THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DEPARTMENT OF CHEMISTRY

A MODEL SYSTEM FOR THE SYNTHESIS OF LECANINDOLE D AND ITS BENZOFURAN ANALOG

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ABSTRACT

This thesis details work towards the total synthesis of lecanindole D, an indole sesquiterpenoid with potent and selective agonist activity toward the progesterone receptor. Phosphoniosilylation and conjugate addition are evaluated for the β-substitution of a sterically hindered enone, applicable towards the total synthesis of lecanindole D. The efforts towards construction of the benzofuran analog of lecanindole D are also given, while the completion of the benzofuran analog model system is ongoing.

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I would like to thank Dr. Feldman for the opportunity to learn and work in his research group. I was challenged to think critically and independently throughout my time in the lab, while simultaneously provided enough scaffolding to grow as a research chemist.

I would also like to thank Inanllely Gonzalez for her support and guidance throughout my time and research on my lecanindole D model systems. Ina was a true mentor, friend, and an invaluable asset in the editing of this thesis.

Chapter 1

Introduction

Background Information

Human progesterone receptor (hPR) agonists have been important drug targets because of their role in the female reproductive cycle ever since their approval for menstrual regulation in 1957 and oral contraception in 1959.[1] All current commercial hPR agonists, also known as progestins, are steroidal in nature.[2] While all hPR agonists have the expected progestational effect, they can also interact with other hormone receptors, such as the mineralocorticoid (hMR) and androgen receptors (hAR), to varying degrees. These interactions lead to side effects, such as increased blood pressure, weight gain and decline of libido. Side effects are the primary reason for discontinuation of oral contraceptive treatment.[1] Though steroids are a safe and effective pharmaceutical class, the development of nonsteroidal progestins has the potential to improve the clinical profile and reduce side effects due to their greater selectivity for the hPR.

Lecanindole D (**1**) is a highly selective nonsteroidal hPR agonist isolated from the terrestrial fungus, *Verticillium lecanii 6144*.[2] Isolated alongside lecanindoles A-C (**2**-**4**, Figure 1), lecanindole D was the only compound to exhibit progestin activity in a cell-based luciferase reporter assay.[2] Lecanindole D appears to bind tightly to the hPR with high specificity (Table 1). It is competitive with progesterone due to its EC_{50} of 1.1 ± 0.4 nM, which is about the same as that of the natural ligand. While an EC_{50} over 10,000 nM makes it practically inactive for the hMR and hAR. Compared to current steroidal progestins, lecanindole D's specificity for the hPR shows great promise as a starting point for use as an oral contraceptive design with fewer side effects. Due to its promising medical utility, a synthetic route for lecanindole D is of great interest.

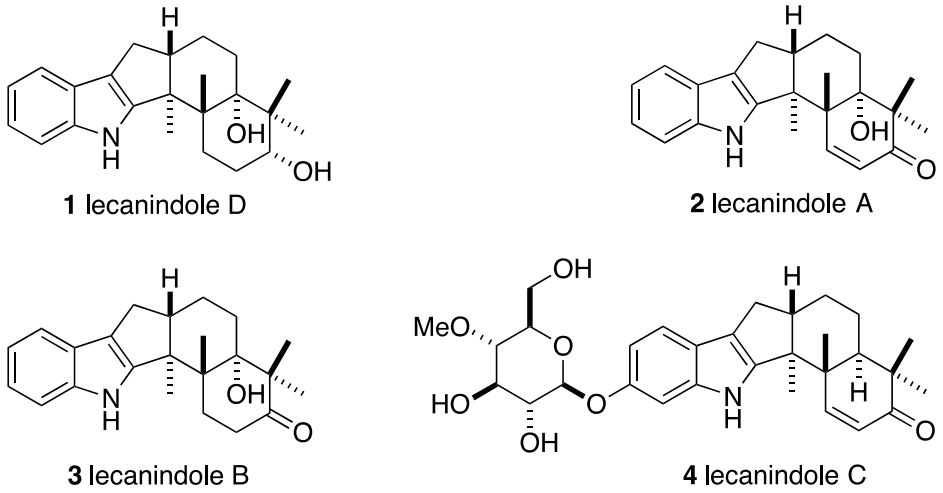

Figure 1. The lecanindoles A-D.

Table 1. Half maximal effective concentrations of progestins

Ligand	EC_{50} (nM) for Receptor		
	Progesterone	Mineralocorticoid	Androgen
progesterone	0.7	> 1000	> 100
gestodene	0.02	---	0.23
drospirenone	1.7	> 1000	> 100
lecanindole D	1.1	>10000	> 10000

Model System of Lecanindole D

The structure of lecanindole D introduces several synthetic challenges, such as the trans indane ring junction, as well as the two all-carbon quaternary stereogenic centers. Based upon prior work in our research group, an allenyl azide cyclization can produce the required trans indane in good yield and high stereoselectivity with the use of the pure *E*-alkenyl sulfide **5-*E***, while the use of the *Z*-alkenyl sulfide **5-*Z*** results in a significant decrease of the desired trans indane ring stereochemistry (Figure 2).[3] The current

synthetic route for lecanindole D is outlined briefly below and is centered around a key allenyl azide cyclization (Figure 3). The required *E*-alkenyl sulfide is introduced through the β-substitution of the starting enone.

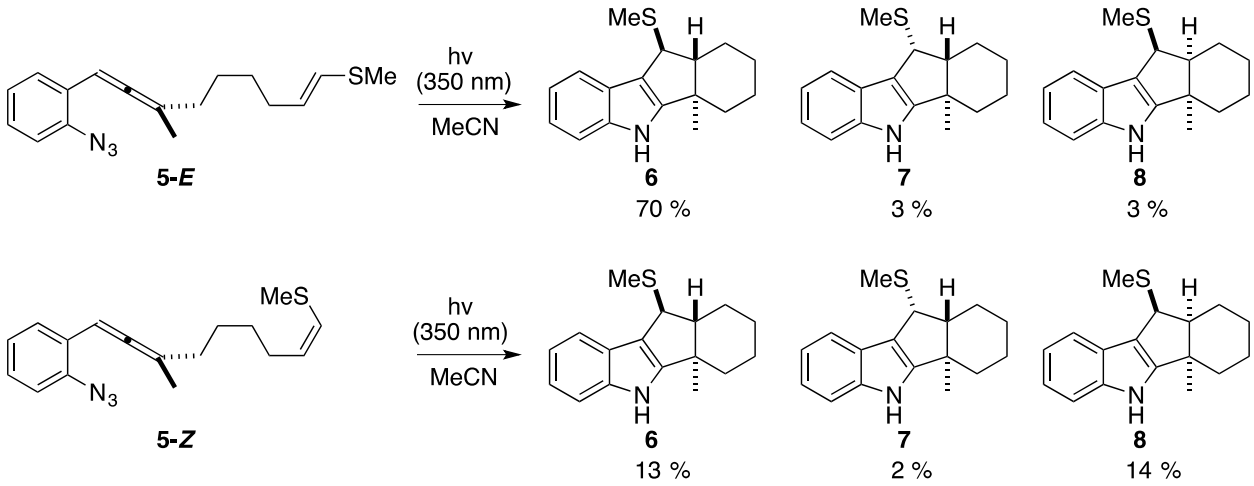

Figure 2. Allenyl azide cyclization of *E*- and *Z*-alkenyl sulfides.

The model system in question investigates the feasibility of this sterically hindered β-substitution with the required *E*-alkenyl sulfide containing chain. Two approaches to the β-substitution of model system **13** were investigated, phosphoniosilylation and conjugate addition (Figure 4). The phosphoniosilylation approach attempts to form the intermediate ylide **15**, which can afford the β-substituted enone **17** via a Wittig reaction.[4] The second approach is the conjugate addition of an organocuprate reagent, followed by the subsequent oxidation of the derived enolate with *N-tert*-butylbenzenesulfinimidoyl chloride to give the one-pot β-substitution of enones as reported by Matsuo and Aizawa.[5] Lithium enolates such as **18** react with *N-tert*-butylbenzenesulfinimidoyl chloride to give β-elimination under mild conditions (-78 °C).[5]

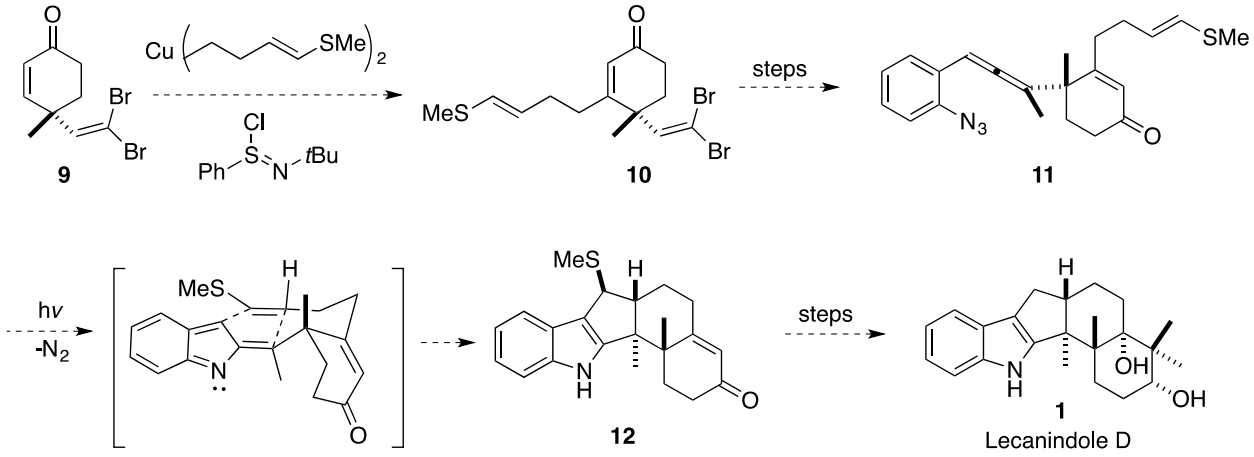

Figure 3. Proposed lecanindole D synthetic route.

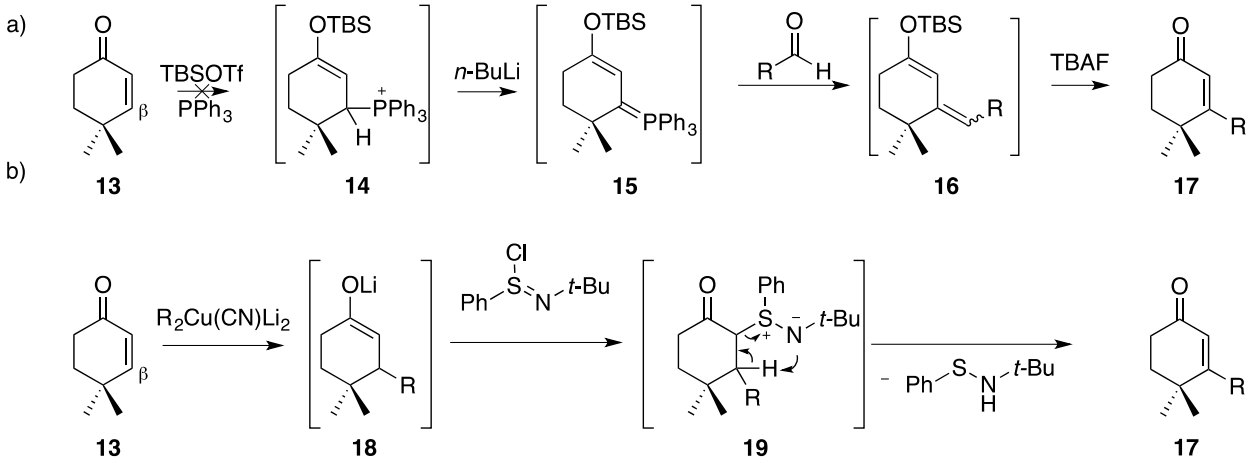

Figure 4. β-Substitution via: (a) phosphoniosilylation and (b) conjugate addition.

Benzofuran Analog

The reason for lecanindole D's specificity for the hPR is unclear. All crystallographically characterized ligand binding domains (LBD) for the hPR display a directional H-bond acceptor at the C(3) carbonyl of the steroid that forms strong H-bonds to the LBD.[6] Such interactions are not possible with lecanindole D due to the lack of equivalent H-bond acceptor functionality at C(3). Instead, calculations using the Glide module of the Schrodinger 2011 software package[7] identify a strong and

directional H-bond attachment between the indole N-H and the hPR LBD. By preparing the benzofuran analog **20** (Figure 5), the significance of the indole N-H binding can be tested.

Figure 5. Benzofuran analog of lecanindole D.

The model system of the benzofuran analog is modified slightly from that of the allenyl azide cyclization used in lecanindole D, due to the obvious absence of nitrogen in the analog. Instead, the key step is a Lewis acid mediated cyclocondensation (Figure 6). Prior work in the group revealed a similar transformation, using a benzylated indole in place of the benzofuran core, resulting in the desired trans indane stereochemistry as the major product (Figure 7).[3]

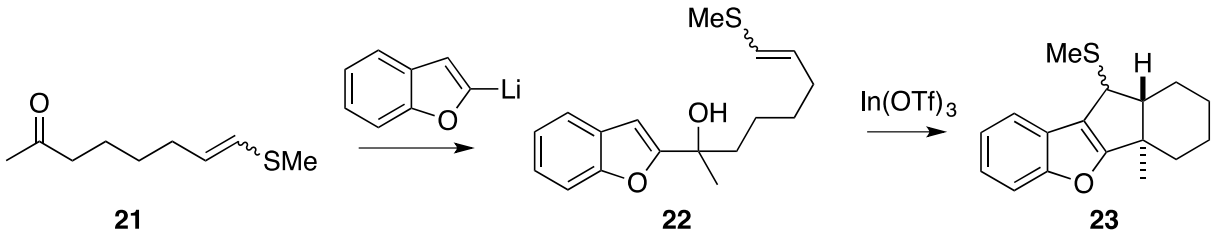

Figure 6. Benzofuran model system analog.

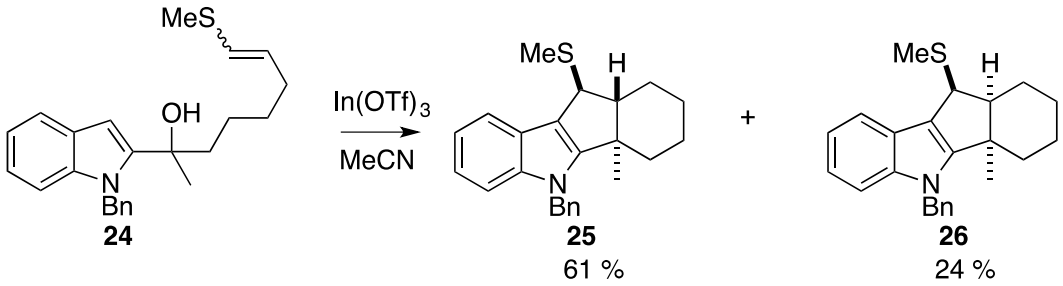

Figure 7. Indium triflate mediated [3 + 2] cyclocondensation of *N*-benzylindole alkenyl sulfide substrate.

Chapter 2

Results and Discussion

Phosphoniosilylation

Investigations into the feasibility of β-substitution began with phosphoniosilylation of sterically hindered model enone **27**. Attempts at phosphoniosilylation with benzaldehyde failed to afford any substantial formation of the desired silyl ether **28** (Figure 8). Instead **29** was obtained as the major product, likely the result of competing deprotonation at the ketone α-position (Figure 9).

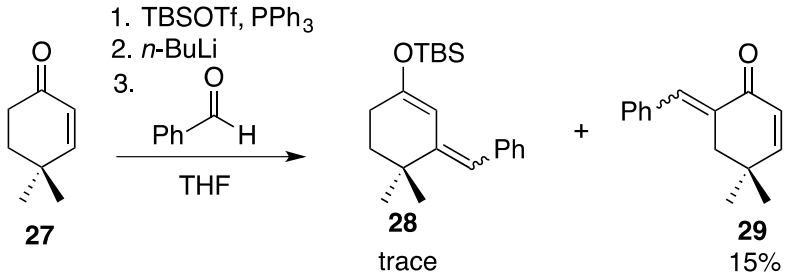

Figure 8. Phosphoniosilylation of a hindered enone.

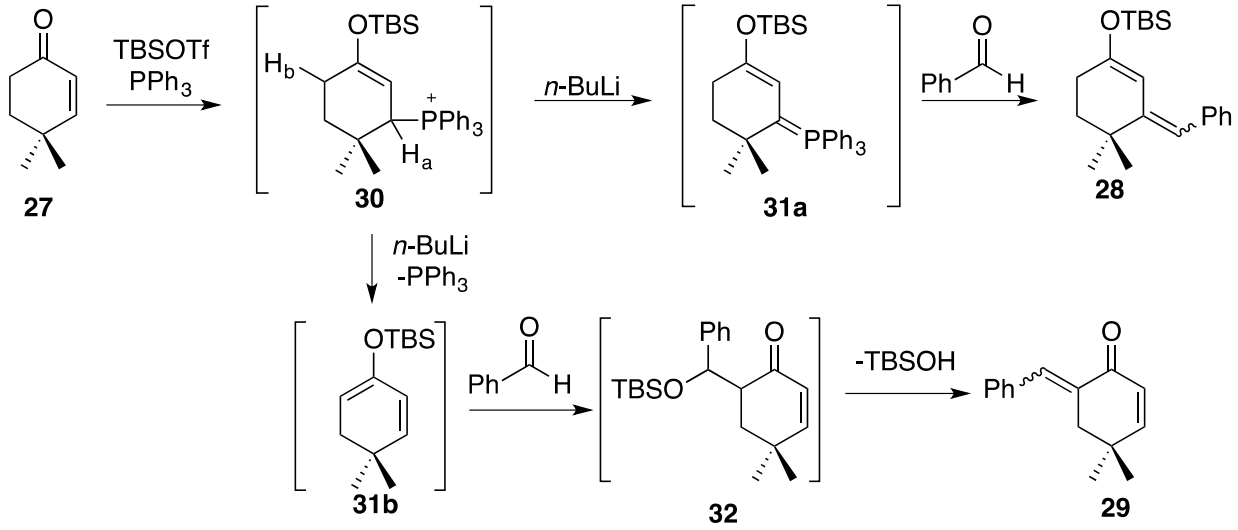

Figure 9. Competing deprotonations during phosphoniosilylation.

Instead of the formation of ylide **31a**, deprotonation of the sterically accessible proton, H_b would result in the elimination of triphenylphosphine and the formation of silyl ether **31b**. Upon nucleophilic addition to benzaldehyde and subsequent elimination of *tert*-butyldimethylsilanol, this unwanted deprotonation results in the formation of **29**. In order to circumvent the steric issue exerted by triphenylphosphonine, other phosphines with smaller Tolman cone angles were screened (Figure 10).[8] However, phosphoniosilylation of the hindered enones failed to give the desired products. Thus, the steric obstacle at the deprotonation site proved to be insurmountable. Control experiments on the unhindered cyclohexenone gave the desired products, supporting the unfavorable sterics hypothesis (Figure 11). However, the adjacent methyls cannot be removed in the lecanindole D synthetic route (Figure 2). Therefore, it was necessary to continue efforts towards β-substitution by studying conjugate addition.

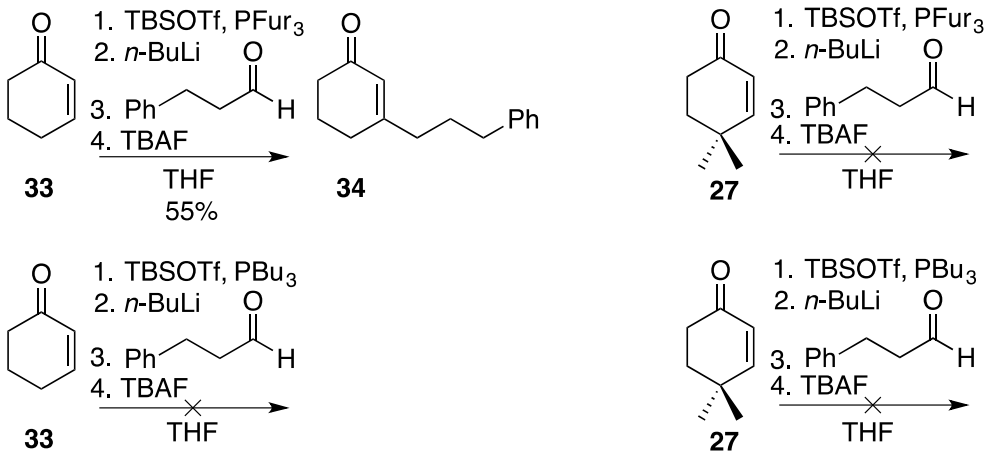

Figure 10. Phosphoniosilylation with phosphines of smaller Tolman cone angles.

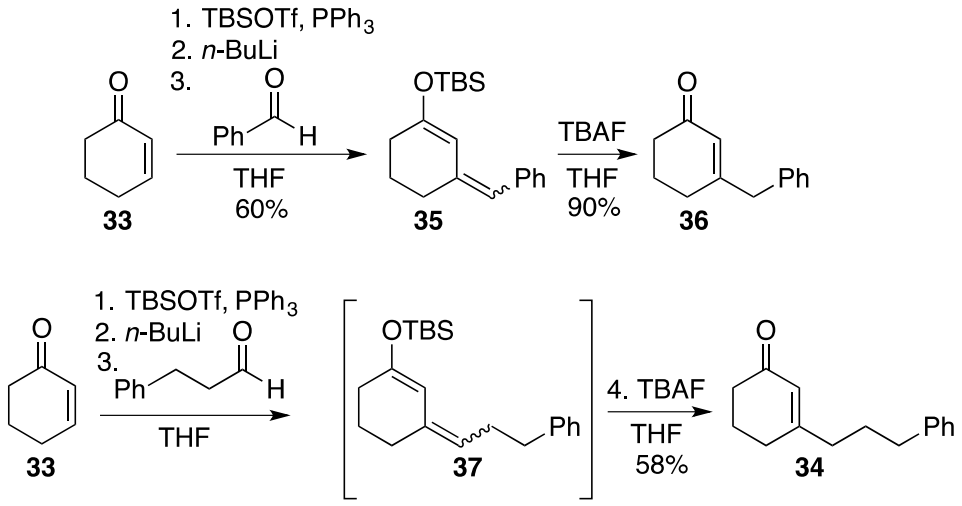

Figure 11. Phosphoniosilylation control experiments.

Conjugate Addition

The conjugate addition of *n*-butyl cyanocuprate to enone **6** afforded the trisubstituted cyclohexane **38** in moderate yield (Figure 12). Having demonstrated the viability of conjugate addition to the sterically hindered β-position, the experiment was repeated with the inclusion of *N*-*tert*-butylbenzenesulfinimidoyl chloride to afford the β-substituted enone **39** in good yield.[5]

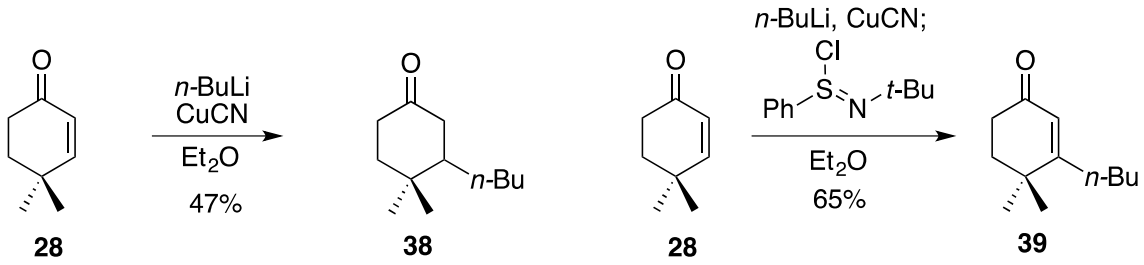

Figure 12. Cyanocuprate conjugate addition.

After the success of the simple alkyl substitution, synthesis of the more complex thiomethyl cyanocuprate was sought for its application towards the model system of lecanindole D. Initial attempts focused on the formation the mixture of *E* and *Z* isomers through a Wittig reaction on 3-chloropropanal (**34**), which was synthesized from its diethyl acetal using trifluoroacetic acid mediated deacetalization

(Figure 13).[9] However, the attempted Wittig reaction failed to yield **42**, as did reactions testing the quality of the ylide reagent. In the interest of time, synthesis of **44** proceeded through substitution of halide **43** with thiomethoxide. Chlorination of **44** via *N*-chlorosuccinimide, followed by elimination with $CaCO_3$ only provided trace amounts of the desired product **46**.[10]

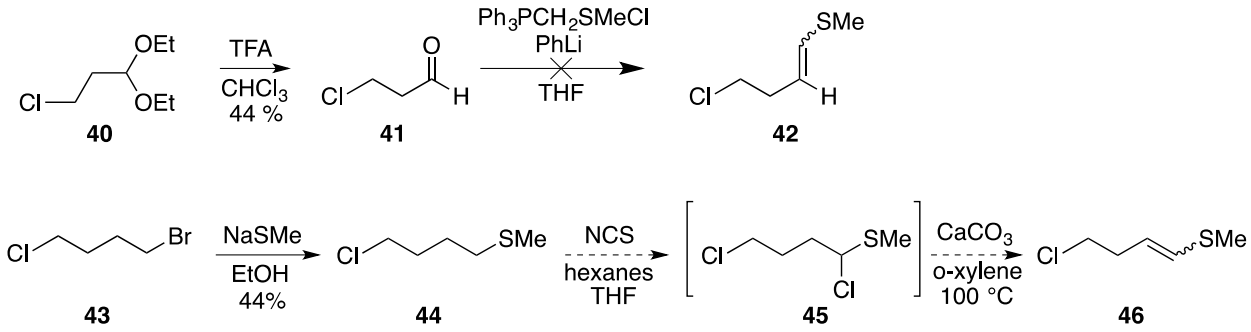

Figure 13. Attempts at thiomethyl cyanocuprate precursor.

The final, successful approach towards the synthesis of the required chain was the formation of the *E*-alkenyl sulfide via hydrozirconation of the corresponding terminal alkyne (Figure 14).[11] This approach would only provide the *E*-alkenyl sulfide, which is required for the model system of lecanindole D (Figures 2, 3). The initial attempt, using MeSCl as the electrophile with intermediate alkenyl zirconate **48**, proved to be unsuccessful, even when the reagent was freshly distilled. MeSCl was prepared from methyl disulfide and SO_2Cl_2, and used immediately as reported by Zhong and Huang.[11] However, reaction of the vinyl zirconium intermediate **48** with iodine delivered the vinyl iodide **50** in good yield. The alkenyl iodide was successfully converted into the desired *E*-alkenyl sulfide through a magnesium-halogen exchange with *i*-PrMgCl·LiCl followed by quenching with methyl disulfide.[12] Moreover, no isomerization of the *E*-alkenyl sulfide to the *Z*-alkenyl sulfide was observed.

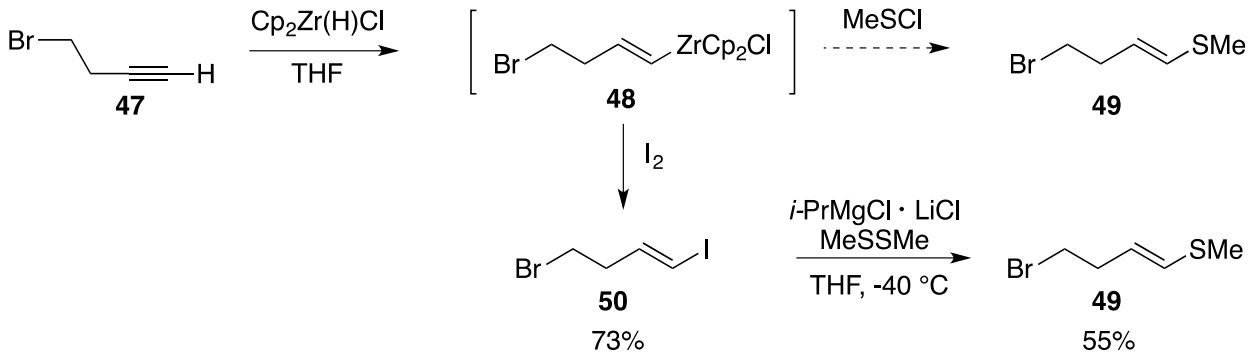

Figure 14. Preparation of the E-alkenyl sulfide via hydrozirconation.

Primary attempts to form the Grignard from bromide **49** showed no consumption of starting material. However unpublished work by Inanllely Gonzalez successfully details the lithium-halogen exchange of **49** followed by formation of the cuprate (Figure 15). The conjugate addition of this cuprate successfully installed the required *E*-alkenyl sulfide into the current synthetic route of lecanindole D (Figure 3).

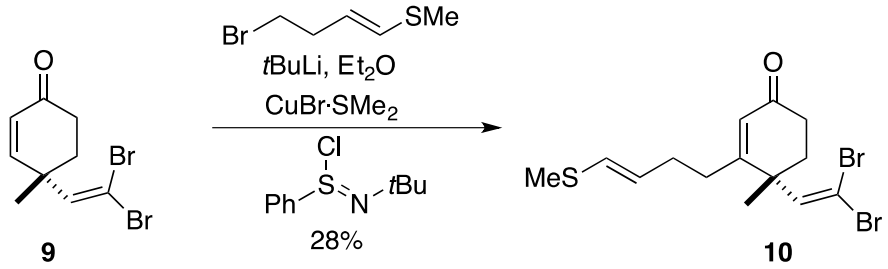

Figure 15. Conjugate addition of the requisite *E*-alkenyl sulfide.

Benzofuran Model System

The benzofuran model system is centered on a Lewis acid mediated cyclocondensation of the benzofuran alkenyl sulfide substrate **22** (Figure 6). The synthesis for the cyclization precursor was completed in 3 steps from 1-methylcyclohexene. Ozonolysis of **51** afforded **52** in moderate yield (Figure 16). The next step required a selective Wittig reaction of an aldehyde in the presence of a ketone, which was accomplished in moderate yield. The resultant vinyl adducts were treated with lithiated benzofuran to

produce **22** and **54**, respectively, in excellent and moderate yields. Attempts to promote a Lewis acid mediated cyclocondensation with $In(OTf)_3$ proved to be unsuccessful, as only the intermediate aldehydes **56** and **57** were observed (Figure 16). Other Lewis acids, such as $Sc(OTf)_3$ and $Yt(OTf)_3$, resulted in similar results.

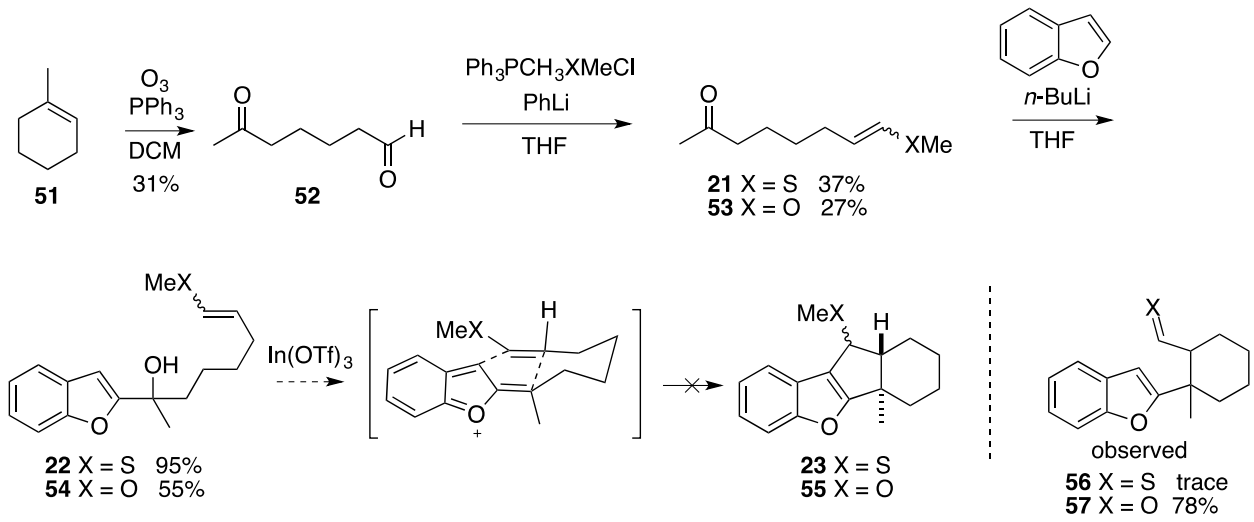

Figure 16. Benzofuran model system.

Attempted Lewis acid mediated cyclocodensations of **22** were messy with no clear major product, but those of **54** were cleaner with **57** as the major product. Attempts to force the complete cyclization have been unsuccessful. Investigations into similar chemistry by Smith and Cui[13] have focused on the transformation from the aldehyde to the mesylate (Figure 17). Experiments are underway to use a Lewis acid with **59** to enhance the mesylate leaving group and encourage cyclization via the oxygen lone pair.

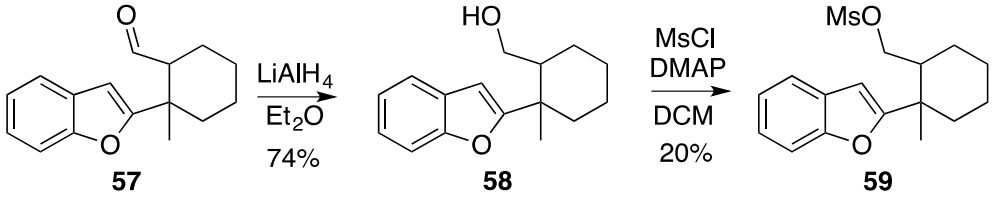

Figure 17. Attempted cyclization of the partial cyclized aldehyde.

Chapter 3

Conclusion

The work described herein addresses a model system for the β-substitution of a sterically hindered enone for the application towards the total synthesis of lecanindole D. The current approach is conjugate addition and subsequent oxidation with *N*-*tert*-butylbenzenesulfinimidoyl chloride. The cuprate precursor was successfully synthesized with the required *E*-alkenyl sulfide, vital for the trans indane stereochemistry observed in allenyl azide cyclizations. The efforts towards construction of the benzofuran analog of lecanindole D were also presented. Work towards the complete cyclization, and completion of the benzofuran analog model system, is ongoing.

Chapter 4

Experimental

Experimental Section

General Methods. All reactions were performed using Schlenk glassware under nitrogen atmosphere unless otherwise indicated. Solvents were purified by passage through activated alumina columns. All reagents were used as supplied without further purification unless otherwise noted. NMR spectra were obtained using a Brüker Avance DPX-300, Brüker Avance CDPX-300, Brüker Avance-360, or a Brüker Ultrashield DRX-400 spectrometer.

8-(Methylthio)oct-7-en-2-one (21). To a solution of (methyl thiomethyl)triphenyl phosphonium chloride (6.0 g, 17 mmol) in THF (30 mL) was added PhLi (1.9 M, 8.8 mL, 17 mmol) at -78 °C. The reaction was stirred at that temperature for 45 min. The resulting solution was added dropwise via pipette to a solution of **52** (1.9 g, 15 mmol) in THF (60 mL) at -78 °C. The reaction was warmed to room temperature and stirred for 2 h. The reaction was quenched with sat. NH_4Cl (aq) (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over $NaSO_4$, and concentrated *in vacuo*. The crude mixture was purified on SiO_2 (95% hexanes / 5% EtOAc) to afford the product **21** as an oil (1.0 g, 37%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (d, J = 14.9 Hz, 1H), 5.41 (m, 1H), 2.43 (t, J = 7.2 Hz, 2H), 2.23 (s, 3H), 2.09 (m, 5H), 1.60 (m, 2H), 1.38 (m, 2H). Spectral data are in agreement with the literature.[3]

2-(Benzofuran-2-yl)-8-(methylthio)oct-7-en-2-ol (22). To a solution of benzofuran (0.38 mL, 3.5 mmol) in THF (150 mL) was added *n*-BuLi (2.5 M, 1.4 mL, 3.5 mmol) dropwise at -78 °C. The reaction was allowed to stir for 20 min at that temperature before **21** was added dropwise. The resulting mixture was stirred for 10 min at -78 °C before being warmed to room temperature to stir for 45 min. The

reaction mixture was quenched with sat. NH_4Cl (aq) (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified on SiO_2 (70% hexanes / 30% Et_2O) to afford the product **22** as an oil (0.80 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (m, 1H), 7.45 (m, 1H), 7.21 (m, 2H), 6.58 (s, 1H), 5.92 (d, *J* = 15 Hz, 1H), 5.48–5.37 (m, 1H), 2.24 (br, 1H), 2.23 (m, 2H), 2.07 (s, 3H), 1.93 (m, 2H), 1.62 (s, 3H), 1.30–1.10 (m, 5H).

6-Benzylidene-4,4-dimethylcyclohex-2-en-1-one (29). To a solution of triphenylphosphine (2.1g, 8.0 mmol) in THF (12 mL) was added *tert*-butyldimethylsilyl triflate (0.92 mL, 4.0 mmol) at room temperature. 4,4-Dimethylcyclohex-2-en-1-one (0.50 mL, 4.0 mmol) was added dropwise to the solution. The reaction mixture was left to stir for 1.5 h, then cooled to -78 °C before *n*-BuLi (1.6 mL, 4.0 mmol) was added and left to stir. After 10 min, benzaldehyde (0.41 mL, 4.0 mmol) was added at -78 °C and the reaction was allowed to warm to room temperature and left to stir overnight. The reaction mixture was poured into petroleum ether (80 mL) and filtered through a plug of neutral alumina. The filtrate was concentrated *in vacuo*. The compound was purified on SiO_2 (75% hexanes / 25% EtOAc) to afford the product **29** as an oil (97 mg, 15%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.43–7.31 (m, 5H), 6.77 (d, *J* = 10 Hz, 2H), 6.07 (d, *J* = 10 Hz, 2H), 2.84 (s, 2H), 1.13 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 189.0, 159.5, 136.6, 136.1, 133.9, 130.1, 128.8, 128.5, 128.1, 126.8, 41.1, 32.0, 29.1.

3-(3-Phenylpropyl)cyclohex-2-en-1-one (34). To a solution of tri-2-furylphosphine (93 mg, 0.40 mmol) in THF (1.2 mL) was added *tert*-butyldimethylsilyl triflate (0.92 mL, 4.0 mmol) at room temperature. Cyclohexenone (39 μL, 0.40 mmol) was added dropwise at room temperature and allowed to stir for 1.5 hr. The reaction was cooled to -78 °C and *n*-BuLi (160 μL, 0.40 mmol) was added and allowed to stir at that temperature for 15 min. Hydrocinnamaldehyde (53 μL, 0.40 mmol) was added at -78 °C and the reaction was allowed to warm to room temperature and left to stir overnight. The reaction mixture was cooled to 0°C and tetrabutylammonium fluoride (0.80 mL of a 1.0 M soln in THF, 0.80 mmol) was added and allowed to stir for 45 min at that temperature. The solution was quenched with sat. NH_4Cl (aq) (1

mL) and extracted with Et_2O (3 x 1 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The compound was purified on SiO_2 (70% hexanes / 30% Et_2O) to afford the product **34** as an oil (47 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.21–7.16 (m, 3H), 5.89 (s, 1H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.36 (t, *J* = 6.3 Hz, 2H), 2.25 (m, 4H), 1.97 (p, *J* = 6.4 Hz, 2H), 1.77 (m, 2H).

((3-Benzylidenecyclohex-1-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (35). To a solution of triphenylphosphine (1.3 g, 5.0 mmol) in THF (15 mL) was added *tert*-butyldimethylsilyl triflate (1.15 mL, 5.0 mmol) at room temperature. Cyclohexenone (0.48 mL, 5.0 mmol) was added dropwise at room temperature and allowed to stir for 1.5 h. The reaction was cooled to -78 °C and *n*-BuLi (2 mL, 5.0 mmol) was added and allowed to stir at that temperature for 30 min. Benzaldehyde (0.51 mL, 5.0 mmol) was added at -78 °C and the reaction was allowed to warm to room temperature and left to stir for 1 h. The precipitate was filtered and the filtrate was concentrated *in vacuo*. The product was purified on SiO_2 (67% hexanes / 33% Et_2O) to afford the product **35** as an oil (0.90 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.16 (m, 5H), 6.10–6.02 (m, 1H), 5.58 (s, 1H), 2.59 (t, *J* = 5.8 Hz, 2H), 2.22 (t, *J* = 6.0 Hz, 2H), 1.77 (quint, *J* = 6.1 Hz, 2H), 0.94 (s, 9H), 0.17 (s, 6H).

3-Benzylcyclohex-2-en-1-one (37). To a solution of **35** (0.90 g, 3.0 mmol) in THF (15 mL) was added tetrabutylammonium fluoride (8.5 mL of a 1.0 M soln in THF, 8.5 mmol) at 0 °C. After 30 min, the reaction was quenched with sat. NH_4Cl (aq) (10 mL) and extracted with ether (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The compound was purified on SiO_2 (75% hexanes / 25%EtOAc) to afford the product **37** as an oil (0.51 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.10 (m, 5H), 5.87 (s, 1H), 3.51 (s, 2H), 2.35 (t, *J* = 6 Hz, 2H), 2.25 (t, *J* = 8 Hz, 2H), 1.95 (quint, *J* = 7 Hz, 2H). Spectral data are in agreement with the literature.[14]

3-Butyl-4,4-dimethylcyclohexan-1-one (38). Copper(I) cyanide (35 mg, 0.39 mmol) was suspended in Et_2O (2 mL) and cooled to -78 °C. To the suspension was added *n*-BuLi (0.28 mL of a 2.5 M soln in hexanes, 0.7 mmol) at that temperature, after which the mixture was warmed to 0 °C and

allowed to stir for 10 min. The solution was then cooled to -23 °C and 4,4-dimethylcyclohex-2-en-1-one (50 μL, 0.35 mmol) was added and stirred at -23 °C for 40 min. The reaction was quenched with sat. NH_4Cl (5 mL) and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified on SiO_2 (95% hexanes / 5% Et_2O) to afford **38** as a yellow oil (30 mg, 47%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.44–2.0 (m, 4H), 1.74–1.21 (m, 9H), 1.21 (s, 3H), 1.02 (s, 3H), 0.88 (t, *J* = 7.2 Hz, 3H). Spectral data are in agreement with the literature.[15]

3-Butyl-4,4-dimethylcyclohex-2-en-1-one (39). Copper(I) cyanide (15 mg, 0.17 mmol) was suspended in Et_2O (2 mL) and cooled to -78 °C. To the suspension was added *n*-BuLi (0.12 mL of a 2.5 M soln in hexanes, 0.31 mmol) at that temperature, after which the mixture was warmed to 0 °C and allowed to stir for 10 min. The solution was cooled to -23 °C and 4,4-dimethylcyclohex-2-en-1-one (22 μL, 0.15 mmol) was added and stirred at -23 °C for 20 min. To the solution was added *N-tert*-butylbenzenesulfinimidoyl chloride (100 mg, 0.46 mmol) in Et_2O (1 mL) at -78 °C. The reaction was allowed to stir at that temperature for 1 h before sat. NH_4Cl (5 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The compound was purified on SiO_2 (95% hexanes / 5% Et_2O) to afford **39** as a yellow oil (18 mg, 65%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (s, 1H), 2.44 (t, *J* = 6 Hz, 2H), 2.18 (t, *J* = 5 Hz, 2H), 1.84 (t, *J* = 5 Hz, 2H), 1.56–1.25 (m, 5H), 1.18 (s, 6H), 0.93 (t, *J* = 8 Hz, 3H).

3-Chloropropanal (41). To a solution of 3-chloro-1,1-diethoxypropane (1 mL, 6 mmol) in $CHCl_3$ (30 mL) was added trifluoroacetic acid (1.89 mL, 24 mmol) dropwise at room temperature. The solution was heated to 75 °C and refluxed overnight. The solution was cooled to room temperature, then H_2O (30 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford **41** as a yellow oil (0.441 g, 44%). The product was used without further purification. ^1H NMR (400 MHz,

$CDCl_3$) δ 9.88 (d, *J* = 1.8 Hz, 1H), 3.80 (t, *J* = 6.4 Hz, 2H), 2.93 (dt, *J* = 1.8 Hz, 5.8Hz, 2H). Spectral data are in agreement with the literature.[16]

(4-Chlorobutyl)(methyl)sulfane (44). Sodium thiomethoxide (0.51 g, 7.3 mmol) was dissolved in EtOH (13 mL) and cooled to 0 °C. To the stirred solution was quickly added 1-bromo-4-chlorobutane (0.78 mL, 6.7 mmol). The solution was stirred at 0 °C for 15 min before being allowed to warm to room temperature and left to stir overnight. The solvent was removed via rotary evaporation and the sample was redissolved in hexanes. The precipitate was filtered through a plug of neutral alumina. The filtrate was concentrated *in vacuo* to afford **44** as a pungent oil (0.42 g, 44%). The sample was stored at -30 °C overnight and used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (t, *J* = 4.6 Hz, 2H), 2.53 (t, *J* = 7.1 Hz, 2H), 2.11 (s, 3H), 1.89 (m, 2H), 1.77 (m, 2H). Spectral data are in agreement with the literature.[17]

(*E*)-(4-Bromobut-1-en-1-yl)(methyl)sulfane (49). To a solution of **50** (1.84 g, 7.0 mmol) in THF (2.8 mL) at -40 °C was added dropwise *i*-PrMgCl•LiCl (1.3M soln in THF, 5.9 mL, 7.7 mmol) over 3 hours. The reaction was left to stir at that temperature overnight. To the solution was added methyl disulfide (0.86 mL, 7.7 mmol). After allowing the reaction mixture to warm to room temperature, it was immediately quenched with sat. NH_4Cl (aq) (3 mL) and extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The compound was purified on SiO_2 (100% hexanes) to afford the product **49** as an oil (0.71 g, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, *J* = 12 Hz, 1H), 5.35 (m, 1H), 3.37 (t, *J* = 8.0 Hz, 2H), 2.65 (m, 2H), 2.25 (s, 3H).

(*E*)-4-Bromo-1-iodobut-1-ene (50). To a solution of 4-but-1-yne (0.9 mL, 9.7 mmol) in THF (70 mL) was added half of a portion of the zirconocene hydrochloride (1.5 g, 5.8 mmol). The reaction was allowed to stir until the mixture became a homogenous solution, and then the second portion of the zirconocene hydrochloride (1.5 g, 5.8 mmol) was added and left to stir until the mixture became a homogeneous solution. Iodine (2.5 g, 9.7 mmol) was added and stirred for 30 min. The resulting product

50 was filtered through a silica plug and used without further purification. ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.52 (m, 1H), 6.22 (d, *J* = 16 Hz, 1H), 3.38 (t, *J* = 8 Hz, 2H), 2.62 (m, 2H).

6-Oxoheptanal (52). Ozone was bubbled through a solution of 1-methylcyclohexene (6.2 mL, 52 mmol) in DCM (0.88 L) at -78 °C until the solution turned blue. The reaction mixture was warmed to room temperature and triphenylphosphine (18.3 g, 62 mmol) was added. The solution was left to stir at that temperature overnight. The reaction mixture was concentrated *in vacuo* and a 50:50 mixture of hexanes and Et_2O (100 mL) was added and a precipitate was formed. The precipitate was filtered and the filtrate was purified on SiO_2 (gradient: 100% hexanes to 30% EtOAc / 70% hexanes) to afford the product **52** as an oil (2.0 g, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 2.46 (m, 4H), 2.13 (s, 3H), 1.60 (m, 4H). Spectral data are in agreement with the literature.[18]

8-Methoxyoct-7-en-2-one (53). To a solution of (methoxy methyl)triphenyl phosphonium chloride (6.17g, 18 mmol) in THF (30 mL) was added PhLi (1.9 M, 9.5 mL, 18 mmol) at -78 °C. The reaction was stirred at that temperature for 60 min then cannulated dropwise to a solution of **52** (2.1 g, 16 mmol) in THF (60 mL) at -78 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with sat. NH_4Cl (aq) (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude compound was purified on SiO_2 (gradient 90% hexanes / 10% Et_2O to 70% hexanes / 30% Et_2O) to afford the product **53** as an oil (0.70 g, 27%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (d, *J* = 12 Hz, 1H), 4.70 (m, 1H), 3.49 (s, 3H), 2.42 (m, 2H), 2.06 (s, 3H), 1.91 (m, 2H), 1.60 (m, 2H), 1.33 (m, 2H).

2-(Benzofuran-2-yl)-8-methoxyoct-7-en-2-ol (54). To a solution of benzofuran (0.41 mL, 3.8 mmol) in THF (150 mL) was added *n*-BuLi (2.5 M, 1.8 mL, 4.5 mmol) dropwise at -78 °C. The reaction was allowed to stir for 20 min at that temperature before **53** was added dropwise. The reaction was stirred for 10 min at -78 °C before being warmed to room temperature and left to stir for 45 min. The reaction was quenched with sat. NH_4Cl (aq) (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was

purified on SiO_2 (70% hexanes / 30% Et_2O) to afford the product **54** as an oil (0.594 g, 55%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (m, 1H), 7.45 (m, 1H), 7.21 (m, 2H), 6.58 (s, 1H), 6.22 (d, *J* = 16 Hz, 1H), 4.66 (m, 1H), 3.57 (s, 3H), 3.50 (s, 1H), 2.10 (m, 2H), 1.62 (s, 3H), 1.92 (m, 2H), 1.27 (m, 4H).

2-(Benzofuran-2-yl)-2-methylcyclohexane-1-carbaldehyde (57). To a suspension of $In(OTf)_3$ (10 mg, 0.018 mmol) in MeCN (12 mL) was added **54** (25 mg, 0.090 mmol) . The reaction was stirred at room temperature overnight. The reaction was quenched with sat. NH_4Cl (aq) (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified on SiO_2 (97% hexanes / 3% Et_2O) to afford the product **57** as an oil (17 mg, 78%). ^1H NMR (300 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.52 (m, 2H), 7.45 (m, 2H), 6.49 (s, 1H), 2.44 (m, 1H), 2.20 (m, 2H), 1.90 (m, 2H), 1.49 (m, 2H), 1.28 (s, 3H), 0.89 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 204.7, 164.6, 154.6, 128.6, 123.8, 122.8, 120.8, 111.1, 101.7, 54.9, 44.0, 38.4, 38.1, 24.7, 22.1, 21.5, 17.9, 1.1.

(2-(Benzofuran-2-yl)-2-methylcyclohexyl)methanol (58). To a suspension of $LiAlH_4$ (4 mg, 0.08 mmol) in Et_2O (1 mL) was added a solution of **57** (20 mg, 0.08 mmol) in Et_2O (1 mL) at room temperature. The reaction mixture was refluxed overnight, and then quenched with consecutive addition of H_2O (12 μL), 15% NaOH (12 μL), and H_2O (37 μL). The aqueous layer was extracted with Et_2O (3 x 1 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The product **58**, an oil, (15 mg, 74%) was used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 1H), 7.42 (m, 1H), 7.19 (m, 2H), 6.44 (s, 1H), 3.53 (m, 1H), 3.30 (t, *J* = 8 Hz, 1H), 2.23 (m, 1H), 2.0 (dt, *J* = 8 Hz, 4Hz, 1H), 1.84 (m, 1H), 1.63 (m, 1H), 1.54 (m, 3H), 1.34 (s, 3H), 1.25 (s, 3H), 0.86 (m, 2H).

(2-(Benzofuran-2-yl)-2-methylcyclohexyl)methyl methanesulfonate (59). To a solution of **58** (15 mg, 0.060 mmol) in DCM (2 mL) at 0 °C was added mesyl chloride (5.7 μL, 0.07 mmol) and 4-dimethylaminopyridine (12 mg, 0.10 mmol). The reaction was stirred at 0 °C for 1 h then quenched with sat. $NaHCO_3$ (aq) (1 mL) and extracted with Et_2O (3 x 1 mL). The combined organic layers were washed

with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified on SiO_2 (75% hexanes / 25% Et_2O) to afford the product **59** as an oil (4 mg, 20%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 1H), 7.42 (m, 1H), 7.19 (m, 2H), 6.47 (s, 1H), 4.00 (m, 1H), 3.92 (m, 1H), 2.75 (s, 3H), 2.02–1.40 (m, 9H) 1.34 (s, 3H).

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