Total Synthesis of Resveratrol Oligomers: A Modular Biomimetic Approach via Persistent Radicals

by

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DEDICATION

To Jordan, Christine, and Allen – for your unwavering support

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"The mountains are calling and I must go."
-John Muir

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LIST OF ABBREVIATIONS

°C	degrees Celsius
[O]	oxidant
δ	chemical shift (ppm)
μL	microliters
μM	micromolar
Ac	acetyl
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
ATRA	atom transfer radical addition
BDE	bond dissociation enthalpy
Bn	benzyl
Boc	tert-butyloxycarbonyl
BRSM	yield based on recovered starting material
Bu	n-butyl
Cbz	carboxybenzyl
Cp	cyclopentadienyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DFT	density functional theory
DHB	dihydrobenzofuran
DHBs	dihydrobenzofurans
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDG	electron-donating group
eq	equivalents
ESI	electrospray ionization
Et	ethyl
EtOH	ethanol
EWG	electron-withdrawing group
FTIR	Fourier transform infrared spectroscopy
g	grams
HAT	hydrogen atom transfer
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HRP	horseradish peroxidase
HSQC	heteronuclear single quantum coherence
HMBC	heteronuclear multiple bond correlation
HWE	Horner–Wadsworth–Emmons reaction
Hz	Hertz
IBX	2-iodoxybenzoic acid
iPr	isopropyl

J	coupling constant (Hz)
KHMDS	potassium bis(trimethylsilyl)amide
KOH	potassium hydroxide
kr	radical recombination rate constant
L	liters
LiHMDS	lithium bis(trimethylsilyl)amide
LiOAc	lithium acetate
m	multiplet
M	molar concentration
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligrams
MHz	megahertz
min	minutes
mm	millimeters
mmol	millimoles
MOM	methoxymethyl
mol	mole
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
NaOMe	sodium methoxide
$Na_2S_2O_3$	sodium thiosulfate
H_2O_2	hydrogen peroxide
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
Tf	triflate

Pd/C	palladium on carbon
PG	protecting group
PhLi	phenyllithium
Piv	pivalate
PMB	para-methoxybenzyl
PPh_3	triphenylphosphine
ppm	parts per million
PRE	persistent radical effect
PSIG	pounds per square inch gauge
q	quartet
QMD	quinone methide dimer
RSE	radical stabilization energy
rt	room temperature
s	singlet
t	triplet
TBAF	tetra-n-butylammonium fluoride
TBDPS	tert-butyldiphenylsilyl
TBS	tert-butyldimethylsilyl
tBu	tert-butyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
TEA	triethylamine
TEAOAc	triethylammonium acetate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl

ABSTRACT

This thesis describes the development of scalable, practical routes to resveratrol oligomers, a class of polyphenolic natural products with broad biological activities including anticancer, antifungal, and anti-inflammatory properties. The approach uses carbon-centered radicals, which have fascinated chemists since their discovery over 120 years ago. This thesis reports studies on the synthesis of resveratrol dimers and trimers by exploiting the persistent radical effect, a kinetic phenomenon wherein long-lived radicals selectively react with a short-lived partner. Central to this strategy is a bis-quinone methide intermediate that exists in equilibrium with persistent phenoxy radicals, enabling selective radical coupling and cyclization of simple resveratrol building blocks into complex oligomeric architectures with an emphasis throughout on reproducible, scalable chemical processes. Chapter 1 summarizes the history of the persistent radical effect and its application in natural product synthesis, followed by a review of resveratrol oligomer biosynthesis and prior synthetic approaches. The chapter concludes with the Stephenson laboratory's past efforts towards resveratrol oligomers, including the persistent radical equilibrium between a bis-quinone methide dimer and its component phenoxy radicals. Chapter 2 describes the development of a scalable method for the synthesis of trans-2,3-diaryl dihydrobenzofurans using the persistent radical effect. To implement this strategy in the total synthesis of resveratrol oligomers, the C3 blocking group was adapted from *tert*-butyl to triisopropylsilyl. This strategy was validated experimentally and a scalable synthesis of the bis-quinone methide reagent was achieved through a series of process chemistry optimizations. Chapter 3 reports the first selective, biomimetic total synthesis of five resveratrol dimers, delta-viniferin, epsilon-viniferin, gnetin C,

ampelopsin B, and ampelopsin F. Selective protection of resveratrol provided differentially functionalized monomers that, upon microwave-assisted radical oligomerization, gave controlled access to C3, C10, and C12 dihydrobenzofuran regioisomers. This study validated the use of a microwave oligomerization as an enabling strategy, establishing a general platform for higher order oligomer synthesis.

Chapter 4 describes synthetic efforts toward six resveratrol trimers. The first half of the chapter details studies toward davidiol A and distichol, two indane-derived trimers whose synthesis required development of a protected indane dimer core. Investigation of carbon-silyl protecting groups revealed an unexpected change in cyclization selectivity compared to carbon-tert-butyl groups, a mechanistically informative result that guided route redesign. The steric demands of the fully protected indane core presented challenges to dihydrobenzofuran formation, and the approach was set aside to pursue more tractable targets. The second half of the chapter redirects toward laetevirenol C, D, E, and parthenocissin B, a related set of indane-derived trimers whose core was forged via a direct silver-mediated oxidation strategy. Oligomerization of these cores provided divergent access to trimeric scaffolds, with final deprotection efforts currently underway. This chapter concludes with a discussion of future directions, outlining how the dimeric intermediates and synthetic methods developed throughout this thesis provide a clear and practical path toward a broad array of resveratrol trimers and higher order oligomers.

Chapter 1 Radicals in Natural Products: de Novo Syntheses and Resveratrol Oligomer Biosynthesis

1.1 Introduction

In 1900 Professor Moses Gomberg published the first instance of trivalent carbon (**1.2**, Figure 1.1), research conducted at the University of Michigan.[1] This serendipitous finding arose from attempts to prepare hexaphenylethane (**1.4**) from triphenylmethyl chloride (**1.1**). A white crystalline solid was isolated, with elemental analysis not matching hexaphenylethane (**1.4**). Upon further analysis it was found to be dimer **1.3** which Gomberg hypothesized formed via reaction with oxygen. By using a carbon dioxide atmosphere tertiary carbon centered radical **1.2** was formed, which dimerized with **1.5** forming **1.6**. There was no direct evidence of **1.2** presented in Gomberg's original publication, but an array of experiments including trapping of **1.2** with chlorine, bromine, and iodine providing rationale for the formation of **1.2** *in situ.*

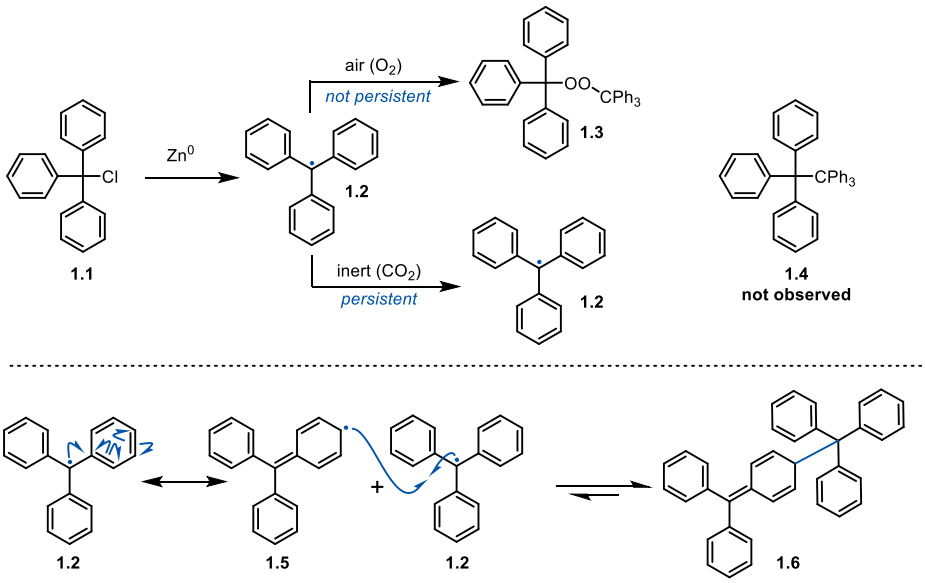


Figure 1.1 Gomberg's discovery of the triphenylmethyl radical

While Gomberg saw the promise of this finding, famously attempting to "reserve the field for myself," the publication was met with fierce skepticism.[2] It was not until 1968 that the equilibrium between **1.2** and **1.6** was thoroughly investigated, finding that 99.99% of the material isolated by Gomberg was **1.6**.[3] The intense research interest surrounding Gomberg's trivalent carbon has grown into the field of radical chemistry. With humble beginnings as an academic intellectual curiosity, radical chemistry has evolved into an indispensable tool for the selective synthesis of a vast array of organic architectures.

1.2 Radical Stability and Persistence

The Gomberg radical (**1.2**) epitomizes both concepts of "stability" and "persistence," first conceptually introduced by David Griller and Keith Ingold in 1976.[4] Stability is a thermodynamic parameters, where the C-H bond dissociation energy must be lower than corresponding alkane, such as methane (105 kcal/mol) for triphenylmethane, to be considered "stable." This is a rather low bar, as many C-H bonds fulfill its criteria, including triphenylmethane (**1.2,** 81 kcal/mol).[5] Persistence is instead a kinetic parameter, where a radical must have a "lifetime significantly greater than methyl radical under the same conditions." By this definition triphenylmethane is also a persistent radical, as it has appreciable lifetime under an atmosphere of carbon dioxide. This underscores the importance of rigorous Schlenk line technique when working with radicals, as even small quantities of trace impurities such as oxygen can affect the persistence of a radical equilibrium.

The persistence of radicals is often dictated by their propensity to undergo 1st and 2nd order decay (Figure 1.2). These pathways are present even under inert conditions and are therefore innate to any radical system. A 1st order decay pathway of **1.7** is provided as an example where β-scission provides an olefin (**1.8**), and a methyl radical (**1.9**). While this process does produce a radical,

radical persistence is discerned for an individual radical species, and the lifetime of the methyl radical will be low in nearly all cases due to homocoupling and other decay pathways. Alternatively, there are two predominant 2nd order decay pathways. Radical-radical coupling of two equivalents of **1.10** forms dimer **1.11**. Alternatively, hydrogen atom transfer alpha to the radical of **1.12** with **1.10** forms an olefin (**1.13**) and alkane (**1.14**).

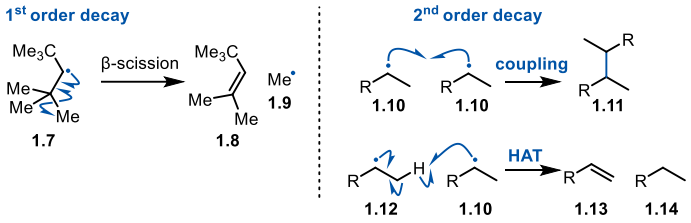
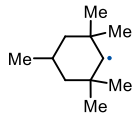
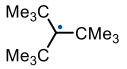
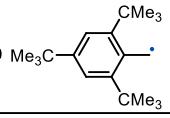


Figure 1.2 Carbon centered radical decay pathways

Over a series of publications Ingold and co-workers used electron paramagnetic resonance spectroscopy to probe the stability and persistence of organic free radicals.[6–9] A selection of this data is provided for comparison (Table 1.1). The radical half-life is presented as its *common* logarithm (base 10) out of convenience. To probe sterics both methyl (**1.19**) and ethyl (**1.15**) were probed, with neither demonstrating persistence with micro-second lifetimes. Notably the ethyl does represent a more than doubling of the radical lifetime (20 to 51 μs), yet this change is inconsequential. The addition of two flanking *tert*-butyl groups (**1.16**) shields the radical from coupling, therefore significantly extending its half-life to more than a minute (63 sec). This principle holds true for ring systems such as **1.17** where adjacent dimethyl groups suppress coupling, resulting in 1st order decay kinetics. A *tris*-*tert*-butyl (**1.18**) retains this trend as well. Notably **1.19**, the substituted toluene derived radical is not persistent even with the strong resonance contribution present. This is due to dimerization approaching the diffusion-controlled limit.[8]

Table 1.1 Radical lifetimes, persistence, and decay kinetics

Label	Radical	Log ($T_{1/2}$ / sec)	Persistent?	Decay Kinetics
1.9		-4.7	No	2
1.15		-4.3	No	2
1.16		1.8	Yes	2
1.17		2.4	Yes	1
1.18		2.7	Yes	2
1.19		-3.4	No	2

Of the many unique properties of radicals, the trends in coupling when both transient and persistent radicals are present is dictated by the persistent radical effect.[10,11] This term, first coined in 1991 by Finke and Daihk,[12,13] had experimental evidence as far back as 1936 by Bachmann and Wieslogle (Figure 1.3).[14] It was found that pentaphenylethane (**1.20**), when heated to 100 °C in DCE (**1.21**), returns starting material (**1.20**) in 87% yield while also producing a small portion (2%) of **1.24**. This contrasts to the behavior of **1.20** under an oxygen atmosphere which is consumed in mere minutes. From this experiment a set of two peroxides were formed (**1.25, 1.26**). The combination of these results illustrates that C-C bond cleave is present under thermolysis conditions, providing the transient radical **1.22** and the persistent Gomberg racial **1.23**. The persistent radical effect dictates that the coupling of a transient and persistent radical selectively produces **1.20**, and by analogy **1.25**, while the coupling of two transient radicals (**1.22**) rapidly depletes the effective concentration of this species, thereby further promoting the transient-persistent coupling mode.

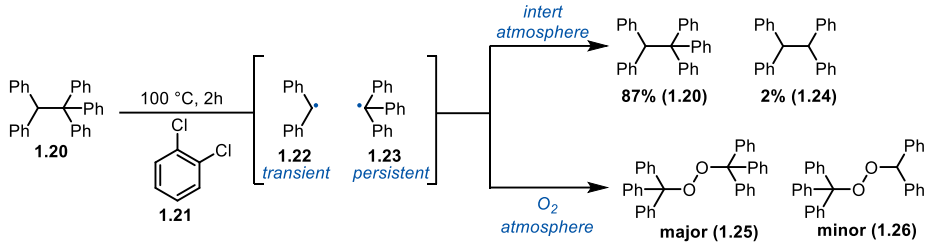


Figure 1.3 Bachmann and Wiselogle's experimental evidence for persistent radical effect

A single transformation which contains all elements of the persistent radical effect is the Barton reaction (Figure 1.4).[15–18] An *in situ* generated nitrile ester (**1.25**) undergoes photolysis, providing persistent NO radical (**1.26**) and alkoxy radical (**1.27**). Intramolecular hydrogen atom transfer generated transient carbon centered radical (**1.28**) which selectively couples with persistent NO radical (**1.26**) which after tautomerization provides oxime **1.29**. The coupling of two persistent NO radicals (**1.26**) is thermodynamically unfavorable and reversible, thereby not depleting the concentration of **1.26**. In contrast transient primary radical **1.28** can irreversibly dimerize, rapidly depleting the concentration of **1.28**, thereby promoting persistent radical effect derived coupling of **1.26** and **1.28**.

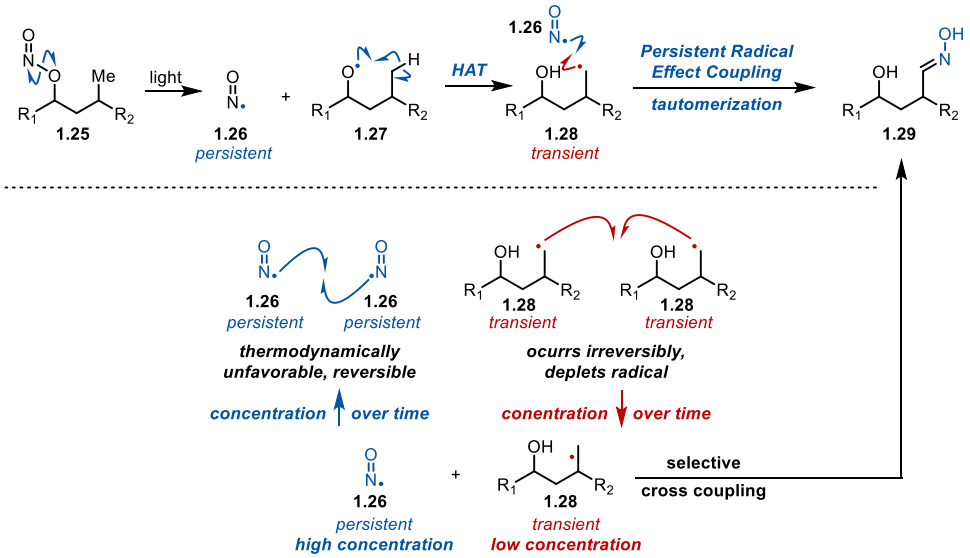


Figure 1.4 Barton reaction as a pedagogical case of the persistent radical effect

1.3 Selected examples of the use of persistent radicals in total synthesis

The uses of persistent radicals in total synthesis are sparce, and frequently rely on either named reactions (Barton reaction) or the use of a commercial persistent radical equivalent (TEMPO).[19–21] One elegant example of the use of persistent radicals in total synthesis was published by Jahn and co-workers in 2015 (Figure 1.5).[22] The authors reported a tempo adduct (**1.30**) which upon heating in *tert*-butanol homolyzes, giving persistent TEMPO radical **1.31** and transient secondary carbon centered radical **1.32**. An 8-*exo-trig* cyclization is rapid due to its intramolecular nature, providing **1.33** which couples with **1.31**, providing the key caged intermediate (**1.34**). The use of a tempo adduct (**1.31**) which can reversibly homolyze to form **1.31** and **1.32** effectively decreases the concentration of **1.32** in solution, which reduces homocoupling of **1.32**, and unproductive pathway. Only six more steps were required to complete the synthesis of bicyclomycin (**1.35**). The Jahn group has utilized a similar strategy in the synthesis of mechanistically related natural products.[23]

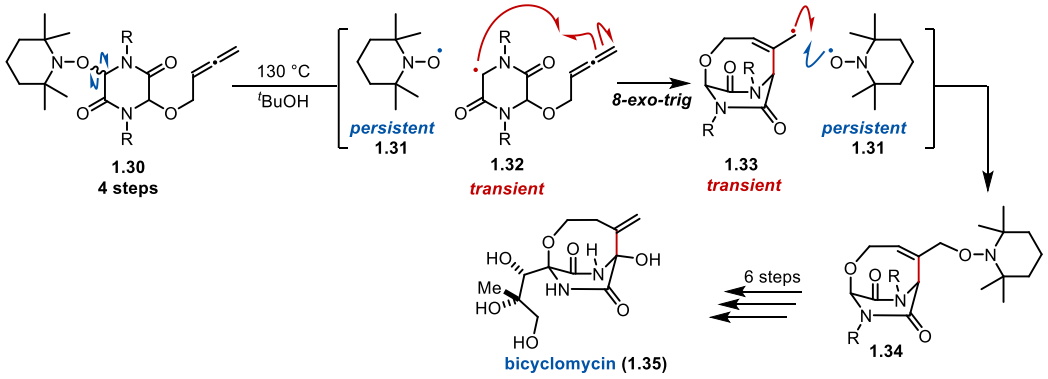


Figure 1.5 Jahn's synthesis of bicylomycin via a TEMPO adduct

A conceptually similar strategy was used by Theodorakis and co-workers in their synthesis of fusarisetin A published in 2018 (Figure 1.6).[24] Preparation of key substrate included transforming Aldehyde **1.36** into beta-keto ester **1.37**. Deprotonation with LiHMDS followed by ferrocene single electron oxidation produced TEMPO adduct **1.38**. Mechanistically, following

single electron oxidation a transient carbon centered radical (**1.40**) is produced, which exists in dynamic equilibrium with **1.42**. A *5-exo-trig* cyclization of **1.40** gave transient radical **1.43** which could selectively couple with TEMPO radical **1.41** via the persistent radical effect. Steroid core **1.38** was elaborated to the natural product fusaristetin A, with the synthesis being just 9 steps and 9.9% overall yield.

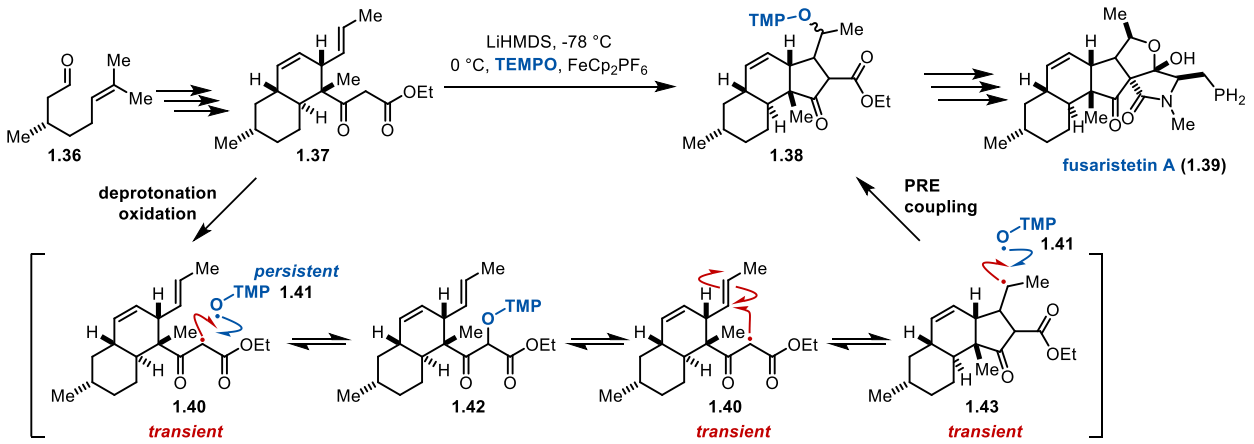


Figure 1.6 Theodorakis' synthesis of fusarisetin A via a TEMPO adduct

1.4 Introduction to Resveratrol Oligomers

Resveratrol (**1.44**, Figure 1.7) was first isolated from *vitis viniferia*, the common grapevine in 1977 by Langcake and Pryce.[25] It was detected after irradiating the leaf with 260 nm (ultraviolet) light. This acted as an abiotic stressor on the plant, which allowed the detection of resveratrol (**1.44**) followed by the dimer ε-viniferin (**1.45**) and the resveratrol trimer α-viniferin (**1.46**). This order of isolation lent credence to the postulation by Langcake and Pryce that resveratrol is directly oligomerized to the higher order species. This mode of detection after exposure of the plant to a biotic or abiotic stress classify these compounds as phytoalexins, which are antimicrobial compounds which act as broad-spectrum defense agents.

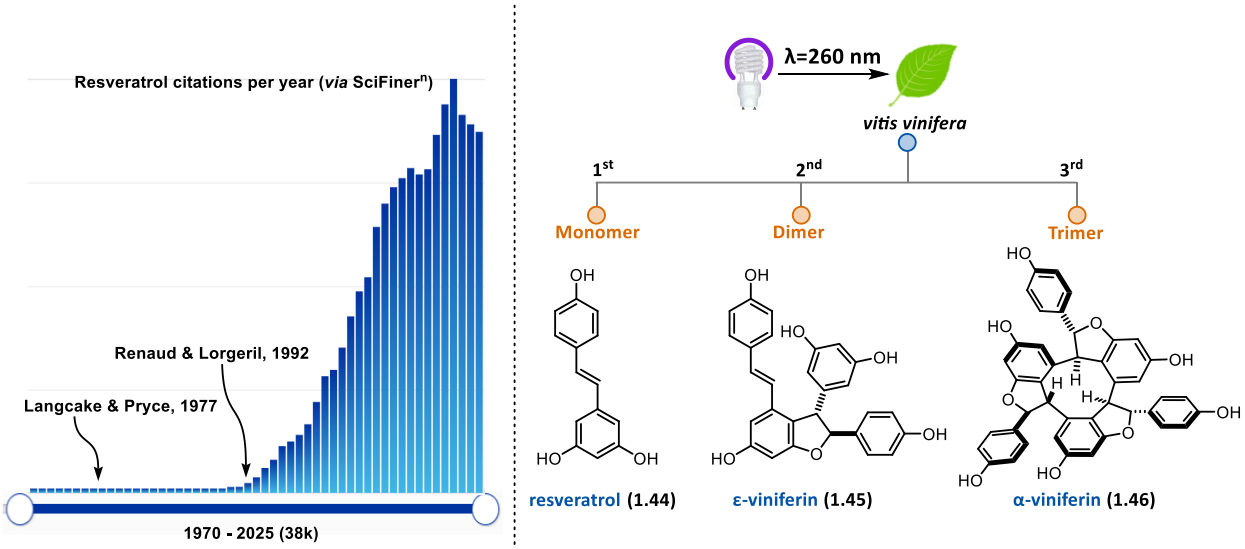


Figure 1.7 Introduction to resveratrol oligomers: isolation and rise to fame

Resveratrol and its oligomers remained in a class of relative obscurity until 1992 when Renaud and Lorgeril reported an epidemiological study.[26] Their study relates to the French Paradox, an observation that France has low levels of coronary artery disease despite having diets high in saturated fats. They postulated that the resveratrol found in wine provided cardioprotective properties (Figure 1.8). More specifically, they proposed that through a hemostatic mechanism resveratrol prevents atherosclerosis.

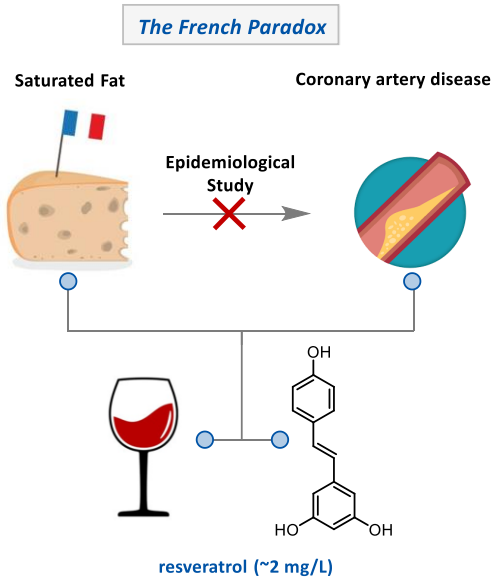


Figure 1.8 Resveratrol postulated as an explanation of the French Paradox

While Renaud and Lorgeril's study has resulted in an explosion of interest into resveratrol and its oligomers, over the past 30 years the role of resveratrol in health remains opaque.[27–30] Resveratrol has failed more than 50 clinical trials and has not been approved for a single indication.[31] This is due to a variety of factors, including less than 1% of resveratrol is orally bioavailable.[32] In addition to resveratrol (**1.44**, Figure 1.9), more than 300 resveratrol oligomers have been isolated, from dimer to octamer, with even multiplicities best represented.[33] These higher order oligomers of resveratrol also provide intriguing biology, including anticancer, anti-inflammatory, and antifungal activity.[34] The biological properties of these resveratrol oligomers is underexplored, partially due to the requirement of isolation from suitable plant matter. To expand the biological studies of oligomers beyond those easily isolated, the Stephenson lab sought to develop scalable, modular routes to these natural products. To accomplish this, we turned to the biosynthesis of these oligomers for inspiration.

Biosynthetically the resveratrol oligomers are synthesized via enzymatic oxidation of resveratrol (**1.44**, Figure 1.9), providing a delocalized radical, with resonance across C3 (**1.44a**), C8 (**1.44b**), C10 (**1.44c**), and C12 (**1.44d**). The resveratrol dimers δ-viniferin (**1.48**, C3-C8 coupling), pallidol (**1.50**, C8-C8 coupling), and ampelopsin B (**1.52**, C10-C8 coupling) demonstrate the structural diversity obtainable from a small subset of radical coupling and cyclizations. The enzymes which catalyze these transformation have not been isolated,[33] but are thought to proceed via an oxidation followed by dirigent protein templating (from the Latin word *dirigere* meaning to steer or guide). For the related polyphenolic class of lignans Davin and Lewis have demonstrated the utility of dirigent proteins to mediate stereoselective phenol dimerization.[35,36] In the presence of a chemical or enzymatic oxidant the dirigent protein, though not itself an oxidase, facilitates stereoselective coupling that is racemic in its absence.

Synthetic chemists have been motivated to synthesize the resveratrol oligomers to both deduce their biosynthetic pathways and provide material to biologists eager to explore their bioactivity.[33] The earliest work on synthesizing resveratrol oligomers consisted of the direct oxidation of resveratrol with the promiscuous horseradish peroxidase (**1.44**, Figure 1.9) resulting in a smattering of dimers and higher order phenols in an unselective fashion.[37–40] Selectivity can be obtained through judicious control of metal and temperature in some cases.[41–43] These methods primarily synthesize δ-viniferin (**1.48**) as C3-C8 is the predominant unselective coupling mode. The use of C3 *tert*-butyl groups on resveratrol (**1.53**) diverts enzymatic selectivity from C3-C8 to C8-C8 as reported by Hou and co-workers in their 2006 total synthesis of quadrangularin A.[44] Sparce examples exist of the synthesis of higher order oligomers (trimers, tetramers, etc.) with unselective oxidations, primarily due to challenges in detection and isolation of the complex mixtures generated.[33]

Of the *de novo* methods used to synthesize resveratrol oligomers, many utilize activation of phenols (**1.54**) to their corresponding quinones (**1.55**) followed by inter and intramolecular cyclizations to construct the natural product cores (**1.56**).[45–48] One subset of this reactivity which has been highly successful in the synthesis of diversified trimers and tetramers was reported by Snyder and co-workers in 2011.[49] The authors utilized electrophilic bromination of pre-synthesized dimers (**1.57**) to from diversified cores (**1.58**). A robust eight-step synthetic sequence was developed to synthesize dihydrobenzofurans (DHBs, **1.59**) from the halogenated cores.

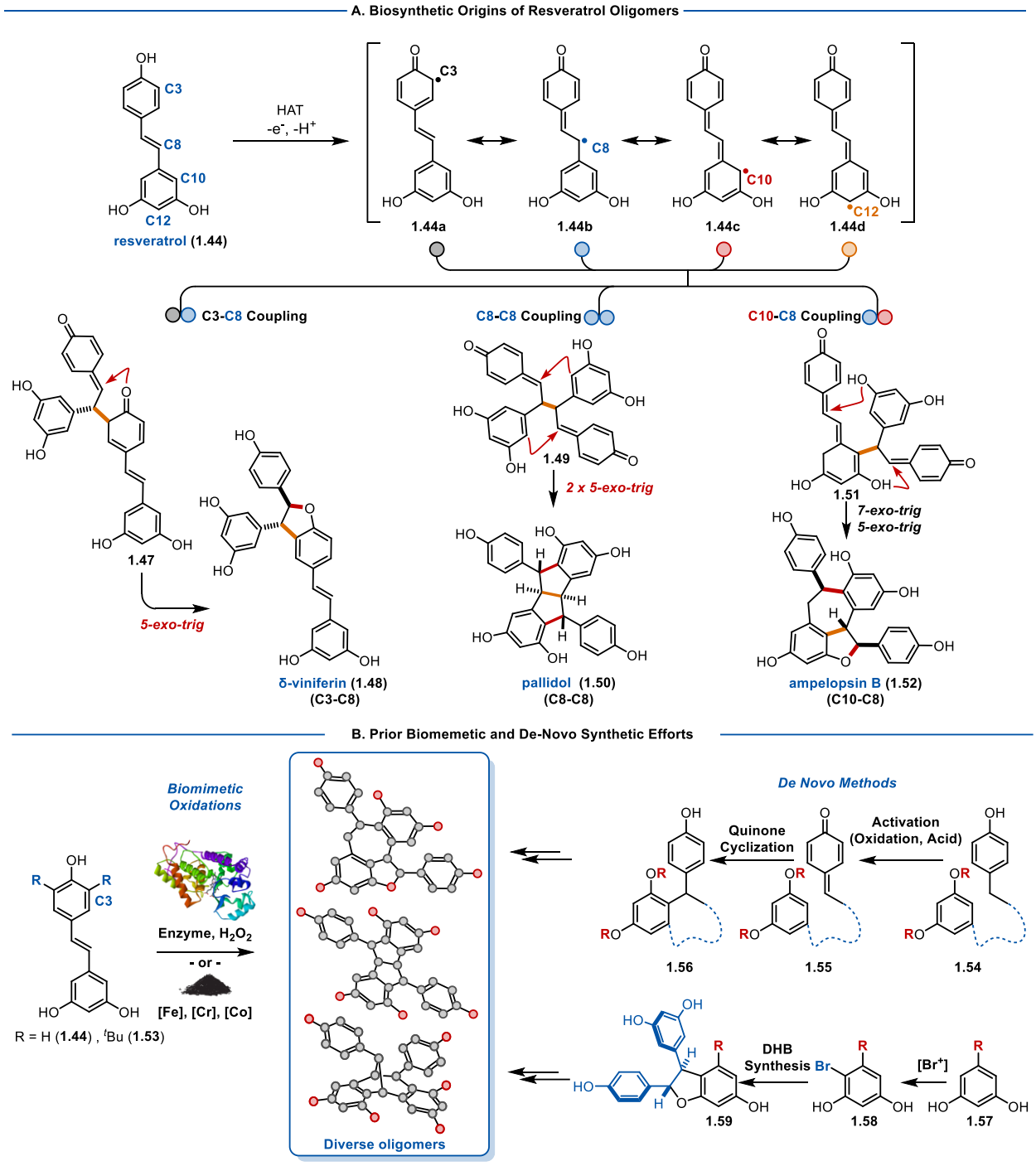


Figure 1.9 A. Resveratrol oligomer biosynthesis and coupling pathways B. Prior biomimetic and de-novo synthetic efforts towards resveratrol oligomers

1.4.1 Total Synthesis of pallidol and quadrangularin A via *bis*-quinone methide cyclization

In 2012, following a departmental seminar given by Professor Scott Snyder at Boston University the Stephenson lab became interested in the synthesis of resveratrol oligomers. This interest was piqued by the opportunity to apply photoredox catalysis to the oxidation of resveratrol, which was being applied to other synthetic projects in the Stephenson lab.[50–53]

We chose to use protected resveratrol **1.60** (Figure 1.10) with C3 *tert*-butyl groups and southern benzyl protection of the resorcinol. This approach was jointly motivated by Hou's efforts with C3 protection and the desire to dampen the reactivity of the resorcinol during oxidation.[44] Through extensive screening of photochemical reaction conditions and judicious control studies we found that potassium *tert*-butoxide in CCl_4 irradiated in an oxygen atmosphere provided 60-80% yield of *bis*-quinone methide (BQM, **1.61**, **1.62**). Due to challenges with scaling this reactivity, we instead switched to the chemical oxidant ferrocenium hexafluorophosphate. This provided yields exceeding 95% at scale of an approximately 1:1 ratio of the *meso* (**1.61**) and C_2-symmetric (**1.62**) BQM diastereomers. We found that subjecting this mixture to the strong Lewis acid BF_3•OEt_2 proceeded through a 1:1 mixture of **1.63** (originating from *meso*, **1.61**) and **1.64** (originating from C_2-symmetric**, 1.62**). The difference in cyclization pathways is due to the conformation of diastereomers. Both **1.63** and **1.64** can cyclize (*5-exo-trig*), forming **1.65** and **1.66**, but this point is where the divergence occurs. Diastereomer **1.65** cannot further cyclize due to relative configuration, thereby yielding indane **1.67** once redrawn, while **1.66** can undergo a 2nd *5-exo-trig* cyclization to the pallidol core (**1.68**). Attempts to isomerize quinone **1.67** to the core of quadrangularin A **1.69** with base or acid were unsuccessful. The pallidol core **1.68** smoothly undergoes deprotection via retro-Friedel-Crafts conditions ($AlCl_3$, 80%) to form pallidol (**1.50**).

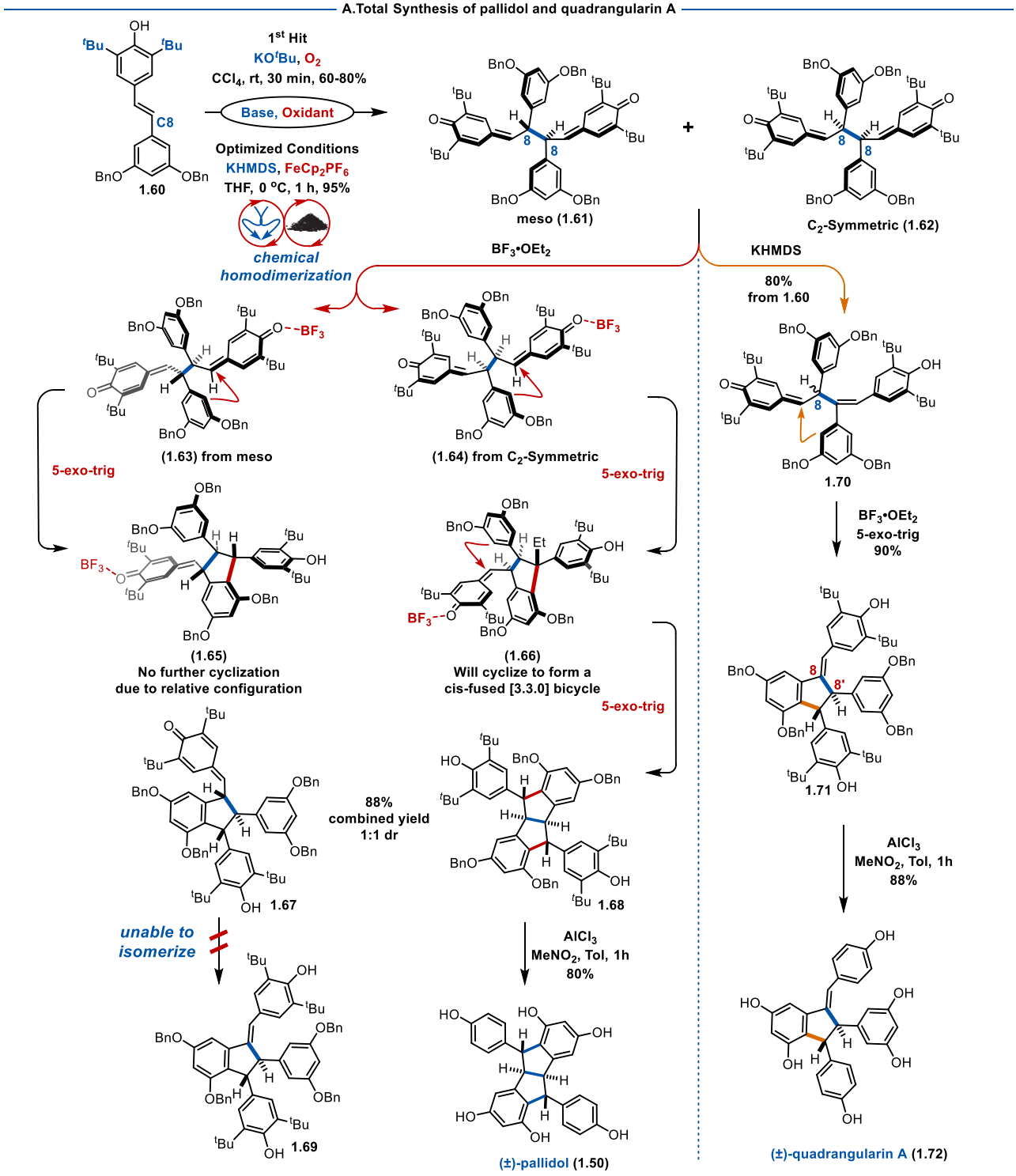


Figure 1.10 Total synthesis of pallidol and quadrangularin A

To synthesize quadrangularin A (**1.72**) the BQM diastereomer mixture generated from **1.60** was subjected to a 2nd aliquot of KHMDS, providing tautomer **1.70** in 80% yield. The same cyclization conditions (BF_3•OEt_2) generated indane **1.71**. Deprotection with $AlCl_3$ was uneventful providing quandrangularin A (**1.72**). To complement our synthetic work, we collaborated with the lab of Professor Derek Pratt (University of Ottawa) to investigate the peroxyl radical trapping ability of these motifs. We found that the natural products synthesized (**1.50**, **1.72**) are not kinetically competitive radical-trapping antioxidants under biologically relevant conditions. This synthesis was the Stephenson labs first foray into resveratrol oligomer total synthesis and motivated us to pursue the synthesis of higher order oligomers (trimers, tetramers, etc.).

1.4.2 Discovery of a persistent radical equilibrium

One of our first attempts to explore novel cyclizations of our BQM (**1.61**, **1.62**, Figure 1.11) produced a result which was confounding on first analysis.[54] The diastereomer BQM mixture (**1.61**, **1.62**) when subjected to TFA in nitromethane produced a single diastereomer of quinone indane (**1.67**) in greater than 90% yield. Our initial efforts to explain this reactivity included subjecting both **1.70** and **1.69** to the same conditions (TFA, **$MeNO_2$**) to replicate the reactivity. In both cases no conversion was observed. This prompted a reanalysis of results, and upon careful observation it was noted that the BQM (**1.61**, **1.62**) when exposed to heat turned from pale yellow to green, returning to yellow upon cooling. A crossover experiment of two BQMs (**1.61/1.62 and 1.74**) upon mild heating in $CDCl_3$ (50 °C) allowed detection of **1.76**, the radical crossover product. This material was also characterized by ^{1}H NMR, thereby confirming our suspicions that a persistent radical equilibrium was in effect. The bond dissociation energy was measured as 17 kcal/mol via EPR spectroscopy which was also consistent with the room temperature formation of a phenoxy radical.[54] These studies were prompted by similar work reported in 1969 by Becker,[55]

wherein the author disclosed the equilibration of BQMs in chloroform with the corresponding phenoxy radicals through a homolytic C-C bond cleavage. This property is akin to that of Gomberg's triphenylmethyl radical.[1,3] These mechanistic findings support the conclusion that when **1.61**/**1.62** is treated with acid the *meso* diastereomer freely cyclizes, while the persistent radical equilibrium scrambles the C8 stereocenters, allowing the irreversible cyclization to **1.67** to ultimately consume all starting material.

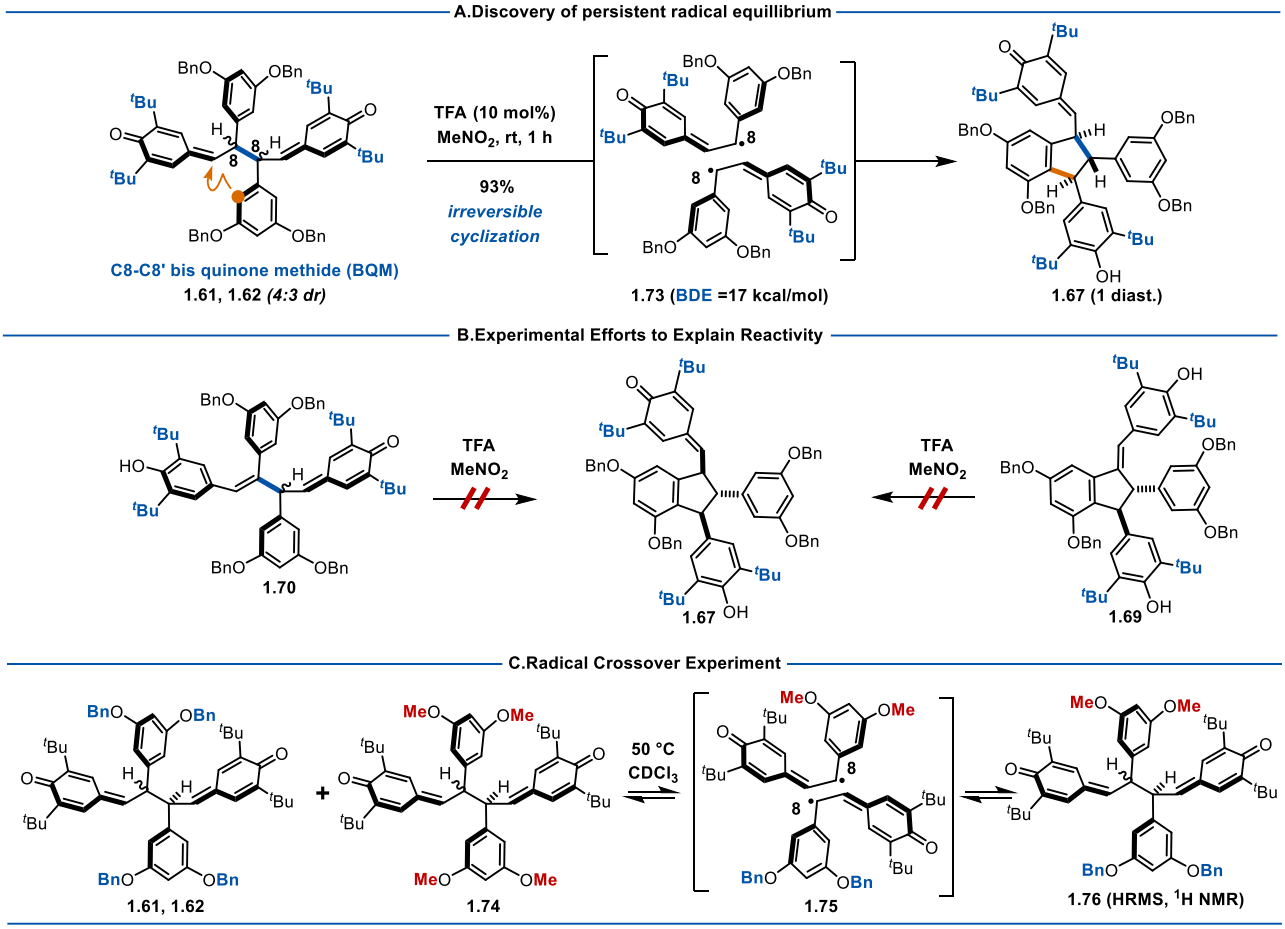


Figure 1.11 Discovery of a BQM persistent radical equilibrium and control experiments

1.4.3 Total synthesis of resveratrol tetramers via a persistent radical equilibrium

With the properties of BQM **1.61**/**1.62** fully characterized, we sought to apply this framework to the total synthesis of resveratrol tetramers.[54] We began by synthesizing a *tert*-butyl protected dimer ε-viniferin via a Wittig reaction (not shown) of a protected aldehyde and

phosphonium salt, mirroring work reported by the Snyder lab in their synthesis of caraphenol A.[48] This route produced **1.77** (Figure 1.12) in 17% yield over 9 steps (LLS). Using the same oxidative dimerization conditions produced BQM tetramer **1.79** as a single diastereomer. This selectivity was remarkable, as this dimerization of **1.77** could produce a set of six diastereomers (three homochiral, three heterochiral) but experimentally produces only one. This BQM tetramer (**1.79**) exhibits the same radical characteristics by EPR as the radical dimer (**1.61/1.62**).

We chose to use similar cyclization conditions as our dimers publication (BF_3•OEt_2) to cyclize our tetramer, and two *5-exo-trig* cyclizations produced the core of nepalensinol B (**1.87**, 44%). The minor product was a 9:1 dr of vateriaphenol C core **1.81** to hopeaphenol core **1.83** (9%) by consecutive *7-exo-trig* cyclizations. Attempts to elaborate these tetrameric cores to the corresponding natural products was unsuccessful. The Retro-Friedel-Crafts conditions ($AlCl_3$) which were used to deprotect resveratrol dimers were unsuitable as the tetramers contained dihydrobenzofurans, acid labile heterocycles. A screening of other acidic conditions did not reveal any productive reactivity.

We aimed to retain the same strategy but instead choose a C3 protecting group which was more labile to deprotection. Trimethylsilyl (TMS) was chosen, and the corresponding dimer (**1.78**) was synthesized (9 steps LLS, 16%). The oxidative dimerization of **1.78** provided tetrameric BQM **1.80** in 63% yield. Lewis acid cyclizations, analogous to those previously used, provided 59% of **1.88**, the nepalensinol B core, and 15% of a 9:1 mixture of *7-exo-trig* products (**1.82**, **1.84**). Subsequent hydrogenolysis (Pd/C, $\mathbf{H_2}$) and TMS deprotection (TFA, CH_2Cl_2/$MeNO_2$) provided nepalensinol B (**1.89**) and a 9:1 mixture of vateriaphenol:hopeaphenol (**1.85**, **1.86**). This work demonstrated the utility of BQMs in diastereoselective cyclizations, as the radical equilibrium promotes exquisite selectivity.

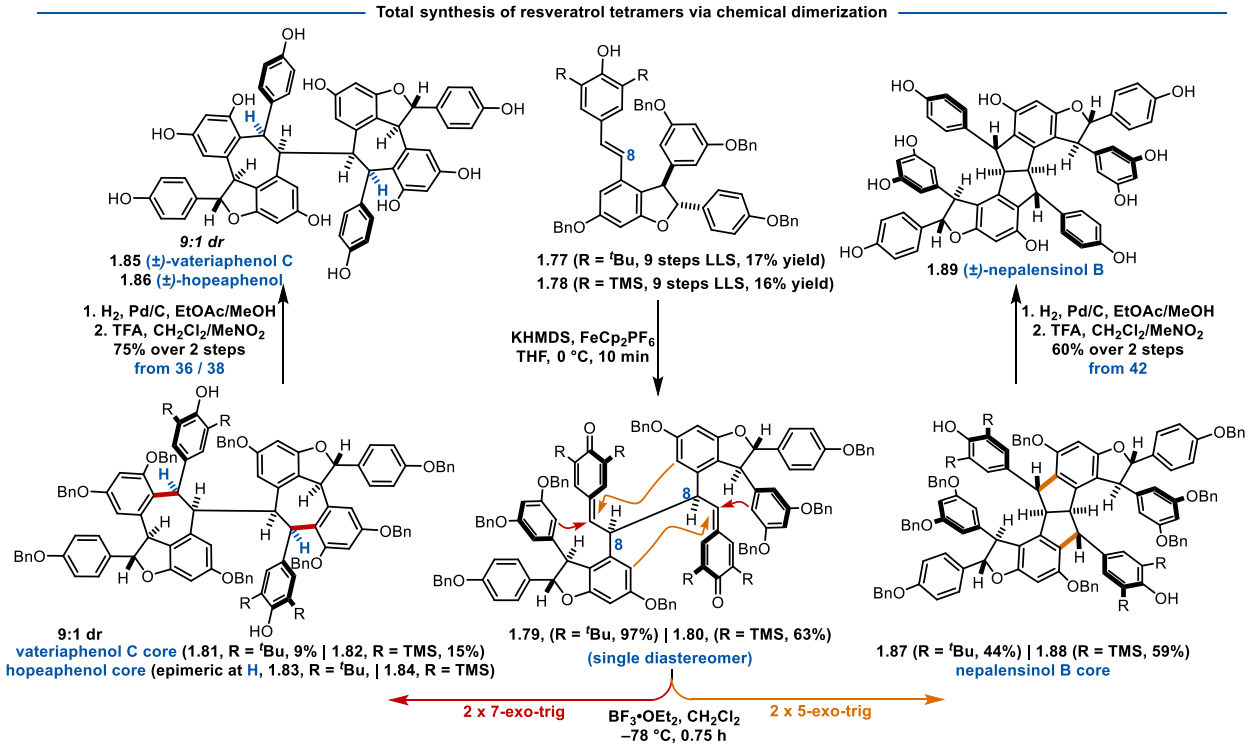


Figure 1.12 Total synthesis of resveratrol tetramers via a chemical dimerization and cyclization

Exploration of other uses for BQM persistent radical

Upon completing our 1st publication on resveratrol tetramers, we sought to leverage the persistent radical nature of our BQM (**1.73**, Figure 1.13) for other productive chemistry. As we had demonstrated that this BQM was likely a key intermediate in the biosynthesis of resveratrol oligomers, we developed a mechanistic hypothesis for the synthesis of dihydrobenzofurans (**1.94**) from a BQM (**1.73**) and a phenol (**1.90**). Gratifyingly we found early success in this method. Heating the two starting materials (**1.73**, **1.90**) in acetone to 100 °C in a sealed tube for 24 h formed 82% of DHB (**1.94**) which was assigned as a 10:1 mixture of *trans*:*cis* diastereomers. Near quantitative amounts of stilbene (**1.60**) were also isolated. This led to the mechanistic hypothesis that hydrogen atom transfer between phenoxy radical (**1.73**) and phenol (**1.90**) provides a set of two radicals. One is transient (**1.91**), while the other persistent (**1.92**), which allows selective cross coupling via the persistent radical effect, which governs the kinetic selectivity in these

systems.[4,10,11] Tautomerization provides **1.93** and cyclization yields DHB (**1.94**), with the isolation of **1.60** providing evidence for the proposed mechanism. Attempts to remove the C3 *tert*-butyl groups were unsuccessful, as the use of $AlCl_3$ or other acidic conditions resulted in the degradation of the DHB ring.

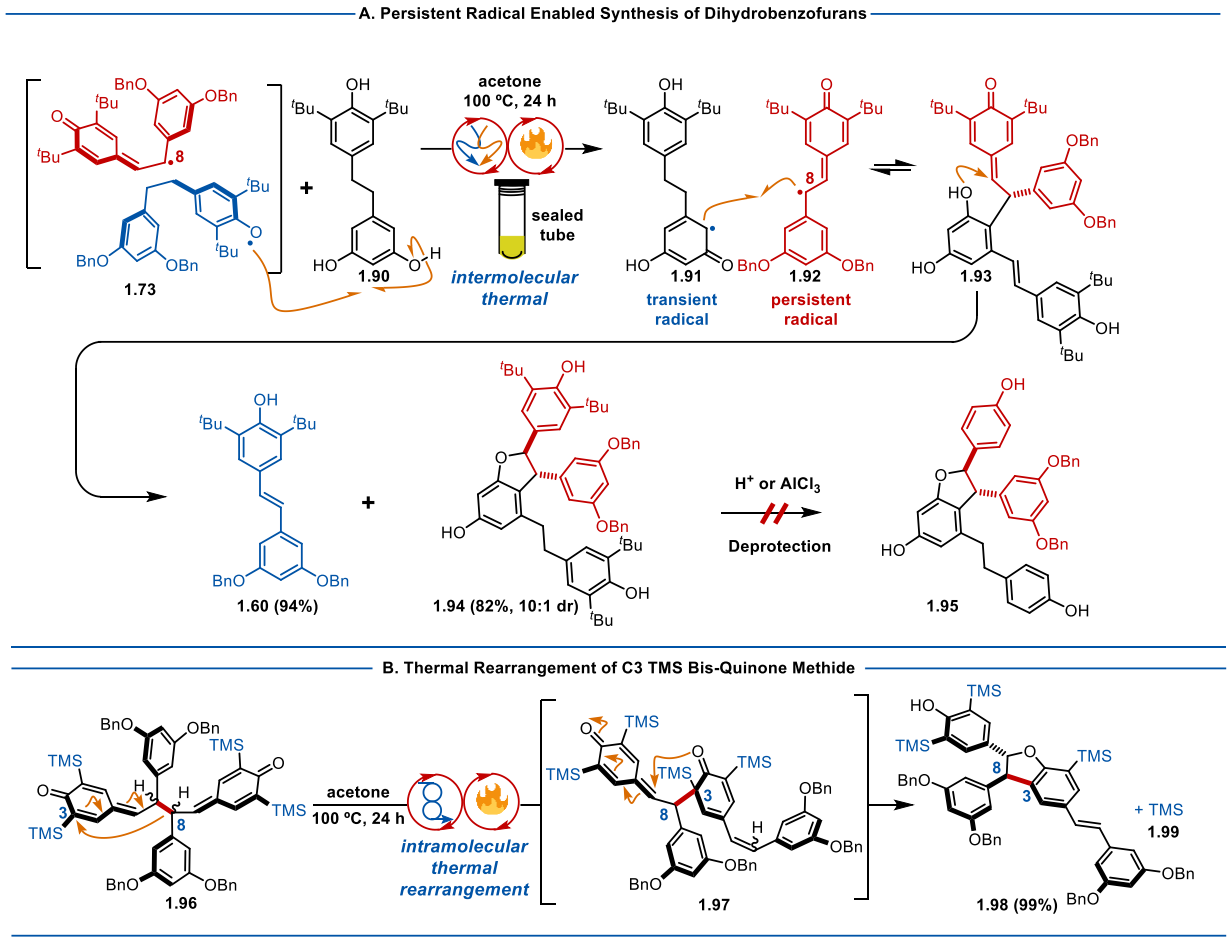


Figure 1.13 Persistent radical effect synthesis of dihydrobenzofurans and discovery of a thermal C3-C8 rearrangement of silyl BQM

To circumvent the challenges associated with C3 *tert*-butyl groups TMS were substituted, as we saw success with this method in the synthesis of tetramers. A BQM with C3 TMS groups (**1.96**) when subjected to our thermal oligomerization conditions does not produce any intermolecular DHB product. Instead, an intramolecular, C3-C8 rearranged DHB is formed (**1.98**)

alongside one equivalent of TMS (**52**). Additional computational investigations provided mechanistic clarity, as a C3 TMS BQM (**1.96**) has a 7.4 kcal/mol while the C3 *tert*-butyl BQM (**1.73**) has a 13.9 kcal/mol barrier to rearrangement.[56] This is consistent with the experimental evidence that **1.96** rearranges intramolecularly, forming DHB while **1.73** does not. This rearrangement effectively degrades the BQM reagent (**1.96**) and outcompetes the formation of any intermolecular DHB products.

1.4.4 Total synthesis of resveratrol tetramers vitisin A and D

Eager to utilize our newfound C3-C8 thermal rearrangement, we set our sights on vitisin A (**1.103**, Figure 1.14) and D (**58**), resveratrol tetramers which we were to synthesize from a suitable tetrameric BQM.[56] Our synthetic efforts began by preparing a similar protected ε-viniferin dimer (**1.99**) as was used in our first tetramer publication.[54] This synthesis was completed in 16% overall yield with 14 steps along the longest linear sequence. In 2018 our lab published an electrochemical method to enable the scalable and tunable synthesis of a range of BQMs.[57] We presented a substrate scope of differentially protected BQMs, but further discussion of this work lays outside the scope of this account. We utilized our electrochemical method in the dimerization of **1.99** to BQM tetramer (**1.100**) in 63% yield, forming a single diastereomer, as was the case with past studies of tetramers. The intramolecular rearrangement to key intermediate **1.101** proceeded smoothly (80%). We next sought to find conditions suitable to convert **1.101** to different vitisin tetramers. Exposure of **1.101** to HCl in methanol provided vitisin A (**1.103**, 60%). Mechanistically this proceeds via DHB ring opening (**1.102**) and 7-*exo*-*trig* cyclization. Acidic rearrangements and cyclizations are known in the resveratrol oligomers, and were key in initial studies of their biosynthesis.[58,59] Alternatively, the use of HF and TEA deprotected all silyl protected oxygens (not drawn) which upon treatment with mild protodesilylation conditions (TMS-Cl, KI, H_2O) providing vitisin D (**1.105**) in 85% yield. Mechanistically this proceeds via stilbene protonation of vitisin A

(**1.104**) and *7-exo-trig* cyclization. Attempts to synthesize vitisin B (not drawn), the uncyclized deprotection product of **1.101** were unsuccessful. The challenge was in removing all silyl groups while also preventing any cyclization products which occur in the presence of even weak acid. This tetramer synthesis demonstrated the synthetic utility of the intramolecular C3-C8 rearrangement of BQM tetramers.

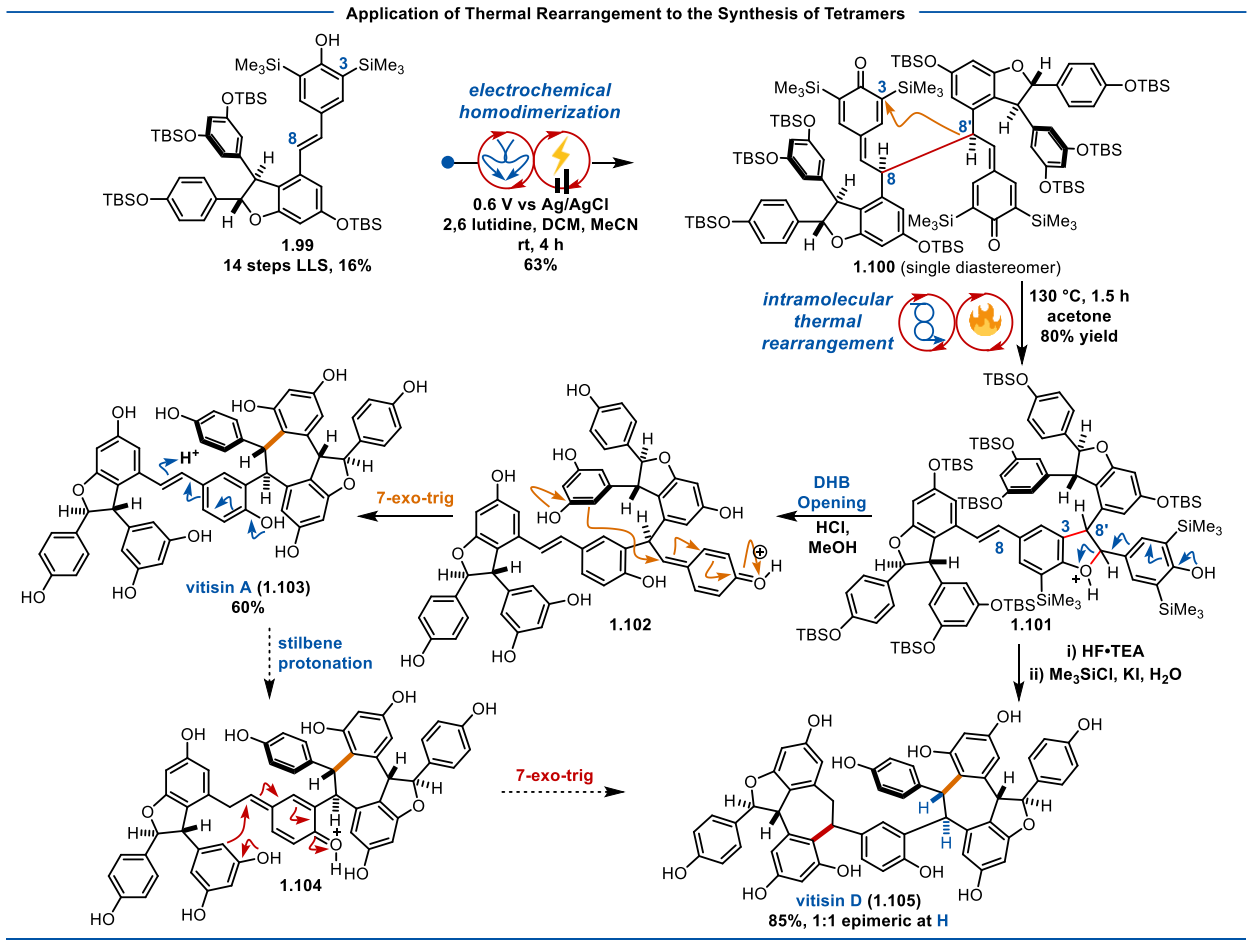


Figure 1.14 Total synthesis of vitisin A and D via a thermal C3-C8 BQM tetramer rearrangement

1.5 Conclusions

The background provided in this chapter illustrates the utility of radicals in the synthesis of complex natural products. Persistent radicals provide a means to selectively engage transient species, enabling transformations that are otherwise challenging. This chapter introduced the resveratrol oligomers as a diverse class of polyphenolic natural products. The principles of stability and persistence were further illustrated by the Stephenson labs synthesis of resveratrol dimers and tetramers which utilize a C3 *tert*-butyl protected BQM which exists as a persistent radical. The discovery of the intramolecular C3–C8 rearrangement of C3 TMS BQMs allowed the synthesis of additional resveratrol tetramers. The work presented here underscores that radicals are not only versatile synthetic tools but also a platform for uncovering mechanistic insights. The strategies and synthesis presented in this thesis build upon the concepts illustrated above.

Chapter 2 Development of a Labile Protecting Group in the Synthesis of Trans-2,3-diaryl Dihydrobenzofurans

2.1 Introduction

[1]The dihydrobenzofuran (**2.1**), and its fully unsaturated congener the benzofuran (**2.2**) are a set of benzo-fused heterocycles which are present in a variety of both natural products (**2.2-2.4**) and drugs (**2.5-2.7**, Figure 2.1).[60,61] The structural diversity and therapeutic applications of this class of molecules is wide. Lithosperic acid (**2.3**), was isolated in 1963 by Jonson and co-workers from the roots of *Lithospermum ruderale*, a flowering plant of the borage family.[62] This natural isolate was found by various research groups to contain anti-HIV activity by inhibiting HIV-1 integrase activity.[63] It has also attracted the attention of synthetic chemists as demonstrated by multiple total syntheses using varied strategies including C-H activation,[64] chromanone to dihydrobenzofuran rearrangement,[65] and palladium-catalyzed annulation.[66] Heliannuol G (**2.4**) was first isolated in 1999 and found to have varied phytotoxic allelopathic activities.[67] An enantioselective synthesis followed shortly thereafter by the Shishido group in 2005, but their prepared sample did not match the NMR spectra from the isolated natural products.[68] A follow up report revised the structure and synthesized the natural product.[69] This theme continues with the

[1] Portions of this chapter have been published in: Roldan, B.J.; Hammerstad, T.A.; Galliher, M.S.; Pratt, A.D.; Stephenson, C.R.J. Leveraging persistent radicals in the formation of trans-2,3-diaryl-dihydrobenzofurans. *Angew. Chem. Int. Ed.* **2023**, 62, e2023058

resveratrol trimer caraphenol A (**2.5**), isolated in 2001, but misassigned as vicinal coupling constants are a notoriously poor predictor of relative configuration.[70]

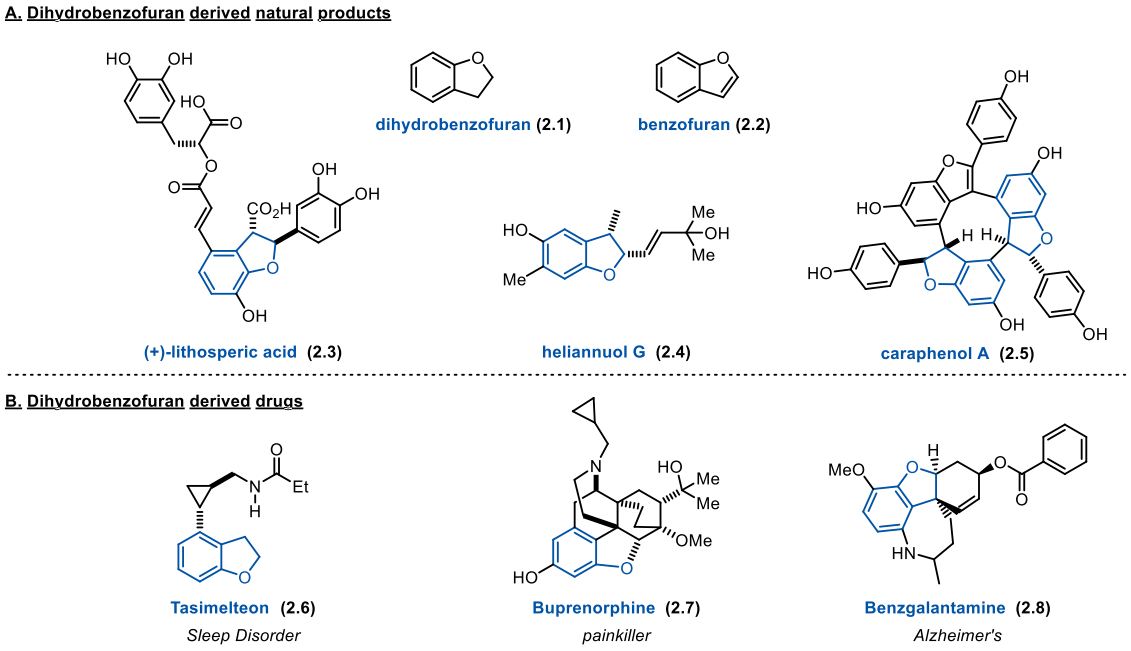


Figure 2.1 Summary of dihydrobenzofuran containing natural products and drugs

Dihydrobenzofurans derived drugs include Tasimelteon (**2.6**), a selective dual melatonin receptor agonist used in the treatment of Non-24-Hour Sleep-Wake Disorder.[71] This most commonly presents in the blind without light perception resulting in the extension of the 24-hour circadian rhythm cycle. This active pharmaceutical ingredient is also the subject of total synthesis, accomplished in only four steps in 48% yield from a vinyl dihydrobenzofuran building block.[72] Buprenorphine (**2.7**) is a potent painkiller medication which is also indicated for the treatment of opioid addition.[73,74] This small molecule dissociates from opioid receptors slowly, resulting in a long duration of action and relief from pain or withdrawal symptoms for upwards of 24 hours. Buprenorphine has many advantages over methadone, an alternative treatment due to its improved safety profile, including a lower risk of overdose and respiratory depression.[75–77] These properties are notable as Buprenorphine was originally developed in the 1960s as a synthetic opioid, and

shares many structural features with other poppy alkaloids including morphine.[78] Benzgalantamine (**2.8**) is indicated for Alzheimer's patients, and was originally designed to minimize side effects.[79] This pharmaceutical is a pro-drug, in which the parent molecule is cleaved *in vivo* to unveil the drug.[80–82] This strategy has a few key advantages, including the ability to optimize the physicochemical, biopharmaceutical, and pharmacokinetic properties while also enabling the delivery of the bioactive molecule. In the case of benzgalantamine, the benzoyl group is cleaved *in vivo*, yielding galantamine.[79] This approach avoids many of the challenges with directly dosing galantamine, as benzgalantamine can pass through the stomach, avoiding many of the gastrointestinal effects associated with other peripheral cholinesterase inhibitors.[79]

2.2 Existing methods to synthesis dihydrobenzofurans

Due to the large number of applications of dihydrobenzofurans, as outlined in Section 2.1, organic chemists have devised numerous creative methods for their synthesis.[83] An overview of these strategies is outlined below, focused on summarizing key aspects of each synthesis (Figure 2.2). The formation of the O-alkyl bond (Figure 2.2, **A**), as demonstrates by Panda and co-workers,[84] begins with an allylic alcohol (**2.9**), primed for a Sharpless Asymetric Epoxidation (**2.8**).[85,86] A standard palladium catalyzed hydrogenation unveils the phenol (**2.9**) which cyclizes under basic conditions to yield the DHB (**2.10**).[87] This strategy was used in the synthesis of heliannuols G and H, related natural products depicted above (Figure 2.1).[88] While this strategy requires prefunctionalization, it allows access to both enationmers of the DHB due to the availability of both (+) and (-) diethyltartrate.[89]

A second approach by Buchwald and co-workers form the O-aryl bond via palladium catalysis (Figure 2.2, B).[90] Key features of this system include the use of di-*tert*-butylphosphinobiaryl ligand and that the mild carbonate bases used allowed the coupling of

enantioenriched substrates without erosion of optical purity. This method was highlighted by the synthes of MKC-242, an antidepressant which was in clinical trials at the time of publication.[91]

Another precious metal approach uses rhodium published as a series of publication from the Davies lab (Figure 2.2, C).[92,93] The decomposition of aryl diazoacetates by a chiral rhodium complex proceeds via intermolecular C-H insertions with both excellent yields and high levels of enantioselectivity. One challenge with this method can stem from the lack of thermal stability of these diazo compounds which has been tracked by differential scanning calorimetry.[94] This method heats a sample and measures the resulting heat flow and can be used to track melting, crystallization, glass transitions, and uncontrolled spontaneous exotherms.[95] Despite these challenges, diazo compounds still see use in process chemistry and industrial scale manufacturing due to their high enantioselectivity in a variety of reactions in well-tuned systems.[96]

Two-component annulations of 1,3-dienes with *o*-iodoaryl acetates, commonly known as a Larock annulation are also well reported.[97] These reactions proceed via a standard mechanism of the substrate (**2.18**) adding to the palladium center via oxidative addition, followed by intramolecular phenol coordination, acetate hydrolysis, and a reductive elimination. This complete cycle regenerated the palladium (0) catalyst. Terminal, cyclic, and internal 1,3 dienes are tolerated as well as both electron-deficient and rich *o*-iodiaryl acetates. Similarly protected amine and free carboxylic acetate functionalities process via a similar mechanism to yield protected indoline and lactones respectively.

A final strategy uses a ring contraction was published by Kampoor and co-workers starting with flavanones (**2.20**, Figure 2.2).[98] In the presence of perchloric acid, trimethyl orthoformate, and thallium (**III**) nitrate an enol ether (**2.21**) is formed, followed by orthoformate addition (**2.22**) and ring contraction to the DHB. A key detractor of this method is the use of 70% perchloric acid,

which is known to have significant safety liabilities.[99] While safer than the anhydrous form, which is known to spontaneously explode, the aqueous solution can still be prone to the formation of unstable perchlorates. These often form at the bottle cap and have been reported to explode from friction when attempting to unscrew the bottle.

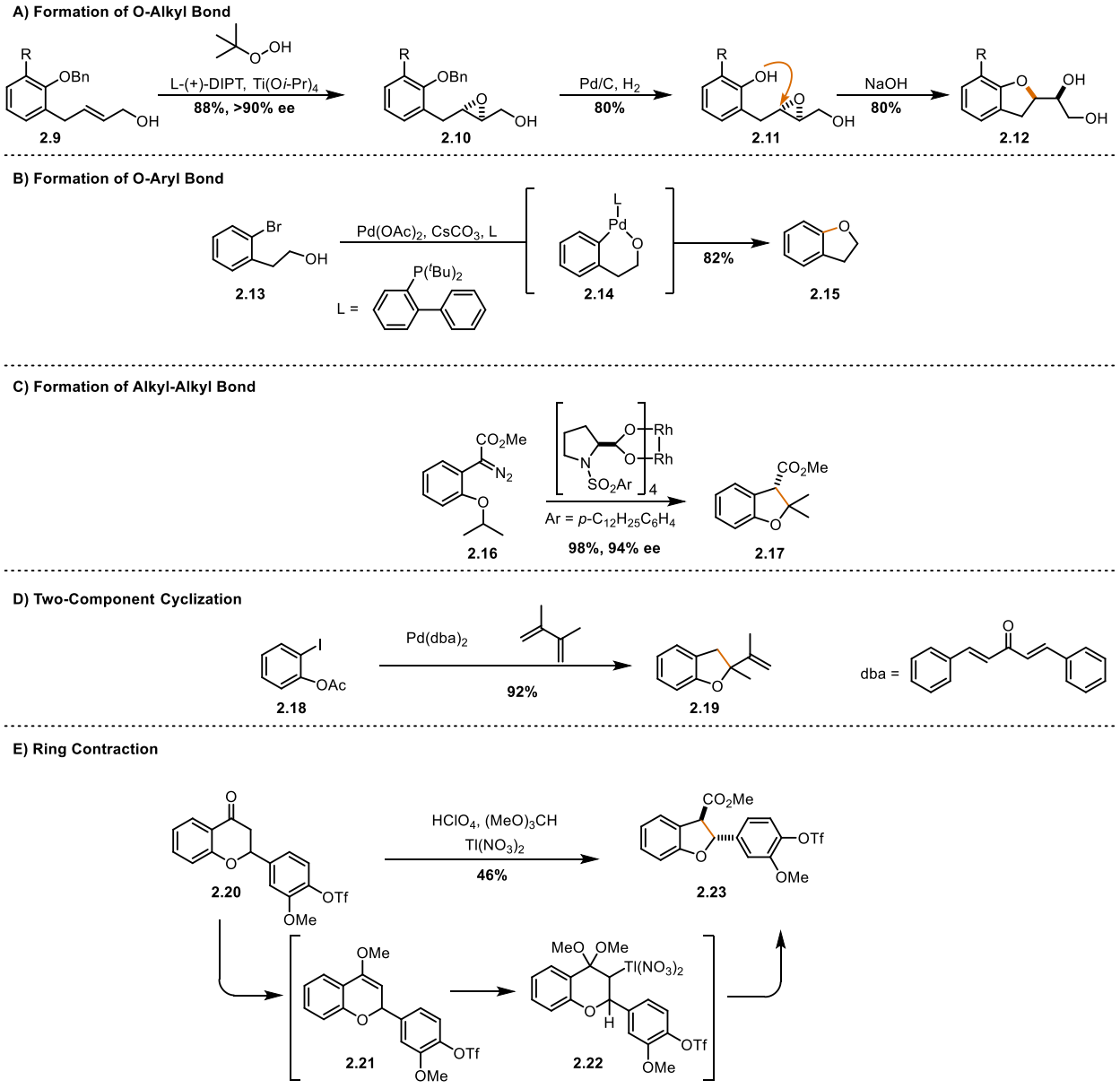


Figure 2.2 Summary of strategies towards dihydrobenzofurans

An example of DHB synthesis towards a complex natural product is Snyder's use of a homologation sequence towards carasiphenol C (**2.31**, Figure 2.3).[100] In summarizing only the

DHB synthesis we being with a protected pallidol core (**2.24**), which has a single aromatic halogen. This feature is key to selectivity, as the placement of this halogen determines the DHB positioning. A more thorough review of this strategy is presented in Chapter 4. Lithium halogen exchange provides a carbanion which attacks a protected aldehyde (**2.25**) without selectivity in 77% yield.[101]

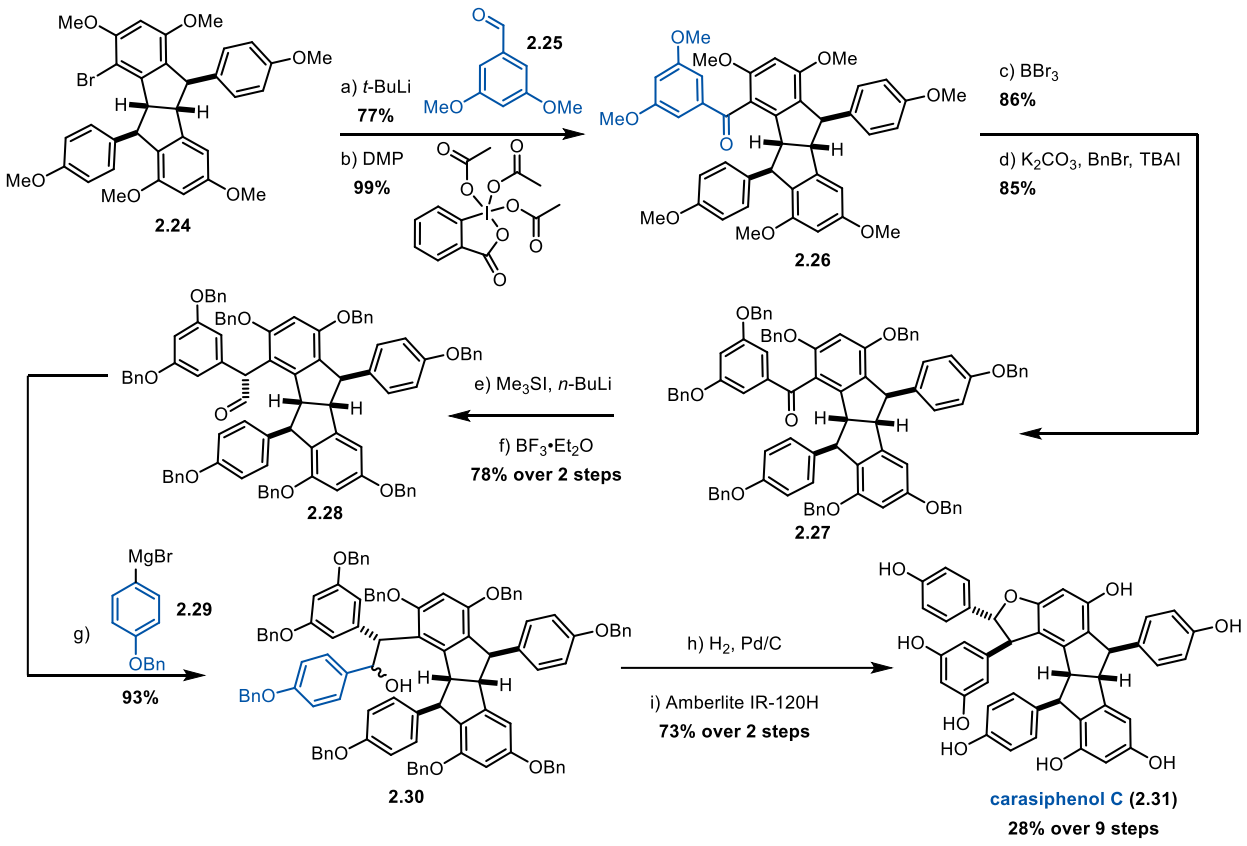


Figure 2.3 Snyder's total synthesis of carasiphenol C via a homologation sequence

This in inconsequential as an oxidation with Dess-Martin Periodinane ablates the configuration, forming the ketone (**2.26**) in quantitative yield.[102,103] A protecting group switch from methyl to benzyl is accomplished in two steps using standard conditions (**2.27**).[87] A Johnson-Corey-Chaykovsky reaction transfers a methylene in good diastereoselectivity and yield.[104–106] A subsequent Meinwald rearrangement effectively finished the homologation efforts yielding a homobenzylic aldehyde (**2.28**).[107] Simple Grignard addition provides a benzylic alcohol (**2.30**).[108] A global reduction with hydrogen gas and palladium on carbon reveals all phenols, followed by

the use of an acidic resin (Amberlite IR-120H) promotes intramolecular cyclization yielding carasiphenol C (**2.31**).[109] This nine step sequence proceeds in with 28% overall yield, and provides a framework for DHB diversification of halogenated phenolic scaffolds. The Snyder lab has used this method to great effect in their total synthetic efforts.

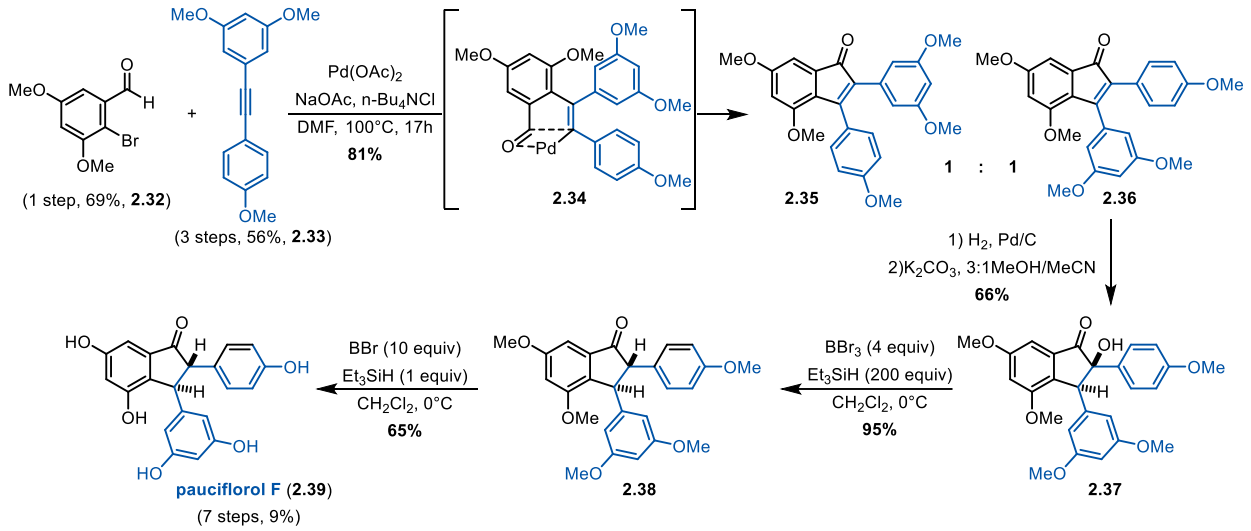


Figure 2.4 Sarpong's total synthesis of pauciflorol F via a Larock annulation

The Sarpong lab pursued the synthesis of pauciflorol F beginning with a set of two methyl protected building blocks (**2.32**, **2.33**, Figure 2.4).[110] When using Larock's original conditions for annulation, a 1:1 regioisomeric mixture of indenones was formed (**2.35**, **2.36**).[111] This was a known limitation of the method, but the isomers were separable by silica gel column chromatography which allowed the isolation of the desired isomer (**2.36**). The strategy was to reduce the olefin (**2.36**) with standard palladium / hydrogen conditions and then epimerize the stereocenter α to the carbonyl. Instead, the α-hydroxy indanone (**2.37**) was isolated. To identify this unexpected product infared spectroscopy and ^{13}C NMR were used, both suggested the presence of a quaternary O-H. It was possible to in one pot hydrogenate and epimerize **2.36** using condition originally reported by Zimmerman (H_2, Pd/C, KOH) avoiding the oxygenation (yielding 2.38).[112] Based on literature precdent, it was postulated that the avoidance of molecular oxygen was key in isolating the desired

intermediate (**2.38**).[113,114] It was found experimentally that a reductant must be present, in varying quantities, for the conversion of **2.37** to **2.38** and **2.38** to **2.39** as yields significantly suffer otherwise. A single step procedure to convert **2.37** to **2.39** also proved elusive. This synthesis assembled pauciflorol F in 9% overall yield over 7 steps.

2.3 Development of a method for the synthesis of trans-2,3-diaryl dihydrobenzofurans

With an eye on the modular total synthesis of resveratrol oligomers, the Stephenson lab formed an initial hypothesis for the radical based synthesis of DHBs. This was rooted in the physical organic experiments confirming a persistent radical equilibrium between a bis-quinone methide (**2.40**) and two equivalents of a persistent radical stilbene (**2.45**, **2.51**, Figure 2.5).

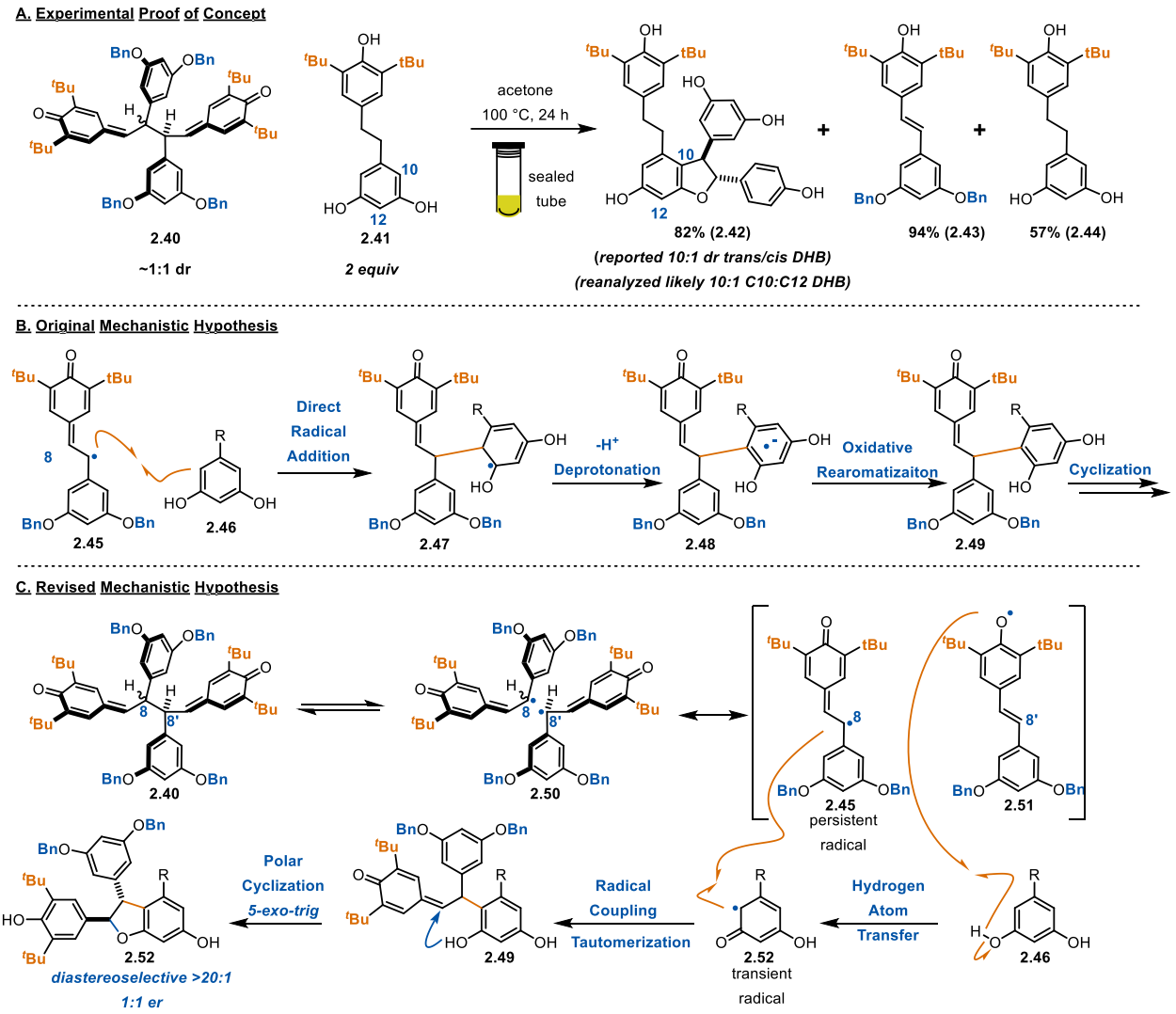


Figure 2.5 Proof of concept and mechanistic hypotheses in the synthesis of DHBs

See Section 1.2 for a review of this phenomenon. The first experimental validation was acquired by reacting a C3-^{t}Bu protected BQM (**2.40**) with a C3-^{t}Bu dihydrostilbene (**2.41**, 2 equiv) in acetone at 100 °C for 24 hours. From this reaction was isolated the DHB (**2.42**) in 82% yield, which was reported as a ~10:1 ratio of trans:cis DHB. After further analysis, and due to the isolation of the C12 DHB in later studies (see Section 3.4) it is likely that instead of a mixture of diastereomers a 10:1 mixture of C10:C12 DHB was present. In addition to starting material (**2.44**, 57%), a fully protected stilbene (**2.43**) was also isolated in 94% yield. The initial mechanistic hypothesis (**B**, Figure 2.5) was that one equivalent of the persistent radical (**2.45**) would undergo

direct radical addition to a phenol (**2.46**) yielding **2.47**. As reported by Curran and Studer these cyclohexadienyl radicals, such as **2.47**, are acidic and can be deprotonated to a radical anion (**2.48**).[115] A final oxidative aromatization provides **2.49** which can cyclize to form DHB.

After conversations with Professor Pratt from the University of Ottawa and a re-analysis of our mechanistic evidence we postulated a related mechanism (**B**, Figure 2.5). The same thermal homolysis occurs yielding two equivalents of persistent radical (**2.50**). These persistent radicals (**2.45**, **2.51**) are drawn based on their reactivity in the mechanism. The oxygen persistent radical and the resorcinol undergo hydrogen atom transfer, producing one equivalent of **2.43** aligning with our experimental findings. The transient radical (**2.52**) couples with the persistent C8 radical (**2.45**) forging the key C-C bond selectively via the persistent radical effect (See section 1.2). A subsequent tautomerization provides **2.49** which spontaneously closes the DHB ring via a polar *5-exo-trig* cyclization. While the diastereoselectivity of this reaction is exquisite, with no cis DHB detected, the product is a 1:1 mixture of enantiomers.

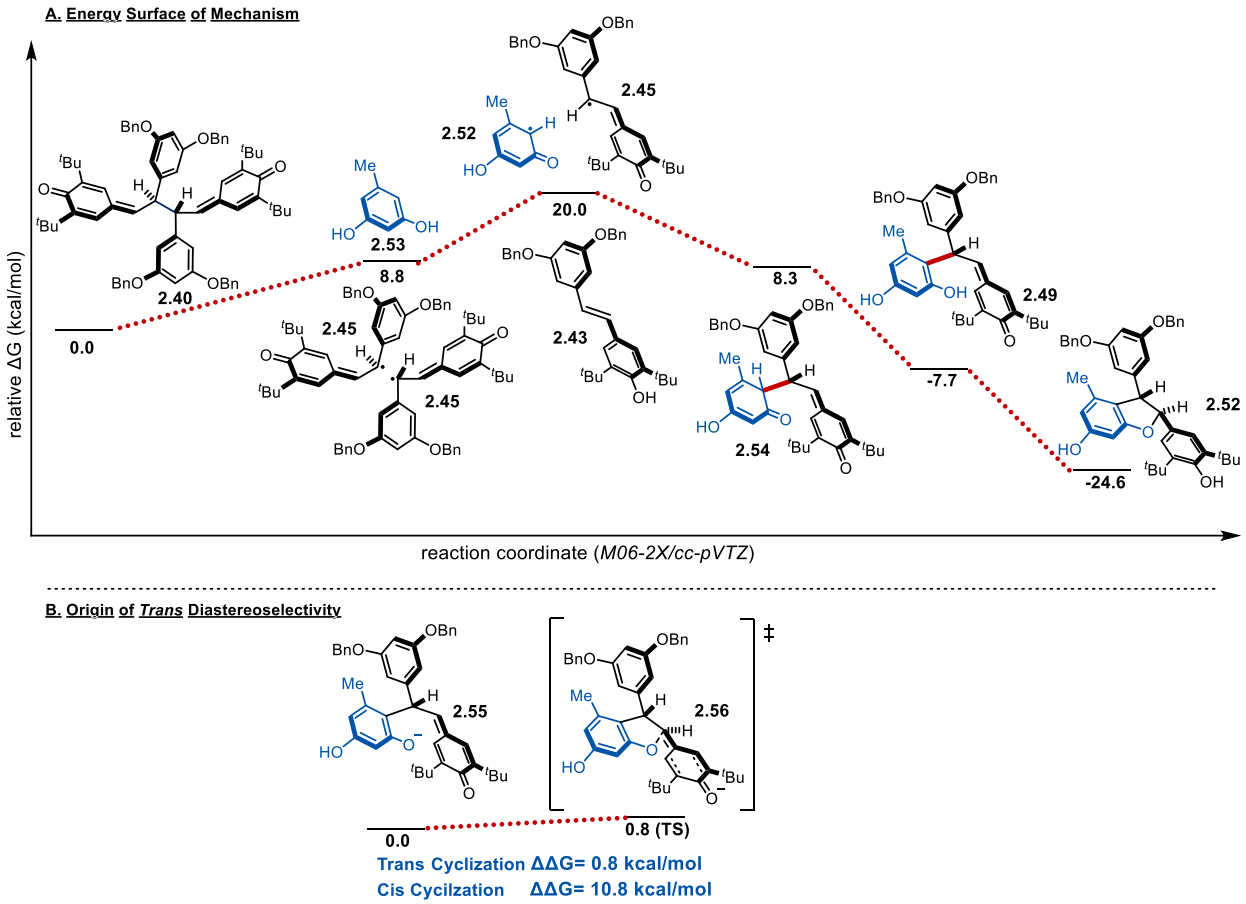


Figure 2.6 Density functional calculations of DHB mechanism

When reanalyzing the mechanism of DHB formation through the lens of density functional theory calculations (M062-2X/cc-pVTZ level of theory) a few key components come into focus (**A**, Figure 2.6).[116,117] The hydrogen atom abstraction of **11R** with **2.46** is slightly endergonic (8.8 kcal/mol).[118] A transition state was not directly calculated as when the bond dissociation of phenols are matched, as is this case, the reaction is very fast.[119] The coupling of transient radical (**2.52**) and persistent radical (**2.45**) is exothermic (11.7 kcal/mol). While this radical coupled intermediate (**2.54**) is higher in energy than the starting material, which could suggest a reversible radical coupling, the tautomerization to restore aromaticity to the orcinol ring is irreversible (16 kcal/mol). The final cyclization is also steeply downhill (16.9 kcal/mol) producing the DHB (**2.52**). A well-defined transition state between **2.49** and **2.52** could not be located, likely due to challenges in

forming a zwitterionic species. Alternatively, the conjugate base of the phenol (**2.55**) undergoes a near barrierless cyclization (0.8 kcal/mol) to **2.56**. The key is that the trans cyclization is 10 kcal/mol more favorable than the cis, providing computational rationale for the high diastereoselectivity observed.

With the mechanistic details in hand, the scope of the DHB reaction was probed (Figure 2.7). In each case the BQM (**2.40**) was stirred overnight in acetone with a phenol of interest at 120 °C in a glass sealed tube. These reactions were ran behind a blast shield, and cooled completely before unscrewing the lid. The main tool used to rationalize the yield of each reaction is the persistence of the phenoxy radical derived from the starting material. As a baseline the BQM (**2.40**) undergoes thermal bond homolysis to form a set of two persistent radicals in solution. The first basic requirement is that the phenoxy radical obtained after HAT of the substrate (**2.52**, Figure 2.6) must be sufficiently long live (persistent) to find the BQM radical (**2.45**, Figure 2.6) in solution. If this is not the case the radical coupling will be highly unfavorable due to the low population of the substrate radical (**2.52**, Figure 2.6) in solution. Alternatively, if the phenoxy radical (**2.52**, Figure 2.6) is too persistent, it may have low reactivity towards the BQM radical as this would be the coupling of two persistent radicals, generally unfavorably. Highly stability phenoxy radicals derived from starting material HAT can also undergo homocoupling or disproportionation if there is an ortho or para heteroatom substituent.

We found that resorcinol as a substrate gave a paltry yield of 9% (**2.56**). This was attributed to the low persistence of this unstabilized radical, resulting in a low concentration of resorcinol radical in solution. Along the series from **2.56** to **2.59** both the stability and persistence of the starting material derived radical increases, thereby also increasing the yield. The ester derived DHB provided 49% yield (**2.57**), similar to the methyl (**2.58**).

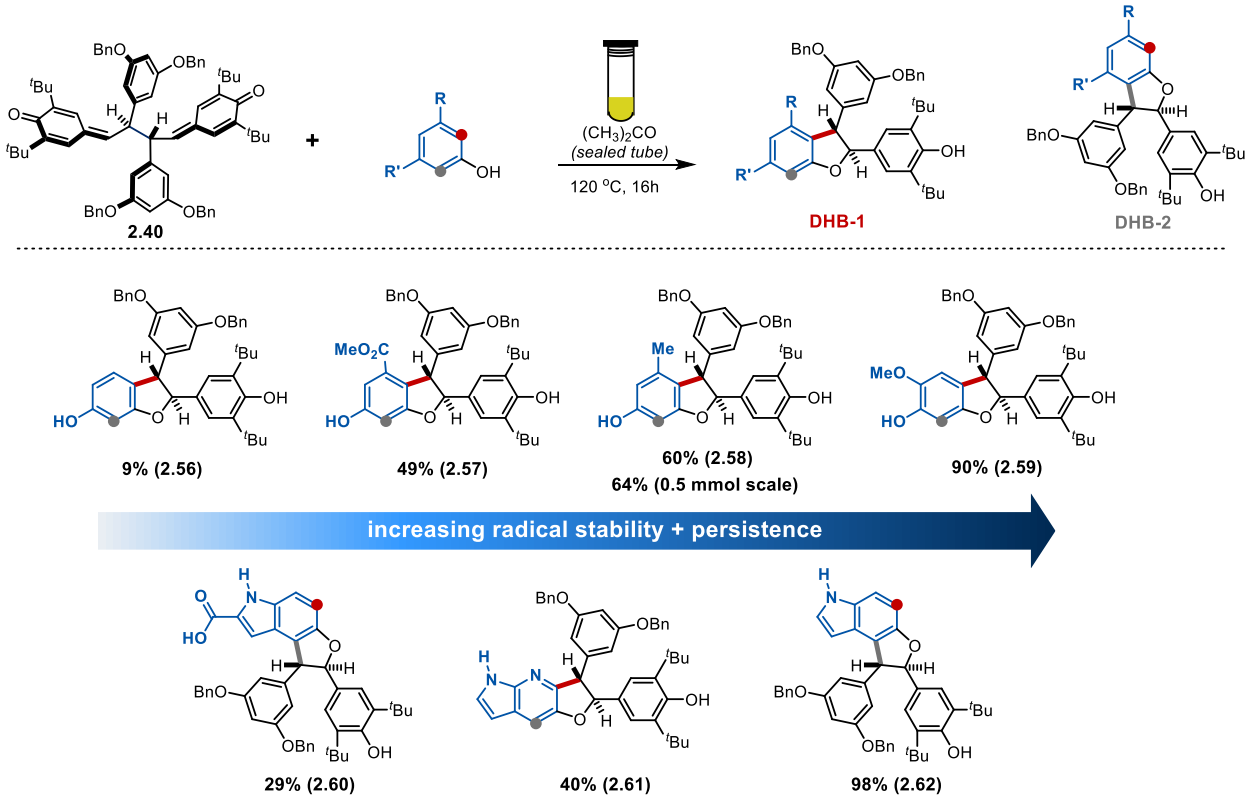
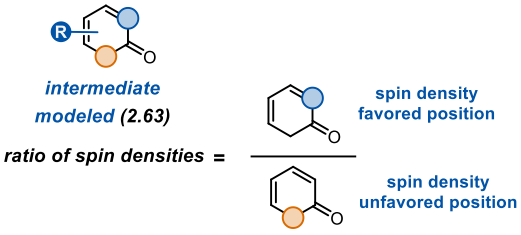


Figure 2.7 Selected substrate scope in the persistent radical synthesis of DHBs

The methyl substituted ring was also scaled to 0.5 mmol scale without depreciation in yield (64%). The guaiacol derived DHB (**2.59**) provided an excellent (90%) yield. This was attributed to dual factors as the guaiacol derived radical is both stabilized ortho hydrogen bonding which both suppresses homocoupling and increases persistence of the resulting radical. A similar series is seen from **2.60** to **2.62**, with yields ranging from 29% to 98% again attributed to the radical stabilities. This is not a perfect system for predicting yields, as there are many factors at play in any organic mechanism, but we feel strongly that the trends hold true for a variety of stabilized, and unstabilized radicals.

Table 2.1 Summary of computational efforts to predict regioselectivity



Not correlated with experimental outcome:
1. Mulliken Charge
2. APT Charge
3. NBO Charge

substrate	*ratio of spin densities*
2.56	+1.54
2.57	+2.94
2.58	+1.28
2.59	+2.28
2.60	+1.58
2.61	0.79*
2.62	+2.56

M06-2X/cc-pVTZ

**does not match experimentally observed isomer*

To predict the regioselectivity of the reaction, we explored the properties of the phenoxy radical derived from each starting material (**2.63**, Table 2.1). At the M06-2X/cc-pVTZ level of theory[117,120] we calculated the Mulliken spin density of each delocalized radical system (**2.63**).[121] This calculation outputs a number per atom indicating the spin density at that position. By taking the more favored spin density adjacent to the oxygen on the ring divided by the less favored spin density a ratio of spin densities was obtained. This data is displayed for a range of substrates matching the figure above (Figure 2.1). For all substrates save one this was a good descriptor of the radical localization. Other methods which were attempted to correlate with the experimental outcome include the Mulliken charge, APT charge, and NBO charge.[122,123] Notably there were no simple phenol derived systems where a mixture of two regioisomers was observed.

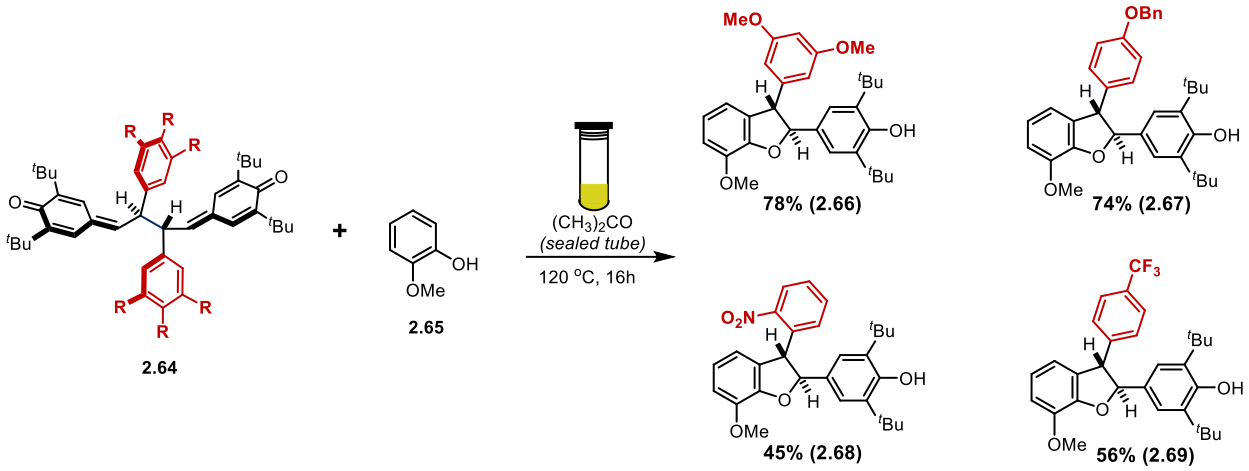


Figure 2.8 Exploration of differentially substituted BQMs

A scope of varied BQMs (**2.64**) each reacting with guaiacol (**2.65**) is displayed (Figure 2.8). The yields vary from 45-78% (**2.66-2.69**) and it is challenging in this small of a yield range to draw meaningful conclusions about how the substituents may fine tune the stability of the BQM radical. The dimethoxy (**2.66**) could be of use in our total synthetic efforts towards resveratrol oligomers, with the other products (**2.67-2.69**) showing an interesting range of products not directly related to other synthetic efforts in the Stephenson lab.

We produced a graphic to summarize the substrates which are synthetically useful to allow practitioners of chemistry to determine if our method is suitable for their research application (Figure 2.9). This essentially displayed phenols (2.71-2.74) which are stabilized and would have adequate persistence in solution to couple efficiently with the BQM radical (2.70) and unstabilized phenols (2.76-2.79) which do not undergo coupling effectively.

In an effort to extend our methodology to other heterocyclic rings, we attempted substrates containing amine or thiol functionality (**2.83-2.86**, Figure 2.10). When analyzing these reaction mixtures, no DHB was ever detected by ^{1}H NMR or HRMS. Often these reactions turned an opaque dark brown or red color while most successful substrates had a crude reaction mixture that was translucent yellow or orange.

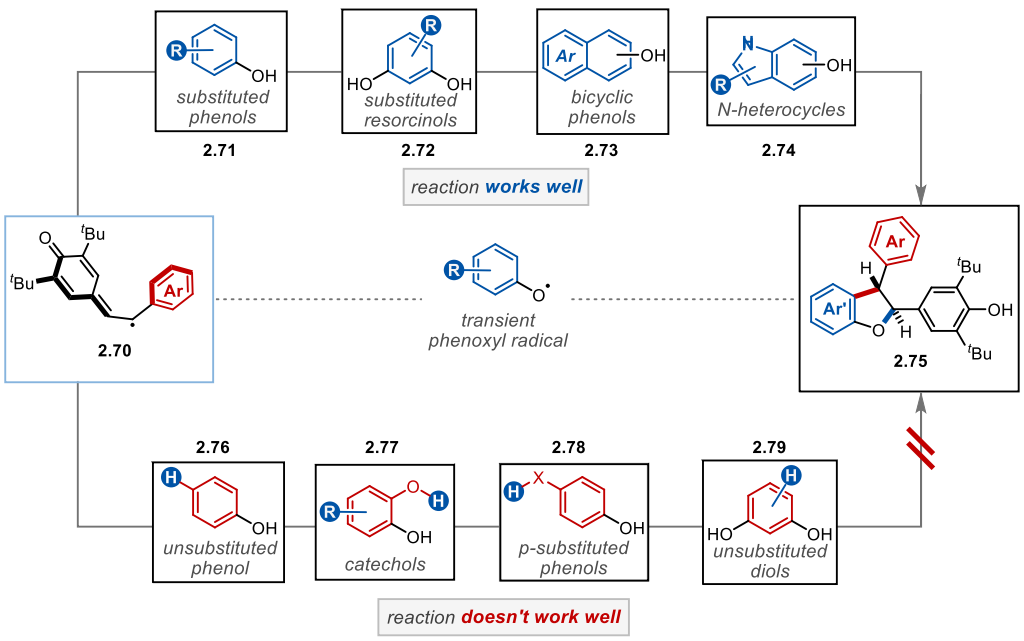


Figure 2.9 Summary of substrates and their propensity to participate in DHB reaction

The use of silica gel column chromatography under argon gas to prevent oxidative decomposition was also attempted, without success. Originally, substrates **2.88-2.90** were presumed product based on their indicative ^{1}H NMR signals being similar to those of the desired DHB product. After a thorough reanalysis of 2D NMRs (HSQC, HMBC) it was determined to instead be tautomerized BQM (**2.82**). The formation of this unexpected byproduct was not more thoroughly mechanistically investigated. As all substrates which provide this product (**2.88-2.90**) contain either amide or amine functionality, it is possible that a simple base mediated deprotonation is occurring with these substrates. This tautomerized product is desirable in some of our total synthetic efforts and this result was earmarked for further exploration and optimization in the future.

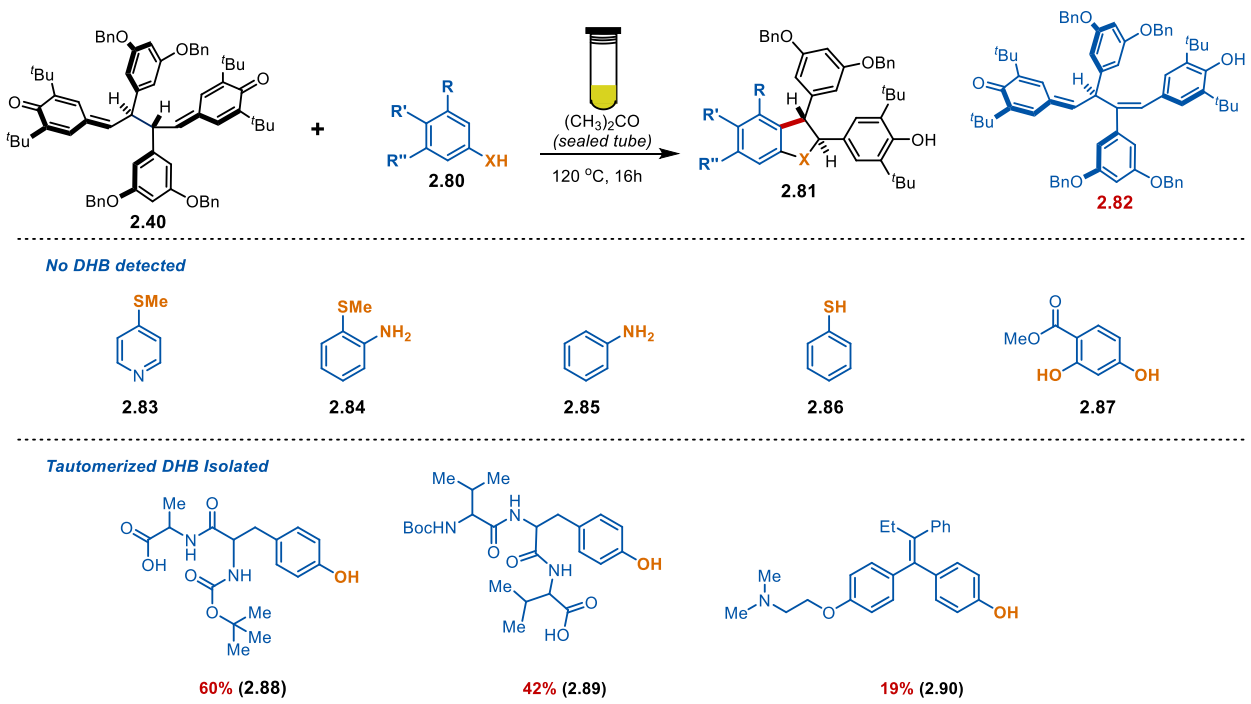


Figure 2.10 Unsuccessful substrates and unexpected byproducts

Another item worth noting is that many of the DHB products contain easily oxidized phenols, and that their isolation and storage is not trivial.[124] These types of products are known to be oxidizable by air, and many of the white or tan foams produced in our research turned to brown or black amorphous solids upon standing under an air or nitrogen atmosphere. The most successful storage methods included under vacuum on a Schlenk line, or sealed under an atmosphere of argon in the freezer. At the request of reviewer some of the compounds were re-purified by preparatory TLC to remove some baseline impurities. In addition to this exercise, and TLC stability study was completed to demonstrate the oxidative liabilities of these molecules and the challenges in isolating them (Figure 2.11). In this exercise a crude reaction mixture was spotted on two thin layer chromatography (TLC) plates, **A** and **B**. The plate labelled **A** was immediately developed and then let sit for 1 hour. Plate **B** was let sit, open to air, for 1 hour before elution.

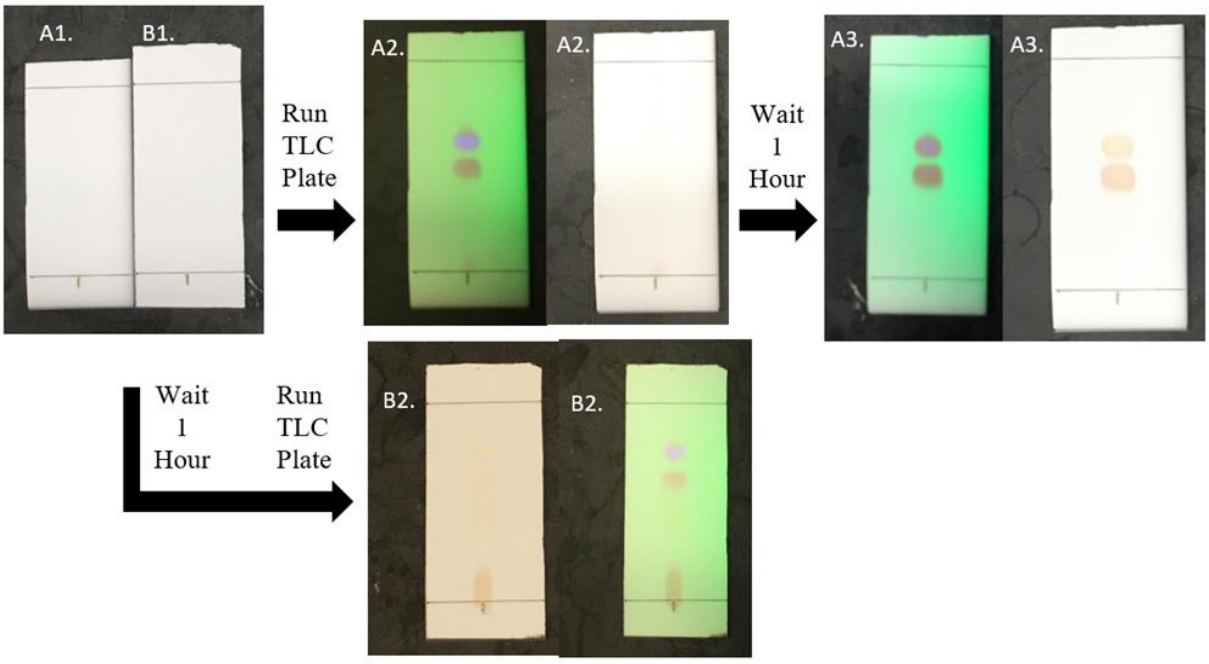


Figure 2.11 TLC studies demonstrating the oxidative sensitives of DHB products

When comparing **A3** to **B2** it can be seen that **B2** has a large streaking impurity at the baseline, visualizable even without UV (254 nm) that is absent in **A3**. This provides credence to the hypothesis that these molecules are air oxidizable and must be handled with caution.

2.4 History of the use of C3 *tert*-butyl protecting groups and intro to silyl protecting groups

In developing a reaction to synthesize a diverse array of DHBs (**Section 2.3**) the Stephenson lab had a keen eye of applying this methodology to the total synthesis of resveratrol oligomers. For this to be an operable strategy, all protecting groups used on the BQM must be removable under conditions which do not degrade the electron rich phenolic rings presents in the resveratrol oligomer natural products. The phenolic benzyl groups can be removed using Pd/C and H_2 as most resveratrol oligomers do not contain olefins which would also be reduced.[87] The *tert*-butyl group pose a challenge as they are typically removed with *retro*-Fridel Crafts conditions, employing superstoichometric amounts of $AlCl_3$, a potent Lewis acid.[125–128] During his PhD studies Matthew Galliher put great effort into finding conditions to remove the C3 *tert*-butyl

groups which stood between the Stephenson lab and numerous resveratrol oligomers. A summary of these efforts are shown on a model substrate, which was originally labelled as an unnatural C8-C12 DHB, related to carasiphenol C (Figure 2.12).[129,130] It was later recognized as the direct precursor of the resveratrol oligomer leachianol D.[131]

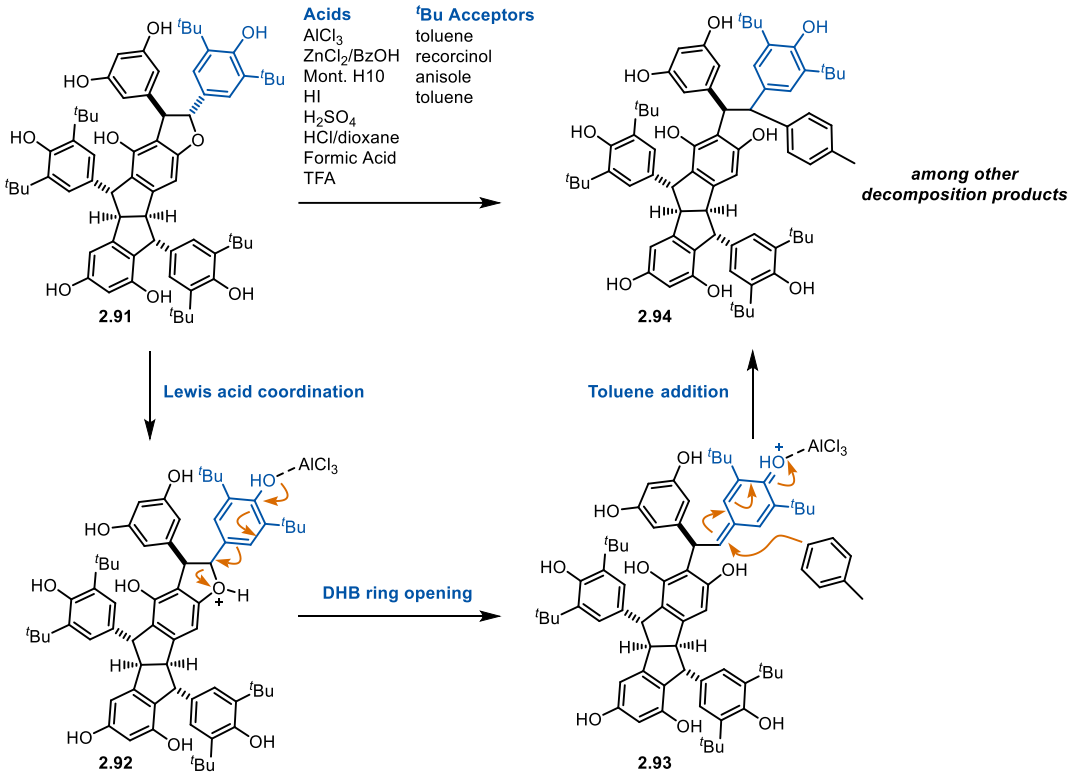


Figure 2.12 Attempts to remove ^{t}Bu protecting groups

An extensive screening operation was conducted, with a variety of Brønsted and Lewis acids screened, in addition to *tert*-butyl acceptors. These acceptors are key as the *tert*-butyl groups each are deprotected as their *tert*-butyl cation which must be trapped by a large excess of an electron rich acceptor, such as toluene or anisole. This prevents these cation(**s**) from being trapped by one of the electron rich phenols present on the substrate. Another complication is that the DHB rings present (**2.91**) can be opened by the Lewis acid (**2.92**) allowing a competent nucleophile to attack the quinone (**2.93**) leading to irreversible degradation. This is mechanistically know by the

rearrangement of resveratrol dimers and trimers in a variety of both Brønsted and Lewis acids.[132–135] Ultimately no conditions were found to remove the C3 *tert*-butyl groups.

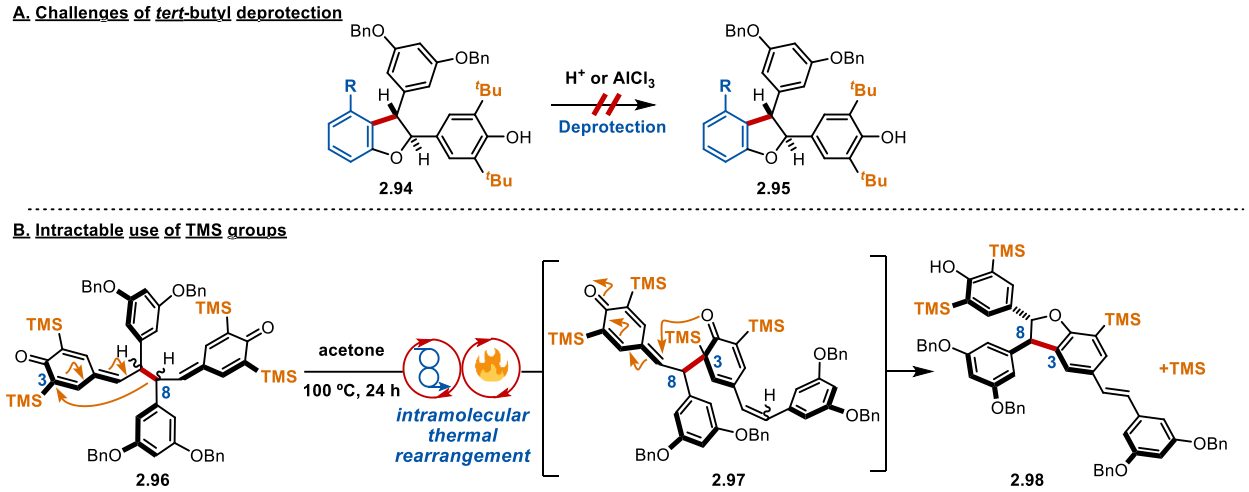


Figure 2.13 Summary of challenges in developing a labile C3 protecting group

The challenges in developing a suitable protecting group are summarized above and include primarily that *tert*-butyl group are too stable to be selectively removed (A, Figure 2.13). Small silyl groups are prone to intramolecular C3-C8 rearrangement (B, Figure 2.13) as was used elegantly by Kevin Romero from our lab in the synthesis of tetrameric resveratrol oligomer natural products, the vitisins (see section 1.4 for further discussion).[56]

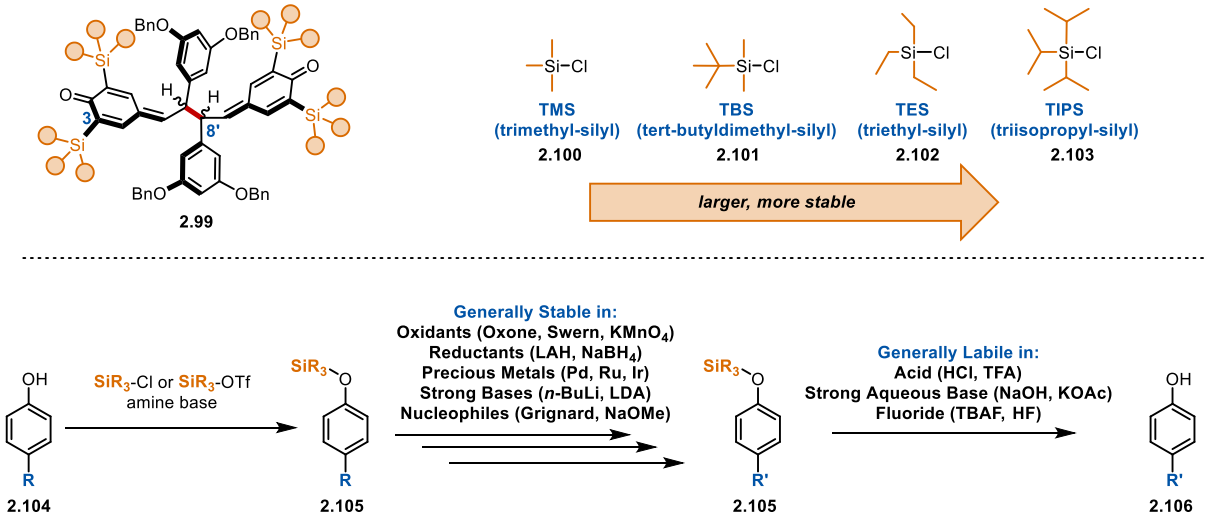


Figure 2.14 Summary of silyl groups and their synthetic utility

With the known challenges with previous C3 protection methods, we chose to evaluate larger C3 silyl protecting groups in an effort to prevent the thermal C3-C8 intramolecular rearrangement while also allowing facile deprotection (Figure 2.14). As a brief overview, silicon based protecting groups are popular for the temporary protection of alcohols,[136] phenols,[87] and occasionally amines.[137,138] As the protecting group becomes larger (**2.100-2.103**) the stability increases. It was postulated that the same trends that govern the stability of heteroatom protection could remain intact for carbon protection. These silyl groups are most commonly introduced as their chloride or triflate, via simple nucleophilic displacement in the presence of an amine base.[87] These groups are remarkably stable to oxidants, reductants, and a variety of other conditions (Figure 2.14). The main conditions for deprotection include acid, fluoride, and strong aqueous base returning the phenol. The tunability, and ease of protection and deprotection are key features which make this group of protecting groups so widely adopted. It was ~50 years ago that E.J. Corey and co-workers reported the first use of *tert*-butyldimethylsilane (TBS) as a hydroxyl protecting group.[139,140] Interestingly, the TBS group remains popular, with >35,000 known compounds containing TBS protected phenols compared to TMS (~6000), TES (~900), and TIPS **(~10,000).**[141]

One of the many masterful examples of the selective use of silyl groups in total synthesis is present in Holton's landmark total synthesis of taxol (Figure 2.15).[142–144] This natural product which is currently approved for use as an broad spectrum anticancer agent was first isolated from the pacific yew tree.[145–147] Beginning with a chiral secondary alcohol (**2.107**) a TES group introduced with standard amine conditions yielding **2.108**. Following Grob Fragmentation[148,149] a TBS ether is introduced via the triflate (**2.110**). These two silyl protected phenols are stable through the subsequent 20 synthetic steps including Aldol addition,[150–152] Swern Oxidation,[153] Chan

Rearrangement,[154] SmI_2,[155–158] Red-Al reduction,[159,160] ozonolysis,[161–164] diazomethane[165] and two uses of *p*-toluene sulfonic acid.[166]

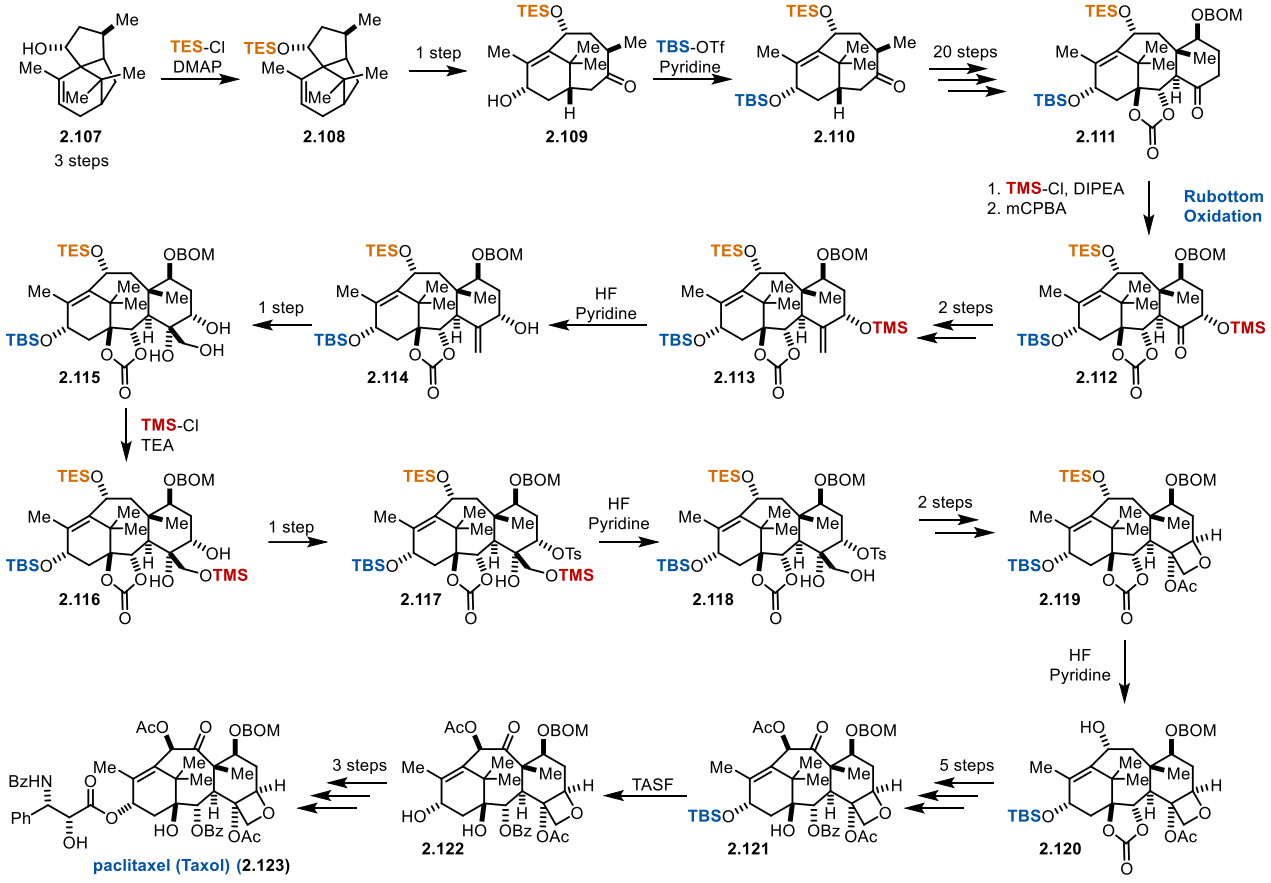


Figure 2.15 Holton's total synthesis of paclitaxel (Taxol) highlighting silyl protection

A subsequent Rubottom Oxidation introduces a TMS group (**2.112**).[167] After two more synthetic steps HF and pyridine is used to selectively remove the TMS ether (**2.114**). The selective removal of silyl ethers has been studied extensively, and covered in a series of excellent reviews by Crouch.[168–170] After a osmium mediated dihydroxylation,[171,172] the TMS group is selectively added to the less sterically hindered primary alcohol (**2.116**). This is also temporary as after tosyl protection of the adjacent alcohol the TMS is removed with the same selectivity as before (**2.118**). Following closure of the oxetane ring (**2.119**) the TES ether is removed, again with HF and pyridine (**2.120**). This demonstrates how small changes in temperature and solvent can affect the

selective deprotection of silyl ethers. TASF,[173] a source of anhydrous fluoride, is used to remove the final silyl group (**2.122**). Three subsequent steps are required to unveil the scaffold of paclitaxel (Taxol, **2.123**).

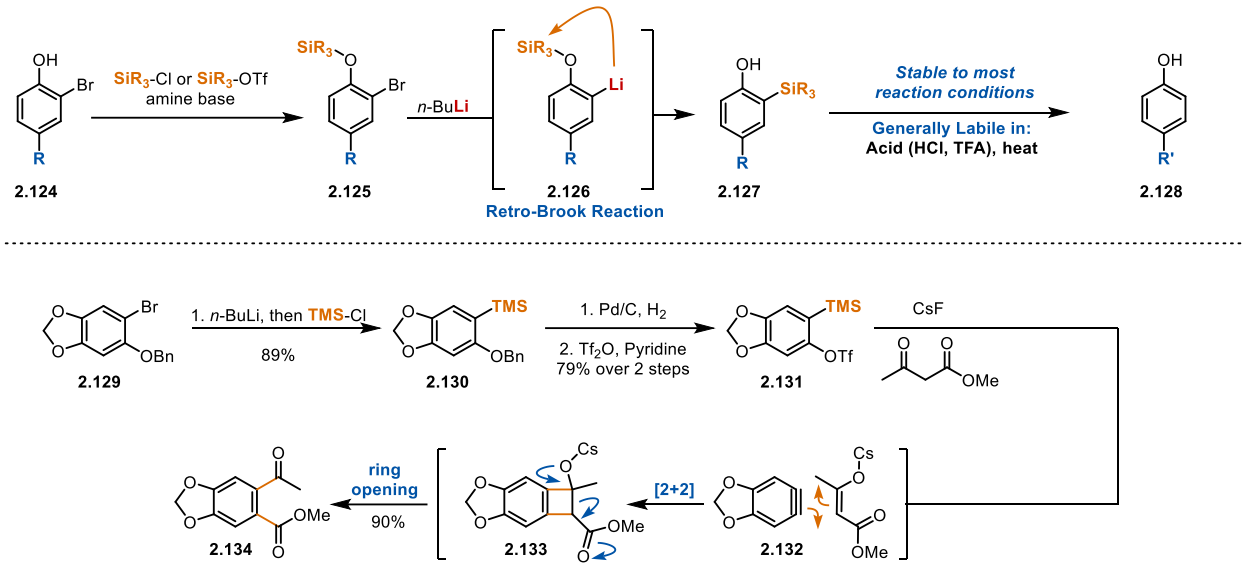


Figure 2.16 Overview of the C-Si bond in protection and reactivity

The use of a carbon silicon bond in aromatic systems is rare in comparison to the breadth and depth of phenolic oxygen silicon protection (Figure 2.16). Common installation of this protection is via first standard silyl protection of an alcohol (**2.125**) followed by an organolithium reagent (*n*-BuLi, PhLi). Following lithium halogen exchange,[174,175] a retro-Brook rearrangement occurs (O→C Si rearrangement).[176–179] This is the microscopic reverse of the more common Brook rearrangement (C→O Si rearrangement)[180–185] and an analog to the classic [1,2] Wittig rearrangement.[186,187] The driving force for both the retro-Brook and Wittig rearrangement is the same, the transfer of charge from a carbanion to a oxyanion. The C-Si bonds forged in this reaction are inert in nearly all reactions conditions save acid and fluoride.[87] Another synthetic route is shown as direct lithium halogen exchange followed by the addition of TMS chloride is also operable (**2.130**). Aromatic carbon silicon protection is most commonly used in the formation of arynes (**2.132**) as opposed to Koybayashi procedure from a benzene diazonium carboxyalate.[188]

In the example shown above the benzyne, generated via fluoride mediated elimination, reacts with a β-ketoester (**2.133**) effectively acyl-alkylating the substrate (**2.134**).

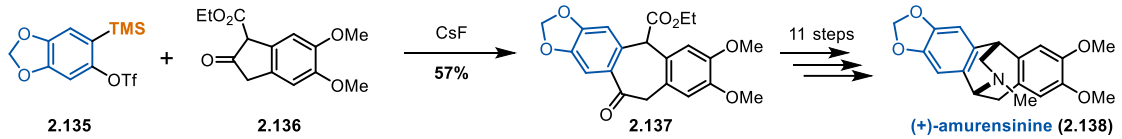
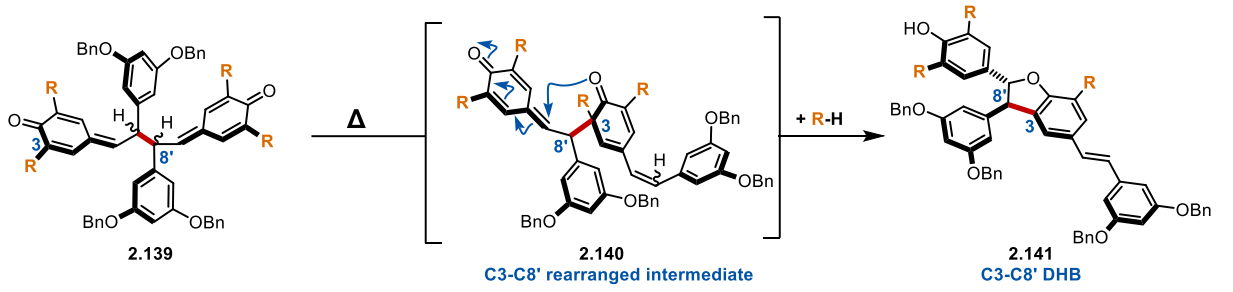


Figure 2.17 Stoltz's total synthesis of (+)-amurensinine via a benzyne acyl-alkylation

This method of benzyne generation has also found many use in natural product total synthesis due to the level of complexity generated in a single step (Figure 2.17).[189–194] Stoltz's synthesis of (+)-amurensinine uses the same methodology as above (Figure 2.16), but has a cyclic β-ketoester instead of acyclic.[195] This method is not enantioselective, but a second oxidative kinetic resolution renders the route enantiopure. A total of 11 additional steps were required to complete the synthesis of (+)-amurensinine.

2.5 Development of a labile C3 silyl protecting group

In choosing a C3 protecting group we used a computational planning approach, with the goal being to reduce the synthetic burden of having to synthesize multiple BQM reagents. The key was to find a C3 silyl protecting group of similar thermal stability of *tert*-butyl (Figure 2.18). The C3 TMS group (entry 2) is known to thermally rearrange and has a ΔH of 8.2 kcal/mol between **2.140** and **2.139**. The *tert*-butyl has a ΔH of 13.8 kcal/mol and was known to not rearrange before 150 °C. The ΔH of the rearrangement of four additional silyl groups was calculated (entries 3, **5-7**). We recognized at this point in planning that if too large a silyl group were chosen it was feasible that the steric bulk would prevent any productive DHB formation even in the even the reagent is thermally stable. The two most promising choices based on the calculations were entry 6, triisopropylsilyl (TIPS) and entry 7 *tert*-butyldiphenylsilyl (TBDPS).



Entry	R Group	ΔH (2.140-2.139)	Thermal Rearrangement Occurs?
1	bromine	8.0	
2	**trimethylsilyl (TMS)**	**8.2**	**yes**
3	tert-butyldimethylsilyl (TBS)	11.2	
4	**tert-butyl (^{t}Bu)**	**13.8**	**no**
5	triethylsilyl (TES)	14.6	
6	tert-butyldiphenylsilyl (TBDPS)	21.8	
7	triisopropylsilyl (TIPS)	22.8	

Calculated at M06-2X / cc-pVDZ level of theory

Figure 2.18 Computational consideration of required silyl group size

Of these two options, TIPS was chosen to explore first as the presence of aromatic protons in the TBDPS protecting group would create many ^{1}H NMR throughout the synthesis of both the BQM reagent and other synthetic intermediates on the route towards natural products.

The synthesis of the *di*-TIPS stilbene began by synthesizing a benzyl phosphonium salt which our lab has previously used in the synthesis of resveratrol oligomers (**2.146**, Figure 2.19).[54,196] Key process improvements are highlighted and were discovered through the need to scale this route to more than 100 g of phosphonium salt. The benzyl bromide protection (**2.143**) requires the use of an addition funnel for the BnBr to prevent exotherm issues. This reaction was executed on 238 mmol of **2.142** with 63 mL of BnBr on its largest scale. The LAH reduction of **2.143** is the most challenging reaction to scale due to the large exotherm issues known.[197] The switch from loose LAH powder to 0.5 g LAH pellets made the most accident prone portion of this reaction, weighing out the LAH, more manageable. The reaction was quenched with Glauber's salt ($Na_2SO_4 \cdot 10\ H_2O$) which was more controlled than the direct addition of water as advised by the Fieser workup.[198] This worked well on up to 243 mmol of ester (**2.143**) using ~15 g of LAH.

The Appel bromination[199,200] underwent no large modifications and proceeded smoothly with the requirement of a large silica gel hand column. A ratio of 10 g silica / 1 g substrate was usually sufficient to remove all triphenylphosphine oxide. Failure to remove all triphenylphosphine oxide via skipping the hand column or poor technique will result in this impurity in the final salt.

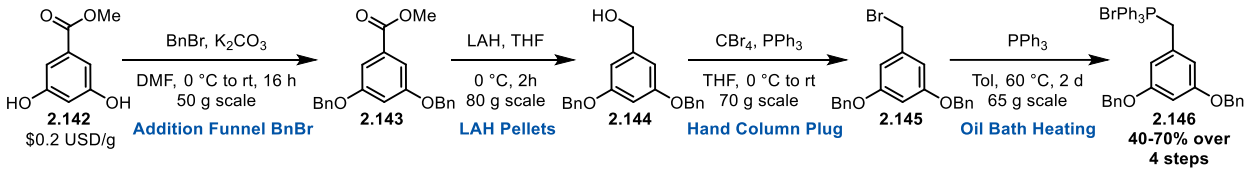


Figure 2.19 Synthesis of benzyl phosphonium salt, highlighting key process parameters

Final salt formation gives purest material (**2.146**) when oil bath heating is used. This reduces the temperature gradient in the reaction and prevents the brown/black discolorment of salt that accumulates on the walls of the flask.

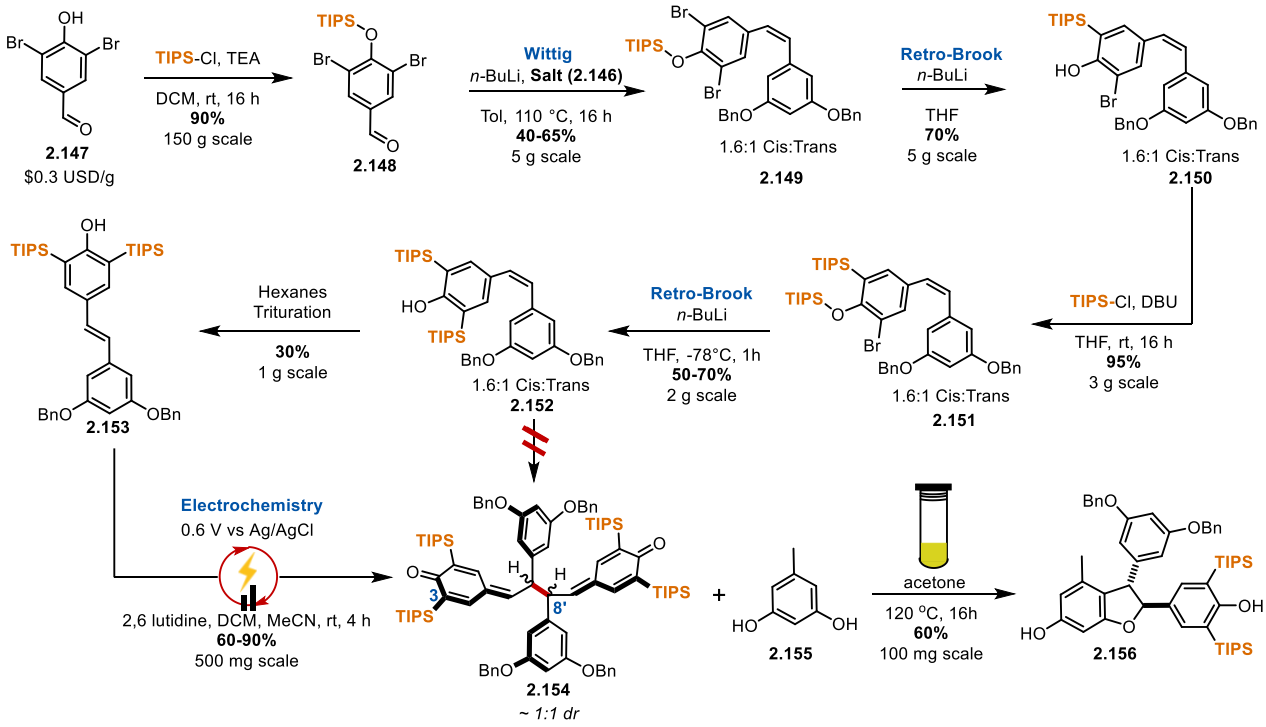
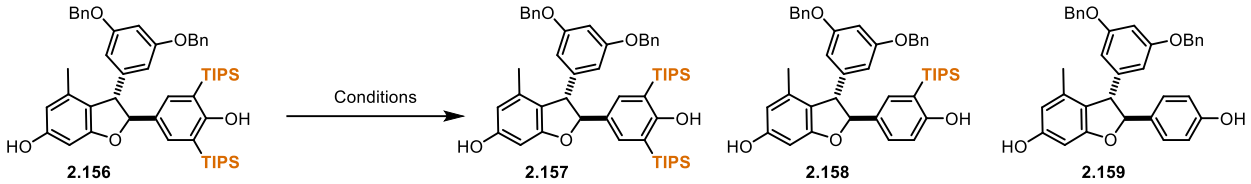


Figure 2.20 Synthesis and validation of C3-TIPS BQM (2.154)

The synthesis of the BQM (**2.154**, Figure 2.20) commenced with an the TIPS protection of an aldehyde (**2.147**).[118] After aqueous workup a trituration in acetonitrile allowed 150 g to be synthesized at once in >90% yield. Wittig olefination of aldehyde (**2.148**) with salt (**2.146**, Figure 2.19) gave, in moderate yield, a 1.6:1 ratio of *cis* to *trans* olefin (**2.149**). The first Retro-Brook rearrangement proceeded smoothly in 70% yield (**2.150**). The second TIPS protection required DBU, as weaker amine bases provided no conversion (**2.151**). A second Retro-Brook afforded the *di*-C3-protected stilbene of interest (**2.152**). When attempting electrochemistry on this material varied results were obtained, based on the exact ratio of *trans* stilbene present in the mixture. It appeared that the *cis* stilbene inhibited the reaction, being more than a non-reacting bystander. Column chromatography under a variety of solvent systems was unsuccessful to separate the stilbene isomers (**2.151**). Upon screening solvents, it was found that *cis*-**2.152** is soluble in hexanes, while *trans*-**2.152** is not. This allowed filtration, collecting *trans* stilbene (**2.153**) cleanly, while only in 30% yield (78% recovery relative to *trans* present in mixture). This stilbene was competent under the standard electrochemical conditions our lab previously reported and ~300 mg of BQM (**2.154**) was synthesized via this route.[57] Gratifyingly, this BQM smoothly produced DHB (**2.156**) in yields similar to the C3-*tert*-butyl BQM.[118] This C3-TIPS-BQM was also thermally stable beyond 150 °C.

Table 2.2 Screening of C3-TIPS-DHB deprotection conditions



Entry		Yield[a] 2.157	2.158	2.159
1	TBAF (5 eq), THF, rt, 16 h		80%	
2	TBAF (3 eq), THF, reflux, 16 h		90%	
3	CsF (10 eq), MeOH/H_2O, 90 °C, 24 h		60%[b]	
4	HCl (aq, 20 eq), MeOH, 50 °C, 16h		15%	20%[b]
5	TFA (20 eq), MeOH, rt, 16h		15%	15%[b]
6	TEA•HF (10 eq), MeOH, reflux, 2d	30%	25%	
7	HCl (0.5M, MeOH), reflux, 16h			90%[c]
8	HCl (0.5M, MeOH), rt, 40 h	50%	50%	

[a] *Yields determined by ^{1}H NMR (10 mg scale)*
[b] *Other unidentified degradation products*
[c] *Confirmed via HRMS*

A variety of fluoride and acidic conditions were screened in an attempt to remove the C3-TIPS protecting group without degrading the DHB ring (

Table 2.2).[87] While the mechanistic rationale is not fully understood, the removal of a single TIPS group was observed under most fluoride conditions (**2.158**). The use of refluxing 0.5 M methanolic HCl smoothly removed the C3 TIPS protecting groups (**2.159**). As this screening was on 10 mg of DHB (**2.156**) per trial a scale up was completed to experimentally validate this approach on a synthetically useful scale. Utilized the same conditions, both the exhaustive TIPS deprotection in acid (**2.159**) and the partial TIPS deprotection in fluoride (**2.158**) were scalable (150 mg scale). Both products can be benzyl deprotected using standard hydrogenolysis conditions (Pd/C, H_2).

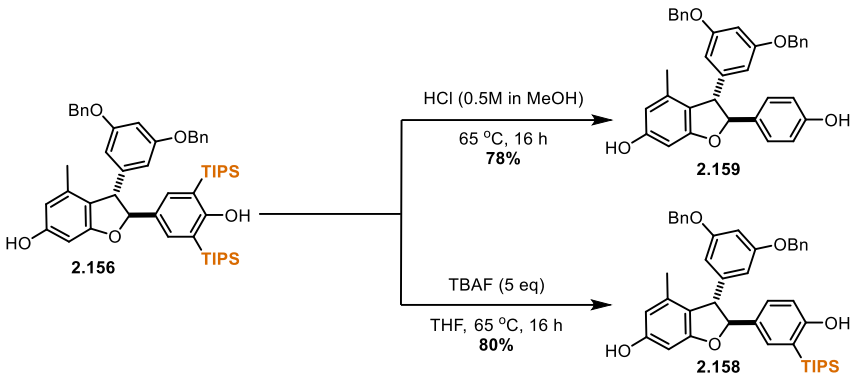


Figure 2.21 Scaled validation of C3-TIPS deprotection

With an eye on scalability the route to **2.153** as multiple grams would be required to explore the use of TIPS-BQM in the total synthesis of resveratrol oligomers. The main challenge with the 1st generation route was two-fold (Figure 2.20 Synthesis and validation of C3-TIPS BQM (**2.154**). The trituration to recover only 30% of **2.153** was intractable and the stepwise TIPS protection Retro-Brook sequence was inefficient.

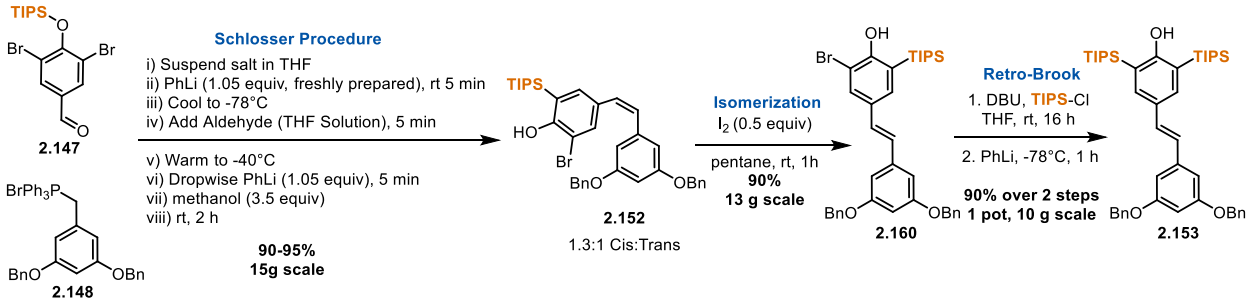


Figure 2.22 Optimized synthesis of C3-stilbene (2.153)

The strategy was use the Schlosser modification of the Wittig reaction to yield only the *trans*-alkene (Figure 2.22).[201–207] Following the preparation of fresh PhLi,[208–210] as was reported necessary, the Schlosser procedure[211] yielded a 1.3:1 mixture of *cis* to *trans* alkene isomers in addition to Retro-Brook rearrangement (**2.152**). This was a welcome surprise, as it did eliminate one step from the synthetic sequence, and when using freshly prepared PhLi was scalable above 10 g scale in excellent yields (90-95%). The final challenge was in efficient isomerization of the alkene to avoid a low recovery trituration step. The isomerization of alkenes, including stilbenes,

is known using molecular iodine,[212–215] through a radical mechanism.[216] This property was merged with the past solubilities studies using pentane in a dynamic kinetic resolution, obtaining *trans* isomer in 90% yield on >10 g scale (**2.160**). Through the course of the reaction the *trans* isomer precipitates from the pentane solvent, driving the reaction to completion. The final optimization was a one pot TIPS protection Retro-Brook sequence in the final step of the synthesis (**2.153**). Using standard electrochemical conditions this route was able to produce > 5 g batches of TIPS-BQM (**2.154**, Figure 2.20). This was deemed adequate for the use of this material towards the total synthesis of resveratrol oligomers.

2.6 Conclusions

In this chapter we began with a mechanistic foundation rooted in the persistent radical effect, a practical method for DHB formation using a C3 tert-butyl bis-quinone methide. The central challenge was removing the C3 tert-butyl group from the resulting DHB products without degradation. We identified the triisopropylsilyl group as a thermally stable bis-quinone methide capable of preventing a intramolecular C3-C8 rearrangement pathway. The C3-TIPS BQM was shown to be thermally stable beyond 150 °C, competent in DHB formation, and cleanly deprotected under refluxing methanolic HCl conditions on synthetically useful scale. We developed a scalable synthetic route to this C3-TIPS BQM, enabling the exploration of complex molecules using this building block.

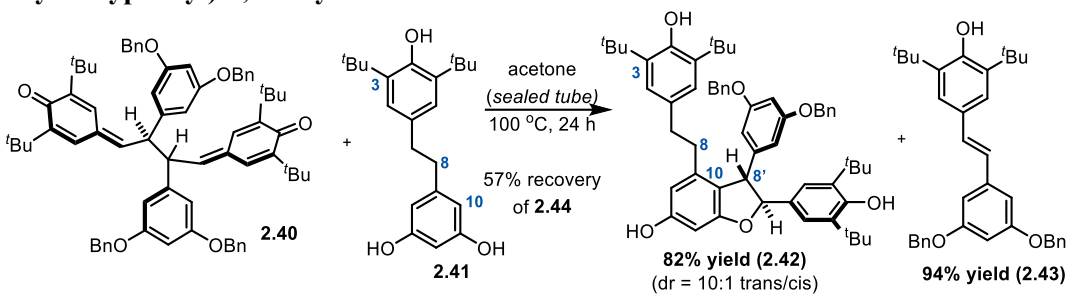
2.7 Experimental Procedures and Spectral Data

General Procedures: Unless specifically noted otherwise, all glassware was flame-dried under vacuum (~0.5 Torr) and cooled under inert atmosphere (N2 or Ar) prior to use. Each reaction container was charged with a Teflon/PTFE-coated magnetic stir bar and sealed with a rubber septum to maintain a positive pressure of inert atmosphere (N2 or Ar). Reagents sensitive to the atmosphere were transferred via syringe or cannula as necessary. Reaction conversion was evaluated using analytical thin-layer chromatography (TLC) using Merck silica gel 60 F254 TLC plates. TLC plates were visualized under a dual short wave/long wave UV lamp and/or stained using solutions of p-anisaldehyde or potassium permanganate or ceric ammonium molybdate. Stained plates were developed over a heat gun as needed. Reactions were purified via flash column chromatography either with RediSep®RF Gold silica columns using a Teledyne Isco CombiFlash RF automated purification system or manually using 230-400 mesh silica gel. Either sodium sulfate or magnesium sulfate were utilized to exclude water from worked up reactions, and the solvent was removed on Büchi rotary evaporators and/or a Welch vacuum pump. All electrochemical experiments were acquired using either a CH1620E electrochemical analyzer (from CH Instruments) or a uSTAT4000 4-Channel Potentiostat/Galvanostat (from Metrohm USA). Cyclic voltammetry measurements were performed in five-neck cells (3 mL) using a three-electrode set-up in which the working electrode was glassy carbon (3 mm diameter), the counter/auxiliary electrode was a platinum wire, and the reference electrode was Ag/AgCl (3 M KCl, from CHInstruments). Bulk electrolysis experiments were performed on discovery scale in open 10-mL vials and in a beaker of the appropriate size (15 – 40 mL) for the subsequent scale-up experiments. These reactions used RVC panels (reticulated vitreous carbon, 100 ppi, 0.25 inch thickness, 3% relative density, from McMaster Carr) as the working or counter/auxiliary electrodes and a Ag/AgCl (3 M KCl) reference electrode.

Reaction Materials: Commercially available reagents were used without further purification unless specified. Organic solvents (acetonitrile, dichloromethane, diethyl ether, dimethylformamide, dimethyl sulfoxide, methanol, tetrahydrofuran, and toluene) and amine bases (triethylamine, pyridine, N,N-diisopropylethylamine, and diisopropylamine) were purified prior to use with a Phoenix Solvent Drying System from JC-Meyer Solvent Systems and PureSolv Micro amine drying columns from Innovative Technology, respectively, and kept under a pressure of argon. Solutions of organolithium reagents and Grignard reagents were purchased from Acros Organics and titrated prior to use.

Product Analysis: Product names were obtained using ChemDraw Professional 16.0 from Perkin Elmer. For racemic compounds, the name corresponds to the depicted structure. Nuclear magnetic resonance (NMR) spectra were obtained using an internal deuterium lock on Varian Inova 500 or Varian VNMR 500 and 700 spectrometers. For ^{1}H spectra, chemical shifts were referenced to the center line of the residual solvent signal (CDCl3: δ 7.26; acetone-d6: δ 2.05; benzene-d6: δ 7.16; DMSO: δ 2.50) and are reported in parts per million (ppm). Signal multiplicity is reported as follows: (br = broad, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet), and the associated coupling constants are given in Hertz. For ^{13}C spectra, experiments were completely heterodecoupled (broadband) and chemical shifts are reported as ppm using the center line of the solvent signal as reference (CDCl3: δ 77.16; acetone-d6: δ 29.92; benzene-d6: δ 128.06; DMSO: δ 39.52). ^{19}F NMR chemical shifts were reported as δ, parts per million, relative to CFCl3 at 0.0 ppm. All ^{13}C NMR spectra are proton-decoupled. All ^{19}F NMR spectra are proton-coupled. High-resolution mass spectra (HRMS) were acquired using a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer using electrospray ionization (ESI), positive ion mode. We thank James Windak and Paul Lennon at the University of Michigan, Department of Chemistry Instrumentation Facility for conducting the HRMS experiments. Infrared spectra were acquired using a Perkin-Elmer Spectrum BX FT-IR spectrophotometer using an ATR mount with a ZnSe crystal.

(2.42) (2R,3R)-3-(3,5-bis(benzyloxy)phenyl)-4-(3,5-di-tert-butyl-4-hydroxyphenethyl)-2-(3,5-di-tert-butyl-4- hydroxyphenyl)-2,3-dihydrobenzofuran-6-ol



A 4 dram vial equipped with a magnetic stirring bar was charged with starting bis-quinone methide **2.40** (300 mg, 0.289 mmol, 1.00 equiv) and dihydrostilbene **2.41** (198 mg, 0.577 mmol, 2.00 equiv). The materials were dissolved/suspended in acetone (5.75 mL), and the vial was sealed tightly. The slowly stirring mixture was then heated to 100 °C for 12 h, over the course of which it becomes homogeneous and yellow-green and eventually yellow-orange. The vial was removed from the heat and allowed to cool to room temperature. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO2 (10% – 20% of a 2:1 EtOAc/CH2Cl2 mixture in Hexanes, followed by a flush at 100% of the 2:1 EtOAc/CH2Cl2) to yield dihydrobenzofuran **2.42** as a separable mixture of trans-(182 mg, 0.211 mmol, 74% yield), and cis-(23 mg, 0.027 mmol, 10% yield) isomers, the disproportionation product stilbene **2.43** (142 mg, 0.273 mmol, 94%) and recovered dihydrostilbene **2.41** (113 mg, 0.330 mmol, 58%).

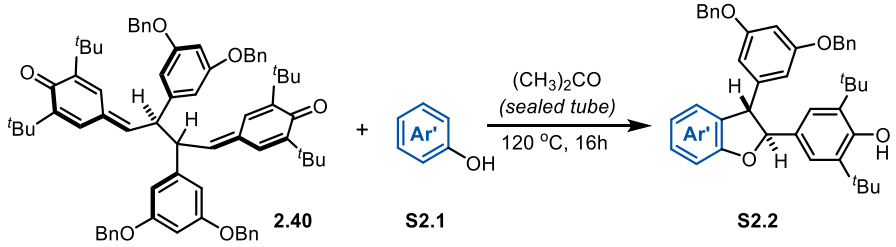
Data for *trans*-dihydrobenzofuran **2.42a**:

TLC (Hexanes/EtOAc, 80:20), R_F:	0.32 (UV, p-anisaldehyde (red));
^{1}H NMR (500 MHz, CDCl3, 25 °C) δ:	7.42 – 7.27 (m, 10H), 7.10 (s, 2H), 6.75 (s, 2H), 6.51 (br s, 1H), 6.46 (s, 2H), 6.34 (s, 1H), 6.22 (s, 1H), 5.42 (d, J = 6.0 Hz, 1H), 5.22 (s, 1H), 5.00 (s, 1H), 4.94 (s, 4H), 4.77 (s, 1H), 4.42 (d, J = 6.0 Hz, 1H), 2.68 – 2.32 (m, 4H), 1.40 (s, 18H), 1.36 (s, 18H);
^{13}C NMR (175 MHz, CDCl3, 25 °C) δ:	161.5, 160.5, 156.9, 154.0, 152.1, 146.2, 140.8, 136.9, 136.2, 135.8, 132.4, 132.2, 128.8, 128.2, 127.8, 125.0, 122.7, 120.5, 108.8, 107.4, 100.5, 95.5, 94.2, 70.2, 56.5, 36.5, 35.5, 34.6, 34.4, 30.53, 30.46;
HRMS (ESI):	*m/z* calculated for $C_{58}H_{69}O_6$ [M+H]+ : 861.5089, found 861.5085;
FTIR (neat) cm^{-1} :	2916 (w), 1594 (w), 1435 (m), 1361 (s), 1222 (s), 1157 (m), 908 (s), 727 (s). 25

Data for *cis*-dihydrobenzofuran (reassigned to C12 regioisomer) **2.42b**:

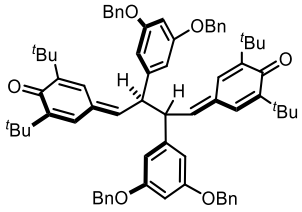
TLC (Hexanes/EtOAc, 80:20), R_F:	0.46 (UV, p-anisaldehyde (red));
^{1}H NMR (500 MHz, CDCl3, 25 °C) δ:	7.44 – 7.27 (m, 10H), 7.12 (s, 2H), 7.02 (s, 2H), 6.58 (br, s, 1H), 6.53 (br s, 2H), 6.45 (s, 1H), 6.30 (s, 1H), 5.42 (d, J = 8.7 Hz, 1H), 5.24 (s, 1H), 5.06 (s, 1H), 4.99 (s, 4H), 4.51 (d, J = 8.7 Hz, 1H), 4.34 (br s, 1H), 2.85 (br s, 4H), 1.44 (s, 18H), 1.42 (s, 18H);
^{13}C NMR (175 MHz, CDCl3, 25 °C) δ:	161.5, 160.8, 154.1, 152.7, 152.2, 145.8, 142.7, 136.8, 136.2, 136.0, 132.6, 130.7, 128.8, 128.3, 127.9, 125.1, 123.1, 112.4, 109.3, 107.4, 103.0, 101.3, 94.22, 70.4, 55.6, 38.8, 38.0, 34.6, 34.5, 30.6, 30.5;
HRMS (ESI):	*m/z* calculated for $C_{58}H_{69}O_6$ [M+H]+ : 861.5089, found 861.5080;
FTIR (neat) cm^{-1} :	3637 (m), 2954 (m), 2873 (m), 1593 (s), 1434 (s), 1361 (m), 1316 (m), 1233 (m), 1213 (m), 1155 (s), 1120 (m), 1056 (s), 908 (s), 726 (s), 695 (s).

General procedure for intermolecular radical addition

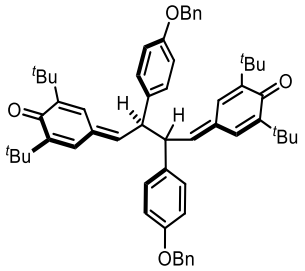


In a flame-dried 15mL sealed tube capped with a septa under inert atmosphere, bisquinone methide dimer (**2.40**, 2 equiv) and aryl phenol (**S2.1**, 1 equiv) were added and the solids were dissolved/suspended in dry acetone (0.025M, reagent grade purity) that had been previously sparged with N2 (18G needle, 10 min). The tube was capped and the mixture was stirred at 120 °C for 16 h. Upon completion, the reaction was transferred to a round bottom flask and concentrated *in vacuo* to provide a foam and the residue was purified with flash chromatography (0-10% EtOAc in hexanes gradient) to afford dihydrobenzofuran **S2.2**.

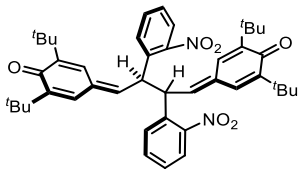
The following substrates were acquired from previous investigations reported by our group.[54,56,57,196]



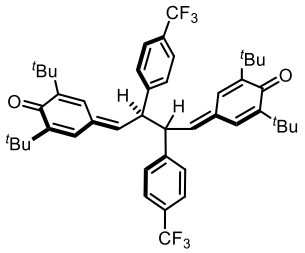
(S2.3) 4,4'-((2R,3S)-2,3-bis(3,5-bis(benzyloxy)phenyl)butane-1,4-diylidene)bis(2,6-di-tert-butylcyclohexa-2,5-dien-1-one)



(S2.4) 4,4'-((2R,3S)-2,3-bis(4-(benzyloxy)phenyl)butane-1,4-diylidene)bis(2,6-di-tert-butylcyclohexa-2,5-dien-1-one)



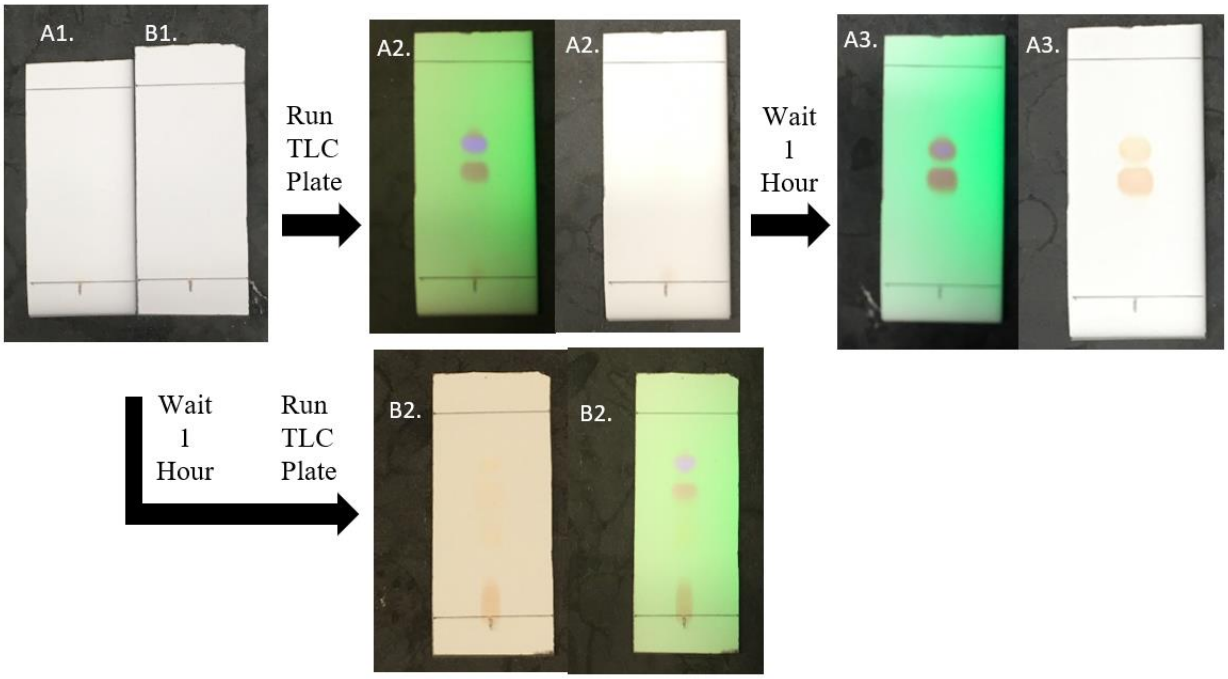
(S2.5) 4,4'-((2R,3S)-2,3-bis(2-nitrophenyl)butane-1,4-diylidene)bis(2,6-di-tert-butylcyclohexa-2,5-dien-1-one)



(S2.6) 4,4'-((2R,3S)-2,3-bis(4-(trifluoromethyl)phenyl)butane-1,4-diylidene)bis(2,6-di-te rt-butylcyclohexa-2,5-dien-1-one)

Note on compound stability

Many of the electron rich phenols synthesized in this publication are not stable to air. This is due to their low oxidation potential, and their propensity to ring open the newly formed dihydrobenzofurans. This property was observed in a number of ways through this research, including the storage of compounds. All dihydrobenzofurans stored under air degraded, often going from a pale colored foam to a red / brown viscous liquid, indicating some chemical change. NMRs of these materials showed the growth of a large number of small intractable impurities. For this reason, the preferred method of storage for these compounds is under vacuum, or in an inert atmosphere such as a glovebox. We found that storage in parafilm sealed vials was not sufficient to prevent degradation on a week or month timescale. A TLC study is shown below as experimental evidence of this phenomenon.



The above image displays a simple TLC control demonstrating the lack of these compounds' stability. TLC plates both A and B are spotted at time zero, with plate A being eluted with 30% ethyl acetate and 70% hexanes. The spots are only visible by UV detection, but not in normal light as shown in plate A2. After waiting for one hour, the UV detection is still efficient as seen in plate A3, but the spots are also visible as brownish red dot spots by the naked eye. On the contrary if plate A1 is let sit for 1 hour followed by eluting of the plate, the two spots with a higher R_f are still present and not visible, but a significant baseline impurity has also formed. We believe this to be of oxidation or dihydrobenzofuran ring opening, and some of the NMRs included show small peaks indicative of degradation.

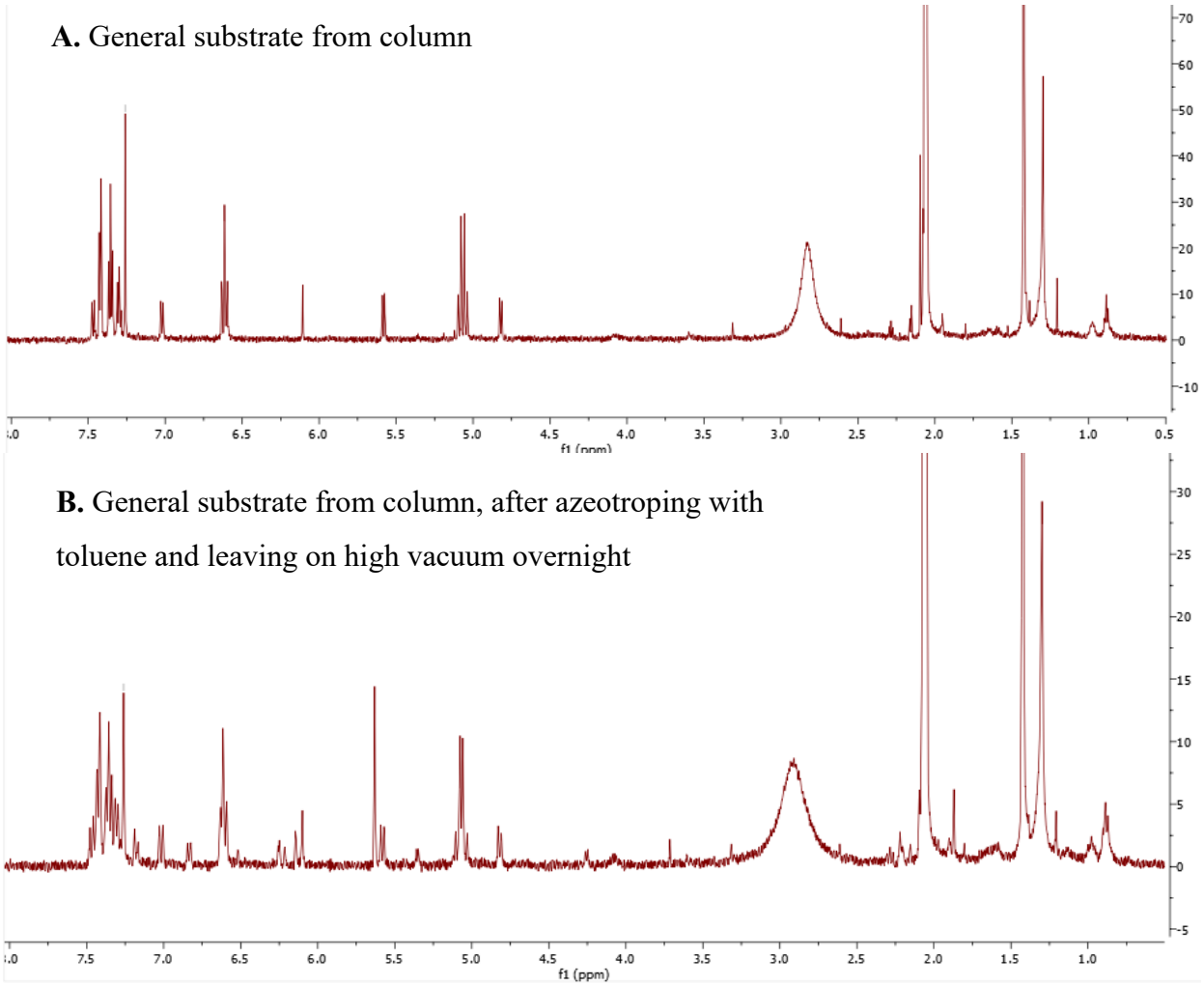
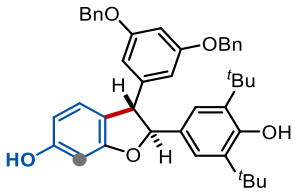


Figure 2.23 Compounds stability analysis by ^{1}H NMR

The figure above depicts a case of compound instability in which azeotroping the product with toluene and leaving on high vacuum overnight resulted in the growth impurities associated with the handling of the compound. This further illustrates some of the purification and material handling consideration when exploring the chemistry of electron rich, easily oxidized molecules.

Selected Scope of phenols: To view full scope, please reference the original publication.[118]

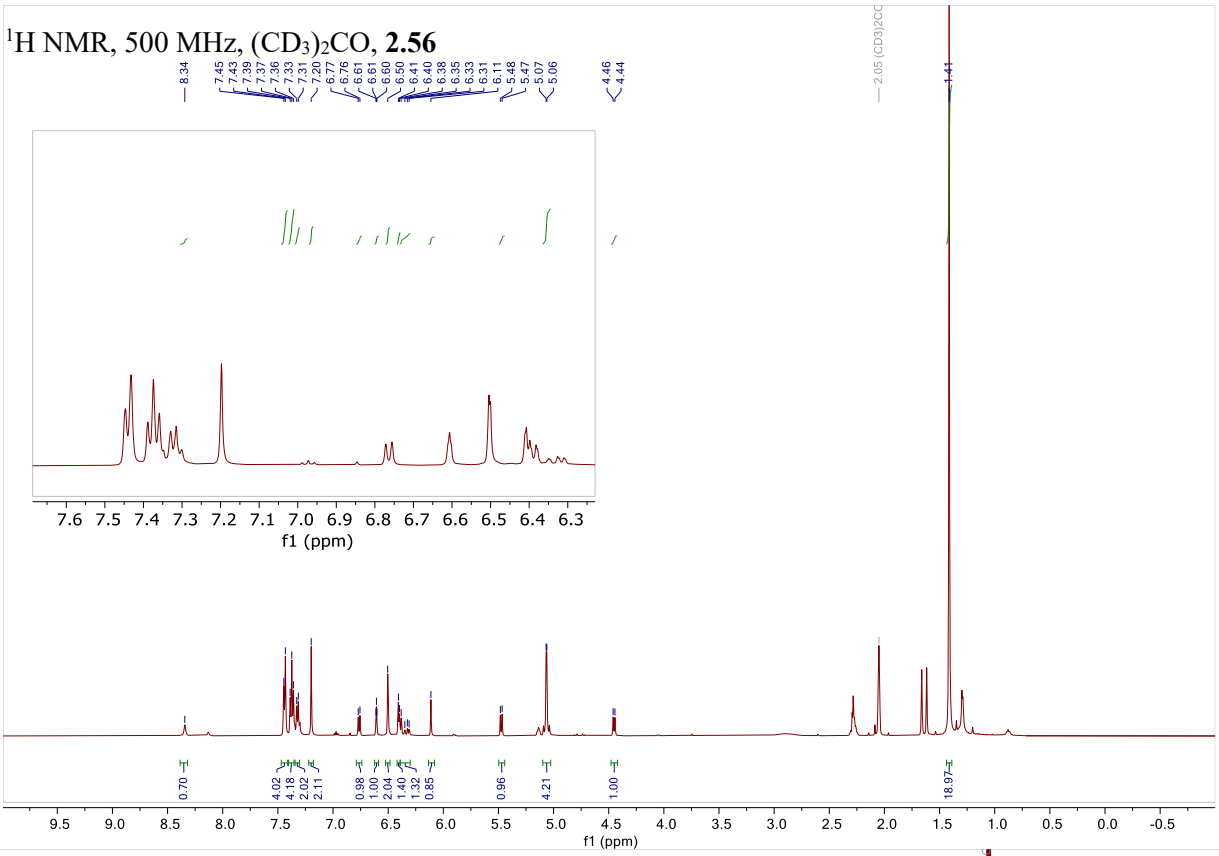


(2.56) 3-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-6-ol

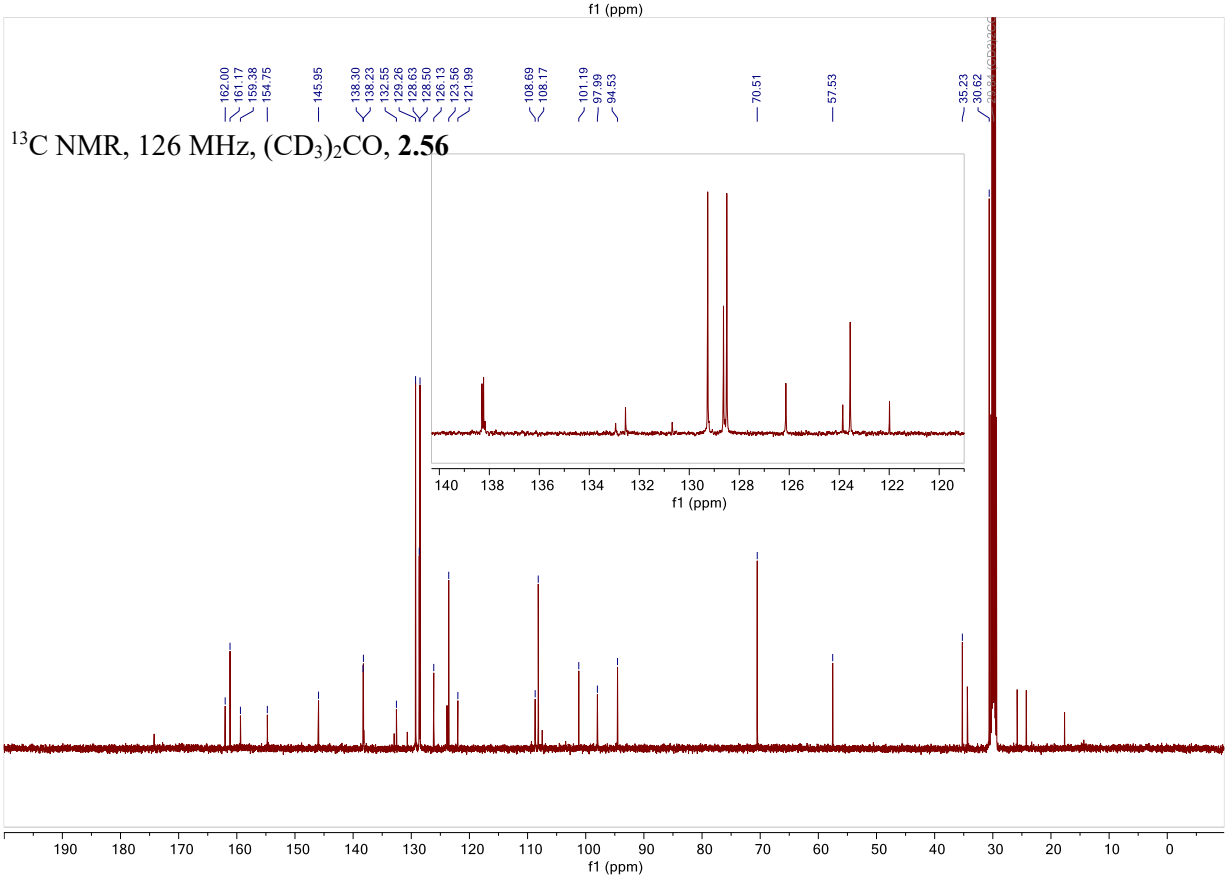
Commercially available resorcinol (11 mg, 0.10 mmol) and **2.40** (208 mg, 0.20 mmol) were subjected to the general procedure for intermolecular radical addition. The product was purified by column chromatography (0-20% ethyl acetate in hexanes) to afford 3-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-6-ol (**2.56**, 6 mg, 9% yield).

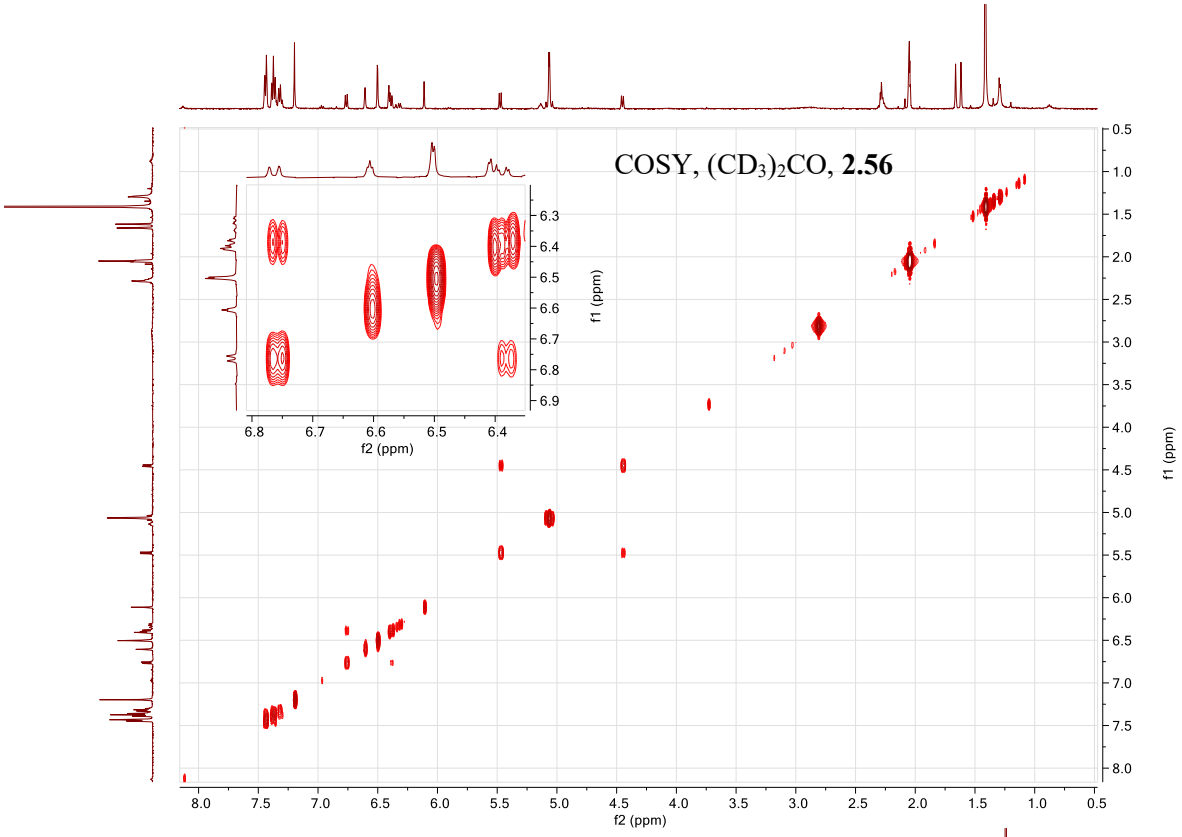
R_F (Hexanes/EtOAc, 70:30):	0.54 (UV potassium permanganate);
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 25 °C) δ:	8.34 (s, 1H), 7.44 (d, *J* = 6.8 Hz, 4H), 7.37 (t, *J* = 7.5 Hz, 4H), 7.32 (d, *J* = 7.1 Hz, 2H), 7.20 (s, 2H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.61 (t, *J* = 2.2 Hz, 1H), 6.50 (s, 2H), 6.40 (d, *J* = 4.4 Hz, 1H), 6.39 – 6.30 (m, 1H), 6.11 (s, 1H), 5.47 (d, *J* = 8.1 Hz, 1H), 5.06 (d, *J* = 3.3 Hz, 4H), 4.45 (d, *J* = 8.2 Hz, 1H), 1.41 (s, 18H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$, 25 °C) δ:	162.0, 161.2, 159.4, 154.8, 146.0, 138.3, 138.2, 132.6, 129.3, 128.6, 128.5, 126.1, 123.6, 122.0, 108.7, 108.2, 101.2, 98.0, 94.5, 70.5, 57.5, 35.2, 30.6.
HRMS (ESI):	*m/z* calculated for $C_{42}H_{45}O_5^+$ ($[M+H]^+$): 629.3262, found 629.3251
FTIR (neat) cm^{-1} :	3625 (br), 3365 (br), 2957 (w), 1707 (w), 1594 (s), 1497 (m), 1453 (m), 1372 (w), 1300 (w), 1234 (w), 1146 (vs), 1056 (m), 1029 (m), 960 (m), 881 (w), 737 (m), 696 (m) cm^{-1}

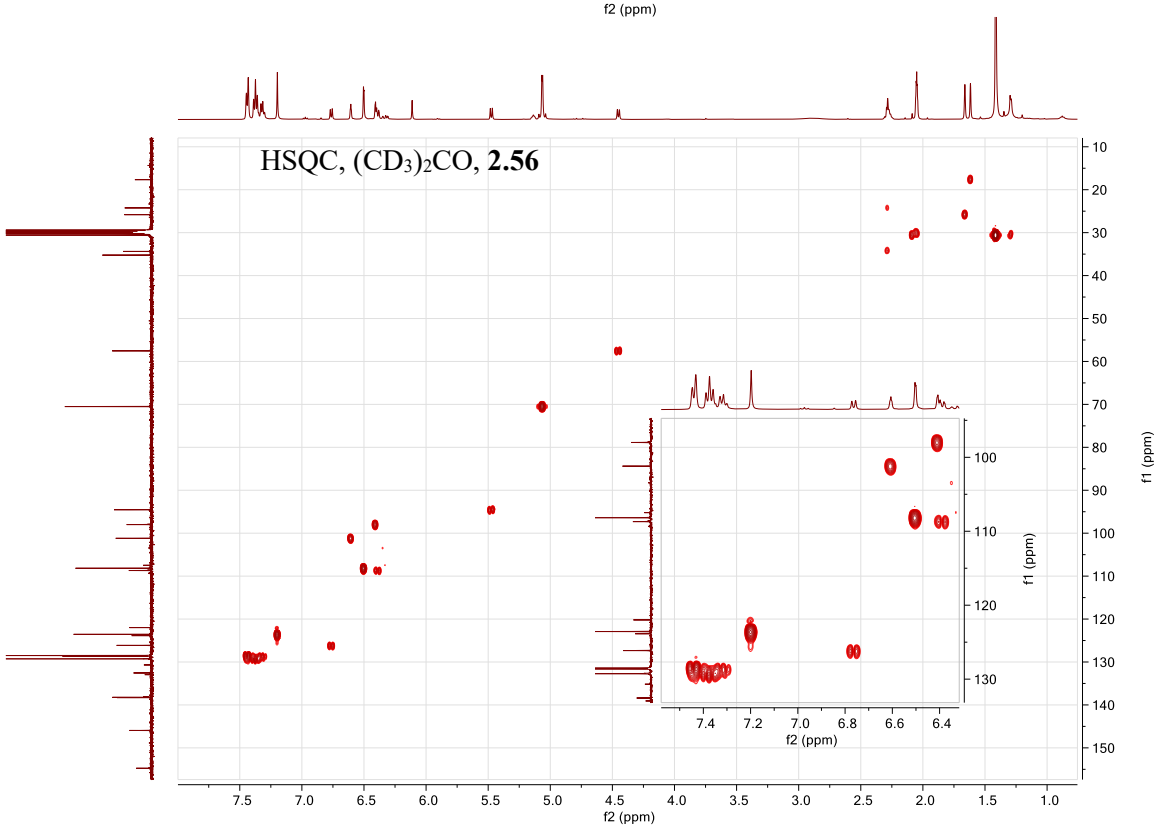
^{1}H NMR, 500 MHz, $(CD_3)_2CO$, **2.56**

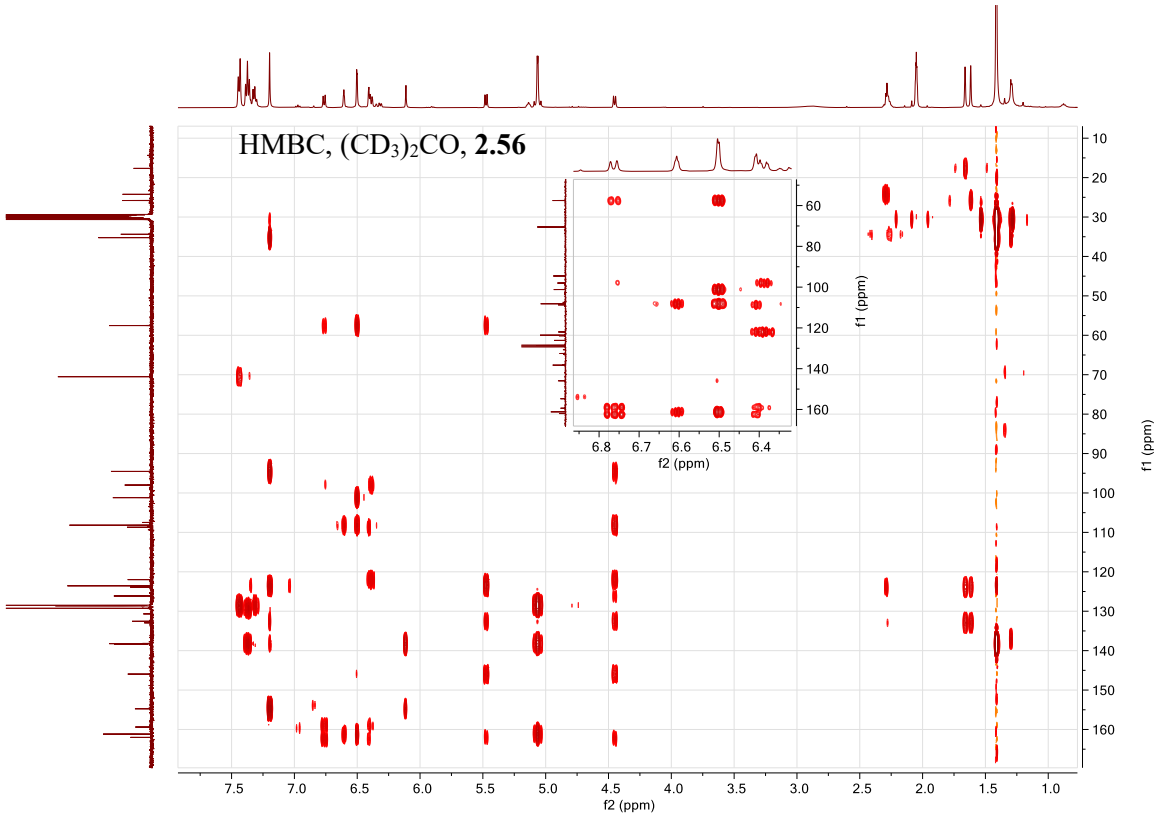


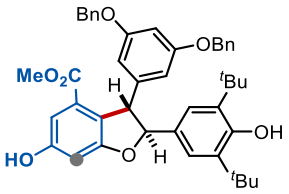
^{13}C NMR, 126 MHz, $(CD_3)_2CO$, **2.56**




COSY, (CD3)2CO, 2.56
f1 (ppm)
f2 (ppm)


HSQC, (CD3)2CO, 2.56
f1 (ppm)
f2 (ppm)


HMBC, (CD3)2CO, 2.56
f2 (ppm)
f1 (ppm)

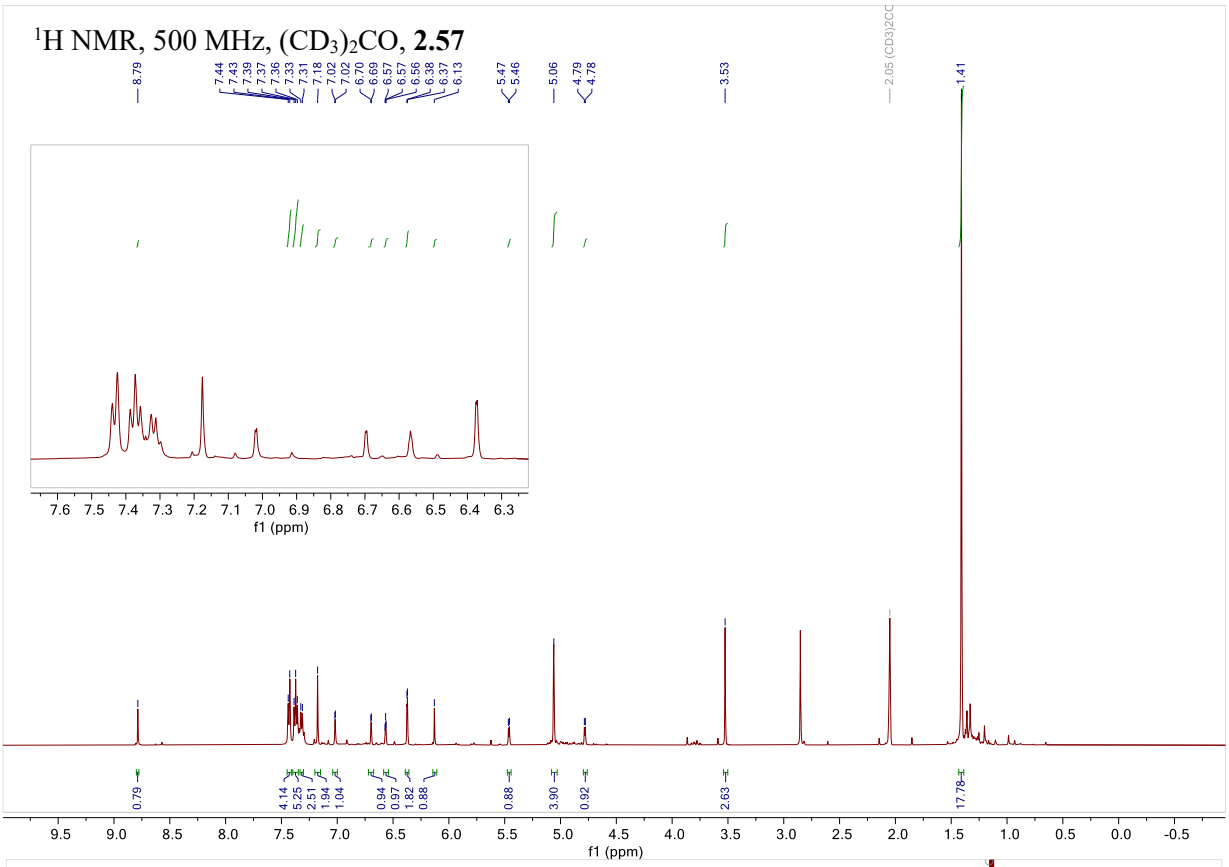


(2.57) methyl 3-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-4-hydroxy-2,3-dihydrobenzofuran-6-carboxylate

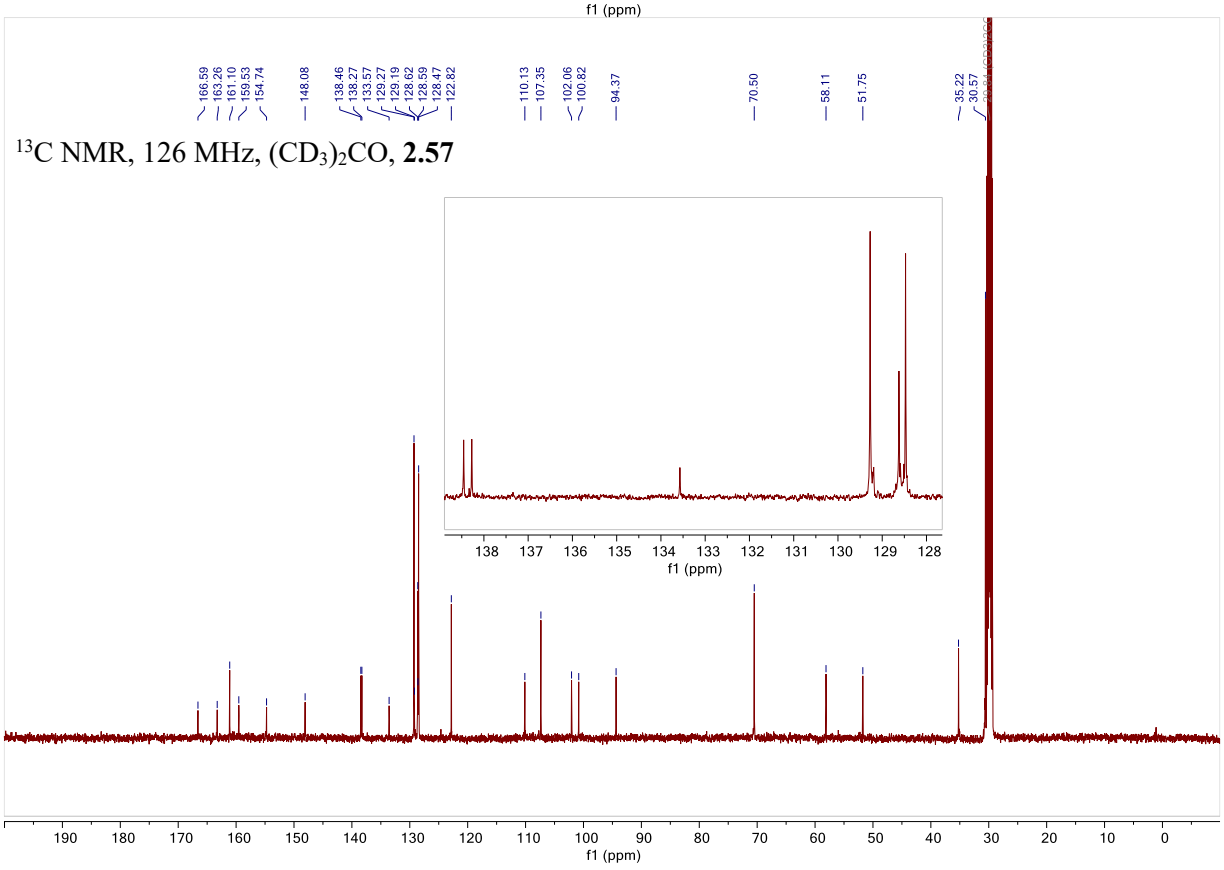
Commercially available methyl 3,5-dihydroxybenzoate (8.41 mg, 0.05 mmol) and **2.40** (104 mg, 0.10 mmol) were subjected to the general procedure for intermolecular radical addition. The product was purified by column chromatography (0-20% ethyl acetate in hexanes) to afford methyl 3-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-4-hydroxy-2,3-dihydrobenzofuran-6-carboxylate (**2.57**, 12.8 mg, 37% yield).

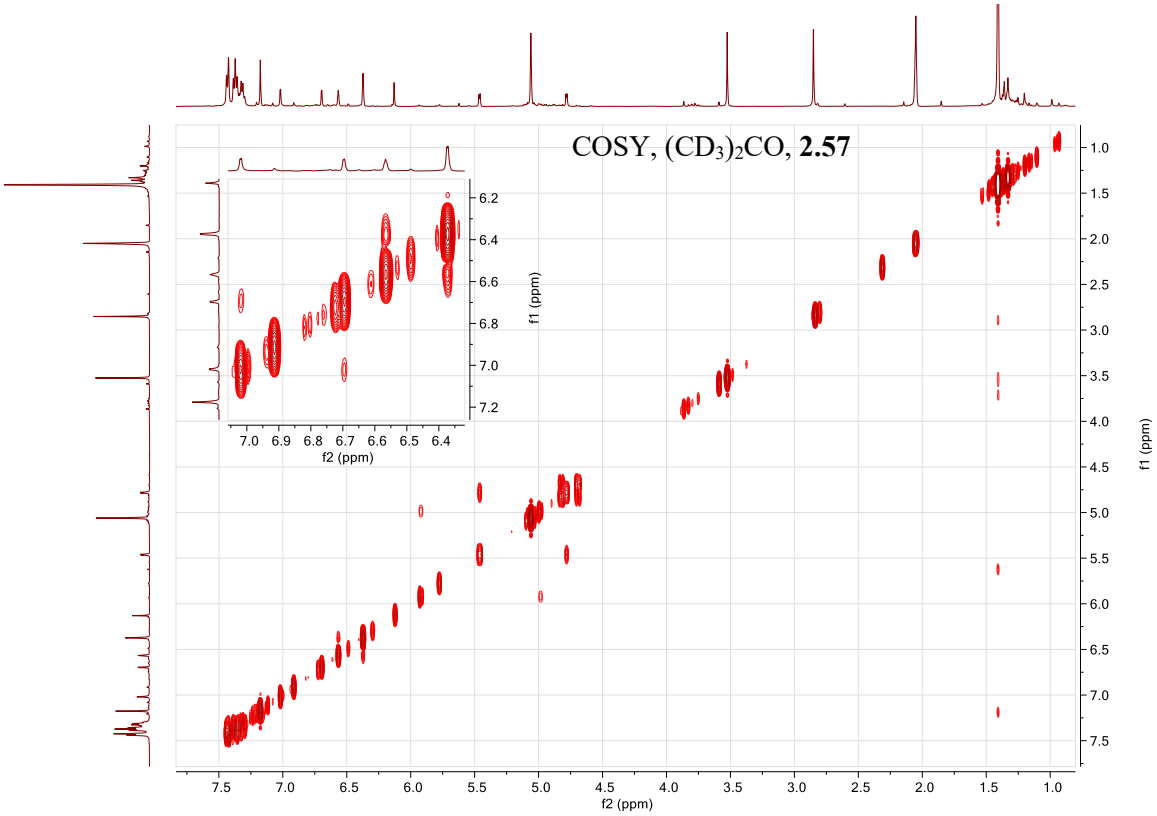
R_F (Hexanes/EtOAc, 70:30):	0.64 (UV, potassium permanganate);
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 25 °C) δ:	8.79 (s, 1H), 7.43 (d, *J* = 7.0 Hz, 4H), 7.37 (t, *J* = 7.4 Hz, 5H), 7.32 (d, *J* = 7.3 Hz, 3H), 7.18 (s, 2H), 7.02 (d, *J* = 2.3 Hz, 1H), 6.70 (d, *J* = 2.4 Hz, 1H), 6.57 (t, *J* = 2.3 Hz, 1H), 6.37 (d, *J* = 2.3 Hz, 2H), 6.13 (s, 1H), 5.46 (d, *J* = 4.5 Hz, 1H), 5.06 (s, 4H), 4.78 (d, *J* = 4.4 Hz, 1H), 3.53 (s, 3H), 1.41 (s, 18H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$, 25 °C) δ:	166.6, 163.3, 161.1, 159.5, 154.7, 148.1, 138.5, 138.3, 133.6, 129.3, 129.2, 128.62, 128.59, 128.5, 122.8, 110.1, 107.4, 102.1, 100.8, 94.4, 70.5, 58.1, 51.8, 35.2, 30.6.
HRMS (ESI):	*m/z* calculated for $C_{44}H_{47}O_7^+$ ($[M+H]^+$): 687.3316, found 687.3303
FTIR (neat) cm^{-1} :	3627 (br), 3407 (w), 2955 (w), 1712 (m), 1593 (s), 1436 (s), 1361 (m), 1290 (w), 1216 (m), 1153 (vs), 1056 (m), 1028 (m), 1003 (w), 882 (w), 737 (m), 696 (s) cm^{-1}

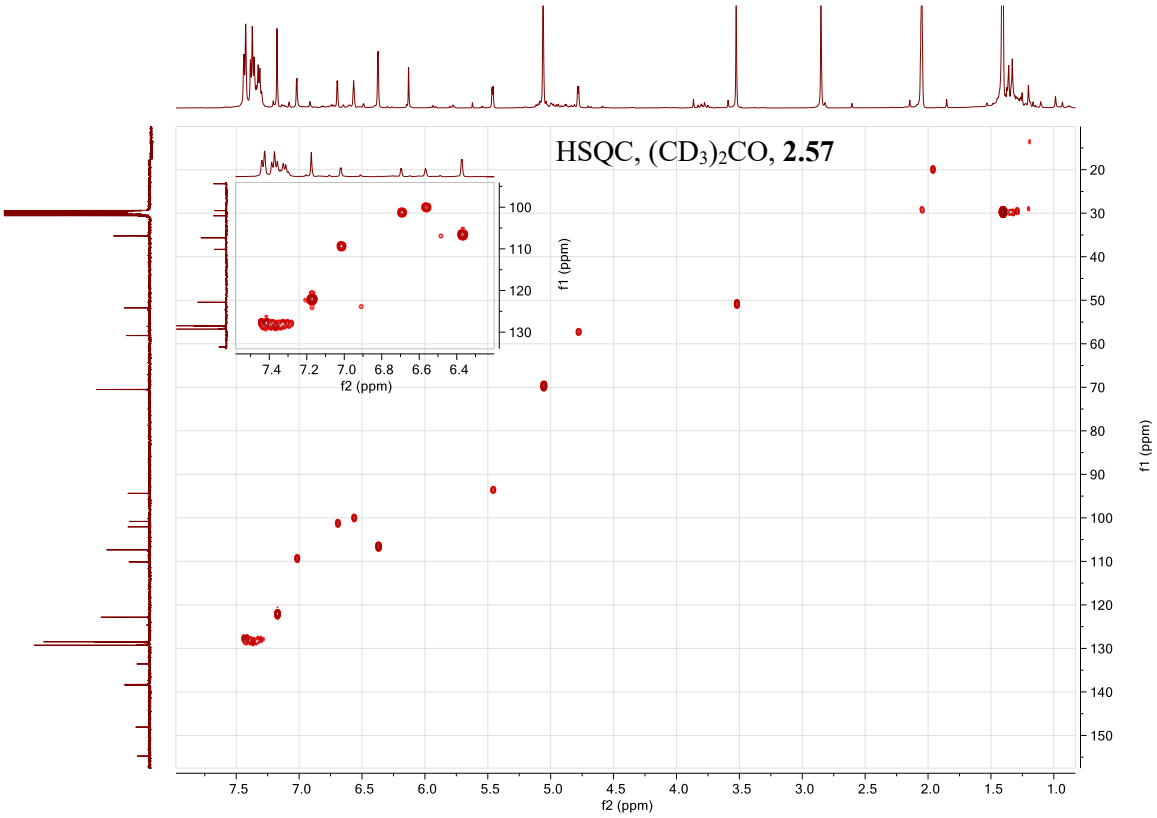
^{1}H NMR, 500 MHz, $(CD_3)_2CO$, **2.57**

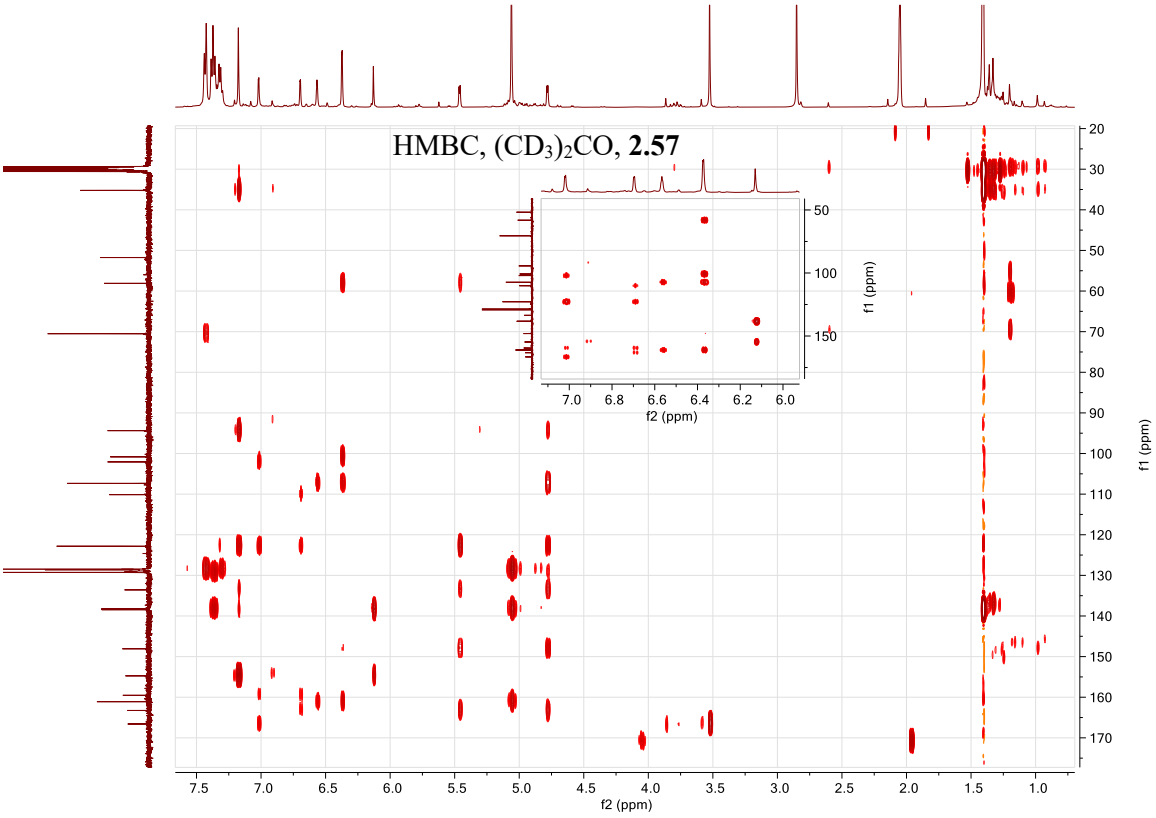


^{13}C NMR, 126 MHz, $(CD_3)_2CO$, **2.57**




COSY, $(CD_3)_2CO$, **2.57**
f2 (ppm)
f1 (ppm)


HSQC, $(CD_3)_2CO$, **2.57**
f2 (ppm)
f1 (ppm)


HMBC, (CD3)2CO, 2.57
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
20
30
40
50
60
70
80
90
100
110
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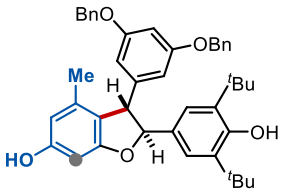
7.0
6.8
6.6
6.4
6.2
6.0
50
100
150

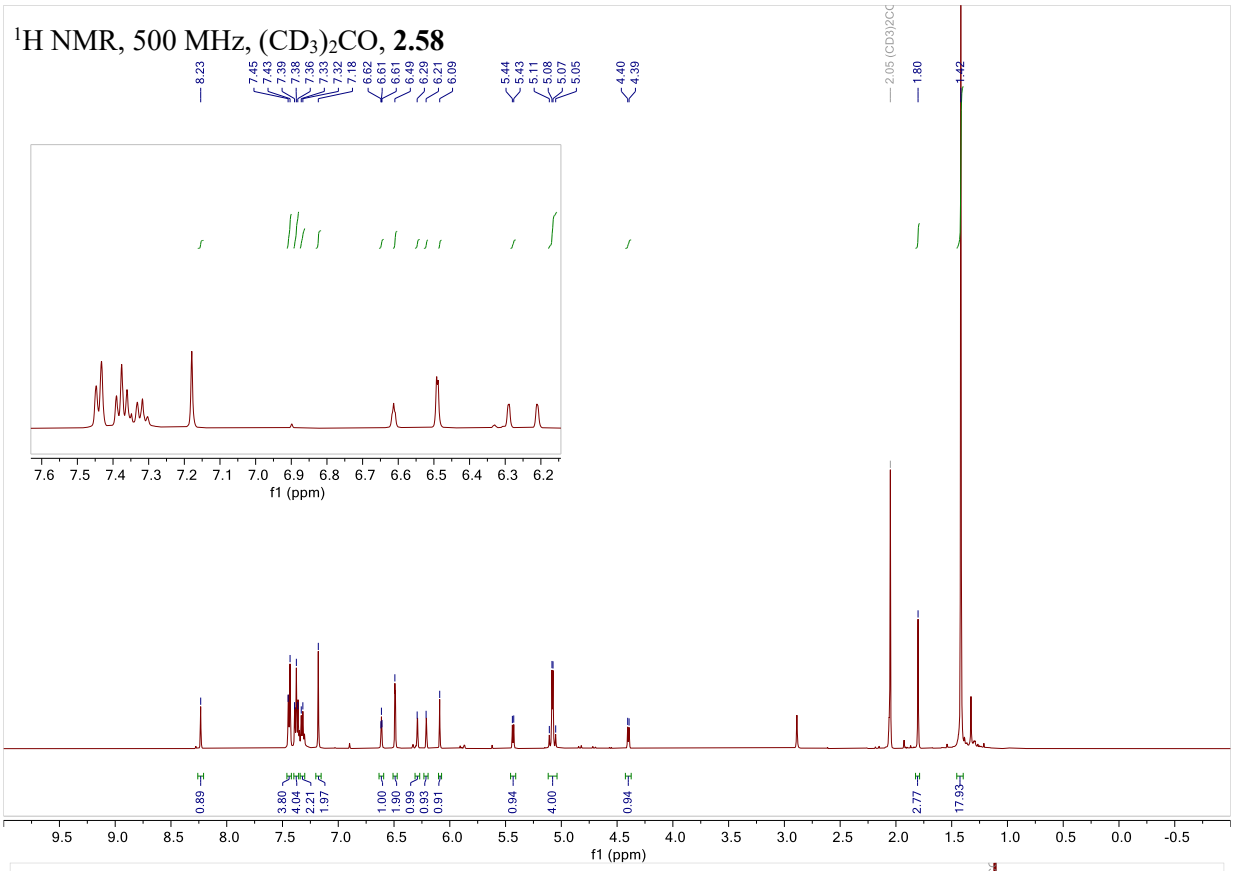


(2.58) 3-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-4-methyl-2,3-dihydrobenzofuran-6-ol

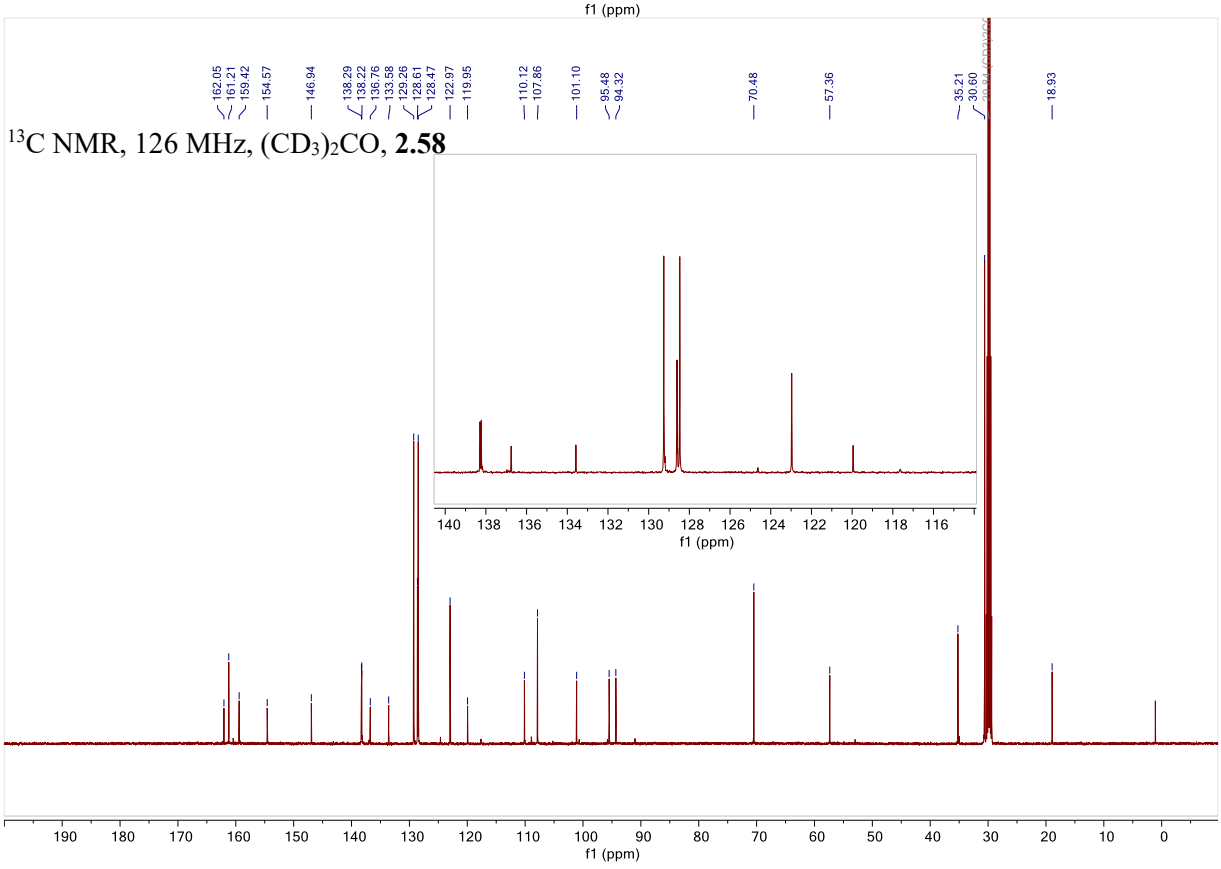
Commercially available orcinol (12.4 mg, 0.10 mmol) and **2.40** (208 mg, 0.20 mmol) were subjected to the general procedure for intermolecular radical addition. The product was purified by column chromatography (0-20% ethyl acetate in hexanes) to afford 3-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-4-methyl-2,3-dihydrobenzofuran-6-ol (**2.58**, 38.7 mg, 60% yield). **Scale-up:** Run at 0.50 mmol scale (207 mg, 64% yield).

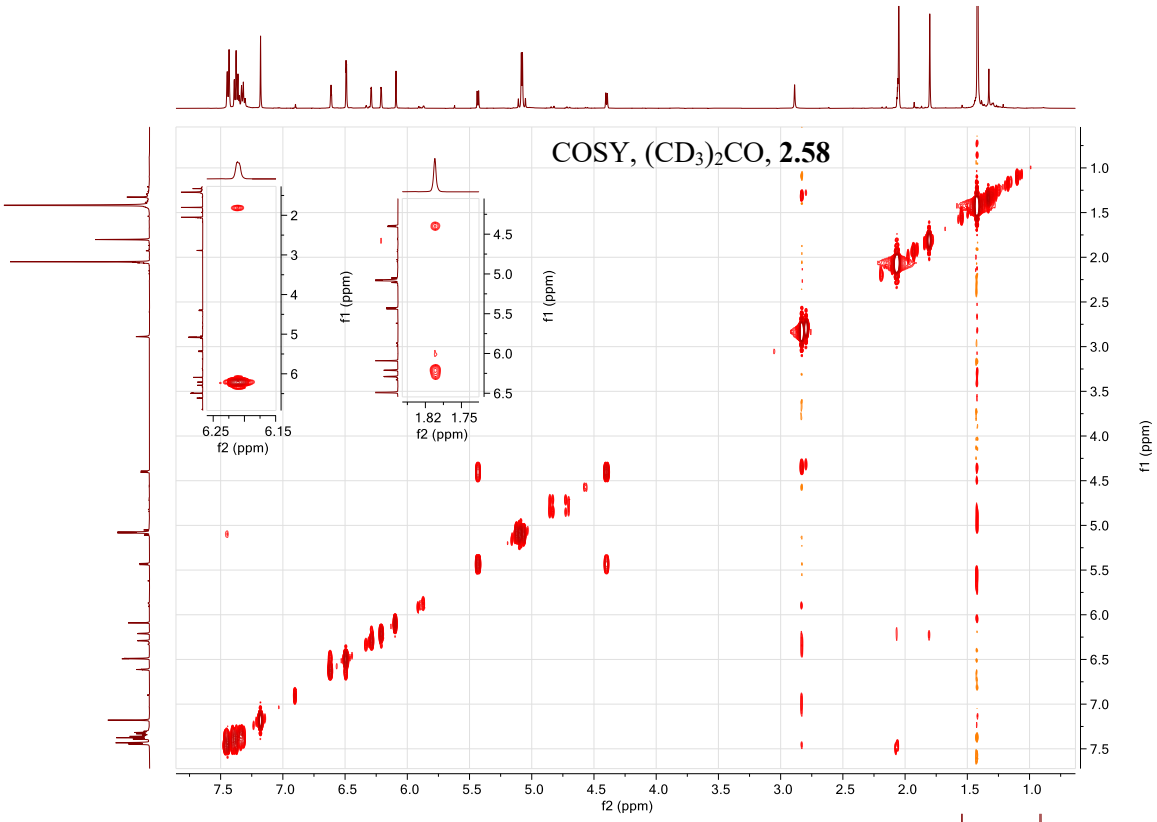
R_F (Hexanes/EtOAc, 70:30):	0.5 (UV, potassium permanganate);
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 25 °C) δ:	8.23 (s, 1H), 7.44 (d, *J* = 8.8 Hz, 4H), 7.40 – 7.36 (m, 4H), 7.32 (d, *J* = 7.1 Hz, 2H), 7.18 (s, 2H), 6.61 (t, *J* = 2.3 Hz, 1H), 6.49 (s, 2H), 6.29 (s, 1H), 6.21 (s, 1H), 6.09 (s, 1H), 5.43 (d, *J* = 6.1 Hz, 1H), 5.12 – 5.04 (m, 4H), 4.40 (d, *J* = 6.1 Hz, 1H), 1.80 (s, 3H), 1.42 (s, 18H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$, 25 °C) δ:	162.1, 161.2, 159.4, 154.6, 146.9, 138.3, 138.2, 136.8, 133.6, 129.3, 128.6, 128.5, 123.0, 120.0, 110.1, 107.9, 101.1, 95.5, 94.3, 70.5, 57.4, 35.2, 30.6, 18.9.
HRMS (ESI):	*m/z* calculated for $C_{43}H_{47}O_5^+$ ($[M+H]^+$): 643.3418, found 643.3414
FTIR (neat) cm^{-1} :	3626 (br), 3387 (br), 2956 (w), 1703 (m), 1593 (s), 1452 (s), 1360 (m), 1290 (w), 1233 (m), 1153 (vs), 1055 (s), 1028 (m), 972 (w), 881 (m), 736 (s), 696 (s) cm^{-1}

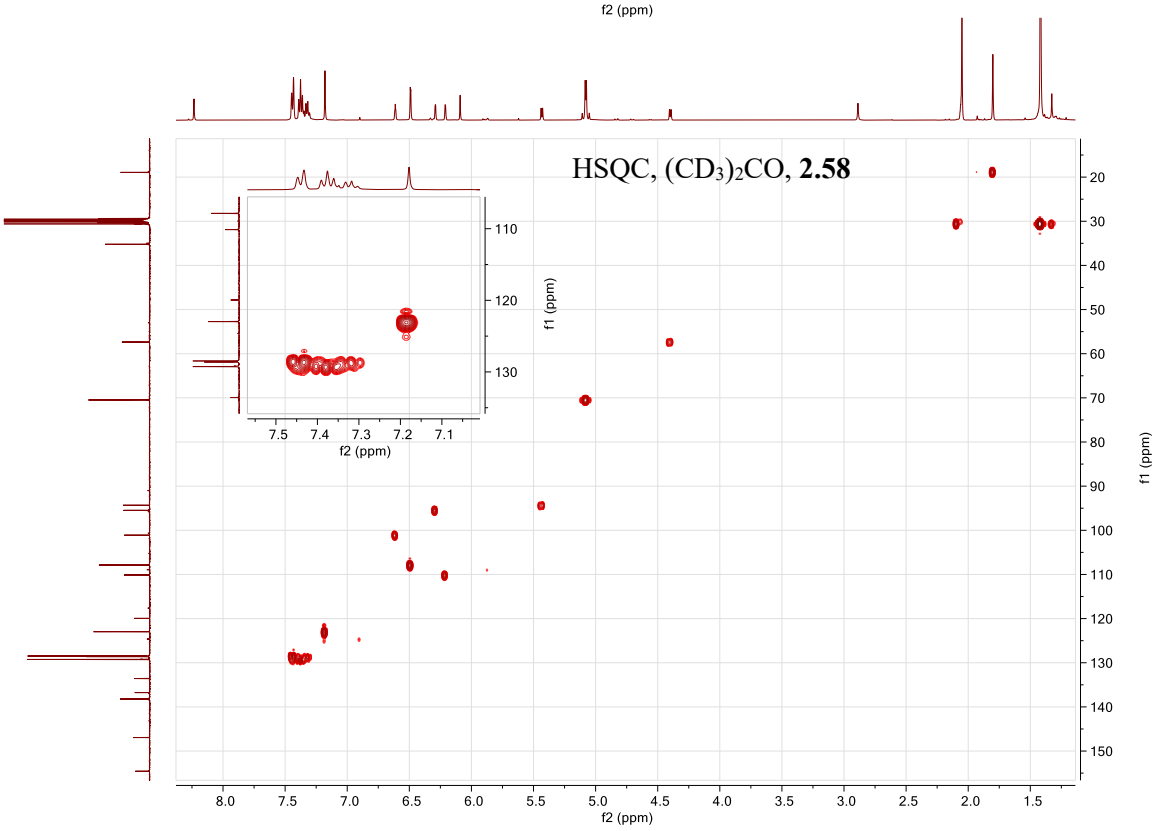
^{1}H NMR, 500 MHz, $(CD_3)_2CO$, **2.58**

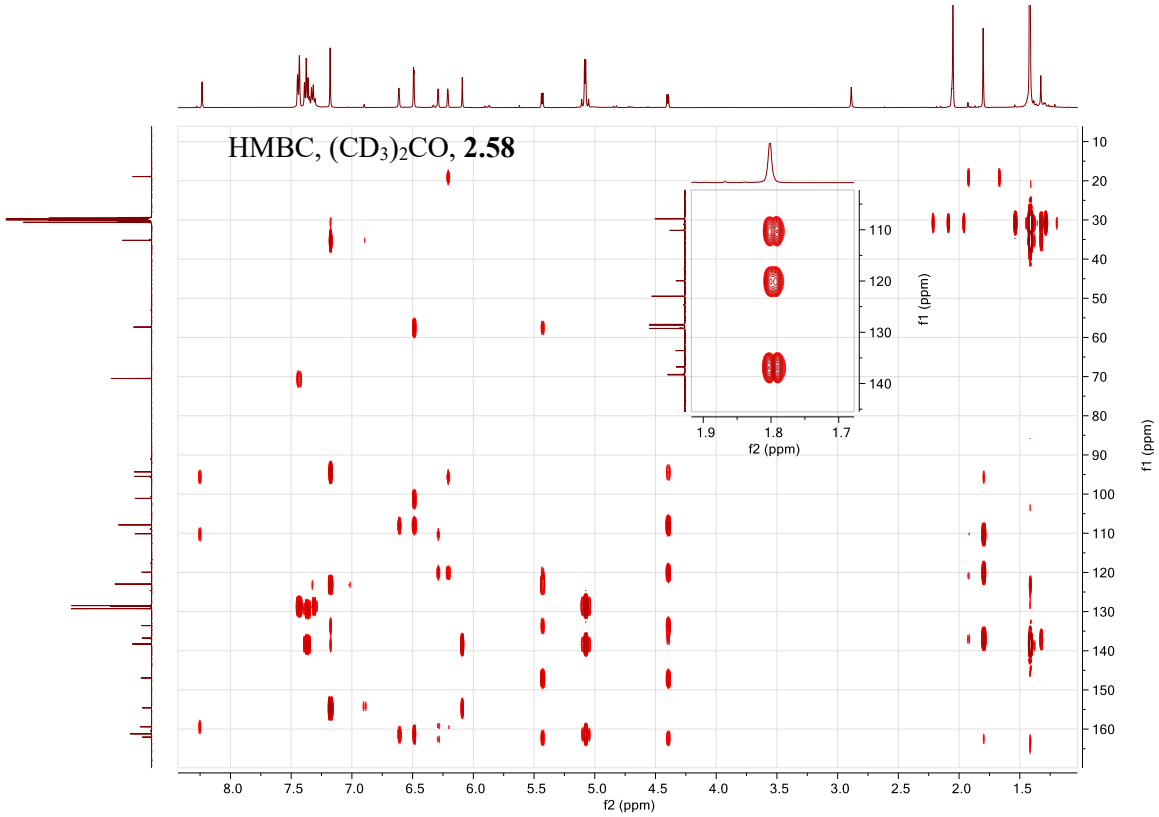


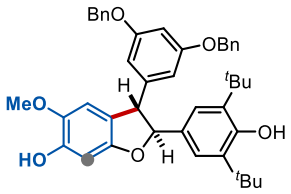
^{13}C NMR, 126 MHz, $(CD_3)_2CO$, **2.58**




COSY, (CD3)2CO, 2.58
f2 (ppm)
f1 (ppm)


HSQC, (CD3)2CO, 2.58
f2 (ppm)
f1 (ppm)


HMBC, (CD3)2CO, 2.58
f2 (ppm)
f1 (ppm)

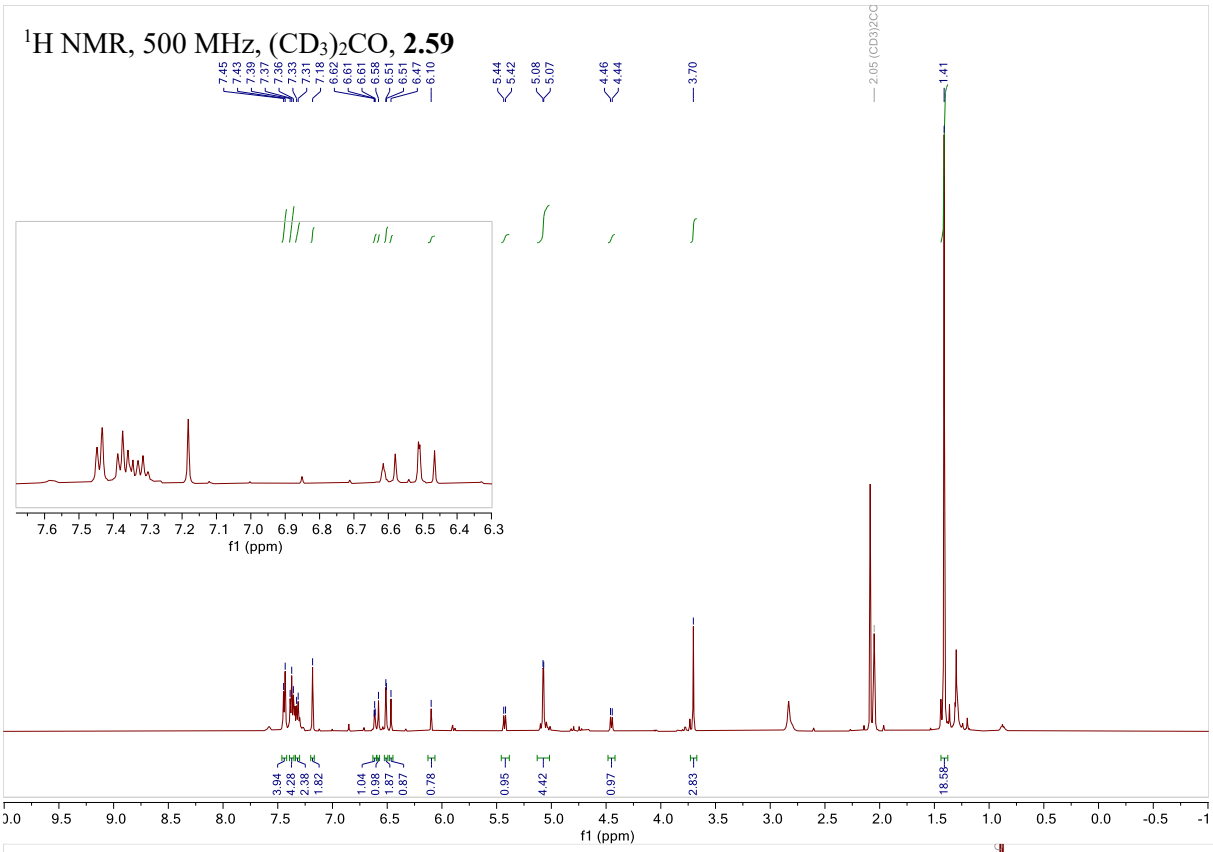


(2.59) (2S)-3-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-5-methoxy-2,3-dihydrobenzofuran-6-ol

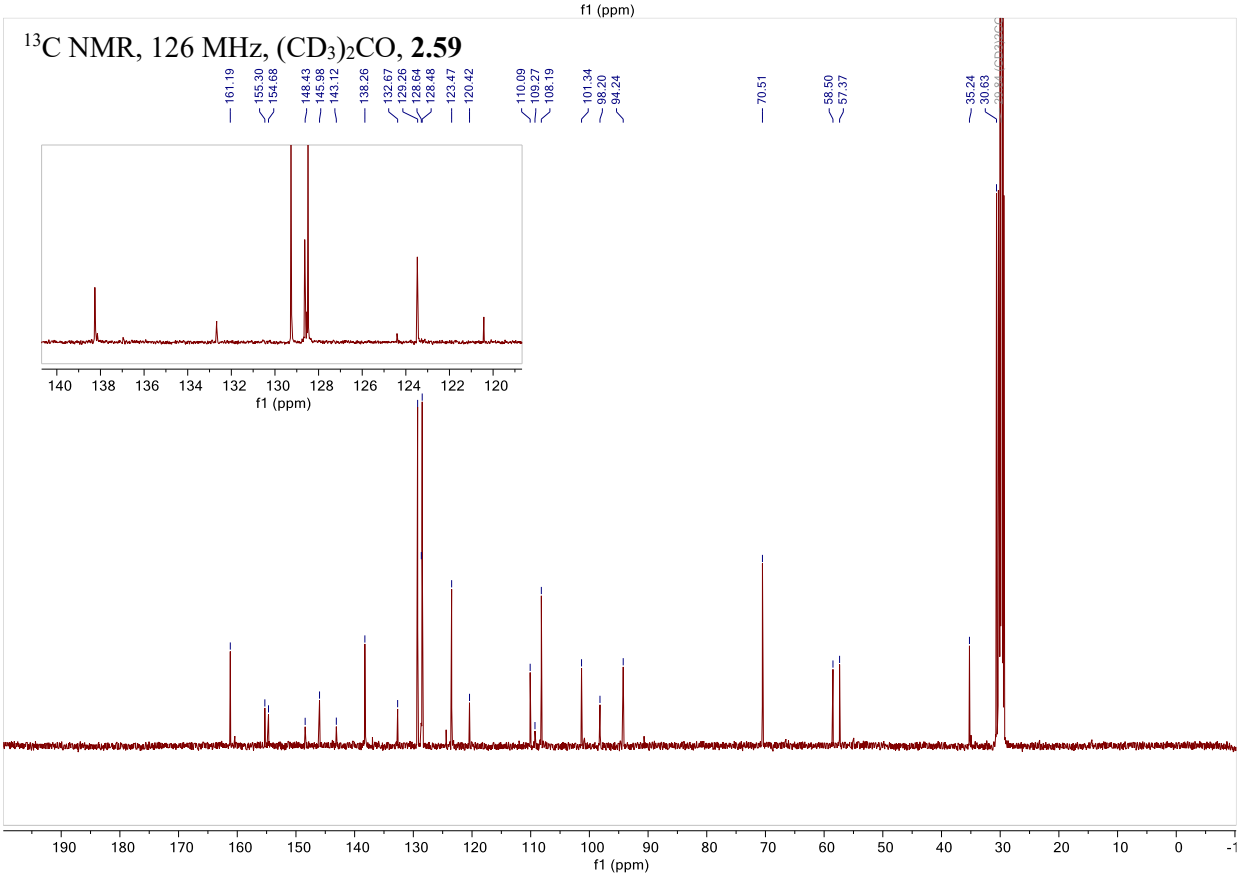
Commercially available 4-methoxybenzene-1,3-diol (14 mg, 0.10 mmol) and **2.40** (208 mg, 0.20mmol) were subjected to the general procedure for intermolecular radical addition. The product was purified by column chromatography (0-15% ethyl acetate in hexanes) to afford (2S)-3-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-5-methoxy-2,3-dihydrobenzofuran-6-ol (**2.59**, 59.0 mg, 90% yield). Due to **2.59** being very oxidatively sensitive, there are minor impurities in the spectra that correspond with oxidative degradation.

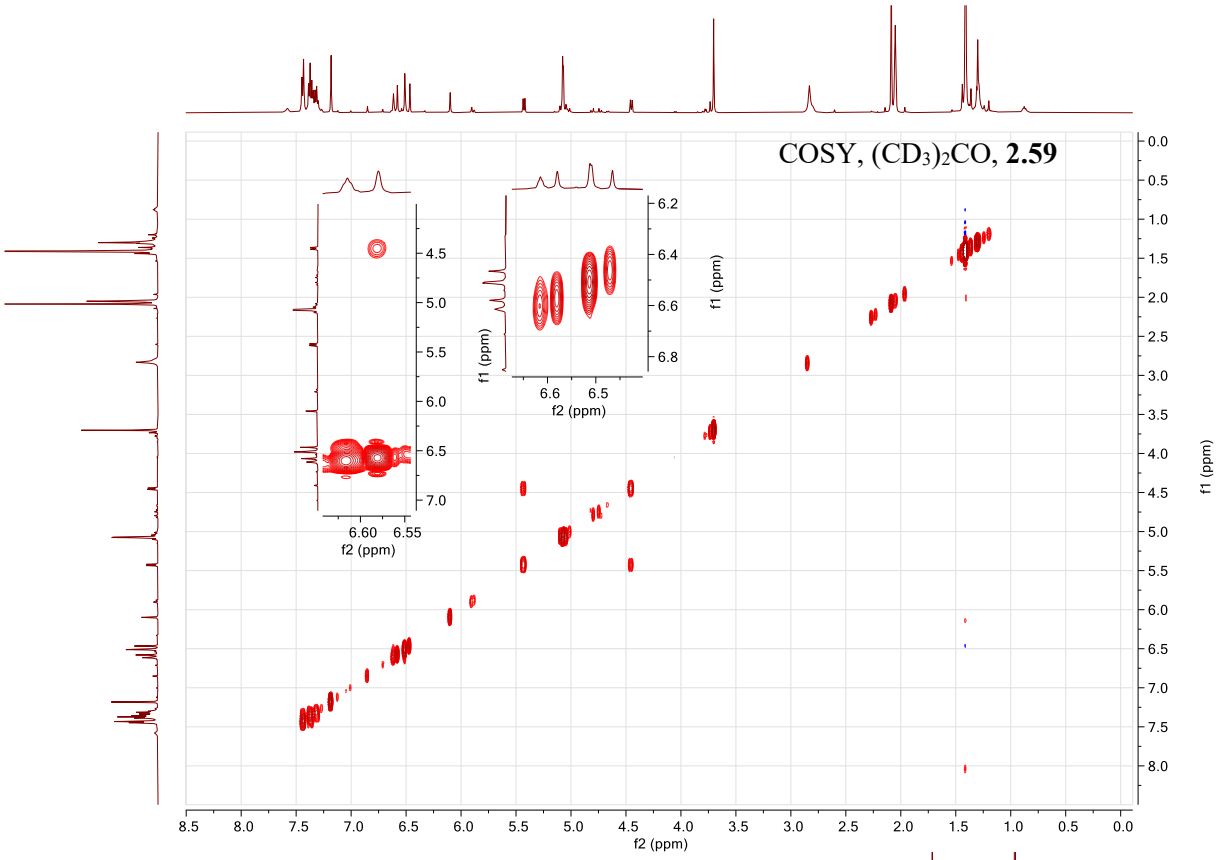
R_F (Hexanes/EtOAc, 70:30):	0.49 (UV, (UV, potassium permanganate);
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 25 °C) δ:	7.44 (d, J = 7.3 Hz, 4H), 7.37 (t, J = 7.4 Hz, 4H), 7.32 (d, J = 7.3 Hz, 2H), 7.18 (s, 2H), 6.61 (t, J = 2.3 Hz, 1H), 6.58 (s, 1H), 6.51 (d, J = 2.4 Hz, 2H), 6.47 (s, 1H), 6.10 (s, 1H), 5.43 (d, J = 8.3 Hz, 1H), 5.07 (d, J = 3.4 Hz, 4H), 4.45 (d, J = 8.1 Hz, 1H), 3.70 (s, 3H), 1.41 (s, 18H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$, 25 °C) δ:	161.2, 155.3, 154.7, 148.4, 146.0, 143.1, 138.3, 132.7, 129.3, 128.6, 128.5, 123.5, 120.4, 110.1, 109.3, 108.2, 101.3, 98.2, 94.2, 70.5, 58.5, 57.4, 35.2, 30.6.
HRMS (ESI):	*m/z* calculated for $C_{43}H_{47}O_6^+$ ($[M+H]^+$): 659.3367, found 659.3364
FTIR (neat) cm^{-1} :	2956 (w), 1710 (w), 1594 (m), 1496 (m), 1439 (m), 1358 (w), 1214 (m), 1148 (vs), 1056 (m), 884 (w), 835 (w), 737 (m), 697 (s) cm^{-1}

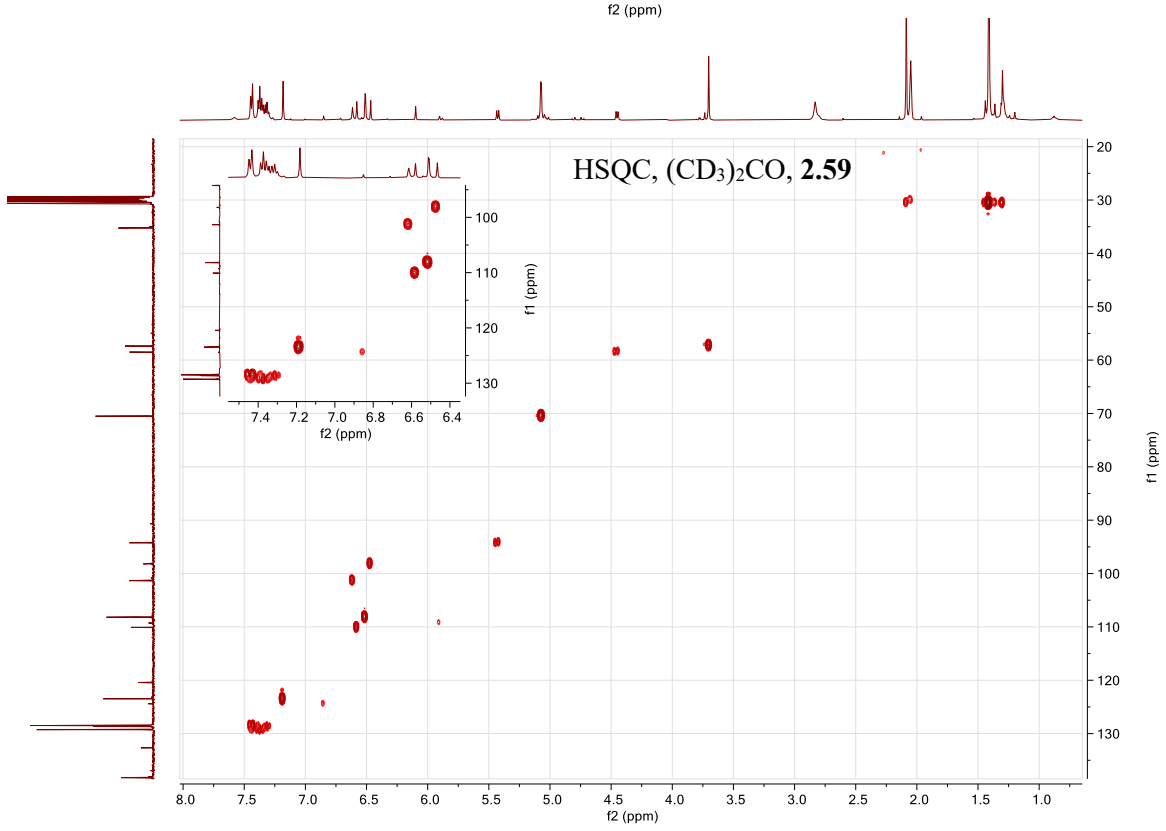
^{1}H NMR, 500 MHz, $(CD_3)_2CO$, **2.59**

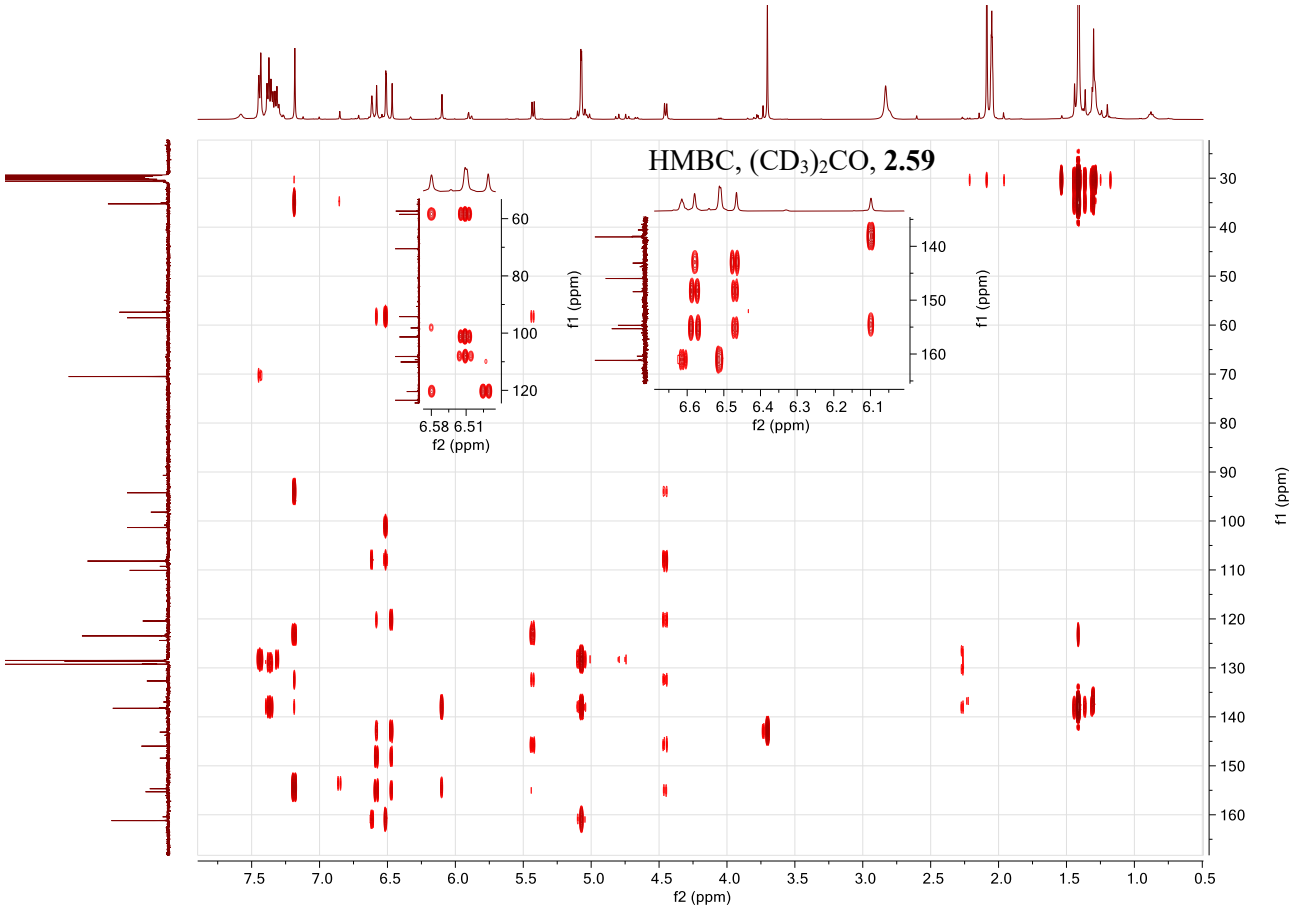


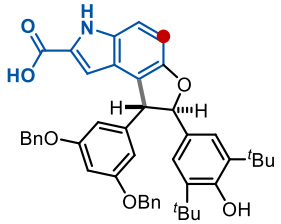
^{13}C NMR, 126 MHz, $(CD_3)_2CO$, **2.59**




COSY, (CD3)2CO, 2.59
f2 (ppm)
f1 (ppm)


HSQC, (CD3)2CO, 2.59
f2 (ppm)
f1 (ppm)


HMBC, (CD3)2CO, 2.59
f2 (ppm)
f1 (ppm)
6.58 6.51
6.6 6.5 6.4 6.3 6.2 6.1

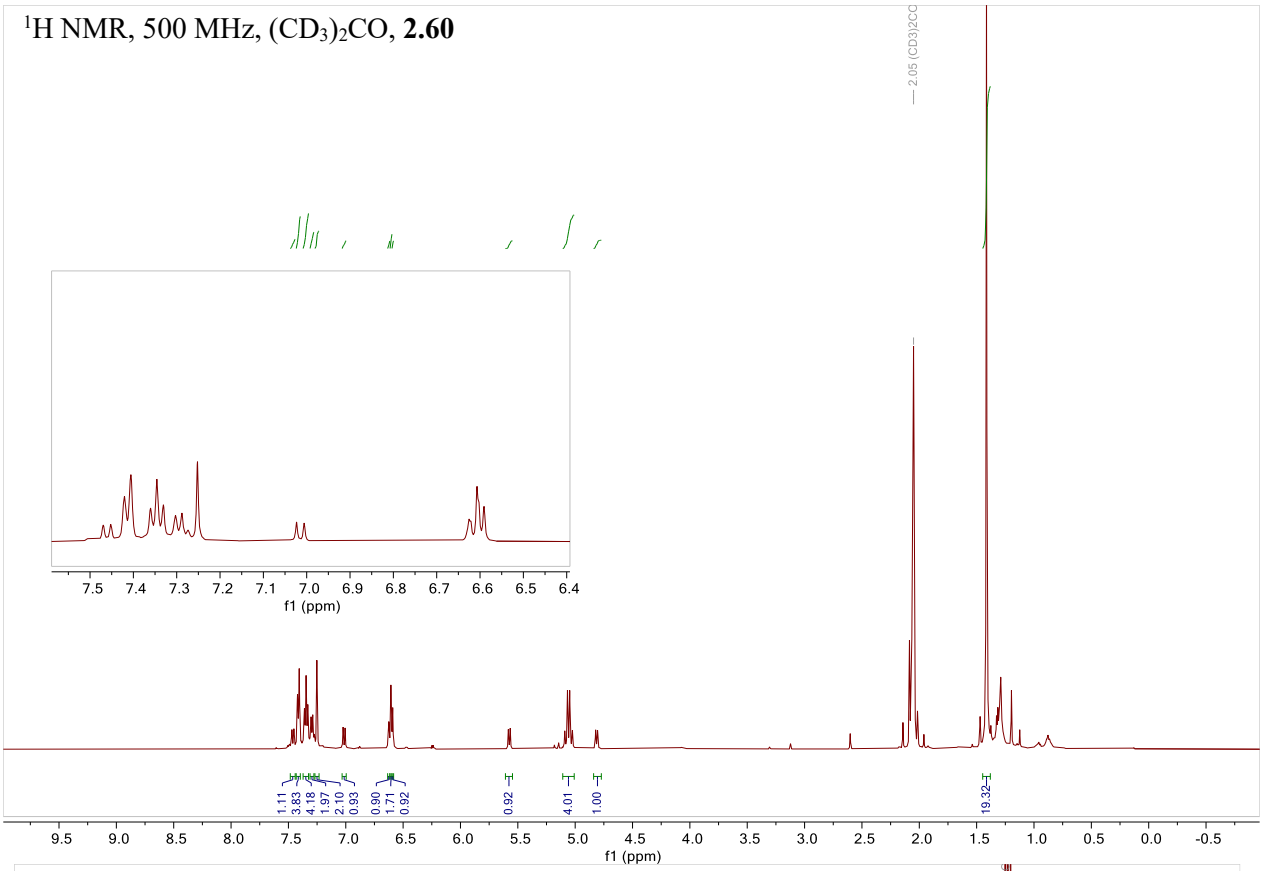


(2.60) (2R)-1-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-1,6-dihydro-2H-furo[3,2-e]indole-7-carboxylic acid

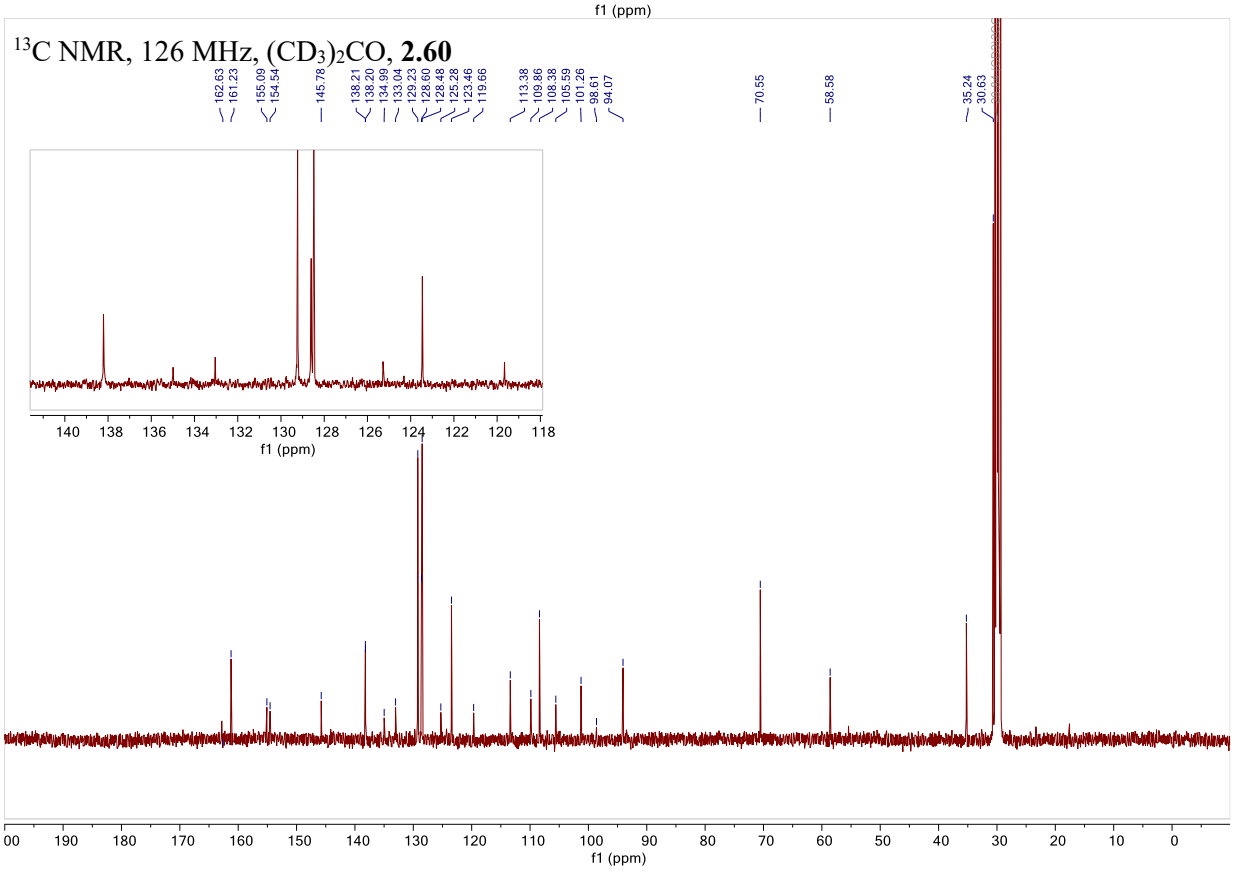
Commercially available 5-hydroxy-1H-indole-2-carboxylic acid (17.7 mg, 0.10 mmol) and **2.40** (208 mg, 0.20mmol) were subjected to the general procedure for intermolecular radical addition. The product was purified by column chromatography (10-80% ethyl acetate in hexanes) to afford (2R)-1-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-1,6-dihydro-2H-furo[3,2-e]indole-7-carboxylic acid (**2.60**, 20.0 mg, 29% yield).

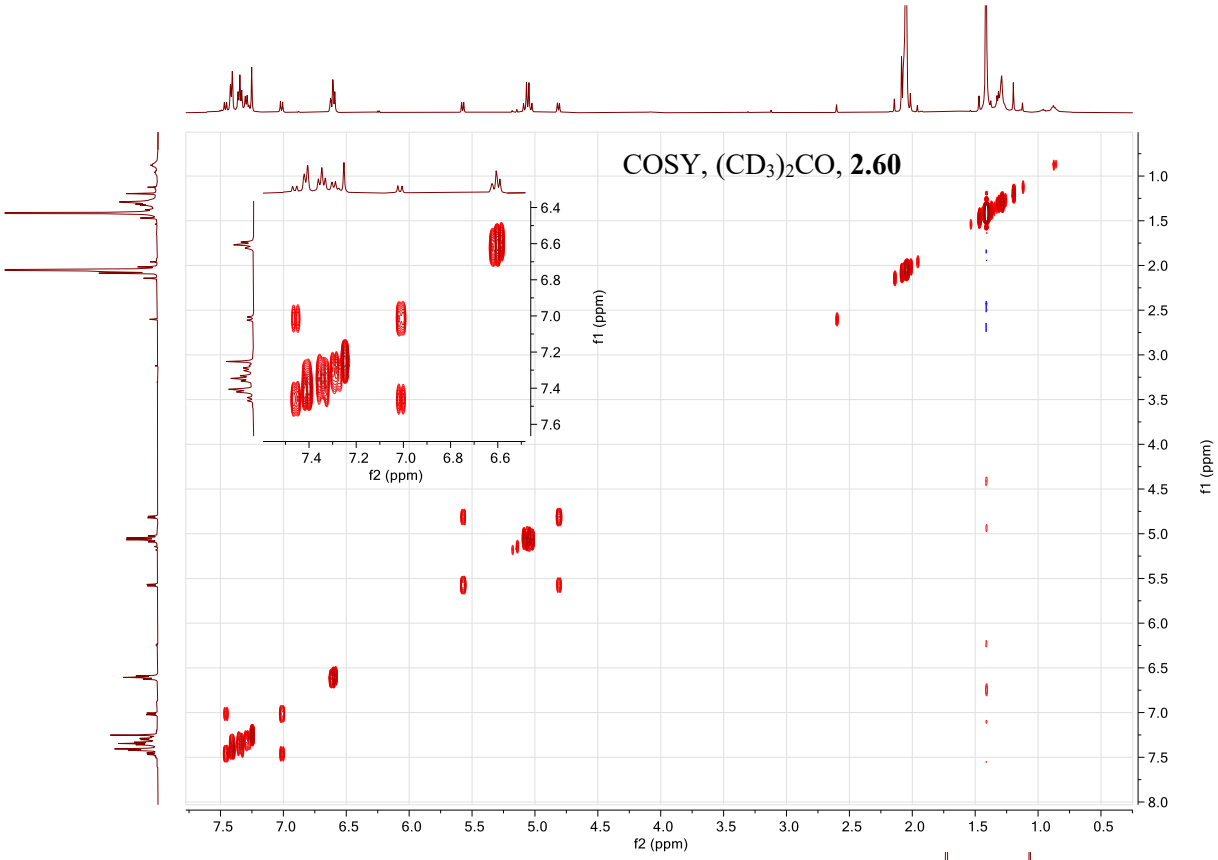
R_F (Hexanes/EtOAc, 30:70):	0.26 (UV, potassium permanganate);
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 25 °C) δ:	7.46 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 7.3 Hz, 4H), 7.35 (t, *J* = 7.5 Hz, 4H), 7.30 (d, *J* = 7.2 Hz, 2H), 7.25 (s, 2H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 6.61 (s, 2H), 6.59 (s, 1H), 5.57 (d, *J* = 8.1 Hz, 1H), 5.11 – 5.01 (m, 4H), 4.81 (d, *J* = 8.2 Hz, 1H), 1.41 (s, 18H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$, 25 °C) δ:	162.63, 161.23, 155.09, 154.54, 145.78, 138.21, 138.20, 134.99, 133.04, 129.23, 128.60, 128.48, 125.28, 123.46, 119.66, 113.38, 109.86, 108.38, 105.59, 101.26, 98.61, 94.07, 70.55, 58.58, 35.24, 30.63.
HRMS (ESI):	*m/z* calculated for $C_{45}H_{46}NO_6^+$ ($[M+H]^+$): 696.3320, found: 696.3319
FTIR (neat) cm^{-1} :	3627 (br), 2957 (w), 1704 (s), 1594 (s), 1531 (m), 1437 (s), 1362 (m), 1213 (s, br), 1155 (vs), 1121 (m), 1056 (m), 1028 (w), 967 (w), 881 (w), 772 (w), 737 (m), 696 (s) cm^{-1}

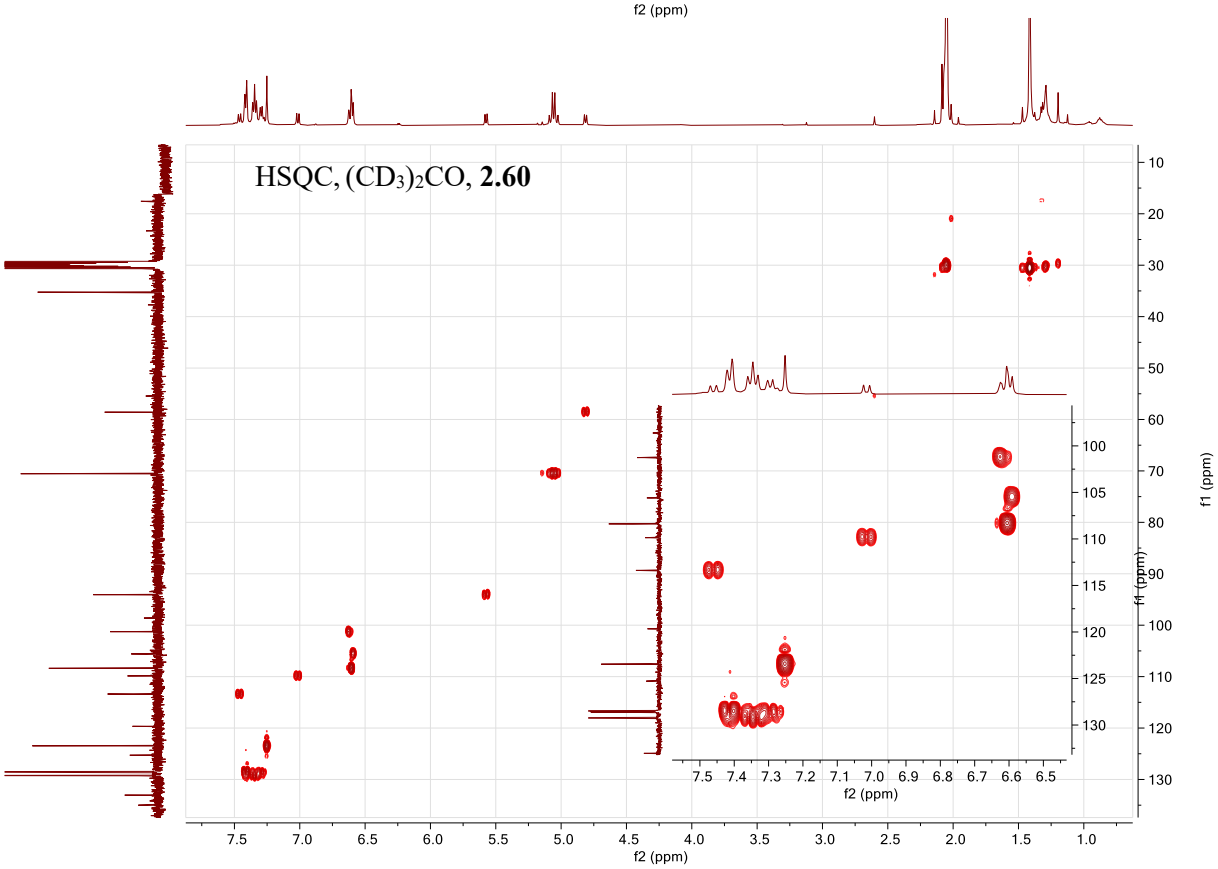
^{1}H NMR, 500 MHz, $(CD_3)_2CO$, **2.60**

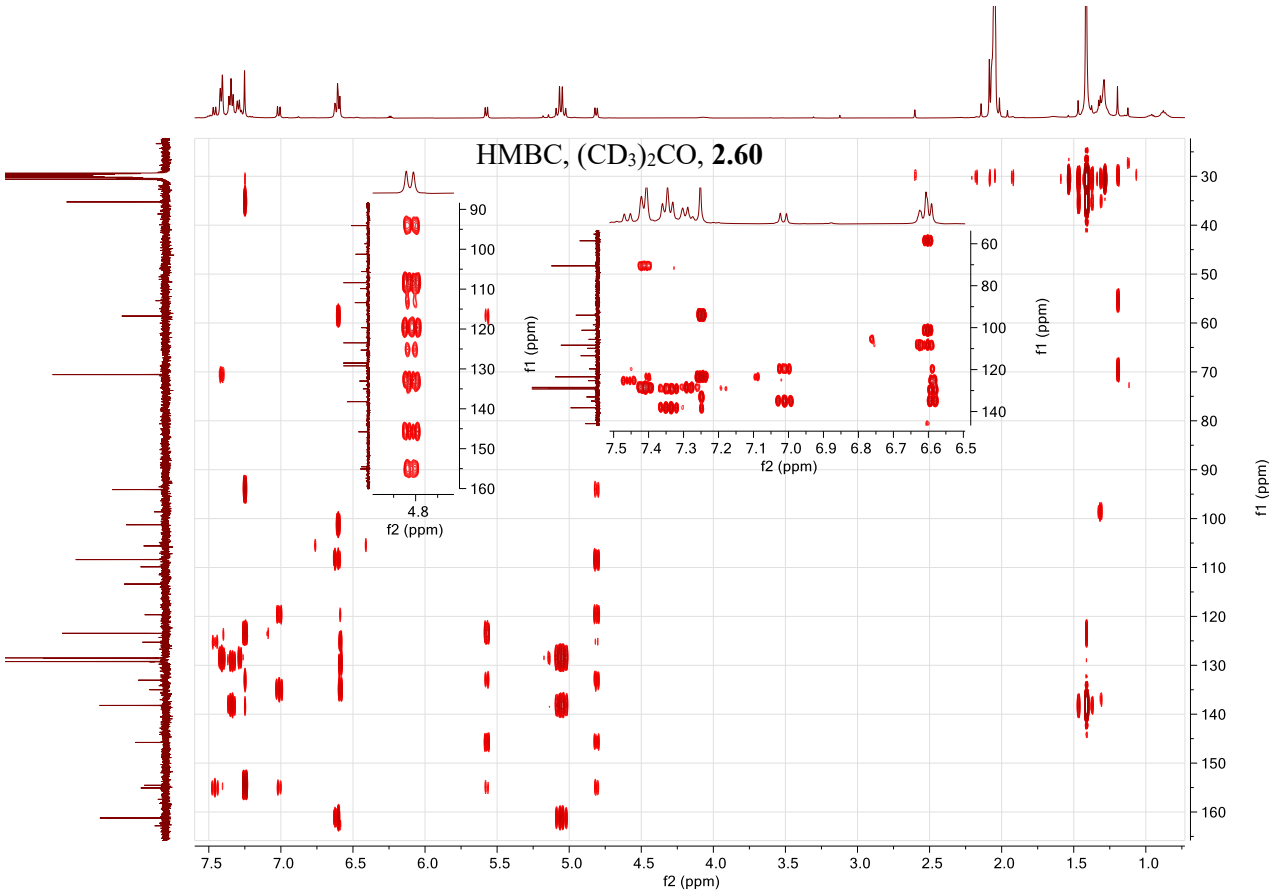


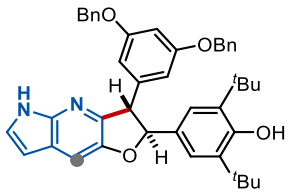
^{13}C NMR, 126 MHz, $(CD_3)_2CO$, **2.60**




COSY, $(CD_3)_2CO$, **2.60**
f2 (ppm)
f1 (ppm)


HSQC, $(CD_3)_2CO$, **2.60**
f2 (ppm)
f1 (ppm)


HMBC, (CD3)2CO, 2.60
f2 (ppm)
f1 (ppm)

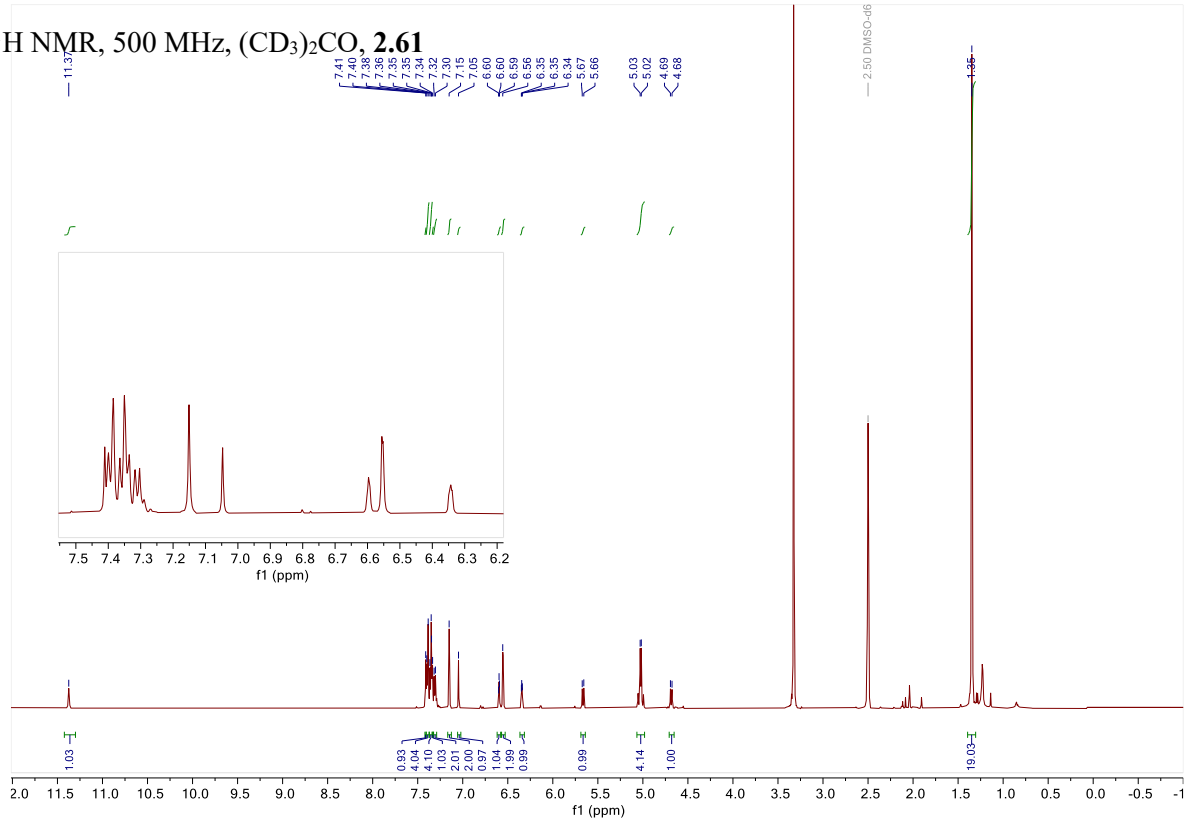


(2.61) 4-((2S)-3-(3,5-bis(benzyloxy)phenyl)-3,5-dihydro-2H-furo[3,2-b]pyrrolo[3,2-e]pyridin-2-yl)-2,6-di-tert-butylphenol

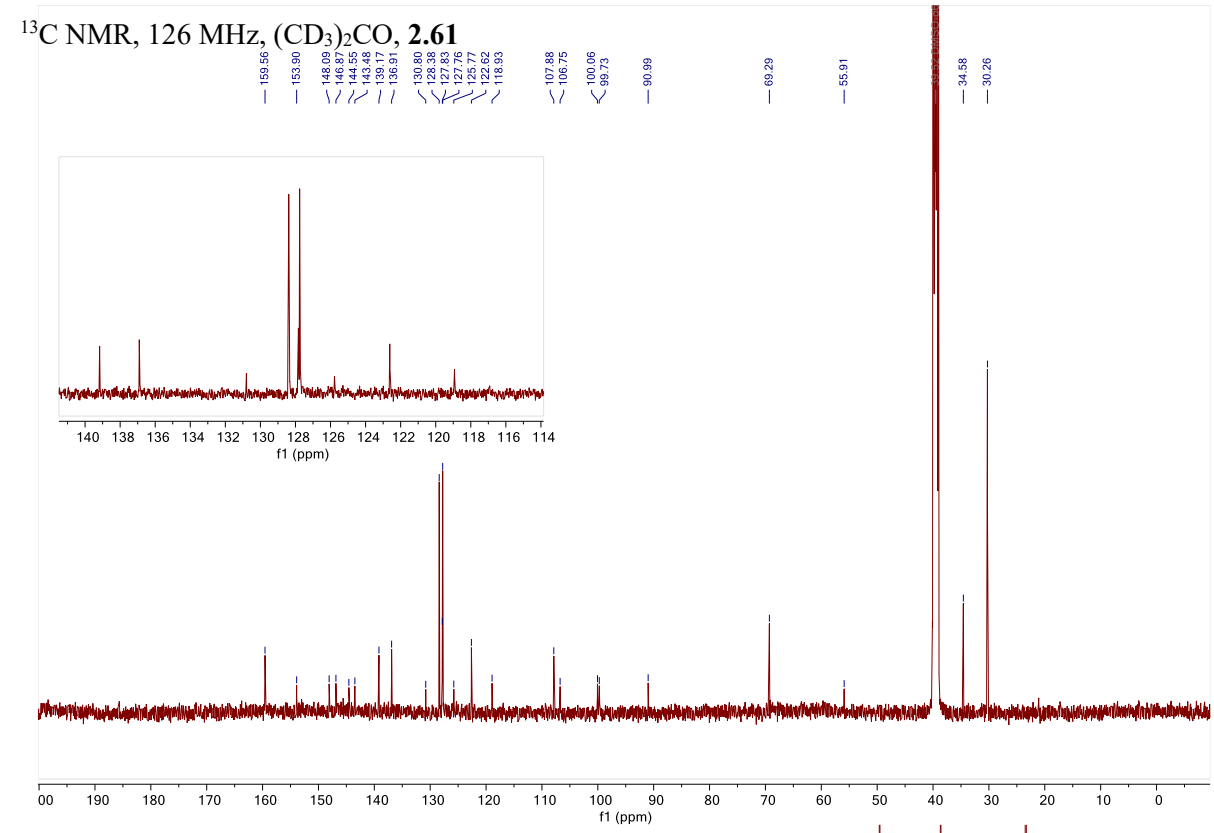
Commercially available 1H-pyrrolo[2,3-b]pyridin-5-ol (13.4 mg, 0.10 mmol) and **2.40** (208 mg, 0.20mmol) were subjected to the general procedure for intermolecular radical addition. The product was purified by column chromatography (0-40% ethyl acetate in hexanes) to afford 4-((2S)-3-(3,5-bis(benzyloxy)phenyl)-3,5-dihydro-2H-furo[3,2-b]pyrrolo[3,2-e]pyridin-2-yl)-2,6-di-tert-butylphenol (**2.61**, 25.0 mg, 38% yield).

$\mathbf{R_F}$ (Hexanes/EtOAc, 70:30):	0.28 (UV, potassium permanganate);
^{1}H NMR (500 MHz, *dmso*, 25 °C) δ:	11.37 (s, 1H), 7.41 (s, 1H), 7.39 (d, J = 7.8 Hz, 4H), 7.37 – 7.34 (m, 4H), 7.34 (s, 1H), 7.31 (d, J = 7.2 Hz, 2H), 7.15 (s, 2H), 7.05 (s, 1H), 6.60 (t, J = 2.4 Hz, 1H), 6.56 (s, 2H), 6.36 – 6.32 (m, 1H), 5.66 (d, J = 8.7 Hz, 1H), 5.02 (d, J = 6.3 Hz, 4H), 4.69 (d, J = 8.7 Hz, 1H), 1.35 (s, 18H).
^{13}C NMR (126 MHz, *dmso*, 25 °C) δ:	159.6, 153.9, 148.1, 146.9, 144.6, 143.5, 139.2, 136.9, 130.8, 128.4, 127.83, 127.76, 125.8, 122.6, 118.9, 107.9, 106.8, 100.1, 99.7, 91.0, 69.3, 55.9, 34.6, 30.3.
HRMS (ESI):	*m/z* calculated for $C_{43}H_{45}N_2O_4^+$ ($[M+H]^+$): 653.3374, found: 653.3365
FTIR (neat) cm^{-1} :	3624, 3420, 2956, 1594, 1437, 1345, 1225, 1149, 1056, 1028, 887, 798, 737, 694 cm^{-1}

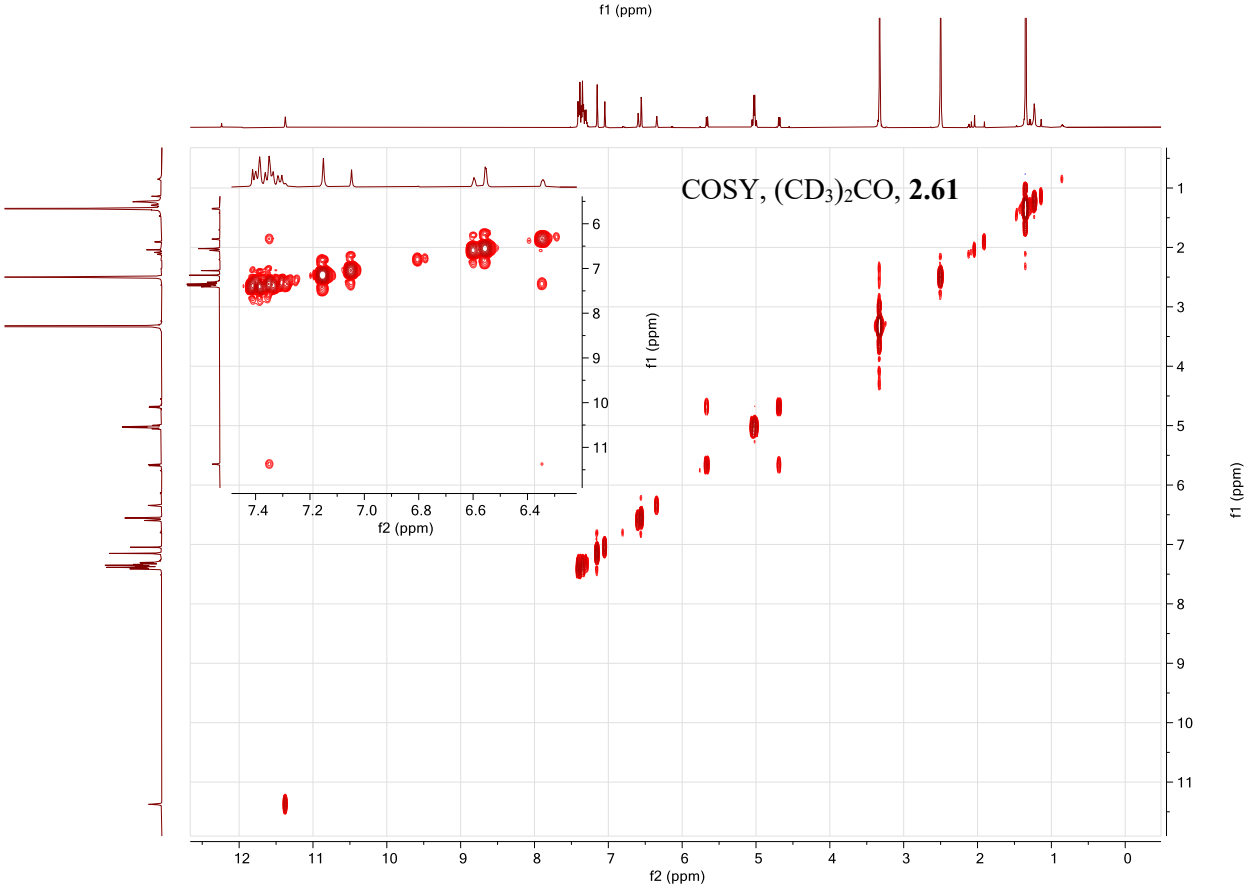
^{1}H NMR, 500 MHz, $(CD_3)_2CO$, **2.61**

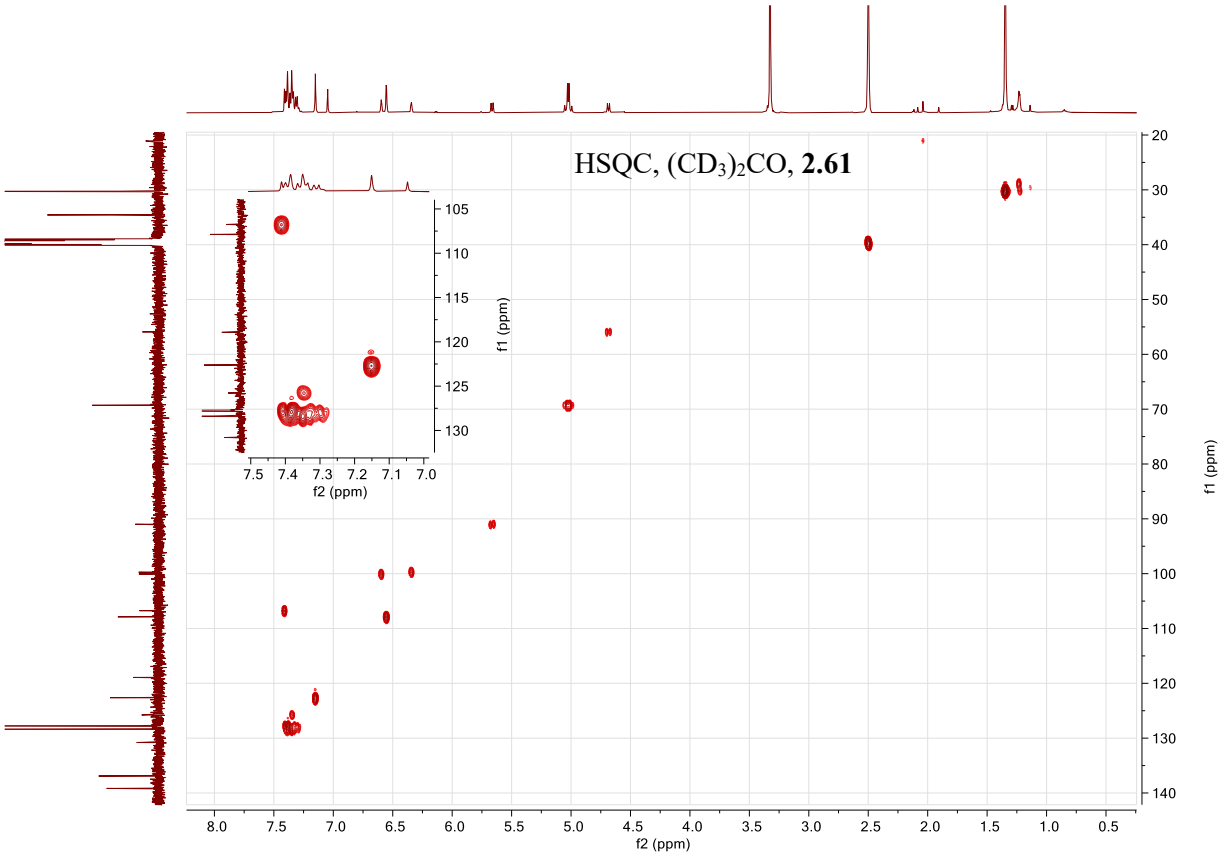


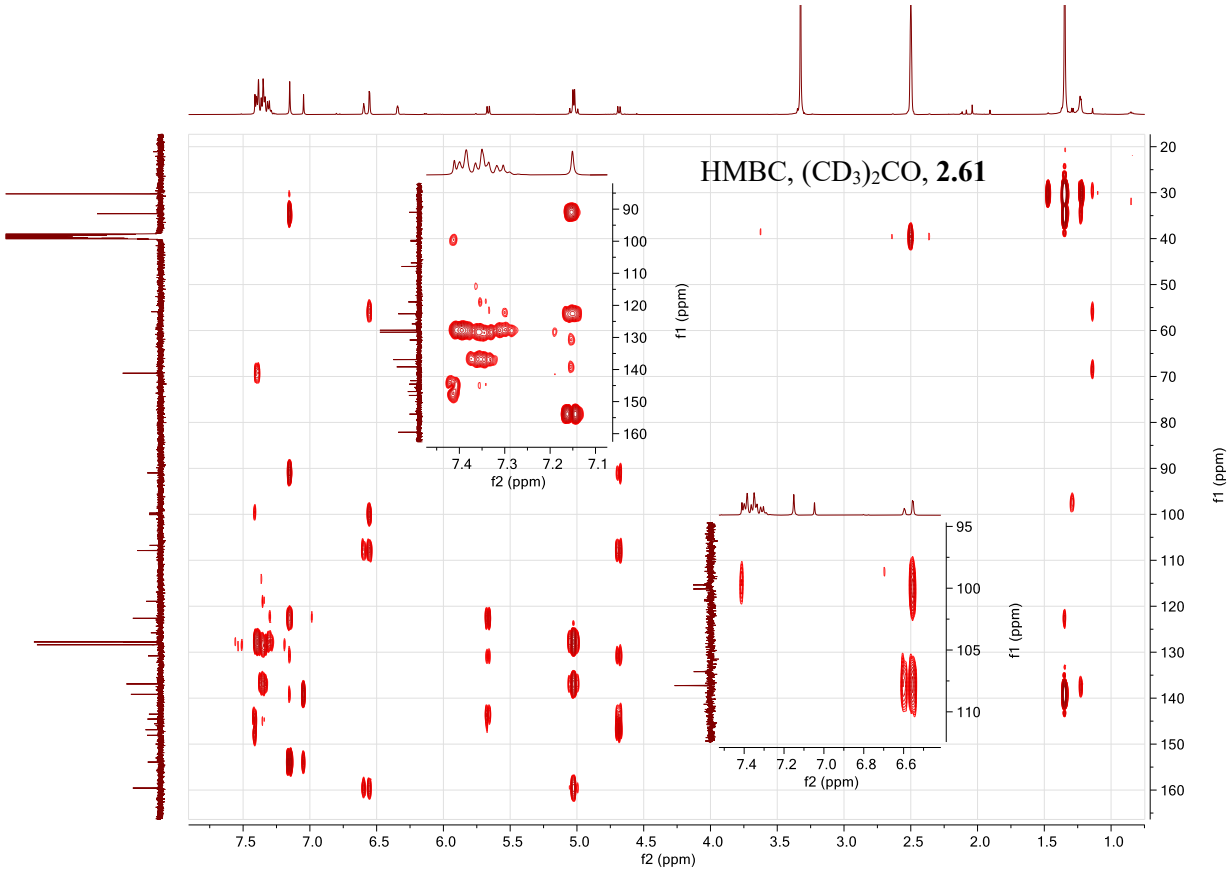
^{13}C NMR, 126 MHz, $(CD_3)_2CO$, **2.61**

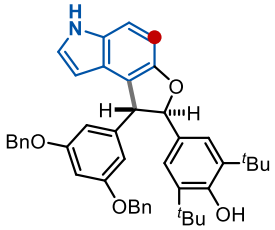


COSY, $(CD_3)_2CO$, **2.61**



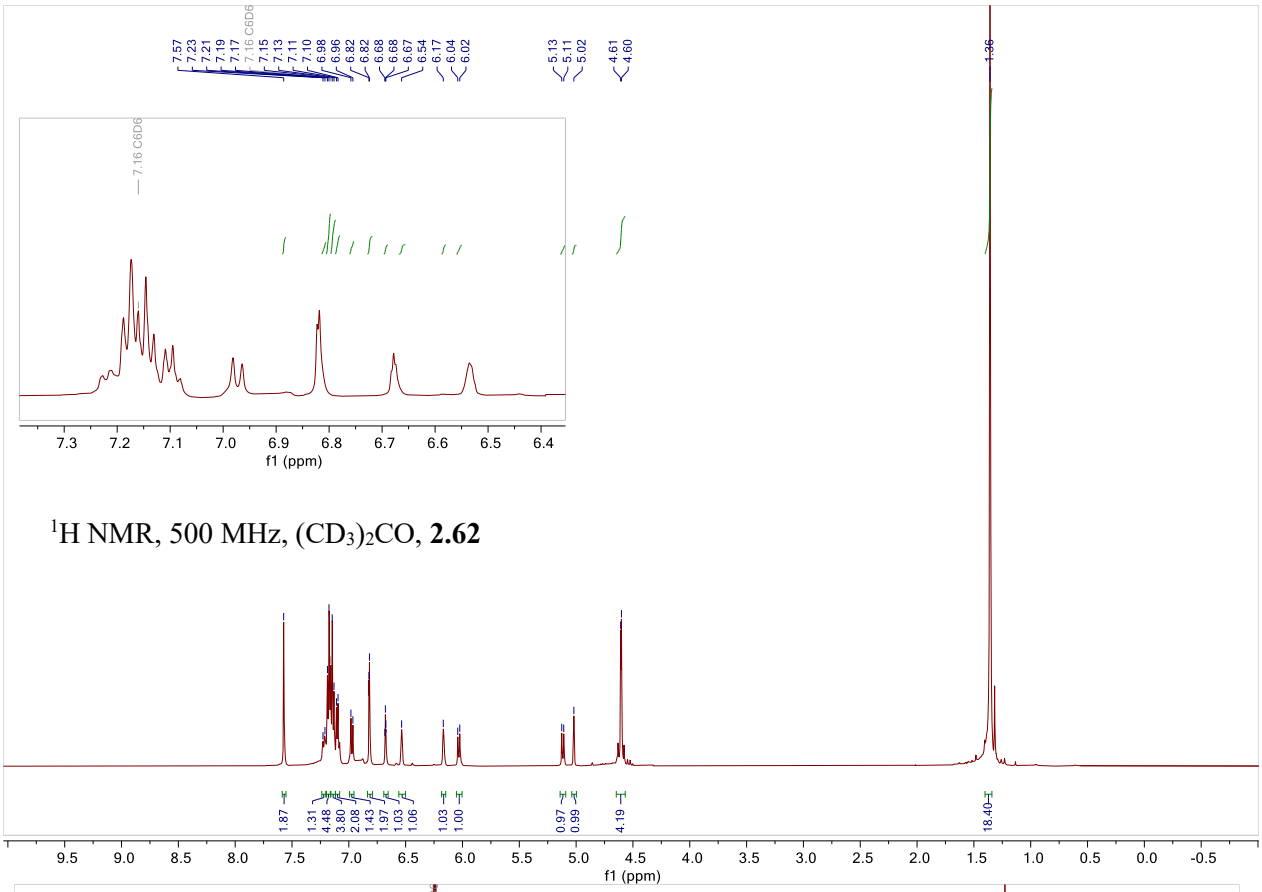

HSQC, $(CD_3)_2CO$, **2.61**
f2 (ppm)
f1 (ppm)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
20 30 40 50 60 70 80 90 100 110 120 130 140
7.5 7.4 7.3 7.2 7.1 7.0
105 110 115 120 125 130


HMBC, $(CD_3)_2CO$, **2.61**
f2 (ppm)
f1 (ppm)

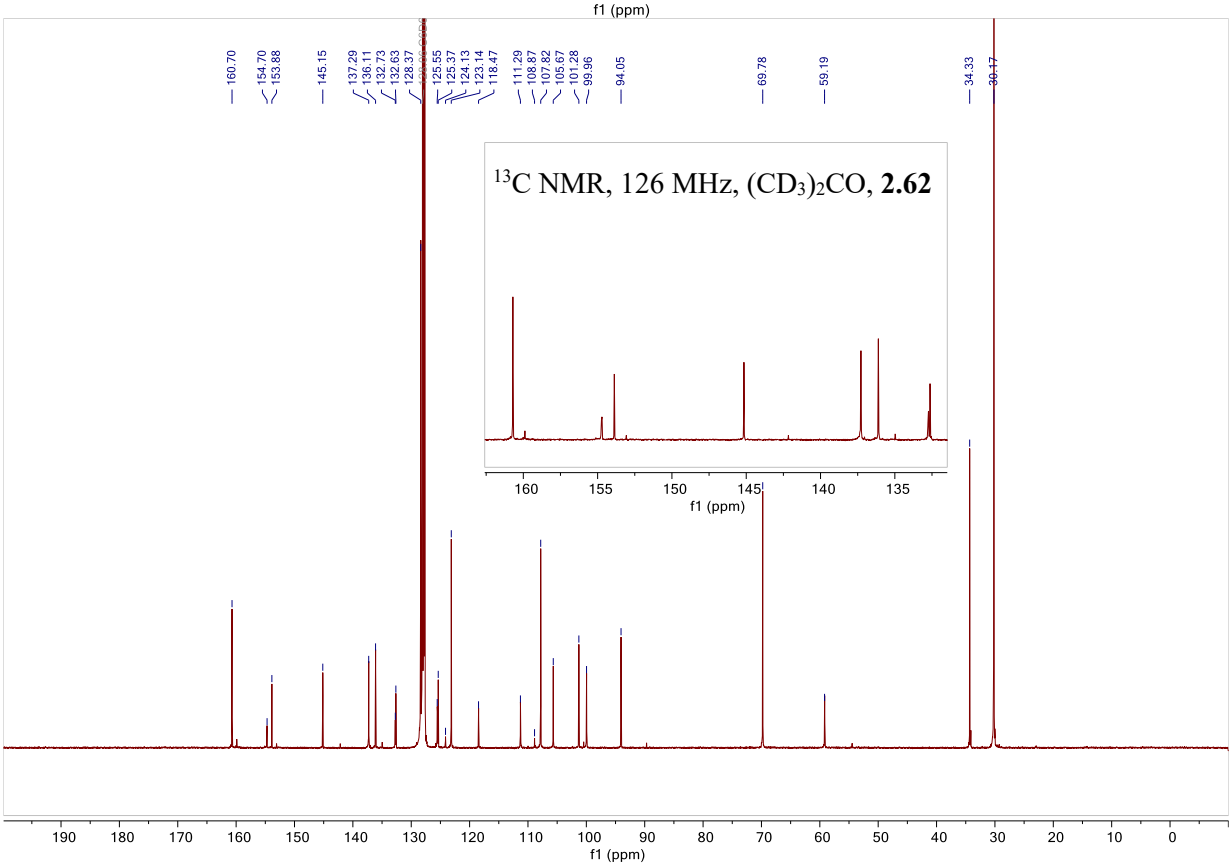


(2.62) 4-(3-(3,5-bis(benzyloxy)phenyl)-3,6-dihydro-2H-furo[2,3-e]indol-2-yl)-2,6-di-tert-butylphenol
Commercially available 1H-indol-5-ol (13.3 mg, 0.10 mmol) and **2.40** (208 mg, 0.20mmol) were subjected to the general procedure for intermolecular radical addition. The product was purified by column chromatography (0-25% ethyl acetate in hexanes) to afford 4-(3-(3,5-bis(benzyloxy)phenyl)-3,6-dihydro-2H-furo[2,3-e]indol-2-yl)-2,6-di-tert-butylphenol (**2.62,** 64.0 mg, 98% yield).

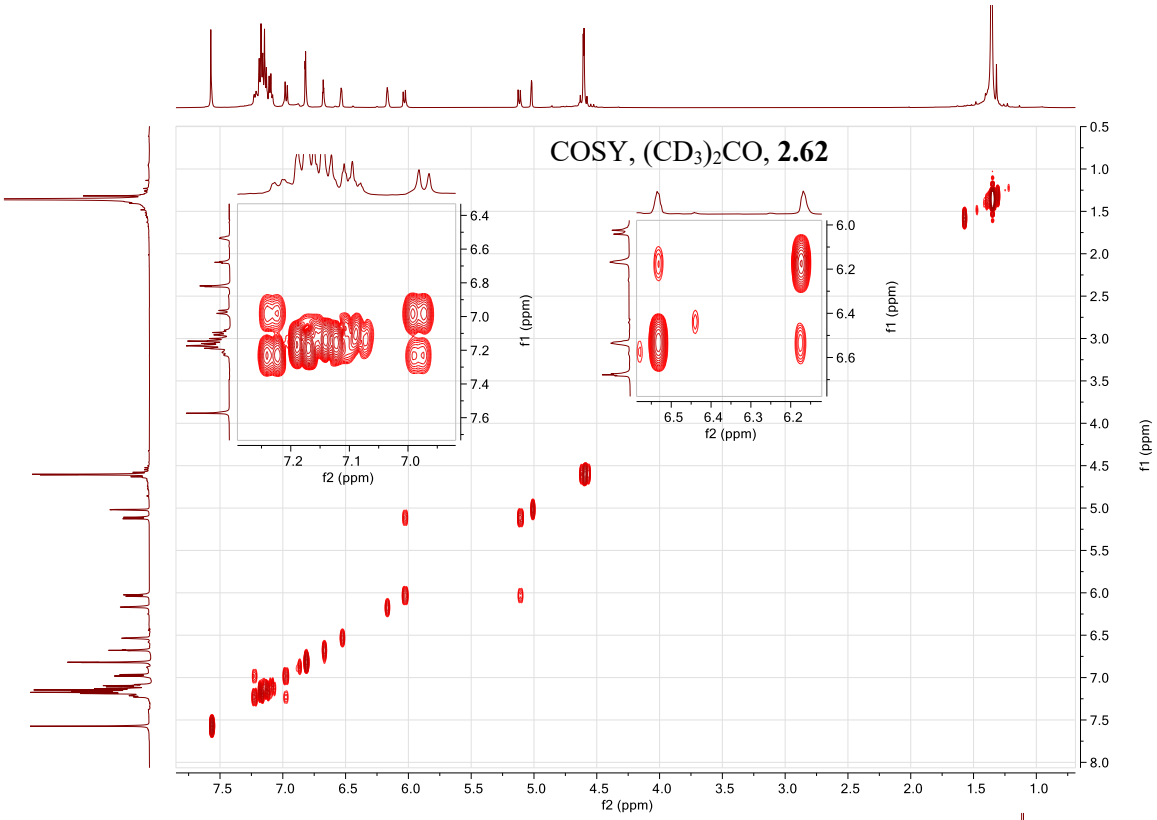
R_F (Hexanes/EtOAc, 70:30):	0.42 (UV, potassium permanganate);
^{1}H NMR (500 MHz, C_6D_6, 25 °C) δ:	7.57 (s, 2H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.18 (d, *J* = 6.7 Hz, 4H), 7.14 (d, *J* = 7.8 Hz, 4H), 7.10 (d, *J* = 6.9 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.82 (d, *J* = 2.3 Hz, 2H), 6.68 (t, *J* = 2.3 Hz, 1H), 6.54 (s, 1H), 6.17 (s, 1H), 6.03 (d, *J* = 8.8 Hz, 1H), 5.12 (d, *J* = 8.9 Hz, 1H), 5.02 (s, 1H), 4.60 (d, *J* = 3.5 Hz, 4H), 1.36 (s, 18H).
^{13}C NMR (126 MHz, C_6D_6, 25 °C) δ:	160.7, 154.7, 153.9, 145.2, 137.3, 136.1, 132.7, 132.6, 128.4, 125.6, 125.4, 124.1, 123.1, 118.5, 111.3, 108.9, 107.8, 105.7, 101.3, 100.0, 94.1, 69.8, 59.2, 34.3, 30.2.
HRMS (ESI):	*m/z* calculated for $C_{44}H_{46}NO_4^+$ ($[M+H]^+$): 652.3421, found 652.3412
FTIR (neat) cm^{-1} :	3621 (br), 3420 (br), 2956 (w), 1593 (s), 1437 (s), 1323 (w), 1226 (m), 1149 (vs), 1053 (s), 1028 (w), 887 (m), 798 (m), 734 (s), 694 (vs) cm^{-1}

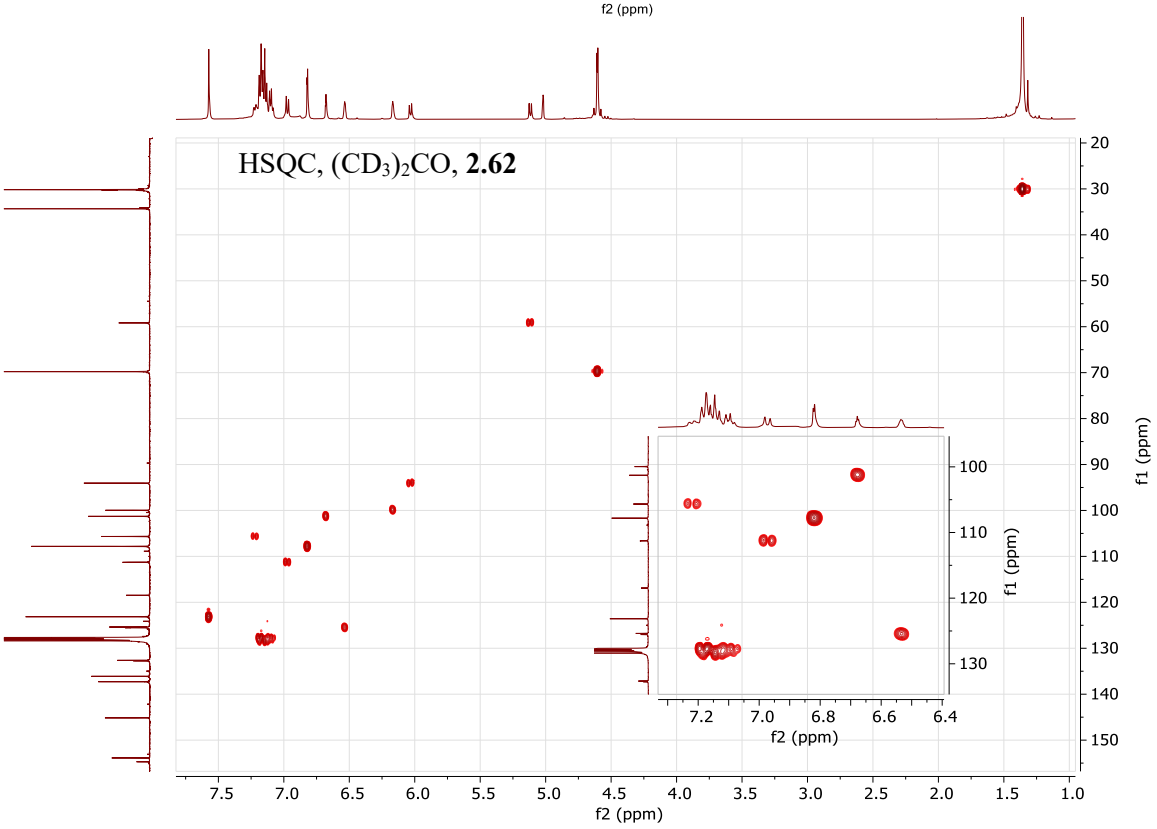


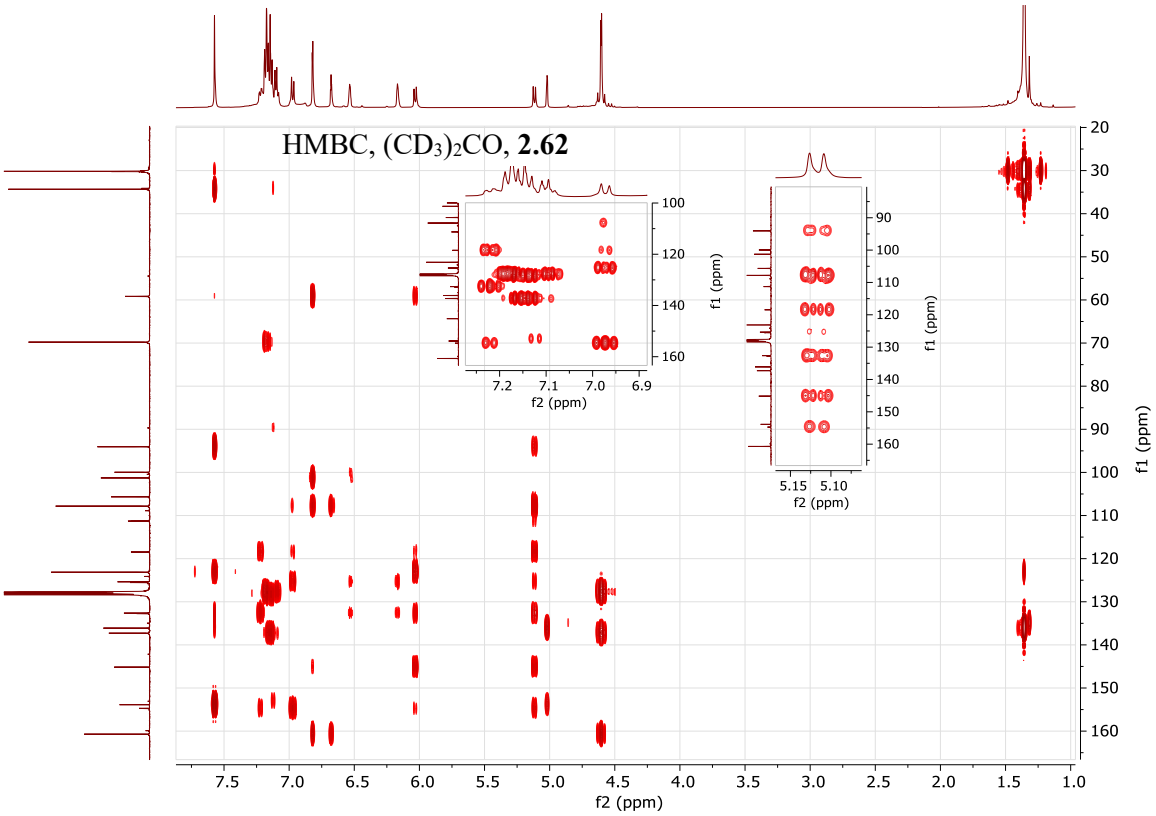
^{1}H NMR, 500 MHz, $(CD_3)_2CO$, **2.62**

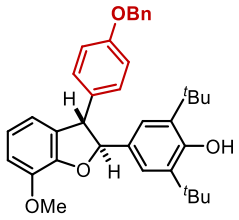


^{13}C NMR, 126 MHz, $(CD_3)_2CO$, **2.62**


COSY, (CD3)2CO, 2.62
f2 (ppm)
f1 (ppm)


HSQC, (CD3)2CO, 2.62
f2 (ppm)
f1 (ppm)

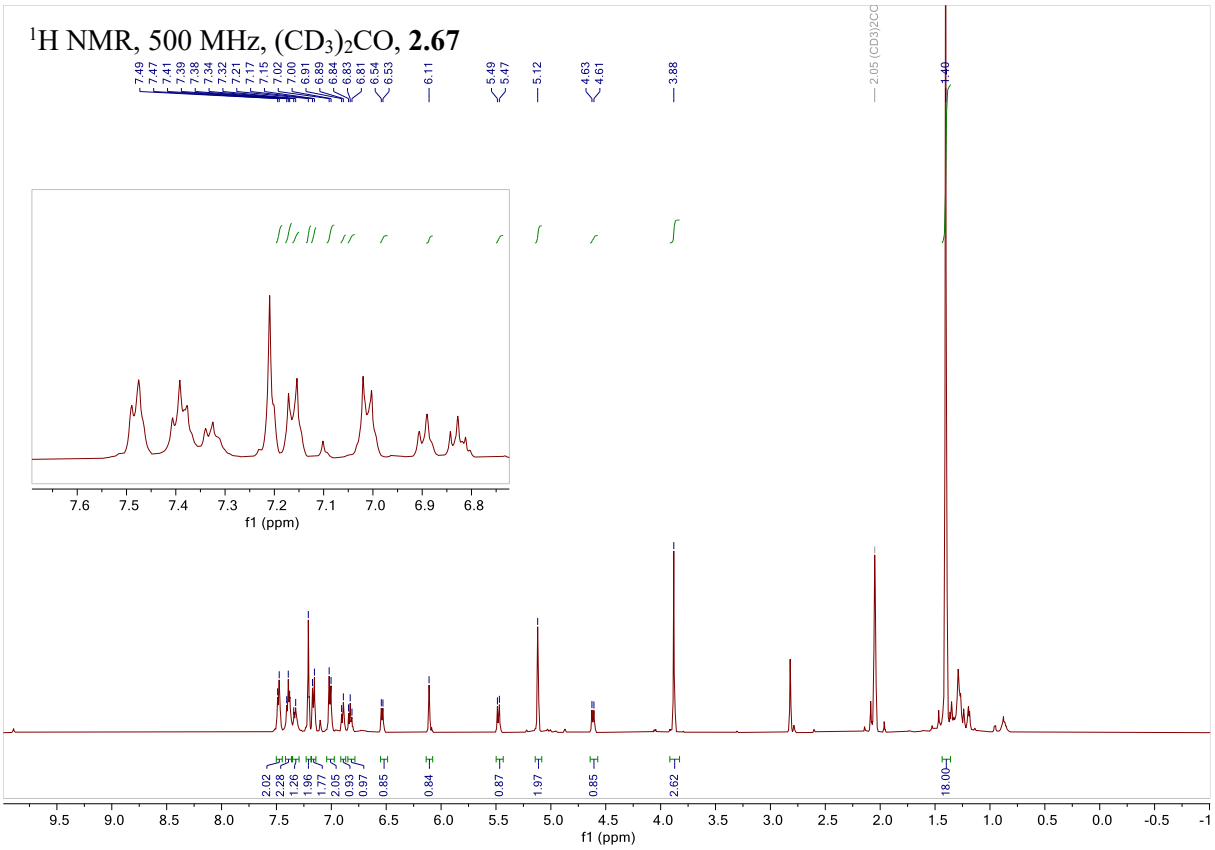

HMBC, (CD3)2CO, 2.62
f2 (ppm)
f1 (ppm)



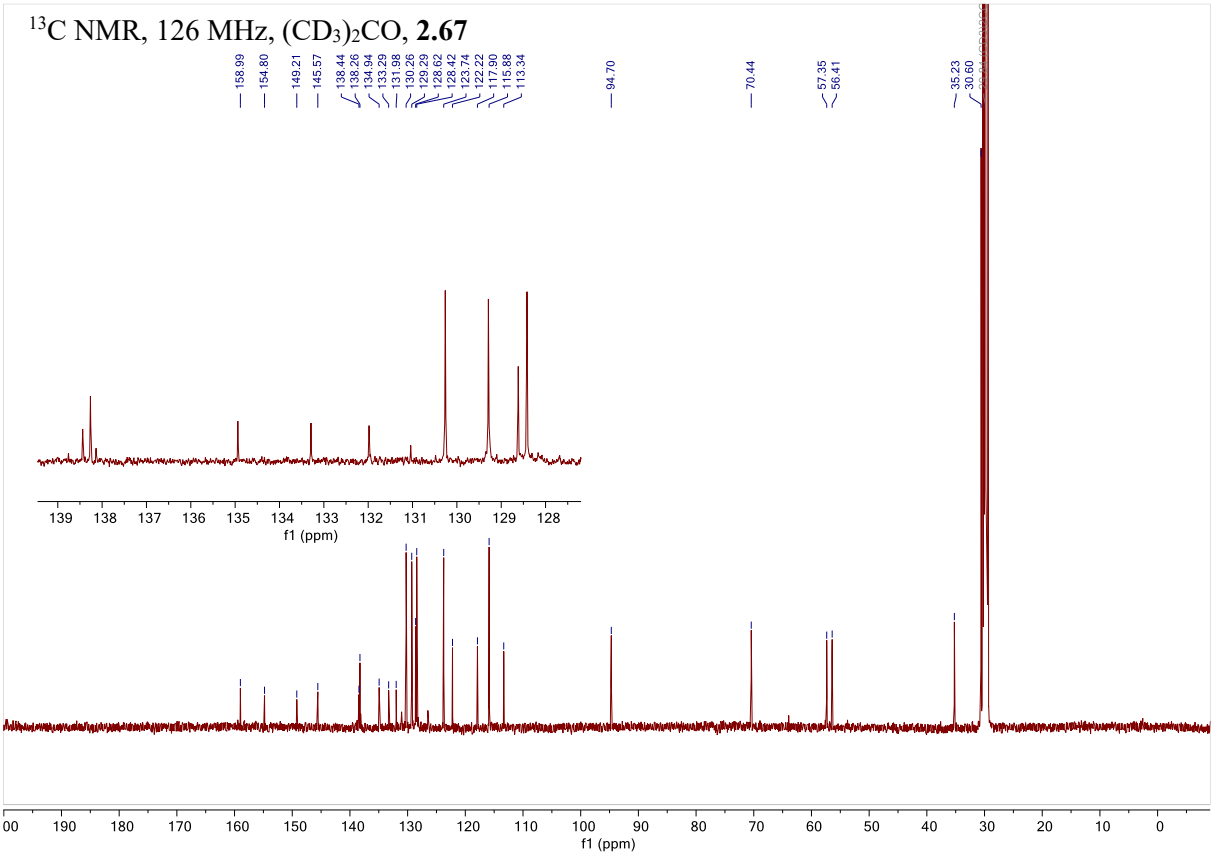
(**2.67**) **4-(3-(4-(benzyloxy)phenyl)-7-methoxy-2,3-dihydrobenzofuran-2-yl)-2,6-di-tert-butylphenol**
Commercially available 2-methoxyphenol (6.3 mg, 0.05 mmol) and **S2.4** (84mg, 0.10 mmol) were subjected to the general procedure for intermolecular radical addition. The product was purified by column chromatography (0-20% ethyl acetate in hexanes) to afford 4-(3-(4-(benzyloxy)phenyl)-7-methoxy-2,3-dihydrobenzofuran-2-yl)-2,6-di-tert-butylphenol (**2.67**, 20 mg, 73% yield).

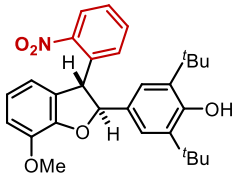
R_F (Hexanes/EtOAc, 80:20):	0.57 (UV potassium permanganate)
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 25 °C) δ:	7.48 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 6.7 Hz, 2H), 7.33 (d, *J* = 8.9 Hz, 1H), 7.21 (s, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.83 (t, *J* = 7.8 Hz, 1H), 6.54 (d, *J* = 7.4 Hz, 1H), 6.11 (s, 1H), 5.48 (d, *J* = 9.0 Hz, 1H), 5.12 (s, 2H), 4.62 (d, *J* = 9.0 Hz, 1H), 3.88 (s, 3H), 1.40 (s, 18H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$, 25 °C) δ:	159.0, 154.8, 149.2, 145.6, 138.4, 138.3, 134.9, 133.3, 132.0, 130.3, 129.3, 128.6, 128.4, 123.7, 122.2, 117.9, 115.9, 113.3, 94.7, 70.4, 57.4, 56.4, 35.2, 30.6.
HRMS (ESI)	*m/z* calculated for $C_{36}H_{41}O_4^+$ ($[M+H]^+$): 537.2999, found 537.2991
FTIR (neat) cm^{-1} :	3631 (m), 2956 (s, br), 1611 (m), 1510 (vs), 1490 (m), 1455 (m), 1284 (m), 1237 (vs), 1159 (w), 1083 (s), 1025 (m), 885 (w), 829 (m), 735 (m), 697 (m) cm^{-1}

^{1}H NMR, 500 MHz, $(CD_3)_2CO$, **2.67**



^{13}C NMR, 126 MHz, $(CD_3)_2CO$, **2.67**

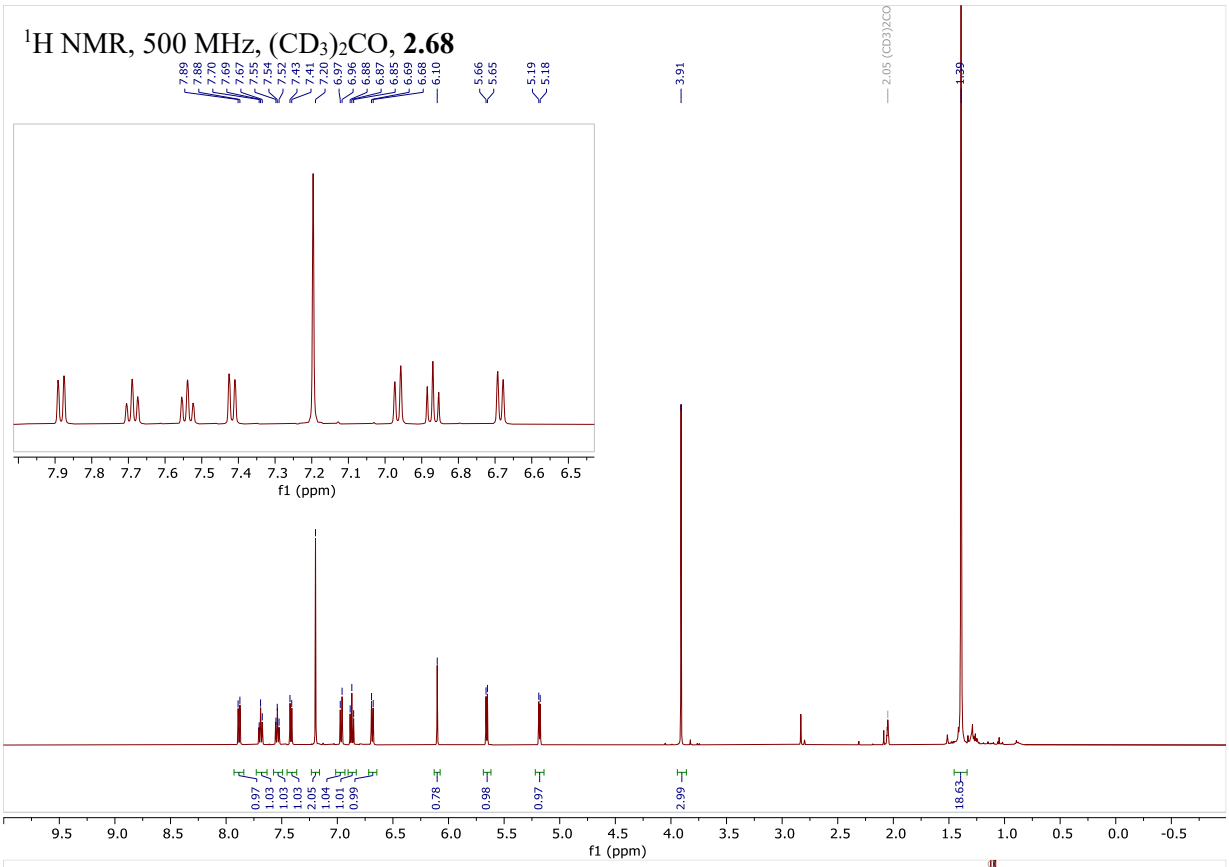


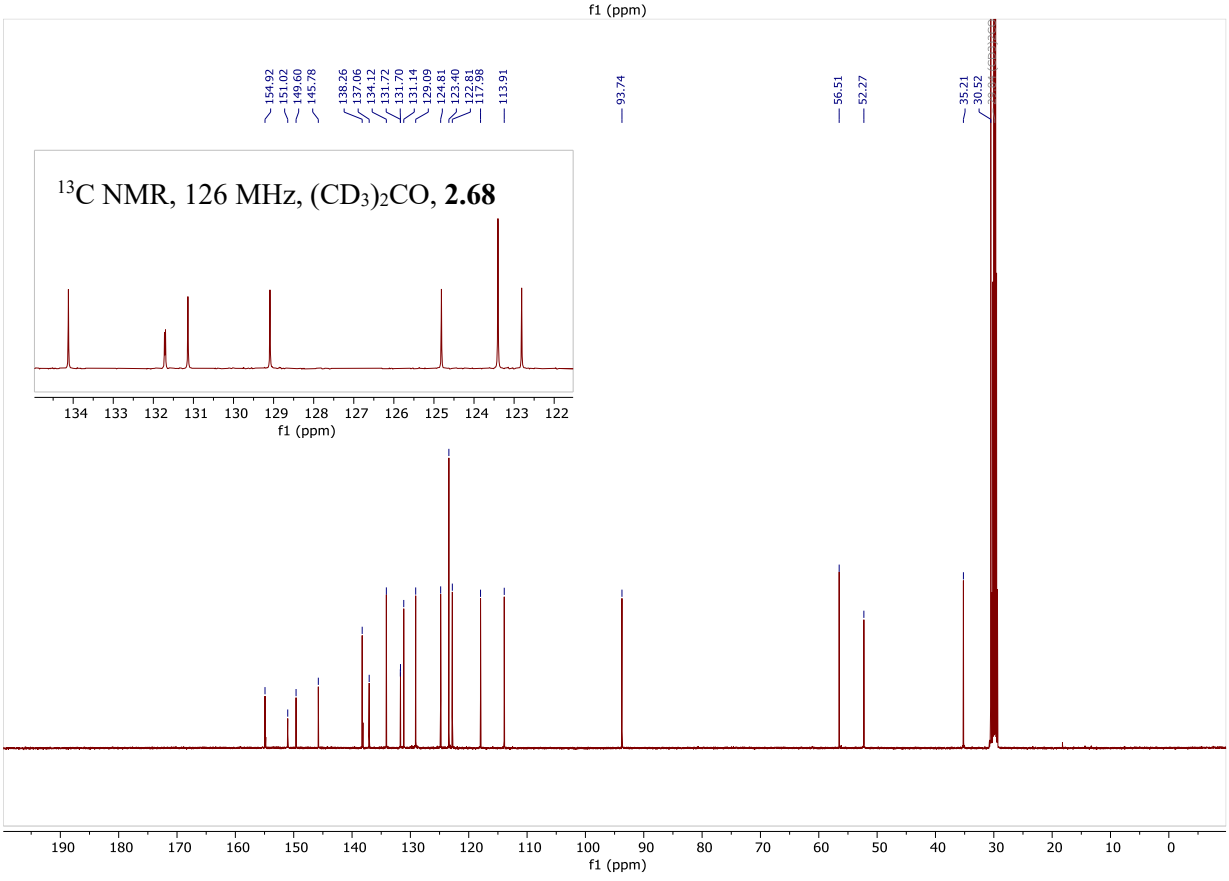


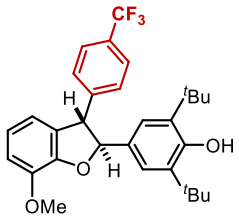
(2.68) 2,6-di-tert-butyl-4-(7-methoxy-3-(2-nitrophenyl)-2,3-dihydrobenzofuran-2-yl)phenol

Commercially available 2-methoxyphenol (7.0 mg, 0.05 mmol) and **S2.5** (80 mg, 0.10 mmol) were subjected to the general procedure for intermolecular radical addition. The product was purified by column chromatography (0-20% ethyl acetate in hexanes) to afford 2,6-di-tert-butyl-4-(7-methoxy-3-(2-nitrophenyl)-2,3-dihydrobenzofuran-2-yl)phenol (**2.68**, 18 mg, 67% yield).

R_F (Hexanes/EtOAc, 80:20):	0.49 (UV potassium permanganate)
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 25 °C) δ:	7.88 (d, *J* = 8.1 Hz, 1H), 7.69 (t, *J* = 7.0 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.20 (s, 2H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.87 (t, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 6.10 (s, 1H), 5.66 (d, *J* = 6.4 Hz, 1H), 5.18 (d, *J* = 6.3 Hz, 1H), 3.91 (s, 3H), 1.39 (s, 18H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$, 25 °C) δ:	154.9, 151.0, 149.6, 145.8, 138.3, 137.1, 134.1, 131.72, 131.70, 131.1, 129.1 124.8, 123.4, 122.8, 117.98, 113.9, 93.7, 56.5, 52.3, 35.2, 30.5.
HRMS (ESI)	*m/z* calculated for $C_{29}H_{34}NO_5^+$ ($[M+H]^+$): 476.2429, found 476.2428
FTIR (neat) cm^{-1} :	2928 (vs, br), 1528 (s), 1458 (m), 1359 (w) cm^{-1}


^{1}H NMR, 500 MHz, $(CD_3)_2CO$, **2.68**
7.89 7.88 7.70 7.69 7.67 7.55 7.54 7.52 7.43 7.41 7.20 6.97 6.96 6.88 6.87 6.85 6.69 6.68 6.10 5.66 5.65 5.19 5.18 3.91 2.05 (CD3)2CO 1.39
0.97 1.03 1.03 1.03 2.05 1.04 1.01 0.99 0.78 0.98 0.97 2.99 18.63
f1 (ppm)


^{13}C NMR, 126 MHz, $(CD_3)_2CO$, **2.68**
154.92 151.02 149.60 145.78 138.26 137.06 134.12 131.72 131.70 131.14 129.09 124.81 123.40 122.31 117.98 113.91 93.74 56.51 52.27 35.21 30.52
f1 (ppm)

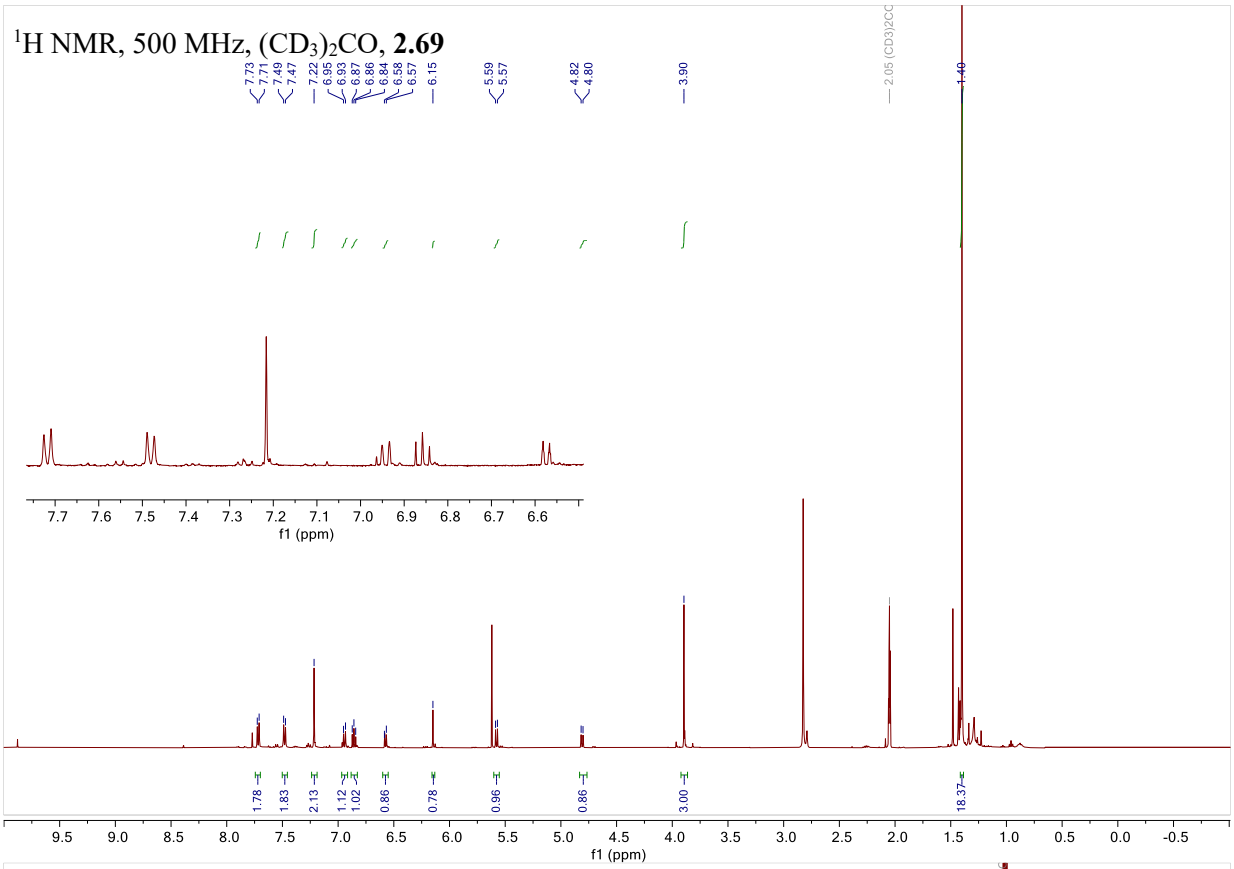


(2.69) 2,6-di-tert-butyl-4-(7-methoxy-3-(4-(trifluoromethyl)phenyl)-2,3-dihydrobenzofuran-2-yl)phenol

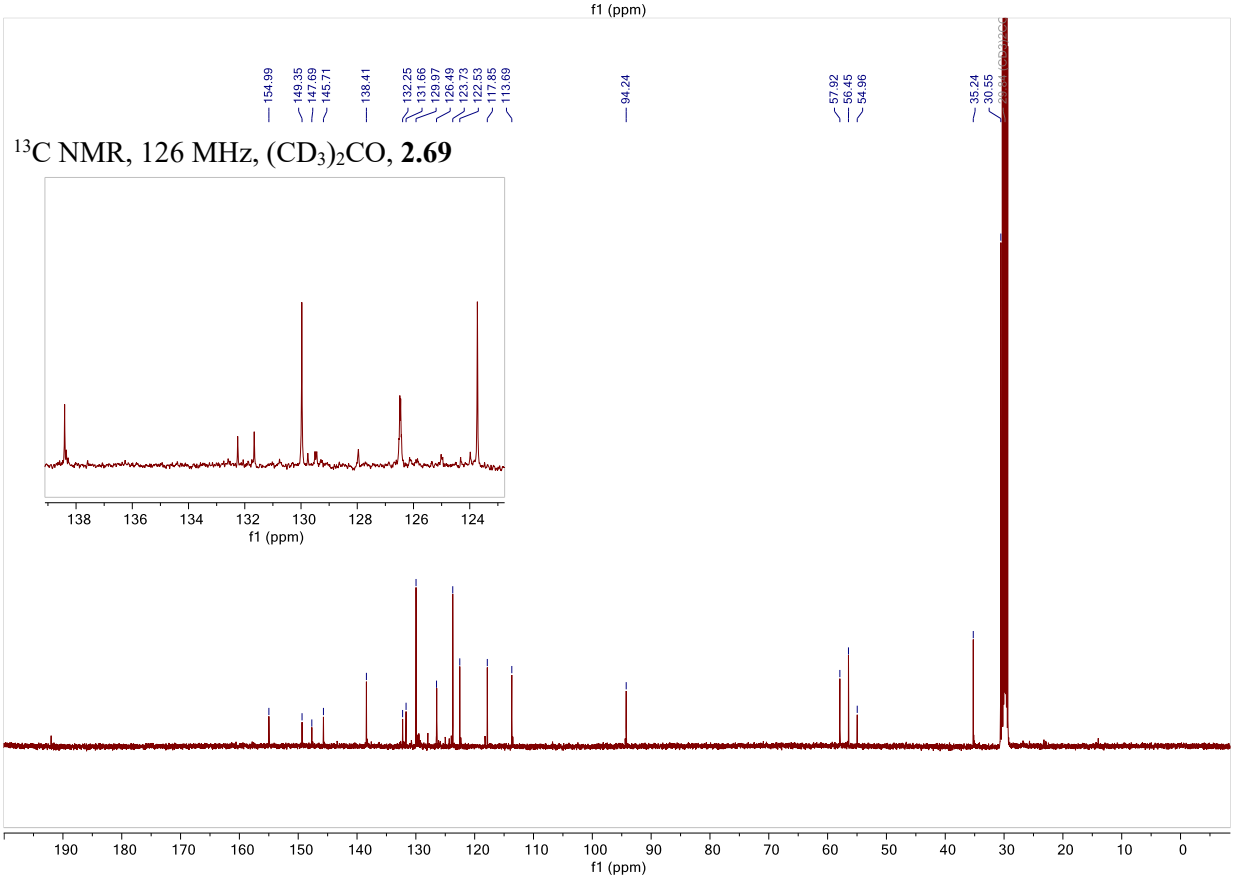
Commercially available 2-methoxyphenol (6.2 mg, 0.05 mmol) and **S2.6** (75 mg, 0.10 mmol) were subjected to the general procedure for intermolecular radical addition. The product was purified by column chromatography (0-20% ethyl acetate in hexanes) to afford 2,6-di-tert-butyl-4-(7-methoxy-3-(4-(trifluoromethyl)phenyl)-2,3-dihydrobenzofuran-2-yl)phenol (**2.69**, 14 mg, 56% yield).

R_F (Hexanes/EtOAc, 90:10):	0.47 (UV potassium permanganate)
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 25 °C) δ:	7.72 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.22 (s, 2H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.86 (t, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 8.6 Hz, 1H), 6.15 (s, 1H), 5.58 (d, *J* = 8.5 Hz, 1H), 4.81 (d, *J* = 8.5 Hz, 1H), 3.90 (s, 3H), 1.40 (s, 18H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$, 25 °C) δ:	155.0, 149.4, 147.7, 145.7, 138.4, 132.3, 131.7, 130.0, 126.5, 123.7, 122.5, 117.9, 113.7, 94.2, 57.9, 56.5, 55.0, 35.2, 30.6
^{19}F NMR (471 MHz, $(CD_3)_2CO$) δ:	-62.90 ppm
HRMS (ESI)	*m/z* calculated for $C_{30}H_{34}F_3O_3^+$ ($[M+H]^+$): 499.2455, found 499.2449
FTIR (neat) cm^{-1} :	3639 (br), 2958 (m), 1617 (w), 1438 (m), 1324 (vs), 1214 (w), 1164 (m), 1124 (s), 1086 (w), 1067 (s), 1018 (w), 944 (w), 837 (w), 770 (w) cm^{-1}

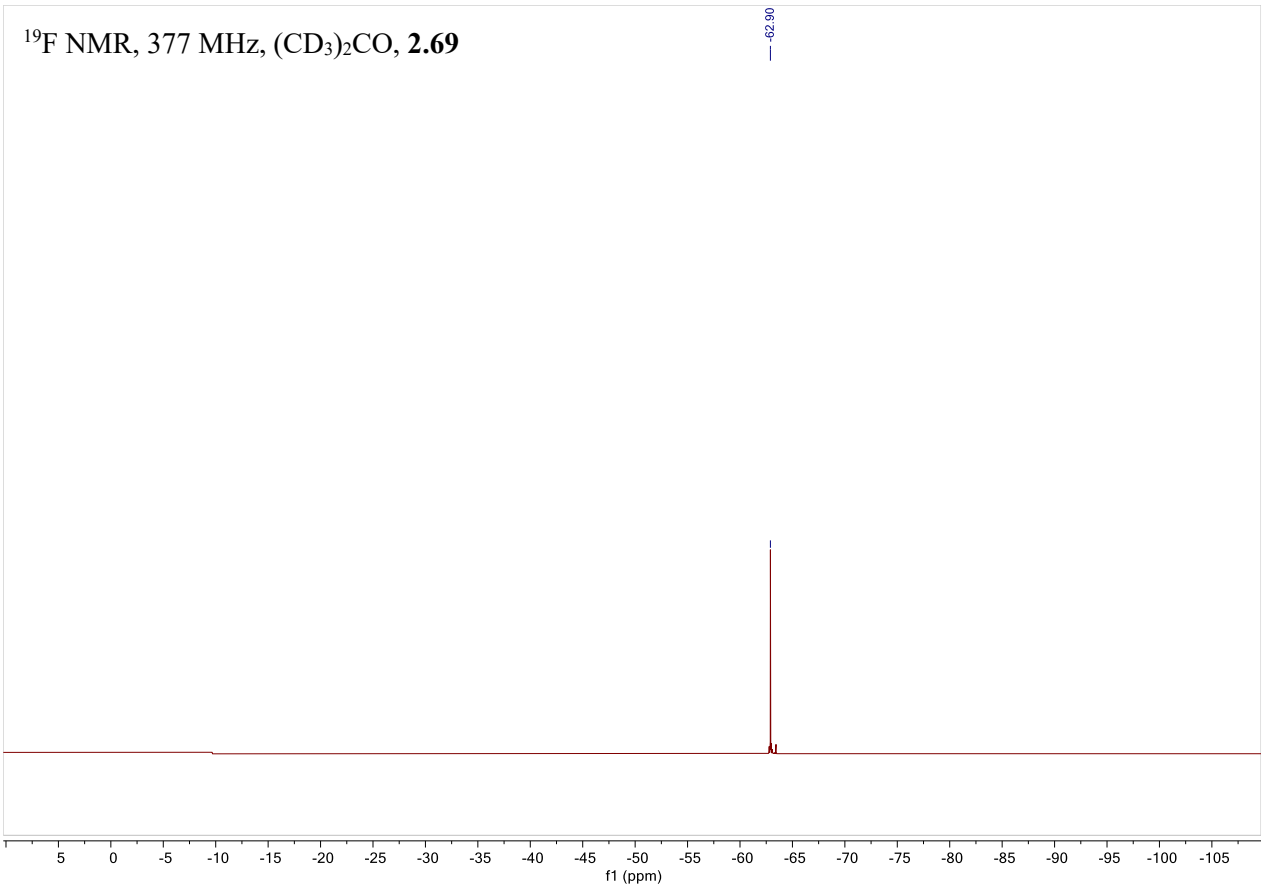
^{1}H NMR, 500 MHz, $(CD_3)_2CO$, **2.69**



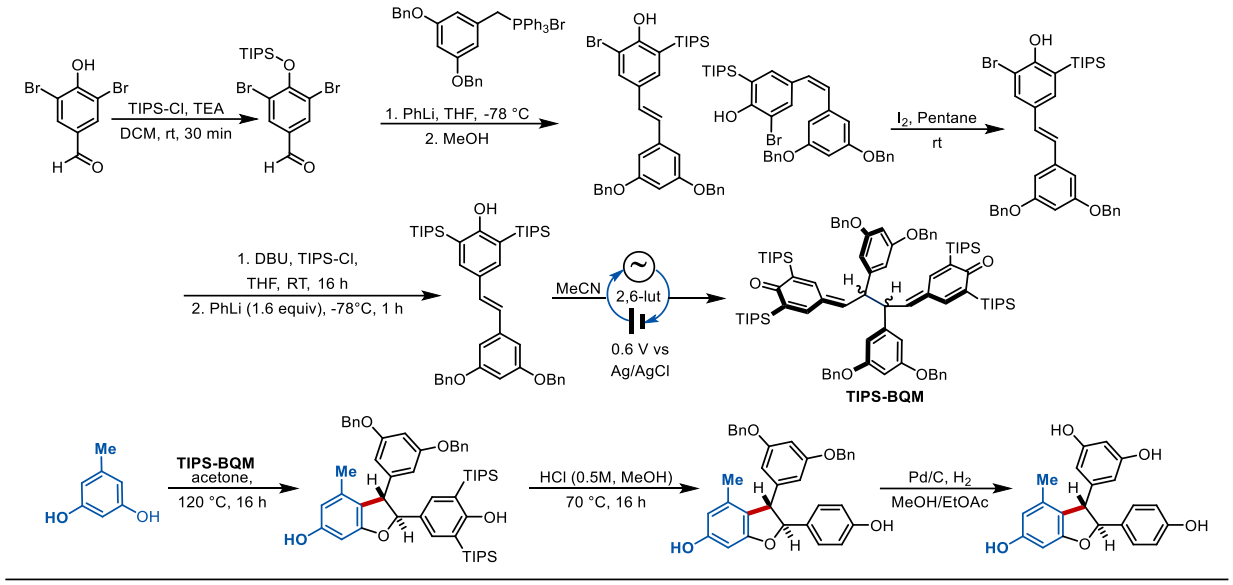
^{13}C NMR, 126 MHz, $(CD_3)_2CO$, **2.69**

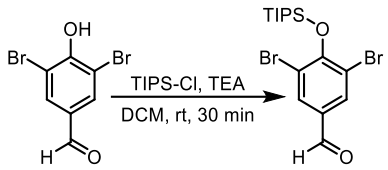


^{19}F NMR, 377 MHz, $(CD_3)_2CO$, **2.69**



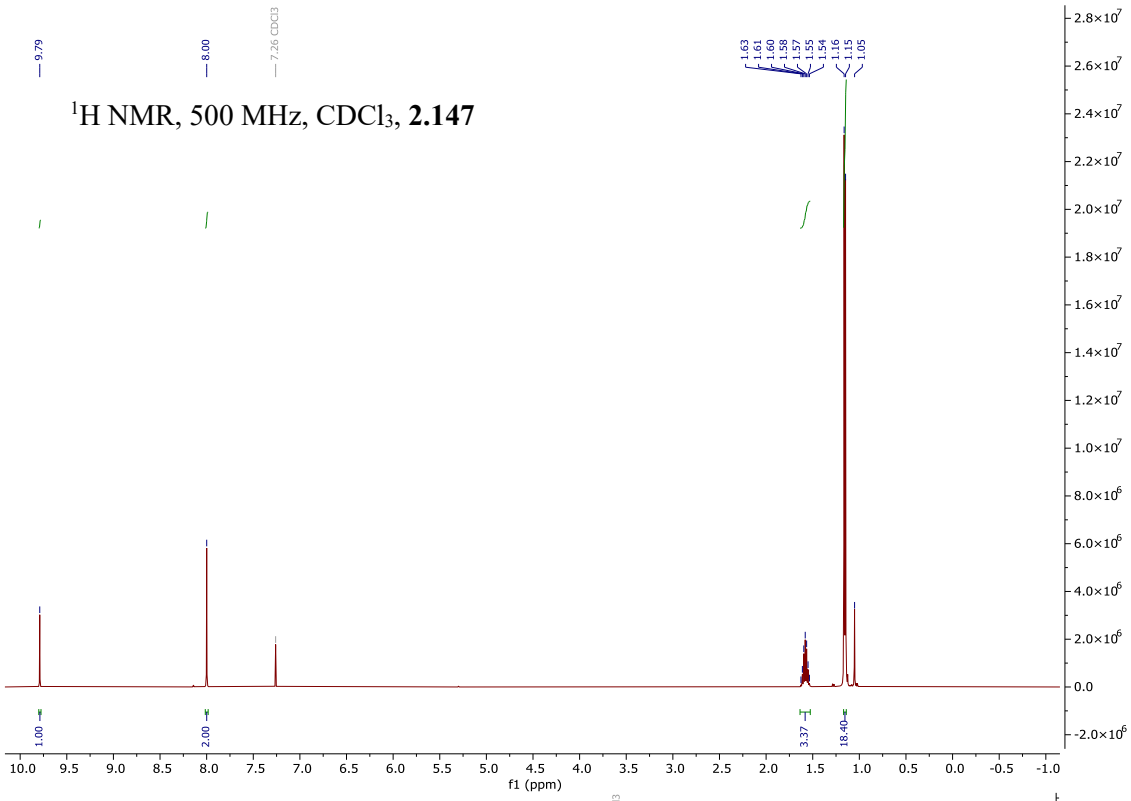
Synthesis and deprotection of TIPS-DHB



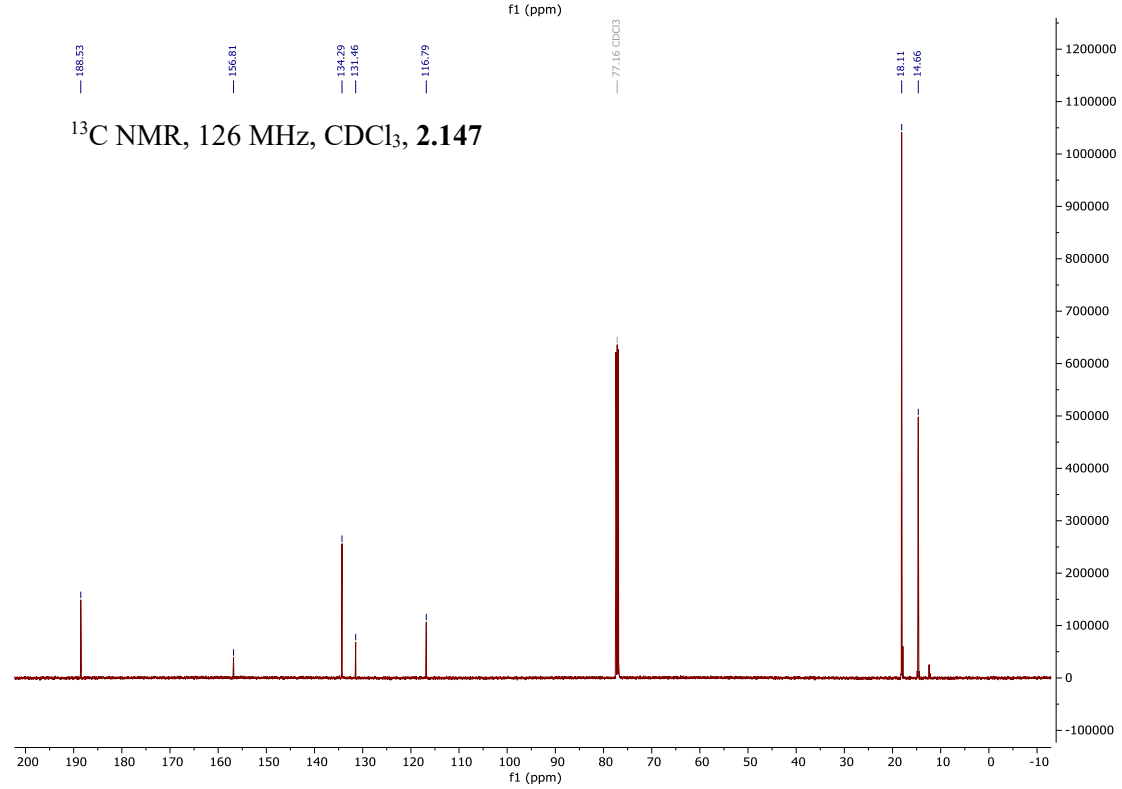


(2.147) (3,5-dibromo-4-((triisopropylsilyl)oxy)benzaldehyde) A 250 mL RBF was charged with commercially available aldehyde (5.0 g, 18 mmol, 1.0 equiv) and dissolved in DCM (89 mL). Triethylamine was added dropwise (3.0 mL, 21 mmol, 1.2 equiv), followed by triisopropylsilyl chloride (4.2 mL, 20 mmol, 1.1 equiv). The reaction was monitored by TLC and upon completion (approximately 30 minutes) the reaction was quenched with water (50 mL). The organic layer was separated, and the aqueous was washed with additional DCM (2 x 50 mL). The combined organics were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-5% EtOAc in Hexanes) to yield the product as a white powder (7.2 g, 92%).

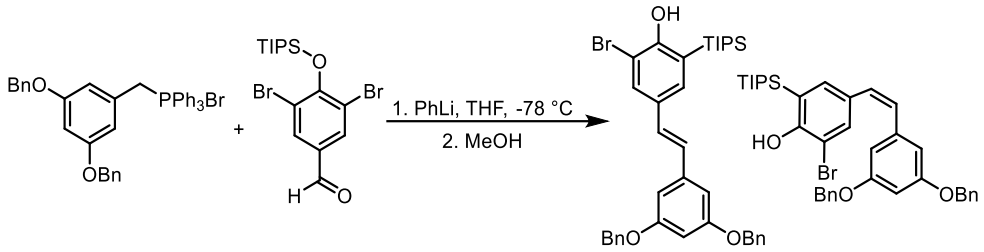
TLC (Hexanes/EtOAc, 95:5), R_F:	0.47 (UV, potassium permanganate)
^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ:	δ= 9.79 (s, 1H), 8.00 (s, 2H), 1.58 (hept, J = 7.6 Hz, 3H), 1.16 (d, J = 7.6 Hz, 18H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ:	δ= 188.5, 156.8, 134.3, 131.5, 116.8, 18.1, 14.7.
HRMS (ESI):	*m/z* calculated for $C_{16}H_{24}Br_2O_2Si$ ($[M+H]^+$): 434.9912, found 434.9970.
FTIR (neat) cm^{-1} :	ν̃= 3062 (w), 2945 (w), 2867 (w), 1455 (m), 1290 (m), 880 (s), 742 (m), 684 (vs)



^{1}H NMR, 500 MHz, $CDCl_3$, **2.147**

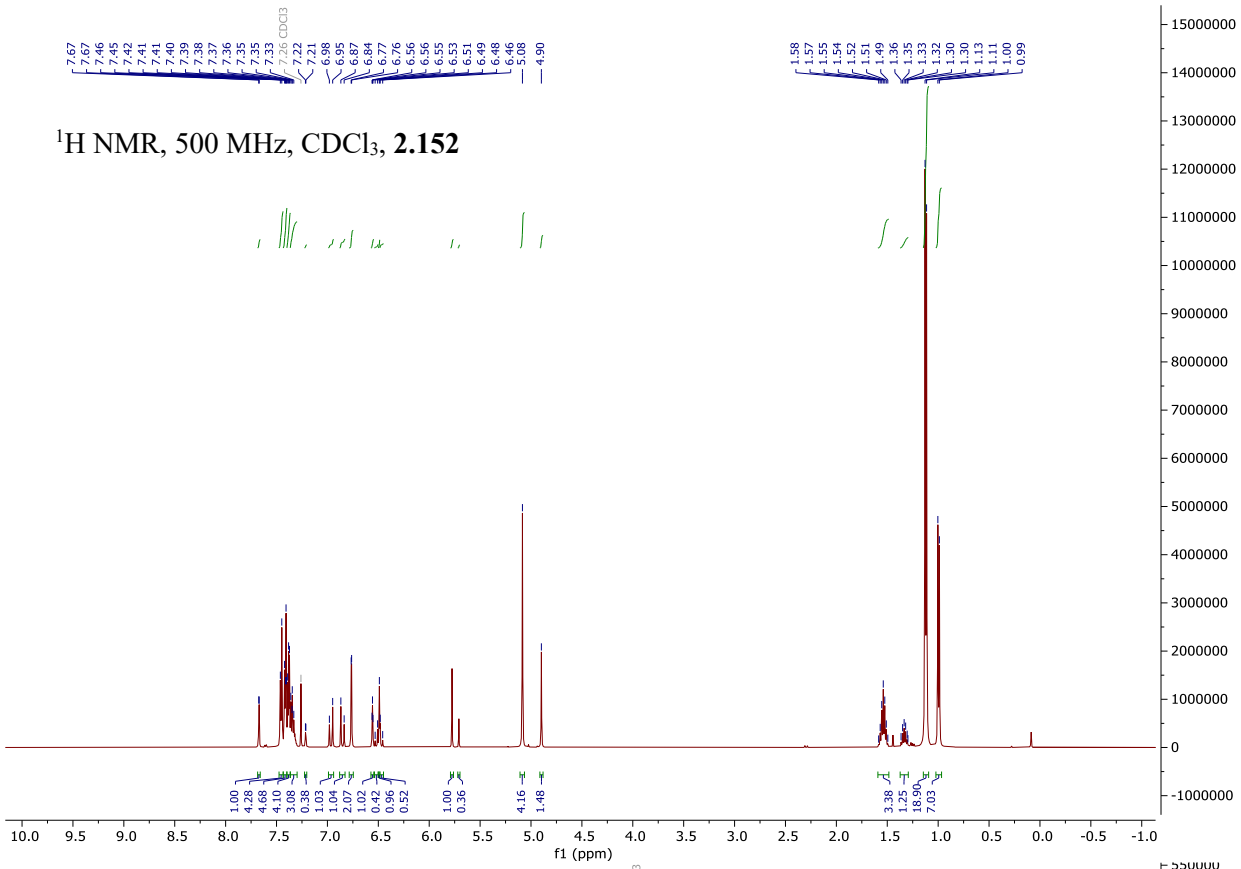


^{13}C NMR, 126 MHz, $CDCl_3$, **2.147**

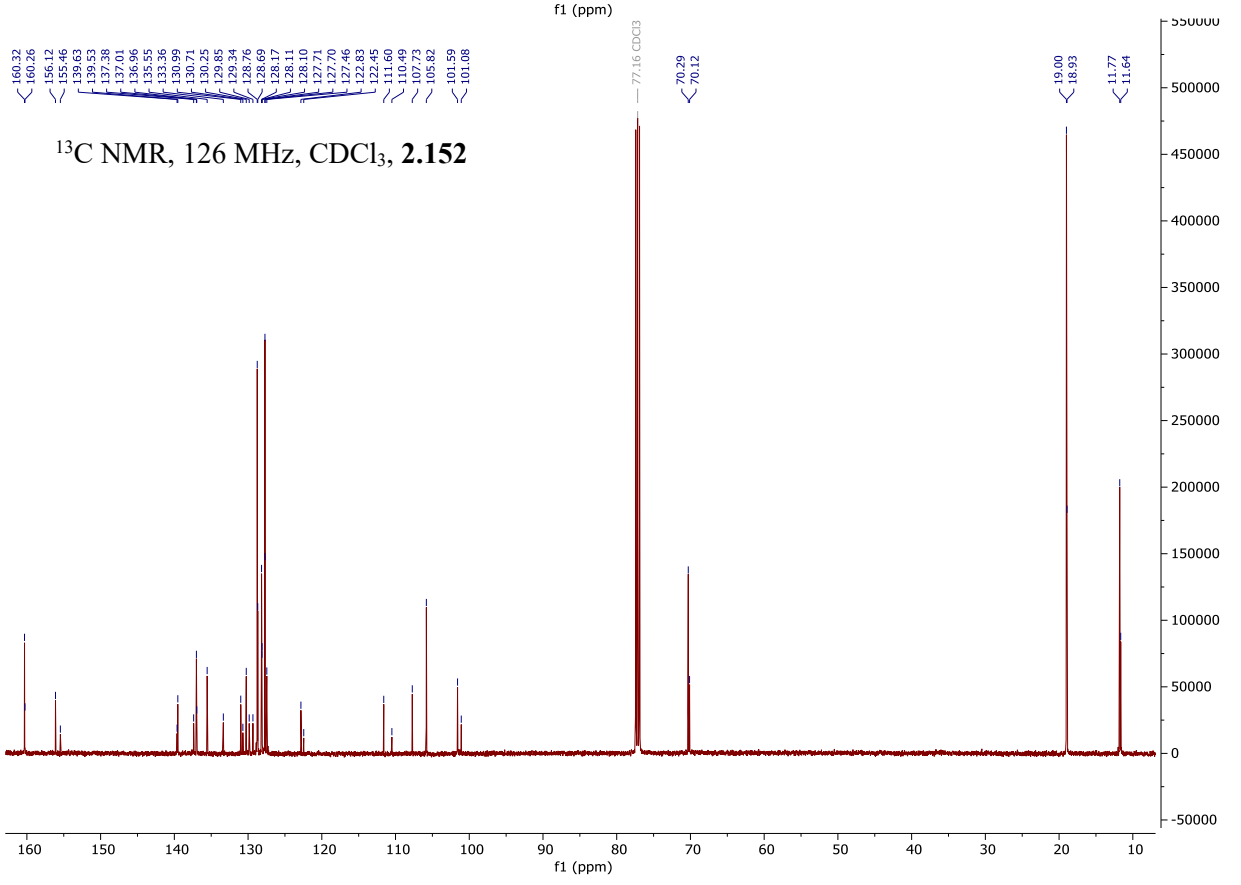


(2.152) (E/Z)-4-(3,5-bis(benzyloxy)styryl)-2-bromo-6-(triisopropylsilyl)phenol) A 2 dram vial was charged with phosphonium salt (acquired from previous synthetic studies) (200 mg, 0.31 mmol, 1.0 equiv) and dry THF (1.1 mL). While stirring at room temperature PhLi (1.10 M), freshly prepared[2] (0.31 mL, 0.34 mmol, 1.1 equiv) was added dropwise, turning the cloudy solution a brilliant red color. Upon colling to -78 °C, the aldehyde was added as a solution in dry diethyl ether (135 mg, 0.31 mmol, 1 equiv, 0.443 mL). This temperature was held for 5 miuntes. Upon warming to -40 °C another equivalent of PhLi was added (0.31 mL, 0.34 mmol, 1.1 equiv). After 5 minutes methanol (0.044 mL, 3.5 equiv) was added, and the solution was let warm to room temperature and stir for two hours. The reaction was quenched with water (5 mL) and then extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-10% EtOAc in Hexanes) to yield the product as a viscous amorphous tan liquid (190 mg, 95%, 2.7:1 trans:cis).

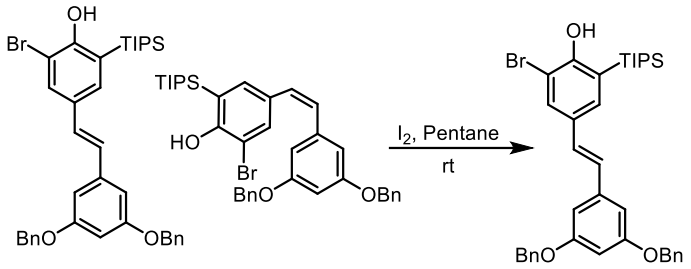
TLC (Hexanes/EtOAc, 95:5), R_F:	0.42 (UV, potassium permanganate)
^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ:	δ= 7.67 (major trans, d, J = 2.0 Hz, 1H), 7.46 (Bn, Overlapping, J = 7.0 Hz, 4H), 7.41 (Bn, Overlapping, d, J = 7.3 Hz, 4H), 7.40 – 7.32 (Bn, Overlapping, m, 4H), 7.21 (minor cis, d, J = 2.1 Hz, 2H), 6.96 (olefin, major trans, d, J = 16.2 Hz, 1H), 6.85 (olefin, major trans, d, J = 16.2 Hz, 1H), 6.76 (major trans, d, J = 2.3 Hz, 2H), 6.56 (major trans, t, J = 2.2 Hz, 1H), 6.52 (minor cis, d, J = 12.1 Hz, 1H), 6.49 (minor cis, s, 2H), 6.47 (minor cis, d, J = 12.3 Hz, 1H), 5.78 (major trans, s, 1H), 5.71 (minor cis, s, 1H), 5.08 (benzylic, major cis, s, 4H), 4.90 (benzylic, minor trans, s, 4H), 1.54 (TIPS tertiary, major trans, hept, J = 7.5 Hz, 3H), 1.33 (TIPS tertiary, minor cis, h, J = 7.5 Hz, 3H), 1.12 (TIPS primary, major trans, d, J = 7.5 Hz, 18H), 1.00 (TIPS primary, minor cis, d, J = 7.5 Hz, 18H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ:	δ= 160.3, 160.3, 156.1, 155.5, 139.6, 139.5, 137.4, 137.0, 137.0, 135.5, 133.4, 131.0, 130.7, 130.2, 129.8, 129.3, 128.8, 128.7, 128.2, 128.1, 128.1, 127.7, 127.7, 127.5, 122.8, 122.4, 111.6, 110.5, 107.7, 105.8, 101.6, 101.1, 70.3, 70.1, 19.0, 18.9, 11.8, 11.6.
HRMS (ESI):	*m/z* calculated for $C_{37}H_{43}BrO_3Si$ ($[M+H]^+$): 643.2243, found 643.2203
FTIR (neat) cm^{-1} :	ν̃= 3466 (br), 3029 (w), 2940 (w), 2864 (w), 1591 (m), 1293 (w), 1160 (m), 1144 (vs), 1076 (w), 1062 (m), 1043 (m), 959 (m), 882 (m), 815 (w), 753 (m), 727 (vs), 690 (s), 673 (vs)



^{1}H NMR, 500 MHz, $CDCl_3$, **2.152**



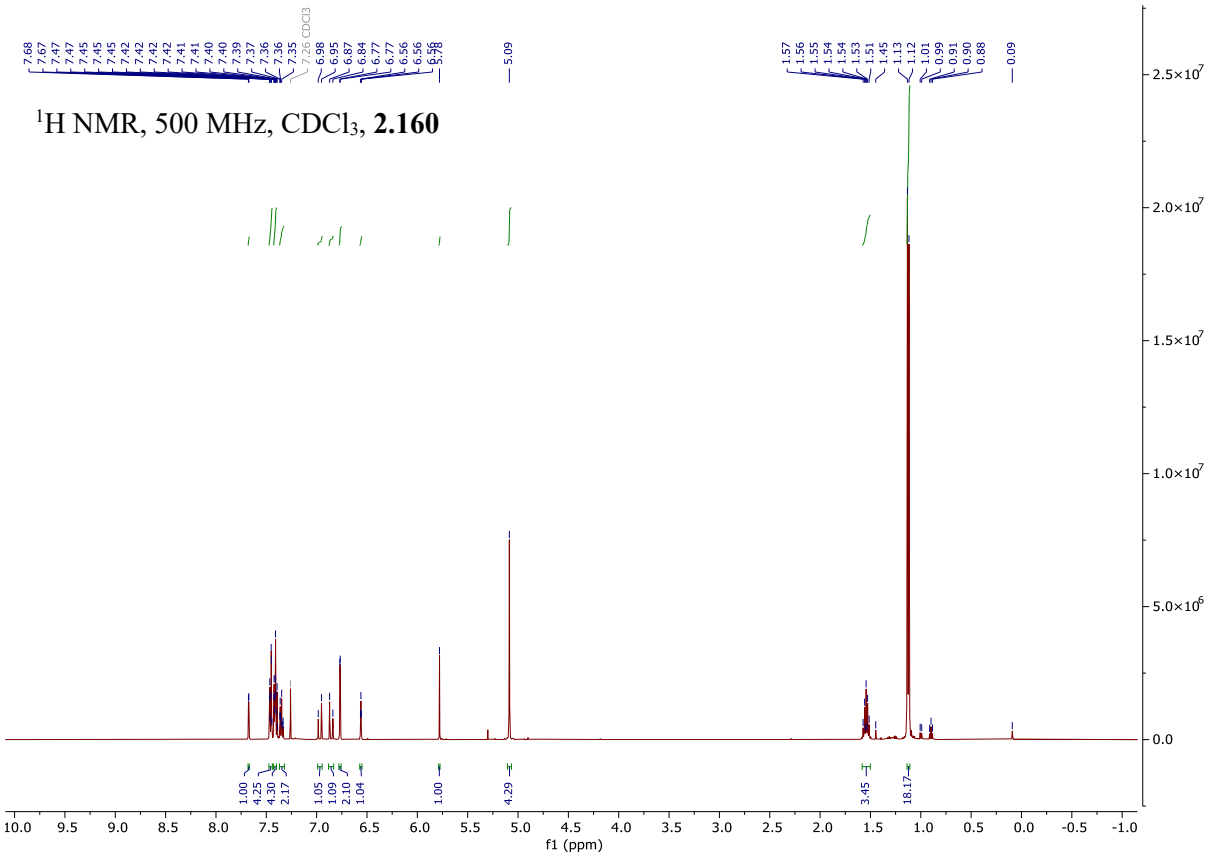
^{13}C NMR, 126 MHz, $CDCl_3$, **2.152**



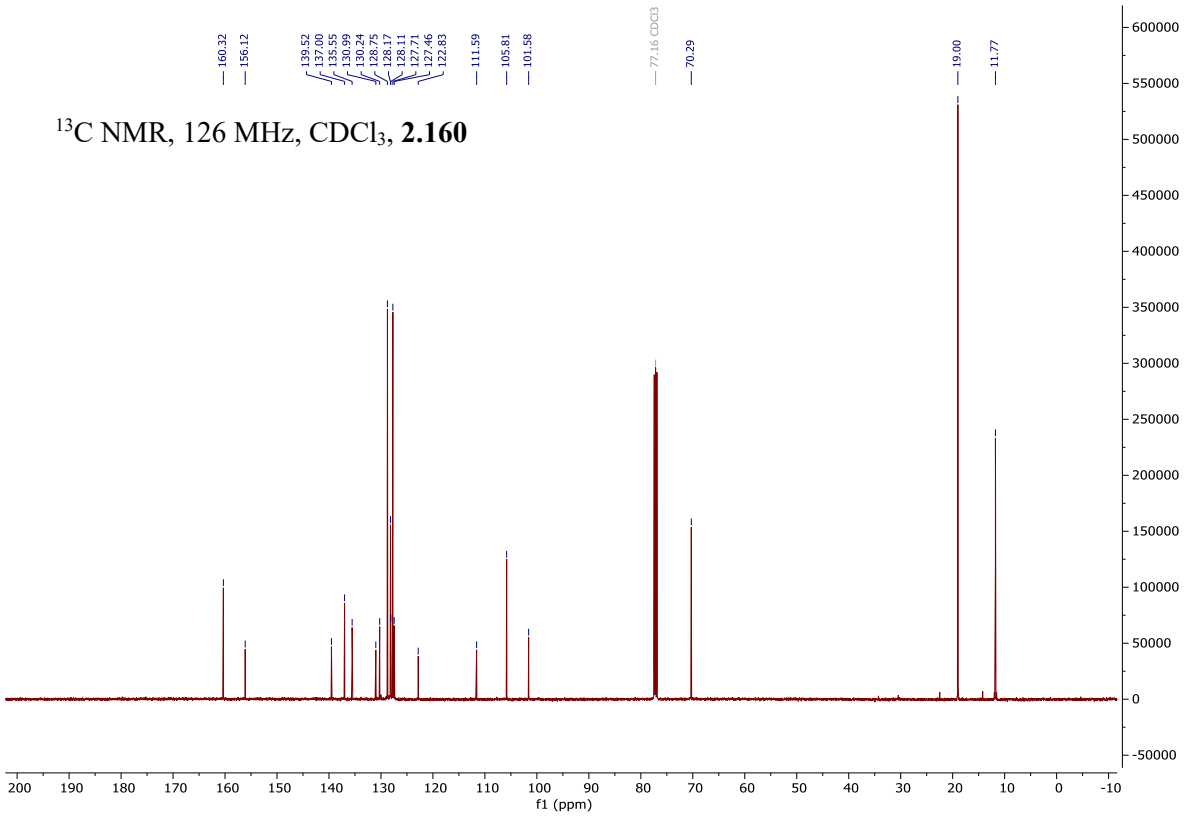
(2.160) (E)-4-(3,5-bis(benzyloxy)styryl)-2-bromo-6-(triisopropylsilyl)phenol) A 9.5 dram vial was charged with the alkene isomer mixture (1.0 gram, 1.0 equiv, 2.7:1 trans:cis), iodine (394 mg, 1.0 equiv), and pentane (6.2 mL). The reaction was stirred for one hour at room temperature, when it was quenched with a saturated sodium thiosulfate solution (10 mL) and diluted with DCM (10 mL). The reaction was decolorized from dark to light purple while stirring for 10 minutes. The organic layer was separated, and the aqueous layer was washed with DCM (2 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-10% EtOAc in Hexanes) to yield the product as an amorphous off white powder (760 mg, 76%, pure trans).

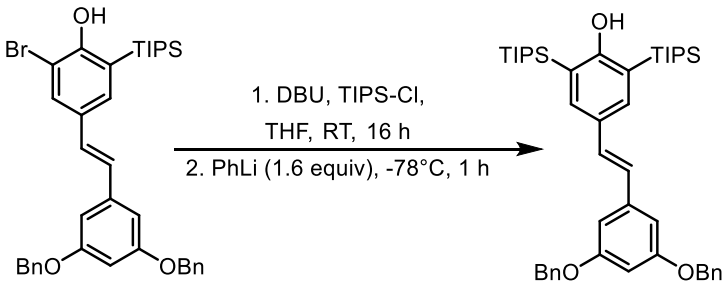
TLC (Hexanes/EtOAc, 95:5), R_F:	0.43 (UV, potassium permanganate)
^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ:	δ= 1H NMR (500 MHz, CDCl3) δ 7.68 (d, J = 2.0 Hz, 1H), 7.47 – 7.44 (m, 4H), 7.43 – 7.39 (m, 4H), 7.37 – 7.33 (m, 2H), 6.97 (d, J = 16.2 Hz, 1H), 6.86 (d, J = 16.2 Hz, 1H), 6.77 (d, J = 2.2 Hz, 2H), 6.56 (t, J = 2.2 Hz, 1H), 5.78 (s, 1H), 5.09 (s, 4H), 1.54 (hept, J = 7.5 Hz, 3H), 1.13 (d, J = 7.5 Hz, 18H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ:	δ= 160.3, 156.1, 139.5, 137.0, 135.5, 131.0, 130.2, 128.8, 128.2, 128.1, 127.7, 127.5, 122.8, 111.6, 105.8, 101.6, 70.3, 19.0, 11.8.
HRMS (ESI):	*m/z* calculated for $C_{37}H_{43}BrO_3Si$ ($[M+H]^+$): 643.2243, found 643.2231
FTIR (neat) cm^{-1} :	ν̃= 3466 (br), 3029 (w), 2940 (w), 2865 (w), 1592 (w), 1162 (w), 1144 (vs), 1043 (w), 959 (m), 815 (w), 754 (m), 727 (vs), 690 (s), 674 (vs)

^{1}H NMR, 500 MHz, $CDCl_3$, **2.160**



^{13}C NMR, 126 MHz, $CDCl_3$, **2.160**

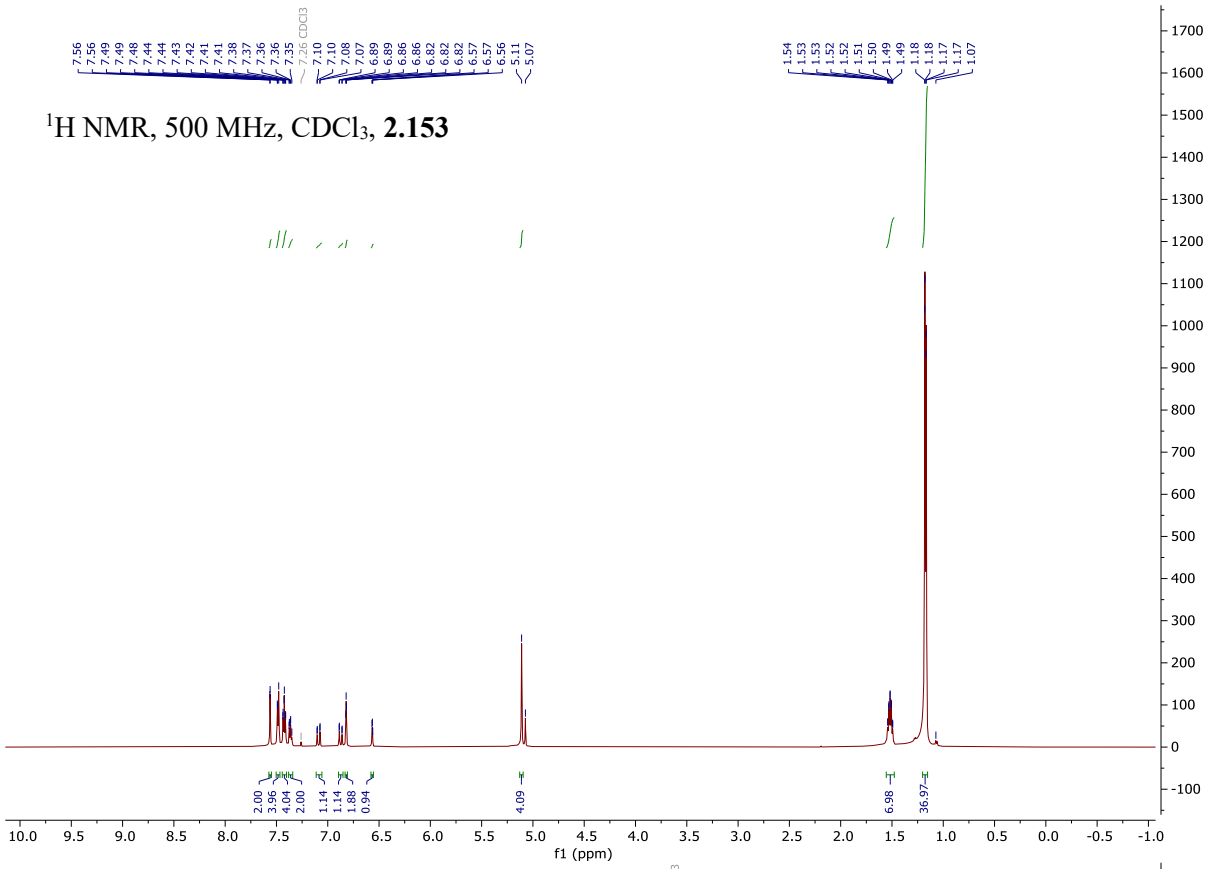




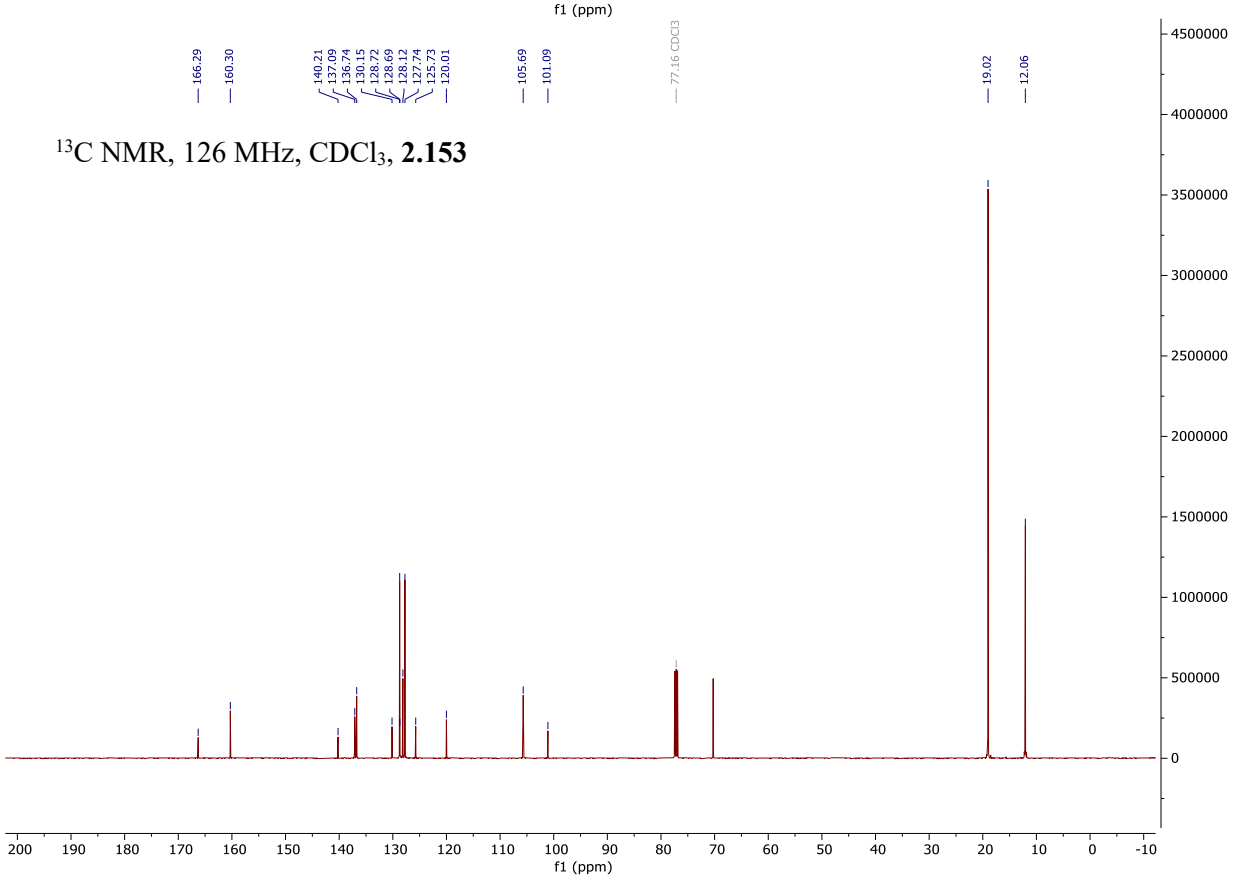
(2.153) (E)-4-(3,5-bis(benzyloxy)styryl)-2,6-bis(triisopropylsilyl)phenol A 2 dram vial was charged with the alkene (100 mg, 155 mmol, 1.0 equiv) and THF (1.55 mL). At 0 °C the DBU (38 µL, 249 mmol, 1.6 equiv) and TIPS-Cl (53 µL, 249 mmol, 1.6 equiv) were added dropwise. The vial was let warm to room temperature and react overnight (14 hours). After cooling to -78 °C freshly prepared PhLi (1.2 M) was added (53 µL, 249 mmol, 1.6 equiv). After 1 hour at -78 °C the reaction was quenched with water (5 mL) and then extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-10% EtOAc in Hexanes) to yield the product as a white powder (103 mg, 92%, trans, no racemization observed).

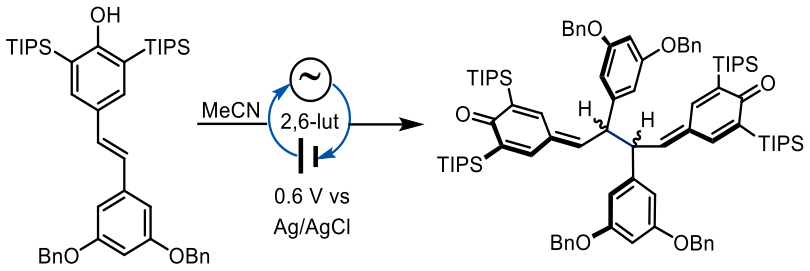
TLC (Hexanes/EtOAc, 95:5), R_F:	0.53 (UV, potassium permanganate)
^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ:	δ= 7.56 (s, 1H), 7.49 (d, J = 8.2 Hz, 4H), 7.42 (td, J = 7.5, 1.7 Hz, 4H), 7.36 (dd, J = 8.1, 6.3 Hz, 2H), 7.09 (dd, J = 16.2, 1.4 Hz, 1H), 6.87 (dd, J = 16.2, 1.4 Hz, 1H), 6.82 (t, J = 1.9 Hz, 2H), 6.57 (df, J = 2.1 Hz, 1H), 5.11 (s, 4H), 1.52 (hept, J = 8.6 Hz, 6H), 1.17 (dd, J = 7.5, 1.6 Hz, 36H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ:	δ= 166.3, 160.3, 140.2, 137.1, 136.7, 130.1, 128.7, 128.7, 128.1, 127.7, 125.7, 120.0, 105.7, 101.1, 19.0, 12.1.
HRMS (ESI):	*m/z* calculated for $C_{46}H_{64}O_3Si_2$ ($[M+H]^+$): 721.4472, found 721.4457.
FTIR (neat) cm^{-1} :	ν̃= 3590 (w), 2945 (w), 2865 (w), 1589 (m), 1150 (vs), 1061 (m), 1043 (w), 957 (w), 882 (m), 741 (s), 712 (w), 698 (m), 678 (s)

^{1}H NMR, 500 MHz, $CDCl_3$, **2.153**



^{13}C NMR, 126 MHz, $CDCl_3$, **2.153**

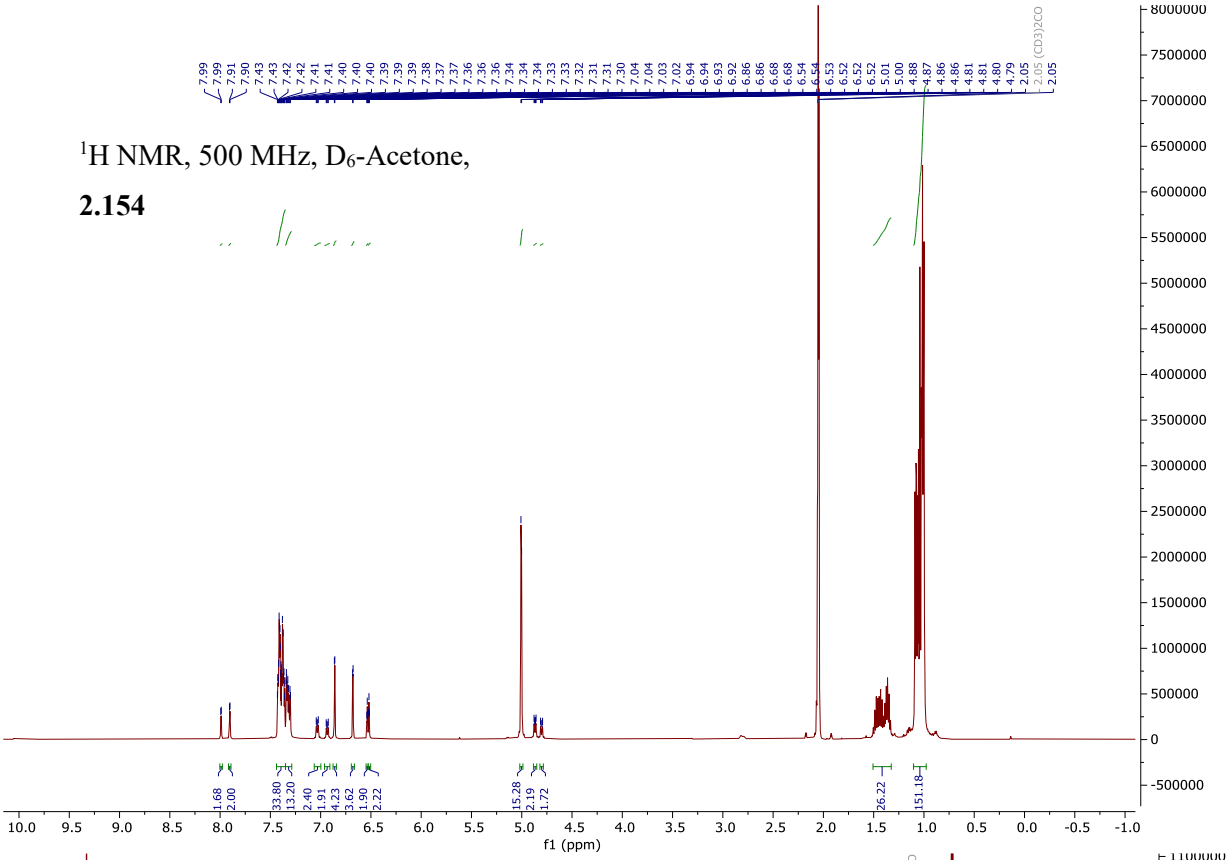




(2.154) (4,4'-((2R,3S)-2,3-bis(3,5-bis(benzyloxy)phenyl)butane-1,4-diylidene)bis(2,6-bis(triisopropylsilyl)cyclohexa-2,5-dien-1-one)

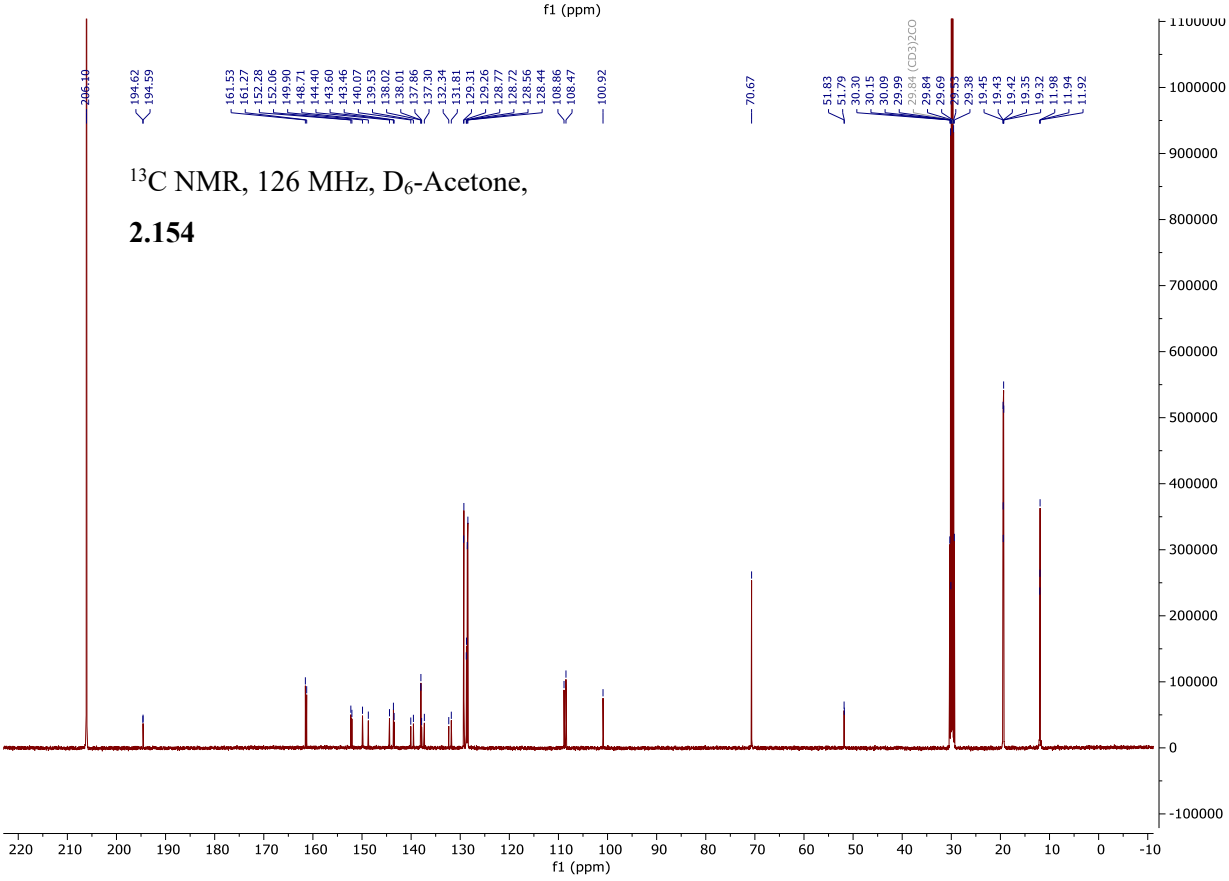
This preparation utilizes the conditions from our previous publicaiton.[1] The starting phenol (790 mg, 1.10 mmol, 1.0 equiv) was added to a 150 mL beaker with KPF_6 (806 mg, 4.38 mmol, 4.0 equiv) and 2,6-lutidine (454 µL, 2.19 mmol, 2.0 equiv) and dissolved in acetonitrile (mL). Two pieces of 4 x 2-inch RVC panel (0.25 inch thickness) were cut. To each, a hole was made near one end, and copper wire was placed through the hole and wrapped around the top of each electrode. One end of the wire was left free to connect to the alligator clips. These electrodes were carefully placed into the beaker along with the reference electrode (Ag/AgCl in 3 M KCl) and a divider. The alligator clips were connected such that the reference and working electrodes were adjacent to each other, while the counter electrode was opposite the divider. Care was taken to ensure the copper wire was not submerged in solvent, nor the active components of the alligator clips touching each other. The reaction was stirred at 750 rpm for 1-2 h at a constant voltage of 0.6 V. A chronoampergram was recorded to follow the course of the reaction. Upon completion of the reaction, the electrodes were removed and rinsed into a collection flask with DCM (~200 mL). The contents of the reaction vial were also rinsed into the collection flask. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-30% EtOAc in Hexanes) to yield the product as a bright yellow foam (645 mg, 81%, 1.2:1 mixture of diastereomers).

TLC (Hexanes/EtOAc, 80:20), R_F:	0.66 (UV, potassium permanganate);
^{1}H NMR (500 MHz, D_6-Acetone, 25 °C) δ:	δ= 7.99 (minor diastereomer, d, J=2.5, 2H), 7.90 (major diastereomer, d, J=2.5, 2H), 7.44 – 7.29 (overlapping, m, 40H), 7.07 – 7.00 (major diastereomer, m, 2H), 6.96 – 6.91 (minor diastereomer, m, 2H), 6.86 (major diastereomer, d, J=2.2, 4H), 6.68 (minor diastereomer, d, J=2.2, 4H), 6.54 (major diastereomer, t, J=2.2, 2H), 6.52 (minor diastereomer, t, J=2.2, 2H), 5.00 (overlapping, 16H), 4.90 – 4.84 (major diastereomer, m, 2H), 4.83 – 4.77 (minor diastereomer, m, 2H), 1.51 – 1.32 (overlapping, m, 24H), 1.12 – 0.97 (overlapping, m, 144H).
^{13}C NMR (126 MHz, D_6-Acetone, 25 °C) δ:	δ= 206.1, 194.6, 194.6, 161.5, 161.3, 152.3, 152.1, 149.9, 148.7, 144.4, 143.6, 143.5, 140.1, 139.5, 138.0, 138.0, 137.9, 137.3, 132.3, 131.8, 129.3, 129.3, 128.8, 128.7, 128.6, 128.4, 108.9, 108.5, 100.9, 70.7, 51.8, 51.8, 30.3, 30.1, 30.1, 30.0, 29.8, 29.7, 29.5, 29.4, 19.5, 19.4, 19.4, 19.3, 19.3, 12.0, 11.9, 11.9.
HRMS (ESI):	*m/z* calculated for $C_{92}H_{126}O_6Si_4$ ($[M+H]^+$): 1439.8709, found 1439.8663
FTIR (neat) cm^{-1} :	ν̃= 2943 (w), 2865 (w), 2230 (w), 1591 (vs), 1157 (s), 1052 (m), 1028 (w), 1020 (w), 883 (m), 837 (w), 806 (m), 734 (m), 695 (m)



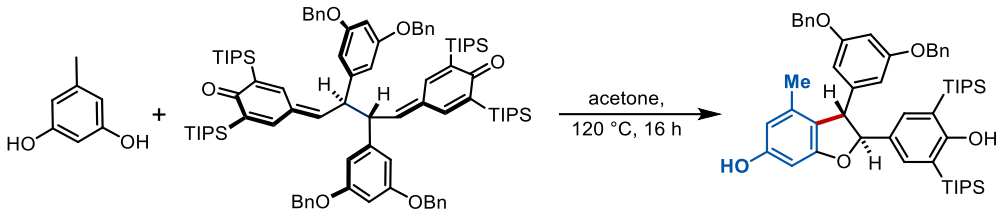
^{1}H NMR, 500 MHz, D_6-Acetone,

2.154



^{13}C NMR, 126 MHz, D_6-Acetone,

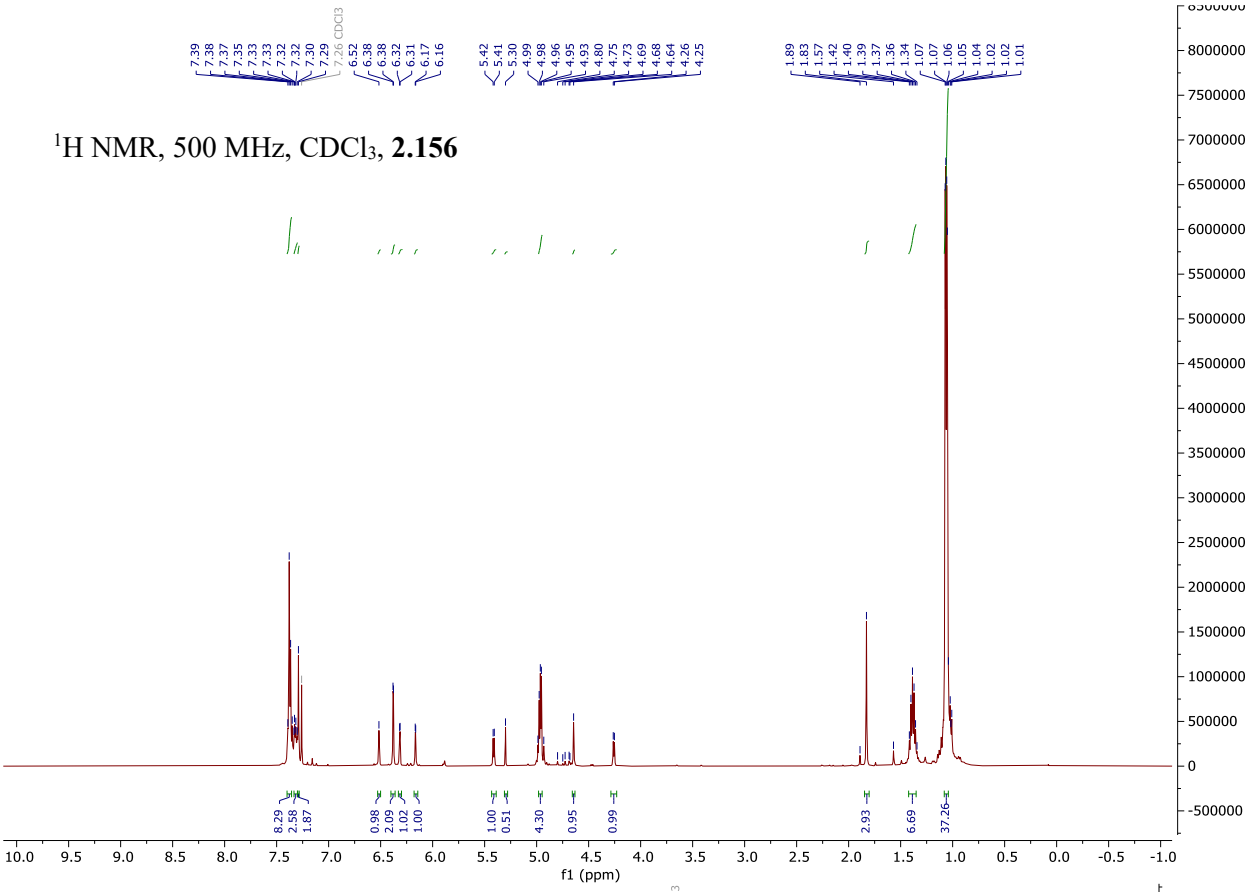
2.154



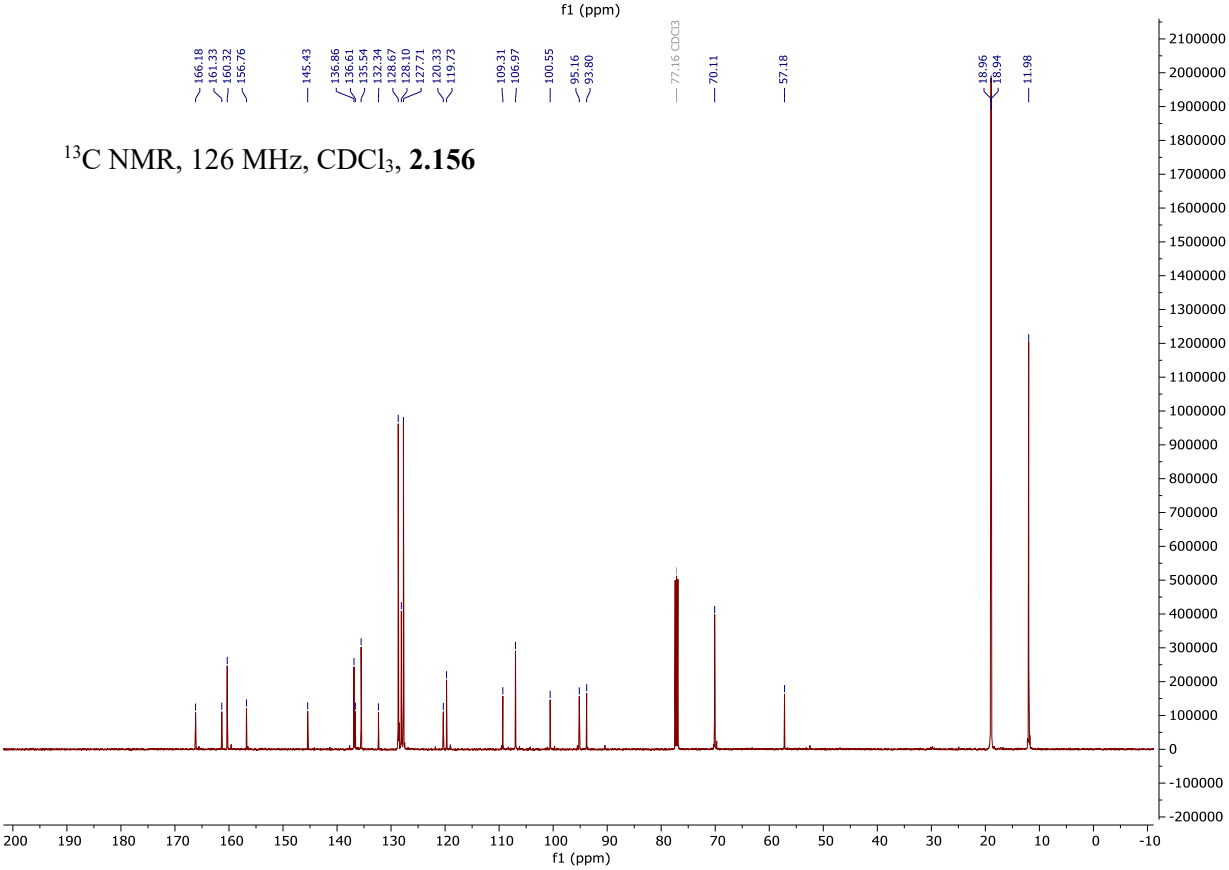
(2.156) (2S)-3-(3,5-bis(benzyloxy)phenyl)-2-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)-4-methyl-2,3-dihydrobenzofuran-6-ol In a flame-dried 15mL sealed tube capped with a septa under inert atmosphere, bisquinone methide dimer (175 mg, 121 mmol, 2 equiv) and aryl phenol (11.3 mg, 91.1 mmol, 1.5 equiv) were added and the solids were dissolved/suspended in dry acetone (0.05M, reagent grade purity) that had been previously freeze-pump-thawed (three times) to rigorously degas the solvent. The tube was capped and the mixture was stirred at 120 °C (oil bath) for 16 h. Upon completion. the reaction was transferred to a round bottom flask and concentrated *in vacuo* to provide residue which was purified with flash chromatography (0%-20% EtOAc in Hexanes) to afford the dihydrobenzofuran product as a tan foam (45.7 mg, 60%).

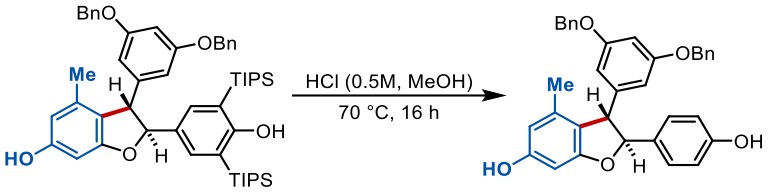
TLC (Hexanes/EtOAc, 80:20), R_F:	0.47 (UV, potassium permanganate)
^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ:	δ= 7.37 (d, J=6.6, 8H), 7.34 – 7.30 (m, 2H), 7.29 (s, 2H), 6.52 (t, J=2.3, 1H), 6.38 (d, J=2.2, 2H), 6.32 (d, J=2.2, 1H), 6.17 (d, J=2.2, 1H), 5.41 (d, J=5.6, 1H), 5.30 (s, 1H), 5.02 – 4.91 (m, 4H), 4.64 (s, 1H), 4.26 (d, J=5.6, 1H), 1.83 (s, 3H), 1.38 (h, J=7.2, 6H), 1.06 (dd, J=7.5, 3.1, 36H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ:	δ= 166.2, 161.3, 160.3, 156.8, 145.4, 136.9, 136.6, 135.5, 132.3, 128.7, 128.1, 127.7, 120.3, 119.7, 109.3, 107.0, 100.6, 95.2, 93.8, 70.1, 57.2, 19.0, 18.9, 12.0.
HRMS (ESI):	*m/z* calculated for $C_{53}H_{70}O_5Si_2$ ($[M+H]^+$): 843.4840, found 843.4826
FTIR (neat) cm^{-1} :	ν̃= 3601 (w), 2944 (w), 2890 (w), 2865 (w), 1595 (m), 1455 (w), 1156 (vs), 1055 (w), 883 (w), 733 (vs), 696 (w)

^{1}H NMR, 500 MHz, $CDCl_3$, **2.156**



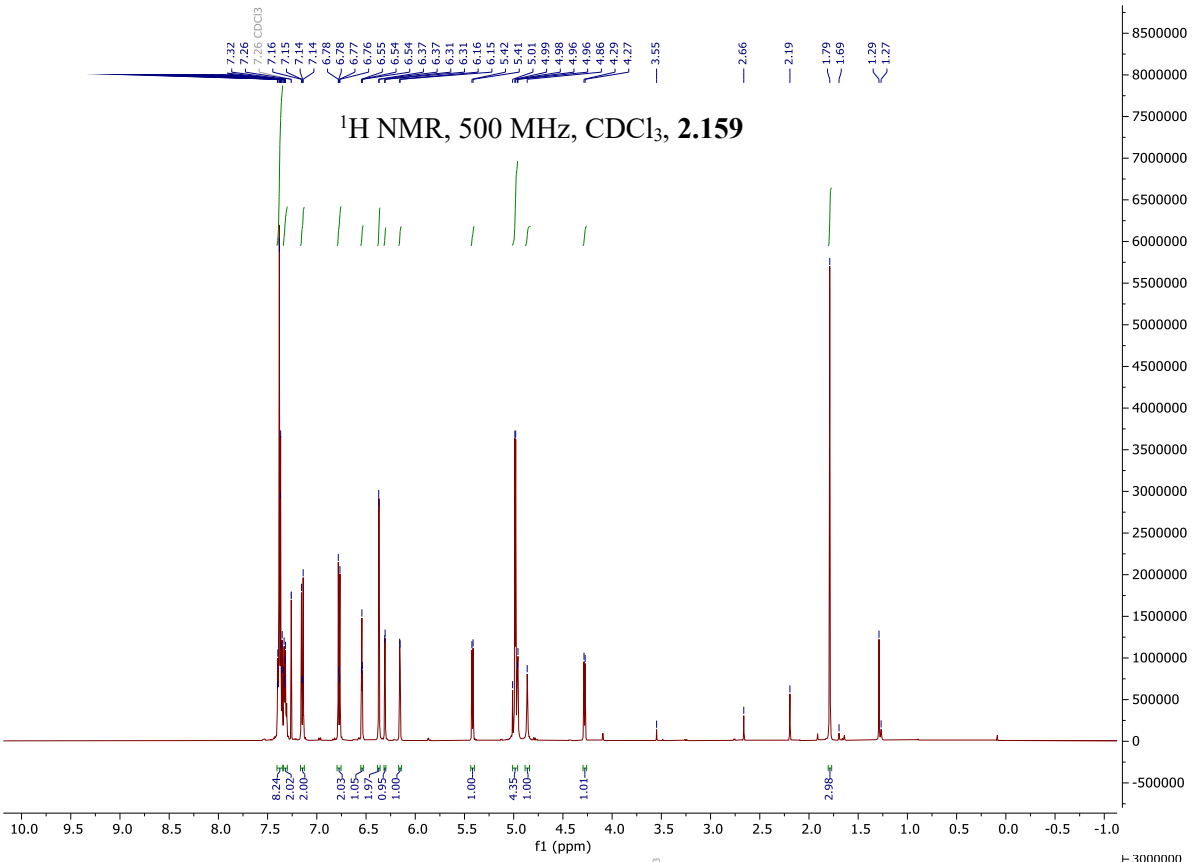
^{13}C NMR, 126 MHz, $CDCl_3$, **2.156**



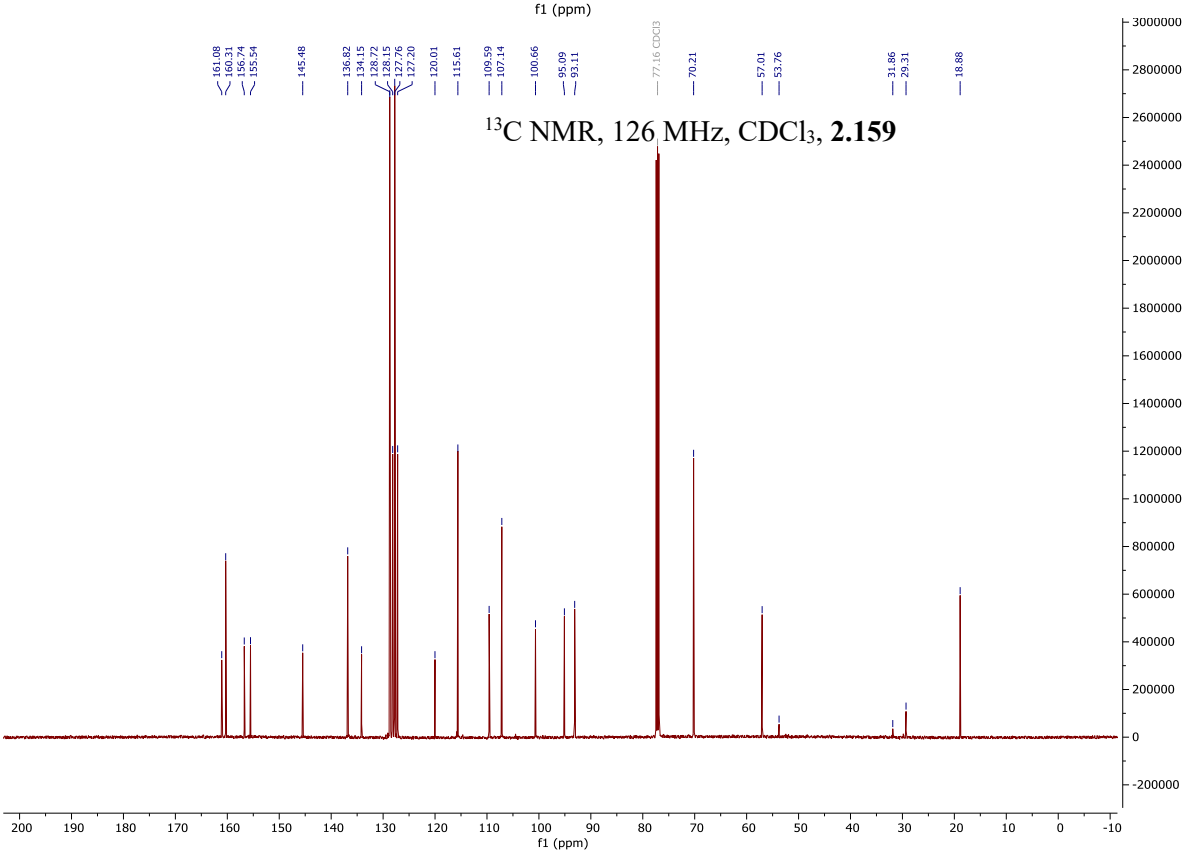


(2.159) ((2S)-3-(3,5-bis(benzyloxy)phenyl)-2-(4-hydroxyphenyl)-4-methyl-2,3-dihydrobenzofuran-6-ol) A 9.5 dram vial was charged with the TIPS protected DHB (65 mg, 0.95 mmol, 1 equiv) and a solution of HCl (9.5 mL, 0.5 M in methanol). The reaction was refluxed (oil bath set to 70 °C) for 16 h. The reaction was quenched with $NaHCO_3$ (10 mL, saturated solution) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-60% EtOAc in Hexanes) to yield the product as a light tan foam (34.2 mg, 68%).

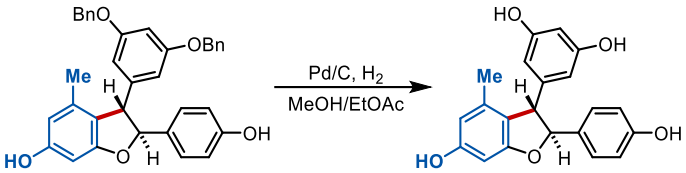
TLC (Hexanes/EtOAc, 80:20), R_F:	0.04 (UV, potassium permanganate)
^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ:	δ = 7.41 – 7.35 (m, 8H), 7.34 – 7.29 (m, 2H), 7.18 – 7.11 (m, 2H), 6.81 – 6.73 (m, 2H), 6.54 (t, J=2.3, 1H), 6.37 (d, J=2.2, 2H), 6.31 (d, J=2.2, 1H), 6.16 (d, J=2.2, 1H), 5.42 (d, J=5.8, 1H), 4.98 (d, J=4.1, 3H), 4.96 (s, 1H), 4.86 (s, 1H), 4.28 (d, J=5.8, 1H), 1.79 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ:	δ= 161.1, 160.3, 156.7, 155.5, 145.5, 136.8, 134.1, 128.7, 128.2, 127.8, 127.2, 120.0, 115.6, 109.6, 107.1, 100.7, 95.1, 93.1, 70.2, 57.0, 18.9.
HRMS (ESI):	*m/z* calculated for $C_{35}H_{30}O_5$ ($[M+H]^+$): 531.2171, found 531.2155
FTIR (neat) cm^{-1} :	ν̃= 3392 (br), 3033 (w), 2922 (w), 1594 (vs), 1453 (w), 1154 (vs), 1124 (s), 1055 (m), 831 (w), 733 (vs), 696 (m)



^{1}H NMR, 500 MHz, $CDCl_3$, **2.159**

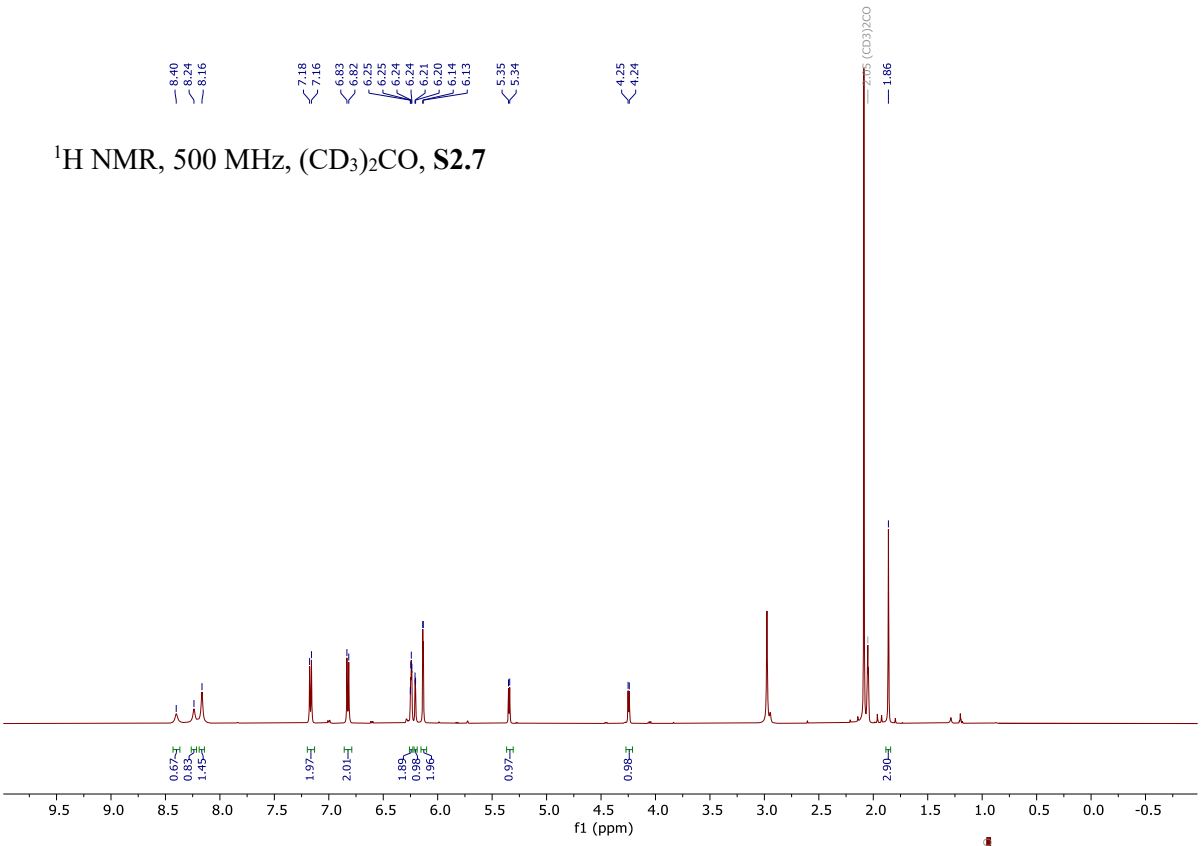


^{13}C NMR, 126 MHz, $CDCl_3$, **2.159**

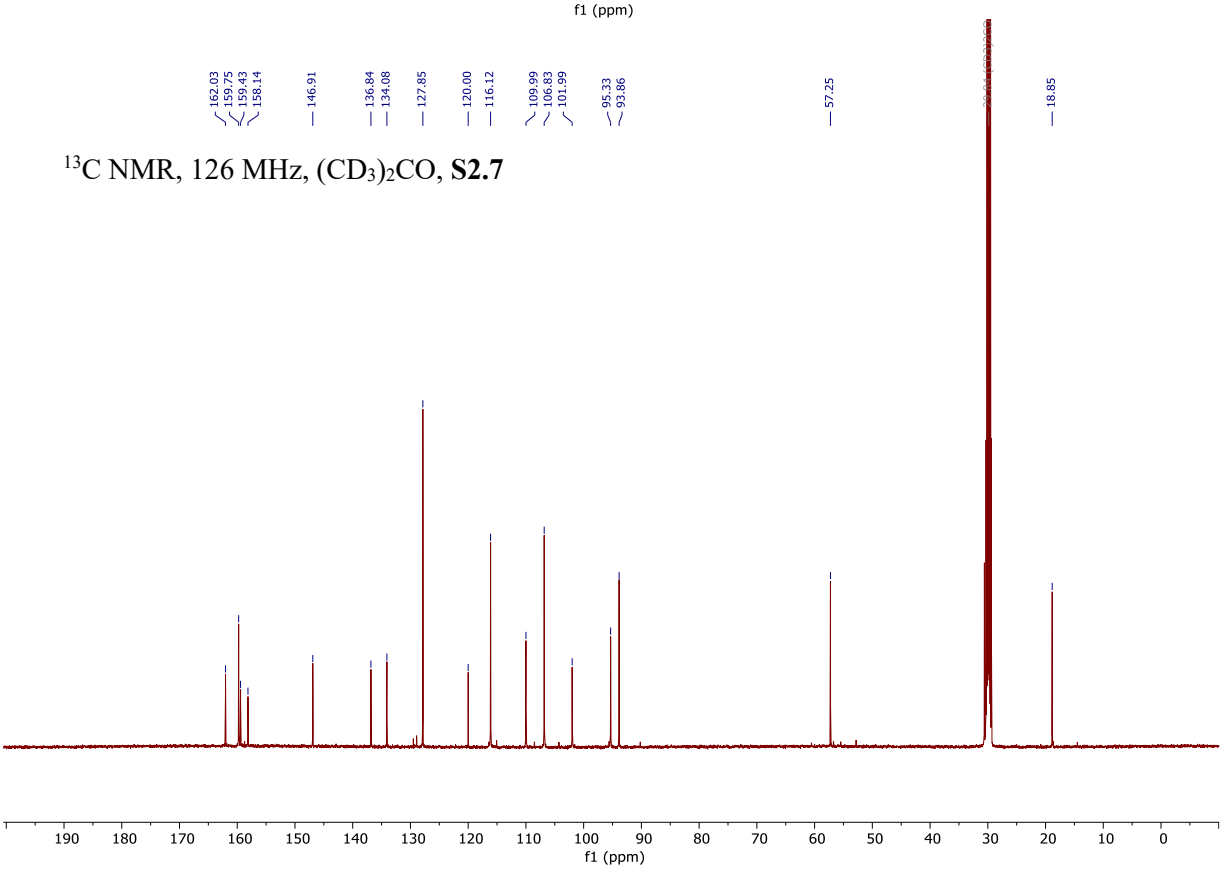


(S2.7) (5-((2S)-6-hydroxy-2-(4-hydroxyphenyl)-4-methyl-2,3-dihydrobenzofuran-3-yl)benzene-1,3-diol) A 4-dram vial was charged with Pd/C (23 mg, 1 equiv) and the benzyl protected DHB (35 mg, 0.066 mmol, 1 equiv) was added as a solution in degassed methanol (6.6 mL, 0.01M). The reaction mixture was thoroughly sparged with H_2 (g), and let react under an atmosphere of H_2. After 16 h, the solution was sparged with argon, celite was added to the vial, which was then filtered over a bed of celite, washing continuously with ethyl acetate. Care was taken to ensure the filter bed did not go dry. The organic extract was purified by flash chromatography over SiO_2 (0%-60% EtOAc in Hexanes) to yield the product as a light tan oil (18.9 mg, 82%).

TLC (Hexanes/EtOAc, 60:40), R_F:	0.14 (UV, potassium permanganate)
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 25 °C) δ:	δ 8.40 (s, 1H), 8.24 (s, 1H), 8.16 (s, 1H), 7.17 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.26 – 6.23 (m, 2H), 6.21 (d, J = 2.5 Hz, 1H), 6.13 (d, J = 2.3 Hz, 2H), 5.34 (d, J = 5.6 Hz, 1H), 4.25 (d, J = 5.5 Hz, 1H), 1.86 (s, 3H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$, 25 °C) δ:	δ 162.0, 159.8, 159.4, 158.1, 146.9, 136.8, 134.1, 127.9, 120.0 116.1, 109.99, 106.8, 101.99, 95.3, 93.9, 57.3, 18.9.
HRMS (ESI):	*m/z* calculated for $C_{21}H_{18}O_5$ ($[M-H]^+$): 349.1076, found 349.1077
FTIR (neat) cm^{-1} :	ν̃= 3353 (br), 2923 (w), 1687 (s), 1597 (s), 1516 (w), 1452 (m), 1337 (w), 1258 (s), 1156 (s), 1144 (s), 1123 (vs), 1004 (s), 971 (m), 831 (s), 693 (s), 672 (w)



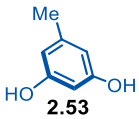
^{1}H NMR, 500 MHz, $(CD_3)_2CO$, **S2.7**



^{13}C NMR, 126 MHz, $(CD_3)_2CO$, **S2.7**

2.8 Computational Details

All density functional theory (DFT) calculations were performed using the Gaussian 16 package. Optimized geometries were carried out at the M062X [217] / cc-pVTZ [218] level of theory, with a conductor-like polarizable continuum *model* (*CPCM*) in acetone. All optimized ground state geometries were confirmed to have zero imaginary frequencies, while transition states had one.



2.53

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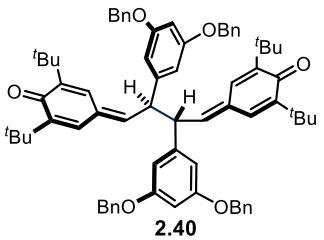

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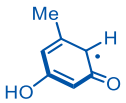

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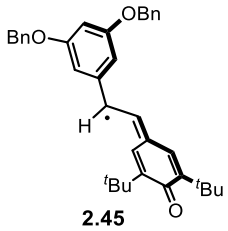

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C 1.93553200 -1.31016500 0.80491700
H 1.90554800 -0.33706400 0.32841900
H 2.40670600 -2.36515000 2.56694400
C 4.52315700 1.08529100 7.17437900
H 4.77092900 0.58024800 8.10229000
H 3.74562900 1.82803600 7.36052600
H 5.41279600 1.57918200 6.78008900
C 3.75390500 4.36389800 3.57344200
H 3.67427900 5.25841300 2.96429500
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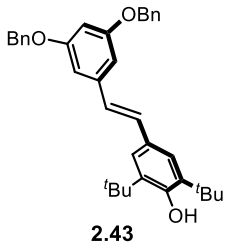

2.43

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C 4.05578600 -6.23337600 1.09158400
C 3.18813700 -7.96615100 -0.91932100
C 4.16725600 -8.39469200 -0.02986900
C 4.58136400 -7.50942500 0.96551200
O 2.56826000 -4.58306800 0.30777800

C 4.53420200 -5.28477900 2.19898900
C 3.36562700 -4.90674700 3.12357300
H 2.57863100 -4.38139000 2.59093400
H 3.73169800 -4.26132100 3.92418900
H 2.94071900 -5.80225500 3.58035000
C 5.60610500 -5.93831900 3.07661400
H 5.90981500 -5.22666700 3.84457700
H 6.49352800 -6.20760300 2.50246400
H 5.23164900 -6.83104800 3.57912500
C 5.16187600 -4.02071900 1.58940900
H 4.44868400 -3.45817400 0.99449800
H 6.01049900 -4.28777700 0.95724100
H 5.52816300 -3.37612800 2.39061300
C 1.53249500 -6.27484200 -1.86206000
C 1.22073500 -7.39511500 -2.86074100
H 2.09691600 -7.66636700 -3.44962100
H 0.45031200 -7.04655800 -3.54846200
H 0.84429800 -8.28778200 -2.36122600
C 0.20380700 -5.96772400 -1.14379100
H -0.54683400 -5.67473600 -1.87876500
H 0.25441600 -5.17524700 -0.39815400
H -0.15137300 -6.86263100 -0.63203300
C 2.00871400 -5.07680200 -2.70672300
H 2.89949100 -5.35648200 -3.26994300
H 2.26120900 -4.18171100 -2.13938000
H 1.22878800 -4.80056900 -3.41727100
H 2.87218800 -8.65803600 -1.68598700
C 4.71185200 -9.74620700 -0.18231400
C 5.65015900 -10.32325600 0.57427100
C 6.18432800 -11.68047200 0.40401600
C 5.76563600 -12.53722600 -0.61486400
C 7.15161800 -12.12049000 1.30486500
C 6.31016300 -13.80858600 -0.72100100
C 7.69217700 -13.39701000 1.19154800
C 7.27978900 -14.25854200 0.17838900
H 5.02050900 -12.24320400 -1.33948400
H 7.49637100 -11.47860000 2.10426400
H 7.69780400 -15.24655400 0.08922500
O 8.62596000 -13.72964000 2.11697800
O 5.84260400 -14.56933800 -1.74288800
C 9.20650700 -15.01931800 2.04313300
H 9.91717600 -15.07887800 2.86118100
H 9.72985300 -15.16076400 1.09589900
H 8.45056700 -15.79771500 2.16086700
C 6.36671600 -15.87573300 -1.89859400
H 5.86620500 -16.30150900 -2.76238000
H 6.16040400 -16.48985600 -1.02031100

H 7.44273200 -15.84904100 -2.07912400
H 1.91129200 -4.40278100 -0.36695000
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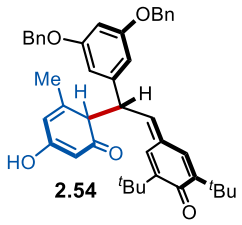

M062X / cc-pVTZ Free Energy = -1579.618229

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C 4.77101800 -6.02879500 0.94979200
C 3.96255900 -7.66719800 -1.24272300
C 5.07257500 -8.05713500 -0.39811800
C 5.41646000 -7.18186700 0.70189100
O 3.02841600 -4.59180300 0.25754200
C 5.15258600 -5.11094400 2.10834600
C 3.96976300 -4.96204600 3.07900500
H 3.10925400 -4.51216300 2.59269100
H 4.26821900 -4.32915300 3.91666400
H 3.68026200 -5.93580600 3.47804900
C 6.33326600 -5.67382400 2.90295700
C 5.57282300 -3.73165500 1.57439200
H 4.75860500 -3.24207600 1.04867400
H 6.42241400 -3.82935300 0.89616700
H 5.87925000 -3.10005900 2.41016000
C 2.09060500 -6.14255400 -1.96504600
C 1.84892200 -7.19091200 -3.05307500
H 2.71651200 -7.30577200 -3.70449300
H 1.00840500 -6.87173700 -3.66960300
H 1.60153100 -8.16503800 -2.62851700
C 0.79875100 -6.02522400 -1.14022500
H -0.03208400 -5.77695600 -1.80321600
H 0.87956400 -5.25345000 -0.38035500
H 0.57019400 -6.97553500 -0.65438400
C 2.38930800 -4.80769400 -2.66628400
H 3.29373600 -4.89051500 -3.27162800
H 2.51918000 -4.00142700 -1.95028300
H 1.56068400 -4.55486600 -3.33035400
C 5.74961100 -9.18898800 -0.68448000
C 6.92910100 -9.72855800 0.08144000

C 6.98164900 -11.24410900 -0.00573700
C 5.86839700 -11.94890600 0.44172900
C 8.08134100 -11.93414100 -0.49060900
C 5.85620400 -13.33704700 0.39820500
C 8.06326100 -13.32812900 -0.53039100
C 6.95549800 -14.04527600 -0.08971400
H 5.00114500 -11.43159900 0.83149800
H 8.97096800 -11.43646400 -0.85026900
H 6.94696800 -15.12138900 -0.12292000
O 9.18150400 -13.91391200 -1.02160600
O 4.73094400 -13.93719600 0.85505400
C 8.24820500 -9.01978900 -0.30268900
H 6.75429400 -9.49339200 1.13247000
C 8.59117200 -9.15735100 -1.78629600
C 9.38235300 -9.26936500 0.65847000
C 10.64147000 -9.30666500 0.21108600
C 10.94366800 -9.20477300 -1.20410500
C 9.98229800 -9.12841500 -2.15474000
O 12.22914000 -9.21597300 -1.58255100
O 7.69318200 -9.24088300 -2.61286700
H 12.81140900 -9.28880800 -0.81779400
C 4.67341600 -15.35282600 0.83573300
H 3.70251500 -15.62116700 1.23943500
H 5.45832300 -15.78599300 1.45791700
H 4.76212400 -15.73535000 -0.18237600
C 9.21735900 -15.32841500 -1.09327900
H 10.18441700 -15.58551500 -1.51313900
H 8.42619200 -15.70808600 -1.74196000
H 9.12090000 -15.77386100 -0.10174300
H 3.72408100 -8.34551200 -2.05086500
H 7.22586800 -5.77683400 2.28302900
H 6.10071900 -6.64444600 3.34433100
H 6.57017200 -4.98709200 3.71566100
H 6.23119200 -7.48562800 1.34281100
C 9.06750800 -9.38755800 2.11514000
H 8.46046000 -8.54433500 2.45223800
H 9.97888000 -9.41826900 2.70655400
H 8.49633500 -10.29762600 2.31192800
H 5.42408600 -9.77470300 -1.53420800
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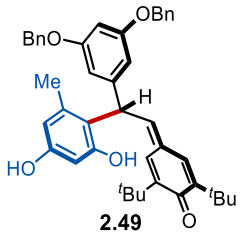

2.49

M062X / cc-pVTZ Free Energy = -1579.643757

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C 5.06898000 -6.24284200 1.04059300
C 3.87806700 -7.95229700 -0.91293100
C 4.99176400 -8.40913800 -0.10792700
C 5.53111100 -7.49369200 0.87443900
O 3.50173500 -4.63906000 0.29846000
C 5.67064500 -5.28021400 2.06076100
C 4.60222700 -4.83396500 3.07198900
H 3.79608600 -4.29151200 2.58713300
H 5.06170300 -4.18341000 3.81830200
H 4.18377900 -5.69864100 3.59022900
C 6.80279600 -5.94171900 2.85055900
C 6.25941000 -4.05525300 1.34225700
H 5.49493400 -3.50702200 0.79931400
H 7.03739900 -4.36351000 0.64143200
H 6.71226200 -3.38778400 2.07763100
C 2.17251000 -6.25548400 -1.66302800
C 1.69943100 -7.36178000 -2.60836900
H 2.48420400 -7.66341300 -3.30367000
H 0.85942200 -6.98919500 -3.19494800
H 1.36127300 -8.24365300 -2.06217300
C 0.98258700 -5.87088900 -0.76908800
H 0.14085300 -5.57184300 -1.39641800
H 1.23086200 -5.04728800 -0.10599500
H 0.66772400 -6.72517900 -0.16708700
C 2.58975500 -5.05511200 -2.52789900
H 3.42186000 -5.32739300 -3.17965400
H 2.88577400 -4.20717100 -1.91729800
H 1.75100700 -4.75525700 -3.15890000
C 5.50672700 -9.63678800 -0.31814900
C 6.68049500 -10.23506000 0.42324200
C 6.75424800 -11.74480400 0.22261600
C 5.59599900 -12.49313300 0.40705000
C 7.94226600 -12.38393600 -0.09330500
C 5.62923400 -13.87483100 0.26770500
C 7.96875100 -13.77061600 -0.23093600
C 6.81717000 -14.53240500 -0.05488600
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H 8.85915000 -11.83142200 -0.24234400
H 6.84168300 -15.60322800 -0.16395800
O 9.17366900 -14.30740800 -0.54443400
O 4.45418200 -14.52150100 0.46638200
C 7.97876600 -9.50576200 0.13094200
H 6.46937400 -10.09311100 1.48580100
C 8.34589700 -9.24094800 -1.19115200
C 8.84623200 -9.10846900 1.15215700
C 10.01946700 -8.42412000 0.84493300
C 10.34505900 -8.14545200 -0.47556600
C 9.51266100 -8.56046200 -1.50439700
O 11.47649000 -7.47741900 -0.82242800
O 7.51405500 -9.69696000 -2.16545800
H 9.78246100 -8.35758900 -2.53261200
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C 4.43816600 -15.93208800 0.33828300
H 3.41720100 -16.24218300 0.53642400
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H 8.61331300 -16.05912200 -1.50714600
H 8.98775300 -16.22552200 0.22731700
H 3.48719100 -8.66451000 -1.62723900
H 7.61733500 -6.26987400 2.20078400
H 6.44521600 -6.79999900 3.42228100
H 7.21058200 -5.21824100 3.55666800
H 6.35297800 -7.84998600 1.47685000
C 8.54852400 -9.42840600 2.59348700
H 8.39174800 -10.49922500 2.73264500
H 7.64801400 -8.92107000 2.94623800
H 9.37258000 -9.11833900 3.23141700
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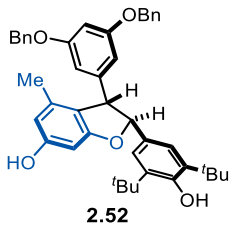

2.52

M062X / cc-pVTZ Free Energy = -1579.670672

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C 4.42676800 -7.92398700 -0.84451300
C 5.79561000 -7.74931900 -0.71798700
C 6.28118300 -6.53344300 -0.26837400
O 3.23940700 -4.64718100 0.25834400
C 5.99792700 -4.14418800 0.56599900
C 5.49214200 -3.84607900 1.98671600
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H 5.92904800 -2.90939700 2.33805800
H 5.79932400 -4.63889400 2.67101100
C 7.52842300 -4.16915100 0.63108100
C 5.60520200 -3.00458100 -0.38783100
H 4.52817900 -2.87900800 -0.44813100
H 5.99059500 -3.20104000 -1.38983600
H 6.04355100 -2.06899600 -0.03536100
C 2.00755200 -7.14569500 -0.68366500
C 1.70175200 -8.55697000 -1.19777500
H 2.13860100 -8.73172700 -2.18104200
H 0.62143600 -8.67105700 -1.28671400
H 2.06376300 -9.32355500 -0.51238000
C 1.29313900 -7.02805200 0.67714500
H 0.22515500 -7.20353400 0.54256500
H 1.40286700 -6.06524400 1.17479200
H 1.67944800 -7.78458300 1.36076500
C 1.40621400 -6.17779700 -1.72148700
H 1.87606100 -6.34160000 -2.69168800
H 1.52126900 -5.12020400 -1.48698500
H 0.33791800 -6.37268300 -1.82275400
C 6.70864900 -8.91369200 -1.01285700
C 6.79527600 -9.91300000 0.18792900
C 6.76001500 -11.36046000 -0.25614300
C 5.56971400 -12.06871000 -0.16517700
C 7.88757400 -11.96367400 -0.79777800
C 5.50783200 -13.38379100 -0.61784700
C 7.81772000 -13.27697900 -1.25113000
C 6.62966200 -14.00314800 -1.16581800
H 4.68125700 -11.61762400 0.25707200
H 8.82906100 -11.43515900 -0.86945400
H 6.58157000 -15.02149800 -1.51197700
O 8.96269400 -13.78850200 -1.76569500
O 4.30847400 -14.00116000 -0.48585700
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C 8.76985900 -8.67631000 -0.10880700
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C 9.97641600 -9.32392100 2.25915100
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C 10.03058800 -8.16218800 0.12271000
O 11.86348700 -7.99670200 1.57539300
O 8.05534200 -8.45531900 -1.24526200
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H 10.47319700 -9.56945900 3.19020300
H 12.17255300 -8.28856100 2.43909300
C 4.19535400 -15.34183600 -0.92890500
H 3.16965000 -15.63891400 -0.73547600
H 4.87337700 -15.99597800 -0.37809800
H 4.40137800 -15.42082200 -1.99768900
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H 9.94635300 -15.32791800 -2.60446700
H 8.22932100 -15.24185700 -3.05405500
H 8.70168800 -15.82156200 -1.43618700
H 7.97458700 -4.33831200 -0.34981700
H 7.89391800 -4.93600900 1.31568200
H 7.87864100 -3.20277900 0.99450600
C 8.00437500 -10.74425100 2.96066400
H 7.02406000 -10.34542500 3.22593000
H 8.58230400 -10.87899500 3.87215000
H 7.83891300 -11.72324100 2.50608400
H 6.38475100 -9.42429800 -1.91842100
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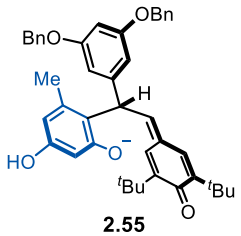

2.55

M062X / cc-pVTZ Free Energy = -1579.174357

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C 4.50750000 -7.65897100 -1.39529300
C 5.34795700 -8.24793400 -0.37635200
C 5.25761800 -7.69753300 0.95677900
O 2.87924400 -5.10325400 0.45505700
C 4.38021600 -6.09253500 2.68719100
C 2.94937400 -6.21113400 3.23603500
H 2.24389900 -5.64728700 2.63297700
H 2.92038100 -5.82830500 4.25796000
H 2.63695300 -7.25678300 3.25875400
C 5.30365900 -6.84764900 3.64619000
H 5.21811700 -6.40566800 4.63916000
H 6.34922800 -6.78022500 3.34033100
H 5.03199300 -7.90146900 3.72503800
C 4.82298300 -4.62037800 2.68580400
H 4.17465300 -4.01042700 2.06380300
H 5.84746400 -4.53304500 2.31900600
H 4.79571800 -4.23256700 3.70592500
C 2.79845900 -6.01986400 -2.26088800
C 2.99073100 -6.74323100 -3.59545200
H 4.01977200 -6.67128700 -3.95061600
H 2.34611600 -6.28110300 -4.34358500
H 2.72060200 -7.79805200 -3.52631300
C 1.31383500 -6.13903000 -1.88090200
H 0.69950000 -5.73106100 -2.68589300
H 1.09272000 -5.59746700 -0.96575900
H 1.03950300 -7.18683600 -1.74530000
C 3.16750100 -4.54357200 -2.47804900
H 4.21418800 -4.45380200 -2.77448100
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H 5.86458800 -8.15536400 1.72291400
C 6.16966200 -9.27114900 -0.71157600
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C 5.61203400 -11.89892400 0.35151100
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C 6.38993500 -14.09862400 0.98408500
H 4.77737800 -11.25823000 0.09977600
H 8.96696800 -11.87781700 0.72707200
H 6.23376800 -15.14053300 1.21647600
O 8.65084700 -14.50384300 1.35216800
O 4.05396300 -13.62218700 0.58705200
C 8.53614200 -9.65338100 -0.50451400

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C 8.82418900 -10.30816500 -1.75757300
C 9.43492300 -8.75332800 0.06354100
C 10.66451600 -8.49869500 -0.54572200
C 10.98048800 -9.15244200 -1.73688400
C 10.10064600 -10.02974600 -2.33159600
O 12.18319300 -8.93448400 -2.36220400
O 7.98848300 -11.08687000 -2.31521700
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C 9.11144200 -8.02016600 1.34375900
H 8.20757300 -7.41526500 1.23780300
H 8.94335600 -8.70817400 2.17468000
H 9.92742400 -7.35538800 1.62036000
H 11.36655200 -7.80443500 -0.10022400
C 3.74993100 -14.97283200 0.88019000
H 2.67414000 -15.07304100 0.77592300
H 4.04259100 -15.22865800 1.90024300
H 4.24810600 -15.64782000 0.18183900
C 9.99427000 -14.05884100 1.38149400
H 10.59458600 -14.92112800 1.65439600
H 10.13052200 -13.26971400 2.12314100
H 10.30725900 -13.69056400 0.40269800
H 7.18901800 -9.48884200 1.13391200
H 10.36661300 -10.51068300 -3.26445000
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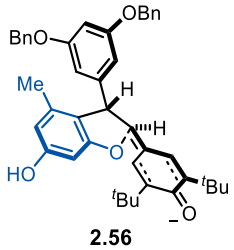

2.56

(TS, Trans Cyclization) M062X / cc-pVTZ Free Energy = -1579.173099

```
-1 1
C -4.02695100 -0.63992600 0.35535500
C -3.39875300 -1.76749900 -0.35827800
C -3.15508100 0.43377500 0.87193200
C -2.05052200 -1.77158900 -0.51646000
C -1.20012900 -0.74039400 -0.01652000
C -1.81526200 0.34514200 0.67709300
O -5.25666400 -0.59469200 0.52072300
C -3.78383700 1.61783600 1.60702900
C -4.53161700 1.13475000 2.85971600
H -5.33119400 0.44804100 2.59765100
```

H -4.95990400 1.99110700 3.38520000
H -3.84321400 0.63097500 3.54120500
C -2.72659900 2.62574400 2.06596100
C -4.75452600 2.36280800 0.67684200
H -5.55643600 1.71019000 0.34364600
H -4.22324700 2.74365000 -0.19767400
H -5.18914100 3.21432800 1.20495200
C -4.28345100 -2.89050700 -0.90037900
C -3.45982300 -3.96886000 -1.60816800
H -2.91615600 -3.56659200 -2.46445900
H -4.13238200 -4.74555300 -1.97436600
H -2.74250000 -4.43870400 -0.93328300
C -5.04210500 -3.57331300 0.24858700
H -5.65911800 -4.38269200 -0.14791000
H -5.68225200 -2.86728800 0.76960500
H -4.33844200 -4.00501200 0.96316200
C -5.28392700 -2.33174800 -1.92453900
H -4.75284400 -1.87843400 -2.76385800
H -5.92978800 -1.58402200 -1.47340300
H -5.90237400 -3.14289700 -2.31515400
C 0.15287700 -0.77789800 -0.27687400
C 1.14282300 0.16515400 0.36431800
C 2.54286800 -0.42184200 0.38923200
C 3.16168600 -0.67924500 1.60394900
C 3.20933600 -0.69786100 -0.80033600
C 4.44975200 -1.20960000 1.63161600
C 4.49082400 -1.23098500 -0.76409700
C 5.12958000 -1.49248600 0.45047900
H 2.66180600 -0.47479500 2.54173600
H 2.73243300 -0.50556300 -1.75207900
H 6.12441700 -1.90353000 0.47258900
O 5.06906100 -1.47459900 -1.96885000
O 4.97633500 -1.42524500 2.86424700
C 1.08916700 1.49885900 -0.35713900
H 0.83393900 0.30810000 1.40200400
C 0.71909700 1.38688000 -1.72494900
C 1.36514700 2.72101700 0.23161500
C 1.28927100 3.88557300 -0.53873400
C 0.93402000 3.79407800 -1.88183700
C 0.64725500 2.57776100 -2.47943300
O 0.85026600 4.91245700 -2.67068200
O 0.46079000 0.21476000 -2.19660100
H 1.06411900 5.68653600 -2.14091500
C 6.28258800 -1.96485700 2.94340400
H 6.50941900 -2.05716100 4.00080400
H 7.01091500 -1.30247600 2.47199000
H 6.33069700 -2.94922400 2.47417600

```
C 6.37608500 -2.01715200 -1.98493900
H 6.64406600 -2.13171100 -3.03054200
H 6.40454400 -2.99191100 -1.49447900
H 7.08751000 -1.34621500 -1.49991900
H -2.16643000 3.03937900 1.22479700
H -2.01772500 2.17842200 2.76514300
H -3.22266400 3.45222900 2.57630300
H -1.16673100 1.12797200 1.04427800
C 1.73091400 2.80582300 1.68989700
H 0.90506000 2.46664900 2.32064100
H 1.97255600 3.82811300 1.97419900
H 2.58844800 2.17115900 1.91974800
H -1.56361000 -2.58138900 -1.04485000
H 0.36855000 2.54163800 -3.52418000
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H 0.55183600 -1.67255400 -0.73711100
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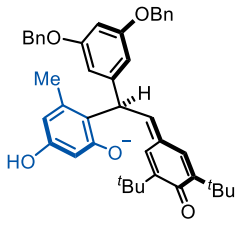


S2.8

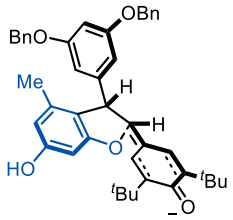
(Cis Cyclization Precursor) M062X / cc-pVTZ Free Energy = -1579.160065

-1 1

C	11.26279200	-3.55972800	7.92969600
C	9.95611700	-4.11186800	8.37904800
C	11.97207500	-4.21491200	6.79424600
C	9.45783800	-5.18079500	7.73100800
C	10.13227200	-5.82241700	6.62485000
C	11.41289900	-5.29133300	6.20932500
O	11.75057400	-2.58040700	8.48717700
C	13.30574900	-3.63789500	6.32553500
C	14.33895400	-3.67803600	7.46281100
H	14.02574500	-3.07254900	8.30839500
H	15.29513900	-3.29952800	7.09610600
H	14.49096100	-4.70466800	7.80125900
C	13.87443800	-4.44113400	5.15419800
C	13.11233400	-2.19064300	5.84416600
H	12.75109700	-1.54906500	6.64287000

H	12.40108500	-2.15875100	5.01658600
H	14.06566800	-1.79863800	5.48439200
C	9.23126300	-3.44603800	9.54667200
C	10.09758600	-3.51005600	10.81473800
H	10.31040400	-4.54802000	11.07714400
H	9.55711700	-3.05549800	11.64732500
H	11.03768600	-2.98283200	10.68081900
C	8.90577800	-1.98262800	9.20741900
H	8.35958300	-1.53049700	10.03758200
H	8.27335800	-1.93050200	8.31924400
H	9.80851200	-1.40573000	9.02909200
C	7.90891800	-4.15069200	9.85724900
H	8.06240400	-5.19383400	10.13776900
H	7.22338600	-4.11676100	9.00912800
H	7.42816500	-3.64631600	10.69588500
C	9.54104500	-6.86005500	5.99226100
C	10.09275700	-7.58012200	4.79679500
C	9.44508200	-8.94297900	4.59100900
C	9.14995700	-9.73503700	5.69699900
C	9.20190700	-9.43836000	3.31730200
C	8.60990300	-11.00441600	5.52725600
C	8.66272900	-10.71075300	3.15376700
C	8.35655400	-11.51065000	4.25289800
H	9.34346100	-9.38995900	6.70427400
H	9.41772800	-8.84308100	2.44129400
H	7.93638900	-12.49322000	4.12227300
O	8.45731000	-11.10551400	1.87072400
O	8.35608200	-11.70001500	6.66568800
C	10.14803900	-6.69397300	3.56502300
H	11.14987400	-7.78961800	4.99715700
C	11.44754300	-6.54221800	2.95763000
C	9.02663200	-6.06831600	3.03664000
C	9.12797400	-5.27408300	1.89100100
C	10.37393100	-5.10824000	1.29200400
C	11.50537100	-5.71091600	1.80253700
O	10.52107900	-4.33563300	0.16587300
O	12.48488800	-7.11125000	3.43453700
H	12.45893800	-5.56519100	1.31102300
H	8.25037100	-4.79416900	1.47438300
H	9.66321100	-3.97469600	-0.07740000
C	7.80981500	-13.00017200	6.54366800
H	7.68811200	-13.37424500	7.55530500
H	8.48181400	-13.65942500	5.99124300
H	6.83809800	-12.97398000	6.04722100
C	7.90756000	-12.39063600	1.64900700
H	7.82665700	-12.50461300	0.57261100

H	6.91674600	-12.47811100	2.09866100
H	8.55734800	-13.17135800	2.04866200
H	8.50615300	-5.60827500	8.01846000
H	13.19565700	-4.45773500	4.29955700
H	14.07764200	-5.47551400	5.43319000
H	14.81317500	-3.98467300	4.83754400
H	11.91138100	-5.79335600	5.38883000
C	7.67442100	-6.20928000	3.69047100
H	6.87939600	-5.93493300	2.99859500
H	7.49476100	-7.22999100	4.03063900
H	7.59561100	-5.55728700	4.56351600
H	8.57113000	-7.18033100	6.36331600



S2.9

(TS, Cis Cyclization) M062X / cc-pVTZ Free Energy = -1579.160065

-1 1

C	3.29741000	-0.72025100	0.58725300
C	3.35877800	-0.94193200	-0.86978700
C	2.05667800	-0.15846700	1.15380600
C	2.28338400	-0.60847700	-1.62873400
C	1.08309700	-0.05175600	-1.09098400
C	1.03421700	0.15808800	0.32067600
O	4.26075200	-1.00284800	1.31831400
C	1.94616200	0.04954500	2.66422500
C	3.01444900	1.04361100	3.14494500
H	4.01401900	0.67969800	2.92411100
H	2.92265100	1.19134800	4.22325000
H	2.87631000	2.01137200	2.65855000
C	0.57811800	0.61446500	3.05751600
C	2.11222800	-1.29114100	3.39710900
H	3.08535900	-1.73016700	3.19749300
H	1.33746400	-1.99282000	3.08033800
H	2.00873700	-1.13770600	4.47351400
C	4.62697800	-1.54207000	-1.47795700
C	5.83249300	-0.62814800	-1.20663000
H	5.66962300	0.35544700	-1.65166100

H	6.72914700	-1.05848400	-1.65816100
H	5.99995200	-0.50708300	-0.14033900
C	4.88977700	-2.93735900	-0.88976500
H	5.79079800	-3.36219800	-1.33778200
H	4.05532300	-3.60530000	-1.11264000
H	5.02263200	-2.88992100	0.18724400
C	4.50762100	-1.70144100	-2.99534600
H	4.35330200	-0.74242800	-3.49247200
H	3.68863500	-2.36838400	-3.26948400
H	5.43268500	-2.13240200	-3.38036900
C	0.05349700	0.29263600	-1.94250800
C	-1.33727200	0.72704400	-1.54022700
C	-2.22288100	-0.37542900	-0.98302500
C	-1.75919200	-1.42992400	-0.20812500
C	-3.57966000	-0.29801300	-1.27996600
C	-2.65500200	-2.36780700	0.29896700
C	-4.46915700	-1.23386500	-0.76928000
C	-4.01954900	-2.28144900	0.03471100
H	-0.71373300	-1.55180300	0.02747400
H	-3.96695700	0.50718200	-1.89056200
H	-4.70698500	-3.00984900	0.42975100
O	-5.77388400	-1.05815100	-1.09906500
O	-2.10680300	-3.35215700	1.05641400
C	-1.21118500	2.03496500	-0.76212400
H	-1.80641200	1.01345700	-2.48563900
C	-0.26893900	2.85828700	-1.45548900
C	-1.82636500	2.47660600	0.39960000
C	-1.53911700	3.76894000	0.86761000
C	-0.65266300	4.58744200	0.18098200
C	-0.01129400	4.15164000	-0.96653100
O	-0.36361400	5.85416200	0.61966500
O	0.31844100	2.35298800	-2.48970900
H	0.69433200	4.79429900	-1.47576200
H	-2.00728400	4.12636100	1.77697000
H	-0.86226400	6.02901000	1.42370800
C	-2.97011100	-4.33388000	1.59964900
H	-2.33916800	-5.01517000	2.16154600
H	-3.48627500	-4.88377500	0.81062900
H	-3.70524100	-3.88389100	2.26931600
C	-6.71692900	-1.99203600	-0.60584200
H	-7.68392300	-1.67389700	-0.98231900
H	-6.73509800	-1.99383200	0.48545700
H	-6.49967000	-2.99869900	-0.96736300
H	2.30416900	-0.75935300	-2.70064000
H	-0.23152900	-0.06416800	2.77968100
H	0.38532000	1.58432600	2.59326900

H	0.54688700	0.74753600	4.13973500
H	0.12328700	0.57345300	0.72305700
C	-2.77883400	1.64692100	1.22795800
H	-2.98154300	2.15102900	2.17142600
H	-3.72819500	1.48847600	0.71649200
H	-2.37075400	0.66084000	1.44918500
H	0.16483500	-0.00493300	-2.97806600

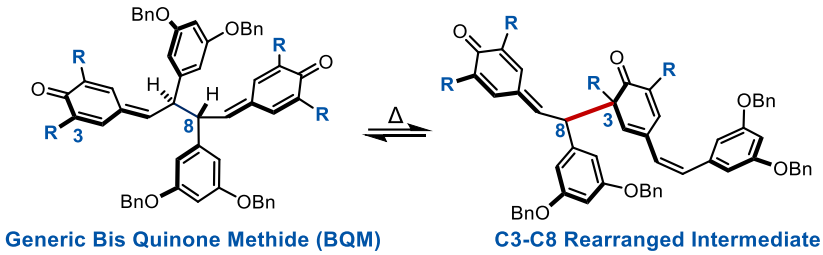


Table 2.3 Computed ground state enthalpy values for a variety of C3 substituted BQM and C3-C8 rearranged intermediates.

BQM R Group	BQM Enthalpy (Ha)	C3-C8 Enthalpy (Ha)	ΔH (kcal)	ΔH ratio (relative to ^{t}Bu)
trimethylsiliyl (TMS)	-3164.541946	-3164.528826	8.233	0.60
tert-butyldimethylsilyl (TBS)	-3635.710449	-3635.692605	11.197	0.81
tert-butyl (^{t}Bu)	-2158.876227	-2158.854212	13.814	1.00
triethyl-silyl (TES)	-3635.67433	-3635.651063	14.600	1.06
tert-butyldiphenylsilyl (TBDPS)	-5168.738514	-5168.70385	21.752	1.57
triisopropylsilyl (TIPS)	-4106.832718	-4106.796415	22.780	1.65

Optimized geometries were carried out at the M062X / cc-pVDZ level of theory, with a conductor-like polarizable continuum *model* (*CPCM*) in acetone. These computations mirror those done our previous publication.[54]

S2.10, BQM, R = TMS

0 1

C	1.41049400	-4.41852400	-1.58280200
C	0.94454700	-3.07175800	-1.98536600
C	1.91214800	-4.62436700	-0.20141800
C	1.30575800	-2.02373000	-1.21289300
C	2.15979400	-2.18148000	-0.03409300
C	2.30849100	-3.53484900	0.49765100
Si	1.90851400	-6.38308200	0.51555900

C	0.09349100	-6.85372900	0.71763700
H	-0.00447500	-7.85881200	1.15598400
H	-0.40481100	-6.85729900	-0.26393700
H	-0.43057200	-6.13805800	1.36835900
C	2.74046800	-7.66542000	-0.58691700
H	2.47540700	-8.67508100	-0.23607700
H	3.83244500	-7.56809000	-0.53212200
H	2.40929500	-7.54557900	-1.62690500
C	2.78642900	-6.32505200	2.18203000
H	3.84464600	-6.05062700	2.04562900
H	2.75531100	-7.31878600	2.65497000
H	2.31559400	-5.60996400	2.87375400
Si	-0.03566700	-2.92257500	-3.60327900
C	-1.56982600	-4.00597600	-3.46673700
H	-1.26930700	-5.05159800	-3.30401900
H	-2.16749500	-3.95508500	-4.38984400
H	-2.20536600	-3.68981800	-2.62604700
C	1.00596600	-3.45901700	-5.07694900
H	1.96990100	-2.93006600	-5.09371400
H	0.47052600	-3.24874700	-6.01591600
H	1.19608200	-4.54117500	-5.02172200
C	-0.52406600	-1.10959700	-3.79379600
H	-1.11221500	-0.75684400	-2.93250700
H	-1.13945000	-0.97976500	-4.69731100
H	0.36224000	-0.46456500	-3.89839500
H	2.75319400	-3.64838000	1.49001100
O	1.38677400	-5.35044300	-2.39236500
C	4.04543600	-1.08689800	1.30219200
C	4.15771900	0.21232300	2.08624500
C	3.81169200	1.43948300	1.51367700
C	4.00932600	2.62304500	2.22590000
C	4.61852200	2.61105900	3.47799000
C	4.99468600	1.38445400	4.03342500
C	4.71936400	0.19048300	3.36609600
H	3.37401900	1.53063100	0.52122900
H	5.03203900	-0.74416300	3.83260500
H	4.82115100	3.53951200	4.01692400
O	5.64962600	1.31442600	5.22246500
O	3.60422100	3.77456400	1.61905900
H	6.20023200	2.10884800	5.32315000
H	3.67568500	4.50419100	2.24834200
H	5.59514900	5.14583400	2.26168700
H	7.46606500	0.50584400	6.81978000
C	6.68714200	5.24406100	2.31462600
H	6.95077400	6.25398300	1.96348300
O	5.82254900	-6.19738200	0.11391100

C	5.41929500	-5.04624600	-0.49492900
C	4.81211000	-5.03523500	-1.74801100
H	7.02020000	5.12426500	3.35401900
C	5.61665800	-3.86200500	0.21624000
C	8.42875200	1.03700100	6.80121600
C	4.43737700	-3.80903000	-2.30528900
H	5.75200200	-6.92760400	-0.51478200
O	3.78435700	-3.74005400	-3.49548800
C	4.71242200	-2.61448900	-1.63886500
C	5.27240500	-2.63525600	-0.35826900
H	5.58021600	3.62861400	-0.31700200
H	4.60987000	-5.96411500	-2.28633800
C	5.38467800	-1.33537500	0.42470000
H	6.05257100	-3.95223200	1.20957400
H	3.23196200	-4.53339000	-3.59518800
H	8.23606200	2.11868400	6.74554400
H	8.96611800	0.82865300	7.73951000
H	4.40092200	-1.68016600	-2.10681400
H	9.07327500	-1.95646900	5.62012800
C	6.63795800	3.90422800	-0.45462500
C	7.12023700	1.11398100	1.22829100
Si	7.51819800	3.96246600	1.21063100
C	7.27074000	-0.23945200	1.75936600
C	7.51672000	2.20357300	1.92716000
H	6.66741000	4.89821200	-0.92715600
C	8.12631900	-0.39688600	2.93708800
C	8.02046300	1.99774300	3.30781700
C	8.48774600	0.65116400	3.70943200
O	8.04504500	2.92956200	4.11744600
Si	9.46947400	0.50194700	5.32640800
C	9.95915200	-1.31080400	5.51580400
H	8.38894900	-1.42120900	3.22274900
H	10.57469600	-1.44076300	6.41919400
H	7.10865600	3.18995400	-1.14728700
C	9.33259500	4.43432600	1.00569000
H	10.54744500	-1.66268200	4.65425800
H	9.42905400	5.43960800	0.56745600
C	11.00285600	1.58636000	5.18915500
H	9.83264000	4.43799400	1.98637300
H	10.70163800	2.63192700	5.02738800
H	11.60139500	1.53520600	6.11168700
H	9.85601100	3.71921700	0.35383000
H	11.63780200	1.27108000	4.34768700
C	6.56324000	-1.31605600	1.34501200
H	5.43337300	-0.49382500	-0.28206900
H	1.04414500	-0.99931100	-1.49915100

H	6.67407500	1.22752500	0.23658600
H	6.78494600	-2.25503600	1.85912400
C	2.86772100	-1.10537400	0.38081500
H	2.64764000	-0.16641300	-0.13403500
H	3.99615100	-1.92897600	2.00828100

S2.11, C3-C8 Rearranged Intermediate, R = TMS

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C	4.38580700	3.74812400	-0.23283400
C	3.96596700	3.35715200	1.13522400
C	4.39846700	2.72329100	-1.30834200
C	3.62881300	2.07131700	1.38173500
C	3.68411600	1.03286100	0.35381100
C	4.05541500	1.45340800	-0.99854100
Si	4.94768700	3.29230000	-3.03214400
C	3.79538100	4.64801500	-3.64621000
H	4.10086200	4.99702000	-4.64471500
H	3.82660100	5.49628400	-2.94793200
H	2.75875500	4.28429600	-3.71001400
C	6.72074600	3.91894700	-2.93608800
H	7.06137800	4.28225600	-3.91807000
H	7.40299000	3.11982600	-2.60854700
H	6.77633400	4.74490400	-2.21277400
C	4.85455600	1.79596100	-4.18195900
H	5.52302900	0.98758700	-3.84682000
H	5.16128100	2.08376200	-5.19945100
H	3.82991000	1.39685300	-4.24071900
Si	4.04018700	4.67811100	2.49410400
C	2.89762600	6.11144000	2.06432000
H	3.21002900	6.55094700	1.10634500
H	2.93640300	6.88959500	2.84217500
H	1.85595500	5.76960900	1.96944900
C	5.81889100	5.27508500	2.66407300
H	6.47423900	4.45739600	3.00118300
H	5.88432100	6.09414700	3.39716900
H	6.18107900	5.64029000	1.69223400
C	3.49612500	3.84402900	4.09819800
H	2.45468900	3.49092300	4.03774300
H	3.56496800	4.54993900	4.93995600
H	4.14457700	2.98114000	4.31983700
H	4.06785300	0.67091200	-1.76518400
O	4.72106300	4.90637000	-0.47508300
C	3.21679900	-0.93415200	1.93044300

C	2.00807100	-1.85380900	1.87944000
C	1.01102000	-1.71072100	2.84574200
C	-0.09067800	-2.56900300	2.84866000
C	-0.20897300	-3.57515400	1.88800600
C	0.77486200	-3.69191800	0.90318500
C	1.87305200	-2.83250100	0.88927700
H	1.05945300	-0.92793800	3.60170300
H	2.59871300	-2.95225300	0.08610100
H	-1.06878900	-4.25098100	1.89553100
O	0.71786700	-4.63319800	-0.07336500
O	-1.02129800	-2.37846400	3.81703100
H	-0.08773300	-5.15524900	0.03322000
H	-1.73712000	-3.01616300	3.69942600
H	3.84776400	-1.31897800	6.36981600
H	8.94827300	0.24512300	4.37023100
C	3.60768800	-1.08495100	5.32072600
H	2.51512600	-1.09547600	5.21334600
O	8.92919400	-8.41580800	-1.76358800
C	7.64561300	-7.96954000	-1.75754800
C	6.62594400	-8.64228200	-2.44003600
H	3.99059000	-0.07966300	5.09195100
C	7.37702200	-6.81067500	-1.03697000
C	8.51898600	1.09083400	3.81131500
C	5.32597100	-8.13822800	-2.39040400
H	8.98027400	-9.22161100	-2.29307200
O	4.28935700	-8.74366100	-3.02679600
C	5.04555100	-6.97625600	-1.67224900
C	6.07073100	-6.30461900	-0.99621100
H	2.56306600	-3.93594100	3.69076700
H	6.84567700	-9.55463800	-3.00189800
C	5.72173100	-5.07773000	-0.26465400
H	8.20209300	-6.33192600	-0.51247500
H	4.61781400	-9.52606400	-3.48777400
H	7.57273800	1.38510300	4.28711900
H	9.22410900	1.93433100	3.87204600
H	4.02050800	-6.60565700	-1.65287300
H	10.21961100	-0.84156800	1.72849300
C	3.53643300	-4.00298700	4.19920100
C	4.94199100	-2.82168500	1.57625300
Si	4.44682800	-2.35444300	4.21749900
C	6.18945000	-3.02586000	1.08429900
C	4.55757600	-1.63483100	2.37186200
H	4.14271800	-4.77779000	3.70633200
C	7.18952000	-1.97948600	1.27269800
C	5.62506500	-0.56964900	2.50598800
C	6.95981400	-0.81334000	1.92804200

O	5.37736800	0.48214800	3.09499300
Si	8.20003700	0.62363800	2.01571700
C	9.80273500	0.03527200	1.20880600
H	8.17331800	-2.15644400	0.82334400
H	10.55588400	0.83734700	1.24728600
H	3.35933200	-4.32107300	5.23888500
C	6.21959000	-2.61695600	4.79156700
H	9.64930800	-0.22701200	0.15048100
H	6.78790700	-3.22230200	4.06910800
C	7.47353500	2.06761700	1.05259900
H	6.73681000	-1.65529900	4.92828200
H	6.52200000	2.37326000	1.51279300
H	8.15702500	2.93117600	1.04823500
H	6.21615300	-3.14784800	5.75651600
H	7.27230700	1.77954100	0.00857500
C	6.57578700	-4.23844700	0.34363500
H	3.34548400	1.77204500	2.39097900
C	3.47503000	-0.28374800	0.59778100
H	3.57738500	-0.97050300	-0.25032900
H	3.02191300	-0.16564500	2.68589200
H	4.65200600	-4.84457000	-0.25001000
H	7.65146900	-4.42968600	0.28261800
H	4.19012800	-3.60476800	1.46698200

S2.12, BQM, R = TBS

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C	0.13955300	-4.36603700	-1.59102700
C	0.32192400	-3.13304500	-2.39475800
C	0.62588100	-4.40166500	-0.18635800
C	1.00877700	-2.10470300	-1.84776100
C	1.66925300	-2.19533700	-0.54752400
C	1.38903400	-3.37785400	0.26277000
Si	0.15692300	-5.90138500	0.88765600
C	1.40343000	-7.31743800	0.55866000
C	-1.61510000	-6.43614900	0.54407600
H	-1.95785800	-7.13903500	1.31903800
H	-1.69541500	-6.91204000	-0.44230700
H	-2.28548700	-5.56290000	0.55399700

C	0.28534100	-5.35589400	2.69325600
H	1.28504200	-4.97646000	2.95242900
H	0.06789600	-6.20321300	3.36255600
H	-0.44887100	-4.56321900	2.90423000
Si	-0.29989500	-3.10512400	-4.19048200
C	-2.21477800	-3.08858900	-4.27752000
C	0.41171000	-4.60115900	-5.09622700
H	1.51169000	-4.57089100	-5.04857000
H	0.11531400	-4.60924100	-6.15649200
H	0.07424000	-5.52886600	-4.61471700
C	0.39693200	-1.53172200	-4.97016900
H	-0.01093900	-0.61979000	-4.50595600
H	0.15486900	-1.49774700	-6.04319200
H	1.49359200	-1.51965300	-4.86750600
H	1.77515200	-3.39262000	1.28580300
O	-0.41007500	-5.35248600	-2.07908500
C	3.66950700	-1.35056700	0.79400600
C	3.76824300	-0.16212600	1.72998700
C	3.56855600	1.14361500	1.27419700
C	3.76303800	2.21474800	2.14706000
C	4.17899800	2.00258300	3.46244900
C	4.36959400	0.69343400	3.90895200
C	4.15186300	-0.38540400	3.05194600
H	3.25426500	1.36751600	0.25502000
H	4.32127300	-1.39341500	3.43193400
H	4.34830800	2.84726300	4.13551700
O	4.76821100	0.40363600	5.17328100
O	3.54459500	3.46193600	1.64867500
H	4.95727400	1.21988100	5.65535200
H	3.67083400	4.11473400	2.34982100
H	5.75931500	4.35218200	2.69672500
H	10.46426200	-2.68602200	3.86596000
C	6.83844800	4.53480300	2.59492700
H	6.98160100	5.59311900	2.32619200
O	4.64992400	-6.28099400	-1.12255500
C	4.55239700	-4.99660600	-1.54737200
C	4.12493800	-4.66841400	-2.83553500
H	7.33183400	4.33677500	3.55654900
C	4.89699000	-3.99852700	-0.63187800
C	9.88366200	-2.49938600	4.78280100
C	4.10774700	-3.32650800	-3.22032700
H	4.20329900	-6.86626300	-1.74944800
O	3.69839100	-2.92875200	-4.45436700
C	4.50331600	-2.32819200	-2.33109400
C	4.86494100	-2.66011900	-1.02428100
H	5.42484900	3.16103500	-0.03981300

H	3.82861200	-5.45302700	-3.53697400
C	5.04164700	-1.53862900	-0.01671900
H	5.17200200	-4.31062300	0.37554900
H	3.46246000	-3.70385300	-4.98106300
H	8.98589000	-3.13518400	4.75658100
H	10.49627000	-2.82257100	5.63865600
H	4.46828200	-1.29087600	-2.66572900
H	11.53262400	0.28321400	3.91293100
C	6.44584300	3.49880300	-0.27564800
C	6.88443900	0.61645800	1.12560000
Si	7.54285800	3.40304100	1.26000900
C	6.92666300	-0.79054700	1.51791900
C	7.51358200	1.58734000	1.82600600
H	6.37687100	4.53926000	-0.62753800
C	7.78979300	-1.14009500	2.64526200
C	8.24806200	1.21827600	3.06144400
C	8.40655000	-0.21497500	3.41580400
O	8.73553100	2.09360100	3.77534200
Si	9.46799200	-0.66037500	4.92994700
C	11.07088900	0.32910500	4.91142400
H	7.88092800	-2.20698000	2.87570900
H	11.78824900	-0.08198400	5.63817000
H	6.84301300	2.88961000	-1.10315100
C	9.33501100	3.92663100	0.80533900
H	10.87859100	1.38474500	5.14643300
C	8.47646500	-0.35726400	6.54119900
C	6.15583300	-1.75284500	0.95583400
H	5.19197900	-0.59991100	-0.56799600
H	1.18616200	-1.18762100	-2.41934700
H	6.32549600	0.87892400	0.22533100
H	6.28105900	-2.77238500	1.33476500
C	2.58363800	-1.24890000	-0.22874000
H	2.65791300	-0.39314400	-0.90938000
H	3.54217700	-2.26263300	1.39307300
C	0.85245400	-8.63135600	1.12602100
H	-0.07176600	-8.93802000	0.61203200
H	0.63161100	-8.55220400	2.20320400
H	1.59145400	-9.44230400	1.00054600
C	2.72348400	-6.97019000	1.25839400
H	2.60598300	-6.97034500	2.35341200
H	3.09929200	-5.98132200	0.94746700
H	3.50546000	-7.70506500	1.00130700
C	1.64177400	-7.47762700	-0.94780100
H	2.36386500	-8.29750500	-1.12648400
H	2.04027000	-6.54866300	-1.38790100
H	0.71360500	-7.71527900	-1.48848200

C	-2.76665300	-2.22093300	-3.13961200
H	-2.54463700	-2.66134500	-2.15508800
H	-3.86306000	-2.12627700	-3.22895800
H	-2.34294600	-1.20280500	-3.15448200
C	-2.64058500	-2.48484500	-5.62391300
H	-2.33081200	-1.43262000	-5.71934600
H	-3.73969700	-2.52018000	-5.72167500
H	-2.21711000	-3.04195500	-6.47636200
C	-2.79120700	-4.50554100	-4.16558000
H	-2.48342600	-4.99973900	-3.23355000
H	-2.46153400	-5.13925100	-5.00433500
H	-3.89440400	-4.46323500	-4.19445400
C	9.26339300	5.03965400	-0.25095100
H	8.81136900	4.68812600	-1.19114500
H	10.27986300	5.40269200	-0.48293000
H	8.67880100	5.90543400	0.10310100
C	10.09432300	4.45995800	2.02710500
H	9.60639100	5.35535300	2.44415700
H	11.11866000	4.74828200	1.73135300
H	10.15895100	3.70958800	2.82661000
C	10.09071900	2.72758700	0.21918400
H	9.55637400	2.28046300	-0.63562500
H	10.23789000	1.93750500	0.97244200
H	11.08705600	3.04243200	-0.13761700
C	7.88695200	1.05779300	6.56685200
H	8.66014900	1.83421600	6.47068900
H	7.34891800	1.21866000	7.51936500
H	7.17950900	1.20159200	5.73618300
C	7.33149600	-1.37390600	6.63067600
H	6.65005300	-1.29013000	5.76923100
H	6.73230700	-1.19031900	7.54034900
H	7.70661000	-2.40788700	6.68652700
C	9.41562200	-0.53317300	7.74191900
H	10.22297300	0.21575600	7.73798200
H	9.87864100	-1.53328100	7.76032000
H	8.85366700	-0.41323500	8.68487900

S2.13, C3-C8 Rearranged Intermediate, R = TBS

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C	4.19107000	3.79958600	-0.62149400
C	3.91428800	3.42387900	0.79254900
C	4.16990400	2.75359100	-1.67700200
C	3.66331900	2.12634900	1.08185200
C	3.63776400	1.07751800	0.06399500

C	3.89191900	1.48020100	-1.31831000
Si	4.54738500	3.26598200	-3.46797400
C	3.63114700	4.84573300	-3.92587200
H	3.68329200	5.02142400	-5.01139400
H	4.05504600	5.70714500	-3.39285800
H	2.57068300	4.76221900	-3.64271100
C	6.44107100	3.46437800	-3.68452500
C	3.93411900	1.86545700	-4.58322700
H	4.40727500	0.89980700	-4.34949700
H	4.14979200	2.09590700	-5.63823500
H	2.84400100	1.74739500	-4.48178900
Si	4.01570600	4.85272600	2.05413100
C	2.74575400	6.15993100	1.56540900
H	2.93565000	6.46234800	0.52617900
H	2.82480900	7.04870100	2.20968900
H	1.71831000	5.77156300	1.63320400
C	5.75626700	5.57697700	1.96301700
H	6.51786100	4.83300200	2.24073700
H	5.86005500	6.44694500	2.62944800
H	5.94831300	5.90102000	0.93032700
C	3.66566500	4.25387100	3.84643300
H	3.85477700	0.68457800	-2.07016500
O	4.44026300	4.96645000	-0.91742500
C	3.21069400	-0.87872900	1.67487300
C	1.89844300	-1.64308300	1.70265300
C	0.98156500	-1.34551200	2.71302300
C	-0.24081600	-2.01718400	2.77090000
C	-0.56041400	-2.98787300	1.82031900
C	0.34565100	-3.25577400	0.79156500
C	1.56529100	-2.58213900	0.72137100
H	1.18816500	-0.57845500	3.45893900
H	2.22148500	-2.81108900	-0.11733500
H	-1.51496600	-3.51943200	1.86955300
O	0.09155500	-4.17318600	-0.17547600
O	-1.08254200	-1.68661500	3.78219300
H	-0.78276800	-4.55630300	-0.02874300
H	-1.89820700	-2.19667600	3.69589800
H	4.05840600	-1.37794500	6.00669600
H	9.10732000	-0.11704000	3.72335500
C	3.70093900	-1.22897300	4.97607500
H	2.61295000	-1.38085400	4.96473400
O	7.94181500	-7.70570100	-3.86068100
C	7.02130800	-7.76939900	-2.86336200
C	6.33135100	-8.95005700	-2.56789100
H	3.93586500	-0.19553100	4.67947800
C	6.78072600	-6.60392900	-2.14275400

C	8.62068200	0.76983900	3.28941000
C	5.38958000	-8.94891300	-1.53832100
H	8.00521500	-8.56963900	-4.28720500
O	4.68230100	-10.05902900	-1.20199000
C	5.14056700	-7.78650000	-0.80980100
C	5.84039800	-6.61068200	-1.10387900
H	6.52364700	-9.86091900	-3.14206600
C	5.55427500	-5.41606800	-0.29464600
H	7.32581200	-5.70497900	-2.42553600
H	4.94964300	-10.78794500	-1.77625100
H	7.69948100	0.97780400	3.85251100
H	9.29899100	1.62879100	3.40616500
H	4.40145100	-7.81851400	-0.00942500
C	3.94702800	-4.23250600	4.07951900
C	4.77931100	-2.84353700	1.10217600
Si	4.60217600	-2.43842600	3.84883600
C	5.98351900	-3.08416300	0.52265800
C	4.52115600	-1.69142100	1.98867200
C	7.02987100	-2.07451300	0.64786800
C	5.64464300	-0.67268000	2.06723600
C	6.91595700	-0.92550900	1.36298200
O	5.47903500	0.35944800	2.71661900
Si	8.17657500	0.50774200	1.47414900
C	9.77000100	0.13551700	0.47084000
H	7.95103400	-2.27542200	0.09357400
C	6.43480800	-2.45906300	4.29988000
H	7.03369300	-2.98861600	3.54341600
C	7.32564600	2.04175000	0.77881300
H	6.82054000	-1.43352700	4.39559800
H	6.55261200	2.37180500	1.48811700
H	8.03634700	2.86728000	0.61811100
H	6.57099300	-2.97067500	5.26549800
H	6.82678400	1.82174900	-0.17980400
C	6.27782300	-4.28361400	-0.27498000
H	3.49854600	1.81941600	2.11325000
C	3.41524100	-0.23258700	0.32984100
H	3.43584600	-0.92323400	-0.52137900
H	3.15573800	-0.10769000	2.44904700
H	4.67666600	-5.50193000	0.35399300
H	7.18677800	-4.22678400	-0.88163000
H	3.96004700	-3.54859400	0.94994000
C	3.78056900	-4.40846100	5.60103200
H	4.70521400	-4.17817600	6.15468700
H	3.51855100	-5.45737300	5.82191700
H	2.97628200	-3.77178100	5.99975800
C	4.98314700	-5.25336300	3.58770600

H	5.92999400	-5.17243300	4.14266100
H	5.21675300	-5.13637900	2.51837500
H	4.59671500	-6.27654000	3.73837000
C	2.59480000	-4.52233600	3.42069300
H	2.23509900	-5.51435600	3.74659900
H	1.82833300	-3.78012200	3.69350000
H	2.66131800	-4.54366600	2.32309600
C	10.47421700	-1.13473600	0.96701000
H	11.41344300	-1.29018300	0.40732100
H	10.73626600	-1.05704700	2.03393600
H	9.86388200	-2.04128300	0.84348400
C	10.73482100	1.31594300	0.67123800
H	10.29695800	2.26884900	0.33587700
H	11.65514900	1.15066800	0.08407100
H	11.03107500	1.42779700	1.72567400
C	9.45648000	0.02703100	-1.02766400
H	8.75586900	-0.78988200	-1.25966700
H	10.38317300	-0.15700200	-1.59954400
H	9.01158700	0.95955300	-1.40890000
C	2.26966500	3.62958400	3.98172200
H	2.07558600	3.36628300	5.03688200
H	2.15115100	2.71202500	3.38634300
H	1.48078000	4.33088200	3.66705500
C	6.72357500	4.10713700	-5.04888200
H	6.29263000	3.52325500	-5.87892700
H	7.81236900	4.17238900	-5.22116800
H	6.31639300	5.12867300	-5.10430400
C	7.03206000	4.34689400	-2.57839600
H	6.55220500	5.33604200	-2.53722000
H	8.11315800	4.49216700	-2.75484100
H	6.91071200	3.88492600	-1.58615800
C	7.10161300	2.08143500	-3.62670500
H	6.85611900	1.55318100	-2.68952100
H	8.20058600	2.18078900	-3.67572000
H	6.78878800	1.44238400	-4.46743300
C	3.71773400	5.48863200	4.76129900
H	2.94149100	6.22524900	4.50157800
H	4.69580700	5.99263200	4.71535700
H	3.55091500	5.18559300	5.81005800
C	4.73712000	3.26051500	4.31807900
H	5.73819800	3.72097900	4.30668600
H	4.78907700	2.34924400	3.70395200
H	4.53187200	2.95214600	5.35956800

S2.14, BQM, R = ^{t}Bu

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C	1.03791300	-4.56514700	-1.49726200
C	0.85684100	-3.19301100	-2.06341900
C	1.81400200	-4.72787000	-0.22636500
C	1.40928500	-2.15048700	-1.40892600
C	2.24583500	-2.30266800	-0.22642200
C	2.38594000	-3.63885400	0.33284900
C	1.90259500	-6.12191900	0.39903500
C	0.48613400	-6.60417400	0.76253700
H	0.54679900	-7.59426400	1.24085400
H	-0.14747200	-6.68441500	-0.12860400
H	0.01423500	-5.90983600	1.47466200
C	2.55380900	-7.12141500	-0.57405500
H	2.62027000	-8.10832600	-0.08952000
H	3.57485400	-6.79269600	-0.81629000
H	1.97666000	-7.21856400	-1.49946400
C	2.74627500	-6.10599700	1.67819200
H	3.78500300	-5.80301800	1.47414800
H	2.77226600	-7.12021100	2.10298600
H	2.31954200	-5.43682300	2.44062800
C	0.08418100	-3.03539800	-3.37304100
C	-1.35476600	-3.55816400	-3.21805100
H	-1.36742500	-4.62297100	-2.96085900
H	-1.89936900	-3.41741500	-4.16487800
H	-1.88554400	-2.99590500	-2.43417700
C	0.81595900	-3.81012100	-4.48533900
H	1.85411900	-3.45223700	-4.57092000
H	0.31035500	-3.63956400	-5.44869000
H	0.82212300	-4.88666800	-4.27774200
C	0.00835500	-1.56556900	-3.79845600
H	-0.50889400	-0.94951100	-3.04716400
H	-0.55723800	-1.49180500	-4.73861000
H	1.00813200	-1.14006200	-3.97407600
H	2.97072100	-3.74243700	1.24444000
O	0.55278300	-5.54065100	-2.05980000
C	4.01020800	-1.17493300	1.24518300
C	3.97537800	0.06287300	2.12294800
C	3.70394300	1.32351500	1.58562200
C	3.81051400	2.45660600	2.39125700
C	4.21330300	2.35329700	3.72292400
C	4.48333800	1.08932300	4.25233200
C	4.34466200	-0.05264800	3.46296600
H	3.41926500	1.47233200	0.54455100
H	4.57893200	-1.02078300	3.90655900
H	4.31744800	3.24792800	4.34287100
O	4.88936700	0.91111800	5.53550300

O	3.53228500	3.65302900	1.80636200
H	4.99554000	1.77277900	5.95979900
H	3.67073300	4.36327500	2.44680500
H	5.85450400	4.37077800	2.54288400
H	7.57709500	1.03061500	6.29657000
C	6.87543400	4.69975200	2.30050700
H	6.80865700	5.68676300	1.81621900
O	5.89724500	-6.07509000	-0.07887300
C	5.61945600	-4.87876800	-0.66418200
C	5.21721600	-4.77572300	-1.99604200
H	7.45279000	4.79680500	3.22579800
C	5.72603400	-3.74547400	0.14115600
C	8.61513000	1.38881600	6.21080000
C	4.94766800	-3.51183700	-2.52590000
H	5.75842600	-6.78551300	-0.71903900
O	4.54216000	-3.33389700	-3.80927100
C	5.08637500	-2.36966400	-1.73681700
C	5.45518600	-2.48490800	-0.39665500
H	5.64393300	3.38137000	0.25253100
H	5.11313400	-5.67049300	-2.61579700
C	5.42042100	-1.24690900	0.48083600
H	6.01021400	-3.89404000	1.18240400
H	4.43547600	-4.19566500	-4.23322200
H	8.60860200	2.46536400	6.00321900
H	9.12096800	1.21839400	7.17405200
H	4.85249900	-1.40159800	-2.18076800
H	8.42355200	-1.28130800	5.69937500
C	6.68250600	3.68465300	0.04815700
C	7.04420100	1.21737300	1.39298900
C	7.52663700	3.70063300	1.32701700
C	7.18483400	-0.11881900	1.95211000
C	7.61591300	2.30651900	1.95218400
H	6.65608600	4.69892100	-0.37648300
C	8.02169000	-0.27085100	3.13441400
C	8.39232300	2.14391600	3.22289900
C	8.57395200	0.77178500	3.78888300
O	8.87758400	3.11947000	3.78523800
C	9.34691000	0.61431700	5.09834600
C	9.42319500	-0.85550700	5.52370600
H	8.13270100	-1.28745600	3.51397800
H	9.98887700	-0.92913700	6.46381700
H	7.10915200	3.01571000	-0.71453000
C	8.94280400	4.18341900	0.96307300
H	9.94057600	-1.47139000	4.77236100
H	8.88162100	5.17352000	0.48484100
C	10.78568800	1.13746700	4.94310300

H	9.57667900	4.26383200	1.85400200
H	10.79801200	2.20227700	4.68590500
H	11.33049700	0.99686200	5.88983300
H	9.41471400	3.48930100	0.25074200
H	11.31647400	0.57534900	4.15913400
C	6.51679100	-1.20640600	1.49710200
H	5.46032200	-0.35909800	-0.16563600
H	1.29864200	-1.13387700	-1.78858500
H	6.45914100	1.32087300	0.48156900
H	6.71715300	-2.14756100	2.01800400
C	2.91405700	-1.21523300	0.22867800
H	2.71413800	-0.27407800	-0.29239800
H	3.97018800	-2.06287000	1.89146600

S2.15, C3-C8 Rearranged Intermediate, R = ^{t}Bu

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C	4.41590100	3.71143500	-0.21193500
C	4.01556200	3.34180100	1.18295000
C	4.62874400	2.62023800	-1.21536400
C	3.81028300	2.04116900	1.48231100
C	4.00963200	0.97042100	0.51766200
C	4.41965700	1.34361000	-0.83059200
C	5.07910500	2.99957800	-2.62654600
C	4.02132500	3.89640400	-3.29499000
H	4.34157200	4.13844100	-4.32062600
H	3.88434300	4.83090200	-2.73956800
H	3.05492600	3.37213500	-3.35466800
C	6.42931900	3.73679900	-2.56279700
H	6.76534600	3.97556400	-3.58412400
H	7.19468300	3.09884000	-2.09322700
H	6.34751500	4.66942600	-1.99328100
C	5.26407300	1.75643300	-3.50259700
H	6.03019100	1.07961500	-3.09417800
H	5.59168800	2.06788500	-4.50510600
H	4.32541500	1.19314000	-3.61662300
C	3.87085800	4.45303800	2.22362900
C	2.76062700	5.43235100	1.80316300
H	2.99863700	5.91773400	0.84996700
H	2.64481200	6.20876900	2.57578900
H	1.79933800	4.90455800	1.70414300
C	5.20735900	5.20387600	2.37138700
H	6.00520300	4.51127700	2.68195800
H	5.10712600	5.97726100	3.14909600
H	5.50080600	5.68702400	1.43269100
C	3.50651100	3.87748800	3.59667300

H	2.53292700	3.36386100	3.57819900
H	3.43629900	4.69952200	4.32373800
H	4.26879500	3.16817700	3.95441300
H	4.56408400	0.51929700	-1.53068200
O	4.56709900	4.88585100	-0.52724600
C	3.49763300	-0.95942600	2.13728400
C	2.29160900	-1.86492900	1.92314300
C	1.14075100	-1.67570700	2.68908700
C	0.03408500	-2.50849100	2.50585300
C	0.06345500	-3.53560900	1.56033500
C	1.20566700	-3.69690700	0.77310500
C	2.30625200	-2.85989700	0.93991100
H	1.07178300	-0.88349100	3.43393600
H	3.15885700	-3.00389700	0.27865500
H	-0.80065300	-4.19258800	1.42764800
O	1.30686600	-4.66265800	-0.17876100
O	-1.05128400	-2.27425300	3.28570700
H	0.48661800	-5.17195300	-0.20808300
H	-1.74964800	-2.89955700	3.05323300
H	3.81846100	-1.38832500	6.19713700
H	9.03362700	-0.19809000	3.85350200
C	3.76645100	-1.09256300	5.13796900
H	2.70484600	-1.09371300	4.85490700
O	8.52740300	-8.04846600	-2.43661200
C	7.26524900	-7.61130900	-2.18630500
C	6.14327600	-8.22847600	-2.75045500
H	4.16586800	-0.07656600	5.04189000
C	7.12474300	-6.52035800	-1.33478500
C	8.57999600	0.71453900	3.43567800
C	4.87139600	-7.73965600	-2.44921200
H	8.48596700	-8.80750800	-3.03196600
O	3.74223000	-8.29645500	-2.96109700
C	4.71771500	-6.64606800	-1.59794900
C	5.84536900	-6.03003700	-1.04258900
H	2.91344300	-3.48959400	3.82352400
H	6.26273500	-9.08833200	-3.41595300
C	5.62457700	-4.87236500	-0.16383500
H	8.02483600	-6.08413000	-0.90468400
H	3.98815700	-9.03400900	-3.53389100
H	7.75315400	1.02942900	4.08306200
H	9.34480900	1.50657900	3.43795500
H	3.71376300	-6.27941600	-1.38098300
H	9.83181500	-0.78647500	1.50244700
C	3.84614300	-3.46376000	4.40442200
C	5.16570600	-2.83919400	1.97873300
C	4.56573400	-2.10654600	4.30972400

C	6.26789700	-2.89604100	1.20664900
C	4.77521800	-1.64970300	2.79757100
H	4.48895300	-4.29236600	4.07518000
C	7.22763400	-1.79033300	1.24240100
C	5.82436400	-0.51304700	2.77224200
C	7.07512000	-0.66379700	1.97535600
O	5.58167200	0.51532400	3.38388400
C	8.10094400	0.46924800	1.99335300
C	9.32596100	0.12228100	1.14160100
H	8.12101300	-1.91385400	0.62744000
H	10.04603400	0.95144500	1.19430200
H	3.58928800	-3.64748400	5.45854600
C	5.95835400	-2.27698100	4.94135000
H	9.06000400	-0.02078800	0.08324000
H	6.60769000	-2.89736400	4.30215800
C	7.47148900	1.75291300	1.42007700
H	6.44987600	-1.30754100	5.10764100
H	6.62591200	2.09208900	2.03000000
H	8.22875200	2.55266700	1.39234600
H	5.86369700	-2.77871000	5.91636300
H	7.11393400	1.58490800	0.39138700
C	6.55945600	-4.03926900	0.32322900
H	3.53153400	1.75692400	2.49342800
C	3.88461100	-0.34603500	0.81542000
H	4.10373700	-1.05599300	0.01105000
H	3.21135700	-0.16766100	2.83691700
H	4.57404800	-4.68741300	0.08187300
H	7.60679300	-4.17177600	0.03494500
H	4.49409400	-3.69498700	2.00747200

S2.16, BQM, R = TES

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C	1.24431700	-4.00980000	-1.66266200
C	0.78116600	-2.63663600	-1.97622700
C	1.69647600	-4.31886100	-0.28300800
C	1.12810900	-1.65152600	-1.11620100
C	1.97165400	-1.89817200	0.05390300
C	2.09231500	-3.28590300	0.49635100
Si	1.58850000	-6.12643900	0.29760400
C	-0.26295000	-6.52626400	0.22415900
C	2.63261200	-7.29389600	-0.76585300
C	2.20816600	-6.20906600	2.08600300
Si	-0.19568700	-2.31384300	-3.57820700
C	-1.91335100	-3.10080700	-3.42186200

C	0.67583600	-2.98971200	-5.11422000
C	-0.36953800	-0.43344700	-3.74917300
H	2.48750900	-3.46860500	1.49917000
O	1.25431800	-4.88635600	-2.53237700
C	3.90866000	-0.97462900	1.41825600
C	4.06671000	0.18320400	2.38690900
C	3.79315300	1.49632000	1.99780100
C	4.08780900	2.55034900	2.86415800
C	4.68322500	2.31472000	4.10336900
C	4.94049400	0.99657600	4.49082000
C	4.61503900	-0.06507600	3.64534800
H	3.35008400	1.74714400	1.03519400
H	4.84622000	-1.07855400	3.97504800
H	4.92572100	3.14641700	4.77042300
O	5.50397800	0.68878500	5.68544500
O	3.77389100	3.80299200	2.43814900
H	5.80097800	1.50071700	6.12022000
H	4.01232700	4.44147500	3.12342100
C	6.92189000	5.37158700	1.95402500
O	5.84149400	-5.84012800	-0.38966200
C	5.34975500	-4.65181200	-0.83851100
C	4.65489100	-4.54115200	-2.04053200
C	5.55363200	-3.53601500	-0.02406800
C	8.68206700	1.23000600	6.43664600
C	4.20502500	-3.28343400	-2.45081000
H	5.69629200	-6.51648500	-1.06472000
O	3.49052100	-3.12521000	-3.59688500
C	4.47119200	-2.15240600	-1.67957900
C	5.11262500	-2.27853600	-0.44387900
H	4.45378500	-5.41871100	-2.65956100
C	5.20663800	-1.06194800	0.46329000
H	6.07154800	-3.69696400	0.91997500
H	2.94161500	-3.91626700	-3.73446900
H	4.09761800	-1.18955100	-2.02943700
C	6.74479200	4.04737300	-0.83527900
C	7.10471600	1.31624800	1.05371600
Si	7.73268500	4.12941500	0.78180100
C	7.20116100	-0.00689900	1.66623100
C	7.73656400	2.39798600	1.56482600
C	8.12388200	-0.15482500	2.79070300
C	8.51773800	2.24793000	2.81908100
C	8.73862300	0.89386200	3.38268000
O	8.97975800	3.24058000	3.38120000
Si	9.77441300	0.73452000	4.96754900
C	10.23977500	-1.09064200	5.17821000
H	8.24481600	-1.16838300	3.18923800

C	9.52605400	4.60511500	0.41771000
C	11.34834800	1.77564200	4.86770000
C	6.41684900	-1.06157800	1.34039000
H	5.18228800	-0.15522200	-0.15757900
H	0.87381700	-0.60709700	-1.32506800
H	6.51196600	1.41258300	0.14047600
H	6.59930300	-1.98671700	1.89668700
C	2.70292400	-0.86971400	0.54298500
H	2.50202700	0.11858900	0.11688400
H	3.89316800	-1.91746000	1.98466800
C	0.93566000	0.26665800	-4.14651500
H	-0.76763600	-0.01876900	-2.80684600
H	-1.14810200	-0.23551600	-4.50525500
H	1.75341500	0.02979900	-3.44685100
H	0.82616600	1.36082100	-4.17843500
H	1.27013900	-0.06204600	-5.14235900
C	-0.10691100	-2.67476000	-6.39455700
H	0.79162000	-4.07786800	-4.98502200
H	1.68975300	-2.56171400	-5.16526100
H	-1.12409900	-3.09652000	-6.35887200
H	0.38718800	-3.08358300	-7.28823300
H	-0.21093000	-1.58835800	-6.54531100
C	-1.94097800	-4.61907300	-3.63211800
H	-2.57525900	-2.60557800	-4.15359100
H	-2.31480600	-2.84084900	-2.42788000
H	-1.61594300	-4.88145400	-4.65109000
H	-2.95098200	-5.03125000	-3.49007100
H	-1.25845200	-5.13527500	-2.94158700
C	-0.65568600	-7.98495200	0.47883800
H	-0.63056500	-6.20626500	-0.76516800
H	-0.75365500	-5.86425400	0.95872700
H	-0.29865400	-8.63774200	-0.33143700
H	-1.74763400	-8.10546000	0.53665000
H	-0.23311700	-8.36591000	1.42216000
C	3.72005300	-5.99896100	2.23498300
H	1.92354800	-7.19486000	2.49311300
H	1.64984000	-5.47074400	2.68752500
H	4.29167300	-6.73416200	1.64903000
H	4.04487800	-6.07989200	3.28311600
H	4.02996200	-5.00979500	1.86203000
C	2.80308700	-8.70254400	-0.18413900
H	3.61835300	-6.81329000	-0.86096200
H	2.19591100	-7.31815300	-1.77634700
H	3.27410300	-8.67099000	0.81080600
H	3.43575200	-9.33414700	-0.82633900
H	1.83928900	-9.21845500	-0.06929100

C	12.30933800	1.51957000	6.03342300
H	11.04940400	2.83337700	4.82256400
H	11.84375200	1.56200200	3.90524700
H	11.82991200	1.72912100	7.00290300
H	13.20652300	2.15288600	5.97021200
H	12.64815400	0.47169800	6.05839100
C	11.21125200	-1.60867300	4.11201400
H	9.31764600	-1.69723800	5.19412300
H	10.68088200	-1.20654200	6.18333400
H	10.79280500	-1.49818300	3.09934600
H	11.45790400	-2.67079500	4.25722400
H	12.15671400	-1.04444300	4.13108600
C	8.00301400	2.59812000	6.32181000
H	9.29244900	1.18126900	7.35460000
H	7.92016700	0.43710500	6.52933300
H	8.73630300	3.41401600	6.24520900
H	7.36306800	2.81173700	7.19584200
H	7.39216500	2.66250100	5.40642800
C	6.85199200	6.78903700	1.37627200
H	7.49020300	5.35153900	2.89662600
H	5.91006900	4.99376600	2.17387900
H	7.85800000	7.18182200	1.16276300
H	6.36684100	7.49432800	2.06782100
H	6.28471100	6.81223800	0.43192100
C	5.22916600	3.93588500	-0.63522400
H	7.11874900	3.20241800	-1.43928800
H	6.98435600	4.95354900	-1.41835700
H	4.96697200	3.04526500	-0.04280700
H	4.68940100	3.87641700	-1.59243700
H	4.83151700	4.79838500	-0.07943500
C	10.26022000	3.58065600	-0.45384000
H	10.03779700	4.72607300	1.38573700
H	9.52941100	5.59393500	-0.07211100
H	10.28012000	2.59119100	0.02932500
H	11.30185600	3.87687100	-0.64629800
H	9.76728100	3.45613300	-1.43095500

S2.17, C3-C8 Rearranged Intermediate, R = TES

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C	4.50004600	3.76527400	-0.44626400
C	4.03895100	3.43566300	0.92457700
C	4.64084000	2.68068500	-1.44981100
C	3.75120200	2.14819700	1.22729900
C	3.86728300	1.06136100	0.25628300
C	4.32080300	1.41766300	-1.08795600

Si	5.28407400	3.14674900	-3.17901800
C	4.35756000	4.62795500	-3.92338800
C	7.15539200	3.43395100	-3.08302300
C	4.97432800	1.64918800	-4.30369600
Si	3.87253200	4.82080000	2.21823400
C	2.34184500	5.87332700	1.84143800
C	5.42579600	5.90673200	2.27464300
C	3.62188100	3.94495200	3.88421000
H	4.40578400	0.59396700	-1.80514200
O	4.76713200	4.92591500	-0.75418400
C	3.24710600	-0.80295700	1.89025700
C	1.95944400	-1.60529400	1.87093100
C	0.98716700	-1.31322200	2.83012000
C	-0.19167500	-2.05827500	2.88030400
C	-0.41533600	-3.09222400	1.96920600
C	0.54769400	-3.35862700	0.99288000
C	1.72962600	-2.61872700	0.93652400
H	1.12555400	-0.51301900	3.55700200
H	2.43800400	-2.85092100	0.14243600
H	-1.33813500	-3.67775000	2.01024600
O	0.38709900	-4.33601500	0.06545400
O	-1.08553700	-1.73806400	3.84978000
H	-0.46929100	-4.76266500	0.19733900
H	-1.85987000	-2.30995300	3.76995800
C	3.55195800	-0.92086400	5.33657300
O	8.93308500	-8.45438300	-1.44769700
C	7.70785800	-7.89880100	-1.63957600
C	6.78302000	-8.44064400	-2.53886800
C	7.39921800	-6.76380500	-0.89706500
C	8.34013800	0.94392500	4.26045200
C	5.53718400	-7.82976800	-2.68464100
H	9.01891700	-9.23171800	-2.01401100
O	4.59191200	-8.30572100	-3.53636900
C	5.21784800	-6.69068000	-1.94622100
C	6.14979800	-6.14866600	-1.05394200
H	7.03233200	-9.33573300	-3.11592600
C	5.77140800	-4.93697500	-0.31051200
H	8.14488500	-6.39227300	-0.19636100
H	4.93889100	-9.08641900	-3.98653900
H	4.23723000	-6.23553600	-2.08457900
C	3.02630500	-3.80726200	4.13519900
C	4.90960400	-2.75235300	1.60724400
Si	4.20877900	-2.32186000	4.23926500
C	6.18116300	-2.98287600	1.19664200
C	4.51117200	-1.57792500	2.41866700
C	7.20179100	-1.97939100	1.48626200

C	5.60183700	-0.54736400	2.63945400
C	6.96530100	-0.81644200	2.14344400
O	5.34465200	0.50217700	3.22727100
Si	8.23483000	0.57684700	2.40216600
C	9.90035200	-0.04535300	1.73204100
H	8.20831200	-2.18869700	1.10827600
C	5.89684900	-2.91146100	4.87547900
C	7.64617400	2.08223300	1.41446100
C	6.58589200	-4.18159500	0.44388100
H	3.44172500	1.89095400	2.24049700
C	3.60412500	-0.23750000	0.54367700
H	3.73308600	-0.96711600	-0.26450500
H	3.10550400	0.01896500	2.59623700
H	4.72511400	-4.63434600	-0.42331400
H	7.64901800	-4.43513200	0.50163500
H	4.14135300	-3.50065700	1.40321800
C	2.62423800	-1.39971200	6.45921000
H	3.03782900	-0.17421400	4.71352400
H	4.42616400	-0.38913600	5.74558600
H	1.74138200	-1.91966800	6.05347200
H	2.26129800	-0.55682600	7.06564100
H	3.13682300	-2.09622200	7.14093300
C	3.14560600	-4.78913300	5.30835600
H	3.23463500	-4.34462100	3.19565400
H	1.99130700	-3.44270700	4.04871400
H	4.16095700	-5.20674500	5.38371100
H	2.45166700	-5.63404700	5.18690200
H	2.91100800	-4.30852400	6.27002100
C	5.98465100	-2.99687800	6.40571300
H	6.67413800	-2.22373500	4.50562300
H	6.11810500	-3.89179700	4.42037300
H	5.80091900	-2.01545400	6.86929300
H	6.98060700	-3.33151700	6.73129900
H	5.24927800	-3.70051000	6.82369800
C	9.64116100	1.60235500	4.73179000
H	8.19498400	-0.01325600	4.79157100
H	7.46566500	1.56251500	4.51844500
H	10.51313400	0.96438700	4.51880300
H	9.62978000	1.79057400	5.81596100
H	9.81189600	2.56880400	4.23282800
C	8.21461800	3.42315400	1.89343100
H	6.54635800	2.10108400	1.48936900
H	7.88435300	1.91364700	0.34901400
H	7.95362800	3.60371900	2.94846500
H	7.81298700	4.26542400	1.30959100
H	9.31256100	3.45972600	1.81497000

C	10.92124300	1.05924000	1.42822700
H	9.70139500	-0.60562000	0.80194700
H	10.32230800	-0.77610300	2.44421200
H	10.53353600	1.75228900	0.66587500
H	11.86610300	0.64468200	1.04612800
H	11.15965800	1.65533000	2.32162000
C	5.17818100	7.31769300	2.82318400
H	5.82779600	5.96471000	1.25168200
H	6.18319800	5.38639800	2.88486300
H	4.47218500	7.87226400	2.18652500
H	6.10921300	7.90247500	2.86852000
H	4.75259600	7.29706100	3.83850200
C	3.70644500	4.87473000	5.09979300
H	4.37791600	3.14401900	3.96691900
H	2.64036400	3.43850200	3.86775900
H	4.70286500	5.33656600	5.17549400
H	3.52262300	4.33605700	6.04146000
H	2.97000000	5.69159200	5.03886800
C	2.31250200	6.53478600	0.45958400
H	2.27629800	6.64156300	2.63250300
H	1.45608500	5.22853200	1.97393400
H	3.21857800	7.13212000	0.27741400
H	1.43925900	7.19498700	0.34692000
H	2.27365400	5.78111200	-0.33977800
C	5.01556100	6.00071200	-3.75168300
H	3.33602400	4.64089500	-3.50757200
H	4.24278700	4.40315800	-4.99937700
H	5.06979200	6.27199400	-2.68956800
H	4.45036200	6.78315500	-4.28036700
H	6.03994600	6.00514000	-4.15700500
C	3.49327800	1.37502600	-4.58827200
H	5.45913600	0.75714200	-3.86994700
H	5.50957100	1.84322900	-5.24984000
H	2.93564200	1.17240400	-3.66057400
H	3.35234500	0.51279500	-5.25711100
H	3.01489200	2.24430400	-5.06525500
C	7.64535500	4.31172400	-1.92677200
H	7.47971800	3.85254900	-4.05236400
H	7.62094600	2.43458200	-3.01724500
H	7.20952700	5.31983600	-1.96994900
H	8.74203800	4.40910300	-1.93128400
H	7.35042200	3.88082100	-0.95800700

S2.18, BQM, R = TBDPS

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C	-0.05456900	-4.15179800	-1.45930900
C	0.01182000	-3.12713700	-2.53253800
C	0.64527700	-3.91023800	-0.17813300
C	0.60647100	-1.93720800	-2.26154300
C	1.34024200	-1.69479400	-1.02875600
C	1.29419400	-2.73360600	-0.01298700
Si	0.64380800	-5.15481900	1.27538700
C	0.79632000	-7.02307000	0.84980700
C	-0.94700300	-4.90471000	2.26496200
C	2.11478400	-4.51607900	2.30399300
Si	-0.57523000	-3.52724700	-4.30627500
C	-2.37175000	-4.17046400	-4.49875200
C	0.63723100	-4.81475700	-5.01998600
C	-0.26985800	-1.88721600	-5.22005500
H	1.80442600	-2.53415300	0.92773300
O	-0.69858800	-5.18971800	-1.62894100
C	3.30403900	-0.50744700	0.03513500
C	3.38664800	0.81981100	0.75990200
C	3.13195700	2.02451700	0.09822100
C	3.30537900	3.22669700	0.78293100
C	3.77422700	3.24558400	2.09593800
C	4.04588300	2.03692000	2.73834300
C	3.81745100	0.82374200	2.08783900
H	2.79905700	2.06281000	-0.93854900
H	4.03255900	-0.10795800	2.61379100
H	3.94179200	4.19690200	2.60884500
O	4.55259900	1.99175600	3.99727100
O	3.04028200	4.38113500	0.10914100
H	4.75428600	2.89575000	4.28113300
H	3.25716700	5.12826500	0.68556200
C	6.80745200	4.70555600	2.23544100
O	3.33466900	-5.26085900	-2.08858900
C	3.75745900	-4.03382800	-2.47523800
C	3.81071400	-3.66069600	-3.82214900
C	4.12895600	-3.13899100	-1.47264900
C	8.20854800	-2.96865000	4.47980300
C	4.22286800	-2.36993200	-4.14827500
H	3.00849600	-5.74242900	-2.86476000
O	4.29068100	-1.94767000	-5.44224000
C	4.55190300	-1.44747400	-3.15096600
C	4.49834900	-1.83666100	-1.81250600
H	3.52365700	-4.37173000	-4.60370500
C	4.68997700	-0.79569700	-0.72563500
H	4.03939700	-3.46592000	-0.43508700
H	4.04476500	-2.68374600	-6.02038100
H	4.83690000	-0.43514300	-3.43961300

C	7.37664100	3.62362400	-0.62291600
C	6.76994600	0.93051500	0.77428800
Si	7.88856400	3.52559400	1.20520200
C	6.50046600	-0.47292100	1.05293300
C	7.47478900	1.71084000	1.62968400
C	7.10592700	-1.05355200	2.24495300
C	7.92184000	1.13305200	2.91768600
C	7.76267700	-0.31644800	3.17356600
O	8.43500900	1.86383000	3.76857400
Si	8.35063100	-1.09537500	4.81623200
C	10.18558300	-0.80821300	5.21740200
H	6.95704100	-2.12802300	2.38879900
C	9.73866800	3.98883400	1.46425900
C	7.26238700	-0.51273000	6.28709400
C	5.64823600	-1.24039800	0.32999200
H	5.00234500	0.15174300	-1.18565700
H	0.64633700	-1.14612400	-3.01460200
H	6.39511200	1.34468600	-0.16440000
H	5.54005100	-2.28576100	0.64046200
C	2.18455700	-0.63479100	-0.95084700
H	2.15887700	0.09237200	-1.77010000
H	3.21639800	-1.29492200	0.79432600
C	1.39021700	-7.74026800	2.07246900
H	0.78435300	-7.56873600	2.97723400
H	2.41974800	-7.41828300	2.28834000
H	1.40498200	-8.82849000	1.88854100
C	1.67909000	-7.27877700	-0.37656000
H	2.70702000	-6.90979400	-0.25193300
H	1.25678400	-6.79011200	-1.26692600
H	1.73019100	-8.36517100	-0.57017100
C	-0.60101400	-7.60456900	0.58228700
H	-0.50322600	-8.67570700	0.33277100
H	-1.09246900	-7.09621400	-0.25845400
H	-1.24997900	-7.52162400	1.46707700
C	-3.29033500	-3.45747300	-3.49742800
H	-3.00235200	-3.70609500	-2.46400800
H	-4.33484000	-3.78199300	-3.64584100
H	-3.26379300	-2.36091600	-3.60007600
C	-2.83566800	-3.91801700	-5.94276400
H	-2.90675200	-2.85156000	-6.19547300
H	-3.83305800	-4.36662700	-6.09021000
H	-2.15299900	-4.38935500	-6.66932900
C	-2.44836800	-5.68520500	-4.25178300
H	-2.10873800	-5.95234300	-3.24329200
H	-1.84382900	-6.24168100	-4.98464800
H	-3.49655600	-6.01247400	-4.36654300

C	10.09908800	5.11310300	0.47922800
H	10.05039700	4.79287900	-0.57087600
H	11.12646300	5.46227700	0.68027700
H	9.42770800	5.98032400	0.59568800
C	9.97903200	4.52335200	2.88509200
H	9.40348800	5.44296400	3.07207100
H	11.04952600	4.76889700	2.99886100
H	9.70863400	3.78461100	3.65127400
C	10.64619500	2.77191200	1.23629600
H	10.50810200	2.31493100	0.24394600
H	10.46419200	1.99367900	1.99323000
H	11.70448700	3.07567600	1.31666700
C	7.43738100	0.99590500	6.51878600
H	8.49615400	1.28764200	6.59328500
H	6.93743900	1.27221600	7.46399600
H	6.98308600	1.57781800	5.70528300
C	5.77176400	-0.77432500	6.02558100
H	5.43287400	-0.27956000	5.10081000
H	5.17462700	-0.35700200	6.85554900
H	5.52858700	-1.84520300	5.96123300
C	7.72647000	-1.24823200	7.55436400
H	8.77024900	-0.99603000	7.79810500
H	7.66101600	-2.34320700	7.46285700
H	7.09869300	-0.94509500	8.41010600
C	1.92802800	-3.52102600	3.27790700
C	3.43780100	-4.82656600	1.93908400
C	4.52621200	-4.16849600	2.51418300
C	3.01110100	-2.84421400	3.84537800
C	4.31230700	-3.16215800	3.45912000
H	2.83888800	-2.06064800	4.58598900
H	5.16034000	-2.63136000	3.89494800
H	3.62668500	-5.58258800	1.17213700
H	5.54697900	-4.43791100	2.22862300
H	0.91424100	-3.24287300	3.57697300
C	-1.25387400	-0.90649200	-5.41951500
C	-0.93518700	0.34654100	-5.94621000
C	0.38374400	0.65550600	-6.27485100
C	1.38492900	-0.29339000	-6.06777100
C	1.05309900	-1.54280800	-5.54787300
H	2.42865700	-0.07051800	-6.29524900
H	1.85350600	-2.26108700	-5.36627100
H	-2.29225700	-1.10797700	-5.15025700
H	-1.72252600	1.08737600	-6.09297700
H	0.63099900	1.63672000	-6.68279700
C	-2.12365400	-4.48581800	1.62520500
C	-3.32444100	-4.37631100	2.32569900

C	-3.37066600	-4.68511700	3.68453600
C	-2.21283400	-5.10353900	4.33941700
C	-1.01470200	-5.21234800	3.63371700
H	-0.11317600	-5.53318100	4.16367500
H	-2.10465200	-4.25168700	0.55767800
H	-4.22773800	-4.04938900	1.80844400
H	-4.30915600	-4.59857600	4.23420300
H	-2.24246900	-5.34466300	5.40314000
C	1.18382600	-4.69071300	-6.30729300
C	2.09779500	-5.62397100	-6.80553200
C	2.47707000	-6.71636800	-6.02724400
C	1.00624000	-5.94415800	-4.26547800
C	1.91490400	-6.88311300	-4.75940700
H	0.55877300	-6.09981900	-3.28119500
H	2.17339500	-7.75707400	-4.15644200
H	3.18974300	-7.44655100	-6.41316000
H	0.89718800	-3.84490000	-6.93705500
H	2.50633700	-5.50123200	-7.81025500
C	9.03517700	-3.49148800	3.46569400
C	7.33944100	-3.86331700	5.12030900
C	7.28409500	-5.21328600	4.76272200
C	8.10629500	-5.70214800	3.75143400
C	8.98747700	-4.83501800	3.10214800
H	6.68161900	-3.51514300	5.91750000
H	6.59073400	-5.88046500	5.27680100
H	9.73524500	-2.82874700	2.94801400
H	8.06465000	-6.75548400	3.47021700
H	9.64110000	-5.20809900	2.31218000
C	10.85260700	0.41716400	5.04549700
C	12.18998200	0.56772700	5.41309100
C	12.89158000	-0.49894900	5.97151600
C	10.91305000	-1.87080000	5.78411700
C	12.24730500	-1.72018300	6.16045600
H	10.43162200	-2.84061400	5.93226100
H	12.78507300	-2.56229700	6.59887300
H	12.68430700	1.52885500	5.26207800
H	13.93725200	-0.37943800	6.25948900
H	10.31616000	1.26630400	4.62354800
C	6.05870400	3.94598000	-0.97778200
C	5.59498200	3.81651200	-2.28775800
C	6.45228200	3.35436300	-3.28404900
C	7.76857500	3.02295600	-2.95817800
C	8.21926100	3.15241500	-1.64534200
H	5.36131900	4.29170400	-0.21785400
H	4.55956200	4.07694500	-2.51494700
H	6.09940600	3.24945000	-4.31121300

H	8.44614600	2.65444300	-3.72975000
H	9.24704200	2.86239500	-1.41682100
C	6.22376500	5.85737600	1.68453700
C	5.41793500	6.70449500	2.45203400
C	5.19718500	6.42744700	3.80043300
C	5.80505500	5.31105400	4.37987100
C	6.59816600	4.46158500	3.60600900
H	6.39641500	6.10386200	0.63408400
H	4.97657700	7.59356300	1.99734600
H	7.07854600	3.59825500	4.07248900
H	4.57402700	7.08951400	4.40339000
H	5.67133300	5.10946300	5.44529800

S2.19, C3-C8 Rearranged Intermediate, R = TBDPS

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C	4.53623700	3.90979200	-0.43779400
C	4.01205500	3.72461000	0.94037300
C	4.90144000	2.72113200	-1.24684200
C	4.00304900	2.48383400	1.48283900
C	4.44733200	1.31708800	0.74000500
C	4.84557200	1.50642100	-0.64873500
Si	5.43644800	2.87317700	-3.07434500
C	4.00596700	3.47047100	-4.15767300
C	6.94914400	4.03184200	-3.33078100
C	5.83449200	1.06747500	-3.52625800
Si	3.18891400	5.19481900	1.82705800
C	1.63160800	5.62366300	0.83900300
C	4.33345800	6.71959300	2.07267000
C	2.63561200	4.41925000	3.47002000
H	5.11615900	0.59902200	-1.19697000
O	4.63489800	5.04450200	-0.90660400
C	4.14111000	-0.37334900	2.64996500
C	2.68617900	-0.78599900	2.75022000
C	1.94449900	-0.26771700	3.80854300
C	0.63217300	-0.69666200	4.00756100
C	0.04849800	-1.61648800	3.13667200
C	0.78882600	-2.09109800	2.05075800
C	2.10072200	-1.66970200	1.84171400
H	2.37349500	0.46269200	4.49368000
H	2.64434700	-2.06776200	0.98484600
H	-0.97252600	-1.97029500	3.30503600
O	0.28637500	-3.00655400	1.18048000
O	-0.02280500	-0.19189500	5.08711800
H	-0.62684700	-3.20483900	1.42465400

H	-0.89633700	-0.60053300	5.14607200
C	4.57683600	-0.92682400	6.28670800
O	7.27568400	-6.70951500	-3.98375000
C	6.24894900	-5.88335100	-3.65807700
C	5.22206300	-5.58547400	-4.56151300
C	6.25388500	-5.33107800	-2.37934900
C	9.77109800	-0.11567300	4.03417500
C	4.18017100	-4.74852100	-4.15836900
H	7.15200300	-7.02828200	-4.88690900
O	3.16470100	-4.39800400	-4.99127300
C	4.16072500	-4.21176500	-2.87232900
C	5.21367900	-4.47765300	-1.99134400
H	5.23221400	-6.01124200	-5.56891100
C	5.23088100	-3.75499600	-0.71082000
H	7.06890500	-5.58920700	-1.70455800
H	3.30492600	-4.80937300	-5.85396800
H	3.34592600	-3.54347500	-2.59392300
C	3.20354600	-3.33719900	5.00633400
C	5.31099800	-2.55667200	2.08760200
Si	4.78104400	-2.25684300	4.92965500
C	6.32542700	-2.59838700	1.19111900
C	5.18034700	-1.49426800	3.13758300
C	7.41274200	-1.61994900	1.26733200
C	6.45340200	-0.66378500	3.28220200
C	7.47173000	-0.65286300	2.21241800
O	6.60289400	0.05723100	4.25692800
Si	8.89438800	0.57910800	2.50332500
C	10.05886400	0.43522300	1.00993600
H	8.18966600	-1.68365000	0.49848000
C	6.22926700	-3.47078500	5.35901200
C	8.38575900	2.42963600	2.63030500
C	6.32899700	-3.48185100	0.01240800
H	3.60541600	2.32255500	2.48712600
C	4.47457700	0.06291900	1.24819000
H	4.76001700	-0.72904300	0.54995500
H	4.28794500	0.46101700	3.35079600
H	4.27437600	-3.32250900	-0.39951700
H	7.30775100	-3.81301100	-0.34924300
H	4.50988200	-3.28881000	1.98303100
C	3.31457100	-0.55464700	6.77873200
C	3.17762700	0.34181800	7.84140300
C	4.30528900	0.89934400	8.43757400
C	5.70040900	-0.35077600	6.90959600
C	5.57060800	0.54877800	7.96457000
H	6.70242300	-0.59853200	6.55866100
H	6.46455700	0.97476900	8.42302900

H	2.18064700	0.59314500	8.20770400
H	4.20125300	1.59832500	9.26909400
H	2.40838500	-0.97579700	6.34004900
C	2.62283000	-4.02348300	3.92804600
C	1.53548000	-4.88131600	4.09480800
C	1.57325000	-4.45353300	6.45839900
C	2.65465400	-3.59155500	6.27928600
H	3.00366800	-3.89563700	2.91787700
C	7.61743800	-2.95225100	4.96066600
H	7.71160900	-2.83935800	3.86852300
H	8.38183400	-3.68505600	5.27356300
H	7.87961200	-1.98738900	5.42099600
C	5.99677600	-4.80606900	4.63003200
H	5.06367500	-5.29219700	4.95028200
H	6.83214400	-5.49048200	4.85850600
H	5.96440200	-4.68502600	3.53553200
C	6.21342500	-3.75469600	6.86926000
H	6.44587000	-2.86024800	7.46433900
H	6.97083900	-4.52307600	7.10163300
H	5.23846300	-4.14413000	7.20219000
C	10.51344900	-1.30121500	3.91087400
C	11.06847500	-1.93003800	5.02540700
C	10.88454600	-1.38485000	6.29506900
C	10.14700700	-0.21011000	6.44117400
C	9.59623600	0.41367500	5.32176300
H	10.65527400	-1.75053500	2.92339400
H	11.63949100	-2.85170000	4.90244300
H	11.31294100	-1.87569400	7.17020200
H	9.00447600	1.31979300	5.45988300
H	9.99582300	0.22093300	7.43228600
C	9.55250500	0.44230100	-0.30359600
C	10.40174400	0.42169700	-1.40956000
C	11.78481100	0.39501800	-1.22643200
C	12.30919200	0.39251100	0.06400000
C	11.45340900	0.41306600	1.16681100
H	8.47032100	0.47663800	-0.46909900
H	13.38958500	0.37744400	0.21524700
H	11.88277800	0.41524500	2.17204200
H	9.98707200	0.43339500	-2.42010500
H	12.45074700	0.38057000	-2.09029400
C	7.92765900	2.90414400	1.24174200
H	8.74766400	2.88750100	0.50951600
H	7.56175300	3.94357300	1.31374800
H	7.09717500	2.29293800	0.84727900
C	7.26191600	2.76083700	3.62180800
H	6.29666100	2.35209800	3.28572900

H	7.16562400	3.85956200	3.67650600
H	7.43638300	2.37942800	4.63564500
C	9.65178200	3.21208500	3.01995300
H	10.48675600	3.00963000	2.32998200
H	9.98798500	2.97242600	4.04039100
H	9.44162900	4.29471800	2.97894400
C	4.86318500	0.21516300	-4.07579700
C	5.09322600	-1.15548800	-4.22027200
C	7.04747500	0.48385300	-3.11985300
C	7.28372100	-0.88440900	-3.25224800
C	6.30381600	-1.70976900	-3.80602200
H	8.23178500	-1.30995800	-2.91548400
H	6.47735600	-2.78368500	-3.90450500
H	3.89838500	0.62522300	-4.38407000
H	4.31912500	-1.79830000	-4.64608400
H	7.82084800	1.11104600	-2.66861800
C	3.95857300	3.12064600	-5.51784500
C	3.01954000	4.34287400	-3.66933900
C	2.01794900	4.83636100	-4.50523400
C	1.98448000	4.47129600	-5.85052000
C	2.95948600	3.61338400	-6.35749200
H	1.20214400	4.85866100	-6.50513600
H	2.94315700	3.32673800	-7.41024300
H	3.04556500	4.66649400	-2.62726500
H	1.26723000	5.51773500	-4.10110300
H	4.71209500	2.44403000	-5.93115700
C	7.85035700	4.02616400	-2.08974200
H	8.72768700	4.67517800	-2.25797500
H	7.31139100	4.41046400	-1.20961500
H	8.22895300	3.02121300	-1.84008100
C	6.46527800	5.46813700	-3.58538000
H	5.87194700	5.53292200	-4.51026600
H	7.34151900	6.13068800	-3.69668400
H	5.84938100	5.84014600	-2.75537100
C	7.74175500	3.56940900	-4.56257900
H	8.19162600	2.57471900	-4.42852000
H	8.55653400	4.28572800	-4.76630800
H	7.10425100	3.53170900	-5.46135600
C	1.29951600	4.03971400	3.66608500
C	0.92104400	3.26457400	4.76389500
C	1.87777300	2.84488100	5.68496900
C	3.21552300	3.20936200	5.51402100
C	3.58244000	3.99533200	4.42163100
H	0.54239400	4.33547100	2.93597100
H	3.97112300	2.86179700	6.22234900
H	4.63854500	4.25015500	4.28981800

H	-0.12013500	2.96338600	4.88761500
H	1.58655600	2.21236500	6.52428000
C	1.23551500	4.87448600	-0.27834700
C	0.07229800	5.18557400	-0.98440300
C	-0.72447400	6.25471400	-0.57905500
C	-0.35700900	7.00575300	0.53776300
C	0.80715100	6.68977800	1.23591300
H	1.07488500	7.28665500	2.11252800
H	-1.63410700	6.50070400	-1.12907100
H	-0.97929400	7.83984700	0.86555700
H	1.83688700	4.02257000	-0.60594300
H	-0.21077100	4.58561900	-1.85112800
C	5.79754400	6.25835800	2.06509200
H	6.07134400	5.84333300	1.08296900
H	6.46184400	7.11575200	2.27151700
H	5.99543100	5.49089800	2.83039400
C	4.13511600	7.73706300	0.93977600
H	3.12361400	8.16967100	0.95179000
H	4.29925200	7.27583200	-0.04376100
H	4.85635500	8.56383800	1.06396200
C	4.02290100	7.39682300	3.41590100
H	4.21651700	6.73224500	4.27099700
H	2.97193400	7.72159400	3.48265900
H	4.65492600	8.29451400	3.53121500
C	1.00161800	-5.09719900	5.36260500
H	0.15367900	-5.77036700	5.49858400
H	1.10914500	-5.37823900	3.22165800
H	1.17873600	-4.62165900	7.46174900
H	3.07678200	-3.10428400	7.16018000

S2.20, BQM, R = TIPS

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C	1.00092100	-4.23370100	-1.75829500
C	0.79673300	-2.82979100	-2.19026100
C	1.80215400	-4.52928700	-0.54436600
C	1.39897700	-1.85184600	-1.47575500
C	2.28830100	-2.11793200	-0.34691000
C	2.42413900	-3.50665500	0.08677200
Si	1.69523900	-6.34155700	0.06033400
C	-0.18107500	-6.59069200	0.43141000
C	2.27658000	-7.50947900	-1.33559300
C	2.82672900	-6.42226500	1.60597700
Si	-0.31782700	-2.53397000	-3.70986300
C	-2.13727800	-2.81440500	-3.18037500
C	0.23905600	-3.71518300	-5.10713300

C	-0.10595600	-0.68996200	-4.16308700
H	3.01885400	-3.70096200	0.98181400
O	0.49900300	-5.16078700	-2.39637200
C	4.12620300	-1.16471900	1.14568900
C	4.07794900	-0.14057200	2.26180300
C	3.92439600	1.21471800	1.96716900
C	4.10356100	2.16328900	2.97432600
C	4.42311000	1.77057100	4.27637400
C	4.53493800	0.40937100	4.56634700
C	4.36301200	-0.54701200	3.56363400
H	3.70150400	1.57010600	0.96052600
H	4.49327300	-1.59921400	3.81823600
H	4.56630400	2.51829700	5.06135000
O	4.82614500	-0.04599800	5.81099900
O	3.96954800	3.46827300	2.62513400
H	5.00361400	0.70691700	6.39126600
H	4.27670600	4.02934700	3.35144400
C	6.57877500	5.39478700	2.13197200
O	6.43737500	-5.50501800	-1.18142000
C	5.96186500	-4.27097600	-1.49379600
C	5.42813900	-3.97646000	-2.74961600
C	6.01884900	-3.29852200	-0.49320200
C	9.04343700	1.80049000	6.53738900
C	4.99400200	-2.67590700	-3.01399700
H	6.30995400	-6.09488400	-1.93654600
O	4.47325700	-2.31081600	-4.21260300
C	5.08585400	-1.68777800	-2.03404700
C	5.57436400	-2.00354700	-0.76661300
H	5.36677200	-4.74943800	-3.52053300
C	5.47640500	-0.95143100	0.32110900
H	6.41682100	-3.59174400	0.47786300
H	4.33604300	-3.09623900	-4.75944100
H	4.72644100	-0.68575400	-2.27131400
C	6.93829500	4.11682700	-0.68712400
C	7.16987500	1.47458700	1.22159700
Si	7.73461700	4.31718000	1.04782100
C	7.30120900	0.12099400	1.75637400
C	7.77907700	2.54828300	1.77939600
C	8.19054200	-0.06200200	2.90163000
C	8.58224700	2.33740200	3.01057500
C	8.79510300	0.96745100	3.53571100
O	9.08491100	3.29557200	3.60143200
Si	9.89062300	0.86539200	5.09147700
C	10.06849800	-0.95127300	5.65590300
H	8.30860300	-1.08871000	3.25868200
C	9.56104500	4.86466000	0.92654900

C	11.59302600	1.62652600	4.70286400
C	6.61048800	-0.95099900	1.29626300
H	5.38910100	0.03304800	-0.15790700
H	1.28309500	-0.80036600	-1.75861500
H	6.57368000	1.60003800	0.31544400
H	6.81853200	-1.91127400	1.78164100
C	2.97998600	-1.08407100	0.19075500
H	2.76143400	-0.08438600	-0.20232600
H	4.18988500	-2.16786500	1.58845000
C	1.27877000	-0.36699600	-4.73955300
H	2.10174200	-0.79897400	-4.14810000
H	1.43648200	0.72231100	-4.80375400
H	1.37407200	-0.76455400	-5.76294600
C	-0.27819300	-3.32577100	-6.49780400
H	-1.37090200	-3.21201400	-6.52884300
H	-0.00305700	-4.09291700	-7.24057200
H	0.16668900	-2.37604900	-6.83587200
C	-2.31124200	-3.84760000	-2.06101700
H	-2.00193500	-4.85012500	-2.39269300
H	-3.36784500	-3.90091900	-1.75075300
H	-1.71163900	-3.59454700	-1.17297800
C	-0.52037300	-7.03060600	1.85923400
H	-0.22604100	-8.07778900	2.03352300
H	-1.60747300	-6.96816500	2.02978300
H	-0.02685500	-6.40906000	2.62206200
C	4.29280000	-6.18814200	1.20948000
H	4.70004400	-7.06805600	0.68664500
H	4.92132600	-6.02814600	2.10192600
H	4.42939500	-5.32867300	0.53742700
C	2.65678000	-8.90671300	-0.83380500
H	3.58970500	-8.88128200	-0.24805200
H	2.82234800	-9.59465900	-1.67931200
H	1.87626100	-9.34951700	-0.19414500
C	12.64488700	1.19998900	5.73313800
H	12.31682700	1.39341400	6.76756600
H	13.59195000	1.74214800	5.57869800
H	12.86925300	0.12352600	5.65595900
C	10.77702100	-1.86947900	4.65275500
H	10.22814100	-1.95156600	3.70181200
H	10.88083900	-2.88889700	5.05979000
H	11.78637300	-1.50535900	4.41080800
C	9.61676400	3.19289800	6.81592600
H	10.69024200	3.15691800	7.05556400
H	9.10134900	3.65989300	7.67175200
H	9.48769300	3.84400800	5.93888700
C	6.77735900	6.90424000	1.95510900

H	7.70809500	7.23575200	2.44049000
H	5.95010600	7.46422200	2.42168400
H	6.82657700	7.20427400	0.89669400
C	5.41384500	3.95464500	-0.59811700
H	5.09688200	3.28570200	0.21729700
H	5.00034600	3.57357400	-1.54664900
H	4.93494000	4.92823300	-0.40442700
C	10.33282800	3.85262100	0.06708400
H	10.20213500	2.81865800	0.42290500
H	11.41185200	4.07632000	0.07546100
H	10.00095100	3.88317000	-0.98443400
C	-1.21405700	-0.14369000	-5.07229800
H	-0.20535300	-0.16538900	-3.19323800
H	-1.22213800	-0.65065800	-6.05007300
H	-1.06543600	0.93194800	-5.26365200
H	-2.21137500	-0.26506400	-4.62369600
C	1.76456000	-3.87869900	-5.15700700
H	-0.19205700	-4.68999400	-4.82451800
H	2.24295700	-2.93030200	-5.45048900
H	2.04401900	-4.64282000	-5.90243800
H	2.17893300	-4.18361300	-4.18372100
C	-3.05428700	-3.16350300	-4.35912300
H	-2.45231500	-1.83196300	-2.78004500
H	-2.76623600	-4.13016500	-4.80354400
H	-3.02718900	-2.40579000	-5.15676000
H	-4.10005400	-3.25677700	-4.02321200
C	3.40046400	-6.90376400	-2.18164500
H	1.39433800	-7.60244800	-1.98736600
H	4.28656600	-6.68290400	-1.56544500
H	3.07569200	-5.96447200	-2.65374600
H	3.70426500	-7.60049400	-2.98247200
C	2.74016300	-7.68275400	2.47751100
H	2.49840600	-5.56818900	2.22981000
H	3.00907300	-8.58494800	1.90857600
H	1.74207700	-7.83891100	2.90330000
H	3.45078600	-7.60817200	3.31767300
C	-0.87956200	-7.50326300	-0.58321400
H	-0.59668400	-5.57593100	0.29534600
H	-0.48036800	-8.53038500	-0.54020900
H	-0.75802400	-7.12954100	-1.60897900
H	-1.95879400	-7.56173100	-0.36506100
C	8.74487300	-1.55799400	6.14308000
H	10.72720700	-0.87006500	6.54187400
H	7.98564800	-1.60713600	5.34598100
H	8.30726800	-0.97239200	6.96563400
H	8.89817900	-2.58474100	6.51399000

C	12.06956200	1.35953700	3.27170600
H	11.42926800	2.71269800	4.79908900
H	12.17154200	0.28218100	3.06424600
H	13.05444400	1.82284800	3.09552000
H	11.36869200	1.77531900	2.53240100
C	7.52588700	1.87765200	6.32905900
H	9.23329500	1.16798900	7.42487900
H	7.02501400	2.28192000	7.22720000
H	7.09594500	0.89096300	6.09685800
H	7.29540800	2.54965800	5.48575700
C	6.57254700	5.02941000	3.62004800
H	5.58356900	5.13648800	1.73152700
H	7.53558900	5.25552200	4.10068700
H	6.39307600	3.95223200	3.77458500
H	5.79142600	5.60232800	4.15559300
C	9.83613900	6.29390300	0.44357000
H	9.93024900	4.77932700	1.96095600
H	10.92321400	6.47820200	0.42042000
H	9.38999800	7.05139900	1.10085900
H	9.45812000	6.47205300	-0.57388200
C	7.28083600	5.21518100	-1.70068300
H	7.36391300	3.17273800	-1.07488000
H	6.99287600	6.21330400	-1.33225000
H	6.73780500	5.04975700	-2.64618900
H	8.35362100	5.24204700	-1.93681400

S2.21, C3-C8 Rearranged Intermediate, R = TIPS

0 1

C	4.07165800	3.83899500	-0.23840100
C	3.79637100	3.32315700	1.12638200
C	4.32707800	2.88944600	-1.35295000
C	3.75829100	1.98063700	1.29999200
C	4.04294600	1.02417500	0.23756700
C	4.33410400	1.56416000	-1.08631100
Si	4.66979100	3.62025700	-3.08163700
C	3.25461100	4.80080300	-3.60345000
C	6.45542900	4.31568600	-3.09785300
C	4.66563300	2.13432700	-4.29184800
Si	3.58424300	4.51206400	2.61679900
C	2.04362700	5.62738300	2.37951100
C	5.23236500	5.42659000	2.96173000
C	3.31814000	3.33003100	4.10930800
H	4.54102200	0.83340200	-1.87497000
O	4.10086600	5.04915500	-0.45888700

C	3.62178800	-1.07026000	1.66555100
C	2.59525000	-2.05683400	1.10577000
C	1.23938500	-1.81644400	1.32477100
C	0.27924800	-2.68160400	0.79680400
C	0.65817100	-3.78213000	0.02664200
C	2.01444800	-3.98250800	-0.24029000
C	2.97737200	-3.11860400	0.27614400
H	0.89877200	-0.96413100	1.90983200
H	4.01708800	-3.29194000	0.00145700
H	-0.09458400	-4.46752500	-0.37248100
O	2.46225500	-5.01986300	-0.99872500
O	-1.01849500	-2.40834000	1.08602600
H	1.70865400	-5.52970000	-1.32367800
H	-1.58539900	-3.05880500	0.65187800
C	4.21605800	-0.19745300	5.28735900
O	8.78763100	-9.55801600	0.48850800
C	7.61950300	-8.95044400	0.15206800
C	6.65253000	-9.58949800	-0.63157300
C	7.41168200	-7.65886200	0.62624300
C	8.73382400	1.18718400	3.54940000
C	5.46712100	-8.91836400	-0.93561900
H	8.80329100	-10.44448200	0.10612900
O	4.48750300	-9.48527800	-1.68910800
C	5.24744100	-7.62416200	-0.46684800
C	6.22321400	-6.98858500	0.30976300
H	6.82200900	-10.60688300	-0.99597700
C	5.94687800	-5.61687600	0.76011500
H	8.18042600	-7.20877700	1.25250200
H	4.76901700	-10.37012600	-1.95437400
H	4.31918400	-7.11276000	-0.72337400
C	2.58194500	-2.81279600	4.30443900
C	5.24367100	-3.04257900	2.11797100
Si	4.28610300	-1.91470800	4.44918600
C	6.48890400	-3.38243500	1.70411400
C	4.84456300	-1.67208300	2.51348800
C	7.51621500	-2.34693000	1.64493200
C	5.96499900	-0.64641400	2.44838200
C	7.31821100	-1.04905800	1.99647100
O	5.72676300	0.52790600	2.72022900
Si	8.65516800	0.31943800	1.85162200
C	10.30137200	-0.58336100	1.45900500
H	8.50310000	-2.66798000	1.29591600
C	5.50586400	-3.09971100	5.32813500
C	8.14532600	1.53685000	0.47072800
C	6.83283500	-4.74935600	1.27869700
H	3.58333000	1.56282600	2.28787300

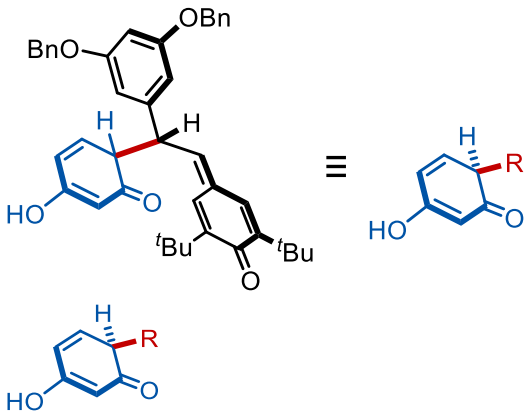
C	4.07851300	-0.31575300	0.43865200
H	4.39397500	-0.94421100	-0.40227600
H	3.08205600	-0.37345400	2.31954100
H	4.91243100	-5.29070700	0.60963600
H	7.88771400	-5.03157800	1.35472200
H	4.48905800	-3.82748300	2.20870200
C	3.25458000	-0.12282000	6.48480400
H	2.20079600	-0.19166200	6.19277300
H	3.38839300	0.84006800	7.00565000
H	3.45534200	-0.91652000	7.22256100
C	2.38288400	-4.07248800	5.15945300
H	3.22649400	-4.77484500	5.09680600
H	1.48017100	-4.60686400	4.82105500
H	2.22487100	-3.82133700	6.21916500
C	5.16168200	-3.23337000	6.82102300
H	5.40775700	-2.30423300	7.35842300
H	5.76055900	-4.03775300	7.27808800
H	4.10444000	-3.45883100	7.00984700
C	9.44000900	2.54719200	3.57759400
C	9.30004500	2.45564800	0.04568600
H	9.76205900	2.98532900	0.89107500
H	8.94825000	3.21338000	-0.67163900
H	10.09199100	1.87808100	-0.45746100
C	11.54999400	0.25102300	1.77958600
H	11.58544500	1.17058000	1.17477700
H	12.46460500	-0.32275800	1.55515700
H	11.59551900	0.54698400	2.83654500
C	5.04604000	6.67982200	3.82772600
H	4.50509600	7.46241300	3.27246100
H	6.02460200	7.10027700	4.11285500
H	4.48609500	6.48089700	4.75345200
C	3.61505800	3.93437100	5.48790800
H	4.64393200	4.31742200	5.55545200
H	3.49720400	3.16763300	6.27304400
H	2.93226300	4.76079200	5.73878300
C	2.18608900	6.72821100	1.32077900
H	2.99911800	7.42556700	1.58140400
H	1.25596200	7.31793400	1.26280400
H	2.41248900	6.32624500	0.32720200
C	3.50659100	6.29855100	-3.39631900
H	3.76510200	6.50891900	-2.34827700
H	2.59695900	6.87191200	-3.64254600
H	4.31349500	6.67474500	-4.03888500
C	3.28011700	1.50508600	-4.47506700
H	2.82346100	1.20339100	-3.51992500
H	3.33392100	0.61320500	-5.12117000

H	2.59116500	2.21599300	-4.96031300
C	6.93837400	4.83658600	-1.74173300
H	6.35150300	5.70872000	-1.41745700
H	7.99882400	5.13694300	-1.79699300
H	6.84365200	4.06943600	-0.95624700
C	5.25619400	2.50233700	-5.65861300
H	5.33660400	1.37912800	-3.83985600
H	4.67796700	3.30857900	-6.14114200
H	5.23351200	1.63630500	-6.34073800
H	6.30078700	2.83825300	-5.58297600
C	6.74083300	5.35560100	-4.19080900
H	7.04786000	3.40954600	-3.33468700
H	6.37755200	6.34557400	-3.87930300
H	6.26983500	5.11548700	-5.15621800
H	7.82570300	5.44990900	-4.36155000
C	10.40275200	-1.10968500	0.01951700
H	10.30521200	-1.45336300	2.14343500
H	10.52591600	-0.27627900	-0.68968700
H	9.51692600	-1.67727600	-0.30233200
H	11.28320000	-1.76327700	-0.09508100
C	1.93535300	4.39931400	-2.92624500
H	3.14243300	4.62154700	-4.68999200
H	1.96953400	4.64807400	-1.85447900
H	1.71712100	3.32463100	-3.01444200
H	1.09125700	4.95329100	-3.36862100
C	6.08288300	5.75884900	1.73320600
H	5.79696300	4.68347800	3.55787600
H	5.56745100	6.46193300	1.06225500
H	6.31426300	4.86043300	1.14287300
H	7.03799500	6.21458100	2.04505400
C	1.94482200	2.64463000	4.11520600
H	4.09388600	2.55687900	3.94545100
H	1.14285400	3.36502900	4.34058300
H	1.89864900	1.85984100	4.89064800
H	1.69364500	2.18191500	3.14739800
C	1.54445600	6.24606100	3.69435000
H	1.26672100	4.92073900	2.03061100
H	2.27753600	6.95532700	4.10866300
H	1.33223100	5.49399100	4.46704400
H	0.61375100	6.80992900	3.51714000
C	9.27928600	0.24845600	4.63153200
H	7.66971900	1.37439900	3.76632600
H	10.36267300	0.08279300	4.51880700
H	8.79205400	-0.73856400	4.60129000
H	9.11703900	0.66973600	5.63791700
C	7.56652600	0.83653400	-0.76446900

H	7.34175500	2.15083700	0.92160200
H	8.33059100	0.22747900	-1.27245500
H	7.20018200	1.58084600	-1.49265200
H	6.72652100	0.17509400	-0.50635500
H	10.49519500	2.48166500	3.26829900
H	9.42513700	2.96219900	4.59931700
H	8.94048400	3.27564700	2.92173300
C	7.00132300	-2.79432700	5.20305700
H	5.32614700	-4.07680900	4.84397200
H	7.26529900	-1.89051900	5.77067400
H	7.32427300	-2.65029500	4.16530800
H	7.59088800	-3.62500200	5.62508300
C	1.35131100	-1.90712100	4.47115900
H	2.58682600	-3.16237700	3.25888400
H	1.09477400	-1.80892700	5.53625400
H	0.47629600	-2.34123200	3.96179300
H	1.49739000	-0.88944200	4.07537100
C	5.60080600	0.28960300	5.74654900
H	3.85813400	0.49775300	4.50753500
H	5.89661000	-0.22032600	6.67778000
H	5.56470200	1.37035300	5.96405000
H	6.39349500	0.12890400	5.00591200

Regioselectivity Energies and Coordinates

Optimized geometries were carried out at the M062X / cc-pVTZ level of theory, with a conductor-like polarizable continuum *model* (*CPCM*) in acetone. Free energies listed in Hartree.

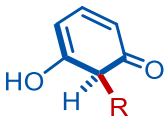


S2.22
Free Energy = -1540.330396

0 1

C	3.67853600	-5.90279900	0.20448900
C	3.37483700	-6.80400200	-0.94132200
C	4.80283700	-6.25389300	1.12332000
C	4.14014900	-7.89496000	-1.11611500
C	5.24446700	-8.24249400	-0.24472100
C	5.51341700	-7.36839000	0.87778600
O	3.01608200	-4.89045700	0.39575100
C	5.10149200	-5.33849600	2.30769600
C	3.88002600	-5.25968200	3.23804800
H	3.01812400	-4.83717600	2.73012900
H	4.12156300	-4.63168100	4.09744600
H	3.61940400	-6.25268600	3.60859700
C	6.27792000	-5.86090800	3.13543500
H	6.45456400	-5.17766200	3.96621600
H	7.19554300	-5.91480300	2.54708000
H	6.07344200	-6.84796800	3.55315400
C	5.47572000	-3.93282200	1.80971900
H	4.65874000	-3.47253400	1.26225600
H	6.35254000	-3.97984800	1.16143700
H	5.72224700	-3.30158600	2.66533300
C	2.21544500	-6.45422300	-1.87082300
C	2.05650800	-7.49697700	-2.97924100
H	2.94621200	-7.55890000	-3.60761500
H	1.21819400	-7.21096100	-3.61474500
H	1.84670700	-8.48840900	-2.57497500
C	0.89720100	-6.41342000	-1.08120800
H	0.07357600	-6.19648100	-1.76385800
H	0.91825300	-5.65014600	-0.30882400
H	0.70310500	-7.38116000	-0.61521800
C	2.46660600	-5.09594400	-2.54529300
H	3.39156900	-5.12433400	-3.12401300
H	2.53395000	-4.29444600	-1.81549700
H	1.64622000	-4.87587000	-3.23086500
H	3.95905400	-8.57237600	-1.93975400
H	6.32571800	-7.63961600	1.53597900
C	5.98224200	-9.33631700	-0.52633500
C	7.17197500	-9.82739000	0.25489800
H	5.71292800	-9.92147800	-1.39649500
C	7.28250900	-11.34049000	0.17030600
C	6.16466100	-12.08454000	0.53539400
C	8.43786900	-11.99214600	-0.23086300
C	6.20460700	-13.47218500	0.49559100

C	8.47213400	-13.38565600	-0.26725800
C	7.36110300	-14.14161900	0.09290800
H	5.25266800	-11.59882000	0.85773300
H	9.33370200	-11.46406400	-0.52511000
H	7.39259100	-15.21733300	0.06179900
O	9.64384600	-13.93162700	-0.67306700
C	9.73587400	-15.34397700	-0.73426700
H	9.00928400	-15.75426300	-1.43760500
H	9.58237100	-15.78998500	0.24984900
O	5.06981900	-14.11145900	0.86884300
C	5.06233800	-15.52806200	0.84513900
H	5.81268000	-15.93618300	1.52432300
H	5.24020300	-15.90472200	-0.16349300
C	8.45899700	-9.06194600	-0.12493100
H	6.99740500	-9.59454600	1.30853200
C	8.88489400	-9.24388800	-1.57800000
C	9.55193500	-9.21884900	0.88098700
H	8.19524500	-7.99325600	-0.08247400
C	10.83731500	-9.23354100	0.53590000
C	11.21366100	-9.17742800	-0.86961600
C	10.29807600	-9.17721000	-1.86715600
O	12.51592000	-9.15574700	-1.18311400
O	8.04143700	-9.39410200	-2.44984700
H	10.61307900	-9.20037400	-2.90045900
H	11.62155700	-9.30050800	1.27890400
H	13.06327500	-9.17693400	-0.38984500
H	4.07366600	-15.83052000	1.17486300
H	10.74003500	-15.56695100	-1.08005100
H	9.26319200	-9.26694600	1.92398400



S2.23

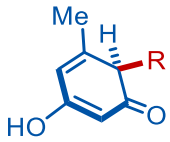
Free Energy = -1540.331043

0 1

C	3.44926500	-5.93076500	0.08536300
C	3.42675000	-6.67853700	-1.20337700
C	4.41490200	-6.34615000	1.14780900
C	4.27137300	-7.71215900	-1.35667500
C	5.20224500	-8.13880900	-0.33113200
C	5.21557500	-7.39984100	0.91499800
O	2.68835400	-4.99082600	0.27493200
C	4.45508600	-5.56378200	2.45750700
C	3.09523500	-5.64915400	3.16971200

H	2.30319500	-5.20782800	2.57212500
H	3.15325500	-5.11693700	4.12084900
H	2.84073900	-6.68940100	3.38022200
C	5.51176800	-6.12569300	3.41168100
H	5.50960600	-5.53330300	4.32670100
H	6.51409200	-6.07480700	2.98280900
H	5.30285000	-7.16141200	3.68455000
C	4.81486800	-4.09435700	2.18298100
H	4.07160400	-3.61147200	1.55552500
H	5.78788700	-4.02625600	1.69322200
H	4.87552000	-3.55573900	3.13027100
C	2.45037600	-6.24432900	-2.29352600
C	2.58186700	-7.12252400	-3.53960800
H	3.58128200	-7.06291300	-3.97309400
H	1.87072700	-6.77788600	-4.29051400
H	2.35849800	-8.16823900	-3.32314100
C	1.00340500	-6.36877300	-1.78961700
H	0.31690000	-6.08856900	-2.59062900
H	0.82136200	-5.72379800	-0.93499300
H	0.78704600	-7.40010100	-1.50532600
C	2.73694100	-4.79441100	-2.71613100
H	3.75801900	-4.70202100	-3.09046300
H	2.60270400	-4.10345200	-1.88900300
H	2.05566100	-4.51164400	-3.52066100
H	4.28985700	-8.28092600	-2.27648800
H	5.91405300	-7.71826400	1.67517200
C	6.02994800	-9.17427800	-0.57865100
C	7.03159200	-9.72478700	0.39125000
H	5.96622200	-9.64774400	-1.55042800
C	7.34137400	-11.19463200	0.17880900
C	7.43163600	-12.01739900	1.29304200
C	7.57243100	-11.71722200	-1.08801500
C	7.75601600	-13.36248600	1.14185100
C	7.89558200	-13.06256500	-1.23151400
C	7.99067000	-13.90080800	-0.12150600
H	7.25734100	-11.63044900	2.28843800
H	7.52513600	-11.10468200	-1.97751100
H	8.23758800	-14.94223100	-0.23849400
O	8.10917800	-13.48585200	-2.50097500
C	8.44226900	-14.84767300	-2.70428400
H	7.64228100	-15.50361500	-2.35685900
H	9.37196500	-15.10503600	-2.19399300
O	7.82247800	-14.08803700	2.28396900
C	8.14542100	-15.46377500	2.18239400
H	9.13299300	-15.60340100	1.73952200
H	7.40132500	-15.99875900	1.58989300

C	10.40412200	-9.62942400	-0.89568800
C	9.09085100	-9.01166300	-0.92076900
C	10.98354800	-9.95331300	0.27660100
C	10.37437400	-9.72430300	1.56549700
C	9.14378100	-9.19567000	1.62400300
C	8.34915600	-8.86176200	0.40302500
O	8.46886800	-8.92184400	2.75598300
O	8.55260500	-8.63303900	-1.94880700
H	8.99154600	-9.16220200	3.53091100
H	8.14593400	-15.84991000	3.19656100
H	8.57137200	-14.97063100	-3.77474200
H	6.62630000	-9.62590300	1.39617800
H	8.03760200	-7.81641700	0.48135000
H	10.91765200	-9.97215900	2.46687200
H	10.89450500	-9.79464900	-1.84425200
H	11.96964100	-10.40057000	0.27014900



2.54

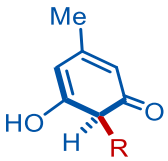
Free Energy = -1579.618488

0 1

C	3.95758000	-5.94728600	0.22560700
C	3.63096900	-6.85532100	-0.90773700
C	5.10975600	-6.28499300	1.11410600
C	4.39185300	-7.94850600	-1.09071900
C	5.51426800	-8.29011600	-0.24158000
C	5.81255500	-7.40321200	0.86245000
O	3.29099200	-4.94027200	0.43242600
C	5.44362300	-5.35377300	2.27663100
C	4.25649300	-5.27353700	3.25017900
H	3.37289400	-4.86542600	2.76847300
H	4.52325700	-4.63200000	4.09196000
H	4.01884300	-6.26385800	3.64267800
C	6.65443600	-5.85622700	3.06632500
H	6.85760500	-5.16029000	3.88033900
H	7.54933200	-5.91125000	2.44360800
H	6.47381200	-6.83873300	3.50572600
C	5.78737500	-3.95119600	1.74869200
H	4.94719600	-3.50514000	1.22496900
H	6.64100200	-3.99887000	1.07017800
H	6.05846500	-3.30722700	2.58720400

C	2.45235900	-6.51182400	-1.81529400
C	2.27538600	-7.55754300	-2.91818900
H	3.15408200	-7.61974800	-3.56186400
H	1.42554800	-7.27427900	-3.53948300
H	2.07405600	-8.54828600	-2.50799000
C	1.14925600	-6.47320100	-1.00085600
H	0.31209200	-6.26010400	-1.66813300
H	1.18292600	-5.70833200	-0.23055200
H	0.96698600	-7.44054200	-0.52928200
C	2.68628700	-5.15443200	-2.49765800
H	3.59920900	-5.18192500	-3.09525600
H	2.76688700	-4.35126400	-1.77101200
H	1.85149700	-4.93747000	-3.16665100
H	4.19192800	-8.63209800	-1.90486400
H	6.64112400	-7.66767700	1.50311600
C	6.24227500	-9.39003000	-0.52739300
C	7.43967100	-9.88041800	0.24377500
H	5.94717900	-9.98702000	-1.38036500
C	7.55852800	-11.39211000	0.15307500
C	6.47111800	-12.14636000	0.58316500
C	8.69426600	-12.03206000	-0.31730600
C	6.52064700	-13.53362000	0.53671500
C	8.73830300	-13.42532300	-0.35964100
C	7.65702300	-14.19161000	0.06376900
H	5.57637200	-11.66886400	0.96141300
H	9.56608600	-11.49496400	-0.66367600
H	7.69644800	-15.26695700	0.02860200
O	9.88818700	-13.96012700	-0.83573100
C	9.98783400	-15.37152000	-0.90809000
H	9.22345700	-15.78512800	-1.56806000
H	9.89753900	-15.82222700	0.08165100
O	5.41623700	-14.18385500	0.97556500
C	5.41957100	-15.60048000	0.94830100
H	6.21261600	-16.00342200	1.58040000
H	5.54017700	-15.97305200	-0.07024000
C	8.72891000	-9.11488500	-0.13199200
H	7.24939000	-9.65565000	1.29441800
C	9.08723200	-9.23900000	-1.61297300
C	9.86685800	-9.31300600	0.83665900
H	8.48283700	-8.04511100	-0.03585600
C	11.12931500	-9.28999100	0.39762000
C	11.43546800	-9.17212100	-1.01562200
C	10.47761200	-9.14254700	-1.97246600
O	12.72220600	-9.12045100	-1.38655200
O	8.19966800	-9.36780900	-2.44493500
H	10.74253300	-9.11856100	-3.01944300

H	13.30359900	-9.16245500	-0.61883200
H	10.97111900	-15.58478000	-1.31464400
H	4.45494700	-15.91233500	1.33546200
H	11.95659300	-9.37165800	1.09271000
C	9.54813500	-9.45050100	2.29078100
H	8.89784600	-8.63949000	2.62611900
H	10.45582000	-9.43825700	2.88850000
H	9.02109100	-10.38824600	2.48082800



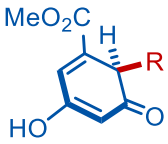
S2.24

Free Energy = -1579.620435

0 1

C	3.48633100	-5.94460700	0.08656900
C	3.44643000	-6.70284100	-1.19534200
C	4.46409700	-6.35325100	1.14009800
C	4.29206800	-7.73513800	-1.35333700
C	5.24119600	-8.14933800	-0.33991600
C	5.26588300	-7.40520400	0.90248000
O	2.72947800	-5.00139700	0.27779200
C	4.51641600	-5.56533900	2.44608700
C	3.16302600	-5.64721100	3.17086900
H	2.36571400	-5.20852100	2.57833900
H	3.22946500	-5.11075600	4.11908300
H	2.91028200	-6.68648000	3.38827700
C	5.58132200	-6.12360000	3.39325600
H	5.58700500	-5.52779700	4.30605000
H	6.58006700	-6.07429800	2.95584300
H	5.37458400	-7.15826100	3.67167200
C	4.87417800	-4.09722200	2.16211800
H	4.12589500	-3.61716700	1.53845300
H	5.84318500	-4.03156200	1.66412000
H	4.94262700	-3.55423300	3.10640400
C	2.45376500	-6.27907700	-2.27490900
C	2.56656700	-7.16905300	-3.51446600
H	3.55891500	-7.11266400	-3.96432300
H	1.84332700	-6.83231200	-4.25738000
H	2.34787300	-8.21288600	-3.28450500
C	1.01448700	-6.39836100	-1.74834900
H	0.31605300	-6.12483800	-2.54132800
H	0.84569600	-5.74577700	-0.89677000
H	0.80205500	-7.42703900	-1.45174400

C	2.73397600	-4.83330600	-2.71563700
H	3.74942500	-4.74466600	-3.10586200
H	2.61201500	-4.13448800	-1.89322000
H	2.04089400	-4.55810500	-3.51269900
H	4.29930500	-8.31019100	-2.26940300
H	5.97376900	-7.71840600	1.65595300
C	6.07826300	-9.17475900	-0.59801700
C	7.10757900	-9.70822900	0.35237400
H	6.00442000	-9.65281600	-1.56694500
C	7.42652000	-11.17549300	0.13748200
C	7.50678700	-12.00483600	1.24760200
C	7.67426900	-11.68892300	-1.12989500
C	7.83751900	-13.34783600	1.09155600
C	8.00461000	-13.03200100	-1.27808900
C	8.08960500	-13.87707400	-0.17227400
H	7.32077600	-11.62422500	2.24320500
H	7.63224600	-11.07029700	-2.01567700
H	8.34177600	-14.91681300	-0.29299800
O	8.23466900	-13.44665600	-2.54758800
C	8.57549200	-14.80589700	-2.75527900
H	7.77412600	-15.46708900	-2.42124200
H	9.50018600	-15.06278100	-2.23572000
O	7.89261900	-14.08074600	2.22974600
C	8.21990300	-15.45503000	2.12303300
H	9.21318000	-15.58964700	1.69148200
H	7.48439300	-15.98767700	1.51784000
C	10.43869100	-9.49869900	-1.06773800
C	9.10873900	-8.93294600	-1.02344800
C	11.09443100	-9.85274000	0.06020200
C	10.50720300	-9.67893100	1.37558900
C	9.26705700	-9.19143900	1.50350300
C	8.41458300	-8.83349700	0.33041600
O	8.63416400	-8.98137100	2.67374200
O	8.51326800	-8.55315500	-2.02159400
H	9.19498200	-9.24121900	3.41501400
H	8.20879000	-15.84793700	3.13454900
H	8.71757900	-14.92180800	-3.82488300
H	6.72413600	-9.60999000	1.36591700
H	8.09702500	-7.79363900	0.45116800
H	11.09239800	-9.94084000	2.24814900
H	10.89263200	-9.61519100	-2.04255700
C	12.47089600	-10.43461800	0.01561800
H	12.84021100	-10.52021800	-1.00266200
H	12.46948100	-11.42225600	0.48067100
H	13.15649300	-9.81405600	0.59538800



S2.25

Free Energy = -1768.168104

0 1

C	3.92291500	-5.85200900	0.11713800
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C	5.00394000	-6.18106500	1.09405300
C	4.56458400	-7.77016400	-1.23639500
C	5.60805900	-8.11245800	-0.29159200
C	5.77389700	-7.26070200	0.86920100
O	3.19237000	-4.88666000	0.30348700
C	5.19303300	-5.28189400	2.31297900
C	3.92165100	-5.28466900	3.17759500
H	3.06785500	-4.88999600	2.63497500
H	4.08789900	-4.66876000	4.06327600
H	3.69068700	-6.29818000	3.51043400
C	6.34843400	-5.76767600	3.19003900
H	6.44869400	-5.09539500	4.04256100
H	7.29650200	-5.77221200	2.65077700
H	6.17387000	-6.77346600	3.57483100
C	5.52280400	-3.84800300	1.86677000
H	4.71505600	-3.41415600	1.28492300
H	6.43490600	-3.83690000	1.26735200
H	5.69123500	-3.22658200	2.74814400
C	2.65190800	-6.36942400	-2.09017400
C	2.63533400	-7.35982600	-3.25638400
H	3.57825300	-7.35432500	-3.80521900
H	1.84345900	-7.07536000	-3.94954000
H	2.43473700	-8.37805700	-2.91988300
C	1.27284300	-6.42746500	-1.41360200
H	0.49864300	-6.21102100	-2.15205000
H	1.19405600	-5.70560700	-0.60598900
H	1.08757900	-7.42578900	-1.01316200
C	2.89137000	-4.96853100	-2.67598300
H	3.86224200	-4.92506300	-3.17283700
H	2.85654300	-4.20285200	-1.90645800
H	2.12201900	-4.75150100	-3.41925500
H	4.47315400	-8.42244200	-2.09438600
H	6.56142000	-7.51201800	1.56752200

C	6.39478000	-9.17889000	-0.54152100
C	7.49429900	-9.66839200	0.35392800
H	6.21463500	-9.74252700	-1.44871000
C	7.71721900	-11.16462200	0.26414900
C	7.68195800	-11.91163800	1.43304800
C	8.00586800	-11.78254700	-0.94640400
C	7.95588600	-13.27691100	1.39654300
C	8.26818800	-13.14901600	-0.97666900
C	8.25220700	-13.91046700	0.19267000
H	7.44895200	-11.45498300	2.38702000
H	8.03043600	-11.23141900	-1.87649400
H	8.46073800	-14.96642700	0.16400300
O	8.53769100	-13.67085800	-2.19574300
C	8.81420800	-15.05804500	-2.28537700
H	7.96426100	-15.65005100	-1.94230900
H	9.70005500	-15.31951700	-1.70438000
O	7.92350200	-13.91643900	2.58888200
C	8.19817800	-15.30712300	2.60785400
H	9.20515100	-15.51176000	2.24075800
H	7.47159600	-15.85742200	2.00806600
C	8.83682600	-8.89420600	0.13998800
H	7.20231700	-9.45075200	1.37946600
C	9.32523400	-8.95831800	-1.30425400
C	9.85092900	-9.30762000	1.16706900
H	8.61558300	-7.83657900	0.32667100
C	11.10470400	-9.61971700	0.84416500
C	11.54111500	-9.61652200	-0.54814300
C	10.70245900	-9.30994400	-1.55926900
O	12.81200800	-9.93376200	-0.81685700
O	8.55094400	-8.69495900	-2.21161000
H	11.04396000	-9.32815100	-2.58400500
H	13.30523400	-10.13338000	-0.01295300
H	8.99711300	-15.26184700	-3.33535200
H	8.12049300	-15.61613000	3.64507800
H	11.84147100	-9.85667300	1.60096100
C	9.42362200	-9.15340100	2.59407500
O	9.83290600	-10.00203100	3.53165800
O	8.71305300	-8.22978300	2.90937800
C	10.44597700	-11.27465500	3.27922300
H	11.52091100	-11.18949100	3.41891800
H	10.21620100	-11.63925400	2.28278200
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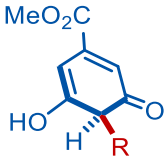

S2.26

Free Energy = -1768.179003

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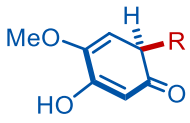
C	3.58598900	-5.99872000	0.07380900
C	3.59055000	-6.73497800	-1.22215700
C	4.55302200	-6.40142100	1.14029500
C	4.46334500	-7.74388200	-1.38012300
C	5.40151800	-8.15308000	-0.35372700
C	5.38349000	-7.43021300	0.90175600
O	2.80219800	-5.07875200	0.26577000
C	4.56191600	-5.63380700	2.45920700
C	3.19785800	-5.75992900	3.15719600
H	2.40122300	-5.32998000	2.55744900
H	3.23457000	-5.23795400	4.11500500
H	2.96591900	-6.80827800	3.35295700
C	5.62280300	-6.18148500	3.41701800
H	5.59750600	-5.60037100	4.33886200
H	6.62780000	-6.10116700	2.99896300
H	5.43616200	-7.22504400	3.67568100
C	4.88851400	-4.15303900	2.20481000
H	4.13868500	-3.68056500	1.57723900
H	5.86339300	-4.05568000	1.72380400
H	4.92870400	-3.62461900	3.15888800
C	2.61038200	-6.31545200	-2.31452900
C	2.77114000	-7.17924400	-3.56723700
H	3.77102600	-7.09021700	-3.99452000
H	2.05556600	-6.84634200	-4.31920400
H	2.57341000	-8.23215700	-3.36095200
C	1.16392300	-6.47959000	-1.82063500
H	0.47571700	-6.20919700	-2.62352900
H	0.96092300	-5.84669500	-0.96168700
H	0.97104600	-7.51830200	-1.54654400
C	2.86417400	-4.85527900	-2.72278900
H	3.88498600	-4.73487500	-3.08980000
H	2.70798700	-4.17484200	-1.89078600
H	2.18123400	-4.58230200	-3.52927200
H	4.50338200	-8.30231700	-2.30551300
H	6.08306400	-7.73969200	1.66436900
C	6.26758100	-9.15370300	-0.61141700
C	7.29071800	-9.67799000	0.35051300
H	6.22535400	-9.61644500	-1.58986100
C	7.65316300	-11.13216300	0.11554800

C	7.73004200	-11.98056300	1.21085000
C	7.94529000	-11.61270000	-1.15542100
C	8.10329900	-13.31044100	1.03685200
C	8.31865300	-12.94252400	-1.32160000
C	8.40170500	-13.80635200	-0.23033100
H	7.51035300	-11.62541200	2.20895600
H	7.90176400	-10.98133600	-2.03236900
H	8.68740600	-14.83567700	-0.36497400
O	8.59053100	-13.32449300	-2.59244100
C	8.97679500	-14.66887000	-2.81827100
H	8.18786100	-15.35974700	-2.51651500
H	9.89630100	-14.90844700	-2.28164600
O	8.15210800	-14.06356300	2.16121500
C	8.52591700	-15.42469200	2.03717800
H	9.53340900	-15.51895700	1.62864600
H	7.82300900	-15.96818000	1.40365100
C	10.60665800	-9.43534200	-1.03568700
C	9.28308900	-8.82424200	-0.97903400
C	11.23053900	-9.80686700	0.09814400
C	10.65880000	-9.64497100	1.41572200
C	9.42369000	-9.14190600	1.54006700
C	8.57709600	-8.76723200	0.36745900
O	8.78535100	-8.94035100	2.70648500
O	8.72826600	-8.38733500	-1.97082600
H	9.33401400	-9.22091100	3.44959800
H	8.50230400	-15.83716600	3.04060600
H	9.14730600	-14.75877000	-3.88617300
H	6.88968200	-9.60536700	1.35934900
H	8.23058800	-7.74007500	0.50910500
H	11.24718500	-9.93065500	2.27554600
H	11.06347500	-9.54928900	-2.00685600
C	12.60274900	-10.41499900	0.05528200
O	13.07599300	-10.54685800	-1.17682400
O	13.20447600	-10.74759200	1.04511900
C	14.38312500	-11.12293500	-1.28137700
H	15.10571200	-10.50455200	-0.75412000
H	14.60739900	-11.15503100	-2.34113700
H	14.38331000	-12.12455100	-0.85786500



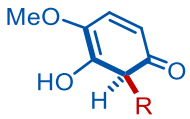
S2.27

Free Energy = -1654.82895

0 1

C	3.90795500	-5.96326900	0.26564000
C	3.56755000	-6.86077700	-0.87251100
C	5.08605700	-6.29538000	1.12191000
C	4.33806200	-7.94108700	-1.08676000
C	5.48428300	-8.27834900	-0.26732400
C	5.79756900	-7.40081200	0.84075900
O	3.23204800	-4.96919500	0.50137500
C	5.43660100	-5.37198400	2.28580700
C	4.27295200	-5.31607700	3.28896100
H	3.37335100	-4.91234500	2.83408900
H	4.55358500	-4.68129000	4.13134800
H	4.05582600	-6.31337400	3.67566600
C	6.67213500	-5.86784200	3.04072700
H	6.88706400	-5.17709500	3.85616400
H	7.55212000	-5.90769600	2.39634600
H	6.51289000	-6.85628100	3.47456400
C	5.75007800	-3.96015800	1.76383500
H	4.89243900	-3.52020700	1.26364600
H	6.58850800	-3.99033700	1.06565500
H	6.03196300	-3.32051500	2.60209600
C	2.36498000	-6.52052700	-1.74927100
C	2.17832300	-7.55266600	-2.86334600
H	3.04388700	-7.59381000	-3.52622100
H	1.31181700	-7.27189900	-3.46233300
H	1.99870100	-8.55179700	-2.46357500
C	1.07940700	-6.51130100	-0.90658700
H	0.22536300	-6.30014900	-1.55276100
H	1.11942300	-5.75698500	-0.12623600
H	0.92014100	-7.48760100	-0.44528700
C	2.56585400	-5.15031600	-2.41649100
H	3.46656600	-5.15611700	-3.03293200
H	2.64995800	-4.35639600	-1.68010800
H	1.71453900	-4.93596000	-3.06518800
H	4.12858200	-8.61698000	-1.90490200
H	6.64655400	-7.66045100	1.45585900
C	6.21970700	-9.36466500	-0.58318700
C	7.44585100	-9.84599500	0.14604200
H	5.91667900	-9.95170100	-1.44098500
C	7.56125200	-11.35818400	0.05265600
C	6.47829200	-12.10779500	0.50248400

C	8.68175700	-12.00503000	-0.44362100
C	6.51726400	-13.49507100	0.45111500
C	8.71523600	-13.39805300	-0.49203200
C	7.63831600	-14.15927100	-0.04841500
H	5.59423500	-11.62620100	0.90018900
H	9.55157000	-11.47302600	-0.80084400
H	7.66964000	-15.23471500	-0.08849800
O	9.85184900	-13.93893100	-0.99397500
C	9.94043200	-15.35055800	-1.07257900
H	9.15962000	-15.75719400	-1.71751800
H	9.86786700	-15.80389000	-0.08252800
O	5.41742700	-14.13916300	0.91146800
C	5.41063000	-15.55552300	0.87963800
H	6.21398800	-15.96592800	1.49372500
H	5.50745400	-15.92571000	-0.14232800
C	8.70968000	-9.06133700	-0.27758100
H	7.31022100	-9.61806800	1.20636800
C	9.07229300	-9.23264100	-1.74824200
C	9.83737100	-9.23099900	0.69306400
H	8.42654600	-7.99902300	-0.22690300
C	11.10452800	-9.25484900	0.28198400
C	11.43023100	-9.19024100	-1.15003300
C	10.47329900	-9.17077100	-2.10181900
O	12.72263300	-9.18036600	-1.47434800
O	8.19460300	-9.36978100	-2.58678900
H	10.74278300	-9.18178100	-3.14797300
H	13.25027200	-9.22811700	-0.66295700
H	10.91350900	-15.56929100	-1.50029800
H	4.45223900	-15.86235600	1.28588500
H	9.58540000	-9.27394000	1.74361700
O	12.21966600	-9.34767000	1.04147500
C	12.03335000	-9.43499100	2.44616000
H	11.52451800	-8.54427100	2.81673200
H	13.02334200	-9.50633300	2.88252600
H	11.44968200	-10.32217300	2.69517000



S2.28

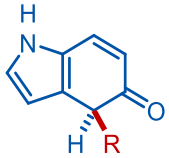
Free Energy = -1654.823893

0 1

C	3.67459700	-5.98694400	-0.01613400
C	3.66522900	-6.72578200	-1.31067700

C	4.63855800	-6.40105700	1.04894100
C	4.52074000	-7.74951500	-1.46743800
C	5.45155200	-8.17354100	-0.44023200
C	5.45077200	-7.44487500	0.81270900
O	2.90476500	-5.05531000	0.17575700
C	4.66481500	-5.62732600	2.36396800
C	3.30188300	-5.72827500	3.06819300
H	2.50955500	-5.28815800	2.47011800
H	3.35126500	-5.20290000	4.02359100
H	3.05400100	-6.77190800	3.26958600
C	5.72102900	-6.18715900	3.31973800
H	5.70972500	-5.60058700	4.23844600
H	6.72502200	-6.12723300	2.89625500
H	5.51866700	-7.22622300	3.58485500
C	5.01409600	-4.15325600	2.10083400
H	4.26998000	-3.67192100	1.47317500
H	5.98887000	-4.07406400	1.61628400
H	5.06589800	-3.62067600	3.05203600
C	2.68986400	-6.29287800	-2.40208300
C	2.83533900	-7.16095400	-3.65367300
H	3.83604500	-7.08865500	-4.08218800
H	2.12429400	-6.81778400	-4.40531400
H	2.62099700	-8.21024400	-3.44555300
C	1.24186400	-6.43431100	-1.90562600
H	0.55652800	-6.15522500	-2.70800200
H	1.04964700	-5.79674800	-1.04767100
H	1.03386400	-7.46946500	-1.62914900
C	2.96504500	-4.83734600	-2.81293100
H	3.98700100	-4.73284200	-3.18161100
H	2.82035000	-4.15341100	-1.98172300
H	2.28504700	-4.55528400	-3.61876900
H	4.54969200	-8.31128000	-2.39124800
H	6.14901700	-7.76236500	1.57381500
C	6.29222700	-9.19771300	-0.69001700
C	7.29801100	-9.73700700	0.28078300
H	6.23819300	-9.66563700	-1.66548600
C	7.68109900	-11.18322800	0.03085700
C	7.84642000	-12.02024500	1.12441000
C	7.93786800	-11.65960300	-1.24988600
C	8.28299000	-13.32949500	0.94098600
C	8.38267700	-12.96501000	-1.42531200
C	8.55959400	-13.81602200	-0.33481800
H	7.65597400	-11.66902900	2.13001300
H	7.84240300	-11.03375900	-2.12630700
H	8.89995600	-14.82768900	-0.47627200
O	8.63478400	-13.33546600	-2.70466400

C	9.11722600	-14.64694300	-2.93709700
H	8.39404600	-15.39582100	-2.60982400
H	10.06806000	-14.81068000	-2.42685100
O	8.41805300	-14.07156600	2.06620000
C	8.86998000	-15.40776200	1.93350600
H	9.86567200	-15.44238300	1.48806900
H	8.17927800	-15.99742800	1.32850800
C	10.59206700	-9.79478000	-0.90452000
C	9.35588400	-8.99612400	-0.96167000
C	11.13213300	-10.11408700	0.28779500
C	10.53051200	-9.72997600	1.55306600
C	9.34568300	-9.11559500	1.57776800
C	8.58514200	-8.81556400	0.33179000
O	8.66815500	-8.73776600	2.68836700
O	8.91774000	-8.54696000	-2.00159600
H	9.15203700	-8.99863200	3.48087500
H	8.90884900	-15.81509300	2.93858600
H	9.26300500	-14.72981000	-4.00927100
H	6.88001600	-9.67826700	1.28442500
H	8.23348500	-7.78286000	0.36781500
H	11.05275000	-9.96652500	2.47015100
H	12.05498300	-10.67432400	0.33296200
O	11.07216500	-10.11788900	-2.12486800
C	12.21502900	-10.95174500	-2.15247800
H	13.07149300	-10.45759900	-1.68915400
H	12.42826800	-11.14703000	-3.19831900
H	12.01670700	-11.89280000	-1.63354200



S2.29

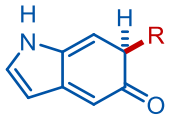
Free Energy = -1596.655726

0 1

C	4.41197900	-6.31761300	-0.08211000
C	5.22679500	-6.73212000	-1.26039400
C	4.55617300	-7.07161900	1.19833800
C	6.06133000	-7.77491500	-1.12283400
C	6.21022200	-8.52283300	0.11276300
C	5.40367900	-8.11301500	1.24584200
O	3.63721900	-5.37357900	-0.16250600
C	3.74501900	-6.62709300	2.41266400
C	2.23996900	-6.72512100	2.11671100
H	1.94958300	-6.07075500	1.30015400

H	1.67831100	-6.44126000	3.00856300
H	1.96902400	-7.75080800	1.86004000
C	4.03676800	-7.50899400	3.62913600
H	3.44967700	-7.14835500	4.47394600
H	5.09059800	-7.47394400	3.91004700
H	3.75966600	-8.54913100	3.44995900
C	4.11590000	-5.18345700	2.79010600
H	3.88196100	-4.48770300	1.98953000
H	5.18104700	-5.11337500	3.01891500
H	3.55929900	-4.88946900	3.68175900
C	5.08653000	-5.95668400	-2.56757000
C	6.00042000	-6.52760700	-3.65395400
H	7.05224100	-6.46901000	-3.37005900
H	5.86820500	-5.94656300	-4.56678200
H	5.75879000	-7.56696300	-3.88125300
C	3.64148200	-6.04429400	-3.08453100
H	3.56729700	-5.51909000	-4.03849900
H	2.93997800	-5.59685100	-2.38660200
H	3.35893500	-7.08550300	-3.24980900
C	5.48105000	-4.48611200	-2.35610700
H	6.51207600	-4.41566100	-2.00486200
H	4.83102700	-3.99818300	-1.63582600
H	5.41096900	-3.95339900	-3.30621200
H	6.67443700	-8.10613800	-1.95016400
H	5.52623800	-8.66410700	2.16438700
C	7.10716500	-9.52842200	0.15689500
C	7.47457700	-10.37069400	1.33619600
H	7.68658200	-9.70973500	-0.74336400
C	7.51080400	-11.86090000	1.03850000
C	7.76581200	-12.73372500	2.09165800
C	7.29881200	-12.36893200	-0.23368500
C	7.82676100	-14.10248900	1.86650400
C	7.36234000	-13.74454300	-0.45388200
C	7.63239800	-14.62667700	0.58713800
H	7.91525000	-12.37176000	3.10022400
H	7.08102300	-11.73468100	-1.07988300
H	7.68148000	-15.68796900	0.41291000
O	7.14704000	-14.14406300	-1.73052500
C	7.19925300	-15.53126500	-2.01282800
H	6.44013400	-16.07528900	-1.44825900
H	8.18511400	-15.94084000	-1.78623100
O	8.07975400	-14.87295300	2.95199500
C	8.15096700	-16.27670400	2.77371300
H	8.35817100	-16.69544300	3.75320900
H	8.95499300	-16.54488700	2.08632600
C	10.26253300	-7.51018400	0.86109200

C	9.34713900	-7.33397400	1.83580700
C	10.56318300	-8.82767000	0.39473500
C	9.94750300	-9.96971400	0.86615900
C	8.86002700	-9.87761300	1.88545300
C	8.64234800	-8.46345100	2.43755200
N	11.48956300	-9.20003700	-0.54116200
C	11.47449300	-10.55158500	-0.66988000
C	10.52466800	-11.06709900	0.19013400
H	12.09532600	-8.57430000	-1.04594500
H	12.13646700	-11.04893000	-1.35689700
H	10.28448500	-12.11028100	0.30967800
O	7.85184300	-8.30781900	3.35536700
H	6.77291000	-10.21427900	2.15329600
H	9.09056300	-10.50113300	2.75107100
H	9.10669600	-6.35331800	2.22108800
H	10.78130500	-6.66119200	0.43257100
H	7.00137000	-15.63149600	-3.07510600
H	7.20522800	-16.67380800	2.40130500



S2.30

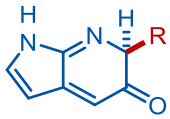
Free Energy = -1596.637362

0 1

C	4.08959500	-5.97743800	0.03117300
C	4.40383200	-6.56617800	-1.30216300
C	4.62157800	-6.64029900	1.26087400
C	5.15067600	-7.68162600	-1.34712600
C	5.67051100	-8.34009900	-0.16426800
C	5.35486900	-7.75752900	1.12494800
O	3.40380000	-4.96813800	0.12079900
C	4.31034200	-6.02869600	2.62376000
C	2.79159300	-6.00880600	2.86199300
H	2.27973000	-5.39871200	2.12368800
H	2.58843500	-5.60117800	3.85385400
H	2.38734600	-7.02188200	2.82432100
C	4.94511800	-6.83840900	3.75691400
H	4.70367100	-6.36231200	4.70726300
H	6.03235800	-6.87682000	3.66916300
H	4.56284000	-7.85988800	3.78919300
C	4.87479300	-4.60062700	2.70223700
H	4.42126800	-3.95014000	1.96016400
H	5.95558200	-4.60997400	2.55025500

H	4.67726400	-4.19009400	3.69398600
C	3.86811900	-5.88265600	-2.55741200
C	4.30275900	-6.62475800	-3.82295900
H	5.38888400	-6.65365700	-3.92224500
H	3.90151300	-6.10368000	-4.69233000
H	3.92414400	-7.64773900	-3.84257500
C	2.33116100	-5.86397900	-2.53582100
H	1.96303600	-5.40315200	-3.45424700
H	1.95038000	-5.30139400	-1.68849900
H	1.93912300	-6.88145400	-2.48831800
C	4.41053800	-4.44737000	-2.65257500
H	5.50154800	-4.45422800	-2.68354200
H	4.08742200	-3.84117400	-1.81130300
H	4.04993500	-3.98602400	-3.57367400
H	5.40338000	-8.14162900	-2.29295500
H	5.74088800	-8.25585300	2.00202900
C	6.43491400	-9.44274400	-0.30057100
C	7.06253900	-10.20797900	0.82321500
H	6.62688100	-9.79606600	-1.30816800
C	7.32014000	-11.66369000	0.49096800
C	6.95485700	-12.63166500	1.41781300
C	7.94231700	-12.04282000	-0.69204900
C	7.21812200	-13.97410400	1.16483200
C	8.20334400	-13.38689600	-0.93859700
C	7.84605900	-14.36812700	-0.01531900
H	6.47631400	-12.35786600	2.34826000
H	8.24692800	-11.32131000	-1.43725600
H	8.04763900	-15.40745700	-0.21153500
O	8.81807400	-13.66273300	-2.11548000
C	9.11082600	-15.01608500	-2.41382900
H	8.19892200	-15.61348500	-2.46396100
H	9.78638100	-15.44444500	-1.67144700
O	6.82794500	-14.84644600	2.12633200
C	7.07428600	-16.22520400	1.91555100
H	6.69108800	-16.73850200	2.79157300
H	8.14312100	-16.42265900	1.81714700
C	9.39802700	-9.39476800	0.23455300
C	8.37607500	-9.48743700	1.31564000
C	10.56222600	-10.02429300	0.38992300
C	10.90874900	-10.78843300	1.59975300
C	10.05956200	-10.85600000	2.66338600
C	8.79402600	-10.17562100	2.61620000
N	11.65304400	-10.13559500	-0.46723100
C	12.60044800	-10.91526800	0.12456100
C	12.21313300	-11.33159600	1.36308500
H	11.70914900	-9.75195400	-1.39407000

H	12.78701700	-11.94702900	2.03257900
O	8.00994500	-10.14432700	3.56302700
H	9.59519500	-15.01392300	-3.38498700
H	6.55413800	-16.58580700	1.02645700
H	6.40651300	-10.18281000	1.69174600
H	9.15816600	-8.84188700	-0.66538900
H	8.06240300	-8.47704900	1.59441700
H	10.31633100	-11.39252700	3.56649600
H	13.52069000	-11.12616200	-0.39652800



S2.31

Free Energy = -1612.702081

0 1

C	4.02642500	-6.77112000	-0.20027700
C	4.99500100	-6.32315100	-1.24243800
C	4.50387500	-7.66668500	0.89622900
C	6.26743000	-6.74605100	-1.15663600
C	6.74603200	-7.61277200	-0.09768100
C	5.79686500	-8.02912100	0.91426400
O	2.85763600	-6.40978000	-0.23926100
C	3.51168600	-8.14264500	1.95328800
C	2.37802600	-8.94159800	1.28956700
H	1.81377200	-8.33032200	0.59146700
H	1.69829200	-9.30968100	2.06005800
H	2.78256900	-9.80390200	0.75641700
C	4.18573000	-9.06358000	2.97396200
H	3.44138200	-9.38726600	3.70169100
H	4.98353300	-8.55368600	3.51671000
H	4.60438300	-9.95500900	2.50198100
C	2.93186600	-6.94255100	2.71878700
H	2.38820100	-6.27355500	2.05807200
H	3.72998800	-6.38212800	3.20878000
H	2.24912400	-7.30236500	3.49061000
C	4.50530200	-5.40749100	-2.36137200

C	5.63737200	-5.05868800	-3.32994900
H	6.45031200	-4.53100900	-2.82897000
H	5.24543900	-4.40540000	-4.10967200
H	6.04532600	-5.94791000	-3.81282200
C	3.39986600	-6.10309300	-3.17205000
H	3.08703000	-5.45086100	-3.98944600
H	2.53389400	-6.32709900	-2.55601300
H	3.77374600	-7.03222600	-3.60588000
C	3.97568500	-4.08921700	-1.77403500
H	4.76056000	-3.58118500	-1.21086900
H	3.12611200	-4.25690500	-1.11849700
H	3.66419600	-3.43115300	-2.58726500
H	7.00159500	-6.44944400	-1.89358800
H	6.16848300	-8.66835100	1.70060400
C	8.03153900	-8.01516700	-0.09110600
C	8.66102000	-8.90174500	0.94906200
H	8.67778800	-7.67446800	-0.89290000
C	8.04092300	-10.28576900	1.04122600
C	7.77592500	-10.82290200	2.29457500
C	7.77012100	-11.02437600	-0.10244600
C	7.24069800	-12.10279200	2.40189100
C	7.24904100	-12.30954400	0.01335300
C	6.97663200	-12.86322400	1.26391000
H	7.97465200	-10.26034700	3.19740200
H	7.95661600	-10.62344100	-1.08897400
H	6.56401400	-13.85412800	1.34844500
O	7.02985900	-12.96525200	-1.15218000
C	6.50212300	-14.27849400	-1.09050800
H	5.51953000	-14.28491100	-0.61576200
H	7.17367200	-14.94596200	-0.54777200
O	6.99653100	-12.53917200	3.66111500
C	6.43950100	-13.83171200	3.82299700
H	6.32084200	-13.97811200	4.89170000
H	7.10451100	-14.59872400	3.42252200
N	10.43273800	-9.52384200	-0.62139300
C	10.19971500	-8.99841700	0.70768800
C	10.94492600	-10.68029000	-0.67269900
C	11.41252800	-11.53587700	0.45421500
C	11.35104500	-11.05284300	1.71100800
C	10.80261100	-9.72275100	1.90983500
N	11.18110600	-11.41333400	-1.82052700
C	11.71446000	-12.63345000	-1.47700800
C	11.87793200	-12.75965000	-0.13728700
H	10.93146300	-11.11804300	-2.74878200
H	12.28497100	-13.61194100	0.37624500
O	10.76471800	-9.18143500	3.00415300

H	6.40940100	-14.61566600	-2.11783700
H	5.46568500	-13.90281000	3.33556400
H	8.55501300	-8.42612600	1.92690300
H	10.57866900	-7.97411300	0.73789700
H	11.70214700	-11.59967400	2.57567700
H	11.94935900	-13.34646200	-2.25065500



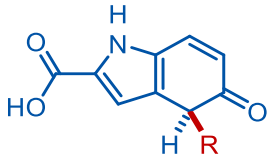
S2.32

Free Energy = -1612.703056

0 1

C	4.40966800	-6.31002800	-0.06585600
C	5.22586600	-6.72598000	-1.24323000
C	4.53450900	-7.07770600	1.20947800
C	6.05163800	-7.77541500	-1.10702000
C	6.18877800	-8.53072100	0.12616600
C	5.37392200	-8.12507200	1.25542000
O	3.64949200	-5.35477100	-0.14220100
C	3.71487000	-6.63795600	2.41953200
C	2.21228100	-6.71263200	2.10461200
H	1.93994900	-6.04385400	1.29354900
H	1.64408600	-6.43308800	2.99360100
H	1.93111300	-7.73123700	1.83136000
C	3.98038700	-7.53842700	3.62834900
H	3.38541800	-7.18227500	4.46945800
H	5.03020600	-7.51757500	3.92543100
H	3.69508100	-8.57323100	3.43209300
C	4.10061500	-5.20399100	2.81854200
H	3.88440400	-4.49556700	2.02415300
H	5.16403500	-5.15084800	3.05955600
H	3.53815000	-4.91370000	3.70767500
C	5.09772500	-5.94290900	-2.54692100
C	6.00783900	-6.51941300	-3.63351400
H	7.05967000	-6.47241000	-3.34760200
H	5.88322800	-5.93384600	-4.54447700
H	5.75596700	-7.55544700	-3.86486400
C	3.65291900	-6.01215400	-3.06743600
H	3.58722100	-5.48242000	-4.01946100
H	2.95467000	-5.55930900	-2.36970600
H	3.35884200	-7.04937300	-3.23752700
C	5.50824900	-4.47784600	-2.32761700
H	6.53894600	-4.42054500	-1.97316000
H	4.86165800	-3.98548200	-1.60728100

H	5.44696000	-3.94054600	-3.27570900
H	6.66696700	-8.10676000	-1.93253500
H	5.47987900	-8.68726300	2.16929700
C	7.08112400	-9.54038500	0.17053400
C	7.44224000	-10.38563100	1.35129300
H	7.66406600	-9.72192300	-0.72727600
C	7.48821300	-11.87521800	1.05383500
C	7.74173100	-12.74657400	2.10835900
C	7.28807400	-12.38215800	-0.22051200
C	7.81088400	-14.11493500	1.88247000
C	7.35935800	-13.75749400	-0.44096200
C	7.62664700	-14.63871800	0.60150400
H	7.88232300	-12.38494300	3.11831100
H	7.07206900	-11.74824900	-1.06735600
H	7.68172100	-15.69966600	0.42692600
O	7.15401300	-14.15713200	-1.71875800
C	7.21340500	-15.54413900	-2.00145900
H	6.45292000	-16.09122900	-1.44176100
H	8.19950400	-15.94977700	-1.76905000
O	8.06094300	-14.88465600	2.96866100
C	8.13963100	-16.28818100	2.79016500
H	8.34289400	-16.70623300	3.77074500
H	8.94904700	-16.55215100	2.10753100
N	10.24161200	-7.52438300	0.80324700
C	9.36568500	-7.35763500	1.72394700
C	10.50253500	-8.81730500	0.42512700
C	9.91926100	-9.97763200	0.88846400
C	8.82759300	-9.89392700	1.90198400
C	8.63108700	-8.46558300	2.39707700
N	11.43866000	-9.14652300	-0.51428700
C	11.46283000	-10.49593200	-0.65515800
C	10.52749700	-11.04860600	0.20054100
H	12.01848500	-8.48554500	-1.00569000
H	12.13845800	-10.96885000	-1.34572400
H	10.31753100	-12.09956700	0.30838200
O	7.86146300	-8.21738700	3.30156300
H	6.73739400	-10.23049400	2.16628100
H	9.05363900	-10.49808900	2.78245100
H	9.12862300	-6.35491300	2.06410000
H	7.02238400	-15.64443600	-3.06495600
H	7.19790800	-16.68921900	2.41195600



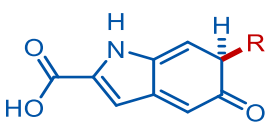
S2.33

Free Energy = -1596.655726

0 1

C	4.40917800	-6.30386100	-0.06076000
C	5.19031400	-6.70263800	-1.26750300
C	4.58697500	-7.07694700	1.20460000
C	6.03062900	-7.74467400	-1.16658900
C	6.21532300	-8.50803800	0.05513500
C	5.43716600	-8.11675600	1.21466800
O	3.63506800	-5.35758100	-0.10576800
C	3.80716200	-6.65189700	2.44597100
C	2.29501700	-6.74461700	2.18661600
H	1.98423700	-6.07720200	1.38840800
H	1.75662200	-6.47471100	3.09691200
H	2.01674200	-7.76596500	1.92072300
C	4.12822700	-7.55372100	3.64023400
H	3.56119800	-7.20776800	4.50459500
H	5.18821200	-7.52207600	3.89751300
H	3.84759400	-8.59096400	3.45032800
C	4.18910100	-5.21481100	2.83715400
H	3.93454800	-4.50582200	2.05472700
H	5.25995700	-5.14889800	3.03884500
H	3.65642600	-4.93549900	3.74790900
C	5.01063400	-5.91204100	-2.56058600
C	5.89123100	-6.47030500	-3.68047400
H	6.95116600	-6.41342600	-3.42827500
H	5.73067700	-5.87956000	-4.58242100
H	5.64360300	-7.50743500	-3.91146800
C	3.55045900	-5.99448500	-3.03416900
H	3.44766200	-5.45913200	-3.97976700
H	2.87026000	-5.55457900	-2.31078700
H	3.26286700	-7.03388800	-3.20200000
C	5.41137500	-4.44382000	-2.34439600
H	6.45221500	-4.37692700	-2.02269600
H	4.78272800	-3.96360600	-1.60038000
H	5.31375700	-3.90098600	-3.28628300
H	6.62118800	-8.06390100	-2.01474300
H	5.58289700	-8.68150400	2.12136600
C	7.11639600	-9.51067200	0.06185800
C	7.51516900	-10.36736200	1.22064700
H	7.67186700	-9.67736500	-0.85630800

C	7.53681000	-11.85486000	0.91028900
C	7.79195500	-12.73648200	1.95587200
C	7.33170700	-12.34939200	-0.36819100
C	7.85944100	-14.10292800	1.71683600
C	7.40136200	-13.72280800	-0.60219300
C	7.67229500	-14.61404000	0.43098700
H	7.93805300	-12.38305200	2.96803600
H	7.11550100	-11.70722600	-1.20870500
H	7.72622800	-15.67329000	0.24600100
O	7.19195900	-14.10982300	-1.88279700
C	7.25272800	-15.49388400	-2.18015300
H	6.49482900	-16.04791600	-1.62386300
H	8.24028000	-15.90004300	-1.95497400
O	8.11178800	-14.88302200	2.79450700
C	8.18970700	-16.28497700	2.60253700
H	8.39536100	-16.71218600	3.57863300
H	8.99733000	-16.54254200	1.91541000
C	10.35868000	-7.57859500	0.59630300
C	9.47132500	-7.36149500	1.58119500
C	10.62489200	-8.92552000	0.17078700
C	9.98951100	-10.03929400	0.69538200
C	8.92376200	-9.89592300	1.73068800
C	8.75695700	-8.46209500	2.24160700
N	11.52074100	-9.33893100	-0.75754800
C	11.48036600	-10.69825100	-0.84162600
C	10.53127700	-11.16645800	0.05497800
H	12.14187000	-8.76419700	-1.30743600
H	10.26119700	-12.19577300	0.23331300
O	7.99943100	-8.25094700	3.17104800
H	6.84286000	-10.21208200	2.06194400
H	9.15700900	-10.50237000	2.60733000
H	9.25178300	-6.36627000	1.94112400
H	7.05864700	-15.58326700	-3.24403200
H	7.24686900	-16.68206100	2.22304000
H	10.88316000	-6.75701200	0.12546300
C	12.37450900	-11.36956400	-1.78465400
O	12.30593300	-12.70547100	-1.84574500
O	13.14904400	-10.76877300	-2.48724100
H	11.64310700	-13.05587200	-1.23852900



S2.34

Free Energy = -1596.637362

0 1

C	4.12219300	-5.97306000	0.03702400
C	4.40059000	-6.57340800	-1.29933800
C	4.66526000	-6.63997200	1.26002100
C	5.13389200	-7.69721400	-1.35349400
C	5.67093000	-8.35518700	-0.17771700
C	5.38276500	-7.76610700	1.11513600
O	3.45688400	-4.95121300	0.13472900
C	4.38432200	-6.02054300	2.62583400
C	2.86977800	-5.97450600	2.88630100
H	2.35731800	-5.35696100	2.15463900
H	2.68831300	-5.56202500	3.88032400
H	2.44790700	-6.98063900	2.85644300
C	5.02195500	-6.83835800	3.75150600
H	4.80121800	-6.35699300	4.70421300
H	6.10716700	-6.89384800	3.64898800
H	4.62411500	-7.85363300	3.79078000
C	4.97430900	-4.60220500	2.69211900
H	4.52258000	-3.94634000	1.95372200
H	6.05268000	-4.63084300	2.52613600
H	4.79678600	-4.18517500	3.68493600
C	3.84660100	-5.89051300	-2.54691200
C	4.24051600	-6.64828400	-3.81649600
H	5.32340400	-6.69298600	-3.94165800
H	3.82568500	-6.12835800	-4.68014100
H	3.84760100	-7.66606000	-3.81877400
C	2.31100700	-5.84790300	-2.49003300
H	1.92898600	-5.38952900	-3.40396300
H	1.95840500	-5.27191300	-1.63952100
H	1.90457400	-6.85868600	-2.42424700
C	4.40847600	-4.46443700	-2.66512600
H	5.49822700	-4.48816600	-2.72110900
H	4.11394800	-3.84741000	-1.82126600
H	4.03367200	-4.00424300	-3.58110700
H	5.36269900	-8.16454700	-2.30177500
H	5.77623100	-8.26672400	1.98752000
C	6.42648800	-9.46222900	-0.32512200
C	7.07212200	-10.22765100	0.78830800
H	6.59880000	-9.81992200	-1.33465600
C	7.32040500	-11.68475600	0.45508000
C	6.96618000	-12.65014800	1.38898400
C	7.92932400	-12.06642900	-0.73387600
C	7.23000600	-13.99291100	1.13793300
C	8.19333100	-13.41058500	-0.97723200

C	7.84885500	-14.38911500	-0.04631900
H	6.49567300	-12.37526600	2.32326800
H	8.22303000	-11.34717200	-1.48552800
H	8.05229100	-15.42851600	-0.24034400
O	8.79874300	-13.68844700	-2.15799000
C	9.09848800	-15.04133200	-2.45198300
H	8.19040500	-15.64522800	-2.49183700
H	9.78299500	-15.46097600	-1.71282600
O	6.85086000	-14.86268000	2.10564500
C	7.09826700	-16.24175000	1.89720100
H	6.72398700	-16.75282800	2.77833000
H	8.16661400	-16.43713700	1.78994700
C	9.39076600	-9.41296400	0.14279200
C	8.40163400	-9.50841200	1.25279800
C	10.53324500	-10.09518400	0.23713200
C	10.88492900	-10.90583400	1.41333200
C	10.08714000	-10.96580200	2.50908600
C	8.84873400	-10.22009700	2.52827500
N	11.58322800	-10.23290400	-0.66076500
C	12.51060200	-11.07846300	-0.12690400
C	12.15685400	-11.51047500	1.11400200
H	11.64660400	-9.84705500	-1.58820600
H	12.70972400	-12.16436900	1.76691500
O	8.11944100	-10.16922300	3.51184300
H	9.57513100	-15.04059400	-3.42693100
H	6.57095900	-16.60626000	1.01397800
C	13.71392800	-11.37827600	-0.94804900
O	14.59512600	-12.24204100	-0.45010100
O	13.88401300	-10.86303200	-2.01894100
H	14.31752800	-12.59426500	0.40457000
H	6.43450700	-10.19711200	1.67052800
H	9.14056900	-8.82774700	-0.73293200
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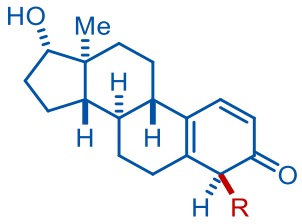
H	10.35518800	-11.53535200	3.38798200



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C	7.18018500	-5.08868200	7.37305300
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C	6.23761100	-6.05266900	7.70774300
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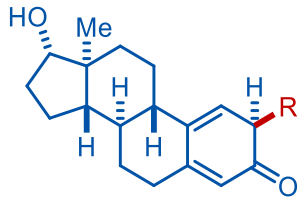

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H	5.06476500	-9.73390000	5.09116500
H	6.66701100	-9.01550400	5.32345100
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C	9.04243600	-2.92552500	0.41774700
C	9.01384800	-4.08217300	-0.47384700

O	5.78915100	-3.82990000	-1.92473400
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H	13.67167900	0.86040000	4.02857200
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H	13.02667900	0.83951800	0.35317400
H	14.01848700	-0.44808700	-0.31529500
O	15.27194000	-0.43690600	1.95040600
H	13.97430400	-1.35704600	3.25709900
H	15.63162600	-1.29816600	1.71777200
H	13.76929000	-2.82378600	0.48578000
H	12.96275100	-3.12288800	2.02179100

Chapter 3 Total Synthesis of a Diverse Array of Resveratrol Dimers

3.1 Introduction

[2] The resveratrol dimers represent a diverse class of polyphenolic compounds, with over 100 isolated to date. They are produced by a small set of phylogenetically distinct plant families.[219] With the biosynthetic pathways not fully explored, it can be difficult to draw conclusions from how their distribution through the plant kingdom affects their structure, or mechanism of action. Nevertheless there exists key structural features and mechanistic pathways which seem reasonable and are used to explain the occurrence of the resveratrol dimers.[33]

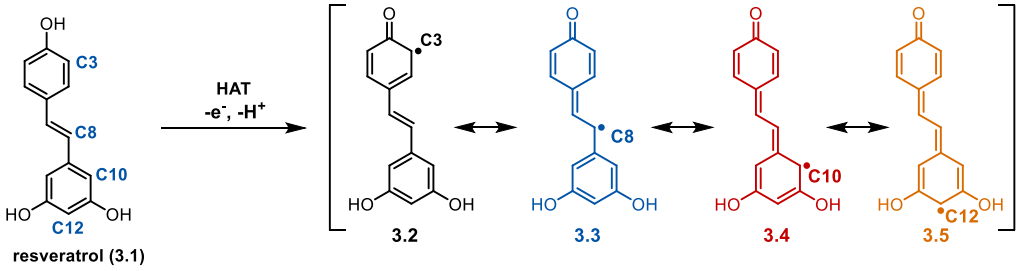


Figure 3.1 Oxidation of resveratrol yields C3, C8, C10, and C12 radical resonance forms

As more thoroughly discussed in Section 1.4, Langcake and Pryce postulated that the resveratrol oligomers arise from the oxidative generation of phenoxy radicals.[25] The coupling of these C8 these radicals is dominated by C8-C10', C8-C8', and C8-C3' (Figure 3.1). Following dimerization various regiodivergent nucleophilic trappings, Friedel-Crafts reactions and

[2] Portions of this chapter appear in: Hammerstad, T.A.; Roldan, B.J.; Schoenmakers, K.; Warner, A.; Kapenga, O.; Galliher, M.S.; Snyder, R.; Stephenson, C.R.J.; Total Synthesis of Five Diverse Resveratrol Dimers via a Biomimetic Radical Oligomerization. *Submitted*

tautomerizations finish the core diversifications. While the structural diversity is impressive, almost all resveratrol oligomers can be retroactively mapped onto these simple disconnections.

The C3-C8' dimers represent the least structurally diverse class of oligomers (Figure 3.2).[33] Coupling of the C3 (**3.3**) and C8 (**3.2**) followed by tautomerization yields **3.6** which can undergo *5-exo-trig* cyclization forming δ-viniferin (**3.7**). This natural product, isolated recently in comparison (1998) to others, is also referred to as the resveratrol-*trans*-dehydrodimer and is found in many resveratrol producing plants.[220] Kouzi and co-workers who reported the isolation of δ-viniferin from grapevine pathogen *Botrytis*.[221] This finding provides evidence that the resveratrol dimers are not exclusively synthesized by the plant and that extracellular organisms may also play a role in their biosynthesis.

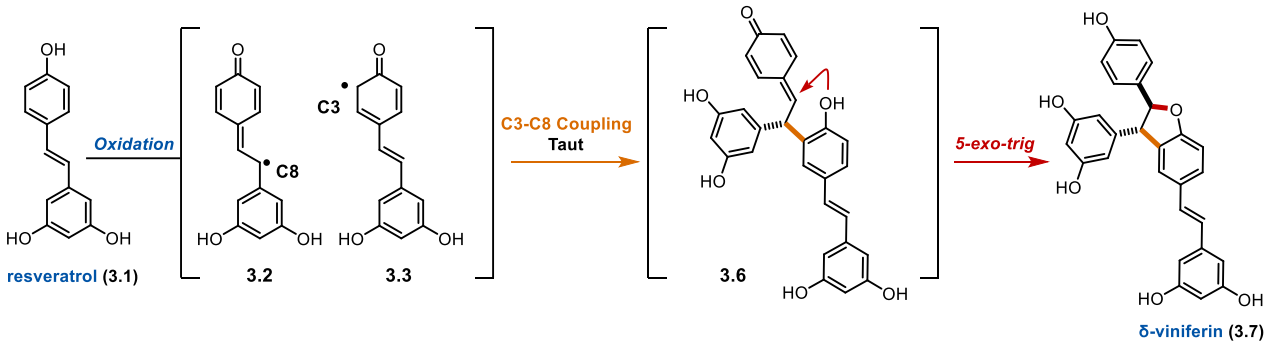


Figure 3.2 Biosynthesis of selected C3-C8 dimers

In contrast the C8-C10 coupling mode is by far the most well represented for the resveratrol oligomers (Figure 3.3).[33] This can be rationalized by combinatorics, as the coupled dimer (**3.8**) has many distinct reactivity modes available to it. This can be further realized by comparison, as the C3-C8 class (Figure 3.2) proceed via an intermediate (**3.6**) which lacks mechanistically diverse options. The parent molecule of the C8-C10 dimers, ε-viniferin (**3.9**, Figure 3.3),[25] formed via oxa-addition to the quinone, has been found in both enantiomeric forms, which is rare for the resveratrol oligomers.[222] In an acidic environment the quinone can be regenerated (**3.10**) allowing a subsequent *7-exo-trig* cyclization yielding ampelopsin B (**3.11**).[223]

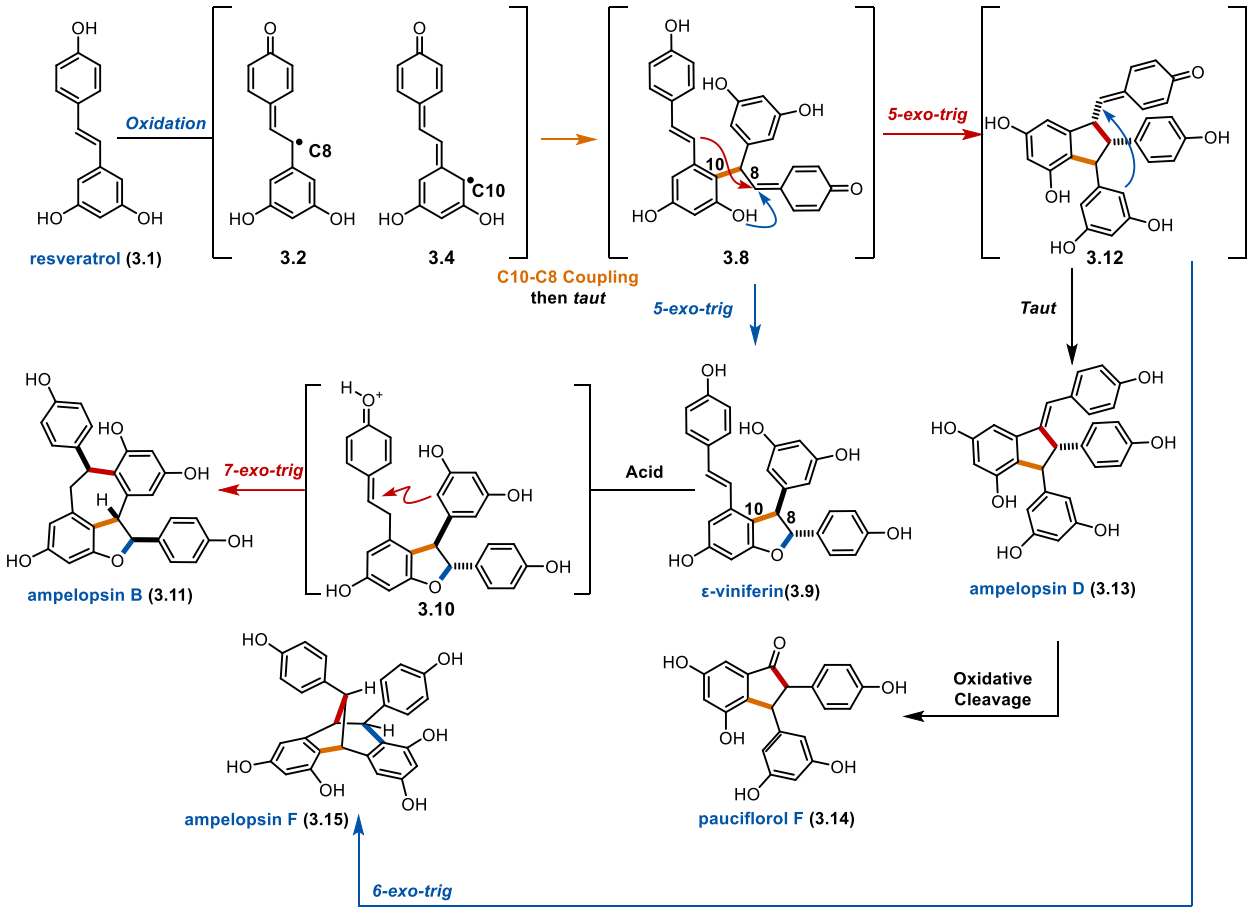


Figure 3.3 Biosynthesis of selected C8-C10 dimers

Instead continuing from intermediate **3.8** a carbogenic *5-exo-trig* provides **3.12** which upon tautomerization affords ampelopsin D (**3.13**).[224] Oxidative cleavage of the olefin of ampelopsin D results in pauciflorol F (**3.14**).[225] Ampelopsin F (**3.15**)[226] is generated via a *6-exo-trig* cyclization of **3.12** providing the caged [3.2.1] core. Methanolic trapping of the quinone (**3.12**) provides solid evidence of its existence as is the case with viniferethers A/B (not drawn).[227]

The C8-C8 dimers pose an inflection point as the dimeric intermediate (**3.16**, **3.19**, Figure 3.4) generates vicinal stereocenters. This feature is not present in the C8-C3 and C8-C10 dimers. The C_2-symmetric diastereomer has the correct relative configuration to undergo serial *5-exo-trig* cyclizations to form pallidol (**3.17**).[228] The product of water addition, restrytisol A (**3.18**) is also derived from this diastereomer.[229] The *meso* diastereomer (**3.19**) also offers divergent reactivities

with *5-exo-trig* yielding quadrangularin A (**3.20**)[230] which was originally isolated as cyphostemmin B.[231] This product is not capable of a second cyclization, as the formation of a *trans*-fused bicyclo[3.3.0]octane is energetically unfavorable.[232]

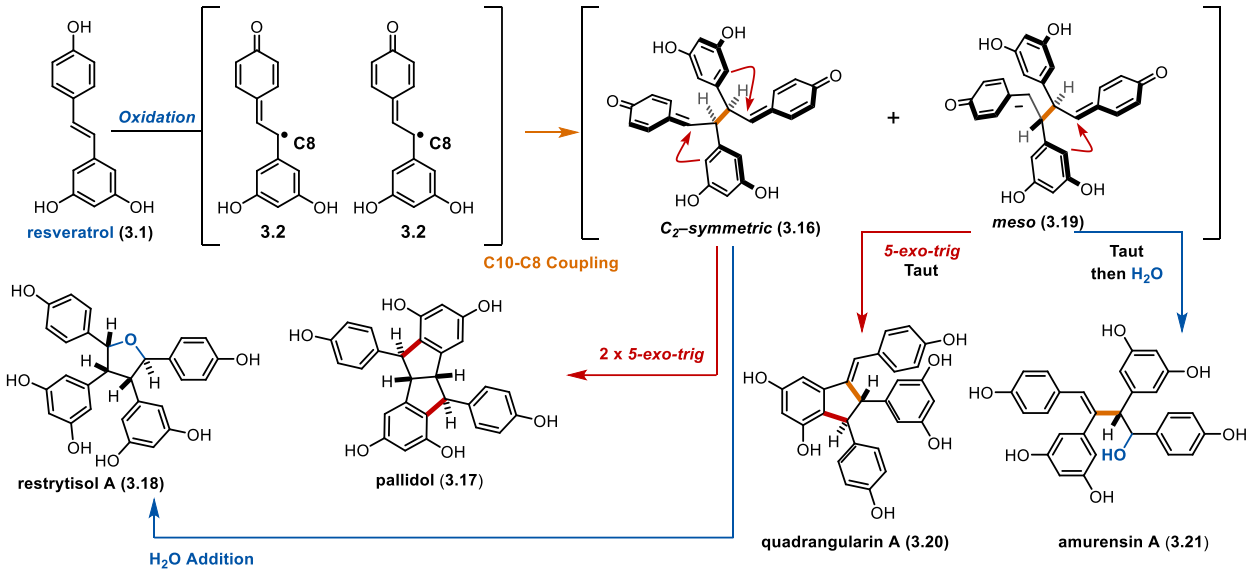


Figure 3.4 Biosynthesis of the C8-C8 dimers

The *meso* diastereomer can undergo tautomerization, followed by water addition to the quinone forming amurensin A (**3.21**). It is important to note that the addition of water and low molecular weight alcohols (MeOH, EtOH) should be viewed with skepticism as these natural products could simply be isolation artifacts.

3.2 Existing enzymatic and chemical oxidations towards resveratrol dimers

Many of the biosynthetic hypotheses of the resveratrol oligomers are directly supported by experiments, namely the oxidation of resveratrol and its derivatives. These studies draw on a rich history of mechanistic work completed on the lignans, another polyphenolic class of natural products.[233] When (E)-isoeugenol (**3.22**) is oxidized with horseradish peroxidase the predominant product is licarin A (65%, **3.23**).[234,235] This provides evidence that dihydrobenzofuran containing polyphenolic natural products may form via similar radical intermediates. The other products isolated (**3.24-3.27**) also have mechanistic similarities as the trapping of a homobenzylic radical

by a phenoxy radical (**3.24**, **3.25**) or quinone trapping by water (**3.26**, **3.27**) are evident. Earlier studies by Freudenberg also report the enzymatic oxidation of lignan related phenols (E-coniferyl alcohol, not drawn) resulted in approximately 30 dimeric and oligomeric adducts.[236] The common theme among these unselective oxidation attempts is the synthesis of a large number of mechanistically related dimers, often in low yield.

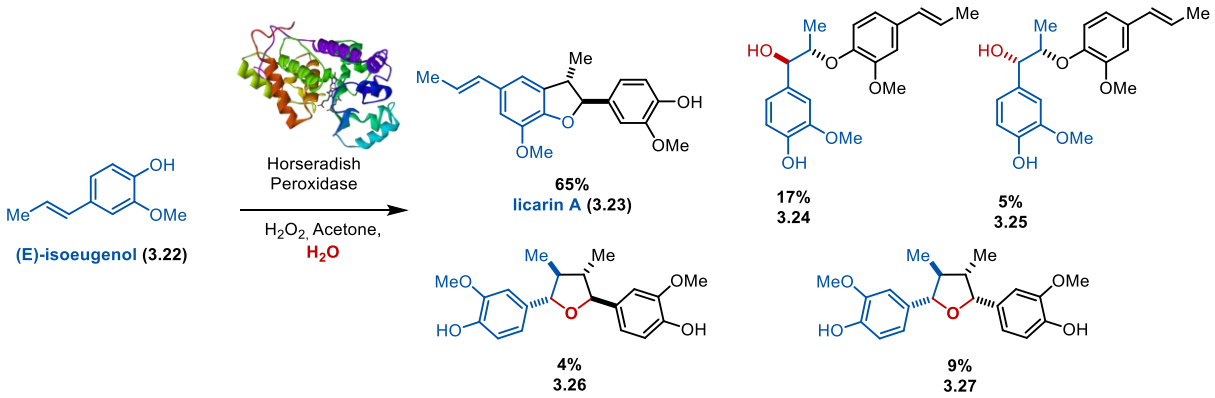


Figure 3.5 Enzymatic oxidation of (E)-isoeugenol (3.22) provides licarin A (3.23)

Following precedent for related phenolic systems, as outlined above (Figure 3.5),[234,235] Langcake and Pryce reported the dimerization of resveratrol (**3.1**) to δ-viniferin (**3.7**) in a 41% yield (Figure 3.6).[237] This publication also reports that δ-viniferin has similar *in vitro* and *in vivo* antifungal properties as ε-viniferin. All products were isolated as single diastereomers and racemic. The phenols are key to activity, as dimerization product of *trans*-4-hydroxystilbene shows no activity. This seminal report has been highly influential as most biosynthetic studies on the resveratrol oligomers have been conducted using horseradish peroxidase.[33] This is likely due to its promiscuity in phenol oxidations, and its commercial availability. Since this report there have been many studies demonstrating the dimerization of resveratrol using inorganic,[42,43] organic,[238] and photochemical oxidations.[239] The most successful simple oxidation strategy was reported by Sako in which δ-viniferin could be synthesized in 97% yield with silver acetate.[41]

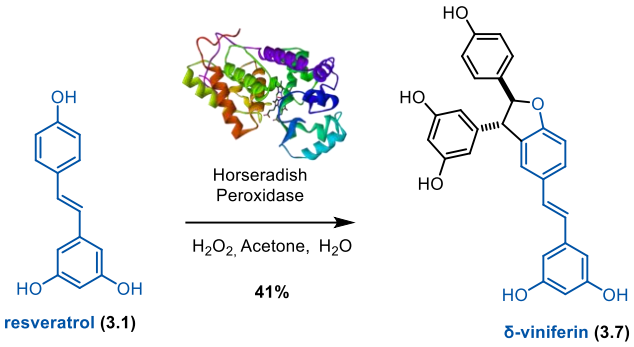


Figure 3.6 Langcake and Pryce enzymatic oxidation of resveratrol (3.1) to δ-viniferin (3.7)

Another nuance is presented by Hamann and co-workers who found that *B. cinera* is capable of producing an array of C8-C8' dimers (Figure 3.7) when resveratrol is added to its fermentation broth.[38] All natural products isolated were found to be in their optically active forms. The authors postulate that fungi may produce oligomers via fungal laccase activity, in addition to inducing expression in plants. It is important to note that *B. cinera* is the same necrotrophic fungus which was by Langcake and Pyrce in their seminal isolation efforts of resveratrol.[25] This lends credence to the hypothesis that fungi utilize oxidative catalysis to detoxify resveratrol which provides further evidence that resveratrol oligomers are not solely plant metabolites.

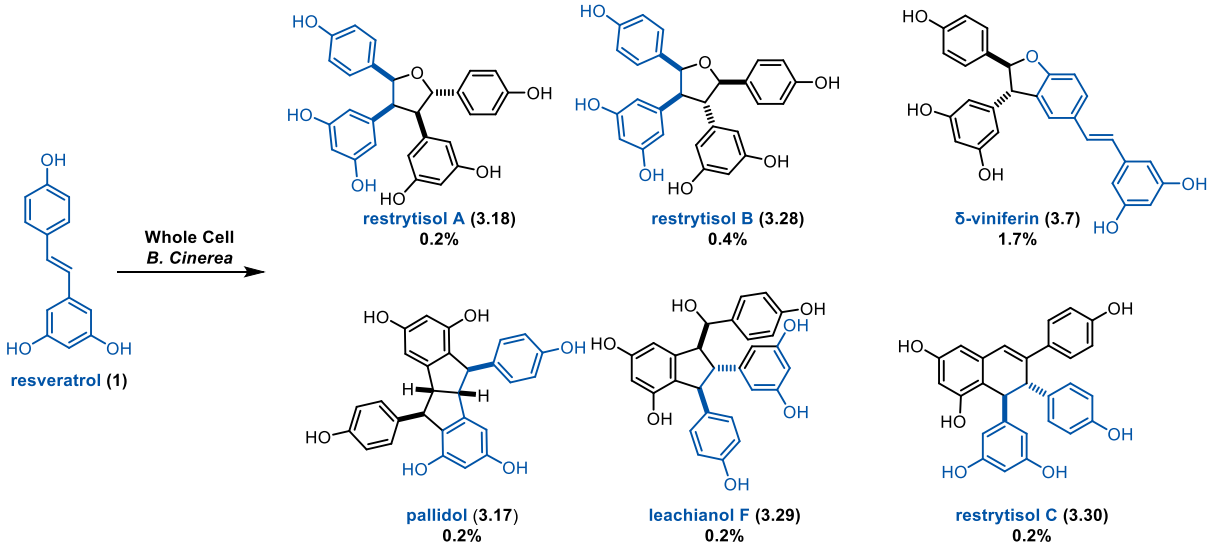


Figure 3.7 Hamann's Dimerization of resveratrol using whole cell *B. Cinera*

In 1998 Pezet and co-workers isolated a laccase-like stilbene oxidase from *B. cineara*, the same pathogen used by Hamann.[240] This 32-kDa laccase was purified vis SDS-PAGE (single band) and was used to catalyze the oxidation of resveratrol to ε-viniferin in 1h at a 30 °C incubation in 97.13% yield (Figure 3.8). It is unclear what affords this selectivity as most enzyme preferentially form δ-viniferin. The other caveat is that this method was performed on µg scale and has not been validated on a more preparatively useful scale.

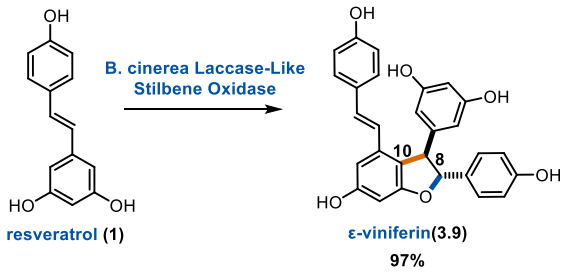
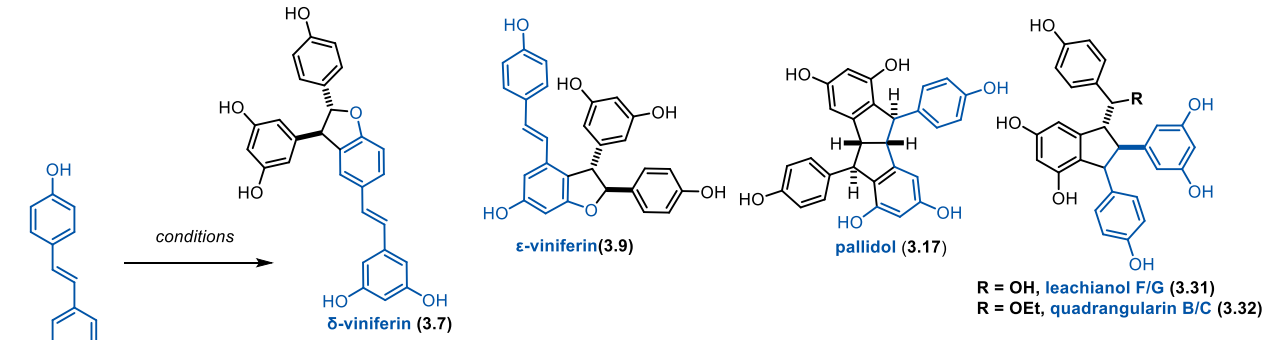


Figure 3.8 Pezet's oxidation of resveratrol with laccase-like stilbene oxidase

A more practical synthesis of ε-viniferin was reported in 2004 by Yao and co-workers.[241] This reaction used one equivalent of $FeCl_3$ in methanol for 49 hours producing a 30% yield of ε-viniferin. This reaction was effectively scaled to 500 mg and was used in the synthesis of ampelopsin B.[242]

A year later Niwa and co-workers reported similar oxidative conditions to generate ε-viniferin.[42] This work used precise temperature control and reported a degree of transformation, which is more commonly referred to as a yield "by remaining starting material." The use of HPLC quantification provides additional credibility of the study and allowed the reporting of minor products. The use of thallium nitrate gave 30.1% yield of ε-viniferin with 56% recovered resveratrol (Table 3.1). The variety of enzymes were also used and leachinol F/G (**3.31**) and quadrangularin B/C (diastereomers) were only under these conditions. It is not fully understood how the conditions presented prevent overoxidation.[243]

Table 3.1 Niwa's chemical and enzymatic oxidations of resveratrol to dimers



Reagent / Peroxidase	Solvent	Temperature (°C)	Time	3.9 (%)	3.7 (%)	3.17 (%)	3.31 (%)	3.32 (%)
$Tl(NO_3)_3$	MeOH	-50	5 min	30.1				
$Tl(NO_3)_3$	MeOH	-30	5 min	3.9				
$K_3[Fe(CN)_6]$	MeOH	25	10 min	21.9	22.5	15.7		
$Ce(SO_4)_2$	MeOH	-50	26 h	3.7	8.4			
$FeCl_3$	Acetone	25	20 h	0.9	97.0	1.5		
MnO_2	DCM	25	24 h		91.0	9.0		
Glycine max	Acetone	27	30 min		21.4	7.2	1.8	
Athyomyces ramosus	Acetone	27	30 min		18.4	7.4	4.6	
Horseradish	Acetone	27	30 min		12.6	10.2		
Glycine max	EtOH	27	30 min		12.1	9.5	5.2	8.6
Athyomyces ramosus	EtOH	27	30 min		13.1	5.0	4.6	8.2

*All yields Degree of transformation (%DT) = (mole product x 2)/(mol of resveratrol x 100) calculated via HPLC peak area

In 2006 Hou and co-workers reported one of the first biomimetic total syntheses of a resveratrol dimer, quadrangularin A (**3.20**, Figure 3.9).[44] The key advancement that allowed this effort was the use of 2,6 di-^{t}Bu blocking group on the stilbene (**3.37**) to prevent the standard C3-C8 coupling seen with unprotected resveratrol. This again draws on earlier work in lignan biosynthesis were Müller[244] and Wallis[245] both employed the use of blocking groups (^{t}Bu or OMe) to direct reactivity. The authors reported that their choice of the use of ^{t}Bu groups was also guided by the knowledge that their removal was well precedented.[246–248] This synthesis began with a simple phenolic acid (**3.33**) which was Fischer esterified,[249] benzylated,[87] reduced with LAH, chlorinated, and the halide displaced with triphenyl phosphine affording phosphonium salt (**3.34**). A simple Wittig reaction gave stilbene (**3.36**) in 91% yield. The removal of the Bn protecting groups proceeded smoothly (**3.37**, 78%). The author's original hypothesis was validated by the synthesis of quinone (**3.38**) using standard horseradish peroxidase conditions.

Tautomerization provided **3.39** in 95% yield (BRSM) followed by standard Lewis acid deprotection ($AlCl_3$). This synthesis was highly influential and many research groups, including the Stephenson lab, have utilized C3 blocking groups in the total synthesis of oligomers.

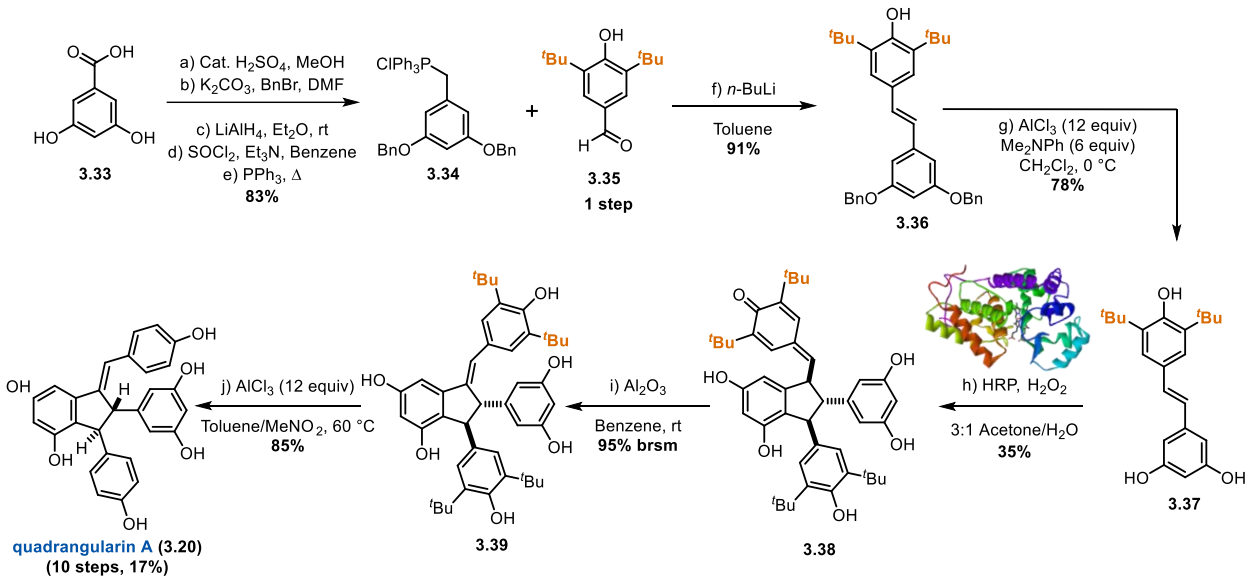


Figure 3.9 Hou's biomimetic total synthesis of quadrangularin A

In 2014 the Li group reported an application of *tert*-butyl blocking groups in the synthesis of pallidol via tetraarylfuran intermediates (Figure 3.10). The assembly of stilbene **3.41** occurs via a standard strategy of alkene formation (**3.40**) and acyl protection (**3.41**). Oxidation with hydrated iron trichloride provided two furan analogues of natural products in a 48% combined yield (**3.42**, **3.43**). Deprotection with strong acid provided pallidol (**3.17**) and not the desired furan natural products. Attempts were made to first remove the acetyl protecting groups followed by aluminum trichloride deprotection of the *tert*-butyl groups, but was unsuccessful. While not provided in the original publication, the reversion of **3.43** to a *bis*-quinone methide core (**3.45**) prior to cyclization is logical. It is unclear whether the acetyl protecting groups are removed before or after cyclization to the pallidol core.

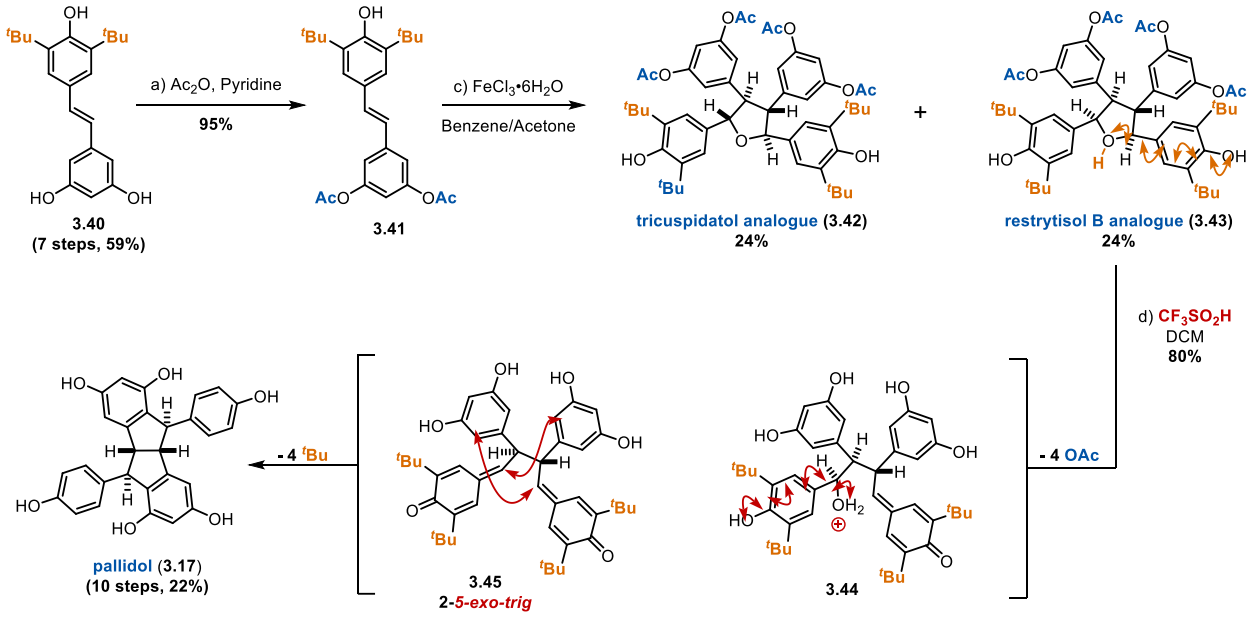
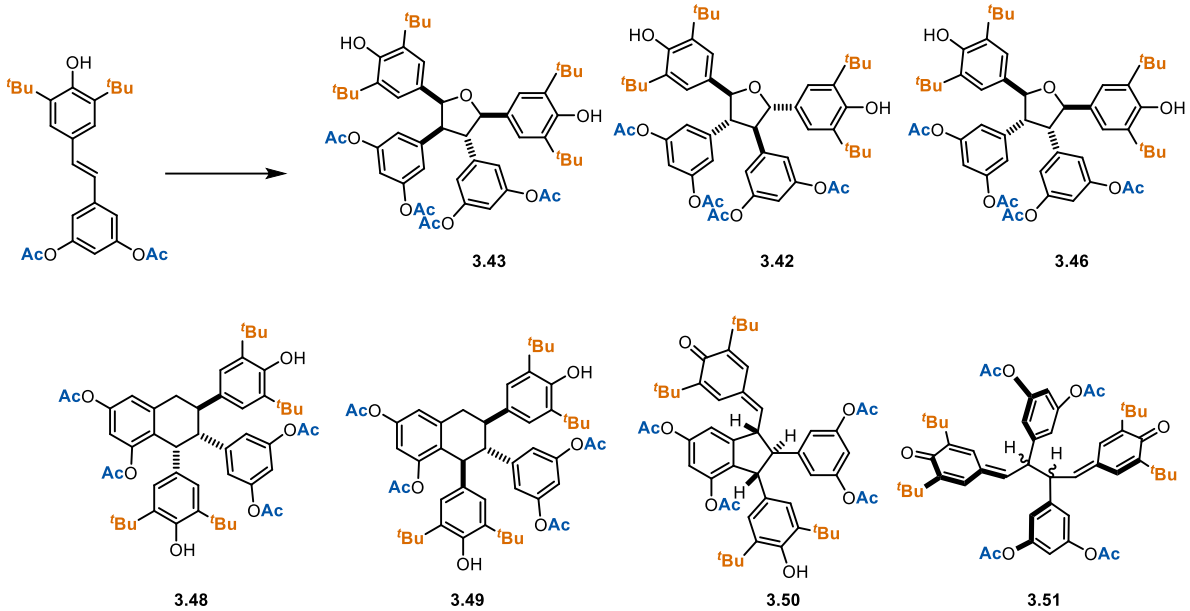


Figure 3.10 Li's biomimetic synthesis of pallidol via tetraarylfuran intermediates

This strategy of oxidative iron conditions was expanded in 2016 with another publication from the Li group (Table 3.2).[250] This study provides further insight into the influence of solvent and iron salt on the product distribution. Most notably a 2:1 ratio of acetone to benzene yields 95% *bis*-quinone methide (**3.51**). A mixture of the resformicol A precursor (**3.48**) and unnatural diastereomer (**3.49**) were both successfully deprotected with triflic acid (86%). As expected, the substituted tetrahydrofuan rings (**3.42**, **3.43**, **3.46**) could not be deprotected due to the propensity of this motif to extrude water and form pallidol under acidic conditions. More recently the Li group also has published a series of biomimetic oxidations using C3 halogen (**Br**, **I**) and methoxy (**OMe**) groups towards the synthesis of resveratrol oligomers and closely related analogues.[251–254]

Table 3.2 Li's oxidation of *tert*-butyl protected resveratrol with iron salts



Oxidant (eq)	Solvent(s)	Time (h)	Product (yield)	Product (yield)	Total Yield
$FeCl_3$•$6H_2O$ (1.5)	benzene-acetone (2:1)	24	3.43 (24%)	3.42 (24%)	48
$FeCl_3$•$6H_2O$ (1.5)	acetone	24	3.43 (44%)	3.42 (44%)	88
$FeCl_3$•$6H_2O$ (1.5)	benzene	5	complex		
$FeCl_3$•$6H_2O$ (1.5)	DCM	24	3.42 (26%)	3.46 (26%)	52
$FeCl_3$ (3.0)	benzene-acetone (2:1)	24	3.42 (38%)	3.42 (38%)	76
$FeCl_3$ (5.0)	acetone	3	3.42 (36%)	3.42 (22%)	58
$FeCl_3$ (2.0)	benzene	2	3.48/3.49 (21%)	3.51 (13%)	34
$FeCl_3$ (2.0)	DCM	5	complex		
$FeCl_3$•$6H_2O$ (5.0)	acetone-benzene (2:1)	3	*meso*-13a/b (95%)		95

*All reactions ran at room temperature

A more contemporary example of this strategy was employed by Iwabuchi and co-workers (Figure 3.11).[255] The use of a chromium salen catalyst (**3.53**) allowed the dimerization of electron rich resorcinols (**3.52**) to the corresponding quadrangularin A core (**3.54**). In contrast when less electron rich rings are used without the key 3,5 OH resorcinol ring (**3.55**) the *bis*-quinone methide is isolated (**3.56**). This trend is likely conserved throughout the resveratrol oligomers but has not been thoroughly investigated as the synthesis of closely related natural product analogues is not of high scientific interest.

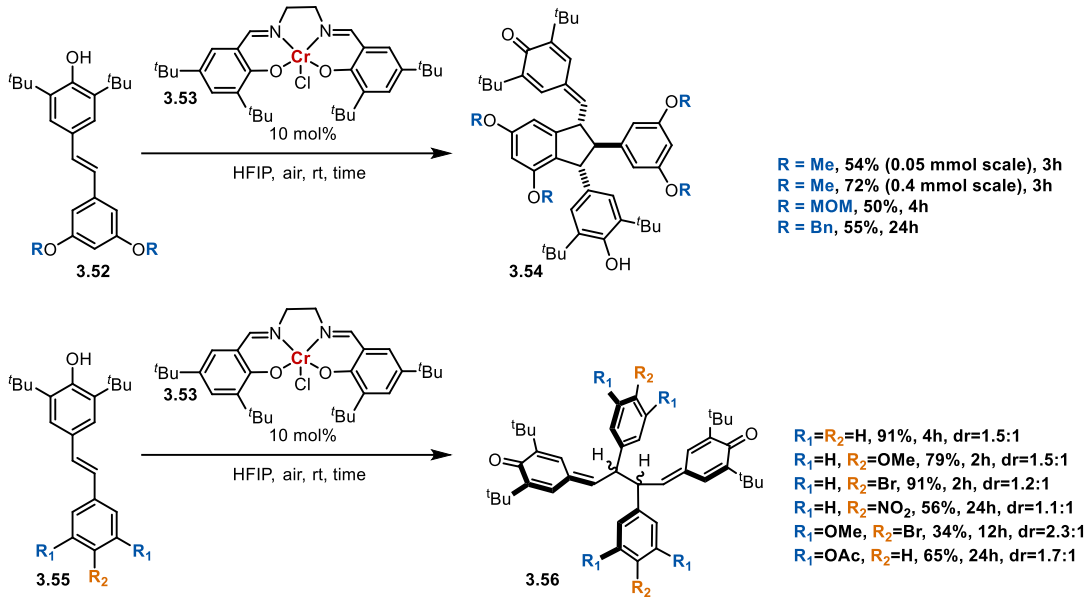
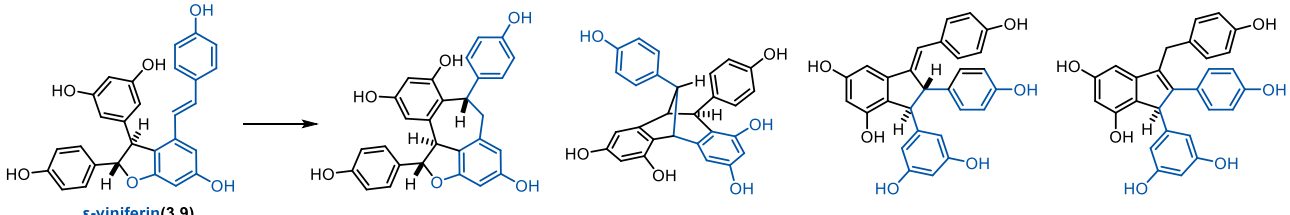


Figure 3.11 Iwabuchi's aerobic dimerization of hydroxystilbenoids with chromium

A final key example of biomimetic work was completed in 2002 by Niwa and co-workers in a series of biosynthetically relevant conversions of ε-viniferin (**3.9**, Table 3.3).[256] This work was undertaken in an effort to determine the absolute configuration of ampeolopsins A (not drawn), B (**3.11**), F (**3.15**), and D (**3.13**). This study also helped set the record straight that quadrangularin A and ampelopsin D are distinct compounds, while their ^{1}H and ^{13}C NMR spectra are "*very similar*."[256] The change in product as a function of acid, temperature, and time demonstrate the pervasive nuance of the class, and provide insights into how a plant, or family, could synthesize a relatively small number of oligomers which then rearrange to a more significant population.

Table 3.3 Niwa's acidic interconversions of ε-viniferin to diverse dimers



	ampelopsin B (3.11)	ampelopsin F (3.15)	ampelopsin D (3.13)	isoampelopsin D (3.57)
aq. HCl, rt 50h	38%	8%	---	---
$TfOH/CH_3NO_2$, rt 10h	---	38%	---	---
TfOH/MeOH, reflux, 7d	---	21%	14%	8%
H_2SO_4/MeOH, reflux, 5d	13%	19%	6%	10%

3.3 Selected *de novo* approaches to resveratrol dimers

In the realm of *de novo* approaches to resveratrol oligomers the Snyder lab (U Chicago) has provided many of the most flexible and elegant approaches. In 2007 the Snyder research group published a divergent approach to the synthesis of indane derived resveratrol dimers (Figure 3.12, Figure 3.13).[257] The total synthesis of both pauciflorol F (**3.14**) and ampelopsin D (**3.13**, Figure 3.12) began with a methyl protected stilbene derivative (**3.58**) which was synthesized in 66% yield over 6 steps.

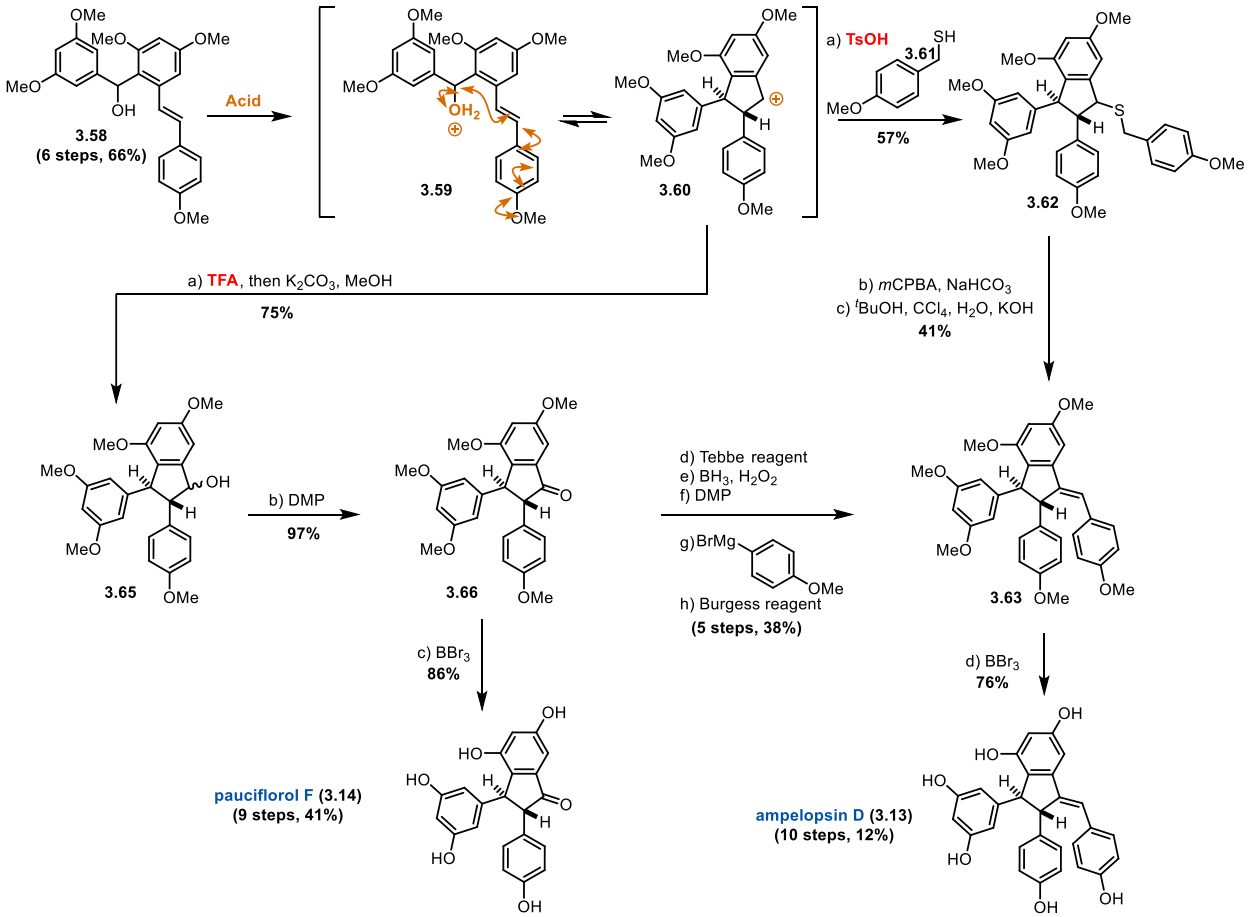


Figure 3.12 Snyders' synthesis of ampelopsin D and pauciflorol F

In the presence of acid the secondary alcohol acts as a leaving group and cyclization via the stilbene (**3.59**) provides a secondary carbocation (**3.60**) which can be diversified by judicious choice of reaction conditions. Trapping with a thiol (**3.61**) yields **3.62** which can be oxidized to

the corresponding sulfone and converted to olefin via a Meyers[258] modified Ramberg–Bäcklund[258] reaction (**3.63**). A final deprotection with BBr_3 provided ampelopsin D (**3.13**) in 12% overall yield across 10 steps. By instead treating hypothetical intermediate **3.60** with TFA followed by hydrolysis provides **3.65**. Standard DMP oxidation[259] followed by BBr_3 deprotection gave pauciflorol F (**3.14**, 41% over 9 steps). By varying the identity of the intermediate before acidification (**3.58**) the Snyder lab was able to achieve the same reactivity towards isopauciflorol F (**3.73**, Figure 3.13) and quadrangularin A (**3.20**, Figure 3.13). In this work they also disclosed a route from **3.71** to **3.70** via Tebbe olefination,[260] hydroboration oxidation, DMP oxidation, Grignard addition, and Burgess dehydration.[261] This effectively allows the interconversion from isopauciflorol F (**3.7**) and quadrangularin A (**3.20**).

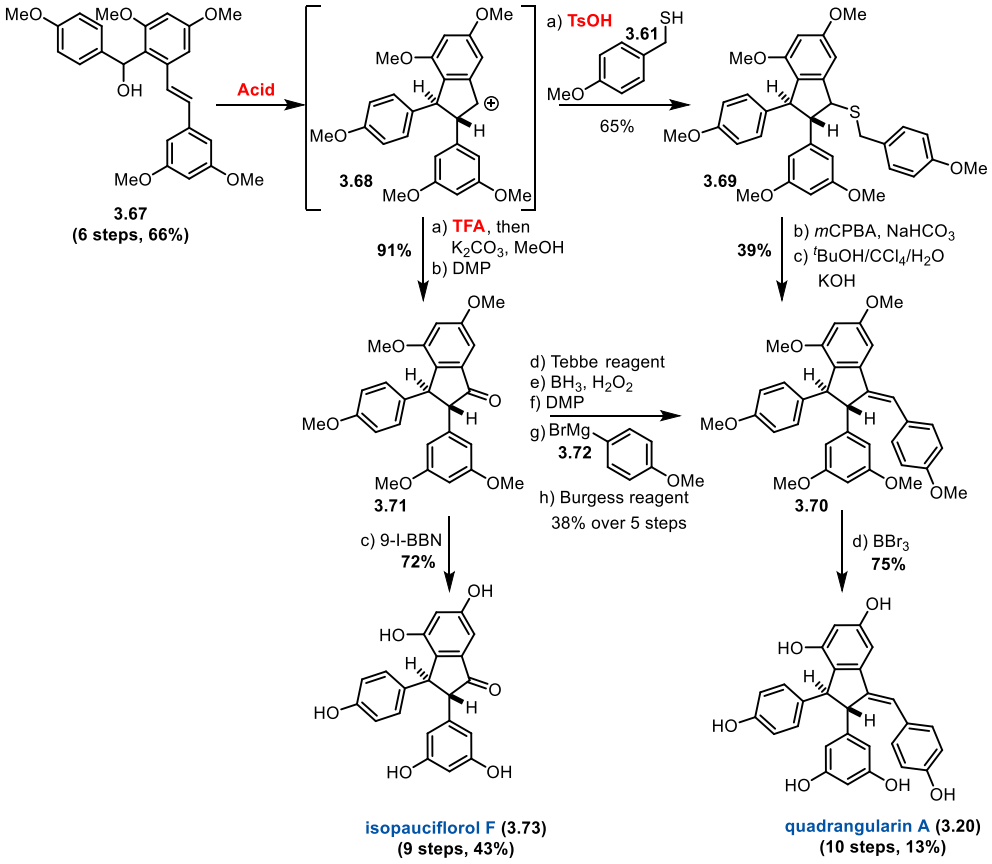


Figure 3.13 Snyders' synthesis of isopauciflorol F and quadrangularin A

A subsequent publication by the Snyder lab utilized electrophilic halogenations of the same indane cores to access ampelopsin F (**3.15**, Figure 3.14) and pallidol (**3.17**, Figure 3.14).[262] This strategy was employed as the addition of halogens to alkenes is reversible, thereby allowing stereochemical scrambling which could allow the required configuration for cyclization.[263] Exposure of **3.63** to NBS provided bicyclo[3.3.0]octatane (**3.75**). The synthesis of Ampelopsin F (**3.15**) was completed by global dehalogenation (TTMSS, AIBN) and methyl deprotection (BBr_3) in 80% yield. Completing a similar set of transformations with protected quadrangularin A (**3.70**) provides pallidol (**3.17**) in 9% overall yield over 12 steps. A similar strategy was used by the Snyder group in the synthesis of dimers Caraphenol B and C in 2011[264] as well as Hopeanol and Hopeahainol A in 2012.[265] This collection of dimer synthesis demonstrates how judicious planning and careful retrosynthetic analysis can provide divergent synthesis of resveratrol dimers with similar reaction conditions.

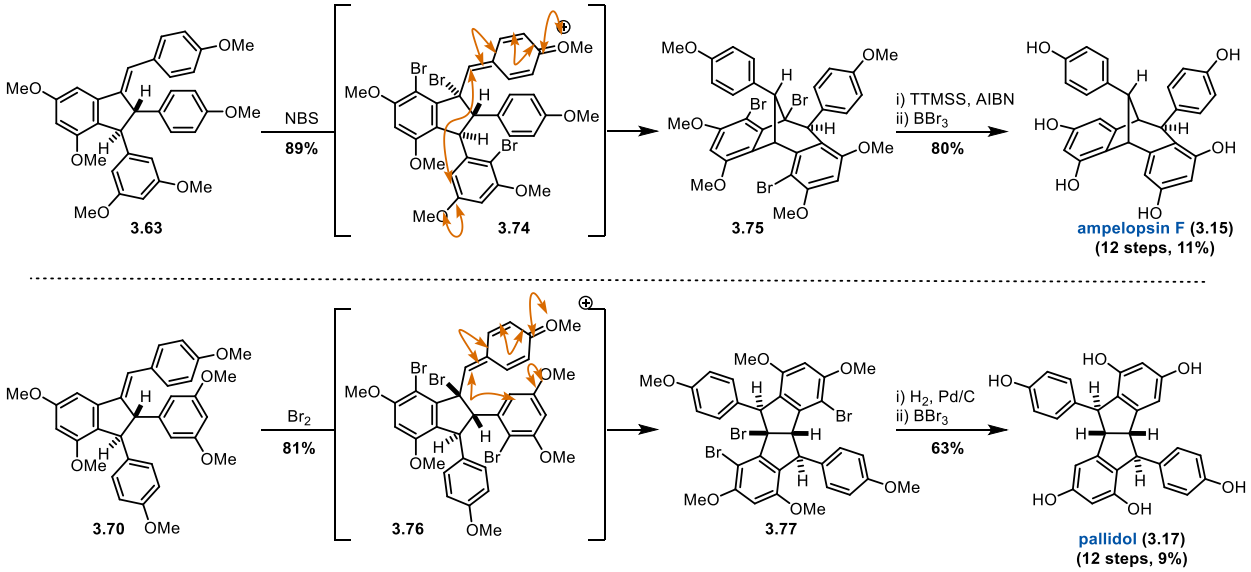


Figure 3.14 Snyders' synthesis of ampelopsin F and pallidol

In 2010 Chen and co-workers disclosed a synthesis of malibatol A (**3.80**, Figure 3.15) and shoreaphenol (**3.81**, Figure 3.15) via a direct benzofuran synthesis strategy.[46] A diversified permethyl protected core, similar to those used by the Snyder lab, was synthesized in 47% yield

over 6 steps (**3.78**). Benzylic deprotonation by LiTMP initiated cyclization onto the carbonyl, followed by acidic elimination of the resultant alcohol forming benzofuran (**3.79**). Ring closure was affected by NBS, followed by BBr_3 methyl deprotection unveiling malibatol A (**3.80**). Chromium oxidation completed the synthesis of closely related shoreaphenol (**3.81**).

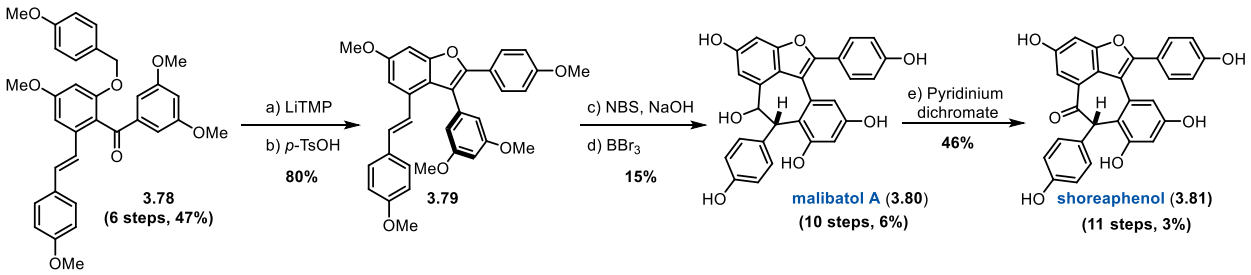


Figure 3.15 Chen's synthesis of malibatol A and shoreaphenol

A more contemporary example of dimer synthesis comes from the Elofsson lab and was designed with flexibility to allow analogue synthesis.[266] The *cis* dihydrobenzofuran (**3.82**) is formed via Pd/C H_2 reduction of a benzofuran, setting the configuration. A phosphonate (**3.83**), synthesized in four steps is coupled with base forming the core of ampelopsin B (**3.84**). This route uses the cyclopropyl methyl as a phenol protecting group which is labile in acid, but not base.[87] This rare phenol protecting group is removed with aqueous HCl in a THF co-solvent yielding ampelopsin B (**3.11**, 21%). It is key to note that the dihydrobenzofuran epimerizes from *cis* (**3.84**) to *trans* (**3.11**) in this transformation, which requires the opening on the DHB to a quinone which can cyclize with the thermodynamically favored *trans* configuration. In their synthesis of ε-viniferin (**3.9**) the use of acid in the final step would cyclize to ampelopsin B (**3.11**) so therefore must be avoided. Due to this nuance the dihydrobenzofuran was pre-synthesized as *trans* by epimerizing the *cis* dihydrobenzofuran earlier in the route. This allows the deprotection of the *trans* dihydrobenzofuran (**3.87**) with base (KOH), providing ε-viniferin without the need to epimerize, while avoiding the use of acid.

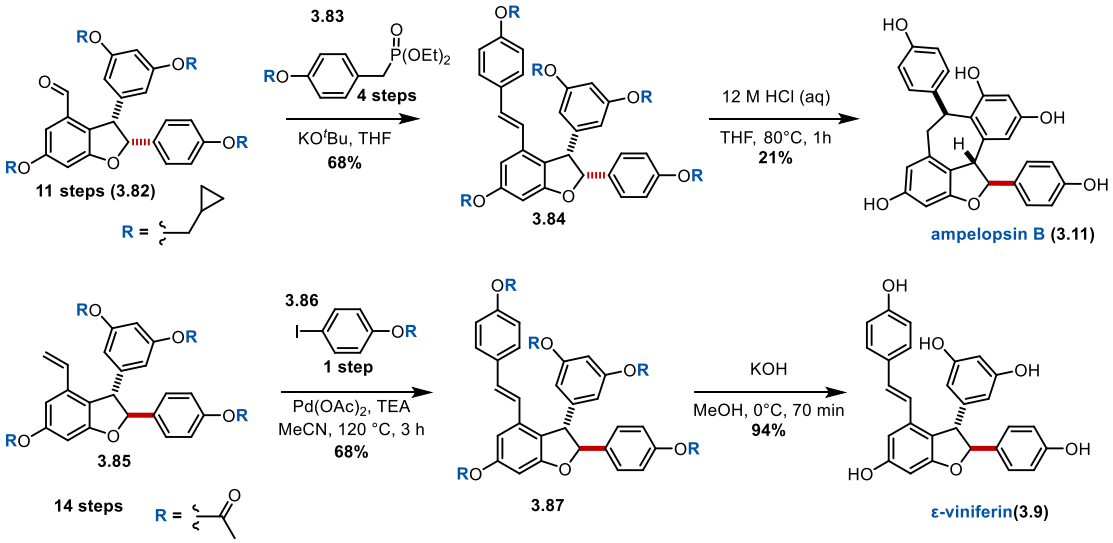


Figure 3.16 Elofsson's synthesis of ampelopsin B and ε-viniferin

3.4 Synthesis of dihydrobenzofuran derived resveratrol dimers

With the development of a TIPS-BQM completed (see Section 2.5), the Stephenson lab turned to applying this methodology to resveratrol dimers (Figure 3.17). The strategy was to synthesize protected resveratrol monomers (**3.88**) and then forms dihydrobenzofuran via thermal reactivity with a *bis*-quinone methide (**3.89**). The regioselectivity to synthesize both ε-viniferin (**3.9**) and δ-viniferin (**3.7**) was known, but gnetin C (**3.90**) was not accessible.

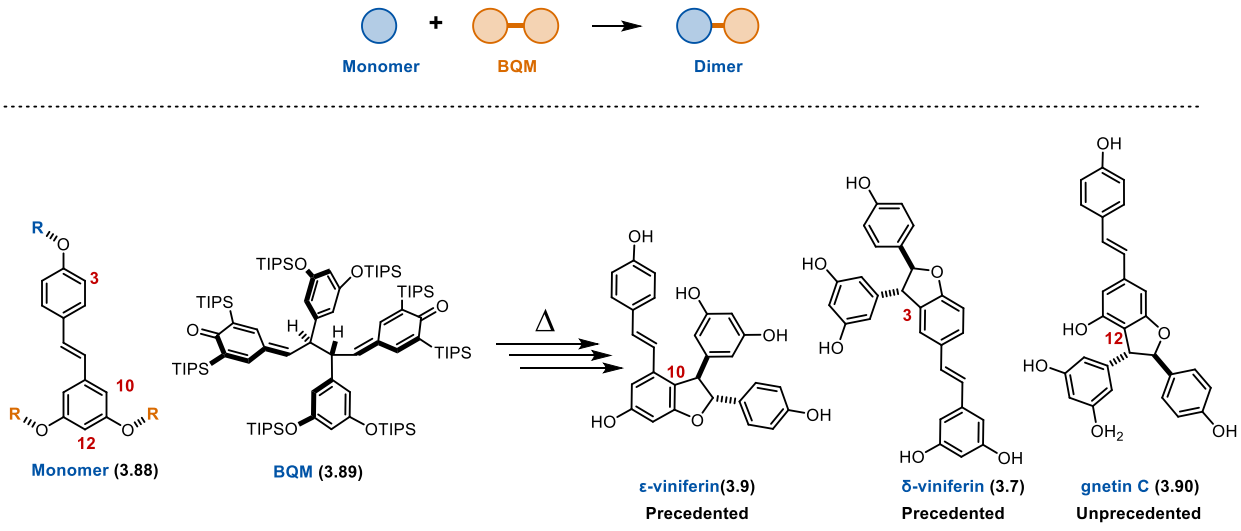


Figure 3.17 Stephenson lab's strategy for synthesizing resveratrol dimers

With the experimental precedent in mind, we also chose to explore a computational examination of the C10 vs C12 selectivity (Figure 3.18). The transient radical (**3.94**), generated from hydrogen atom transfer couples with a persistent BQM radical (**3.95**) forming the key C10-C8 bond (**3.96**). We postulate this endergonic coupling is the irreversible selectivity determining step whereas the product of this coupling proceeds downhill through tautomerization and cyclization forming the DHB. This suggests the radical population of the resorcinol radical (**3.94**) determines the C10 vs C12 product distribution. Density functional theory calculations for the SCF spin density (M062X / cc-PVTZ) of **3.99** show delocalization of the radical singly occupied molecular orbital through the resorcinol ring.

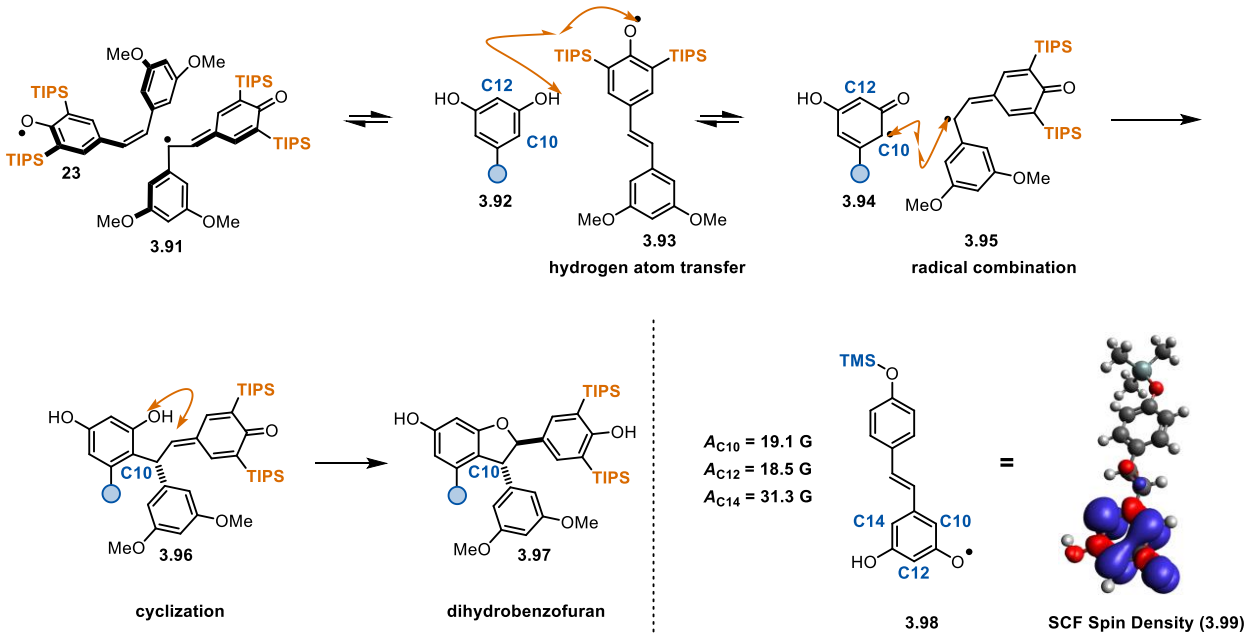


Figure 3.18 Computational investigation of C10 vs C12 DHB selectivity

The radical population was further probed with DFT-EPR. The hyperfine coupling constants indicate that the radical is most localized at C10 (19.1 G, **3.98**) and C14 (31.3 G, **3.98**), which are symmetrically degenerate and converge to the same C10 DHB product. These dominant

couplings are consistent with the experimental hypothesis that radical reactivity is centered at C10, while the additional contribution at C12 (18.5 G, **3.98**) suggests the feasibility of a minor C12 product as well.

We chose to target blocking groups as a strategy to unlock C12 dihydrobenzofuran reactivity (Figure 3.19). From a simple phenol unselective protections were attempted, often in low yield, to synthesize a variety of probes. These included the use of different phenolic protecting groups (**3.102**, **3.103**), halogenated blocking groups (**3.105**, **3.108**, **3.112**), and silyl blocking groups (**3.107**, **3.109**). These substrates were then subjected to standard *bis*-quinone methide thermal oligomerization and in most cases no DHB was detected (**3.102-3.107**). In cases where DHB was detected via crude ^{1}H NMR, we were unable to cleanly isolate any DHB products. This was likely the case as low molecular weight phenols with tangential blocking groups are poor substrates for the reaction. This strategy was abandoned, and it was decided to focus on the C3 and C10 dimers which were known to proceed smoothly.

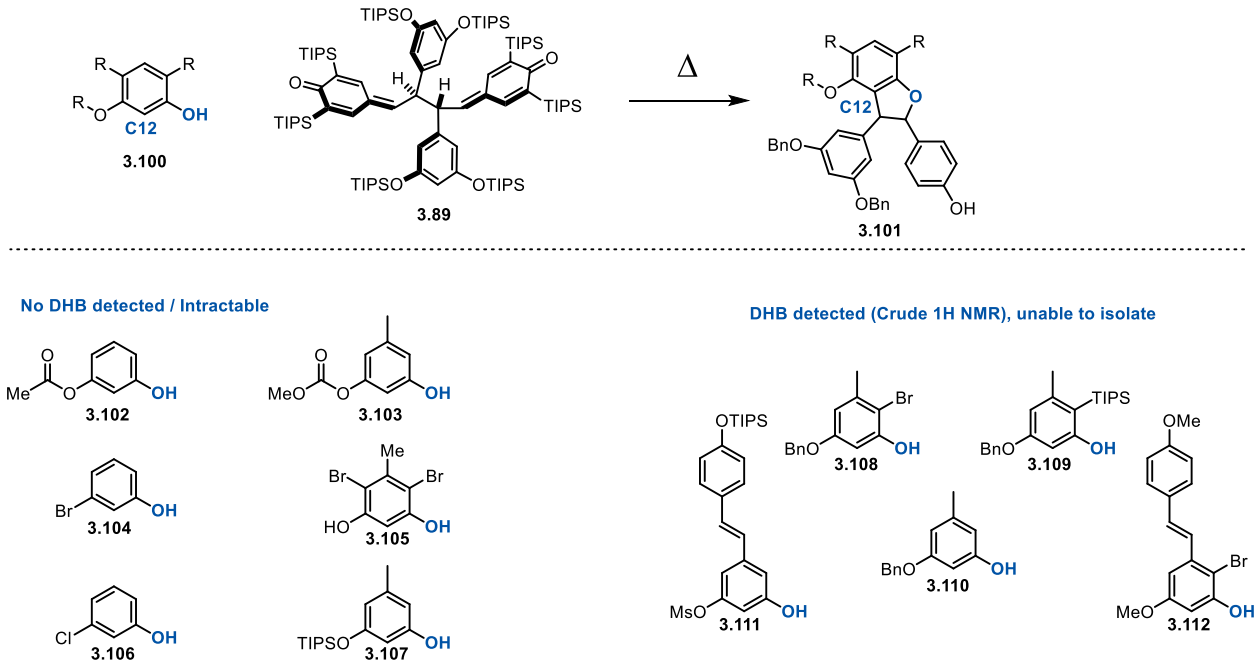


Figure 3.19 Attempts to unlock C12 dihydrobenzofuran reactivity with blocking groups

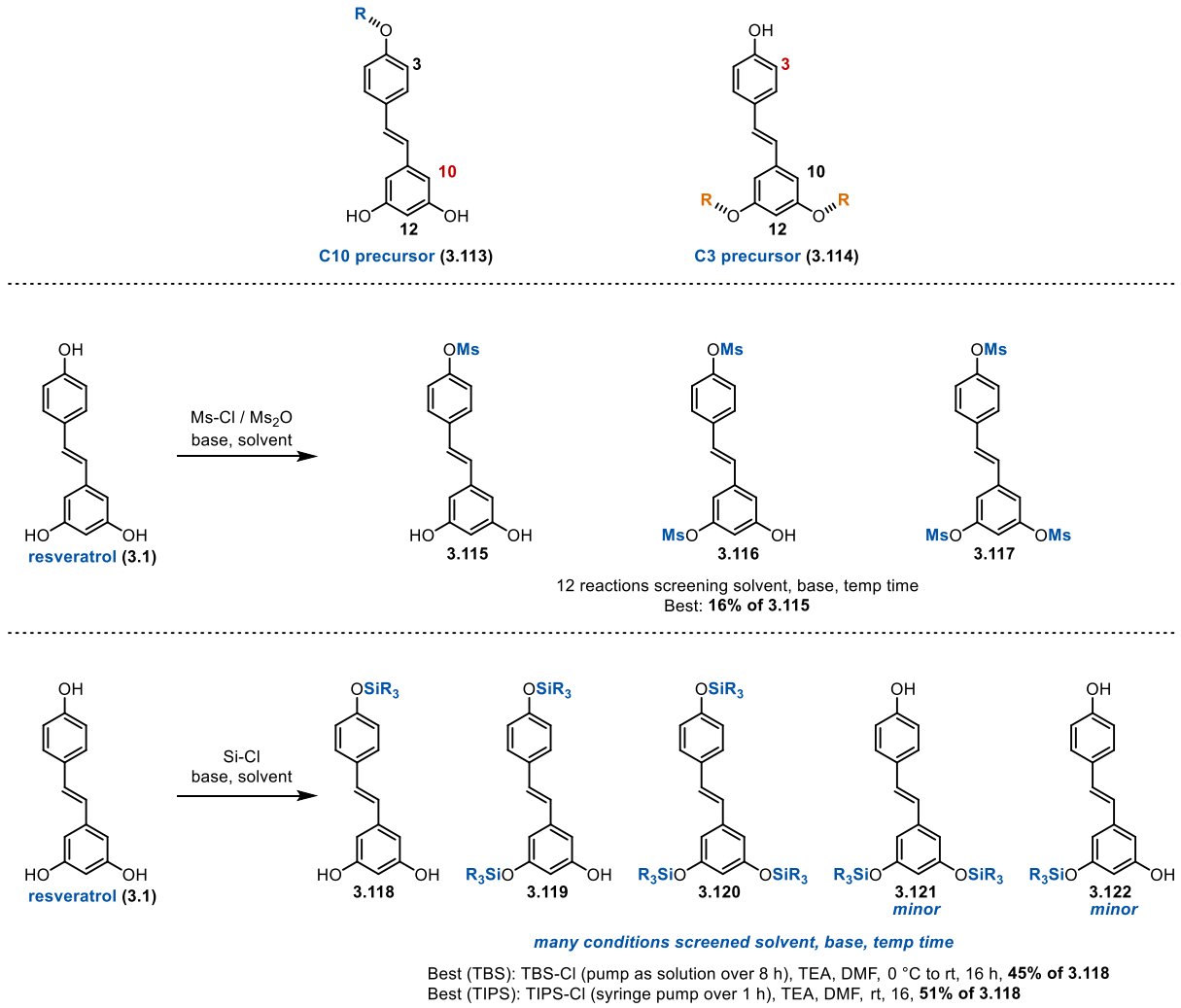


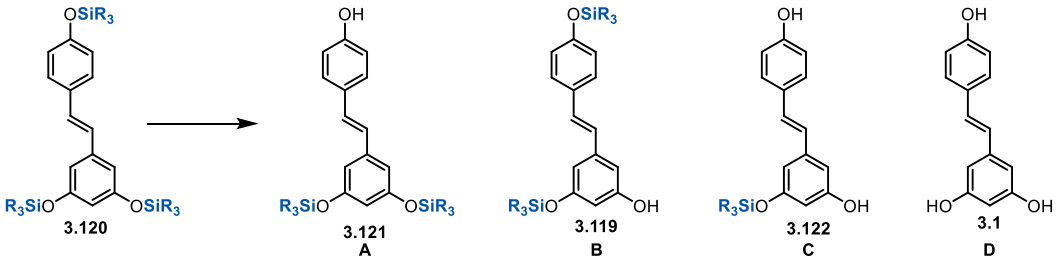
Figure 3.20 Strategy and synthesis of mono protected resveratrol

To selectively access C10 and C3 resveratrol dimers a suitably protected resveratrol monomer was required (Figure 3.20). The C10 precursor (**3.113**) and C3 precursor (**3.114**) both require selective protection of resveratrol to avoid a long stepwise sequence involving stilbene synthesis. Initially the protected group used was deemed not critical, and instead the selectivity of their reaction with resveratrol was studied. The methanesulfonate protecting group, added via the chloride or anhydride to resveratrol, was largely unselective forming mixed ratios of products (**3.115-3.117**). Screening the solvent, base, temperature, and equivalents of electrophile were unsuccessful at increasing the yield of 3.115 above ~15%. While low, this product could be

cleanly isolated, and this route was occasionally used for streamlined access to a suitable C10 dihydrobenzofuran precursor.

Silyl groups (TBS / TIPS), as their chloride, were screened for reactivity. Both the TBS and TIPS were found suitable C10 dihydrobenzofuran precursor in ~50% yield (**3.118**). One of the minor products (**3.121**) was also of interest as a C3 precursor (**3.114**) but was unable to be optimized beyond ~10% yield. The isolation of this product was also complicated by the polarity of **3.119** being nearly identical in multiple solvent systems. All individual sets of isomers (1-TIPS / 2-TIPS / 3-TIPS) were able to be easily separated by silica gel column chromatography.

Table 3.4 Selective deprotection of *tri*-silylated resveratrol



SM R	Reagent (equiv)	Solvent	Temp °C	Major Product	Conversion
TBS	TBAF	THF	-78	C	75%
TBS	LiOAc (0.1)	50:1 DMF:H_2O	RT	C	100%
TIPS	LiOAc (0.1)	50:1 DMF:H_2O	RT	1:1 A:B	10%
TBS	KOAc (0.1)	50:1 DMF:H_2O	RT	C	100%
TIPS	KOAc (0.1)	50:1 DMF:H_2O	RT	1:1 A:B	10%
TBS	$CuBr_2$ (0.05)	MeCN	RT	B	20%
TIPS	$CuBr_2$ (0.05)	MeCN	RT	1:2 A:B	5%
TBS	DBU (1.0)	10:1 DMF:H_2O	RT	D	75%
TIPS	DBU (1.0)	10:1 DMF:H_2O	RT	D	20%
TBS	-	10:2 DMSO:H_2O	70	-	0%
TIPS	-	10:2 DMSO:H_2O	70	-	0%
TIPS	KOAc (1.0)	50:1 DMF:H_2O	RT	C	100%
TIPS	KOAc (0.1)	50:1 DMF:H_2O	50	1:2 A:B	10%
TIPS	KOAc (1.0)	50:1 DMF:H_2O	0	2:1 A:B	10%
TIPS	HCl (1.0)	MeOH	RT	-	0%
TIPS	NaOH(0.5)	MeOH / H_2O	RT	-	0%
TIPS	NaOH(0.5)	MeOH / H_2O	50	1:2 A:B	5%
TIPS	**KOAc (0.2)**	**50:1 DMF:H_2O**	**RT, 48h**	**1:1 A:B**	**10%**

Fully Optimized KOAc (1 eq), 25:1 DMF:H_2O, rt, 2h, **51% A (3.121)**

Due to the selectivity observed in the mono protection of resveratrol with silyl groups to synthesize a C10 precursor, we also examined if the selective deprotection of a *tri*-silylated precursor (**3.120**, Table 3.4) could be a feasible alternative. This approach was weakly precedented

as only a few non general approaches using base,[267,268] (LiOAc, KOAc) or acid[269,270] were known. Considering this a screening campaign was commenced with either 3-TBS or 3-TIPS resveratrol, each synthesized in a single step (**3.120**, Table 3.4). The major deprotection products are depicted (**3.121**, **3.119**, **3.122**, **3.1**, Table 3.4). A variety of additives were screened including fluoride (TBAF) and base (LiOAc, KOAc, NaOH) with monobasic acetate showing most promise. A biphasic mixture was found promising, and fully optimized conditions (25:1 DMF:H_2O, 1 eq KOAc, rt, 2h) were reached proving 51% yield of desired C3 precursor (**3.121**). This reaction performed best on scales less than 500 mg due to the rigorous stirring requirements in the biphasic solution.

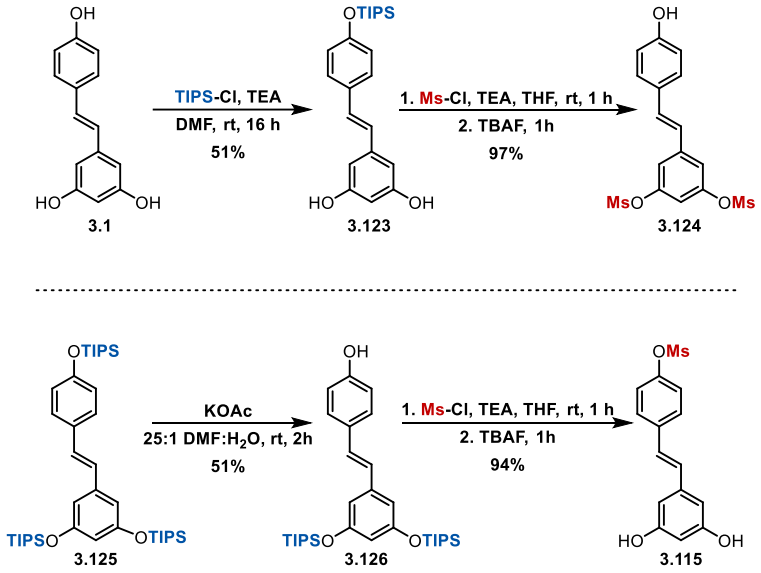
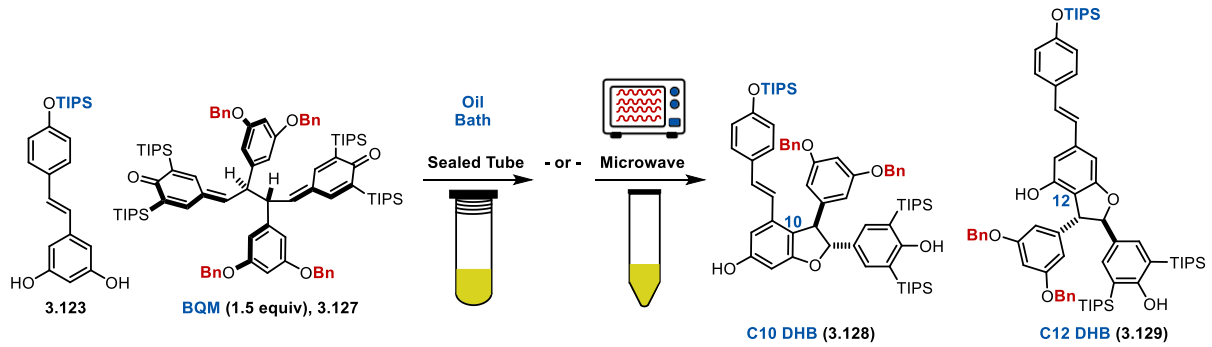


Figure 3.21 Finalized conditions for the derivatization of resveratrol to protected monomers

With two approaches to derivatize resveratrol optimized we synthesized two additional complimentary protected resveratrol building blocks (**3.124**, **3.115**, Figure 3.21). They were each synthesized from the silylated C10 and C3 precursors (**3.123**, **3.126**) via a mesylation (Ms-Cl) and deprotection sequence. These two operations were conducted in one pot with methanol quenching of the excess Ms-Cl between steps. This provided **3.124** and **3.115** in greater than 90% yield over

two steps. The mesyl protecting group was chosen as it is deprotected orthogonally to the silyl groups (labile in base, instead of acid).[87]

Table 3.5 Evaluation of C10 DHB formation via sealed tube and microwave irradiation



C. Table of Oligomerization Optimization

Reactor / Heating	Solvent	Temp (°C)	Time (h)	3.128 (%)	3.129 (%)
Sealed Tube / Oil Bath	Acetone	120	16	35	4
Microwave Vial	Acetone	120	16	42	8
Microwave Vial	**Acetone**	**100**	**10**	**55**	**14**
Microwave Vial	Acetone	80	10	29	4
Microwave Vial	Acetone	100	6	48	9
Microwave Vial	MeCN	100	10	42	13
Microwave Vial	THF	100	10	27	8

We chose to evaluate our C10 dimer precursor first, screening with both oil bath heating, which was standard for this method,[118] and microwave irradiation (Table 3.5). Yields between 30% and 40% were observed when phenol **3.123** was stirred with *bis*-quinone methide (**3.127**) in a sealed tube at 120 °C overnight. Changing to microwave irradiation saw a small but detectable jump in yield, which grew once temperature and time was optimized to 10 h at 100 °C. Until this point the second small portion of dihydrobenzofuran detected by crude ^{1}H NMR, but never isolated was assumed to be the *cis* diastereomer. It was only upon isolation under microwave irradiation conditions that **3.129** was isolated, the C12 DHB and gnetin C precursor (**3.129**, Table 3.5). This was gratifying, as this C12 DHB product was elusive in earlier studies. This assignment also requires reconsidering past results in which the *cis* DHB was reported. While these

experiments were not repeated, it is our hypothesis that all cases were of the C12, or adjacent regioisomer and not another diastereomer.

In addition to microwave irradiation being more reproducible and higher yielding, practical safety considerations also motivated the change of heating (Figure 3.22).[271] In addition to a lower operating temperature, the operating pressure is reduced from 6 atm to 3.7 atm (Figure 3.22).[272] The continuous monitoring of pressure and temperature as well as secondary containment ensures that microwave irradiation is a safer process. This technique is also known to accelerate thermal reactions and prevent of hot spots.[271]

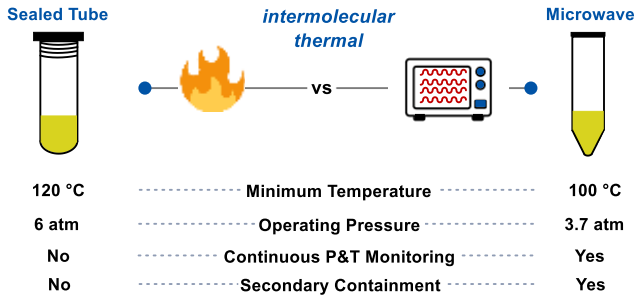
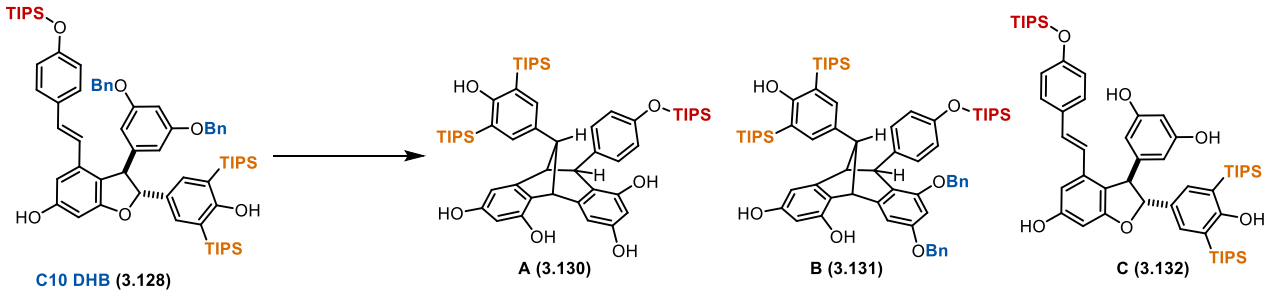


Figure 3.22 Practical considerations motivating the use of microwave irradiation

With C10 DHB in hand (**3.128**, Table 3.6), the core of ε-viniferin, we first attempted standard BCl_3 deprotection conditions with pentamethylbenzene as a benzyl cation trap.[273] We found that in addition to deprotection a skeletal rearrangement occurred yielding the scaffold of ampelopsin F in 52% yield (**3.130**). This type of rearrangement is known to be operable on similar substrates under similar Lewis or Brønsted acidic conditions.[256] This reaction proved challenge to optimize as competing debenzylation and cyclization pathways made monitoring by TLC or ^1H NMR unproductive. There was a large influence on the rate of addition of BCl_3 and quench procedure. To achieve cyclization without benzyl deprotection BF_3 was used, with no conversion observed. Toluene as a radical cation trap instead of pentamethylbenzene did not improve

reactivity. Ultimately it was decided that a system without benzyl groups would be more straightforward to optimize.

Table 3.6 Lewis acid deprotection of C10 DHB results in skeletal rearrangement



Reagent (eq)	Solvent	Additive (eq)	Temp (°C)	Time (h)	Yield A (%)	Yield B (%)	Yield C (%)	Note
BCl_3 (3)	DCM	Me_5-Benzene (5)	-78	2	52			$NaHCO_3$ quench at -78 °C
BCl_3 (3)	DCM	Me_5-Benzene (20)	-78	2	18			
BCl_3 (3)	DCM	Me_5-Benzene (5)	-78	2	9			TEA quench at -78 °C
BCl_3 (3)	DCM	Me_5-Benzene (5)	-78	2	8			TEA quench at rt
BCl_3 (3)	DCM	Me_5-Benzene (5)	-78	2	12			$NaHCO_3$ quench at -78 °C
BF_3 (3)	DCM		-78	2				no conversion
BF_3 (10)	DCM		-78	3				no conversion
BF_3 (10)	DCM		-78 to rt	4				decomposition
TfOH (10)	DCM		rt	6				decomposition
BCl_3 (4)	DCM	Toluene (8)	-78	2	4	3	3	
BCl_3 (8)	DCM	Toluene (14)	-78	3	3	2	3	

To synthesize a fully TIPS protected DHB, a BQM (**3.133**) bearing eight TIPS protecting groups was used. This was synthesized in two steps by debenzylation and reprotection with TIPS-Cl of the 2-TIPS, 2-Bn trans stilbene (Figure 2.22). For a more elaborate discussion on methods to synthesize fully silyl protected stilbene units see Section 4.6. Under standard microwave reaction conditions, the C12 DHB (**3.134**, Figure 3.23) and C10 DHB (**3.135**, Figure 3.23) were prepared.

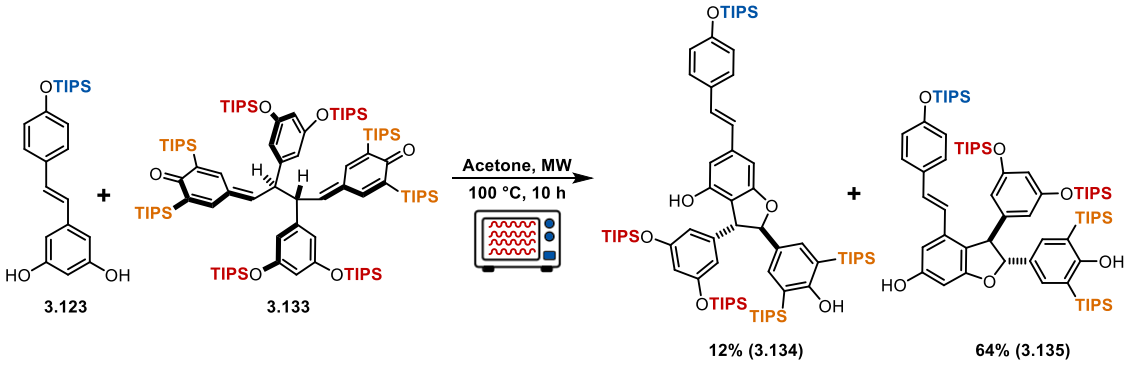
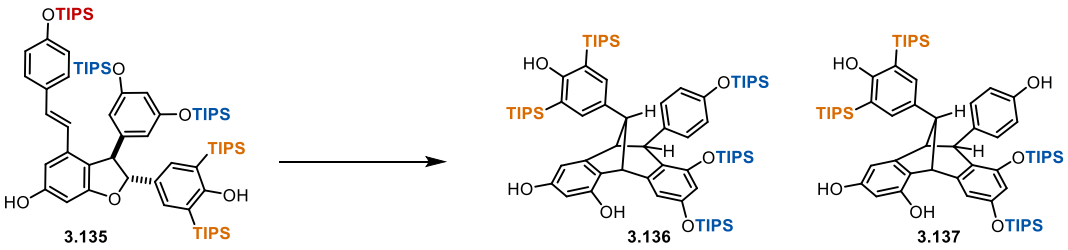


Figure 3.23 Synthesis of C10 and C12 DHB dimers with 8-TIPS BQM (3.133)

The fully TIPS protected C10 DHB (**3.135**, Table 3.7) was subjected to a battery of cyclization conditions. This substrate proved simpler to cyclize with a variety of Lewis acids (BCl_3, BBr_3, $AlCl_3$, $\mathbf{B(C_6H_5)_3}$). In many cases both the cyclized fully TIPS protected product (**3.136**) and the loss of a single TIPS group (**3.137**) were observed. While this product (**3.137**) is interesting, it is not immediately useful and was therefore optimized against. Due to the simplicity of use and reproducible reactivity BCl_3 was chosen as the desired cyclization reagent.

Table 3.7 Lewis acid screening of 5-TIPS ε-viniferin towards ampelopsin F



Reagent (eq)	Solvent	Additive	Temp (°C)	Time (h)	yield 3.136	yield 3.137	Note
BCl_3 (1.5)	DCM		-78	2	40%		
BBr_3 (1.5)	DCM		-78	2	40%		
$AlCl_3$ (4)	DCM		-78 to rt	6	20%	10%	TIPS loss at -78 °C
$TiCl_4$ (4)	DCM		-78 to rt	6			Solution turned black
$AlCl_3$ (4)	DCM		-78 to rt	4	20%	10%	TIPS loss at -78 °C
$AlCl_3$ (4)	Toluene		110	2	20%	10%	Slow conversion by TLC
$Sc(OTf)_3$ (4)	DCM		-78 to 40	6	20%		Conversion only at reflux
$B(C_6F_5)$ (4)	DCM		-78 to 40	6	40%		Conversion only at reflux
$Sc(OTf)_3$ (4)	Toluene		110	8			>4 products
$B(C_6F_5)$ (4)	DCM		40	16	20%	20%	
$AlCl_3$ (4)	DCM	N,N-Dimethylaniline	rt to 40	4	20%	10%	No conversion
$AlCl_3$ (8)	DCM		rt	2	8%	24%	
$AlCl_3$ (8)	DCM		rt	8		52%	

With screening complete, the finalized synthesis of ampelopsin F proceeded smoothly (Figure 3.24). Key to this was the change from benzyl protecting groups (**3.128**, Figure 3.24) which were first used in the discovery of the skeletal rearrangement to the core of ampelopsin F (**3.130**). In the finalized route protected C10 dimer (**3.135**) is converted to the core of ampelopsin F (**3.316**) in 73% yield. Final methanolic HCl deprotection provides ampelopsin F (**3.15**) in 77% yield.

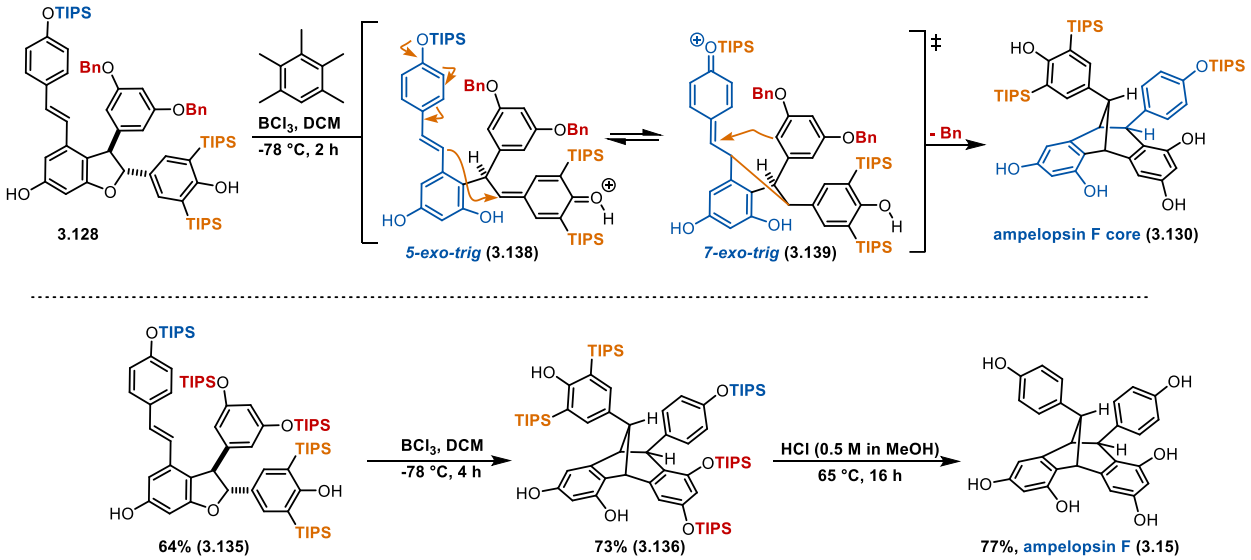


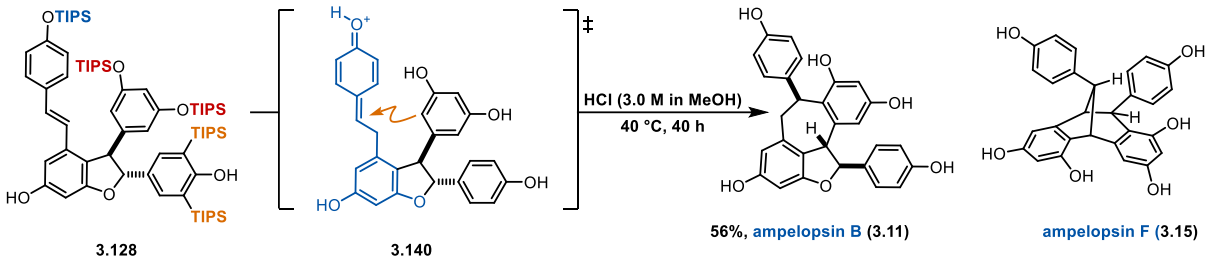
Figure 3.24 Finalized conditions for total synthesis of ampelopsin F (3.15)

Returning to the fully TIPS protected C10 DHB (**3.128**,

Table 3.8), we sought to remove the silyl protecting group while preserving the core of ε-viniferin which was not possibly while using benzyl protecting groups. Treating **3.128** with methanolic HCl produced a mixture of ampelopsin B (**3.11**) and ampelopsin F (**3.15**). The precise temperature and time of reaction determined the ratio of these products, as estimated by crude ^{1}H NMR. Both natural products are accessed via quinone formation once the silyl groups are removed (**3.140**,

Table 3.8). Finalized conditions were the use of 3 M HCl in MeOH at 40 °C for 40 hours provided a 56% yield of ampelopsin B (**3.11**) with only trace amounts of ampelopsin F (**3.15**) detected. These findings illustrate the lability of resveratrol dimers to acid, and how small changes in reaction conditions can alter the experimental outcome of these cyclizations.

Table 3.8 Finalized conditions for total synthesis of ampelopsin B (3.11)



Conditions	Time	Temp (°C)	Ratio (3.11:3.15)	Note
HCl (0.5 M in MeOH)	120 h	rt	0:1	
HCl (0.5 M in MeOH)	16 h	80	1:1	
HCl (3 M in MeOH)	16 h	30	3:1	
HCl (3 M in H_2O), 10% MeOH	16 h	80	0:0	80% SM Recovery
HCl (4 M in Dioxane)	16 h	80	0:0	40% SM recovery

The synthesis of gnetin C was comparatively straightforward as refluxing methanolic HCl proceeded smoothly (71%, **3.90**, Figure 3.25). This C12 product contrasts the C10 with its lower complexity of deprotection as the DHB is distal to other reactive functionality. This method does not prevent DHB ring opening to its tautomer (**3.141**, Figure 3.25), but rather there are no competing pathways to effectively intramolecularly trap the resulting quinone.

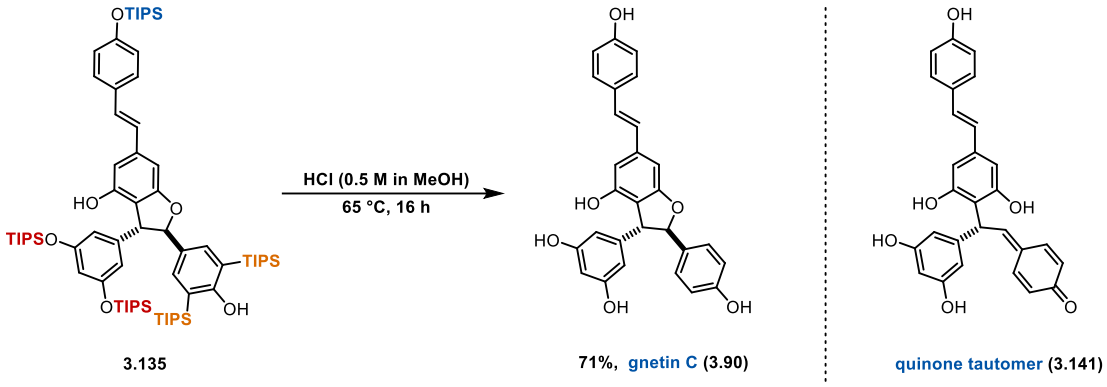


Figure 3.25 Finalized conditions for the total synthesis of gnetin C

Returning to the elusive synthesis of ε-viniferin (**3.9**, Figure 3.26) we chose to use a mesylate protected resveratrol (**3.115**, Figure 3.26). The microwave DHB synthesis gave 67% of **3.142** in addition to 11% of the C12 DHB (**3.143**) which was not utilized further. The use of methanolic HCl cleanly removed the four TIPS groups but left the core uncyclized. The mesylate stability in acid was key, as it prevented quinone formation and the formation of ampelopsin B or ampelopsin F scaffolds. A final basic hydrolysis provided ε-viniferin in 75% yield.

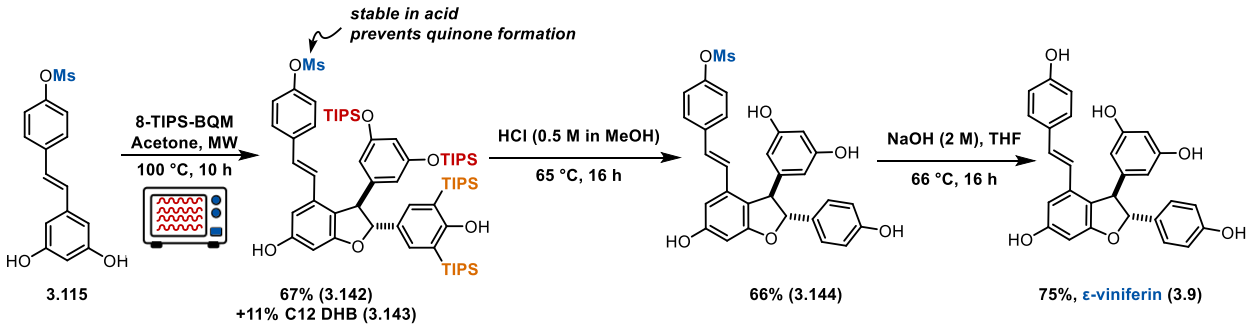
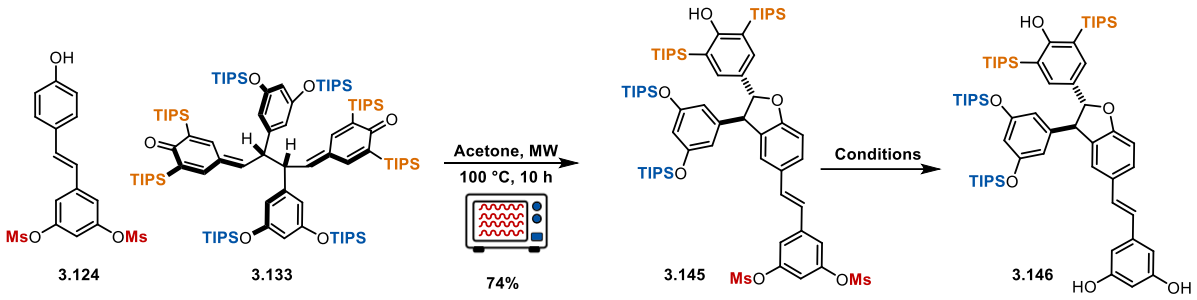


Figure 3.26 Finalized conditions for the total synthesis of ε-viniferin

The final dimer targeted was the C3 DHB, δ-viniferin (**3.7**, Figure 3.17). We began with our mesylate protected resveratrol (**3.124**, Table 3.9) which produced C3 DHB via microwave oligomerization in 74% yield (**3.145**). This protected resveratrol monomer (**3.124**) was selected to aid in the separation of **3.145** from the stilbene byproduct of the DHB reaction. Attempts to remove the mesylate from **3.145** were unsuccessful using a set of diverse conditions (MeMgBr, NaOH,

TBAF, MeLi, Table 3.9).[87] In all cases decomposition was observed, likely via quinone formation and trapping, leading to a smattering of unproductive reactivity.

Table 3.9 Attempts to synthesize δ-viniferin via mesylate protection of resveratrol



Conditions	Time	Temp	Result
MeMgBr (10 equiv)	2 h	rt	decomposition
NaOH (2M), THF	16 h	rt	decomposition
TBAF (6 equiv)	16 h	0 °C to rt	decomposition
MeLi (15 equiv)	1 h	rt	Ms removal and DHB decomposition

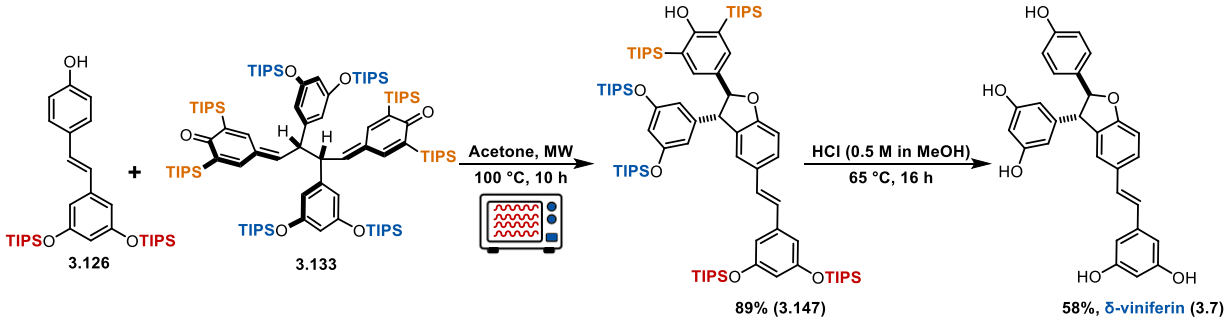


Figure 3.27 Finalized conditions for the total synthesis of δ-viniferin

We pivoting to a silyl protected resveratrol (**3.126**, Figure 3.27). Microwave oligomerization gave DHB in 89% ^{1}H qNMR yield (**3.147**). Final deprotection with methanolic HCl provided δ-viniferin in 56% yield (**3.7**, Figure 3.27). As with the C12 DHB, the C3 (**3.147**) is facile to deprotection as there are no adjacent functionalities to trap the quinone intermediate (not drawn) of the methanolic HCl deprotection.

3.5 Conclusions

In Summary, we have developed a unifying strategy for the total synthesis of five resveratrol dimers from resveratrol by the selective synthesis of C3, C10, and C12 DHBs. By

combining bis-quinone methide oligomerization with carefully designed protecting group strategies, a range of structurally diverse resveratrol dimers were synthesis: ε-viniferin, δ-viniferin, ampelopsin B, ampelopsin F, and gnetin C. These results build on a rich history of biomimetic syntheses while demonstrating exquisite regiocontrol.

Overall, this work establishes a general and modular approach to resveratrol dimer synthesis that integrates mechanistic insight with practical synthetic design. Beyond providing streamlined access to these dimers, this chemistry establishes a broadly applicable platform for the stepwise oligomerization of resveratrol, enabling the efficient synthesis of higher-order dimers, trimers, and beyond.

3.6 Experimental Procedures and Spectral Data

General Procedures: Unless specifically noted otherwise, all glassware was flame-dried under vacuum (~0.5 Torr) and cooled under inert atmosphere (N_2 or Ar) prior to use. Each reaction container was charged with a Teflon/PTFE-coated magnetic stir bar and sealed with a rubber septum to maintain a positive pressure of inert atmosphere (N_2 or Ar). Reagents sensitive to the atmosphere were transferred via syringe or cannula as necessary. Reaction conversion was evaluated using analytical thin-layer chromatography (TLC) using Merck Supelco® silica gel 60 F_{254} TLC plates. TLC plates were visualized under a dual short wave/long wave UV lamp and/or stained using a solution of potassium permanganate. Stained plates were developed over a heat gun as needed. These same TLC plates were used for preparative TLC when required.

Reactions were purified via flash column chromatography with either Biotage® Sfär Silica D columns (standard separation) or Biotage® Sfär Silica HC D columns (challenging separations) using a Biotage® Isolera One automated chromatography system. Some reaction were also purified manually using SilicaFlash® Irregular Silica Gel (F60, 40-63 μm, 60 Å). Organic solutions were dried with either sodium sulfate or magnesium sulfate prior to column chromatography. Solvent was removed on a Büchi rotary evaporator and/or a Welch vacuum pump. All electrochemical experiments were done using a PINE research WaveNow system. The reference electrode was Ag/AgCl (3 M KCl, from CH Instruments). Bulk electrolysis experiments were performed in open 10-mL vials and in beakers of the appropriate size (20 – 500 mL). The reactions used RVC panels (reticulated vitreous carbon, 100 ppi, 0.25 inch thickness, 3% relative density, from ERG) as the working or counter/auxiliary electrodes and a Ag/AgCl (3 M KCl) reference electrode.

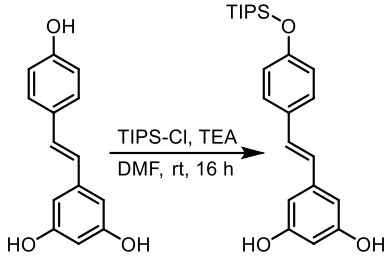
Product names were abbreviated for clarity. For racemic compounds, the name corresponds to the depicted structure. Nuclear magnetic resonance (NMR) spectra were obtained using an internal deuterium lock on Varian Inova 500 or Varian VNMR 500 and 700 spectrometers. For 1H spectra, chemical shifts were referenced to the center line of the residual solvent signal (CDCl3: δ 7.26; acetone-d6: δ 2.05; benzene-

d6: δ 7.16; DMSO: δ 2.50) and are reported in parts per million (ppm). Signal multiplicity is reported as follows: (br = broad, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet), and the associated coupling constants are given in Hertz. For 13C spectra, experiments were completely heterodecoupled (broadband) and chemical shifts are reported as ppm using the center line of the solvent signal as reference (CDCl3: δ 77.16; acetone-d6: δ 29.92; benzene-d6: δ 128.06; DMSO: δ 39.52). 19F NMR chemical shifts were reported as δ, parts per million, relative to CFCl3 at 0.0 ppm. All 13C NMR spectra are proton- 58 decoupled. High-resolution mass spectra (HRMS) were acquired using a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer using electrospray ionization (ESI), positive ion mode. Infrared spectra were acquired using a Perkin-Elmer Spectrum BX FT-IR spectrophotometer using an ATR mount with a ZnSe crystal.

Reaction Materials: Commercially available reagents were used without further purification unless specified. Organic solvents (acetonitrile, dichloromethane, diethyl ether, dimethylformamide, dimethyl sulfoxide, methanol, tetrahydrofuran, and toluene) were purified/dried prior to use with a Phoenix Solvent Drying System from JC-Meyer Solvent System. Amine bases (triethylamine, pyridine, N,N-diisopropylethylamine, and diisopropylamine) were also purified/dried prior to use s and PureSolv Micro amine drying columns from Innovative Technology. Both systems were kept under a pressure of argon.

Product Analysis: Product names were abbreviated for clarity. Nuclear magnetic resonance (NMR) spectra were obtained using an internal deuterium lock on Varian VNMR 500 or 700 spectrometers. Other instruments used include a Bruker Advance Neo 500 and Bruker Avance 400 / 600 MHz spectrometers. For ^{1}H spectra, chemical shifts were referenced to the center line of the residual solvent signal ($CDCl_3$: δ 7.26; acetone-d6: δ 2.05) and are reported in parts per million (ppm). Signal multiplicity is reported as follows: (br = broad, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet), and the associated coupling constants are given in Hertz. For ^{13}C spectra, experiments were completely heterodecoupled (broadband) and chemical shifts are reported as ppm using the center line of the solvent signal as reference (CDCl3: δ 77.16; acetone-d6: δ 29.92). High-resolution mass spectra (HRMS) were acquired using a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer using electrospray ionization (ESI), positive ion mode. Infrared spectra were acquired using a PerkinElmer Frontier FTIR equippted with universal ATR sampling.

Resveratrol derivatization



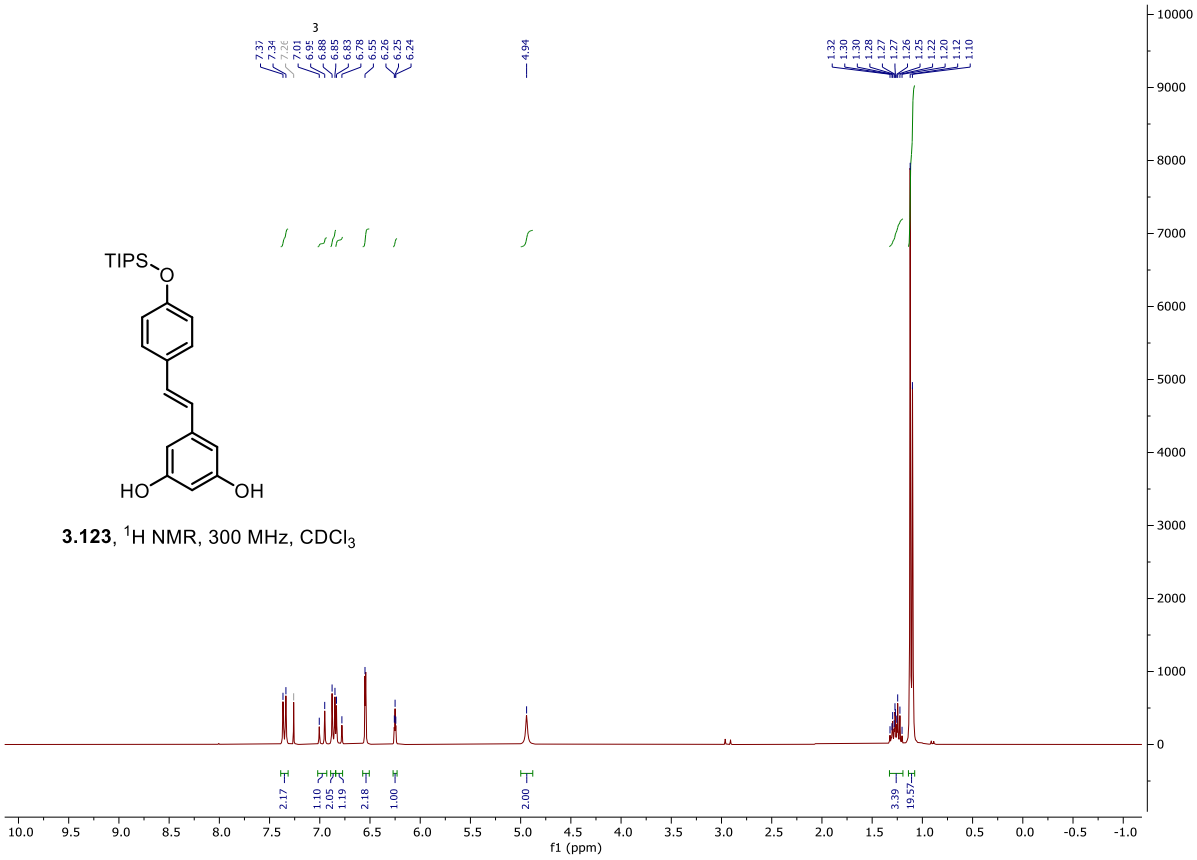
(3.123) (E)-5-(4-((triisopropylsilyl)oxy)styryl)benzene-1,3-diol

In a flame-dried 250 mL RBF was added resveratrol (3.00 g, 13.1 mmol, 1 equiv), DMF (33 mL, 0.4 M), and TEA (2.2 mL, 15.8 mmol, 1.2 equiv). To an addition funnel was added TIPS-Cl (3.38 mL, 15.8

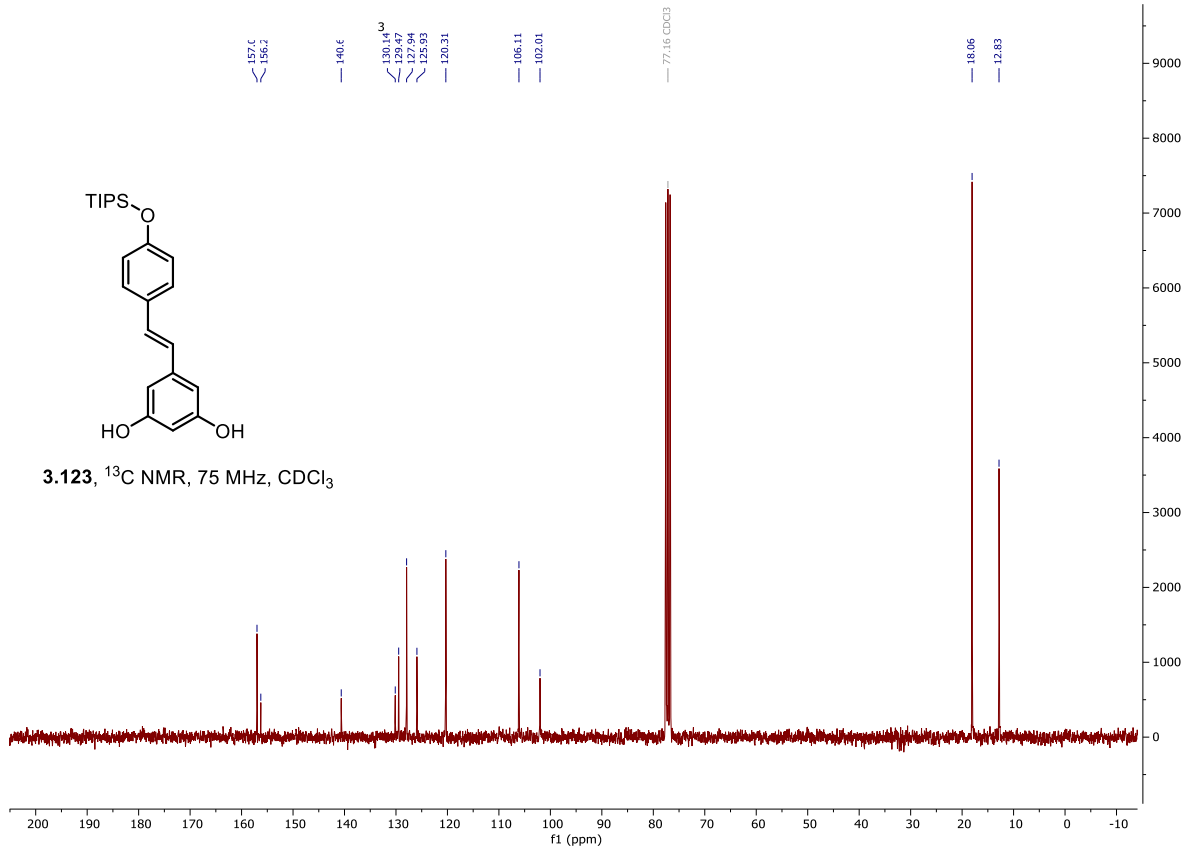
mmol, 1.2 equiv) and DMF (33 mL). The TIPS-Cl solution in DMF was added dropwise over 1 hour via syringe pump the vigorously stirred reaction. After 16 hours at rt the reaction was quenched with water (40 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with sat. LiCl (40 mL x 2) and brine (40 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-15% EtOAc in Hexanes) to yield the product as a yellow viscous crystalline foam (2.6 g, 51%).

Other conditions attempted in optimization: 1) TEA (0.8 equiv), TIPS-Cl (0.8 equiv), DMF (0.4 M), rt, 16 h, 37% desired mono TIPS product. 2) TEA (1.2 equiv), TIPS-Cl (1.2 equiv), DMF (0.2 M), rt, 16 h, 28% desired mono TIPS product.

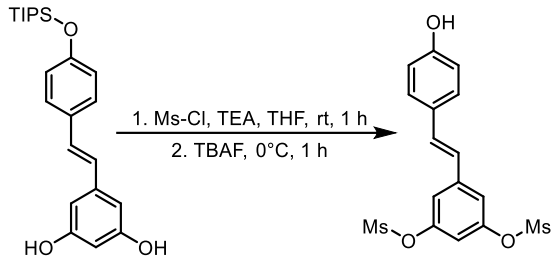
TLC (Hexanes/EtOAc, 80:20), R_F:	0.23 (UV, potassium permanganate)
^{1}H NMR (300 MHz, $CDCl_3$, 25 °C)	δ = 7.35 (d, J=8.8, 2H), 6.98 (d, J=16.3, 1H), 6.86 (d, J=8.6, 2H), 6.81 (d, J=16.2, 1H), 6.55 (s, 2H), 6.25 (t, J=2.2, 1H), 4.94 (s, 2H, OH), 1.33 – 1.19 (m, 3H), 1.11 (d, J=6.7, 18H).
^{13}C NMR (75 MHz, $CDCl_3$, 25 °C)	δ = 157.0, 156.3, 140.6, 130.1, 129.5, 127.9, 125.9, 120.3, 106.1, 102.0, 18.1, 12.8.
HRMS (ESI):	*m/z* calculated for $C_{23}H_{32}O_3Si$ ($[M+H]^+$): 385.2193, found 385.2192
FTIR (neat) cm^{-1} :	$\tilde{\nu}$= 3302 (br), 2944 (m), 2366 (m), 2190 (m), 1599 (m), 1510 (vs), 1270 (s), 915 (w), 670 (s), 662 (w)



3.123, ^{1}H NMR, 300 MHz, $CDCl_3$



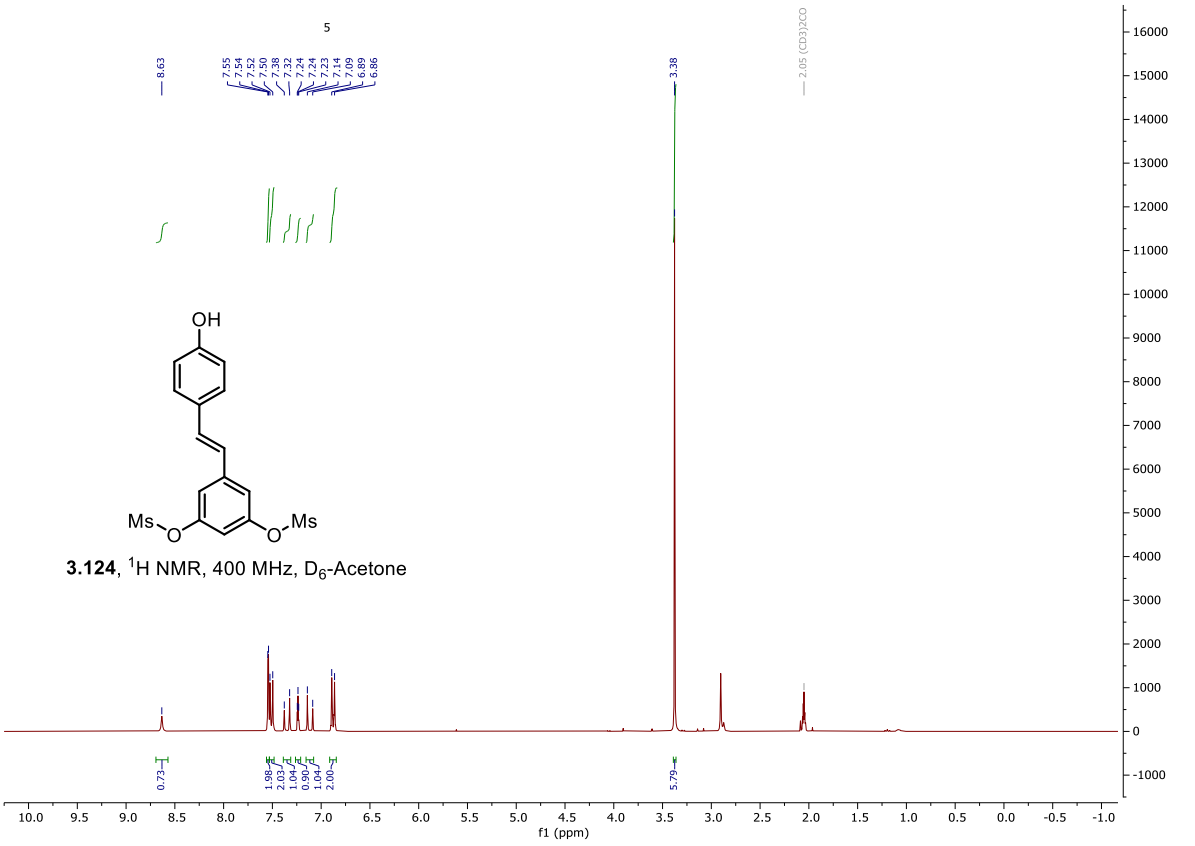
3.123, ^{13}C NMR, 75 MHz, $CDCl_3$



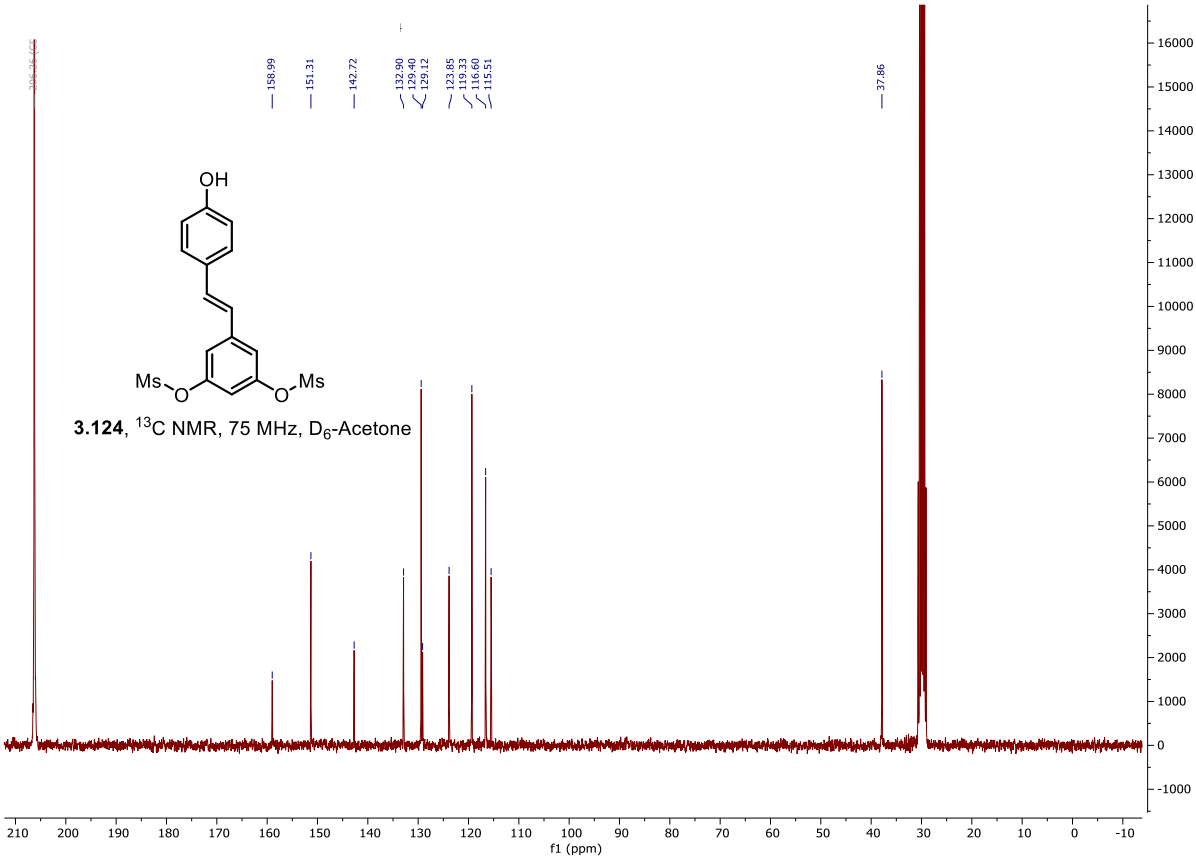
(3.124) (E)-5-(4-hydroxystyryl)-1,3-phenylene dimethanesulfonate

To a 12 dram vial was added stilbene (300 mg, 780 µmol, 1.0 equiv), THF (15.6 mL, 0.05 M), TEA (326 µL, 2.34 mmol, 3.0 equiv), and Ms-Cl dropwise (182 µL, 2.34 mmol, 3.0 equiv). The reaction was stirred at room temperature for 1 hour. Monitoring by TLC indicated full conversion, and the temperature was lowered to 0 °C. TBAF (1.17 mL of a 1 M solution in THF, 1.17 mmol, 1.5 equiv) was added dropwise. After 1 h the reaction was diluted with $NaHCO_3$ (10 mL). The contents were transferred to a separatory funnel and the mixture was extracted with EtOAc (3 x 10mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (20%-80% EtOAc in Hexanes) to yield the product as an amorphous white solid (292 mg, 97%).

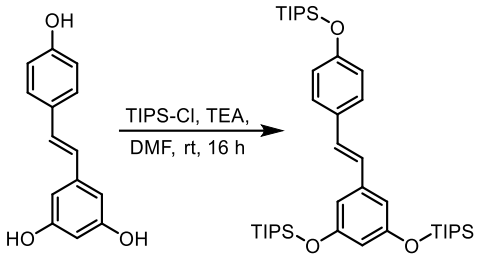
TLC (Hexanes/EtOAc, 60:40), R_F:	0.33 (UV, potassium permanganate)
^{1}H NMR (400 MHz, D_6-Acetone, 25 °C)	δ = 8.63 (s, 1H, OH), 7.54 (d, J=2.2, 2H), 7.51 (d, J=8.6, 2H), 7.35 (d, J=16.4, 1H), 7.24 (t, J=2.2, 1H), 7.11 (d, J=16.4, 1H), 6.88 (d, J=8.7, 2H), 3.38 (s, 6H).
^{13}C NMR (75 MHz, D_6-Acetone, 25 °C)	δ = 159.0, 151.3, 142.7, 132.9, 129.4, 129.1, 123.9, 119.3, 116.6, 115.5, 37.9.
HRMS (ESI):	*m/z* calculated for $C_{16}H_{16}O_7S_2$ ($[M+NH_4]^+$): 402.0681, found 407.0677
FTIR (neat) cm^{-1} :	ν̃= 3469 (w), 3033 (w), 2942 (w), 1602 (w), 1362 (m), 1173 (s), 1142 (w), 1107 (m), 957 (vs), 821 (m), 796 (vs), 727 (w)



3.124, ^{1}H NMR, 400 MHz, D_6-Acetone



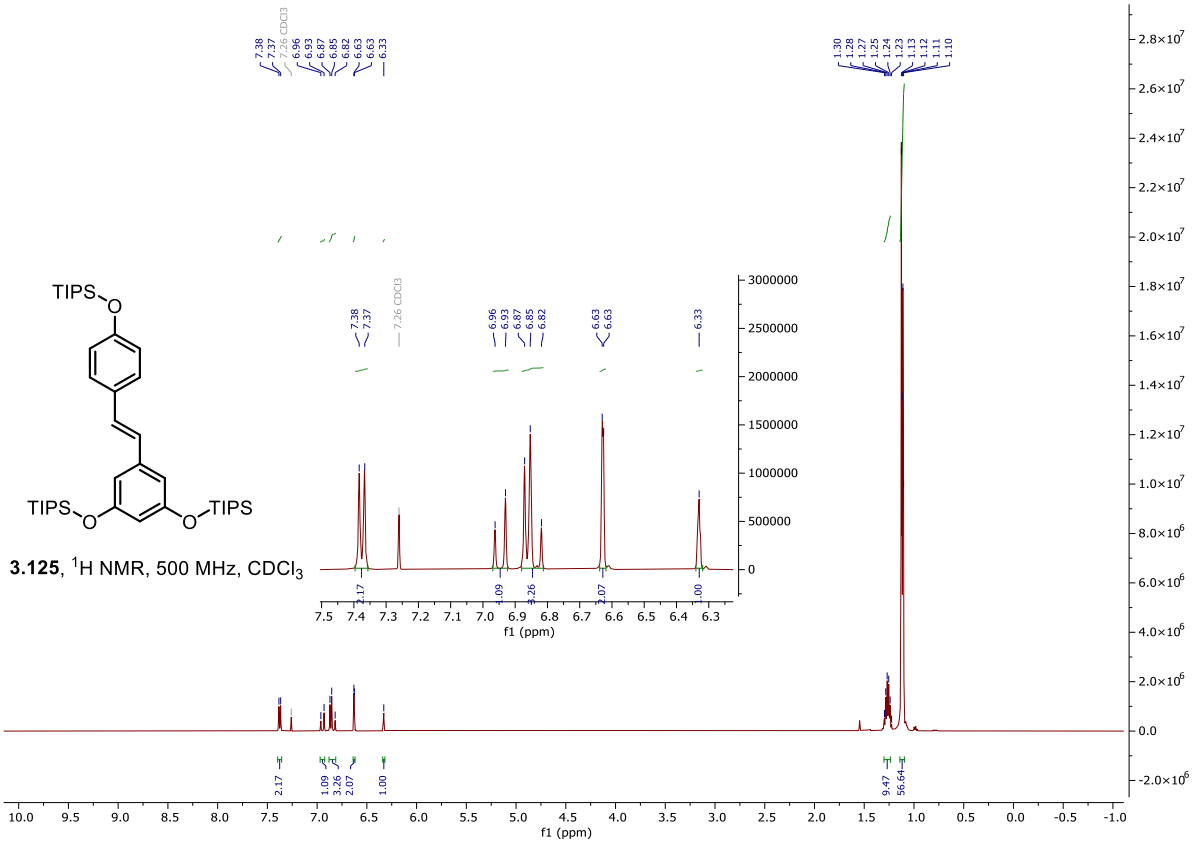
3.124, ^{13}C NMR, 75 MHz, D_6-Acetone



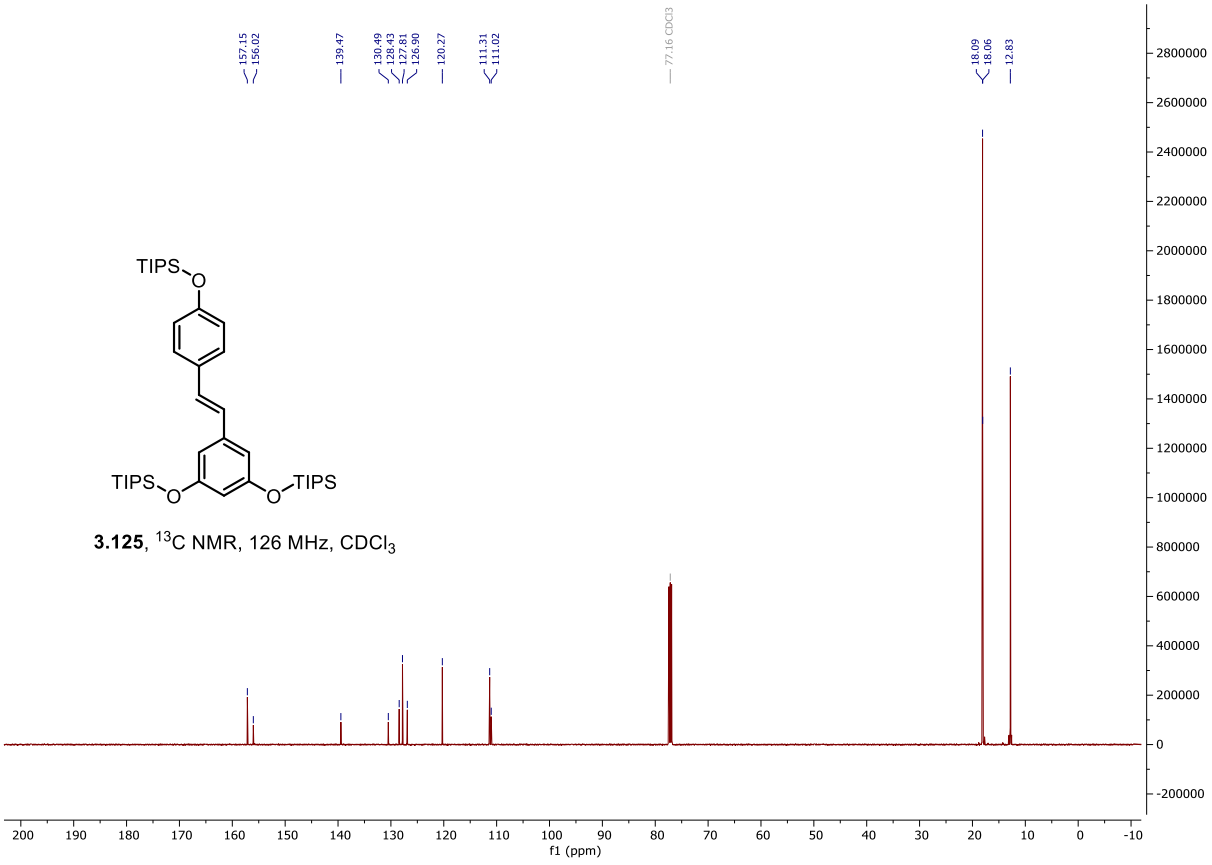
(3.125) (E)-((5-(4-((triisopropylsilyl)oxy)styryl)-1,3-phenylene)bis(oxy))bis(triisopropylsilane)

In a flame-dried 50 mL RBF was added resveratrol (3.00 g, 13.1 mmol, 1 equiv), DMF (13.1 mL, 1.0 M), then dropwise TEA (9.16 mL, 65.7 mmol, 5.0 equiv), and TIPS-Cl (14.1 mL, 65.7 mmol, 5.0 equiv). A large stir bar was used at a high spin rate to ensure adequate mixing as the mixture became cloudy and viscous over the course of the reaction. After 16 hours at rt the reaction was quenched with water (20 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with sat. LiCl (30 mL x 2) and brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-5% EtOAc in Hexanes) to yield the product as a viscous opaque liquid. (9.1 g, 99%).

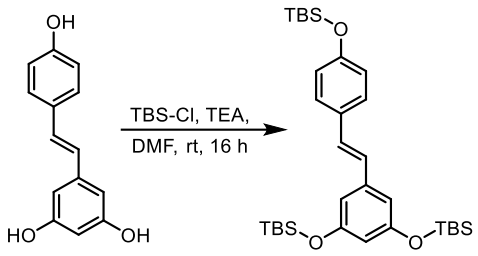
TLC (Hexanes/EtOAc, 95:5), R_F:	0.91 (UV, potassium permanganate)
^{1}H NMR (500 MHz, $CDCl_3$, 25 °C)	δ = 7.38 (d, J=8.3, 3H), 6.95 (d, J=16.2, 1H), 6.85 (d, J=16.2, 1H), 6.84 (s, 2H), 6.63 (d, J=2.2, 2H), 6.33 (s, 1H), 1.31 – 1.22 (m, 9H), 1.12 (dd, J=7.5, 3.6, 54H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C)	δ = 157.2, 156.0, 139.5, 130.5, 128.4, 127.8, 126.9, 120.3, 111.3, 111.0, 18.1, 18.1, 12.8.
HRMS (ESI):	*m/z* calculated for $C_{41}H_{72}O_3Si_3$ ($[M+H]^+$): 697.4862, found 697.4862
FTIR (neat) cm^{-1} :	ν̃= 2892 (m), 2867 (m), 1580 (m), 1508 (m), 1270 (m), 1168 (vs), 1014 (m), 881 (vs), 762 (w), 681 (vs), 660 (m)



3.125, ^{1}H NMR, 500 MHz, $CDCl_3$



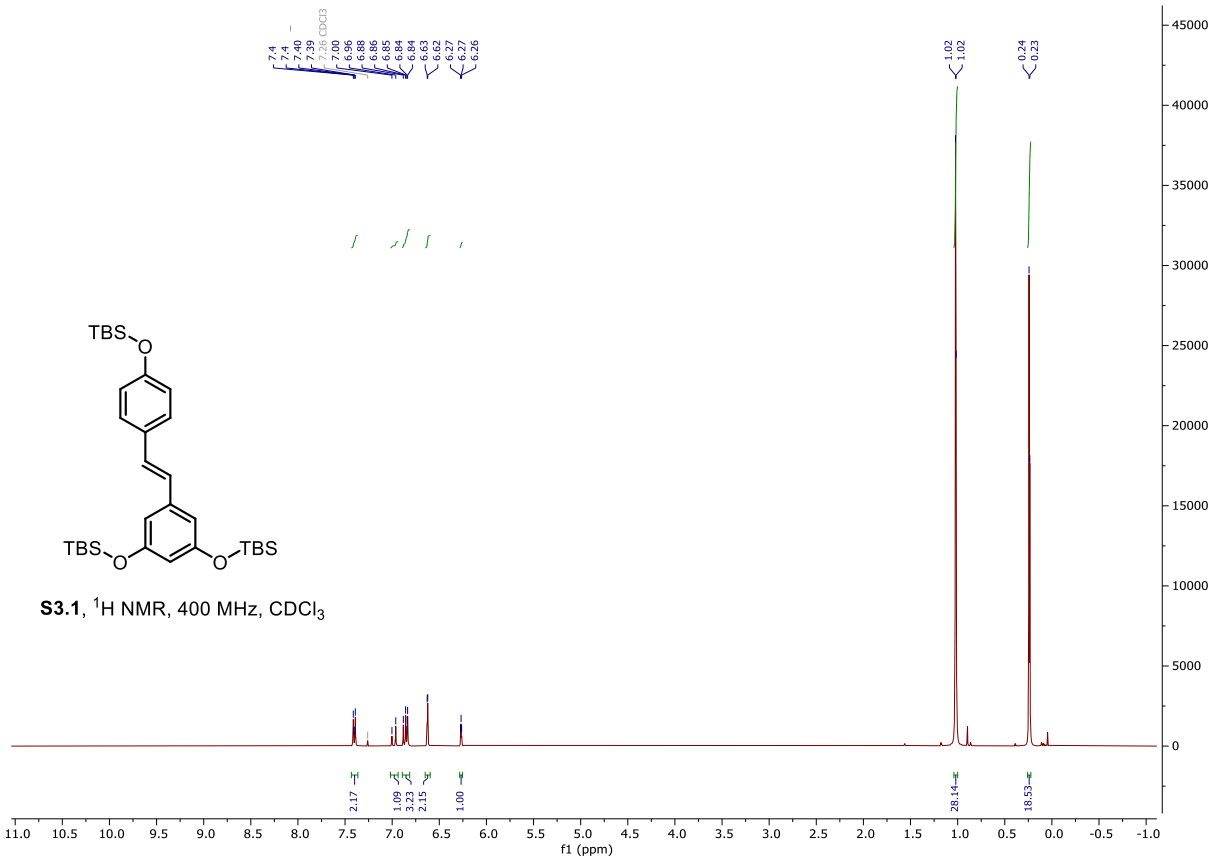
3.125, ^{13}C NMR, 126 MHz, $CDCl_3$



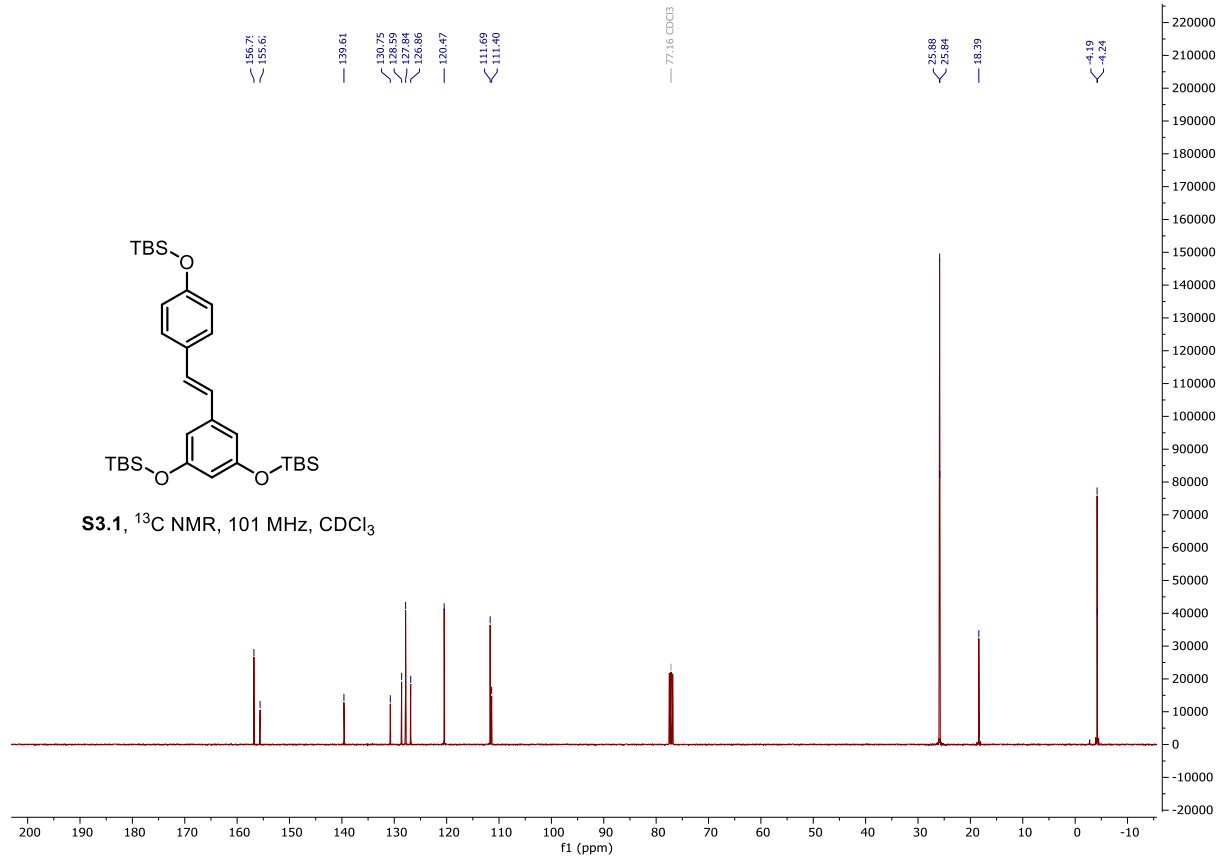
(S3.1) (E)-((5-(4-((tert-butyldimethylsilyl)oxy)styryl)-1,3-phenylene)bis(oxy))bis(tert-butyldimethylsilane)

In a flame-dried 50 mL RBF was added resveratrol (3.00 g, 13.1 mmol, 1 equiv), DMF (13.1 mL, 1.0 M), then dropwise TEA (9.16 mL, 65.7 mmol, 5.0 equiv), and TBS-Cl (9.9 g, 65.7 mmol, 5.0 equiv) as a solid. A large stir bar was used at a high spin rate to ensure adequte mixing as the mixture became cloudy and viscous over the course of the reaction. After 16 hours at rt the reaction was quenched with water (20 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with sat. LiCl (30 mL x 2) and brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-5% EtOAc in Hexanes) to yield the product as a viscous opaque liquid. (9.1 g, 99%).

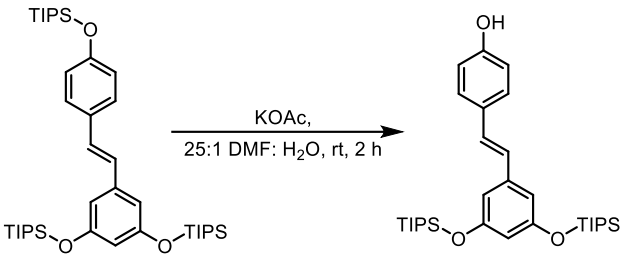
TLC (Hexanes/EtOAc, 95:5), R_F:	0.90 (UV, potassium permanganate)
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C)	δ = 7.40 (d, J=8.6, 2H), 6.98 (d, J=16.2, 1H), 6.90 – 6.81 (m, 3H), 6.63 (d, J=2.2, 2H), 6.27 (t, J=2.1, 1H), 1.02 (d, J=2.7, 27H), 0.24 (d, J=3.3, 18H).
^{13}C NMR (101 MHz, $CDCl_3$, 25 °C)	δ = 156.8, 155.6, 139.6, 130.8, 128.6, 127.8, 126.9, 120.5, 111.7, 111.4, 25.9, 25.8, 18.4, -4.2, -4.2.
HRMS (ESI):	*m/z* calculated for $C_{32}H_{54}O_3Si_3$ ($[M+H]^+$): 571.3454, found 571.3455
FTIR (neat) cm^{-1} :	ν̃= 2958 (w), 2931 (w), 2887 (w), 2859 (w), 1583 (m), 1509 (m), 1253 (vs), 1165 (vs), 1031 (w), 912 (m), 877 (m), 829 (vs), 813 (vs), 778 (vs)



S3.1, ^{1}H NMR, 400 MHz, $CDCl_3$



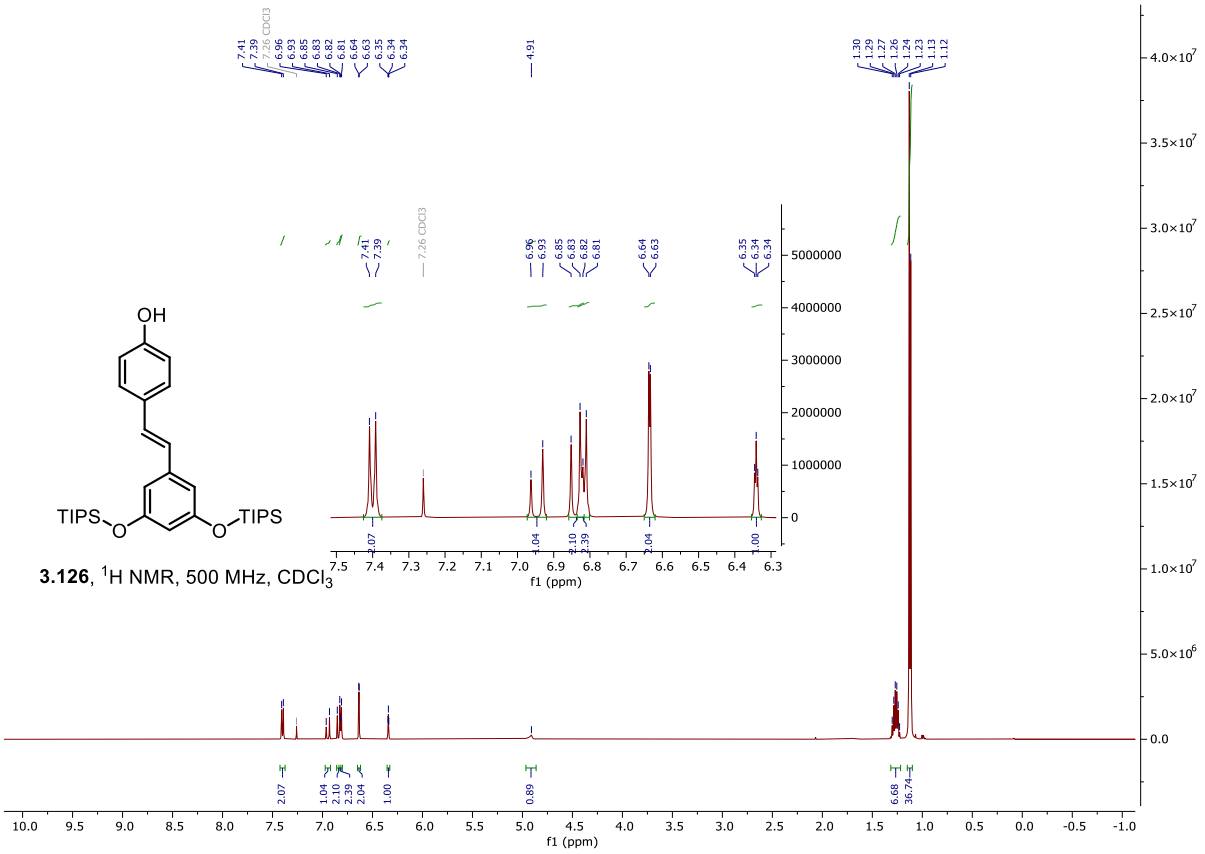
S3.1, ^{13}C NMR, 101 MHz, $CDCl_3$



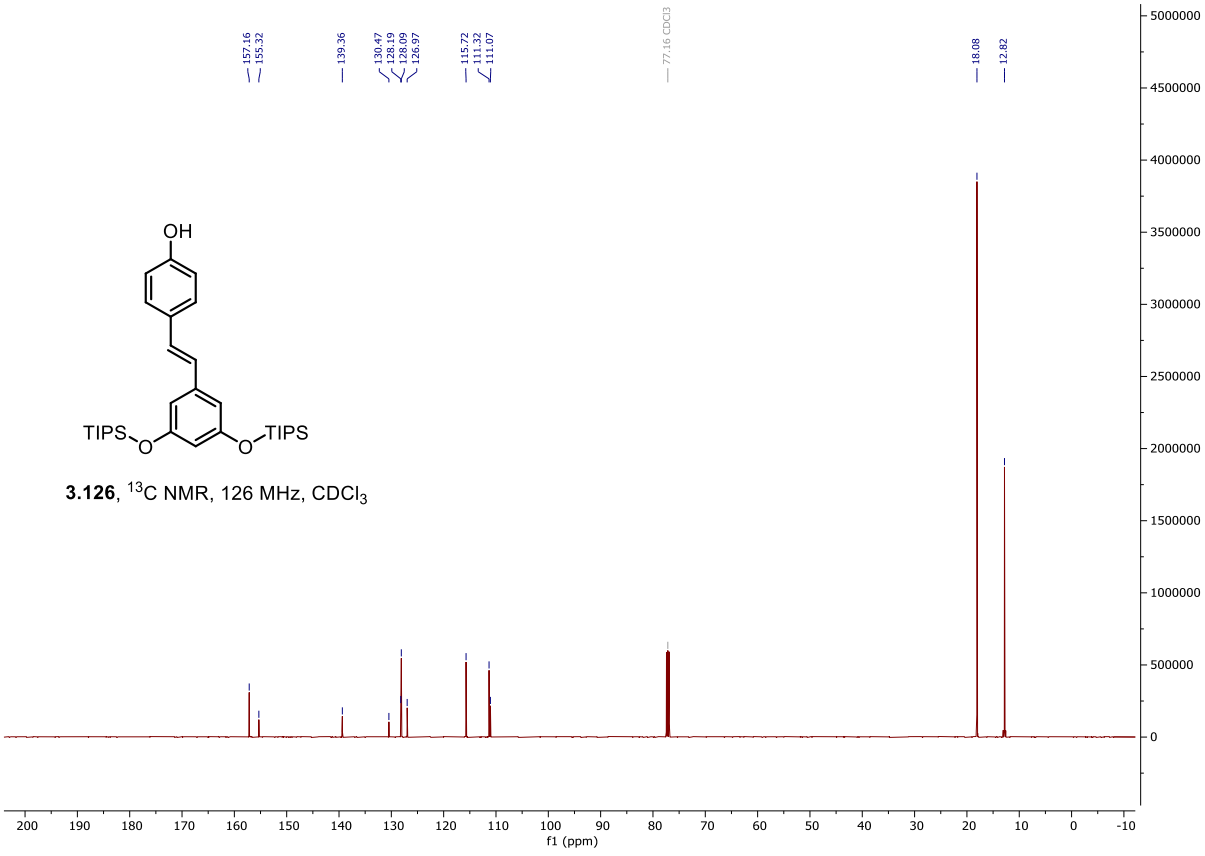
(3.126) (E)-4-(3,5-bis((triisopropylsilyl)oxy)styryl)phenol

To a 4 dram vial was added stilbene (300 mg, 0.43 mmol, 1 equiv) and 25:1 DMF:H_2O (2.2 mL, 0.2 M). This mixture was stirred vigorously for 10 minutes until well incorporated. KOAc (42 mg, 0.43 mmol, 1 equiv) was added as a solid. After 2 hours the reaction was added to a separatory funnel containing water (20 mL). The mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with sat. LiCl (30 mL x 2) and brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-15% EtOAc in Hexanes) to yield the product as a viscous opaque yellow liquid. (118 mg, 51%).

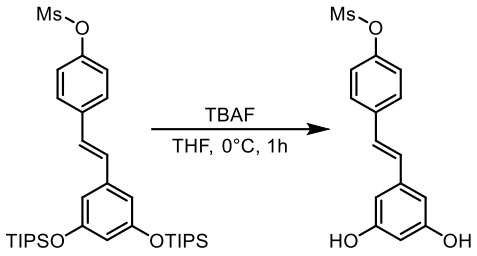
TLC (Hexanes/EtOAc, 90:10), R_F:	0.43 (UV, potassium permanganate)
^{1}H NMR (500 MHz, $CDCl_3$, 25 °C)	δ = 7.40 (d, J=8.6, 1H), 6.95 (d, J=16.3, 1H), 6.84 (d, J=16.3, 1H), 6.82 (d, J=8.6, 1H), 6.64 (d, J=2.1, 2H), 6.34 (t, J=2.2, 1H), 4.91 (s, 1H, OH), 1.26 (m, 3H), 1.12 (d, J=7.4, 36H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C)	δ = 157.2, 155.3, 139.4, 130.5, 128.2, 128.1, 127.0, 115.7, 111.3, 111.1, 18.1, 12.8.
HRMS (ESI):	*m/z* calculated for $C_{32}H_{52}O_3Si_2$ ($[M+H]^+$): 541.3528, found 541.3528
FTIR (neat) cm^{-1} :	ν̃= 2945 (w), 2867 (w), 1579 (s), 1441 (w), 1170 (vs), 1033 (w), 1015 (m), 882 (m), 838 (w), 684 (m)



3.126, ^{1}H NMR, 500 MHz, $CDCl_3$



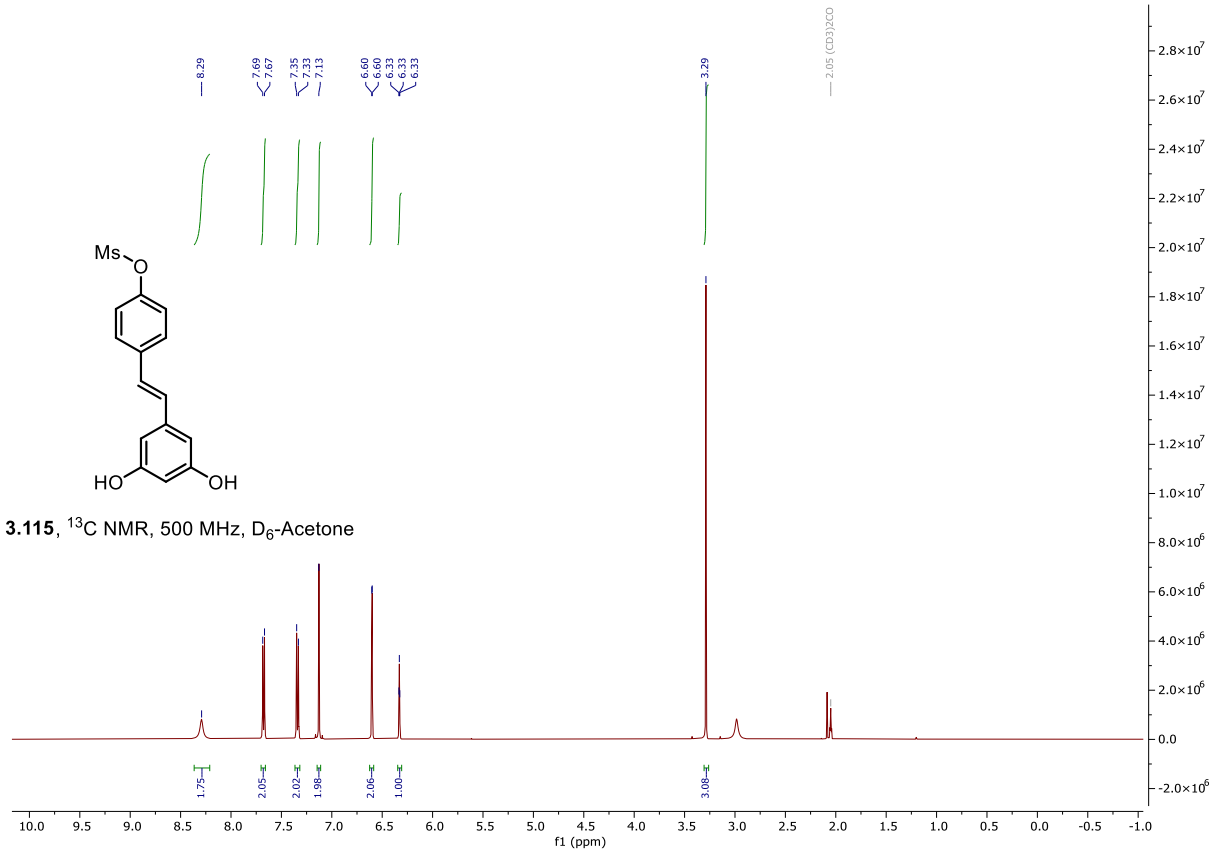
3.126, ^{13}C NMR, 126 MHz, $CDCl_3$



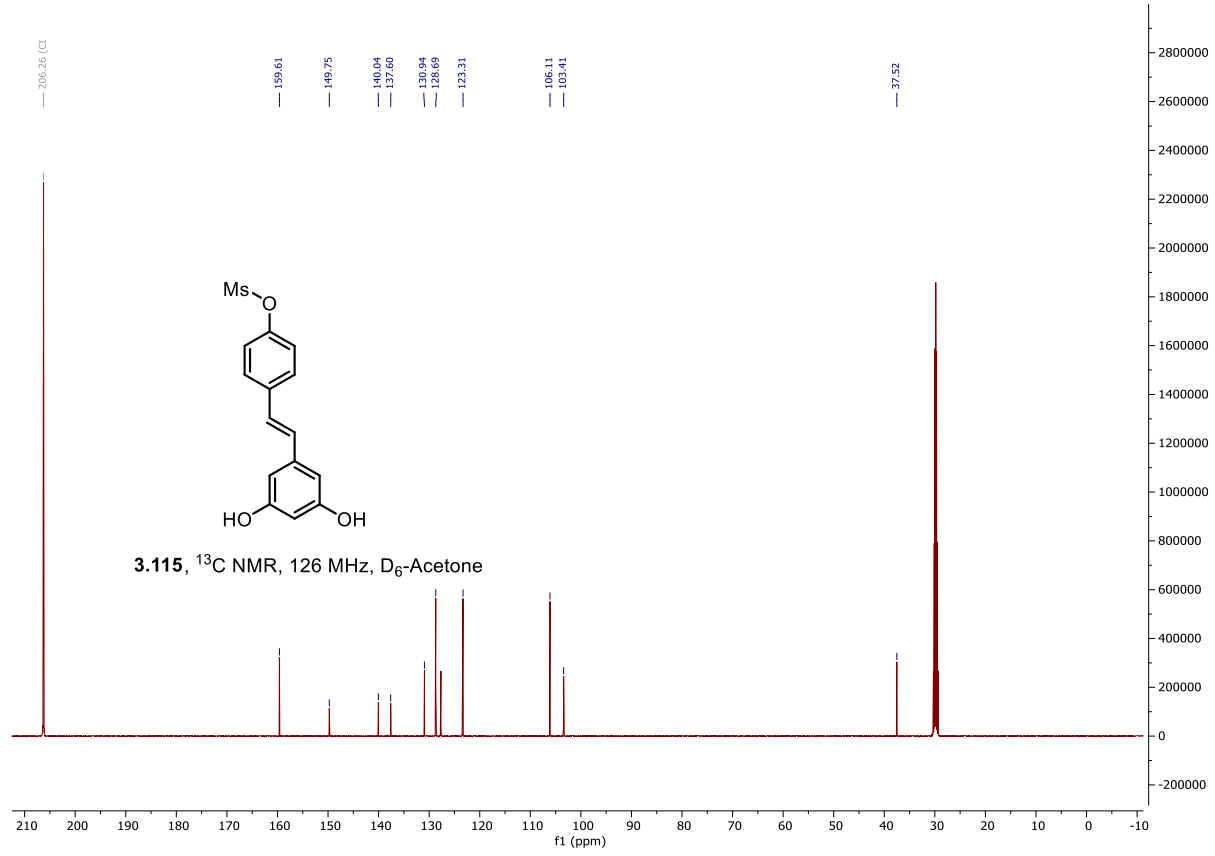
(3.115) (E)-4-(3,5-dihydroxystyryl)phenyl methanesulfonate

To an 11 dram vial was added stilbene (300 mg, 0.485 mmol, 1 equiv) and THF (9.7 mL, 0.05 M). The solution was cooled to 0 °C. TBAF (1.2 mL, 1.2 mmol, 2.5 equiv, 1 M solution in THF) was added. The solution was stirred for 1 h before diluting with sat $NaHCO_3$ (5 mL). The reaction was transferred to a separatory funnel containing water (20 mL). The mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuum and the crude material was purified by flash chromatography over SiO_2 (0%-20% Acetone in DCM) to yield the product as a tan amorphous solid (140 mg, 94%).

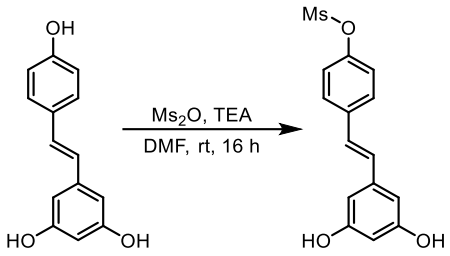
TLC (DCM/Acetone, 90:10), R_F:	0.16 (UV, potassium permanganate)
^{1}H NMR (500 MHz, D_6-Acetone, 25 °C)	δ = 8.29 (s, 2H, OH), 7.68 (d, J=8.8, 1H), 7.34 (d, J=8.8, 1H), 7.13 (s, 1H), 6.60 (d, J=2.3, 2H), 6.33 (t, J=2.1, 1H), 3.29 (s, 3H).
^{13}C NMR (126 MHz, D_6-Acetone, 25 °C)	δ = 159.6, 149.7, 140.0, 137.6, 130.9, 128.7, 123.3, 106.1, 103.4, 37.5.
HRMS (ESI):	*m/z* calculated for $C_{15}H_{14}O_5S$ ($[M+H]^+$): 307.0635, found 307.0636
FTIR (neat) cm^{-1} :	$\tilde{\nu}$= 3380 (br), 3031 (w), 2937 (w), 1347 (m), 1142 (vs), 870 (m), 840 (m)



3.115, ^{13}C NMR, 500 MHz, D_6-Acetone



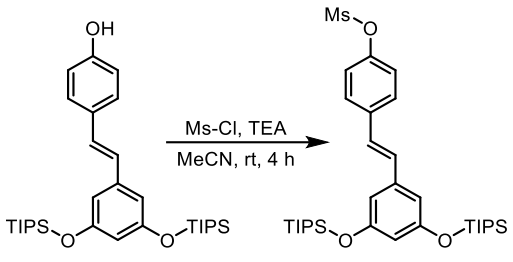
3.115, ^{13}C NMR, 126 MHz, D_6-Acetone



(3.115) (E)-4-(3,5-dihydroxystyryl)phenyl methanesulfonate

Alternative Procedure

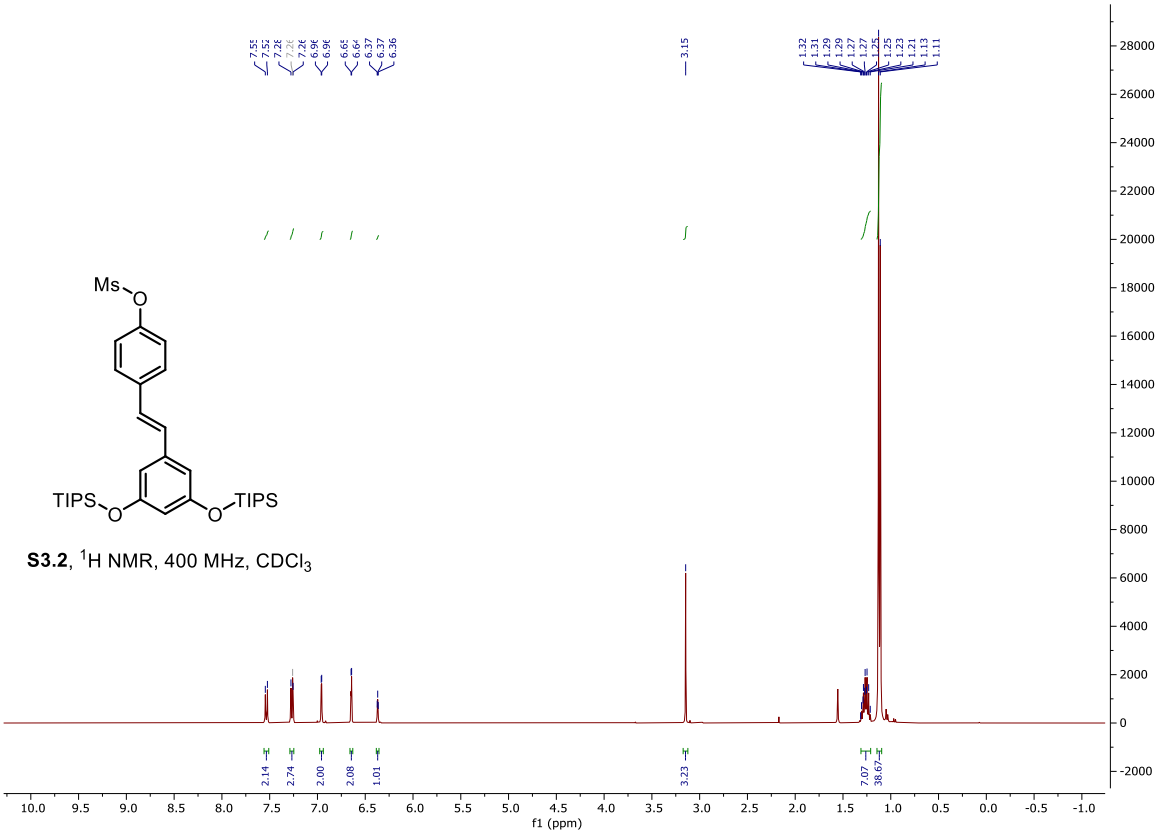
To a 50 mL RBF was added resveratrol (1.0 g, 4.4 mmol, 1 equiv), DMF (22 mL, 0.2 M), and TEA (0.85 mL, 6.1 mmol, 1.4 equiv). The solution was stirred vigorously during the addition of methanesulfonic anhydride (1.4 g, 6.1 mmol, 1.4 equiv) dissolved in 4.4 mL of DMF over 6 hours via syringe pump. The solution was let stir for a total of 16 hours before transferred to a separatory funnel containing water (100 mL). The mixture was extracted with diethyl ether (3 x 40 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-20% Acetone in DCM) to yield the product as a tan amorphous solid (251 mg, 19%). The yield of this reaction is highly dependent on the rate of electrophile addition and stirring.



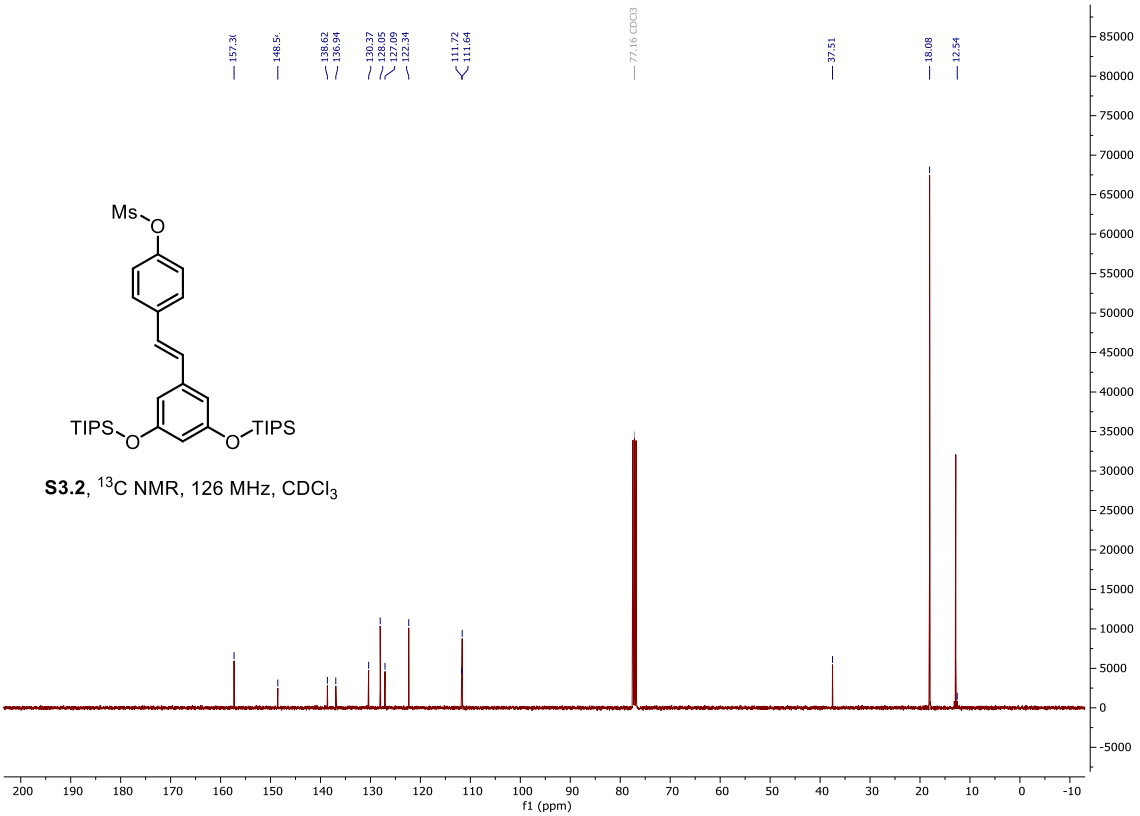
(S3.2) (E)-4-(3,5-bis((triisopropylsilyl)oxy)styryl)phenyl methanesulfonate

If a stepwise procedure is desired towards compound **14,** this preparation can be used to isolate **S2**. To a 4 dram vial was added phenol (100 mg, 185 µmol, 1.0 equiv), acetonitrile (1.23 mL, 0.15 M), TEA (38.6 µL, 277 µmmol, 1.5 equiv), and Ms-Cl dropwise (18.6 µL, 240 µmol, 1.3 equiv). The reaction was stirred at room temperature for 4 hours and quenched with water (10 mL). The mixture was extracted with diethyl ether (3 x 10mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-15% EtOAc in Hexanes) to yield the product as an amorphous white solid (91 mg, 80%).

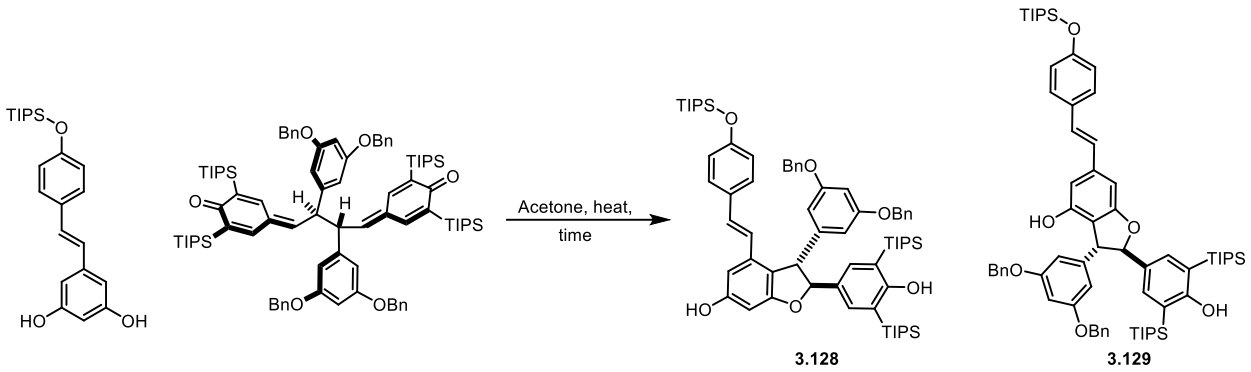
TLC (Hexanes/EtOAc, 90:10), R_F:	0.30 (UV, potassium permanganate)
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C)	δ = 7.53 (d, J=8.8, 2H), 7.27 (d, J=8.8, 2H), 6.96 (d, J=2.1, 2H), 6.65 (d, J=2.2, 2H), 6.37 (t, J=2.2, 1H), 3.15 (s, 3H), 1.31 – 1.21 (m, 7=6H), 1.12 (d, J=7.0, 36H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C)	δ = 157.3, 148.5, 138.6, 136.9, 130.4, 128.0, 127.1, 122.3, 111.7, 111.6, 37.5, 18.1, 12.5.
HRMS (ESI):	*m/z* calculated for $C_{33}H_{54}O_5SSi_2$ ($[M+H]^+$): 619.3309, found 619.3303
FTIR (neat) cm^{-1} :	ν̃= 2945 (m), 2868 (m), 1578 (w), 1350 (w), 1173 (vs), 1150 (vs), 1015 (w), 880 (s), 859 (vs), 761 (w), 683 (vs)



S3.2, ^{1}H NMR, 400 MHz, $CDCl_3$



S3.2, ^{13}C NMR, 126 MHz, $CDCl_3$

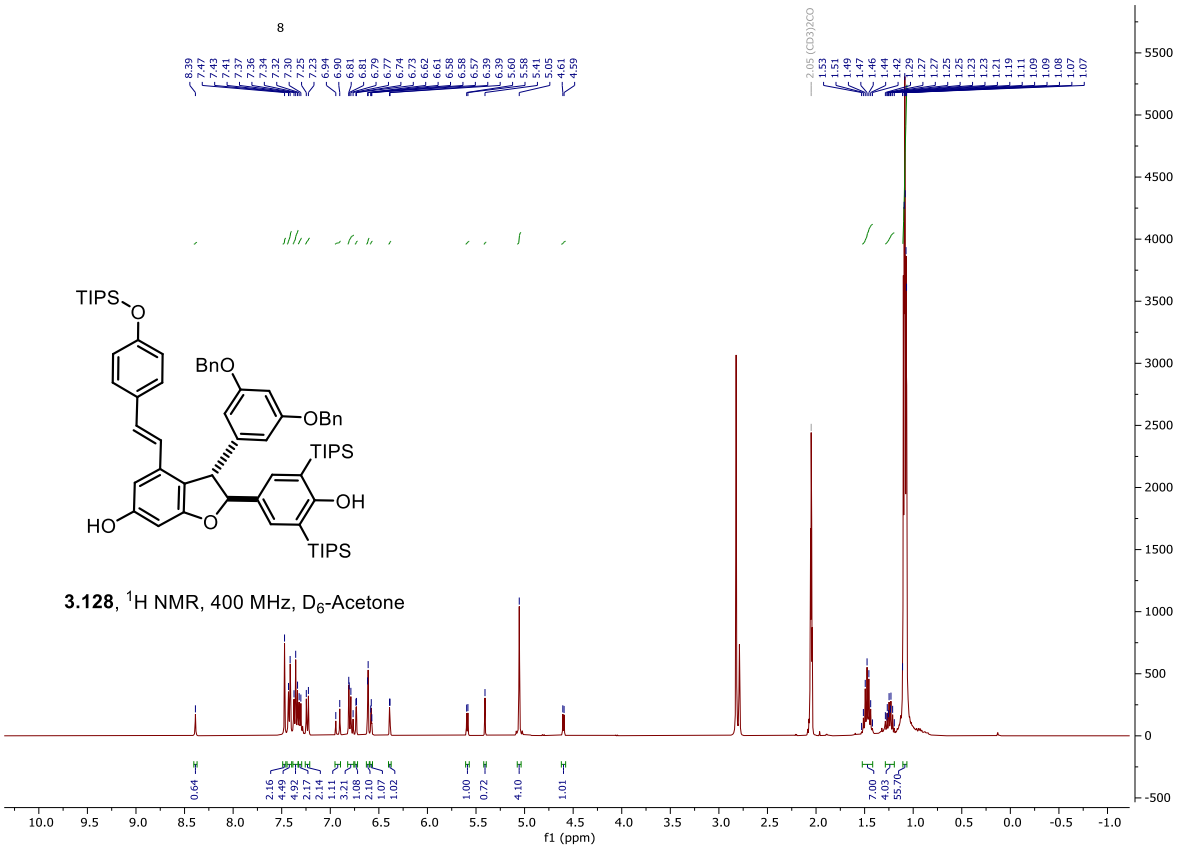


(3.128) 2-Bn 3-TIPS ε-viniferin and (3.129) 2-Bn 3-TIPS gnetin C

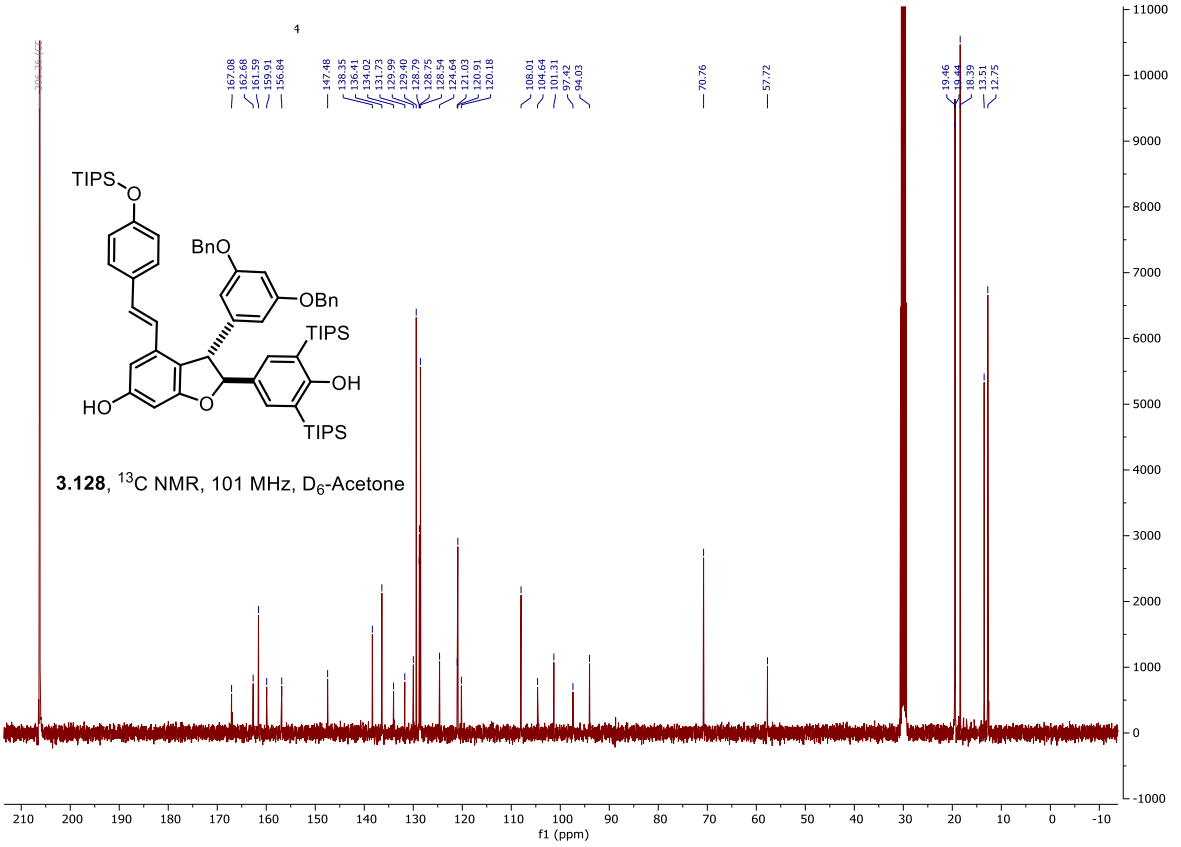
In a flame-dried 0.5-2 mL microwave vial was added stilbene (15 mg, 39 μmol, 1.0 equiv), bis-quinone methide dimer (110 mg, 78 μmol, 2 equiv), and acetone (1.6 mL, 0.025M). The suspension was freeze-pump-thawed (three cycles) to rigorously degas the solution. The tube was capped, and the mixture was reacted at 100 °C for 10 hours with stirring in a Biotage Initiator+ microwave reactor. The crude was transferred to a round bottom flask and concentrated *in vacuo* and purified by flash chromatography over SiO_2 (0%-20% EtOAc in Hexanes) to afford 2-Bn 3-TIPS ε-viniferin (16) as a light tan foam (23.6 mg, 55%) and 2-Bn 3-TIPS gnetin C (17) (6.2 mg, 14%) as a light tan foam.

Characterization for (3.128) 2-Bn 3-TIPS ε-viniferin

TLC (Hexanes/EtOAc, 90:10), R_F:	0.23 (UV, potassium permanganate)
^{1}H NMR (400 MHz, D_6-Acetone, 25 °C)	δ = 8.39 (s, 1H, OH), 7.47 (s, 2H), 7.42 (d, J=6.7, 4H), 7.36 (t, J=7.2, 4H), 7.31 (d, J=7.0, 2H), 7.24 (d, J=8.7, 2H), 6.92 (d, J=16.3, 1H), 6.82 – 6.76 (m, 3H), 6.73 (d, J=2.1, 1H), 6.61 (d, J=2.3, 2H), 6.58 (t, J=2.2, 1H), 6.39 (d, J=2.1, 1H), 5.59 (d, J=5.1, 1H), 5.41 (s, 1H, OH), 5.05 (s, 4H), 4.60 (d, J=5.1, 1H), 1.47 (h, J=7.5, 6H), 1.29 – 1.19 (m, 3H), 1.11 – 1.06 (m, 54H).
^{13}C NMR (101 MHz, D_6-Acetone, 25 °C)	δ = 167.1, 162.7, 161.6, 159.9, 156.8, 147.5, 138.3, 136.4, 134.0, 131.7, 130.0, 129.4, 128.8, 128.7, 128.5, 124.6, 121.0, 120.9, 120.2, 108.0, 104.6, 101.3, 97.4, 94.0, 70.8, 57.7, 19.5, 19.4, 18.4, 13.5, 12.8.
HRMS (ESI):	*m/z* calculated for $C_{69}H_{94}O_6Si_3$ ($[M+H]^+$): 1103.6436, found 1103.6428
FTIR (neat) cm^{-1}:	ν̃= 2866 (w), 1595 (vs), 1509 (s), 1461 (w), 1273 (m), 1158 (vs), 884 (vs), 693 (m), 671 (w)



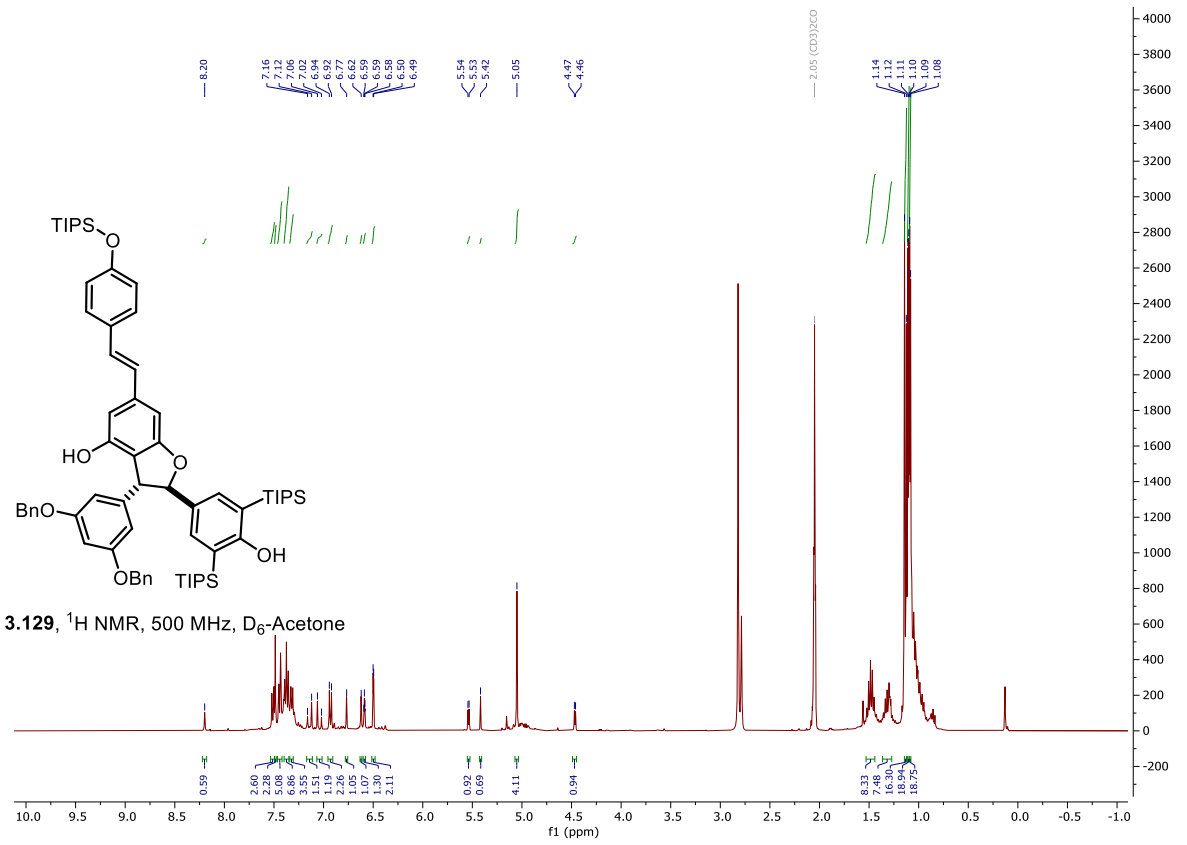
3.128, ^{1}H NMR, 400 MHz, D_6-Acetone



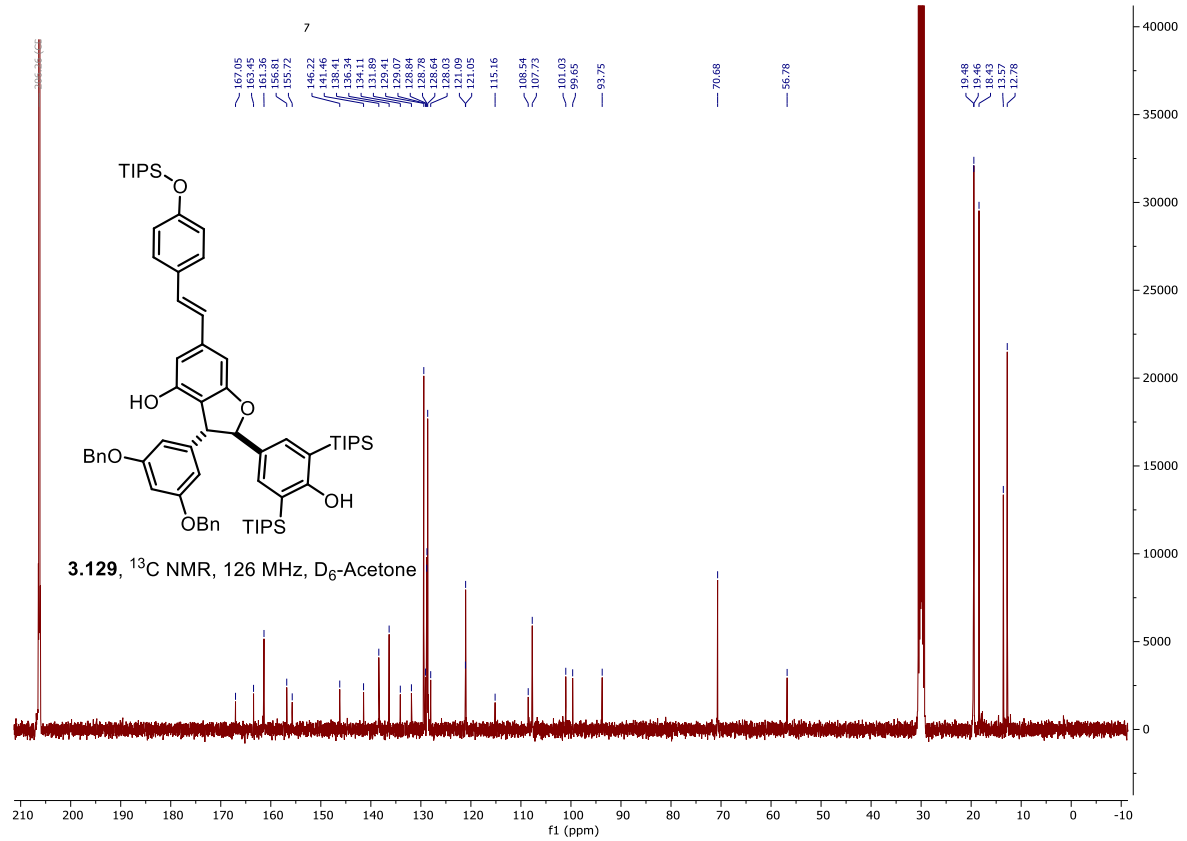
3.128, ^{13}C NMR, 101 MHz, D_6-Acetone

Characterization for (3.129) 2-Bn 3-TIPS gnetin C

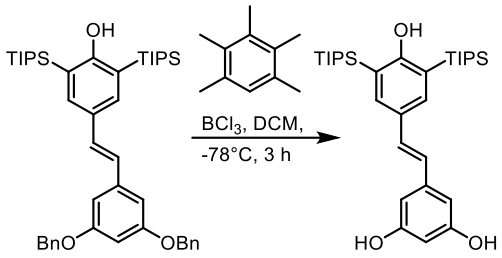
TLC (Hexanes/EtOAc, 90:10), R_F:	0.33 (UV, potassium permanganate)
^{1}H NMR (500 MHz, D_6-Acetone, 25 °C)	δ = 8.20 (s, 1H, OH), 7.51 (d, J=8.6, 2H), 7.49 (s, 2H), 7.44 (d, J=6.8, 4H), 7.40-7.36 (m, 6H), 7.34-7.32 (m, 4H), 7.14 (d, J=16.4, 1H), 7.04 (d, J=16.3, 1H), 6.93 (d, J=8.6, 2H), 6.77 (s, 1H), 6.62 (s, 1H), 6.59 (t, J=2.3, 1H), 6.50 (d, J=2.3, 2H), 5.54 (d, J=4.6, 1H), 5.42 (s, 1H, OH), 5.05 (s, 4H), 4.47 (d, J=4.7, 1H), 1.49 (p, J=7.5, 6H), 1.36 – 1.27 (m, 3H), 1.13 (d, J=7.3, 18H), 1.10 (d, J=3.7, 18H), 1.09 (d, J=3.7, 18H).
^{13}C NMR (126 MHz, D_6-Acetone, 25 °C)	δ = 167.1, 163.4, 161.4, 156.8, 155.7, 146.2, 141.5, 138.4, 136.3, 134.1, 131.9, 129.4, 129.1, 128.8, 128.8, 128.6, 128.0, 121.1, 121.1, 115.2, 108.5, 107.7, 101.0, 99.7, 93.8, 70.7, 56.8, 19.5, 19.5, 18.4, 13.6, 12.8.
HRMS (ESI):	*m/z* calculated for $C_{69}H_{94}O_6Si_3$ ($[M+H]^+$): 1103.6436, found 1103.6430
FTIR (neat) cm^{-1}:	ν̃= 2945 (m), 2866 (vs), 1599 (vs), 1509 (m), 1464 (m), 1404 (w), 1271 (m), 1160 (vs), 1058 (w), 1018 (w), 917 (w), 882 (m), 695 (w), 668 (w)



3.129, ^{1}H NMR, 500 MHz, D_6-Acetone



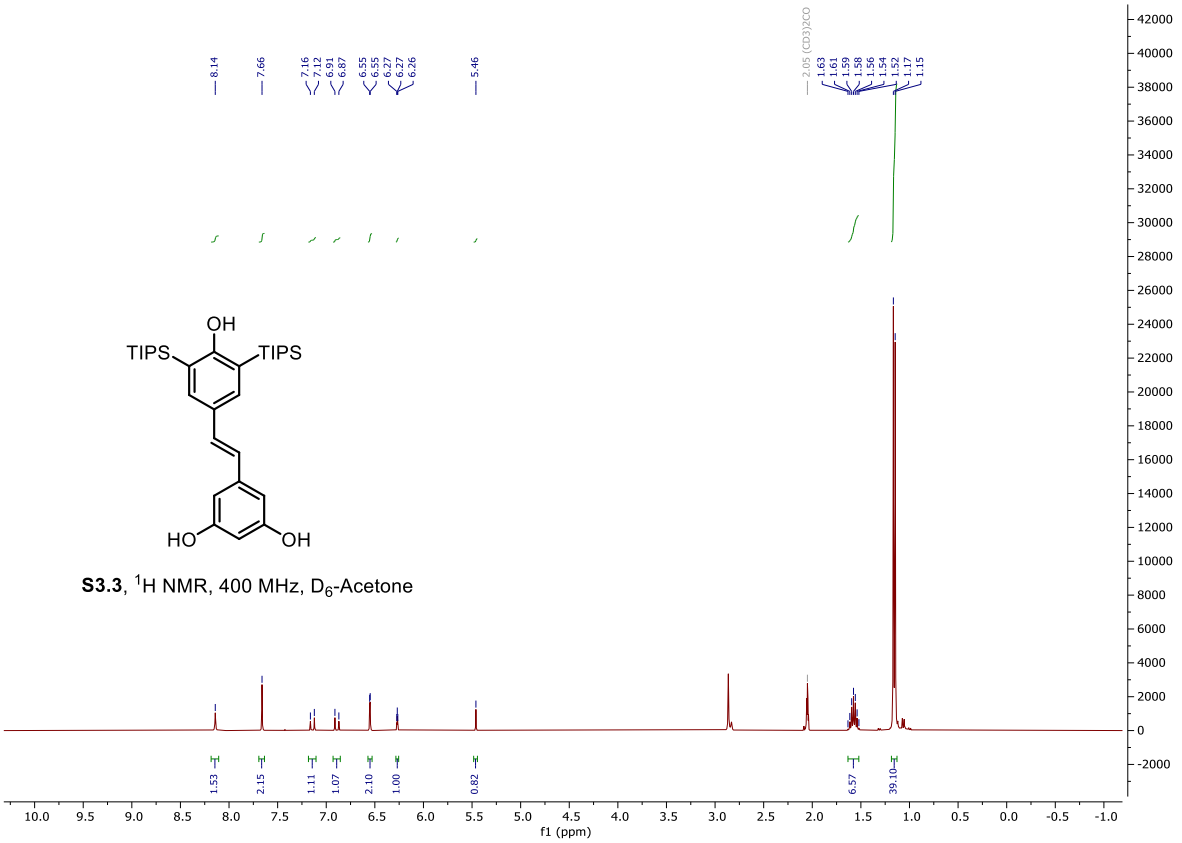
3.129, ^{13}C NMR, 126 MHz, D_6-Acetone



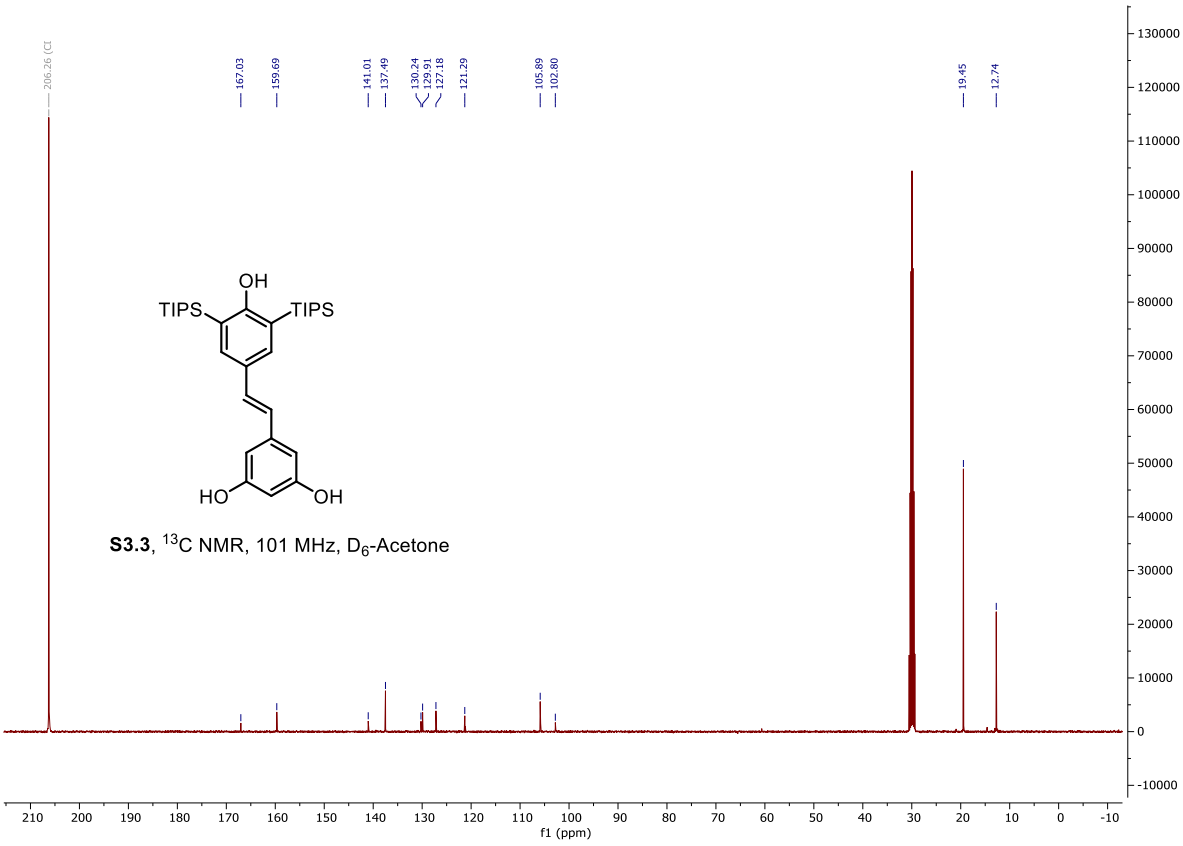
(S3.3) (E)-5-(4-hydroxy-3,5-bis(triisopropylsilyl)styryl)benzene-1,3-diol

This stilbene was obtained through the same synthetic sequence presented in chapter 2. To a 250 mL RBF was added phenol (2.58 g, 3.6 mmol, 1.0 equiv), DCM (179 mL, 0.02 M), and pentamethylbenzene (10.6 g, 71.5 mmol, 20 equiv). The solution was cooled to -78 °C and boron trichloride (21.5 mL, 21.5 mmol, 6 equiv, 1 M solution in DCM) was added dropwise. The solution turned a brilliant red color. After 3 hours, with TLC monitoring the reaction was quenched at -78 °C with 2 mL of a sat $NaHCO_3$ solution dropwise. Loss of 1 or 2 TIPS groups can be seen below the product spot by TLC. Optimal yield is obtained at approximately 90% conversion. As the reaction warmed to room temperature over 30 minutes the solution decolorized. The reaction was extracted with diethyl ether (3 x 100mL). The combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-30% EtOAc in Hexanes) to yield the product as a translucent pale-yellow viscous foam (1.25 g, 65%).

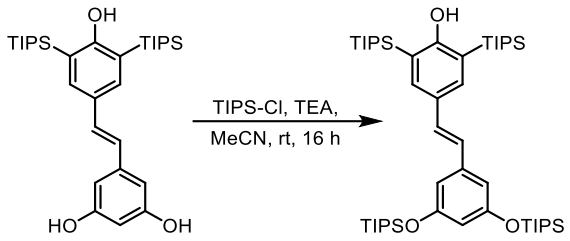
TLC (Hexanes/EtOAc, 80:20), R_F:	0.14 (UV, potassium permanganate)
^{1}H NMR (400 MHz, D_6-Acetone, 25 °C)	δ = 8.14 (s, 2H, OH), 7.66 (s, 2H), 7.14 (d, J=16.2, 1H), 6.89 (d, J=16.2, 1H), 6.55 (d, J=2.2, 2H), 6.27 (t, J=2.2, 1H), 5.46 (s, 1H, OH), 1.58 (p, J=7.5, 6H), 1.16 (d, J=7.4, 38H).
^{13}C NMR (101 MHz, D_6-Acetone, 25 °C)	δ = 167.0, 159.7, 141.0, 137.5, 130.2, 129.9, 127.2, 121.3, 105.9, 102.8, 19.5, 12.7.
HRMS (ESI):	*m/z* calculated for $C_{32}H_{52}O_3Si_2$ ($[M+H]^+$): 541.3528, found 541.3529
FTIR (neat) cm^{-1} :	ν̃= 3602 (w), 3379 (br), 2946 (s), 2866 (s), 1591 (m), 1465 (m), 1156 (vs), 882 (vs), 670 (s)



S3.3, ^{1}H NMR, 400 MHz, D_6-Acetone



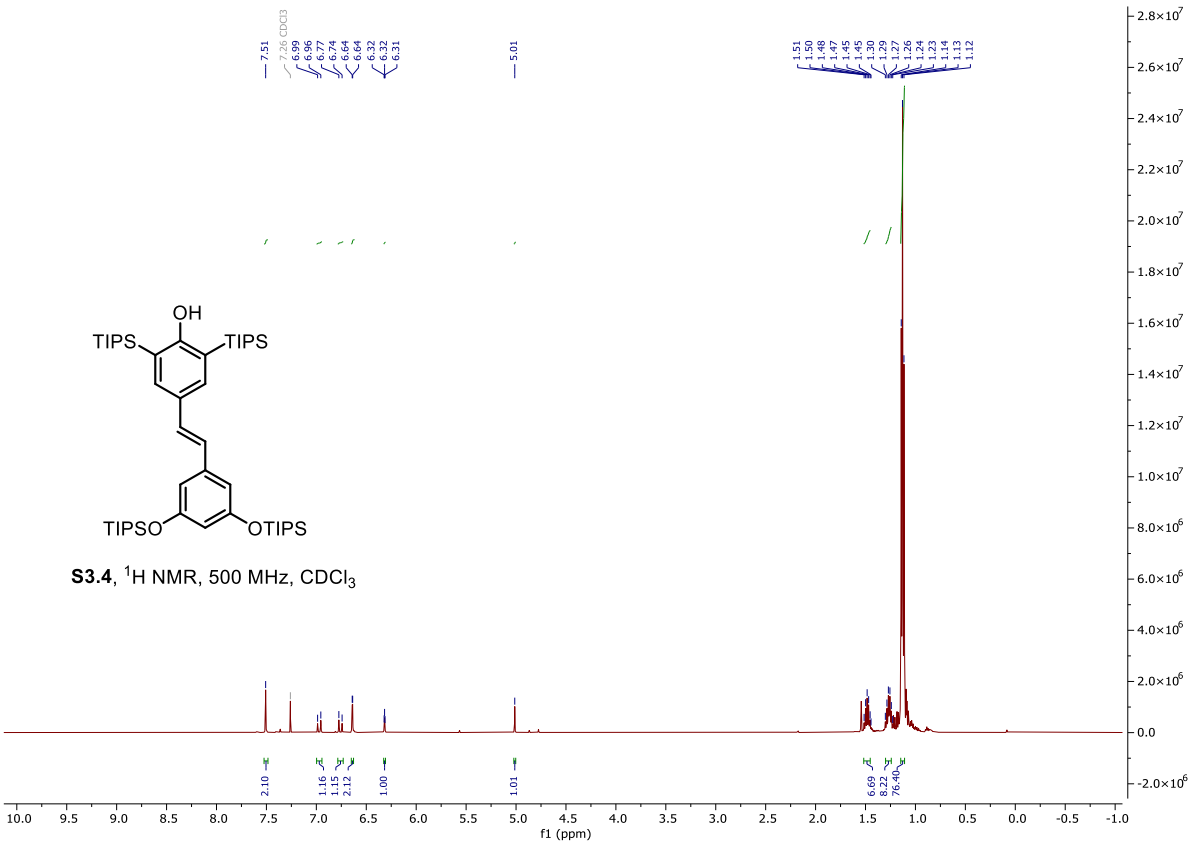
S3.3, ^{13}C NMR, 101 MHz, D_6-Acetone



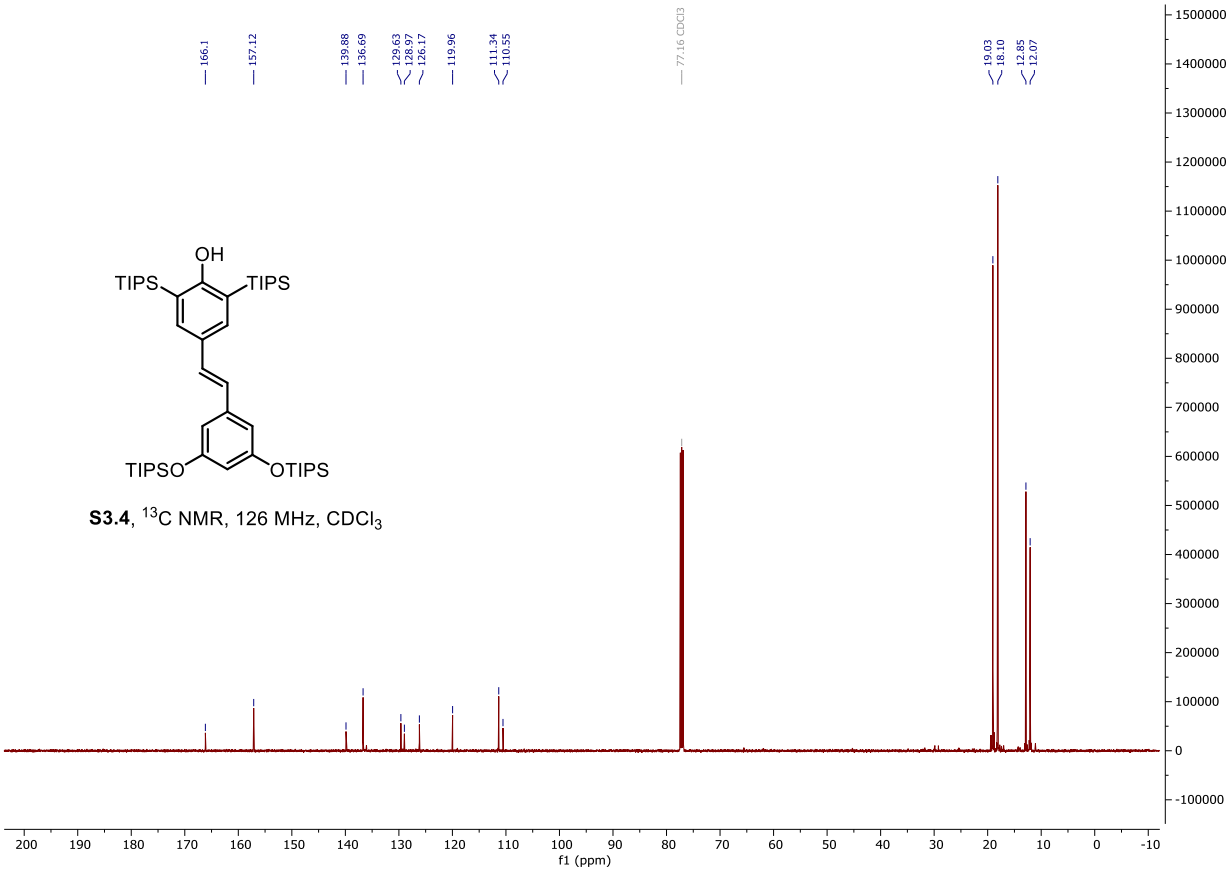
(S3.4) (E)-4-(3,5-bis((triisopropylsilyl)oxy)styryl)-2,6-bis(triisopropylsilyl)phenol

To a 100 mL RBF was added phenol (1.2 g, 2.2 mmol, 1.0 equiv), acetonitrile (44 mL, 0.05 M), TEA (1.2 mL, 8.9 mmol, 4 equiv), and TIPS-Cl dropwise (1.9 mL, 8.9 mmol, 4 equiv). The reaction was stirred at room temperature for 16 hours and quenched with water (40 mL). The mixture was extracted with diethyl ether (3 x 30mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-10% EtOAc in Hexanes) to yield the product as a translucent pale-yellow viscous oil (1.5 g, 79%).

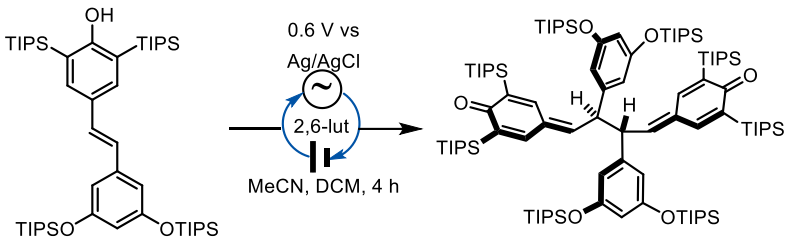
TLC (Hexanes/EtOAc, 95:5), R_F:	0.98 (UV, potassium permanganate)
^{1}H NMR (500 MHz, $CDCl_3$, 25 °C)	δ = 7.51 (s, 2H), 6.97 (d, J=16.1, 1H), 6.76 (d, J=16.1, 1H), 6.64 (d, J=2.3, 2H), 6.32 (t, J=2.3, 1H), 5.01 (s, 1H, OH), 1.48 (p, J=7.4, 6H), 1.30 – 1.24 (m, 6H), 1.13 (t, J=6.8, 72H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C)	δ = 166.2, 157.1, 139.9, 136.7, 129.6, 129.0, 126.2, 120.0, 111.3, 110.6, 19.0, 18.1, 12.9, 12.1.
HRMS (ESI):	*m/z* calculated for $C_{29}H_{24}O_8S$ ($[M+H]^+$): 853.6197, found 853.6205
FTIR (neat) cm^{-1} :	ν̃= 2945 (m), 2866 (m), 1578 (m), 1344 (w), 1170 (m), 1015 (m), 881 (vs), 767 (w), 682 (s), 664 (s)



S3.4, ^{1}H NMR, 500 MHz, $CDCl_3$



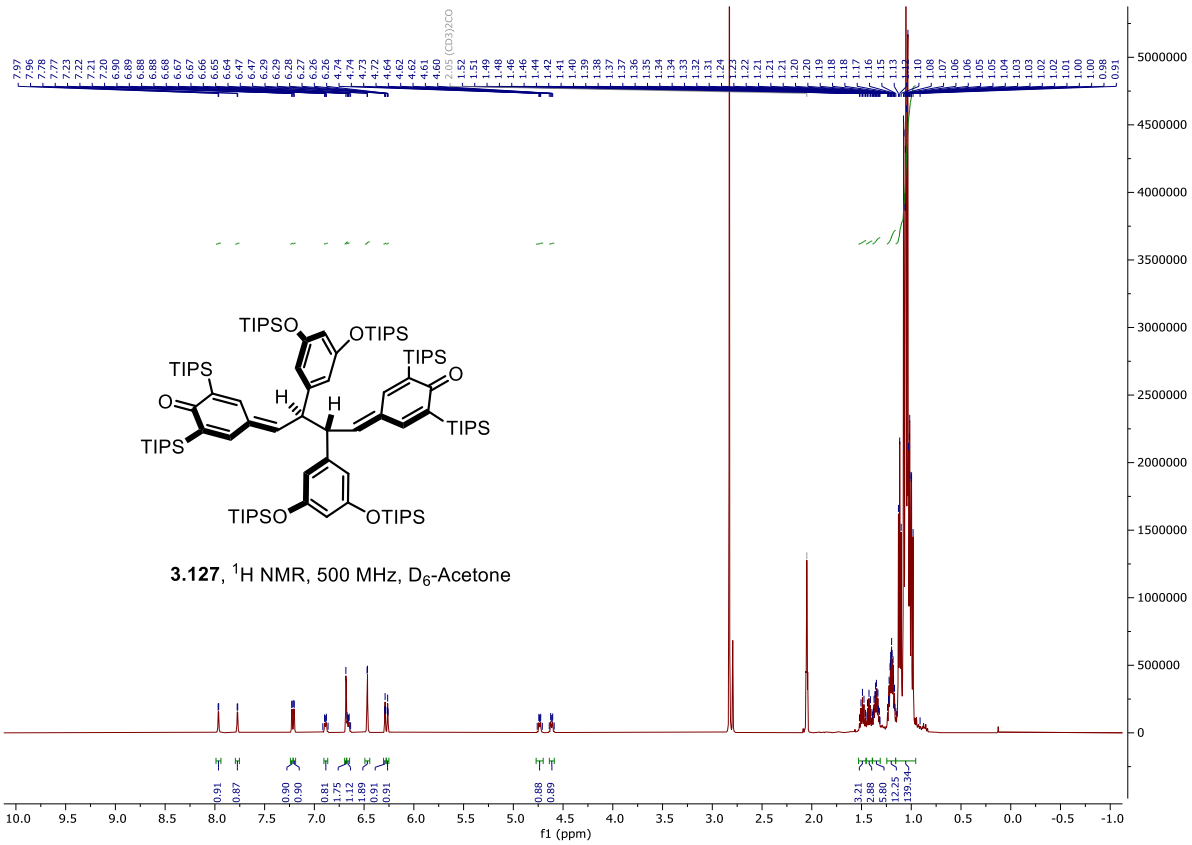
S3.4, ^{13}C NMR, 126 MHz, $CDCl_3$



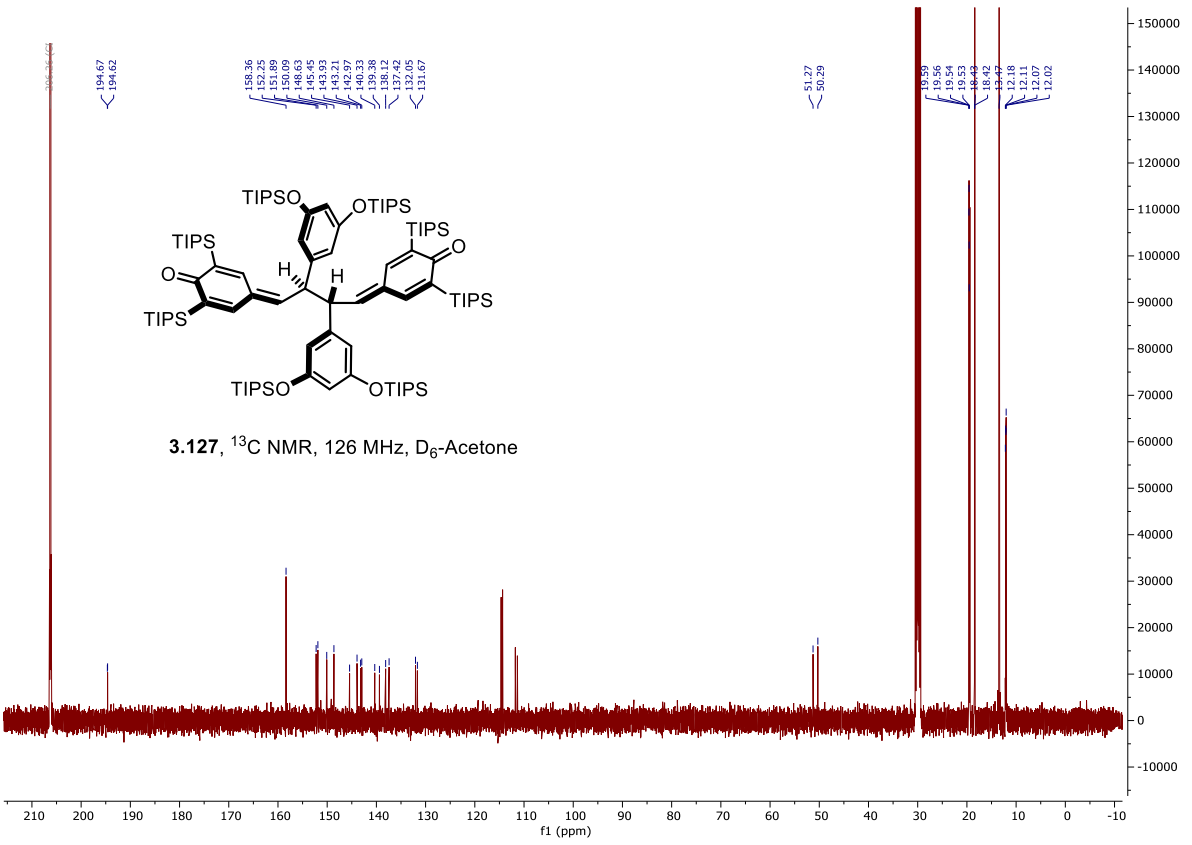
(3.127) 4,4'-((2R)-2,3-bis(3,5-bis((triisopropylsilyl)oxy)phenyl)butane-1,4-diylidene)bis(2,6-bis(triisopropylsilyl)cyclohexa-2,5-dien-1-one)

This preparation utilizes the conditions from our previous publication.[57] To a 150 mL beaker was added stilbene (1.50 g, 1.76 mmol, 1 equiv), KPF_6 (1.29 g, 7.03 mmol, 4 equiv), 2,6-lutidine (204 µL, 1.76 mmol, 1 equiv), and a 2:1 ratio of MeCN:DCM (140 mL total volume, 93 MeCN: 47 DCM, 0.0125M). Two pieces of 8 x 4-inch RVC panel (0.25-inch thickness) were cut. To each, a hole was made near one end, and copper wire was placed through the hole and wrapped around the top of each electrode. One end of the wire was left free to connect to the alligator clips. These electrodes were carefully placed into the beaker along with the reference electrode (Ag/AgCl in 3 M KCl) and a glass divider. The alligator clips were connected such that the reference and working electrodes were adjacent to each other, while the counter electrode was opposite the divider. Care was taken to ensure the copper wire was not submerged in solvent, nor the active components of the alligator clips touching each other. The reaction was stirred at 1000 rpm for 2-5 h at a constant voltage of 0.6 V. A chronoampergram was recorded to follow the course of the reaction. Upon completion of the reaction, the electrodes were removed and rinsed into a collection flask with DCM (~200 mL). The contents of the reaction vial were also rinsed into the collection flask. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-10% EtOAc in Hexanes) to yield the product as a bright yellow foam (1.3 g, 89%, 1:1 mixture of diastereomers).

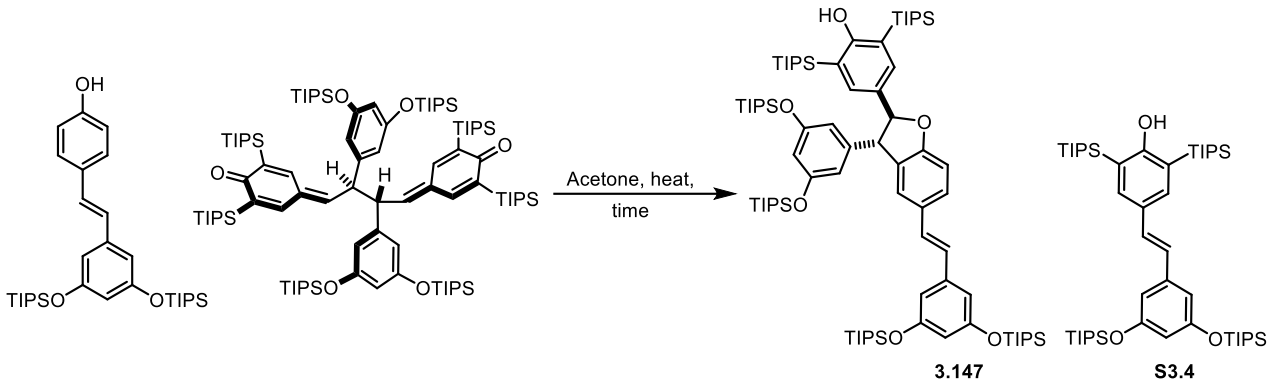
TLC (Hexanes/EtOAc, 95:5), R_F:	0.80 and 0.82 (UV, potassium permanganate)
^{1}H NMR (500 MHz, D_6-Acetone, 25 °C)	1H NMR (500 MHz, Acetone) δ = 7.96 (d, J=2.6, 1H), 7.77 (d, J=2.6, 1H), 7.22 (d, J=2.6, 1H), 7.20 (d, J=2.6, 1H), 6.89 (dd, J=6.6, 2.8, 1H), 6.68 (d, J=2.1, 2H), 6.66 (dd, J=7.3, 2.8, 1H), 6.47 (d, J=2.1, 2H), 6.29 (t, J=2.1, 1H), 6.26 (t, J=2.2, 1H), 4.73 (dd, J=6.6, 2.8, 1H), 4.61 (dd, J=7.3, 2.8, 1H), 1.53 – 1.45 (m, 3H), 1.45 – 1.38 (m, 3H), 1.31-1.38 (m, 6H), 1.25 – 1.15 (m, 12H), 1.16 – 0.96 (m, 144H).
^{13}C NMR (126 MHz, D_6-Acetone, 25 °C)	13C NMR (126 MHz, Acetone) δ = 194.7, 194.6, 158.4, 152.2, 151.9, 150.1, 148.6, 145.4, 143.9, 143.2, 143.0, 140.3, 139.4, 138.1, 137.4, 132.1, 131.7, 51.3, 50.3, 19.6, 19.6, 19.5, 19.5, 18.4, 18.4, 13.5, 12.2, 12.1, 12.1, 12.0.
HRMS (ESI):	*m/z* calculated for $C_{100}H_{182}O_6Si_8$ ($[M+H]^+$): 1,704.2164, found 1704.2126



3.127, ^{1}H NMR, 500 MHz, D_6-Acetone

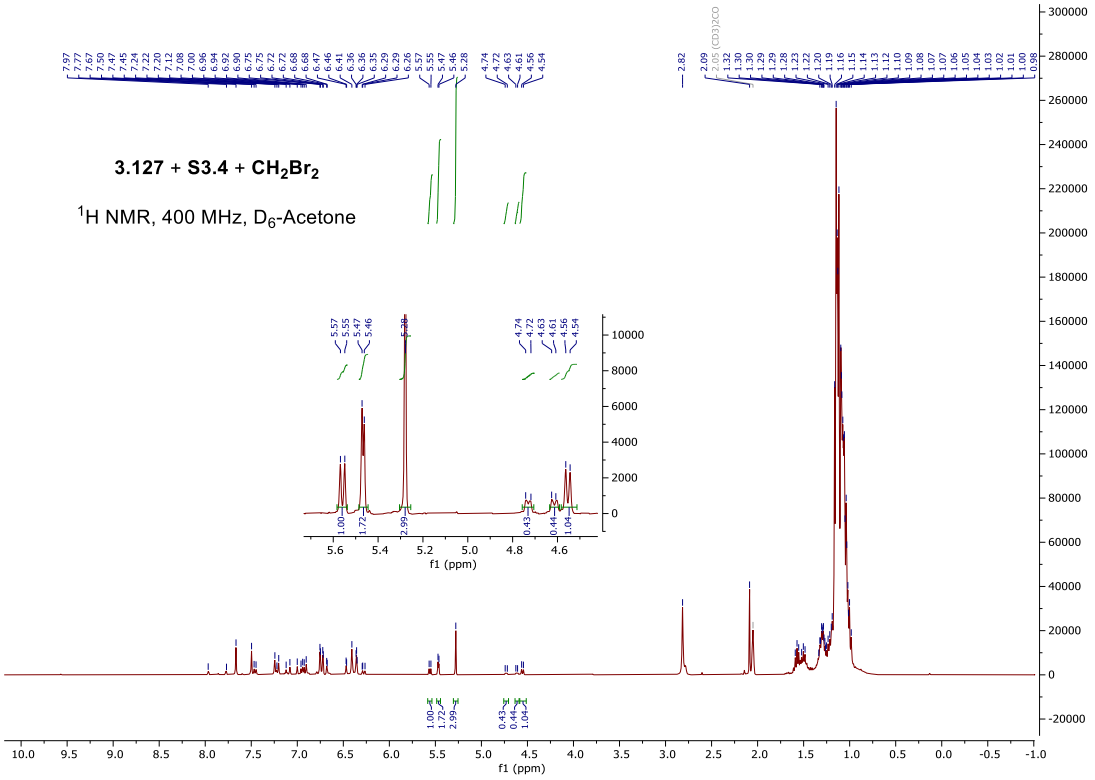


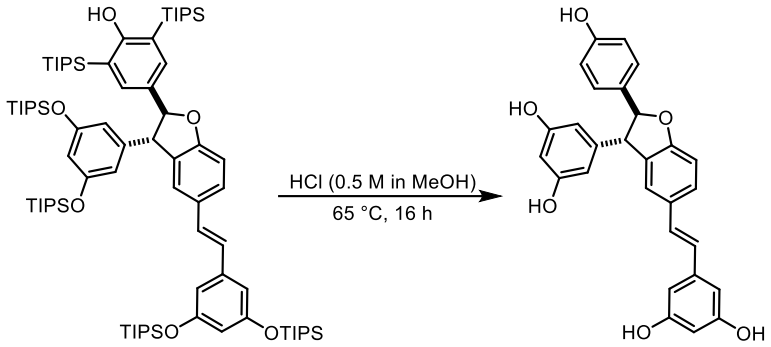
3.127, ^{13}C NMR, 126 MHz, D_6-Acetone



(3.147) 4-((2S,3S)-3-(3,5-bis((triisopropylsilyl)oxy)phenyl)-5-((E)-3,5-bis((triisopropylsilyl)oxy)styryl)-2,3-dihydrobenzofuran-2-yl)-2,6-bis(triisopropylsilyl)phenol

In a flame-dried 0.5-2 mL microwave vial was added stilbene (20 mg, 37 µmol, 1.0 equiv), bis-quinone methide dimer (130 mg, 74 µmol, 2 equiv), and acetone (1.5 mL, 0.025M). The tube was capped, and the mixture was reacted at 100 °C for 16 hours with stirring in a Biotage Initiator+ microwave reactor. The crude was transferred to a round bottom flask and concentrated *in vacuo* and purified by flash chromatography over SiO_2 (0%-10% EtOAc in Hexanes) to afford a mixture of desired product A (6-TIPS δ-viniferin), stilbene byproduct (B), and unreacted bis-quinone methide. Efforts were made to separate these two nonpolar materials including selective recrystallization and silver nitrate doped silica gel chromatography. Ultimately a quantitative proton NMR of the crude with a dibromomethane standard was used to obtain a yield of 89% (46 mg). This material was directly carried forward for deprotection. A ^1H NMR of the crude with standard is shown below.

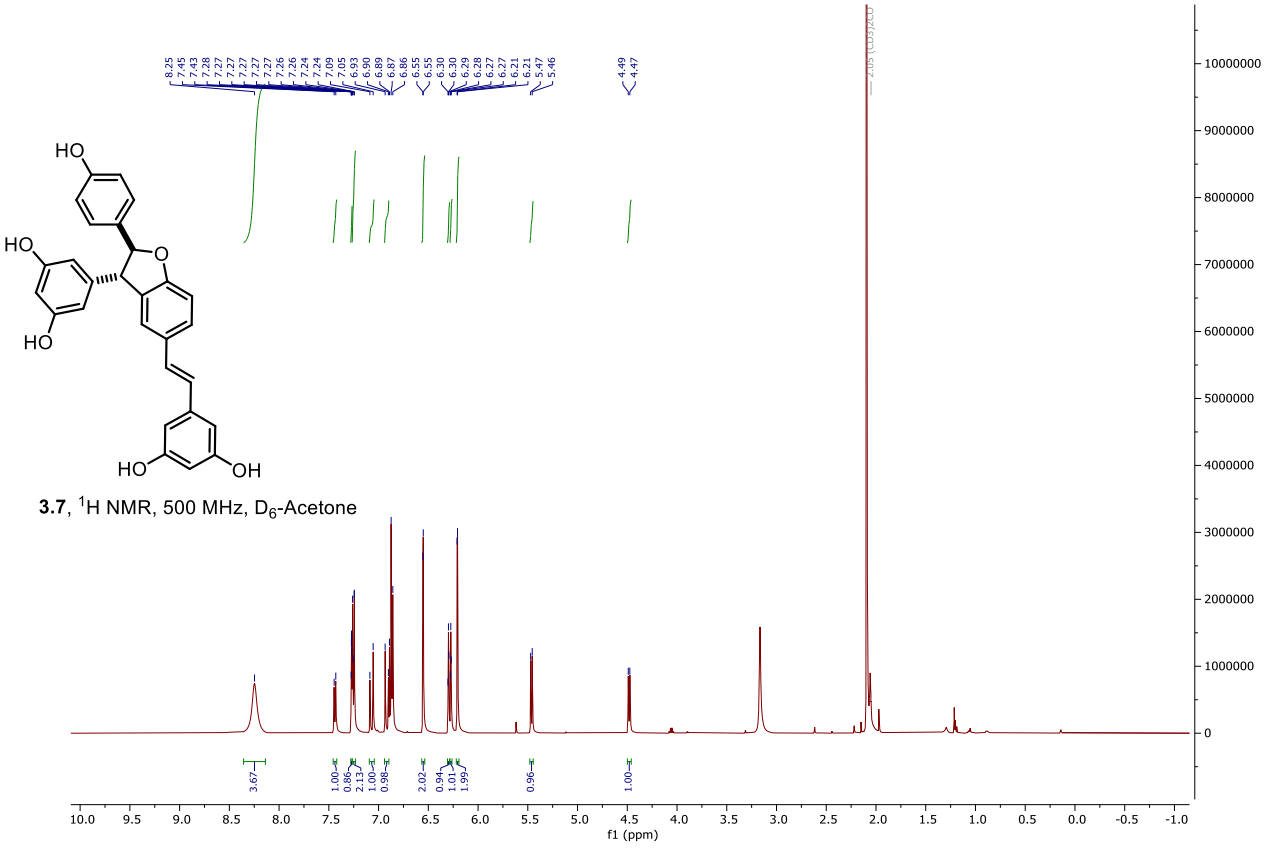




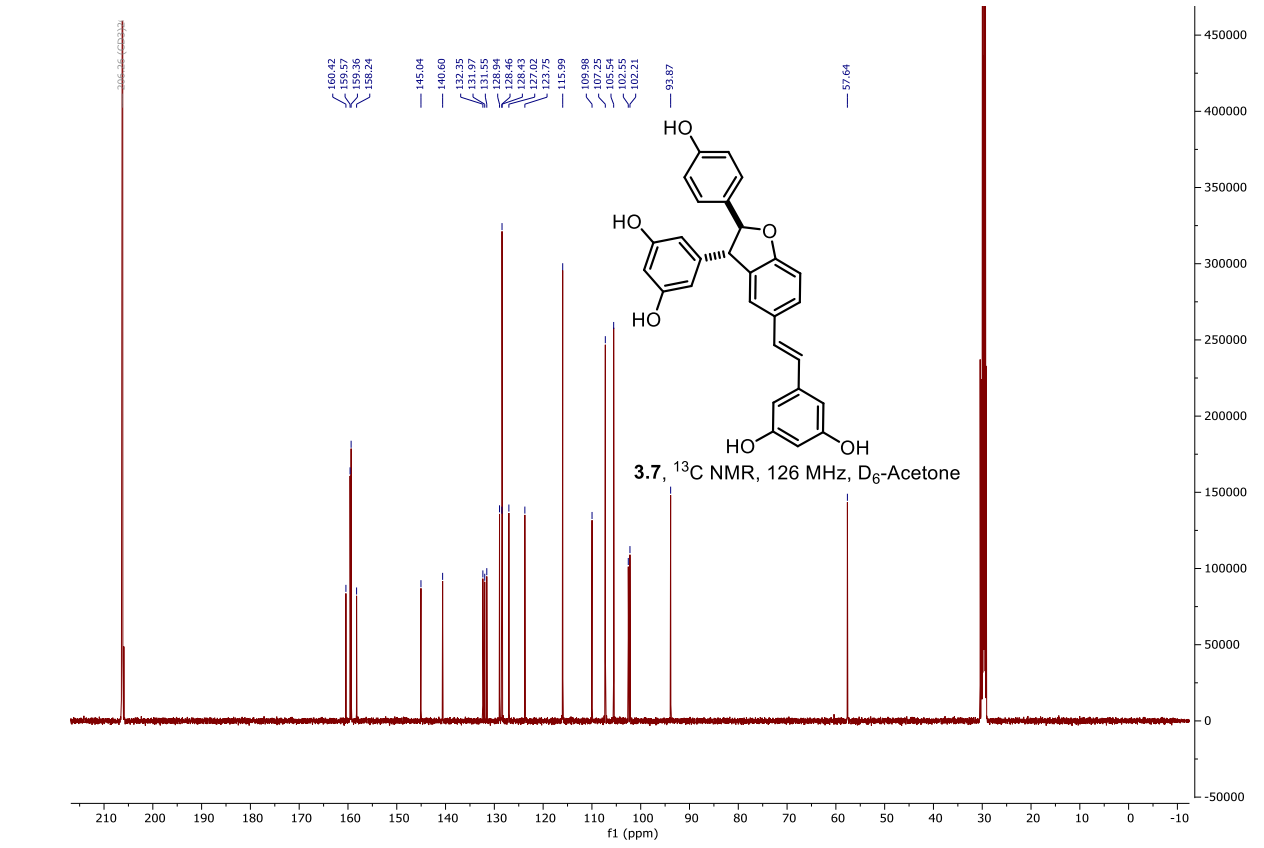
(3.7) δ-viniferin

To a 15 mL sealed tube was added crude reaction mixture with stoichiometry calculated from qNMR of previous reaction (51 mg, 0.037 mmol, 1 equiv), HCl (0.5 M in MeOH, 3.7 mL, 0.5 M). The headspace was filled with argon, the tube was capped and heated in an oil bath set to 80 °C for 16 h. The reaction was concentrated, and the crude material was purified by flash chromatography over SiO_2 (0%-30% Acetone in DCM) to yield the product as a light tan foam (9.7 mg, 58%).

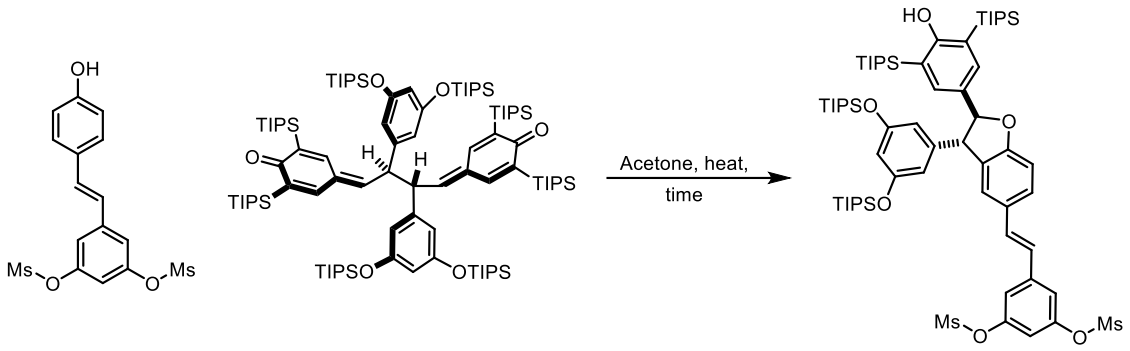
TLC (DCM/Acetone, 70:30), R_F:	0.23 (UV, potassium permanganate)
^{1}H NMR (500 MHz, D_6-Acetone, 25 °C)	δ = 8.25 (br s, 5H, OH), 7.44 (d, J=8.3, 1H), 7.27 (br s, 1H), 7.25 (d, J=8.8, 2H), 7.07 (d, J=16.2, 1H), 6.92 (d, J=16.4, 2H), 6.89 (s, 1H), 6.87 (d, J=8.4, 2H), 6.55 (d, J=2.1, 2H), 6.30 (t, J=2.2, 1H), 6.27 (t, J=2.2, 1H), 6.21 (d, J=2.1, 3H), 5.46 (d, J=8.0, 2H), 4.48 (d, J=8.0, 2H).
^{13}C NMR (126 MHz, D_6-Acetone, 25 °C)	δ = 160.4, 159.6, 159.4, 158.2, 145.0, 140.6, 132.4, 132.0, 131.5, 128.9, 128.5, 128.4, 127.0, 123.7, 116.0, 110.0, 107.3, 105.5, 102.5, 102.2, 93.9, 57.6.
HRMS (ESI):	*m/z* calculated for $C_{28}H_{22}O_6$ ($[M+H]^+$): 455.1495, found 455.1497
FTIR (neat) cm^{-1}:	ν̃= 3295 (br), 1595 (s), 1486 (w), 1259 (m), 1235 (m), 1148 (vs), 832 (m)



3.7, ^{1}H NMR, 500 MHz, D_6-Acetone



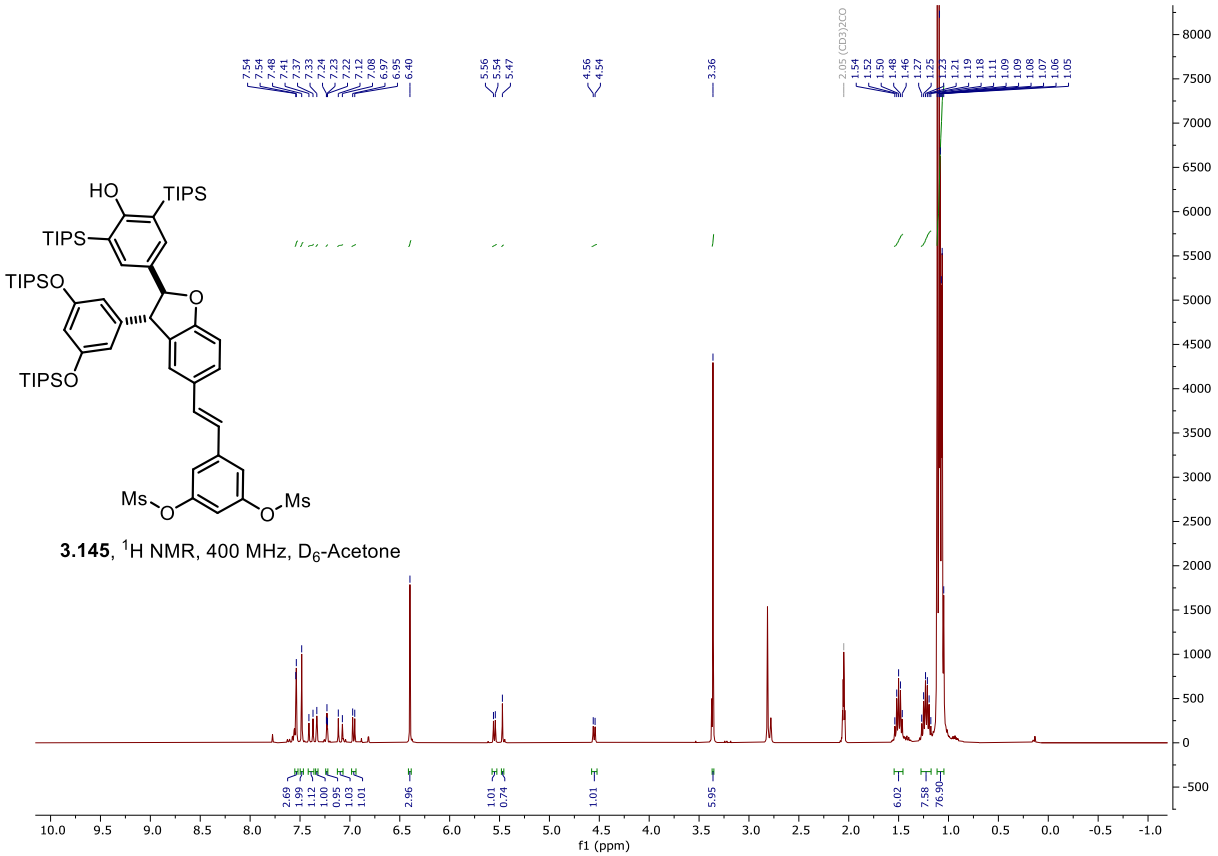
3.7, ^{13}C NMR, 126 MHz, D_6-Acetone



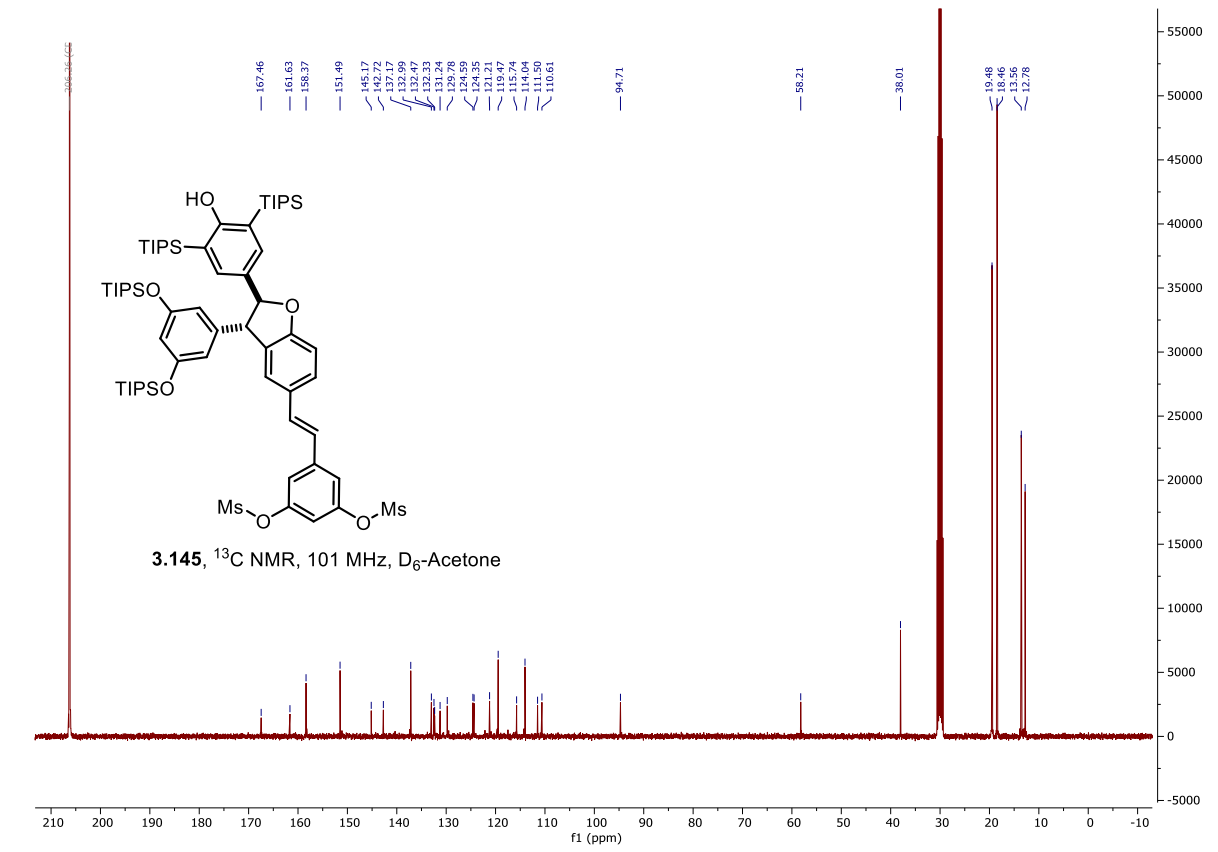
(3.145) 5-((E)-2-((2S,3S)-3-(3,5-bis((triisopropylsilyl)oxy)phenyl)-2-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)-2,3-dihydrobenzofuran-5-yl)vinyl)-1,3-phenylene dimethanesulfonate

In a flame-dried 2 - 5 mL microwave vial was added stilbene (35 mg, 91 µmol, 1.0 equiv), bis-quinone methide dimer (160 mg, 91 µmol, 1 equiv), and acetone (3.6 mL, 0.025M). The tube was capped, and the mixture was reacted at 100 °C for 12 hours with stirring in a Biotage Initiator+ microwave reactor. The crude was transferred to a round bottom flask and concentrated *in vacuo* and purified by flash chromatography over SiO_2 (0%-20% EtOAc in Hexanes) to afford 4-TIPS 2-Ms δ -viniferin as a light tan foam (85.3 mg, 76%).

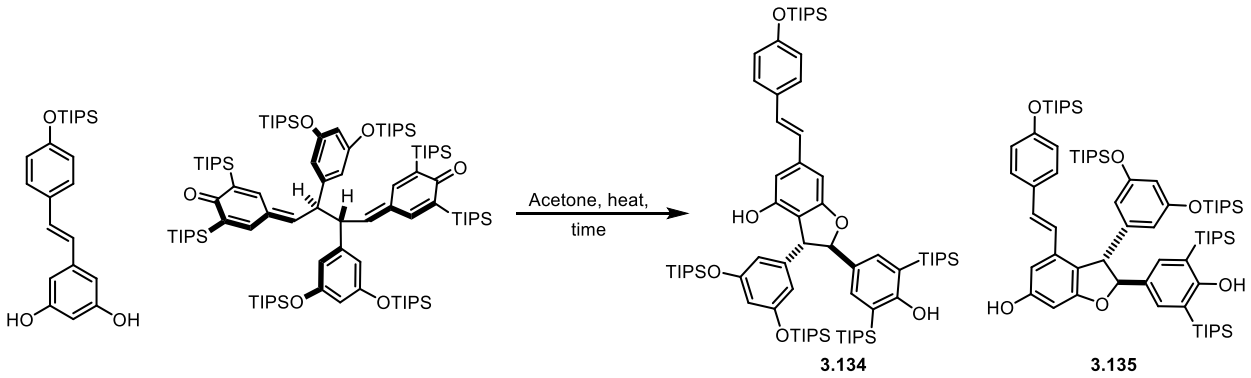
TLC (Hexanes/EtOAc, 80:20), R_F:	0.40 (UV, potassium permanganate)
^{1}H NMR (400 MHz, D_6-Acetone, 25 °C)	δ = 7.54 (d, J=2.2, 3H), 7.48 (s, 2H), 7.39 (d, J=16.4, 1H), 7.33 (s, 1H), 7.23 (t, J=2.1, 1H), 7.10 (d, J=16.4, 1H), 6.96 (d, J=8.3, 1H), 6.40 (s, 3H), 5.55 (d, J=7.4, 1H), 5.47 (s, 1H, OH), 4.55 (d, J=7.4, 1H), 3.36 (s, 6H), 1.50 (p, J=7.5, 6H), 1.22 (dq, J=13.8, 7.2, 6.8, 6H), 1.11 – 1.05 (m, 72H).
^{13}C NMR (101 MHz, D_6-Acetone, 25 °C)	δ = 167.5, 161.6, 158.4, 151.5, 145.2, 142.7, 137.2, 133.0, 132.5, 132.3, 131.2, 129.8, 124.6, 124.3, 121.2, 119.5, 115.7, 114.0, 111.5, 110.6, 94.7, 58.2, 38.0, 19.5, 18.5, 13.6, 12.8.
HRMS (ESI):	*m/z* calculated for $C_{66}H_{106}O_{10}S_2Si_4$ ($[M+H]^+$): 1235.6374, found 1235.6383
FTIR (neat) cm^{-1} :	ν̃= 3604 (w), 2945 (m), 2867 (m), 1588 (w), 1374 (w), 1183 (vs), 962 (vs), 882 (vs), 682 (w)



3.145, ^{1}H NMR, 400 MHz, D_6-Acetone



3.145, ^{13}C NMR, 101 MHz, D_6-Acetone

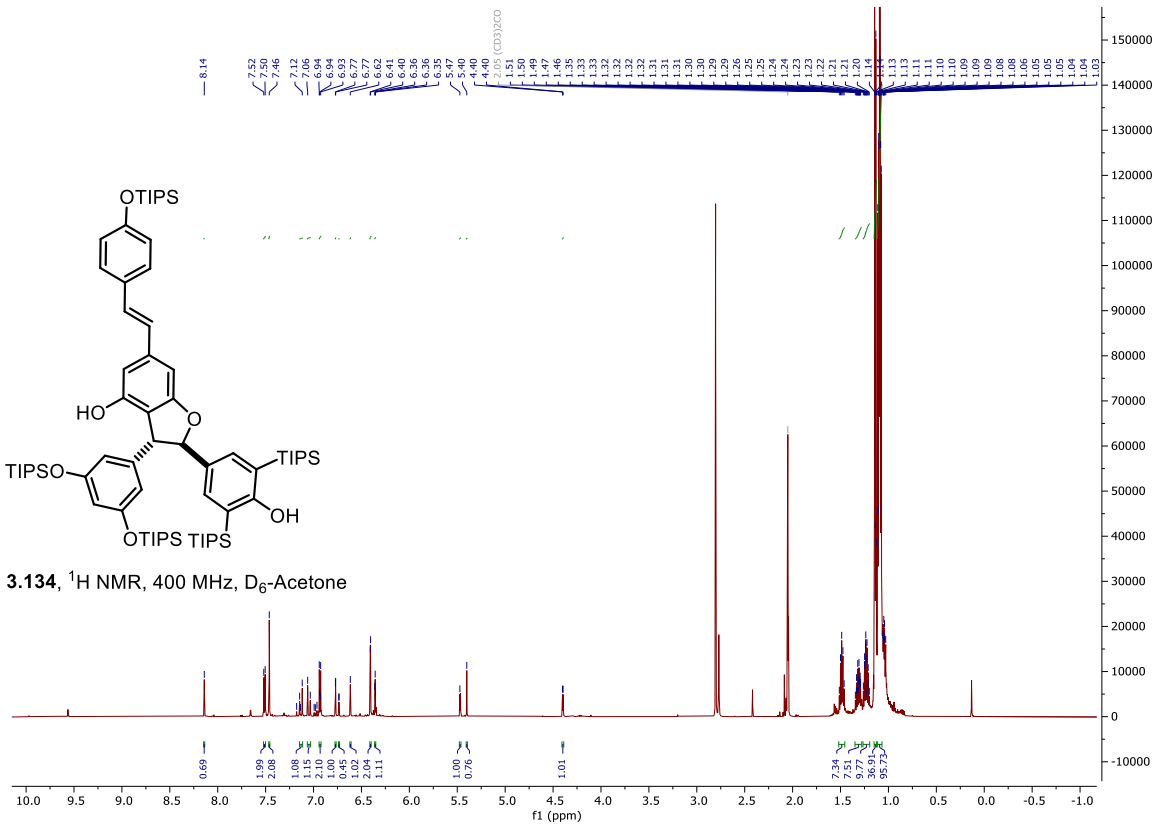


(3.134) 5-TIPS gnetin C and (3.135) 5-TIPS ε-viniferin

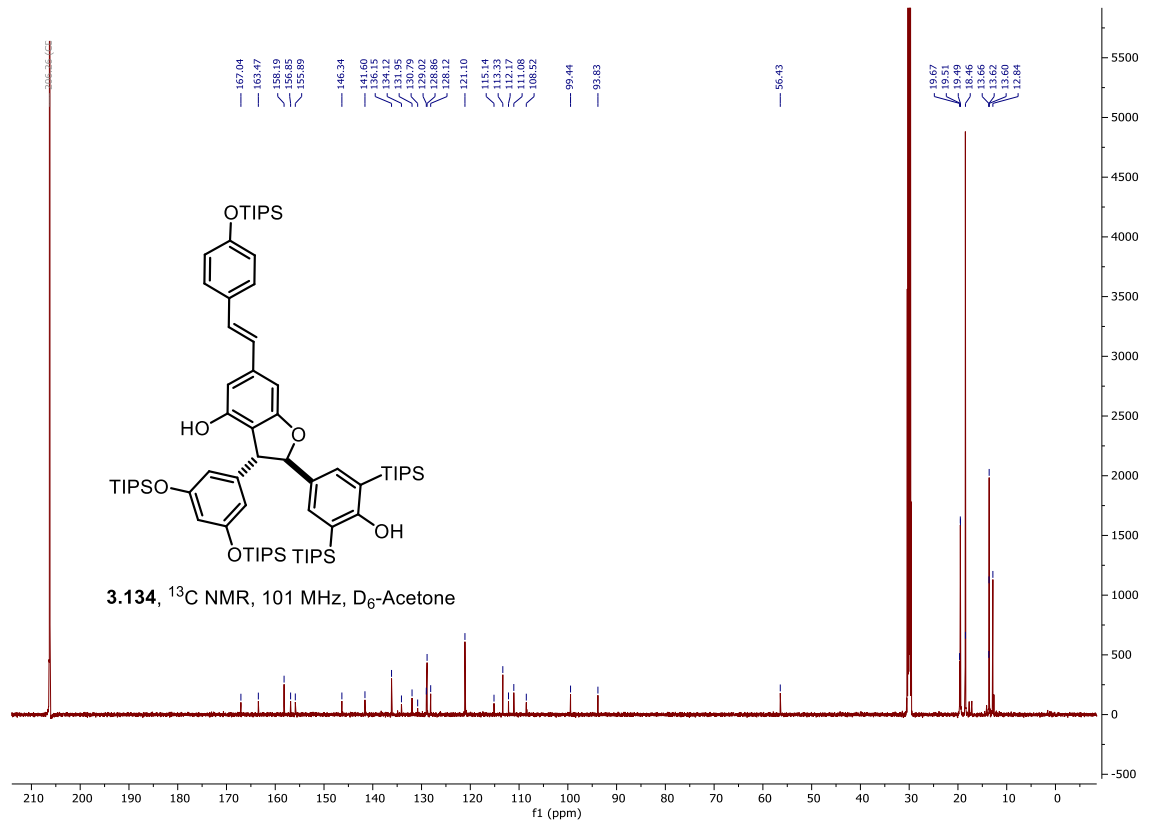
In a flame-dried 10-20 mL microwave vial was added stilbene (20 mg, 468 µmol, 1.0 equiv), bis-quinone methide dimer (180 mg, 702 µmol, 1.5 equiv), and acetone (18.7 mL, 0.025M). The tube was capped, and the mixture was reacted at 100 °C for 10 hours with stirring in a Biotage Initiator+ microwave reactor. The crude was transferred to a round bottom flask and concentrated *in vacuo* and purified by flash chromatography over SiO_2 (0%-15% EtOAc in Hexanes) to afford 5-TIPS ε-viniferin (21) as a light tan foam (370 mg, 64%) and 5-TIPS gnetin C (20) as a light tan foam (60 mg, 12%).

Characterization for (20) 5-TIPS gnetin C

TLC (Hexanes/EtOAc, 90:10), R_F:	0.77 (UV, potassium permanganate)
^{1}H NMR (600 MHz, D_6-Acetone, 25 °C)	δ = 8.14 (s, 1H, OH), 7.51 (d, J=8.7, 2H), 7.46 (s, 2H), 7.13 (d, J=16.3, 1H), 7.05 (d, J=16.3, 1H), 6.93 (d, J=8.7, 2H), 6.77 (d, J=1.5, 1H), 6.62 (s, 1H), 6.41 (d, J=2.3, 3H), 6.36 (t, J=2.2, 1H), 5.47 (s, 1H), 5.40 (s, 1H), 4.40 (d, J=3.9, 1H), 1.49 (p, J=7.5, 6H), 1.35 – 1.27 (m, 6H), 1.23 (m, 6H), 1.13 (m, 36H), 1.09 (m, 54H).
^{13}C NMR (151 MHz, D_6-Acetone, 25 °C)	δ = 167.0, 163.5, 158.2, 156.9, 155.9, 146.3, 141.6, 136.2, 134.1, 131.9, 130.8, 129.0, 128.9, 128.1, 121.1, 115.1, 113.3, 112.2, 111.1, 108.5, 99.4, 93.8, 56.4, 19.7, 19.5, 19.5, 18.5, 13.7, 13.6, 13.6, 12.8.
HRMS (ESI):	*m/z* calculated for $C_{73}H_{122}O_6Si_5$ ($[M+H]^+$): 1235.8161, found 1235.8154
FTIR (neat) cm^{-1} :	ν̃= 3604 (br), 2946 (vs), 2867 (vs), 1593 (w), 1170 (m), 883 (m), 660 (w)



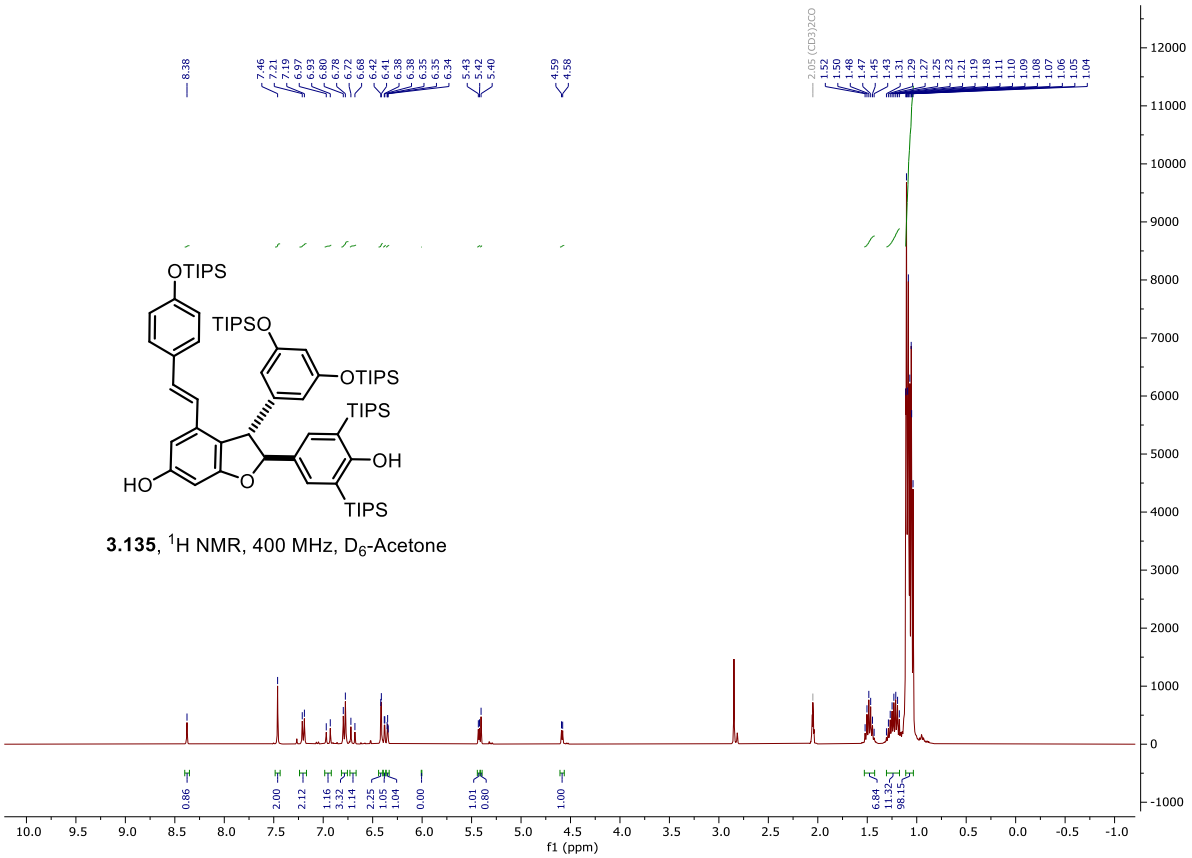
3.134, ^{1}H NMR, 400 MHz, D_6-Acetone



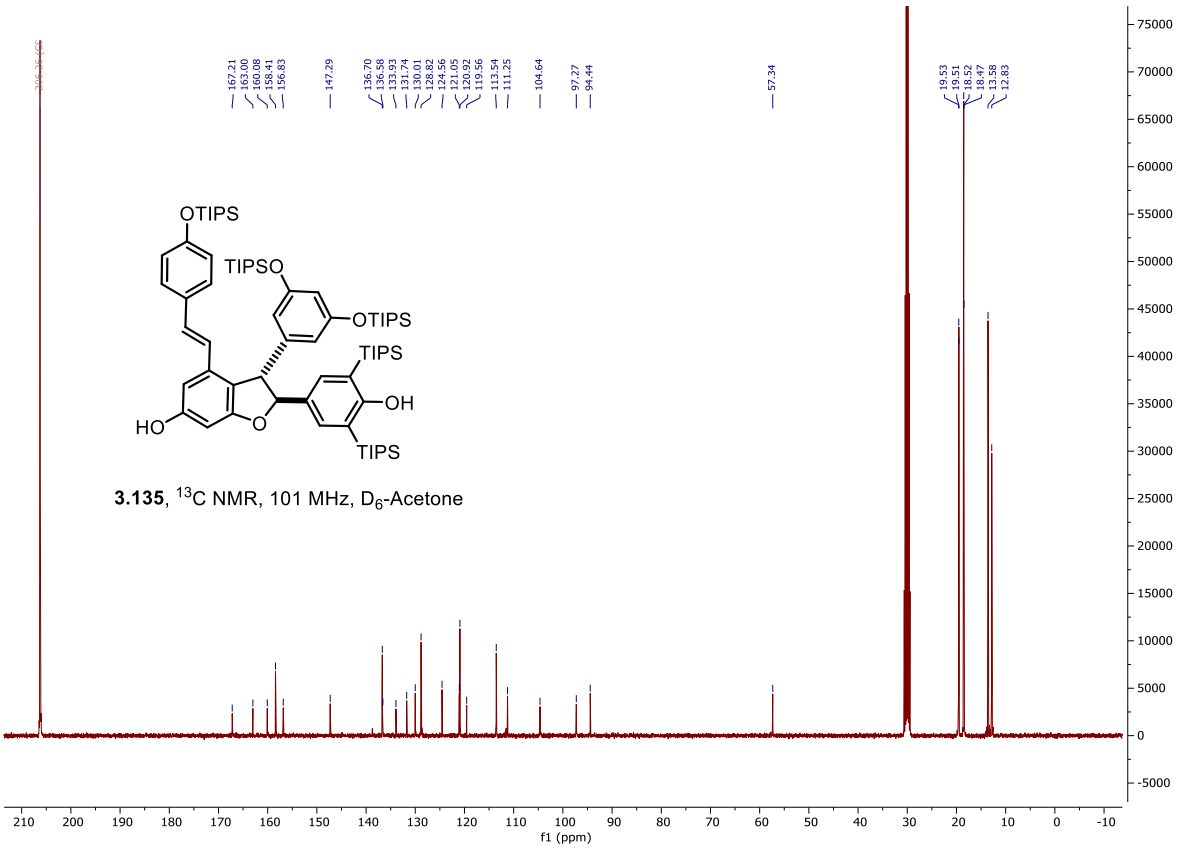
3.134, ^{13}C NMR, 101 MHz, D_6-Acetone

Characterization for (3.135) 5-TIPS ε-viniferin:

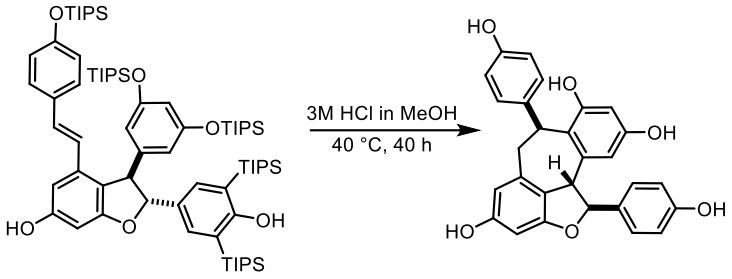
TLC (Hexanes/EtOAc, 90:10), R_F:	0.50 (UV, potassium permanganate)
^{1}H NMR (400 MHz, D_6-Acetone, 25 °C)	δ = 8.38 (s, 1H, OH), 7.46 (s, 2H), 7.20 (d, J=8.7, 2H), 6.95 (d, J=16.3, 1H), 6.79 (d, J=8.4, 3H), 6.70 (d, J=16.3, 1H), 6.42 (d, J=2.3, 2H), 6.38 (d, J=2.1, 1H), 6.35 (t, J=2.2, 1H), 5.43 (d, J=4.7, 1H), 5.40 (s, 1H, OH), 4.58 (d, J=4.7, 1H), 1.48 (h, J=7.1, 6.6, 6H), 1.31 – 1.18 (m, 9H), 1.11 – 1.03 (m, 90H).
^{13}C NMR (101 MHz, D_6-Acetone, 25 °C)	δ = 167.2, 163.0, 160.1, 158.4, 156.8, 147.3, 136.7, 136.6, 133.9, 131.7, 130.0, 128.8, 124.6, 121.0, 120.9, 119.6, 113.5, 111.2, 104.6, 97.3, 94.4, 57.3, 19.5, 19.5, 18.5, 18.5, 13.6, 12.8.
HRMS (ESI):	*m/z* calculated for $C_{73}H_{122}O_6Si_5$ ($[M+H]^+$): 1235.8166, found 1235.8156
FTIR (neat) cm^{-1} :	ν̃= 3604 (w), 3388 (br), 2946 (m), 2892 (w), 2867 (m), 1168 (s), 882 (vs), 683 (s), 668 (s)



3.135, ^{1}H NMR, 400 MHz, D_6-Acetone



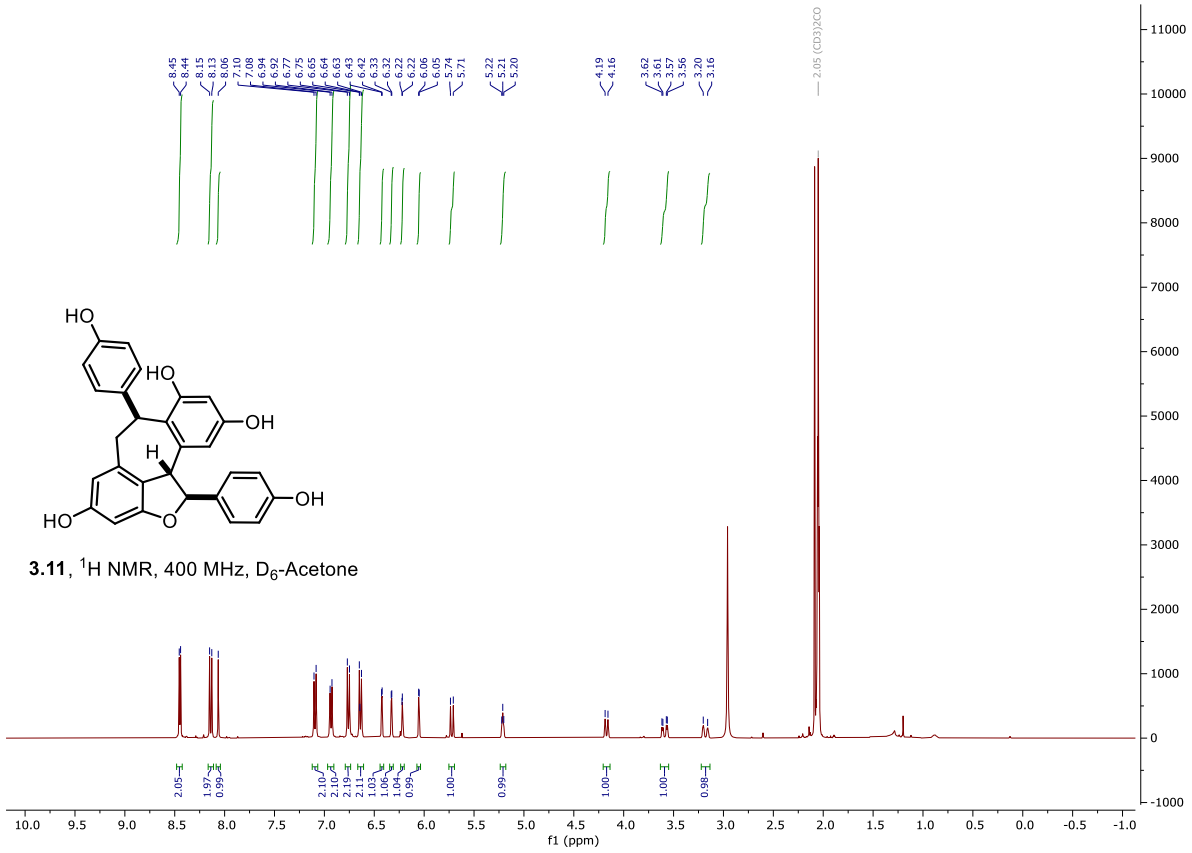
3.135, ^{13}C NMR, 101 MHz, D_6-Acetone



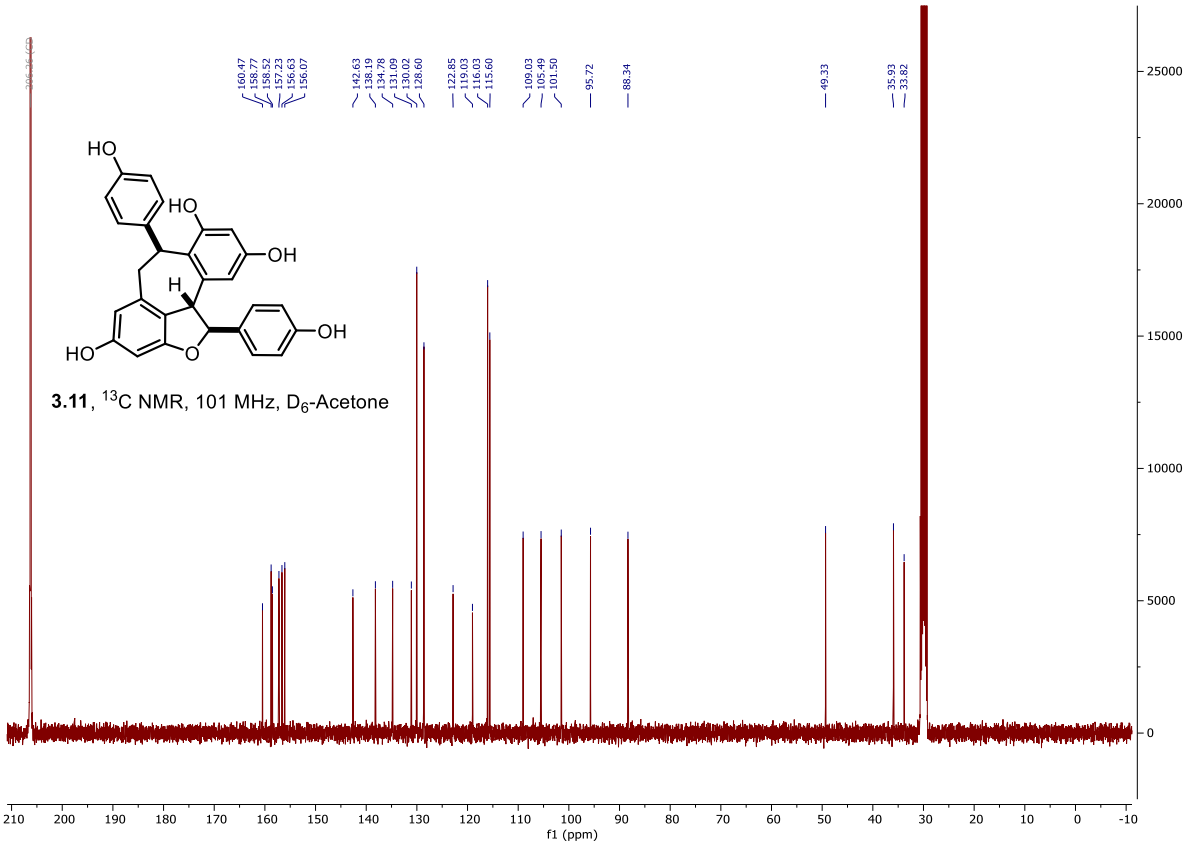
(3.11) ampelopsin B

To a 15 mL sealed tube was added the phenol (20 mg, 16 μmol, 1 equiv), HCl (3.0 M in MeOH, 0.8 mL). The headspace was backfilled with argon, and the reaction was heated refluxed in an oil bath set to 40 °C for 48 h. The crude reaction mixture was concentrated onto celite, and the crude material was purified by flash chromatography over SiO_2 (0%-40% Acetone in DCM) to yield the product as a light tan foam (5.5 mg, 75%).

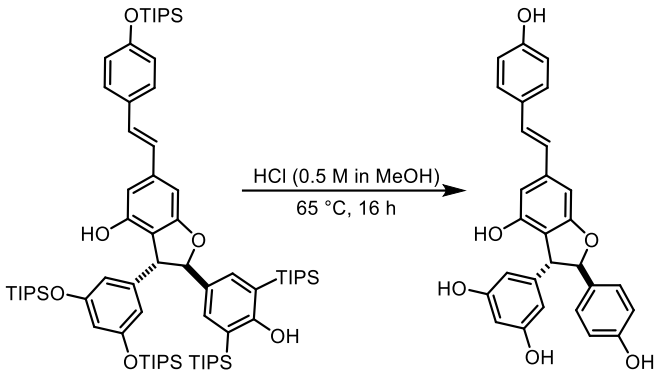
TLC (DCM/Acetone, 70:30), R_F:	0.19 (UV, potassium permanganate)
^{1}H NMR (400 MHz, D_6-Acetone, 25 °C)	δ = 8.45 (s, 1H), 8.44 (s, 1H), 8.15 (s, 1H), 8.13 (s, 1H), 8.06 (s, 1H), 7.09 (d, J=8.5, 2H), 6.93 (br d, J=7.5, 2H), 6.76 (d, J=8.6, 2H), 6.64 (d, J=8.6, 2H), 6.42 (d, J=2.3, 1H), 6.33 (d, J=2.2, 1H), 6.22 (br s, 1H), 6.05 (d, J=2.1, 1H), 5.72 (d, J=11.4, 1H), 5.21 (t, J=4.1, 1H), 4.17 (br d, J=11.4, 1H), 3.59 (dd, J=17.7, 3.9, 1H), 3.18 (br d, J=17.5, 1H).
^{13}C NMR (101 MHz, D_6-Acetone, 25 °C)	δ = 160.5, 158.8, 158.5, 157.2, 156.6, 156.1, 142.6, 138.2, 134.8, 131.1, 130.0, 128.6, 122.9, 119.0, 116.0, 115.6, 109.0, 105.5, 101.5, 95.7, 88.3, 49.3, 35.9, 33.8.
HRMS (ESI):	*m/z* calculated for $C_{28}H_{22}O_6$ ($[M+H]^+$): 455.1489, found 455.1490
FTIR (neat) cm^{-1} :	ν̃= 3313 (br), 1688 (w), 1596 (s), 1513 (w), 1446 (w), 1259 (s), 1219 (m), 1174 (s), 1129 (vs), 1010 (w), 834 (vs)



3.11, ^{1}H NMR, 400 MHz, D_6-Acetone



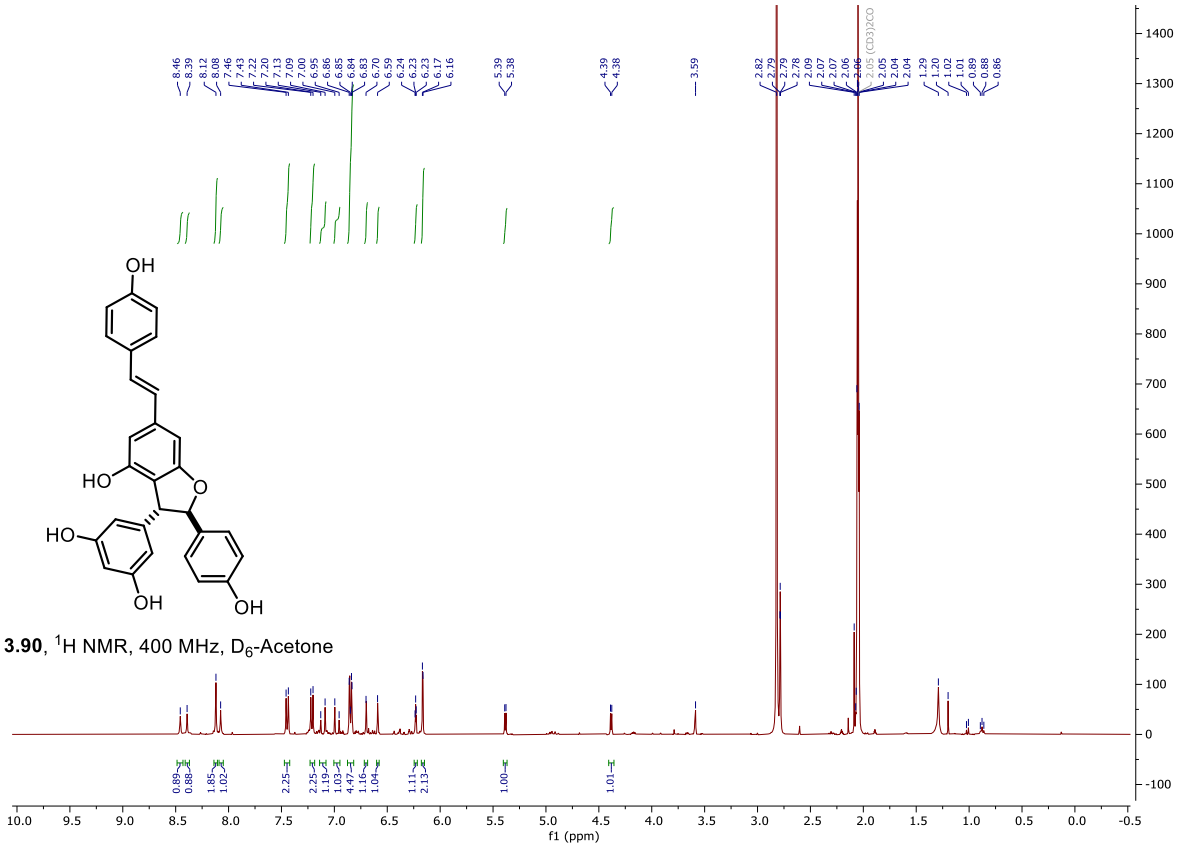
3.11, ^{13}C NMR, 101 MHz, D_6-Acetone



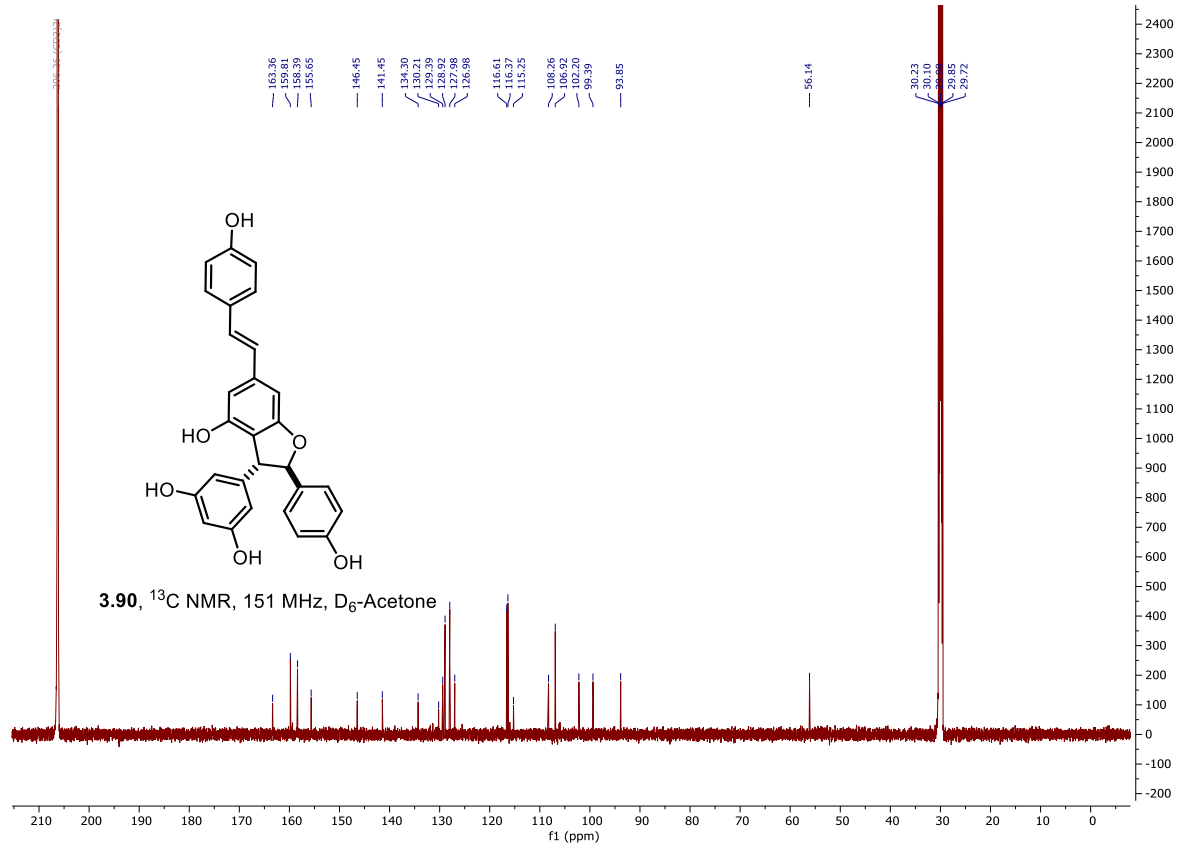
(3.90) gnetin C

To a 15 mL sealed tube was added the phenol (50 mg, 0.048 mmol, 1 equiv), HCl (0.5M in MeOH, 4.0 mL, 0.5 M) and THF (1.6 mL, 0.025 M). The headspace was backfilled with argon, and the reaction was refluxed in an oil bath set to 70 °C for 16 h. The crude reaction mixture was quenched with sat. $NaHCO_3$ (15 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-30% Acetone in DCM) to yield the product as a light-yellow foam (13 mg, 71%).

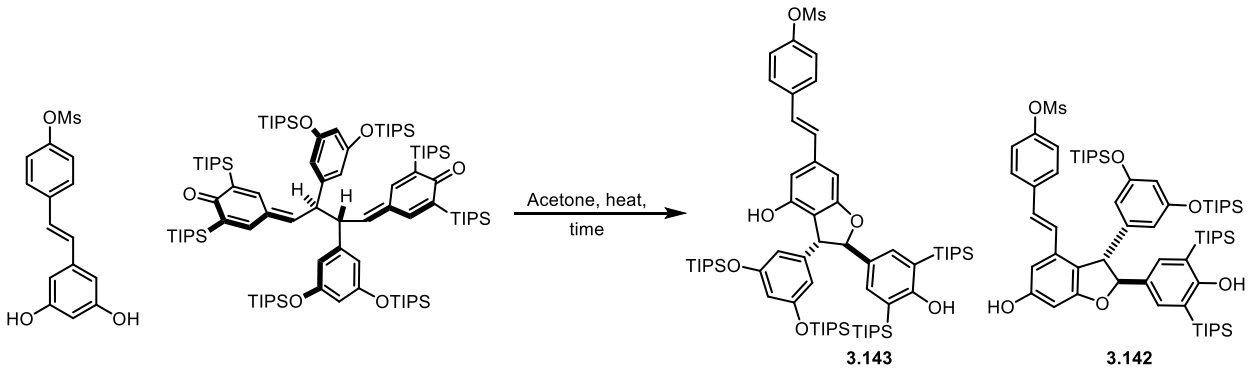
TLC (DCM/Acetone, 70:30), R_F:	0.23 (UV, potassium permanganate)
^{1}H NMR (400 MHz, D_6-Acetone, 25 °C)	δ = 8.46 (s, 1H, OH), 8.39 (s, 1H, OH), 8.12 (s, 2H, OH), 8.08 (s, 1H, OH), 7.45 (d, J=8.6, 2H), 7.21 (d, J=8.5, 2H), 7.11 (d, J=16.4, 1H), 6.98 (d, J=16.4, 1H), 6.88 – 6.81 (m, 4H), 6.70 (br s, 1H), 6.59 (br s, 1H), 6.23 (t, J=2.2, 1H), 6.16 (d, J=2.2, 2H), 5.38 (d, J=4.8, 1H), 4.38 (d, J=4.9, 1H).
^{13}C NMR (151 MHz, D_6-Acetone, 25 °C)	δ = 163.4, 159.8, 158.4, 155.7, 146.4, 141.4, 134.3, 130.2, 129.4, 128.9, 128.0, 127.0, 116.6, 116.4, 115.3, 108.3, 106.9, 102.2, 99.4, 93.8, 56.1.
HRMS (ESI):	*m/z* calculated for $C_{28}H_{22}O_6$ ($[M+H]^+$): 455.1495, found 455.1488
FTIR (neat) cm^{-1} :	ν̃= 2938 (br), 2362 (s), 1603 (m), 1515 (w), 1457 (w), 1251 (w), 1157 (vs), 834 (w), 695 (s)



3.90, ^{1}H NMR, 400 MHz, D_6-Acetone



3.90, ^{13}C NMR, 151 MHz, D_6-Acetone



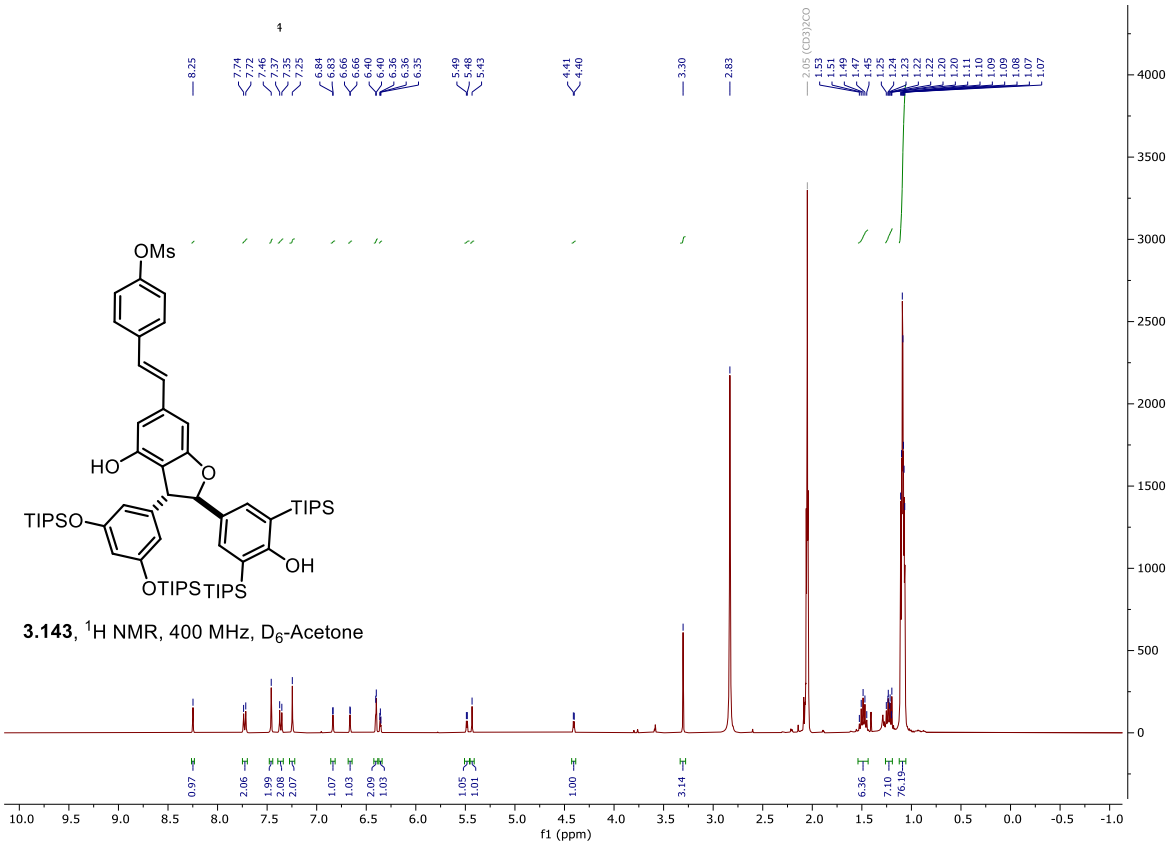
(3.143) 1-Ms 4-TIPS gnetin C and (3.142) 1-Ms 4-TIPS ε-viniferin

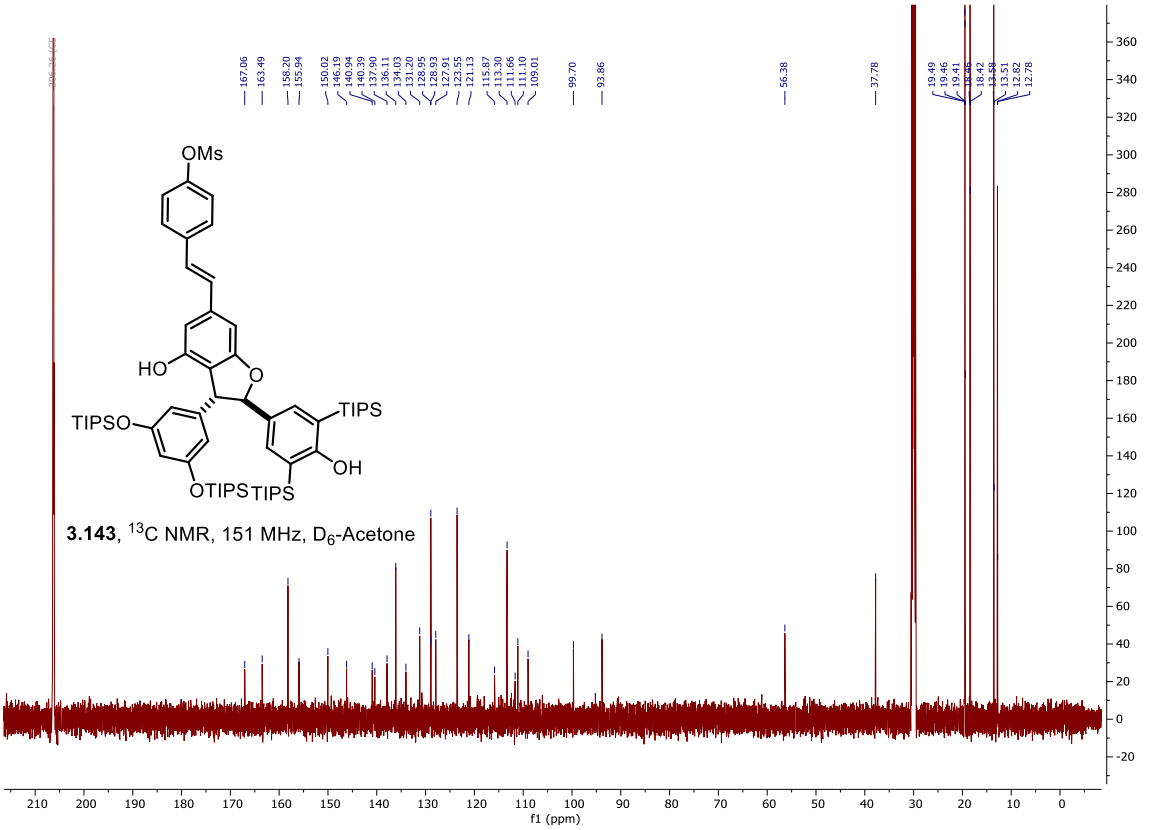
Procedure A: Sealed Tube: In a flame-dried 15mL sealed tube capped with a septa under inert atmosphere stilbene (50 mg, 163 µmol, 1.0 equiv), bis-quinone methide dimer (557 mg, 326 µmol, 2 equiv), and acetone (6.53 mL, 0.025M) were added. The suspension was freeze-pump-thawed (three cycles) to rigorously degas the solution. The tube was capped, and the mixture was stirred at 120 °C (oil bath temperature) for 16 h. The reaction was transferred to a round bottom flask and concentrated *in vacuo* and purified by flash chromatography over SiO_2 (0%-30% EtOAc in Hexanes) to afford 1-Ms 4-TIPS ε-viniferin (31) as a light tan foam (91 mg, 48%).

Procedure B: Microwave Reactor: In a flame-dried 0.5-2 mL microwave vial was added stilbene (20 mg, 65 µmol, 1.0 equiv), bis-quinone methide dimer (140 mg, 82 µmol, 1.25 equiv), and acetone (2.0 mL, 0.025M). The tube was capped, and the mixture was reacted at 100 °C for 16 hours with stirring in a Biotage Initiator+ microwave reactor. The crude was transferred to a round bottom flask and concentrated *in vacuo* and purified by flash chromatography over SiO_2 (0%-30% EtOAc in Hexanes) to afford 1-Ms 4-TIPS ε-viniferin (31) as a light tan foam (46 mg, 57%) and 1-MS 4-TIPS gnetin C (30) (8.8 mg, 11%) as a light tan foam.

Characterization for 1-Ms 4-TIPS gnetin C (30):

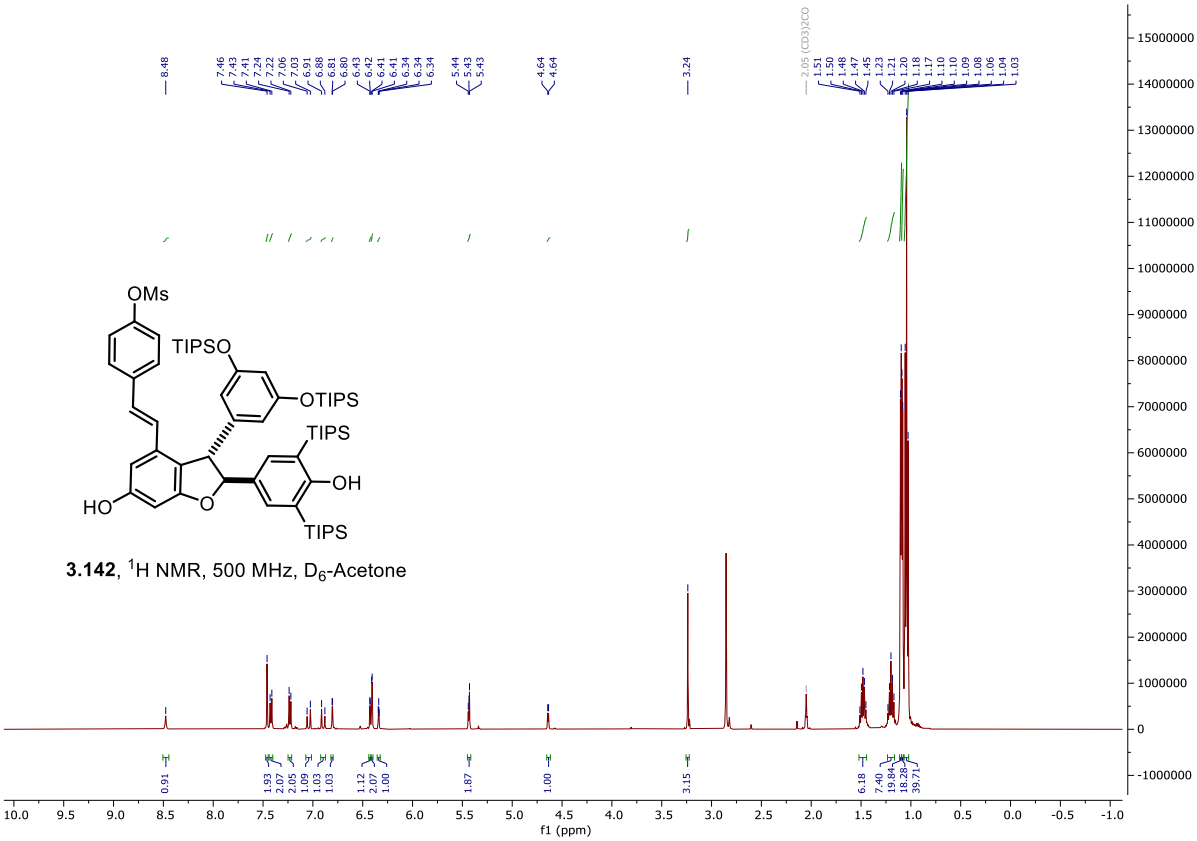
TLC (Hexanes/EtOAc, 80:20), R_F:	0.47 (UV, potassium permanganate)
^{1}H NMR (400 MHz, D_6-Acetone, 25 °C)	δ = 8.25 (s, 1H, OH), 7.73 (d, J=8.7, 2H), 7.46 (s, 2H), 7.36 (d, J=8.7, 2H), 7.25 (s, 2H), 6.84 (d, J=1.2, 1H), 6.66 (d, J=1.3, 1H), 6.40 (d, J=2.2, 2H), 6.36 (t, J=2.2, 1H), 5.48 (d, J=3.7, 1H), 5.43 (s, 1H, OH), 4.41 (d, J=3.7, 1H), 3.30 (s, 3H), 1.48 (q, J=7.5, 6H), 1.31 – 1.16 (m, 6H), 1.13 – 1.04 (m, 72H).
^{13}C NMR (151 MHz, D_6-Acetone, 25 °C)	δ = 167.1, 163.5, 158.2, 155.9, 150.0, 146.2, 140.9, 140.4, 137.9, 136.1, 134.0, 131.2, 128.9, 128.9, 127.9, 123.5, 121.1, 115.9, 113.3, 111.7, 111.1, 109.0, 99.7, 93.9, 56.4, 37.8, 19.5, 19.5, 19.4, 18.5, 18.4, 13.6, 13.5, 12.8, 12.8.
HRMS (ESI):	*m/z* calculated for $C_{65}H_{104}O_8SSi_4$ ($[M+H]^+$): 1157.6602, found 1157.6576
FTIR (neat) cm^{-1} :	ν̃= 2946 (s), 2868 (s), 1588 (m), 1175 (vs), 1152 (s), 1017 (w), 882 (s), 686 (w)


OMs
HO
O
TIPSO
TIPS
OH
OTIPS
TIPS
3.143, 1H NMR, 400 MHz, D6-Acetone
f1 (ppm)

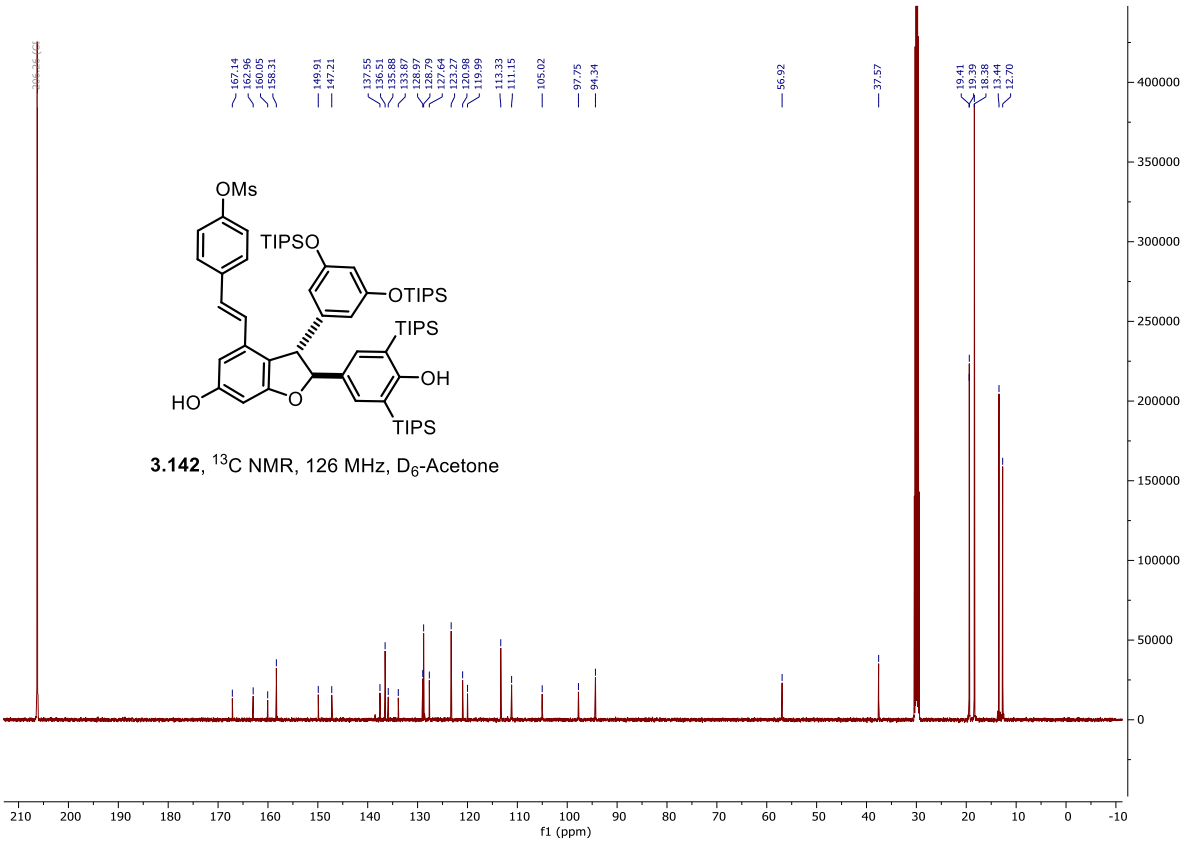

OMs
HO
O
TIPSO
TIPS
OH
OTIPS
TIPS
3.143, 13C NMR, 151 MHz, D6-Acetone
f1 (ppm)

Characterization for (3.142) 1-Ms 4-TIPS ε-viniferin

TLC (Hexanes/EtOAc, 80:20), R_F:	0.42 (UV, potassium permanganate)
^{1}H NMR (500 MHz, D_6-Acetone, 25 °C)	δ = 8.48 (s, 1H, OH), 7.46 (s, 2H), 7.42 (d, J=8.8, 2H), 7.23 (d, J=8.8, 2H), 7.04 (d, J=16.4, 1H), 6.90 (d, J=16.4, 1H), 6.80 (d, J=2.1, 1H), 6.43 (d, J=2.1, 1H), 6.41 (d, J=2.3, 2H), 6.34 (t, J=2.3, 1H), 5.44 (d, J=4.64, 1H), 5.43 (s, 1H), 4.64 (d, J=4.3, 1H), 3.24 (s, 3H), 1.48 (p, J=7.5, 6H), 1.20 (p, J=7.4, 6H), 1.10 (d, J=4.0, 18H), 1.09 (d, J=4.0, 18H), 1.04 (t, J=7.3, 36H).
^{13}C NMR (126 MHz, D_6-Acetone, 25 °C)	δ = 167.1, 163.0, 160.1, 158.3, 149.9, 147.2, 137.5, 136.5, 135.9, 133.9, 129.0, 128.8, 127.6, 123.3, 121.0, 120.0, 113.3, 111.2, 105.0, 97.8, 94.3, 56.9, 37.6, 19.4, 19.4, 18.4, 13.4, 12.7.
HRMS (ESI):	*m/z* calculated for $C_{65}H_{104}O_8SSi_4$ ($[M+H]^+$): 1,157.6602, found 1157.6572
FTIR (neat) cm^{-1} :	ν̃= 3387 (br), 2866 (w), 1589 (s), 1449 (w), 1168 (vs), 1150 (s), 1015 (m), 880 (vs), 864 (s), 837 (m), 758 (w), 684 (m)



3.142, ^{1}H NMR, 500 MHz, D_6-Acetone



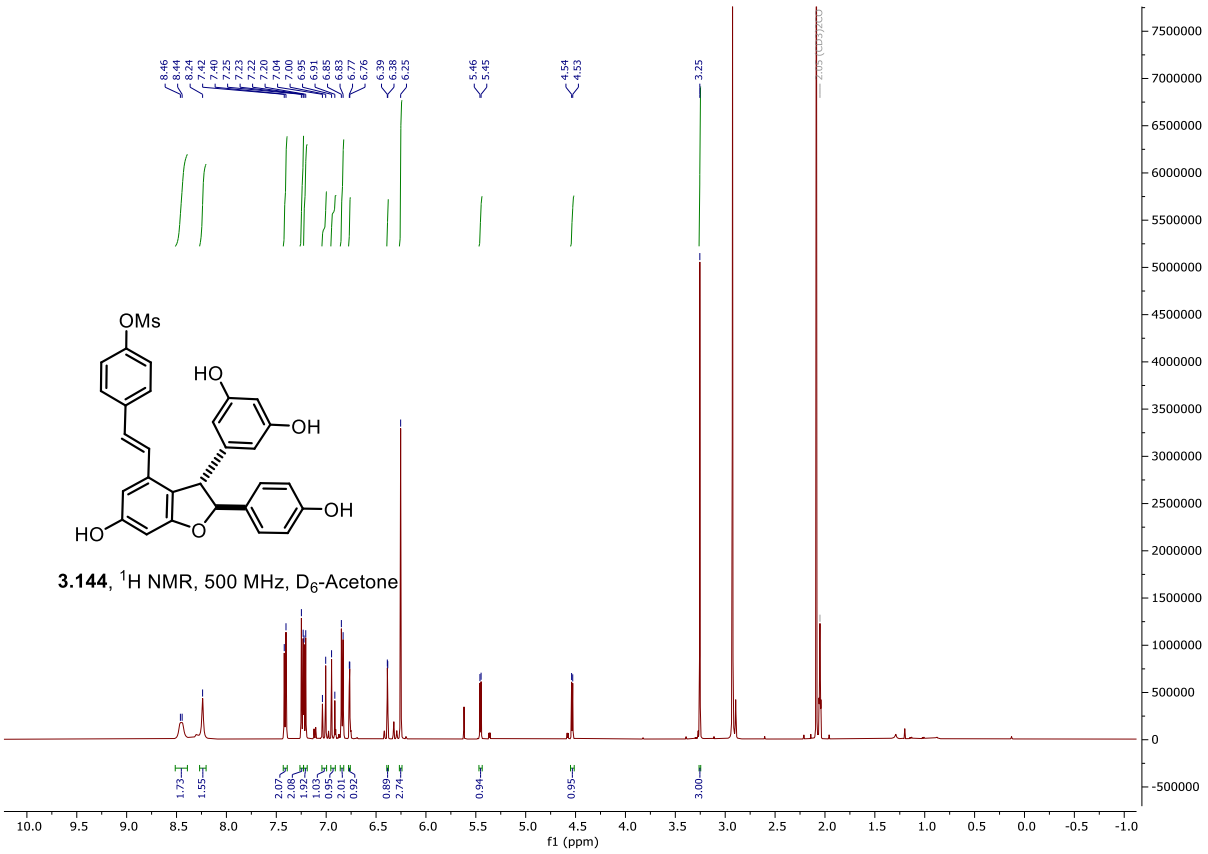
3.142, ^{13}C NMR, 126 MHz, D_6-Acetone

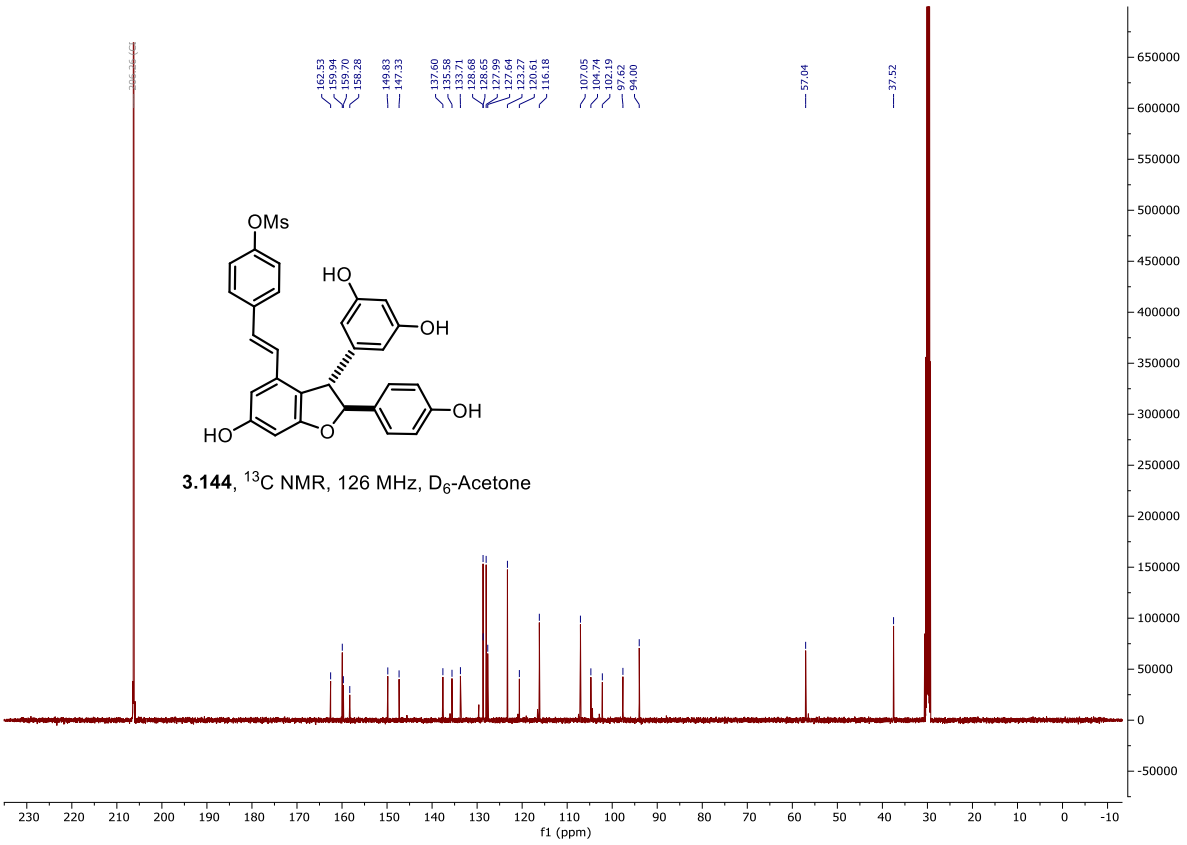


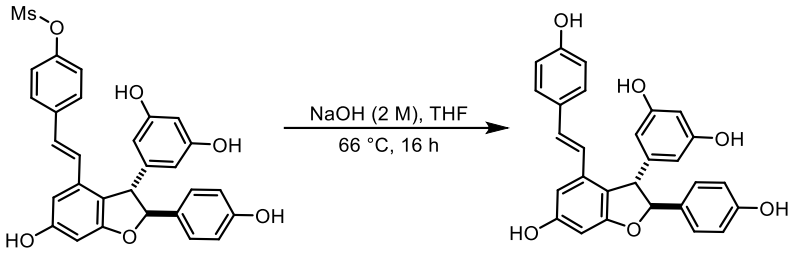
(3.144) 4-((E)-2-((2S,3S)-3-(3,5-dihydroxyphenyl)-6-hydroxy-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-4-yl)vinyl)phenyl methanesulfonate

To a 12-dram vial was added the phenol (89 mg, 0.769 mmol, 1 equiv) and HCl (0.5M in MeOH, 7.7 mL, 0.5 M). The headspace was backfilled with argon, and the reaction was refluxed in an oil bath set to 70 °C for 16 h. The reaction was added to a separatory funnel containing water (20 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-30% Acetone in DCM) to yield the product as a light tan foam (27 mg, 66%).

TLC (DCM/Acetone, 70:30), R_F:	0.37 (UV, potassium permanganate)
^{1}H NMR (500 MHz, D_6-Acetone, 25 °C)	δ = 8.45 (br s, 2H, OH), 8.24 (br s, 2H, OH), 7.41 (d, J=8.8, 2H), 7.24 (d, J=8.8, 2H), 7.21 (d, J=8.6, 2H), 7.02 (d, J=16.4, 2H), 6.93 (d, J=16.4, 2H), 6.84 (d, J=8.8, 2H), 6.77 (d, J=2.3, 1H), 6.38 (d, J=2.1, 1H), 6.25 (s, 3H), 5.45 (d, J=5.6, 1H), 4.53 (d, J=5.6, 1H), 3.25 (s, 3H).
^{13}C NMR (126 MHz, D_6-Acetone, 25 °C)	δ = 162.5, 159.9, 159.7, 158.3, 149.8, 147.3, 137.6, 135.6, 133.7, 128.7, 128.7, 128.0, 127.6, 123.3, 120.6, 116.2, 107.1, 104.7, 102.2, 97.6, 94.0, 57.0, 37.5.
HRMS (ESI):	*m/z* calculated for $C_{29}H_{24}O_8S$ ($[M+H]^+$): 533.1265, found 533.1264
FTIR (neat) cm^{-1} :	ν̃= 3344 (br), 1596 (m), 1356 (m), 1260 (w), 1172 (m), 1144 (vs), 1125 (m), 1002 (w), 968 (w), 875 (m), 834 (m)


OMs
HO
OH
HO
OH
O
3.144, 1H NMR, 500 MHz, D6-Acetone
f1 (ppm)

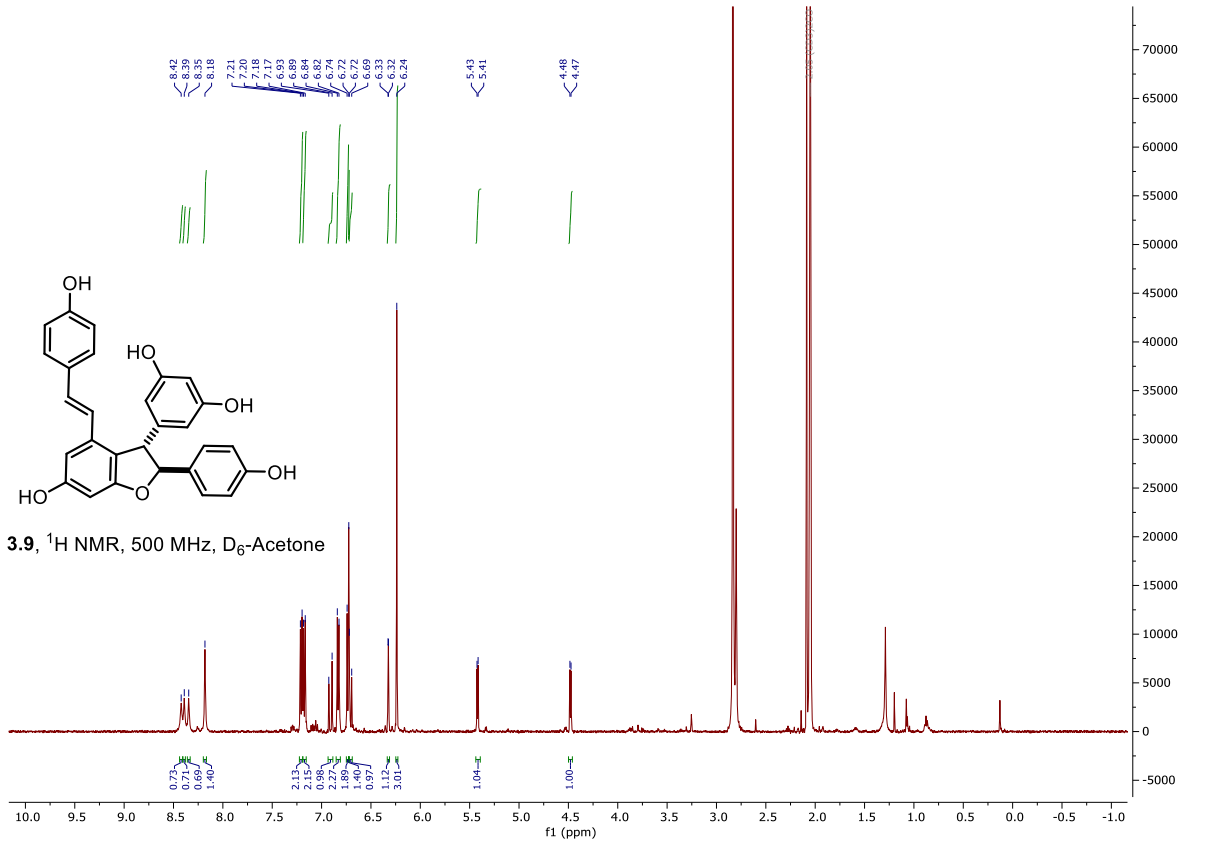

OMs
HO
OH
HO
OH
O
3.144, 13C NMR, 126 MHz, D6-Acetone
f1 (ppm)



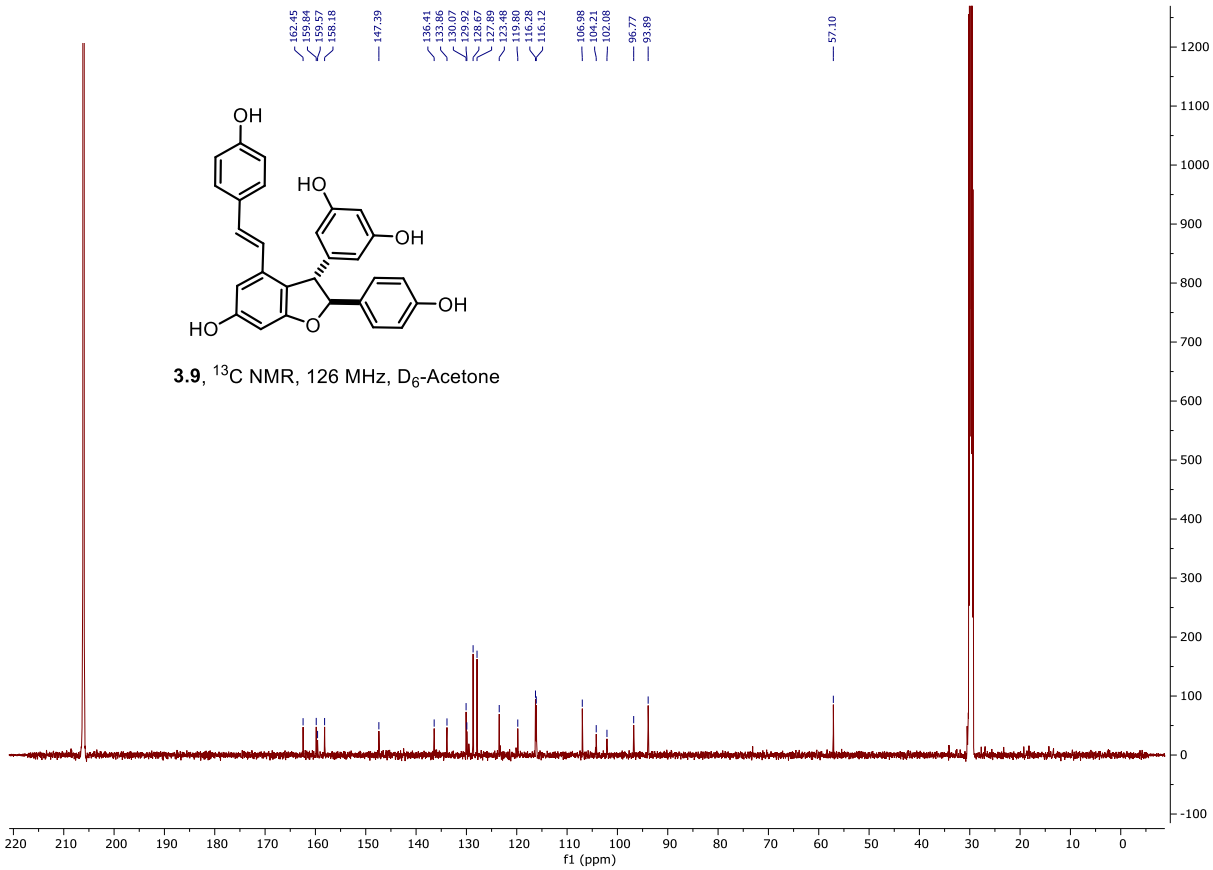
(3.9) ε-viniferin

To a 15 mL sealed tube was added the phenol (36 mg, 0.068 mmol, 1 equiv), NaOH (2.7 mL, 2M), and THF (2.7 mL, 0.025 M). The headspace was filled with argon, the tube was capped and heated in an oil bath set to 80 °C for 16 h. The reaction was added to a separatory funnel containing water (20 mL) and sat. NH_4Cl (20 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-40% Acetone in DCM) to yield the product as a pale-yellow foam (23 mg, 75%).

TLC (DCM/Acetone, 70:30), R_F:	0.27 (UV, potassium permanganate)
^{1}H NMR (500 MHz, D_6-Acetone, 25 °C)	δ = 8.42 (s, 1H, OH), 8.39 (s, 1H, OH), 8.35 (s, 1H, OH), 8.18 (s, 1H, OH),7.21 (d, J=8.5, 2H), 7.17 (d, J=8.7, 2H), 6.91 (d, J=16.4, 1H), 6.83 (d, J=8.5, 2H), 6.74 (d, J=8.5, 2H), 6.73 (d, J=2.0, 1H), 6.71 (d, J=16.4, 1H), 6.75 – 6.69 (m, 4H), 6.32 (d, J=2.0, 1H), 6.24 (s, 3H), 5.42 (d, J=5.3, 1H), 4.48 (d, J=5.5, 1H).
^{13}C NMR (126 MHz, D_6-Acetone, 25 °C)	δ = 162.5, 159.8, 159.6, 158.2, 147.4, 136.4, 133.9, 130.1, 129.9, 128.7, 127.9, 123.5, 119.8, 116.3, 116.1, 107.0, 104.2, 102.1, 96.8, 93.9, 57.1.
HRMS (ESI):	*m/z* calculated for $C_{28}H_{22}O_6$ ($[M+H]^+$): 455.1495, found 455.1508
FTIR (neat) cm^{-1} :	ν̃= 3338 (br), 2361 (s), 2343 (w), 1605 (vs), 1514 (vs), 1243 (w), 1172 (m)

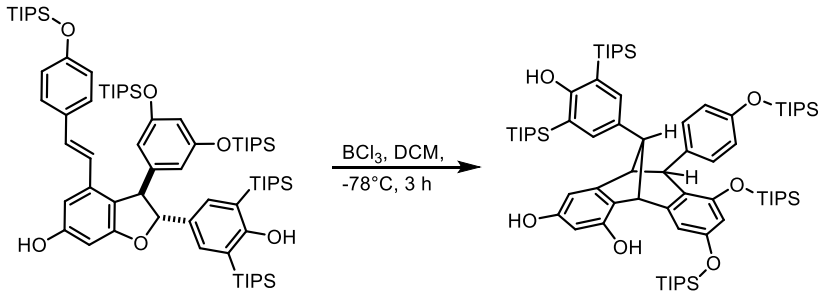


3.9, ^{1}H NMR, 500 MHz, D_6-Acetone



3.9, ^{13}C NMR, 126 MHz, D_6-Acetone

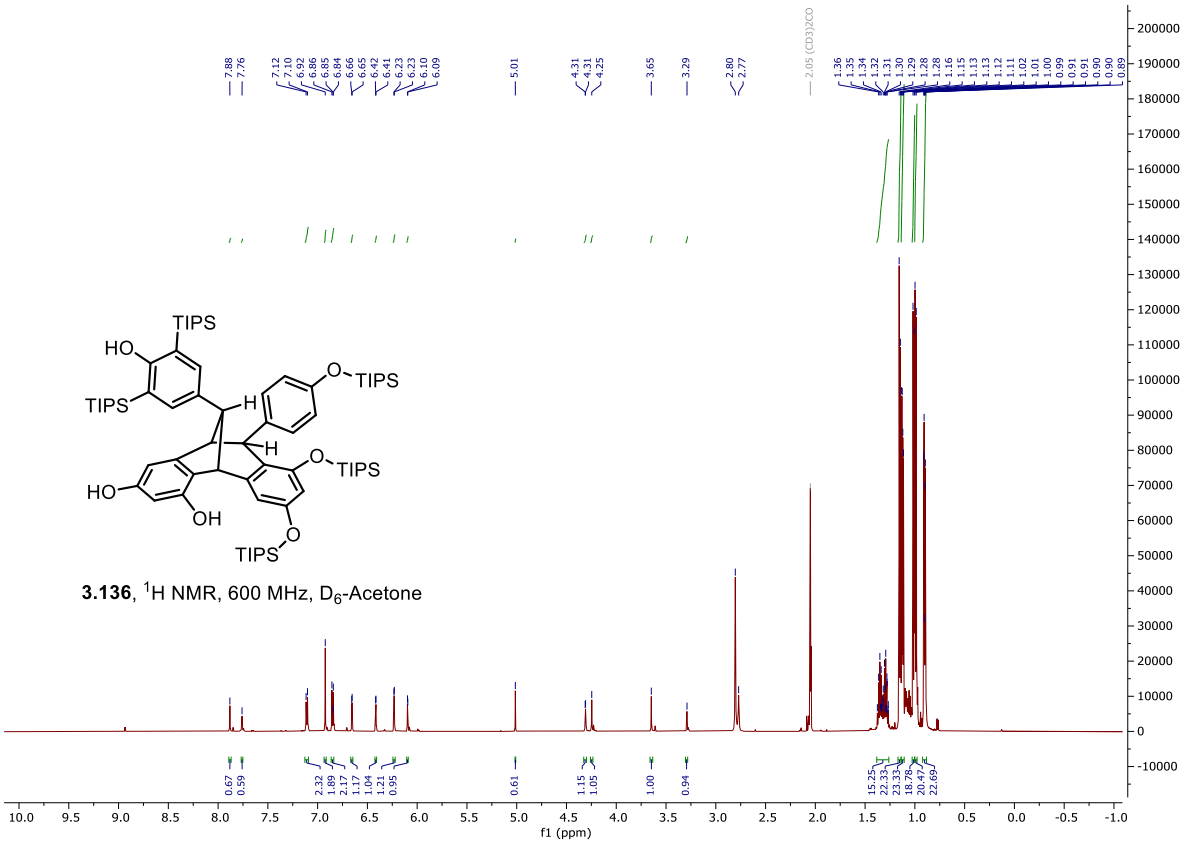
Synthesis of ampelopsin F



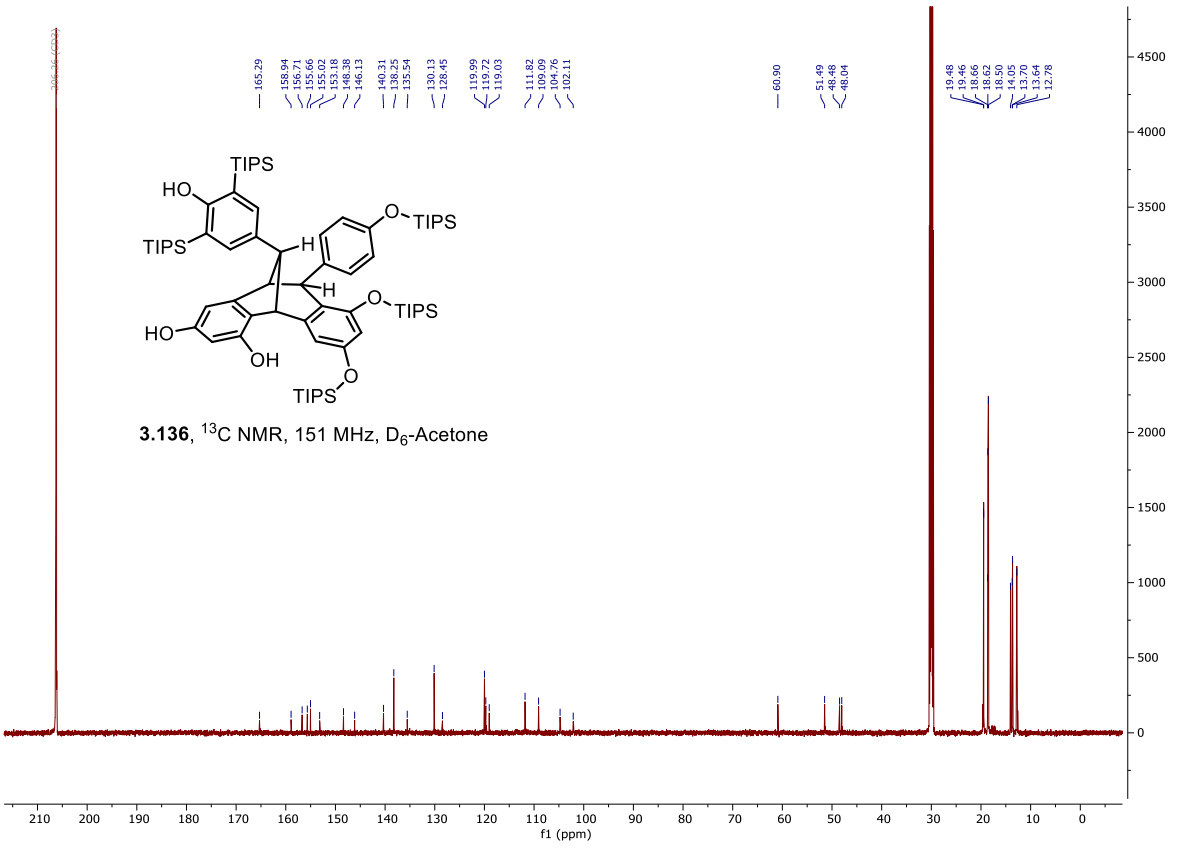
(3.136) 5-TIPS ampelopsin F

To a 2 dram vial was added the phenol (20 mg, 16 µmol, 1 equiv) and BCl_3 (1 M in DCM, 49 µL, 3.0 equiv) at -78 °C. After 3 hours the reaction was added to a separatory funnel containing water (20 mL). The mixture was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-20% EtOAc in Hexanes) to yield the product as a light tan foam. (14.6 mg, 73%).

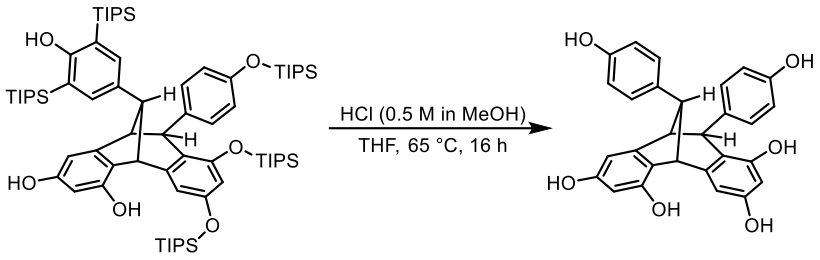
TLC (Hexanes/EtOAc, 85:15), R_F:	0.29 (UV, potassium permanganate)
^{1}H NMR (600 MHz, D_6-Acetone, 25 °C)	δ = 7.88 (s, 1H, OH), 7.76 (s, 1H, OH), 7.11 (d, J=8.4, 2H), 6.92 (s, 2H), 6.85 (d, J=8.6, 2H), 6.66 (d, J=2.4, 1H), 6.42 (d, J=2.0, 1H), 6.23 (d, J=2.4, 1H), 6.10 (d, J=1.9, 1H), 5.01 (s, 1H, OH), 4.31 (d, J=2.1, 1H), 4.25 (br s, 1H), 3.65 (s, 1H), 3.29 (br s, 1H), 1.40 – 1.25 (m, 15H), 1.15 (d, J=7.4, 18H), 1.12 (dd, J=7.5, 4.0, 18H), 1.01 (d, J=7.5, 18H), 0.99 (d, J=7.5, 18H), 0.90 (dd, J=7.5, 1.8, 18 H).
^{13}C NMR (151 MHz, D_6-Acetone, 25 °C)	δ = 165.3, 158.9, 156.7, 155.7, 155.0, 153.2, 148.4, 146.1, 140.3, 138.2, 135.5, 130.1, 128.4, 120.0, 119.7, 119.0, 111.8, 109.1, 104.8, 102.1, 60.9, 51.5, 48.5, 48.0, 19.5, 19.5, 18.7, 18.6, 18.5, 14.1, 13.7, 13.6, 12.8.
HRMS (ESI):	*m/z* calculated for $C_{73}H_{122}O_6Si_5$ ($[M+H]^+$): 1235.8161, found 1235.8179
FTIR (neat) cm^{-1} :	ν̃= 3359 (br), 2945 (m), 2867 (s), 2361 (vs), 2339 (m), 1601 (w), 1507 (m), 1464 (s), 1262 (s), 1013 (w), 919 (m), 882 (vs), 858 (m), 838 (s), 788 (w), 684 (vs), 662 (vs)



3.136, ^{1}H NMR, 600 MHz, D_6-Acetone



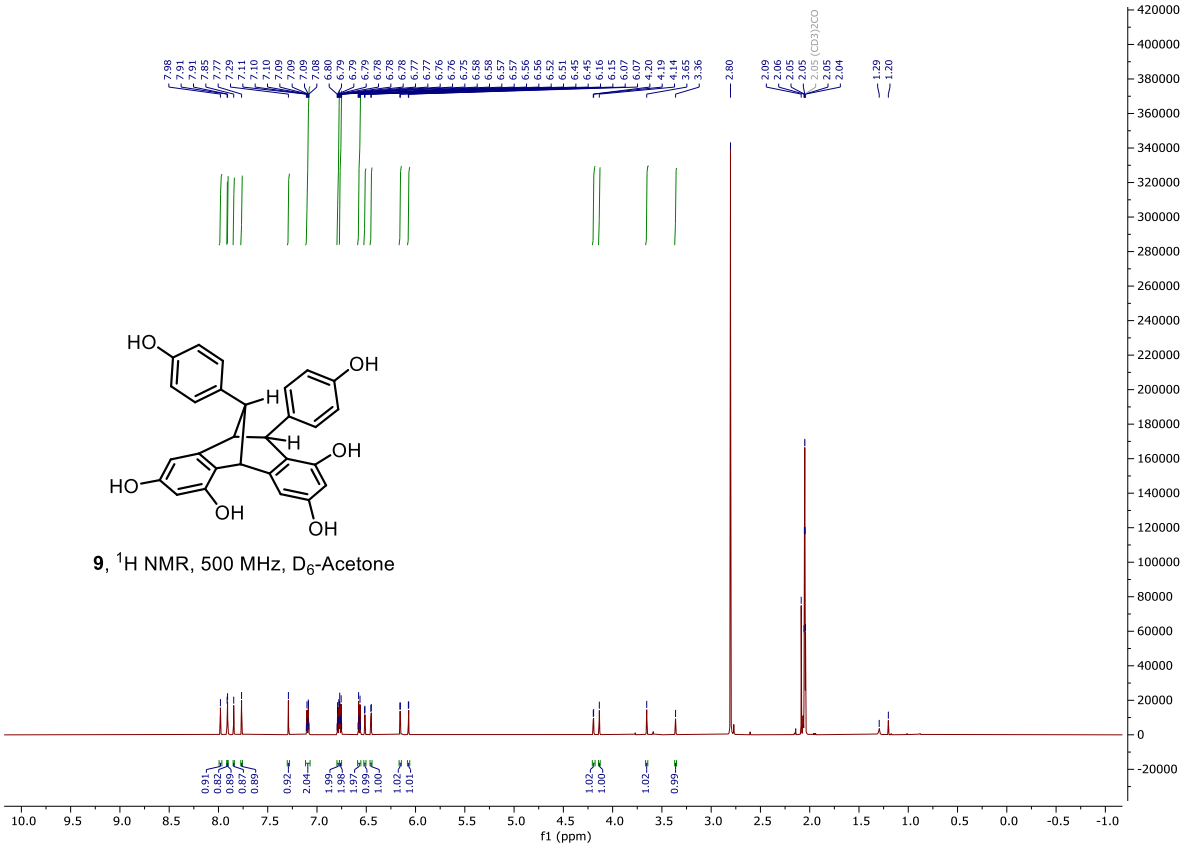
3.136, ^{13}C NMR, 151 MHz, D_6-Acetone



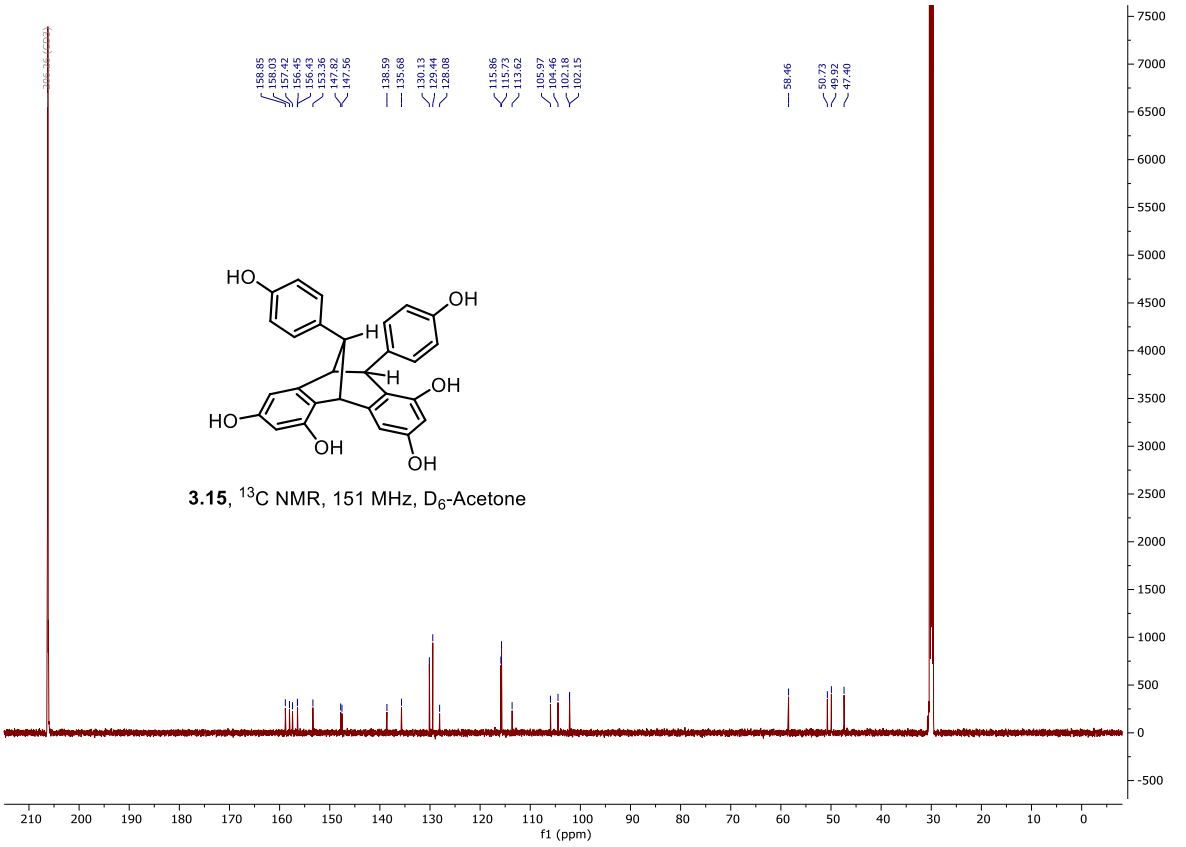
(3.15) ampelopsin F

To a 15 mL sealed tube was added phenol (22.8 mg, 0.021 mmol, 1 equiv) and HCl (0.5M in MeOH, 2.1 mL, 0.5 M), and THF (0.845 mL, 0.025 M). The headspace was backfilled with argon, and the reaction was refluxed in an oil bath set to 70 °C for 16 h. The reaction was concentrated and purified by preparative TLC 50:50 DCM/Acetone to yield the product as a light tan foam (7.4 mg, 77%).

TLC (DCM/Acetone, 70:30), R_F:	0.08 (UV, potassium permanganate)
^{1}H NMR (600 MHz, D_6-Acetone, 25 °C)	δ = 7.98 (s, 1H, OH), 7.91 (s, 1H, OH), 7.91 (s, 1H, OH), 7.85 (s, 1H, OH), 7.77 (s, 1H, OH), 7.29 (s, 1H, OH), 7.12 – 7.07 (m, 2H), 6.80 – 6.77 (m, 2H), 6.77 – 6.75 (m, 2H), 6.52 (d, J=2.0, 1H), 6.45 (d, J=2.4, 1H), 6.16 (d, J=2.4, 1H), 6.07 (d, J=2.0, 1H), 4.19 (d, J=2.0, 1H), 4.14 (s, 1H), 3.65 (br s, 1H), 3.36 (br s, 1H).
^{13}C NMR (151 MHz, D_6-Acetone, 25 °C)	δ = 158.9, 158.0, 157.4, 156.5, 156.4, 153.4, 147.8, 147.6, 138.6, 135.7, 130.1, 129.4, 128.1, 115.9, 115.7, 113.6, 106.0, 104.5, 102.2, 102.1, 58.5, 50.7, 49.9, 47.4.
HRMS (ESI):	*m/z* calculated for $C_{28}H_{22}O_6$ ($[M+H]^+$): 455.1495, found 455.1482
FTIR (neat) cm^{-1} :	ν̃= 3322 (br), 2924 (w), 1687 (m), 1599 (s), 1512 (s), 1461 (w), 1332 (w), 1259 (vs), 1173 (w), 1139 (w), 839 (w)



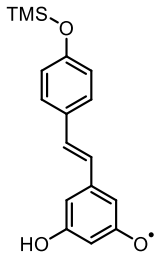
9, ^{1}H NMR, 500 MHz, D_6-Acetone



3.15, ^{13}C NMR, 151 MHz, D_6-Acetone

3.7 Computational Details

All density functional theory (DFT) calculations were performed using the Gaussian 16 package (Revision C.01). The numerical values presented in the manuscript were computed at the M062X / cc-PVTZ level of theory. All calculations are presented in the gas phase, without solvent corrections, unless otherwise noted. Computations were completed under default temperature conditions (T = 298.15 K). The triisopropylsilyl group was truncated to trimethylsilyl for computational simplicity. Following the numerical values are the xyz coordinates from which the values were derived. All optimized ground state geometries were confirmed to have zero imaginary frequencies, while transition states had one.



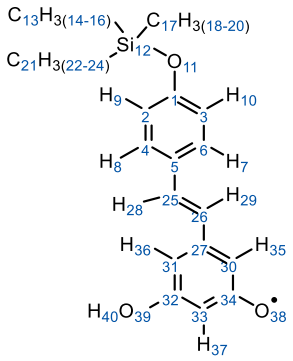
3.98

M062X / cc-PVTZ

0 2

C	-2.08998800	-1.24481900	-0.44351400
C	-3.37051700	-0.69900700	-0.48243700
C	-0.99731300	-0.39750500	-0.23611400
C	-3.54273900	0.66727300	-0.31935600
C	-2.46271800	1.52590500	-0.11600800
C	-1.18210700	0.95914900	-0.07565900
H	-0.31429300	1.58395000	0.08587600
H	-4.54431400	1.07781800	-0.35144300
H	-4.23262500	-1.33246600	-0.63556400
H	-0.00750900	-0.83166900	-0.20385400
O	-1.83674300	-2.56181400	-0.58815300
Si	-2.85414300	-3.84318500	-1.00264000
C	-3.64769800	-3.49760400	-2.65632000
H	-4.33752900	-2.65484200	-2.62621100
H	-4.20764600	-4.37689700	-2.97952300
H	-2.88454600	-3.28971100	-3.40735900
C	-1.69177800	-5.29193800	-1.10534300
H	-0.92547300	-5.12052100	-1.86171600
H	-2.23712100	-6.19818300	-1.37156600
H	-1.19897600	-5.46050100	-0.14740100
C	-4.12384300	-4.11027300	0.34024300

H	-4.85868800	-3.30833200	0.39971100
H	-3.63545900	-4.20115700	1.31130400
H	-4.66085800	-5.04053500	0.14621900
C	-2.71680000	2.95816300	0.04362700
C	-1.79664800	3.91507300	0.19706900
C	-2.05703700	5.34855300	0.35520600
H	-3.76756300	3.22711400	0.02452600
H	-0.74535700	3.65202500	0.20658600
C	-1.00005000	6.21796200	0.46642300
C	-3.36787100	5.87834500	0.40021600
C	-3.60088700	7.25864500	0.55355000
C	-2.55502700	8.13316800	0.66297300
C	-1.19971600	7.64345100	0.62352900
H	0.02188100	5.86369500	0.43938400
H	-4.22398600	5.22168900	0.31969000
H	-2.72414900	9.19388700	0.78138100
O	-0.22829700	8.41731200	0.72174600
O	-4.86218900	7.75088600	0.59711100
H	-5.50639800	7.03965800	0.51721200



3.98, with atom labeling

M062X / cc-PVTZ, Prop=EPR

Isotropic Fermi Contact Couplings

Atom	a.u.	MegaHertz	Gauss	10(-4) cm-1
1 C(13)	-0.00197	-2.21534	-0.79049	-0.73896
2 C(13)	0.00121	1.35632	0.48397	0.45242
3 C(13)	0.00110	1.23407	0.44035	0.41164
4 C(13)	-0.00202	-2.26697	-0.80891	-0.75618
5 C(13)	0.00309	3.47585	1.24027	1.15942
6 C(13)	-0.00175	-1.96336	-0.70058	-0.65491

7	H(1)	0.00014	0.64461	0.23001	0.21502
8	H(1)	0.00016	0.73569	0.26251	0.24540
9	H(1)	-0.00004	-0.20048	-0.07154	-0.06687
10	H(1)	-0.00004	-0.18218	-0.06501	-0.06077
11	O(17)	-0.00026	0.16057	0.05729	0.05356
12	Si(29)	0.00002	-0.01737	-0.00620	-0.00579
13	C(13)	-0.00001	-0.01319	-0.00471	-0.00440
14	H(1)	0.00000	0.00279	0.00099	0.00093
15	H(1)	0.00000	0.01092	0.00390	0.00364
16	H(1)	0.00000	0.00191	0.00068	0.00064
17	C(13)	0.00002	0.02012	0.00718	0.00671
18	H(1)	-0.00000	-0.00490	-0.00175	-0.00164
19	H(1)	0.00000	0.01189	0.00424	0.00396
20	H(1)	-0.00000	-0.00450	-0.00161	-0.00150
21	C(13)	-0.00002	-0.02436	-0.00869	-0.00813
22	H(1)	-0.00000	-0.00005	-0.00002	-0.00002
23	H(1)	0.00000	0.00193	0.00069	0.00065
24	H(1)	0.00000	0.00608	0.00217	0.00203
25	C(13)	-0.00963	-10.82107	-3.86123	-3.60952
26	C(13)	0.00937	10.53050	3.75754	3.51260
27	C(13)	-0.03951	-44.41580	-15.84866	-14.81552
28	H(1)	0.00073	3.25542	1.16161	1.08589
29	H(1)	-0.00067	-2.98041	-1.06349	-0.99416
30	C(13)	0.04759	53.49649	19.08888	17.84451
31	C(13)	0.07793	87.61294	31.26248	29.22453
32	C(13)	-0.04150	-46.65348	-16.64712	-15.56192
33	C(13)	0.04609	51.81073	18.48736	17.28220
34	C(13)	-0.04142	-46.56074	-16.61403	-15.53099
35	H(1)	-0.00482	-21.55416	-7.69106	-7.18969
36	H(1)	-0.00712	-31.82861	-11.35724	-10.61688
37	H(1)	-0.00468	-20.92246	-7.46565	-6.97898
38	O(17)	0.09877	-59.87305	-21.36419	-19.97150
39	O(17)	-0.00285	1.72819	0.61666	0.57646
40	H(1)	0.00011	0.48717	0.17384	0.16250

Chapter 4 Total Synthesis of Resveratrol Trimers

4.1 Introduction

The resveratrol trimers exhibit the same coupling patterns, cyclizations, and rearrangements as the resveratrol dimers (chapter 3), but are structurally distinct due to the combinatorial explosion of diversity displayed in their structures. Nearly all trimers are hypothetically biosynthesized via the radical coupling of resveratrol (**4.1**) and a resveratrol dimer in a 1 + 2 fashion. Following this coupling divergent cyclizations transform a single motif into many cores via disparate cyclization pathways.

The C3-C8 trimers are the simplest and least diverse subclass, similarly to the C3-C8 dimers. Resveratrol (**4.1**, Figure 4.1) and the dimer parthenocissin B (**4.2**) are oxidized to a set of radicals which exhibit a C3-C8 coupling pattern (**4.3**). A *5-exo-trig* cyclization closes the dihydrobenzofuran, forming parthenocissin B (**4.3**). Notably the other *trans* dihydrobenzofuran diastereomer has also been isolated (laetevirenol E, not drawn).[274] This complicates the assumption that these trimers are deliberate enzymatic oxidation products and provides evidence they are the produce of unselective oxidative radical couplings. The linear dimer amurensin A (**4.5**) can undergo a similar C3-C8 coupling and cyclize to form wenchowenol (**4.7**).[275]

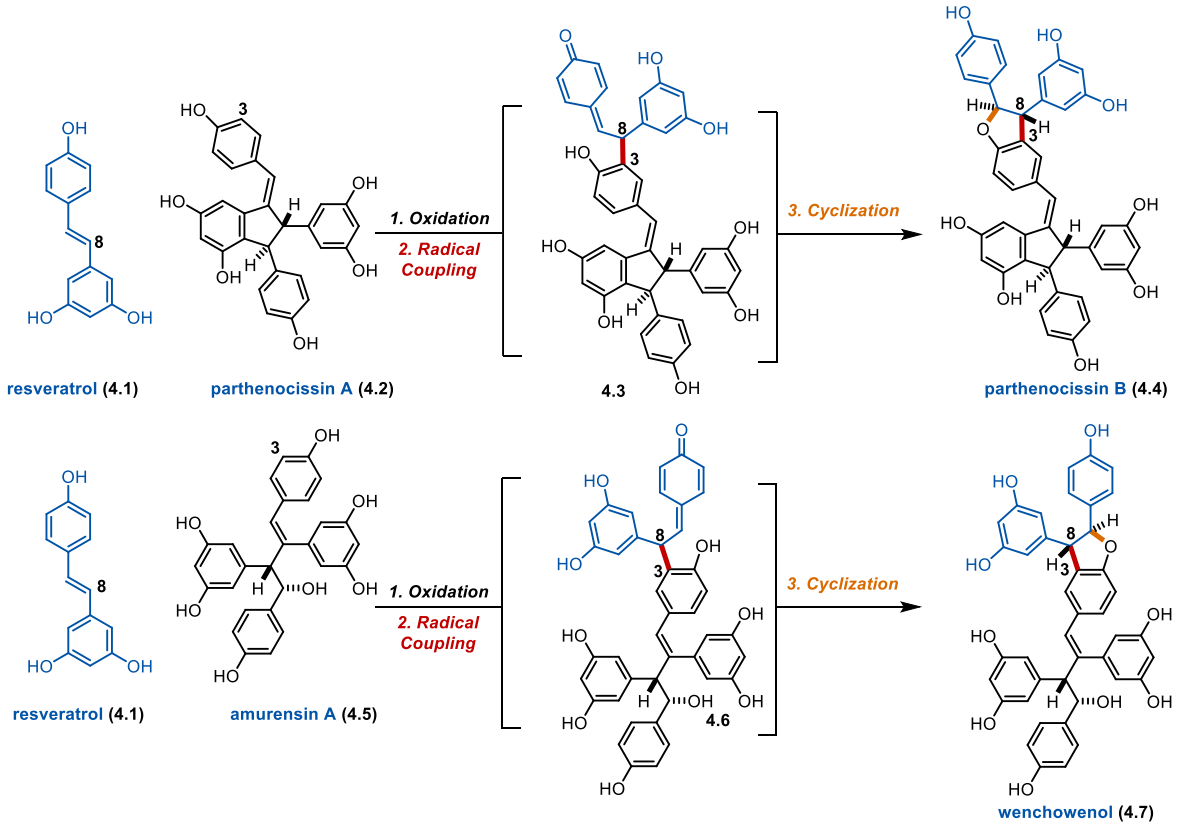


Figure 4.1 Biosynthesis of selected C3-C8 resveratrol trimers

The C8-C8 trimers represent a more diverse class, originating from the oxidative radical coupling of ε-viniferin (**4.8**, Figure 4.2) and resveratrol (**4.1**, Figure 4.2). The key intermediate (**4.9**), has three divergent pathways shown. Simple trapping of both quinone methide's by water give trimer nepalensinol C (**4.10**).[276] Returning to **4.9** there are two divergent *5-exo-trig* cyclizations conformationally feasible. Cyclization through the resorcinol originating from resveratrol provides **4.11** which is poised for an *8-exo-trig* cyclization forming distichol (**4.12**). Two epimers of distichol in canaliculatol[277] and stenophyllol B[278] are also known (not drawn). Alternatively, if **4.9** undergoes *5-exo-trig* from ε-viniferin originating resorcinol **4.13** is produced. Again, with divergent pathways, carasiphenol C (**4.14**)[279] arises from *5-exo-trig* while ampelopsin C (**4.15**)[280] from *7-exo-trig*. Nucleophilic trapping of **4.13** with water yields nepalensinol A (**4.16**).[280] These trimers represent a class where most mechanistically valid divergent pathways are

represented in natural isolated. This is a common theme among the resveratrol trimer and tetramers.

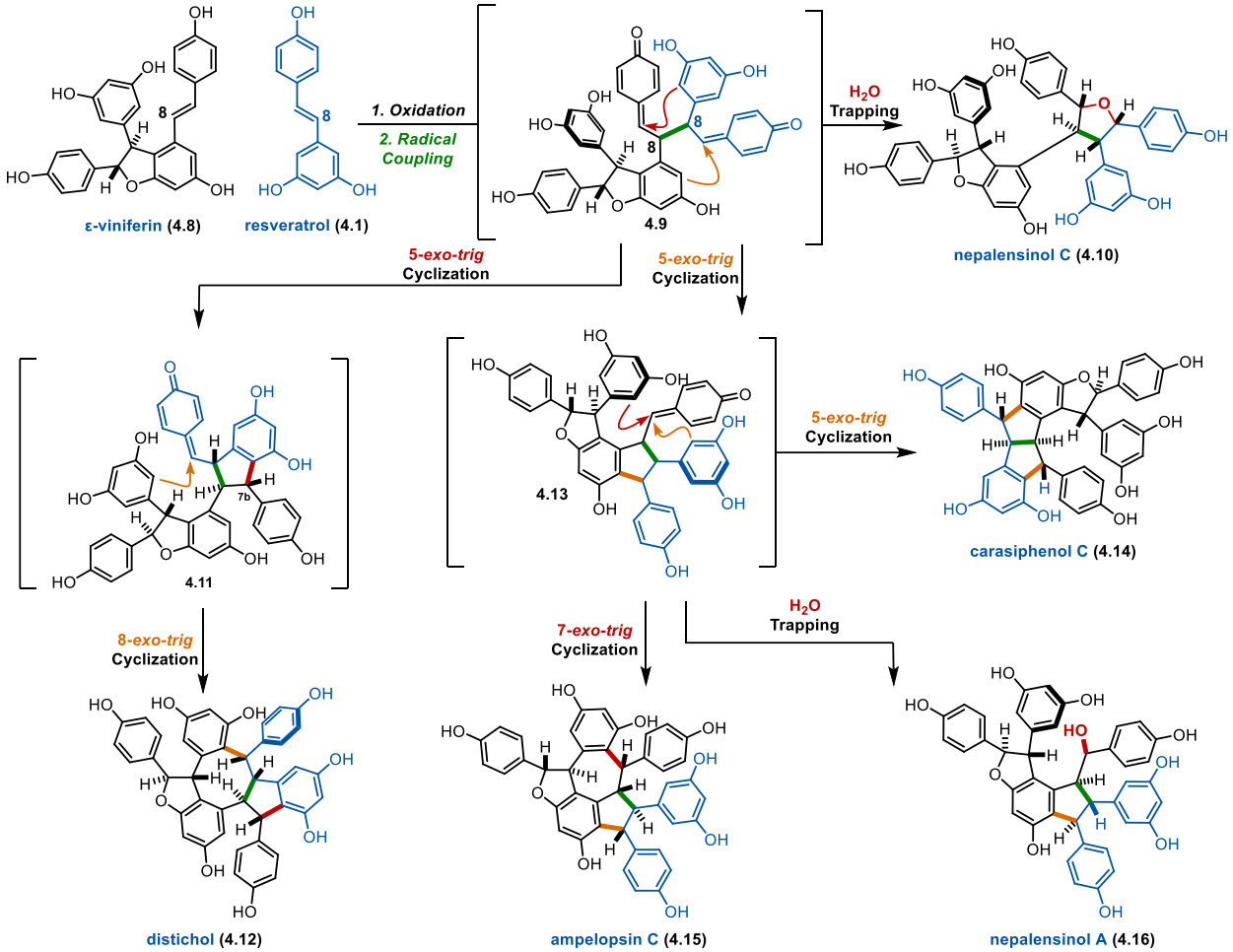


Figure 4.2 Biosynthesis of selected C8-C8 resveratrol trimers

As a brief aside, the resveratrol C8-C8 tetramers are biosynthesized via a dimerization of ε-viniferin (**4.8**, Figure 4.3). Oxidative radical coupling provides **4.17** with each half of the tetramers containing two distinct resorcinol nucleophiles, with cyclization within the same ε-viniferin dimer and cross cyclization represented. The two reactive quinone methides present many diversifying cyclization pathways. Two equivalent *8-exo-trig* cyclizations give symmetrical tetramer vaticaffinol (**4.18**).[281] Other products of symmetrical cyclization include ampelopsin H (**4.19**, 2 x *5-exo-trig*)[282] and hopeaphenol (**4.22**, 2 x *7-exo-trig*).[283] In contrast two unsymmetrical

cyclizations produce diversified products such as viniferol A (**4.20**, 1 x *5-exo trig*, 1 x *8-exo-trig*)[284] and hemsleyanol C (**4.21**, 1 x *5-exo-trig*, 1 x *7-exo-trig*).[285] The series depicted represents only a small number of known C8-C8 tetramers but efficiently illustrates how the same principles of coupling and cyclization produce the structural diversity of the dimers and trimers apply in whole with the tetramers.

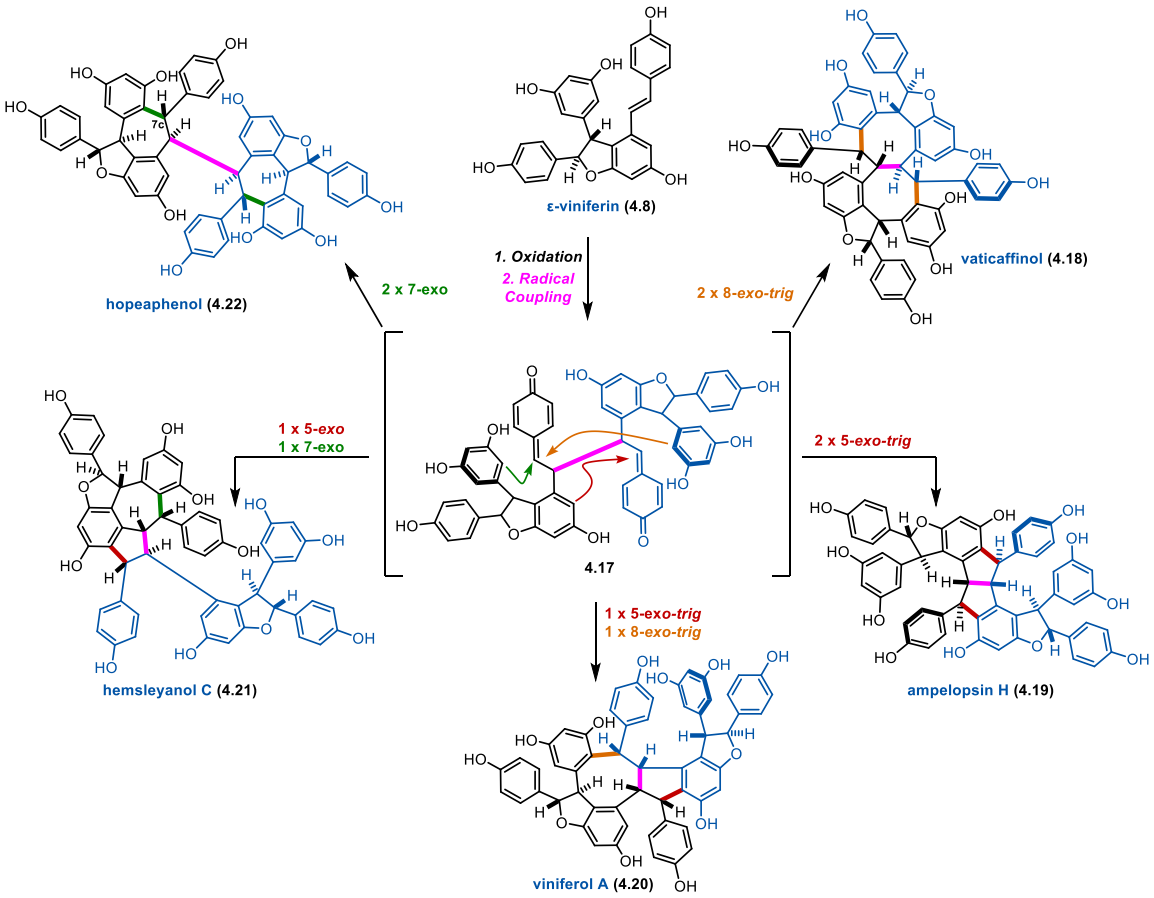


Figure 4.3 Biosynthesis of selected C8-C8 resveratrol tetramers

The coupling of resveratrol (**4.1**, Figure 4.4) and ε-viniferin (**4.8**, Figure 4.4) diverges with both C8-C10 and C10-C8 patterns forming two *mono*-quinone intermediates (**4.23**, **4.28**). A single *5-exo-trig* of intermediates **4.23** yields trimer gnetin H (**4.24**).[286] Protonation of the stilbene in gnetin H would allow *7-exo-trig* cyclization providing vitisin E (**4.25**).[287] Returning to **4.23** a *5-*

exo-trig through the stilbene forms indane **4.26**, which after subsequent *7-exo-trig* form the fused ring scaffold of vaticanol A (**4.27**).[288]

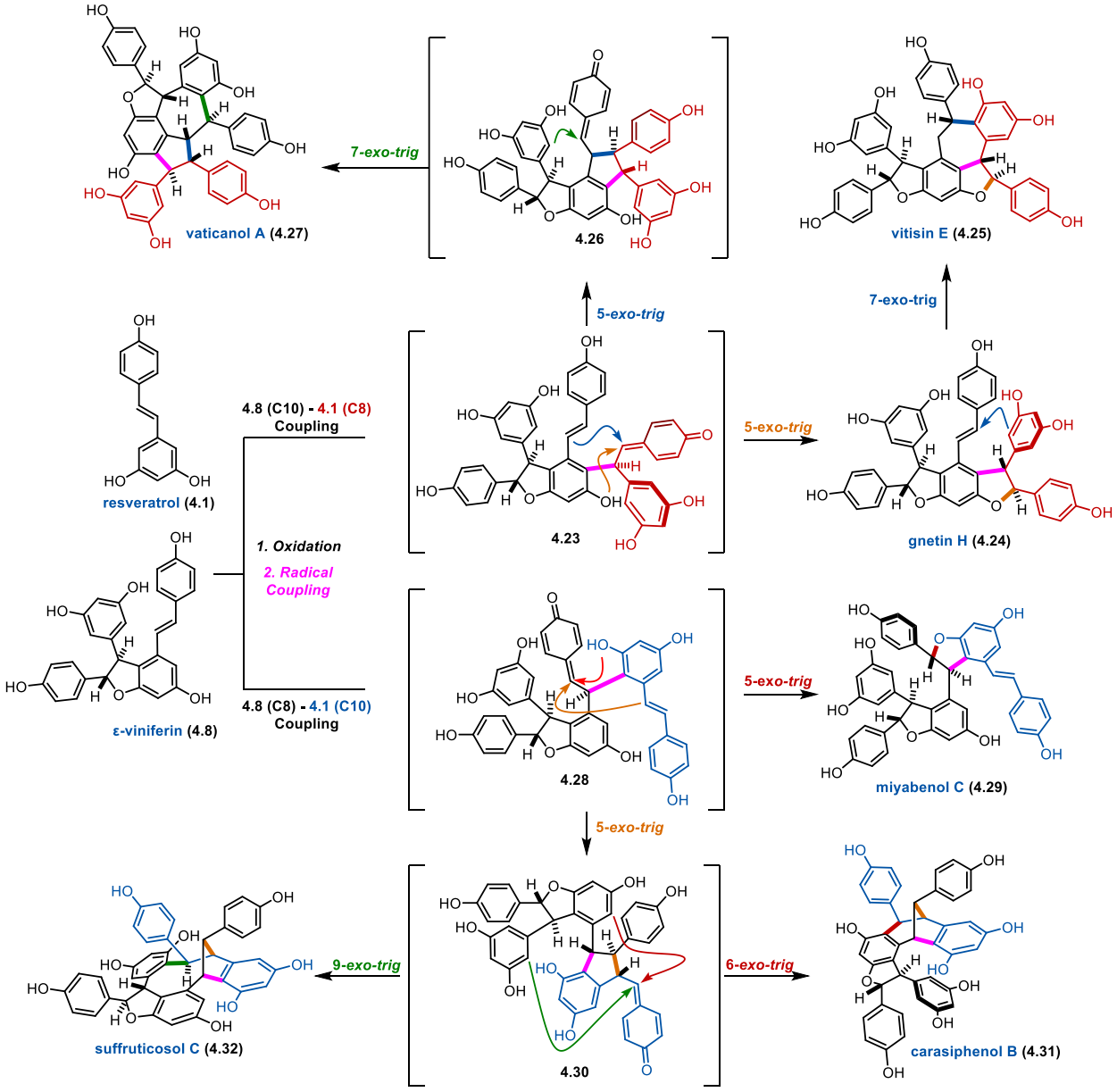


Figure 4.4 Biosynthesis of selected C8-C10 and C10-C8 resveratrol trimers

The C8-C10 coupling pattern provides **4.28** which after *5-exo-trig* through resveratrol originating resorcinol provides *di*-dihydrobenzofuran miyabenol C (**4.29**).[289] Alternatively *5-exo-trig* of stilbene originating from resveratrol in **4.28** provides **4.30**, which can cyclize via *6-exo-trig* to

the bicyclo[3.2.1] core of carasiphenol B (**4.31**),[290] or *9-exo-trig* to form the bicyclo[5.2.1] core of suffruticosol C (**4.32**).[291]

4.2 Biomimetic enzymatic oligomerizations and chemical interconversions towards resveratrol trimers

The earliest biomimetic oxidations towards resveratrol trimers were conducted Niwa and co-workers (2006, Figure 4.5).[292] In this study ε-viniferin and resveratrol were oxidatively coupling using horseradish peroxidase and hydrogen peroxide yielding davidiol A (**4.32**) in 1.1% yield. This study was initiated to determine the absolute configuration of davidiol A by analogy as (+) ε-viniferin was used in its synthesis. On this front even the low yield isolated was sufficient to confirm the configuration of the trimer. In 2012 the Pan group also reported a horseradish peroxidase oxidation of the same starting materials and in addition to isolating davidiol A in 3.3% yield, wilsonol A (**4.33**) was detected.[293] This oxidation was reported alongside the isolation of isolation of bicylco[3.2.1] trimer wilsonol B. The radical scavenging abilities of the wilsonol's against both singlet oxygen (generated via rose bengal photoirradiation in air) and the nitrogen centered persistent radical of 1-diphenyl-2-picrylhydrazyl.[293]

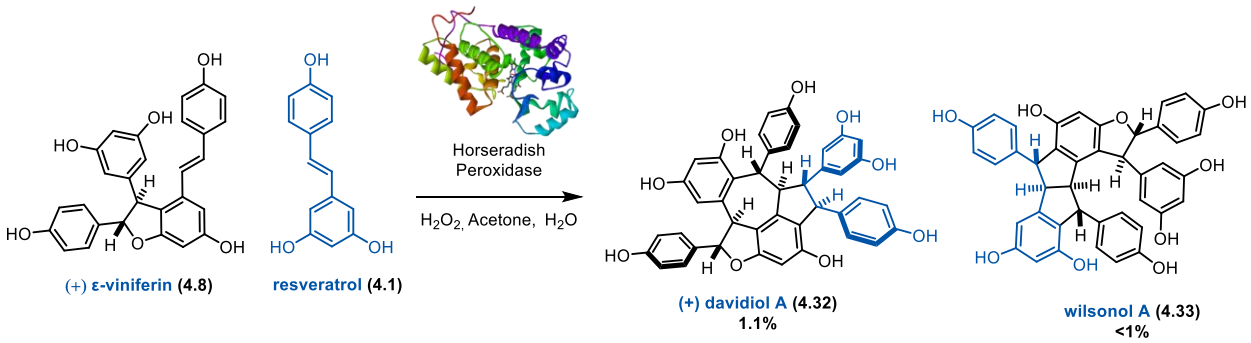


Figure 4.5 Peroxidase coupling of (+) ε-viniferin and resveratrol by Niwa and Pan groups

The Winterhalter group reported similar work to Pan and co-workers, instead using (-) ε-viniferin (**4.8**, Figure 4.6) and resveratrol (**4.1**, Figure 4.6).[294] This oxidation was scaled to 214 mg of (-) ε-viniferin and 416 mg of resveratrol. This allowed the isolation of 4 mg of resviniferin A

(**4.34**, 0.6%) and 8 mg of resviniferin B (**4.35**, 1.2%) which is an impressive feat. The authors were unable to assign the relative configuration of these unnatural stilbene trimers.

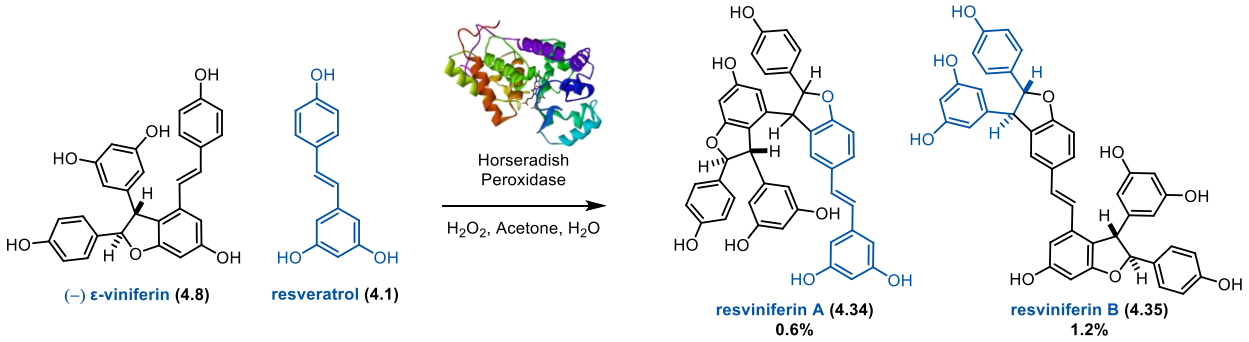


Figure 4.6 Peroxidase coupling of (-) ε-viniferin and resveratrol by Winterhalter group

In the same study that Pan isolated davidiol A, they established the biosynthetic origins of the C8-C10 trimers (Figure 4.7).[293] The authors isolated 3.4% yield of *di*-dihydrobenzofuran gnetin H (**4.24**, Figure 4.7). Subjecting this trimer to vigorous acid (conc. H_2SO_4, MeOH, **reflux**, 20 h) provided a diverse array of cyclization products including ampelopsin G (**4.36**, 4.5%), wilsonol B (**4.37**, 2.7%), amurensin G (**4.38**, 8.4%), and vitisin E (**4.45**, 34%). The isolation of these products was enabled by preparative HPLC. This study highlights that even in forcing conditions simple cyclization onto protonated stilbene giving vitisin E (**4.25**) is energetically favorable compared to dihydrobenzofuran ring opening and cascade cyclization to caged structures **4.36** and **4.37**.

Another key study by the Pan group displayed the biogenic relationship with resveratrol tetramers through dimerization of (+) ε-viniferin (**4.8**, Figure 4.8).[295] The authors were able to isolate hopeaphenol (**4.22**, 9%), vitisin B (**4.39**, 6%), vitisin C (**4.40**, 3%) and isohopeaphenol (**4.41**, 1%). Both **4.22** and **4.41** represent dimerization followed by cyclization onto the nascent quinone (not drawn). In contrast, **4.39** and **4.40** undergo dihydrobenzofuran formation but no further derivatization under the enzymatic conditions.

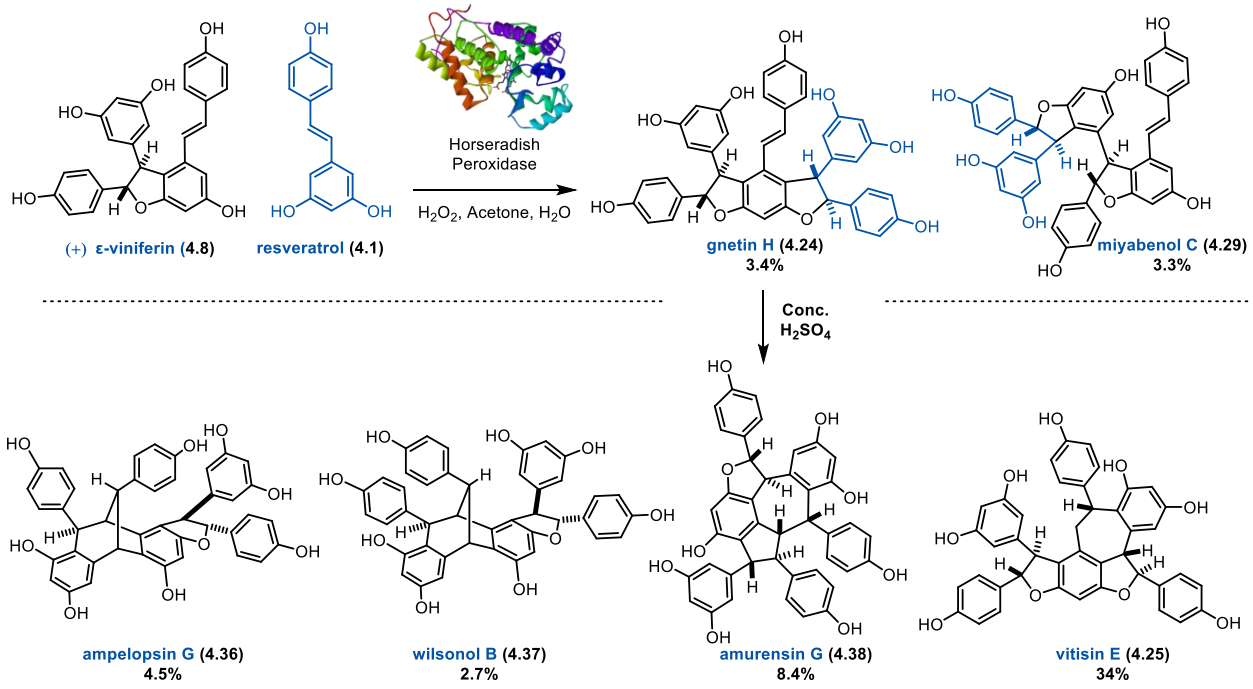


Figure 4.7 Pan's enzymatic oxidation to C10-C8 trimer gnetin H and its acidic rearrangements

The conversion of vitisin B (**4.39**) with aqueous HCl at room temperature quantitatively cyclizes to vitisin A (**4.42**, 100%). A second exposure to vigorous acid (refluxing H_2SO_4) is required to form vitisin D (**4.43**, 37%). This is a rare example of insight into the energetics of these cyclizations as this result provides evidence that the ring opening of a dihydrobenzofuran, as required to reach vitisin A (**4.42**), has a lower energy barrier to activation relative to stilbene protonation, as required to access vitisin D (**4.43**). This contrasts hopeaphenol (**4.22**) and isohopeaphenol (**4.41**) which both are able to cyclize via intramolecular quinone attack upon enzymatic oxidation at room temperature.

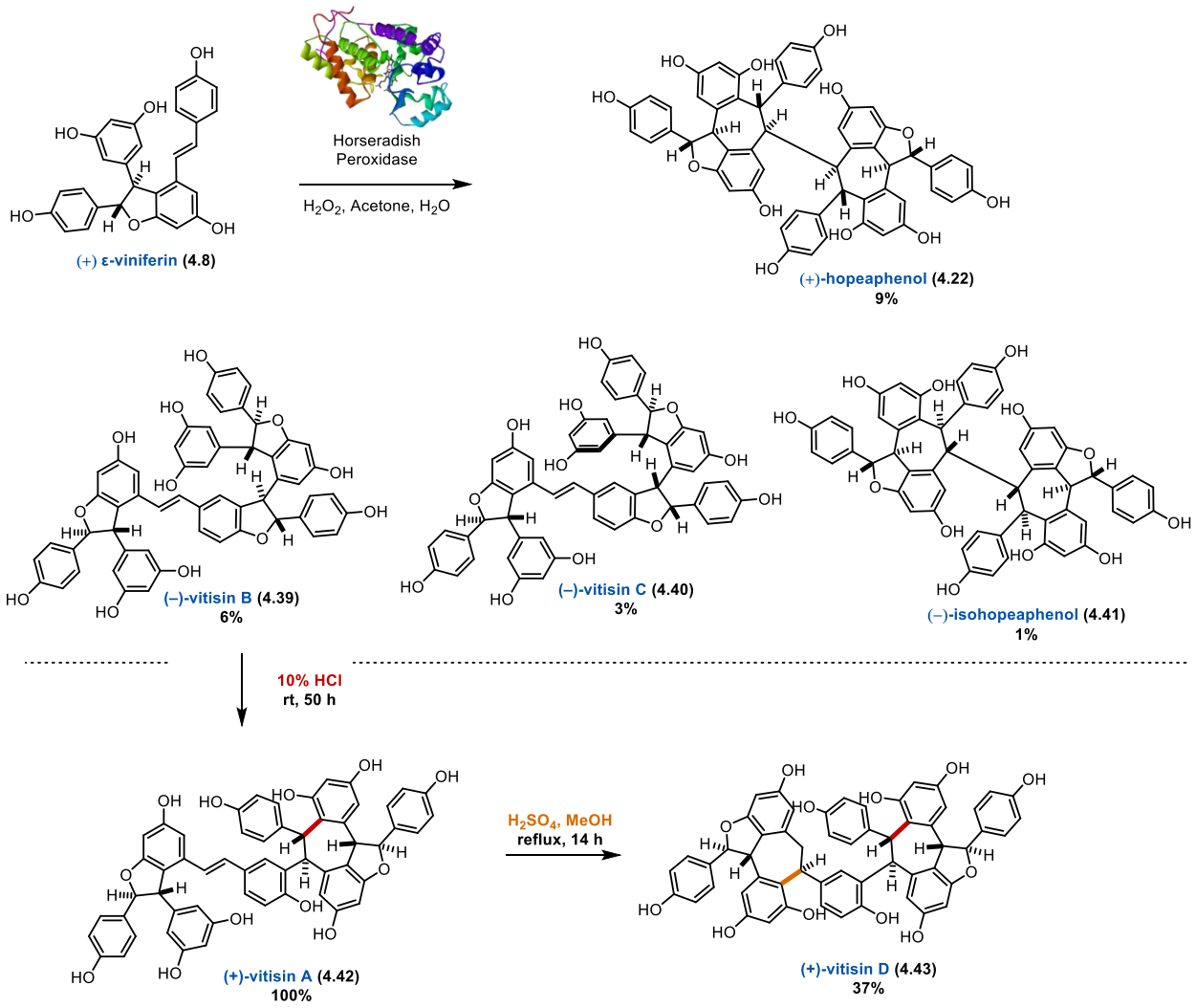


Figure 4.8 Niwa's enzymatic oxidation to resveratrol tetramers and their acid mediated cyclizations

Chemical oxidation to selectively form higher order oligomers is scarcely reported, largely due to the challenges in selectivity encountered when attempting any system more complex than the dimerization of resveratrol. The Sako group has reported a highly productive dimerization of (+) ε-viniferin (**4.8**, Figure 4.9) to vitisin B (**4.39**, Figure 4.9).[296] This transformation requires equimolar silver acetate suspended in dry methanol at 50 °C for one hour.

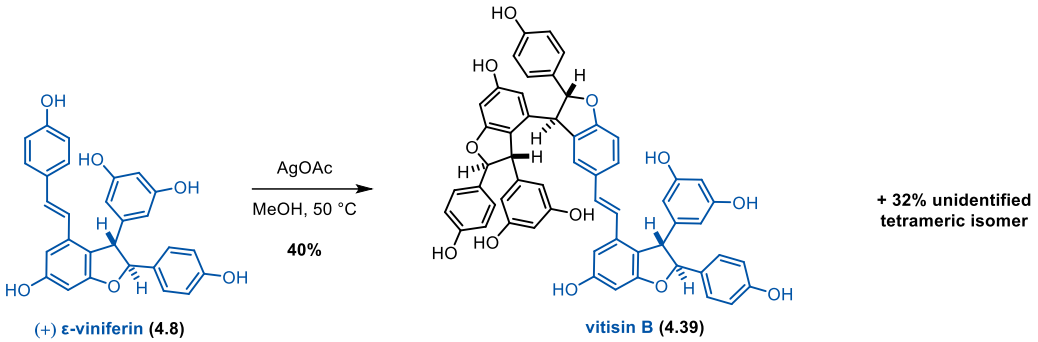


Figure 4.9 Sako's chemical oxidation of (+) ε-viniferin (4.8) to vitisin B (4.39)

Impressively, the use of standard column chromatography (10:1 chloroform: methanol) was sufficient to isolate 40% (9 mg) of vitisin B (**4.39**). The authors also note the formation of a silver mirror during the reaction, which is consistent with the reduction of their silver acetate to metallic silver.[297]

4.3 De novo approaches to resveratrol trimers

The number of publications disclosing *de novo* approaches to resveratrol trimers and tetramers is scarce. At present, these reports wholly originate from the Stephenson[54,56] (see section) and Snyder[47,49] research groups. No reports of selective syntheses of pentamers or higher order oligomers are known.

The Snyder groups 2011 approach to dihydrobenzofuran containing trimers and tetramers was based on a stepwise oligomerization strategy (Figure 4.10).[49] This report details the use of bromination reagents: *n*-bromo succinimide (NBS) molecular bromine, and bromodiethylsulfonium bromopentachloroantimonate (BDSB). The final reagent, BDSB, was a custom bromonium reagent which the Snyder lab has recently reported for use in halonium-induced polyene cyclizations.[298] The key is that this first halogenation is selectivity determining, as this aromatic halogen (**4.45**, Figure 4.10) determines the placement of the final dihydrobenzofuran (**4.47**). The Snyder lab developed an eight step sequence which proceeds via

extension/homologation (**4.46**) to an aldehyde, followed by dihydrobenzofuran synthesis (**4.47**). The specifics of this route were covered in **section 2.2**.

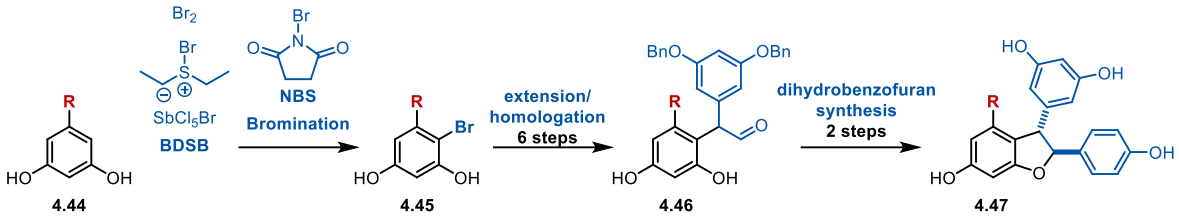


Figure 4.10 Snyder's dihydrobenzofuran synthesis *en route* to resveratrol trimers and tetramers

The first example of this chemistry in action is in the synthesis of a pallidol derived trimer and tetramer (**4.14**, **4.19**, Figure 4.11). A *tri*-brominated pallidol core, synthesized via the bromination of protected quadrangularin A (not shown), required halogen repositioning (**4.48**). This process is conceptually similar to a halogen dance[299] and exploits small reactivity difference in halogenated intermediates. By first removing both aromatic halogens with two equivalents of *n*-BuLi a re-halogenation with NBS proceeded with selectivity distal to the remaining aliphatic bromide. The authors remarked this selectivity was likely steric in nature. Once the halogen was correctly placed, the homologation sequence and dihydrobenzofuran synthesis provided carasiphenol C (**4.14**) in 3% yield over 20 steps. Similarly the bromination of **4.50** provided directly the *di*-bromide **4.51** which was converted to the *di*-dihydrobenzofuran ampelopsin H (**4.19**) in 2% yield over 20 steps.

Continuing with the same strategy a *per*-methylated ampelopsin F (**4.52**, Figure 4.12) was subjected to empirical halogenation conditions. The use of one equivalent of NBS provided **4.53** in 99% yield, which was homologated and followed by ring closure to provide carasiphenol B (**4.21**) in 3% yield over 20 steps. The most challenging halogenation was the formation of **4.54**, which required the use of sub-stoichiometric quantities of BDSB, as even at a cryogenic temperature (-78 °C) the dibromide (**4.56**) was formed. This impurity could not be separated from

the mono-bromide (**4.54**) complicating this route. The synthesis of ampelopsin G (**4.55**, 20 steps, 0.5% yield) was completed with the standard homologation and dihydrobenzofuran synthesis procedure. Comparatively the synthesis of **4.56** was simple as excess NBS provided it in quantitative yield. Resveratrol tetramer vaticanol C (**4.57**) was completed in 20 steps and 0.5% overall yield.

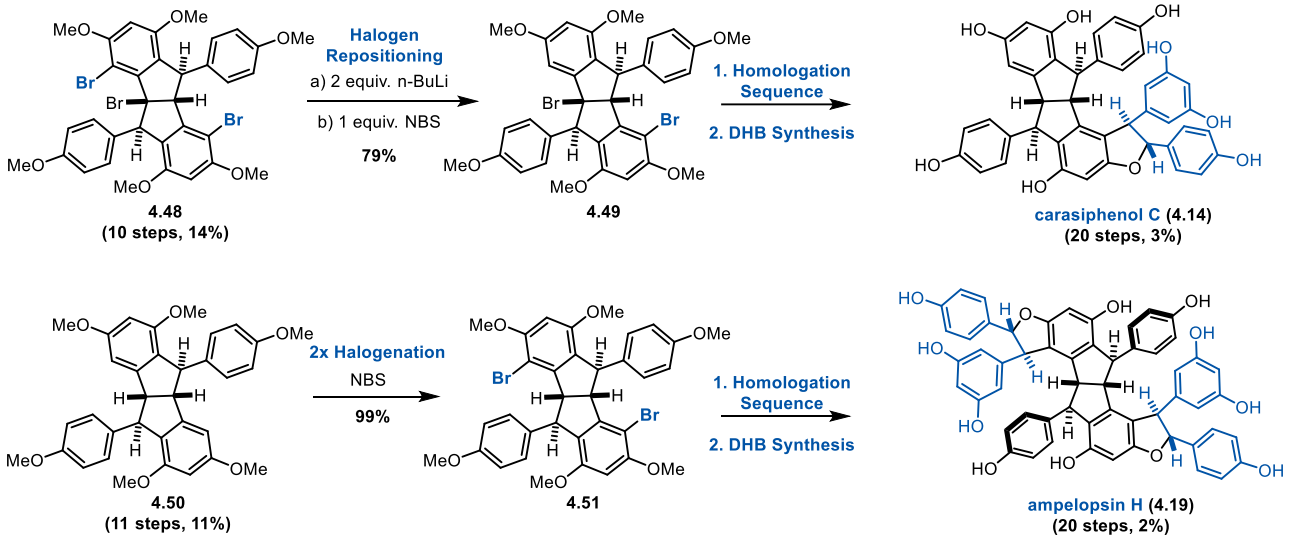


Figure 4.11 Snyder's total synthesis of pallidol derived trimer carasiphenol C and tetramer ampelopsin H

The key takeaways from this study are the use of stepwise oligomerization directed by halogens in the synthesis of dihydrobenzofurans. Due to the publication venue (**Nature**) many of the synthetic details are provided only in the supporting information. This report included an incredible amount of synthetic work, as the dimers presented as starting materials for this publication must be synthesized through stepwise paths as well. Furthermore, the homologation and dihydrobenzofuran sequence hid much of the synthetic complexity of the route, as this sequence along required eight synthetic steps.

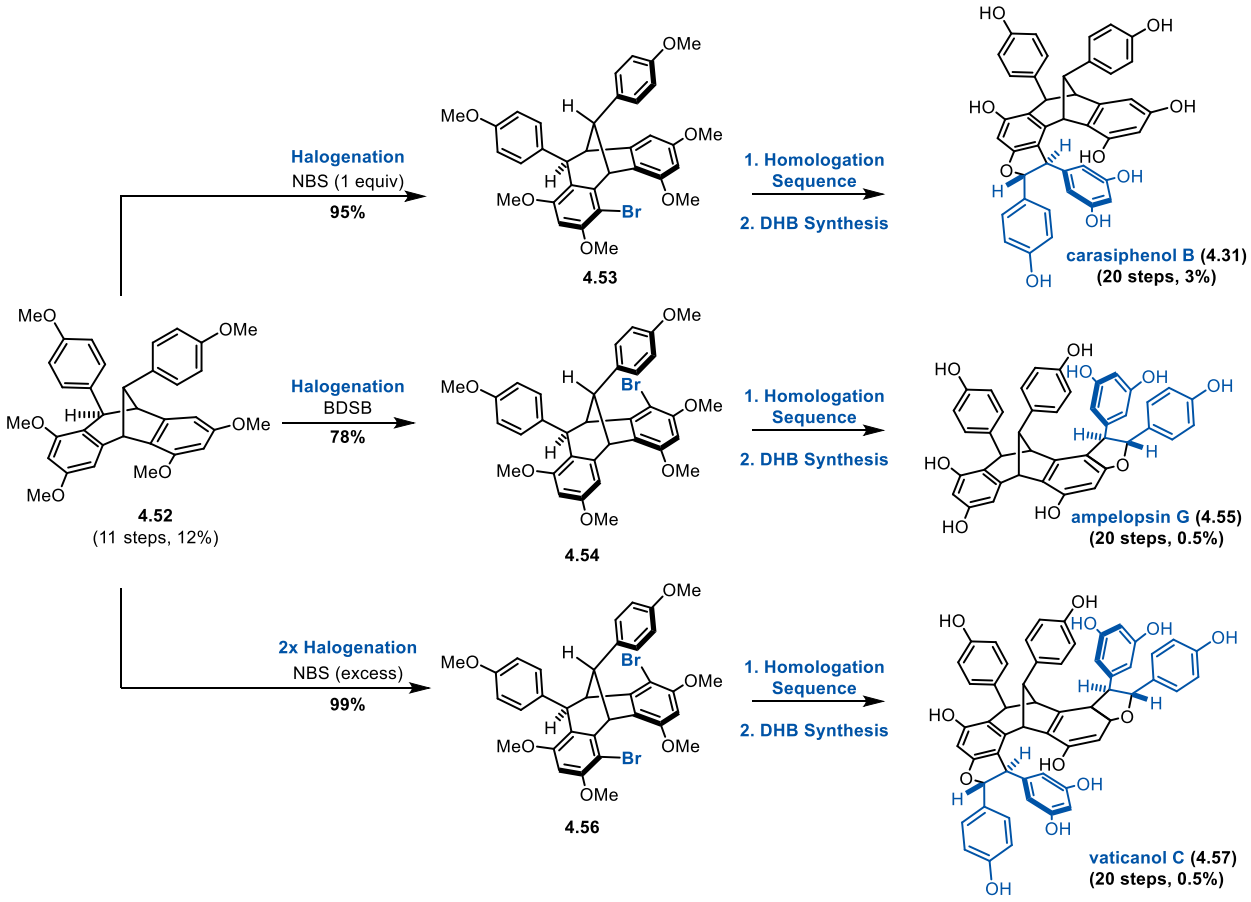


Figure 4.12 Snyder's total synthesis of ampelopsin F derived trimers and tetramers

A *tour de force* in organic synthesis which highlights the efficiency of Synder's homologation and dihydrobenzofuran synthesis procedure was reported in 2014 in the synthesis of caraphenol A (**4.67**, Figure 4.13).[48] This 9-member ring trimer was synthesized via a protected ketone (**4.58**), three steps removed from 3,5-dibenzyloxybenzyl alcohol (not shown). The standard homologation sequence and dihydrobenzofuran synthesis provided **4.59**, which was sequentially oxidized with DMP and $NaClO_2$ (Pinnick oxidation)[300] to a carboxylic acid which was alkylated with **4.60** providing ester **4.61**. A creative anionic Fries rearrangement provided ketone **4.62**.[301,302] A short benzofuran synthesis closed the ring, notably missing the reduction (H_2, Pd/C) and epimerization (HCl, MeOH) used in Snyder's dihydrobenzofuran synthesis. Thermal conversion of atropisomer[303,304] affords **4.64** which is sequentially oxidized (DMP) and attacked with vinyl

lithium providing allylic alcohol **4.65**. Methanesulfonic acid (MsOH) promotes the key *9-exo-trig* cyclization followed by oxidation to diol (OsO_4) and periodate cleavage ($NaIO_4$) to give aldehyde **4.66**. Final dihydrobenzofuran synthesis affords carasiphenol C (**4.67**) in 8% overall yield over 23 steps. More than 600 mg of this trimer was synthesized, with all steps conducted on gram scale and an average yield >89%. The scale and efficiency of this route is unprecedented not just in the resveratrol oligomer class, but among any total syntheses of similar length and complexity.[305]

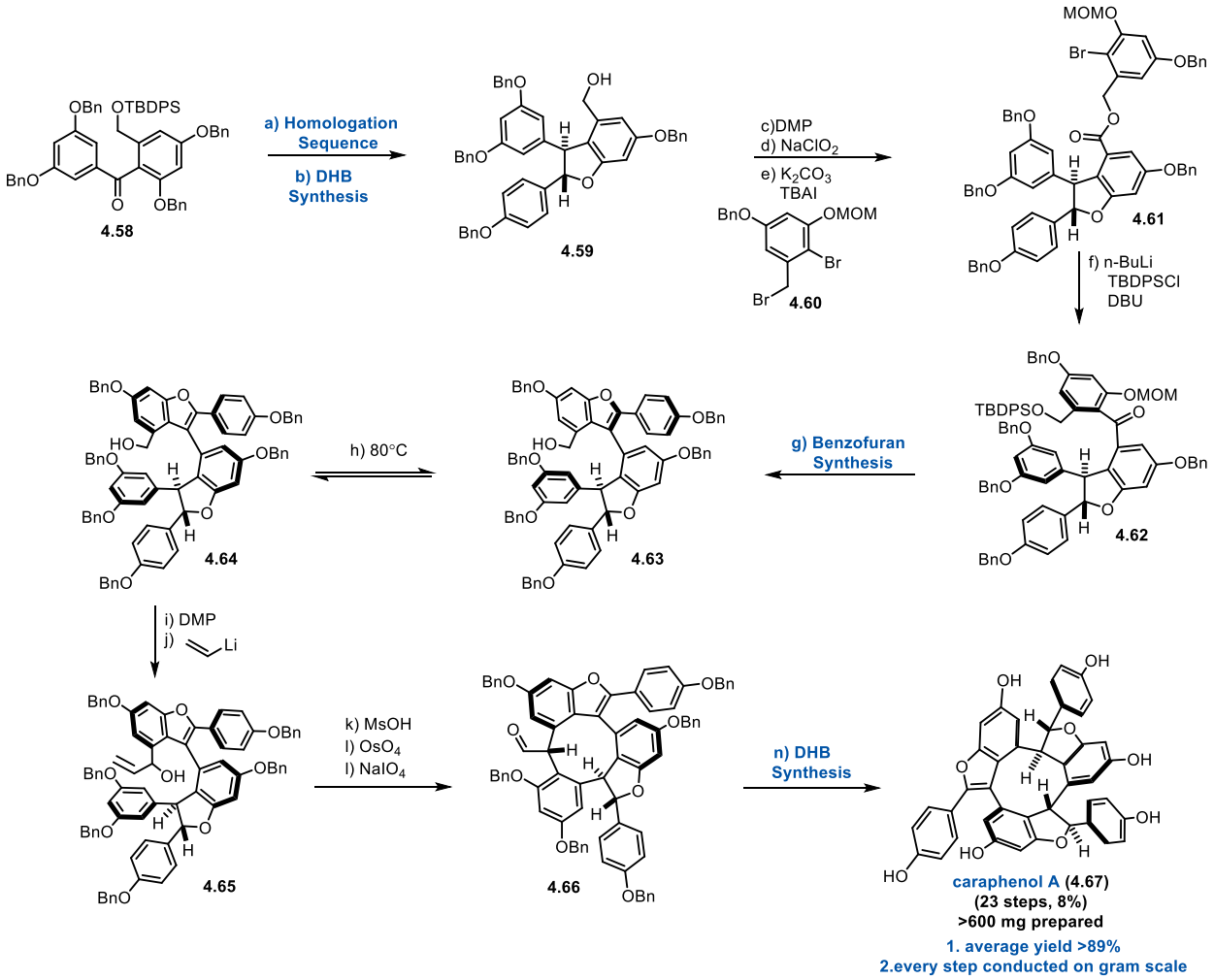


Figure 4.13 Snyder's gram scale synthesis of caraphenol A via homologation and DHB synthesis

The Snyder lab's synthesis of [7,5] carbocycle trimer vaticanol A (**4.27**, Figure 4.14) follows a similar mechanistic logic as past syntheses from the same group. Protected pauciflorol

F (**4.68**) was obtained from their past synthetic studies on the molecule in eights steps and 44% yield.[257,262]

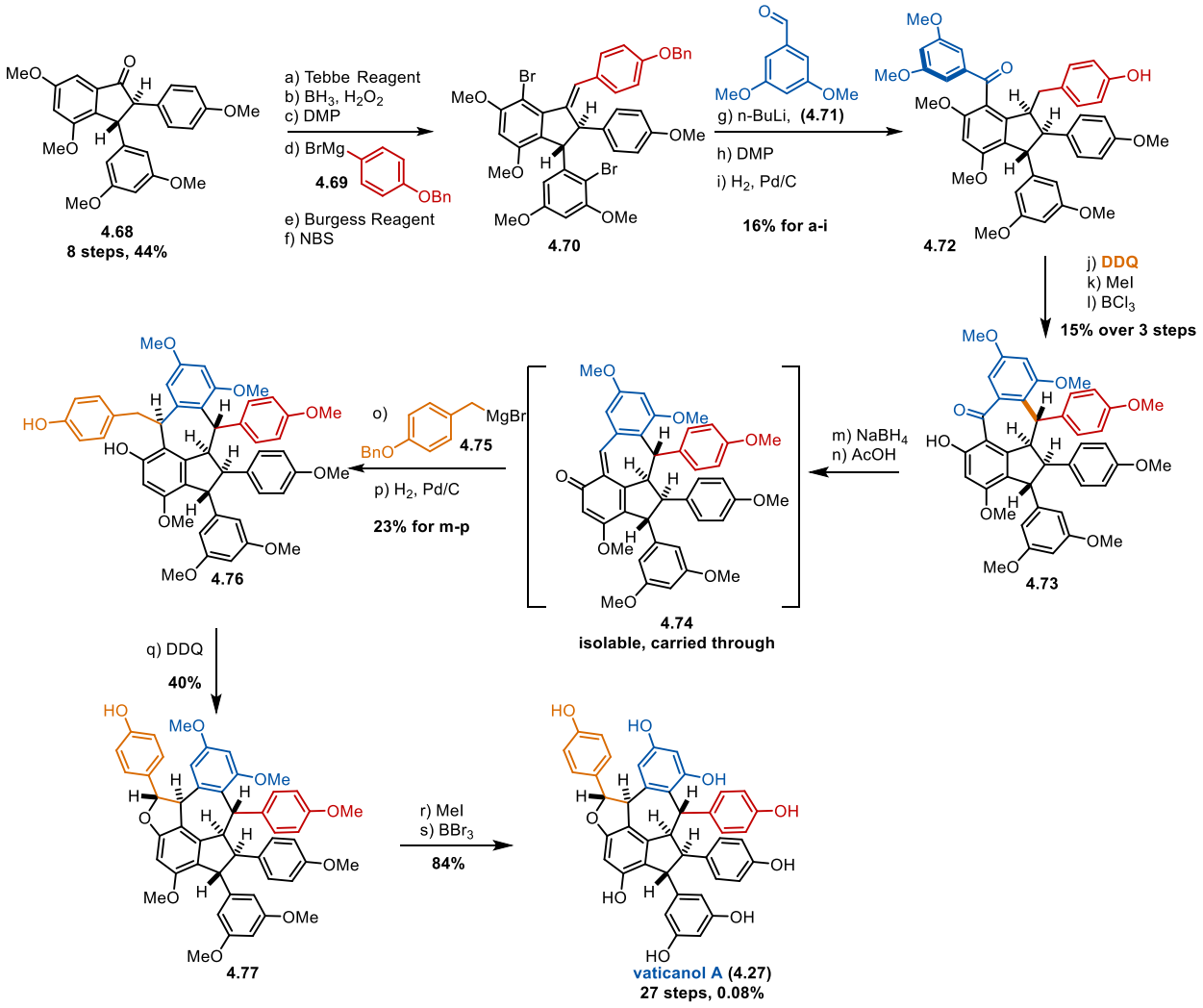


Figure 4.14 Snyder's total synthesis of resveratrol trimer vaticanol A

Homologation proceeded via Tebbe olefination, hydroboration, DMP oxidation, Grignard addition (with **4.69**) and dehydration. Bromination (NBS) afforded **4.70** with differential protection on the recently added phenol. Lithium halogen exchange (*n*-BuLi) and addition of electrophile (**4.71**) was succeeded by oxidation (DMP) and benzyl protecting group removal (**H2**, Pd/C) to generate **4.72** in 16% over 9 steps. A screen of oxidants found that DDQ was uniquely able to cyclize **4.72** with other oxidants found to be unreactive (CAN, Ag_2O, $PhI(OAc)_2$, MnO_2,

etc.). This transformation produced a 1:1 mixture of diastereomers. Re-methylation and selective demethylation of a single phenol provided **4.73**. This was rationalized as electrostatic control from the proximal carbonyl. Borohydride reduction and acidic elimination of secondary alcohol provided *ortho*-quinone methide (**4.74**) which was attacked with Grignard (**4.75**) and deprotected (H_2, Pd/C) to form **4.76**. Another DDQ oxidation generated quinone which spontaneously cyclized to dihydrobenzofuran (**4.77**). The authors noted that global de-methylation with BBr_3 was unsuccessful initially and required protection of the lone phenol with MeI for deprotection to be successful. They suggested the solubility profile in the deprotection is critical to success. Vaticanol A (**4.27**) was synthesized in 27 steps and 0.08% overall yield. This contrasts from the Synder groups synthesis of caraphenol A (**4.67**, Figure 4.13) which was published in the same year. The synthesis of vaticanol A is more typical in its overall yield considering the complexity and length of the synthesis with 0.9 mg of the natural product synthesized.

4.4 The use of C3 *tert*-butyl protection towards resveratrol trimers davidiol A and distichol

The Stephenson lab has a longstanding interest in the total synthesis of the indane derived resveratrol trimers davidiol A (**4.77**, Figure 4.15)[292] and distichol (**4.80**, Figure 4.15).[306] First postulated in the PhD thesis of Dr. Bryan Matsuura,[307] and also mentioned by Dr. Mitch Keylor,[308] distichol was listed as a synthetic target for further exploration. The first synthetic studies towards these molecules were completed by Dr. Kevin Romero, being the first to synthesize the core of the molecules.[309] This work was continued by both Dr. Bec Roldan[310] and Dr. Matthew Galliher,[311] in efforts to remove the *tert*-butyl protecting groups and find creative solutions to synthesize the core of the molecule more efficiently.

All synthetic studies in the Stephenson lab have followed a stepwise oligomerization strategy where a phenol (**4.79**, **4.82**, Figure 4.15) is oligomerized via a radical coupling to form a

dihydrobenzofuran (**4.78**, **4.81**). A final *5-exo-trig* cyclization provides the natural product davidiol A (**4.77**) or distichol (**4.80**). The selectivity determining step is the radical coupling in the dihydrobenzofuran synthesis. The Stephenson lab has used three key indane cores (**4.83**, **4.84**, **4.85**). The first, **4.83**, has two sites for radical oligomerization, with both davidiol A and distichol synthesizable from a single divergent indane. This strategy was first used by Dr. Kevin Romero and remains the most robust synthetic method. To achieve selectivity in dihydrobenzofuran synthesis a differentiation of the phenols is required. Indane **4.84** achieves this by selective protection of the resorcinol rings, a strategy first employed by Dr. Bec Roldan. A final strategy used by Dr. Matthew Galliher takes advantage of alkene geometry to block the eastern resorcinol ring of **4.85** providing selectivity towards davidiol A.

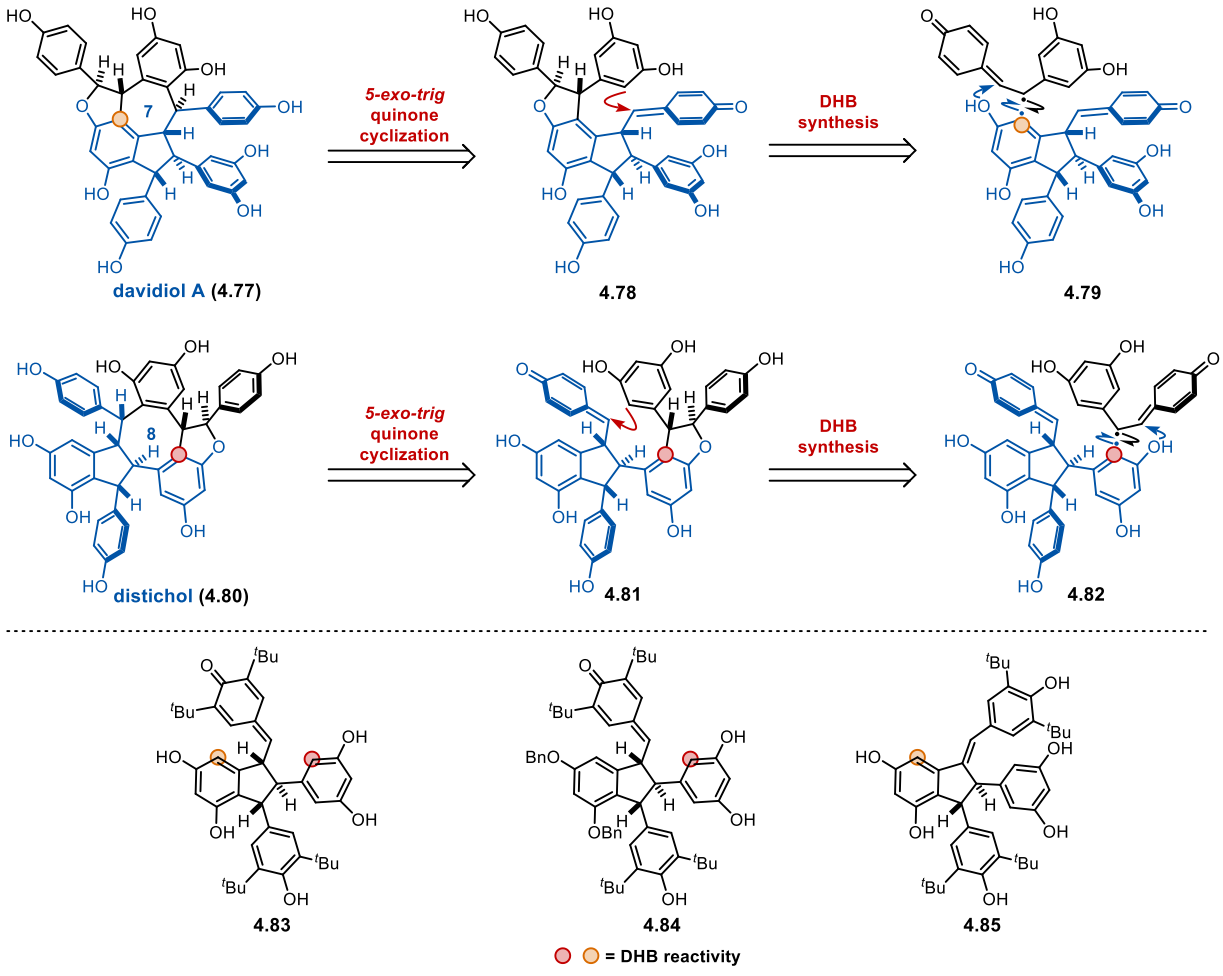


Figure 4.15 Synthetic strategy and elements of control towards davidiol A and distichol

As a brief review of Dr. Kevin Romero's work towards davidiol A and distichol *bis*-quinone methide (**4.86**, Figure 4.16) is cyclized with trifluoroacetic acid in nitromethane to indane **4.87**. This cyclization generated exclusively *trans* diastereomer via persistent radical equilibrium mediated cyclization. A complete reduction ($NaBH_4$, Pd/C, H_2) followed by reoxidation (DDQ) provided **4.83** the substrate for oligomerization with *bis*-quinone methide (**4.86**). Microwave irradiation for three hours at 100 °C affords the two trimeric indanes **4.88** (18%) and **4.90** (30%). The approximately double yield of **4.90** can be rationalized as the two resorcinol sites are equivalent via rotation. Each trimer is elaborated via cyclization onto the quinone with acid (TFA) and benzyl deprotection (Pd/C, H_2) to form the *hexa-tert*-butylated natural product analogues **4.89** and **4.91**.

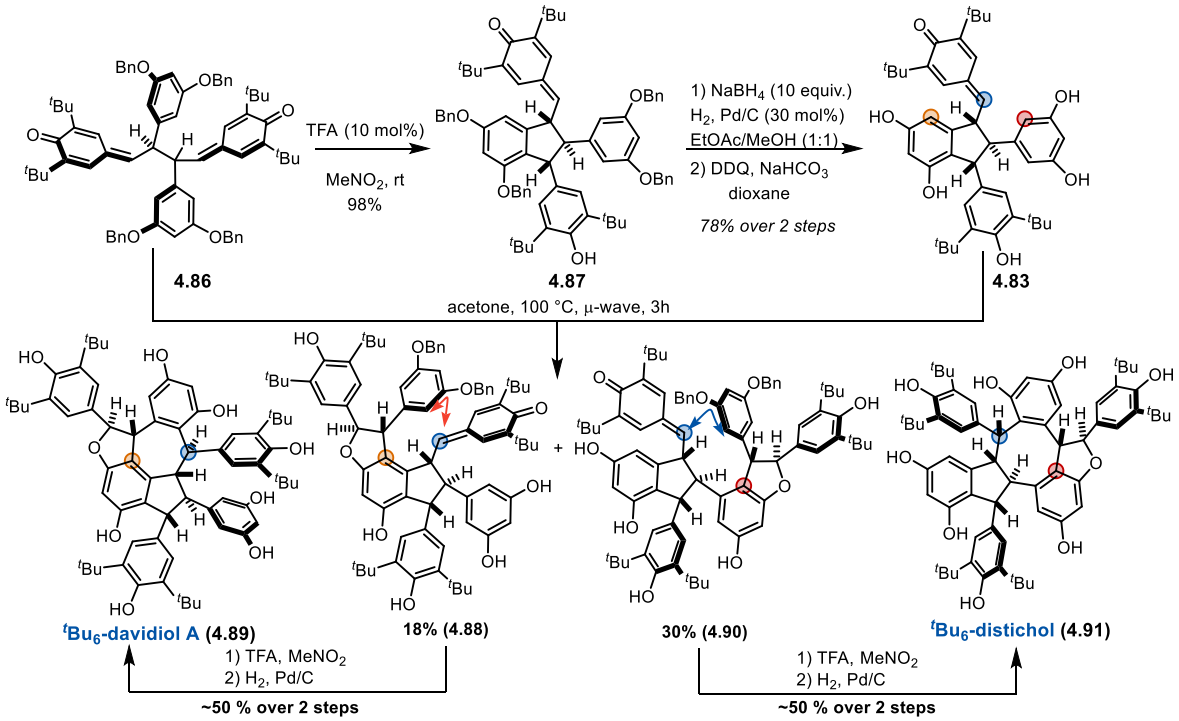


Figure 4.16 Dr. Kevin Romero's approach to ^{t}Bu$_6$-davidiol A and to ^{t}Bu$_6$-distichol

In 2022 we were motivated to build on the result of Dr. Bec Roldan (Figure 4.17) in the formation of a crossover indane (**4.84**). The hypothesis was that this method could streamline the

synthesis of *tert*-butylated trimers which would allow a more rigorous screening of deprotection conditions. The mechanistic rationale for this cyclization selectivity was not fully understood at the time.

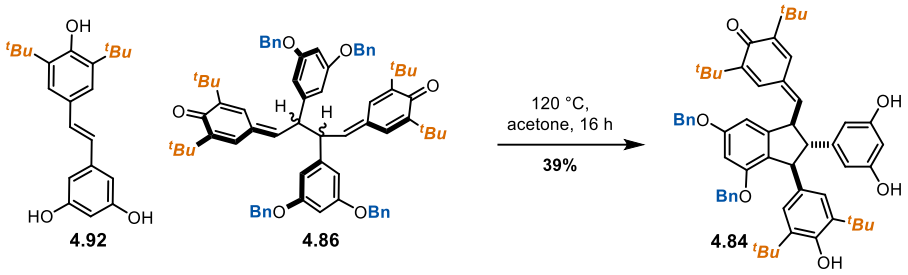
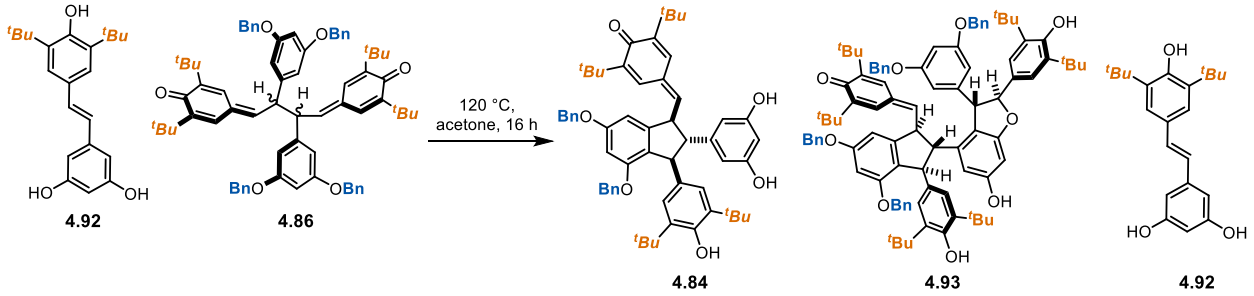


Figure 4.17 Dr. Bec Roldan's crossover cyclization to form partially benzylated indane

Building on Dr. Roldan's earlier studies we pursued a one pot strategy where crossover indane (**4.84**, Figure 4.18) would form dihydrobenzofuran (**4.93**) in a single reaction. A screen of conditions found that the key parameter was temperature, with at least 100 °C required for trimer formation. These studies provided weak validation of this strategy, but it was challenging to cleanly isolate trimeric material which existed as a set of *trans* dihydrobenzofuran diastereomers in a reaction mixture containing > 10 minor products.



Temp (°C)	Time (h)	Conc. (M)	4.84 (%)	4.93 (%)
130	19	0.02	7	13
130	16	0.02	25	6
80	16	0.05	20	0
80	16	0.05	23	0
80	32	0.05	48	0
90	16	0.05	22	0
100	16	0.05	44	7
120	16	0.05	47	15
120	40	0.05	7	24

Figure 4.18 One pot thermal crossover dihydrobenzofuran oligomerization towards distichol

To more closely follow the precedent of Dr. Kevin Romero we synthesized *bis*-quinone methide **4.97** via Wittig coupling and electrochemical homodimerization. This dimer was designed with TIPS instead of the Bn blocking groups previously used, as it was hypothesized that after cyclization the resultant indane could be deprotected with fluoride or acid, avoiding the reduction and re-oxidation technique formerly employed.

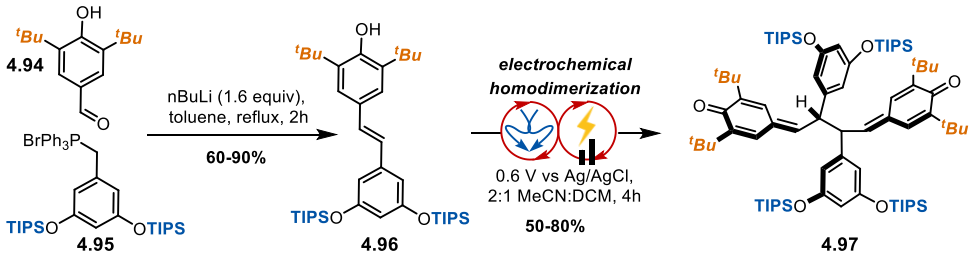
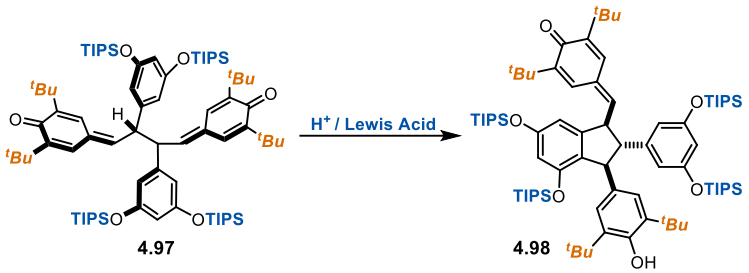


Figure 4.19 Synthesis of C3 *tert*-butyl O-TIPS *bis*-quinone methide

The strategy was to directly cyclize **4.97** (Table 4.1) to indane **4.98** through either Brønsted or Lewis acidic conditions. The standard nitromethane and trifluoroacetic acid conditions struggled to convert the starting material and resulted in 15% of **4.97**. The mass balance was unreacted starting material. It is likely the nitromethane conditions are highly substrate specific, as with **4.86**, the original substrate, partial solubility was observed, a characteristic that is not well conserved when substituting benzyl ethers for the large alkyl derived TIPS. Heating the reaction often led to higher conversion but was observed alongside decomposition of the starting material **4.97**. Desilylation with TBAF to increase nucleophilicity of the resorcinol ring nucleophile also led to decomposition.

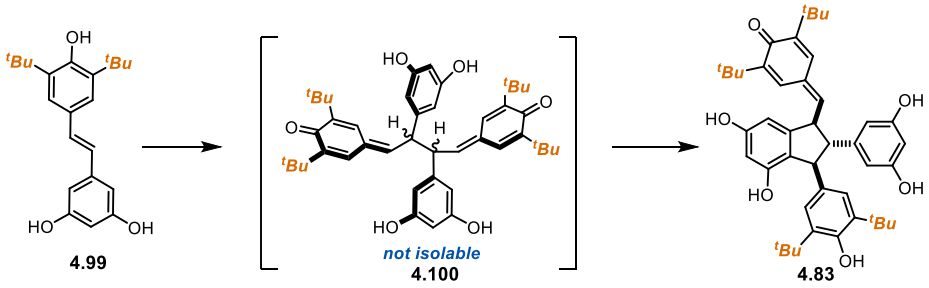
Table 4.1 Attempts to cyclize *tert*-butyl, TIPS protected BQM to indane



Temp (°C)	Time (h)	Solvent	Reagent	4.98 (%)
120	16	acetone	$ZnCl_2$	<5
120	16	acetone	-	10
120	16	acetone	$Zn(OTf)_2$	<5
120	16	acetone	$Sc(OTf)_3$	-
120	16	acetone	$Bi(OTf)_3$	-
rt	16	nitromethane	TFA	15
rt	18	acetone	TFA	10
rt	16	ethanol	HCl	-
120	16	acetonitrile	-	-
120	2	DMF	-	-
120	2	acetone	-	-
140	16	acetone	-	-
120	16	acetone	TFA	25
120	16	acetone	TFA	35
120	16	acetone	TFA	10
120	16	acetone	TBAF	10

To circumvent the issues with *bis*-quinone methide cyclization a stilbene (**4.99**, Table 4.2) was employed in direct oxidation and cyclization to **4.83**. This strategy would directly provide free resorcinol indane required for dihydrobenzofuran oligomerization studies towards trimers. In the quest for synthetic efficiency this reaction was thoroughly optimized. Chronologically this was not the first time this reaction had been explored which explains the persistence to use silver acetate as oxidant (see Section 4.5). In this transformation the stilbene (**4.99**) undergoes single electron oxidation and radical coupling to **4.100** followed by *5-exo-trig* cyclization to **4.83**. Fortunately, the *bis*-quinone methide **4.100** was identifiable via crude ^{1}H NMR which greatly aided in optimization. A brief screen of conditions found that elevated temperatures led to degradation and DCM as optimal solvent. In many of the DCM trials crude ^{1}H NMR revealed mostly **4.100** with less than 10% **4.83**.

Table 4.2 Direct oxidation cyclization cascade of C3 *tert*-butyl stilbene



Solvent	Temp (°C)	Oxidant (eq)	Additive (eq)	Time	Yield (^{1}H NMR)	
THF	rt	AgOAc (3)		16	15%	
DCM	40	AgOAc (6)		16	30% (dirty)	Elevated Temperature = Degradation
Acetone	70	AgOAc (6)		16	unknown byproduct	
THF	70	AgOAc (6)		16	degradation	
DCM	rt	AgOAc (6)		16	dirty	
Acetone	rt	AgOAc (6)		16	40%	
THF	rt	AgOAc (6)		16	35%	
THF	rt	AgOAc (6)		16	unknown byproduct	
DCM	rt	Ag_2O (2)		16	No conversion	Literature Conditions = Unreliable
Acetone	rt	AgOAc (2)		16	BQM (85%)	
DCM	rt	AgOAc (4)		16	30%	
THF	rt	AgOAc (4)		16	35%	
DCM	rt	AgOAc (4)	$ZnCl_2$ (15)	2+4	15%	Filter off Metal (2h) and Add Lewis Acid
THF	rt	AgOAc (4)	$ZnCl_2$ (15)	2+4	degradation	
DCM	rt	AgOAc (4)	$ZnCl_2$ (2)	2+4	<10%	Filter off Metal (2h) and Add Lewis Acid
DCM	rt	AgOAc (4)	$ZnBr_2$ (2)	2+4	<10%	
DCM	rt	AgOAc (4)	$ZnOTf_2$ (2)	2+4	15%	
DCM	rt	AgOAc (4)	TFA (0.5)	2+4	degradation	
DCM	rt	AgOAc (4)	$ZnCl_2$ (2)	2+4	20%	No Filter (2h) and Add Lewis Acid
DCM	rt	AgOAc (4)	$ZnBr_2$ (2)	2+4	80%	
DCM	rt	AgOAc (4)	$ZnOTf_2$ (2)	2+4	40%	
DCM	rt	AgOAc (4)	TFA (0.5)	2+4	degradation	
DCM	rt	AgOAc (4)	$ZnBr_2$ (2)	2+1	40%	Filter off Metal (2h) and Add Lewis Acid Glovebox $ZnCl_2$
DCM	rt	AgOAc (4)	$ZnCl_2$ (2)	2+1	70%	
DCM	rt	AgOAc (4)	$ZnCl_2$ (2)	2+1	80% (40% isolated)	
DCM	rt	AgOAc (4)	$ZnCl_2$ (4)	2+1	<30%	
DCM	rt	AgOAc (4)	$ZnCl_2$ (1)	2+1	40%	
DCM	rt	AgOAc (4)	$ZnCl_2$ (2+2)	2+1	<20%	
DCM	rt	AgOAc (4)	$ZnCl_2$ (2)	2+X	30-70%	X of 1 h good for small scale (<50 mg) for 50-200 mg need 2 h
DCM	rt	AgOAc (4)	$ZnCl_2$ (2)	2+2	27% 27 mg	50 °C rotavap dry load
DCM	rt	AgOAc (4)	$ZnCl_2$ (2)	2+2	42% 42 mg	20 °C rotavap dry load
DCM	rt	AgOAc (4)	$ZnCl_2$ (2)	2+2	49% 49 mg	20 °C rotavap dry load

This motivated us to find a cyclization inducing reagent which could help push the reaction to completion. Initial efforts to filter the reaction and remove the silver acetate followed by addition of Lewis acid were uniformly unsuccessful. We postulate this was due to the instability of **4.100**. Ultimately zinc chloride fresh from the glovebox was required, with reaction time of 2+2,

indicating two hours of stirring with silver acetate followed by two hours of reaction time after addition of zinc chloride. The quality of Lewis acid is paramount, as over the course of optimization the zinc salts (chloride, bromide) saw a drop in yield as they became contaminated with water. A workup procedure involving cold evaporation of solvent led to a ~50% yield which was found to be reproducible irrespective of scale. This was deemed adequate for further studies given the complexity of optimization and value of product synthesized.

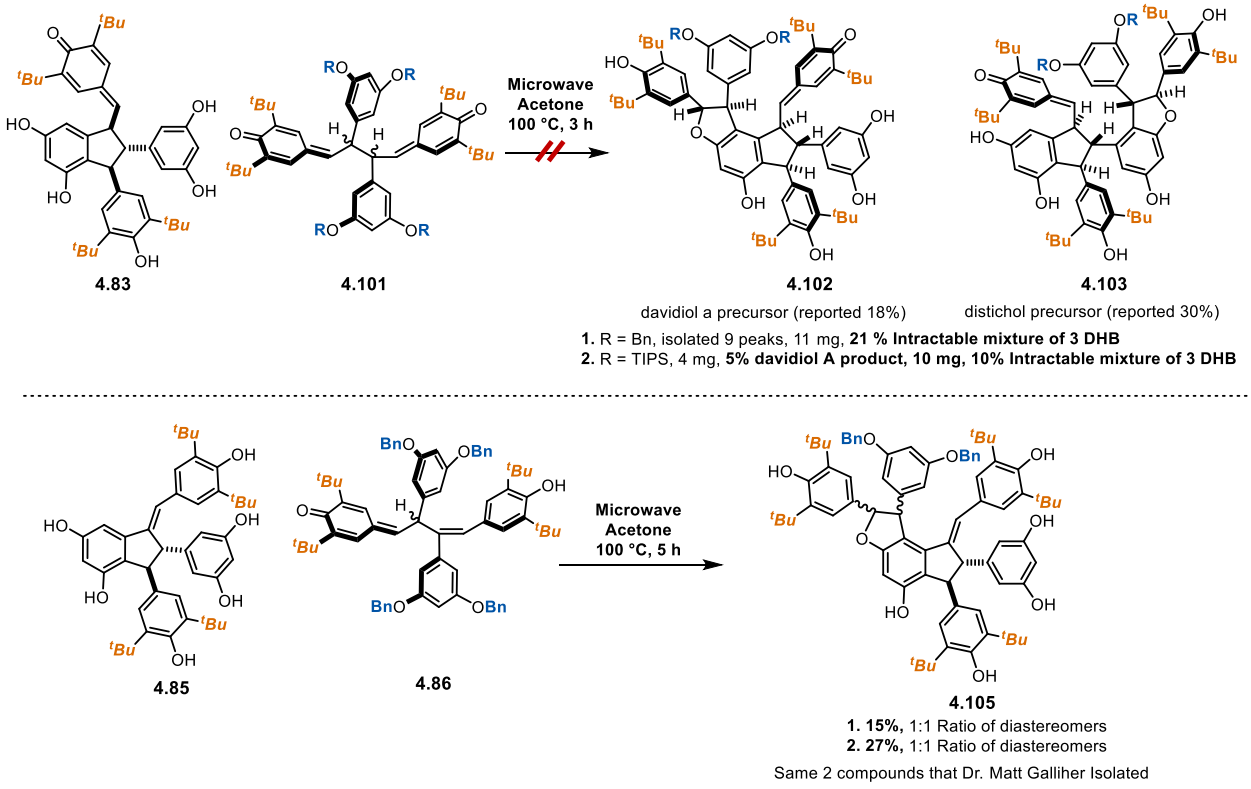


Figure 4.20 Microwave oligomerization replication of Stephenson lab precedent towards davidiol A and distichol

With indane dimer in hand (**4.83**, Figure 4.20) a replication of Dr. Kevin Romero's conditions was attempted. From silica gel column chromatography nine peaks were isolated, with one of them containing 21% of a mixture of three intractable dihydrobenzofurans. The use of a silylated *bis*-quinone methide **4.101** aided in the chromatographic isolation of **4.102** (5 mg, 5%) while **4.103** was isolated as a mixture of at least three dihydrobenzofurans. The use of preparative

TLC did provide useful. In contrast the use of **4.85** was cleanly oligomerized with **4.86** to **4.105** using the conditions reported by Dr. Matthew Galliher in similar yields. The spectral data for the two *trans*-dihydrobenzofuran diastereomers isolated matched those previously reported.[311]

To prepare another unique indane core the crossover cyclization developed by Dr. Bec Roldan was examined. A short optimization campaign, aided by the use of a microwave reactor, provided a distribution of cyclized products (**4.84**, **4.87**, **4.101**, Figure 4.21). The yield of **4.84** is comparable to past reports (41% vs 39%) but the isolation of **4.87** and detection of **4.101** was novel. Subjecting the crossover indane dimer (**4.84**) to microwave oligomerization conditions provided a set of five fraction after silica gel column chromatography, none of which contained any distinctive dihydrobenzofuran peaks via ^{1}H, COSY, or HSQC NMR techniques.

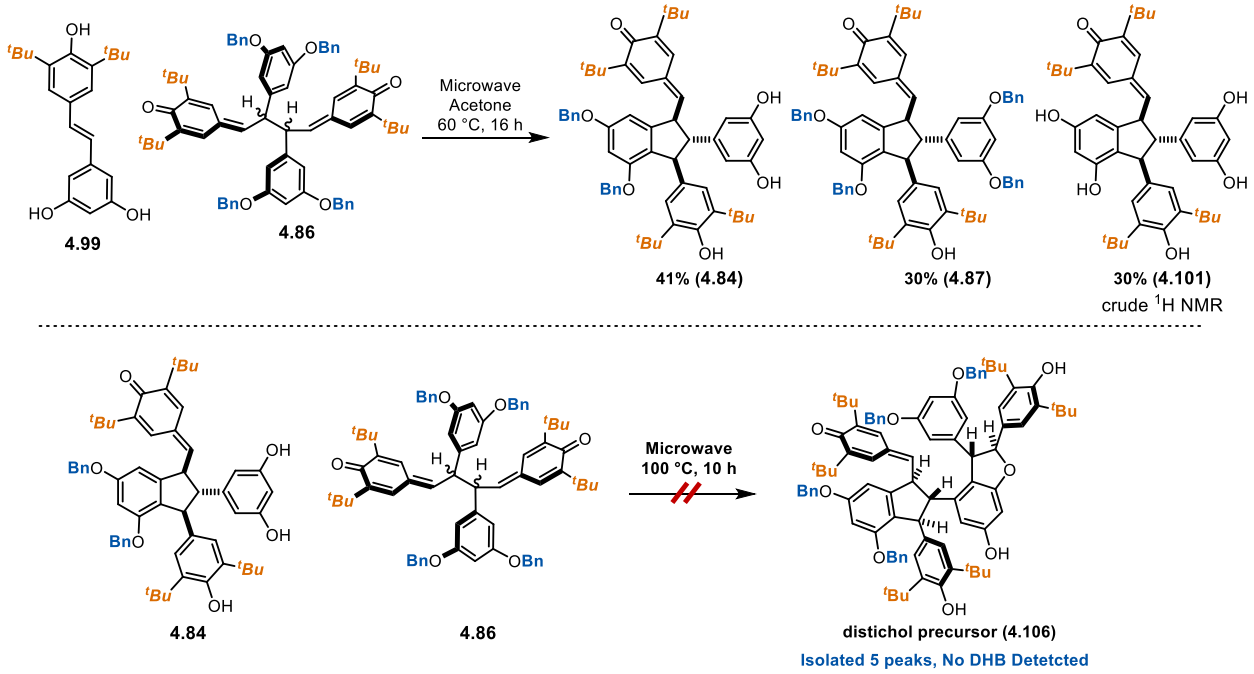


Figure 4.21 Crossover cyclization in a stepwise strategy towards distichol

A final strategy briefly explored was the reductive ring opening of a dihydrobenzofuran to aid in *tert*-butyl deprotection (Figure 4.22). This strategy was first reported by Dr. Matthew Galliher.[311] A model substrate derived from orcinol (**4.107**) was prepared and subjected to

reductive conditions. While DIBAL-H, borane, and LAH did not yield productive chemistry, the same conditions previously reported ($LiBHEt_3$, super hydride) did cleanly ring open the dihydrobenzofuran (**4.109**).

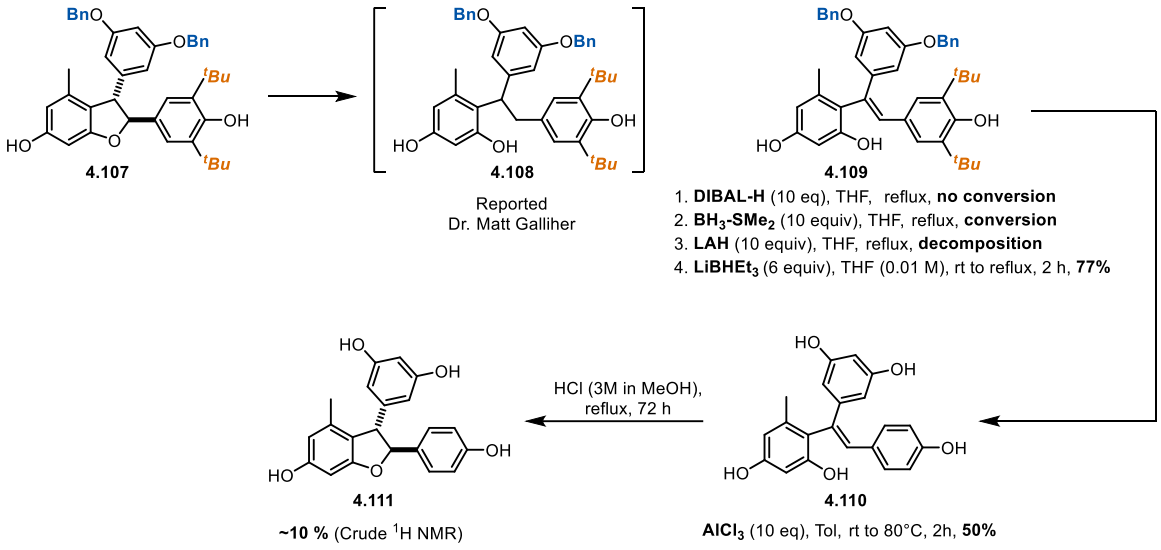


Figure 4.22 Reductive ring opening of dihydrobenzofuran as a *tert*-butyl removal strategy

Notably the compound isolated and characterized differs in unsaturation to that reported by Dr. Matt Galliher (**4.108**). The removal of the *tert*-butyl groups with aluminum chloride provided **4.110** in 50% yield. Ring close to the dihydrobenzofuran was detected in refluxing 3M methanolic HCl, but this route was not further explored.

4.5 Synthetic studies towards davidiol A and distichol with C3 silyl groups

To find an all-encompassing solution to the challenges encountered using C3 *tert*-butyl groups, a revised strategy was proposed. This consisted of two main strategic changes. First, altering the indane core from **4.83** (Figure 4.23) with *tert*-butyl groups to silyl groups (**4.112**) to allow for their removal at the end of the synthesis and second the use of TIPS protected *bis*-quinone methide **4.113** which was validated on resveratrol dimers (see Chapter 3).

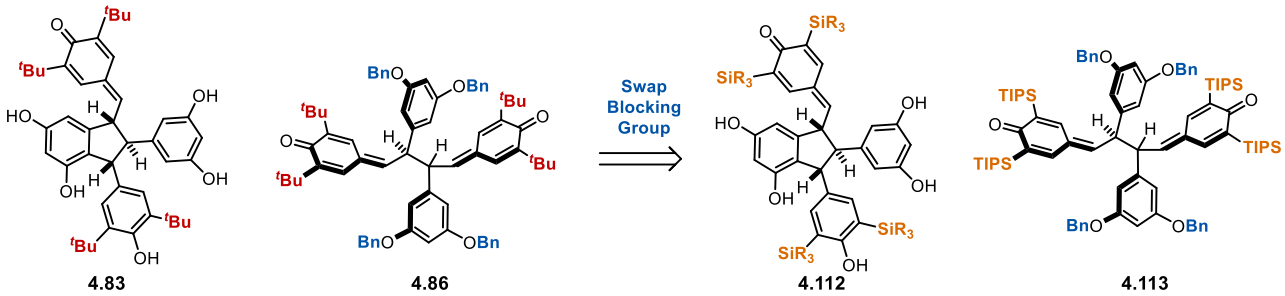
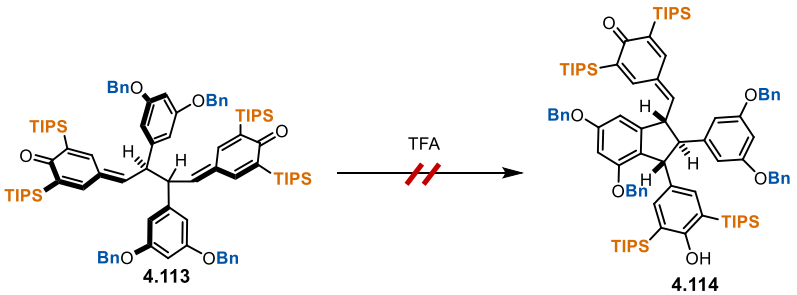


Figure 4.23 Synthetic strategy of using C3 silyl groups on indane core

While these changes were not trivial and their synthesis was unknown, it was determined that these risks were warranted given the great challenges associated with removal of the C3 *tert*-butyl groups.

4.5.1 The use of C3 TIPS groups

From the outset the strategy was to follow the steps precedented in the use of *tert*-butyl protecting groups in the synthesis of an indane (**4.114**, Figure 4.24) from BQM (**4.113**). The use of sub stoichiometric equivalents of TFA resulted in no conversion even at elevated temperatures. Disproportionation to stilbene was also observed in some instances. Increasing the molar equivalents of acid resulted in small quantities of cyclized products, along with decomposition, likely from removal of the C3 TIPS groups.



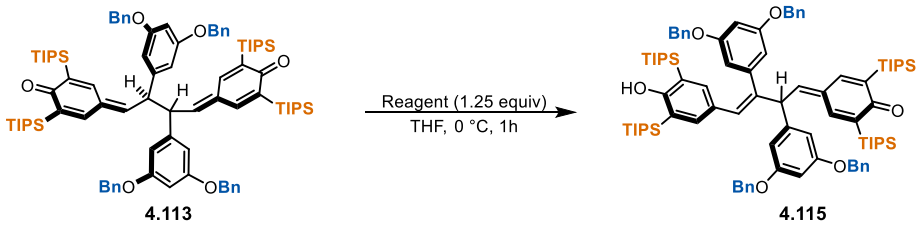
TFA equiv	Solvent	Temp (°C)	Time (h)	Result
0.1	$MeNO_2$	RT	2	No conversion, solubility issues
0.1	Acetone	RT	2	No conversion
0.1	Acetone	RT	16	No conversion
0.1	Acetone	50	16	No conversion
0.1	Acetone	120	16	TIPS-OBn-Stilbene Monomer
3.0	Acetone	120	16	~20% product, intractable

Figure 4.24 Attempts to cyclize TIPS BQM with trifluoroacetic acid

These results confirm that Brønsted acid cyclization is substrate dependent as the *tert*-butyl BQM, with partial solubility, cyclized under these conditions in near quantitative yield.

An alternative strategy of tautomerization followed by cyclization was pursued as these conditions employed strong Lewis acid for cyclization which was postulated to circumvent the lower propensity for cyclization of the TIPS BQM. Direct exposure of **4.113** to strong Lewis acid (BCl_3, BF_3) led to a low yield of many cyclized products, as analogous chemistry was reported the Stephenson lab.[196] The use of various strong bases (Table 4.3) provided the tautomer **4.115** in synthetically useful yields. The source of strong base and counterion were likely inconsequential, but it was paramount to use the correct molar equivalence. This was required as excess base led to decomposition, whereas substoichiometric quantities left BQM (**4.113**) which was inseparable from tautomer **4.115**. Ultimately preparing a stock solution of NaHMDS from a solid stored in the glovebox provided the most consistent yields (70-80%) when reacted for 1 hour at 0 °C with slow addition of the base to minimize exotherm.

Table 4.3 Tautomerization of TIPS BQM with strong base



Reagent	Scale (mg)	Yield (%)
KHMDS (glovebox)	15	57
LiHMDS (bottled solution)	15	43
NaHMDS (glovebox)	15	71
KO^{t}Bu, 18-crown-6	15	59
NaHMDS (glovebox)	100	73
NaHMDS (glovebox)	100	74

With **4.115** in hand (Figure 4.25) cyclization with boron trifluoride at cryogenic temperatures was precedented with *tert*-butyl groups to provide *5-exo-trig* cyclization to indane (analogue to **4.116**). Instead, *6-exo-trig* cyclization to **4.117** in 40-70% yield occurred. Varying temperature, reaction time, and equivalents of Lewis acid was found to have no effect on this

selectivity. The *6-exo-trig* product was not immediately identified, and it was only after benzyl deprotection to **4.118** and the structure was rigorously characterized by 1D and 2D NMR, HRMS, and single X-ray crystallography that the structure was confirmed. The origins of this selectivity are not fully understood, but we hypothesized that it was the conformation of the tautomer with large silyl groups preferenced the molecule for *6-exo-trig* cyclization. While not immediately synthetically useful, this dimeric resveratrol core is the same as gnetifolin P and the synthesis of this *ortho*-methoxy variant is being explore by a talented 1st year PhD student Sarah Maffett.[312] We also postulate that the TIPS deprotected derivative of **4.118** (not shown) is also a natural product, but has not yet been isolated.

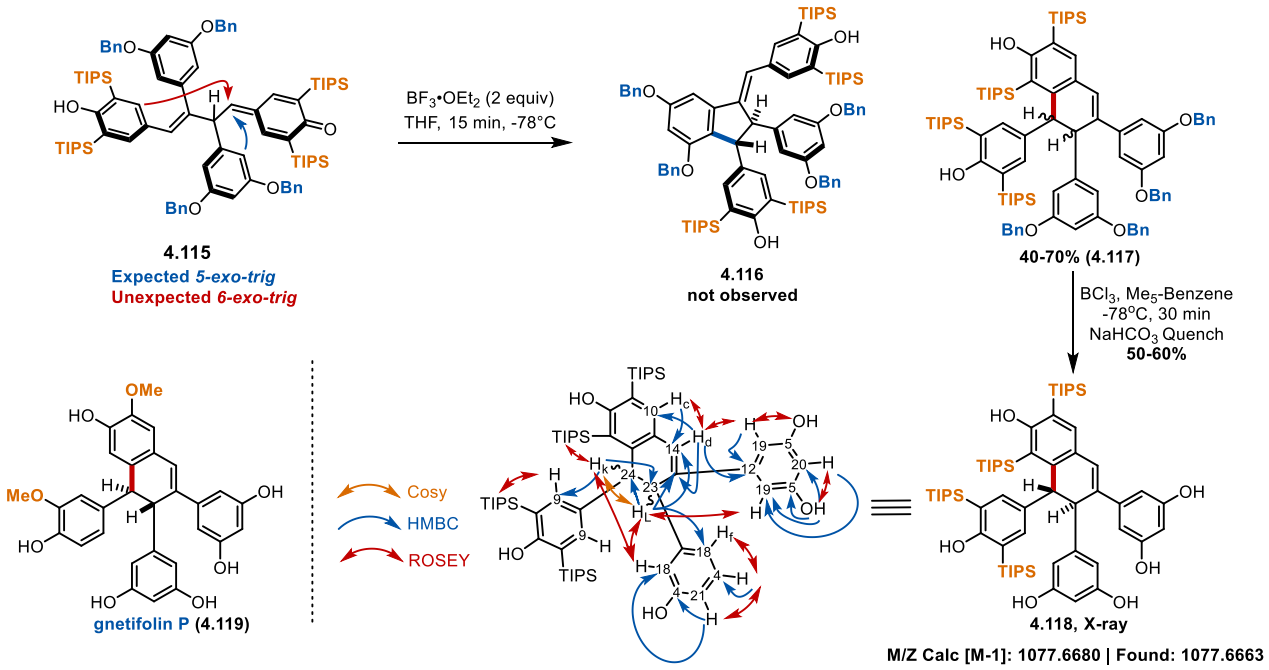


Figure 4.25 Lewis acid cyclization of BQM tautomer provides unexpected *6-exo-trig* cyclization

We chose to revisit the Lewis acid cyclization of BQM **4.113** (Figure 4.26) and quickly found that strong Lewis acids were not productive (entries 1 and 2). Screening with a weak Lewis acid ($ZnCl_2$) to allow for diastereoselectivity via persistent radical equilibrium found success using $ZnCl_2$ (1 M solution in THF) at 120 °C in a sealed tube for 1 hour. This provided quantitative

conversion to indane **4.114** and was found to be highly scalable. Approximately one gram of this material was prepared. Solid $ZnCl_2$ was less reproducible, even when dissolved into a THF stock solution, due to its hygroscopic nature. Removal of phenolic benzyl protected groups with reported conditions of Pd/C, H_2 and $NaBH_4$ to ensure complete quinone reduction provided **4.120** in 40-70% yield. The re-oxidation to quinone **4.121** with DDQ was difficult to analyze and reproduce due to the large quantities of highly UV active oxidant required to observe any conversion. This is another instance where the additional steric bulk of the TIPS protected indane alters reactivity.

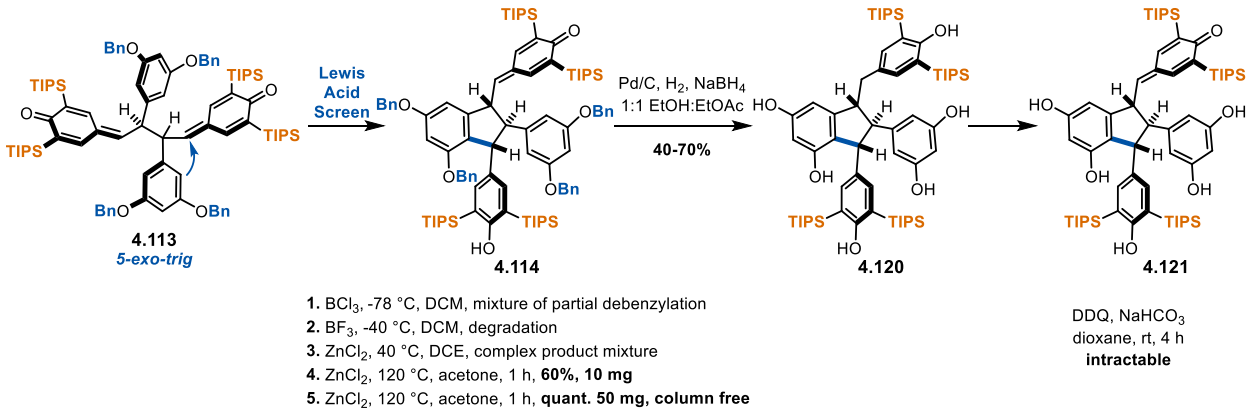


Figure 4.26 Lewis acid cyclization of TIPS BQM

To circumvent the challenges in re-oxidation an alternative strategy was proposed where reversible nucleophilic addition to quinone (**4.114**, Figure 4.27) allows for reductive deprotection of the benzyl ethers without quinone reduction. Nucleophilic 1,6 addition to quinone is well precedented[313,314] and irreversible addition was demonstrated on a similar system using PhLi by Dr. Mitch Keylor.[308] We found that while various nucleophiles are competent for addition (NaOMe, KOMe) the use of methanolic HCl provides scalable and reproducible quantities of **4.112** as a 1:1 ratio of diastereomers. We postulated that the solvent quantities of nucleophile (MeOH) help drive this reaction to completion. Removal of benzyl groups with standard hydrogenolysis conditions (Pd/C, H_2) provide **4.123** in excellent yield (>95%).

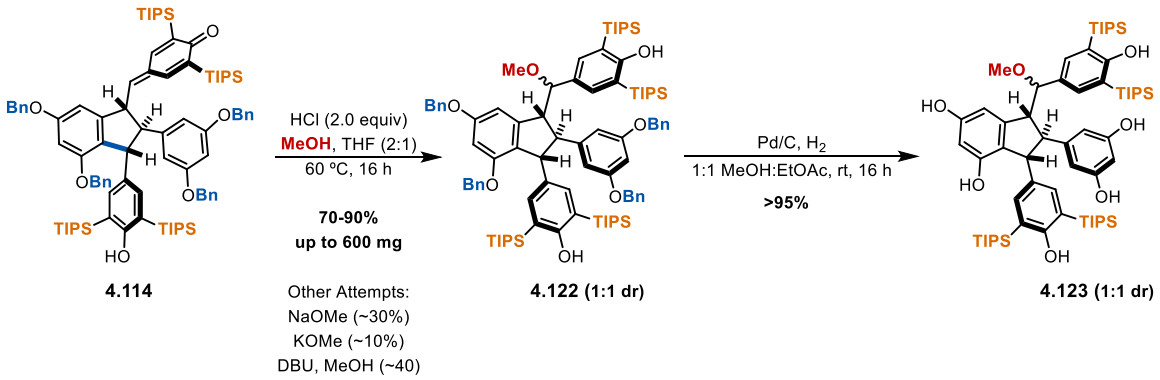


Figure 4.27 1,6 methanol addition to *para*-quinone methide as temporary protection

The oligomerization of **4.123** (Figure 4.28) with BQM (**4.113**) under standard conditions (120 °C, 16 h, **acetone**, **sealed tube**) cleanly returned starting materials. Changing solvent to allow for higher temperatures to be screened without surpassing the pressure rating of the sealed tube 60 PSIG (tested by ChemGlass to withstand 150 PSIG).[315] This chemistry was also briefly revisited using a Biotage microwave reactor which can withstand 30 bar (~453 PSIG)[316] using acetone heated to 180 °C and in all cases no productive DHB formation was observed. Trace amounts of unidentified trimer were detected via crude ^{1}H NMR in some cases but attempts to isolate this material were unsuccessful.

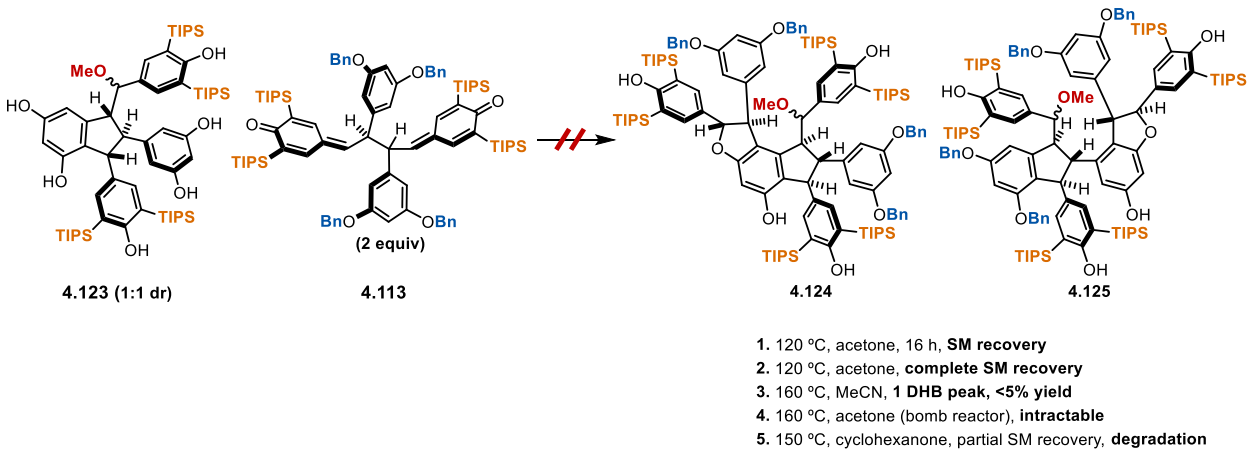
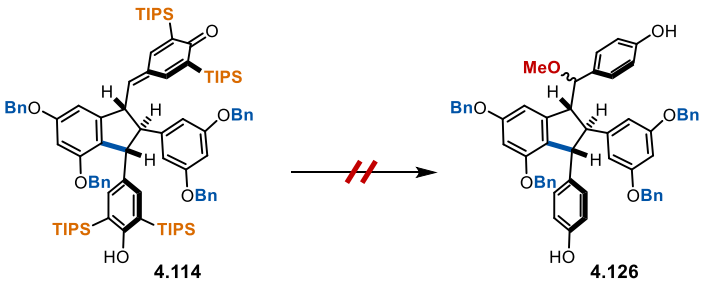


Figure 4.28 Attempts at DHB oligomerization of TIPS protected indane to trimer

To circumvent the challenges associated with thermal DHB formation on a sterically encumbered indane core we attempted to remove the TIPS protecting groups prior to

oligomerization (Figure 4.29). A series of acidic conditions, similar to those successful in past studies, were unable to cleanly convert TIPS protected indane **4.114** to **4.126**. Either patrial TIPS removal or decomposition was observed in all trials.



Reagent	Solvent	Temp	Result
0.5 M HCl	MeOH	80 °C	methanol addition, partial TIPS removal
0.5 M HCl	MeOH	23 °C	methanol addition
0.5 M HCl	MeOH	40 °C	methanol addition, partial TIPS removal
0.5 M HCl	MeOH	60 °C	methanol addition, partial TIPS removal
0.5 M HCl	Diethyl Ether	40 °C	intractable partial TIPS removal
0.5 M HCl	Dioxane	80 °C	intractable partial TIPS removal
0.5 M HCl	MeOH/EtOAc	70 °C	methanol addition, partial TIPS removal

Figure 4.29 Attempts to remove TIPS protecting groups from TIPS-Bn indane

To circumvent the challenges associated with the use of TIPS indane (**4.123**, Figure 4.30) we chose to synthesize dimeric indanes with smaller silyl protecting groups (**4.127**) such as TMS, TBS, or TES, which we hypothesized may be competent in thermal DHB chemistry.

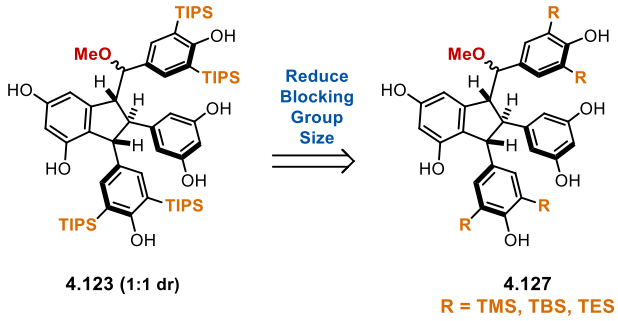


Figure 4.30 Strategy to reduce blocking group size on indane core

4.5.2 The use of C3 TMS groups

The TMS protected indane was the first explored as we hypothesized the smallest silyl protecting group would have the highest chance of success for oligomerization to trimer. The goal was to lighten the synthetic burden and avoid synthesizing the TBS and TES protected indanes if unnecessary. The TMS protected BQM were known from past Stephenson lab precedent.[54,57,56] We were motivated to test the approach developed for C3 TIPS BQM towards the TMS variant as the precursors, such as phosphonium salt **4.129** (Figure 4.31) and aldehyde **4.128** were already synthesized. This route commenced with a Wittig olefination of aldehyde (**4.128**) with phosphonium salt (**4.129**) which after one pot TBAF silyl deprotection provided stilbene **4.130**. A series of two silyl protection retro-Brook sequences provided *di*-TMS protected stilbene **4.132**. Standard electrochemical homodimerization gave BQM in 40-70% yield. Attempts to directly cyclize BQM (**4.133**) with analogous conditions as previously ($ZnCl_2$, acetone, reflux) yielded only decomposition. Strong acids (BF_3, **$TiCl_4$**) did not improve the results. The lability of the silyl groups forced us to use tautomerization (NaHMDS) as a strategy to control reactivity providing adequate quantities of tautomer **4.135** to explore BCl_3 cyclization. As with the C3 TIPS groups, the TMS also afford only *6-exo-trig* product (**4.136**, 30%). Hydrogenolysis (Pd/C, H_2) provided dimer **4.137** which was fully characterized by 2D NMR experiments. This cyclization product refuted the previous hypothesis that silyl group size dictates the *5-exo-trig* vs *6-exo-trig* selectivity, suggesting that a stereoelectronic effect is present. This selectivity is not fully understood, and it is remarkable that the change from C3 *tert*-butyl to trimethylsilyl provides a complete change in cyclization selectivity. With the TMS protected indane out of synthetic reach, we decided to pursue both the TBS and TES protected variants, which are similar in steric considerations.

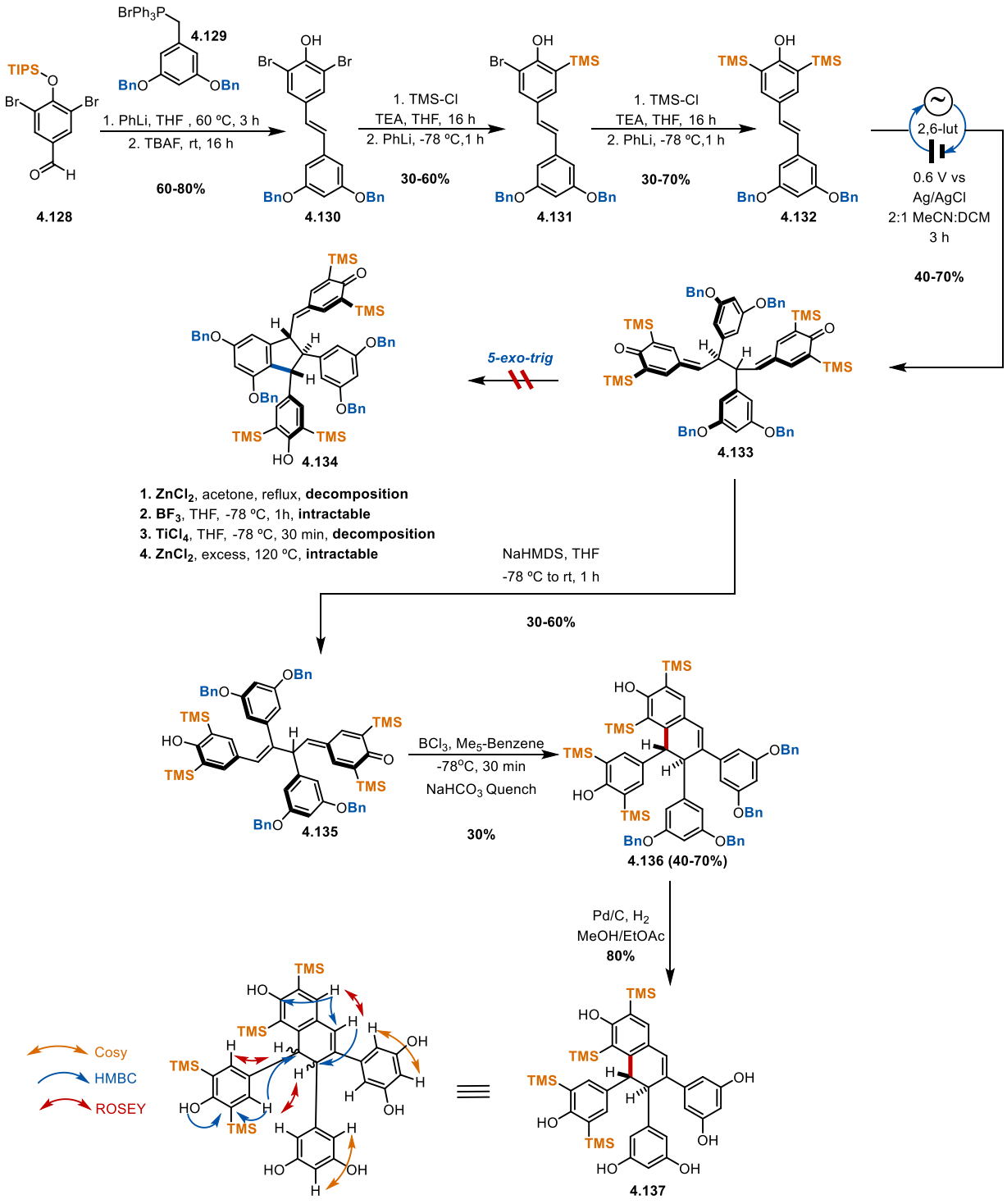


Figure 4.31 Attempts to synthesize TMS protected indane core thwarted by *6-exo-trig* cyclization

4.5.3 The use of C3 TBS groups

Chronologically the TBS indane was pursued first as we were waiting for adequate quantities of TES-Cl to be delivered. We first attempted the same sequence as was used for both TIPS and TMS protection with an iterative Wittig and retro-Brook sequence (not shown).

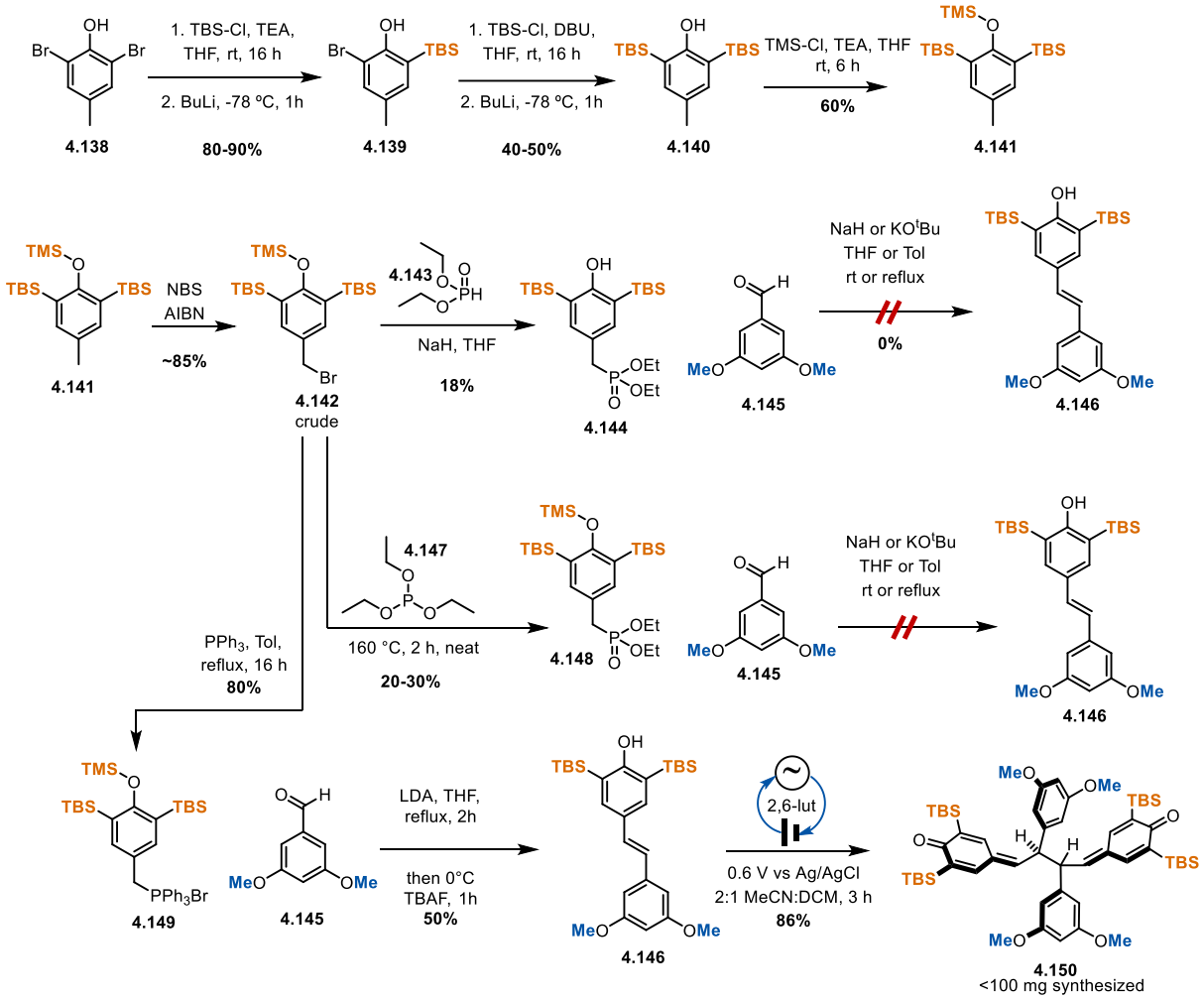


Figure 4.32 Synthesis of C3 TMS Phenolic OMe BQM

We had difficulties with the retro-Brook rearrangements and as we were unable to separate the starting material from products, this route was abandoned. We chose to follow a similar route to past Stephenson lab precedent and began with a simple brominated phenol (**4.138**, Figure 4.32).[54,56] This substrate was amenable to sequential TBS protection and retro-Brook which after two cycles provided **4.140** in 30-40% yield over 4 steps. TMS protection of

phenol in 60% yield gave **4.141** which was brominated (NBS) to provide key intermediate **4.142** which diverged in search of a suitable olefination method. Formation of phosphate (**4.148**) via nucleophilic displacement with phosphonic acid diethyl ester (**4.143**) proceeded with TMS deprotection. The use of various bases and solvents did not provide olefin (**4.146**) when attempted with simple aldehyde **4.145**. The methyl protection of this aldehyde was chosen as the simplest model system for reactivity given the challenges already encountered in this synthetic route. The use of triethyl phosphite (**4.147**) in an Arbuzov reaction retained the phenolic TMS group in **4.148**. This reaction required neat conditions and distillation of the product to obtain sufficiently pure material by removing residual phosphite. Unfortunately, this phosphonate (**4.148**) was also not competent to form olefin (**4.146**) in a variety of conditions. Instead converting bromide (**4.142**) to phosphonium salt (**4.149**) proved fruitful. With LDA the Wittig proceeded smoothly and one pot desilylation (TBAF) gave olefin (**4.146**). This material was electrochemically oxidized to BQM (**4.150**), but inefficiencies of this synthetic route led to <100 mg synthesized. As each of the C3 silyl groups had presented individual nuances, we chose to pursue TES indane protection as it may be more straightforward.

4.5.4 The use of C3 TES groups

The synthesis of a TES stilbene was also attempted first via the iterative sialylation and retro-brook sequences which were successful for the TIPS analogue. Issues with overprotection and separation of byproducts plagued this route. Following the route which was successful for the TBS analogue was instead attempted (Figure 4.33). Beginning with the same simple phenol **4.138** (Figure 4.33) TES protection followed by retro-Brook rearrangement twice provided **4.512** in synthetically useful yields. A *bis*-TMS acetamide (**4.153**) was found more successful than TMS-Cl for the final phenol protection (**4.154**). Free radical bromination gave **4.155**, which

unfortunately was not a competent substrate for phosphonium salt formation. Even with rigorously pure starting material the addition of triphenylphosphine in refluxing toluene provided no precipitate (salt, **4.156**).

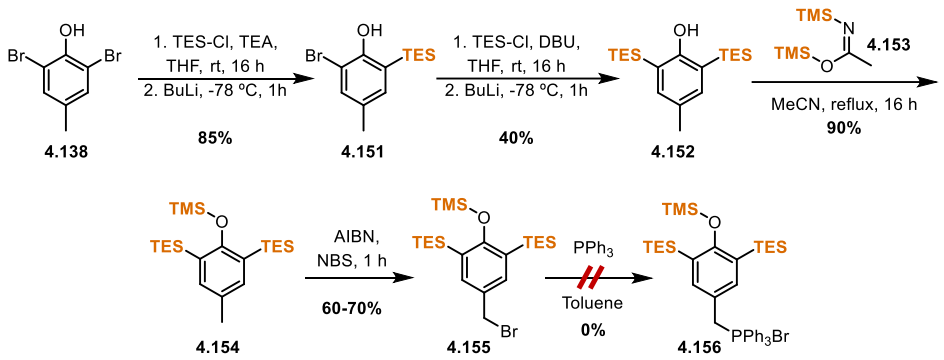
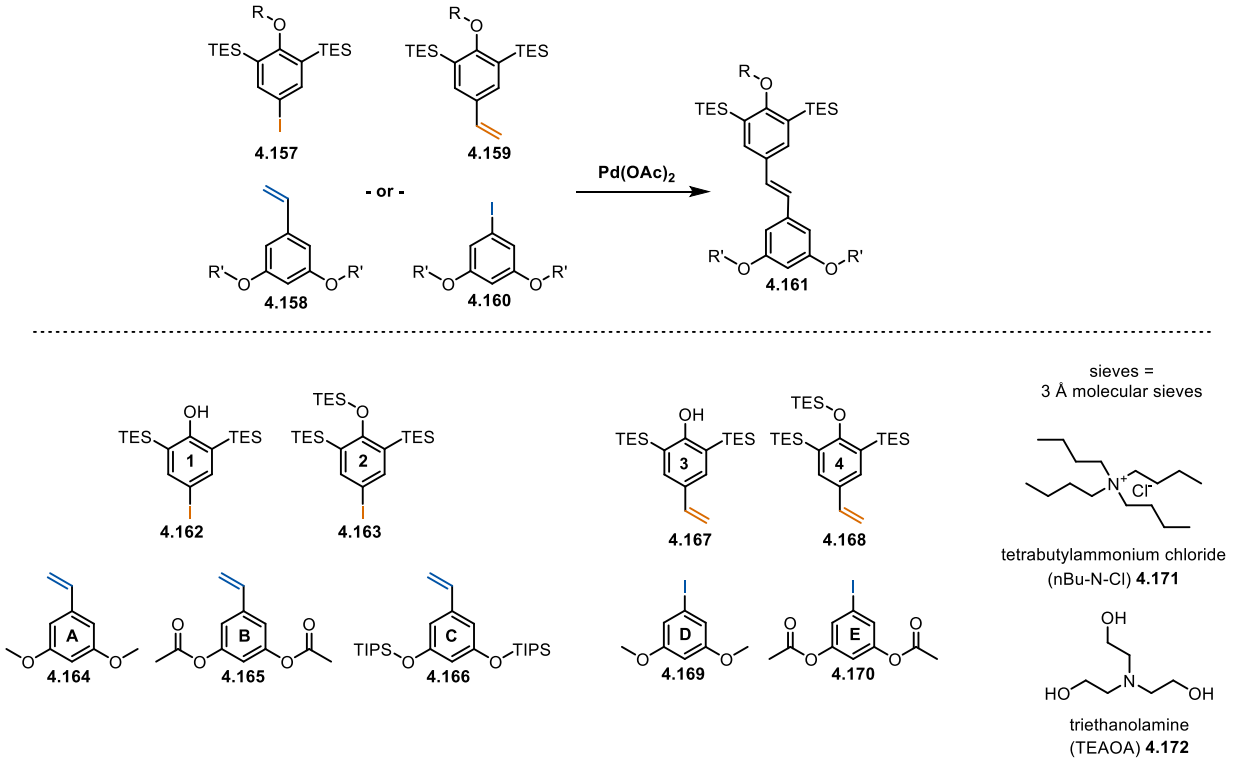


Figure 4.33 Attempts to synthesize TES protected phosphonium salt

We turned to other classical methods of alkene formation, and first explored a Heck reaction strategy (Table 4.4).[317] An aryl halide (**4.157**, **4.160**) would react with a vinyl arene (**4.158**, **4.159**) with palladium acetate to form stilbene (**4.161**). As it was not known which coupling partners would be effective, a variety of aryl iodides (**4.162**, **4.163**, **4.169**, **4.170**) and vinyl arenes (**4.146-4.166**, **4.167**, **4.168**) were synthesized in 1-4 steps from commercial material using the same methods described earlier. A screening of bases ($NaHCO_3$, KOAc, TEA, TEAOA), solvents (MeCN, DMF, H_2O), and additives (PPh_3, nBu-N-Cl, sieves) found conditions (**4.168**, **4.169**, TEAOA, DMF, **100 °C**, 16 h) provided a 46% yield by ^1H NMR. Attempts to isolate this material, cleanly provided stilbene in 25-35% yield.

Table 4.4 Synthesis of C3 TES stilbene via Heck coupling



Phenol (#)	Recorcinol	Base	Additive	Solvent	Temp(°C)	Time(h)	^{1}H NMR Yield*
4	D	$NaHCO_3$	PPh_3, nBu-N-Cl	MeCN	90	3	15%
4	D		nBu-N-Cl, sieves	DMF	90	3	6%
4	D	KOAc	nBu-N-Cl, sieves		90	3	20% (desilyated)
3	D	TEAOA			100	16	45% (desilyated)
3	D	TEA			100	16	45% (desilyated)
4	D	TEAOA			100	16	32% (~50% RSM)
1	A	TEAOA			100	16	9% (desilyated)
2	A	TEAOA			100	16	7% (desilyated)
3	E	TEAOA			100	16	20% (desilyated)
4	D	TEAOA			100	40	46%
4	D	TEAOA	nBu-N-Cl		100	16	45% (desilyated)
4	D	TEAOA	nBu-N-Cl, sieves	MeCN	100	16	35% (desilyated)
4	D	TEAOA		DMF	100	16	48% (desilyated)
4	D	K_2CO_3	nBu-N-Cl	H_2O/DMF	100	16	28%

*desilylated refers to northern phenol, labelled r

Upon further screening we found success in an olefin metathesis approach (Figure 4.34).[318,319] Aldehyde (**4.128**) is converted to olefin (**4.173**) via a scalable Wittig reaction. The previous challenges with TES overprotection were leveraged in a one pot iterative sialylation strategy. After tuning reaction conditions **4.174** could be synthesized on >10-gram scale with DBU and TES-Cl added to phenol **4.173** followed by dropwise addition of *n*BuLi over four hours. The

key to this reaction succeeding was that TES protection of the phenol is operative at cryogenic temperatures, as this allows subsequent phenol sialylation retro-Brook sequences in a single pot. The byproduct, triethyl-butyl-silane (**4.175**), was removed via Kugelrohr distillation, which arose from *n*BuLi addition to TES-Cl. The other olefin was synthesized via PMB protection of phenol (**4.177**) followed by NaH Wittig (**4.178**). The PMB protecting group was chosen as the ^{1}H NMR has two set of symmetrical resonances, and this group offers additional acidic and oxidative deprotection flexibilities compared to Bn.[87] A large set of conditions were screened for olefin metathesis with Grubbs II catalyst to form stilbene **4.175**. The final conditions were found serendipitously, as refluxing DCM with a loosely fitted cap resulted in a thick paste, which when stirred for two hours, followed by desilylation with TBAF gave olefin (**4.15**) in 42% isolated yield. This reaction was challenging to scale due to the complicating stirring profile of the viscous reaction mixture. Electrochemistry gave BQM (**4.176**) in good yield under standard conditions.

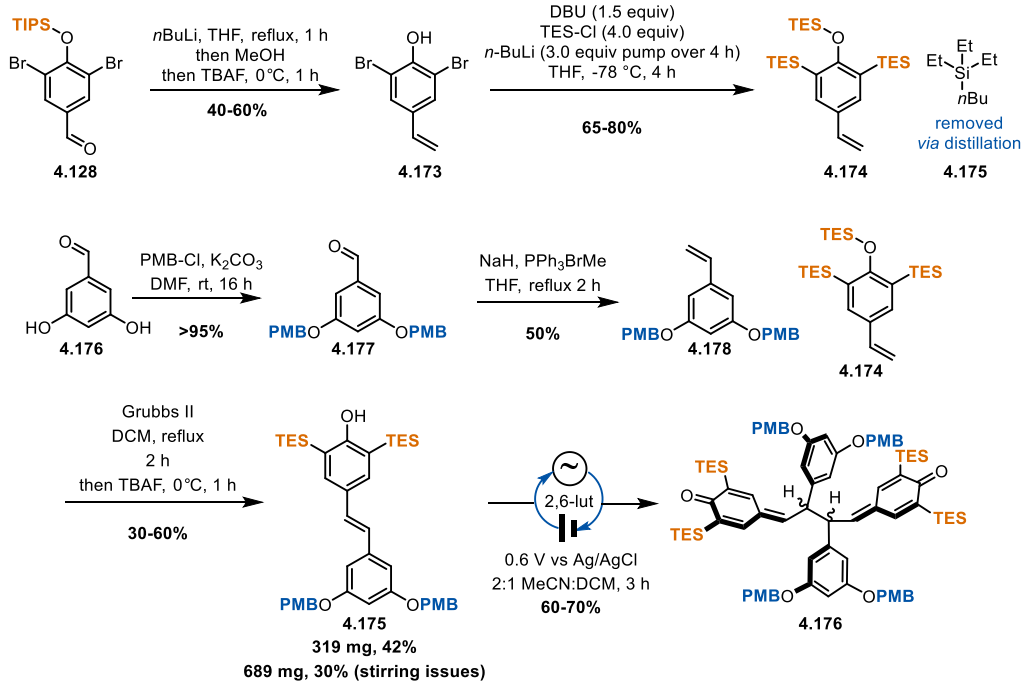
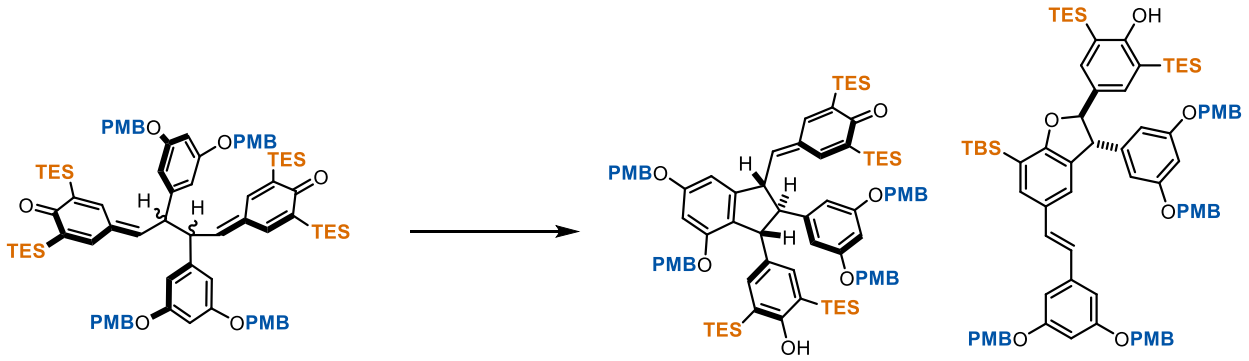


Figure 4.34 Synthesis of TES, PMB protected BQM

The TES protected BQM (**4.176**, Figure 4.34) was subjected to thermal zinc chloride conditions (120 °C) which were competent for the TIPS analogue, but only C3-C8 rearranged product was isolated (**4.178**). This again underscores the nuances of each C3 protecting group and how re-optimization is often required when thermal chemistry is used. This is due to the varying barriers to C3-C8 rearrangement (**4.178**) versus productive cyclization (**4.177**).

Table 4.5 Optimization of *5-exo-trig* cyclization of TES, PMB BQM



Conditions (all 25 mg scale)	Result
$ZnCl_2$, 120°C, Acetone, 1 h	C3-C8 rearrangement
0.5 M HCl in MeOH, rt, 1 h	Intractable
5 eq HCl in MeOH, rt, 3 h	Intractable
0.5 M HCl in MeOH, -78°C, 3h	Intractable
BF_3, -78°C, 30 min	3 products isolated, <20% product
$ZnCl_2$ (1M Solution in THF), 3 days	40% yield
8 equiv $ZnCl_2$ Solid (old), Acetone, rt, 3h	No Conversion
8 equiv $ZnCl_2$ Solid (new), Acetone, rt, 3h	35%
8 equiv $ZnCl_2$ Solid (new), $CH2Cl_2$, rt, 3h	Degradation
8 equiv $ZnCl_2$ Solid (new), MeCN, rt, 3h	25%, with 50% starting material
8 equiv $ZnCl_2$ Solid (new), MeCN, rt, 16h	40%
4 equiv $B(C_6F_5)_3$, Acetone, rt, 3h	Intractable Mess
8 equiv $ZnCl_2$ Solid (new), Acetone, 50 °C, 3h	Cyclization with various deprotections
8 equiv $ZnCl_2$ Solid (new), Acetone, rt, 3h, rt	54%
8 equiv $ZnCl_2$ Solid (new), Acetone, rt, 3h, 30 °C	36%
8 equiv $ZnCl_2$ Solid (new), Acetone, rt, 3h, 35 °C	51%
8 equiv $ZnCl_2$ Solid (new), Acetone, rt, 3h, 40 °C	67%

*old indicates "old" bottle of $ZnCl_2$ with water present
**new inidicates "new" bottle of anhydrous $ZnCl_2$

A brief screen of acids found that zinc chloride over three days formed 40% yield of desired product (**4.177**) without any C3-C8 rearrangement (**4.178**) detected. Using eight equivalents of anhydrous zinc chloride was required for expedient conversion, with fine temperature control (40 °C for 3 h), 67% of the *5-exo-trig* product was isolated.

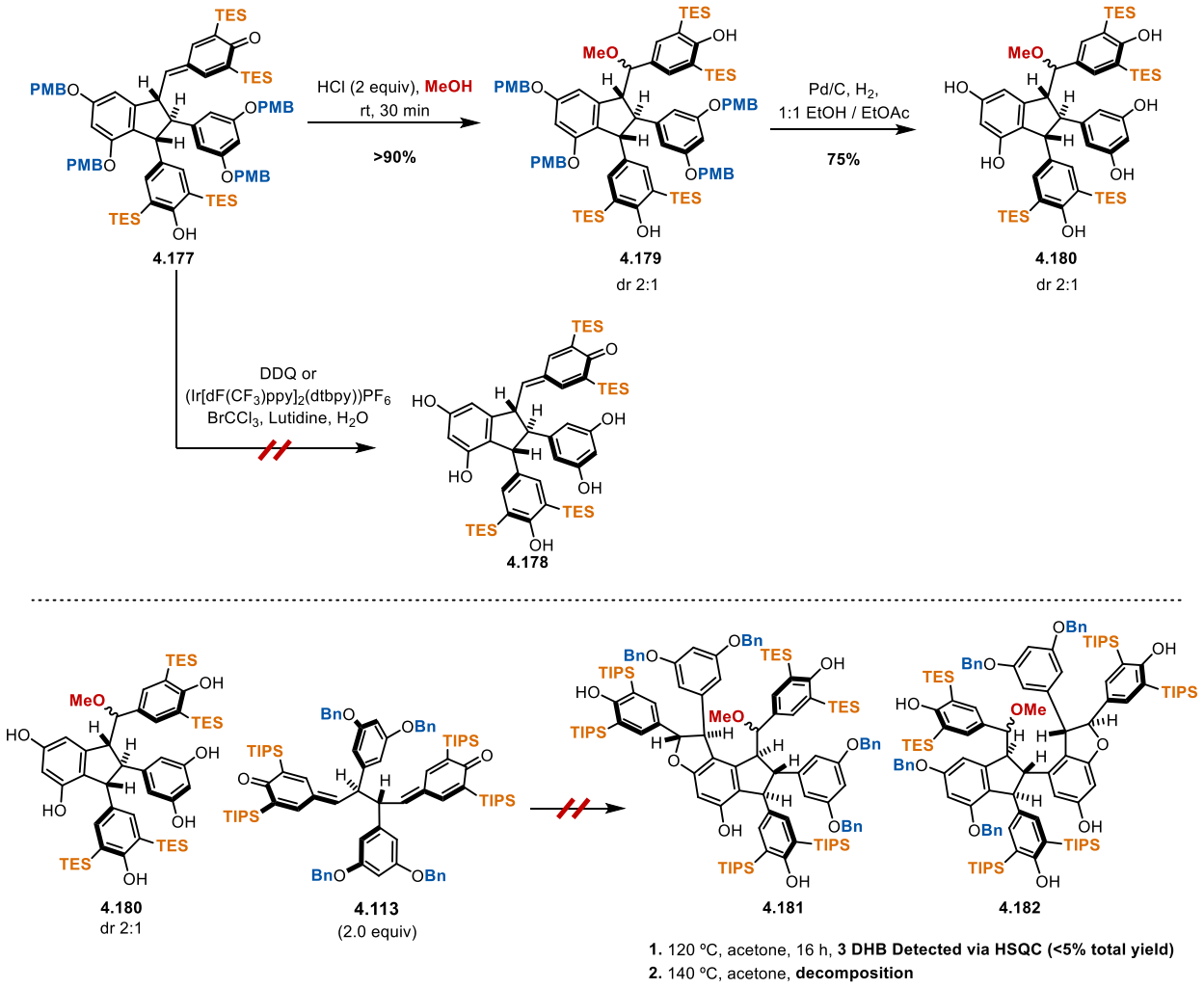


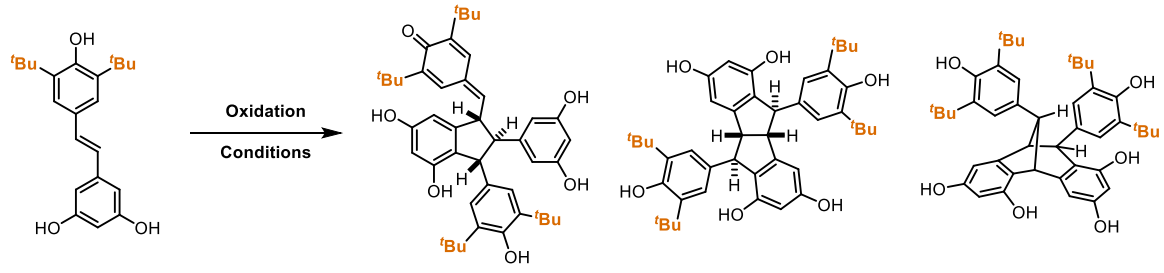
Figure 4.35 Elaboration of cyclized TES indane to core and attempted oligomerization

4.5.5 Revisiting the use of C3 TMS protecting groups via a direct oxidation strategy

To effectively utilize the phenolic PMB protecting groups of **4.177** (Figure 4.35) effectively we attempted oxidative (DDQ)[87] and photoredox conditions towards **4.178**.[320] We did not find success with either of these methods and instead chose to pursue a similar route to past silyl protected indane dimers of methanol protection of quinone. This proceeded smoothly (>90%, **4.179**), and hydrogenolysis (Pd/C, H_2) gave **4.180** in sufficient quantities for oligomerization studies. When **4.180** was mixed with **4.113** with acetone at 120 °C for 16 hours less than 5% of trimeric material (**4.181**, **4.182**) was detected by HSQC. Further heating to 140 °C resulted in

decomposition of the indane core (**4.180**). This strategic approach was put on hold to pursue the synthesis of resveratrol dimers.

After the completion of the synthesis of resveratrol dimers we were motivated to revisit the synthesis of distichol and davidiol A using a direct oxidation strategy. Our approach was inspired by a study by Li and co-workers published in 2010 (Figure 4.36).[321] They utilized a C3 *tert*-butyl protected resveratrol monomer (**4.184**) and subjected it to myriad chemical oxidation conditions. The authors reported the major product, conversion, and recovered starting material for each reaction, with most providing indane (**4.185**). We sought to replicate this approach using TMS groups to synthesize the C3 TMS indane which had resisted synthesis via *bis*-quinone methide cyclization (see Section 4.5.2).



4.184 4.185 4.186 4.187

Oxidant	Solvent	Temperature (°C)	Time (h)	Major Product	Conversion(%)	Recovered SM
Ag_2O	MeOH	25	6	4.185	22	12
Ag_2O	MeOH	25	24	4.185	48	29
Ag_2CO_3	MeOH	25	6	4.185	19	13
Ag_2CO_3	MeOH	25	24	4.185	59	64
MnO_2	DCM	25	24	4.185	16	24
MnO_2	DCM	25	24	4.185	54	76
$FeCl_3{\cdot}6H_2O$	DCM	25	24	4.186	55	45
$FeCl_3{\cdot}6H_2O$	DCM	25	3	4.187	45	25

Figure 4.36 Li's oxidation of *tert*-butyl protected resveratrol to dimers

We began by synthesizing C3 TMS resveratrol **4.196** (Figure 4.37). This began with ethylene glycol protection of **4.188**, forming dioxolane **4.189**. Two silyl protection retro-Brook sequences provided **4.191**. The challenge in this set of 4 operations is overprotection of the phenol with TMS which provides a mixture of inseparable products. Acidic deprotection returns aldehyde (**4.192**) which requires careful TLC tracking to find an endpoint that maximizes yield as both

starting material and degradation (loss of TMS) are present upon reaction quench. The synthesis of this aldehyde followed closely a reported route.[322] The Wittig of unprotected aldehyde (**4.193**) and TIPS phosphonium salt (**4.194**) was not known and using reported conditions (nBuLi, THF, **reflux**, 30 min)[323] resulted in no product formation. Approximately 30 trials were required to hone the conditions to 2.8 equiv of *n*BuLi, 2.2 equiv of salt (**4.194**) in toluene at 60 °C for 16 hours. The use of THF was not productive across a range of conditions, other bases (KHMDS, NaH) performed worse, and elevated temperatures in toluene (**>60 C**) resulted in degradation of the product (loss of TMS). Desilylation of **4.195** with TBAF proceeded smoothly providing **4.196** in excellent yields (85-90%). This route was chosen as the use of phenolic Bn protecting groups would have been challenging to remove while preserving the TMS groups.

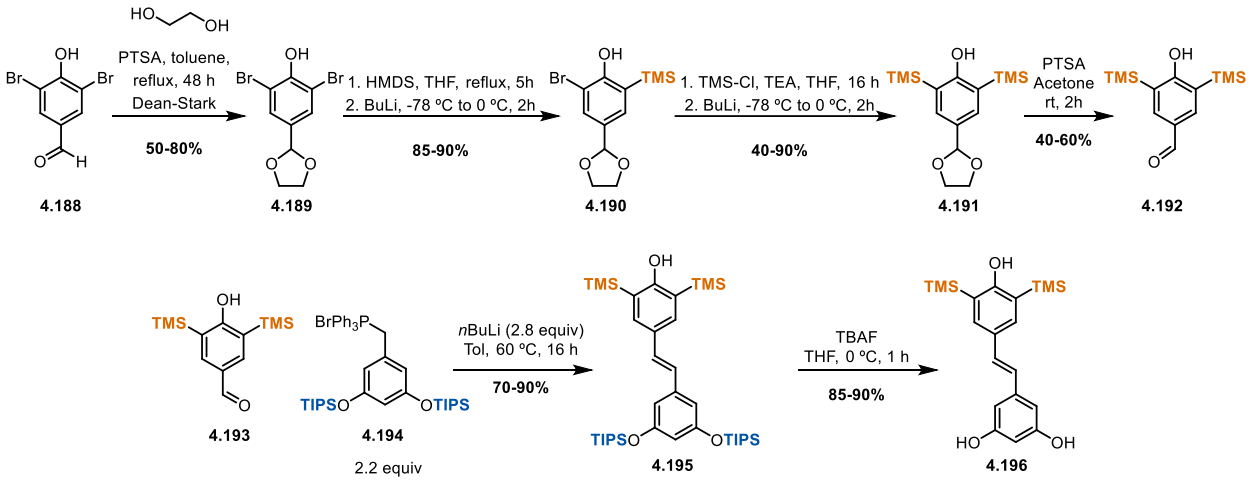
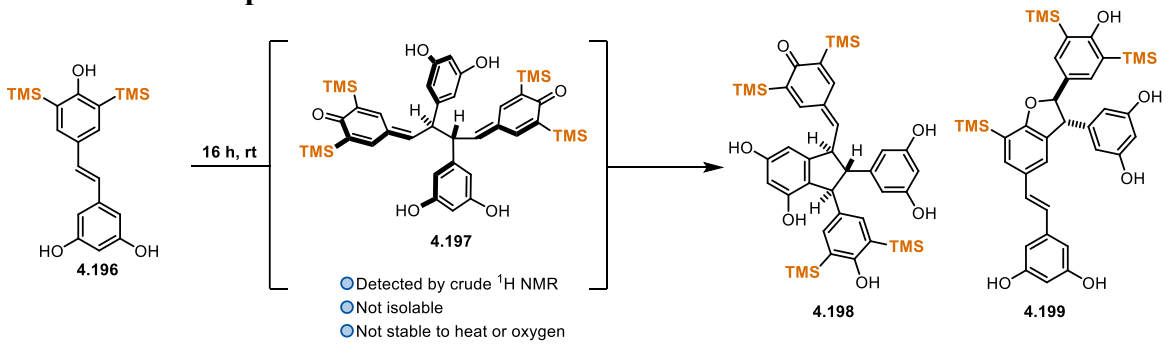


Figure 4.37 Synthesis of C3 TMS resveratrol

We explored chemical oxidation of TMS stilbene (**4.196**, Table 4.6) and had success in our first trial using silver carbonate isolating 53% of **4.198** and approximately 20% of **4.199**. Unfortunately, attempts to replicate this reactivity were unsuccessful for ~50 trials.

Table 4.6 Initial optimization of silver oxidation of C3 TMS resveratrol

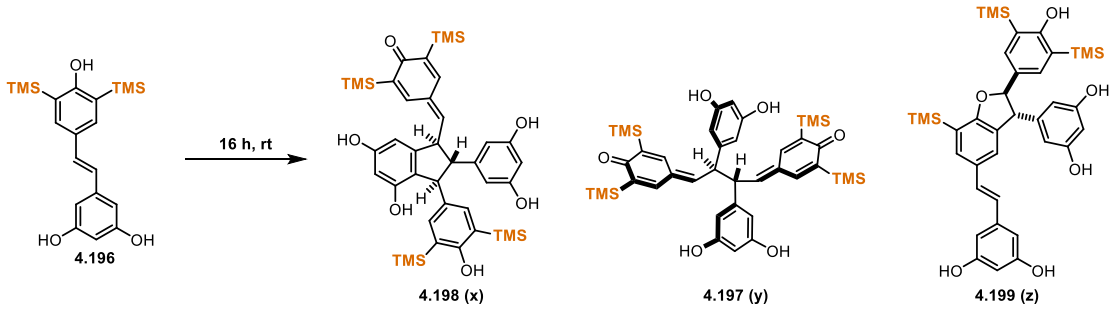


Scale	Degassing Procedure	Solvent	Oxidant	Result (^{1}H NMR)	
40 mg	Ar Headspace	DCM bottle old	Ag_2CO_3 (1.2 eq)	**53% isolated**	
180 mg	Ar Headspace	DCM bottle old		SM Recovery	
140 mg	Ar Sparge	DCM bottle old		SM Recovery	
160 mg	Ar Sparge	DCM bottle new		Messy, went dry	
50 mg	Air Headspace	DCM bottle new		SM Recovery	
50 mg	Ar Headspace	DCM bottle new		SM Recovery	
50 mg	Ar Sparge	DCM bottle new		64%	
200 mg	Ar Sparge	DCM bottle new		SM Recovery	
173 mg	Freeze-Pump-Thaw	DCM bottle new		SM Recovery	
50 mg	Sparge	DCM bottle old		SM Recovery	
50 mg	Sparge	DCM bottle new		SM Recovery	
50 mg (MnO_2)	Sparge	DCM bottle new		SM Recovery	
40 mg	Ar Headspace	DCM bottle old		**53% (product + 4.199)**	
180 mg	Ar Headspace	DCM bottle old		SM Recovery	
140 mg	Ar Sparge	DCM bottle old		SM Recovery	
160 mg	Ar Sparge	DCM bottle new		Messy, went dry	
50 mg	Air Headspace	DCM bottle new		SM Recovery	
50 mg	Ar Headspace	DCM bottle new		SM Recovery	
50 mg	Ar Sparge	DCM bottle new		**64% (4.198)**	
200 mg	Ar Sparge	DCM bottle new		SM Recovery	
173 mg	Freeze-Pump-Thaw	DCM bottle new		SM Recovery	
50 mg	Sparge	DCM bottle old		SM Recovery	
50 mg	Sparge	DCM bottle new		SM Recovery	
50 mg	Sparge	DCM bottle new	MnO_2 (1.2 eq)	SM Recovery	
30 mg	Sparge 5 min	DCM bottle old	Ag_2CO_3 (1.2 eq)	~20% yield, 4 products	
30 mg	Sparge 10 min	DCM bottle old	Ag_2CO_3 (1.2 eq)	~20% yield, 4 products	
30 mg	Sparge 30 min	DCM bottle old	Ag_2CO_3 (1.2 eq)	~20% yield, 4 products	
30 mg	Sparge 30 min	DCM bottle new	Ag_2CO_3 (1.2 eq)	~20% yield, 4 products	
30 mg	Sparge 30 min	DCM bottle new	$AgCO_3$ (3 eq)	~20% yield, 4 products	
30 mg	Sparge 30 min	DCM bottle new	$AgCO_3$ (8 eq)	~20% yield, 4 products	
30 mg	Ar Headspace	DCM bottle new	Ag_2CO_3 (1.2 eq)	~20% yield, 4 products	
30 mg	Ar Headspace	DCM bottle new	Ag_2CO_3 (1.2 eq)	~20% yield, 4 products	rigorously purify starting material
30 mg	Sparge 30 min	DCM bottle new	Ag_2CO_3 (1.2 eq)	SM Recovery	
30 mg	Sparge 30 min	DCM bottle new	$AgCO_3$ (3 eq)	SM Recovery	
30 mg	Sparge 30 min	DCM bottle new	$AgCO_3$ (8 eq)	SM Recovery	
30 mg	Ar Headspace	DCM bottle new	Ag_2CO_3 (1.2 eq)	SM Recovery	
30 mg	Ar Headspace	DCM bottle new	Ag_2CO_3 (1.2 eq)	SM Recovery	
30 mg	Ar Headspace	DCM bottle new	Ag_2CO_3 (1.2 eq)	SM Recovery	
30 mg	Ar Headspace	DCM bottle new	Ag_2CO_3 (1.2 eq)	SM Recovery	
30 mg	Ar Headspace	DCM bottle new	Ag_2CO_3 (1.2 eq)	SM Recovery	
30 mg	Ar Headspace	Benzene, reflux	Ag_2CO_3 (1.2 eq)	~10% yield, messy	
30 mg	Ar Headspace	DCM, reflux	Fetizon Reagent (4 eq)	messy	
30 mg	Air Headspace	DCM	Ag_2CO_3 (1.2 eq)	SM Recovery	
30 mg	Ar Headspace	DCM bottle new	Ag_2CO_3 (1.2 eq)	SM Recovery	
30 mg	Ar Headspace	DCM, water 100 eq	Ag_2CO_3 (1.2 eq)	~50% yield	switch from Ag_2CO_3 to other silver salts
30 mg	Ar Headspace	DCM bottle new	Ag_2O (1.5 eq)	SM Recovery	
30 mg	Ar Headspace	DCM bottle new	$AgNO_3$ (1.5 eq)	SM Recovery	
30 mg	Ar Headspace	DCM bottle new	AgOAc (1.5 eq)	~30% yield, 3 products	
30 mg	Ar Sparge	DCM bottle new	AgOAc (1.5 eq)	~30% yield, 3 products	
30 mg	Ar Headspace	DCM bottle new	AgOAc (3.0 eq)	~50% yield, 2 products	
30 mg	Ar Headspace	DCM, 1/2 M	AgOAc (1.5 eq)	~30% yield, 3 products	
160 mg	**Ar Headspace**	**DCM bottle new**	**AgOAc (3.0 eq)**	**40% isolated yield**	

We varied the degassing procedure (sparge with argon, argon headspace, freeze pump thaw), DCM used ("new" vs "old"), and time of reaction in attempts to replicate our first trials. Inexplicably there were occasionally hits, and we assumed that this was due to starting material purity. After rigorously purifying the stilbene (**4.196**) we did not find any improvements in reactivity. We then decided to abandon our initial hit and reoptimize the system using other silver salts ($AgNO_3$, AgOAc). We quickly found that the use of silver acetate was productive, and we detected three species by ^{1}H NMR in deuterated acetone (**4.197**, **4.198**, **4.199**). Using three equivalents of silver acetate in DCM for 16 hours converted all starting material to 40% of indane **4.198** with approximately 30% of C3-C8 rearranged dimer **4.199** (detected by ^{1}H NMR, not isolated).

We sought to increase the yield of the reaction via further optimization, to select for indane (**4.198**, Table 4.6**)** over C3-C8 rearrangement (**4.199**). We screened a variety of solvents, and found a large effect on the product distribution with acetone providing mostly **4.199** and THF giving a 3.2:1 ratio of **4.198 : 4.199**. Cooling the reaction to 5 °C slowed cyclization from BQM (**4.197**) as no indane (**4.198**) was detected overnight. Allowing this reaction to warm to room temperature over another 24 hours provided a similar ratio of indane : C3-C8 rearranged product (2.8:1) as the analogous reaction ran at room temperature for 16 hours. This provides evidence that the BQM (**4.197**) is metastable, and cyclization to **4.198** or C3-C8 rearrangement (**4.199**) are competing irreversible pathways. It is now known if there is a preference for the *meso* or *D/L* diastereomer of **4.197** to undergo C3-C8 rearrangement. Less than one equivalent of silver acetate returns starting material, while even a small excess (1.1 equiv) does complete the reaction. It appears from crude kinetics studies that the silver acetate is participating in the oxidation of stilbene (**4.196**) to BQM (**4.197**) but not in the cyclization to indane (**4.198**). The optimization of the workup procedure was

a separate endeavor. The optimized procedure was quenching the reaction with Aq $NaHCO_3$ (basify), Aq $Na_2S_2O_3$ (silver sequestration), and extraction with DCM (3x). Rotavaping with a room temperature rotavap bath and column chromatography (wet load in DCM) provided adequate quantities of **4.198**.



Solvent (M)	Salt	Result (Ratios x:y:z) crude ^{1}H NMR	Notes
Benzene (0.05)	AgOAc (3 eq)	1 : 3.4 : 0	
Acetone (0.05)	AgOAc (3 eq)	1 : 0 : 3.2	
Methanol (0.05)	AgOAc (3 eq)	Degradation	
MeCN (0.05)	AgOAc (3 eq)	0 : 0 : 1	Degradation
THF (0.05)	AgOAc (3 eq)	2.7 : 0 : 1	
DCM/Acetone (0.05)	AgOAc (3 eq)	1 : 0 : 1.8	
THF (0.05)	AgOAc (3 eq)	0 : 0 : 1	50 °C, Degradation
THF (0.05)	AgOAc (6 eq)	2.6 : 0 : 1	
Et_2O (0.05)	AgOAc (3 eq)	1.6 : 0 : 1	
DCM/THF (0.05)	AgOAc (3 eq)	1 : 0 : 1.6	
THF (0.01)	AgOAc (3 eq)	2.5 : 0 : 1	
THF (0.05)	**AgOAc (1.5 eq)**	**3.2 : 0 : 1**	
THF (0.05)	AgOAc (1.5 eq)	SM	$ZnCl_2$ (2 eq)
THF (0.05)	AgOAc (1.5 eq)	0 : 34 : 1 → rt, o/n → 2.8 : 0 : 1	5 °C
THF (0.05)	AgOAc (1.1 eq)	2.7 : 0 : 1	
THF (0.05)	AgOAc (0.5 eq)	0 : 6: 1	Mostly SM

We tested our original hypothesis of dihydrobenzofuran oligomerization of TMS indane (**4.198**, Figure 4.38) with BQM (**4.113**) and found only decomposition at both 120 °C and 100 °C in the microwave reactor. This result parallels the TES protected indane, as the core is not sufficiently stable to endure the thermal conditions required for DHB formation.

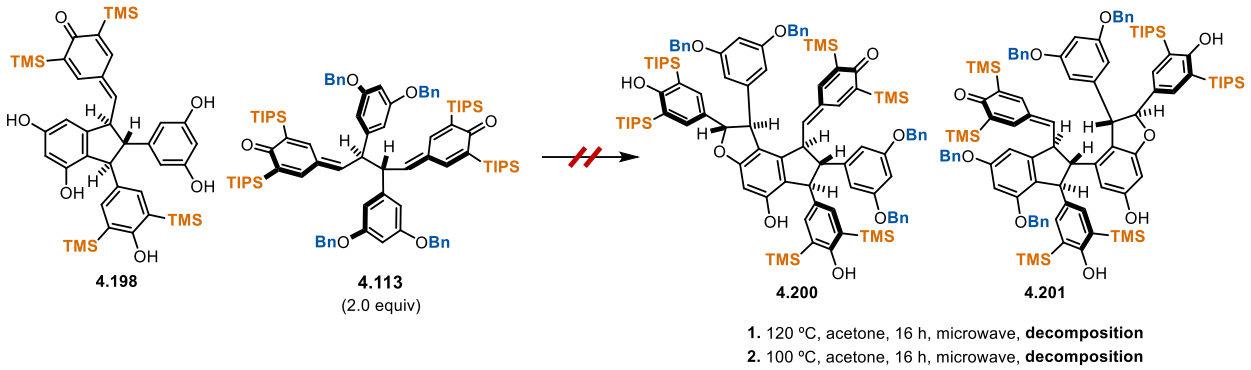


Figure 4.38 Attempts to oligomerize TMS indane to trimers

To circumvent the challenges associated with TMS groups present on the indane, we chose to remove them and replace the C3 protection with direct phenol protection as an alternative strategy. The first operation in this sequence was the methanesulfonate protection of **4.198** (Figure 4.39). Key reaction parameters included the use of Ms-Cl instead of methanesulfonic anhydride, with careful temperature control (0 °C), and 0.02 M to obtain **4.202** in 63% yield. These conditions prevent partial TMS deprotection (**4.203**, **4.204**), which is presumably from the HCl generated *in situ* coupled with poor temperature control.

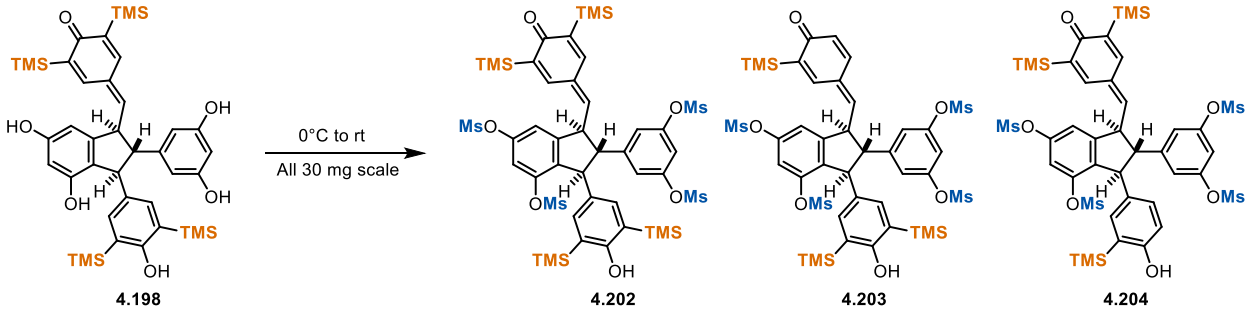
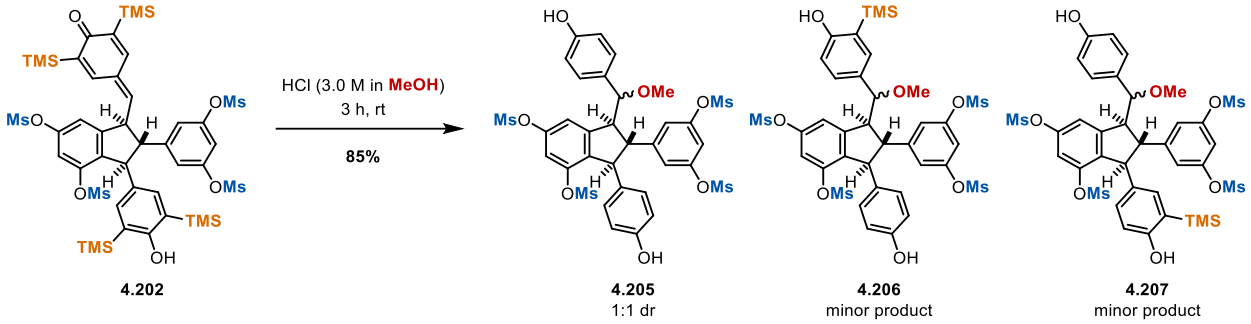


Figure 4.39 Methanesulfonate protection of C3 TMS indane

To remove the C3 TMS groups of **4.202** (Figure 4.40) and achieve methanol protection of the HCl (3M in MeOH) was used. Room temperature for 3 h was sufficient to provide 85% yield of **4.205** as an inconsequential 1:1 mixture of diastereomers. Minor by products included indane cores with a single TMS remaining. From crude ^{1}H NMR it was apparent that methanol protection of quinone proceeded near quantitatively in the first 30 minutes of reaction time while TMS removal was more sluggish.



4.202 **4.205** 1:1 dr **4.206** minor product **4.207** minor product

Figure 4.40 Methanolic HCl deprotection of TMS, Ms Indane

We chose methoxymethyl as an acid labile, base stable, protecting group for the indane (**4.208**, Figure 4.41).[87] The rationale was to allow MOM group removal concurrently with quinone generation in acid. The use of acetonitrile and finely powdered K_2CO_3 were found vital in achieving consistent reactivity with optimized yield providing 370 mg of **4.208** in 79% yield with only trace quantities of partial MOM protected byproduct **4.209**.

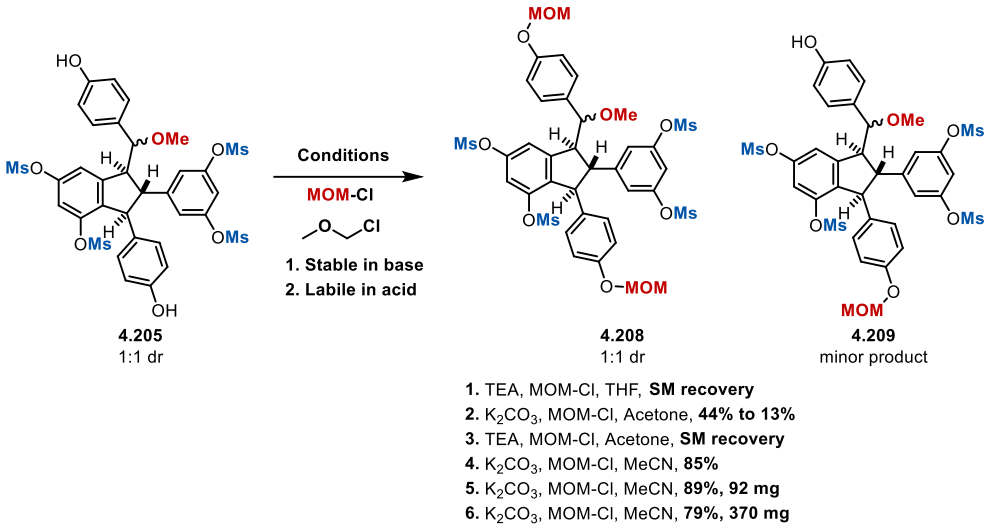


Figure 4.41 MOM protection of Ms, methanol adduct indane

The final task to prepare the indane core was removal of the methanesulfonate protecting groups of **4.208** providing **4.210** (Figure 4.42). The challenge with optimizing a reaction where four protecting groups are removed was that if partial deprotection was observed, a combinatorial nightmare of products was observed. This limited knowledge gained from incomplete reactions. The use of caustic soda (NaOH) gave partial deprotection, while LiHMDS and K_2CO_3 were intractable. The use of excess methyl Grignard was promising on small scale (5.6 mg, 43%). Upon scaling this reaction, the yield improved (90-95%) as it was challenging to isolate small quantities of product from the magnesium emulsions formed during aqueous workup.

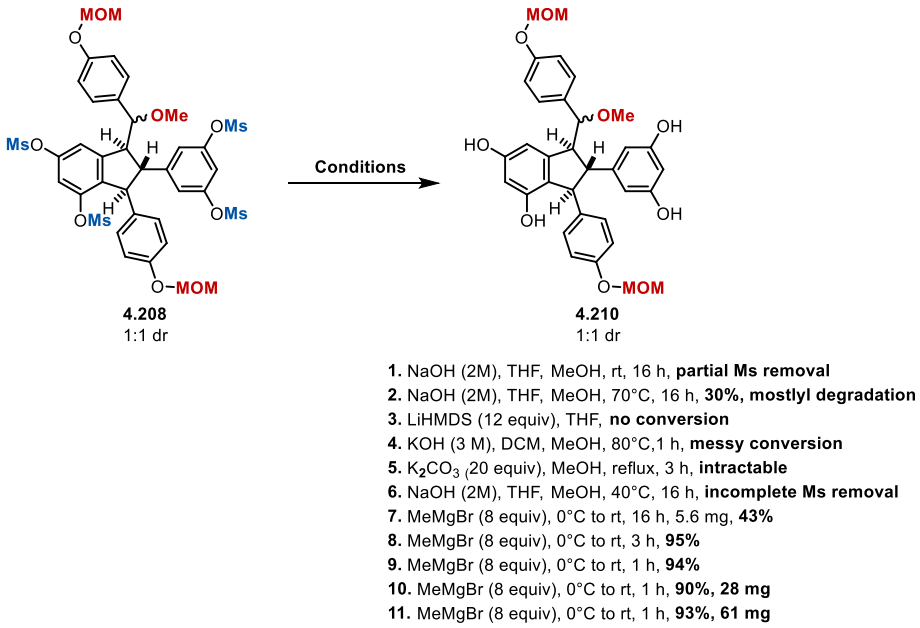


Figure 4.42 Methanesulfonate deprotection screening of MOM, methanol adduct Indane

One formidable challenge when oligomerizing **4.210** (Figure 4.43**)** with a BQM (**4.113)** is the set of diastereomers produced.

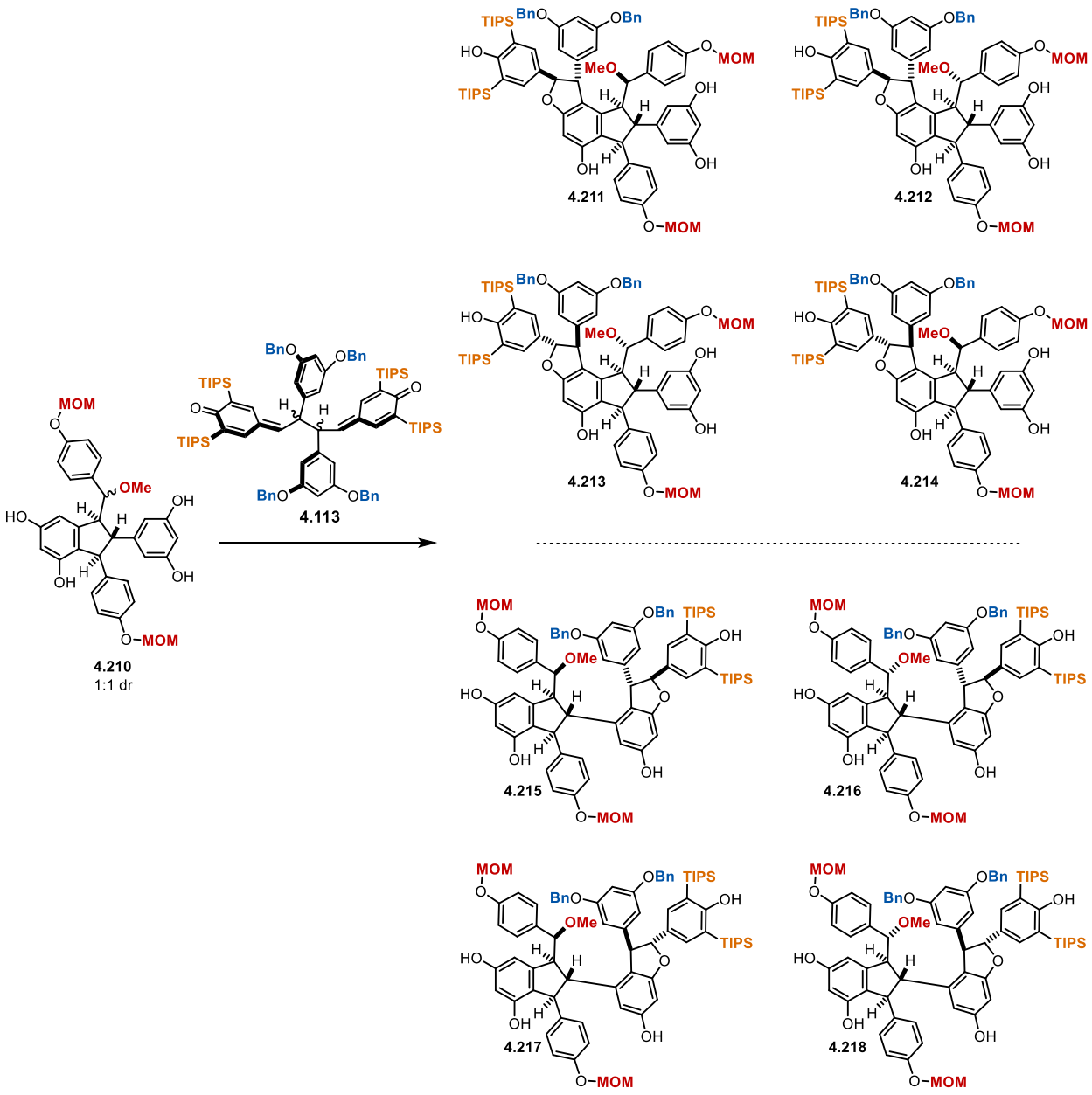
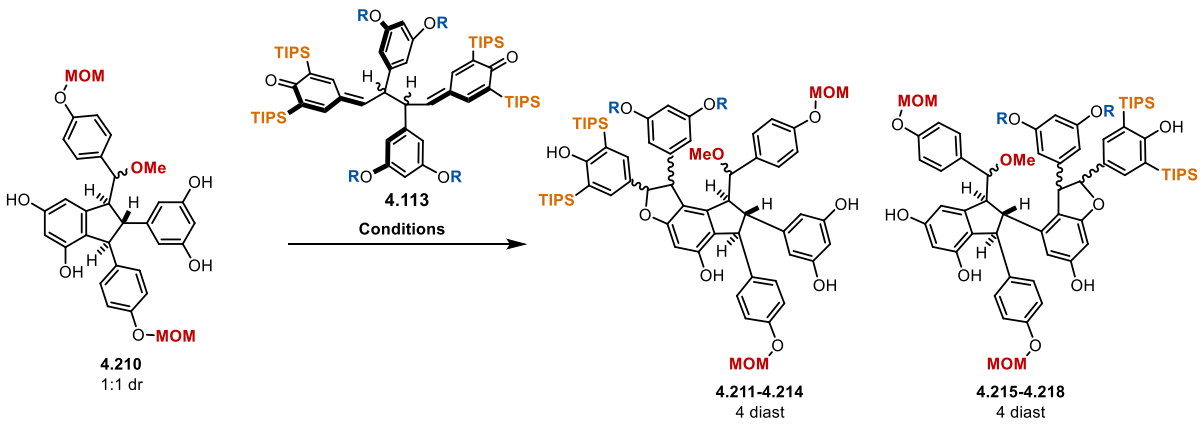


Figure 4.43 Diastereomers feasibly produced from DHB oligomerization of MOM, methanol protected indane

With **4.210** as a 1:1 ratio of diastereomers a set of eight mono-DHB diastereomers could be produced (**4.211-4.218**). While each methanol adduct epimer, such as **4.211** and **4.212**,

degenerates upon quinone formation, they represent distinct entities when purifying and analyzing this reaction. This rudimentary analysis also excludes any tetramers formed from DHB addition to trimer, which would result in another 16 distinct molecules (not drawn, 2 *trans* DHB diastereomers originating from each trimer drawn). This analysis also excludes the possibility of rotamers or atropisomer, which are feasible due to the high steric congestion of these systems and enantiomers, which are present but degenerate by standard NMR methods. These elements of selectivity are discussed to provide a framework for the design of future systems which could reduce the complexity of the system designed.

Table 4.7 DHB oligomerization of MOM, methanol protected indane

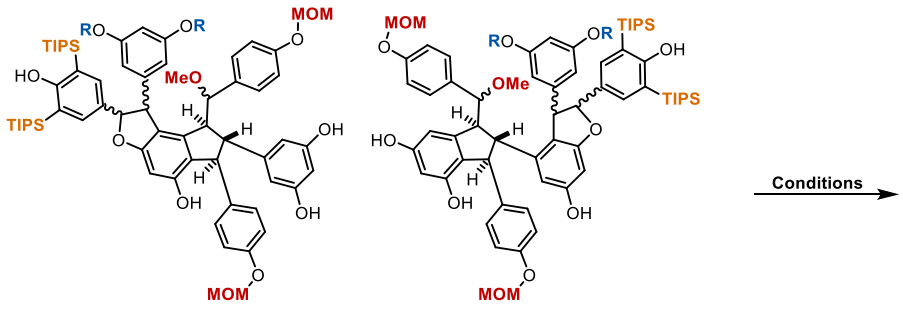


R	BQM Equiv	Conditions	Trimer % (mg)	BQM remaining?	Indane remaining	Davidiol A Precursor % (mg)	Distichol Precursor (%) mg	Confident 2D?
Bn	2	Acetone, 24 h, 120°C	44 % (19), Dirty	0%	0%			No
C3-tBu, Bn	1.5	Microwave, 3 h, 100°C	39% (14)	Yes	5%			Yes (after prep TLC)
Bn	1.5	Microwave, 3 h, 100°C	37% (16)	Yes	5%	6% (2.6)	22% (9.4)	Yes (after prep TLC)
TBS	1.5	Microwave, 3 h, 100°C	32% (14)	No	60%	Inseparable	Inseparable	No
TBS	2.0	Microwave, 3 h, 100°C	39% (21)	No	5%			
TBS	2.0	Microwave, 3 h, 100°C	38% (18)	No	24%			
TIPS	2.0	Microwave, 3 h, 100°C	44% (22)	Yes	57%			
TIPS	2.0	Microwave, 6 h, 100°C	56% (28)	Yes	18%			

Exposure of **4.120** (Table 4.7) to BQM (**4.113**) in a sealed tube at 120 °C consumed all starting material but did not return any clean trimeric material (**4.211-4.218**). The use of the microwave reactor at 100 °C for 3 hours returned starting material, but also small quantities of davidiol A (**4.211-4.214**, 6%, 2.6 mg) and distichol (**4.215-4.218**, 22%, 9.4 mg). The assignments

are tentative as even after multiple preparatory TLC separations all NMR represent mixed fraction of trimeric dihydrobenzofuran material.

Table 4.8 Attempts to converge trimeric material via cyclization



R	Conditions	Spots Isoalted (prep TLC)	Conclusion
TBS	3.0 M HCl in MeOH, rt, 3 h	7	1 promising fraction, MOM and TBS removed, Cyclized, <2 mg
TBS	0.5 M HCl in MeOH, reflux, 16 h	13	No fraction containing both DHB and intact indane core
TIPS	4 equiv of TBAF, 1:1 THF:MeOH, 0°C	5	4 fractions containing multiple DHB each, no reduction in complexity
TIPS	1, then 10, then 100 eq of TFA in 60% nitromethane in methanol	3	Degradation of indane core without loss of MOM group

To reduce the complexity of trimeric fractions, or allow chromatography separation, a series of cyclization conditions (Table 4.8). Trimeric fractions (**4.211-4.218**) were subjected to 3.0 M HCl in MeOH and after 7 spots were isolated by preparative TLC only a single fraction contained distinctive DHB peaks which could be cyclized with concurrent loss of both MOM and TBS protecting groups. Refluxing 0.5 M HCl in methanol resulted in complete DHB degradation. TBAF did not reduce the complexity of the mixture and TFA also resulted in degradation of the indane ring.

4.6 Synthetic studies towards laetevirenol C, D, E and parthenocissin B

After our efforts towards the total synthesis of distichol and davidiol A were stymied, we sought new synthetic targets. We located a set of four resveratrol trimers, laetevirenol C, D, E, and parthenocissin B (**4.219-4.222**, Figure 4.44) of structural similarity.[324,325] We envisioned their synthesis from a suitably protected indane core, with the blue fragment introduced via our microwave persistent radical oligomerization with a suitable bis-quinone methide. The

oligomerization is diastereoselective, but not enantioselective we planned to synthesize both laetevirenol C (**4.129**) and laetevirenol D (**4.220**) from the same indane starting material in a divergent synthesis.

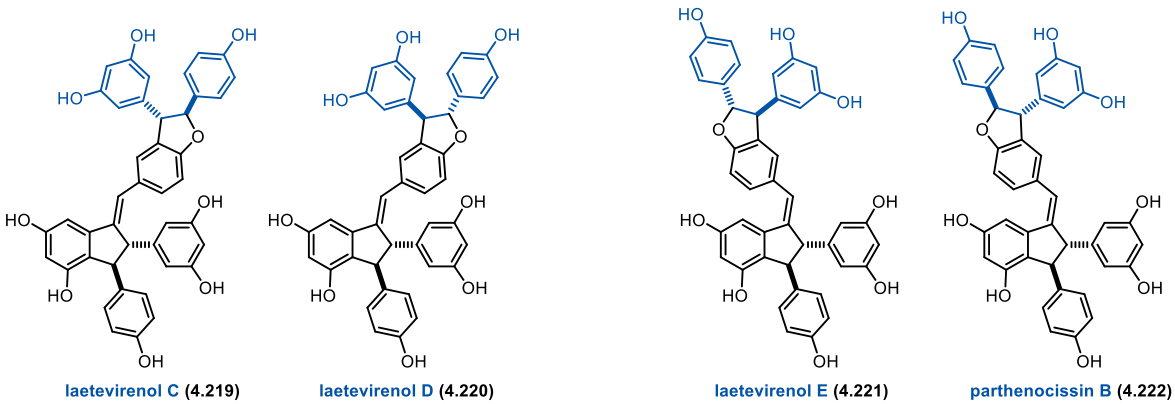


Figure 4.44 Structures of laetevirenol C, D, E, and parthenocissin B

Our strategy was motivated by the efforts of the isolation team of Jiang and co-workers who first isolated the laetevirenol family of trimers in 2008 (Figure 4.45).[325] The authors reported irradiating quadrangularin A (**4.223**, Figure 4.45) with UVA light (> 300 nm) and observing a scrambling of the olefin geometry obtaining a 30% yield of parthenocissin A (**4.224**). More notably, the authors subjected quadrangularin A to oxidative radical conditions (Horseradish Peroxidase, H_2O_2) in the presence of resveratrol. The obtained a 14% yield of laetevirenol C and 14% of laetevirenol D. The combined yield of 28% is remarkable for this type of unprotected oxidation of resveratrol and unprotected indane. The 1:1 ratio of dihydrobenzofuran diastereomers implies that the radical coupling does not occur in the pocket of the enzyme, but rather an oxidation of resveratrol produces a set of radicals which couple and cyclize, similar to the DHB mechanism we originally proposed. This could also be influenced by the lack of dirigent enzymes present in solution. The isolation of other dihydrobenzofuran products is not noted. The regioselectivity between the phenols present is promising, as it could allow for the use of our microwave oligomerization to have the same privileged selectivity. Analogous chemistry was reported for the

oxidative enzymatic coupling of parthenocissin A (**4.224**) to synthesize both laetevirenol E (**4.221**) and parthenocissin B (**4.222**). The set of four trimers were also demonstrated to photochemically isomerize similarly to their indane dimer starting materials.

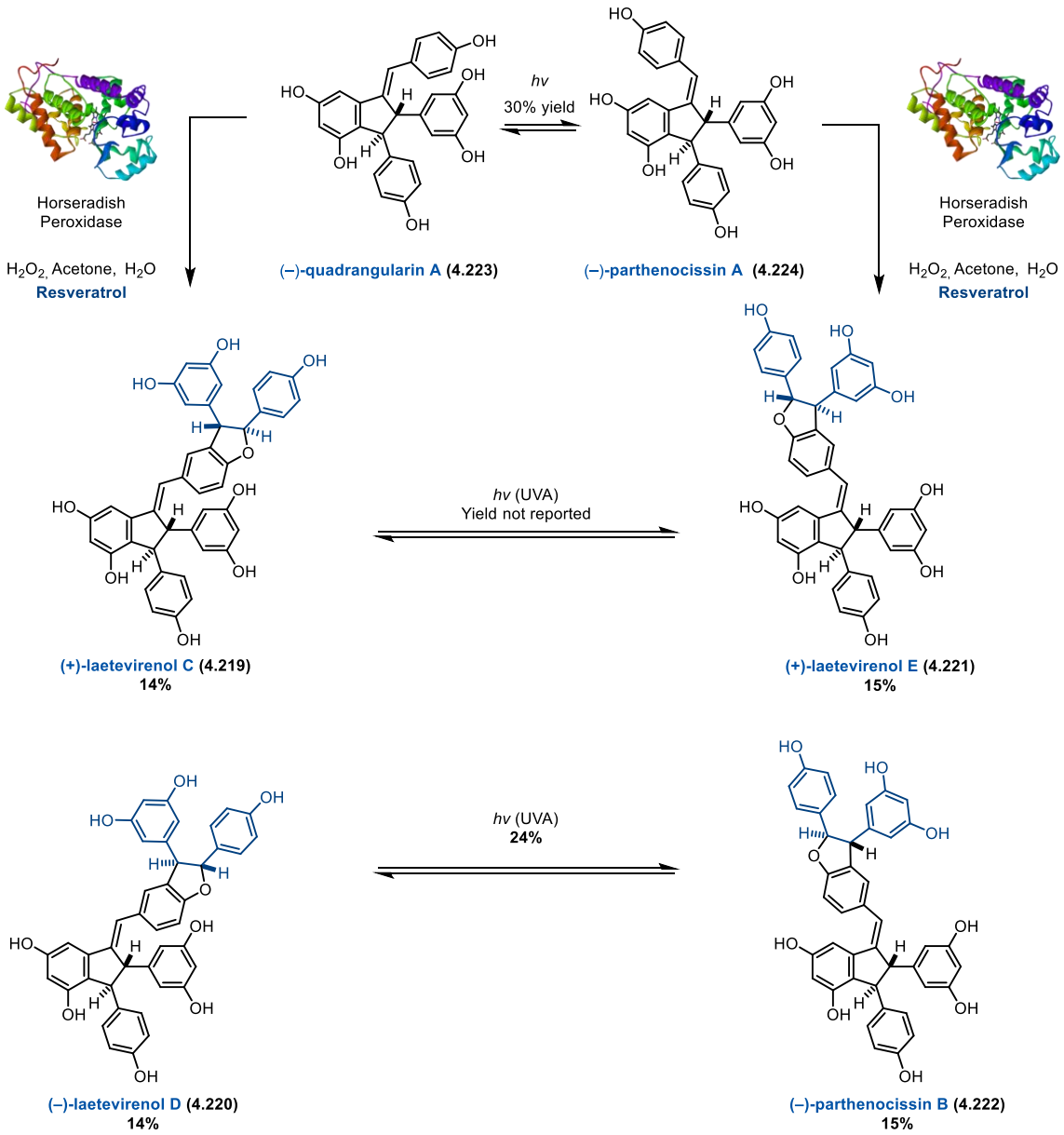


Figure 4.45 Biomimetic interconversions of indane derived resveratrol trimers

We chose to follow a similar biomimetic route towards this class of resveratrol trimers by oligomerizing a suitable indane (**4.223**, Figure 4.46) with a bis-quinone methide (**4.224**) to divergently synthesize the core of laetevirenol C and D in a single step.

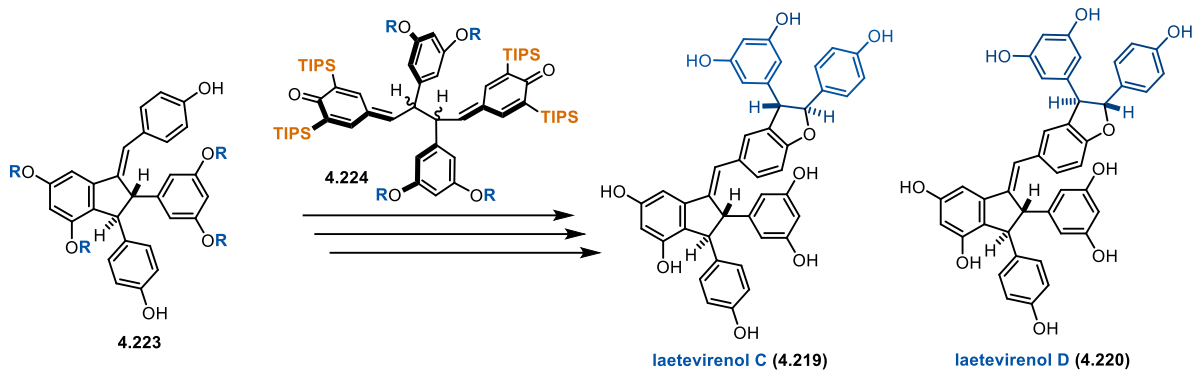


Figure 4.46 Synthetic strategy towards resveratrol trimers laetevirenol C and D

We began our efforts to synthesize a suitable core with **4.205** (Figure 4.47) a molecule which we had from our previous studies towards davidiol A and distichol. There were sparse reports of aliphatic alcohol elimination, but no studies on methyl ethers.[326] We found only degradation when subjecting **4.205** to BCl_3 or $AlCl_3$.

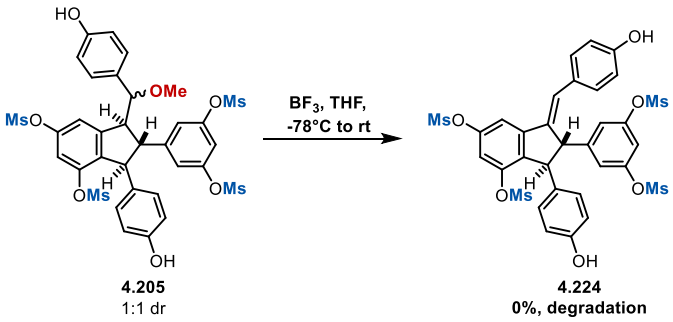


Figure 4.47 Attempts to eliminate aliphatic methyl ether to olefin on indane core

To circumvent our challenge with methoxide elimination we returned to the quinone oxidation state (**4.202**, Figure 4.48) with the aim of removing the TMS groups and isomerizing the olefin in a single step (**4.224**). We found early success using concentrated aqueous HCl with an organic co-solvent. Removal of the toluene allowed for clean production of **4.224**. This reaction was solely selective for the olefin drawn, with none of the other isomer detected. This isomer is

also the predominant product of photochemical isomerization, suggesting it is the thermodynamic product.[325]

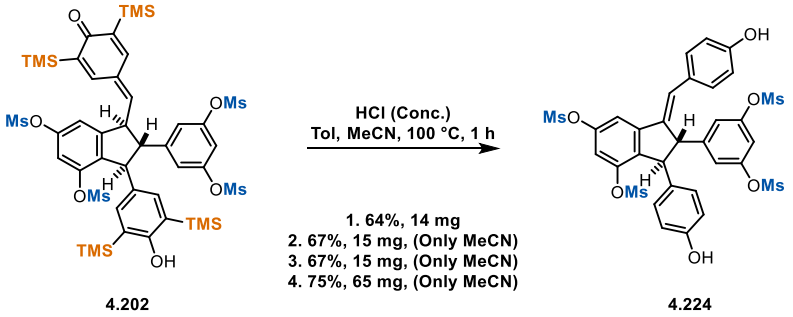


Figure 4.48 Acidic TMS deprotection and quinone to olefin isomerization screening

With **4.224** in hand, we utilized our microwave oligomerization conditions with bis-quinone methide **4.225** (Figure 4.49) bearing eight TIPS groups. This produced **4.226** in 48% yield, as a 1:1 mixture of *trans* DHB diastereomers with 21% recovered indane. Elongating the reaction time to 16 hours did increase the reaction yield (74%). Attempts to remove the mesyl protecting groups with hydrides, nucleophiles, and bases were unsuccessful to access **4.227**.[87] The challenge was then if partial deprotection was observed, the statistical mixture of deprotections was intractable to analyze.

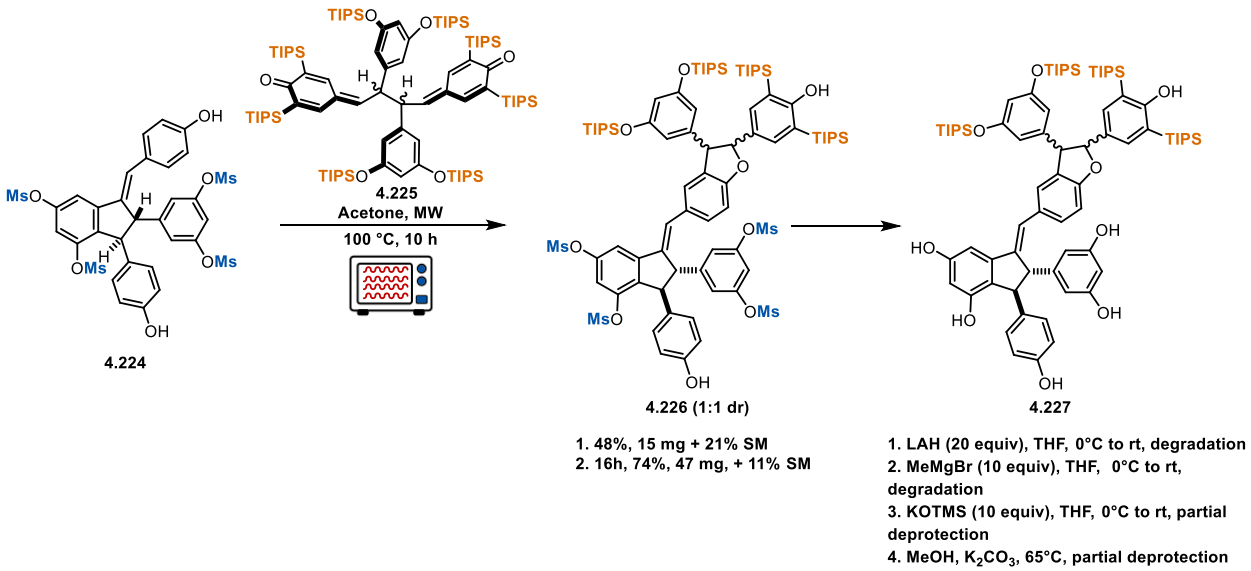


Figure 4.49 Oligomerization of mesyl protected indane towards laetevirenol C/D

To determine if the core of the molecule was stable to acid, standard methanol HCl conditions were used to remove the silyl blocking groups (**4.228**, Figure 4.50). We found good yield (74%) for this transformation but did not attempt at this stage the removal of the mesyl groups as the known challenges and low material available prompted a reconsideration of the protection strategy.

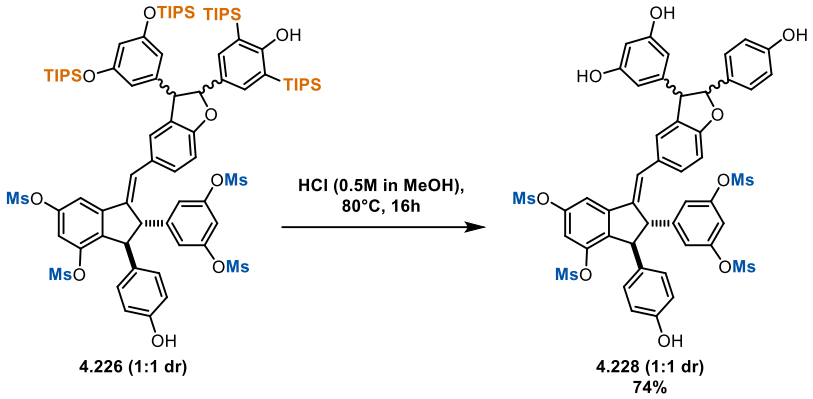
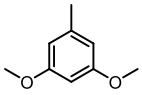
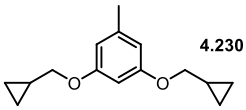
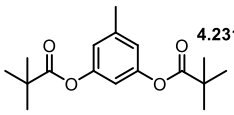


Figure 4.50 Acidic deprotection of TIPS, mesyl protected laetevirenol C/D

To generate data on the resorcinol system we were interested in a set of three molecules were synthesized (**4.229-4.231**, Table 4.9) with protecting groups which could be suitable to protect the indane in the developed route. The analysis was simply completed by TLC, as the large differences in polarity, along with co-spotting the parent orcinol made analysis rapid. Notably, the protection must survive refluxing aqueous HCl but be labile to other conditions which the trimeric core tolerates. The methyl ether (**4.229**) was found to be too stable, while the cyclopropylmethyl (**4.230**) labile in acid. The pivalate showed promise as it was uniquely labile in methanolic HCl compared to aqueous HCl.

Table 4.9 Analysis of phenolic protecting group stability in a variety of acids

	Protecting Group	Condition: Analysis by TLC, anisaldehyde stain — 0.5M HCl in MeOH, 80°C	MeCN and Aq HCl, rt	MeCN and Aq HCl, 100°C	Conclusion
 4.229	Methyl	Stable	Stable	Stable	too stable
 4.230	Cyclopropylmethyl	Partially Stable 50/50 mono-di	Mostly Stable 80% di	Not Stable 80% fully deprotected	too labile in acid
 4.231	Pivalate	Fully Deprotected	Mostly Stable >90% di	Med Stable 10:30:70	promising

Our efforts to protect our indane (**4.198**, Figure 4.51) was met with tepid success. A variety of conditions produced no more than 40% of the tetra-pivalate product, while cyclopropylmethyl, Bn, and PMB met similar fates. The use of MOM-Cl was extensively studies, including the preparation and distillation of fresh MOM-Cl.[327] There appeared to be nonlinear kinetics where after approximately 5 hours of reaction time the conversion would stall, and then revert slowly towards the starting material. The addition of excess electrophile, base, or temperature ramp did not alleviate this issue.

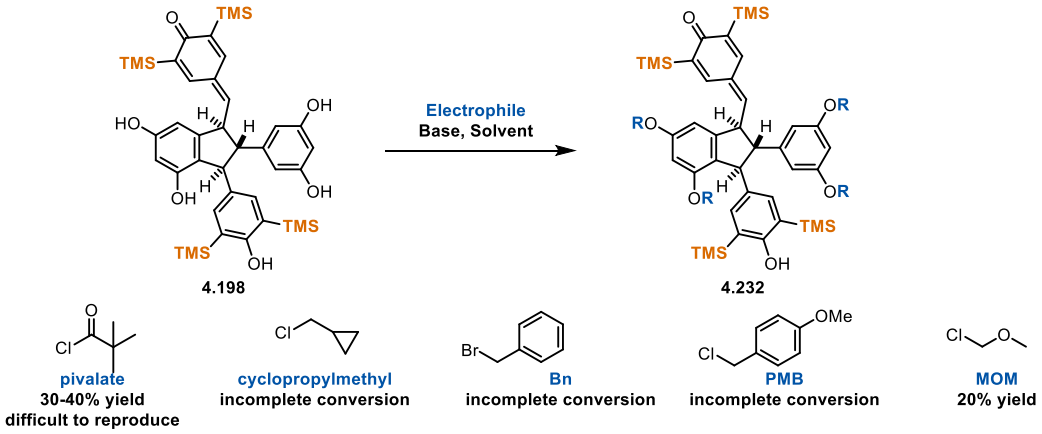


Figure 4.51 Summary of unsuccessful indane protecting groups

As the use of mesyl was successful until final deprotection, it was hypothesized that triflate protection, which is more labile, may be the solution. While triflic anhydride protection of **4.198**

(Figure 4.52) resulted in degradation, a substituted amine triflate source provided the olefin **4.234** in good yield (60-90%). This isomerization was unexpected, and it was determined through control experiments that the TEA was responsible for this reactivity. This likely occurs via an addition elimination mechanism, and the presence of the mono-triflate amine byproduct and longer reaction times allow this isomerization from quinone to olefin to occur. Acidic deprotection with HCl in dioxane provided **4.235** cleanly, suitable for microwave oligomerization.

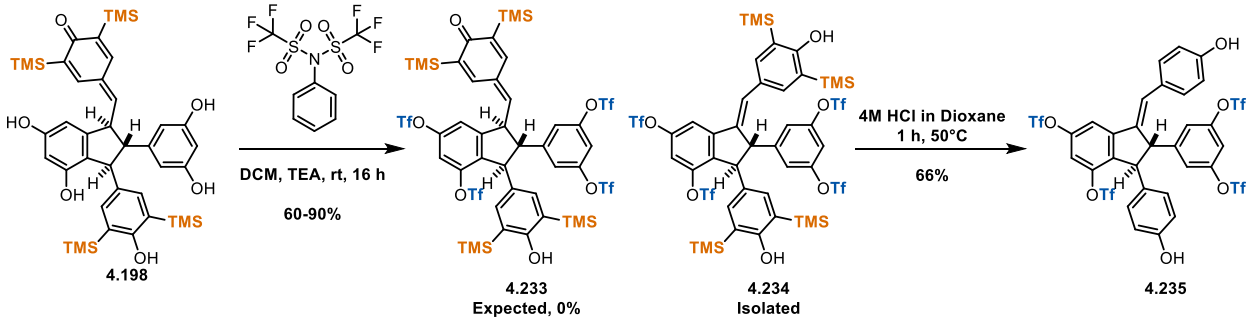


Figure 4.52 Elaboration of triflate protected indane

The microwave reactivity of **4.235** (Figure 4.53) with **4.236** provided the expected trimeric core (**4.237**) again as a 1:1 mixture of diastereomers. The use of a bis-quinone methide with 8 TIPS protecting groups provided a reduced yield (39%). We propose that the steric bulk of this system requires the use of a smaller BQM reagent. The removal of the triflate protected groups was again unsuccessful with a variety of reagents leading to degradation.

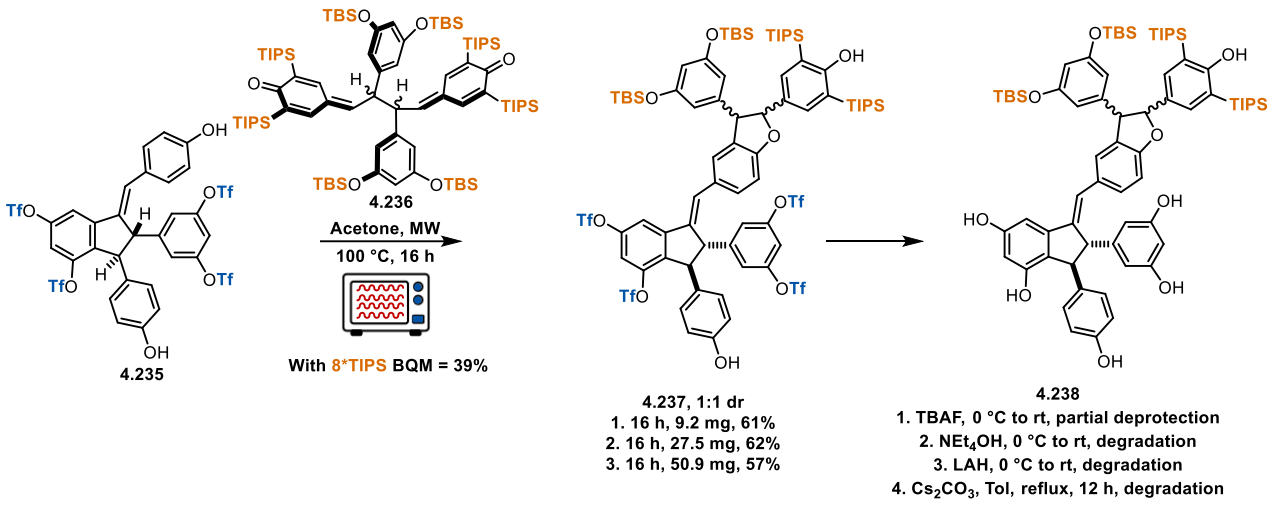


Figure 4.53 Microwave oligomerization of triflate protected indane

It is worth noting that the synthesis of **4.243** (Figure 4.54), the precursor to **4.236** (Figure 4.53) evolved over the course of our synthetic studies. A practical and scalable route was devised from **4.189** (Figure 4.54). The aldehyde (**4.241**) and phosphonium salt (**4.194**) were gave **4.242**, the trans olefin which could be deprotected with TBAF to provide **4.243**. This expedited route is both more scalable and reproducible to the previous route to **4.243**. The use of a TBS protected phosphonium salt, analogous to **4.194** was unsuccessful in a variety of conditions, with a silyl group switching strategy from TIPS to TBS being the valid alternative.

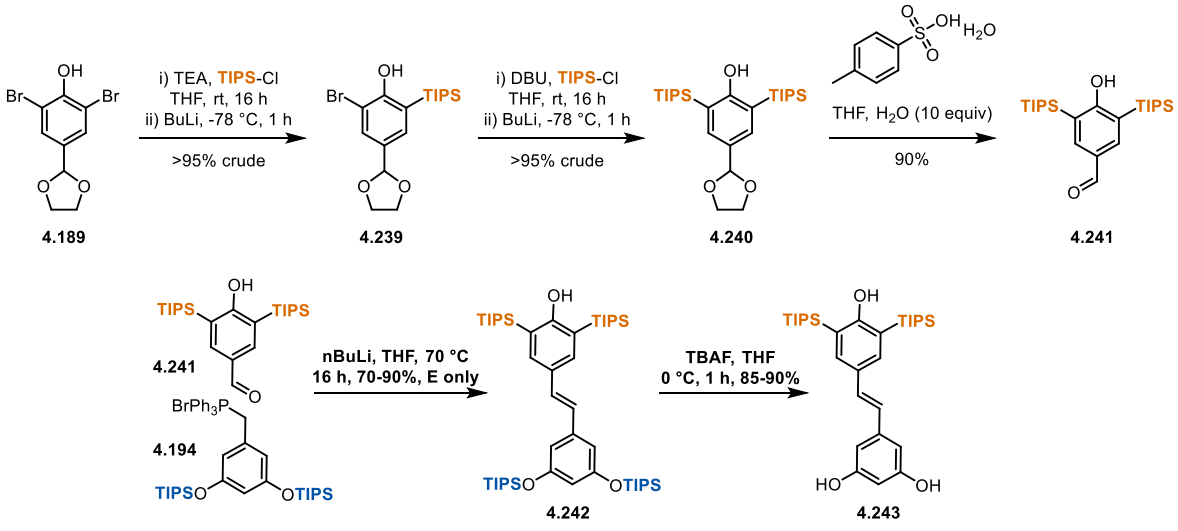
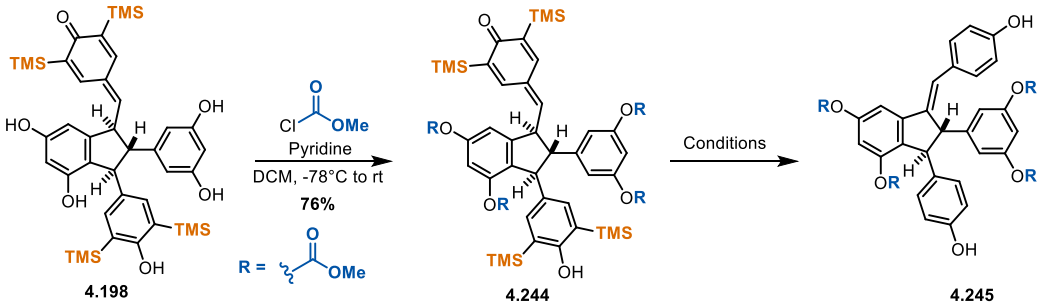


Figure 4.54 Revised synthesis of C3-TIPS protected stilbene

After careful consideration it was determined that a more acid labile phenolic protecting group was required, to allow global deprotection after microwave oligomerization. After exploring both carbonate and carbamate protection, the methyl carbonate was chosen as a suitable candidate (**4.224**, Figure 4.55). Initial efforts to remove the carbon TMS groups but retain the phenolic carbonate protection were unsuccessful in synthesizing **4.245**.

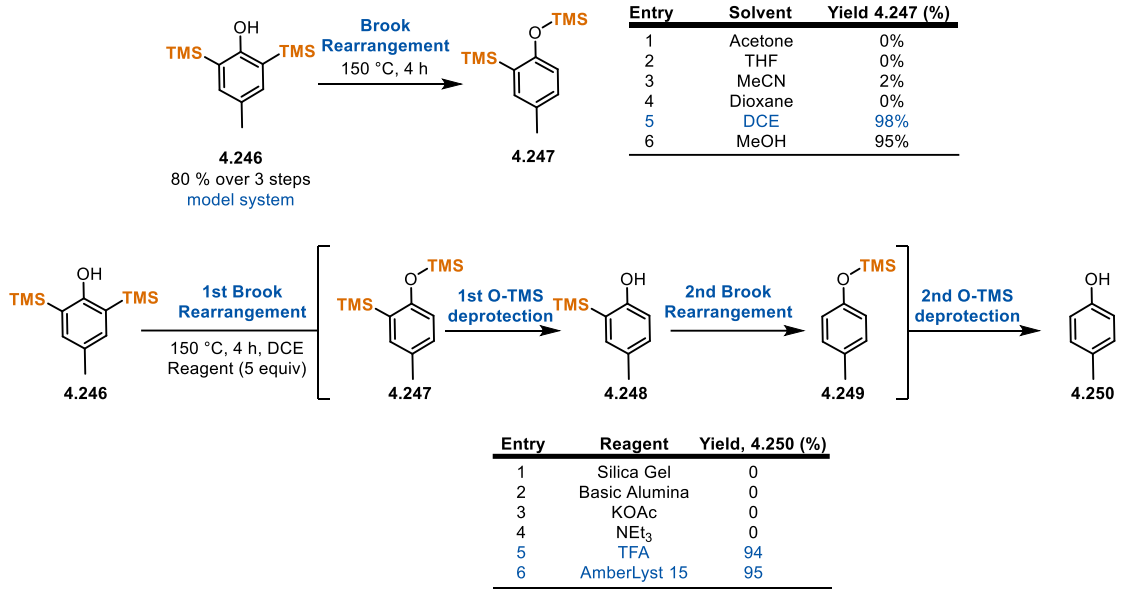


Entry	Acid	Solvent	Temp. (°C)	Yield (%)
1	TFA	MeOH	rt	6% (low conversion)
2	TFA	THF	66	0% (degradation
3	HCl	MeOH	rt	14% (low conversion)
4	HCl	MeOH	65	0% (degradation)
5	HCl	DCM	40	0% (degradation)

Figure 4.55 Methyl carbonate protection of indane

Instead of a single acidic deprotection step we turned to the Brook rearrangement as a solution to find locate conditions for the removal of C3-TMS groups (Figure 4.56). This rearrangement from carbon-silicon to oxygen-silicon bond is documented for aromatic systems, though not extensively.[328–331] Large solvent effects on the rate of rearrangement are known.[332] We chose to screen conditions in the microwave reactor to achieve consistent, reproducible heating. We used model substrate **4.246** and screened solvents for the Brook rearrangement to **4.247**. Both methanol and DCE were found to be superior solvents, with near quantitative conversion by crude ^{1}H NMR. The full elaboration of this method includes elaborating **4.246** to **4.250** in a single pot, with subsequent Brook rearrangements and O-TMS deprotections. The use of basic reagents (basic alumina, KOAc) did not provide any product and instead returned starting material **4.246**, indicating that they inhibit the Brook rearrangement. Both TFA and AmberLyst 15 provided near

quantitative conversion to **4.250**. AmberLyst 15 is a strongly acidic catalyst which is known to be industrially useful for esterification and phenol alkylation reactions.[333]



Entry	Solvent	Yield 4.247 (%)
1	Acetone	0%
2	THF	0%
3	MeCN	2%
4	Dioxane	0%
5	DCE	98%
6	MeOH	95%

Entry	Reagent	Yield, 4.250 (%)
1	Silica Gel	0
2	Basic Alumina	0
3	KOAc	0
4	NEt_3	0
5	TFA	94
6	AmberLyst 15	95

Figure 4.56 Brook rearrangement as a strategy for carbon TMS deprotection

When returning to the system of interest (**4.244**, Figure 4.57) we found that adjusting the temperature to 75 °C was crucial for clean reactivity with the AmberLyst 15 reagent. Notable, the use of the same equivalents of TFA under the same conditions provides degradation through deprotection of the methyl carbonate protecting groups.

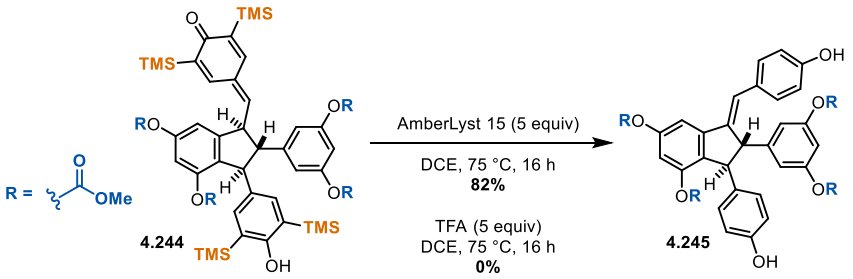


Figure 4.57 Use of AmberLyst 15 for TMS deprotection

The microwave oligomerization of **4.245** (Figure 4.58) proceeded smoothly with the TBS protected bis-quinone methide (**4.236**), providing 64% of a 1:1 diastereomer mixture of trimeric

cores (**4.246**, **4.247**). The resorcinol TIPS protection (**4.225**) of the bis-quinone methide performed significantly worse (26%) reinforcing the steric considerations of the BQM reagent.

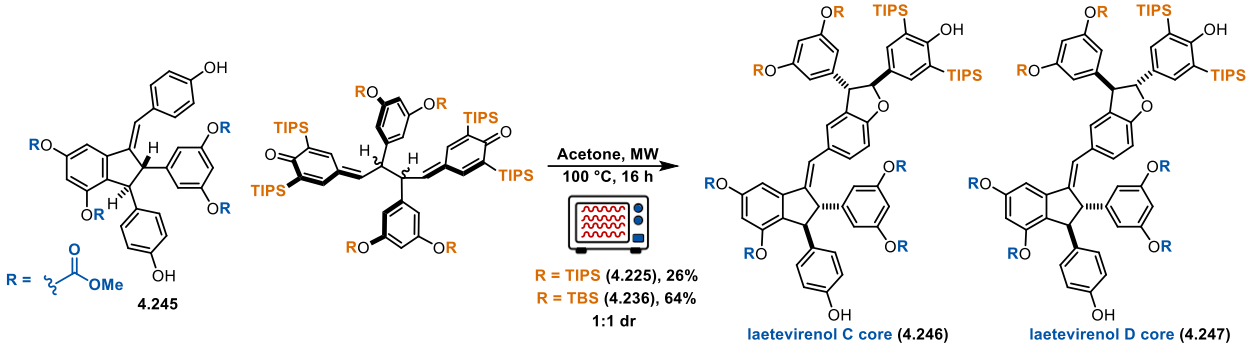


Figure 4.58 Microwave oligomerization of methyl carbonate protected indane

The deprotection of **4.246/4.247 (**Figure 4.59**)** with acid produced an internalization of the olefin in high yield, giving **4.248**. This rearrangement is not documented for this trimeric system, but has been reported on simpler indanes.[334,335] Notably this isomerization was not observed when the indane core remained protected with a mesyl or triflate group. A series of acids were screened on **4.245** (Figure 4.58) and did not locate conditions to remove the methyl carbonate protecting groups while preventing olefin isomerization. Due to this conclusion, we chose to pursue a Brook rearrangement strategy to remove the carbon TIPS groups present on the trimer cores.

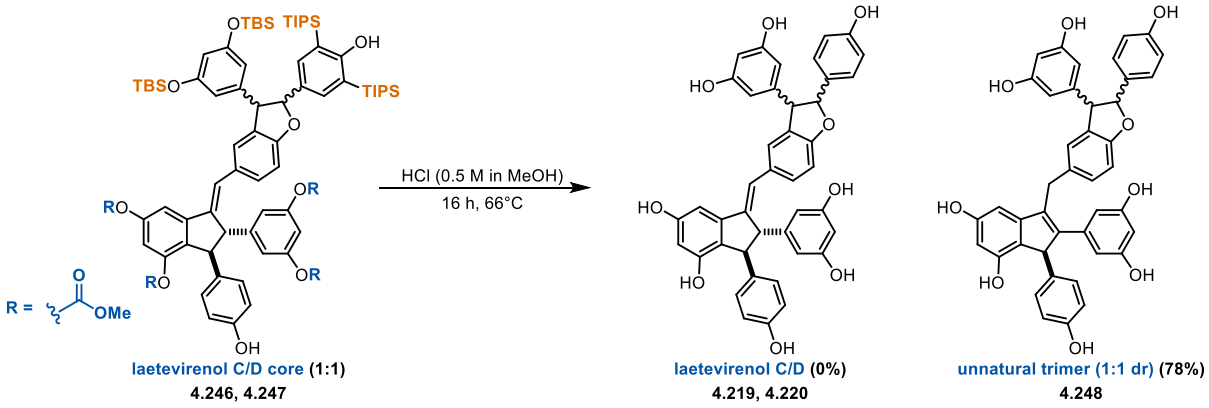


Figure 4.59 Acidic deprotection of laetevirenol C/D with methyl carbonate core

We screened conditions for the Brook rearrangement of **4.249** (Figure 4.60) finding that DCE is the superior solvent at 150 °C for 4 hours, or 175 °C for 2 hours, providing **4.250**. The use

of fluoride, or acid in DCE did not result in the conversion to **4.251** or **4.252**, instead returning only **4.249**, with inhibition of the Brook rearrangement. This led us to instead consider a two step deprotection strategy, where **4.249** is Brook rearranged to the O-Silyl compound (not drawn) and subsequently fluoride deprotected (TBAF). This sequence ran twice provided **4.252**, thereby validating this strategy on a model system.

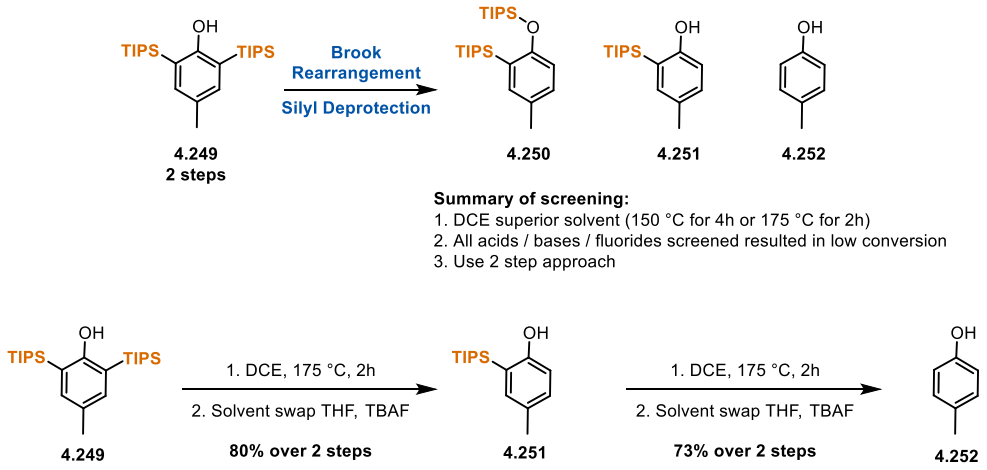


Figure 4.60 Use of a Brook rearrangement strategy for the removal of C3 TIPS groups

The first step in applying this strategy to the core of laetevirenol C/D was carbonate deprotection (**4.246/4.247**, Figure 4.61). The use of methanolic ammonia provided **4.253**. The Brook rearrangement to **4.254** was executed at 200 °C in tetrachloroethane as it allows for this high temperature reactivity under lower pressure conditions than DCE. This reaction at 175 °C for 4 hours resulted in incomplete conversion of the starting material. The TBAF deprotection to **4.255** removed the 3 oxygen-silyl groups. The final Brook rearrangement and subsequent TBAF deprotection require further optimization. This sequence is promising in unlocking the synthesis of laetevirenol C/D.

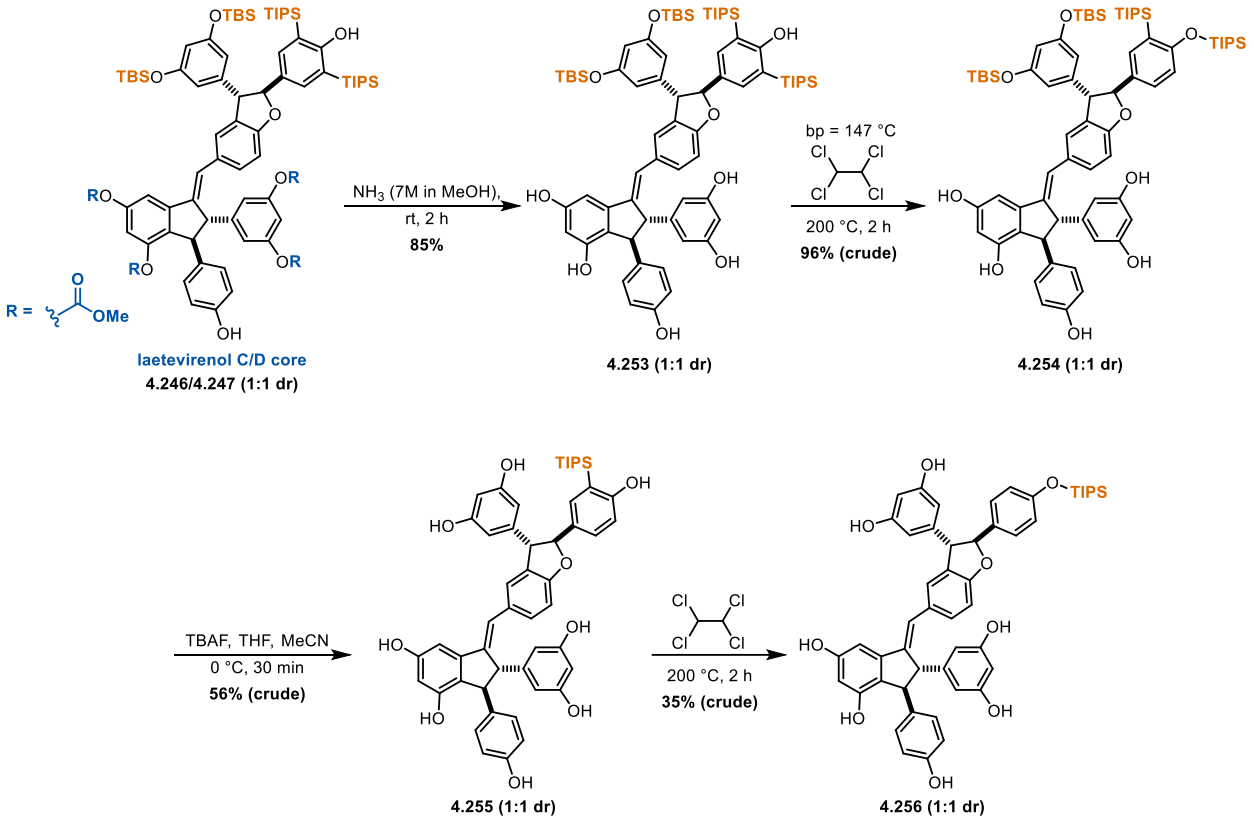


Figure 4.61 Brook rearrangement strategy to remove C-TIPS groups towards laetevirenol C/D

We have preliminary data towards the total synthesis of laetevirenol E (**4.221**, Figure 4.62) and parthenocissin B (**4.22**). The synthetic sequence towards these trimers will be largely conserved from the current synthetic route, the isomerization of the olefin being the main concern. While the original publication demonstrated the photochemical isomerization of the alkene trimers, a more elegant strategy would be controlling this selectivity earlier in the synthetic route. A plan could include photochemistry on the indane dime, such as **4.224**, which we have confirmed isomerizes to **4.257**, while the separation of these two is challenging.

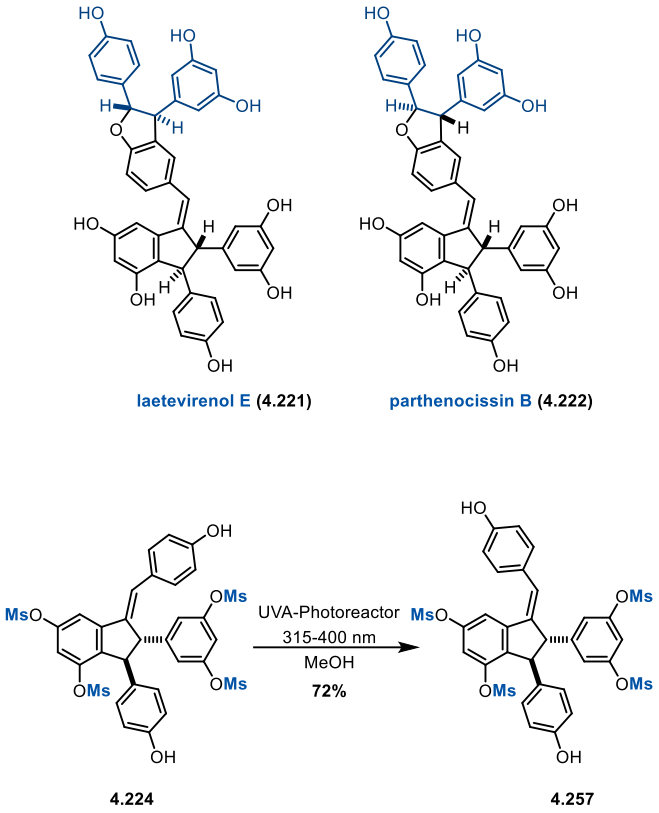


Figure 4.62 Preliminary efforts towards laetevirenol E and parthenocissin B

We believe these synthetic studies demonstrate the broad applicability of the microwave oligomerization methods developed herein. Discovering the same diastereoselectivity along a similar synthetic route as was proposed by the original isolation team is deeply rewarding, and we plan to report he finished synthesis of this set of four resveratrol trimers in due course. The completion of their synthesis is left to Sarah Maffett, a talented 1st year PhD student who I have had the honor of mentoring on this project.

4.7 Conclusions and future directions

In considering the future synthetic efforts of the Stephenson lab towards resveratrol oligomers there persists a few main themes. The use of dihydrobenzofuran formation (see Chapter 2) remains a robust strategy for the synthesis of higher order oligomers, with the elaboration of dimers (see Chapter 3) and trimers (see Chapter 4) provide a framework which can be built upon.

The dimeric intermediates synthesized provide opportunities for further oligomerization (Figure 4.63). For example, **4.259** is a partially protected dimer which could be elaborated to carasiphenol B (**4.250**), ampelopsin G (**4.260**), and vaticanol C (**4.261**) through a successive oligomerization strategy. The stability of the ampelopsin F core of these molecules would prevent some of the rearrangement challenges with other dimeric cores. The dimer **4.262** represents another diversified core capable of oligomerization towards gnetin H (**4.263**), vitisin E (**4.264**), and resviniferin B (**4.265**). Additionally, the dimer **4.224**, after a simple protecting group dance could provide **4.266**, capable of oligomerization to the core of both nepalensinol A (**4.267**) and cystilbenetrimerol A (**4.268**).

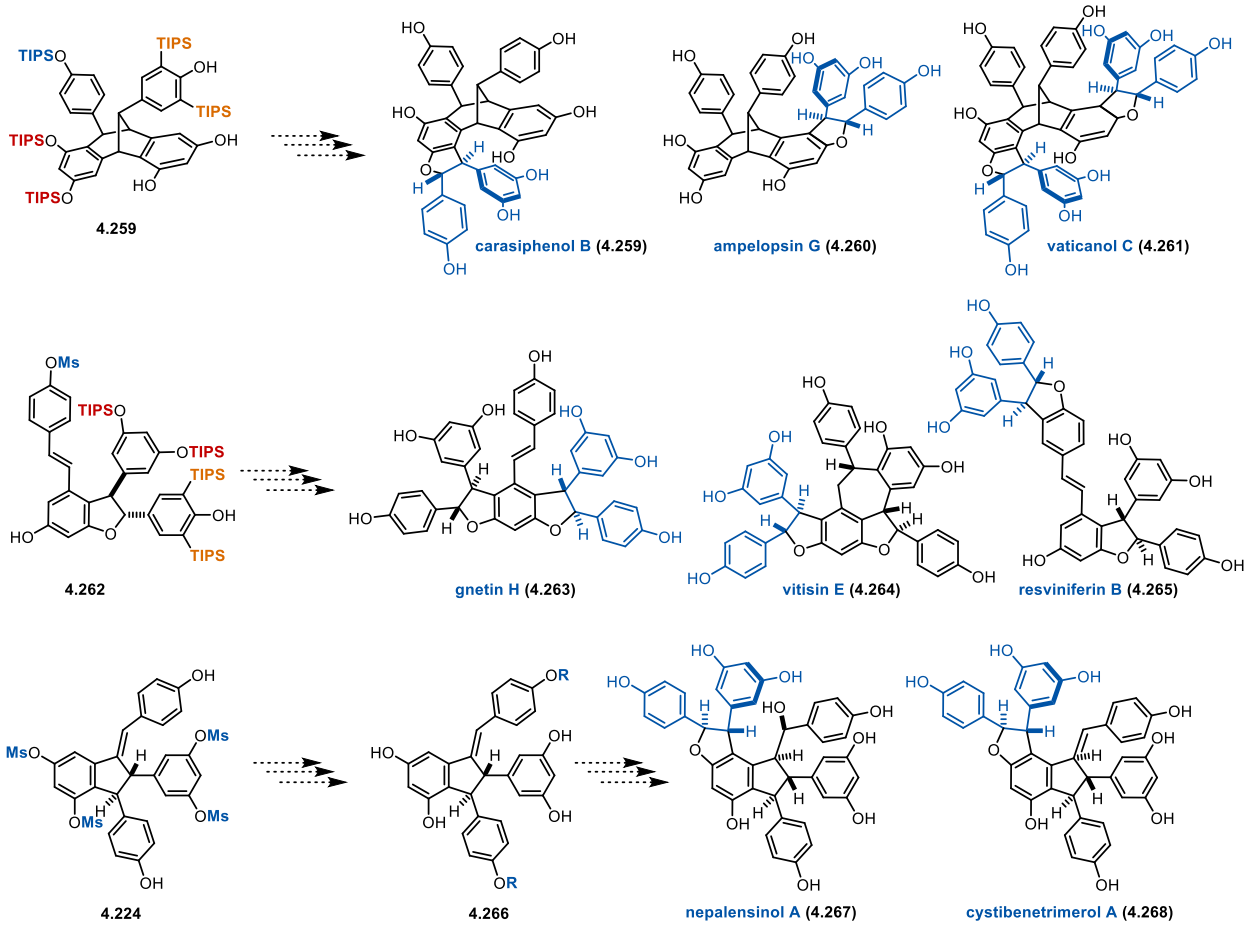


Figure 4.63 Synthetic future directions from dimers synthesized

These synthetic opportunities represent a small fraction of the future direction possible. This is due to the breadth of selective, biomimetic chemistry the Stephenson lab has developed towards resveratrol oligomers. The combined knowledge of the last decade has enabled the judicious selection of targets, and their synthesis. While no total synthesis is simple, the ability to predict the regioselectivity and diastereoselectivity of the reactions disclosed herein allows a rigorous analysis of any proposed total synthesis.

4.8 Experimental Procedures and Spectral Data

General Procedures: Unless specifically noted otherwise, all glassware was flame-dried under vacuum (~0.5 Torr) and cooled under inert atmosphere (N_2 or Ar) prior to use. Each reaction container was charged with a Teflon/PTFE-coated magnetic stir bar and sealed with a rubber septum to maintain a positive pressure of inert atmosphere (N_2 or Ar). Reagents sensitive to the atmosphere were transferred via syringe or cannula as necessary. Reaction conversion was evaluated using analytical thin-layer chromatography (TLC) using Merck Supelco® silica gel 60 F_{254} TLC plates. TLC plates were visualized under a dual short wave/long wave UV lamp and/or stained using a solution of potassium permanganate. Stained plates were developed over a heat gun as needed. These same TLC plates were used for preparative TLC when required.

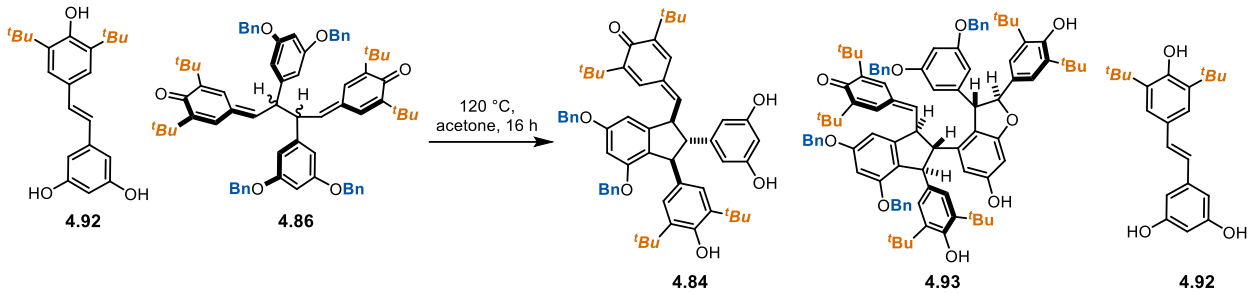
Reactions were purified via flash column chromatography with either Biotage® Sfär Silica D columns (standard separation) or Biotage® Sfär Silica HC D columns (challenging separations) using a Biotage® Isolera One automated chromatography system. Some reaction were also purified manually using SilicaFlash® Irregular Silica Gel (F60, 40-63 μm, 60 Å). Organic solutions were dried with either sodium sulfate or magnesium sulfate prior to column chromatography. Solvent was removed on a Büchi rotary evaporator and/or a Welch vacuum pump. All electrochemical experiments were done using a PINE research WaveNow system. The reference electrode was Ag/AgCl (3 M KCl, from CH Instruments). Bulk electrolysis experiments were performed in open 10-mL vials and in beakers of the appropriate size (20 – 500 mL). The reactions used RVC panels (reticulated vitreous carbon, 100 ppi, 0.25 inch thickness, 3% relative density, from ERG) as the working or counter/auxiliary electrodes and a Ag/AgCl (3 M KCl) reference electrode.

Product names were abbreviated for clarity. For racemic compounds, the name corresponds to the depicted structure. Nuclear magnetic resonance (NMR) spectra were obtained using an internal deuterium lock on Varian Inova 500 or Varian VNMR 500 and 700 spectrometers. For 1H spectra, chemical shifts were referenced to the center line of the residual solvent signal (CDCl3: δ 7.26; acetone-d6: δ 2.05; benzene-d6: δ 7.16; DMSO: δ 2.50) and are reported in parts per million (ppm). Signal multiplicity is reported as follows: (br = broad, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet), and the associated coupling constants are given in Hertz. For 13C spectra, experiments were completely heterodecoupled (broadband) and chemical shifts are reported as ppm using the center line of the solvent signal as reference (CDCl3: δ 77.16; acetone-d6: δ 29.92; benzene-d6: δ 128.06; DMSO: δ 39.52). 19F NMR chemical shifts were reported as δ, parts per million, relative to CFCl3 at 0.0 ppm. All 13C NMR spectra are proton- 58 decoupled. High-resolution mass spectra (HRMS) were acquired using a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer using electrospray ionization (ESI), positive ion mode. Infrared spectra were acquired using a Perkin-Elmer Spectrum BX FT-IR spectrophotometer using an ATR mount with a ZnSe crystal.

Reaction Materials: Commercially available reagents were used without further purification unless specified. Organic solvents (acetonitrile, dichloromethane, diethyl ether, dimethylformamide, dimethyl sulfoxide, methanol, tetrahydrofuran, and toluene) were purified/dried prior to use with a Phoenix Solvent Drying System from JC-Meyer Solvent System. Amine bases (triethylamine, pyridine, N,N-diisopropylethylamine, and diisopropylamine) were also purified/dried prior to use s and PureSolv Micro amine drying columns from Innovative Technology. Both systems were kept under a pressure of argon.

Product Analysis: Product names were abbreviated for clarity. Nuclear magnetic resonance (NMR) spectra were obtained using an internal deuterium lock on Varian VNMR 500 or 700 spectrometers. Other instruments used include a Bruker Advance Neo 500 and Bruker Avance 400 / 600 MHz spectrometers. For ^{1}H spectra, chemical shifts were referenced to the center line of the residual solvent signal ($CDCl_3$: δ 7.26; acetone-d6: δ 2.05) and are reported in parts per million (ppm). Signal multiplicity is reported as follows: (br = broad, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet), and the associated coupling constants are given in Hertz. For ^{13}C spectra, experiments were completely heterodecoupled (broadband) and chemical shifts are reported as ppm using the center line of the solvent signal as reference ($CDCl_3$: δ 77.16; acetone-d6: δ 29.92). High-resolution mass spectra (HRMS) were acquired using a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer using electrospray ionization (ESI), positive ion mode. Infrared spectra were acquired using a PerkinElmer Frontier FTIR equippted with universal ATR sampling. All NMR spectra were acquired at room temperature (~22 °C) unless otherwise noted.

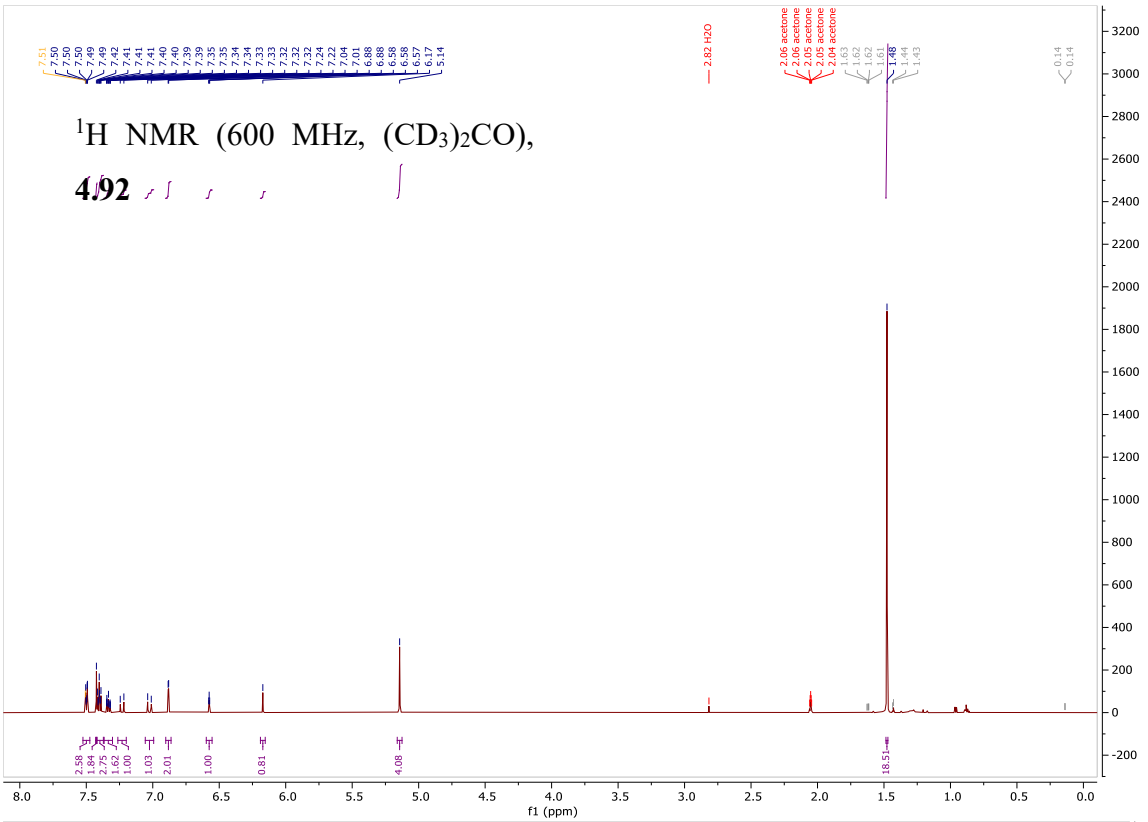
4.8.1 Towards davidiol A and distichol



(4.93) 4-(((1S,2S,3S)-4,6-bis(benzyloxy)-2-((2S,3S)-3-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-6-hydroxy-2,3-dihydrobenzofuran-4-yl)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2,3-dihydro-1H-inden-1-yl)methylene)-2,6-di-tert-butylcyclohexa-2,5-dien-1-one

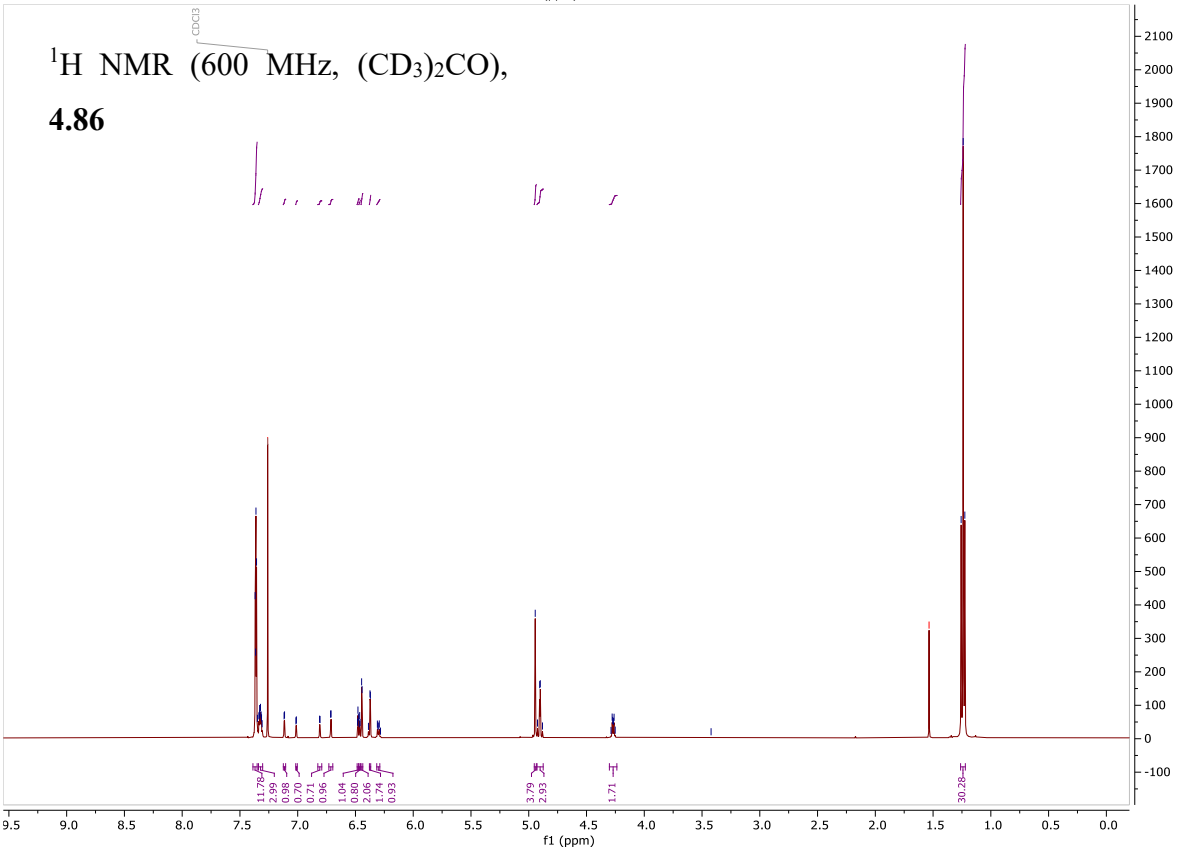
Representative procedure: In a flame-dried sealed tube added stilbene (50 mg, 150 µmol, 1 equiv), BQM (30mg, 289 µmol, 2 equiv), and acetone (12 mL, 0.12 M). The tube was capped with argon, sealed, and heated to 120 °C overnight (16 h). The crude reaction mixture was concentrated and purified by flash chromatography over SiO_2 (0%-30% EtOAc in Hexanes).

^{1}H NMR (600 MHz, $(CD_3)_2CO$), **4.92**	δ = 7.50 (d, J=7.9, 4H), 7.42 (s, 2H), 7.40 (d, J=7.8, 4H), 7.33 (t, J=7.4, 2H), 7.23 (d, J=16.3, 1H), 7.02 (d, J=16.3, 1H), 6.88 (d, J=2.2, 2H), 6.58 (t, J=2.2, 1H), 6.17 (s, 1H), 5.14 (s, 4H), 1.48 (s, 19H).
^{1}H NMR (600 MHz, $CDCl_3$), **4.86**	δ = 7.39 – 7.35 (m, 12H), 7.34 – 7.30 (m, 3H), 7.12 (d, J=2.3, 1H), 7.01 (d, J=2.4, 1H), 6.81 (d, J=2.4, 1H), 6.71 (d, J=2.4, 1H), 6.48 (t, J=2.2, 1H), 6.46 (t, J=2.2, 1H), 6.44 (d, J=2.2, 2H), 6.37 (d, J=2.2, 2H), 6.32 – 6.29 (m, 1H), 4.94 (s, 4H), 4.93 – 4.87 (m, 3H), 4.30 – 4.24 (m, 2H), 1.26 – 1.22 (m, 30H).
^{1}H NMR (600 MHz, $(CD_3)_2CO$), **4.84**	δ = 8.13 (s, 2H), 7.42 (d, J=7.0, 2H), 7.36 (t, J=7.5, 4H), 7.32 – 7.29 (m, 2H), 7.25 (d, J=2.4, 1H), 7.09 (d, J=2.4, 1H), 7.05 (s, 1H), 6.91 (s, 2H), 6.58 (d, J=2.3, 2H), 6.53 (t, J=2.2, 1H), 6.33 (d, J=2.1, 1H), 6.16 (dd, J=2.2, 1.0, 1H), 5.85 (s, 1H), 5.06 – 4.96 (m, 5H), 4.76 (t, J=9.8, 1H), 4.48 (d, J=9.1, 1H), 3.15 (d, J=9.3, 1H), 1.34 (s, 18H), 1.26 (s, 9H), 1.22 (s, 9H).



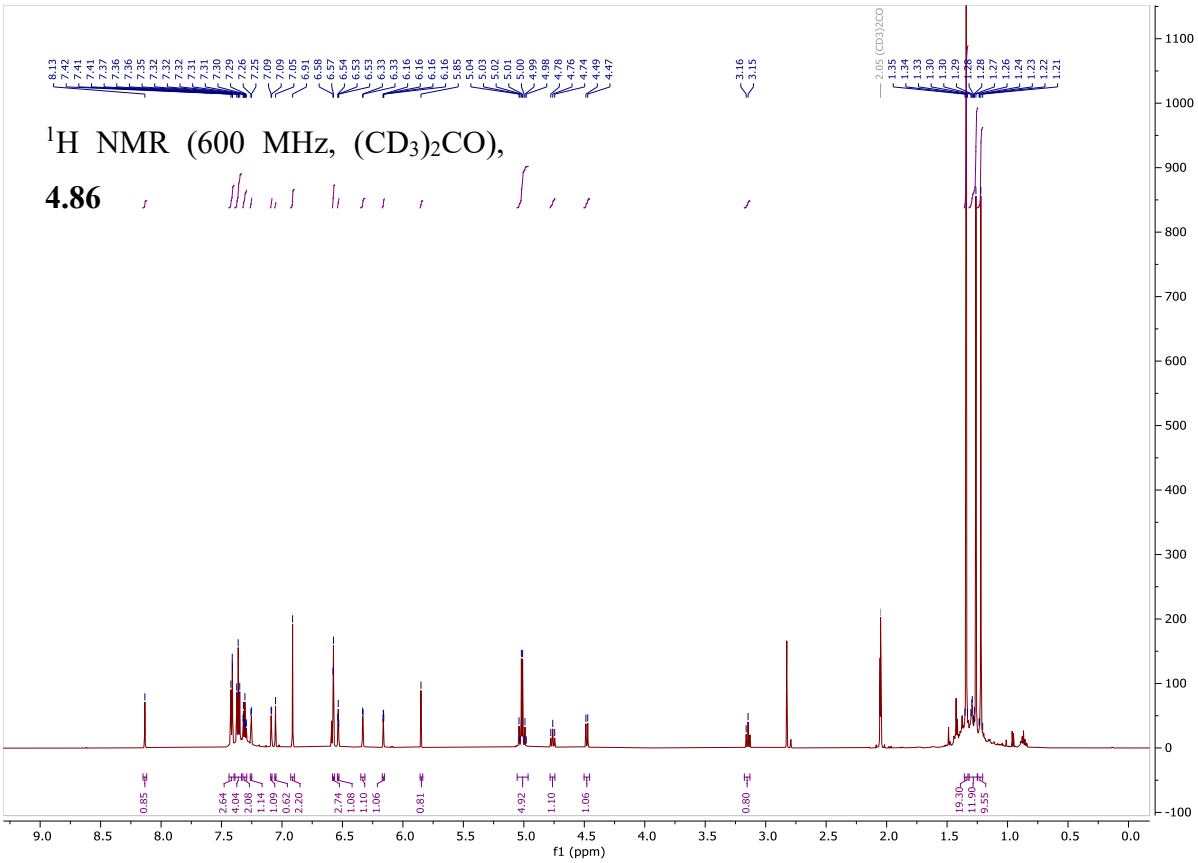
^{1}H NMR (600 MHz, $(CD_3)_2CO$),

4.92



^{1}H NMR (600 MHz, $(CD_3)_2CO$),

4.86



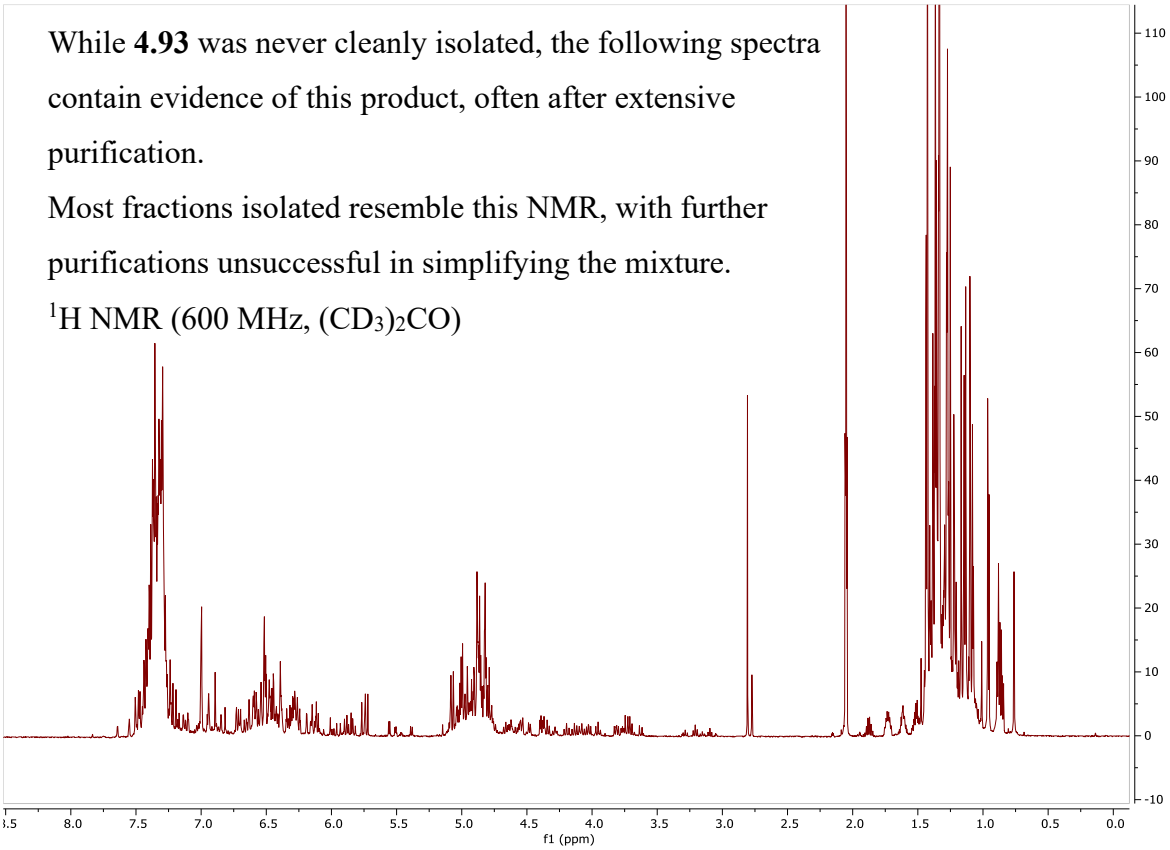
^{1}H NMR (600 MHz, $(CD_3)_2CO$),

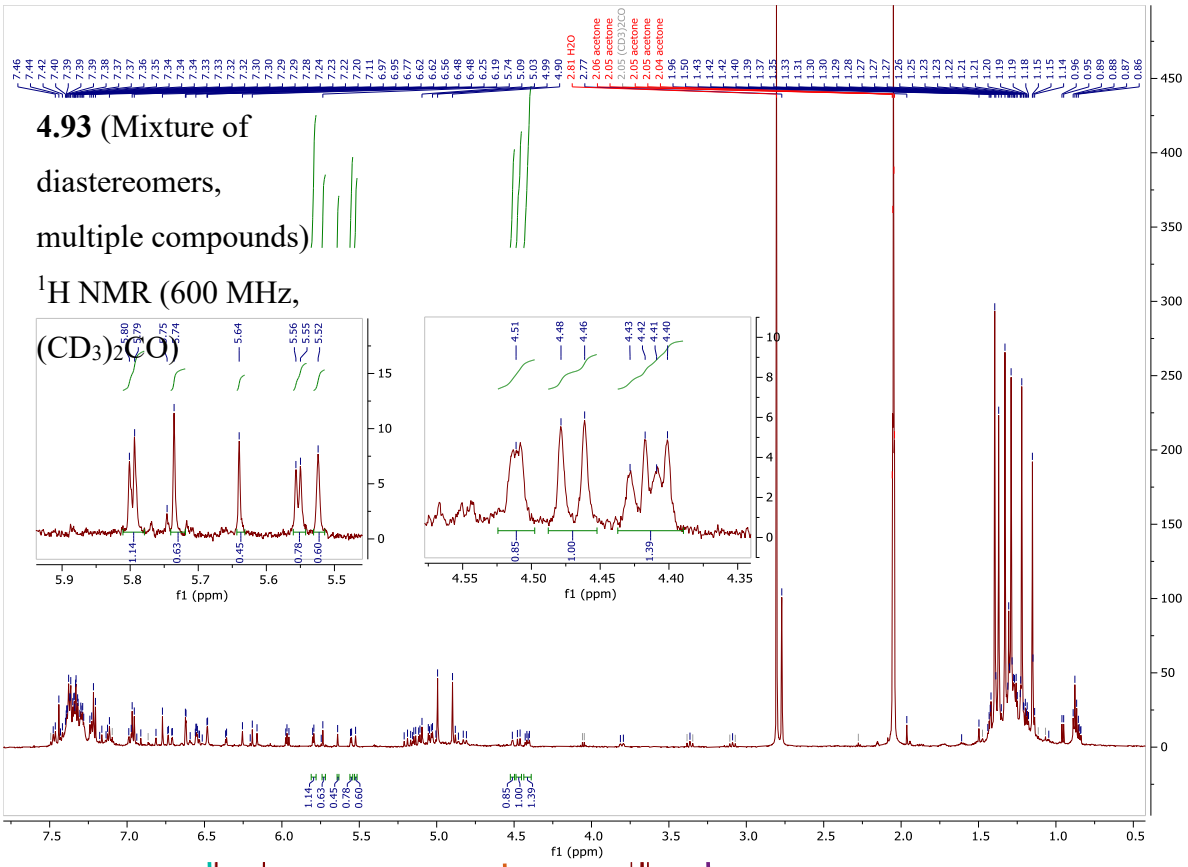
4.86

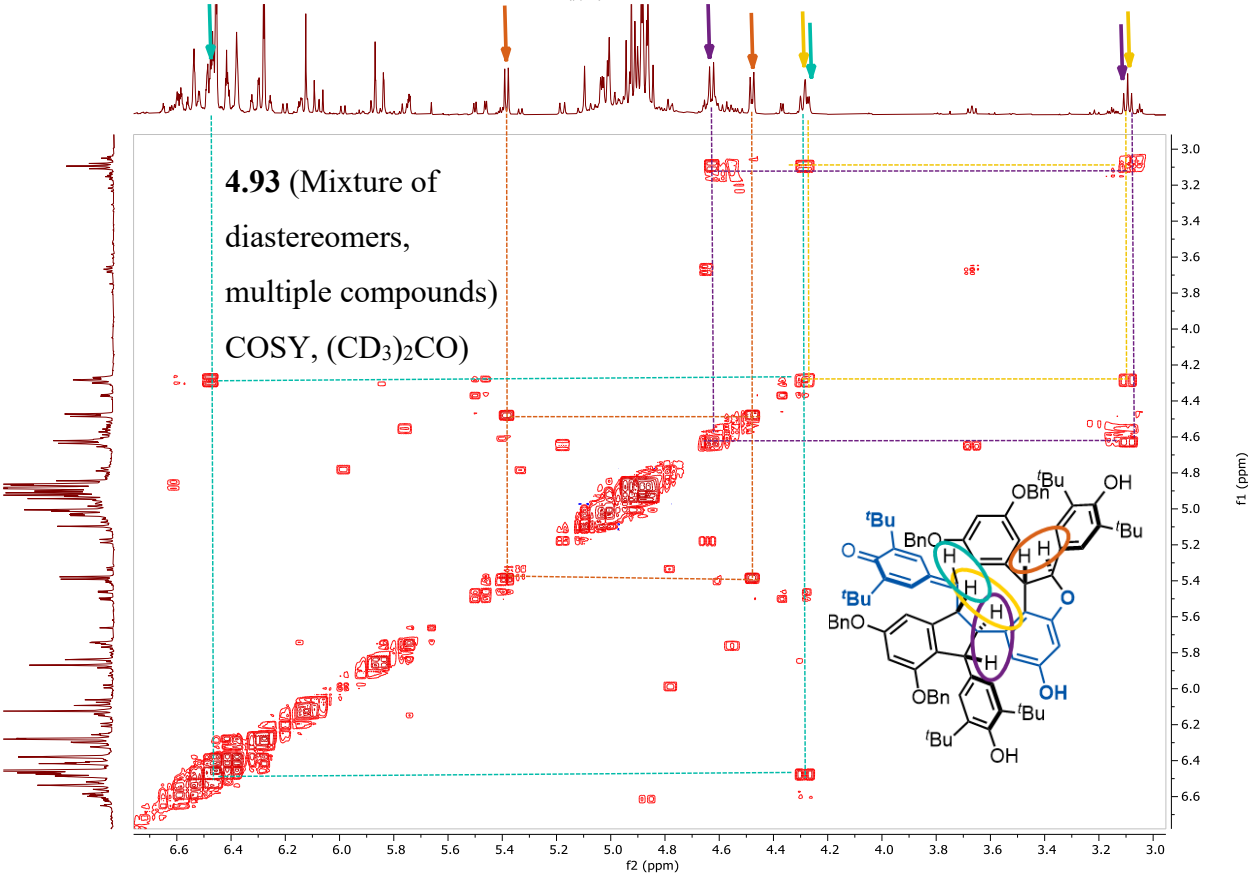
While **4.93** was never cleanly isolated, the following spectra contain evidence of this product, often after extensive purification.

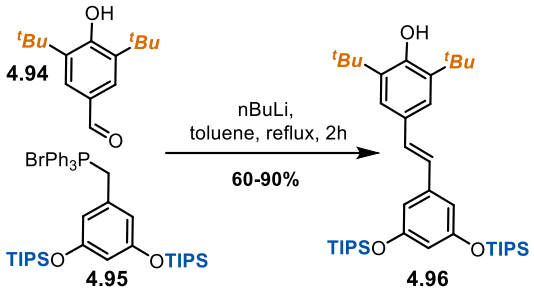
Most fractions isolated resemble this NMR, with further purifications unsuccessful in simplifying the mixture.

^{1}H NMR (600 MHz, $(CD_3)_2CO$)




4.93 (Mixture of diastereomers, multiple compounds)
1H NMR (600 MHz, (CD3)2CO)
f1 (ppm)


4.93 (Mixture of diastereomers, multiple compounds)
COSY, (CD3)2CO
f2 (ppm)
f1 (ppm)

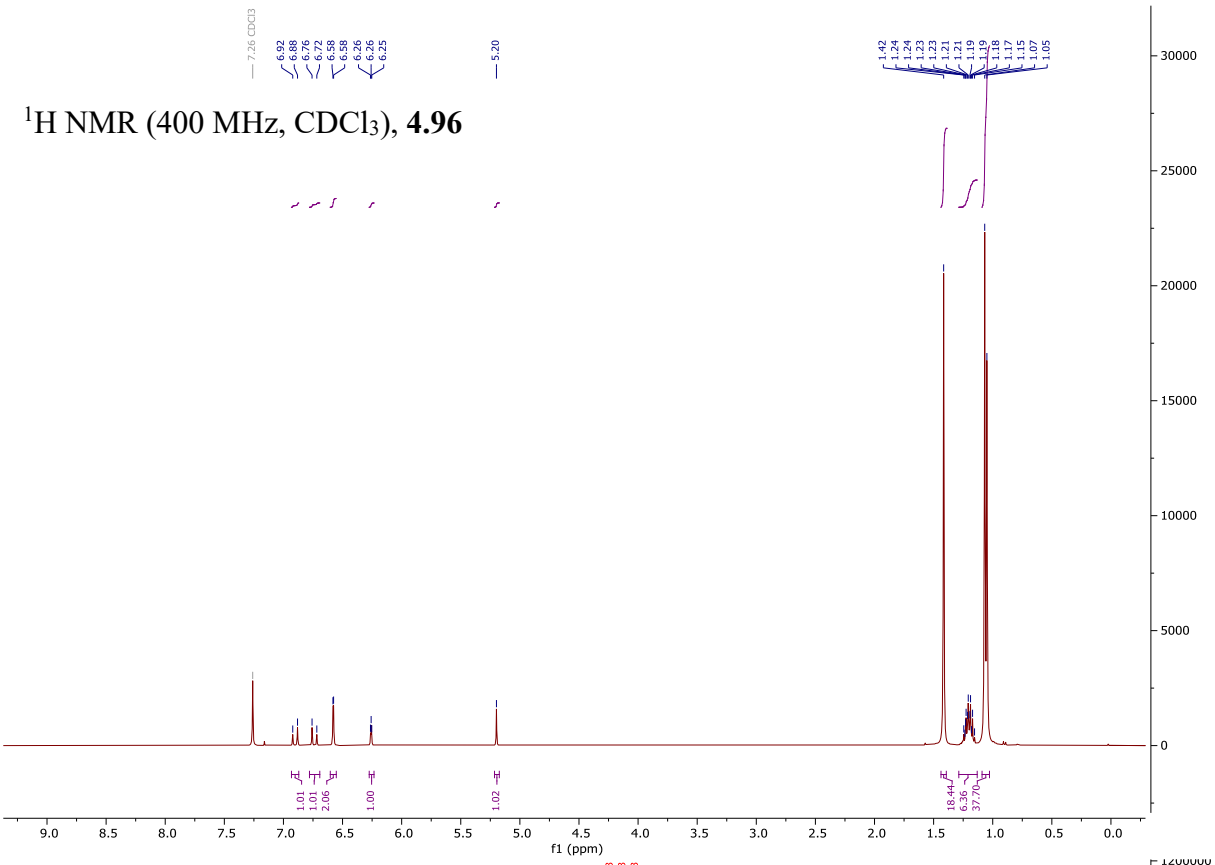


(4.96) (E)-4-(3,5-bis((triisopropylsilyl)oxy)styryl)-2,6-di-tert-butylphenol

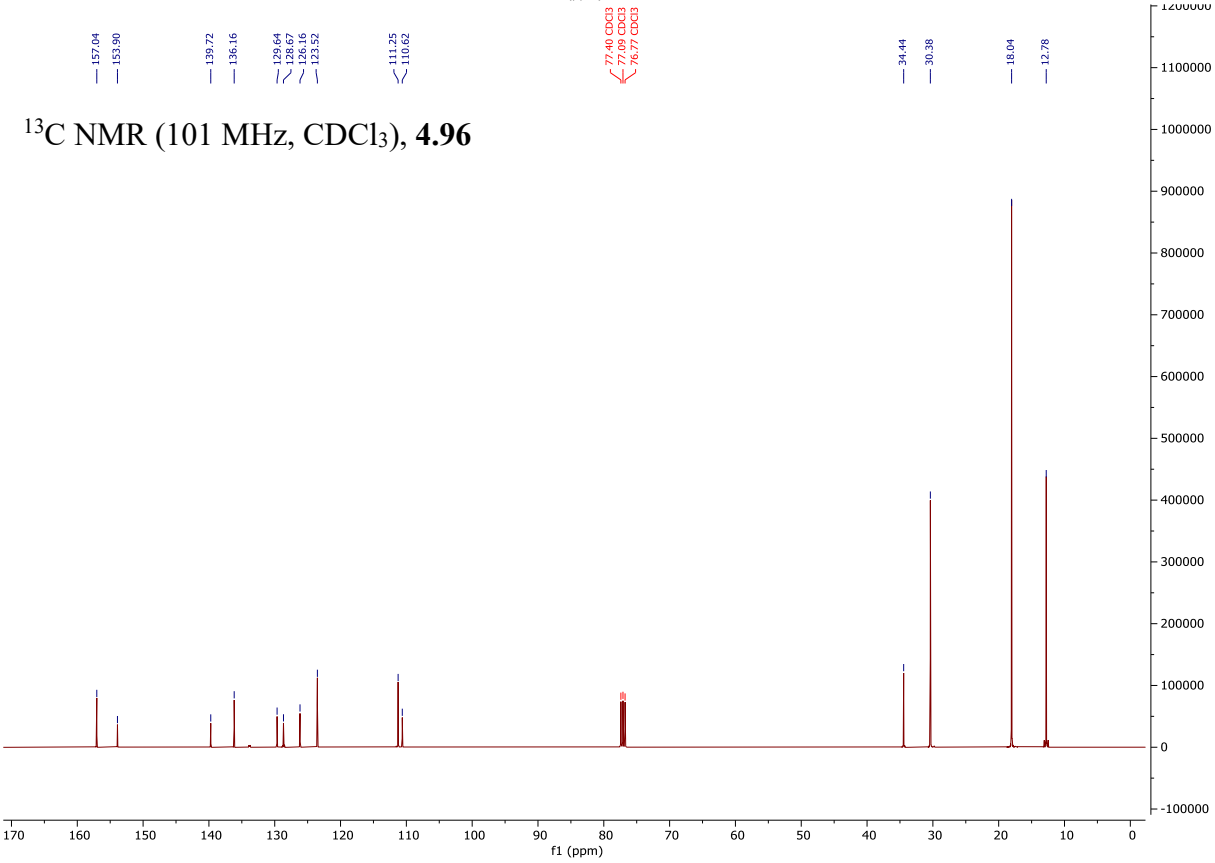
In a flame-dried 25 mL RBF was added salt (200 mg, 257 µmol, 1.3 equiv), toluene (2.5 mL, 0.1 M), and nBuLi (107 µL, 1.3 equiv). The bright red solution was stirred for 5 min before addition of aldehyde (46 mg, 198 µmol, 1 equiv) as a solid. The solution was heated to reflux (110 °C) for 2 h, upon which methanol was added to quench the reaction. The reaction was additionally quenched with water (20 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-15% EtOAc in Hexanes) to yield the product as an amorphous white powder (78 mg, 60%).

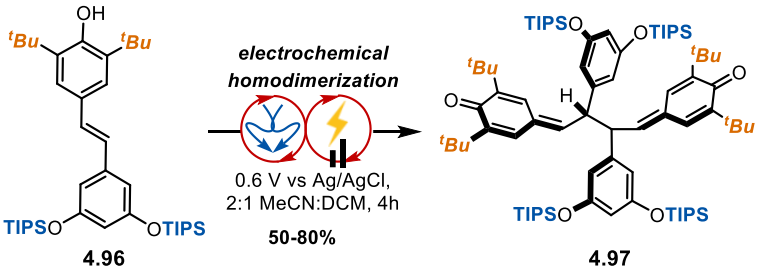
^{1}H NMR (400 MHz, $CDCl_3$)	δ = 6.90 (d, J=16.1, 1H), 6.74 (d, J=16.2, 1H), 6.58 (d, J=2.2, 2H), 6.26 (t, J=2.2, 1H), 5.20 (s, 1H), 1.42 (s, 18H), 1.20 (ddt, J=13.6, 10.2, 6.4, 6H), 1.06 (d, J=7.4, 38H).
^{13}C NMR (101 MHz, $CDCl_3$)	δ = 157.0, 153.9, 139.7, 136.2, 129.6, 128.7, 126.2, 123.5, 111.3, 110.6, 77.4, 77.1, 76.8, 34.4, 30.4, 18.0, 12.8.

^{1}H NMR (400 MHz, $CDCl_3$), **4.96**



^{13}C NMR (101 MHz, $CDCl_3$), **4.96**



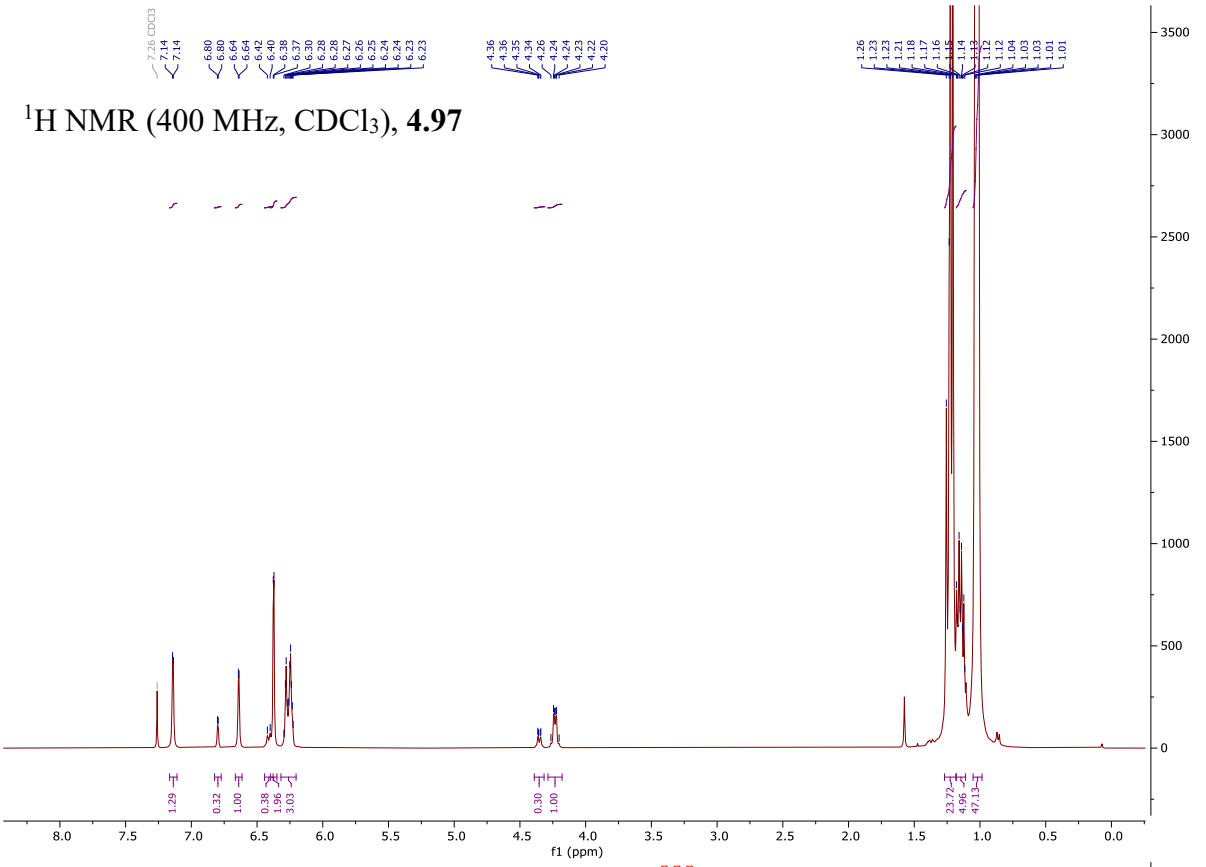


(4.97) 4,4'-((2R,3S)-2,3-bis(3,5-bis((triisopropylsilyl)oxy)phenyl)butane-1,4-diylidene)bis(2,6-di-tert-butylcyclohexa-2,5-dien-1-one)

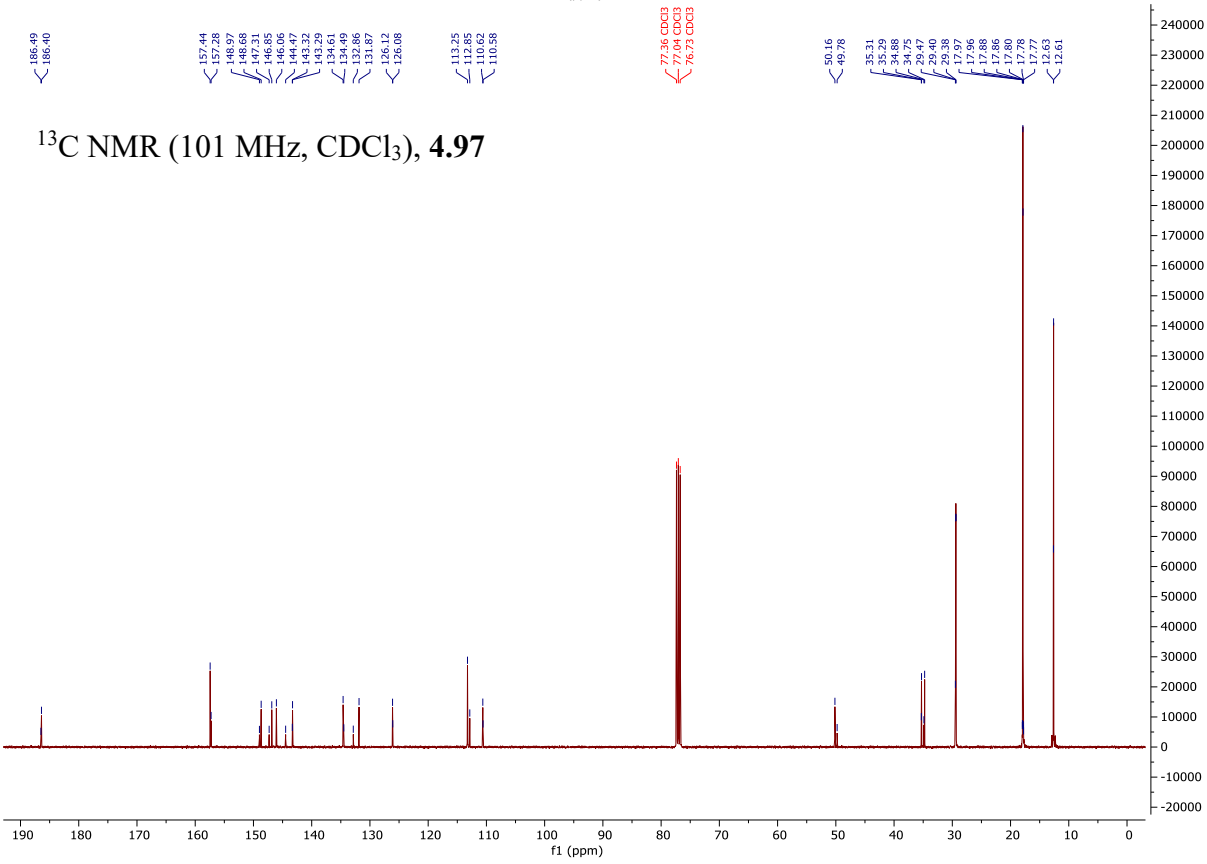
The starting phenol (1.6 g, 2.4 mmol, 1.0 equiv) was added to a 250 mL beaker with KPF_6 (1.8 g, 9.8 mmol, 4.0 equiv) and 2,6-lutidine (0.28 mL, 2.4 mmol, 1.0 equiv) and dissolved in acetonitrile (133 mL) and dichloromethane (67 mL). Two pieces of 4 x 2-inch RVC panel (0.25-inch thickness) were cut. To each, a hole was made near one end, and copper wire was placed through the hole and wrapped around the top of each electrode. One end of the wire was left free to connect to the alligator clips. These electrodes were carefully placed into the beaker along with the reference electrode (Ag/AgCl in 3 M KCl) and a divider. The alligator clips were connected such that the reference and working electrodes were adjacent to each other, while the counter electrode was opposite the divider. Care was taken to ensure the copper wire was not submerged in solvent, nor the active components of the alligator clips touching each other. The reaction was stirred at 750 rpm for 1-2 h at a constant voltage of 0.6 V. A chronoampergram was recorded to follow the course of the reaction. Upon completion of the reaction, the electrodes were removed and rinsed into a collection flask with DCM (~200 mL). The contents of the reaction vial were also rinsed into the collection flask. The solvent was removed in vacuo, and the crude material was purified by flash chromatography over SiO_2 (0%-30% EtOAc in Hexanes) to yield the product as a bright yellow foam (948 mg, 59%, 3.3:1 mixture of diastereomers).

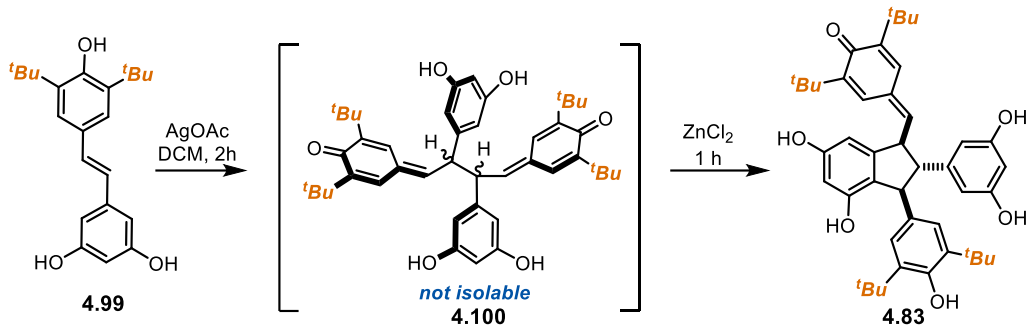
^{1}H NMR (400 MHz, $CDCl_3$)	δ = 7.14 (d, J=2.3, 1H), 6.80 (d, J=2.4, 0H), 6.64 (d, J=2.3, 1H), 6.41 (d, J=8.4, 0H), 6.37 (d, J=2.1, 2H), 6.26 (ddd, J=11.1, 5.5, 2.7, 3H), 4.39 – 4.32 (m, 0H), 4.23 (dd, J=6.6, 2.7, 1H), 1.23 (dd, J=11.7, 8.2, 24H), 1.18 – 1.11 (m, 5H), 1.05 – 0.98 (m, 47H).
^{13}C NMR (101 MHz, $CDCl_3$)	δ = 186.5, 186.4, 157.4, 157.3, 149.0, 148.7, 147.3, 146.9, 146.1, 144.5, 143.3, 143.3, 134.6, 134.5, 132.9, 131.9, 126.1, 126.1, 113.2, 112.9, 110.6, 110.6, 77.4, 77.0, 76.7, 50.2, 49.8, 35.3, 35.3, 34.9, 34.8, 29.5, 29.4, 29.4, 18.0, 18.0, 17.9, 17.9, 17.8, 17.8, 17.8, 12.6, 12.6.

^{1}H NMR (400 MHz, $CDCl_3$), **4.97**



^{13}C NMR (101 MHz, $CDCl_3$), **4.97**



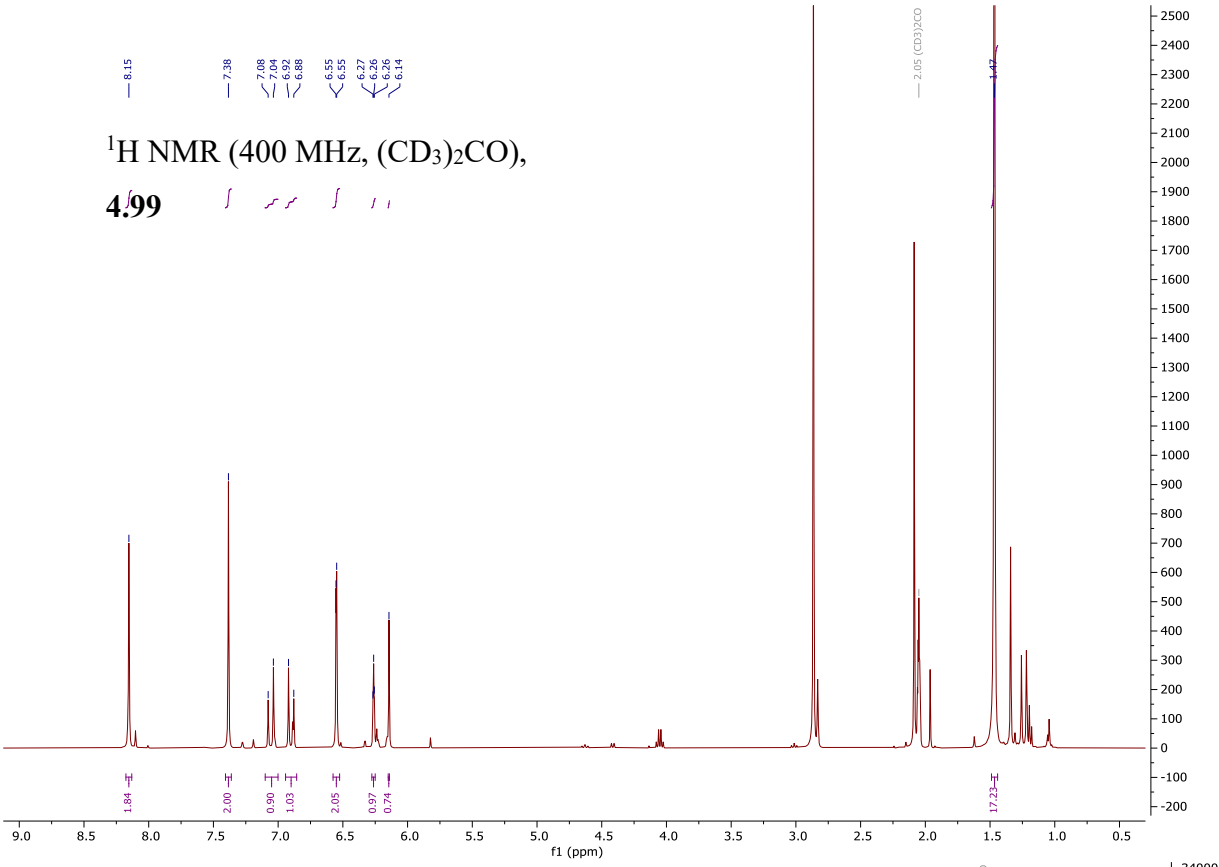


(4.83) 2,6-di-tert-butyl-4-(((1S,2S,3S)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-(3,5-dihydroxyphenyl)-4,6-dihydroxy-2,3-dihydro-1H-inden-1-yl)methylene)cyclohexa-2,5-dien-1-one

Representative procedure: In a flame-dried 25 mL RBF was added stilbene (160 mg, 470 µmol, 1 equiv), silver acetate (314 mg, 1.88 mmol, 4.0 equiv), and DCM (9.4 mL, 0.05 M). The reaction was stirred vigorously for 2 h, after which time a crude ^{1}H NMR was acquired to confirm full consumption of stilbene, with mostly BQM present, and small quantities of indane. Fresh zinc chloride from the glovebox was added (128 mg, 0.94 mmol, 2.0 equiv). After another 1 hour of reaction time the reaction was concentrated and the crude material was purified by flash chromatography over SiO_2 (0%-40% EtOAc in Hexanes) to yield the product as a yellow foam (87 mg, 55%).

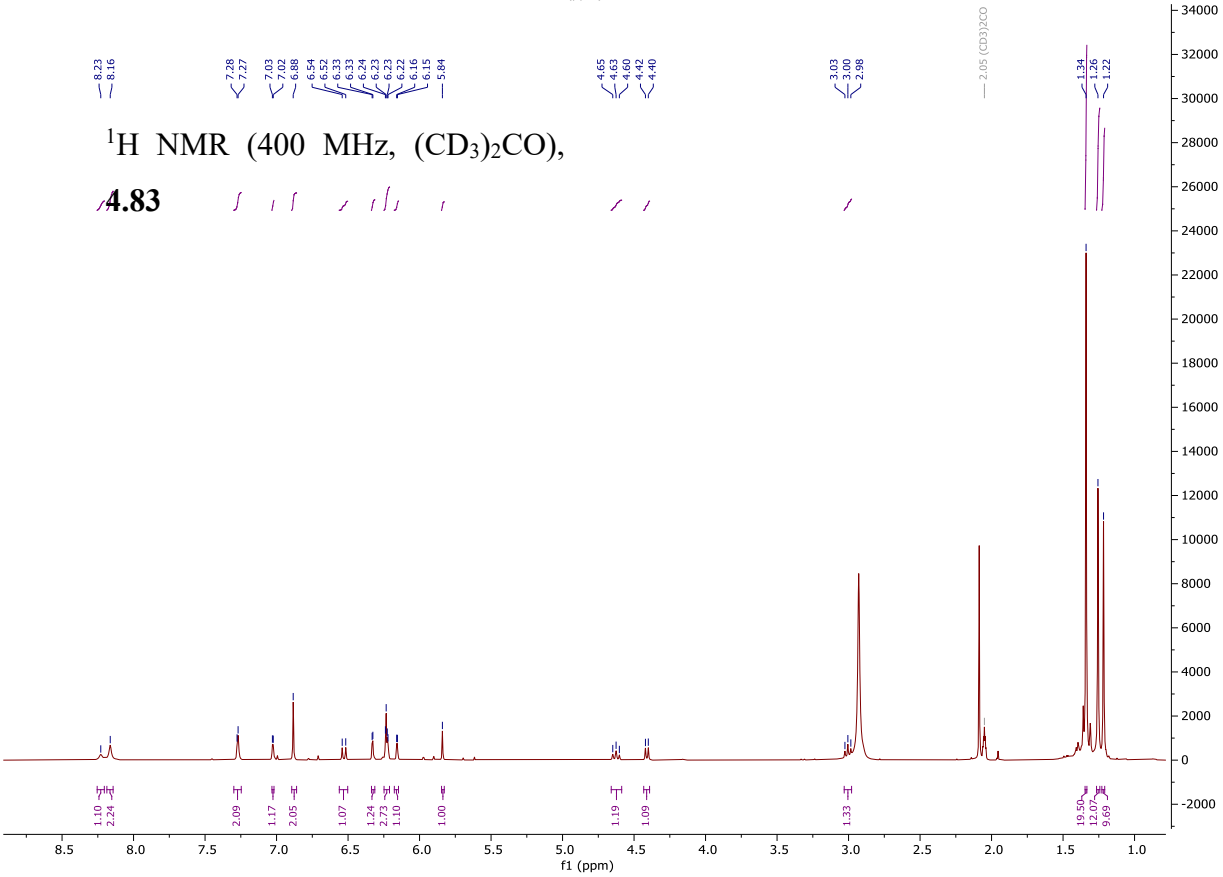
^{1}H NMR (400 MHz, $(CD_3)_2CO$), **4.99** δ = 8.15 (s, 2H), 7.38 (s, 2H), 7.06 (d, J=16.2, 1H), 6.90 (d, J=16.3, 1H), 6.55 (d, J=2.1, 2H), 6.26 (t, J=2.1, 1H), 6.14 (s, 1H), 1.47 (s, 18H).

^{1}H NMR (400 MHz, $(CD_3)_2CO$), **4.83** δ = 8.23 (s, 1H), 8.16 (s, 2H), 7.27 (d, J=2.9, 2H), 7.03 (d, J=2.4, 1H), 6.88 (s, 2H), 6.53 (d, J=9.9, 1H), 6.33 (d, J=2.1, 1H), 6.25 – 6.21 (m, 3H), 6.16 (d, J=2.1, 1H), 5.84 (s, 1H), 4.63 (t, J=9.2, 1H), 4.41 (d, J=8.0, 1H), 3.00 (t, J=8.3, 1H), 1.34 (s, 18H), 1.26 (s, 12H), 1.22 (s, 10H).



^{1}H NMR (400 MHz, $(CD_3)_2CO$),

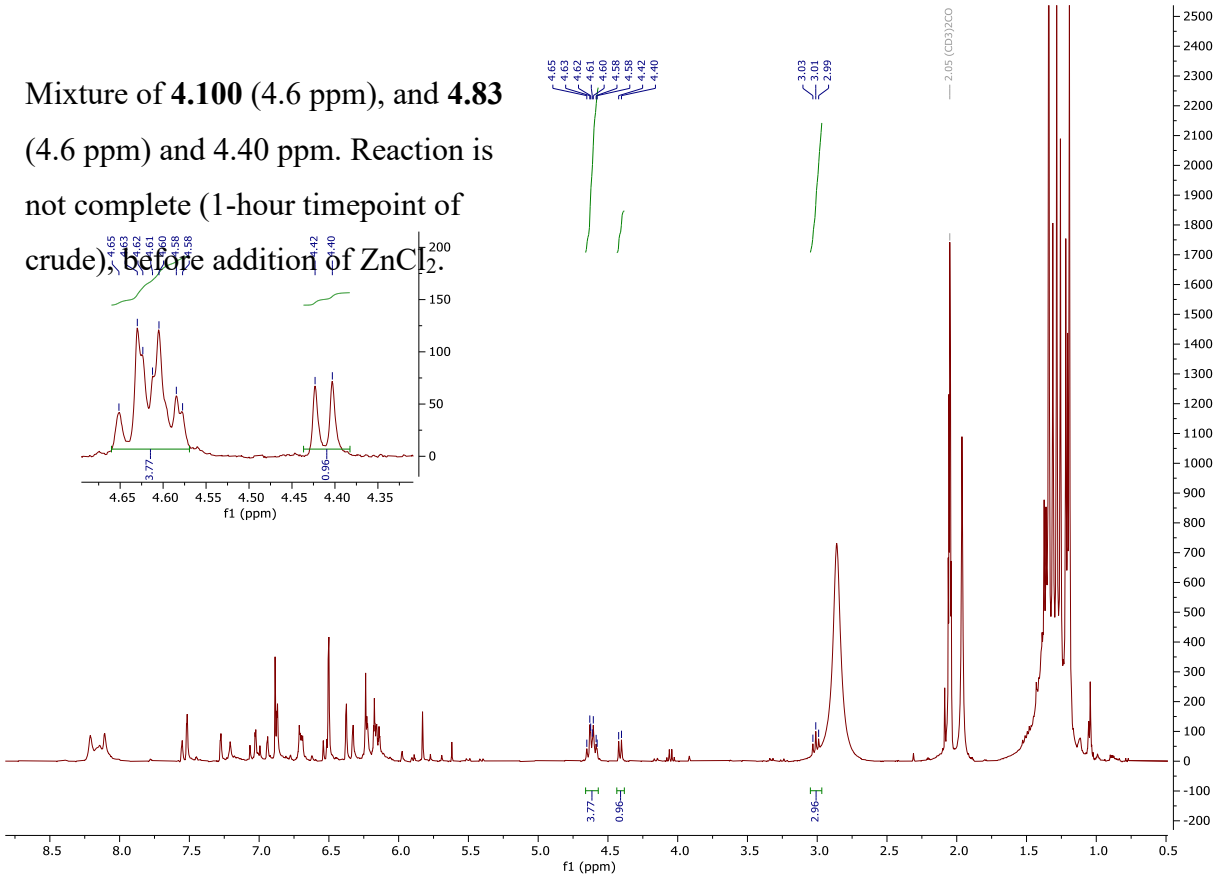
4.99

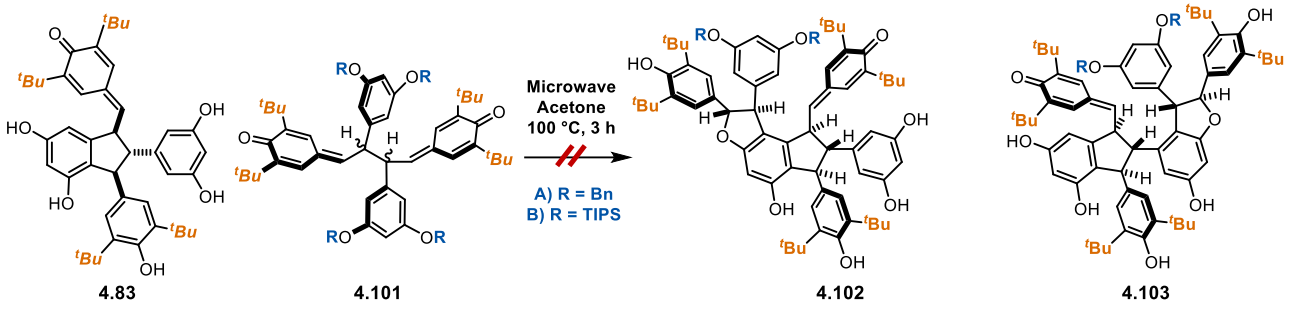


^{1}H NMR (400 MHz, $(CD_3)_2CO$),

4.83

Mixture of **4.100** (4.6 ppm), and **4.83** (4.6 ppm) and 4.40 ppm. Reaction is not complete (1-hour timepoint of crude), before addition of $ZnCl_2$.

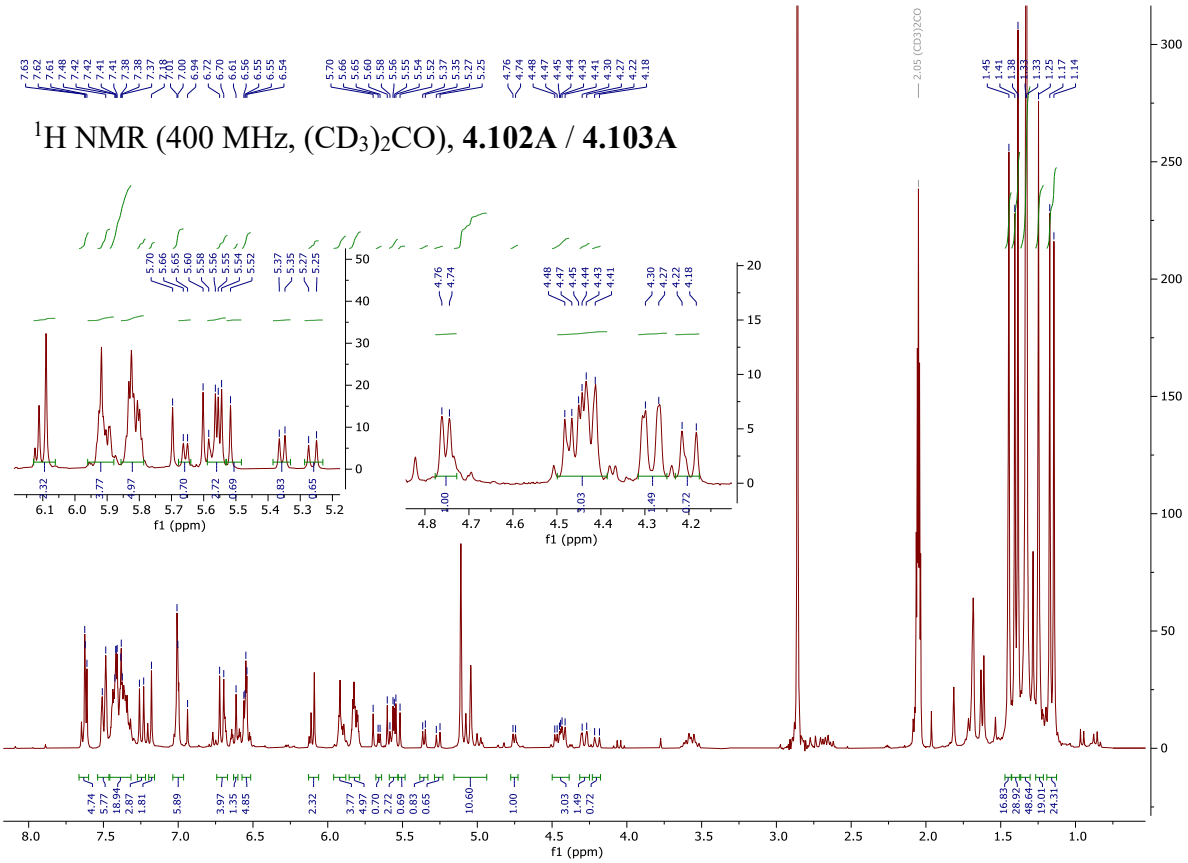


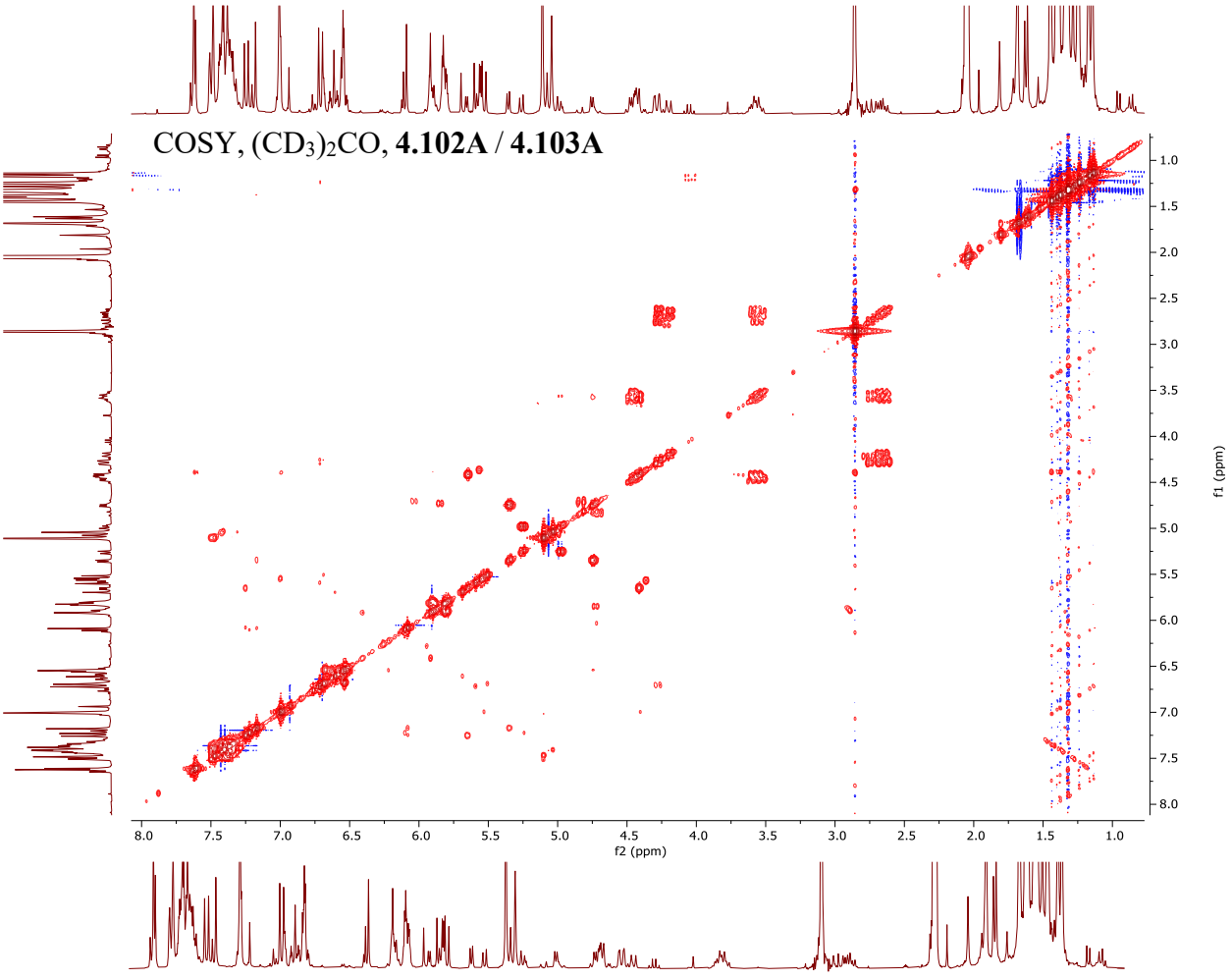


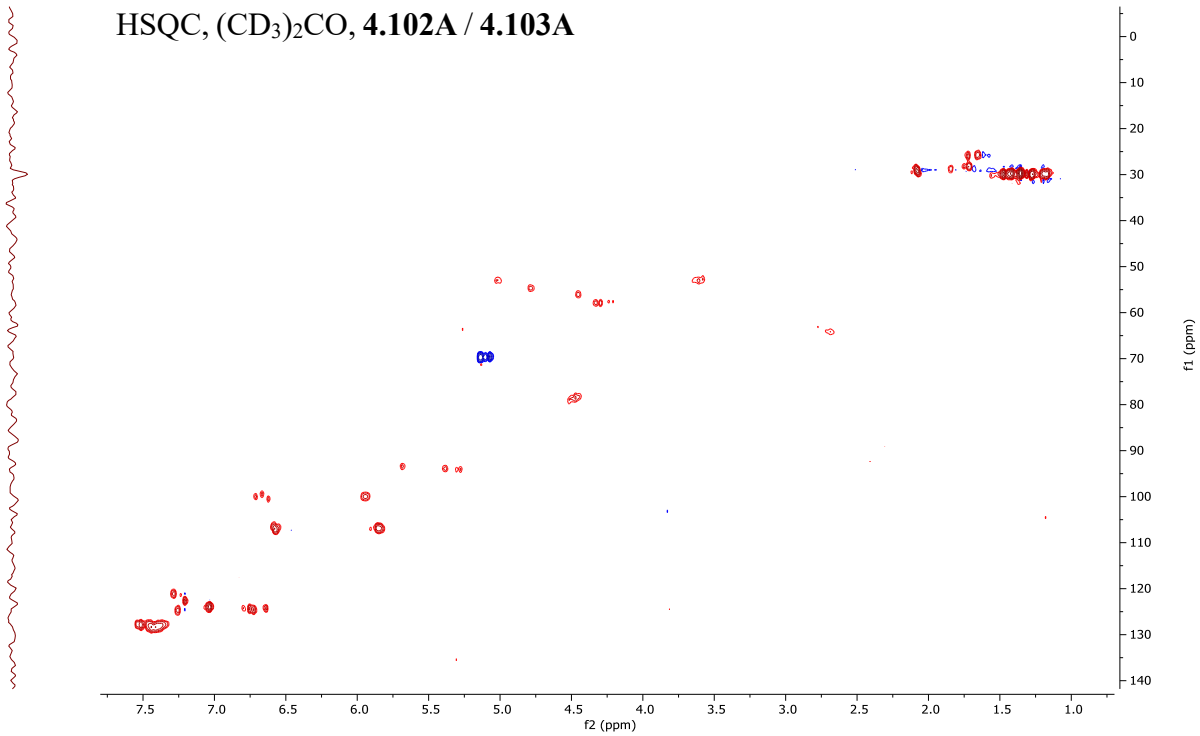
(4.102 / 4.103) 4-(((1S,2S,6S,8S)-1-(3,5-bis(benzyloxy)phenyl)-2,6-bis(3,5-di-tert-butyl-4-hydroxyphenyl)-7-(3,5-dihydroxyphenyl)-5-hydroxy-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)methylene)-2,6-di-tert-butylcyclohexa-2,5-dien-1-one

Representative procedure: In a flame-dried 2 mL microwave vial was added indane (30 mg, 44 µmol, 1 equiv), BQM (92 mg, 88 µmol, 2 equiv), and acetone (1.8 mL, 0.025 M). The headspace was capped with argon, and the vial was reacted at 100 °C for 3 hours in a Biotage microwave reactor. The reaction mixture was concentrated and purified by flash chromatography over SiO_2 (0%-40% EtOAc in Hexanes). Preparatory TLC was also used to further purify the trimeric fractions.

Following spectra are for **4.102A** / **4.103A**, mixture of ~3 dihydrobenzofurans

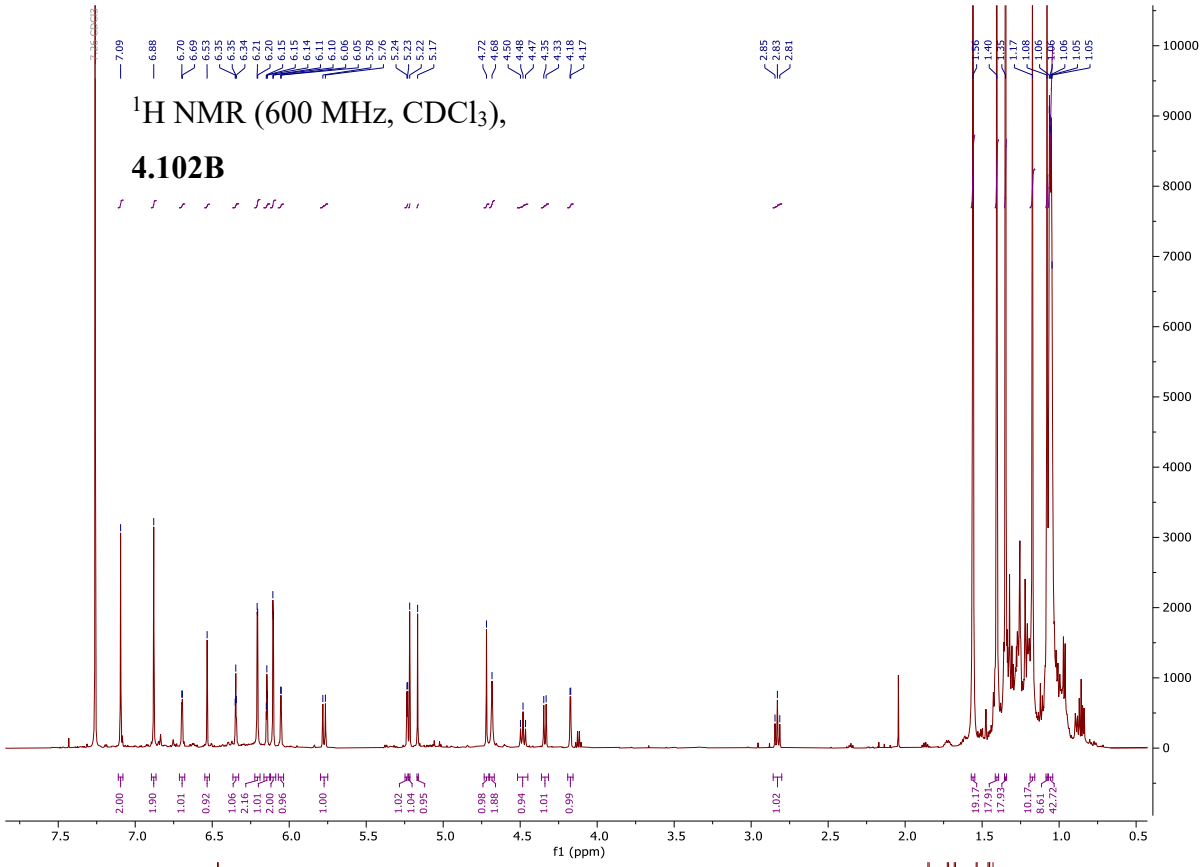



COSY, (CD3)2CO, 4.102A / 4.103A
f2 (ppm)
f1 (ppm)


HSQC, (CD3)2CO, 4.102A / 4.103A
f2 (ppm)
f1 (ppm)

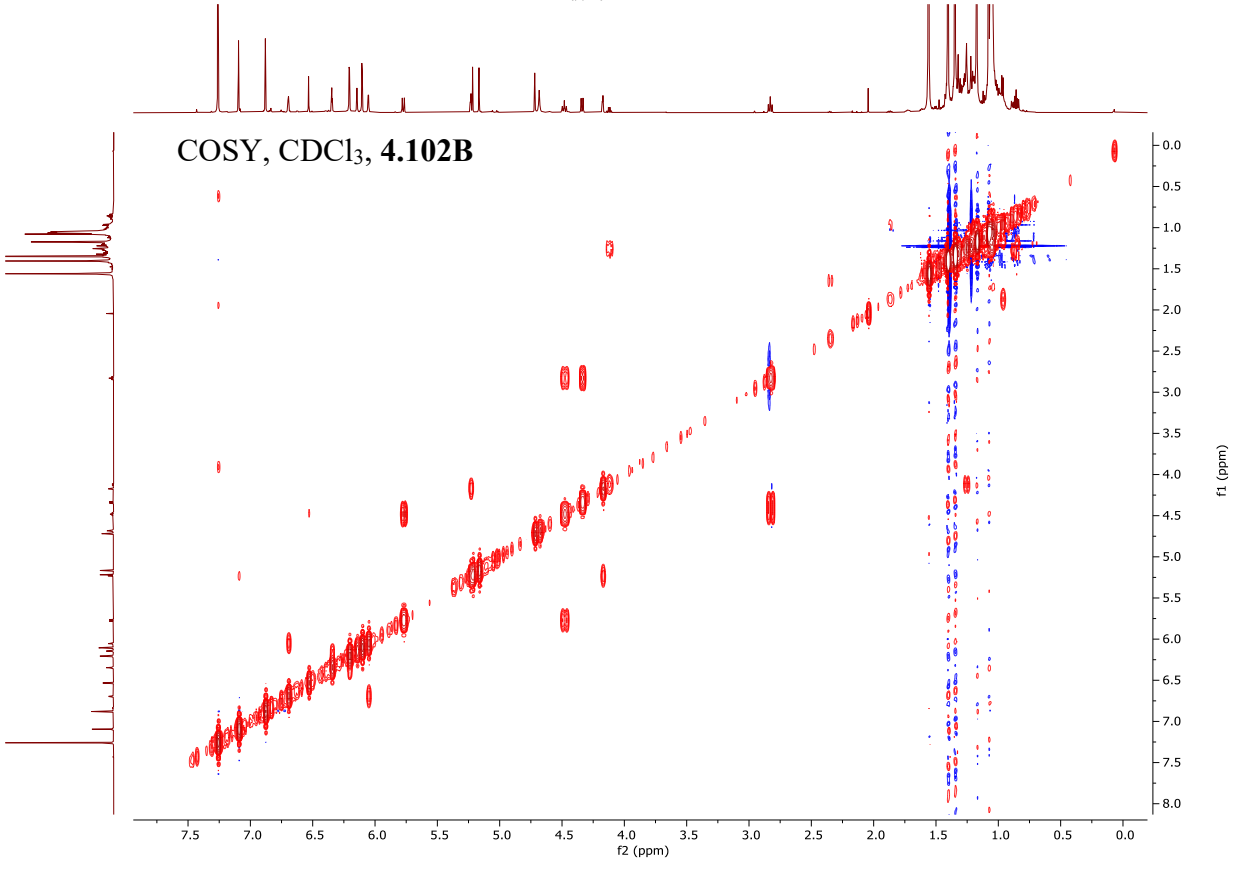
Following spectra are for **4.102B**. Assignment is tentative based on <1 mg isolated. There was insufficient material for a suitable carbon NMR, HSQC, or other 2D NMR technique.

^{1}H NMR (600 MHz, $CDCl_3$), **4.102B**	δ = 7.09 (s, 2H), 6.88 (s, 2H), 6.70 (d, J=2.4, 1H), 6.53 (s, 1H), 6.35 (t, J=2.2, 1H), 6.21 (d, J=2.2, 2H), 6.15 (t, J=2.2, 1H), 6.10 (d, J=2.2, 2H), 6.05 (d, J=2.3, 1H), 5.77 (d, J=10.0, 1H), 5.23 (d, J=2.8, 1H), 5.22 (s, 1H), 5.17 (s, 1H), 4.72 (s, 1H), 4.68 (s, 2H), 4.48 (t, J=9.9, 1H), 4.34 (d, J=9.3, 1H), 4.17 (d, J=2.8, 1H), 2.83 (t, J=9.3, 1H), 1.56 (s, 18H), 1.40 (s, 18H), 1.35 (s, 18H), 1.17 (s, 9H), 1.08 (s, 9H), 1.07 – 1.04 (m, 36H).

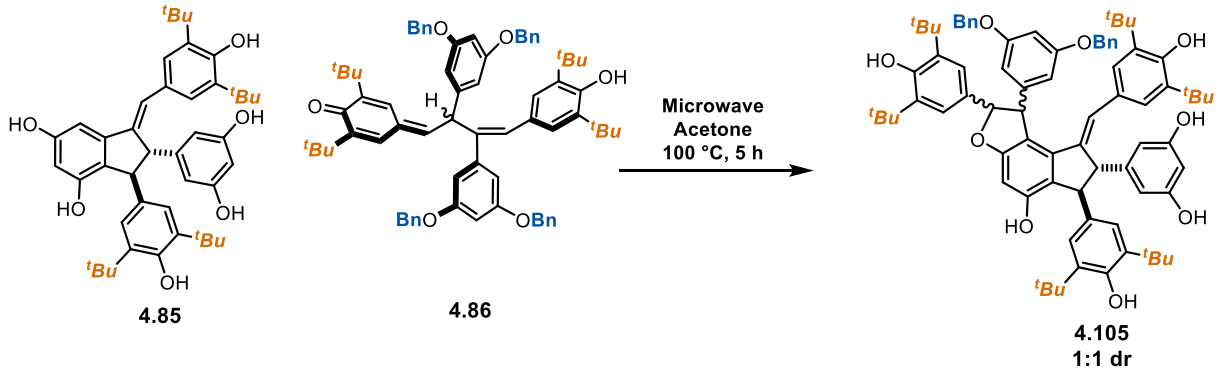


^{1}H NMR (600 MHz, $CDCl_3$),

4.102B



COSY, $CDCl_3$, **4.102B**

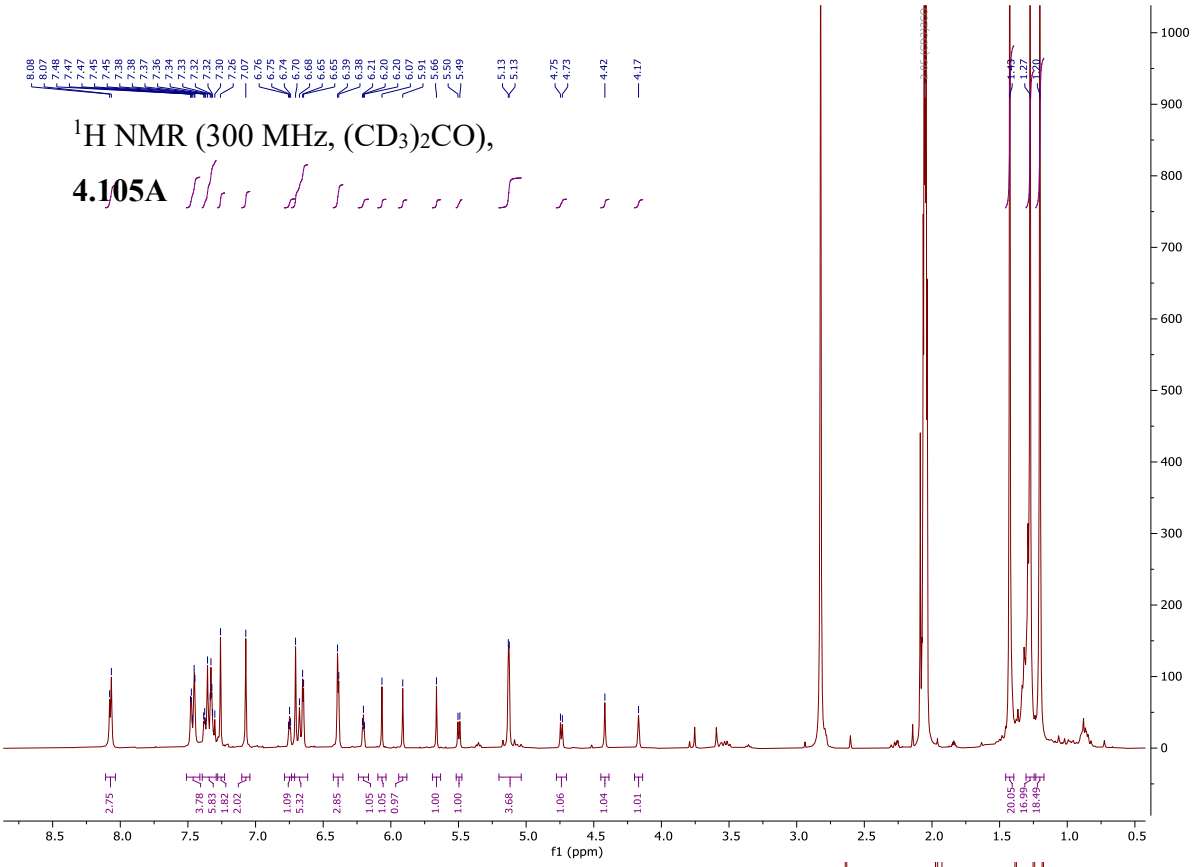


4.85 4.86 4.105
1:1 dr

(4.105) 5-((6S,7S)-1-(3,5-bis(benzyloxy)phenyl)-8-((E)-3,5-di-tert-butyl-4-hydroxybenzylidene)-2,6-bis(3,5-di-tert-butyl-4-hydroxyphenyl)-5-hydroxy-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-7-yl)benzene-1,3-diol

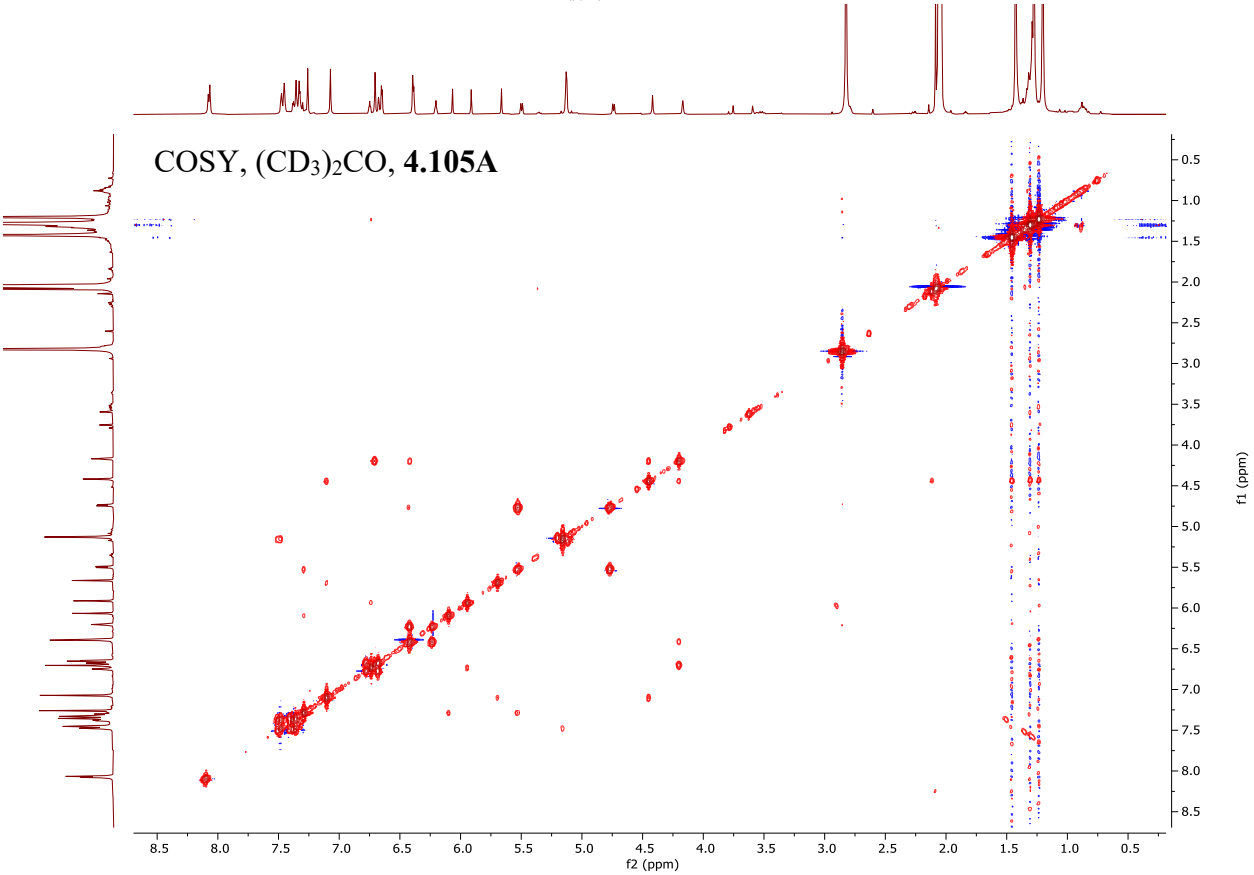
In a flame-dried 2 mL microwave vial was added indane (20 mg, 29 µmol, 1 equiv), BQM (61 mg, 59 µmol, 2 equiv), and acetone (1.2 mL, 0.025 M). The headspace was capped with argon, and the vial was reacted at 100 °C for 5 hours in a Biotage microwave reactor. The reaction mixture was concentrated and purified by flash chromatography over SiO_2 (0%-40% EtOAc in Hexanes). Preparatory TLC was also used to further purify the trimeric fractions. The light tan oil products were isolated as a 1:1 mixture of *trans* DHB diastereomers, labelled simply as **A** and **B** as the exact identity was not determined.

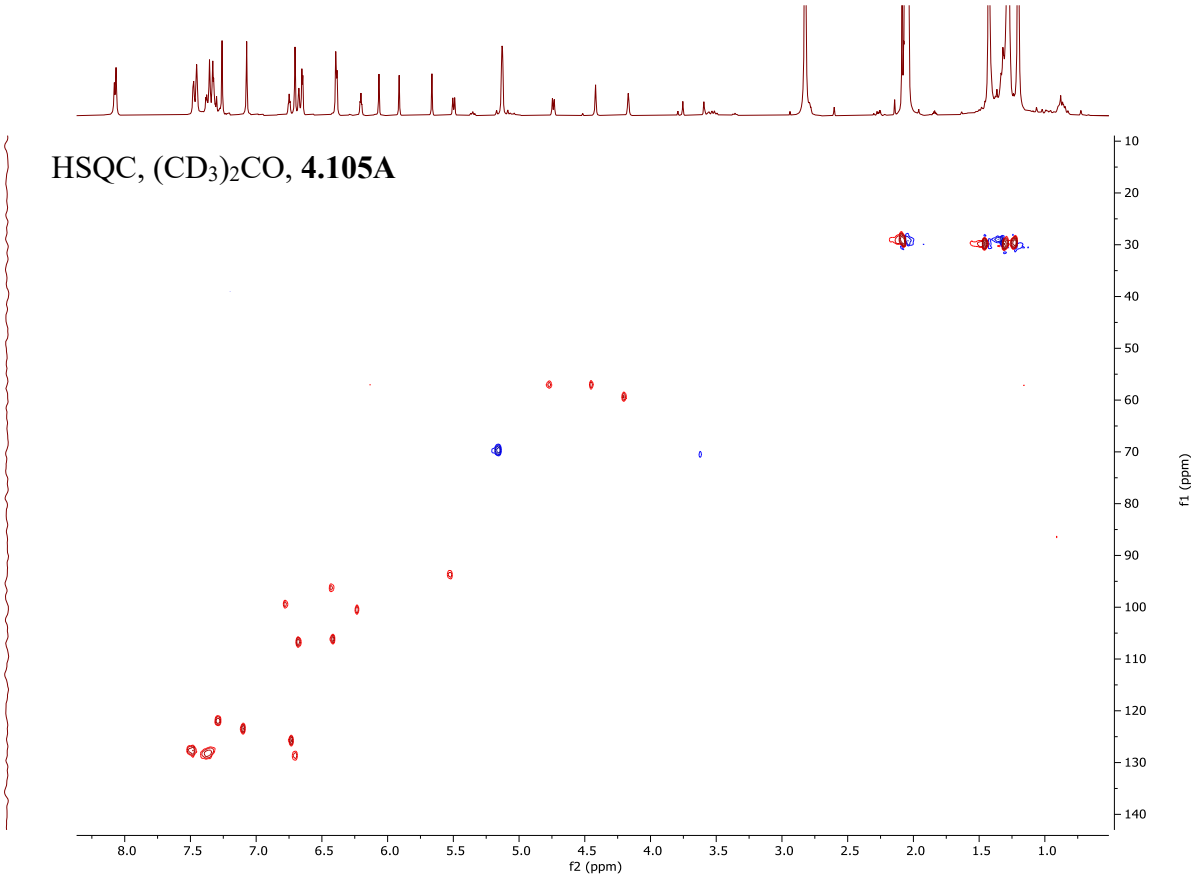
^{1}H NMR (300 MHz, $(CD_3)_2CO$), **4.105A** δ = 8.07 (d, J=3.9, 2H), 7.51 – 7.41 (m, 4H), 7.39 – 7.29 (m, 6H), 7.26 (s, 2H), 7.07 (s, 2H), 6.75 (t, J=2.3, 1H), 6.73 – 6.61 (m, 5H), 6.39 (d, J=2.8, 3H), 6.20 (t, J=2.2, 1H), 6.07 (s, 1H), 5.91 (s, 1H), 5.66 (s, 1H), 5.50 (d, J=4.2, 1H), 5.13 (d, J=2.0, 4H), 4.74 (d, J=4.2, 1H), 4.42 (s, 1H), 4.17 (s, 1H), 1.43 (s, 18H), 1.27 (s, 18H), 1.20 (s, 18H).



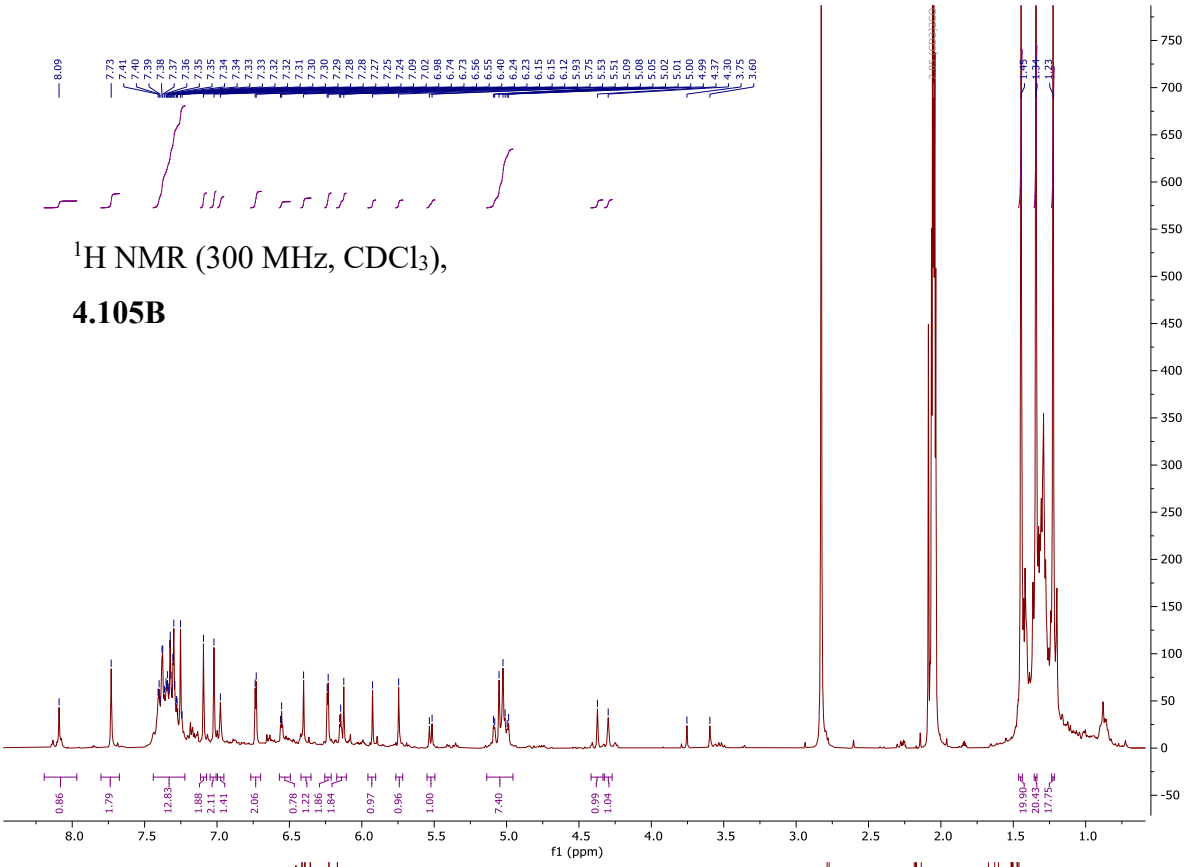
^{1}H NMR (300 MHz, $(CD_3)_2CO$),

4.105A



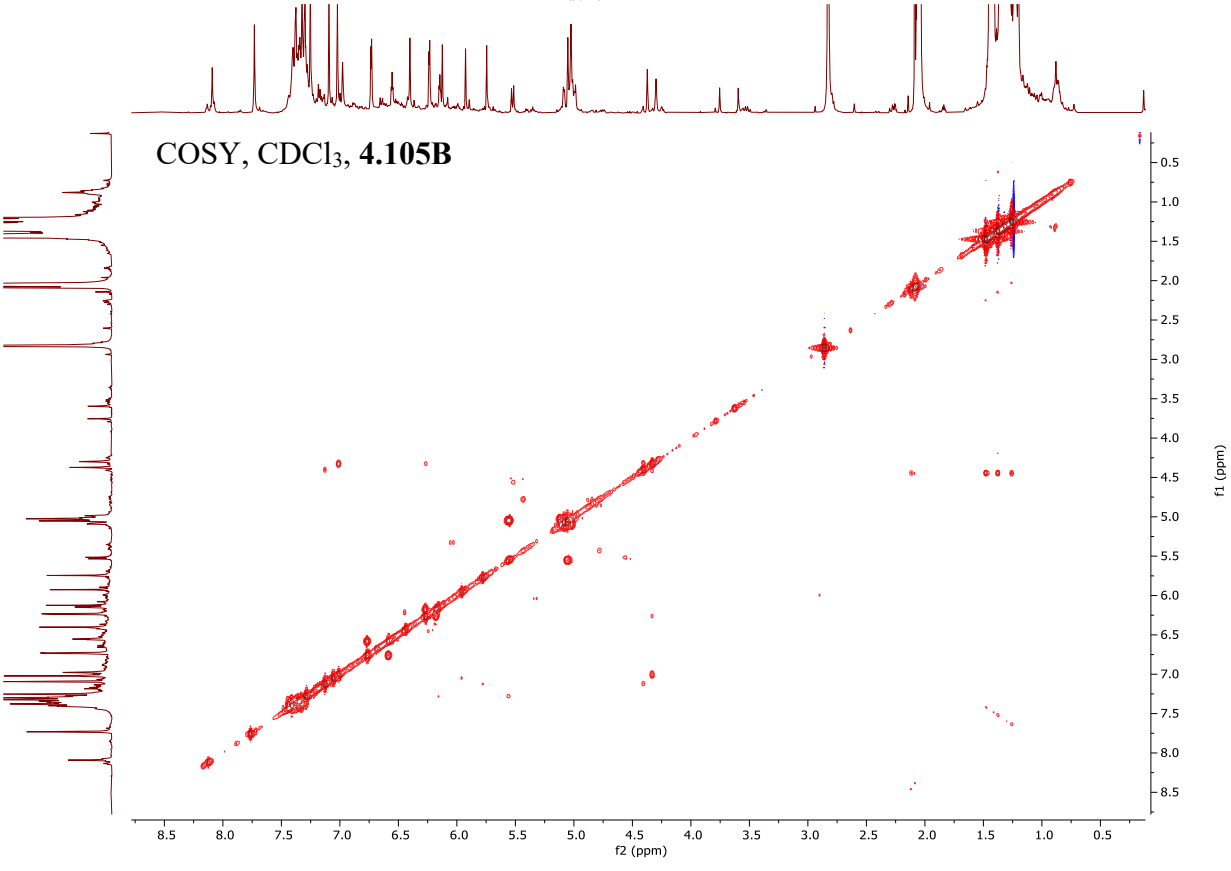


^{1}H NMR (300 MHz, $(CD_3)_2CO$), **4.105B** δ = 8.09 (s, 1H), 7.73 (s, 2H), 7.44 – 7.22 (m, 13H), 7.09 (s, 2H), 7.02 (s, 2H), 6.98 (s, 1H), 6.73 (d, J=2.3, 2H), 6.56 (d, J=2.3, 1H), 6.40 (s, 1H), 6.24 (d, J=2.1, 2H), 6.17 – 6.11 (m, 2H), 5.93 (s, 1H), 5.75 (s, 1H), 5.52 (d, J=5.6, 1H), 5.14 – 4.96 (m, 7H), 4.37 (s, 1H), 4.30 (s, 1H), 1.45 (s, 18H), 1.34 (s, 18H), 1.23 (s, 18H).

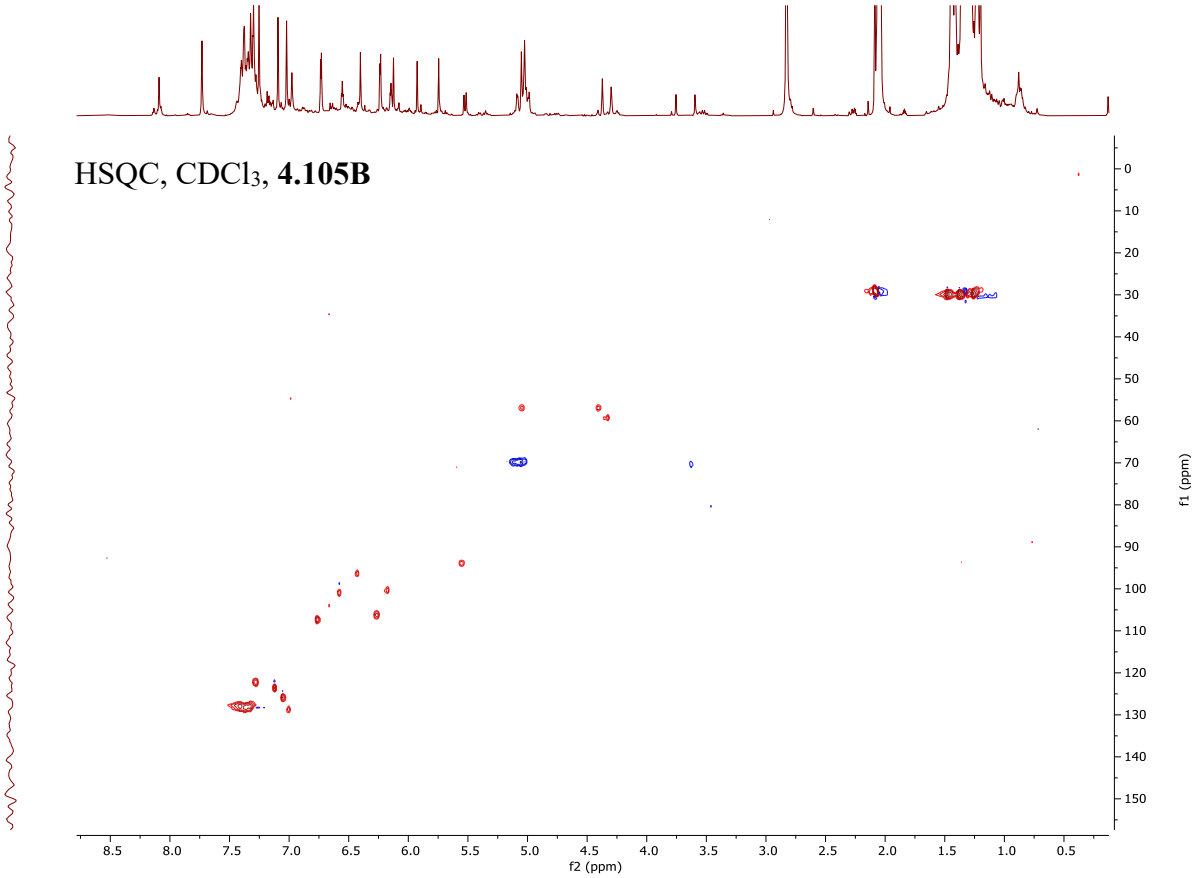


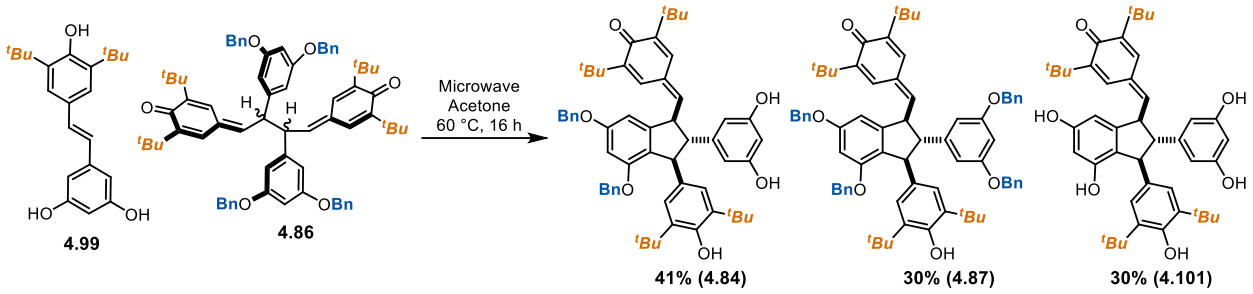
^{1}H NMR (300 MHz, $CDCl_3$),

4.105B



COSY, $CDCl_3$, **4.105B**

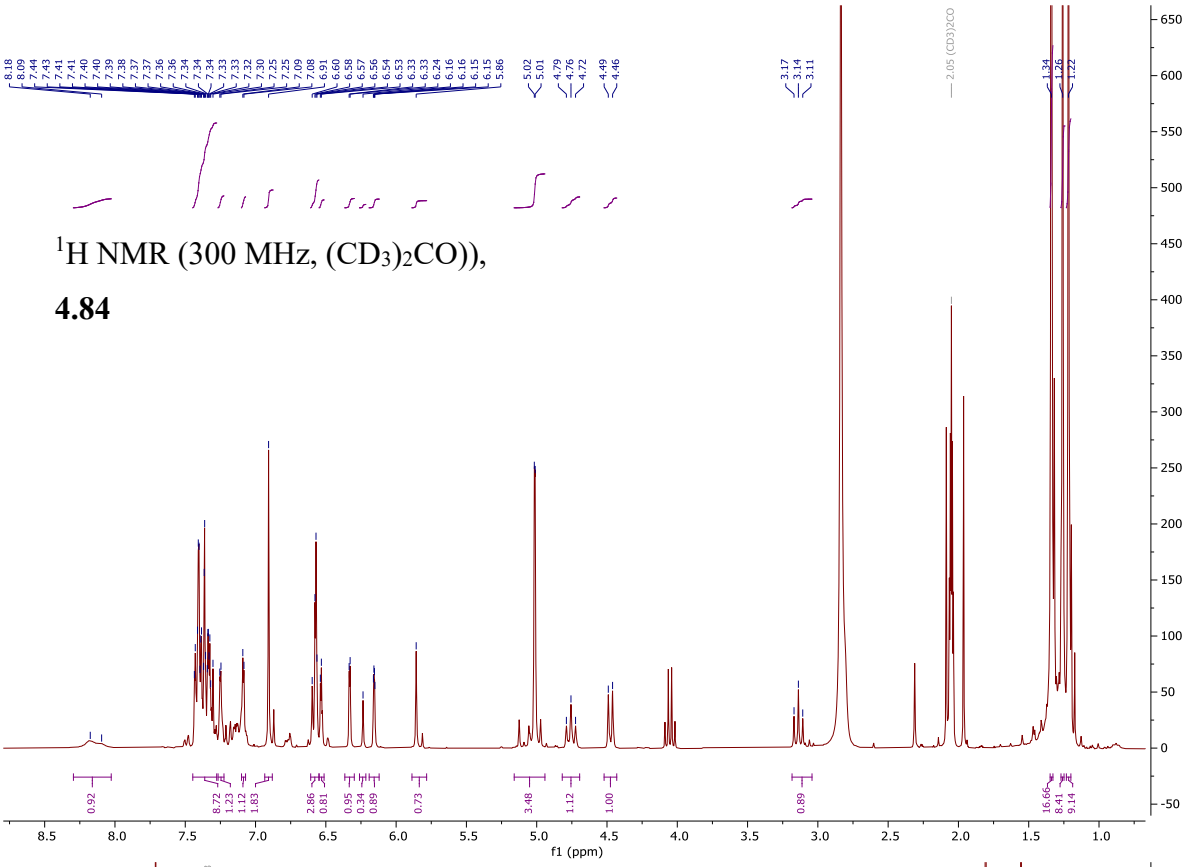

HSQC, CDCl3, 4.105B
f2 (ppm)
f1 (ppm)



(4.84) 4-(((1S,2S,3S)-4,6-bis(benzyloxy)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-(3,5-dihydroxyphenyl)-2,3-dihydro-1H-inden-1-yl)methylene)-2,6-di-tert-butylcyclohexa-2,5-dien-1-one

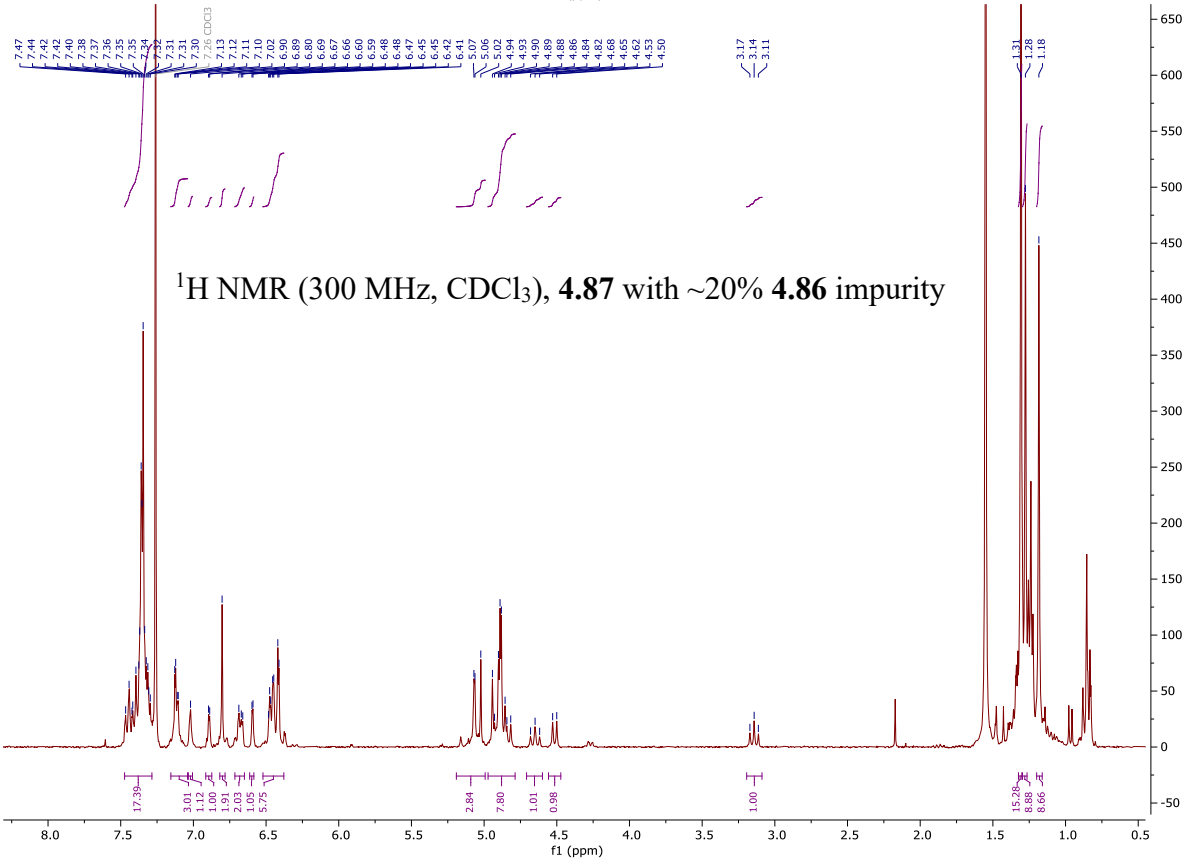
In a flame-dried 2 mL microwave vial was added stilbene (30 mg, 88 µmol, 1 equiv), BQM (92 mg, 88 µmol, 1 equiv), and acetone (1.8 mL, 0.005 M). The headspace was capped with argon, and the vial was reacted at 60 °C for 16 hours in a Biotage microwave reactor. The reaction mixture was concentrated and purified by flash chromatography over SiO_2 (0%-40% EtOAc in Hexanes). All products were isolated as a tan foams (**4.84**, 31 mg, 41%), (**4.87**, 18 mg, 30%), (**4.101**, 27 mg, 30%).

^{1}H NMR (300 MHz, $(CD_3)_2CO$), **4.84**	δ = 8.14 (d, J=24.3, 1H), 7.45 – 7.28 (m, 9H), 7.25 (d, J=2.4, 1H), 7.09 (d, J=2.4, 1H), 6.91 (s, 2H), 6.61 – 6.55 (m, 3H), 6.54 (d, J=2.2, 1H), 6.33 (d, J=2.1, 1H), 6.24 (s, 1H), 6.16 (dd, J=2.1, 1.0, 1H), 5.86 (s, 1H), 5.01 (d, J=1.8, 4H), 4.76 (t, J=9.8, 1H), 4.48 (d, J=9.1, 1H), 3.14 (t, J=9.3, 1H), 1.34 (s, 18H), 1.26 (s, 9H), 1.22 (s, 9H).
^{1}H NMR (300 MHz, $CDCl_3$), **4.87** with ~20% **4.86** impurity	δ = 7.47 – 7.29 (m, 17H), 7.12 (dd, J=5.2, 2.0, 3H), 7.02 (s, 1H), 6.89 (d, J=2.4, 1H), 6.80 (s, 2H), 6.71 – 6.65 (m, 2H), 6.59 (d, J=2.1, 1H), 6.52 – 6.38 (m, 6H), 5.19 – 4.99 (m, 3H), 4.97 – 4.79 (m, 8H), 4.65 (t, J=9.4, 1H), 4.51 (d, J=8.5, 1H), 3.14 (t, J=8.7, 1H), 1.31 (s, 18H), 1.28 (s, 9H), 1.18 (s, 9H).
^{1}H NMR (300 MHz, $(CD_3)_2CO$), **4.101**	δ = 8.17 (s, 1H), 8.11 (s, 2H), 7.28 (d, J=2.3, 1H), 7.21 (s, 1H), 7.03 (d, J=2.4, 1H), 6.89 (s, 2H), 6.53 (d, J=10.0, 1H), 6.33 (d, J=2.1, 1H), 6.23 (q, J=1.9, 3H), 6.16 (dd, J=2.2, 1.0, 1H), 5.83 (s, 1H), 4.63 (t, J=9.1, 1H), 4.41 (d, J=8.0, 1H), 3.01 (t, J=8.3, 1H), 1.34 (s, 17H), 1.26 (s, 9H), 1.22 (s, 9H).

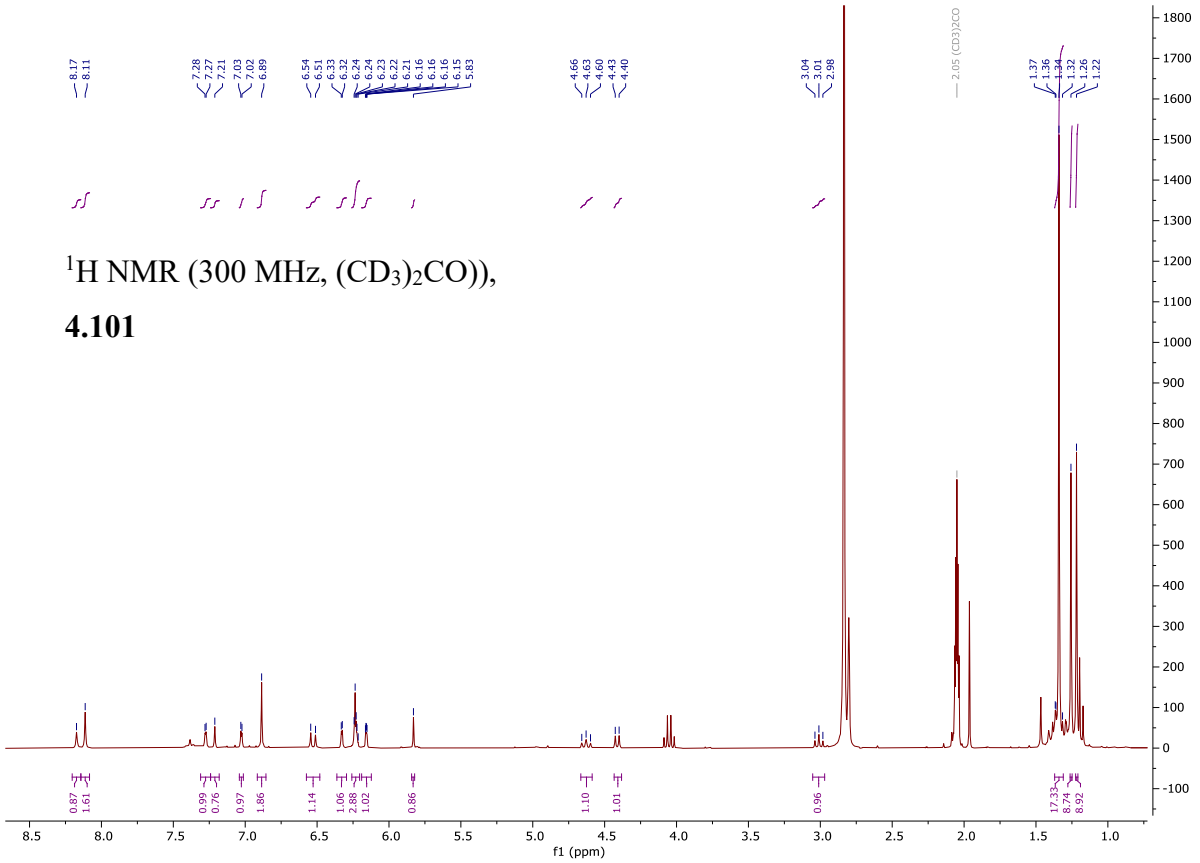


^{1}H NMR (300 MHz, $(CD_3)_2CO$)),

4.84

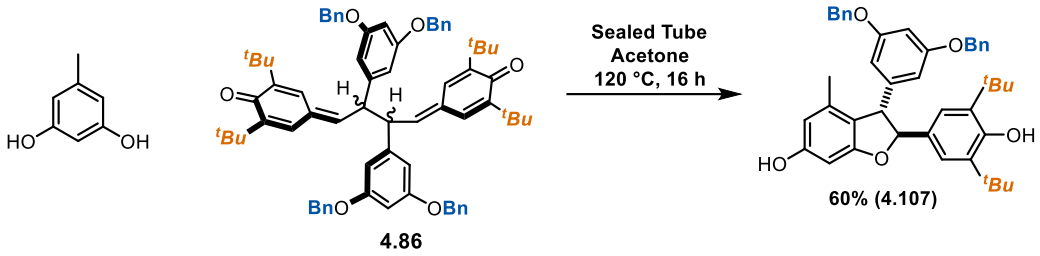


^{1}H NMR (300 MHz, $CDCl_3$), **4.87** with ~20% **4.86** impurity



^{1}H NMR (300 MHz, $(CD_3)_2CO$)),

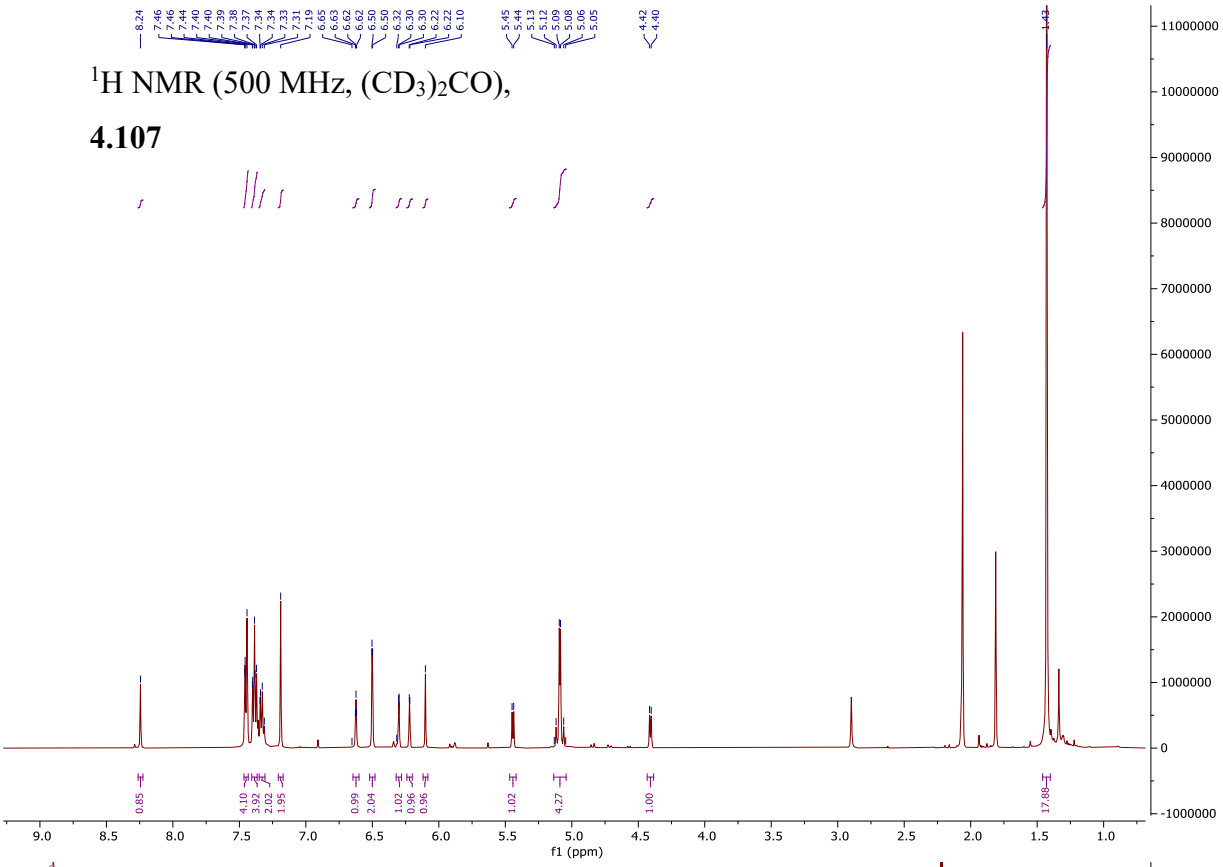
4.101



(4.107) (2S,3S)-3-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-4-methyl-2,3-dihydrobenzofuran-6-ol

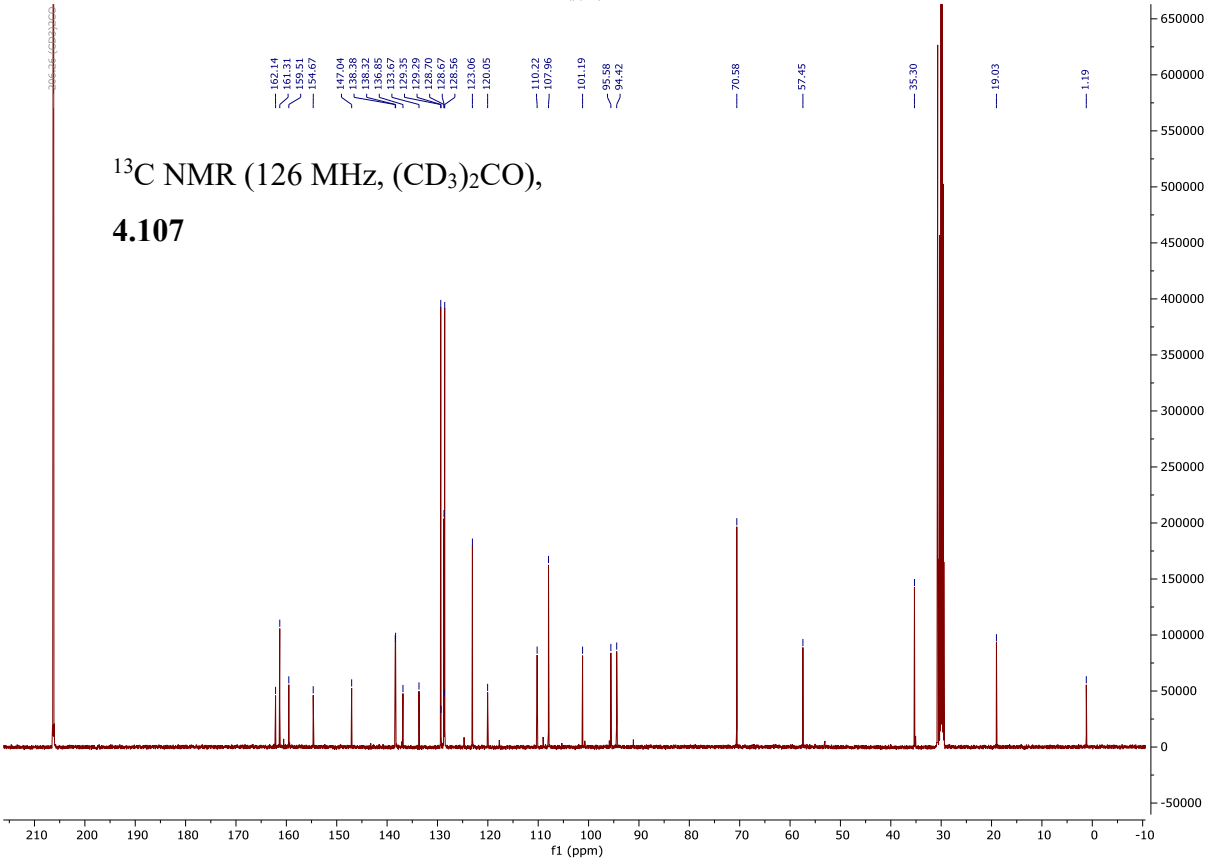
In a flame dried sealed tube phenol (12.4 mg, 0.10 mmol, 1 equiv) and BQM (208 mg, 0.20 mmol, 2 equiv) were suspended in acetone (4.0 mL, 0.025 M) and the tube was capped with argon and sealed. The reaction was heated to 120 °C for 16 hours. The reaction mixture was concentrated and purified by column chromatography SiO_2 (0-20% ethyl acetate in hexanes) to afford the product as a tan solid (38.7 mg, 60%).

^{1}H NMR (500 MHz, $(CD_3)_2CO$), **4.107**	δ = 8.24 (s, 1H), 7.45 (d, J=7.0, 4H), 7.41 – 7.37 (m, 4H), 7.35 – 7.31 (m, 2H), 7.19 (s, 2H), 6.62 (t, J=2.2, 1H), 6.50 (d, J=2.2, 2H), 6.30 (d, J=2.1, 1H), 6.22 (d, J=2.2, 1H), 6.10 (s, 1H), 5.44 (d, J=6.1, 1H), 5.14 – 5.04 (m, 4H), 4.41 (d, J=6.1, 1H), 1.43 (s, 18H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$), **4.107**	δ = 162.1, 161.3, 159.5, 154.7, 147.0, 138.4, 138.3, 136.9, 133.7, 129.3, 129.3, 128.7, 128.7, 128.6, 123.1, 120.0, 110.2, 108.0, 101.2, 95.6, 94.4, 70.6, 57.5, 35.3, 19.0, 1.2.



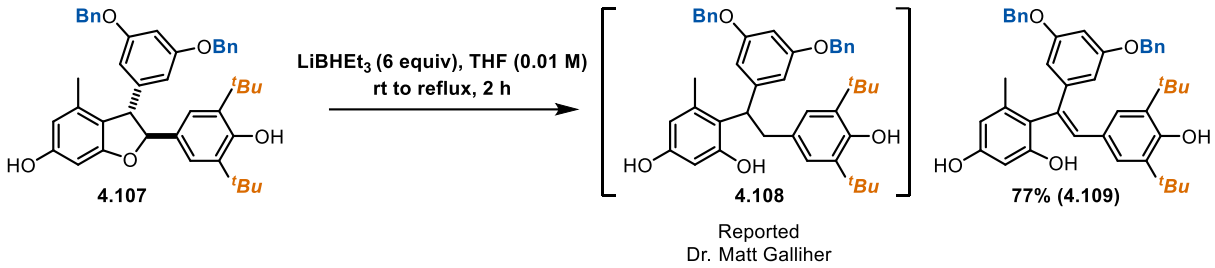
^{1}H NMR (500 MHz, $(CD_3)_2CO$),

4.107



^{13}C NMR (126 MHz, $(CD_3)_2CO$),

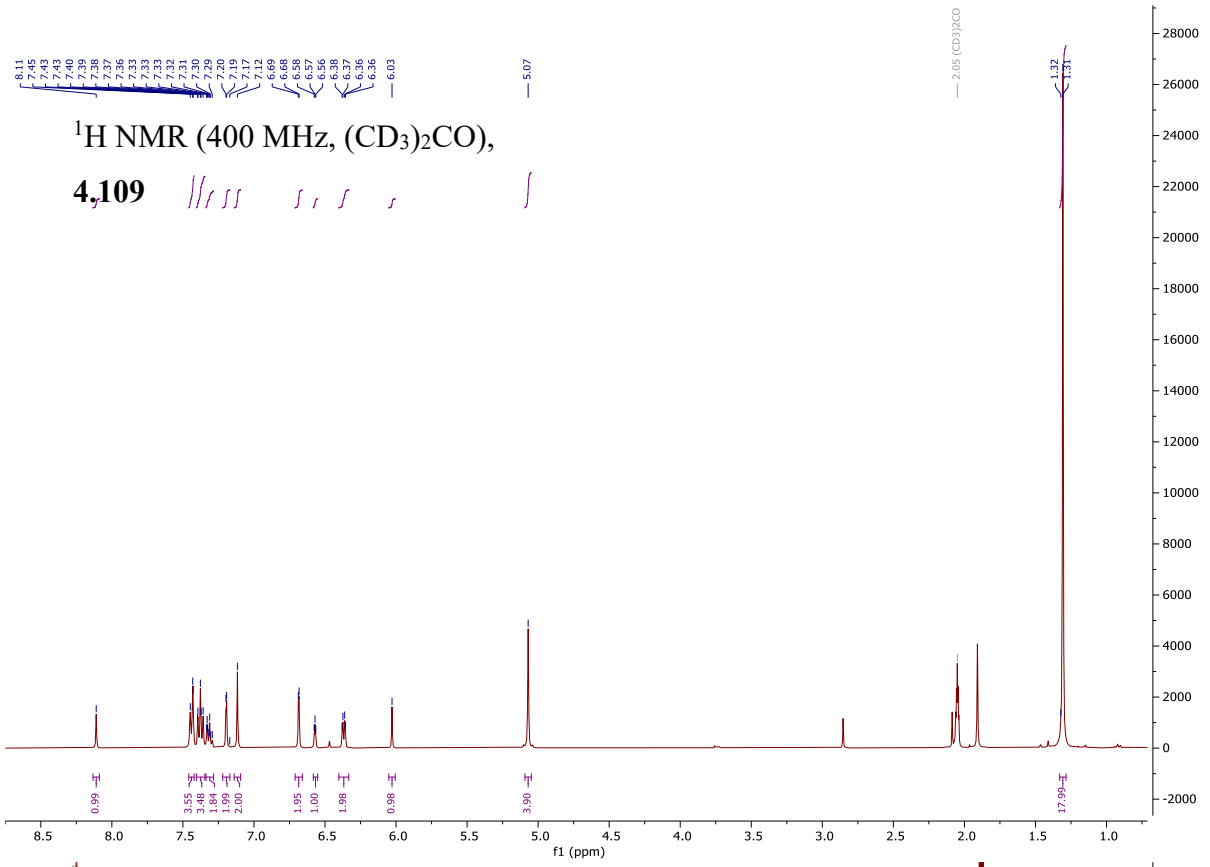
4.107



(4.109) (E)-4-(1-(3,5-bis(benzyloxy)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)vinyl)-5-methylbenzene-1,3-diol

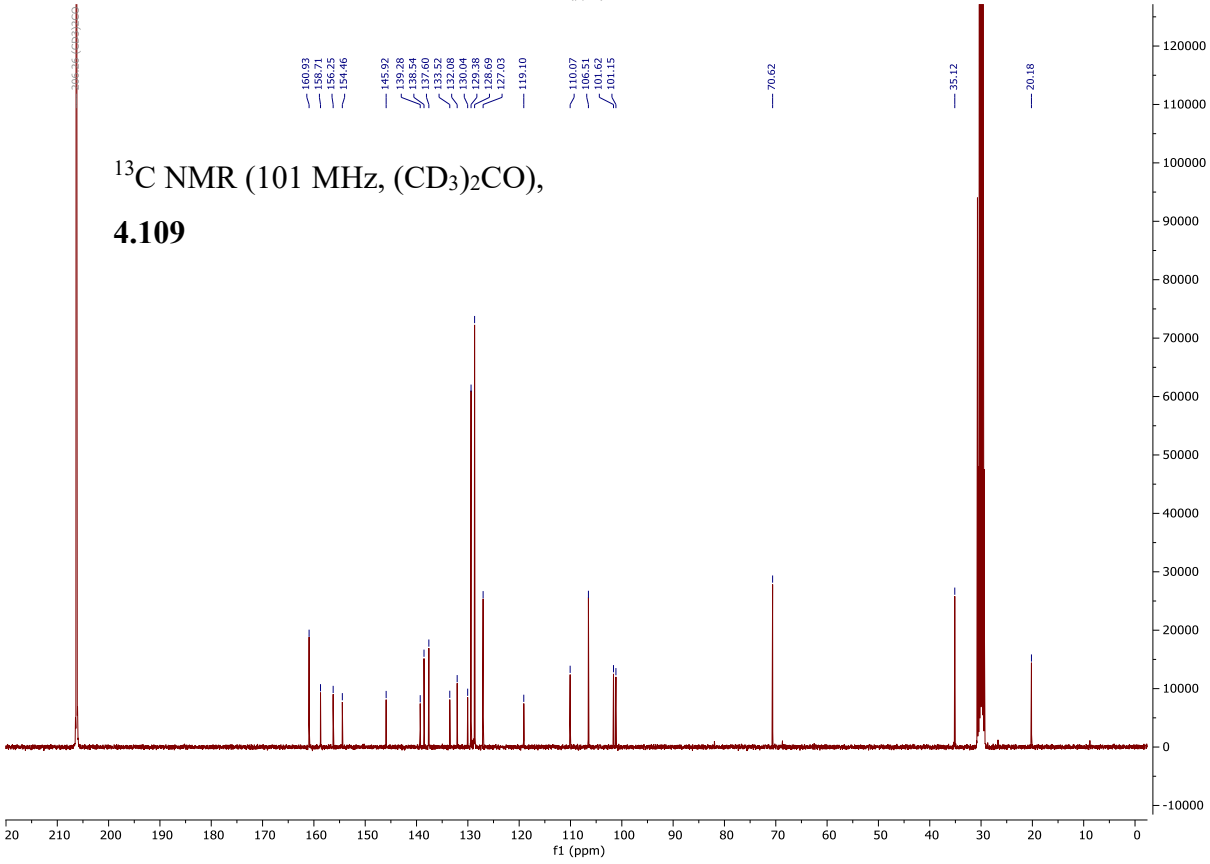
In a 50 mL flame dried RBF was added DHB (128 mg, 0.199 mmol, 1 equiv), THF (20 mL, 0.01 M), and dropwise super hydride (1.2 mL, 1.19 mmol, 6 equiv, 1 M in THF solution) at room temperature. Upon observation of low conversion by TLC the mixture was heated to reflux for 2 hours. The reaction was quenched with methanol (2 mL) and water (10 mL). The mixture was extracted with diethyl ether (3 x 20 mL), dried with brine (20 mL), $MgSO_4$ and filtered. The crude reaction mixture was purified by column chromatography SiO_2 (0-20% ethyl acetate in hexanes) to afford the product as an off white foam (98 mg, 77%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$), **4.109**	δ = 8.11 (s, 1H), 7.44 (d, J=6.8, 4H), 7.41 – 7.35 (m, 3H), 7.34 – 7.28 (m, 2H), 7.19 (d, J=2.0, 2H), 7.12 (s, 2H), 6.68 (d, J=2.2, 2H), 6.57 (t, J=2.2, 1H), 6.40 – 6.33 (m, 2H), 6.03 (s, 1H), 5.07 (s, 4H), 1.31 (s, 18H).
^{13}C NMR (101 MHz, $(CD_3)_2CO$), **4.109**	δ = 160.9, 158.7, 156.2, 154.5, 145.9, 139.3, 138.5, 137.6, 133.5, 132.1, 130.0, 129.4, 128.7, 127.0, 119.1, 110.1, 106.5, 101.6, 101.1, 70.6, 35.1, 20.2.
HRMS (ESI):	m/z calculated for $C_{43}H_{46}O_5$ ([M+H]+): 643.3418, found 643.3411



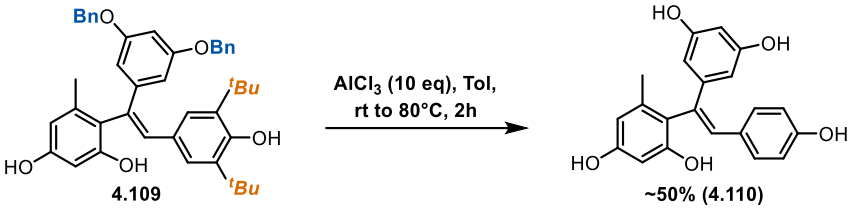
^{1}H NMR (400 MHz, $(CD_3)_2CO$),

4.109



^{13}C NMR (101 MHz, $(CD_3)_2CO$),

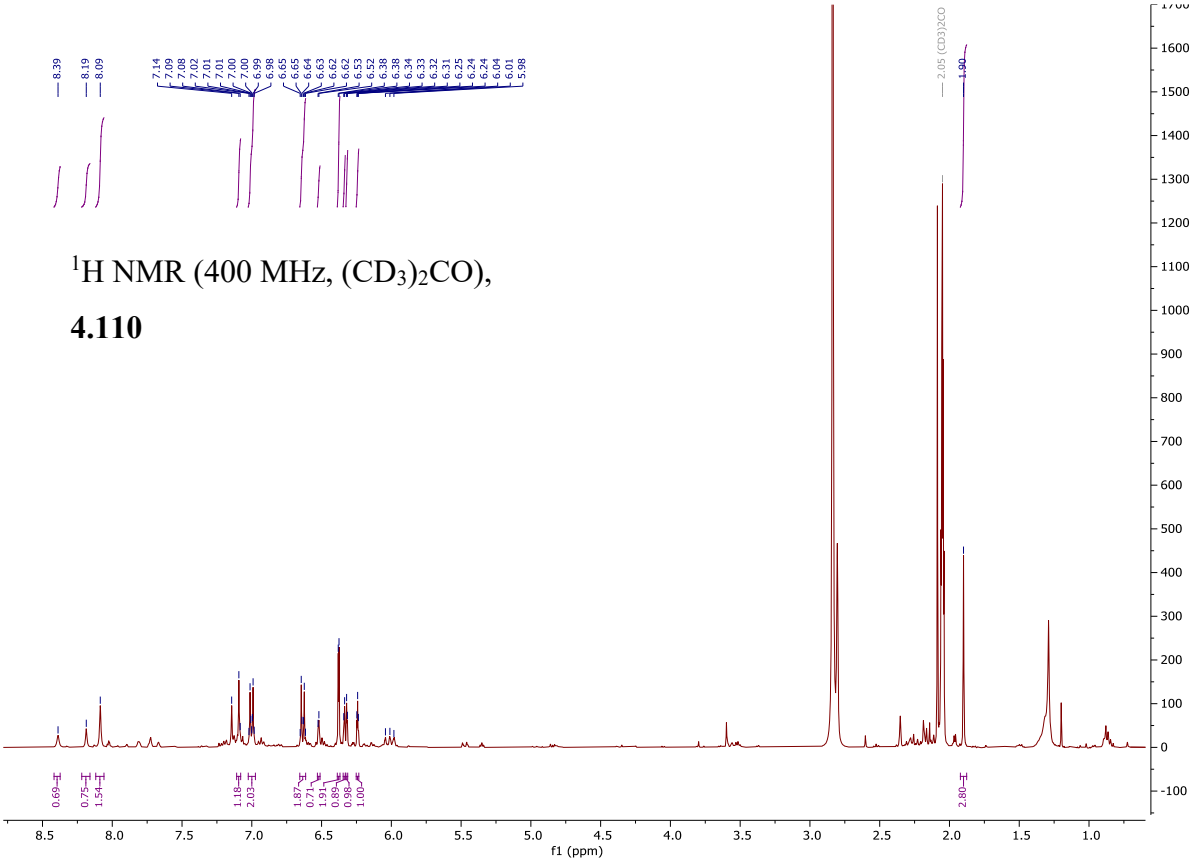
4.109



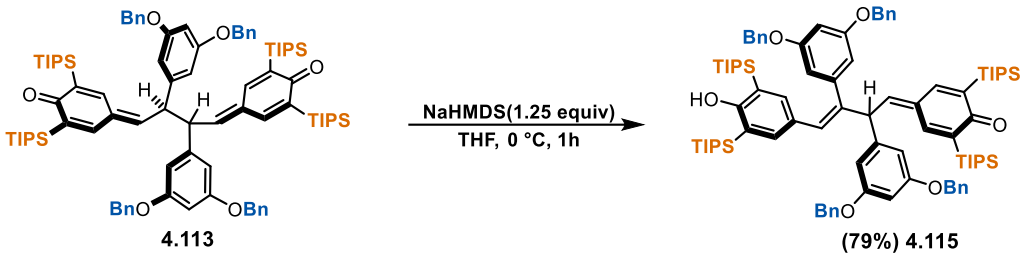
(4.110) (E)-4-(1-(3,5-dihydroxyphenyl)-2-(4-hydroxyphenyl)vinyl)-5-methylbenzene-1,3-diol

In a 2-dram vial was added starting material (10 mg, 16 µmol, 1 equiv), aluminum chloride (21 mg, 0.16 mmol, 10 equiv), and toluene (3.1 mL, 0.005 M). The reaction was heated to 80 °C for 2 hours. The reaction was quenched with methanol (1 mL) and water (5 mL). The mixture was extracted with ethyl acetate (3 x 5 mL), dried with brine (5 mL), $MgSO_4$ and filtered. The crude reaction mixture was purified by column chromatography SiO_2 (0-20% ethyl acetate in hexanes), followed by preparatory TLC to afford the product as a brown residue slightly contaminated with silica gel (3.2 mg, 59%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$), **4.110** δ = 8.39 (s, 1H), 8.19 (s, 1H), 8.09 (s, 2H), 7.09 (s, 1H), 7.03 – 6.97 (m, 2H), 6.66 – 6.61 (m, 2H), 6.52 (d, J=2.4, 1H), 6.38 (d, J=2.2, 2H), 6.34 (d, J=2.4, 1H), 6.32 (d, J=2.4, 1H), 6.24 (t, J=2.2, 1H), 1.90 (s, 3H).



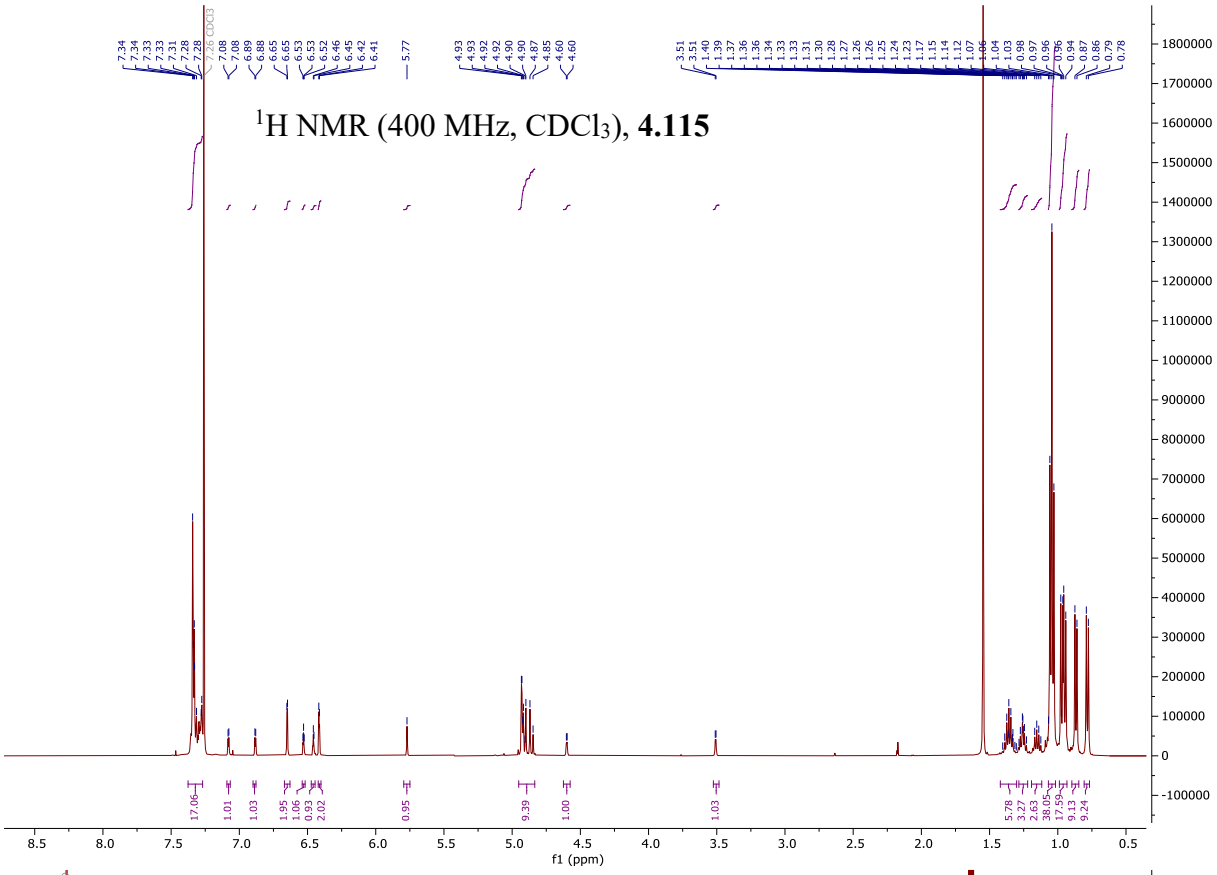
^{1}H NMR (400 MHz, $(CD_3)_2CO$), **4.110**



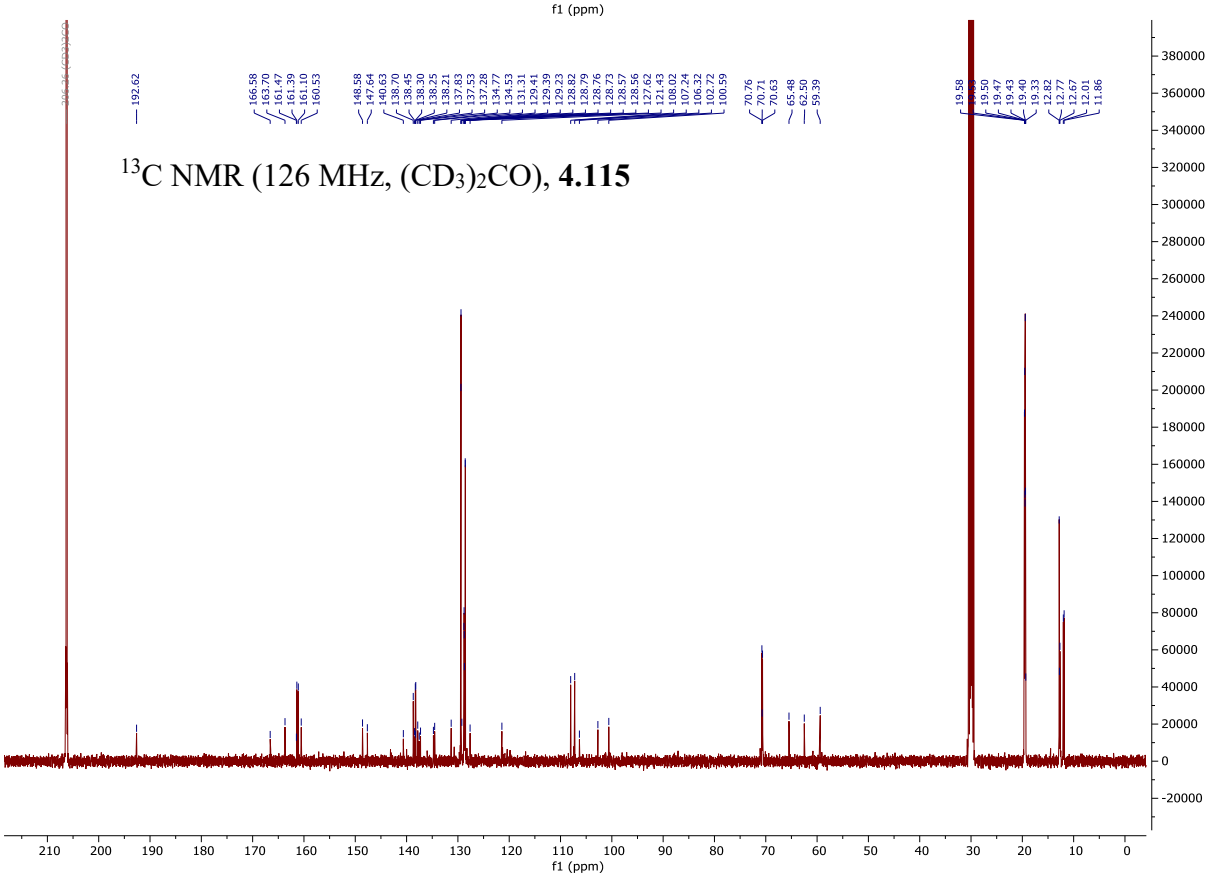
(4.115) (Z)-4-(2,3-bis(3,5-bis(benzyloxy)phenyl)-4-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)but-3-en-1-ylidene)-2,6-bis(triisopropylsilyl)cyclohexa-2,5-dien-1-one

In a 50 mL flame dried RBF was added BQM (1.00 g, 694 µmol, 1 equiv) and THF (35 mL, 0.02 M). The solution was cooled to 0 °C and then NaHMDS dropwise (179 µL, 868 µmol, 1.25 equiv, as a solution in THF, 5 mL, prepared freshly from solid removed from glovebox). The mixture was let stir for 1 hour after which the reaction was quenched with methanol (5 mL) and water (30 mL). The mixture was extracted with ether (3 x 30 mL), dried with brine (100 mL), $MgSO_4$ and filtered. The crude reaction mixture was purified by column chromatography SiO_2 (0-20% ethyl acetate in hexanes) to afford the tautomer as a pale-yellow foam (786 mg, 77%).

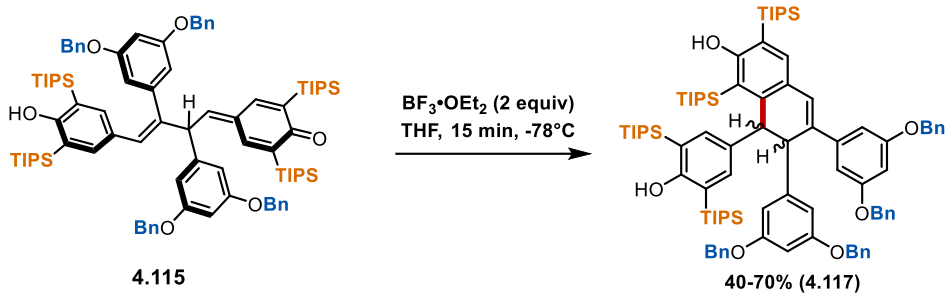
^{1}H NMR (400 MHz, $CDCl_3$), **4.115**	δ = 7.38 – 7.27 (m, 16H), 7.08 (d, J=3.0, 1H), 6.88 (d, J=3.0, 1H), 6.65 (d, J=2.2, 2H), 6.53 (t, J=2.2, 1H), 6.46 (d, J=2.2, 1H), 6.42 (d, J=2.2, 2H), 5.77 (s, 1H), 4.95 – 4.83 (m, 8H), 4.60 (d, J=2.8, 1H), 3.51 (d, J=2.9, 1H), 1.36 (p, J=7.5, 6H), 1.29 – 1.22 (m, 3H), 1.15 (q, J=7.5, 3H), 1.04 (t, J=7.3, 36H), 0.96 (dd, J=10.9, 7.5, 18H), 0.87 (d, J=7.5, 9H), 0.78 (d, J=7.5, 9H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$), **4.115**	δ = 192.6, 166.6, 163.7, 161.5, 161.4, 161.1, 160.5, 148.6, 147.6, 140.6, 138.7, 138.4, 138.3, 138.2, 138.2, 137.8, 137.5, 137.3, 134.8, 134.5, 131.3, 129.4, 129.4, 129.2, 128.8, 128.8, 128.8, 128.7, 128.6, 128.6, 127.6, 121.4, 108.0, 107.2, 106.3, 102.7, 100.6, 70.8, 70.7, 70.6, 65.5, 62.5, 59.4, 19.6, 19.5, 19.5, 19.5, 19.4, 19.4, 19.3, 12.8, 12.8, 12.7, 12.0, 11.9.



^{1}H NMR (400 MHz, $CDCl_3$), **4.115**



^{13}C NMR (126 MHz, $(CD_3)_2CO$), **4.115**

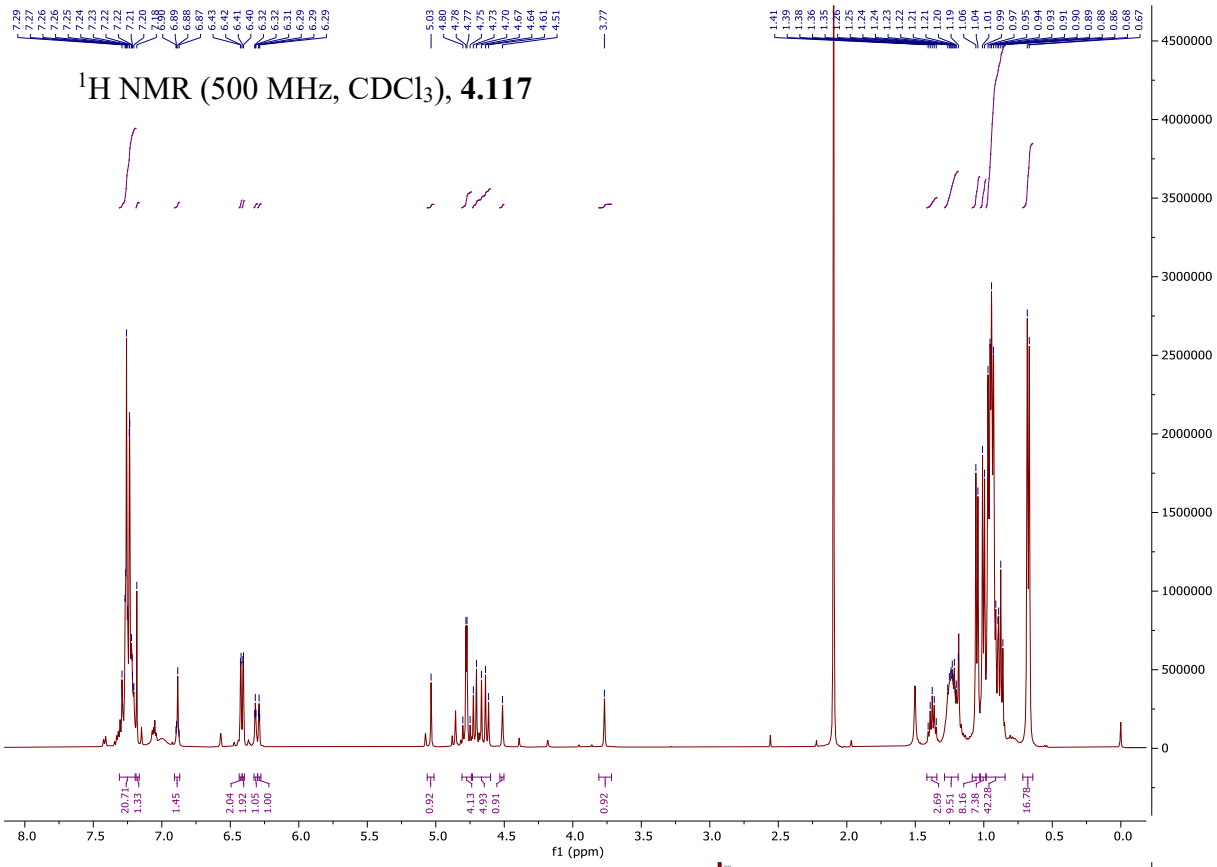


(4.117) 6,7-bis(3,5-bis(benzyloxy)phenyl)-8-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)-1,3-bis(triisopropylsilyl)-7,8-dihydronaphthalen-2-ol

In a 2-dram vial was added starting material (26 mg, 18 µmol, 1 equiv) and THF (1.8 mL, 0.01 M). The solution was cooled to -78 °C and BF_3•OEt_2 (9.6 µL, 37 µmol, 2 equiv, 48 wt% solution) was added dropwise. After 15 minutes the reaction was quenched with methanol (1 mL) and water (2 mL). The mixture was extracted with ether (3 x 3 mL), dried with brine (10 mL), $MgSO_4$ and filtered. The crude reaction mixture was purified by column chromatography SiO_2 (0-20% ethyl acetate in hexanes) to afford the product as a brown oil (17 mg, 64%). This product was difficult to identify as the inequivalent benzyl protecting groups obscured the spectral interpretation.

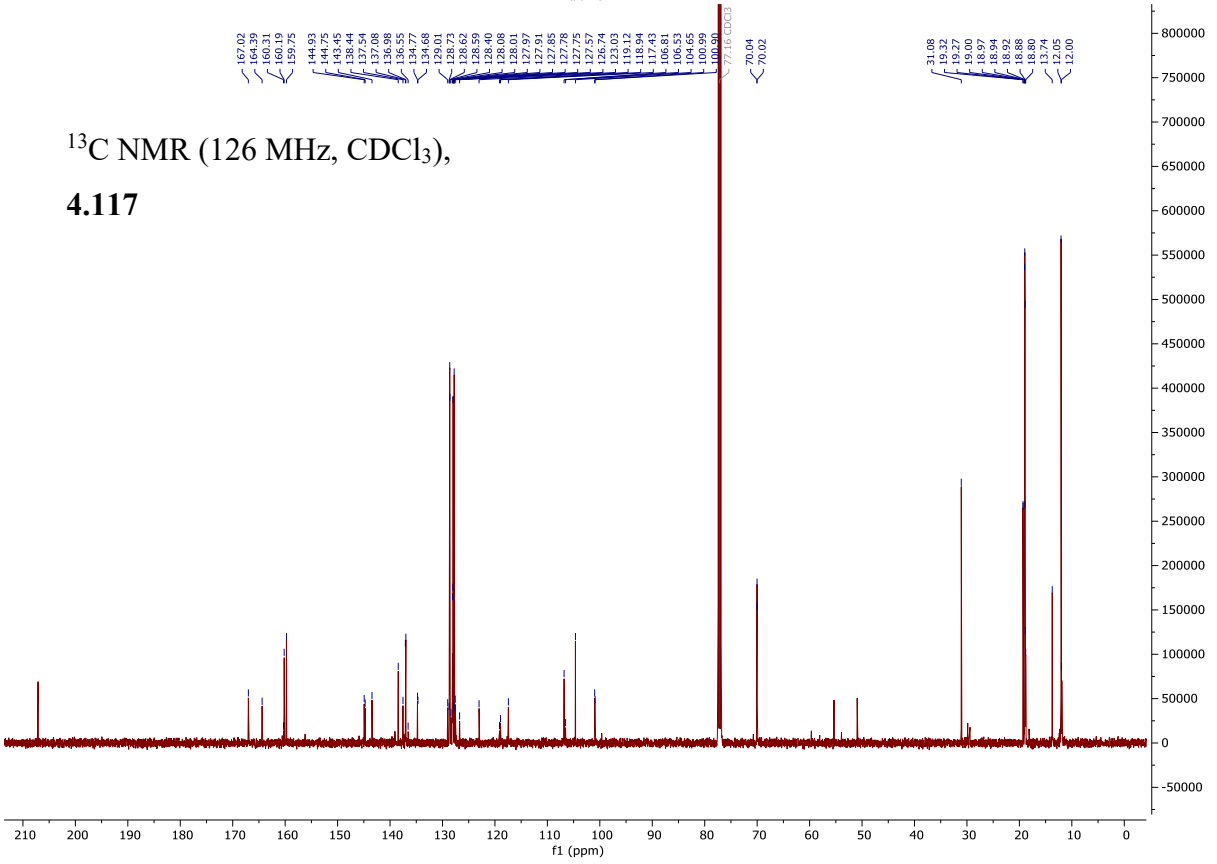
^{1}H NMR (500 MHz, $CDCl_3$), **4.117**	δ = 7.31 – 7.19 (m, 21H), 7.18 (s, 1H), 6.88 (s, 1H), 6.42 (d, J=2.2, 2H), 6.41 (d, J=2.2, 2H), 6.32 (t, J=2.4, 1H), 6.29 (t, J=2.2, 1.8, 1H), 5.03 (s, 1H), 4.81 – 4.74 (m, 4H), 4.73 – 4.60 (m, 5H), 4.51 (s, 1H), 3.77 (s, 1H), 1.38 (p, J=7.4, 3H), 1.29 – 1.19 (m, 10H), 1.05 (d, J=7.5, 8H), 1.00 (d, J=7.5, 7H), 0.98 – 0.84 (m, 42H), 0.68 (d, J=7.3, 17H).
^{13}C NMR (126 MHz, $CDCl_3$), **4.117**	δ = 167.0, 164.4, 160.3, 160.2, 159.7, 144.9, 144.7, 143.4, 138.4, 137.5, 137.1, 137.0, 136.6, 134.8, 134.7, 129.0, 128.7, 128.6, 128.6, 128.4, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 126.7, 123.0, 119.1, 118.9, 117.4, 106.8, 106.5, 104.6, 101.0, 100.9, 70.0, 70.0, 31.1, 19.3, 19.3, 19.0, 19.0, 18.9, 18.9, 18.9, 18.8, 13.7, 12.1, 12.0.

^{1}H NMR (500 MHz, $CDCl_3$), **4.117**



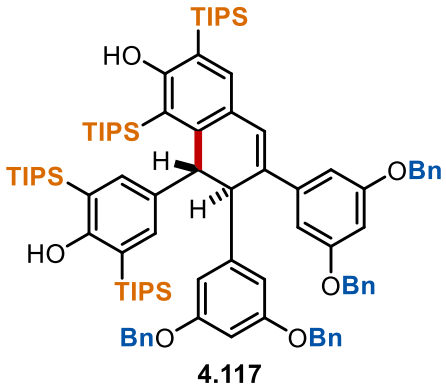
^{13}C NMR (126 MHz, $CDCl_3$),

4.117

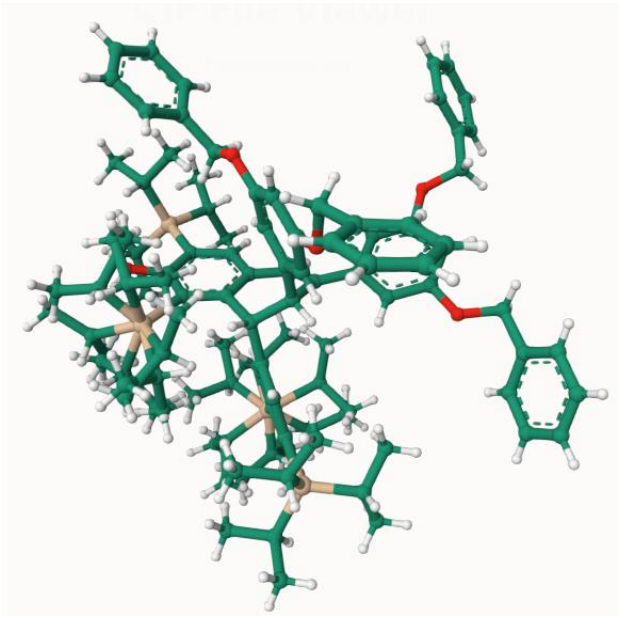


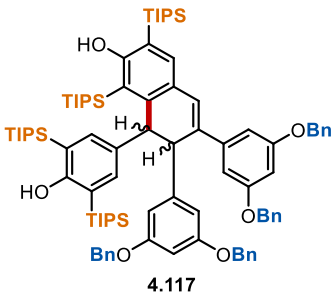
X-ray Crystallography

Crystals suitable for X-ray diffraction were grown from slow evaporation from DCM. We thank the crystallographer, Fengrui Qu, for acquiring the X-ray data. It was reported that the connectivity of the crystal could be readily deduced, but that the data was not recommended for publication.



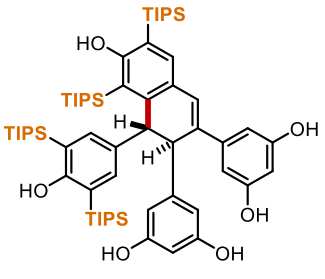
4.117





4.117

BCl_3, Me_5-Benzene
DCM, -78°C, 30 min
$NaHCO_3$ Quench

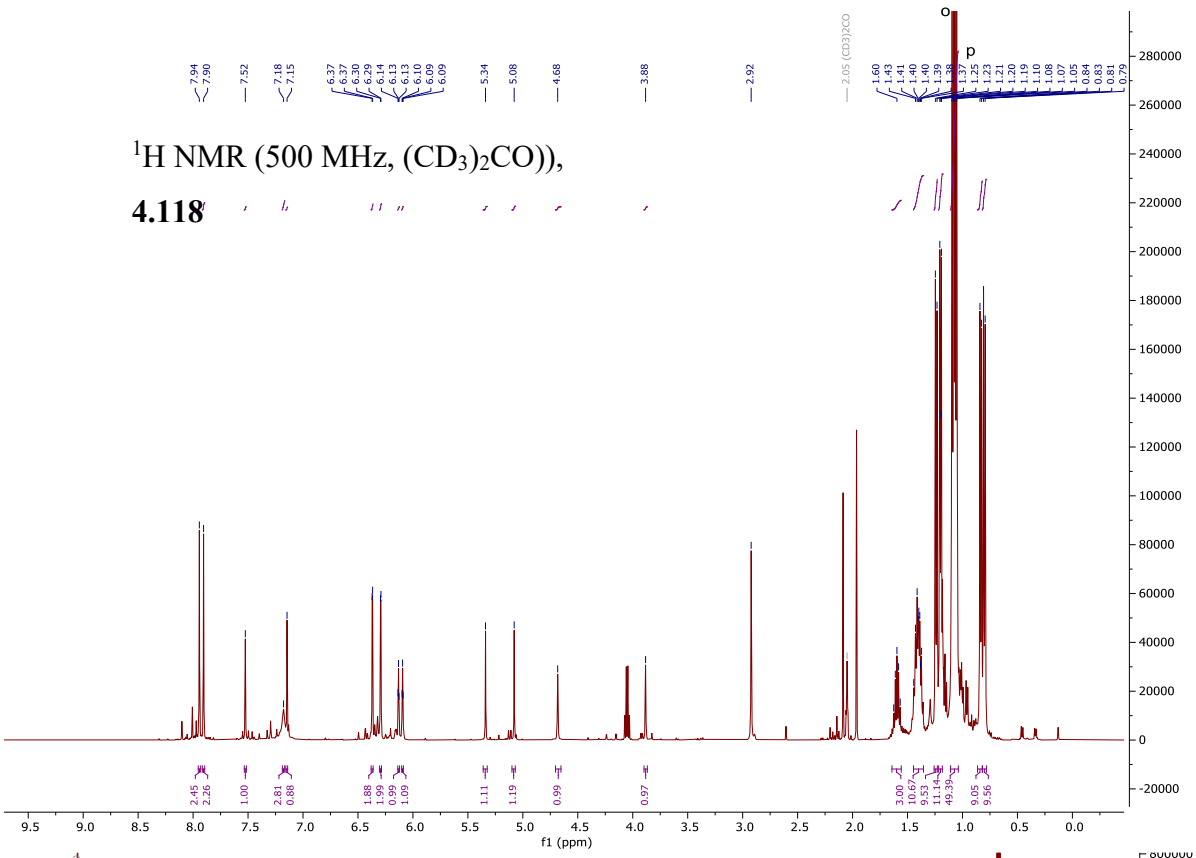


50-60% (4.118)

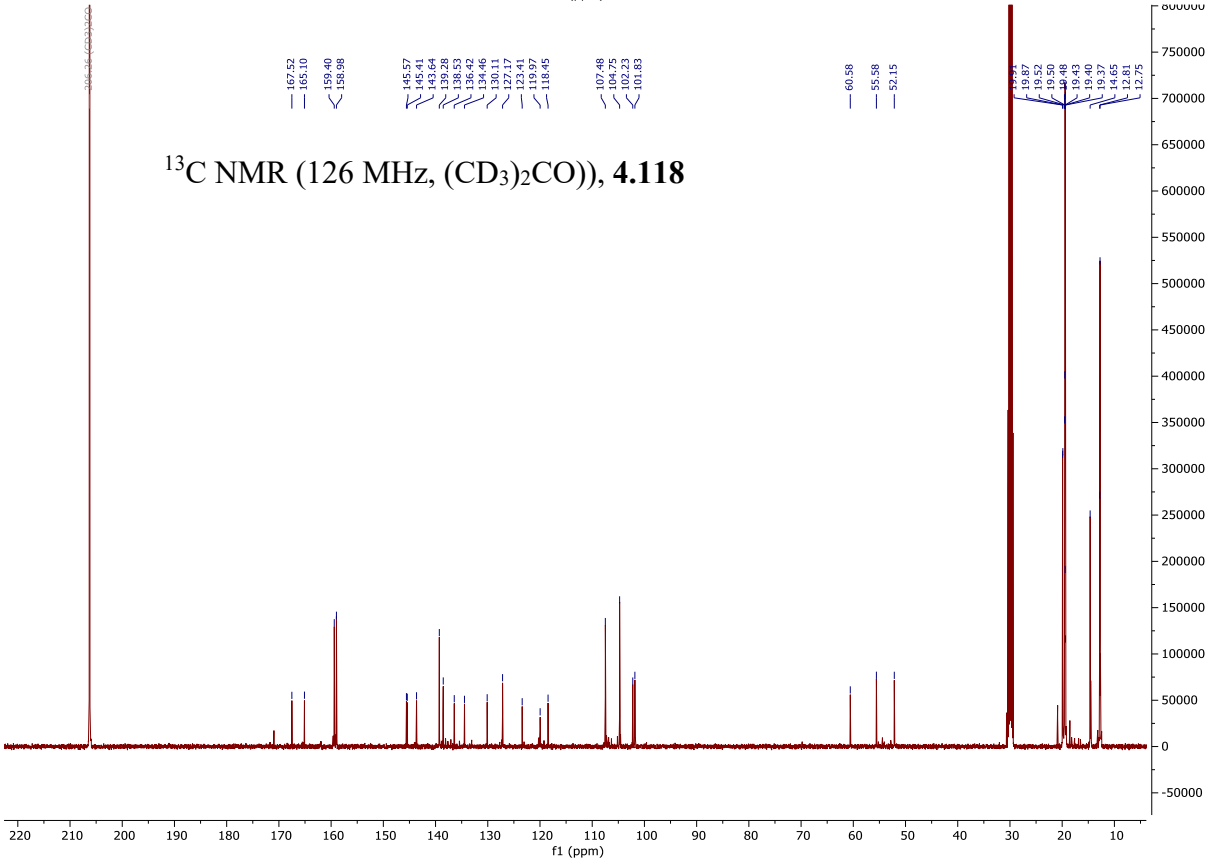
(4.118) 5,5'-((2R)-7-hydroxy-1-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)-6,8-bis(triisopropylsilyl)-1,2-dihydronaphthalene-2,3-diyl)bis(benzene-1,3-diol)

In a 4-dram vial was added starting material (100 mg, 69 μmol, 1 equiv), pentamethylbenzene (206 mg, 1.38 mmol, 20 equiv), and DCM (6.9 mL, 0.01 M). The solution was cooled to -78 °C and BCl_3 (833 μL, 833 μmol, 12 equiv, 1.0 M in DCM) was added dropwise. After 30 minutes the reaction was quenched with Sat. $NaHCO_3$ (aq) (1 mL) at -78 °C. The solution was let warm to room temperature before addition of DCM (5 mL) for extraction. The combined organics were dried with brine (10 mL), $MgSO_4$ and filtered. The crude reaction mixture was purified by column chromatography SiO_2 (0-50% ethyl acetate in hexanes) to afford the product as a tan foam (39 mg, 52%).

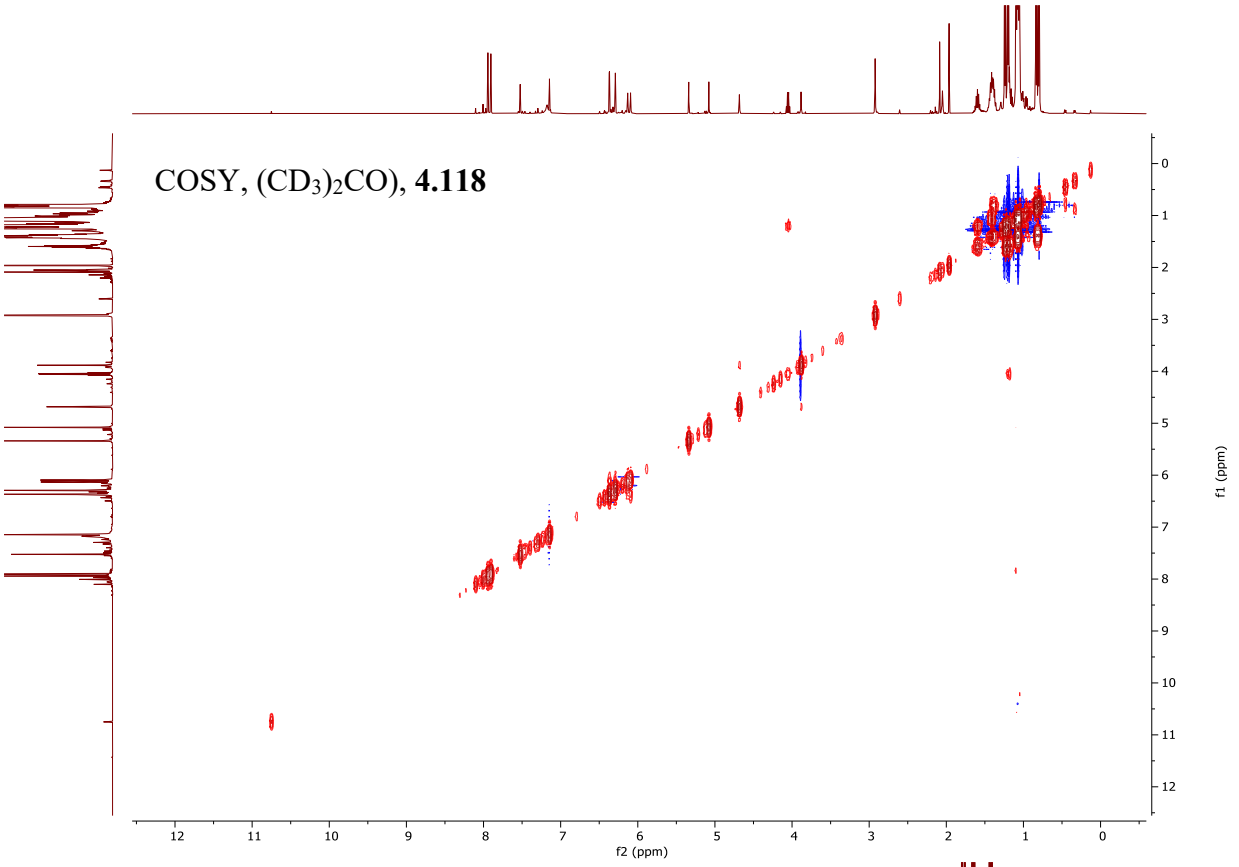
^{1}H NMR (500 MHz, $(CD_3)_2CO$)), **4.118**	δ = 7.94 (s, 2H), 7.90 (s, 2H), 7.52 (s, 1H), 7.18 (s, 1H), 7.15 (s, 1H), 6.37 (d, J=2.1, 2H), 6.29 (d, J=2.2, 2H), 6.14 – 6.12 (m, 1H), 6.10 – 6.09 (m, 1H), 5.34 (s, 1H), 5.08 (s, 1H), 4.68 (s, 1H), 3.88 (s, 1H), 1.60 (p, J=7.4, 3H), 1.45 – 1.35 (m, 9H), 1.24 (d, J=7.5, 9H), 1.22 – 1.18 (m, 9H), 1.07 (dd, J=14.0, 7.4, 36H), 0.83 (d, J=7.4, 9H), 0.80 (d, J=7.4, 9H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$)), **4.118**	δ = 167.5, 165.1, 159.4, 159.0, 145.6, 145.4, 143.6, 139.3, 138.5, 136.4, 134.5, 130.1, 127.2, 123.4, 120.0, 118.5, 107.5, 104.8, 102.2, 101.8, 60.6, 55.6, 52.1, 19.9, 19.9, 19.5, 19.5, 19.5, 19.4, 19.4, 19.4, 14.6, 12.8, 12.8.



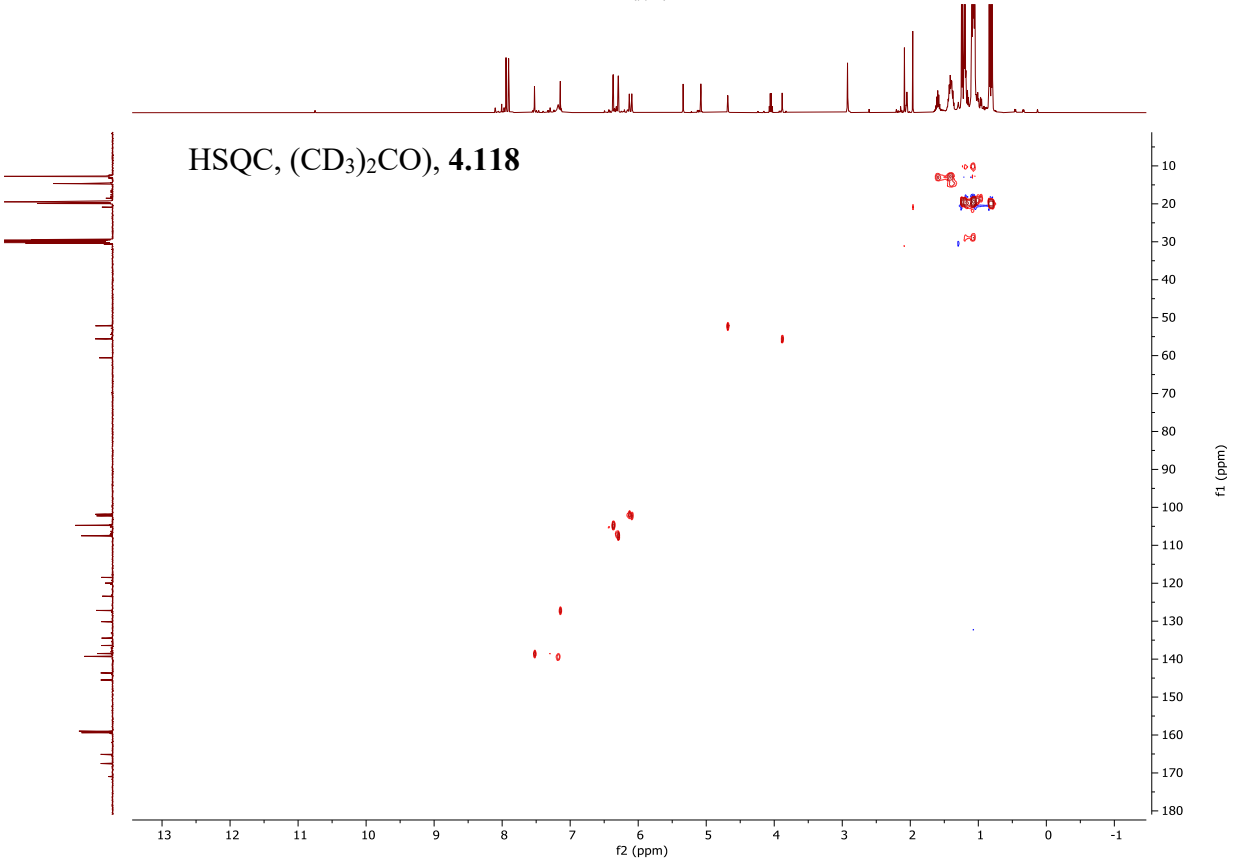
^{1}H NMR (500 MHz, $(CD_3)_2CO$)), **4.118**



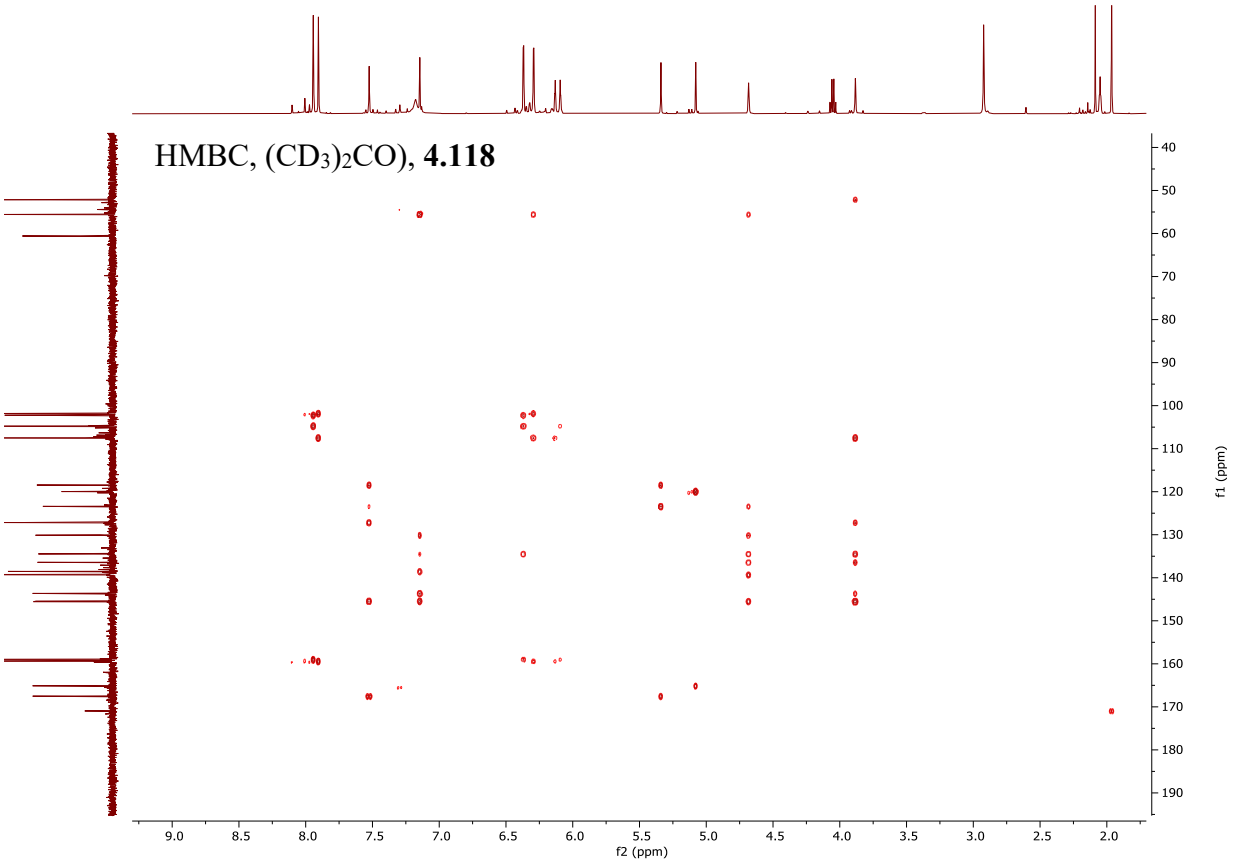
^{13}C NMR (126 MHz, $(CD_3)_2CO$)), **4.118**

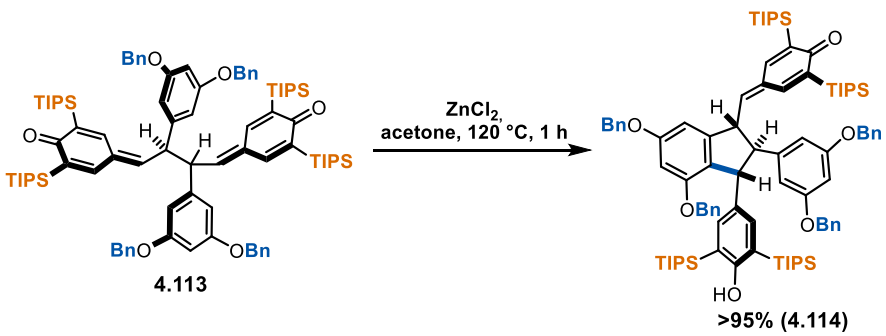


COSY, $(CD_3)_2CO$), **4.118**



HSQC, $(CD_3)_2CO$), **4.118**


HMBC, (CD3)2CO), 4.118
f2 (ppm)
f1 (ppm)

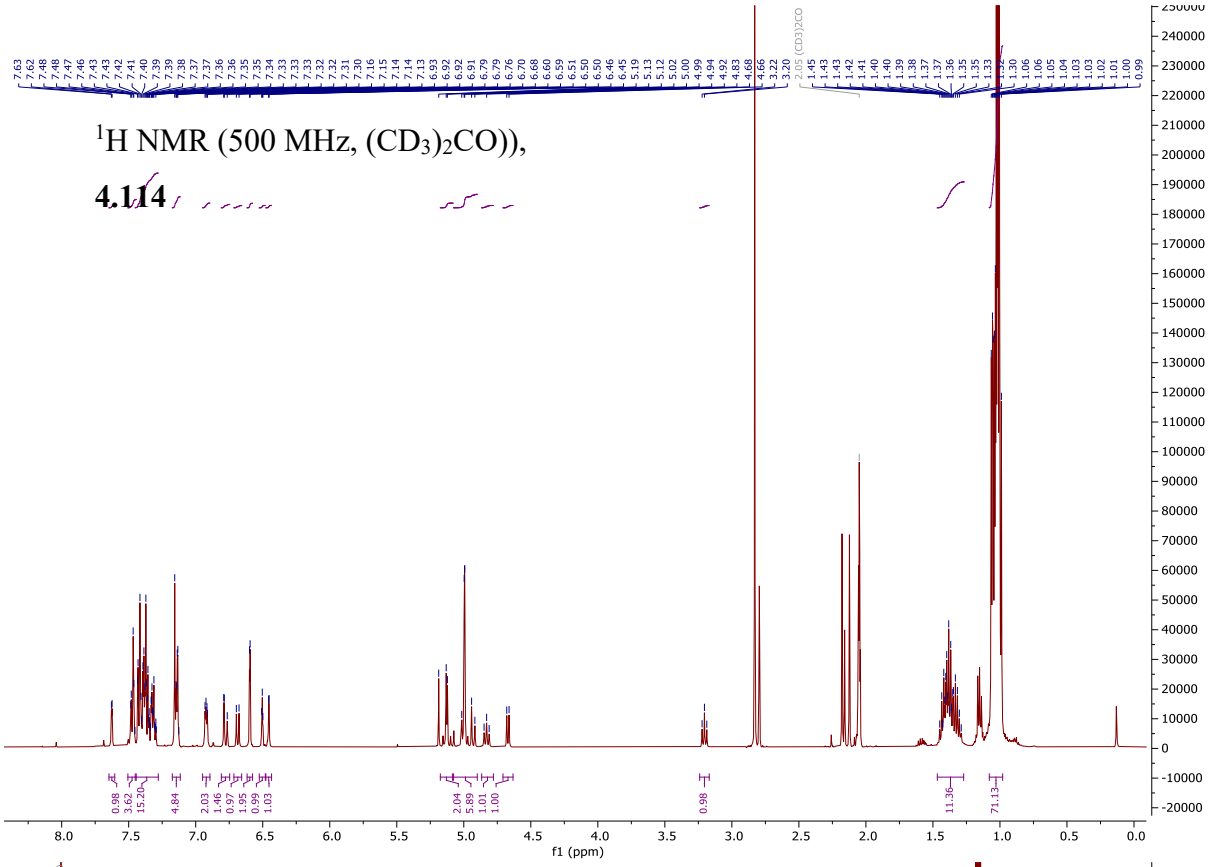


(4.114) 4-(((1R,2R,3R)-4,6-bis(benzyloxy)-2-(3,5-bis(benzyloxy)phenyl)-3-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)-2,3-dihydro-1H-inden-1-yl)methylene)-2,6-bis(triisopropylsilyl)cyclohexa-2,5-dien-1-one

In a sealed tube was added starting material (50 mg, 35 µmol, 1 equiv), $ZnCl_2$ (69 µL, 69 µmol, 2 equiv, 1.0 M solution in THF), and acetone (3.5 mL, 0.01 M). The sealed tube was capped and heated to 120 °C for 1 h in an oil bath. The crude solution was partitioned between ether (20 mL) and water (20 mL). The organics were dried with brine (20 mL) and $MgSO_4$. This organic extract was in sufficient purity for further reaction (~90%), but if desired the residue could be subjected to column chromatography SiO_2 (0-20% ethyl acetate in hexanes) to afford the product as a tan foam (47 mg, 94%).

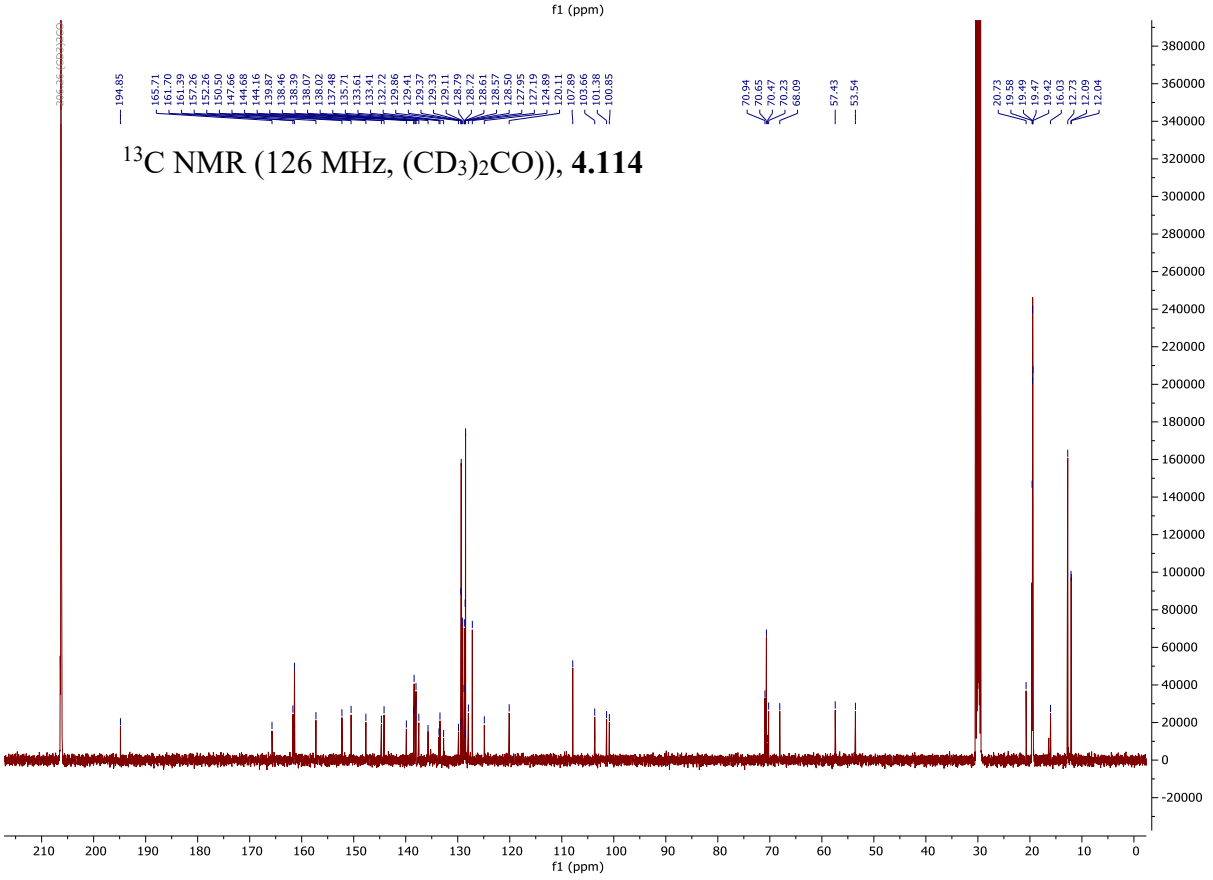
^{1}H NMR (500 MHz, $(CD_3)_2CO$)), **4.114** δ = 7.63 (d, J=2.7, 1H), 7.51 – 7.44 (m, 4H), 7.45 – 7.28 (m, 15H), 7.17 – 7.12 (m, 5H), 6.92 (dd, J=6.5, 2.9, 2H), 6.81 – 6.75 (m, 1H), 6.69 (d, J=10.0, 1H), 6.60 (d, J=2.2, 2H), 6.50 (t, J=2.2, 1H), 6.45 (d, J=2.0, 1H), 5.13 (d, J=4.5, 2H), 5.08 – 4.90 (m, 6H), 4.83 (t, J=9.5, 1H), 4.67 (d, J=8.7, 1H), 3.20 (t, J=8.8, 1H), 1.47 – 1.27 (m, 11H), 1.08 – 0.98 (m, 71H).

^{13}C NMR (126 MHz, $(CD_3)_2CO$)), **4.114** δ = 194.8, 165.7, 161.7, 161.4, 157.3, 152.3, 150.5, 147.7, 144.7, 144.2, 139.9, 138.5, 138.4, 138.1, 138.0, 137.5, 135.7, 133.6, 133.4, 132.7, 129.9, 129.4, 129.4, 129.3, 129.1, 128.8, 128.7, 128.6, 128.6, 128.5, 128.0, 127.2, 124.9, 120.1, 107.9, 103.7, 101.4, 100.9, 70.9, 70.7, 70.5, 70.2, 68.1, 57.4, 53.5, 20.7, 19.6, 19.5, 19.5, 19.4, 16.0, 12.7, 12.1, 12.0.

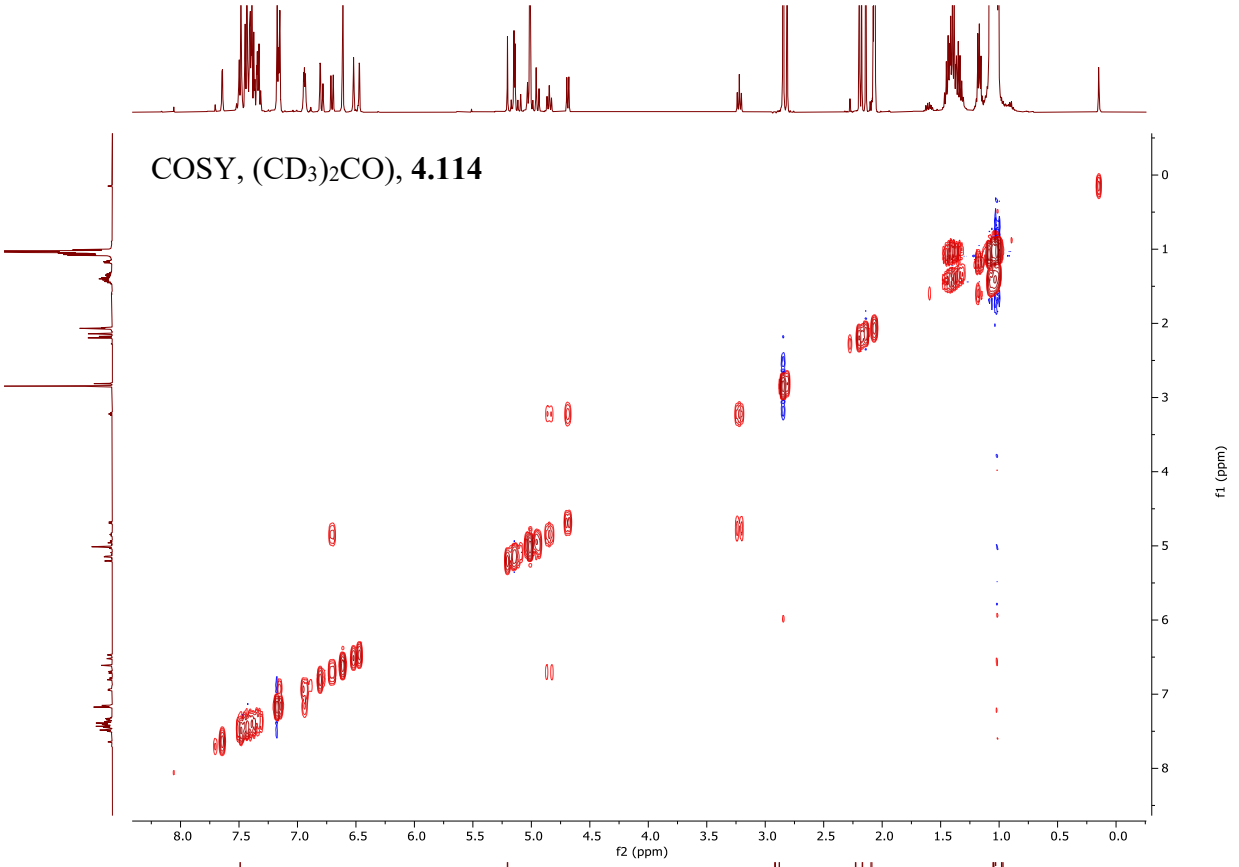


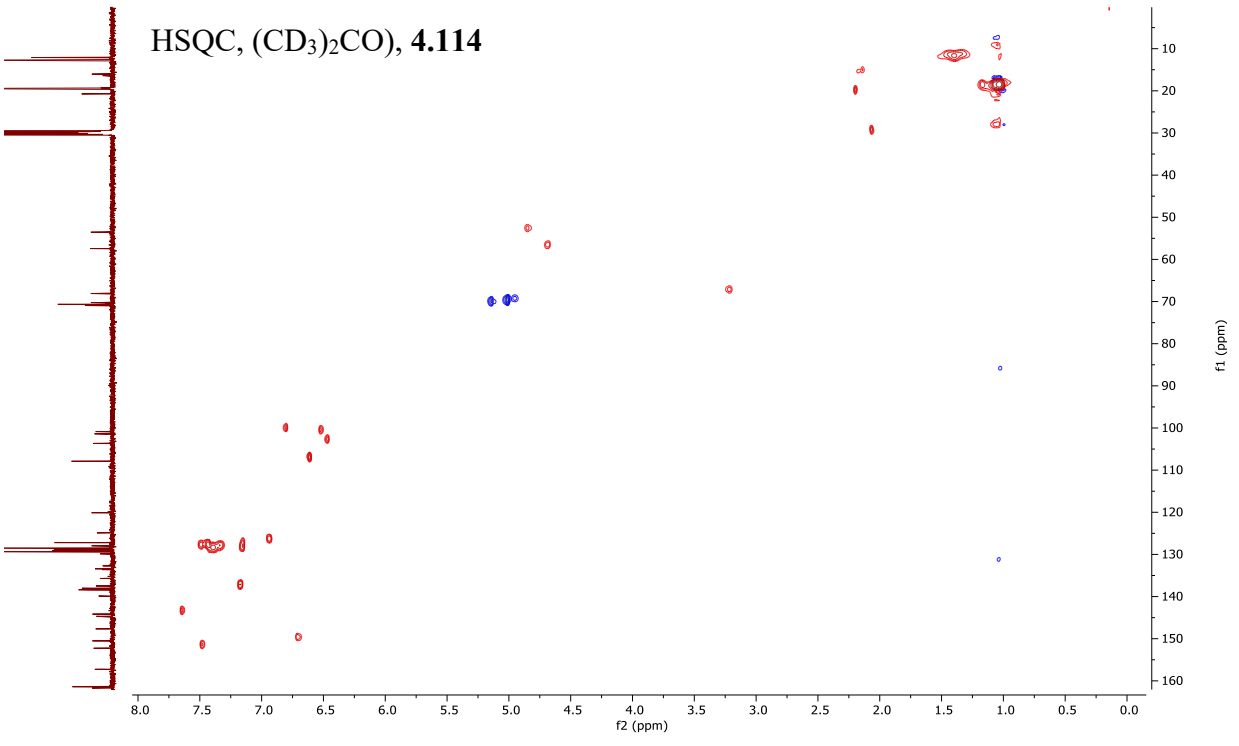
^{1}H NMR (500 MHz, $(CD_3)_2CO$)),

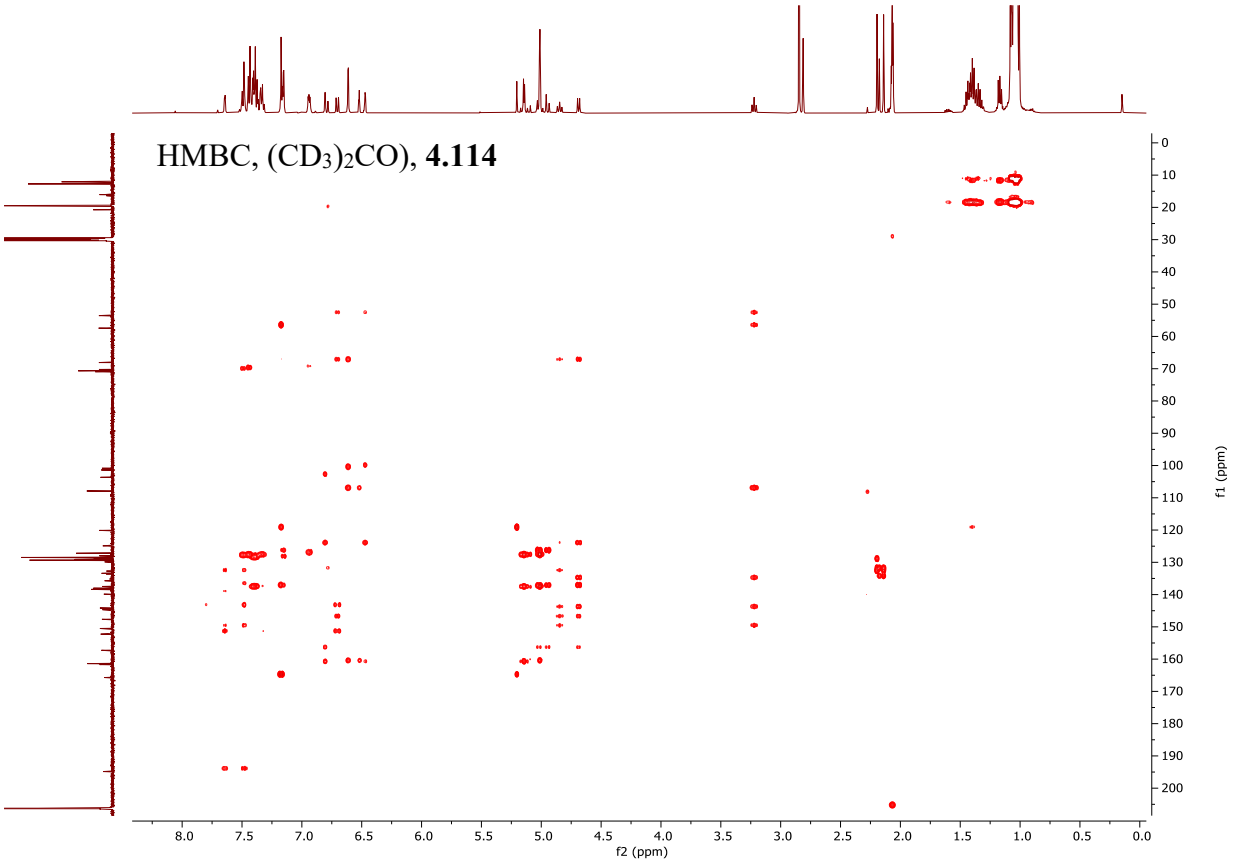
4.114

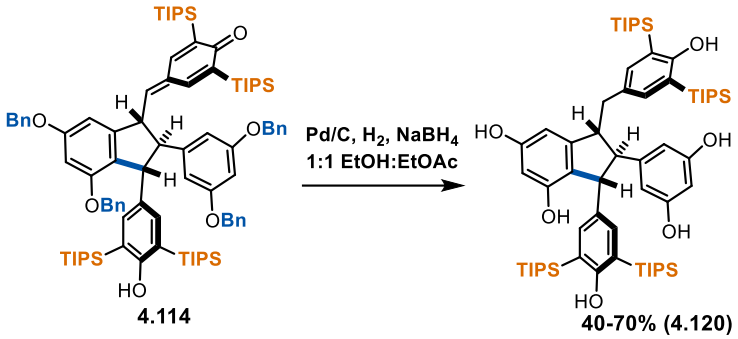


^{13}C NMR (126 MHz, $(CD_3)_2CO$)), **4.114**


COSY, $(CD_3)_2CO$), **4.114**
f2 (ppm)
f1 (ppm)


HSQC, $(CD_3)_2CO$), **4.114**
f2 (ppm)
f1 (ppm)


HMBC, (CD3)2CO), 4.114
f2 (ppm)
f1 (ppm)

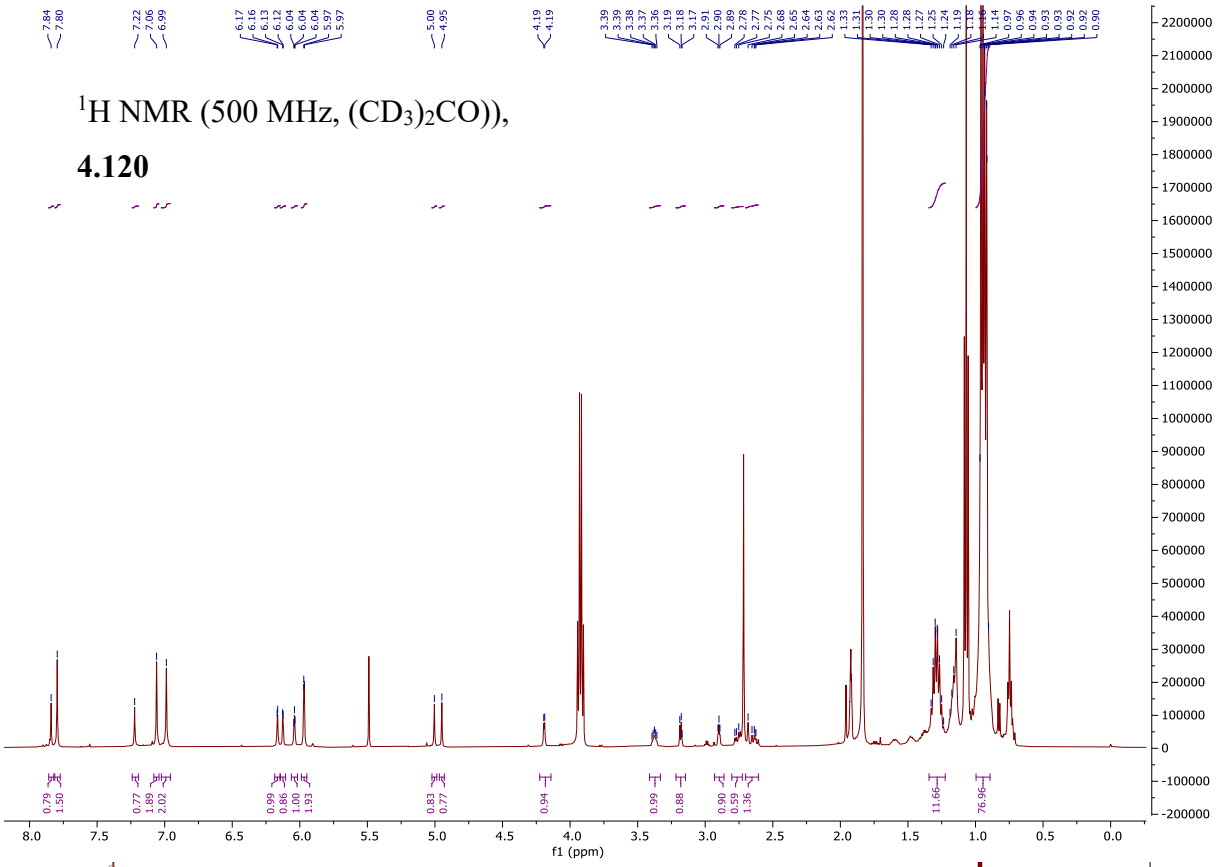


(4.120) (1R,2R,3R)-2-(3,5-dihydroxyphenyl)-1-(4-hydroxy-3,5-bis(triisopropylsilyl)benzyl)-3-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)-2,3-dihydro-1H-indene-4,6-diol

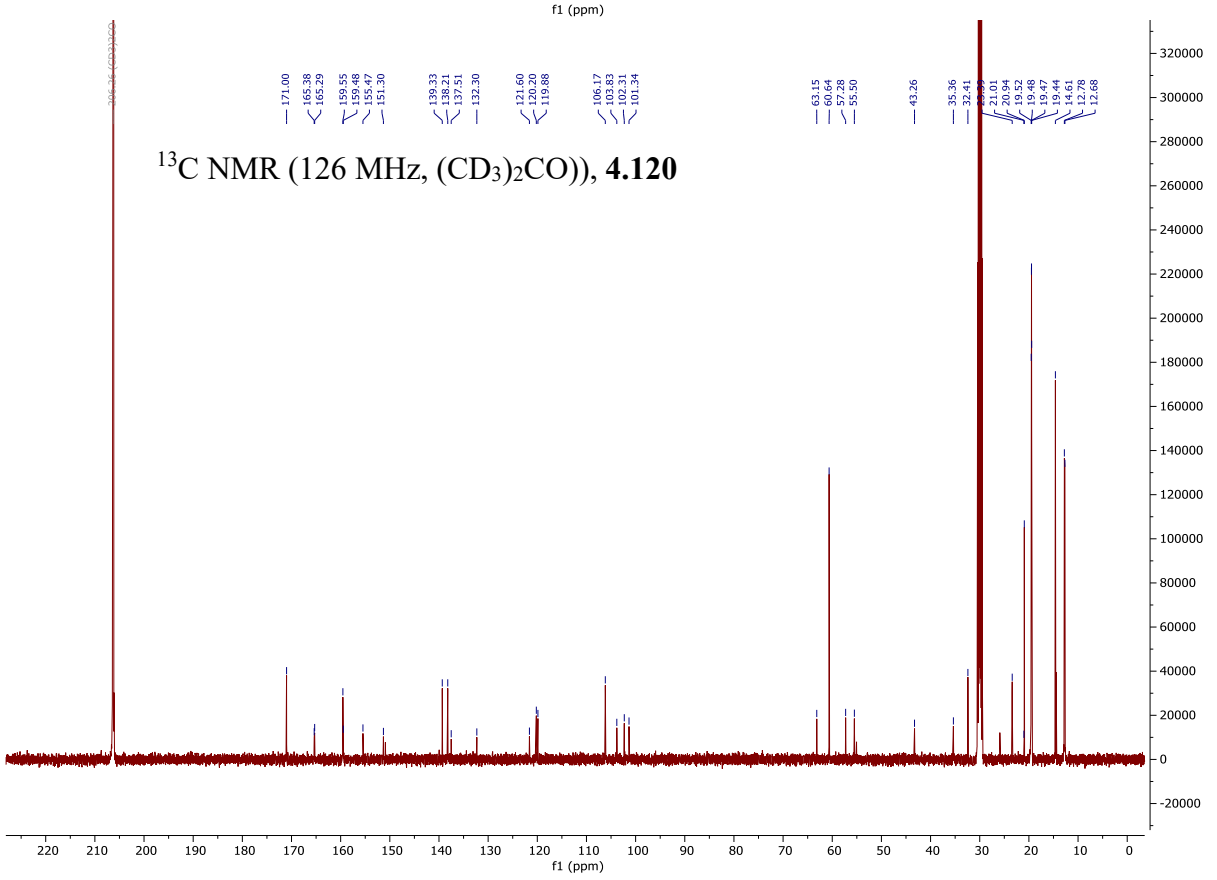
In a 2-dram vial was added starting material (20 mg, 14 µmol, 1 equiv), Pd/C (5 mg, 14 µmol, 1 equiv, 30 wt% on carbon), $NaBH_4$ (5 mg, 140 µmol, 10 equiv) and MeOH (1.4 mL, 0.01 M). The solution was sparged with hydrogen gas for 10 minutes and then let react for 16 hours under an atmosphere of hydrogen. The completed reaction was sparged with argon, filtered to remove solids, and concentrated. This crude organic was subjected to column chromatography SiO_2 (0-50% ethyl acetate in hexanes) to afford the product as a brown residue (8 mg, 51%).

^{1}H NMR (500 MHz, $(CD_3)_2CO$)), **4.120** δ = 7.84 (s, 1H), 7.80 (s, 1H), 7.22 (s, 1H), 7.06 (s, 2H), 6.99 (s, 2H), 6.17 (d, J=2.1, 1H), 6.13 (d, J=2.1, 1H), 6.04 (t, J=2.2, 1H), 5.97 (d, J=2.2, 2H), 5.00 (s, 1H), 4.95 (s, 1H), 4.19 (d, J=3.5, 1H), 3.41 – 3.33 (m, 1H), 3.18 (d, J=5.3, 1H), 2.90 (t, J=3.7, 1H), 2.80 – 2.73 (m, 1H), 2.70 – 2.61 (m, 1H), 1.34 – 1.22 (m, 12H), 1.00 – 0.89 (m, 72H).

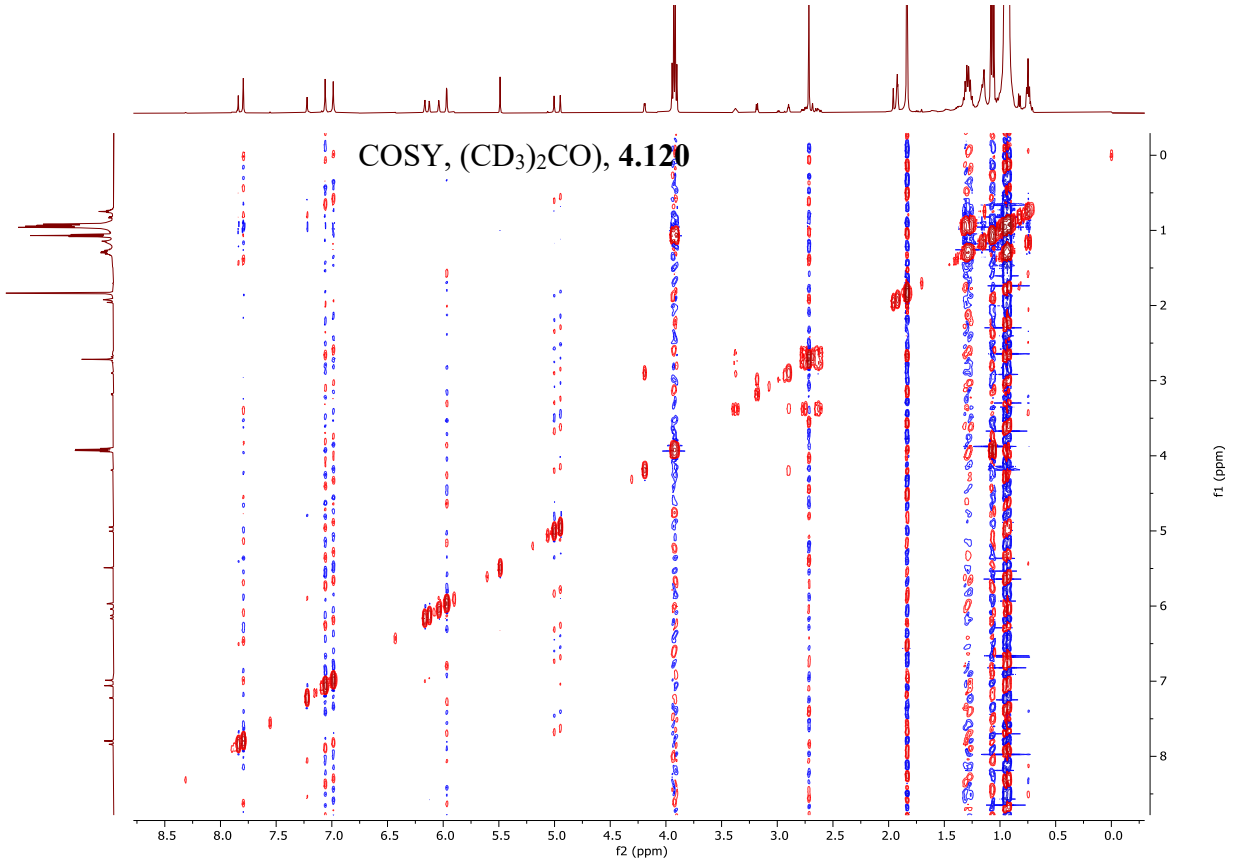
^{13}C NMR (126 MHz, $(CD_3)_2CO$)), **4.120** δ = 171.0, 165.4, 165.3, 159.5, 159.5, 155.5, 151.3, 139.3, 138.2, 137.5, 132.3, 121.6, 120.2, 119.9, 106.2, 103.8, 102.3, 101.3, 63.2, 60.6, 57.3, 55.5, 43.3, 35.4, 32.4, 23.4, 21.0, 20.9, 19.5, 19.5, 19.5, 19.4, 14.6, 12.8, 12.7.

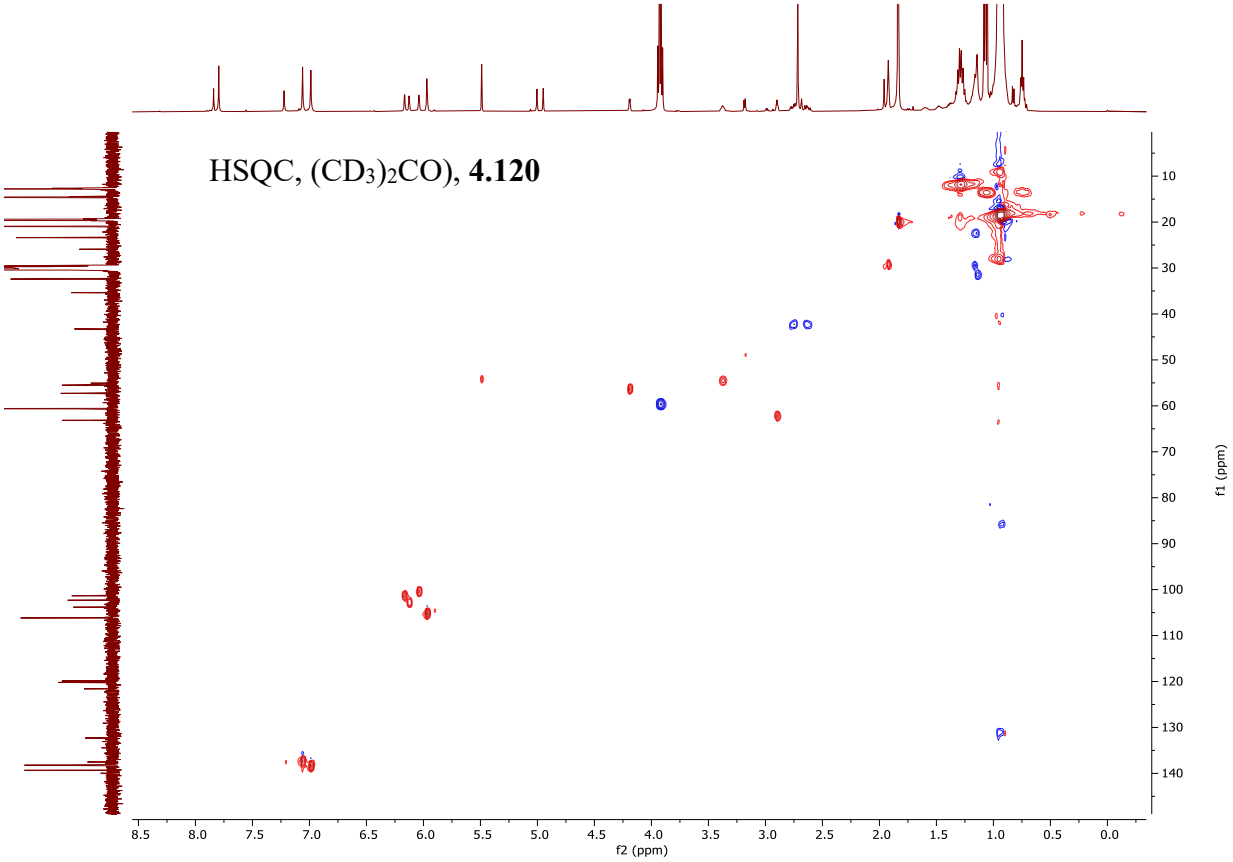


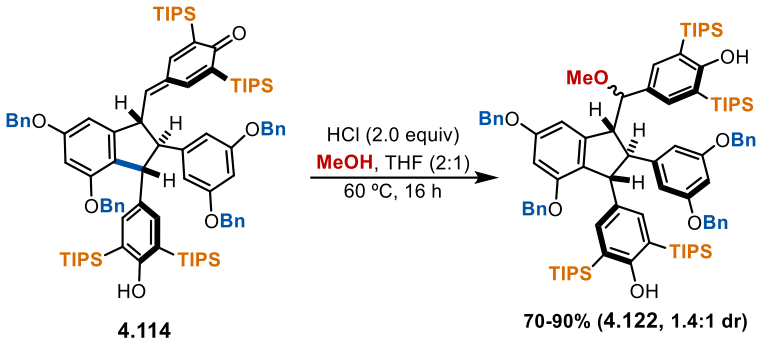
^{1}H NMR (500 MHz, $(CD_3)_2CO$)), **4.120**



^{13}C NMR (126 MHz, $(CD_3)_2CO$)), **4.120**


COSY, $(CD_3)_2CO$), **4.120**
f2 (ppm)
f1 (ppm)

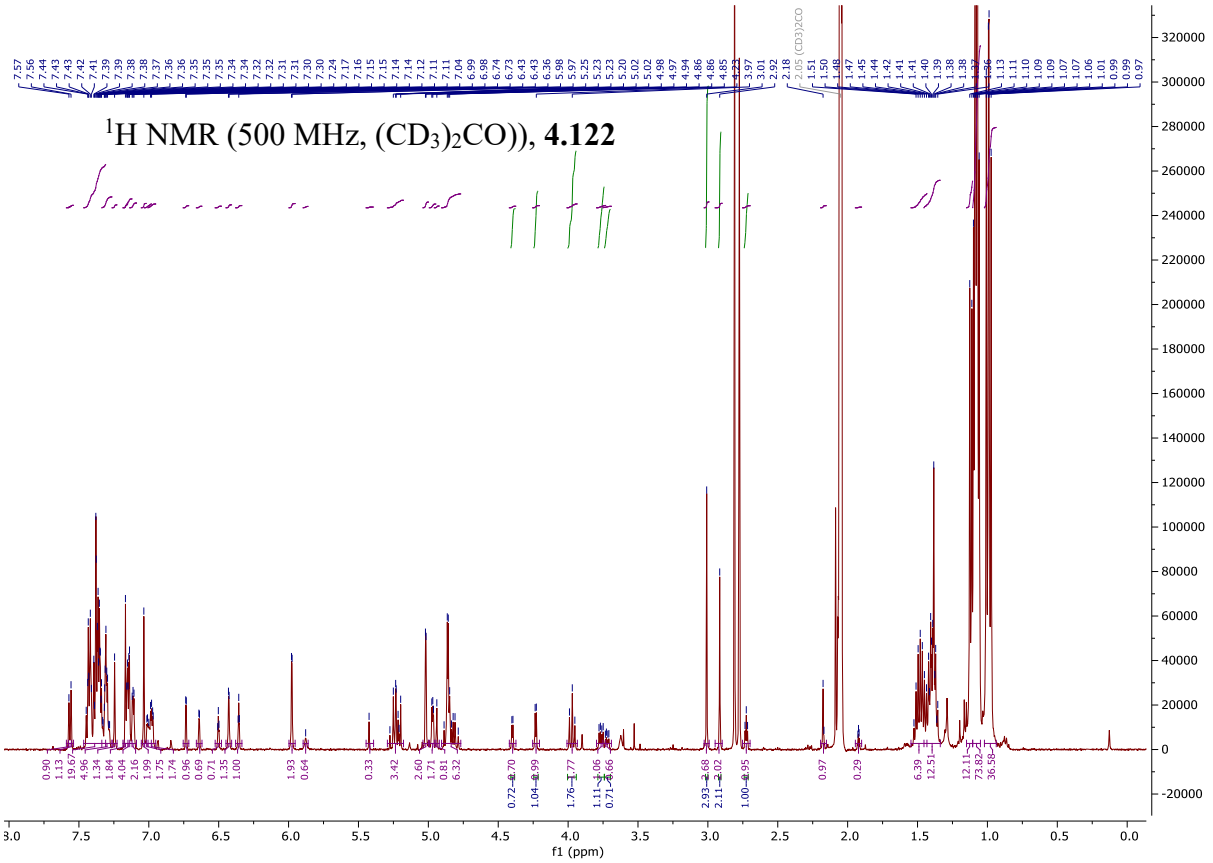

HSQC, $(CD_3)_2CO$), **4.120**
f2 (ppm)
f1 (ppm)

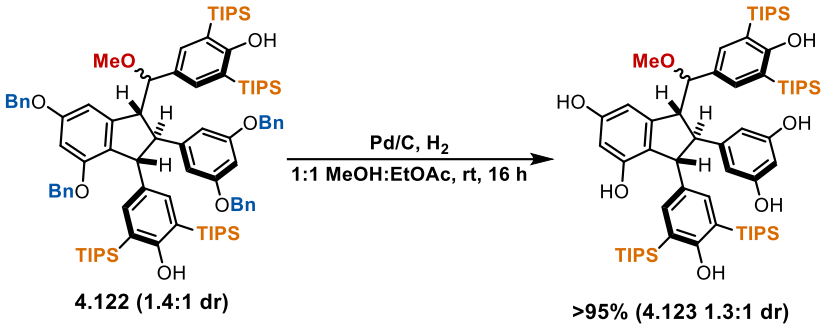


(4.122) 4-((1R,2S,3R)-5,7-bis(benzyloxy)-2-(3,5-bis(benzyloxy)phenyl)-3-((4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)(methoxy)methyl)-2,3-dihydro-1H-inden-1-yl)-2,6-bis(triisopropylsilyl)phenol

In a 2-dram vial was added starting material (300 mg, 280 µmol, 1 equiv), HCl (833 µL, 417 µmol, 2 equiv, 0.5 M solution in MeOH), MeOH (20 mL, 0.01 M) and THF (10 mL, 0.02 M). The reaction was heated to 60 °C for 16 h. The mixture was quenched with sat. $NaHCO_3$ (aq) (20 mL) and extracted with either (3 x 20 mL). The organics were dried with brine (20 mL) and $MgSO_4$. The crude organic residue was subjected to column chromatography SiO_2 (0-30% ethyl acetate in hexanes) to afford the product as a pale yellow foam (232 mg, 76%) as a 1.4:1 mixture of diastereomers about addition of MeOH to the quinone. Due to the complexity of the spectral interpretation of the inseparable mixture, the major diastereomer was not identified.

^{1}H NMR (500 MHz, $(CD_3)_2CO$)), **4.122** δ = 7.57 (s, 1H), 7.56 (s, 1H), 7.47 – 7.31 (m, 20H), 7.34 – 7.26 (m, 5H), 7.24 (s, 1H), 7.17 (s, 2H), 7.15 (dd, J=7.3, 2.7, 4H), 7.14 – 7.09 (m, 2H), 7.04 (s, 2H), 7.03 – 6.98 (m, 2H), 6.98 (dd, J=6.6, 2.8, 2H), 6.73 (d, J=2.1, 1H), 6.64 (d, J=2.1, 1H), 6.50 (t, J=2.3, 1H), 6.43 (d, J=2.2, 1H), 6.36 (t, J=2.3, 1H), 5.98 (d, J=2.2, 2H), 5.88 (s, 1H), 5.42 (s, 0H), 5.29 – 5.18 (m, 3H), 5.02 (d, J=1.9, 3H), 4.99 – 4.95 (m, 2H), 4.94 (s, 1H), 4.91 – 4.77 (m, 6H), 4.40 (d, J=3.8, 1H), 4.23 (d, J=4.3, 1H), 3.97 (t, J=9.6, 2H), 3.76 (dd, J=10.0, 4.9, 1H), 3.72 (dd, J=8.8, 3.7, 1H), 3.01 (s, 3H), 2.92 (s, 2H), 2.73 (t, J=4.5, 1H), 2.18 (s, 1H), 1.92 (t, J=2.2, 0H), 1.48 (dt, J=15.0, 7.5, 6H), 1.40 (dt, J=10.6, 7.2, 13H), 1.12 (d, J=7.5, 12H), 1.08 (td, J=7.4, 5.1, 74H), 0.99 (dd, J=9.9, 7.4, 37H).

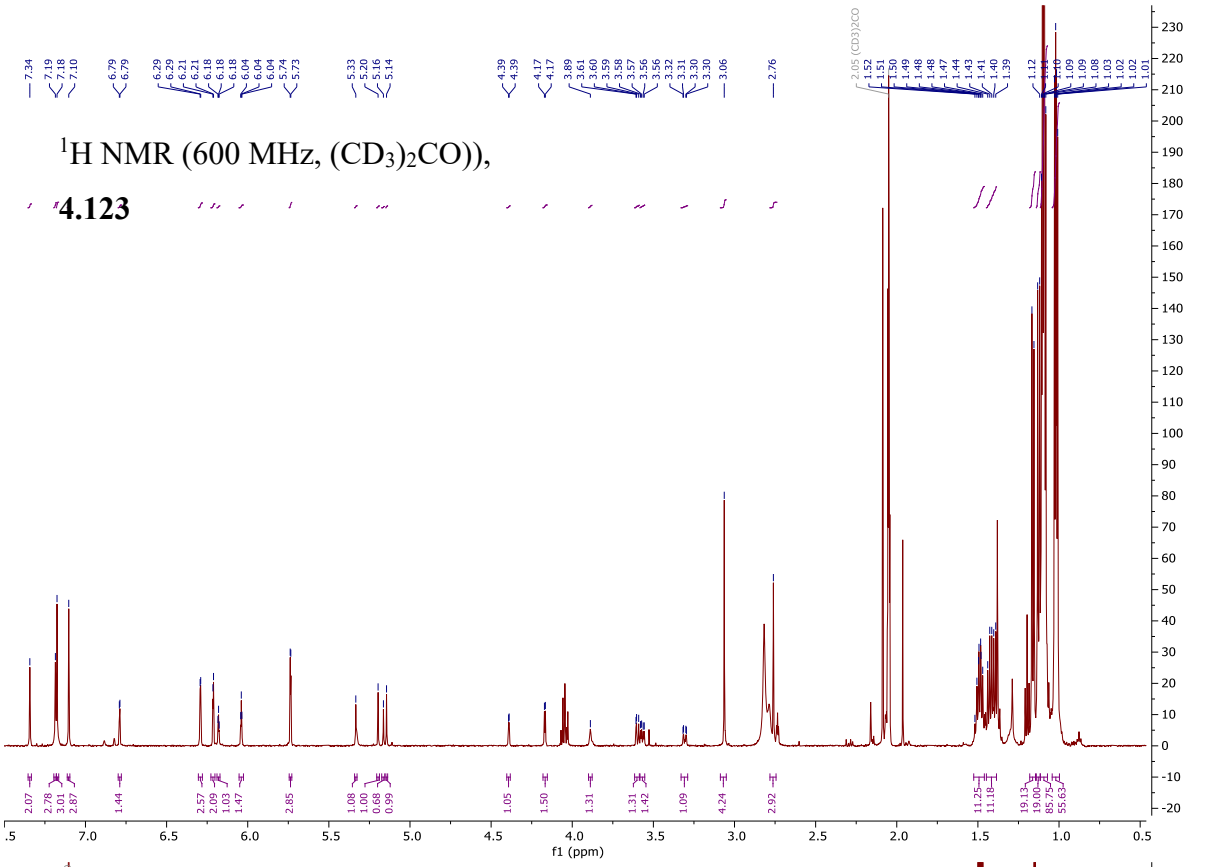

^{1}H NMR (500 MHz, $(CD_3)_2CO$)), **4.122**
f1 (ppm)



(4.123) (1R,2S,3R)-2-(3,5-dihydroxyphenyl)-3-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)-1-((4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)(methoxy)methyl)-2,3-dihydro-1H-indene-4,6-diol

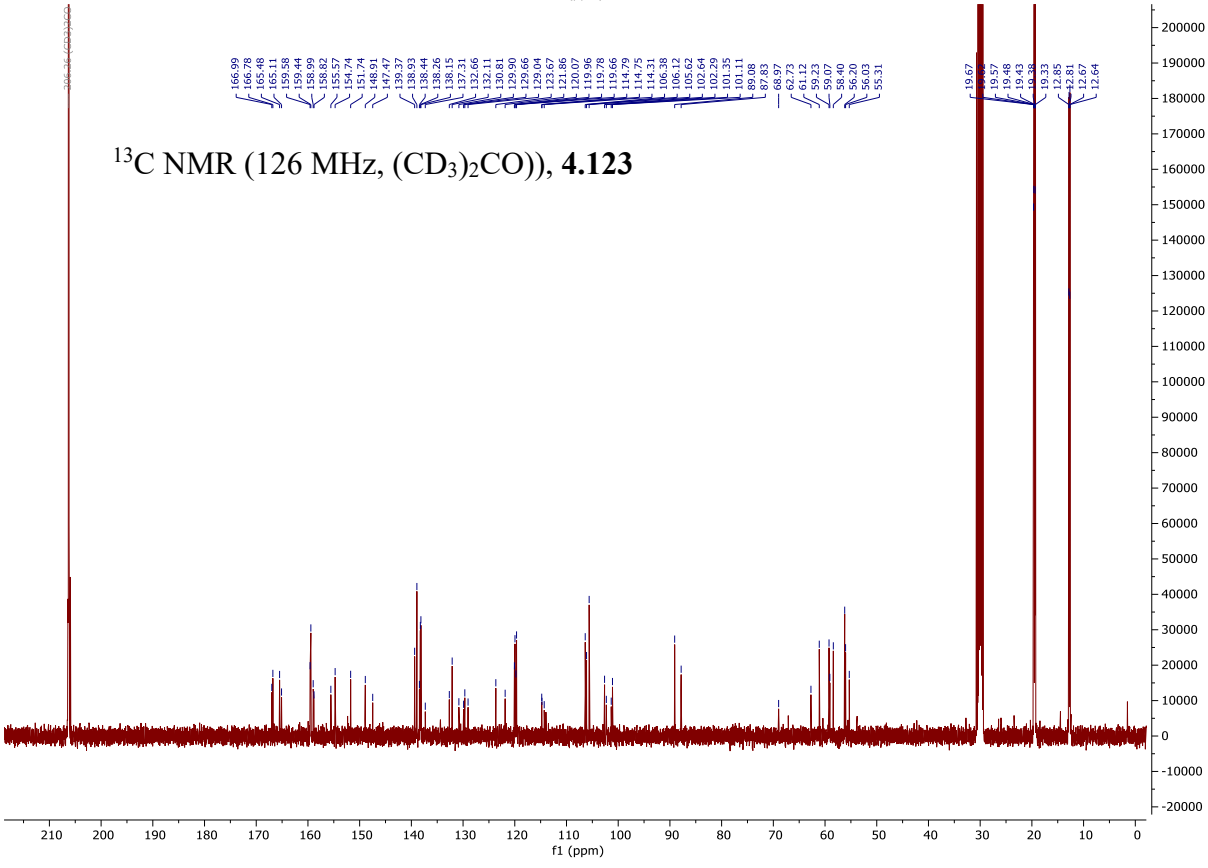
In a 25 mL RBF was added starting material (100 mg, 68 µmol, 1 equiv), Pd/C (72 mg, 68 µmol, 1 equiv, 30 wt% on carbon), EtOAc (3.5 mL, 0.01 M), and MeOH (3.5 mL, 0.01 M). The solution was sparged with hydrogen gas for 10 minutes and then let react for 16 hours under an atmosphere of hydrogen. The completed reaction was sparged with argon, filtered to remove solids, and concentrated. This filtered organic were of sufficient purity for further reactions.

^{1}H NMR (600 MHz, $(CD_3)_2CO$)), **4.123**	δ = 7.34 (s, 2H), 7.19 (s, 3H), 7.18 (s, 3H), 7.10 (s, 3H), 6.79 (d, J=2.2, 1H), 6.29 (d, J=2.1, 3H), 6.21 (d, J=2.2, 2H), 6.18 (t, J=2.2, 1H), 6.04 (t, J=2.2, 1H), 5.74 (d, J=2.2, 3H), 5.33 (s, 1H), 5.20 (s, 1H), 5.16 (s, 1H), 5.14 (s, 1H), 4.39 (d, J=2.1, 1H), 4.17 (d, J=3.4, 1H), 3.89 (s, 1H), 3.62 – 3.59 (m, 1H), 3.57 (dd, J=9.7, 3.9, 1H), 3.33 – 3.29 (m, 1H), 3.06 (s, 4H), 2.76 (s, 3H), 1.49 (td, J=7.7, 6.2, 11H), 1.41 (dt, J=14.7, 7.5, 11H), 1.16 (d, J=7.5, 19H), 1.13 (d, J=7.5, 19H), 1.10 (dt, J=7.8, 4.2, 86H), 1.02 (dd, J=7.5, 4.4, 56H).
^{13}C NMR (126 MHz, $(CD_3)_2CO$)), **4.123**	δ = 167.0, 166.8, 165.5, 165.1, 159.6, 159.4, 159.0, 158.8, 155.6, 154.7, 151.7, 148.9, 147.5, 139.4, 138.9, 138.4, 138.3, 138.2, 137.3, 132.7, 132.1, 130.8, 129.9, 129.7, 129.0, 123.7, 121.9, 120.1, 120.0, 119.8, 119.7, 114.8, 114.7, 114.3, 106.4, 106.1, 105.6, 102.6, 102.3, 101.4, 101.1, 89.1, 87.8, 69.0, 62.7, 61.1, 59.2, 59.1, 58.4, 56.2, 56.0, 55.3, 19.7, 19.6, 19.6, 19.5, 19.4, 19.4, 19.3, 12.8, 12.8, 12.7, 12.6.

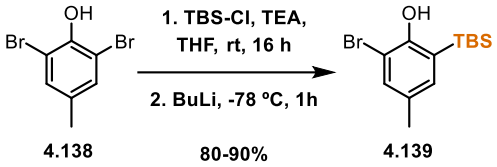


^{1}H NMR (600 MHz, $(CD_3)_2CO$)),

4.123



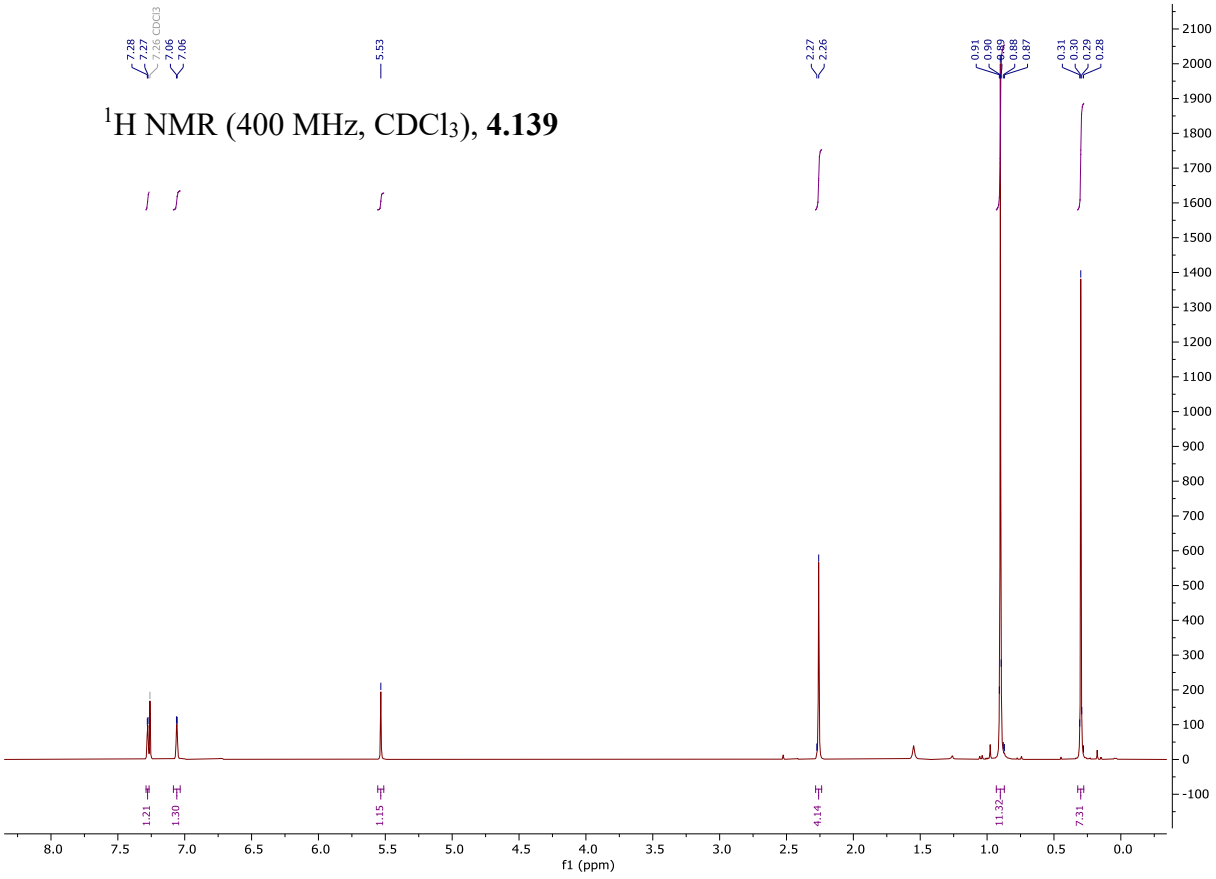
^{13}C NMR (126 MHz, $(CD_3)_2CO$)), **4.123**

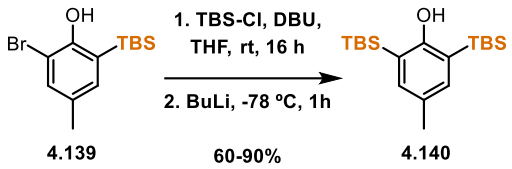


(4.139) 2-bromo-6-(tert-butyldimethylsilyl)-4-methylphenol

In a 50 mL RBF was added starting material (500 mg, 1.88 mmol, 1 equiv), THF (19 mL, 0.1 M), TEA (314 µL, 2.26 mmol, 1.2 equiv), and TBS-Cl as a solid (368 mg, 2.44 mmol, 1.3 equiv). The solution was to stir for 16 hours at room temperature. The solution was then cooled to -78 °C and BuLi (1.11 mL, 2.44 mmol, 1.3 equiv) dropwise. After 1 hour the reaction was quenched with MeOH (5 mL) and sat. $NaHCO_3$ (aq) (20 mL). The mixture was extracted with either (3 x 20 mL). The organics were dried with brine (20 mL) and $MgSO_4$. The crude organic residue was subjected to column chromatography SiO_2 (0-10% ethyl acetate in hexanes) to afford the product as an opaque viscous oil (488 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$), **4.139** δ = 7.28 (d, J=2.1, 1H), 7.06 (d, J=2.1, 1H), 5.53 (s, 1H), 2.26 (s, 4H), 0.90 (s, 11H), 0.30 (s, 6H).



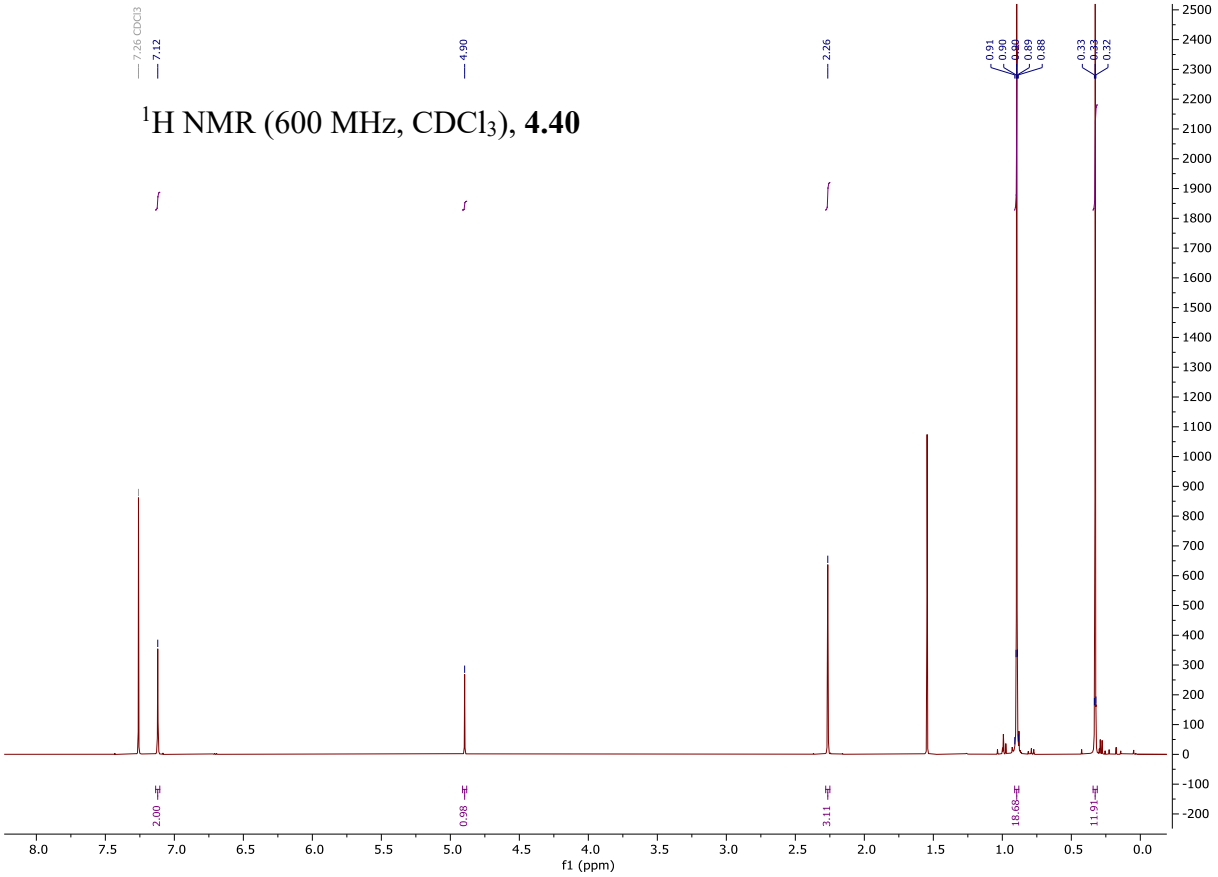


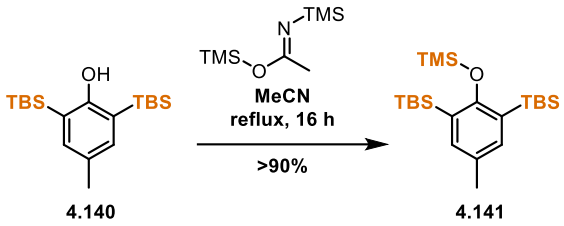
(4.140) 2,6-bis(tert-butyldimethylsilyl)-4-methylphenol

To a 500 mL RBF was added starting material (9.3 g, 31.1 mmol, 1 equiv), THF (207 mL, 0.15 M), DBU (6.1 mL, 40.4 mmol, 1.3 equiv), and TBS-Cl as a solid (6.6 g, 43.5 mmol, 1.4 equiv). The solution was to stir for 16 hours at room temperature. The solution was then cooled to -78 °C and BuLi (17.8 mL, 43.5 mmol, 1.4 equiv) dropwise. After 1 hour the reaction was quenched with MeOH (10 mL), sat. $NaHCO_3$ (aq) (60 mL), and water (60 mL). The mixture was extracted with either (3 x 80 mL). The organics were dried with brine (100 mL) and $MgSO_4$. The crude organic residue was subjected to column chromatography SiO_2 (0-10% ethyl acetate in hexanes) to afford the product as an opaque viscous oil (8.69 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$), **4.140** δ = 7.12 (s, 2H), 4.90 (s, 1H), 2.26 (s, 3H), 0.90 (s, 18H), 0.33 (s, 12H).

^{1}H NMR (600 MHz, $CDCl_3$), **4.40**



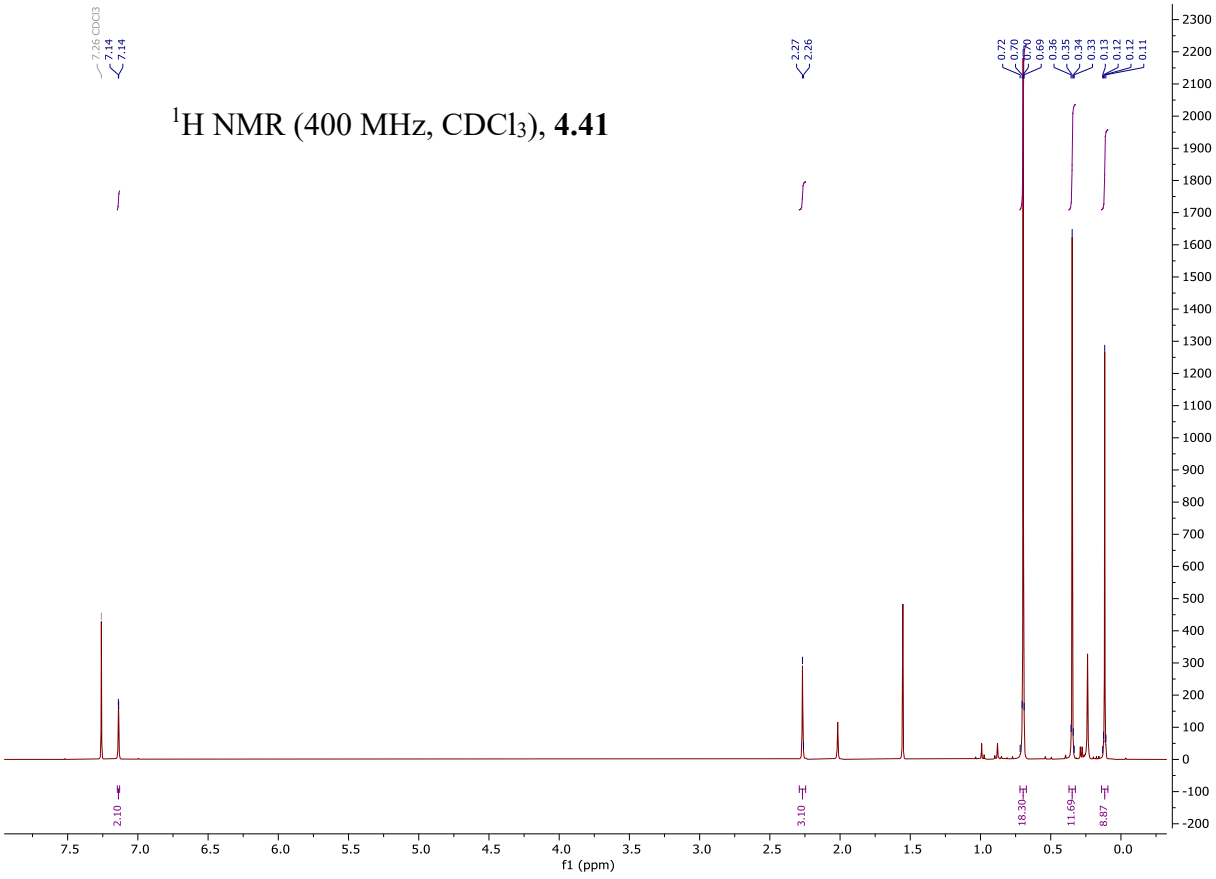


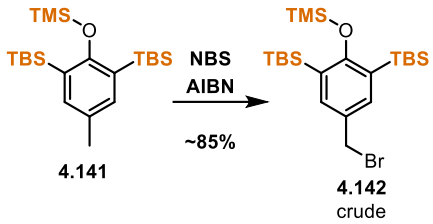
(4.141) 2,6-bis(tert-butyldimethylsilyl)-4-methylphenol

To a 50 mL RBF was added starting material (1.0 g, 2.9 mmol, 1 equiv), MeCN (11.9 mL, 0.25 M), and acetamide (1.8 mL, 7.4 mmol, 2.5 equiv). The solution was heated to reflux (82 °C) for 16 hours. As the TMS protected product is known to be labile, the purification consisted of concentration of the crude to an oil, followed by distillation to remove the access acetamide (1.2 g, 2.9 mmol, 100%) the yield is inflated due to the lower purity of the product.

^{1}H NMR (400 MHz, $CDCl_3$), **4.141** δ = 7.14 (d, J=0.8, 2H), 2.27 (s, 3H), 0.70 (s, 18H), 0.35 (s, 12H), 0.12 (s, 9H).

^{1}H NMR (400 MHz, $CDCl_3$), **4.41**

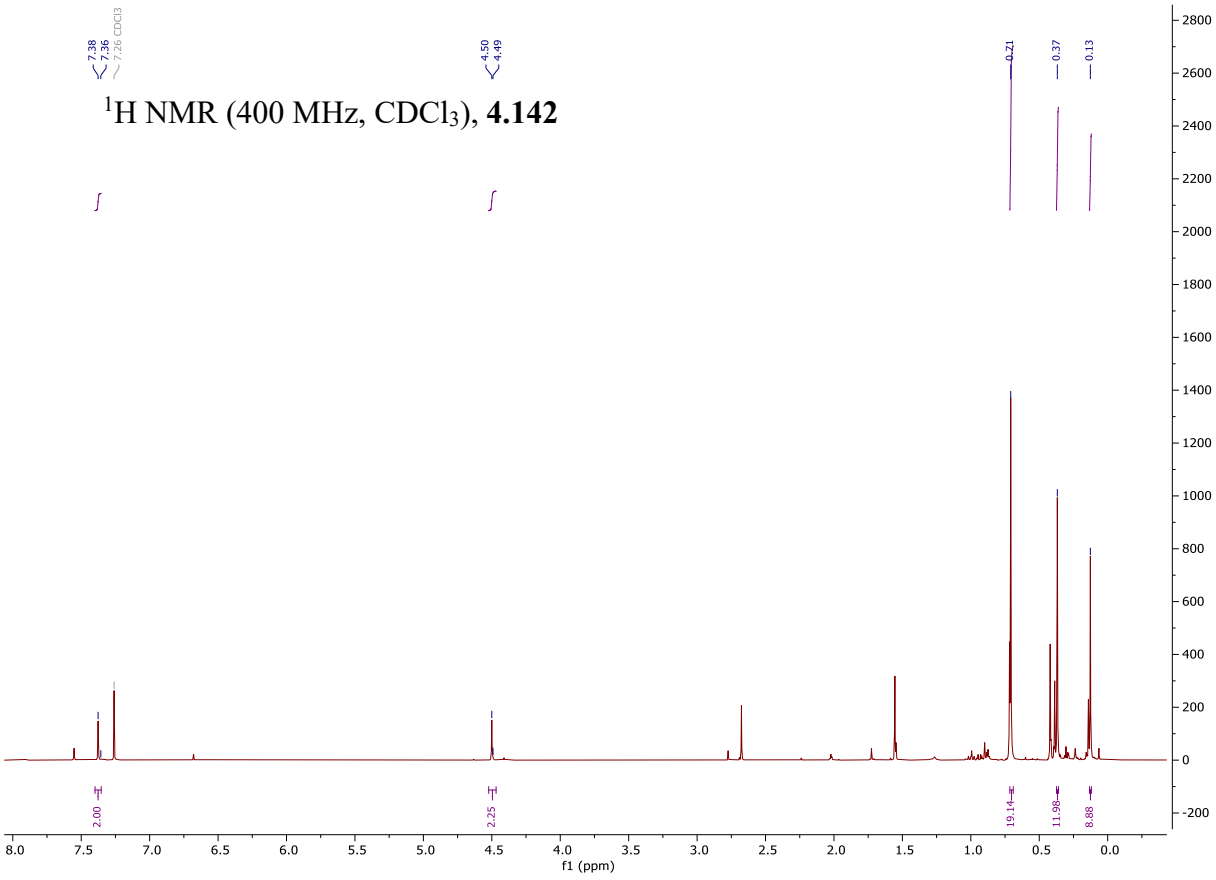


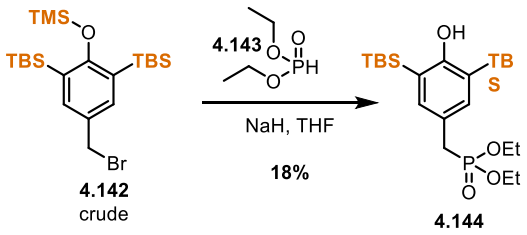


(4.142) (5-(bromomethyl)-2-((trimethylsilyl)oxy)-1,3-phenylene)bis(tert-butyldimethylsilane)

To a 50 mL RBF was added starting material (1.2 g, 3.0 mmol, 1 equiv), CCl_4 (30 mL, 0.1 M), NBS (685 mg, 3.8 mmol, 1.3 equiv), and AIBN (49 mg, 0.3 mmol, 0.1 equiv). The solution was heated to reflux (77 °C) for 3 hours. After cooling to room temperature the solution was filtered over a sinter funnel fitted with a filter paper, eluting with hexanes. The filtrate was concentrated to afford the product as a viscous yellow oil which is not stable to light, and should be carried forward immediately (1.2 g, 83%, ~80% pure)

^{1}H NMR (400 MHz, $CDCl_3$), **4.142** δ = 7.38 (s, 2H), 4.50 (s, 2H), 0.71 (s, 18H), 0.37 (s, 12H), 0.13 (s, 9H).

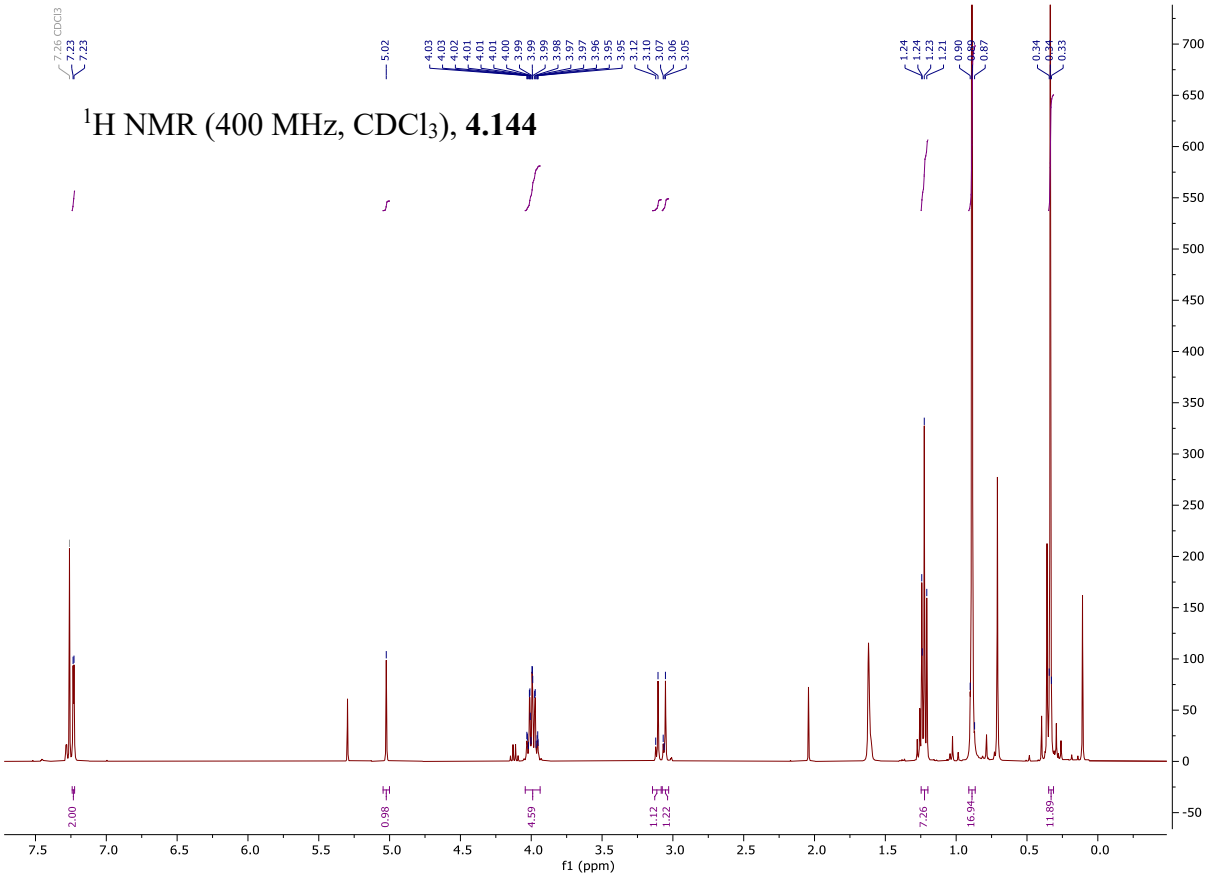


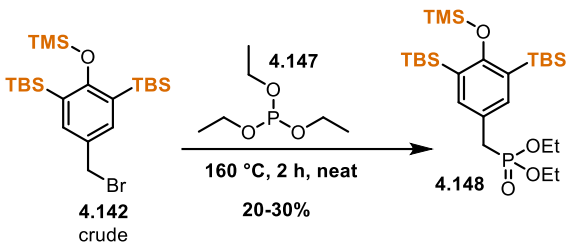


(4.144) diethyl (3,5-bis(tert-butyldimethylsilyl)-4-hydroxybenzyl)phosphonate

To a 10 mL RBF at 0 °C was added THF (4.4 mL, 0.3 M), NaH (69 mg, 1.7 mmol, 1.3 equiv, 60 wt% in mineral oil) and diethyl phosphonate (221 mg, 1.6 mmol, 1.2 equiv). After 30 minutes the starting material (650 mg, 1.3 mmol, 1 equiv) was added. After 3 hours of reaction time the reaction was quenched with MeOH (1 mL), sat. $NaHCO_3$ (aq) (6 mL), and water (6 mL). The mixture was extracted with ether (3 x 10 mL). The organics were dried with brine (10 mL) and $MgSO_4$. The crude organic residue was subjected to column chromatography SiO_2 (0-40% ethyl acetate in hexanes) to afford the product as an amorphous white solid (110 mg, 18%).

^{1}H NMR (400 MHz, $CDCl_3$), **4.144** δ = 7.23 (d, J=2.6, 2H), 5.02 (s, 1H), 4.04 – 3.94 (m, 4H), 3.11 (d, J=6.5, 1H), 3.06 (d, J=6.3, 1H), 1.23 (t, J=7.1, 6H), 0.89 (s, 12H), 0.34 (s, 9H).

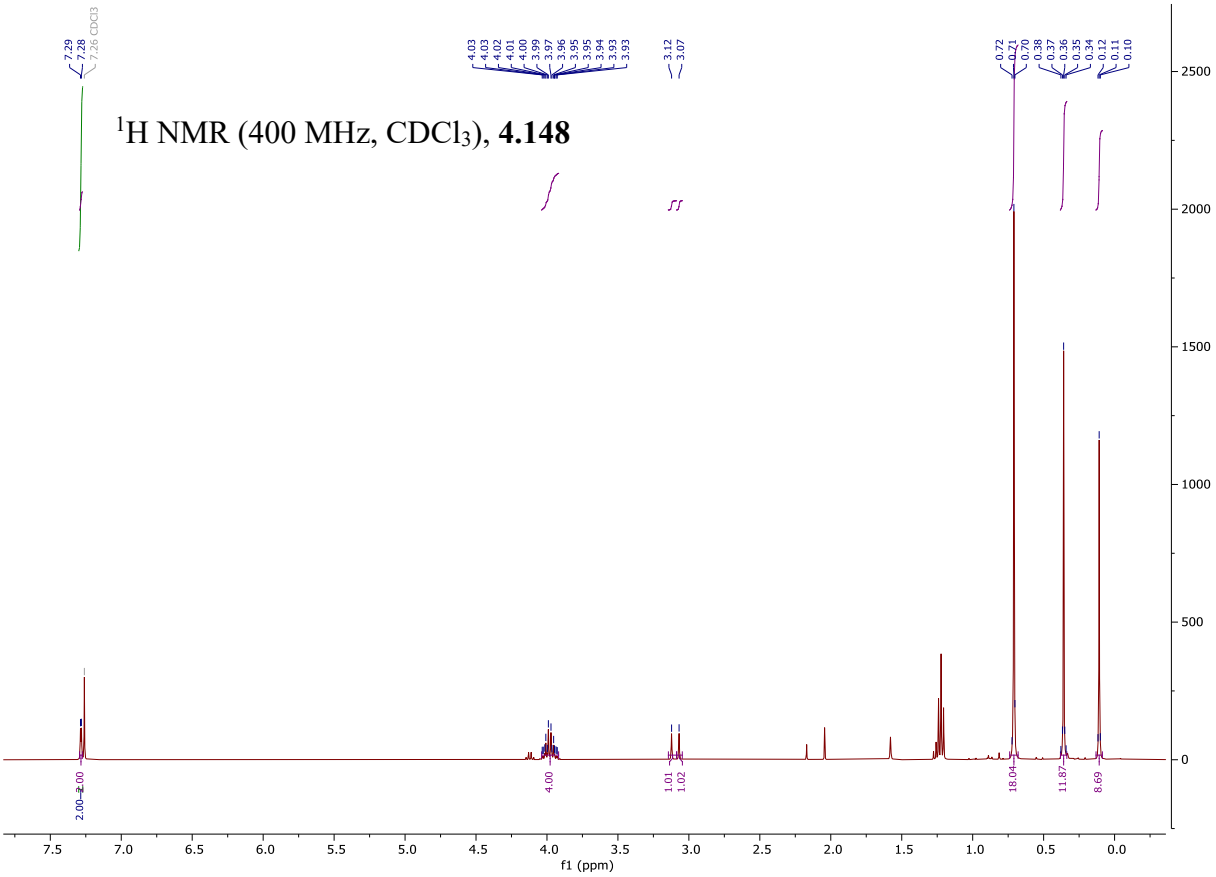


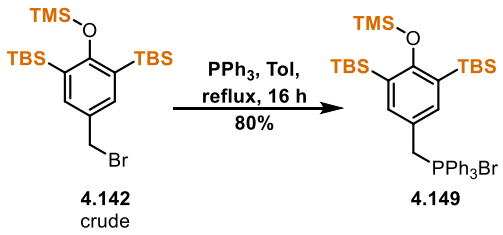


(4.148) diethyl (3,5-bis(tert-butyldimethylsilyl)-4-((trimethylsilyl)oxy)benzyl)phosphonate

To a 10 mL RBF was added starting material (1.2 g, 2.5 mmol, 1 equiv) and triethyl phosphite (1.1 mL, 6.2 mmol, 2.5 equiv). The residue was heated to 100 °C for 16 hours. The excess triethyl phosphite was removed via short path vacuum distillation to afford the product as a colorless oil (360 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$), **4.148** δ = 7.28 (d, J=2.6, 2H), 3.99 (hept, J=7.2, 4H), 3.12 (s, 1H), 3.07 (s, 1H), 0.71 (s, 18H), 0.36 (s, 12H), 0.11 (s, 9H).





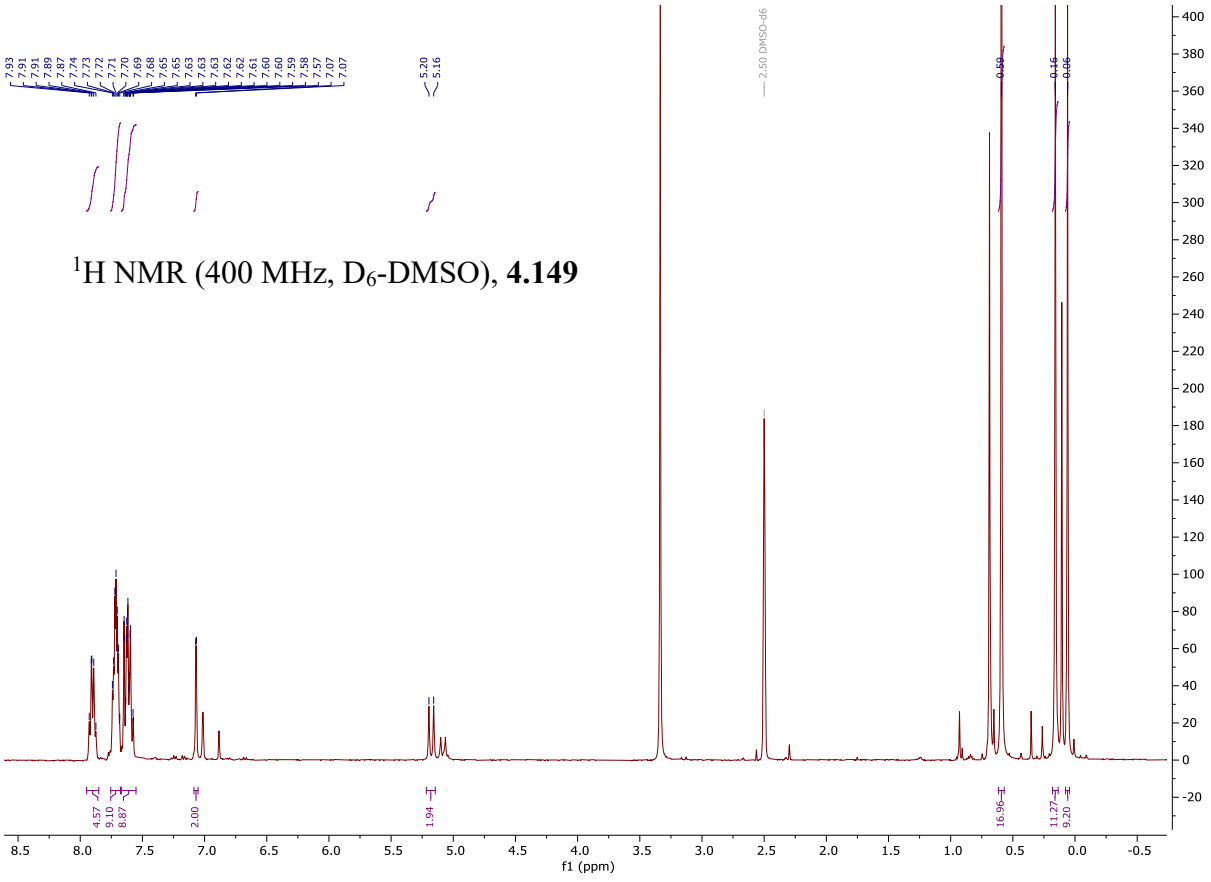
4.142
crude

4.149

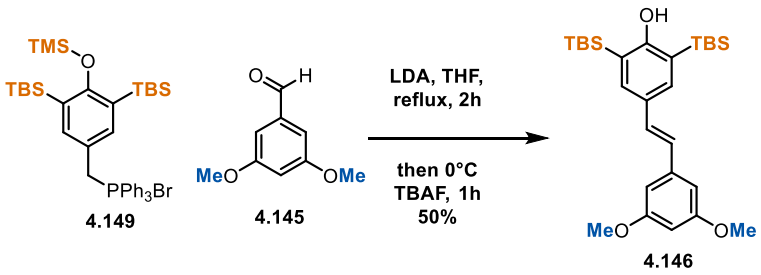
(4.149) (3,5-bis(tert-butyldimethylsilyl)-4-((trimethylsilyl)oxy)benzyl)bromotriphenyl-l5-phosphane

To a 50 mL RBF was added starting material (1.4 g, 3.0 mmol, 1 equiv), toluene (15 mL, 0.2 M), and triphenylphosphine (1.2 g, 4.4 mmol, 1.5 equiv). The reaction was heated to reflux (110 °C) for 16 hours. The reaction slurry was cooled, and filtered, washing the filter cake with hexanes to obtain the product as a white to tan powdered solid (1.8 g, 80%). As the alkyl bromide starting material was used as crude, and the product was purified via filtration the final purity is only ~70% as a mixture with unreacted starting material.

^{1}H NMR (400 MHz, D_6-DMSO), **4.149** δ = 7.95 – 7.85 (m, 5H), 7.71 (tt, J=7.9, 4.0, 9H), 7.67 – 7.55 (m, 9H), 7.07 (d, J=2.5, 2H), 5.18 (d, J=15.3, 2H), 0.59 (s, 18H), 0.16 (s, 12H), 0.06 (s, 9H).



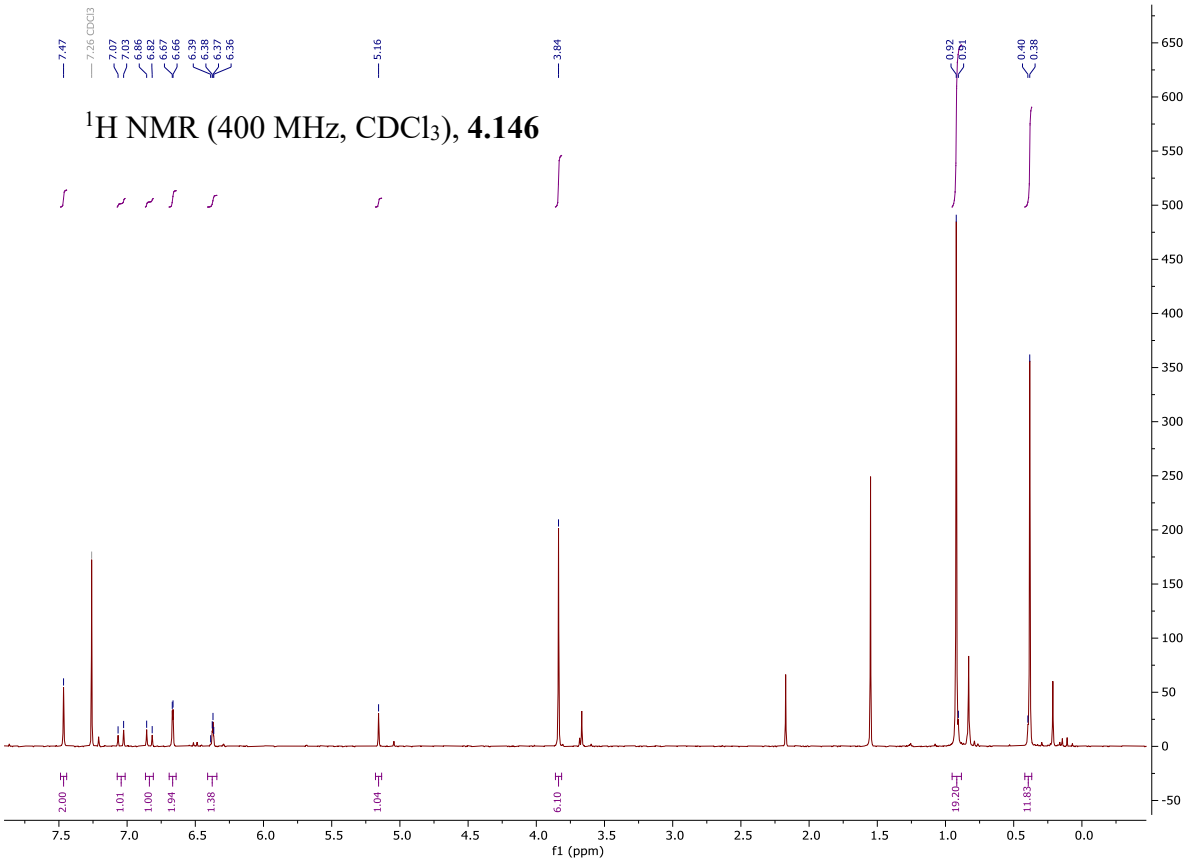
^{1}H NMR (400 MHz, D_6-DMSO), **4.149**

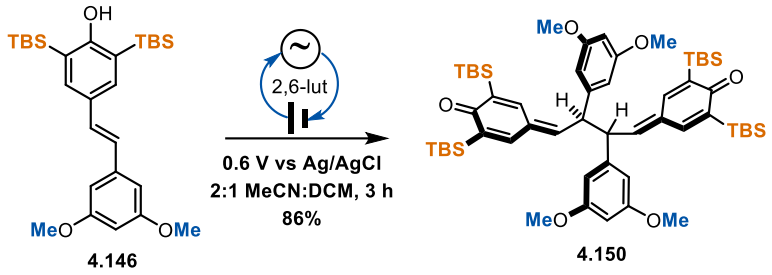


(4.146) (E)-2,6-bis(tert-butyldimethylsilyl)-4-(3,5-dimethoxystyryl)phenol

To a 25 mL RBF was added phosphonium salt (248 mg, 0.33 mmol, 1.1 equiv), THF (6 mL, 0.05 M) and LDA (0.55 mmol, 1.5 equiv) which was freshly prepared from 72 µL diisopropylamine and 184 µL of BuLi in 2 mL THF. After 10 minutes the aldehyde (50 mg, 0.3 mmol, 1 equiv) was added as a solid. The solution was heated to reflux (66 °C) for 2 hours. The reaction slurry was cooled to 0 °C and TBAF (361 µL, 361 µmol, 1.2 equiv, 1.0 M solution in THF) was added. After 1 hour the reaction was quenched with Sat. $NaHCO_3$ (aq). The solution was let warm to room temperature before addition of ether for extraction. The combined organics were dried with brine, $MgSO_4$ and filtered. The crude reaction mixture was purified by column chromatography SiO_2 (0-10% ethyl acetate in hexanes) to afford the product as an amorphous white powder (73 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$), **4.146** δ = 7.47 (s, 2H), 7.05 (d, J=16.2, 1H), 6.84 (d, J=16.2, 1H), 6.67 (d, J=2.2, 2H), 6.37 (t, J=2.3, 1H), 5.16 (s, 1H), 3.84 (s, 6H), 0.92 (s, 18H), 0.38 (s, 12H).

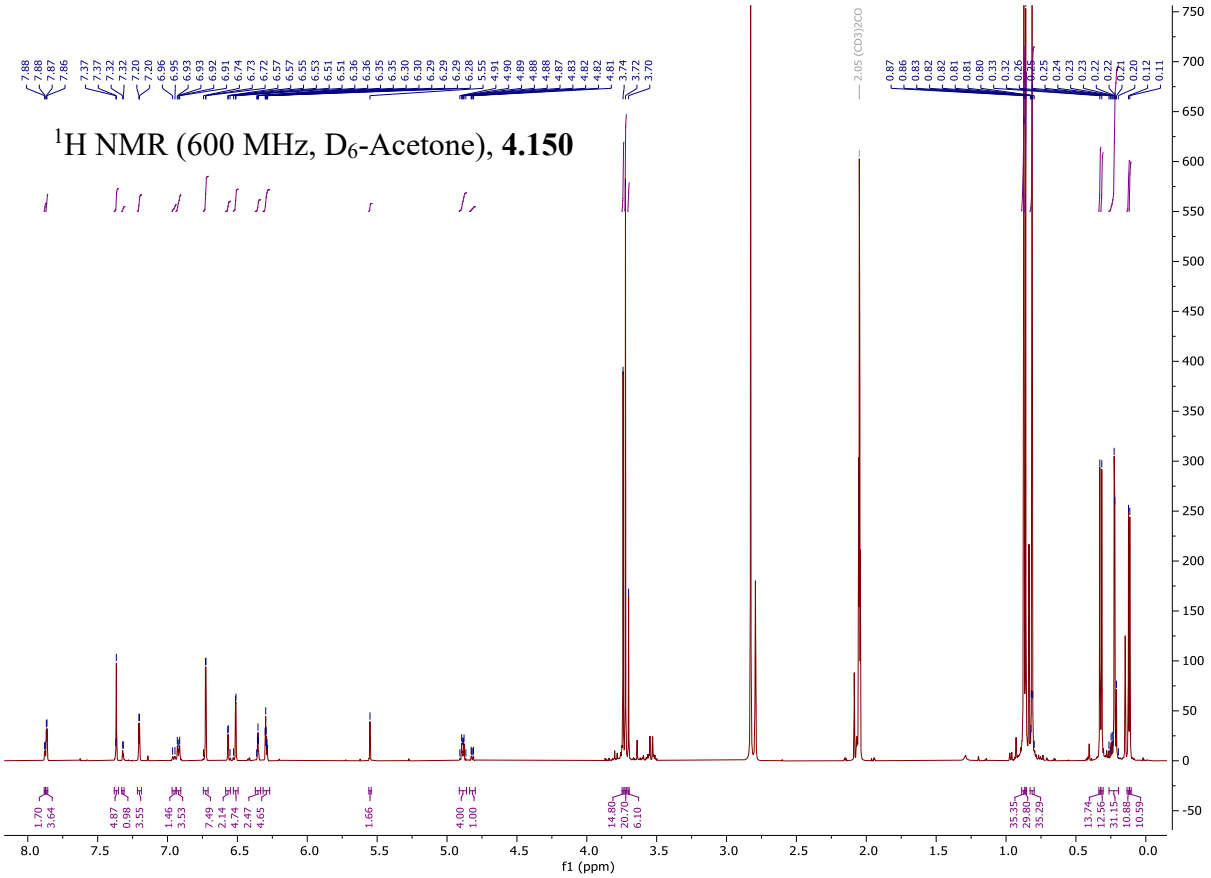


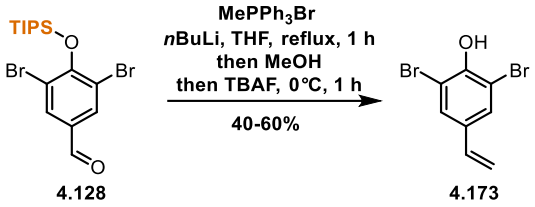


(4.150) 4-((2R,3S)-4-(3,5-bis(tert-butyldimethylsilyl)-4-oxocyclohexa-2,5-dien-1-ylidene)-2,3-bis(3,5-dimethoxyphenyl)butylidene)-2,6-bis(tert-butyldimethylsilyl)cyclohexa-2,5-dien-1-one

The starting phenol (73 mg, 0.15 mmol, 1.0 equiv) was added to a 25 mL beaker with KPF_6 (110 mg, 0.6 mmol, 4.0 equiv) and 2,6-lutidine (17 µL, 0.15 mmol, 1.0 equiv) and dissolved in acetonitrile (8 mL) and dichloromethane (4 mL). Two pieces of 1 x 2-inch RVC panel (0.25-inch thickness) were cut. To each, a hole was made near one end, and copper wire was placed through the hole and wrapped around the top of each electrode. One end of the wire was left free to connect to the alligator clips. These electrodes were carefully placed into the beaker along with the reference electrode (Ag/AgCl in 3 M KCl) and a divider. The alligator clips were connected such that the reference and working electrodes were adjacent to each other, while the counter electrode was opposite the divider. Care was taken to ensure the copper wire was not submerged in solvent, nor the active components of the alligator clips touching each other. The reaction was stirred at 750 rpm for 1-2 h at a constant voltage of 0.6 V. A chronoampergram was recorded to follow the course of the reaction. Upon completion of the reaction, the electrodes were removed and rinsed into a collection flask with DCM (~20 mL). The contents of the reaction vial were also rinsed into the collection flask. The solvent was removed in vacuo, and the crude material was purified by flash chromatography over SiO_2 (0%-10% EtOAc in Hexanes) to yield the product as a bright yellow foam (61 mg, 84%, 4.0:1 mixture of diastereomers).

^{1}H NMR (600 MHz, D_6-Acetone), **4.150** δ = 7.88 (d, J=2.8, 2H), 7.86 (d, J=2.6, 4H), 7.37 (s, 5H), 7.32 (d, J=2.6, 1H), 7.20 (d, J=2.6, 4H), 6.96 (d, J=10.1, 1H), 6.92 (dd, J=7.3, 2.9, 4H), 6.73 (d, J=2.2, 7H), 6.57 (d, J=2.2, 2H), 6.51 (d, J=2.2, 5H), 6.35 (t, J=2.3, 2H), 6.29 (dt, J=5.7, 2.2, 5H), 5.55 (s, 2H), 4.91 – 4.86 (m, 4H), 4.84 – 4.80 (m, 1H), 3.74 (s, 15H), 3.72 (s, 21H), 3.70 (s, 6H), 0.87 (s, 35H), 0.86 (s, 30H), 0.81 (s, 35H), 0.33 (s, 14H), 0.32 (s, 13H), 0.26 – 0.20 (m, 31H), 0.12 (s, 11H), 0.11 (s, 11H).

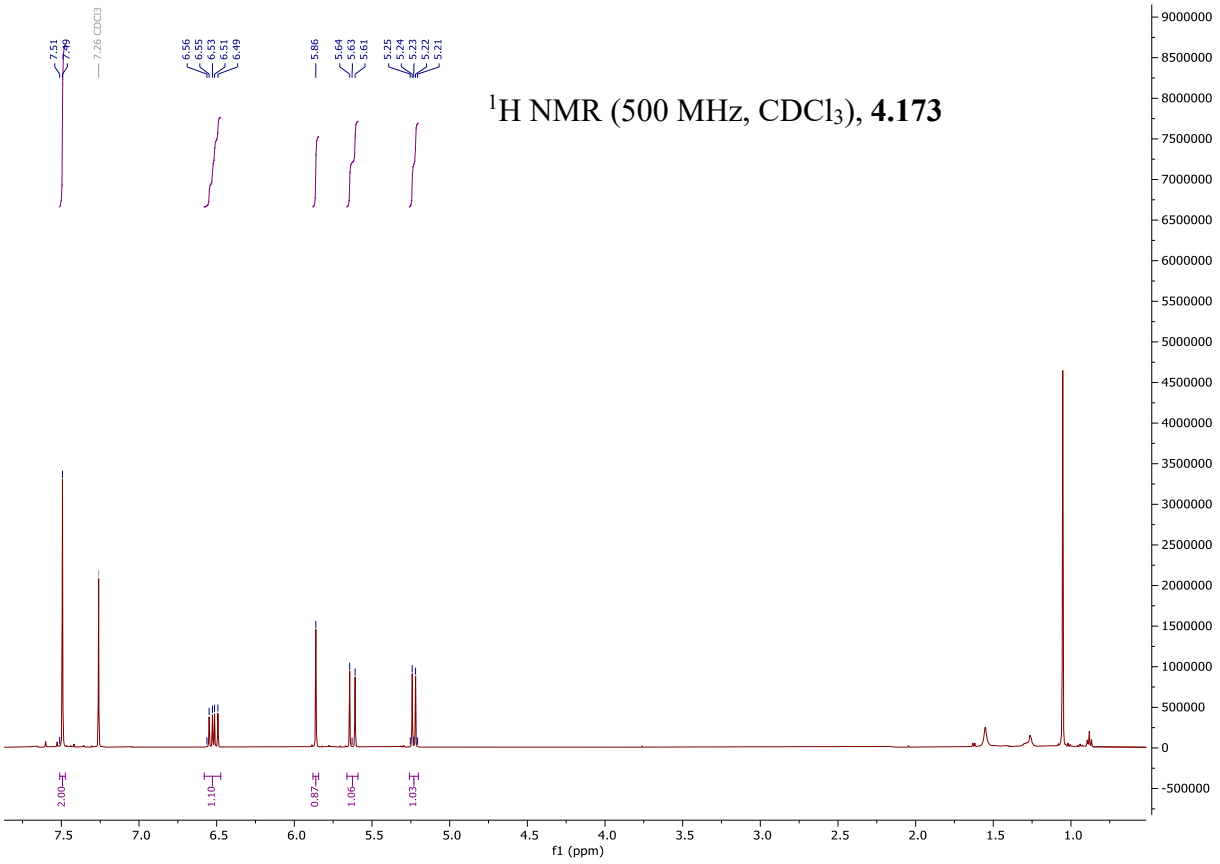

^{1}H NMR (600 MHz, D$_6$-Acetone), **4.150**
f1 (ppm)



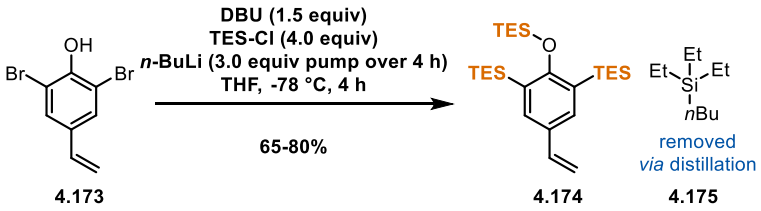
(4.173) 2,6-dibromo-4-vinylphenol

To a 100 mL RBF was added phosphonium salt (2.0 g, 5.5 mmol, 1.2 equiv), THF (35 mL, 0.13 M) and BuLi (2.6 mL, 6.0 mmol, 1.3 equiv). After 10 minutes the aldehyde (2.0 g, 4.6 mmol, 1 equiv) was added as a solid. The solution was heated to reflux (66 °C) for 1 hour. The reaction slurry was cooled to 0 °C and TBAF (6.9 mL, 6.9 mol, 1.5 equiv, 1.0 M solution in THF) was added. After 1 hour the reaction was quenched with Sat. $NaHCO_3$ (aq). The solution was let warm to room temperature before addition of ether for extraction. The combined organics were dried with brine, $MgSO_4$ and filtered. The crude reaction mixture was purified by column chromatography SiO_2 (0-10% ethyl acetate in hexanes) to afford the product as an amorphous white powder (793 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$), **4.173** δ = 7.49 (s, 2H), 6.52 (dd, J=17.5, 10.8, 1H), 5.86 (s, 1H), 5.63 (d, J=17.5, 1H), 5.23 (d, J=10.9, 1H).



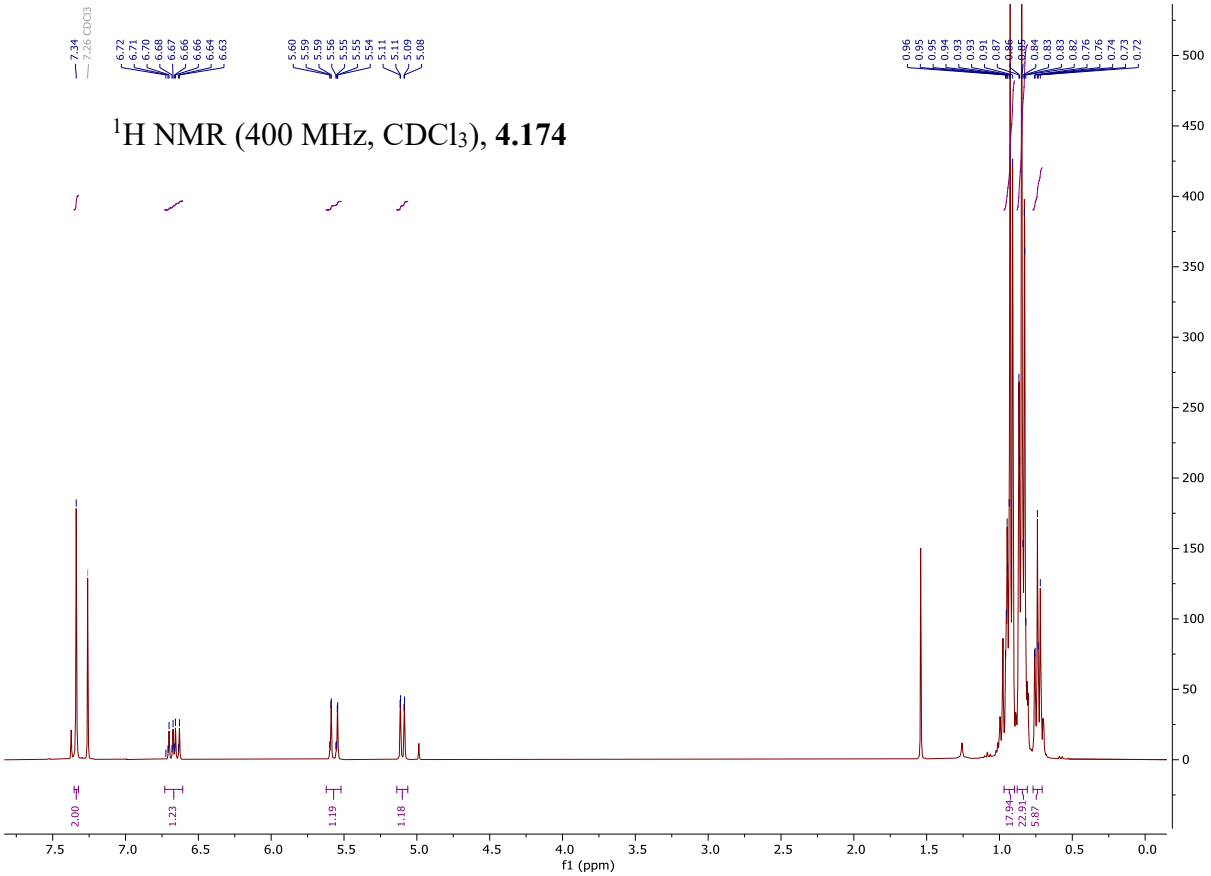
^{1}H NMR (500 MHz, $CDCl_3$), **4.173**

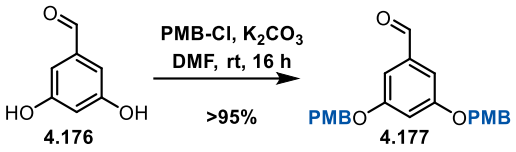


(4.174) (2-((triethylsilyl)oxy)-5-vinyl-1,3-phenylene)bis(triethylsilane)

To a 50 mL RBF was added starting material 500 mg, 1.8 mmol, 1 equiv), THF (9 mL, 0.2 M), DBU (407 µL, 2.7 mmol, 1.5 equiv) and TES-Cl (906 µL, 5.4 mmol, 3 equiv). After 10 minutes of stirring the reaction was cooled to -78 °C. BuLi (2.2 mL, 5.4 mmol, 3 equiv) was added via syringe pump over 3 hours. The reaction was quenched with methanol (3 mL). The solution was let warm to room temperature before addition of ether for extraction. The combined organics were dried with brine, $MgSO_4$ and filtered. The crude reaction mixture was purified by column chromatography SiO_2 (0-10% ethyl acetate in hexanes) to afford a viscous oil which was further purified via distillation to remove the silane impurity, providing the product as a translucent viscous oil (561 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$), **4.174** δ = 7.34 (s, 2H), 6.73 – 6.61 (m, 1H), 5.62 – 5.52 (m, 1H), 5.10 (dd, J=10.8, 1.2, 1H), 0.93 (dd, J=8.8, 6.3, 18H), 0.88 – 0.81 (m, 21H), 0.77 – 0.71 (m, 6H).

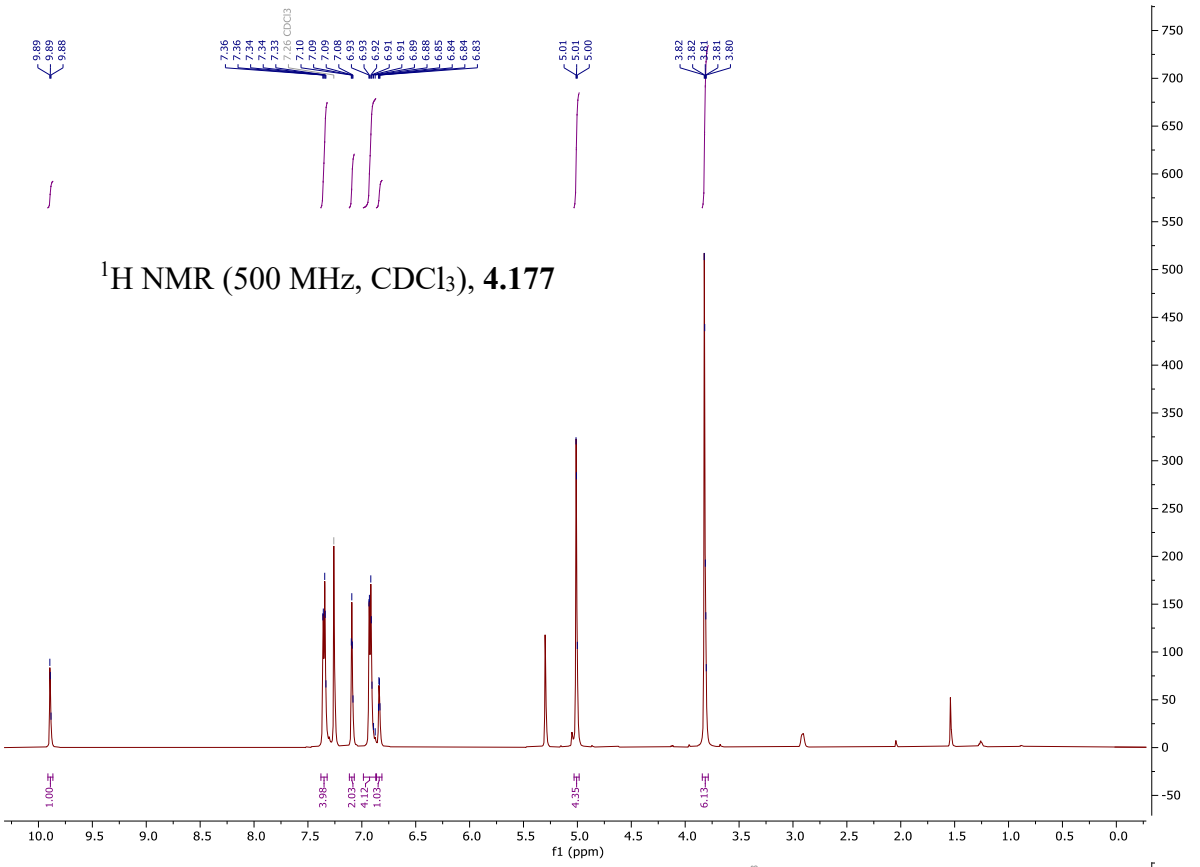




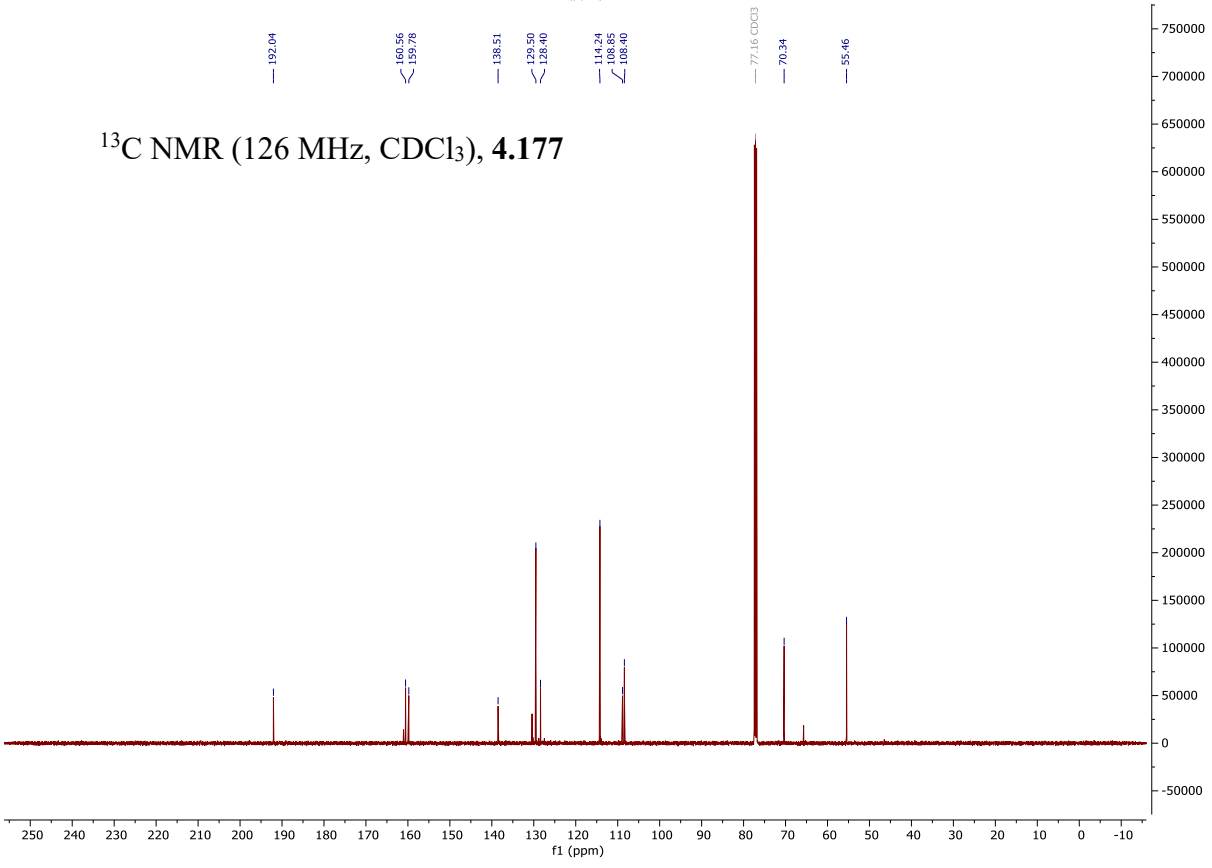
(4.177) (2-((triethylsilyl)oxy)-5-vinyl-1,3-phenylene)bis(triethylsilane)

To a 50 mL RBF was added starting material (500 mg, 3.6 mmol, 1 equiv), THF (18 mL, 0.2 M), K_2CO_3 (3.0 g, 21.7 mmol, 6 equiv) and PMB-Cl (1.08 mL, 8.0 mmol, 2.2 equiv). The mixture was stirred at 70 °C for 16 hours. The reaction was quenched with Sat. $NaHCO_3$ (aq) (10 mL). The solution was extracted with ether (3 x 20 mL). The combined organics were dried with brine (30 mL), $MgSO_4$ and filtered. The crude reaction mixture was purified by column chromatography SiO_2 (0-50% ethyl acetate in hexanes) to afford the product as a tan foam (1.3 g, 96%).

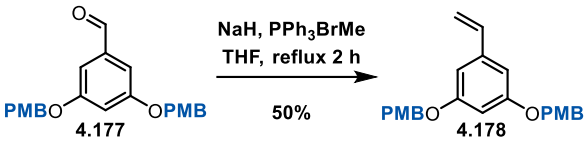
^{1}H NMR (500 MHz, $CDCl_3$), **4.177**	δ = 9.89 (d, J=2.0, 1H), 7.38 – 7.32 (m, 4H), 7.09 (q, J=3.1, 2.7, 2H), 6.99 – 6.87 (m, 4H), 6.84 (q, J=2.4, 1H), 5.01 (d, J=2.1, 4H), 3.82 (dd, J=5.2, 2.1, 6H).
^{13}C NMR (126 MHz, $CDCl_3$), **4.177**	δ = 192.0, 160.6, 159.8, 138.5, 129.5, 128.4, 114.2, 108.9, 108.4, 70.3, 55.5.



^{1}H NMR (500 MHz, $CDCl_3$), **4.177**



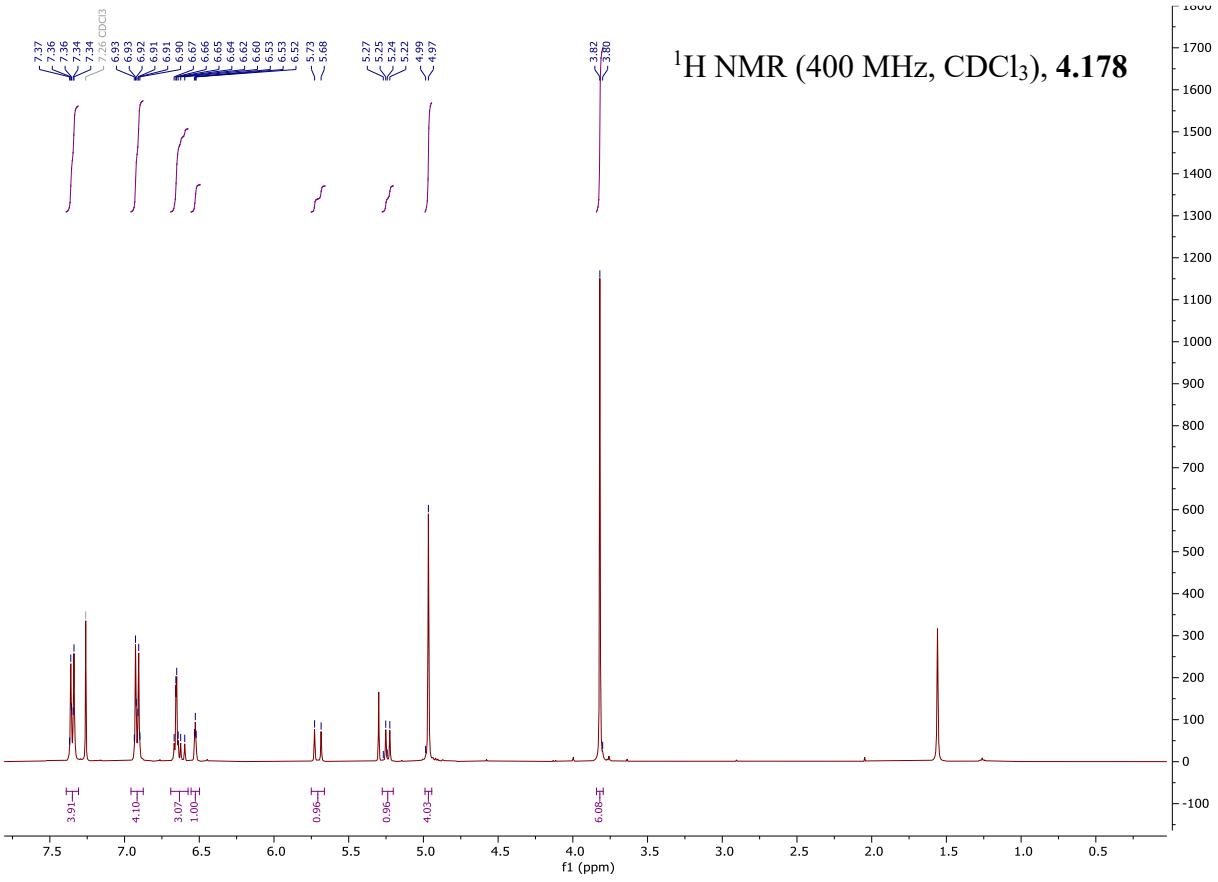
^{13}C NMR (126 MHz, $CDCl_3$), **4.177**

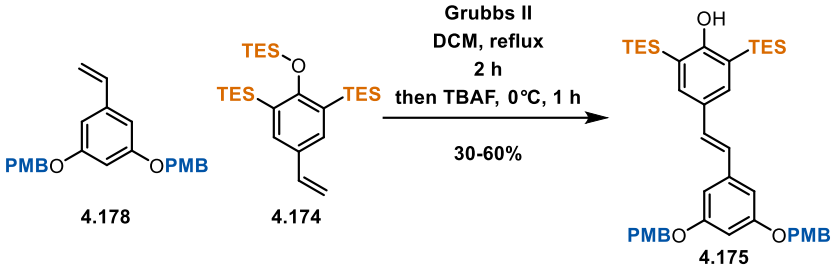


(4.178) 4,4'-(((5-vinyl-1,3-phenylene)bis(oxy))bis(methylene))bis(methoxybenzene)

To a 250 mL RBF was added phosphonium salt (11 g, 30 mmol, 2.3 equiv), THF (150 mL, 0.15 M) and sodium hydride (1.2 g, 30 mmol, 2.3 equiv, 60 wt% in mineral oil). After 10 minutes the aldehyde (5.0 g, 13 mmol, 1 equiv) was added as a solid. The solution was heated to reflux (66 °C) for 2 hours. The reaction slurry was cooled to 0 °C and was quenched with Sat. $NaHCO_3$ (aq). The solution was let warm to room temperature before addition of ether for extraction. The combined organics were dried with brine, $MgSO_4$ and filtered. The crude reaction mixture was purified by column chromatography SiO_2 (0-20% ethyl acetate in hexanes) to afford the product as an amorphous white powder (2.5 g, 50%).

^{1}H NMR (400 MHz, $CDCl_3$), **4.178** δ = 7.39 – 7.31 (m, 4H), 6.96 – 6.87 (m, 4H), 6.69 – 6.57 (m, 3H), 6.53 (t, J=2.3, 1H), 5.71 (d, J=17.4, 1H), 5.24 (d, J=10.8, 1H), 4.97 (s, 4H), 3.82 (s, 6H).

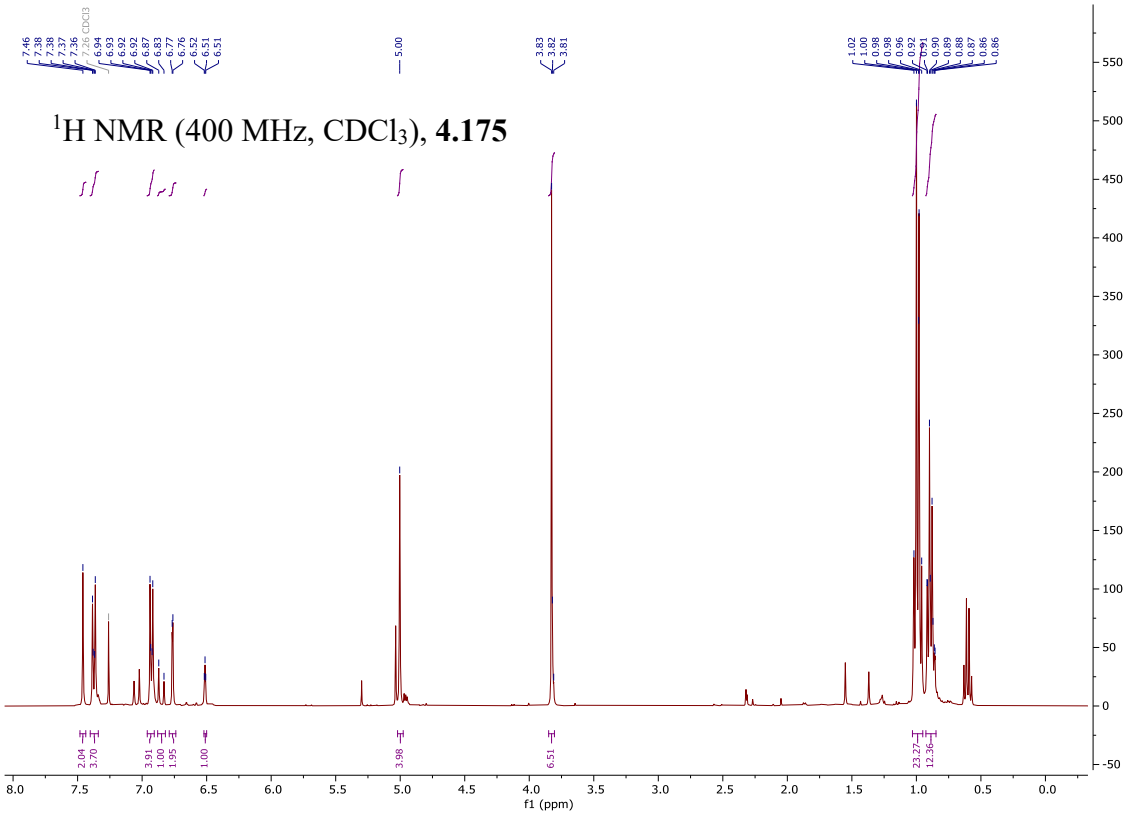


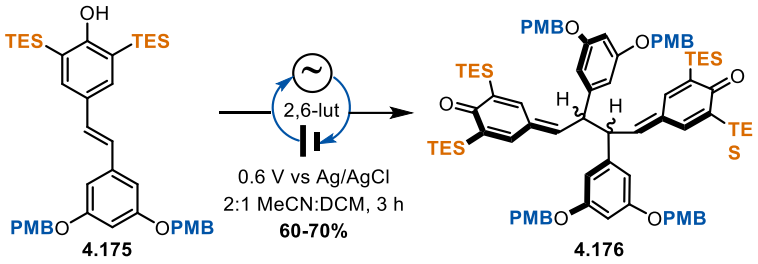


(4.175) (E)-4-(3,5-bis((4-methoxybenzyl)oxy)styryl)-2,6-bis(triethylsilyl)phenol

To a 100 mL RBF was added PMB protected resorcinol (1.3 g, 3.4 mmol, 1 equiv), TES protected phenol (1.6 g, 3.4 mmol, 1 equiv), Grubbs II catalyst (284 mg, 0.34 mmol, 0.1 equiv), and DCM (34 mL, 0.1 M). The flask was heated with a purge needle to reflux (40 °C) for 2 hours. This resulted in the reaction concentrating to a thick black sludge over the first 30 minutes of reactivity. THF was added (34 mL, 0.1 M) and the solution was cooled to 0 °C. TBAF (5 mL, 5 mmol, 1.5 equiv, 1 M solution in THF) was added, and let stir for 1 hour. The reaction slurry was quenched with Sat. $NaHCO_3$ (aq). The solution was let warm to room temperature before addition of ether for extraction. The combined organics were dried with brine, $MgSO_4$ and filtered. The crude reaction mixture was purified by column chromatography SiO_2 (0-20% ethyl acetate in hexanes) to afford the product as an amorphous yellow powder (889 mg, 38%).

^{1}H NMR (400 MHz, $CDCl_3$), **4.175** δ = 7.46 (s, 2H), 7.40 – 7.34 (m, 4H), 6.96 – 6.91 (m, 4H), 6.85 (d, J=16.2, 1H), 6.76 (d, J=2.2, 2H), 6.51 (t, J=2.2, 1H), 5.00 (s, 4H), 3.82 (d, J=2.5, 7H), 1.03 – 0.95 (m, 18H), 0.93 – 0.85 (m, 12H).

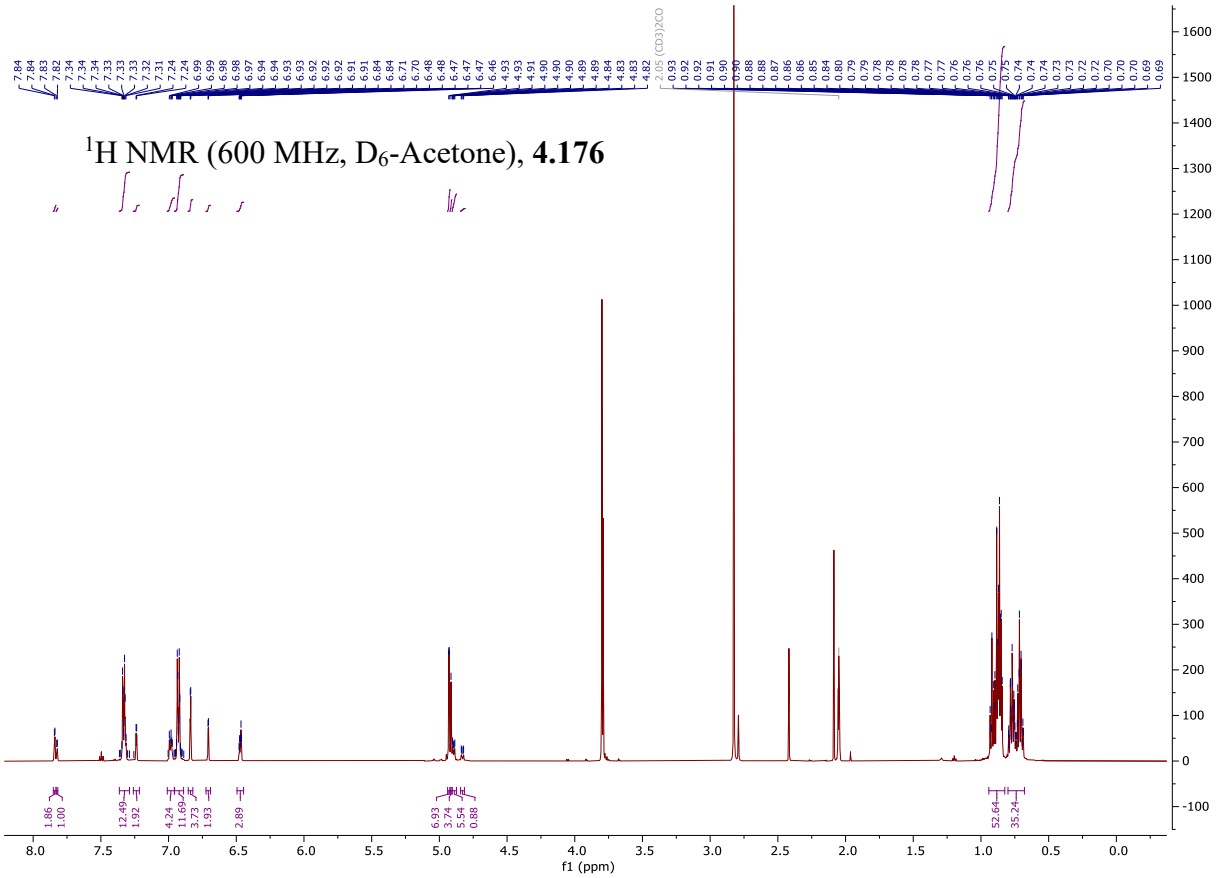


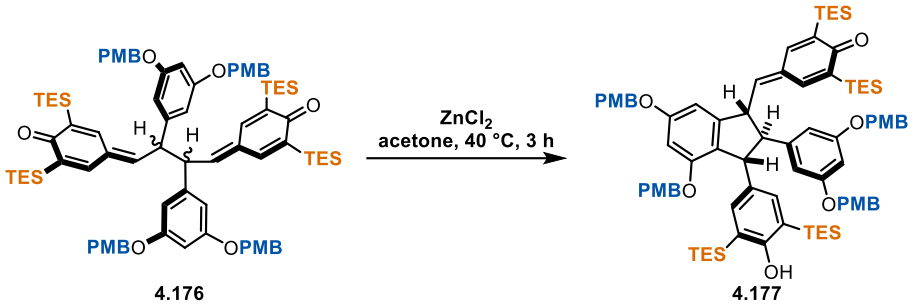


(4.176) 4,4'-((2R)-2,3-bis(3,5-bis((4-methoxybenzyl)oxy)phenyl)butane-1,4-diylidene)bis(2,6-bis(triethylsilyl)cyclohexa-2,5-dien-1-one)

The starting phenol (320 mg, 0.46 mmol, 1.0 equiv) was added to a 50 mL beaker with KPF_6 (340 mg, 1.8 mmol, 4.0 equiv) and 2,6-lutidine (53 µL, 0.46 mmol, 1.0 equiv) and dissolved in acetonitrile (26.6 mL) and dichloromethane (13.3 mL). Two pieces of 2 x 4-inch RVC panel (0.25-inch thickness) were cut. To each, a hole was made near one end, and copper wire was placed through the hole and wrapped around the top of each electrode. One end of the wire was left free to connect to the alligator clips. These electrodes were carefully placed into the beaker along with the reference electrode (Ag/AgCl in 3 M KCl) and a divider. The alligator clips were connected such that the reference and working electrodes were adjacent to each other, while the counter electrode was opposite the divider. Care was taken to ensure the copper wire was not submerged in solvent, nor the active components of the alligator clips touching each other. The reaction was stirred at 750 rpm for 1-2 h at a constant voltage of 0.6 V. A chronoampergram was recorded to follow the course of the reaction. Upon completion of the reaction, the electrodes were removed and rinsed into a collection flask with DCM (~40 mL). The contents of the reaction vial were also rinsed into the collection flask. The solvent was removed in vacuo, and the crude material was purified by flash chromatography over SiO_2 (0%-10% EtOAc in Hexanes) to yield the product as a bright yellow foam (61 mg, 84%, 1.8:1 mixture of diastereomers).

^{1}H NMR (600 MHz, D_6-Acetone), **4.176** δ = 7.84 (d, J=2.6, 2H), 7.82 (d, J=2.6, 1H), 7.36 – 7.29 (m, 12H), 7.24 (d, J=2.6, 2H), 6.98 (dd, J=9.0, 4.2, 4H), 6.96 – 6.89 (m, 12H), 6.84 (d, J=2.2, 4H), 6.71 (d, J=2.2, 2H), 6.47 (dt, J=6.3, 2.2, 3H), 4.93 (d, J=1.6, 7H), 4.91 (s, 4H), 4.91 – 4.87 (m, 6H), 4.83 (dd, J=7.8, 2.5, 1H), 0.94 – 0.82 (m, 53H), 0.80 – 0.68 (m, 35H).

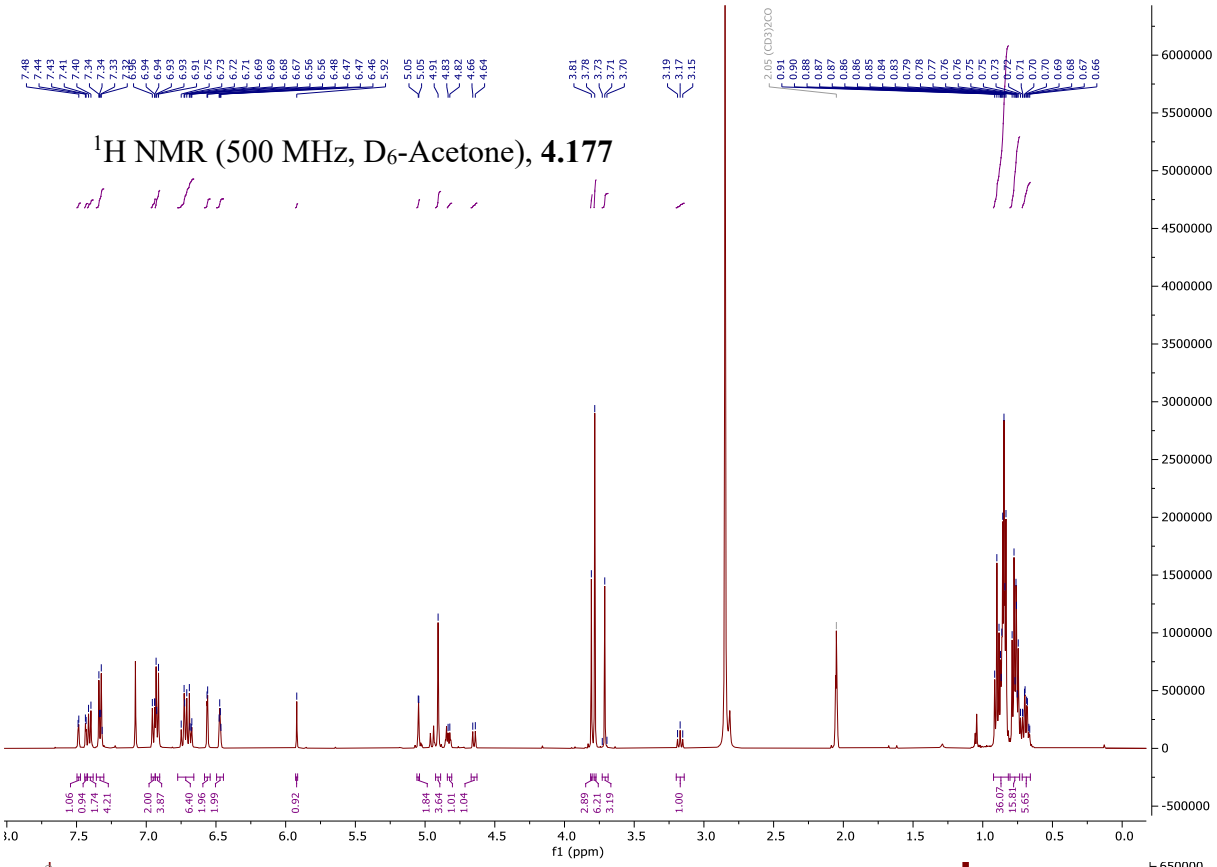

^{1}H NMR (600 MHz, D$_6$-Acetone), **4.176**
f1 (ppm)



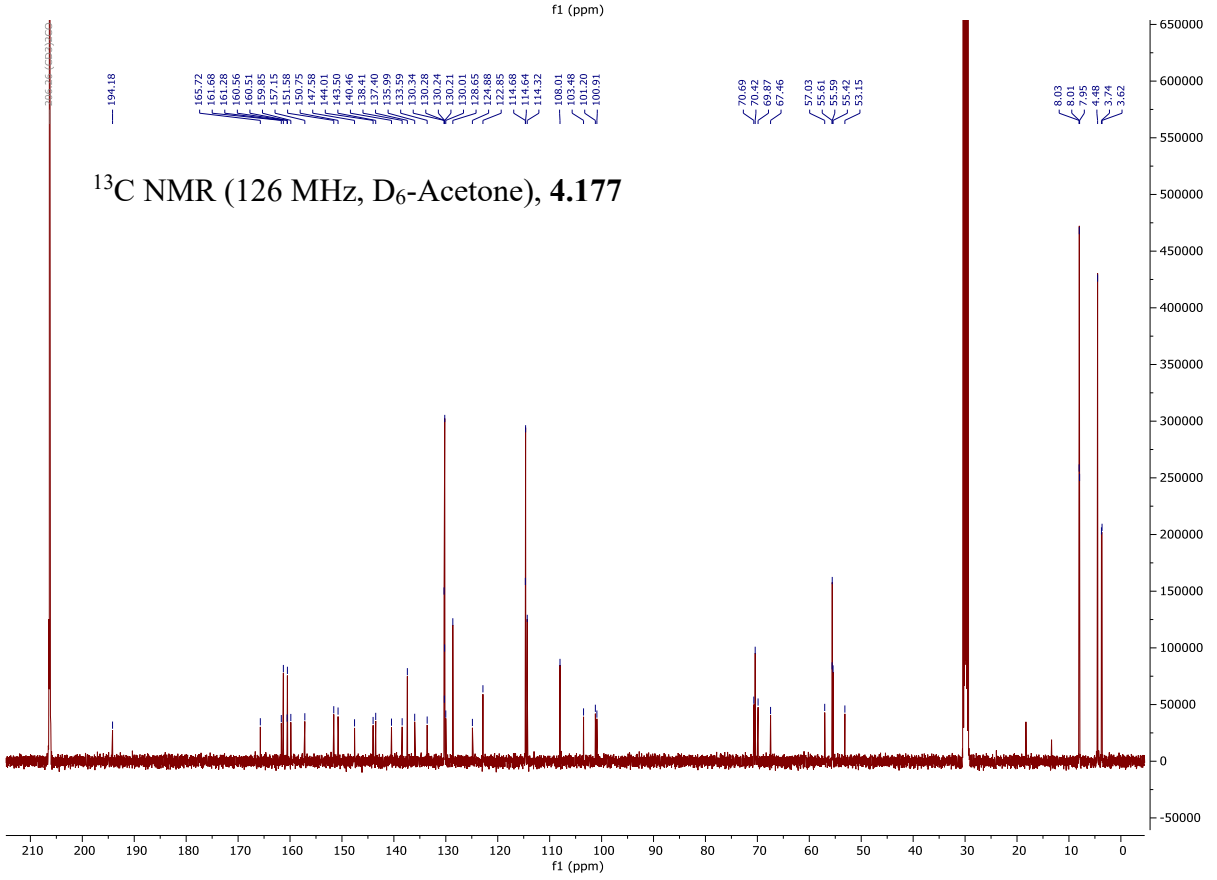
(4.177) 4-(((1R,2R,3R)-2-(3,5-bis((4-methoxybenzyl)oxy)phenyl)-3-(4-hydroxy-3,5-bis(triethylsilyl)phenyl)-4,6-bis((4-methoxybenzyl)oxy)-2,3-dihydro-1H-inden-1-yl)methylene)-2,6-bis(triethylsilyl)cyclohexa-2,5-dien-1-one

In a sealed tube was added starting material (205 mg, 148 µmol, 1 equiv), $ZnCl_2$ (161 mg, 1.2 mmol, 8 equiv, solid), and acetone (3.0 mL, 0.05 M). The sealed tube was capped and heated to 40 °C for 3 h in an oil bath. The crude solution was partitioned between ether (20 mL) and water (20 mL). The organics were dried with brine (20 mL) and $MgSO_4$. This organic extract was in sufficient purity for further reaction (~90%), but if desired the residue could be subjected to column chromatography SiO_2 (0-20% ethyl acetate in hexanes) to afford the product as a tan foam (134 mg, 65%).

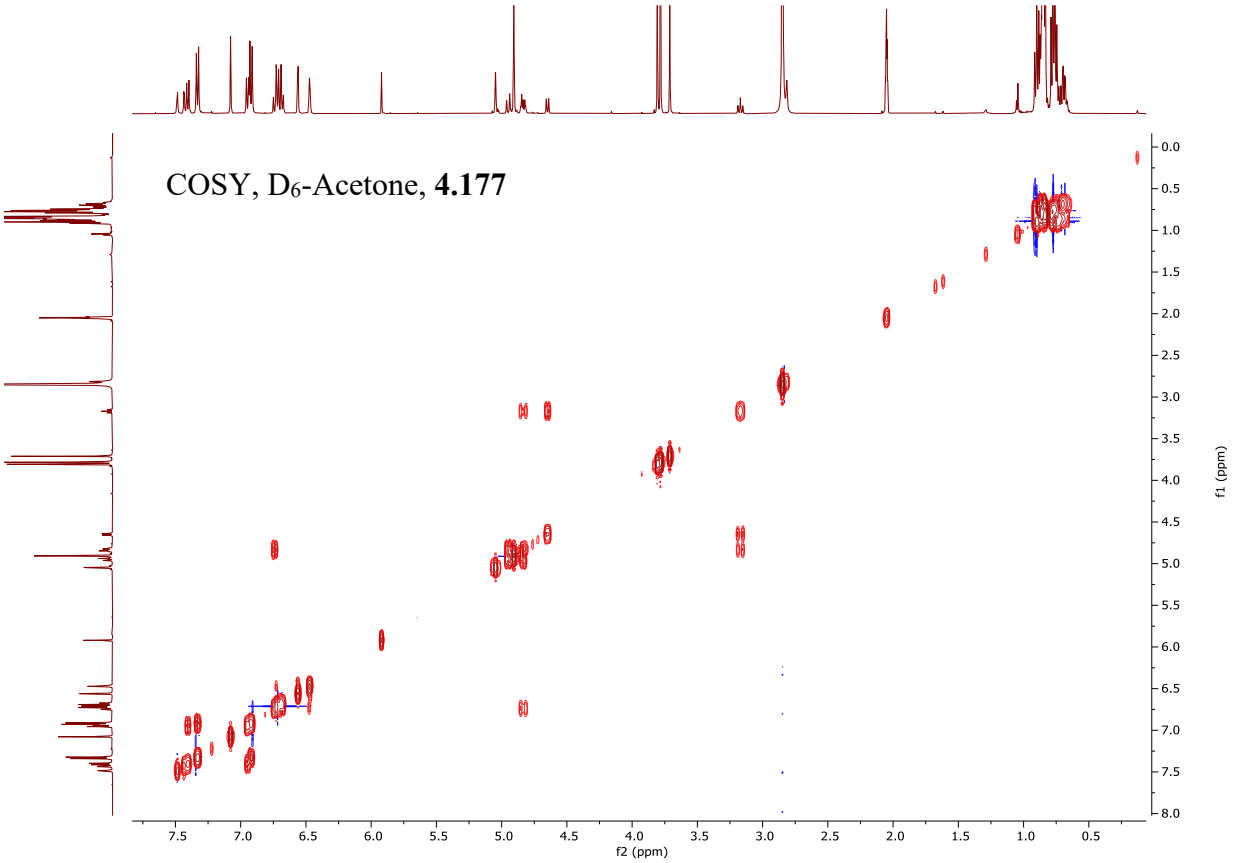
^{1}H NMR (500 MHz, D_6-Acetone), **4.177**	δ = 7.49 (d, J=2.6, 1H), 7.43 (d, J=2.6, 1H), 7.41 (d, J=8.6, 2H), 7.36 – 7.30 (m, 4H), 6.95 (d, J=8.7, 2H), 6.92 (d, J=8.6, 4H), 6.77 – 6.66 (m, 6H), 6.56 (d, J=2.2, 2H), 6.47 (t, J=2.1, 2H), 5.92 (s, 1H), 5.05 (d, J=1.9, 2H), 4.91 (s, 4H), 4.83 (d, J=6.2, 1H), 4.65 (d, J=9.2, 1H), 3.81 (s, 3H), 3.78 (s, 6H), 3.71 (s, 3H), 3.17 (t, J=9.3, 1H), 0.92 – 0.82 (m, 36H), 0.80 – 0.74 (m, 16H), 0.69 (qd, J=8.4, 7.8, 2.4, 6H).
^{13}C NMR (126 MHz, D_6-Acetone), **4.177**	δ = 194.2, 165.7, 161.7, 161.3, 160.6, 160.5, 159.8, 157.2, 151.6, 150.8, 147.6, 144.0, 143.5, 140.5, 138.4, 137.4, 136.0, 133.6, 130.3, 130.3, 130.2, 130.2, 130.0, 128.7, 124.9, 122.9, 114.7, 114.6, 114.3, 108.0, 103.5, 101.2, 100.9, 70.7, 70.4, 69.9, 67.5, 57.0, 55.6, 55.6, 55.4, 53.1, 8.0, 8.0, 7.9, 4.5, 3.7, 3.6.

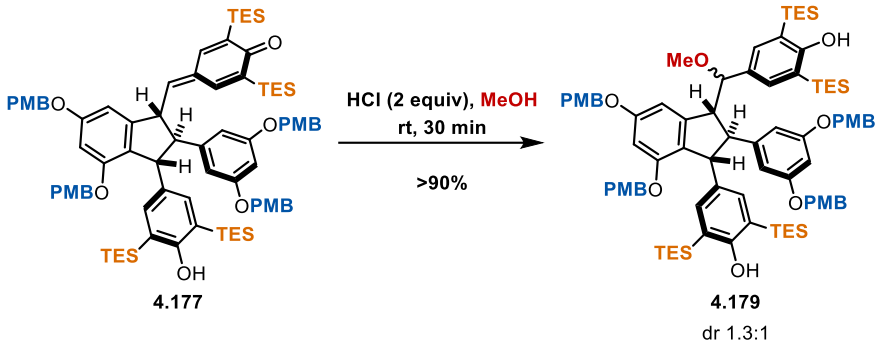


^{1}H NMR (500 MHz, D$_6$-Acetone), **4.177**



^{13}C NMR (126 MHz, D$_6$-Acetone), **4.177**

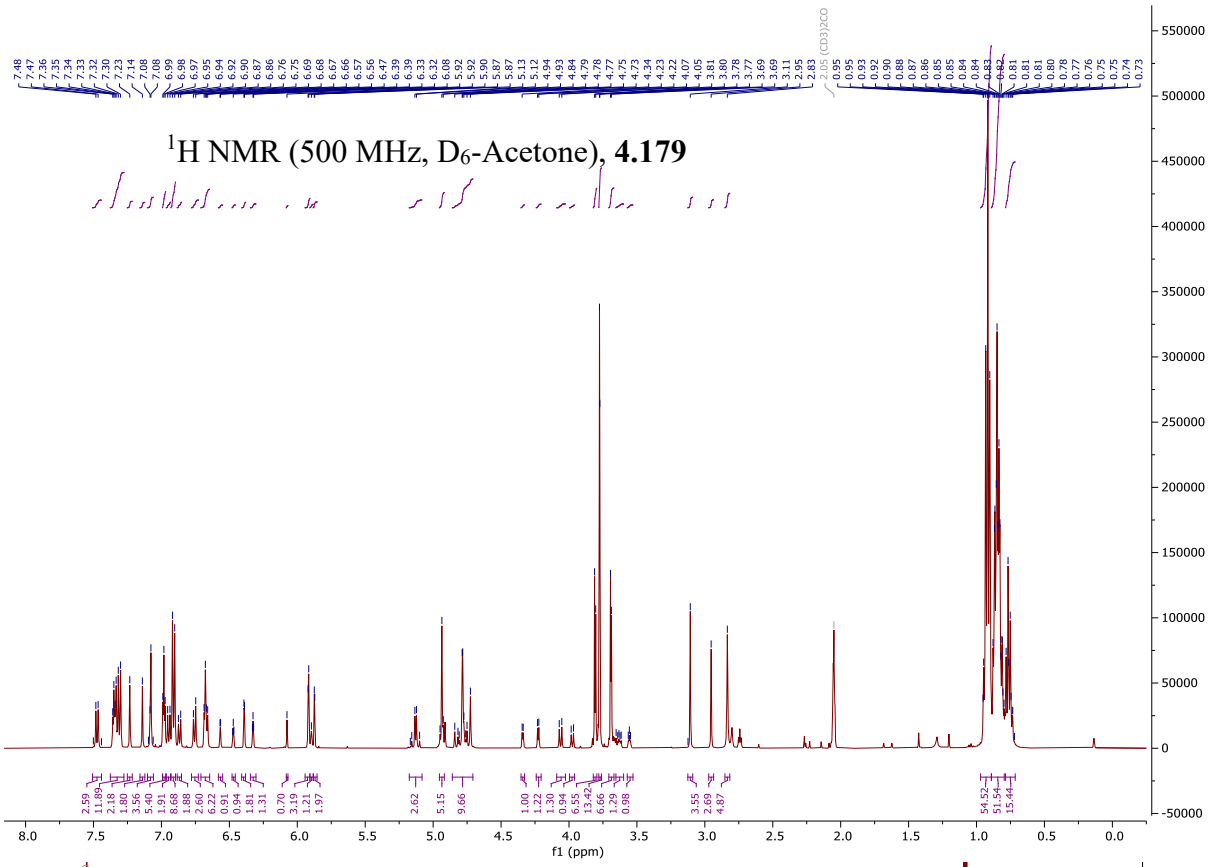

COSY, D6-Acetone, 4.177
f2 (ppm)
f1 (ppm)

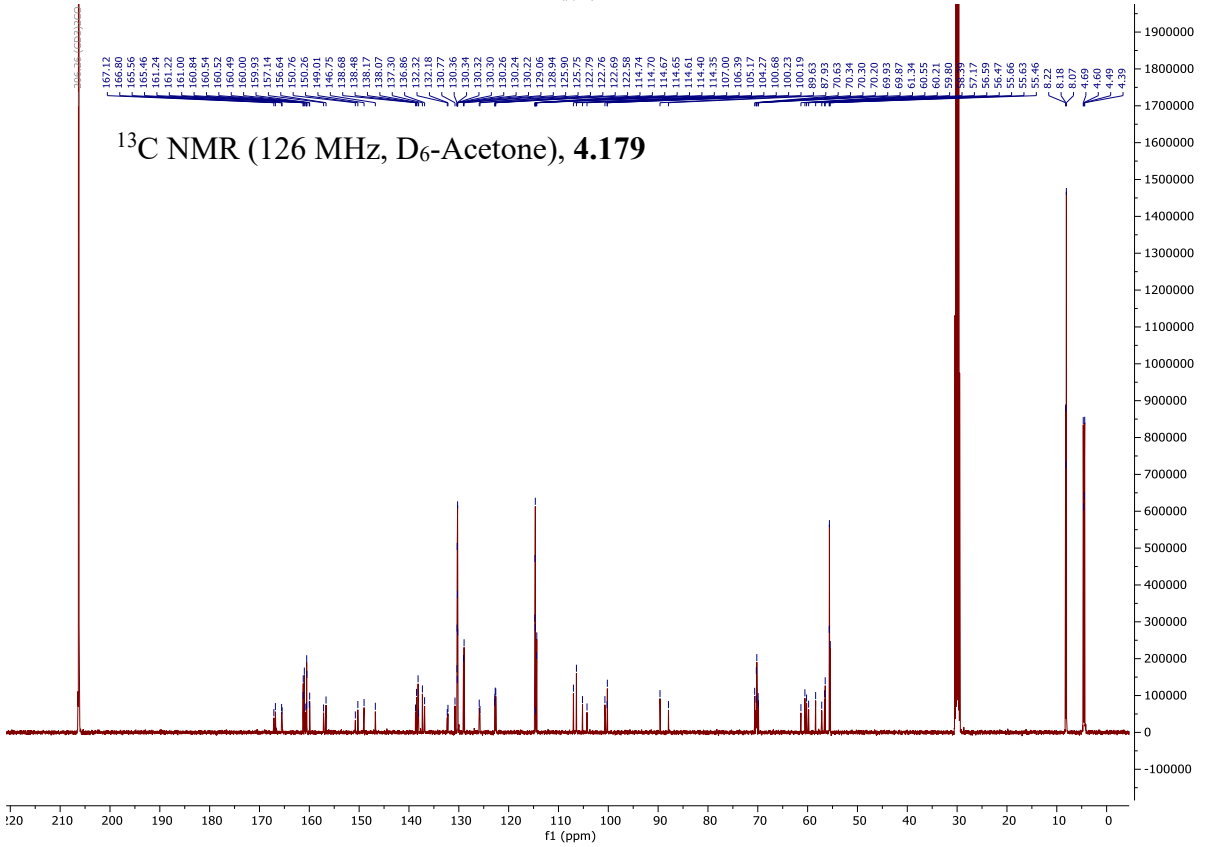


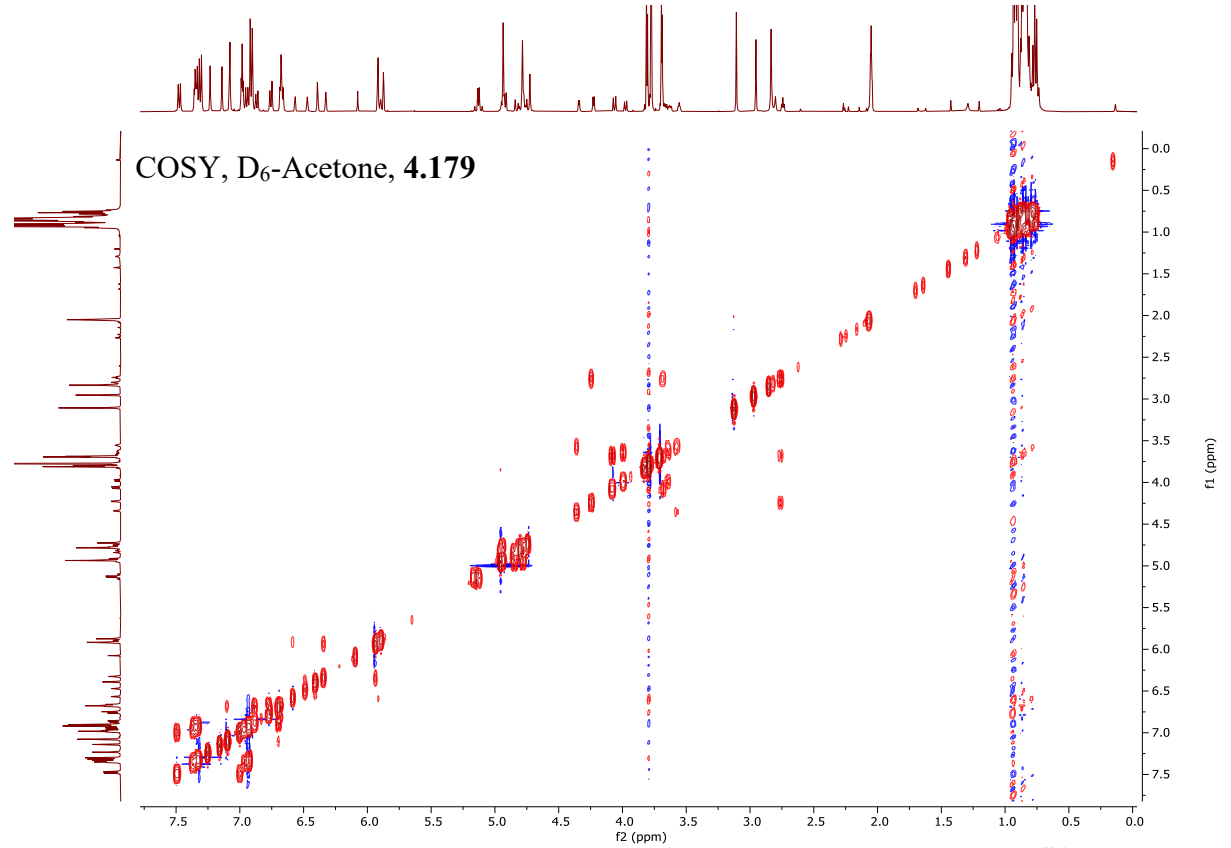
(4.179) 4-((1R,2S,3R)-2-(3,5-bis((4-methoxybenzyl)oxy)phenyl)-3-((4-hydroxy-3,5-bis(triethylsilyl)phenyl)(methoxy)methyl)-5,7-bis((4-methoxybenzyl)oxy)-2,3-dihydro-1H-inden-1-yl)-2,6-bis(triethylsilyl)phenol

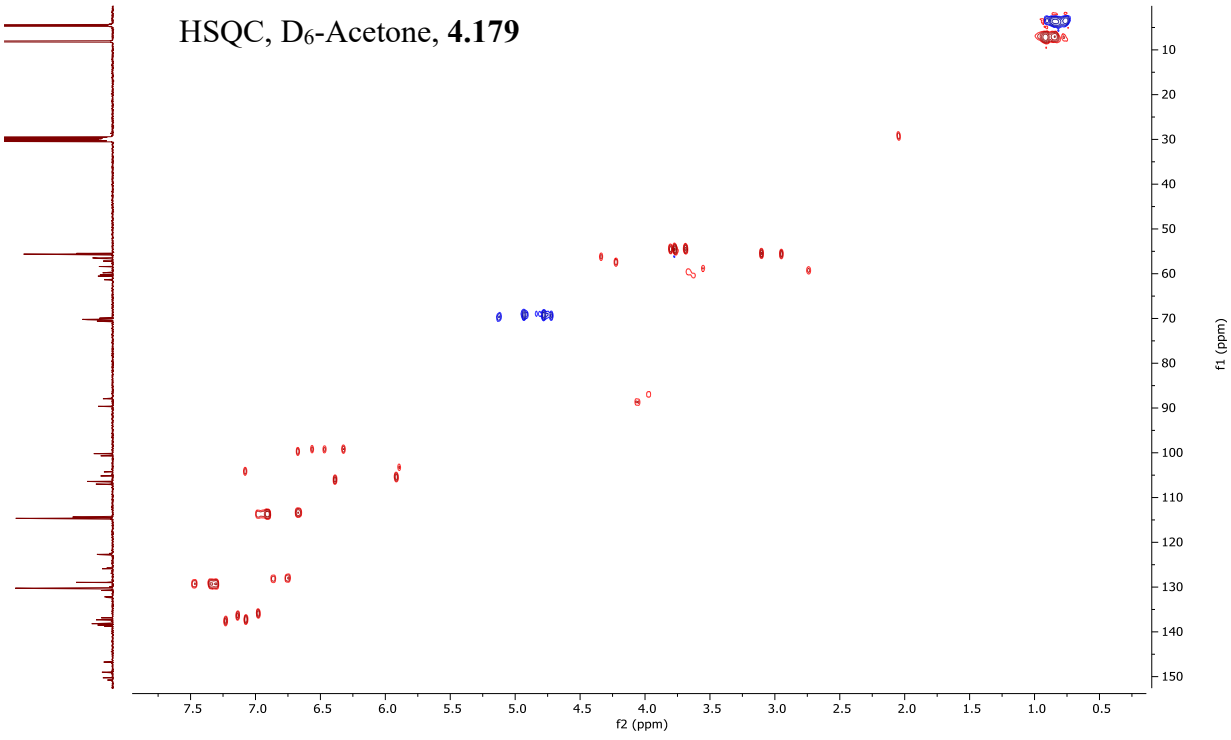
In a 2-dram vial was added starting material (42 mg, 30 µmol, 1 equiv), HCl (120 µL, 60 µmol, 2 equiv, 0.5 M solution in MeOH), MeOH (30 mL, 0.01 M) and THF (1.5 mL, 0.02 M). The reaction was stirred for 30 minutes at room temperature. The mixture was quenched with sat. $NaHCO_3$ (aq) (20 mL) and extracted with either (3 x 20 mL). The organics were dried with brine (20 mL) and $MgSO_4$. The crude organic residue was subjected to column chromatography SiO_2 (0-30% ethyl acetate in hexanes) to afford the product as a tan foam (39 mg, 91%) as a 1.3:1 mixture of diastereomers about addition of MeOH to the quinone. Due to the complexity of the spectral interpretation of the inseparable mixture, the major diastereomer was not identified.

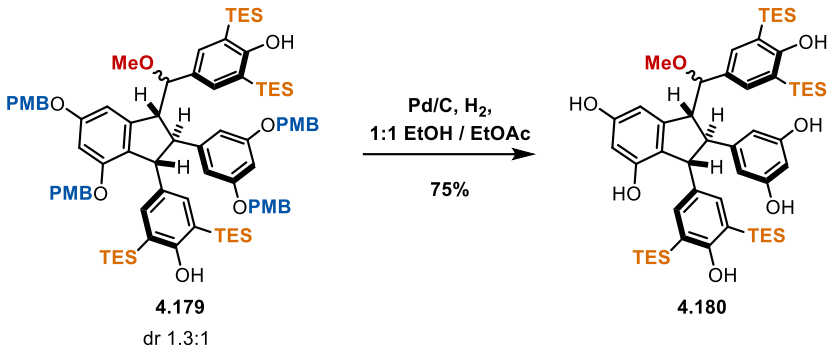
^{1}H NMR (500 MHz, D_6-Acetone), **4.179**	δ = 7.47 (d, J=8.3, 3H), 7.38 – 7.28 (m, 12H), 7.23 (s, 2H), 7.14 (s, 2H), 7.08 (d, J=3.1, 4H), 6.98 (t, J=4.3, 5H), 6.95 (d, J=8.5, 2H), 6.91 (d, J=8.3, 9H), 6.87 (d, J=8.4, 2H), 6.76 (d, J=8.5, 3H), 6.67 (q, J=4.6, 6H), 6.57 (d, J=2.0, 1H), 6.47 (d, J=2.2, 1H), 6.39 (d, J=2.2, 2H), 6.32 (d, J=2.3, 1H), 6.08 (s, 1H), 5.92 (d, J=2.4, 3H), 5.90 (s, 1H), 5.87 (d, J=1.7, 2H), 5.18 – 5.08 (m, 3H), 4.94 (s, 5H), 4.86 – 4.71 (m, 10H), 4.34 (d, J=3.9, 1H), 4.23 (d, J=4.6, 1H), 4.06 (d, J=9.4, 1H), 3.98 (d, J=8.4, 1H), 3.81 (d, J=4.2, 7H), 3.77 (d, J=1.3, 13H), 3.69 (d, J=3.3, 7H), 3.65 – 3.60 (m, 1H), 3.56 (t, J=4.0, 1H), 3.11 (s, 4H), 2.95 (s, 3H), 2.83 (s, 5H), 0.92 (q, J=7.4, 55H), 0.84 (dtd, J=15.9, 8.7, 7.8, 3.5, 52H), 0.77 (dd, J=8.8, 6.3, 15H).
^{13}C NMR (126MHz, D_6-Acetone), **4.179**	δ = 167.1, 166.8, 165.6, 165.5, 161.2, 161.2, 161.0, 160.8, 160.5, 160.5, 160.5, 160.0, 159.9, 157.1, 156.6, 150.8, 150.3, 149.0, 146.7, 138.7, 138.5, 138.2, 138.1, 137.3, 136.9, 132.3, 132.2, 130.8, 130.4, 130.3, 130.3, 130.3, 130.3, 130.2, 130.2, 129.1, 128.9, 125.9, 125.7, 122.8, 122.8, 122.7, 122.6, 114.7, 114.7, 114.7, 114.6, 114.6, 114.4, 114.3, 107.0, 106.4, 105.2, 104.3, 100.7, 100.2, 100.2, 89.6, 87.9, 70.6, 70.3, 70.3, 70.2, 69.9, 69.9, 61.3, 60.5, 60.2, 59.8, 58.4, 57.2, 56.6, 56.5, 55.7, 55.6, 55.5, 8.2, 8.2, 8.1, 4.7, 4.6, 4.5, 4.4.


^{1}H NMR (500 MHz, D$_6$-Acetone), **4.179**
f1 (ppm)


^{13}C NMR (126 MHz, D$_6$-Acetone), **4.179**
f1 (ppm)


COSY, D6-Acetone, 4.179
f2 (ppm)
f1 (ppm)

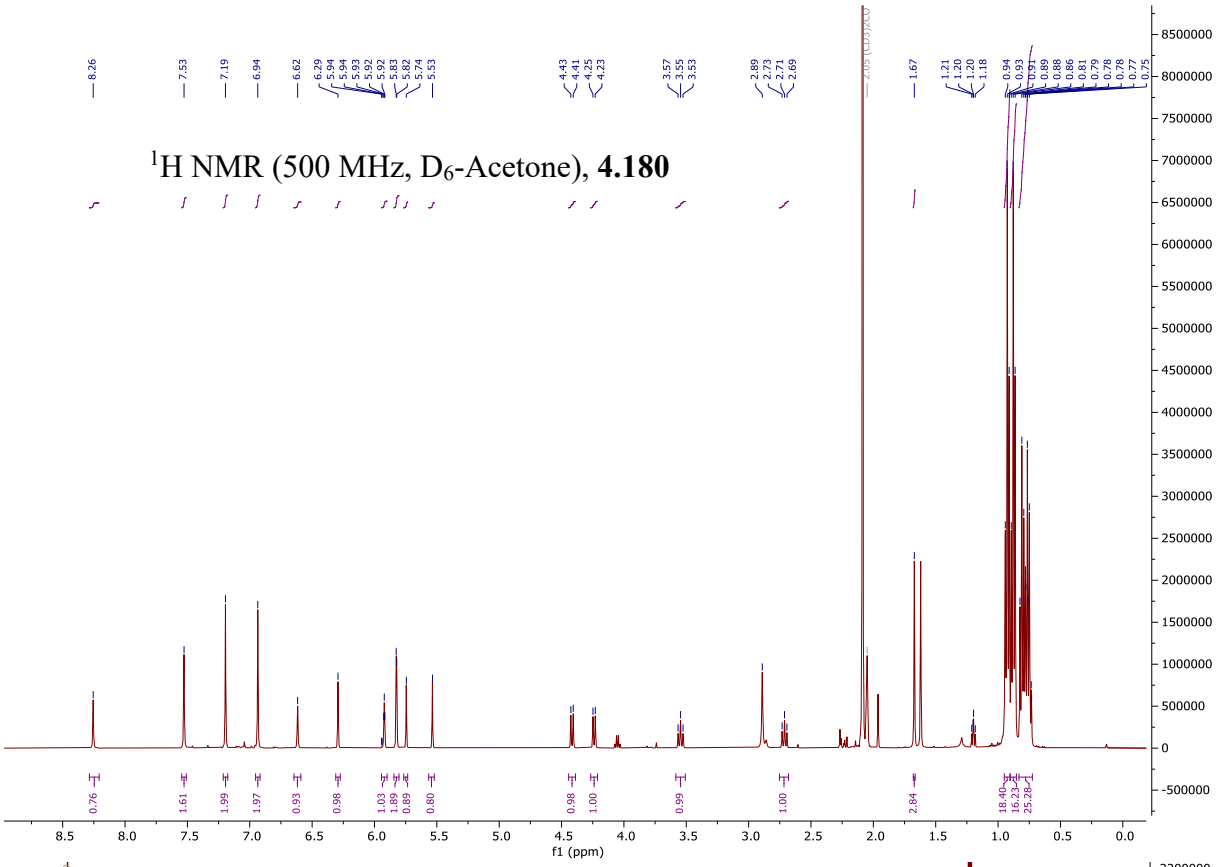

HSQC, D6-Acetone, 4.179
f2 (ppm)
f1 (ppm)



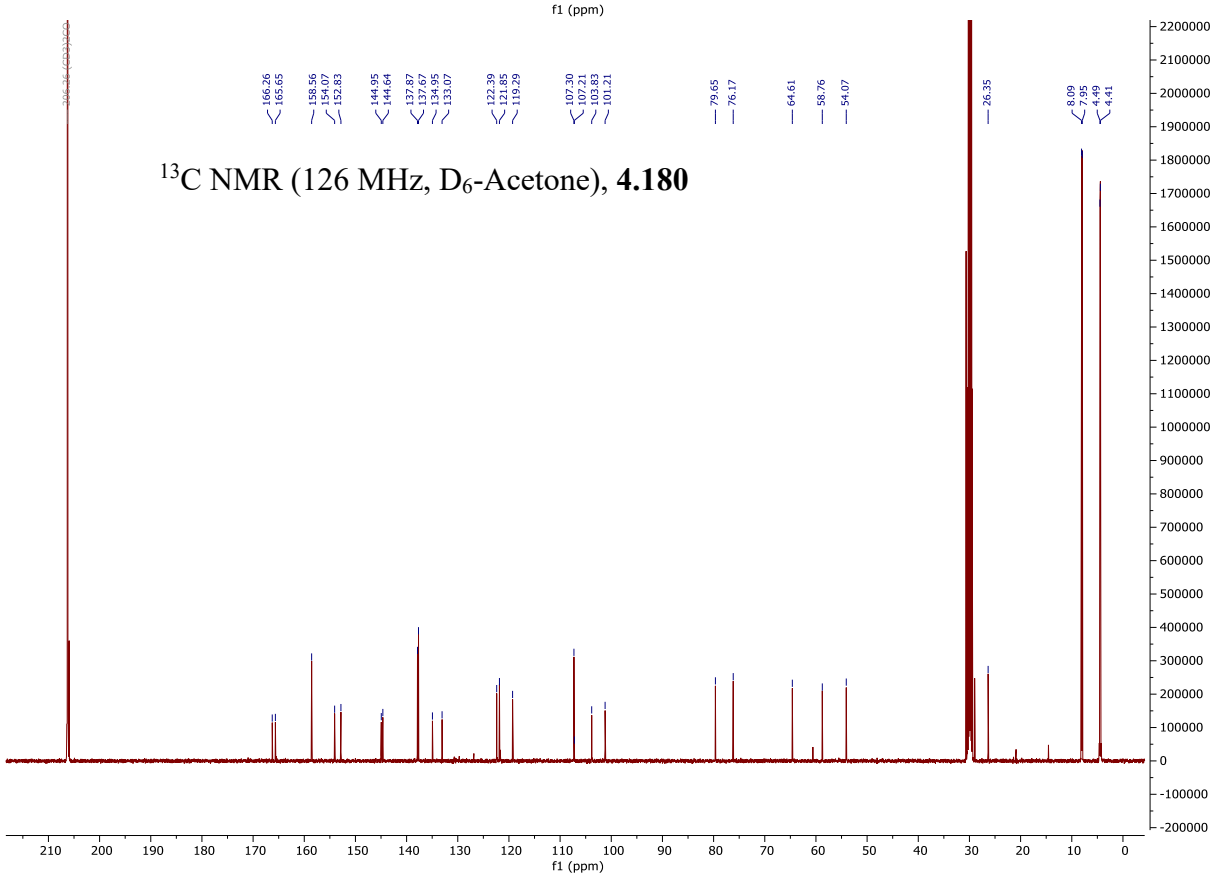
(4.180) (1R,2S,3R)-2-(3,5-dihydroxyphenyl)-3-(4-hydroxy-3,5-bis(triethylsilyl)phenyl)-1-((4-hydroxy-3,5-bis(triethylsilyl)phenyl)(methoxy)methyl)-2,3-dihydro-1H-indene-4,6-diol

In a 25 mL RBF was added starting material (120 mg, 84 µmol, 1 equiv), Pd/C (20 mg, 17 µmol, 0.2 equiv, 30 wt% on carbon), EtOAc (4 mL, 0.01 M), and EtOH (4 mL, 0.01 M). The solution was sparged with hydrogen gas for 10 minutes and then let react for 16 hours under an atmosphere of hydrogen. The completed reaction was sparged with argon, filtered to remove solids, and concentrated. The crude organic residue was subjected to column chromatography SiO_2 (0-50% ethyl acetate in hexanes) to afford the product as a tan foam (60 mg, 75%). A single diastereomer is shown below, with other mixed fractions also isolated.

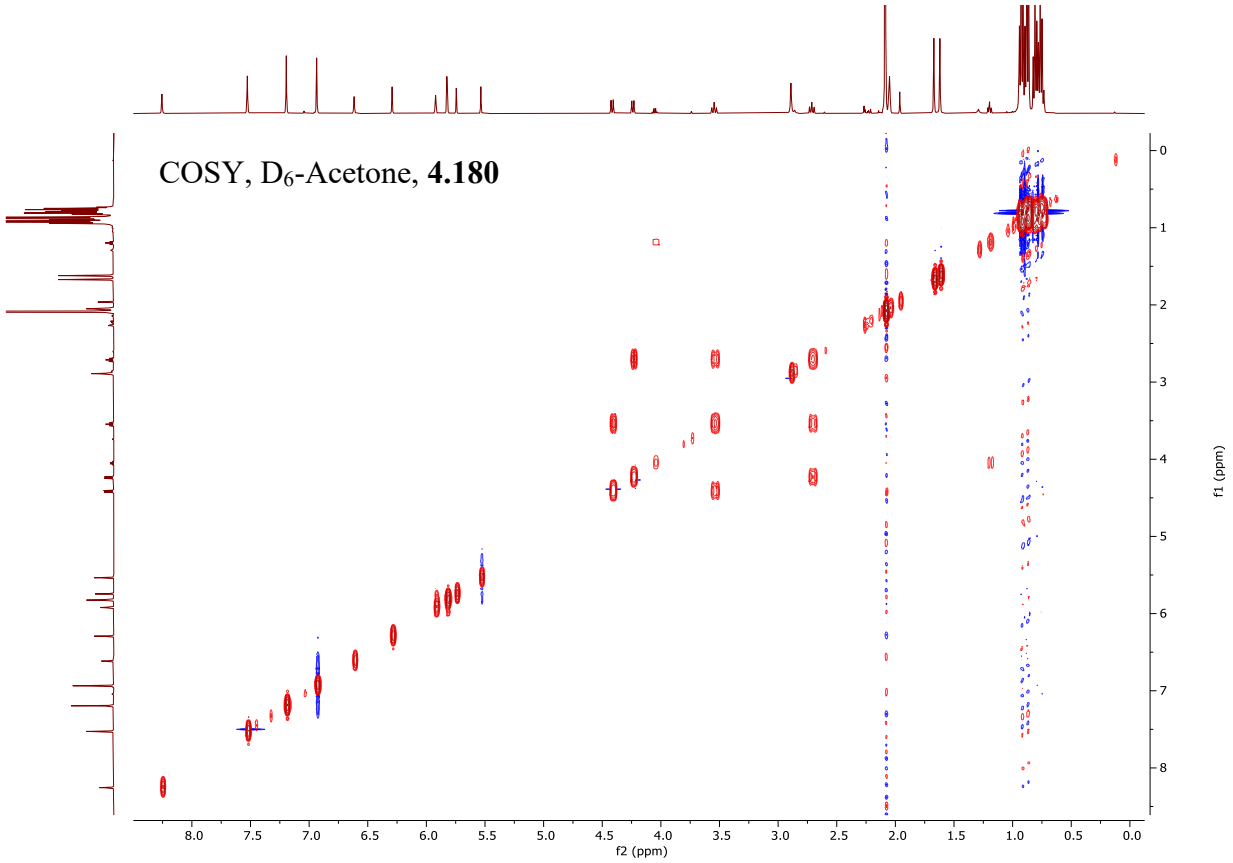
^{1}H NMR (500 MHz, D_6-Acetone), **4.180**	δ = 8.26 (s, 1H), 7.53 (s, 2H), 7.19 (s, 2H), 6.94 (s, 2H), 6.62 (s, 1H), 6.29 (s, 1H), 5.92 (t, J=2.2, 1H), 5.82 (d, J=2.2, 2H), 5.74 (s, 1H), 5.53 (s, 1H), 4.42 (d, J=9.5, 1H), 4.24 (d, J=9.1, 1H), 3.55 (t, J=9.9, 1H), 2.71 (t, J=9.7, 1H), 1.67 (s, 3H), 0.93 (t, J=7.8, 18H), 0.88 (t, J=7.8, 18H), 0.83 – 0.73 (m, 24H).
^{13}C NMR (126MHz, D_6-Acetone), **4.180**	δ = 166.3, 165.6, 158.6, 154.1, 152.8, 144.9, 144.6, 137.9, 137.7, 134.9, 133.1, 122.4, 121.9, 119.3, 107.3, 107.2, 103.8, 101.2, 79.6, 76.2, 64.6, 58.8, 54.1, 26.3, 8.1, 7.9, 4.5, 4.4.

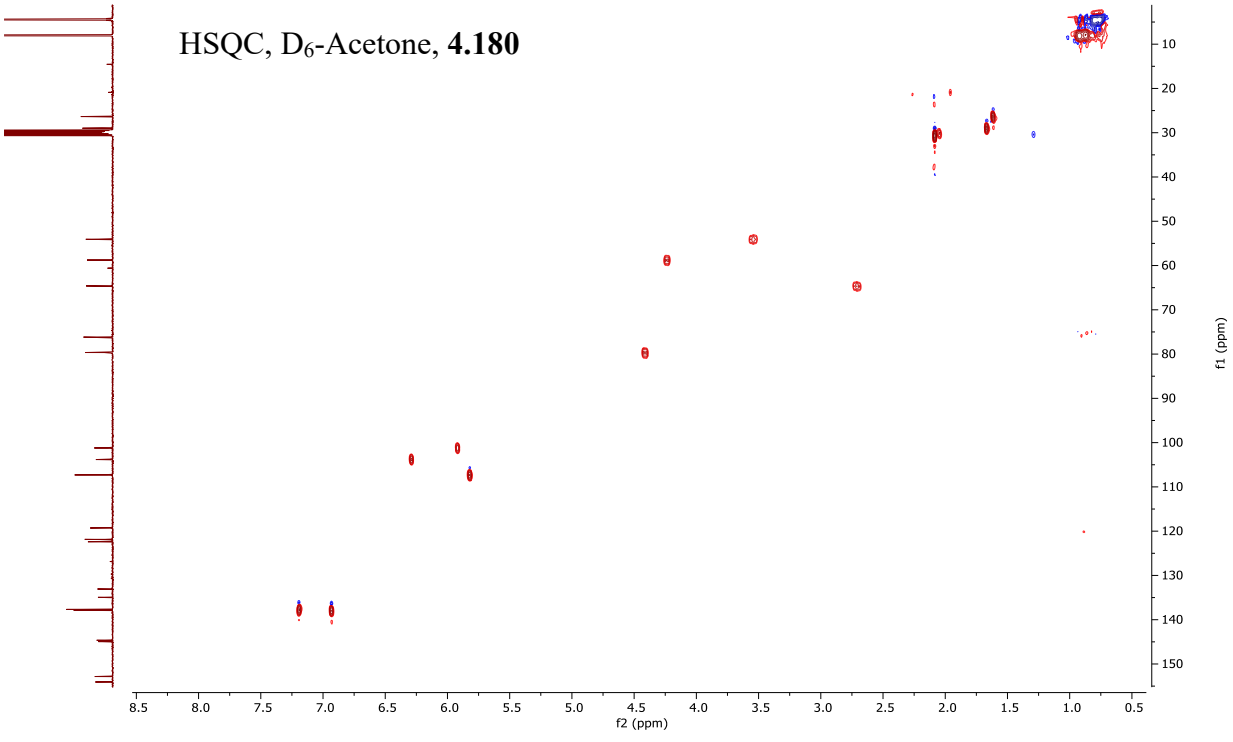


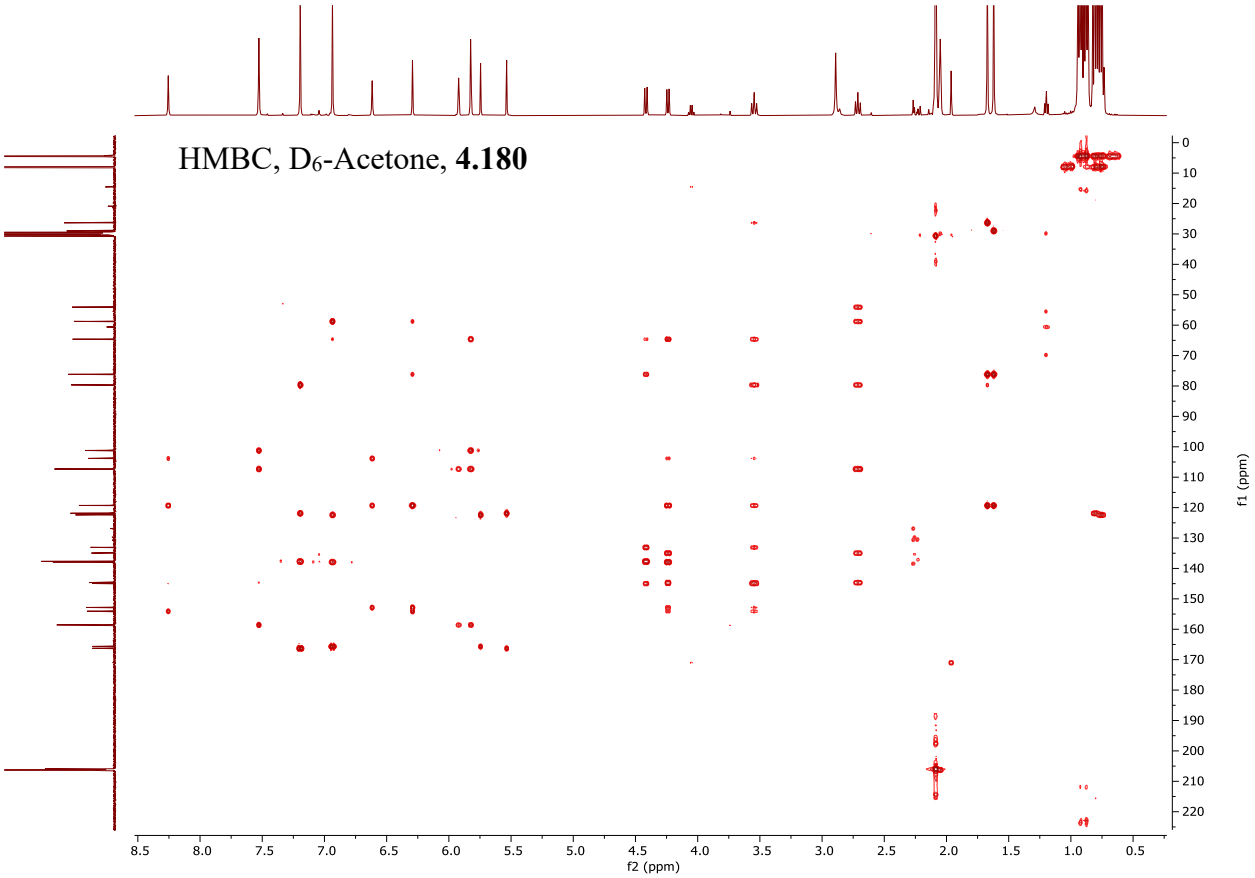
^{1}H NMR (500 MHz, D_6-Acetone), **4.180**

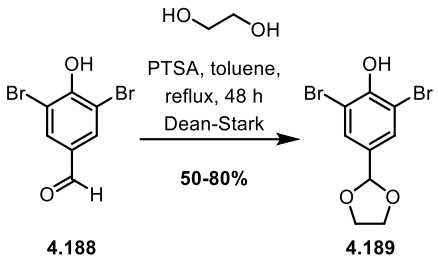


^{13}C NMR (126 MHz, D_6-Acetone), **4.180**


COSY, D6-Acetone, 4.180
f2 (ppm)
f1 (ppm)


HSQC, D6-Acetone, 4.180
f2 (ppm)
f1 (ppm)

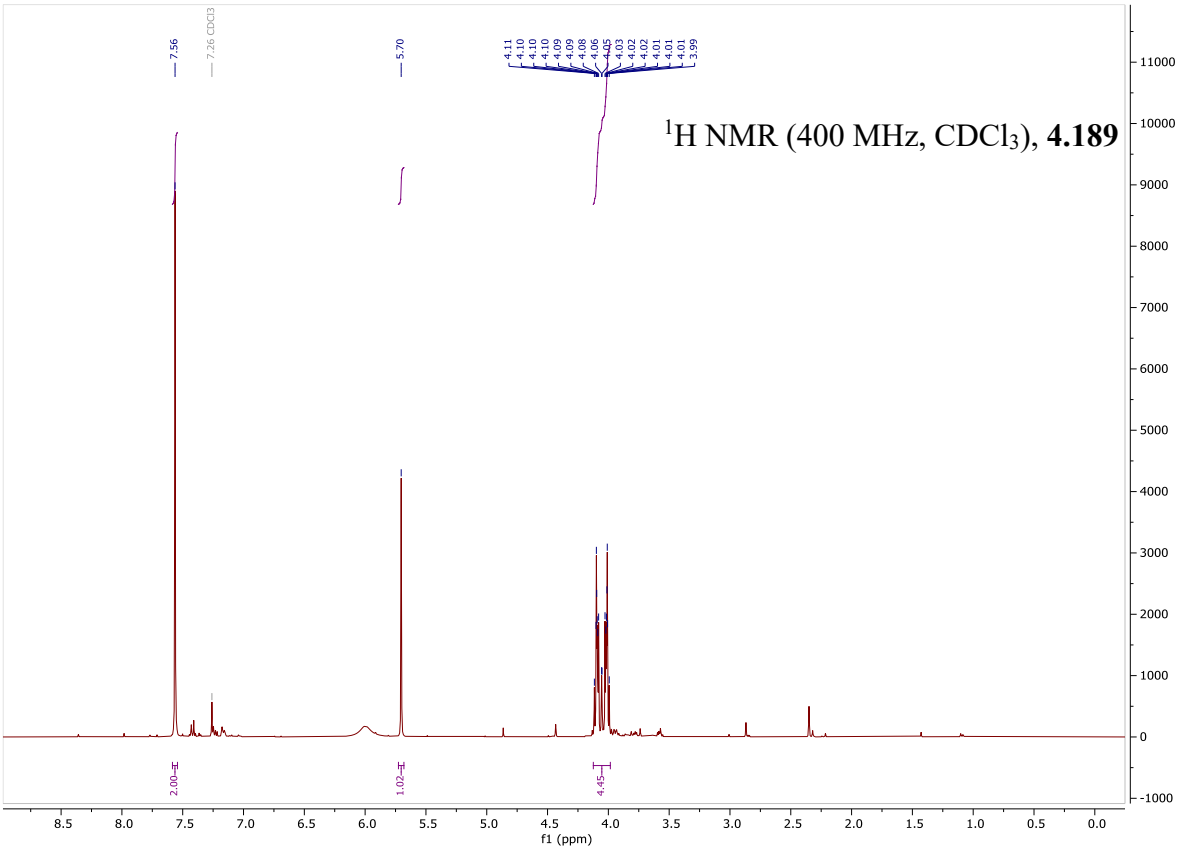

HMBC, D6-Acetone, 4.180
f2 (ppm)
f1 (ppm)

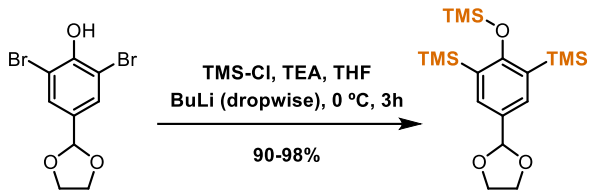


(4.189) 2,6-dibromo-4-(1,3-dioxolan-2-yl)phenol

In a 500 mL RBF was added starting material (40 g, 143 mmol, 1 equiv), ethylene glycol (80 mL, 1.4 mol, 10 equiv), p-toluene sulfonic acid (5.4 g, 28 mmol, 0.2 equiv), and toluene (286 mL, 0.5 M). The solution was heated to reflux (110 °C) with a Dean-Stark trap for 48 hours. The reaction was cooled to room temperature and potassium carbonate was added to quench (7.9 g, 57 mmol, 0.4 equiv). The mixture was stirred for 30 minutes, then concentrated near dryness. The crude residue was suspended in ether (500 mL) and washed with water (4 x 800 mL) to remove excess glycol. The organics were washed with brine (400 mL) and dried over excess $MgSO_4$. This crude product was carried forward in sufficient purity as a brown to tan oil which solidified under vacuum over 3-5 days (39 g, 84%). Spectral data matches previous reports of this compound.[336]

^{1}H NMR (400 MHz, $CDCl_3$), **4.189** δ = 7.56 (s, 2H), 5.70 (s, 1H), 4.12 – 3.98 (m, 4H).



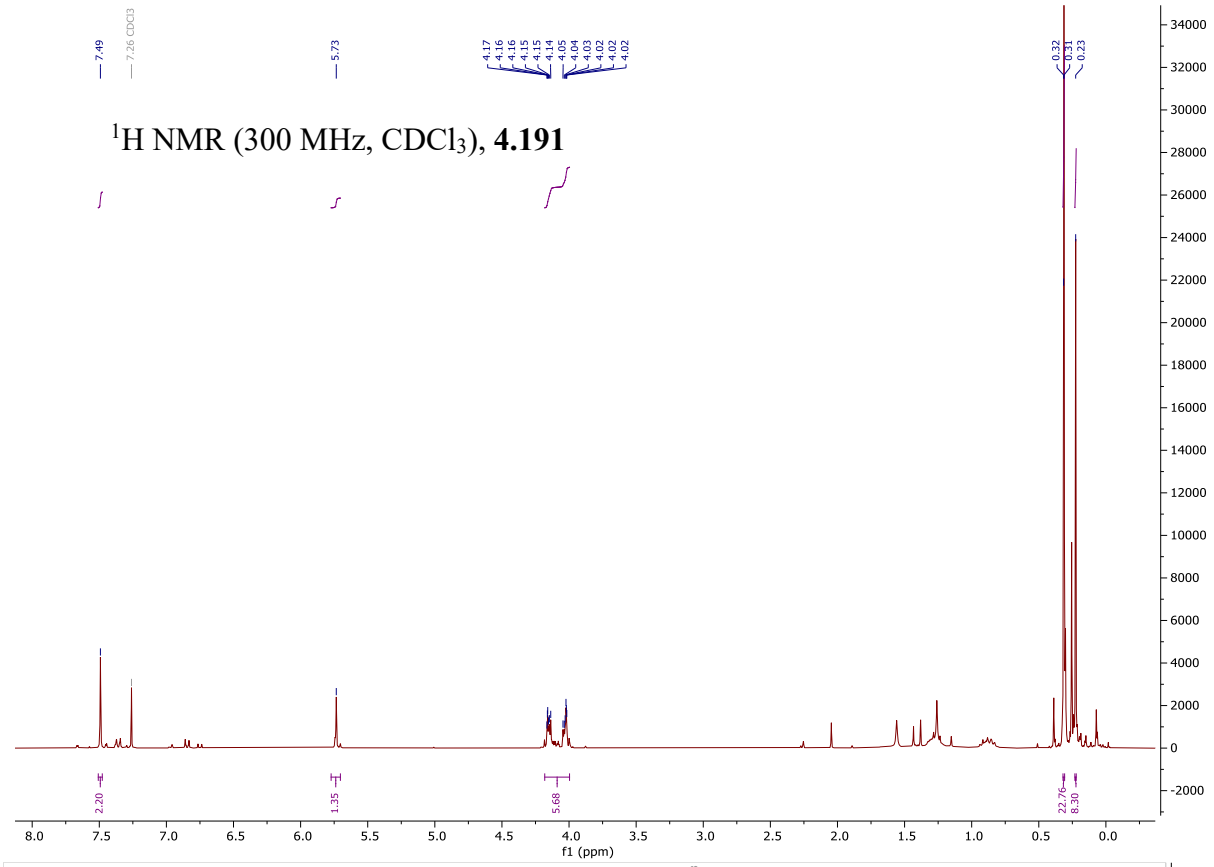


(4.191) 4-(1,3-dioxolan-2-yl)-2,6-bis(trimethylsilyl)phenol

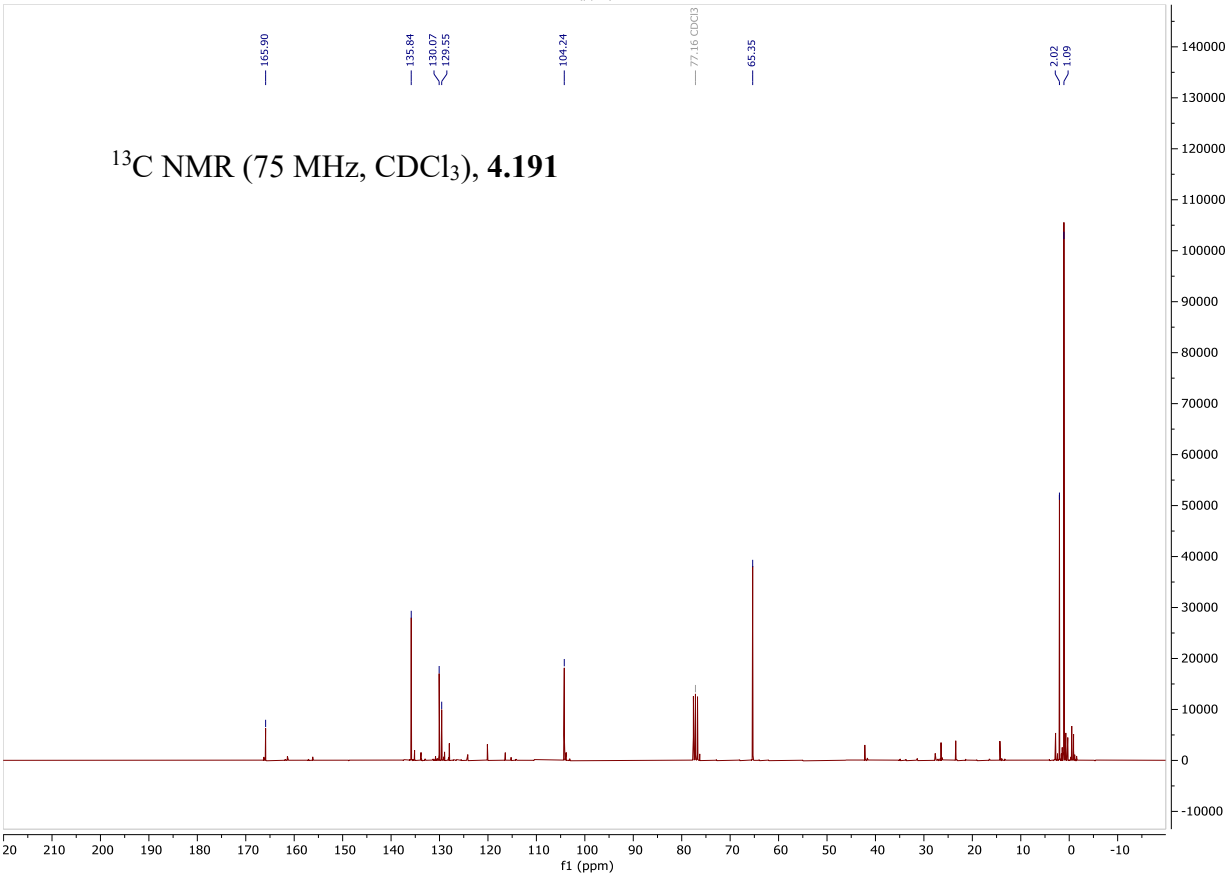
In a 2 L RBF was added starting material (43 g, 133 mmol, 1 equiv), THF (665 mL, 0.2 M), TEA (28 mL, 199 mmol, 1.5 equiv), and TMS-Cl (84 mL, 665 mmol, 5 equiv). This viscous cloudy slurry was stirred for 15 minutes before cooling to 0 °C. BuLi (343 mL, 531 mmol, 4.0 equiv) was added dropwise via cannula over 3 hours. The reaction was monitored by crude ^{1}H NMR. After 1 additional hour of stirring the reaction was quenched with methanol (20 mL) and let warm to room temperature. To the crude was added ether (800 mL) and water (800 mL). The organic extract was washed with water (800 mL) and brine (400 mL), then dried over excess $MgSO_4$. This crude product was carried forward in sufficient purity as a viscous tan oil (50 g, 98%).

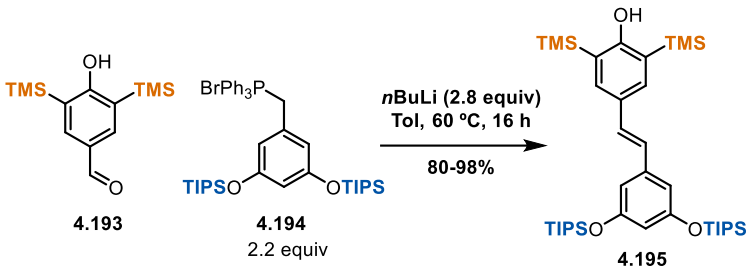
TLC (Hexanes/EtOAc, 90:10), RF:	0.50 (UV, potassium permanganate)
^{1}H NMR (300 MHz, $CDCl_3$), **4.191**	δ = 7.49 (s, 2H), 5.73 (s, 1H), 4.18 – 4.00 (m, 4H), 0.31 (d, J=0.9, 18H), 0.23 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$), **4.191**	δ = 165.9, 135.8, 130.1, 129.6, 104.2, 65.3, 2.0, 1.1.
HRMS (ESI):	m/z calculated for $C_{18}H_{34}O_3Si_3$ ([M+H]+): 383.1888, found 383.1888
FTIR (neat) cm^{-1} :	$\tilde{\nu}$ = 2955 (w), 2895 (w), 1392 (w), 1363 (w), 1253 (m), 1216 (m), 1088 (m), 912 (m), 838 (vs), 751 (w)

^{1}H NMR (300 MHz, $CDCl_3$), **4.191**



^{13}C NMR (75 MHz, $CDCl_3$), **4.191**



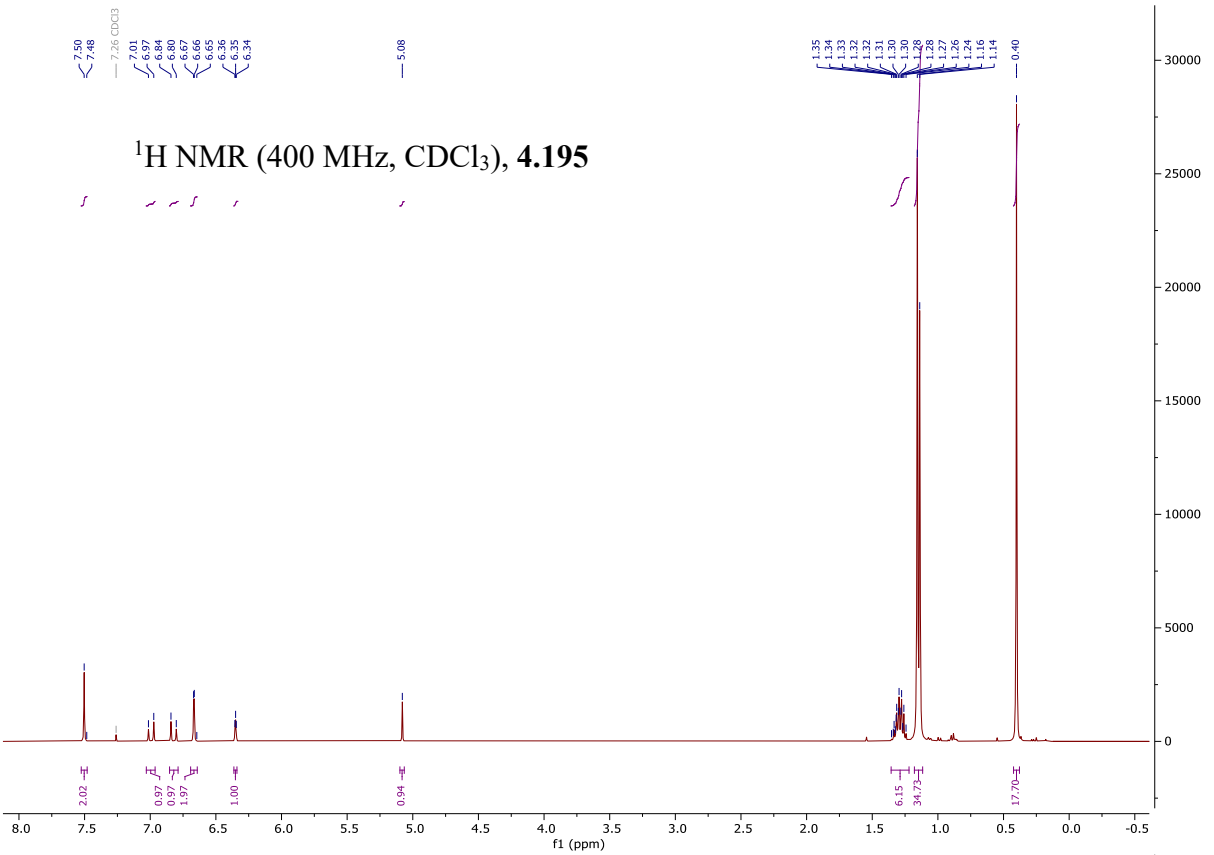


(4.195) (E)-4-(53,5-bis((triisopropylsilyl)oxy)styryl)-2,6-bis(trimethylsilyl)phenol

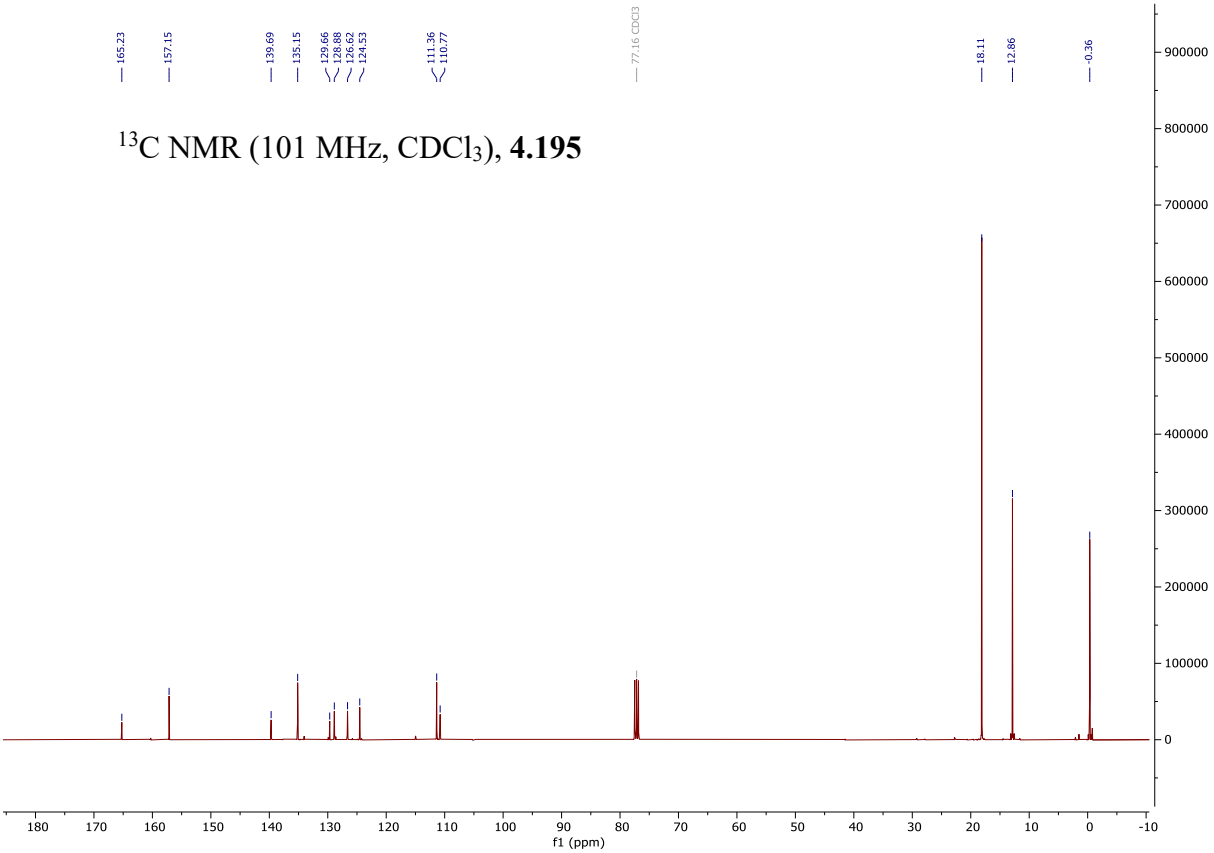
In a 25 mL RBF was added phosphonium salt (1.9 g, 2.5 mmol, 2.2 equiv), toluene (8 mL, 0.15 M), and BuLi (1.26 mL, 3.15 mmol, 2.8 equiv). The bright red solution was let stir for 10 minutes. The aldehyde (300 mg, 1.13 mmol, 1 equiv) was added as a solution in toluene (2 mL). The reaction was heated to 60 °C in an oil bath for 16 hours before quenching with methanol (2 mL). The crude reaction mixture was concentrated onto silica gel for purification by flash chromatography over SiO_2 (0%-15% EtOAc in Hexanes) to yield the product as a yellow viscous crystalline foam (750 mg, 97%). Occasionally excess aldehyde is present in the product, which is inconsequential and can be easily separated once the O-TIPS groups are removed via TBAF in the next synthetic step. The equivalents of BuLi required varies from 2.2 equiv to 4.0 equiv depending on the quality of the phosphonium salt. It is prudent to run a test reaction using the salt of interest before scaling the reaction.

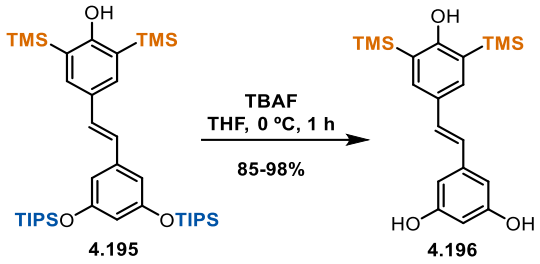
^{1}H NMR (400 MHz, $CDCl_3$), **4.195**	δ = 7.50 (s, 2H), 6.99 (d, J=16.2, 1H), 6.82 (d, J=16.2, 1H), 6.67 (d, J=2.1, 2H), 6.35 (t, J=2.2, 1H), 5.08 (s, 1H), 1.29 (ddt, J=13.6, 10.2, 6.5, 6H), 1.15 (d, J=7.4, 36H), 0.40 (s, 18H).
^{13}C NMR (101 MHz, $CDCl_3$), **4.195**	δ = 165.2, 157.1, 139.7, 135.1, 129.7, 128.9, 126.6, 124.5, 111.4, 110.8, 18.1, 12.9, -0.4.

^{1}H NMR (400 MHz, $CDCl_3$), **4.195**



^{13}C NMR (101 MHz, $CDCl_3$), **4.195**

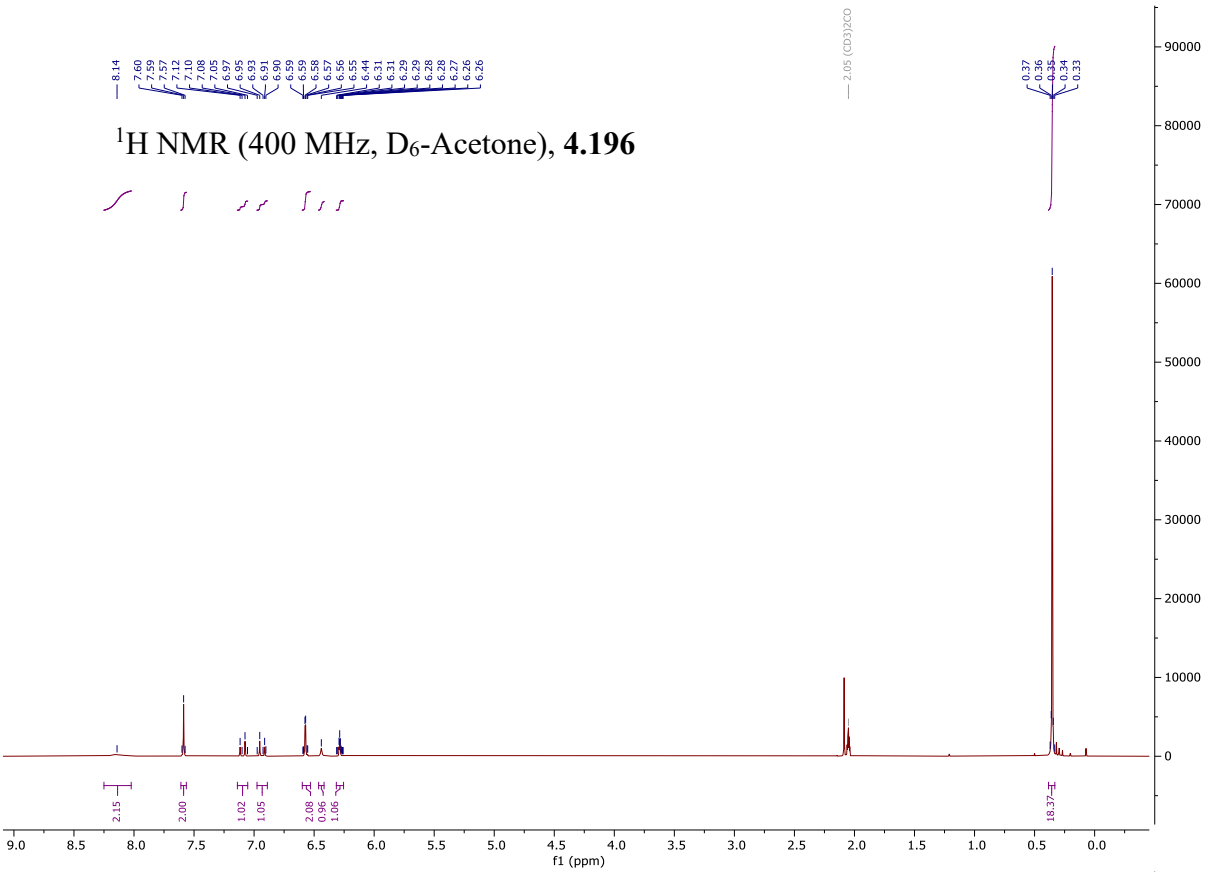




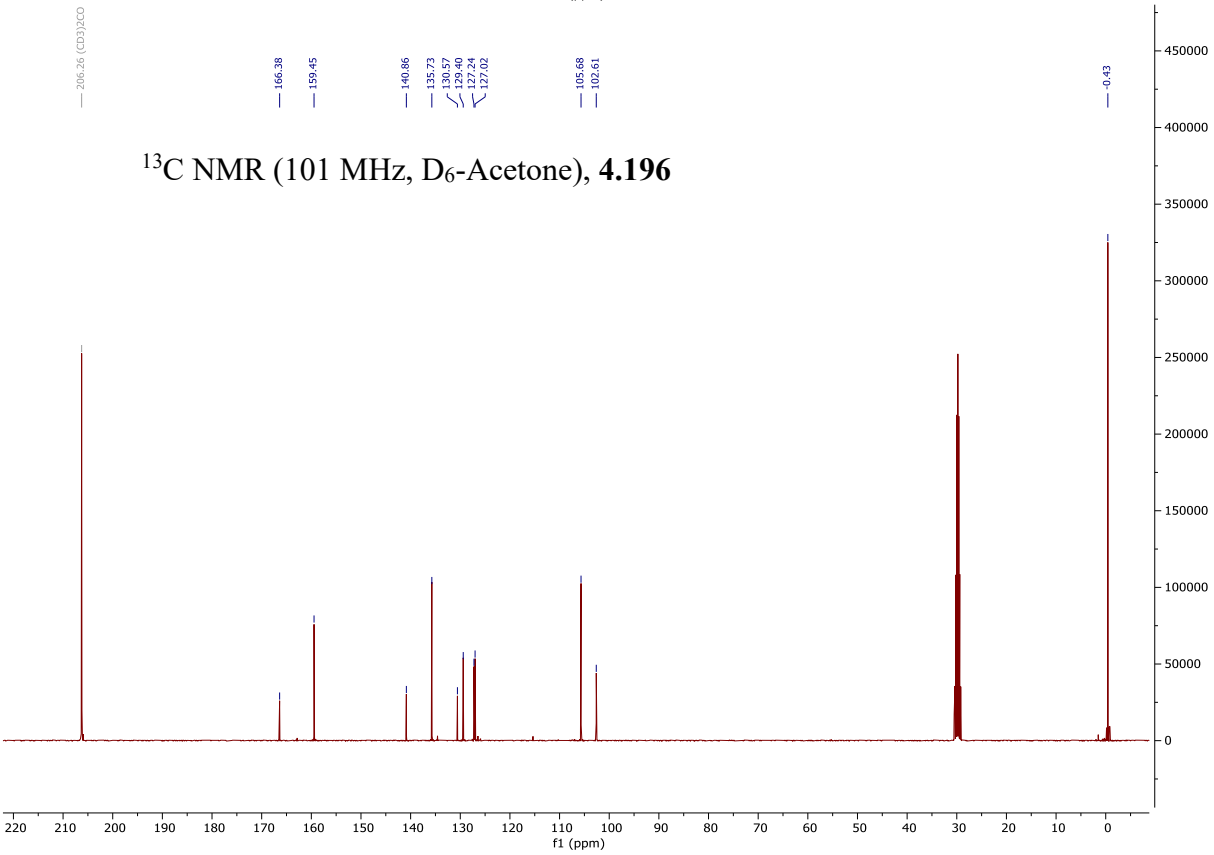
(4.196) (E)-5-(4-hydroxy-3,5-bis(trimethylsilyl)styryl)benzene-1,3-diol

In a 250 mL RBF was added starting material (2.6 g, 3.8 mmol, 1 equiv), THF (76 mL, 0.05 M), and TBAF (8.7 mL, 8.7 mmol, 2.3 equiv) at 0 °C. After 1 hour of reaction time mixture was quenched with sat. $NaHCO_3$ (aq) (80 mL) and extracted with ether (3 x 80 mL). The organics were dried with brine (80 mL) and $MgSO_4$. The crude organic residue was subjected to column chromatography SiO_2 (0-50% ethyl acetate in hexanes) to afford the product as a tan foam (1.38 g, 98%).

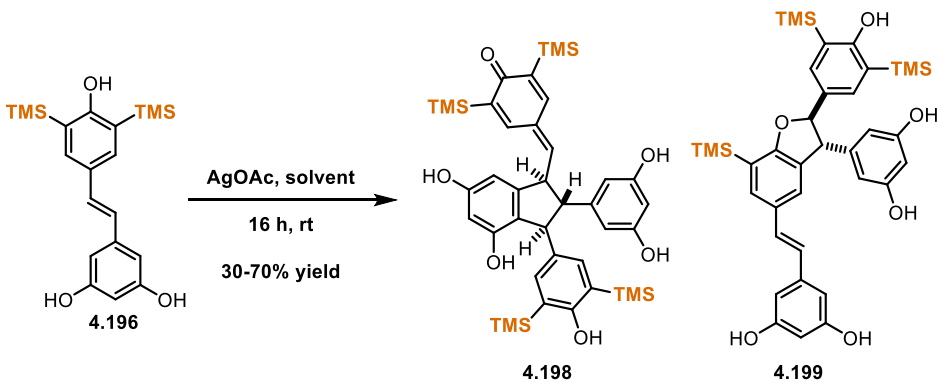
^{1}H NMR (400 MHz, D_6-Acetone), **4.196**	δ = 8.14 (s, 2H), 7.59 (s, 2H), 7.10 (d, J=16.3, 1H), 6.93 (d, J=16.3, 1H), 6.57 (d, J=2.2, 2H), 6.44 (s, 1H), 6.29 (t, J=2.2, 1H), 0.35 (s, 18H).
^{13}C NMR (101 MHz, D_6-Acetone), **4.196**	δ = 166.4, 159.5, 140.9, 135.7, 130.6, 129.4, 127.2, 127.0, 105.7, 102.6, -0.4.



^{1}H NMR (400 MHz, D_6-Acetone), **4.196**



^{13}C NMR (101 MHz, D_6-Acetone), **4.196**



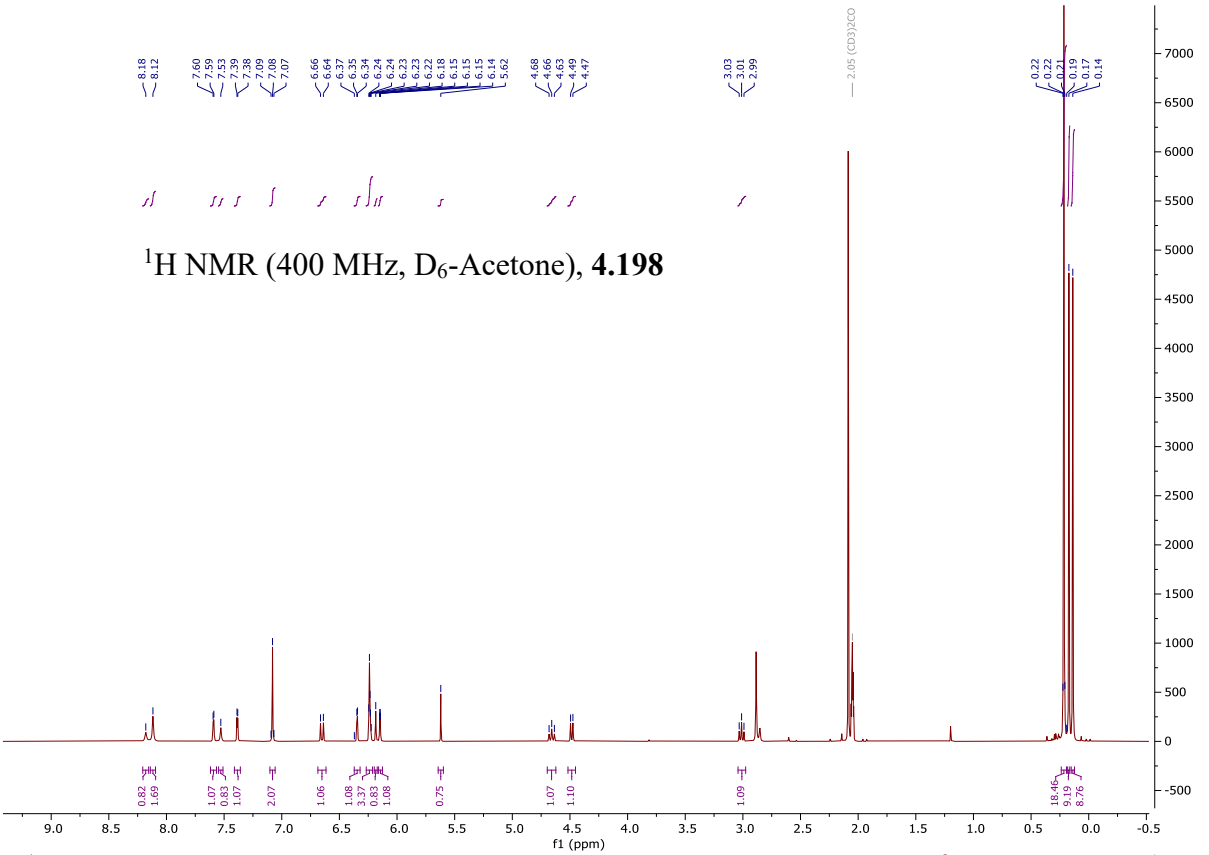
(4.198) 4-(((1S,2S,3S)-2-(3,5-dihydroxyphenyl)-4,6-dihydroxy-3-(4-hydroxy-3,5-bis(trimethylsilyl)phenyl)-2,3-dihydro-1H-inden-1-yl)methylene)-2,6-bis(trimethylsilyl)cyclohexa-2,5-dien-1-one

Original procedure: To a 25 mL RBF was added starting material (260 mg, 0.69 mmol, 1 equiv), silver acetate (348 mg, 2.1 mmol, 3 equiv) and THF (14 mL, 0.05 M). After 16 hours of reaction time at room temperature the mixture was concentrated onto silica and purified via flash chromatography over SiO_2 (0%-80% EtOAc in Hexanes) to yield the product as a yellow foam (145 mg, 56%). After approximately 6 months of using this procedure, the yields started suffering due to low conversion from the BQM intermediate to the product. To remedy the reproducibility challenges a new procedure was optimized.

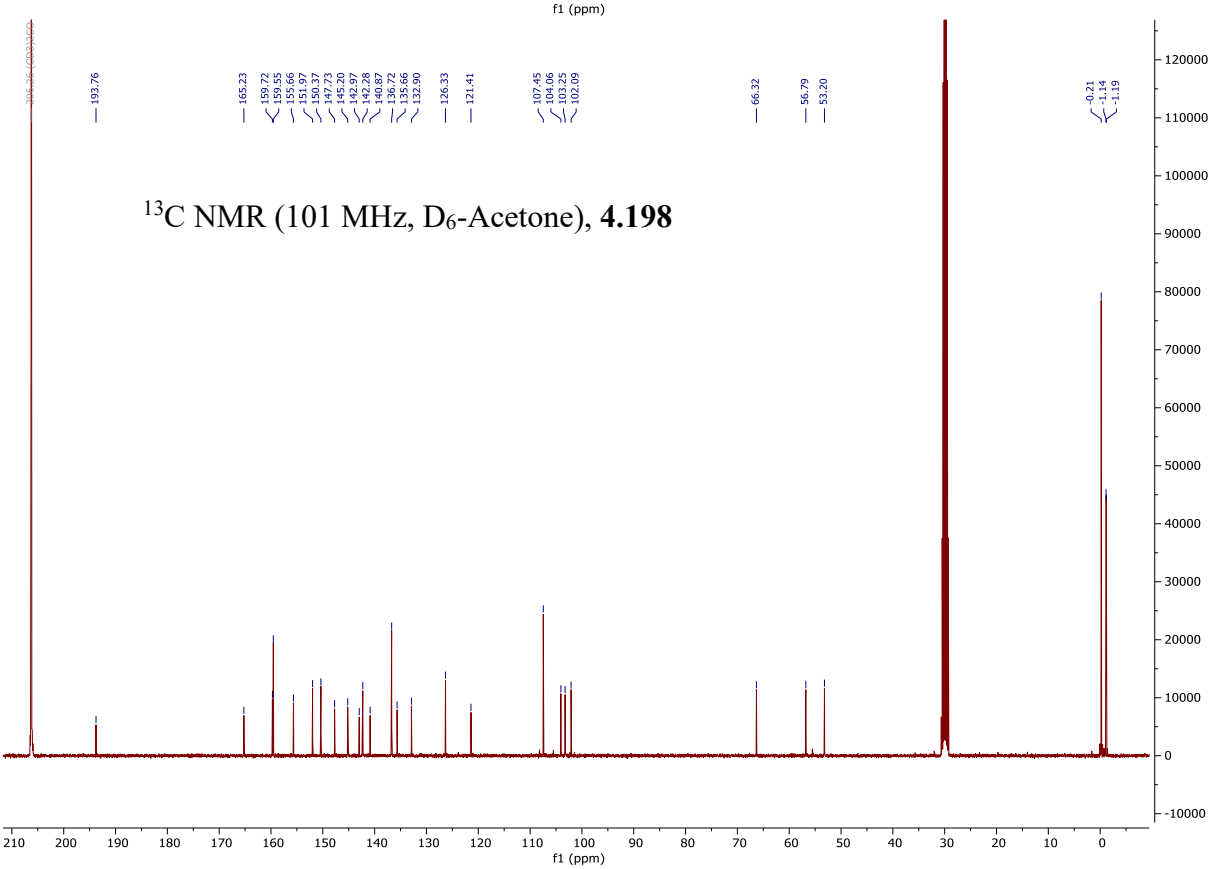
New optimized procedure: To a 100 mL RBF was added starting material (1.4 g, 3.7 mmol, 1 equiv), silver acetate (1.85 g, 11.1 mmol, 3 equiv), THF (74 mL, 0.05 M), and deionized water (6.67 mL, 370 mmol, 100 eq). After 16 hours of reaction time at room temperature the mixture was diluted with Sat. $NaHCO_3$ (aq) (200 mL) and Sat. $Na_2S_2O_3$ (aq) (200 mL). The aqueous was extracted with DCM (4 x 150 mL) and concentrated at 25 °C via rotavapor evaporation. The viscous red crude was dissolved in DCM for wet load for flash chromatography over SiO_2 (0%-60% Acetone in DCM) to yield the product as a yellow foam (717 mg, 58%). The column fractions were also concentrated at 25 °C. The yield of dihydrobenzofuran varied from 10-25% depending on the individual conditions.

TLC (DCM/Acetone, 95:5), RF:	0.44 (UV, potassium permanganate)
^{1}H NMR (400 MHz, D_6-Acetone), **4.198**	δ = 8.18 (s, 1H), 8.12 (s, 2H), 7.59 (d, J=2.6, 1H), 7.53 (s, 1H), 7.38 (d, J=2.6, 1H), 7.08 (s, 2H), 6.65 (d, J=10.0, 1H), 6.35 (d, J=2.1, 1H), 6.24 (q, J=1.9, 3H), 6.18 (s, 1H), 6.15 (dd, J=2.1, 1.0, 1H), 5.62 (s, 1H), 4.66 (t, J=9.2, 1H), 4.48 (d, J=8.1, 1H), 3.01 (t, J=8.3, 1H), 0.22 (s, 18H), 0.17 (s, 9H), 0.14 (s, 9H).
^{13}C NMR (101 MHz, D_6-Acetone), **4.198**	δ = 193.8, 165.2, 159.7, 159.5, 155.7, 152.0, 150.4, 147.7, 145.2, 143.0, 142.3, 140.9, 136.7, 135.7, 132.9, 126.3,

	121.4, 107.5, 104.1, 103.2, 102.1, 66.3, 56.8, 53.2, -0.2, -1.1, -1.2.
HRMS (ESI):	m/z calculated for $C_{40}H_{54}O_6Si_4$ ([M+H]+): 743.3070, found 743.3068
FTIR (neat) cm^{-1} :	ν˜= 3365 (br), 2954 (w), 2899 (w), 1598 (w), 1583 (w), 1246 (s), 1158 (w), 1135 (w), 834 (vs), 694 (w)

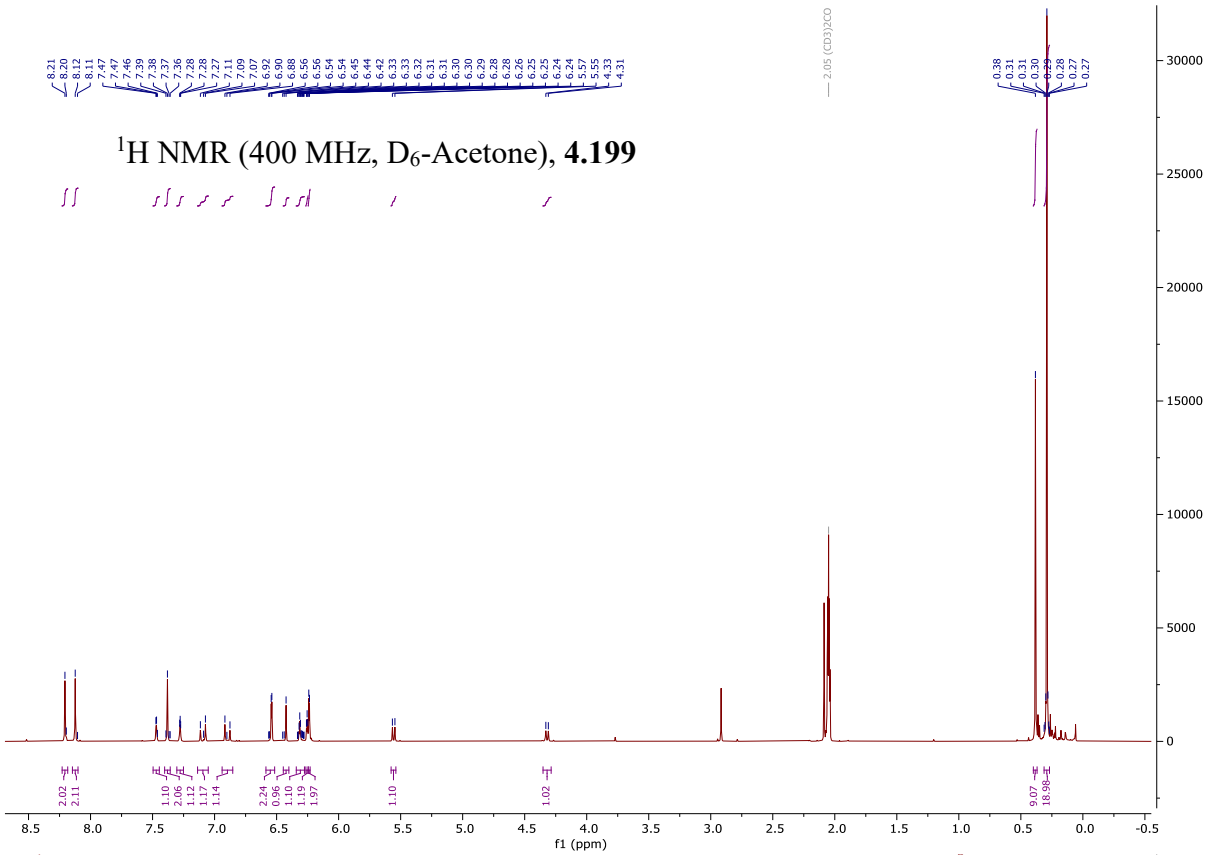


^{1}H NMR (400 MHz, D_6-Acetone), **4.198**

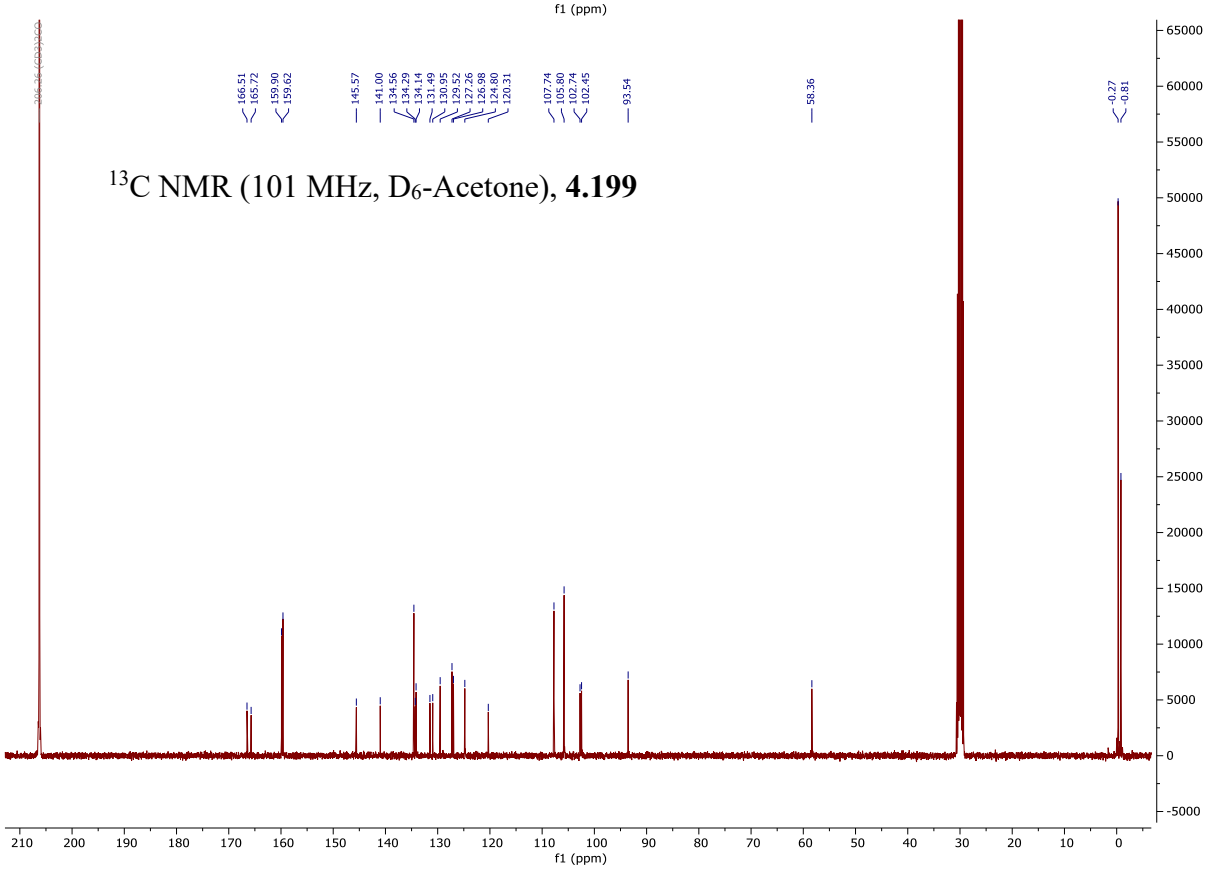


^{13}C NMR (101 MHz, D_6-Acetone), **4.198**

TLC (DCM/Acetone, 95:5), RF:	0.11 (UV, potassium permanganate)
^{1}H NMR (400 MHz, D_6-Acetone), **4.199**	δ = 8.21 (s, 2H), 8.12 (s, 2H), 7.47 (d, J=2.0, 1H), 7.38 (s, 2H), 7.28 (t, J=1.6, 1H), 7.09 (d, J=16.3, 1H), 6.90 (d, J=16.3, 1H), 6.54 (d, J=2.2, 2H), 6.42 (s, 1H), 6.31 (t, J=2.2, 1H), 6.25 (t, J=2.2, 1H), 6.24 (d, J=2.2, 2H), 5.56 (d, J=8.1, 1H), 4.32 (d, J=8.1, 1H), 0.38 (s, 9H), 0.29 (s, 18H).
^{13}C NMR (101 MHz, D_6-Acetone), **4.199**	δ = 166.5, 165.7, 159.9, 159.6, 145.6, 141.0, 134.6, 134.3, 134.1, 131.5, 130.9, 129.5, 127.3, 127.0, 124.8, 120.3, 107.7, 105.8, 102.7, 102.5, 93.5, 58.4, -0.3, -0.8.
HRMS (ESI):	m/z calculated for $C_{37}H_{46}O_6Si_3$ ([M+H]+): 671.2675, found 671.2666
FTIR (neat) cm^{-1} :	$\tilde{\nu}$= 3365 (br), 2955 (w), 2898 (w), 1596 (m), 1400 (w), 1338 (w), 1308 (w), 1248 (m), 1159 (m), 838 (vs)

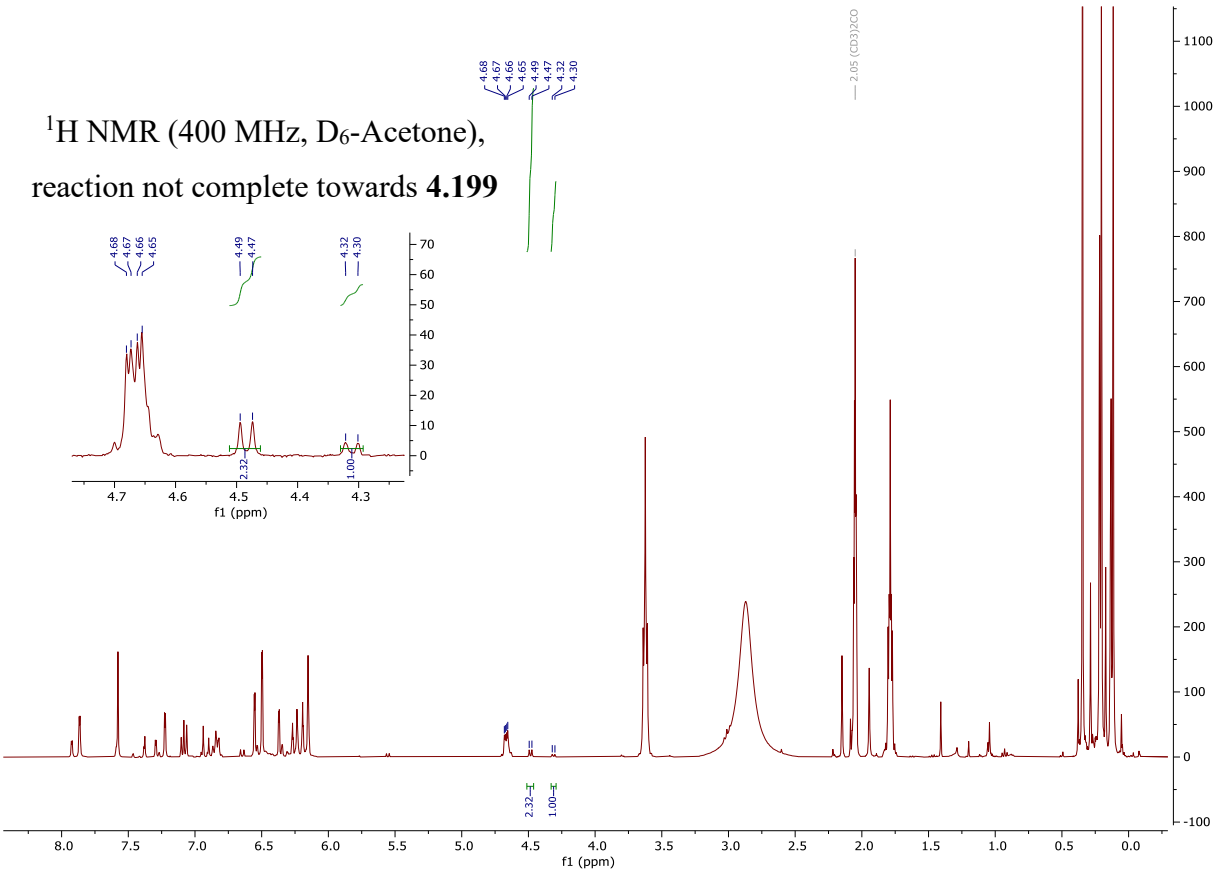


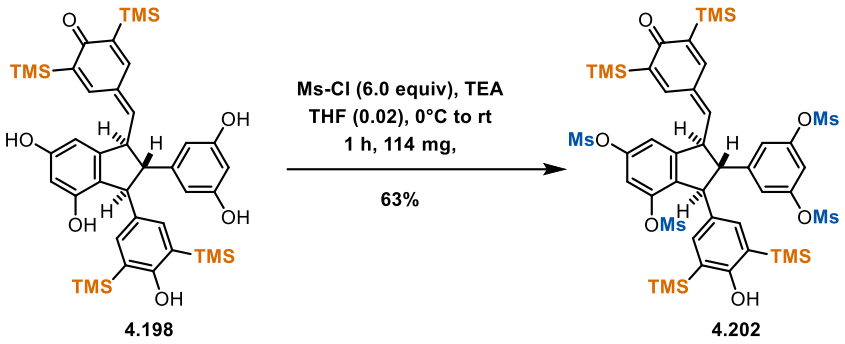
^{1}H NMR (400 MHz, D_6-Acetone), **4.199**



^{13}C NMR (101 MHz, D_6-Acetone), **4.199**

This NMR is of a reaction which is not complete yet, with mostly BQM intermediate (~4.65 ppm), with both indane (4.49 ppm) and rearranged DHB (4.30) present.

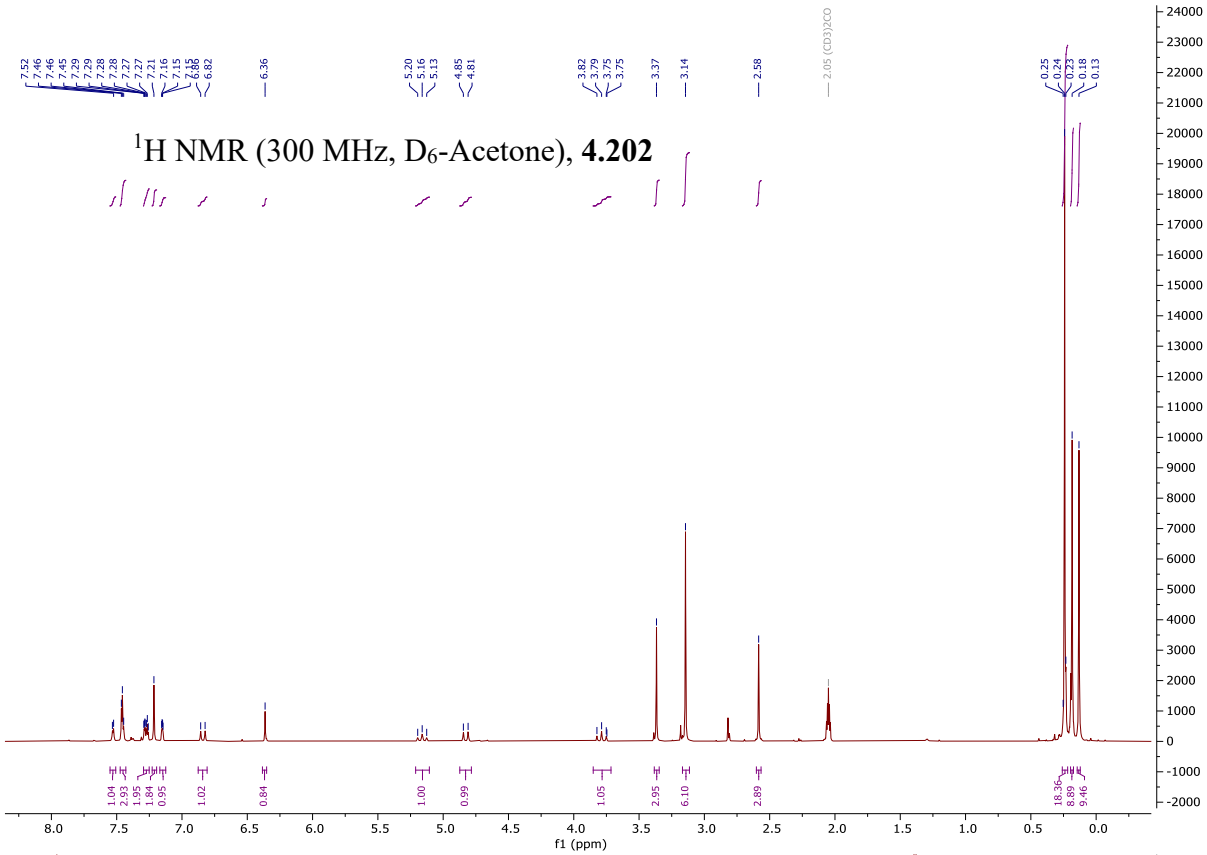




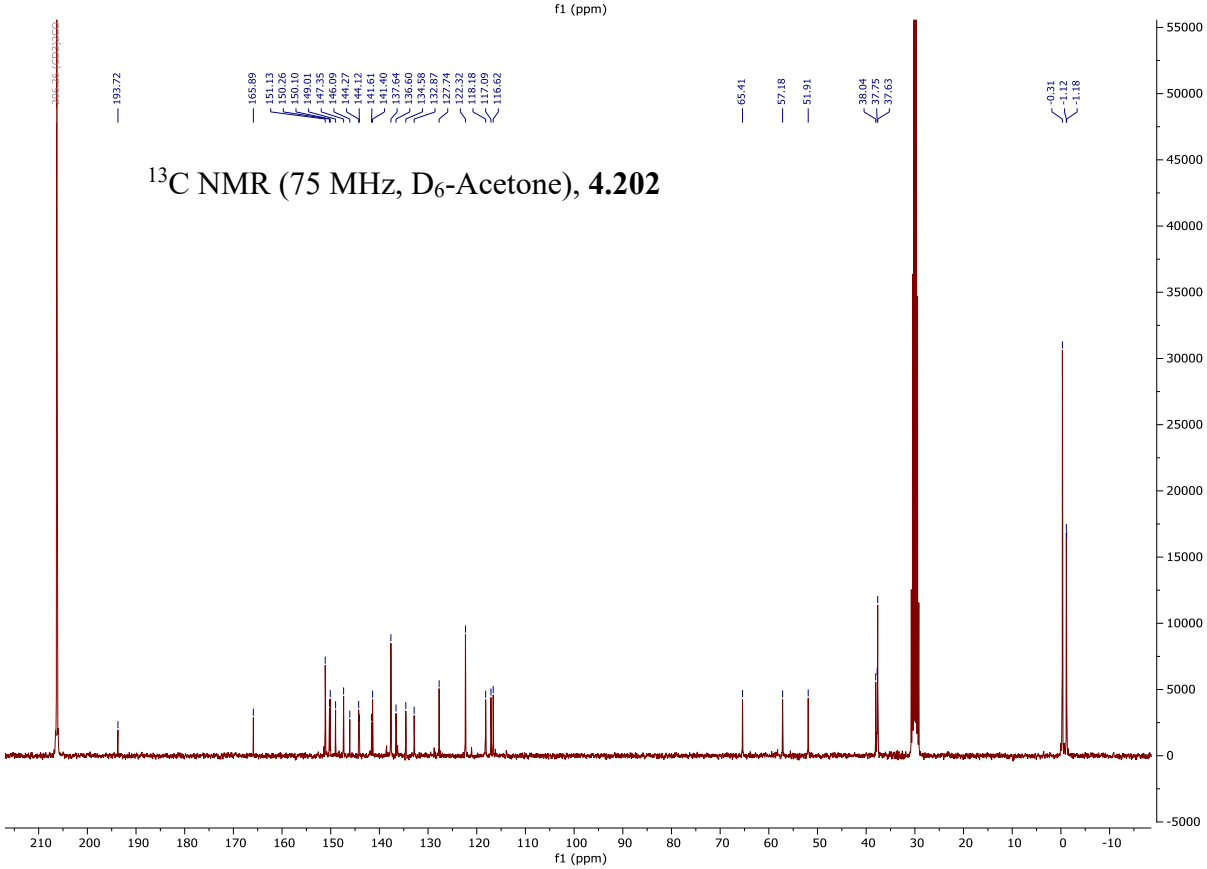
(4.202) (1S,2S,3S)-2-(3,5-bis((methylsulfonyl)oxy)phenyl)-3-(4-hydroxy-3,5-bis(trimethylsilyl)phenyl)-1-((4-oxo-3,5-bis(trimethylsilyl)cyclohexa-2,5-dien-1-ylidene)methyl)-2,3-dihydro-1H-indene-4,6-diyl dimethanesulfonate

To a 100 mL RBF was added starting material (900 mg, 1.2 mmol, 1 equiv), THF (61 mL, 0.02 M), TEA (1.0 mL, 7.3 mmol, 6 equiv), and Ms-Cl dropwise (566 µL, 7.3 mmol, 6 equiv) at 0 °C. After 1 hour of reaction time the mixture was diluted with Sat. $NaHCO_3$ (aq) (100 mL) and ether (100 mL). The aqueous was extracted with additional ether (2 x 50 mL) and the combined organic extracts were dried with brine and $MgSO_4$. The crude residue was purified via flash chromatography over SiO_2 (0%-40% EtOAc in Hex) to yield the product as a white foam (810 mg, 63%).

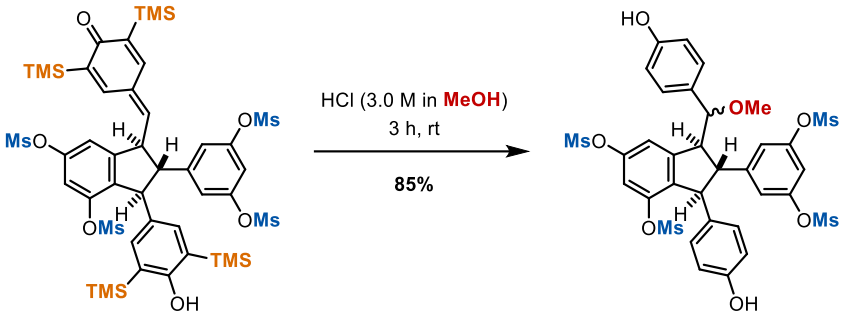
TLC (Hexanes/EtOAc, 70:30), RF:	0.17 (UV, potassium permanganate)
^{1}H NMR (300 MHz, D_6-Acetone), **4.202**	δ = 7.53 (d, J=2.7, 1H), 7.46 (t, J=2.6, 3H), 7.29 – 7.25 (m, 2H), 7.21 (s, 2H), 7.15 (dd, J=2.1, 1.1, 1H), 6.84 (d, J=10.2, 1H), 6.36 (s, 1H), 5.16 (t, J=10.3, 1H), 4.83 (d, J=10.9, 1H), 3.79 (t, J=10.7, 1H), 3.37 (s, 3H), 3.14 (s, 6H), 2.58 (s, 3H), 0.24 (s, 18H), 0.18 (s, 9H), 0.13 (s, 9H).
^{13}C NMR (75 MHz, D_6-Acetone), **4.202**	δ = 193.7, 165.9, 151.1, 150.3, 150.1, 149.0, 147.4, 146.1, 144.3, 144.1, 141.6, 141.4, 137.6, 136.6, 134.6, 132.9, 127.7, 122.3, 118.2, 117.1, 116.6, 65.4, 57.2, 51.9, 38.0, 37.7, 37.6, -0.3, -1.1, -1.2.
HRMS (ESI):	m/z calculated for $C_{44}H_{62}O_{14}S_4Si_4$ ([M+H]+): 1055.2172, found 1055.2159
FTIR (neat) cm^{-1} :	ν̃= 3603 (br), 3027 (w), 2954 (w), 1591 (w), 1403 (w), 1370 (s), 1332 (w), 1247 (m), 1182 (vs), 1110 (m), 994 (w), 962 (s), 839 (vs), 797 (vs), 776 (w)



^{1}H NMR (300 MHz, D_6-Acetone), **4.202**



^{13}C NMR (75 MHz, D_6-Acetone), **4.202**



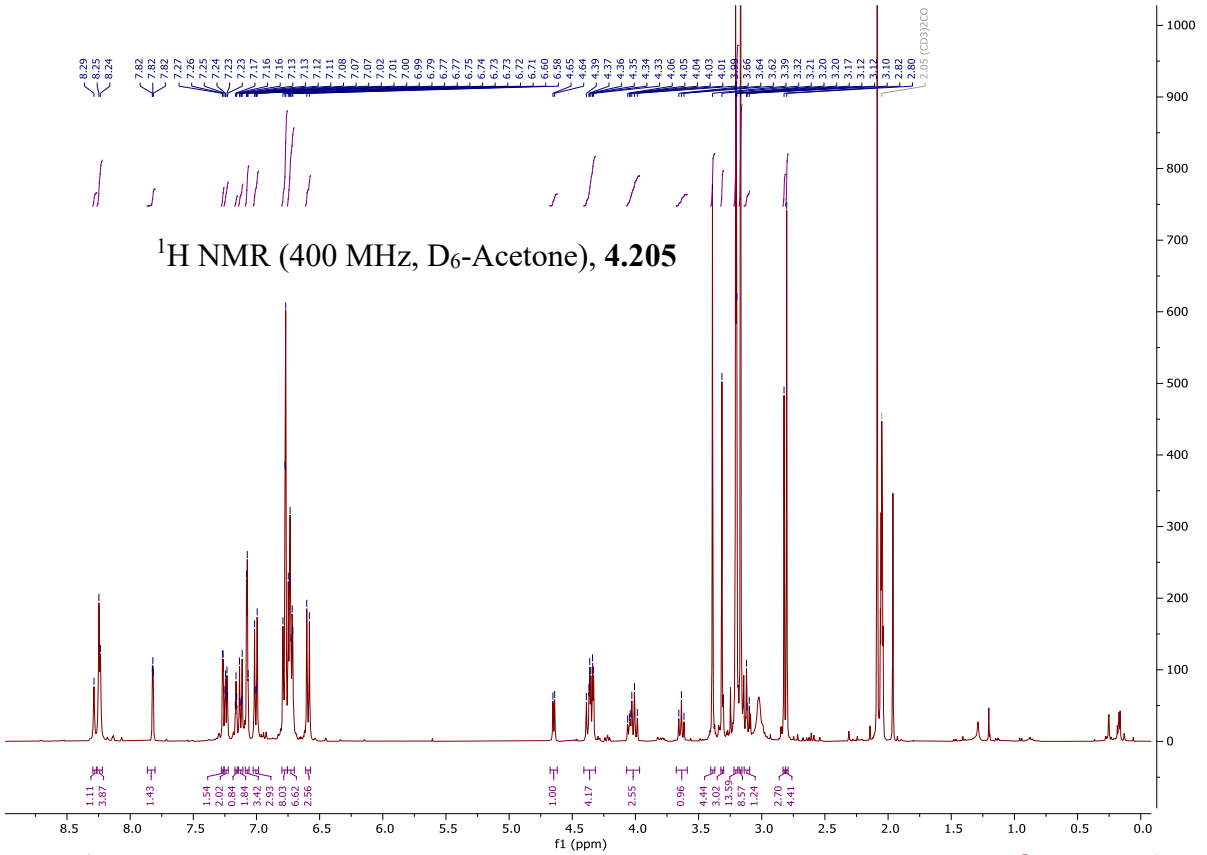
4.202 **4.205**
1:1 dr

(4.205) (1S,2R,3S)-2-(3,5-bis((methylsulfonyl)oxy)phenyl)-3-(4-hydroxyphenyl)-1-((4-hydroxyphenyl)(methoxy)methyl)-2,3-dihydro-1H-indene-4,6-diyl dimethanesulfonate

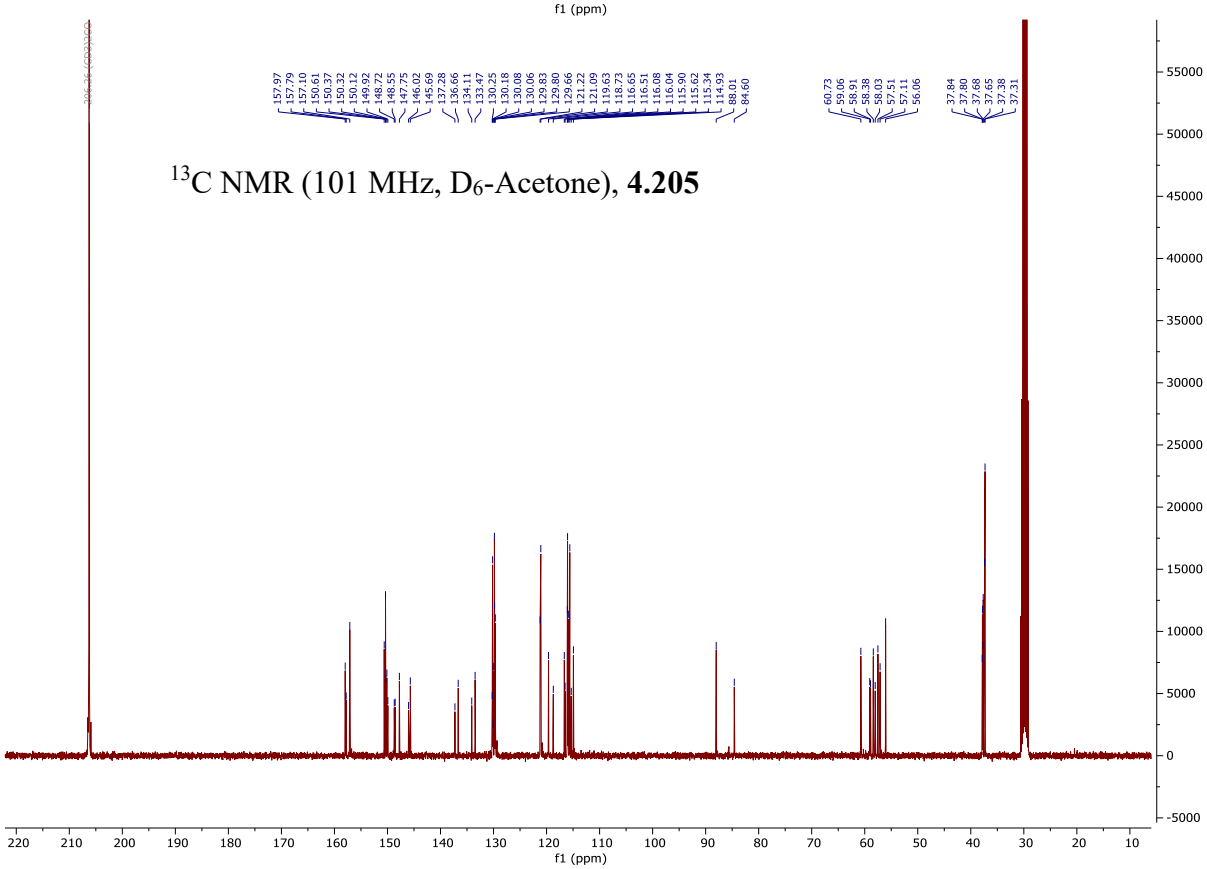
To a 2-dram vial was added starting material (100 mg, 95 µmol, 1 equiv) and 3 M HCl in MeOH (1.6 mL, 4.7 mmol, 50 equiv). After 3 hours of reaction time the mixture was diluted with Sat. $NaHCO_3$ (aq) (10 mL) and ether (10 mL). The aqueous was extracted with additional ether (2 x 5 mL) and the combined organic extracts were dried with brine and $MgSO_4$. The crude residue was purified via flash chromatography over SiO_2 (0%-60% EtOAc in Hex) to yield the product as a white foam (64 mg, 85%) as a 1:1 mixture of diastereomers about methanol addition to quinone.

^{1}H NMR (400 MHz, D_6-Acetone), **4.205** δ = 8.29 (s, 1H), 8.24 (d, J=4.8, 4H), 7.86 – 7.80 (m, 1H), 7.27 (d, J=2.2, 2H), 7.26 – 7.22 (m, 2H), 7.16 (t, J=2.2, 1H), 7.14 – 7.11 (m, 2H), 7.08 (d, J=2.3, 3H), 7.03 – 6.98 (m, 3H), 6.80 – 6.76 (m, 8H), 6.73 (td, J=5.8, 2.9, 7H), 6.59 (d, J=8.4, 3H), 4.65 (d, J=5.5, 1H), 4.41 – 4.32 (m, 4H), 4.07 – 3.97 (m, 3H), 3.64 (t, J=8.2, 1H), 3.39 (s, 4H), 3.32 (s, 3H), 3.22 – 3.19 (m, 14H), 3.17 (s, 9H), 3.11 (d, J=8.8, 1H), 2.82 (s, 3H), 2.80 (s, 4H).

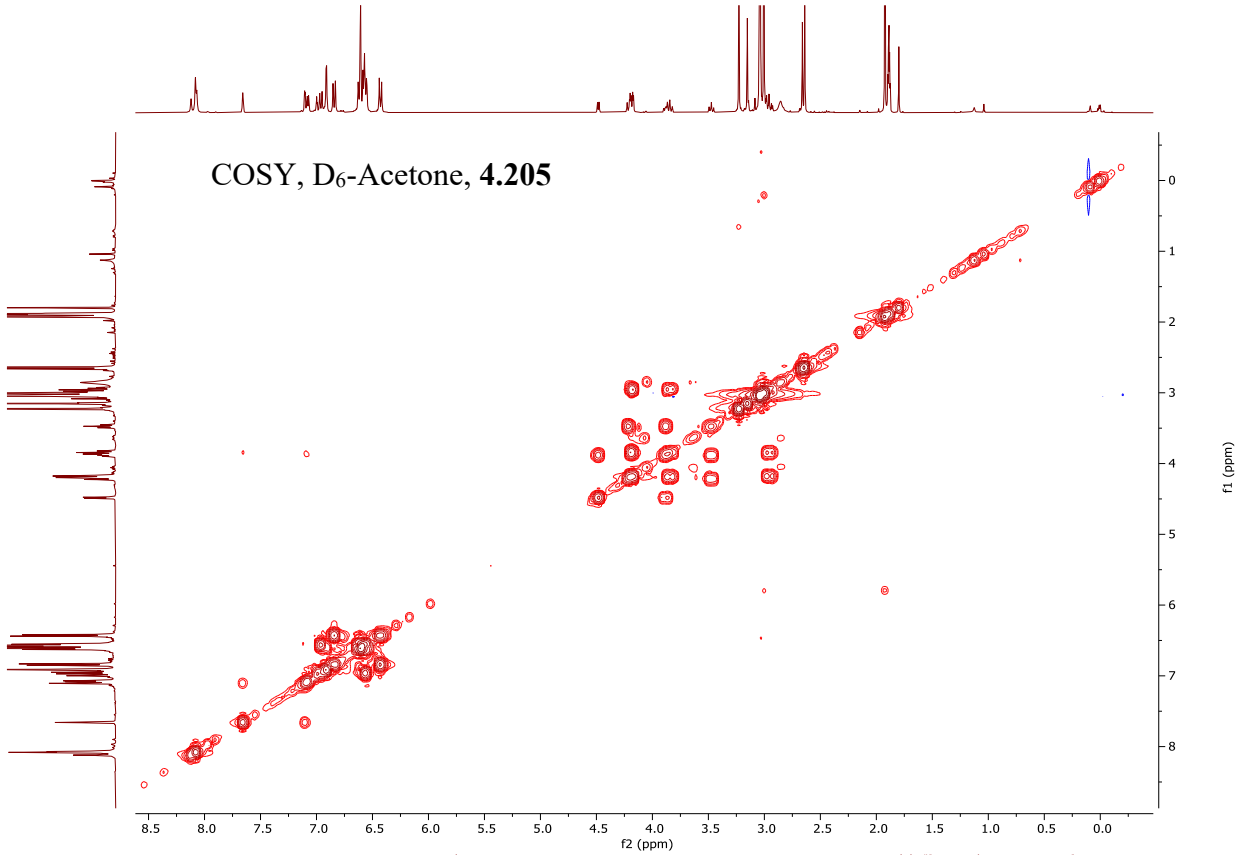
^{13}C NMR (101 MHz, D_6-Acetone), **4.205** δ = 158.0, 157.8, 157.1, 150.6, 150.4, 150.3, 150.1, 149.9, 148.7, 148.6, 147.7, 146.0, 145.7, 137.3, 136.7, 134.1, 133.5, 130.2, 130.2, 130.1, 130.1, 129.8, 129.8, 129.7, 121.2, 121.1, 119.6, 118.7, 116.7, 116.5, 116.1, 116.0, 115.9, 115.6, 115.3, 114.9, 88.0, 84.6, 60.7, 59.1, 58.9, 58.4, 58.0, 57.5, 57.1, 56.1, 37.8, 37.8, 37.7, 37.7, 37.4, 37.3.

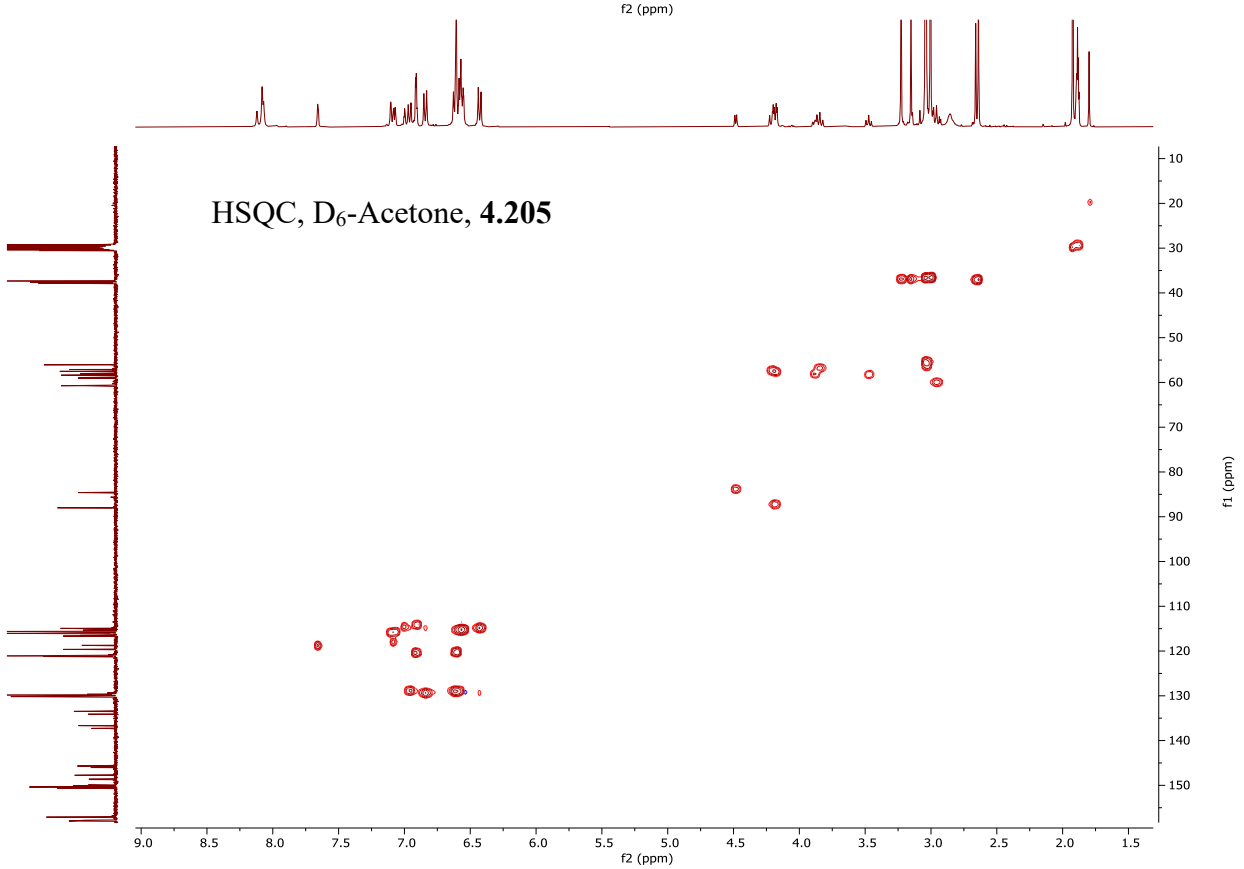


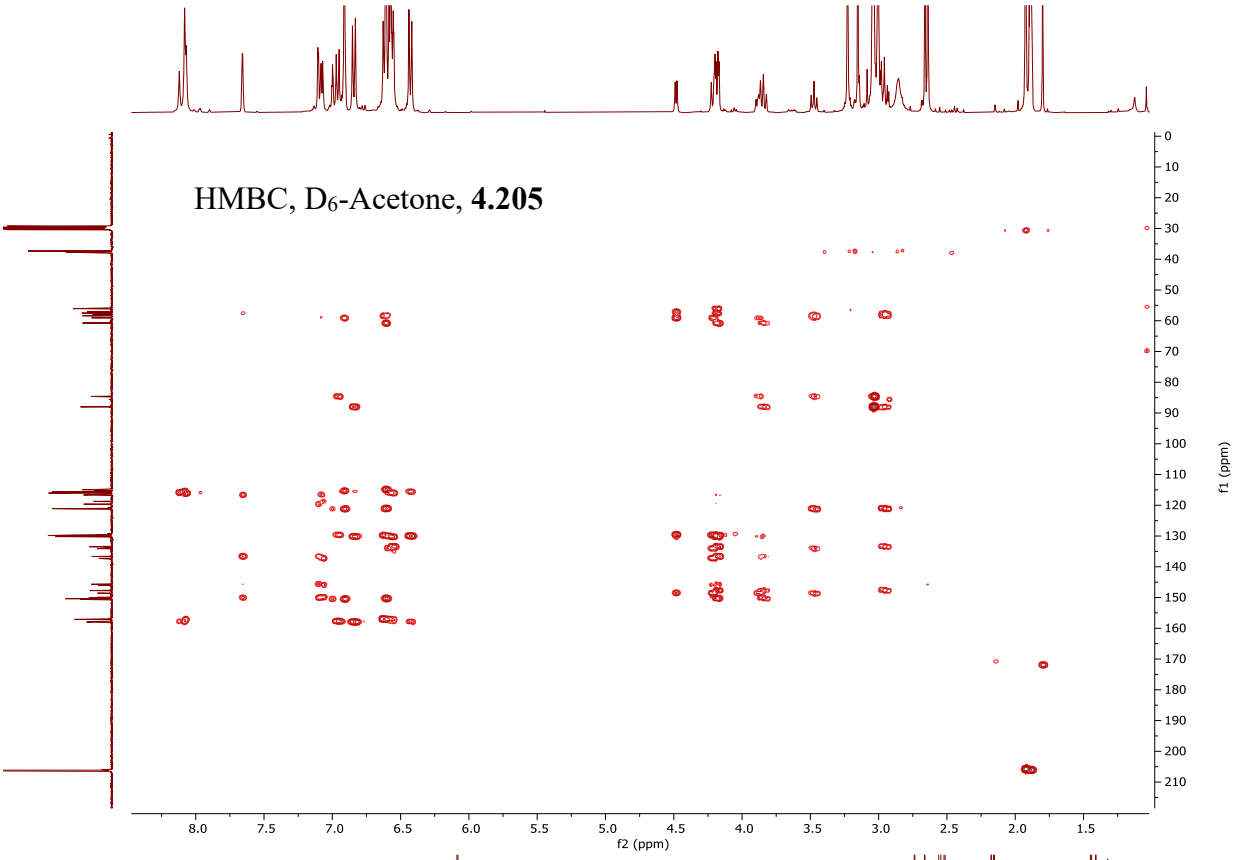
^{1}H NMR (400 MHz, D$_6$-Acetone), **4.205**

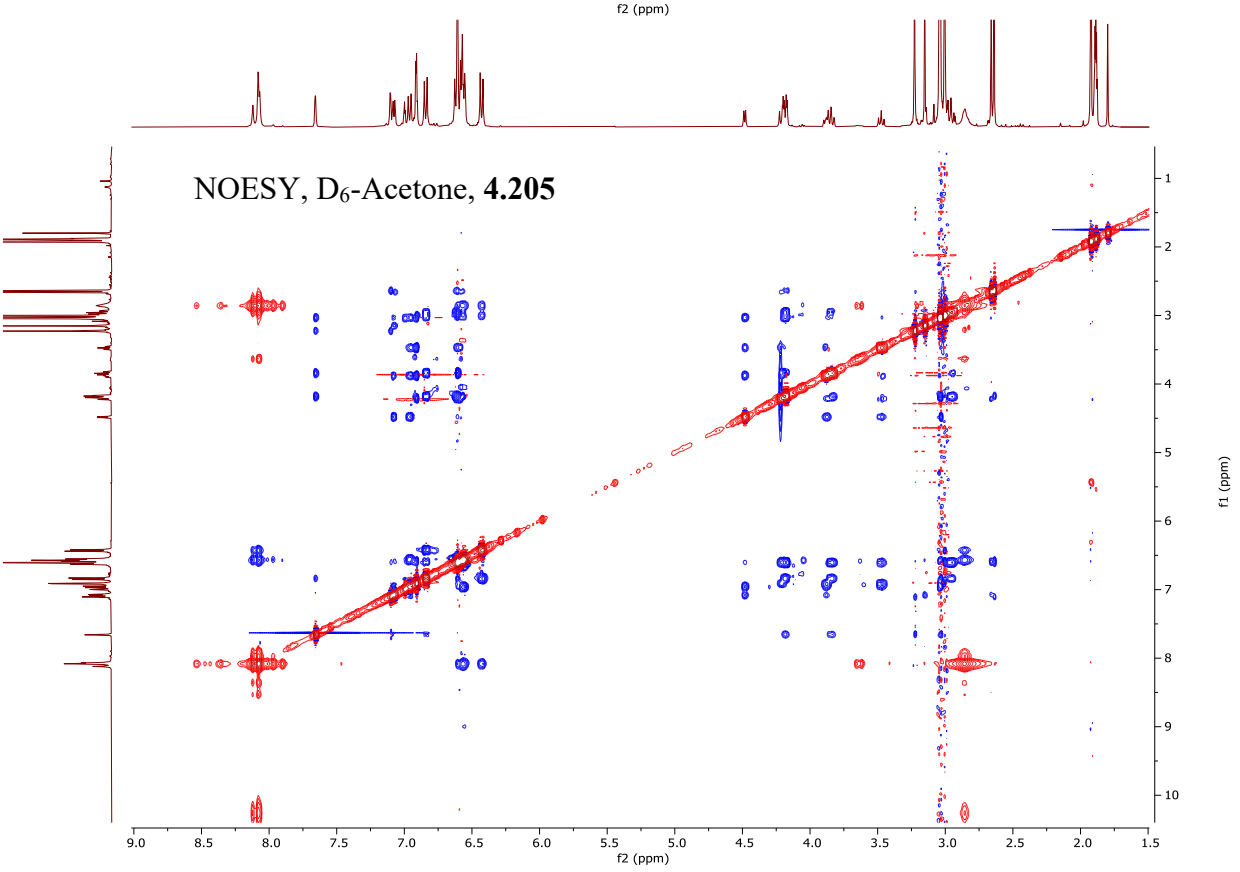


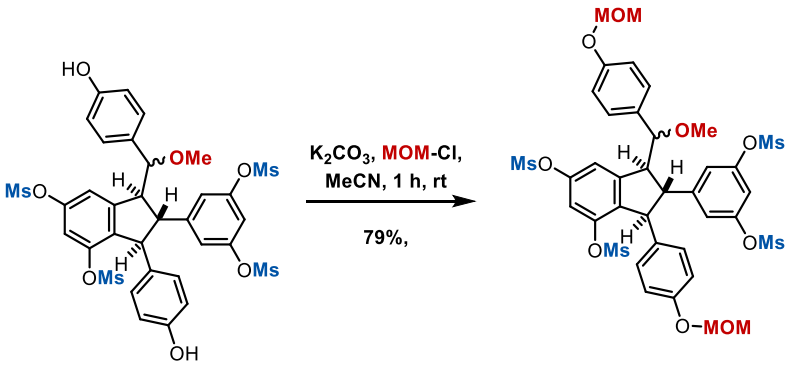
^{13}C NMR (101 MHz, D$_6$-Acetone), **4.205**


COSY, D6-Acetone, 4.205
f2 (ppm)
f1 (ppm)


HSQC, D6-Acetone, 4.205
f2 (ppm)
f1 (ppm)


HMBC, D6-Acetone, 4.205
f2 (ppm)
f1 (ppm)

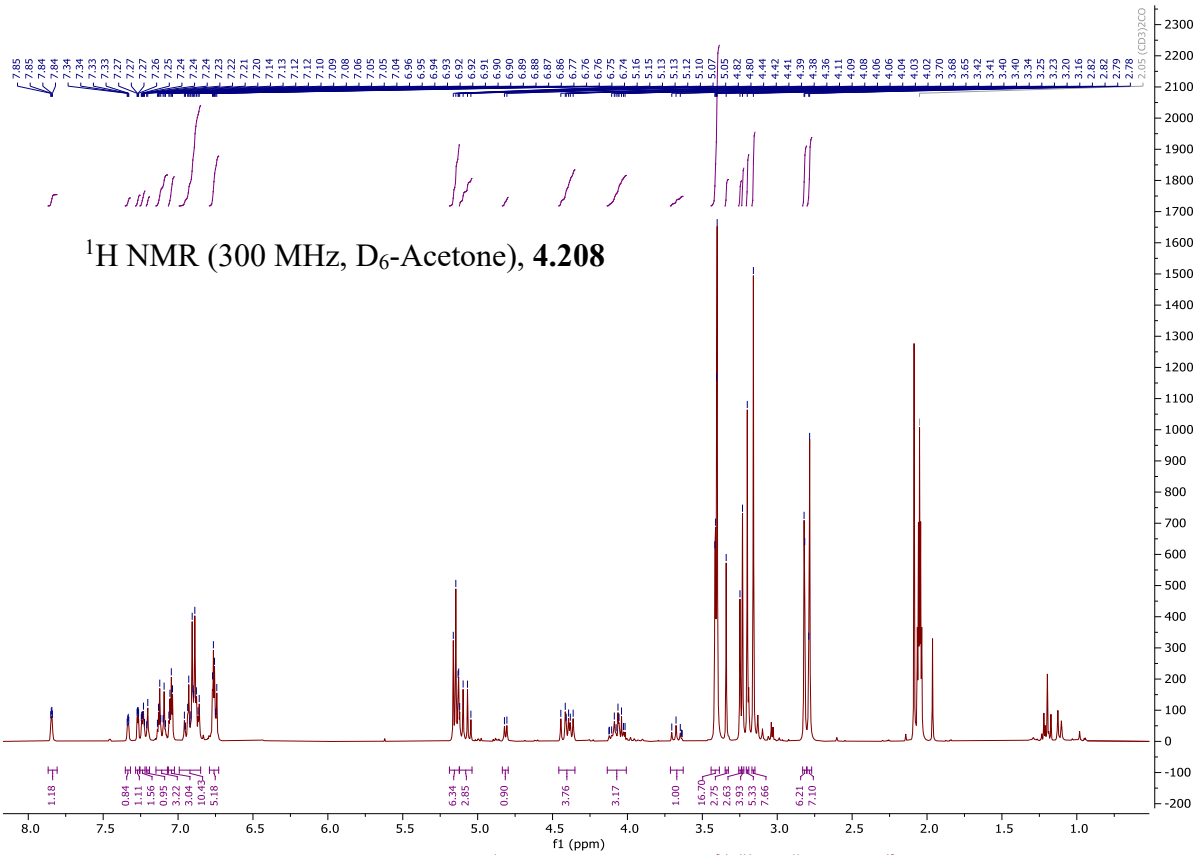

NOESY, D6-Acetone, 4.205
f2 (ppm)
f1 (ppm)



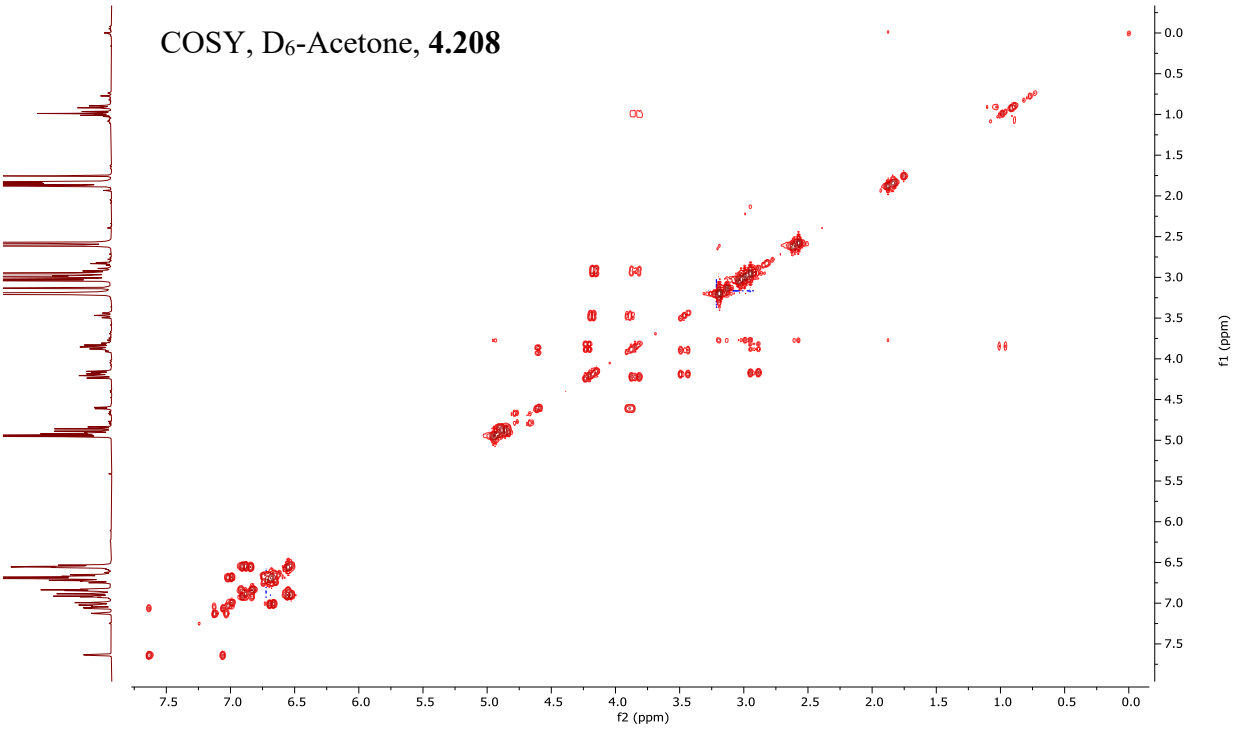
(4.208) (1S,2R,3S)-2-(3,5-bis((methylsulfonyl)oxy)phenyl)-1-(methoxy(4-(methoxymethoxy)phenyl)methyl)-3-(4-(methoxymethoxy)phenyl)-2,3-dihydro-1H-indene-4,6-diyl dimethanesulfonate

To a 25 mL RBF was added starting material (1.12 g, 1.4 mmol, 1 equiv), K_2CO_3 (1.2 g, 8.4 mmol, 6 equiv), MeCN (14 mL, 0.1 M), and MOM-Cl dropwise (639 µL, 8.4 mmol, 6 equiv). After 1 hour of reaction time the mixture was diluted with Sat. $NaHCO_3$ (aq) (20 mL) and ether (20 mL). The aqueous was extracted with additional ether (2 x 10 mL) and the combined organic extracts were dried with brine and $MgSO_4$. The crude residue was purified via flash chromatography over SiO_2 (0%-60% EtOAc in Hex) to yield the product as a white foam (980 mg, 79%) as a 1:1 mixture of diastereomers about methanol addition to quinone.

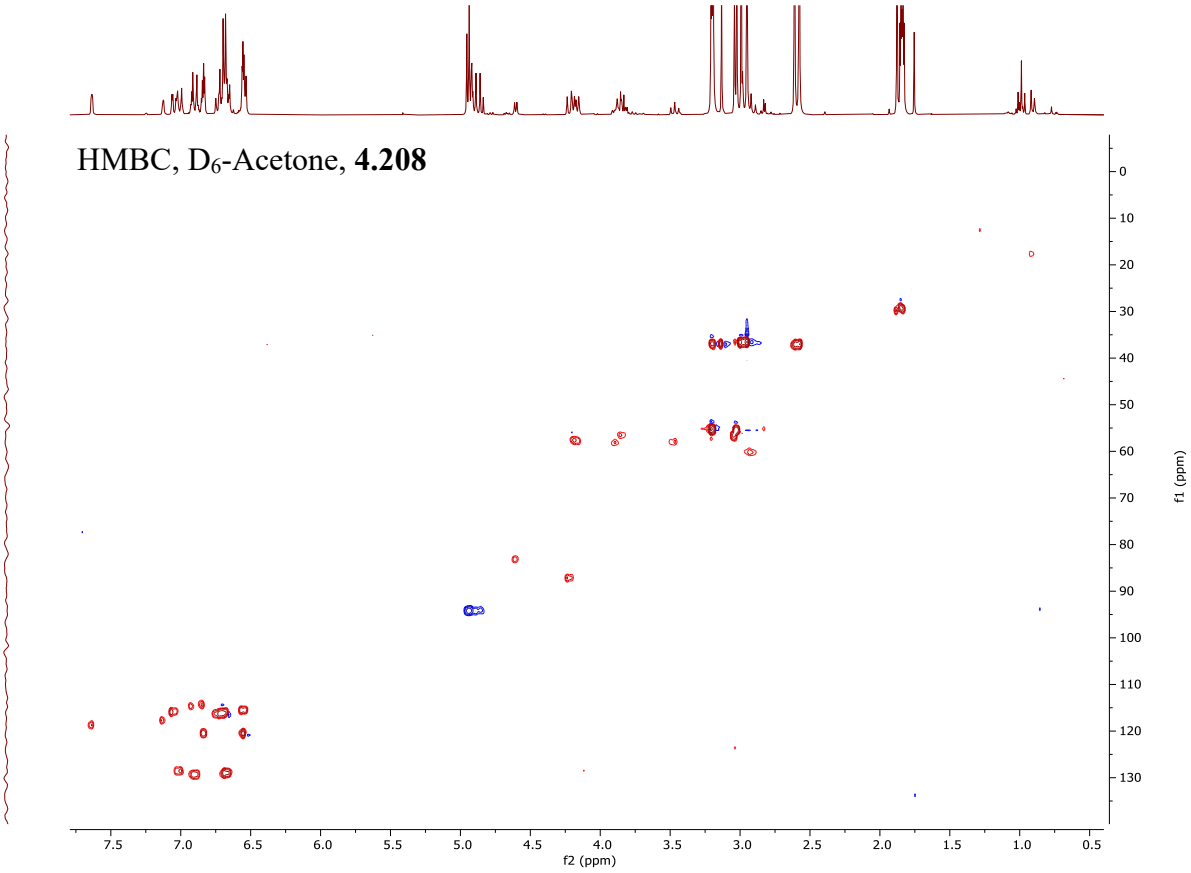
^{1}H NMR (300 MHz, D_6-Acetone), **4.208** δ = 7.84 (dd, J=2.2, 1.1, 1H), 7.33 (dd, J=2.2, 1.1, 1H), 7.27 (dd, J=2.2, 0.8, 1H), 7.24 (dt, J=4.3, 1.4, 2H), 7.21 (d, J=2.2, 1H), 7.15 – 7.07 (m, 3H), 7.06 – 7.02 (m, 3H), 6.99 – 6.85 (m, 10H), 6.79 – 6.73 (m, 5H), 5.15 (t, J=5.4, 6H), 5.12 – 5.04 (m, 3H), 4.81 (d, J=4.9, 1H), 4.46 – 4.35 (m, 4H), 4.13 – 4.01 (m, 3H), 3.68 (t, J=8.5, 1H), 3.44 – 3.39 (m, 17H), 3.34 (s, 3H), 3.25 (s, 3H), 3.23 (s, 4H), 3.20 (s, 5H), 3.16 (s, 8H), 2.82 (d, J=1.3, 6H), 2.79 (d, J=1.8, 7H.

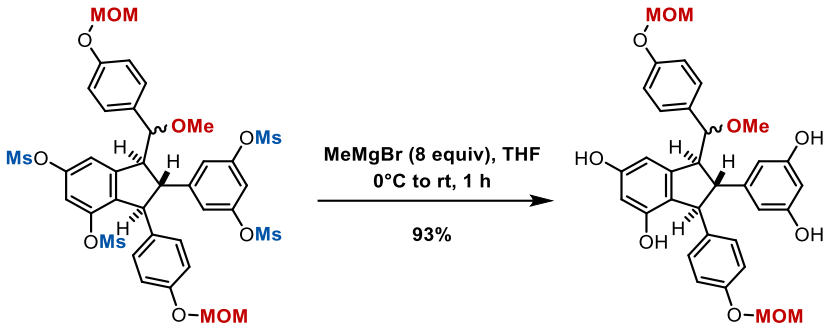


^{1}H NMR (300 MHz, D_6-Acetone), **4.208**



COSY, D_6-Acetone, **4.208**


HMBC, D6-Acetone, 4.208
f2 (ppm)
f1 (ppm)



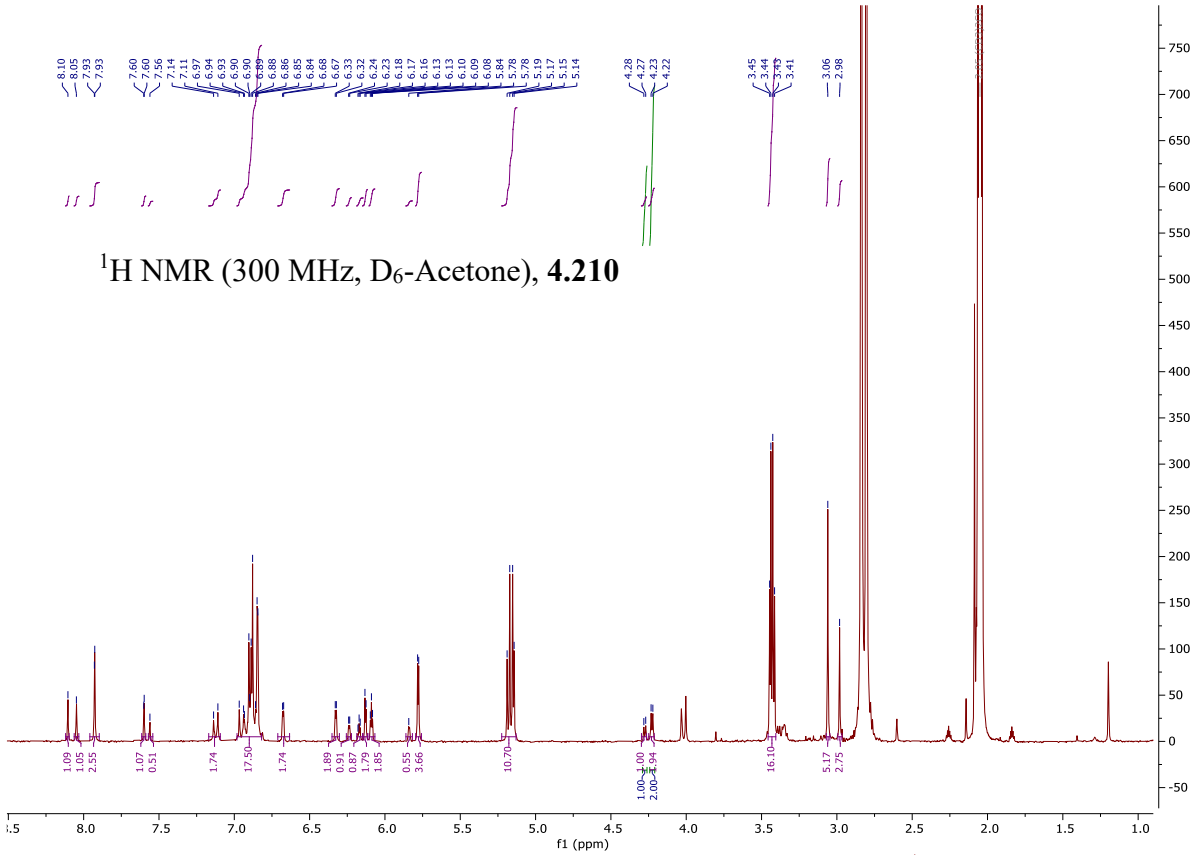
4.208
1:1 dr

4.210
2:1 dr

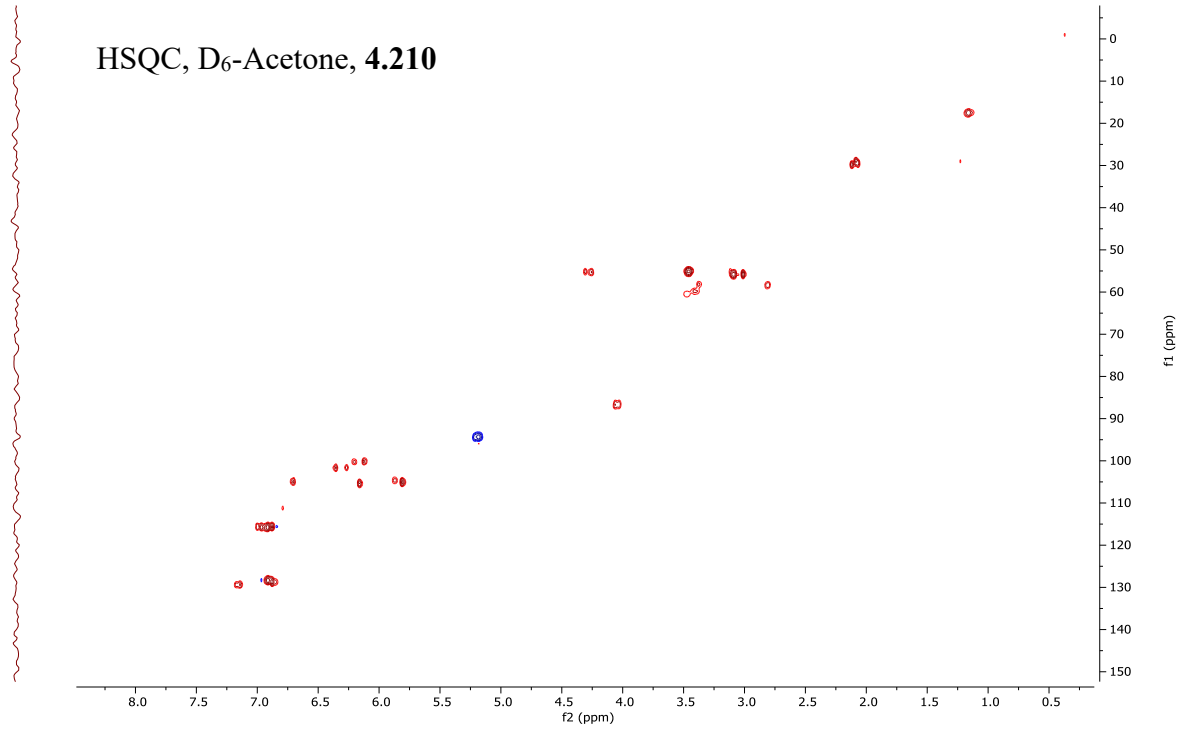
(4.210) (1S,2R,3S)-2-(3,5-dihydroxyphenyl)-1-(methoxy(4-(methoxymethoxy)phenyl)methyl)-3-(4-(methoxymethoxy)phenyl)-2,3-dihydro-1H-indene-4,6-diol

To a 25 mL RBF was added starting material (400 mg, 451 µmol, 1 equiv), THF (9 mL, 0.05 M), and MeMgBr (1.2 mL, 3.6 mmol, 8 eq, 3 M solution) dropwise at 0 °C. After 1 hour of reaction time the mixture was quenched with methanol (1 mL) with vigorous bubbling. The solution was diluted with Sat. $NaHCO_3$ (aq) (10 mL) and EtOAc (20 mL). The aqueous was extracted with additional ether (2 x 10 mL) and the combined organic extracts were dried with brine and $MgSO_4$. The crude residue was purified via flash chromatography over SiO_2 (0%-60% EtOAc in Hex) to yield the product as a white foam (240 mg, 93%) as a 2:1 mixture of diastereomers about methanol addition to quinone.

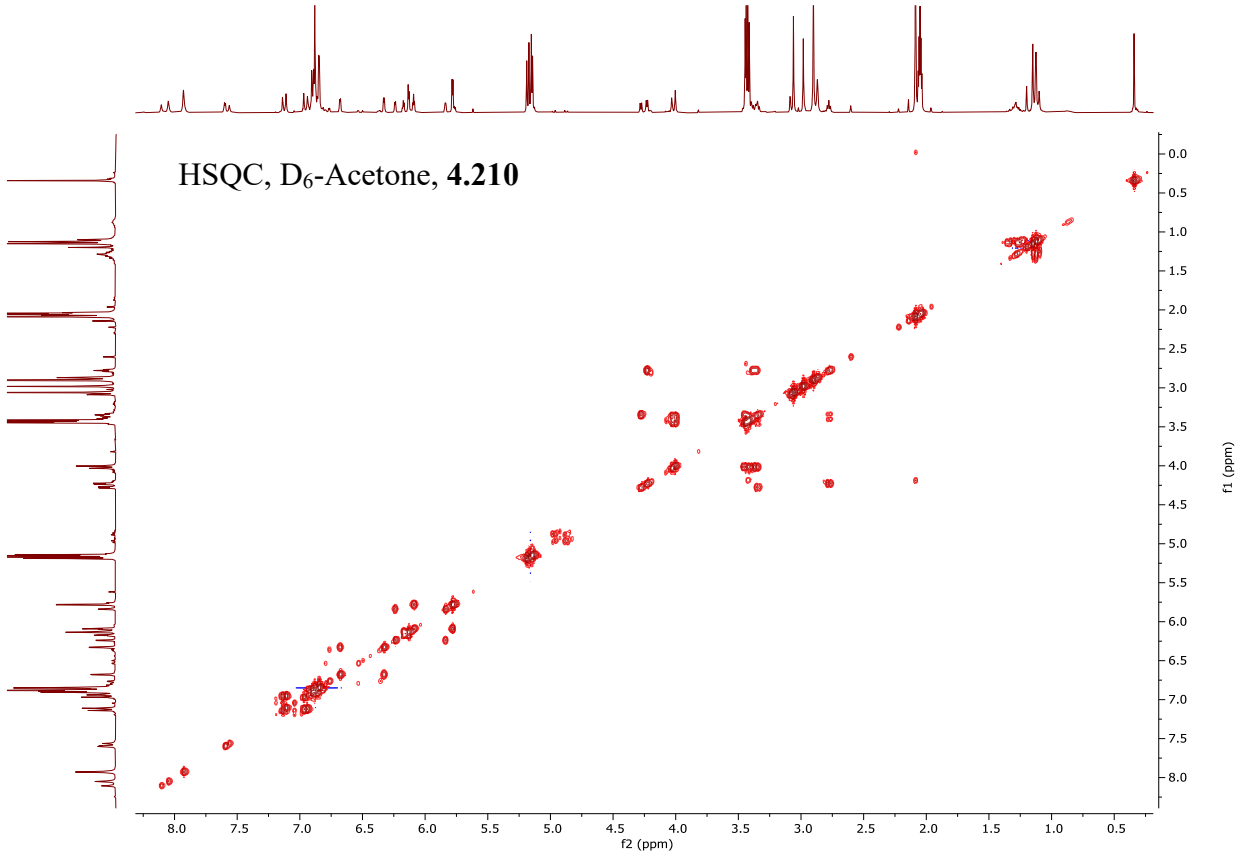
^{1}H NMR (300 MHz, D_6-Acetone), **4.210** δ = 8.10 (s, 1H), 8.05 (s, 1H), 7.93 (d, J=0.7, 3H), 7.60 (d, J=0.8, 1H), 7.56 (s, 1H), 7.12 (d, J=8.6, 2H), 6.98 – 6.82 (m, 18H), 6.68 (d, J=2.1, 2H), 6.33 (d, J=2.2, 2H), 6.24 (d, J=2.1, 1H), 6.17 (t, J=2.2, 1H), 6.13 (d, J=2.2, 2H), 6.09 (t, J=2.2, 2H), 5.84 (s, 1H), 5.78 (d, J=2.2, 4H), 5.22 – 5.13 (m, 11H), 4.28 (d, J=3.7, 1H), 4.23 (d, J=3.5, 2H), 3.46 – 3.41 (m, 16H), 3.06 (s, 5H), 2.98 (s, 3H).

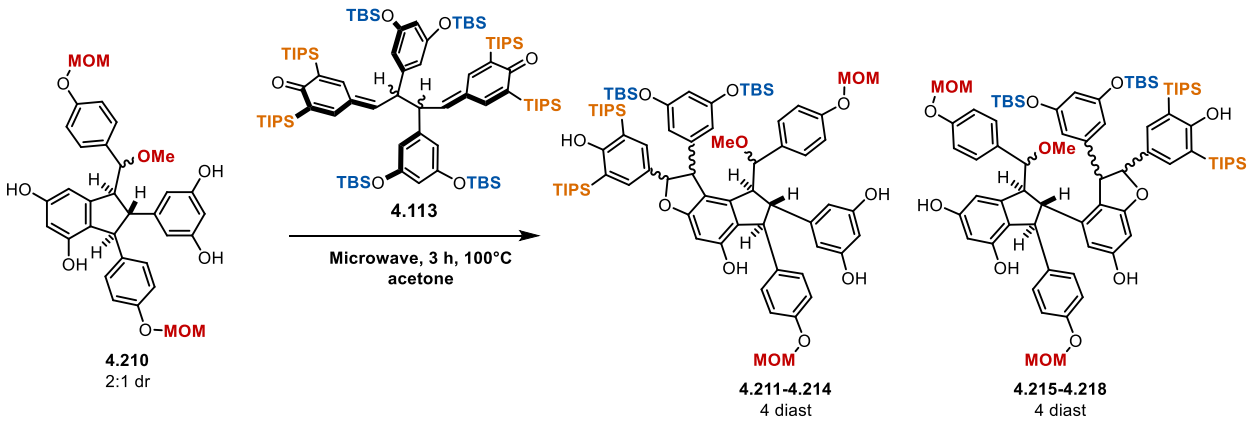


^{1}H NMR (300 MHz, D_6-Acetone), **4.210**



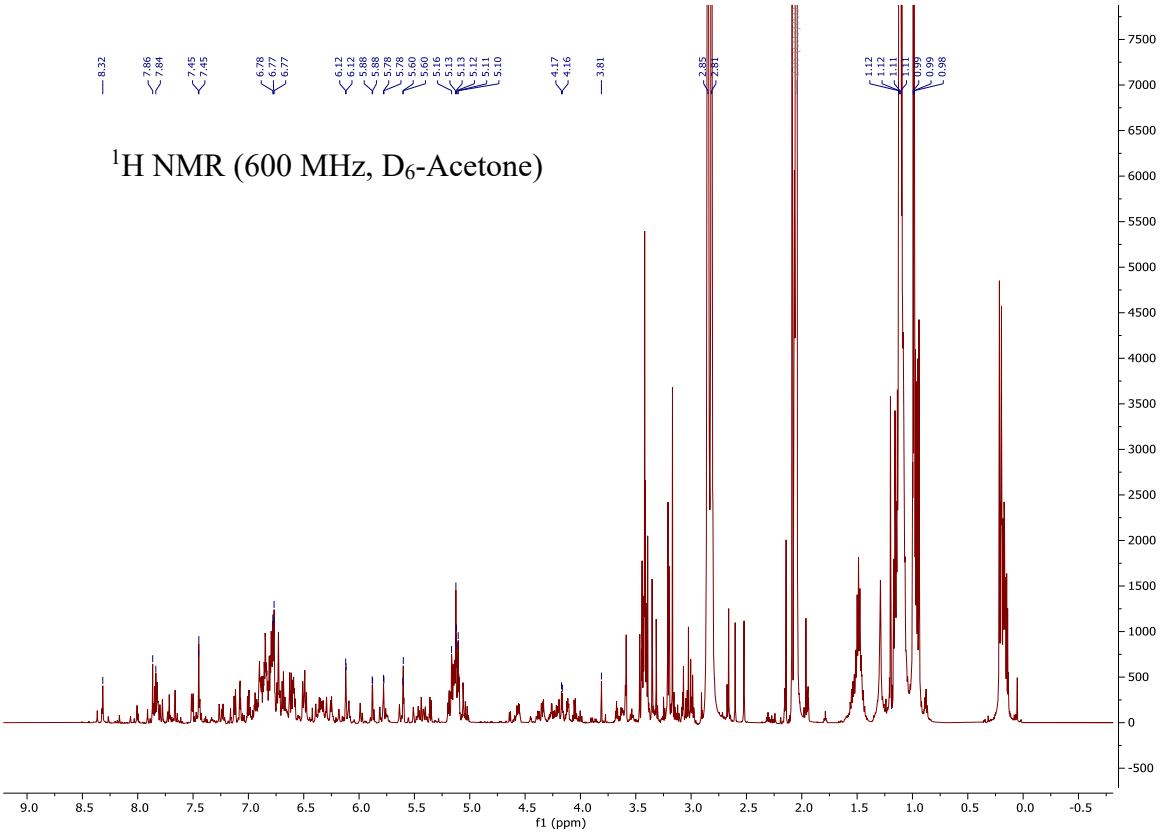
HSQC, D_6-Acetone, **4.210**

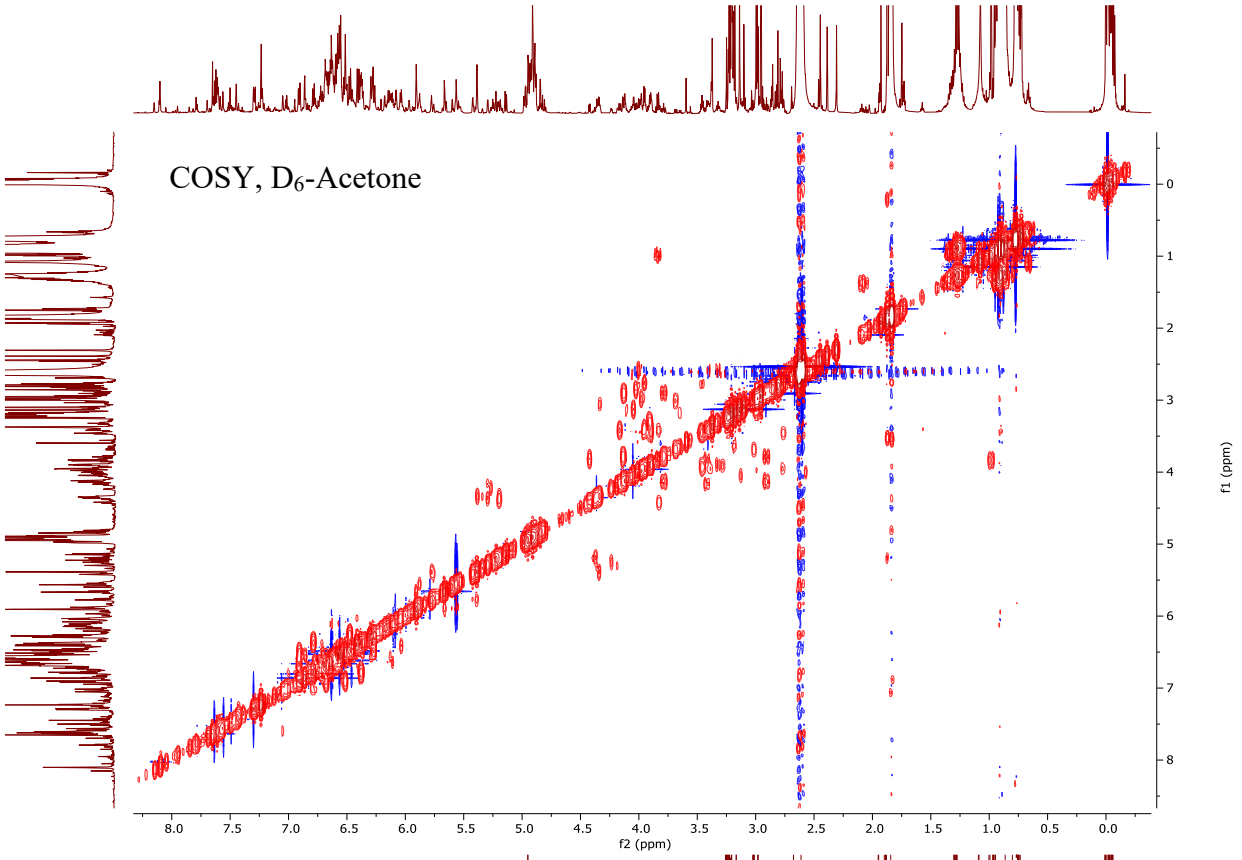

HSQC, D6-Acetone, 4.210
f2 (ppm)
f1 (ppm)

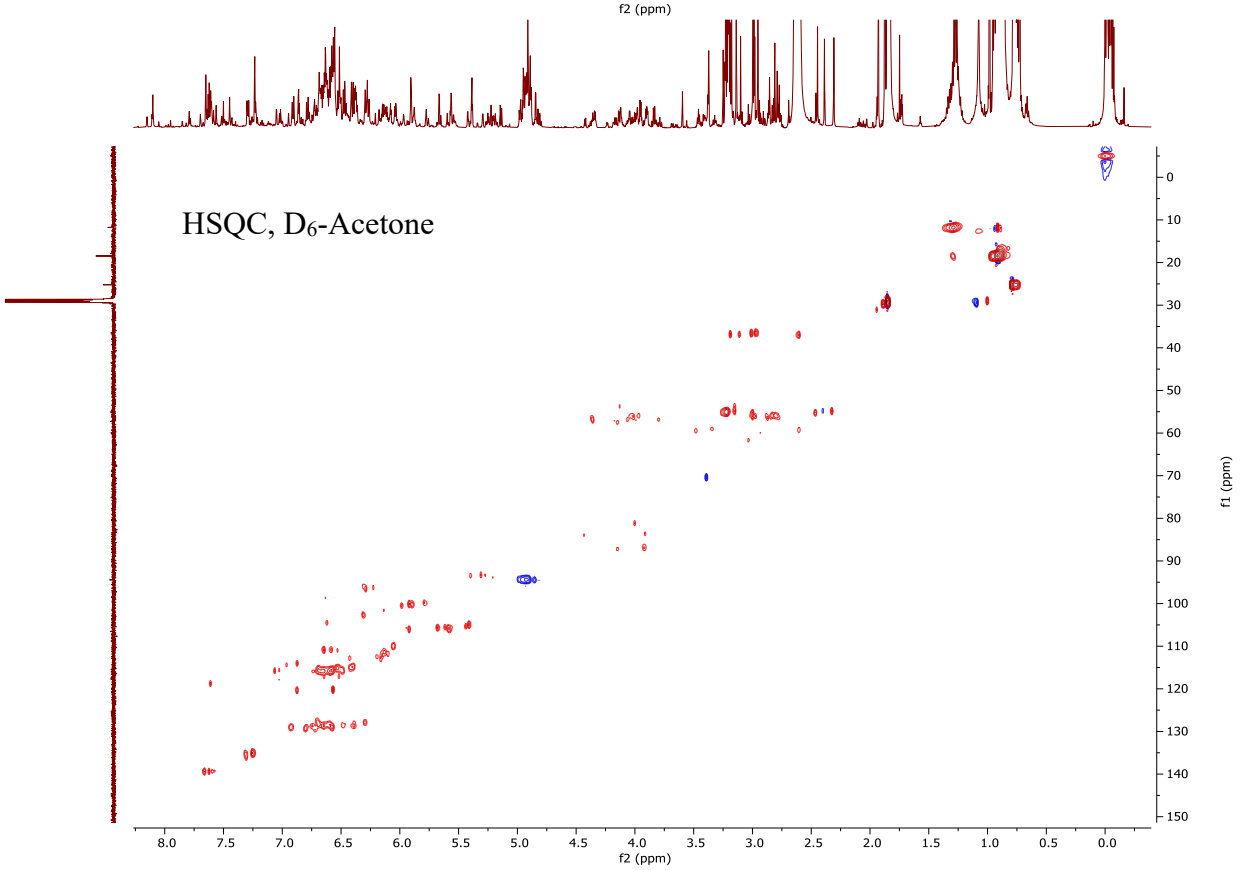


(4.211-4.218) 5-((6S,7R,8S)-1-(3,5-bis((tert-butyldimethylsilyl)oxy)phenyl)-5-hydroxy-2-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)-8-(methoxy(4-(methoxymethoxy)phenyl)methyl)-6-(4-(methoxymethoxy)phenyl)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-7-yl)benzene-1,3-diol

Representative procedure: In a flame-dried 2 mL microwave vial was added indane (19 mg, 33 µmol, 1 equiv), BQM (76 mg, 50 µmol, 2 equiv), and acetone (1.7 mL, 0.02 M). The headspace was capped with argon, and the vial was reacted at 100 °C for 3 hours in a Biotage microwave reactor. The reaction mixture was concentrated and purified by flash chromatography over SiO_2 (0%-40% EtOAc in Hexanes). Preparatory TLC was also used to further purify the trimeric fractions. Trimeric fractions after 1 round of flash chromatography over SiO_2 and 1 round of preparatory TLC.

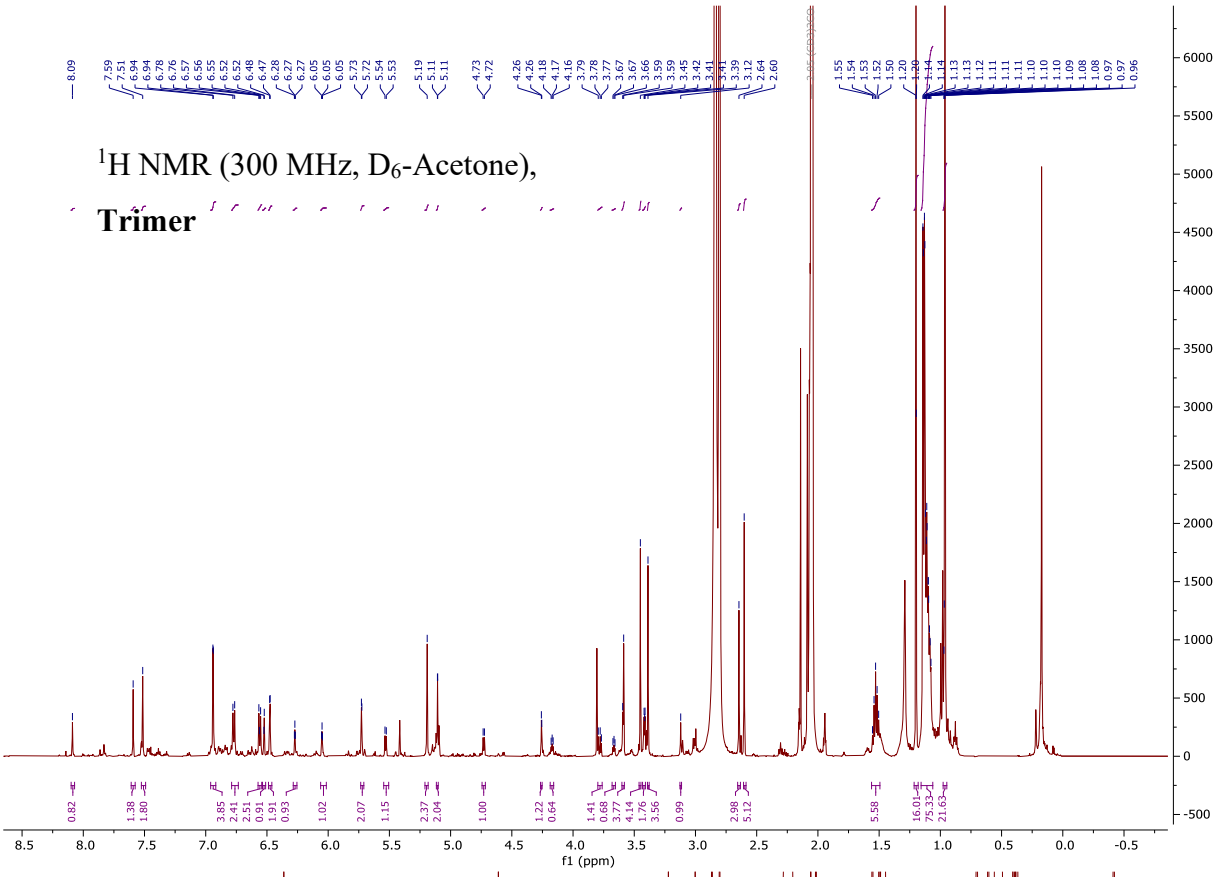


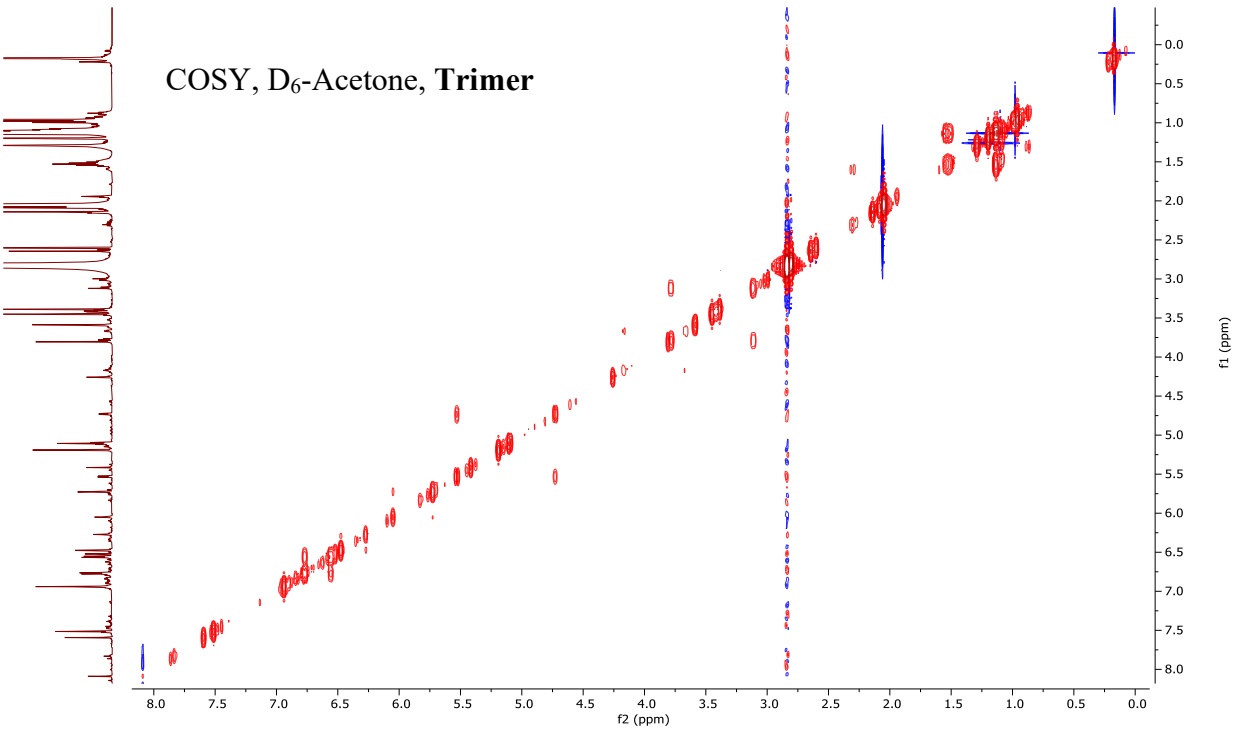

COSY, D6-Acetone
f2 (ppm)
f1 (ppm)

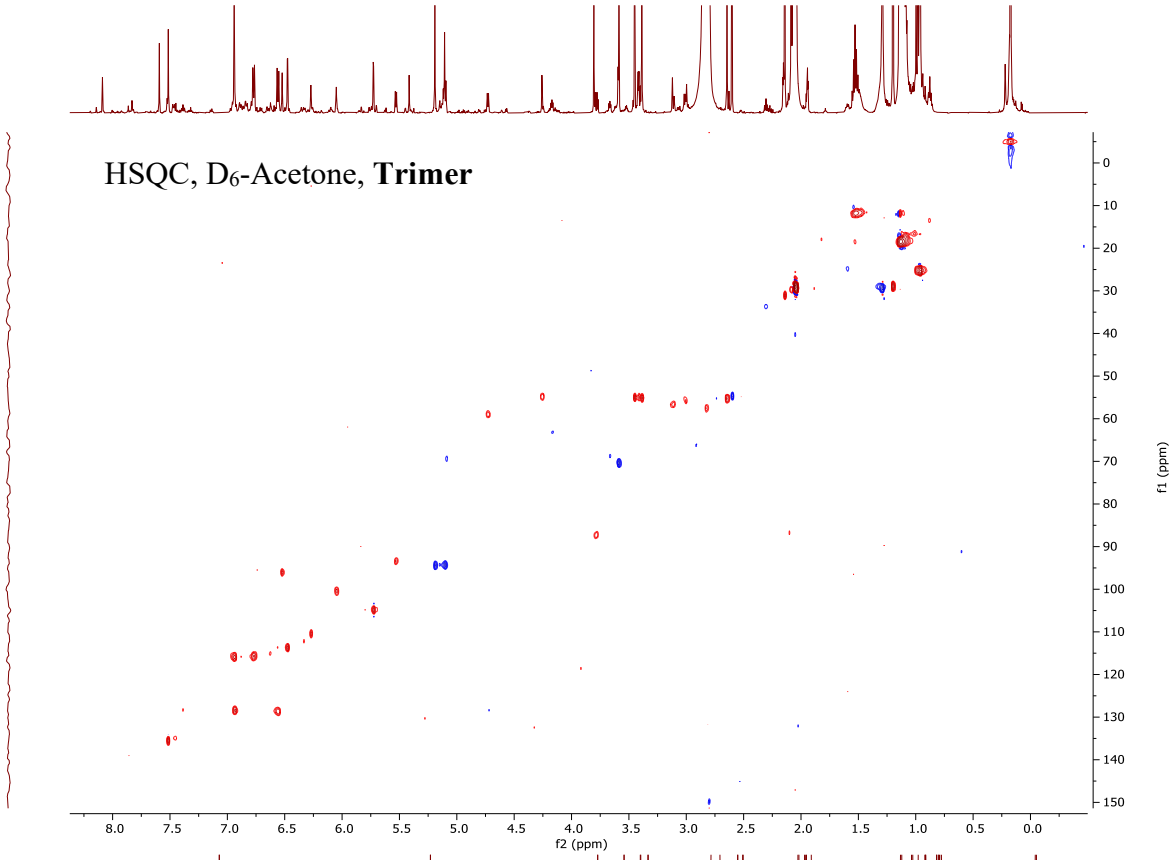

HSQC, D6-Acetone
f2 (ppm)
f1 (ppm)

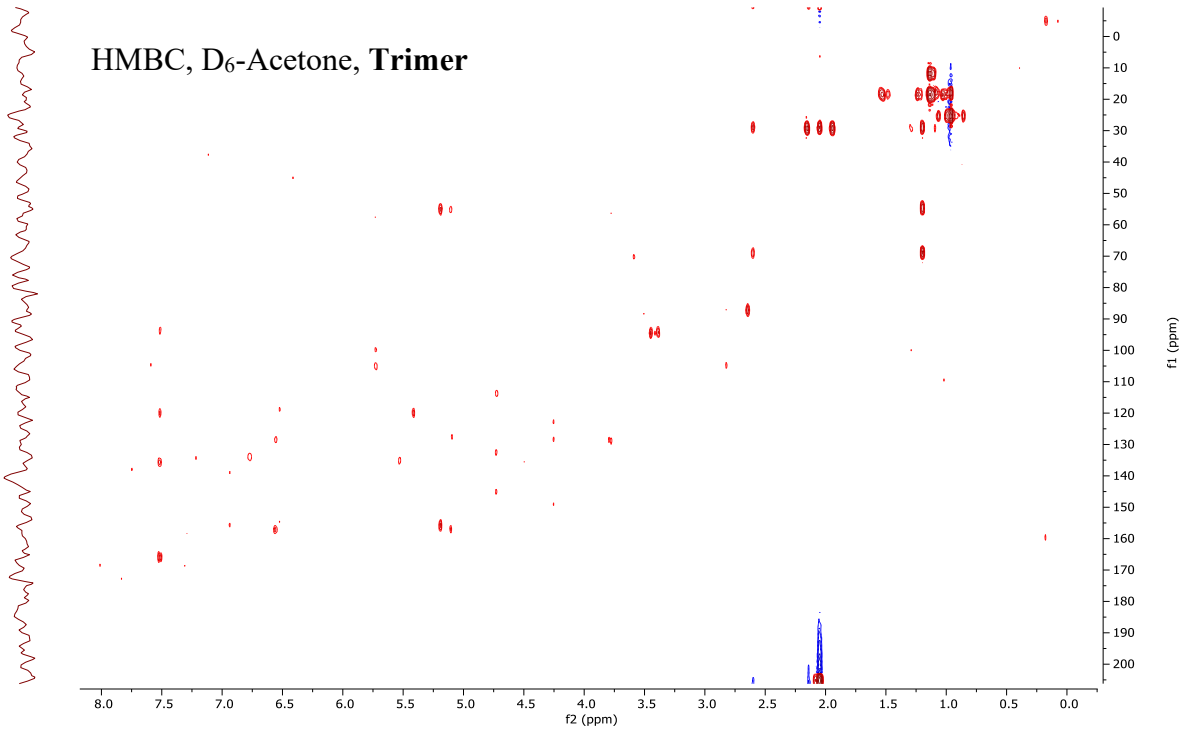
From the preparatory TLC a single fraction was of adequate quality to provide line listings, as shown below. Insufficient material was isolated to provide a rigorous interrogation of the connectivity via HMBC.

^{1}H NMR (300 MHz, D_6-Acetone), **Trimer**	δ = 8.09 (s, 1H), 7.59 (s, 1H), 7.51 (s, 2H), 6.94 (d, J=1.7, 4H), 6.77 (d, J=8.6, 2H), 6.56 (d, J=8.5, 3H), 6.52 (d, J=1.5, 1H), 6.48 (d, J=2.2, 2H), 6.27 (t, J=2.3, 1H), 6.05 (d, J=2.2, 1H), 5.73 (d, J=2.2, 2H), 5.53 (d, J=6.5, 1H), 5.19 (s, 2H), 5.11 (d, J=1.2, 2H), 4.73 (d, J=6.5, 1H), 4.26 (d, J=1.9, 1H), 4.19 – 4.16 (m, 1H), 3.80 – 3.76 (m, 1H), 3.68 – 3.65 (m, 1H), 3.59 (d, J=4.7, 4H), 3.45 (s, 4H), 3.43 – 3.41 (m, 2H), 3.39 (s, 4H), 3.12 (s, 1H), 2.64 (s, 3H), 2.60 (s, 5H), 1.53 (p, J=7.5, 6H), 1.20 (d, J=1.5, 16H), 1.16 – 1.06 (m, 75H), 0.96 (s, 22H).

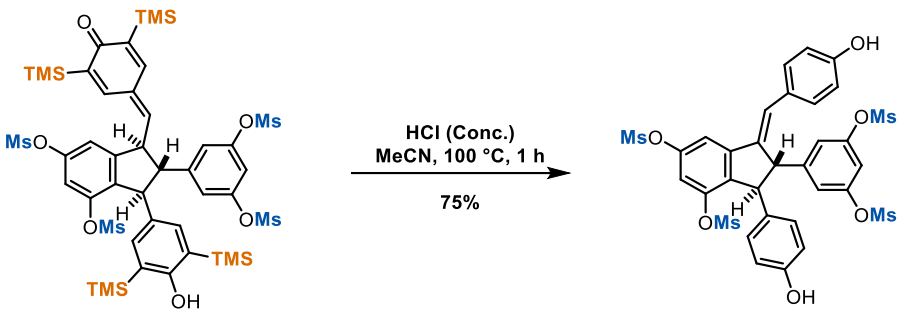

^{1}H NMR (300 MHz, D_6-Acetone),
Trimer
f1 (ppm)


COSY, D_6-Acetone, **Trimer**
f2 (ppm)
f1 (ppm)


HSQC, D6-Acetone, **Trimer**
f2 (ppm)
f1 (ppm)


HMBC, D6-Acetone, **Trimer**
f2 (ppm)
f1 (ppm)

4.8.2 Towards laetevirenol C, D, E and parthenocissin B

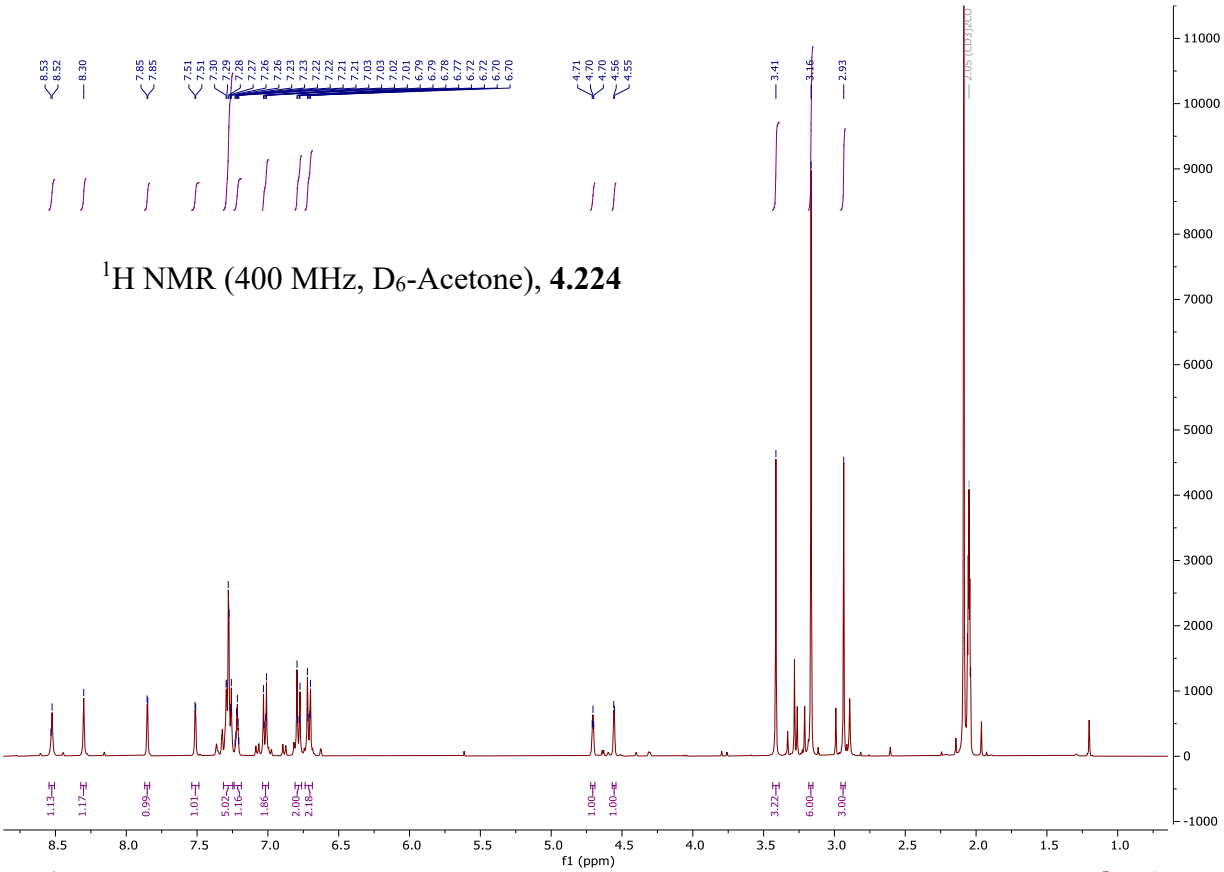


4.202 4.224

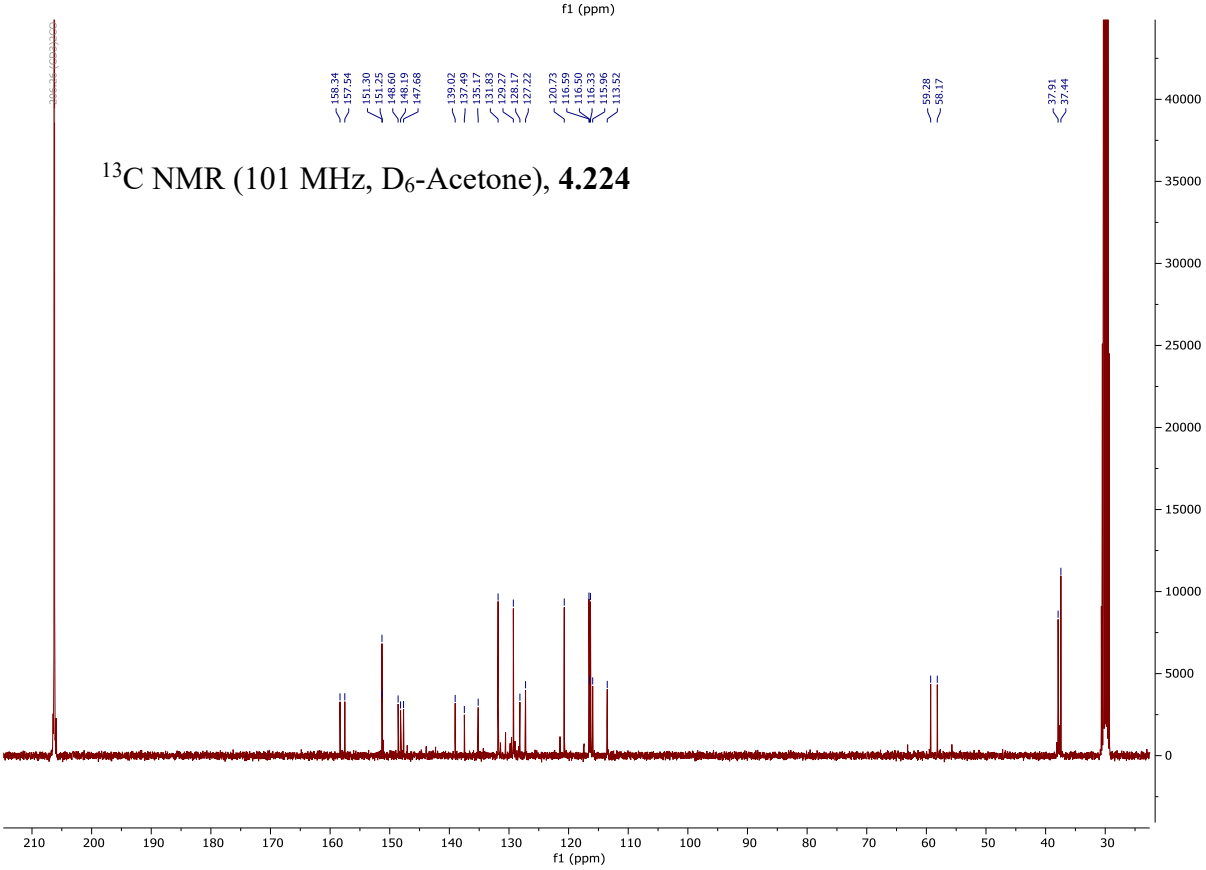
(4.224) (2S,3S)-2-(3,5-bis((methylsulfonyl)oxy)phenyl)-1-((E)-4-hydroxybenzylidene)-3-(4-hydroxyphenyl)-2,3-dihydro-1H-indene-4,6-diyl dimethanesulfonate

In a 2-dram vial was added starting material (105 mg, 99 µmol, 1 equiv), MeCN (2 mL, 0.05 M), and HCl (414 µL, 5 mmol, 50 equiv, 12 M in H_2O). The solution was heated to reflux (100 °C) for 1 hour. The reaction was diluted with Sat. $NaHCO_3$ (aq) (1 mL), water (1 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-45% EtOAc in Hexanes) to yield the product as a white foam (57 mg, 75%).

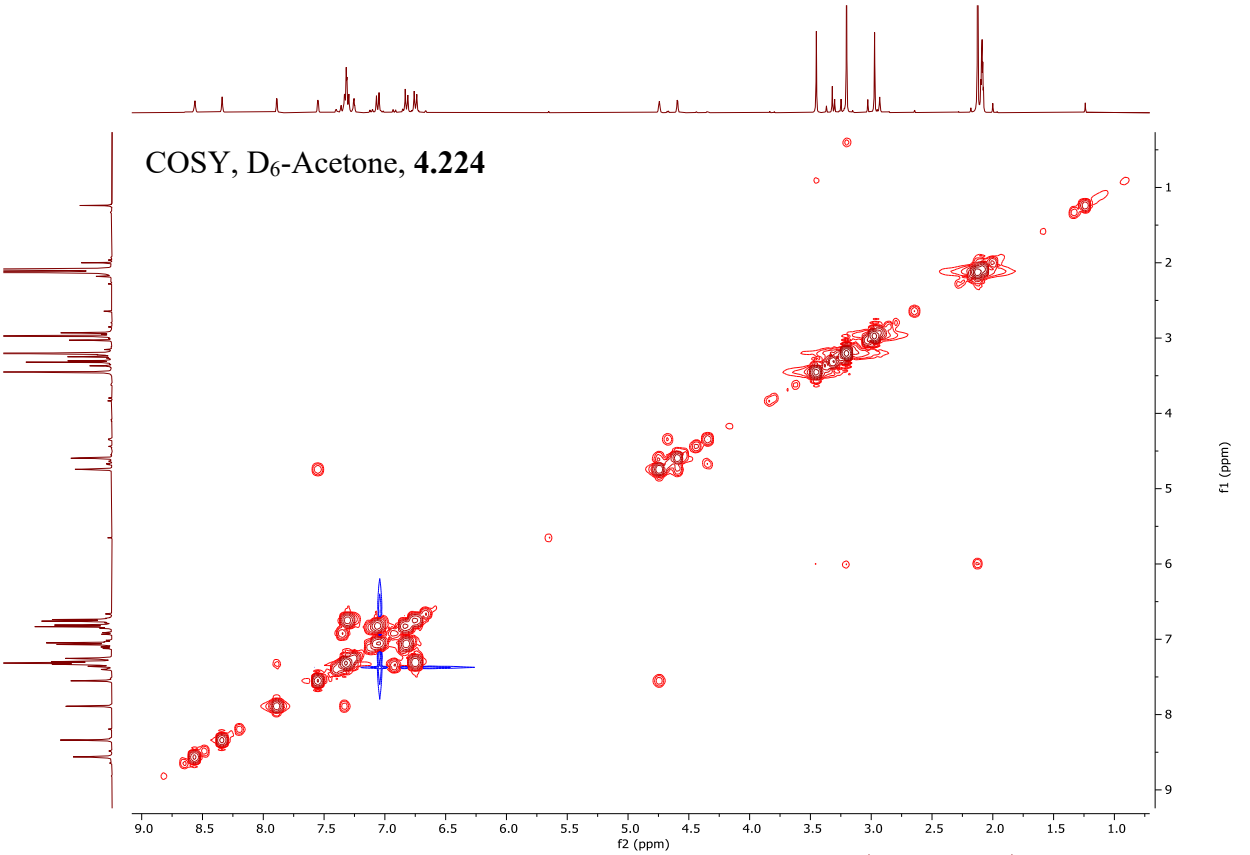
TLC (DCM/Acetone, 80:20), RF:	0.17 (UV, potassium permanganate)
^{1}H NMR (400 MHz, D_6-Acetone), **4.224**	δ = 8.53 (d, J=3.3, 1H), 8.30 (s, 1H), 7.85 (d, J=2.0, 1H), 7.51 (d, J=2.0, 1H), 7.28 (td, J=6.3, 2.0, 4H), 7.22 (q, J=2.3, 1H), 7.04 – 7.00 (m, 2H), 6.81 – 6.76 (m, 2H), 6.74 – 6.69 (m, 2H), 4.70 (t, J=2.2, 1H), 4.56 (d, J=2.3, 1H), 3.41 (s, 3H), 3.16 (s, 6H), 2.93 (s, 3H).
^{13}C NMR (101 MHz, D_6-Acetone), **4.224**	δ = 158.3, 157.5, 151.3, 151.3, 148.6, 148.2, 147.7, 139.0, 137.5, 135.2, 131.8, 129.3, 128.2, 127.2, 120.7, 116.6, 116.5, 116.3, 116.0, 113.5, 59.3, 58.2, 37.9, 37.4.
HRMS (ESI):	m/z calculated for $C_{32}H_{30}O_{14}S_4$ ([M+H]+): 767.0591, found 767.0611
FTIR (neat) cm^{-1} :	ν̃= 3472 (br), 3029 (w), 2938 (w), 1514 (w), 1365 (s), 1179 (vs), 1108 (w), 992 (w), 963 (s), 799 (m)

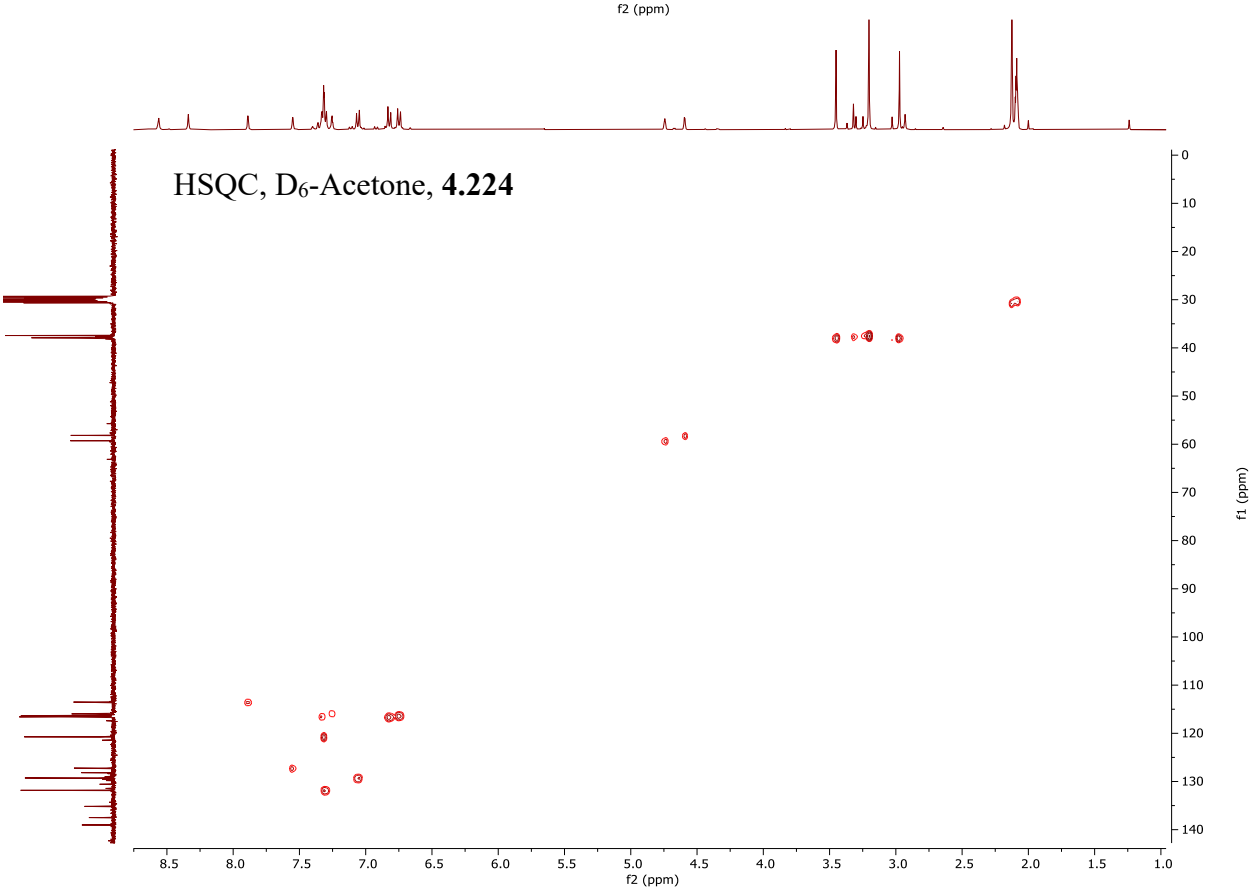


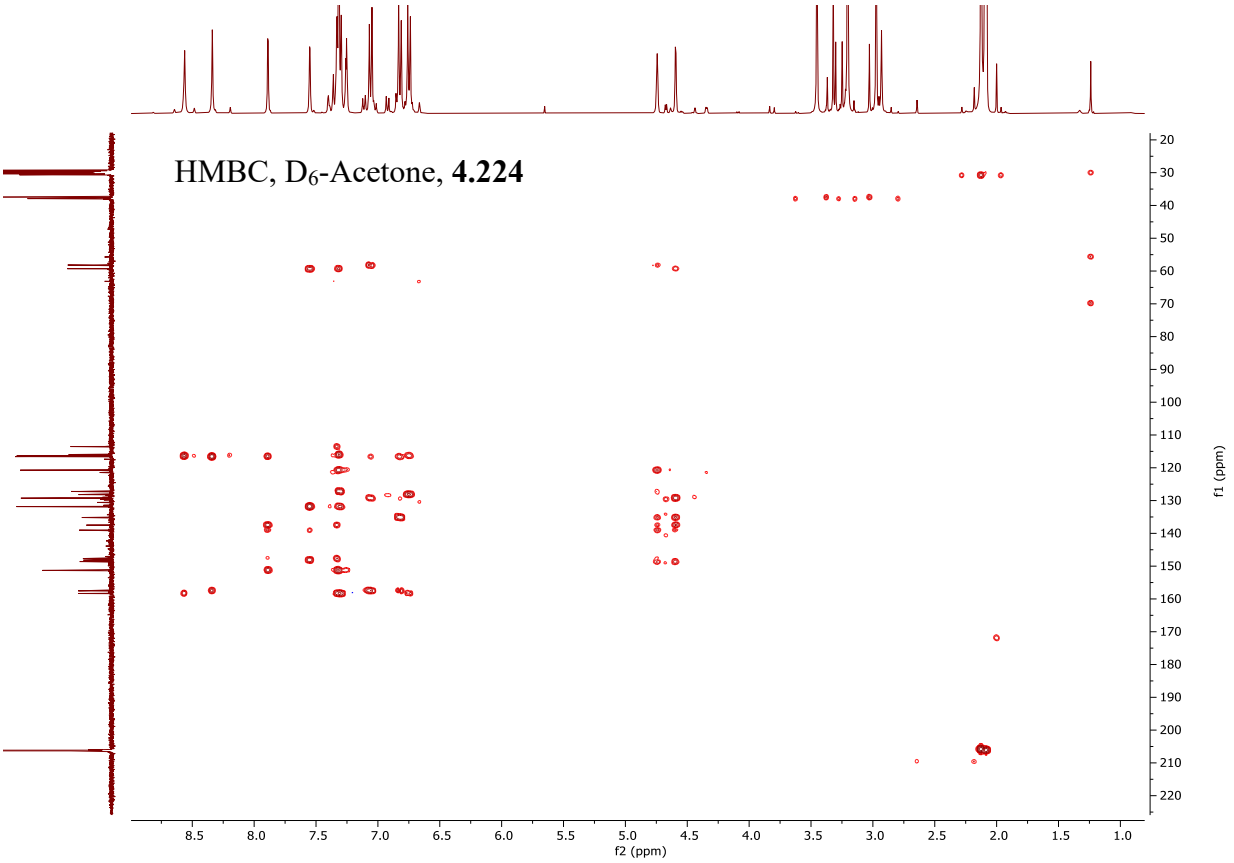
^{1}H NMR (400 MHz, D_6-Acetone), **4.224**

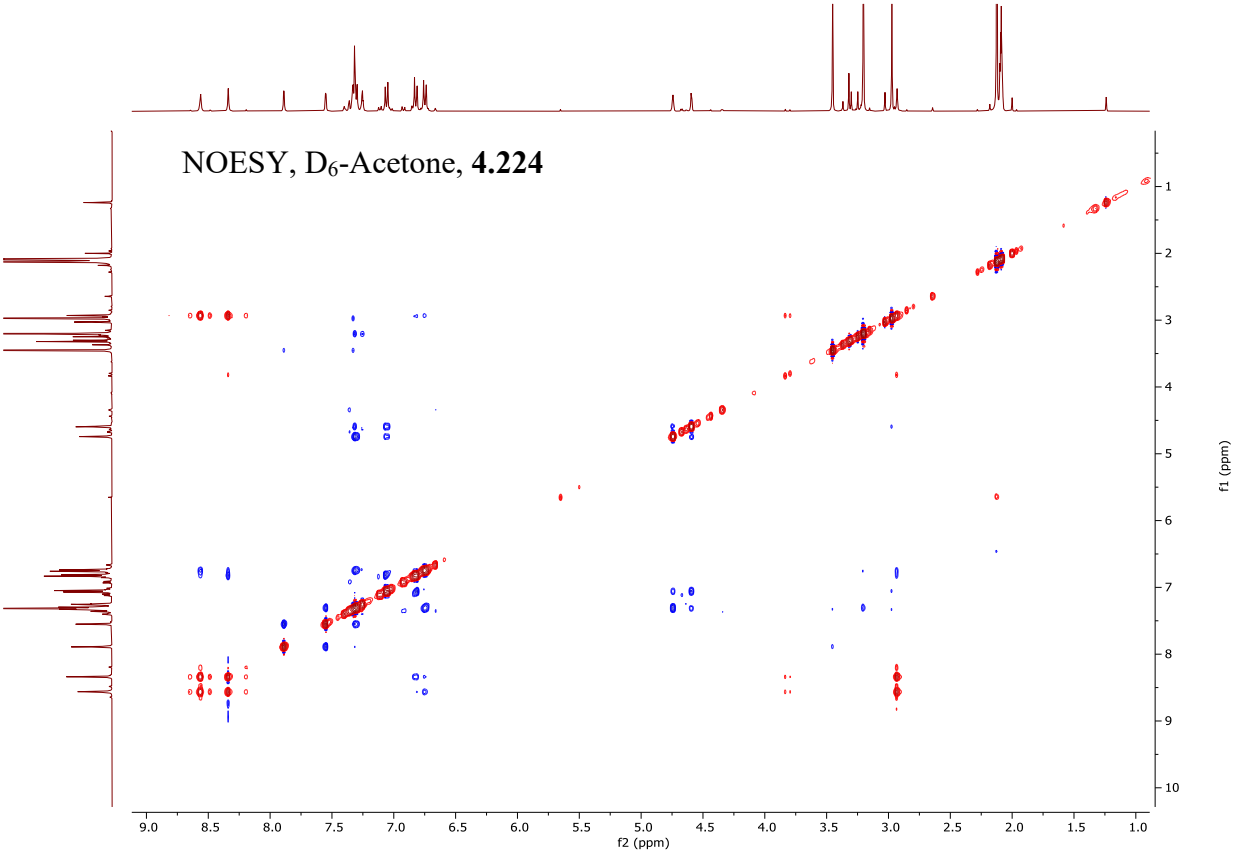


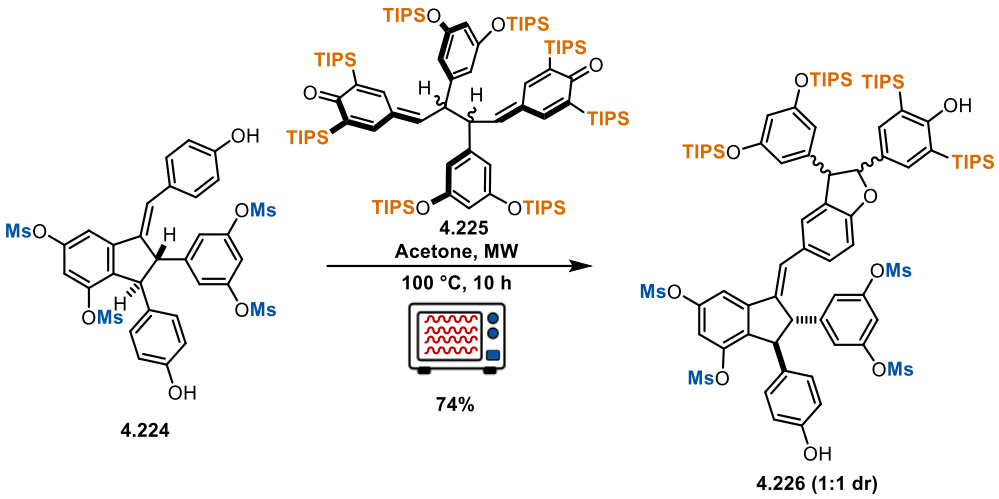
^{13}C NMR (101 MHz, D_6-Acetone), **4.224**


COSY, D6-Acetone, 4.224
f2 (ppm)
f1 (ppm)


HSQC, D6-Acetone, 4.224
f2 (ppm)
f1 (ppm)


HMBC, D6-Acetone, 4.224
f2 (ppm)
f1 (ppm)

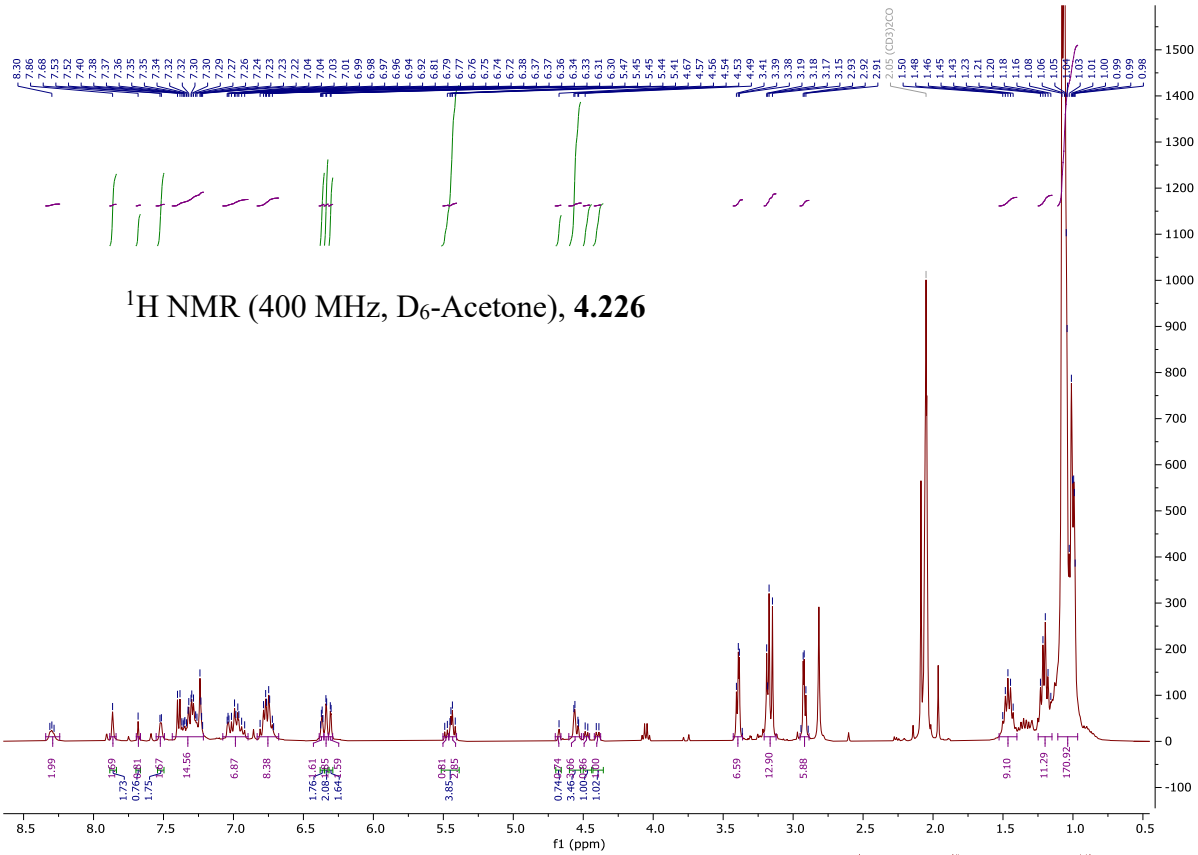

NOESY, D6-Acetone, 4.224
f2 (ppm)
f1 (ppm)



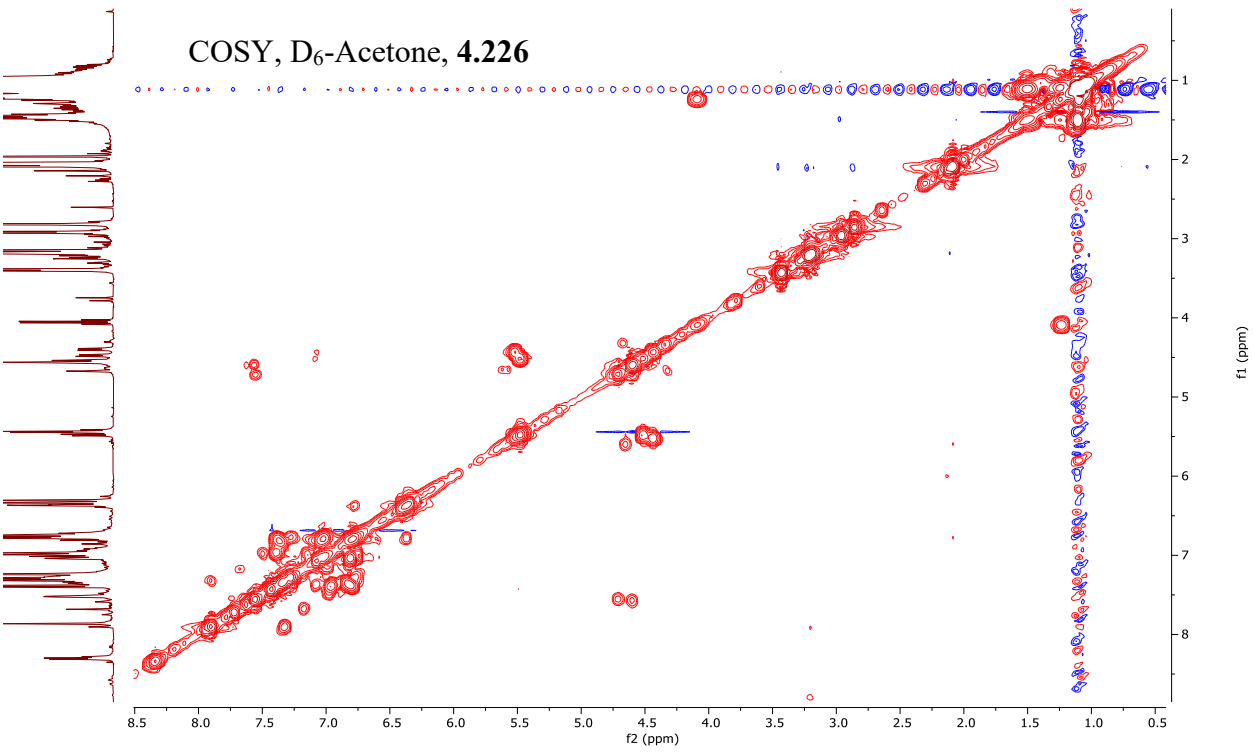
(4.226) (2S,3S,E)-2-(3,5-bis((methylsulfonyl)oxy)phenyl)-1-((3-(3,5-bis((triisopropylsilyl)oxy)phenyl)-2-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)-2,3-dihydrobenzofuran-5-yl)methylene)-3-(4-hydroxyphenyl)-2,3-dihydro-1H-indene-4,6-diyl dimethanesulfonate

In a flame-dried 5 mL microwave vial was added indane (57 mg, 74 µmol, 1 equiv), BQM (189 mg, 111 µmol, 1.5 equiv), and acetone (3.0 mL, 0.025 M). The headspace was capped with argon, and the vial was reacted at 100 °C for 16 hours in a Biotage microwave reactor. The reaction mixture was concentrated and purified by flash chromatography over SiO_2 (0%-40% EtOAc in Hexanes). The product was isolated as a tan foam (71 mg, 74%), 1:1 mixture of *trans* DHB diastereomers.

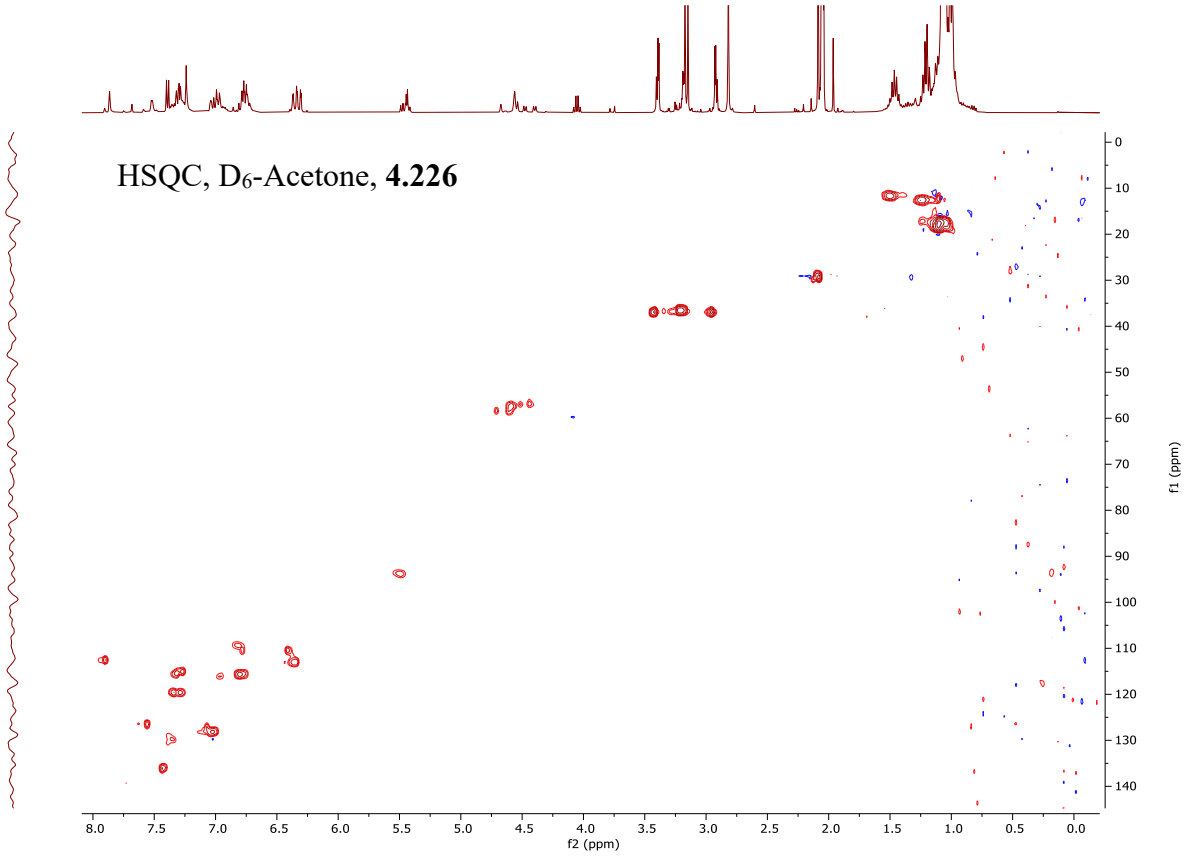
^{1}H NMR (400 MHz, D_6-Acetone), **4.226** δ = 8.34 – 8.24 (m, 2H), 7.86 (s, 2H), 7.68 (s, 1H), 7.52 (d, J=4.0, 2H), 7.44 – 7.22 (m, 15H), 7.08 – 6.90 (m, 7H), 6.83 – 6.68 (m, 8H), 6.37 (q, J=2.2, 2H), 6.34 (d, J=2.1, 2H), 6.31 (d, J=2.2, 2H), 5.48 (d, J=7.5, 1H), 5.46 – 5.41 (m, 3H), 4.67 (s, 1H), 4.60 – 4.51 (m, 3H), 4.48 (d, J=7.6, 1H), 4.40 (d, J=7.5, 1H), 3.43 – 3.36 (m, 7H), 3.21 – 3.12 (m, 13H), 2.95 – 2.89 (m, 6H), 1.46 (p, J=7.4, 9H), 1.21 (q, J=7.4, 11H), 1.11 – 0.97 (m, 171H).

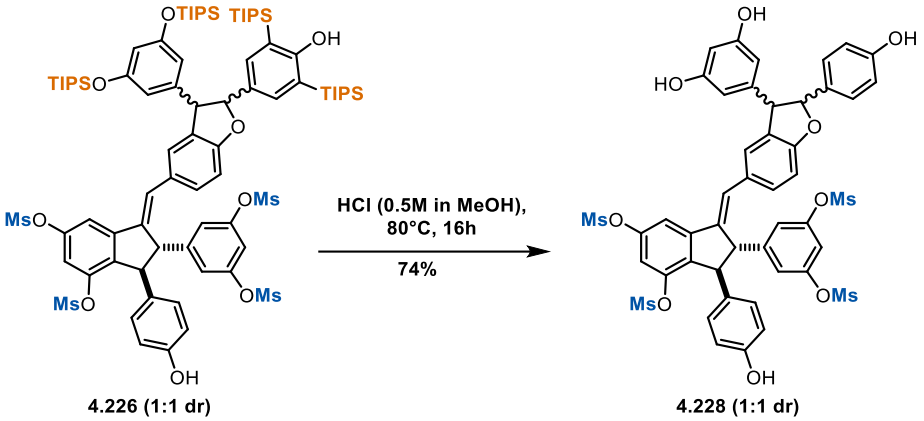


^{1}H NMR (400 MHz, D_6-Acetone), **4.226**



COSY, D_6-Acetone, **4.226**

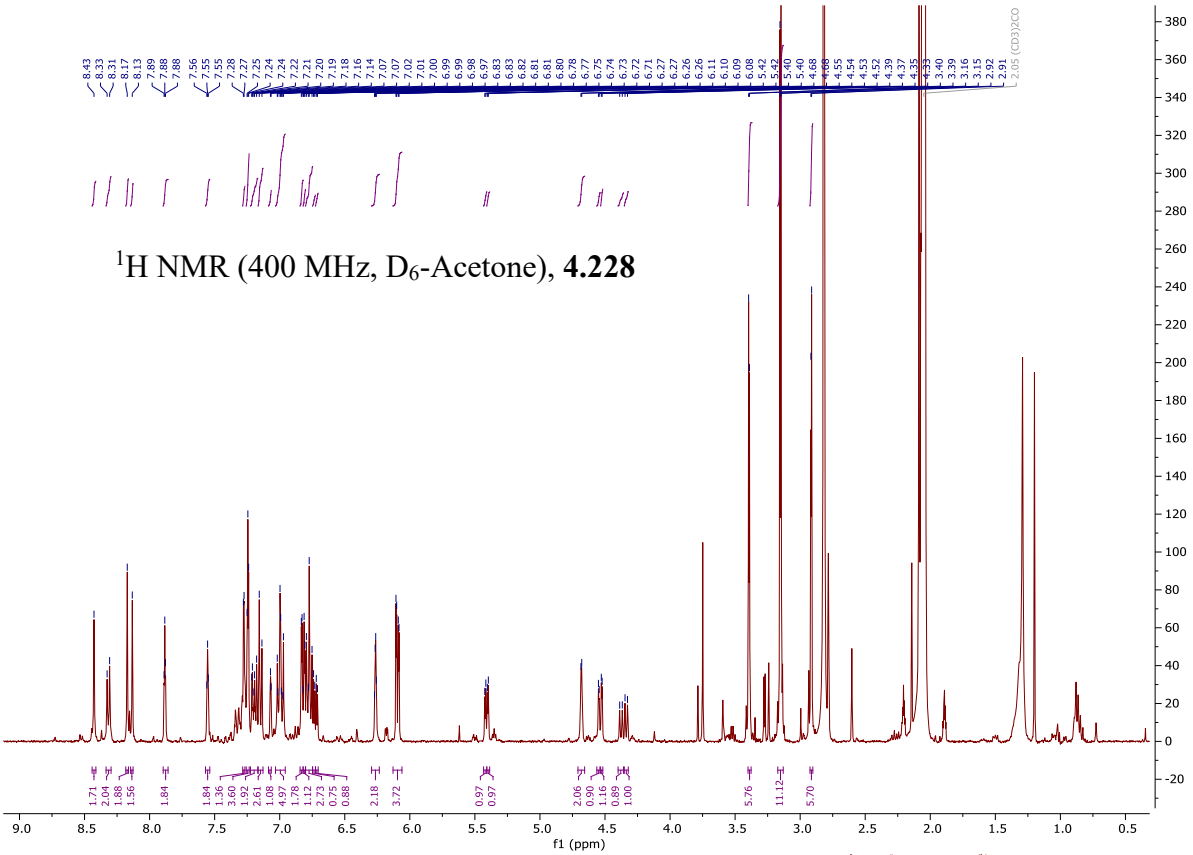

HSQC, D6-Acetone, 4.226
f2 (ppm)
f1 (ppm)



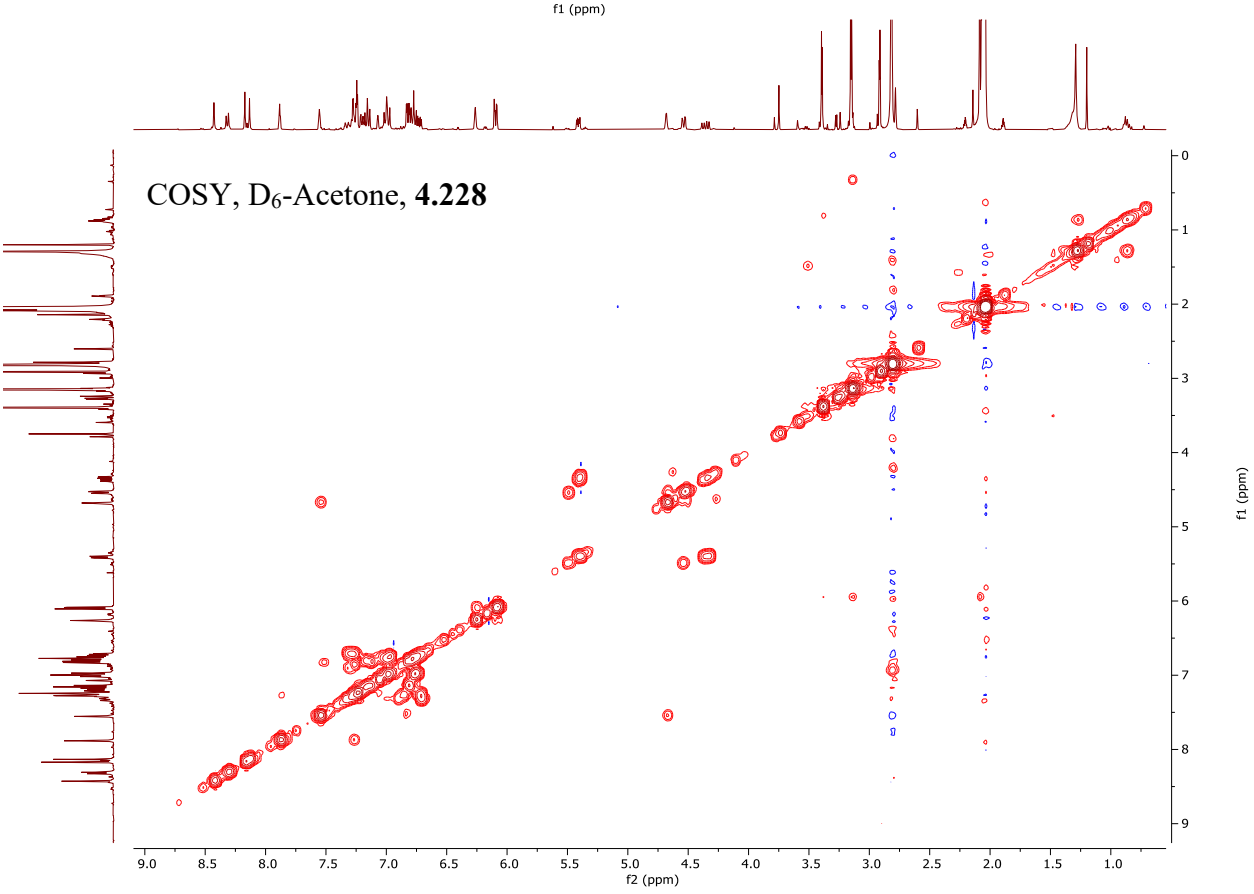
(4.228) (2S,3S,E)-2-(3,5-bis((methylsulfonyl)oxy)phenyl)-1-((3-(3,5-dihydroxyphenyl)-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-5-yl)methylene)-3-(4-hydroxyphenyl)-2,3-dihydro-1H-indene-4,6-diyl dimethanesulfonate

In a 2-dram vial was added starting material (15 mg, 9 µmol, 1 equiv) and HCl (0.9 mL, 0.46 mmol, 50 equiv, 0.5 M in MeOH). The capped vial was heated to 80 °C for 16 hours. The reaction mixture was diluted with Sat. $NaHCO_3$ (aq) (1 mL), water (1 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The reaction mixture was concentrated and purified by preparatory TLC (20% Acetone in DCM). The product was isolated as a brown residue (6.8 mg, 74%), 1:1 mixture of *trans* DHB diasteromers.

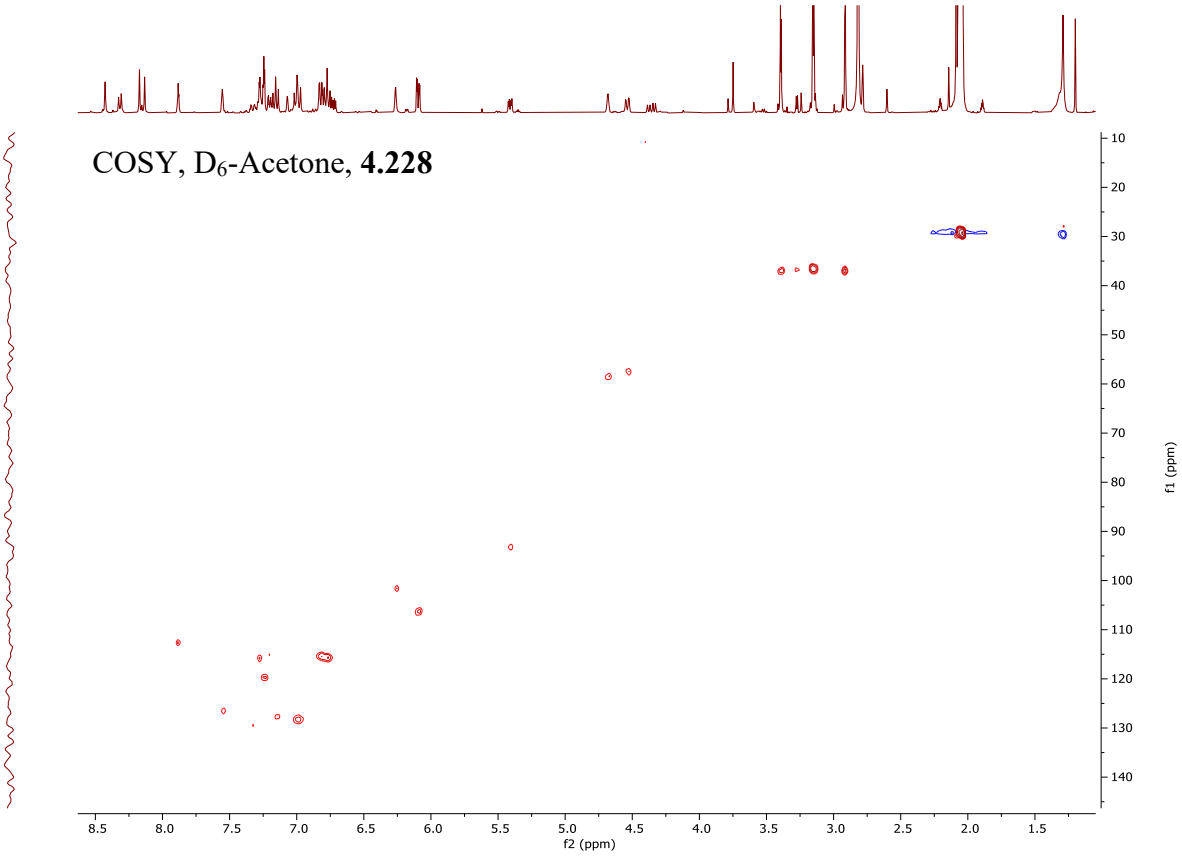
^{1}H NMR (400 MHz, D_6-Acetone), **4.228** δ = 8.43 (s, 2H), 8.32 (d, J=7.7, 2H), 8.17 (s, 2H), 8.13 (s, 2H), 7.88 (t, J=2.1, 2H), 7.55 (d, J=2.3, 2H), 7.28 (d, J=2.0, 1H), 7.24 (t, J=2.4, 4H), 7.22 – 7.17 (m, 2H), 7.15 (d, J=8.2, 3H), 7.07 (d, J=1.9, 1H), 7.00 (dd, J=10.5, 8.5, 5H), 6.83 (d, J=2.3, 2H), 6.81 (d, J=2.3, 1H), 6.77 (t, J=8.7, 3H), 6.74 (d, J=3.7, 1H), 6.71 (d, J=3.7, 1H), 6.26 (q, J=2.0, 2H), 6.09 (dd, J=7.2, 2.2, 4H), 5.42 (d, J=3.3, 1H), 5.40 (d, J=3.0, 1H), 4.68 (d, J=2.5, 2H), 4.55 (d, J=2.3, 1H), 4.53 (d, J=2.5, 1H), 4.38 (d, J=8.0, 1H), 4.34 (d, J=7.7, 1H), 3.39 (d, J=2.6, 6H), 3.15 (d, J=3.2, 12H), 2.91 (d, J=2.2, 6H).

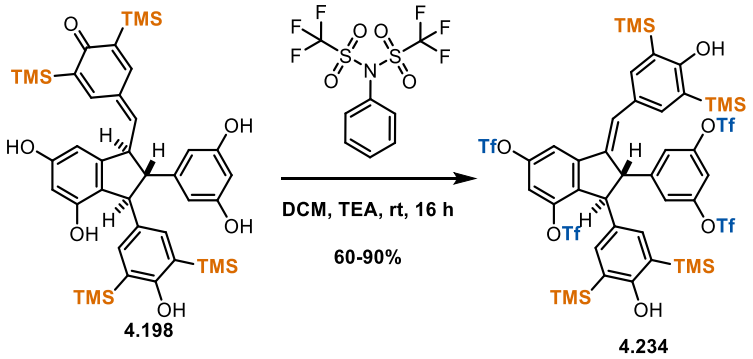


^{1}H NMR (400 MHz, D_6-Acetone), **4.228**



COSY, D_6-Acetone, **4.228**

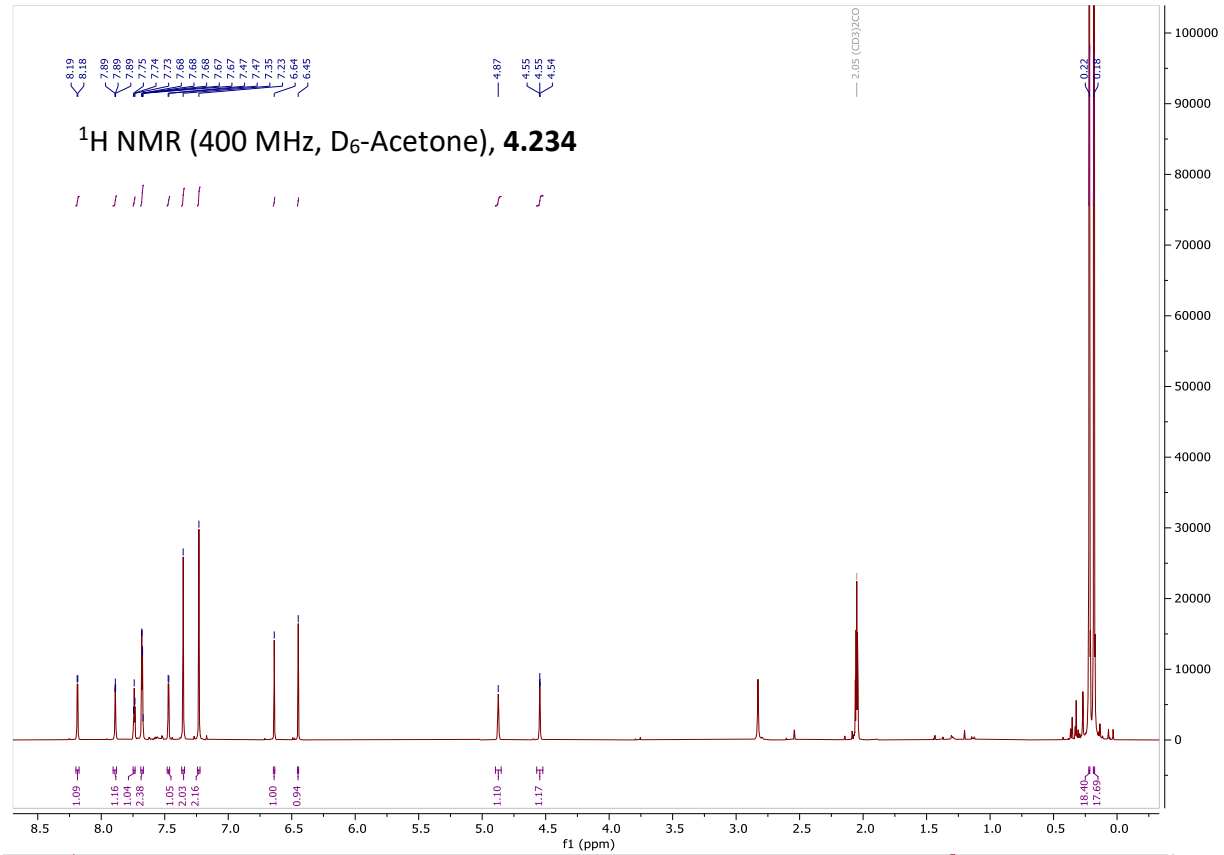

COSY, D6-Acetone, 4.228
f2 (ppm)
f1 (ppm)

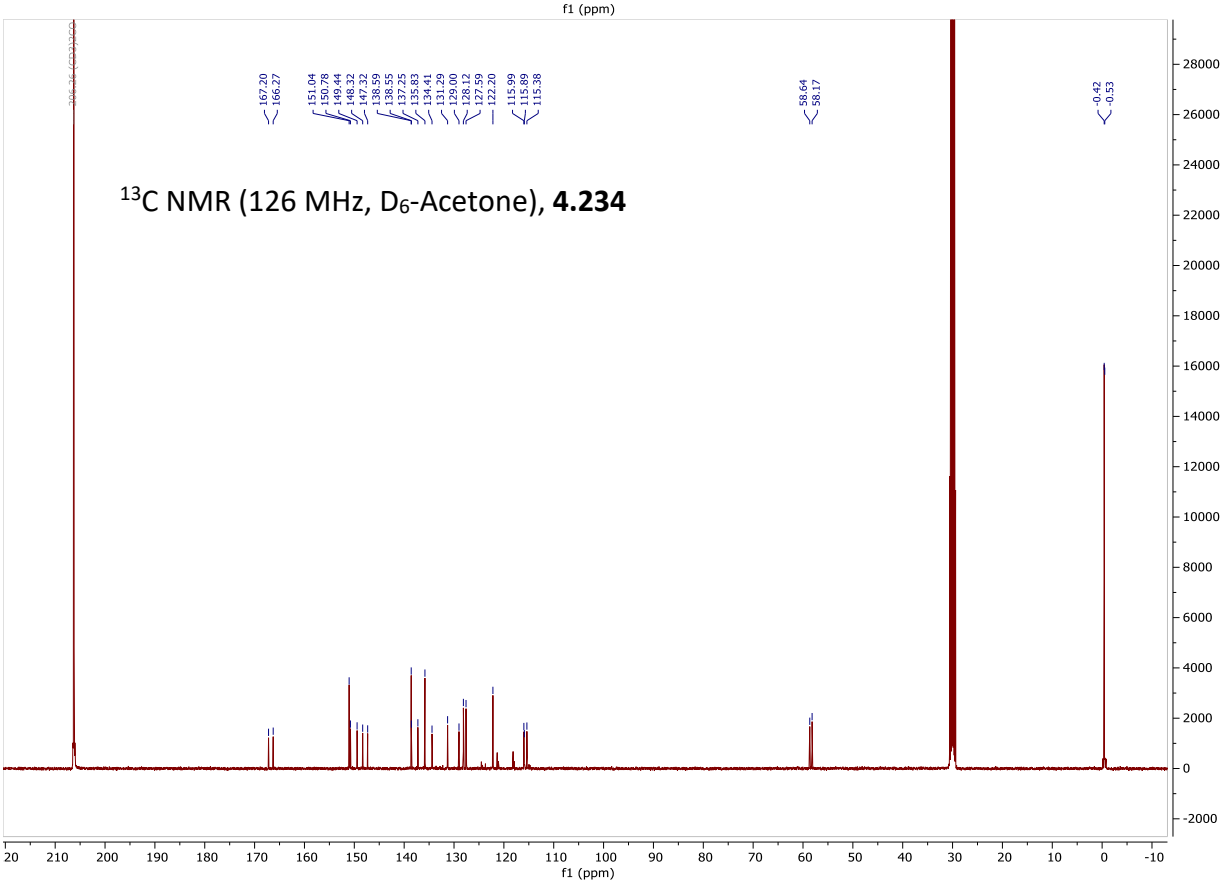


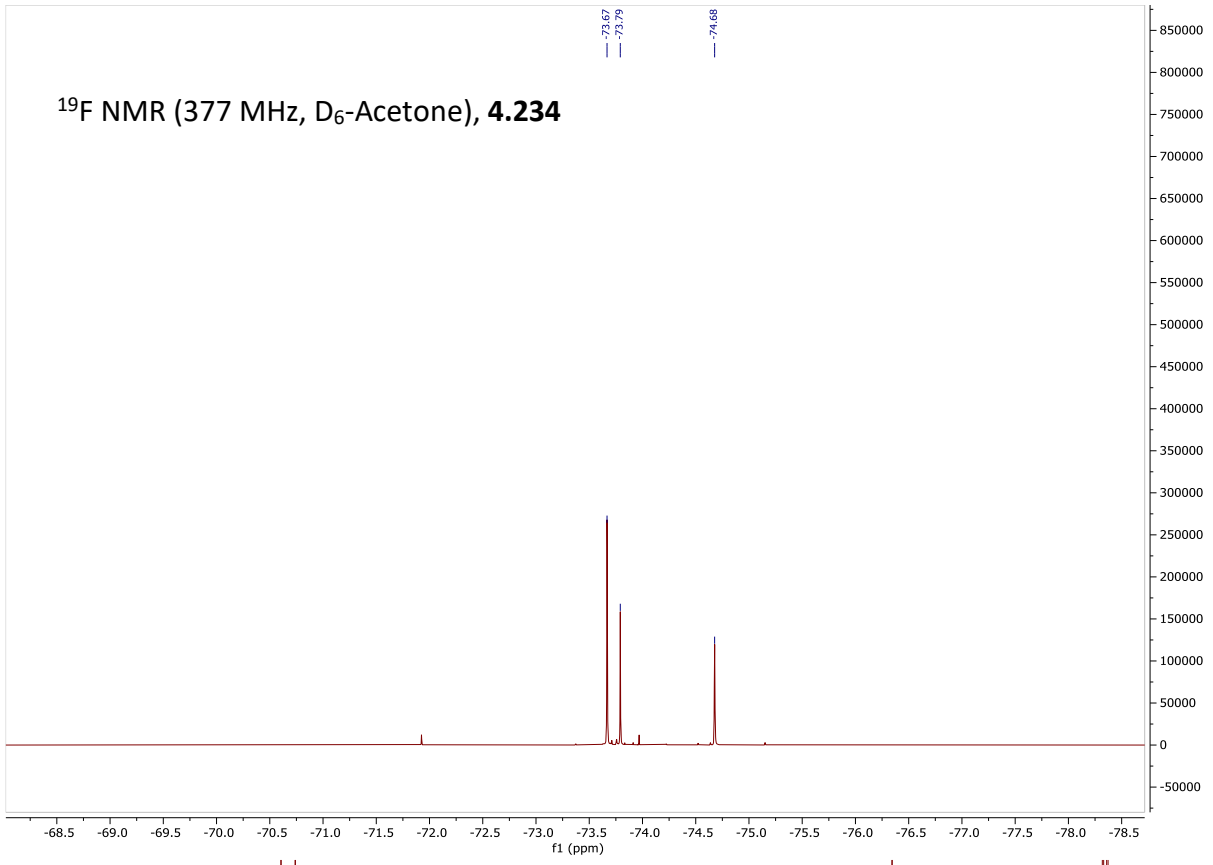
(4.234) (2S,3S)-2-(3,5-bis(((trifluoromethyl)sulfonyl)oxy)phenyl)-1-((Z)-4-hydroxy-3,5-bis(trimethylsilyl)benzylidene)-3-(4-hydroxy-3,5-bis(trimethylsilyl)phenyl)-2,3-dihydro-1H-indene-4,6-diyl bis(trifluoromethanesulfonate)

In a flame-dried 2 mL vial was added indane (50 mg, 67 µmol, 1 equiv), DCM (0.27 mL, 0.25 M), TEA (47 µL, 340 µmol, 5 equiv), and phenyl triflimide (120 mg, 340 µmol, 5 equiv). The headspace was capped with argon, and the reaction was let stir overnight. The reaction mixture was directly transferred to purification by flash chromatography over SiO_2 (0%-40% EtOAc in Hexanes). The product was isolated as a tan foam (70 mg, 82%)

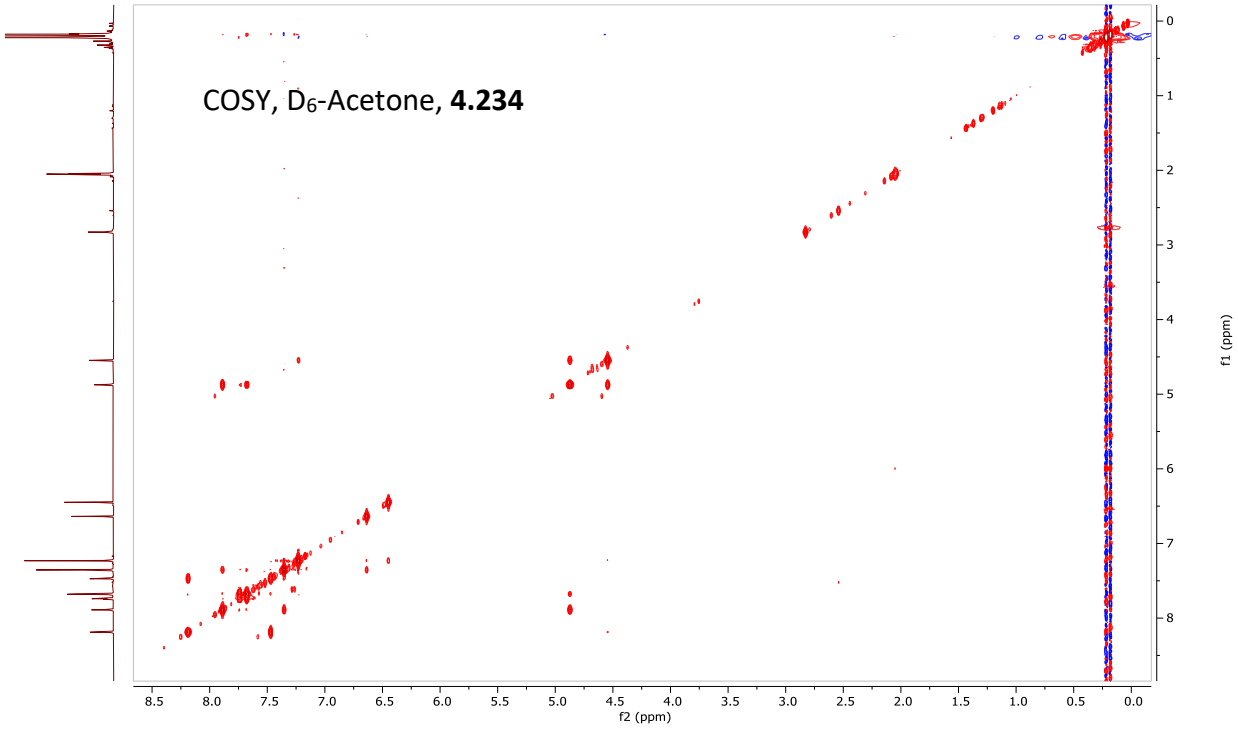
TLC (Hexanes/EtOAc, 80:20), R_f:	0.70 (UV, potassium permanganate)
^{1}H NMR (400 MHz, D_6-Acetone), **4.234**	δ = 8.19 (d, J=2.1, 1H), 7.91 – 7.88 (m, 1H), 7.74 (t, J=2.2, 1H), 7.68 (dd, J=2.2, 0.7, 2H), 7.47 (d, J=2.1, 1H), 7.35 (s, 2H), 7.23 (s, 2H), 6.64 (s, 1H), 6.45 (s, 1H), 4.87 (s, 1H), 4.57 – 4.52 (m, 1H), 0.22 (s, 18H), 0.18 (s, 18H).
^{13}C NMR (126 MHz, D_6-Acetone), **4.234**	δ = 167.2, 166.3, 151.0, 150.8, 149.4, 148.3, 147.3, 138.6, 138.6, 137.2, 135.8, 134.4, 131.3, 129.0, 128.1, 127.6, 122.2, 116.0, 115.9, 115.4, 58.6, 58.2, -0.4, -0.5.
HRMS (ESI):	*m/z* calculated for $C_{44}H_{50}F_{12}O_{14}S_4Si_4$ ($[M+H]^+$): 1271.1042, found 1271.1037
FTIR (neat) cm^{-1} :	ν̃= 3608 (br), 2957 (w), 1429 (m), 1245 (m), 1211 (vs), 1137 (vs), 975 (m), 839 (vs), 607 (w)


^{1}H NMR (400 MHz, D$_6$-Acetone), **4.234**
f1 (ppm)

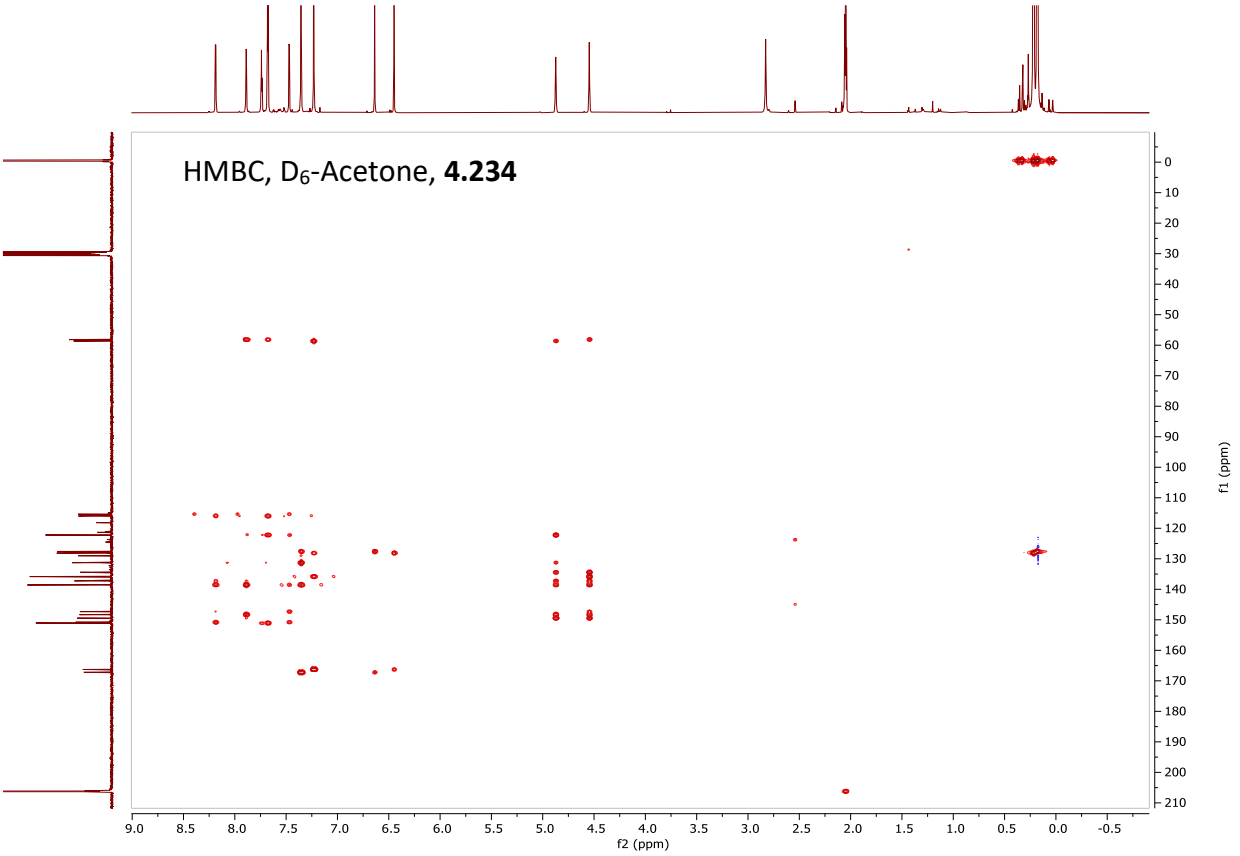

^{13}C NMR (126 MHz, D$_6$-Acetone), **4.234**
f1 (ppm)

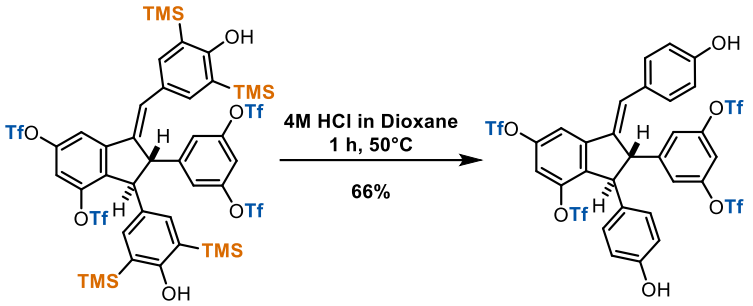


^{19}F NMR (377 MHz, D_6-Acetone), **4.234**



COSY, D_6-Acetone, **4.234**


HMBC, D6-Acetone, 4.234
f2 (ppm)
f1 (ppm)

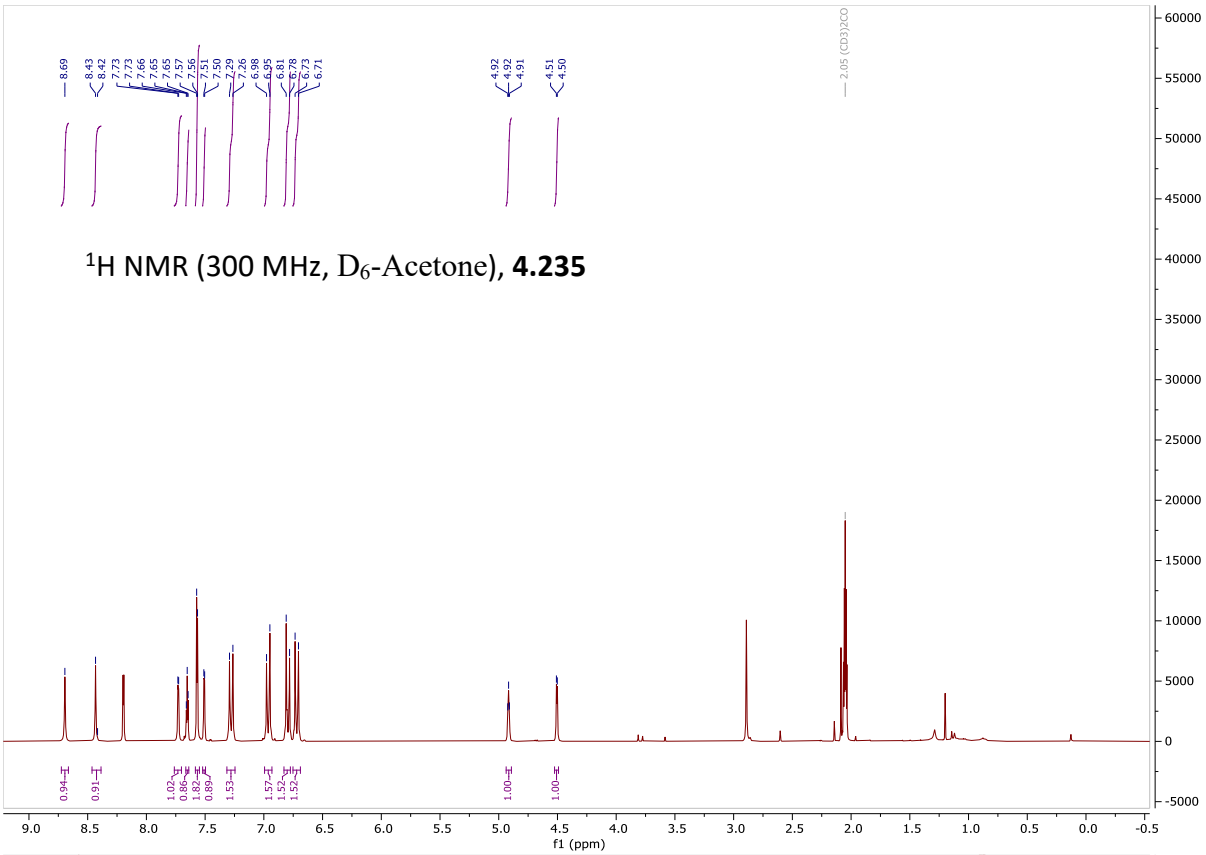


4.234 4.235

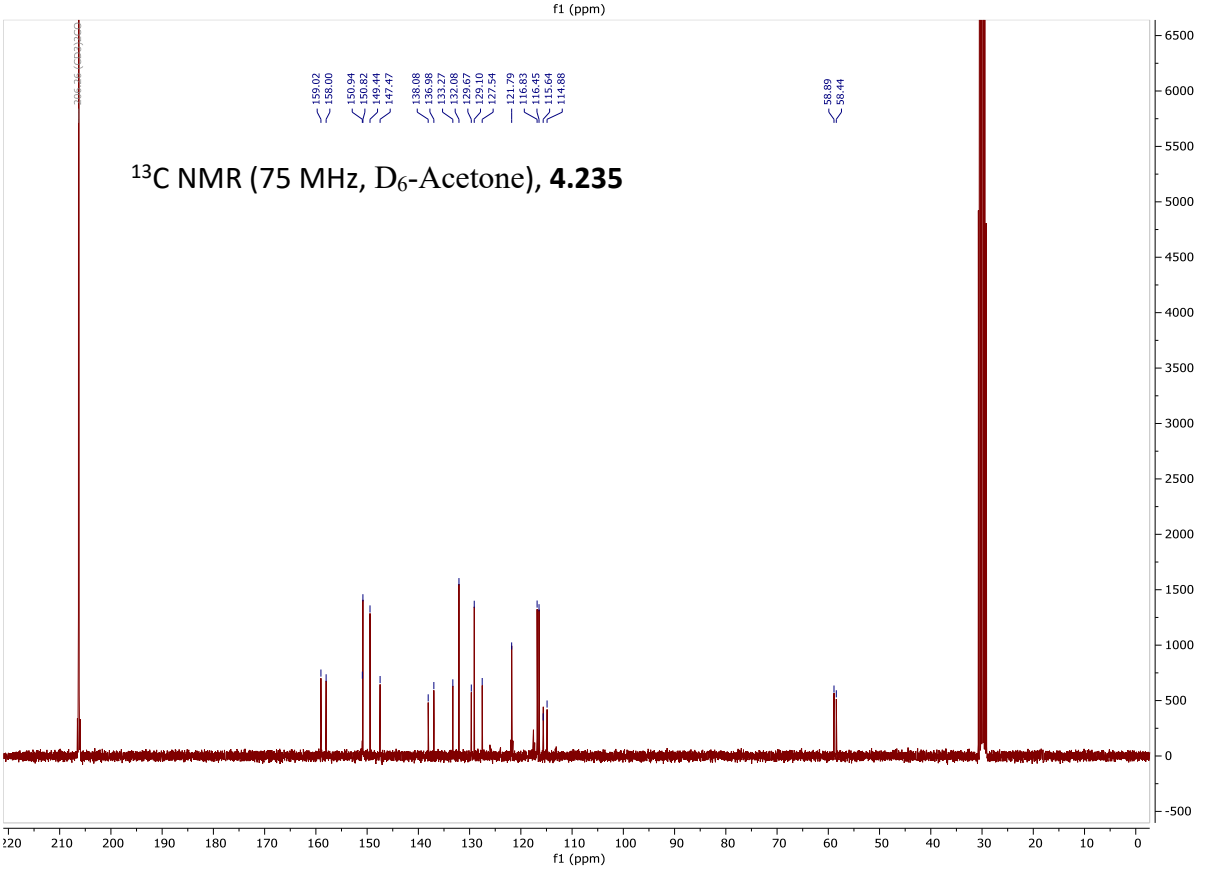
(4.235) (2S,3S)-2-(3,5-bis(((trifluoromethyl)sulfonyl)oxy)phenyl)-1-((E)-4-hydroxybenzylidene)-3-(4-hydroxyphenyl)-2,3-dihydro-1H-indene-4,6-diyl bis(trifluoromethanesulfonate)

In a flame-dried 4 mL vial was added indane (400 mg, 315 µmol, 1 equiv) and 4M HCl in Dioxane (3.9 mL, 15.7 mmol, 50 equiv). The reaction was heated to 50 °C for 1 hour. The reaction was quenched with sat. $NaHCO_3$ (aq) (5 mL). The mixture was extracted with ethyl acetate ether (3 x 5 mL). The organics were dried with brine (10 mL) and $MgSO_4$. The crude organics were purified by flash chromatography over SiO_2 (0%-40% EtOAc in Hexanes). The product was isolated as a tan foam (204 mg, 66%)

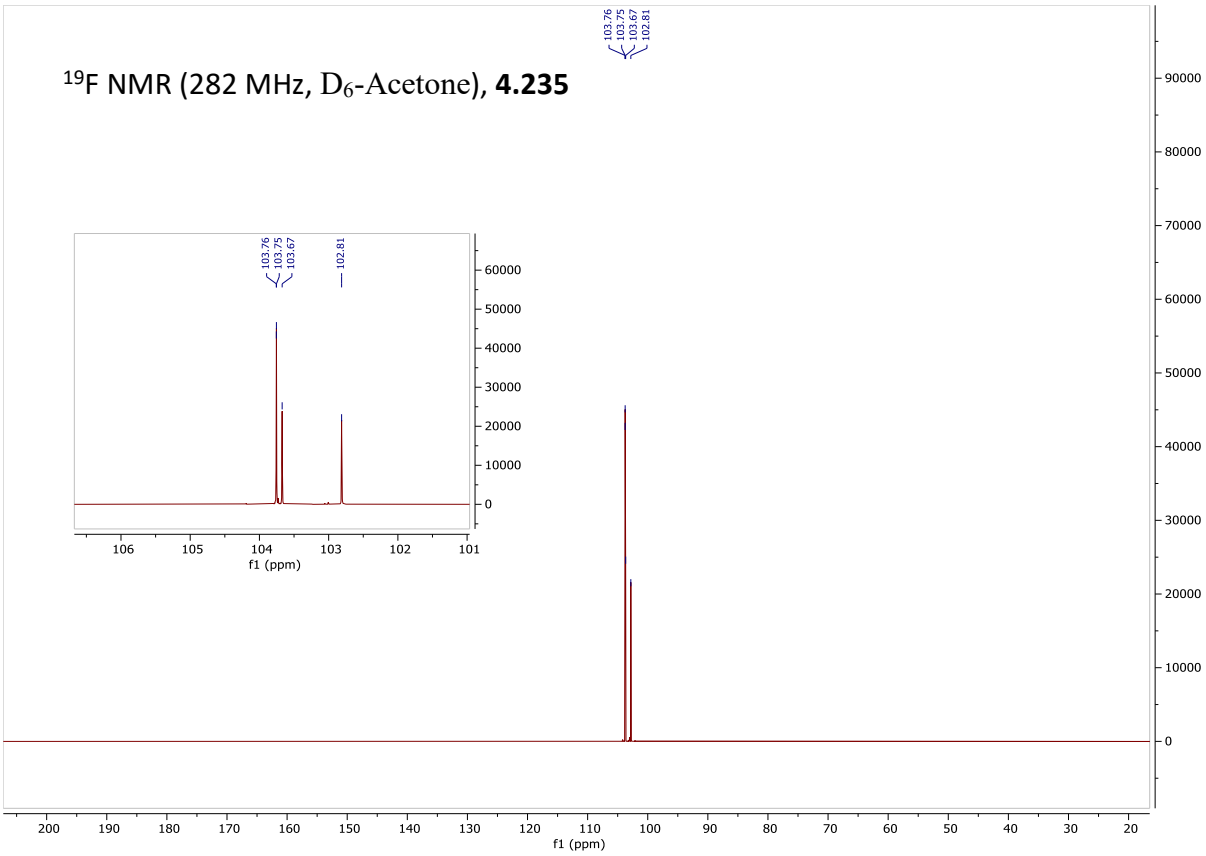
TLC (Hexanes/EtOAc, 60:40), R_F:	0.52 (UV, potassium permanganate)
^{1}H NMR (300 MHz, D_6-Acetone), **4.235**	δ = 8.69 (s, 1H), 8.43 (s, 1H), 7.73 (d, J=1.9, 1H), 7.65 (t, J=2.2, 1H), 7.57 (d, J=2.2, 2H), 7.51 (d, J=2.0, 1H), 7.28 (d, J=8.7, 2H), 6.96 (d, J=8.6, 2H), 6.80 (d, J=8.6, 2H), 6.72 (d, J=8.7, 2H), 4.92 (t, J=2.2, 1H), 4.51 (d, J=2.3, 1H).
^{13}C NMR (75 MHz, D_6-Acetone), **4.235**	δ = 159.0, 158.0, 150.9, 150.8, 149.4, 147.5, 138.1, 137.0, 133.3, 132.1, 129.7, 129.1, 127.5, 121.8, 116.8, 116.5, 115.6, 114.9, 58.9, 58.4.
HRMS (ESI):	*m/z* calculated for $C_{32}H_{18}F_{12}O_{14}S_4$ ($[M+H]^+$): 982.9460, found 982.9495
FTIR (neat) cm^{-1} :	$\tilde{\nu}$= 3369 (br), 1514 (w), 1427 (s), 1245 (s), 1212 (vs), 1175 (w), 1137 (vs), 974 (s), 827 (w), 802 (w)

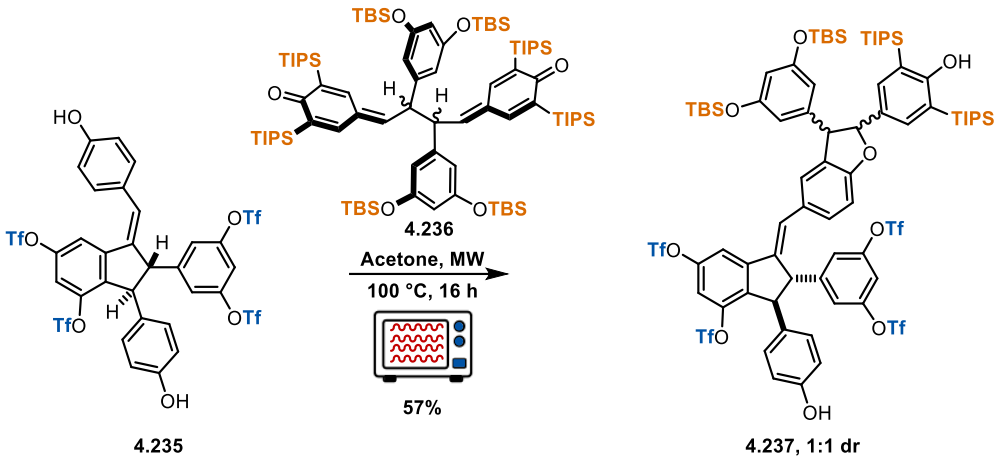


^{1}H NMR (300 MHz, D_6-Acetone), **4.235**



^{13}C NMR (75 MHz, D_6-Acetone), **4.235**

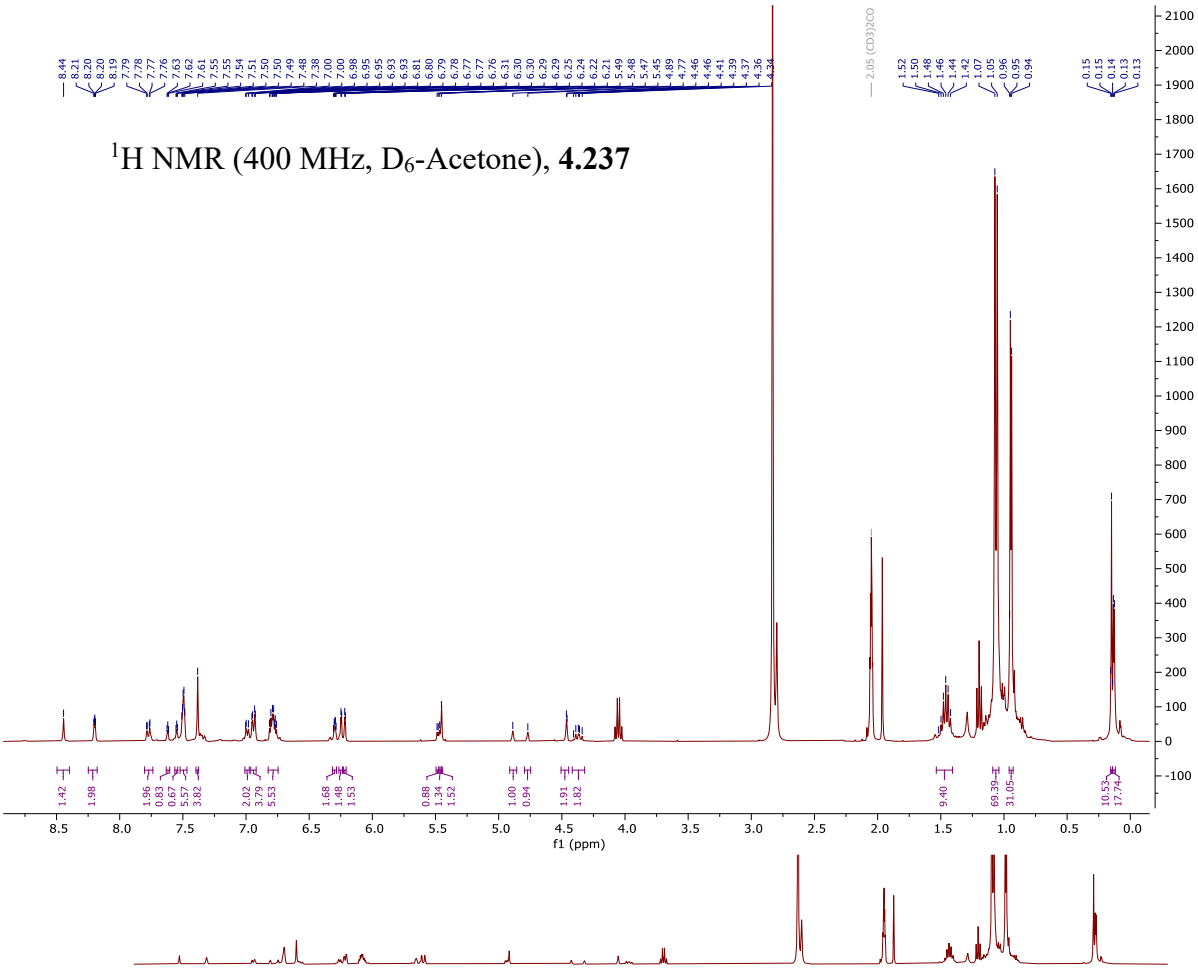

19F NMR (282 MHz, D6-Acetone), 4.235
103.76
103.75
103.67
102.81
f1 (ppm)



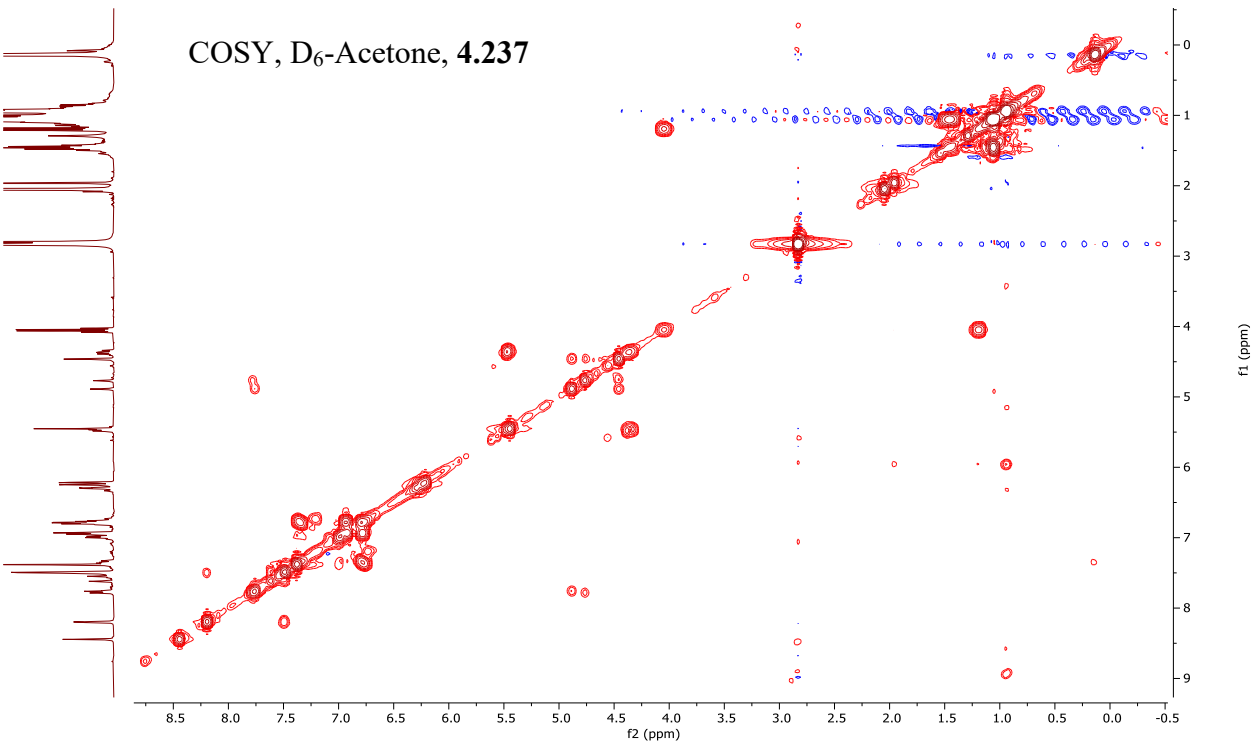
(4.237) (2S,3S,E)-2-(3,5-bis(((trifluoromethyl)sulfonyl)oxy)phenyl)-1-((3-(3,5-bis((tert-butyldimethylsilyl)oxy)phenyl)-2-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)-2,3-dihydrobenzofuran-5-yl)methylene)-3-(4-hydroxyphenyl)-2,3-dihydro-1H-indene-4,6-diyl bis(trifluoromethanesulfonate)

In a flame-dried 2 mL microwave vial was added indane (15 mg, 15 µmol, 1 equiv), BQM (35 mg, 23 µmol, 1.5 equiv), and acetone (0.6 mL, 0.025 M). The headspace was capped with argon, and the vial was reacted at 100 °C for 16 hours in a Biotage microwave reactor. The reaction mixture was concentrated and purified by flash chromatography over SiO_2 (0%-40% EtOAc in Hexanes). The product was isolated as a tan foam (15 mg, 57%)

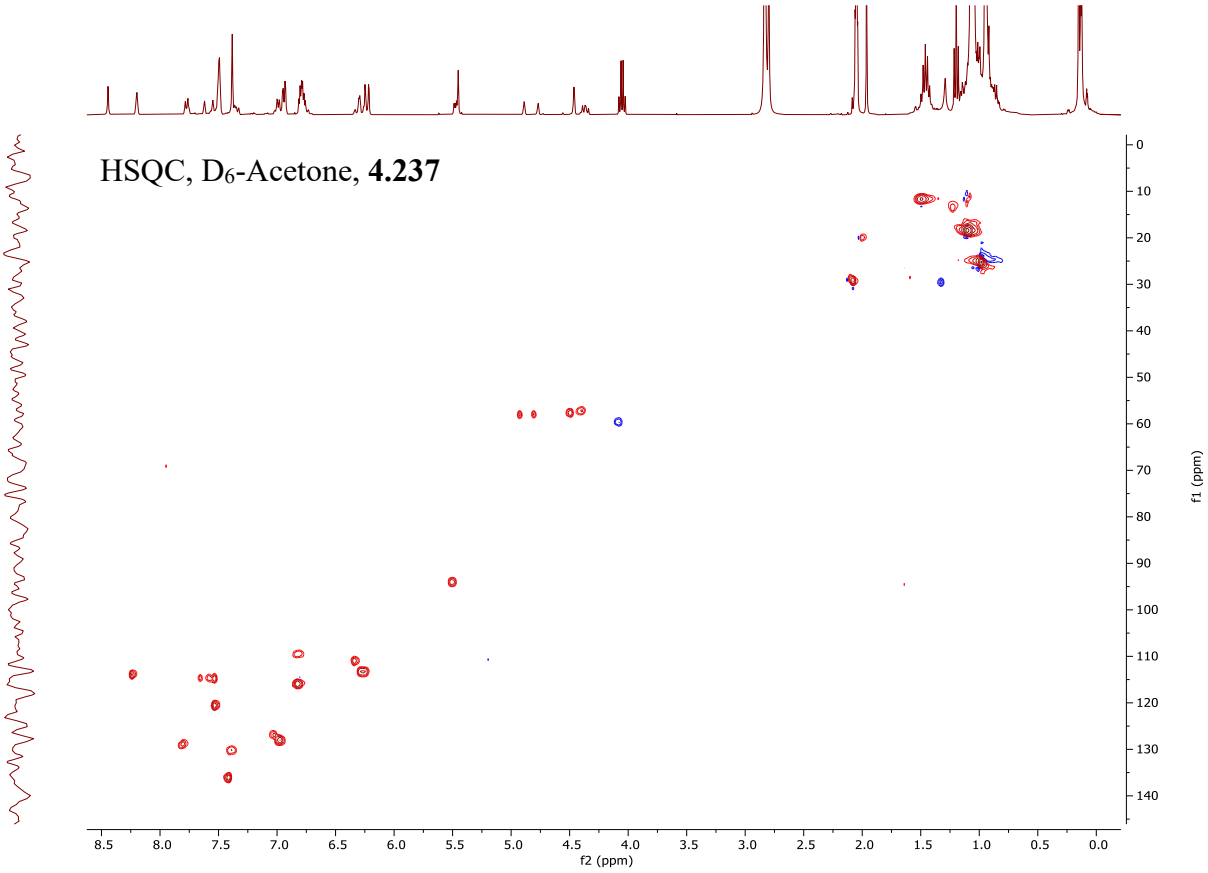
^{1}H NMR (400 MHz, D_6-Acetone), **4.237** δ = 8.44 (s, 1H), 8.20 (dd, J=3.5, 2.1, 2H), 7.77 (dd, J=8.6, 1.8, 2H), 7.62 (t, J=2.3, 1H), 7.55 (t, J=2.2, 1H), 7.50 (dt, J=5.4, 2.4, 6H), 7.38 (s, 4H), 6.99 (d, J=7.1, 2H), 6.96 – 6.92 (m, 4H), 6.79 (dq, J=8.9, 4.1, 6H), 6.30 (dt, J=3.9, 2.2, 2H), 6.25 (d, J=2.2, 1H), 6.22 (d, J=2.2, 2H), 5.48 (d, J=3.6, 1H), 5.47 (s, 1H), 5.45 (s, 2H), 4.89 (s, 1H), 4.77 (s, 1H), 4.46 (d, J=2.0, 2H), 4.36 (dd, J=11.8, 8.4, 2H), 1.46 (p, J=7.5, 9H), 1.06 (d, J=7.4, 69H), 0.94 (d, J=4.0, 31H), 0.15 (d, J=2.5, 11H), 0.14 – 0.12 (m, 18H).

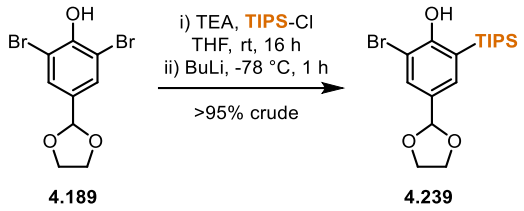


^{1}H NMR (400 MHz, D$_6$-Acetone), **4.237**



COSY, D$_6$-Acetone, **4.237**


HSQC, D6-Acetone, 4.237
f2 (ppm)
f1 (ppm)

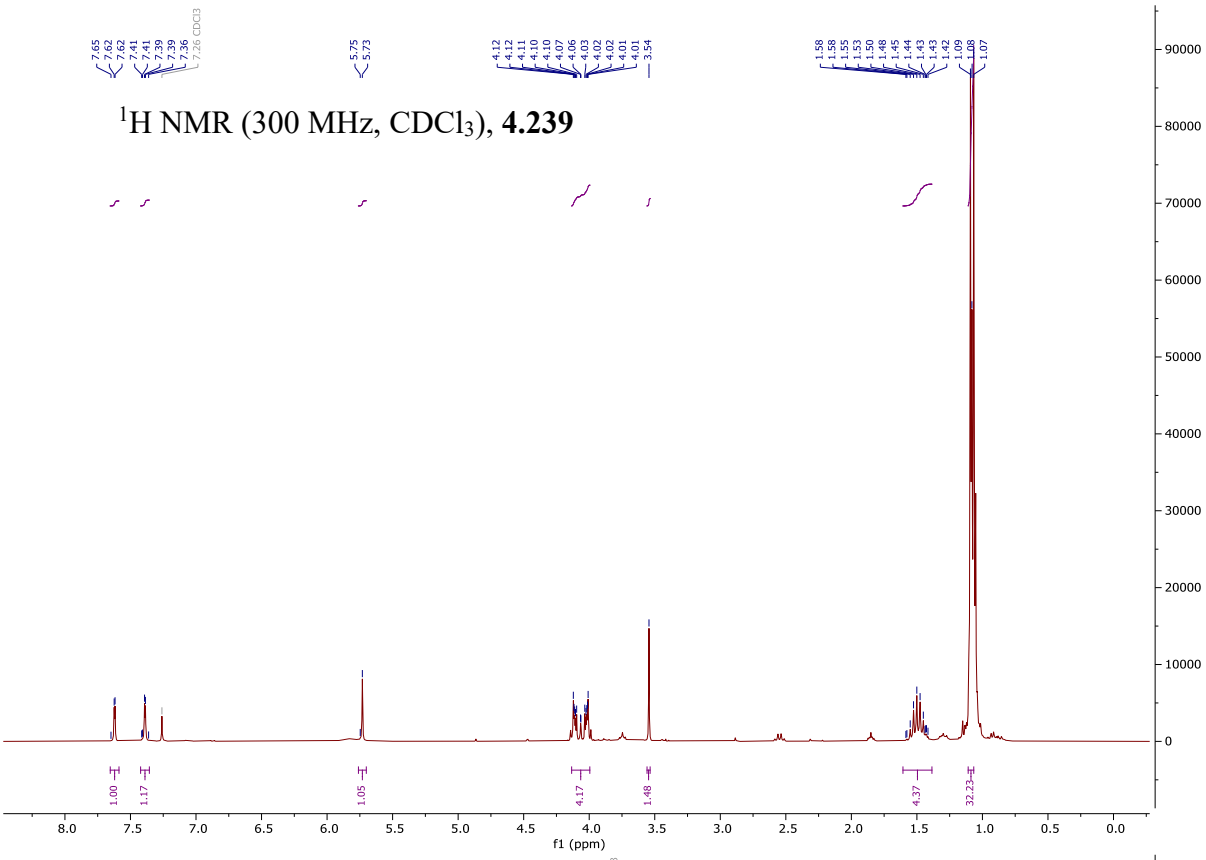


(4.239) 2-bromo-4-(1,3-dioxolan-2-yl)-6-(triisopropylsilyl)phenol

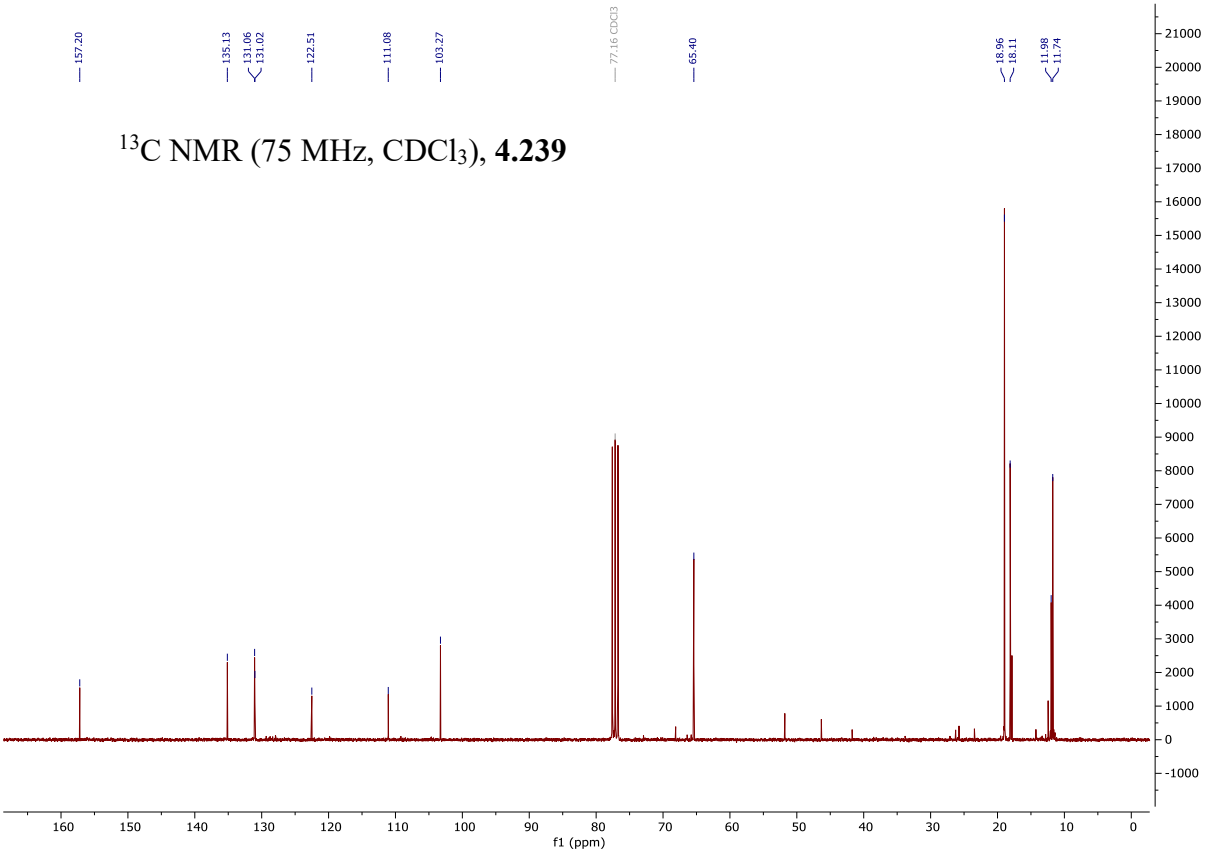
In a 100 mL RBF was added starting material (15 g, 46 mmol, 1 equiv), THF (46 mL, 1.0 M), TEA (10 mL, 74 mmol, 1.6 equiv), and TIPS-Cl (16 mL, 74 mmol, 1.6 equiv). The solution was to stir for 16 hours at room temperature. The solution was then cooled to -78 °C and BuLi (48 mL, 74 mmol, 1.6 equiv) dropwise. After 1 hour the reaction was quenched with MeOH (10 mL) and sat. $NaHCO_3$ (aq) (40 mL). The mixture was extracted with ether (3 x 40 mL). The organics were dried with brine (60 mL) and $MgSO_4$. The crude organic residue was a brown to tan solid which was in sufficient purity for subsequent reactions (18.1 g, 97%).

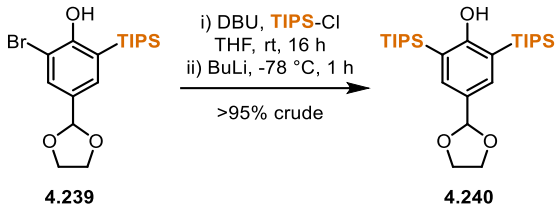
TLC (Hexanes/EtOAc, 90:10), RF:	0.44 (UV, potassium permanganate)
^{1}H NMR (300 MHz, $CDCl_3$), **4.239**	δ = 7.62 (d, J=2.0, 1H), 7.39 (d, J=2.0, 1H), 5.73 (s, 1H), 4.13 – 4.00 (m, 4H), 3.54 (s, 1H), 1.49 (h, J=7.4, 3H), 1.11 – 1.07 (m, 18H).
^{13}C NMR (75 MHz, $CDCl_3$), **4.239**	δ = 157.2, 135.1, 131.1, 131.0, 122.5, 111.1, 103.3, 65.4, 19.0, 18.1, 12.0, 11.7.
HRMS (ESI):	m/z calculated for $C_{18}H_{29}BrO_3Si$ ([M+H]+): 401.1142, found 401.1139
FTIR (neat) cm^{-1} :	$\tilde{\nu}$ = 3511 (br), 2943 (m), 2888 (m), 2864 (s), 1235 (w), 1077 (vs), 881 (vs), 678 (w)

^{1}H NMR (300 MHz, $CDCl_3$), **4.239**



^{13}C NMR (75 MHz, $CDCl_3$), **4.239**

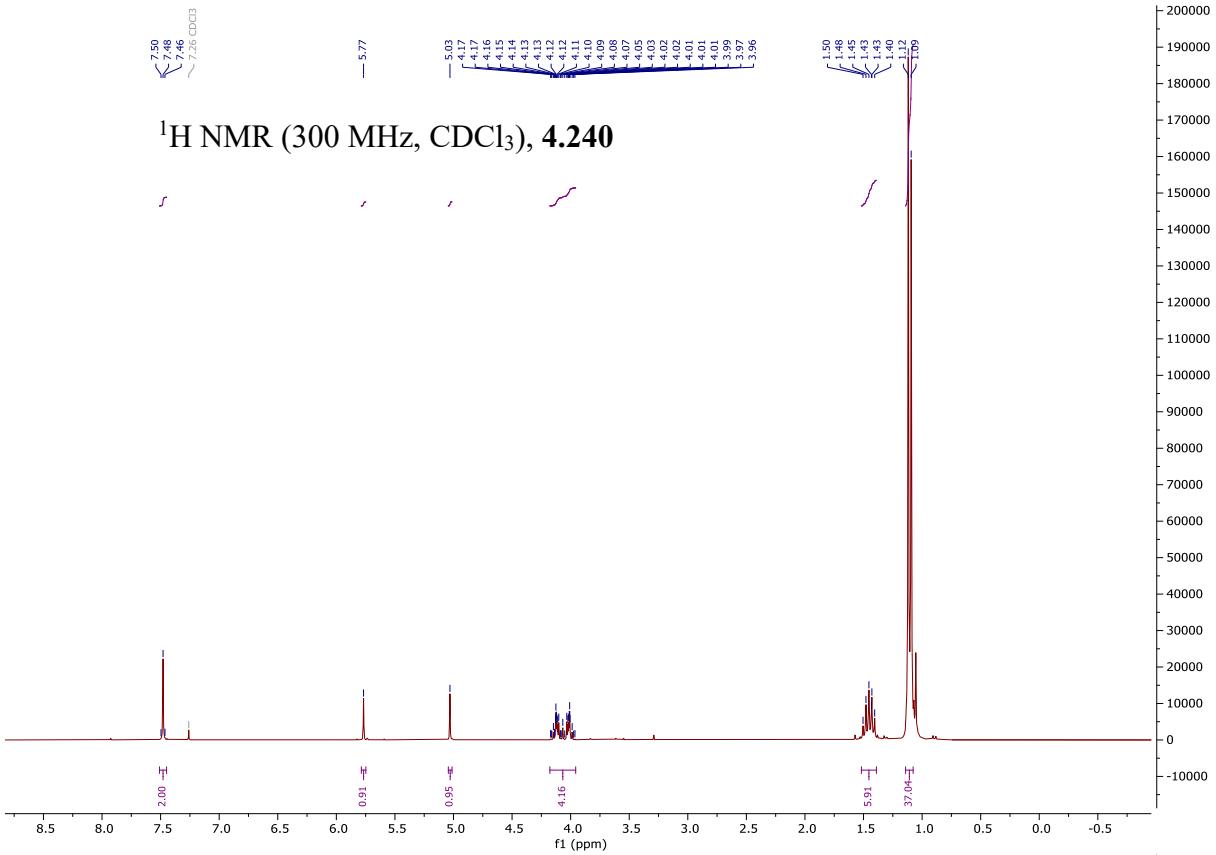




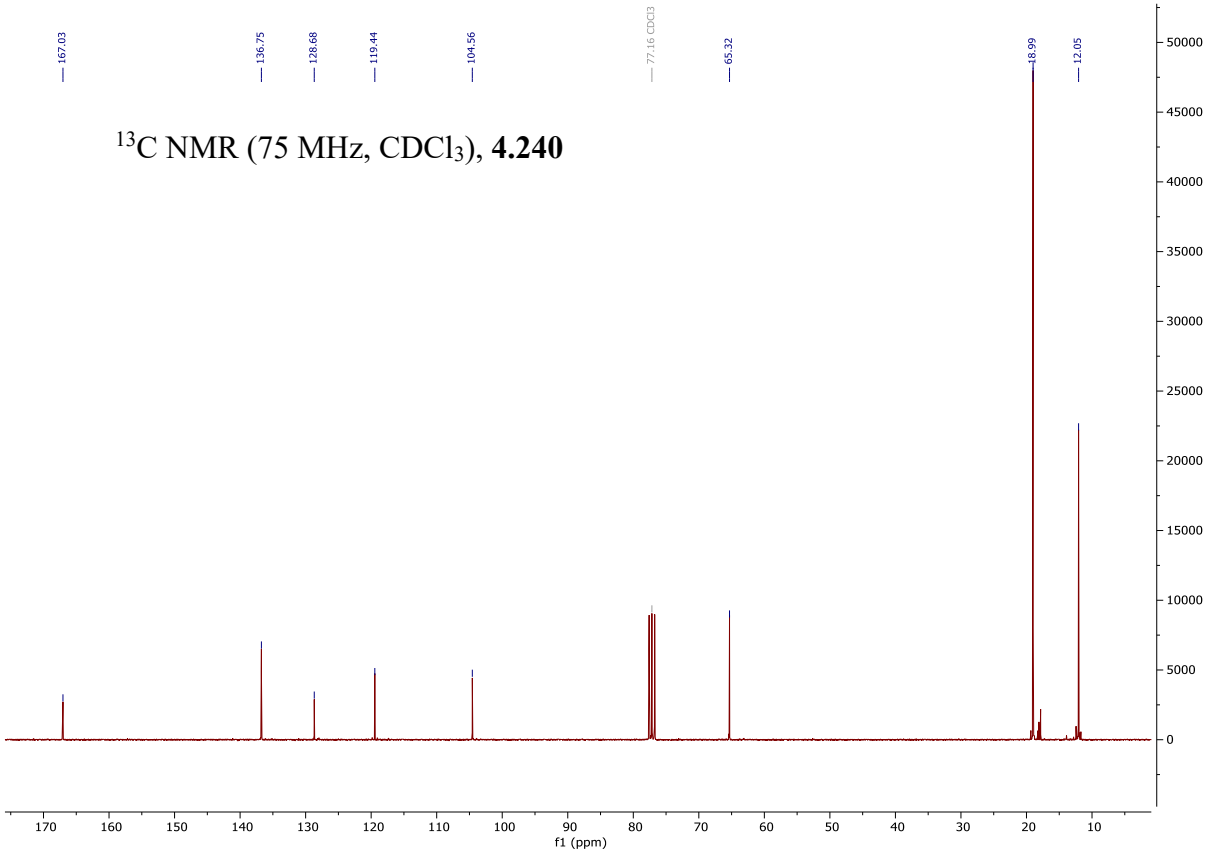
(4.240) 4-(1,3-dioxolan-2-yl)-2,6-bis(triisopropylsilyl)phenol

In a 100 mL RBF was added starting material (3.7 g, 9 mmol, 1 equiv), THF (46 mL, 0.2 M), DBU (2.2 mL, 15 mmol, 1.6 equiv), and TIPS-Cl (3.2 mL, 15 mmol, 1.6 equiv). The solution was to stir for 16 hours at room temperature. The solution was then cooled to -78 °C and BuLi (9.5 mL, 15 mmol, 1.6 equiv) dropwise. After 1 hour the reaction was quenched with MeOH (10 mL) and sat. $NaHCO_3$ (aq) (40 mL). The mixture was extracted with ether (3 x 40 mL). The organics were dried with brine (60 mL) and $MgSO_4$. The crude organic residue was a brown to tan solid which was in sufficient purity for subsequent reactions (4.2 g, 95%).

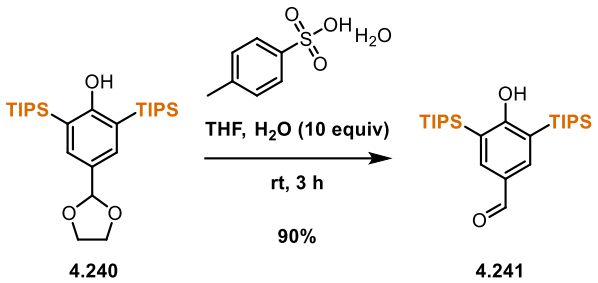
TLC (Hexanes/EtOAc, 90:10), RF:	0.55 (UV, potassium permanganate)
^{1}H NMR (300 MHz, $CDCl_3$), **4.240**	δ = 7.48 (s, 2H), 5.77 (s, 1H), 5.03 (s, 1H), 4.18 – 3.96 (m, 4H), 1.52 – 1.39 (m, 6H), 1.11 (d, J=7.5, 36H).
^{13}C NMR (75 MHz, $CDCl_3$), **4.240**	δ = 167.0, 136.7, 128.7, 119.4, 104.6, 65.3, 19.0, 12.1.
HRMS (ESI):	m/z calculated for $C_{27}H_{50}O_3Si_2$ ([M+H]+): 479.3371, found 479.3370
FTIR (neat) cm^{-1} :	$\tilde{\nu}$ = 3364 (br), 2944 (w), 2865 (s), 1088 (s), 908 (w), 881 (vs), 757 (w), 732 (vs), 675 (vs)



^{1}H NMR (300 MHz, $CDCl_3$), **4.240**



^{13}C NMR (75 MHz, $CDCl_3$), **4.240**



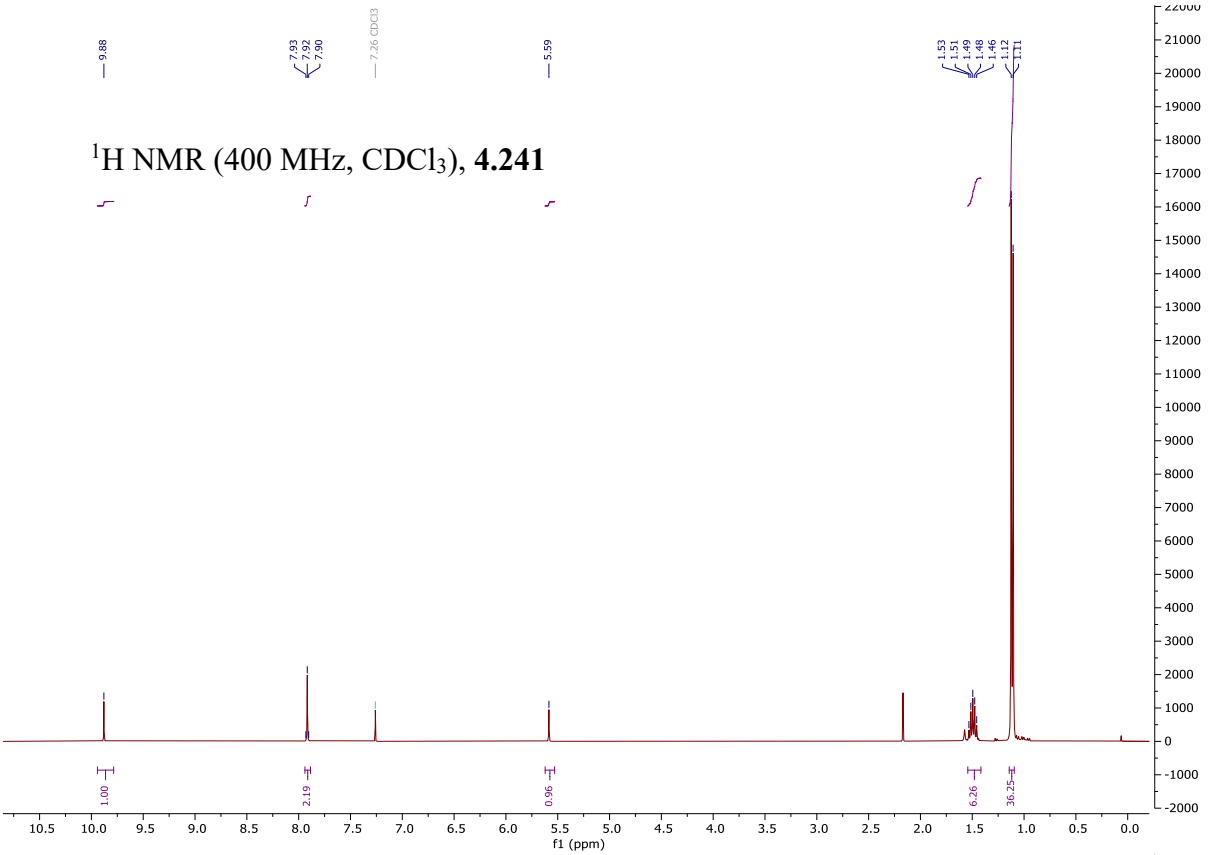
4.240 4.241

(4.241) 4-hydroxy-3,5-bis(triisopropylsilyl)benzaldehyde

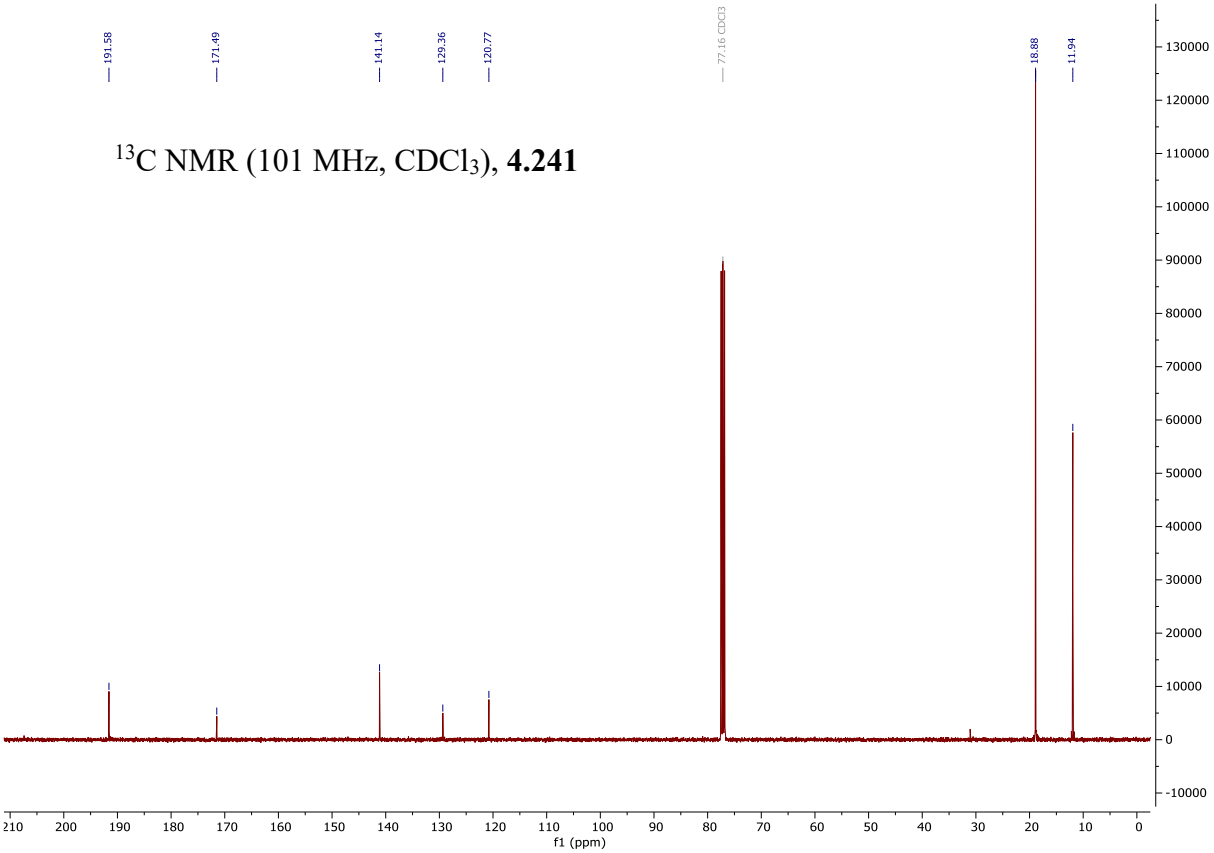
In a 50 mL RBF was added starting material (1.0 g, 2 mmol, 1 equiv), THF (21 mL, 0.1 M), and p-toluene sulfonic acid monohydrate (120 mg, 96 µmol, 0.3 equiv). The solution was stirred at room temperature for 3 hours. The reaction was diluted with water (30 mL) and extracted with ether (3 x 40 mL). The organics were dried with brine (60 mL) and $MgSO_4$. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-30% EtOAc in Hexanes) to yield the product as an amorphous white solid (815 mg, 90%).

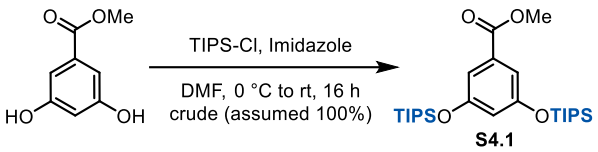
TLC (Hexanes/EtOAc, 90:10), RF:	0.55 (UV, potassium permanganate)
^{1}H NMR (400 MHz, $CDCl_3$), **4.241**	δ = 7.48 (s, 2H), 5.77 (s, 1H), 5.03 (s, 1H), 4.18 – 3.96 (m, 4H), 1.52 – 1.39 (m, 6H), 1.11 (d, J=7.5, 36H).
^{13}C NMR (101 MHz, $CDCl_3$), **4.241**	δ = 191.6, 171.5, 141.1, 129.4, 120.8, 18.9, 11.9.
HRMS (ESI):	m/z calculated for $C_{25}H_{46}O_2Si_2$ ([M+H]+): 435.3109, found 435.3106
FTIR (neat) cm^{-1} :	$\tilde{\nu}$ = 3588 (m), 2949 (vs), 2866 (vs), 1688 (s), 1573 (s), 1214 (m), 882 (s), 768 (w), 673 (s)

^{1}H NMR (400 MHz, $CDCl_3$), **4.241**



^{13}C NMR (101 MHz, $CDCl_3$), **4.241**

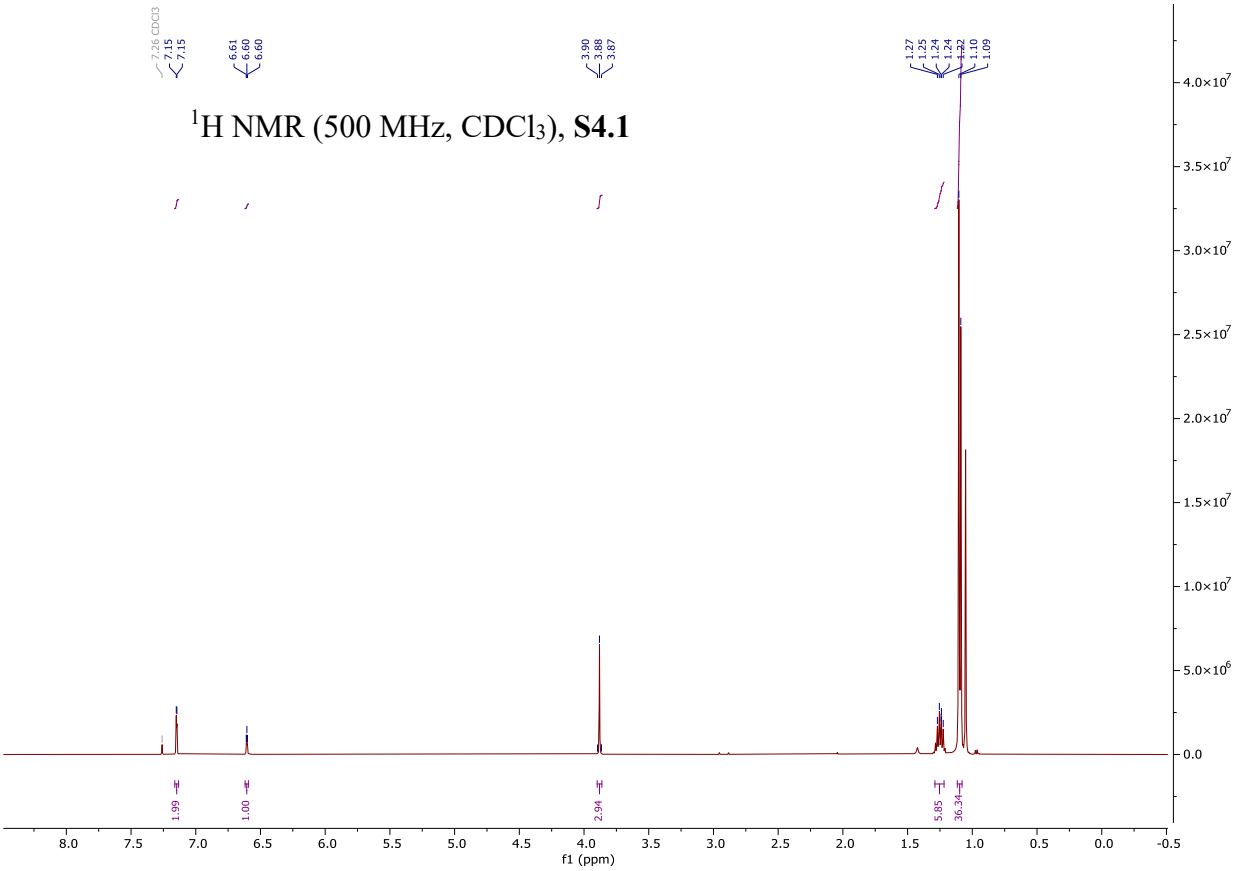


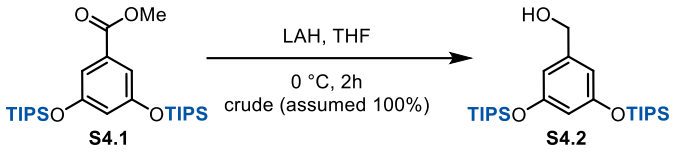


(S4.1) methyl 3,5-bis((triisopropylsilyl)oxy)benzoate

In a 500 mL RBF was added starting material (40 g, 238 mmol, 1 equiv), DMF (190 mL, 1.25 M), imidazole (42 g, 618 mmol, 2.6 equiv), and TIPS-Cl (112 mL, 523 mmol, 2.2 equiv) at 0 °C. The solution warmed to room temperature and was let stir for 16 hours. The reaction was diluted with water (200 mL) and extracted with ethyl acetate (5 x 200 mL). The organics were washed with water (5 x 500 mL) and dried with brine (1000 mL) and $MgSO_4$. The solvent was removed in vacuo and the crude material was deemed in sufficient purity for subsequent reactions. The product was isolated as a viscous tan oil (assumed 100%).

^{1}H NMR (500 MHz, $CDCl_3$), **S4.1** δ = 7.15 (d, J=2.3, 2H), 6.60 (t, J=2.3, 1H), 3.88 (s, 3H), 1.29 – 1.22 (m, 6H), 1.10 (d, J=7.5, 36H).

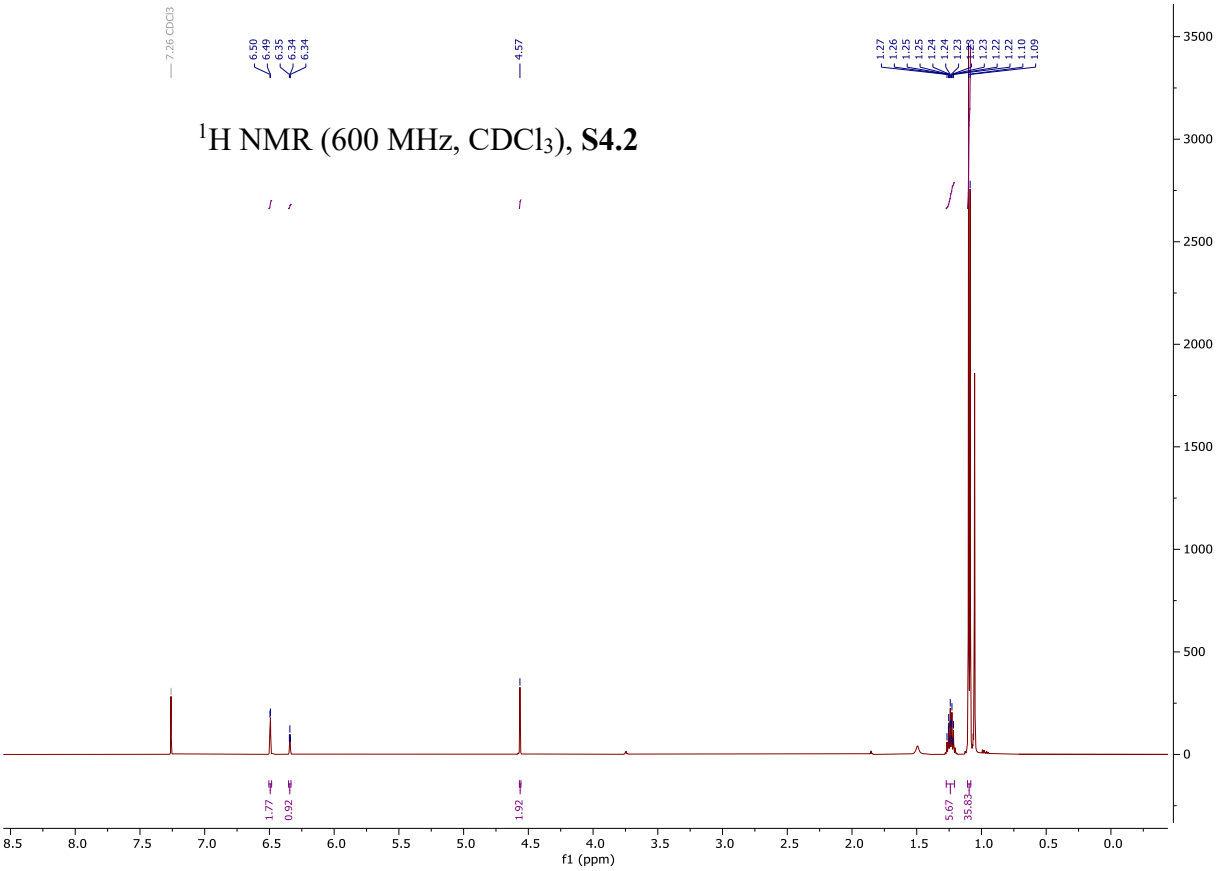


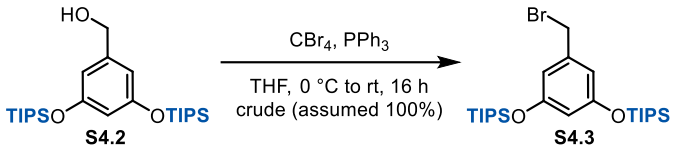


(S4.2) (3,5-bis((triisopropylsilyl)oxy)phenyl)methanol

In a 5 L, 3 neck RBF was added LAH (13.5 g, 356 mmol, 1.5 equiv), THF (1.0 L, 1.2 M) and starting material (114 g, 238 mmol, 1 equiv) as a solution of THF (200 mL) dropwise via addition funnel at 0 °C. The reaction was stirred at 0 °C for 2 hours. Upon full conversion of the starting material, assessed by TLC, the reaction was quenched with solid Glauber's salt, followed by methanol, and water. $MgSO_4$ (~50 g) was added as desiccant. The reaction was filtered, washing with ether (500 mL) and concentrated to dryness. The crude material was deemed in sufficient purity for subsequent reactions. The product was isolated as a viscous clear oil (assumed 100%).

^{1}H NMR (600 MHz, $CDCl_3$), **S4.2** δ = 6.49 (d, J=2.2, 2H), 6.34 (t, J=2.2, 1H), 4.57 (s, 2H), 1.27 – 1.21 (m, 6H), 1.09 (d, J=7.5, 36H).

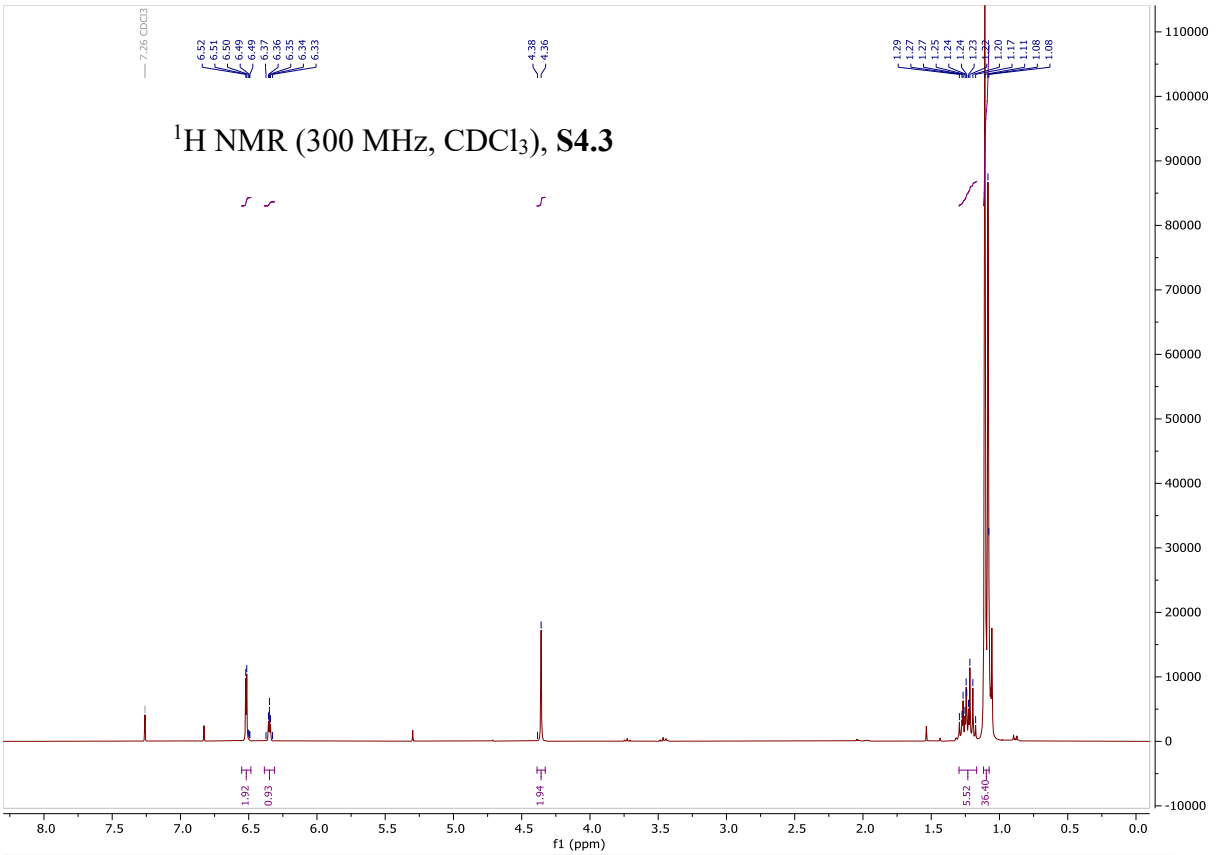




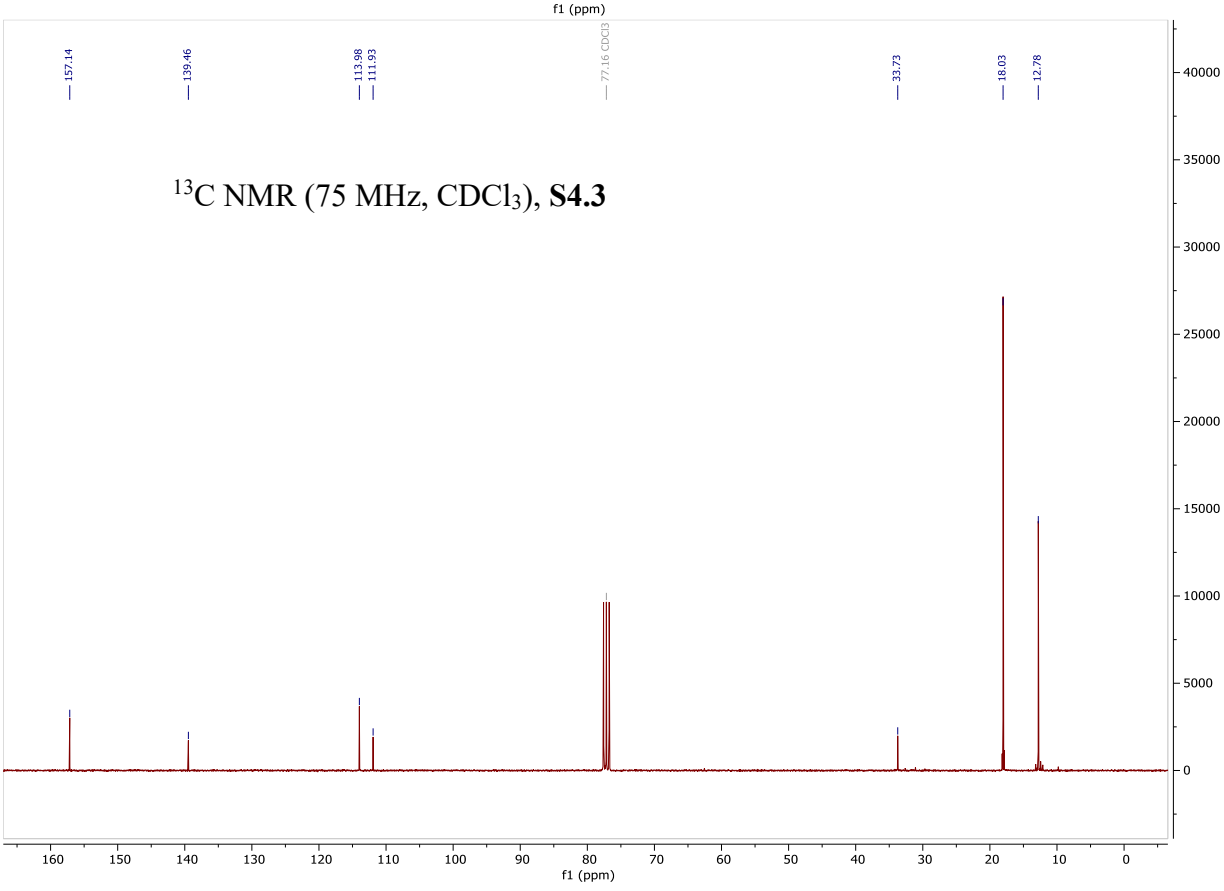
(S4.3) ((5-(bromomethyl)-1,3-phenylene)bis(oxy))bis(triisopropylsilane)

In a 500 mL RBF was added secondary alcohol (40 g, 88 mmol, 1 equiv), CBr_4 (37 g, 110 mmol, 1.25 equiv) and THF (220 mL, 0.4 M). The PPh_3 (29 g, 110 mmol, 1.25 equiv) was added as a solution in THF (60 mL) to a cooled (0 °C) reaction slurry. The reaction was shieled from light and let warm to room temperature overnight. Full consumption of alcohol was monitored by TLC. The reaction was diluted with with sat. $NaHCO_3$ (aq) (200 mL) and sat. $Na_2S_2O_3$ (aq) (200 mL) and extracted with ethyl acetate (3 x 200 mL). The organics were dried with brine (200 mL) and $MgSO_4$. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (10% EtOAc in Hexanes) using a large hand column (700 g silica). The semi-crude material was deemed in sufficient purity for subsequent reactions. The product was isolated as a viscous clear oil (assumed 100%).

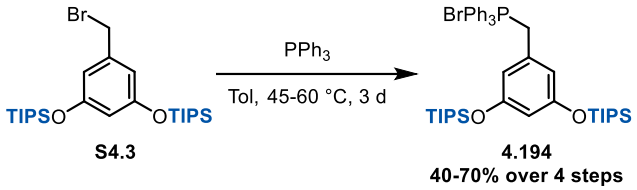
TLC (Hexanes/EtOAc, 90:10), RF:	0.86 (UV, potassium permanganate)
^{1}H NMR (300 MHz, $CDCl_3$), **S4.3**	δ = 6.52 (d, J=2.2, 2H), 6.35 (t, J=2.2, 1H), 4.36 (s, 2H), 1.30 – 1.17 (m, 6H), 1.10 (d, J=6.8, 36H).
^{13}C NMR (75 MHz, $CDCl_3$), **S4.3**	δ = 157.1, 139.5, 114.0, 111.9, 33.7, 18.0, 12.8.
HRMS (ESI):	m/z calculated for $C_{25}H_{47}BrO_2Si_2$ ([M+H]+): 515.2371, found 515.2365
FTIR (neat) cm^{-1} :	$\tilde{\nu}$ = 2867 (w), 1587 (m), 1451 (m), 1344 (w), 1172 (vs), 1031 (w), 1014 (w), 882 (m), 761 (w), 685 (m)



^{1}H NMR (300 MHz, $CDCl_3$), **S4.3**



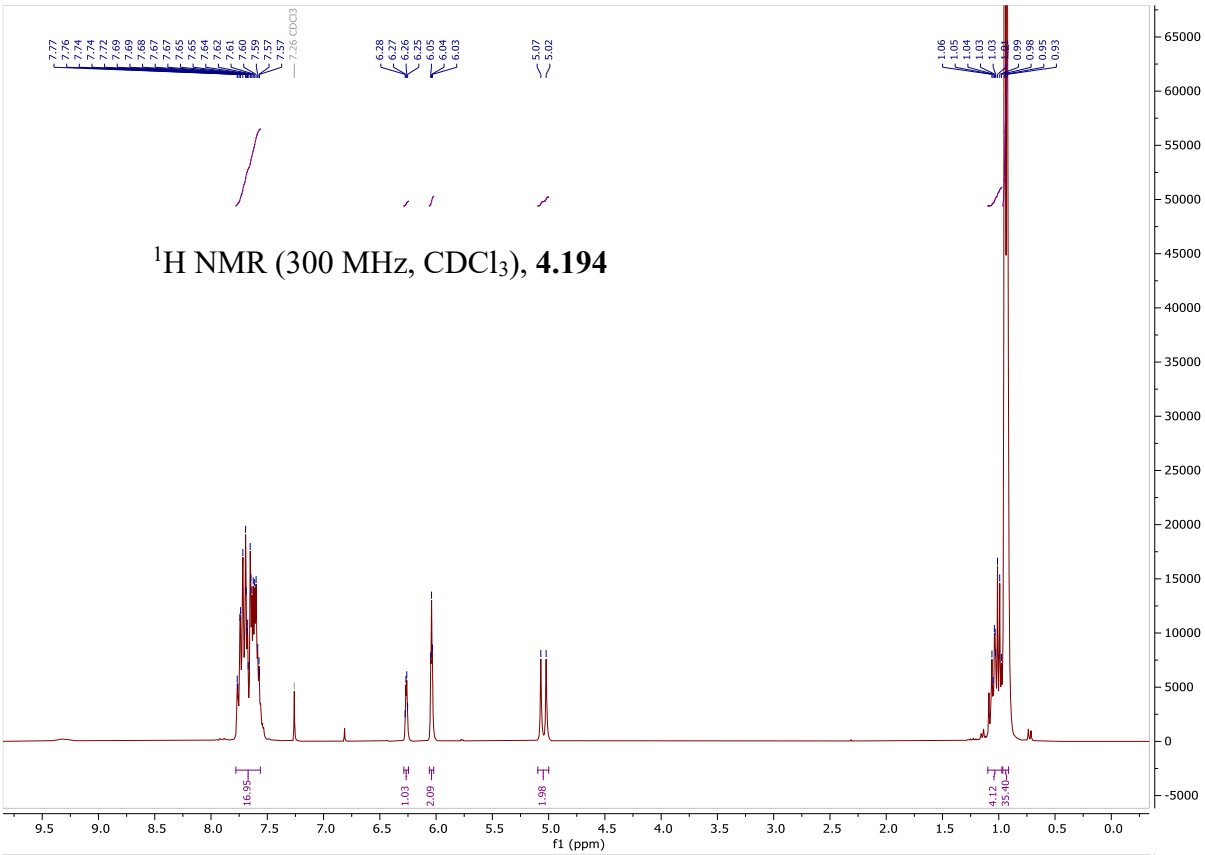
^{13}C NMR (75 MHz, $CDCl_3$), **S4.3**



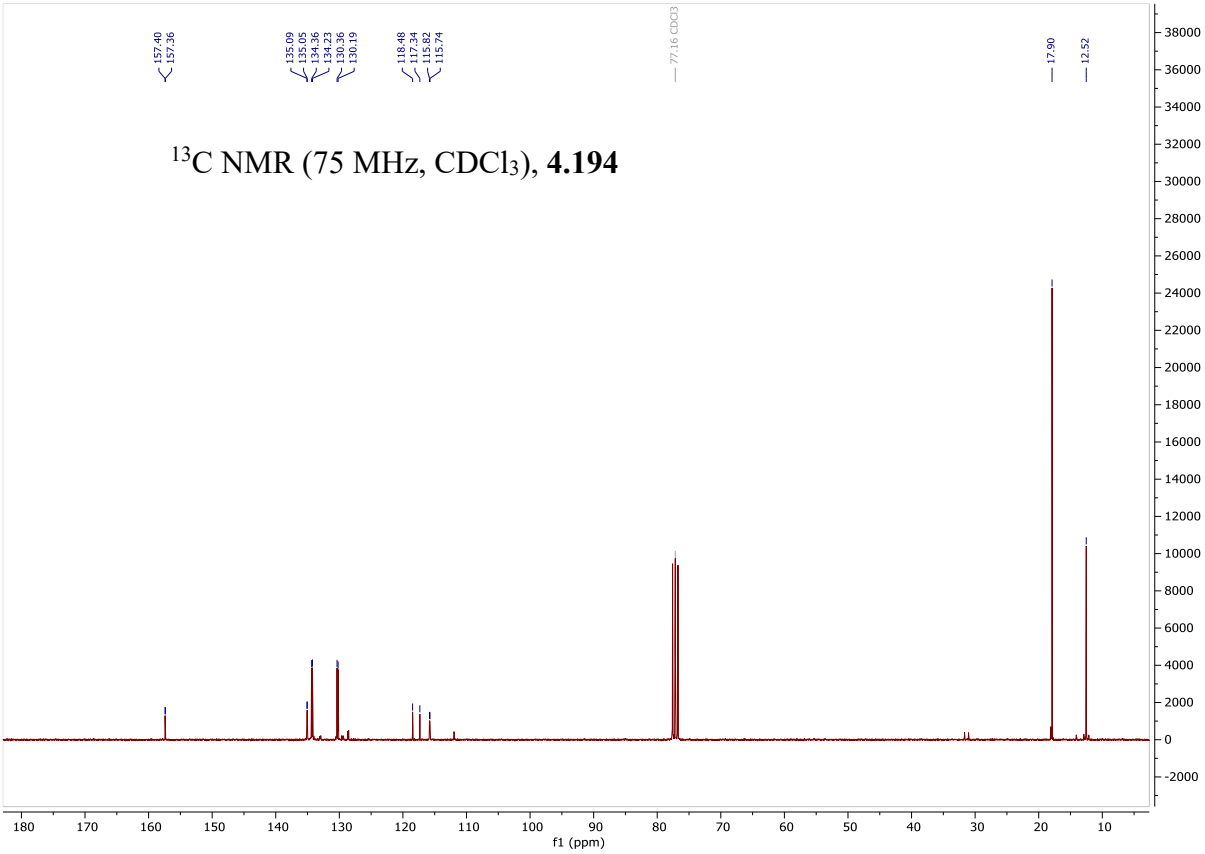
(4.194) (3,5-bis((triisopropylsilyl)oxy)benzyl)bromotriphenyl-l5-phosphane

In a 500 mL RBF was added the alkyl bromide (46 g, 88 mmol, 1 equiv), toluene (253 mL, 0.35 M), and triphenylphosphine (46 g, 177 mmol, 2 equiv). The reaction was heated to 45 °C for 48 hours, followed by 60 °C for another 24 hours in an oil bath. The reaction was let cool to room temperature before filtering and washing with hexanes (500 mL). The salt was dried (high vacuum), providing a free flowing white amorphous solid.

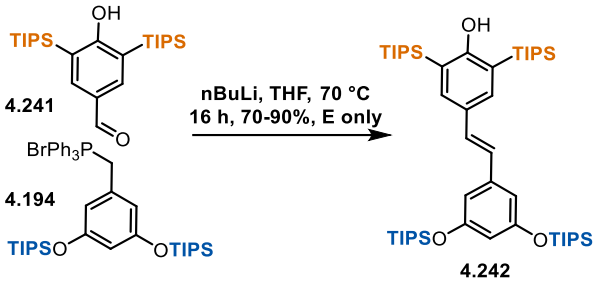
^{1}H NMR (300 MHz, $CDCl_3$), **4.194**	δ = 7.78 – 7.56 (m, 15H), 6.26 (q, J=2.2, 1H), 6.04 (t, J=2.4, 2H), 5.05 (d, J=14.2, 2H), 1.10 – 0.97 (m, 6H), 0.94 (d, J=6.2, 35H).
^{13}C NMR (75 MHz, $CDCl_3$), **4.194**	δ = 157.4, 157.4, 135.1, 135.0, 134.4, 134.2, 130.4, 130.2, 118.5, 117.3, 115.8, 115.7, 17.9, 12.5.



^{1}H NMR (300 MHz, $CDCl_3$), **4.194**

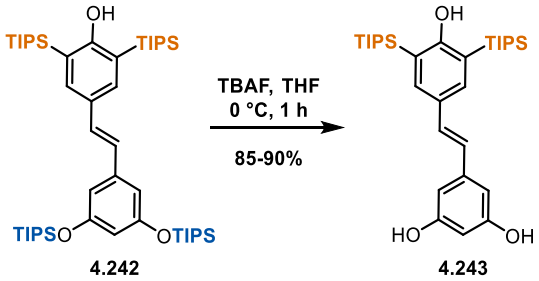


^{13}C NMR (75 MHz, $CDCl_3$), **4.194**



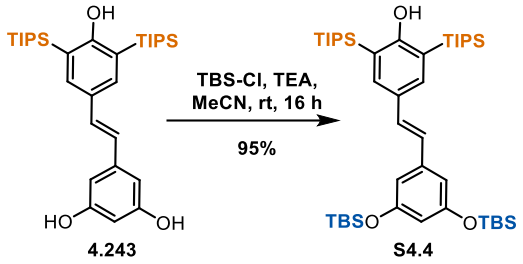
(4.242) (E)-4-(3,5-bis((triisopropylsilyl)oxy)styryl)-2,6-bis(triisopropylsilyl)phenol

In a 250 mL RBF was added phosphonium salt (12 g, 15 mmol, 2.2 equiv), THF (46 mL, 0.15 M), and BuLi (20 mL, 30 mmol, 4.4 equiv). The bright red solution was let stir for 10 minutes. The aldehyde (3 g, 6.9 mmol, 1 equiv) was added as a solution in THF (10 mL). The reaction was heated to 70 °C in an oil bath for 16 hours before quenching with methanol (5 mL). The crude reaction mixture was concentrated onto silica gel for purification by flash chromatography over SiO_2 (0%-15% EtOAc in Hexanes) to yield the product as a yellow to white viscous crystalline foam (5.1 g, 87%). Spectral data for this compound are identical to those reported in chapter 3.



(4.243) (E)-5-(4-hydroxy-3,5-bis(triisopropylsilyl)styryl)benzene-1,3-diol

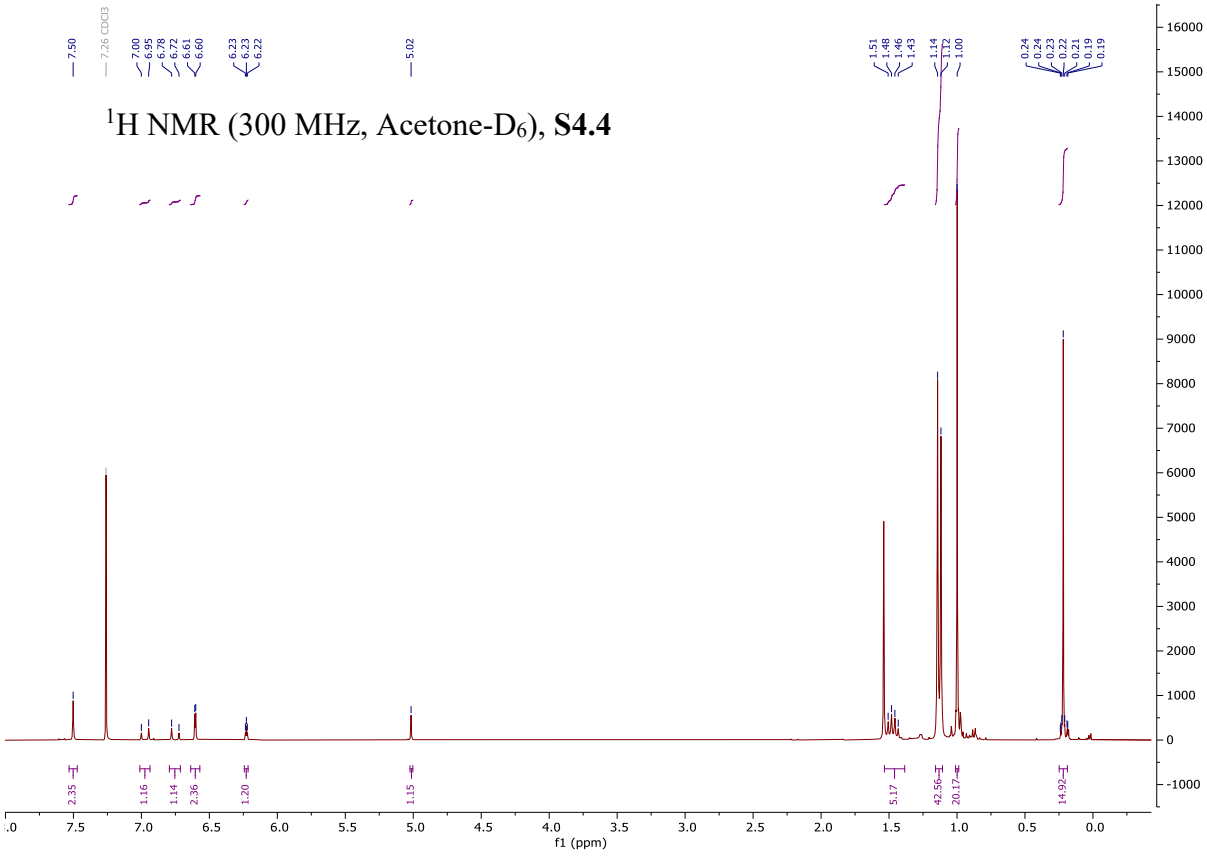
In a 250 mL RBF was added starting material (5.9 g, 6.9 mmol, 1 equiv), THF (140 mL, 0.05 M), and TBAF (15 mL, 15 mmol, 2.2 equiv, 1.0 M solution in THF) at 0 °C. After 1 hour of reaction time mixture was quenched with sat. $NaHCO_3$ (aq) (80 mL) and extracted with ether (3 x 80 mL). The organics were dried with brine (80 mL) and $MgSO_4$. The crude organic residue was subjected to column chromatography SiO_2 (0-50% ethyl acetate in hexanes) to afford the product as a tan foam (3.2 g, 85%). Spectral data for this compound are identical to those reported in chapter 3.

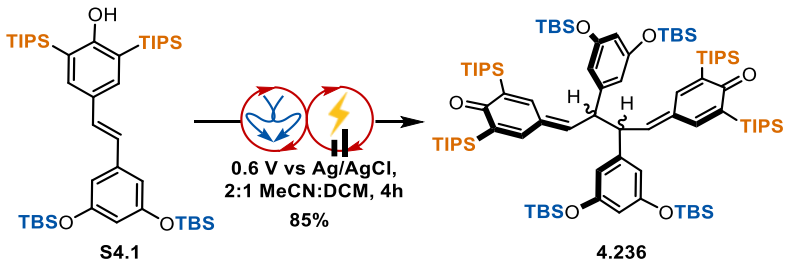


(S4.4) (E)-4-(3,5-bis((tert-butyldimethylsilyl)oxy)styryl)-2,6-bis(triisopropylsilyl)phenol

In a 50 mL RBF was added starting material (640 mg, 1.2 mmol, 1 equiv), MeCN (24 mL, 0.05 M), TEA (0.66 mL, 5 mmol, 4 equiv), and TBS-Cl (713 mg, 5 mmol, 4 equiv). After 16 hour of reaction time mixture was quenched with water (50 mL) and extracted with ether (3 x 50 mL). The organics were dried with brine (50 mL) and $MgSO_4$. The crude organic residue was subjected to column chromatography SiO_2 (0-10% ethyl acetate in hexanes) to afford the product as a viscous opaque oil (860 mg, 95%).

^{1}H NMR (300 MHz, D_6-Acetone), **S4.4** δ = 7.50 (s, 2H), 6.97 (d, J=16.2, 1H), 6.75 (d, J=16.2, 1H), 6.60 (d, J=2.2, 2H), 6.23 (t, J=2.2, 1H), 5.02 (s, 1H), 1.47 (q, J=7.4, 6H), 1.13 (d, J=7.4, 36H), 1.00 (s, 18H), 0.22 (s, 18H).

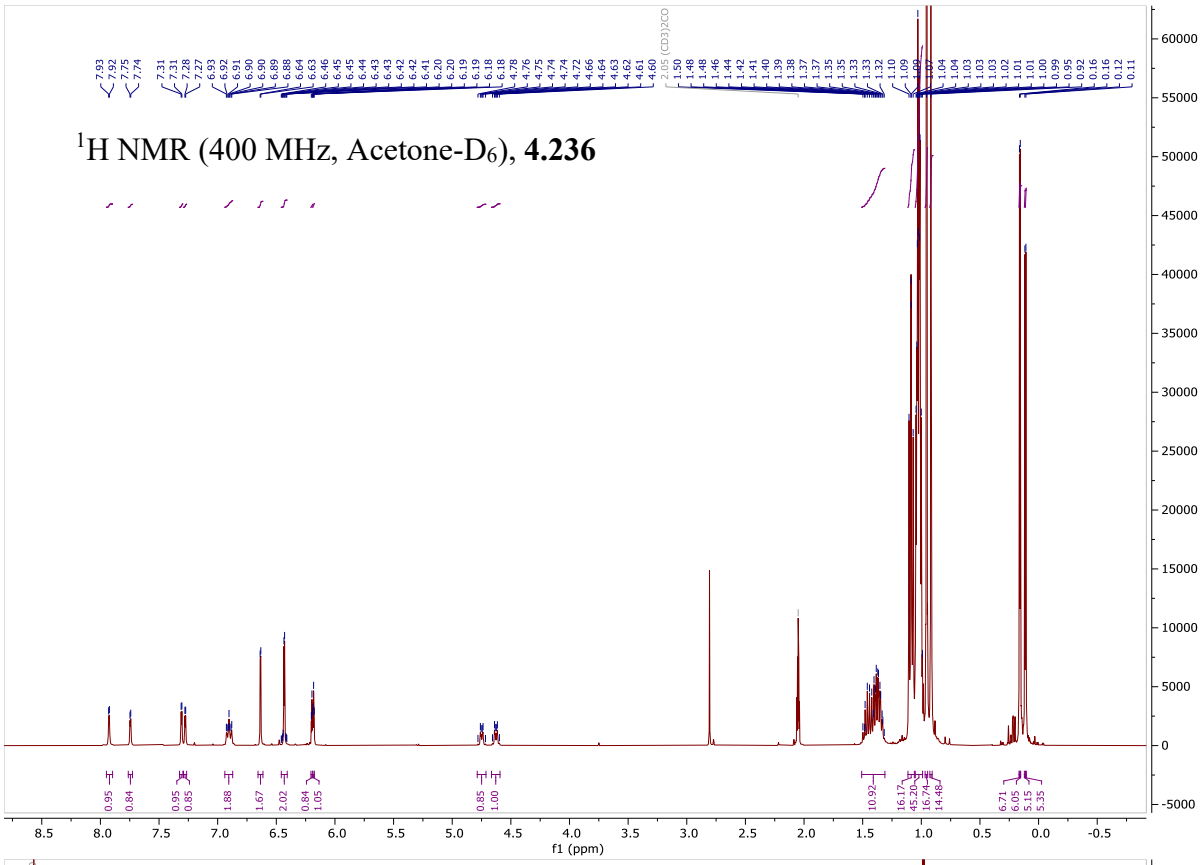


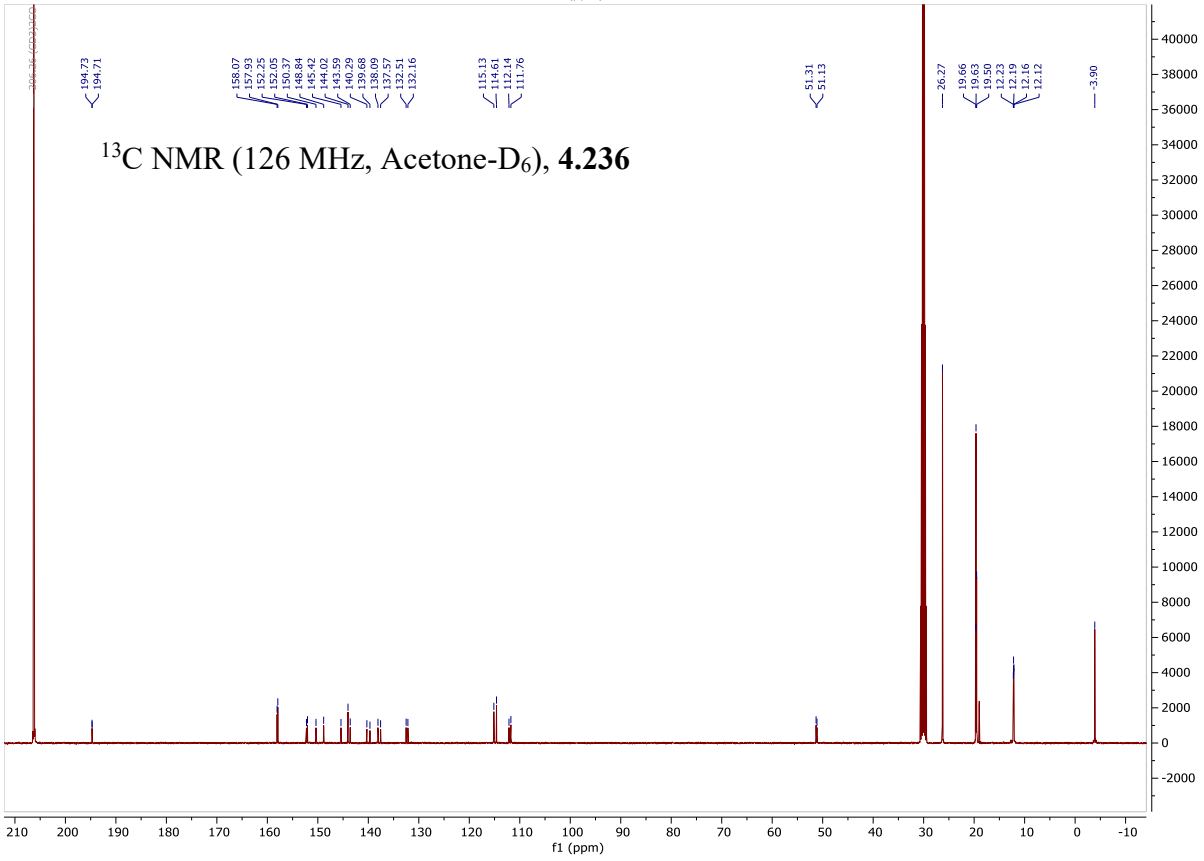


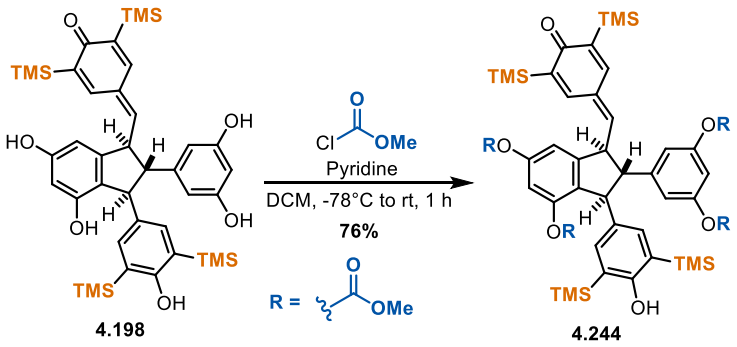
(4.236) 4-hydroxy-3,5-bis(triisopropylsilyl)benzaldehyde

The starting phenol (4.3 g, 5.6 mmol, 1.0 equiv) was added to a 500 mL beaker with KPF_6 (4.1 g, 22 mmol, 4.0 equiv) and 2,6-lutidine (644 µL, 5.6 mmol, 1.0 equiv) and dissolved in acetonitrile (300 mL) and dichloromethane (150 mL). Two pieces of 4 x 10-inch RVC panel (0.25-inch thickness) were cut. To each, a hole was made near one end, and copper wire was placed through the hole and wrapped around the top of each electrode. One end of the wire was left free to connect to the alligator clips. These electrodes were carefully placed into the beaker along with the reference electrode (Ag/AgCl in 3 M KCl) and a divider. The alligator clips were connected such that the reference and working electrodes were adjacent to each other, while the counter electrode was opposite the divider. Care was taken to ensure the copper wire was not submerged in solvent, nor the active components of the alligator clips touching each other. The reaction was stirred at 750 rpm for 1-2 h at a constant voltage of 0.6 V. A chronoampergram was recorded to follow the course of the reaction. Upon completion of the reaction, the electrodes were removed and rinsed into a collection flask with DCM (~100 mL). The contents of the reaction vial were also rinsed into the collection flask. The solvent was removed in vacuo, and the crude material was purified by flash chromatography over SiO_2 (0%-10% EtOAc in Hexanes) to yield the product as a bright yellow foam (3.6 g, 85%, 1.1:1 mixture of diastereomers).

TLC (Hexanes/EtOAc, 95:5), RF:	0.87 (UV, potassium permanganate)
^{1}H NMR (400 MHz, Acetone-D_6), **4.236**	δ = 7.93 (d, J=2.5, 1H), 7.74 (d, J=2.6, 1H), 7.31 (d, J=2.5, 1H), 7.28 (d, J=2.5, 1H), 6.94 – 6.87 (m, 2H), 6.63 (d, J=2.2, 2H), 6.43 (d, J=2.2, 2H), 6.20 (t, J=2.2, 1H), 6.18 (t, J=2.2, 1H), 4.75 (dd, J=6.5, 2.7, 1H), 4.67 – 4.59 (m, 1H), 1.51 – 1.31 (m, 11H), 1.09 (dd, J=7.5, 6.6, 16H), 1.05 – 0.99 (m, 45H), 0.95 (s, 17H), 0.92 (s, 14H), 0.16 (s, 7H), 0.16 (s, 6H), 0.12 (s, 5H), 0.11 (s, 5H).
^{13}C NMR (126 MHz, Acetone-D_6), **4.236**	δ = 194.7, 194.7, 158.1, 157.9, 152.3, 152.1, 150.4, 148.8, 145.4, 144.0, 143.6, 140.3, 139.7, 138.1, 137.6, 132.5, 132.2, 115.1, 114.6, 112.1, 111.8, 51.3, 51.1, 26.3, 19.7, 19.6, 19.5, 12.2, 12.2, 12.2, 12.1, -3.9.
HRMS (ESI):	m/z calculated for $C_{88}H_{158}O_6Si_8$ ([M+H]+): 1536.0285, found 1536.02553
FTIR (neat) cm^{-1} :	ν̃= 2942 (w), 2864 (m), 1592 (vs), 1450 (w), 1254 (w), 1167 (m), 1029 (w), 882 (w), 830 (s), 814 (w), 781 (w)


^{1}H NMR (400 MHz, Acetone-D6), 4.236
f1 (ppm)

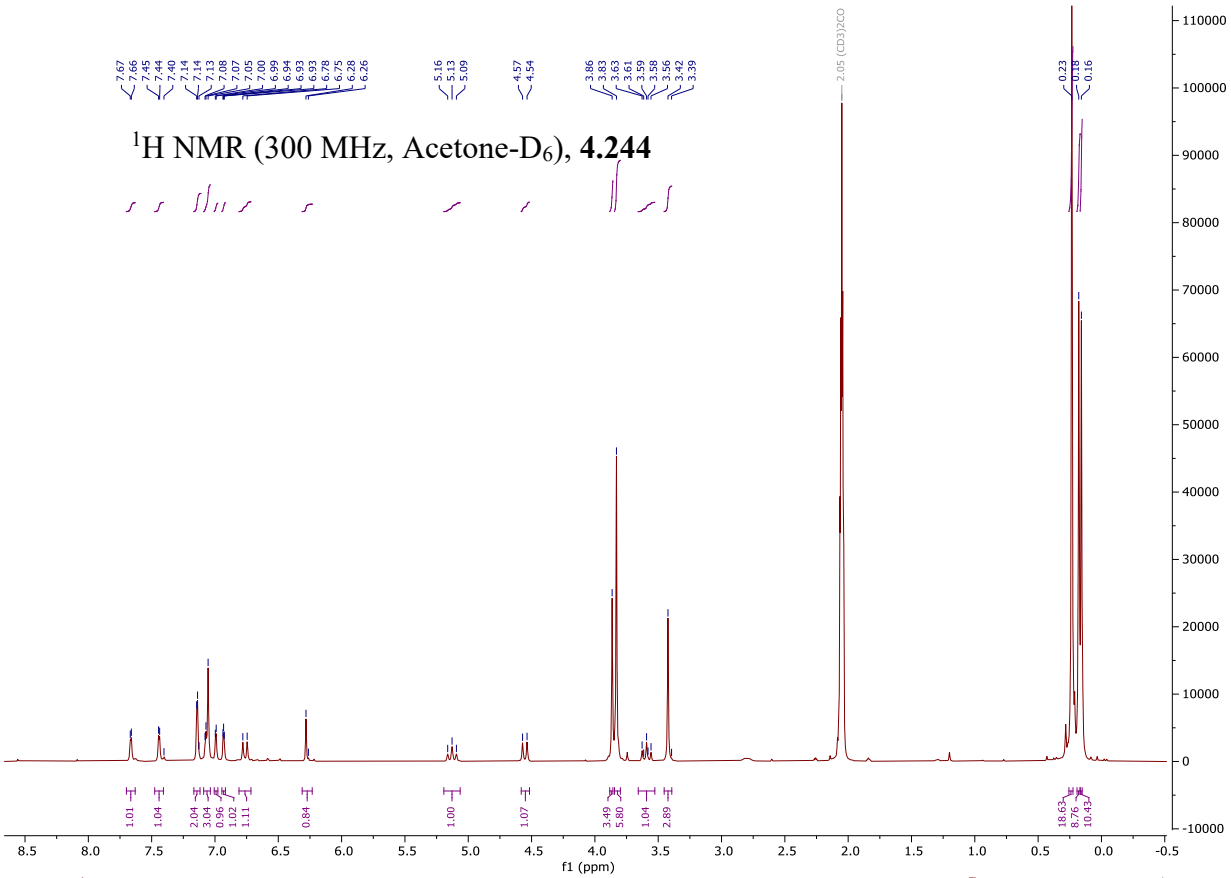

^{13}C NMR (126 MHz, Acetone-D6), 4.236
f1 (ppm)



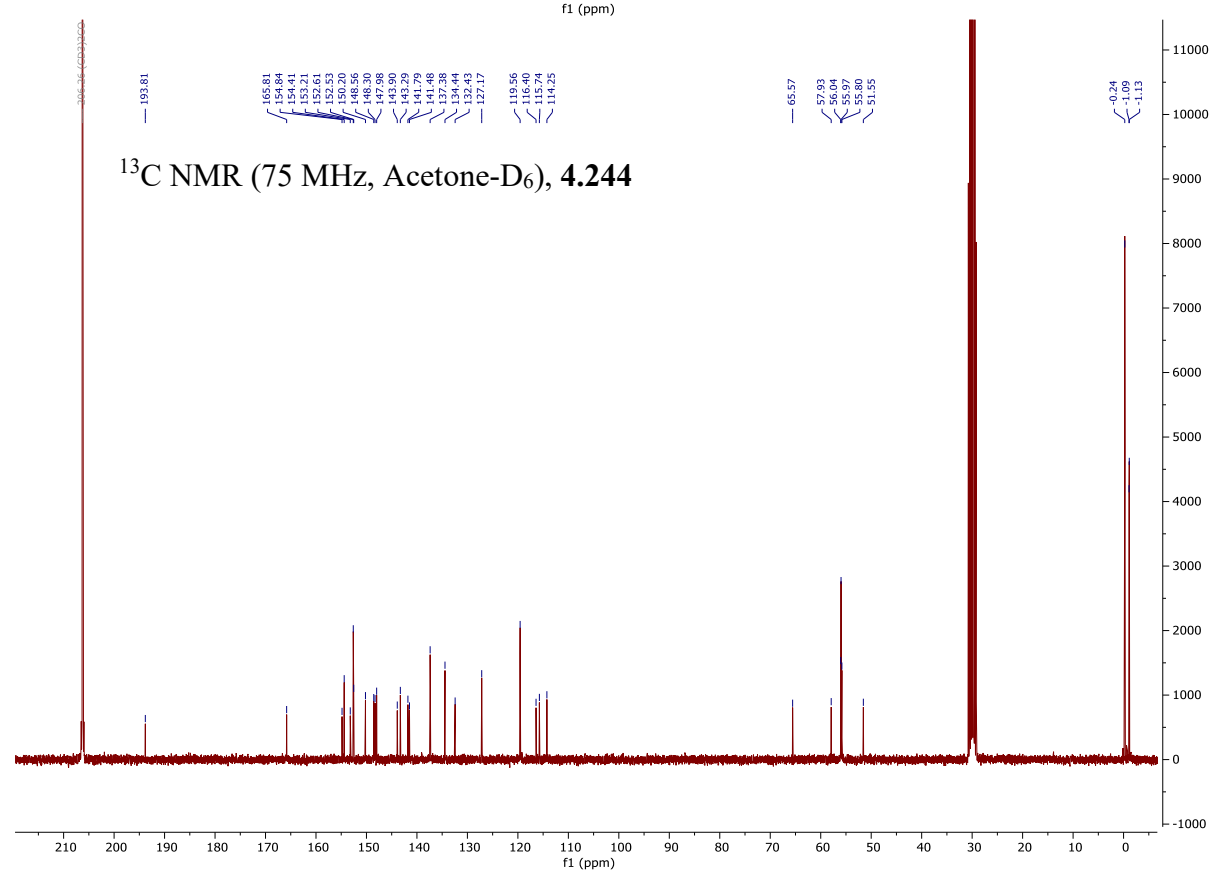
(4.244) 5-((1S,2S,3S)-3-(4-hydroxy-3,5-bis(trimethylsilyl)phenyl)-4,6-bis((methoxycarbonyl)oxy)-1-((4-oxo-3,5-bis(trimethylsilyl)cyclohexa-2,5-dien-1-ylidene)methyl)-2,3-dihydro-1H-inden-2-yl)-1,3-phenylene dimethyl bis(carbonate)

In a 10 mL RBF was added starting material (142 mg, 0.191 mmol, 1 equiv), DCM (2.4 mL, 0.08 M), and pyridine (155 µL, 1.9 mmol, 10 equiv) and the solution was cooled to -78 °C. Methyl chloroformate (118 µL, 1.5 mmol, 8 equiv) was added dropwise. The solution was slowly warmed to room temperature over the course of 1 hour. The reaction was diluted with water (10 mL) and extracted with ether (3 x 10 mL). The organics were dried with brine (20 mL) and $MgSO_4$. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-30% EtOAc in Hexanes) to yield the product as a pale white foam (142 mg, 76%).

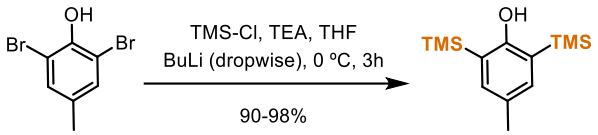
TLC (Hexanes/EtOAc, 80:20), RF:	0.40 (UV, potassium permanganate)
^{1}H NMR (300 MHz, Acetone-D_6), **4.244**	δ = 7.66 (d, J=2.6, 1H), 7.44 (d, J=2.6, 1H), 7.14 (d, J=2.2, 2H), 7.06 (d, J=5.1, 3H), 6.99 (d, J=2.1, 1H), 6.93 (d, J=1.8, 1H), 6.76 (d, J=10.3, 1H), 6.28 (s, 1H), 5.13 (t, J=10.3, 1H), 4.55 (d, J=10.7, 1H), 3.86 (s, 3H), 3.83 (s, 6H), 3.59 (t, J=10.6, 1H), 3.42 (s, 3H), 0.23 (s, 18H), 0.18 (s, 9H), 0.16 (s, 9H).
^{13}C NMR (75 MHz, Acetone-D_6), **4.244**	δ = 193.8, 165.8, 154.8, 154.4, 153.2, 152.6, 152.5, 150.2, 148.6, 148.3, 148.0, 143.9, 143.3, 141.8, 141.5, 137.4, 134.4, 132.4, 127.2, 119.6, 116.4, 115.7, 114.3, 65.6, 57.9, 56.0, 56.0, 55.8, 51.6, -0.2, -1.1, -1.1.
HRMS (ESI):	m/z calculated for $C_{48}H_{62}O_{14}Si_4$ ([M+H]+): 975.3289, found 975.3295
FTIR (neat) cm^{-1} :	ν̃= 3608 (br), 2957 (w), 1769 (s), 1596 (w), 1440 (w), 1240 (vs), 1197 (w), 1155 (w), 841 (s)



^{1}H NMR (300 MHz, Acetone-D$_6$), **4.244**



^{13}C NMR (75 MHz, Acetone-D$_6$), **4.244**

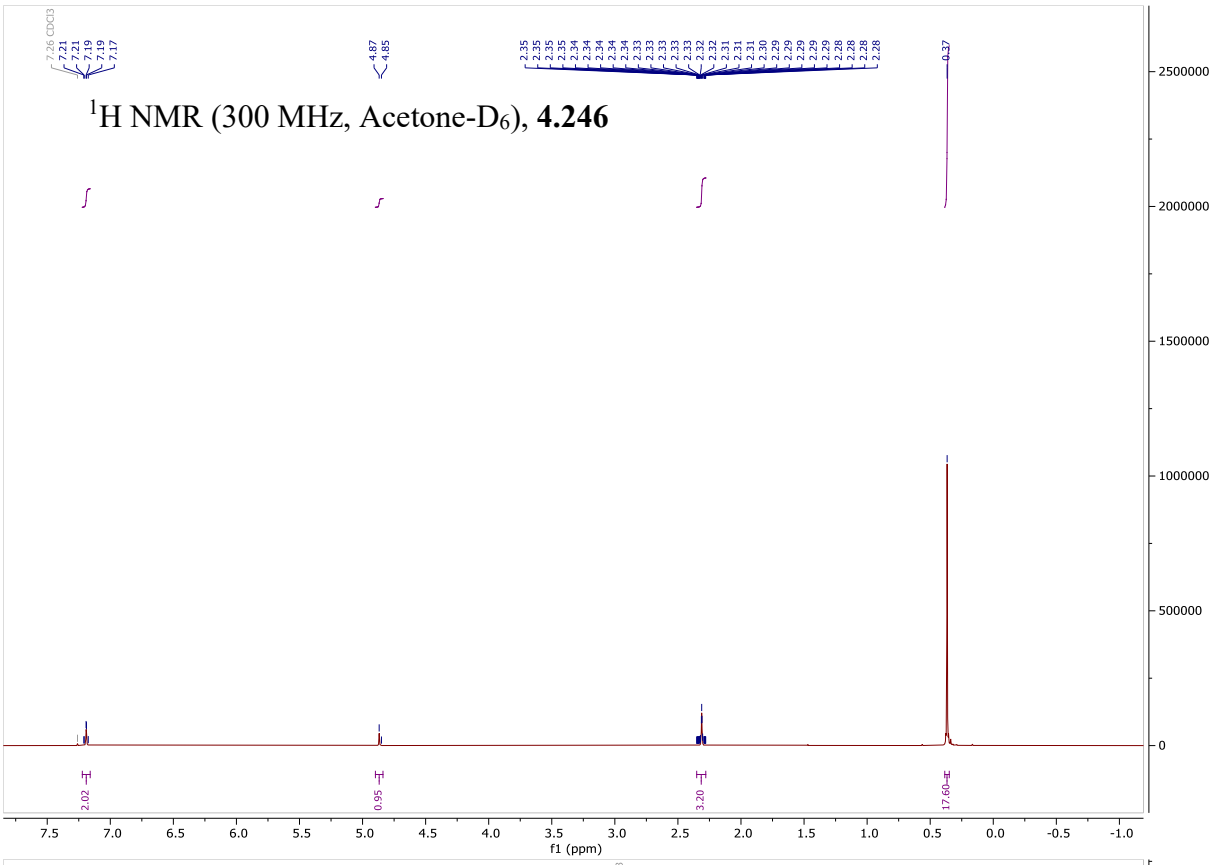


4.246

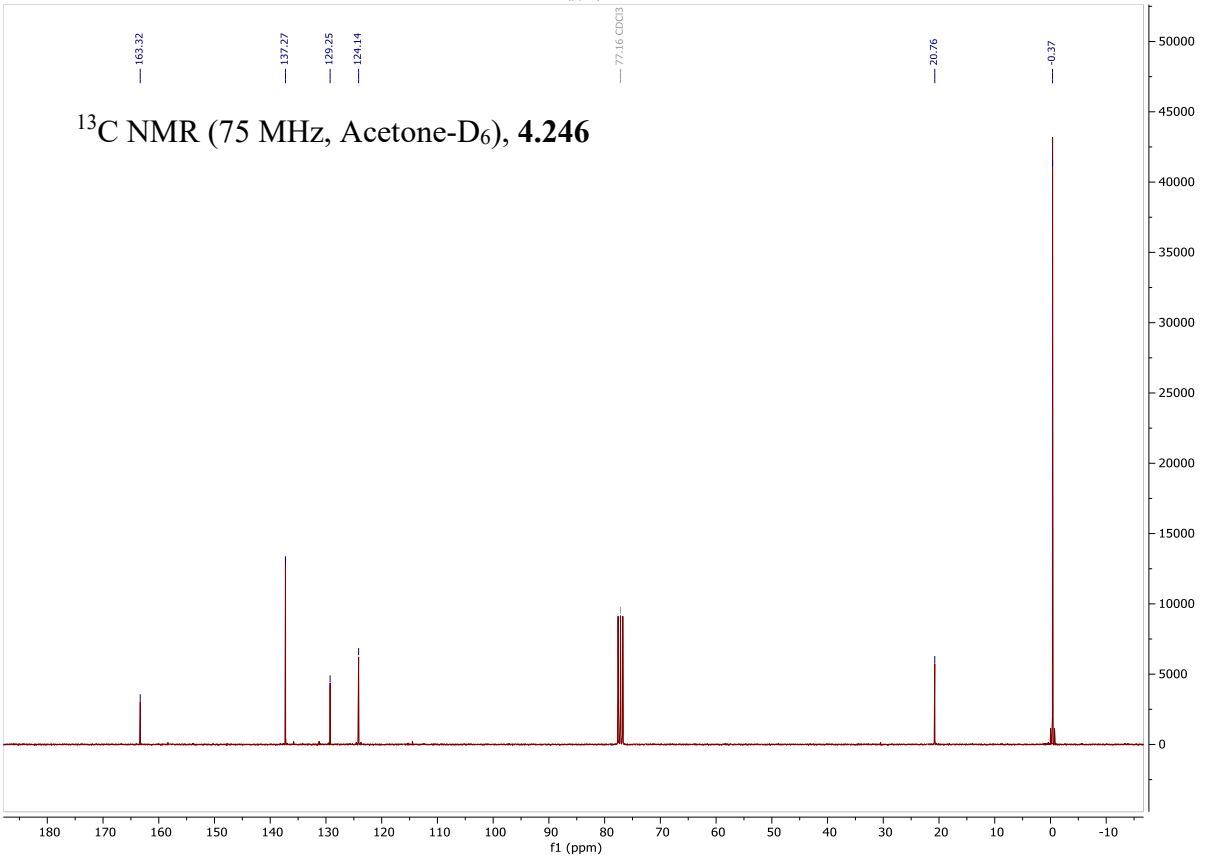
(4.246) 4-methyl-2,6-bis(trimethylsilyl)phenol

In a 100 mL RBF was added starting material (2.0 g, 7.5 mmol, 1 equiv), THF (38 mL, 0.2 M), TEA (1.6 mL, 11 mmol, 1.5 equiv), and TMS-Cl (4.8 mL, 38 mmol, 5 equiv). This viscous cloudy slurry was stirred for 15 minutes before cooling to 0 °C. BuLi (19 mL, 30 mmol, 4.0 equiv) was added dropwise via syringe pump over 3 hours. The reaction was monitored by crude ^{1}H NMR. After 1 additional hour of stirring the reaction was quenched with methanol (20 mL) and let warm to room temperature. To the crude was added ether (80 mL) and water (80 mL). The organic extract was washed with water (80 mL), with Sat. $NaHCO_3$ (aq) (80 mL), and brine (400 mL), then dried over $MgSO_4$. The solvent was removed in vacuo and the crude material was purified by flash chromatography over SiO_2 (0%-10% EtOAc in Hexanes) to yield the product as an amorphous white to yellow solid (1.8 g, 94%).

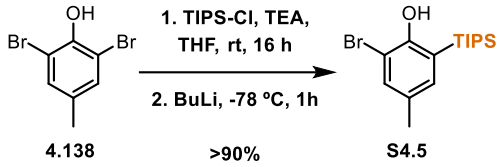
TLC (Hexanes/EtOAc, 95:5), RF:	0.77 (UV, potassium permanganate)
^{1}H NMR (300 MHz, Acetone-D_6), **4.246**	δ = 7.19 (d, J=0.9, 2H), 4.87 (s, 1H), 2.31 (t, J=0.7, 3H), 0.37 (s, 18H).
^{13}C NMR (75 MHz, Acetone-D_6), **4.246**	δ = 163.3, 137.3, 129.3, 124.1, 20.8, -0.4.
HRMS (ESI):	m/z calculated for $C_{13}H_{24}OSi_2$ ([M+H]+): 253.1438, found 253.1454
FTIR (neat) cm^{-1} :	ν̃= 3618 (br), 2956 (w), 1574 (w), 1400 (m), 1249 (m), 1167 (m), 855 (vs), 836 (vs)



^{1}H NMR (300 MHz, Acetone-D$_6$), **4.246**



^{13}C NMR (75 MHz, Acetone-D$_6$), **4.246**

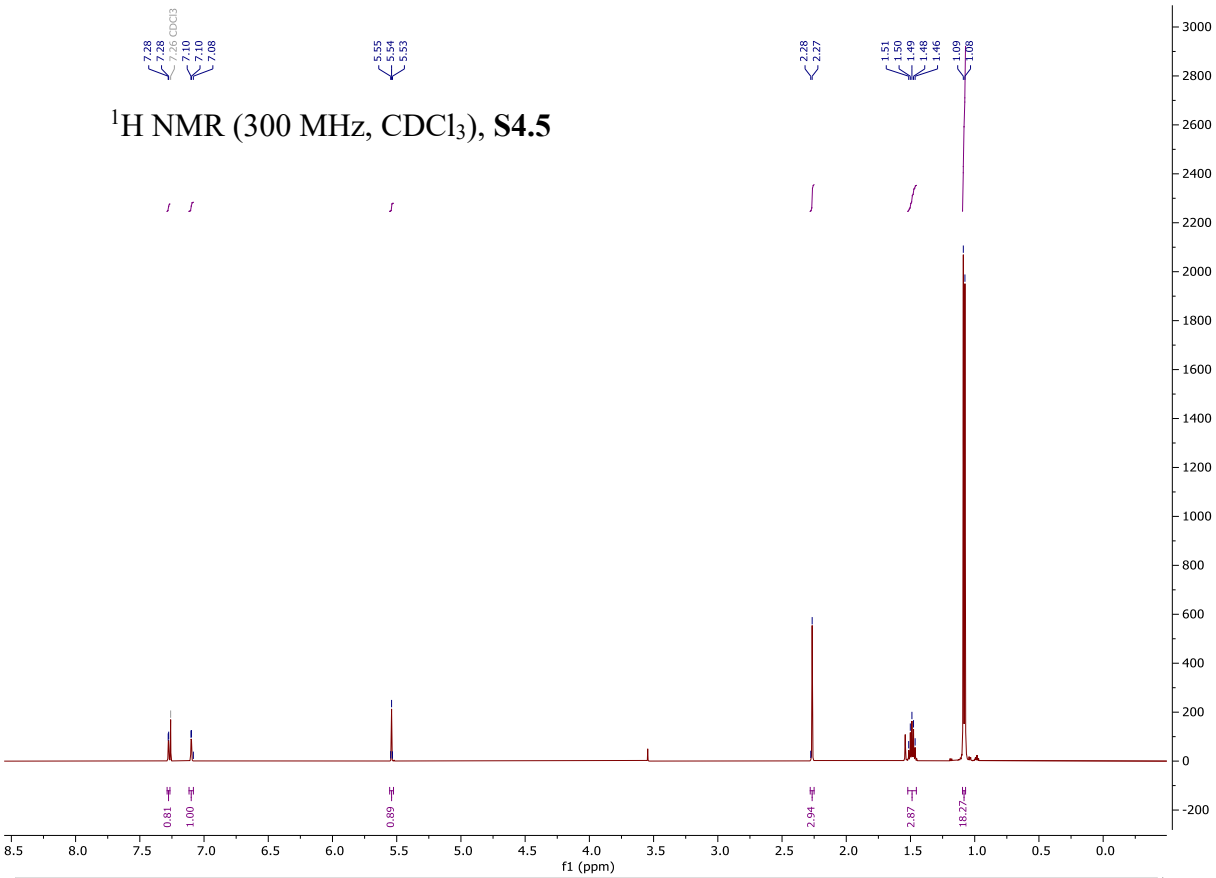


(S4.5) 4-methyl-2,6-bis(triisopropylsilyl)phenol

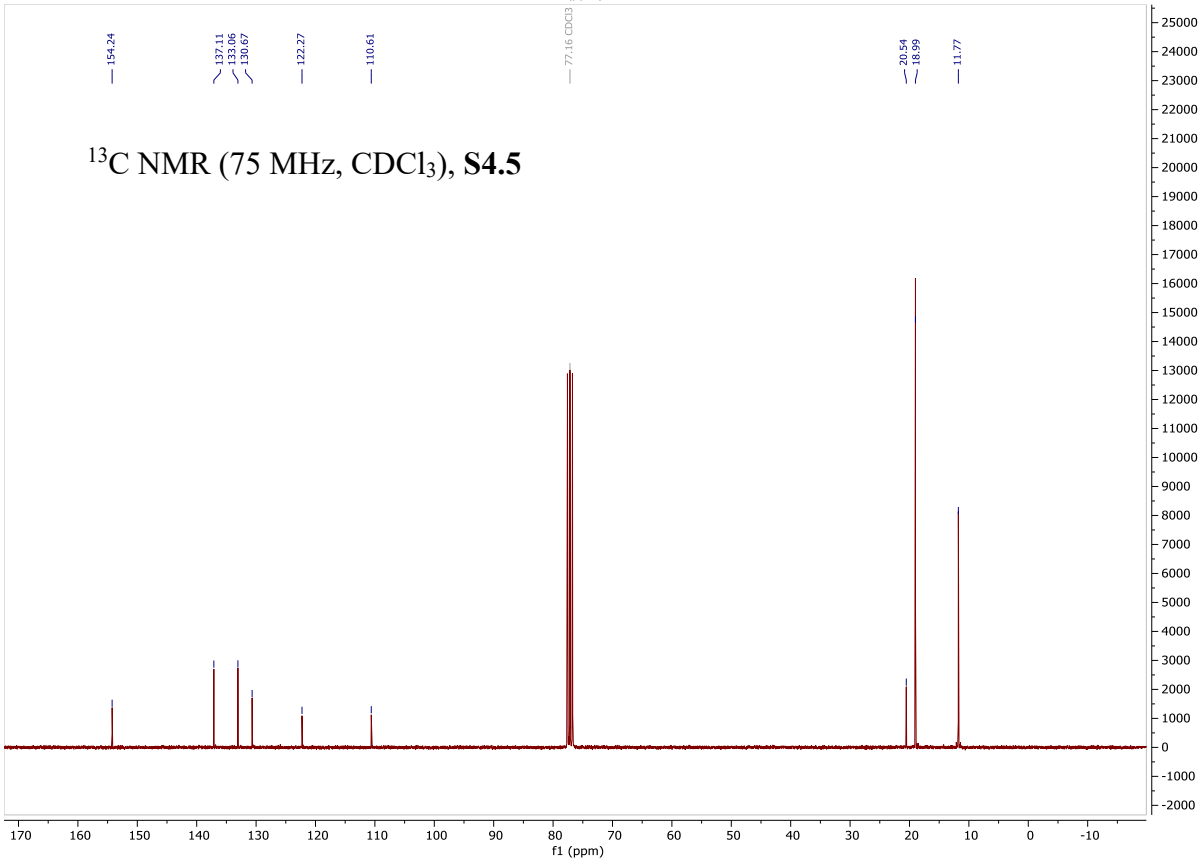
In a 50 mL RBF was added phenol **4.138** (4.0 g, 15 mmol, 1 equiv), THF (15 mL, 1.0 M), TEA (3.35 mL, 24.1 mmol, 1.6 equiv), and TIPS-Cl (5.2 mL, 24 mmol, 1.6 equiv). The solution was to stir for 16 hours at room temperature. The solution was then cooled to -78 °C and BuLi (9.8 mL, 24 mmol, 1.6 equiv) dropwise. After 1 hour the reaction was quenched with MeOH (20 mL) and sat. $NaHCO_3$ (aq) (50 mL). The mixture was extracted with ether (3 x 40 mL). The organics were dried with brine (40 mL) and $MgSO_4$. The crude organic residue was deemed to be sufficient purify for subsequent reactions. Average purity is depicted below of the amorphous white solid (5.0 g, 98%).

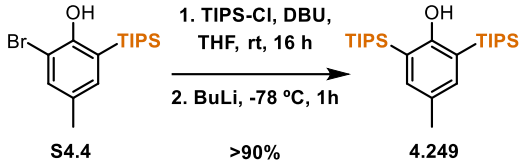
TLC (Hexanes/EtOAc, 90:10), RF:	0.86 (UV, potassium permanganate)
^{1}H NMR (300 MHz, $CDCl_3$), **S4.5**	δ = 7.28 (dd, J=2.1, 0.8, 1H), 7.10 (dt, J=2.1, 0.7, 1H), 5.54 (s, 1H), 2.27 (d, J=0.7, 3H), 1.49 (ddd, J=14.8, 8.5, 7.6, 3H), 1.08 (d, J=7.5, 18H).
^{13}C NMR (75 MHz, $CDCl_3$), **S4.5**	δ = 154.2, 137.1, 133.1, 130.7, 122.3, 110.6, 20.5, 19.0, 11.8.
HRMS (ESI):	m/z calculated for $C_{16}H_{27}BrOSi$ ([M+H]+): 343.1087, found 343.1093
FTIR (neat) cm^{-1} :	ν̃ = 3505 (m), 2943 (vs), 2864 (vs), 1449 (m), 1388 (w), 1245 (w), 1077 (s), 900 (w), 882 (w), 678 (w)

^{1}H NMR (300 MHz, $CDCl_3$), **S4.5**



^{13}C NMR (75 MHz, $CDCl_3$), **S4.5**

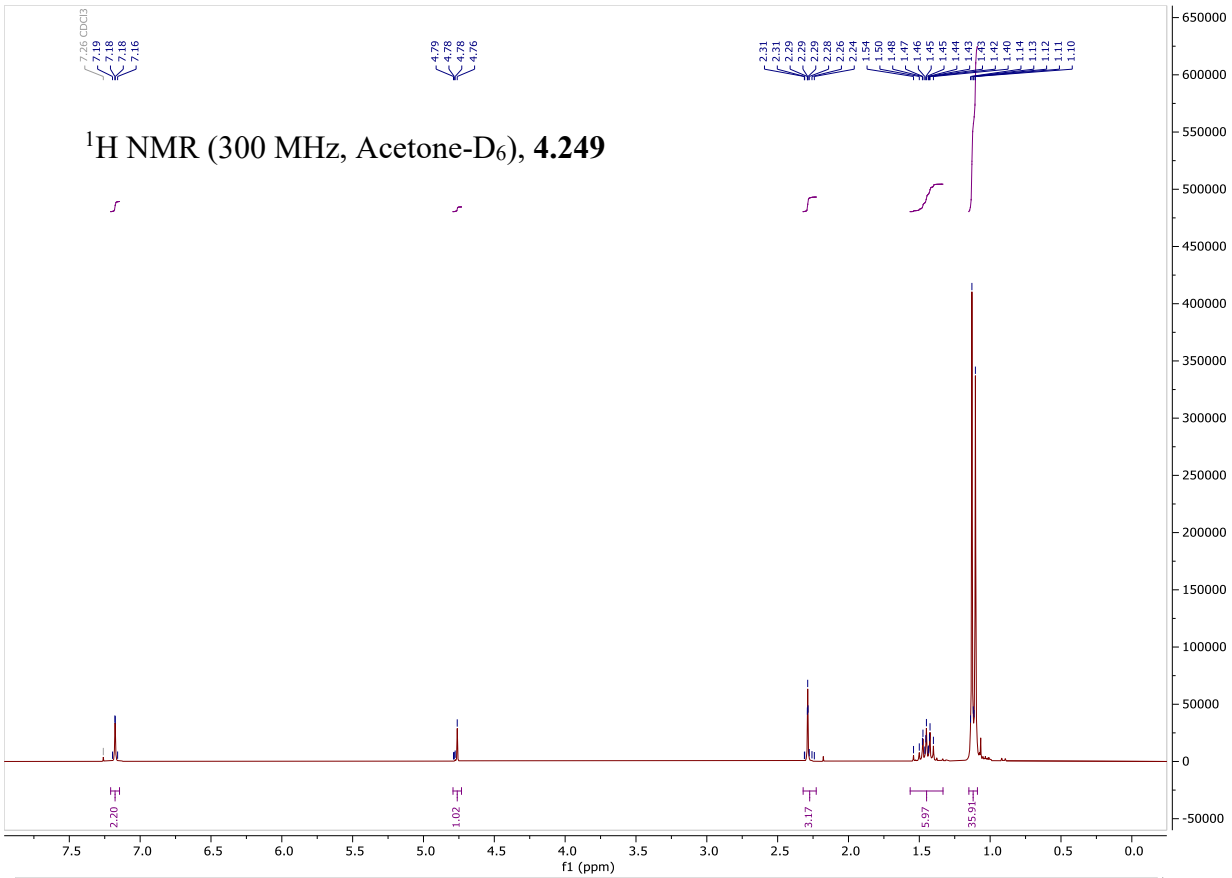




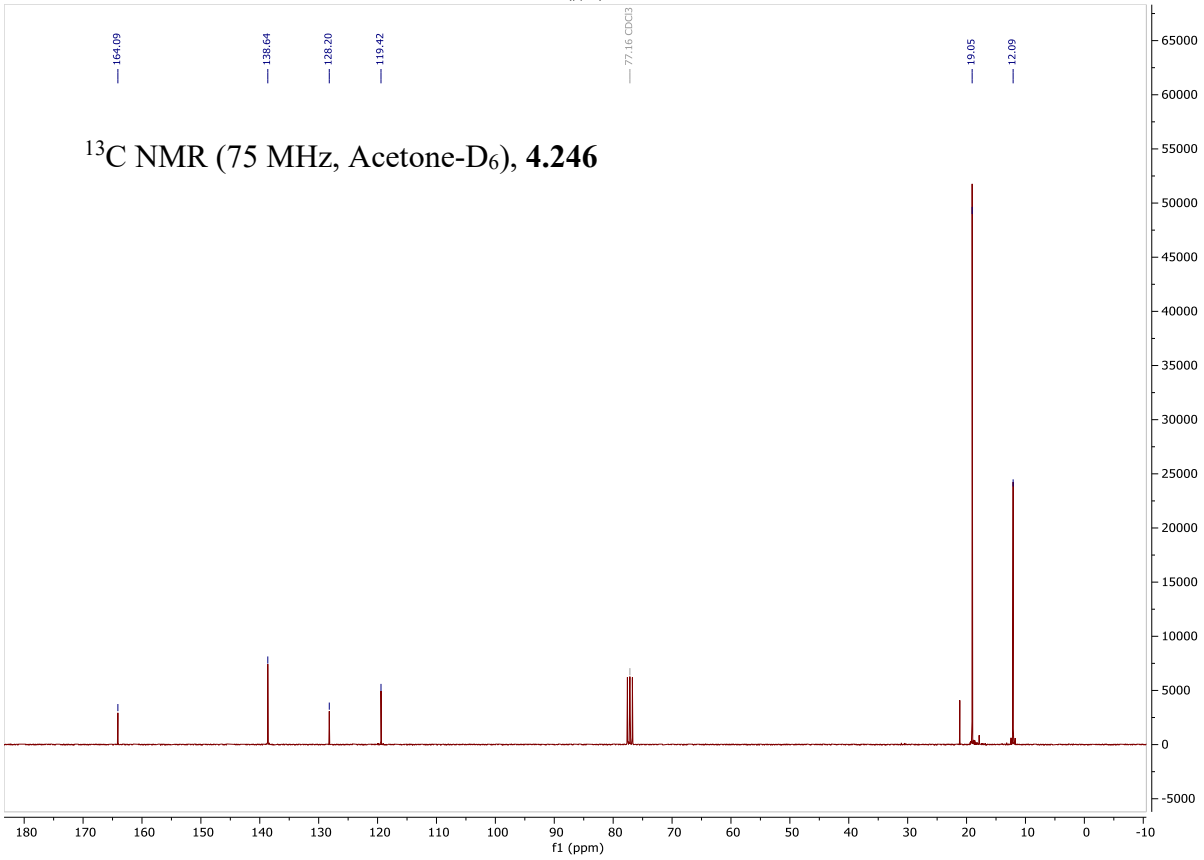
(4.249) 4-methyl-2,6-bis(triisopropylsilyl)phenol

To a 500 mL RBF was added starting material (5.0 g, 15 mmol, 1 equiv), THF (15 mL, 1.0 M), DBU (3.2 mL, 24 mmol, 1.3 equiv), and TIPS-Cl (5.2 g, 24 mmol, 1.6 equiv). The solution was to stir for 16 hours at room temperature. The solution was then cooled to -78 °C and BuLi (9.8 mL, 24 mmol, 1.6 equiv) dropwise. After 1 hour the reaction was quenched with MeOH (20 mL) and sat. $NaHCO_3$ (aq) (50 mL). The mixture was extracted with ether (3 x 40 mL). The organics were dried with brine (40 mL) and $MgSO_4$. The crude organic residue was subjected to column chromatography SiO_2 (0-10% ethyl acetate in hexanes) to afford the product as an clear viscous oil which solidifies after ~4 days to an amorphous white solid (5.0 g, 97%).

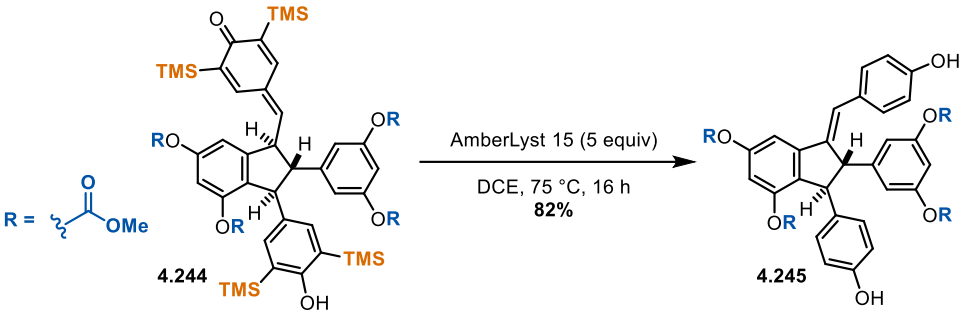
TLC (Hexanes/EtOAc, 95:5), RF:	0.87 (UV, potassium permanganate)
^{1}H NMR (300 MHz, Acetone-D_6), **4.249**	δ = 7.18 (d, J=0.8, 2H), 4.76 (s, 1H), 2.29 (d, J=0.7, 3H), 1.56 – 1.33 (m, 6H), 1.12 (d, J=7.4, 36H).
^{13}C NMR (75 MHz, Acetone-D_6), **4.246**	δ = 164.1, 138.6, 128.2, 119.4, 19.1, 12.1.
HRMS (ESI):	m/z calculated for $C_{25}H_{48}OSi_2$ ([M+H]+): 421.3316, found 421.3307
FTIR (neat) cm^{-1} :	ν̃= 3612 (m), 2945 (m), 2865 (vs), 1401 (s), 882 (m), 670 (w), 642 (w)



^{1}H NMR (300 MHz, Acetone-D$_6$), **4.249**



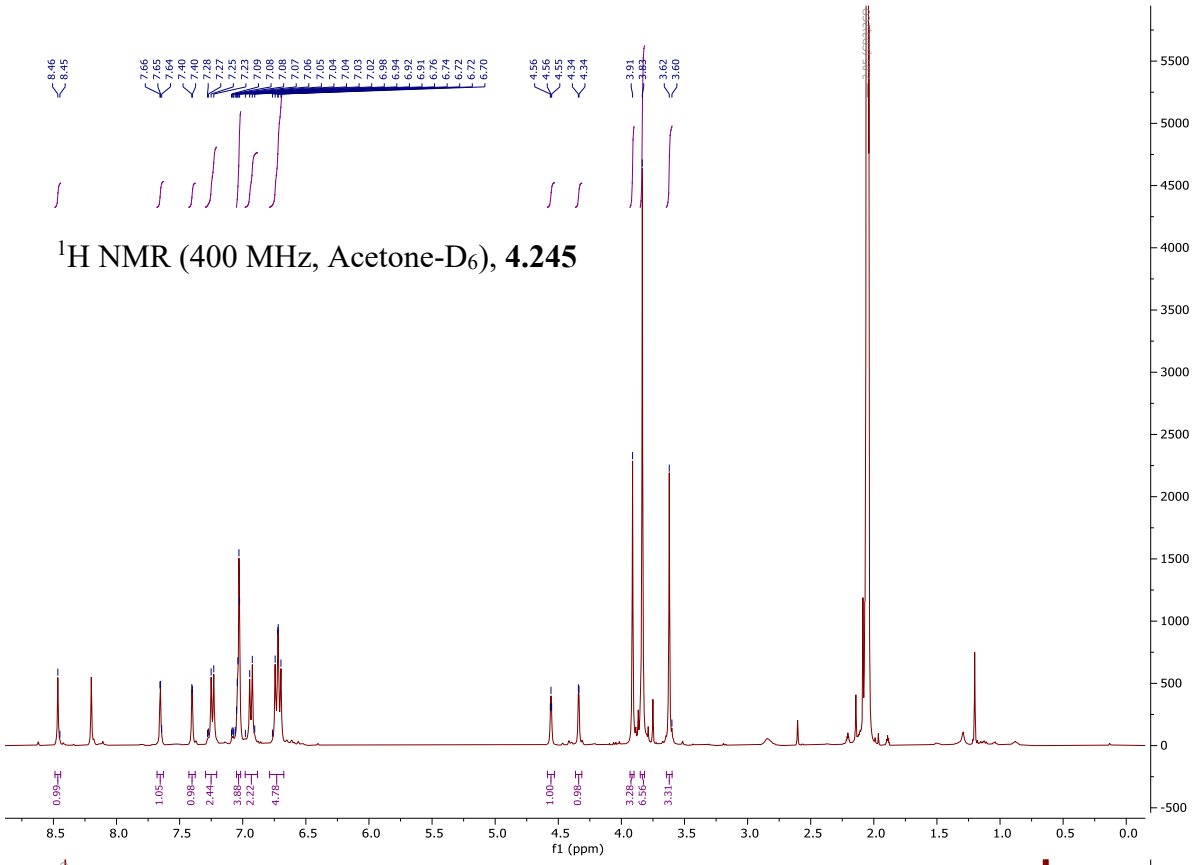
^{13}C NMR (75 MHz, Acetone-D$_6$), **4.246**



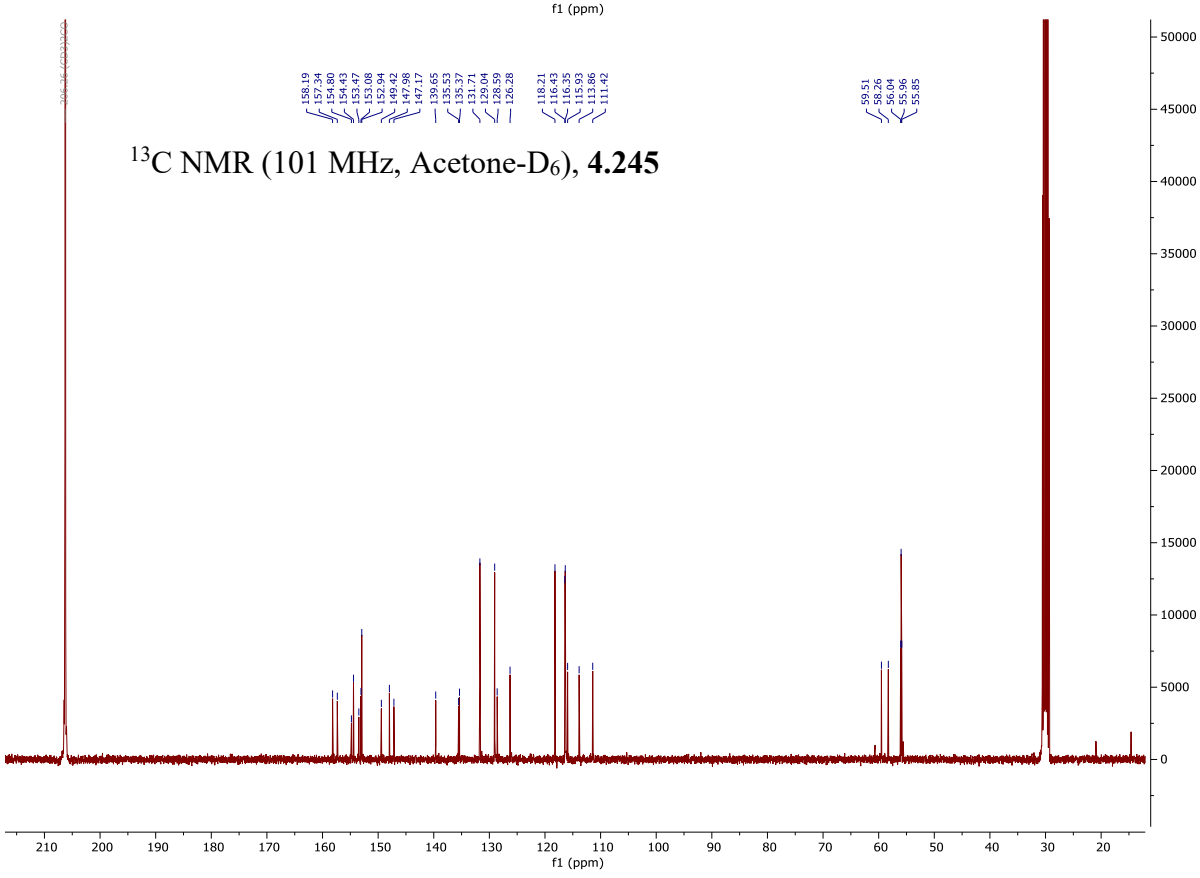
(4.245) 5-((2S,3S)-1-((E)-4-hydroxybenzylidene)-3-(4-hydroxyphenyl)-4,6-bis((methoxycarbonyl)oxy)-2,3-dihydro-1H-inden-2-yl)-1,3-phenylene dimethyl bis(carbonate)

In a 10 mL flame dried microwave vial was added starting material (114 mg, 117 µmol, 1 equiv), DCE (7.8 mL, 0.015 M) and AmberLyst 15 resin (184 mg, 0.58 mmol, 5 equiv). The vial was capped with argon, sealed, and reacted at 75 °C for 16 hours in a Biotage microwave reactor. The crude organics were filtered over cotton and concentrated to dryness. The crude material was purified by flash chromatography over SiO_2 (0%-50% EtOAc in Hexanes) to yield the product as a pale white foam (66 mg, 82%).

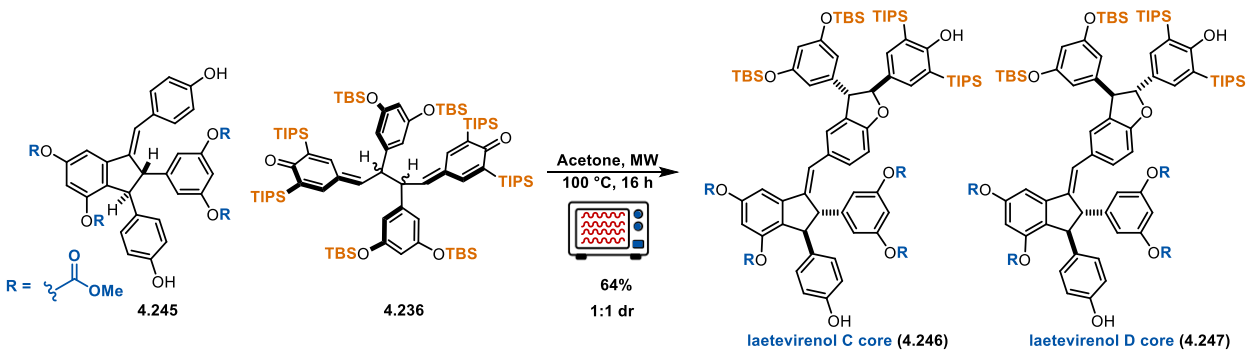
TLC (Hexanes/EtOAc, 50:50), RF:	0.38 (UV, potassium permanganate)
^{1}H NMR (400 MHz, Acetone-D_6), **4.245**	δ = 8.46 (s, 1H), 7.65 (d, J=2.0, 1H), 7.40 (d, J=1.9, 1H), 7.24 (d, J=8.4, 2H), 7.05 – 7.02 (m, 3H), 6.93 (d, J=8.2, 2H), 6.79 – 6.67 (m, 4H), 4.56 (d, J=2.1, 1H), 4.34 (d, J=2.0, 1H), 3.91 (s, 3H), 3.83 (s, 7H), 3.62 (s, 3H).
^{13}C NMR (101 MHz, Acetone-D_6), **4.245**	δ = 158.2, 157.3, 154.8, 154.4, 153.5, 153.1, 152.9, 149.4, 148.0, 147.2, 139.6, 135.5, 135.4, 131.7, 129.0, 128.6, 126.3, 118.2, 116.4, 116.4, 115.9, 113.9, 111.4, 59.5, 58.3, 56.0, 56.0, 55.8.
HRMS (ESI):	m/z calculated for $C_{36}H_{30}O_{14}$ ([M+H]+): 687.1708, found 687.1647
FTIR (neat) cm–1 :	ν̃= 3428 (br), 2960 (w), 1763 (m), 1603 (w), 1513 (w), 1439 (m), 1236 (vs), 1173 (m), 1152 (w), 964 (w), 942 (w)



^{1}H NMR (400 MHz, Acetone-D$_6$), **4.245**



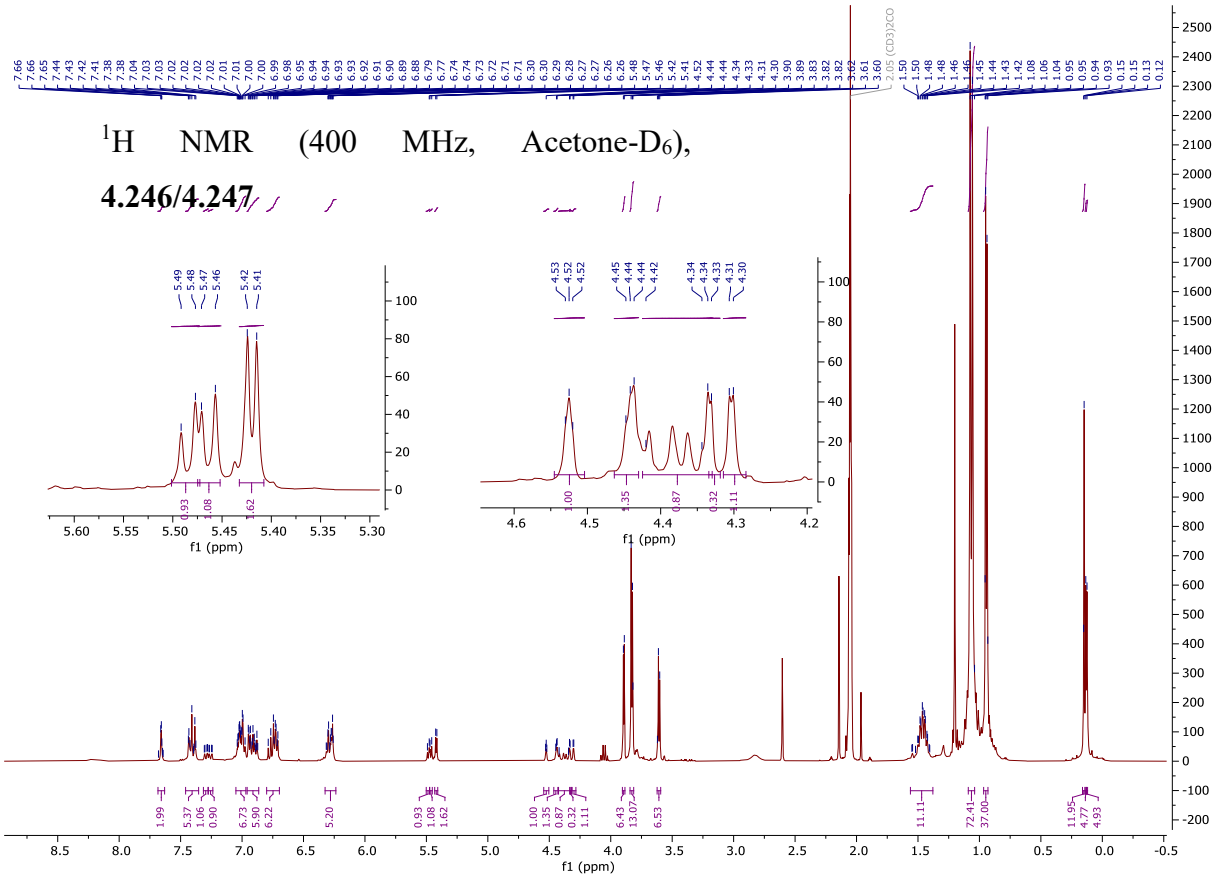
^{13}C NMR (101 MHz, Acetone-D$_6$), **4.245**



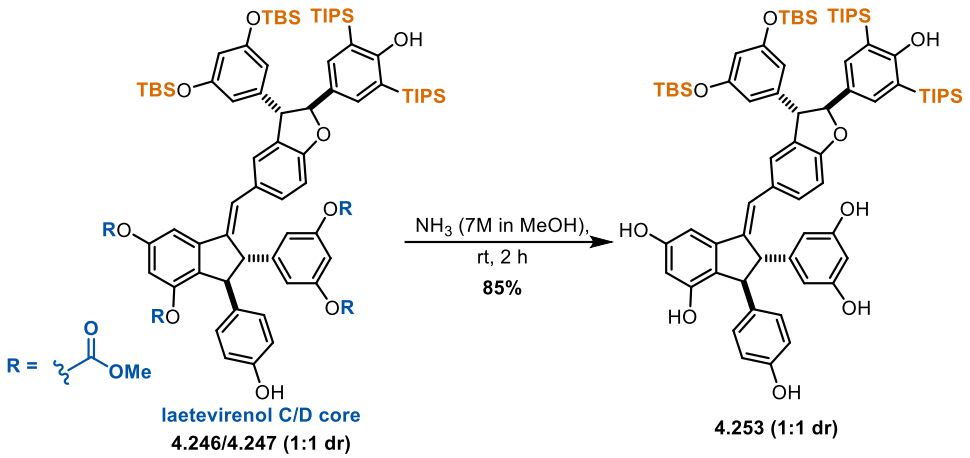
(4.246/4.247) 5-((2S,3S,E)-1-(((2S,3S)-3-(3,5-bis((tert-butyldimethylsilyl)oxy)phenyl)-2-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)-2,3-dihydrobenzofuran-5-yl)methylene)-3-(4-hydroxyphenyl)-4,6-bis((methoxycarbonyl)oxy)-2,3-dihydro-1H-inden-2-yl)-1,3-phenylene dimethyl bis(carbonate)

In a 2 mL flame dried microwave vial indane was added indane (37 mg, 55 µmol, 1 equiv), bis-quinone methide (151 mg, 98 µmol, 1.8 equiv), and acetone (2 mL, 0.025 M). The vial was capped with argon, sealed, and reacted at 100 °C for 16 hours in a Biotage microwave reactor. The crude organics were concentrated to dryness and purified by flash chromatography over SiO_2 (0%-50% EtOAc in Hexanes) to yield the product as a pale white to yellow foam (51 mg, 64%) as a 1:1 mixture of *trans* DHB disatereomers.

^{1}H NMR (400 MHz, Acetone-D_6), **4.246/4.247** δ = 7.66 (t, J=1.7, 2H), 7.46 – 7.35 (m, 5H), 7.29 (dd, J=8.4, 1.9, 1H), 7.26 (dd, J=8.5, 1.8, 1H), 7.05 – 6.97 (m, 7H), 6.96 – 6.86 (m, 6H), 6.80 – 6.70 (m, 6H), 6.32 – 6.24 (m, 5H), 5.48 (d, J=5.8, 1H), 5.46 (d, J=5.6, 1H), 5.42 (d, J=3.8, 2H), 4.53 (d, J=2.0, 1H), 4.46 – 4.43 (m, 1H), 4.38 (d, J=33.8, 1H), 4.33 (s, 0H), 4.30 (d, J=2.3, 1H), 3.89 (d, J=3.0, 6H), 3.83 (d, J=4.3, 13H), 3.61 (d, J=4.2, 7H), 1.56 – 1.38 (m, 11H), 1.07 (d, J=7.4, 72H), 0.94 (d, J=4.3, 37H), 0.15 (d, J=1.5, 12H), 0.13 (s, 5H), 0.12 (s, 5H).



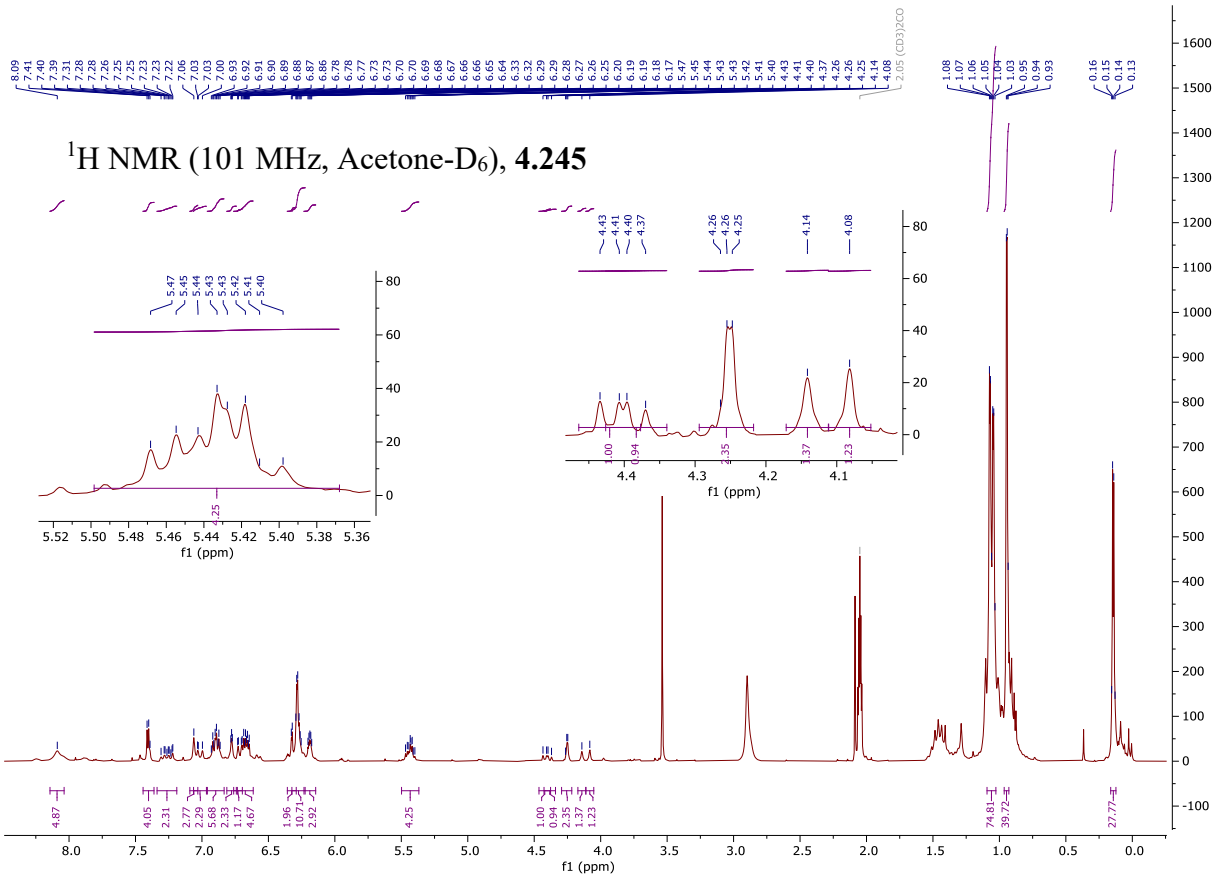
^{1}H NMR (400 MHz, Acetone-D_6), **4.246/4.247**

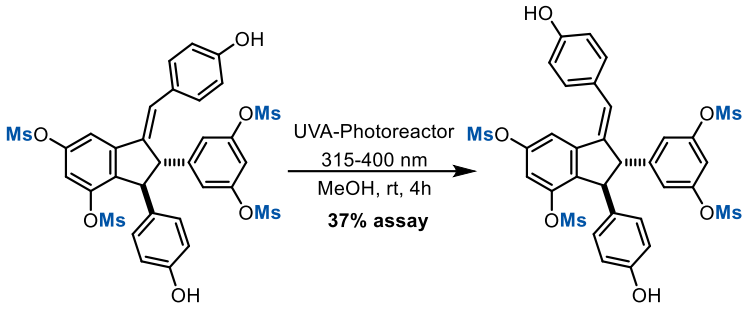


(4.253) (2S,3S,E)-1-(((2S,3S)-3-(3,5-bis((tert-butyldimethylsilyl)oxy)phenyl)-2-(4-hydroxy-3,5-bis(triisopropylsilyl)phenyl)-2,3-dihydrobenzofuran-5-yl)methylene)-2-(3,5-dihydroxyphenyl)-3-(4-hydroxyphenyl)-2,3-dihydro-1H-indene-4,6-diol

In a 1 dram flame dried vial was added starting material (19 mg, 13 µmol, 1 equiv) and NH_3 (93 µL, 0.65 mmol, 50 equiv, 7N solution in methanol). The reaction was stirred at room temperature for 2 hours before concentrating and passing through a pipette column silica gel plug (isocratic elution 20% methanol in DCM). This afforded a semi-crude product as a tan residue (13 mg, 85%).

TLC (MeOH/DCM, 80:20), R_F:	0.69 (UV, potassium permanganate)
^{1}H NMR (300 MHz, D_6-Acetone, 25 °C)	δ = 8.09 (s, 5H), 7.41 (d, J=3.7, 4H), 7.34 – 7.19 (m, 2H), 7.06 (s, 3H), 7.06 – 6.97 (m, 2H), 6.89 (ddd, J=8.3, 5.2, 2.5, 6H), 6.78 (t, J=1.7, 2H), 6.73 (d, J=1.6, 1H), 6.68 (ddd, J=8.4, 5.7, 2.9, 5H), 6.32 (d, J=2.1, 2H), 6.28 (p, J=2.2, 11H), 6.19 (dt, J=4.1, 2.1, 3H), 5.43 (tq, J=6.0, 3.9, 4H), 4.42 (d, J=8.2, 1H), 4.38 (d, J=7.9, 1H), 4.25 (d, J=2.3, 2H), 4.14 (s, 1H), 4.08 (s, 1H), 1.06 (dd, J=7.5, 2.2, 75H), 0.94 (d, J=1.9, 40H), 0.14 (d, J=2.6, 28H).
HRMS (ESI):	*m/z* calculated for $C_{72}H_{100}O_9Si_4$ ($[M+H]^+$): 1221.6517, found 1221.649
FTIR (neat) cm^{-1} :	ν̃= 3367 (br), 2929 (s), 2864 (m), 1597 (vs), 1464 (w), 1254 (w), 1158 (s), 839 (vs)

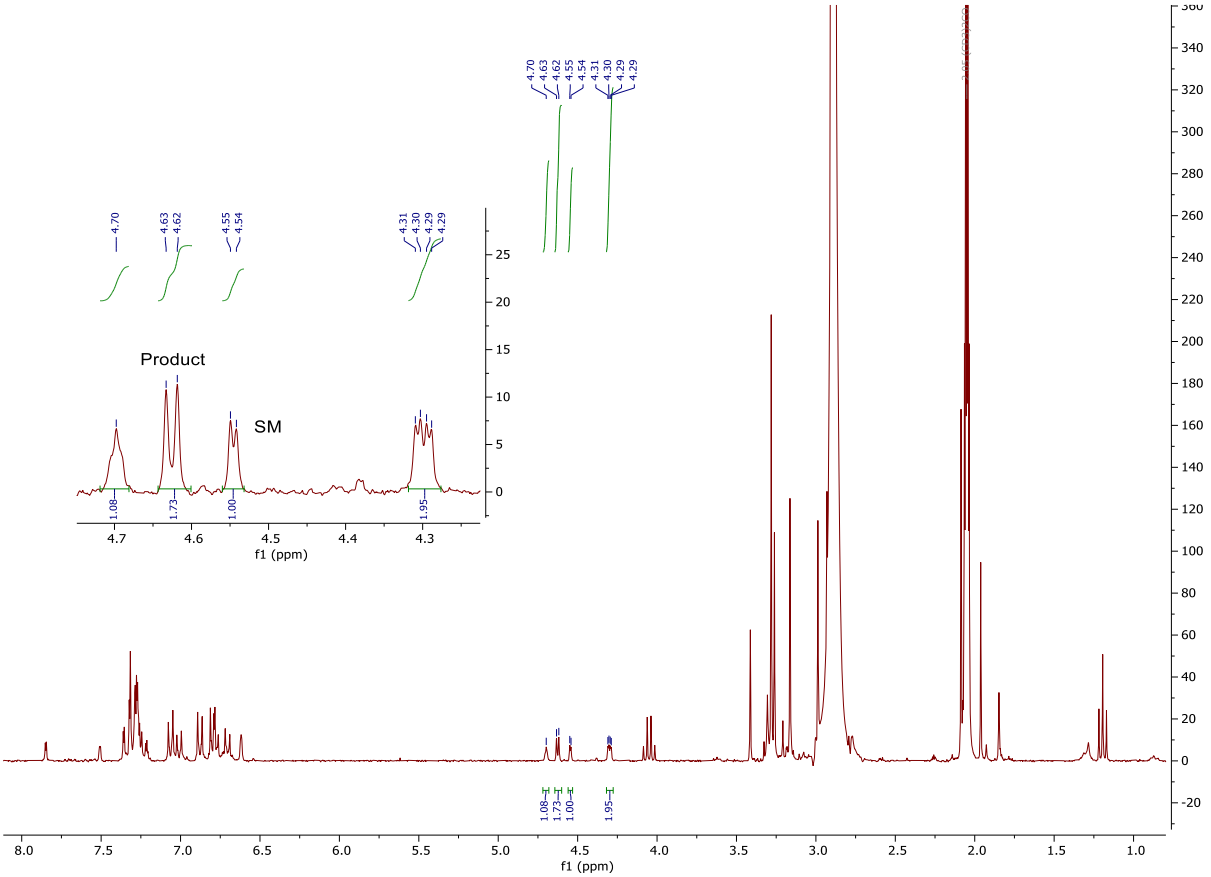

^{1}H NMR (101 MHz, Acetone-D$_6$), **4.245**
f1 (ppm)



4.224 **4.257**

(4.257) (2S,3S)-2-(3,5-bis((methylsulfonyl)oxy)phenyl)-1-((Z)-4-hydroxybenzylidene)-3-(4-hydroxyphenyl)-2,3-dihydro-1H-indene-4,6-diyl dimethanesulfonate

In a flame dried pyrex flask was added starting material(10 mg, 13 µmol, 1 equiv) and methanol (0.5 mL, 0.025 M). The substrate was irradiated with UVA light for 4 hours. A crud reaction aliquot was dried, and a ^{1}H NMR was obtained, indicating a 1.7 : 1 ratio of stating material to isomerized product. This corresponds to a 37% assay yield. The products were not separated on this scale.



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