THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DEPARTMENT OF CHEMISTRY

PROGRESS TOWARDS A TOTAL SYNTHESIS OF LECANINDOLE D

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A thesis
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in Chemistry
with honors in Chemistry

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Abstract

This thesis details steps towards the development of a synthetic route to the natural product lecanindole D, an indolosesquiterpenoid isolated from the fermentation broth of the terrestrial fungus *Verticillium lecanii* 6144. Lecanindole D was found to be a potent and selective non-steroidal progesterone receptor (PR) agonist. It is hoped that synthesis of this compound and subsequent medicinal chemistry studies could yield a medically useful PR agonist with an improved therapeutic profile. The synthesis of this fused 5-ring system features the stereoselective coupling of the E-ring generated from geraniol with a chiral imide derived from 3-indolepropionic acid. The key step is an intramolecular cationic cyclization of an indolidene intermediate with a pendant olefin to form the D ring. Work towards a complete E ring model forms the basis of this thesis.

TABLE OF CONTENTS

Section Page

Acknowledgements

Firstly, I would like to thank Dr. Kenneth Feldman for accepting me into his research group during my junior year and for being both an outstanding academic advisor and teacher. The counsel that Dr. Feldman provided while I was an underclassman trying to find the right major and later as an upperclassman applying for internships and graduate school has been invaluable in getting me where I am today.

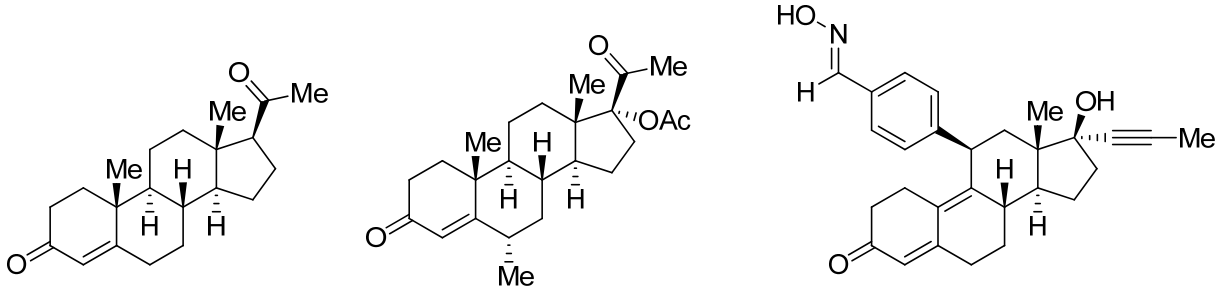
I also want to thank the graduate students in Dr. Feldman's research group who mentored me while I learned the basics of working in lab. Without their guidance I would have not have been able to accomplish much of what is presented in this thesis. I thank them for their patience and willingness to pass on their experience.

Introduction

I. Background

Progesterone receptor (PR) agonists and antagonists have been used for female oral contraception since 1959, for post-menopausal hormone therapy since 1957, and for treating gynecological disorders.[1] Currently, all such medications on the market are steroidal in nature.[2] While these synthetic analogues of progesterone, known as progestins, (Figure 1), have proven to be safe and effective, the interaction of this class of compounds with other steroid receptors is responsible for a variety of side effects. Loss of libido is attributable to androgen receptor (AR) agonism, weight gain and increased blood pressure arise from mineralocorticoid receptor (MR) agonism, and breast tenderness stems from estrogen receptor (ER) agonism.[1] These issues provide an impetus to discover non-steroidal PR agonists or antagonists which could be used as female contraceptives and post menopausal medications with improved clinical profiles.

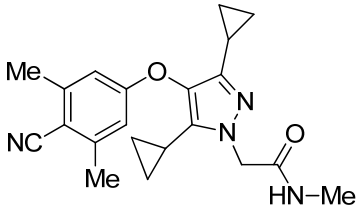
Figure 1: Endogenous progesterone and examples of steroidal PR modulators



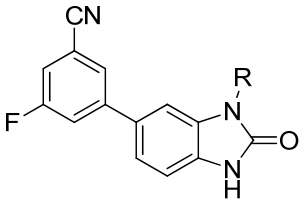
Indeed, considerable effort by medicinal chemists in the pharmaceutical industry and academia has already been devoted to identifying new nonsteroidal PR modulators. Some of the most potent leads include (Figure 2): functionalized pyrazoles with pendant chlorophenol moieties under development by Pfizer (exemplified by **4**) with IC_{50}'s in the single digit nanomolar range, 6-aryl-1,3-dihydrobenzimidazole-2-ones by Terefenko (exemplified by **5**)

which also have single digit nanomolar IC_{50}'s, and a series of tetrahydrobenzindolones (exemplified by **6**) isolated from a fungal fermentation broth by Khrihara et al among others.[3] In 2004, Pfizer disclosed the structure of Tanaproget[4] (**7**) (Figure 2) which was found to have an EC_{50} of 0.15 nM against PR in a T47D alkaline phosphatase assay while having only weak interactions with other steroid receptors, making it a potent and selective drug candidate.[3]

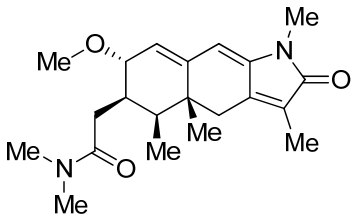
Figure 2: A selection of new nonsteroidal PR modulator leads and drug candidate Tanaproget (**7**).



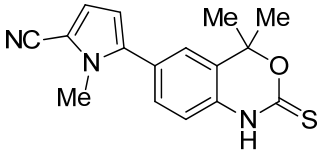
4
pyrazole based PR agonist



5
Benzimidazolone based antagonist
R = cyclobutyl or cyclopentyl



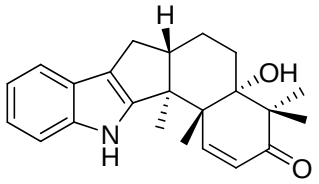
6
Tetrahydrobenzindolone based
PR modulator



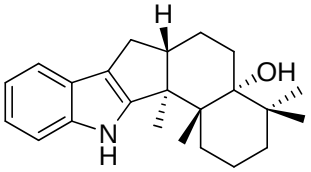
7
Tanaproget

Four indolosesquiterpenes were isolated and characterized by Roll and coworkers from extracts of a fermentation broth of the fungus *Verticillium lecanii* 6144 (Figure 3).[2] The results of a cell-based luciferase reporter assay indicated that while lecanindoles A – C (**8 – 10**) were inactive with the PR, lecanindole D had an EC_{50} of 1.1 +/- 0.4 nM. When tested against other steroid receptors, lecanindole D was found to be only a weak agonist of ER_{α} (EC_{50} > 10 μM) and a weak antagonist of the Glucocorticoid receptor, MR, and ER_{β} at micromolar IC_{50} concentrations.[2] This activity profile suggests that lecanindole D would be a good lead for the development of a nonsteroidal PR agonist with reduced side effects.

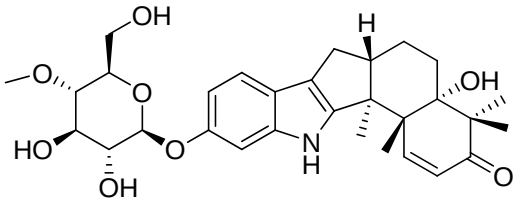
Figure 3: Lecanindoles A through C (**8** through **10** respectively) and D (**11**) with labeled rings



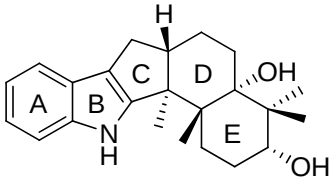
8
Lecanindole A



9
Lecanindole B



10
Lecanindole C

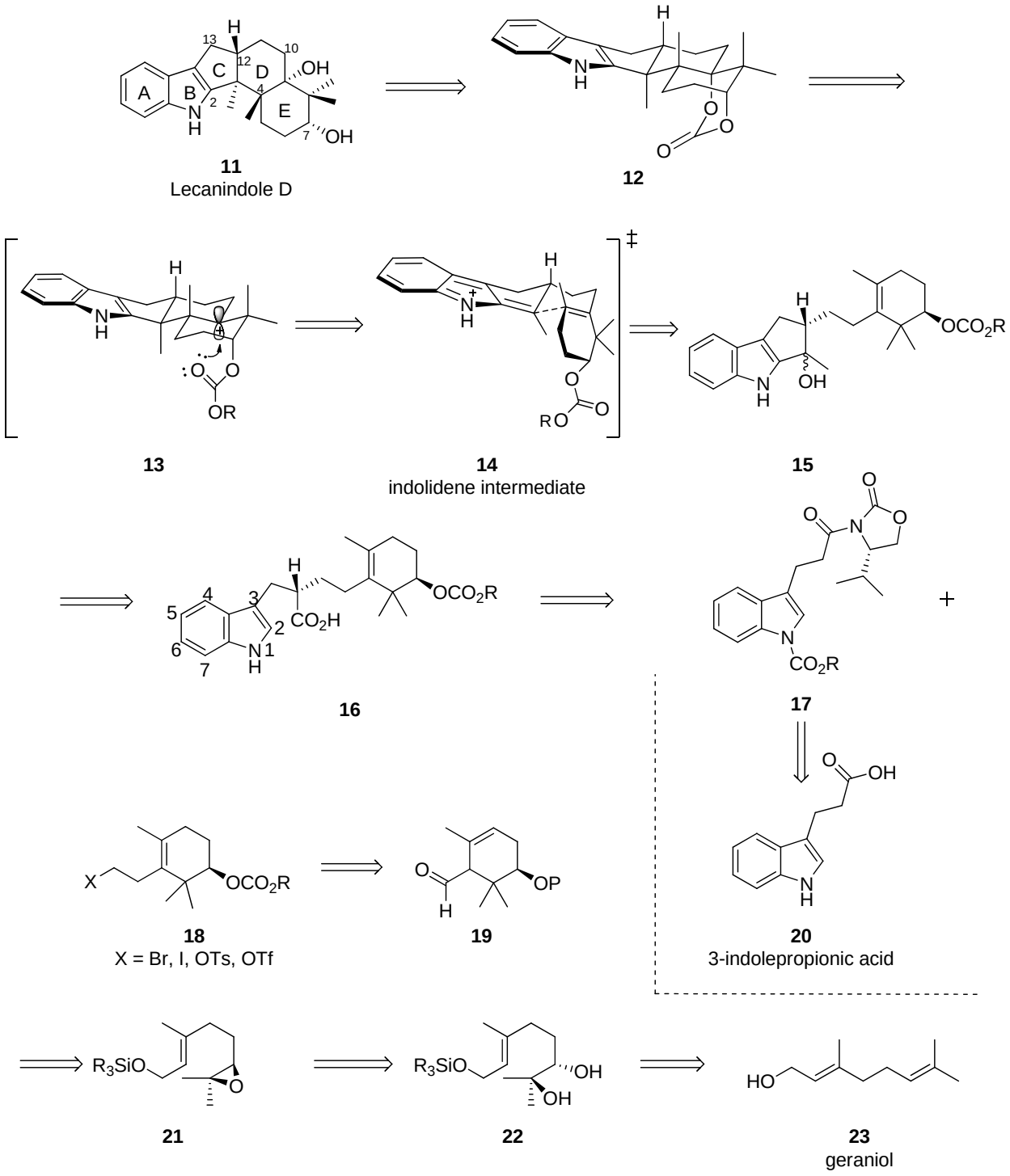


11
Lecanindole D

II. Lecanindole D Synthesis

In the interest of following up on this lead for an improved, medically useful PR agonist, a synthesis of this compound was designed by Dr. Kenneth Feldman. It is hoped that a total synthesis will provide more material for further biological testing and a framework for medicinal chemistry studies. The synthesis features a key acid-catalyzed cationic cyclization of indole **15** to form the D ring (Scheme 1). The resulting tertiary carbocation hopefully will be trapped by the pendant carbonate to form **12,** which should be easily reducible to afford lecanindole D (**11**). Examples of trapping of carbocations by proximal carbonyl compounds can be found in the realm of carbohydrate chemistry, where carbonyls such as pivaloyloxy groups anchimerically stabilize vicinal carbocations by transiently forming dioxolane rings in highly stereoselective reactions.[5]

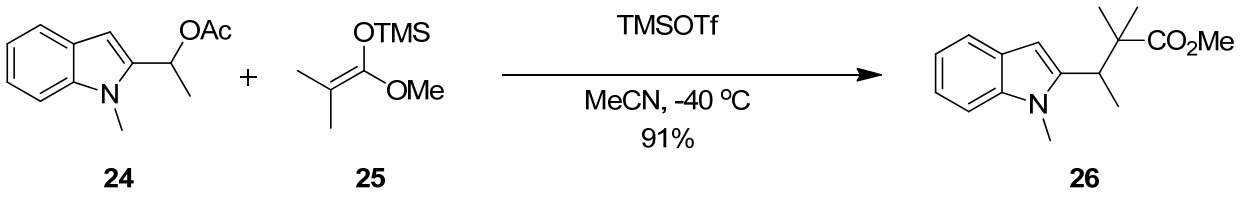
Scheme 1: Lecanindole D retrosynthesis



Formation of indole-2-alkyl or indole-3-alkyl indolidenes by Lewis-acid catalyzed E1 elimination of alcohols from indol-2-yl carbinols and subsequent addition of pi nucleophiles

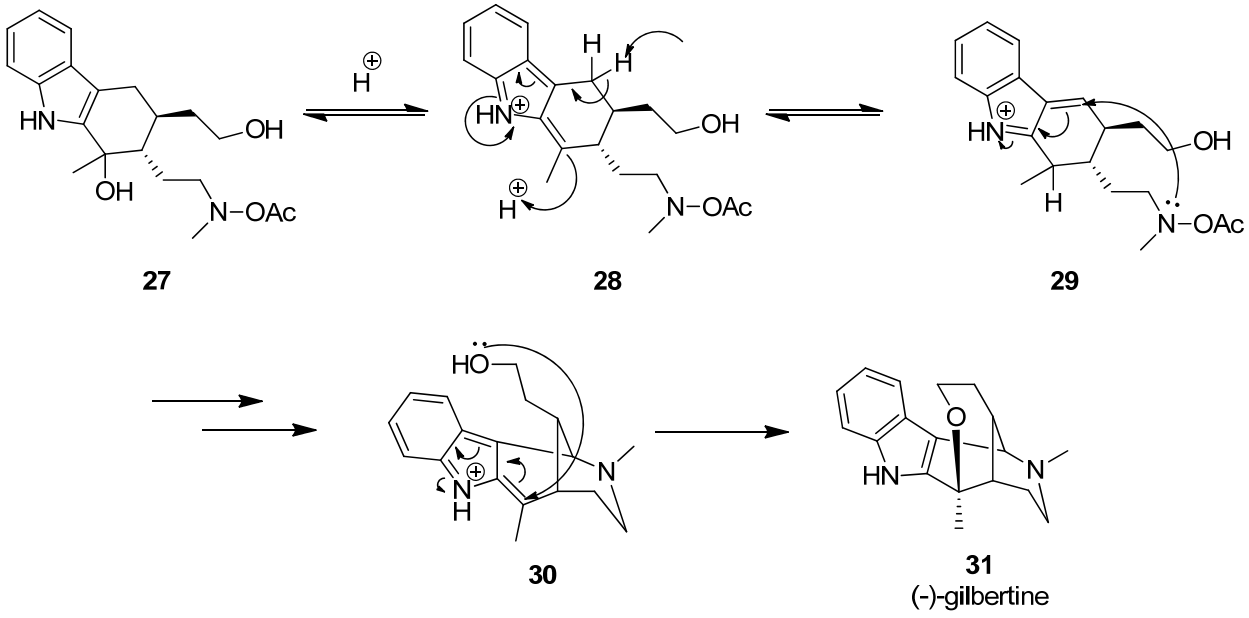
under a variety of conditions is well documented in the literature.[6-8] Martin et al. has reported conditions for the addition of silyl ketene acetals **25** to indol-2-yl carbonyls (Scheme 2).[7] A particularly illustrative example of this type of reactivity in natural product synthesis was reported during the synthesis of (-)-gilbertine (**31**) by Blechert et al.[6] In the final step of the route, an acid catalyzed E1 elimination of indol-2-carbinol **27** facilitates entry into the indolidene manifold (Scheme 3). Blechert proposes that the cationic cascade features intramolecular nucleophilic attack at the indole-2-alkyl position by the primary alcohol and at the indole-3-alkyl position by the hydroxylamine acetate.[6]

Scheme 2: Martin conditions for π nucleophile addition to indol-2-yl carbinols



24 **25** **26**

Scheme 3: Synthesis of (-)-gilbertine (**31**) by Blechert et al. via cationic indolidene cyclization cascade.



27 **28** **29**

30

31
(-)-gilbertine

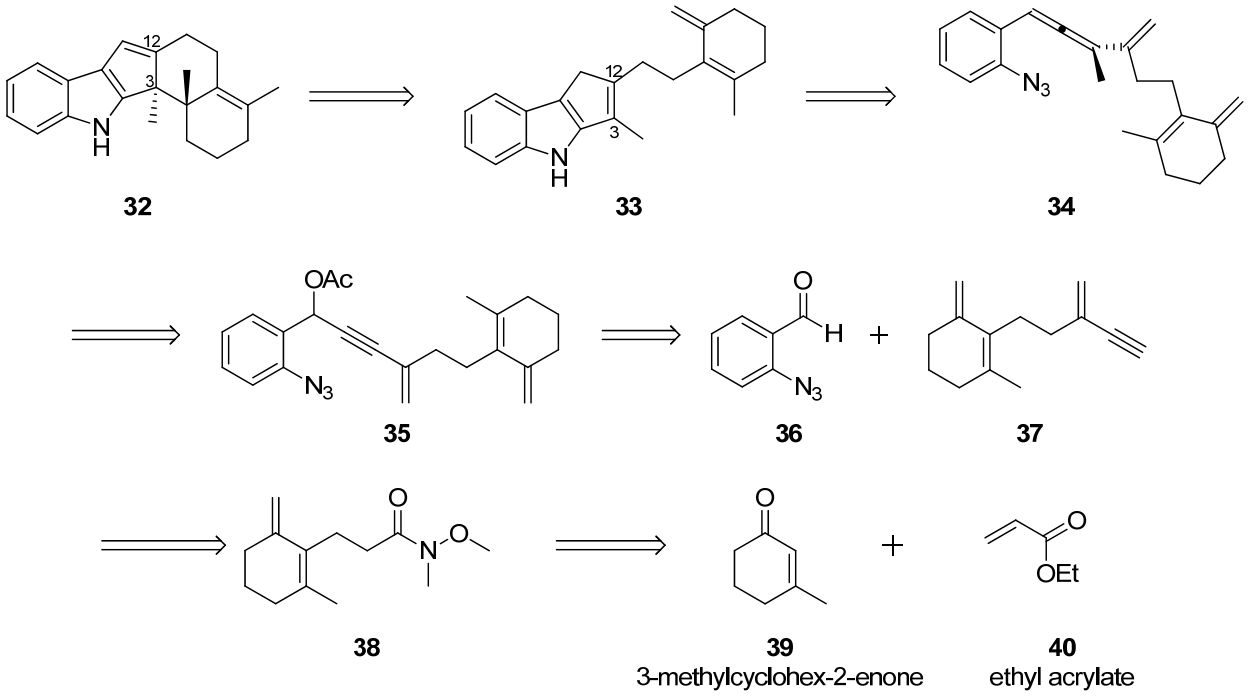
Alcohol **15** can be reached from **16** by the cyclization of the nucleophilic 2-position of the indole ring onto an activated derivative of the carboxylic acid (Scheme 1). Acid **16** is the product of an asymmetric alkylation onto chiral imide **17**, derived from 3-indolepropionic acid (**20**). Alkyl halide **18** defines the E ring of lecanindole D (Scheme 1).

E ring precursor **18** should be accessible from geraniol (**23**) (Scheme 1). **18** may be prepared by isomerizing the β – γ alkene of aldehyde **19**, which in turn will be available through cyclization of chiral epoxide **21**.[9] Cyclization substrate **21** may be formed from diol **22**, which can be prepared through the enantioselective dihydroxylation of the silyl ether of geraniol (**23**).

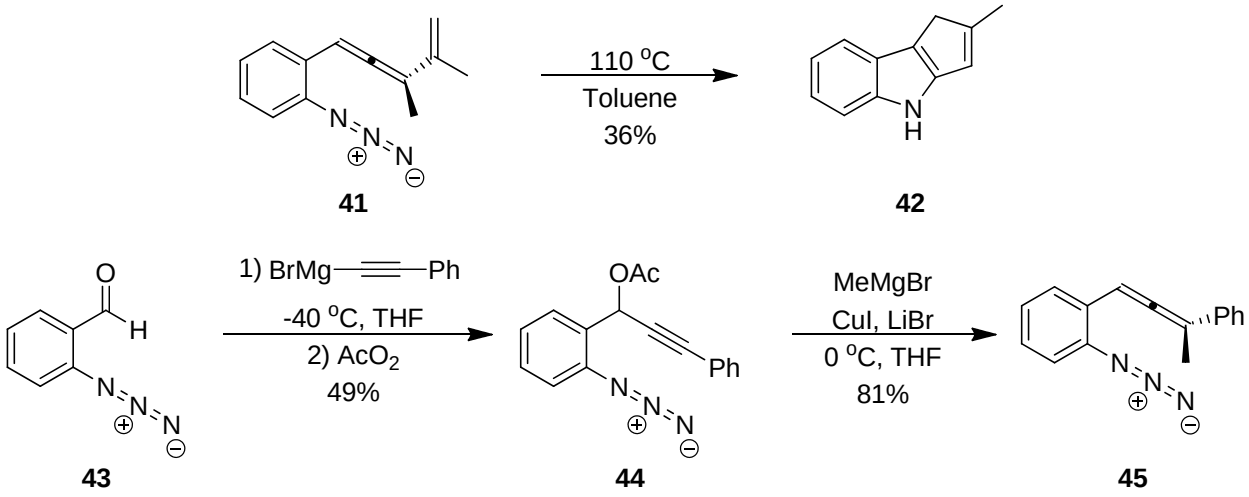
III. First Generation Lecanindole D Model System

In order to demonstrate the viability of the key cyclization, model system **32** was devised in which a simplified indolidene precursor, **33**, undergoes a cationic cyclization with a tethered diene π-nucleophile (Scheme 4).[10] The 1,2-cyclopentannelated indole **33** can be constructed in a single step from **34** utilizing allenyl azide thermolysis chemistry that was developed by the Feldman group (Scheme 5).[11] Addition of the lithiate of alkyne **37** to aldehyde **36,** followed by acylation of the derived alkoxide with acetic anhydride, should give alkynyl azide **35** (Scheme 4), again following previous work from the Feldman group (Scheme 5, **43** – **45**).[11] Alkyne **37** could be accessed by the addition of TBS-acetylene into Weinreb amide **38**,[10] followed by olefination of the resulting ketone and removal of the TBS group. Diene **38** could be constructed from 3-methylcyclohex-2-enone (**39**) and ethyl acrylate (**40**) by a Bayless-Hillman reaction[12] followed by the nucleophilic addition of methylmagnesium bromide into the ketone, E2 elimination of the resulting tertiary alcohol, and finally nucleophilic acyl substitution with *N*,O-dimethyl-hydroxylamine to form a standard Weinreb amide.[13]

Scheme 4: First generation model system retrosynthesis.



Scheme 5: Allenyl azide chemistry

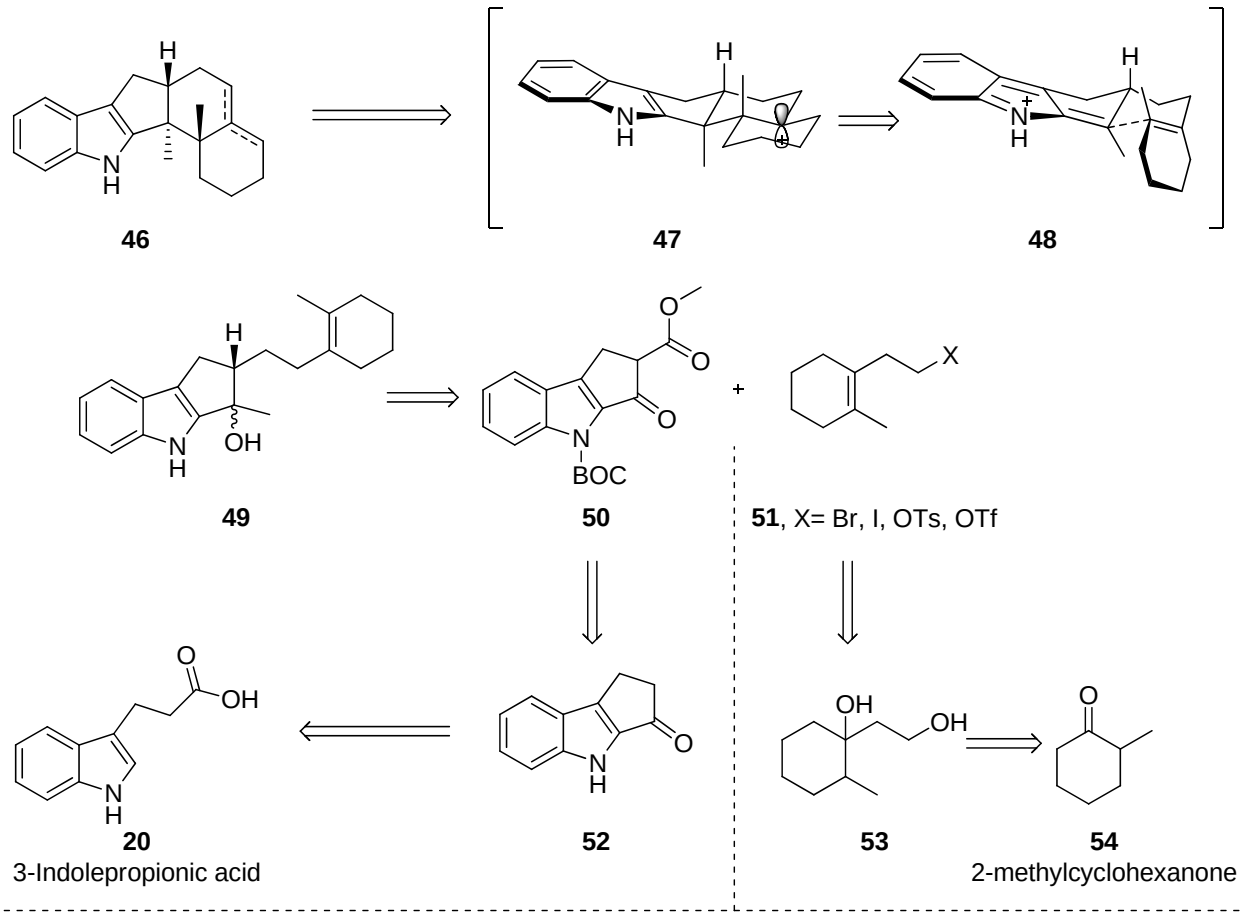


IV. Second Generation Lecanindole D Model System

After problems arose in executing the chemistry described in Scheme 4, a new approach to a model cationic cyclization precursor was required. The improved second generation model system, fused pentacycle **46**, features an indole-2-yl carbinol indolidene precursor **49** (Scheme

6). Elimination of the 2-yl hydroxyl group of **49** is expected to generate indolidene **48** which should cyclize to afford tertiary carbocation **47**. The cyclization of carbocation **47** will be critical in determining whether the D ring forms with the proper regiochemistry and stereochemistry. One potential problem with this model system is that it may be difficult to assess the outcome(s) of this key step through NMR spectroscopy. While we think that elimination leading to one of the internal alkenes **46** will occur most quickly, there is the potential for a variety of methyl shifts and rearrangements. Nevertheless, successful synthesis and characterization of products arising from **47** will indicate whether the D ring can be formed efficiently in this manner.

Scheme 6: Second generation model system retrosynthesis



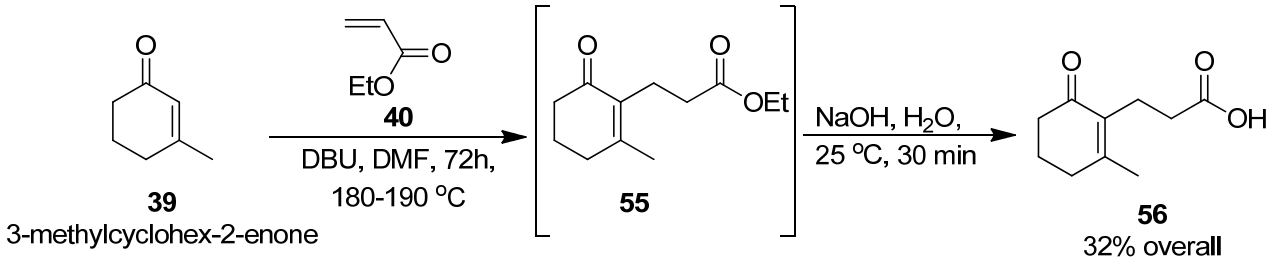
A retrosynthetic analysis of the new model system **49** (Scheme 6) suggested coupling of beta-keto ester **50** and cyclohexene **51**. Synthesis of cyclohexene **51** could be accomplished by (1) elimination of the tertiary alcohol, and (2) activation of the primary alcohol of diol **53** as a leaving group. 2-Methylcyclohexanone (**54**) could be converted to diol **53** by 1-2 addition of the enolate of an acetate ester to the ketone of **54** via a Reformatsky reaction[14] and subsequent reduction of the ester to the primary alcohol. Alkylation with the soft enolate of beta-keto ester **50** to produce **49** should be superior to alkylation with the hard enolate of ketone **52** which may be more prone to elimination side reactions. Beta-keto esters such as **50** can be prepared from enolates using Mander's reagent.[15] The synthesis of ketone **52** from 3-indolepropionic acid (**20**) using polyphosphoric acid has been demonstrated previously by Hoornaert et al.[16]

Results and Discussion

I. Progress towards the First Generation Model System

Initial efforts towards the lecanindole D model system were based on the first retrosynthetic analysis depicted in Scheme 4. Weinreb amide diene **38** was synthesized in five steps from commercially available 3-methylcyclohex-2-enone (**39**). Following the unpublished work of Paul Munson and Megan Nines,[10] the synthesis began with 1,4 addition of **39** into ethyl acrylate (**40**) via a Bayless-Hillman reaction[12] catalyzed by 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) at high temperature (Scheme 7). The reaction was carried out in a steel bomb to prevent the evaporation of the DMF (bp 153 ^{o}C). Saponification of intermediate ester **55** in aqueous NaOH gave acid **56** (Scheme 7) in only 32% yield.

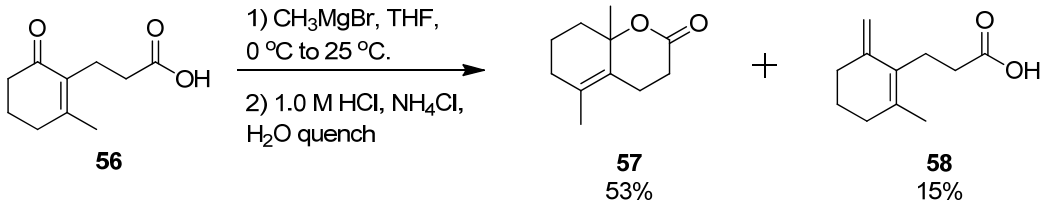
Scheme 7: Bayless-Hillman reaction of 3-methylcyclohex-2-enone and ethyl acrylate and subsequent saponification



Addition of MeMgBr led to a mixture primarily consisting of lactone **57**, and exo-diene **58** (Scheme 8). After addition of the methyl anion to the ketone to give the corresponding tertiary alkoxide, it is apparent that the reaction may terminate in multiple ways upon acid addition. Addition of the derived alcohol to the carboxylic acid leads to lactone **57**. In addition, elimination of the tertiary alcohol apparently occurs through deprotonation at one of the methyl substituents of the cyclohexene ring, to give exo-diene **58**. Other vinyl proton peaks in the ^{1}HNMR spectrum of the crude reaction mixture indicated the presence of another diene side

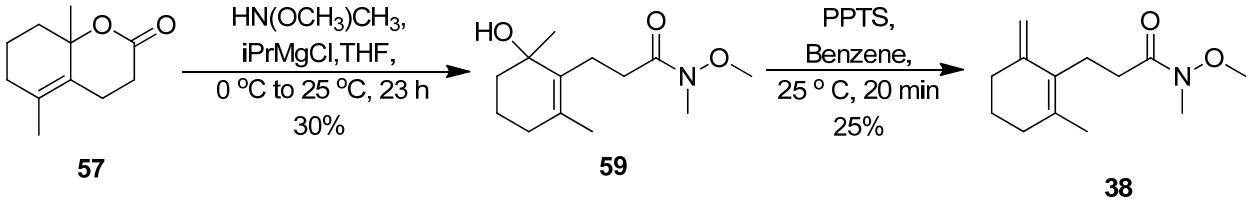
product(s), which was not fully characterized. A likely possibility is the product of the elimination of a methylene proton in the ring to give the corresponding endo-diene.

Scheme 8: Treatment of α,β-unsaturated ketone **56** with MeMgBr



Ring opening of lactone **57** with *N*,O-dimethylhydroxylamine / iPrMgCl gives *N*-methoxy *N*-methyl amide **59**, which can be dehydrated directly to exo-diene amide **60** in the presence of pyridinium *p*-toluenesulfonate (PPTS) (Scheme 9). The generation of other alkene elimination products appears to have occurred in this reaction as evidenced by the presence of additional vinyl peaks in the crude ^{1}HNMR spectrum.

Scheme 9: Ring opening of lactone **57** to give hydroxyl Weinreb amide **59** followed by alcohol elimination

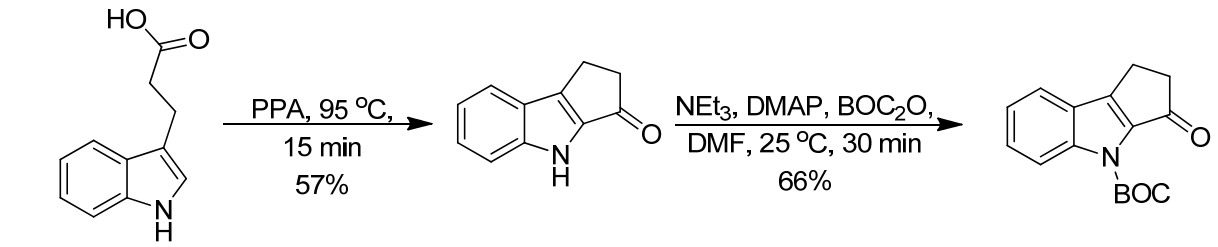


At this stage in the route to model system **32**, new concerns were raised over the feasibility of the cationic cyclization of indolidene precursor **33**. As a result, it was decided that a different model system should be pursued.

II. Progress towards the Second Generation Model System

The preparation of β-ketoester **50** commenced from the cyclization of **20** via polyphosphoric acid treatment in which the nucleophilic 2 position of the indole attacked the tethered and activated carboxylic acid to give ketone **52** (Scheme 10). Although this reaction proceeded in satisfactory yield (57%) for our purposes, the workup of the reaction was difficult due to the viscosity of the polyphosphoric acid solution. Filtrations proceeded slowly and it is suspected that much of the yield loss was due to an inability to separate the product from the polyphosphoric acid matrix. The synthesis proceeded with the *N*-BOC protection of the indole ketone **52** (Scheme 10).

Scheme 10: Cyclization and BOC protection of 3-Indolepropionic acid



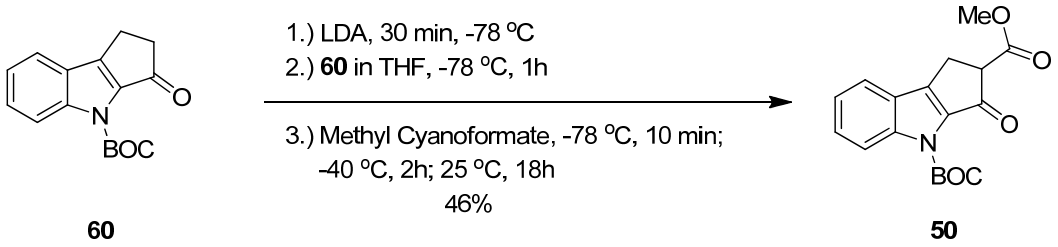
20
3-Indole Propionic Acid

52

60

Mander's reagent (methyl cyanoformate) was used to functionalize the alpha position of ketone **60** by forming the kinetic enolate with LDA and subsequent acylation (Scheme 11) to obtain β-keto ester **50**. This reaction proved to be exceedingly sensitive to changes in concentration and temperature. Allowing the reaction to warm above -40 ^{o}C in the two hours following methyl cyanoformate addition resulted in degradation of the material. Concentrations of **60** above 0.1 M at the outset of the reaction also provided extremely poor yields, with much degradation.

Scheme 11: Synthesis of Beta-keto ester **50**

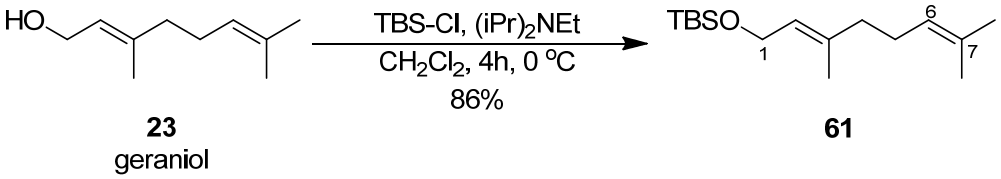


60 **50**

III. E Ring Synthesis

The route was started by protection of geraniol (**23**) as its *t*-butyl dimethyl silyl (TBS) ether. This reaction proceeded easily and in high yield (86%) to provide silyl ether **61** (Scheme 12). The sterically bulky TBS group is thought to be essential for directing the regiochemistry of the next reaction, a Sharpless asymmetric dihydroxylation of the C(6) – C(7) alkene of **61**.

Scheme 12: TBS protection of geraniol

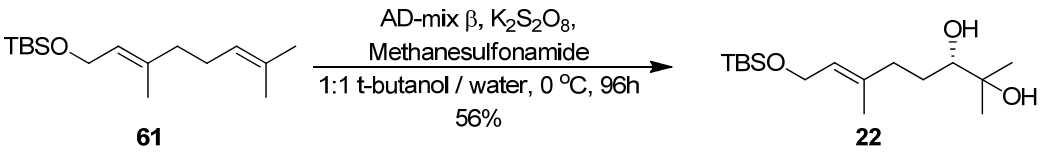


23
geraniol

61

Applying Sharpless' rule for determining the outcome of a stereoselective dihydroxylation,[17] it was anticipated that AD-mix β would provide the desired *S* stereochemistry at C(6) to yield diol **22** (Scheme 13). This reaction proved to be operationally difficult. Temperature had to be controlled carefully because the optimal cold temperature of the reaction is also close to the freezing point of the solution. Indeed, freezing of one batch stalled the reaction and necessitated a significant extension of the reaction time. Special care must be taken to ensure that stirring of the reaction solution is not impeded by precipitated salts. In order to drive the reaction to completion, additional potassium persulfate oxidant was added to the reaction mixture.

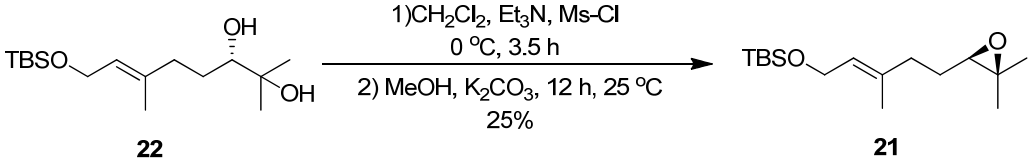
Scheme 13: Asymmetric dihydroxylation of TBS protected geraniol



61 **22**

The last step towards E ring construction that time allowed to be completed was the conversion of diol **22** into the corresponding epoxide **21** (Scheme 19). Since the mesylation and subsequent S_N2 displacement occurred *in situ*, it was not immediately clear whether stereochemistry was inverted or retained at C(6). However, it is believed that the secondary hydroxyl group was mesylated based on studies of asymmetric dihydroxylation and epoxidation of terpene acetates conducted by Garlaschelli et al.[18]

Scheme 14: Mesylation and subsequent S_N2 substitution to form epoxide **21**



22 **21**

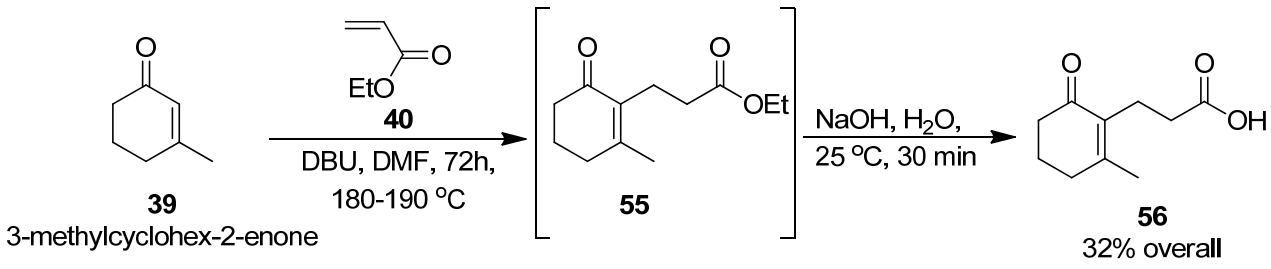
Conclusions

The work described herein represents progress towards a total synthesis of lecanindole D, a natural product that has been identified as a potent and selective progesterone receptor agonist. Several steps towards a model system of the key step of the reaction were presented as well as four steps towards a synthesis of the E ring of the real system. Work towards a lecanindole D total synthesis is ongoing and it is hoped that the methods presented in this thesis will help in the eventual attainment of a complete, efficient synthetic route.

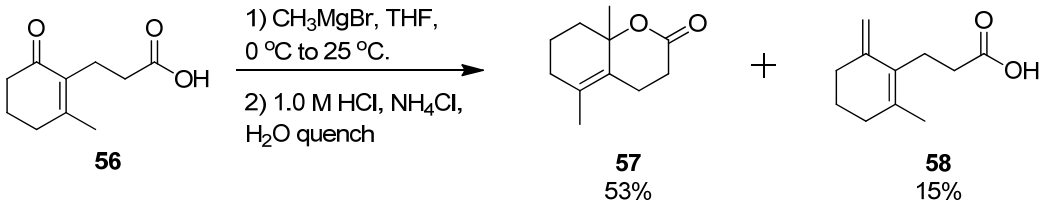
Experimental Section

General Experimental Methods. Unless otherwise stated, reactions were carried out in flame-dried glassware under nitrogen atmosphere. Dry THF, CH_2Cl_2, and DMF were obtained from an alumina column solvent purification system. Water was obtained from a laboratory distilled water line. All reagents were purchased commercially and used without further purification. NMR spectra were taken on Bruker 300 MHz, 360 MHz, or 400 MHz spectrometers at 25 ^oC using spectroscopically homogeneous samples. NMR spectra are reported in ppm and are calibrated to residual proton peaks in the deuterated solvent ($CHCl_3$ = 7.26 ppm, $OS(CH_3)_2$ = 2.54 ppm). IR spectra were taken on a Perkin Elmer 1600 FTIR spectrometer with neat samples on KBr salt plates. Mass spectral data was obtained using an Applied Biosystems AP_1 150EX spectrometer. Concentration *in vacuo* refers to rotary evaporation at temperatures of 25 ^oC to 45 ^oC at reduced pressure (10 – 30 torr) followed by at least 10 minutes of exposure to a vacuum of approximately 1 torr. Reactions and purifications were monitored using TLC Silica gel 60 F_{254} plates from EMD Chemicals Inc. visualized with UV light, and $KMnO_4$, anisaldehyde, or phosphomolybdic acid. All flash chromatography was performed using the method of Still, Khan and Mitra[19] with Silicycle sicili flash p60 (230 – 400 mesh) gel.

I. First Generation Model System



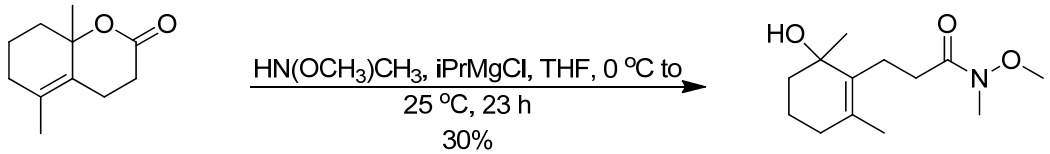
3-(2-Methyl-6-oxocyclohex-1-en-1-yl)propanoic Acid (57). Enone **39** (4.86 g, 44.1 mmol), ethyl acrylate (**40**) (9.25 mL, 52.9 mmol), DMF (75.0 mL), and DBU were charged to a round bottom flask inside a steel bomb. The bomb was sealed and heated to 195 ^{o}C and a magnetic stir bar was used to stir the reaction mixture for 88 h. After cooling to room temperature, the mixture was diluted with Et_2O (100 mL) and rinsed with water (1 x 40 mL) and brine (1 x 40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a brown oil. 1.0M NaOH (46.2 mL, 46.2 mmol) was added to the neat oil (4.86 g) and the reaction mixture was stirred for 30 min at 25 ^{o}C. The reaction mixture turned from brown to orange. The reaction mixture was washed with Et_2O (2 x 25 mL). The aqueous phase was then acidified with 1.0 M HCl and extracted with EtOAc (4 x 30 mL). The organic fractions were washed with water (1 x 50 mL) and brine (1 x 50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. The oil was purified via flash chromatography with 10 – 65% EtOAc in hexanes as eluent to yield **56** (2.57 g, 32%) as a white, crystalline solid (m.p. unknown). ^{1}HNMR (300 MHz, $CDCl_3$) δ 2.59 (t, J = 7.45 Hz, 2H), 2.40 – 2.30 (m, 6H), 2.14 (s, 1H), 1.95 – 1.87 (m, 5H).



56 **57** 53% **58** 15%

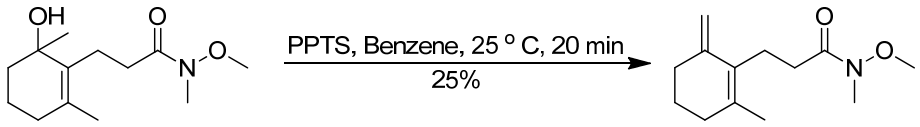
5,8a-Dimethyl-3,4,6,7,8,8a-hexahydro-2H-chromen-2-one (**57**) and **3-(2,6-Dimethylcyclohexa-1,5-dien-1-yl)propanoic Acid** (**58**). Methylmagnesium bromide (3.0M in THF, 0.49 mL, 1.5 mmol) was added dropwise over 12 min to a solution of **56** (105 mg, 0.575 mmol) in THF (6.0 mL) at 0 ^{o}C while stirring. The reaction solution was allowed to warm to 25 ^{o}C and stirred for 45 min before adding to ice cold 1.0M HCl (10 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL). The organic fractions were collected, washed with water (1 x

80 mL) and brine (1 x 80 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a yellow oil. The crude product was purified via flash chromatography with 5 – 40% EtOAc in hexanes as eluent to yield lactone **57** (360 mg, 53%) as a clear, colorless oil. IR (thin film) 2940, 1732 cm^{-1}; ^{1}HNMR (360 MHz, $CDCl_3$) δ 2.77 – 2.60 (m, 2H), 2.52 – 2.45 (m, 2H), 2.05 – 1.97 (m, 2H) 1.91 – 1.73 (m, 2H), 1.63 – 1.55 (m, 2H), 1.60 (s, 3H), 1.49 (s, 3H); ^{13}CNMR (360 MHz, $CHCl_3$) δ 171.8, 131.1, 125.9, 83.0, 37.5, 31.7, 30.6, 27.1, 20.9, 19.7, 19.1. Purification of the curde product also afforded exo-diene **58** (118 mg, 15%). ^{1}HNMR (360 MHz, $CDCl_3$) δ 4.84 (s, 1H), 4.72 (s, 1H), 2.66 – 2.61 (m, 2H), 2.57 – 2.51 (m, 2H), 2.48 – 2.41 (m, 2H), 2.37 – 2.29 (m, 2H), 1.80 (s, 3H), 1.64 – 169 (m, 2H).



57 **59**

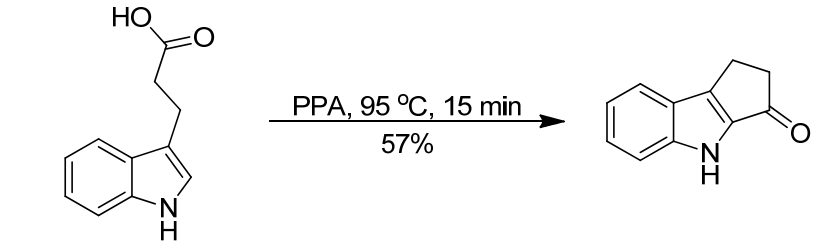
3-(6-Hydroxy-2,6-dimethylcyclohex-1-en-1-yl)-N-methoxypropanamide (**59**). A solution of *N*,O-dimethylhydroxylamine (657 mg, 6.00 mmol) in THF (10 mL) was cooled to 0 °C. Isopropylmagnesium chloride (2.0M, 6.0 mL, 12 mmol) was added dropwise over 5 min followed by a solution of **57** (360 mg, 2.0 mmol) in THF (10 mL). The mixture was warmed to 25 °C and allowed to stir for 23 h before the addition of saturated NH_4Cl (20 mL). The resulting mixture was extracted with EtOAc (3 x 40 mL). The organic layer was washed with water (1 x 60 mL) and brine (1 x 60 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction residue was purified via flash chromatography with 40 – 85% EtOAc in hexanes as eluent to yield **59** (147 mg, 30%) as a clear yellow oil. ^{1}HNMR (360 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.17 (s, 3H), 2.68 – 2.39 (m, 5H), 2.03 – 1.86 (m, 3H), 1.77 – 1.59 (m, 3H), 1.63 (s, 3H), 1.29 (s, 3H).



59 **38**

***N*-methoxy-N-methyl-3-(2-methyl-6-methylenecyclohex-1-en-1-yl)propanamide** (**38**). To a solution of **59** (147 mg, 0.607 mmol) in benzene (3.1 mL) at room temperature was added pyridinium *p*-toluenesulfonate (PPTS) (305 mg, 1.21 mmol). After 20 min, the solution was added to water and extracted with Et_2O (2 x 10 mL). The organic layer was washed with water (1 x 10 mL), and brine (1 x 10 mL) dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified via flash chromatography with 10 – 40 % EtOAc in hexanes as eluent to yield **38** (33.9 mg, 25%) as a clear, oil. ^{1}HNMR (360 MHz, $CDCl_3$) δ 4.87 (s, 1H), 4.69 (s, 1H), 3.66 (s, 3H), 3.18 (s, 3H), 2.60 – 2.49 (m, 4H), 2.34 – 2.28 (m, 2H), 2.11 (t, *J* = 7.2 Hz, 2H), 1.77 (s, 3H), 1.66 (t, *J* = 7.2 Hz, 2H).

II. Second Generation Model System

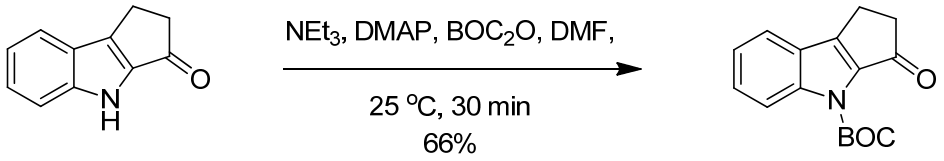


20 **52**

3-Indole Propionic Acid

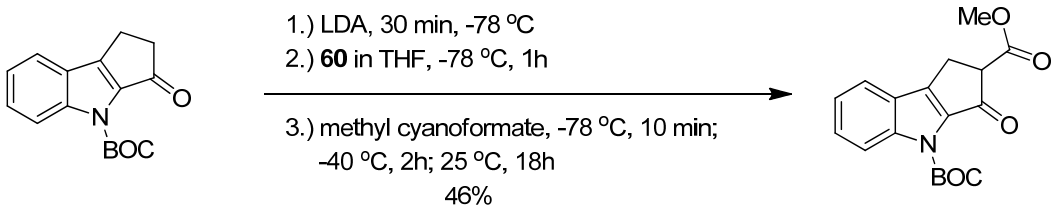
1,2-Dihydrocyclopenta[b]indol-3(4H)-one (**52**). To an open beaker containing polyphosphoric acid (113.7 g, 15 mass equiv) at 95 ºC was added 3-indolepropionic acid (**20**) (7.58 g, 40.1 mmol, 1.0 mass equiv) while stirring. The viscous solution slowly turned from yellow to red/brown. After 15 min, the mixture was diluted with ice water (200 mL). The resulting suspension was filtered and the filtrate was washed with EtOAc. The retentate was allowed to dry over P_2O_5 *in vacuo*. The filtrate was extracted with EtOAc (3 x 100 mL). The

organic fractions were combined, washed with water (2 x 100 mL), and brine (2 x 80 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* over P_2O_5. The dried solids from the filtrate and retentate were combined to afford **52** (3.93 g, 57%) as a coarse brown powder. ^{1}HNMR (300 MHz, DMSO) δ 11.64 (s,1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.36 (t, *J* = 8.4, 7.2 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 3.06 (d, *J* = 4.1 Hz, 2H), 2.92 (d, *J* = 3.6 Hz, 2H).



52 **60**

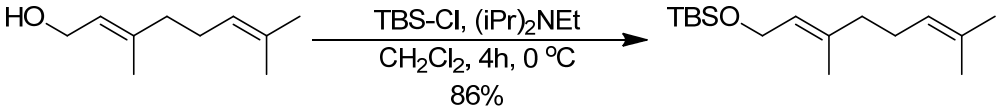
tert-Butyl 3-Oxo-2,3-dihydrocyclopenta[b]indole-4(1H)-carboxylate (**60**). Indole ketone **52** (4.81 g, 30.6 mmol) was dissolved in DMF (306 mL) followed by addition of dimethyl amino pyridine (DMAP) (7.47 g, 61.2 mmol), triethylamine (4.55 mL, 61.2 mmol), and butyloxycarbonyl anhydride (13.3 g, 61.2 mmol) while stirring. The solution was stirred at 25 ^{o}C for 2h and then added to water (150 mL) and EtOAc (150 mL). The reaction mixture was extracted with Et_2O (4 x 100 mL) and the combined organic fractions were washed with water (1 x 150 mL) and brine (1 x 150 mL). The residue was dried over Na_2SO_4, filtered, and concentrated, *in vacuo* to yield a brown solid. The product was purified via flash chromatography with 10-50% EtOAc in hexanes as eluent to yield **60** (5.51 g, 66%). ^{1}HNMR (360 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.1 Hz, 1H), 7.76 (d, *J* = 6.5 Hz, 1H), 7.52 (t, *J* = 9.0, 5.9 Hz, 1H), 7.33 (t, J_1 = 8.1, 5.9 Hz, 1H), 3.02 (app. s, 4H), 1.69 (s, 9H).



60 **50**

4-tert-Butyl-2-methyl-3-oxo-2,3-dihydrocyclopenta[b]indole-2,4(1H)-dicarboxylate (**50**). To a solution of freshly distilled diisopropylamine (61 μL, 0.43 mmol) in THF (2.76 mL) at -78 °C was added *n*-BuLi (2.2 M in hexanes, 0.20 mL, 0.43 mmol). After stirring for 30 min, **60** in THF (1.18 mL) was chilled to -78 °C and added to the LDA solution. Stirring was continued for 1 h during which time the reaction solution turned yellow. Methyl cyanoformate was added dropwise and the mixture was allowed to stir for 10 min at -78 °C before raising the temperature to -40 °C with an acetonitrile / dry ice bath. After 2 h, the solution turned red and was allowed to warm to room temperature with continued stirring for 18 h. The reaction mixture was rinsed into a round bottom flask with Et_2O (2 x 10 mL), concentrated *in vacuo*, re-dissolved in CH_2Cl_2 (1.5 mL) and purified via flash chromatography with 30-100% EtOAc in hexanes as eluent to afford **50** (60 mg, 46%). ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.53 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.33 (dd, *J* = 7.7, 7.3 Hz, 1H), 4.04 (dd, *J* = 6.9, 2.7 Hz, 1H), 3.40 (dd, *J* = 17.4, 2.8 Hz, 1H), 3.25 (dd, *J* = 17.3, 7.0 Hz, 1H), 1.67 (s, 9H).

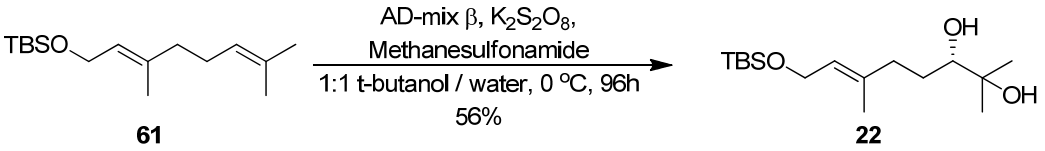
III. Real System: E Ring



23 **61**
geraniol

t-Butyldimethylsilyl Geraniol (**62**). To a solution of geraniol (**23**) (10.04 g, 65.09 mmol) and $(iPr)_2NEt$ (21.52 mL, 130.2 mmol) in dry CH_2Cl_2 (32.6 mL) cooled to 0 °C was added a

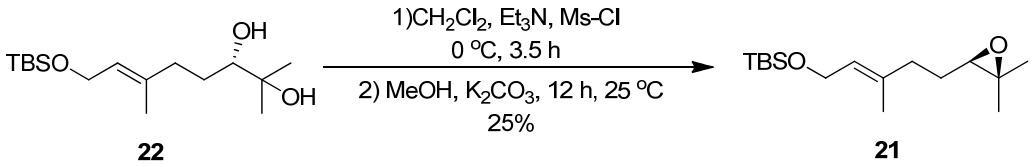
solution of *t*-butyldimethylsilyl (TBDMS) chloride in dry CH_2Cl_2 (13.0 mL) pre-cooled to 0 ^oC while stirring. A white gas was evolved and the solution was allowed to stir for 5h before addition of 1M HCl (20 mL). The organic layer was washed with 1M HCl (2 x 30 mL), and brine (1 x 30 mL). The aqueous layer was extracted with CH_2Cl_2 (1 x 30 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* before purification via flash chromatography with 20-30% EtOAc in hexanes as eluent to yield **61** (15.0 g, 86%). ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.31 (t, *J* = 6.4 Hz, 1H), 5.10 (t, *J* = 5.6 Hz, 1H), 4.20 (d, *J* = 6.4 Hz, 2H), 2.10 (m, 2H), 2.01 (m 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H).



61 **22**

(*S,E*)-8-((tert-Butyldimethylsilyl)oxy)-2,6-dimethyloct-6-ene-2,3-diol (**22**). Methanesulfonamide (1.07 g, 8.47 mmol), AD mix β (11.7 g, 2.3 equiv), and potassium persulfate (4.58 g, 16.9 mmol) were dissolved in 1:1 t-butanol : water (86.4 mL) and cooled to 0 ^oC before adding TBS protected geraniol **61**, dissolved in 10 mL of 1:1 *t*-butanol : water. The mixture separated into two phases and was allowed to stir at 0 ^oC under N_2. After 4 days, the reaction solution was warmed to 25 ^oC and Na_2SO_3 (5.7 g) in water was added. After stirring for 2h, EtOAc (70 mL) was added. The organic layer was washed with water (1 x 30 mL). The combined aqueous fractions were extracted with EtOAc (3 x 50 mL). The organic fractions were combined, washed with brine (1 x 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a cloudy white liquid. The crude material was purified via flash chromatography with 20-50% EtOAc in hexanes as eluent to yield **22** (1.28 g, 56%) as a clear, colorless, viscous liquid. IR (cm^{-1}): 3424 (broad). ^{1}HNMR (360 MHz, $CDCl_3$) δ 5.37 (dd, *J* = 12.7, 6.3 Hz, 1H),

4.18 (d, *J* = 6.3 Hz, 2H), 3.35 (d, *J* = 9.90 Hz, 1H), 2.31 – 2.23 (m, 1H), 2.20 (br, s, 1H), 2.15 – 2.04 (m, 1H), 1.98 (br, s, 1H), 1.72 (s, 3H), 1.64 – 1.56 (m, 1H), 1.48 – 1.36 (m, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 0.89 (s, 9H), 0.13 (s, 6H); ^{13}CNMR (360 MHz, $CDCl_3$) δ 137.0, 124.9, 78.2, 73.1, 60.2, 36.7, 29.6, 26.5, 26.0, 23.3, 18.4, 16.3, -5.1.



22 **21**

(*S*,*E*)-tert-Butyl((5-(3,3-dimethyloxiran-2-yl)-methylpent-2-en-1-yl)oxy)dimethylsilane (**21**)**.** To a solution of **22** (288 mg, 0.953 mmol) in CH_2Cl_2 (11.0 mL), at 0 °C was added Et_3N (314 μL, 2.3 mmol) followed by mesyl chloride (218 mg, 1.10 mmol). After 1.5 h, additional Et_3N (162 μL, 1.2 mmol) was added. After a total of 3.5 h, the CH_2Cl_2 was removed *in vacuo* and replaced with methanol (18.2 mL). To this solution was added K_2CO_3 (382 mg, 2.76 mmol) and the resulting mixture was allowed to stir under N_2 for 21.5 h. The mixture was filtered through Celite and rinsed with CH_2Cl_2 (40 mL) and water (40 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The organic fractions were combined, washed with water (1 x 40 mL) and brine (1 x 40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography with 1.0 – 9.0 % EtOAc in hexanes as eluent to yield **21** (67 mg, 25%) as a clear, colorless oil. ^{1}HNMR (360 MHz, $CDCl_3$) δ 5.33 (t, 1H), 4.18 (d, *J* = 6.3 Hz, 2H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.15 (m, 2H), 1.67-1.64 (m, 2H), 1.62 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}CNMR (360 MHz, $CDCl_3$) δ 136.0, 125.0, 64.1, 60.2, 58.4, 36.1, 27.2, 26.0, 24.9, 18.7, 18.4, 16.4, -5.1.

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Education:

The Pennsylvania State University, University Park, PA: August 2008 –May 2012

- Dean's list six of seven semesters
- Schreyer Honors College: entails a curriculum of honors classes which present subjects in greater depth than normal lectures. I have focused on, and performed well in, various honors chemistry classes.
- Schreyer Scholarship award recipient
- Expected graduation, May 2012
- Majoring in chemistry
- Minor in Engineering Entrepreneurship: an interdisciplinary curriculum designed to teach the skill sets needed to grow an idea into a viable product or business.

Professional Experience:

Feldman Research Group, Penn State University: August 2010 – December 2011

- Developing a first generation total synthesis for Lecanindole D, a highly selective natural product progesterone receptor agonist.
- Have worked on steps in multiple routes.
- Exploring various reaction methodologies and conditions.

Merck Summer Intern: June 2011 – August 2011

- Explored opportunities to reject a problematic analogue impurity from the synthesis of Caspofungin acetate, an intravenous life-saving anti-fungal drug.
- The impurity caused batches to fail specs, preventing exportation in previous years
- Stonewall Technical Operations, Elkton, Virginia
- Awarded a Merck Engineering and Technology Fellowship second time

Merck Summer Intern: June 2010 – August 2010

- Investigated and determined cause of a critical des-fluoro impurity in the synthesis for MK-859, also known as Anacetrapib, a phase III drug for the treatment of hypercholesterolemia.
- Generated a series of recommendations for optimization of the synthesis to prevent impurity formation and save money on plant scale.
- Awarded a Merck Engineering and Technology Fellowship

- Worked with the Chemical Process Development and Commercialization Department in Rahway, New Jersey.

Penn State TA for Organic Chemistry II: August 2009 – May 2010

- Assisted professors Kenneth Feldman (fall 2009) and Scott Phillips (spring 2010) with teaching lecture material to classes of 300 sophomore and junior students.
- Responsibilities included giving recitations, holding regular office hours, writing homework problems, proctoring exams, giving absentee lectures, and grading.

Lab Assistant, East Stroudsburg Univ. Chemistry Dept.: June 2009 – August 2009

- Prepared equipment and solutions for summer general and organic chemistry classes.
- Tested and developed lab procedures for the calorimetric analysis of various foods.

Organizations and Service:

Pennsylvania State University:

- Penn State Professional Chemistry Fraternity (September 2009 – May 2012)
  - Served 1 year as President. Responsibilities include managing committees, directing officers, event planning, managing leases, and upholding the constitution.
  - Professional Chair, 1 semester. Responsibilities included liaising with university faculty and organizing professional events, including faculty talks about current research.
  - THON: participated in yearly fundraiser to help children with cancer.
  - Science outreach volunteer programs: Bellefonte Family Science Night, Science Lions
- Penn State Korean Karate Club (August 2008 – January 2010)