The Thesis Committee for Aurpon W. Mitra
Certifies that this is the approved version of the following thesis:

Synthesis of Caryolanemagnolol and Clovanemagnolol Derivatives for
Molecular Pull-down Experiments

APPROVED BY
SUPERVISING COMMITTEE:

Supervisor:

Dionicio R. Siegel

Guangbin Dong
Synthesis of Caryolanemagnolol and Clovanemagnolol Derivatives for Molecular Pull-down Experiments

by

Aurpon W. Mitra, B.S.

Thesis
Presented to the Faculty of the Graduate School of
The University of Texas at Austin
in Partial Fulfillment
of the Requirements
for the Degree of

Master of Arts

The University of Texas at Austin
December 2011
Abstract

Synthesis of Caryolanemagnolol and Clovanemagnolol Derivatives for Molecular Pull-down Experiments

Aurpon W. Mitra, M.A.
The University of Texas at Austin, 2011

Supervisor: Dionicio R. Siegel

Caryolanemagnolol and clovanemagnolol promote neuronal regeneration in various cell and animal based assays. The protein targets of these natural products are not currently known. Derivatives of caryolanemagnolol and clovanemagnolol were synthesized for the purpose of affinity chromatography. The derivatives are accessed rapidly through optimized procedures.
# Table of Contents

Chapter 1

1.1 Isolation ...........................................................................................................1
1.2 Biological Activity ..........................................................................................2
1.3 Total Synthesis of Caryolanemagnolol and Clovanemagnolol ....................4
1.4 C. elegans .....................................................................................................8
1.5 Target Identification .....................................................................................9
1.6 Synthesis .....................................................................................................11
1.7 Experimental Section .................................................................................16

References .............................................................................................................43
Chapter 1

1.1 Isolation

Bark from the Japanese Bigleaf Magnolia (Magnolia obovata) has been used in China, Japan, and Korea as a traditional medicine. The natural products derived from this bark have prompted investigation for pharmacologically relevant agents. Caryolanemagnolol (1) and clovanemagnolol (2) were isolated from this bark by Fukuyama and coworkers.\textsuperscript{1,2} Their screen was part of a program to identify neurotrophically active natural products. Other compounds isolated included caryophyllene oxide (3), magnolol (4), and eudesmagnolol (5) (Figure 1).\textsuperscript{1} Fukuyama and coworkers postulated that both 1 and 2 occurred from a common intermediate, caryophyllene oxide.\textsuperscript{13} Under acid catalyzed conditions, α-caryophyllene oxide rearranges to form cation 6 which is trapped by magnolol to form caryolanemagnolol (1) (Scheme 1). The same conditions cause β-caryophyllene oxide to form cation 7, which rearranges to cation 8 and is trapped by magnolol to form clovanemagnolol (Scheme 1). Cation 6 does not rearrange because of poor orbital overlap. Barton and coworkers initially studied the acid catalyzed rearrangement of caryophyllene oxide as part of their studies elucidating the structure of caryophyllene.\textsuperscript{13} Eudesmagnolol degraded to 4 and eudesmol (9) when treated with trifluoroacetic acid. It is likely that compounds 1, 2, and 5 arise from the combination of magnolol with an appropriate terpene (Scheme 2).\textsuperscript{1}
Figure 1: Selected terpene natural products from Japanese Big Leaf Magnolia.

Scheme 1: Proposed biosynthesis of caryolanemagnolol and clovnamagnolol.

Scheme 2: Degradation of eudesmagnolol (5).

1.2 Biological Activity

Fukuyama and coworkers observed neurotrophic activity for 1 and 2 in neurons derived from fetal rat cerebral rat hemisphere.² Both compounds accelerated neurite sprouting and neuronal network formation. Choline acetyltransferase (ChAT) activity increased 16 fold and 6 fold for 1 and 2 at 0.1 µM, respectively, leading to an increase in the production of acetylcholine, a neurotransmitter, after 10 days.¹ Magnolol showed only slight neuronal sprouting and ChAT at 10µM. Recently, Siegel and coworkers investigated the neurite growth of hippocampal and cortical neurons when treated with 2.³⁴ When treated with 2 and 4, hippocampal neurons increased neurite growth at 0.01µM, relative to controls. Neurite growth decreased at micromolar concentrations,
indicating off target effects. Treatment of cortical neurons with 2 and 4 showed clovanemagnolol’s ability to promote neurite growth at lower concentrations in comparison to magnolol. Statistically significant neurite growth for magnolol treated cortical neurons occurred at 0.1 µM.

**Figure 2:** Neurite growth in hippocampal neurons. Adapted from Khaing et al.³
Figure 3: Neurite growth for cortical neurons. Adapted from Khaing et al.³

1.3 Total Synthesis of Caryolanemagnolol and Clovanemagnolol

Siegel and coworkers completed syntheses of 1 and 2 in 2010.⁵ Epoxidation of (−)-β-caryophyllene with m-CPBA generated a 1:5 mixture of α:β caryophyllene oxides. Use of the Shi catalyst overrode the inherent selectivity of the epoxide, generating 2.2:1 α:β mixture of epoxides.¹⁵ The α diastereomer of caryophyllene oxide was rearranged with trimethylaluminum and 4-bromophenol (3:1) in dichloromethane at 0 °C to generate 10. Attempts at bromination led only to oxidation of the secondary alcohol. Protection of the secondary alcohol as an acetate followed by bromination with bromine, sodium acetate, and acetic acid yielded the dibromide 11. A Suzuki coupling appended the allyl fragment to form 12. Careful reaction monitoring was necessary to avoid bis-allylation of the 11. A second Suzuki coupling, using cross coupling conditions developed by Fu and
coworkers, generated the penultimate intermediate 13. Global deprotection with lithium aluminum hydride generated caryolanemagnolol (1).

The total synthesis of clovanemagnolol was achieved in similar manner as caryolanemagnolol. Diphenylphosphate, not trimethylaluminum, was necessary to achieve the rearrangement of β-caryophyllene oxide and subsequent trapping with 4-bromophenol. Elimination also accompanied the rearrangement to generate clovone (18). The dibromide 15 was converted to clovanemagnolol using the same synthetic sequence as that of caryolanemagnolol. Siegel and coworkers finally synthesized caryolanemagnolol and clovanemagnolol in one step with diphenylphosphate and magnolol from α-caryophyllene oxide and β-caryophyllene oxide, respectively. These single step syntheses lend credence to the biosynthetic proposal put forth by Barton. Interestingly, while comparing of synthetic caryolanemagnolol and clovanemagnolol to naturally isolated material, it was realized that the published NMR shifts were incorrectly reported.
Scheme 3: Total synthesis of caryolanemagnolol.
Scheme 4: Total synthesis of clovanemagnolol.
Scheme 5: Bio-inspired syntheses of caryolanemagnolol and clovanemagnolol.

1.4 C. elegans

*Caenorhabditis elegans* has been developed by Sydney Brenner as a model organism for higher order biological processes such as neuroregeneration. Over half of the neurotransmitters used by humans are also used by *C. elegans*. *C. elegans* also respond to the same neuroactive compounds. Biological activity in *C. elegans* can potentially translate into possible biological activity in humans. This potential stems, in part, from an overlap in the genes between *C. elegans* and humans. 60%-80% of *C. elegans* genes are homologous with that of humans. The Nobel Prize in Medicine and Physiology in 2002 was awarded for the development of *C. elegans* as a model organism.

*C. elegans* serve as an appealing model for probing biological activity. They are easily grown without especially rigorous conditions. There are no ethical concerns for growing/working as with other species such as chimpanzees. *C. elegans* have the shortest growing time (2-3 days) of possible animal model species. Finally, *C. elegans* have successfully been used to study neurodegenerative diseases such as Alzheimer’s disease and Huntington’s disease. We have since begun using *C. elegans* for assessment of
biological activity for various compounds. We have used *C. elegans* to evaluate analogs of caryolanemagnolol and clovanemagnolol lacking allyl groups (Figure 5). Analogs 19 and 20 have been identified as more extensive promoters of neuronal growth, relative to caryolanemagnolol and clovanemagnolol.

### 1.5 Target Identification

Small molecules are best known as medicinal agents. However, they can also serve as tools for determining those proteins which bind to small molecules. The chief method for identification of small molecule binding proteins is affinity chromatography (Figure 4). The technique relies on small molecules, which are covalently linked to affinity tags (e.g., biotin) or solid matrices (e.g., Agarose beads). A mixture of proteins is incubated with the tagged or immobilized small molecule. Proteins that do not bind to the small molecule are removed through washing. Those small molecule-bound proteins are revealed through subsequent washing with either another drug or a denaturing solution. The method is only effective if the biological activity is not impaired upon linkage to an affinity tag or solid matrix. Negative controls are also necessary to ensure validity of isolated protein targets.

![Figure 4: General method for affinity chromatography. Adapted from Lomenick et al.](image)

Schreiber and coworkers have demonstrated that natural products bearing terminal hydroxymethyl groups are ideal for immobilization to beaded agarose using
1,1’-carbonyldimimidazole (CDI) (Scheme 8). The method involves formation of a mixed imidazolide. The mixture is washed with water to remove excess CDI and imidazole prior to binding to an amino-solid support. Finally, the resin is capped through acylation by the acetate of N-Hydroxysuccinimide. The Schreiber method is particularly useful because of its mild reaction conditions, higher reactivity for coupling to solid support, and lack of solid support prefunctionalization. The promising biological activity of clovanemagnolol prompted us to consider use of caryolanemagnolol and clovanemagnolol for use in molecular pull down experiments.

![Scheme 6: Method for attaching alcohols to beads. Adapted from Wang, X. et al.](image)

The intermediacy of carbocations 6 and 8 offers an opportunity for synthesis of caryolane and clovane analogs via trapping with various nucleophiles. Given our interest in affinity chromatography experiments and the potency of analogs 19 and 20, we selected analogs 21 and 22 for synthesis and subsequent solid support immobilization. We envisioned that 21 and 22 could be derived from a hyboration/oxidation of 23 and 24 (Scheme 7). Our goal thus became synthesis of 23 and 24.

![Figure 5: Analogs of caryolanemagnolol and clovanemagnolol.](image)
Scheme 7: Retrosynthesis of caryolane and clovane derivatives.

1.6 Synthesis

My synthesis began with (−)-caryophyllene oxide (4:1 β:α) (derived from epoxidation of (−)-caryophyllene with m-chloroperoxybenzoic acid (m-CPBA)) in CH₂Cl₂ at 38 °C in the presence of biphenol and diphenyl phosphate to afford 19 and 20 in 48% and 16% yield, respectively. The bridgehead carbocation derived from α-caryophyllene oxide was competitively trapped by diphenyl phosphate, leading to the diphenyl phosphate 25 as the principal by-product. For the β-caryophyllene derived carbocation, diphenylphosphate trapping and elimination formed diphenylphosphate adduct 27 and clovone (19).

Scheme 8: Synthesis of derivatives of caryolanemagnolol and clovanemagnolol.
I next decided to synthesize 24 by a two step sequence involving iodination of 19 followed by a Pd-catalyzed Suzuki coupling with allyl pinacol boronate (Scheme 9). Though I could now access 24, some optimization was necessary.

![Scheme 9: Two step synthesis of 24.](image)

The yield of 27 and 28 initially varied between 60% and 70% yield. Reduction of warming time to one hour, as opposed to 2.5 hours, allowed consistent yields of >85% (Schemes 10 and 11). The remainder of mass balance consisted of polyiodinated compounds according to mass spectrum and NMR analyses.

![Scheme 10: Optimized iodination of 19.](image)

![Scheme 11: Optimized iodination of 20.](image)
reactions lacking LiCl showed complete isomerization of the allyl group.

dilution with ethyl acetate, washed repeatedly with 3N LiCl to remove DMF, and subsequent purification by column chromatography. A couple aspects of this Stille coupling are worthy of mention: the reaction is fast (complete consumption of starting material in 15 minutes by TLC analysis), and the reaction shows no allylic isomerization to the corresponding styrenyl compound. This stands in contrast to reports by Stille, in which significant isomerization was observed. The role of LiCl is notable because reactions lacking LiCl showed complete isomerization of the allyl group.

Scheme 12: Attempted Heck reaction en route to 29.

In many cases the yield of the Suzuki cross coupling declined as the scale of reactions was increased, with yields not exceeding 54% on 42 mg scale. Heck conditions for the coupling of aryl iodides with allylic alcohol showed returned starting material (Scheme 12). Addition of Ag$_2$CO$_3$ as a halide abstraction reagent did not facilitate the reaction. Fortunately, an optimized Stille coupling with allyltributyltin by Sáa and coworkers provided the ideal cross coupling method. In the presence of triphenylphosphine, lithium chloride, (bis)triphenyl phosphine palladium (II) dichloride, and 2 milligrams of 2,6-di-tert-butyl-4-methylphenol (BHT), allyltributylin couples to aryl iodides 27 and 28 in DMF in >75% yield when heated to 120 °C (Schemes 13 and 14). More importantly, the reaction is amenable to scales greater than 42 milligrams (0.079 mmol). The acceptable yield was achieved only by eliminating the work up procedure; rather than washing with potassium fluoride, the reaction was quenched by dilution with ethyl acetate, washed repeatedly with 3N LiCl to remove DMF, and subsequent purification by column chromatography.

Scheme 14:  Stille cross coupling using caryolane iodide 27.

The final step in the synthetic sequence was the hydroboration of terminal olefins. An initial attempt with (9-borabicyclo(3.3.1)nonane (9-BBN) showed that the hydroboration did not occur, even with prolonged heating for more than 8 hours (Scheme 15). Considering perhaps that the presence of phenolic and secondary hydroxyl groups was preventing the reaction, the compound was protected as its bisacetate 30. No hydroboration occurred with 35 either (Scheme 15). Fortunately, hydroboration and oxidative work up of 24 and 25 with borane dimethylsulfide complex cleanly furnished the triols 22 and 23 in 77% (Schemes 16 and 17). The success of the hydroboration came after some optimization; Water was added prior to addition of H₂O₂ and LiOH, and the use of pH=4 phosphate buffer lead to higher yields. Quenching reactions with mineral acid solutions diminished yields of 22 and 23.

Scheme 15:  Proposed hydroboration / oxidation using 9-BBN.
Scheme 16: Hydroboration/oxidation of 23.

Scheme 17: Hydroboration/oxidation of 24.
1.7 Experimental Section

All reactions were performed under an atmosphere of nitrogen. Dichloromethane (CH₂Cl₂), tetrahydrofuran (THF), and toluene (PhMe) were purified using a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). All other reagents were used directly from the supplier without further purification unless noted. Analytical thin-layer chromatography (TLC) were carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD Chemical). Infrared spectra were recorded on a Nicolet 380 FTIR using neat thin film technique. High-resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and reported as m/z (relative intensity). Accurate masses are reported for the molecular ion [M+Na]⁺, [M+H]⁺, [M-H]⁻ or [M⁺]. Nuclear magnetic resonance spectra (¹H NMR and ¹³C NMR) were recorded with a Varian Gemini (400 MHz, ¹H at 400 MHz, ¹³C at 100 MHz). For CDCl₃ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of solvents: CHCl₃ δ H (7.26 ppm) and CDCl₃ δ C (77.0 ppm). Coupling constants are reported in Hertz (Hz). Data for ¹H-NMR spectra are reported as follows: chemical shift (ppm, referenced to protium; s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration).
A solution of β-caryophyllene oxide (2.25 g, 10.21 mmol, 4:1 mixture of β:α
diastereomers) and 2,2’-biphenol (3.80 g, 20.42 mmol, 2 equiv.) in 90 mL CH₂Cl₂ was
placed in a preheated silicone oil bath (38 °C). A solution of diphenyl phosphate (1.27 g,
5.11 mmol, 0.5 equiv.) in 60 mL CH₂Cl₂ was added over 10 minutes to the reaction
vessel. After stirring for 30 minutes, the reaction was removed from the oil bath and
allowed to cool to 23 °C. The reaction mixture was diluted with 300 mL CH₂Cl₂ and
washed with saturated NaHCO₃ solution (3 x 150 mL). Next, the reaction mixture was
washed with 4 N NaOH solution (3 x 150 mL). Finally, the reaction mixture was washed
with 100 mL brine. The extracts were then dried over Na₂SO₄, filtered, and concentrated
in vacuo. The mixture of products were purified by column chromatography (10% ethyl
Acetate/hexanes → 20% ethyl Acetate/hexanes in 5% increments). The mixture of
products was then purified again by column chromatography (dichloromethane → 10%
methanol/dichloromethane) to afford clovanebisphenol 20 (288 mg, 0.708 mmol, 16%)
and caryolanebisphenol 19 (216 mg, 0.531 mmol, 48%). Both compounds were white
foams. The yield values are determined based on the amount of the diastereomeric
epoxide that leads to the desired product.

20

Rf: 0.22 (dichloromethane)

¹H (400 MHz, CDCl₃): δ 0.84 (s, 3H), 0.87 (bs, 1H), 0.90 (s, 3H), 0.94 (s, 3H) 1.02-1.2
(m, 2H), 1.20-1.47 (m, 6H), 1.48-1.72 (m, 4H), 1.79 (dd, J=5.4 and 12.1 Hz, 1H) 1.86-
2.02 (m, 1H), 3.25 (bs, 1H), 4.22 (dd, J= 5.8 and 9.3 Hz), 6.33 (s, 1H), 7.00 (t, J=8.2,
2H) 7.04-7.16(m, 2H), 7.2-7.4 (m, 4H)
$^{13}$C (100 MHz, CDCl$_3$): δ 20.5, 25.3, 25.9, 26.4, 28.3, 31.1, 32.8, 34.5, 35.4, 37.5, 44.2, 44.7, 49.8, 74.7, 89.4, 115.8, 116.9, 120.6, 122.2, 126.7, 128.6, 128.9, 129.0, 131.1, 132.2, 153.5, 155.5

IR: ν 3378, 2947, 1478, 752

HRMS Calculated for C$_{27}$H$_{34}$O$_3$Na$^+([M+Na^+]): 429.2508$ Found: 429.2406

19

R$_f$: 0.33 (dichlromethane)

$^1$H (400 MHz, CDCl$_3$): δ 0.75 (s, 3H), 0.98 (s, 3H), 1.04 (s, 3H), 1.06-1.18(m, 2H), 1.18-1.52 (m, 7H), 1.72 (t, J = 9 Hz, 1H), 1.82 (t, J = 10 Hz, 1H), 1.88-2.06 (m, 2H), 2.28-2.4(m, 1H) 3.29 (bs, 1H) 6.95-7.11(m, 3H) 7.13-7.22(m, 1H), 7.24-7.34(m, 2H) 7.32 (dd, J = 1.71 and 7.52 Hz, 1H) 7.38 (s,1H)

$^{13}$C (100 MHz, CDCl$_3$): δ 20.2, 20.6, 26.4, 28.2, 28.9, 30.2, 34.8, 35.3, 36.2, 38.6, 39.3, 39.6, 43.9, 71.4, 84.5, 118.1, 120.9, 123.6, 123.9, 127.9, 128.3, 128.9, 131.1, 132.3, 133.1, 150.7, 153.6

IR: ν 3352, 2949, 1477, 731

LRMS Calculated for C$_{27}$H$_{34}$O$_3$Na$^+([M+Na^+]) = 429.25$ Found: 429.33
A solution of 19 (1.00 g, 2.460 mmol) and NaOH (197 mg 4.92 mmol, 2 equiv.) in 250 mL of MeOH was first cooled to −78 °C (dry ice/acetone). Once cooled, a solution of Iodine (624 mg, 2.435 mmol, 1 equiv.) in 250 mL MeOH was added and stirred at −78 °C for 30 minutes. After 30 minutes had elapsed, the −78 °C bath was removed and the reaction vessel was allowed to warm to ambient temperature over 1 hour. The reaction mixture was first concentrated under pressure to form a viscous oil, then diluted with 300 mL ethyl acetate, 200 mL of pH=3 phosphate buffer and 300 mL saturated Na₂SO₃. The organic layer was separated from the aqueous layer. The extracts were then washed with 100 mL saturated Na₂SO₃ and with 100 mL brine. The extracts were finally dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting iodophenol was purified by flash chromatography (10% ethyl acetate/hexanes→25% ethyl acetate/hexanes) to afford 27 as a white foam (1.14 g, 2.141 mmol, 87%)

Rᶠ: 0.43 (dichloromethane)

¹H (400 MHz, CDCl₃): δ 0.79 (s, 3H), 0.99 (s, 3H), 1.03 (s,3H) 1.06-1.2 (m, 3H) 1.29-1.51 (m, 5H), 1.85-2.03 (m, 3H), 2.26-2.42 (m, 1H), 3.33(bs, 1H), 6.79(d, J=8.6 Hz, 1H), 7.02 (d, J=8.2 Hz, 1H), 7.16 (td, J= 1.1 and 7.4 Hz, 1H), 7.26-7.34 (m, 2H),7.39 (s, 1H), 7.51-7.57(m, 1H), 7.59 (d, J=1.96 Hz, 1H).

¹³C (100 MHz, CDCl₃): δ 20.2, 20.5, 26.3, 28.1 29.0, 30.2, 34.7, 35.2, 36.3, 38.6, 39.2, 39.7, 44.0, 71.3, 82.7, 84.6, 120.3, 123.3, 123.8, 128. 3, 130.8, 131.1, 132.1, 137.4, 139.2, 150.6, 153.7

IR: ν 3353, 2949, 1489, 732

LRMS Calculated for C₂₇H₃₂O₃I⁺ ([M-H]⁺): 531.45 Found: 531.42
A solution of 20 (990 mg, 2.435 mmol) and NaOH (177 mg 4.43 mmol, 2 equiv.) in 250 mL of MeOH was first cooled to −78 °C (dry ice/acetone). Once cooled, a solution of Iodine (617 mg, 2.435 mmol, 1 equiv.) in 250 mL MeOH was added over 5 minutes and stirred at −78 °C for 30 minutes. The −78 °C bath was then removed and the reaction vessel was allowed to warm to 23 °C over 1 hour. The reaction mixture was first concentrated under pressure to form a viscous oil, then diluted with 300 mL Ethyl Acetate, 200 mL of pH=3 phosphate buffer and 300 mL saturated Na2SO3. The organic layer was separated from the aqueous layer. The extracts were then washed with 100 mL saturated Na2SO3 and with 100 mL brine. The extracts were finally dried over Na2SO4, filtered, and concentrated in vacuo. The resulting iodophenol was purified by flash chromatography (90% dichloromethane/Hexanes→dichloromethane→5% methanol/dichloromethane) to afford 28 as a bright white foam (1.14 g, 2.141 mmol, 88%)

Rf: 0.2 (dichloromethane)

$^1$H (400 MHz, CDCl3): $\delta$ 0.87 (s, 3H), 0.93 (s, 3H) 0.95 (s, 3H) 1.02-1.2 (m, 2H), 1.21-1.69 (m, 9H), 1.80 (dd, $J$= 5.8 and 12.5, 1H) 1.86-2.02 (m, 1H) 3.28 (bs, 1H), 4.25 (dd, $J$=5.4 and 9, 1H), 6.52 (d, $J$= 8 Hz), 6.77 (d, $J$=8.2 Hz, 1H), 7.03 (d, $J$ = 8.2, 1H), 7.07 (t, $J$=7.5Hz, 1H) 7.27 (d, $J$=1.9, 1H), 7.29 (dd, $J$= 1.57 and 7.52, 1H) 7.33-7.42 (m, 1H), 7.53 (dd, $J$ = 2.3 and 10.5, 1H), 7.54 (d, $J$ = 2.0 Hz, 1H)

$^{13}$C (100 MHz, CDCl3): $\delta$ 20.5, 25.3, 25.9, 26.5, 28.2, 31.0, 32.7, 34.3, 35.4, 37.6, 43.8, 44.7, 49.8, 74.8, 82.2, 88.6, 115.1, 119.0, 121.8, 126.7, 129.0, 129.4, 131.8, 137.3, 139.3, 153.5, 155.2

IR: ν 3400, 2949, 1478, 753

HRMS Calculated for C_{27}H_{35}O_3I^+ ([M^+]): 532.1474 Found: 532.1475
An oven dried round bottom flask, with stir bar, was charged with triphenylphosphine (2.208 g, 8.42 mmol, 6 equiv), lithium chloride (960 mg, 22.60 mmol, 16.11 equiv), bis(triphenylphosphine)palladium(II) dichloride (98 mg, 0.140 mmol, 0.1 equiv), 2 mg of 2,6 di-tert-butyl-4-methyl phenol (BHT), and iodophenol 28 (747 mg, 1.403 mmol). The round bottom flask was sealed with a rubber septum, placed under vacuum, and backfilled with N₂. To the reaction vessel was added N,N'-dimethylformamide (14 mL) followed by allyltributylstannane (1.394 g, 1.283 mL, 4.21 mmol, 3 equiv.). The reaction was placed into a pre-heated 120 °C oil bath for 15 minutes. The heating bath was then removed and the reaction was allowed to cool to 23 °C. Once cool, the reaction was diluted with 50 mL EtOAc, washed with 3N aqueous LiCl (5x 15 mL), and washed with 15 mL brine. The extracts were then dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting allylphenol was purified by flash chromatography (50% dichloromethane/hexanes→dichloromethane→10% ethyl acetate/dichloromethane) to afford 23 as a bright white foam (488 mg, 78%).

Rᶠ: 0.47 (35% ethyl Acetate/hexanes)

¹H (400 MHz, CDCl₃): δ 0.84 (s, 3H), 0.91 (s, 3H) 0.95 (s, 3H), 1.02-1.20 (m, 2H), 1.20-1.47 (m, 6H), 1.48-1.67 (m, 4H), 1.79 (dd, J=5.4 and 12.1 Hz, 1H) 1.86-2.02 (m, 1H), 3.24 (bs, 1H), 3.36 (d, J=6.6 Hz, 2H), 4.21 (dd, J=5.4 and 9.3 Hz, 1H) 4.88-5.1 (m, 2H), 4.97-5.1 (m, 2H), 6.31 (s, 1H), 6.94 (d, J= 8.2 Hz, 1H) 7.03-7.16 (m, 4H), 7.29-7.39 (m, 1H)

¹³C (100 MHz, CDCl₃): δ 20.5, 25.3, 26.0, 26.4, 28.2, 31.1, 32.8, 34.4, 35.3, 37.5, 39.2, 44.1, 44.7, 49.8, 74.7, 89.4, 115.2, 115.8, 116.9, 122.1, 126.6, 128.7, 128.9, 129.0, 131.1, 131.8, 132.0, 137.8, 151.8, 155.4

IR: ν 3421, 2948, 1497, 732
HRMS Calculated for $\text{C}_{38}\text{H}_{38}\text{O}_{3}^+([M^+])$: 446.2821 Found: 446.2822
An oven dried round bottom flask, with stir bar, was charged with Triphenylphosphine (887 mg, 3.38 mmol, 6 equiv), lithium chloride (385 mg, 9.08 mmol, 16.11 equiv), Bis(triphenylphosphine)palladium(II) dichloride (39.5 mg, 0.056 mmol, 0.1 equiv), 1 crystal of 2,6-d-tertbutyl-4-methyl phenol (BHT), and iodophenol 27 (300 mg, 0.563 mmol). The round bottom flask was sealed with a rubber septum, placed under vacuum, and backfilled with N₂. To the reaction vessel was added N,N'-dimethylformamide (14 mL) followed by allyltributylstannane (560 mg, 0.515 mL, 1.690 mmol, 3 equiv). The reaction was placed into a pre-heated 120 °C oil bath. After 15 minutes, the heating bath was removed and the reaction was allowed to cool to 23 °C. Once cool, the reaction was diluted with 50 mL EtOAc, washed with 3N aqueous LiCl (5x 15 mL), and 15 mL brine. The extracts were then dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting allylphenol was purified by column chromatography (50% dichloromethane/hexanes → dichloromethane → 10% ethyl acetate/dichloromethane) to afford 24 as a bright white foam (240 mg, 95%).

**Rᶠ**: 0.14 (20% acetone/hexanes)

**¹H (400 MHz, CDCl₃)**: δ 0.74 (s, 3H), 0.98 (s, 3H), 1.04 (s,3H), 1.06 -1.18 (m, 1H) 1.17-1.52 (m, 9H) 1.52-2.06 (m, 4H), 2.25-2.44 (m, 2H) 3.29 (bs, 1H), 3.37 (d, J=6.65 Hz, 2H), 5.0-5.12(m, 2H), 5.91-6.10 (m, 2H), 6.96 (d, J=7.8 Hz, 1H), 7.01 (d, J=8.2 Hz, 1H), 7.09 (bs, 1H), 7.11 (d, J=2.3, 1H) 7.16 (td, J= 1.18 and 7.44 Hz, 1H), 7.22-7.30 (m, 1H), 7.32-7.38 (m, 2H)
\[^{13}\text{C}\] (100 MHz, CDCl\textsubscript{3}): \(\delta\) 13.5, 20.1, 20.6, 26.3, 27.7, 28.2, 28.9, 30.2, 34.8, 34.8, 35.2, 36.0, 38.5, 39.3, 43.7, 53.3, 71.5, 84.4, 115.2, 118.0, 124.0, 127.8, 128.3, 129.0, 131.1, 132.2, 133.2, 137.9, 150.6, 151.9

\textbf{IR}: \nu 3345, 2950, 1497, 731

\textbf{HRMS} Calculated for C\textsubscript{30}H\textsubscript{38}O\textsubscript{3} + ([M+]): 446.2821 Found: 446.2817
To a solution of 23 (488 mg, 1.093 mmol) in dry THF (10.9 mL) was added 1M BH$_3$-SMe$_2$ (7.1 mL, 7.1 mmol, 6.5 equiv.) via syringe. After 10 minutes at 23 °C, the reaction was placed in an 0 °C bath (ice / water) and 1 mL H$_2$O was added. Once the fizzing had subsided, 5 mL each 30 % H$_2$O$_2$ and 5 mL 4N LiOH were added, the ice bath was removed and allowed to stir for 10 minutes. The reaction was diluted with 30 mL pH=3 phosphate buffer and 30 mL brine. The organic layers was separated from the aqueous layer. The aqueous was then extracted with EtOAc (4 x 50 mL). The combined extracts were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The resulting triol was purified by flash chromatography (30% ethyl acetate/hexanes$\rightarrow$60% ethyl acetate/hexanes) to afford 21 as a bright white foam (399 mg, 0.839 mmol, 77%)

Rf: 0.13 (35% ethyl acetate/hexanes)

$^1$H (400 MHz, CDCl$_3$): δ 0.86 (s, 3H), 0.88 (s, 3H), 0.96 (s, 3H) 1.01-1.14 (m, 2H ) 1.16-1.58 (m, 7H) 1.61 (t, J=10.6 Hz, 1H) 1.76-1.98 (m, 3H) 2.35 (s, 1H) 2.68 (t, J=7 Hz, 2H) 3.2 (bs, 1H), 3.64 (t, J=6.5 Hz, 2H), 4.23 (dd, J= 5 Hz and 9Hz, 1H), 6.9 (bs, 1H), 6.92 (d, J=7.8 Hz, 1H), 7.02-7.12(m, 3H) 7.14-7.22 (m, 1H), 7.30-7.40 (m, 2H)

$^{13}$C (100 MHz, CDCl$_3$): δ 20.5, 25.2, 25.2, 25.8, 26.4, 28.2, 31.0, 32.8, 34.0, 34.4, 35.4, 37.5, 44.1, 44.6, 49.7, 61.7, 74.6, 88.9, 115.3, 116.6, 125.1, 126.5, 128.0, 128.5, 128.8, 130.9, 131.9, 133.6, 151.6, 155.5

IR: v3383, 2946, 1036, 736

HRMS Calculated for C$_{30}$H$_{40}$O$_4^+$ ([M$^+$]): 464.2927 Found: 464.2924
To a solution of 24 (150 mg, 0.336 mmol) in dry THF (3.36 mL) was added 1M BH$_3$SMe$_2$ (2.18.1 mL, 6.5 equiv.) via syringe. After 10 minutes 23 °C, the reaction was placed in an 0 °C bath (ice/water) and 1 mL H$_2$O. Once the fizzing had subsided, 1 mL each 30% H$_2$O$_2$ and 1 mL 4N LiOH were added, the ice bath was removed, and allowed to stir for 10 minutes. The reaction was diluted with 15 mL pH=3 phosphate buffer and 15 mL brine. The organic layer was separated from the aqueous layer. The aqueous was then extracted with EtOAc (4x 50 mL). The combined extracts were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The resulting triol was purified by flash chromatography (30% ethyl acetate/hexanes→60% ethyl acetate/hexanes) to afford 22 as a bright white foam (399 mg, 0.839 mmol, 77%).

R$_f$: 0.27 (40% ethyl acetate/hexanes)

$^1$H (400 MHz, CDCl$_3$): δ 0.73 (s, 3H), 0.98(s, 3H), 1.04 (s, 3H) 1.06-1.14(m, 1H), 1.14-1.65(m, 7H), 1.68-1.78(m, 1H), 1.79-2.02 (m, 5H), 2.25-2.39(m, 1H) 2.69 (t, $J$=7.4 Hz, 2H), 3.26 (bs, 1H), 3.64 (t, $J$=6.2 Hz, 2H) 6.95 (d, $J$=8.2 Hz, 1H) 7.03(d, $J$=7.8 Hz, 1H), 7.08-7.14(m, 2H) 7.17(t, $J$=7.43, 1H), 7.22-7.29(m, 7H), 7.3-7.38(m, 1H)

$^{13}$C (100 MHz, CDCl$_3$): δ 20.0, 20.6, 26.4, 28.2, 28.9, 30.2, 31.0, 34.1, 34.8, 35.2, 36.1, 38.3, 39.3, 43.8, 61.6, 71.5, 84.5, 118.1, 124.1, 126.7, 128.3, 128.8, 131.0, 132.1, 133.4, 134.0, 150.8, 151.7

IR: ν 3353, 2932, 2247, 1442

HRMS Calculated for C$_{30}$H$_{40}$O$_4$Na$^+$([M+Na$^+$]): 487.2927 Found: 487.2822
Figure 5: $^1$H NMR spectrum for 20.
Figure 6: $^{13}$C NMR spectrum for 20.
Figure 7: H NMR spectrum for 19.
Figure 8: $^{13}$C NMR spectrum for $^{19}$.
Figure 9: $^{1}$H NMR spectrum for 27.
Figure 10: $^{13}$C NMR spectrum for 27.
Figure 11: $^1$H NMR spectrum for 28.
Figure 12: $^{13}$C NMR spectrum for 28.
Figure 13: $^1$H NMR spectrum for 23.
Figure 14: $^{13}$C NMR spectrum for 23.
Figure 15: $^1$H NMR spectrum 24.
Figure 16: $^{13}$C NMR spectrum 24.
Figure 16: $^1$H NMR spectrum for 21.
Figure 17: $^1$H NMR spectrum for 21.
Figure 18: $^1$H NMR spectrum for 22.
Figure 19: $^{13}$C NMR spectrum for 22.
References