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STUDIES TOWARD THE TOTAL SYNTHESIS OF (±)-CHARTELLINE C AND (–)-PLATENSIMYCIN

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STUDIES TOWARD THE TOTAL SYNTHESIS OF (±)-CHARTELLINE C AND (–)-PLATENSIMYCIN

by

Evan A. Hecker, B.S.

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Dedication

To Cara, my love and my life, whose love and support made this possible.

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STUDIES TOWARD THE TOTAL SYNTHESIS OF (±)-CHARTELLINE C AND (–)-PLATENSIMYCIN

Publication No._____

Evan A. Hecker, Ph.D.

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Supervisor: Philip D. Magnus

Herein is described our work towards the total synthesis of the marine natural product (±)-chartelline C and the potent antibiotic (–)-platensimycin. Part 1 relates the (±)-chartelline C project. The first chapter reviews (±)-chartelline C's isolation, biogeneity, and previously reported studies relevant to the area. Chapter 2 tells of our contributions including the development of a convergent, regioselective assembly of an indole-imidazole compound *en route* to the natural product. Chapter 3 includes the experimental details of this work and the characterization of previously unreported compounds. Part 2 recounts the (–)-platensimycin research project. Chapter 4 discusses the importance of the natural product and the relevant previous research reported. Chapter 5 describes our efforts in this area, culminating in the stereoselective synthesis of an intermediate closely related to a known compound, which was converted to the natural product. Chapter 6 includes the experimental details of this work and the characterization of previously unreported compounds.

Table of Contents

PART 1: STUDIES TOWARD THE SYNTHESIS OF (±)-CHARTELLINE C

Chapter 1: The Chartelline Alkaloids

1.1. ISOLATION

Marine organisms are a rich source of structurally complex and diverse natural products. Alkaloids isolated from such marine organisms have been found to contain unprecedented molecular architectures and often possess compelling biological activity.[1,2] Bryozoans in particular, are invertebrate phyla that have served as a source of biologically active compounds.[3] The difficulty of obtaining large quantities of these organisms for serious investigations has led to fewer studies relative to other sources of natural products.

In 1985, Christophersen reported the isolation and characterization of chartelline A[4] from the marine bryozoan *Chartella papyracea* belonging to the family Flustridae. This was followed in 1987 by the disclosure of chartellines B and C (Figure 1. 1).[5] The three chartellines were collected during a diving expedition in the autumn of 1981, from Roscoff Marine Biological Station in the North Sea. Organic extraction of the lyophilized material, followed by silica gel chromatography of the crude extract yielded 0.07% of a compound whose structure was determined by NMR spectroscopy and confirmed by X-ray analysis to be that shown for chartelline A. Due to the unprecedented and intriguingly complex structure of chartelline A, the remaining alkaloid extracts were further studied. This resulted in the characterization of chartellines B and C, differing only in their halogenation patterns.

Christophersen has also reported the isolation and characterization of chartellamides A and B from the same organism.[6] The absolute stereochemistry was determined to be the same as in the chartellines based on the similarities of their CD

curves. The structurally related alkaloids, securamines A-D, were later isolated from *Securiflustra securifrons*, another member of the family Flustridae.[7, 8]

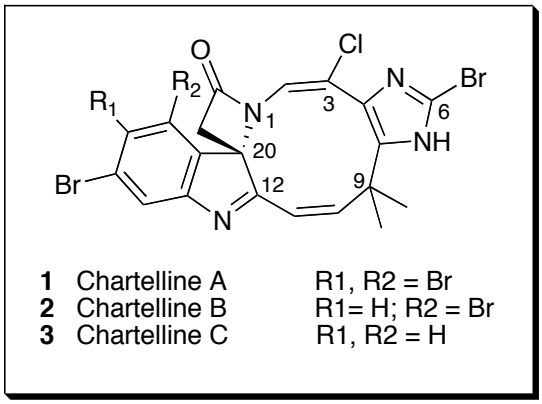


Figure 1. 1: Chartellines and Related Alkaloids

Though they have been tested for anitmicrobial activity, neither chartelline A, nor the crude extracts of alkaloids, have been shown to possess any significant biological activity against both gram-positive and gram-negative bacteria or molds. No significant biological activity has been reported for any of the chartellines, chartellamides, securamines, or securines.

1.2. STRUCTURE

These alkaloids all consist of indole and imidazole subunits linked by an isoprene moiety. In the chartellines A-C (**1 - 3**), the subunits are linked in a 10-membered macrolactam ring with an unprecedented spiro-β-lactam ring at C-20 (chartelline numbering). The X-ray structure of chartelline A[4] reveals its unique structure; it adopts a cup-like conformation wherein the imidazole is orientated under the indole (Figure 1. 2). The configuration around C-20 was determined to be *S* (as shown) by Christophersen.

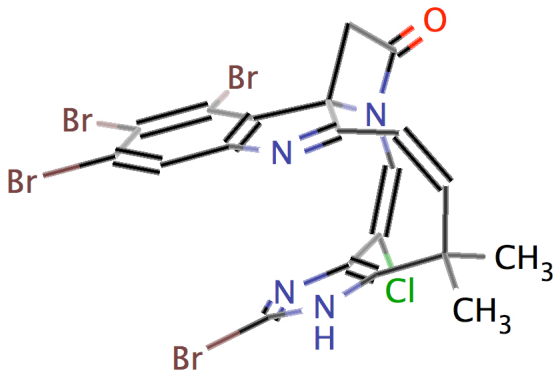


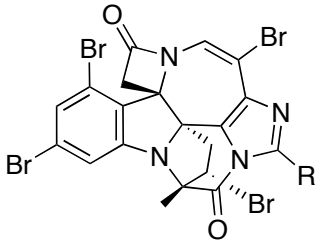
Figure 1. 2: 3-D Representation of chartelline A

Chartellamides A and B (**4**, **5**) also contain a spiro-β-lactam ring but they differ in that they contain a trans-annular link between C-12 (the indole C-2) and C-8 (the imidazole C-5) creating a more compact polycyclic molecule (Figure 1. 3). Additionally, the polyhalogenation pattern is unlike that found in the chartellines.

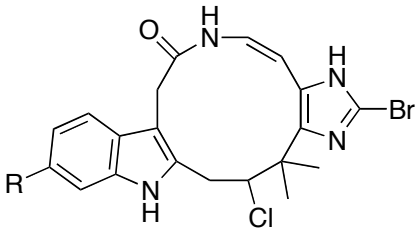
The securamines A-D (**8** – **11**) also are made up of indole and imidazole portions joined by an isoprene unit, though the macrolactam core is different. Securamines contain a γ-lactam where the amide *N* is attached to the indole C-2. While the

chartellines contain a 10-membered macrolactam ring core, the securamines A (**8**) and B (**9**)–differing only in a bromine substituent–have a 9-membered macrolactam ring core. The securamines C (**10**) and D (**11**)–also differing only in bromine substitution–appear to be the product of indole *N* attack at imidazole C-5, giving rise to the compact polycyclic core.

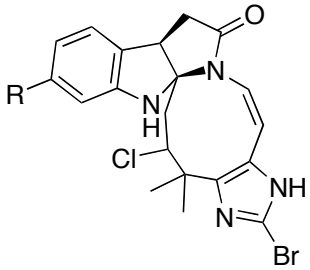
The securines A and B[7] (**6**, **7**) are comprised of a 12-membered macrolactam core, the largest among these alkaloids. They were observed to form when securamines A and B were kept in DMSO solution.



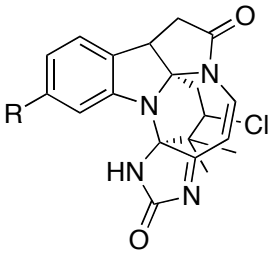
4 Chartellamide A R = H
5 Chartellamide B R = Br



6 Securine A R = H
7 Securine B R = Br



8 Securamine A R = H
9 Securamine B R = Br



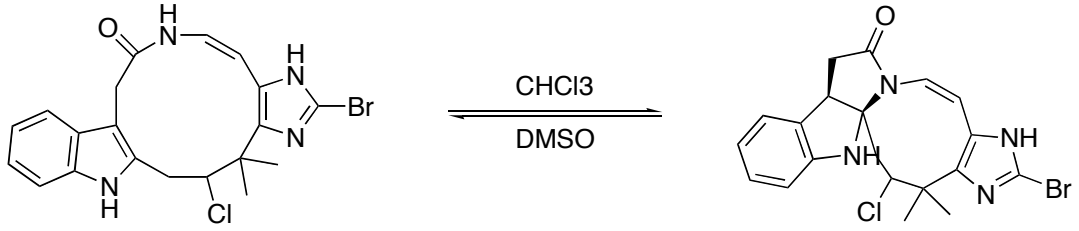
10 Securamine C R = Br
11 Securamine D R = H

Figure 1. 3: Related Alkaloids

1.3. BIOGENETIC RELATIONSHIP

1.3.1. Chartellines, Securamines, and Securines

The chartellines, chartellamides, securamines and securines are all believed to be tryptophan, histamine, and isoprene derived natural products. The aforementioned observation that the securamines open to form the securines when kept in DMSO gives credence to the hypothesis of a common biogeneity of these alkaloids (Scheme 1. 1). Furthermore, dissolution of the securines in $CHCl_3$ gives rise to the reverse ring-closing process, returning the securamines.[9]



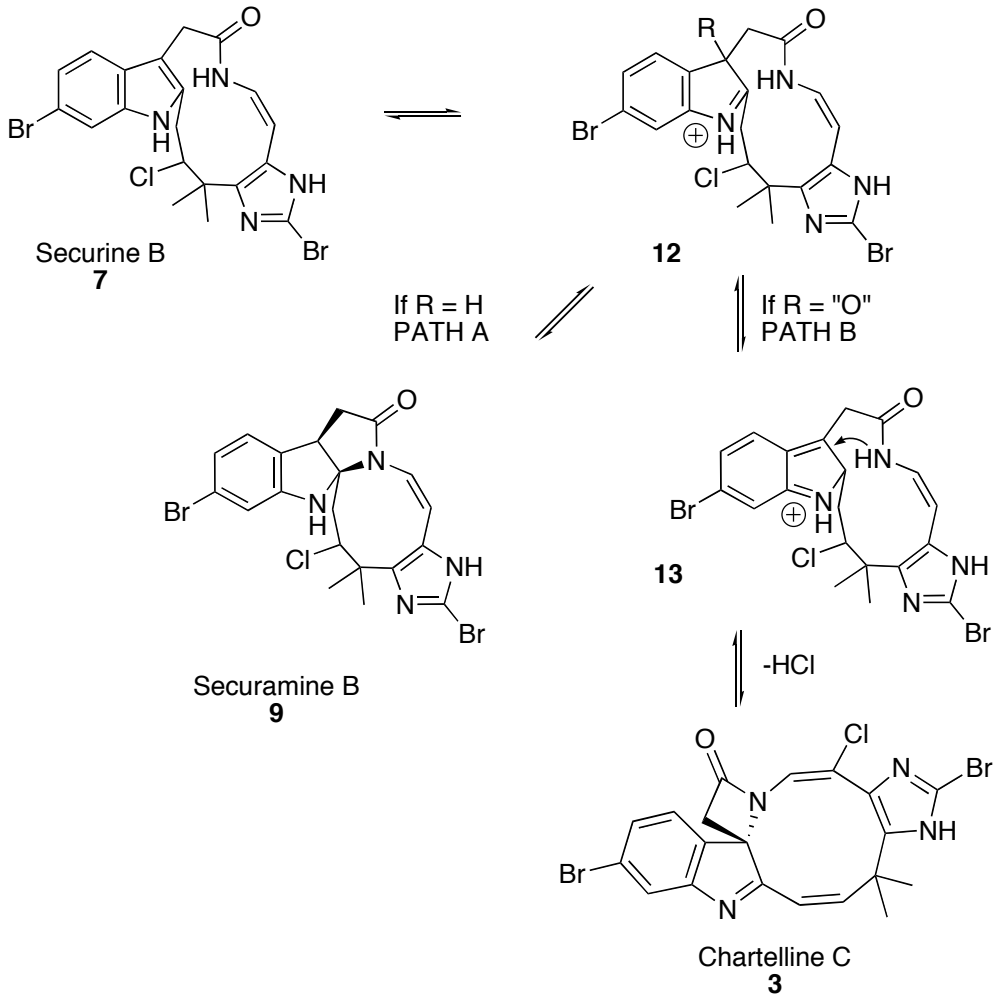
Securine A
6

Securamine A
8

Scheme 1. 1: Solvent dependent equilibrium between securamine and securine

The securines have thus been suggested as a biogenetic precursor to the securamines and chartellines. The common aza-2,4-cyclononadiene system can be converted from the simple macrolactam present in securine **7**, into the skeleton of the securamines *via* protonation of the indole C-3 to give intermediate **12** (R = H) (Path A, Scheme 1. 2), followed by attack of the amide *N* onto the intermediate imine, thus delivering the γ-lactam containing securamines (**9**).[10] Alternatively, an oxidant, such as a hypohalite,[11] could undergo electrophilic attack at the indole C-3 to give an intermediate **13** (R = "O", an oxidant) (Path B, Scheme 1. 2).[12, 13] In this case, the amide *N* would undergo attack at indole C-3 to displace the oxidant (likely *via* an extended iminium)

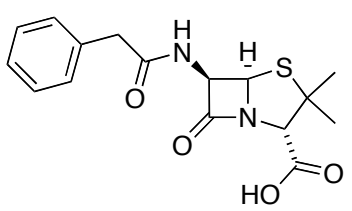
giving rise to the spiro-β-lactam found in the chartellines (**1** – **3**) and chartellamides (**4** – **5**). Loss of HCl installs the lower *cis*-olefin and gives the chartellines.



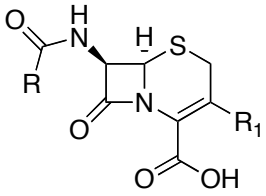
Scheme 1. 2: Possible Biosynthetic Pathways *via* Securine

1.4. β-LACTAM FORMATION

The idea that the unprecedented spiro-β-lactam in the chartellines and chartellamides is biosynthetically derived *via* enzymatic oxidation has its roots in the biosynthesis of the β-lactam antibiotics. The penicillins **14** and cephalosporins **15** (Figure 1. 4), stimulated great interest because of their importance as pharmaceuticals and because of their chemical structure.



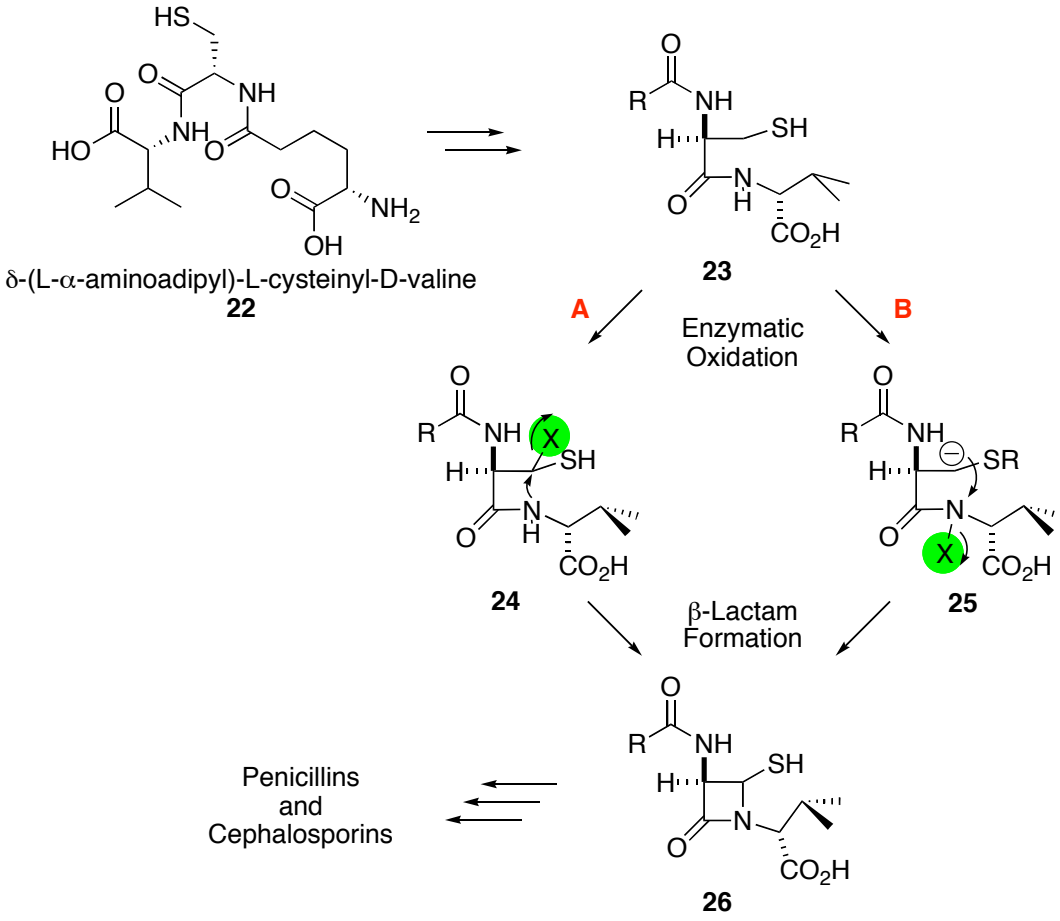
Penicillin G
"penam" class
14



Cephalosporins
"cepham" class
15

Figure 1. 4: Classes of β-Lactam Antiobitics

The extensive research into their biosynthesis led to the conclusion that the "Arnstein tripeptide" δ-(*L*-α-aminoadipyl)-*L*-cysteinyl-*D*-valine **22** was the linear precursor to the antibiotics. Two modes of β-lactam formation from linear **22** were proposed, both involving an enzymatic oxidation of an intermediate **23** (Scheme 1. 3). Path **A** entails oxidation α to the thiol, installing a leaving group (**24**). Displacement by the amide *N*, forms the β-lactam and subsequent enzymatic transformations form the other ring, either providing penam or cepham antibiotics *via* **26**. Path **B** involves oxidizing the amide nitrogen to a hydroxamic acid-like intermediate **25**. In this case, an anion formed α to the thiol would attack the amide nitrogen, furnishing the β-lactam *en route* to the antibiotics. Both paths have been demonstrated to be viable non-enzymatically.

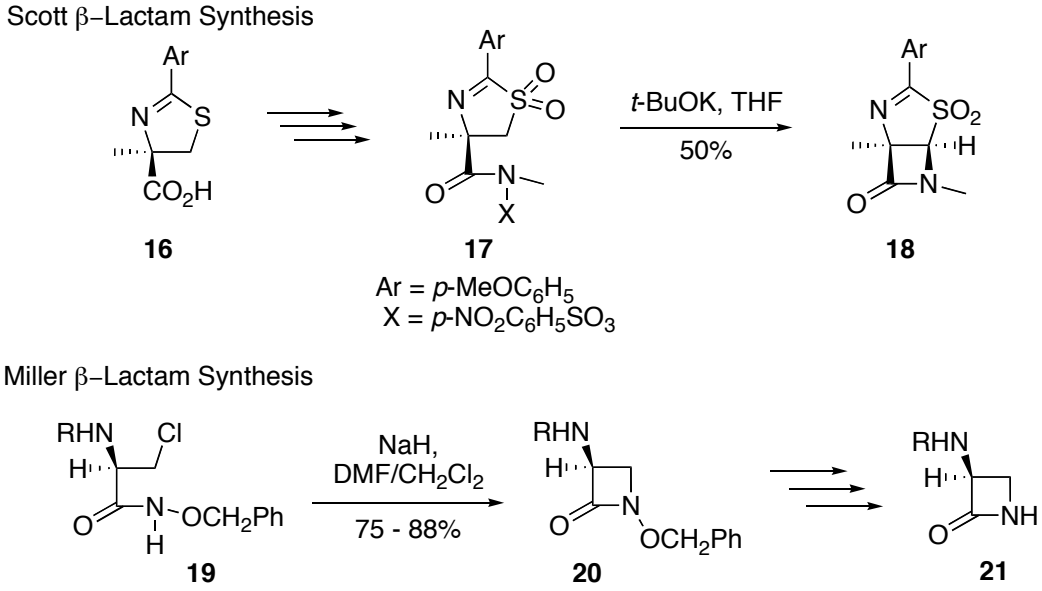


Scheme 1. 3: Enzymatic Pathways for β-Lactam Synthesis

1.4.1. Early examples of β-lactam synthesis

The classical approach to β-lactam synthesis, developed by Sheehan in his groundbreaking synthesis of penicillin, was to use amide bond formation as the key disconnection. The hypothetical biosynthetic pathways represented a different disconnection though.

The two main departures were investigated long before the chartellines were discovered. Path B was demonstrated to be viable by Scott and co-workers[14]. The synthesis of a hydroxamic acid derivative **17** was performed (from **16**). Oxidation of the ring sulfur to the sulfone installed a functional handle for a non-enzymatic anion formation. In fact, treatment of the sulfone with potassium *t*-butoxide provided the β-lactam derivative **18** in 50% yield. While **18** was not a precursor to the penam or cepham antibiotics, it clearly established the capability of β-lactam synthesis *via* carbon to amide nucleophilic dispacement.



Scheme 1. 4: Approaches to β-lactam Synthesis

Path A, Scheme 1. 3 was utilized in work from Miller and co-workers[15, 16] and would find application in the approach to chartelline synthesis (*vide infra*, 1.5.2. Isobe). Miller found that the use of a hydroxamic acid derivative **19** to generate an anion was necessary as the amide failed. In the incidence of treating Cl-containing hydroxamic acid derivatives **20** with NaH, β-lactam formation was observed in 75–88% yields. Once

again, while no clear mapping onto the penam or cepham antibiotics was evident, the route to β-lactam synthesis was shown to be feasible.

1.5. STUDIES TOWARDS THE SYNTHESIS OF CHARTELLINES

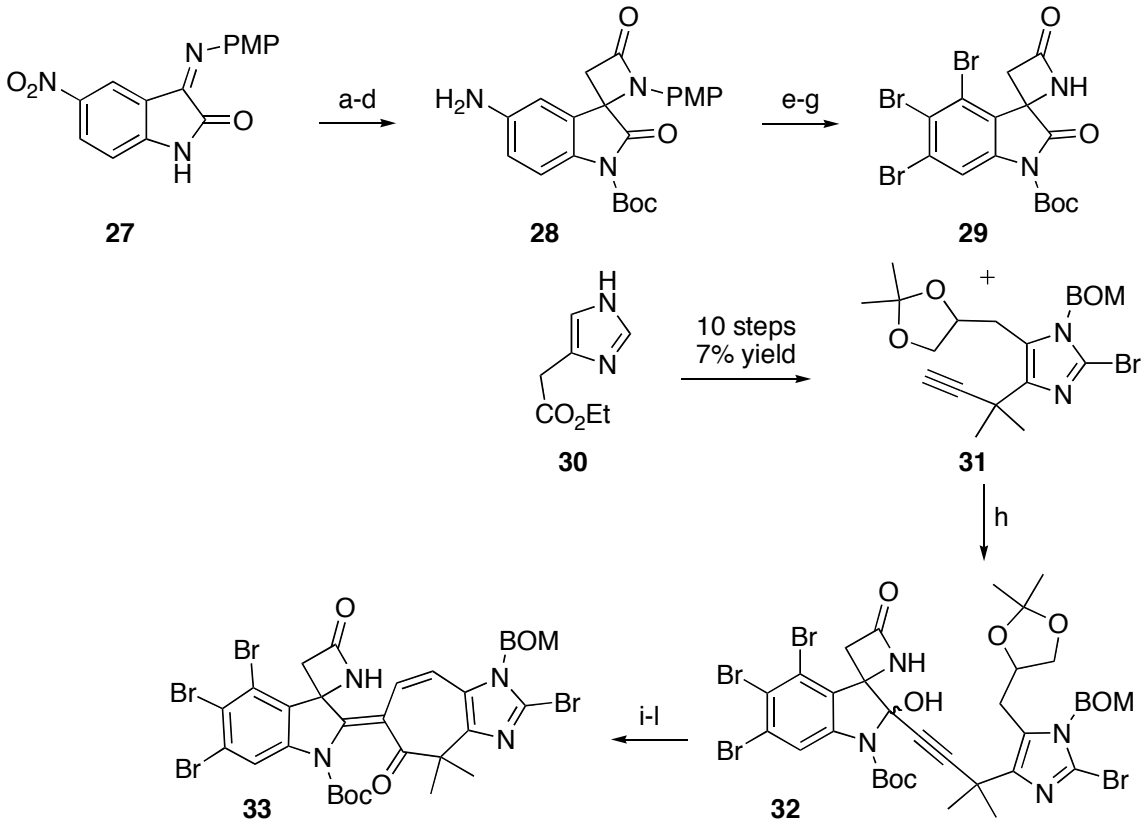
The chartellines were first disclosed in the 1980's, yet the first published report of efforts towards their synthesis did not appear until 2001.[17] Though there has been no reported biological activity, these alkaloids have spurred several research groups to undertake their syntheses due to their complex molecular architecture. The focus of much of the published efforts has been on strategies for the synthesis of the spiro-β-lactam. There has been one total synthesis of chartelline C (**3**).

1.5.1. Weinreb's Studies Toward the Chartellines and Chartellamides

Weinreb and co-workers were the first to report their efforts towards the synthesis of chartelline alkaloids.[17] The strategy involved the early formation of oxindole-3-spiro-β-lactam from an isatin derivative *via* [2+2]-cycloaddition. The rest of the structure would be installed through nucleophilic attack at the oxindole carbonyl. A model study tested the viability of a Staudinger ketene-imine cycloaddition to form the β-lactam. In a system aimed at the total synthesis,[18] the isatin derivative **27** was treated with an *in situ* generated ketene to yield the cycloadduct **28** in 74% from isatin. Reduction of the aromatic nitro and reductive removal of the Cl provided an oxindole (Scheme 1. 5) with the spiro-β-lactam intact. Installation of the three bromines around the indole ring and removal of the lactam protecting group furnished **29**, which was ready for the proposed oxindole acetylene addition.

Acetylenic imidazole fragment **31**, derived in 10 steps and 7% overall yield from 4-substituted imidazole **30**, was treated with LiHMDS and then subjected to the oxindole **29**, resulting in efficient addition into the carbonyl to yield propargyl alcohol **32**.

However, propargyl alcohol **32** could not be converted to chartelline A. Treatment of **32** with acid resulted in the rearranged enone **33**.



Reagents and Conditions: a) $ClCH_2COCl$, NEt_3, CH_2Cl_2, 74% from isatin; b) Boc_2O, NEt_3, CH_2Cl_2, 64%; c) Zn, AcOH, THF; d) $(TMS)_3SiH$, AIBN, PhMe, 100 °C, 88% two steps; e) $BnMe_3NBr_3$, $CaCO_3$, MeOH, CH_2Cl_2, 91%; f) *t*-BuONO, $CuBr_2$, MeCN, 88%, g) CAN, MeCN, 90%; h) LiHMDS, THF, -78 °C, 91%; i) TFA, H_2O, 99%; j) $Pb(OAc)_4$, PhH; k) *p*-TsOH, PhMe; l) Boc_2O, NEt_3, CH_2Cl_2, 55% 3 steps.

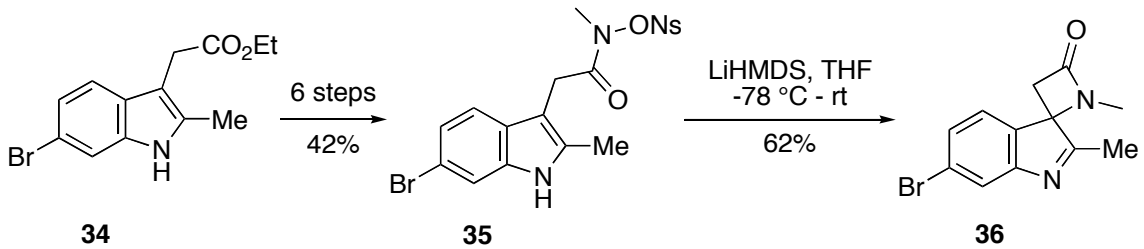
Scheme 1. 5: Weinreb's efforts towards the chartellines

Weinreb's work showed the feasibility of the Staudinger [2+2] cycloaddition to form the spiro-β-lactam **28** and demonstrated its stability by carrying it through the subsequent functionalizations and alkyne addition. Additionally, this strategy has been applied in studies directed toward the total synthesis of chartellamides.[19] However, while

the installation of the imidazole acetylene fragment *via* nucleophilic addition into an oxindole was successful, the advancement of this strategy towards the total synthesis of these alkalkoids has proved unsuccessful to date.

1.5.2. Isobe's Studies Toward the Chartellines

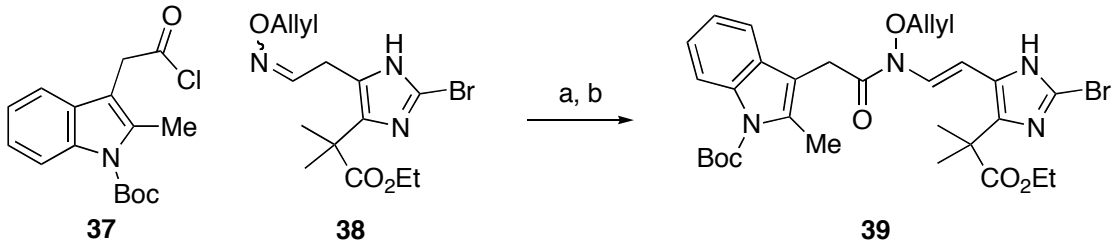
Isobe and co-workers have disclosed several efforts towards the synthesis of the chartellines.[20, 21] An intial disclosure into the synthesis of the β-lactam *via* peptide coupling,[20] though successful in the model compounds, was never progressed towards chartelline C. Their second strategy[21] involved an intramolecular attack of the indole C-3 at an electrophilic *N*-ONs amide (Ns = *p*-nitrobenzenesulfonyl). This approach is obviously rooted in the work done by Scott[14]. They have demonstrated the success of this method in the synthesis of several model indole-3-spiro-β-lactams (Scheme 1. 6).[20] Indole acetate **34** was converted to *O*-Ns hydroxamate **35** in 6 steps and 42% yield. Upon deprotonation of the indole *N*-H with LiHMDS, the *N*-ONs underwent nucleophilic attack to form the spiro-β-lactam **36** in 62% yield. Isobe observed that the indole's 6-Br had a large, negative impact on the efficiency of the reaction.[21] In the absence of the Br, cyclization was facile at –78 °C and with the 6-Br present, the reaction was performed at room temperature with lesser success.



34 **35** **36**

Scheme 1. 6: Isobe's Approach to Spiro-β-lactam Synthesis

Central to this approach is the assumption that this method will be applicable to a more complex substrate containing both an indole and imidazole portion present in the natural product. Towards that end, () a method for the synthesis of an appropriate *N*-ONs hydroxyenamide was sought.[22] Isobe showed that the reaction of an imidazole containing oxime **38** with an indole-3-acetyl chloride **37** provided an *N*-(*O*-allyl) enamide **39**. While the *O*-allyl protecting group was removed easily on simpler substrates, the indole-imidazole containing substrate was left unchanged. Additionally, the process resulted in *E*-enamides exclusively, thereby questioning the relavancy of this approach towards a total synthesis of *Z*-olefin containing chartelline C.



37 **38** **39**

Reagents and Conditions: a) CH_2Cl_2, 3Å MS, Δ; b) *p*-TsOH, CH_3CN, 39%

Scheme 1. 7: Isobe's hydroxyenamide formation

1.5.3. Baran's Total Synthesis of (±)-Chartelline C

Baran and co-workers completed the total synthesis of chartelline C in 2006.[23, 24] The strategy employed therein is based on the supposition that the spiro-β-lactam could arise from a late-stage oxidative cyclization, similar to that proposed in the biosynthesis of these alkaloids (Scheme 1. 2).

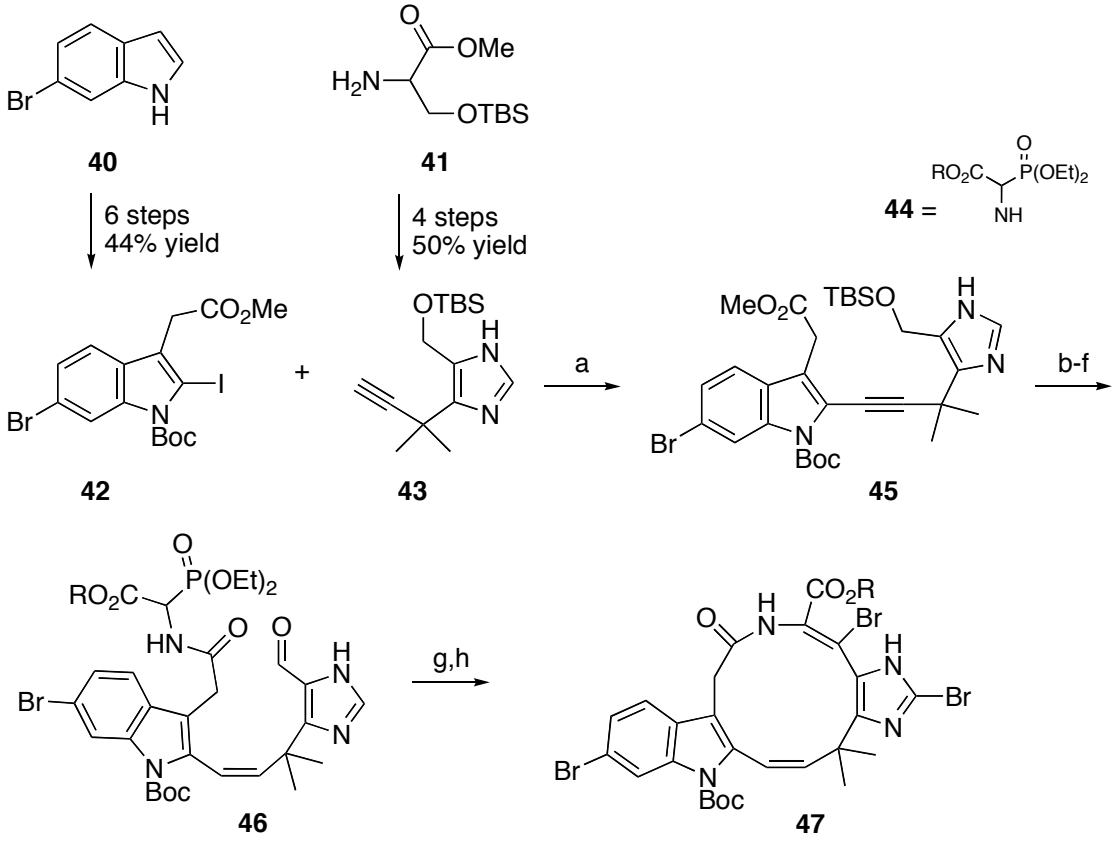
Initial studies on a model system, reported in 2005,[23] established the viability of using a hypervalent bromine (NBS) oxidation on a securine-like macrolactam to instigate

the β-lactam formation. The synthesis of such a macrolactam and the application of the developed method to the real system was reported a year later.[24]

The report commences with the Sonogashira coupling of 6-bromo-2-iodo-indole **42** (derived from 6-bromoindole **40** in 6 steps and 44% yield) with imidazole acetylene **43** (prepared from *O*-TBS serine methyl ester **41** in 4 steps and 50% yield). The Pd catalyzed coupling occurs at the 2-iodo selectively, yielding alkyne **45** in 85% yield (Scheme 1. 9). Reduction of the acetylene with Raney Ni to the *cis*-alkene–leaving the aromatic Br intact–preceded removal of the *O*-TBS and oxidation to the aldehyde. The strategy for formation of the macrolactam was to perform an intramolecular Horner-Wadsworth-Emmons (HWE) on the aldehyde. To do this, the 3-indole acetate was hydrolyzed to the acid and coupled with phosphonate amine **44** to give the HWE precursor **46**. The cyclization provided an enamide **i**n 56% yield, which upon sequential treatment with Br_2 and *N*-bromoacetamide (NBA) gave the tribromo macrolactam **47**.

With a successful synthesis of a polyhalogenated macrolactam **47**, the first such reported in this area, Baran examined the oxidative formation of the spiro-β-lactam. In the initially reported model system, the ring contraction was found to proceed on an *N*-H indole macrolactam upon exposure to NBS. Therefore, the *N*-Boc on the indole **47** was removed thermally (185 °C, neat) in the polyhalogenated system (Scheme 1. 9). The intermediate *N*-H indole was taken up in acetonitrile and upon exposure to NBS at ambient temperature was converted to the β-lactam **50**. While several mechanistic pathways are possible and may likely be operable, the mechanism suggested by Baran is shown (Scheme 1. 9). Bromination at C-20 (indole C-3) would form an intermediate imine **48**. The amide would then attack the imine at the indole C-2, contracting the macrolactam and providing a securamine-like pyrroloindoline. Loss of the indole C-3 bromine, forming the extended imine species **49**, initiates a [1,5]-shift of the amide

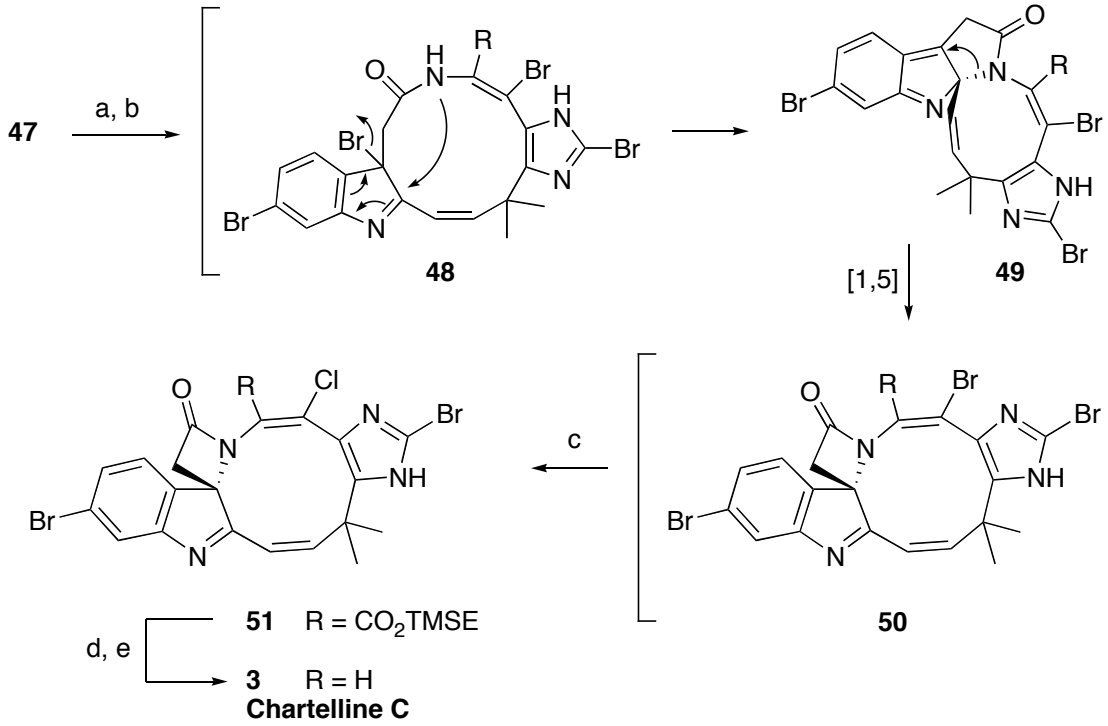
converting the pyrrolindoline **49** into the β-lactam **50**. Upon workup of the reaction with aq. NaCl (brine), the enamide Br mildly exchanged for Cl, generating the chartelline-like **51** in a remarkably facile and efficient 93% yield over the three steps.



Reagents and Conditions: a) $Pd(PPh_3)_4$, CuI, Et_3N, DME, 50 °C, 85%; b) (b) Raney Ni, MeOH, 20 °C, 5 h, 80%; (c) TBAF, THF; (d) MnO_2 CH_2Cl_2, 60% three steps; (e) LiOH, H_2O; iv), THF/H_2O 4:1; (f) **44,** BOPCl, DIPEA, CH_2Cl_2, 0 °C, 89% overall; (g) LiCl, DIPEA, MeCN, 70 °C, 56%; (h) Br_2, $CaCO_3$, PhH, then NBA, PhH, 36%; R = TMSE

Scheme 1. 8: Baran's synthesis of a securine-like macrolactam

Completion of the synthesis required only to remove the ester of the enamide. This was achieved by hydrolysis of the trimethylsilylethyl (TMSE) ester **51** to its acid and a thermal decarboxylation. Heating of the intermediate acid to 200 °C in *o*-dichlorobenzene (DCB) for 5 min, cleanly decarboxylated to provide chartelline C (**3**). Thus, the first total synthesis of a chartelline alkaloid had been achieved in a straightforward and elegant fashion. The work featured a remarkably facile, "biosynthetically inspired" strategy of securine-like macrolactam contraction to form the spiro-β-lactam in the chartellines.



Reagents and Conditions: a) 185 °C, 1.5 min (4x); b) CH_3CN, NBS, then K_2CO_3, 18-crown-6; c) aq. $NaHCO_3$, aq. NaCl, 93%; d) TFA, DCE; e) *o*-DCB, 200 °C, 5 min, 64%; R = CO_2TMSE

Scheme 1. 9: The completion of Baran's total synthesis of chartelline C

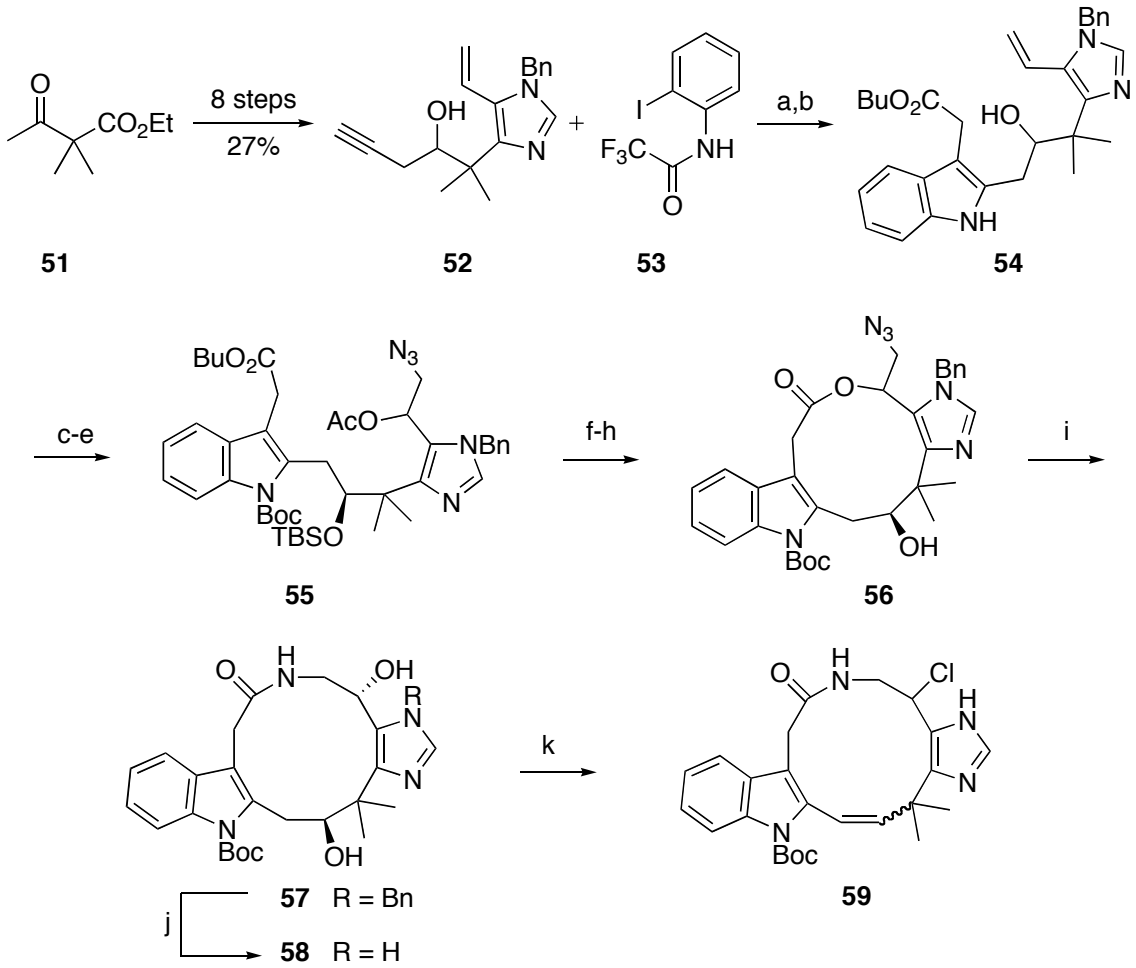
1.6. STUDIES TOWARDS THE SYNTHESIS OF SECURINE AND SECURAMINE

The securines and securamines are biogenetically and structurally related to the chartellines, though there has been only one published report of synthetic effort towards these compounds.

1.6.1. Wood's Studies Toward the Synthesis of Securine A

Wood and co-workers disclosed their work towards the synthesis of securine A,[25] culminating in the synthesis of a securine A carbon skeletal compound (Scheme 1. 10). The strategy entailed the rearrangement of a macrolactone to the macrolactam present in securines.

The work commenced with the synthesis of imidazole **52** in 8 steps and 27% yield from ketone **51**. Coupling of the terminal acetylene to iodoarene **53** followed by a Pd(0) mediated indole formation gave the indole **54**. Protection of the alcohol as its silyl ether preceded functionalization of the vinyl species on the imidazole, which was best achieved *via* iodonium ion formation and opening with acetate. Displacement of the primary iodide with azide gave macrolactone precursor **55**. Hydrolysis of the indole-3-acetate and the benzylic acetate was facile and gave way to a Yamaguchi lactonization to give macrolactone **56**. Reduction of the azide with tributyltin hydride and AIBN provided an intermediate amine that underwent an acyl transfer to the macrolactam **57** in 55% yield. Hydrogenolysis to cleave the imidazole *N*-benzyl to the *N*-H **58** went in 77% yield. Disappointingly, treatment of the diol **58** with tributylphosphine and carbon tetrachloride converted the northern alcohol to a Cl, while the lower hydroxyl was eliminated. The hope was that the converse would occur, providing securine A **6**. The macrolactam **58** exists as a mixture of olefin isomers.



Reagents and Conditions: a) $PdCl_2(PPh_3)_2$, CuI, NEt_3, PhH, 95%; b) $Pd(PPh_3)_4$, Et_2NH, DMF, ethylene glycol, 73%; ICH_2CO_2Bu, *n*-BuLi, 89%; c) TBSCl, imid; d) Boc_2O, Et_3N, 60 °C, 77%; e)ICl, MeCN, NaOAc; e) NaN_3, DMF, 100 °C, 91%; f) LiOH, THF/H_2O, 99°C; g) Yamaguchi's reagent, Et_3N, THF, 74%; h) TBAF, AcOH, 73%; i) Bu_3SnH, PhH, AIBN, 80 °C, 55%; j) H_2, Pd/C, MeOH/EtOAc, 77%; k) PBu_3, MeCN/CCl_4, 55 °C, 68%.

Scheme 1. 10: Wood's Approach to the Securines

While Wood's strategy for macrolactam formation was successful, producing a securine-like **59** containing all of the carbons and nitrogens of the natural product, advancement to the enamide present in securine proved unfruitful.

1.7. CONCLUSIONS

Chartelline A's (**1**) isolation was reported in 1985 followed by chartellines B (**2**) and C (**3**) in 1987. Their disclosure as isolates from the marine bryozoan *Chartella papyracea* described the structurally unprecedented molecules as displaying an unusual "boat-like" conformation and consisting of polyhalogenated indole, imidazole, and isoprene units joined in a macrolactam with a spiro-β-lactam at the indole C-3. Though they were not found to exhibit any significant biological activity, these intriguing alkaloids have generated great interest in the synthetic community. Weinreb, Isobe, and Baran worked towards the total synthesis of the chartellines, each demonstrating different strategies to the β-lactam formation. Baran's work culminated in the total synthesis of chartelline C.

Additional alkaloids consisting of similar structural elements were later reported and are believed to be biogenetically related to the chartellines. The chartellamides (**4**, **5**) and securamines (**8** – **11**) are virtually constitutional isomers of the chartellines, varying in connectivities around the macrolactam and in halogenation patterns. None of these have been shown to possess any biological activity. The chartellamides have been the subject of study by Weinreb. The securines (**6**, **7**), which resulted from the securamines storage in DMSO, are simpler macrolactam stuctures than the other alkaloids discussed. Wood has reported work towards the synthesis of securines. It was suggested by Christophersen that the securines may be biosynthetic precursors to both the chartellines and securamines.

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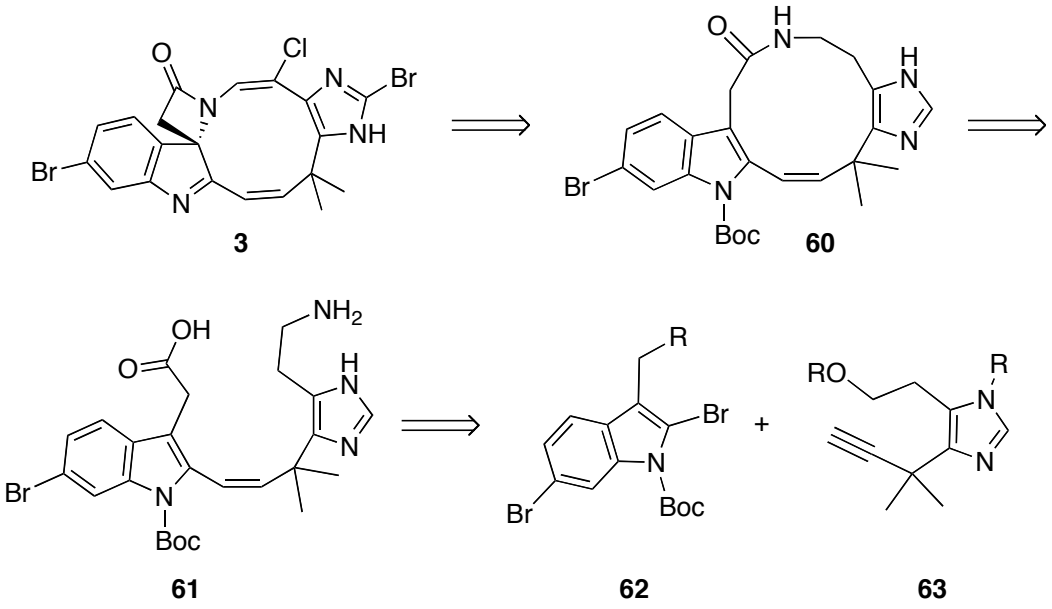
Chapter 2: Efforts Towards the Synthesis of Chartelline C

2.1. Synthetic Strategy

Inspired by the hypothesis that the chartelline alkaloids are biogenetically related to the securines and securamines, our synthetic strategy was based on the supposition that the β-lactam could be accessible *via* oxidation of a suitable substrate. The chartelline C (**3**) skeleton would be formed by a late-stage oxidative cyclization of a securine-like macrolactam (**60**) (Scheme 2. 1). The macrolactam is seen arising from an intramolecular amide formation of an indole-imidazole substrate **61**. The indole-imidazole substrate could arise from the convergent assembly of a 2-halo-indole **62** and an acetylenic imidazole **63**. An acetylene is seen as being advantageous due to the plethora of methods available for its reduction to a *cis*-olefin.



Scheme 2. 1: Synthetic Strategy

Central to this strategy is the ability to selectively halogenate the C-2 of indole in the presence of the 6-Br, a component of the natural product. Additionally, the synthesis of a 2-H-4,5-substituted imidazole presents certain challenges that would need to be met.

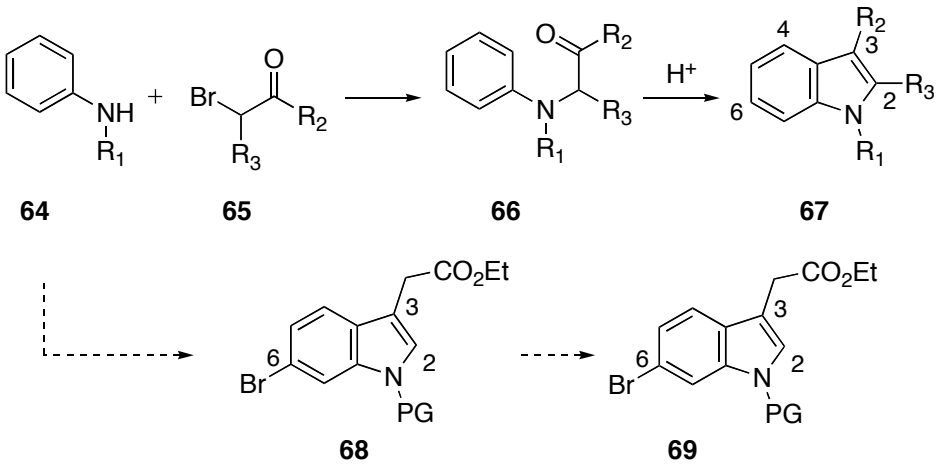
2.2. INDOLE SYNTHESIS

The first objective in our efforts towards the synthesis of chartelline C **3** is the achievement of a 6-bromo indole substrate with the ability to functionalize the 2 position selectively. Also, the presence of an acid surrogate in the 3-position that would be amenable to macrolactamization was sought. In consideration of methods to attach an acetylenic component at the indole C-2, the Sonogoshira cross-coupling[1] of an aryl halide and terminal acetylene seemed a direct solution. Therefore, a selective Sonogashira coupling of a 2-halo-6-bromo indole was initially investigated.

2.2.1. First Generation Indole Synthesis

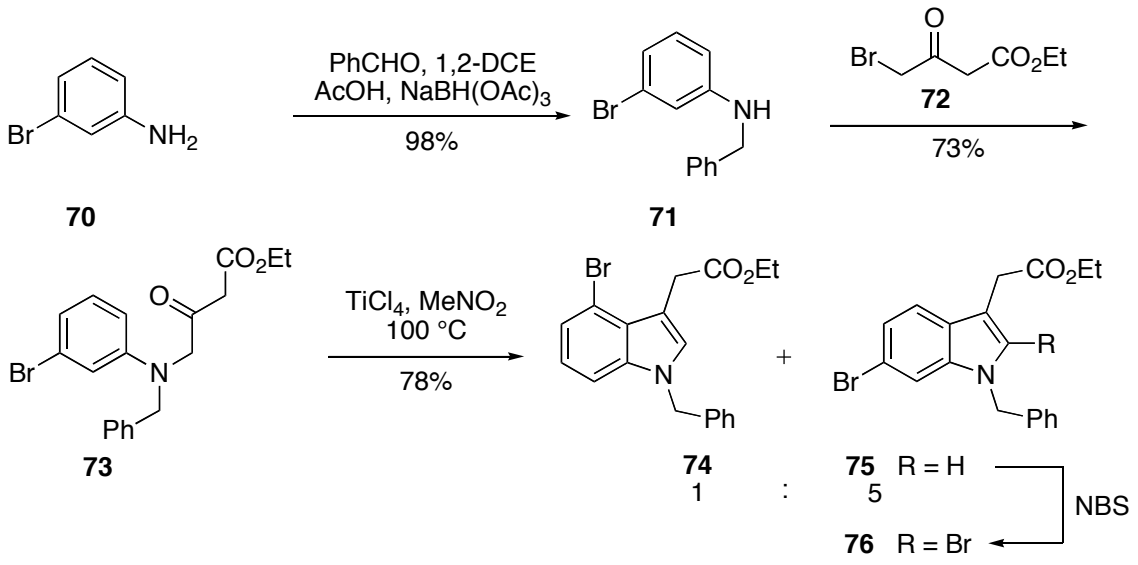
While many methods for the synthesis of indoles have been developed,[2, 3] we desired a flexible route with respect to substitution at indole C-3. Several routes were initially investigated[4] with varied success, leading to the use of the Bischler-Möhlau synthesis to access a suitable substrate.

The Bischler-Möhlau synthesis involves the intramolecular condensation of an α-anilino-ketone to form an indole (Scheme 2. 2). An aniline **64** can be treated with an α-halo ketone **65**, providing the Bischler-Möhlau precursor **66**. Upon heating of the α-anilino ketone **66** with acid present, the electrophilic aromatic addition of the ketone to the arene followed by a dehydration/aromatization provides indole **67**. The R-groups on the α-ketone become the 2,3-substituents on the indole ring produced. This strategy for the synthesis of an indole **68** seemed well-matched.



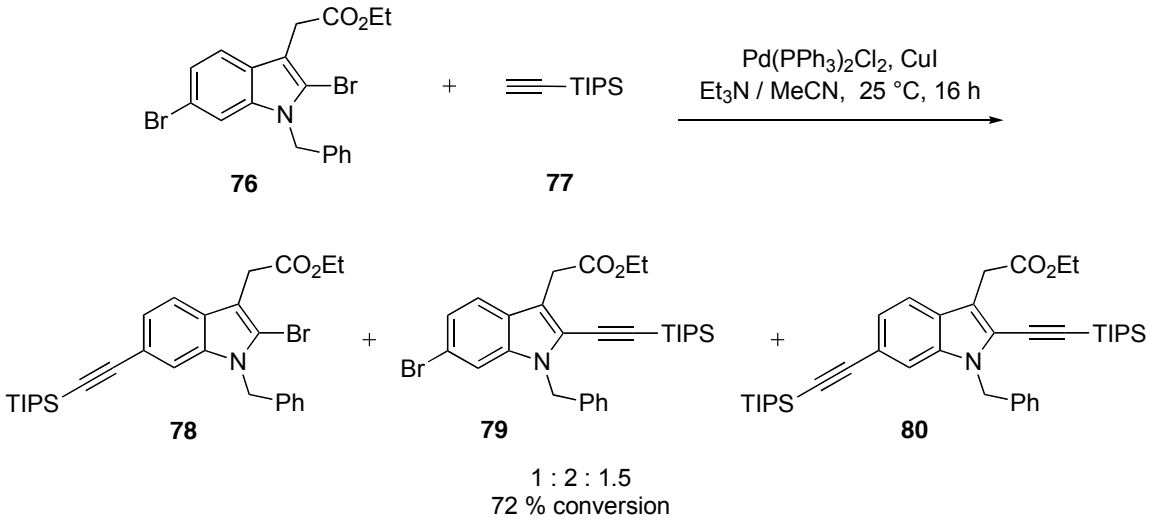
Scheme 2. 2: The Bischler-Möhlau Indole Synthesis

In this case, 3-bromoaniline was the starting aniline **70**. The reductive amination of 3-bromoaniline **70** with benzaldehdye provided *N*-benzyl **71** in 98% yield (Scheme 2. 3). Treatment of aniline **71** with bromo-β-ketoester **72** (prepared from the β-ketoester) gave the Bischler-Möhlau substrate **73**, which upon heating with a Lewis acid, dehydrated to a mixture of 4-bromoindole **74** and the desired 6-bromoindole **75**. After extensive experimentation, it was found that the best results were obtained when $TiCl_4$ was the Lewis acid. A 6-bromo/4-bromo cyclized product ratio of 5:1 was obtained in a combined 78% yield. Bromination at indole C-2 with NBS provided a 2,6-dibromoindole **76** used to investigate the regioselectivity of Sonogashira couplings.



Scheme 2. 3: Bischler-Möhlau Synthesis of 6-Bromoindole **76**

Disappointingly, subjecting indole **76** to a standard set of conditions (Pd(II), CuI, Et_3N) with triisopropylsilylacetylene **77** as the alkyne gave a mixture of 2-coupled (**79**), 6-coupled (**78**), and 2,6-dicoupled products (**80**) (Scheme 2. 4). Although 2-iodo indoles were also investigated, selectivity in a Sonogashira coupling with a 2-halo-6-bromo-*N*-benzyl indole could not be achieved.[4]



Scheme 2. 4: Unsuccessful regioselectivity

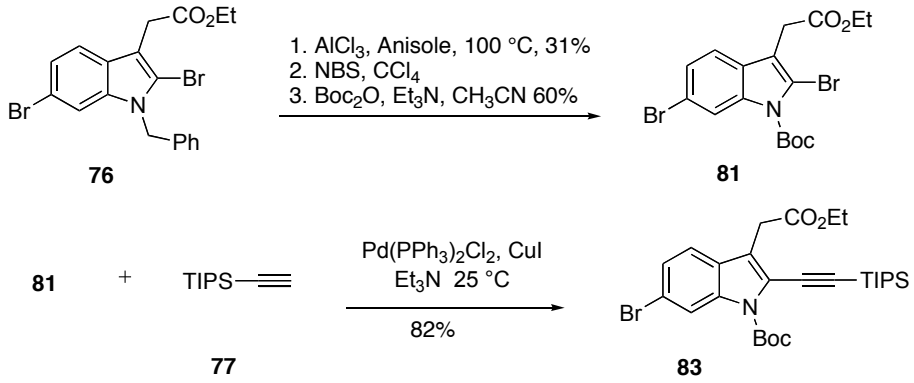
Conversion of the *N*-benzyl indole **75** to an *N*-Boc indole was achieved in a three step process (Scheme 2. 5). Removal of the benzyl group with $AlCl_3$–hydrogenolysis methods gave indolines–followed by bromination of the intermediate indole and Boc protection, furnished *N*-Boc-2,6-dibromoindole **81**. The yield over the three steps was a modest 19%, however enough material for the desired investigative reactions was obtained.

In the event, treatment of indole **81** with triisopropylacetylene **77** in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and NEt_3 delivered only the 2-coupled product **83** in an 82% yield.[4] This result established the necessity of using an *N*-Boc protecting group on the indole for the purpose of obtaining regioselective functionalization of the indole C-2 through Pd cataylzed coupling.

The origin of the regioselectivity is at present unclear. Purely inductive effects could be responsible. As the carbamate withdraws electron density from the indole ring, the proximal C_2–Br bond is weakened relative to the distal C_6–Br. This possibly lowers the activation energy for Pd insertion at C-2, causing the increased rate of C-2 coupling.

While the weakening of the C–Br bond is a reasonable explanation–it agrees with the observations in the literature that aryl iodides are faster to couple than aryl bromides–it is not in agreement with the general observation that more electron rich aryl halides react faster when other factors are equalized.[1]

Alternatively, the carbamate could act as a directing group by a pre-coordination to the Pd. In this case, insertion of Pd into the adjacent C_2–Br bond would be faster based on a steric argument; that the Pd, while coordinated to the carbamate *O*, cannot reach the farther C_6–Br. Both of these arguments are based on the assumption that Pd insertion is the rate determining step, an assumption still up for debate and one that seems substrate dependent. At this point, the cause of the observed selectivity has not been unambiguously determined.



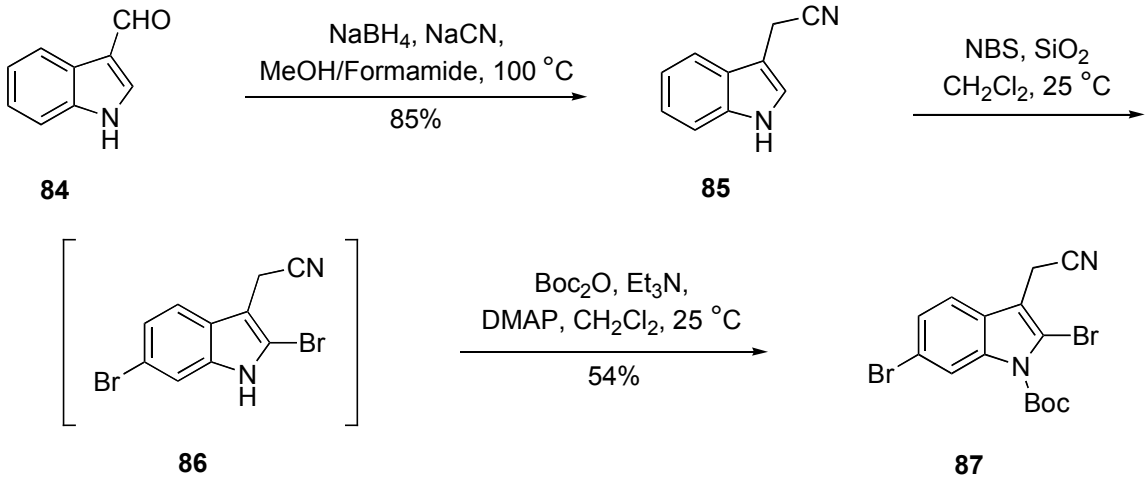
Scheme 2. 5: A regioselective Sonogashira coupling

In any case, this route to 2,6-dibromoindole-3-acetates would not have been amenable to obtaining sufficient quantities of indole **81**. A more direct route was desired.

2.2.2. Second Generation Indole Synthesis

Smith and co-workers have previously demonstrated the regioselective dibromination of certain indoles *via* a SiO_2 mediated bromination with NBS.[5] The examples they showed did not include any with an acetate at C-3; rather a C-3 acetonitrile example was deemed relevant precedence. Clearly, introduction of the nitrogen had been previously planned on arising from the imidazole component of the convergent synthetic plan. It seemed reasonable that considering the large number of known methods of converting nitriles[6] to amides,[7] esters, and acids[8] that substitution of the acetate for an acetonitrile might be advantageous.

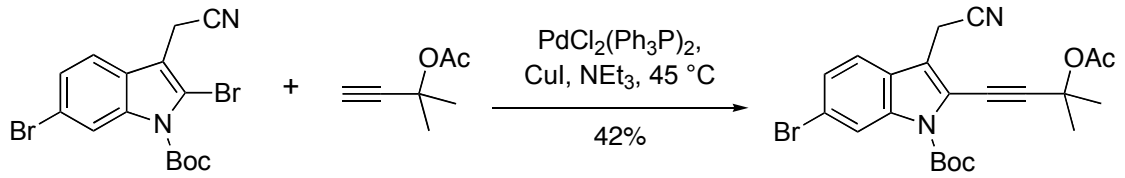
Indole-3-acetontrile[9], though commercially available, was accessed cheaply from indole-3-carboxaldehyde.[10] Reduction of the aldehyde **84** followed by heating with an excess of NaCN produced the indole-3-acetonitrile **85** (Scheme 2. 6). Indole **85**, in accordance with Smith's report, was found to regioselectively brominate at the 2 and 6 positions upon treatment with NBS in the presence of SiO_2 (rigorously dried). While the bromination appeared to work well, the intermediate dibromo indole **86** could not be isolated in appreciable quantities. Such indoles are known to be readily hydrolyzed to oxindoles[11,12] and while no oxindole was observed either, *in situ* protection as its *t*-butyl carbamate allowed for 2,6-dibromo indole **87** to be isolated in 54% yield.



Scheme 2. 6: Synthesis of indole **87**

Normally, bromination of indoles occurs quickest at the 2 position (as in this case) and then at the 5-position, *para* to the nitrogen. The exact cause of the shift in bromination pattern is unclear. It is possible that the silica gel becomes covalently bound to the N, producing an ammonium species. This would shut off the donating effect of the N, the reason for 5-bromination. Now the alkyl substitution presents a tolyl-like arene, directing bromination to the observed 6-position.

The bromination of an indole in the 2 and 6 positions clearly represents a direct route to the desired indole. However, the regioselective cross-coupling had been found on the indole-3-acetate. Gratifyingly, the Sonogashira reaction displayed the same level of control in the test reaction shown (Scheme 2. 7). Indole **87** could be coupled with the propargyl acetate **88** giving only the 2-coupled product **89** in 42% yield. This result was also important because the quaternary carbon in alkyne **88** was a mimic for the steric environment of our proposed substrate en route to chartellines.



87 **88** **89**

Scheme 2. 7: Test Sonogashira coupling of indole **87**

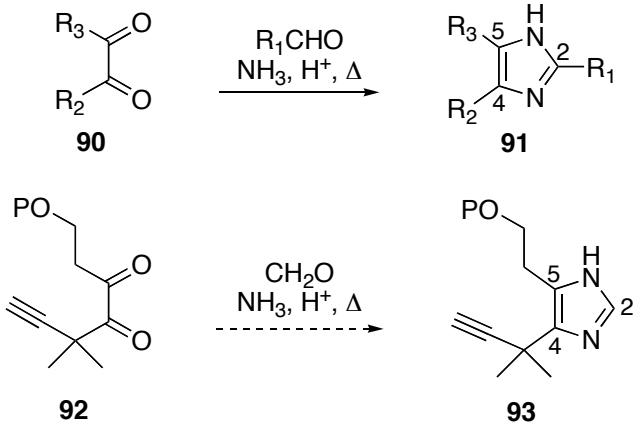
A viable, two-step synthesis of indole **87** and its regioselective functionalization (to **89**) had been established. The synthesis of a suitable alkyne coupling partner was investigated.

2.3. IMIDAZOLE SYNTHESIS

Imidazole is a very common structural motif in alkaloids[13] and as such, there have been many methods developed for their syntheses[14]. Our strategy for the synthesis of the imidazole acetylene envisioned as the coupling partner to indole **87** for the convergent synthesis of chartelline C **3** is discussed herein.

2.3.1. An imidazole coupling partner

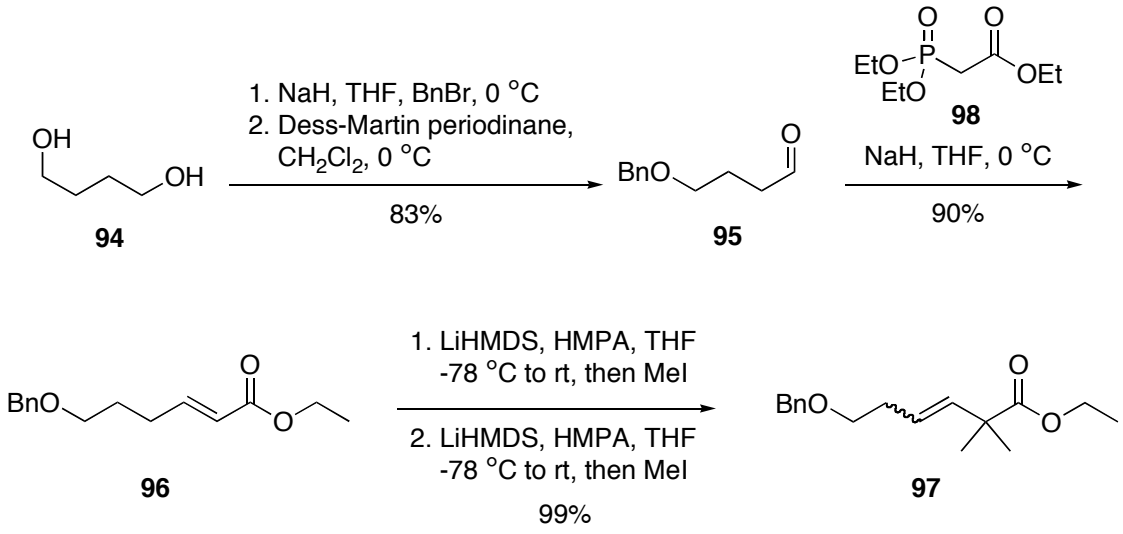
The notion that a 1,2-diketone **90** could be efficiently converted to an imidazole **91** was central to the employed strategy (Scheme 2. 8). As the carbonyl carbons of the 1,2-diketone **90** become the C-4 and C-5 of the imidazole **91**, it seemed a straightforward starting point for investigation into synthesis of the 4,5-disubstituted imidazole **93**. The use of the 1,2-diketone disconnect for imidazole synthesis is usually successful on those dicarbonyls without α-protons; an advantage we have with one carbonyl. Therefore, the synthesis of an α-*gem*-dimethyl 1,2-diketone **92** was the focus.



Scheme 2. 8: The conversion of 1,2-dicarbonyl compounds to imidazoles

The work commenced with the protection of 1,4-butanediol **94** as its mono-benzyl ether (Scheme 2. 9). Oxidation of the primary alcohol to the aldehyde **95** was found to proceed best (83% yield over the two steps) with Dess-Martin periodinane[15] (DMP) as an oxidant. The Horner-Wadsworth-Emmons reaction of the aldehyde with triethylphosphonoacetate gave α,β-unsaturated ester **96** in 90% yield.

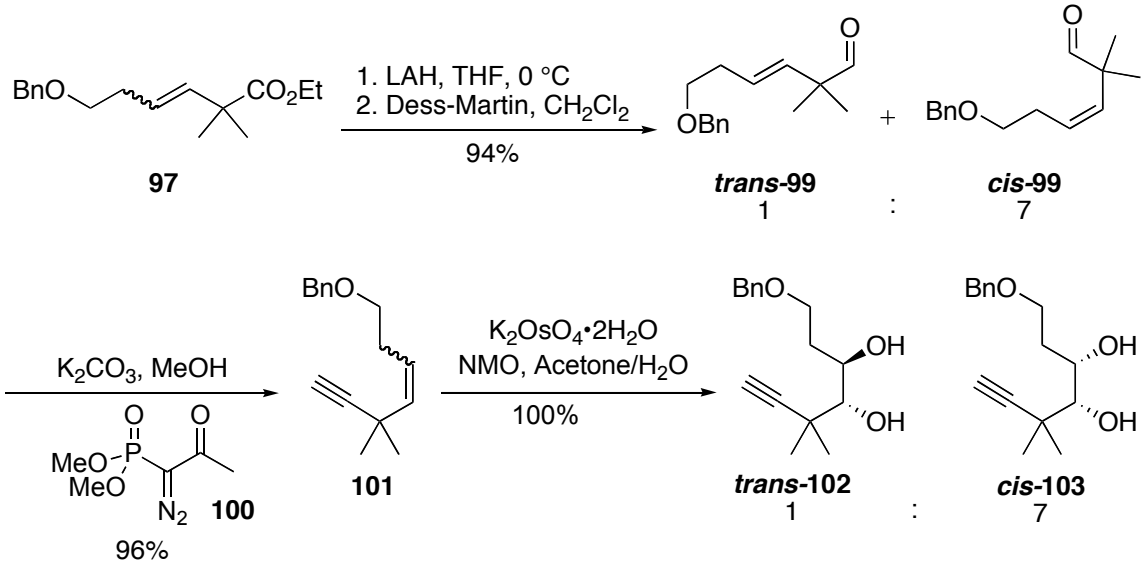
To install the α-*gem*-methyls, a deconjugative alkylation of α,β-unsaturated ester **96** was imagined. During initial investigations into the deconjugative alkylation, it was observed that the addition of HMPA to the reaction had a great impact on its efficiency. The extended enolate was formed upon treatment of α,β-unsaturated ester **96** with LiHMDS at –78 °C, however in the absence of HMPA, quenching of the anion with MeI only produced modest yields of the desired product. The presence of HMPA improved the conversions and yields to quantitative.



Scheme 2. 9: Synthesis of α,β-unsaturated ester **97**

Under the optimized conditions, both alkylations could be carried out sequentially in a one-pot process (99% yield over the two alkylations). The deconjugated olefin in the product was obtained as an inseparable mixture of *E* and *Z* isomers. The olefin would serve as a functional handle for introduction of the 1,2-diketone while the α-*gem*-dimethyl ester **97** would be converted to the terminal alkyne.

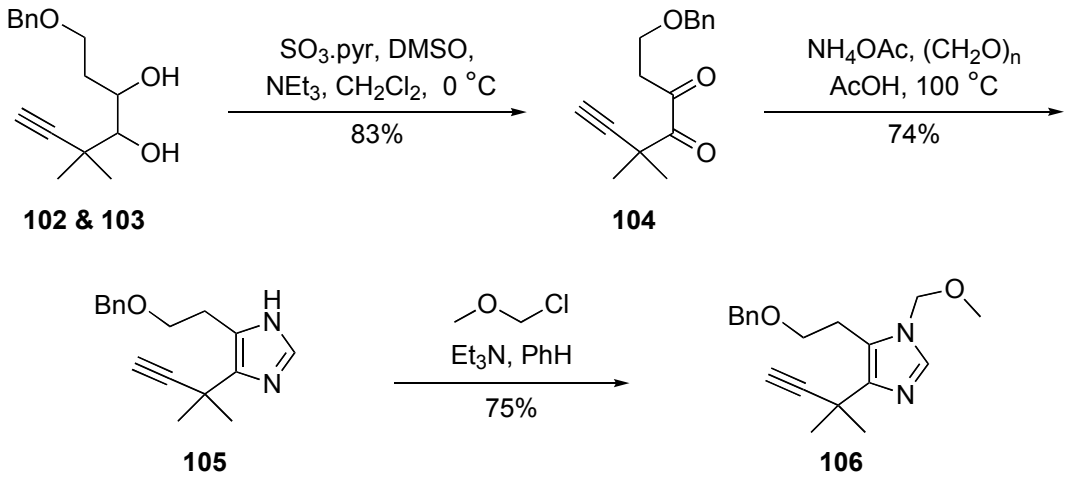
Conversion of the ester to an alkyne was most successfully accomplished in a three-step process (Scheme 2. 10). Reduction with LAH followed by oxidation of the crude alcohol with DMP provided separable aldehydes *trans*-**99** and *cis*-**99** in an approximately 1 : 7 ratio. The homologation of the aldehydes was achieved with the Ohira[16, 17] reagent (**100**). Attempts at the utilization of the two-step Corey-Fuchs protocol for the conversion of aldehydes to alkynes were less successful. Treatment of the aldehydes **99**, carried out as a mixture of olefin isomers in MeOH with K_2CO_3, with the Ohira reagent **100** furnished the terminal alkyne **101** as a mixture of internal olefin isomers in 96% yield.



Scheme 2. 10: Synthesis of diols *trans*-**102** and *cis*-**103**

Dihydroxylation of the internal olefin yielded the diastereomeric diols *trans*-**102** and *cis*-**103** in approximately a 1 : 7 ratio, suggesting that no isomerization occurred during the homologation or dihydroxylation. When potassium osmate dihydrate was employed as the catalytic oxidant, as opposed to OsO_4, the diols could be obtained in a quantitative yield (in all examples NMO was used as the stoichiometric oxidant).

To prepare the 1,2-diketone, the direct precursor to an imidazole, oxidation of the diol was undertaken. In this case, it was found to work most efficiently with SO_3•pyr in DMSO to give an 83% yield of the α-dicarbonyl **104** as a bright yellow oil, diagnostic of this functional group (Scheme 2. 11). With the diketone in hand, conversion to the imidazole[18] was next. To accomplish this, a nitrogen source, an aldehyde source and an acid were necessary. After screening conditions, the use of NH_4OAc, paraformaldehyde, and acetic acid (as solvent) were determined for use. Heating of the α-dicarbonyl to 100 °C in the presence of these reagents provided imidazole **105** in 74% yield. It is worth noting that the reaction, even under these optimized conditions, behaved capriciously. While the yield of product was found to be inconsistent, the reaction always gave a separable mixture of the starting dione **104**, which could be recycled, and the product imidazole **105**.



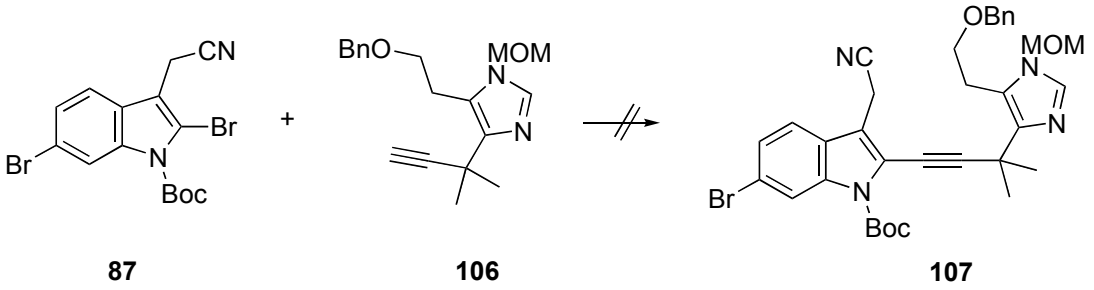
Scheme 2. 11: Synthesis of imidazole **106**

Protection of the imidazole **105** as its methoxymethyl (MOM) aminal, performed with MOMCl in benzene, provided imidazole **106** in 75% yield. Thus, with a synthesis of an imidazole acetylene **106** accomplished, its ability to couple with the indole was investigated.

2.3.2. Unsuccessful Coupling

Application of the previously established conditions (*vide supra*) for the Sonogashira coupling[1] of indole **87** were utilized in the coupling of imidazole **106**. Disappointingly, no product **107** was observed (Scheme 2. 12). At mild temperatures (20 °C to 45 °C), as in the conditions used for simpler alkynes, no reaction occurred and the starting materials were returned (the indole **87** could be recovered quantitatively). Warming of the reaction only led to complex mixtures of products, with no evidence of the desired coupling product. It appeared that temperatures nearing and above 100 °C led to decomposition of the indole, either through loss of the *N*-Boc or reduction of the 2-Br

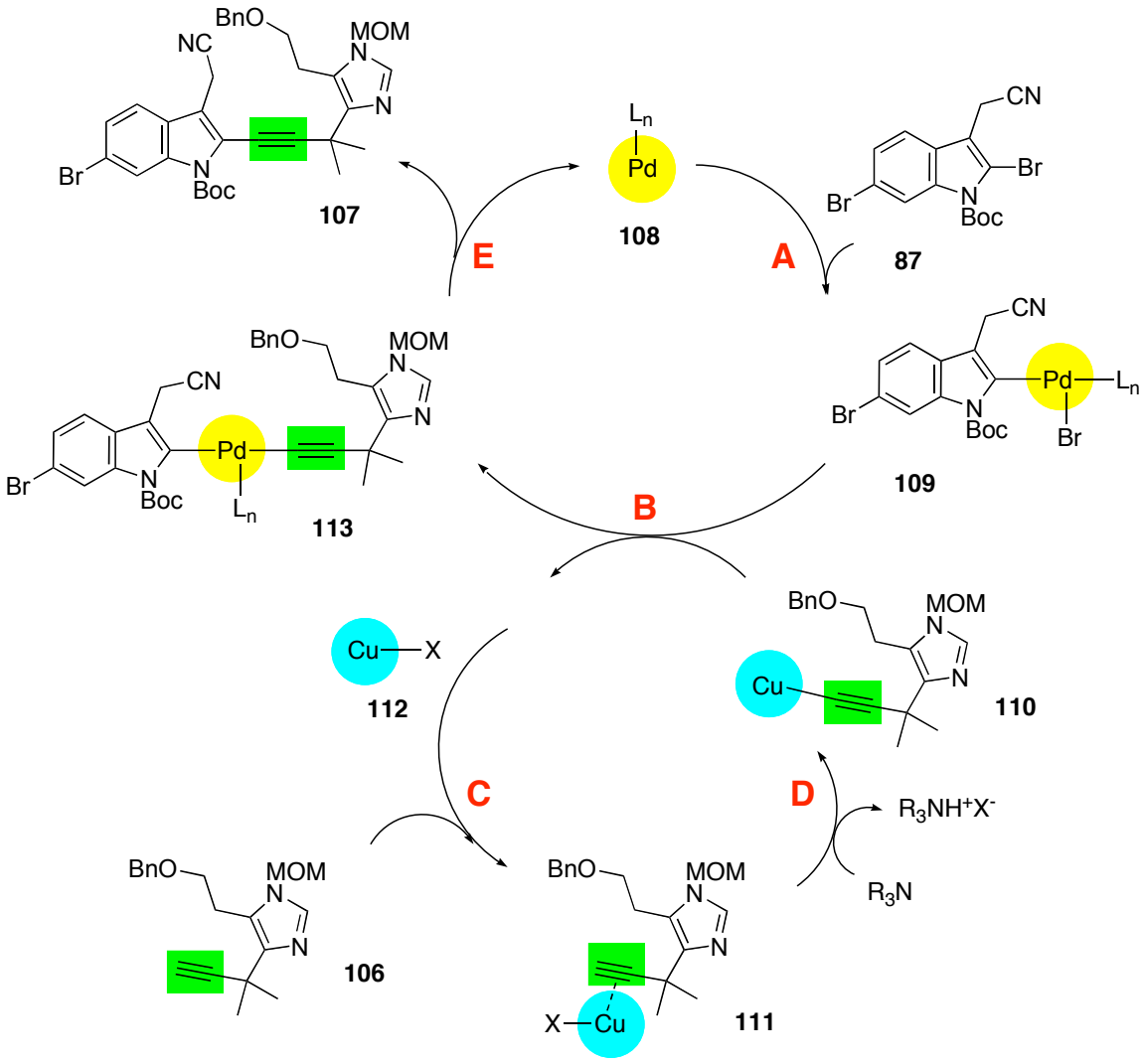
to a 2-H. Additionally, the use of different solvents, amine bases, or Pd sources [$Pd_2(dba)_3$, $Pd(PPh_3)_4$, $Pd(OAc)_2$, and Pd/C] resulted in similar reaction failures.



87 **106** **107**

Scheme 2. 12: The attempted imidazole Sonogashira coupling

The mechanism of the Sonogashira coupling is shown (Scheme 2. 13). The possibly of a 2-H indole product being formed was encouraging. It implied Pd insertion was occurring (**A**, Scheme 2. 13). The ability of a generic Pd catalyst **108** to insert into **87**, forming intermediate **109** (not isolated) meant that the transmetalation of the Cu-acetylide to Pd (**B**) was not taking place, as the ensuing reductive elimination (**E**) is generally considered fast. The lack of transmetalation was surprising, in that it clearly was not an issue for simpler terminal acetylenes, including those with similar steric congestion adjacent to the alkyne. This would limit the possibilities of problems to either the formation of the copper acetylide (**C** or **D**) or in its ability to transmetalate to Pd (**B**).



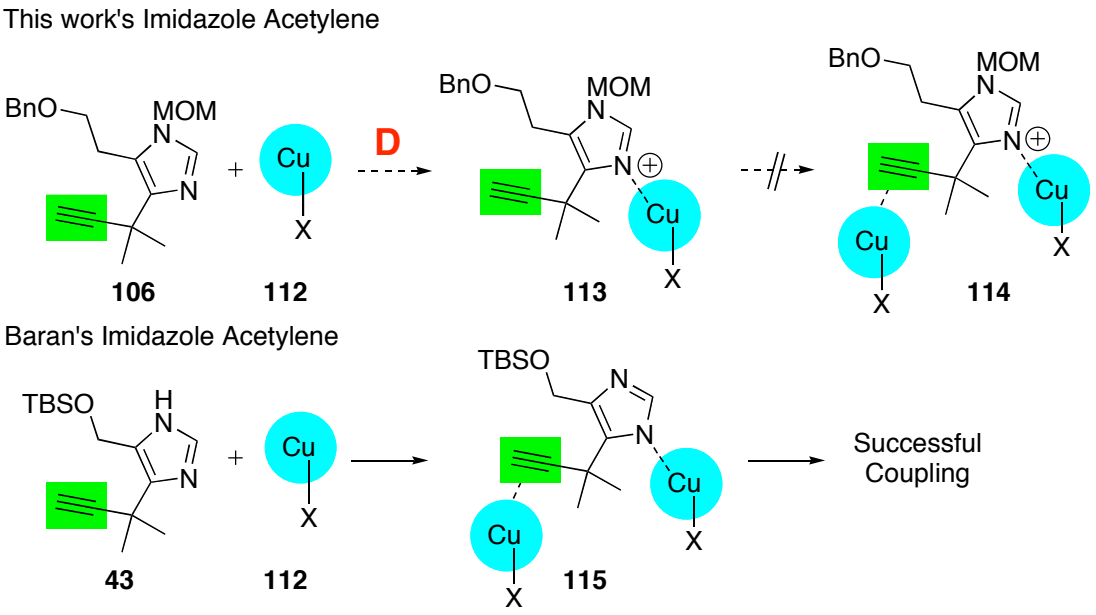
Scheme 2. 13: Mechanism of the attempted Sonogashira coupling of **106** and **87**

In order for the copper acetylide **110** to form, pre-coordination of the Cu(I) salt to the acetylene (**111**) must occur (**C**). The ability of Cu (**112**) to coordinate **106** or the ensuing deprotonation of the alkyne H (**D**) to give **110** seemed the most likely causes.

While there are many examples of Sonogashira coulings where the aryl halide is an imidazole, there are few examples where the acetylenic partner contains an imidazole. We reasoned that the existence of the imidazole *N*-3 might be shutting the reaction off as

this seemed the most obvious structural difference between those couplings discussed herein (*vide supra*, Scheme 1. 8) that worked and those that did not. Either the Cu(I) was bound by the *N* (**113**) and therefore not forming the copper acetylide–which forms *via* initial coordination of the alkyne to the CuI (**114**)–or the copper acetylide was bound by the *N* (dimerized) and therefore unable to transmetalate (Scheme 2. 14). The formation of a imidazolium-copper species **113** may be invoked in either case. This species would be expected to be higher in enegy than the normal copper acetylide and may decompose in an undetermined way. Alternatively, the coordination and formation of an imidazolium **113** could increase the energy necessary for copper to insert into the alkyne C-H bond.

The use of excess CuI, either in the presence of Pd or absence (Castro-Stephens type coupling[19]) did not meet success. These results were made especially troubling by the eventual disclosure by Baran (*vide supra*) of a similar Sonogashira couplings[23, 24] success, reported a year after this approach was abandoned. The conditions disclosed in Baran's report were attempted with our substrates and yet we still had no success with an imidazole acetylene. The conspicuous difference between their successful substrate **43** and our attempted substrate **106** was the absence of a protecting group on the imidazole *N*. The pathway that possibly led to the failure in our case, would not present such a hindrance in theirs. The copper-imidazolium species could lose a proton forming **115**, which is not charged and formation of the copper-acetylide should therefore be relatively unaffected. Owing to these failures, it was decided to look into alternative coupling partners.



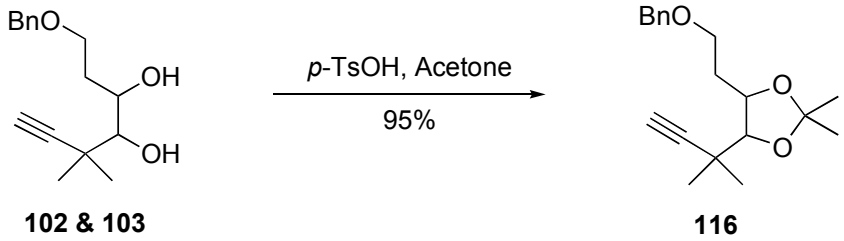
Scheme 2. 14: Possible Problems in Copper Acetylide Formation

2.4. AN ALTERNATIVE IMIDAZOLE SOURCE

2.4.1. First Generation Alternative Coupling Partner

The hypothesis that the presence of a pyridine-like nitrogen was disabling the Sonogashira coupling from occurring led us to pursue an alternative strategy. The options were to pursue an alternative coupling strategy that would be amenable to the imidazole acetylene **106** or pursue an alternative coupling partner that could utilize the already established coupling conditions. The convergent assembly of an acetylenic imidazole precursor and the indole **87** seemed attractive.

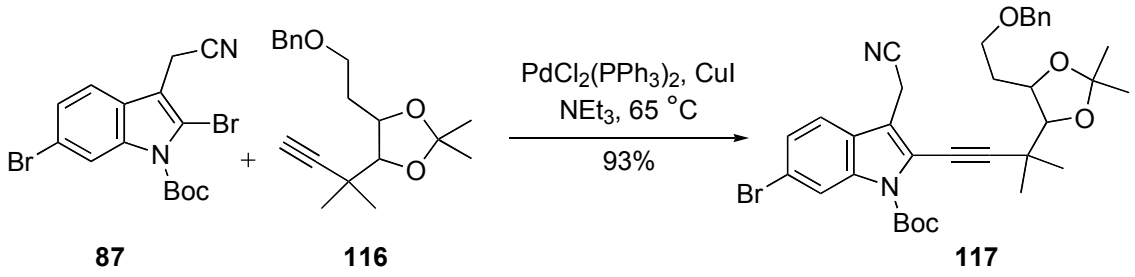
A protected diol was first examined as a substrate. A mixture of diols *trans*-**102** and *cis*-**103** were protected as their 1,2-acetonide **116** by stirring in acetone with catalytic *p*-TsOH in 95% yield (Scheme 2. 15). The acetonide was chosen as a diol protecting group due to its ease of attachment and removal,[20] and the supposed orthogonal relationship with the other protecting groups.



102 & 103 **116**

Scheme 2. 15: Protection of diols **102** and **103**

The key test was in the ability of acetonide **116** to undergo the Sonogashira coupling. In fact, treatment of indole **87**, in the presence of $PdCl_2(PPh_3)_2$, CuI, in triethylamine, with acetonide acetylene **116** produced the desired coupling product **117** (Scheme 2. 16). By heating the reaction to 65 °C, a 93% yield of coupled product **117** could be obtained.



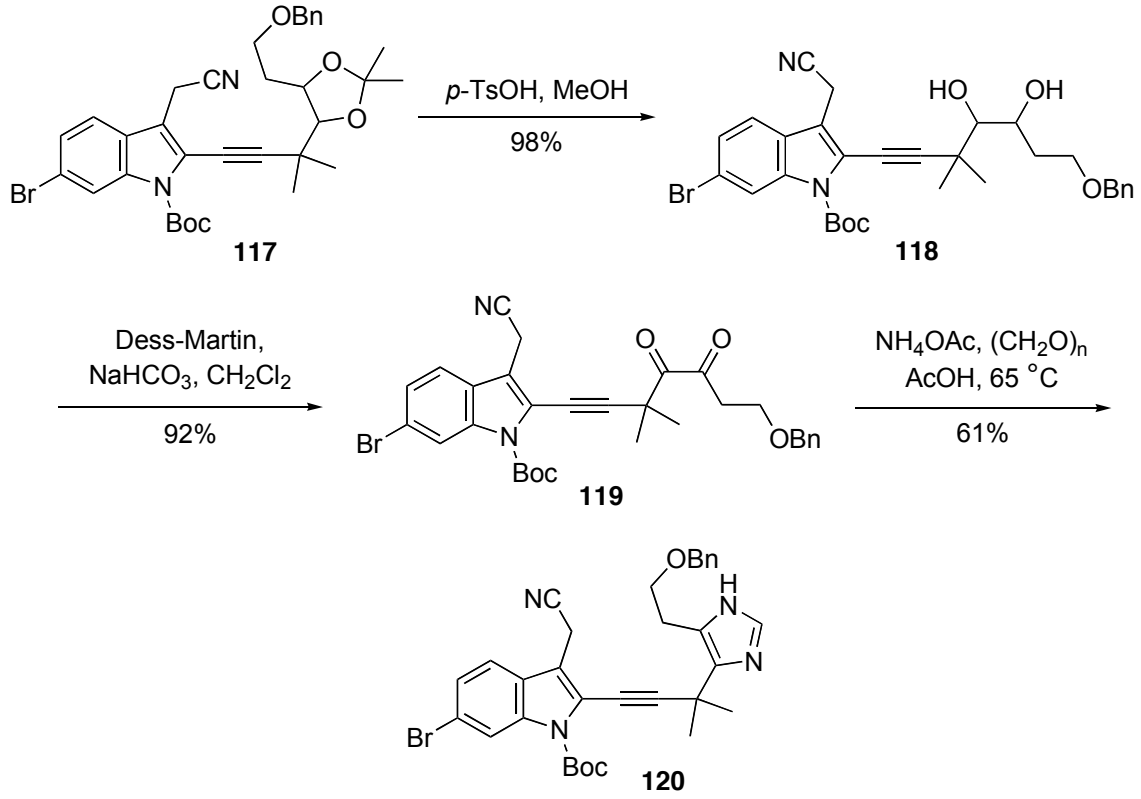
87 **116** **117**

Scheme 2. 16: Acetonide **116** in the Sonogashira coupling

With the successful coupling of indole **87** and acetonide **116**, the objective was to advance the 1,2-acetonide in **117** to an imidazole as in **107**. Removal of the 1,2-acetonide in **117** was achieved mildly by transketalization with MeOH and *p*-TsOH (Scheme 2. 17). The deprotected diol **118** could be obtained near quantitatively (98%) *via* this route. The direct coupling of diols **102** and **103** were successful, albeit in lower yields. It was found to be more efficient to prepare the acetonide, couple it with the indole, and remove the acetonide (87% over three steps) than the direct coupling of the diols (42%). These successful reactions furthered the assumption that the Sonogashira coupling was simply incompatible with our imdiazole acetylene and so this route was further explored.

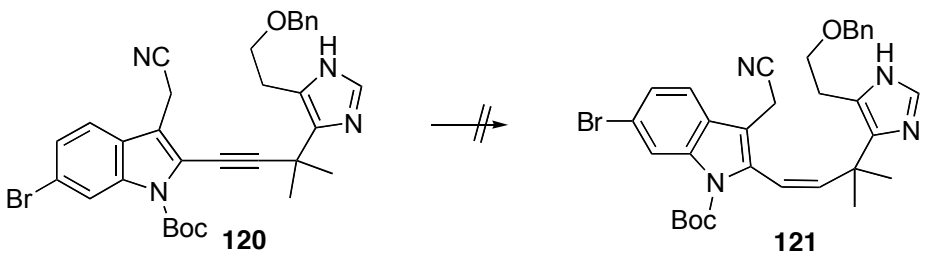
The coupled diol **118** was oxidized to the 1,2-dicarbonyl **119** using Dess-Martin periodinane (Scheme 2. 17). Strangely, while the Dess-Martin reagent was used (*vide supra*) on the uncoupled substrates in lower yielding reactions, the SO_3•pyr and DMSO conditions proved less effective in this case. In any event, the α-dicarbonyl **119** was submitted to the imidazole forming conditions and was degraded by them. However, lowering the temperature of the reaction from 100 °C to 65 °C produced an acceptable yield of 61% of the imidazole **120**. The decomposition of the dione **119** is believed to

arise from the loss of the *N*-Boc on the indole under the acidic conditions. This should be facile, and the resultant unprotected indole might then decompose *via* a gramine-like intermediate (*vide infra*, Scheme 2. 31).



Scheme 2. 17: Advancement of acetonide **117** to indole **120**

With the desired indole imidazole compound **120** in hand, the reduction of the acetylene to a *cis*-olefin was examined (Scheme 2. 18). Initial attempts, using *in situ* generated diimide, returned the starting acetylene unchanged. Hydrogenations with Lindlar's catalyst, Pd on $BaSO_4$, and PtO_2 failed to give the desired product. Hydrogenations with Pd/C or Raney Ni returned complex mixtures of products, probably resulting from hydrogenolysis of the benzyl ether and loss of the aromatic bromide.

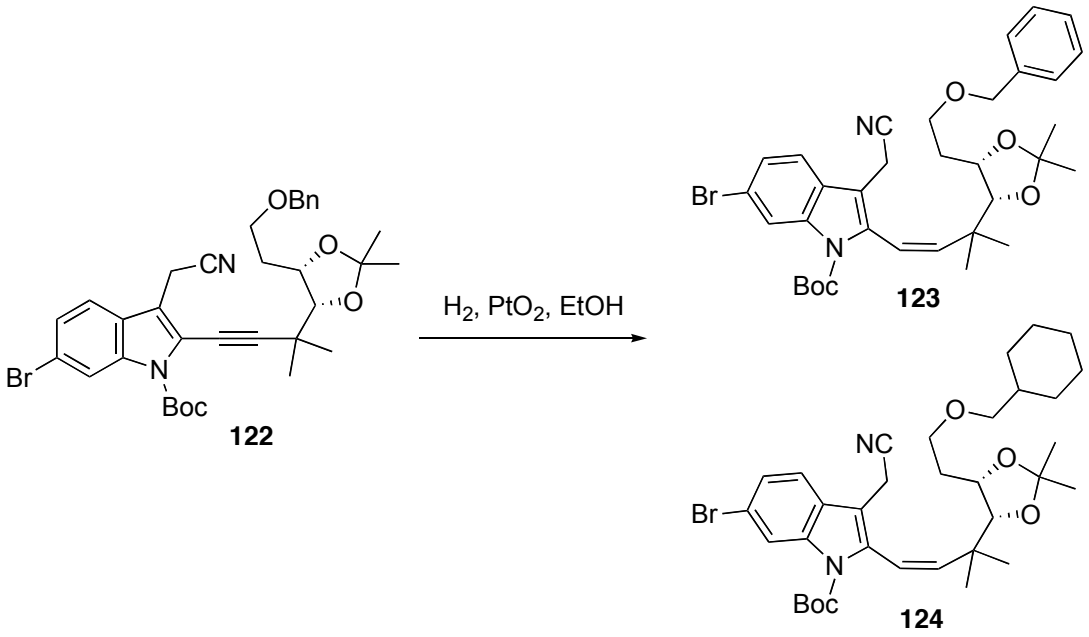


Scheme 2. 18: The unsuccessful hydrogenation of acetylene **121**

In a desire to screen conditions for olefin formation without aromatic bromide loss, acetonide **122** was hydrogenated (Scheme 2. 19). Still, the mild diimide reductions failed. Screening of catalytic hydrogenations resulted in similar trends as observed in the imidazole series. Lindlar's catalyst, Pt/C, Rh/C and Pd on $BaSO_4$ were apparently too mild as they returned the alkyne unchanged. Raney Ni returned a mixture of olefinic compounds, but the aromatic bromide was clearly lost. The use of Pd/C also gave olefinic products, though it appeared that the aromatic bromide and benzyl ether had been lost. Fortunately, PtO_2 (Adam's catalyst) was found to deliver the *cis*-olefin **123**. Unfortunately, the reaction was exceedingly slow, and was unable to be driven to completion cleanly. After lengthy reaction times, an undesirable overreduction appeared. Cyclohexyl **124** was obtained as the major product when the starting material was completely consumed.

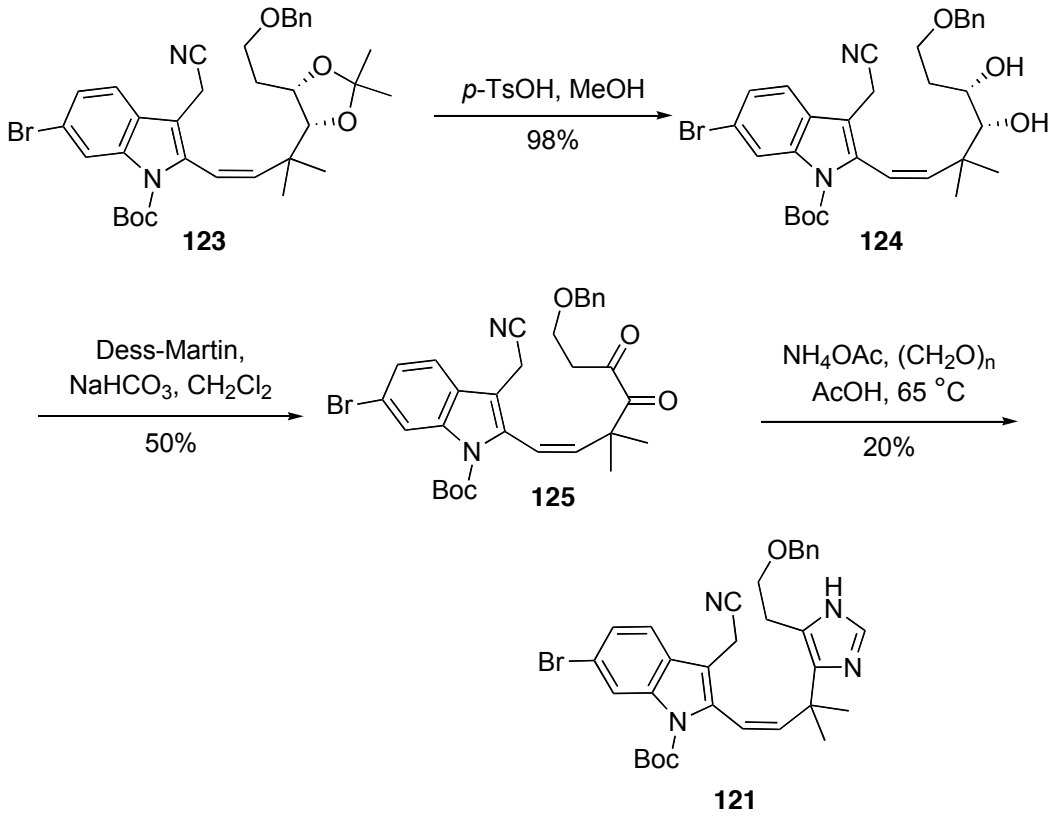
While PtO_2 is known to be resistant to hydrogenolytic removal of benzyl ethers, its use as an aromatic hydrogenation catalyst is known. Further complicating matters, the alkyne and *cis*-olefin were inseparable, and the reaction could only be monitored by ^1H NMR analysis of worked-up aliquots. In fact, it seems the cyclohexyl product **124** was formed from the *cis*-olefin product **123** as no cyclohexyl alkyne species were ever observed. The existence of **124**, while separable from the mixture of starting alkyne **122**

and olefin **123**, presented a problem as the selective removal of the cyclohexylmethylenoxy ether would be extremely difficult.



Scheme 2. 19: The hydrogenation and over-reduction products

In any case, with *cis*-olefin **123** in hand, its advancement to imidazole **121** was explored (Scheme 2. 20). Again, removal of the acetonide was facile, yielding 98% of the diol **124**. The diol was oxidized, using the Dess-Martin periodinane, for a 50% yield of dione **125**. The imidazole **121** could then be formed under the same conditions as before in a modest 20% yield.



Scheme 2. 20: Synthesis of indole-imidazole **121**

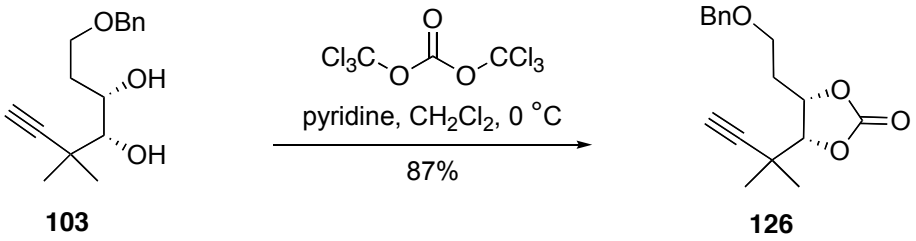
2.4.2. Second-generation coupling partner

The use of a benzyl ether had become a hindrance to the synthesis of chartelline C **3**. As such, an alternative was sought that would be easily removable, yet robust enough for the protocol established thus far. With a high-yielding, scalable route to *O*-benzyl ether diols **102** and **103** established, and a moderate quantity in hand, the alternative protecting group investigation started here.

Initially, removal of the benzyl ether from coupled acetonide **117** was considered. As the incompatibility of hydrogenolysis to the substrate had been established, lewis acids BCl_3 and BBr_3 were tried. However, it appeared that acetonide deprotection

occurred quicker than benzyl ether cleavage. Therefore, an alternative to the acetonide that might allow for benzyl ether cleavage after coupling to the indole was sought.

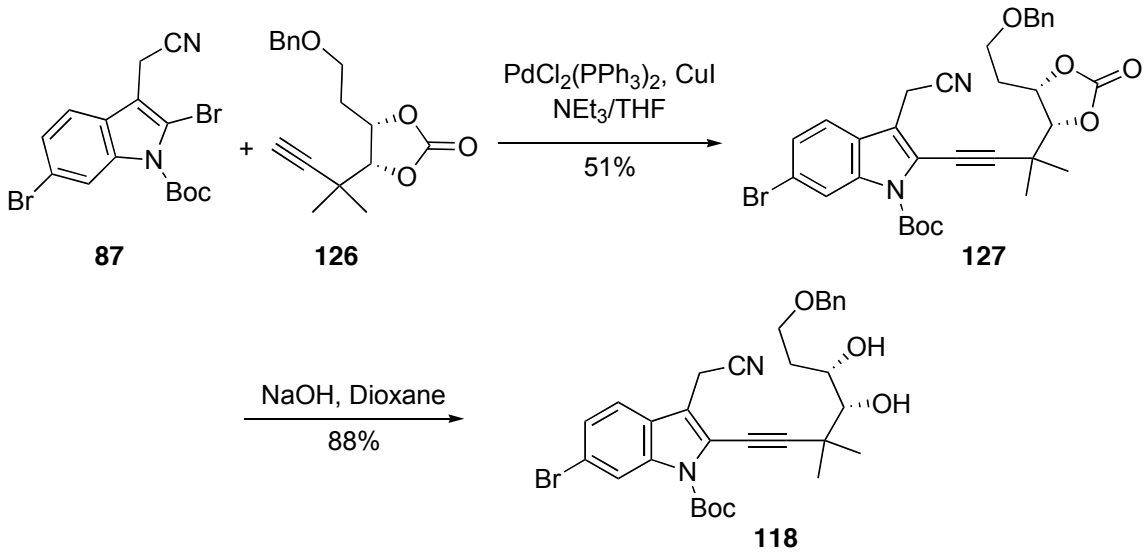
Protection of the early diol intermediate **102** as its 1,2-carbonate **126** was carried out (Scheme 2. 21). Treatment of diol **102** with triphosgene provided the carbonate **126** in 87% yield.



103 **126**

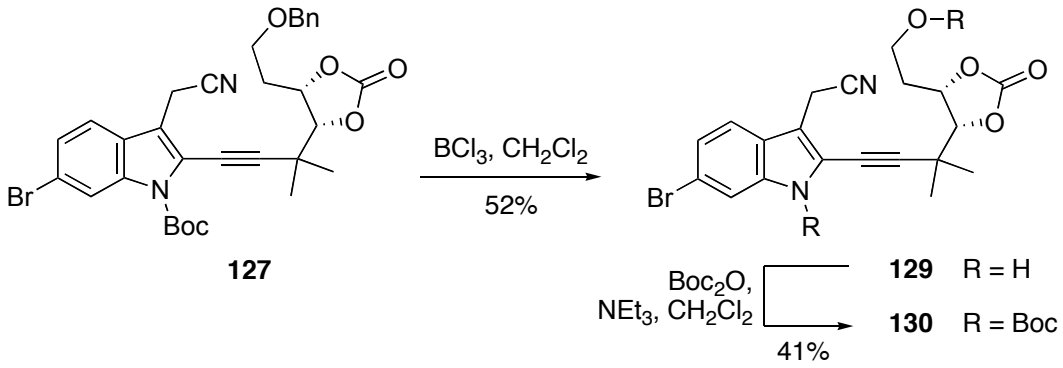
Scheme 2. 21: Carbonate **126** synthesis

The inherent substrate differences associated with the Sonogashira couplings of indole **87** gave us pause with respect to changing from acetonide **116** to carbonate **126**. Gratifyingly, the carbonate had no effect on the coupling's success, and was able to be performed at room temperature without addtional warming(Scheme 2. 22). The reaction of indole **87** and carbonate **126** with $PdCl_2(PPh_3)_2$ and CuI gave coupled alkyne **127** in 51% yield. With the coupled carbonate alkyne **127** in hand, it was worthwhile investigating the removal of the carbonate, as its orthogonal cleavability was essential to the approach. This was achieved mildly with NaOH (aq.) in dioxane to provide diol **128**, identical to that previously synthesized.



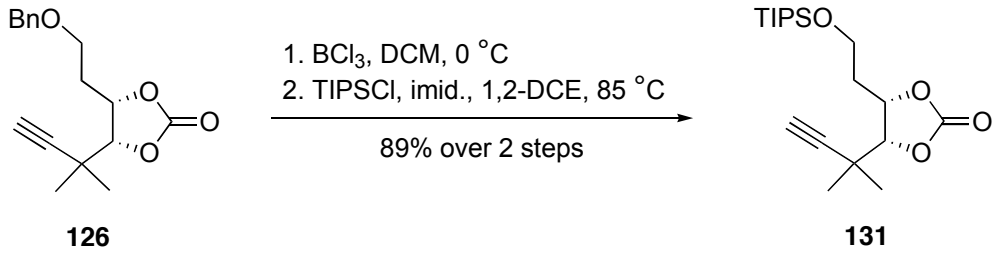
Scheme 2. 22: The coupling of carbonate **126** and indole **87**

Removing the benzyl group while leaving the molecule otherwise intact, however, proved difficult. Treatment of benzyl carbonate compound **127** with BCl_3 (Scheme 2. 23) cleaved the benzyl group but also cleanly removed the *N*-Boc, in the process giving *N*-H indole **129** in 52% yield. None of the desired alcohol, with the *N*-Boc intact, was observed. Attempts to reinstall the *N*-H Boc on the indole returned the bis-Boc product **130** in 41% yield. It seems that exchange of the benzyl group would be best accomplished earlier in the synthesis.



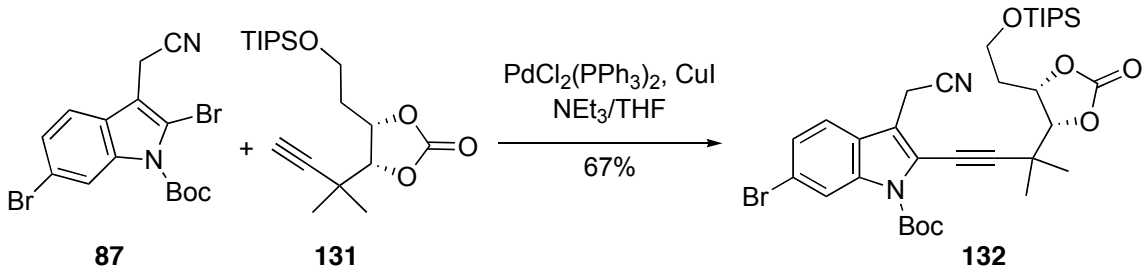
Scheme 2. 23: Attempted benzyl ether cleavage

The viability of a carbonate in the synthesis having been established, the problem of the benzyl ether could be addressed. The choice of silyl ether as protecting group was chosen because they are inert to catalytic hydrogenation and are generally easy to remove upon treatment with fluoride. Therefore, the benzyl ether in carbonate **126** was converted to the triisopropylsilyl ether carbonate **131** in a two-step process and 89% overall yield (Scheme 2. 24).



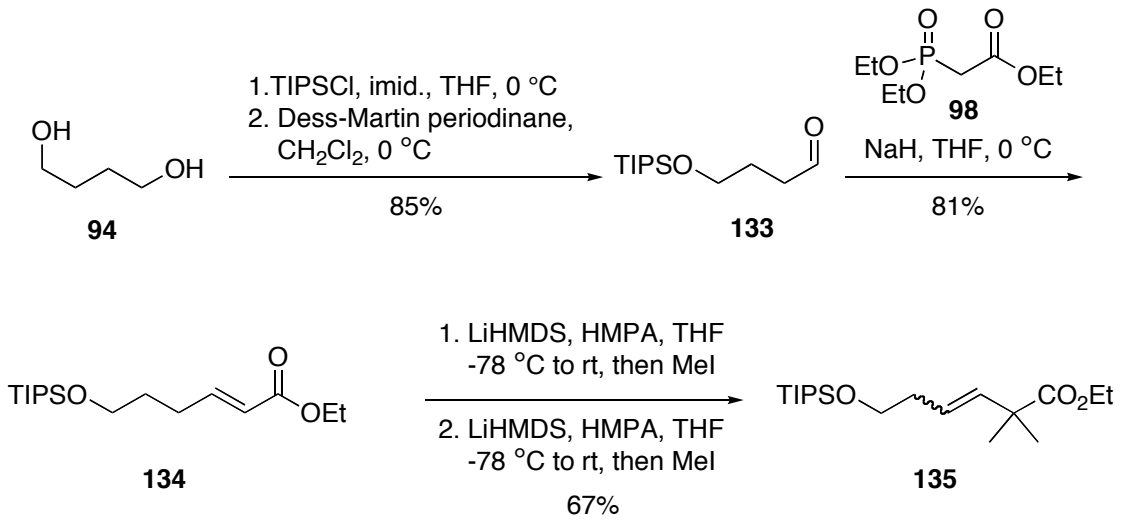
Scheme 2. 24: Carbonate **131** Synthesis

The triisopropylsilyl carbonate **131** was now used in the coupling with indole **87** producing alkyne **132** in 67% yield (Scheme 2. 25).



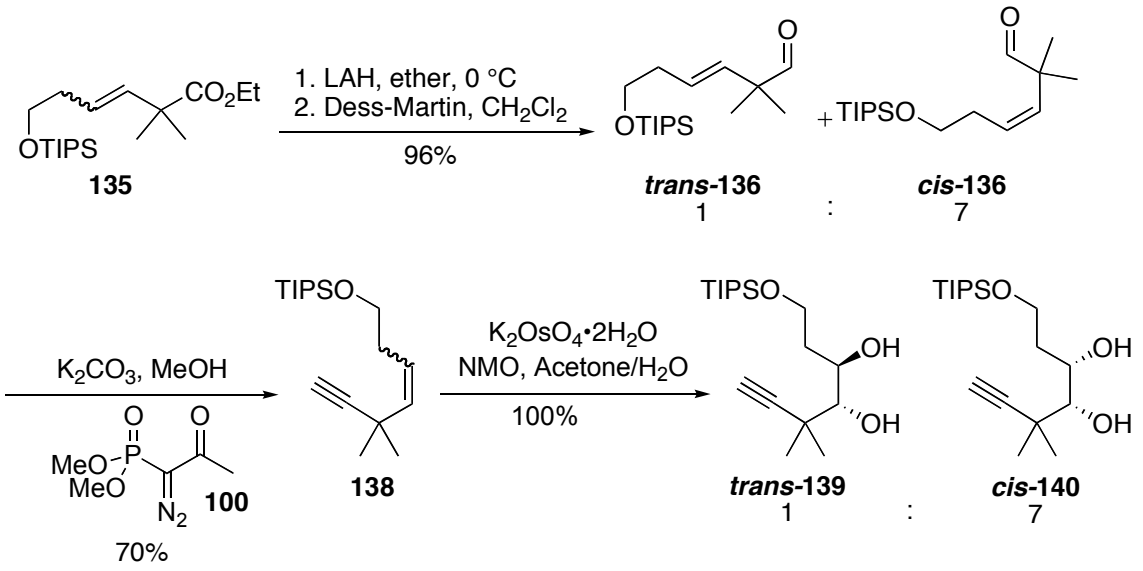
Scheme 2. 25: Coupling of carbonate acetylene **131** and indole **87**

Having shown the capability of the TIPS-carbonate **131** to perform the Sonogashira coupling, the synthesis of **131** from 1,4-butanediol **94** was carried out. The work commenced with the protection of 1,4-butanediol **94** as its mono-silyl ether **i**n 89% yield (Scheme 2. 26). Oxidation of the primary alcohol to the aldehyde **133** was once again best 96% performed with the Dess-Martin periodinane[15] (DMP) as an oxidant. The Horner-Wadsworth-Emmons reaction of the aldehyde with the same phosphonate as before gave α,β-unsaturated ester **134** in 81% yield. The deconjugative alkylation of α,β-unsaturated ester **134** was operated in a step-wise fashion without optimization to a one-pot process to provide the dialkylated **135** in 67% after the two reactions.



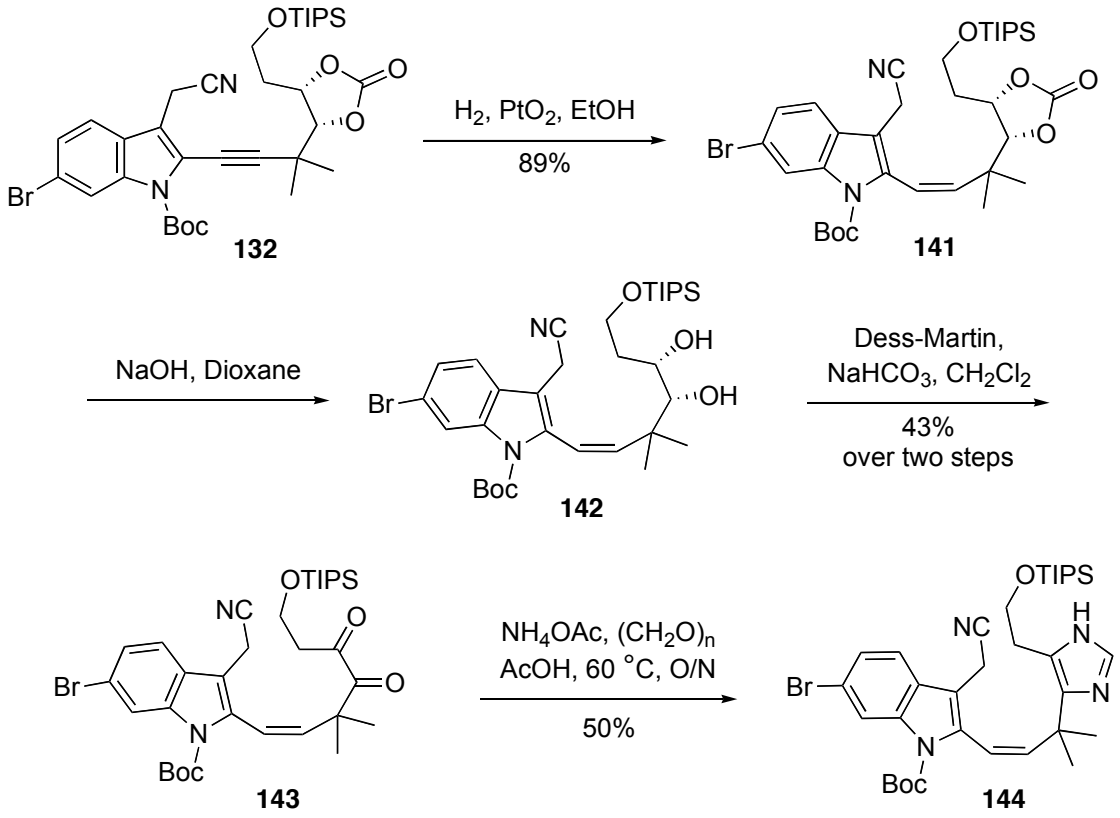
Scheme 2. 26: Synthesis of ester **135**

Conversion of the ester **135** to alkyne **138** was again accomplished in a three-step process (Scheme 2. 27). Reduction with LAH followed by oxidation of the crude alcohol with DMP provided separable aldehydes *trans*-**136** and *cis*-**136** in an approximately 1 : 7 ratio and 96% yield over the two steps. The subsequent homologation of the aldehydes was achieved with the Ohira reagent **100**, providing the alkyne **138** in 70% yield. Dihydroxylation of the internal olefin with potassium osmate dihydrate yielded the TIPS diols *trans*-**139** and *cis*-**140** in approximately 1 : 7 ratio. Interestingly, the *cis*-**140** is obtained as a white solid while the *trans*-**139** exists at room temperature as a colorless oil. In any event, treatment of the diols with triphosgene provided the carbonate **131** spectroscopically identical to that produced before.



Scheme 2. 27: Carbonate diol synthesis

With a more straightforward approach to the synthesis of alkyne **131** established, our attention returned to the coupled carbonate **132**. Hydrogenation of the alkyne **132** to the *cis*-olefin **141** proceeded well using the PtO_2 protocol (89%) (Scheme 2. 28). The carbonate was removed using NaOH (aq.) in dioxane and the crude diol **142** was oxidized using the Dess-Martin reagent for a 43% yield of dione **143** over two steps. The dione **143** could then be converted to the imidazole **144** as before. The product obtained, imidazole **144**, consisted of all the carbon's present in the natural product, chartelline C (**3**).



Scheme 2. 28: Synthesis of imidazole **144**

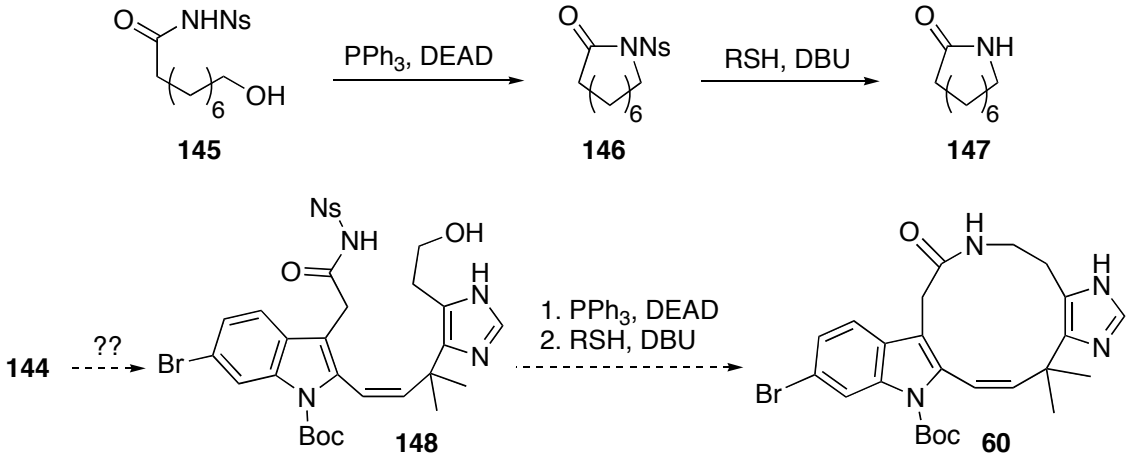
With a compound composed of all of the carbons in the chartelline, securamine, and securine skeletons, the formation of a securine-like macrolactam was the next objective. As the original synthetic strategy was to assemble the lactam bond *via* an intramolecular peptide coupling, necessitating an acid and amine, a re-evaluation was in order. It seemed at the time, counter-productive to install a *N* by converting the silyl ether to an amine, while removing the nitrogen of the nitrile by hydrolyzing it to an acid. Therefore, an alternative macrolactamization strategy was envisaged.

2.5. MACROLACTAMIZATION STRATEGIES

2.5.1. Nitrile to amide hydration

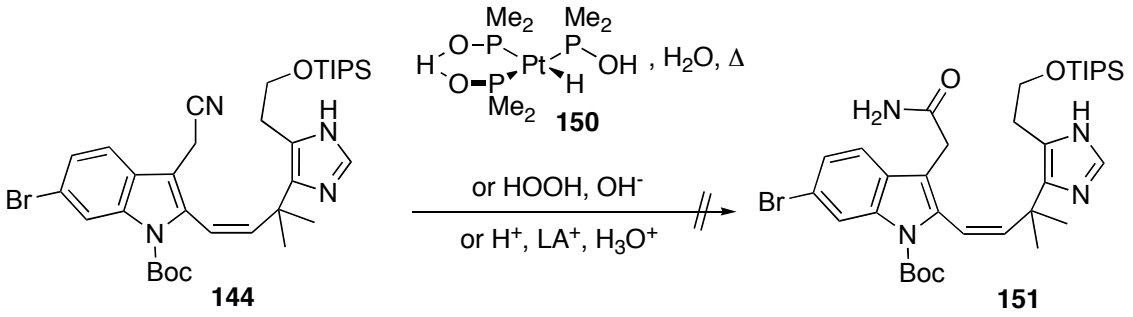
The indole-imidazole compound **144** was a starting point for investigation of macrolactamization strategies. The compound **144** includes an acetonitrile moeity and with a nitrogen already installed, it seemed counter-productive to attempt to remove that nitrogen only to replace the primary triisopropylsiloxy group with an amine to effect the peptide coupling. In an effort to maintain a straightforward approach hydrolysis of the nitrile to an amide[21] was examined.

Two main options were available starting from nitrile **144**. The first, more direct route would be based on the methods developed by Fukuyama,[22, 23] where the lactam **146** and **147** is formed *via* the intramolecular Mitsunobu reaction of an *N*-Ns amide **145** (Scheme 2. 29). This would require the conversion of the nitrile **144** to an *N*-Ns amide **148** and the unmasking of the primary alcohol.



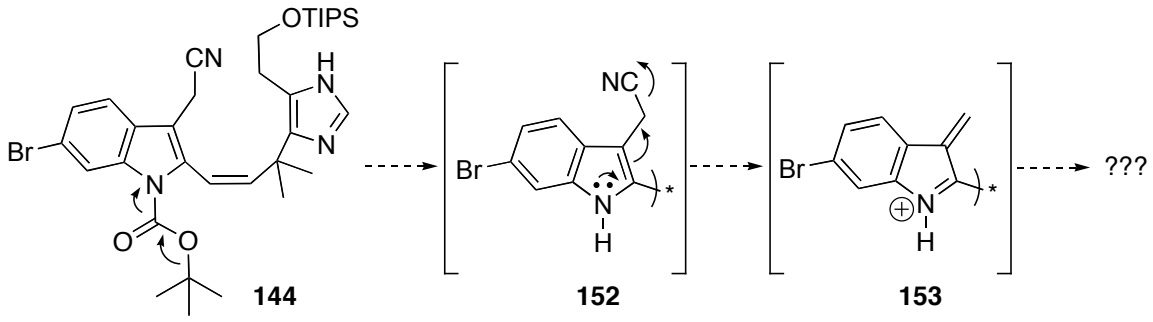
Scheme 2. 29: Fukuyama's macrolactamization and possible application

To achieve the proposed amide intermediate incompatible **148**, hydration of the nitrile was examined. Initially, the classical conditions using basic hydrogen peroxide were explored (Scheme 2. 30). These experiments resulted only in intractable mixtures which clearly exhibited the loss of the *N*-Boc group and showed no evidence of amide formation as determined by IR and ^{1}H NMR spectroscopic analysis of the crude isolates. Catalytic hydration of the nitrile using the homogeneous Pt catalyst **150** developed by Parkins[24, 25] was equally unfruitful. No reaction occurred at ambient temperature and as the reaction was warmed to reflux–the literature conditions call for refluxing in water–decomposition of the starting material was observed. Once again, loss of the *N*-Boc was implicated as the quickest reaction pathway accessible to starting material **144**.



Scheme 2. 30: Failed nitrile hydration

While no indole *N*-H compounds were ever isolated, the lack of the 9H singlet in ^{1}H NMR spectra of the crude reaction products was conspicuous. The loss of the *N*-Boc was not completely unexpected in that *N*-Boc indoles are labile comparably to other *N*-Boc amines. From an *N*-H indole **152** intermediate, decomposition possibly goes through gramine-like pathways **153** (Scheme 2. 31).



Scheme 2. 31: Possible pathways to the decomposition of **144**

2.5.2. Nitrile to acid hydrolysis

Considering the failure of nitrile to amide conversion route, the prospect of a successful acidic hydrolysis seemed less likely. However, acidic hydrolysis was attempted and, not surprisingly, was met with similar failures.

The nitrile **144** was subjected to a variety of Brönsted and Lewis acids in attempts to access either an acid, amide, or imidate. Any non-nitrile product would have, at this point, been deemed a success and the macrolactam strategy would have been adjusted accordingly. Unfortunately, all attempts at the acidic hydrolysis of the nitrile **144** were either too mild, returning starting material, or were too harsh, yielding intractable mixtures.

After these results, the unpleasant conclusion that the nitrile was incompatible with our synthetic strategy was reached. The assumption made early on, that the indole-3-acetonitrile was amenable to our synthetic approach to the synthesis of chartelline C, had been proven false.

2.6. CONCLUSIONS

Studies towards the total synthesis of the complex and unusual marine alkaloid chartelline C **3** were undertaken. The hypothesis that the spiro-β-lactam present in the natural product could be assembled from a suitable macrolactam along a supposed biomimetic pathway guided our synthetic approach. The proposed macrolactam was the intermediate of specific interest as its skeleton resembles that of the natural product securine, implicated in the biosynthesis of chartelline C **3**.

The macrolactam was attempted to be made *via* the convergent assembly of an indole and imidazole acetylene fragments. A 2,6-dibromoindole **87** was coupled selectively to an acetylenic imidazole precursor **131** and was advanced to an indole-imidazole compound **144** containing all of the carbons of the natural products securine and chartelline C **3** was accomplished. The macrolactamization was investigated next

However, it was while this work was progressing that the total synthesis of chartelline C was reported by Baran and co-workers. In view of the inevitable similarity in the possible conversion of **144** into **60**, and hence into chartelline C **3**, to Baran's work, it was decided to discontinue any further work in the area.[26]

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Chapter 3: Experimental Section

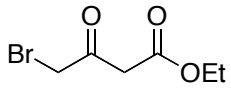
3.1 General Methods.

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet FT-IR spectrophotometer neat unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer at 300 MHz and 75 MHz, respectively and are reported in ppm relative to tetramethylsilane. All NMR spectra were taken with $CDCl_3$ as solvent unless otherwise noted. Mass spectra were obtained on a VG ZAB2E or a Finnigan TSQ70. TLC was performed on glass sheets precoated with silica gel (Silica Gel 60, F254, 0.25mm Layer Thickness). Column chromatographic separations were performed on silica gel (Silica gel 60, 230-400 mesh) under pressure. Solvents and commercial reagents were purified in accordance with Perrin and Armarego or used without further purification.

All moisture sensitive reactions were performed under an atmosphere of Ar, and glassware was pre-dried at 125 °C prior to use. THF and ether were dried by distillation over Na/benzophenone, CH_2Cl_2, Et_3N, CH_3CN, and *i*-Pr_2NH were dried by distillation from CaH_2. All other reagents or solvents were used as received without further purification unless otherwise stated.

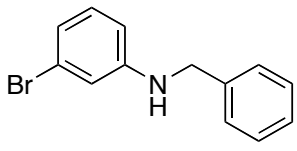
3.2. EXPERIMENTAL CONDITIONS AND CHARACTERIZATIONS

Ethyl 4-bromo-3-oxo-butyrate (72):



Bromine (5.1 mL, 0.1 mmol) was added slowly to a solution of ethyl-3-oxobutanoate (12.7 mL, 0.1 mol) in chloroform (90 mL) over 1 hour. The reaction was stirred at room temperature for 15 hours. Nitrogen gas was then bubbled into the mixture for 2 hours to remove the excess hydrogen bromide. Water (100 mL) was added to the reaction mixture, and the organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The sample was purified by flash-column chromatography (10% EtOAc in hexanes) to give bromide[1,2] **72** (16.59 g, 79 %) as a light-brown oil whose spectral data matched that previously reported: IR (thin film) 1712, 1636 cm^{-1}; ^1H NMR δ 1.30 (t, 2H), 3.72 (s, 2H), 4.05 (s, 2H), 4.22 (q, 3H); ^{13}C NMR δ = 194.4, 166.4, 61.6, 45.8, 33.7, 13.8.

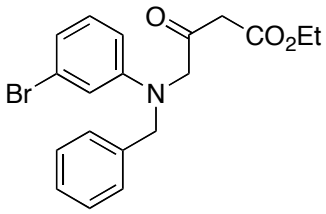
Benzyl-(3-bromo-phenyl)-amine (71):



4-Bromoaniline (6.4 mL, 58.1 mmol) and benzaldehyde (6.0 mL, 59.3 mmol) were dissolved in 1,2-dichloroethane (250 mL). To this solution was added glacial acetic

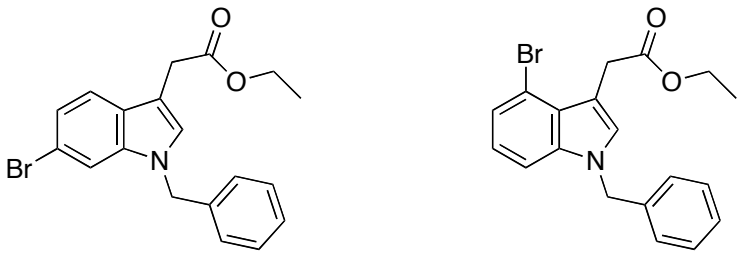
acid (3.6 mL, 62.2 mmol) and sodium trisacetoxyborohydride (16.02 g, 75.6 mmol). The mixture was stirred at room temperature for 18 hours, acidified with 1 N HCl (100 mL) and then neutralized with 4 M aq. NaOH (25 mL). The aqueous layer was extracted with dichloromethane (4 x 50 mL). The combined organic layers were washed with water (150 mL), brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo to give benzyl aniline **71** (14.94 g, 98 %) as a yellow oil whose spectral data matched that previously reported.[3]

Ethyl 4-(*N*-benzyl-*N*-(3-bromophenyl)amino)-3-oxobutanoate (73):



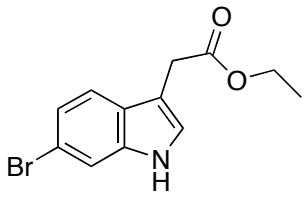
Aniline **71** (9.94 g, 38.0 mmol), bromide **72** (2.66 g, 12.7 mmol) and tetrabutylammonium iodide (0.47 g, 1.27 mmol) were stirred at 40 ºC for 18 hours. The mixture was diluted with ether (100 mL) and washed with sat. aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with ether (3 x 50 mL) and the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The sample was purified by flash-column chromatography (10% EtOAc in hexanes) to give aniline **73** (3.64 g, 73 %) as a pale-tan solid: m.p. 73-75 ºC; IR (neat) 1748, 1718 cm^{-1}; ^1H NMR δ 7.2-7.4 (m, 5H), 7.02 (t, 1H), 6.81 (m, 2H) 6.59 (dd, 1H), 4.60 (s, 2H), 4.25 (s, 2H), 4.20 (q, 3H), 3.42 (s, 2H), 1.25 (t, 3H); ^{13}C NMR δ 200.6, 166.6, 149.4, 137.1, 130.4, 128.6, 127.2, 126.6, 123.3, 120.5, 115.2, 111.0, 61.5, 60.0, 55.2, 46.1, 13.9.

Ethyl 2-(1-benzyl-6-bromo-1H-indol-3-yl)acetate (75) and ethyl 2-(1-benzyl-4-bromo-1H-indol-3-yl)acetate (74):



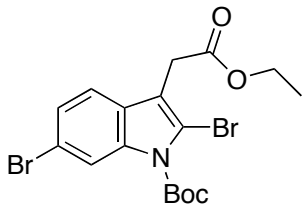
Titanium tetrachloride (0.74 mL, 6.73 mmol) was added to a solution of α-anilino ketone **73** (2.5 g, 6.41 mmol) in nitromethane (30 mL). The mixture was heated at 100 °C for 1 hour, cooled, diluted with ethyl acetate (100 mL) and washed with sat. aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with ethyl acetate (3 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The sample was purified by flash-column chromatography (20:1 hexane/ ethyl acetate) to give a mixture of 6-bromo **75** and 4-bromo **74** cyclized products (1.85 g, 78 %; 5:1 6-bromo:4-bromo) as a pale-tan solid.

Ethyl 2-(6-bromo-1H-indol-3-yl)acetate:



(1-Benzyl-6-bromo-1H-indol-3-yl)-acetic acid ethyl ester (0.056 g, 0.15 mmol) and aluminium trichloride (0.080 g, 0.60 mmol) were heated to 100 ºC in anisole (2 mL) for 1 hour. The mixture was cooled, diluted with ethyl acetate (25 mL) and washed with a solution of Rochelle's salt (25 mL). The aqueous layer was extracted with ethyl acetate (4 x 25 mL) and the combined organic layers washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The sample was purified by flash-column chromatography (10:1 hexane/ ethyl acetate) to give the title compound (0.013 g, 31 %) as a pale-tan solid whose spectral data matched that previously reported.[4]

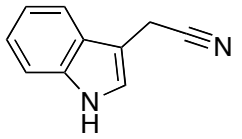
***tert*-butyl 3-((ethoxycarbonyl)methyl)-2,6-dibromo-1H-indole-1-carboxylate (81):**



N-Bromosuccinimide (1.19 g, 6.67 mmol) was added to a solution of ethyl 2-(6-bromo-1H-indol-3-yl)acetate (1.71 g, 6.06 mmol) in anhydrous carbon tetrachloride (15 mL). The reaction was stirred at room temperature for 2.5 hours then diluted with chloroform (100 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (100 mL), water (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give 2,6-dibromo-*N*H-indole as a dark-crimson oil. A solution of this crude oil in acetonitrile (50 mL) was added DMAP (0.148 g, 1.21 mmol) and Boc_2O (3.04 g, 13.9 mmol). The mixture was stirred at room temperature for 4.5 hours, diluted with ether (100 mL) and washed with water (100 mL). The aqueous layer was extracted with diethyl ether (3 x 50

mL), the combined organic layers washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash-column chromatography (SiO_2; 30:1 hexane/diethyl ether) to yield the *N*-Boc indole **81** (1.68 g, 60% from **75**) as a pale-yellow solid: m.p. 72-75 °C; IR (thin film) 2980, 1739, 1346, 1154 cm^{-1}; ^1H NMR δ 8.29 (s, 1H), 7.32 (d, *J* = 1.5Hz, 2H), 4.13 (q, *J* = 7.4 Hz, 2H), 3.71 (s, 2H), 1.68 (s, 9H); ^{13}C NMR δ 169.5, 148.3, 136.7, 133.8, 127.2, 126.1, 119.2, 118.3, 118.2, 116.1, 85.5, 61.0, 31.3, 27.9, 14.0; HRMS for $C_{17}H_{19}NO_4Br_2$ [MH+] *m/z* calc458.9681, found 458.9685.

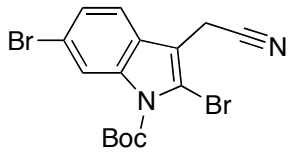
(1H-Indol-3-yl)-acetonitrile (85):



Sodium borohydride (0.023 g, 0.62 mmol) was added to a solution of indole-3-carboxaldehyde **84** (0.068 g, 0.47 mmol) in methanol/formamide (1:1, 8 mL) at room temperature. After stirring for 1h, sodium cyanide (0.237 g, 4.84 mmol) was added and the mixture heated at 100 ºC for 4.5 hours. The solution was cooled and poured into brine (100 mL). The aqueous layer was extracted with chloroform/methanol (95:5; 4 x 50 mL) and the combined organic layers dried (Na_2SO_4) and concentrated *in vacuo*. The crude mixture was purified by flash-column chromatography (SiO_2; $CHCl_3$) to provide indole **85** (0.062 g, 85%) as a colorless oil whose spectral data matched that previously reported[5]: IR (thin film) 2249 cm^{-1}; ^1H NMR δ 8.38 (bs, 1H), 7.62 (d, *J* = 7.8 Hz, 1H),

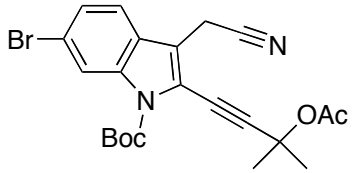
7.41 (d, J = 8.2 Hz, 1H), 7.2-7.3 (m, 2H), 7.15 (s, 1H), 3.86 (s, 2H); ^{13}C NMR δ 136.1, 125.8, 122.9, 122.6, 120.0, 117.8, 111.6, 104.1, 14.1.

***tert*-butyl 2,6-dibromo-3-(cyanomethyl)-1H-indole-1-carboxylate (87):**



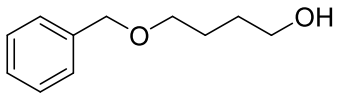
N-Bromosuccinimide (2.49 g, 14.0 mmol) in dichloromethane (100 mL) was added dropwise to a solution of (1H-indol-3-yl)-acetonitrile **85** (1.09 g, 7.0 mmol) in dichloromethane (50 mL) containing oven-dried SiO_2 (> 100 ºC, 28 g) over 1 hour at 23 °C. The mixture was stirred for a further 0.5 hour, filtered, and concentrated *in vacuo* to give 2.2 g of a brown solid. To this solid (3.06 g, 14.0 mmol) in dichloromethane (10 mL), was added DMAP (0.086 g, 0.7 mmol), Boc_2O (3.34 g, 15.29 mmol) and triethylamine (1.07 mL, 7.7 mmol). The mixture was stirred at room temperature for 1 hour and then diluted with DCM (25 mL) and washed with sat. aq. NH_4Cl (2 x 25 mL), brine (25 mL), and concentrated *in vacuo*. The crude mixture was purified by flash-column chromatography (SiO_2, 10% EtOAc in hexanes) to provide the *N*-Boc indole **87** (1.25 g, 43 %) as a white solid after recrystallisation from diethyl ether: m.p. 145-147 ºC; IR (thin film) 2249, 1740 cm^{-1}; ^{1}H NMR δ 8.36 (s, 1H), 7.44 (dd, J = 7.4, 1.5 Hz, 2H), 3.80 (s, 2H), 1.71 (s, 9H); ^{13}C NMR δ 148.0, 136.7, 126.6, 125.7, 119.0, 118.6, 115.7,111.6, 111.2, 86.2, 27.9, 14.5; HRMS for $C_{15}H_{15}N_2O_2Br_2$ [MH+] m/z calc. 412.9500, found 412.9504.

***tert*-butyl 2-(3-acetoxy-3-methylbut-1-ynyl)-6-bromo-3-(cyanomethyl)-1*H*-indole-1-carboxylate (89):**



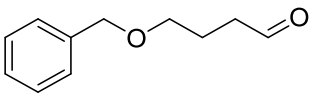
A mixture of 2-methylbut-3-yn-2-yl acetate (**88**) (0.291 g, 2.31 mmol), indole **87** (0.870 g, 2.10 mmol), and $PdCl_2(PPh_3)_2$ (0.074g, 0.105 mmol) in triethylamine (25 mL, distilled over CaH_2) was thoroughly degassed with Ar at 23 °C. To this mixture was added a degassed suspension of CuI (0.060g, 0.311 mmol) in triethylamine (2mL). The reaction was stirred 16h at 23 °C under an atmosphere of Ar. The reaction was filtered over celite, washing with ether and the organic filtrate was concentrated *in vacuo*. Column chromatography (15% EtOAc in hexanes) of the crude residue gave the 2-coupled product **89** as a pale yellow oil which produced a foam *in vacuo* (0.400 g, 42%): R_f = 0.34 (10% EtOAc in hexanes); IR (neat) 2986, 2937, 1738, 1243, 1146 cm^{-1}; ^1H NMR δ 8.39 (s, 1H), 7.43 (dd, J = 8.4, 1.7 Hz, 2H), 3.92 (s, 2H), 2.08 (s, 3H), 1.80 (s, 6H), 1.69 (s, 9H); ^{13}C NMR δ 169.5, 148.5, 136.1, 126.1, 125.8, 120.3, 119.5, 119.4, 118.9, 117.4, 116.6, 101.5, 85.5, 74.5, 72.1, 28.7, 28.6, 28.1, 21.8, 13.5; HRMS for $C_{22}H_{24}N_2O_4Br$ [MH+] m/z calc. 459.0919, found 459.0917.

4-Benzyloxy-1-butanol:



To a solution of 1,4-butanediol **94** (30.0 mL, 0.340 mol) in dry THF (250 mL) at 0 °C was added NaH (60% in mineral oil, 14.2 g, 0.36 mol) slowly. The reaction was stirred for 30 min and benzyl bromide (42 mL, 0.36 mol) and tetrabutylammonium iodide (1.25 g, 3.40 mmol) were added. The reaction was warmed to 23 °C and stirred an additional 4 h. The mixture was quenched with 10% aq. NH_4Cl (100 mL) and washed with water (100 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 150 mL). The combined organic layer was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (gradient elution, 10% EtOAc/hexanes to 100% EtOAc) gave 4-benzyloxy-1-butanol as a pure yellowish oil (52.9 g, 87%) whose spectral data was consistent with that previously reported.[6]

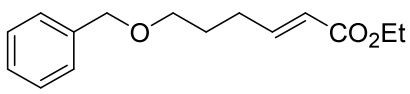
4-Benzyloxy-1-butanal (95):



To a solution of the Dess-Martin periodinane[7] (14.7 g, 35.0 mmol) in dry CH_2Cl_2 (140 mL), at room temperature, was added 4-benzyloxy-1-butanol (5.00 g, 27.8 mmol) as

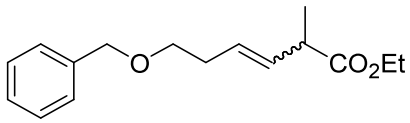
a solution in CH_2Cl_2 (20 mL). A slight exotherm ensued and the solution was stirred 30 min then was diluted in ether (150 mL), poured into aq. NaOH (1M, 100 mL) and stirred until two clear layers were evident. The organic layer was separated, washed with water (150 mL), brine (150 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give aldehyde **95** as a colorless oil (4.67 g, 95%) whose spectral data was consistent with that of previous reports.[8]

Ethyl (2*E*)-6-(benzyloxy)hex-2-enoate (96):



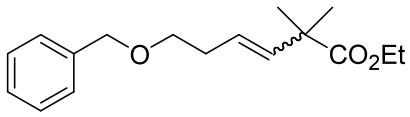
To a solution of triethylphosphonoacetate (1.70 mL, 8.42 mmol) in dry THF (25 mL) at 0 °C was added NaH (60% in mineral oil, 340 mg, 8.42 mmol). The mixture was stirred for 30 min at 0 °C after which the aldehyde **95** (1.0 g, 5.61 mmol) was added as a solution in THF (10 mL) and the reaction was stirred an additional 1.5 h. After warming the reaction to 23 °C, and diluting with ether (50 mL), the solution was washed with water (50 mL) then brine (25 mL), and the organic layer was concentrated *in vacuo*. Purification of the yellow residue by column chromatography (5% EtOAc in hexanes) gave ester[9] **96** as a pure colorless oil (1.26 g, 90%): R_f = 0.29 (5% EtOAc/hexanes); IR (neat) 2980, 2938, 2857, 1717, 1654 cm^{-1}; ^1H NMR δ 7.30 (m, 5H), 6.97 (dt, *J* = 15, 6.9 Hz, 1H), 5.83 (dd, *J* = 15, 1.5 Hz), 4.50 (s, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.50 (t, *J* = 6.3 Hz, 2H), 2.32 (q, *J* = 7.2 Hz, 2H), 1.78 (m, 2H), 1.29 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR δ 14.0, 28.0, 28.7, 59.9, 69.0, 72.7, 121.5, 127.3, 127.4, 128.2, 138.2, 148.3, 166.4; HRMS for $C_{15}H_{21}O_3$ [MH+] *m/z* calc. 249.1491, found 249.1492.

Ethyl 6-(benzyloxy)2-methylhex-3-enoate:



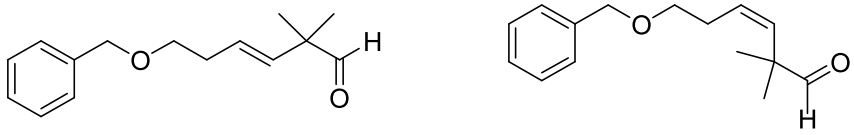
To a solution of 1,1,1,3,3,3-hexamethyldisilazane (distilled from CaH_2, 2.20 mL, 10.45 mmol) in dry THF (15 mL) at −78 °C was added *n*-BuLi (2.4M in hexanes, 4.4 mL, 10.45 mmol) and hexamethylphosphoramide (distilled from CaH_2, 1.82 mL, 10.45 mmol). The solution was stirred for 30 min at −78 °C. The α,β-unsaturated ester **96** (2.16g, 8.71 mmol) was then added as a solution in THF (10 mL) and the reaction was allowed to warm to room temperature over 30 min at which point the solution turned a dark yellow-orange, indicating formation of the anion. Methyl iodide (distilled, 2.0 mL, 32.1 mmol) was then added at −78 °C and the solution was stirred an additional 30 min. The reaction was quenched with 10% aq. NH_4Cl (10 mL) and diluted in ether (25 mL). The organic layer was washed 10% aq NH_4Cl (25 mL), water (25 mL), brine (25 mL), dried over Na_2SO_4, and concentrated. The residue was taken up in ether, filtered over a silica plug, eluting with 10% EtOAc in hexanes. Concentration of the filtrate *in vacuo* gave 2.28g (>99%) of the title compound as a yellowish oil which proved an to be an inseparable mixture of *E*/*Z* olefins: R_f = 0.35 (5% EtOAc/hexanes); IR (neat) 2977, 2934, 2858, 1732 cm^{-1}; ^{1}H NMR δ 7.30 (m, 5H), 5.53 (m, 2H), 4.52 (s, 2H), 4.11 (q, *J* = 4.0 Hz, 2H), 3.50 (m, 3H), 2.44 (q, *J* = 6.3 Hz, 1H), 1.78 (m, 2H), 1.29 (m, 8H); ^{13}C NMR δ 13.8, 17.8, 28.0, 38.1, 60.3, 69.5, 124.7, 127.3, 127.3, 127.5, 128.2, 138.2, 174.6.

Ethyl 6-(benzyloxy)2,2-dimethylhex-3-enoate (XXX):



To a solution of 1,1,1,3,3,3-hexamethyl-disilazane (distilled from CaH_2, 2.20 mL, 10.45 mmol) in dry THF (15 mL) at –78 ºC was added *n*-BuLi (2.4M in hexanes, 4.4 mL, 10.45 mmol). The solution was stirred for 30 min at 0 °C. Ethyl 6-(benzyloxy)2-methylhex-3-enoate (2.28g, 8.67 mmol) was then added as a solution in THF (10 mL) and the reaction was allowed to warm to 23 °C over 30 min at which point the solution turned a dark yellow-orange, indicating formation of the anion. Methyl iodide (distilled, 2.0 mL, 32.1 mmol) was then added at 0 °C and the solution was stirred an additional 30 min. The reaction was quenched with 10% aq. NH_4Cl (10 mL) and diluted in ether (25 mL). The organic layer was washed 10% aq. NH_4Cl (25 mL), water (25 mL), brine (25 mL), dried over Na_2SO_4, and concentrated. The residue was taken up in ether, filtered over a silica plug, eluting with 10% EtOAc in hexanes. Concentration of the filtrate *in vacuo* gave 2.23g (93%) of *gem*-dimethyl ester **97** as a yellowish oil which proved to be an inseparable mixture of *E*/*Z* olefins: R_f = 0.38 (5% EtOAc/hexanes); IR (neat) 2977, 2934, 2858, 1728 cm^{-1}; ^1H NMR δ 7.30 (m, 5H), 5.53 (m, 2H), 4.52 (s, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.50 (t, *J* = 6.6 Hz 3H), 2.34 (m, 2H), 1.34 (s, 6H), 1.29 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR δ 13.9, 24.9, 28.0, 32.8, 60.5, 69.2, 124.7, 127.3, 127.4, 128.1, 135.8, 136.2, 177.2; HRMS for $C_{17}H_{24}O_3$ [MH+] *m*/*z* calc. 277.180370, found 277.181510.

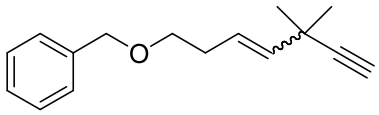
6-(benzyloxy)2,2-dimethylhex-3-enal (*cis*-99 and *trans*-99):



To a stirred solution of the ester **97** (2.20 g, 7.96 mmol) in dry ether (25 mL) at −78 °C was added slowly lithium aluminum hydride (s) until no more starting material was evident in the TLC. The mixture was stirred an additional 10 min and warmed to 0 °C. The reaction was qenched dropwise with Na_2SO_4 (sat. aq.) and poured into potassium sodium tartrate (sat. aq., 25 mL). Extraction with ether (2 x 25 mL) and concentration of the organics gave a colorless oil which was used without further purification. To a solution of the Dess-Martin periodinane (4.05 g, 9.55 mmol) in dry CH_2Cl_2 (35 mL), at 23 °C, was added the intermediate alcohol (7.96 mmol) as a solution in CH_2Cl_2 (10 mL). The solution was stirred 30 min and then poured into 1M aq. NaOH (25 mL) and stirred an additional 20 min. The organic layer was separated, washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give of aldehydes **99** (1.64 g, 89% from **97**) as a yellowish oil whose ^{1}H NMR indicated a mixture of isomeric aldehydes, 7:1 *Z*/*E*. Purification by column chromatography (5% EtOAc in hexanes) readily separated the isomers for characterization purposes: *cis*- **99**: R_f = 0.43 (5% EtOAc/hexanes); IR (neat) 2972, 2931, 2858, 1726 cm^{-1}; ^{1}H NMR δ 9.52 (s, 1H), 7.30 (m, 5H), 5.56 (dt, *J* = 11.4, 7.5 Hz, 1H), 5.40 (dd, *J* = 13.5, 9.6, Hz, 1H), 4.50 (s, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 2.27 (dq, *J* = 6.9, 1.2 Hz, 2H), 1.22 (s, 6H); ^{13}C NMR δ

13.9, 22.5, 22.9, 33.1, 47.5, 69.4, 127.4, 127.5, 128.5, 133.1, 138.1, 202.0; HRMS for $C_{15}H_{19}O_2$ [MH+] *m/z* calc. 231.138505, found 231.138972. *trans*- **99**: R_f = 0.40 (5% EtOAc/hexanes); IR (neat) 2973, 2933, 2859, 1727 cm^{-1}; ^1H NMR δ 9.35 (s, 1H), 7.30 (m, 5H), 5.50 (m, 2H), 4.52 (s, 2H), 3.51 (t, *J* = 6.6 Hz, 2H), 2.39 (q, *J* = 6.6 Hz, 2H), 1.21 (s, 6H); ^{13}C NMR δ 13.9, 21.3, 23.0, 28.9, 47.5, 69.2, 72.7, 127.3, 127.4, 128.1, 133.1, 138.2, 202.9; HRMS for $C_{15}H_{19}O_2$ [MH+] *m/z* calc. 231.138505, found 231.138195.

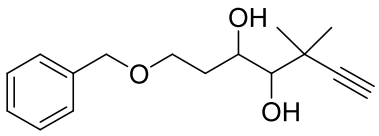
({[5,5-dimethylhept-3-en-6-yn-1-yl]oxy}methyl)benzene (*cis*-101 and *trans*-101):



To a stirred solution of a mixture isomeric aldehydes **99** (390 mg, 1.68 mmol) in methanol (dried over $MgSO_4$ prior to use, 15 mL) with K_2CO_3 (500 mg, 3.70 mmol) was added Ohira's reagent[10,11] (**100**) (390 mg, 2.02 mmol). The reaction was stirred overnight. The mixture was diluted in EtOAc (10 mL), washed with $NaHCO_3$ (sat. aq., 10 mL), water (10 mL), brine (10 mL), and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* gave alkyne **101** as a colorless oil (368 mg, 96%). *trans*-**101**: R_f = 0.67 (5% EtOAc/ hexanes); IR (neat) 3301, 2971, 2929, 2859 cm^{-1}; ^1H NMR δ 7.33 (m, 5H), 5.76 (dt, *J* = 15.6, 6.6 Hz, 1H), 5.40 (d, *J* = 15.0 Hz, 1H), 4.53 (s, 2H), 3.52 (t, *J* = 6.9 Hz, 2H), 2.37 (q, *J* = 6.9 Hz, 2H), 2.24 (s, 1H), 1.36 (s, 6H); ^{13}C NMR δ 25.2, 28.2, 31.0, 68.2, 69.5, 72.6, 108.7, 126.8, 127.3, 127.4, 128.1, 136.3; HRMS for $C_{16}H_{21}O_1$ [MH+] *m/z* calc. 229.159240, found 229.158868. *cis*-**101**: R_f = 0.67 (5% EtOAc/ hexanes); IR (neat) 3301, 2971, 2929, 2859 cm^{-1}; ^1H NMR δ 7.33 (m, 5H), 5.40 (m, 1H),

4.54 (s, 2H), 3.55 (t, J = 6.9 Hz, 2H), 2.77 (q, J = 6. Hz, 2H), 1.22 (s, 6H); ^{13}C NMR δ 25.2, 28.2, 31.0, 68.2, 69.5, 72.6, 108.7, 126.8, 127.3, 127.4, 128.1, 136.3.; HRMS for $C_{16}H_{21}O_1$ [MH+] m/z calc. 229.159240, found 229.158868.

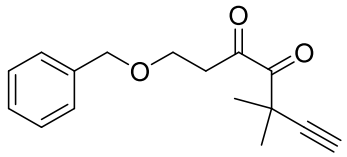
1-(benzyloxy)-5,5-dimethylhept-6-yne-3,4-diol (*cis*-103 and *trans*-102):



A solution of the olefin **101** (610 mg, 2.67 mmol) in wet acetone (10 mL) with 4-methylmorpholine-*N*-oxide (345 mg, 2.94 mmol) and $K_2O_4Os•2H_2O$ (cat.) was stirred overnight. The solution turned black as the osmate was added. Additional 4-methylmorpholine-*N*-oxide was added as needed until the reaction was complete by TLC monitoring (50% EtOAc in hexanes). To this was added 1M aq. $Na_2S_2O_3$ (5 mL) to quench the osmium, and the solution turned to a dark red color. The aqueous mixture was extracted with CH_2Cl_2 (3 x 15 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The diols **102** and **103** were collected in quantitative yield as a mixture of diastereomers (700 mg, 100%) and carried on without purification. Purification by column chromatography (30% EtOAc in hexanes) was performed for characterization purposes: *trans*-**102**: R_f = 0.86 (1:1 EtOAc/ hexanes); IR (neat) 3446, 3297, 2930, 2869 cm^{-1}; ^{1}H NMR δ 7.33 (m, 5H), 4.55 (s, 2H), 4.02 (m, 1H), 3.75 (m, 2H), 3.37 (d, J = 6.0 Hz, 1H), 2.25 (s, 1H), 2.10 (m, 2H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR δ 24.8, 26.5, 35.1, 35.9, 68.3, 69.2, 70.4, 73.4, 78.4, 90.1, 127.8, 127.8, 128.5, 137.8; HRMS for $C_{16}H_{21}O_3$ [M-H] m/z calc. 261.149070, found 261.148940. *cis*-**103**: R_f = 0.66 (1:1 EtOAc/ hexanes); IR (neat) 3420, 3295, 2971, 2929, 2870 cm^{-1}; ^{1}H NMR δ 7.33 (m, 5H), 4.54 (s, 2H), 4.28

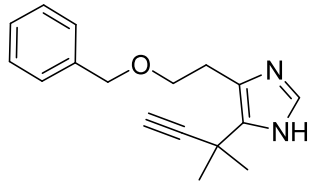
(dd, J = 8.7, 3.6 Hz, 1H), 3.72 (m, 2H), 3.14 (d, J = 8.1 Hz, 1H), 2.21 (s, 1H), 2.10 (m, 1H), 1.75 (m, 1H), 1.27 (s, 6H); ^{13}C NMR δ 26.1, 26.2, 31.7, 34.8, 68.1, 70.9, 71.9, 73.2, 79.0, 89.5, 127.5, 127.6, 128.3, 137.5; HRMS for $C_{16}H_{23}O_3$ [MH+] *m/z* calc. 263.164720, found 263.163444.

1-(benzyloxy)-5,5-dimethyl-hept-6-yne-3,4-dione (104):



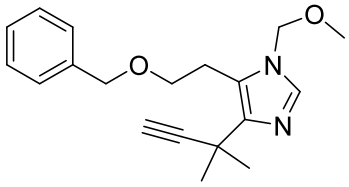
To a solution of the diasteromeric diols (**102** & **103**) (700 mg, 2.67 mmol) in dry CH_2Cl_2 (15 mL) with triethylamine (2.23 mL, 16.0 mmol) was added a solution of SO_3•pyridine complex (2.55g, 16.0 mmol) in dimethylsulfoxide (3.0 mL). The reaction was stirred 2 h and then concentrated *in vacuo* to give a crude brown oil. Extraction of the residue with ether (3 x 15 mL) was followed by washing of the organic layer with water (10 mL), sat. aq. $CuSO_4$ (10 mL), brine (10 mL) and drying over Na_2SO_4. Concentration of the organic layer *in vacuo* gave dione **104** (570 mg, 83%) as a yellow oil: R_f = 0.10 (5% EtOAc/hexanes); IR (neat) 2983, 2872, 1756, 1715 cm^{-1}; ^{1}H NMR δ 7.32 (m, 5H), 4.52 (s, 2H), 3.80 (t, J = 6.0 Hz, 2H), 3.04 (t, J = 6.3 Hz, 2H), 2.33 (s, 1H), 1.51 (s, 6H); ^{13}C NMR δ 13.9, 22.4, 25.8, 39.0, 40.3, 64.1, 72.4, 73.0, 84.9, 127.5, 128.2, 128.2, 137.6, 198.7, 199.1. HRMS for $C_{16}H_{19}O_3$ [MH+] *m/z* calc. 259.133420, found 259.133500.

4-(2-[benzyloxy]ethyl)-5-(2-methylbut-3-yn-2-yl)-1H-imidazole (105):



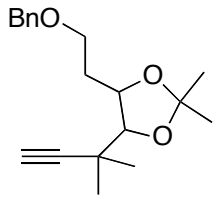
The α-dicarbonyl **104** (84 mg, 0.325 mmol) was dissolved in acetic acid (2 mL). Ammonium acetate (excess) and paraformaldehyde (25 mg, 0.833 mmol) were added. The reaction was heated to 100 °C and stirred for 2 h then cooled to 23 °C. The reaction was slowly poured into sat. aq. $NaHCO_3$ (10 mL) at 0 °C. The aqueous layer was extracted with ether (3 x 15 mL), dried over Na_2SO_4 and concentrated *in vacuo* overnight to provide imidazole **105** (84 mg, 96%) as a brown oil: R_f = 0.10 (5% MeOH/CH_2Cl_2); IR (neat) 3271, 2978, 2929, 1722, 1694 cm^{-1}; ^1H NMR δ 7.32 (m, 5H), 4.57 (s, 2H), 3.79 (t, J = 6.0 Hz, 2H), 3.25 (t, J = 6.0 Hz, 2H), 2.31 (s, 1H), 1.69 (s, 6H); ^{13}C NMR δ 25.5, 29.4, 30.5, 30.6, 69.2, 69.2, 73.0, 89.8, 127.5, 127.6, 128.2, 128.3, 131.8, 137.7; HRMS for $C_{17}H_{21}N_2O_1$ [MH+] *m/z* calc. 269.16538, found 269.163015.

5-(2-[benzyloxy]ethyl)-1-methoxymethyl-4-(2-methylbut-3-yn-2-yl)-imidazole (106):



To a stirred solution of the imidazole **105** (84 mg, 0.31 mmol) in benzene (5 mL) was added chloromethyl methyl ether (50 μL, 0.62 mmol) and triethylamine (86 μL, 0.62 mmol). The reaction was stirred overnight and diluted in EtOAc (20 mL), washed with water (15 mL), brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (2% MeOH in CH_2Cl_2) furnished imidazole **106** (73 mg, 75% yield) as a brown oil: R_f = 0.85 (5% MeOH/CH_2Cl_2); IR (neat) 2928, 2851, 1719 cm^{-1}; ^1H NMR δ 7.51 (s, 1H), 7.32 (m, 5H), 5.23 (s, 2H), 4.49 (s, 2H), 3.70 (t, *J* = 6.9 Hz, 2H), 3.28 (t, *J* = 6.9 Hz, 2H), 3.23 (s, 3H), 2.21 (s, 1H), 1.62 (s, 6H); ^{13}C NMR δ 23.8, 29.5, 30.7, 30.9, 55.5, 68.9, 69.7, 72.8, 90.3, 127.3, 127.5, 128.2, 128.3, 135.5, 138.0; HRMS for $C_{19}H_{25}N_2O_2$ [MH+] *m/z* calc. 313.191603 found 313.190623.

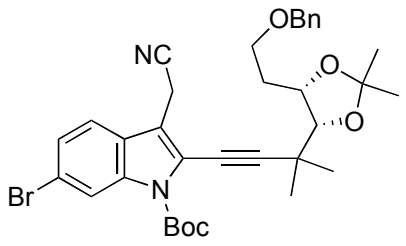
4-[2-(benzyloxy)ethyl]-2,2-dimethyl-5-(2-methylbut-3-yn-2-yl)-1,3-dioxolane (116):



To a solution of diols **102** & **103** (1.430 g, 5.45 mmol) in dry acetone (250 mL) at room temperature was added catalytic *p*-TsOH (200 mg). After stirring for 2h, the reaction was quenched with $NaHCO_3$ (s) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and filtered over a silica plug eluting with 20% EtOAc in hexanes. The collected organics were combined and concentrated to give a clear, brownish oil of acetonide **116** as an otherwise pure mixture of diastereomers (1.557 g, 95%): R_f = 0.46 (20% EtOAc/ hexanes); IR (neat) 2929, 2870 cm^{-1}; ^1H NMR δ 7.33 (m,

5H), 4.54 (s, 2H), 4.34 (m, 1H), 4.14 (m, 1H), 3.84 (d, J = 6.0 Hz, 1H), 3.63 (m, 2H), 3.62 (m, 2H), 2.25 (m, 2H), 2.20 (m, 2H), 1.50 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.34 (s, 6H), 1.29 (s, 6H), 1.26 (s, 3H); ^{13}C NMR δ 24.8, 26.5, 26.7, 27.6, 30.5, 32.3, 35.1, 35.9, 68.3, 69.2, 70.4, 73.4, 78.4, 90.1, 107.2, 127.8, 127.8, 128.5, 137.8; HRMS for $C_{19}H_{27}O_3$ [MH+] m/z calc. 303.1960, found 303.1963.

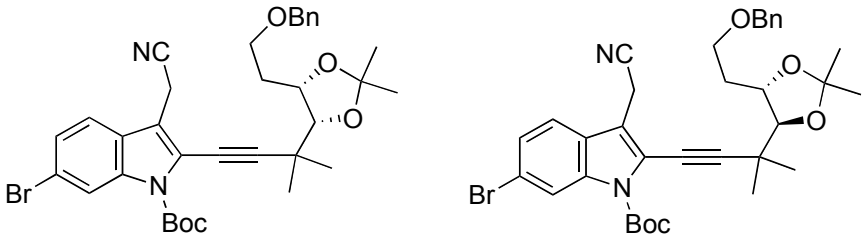
***tert*-Butyl 2-(3-{5-[2-(benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-3-methylbut-1-yn-1-yl)-6-bromo-3-(cyanomethyl)-indole-1-carboxylate (*cis*-117):**



A mixture of *cis*-acetonide alkyne *cis*-**116** (0.686g, 2.27 mmol), indole **87** (0.857g, 2.07 mmol), and $PdCl_2(PPh_3)_2$ (0.073g, 0.104 mmol) in triethylamine (25 mL, distilled over CaH_2) was thoroughly degassed with Ar at room temperature. To this mixture was added a degassed suspension of CuI (0.060g, 0.311 mmol) in triethylamine (2mL). The mixture was heated to 60 °C and stirred overnight under an atmosphere of Ar. The reaction was allowed to cool to room temperature and filtered over celite, washing with ether and the organic filtrate was concentrated *in vacuo*. Column chromatography (10% EtOAc/hexanes) on the crude residue gave the 2-coupled product *cis*-**117** as a red oil which produced a foam *in vacuo* (1.26g, 96%): R_f = 0.26 (10% EtOAc/ hexanes); IR (neat) 2981, 2934, 1739 cm^{-1}; ^1H NMR δ 8.32 (s, 1H), 7.43 (d, J = 2.0 Hz, 2H), 7.33 (m, 5H), 4.50 (s, 2H), 4.45 (m, 1H), 3.95 (d, J = 6.0 Hz, 1H), 3.83 (s, 2H), 3.68 (m, 2H), 2.21 (m, 1H), 1.69 (s, 9H), 1.53 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ 148.4, 138.3, 135.6, 128.1, 127.5, 127.5, 127.4, 127.3, 126.5, 125.8, 120.5, 119.1, 118.8, 115.5, 107.5, 106.1, 85.5, 85.1, 83.2, 74.9, 72.9, 67.4, 33.9,

30.8, 28.0, 26.9, 25.6, 14.0, 14.0, 13.8; HRMS for $C_{34}H_{40}N_2O_5Br$ [MH+] *m/z* calc. 635.2121, found 635.2112.

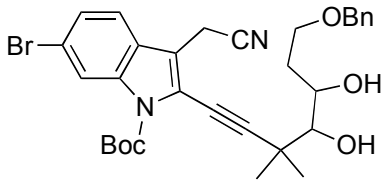
***tert*-Butyl 2-(3-{5-[2-(benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-3-methylbut-1-yn-1-yl)-6-bromo-3-(cyanomethyl)-indole-1-carboxylate (117):**



A mixture of *cis* and *trans* acetonide alkynes **116** (0.665g, 2.20 mmol), indole **87** (0.828 g, 2.00 mmol), and $PdCl_2(PPh_3)_2$ (0.070g, 0.10 mmol) in triethylamine (25 mL, distilled over CaH_2) was thoroughly degassed with Ar at room temperature. To this mixture was added a degassed suspension of CuI (0.057 g, 0.3 mmol) in triethylamine (2mL). The mixture was stirred 16h at 50 °C under an atmosphere of Ar. After cooling to 23 °C, the reaction was filtered over celite, washing with ether, and the organic filtrate was concentrated *in vacuo*. Column chromatography (10% EtOAc/hexanes) on the crude residue gave the 2-coupled products *cis*-**117** and *trans*-**117** as red oil which produced foams *in vacuo* (1.13 g, 89%): *cis*-**117**: characaterized as above. *trans*-**117**: R_f = 0.20 (10% EtOAc/ hexanes); IR (neat) 2981, 2934, 1739 cm^{-1}; ^1H NMR δ 8.32 (s, 1H), 7.43 (d, *J* = 2.0 Hz, 2H), 7.33 (m, 5H), 4.50 (s, 2H), 4.28 (dt, *J* = 7.6, 2.2 Hz, 1H), 3.72 (m, 4H), 2.10 (m, 1H), 1.91 (m, 1H), 1.68 (s, 9H), 1.44 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ 148.4, 138.2, 135.7, 128.1, 127.4, 127.4, 126.5, 125.7, 119.7, 119.1, 118.7, 116.3, 115.7, 108.7, 106.1, 86.5, 85.2, 84.7, 72.9, 67.2, 35.9, 35.3, 28.1,

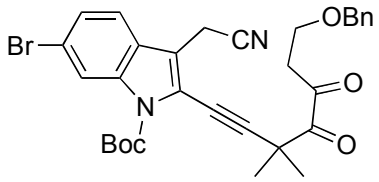
27.9, 27.4, 27.2, 27.1, 25.8, 25.0, 13.5; HRMS for $C_{34}H_{40}N_2O_5Br$ [MH+] *m/z* calc. 635.2121, found 635.2112.

***tert*-butyl 2-[7-(benzyloxy)-4,5-dihydroxy-3,3-dimethylhept-1-yn-1-yl]-6-bromo-3-cyanomethyl-indole-1-carboxylate (118):**



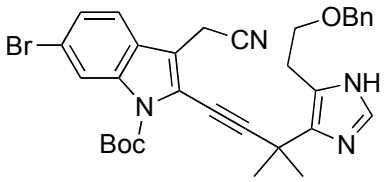
To a stirred solution of the acetonide **117** (1.086 g, 1.71 mmol) in methanol/H_2O (60 mL, 5:1) was added *p*-TsOH (1.0 g). The solution was stirred overnight. The reaction was quenched with sat. aq. K_2CO_3 (25 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were dried over Na_2SO_4 (s) and concentrated *in vacuo*. Column chromatography (1:1 EtOAc:hexanes) of the crude residue yielded the diol **118** as an orange oil (0.911 g, 89%): *cis*-**118** R_f = 0.60 (50% EtOAc/hexanes); IR (neat) 3440, 3268, 2979, 2932, 1739 cm^{-1}; ^1H NMR δ 8.20 (s, 1H), 7.43 (dd, *J* = 2.0 Hz, 2H), 7.33 (m, 5H), 4.54 (s, 2H), 4.06 (m, 1H), 3.83 (s 2H), 3.78 (m, 2H), 3.50 (t, *J* = 6.2 Hz, 1H), 3.45 (d, *J* = 5.6 Hz, 1H), 3.27 (d, *J* = 6.2 Hz, 1H), 2.21 (m, 1H), 2.00 (m, 1H), 1.70 (s, 9H), 1.50 (s, 3H), 1.45 (s, 3H); ^{13}C NMR δ 13.5, 13.6, 24.9, 26.6, 28.0, 32.5, 37.1, 68.5, 72.6, 73.2, 79.8, 85.8, 107.5, 113.6, 115.0, 116.2, 118.9, 119.7, 125.9, 126.7, 127.5, 127.6, 128.2, 128.3, 135.3, 137.6, 148.7; HRMS for $C_{31}H_{35}N_2O_5Br$ [MH+] *m/z* calc. 594.1729, found 594.1738.

***tert*-butyl 2-[7-(benzyloxy)-3,3-dimethyl-4,5-dioxohept-1-yn-1-yl]-6-bromo-3-(cyano-methyl)indole-1-carboxylate (119):**



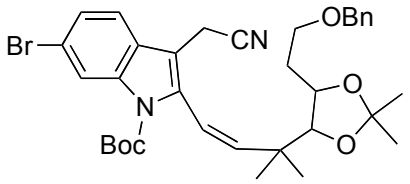
To a stirred solution of the diol **118** (76 mg, 0.128 mmol), in CH_2Cl_2 (10 mL) was added the Dess-Martin reagent (120 mg, 0.282 mmol). The mixture was stirred overnight. The mixture was concentrated and the crude residue was purified by column chromatography (20% EtOAc/hexanes) to give the pure dione **119** as a bright yellow oil (68 mg, 90%): R_f = 0.60 (50% EtOAc/hexanes); IR (neat) 2979, 2928, 2869, 1738, 1732, 1716 cm^{-1}; ^1H NMR δ 8.33 (s, 1H), 7.44 (bs, 2H), 7.27 (m, 5H), 4.54 (s, 2H), 3.82 (t, J = 6.0 Hz, 2H), 3.79 (s, 2H), 3.10 (t, J = 6.0 Hz, 2H), 1.68 (s, 9H), 1.65 (bs, 6H), ^{13}C NMR δ 13.4, 25.8, 28.0, 38.6, 41.5, 64.3, 73.0, 74.4, 85.3, 116.3, 116.6, 118.8, 119.1, 119.2, 119.3, 120.0, 125.7, 126.7, 126.7, 127.4, 128.1, 135.7, 137.5, 148.3, 197.3, 197.9; HRMS for $C_{31}H_{31}N_2O_5Br$ [MH+] m/z calc. 591.1429, found 591.1438.

***tert*-butyl 2-(3-{5-[2-(benzyloxy)ethyl]-1*H*-imidazol-4-yl}-3-methyl-but-1-ynyl)-6-bromo-3-cyanomethyl-indole-1-carboxylate (120):**



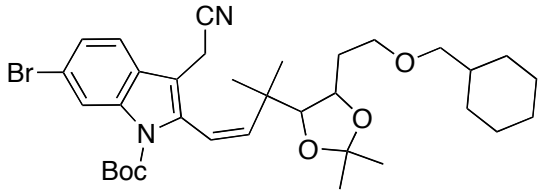
To a stirred solution of dione **119** (57 mg, 0.096 mmol) in acetic acid (2 mL) was added NH_4OAc (40 mg, 0.52 mmol) and paraformaldehyde (3 mg, 0.096 mmol). The solution was heated to 65 °C and stirred 4h. The reaction was allowed to cool to room temperature, at which time the solution was slowly added to a suspension of K_2CO_3 (s) in EtOAc. The mixture was then filtered and the organics concentrated to give a crude orange oil which was determined to be a mixture of starting dione **119** and desired imidazole **120**. Purification by column chromatography (4% MeOH in CH_2Cl_2) gave pure imidazole **120** as a red oil (31 mg, 54%): R_f = 0.40 (4% MeOH in CH_2Cl_2); IR (neat) 3276, 2981, 2916, 1739, 1733, 1558 cm^{-1}; ^1H NMR δ 8.13 (s, 1H), 7.62 (s, 1H), 7.36 (bs, 2H), 7.19 (m, 5H), 4.41 (s, 2H), 3.71 (s, 2H), 3.65 (t, J = 6.0 Hz, 2H), 3.03 (t, J = 6.0 Hz, 2H), 1.65 (s, 6H), 1.56 (s, 9H), ^{13}C NMR δ 13.6, 26.6, 27.9, 28.0, 30.0, 30.1, 32.3, 69.6, 71.2, 73.0, 85.9, 107.7, 115.3, 116.1, 118.9, 119.2, 119.3, 119.9, 120.2, 126.7, 126.8, 127.5, 127.9, 128.2, 131.7, 131.8, 135.5, 137.8, 148.8. HRMS for $C_{32}H_{34}N_4O_3Br$ [MH+] *m/z* calc. 601.1814, found 601.1805.

***tert*-butyl 2-[(1*Z*)-3-{5-[2-(benzyloxy)ethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl}-3-methylbut-1-en-1-yl]-6-bromo-3-(cyanomethyl)-indole-1-carboxylate (123):**



and

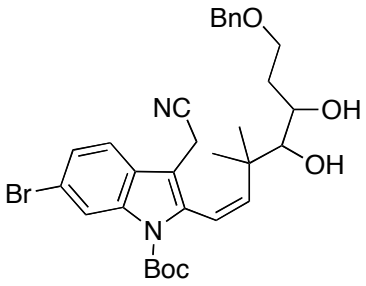
***tert*-butyl 6-bromo-3-(cyanomethyl)-2-[(1*Z*)-3-{5-[2-(cyclohexylmethoxy)ethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl}-3-methylbut-1-en-1-yl]- indole-1-carboxylate (124):**



To a stirred solution of the alkyne **122** (106 mg, 0.167 mmol) in ethanol (5 mL) saturated with H_2 (g) was added PtO_2 (4 mg, 0.019 mmol). The heterogeneous mixture was stirred overnight under an atmosphere of H_2. The mixture was filtered over celite and concentrated *in vacuo*. Column chromatography (20% EtOAc/hexanes) gave recovered alkyne **122** (66 mg), the desired *cis*-olefin **123** as a yellow oil (26 mg), and the over reduced cylohexyl species **124** (8 mg) as a yellow oil. *cis*-olefin **123**: $R_f = 0.26$ (10% EtOAc/hexanes); IR (neat) 2980, 2928, 2852, 1739, 1733, 1370, 1351, 1144, 1122 cm^{-1}; ^1H NMR (some resonances doubled due to carbamate resonance) δ 8.38 (s, 0.5H), 8.32

(s, 0.5H), 7.48 (dd, J = 8.1, 5.2 Hz, 1H), 7.43 (dd, J = 8.1, 5.2 Hz, 1H), 7.35 (m, 5H), 6.33 (d, J = 12.6 Hz, 0.5H), 6.31 (d, J = 12.6 Hz, 0.5H), 6.21 (d, J = 12.6 Hz, 0.5H), 6.11 (d, J = 12.6 Hz, 0.5H), 4.54 (m, 1H), 4.50 (m, 1H), 4.25 (m, 1H), 3.58 – 3.82 (m, 4H), 1.88 (m, 2H), 1.65 (s, 4.5H), 1.64 (s, 4.5H), 1.47 (d, J = 7.5 Hz, 3H), 1.34 (d, J = 2.6 Hz, 3H), 1.03 (s, 3H), 0.89 (d, J = 10.3 Hz, 3H); ^{13}C NMR (some resonances doubled due to carbamate resonance) δ 149.6, 142.6, 142.4, 138.3, 135.8, 134.8, 134.4, 128.1, 128.1, 128.0, 127.4, 127.4, 127.3, 126.4, 126.3, 126.1, 126.1, 119.2, 119.1, 118.8, 118.7, 118.4, 118.3, 117.9, 117.3, 108.0, 107.0, 85.5, 84.9, 84.3, 72.9, 67.4, 67.2, 39.0, 38.7, 34.4, 31.9, 31.6, 31.4, 28.1, 28.0, 27.9, 27.8, 26.5, 25.6, 25.0, 23.9, 22.4, 13.9, 13.9; HRMS for $C_{34}H_{41}N_2O_5Br$ [MH+] m/z calc. 636.2199, found 635.2201; **124**: R_f = 0.42 (10% EtOAc/hexanes); IR (neat) 2980, 2928, 2852, 1739, 1733, 1144, 1122 cm^{-1}; ^{1}H NMR (some resonances doubled due to carbamate resonance) δ 8.38 (s, 0.5H), 8.32 (s, 0.5H), 7.50 (dd, J = 8.3, 8.1 Hz, 1H), 7.42 (dd, J = 8.3, 8.1 Hz, 1H), 6.30 (d, J = 12.6 Hz, 0.5H), 6.29 (d, J = 12.6 Hz, 0.5H), 6.21 (d, J = 12.6 Hz, 0.5H), 6.12 (d, J = 12.6 Hz, 0.5H), 4.20 (m, 1H), 3.70 – 3.80 (m, 3H), 3.5 – 3.57 (m, 2H), 3.21 – 3.25 (m, 2H), 1.10 – 1.85 (m, 11H), 1.67 (s, 4.5H), 1.65 (s, 4.5H), 1.48 (d, J = 5.6 Hz, 3H), 1.34 (d, J = 2.0 Hz, 3H), 1.03 (d, J = 4.0 Hz, 3H), 0.86 (d, J = 13.3 Hz, 3H); ^{13}C NMR (some resonances doubled due to carbamate resonance) δ 149.0, 142.7, 141.4, 134.8, 134.4, 126.4, 126.3, 126.2, 126.1, 119.2, 119.1, 118.8, 118.7, 117.8, 117.2, 116.8, 116.7, 108.0, 107.0, 85.5, 84.9, 74.9, 74.9, 67.9, 67.6, 39.0, 38.7, 37.8, 37.8, 37.7, 31.8, 31.5, 29.9, 29.8, 28.1, 28.1, 28.0, 27.9, 27.8, 27.8, 27.7, 26.5, 25.3, 25.8, 25.7, 25.6, 25.6, 25.5, 13.9, 13.9; HRMS for $C_{34}H_{46}N_2O_5Br$ [MH+] m/z calc. 641.9199, found 641.9201.

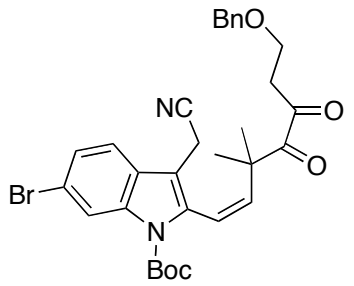
***tert*-butyl 2-[(1*Z*)-7-(benzyloxy)-4,5-dihydroxy-3,3-dimethylhept-1-en-1-yl]-6-bromo-3-(cyanomethyl)-indole-1-carboxylate (124):**



A solution of acetonide **123** (250 mg, 1.56 mmol) in MeOH (15 mL) with *p*-toluenesulfonic acid (500 mg) was stirred at 23 °C for 4h. The solution was diluted in EtOAc (25 mL), washed with sat. aq. $NaHCO_3$ (20 mL), water (20 mL), brine (20 mL) and concentrated. The crude oil was purified by column chromatography (SiO_2, gradient elution, 30% EtOAc in hexanes to 60% EtOAc in hexanes) to yield diol **124** as a colorless oil (210 mg, 89%): R_f = 0.26 (10% EtOAc/hexanes); IR (neat) 3440, 2980, 2928, 1733 cm^{-1}; ^1H NMR (some resonances doubled due to carbamate resonance) δ 8.27 (s, 0.5H), 8.26 (s, 0.5H), 7.49 (dd, *J* = 8.1, 5.2 Hz, 1H), 7.43 (dd, *J* = 8.1, 5.2 Hz, 1H), 7.35 (m, 5H), 6.28 (d, *J* = 12.6 Hz, 0.5H), 6.26 (d, *J* = 12.6 Hz, 0.5H), 6.06 (d, *J* = 12.6 Hz, 0.5H), 6.04 (d, *J* = 12.6 Hz, 0.5H), 4.54 (s, 1H), 4.52 (s, 1H), 3.65 – 3.82 (m, 5H), 3.29 (m, 1H), 1.91 – 2.05 (m, 3H), 1.67 (s, 4.5H), 1.65 (s, 4.5H), 1.60 (m, 1H), 1.26 (s, 3H), 0.86 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (some resonances doubled due to carbamate resonance) δ 149.7, 149.4, 144.1, 143.0, 137.4, 137.3, 135.7, 135.6, 135.2, 135.0, 128.3, 127.6, 127.6, 126.5, 126.3, 126.1, 125.9, 119.2, 119.0, 118.8, 118.3, 118.2, 118.0, 117.0,

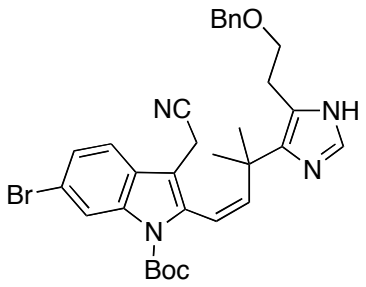
116.9, 116.7, 115.9, 108.1, 108.1, 85.5, 85.1, 81.1, 80.4, 73.2, 72.5, 71.0, 69.1, 67.6, 41.6, 41.5, 32.9, 32.1, 29.5, 28.1, 28.0, 24.7, 24.4, 23.5, 23.4, 21.5, 13.7, 13.6; HRMS for $C_{31}H_{38}N_2O_5Br$ [MH+] *m/z* calc. 597.1964, found 597.1970.

***tert*-butyl 2-[(1*Z*)-7-(benzyloxy)-3,3-dimethyl-4,5-dioxohept-1-en-1-yl]-6-bromo-3-(cyanomethyl)-indole-1-carboxylate (125):**



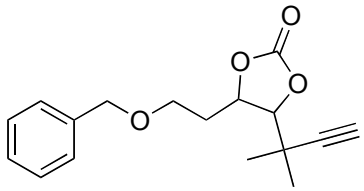
A solution of diol **124** (170 mg, 0.285 mmol) in CH_2Cl_2 (20 mL) was treated with Dess-Martin periodinane (270 mg, 0.627 mmol) and stirred at 23 °C for 16h. The solvent was removed and the residue purified *via* flash column chromatography (SiO_2, gradient elution, 10%, 20%, 30% EtOAc in hexanes) providing dione **125** as a bright yellow oil (81 mg, 48%): R_f = 0.26 (30% EtOAc/hexanes); IR (neat) 2980, 2928, 2869, 1739, 1732, 1716 cm^{-1}; ^1H NMR δ 8.38 (s, 1H), 7.44 (bs, 2H), 7.28 (m, 5H), 6.36 (d, *J* = 11.9 Hz, 1H), 6.02 (d, *J* = 11.9 Hz, 1H), 4.42 (s, 2H), 3.82 (t, *J* = 5.9 Hz, 2H), 3.47 (s, 2H), 2.71 (t, *J* = 5.9 Hz, 2H), 1.68 (s, 9H), 1.27 (bs, 6H), 1.16 (bs, 3H); HRMS for $C_{31}H_{33}N_2O_5Br$ [MH+] *m/z* calc. 593.1639, found 593.1638.

***tert*-butyl 2-[(1Z)-3-{5-[2-(benzyloxy)ethyl]-1*H*-imidazol-4-yl}-3-methylbut-1-en-1-yl}-6-bromo-3-cyanomethyl-indole-1-carboxylate (121):**



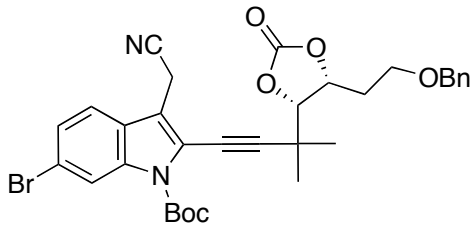
To a stirred solution of dione **125** (90 mg, 0.152 mmol) in acetic acid (8 mL) was added NH_4OAc (40 mg, 0.52 mmol) and paraformaldehyde (30 mg, 0.96 mmol). The solution was heated to 65 °C and stirred 3h. The reaction was allowed to cool to room temperature, at which time the solution was slowly added to a suspension of K_2CO_3 (s) in EtOAc. The mixture was then filtered and the organics concentrated to give a crude orange oil which was determined to be a mixture of starting dione and desired imidazole. Purification by column chromatography (4% MeOH in CH_2Cl_2) gave the pure imidazole **121**as a red oil (18 mg, 20%): R_f = 0.36 (4% MeOH in CH_2Cl_2); IR (neat) 3276, 2981, 2916, 1739, 1733, 1558 cm^{-1}; ^1H NMR δ 8.29 (s, 1H), 7.43 (s, 1H), 7.39 (bs, 2H), 7.33 (m, 5H), 6.57 (d, *J* = 16.4 Hz, 1H), 6.08 (d, *J* = 16.2 Hz, 1H), 4.49 (s, 2H), 3.76 (s, 2H), 3.60 (t, *J* = 5.8 Hz, 2H), 3.00 (t, *J* = 5.8 Hz, 2H), 1.66 (s, 9H), 1.35 (s, 3H), 1.26 (s, 3H); HRMS for $C_{32}H_{36}N_4O_3Br$ [MH+] *m/z* calc. 603.1814, found 603.1805.

4-[2-(Benzyloxy)ethyl)-5-(2-methylbut-3-yn-2-yl)-[1,3]-dioxolan-2-one (126):



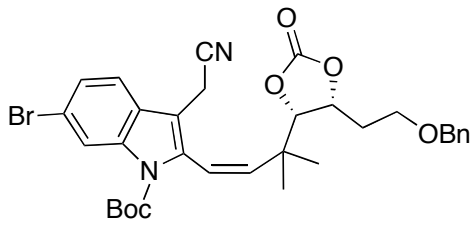
To a stirred solution of the diol **103** (300 mg, 1.14 mmol) in CH_2Cl_2 (10 mL) with pyridine (1 mL) was added triphosgene (413 mg, 1.39 mmol) at 0 °C. The mixture was allowed to slowly warm to room temperature 3h. After cooling back down to 0 °C, the reaction was quenched with 10% aq. NH_4Cl (10 mL). The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2 x 10 mL). The combined organics were washed with 10% aq. NH_4Cl (20 mL) and brine (10mL) and concentrated *in vacuo*. Purification by column chromatography (20% EtOAc in hexanes) gave the carbonate **126** as a yellow oil (300 mg, 92%): R_f = 0.40 (20% EtOAc in hexanes); IR (neat) 3284, 2977, 2937, 2871, 1805, 1799, 1367, 1173 cm^{-1}; ^1H NMR δ 7.35 (m, 5H), 5.04 (m, 1H), 4.53 (s, 2H), 4.39 (d, *J* = 7.4 Hz, 1H), 3.68 (m, 2H), 2.38 (m, 2H), 2.26 (s, 1H), 1.39 (s, 3H), 1.35 (s, 3H), ^{13}C NMR δ 25.8, 26.6, 32.7, 65.8, 72.5, 72.7, 77.2, 83.5, 85.5, 127.4, 127.5, 127.5, 128.2, 137.8, 153.9; HRMS for $C_{17}H_{21}O_4$ [MH+] *m/z* calc. 289.1440, found 289.1440.

***tert*-butyl 2-{3-[(4R,5R)-5-[2-(benzyloxy)ethyl]-2-oxo-1,3-dioxolan-4-yl]-3-methylbut-1-yn-1-yl}-6-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (127):**



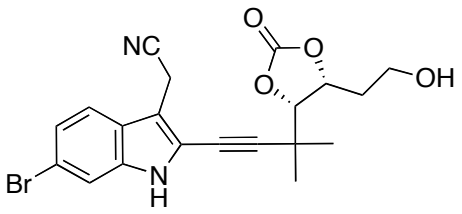
A mixture of alkyne **126** (0.317 g, 1.10 mmol), indole **87** (0.414 g, 1.0 mmol), and $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol) in triethylamine (10 mL) distilled over CaH_2) was thoroughly degassed with Ar at room temperature. To this mixture was added a degassed suspension of CuI (0.029 g, 0.15 mmol) in triethylamine (2mL). The reaction was then heated to 65 °C and stirred overnight under an atmosphere of Ar. The reaction was allowed to cool to room temperature and filtered over celite, washing with ether. The organic filtrate was concentrated *in vacuo*. Column chromatography (30% EtOAc in hexanes) on the crude residue gave the 2-coupled product **127** as a red oil which produced a foam *in vacuo* (0.316 g, 51%): R_f = 0.24 (30% EtOAc in hexanes); IR (neat) 2974, 2929, 1801, 1738, 1732, 1455, 1370, 1148 cm^{-1}; ^1H NMR δ 8.23 (s, 1H), 7.44 (d, *J* = 2.0 Hz, 2H), 7.30 (m, 5H), 5.13 (q, *J* = 7.0 Hz, 1H), 4.55 (d, *J* = 7.3 Hz, 1H), 4.50 (d, *J* = 2.5 Hz, 2H), 3.75 (d, *J* = 3.1 Hz, 1H), 3.70 (m, 2H), 2.46 (dd, *J* = 8.3, 6.5 Hz, 2H), 1.69 (s, 9H), 1.56 (s, 3H), 1.52 (s, 3H); ^{13}C NMR δ 153.9, 148.2, 137.7, 135.5, 128.2, 127.5, 126.6, 125.7, 120.0, 119.5, 119.2, 118.9, 116.2, 102.6, 85.5, 83.6, 83.3, 74.2, 73.2, 65.9, 45.9, 34.3, 29.7, 29.5, 27.9, 26.6, 26.0, 13.4; HRMS for $C_{27}H_{26}N_2O_4Br$ [MH+] *m/z* calc. 521.1076, found 521.1073.

tert-butyl 2-[(1Z)-3-[(4S,5R)-5-[2-(benzyloxy)ethyl]-2-oxo-1,3-dioxolan-4-yl]-3-methylbut-1-en-1-yl]-6-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate:



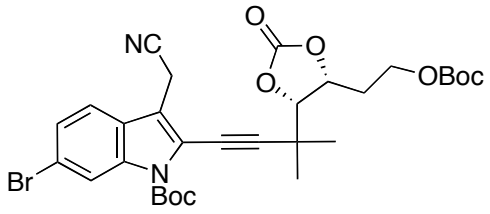
To a stirred solution of the alkyne **127** (0.084 g, 0.135 mmol) in ethanol (10 mL) saturated with H_2 (g) was added PtO_2 (0.005 g, 0.019 mmol). The heterogeneous mixture was stirred overnight under an atmosphere of H_2. The mixture was filtered over celite and concentrated *in vacuo*. Column chromatography (30% EtOAc in hexanes) gave the title compound as a yellow oil (0.040 g, 48%): IR (neat) 2916, 1801, 1739, 1733, 1455, 1142 cm^{-1}; ^1H NMR (some resonances doubled due to carbamate resonance) δ 8.31 (s, 0.5H), 8.25 (s, 0.5H), 7.46 (dd, J = 8.3, 2.5 Hz, 2H), 7.30 (m, 5H), 6.46 (d, J = 12.6 Hz, 1H), 6.08 (d, J = 12.6 Hz, 0.5H), 5.92 (d, J = 12.6 Hz, 0.5H), 4.90 – 5.00 (m, 1H), 4.50 (m, 2H), 4.41 (d, J = 5.1 Hz, 0.5H), 4.38 (d, J = 4.9 Hz, 0.5H), 3.70 (s, 1H), 1.98 – 2.22 (m, 2H), 1.66 (s, 4.5H), 1.58 (s, 4.5H), 1.15 (s, 1.5H), 1.05 (s, 1.5H), 0.99 (s, 1.5H), 0.93 (s, 1.5H); HRMS for $C_{27}H_{28}N_2O_4Br$ [MH+] m/z calc. 523.1232, found 523.1232.

2-(6-bromo-2-{3-[(4S,5R)-5-(2-hydroxyethyl)-2-oxo-1,3-dioxolan-4-yl]-3-methylbut-1-yn-1-yl}-1H-indol-3-yl)acetonitrile (129):



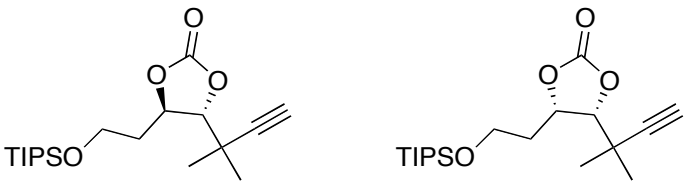
To a stirred solution of the benzyl carbonate **127** (175 mg, 0.282 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added BCl_3 (1 mL, 1.0 M soln in DCM), dropwise. After 30 min., NEt_3 (2 mL) was added and the reaction was quenched with MeOH (10mL). The mixture was concentrated and the crude residue purified by column chromatography (SiO_2, gradient elution, 50% then 100% EtOAc in hexanes) gave the product of benzyl and Boc cleavage **129** (63 mg, 52%) as a yellow oil which decomposed on standing: R_f = 0.24 (50% EtOAc/hexanes); IR (neat) 3446, 2928, 1801 cm^{-1}; ^1H NMR δ 9.00 (s, 1H), 7.45 (d, J = 7.4 Hz, 2H), 7.28 (s, 1H), 5.07 (ddd, J = 7.2, 6.8, 3.7 Hz, 1H), 4.52 (d, J = 7.3 Hz, 1H), 3.95 (m, 1H), 3.81 (m, 1H), 3.81 (s, 2H), 2.40 (m, 2H), 1.52 (s, 3H), 1.48 (s, 3H); HRMS for $C_{20}H_{19}N_2O_4Br$ [MH+] m/z calc. 432.0508, found 432.0516.

***tert*-butyl 6-bromo-2-{3-[(4S,5R)-5-(2-{[(*tert*-butoxy)carbonyl]oxy}ethyl)-2-oxo-1,3-dioxolan-4-yl]-3-methylbut-1-yn-1-yl}-3-(cyanomethyl)-1H-indole-1-carboxylate (130):**



To a stirred solution of *N*-H indole **129** (60 mg, 0.140 mmol) in CH_2Cl_2 (3 mL) with DMAP (19 mg, 0.154 mmol) was added *t*-butyloxycarbonate anhydride (34 mg, 0.154 mmol) dropwise and the reaction was stirred 2h. The reaction was quenched by the addition of 10% aq. NH_4Cl (5 mL). The mixture was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with 10% aq. NH_4Cl (10 mL), brine (10 mL) and concentrated *in vacuo*. Column chromatography (SiO_2, 30% EtOAc in hexanes) gave bis-*t*-butyloxycarbonate **130** (36 mg, 41%) as a yellow oil: R_f = 0.36 (30% EtOAc/hexanes); IR (neat) 2928, 2986, 1801, 1748, 1739 cm^{-1}; ^1H NMR δ 8.23 (s, 1H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.45 (d, *J* = 6.0 Hz, 1H), 5.04 (dd, *J* = 7.2, 3.1 Hz, 1H), 4.98 (d, *J* = 7.3 Hz, 1H), 4.58 (t, *J* = 7.6 Hz, 1H), 4.32 (m, 1H), 4.20 (m, 1H), 2.58 (m, 1H), 1.72 (s, 9H), 1.56 (bs, 6H), 1.45 (s, 9H); ^{13}C NMR δ 170.2, 162.2, 152.9, 135.5, 126.8, 124.7, 120.2, 119., 118.9, 114.4, 102.8, 85.8, 84.9, 83.4, 83.3, 62.9, 60.2, 52.0, 35.9, 34.2, 30.5, 29.5, 28.5, 28.4, 27.9, 27.5, 26.9, 25.8, 20.8, 18.9, 13.9; HRMS for $C_{30}H_{36}N_2O_8Br$ [MH+] *m/z* calc. 631.1655, found 631.1664.

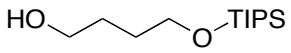
4-(2-Methylbut-3-yn-2-yl)-5-(2-{[tris(propan-2-yl)silyl]oxy}ethyl)-[1,3]dioxolan-2-one (*trans*-131 & *cis*-131):



To a solution of the benzyl ether **126** (3.63g, 12.6 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added 1M BCl_3 in CH_2Cl_2 (16 mL). The mixture was stirred 2h at which time methanol (10 mL) was added slowly at 0 °C to quench the reaction. Concentration of the solution *in vacuo* revealed the crude, brown oil which, by ^{1}H NMR indicated complete removal of the benzyl ether. The crude oil was taken on without further purification. To a stirred solution of the crude alcohol in *N,N*-dimethylformamide (35 mL) was added imidazole (2.0 g) and triisopropylsilylchloride (2.91 g,15.1 mmol). The heterogeneous mixture was stirred for 3h at reflux, overnight at room temperature, and then an additional 3h at reflux. The mixture was diluted in *t*-butylmethylether (100 mL) and washed with 10% aq. NH_4Cl (3 x 50 mL) and brine (30 mL) and then concentrated *in vacuo*. Purification of the crude oil *via* column chromatography (10% EtOAc in hexanes) followed by Kugelrohr distillation of the resultant oil gave the desired carbonates ***trans*-131** and ***cis*-131** as an orange foam (4.19 g, 94%): R_f = 0.80, 0.80 (10% EtOAc in hexanes); IR (neat) 3309, 3263, 2942, 2941, 2868, 1809, 1801 cm^{-1}; ***cis*- 131**: white powder, mp = 86.5 – 89.0 °C; ^{1}H NMR δ 5.08 (m, 1H), 4.43 (d, J = 7.4 Hz, 1H), 3.88 (m, 2H), 2.26 (s, 1H), 2.24 (m, 2H), 1.39 (s, 3H), 1.36 (s, 3H), 1.06 (s, 21H); ^{13}C NMR δ 154.1, 85.3, 83.5, 72.2, 58.7, 32.3, 26.7, 25.5, 17.7, 17.4, 11.9, 11.6; HRMS for

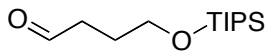
$C_{19}H_{35}O_4Si$ [MH+] *m/z* calc. 355.2305, found 355.2302. ***trans*- 131**: colorless oil; ^1H NMR δ 4.95 (q, *J* = 5.2 Hz, 1H), 4.15 (d, *J* = 5.2 Hz, 1H), 3.89 (t, *J* = 5.8 Hz, 2H), 2.20 (s, 1H), 1.94 (q, *J* = 5.9 Hz, 2H), 1.32 (s, 3H), 1.27 (s, 3H), 1.06 (s, 21H); ^{13}C NMR δ 153.3, 93.5, 85.9, 71.6, 58.4, 46.5, 38.6, 30.7, 24.9, 23.6, 17.9, 11.8; HRMS for $C_{19}H_{35}O_4Si$ [MH+] *m/z* calc. 355.2305, found 355.2302.

4-{[tris(propan-2-yl)silyl]oxy}butan-1-ol:



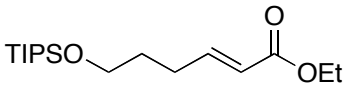
To a stirred solution of 1,4-butanediol **94** (53.17g, 590mmol) and imidazole (8.03g, 118 mmol) in THF (200 mL) at 0 °C was added triisopropylsilyl chloride (22.75 g, 118 mmol). Upon addition, the solution was warmed to 25 °C and stirred for 6 hours. The reaction was washed with ethyl acetate (4 x 200 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purifed by flash column chromatography (SiO_2, 5% EtOAc in hexanes) to provide the title compound as a colorless oil (26 g, 89%) whose spectral data matched those previously reported[12]: R_f = 0.89 (5% EtOAc in hexanes); IR (neat) 3344, 2941, 2866, 2726, 1464 cm^{-1}; ^1H NMR δ 3.78 (t, *J* = 5.7 Hz, 2H), 3.67 (s, 2H), 1.69 (m, 4H), 1.08 (m, 21H); ^{13}C NMR δ 63.5, 62.6, 30.1, 30.0, 17.9, 11.8; HRMS for $C_{13}H_{31}O_2Si$ [MH+] *m/z* calc. 247.2093, found 247.2096.

4-{[tris(propan-2-yl)silyl]oxy}butan-1-al (133):



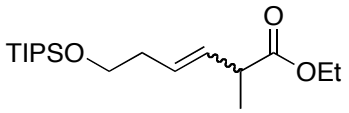
To a solution of the Dess-Martin periodinane (11.5 g, 27.3 mmol) in dry CH_2Cl_2 (160 mL) was added 4-{[tris(propan-2-yl)silyl]oxy}butan-1-ol (5.37 g, 21.84 mmol) in CH_2Cl_2 (40 mL). The solution was stirred 30 min, and then the mixture was diluted in diethyl ether (150 mL). A 1:1 mixture of saturated sodium thiosulfate and saturated sodium bicarbonate (100 mL) was added and the resulting solution was stirred both layers became clear. The organic layer was separated, washed with H_2O (200 mL), brine (200 mL), dried over Na_2SO_4, and then concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% EtOAc in hexanes) gave the aldehyde **133** as a colorless oil (5.06 g, 95%) whose spectral data matched those previously reported[13]: R_f = 0.53 (5% EtOAC in hexanes); IR (neat) 2943, 2892, 2867, 2716, 1729, 1464 cm^{-1}; ^1H NMR δ 9.81 (s, 1H), 3.74 (t, *J* = 5.9 Hz, 2H), 2.55 (t, *J* = 7.0 Hz, 2H), 1.89 (m, 2H), 1.06 (m, 21H); ^{13}C NMR δ 202.2, 62.2, 40.6, 25.5, 17.8, 11.7; HRMS for $C_{13}H_{29}O_2Si$ [MH+] *m/z* calc. 245.1937, found 245.1939.

Ethyl (2*E*)-6-{[tris(propan-2-yl)silyl]oxy}hex-2-enoate (134):



To a solution of triethylphosphonoacetate (8.05 mL, 40.0 mmol) in dry THF (125 mL) at 0 °C was added NaH (1.6 g, 40.0 mmol, 60% dispersion in mineral oil) portionwise. The suspension was stirred for 30 min, and then aldehyde **133** was added as a solution in dry THF (50 mL). The reaction was warmed to 23 °C and stirred 1.5h. The resulting solution was diluted in ether (250 mL), washed with H_2O (250 mL), brine (150 mL), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% EtOAc/hexanes) of the yellow residue gave ester **134** as a colorless oil (6.73g, 81%): R_f= 0.45 (5% EtOAc/hexanes); IR (neat) 2943, 2866, 1724, 1653, 1465, 1109 cm^{-1}; ^1H NMR δ 7.0 (dt, *J* = 15.9 Hz, 7.2 Hz, 1H), 5.81 (d, *J* = 17.6 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.71 (t, *J* = 6.2 Hz, 2H), 2.30 (q, *J* = 6.6 Hz, 2H), 1.70 (m, 2H), 1.29 (t, *J* = 7.3 Hz, 2H), 1.06 (m, 21H); ^{13}C NMR δ 149.1, 121.4, 95.3, 62.4, 60.1, 31.3, 28.7, 18.0, 14.2, 11.9; HRMS for $C_{17}H_{35}O_3Si$ [MH+] *m/z* calc. 315.2355, found 315.2358.

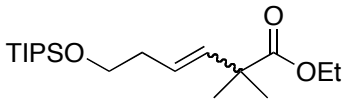
Ethyl 2-methyl-6-{[tris(propan-2-yl)silyl]oxy}hex-3-enoate:



To a solution of 1,1,1,3,3,3- hexamethyldisilazane (distilled from CaH_2, 5.4 mL, 25.68 mmol) in dry THF (40 mL) at –78 °C was added *n*-BuLi (10.85 mL, 25.68 mmol, 2.4 M solution in hexanes) and hexamethylphosphoramide (distilled from CaH_2, 4.5 mL, 25.68 mmol). The resulting solution was stirred 30 min. at –78 °C, and the *α,β*-unsaturated ester **134** (6.73 g, 21.4 mmol) was added as a solution in THF (20 mL).

The solution was warmed to 23 °C over 30 min. After 30 min of stirring, the solution was recooled to –78 °C and iodomethane (distilled, 4.94 mL, 79.2 mmol) was added and the solution stirred 30 min. The reaction was quenched by the addition of sat. aq. NH_4Cl (30 mL) and diluted in ether (75 mL). The organic layer was washed sat. aq. NH_4Cl (75 mL), water (75 mL), and brine (75 mL), dried (Na_2SO_4), and concentrated. Purification by column chromatography (5% EtOAc/hexanes) gave ethyl 2-methyl-6-{[tris(propan-2-yl)silyl]oxy}hex-3-enoate as a colorless oil which proved to be an inseperable mixture of the *E*/*Z* olefins (6.4 g, 91%): R_f = 0.31 (5% EtOAc/hexanes); IR (neat) 2943, 2889, 2867, 2722, 1738, 1464, 1177, 1105 cm^{-1}; ^1H NMR δ 5.52 (m, 4H), 4.11 (q, *J* = 7.2 Hz, 4H), 3.68 (m, 4H), 3.43 (m, 2H), 2.34 (m, 4H), 1.22 (m, 12H), 1.07(s, 42H); ^{13}C NMR δ 174.9, 174.9, 127.9, 62.8, 60.4, 38.3, 31.4, 25.8, 17.9, 14.1, 11.9; HRMS for $C_{18}H_{37}O_3Si$ [MH+] *m*/*z* calc. 329.2512, found 329.2519.

Ethyl 2,2-dimethyl-6-{[tris(propan-2-yl)silyl]oxy}hex-3-enoate (135):



To a solution of 1,1,1,3,3,3-hexamethyldisilazane (distilled from CaH_2, 8.1 mL, 38.35 mmol) in dry THF (60 mL) at –78 °C was added *n*-BuLi (16.28 mL, 38.35 mmol). The solution was stirred for 30 min at 0 °C, and then ethyl 2-methyl-6-{[tris(propan-2-yl)silyl]oxy}hex-3-enoate (10.5 g, 31.96 mmol) was added as a solution in THF (30 mL). The reaction was stirred for 30 min at 23 °C, cooled to 0 °C, methyl iodide (distilled, 7.5 mL, 118.25 mmol) was added and stirred an additional 30 min. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and diluted in ether (100 mL). The organic layer

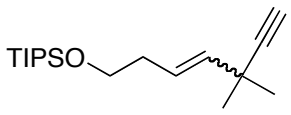
was washed with sat. aq. NH_4Cl (100 mL), water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (5% EtOAc/hexanes) gave the *gem*-dimethyl ester **135** as a colorless oil which proved to be an inseparable mixture of *E*/*Z* olefins (8.10g, 74%). R_f = 0.31 (5% EtOAc/hexanes); IR (neat) 2956, 2929, 2857, 1732, 1256, 1020, 836, 775 cm^{-1}; ^1H NMR δ 5.52 (m, 4H), 4.11 (q, *J* = 7.2 Hz, 4H), 3.68 (m, 4H), 3.43 (m, 2H), 2.34 (m, 4H), 1.22 (m, 12H), 1.07(s, 42H); ^{13}C NMR δ 174.9, 174.9, 136.2, 130.3, 127.9, 125.3, 63.3, 63.2, 63.0, 62.8, 60.4, 38.3, 36.3, 31.4, 31.3, 29.6, 29.5, 25.8, 25.0, 18.0, 17.9, 17.8, 14.1, 14.0, 12.3, 11.9; HRMS for $C_{19}H_{40}O_3Si$ [MH+] *m*/*z* calc. 343.2512, found 343.2519.

(3*Z*)-2,2-dimethyl-6-{[tris(propan-2-yl)silyl]oxy}hex-3-enal (*Z*-137) and (3*E*)-2,2-dimethyl-6-{[tris(propan-2-yl)silyl]oxy}hex-3-enal (*E*-136):

To a stirred solution of ester **135** (8.0 g, 23.35 mmol) in dry ether (250 mL) at –78 °C was slowly added lithium aluminum hydride (s), portionwise until no starting material was evident by TLC. The mixture was stirred an additional 10 min and warmed to 0 °C. The reaction was quenched by the dropwise addition of sat. aq. Na_2SO_4 and then poured into sat. aq. potassium sodium tartrate (100 mL). The suspension was extracted with ether (2 x 100 mL) and the organic phase filtered over celite to remove any remaining aluminum. The washings were concentrated to give a colorless oil which was used without further purification. To a solution of the Dess-Martin periodinane (12.0 g, 28.0 mmol) in dry CH_2Cl_2 (100 mL) was added the intermediate alcohol as a solution in dry

DCM (30 mL). The solution was stirred 30 min, diluted in ether (100 mL), and then poured into a 1:1 sat. aq. sodium thiosulfate/sat. aq sodium bicarbonate solution (100 mL). The solution was stirred until both phases were clear. The organic layer was separated, washed with brine (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (5% EtOAc/hexanes) gave aldehydes *cis*- **137** and *trans*- **136** as a colorless oil (6.7 g, 96% from **135**) which proved to be a mixture of alkene isomeric aldehydes. *cis*- **137**: R_f = 0.42 (5% EtOAc/hexanes); IR (neat) 2959, 2943, 2892, 2866, 1727, 1464, 1106, 883 cm^{-1}; ^1H NMR δ 9.50 (s, 1H), 5.59 (dt, *J* = 11.4, 7.4 Hz, 1H), 5.39 (dt, *J* = 11.4 Hz, 1.5 Hz, 1H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.16 (dq, *J* = 6.0, 1.5 Hz, 2H), 1.20 (s, 6H), 1.04 (s, 21H); ^{13}C NMR δ 203.8, 132.8,131.2, 63.3, 62.7, 47.6, 32.2, 23.2, 17.9, 11.9; *trans*- **136**: R_f = 0.40 (5% EtOAc/hexanes); IR (neat) 2959, 2943, 2892, 2866, 2704, 1728, 1464, 1107, 883 cm^{-1}; ^1H NMR δ 9.35 (s, 1H), 5.60 (m, 1H), 5.40, (m, 1H), 3.68 (m, 2H), 2.29 (m, 2H), 1.17 (s, 6H), 1.04 (s, 21H); ^{13}C NMR δ 202.5, 133.0, 129.1, 62.9, 62.7, 48.4, 36.6, 21.4, 17.9, 11.9; HRMS for $C_{17}H_{35}O_2Si$ [MH+] *m/z* calc. 299.2406, found 299.2404.

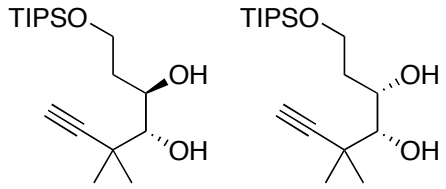
{[5,5-dimethylhept-3-en-6-yn-1-yl]oxy}tris(propan-2-yl)silane (138)



To a stirred solution of aldehydes *cis*- **137** and *trans*- **136** (4.44 g, 15.33 mmol) in methanol (dried over $MgSO_4$ before use, 150 mL) with K_2CO_3 (4.56 g, 33.73 mmol) was added Ohira's reagent (**100**) (3.55g, 18.4 mmol) and the suspension stirred overnight. The mixture was diluted in EtOAc (100 mL), washed with sat. aq. $NaHCO_3$ (100 mL),

water (100mL), brine (100 mL), and concentrated. Purification by column chromatography (SiO_2, hexanes) gave alkyne **138** as a colorless oil (3.1g, 70%). **138**: R_f = 0.24 (hexanes); IR (neat) 3311, 3010, 2942, 2866, 2725, 1464, 1106, 883 cm^{-1}; ^1H NMR δ 5.74 (m, 2H), 5.39 (m, 2H), 3.75 (m, 2H), 3.75 (t, *J*= 6.6 Hz, 2H), 2.67 (q, *J*= 6.4 Hz, 2H), 2.27 (q, J= 6.5 Hz, 2H), 2.23 (s, 1H), 2.18 (s, 1H), 1.38 (s, 6H), 1.30 (s, 6H), 1.07 (s, 42H); ^{13}C NMR δ 137.5, 136.1, 128.4, 124.4, 91.1, 90.0, 69.2, 68.3, 63.2, 63.0, 35.9, 33.2, 31.7, 31.3, 30.7, 29.8, 18.0, 12.0, 11.9; HRMS for $C_{18}H_{35}OSi$ [MH+] *m/z* calc.

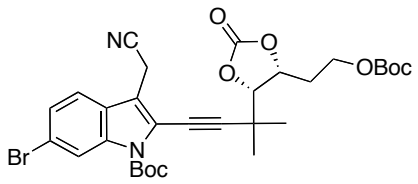
5,5-dimethyl-1-{[tris(propan-2-yl)silyl]oxy}hept-6-yne-3,4-diol (139 & 140):



A solution of the olefin **138** (2.1 g, 7.12 mmol) in wet acetone (30 mL) with 4-methylmorpholine-*N*-oxide (3.34 g, 28.5 mmol) and $K_2O_4Os•2H_2O$ (cat.) was stirred overnight. The solution turned black as the $K_2O_4Os•2H_2O$ was added. Additional 4-methylmorpholine-*N*-oxide was added as needed until the reaction was complete by TLC (1:1 EtOAc:hexanes). To this was added aq. $Na_2S_2O_3$ (1M, 5 mL) to quench the osmate, and the solution turned to a dark red color. The aqueous mixture was extracted with CH_2Cl_2 (3 x 15 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The diols **139** and **140** were collected in quantitative yield as a mixture of diastereomers (2.34 g, 100%) and carried on without purification. Purification by column chromatography (30% EtOAc in hexanes) was performed for characterization purposes only: *cis*-**140**: R_f = 0.64(1:1 EtOAc/ hexanes); IR (neat) 3420, 2943, 2866, 1101 cm^{-1}; ^1H NMR δ 4.32 (dd, *J* = 8.7,

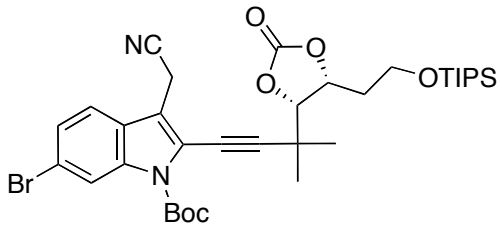
3.6 Hz, 1H), 4.16 (dd, J = 8.9, 3.7 Hz, 1H), 3.69 (m, 2H), 2.18 (s, 1H), 2.02 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H), 1.07 (s, 21H); ^{13}C NMR δ 80.2, 78.4, 70.0, 60.1, 37.6, 33.8, 26.6, 23.4, 20.1, 17.8, 11.7; HRMS for $C_{18}H_{37}O_3Si$ [MH+] m/z calc. 329.2512, found 329.2520. *trans*-**139**: R_f = 0.49 (1:1 EtOAc/ hexanes); IR (neat) 3420, 2943, 2866, 1464, 1104 cm^{-1}; ^{1}H NMR δ 4.04 (m, 1H), 3.98 (m, 1H), 3.78 (m, 2H), 2.19 (s, 1H), 1.87 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H), 1.07 (s, 21H); ^{13}C NMR δ 84.1, 76.6, 61.4, 60.8, 37.9, 24.4, 21.3, 17.9, 16.9, 11.8, 11.8; HRMS for $C_{18}H_{37}O_3Si$ [MH+] m/z calc. 329.2512, found 329.2520.

4-(2-Methylbut-3-yn-2-yl)-5-(2-{[tris(propan-2-yl)silyl]oxy}ethyl)-[1,3]dioxolan-2-one (*cis*-131) and 4-(2-Methylbut-3-yn-2-yl)-5-(2-{[tris(propan-2-yl)silyl]oxy}ethyl)-[1,3]dioxolan-2-one (*trans*-131):



To a stirred solution of the diols **139** and **140** (2.34 g, 7.12 mmol) in CH_2Cl_2 (40 mL) with pyridine (3 mL) was added triphosgene (2.65 g, 8.92 mmol) at 0 °C. The mixture was allowed to slowly warm to room temperature 3h. After cooling back down to 0 °C, the reaction was quenched with 10% aq. NH_4Cl (50 mL). The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2 x 50 mL). The combined organics were washed with 10% aq. NH_4Cl (50 mL) and brine (30mL) and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc in hexanes) gave a mixture of the desired carbonate diastereomers **131**, otherwise pure, as a yellow oil (2.17 g, 86%): *characterized as before*.

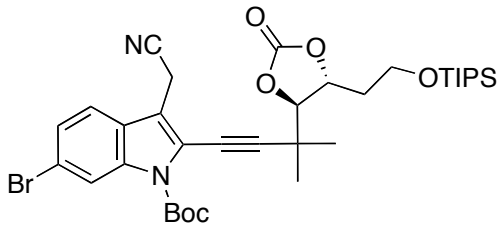
***tert*-butyl 6-bromo-3-(cyanomethyl)-2-{3-methyl-3-[-2-oxo-5-(2-{[tris(propan-2-yl)silyl]oxy}ethyl)-1,3-dioxolan-4-yl]but-1-yn-1-yl}-1H-indole-1-carboxylate (132):**



A mixture of *cis*-acetonide alkyne **131** (0.900 g, 2.54 mmol), indole **87** (0.956 g, 2.31 mmol), and $PdCl_2(PPh_3)_2$ (0.081 g, 0.115 mmol) in triethylamine (25 mL) distilled over CaH_2) was thoroughly degassed with Ar at room temperature. To this mixture was added a degassed suspension of CuI (0.066 g, 0.345 mmol) in triethylamine (2mL). The reaction was then stirred overnight at 23 °C under an atmosphere of Ar. The reaction was filtered over celite, washing with ether, and organic filtrate was concentrated *in vacuo*. Column chromatography (10% EtOAc/hexanes) on the crude residue gave the 2-coupled product **132** as an orange oil which produced a foam *in vacuo* (1.06 g, 67%): R_f = 0.18 (20% EtOAc/ hexanes); IR (neat) 2942, 2865, 1806, 1746, 1354, 1145 cm^{-1}; ^1H NMR δ 8.24 (s, 1H), 7.45 (dd, *J* = 8.1, 4.0 Hz, 2H), 5.16 (dd, *J* = 7.3, 3.0 Hz, 1H), 4.55 (d, *J* = 7.3 Hz, 1H), 3.91 (m, 2H), 3.82 (bs, 2H), 2.35 (m, 2H), 1.70 (s, 9H), 1.59 (s, 3H), 1.52 (s, 3H), 1.02 (m, 21H); ^{13}C NMR δ 154.0, 148.2, 135.5, 126.6, 125.6, 120.6, 119.2, 118.8,

116.2, 113.6, 102.8, 85.4, 83.8, 74.2, 58.8, 34.6, 32.5, 27.9, 27.8, 26.6, 26.0, 17.7, 17.7, 13.4, 11.6; HRMS for $C_{34}H_{46}N_2O_6BrSi$ [MH+] *m/z* calc. 685.2309, found 685.2315.

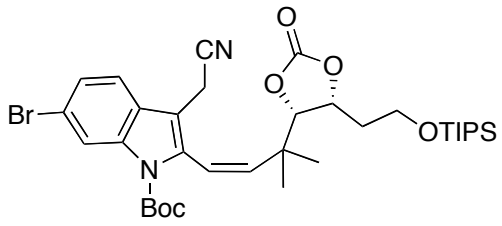
***tert*-butyl 6-bromo-3-(cyanomethyl)-2-{3-methyl-3-[-2-oxo-5-(2-{[tris(propan-2-yl)silyl]oxy}ethyl)-1,3-dioxolan-4-yl]but-1-yn-1-yl}-1H-indole-1-carboxylate (*trans*-132):**



A mixture of *cis*- and *trans*- acetonide alkynes **131** (0.390 g, 1.10 mmol), indole **87** (0.414 g, 1.0 mmol), and $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol) in triethylamine/THF (1:1, 15 mL) distilled over CaH_2) was thoroughly degassed with Ar at room temperature. To this mixture was added a degassed suspension of CuI (0.029 g, 0.15 mmol) in triethylamine (2mL). The reaction was then stirred overnight at 23 °C under an atmosphere of Ar. The reaction was filtered over celite, washing with ether, and organic filtrate was concentrated *in vacuo*. Column chromatography (10% EtOAc/hexanes) on the crude residue gave the 2-coupled products **132** as an orange oil which produced a foam *in vacuo* (0.280 g, 41%): *cis*-**132**: characterized as above. *trans*-**132:** R_f = 0.26 (10% EtOAc/ hexanes); IR (neat) 2942, 2865, 1801, 1739 cm^{-1}; ^1H NMR δ 8.38 (s, 1H), 7.44 (m, 2H), 5.09 (dd, *J* = 4.9, 3.0 Hz, 1H), 4.42 (d, *J* = 4.9 Hz, 1H), 3.75 (d, *J* = 3.1 Hz, 1H), 3.70 – 3.99 (m, 2H), 2.80 (s, 2H), 2.20 (m, 2H), 1.69 (s, 9H), 1.42 (s, 3H), 1.38 (s, 3H), 1.02 (m, 21H); ^{13}C NMR δ 185.4, 154.0, 148.2, 136.9, 126.8, 125.9, 123.2, 118.8,

118.7, 115.9, 111.9, 111.4, 83.4, 83.6, 80.3, 68.5, 58.9, 33.7, 32.6, 29.7, 28.1, 26.6, 25.8, 17.9, 14.6, 12.2, 12.0, 11.8; HRMS for $C_{34}H_{46}N_2O_6BrSi$ [MH+] *m/z* calc. 685.2309, found 685.2315.

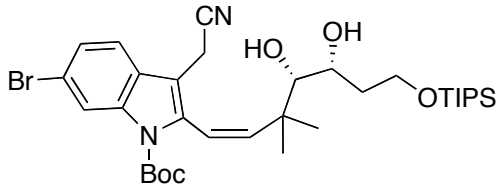
***tert*-butyl 6-bromo-3-(cyanomethyl)-2-[(1Z)-3-methyl-3-[2-oxo-5-(2-{[tris(propan-2-yl)silyl]oxy}ethyl)-1,3-dioxolan-4-yl]but-1-en-1-yl]-1H-indole-1-carboxylate (141):**



A solution of alkyne **132** (0.265 g, 0.385 mmol) in ethanol (20 mL) was saturated with hydrogen gas and then was treated with PtO_2 (35 mg). The heterogeneous mixture was stirred 18h under an atmosphere of H_2. The mixture was filtered over celite and concentrated *in vacuo*. Column chromatography (20% EtOAc/hexanes) yielded the desired *cis*-olefin **141** as a yellow foam (0.158 g, 60%): R_f = 0.36 (10% EtOAc/hexanes); IR (neat) 2942, 2865, 1805, 1739, 1457, 1349, 1122 cm^{-1}; ^1H NMR (some resonances doubled due to carbamate resonance) δ 8.33 (s, 0.5H), 8.27 (s, 0.5H), 7.48 (dd, *J* = 8.1, 5.2 Hz, 1H), 7.46 (dd, *J* = 8.1, 5.2 Hz, 1H), 6.46 (d, *J* = 12.6 Hz, 1H), 6.09 (d, *J* = 12.6 Hz, 0.5H), 5.95 (d, *J* = 12.6 Hz, 0.5H), 5.19 (d, *J* = 7.3 Hz, 1H), 5.01 (m, 1H), 4.43 (d, *J* = 7.2 Hz, 0.5H), 4.38 (d, *J* = 7.2 Hz, 0.5H), 3.87 (m, 2H), 3.71 (bs, 2H), 1.92 – 2.17 (m, 2H), 1.67 (s, 4.5H), 1.66 (s, 4.5H), 1.58 (s, 3H), 1.51 (s, 3H), 1.06 (m, 21H); ^{13}C NMR (some resonances doubled due to carbamate resonance) δ 154.1, 154.0, 149.0, 148.9, 139.4, 138.2, 135.8, 135.7, 133.7, 133.3, 128.1, 126.4, 126.2, 124.9, 121.9, 120.1, 119.8, 119.3, 119.2, 118.9, 118.8, 116.4, 116.3, 108.3, 108.2, 86.2, 82.2, 85.3, 85.1, 58.6, 58.5,

42.5, 39.8, 39.3, 33.2, 33.2, 33.0, 32.9, 32.3, 27.9, 27.9, 27.8, 25.7, 23.8, 22.9, 19.7, 17.7, 17.5, 13.9, 13.8, 11.6, 11.5; HRMS for $C_{34}H_{50}N_2O_6SiBr$ [MH+] *m/z* calc. 689.2622, found 689.2626.

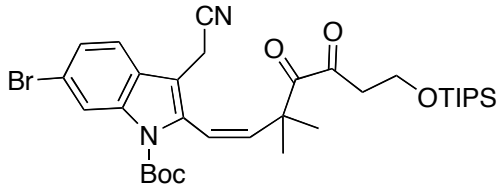
***tert*-butyl 6-bromo-3-(cyanomethyl)-2-[(1Z)-4,5-dihydroxy-3,3-dimethyl-7-{[tris(propan-2-yl)silyl]oxy}hept-1-en-1-yl]-1H-indole-1-carboxylate (142):**



A solution of carbonate **141** (590 mg, 0.858 mmol) in 1,4-dioxane (15 mL) was treated with 10% aq. NaOH (5 mL) was stirred at 23 °C for 4h. The solution was diluted in ether (25 mL), washed with water (20 mL), brine (20 mL) and concentrated. The crude oil was purified by column chromatography (SiO_2, gradient elution, 30% EtOAc in hexanes to 60% EtOAc in hexanes) to yield diol **142** as a colorless oil (453 mg, 80%): R_f = 0.26 (10% EtOAc/hexanes); IR (neat) 3446, 2918, 2866, 1739, 1733, 1094 cm^{-1}; ^1H NMR (some resonances doubled due to carbamate resonance) δ 8.27 (s, 0.5H), 8.26 (s, 0.5H), 7.48 (dd, *J* = 8.1, 5.2 Hz, 1H), 7.42 (dd, *J* = 8.1, 5.2 Hz, 1H), 6.28 (d, *J* = 12.6 Hz, 0.5H), 6.26 (d, *J* = 12.6 Hz, 0.5H), 6.10 (d, *J* = 12.6 Hz, 0.5H), 6.06 (d, *J* = 12.6 Hz, 0.5H), 3.67 – 4.09 (m, 4H), 3.76 (d, *J* = 10.6 Hz, 1H), 3.74 (d, *J* = 8.6 Hz, 1H), 3.33 (dd, *J* = 7.6, 5.9 Hz, 1H), 1.84 – 1.96 (m, 3H), 1.71 (s, 4.5H), 1.68 (s, 4.5H), 1.08 (s, 21H), 1.03 (s, 1.5H), 1.02 (s, 1.5H), 0.87 (s, 3H); ^{13}C NMR (some resonances doubled due to carbamate resonance) δ 144.2, 142.9, 135.6, 135.2, 126.5, 126.2, 126.2, 119.1, 118.8, 118.3, 118.2, 116.8, 116.7, 116.1, 108.1, 85.0, 81.2, 80.2, 73.2, 71.7, 63.2, 61.4, 41.5,

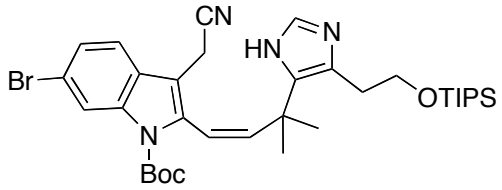
41.2, 34.9, 33.6, 27.9, 27.9, 24.8, 24.6, 23.3, 21.7, 17.7, 13.7, 13.6, 11.5, 11.4; HRMS for $C_{33}H_{52}N_2O_5SiBr$ [MH+] *m/z* calc. 663.2829, found 663.2826.

***tert*-butyl 6-bromo-3-(cyanomethyl)-2-[(1Z)-3,3-dimethyl-4,5-dioxo-7-{[tris(propan-2-yl)silyl]oxy}hept-1-en-1-yl]-1H-indole-1-carboxylate (143):**



A solution of diol **142** (153 mg, 0.231 mmol) in DCM (10 mL) was treated with Dess-Martin periodinane (216 mg, 0.51 mmol) and stirred at 23 °C for 16h. The solvent was removed and the residue purified *via* flash column chromatography (SiO_2, 10% EtOAc in hexanes) providing dione **143** as a bright yellow oil (90 mg, 59%): R_f = 0.75 (30% EtOAc/hexanes); IR (neat) 2928, 2866, 1738, 1732, 1716, 1456, 1295, 1143, 1123 cm^{-1}; ^1H NMR δ 8.34 (s, 1H), 7.44 (dd, *J* = 8.3, 1.5 Hz, 2H), 6.61 (d, *J* = 16.4 Hz, 1H), 6.16 (d, *J* = 16.6 Hz, 1H), 4.03 (t, *J* = 6.0 Hz, 2H), 3.87 (s, 2H), 2.98 (t, *J* = 6.0 Hz, 2H), 1.67 (s, 9H), 1.57 (bs, 3H), 1.43 (bs, 3H), 1.02 (m, 21H); ^{13}C NMR δ 200.0, 197.4, 139.5, 139.2, 136.0, 133.5, 126.5, 125.9, 120.5, 119.3, 118.9, 118.8, 118.7, 108.6, 58.0, 47.7, 40.8, 28.0, 27.8, 25.3, 23.9, 17.6, 13.6, 11.6; HRMS for $C_{33}H_{48}N_2O_5BrSi$ [MH+] *m/z* calc. 659.2516, found 659.2515.

***tert*-butyl 6-bromo-3-(cyanomethyl)-2-[(1Z)-3-methyl-3-[4-(2-{[tris(propan-2-yl)silyl]oxy}ethyl)-1H-imidazol-5-yl]but-1-en-1-yl]-1H-indole-1-carboxylate (144):**



To a stirred solution of dione **143** (140 mg, 0.222 mmol) in acetic acid (14 mL) was added NH_4OAc (420 mg, 5.20 mmol) and paraformaldehyde (58 mg, 1.90 mmol). The solution was heated to 60 °C and stirred 3h. The reaction was allowed to cool to room temperature, at which time the solution was slowly diluted in ether (20 mL) and poured slowly into sat. aq. $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer extracted with ether (2 x 10 mL). The combined organics were washed with brine (10 mL) and concentrated to give a crude orange oil which was determined to be a mixture of starting dione and desired imidazole. Purification by column chromatography (4% MeOH in CH_2Cl_2) gave pure imidazole **144** as a red oil (39 mg, 26% overall yield): R_f = 0.36 (4% MeOH in CH_2Cl_2); IR (neat) 3446, 2916, 1733, 1653, 1558 cm^{-1}; ^1H NMR δ 8.30 (s, 1H), 7.53 (s, 1H), 7.42 (bs, 2H), 6.57 (d, J = 16.3 Hz, 1H), 6.09 (d, J = 16.3 Hz, 1H), 3.80 (s, 2H), 3.95 (t, J = 5.5 Hz, 2H), 2.96 (t, J = 5.5 Hz, 2H), 1.66 (s, 9H), 1.62 (bs, H), 1.05 (m, 21H); ^{13}C NMR δ 148.6, 137.4, 135.1, 131.2, 128.0, 127.8, 126.4, 126.2, 121.2, 120.6, 120.4, 119.2, 118.5, 108.2, 85.8, 35.6, 30.5, 27.9, 27.8,

26.6, 26.0, 17.7, 17.6, 13.4, 11.4; HRMS for $C_{34}H_{49}N_4O_3BrSi$ [MH+] *m/z* calc. 671.2726, found 671.2730.

3.3. REFERENCES

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PART 2: EFFORTS TOWARD THE TOTAL SYNTHESIS OF (–)-PLATENSIMYCIN

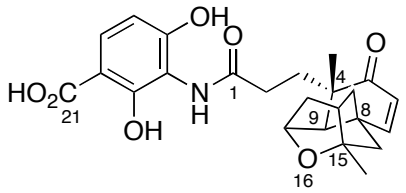
Chapter 4: Platensimycin

4.1. Platensiymycin is a FabF Inhibitor with Potent Antibiotic Properties

The discovery of antibacterial agents and their utility in man's defense against infection could be considered the most important medical advance of the 20th century and and beyond.[1] However, the advances made in the battle against bacteria have slowed as novel targets for antibiotic activity have eluded scientists.[2] The need for new antibiotics and anitbacterial targets is a longstanding and constant problem. The emergence of bacterial resistance to existing treatments means that bacterial infection will forever be a threat to human life and health.[3]

4.1.1. Isolation and Characterization

The search for novel therapeutic agents often, and most successfully, has been rooted in natural products isolation, characterization, and assay.[4] Merck scientists assayed the natural product extracts from a strain of *Streptomyces platensis*, collected from a soil sample in South Africa. The extracts, along with 250,000 other nautral product extracts, were screened in both target-based whole-cell and biochemical assays leading to the identification of a compound with potent antibiotic properties, which was structurally determined to be (–)-platensimycin **160** (Figure 4. 1).[5]



160
(–)-Platensimycin

Figure 4. 1: Platensimycin

Platensimycin was isolated from the fermentation broth of *Streptomyces platensis* in ~2 – 4 mg/L. Based on the spectral data gathered, its structure was assigned as consisting of a 3-aminobenzoic acid and a pentacyclic ketolide joined through an amide linkage. The structure was further confirmed by the X-ray analysis of 6′-bromoplatensimycin.[6,7]

4.1.2. Biological Activity

Platensimycin has been shown to exhibit both *in vitro* and *in vivo* activity against Gram-positive bacteria including methicillin resistant *Staphyloccocus aureus* (MRSA) and vancomycin resistant bacteria, two drug-resistant bacteria afflicting hospitals. The *in vitro* anitbacterial activity of platensimycin against various strains of *S. aureus* (MIC, 0.5 μg/mL) was greater than that of linezolid, a currently used MRSA antibiotic, and with no observable toxicity.

The target of platensimycin was determined to be FabF, an essential component of bacteria fatty acid biosynthesis. It is believed that the antibiotic's activity arises from the inhibition of FabF. Single-enzyme binding assays demonstrated not only that it is a potent inhibitor of FabF (IC_{50} = 48 nM for *S. aureus* and 160 nM for *E. coli*.), but that it is selective in its binding (IC_{50} = 67 μM for FabH). By crippling the bacteria's ability to make fatty acids, it prevents formation of the fatty cell membranes the bacteria needs to

grow.[8,9] While other inhibitors of fatty acid biosynthesis are known, none are clinically used today. Platensimycin clearly represents a new class of antibiotics.[10,11] Its novel mechanism of action represents the first novel target for antibiotics research since the early 1960's.

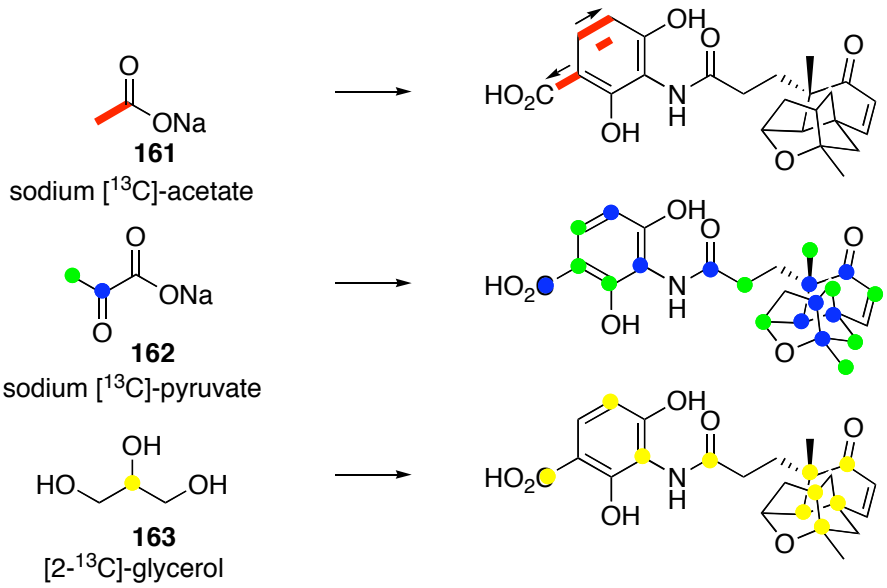
Still, platensimycin is not ready for clinical use. Though *in vivo* activity has been established in a mouse model (a 10^4 – 10^5 fold decrease of infection over a 24 hour period), continuous delivery was necessary to maintain efficacy. This is an indication of a poor pharmacokinetic profile for platensimycin, an issue that would need to be addressed before clinical development.

Structurally, platensimycin's activity is believed to be derived from the anilide portion of the molecule. During initial investigations into platensimycin's mechanism of action, a structure of it bound to a mutant FabF enzyme was obtained. The X-ray revealed that the benzoic acid ring is oriented in the active site of the enzyme, while the ketolide is partially exposed to solvent at the mouth of the binding pocket. Additionally, the benzoic acid carboxylate engages in a strong interaction with active site histidine residues. These observations are circumstantial evidence that point to the benzoic acid being responsible for biological activity. These conclusions were corroborated in later studies on related compounds (*vide infra*).

4.1.3. Biosynthesis

The biosynthetic origin of platensimycin has been examined through feeding studies of labeled precursors.[12] The isotopic incorporations were determined through comparisons of the ^{13}C NMR spectra of the labeled products to that of the natural

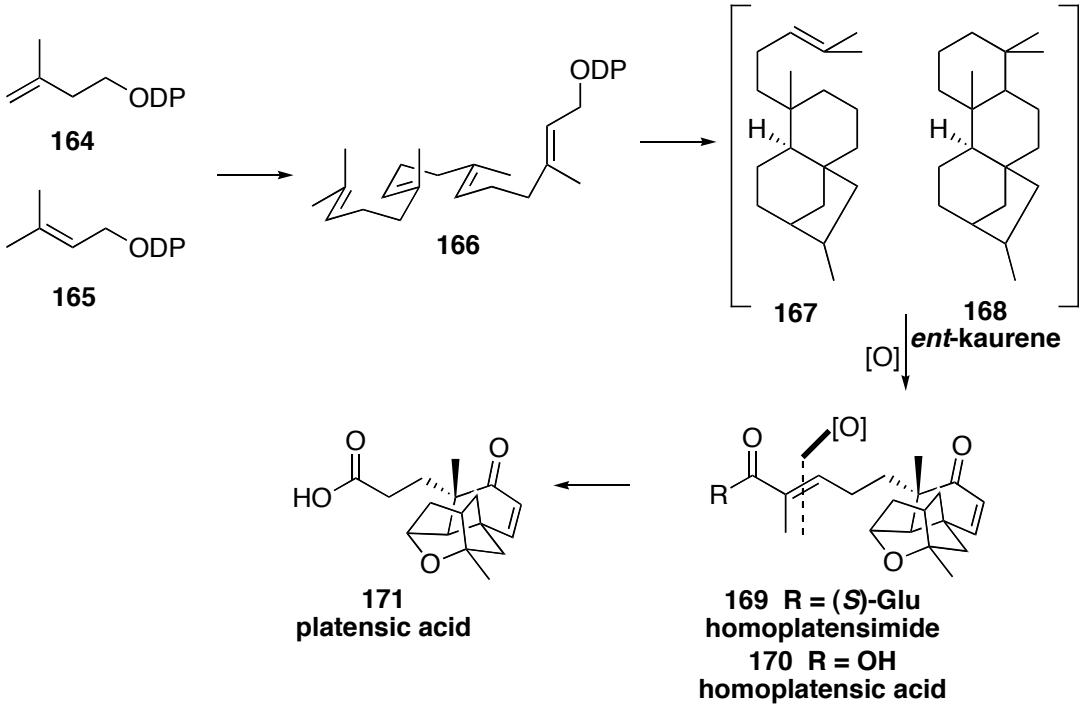
substance (Scheme 4. 1). The likely biosynthetic pathways were deduced based on the results.



Scheme 4. 1: Stable isotope incorporation studies on platensimycin

Feeding the *S. platensis* culture in successive experiments with sodium [1-^{13}C]acetate (**161**) and sodium [2-^{13}C]acetate showed enrichment in only the aromatic anilide portion of the molecule in a tail-tail coupling (red,Scheme 4. 1), indicative of TCA cycle (tricarboxylic acid, aka Krebs or citric acid cycle) participation. When the culture was fed with sodium [2-^{13}C]pyruvate (**162**) and sodium [3-^{13}C]pyruvate (blue and green, Scheme 4. 1), an isotopic enrichment pattern was observed throughout the natural product, indicating that platensimycin is biosynthetically derived from pyruvate. Furthermore, as glycerol is biosynthetically converted to pyruvate, the culture was also fed with [2-^{13}C]glycerol (**163**), confirming the earlier conclusions. These results are consistent with a non-mevalonate terpenoid pathway[13,14] invoked for the biosynthesis of the structurally related *ent*-kaurene class of natural products.

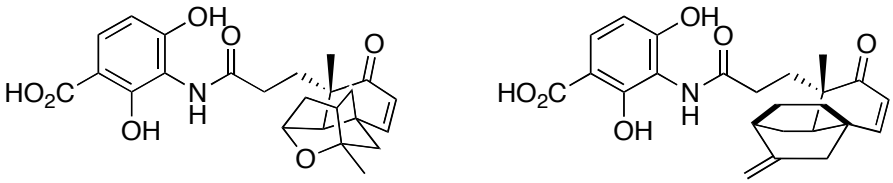
Interest into the biosynthesis of platensimycin and the possible discovery of bioactive congeners led to the isolation of homoplatensimide **169**.[15] The clear mapping of the homoplatensic acid skeleton onto that of the *ent*-kaurenes is further evidence of their biogenetic relationship. The non-mevalonate terpenoid pathway believed to be operative, converts isopentenyl diphosphate **164** and dimethylallyl diphosphate **165** into geranylgeranyl diphosphate **166** which, in turn is cyclized to the skeletons of homoplatensic precursor **167** and *ent*-kaurene **168**. Extensive oxidation of the platensic carbon backbone provides homoplatensic acid **170** and homoplatensimide **169**. Oxidative cleavage of the α,β-unsaturated acid forms the platensic acid structure **171** which couples with the anilide to form the active agent.



Scheme 4. 2: Biosynthesis of platensimycin *via* homoplatensimide **169**

4.1.4. Biological Activity Revisited

The isolation of homoplatensimide **169**, homoplatensic acid **170**, and platensic acid **171** was used not only for biosynthetic studies but in biological assays as well (Scheme 4. 2).[15] The congeners isolated from the fermentation broth, as well as a variety of compounds thus synthetically derived, were assayed. None possessed the 3-aminobenzoic acid moiety present in the natural product and none were found to be active. Therefore, the benzoic acid was deduced to be responsible for and necessary for FabF inhibition.[16] This conclusion has been corroborated in synthetic analog work by Nicolaou where variations on the ketolide portion such as removing the oxygen (carbaplatensimycin)[17] and attaching a simpler hydrophobic group (adamantaplatensimycin),[18] all with the anilide portion present, led to compounds with significant *in vitro* activity, albeit slightly weaker than that of platensimycin. Furthermore, the discovery of platencin[19,20] **172** (Figure 4. 2) as a potent antibiotic whose structural similarities to platensimycin **160** include an identical anilide portion and a similar hydrophobic ketolide lacking the ethereal oxygen, corroborated that conclusion. Thus, the biological activity of platensimycin **160** can be confidently attributed to the aminobenzoic acid moiety.



160
Platensimycin

172
Platencin

Figure 4. 2: Platencin and Platensimycin

4.2. SYNTHESES OF PLATENSIMYCIN

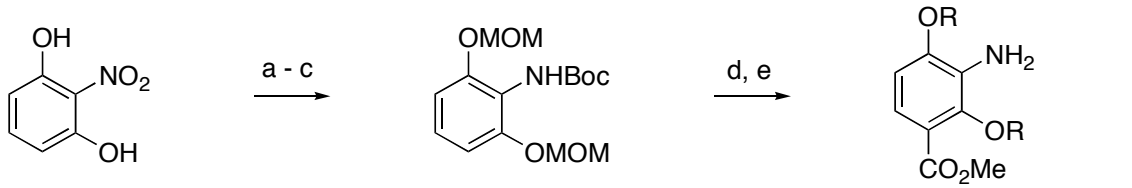
The discovery of platensimycin **160** as a potent antibiotic with a novel mode of action was provocative for scientists interested in new antibiotics. Combined with the compact, deceptively complex, and synthetically intriguing tetracyclic enone acid core, the result was numerous synthetic groups working to synthesize the natural product. Platensimycin's disclosure in 2006 set off a large number of research groups work resulting in the first total synthesis of platensimycin by Nicolaou later in 2006. This work was followed by several formal syntheses, most of which were recently reviewed.[21] Some of the approaches to the synthesis of platensimycin will be discussed herein.

4.2.1. Nicolaou's First Total Synthesis of (±)-Platensimycin

Nicolaou's total synthesis of platensimycin was reported roughly five months after the initial publication in Nature. The strategy utilized by Nicolaou and co-workers involved a late stage combination of the anilide and ketolide portions.[22] The synthesis of a protected version of aniline **175** for coupling to the tetracyclic acid **171** was believed to be necessary at the time. Their approach to the ketolide synthesis involved the intramolecular reductive addition of an aldehyde to a dienone, the product of which was advanced to the ether.

The synthesis of the aniline portion began from 2,5-dihydroxynitrobenzene **173** with the protection of the phenolic OH's as their methoxymethyl ethers (Scheme 4. 3). Hydrogenation of the nitro group and protection of the resultant aniline as its *t*-butyl carbamate gave aniline **174** in 81% over three steps. Directed *ortho* lithiation of aniline **174** was followed by quenching with methyl cyanoformate to install the carboxylate.

Pyrolysis of the intermediate *N*-Boc aniline provided the protected aniline **175a** in 45% over two steps. The aniline **175a** was now ready for coupling to the enone acid **171**.



173 **174** **175 R = H**
Platensimycin Aniline
175a R = MOM

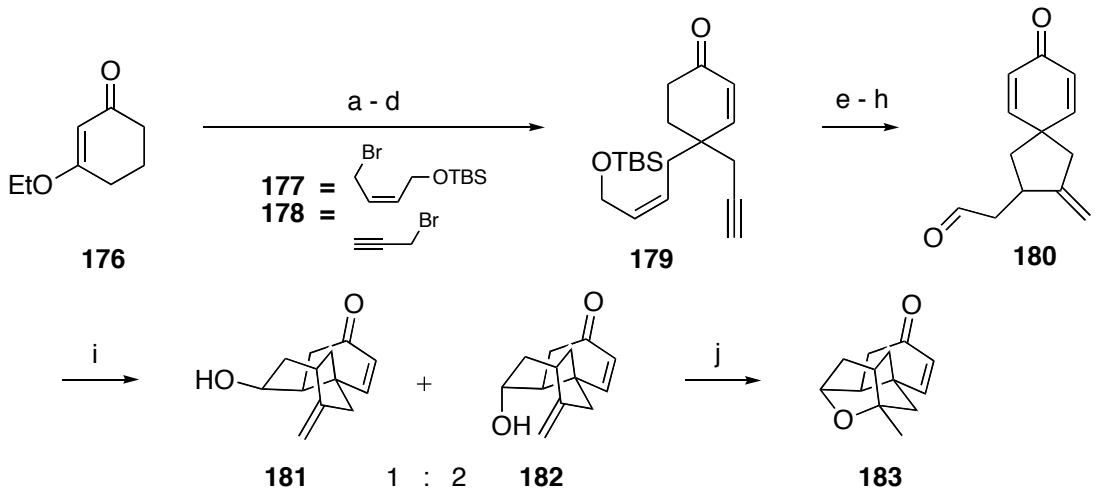
Reagents and Conditions: a) NaH, MOMCl, THF, 0 °C, 82%; b) H_2, 10% Pd/C, MeOH/EtOAc, 99%; c) Boc_2O, 40 °C, 99%; d) *n*-BuLi, TMSCl, -78 °C, then *n*-BuLi, methyl cyanoformate, THF, -78 °C, then 1N aq. HCl, 54%; e) 1,2-DCB, 205 °C (microwave), 83%.

Scheme 4. 3: Nicolaou's synthesis of the platensimycin aniline

The synthesis of the ketolide portion of platensimycin, began with the conversion of vinylogous ester **176** to the γ-disubstitued enone **179** (Scheme 4. 4). The sequential alkylation of ketone **176** with allylic bromide **177** and propargyl bromide **178** followed by the reduction and hydrolysis of the vinylogous ester provided enone **179** in 75% yield over four steps; the TBS protecting group was reinstalled after the hydrolysis step. Cycloisomerization of the enyne **179** using a ruthenium catalyst developed by Trost, formed the spriocyclopentane ring with concomitant isomerization the olefin to an intermediate silyl enol ether. Oxidation of the enone to the dienone using the Saegusa protocol [$Pd(OAc)_2$ catalyzed oxidation of a silyl enol ether] preceded hydrolysis of the silyl enol ether which gave the key aldehyde **180**.

When aldehyde **180** was treated with SmI_2, the aldehyde was reduced to an anion radical which intramolecularly attacked the symmetric dienone, forming the tricyclic compound **182**. The reaction produced a 2 : 1 mixture of alcohol epimers **181** and **182**, of which, only the axial **182** is useful in this work. The ether was formed when axial

alcohol **182** was subjected to TFA, forming the tertiary cation which was trapped by the alcohol. This tetracyclic enone **183** lacked only the methyl and propionyl side chains of platensic acid.



Reagents and Conditions: a) LDA, **178**, THF, -78 °C, 92%; b) LDA, **179**, THF, -78 °C, 97%; c) DIBALH, PhMe, -78 °C, then MeOH, 2N aq. HCl, 22 °C; d) TBSCl, imid, DMF, 84% two steps; e) $[CpRu(MeCN)_3]PF_6$ cat., acetone, 22 °C, 1:1 d.r., 92%; f) LiHMDS, TMSCl, THF -78 °C; g) $Pd(OAc)_2$, MeCN, 22 °C, 68% two steps; h) 1N aq. HCl/THF (1:1), 22 °C, 85%; i) SmI_2, HFIP, THF/HMPA, -78 °C, 2:1 d.r. 46%; j) TFA, DCM, 0 °C, 87%

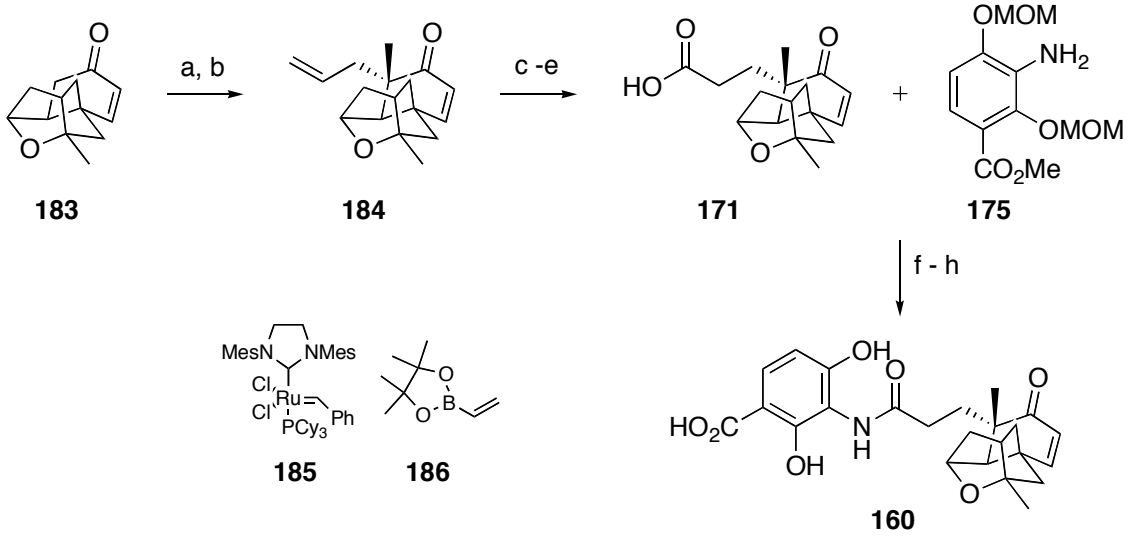
Scheme 4. 4: Nicolaou's first approach to platensic acid

Enone **183** would prove to be the key intermediate in most subsequent formal syntheses. In fact, enone **183** was further elaborated to the natural product through sequential installation of the methyl group, and then allyl group providing **184** as a single isomer (Scheme 4. 5). It was found that this order of alkylations was necessary to achieve the desired stereochemistry, namely the angular methyl.

The allyl moiety in **184** was converted to acid **171** in a three step sequence. Exchange of the vinyl for a vinyl boronate *via* cross-metathesis with boronate **186** using Grubb's second generation catalyst **185** followed by oxidation with trimethylamine *N*-oxide gave an intermediate aldehyde, which was further oxidized to the acid using

sodium hypochlorite. Platensic acid **171** was obtained in 5 steps and 53% yield from the enone **183**. Acid **171** was coupled to aniline **175a** using HATU in 85% yield. The protecting groups were removed and the ester hydrolyzed providing the natural product in racemic form.

Nicolaou and co-workers would produce several different synthetic approaches to platensimycin resulting in several formal syntheses, all intercepting the enone **183**.[23,24] This first route was soon thereafter adapted to be asymmetric.[25] While this first total synthesis of platensimycin was completed quickly, the indirect route to aniline synthesis, the mixture of alcohols produced by the key reductive cyclization, and the awkward installation of the propanoate side chain left room for improvement in this area.



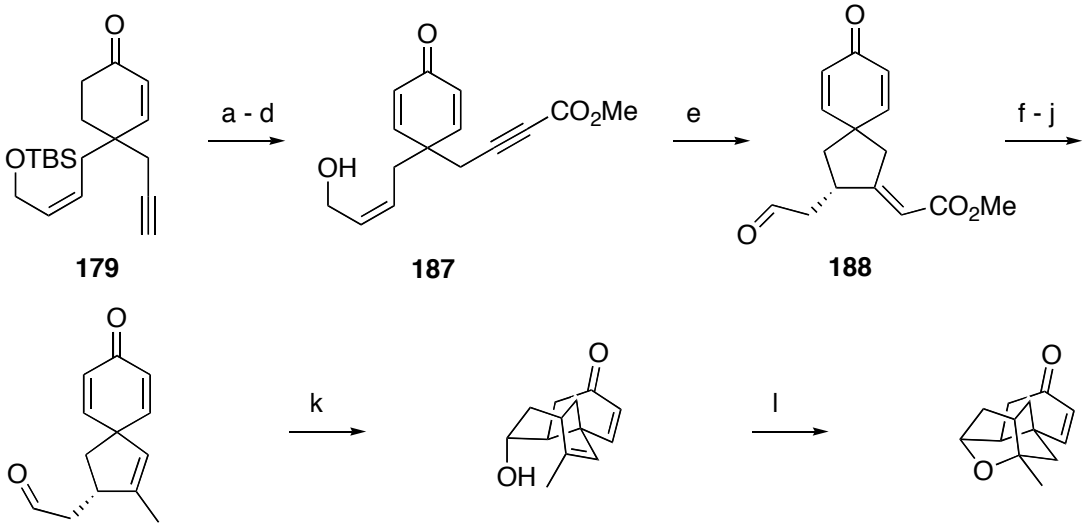
Reagents and Conditions: a) KHMDS, THF/HMPA, MeI, -78 °C, 88%; b) KHMDS, THF/HMPA, allyl Iodide, -78 °C, 79%; c) **185**, **186**, DCM, 85%; d) Me_3NO, THF, 65 °C, 95%; e) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH, H_2O, 95%; f) HATU, Et_3N, DMF, 22 °C, 85%; g) LiOH, THF/H_2O, 45 °C; h) 2N aq. HCl, THF/H_2O, 45 °C, 90% two steps.

Scheme 4. 5: The completion of Nicolaou's first total synthesis of platensimycin

4.2.2. Nicolaou's Synthesis of (–)-Platensimycin

The first total synthesis of platensimycin was racemic, however it was quickly (5 months later) followed by an asymmetric version also by Nicolaou.[25] While two approaches to the ketolide portion were disclosed in this report, only one will be discussed further. The first was an enantioselective synthesis of aldehyde **180** and while this constituted a formal enantioselective route to platensimycin, the issue of a lack of stereoselectivity in the subsequent aldehyde cyclization remained. The other route used a similar strategy as in the racemic synthesis, involving an enantioselective cycloisomerization to set the stereochemistry.

The dienone **179** was made in a similar fashion as before (*vide supra*, Scheme 4. 4). However, in this case, the alkyne had to be carboxylated to methyl ynoate **187**, for the enantiodetermining cycloisomerization step (Scheme 4. 6). In this case, a rhodium catalyst was used for the cyclization, using an (*S*)-BINAP ligand to influence the stereochemical outcome. Enantioenriched enoate aldehyde **188** was obtained in 91% yield and greater than 95% e.e. The enoate, though necessary for the rhodium cycloisomerization, was subsequently excised in a 5 step route to give aldehyde **189**, the reductive cyclization precursor. This substrate **189** differs from that reported in the racemic synthesis (**180**) in the location of the olefin; it is exo to the cyclopentane ring above. This minor change led to a major impact as the only epimer obtained (39% yield) was the desired axial alcohol **190**. No explanation was offered as to the fortuitous results. Cyclization of the ether behaved as before to give enantioenriched enone **183**, constituting a formal synthesis. The enantioselectivity notwithstanding, the synthesis suffers from low yielding key steps and a demonstrable substrate effect for stereoselectivity, both hindrances to analog syntheses and scale-up.



Reagents and Conditions: a) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; b) *n*-BuLi, methyl cyanoformate, THF, -78 °C; c) IBX, MPO, DMSO, 22 °C, 67 % (3 steps); d) 1N aq. HCl/THF (1:2), 0 °C, 91 %; e) [{Rh(cod)Cl}$_2$] (5 mol %), (*S*)-BINAP (11 mol %), $AgSbF_6$ (20 mol %), DCE, 22 °C, 91 %; f) $(CH_2OH)_2$, $CH(OMe)_3$, PPTS, benzene, 60 °C, 90 %; g) 0.6 N aq. LiOH, THF, 0 °C; h) EDC·HCl, CH_2Cl_2, 22 °C; i) visible light, 65 W lamp, *n*-Bu_3SnH, benzene, 22 °C, 49 % (3 steps) ; j) 1N aq. HCl/THF (1:1), 40 °C, 90 %; k) SmI_2, HFIP (1.5 equiv), THF/HMPA (10 :1), 39 %; l) TFA/CH_2Cl_2 (2 :1), 0 °C, 87 %.

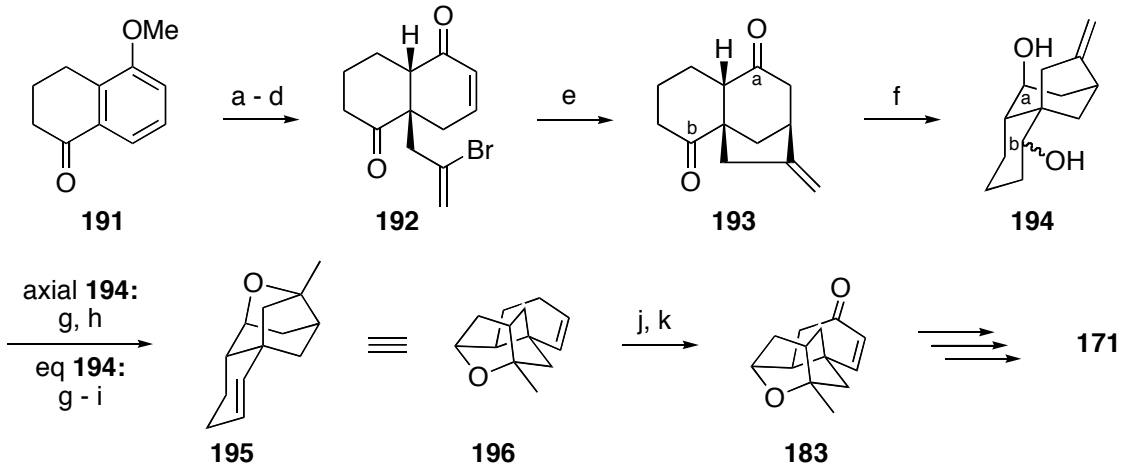
Scheme 4. 6 : Nicolaou's asymmetric approach to (–)-platensimycin

4.2.3. Snider's Formal Synthesis of (±)-Platensimycin

Nicolaou's intermediate **183** was the subject of a formal synthesis by Snider and co-workers reported less than a month following the disclosure of Nicolaou's asymmetric route.[26] Snider's approach is unique from Nicolaou's work in that the enone was installed at a late stage.

The work began with a four-step conversion of 5-methoxytetralone **191** to enones **192** as mixtures of *cis* and *trans* decalins, which were separated and equilibrated to a 6 : 4 ratio (Scheme 4. 7). The desired *cis*-decalin **192** was then reductively cyclized to tricycle

193 by treatment with tributyltin hydride and AIBN. The dione **193** was reduced with L-Selectride to the diol **194**. It was found that C_a was stereoselectively reduced to give the axial alcohol, while C_b was obtained as a 1 : 1 mixture of axial to equatorial alcohols. The alcohol at C_a in diol **194** was cyclized to the ether in the same manner as in Nicolaou's report. The remaining alcohol C_b was eliminated to the olefin **195** under a variety of conditions. The axial **194** was treated with triflic anhydride and then isopropanol to furnish the alkene **195**, while equatorial **194** had to be eliminated *via* the triflate in a step-wise fashion. With alkene **195** in hand, its allylic oxidation was examined and found to be best accomplished in a two-step process. The allylic oxidation with SeO_2 preceded MnO_2 oxidation of the allylic alcohol to enone **193**, intercepting Nicolaou's intermediate.



Reagents and Conditions: a) K, NH_3/Et_2O, *t*-BuOH, -78 °C; b) LiBr; c) 2,3-dibromopropene; 4) conc. HCl/THF, 51% (four steps); e) AIBN, *n*-Bu_3SnH, benzene, 80 °C, 84%; f) L-Selectride, THF, -78 °C, 90%, 1:1 mixture of alcohols; g) TFA, DCM, 0 °C, 81%; h) Tf_2O, Pyr, DCM, -78 °C, then *i*-PrOH, 25 °C, 90% for the axial **194**; i) 1M HCl, silica gel, 84% two steps, equatorial **194**; j) SeO_2, dioxane, microwave, 110 °C, 83%; k) MnO_2, DCM, 25 °C, 94%.

Scheme 4. 7: Snider's formal synthesis

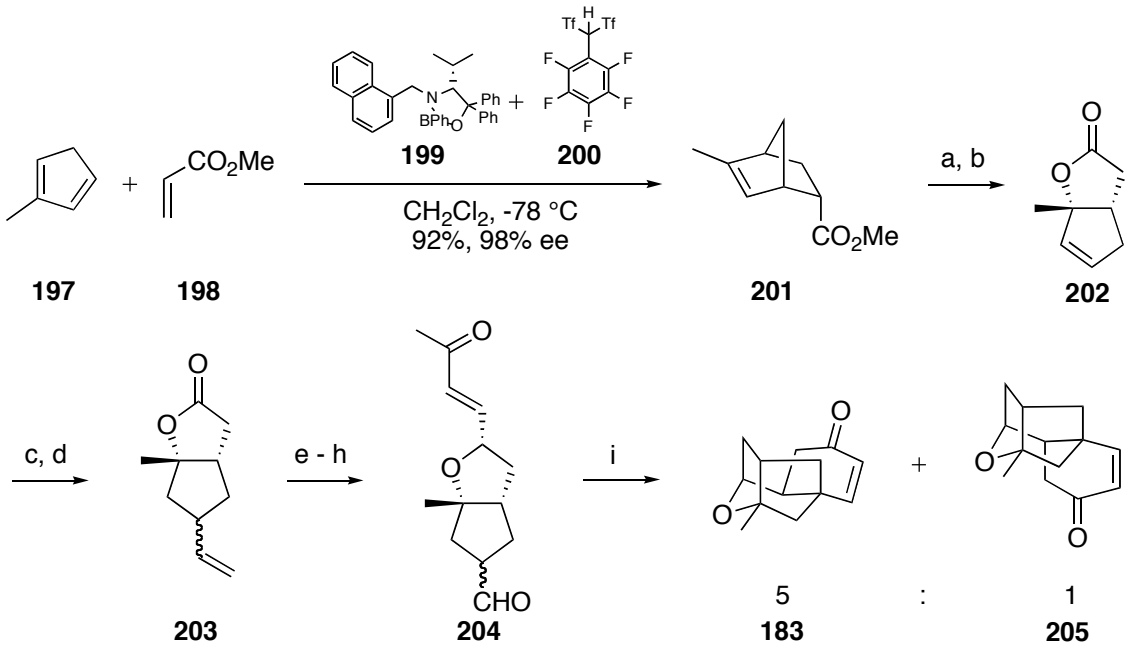
While Snider's route was substantially shorter than Nicolaou's, the lack of stereoselectivity and the resultant iterations required for different substrates to access enone **183** are not ideal.

4.2.4. Yamamoto's Formal Synthesis of (–)-Platensimycin

The enone **183** was also the subject of exploration by Yamamoto and co-workers who devised a unique enantioselective route. The approach by Yamamoto and co-workers involved an enantioselective Diels-Alder to set the stereochemistry early, and used a late stage Robinson annulation to form the cyclohexenone ring.[27]

The synthesis started with the enantioselective Diels-Alder cycloaddition between cyclopentadiene **197** and methyl acrylate **198** (Scheme 4. 8) catalyzed by the chiral oxazaborolidine **199** and the Brönsted acid **200**. The adduct **201** was obtained in 92% yield as a single diastereomer and 99% e.e. The ester was cleaved to a ketone by quenching of the enolate with nitrosobenzene and oxidative decarboxylation. The ketone was treated with basic hydrogen peroxide for a Baeyer-Villiger oxidation with rearrangement to give lactone **202** in 50% yield for the two steps. The lactone was opened *via* S_N2' addition of the vinyl cuprate with subsequent lactonization of the rearranged olefin to yield **203**. The lactone carbonyl was homologated in four steps to an α,β-unsaturated ketone and the vinyl group cleaved to an aldehyde providing key intermediate **204**. Upon treatment of the aldehyde **204** with proline in DMF, the Robinson annulation proceeded to give diastereomeric cyclohexenones **183** and **205** in a 5 : 1 ratio, respectively. The enone **183** intersects both Snider's and Nicolaou's intermediate and constitutes an enantioselective formal synthesis. The brevity and

elegance of the synthesis notwithstanding, the lack of diastereoselectivity in the final step translates to a non-stereoselective synthesis of enone **183** and platensimycin **160**.



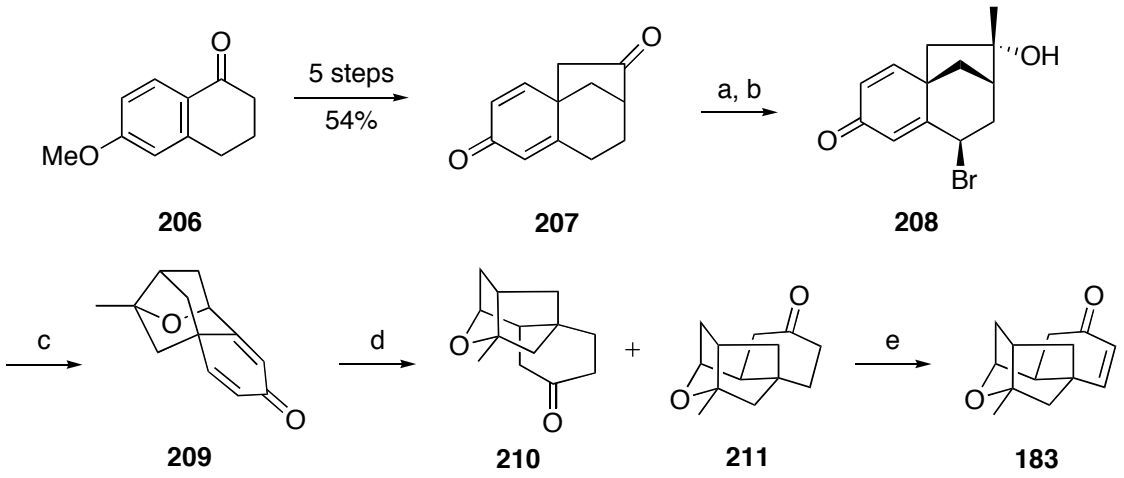
Reagents and Conditions: a) LDA, THF, -78 °C, then PhNO, -78 °C, then LiOH, dioxane/H_2O, 30 °C, 75%; b) H_2O_2/NaOH, Et_2O/H_2O, 0 °C, 68%; c) CuBr•Me_2S, vinylMgBr, THF, -40 °C; d) $HNTf_2$, 1,2-DCE, 70 °C, 81% (2 steps); e) DIBALH, PhMe, -78 °C, then Et_2AlCN, BF_3•OEt_2, 43%; f) DIBALH/*n*-BuLi, -78 °C; g) NaH, $CH_3COCH_2P(O)(OEt)_2$, THF, 0 °C, 65% (2 steps); h) $NaIO_4$, $RuCl_3$, MeCN/H_2O, 59%; i) *L*-Proline, DMF, 5d, then 2N aq. NaOH, 0 °C, 95%, 5 : 1.

Scheme 4. 8: Yamamoto's enantioselective formal synthesis

4.3.5. Mulzer's Formal Synthesis of (±)-Platensimycin

Mulzer and Tiefenbacher reported their protecting group free formal synthesis of platensimycin in 2007.[28] The similarity between the platensic acid core and the *ent*-kaurene structure was observed by Mulzer. Utilizing methods developed by Mander towards the synthesis of kaurene-type diterpenoids,[29] Mulzer took an intermediate disclosed by Mander and converted it to enone **183**.

The tetralone **206** was converted, as per Mander, into dienone **207** in 5 steps and 54% yield (Scheme 4. 9). The advancement of dienone **207** to enone **183** is where Mulzer diverges. The methyl Grignard addition attacked from the outside face of the ketone, which gave the tertiary alcohol. Bromination γ to the dienone carbonyl gave bromide **208** which was closed to the ether under basic conditions. Ether **209** was isolated in 80% yield. Reduction of the dienone **209** to enone **183** was problematic. It was found to be unselective, as the best results were found using Crabtree's Ir catalyst which produced the over-reduced **210** and **211** as a 1.3 : 1 ratio of diastereomers. Oxidation of the cyclohexanone **211** was accomplished with hypervalent iodine providing enone **183** in a short formal synthesis. The lack of stereoselectivity in the hydrogenation again leaves this work short of a selective synthesis.



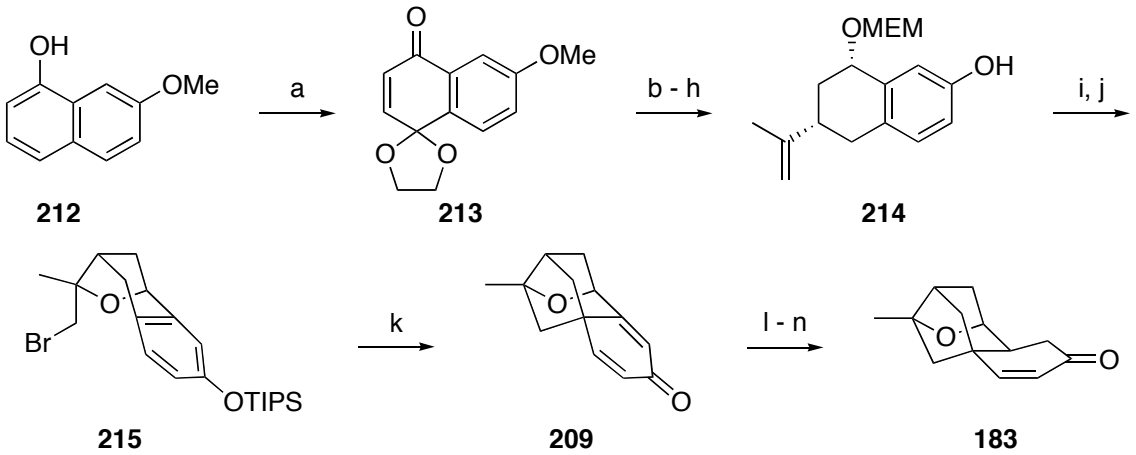
Reagents and Conditions: a) MeMgI, THF, -78 °C, 71% brsm; b) NBS, $(BzO)_2$, CCl_4, reflux, 75%; c) NaOMe, THF, 0 °C, 80% ; d) cat. $[Ir(cod)Py(PCy_3)]PF_6$, H_2 (1 bar), CH_2Cl_2, 78% brsm, **210/211** = 1 : 1.3; e) HIO_3·DMSO, DMSO, cyclohexene, 50 °C, 60%

Scheme 4. 9: Mulzer's formal synthesis

4.3.6. Corey's Formal Synthesis of (–)-Platensimycin

Corey's approach to the formal synthesis of platensimycin was unique among the approaches discussed thus far. Though it intersected with Mulzer's dienone **209**, Corey's and Lalic's approach was different, utilizing an alkylative dienone formation.[30]

Napthol **212** was oxidized, with subsequent *in situ* ketal formation, to enone **213** in 80% yield (Scheme 4. 10). The enantioselective conjugate addition of propenyl-2-trifluoroborate to enone **213** was accomplished in 96% and 94% e.e. The ketone was then reduced to the alcohol, which was protected as its MEM ether. The ketal was removed, and the ketone reduced down to the methylene in a two step process. After phenolic demethylation, the phenol **214** was protected as its trisopropylsilyl ether, which was obtained in eight steps from ketone **213**. Treatment of the olefin in **214** with bromine led to intramolecular opening of the intermediate bromonium ion to form ether **215**. Desilylative alkylation of the phenol gave dienone **209**, which coincided with Mulzer's intermediate. However, Corey improved on Mulzer's work, increasing the diastereoselection of enone hydrogenation. Using a Rh catalyst, with DIOP ligands, enone **209** was reduced giving the cyclohexenone **210** of the desired stereochemistry in 72% yield—the hydrogenation was unspecific and the unwanted diastereomer **211** was isolated as well. The enone was reinstalled providing Nicolaou's intermediate **183** and a formal synthesis was completed. This synthesis, though unique and enantioselective, suffers from the unstereoselective reduction of a dienenone.



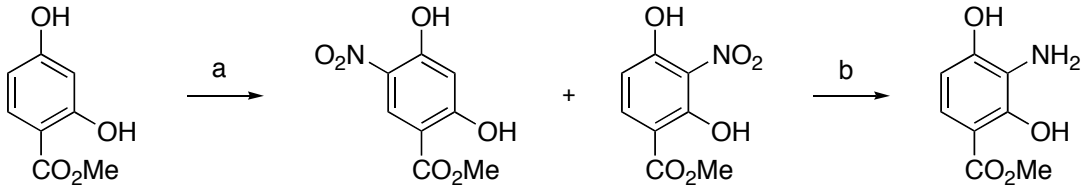
Reagents and Conditions: a) $PhI(O_2CCF_3)_2$, Ethylene glycol, MeCN, 0 °C, 80%; b) propenyl-2-trifluoroborate, (*S*)-BINAP, $[Rh(cod)_2]BF_4$, PhMe, H_2O, Et_3N, 96%, 94% ee; c) $NaBH_4$, MeOH; d) MEMCl, DIEA, DCM; e) TsOH, Acetone, 0 °C; f) DIBALH, DCM, 0 °C; g) Et_3SiH, TFAA, DCM, -20 °C, 79% (five steps); h) PhSH, Cs_2CO_3, DMF, 170 °C, 99%; i) TIPSCl, imid, DCM; j) Br_2, DCM, -78 °C, 84%; k) TBAF, THF, 130 °C, 88%; l) $[Rh(cod)_2]BF_4$, (*R*,*R*)-DIOP, H_2 (600 psi), DCM, 72%; m) TMSOTf, Me_3N, DCM; n) IBX, MPO, DMSO, 80% (two steps).

Scheme 4. 10: Corey's formal synthesis

4.3.7. Giannis' Synthesis of the Platensimcyin Aniline

The synthesis of the platensimycin aniline **175a** by Nicolaou, as discussed above, was indirect and as such was supplanted by a more direct route. Giannis disclosed the synthesis of the platensimycin aniline, both the protected aniline **175a** (used by Nicolaou) and the unprotected aniline **175**.[31]

The commercially available methyl 2,4-dihydroxybenzoic acid **216** was nitrated with HNO_3 and acetic anhydride/acetic acid (Scheme 4. 11) to yield a 1 : 1 mixture of 3-nitro **217** and 5-nitro **218** products in a combined 56% yield (29% of the desired 3-nitro **XXX**). Hydrogenation of 3-nitrobenzoic acid **217** provided the platensimycin aniline **175** in 97% yield. This two-step route, though not selective, is direct and convenient.



216 **218** **217** **175**

Reagents and Conditions: a) HNO_3, Ac_2O, AcOH, 56%, 1:1 ratio; b) H_2, Pd/C, EtOAc, 97%.

Scheme 4. 11: Giannis' synthesis of the platensimycin aniline

4.3. CONCLUSION

Platensimycin (**160**) is a potent, broad spectrum antibiotic whose structural complexity and compelling antibiotic activity has generated great interest in the scientific community. It is a potent and selective inhibitor of FabF which is important for fatty acid biosynthesis and bacterial growth. The biological activity has been shown to be derived from the 3-aminobenzoic acid moiety. Though both *in vitro* and *in vivo* activity have been demonstrated, a poor pharmacokinetic profile has limited the potential for clinical development and spurred the exploration of analogs.

While many approaches to the synthesis of platensimycin have been reported (including several not discussed here[32, 33, 34]), the achievement of a stereospecific route has thus far eluded researchers. The biologically important nature of the target, as well as the draw of a stereoselective synthesis, compelled us to pursue a total synthesis of (-)-platensimycin. Our efforts toward that goal will be presented.

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Chapter 5: Efforts Towards the Total Synthesis of Platensimycin

5.1. INTRODUCTION

Platensimycin, a natural product isolated by Merck scientists from a strain of *Streptomyces platensis*, has recently been discovered to possess potent antibiotic activity against Gram-positive bacteria, including MRSA. While *in vivo* efficacy has been established, a poor pharmacokinetic profile has been implicated and an analogue for clinical development is desirable. Though much research into its total synthesis has been reported, resulting in one total synthesis and numerous formal syntheses, no synthetic approach disclosed thus far has been diastereoselective, leaving room for improvement. Our efforts towards a stereoselective total synthesis of platensimycin will be discussed herein.

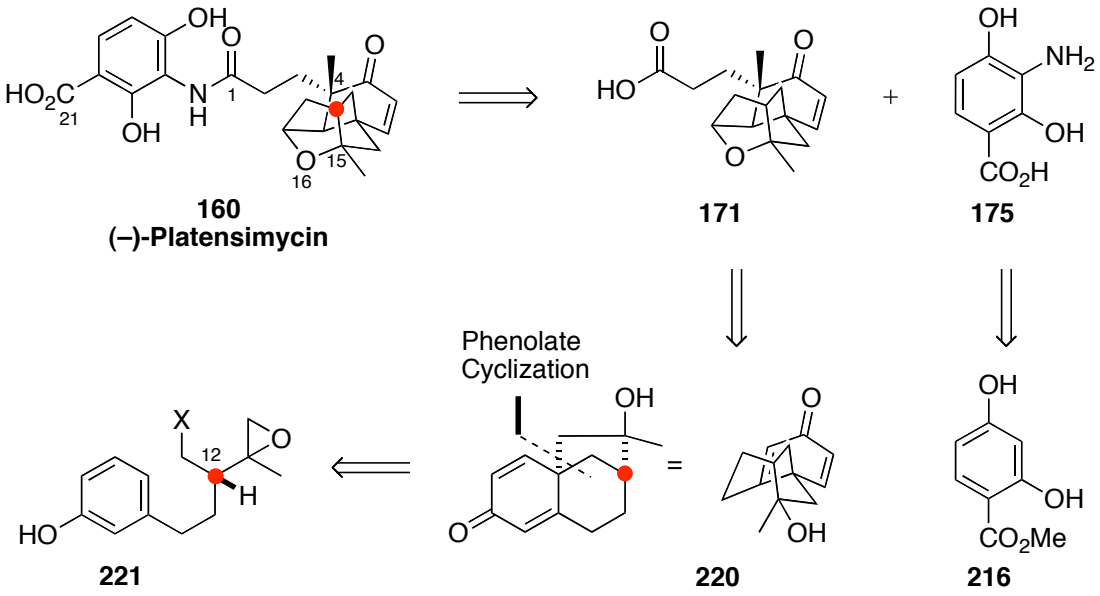
5.1.1. Synthetic Approach

The common disconnection at the amide linkage will be used in this work as well, as it has clearly been established to be a viable route. The aniline **175** and ketolide **171** compounds are the targeted intermediates. The aniline was seen coming from 2,4-dihydroxybenzoate **216**. The enone acid **171**, the more structurally complex target of the two, was seen arising from sequential phenolate cyclizations of **221** to furnish an enone **220** similar to that of Mulzer's.

The key to our proposed stereoselective approach to acid **171** is the ability to use one stereocenter (C_{12}, red) set early, to dictate the stereochemical outcome of later steps wherein the polycyclic ether core could be obtained as a single stereoisomer. The majority of the previously reported formal syntheses relied on late stage hydrogenations to define the stereochemistry of the cyclohexenone core, resulting in mixtures of isomers

and no stereospecificity. To improve on this, it was thought that the core might be best accessed if the proper oxidation state were maintained throughout, eliminating the need for hydrogenation or other reductions. Therefore, the ketolide **171** would be the result of sequential deconjugative alkylations, methyl then propionyl to install the side chains, on dienone **220** followed by hydroboration/oxidation of the deconjugated double bond (Scheme 5. 1). The installed alcohol would then be closed to the ether.

The use of phenolate cyclizations to construct the tricyclic enone **220** was envisioned. Therefore, a phenol of the type **221** was viewed as a starting point for such investigations. The attractive feature of this approach was the belief that the stereochemistry of dienone **220** and subsequent compounds would be controlled by the methine (C-12, platensimycin numbering, highlighted in red) of phenol **221**.

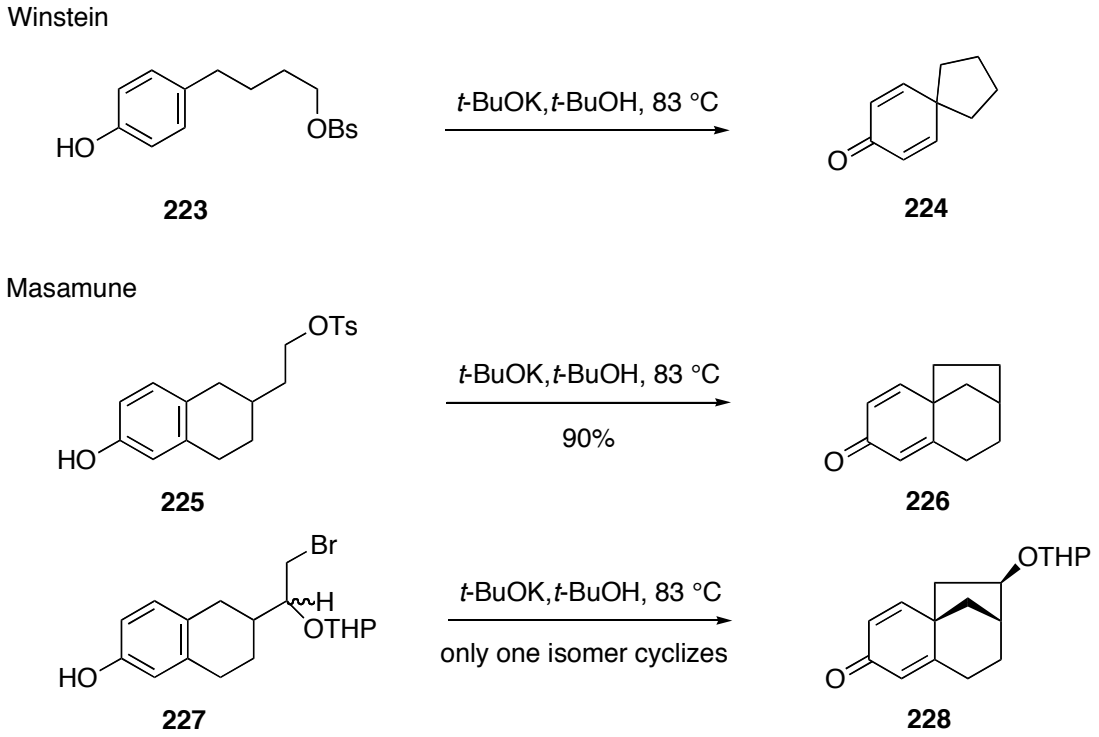


Scheme 5. 1: Synthetic approach to platensimycin **XXX**

5.1.2. Background on the Anionic Phenolate Cyclization[1]

The discovery that some phenols with *para*-substituents containing a leaving group could be cyclized on carbon *via* the participation of the neighboring phenoxide ion by Winstein and Baird[2] inspired numerous research groups to further investigate this powerful reaction. In their seminal report, Winstein and Baird discovered that phenol **223** with a 4-bromobenzenesulfonate (Bs) butanol side chain would cyclize to the dienone **224** under the influence of *t*-BuOK in *t*-BuOH (Scheme 5. 2). That dienones like **224** would be important intermediates for the synthesis of many natural products, including platensimycin (*vide supra*) was soon realized. The utility of phenoxide ion's in the intramolecular displacement of leaving groups for ring formation would soon become a productive area of research.[1]

The similarities between platensimycin and the kaurene class of natural products has been established based on their proposed biosynthesis and structure. So the synthesis of kaurene by Masamune is relevant to this discussion. In a series of papers describing this work, Masamune expanded the scope of the phenolate cyclization first reported by Winstein and Baird. The tetrahydronapthol tosylate **225** was cyclized under the same conditions reported by Winstein to provide the dienone **226** in 90%. The bicyclo-[3.2.1] system is a motif that we hope to target in a synthesis of platensimycin. The account by Masamune of the cyclization chemistry of the protected bromohdyrin **227**, and its conversion to kaurene, was also relevant. A mixture bromohydrin isomers was subjected to the cyclization conditions and it was observed that only one isomeric product was obtained; the product dienone with the "*exo*" tetrahydropyranyl ether **228**. The utility of this cyclization to intall the desired oxygen would be tested in this work (*vide infra*), albeit on a tertiary ether.

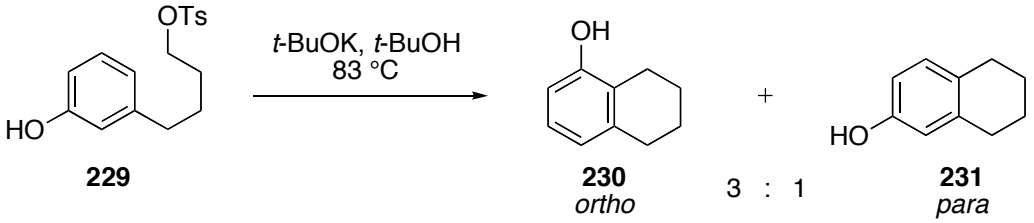


Scheme 5. 2: Development of the phenolate cyclization for the synthesis of dienones

While Masamune (1961) had demonstrated the utility of the phenolate cyclization of tetrahydronaphthols to dienones, the utility of the phenolate cyclization for the synthesis of tetrahydronaphthols had not yet been explored. Murphy and co-workers reported a series of papers (1975) exploring various aspects of the reaction. As our approach to platensimycin relied on the ability to access a tetrahdronaphtol, this was of interest.

Murphy was the first to demonstrate that phenols of the type **229** could undergo ring formation through intramolecular displacement without competing intermolecular ether formation.[3] The phenolic tosylate **229** was cyclized to tetrahydronapthols **230** and **231** in a 3 : 1 ratio (Scheme 5. 3). This so-called Ar_2^-6 reaction[1] has been extended to a

large variety of substrates. The analogous Ar_2^-5, Murphy showed, fails. However, the ratio of *ortho* : *para* products showed some dependence on the reaction conditions.[4] The use of different metal counter-ions gave varying ratios of products, with the *ortho* **230** always predominating. While different solvents were also investigated, *t*-BuOH was found to be superior; no solvolysis was observed.



Scheme 5. 3 : Ar_2^-6 synthesis of tetrahydronaphtols

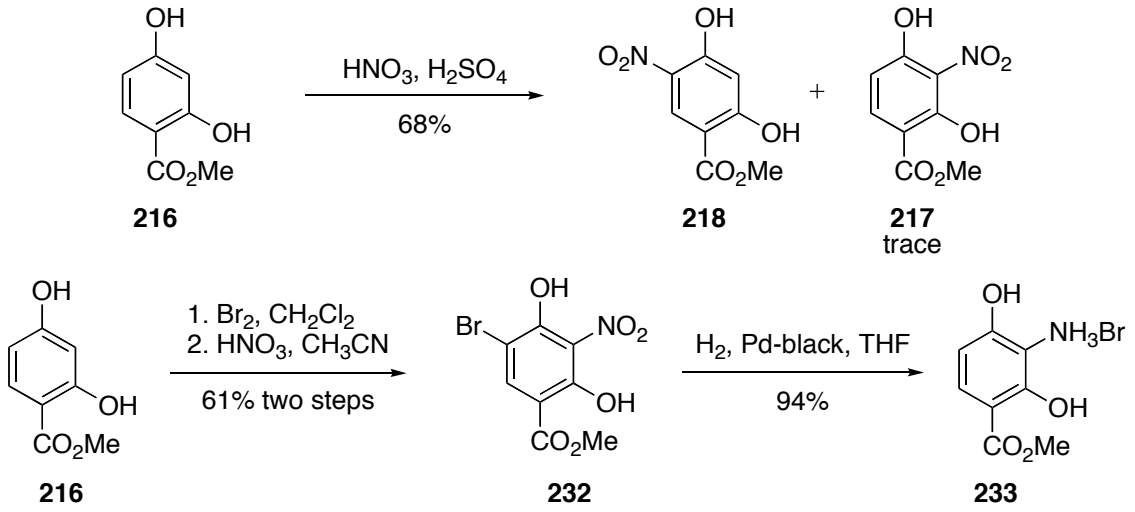
In the end, the utility of the phenolate cyclization in the synthesis of dienones and tetrahydronaphthols is evident. Its application to the stereoselective synthesis of platensimycin will be explored.

5.2. RESULTS AND DISCUSSION

5.2.1. Synthesis of the Platensimycin Aniline

Nicolaou's initial total synthesis[5] addressed the synthesis of an aniline for platensimycin. However, their solution was lengthy (6 steps, including OH deprotection) and included protection of the phenols for the peptide coupling. These two aspects warranted improvement. Our attempts at an improved aniline synthesis were thus initiated. This work, though not published, had been completed before Giannis' disclosure of an improved aniline synthesis.[6]

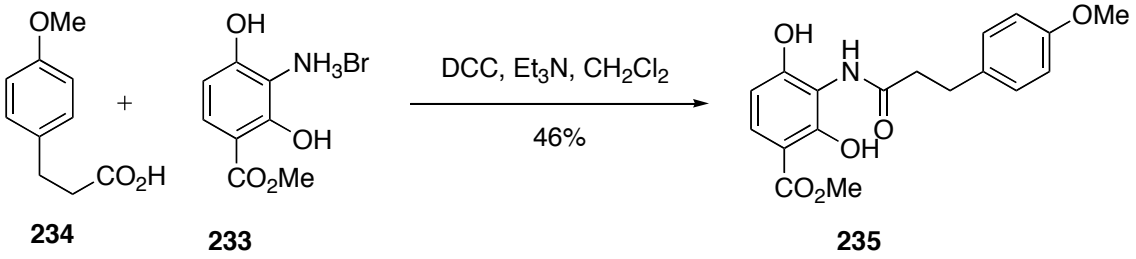
The nitration of methyl 2,4-dihydroxybenzoate (**216**), the commercially available starting material, was examined first. It was found that under the standard nitration protocol, HNO_3 in H_2SO_4, the 5-nitro product **218** was obtained in 68% yield with trace amounts of the desired 3-nitro **217** evident (Scheme 5. 4). The penchant of aryl **216** for "*para*" nitration was expected on the grounds that the 3-position was *ortho* disubstituted and therefore, more hindered. Giannis found that with the addition of acetic anhydride to a nitration protocol, a 1 : 1 mixture of 5-nitro and 3-nitro products could be obtained.



Scheme 5. 4: Synthesis of the platensimycin aniline **233**

The notion to use a removable blocking group to direct nitration was explored. As the nitrobenzene was to be reduced to an aniline in a subsequent step *via* hydrogenation, a blocking group removable by hydrogenolysis for the more reactive 5-position was sought. Bromination of benzoate **216** followed by nitration provided the 3-nitro aryl **232** in 61% yield over the two steps. The bromine was then removed in the subsequent hydrogenation step, providing aniline **233** as its hydrobromide salt.[7]

With a direct and efficient route to the aniline, our attention turned to the aniline's coupling ability. The assumption that the phenols needed to be protected through the peptide coupling was challenged. A simple test coupling with a propionic acid **234** was carried out (Scheme 5. 5). The β-aryl acid **234** was coupled to aniline **233** using the DCC coupling conditions, to afford the amide **235** in 46% yield. Therefore, phenol protection was deemed unnecessary.[8]



234 **233** **235**

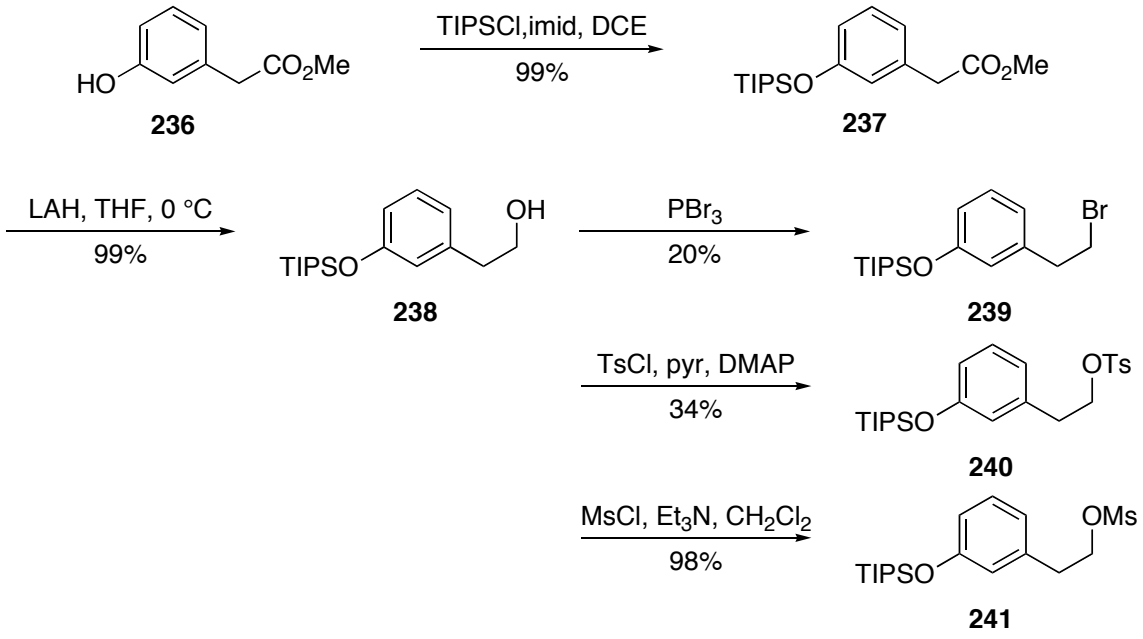
Scheme 5. 5 : Amide coupling of aniline **233**

5.3. STUDIES TOWARD THE SYNTHESIS OF ENONE ACID OF (–)-PLATENSIMYCIN

With a synthesis of the aniline completed, the synthesis of the enone acid **171** was undertaken. The first synthetic target was a phenol of the type **221** with a 3-alkyl substituent suitable for advancement to the dienone **220** (Scheme 5. 1). The spirocyclodienone **220** has been a common structural motif of intermediates used in the synthesis of kaurene natural products, and their synthesis *via* anionic phenolate cyclizations is an established synthetic approach.

5.3.1. First Generation: The Desmethyl Series

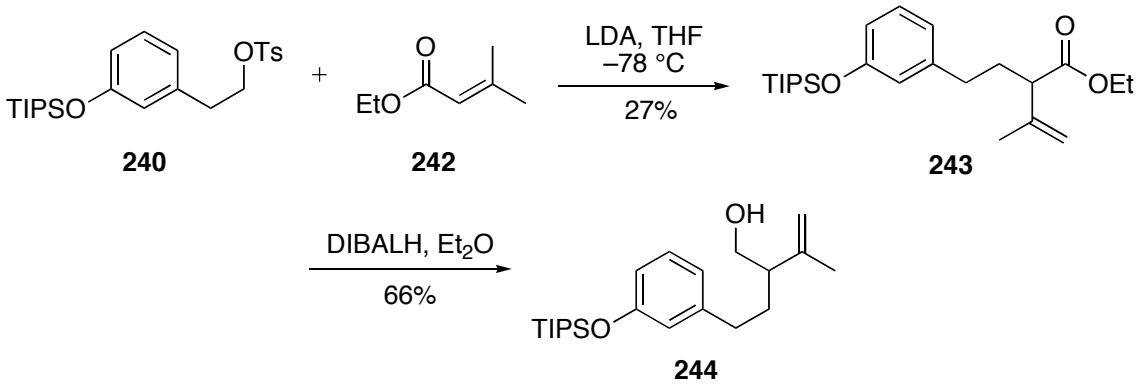
The first targeted intermediate, phenol **221** (the phenolate cyclization substrate) was seen arising from an alkylation of a phenethyl halide, wherein the nucleophilic carbon (C-12) could be set *via* enantioselective alkylation. The synthesis of a phenethyl electrophile began with the protection of commercially available phenol **236** as its triisopropylsilyl ether **237** (Scheme 5. 6). The ester was reduced using LAH, providing the phenethyl alcohol **238**, ready for conversion to a leaving group. The phenethyl alcohol was converted to its bromide **239** (PBr_3, 20%), tosylate **240** (TsCl, pyr, 34%), and mesylate **241** (MsCl, Et_3N, 98%) for investigation into their alkylation potentials.



Scheme 5. 6: The synthesis of phenethyl alkylating agents

Initial investigations were aimed towards a racemic synthesis, thereby testing the credibility of the proposed approach. Ethyl 3,3-dimethylacrylate **242** was chosen as an appropriate nucleophile, including a functional handle for epoxide formation *en route* to phenol **221**. In the event (Scheme 5. 7), the extended enolate of acrylate **242**, formed upon exposure to LDA, was treated with the tosylate **240**. The alkylation product **243** could be obtained, albeit in a disappointing 27% yield. The bromide behaved worse than the tosylate in this reaction, giving primarily a styrene, the product of bromide elimination. The first attempt at the tosylate alkylation, using a roughly 1 : 1 ratio of nucleophile to electrophile gave only 8% of the desired product. Additives such as HMPA and DMPU did not improve the yields. Extending the time of the reaction gave reconjugated acrylate, suggestive that the enolate would rather equilibrate with alkylated product **243** than alkylate with the remaining electrophile. Thus, it was concluded that the enolate of acrylate **242** was not reactive enough for the desired transformation.

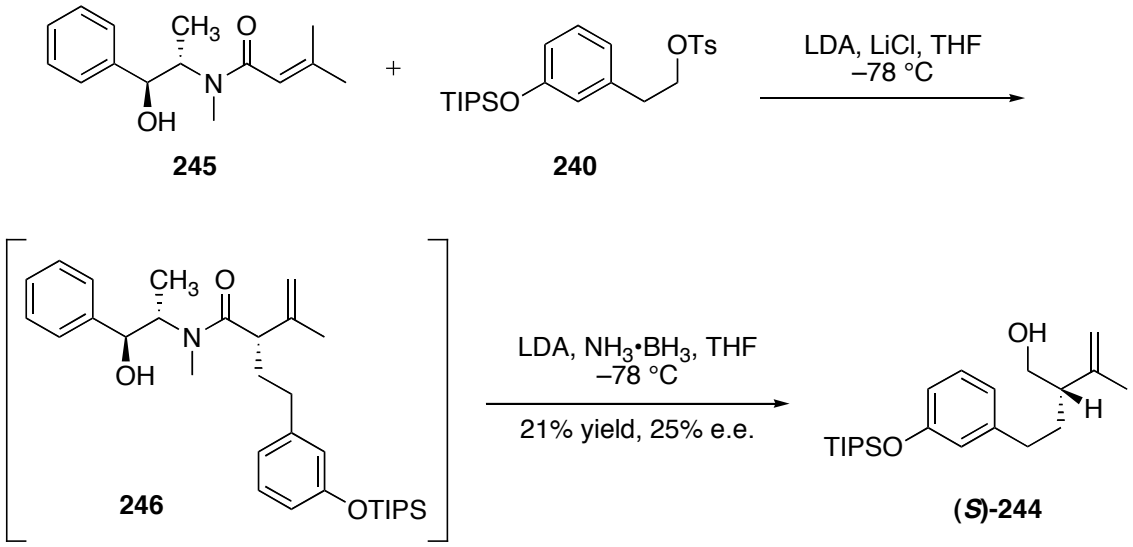
However, the availability of product **243** allowed for further study. Reduction of the ester to the homoallylic alcohol was accomplished with DIBALH in ether to give alcohol **244** in 66% yield.



Scheme 5. 7: The alkylation of phenethyl tosylate **244**

With the success of a racemic alkylation, the investigation of an enantioselective alkylation was begun. The known pseudoephedrine amide **245**,[9] a chiral auxiliary analog of ester **242**, was envisaged as an appropriate nucleophile. There was hope that an enantioselective synthesis could be carried on from the start. While the dianion of pseudoephedrine amide **245**, prepared using the standard protocol,[10] had been alkylated before, only one phenethyl iodide had been used.[11] The common problem of phenethyl alkylation, namely elimination to the styrene, manifested itself in this case.[12] The alkylation of amide **245** with tosylate **240** produced a mixture of pseudoephedrine containing products which could not be separated (Scheme 5. 8). The majority of the tosylate was eliminated. The mixture appeared to contain the desired product **246**, amide starting material **244** and the deconjugated pseudoephedrine amide. The mixture was carried forward, with the reduction to the homoallylic alcohol **244**, corresponding to **(*S*)-244**. As such, the reduction using the known conditions,[13] produced the alcohol

(*S*)-**244**, now readily purified and characterized as before. A meager 21% yield over the two steps was recovered. Using a chiral HPLC trace and through comparison with the racemic alcohol **244**, the enriched alcohol was determined to be of 25% e.e. While further experiments aimed at the optimization of this approach were performed, the enantioselective approach was temporarily discontinued.



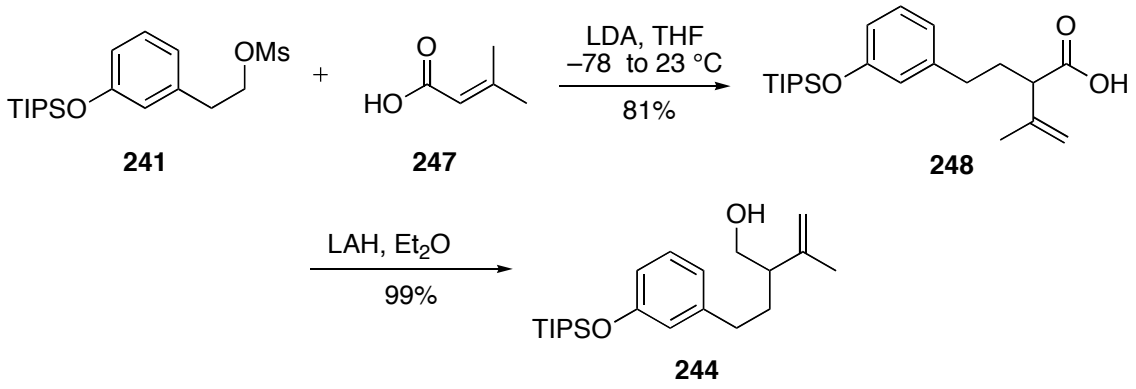
Scheme 5. 8: The pseudoephedrine amide **245** alkylation of tosylate **240**

To achieve an efficient synthesis of platensimycin using this route, clearly improvement into the alkylation of these phenethyl electrophiles was necessary. The reason for the poor yields was believed to be the inertness of the enolate to alkylation, and so a more reactive enolate was desired.

The ethyl acrylate **242**, though commercially available, was economically best accessed in large quantities through the esterification of 3,3-dimethylacrylic acid with EtOH and sulfuric acid, and distillation of the crude mixture. The 3,3-dimethyl acrylic acid **247** starting material was thought to be a rational alternative to the ester *via*

alkylation of its dianion. The use of these dianions in synthesis had been demonstrated,[14] and thus was explored in this case.

In the event, acid **247** was treated with LDA (2.2 eq) and upon warming of the reaction mixture from –78 °C to room temperature, an off-white precipitate formed, indicating the formation of the dianion (Scheme 5. 9). Quenching of the re-cooled (–78 °C) dianion with mesylate **241** provided alkylated acid **248** in 54% yield on the first experiment, doubling the best yield obtained through the ester alkylation. Using an excess of the acid, gave a scalable and reproducible procedure for accessing carboxylates **248**. The acid was reduced using LAH, providing homoallylic alcohol **244** in quantitative yield. It was found that the use of ether was superior to THF and toluene, which produced substandard yields of this reduction. The use of ether gave the desired alcohol cleanly and quantitatively. With improved access to alcohol **244** its utility in the synthesis of platensimycin was examined.

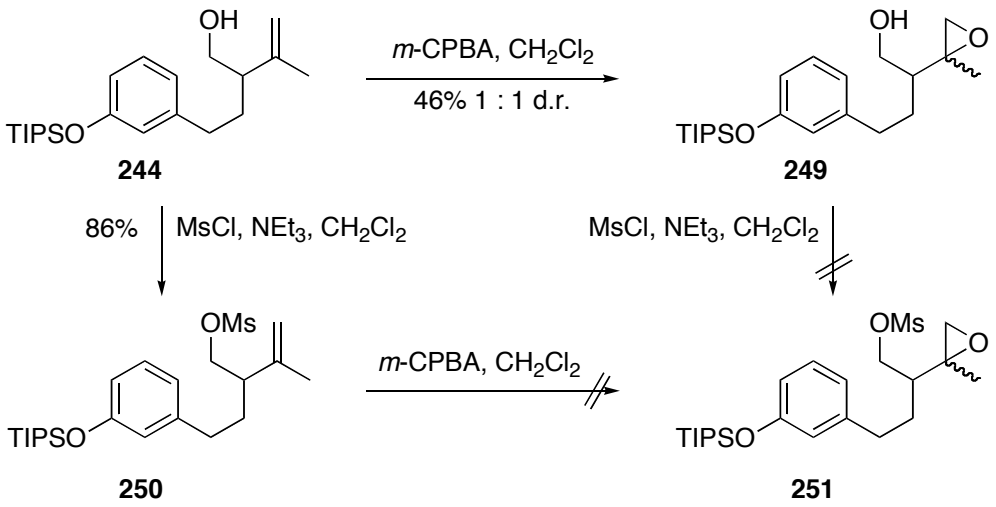


Scheme 5. 9: An improved synthesis of homoallylic alcohol **244**

The strategy envisioned was to use successive phenolate alkylations to form dienone **220**, wherein both the alkylations would be performed in a one-pot process on the doubly activated substrate **221**. To examine this strategy, homoallylic alcohol **244**

would need to be converted to epoxide **251**. The two possibilities were to a) convert the alcohol to a leaving group and then epoxidize the olefin, or b) do it in the reverse order. Both were attempted.

Epoxidation of homoallylic alcohol **244** was accomplished with *m*-CPBA to give an inconsequential mixture of diastereomeric epoxides **249** in a 1 : 1 ratio (Scheme 5. 10). However, the alcohol of **249** proved difficult to convert to a leaving group. Attempts aimed at converting it to a mesylate or tosylate met with decomposition of the starting epoxide. The reaction mixtures clearly indicated the loss of the epoxide, either due to opening by the Cl^- produced in the reaction or by the HCl produced, through its triethylammonium salt. In any case, mesylate **251** was not accessed *via* the epoxide **249**.



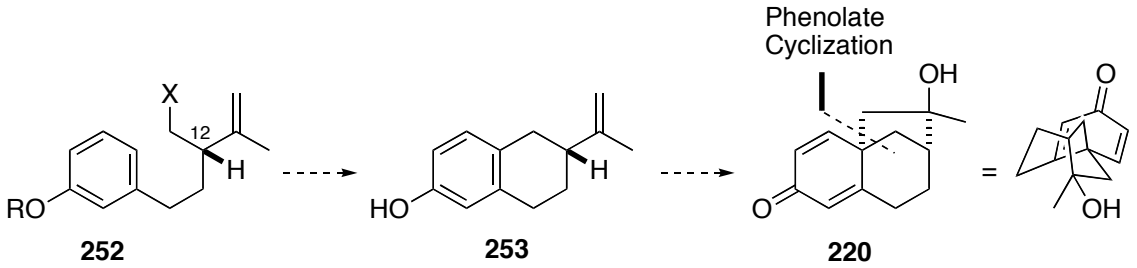
Scheme 5. 10: The failed attempts to synthesize epoxide **251**

While the alcohol **244** could easily be sulfonylated to **250** using MsCl, clean epoxidation of the olefin in **250** was unable to be achieved, even though epoxide **250** was believed to be present in the crude reaction mixtures. All purification attempts led to

decomposition with no discernible products. Some trace amounts of epoxide **251** of reasonable purity were obtained, but it decomposed on standing. It was believed that a stepwise route to dienone formation would be necessary.

5.3.2. Phenolate cyclizations

A slight adjustment to the synthetic approach was made, wherein the two phenolate alkylations would arise through a step-wise route. The synthesis of tetrahydronaphthol **253** from phenol **252** would precede functionalization of the *exo*-propenyl group and cyclization to the dienone **220** (Scheme 5. 11).

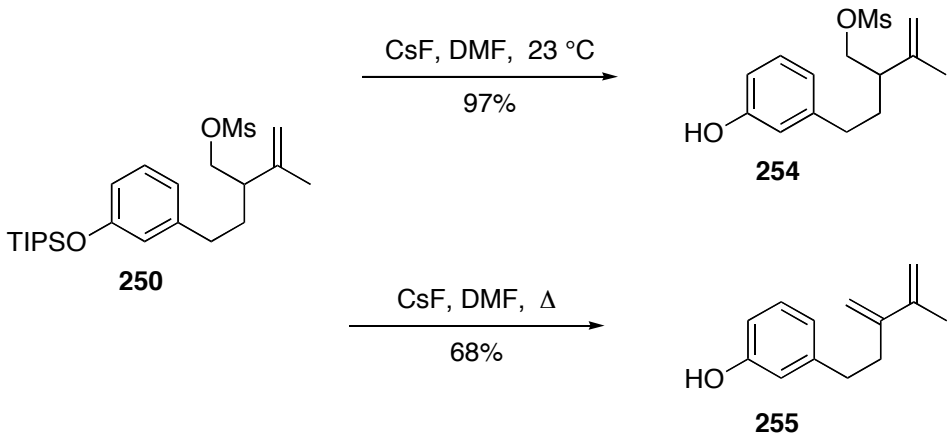


Scheme 5. 11: An adjusted synthetic approach to dienone **220**

With access to mesylate **250** established, its cyclization into the tetrahydronapthol, based on the work of Murphy,[3] was tested. It was thought that removal of the silyl ether and cyclization could be accomplished in one transformation. However, the ratio of *ortho* : *para* cyclized products that would result was unknown as a different mechanism might be operable. The notion that desilylation of the phenol and alkylation of the resultant phenolate anion in the *para* position might be achieved selectively, was explored. Should the reaction behave in a concerted fashion, with

concomitant desilylation and Ar_2^-6 alkylation, the triisopropylsilyl ether might have a steric directing effect.

Aprotic conditions were thought to be necessary to avoid protonation of the phenolate, so silyl ether mesylate **250** was treated with CsF in DMF. This resulted in a single product forming, though different products resulted depending on the temperature at which the experiment was performed (Scheme 5. 12). At room temperature, CsF cleanly and quantitatively removed the silyl ether providing phenol **254** with no cyclization observed. At higher temperatures (150 °C reflux), fluoride behaved as an exceptional base, eliminating the mesylate to the diene **255** cleanly and with complete conversion. All attempts to affect the Ar_2^-6 cyclization from silyl **250** directly led to either phenolic mesylate **254** or diene **255**. Nonetheless, the desilylated phenol **254** could still be cyclized using the established phenolate cyclization conditions, but a one-pot process was not likely to be achieved.

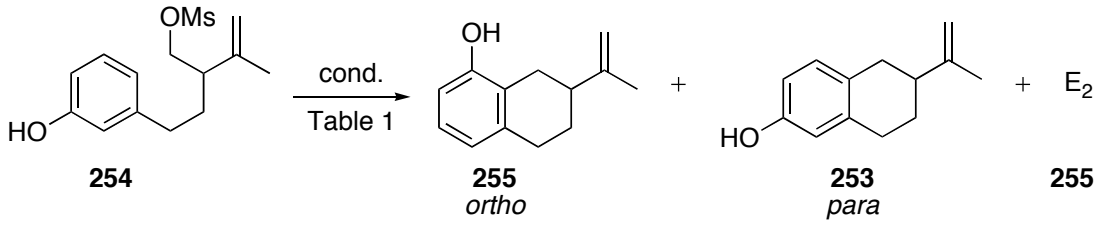


Scheme 5. 12: The attempted one-pot desilylation and phenolate cyclization

Though cyclizations of phenols of the type **254** have been used in synthesis for many years, the reaction has been shown to exhibit substrate dependence. While the

literature reports suggested the desired cyclization would provide an undesired result (predominately *ortho* cyclization), it was prudent to test this compound.

The cyclization of phenol **254** was first instigated with *t*-BuOK in *t*-BuOH at reflux, the standard conditions, which give a mixture of three products with complete conversion (Scheme 5. 13). The products were determined to be the *ortho*-phenol **256** and *para*-phenol **253** (both from the S_N2, Ar_2^-6, cyclization), and the diene **255** from the competing E_2 pathway. The desired *para*-phenol **253** was inseparable from the diene **255**, but the ^{1}H NMR integrations revealed that the *ortho*-phenol **256** was the major product in a ratio of 6 : 2 : 1 (*ortho* : *para* : E_2) with a combined yield of 96%. However, this translates to a meager 20% yield of the desired product. After extensive experimentation (Table 5. 1), the best ratio was obtained through the use of Cs_2CO_3 in *t*-BuOH. The products were obtained in 2 : 1 (*o* : *p*) ratio with trace amounts of the E_2 product diene **255**. The use of strong bases such as potassium hydride and potassium hexamethyldisilazide produced only elimination, while weaker bases such as potassium hydroxide and potassium carbonate gave decomposition or recovered starting material. These results suggest that the effect of the counter-ion is felt in the transition state, directing the carbon-carbon bond formation selectively to the *ortho* position. Ultimately, no conditions could be found wherein the *para* product was formed selectively. Unfortunately, this was a problem that needed to be solved, should a stereoselective synthesis of platensimycin be completed.



254 **255** *ortho* **253** *para* **255**

Scheme 5. 13: The cyclization of phenol **254**

The use of both products, *ortho* **256** and *para* **253**, in exploratory studies is discussed next, while a solution to selective cyclization will be presented later.

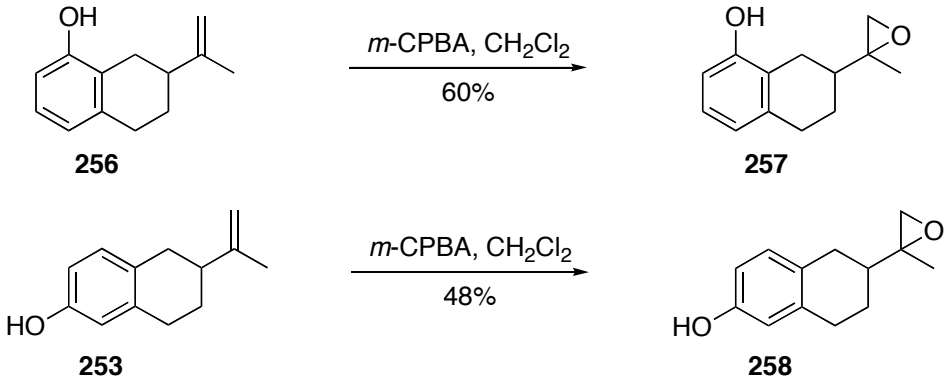
	Conditions	Results *o* : *p* : E_2 (yield)	Notes
1	*t*-BuOK, *t*-BuOH, 83 °C	6 : 2 : 1 (96%)	Classical conditions
2	*t*-BuONa, *t*-BuOH, 83 °C	8 : 2 : 1 (67%)	Tighter counter-ion leads to more *ortho* product
3	*t*-BuOK, *t*-BuOH, 18-crown-6, 83 °C	0 : 0 : 1 (45%)	No counter-ion, increased basicity gave only E_2
4	KH, THF	0 : 0 : 1 (68%)	Strong base gives E_2
5	KHMDS, THF	0 : 0 : 1	Strong base gives E_2
6	KOH, H_2O, 100 °C	Trace amounts	Mostly decomposition
7	Cs_2CO_3, *t*-BuOH, 83 °C	2 : 1 : trace (45%)	Very slow, but best ratio
8	Cs_2CO_3, THF, 65 °C	Trace amounts	Slower, lot of decomp.
9	K_2CO_3, *t*-BuOH, 83 °C	No reaction	

Table 5. 1: Phenolate cyclization conditions

5.3.3. The Advancement of Tetrahydronaphthol 253 to a Dienone

With the utility of the phenolate cyclization established, albeit with its issues, our attention now turned to the synthesis of dienone **220** (Scheme 5. 1). The first attempt was based on the supposition that the phenolate might be used to open an epoxide, giving the dienone **220** directly. The use of phenolates to open epoxides had been demonstrated,[15] though only for the synthesis of larger rings, but its application to this synthesis was loosely relevant.

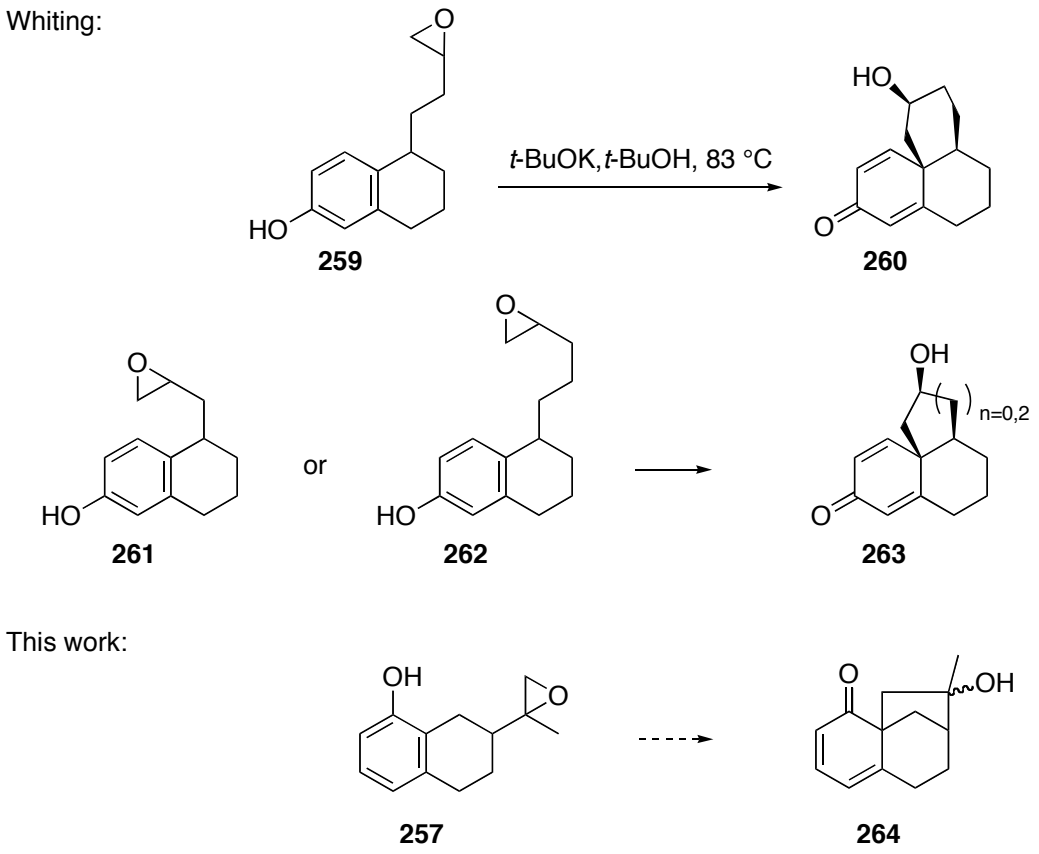
The ability to access larger amounts of pure *ortho*-product **256** governed the decision to carry it forward rather than the *para* **253**, which maps the natural product. Nonetheless, both the *ortho* and *para* phenols were epoxidized, using *m*-CPBA to give epoxides **257** (60%) and **258** (48%), respectively (Scheme 5. 14). With the epoxides in hand, their opening to form dienones was thus investigated.



Scheme 5. 14: Epoxidation of phenols **256** and **253**

5.3.4. The epoxide approach to dienone formation

The intramolecular opening of epoxides by phenoxide for the synthesis of spirocyclodienones was first reported by Whiting and co-workers.[15] However, the application of this to the formation of bicyclo-[3.2.1] systems is unknown. The reaction of epoxide **259** led to opening and spirocycle formation yielding tricycle **260** (Scheme 5. 15). The product resulted from opening at the less-substituted carbon. Interestingly, epoxides **261** (n = 0) and **262** (n = 2), differing slightly in the length of their carbon linkages only, were unreactive under the conditions. Therefore, the epoxide **257**, which differs in the placement of the epoxy side chain on the tetrahydronaphthol ring, was investigated.

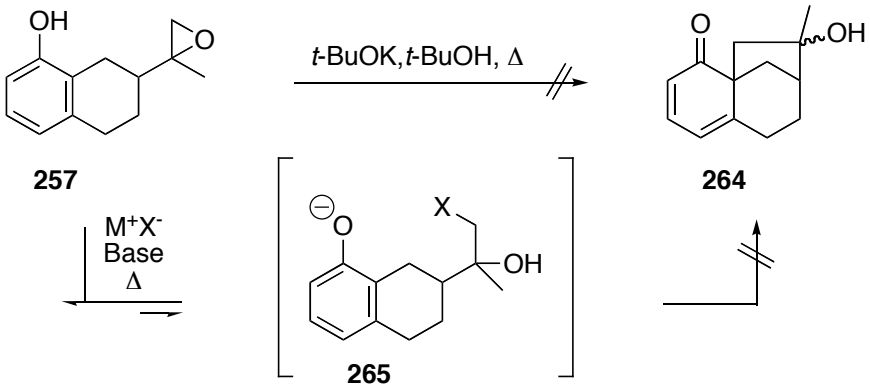


Scheme 5. 15: Whiting's epoxide opening investigations

Treatment of epoxide **257** with *t*-BuOK in *t*-BuOH at reflux only returned unreacted starting material. Further heating of the epoxide in a sealed tube and the use of different bases or solvents, returned the starting epoxide unchanged. It seems the phenol is not able to adopt a conformation wherein the aromatic ring HOMO could attack the epoxide's antibonding σ^* orbital. Therefore, as the phenol could not directly open the epoxide, alternative conditions were explored. The thought was that opening of the epoxide **257** with a halide nucleophile would furnish an intermediate halohydrin **265**. This halohydrin might then be displaced forming the dienone **264**. Even though under the basic conditions, the equilibrium would favor reclosure to the epoxide **257** strongly, the intermediacy of the halide **265** might allow for the irreversible formation of dienone

264. The consumption of the halohydrin, would drive the equilibrium, producing the dieneone **264**. Thus, the second attempt at direct dienone formation was attempted.

To test this hypothesis, the epoxide **XXX** was heated with *t*-BuOK in *t*-BuOH in the presence of a metal halide in a sealed tube. Again, no product dienone was observed. A variety of bases, metal salts, and solvents were tried, but to no avail (Scheme 5. 16). In most cases the epoxide was recovered, as when preformed in *t*-BuOH at reflux. Further heating destroyed the starting material in undetermined ways. In one instance, the use of $Bu_4N^+Br^-$ gave what appeared, but could not be isolated, to be bromohydrin formation as the epoxide was clearly gone, but no dienone was ever observed. As the presence of enone peaks in a ^{1}H NMR spectrum as paired doublets at ~6.8 and 6.0 ppm are diagnostic, their absence was conspicuous.



Scheme 5. 16: The attempted direct opening of epoxide **257**

Some instances using lithium salts gave crude mixtures of products where, no dienone was present, but an aldehyde proton (>9.0 ppm, similarly diagnostic) was observed in the ^{1}H NMR spectrum. Though attempts at isolation of the aldehyde failed,

its presence indicated that the epoxide, at least in the presence of lithium, preferred to open to the cation, which led to rearrangement *via* 1,2-hydride shift to the aldehyde. All in all, the possibility of opening the epoxide directly to the dienone **264** seemed less and less viable.

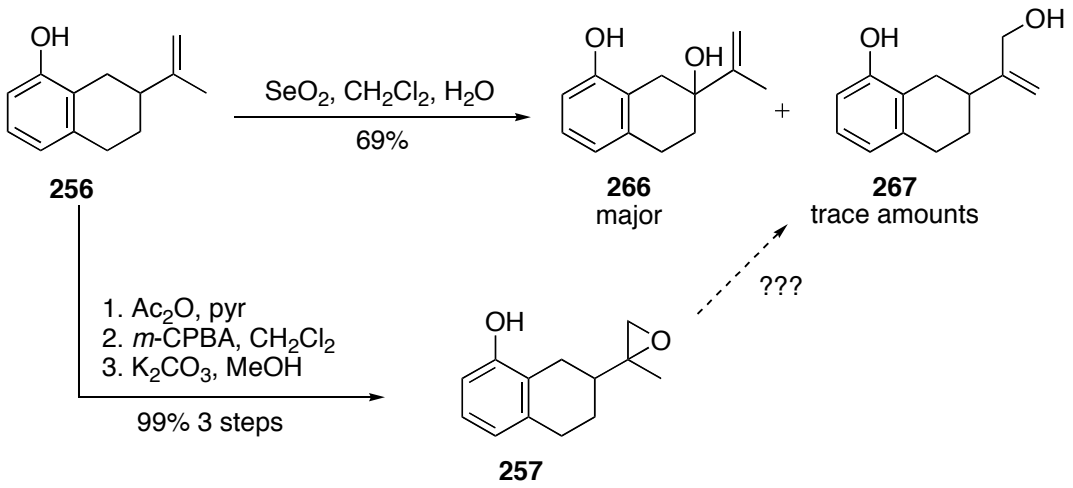
5.3.5. Dienone Formation *via* the Displacement of a Halide

The displacement of aliphatic halides intramolecularly to form dienones has been previously used in the synthesis of natural products by Masamune[16,17] in his work towards the kaurene[18] class of compounds. This strategy was also used by Corey[19] in his formal synthesis of platensimycin. In this case, an allylic halide would be desired as its displacement would furnish a dienone with an *exo*-methylene. Under the proposed route, this could intersect with Nicolaou's intermediate **183**.

The direct allylic oxidation of alkene **256** was the first strategy explored. The use of SeO_2, a standard allylic oxidant, produced the product of allylic oxidation at the undesirable allylic carbon C-12 (**266**) (Scheme 5. 17). The desired methyl group oxidation product **267** was determined to be present only in trace amounts. The major product, alcohol **266** was obtained in 69% yield. While the oxidative rearrangement of alcohol **266** to an aldehyde with an oxygen now on the appropriate carbon seemed a possibility, a more direct alternative was pursued.

The epoxide **257**, already in hand, contained the oxygen attached at the desired appropriate carbon. Considering the variety of methods developed for the conversion of epoxides to allyl alcohols[20] this seemed a more feasible approach. At this point, the epoxidation of alkene **256**, a reaction which did not translate well to scales >30 mg, was optimized. Other epoxidation protocols (i.e. DMDO) gave similarly poor yields and the

hypothesis was that the presence of the phenol was producing undesired side reactions. To prevent this, the phenol was protected as its acetate, which could be epoxidized and deprotected in one-pot to give a quantitative yield of the same epoxide over the three steps (Scheme 5. 17). Additionally, while the *m*-CPBA procedure required column purification, the improved three-step procedure produced pure epoxide as a white powder without the need for further purification.

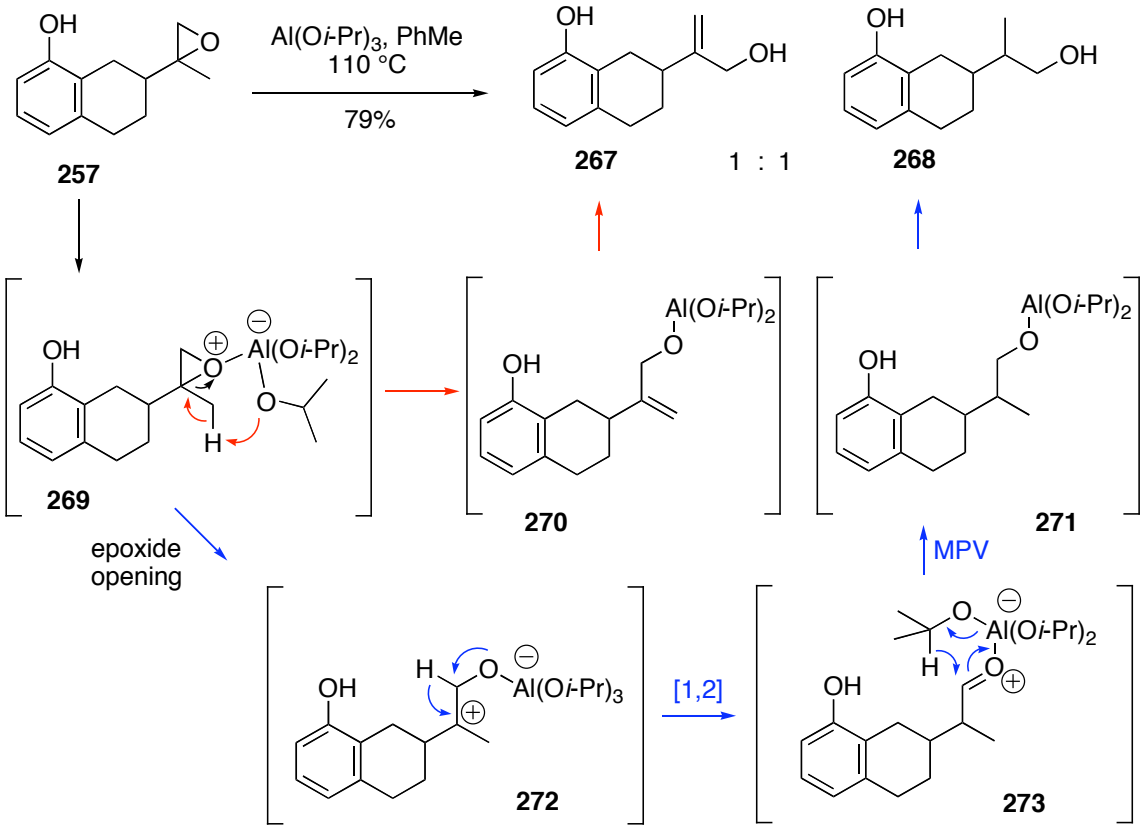


Scheme 5. 17: Allyic oxidation of phenol **256**

The rearrangement of epoxide **257** to allyic alcohol **267** was explored next. Exposure of epoxide **257** to amide bases such as LDA, LDE, and $MgN(i\text{-}Pr)_2$ gave the recovered epoxide at room temperature, and warming led to decomposition. Presumably, the phenolate, formed from deprotonation of the phenol, precludes rearrangement at ambient temperature. Yet heating of the reactions only returned complex mixtures. Using TMSI, generated *in situ*, produced an undetermined product containing silyl groups, but no alkene peaks. This could arise from isomerization of the allylic alcohol double bond to the tetrasubstituted alkene, upon the action of the generated HI.

Nonetheless, this could not be mitigated, and the desired allylic alcohol could not be obtained.

Fortunately, treatment of the epoxide **257** with aluminum triisopropoxide furnished the desired allylic alcohol **267**. However, the aliphatic alcohol **268** was present as well, in an inseparable 1 : 1 mixture and 79% isolated yield (Scheme 5. 18). The unexpected side product, aliphatic alcohol **268**, is understood to arise from the mechanism shown. The epoxide first coordinates to the aluminum giving intermediate **269**. It now has two paths for reaction. The elimination of the epoxide, the desired pathway (red arrows), produces the desired allylic alcohol **267** *via* protonation of the resultant alkoxide **270**. The second path (blue arrows) involves the heterolytic cleavage of the epoxide to the tertiary cation and alkoxide **272**. This alkoxide can then rearrange *via* a 1,2-hydride shift, forming the aldehyde **273**. This pathway was also invoked to explain the observance of aldehyde peaks in earlier experiments with the epoxide **257** (*vide supra*). The aldehyde **273**, still coordinated to the aluminum containing isopropoxide ligands, can then undergo a Meerwein-Pondorf-Verley reduction of the aldehyde to the alcohol **268** after protonation of aluminate **271**.



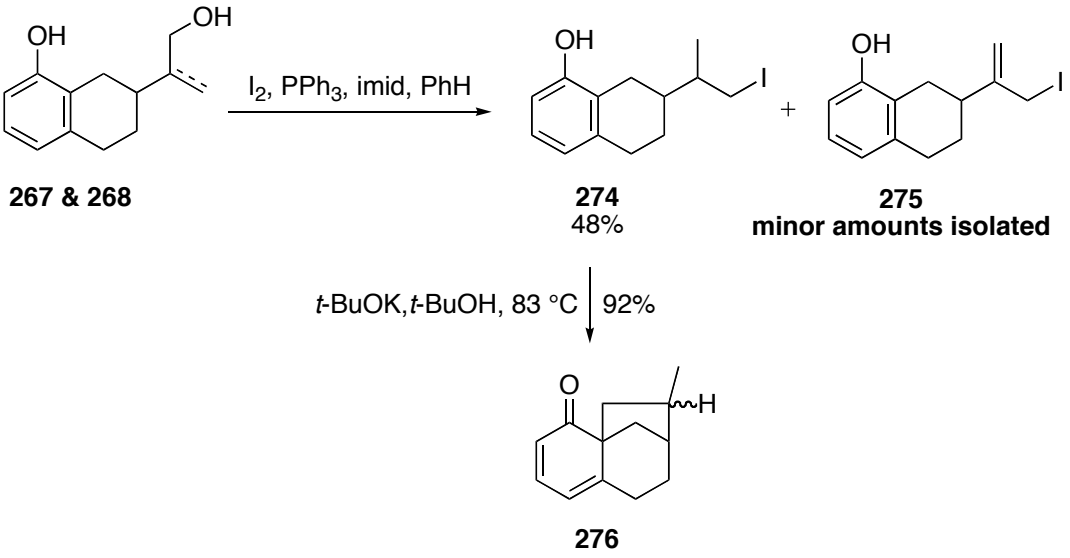
Scheme 5. 18 : Epoxide to allylic alcohol rearrangement and side reaction

5.3.5. Dienone formation

With the alcohols **267** and **268** in hand, their conversion to the dienone was explored. The alcohols, as a 1 : 1 mixture, were treated with I_2, PPh_3, and imidazole to furnish the iodides **274** and **275** (Scheme 5. 19). However, only the aliphatic iodide could be isolated (48% yield, 96% conversion of the aliphatic iodide) in appreciable quantities. The allylic iodide **275** may be extremely reactive, resulting in decomposition upon workup.

Although the relevant allylic iodide could not be obtained in synthetically useful quantities, the less relevant aliphatic iodide **274** could. Reaction of iodide **274** with

t-BuOK in *t*-BuOH at reflux produced the dienone **276** as an inseparable mixture of diastereomers in 92% yield (Scheme 5. 19). Though dienone **276** was not thought to be directly convertible into enone acid **171** and thus platensimycin **160**, the synthesis of a dienone as a model system had been completed.

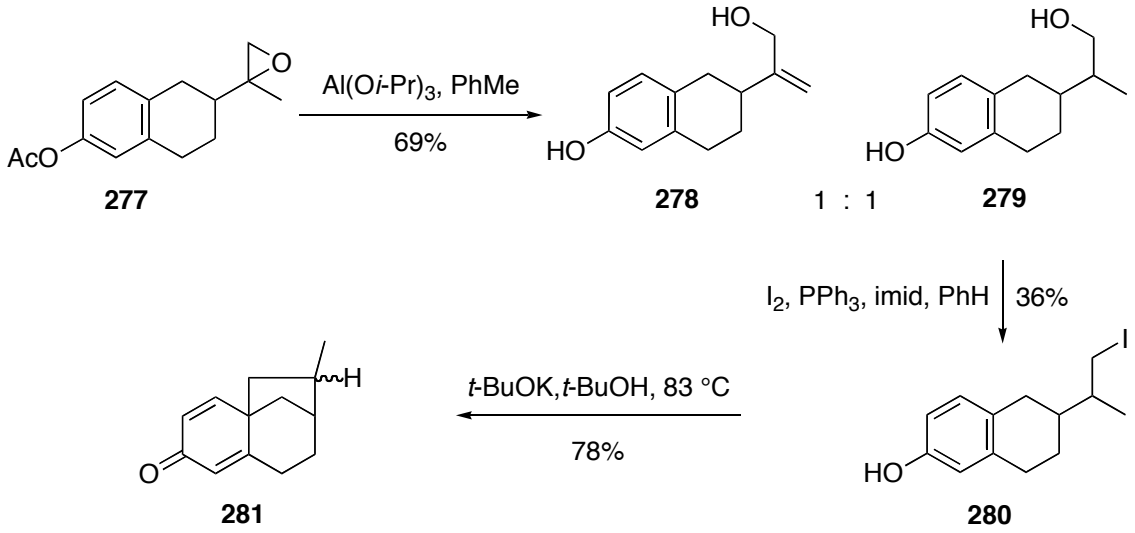


Scheme 5. 19: Dienone **276** synthesis

While access to the dienone **276** was strategically important, it was not obvious that it could be directly converted to platensimcyin. For that, the utility of the halide derived from the *para*-phenol **253** would need to be demonstrated.

The acetate epoxide **277**, derived from *para*-phenol **253** as per Scheme 5. 17, was treated to the allylic rearrangement conditions. It was found that the acetate performed as well as the phenolic epoxides in these rearrangements, resulting in simulateneous deprotection. The allylic alcohol **278** was again obtained as a 1 : 1 mixture with the aliphatic alcohol **279** in 69% total yield (Scheme 5. 20). The iodination of alcohol **279** was performed next. The aliphatic iodide was still the only halide isolated from the

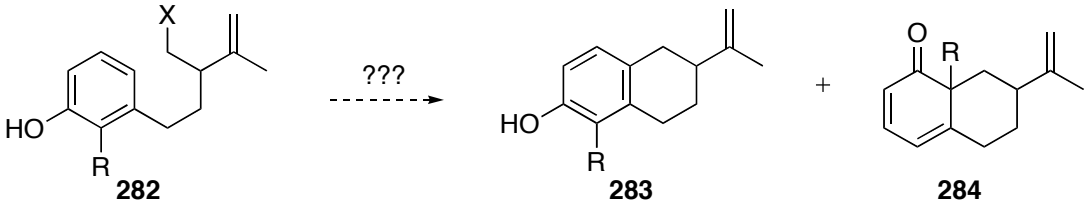
iodination reaction. Treatment of iodide **280** with *t*-BuOK in *t*-BuOH at reflux, as before, produced the cross-conjugated dienone **281**. These compounds were not pursued further, nevertheless, accessing the dienones **276** and **281** was a success.



Scheme 5. 20: Advancement of epoxide **277** to a dienone

5.4. Second Generation Approach: A Blocking Group Solution

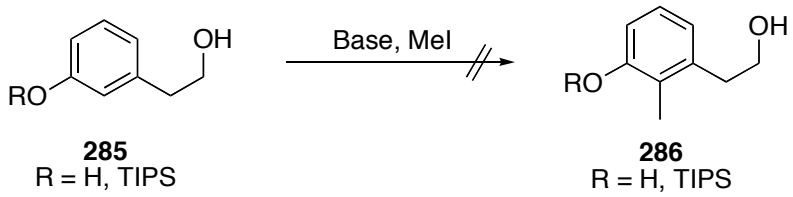
The observation that phenol **254** cyclizes to give primarily the *ortho* cyclized product presented an issue that could not be solved through the desmethyl series phenol **285**. However, installation of a non-H group in the *ortho* position of phenol **254** might direct the cyclization *para*. The use of a similar strategy, using a methyl in the *para* position to direct an *ortho* cyclization was known, so the converse was reasonable.[21] The synthesis of a substrate such as **282** would be targeted (Scheme 5. 21). As the natural product contains a methyl group in this position it seemed the logical choice of R-group.



Scheme 5. 21: Proposed blocking group strategy

5.4.1. A Directed *ortho*-Lithiation Strategy

The phenethylalcohol **285**, used an early intermediate in the desmethyl series above, was available in large quantities from commercially available chemicals and thus was a logical starting point for installing the 2-methyl group directly. Unfortunately, the conversion of aryl **285** to its counterpart 2-methyl aryl **286** proved unfruitful (Scheme 5. 22). Therefore, an alternative course had to be devised. The phenethyl alcohol would be constructed from a suitable 2-substituted phenol.



285
R = H, TIPS

286
R = H, TIPS

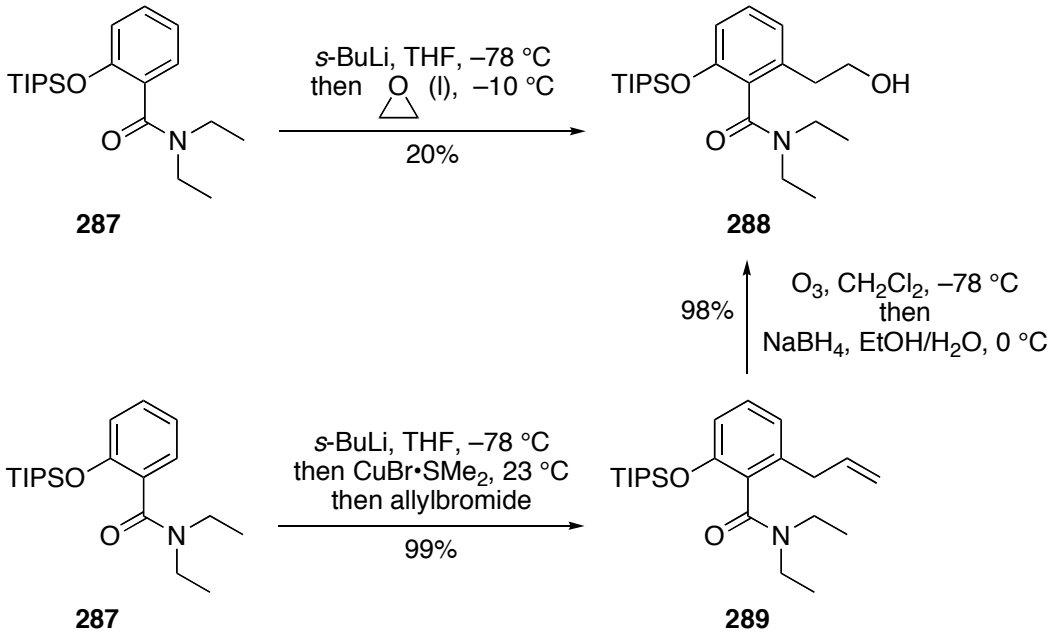
Scheme 5. 22: Attempted conversion of desmethyl phenol **285** to 2-methyl phenol **286**

The *ortho*-directed lithiation and alkylation of aryls is a well established protocol for the synthesis of polysubstituted arenes.[22] Consequently, it was pursued as an strategy for the synthesis of phenol **286**. The known triisopropylsilyl protected benzamide **287** has been used in directed lithiation chemistry and for the purpose of maintaining consistency of the protecting groups, was used first.

Clayden and co-workers used the lithiated triisopropyl benzamide **287** to open epoxides in the presence of BF_3•OEt_2.[23] The extension of this procedure to the opening of ethylene oxide would produce the desired phenethyl alcohol. The lithiation of benzamide **287** was carried out using *s*-BuLi and upon quenching of the aryl lithium with ethylene oxide in the presence of BF_3•OEt_2 returned a complex mixture which appeared to be largely polymeric (Scheme 5. 23). Elimination of the BF_3•OEt_2, the likely instigator of polymerization, gave a 20% yield of the desired phenethylalcohol **288**, however this yield could not be improved at this time.

Alkylating benzamide **287** with allyl bromide, followed by conversion of the allyl **289** to ethanol **288** seemed attractive. However, quenching of the lithiated benzamide with allyl bromide led cleanly to an aryl bromide, the product of lithium halogen exchange and not nucleophilic attack.[24] Interestingly, many examples of lithiated benzamides similar to **287** were transmetalated to an aryl copper or cuprate species for successful alkylation.[25] It proved to be an excellent solution in this case. Transmetalation of the lithiated benzamide with CuBr•SMe_2, followed by quenching with

allyl bromide provided a quantitative yield of the allylated benzamide **289** (Scheme 5. 23).

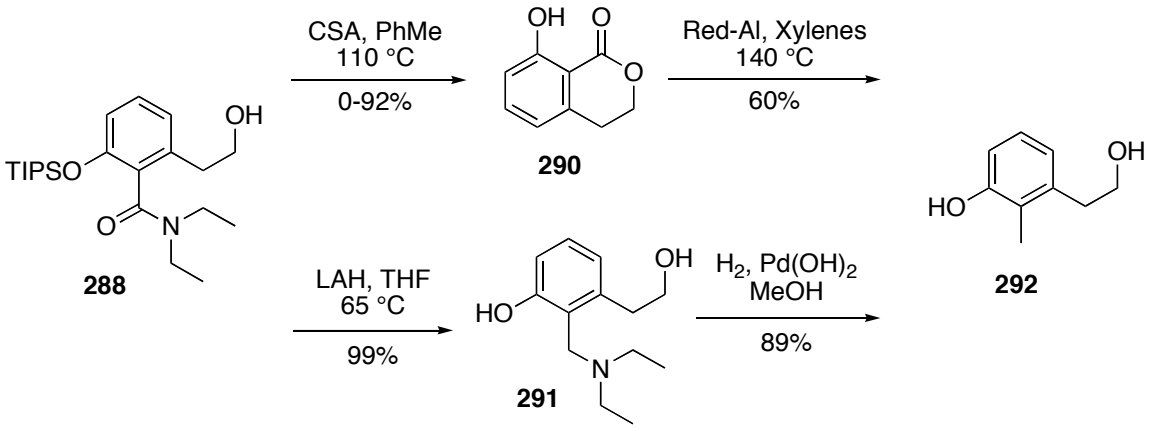


Scheme 5. 23: The directed alkylation of benzamide **287**

The task of converting the allyl **289** to the ethanol **288** was subsequently achieved through ozonolysis and reduction.[26] The allyl was ozonolyzed and then quenched with $NaBH_4$. Reduction of the intermediate secondary ozonide by $NaBH_4$ provided the phenethylalcohol **288** in 98% yield, far better than *via* the initial oxirane opening reactions.

Still, the benzamide carbonyl would need to be reduced to a methyl. The thought of doing this in a two-step process where the amide is converted to the lactone, and the lactone reduced to the methyl was first considered. The first step was to form the lactone[27] **290** (Scheme 5. 24). While there are a few examples of the one-pot aryl epoxide opening and lactone formation,[28] none of those procedures (namely workup of

the alkylation reaction with strong acid) worked in this case. The pure amide **288** could be converted to the lactone under a variety of conditions with varying success, but all of these conditions resulted in quantitative desilylation of the phenol. The best results for lactonization were managed with organic acids such as CSA and TsOH, however these reactions behaved erratically, often returning mostly the deprotected benzamide. Basic conditions using alkaline hydroxides usually returned the seco-acid which was difficult to isolate and resulted in low mass recoveries. Nonetheless, the lactone **290** was reduced to the benzylmethyl **292** using Red-Al in refluxing xylenes for a 60% yield. In the end, another two-step process was found to be superior.

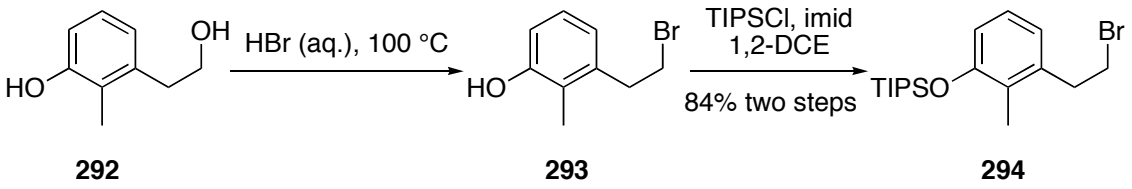


Scheme 5. 24: The reduction of the diethylamide **288** to 2-methylphenol **292**

An alternative two-step process for the reduction of the 2-amide to the 2-methyl is outlined in Scheme 5. 24. Reduction of the benzamide to the diethylbenzyl amine **291** using LAH could be accomplished in refluxing THF (Scheme 5. 24). Once again, deprotection of the silyl ether was facile. Still, the deprotected amine could be obtained in quantitative yield. Hydrogenation of benzyl amine **291** to 2-methylphenol **292** proceeded in 89% yield, but only with $Pd(OH)_2$ as the hydrogenation catalyst.[29] Other Pd

catalysts were completely unreactive. In fact, the only other conditions which returned the desired product involved the heating of amine **291** with a large excess (1000% wt.) of Raney Ni in refluxing EtOH for yields consistently in the 40-50% range. Conversely, hydrogenation with Raney Ni (cat.) and H_2 (g) gave no discernible product.

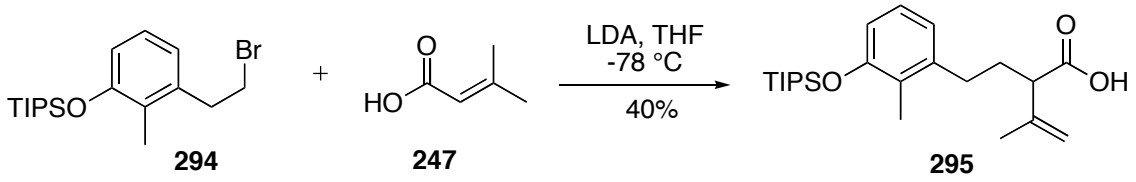
In any case, the 2-methyl-3-phenethanol phenol **292** had been prepared and its conversion to an electrophile had been executed. The diol **292** could be converted to its bromide **293**, for direct comparison to the desmethyl series by refluxing the starting material in 48% HBr (aq.) (Scheme 5. 25). The crude phenol was re-protected as its triisopropylsilyl ether **294** in preparation for the alkylation. The two-step procedure gave bromide **294** in 84% overall.



292 **293** **294**

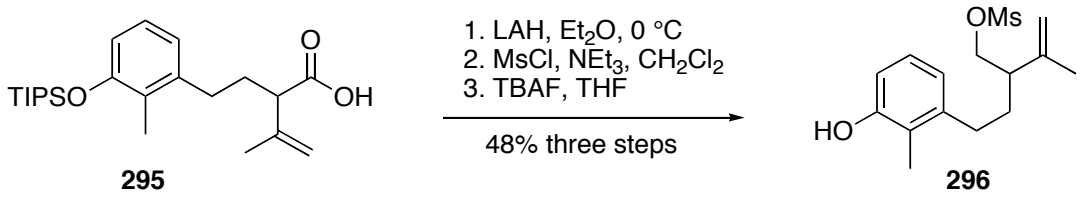
Scheme 5. 25: Synthesis of bromide **294**

The alkylation of bromide **294** with 3,3-dimethylacrylic acid **247** was then performed. Earlier examples of this reaction on the desmethyl bromide **239** gave substantial styrene formation and thus bromide **294** behaved similarly. The enolate of acid **247** was formed with LDA and quenched with bromide **294**. The deconjugated acid **295** was isolated in a mediocre 40% yield (Scheme 5. 26). However, the bromide **294,** accessible in gram quantities, behaved consistently in the alkylation, proceeding in a dependable 40% yield on multigram scales. The issue of a substrate with a better leaving group, i.e. mesylate, was less pressing than whether the 2-methyl "blocking group" had the desired directing effect on the phenolate cyclization.



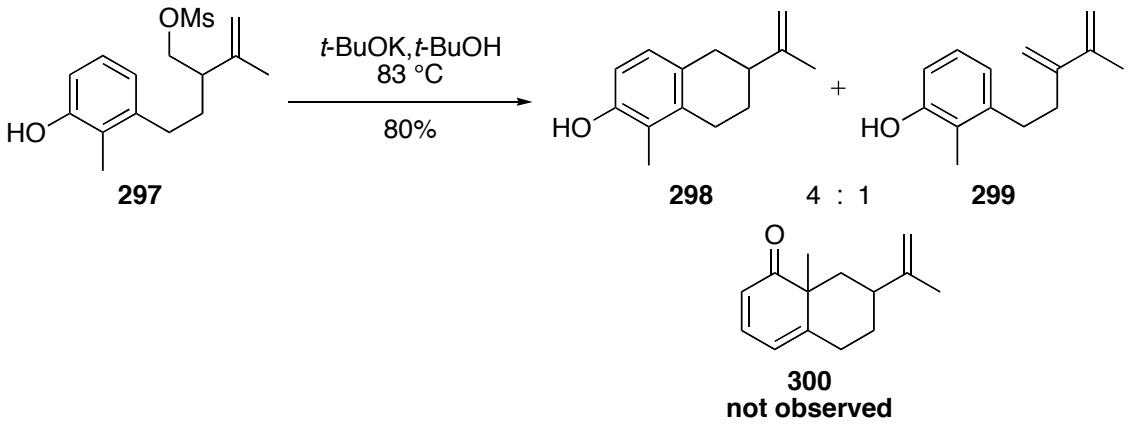
Scheme 5. 26: The alkylation of bromide **294**

The acid **295** was converted to cyclization precursor mesylate **296** in a three-step procedure. The acid was reduced with LAH and the crude alcohol was sulfonylated with MsCl. After removal of the silyl group, phenol **296** was obtained in a 48% yield over the three steps, without any column chromatography (Scheme 5. 27). The phenol mesylate **296** was purified for the subsequent investigations.



Scheme 5. 27: Synthesis of a 2-methyl phenolate cyclization substrate

The hypothesis that a 2-methyl "blocking group" could direct the phenolate cyclization to give the *para*-phenol exclusively was now tested. Gratifyingly, treatment of mesylate **296** with with *t*-BuOK in *t*-BuOH at reflux gave the *para*-phenol **298** with the competing E_2 product, diene **299** in a 4 : 1 ratio and 80% yield (Scheme 5. 28). No *ortho* cyclization product, which would be a dienone **300**, was identified. This confirmed that the existence of a 2-substituent would direct the cyclization *para*. The presence of the elimination product would clearly need to be addressed, but the issue of an improved synthesis of a 2-methyl alkylating agent was more pressing.



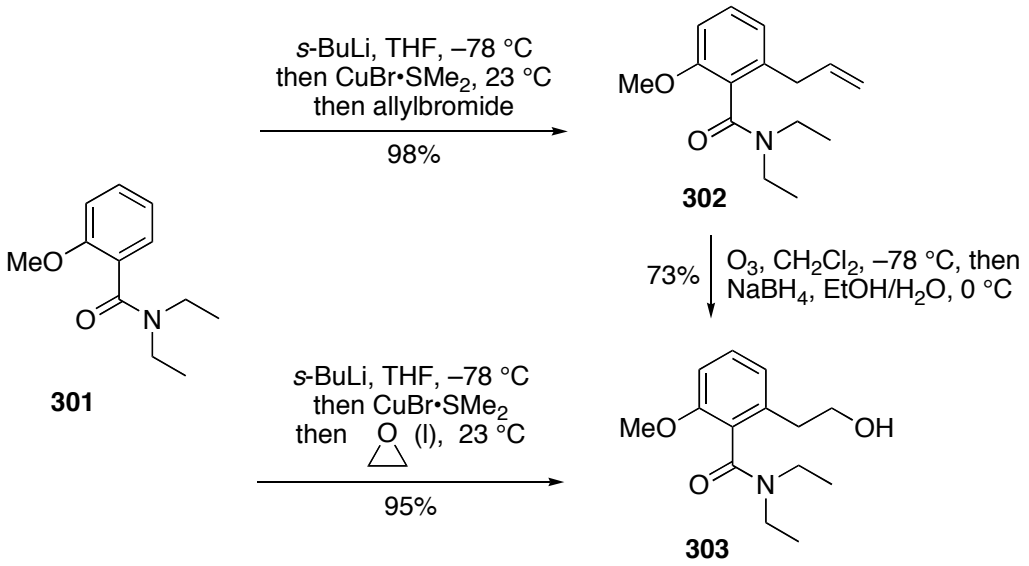
Scheme 5. 28: The *para*-directed phenolate cyclization

The synthesis of bromide **294** was acceptable for the investigative studies described above. However, the difficulty in synthesizing the known silyl ether benzamide **287** (the synthesis from salicylic acid is low-yielding), the loss of the silyl protecting group during amide reduction, and the inefficient performance of the bromide **294** in the alkylation led to the conclusion that a better route could be devised.

5.4.2. An Improved Directed *ortho*-Lithiation Strategy

The choice to use a triisopropylsilyl protected phenol **294** was made for the purposes of direct comparison to the desmethyl series chemistry described above. The desire to change only one variable (the 2-methyl substitution) in the established chemistry overrode the consequences of the silyl ether's lability. With the 2-methyl strategy established, the improved route was devised. The anisic acid derived benzamide[30] **301** was readily synthesized on hundred gram scales and was amenable to distillation, clear advantages for large-scale preparation and purification.

The anisamide **301** was allylated in a similar manner as before.[31] Surprisingly, the use of *s*-BuLi gave ketone products arising from the addition of *s*-BuLi into the diethyl amide. This product had not been observed in the triisopropylsilyl **287**. Switching to *t*-BuLi eliminated this issue and allyl **302** could be obtained in 98% yield (Scheme 5. 29). The allyl **302** behaved in the ozonolysis/reduction protocol as before, providing alcohol **303** in 73% yield.

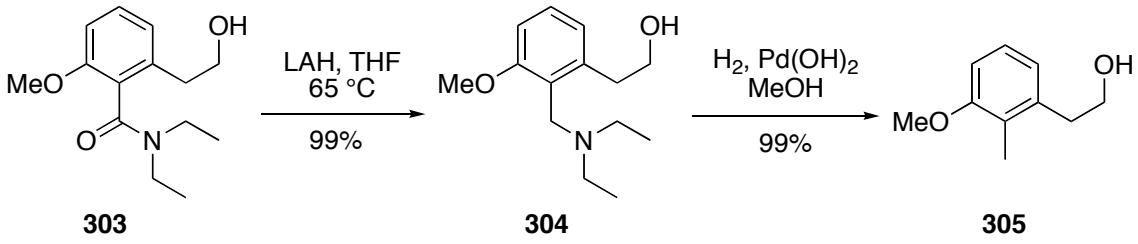


Scheme 5. 29: The anisamide directed alkylation

At this point, the utility of a direct ethylene oxide opening was re-examined. The use of the aryl copper intermediate as a nucleophile (from transmetalation with $CuBr•SMe_2$) had clearly improved the allylation chemistry, so its effect on oxirane openings was tested. By using the aryl copper and raising the temperature at which ethylene oxide addition occurred to 23 °C, the alcohol **303** was optimally acquired in 95% yield (Scheme 5. 29). Another advantage to this benzamide route over the silylated benzamides was found during the isolation of alcohol **303**. Simple trituration of the

crude orange oil (spectroscopically of acceptable purity) with cold ether furnished the pure desired alcohol as a white powder, eliminating the chromatography necessary for the silyl benzamide alcohol **288**.

The effect of changing the phenolic protecting group from a silyl to methyl first manifested itself in the amide reduction. Initial attempts at reducing the amide with LAH in refluxing THF were much slower, giving large amounts of unreacted starting material. Increasing the temperature by switching to LAH in refluxing toluene (65 °C – 110 °C) gave complete consumption of the starting amide, however substantial (as much as 50%) phenolic demethylation occurred. In the end, LAH in refluxing THF for several days allowed the isolation of amine **304** in 99% yield (Scheme 5. 30). The hydrogenation of benzyl amine to the 2-methyl phenethyl alcohol[32] **305** was similarly slowed by the presence of the phenolic methyl but after several days, the desired methyl alcohol could be obtained in quantitative yield (Strem® $Pd(OH)_2$ was found to be essential for reproducability in this reaction).[29] In those instances when time was short, the remaining unreacted amine (obtained through acidic extraction of the organic mixture with H_3PO_4)[33] could be recycled.



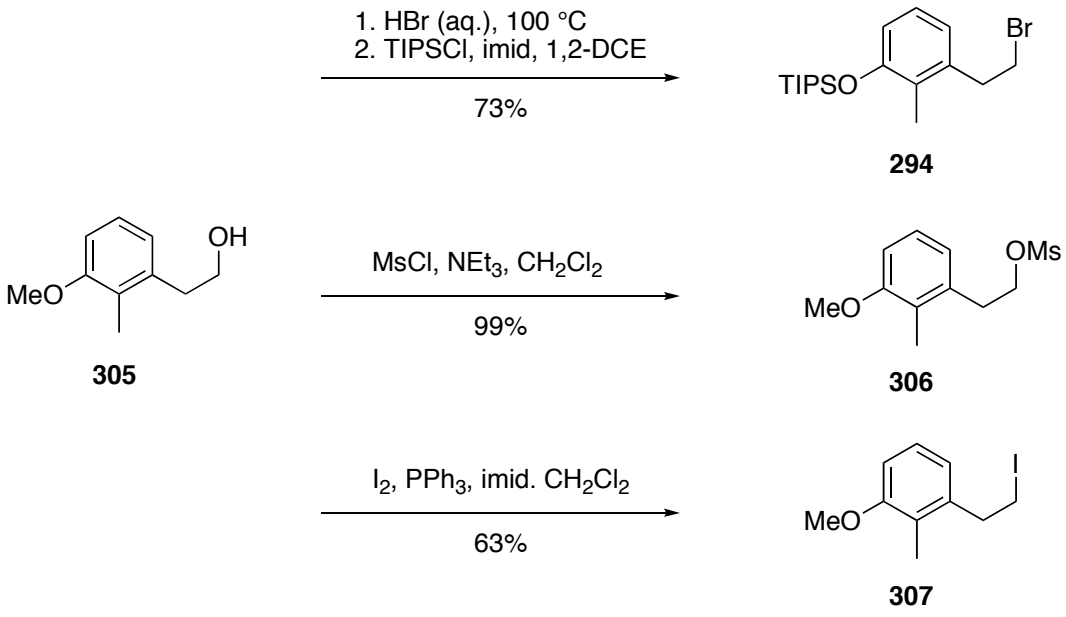
303 **304** **305**

Scheme 5. 30: The synthesis of phenethyl alcohol **305**

The phenolic alcohol **292** had previously been converted to its bromide because of the presence of the diols. In the case of alcohol **305**, the phenol was blocked from

mesylation. Since the removal of the methyl at a later stage had not yet been established, the desire for consistency in later steps led to the conversion of methyl **305** to bromide **294** in the same conditions as before (73% over the two steps) (Scheme 5. 31). The action of HBr was found to cleanly demethylate the anisole **305** to the phenol providing bromide **293**. Should a later substrate prove incompatible with demethylation strategies, the bromide **294** could be used, but now with improved access to it. Additionally, the mesylate **306** (MsCl, NEt_3, 99%) and the iodide **307** (I_2, PPh_3, imid., 63%) were prepared.

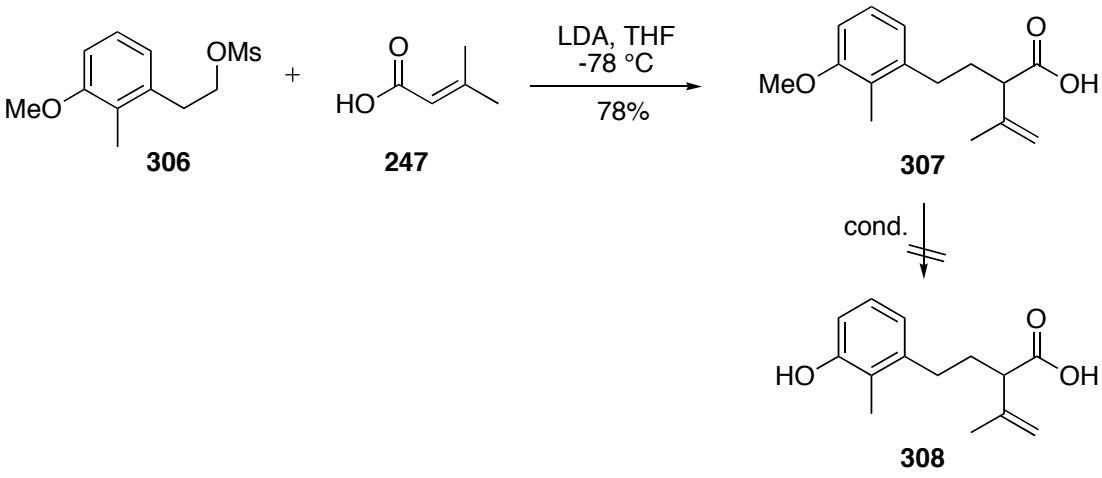
Of the three electrophiles, the mesylate proved the most effective alkylating agent. This was consistent with the observations of earlier alkylations (*vide supra*, Scheme 5. 9) and the mesylate was used from this point on.



Scheme 5. 31 : Conversion of alcohol **305** to electrophiles **294**, **306**, and **307**

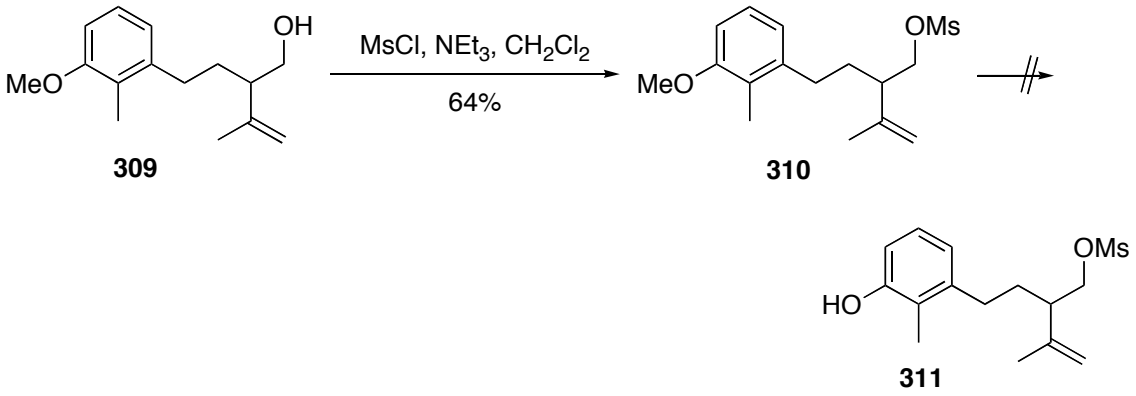
In the alkylation, the dianion of acid **247** was quenched with mesylate **306** to give alkylation product **307** in 78% yield (Scheme 5. 32). The removal of the phenolic methyl

was now examined. Small amounts of the demethylated acid **308** could be obtained in small scale (~10 mg) reactions through the action of BBr_3. Larger scale experiments gave complex mixtures which exhibited the disappearance of the alkenyl protons. This may have occurred through either reconjugation of the olefin to the acid or bromination of the olefin by advantageous Br_2 or a combination of both. The nucleophilic displacement of the methyl from the phenol with thiolates proved equally unsuccessful, giving no evidence of the desired demethylation.



Scheme 5. 32: The alkylation of mesylate **306**

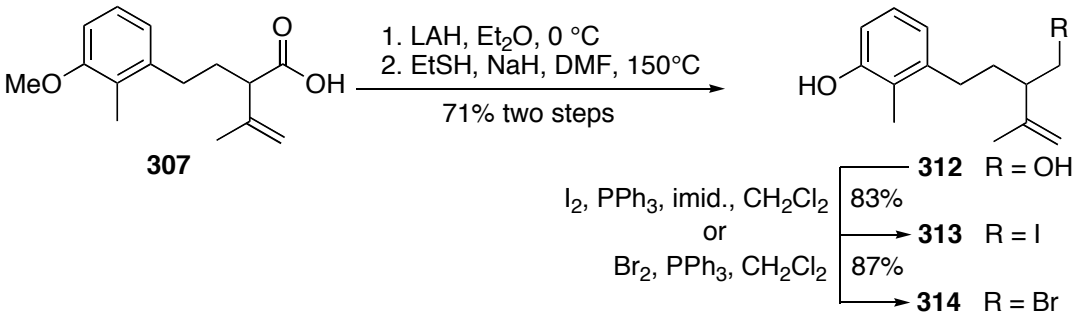
Ultimately, the acid **307** was deemed a poor substrate for demethylation. With that in mind, the reduced acid **309** was converted to its mesylate **310** in an attempt to cleave the phenolic methyl on this substrate (Scheme 5. 33). This would provide the phenolic mesylate **296**, identical to that used in the earlier cyclization example (*vide supra*, Scheme 5. 28). Unfortunately, no conditions for the desired demethylation could be found. The nucleophilic thiolate conditions were clearly incompatible with the presence of an electrophilic mesylate and the use of BBr_3 destroyed the olefin again.



Scheme 5. 33: The attempted demethylation of mesylate **310**

Instead, the acid was reduced to the alcohol using LAH as before in 87% yield (Scheme 5. 34). The phenolic methyl could then be removed under the action of sodium ethanethiolate. Ethanethiol, NaH in DMF at 150 °C provided phenol **312** in 82% yield (or 71% over the two steps). The usage of BBr_3 gave similarly negative results as in the acid, where reaction of the olefin seemed to predominate.

While alcohol **312** could be converted to its iodide **313** or bromide **314** in decent yields (83% and 87% respectively) their utility as phenolate cyclization substrates was questionable. Experiments during the desmethyl series with a bromide instead of the mesylate **296** produced primarily the product of E_2 elimination. Nevertheless, the use of the bromide **314** or iodide **313** in phenolate cyclizations was mandated by the inability to demethylate mesylate **310**. At this point, the problem of competing elimination in the phenolate cyclization to tetrahydronaphthols would need to be solved.

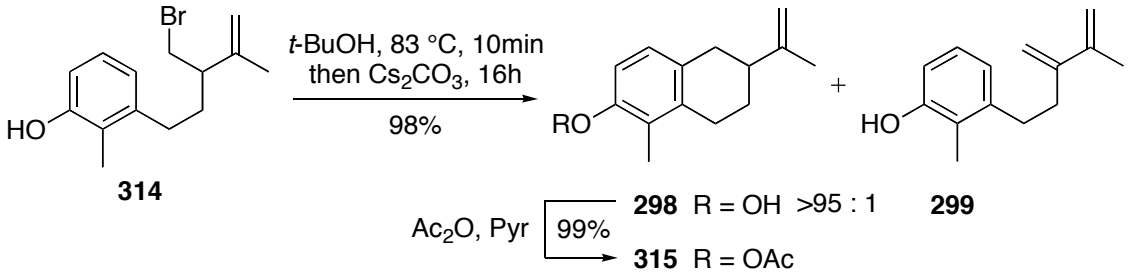


Scheme 5. 34: The demethylation of phenolic **307**

The initial experiments in Ar_2^-6 cyclizations were prepared at room temperature, where the starting material was dissolved in solvent, the base was then added and the reaction heated to the designated temperature and maintained there until the reaction was complete. However, careful examination of the phenolate cyclization revealed this was not optimal. Bromide **314** was chosen for optimization as iodide **313** had a greater propensity for elimination than did the bromide. As no product of intermolecular nucleophilic addition had ever been observed, the concentration of the reaction was not initially considered as a contributing factor when screening the conditions. Nonetheless, it was clear from simple comparisons of side by side reactions that Cs_2CO_3 was an optimal base for the cyclization and that stronger bases such as *tert*-butoxide gave more elimination while weaker bases gave little or no product. The use of aprotic solvents such as THF or DMF also gave greater amounts of E_2. So it was that Cs_2CO_3 in *t*-BuOH was chosen as the optimal base and solvent.

With the base and solvent chosen upon, the temperature at which the reaction was run was called into question. Essentially, which pathway occurrs at lower temperature, S_N2 or E_2 needed to be determined. Nothing happens when the reaction is maintained at room temperature. Slowly warming the suspension in 10 degree increments showed consumption of the bromide. In fact, it was determined that the elimination occurs at

lower temperature. Performing the reaction at 55 °C gave only the diene **299**. In an experiment designed at bypassing the threshold for activation energy for both pathways, the base would not be added until the appropriate temperature had been reached throughout the system. When the base was not added until a solution of the bromide was refluxing rapidly, the elimination product was all but eradicated, appearing in ~10% based on the comparison of the ^{1}H NMR integration. Additionally, when the reaction was performed at dilute concentrations for intramolecular cyclization (~0.005mM) with a great excess of base added after the solution had reached rapid reflux in *t*-BuOH, the desired cyclization product **298** was obtained with virtually no elimination product **299** observable in the ^{1}H NMR spectrum (Scheme 5. 35) (>95% cyclization). These results combine to suggest a mechanism wherein conjugate base of the phenol is responsible for the elimination and not the Cs_2CO_3.



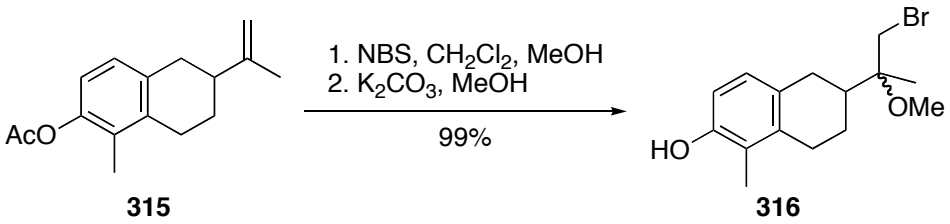
Scheme 5. 35: The optimized phenolate cyclization

The phenol **314** could be protected as its acetate by dissolution in pyridine and acetic anhydride. The reaction was immediately complete and evaporation of the volatiles gave the acetate **315** in quantitative yield, and of acceptable purity. It was determined that this two-step process could be performed in a one-pot process from the bromide **314**. The cyclization was performed and the solvent removed by distillation.

The crude residue was then taken up in acetic anhydride and the excess Cs_2CO_3 served as the base. After workup, the acetate **315** was again obtained in near-quantitative yield for the two steps. With the acetate **315** in hand its conversion to the targeted intermediate dienones could be explored.

5.4.3. Dienone formation

Due to the earlier observations that the allyl halide route was unsuccessful, a bromohydrin intermediate, inspired by the Masamune work,[16] was sought. Treatment of acetate **315** with NBS in DCM with MeOH gave the bromohydrin. The acetate was essential for this reaction's success as the unprotected phenol gave aryl bromination products before bromohydrin formation. The crude reaction mixture was then treated with K_2CO_3 and the acetate was cleaved to phenol **316**. Thus, the phenol bromohydrin **316** was isolated in quantitative yield (Scheme 5. 36). In short, the bromide **314** could be converted to bromohydrins **316** in 3 steps and 99% yield with no column chromatography.

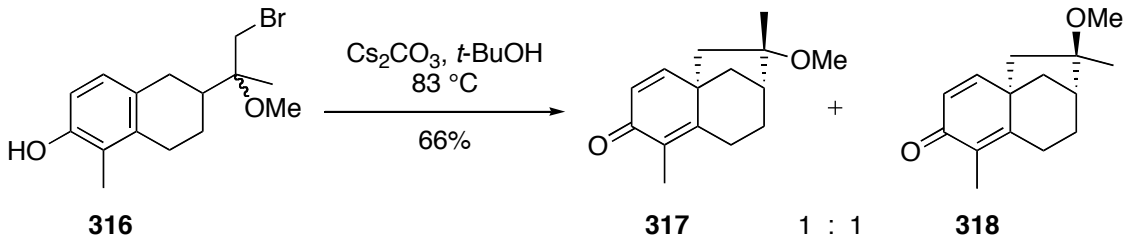


315 **316**

Scheme 5. 36: Bromohydrin formation

The bromohydrin diastereomers were inseparable and at the time this was seen as inconsequential. The ring closure would arise *via* the ionization to the cation, losing any relevance as to the MeOH stereochemistry. The mixture was subjected to the classical

dienone cyclization conditions (*t*-BuOK in *t*-BuOH) and heated for two days until completion. The dienones **317** and **318** were formed in a 1 : 1 ratio and a combined yield of 32% (Scheme 5. 37). This dienone formation proved to be less clean or efficient than earlier examples. This difference in reactivity was understood by the assumption that the S_N2 displacement at the neo-pentyl bromide carbons was more difficult and that competing decomposition may occur. Incidentally, the isolation of both cyclized isomers is contrary to the observation made by Masamune (Scheme 5. 2) that only one isomer of bromohydrin, in his work, was cyclized. The combined yield could be improved to 66% for both isomers by switching to Cs_2CO_3 as the base. The methyl ether epimers were separable at this point.

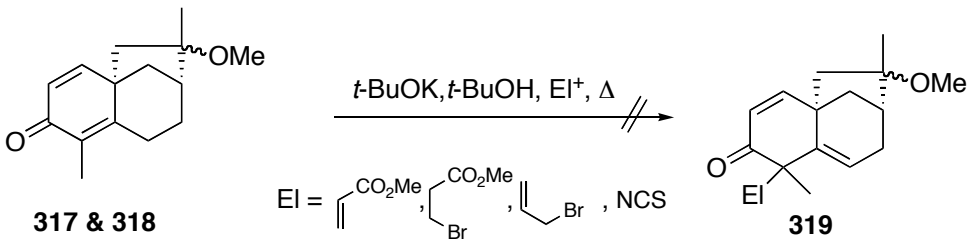


Scheme 5. 37: Cyclization of bromohydrin **316**

The first attempt to convert the dienones **317** and **318** into platensimycin involved the deconjugative alkylations to install the propionate side chain. The resultant trisubstituted olefin would then be hydroborated and oxidized to install the requisite ether oxygen. Classically, dienones of this type have been alkylated using the cyclization conditions of *t*-BuOK in *t*-BuOH. The conjugate addition of the dienone's enolate to an acrylate was envisioned to directly put in the propionate side chain. While Nicolaou's work used an allyl group and functionalized it to the propionate in three steps, a more direct approach was preferable. Unfortunately, no such reaction could be completed.

Under all conditions applied, the starting material was returned unchanged (Scheme 5. 38).

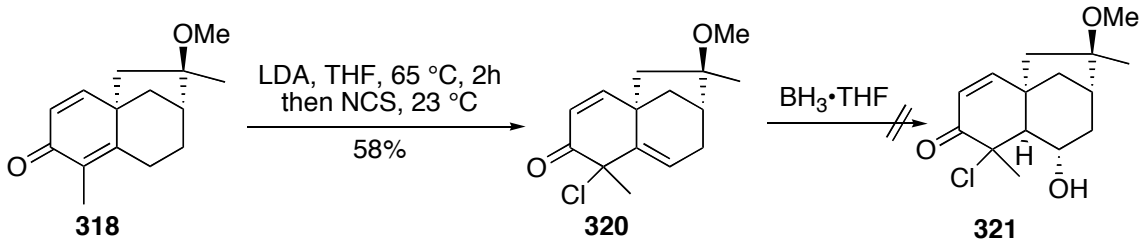
The use of LDA as a base in the alkylation was also explored and was met with similar frustrations when the reaction was performed at ambient temperatures and below. The use of excess methylacrylate as an electrophile to quench the LDA generated enolate produced an initially encouraging result. The starting material was consumed, and a new product was evident. However, the crude reaction mixture could only be described as a polymeric mess and purification of what appeared by ^{1}H NMR to be a deconjugtated enone was not possible. The use of one equivalent of acrylate to quench the same reaction returned the starting dienone unchanged. Its assumed that when a huge excess of acrylate is present, the polymerization pathways did not consume the acrylate so quickly so that some conjugate addition could occur. With only one equivalent in solution, polymerization precludes addition, by consuming all the acrylate before conjugate addition could take place. The use of other electrophiles under these conditions such as the γ-bromopropionate, allyl bromide (as per Nicolaou) and NCS all gave no evidence of product formation.



Scheme 5. 38: Attempted use of dienone **317** and **318**

Although alkylation proved fruitless, an α-chlorine could be installed. To accomplish this, a solution of the dienone **317** with LDA in THF, was heated at reflux

for 2 hours, then cooled and quenched with NCS (Scheme 5. 39). This gave chloride **320** in 58% yield as a single isomer, assumed to be product of chlorine's approach from the less sterically encumbered. This is the stereochemical outcome Nicolaou observed in their allylation work, although the stereochemistry of chlorine **320** was not unambiguously determined. The dienone **317** (believed to be the isomer where the MeO is on the convex face of the bicycle) was the only isomer found to be successful, in α-chlorination. With an α-substituent installed, the hydroboration/oxidation could be explored, and the Cl reductively removed, providing Nicolaou's enone **183**.



Scheme 5. 39: The chlorination of dienone **318**

The utility of isomerized olefin **320** was then tested. With an eye towards ether formation, treatment of olefin **320** to hydroboration (BH_3•THF) was performed. The use of sub-stoichiometric equivalents gave the recovered olefin cleanly, with no evident reduction. Contrast that with the result that an excess of BH_3•THF gave products where the olefin proton and enone proton's were no longer in the ^{1}H NMR spectrum, indicating over reduction. This is consistent with an observation Nicolaou made that borane led to overreduction of a similar enone in their work.[5] Ultimately, chloride **320** could not be converted to the natural product.

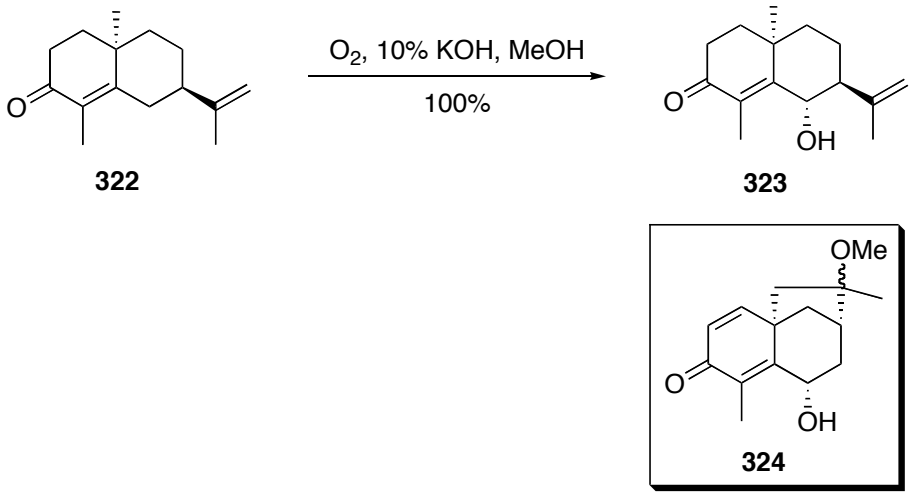
At this point an adjustment to our synthetic approach for the advancement of dienone **317** to platensimycin **160** was in order. A possible solution was found through

the use of autoxidation, nature's way of installing oxygens. Our original goal of a stereoselective synthesis of the platensimycin core might still be achieved, however maintaining the appropriate oxidation state throughout, would not.

5.5. AUTOXIDATION AS AN ENDGAME STRATEGY

The use of autoxidation in organic synthesis has a rich history rooted in steroid chemistry.[34,35] But it was an example of a mild, efficient, and stereoselective autoxidation of a structurally similar dienone that was compelling us to pursue this work. In their synthesis of the sesquiterpene lactone decipienin A, Massanet and co-workers reported a mild autoxidation of an enone very similar in structure to **317** and **318**.[36] The oxidation of 7-*epi*-cyperone **322** with O_2 and methanolic KOH was used as a starting point. The reaction installed an axial oxygen stereoselectively, giving alcohol **323** in 100% yield (Scheme 5. 40). The authors noted that thorough study of that reaction on different substrates revealed a strong substrate dependence. It was observed that the enone α-methyl to the ketone was essential "to prevent decomposition of the molecule," in an unspecified way.

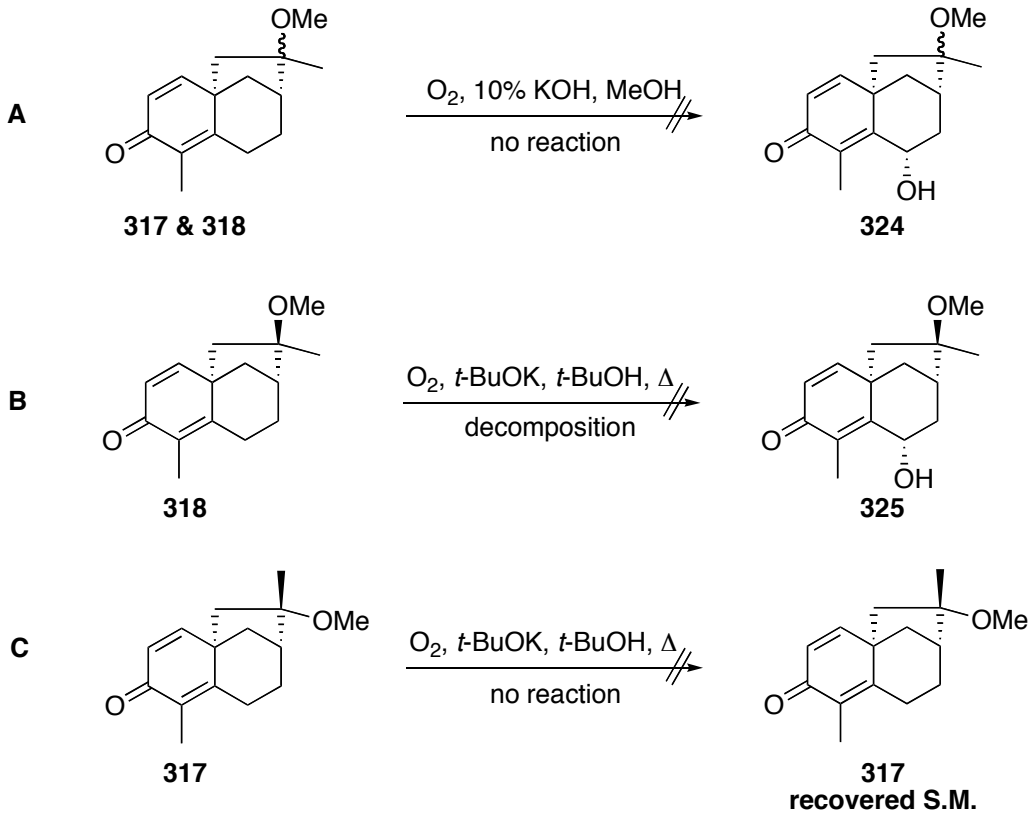
The utility of this reaction to the synthesis of platensimycin from autoxidized dienone **324** warranted further exploration as the dienone **317** contains an α-methyl. However, the subjection of dienones **317** and **318** to the conditions reported by Massanet gave no reaction. The recovery of starting material precluded the decomposition Massanet alluded to in substrates not matched for this procedure. The conclusion was that these conditions were thought to be too mild.



Scheme 5. 40: Massanet's autoxidation of 7-*epi*-cyperone **322** and its possible application to dienone **324**

Classically, the autoxidation of enolates was developed using the ubiquitous *t*-BuOK in *t*-BuOH. However, treatment of dienone **317** to those conditions did not produce the desired alcohol either (Scheme 5. 41). Initially, the mixture of isomers **317** and **318** was used in these reactions. Starting at room temperature and open to air or with a balloon of O_2 attached, the reactions turned yellow immediately upon the addition of *t*-butoxide, but consumption of starting material was observed based on the crude reaction residue. Heating the reaction to reflux open to air, the solution quickly turned brown and upon workup, only the dienone **317**, believed to be the *endo*-OMe epimer, was recovered, quantitatively. The *exo*-OMe **318** however was apparently destroyed. This result was repeated separately with both pure **317** (revcovered quantitatively) and pure **317** (destroyed) and was consistent. The *endo*-OMe was always returned while the *exo*-OMe was not. Additionally frustrating was the inability to recover any new compounds from the reaction; no dienone, enone, alkene or aromatic protons could be resolved in the ^{1}H NMR spectra and thus the fate of **318** could not be deduced. This

disparate reactivity must have a reasonable explanation, but that unfortunately could not be deduced through experimentation.

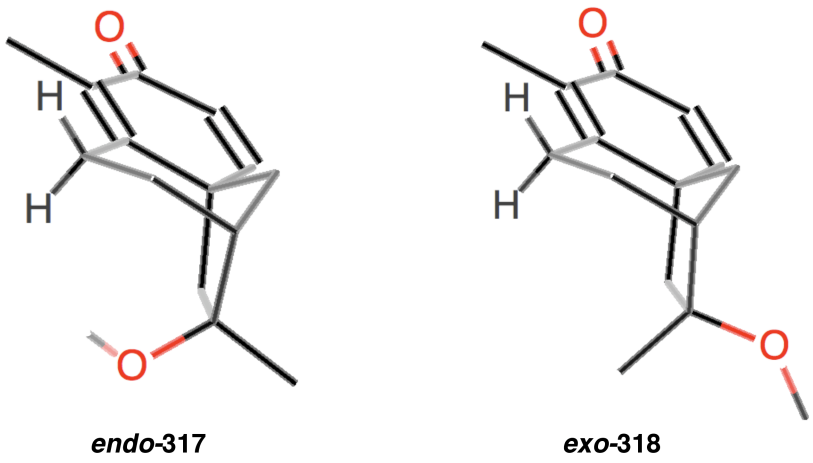


Scheme 5. 41: Attempted autoxidation of dienones

Both of the epimeric dienone ethers were stable to the reaction conditions when they were performed in a degassed sealed tube, absent O_2, as in the attempted deconjugative alkylations (*vide supra*, Scheme 5. 38). So it stands to reason that the decomposition of **318** is likely due to a successful oxidation by the now present O_2 and subsequent decomposition of the product **325** or an intermediate. The lack of reactivity observed in **317** could be simply due to the increased steric compression of having the

OMe inside the bicycle, preventing enolate formation and autoxidation. In any case, it was apparent that these methoxyl dienones were not synthetically useful for autoxidation.

The incongruent reactivities of the epimeric ethers can be understood by examination of their 3-D structures (Figure 5. 1). The unreactive *endo* isomer has the OMe pointing towards the proton to be lost during enolate formation. The axial H is hindered by the CH_3, which is exacerbated by the propellar-like rotation of the OMe. The approach of an incoming base, or subsequent electrophile, is blocked by the OMe. The reactive *exo*-OMe does not contain this steric compression. Enolate formation is likely facile as is the subsequent oxidation and an undetermined decomposition then ensues. This disappointing revelation forced an abandonment of the bromohydrin route. Autoxidation was still believed to be a route worth exploring.



***endo*-317** ***exo*-318**

Figure 5. 1: 3-D structures of dienones **317** & **318**

5.5.1. Second Generation Autoxidation Approach

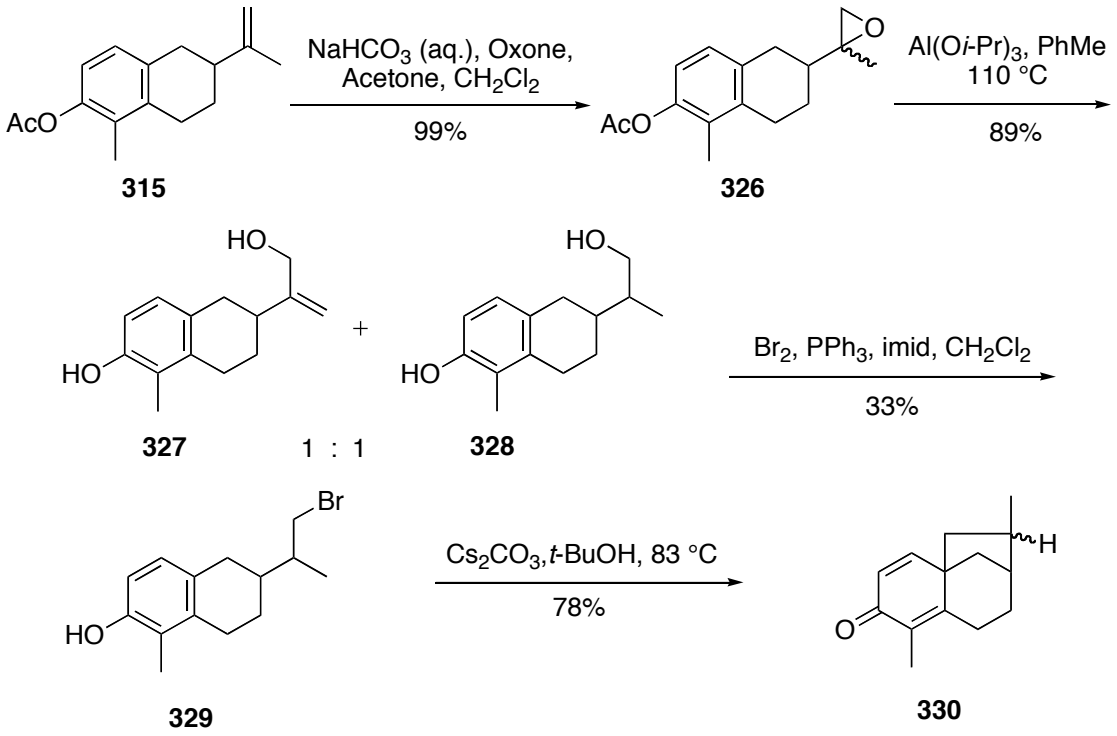
As the methoxyl dienones were unsuccessful in the autoxidation chemistry, the sterically simpler alkene dienones derived from the allyl halide might succeed. To test this, the epoxide to allylic alcohol rearrangement route was instigated on the 2-methyl series.

The acetate **315**, available from the acetylation of the crude phenolate cyclization product (*vide supra,* Scheme 5. 35) was epoxidized using *in situ* generated DMDO, to provide the epoxide **326** as a mixture of diastereomers, cleanly and quantitatively (Scheme 5. 42). This method of epoxide preparation was found to be far superior to *m*-CPBA in its ease of preparation, ease of workup, and its scalable, reliable and efficient results.

The epoxide **326** was available, and it was subjected to the rearrangement conditions found to work best through the desmethyl work. The epoxides **326** were stirred with aluminum triisopropxide in refluxing toluene to provide a 1 : 1 mixture of alcohols in 89% combined yield. Both the allylic alcohol **327** and aliphatic alcohol **328** were obtained as deacetylation occurred *in situ*. The inseparable alcohols were then converted to their bromides, and again, the aliphatic bromide **329** could be isolated in decent yield, while the allylic bromide (as with the iodide) was largely lost. However, trace amounts of the allyic bromide were found to be present with the aliphatic bromides indicative of its viability of formation. Optimization of this bromination, it was thought, would be best accomplished on the pure allylic alcohol **327**, which would have to arise from a different rearrangement procdure.

The aliphatic bromide **329** was cyclized to the dienones **330** as a mixture of methyl epimers. The use of the milder base Cs_2CO_3 in the reaction, though slower,

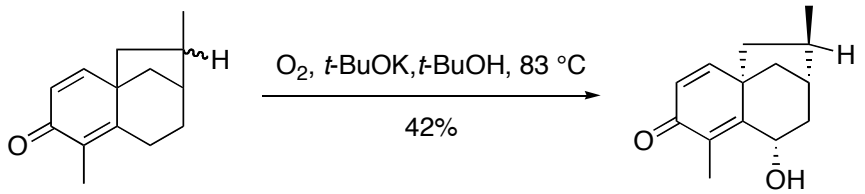
provided a higher yielding reaction than with the *t*-butoxide cases. Also, this reaction seemed concentration dependent as one might expect. Masamune reported the use of 0.001M reaction solutions, which we found to be suitable as well.



Scheme 5. 42: Synthesis of dienone **330**

With the less sterically congested bicyclic dienone, the autoxidation was found to be successful. The 1 : 1 epimer mixture was heated with *t*-BuOK in *t*-BuOH at reflux, furnishing the axial alcohol **331** (Scheme 5. 43) in small amounts. The major product was of oxidation of the *exo*-methyl epimer shown. This is consistent with the rationale for the disparate reactivities in the methoxyl series (**317** and **318**). While trace amounts of the other oxidized product were isolated, that reaction was much slower. The use of

Cs_2CO_3 in DMF at 90 °C open to air produced a 42% yield of the epimer shown. This represents a satisfactory 84% conversion of the epimer.



330 **331**

Scheme 5. 43: The autoxidation of dienone **330**

The success of the autoxidation notwithstanding, the formal synthesis of platensimycin requires an ether formation and selective enone reduction to Nicolaou's intermediate. The second problem, selective enone reduction, was thus explored.

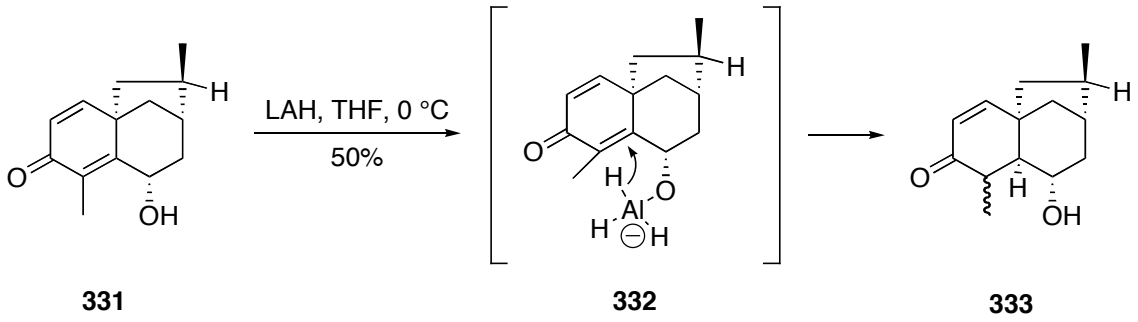
5.5.2. Strategies for the Completion of a Synthesis of (–)-Platensimycin

The oxygen in **331** appeared to be of a single isomer, presumed to be axial based on the examples present in the literature. This was fortuitous and allowed for the possibility of fulfillment of our plan. The stereoselectivity of the approach was at the forefront of our goal. As such, the reduction of the more-substituted enone in **331** was necessary. In all other formal syntheses where a dienone such as these were used, overreduction to the saturated cyclohexanone followed by re-oxidation to the enone was the protocol followed. The use of a hydroxyl directed reduction of the dienone to the less-substituted enone would consititute a straightforward solution to this problem. This proposed solution is one that no other synthetic approach thus far disclosed could boast.

Many methods have been developed for the directed reduction of β-hydroxy ketones but the hydroxyl directed reduction of enones has been less explored. The use of

a coordinated reducing agent, able to deliver a hydride from the same face as the oxygen, yielding the *cis*-decalin ring juncture was desired. It was with this in mind that several conditions using hydride reductants were evaluated.

We began by testing reductants of the enone **331** with $NaBH_4$. In aprotic solvents, the experiment returned a complex mixture that appeared to be allylic alcohols, resulting from reduction of the carbonyl. When the alcohol was exposed to LAH at –78 °C, no reaction occurred, and the starting material was recovered. When the same reaction was performed at 0 °C, workup with MeOH provided a mixture of what was clearly an enone, no longer cross-conjugated, and what appeared to be the over reduced allyic alcohol (Scheme 5. 44). When the reaction was performed again at 0 °C, with the dropwise addition of LAH solution in toluene,[37] the workup produced the desired enone, with trace amounts of the over reduction products. Only one cyclohexanone isomer was obtained from the reaction and it is believed to be that shown, where the hydride was delivered intramolecularly *via* an aluminate intermediate **332**. The reduced alcohol **333** was isolated in 50% yield.



331 **332** **333**

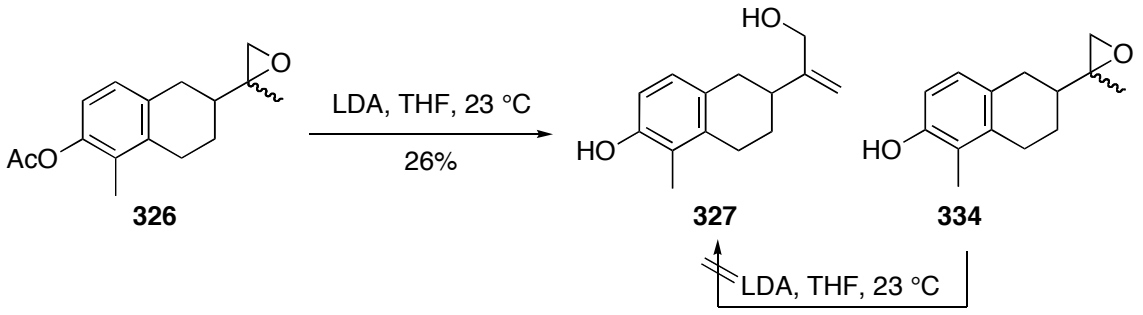
Scheme 5. 44: The stereoselective reduction of dienone **331**

The realization of a stereoselective reduction to an enone **333** opened the door to a completely stereoselective synthesis of platensimycin, if the ether ring can be formed.

The method used by Nicolaou involved the hydration of an alkene with an axial alcohol. It was thought that this strategy might also be viable in this case.

It was at this point that a re-examination of the epoxide to allylic alcohol rearrangement was performed. The acetate **326** had been utilized in the rearrangements using aluminum triisopropoxide with success. The failures of the amide base mediated rearrangements on the desmethyl series was attributed to the presence of the phenol OH, and the acetate had never been explored. This was accessible, easily attempted, and now relevant, so the acetate was investigated further.

The acetate **326** was treated to an excess of LDA in THF at 23 °C and the starting material was quickly consumed. However, workup of the reaction provided the desired allylic alcohol **327** in only 26% yield (Scheme 5. 45. The major product was the deacetylated epoxide **334** which accounted for the mass balance. Attempts to convert the phenolic epoxide **334** to the allylic alcohol by resubjection to the reaction conditions failed, and no product was observed. Heating the reaction destroyed the starting material with no discernible product.

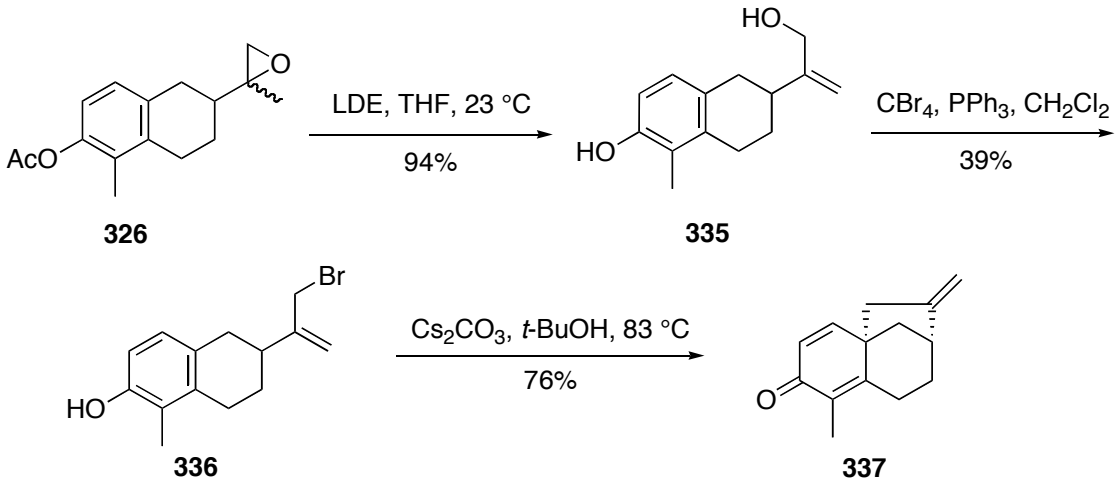


326 **327** **334**

Scheme 5. 45: The conversion of epoxide **326** to allylic alcohol **327**

The use of LDE as the amide base has been traditionally more successful than LDA in these rearrangements. Fortunately, switching to LDE led to complete conversion

of the acetate epoxide **326** to the allylic alcohol **327** in a 94% isolated yield (Scheme 5. 46). The allylic alcohol **327** could now be accessed cleanly and in the absence of the aliphatic alcohol **328**. Its conversion to an allylic halide still presented a problem. The conditions used before (Br_2, PPh_3) were equally unsuccessful on the pure allylic alcohol. The use of CBr_4 as the bromine source improved upon this, allowing for the isolation of the allylic bromide **336** in 39% yield. The problem of isolation still remained, as the reactive allylic bromide is likely decomposing during the column chromatography.



Scheme 5. 46: Synthesis of olefinic dienone **337**

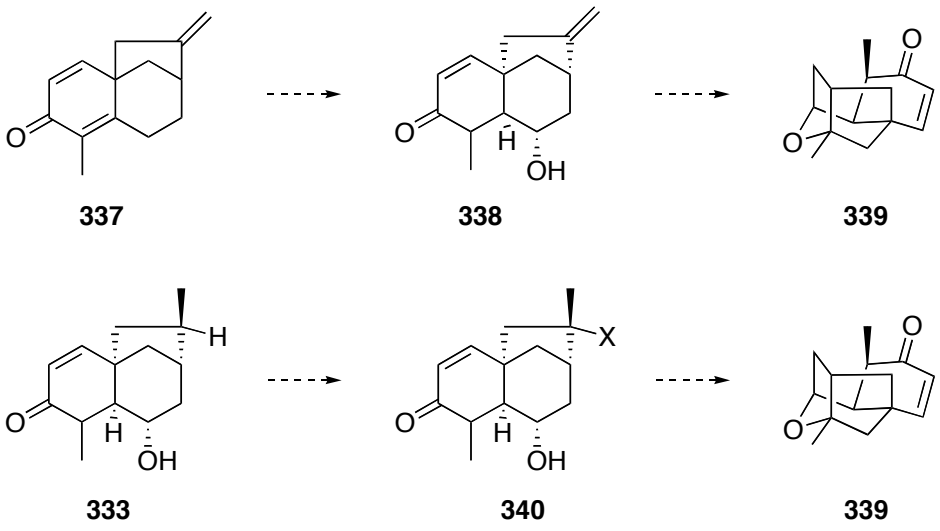
With the allylic bromide available, the cyclization to the olefinic dienone **337** could be performed. Bicycle **337** was obtained in 76% from the allylic bromide. Currently, the autoxidation of **337** is under investigation.

5.5.3. Possible Routes to completion

There are two possible paths to the completion of the formal synthesis of platensimycin from the project's current state. The first, and more direct, is the

autoxidation of **337**, providing the axial oxygen (Scheme 5. 47). The stereoselective hydroxyl directed LAH reduction would provide the enone **338**. Exposure of enone **338** to TFA in DCM (as per Nicolaou) would close the ether ring, and complete a formal synthesis with **339**. The addition of the propionate side chain in a more direct fashion would be explored and the coupling to the synthesized aniline **175** would complete the total synthesis of platensimycin.

Alternatively, the already autoxidized enone **333** might be converted to the natural product *via* oxidation of the methine proton. The hydroxyl radical formed from the axial alcohol, is adjacent to the methine, which could abstract a hydrogen to produce the tertiary radical. Oxidation of that radical to a halide (**340**) and displacement by the oxygen would alternatively complete the formal synthesis (**339**).



Scheme 5. 47: Possible routes to the completion of the synthesis of platensimycin

5.6. CONCLUSIONS

The synthesis of the recently discovered potent antibiotic platensimycin was undertaken. The plan for a stereoselective synthesis, what would be the first in this area, was laid out and the efforts toward achieving it described.

The synthesis of the aniline portion of platensimycin has been completed in a short and efficient three step route.

The synthesis of the tetracyclic enone acid core of platensimycin was investigated. The stereoselective synthesis of an alcohol **333**, lacking only the ether linkage to complete a formal synthesis, was presented. The use of autoxidation to install the oxygen and its utility in the directed enone reduction were described. Efforts to convert **333** to the ether **339** are underway.

An alternative to alcohol **331**, the alkene **337** was also synthesized and expressed. The successful autoxidation of **337** would essentially complete the formal synthesis, as closure of the ether ring, using the known procedure, would yield a methylated compound matching Mulzer's and Corey's intermediates. Its transformation to the natural product is also currently being explored.

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Chapter 6: Experimental Section

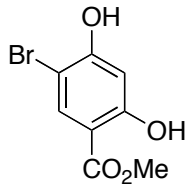
6.1. General Methods

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet FT-IR spectrophotometer neat unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer at 300 MHz and 75 MHz, respectively and are reported in ppm relative to tetramethylsilane. All NMR spectra were taken with $CDCl_3$ as solvent unless otherwise noted. Mass spectra were obtained on a VG ZAB2E or a Finnigan TSQ70. TLC was performed on glass sheets precoated with silica gel (Silica Gel 60, F254, 0.25mm Layer Thickness). Column chromatographic separations were performed on silica gel (Silica gel 60, 230-400 mesh) under pressure. Solvents and commercial reagents were purified in accordance with Perrin and Armarego or used without further purification.

All moisture sensitive reactions were performed under an atmosphere of Ar, and glassware was pre-dried at 125 °C prior to use. THF and ether were dried by distillation over Na/benzophenone, CH_2Cl_2, Et_3N, CH_3CN, and *i*-Pr_2NH were dried by distillation from CaH_2. All other reagents or solvents were used as received without further purification unless otherwise stated.

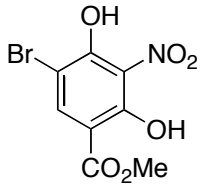
6.2. EXPERIMENTAL CONDITIONS AND CHARACTERIZATIONS

Methyl 5-Bromo- 2,4-Dihydroxybenzoate:



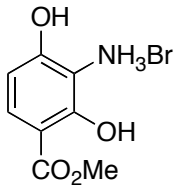
To a stirred solution of the methyl 2,4-dihydroxybenzoate[1] **216** (8g, 48.4 mmol) in dry CH_2Cl_2 (250 mL) at 25 °C was added a solution of Br_2 in dry CH_2Cl_2 (50 mL, 1M solution, 50 mmol) dropwise. The reaction was monitored by TLC (CH_2Cl_2). The addition was stopped when the solution obtained a persistant orange color indicative of excess Br_2. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (250 mL) and extracted with CH_2Cl_2 (3 x 250 mL). The combined organics were dried (Na_2SO_4), and concentrated *in vacuo*. The resulting solid was taken up in CH_2Cl_2, filtered over a silica plug, and eluted with CH_2Cl_2 to give the monobromoaniline with trace amounts of the dibromo product. The dibromo ester could be selectively crystallized and removed out of solution by allowing slow evaporation of the CH_2Cl_2 overnight. The resulting filtrate was concentrated to give pure product (11.53 g, 96%) as a white crystalline solid: mp = 133 - 135 °C; R_f = 0.37 (DCM); IR (neat) 3309, 3080, 2955, 1669, 1444, 1348, 1256 cm^{-1}; ^1H NMR δ 7.97 (s, 1H), 6.63 (s, 1H), 3.94 (s, 3H); ^{13}C NMR δ 52.3, 100.5, 103.9, 107.3, 133.2, 157.9, 162.9, 169.3; HRMS for $C_8H_8O_4Br$ [MH+] *m/z* calc. 246.9606, found 246.9606.

Methyl 5-bromo- 2, 4-dihydroxy-3-nitrobenzoate (232):



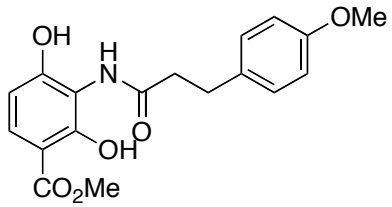
To a stirred solution of the 5-bromo ester (6.0 g, 24.3 mmol) in acetonitrile (300 mL) at 25 °C was added a solution of concentrated nitric acid (15.8N, 7.7 mL, 5.0 eq) in acetonitrile (100 mL) dropwise over 30 min. The solution was stirred at 25 °C for 5 hours and the consumption of starting material was monitored by TLC (40% EtOAc/hexanes). Upon completion, the reaction mixture was poured into ice water. The precipitate was collected, washed with H_2O (2 x 100 mL), ether (1x 50 mL), and recrystallized in methanol to give nitro **232** as a pale yellow powder (4.48 g, 63% yield after recrystallization): mp = 208-209 °C; R_f = 0.47 (40% EtOAc/hexanes); IR (neat) 3192, 3091, 3002, 2951, 1684, 1435, 1321, 1292 cm^{-1}; ^1H NMR δ 8.79 (s, 1H), 4.04 (s, 3H); ^{13}C NMR δ 53.4, 100.3, 106.3, 127.4, 127.5, 157.4, 164.8, 168.9; HRMS for $C_8H_7NO_6Br$ [MH+] *m/z* calc. 291.9457, found 291.9460.

Methyl 3-amino-2, 4-dihydroxybenzoate hydrobromide (233):



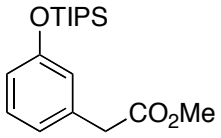
To a solution of nitroaryl **232** (40 mg, 0.14 mmol) in THF (3 mL) was bubbled H_2 (g). To the solution was added Pd black (10 mg cat.) and a balloon of H_2 (g) was attached. The solution was stirred under hydrogen atmosphere for 2 days. The reaction mixture was then filtered over celite, eluted with THF, and the crude filtrate was resubjected to H_2(g) and Pd black for an additional 2 days. The reaction mixture was then filtered over celite, eluted with THF and concentrated *in vacuo*. The resulting dark brown oil was triturated with CH_2Cl_2 to give the HBr salt of aniline hydrobromide **233** as a brown solid (33 mg, 94%): mp = 216 °C (decomposition.); R_f = 0.30 (50% EtOAc/hexanes); IR (salt, diamond press) 3128, 2963, 2883, 1670, 1639, 1476, 1439, 1331, 1204, 1145, 790 cm^{-1}; ^1H NMR (CD_3OD) δ 7.78 (s, 1H), 6.50 (s, 1H) 3.92 (s, 3H); ^{13}C NMR (CD_3OD) δ 52.9, 104.3, 105.5, 112.7, 126.4, 158.6, 164.6, 170.7; HRMS for $C_8H_{10}NO_4$ [MH+] *m/z* calc. 184.0610, found 184.0611.

Methyl 2,4-dihydroxy-3-[3-(4-methoxyphenyl)propanamido]benzoate (235):



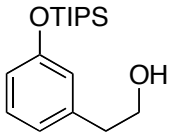
To a stirred solution of 3-(4-methoxyphenyl)propanoic acid **234** (28 mg, 0.157 mmol) in DCM (5 mL) with NEt_3 (1 mL) was added dicyclohexylcarbodiimide (81 mg, 0.393 mmol), aniline hydrobromide **233** (46 mg, 0.173 mmol) and the reaction was stirred at 23 °C for 18h. The mixture was diluted in DCM (10 mL), washed with sat. aq. NH_4Cl, (2 x 5 mL), brine and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 30% EtOAc in hexanes) to yield the amide **235** as a yellow oil (25 mg, 46%): R_f = 0.38 (30% EtOAc/hexanes); IR (neat) 3336, 2929, 2852, 1669, 1617, 1540, 1251 cm^{-1}; ^1H NMR δ 7.40 (s, 1H), 7.14 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.53 (s, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.00 (t, J = 7.4 Hz, 2H), 2.69 (t, J = 7.4 Hz, 2H); ^{13}C NMR δ 172.7, 169.7, 161.2, 158.4, 156.0, 131.8, 129.4, 129.3, 123.2, 118.8, 114.2, 114.1, 106.5, 104.6, 55.2, 52.1, 39.0, 30.9, 24.9; HRMS for $C_{18}H_{20}NO_6$ [MH+] *m/z* calc. 346.1291, found 346.1289.

Methyl 2-(3-{[tris(propan-2-yl)silyl]oxy}phenyl)acetate (237):



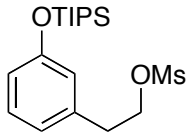
To a stirred solution of methyl 2-(3-hydroxyphenyl)acetate[2] **236** (14.46g, 87.00 mmol) in CH_2Cl_2 (100 mL) at room temperature was added triisopropylsilyl chloride (20.13g, 104.40 mmol) and imidazole (7.07g, 110.5 mmol) and the solution was stirred for 16h. The reaction was poured into sat. aq. NH_4Cl (100 mL), the organic layer separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). Thye combined organics were washed with sat. aq. NH_4Cl (100 mL), brine (100mL) and concentrated. The crude residue was purified by column chromatography (SiO_2, 10% EtOAc in hexanes) to provide silyl ether **237** as an orangish oil (27.8 g, 99%): R_f = 0.65 (10% EtOAc in hexanes); IR (neat) 2946, 2867, 1743, 1489, 1278, 1157 cm^{-1}; ^1H NMR δ 7.16 (dd, J = 8.1, 7.3 Hz, 1H), 6.78 – 6.86 (m, 3H), 3.68 (s, 3H), 3.57 (s, 2H), 1.20 – 1.32 (m, 3H), 1.10 (d, J = 6.8 Hz, 18H); ^{13}C NMR δ 172.8, 156.2, 135.2, 129.4, 121.8, 120.9, 118.6, 51.9, 41.2, 17.9, 12.6; HRMS for $C_{18}H_{31}O_3Si$ [MH+] m/z calc. 323.2042 Da, found 323.2043 Da.

2-(3-{[tris(propan-2-yl)silyl]oxy}phenyl)ethan-1-ol (238):



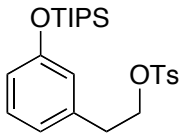
To a stirred suspension of lithium aluminum hydride (16.0 g, 420 mmol) in ether (250 mL) at 0 °C was added ester **237** (22.58 g, 70.0 mmol) in ether (100 mL) dropwise over 30 min. The resulting suspension was stirred 16 h at 23 °C and then quenched by inverse addition *via* cannula to EtOAc (100 mL) at 0 °C and the suspension was stirred 10 min. To this solution was added sat. aq. Na_2SO_4 (20 mL) to quench any remaining lithium salts and the suspension was stirred 30 min, then filtered over Celite and concentrated *in vacuo* to give alcohol **238** as a pale brown oil (20.01 g, 97%) which was used without further purification: R_f = 0.26 (30% EtOAc in hexanes); IR (neat) 2975, 2935, 1629, 1597, 1582, 1468, 1427, 1072, 762 cm^{-1}; ^1H NMR δ 7.16 (t, J = 8.1 Hz, 1H), 6.75 – 6.82 (m, 3H), 3.84 (t, J = 6.6 Hz, 2H), 2.82 (t, J = 6.6 Hz, 2H), 1.20 – 1.32 (m, 3H), 1.10 (d, J = 6.8 Hz, 18H); ^{13}C NMR δ 156.2, 135.2, 128.4, 121.8, 120.8, 118.6, 51.9, 41.1, 17.8, 12.5; HRMS for $C_{17}H_{31}O_2Si$ [MH+] m/z calc. 295.2093 Da, found 295.2094 Da.

2-(3-{[tris(propan-2-yl)silyl]oxy}phenyl)ethyl methanesulfonate (241):



To a stirred solution of alcohol **238** (3.68 g, 12.5 mmol) in CH_2Cl_2 (25 mL) at 0°C with triethylamine (3.0 mL) was added methanesulfonyl chloride (1.16 mL, 15.0 mmol) dropwise over 15 min. The reaction was allowed to stir overnight, after which, the solution was poured into sat. aq. NH_4Cl (50mL), extracted with CH_2Cl_2 (2 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatographic purification of the the crude oil (SiO_2, 20% ethyl acetate in hexanes) gave the mesylate **241** as a yellow oil (4.57 g, 98%): R_f = 0.60 (20% EtOAc in Hexanes); IR (neat) 3447, 2944, 2866, 1603, 1585, 1485, 1355, 1276, 1175, 1004, 970, 882, 689 cm^{-1}; ^1H NMR δ 7.16 (t, J = 8.1 Hz, 1H), 6.75 – 6.82 (m, 3H), 4.40 (t, J = 7.0 Hz, 2H), 3.00 (t, J = 6.8 Hz, 2H), 2.88 (s, 3H), 1.20 – 1.32 (m, 3H), 1.10 (d, J = 6.8 Hz, 18H); ^{13}C NMR δ 156.1, 137.6, 129.4, 121.5, 120.4, 118.2, 60.1, 37.0, 35.3, 17.8, 12.5; HRMS for $C_{18}H_{33}SiO_4S$ [MH+] m/z calc. 373.1876 Da, found 373.1863 Da.

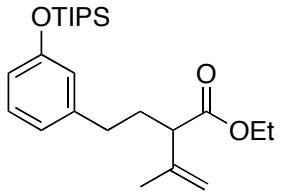
2-(3-{[tris(propan-2-yl)silyl]oxy}phenyl)ethyl 4-methylbenzene-1-sulfonate (240):



To a stirred solution of alcohol **238** (2.00 g, 6.79 mmol) in CH_2Cl_2 (34 mL) with pyridine (2.0 mL) was added 4-methylbenzene-1-sulfonyl chloride (1.43 g, 7.47 mmol).

The reaction was stirred 16h, then dilute in CH_2Cl_2 (25 mL), washed with sat. aq. NH_4Cl (50mL), aq. 20% $CuSO_4$ (20 mL), brine and concentrated. Column chromatographic purification of the the crude residue (SiO_2, 10% ethyl acetate in hexanes) gave the tosylate **240** as a yellow oil (861 mg, 34%): R_f = 0.42 (10% EtOAc in Hexanes); IR (neat) 2920, 2850, 1733, 1177, 667 cm^{-1}; ^1H NMR δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.10 (dd, *J* = 8.1, 7.3 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 7.3 Hz, 1H), 6.64 (s, 1H), 4.18 (t, *J* = 7.3 Hz), 2H), 2.89 (t, *J* = 7.3 Hz, 2H), 2.44 (s, 3H), 1.20 – 1.32 (m, 3H), 1.08 (d, *J* = 6.8 Hz, 18H); ^{13}C NMR (some resonances are overlapping) δ 156.2, 137.6, 129.8, 129.4, 127.8, 121.5, 120.5, 118.3, 111.6, 70.5, 35.2, 29.7, 17.8, 12.6; HRMS for $C_{24}H_{37}O_4SiS$ [MH+] *m/z* calc. 449.2182 Da, found 449.2188 Da.

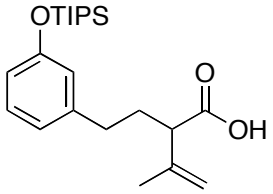
Ethyl 3-methyl-2-(3-{[tris(propan-2-yl)silyl]oxy}phenyl)but-3-enoate (243):



A flame-dried, three-necked 250 mL flask under Ar (g) and equipped with stirbar was charged with diisopropylamine (6.85 mL, 48.9 mmol) and THF (50 mL). The solution was cooled to –78 °C, *n*-BuLi (20.40 mL, 48.90 mmol, 2.4 M in hexanes) and hexamethylphosphoric triamide (HMPA) (8.50 mL, 48.70 mmol) were added *via* syringe. The cold bath was removed, the solution was stirred for 30 min. To the solution, at –78 °C, was added ethyl 3,3-dimethylacrylate **242** (6.7 mL, 47.90 mmol) in a minimal amount of THF (10 mL), *via* cannula and the reaction mixture was stirred at –78 °C for 15 min and at 23 °C for an additional 1 h. The suspension was then re-cooled to –78 °C and tosylate **240** (3.57 g, 9.58 mmol) in a minimal amount of THF (10 mL) was added *via* cannula. The alkylation reaction was allowed to warm to 23 °C and stirred 1.5 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (100 mL), diluted with ether (100 mL) and transferred to a separatory funnel. The organic layer was removed and the aqueous layer extracted with ether (100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated to give a crude oil which was purified by flash column chromatography (SiO_2, 5% ethyl acetate in hexanes) provided ester **243** as a pure, colorless oil (1.05 g, 27%): IR (neat) 2944, 2867, 1733, 1485, 1278 cm^{-1}; ^1H NMR δ 7.12 (t, *J* = 8.6 Hz 1H), 6.73 (m, 2H), 6.70 (s, 1H), 4.93 (s, 1H), 4.89 (s, 1H), 4.15 (q, *J* = 7.1 hz, 2H), 3.03 (t, *J* = 7.5 Hz, 1H), 2.52 (t, *J* = 7.7 Hz, 2H), 2.14 (quintet, *J* = 6.1, 7.8 Hz, 1H), 1.87 (quintet, *J* = 6.1, 7.8 Hz, 1H), 1.76 (s, 3H),

1.26 (t, J = 7.1 Hz, 3H), 1.20 – 1.32 (m, 3H), 1.10 (d, J = 6.8 Hz, 18H); ^{13}C NMR δ 173.5, 156.0, 142.9, 142.2, 129.1, 121.2, 120.1, 117.4, 114.0, 60.5, 52.2, 33.3, 31.6, 20.1, 17.9, 14.2, 12.6; HRMS for $C_{24}H_{41}O_3Si$ [MH+] m/z calc. 405.2825 Da, found 405.2822 Da.

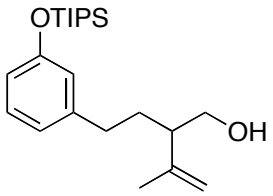
3-methyl-2-(3-{[tris(propan-2-yl)silyl]oxy}phenyl)but-3-enoic acid (248):



A flame-dried, three-necked 500 mL flask under Ar (g) and equipped with stirbar was charged with diisopropylamine (9.75 mL, 69.50 mmol) and THF (100 mL). The solution was cooled to –78 °C and *n*-BuLi (29.0 mL, 69.50 mmol, 2.4 M in hexanes) was added *via* syringe. The cold bath was removed, the solution was stirred for 30 min, and then re-cooled to –78 °C. A solution of 3,3-dimethylacrylic acid **247** (3.16 g, 31.60 mmol) in a minimal amount of THF (20 mL) was added to the reaction flask *via* cannula and the reaction mixture was stirred at –78 °C for 15 min and at 23 °C for an additional 1 h, during which, a white precipitate formed throughout the reaction vessel. The suspension was then cooled to 0 °C and mesylate **241** (11.76 g, 31.60 mmol) in a minimal amount of THF (30 mL) was added *via* cannula. The alkylation reaction was allowed to stir at 0 °C for 3.5 h. The reaction was quenched by the addition of water (100 mL), diluted with ether (100 mL) and transferred to a separatory funnel. The organic layer was removed and the aqueous layer extracted with ether (100 mL). The aqueous layer was acidified with aq. H_3PO_4 (conc.) and extracted with ether (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated to

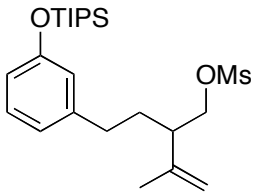
give acid **248** as a yellow oil of sufficient purity (9.59 g, 81%): IR (neat) 2944, 2866, 1705, 1484, 1277, 1157, 882 cm^{-1}; ^{1}H NMR δ 7.13 (t, *J* = 8.1 Hz 1H), 6.77 (m, 3H), 4.99 (s, 1H), 4.95 (s, 1H), 3.08 (t, *J* = 7.5 Hz, 1H), 2.56 (t, *J* = 7.7 Hz, 2H), 2.06 – 2.24 (m, 1H), 1.80 (s, 3H), 1.85 – 1.96 (m, 1H), 1.20 – 1.32 (m, 3H), 1.10 (d, *J* = 6.8 Hz, 18H); ^{13}C NMR δ 179.6, 156.0, 142.7, 141.6, 129.1, 121.2, 120.1. 117.4, 114.8, 51.9, 33.2, 31.3, 20.1, 17.8, 12.6; HRMS for $C_{22}H_{37}O_3Si$ [MH+] *m/z* calc. 377.2512 Da, found 377.2510 Da.

3-methyl-2-[2-(3-{[tris(propan-2-yl)silyl]oxy}phenyl)ethyl]but-3-en-1-ol (244):



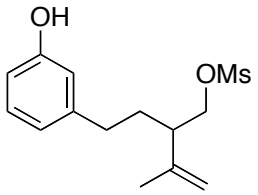
To a stirred solution of ester **243** (1.15 g, 2.84 mmol) in dry ether (25 mL) at 0 °C was added LAH (s) (190 mg, 5.15 mmol). After stirring for four hours, the reaction was quenched with the dropwise addition of sat. aq. Na_2SO_4 until bubbling ceased. The suspension was filtered over celite, the filtrate dried (Na_2SO_4) and concentrated to give the alcohol **244** as a pure, colorless oil (1.02 g, 99%): IR (neat) 3371, 2931, 1585, 1465 cm^{-1}; ^{1}H NMR δ 7.11 (t, *J* = 8.6 Hz 1H), 6.73 (m, 2H), 6.69 (s, 1H), 5.01 (s, 1H), 4.87 (s, 1H), 3.52 (t, *J* = 4.5 Hz, 2H), 2.46 – 2.57 (m, 2H), 2.31 (quintet, *J* = 6.1, 7.8 Hz, 1H), 1.72 (s, 3H), 1.61 – 1.69 (quintet, *J* = 6.8 Hz, 3H), 1.20 – 1.32 (m, 3H), 1.10 (d, *J* = 6.8 Hz, 18H); ^{13}C NMR δ 156.0, 144.6, 143.6, 129.0, 121.0, 120.0, 117.2, 114.4, 63.9, 49.3, 33.2, 30.8, 18.6, 17.9, 12.7; HRMS for $C_{22}H_{39}O_2Si$ [MH+] *m/z* calc. 363.2719 Da, found 363.2717 Da.

3-methyl-2-[2-(3-{[tris(propan-2-yl)silyl]oxy}phenyl)ethyl]but-3-en-1-yl methanesulfonate (250):



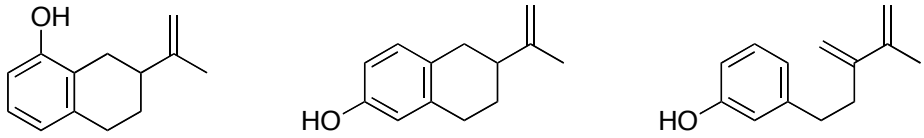
To a stirred solution of alcohol **244** (1.02 g, 2.81 mmol) in DCM (15 mL) with NEt_3 (1.60 mL) was added methansulfonyl chloride (250 μL, 3.09 mmol). After stirring for 3 h, the reaction was poured into sat. aq. NH_4Cl (20 mL) and extracted with DCM (3 x 20 mL). The combined organic extracts were washed with sat. aq. NH_4Cl, brine, dried (Na_2SO_4) and concentrated to give a crude oil, which was chromatographed (SiO_2, 20% EtOAc in hexanes) to give mesylate **250** as a pure, pale-yellow oil (1.07 g, 86%): R_f = 0.40 (20% EtOAc in Hexanes); IR (neat) 2944, 2867, 1602, 1584, 1485, 1357, 1278, 1176, 956, 883, 827, 689 cm^{-1}; ^1H NMR δ 7.12 (t, J = 8.1 Hz, 1H), 6.74 (m, 2H), 6.71 (s, 2H), 4.99 (s, 1H), 4.87 (s, 1H), 4.16 (septet, J = 7.4, 9.5 Hz, 2H), 2.96 (s, 3H), 2.43 – 2.60 (m, 3H), 1.75 (s, 3H), 1.60 – 1.80 (m, 2H), 1.20 – 1.32 (m, 3H), 1.10 (d, J = 6.8 Hz, 18H); ^{13}C NMR δ 154.3, 144.8, 141.9, 126.2, 121.4, 119.9, 115.7, 114.2, 63.9, 37.2, 31.6, 29.9, 22.6, 19.3, 18.0, 13.0; HRMS for $C_{23}H_{41}O_4SiS$ [MH+] m/z calc. 441.3562 Da, found 441.3560 Da.

2-[2-(3-hydroxyphenyl)ethyl]-3-methylbut-3-en-1-yl methanesulfonate (254):



To a stirred solution of triisopropylsilyl ether **250** (2.49 g, 5.65 mmol) in *N,N*-dimethylformamide (10 mL) was added CsF (950 mg, 6.25 mmol) and the reaction stirred overnight. The solution was diluted in methyl *tert*-butyl ether (MTBE) (20 mL) and poured into water (20 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatographic purification (SiO_2, 30% EtOAc in hexanes) gave the phenol **254** as a brownish oil (1.56 g, 97%): R_f = 0.25 (30% EtOAc in Hexanes); IR (neat) 3466, 2938, 1588, 1456, 1350, 1173, 950 cm^{-1}; ^1H NMR δ 7.15 (t, J = 8.1 Hz, 1H), 6.66 – 6.75 (m, 2H), 6.66 (s, 2H), 4.99 (s, 1H), 4.87 (s, 1H), 4.16 (septet, J = 7.5, 6.6 Hz, 2H), 2.98 (s, 3H), 2.43 – 2.64 (m, 3H), 1.74 (s, 3H), 1.66 – 1.84 (m, 2H); ^{13}C NMR δ 155.6, 143.5, 142.5, 129.6, 120.8, 115.2, 114.5, 112.9, 71.3, 45.7, 37.5, 32.7, 30.6, 19.4; HRMS for $C_{14}H_{21}O_4S$ [MH+] *m/z* calc. 285.1161 Da, found 285.1162 Da.

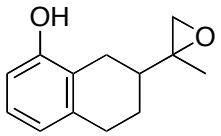
7-(prop-1-en-2-yl)-5,6,7,8-tetrahydro-naphthalen-1-ol (256), 6-(prop-1-en-2-yl)-5,6,7,8-tetrahydro-naphthalen-2-ol (253), and 3-(4-methyl-3-methylidenepent-4-en-1-yl)phenol (255):



To a stirred solution of mesylate **254** (0.104 g, 0.366 mmol) in *tert*-butanol (2 mL) at rapid reflux was added *t*-BuOK (1 mL, 1.0M in *t*-BuOH) and the reaction was stirred at reflux for 16h. The mixture was diluted in ether (10 mL) and washed with H_2O (5 mL), brine (5 mL), and concentrated *in vacuo* to give a yellow oil which was purified by column chromatography (SiO_2, 10% EtOAc in hexanes) to provide *ortho* **256** (38 mg, 55%) and *para* **253** (28 mg with **255**) (96% combined yield) both as yellow oils: **256**: R_f = 0.25 (20% EtOAc in hexanes); IR (neat) 3398, 2928, 1585, 1464, 1259, 887, 766 cm^{-1}; ^1H NMR δ 7.02 (t, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.61 (d, *J* = 7.9 Hz, 1H), 4.82 (s, 2H), 2.84 – 2.94 (m, 3H), 2.36 – 2.50 (m, 2H), 1.96 – 2.02 (m, 1H), 1.85 (s, 3H), 1.59 – 1.73 (m, 1H); ^{13}C NMR δ 153.3, 149.4, 138.3, 126.1, 123.0, 121.2, 111.8, 109.2, 41.4, 29.7, 28.3, 27.6, 20.7; HRMS for $C_{13}H_{17}O$ [MH+] *m/z* calc. 189.1282 Da, found 189.1279 Da. **253**: R_f = 0.20 (20% EtOAc in hexanes); IR (neat) 3398, 2928, 1585, 1464, 1259, 887, 766 cm^{-1}; ^1H NMR δ 6.94 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.58 (s, 1H), 4.79 (s, 1H), 4.77 (s, 1H), 2.77 – 2.83 (m, 2H), 2.61 (d of t, *J* = 11.0, 15.0 Hz, 2H), 2.32 (m, 1H), 1.95 (m, 1H), 1.80 (s, 1H), 1.6 (m, 1H); ^{13}C NMR δ 149.6, 138.7, 130.0, 128.9, 120.9, 114.9, 112.9, 108.9, 41.9, 29.6, 28.0, 20.7, 17.9; HRMS for $C_{13}H_{17}O$ [MH–] *m/z* calc 187.1123 Da, found 187.1126 Da. **255**: R_f = 0.20 (20% EtOAc in

hexanes); IR (neat) 3392, 2927, 1595, 1464, 1274, 1063, 890 cm^{-1}; ^{1}H NMR δ 7.12 (t, *J* = 7.4 Hz, 1H), 6.72 (m, 3H), 5.12 (d, *J* = 8.6 Hz, 2H), 4.98 (d, *J* = 11.5 Hz, 2H), 2.72 (t, *J* = 9.1 Hz, 2H), 2.55 (t, *J* = 9.0 Hz, 2H), 1.92 (s, 3H); ^{13}C NMR δ 156.0, 147.1, 144.0, 129.3, 120.2, 115.2, 113.8, 112.7, 112.5, 112.3, 35.4, 35.1, 21.1; HRMS for $C_{13}H_{17}O$ [MH+] *m/z* calc. 189.1279 Da, found 189.1283 Da.

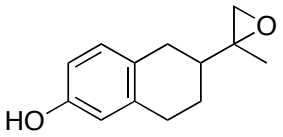
7-(2-methyloxiran-2-yl)-5,6,7,8-tetrahydronapthalen-1-ol (257):



To a stirred solution of acetate **OAc-256** (235 mg, 1.02 mmol) in DCM (10 mL) with $NaHCO_3$ (s) (250 mg) was added *m*-chloroperbenzoic acid (mCPBA) (212 mg, 1.22 mmol). The suspension was stirred for 16 h, after which it was quenched with sat. aq. $NaSO_3$ (10 mL), diluted in DCM (20 mL), washed with sat. aq. $NaHCO_3$ (20 mL), brine (20 mL), and concentrated *in vacuo*. The crude residue was taken up in MeOH (15 mL), K_2CO_3 (s) (300 mg) was added and the suspension stirred for 8 h. The reaction was diluted in DCM (20 mL), poured into sat. aq. NH_4Cl (20 mL), and extracted with DCM (2 x 20 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated to give an inconsequential mixture of diastereomeric epoxides **257** as an off-white powder (210 mg, 100%): mp = 116 – 120 °C; IR (neat) 3390, 2928, 1651, 1587, 1465, 1275 cm^{-1}; ^{1}H NMR δ 6.99 (t, *J* = 7.8 Hz, 2H), 6.70 (d, *J* = 7.8 Hz, 2H), 6.60 (d, *J* = 7.8 Hz, 2H), 2.60 – 3.0 (m, 8H), 2.40 (d of t, *J* = 10.3, 7.4 Hz, 2H), 1.92 – 2.09 (m, 4H), 1.42 – 1.75 (m, 4H), 1.40 (s, 3H), 1.37 (s, 3H); ^{13}C NMR δ 153.6, 153.4, 138.3,

138.2, 136.3, 136.2, 126.2, 122.5, 121.2, 121.1, 111.9, 111.8, 59.5, 53.6, 52.9, 40.8, 40.2, 29.6, 29.3, 25.2, 24.9, 24.7, 23.0, 22.8, 18.6, 17.7; HRMS for $C_{13}H_{17}O_2$ [MH+] *m/z* calc. 205.1229 Da, found 205.1231 Da.

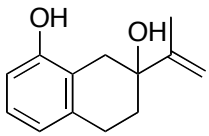
6-(2-methyloxiran-2-yl)-5,6,7,8-tetrahydronapthalen-1-ol (258):



To a stirred solution of acetate **OAc-253** (235 mg, 0.77 mmol) in DCM (10 mL) with $NaHCO_3$ (s) (250 mg) was added *m*-chloroperbenzoic acid (mCPBA) (159 mg, 0.92 mmol). The suspension was stirred for 16 h, after which it was quenched with sat. aq. $NaSO_3$ (10 mL), diluted in DCM (20 mL), washed with sat. aq. $NaHCO_3$ (20 mL), brine (20 mL), and concentrated *in vacuo*. The crude residue was taken up in MeOH (15 mL), K_2CO_3 (s) (300 mg) was added and the suspension stirred for 8 h. The reaction was diluted in DCM (20 mL), poured into sat. aq. NH_4Cl (20 mL), and extracted with DCM (2 x 20 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated to give an inconsequential mixture of diastereomeric epoxides **258** as a purplish waxy solid (117 mg, 74%): mp = 72 – 74 °C; IR (neat) 3390, 2928, 1651, 1587, 1465, 1275 cm^{-1}; ^1H NMR δ 6.94 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.57 (s, 2H), 2.54 – 2.85 (m, 8H), 2.02 (m, 2H), 1.92 – 1.98 (m, 4H), 1.42 – 1.72 (m, 2H), 1.36 (s, 3H), 1.35 (s, 3H), 1.20 – 1.48 (m, 2H); ^{13}C NMR δ 153.6, 137.6, 137.5, 130.1, 129.9, 127.6, 127.5, 115.0, 114.9, 113.1, 59.9,

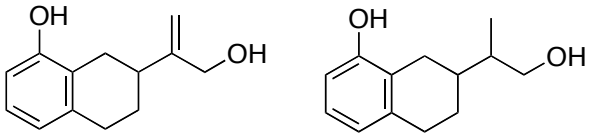
59.7, 53.6, 53.0, 41.1, 40.7, 40.6, 30.7, 30.7, 29.4, 29.2, 25.2, 25.1, 18.5, 17.9; HRMS for $C_{13}H_{17}O_2$ [MH+] *m/z* calc. 205.1229 Da, found 205.1232 Da.

7-(prop-1-en-2-yl)-5,6,7,8-tetrahydro-naphthalen-1, 7-diol (266):



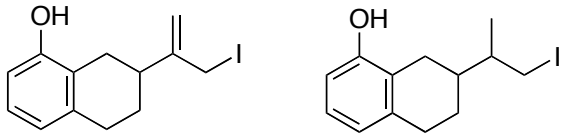
To a stirred solution of SeO_2 (25 mg) in CH_2Cl_2 (2 mL) with water (0.1 mL) was added olefin **256** (12 mg, 0.064 mmol) ain CH_2Cl_2 (1 mL). After stirring overnight, the suspension was concentrated and the crude residue chromatographed to provide diol **266** (9 mg, 69%) as a yellowish oil: R_f = 0.34 (30% EtOAc in Hexanes); IR (neat) 3367, 3349, 2924, 2853, 1464, 1271, 667 cm^{-1}; ^1H NMR δ 7.01 (t, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 5.08 (s, 1H), 4.92 (s, 1H), 2.76 – 3.17 (m, 4H), 2.04 (m, 2H), 1.94 (s, 3H); HRMS for $C_{13}H_{16}O_2$ [MH+] *m/z* calc. 204.1150 Da, found 204.1152 Da.

7-(3-hydoxyprop-1-en-2-yl)-5,6,7,8-tetrahydro-naphthalen-1-ol (267) and 7-(1-hydroxypropan-2-yl)-5,6,7,8-tetrahydronaphthalen-1-ol (268):



A solution of epoxide **257** (9.0 mg, 0.044 mmol) in toluene (1 mL) with alumnium triisopropoxide (25 mg) was stirred at reflux 110 °C for 16 h. The mixture was diluted in EtOAc (10 mL) and washed repeatedly with sat. aq. sodium potassium tartrate (10 mL washings until clear), then washed with brine (10mL) and concentrated *in vacuo* to give an inseperable mixture of allylic alcohol **267** and aliphatic alcohol **268** as an off-white powder (4.0 mg, 44%): **267**: R_f = 0.32 (20% EtOAc in Hexanes); IR (neat) 3420, 2926, 1652, 1635, 667 cm^{-1}; ^1H NMR δ 7.00 (t, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 5.16 (s, 1H), 5.02 (s, 1H), 4.25 (s, 2H), 2.96 (d of d, *J* = 10.4, 11.8 Hz, 1H), 2.86 (m, 2H), 2.46 (d, *J* = 11.8 Hz, 1H), 2.04 – 1.99 (m, 1H), 1.30 – 1.69 (m, 2H), 1.26 (s, 3H); ^{13}C NMR δ 153.3, 152.9, 138.1, 126.1, 122.9, 121.2, 111.8, 108.9, 65.2, 37.2, 29.7, 27.9, 14.2; HRMS for $C_{13}H_{16}O_2$ [MH+] *m/z* calc. 204.1150 Da, found 204.1152 Da. **268**: R_f = 0.32 (20% EtOAc in Hexanes); IR (neat) 3420, 2926, 1652, 1635, 667 cm^{-1}; ^1H NMR δ 6.99 (t, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 7.9 Hz, 1H), 3.76 (m, 1H), 3.64 (m, 1H), 2.79 (m, 3H), 2.36 (m, 1H), 1.69 – 1.93 (m, 3H), 1.39 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 3H); HRMS for $C_{13}H_{18}O_2$ [MH+] *m/z* calc. 206.1160 Da, found 206.1162 Da.

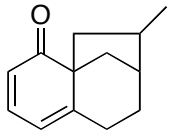
7-(3-iodoprop-1-en-2-yl)-5,6,7,8-tetrahydro-naphthalen-1-ol (275) and 7-(1-iodopropan-2-yl)-5,6,7,8-tetrahydronaphthalen-1-ol (274):



To a stirred solution of a mixture of aliphatic alcohol **268** and allylic alcohol **267** (159 mg, 0.778 mmol) in benzene (10 mL) was added triphenylphosphine (224 mg, 0.856 mmol), imidazole (119 mg, 1.75 mmol), and I_2 (217 mg, 0.856 mmol). The suspension was heated to reflux and stirred for 16 h, after which it was diluted in ether (20 mL), washed with sat. aq. NH_4Cl (20 mL), H_2O (20 mL), and brine (20 mL) and concentrated *in vacuo*. The crude residue was chromatographed (SiO_2, 10% EtOAc in hexanes) to give aliphatic iodide **274** as a brownish oil (120 mg, 48%) and the allylic iodide **275** as a brown oil (6 mg, 3%): **274**: R_f = 0.36 (10% EtOAc in Hexanes); IR (neat) 3420, 2922, 1558, 1260, 1155, 667 cm^{-1}; ^1H NMR δ 7.01 (t, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 3.36 (m, 2H), 2.84 (m, 3H), 2.28 (dt, *J* = 11.8, 4.5 Hz, 1H), 1.93 (m, 3H), 1.29 – 1.52 (m, 2H), 1.11 (d, *J* = 6.7 Hz, 3H); HRMS for $C_{13}H_{17}OI$ [MH+] *m/z* calc. 317.0322 Da, found 317.0318 Da. **275**: R_f = 0.30 (10% EtOAc in Hexanes); IR (neat) 3420, 2922, 1558, 1260, 1155, 667 cm^{-1}; ^1H NMR δ 7.01 (t, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.61 (d, *J* = 7.7 Hz, 1H), 5.35 (s, 1H), 5.05 (s, 1H), 4.09 (d, *J* = 1.2 Hz, 2H), 3.07 (d of d, *J* = 5.2, 1.2 Hz, 1H), 2.88 (d of d, *J* = 4.4, 8.0 Hz, 2H), 2.70 (m, 1H), 2.45 (d of d, *J* = 12.1, 5.1 Hz, 1H), 2.04 – 1.99 (m, 1H), 1.30 – 1.69 (m, 2H), 1.26 (s, 3H); ^{13}C NMR δ 153.2, 150.5, 138.0, 126.3, 122.7, 121.3, 112.9, 111.9, 37.7, 29.7,

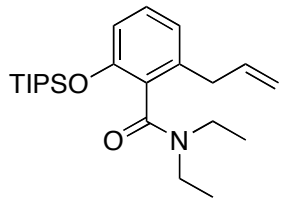
29.6, 28.9, 28.0, 10.1; HRMS for $C_{13}H_{15}OI$ [MH+] *m/z* calc. 315.0222 Da, found 315.0218 Da.

10-methyltricyco[7.2.1.0^{1,6}]dodeca-3,5-dien-2-one (276):



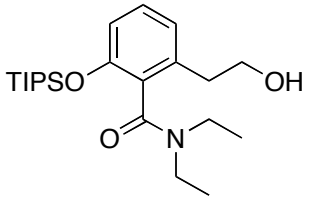
To a solution of aliphatic iodide **274** (80 mg, 0.778 mmol) in *t*-BuOH (12 mL) was added *t*-BuOK (2 mL of 1.0 M solution in *t*-BuOH, prepared from K in *t*-BuOH) and the reaction was stirred at reflux for 16 h. After allowing the reaction to cool to room temperature, it was diluted in H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (20 mL) and concentrated *in vacuo* to provide an inseparable mixture (1:1) of diastereomeric dienones **276** as a brownish oil (44 mg, 92%): IR (neat) 2934, 1660, 1627, 1558 cm^{-1}; ^{1}H NMR δ 7.03 (d of d, *J* = 7.0, 6.1 Hz, 1H), 7.01 (d of d, *J* = 7.0, 6.1 Hz, 1H), 6.07 (d, *J* = 7.3 Hz, 1H), 6.04 (d, *J* = 6.7 Hz, 1H), 5.92 (d of d, *J* = 7.7, 6.1 Hz, 1H), 5.91 (d of d, *J* = 7.7, 6.1 Hz, 1H), 1.20 – 2.80 (m, 20H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (some resonances are overlapping) δ 204.2, 202.2, 162.1, 160.9, 142.9, 142.7, 124.7, 124.2, 112.8, 112.5, 60.8, 51.1, 46.6, 44.5, 44.4, 42.8, 42.6, 36.9, 34.9, 30.1, 29.9, 29.7, 23.0, 15.5; HRMS for $C_{13}H_{17}O$ [MH+] *m/z* calc. 189.1279 Da, found 189.1283 Da.

***N*,*N*-diethyl-2-prop-2-en-1-yl)-6-{[tris(propan-2-yl)silyl]oxy}benzamide (289):**



A stirred solution of diethyl 2-silyloxybenzamide[3] **287** (7.68 g, 21.97 mmol) in THF (100.0 mL) at –78 °C was treated with *s*-BuLi (37 mL, 47.5 mmol, 1.3 M in hexanes) dropwise *via* syringe pump over 20 min and then stirred for 1 h. $CuBr•SMe_2$ (8.88 g, 43.2 mmol) was then added to this solution in one portion and the suspension was warmed to 23 °C and stirred 30 min. After recooling the suspension to –78 °C, allyl bromide (3.7 mL, 43.2 mmol) was added, the cold bath removed and the reaction stirred at 23 °C for 16 h. The reaction was quenched with sat. aq. NH_4Cl (100 mL), and extracted with ether (2 x 100 mL). The combined organics were washed with brine, concentrated, and the residue was chromatographed (SiO_2, 10 % EtOAc in hexanes) to give allylated benzamide **289** as an orangish oil (8.56 g, 100%): R_f = 0.45 (10% EtOAc in hexanes); IR (neat) 2943, 2867, 1639, 1581, 1462, 1280, 1024 cm^{-1}; ^1H NMR δ 7.09 (dd, *J* = 8.1, 7.7 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 5.89 (dt, *J* = 7.2, 9.5 Hz, 1H), 5.02 (m, 2H), 3.80 (quartet, *J* = 6.6 Hz, 4H), 3.27 (m, 2H), 3.00 – 3.1 (dq, *J* = 7.2, 2.2 Hz, 2H), 1.10 (t, *J* = 5.6 Hz, 6H), 1.20 – 1.32 (m, 3H), 1.10 (d, *J* = 6.8 Hz, 18H); ^{13}C NMR δ 167.9, 151.6, 138.0, 136.5, 128.6, 121.4, 116.2, 112.1, 91.8, 43.0, 38.8, 37.0, 17.6, 13.9, 12.9, 12.8; HRMS for $C_{23}H_{40}NO_2Si$ [MH+] *m/z* calc. 390.2828 Da, found 390.2831 Da.

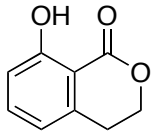
***N*,*N*-diethyl-2-(2-hydroxyethyl)-6-{[tris(propan-2-yl)silyl]oxy}benzamide (288):**



A solution of allyl **289** (4.04 g, 10.37 mmol) in DCM (50 mL) at –78 °C was treated with O_3, continuously bubbling it through the solution until the solution became a persistent pale blue (3 hours). The solution was warmed to 0 °C, and then to this was added dropwise a stirred solution of $NaBH_4$ (3.14 g, 82.96 mmol) in EtOH/H_2O (1 : 1, 50 mL). The reaction was stirred 18 h at 23 °C, then poured into aq. 4M HCl (25 mL) and acidified to pH ~ 1. The solution was extracted with DCM (3 x 50 mL) and the combined organics were washed with H_2O (50 mL), brine (50 mL), and concentrated *in vacuo*. The crude residue was dissolved in ether (40 mL) and filtered over Celite and the solvent evaporated to yield phenethyl alcohol **288** (3.88 g, 95%) as a yellow oil: R_f = 0.68 (EtOAc); IR (neat) 3392, 2942, 1639, 1586, 1469, 1436, 1260 cm^{-1}; ^1H NMR δ 7.15 (t, *J* = 8.1, 7.6 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 3.90 (quintet, *J* = 5.2 Hz, 1H), 3.68 (m, 2H), 3.37 (quintet, *J* = 6.9 Hz, 1H), 3.25 (q, *J* = 7.3 Hz, 1H), 3.07 (q, *J* = 7.3 Hz, 1H), 2.75 (dt, *J* = 13.8, 6.6 Hz, 1H), 2.62 (dd, *J* = 9.1, 4.4 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.20 – 1.32 (m, 3H), 1.00 (t, *J* = 7.4 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 18H); ^{13}C NMR δ 169.4, 151.2, 138.2, 129.4, 128.9, 122.0, 116.3, 36.3, 43.3, 39.7, 36.1,

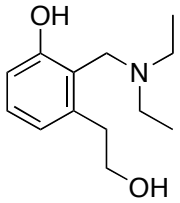
17.9, 14.2, 13.1, 12.8; HRMS for $C_{22}H_{40}NO_3Si$ [MH+] *m/z* calc. 394.2777 Da, found 394.2778 Da.

8-hydroxy-3,4-dihydro-1H-2-benzopyran-1-one (290):



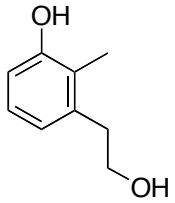
A solution of amide **288** (124 mg, 0.315 mmol) in toluene (6 mL) with camphorsulfonic acid (88 mg, 0.378 mmol) was stirred at reflux for 16h. The reaction was diluted in EtOAc (20 mL) and washed with sat. aq. NH_4Cl (10 mL), H_2O (10 mL), brine (10 mL) and concentrated to give a crude oil which was chromatographed (SiO_2, 20% EtOAc in hexanes) to yield known lactone[4] **290** as a colorless oil (48 mg, 92%): R_f = 0.27 (20% EtOAc in Hexanes); IR (neat) 2925, 2865, 1683, 1464, 1237, 668 cm^{-1}; ^1H NMR δ 7.40 (dd, *J* = 7.6, 8.2 Hz, 1H), 6.89 (d, *J* = 7.6 Hz 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 4.56 (t, *J* = 6.2 Hz, 2H), 3.03 (t, *J* = 6.1 Hz, 2H); ^{13}C NMR δ 162.2, 139.8, 136.2, 117.8, 116.3, 108.4, 68.1, 17.7, 12.2; HRMS for $C_9H_9O_3$ [MH+] *m/z* calc. 165.0552 Da, found 165.0549 Da.

2-[(diethylamino)methyl]-3-(2-hydroxyethyl)phenol (291):



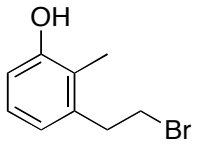
To a stirred suspension of lithium aluminum hydride (s) (0.50 g) in THF (20 mL) at 23 °C was added the amide **288** (850 mg, 2.16 mmol) as a solution in THF (10 mL) *via* addition funnel over 5 min. The mixture was heated to reflux and stirred 2 days. After cooling to 0 °C, the reaction mixture was quenched by dropwise addition to sat. aq. Na_2SO_4 (10 mL) *via* cannula. Upon complete addition, the mixture was diluted in ethyl acetate (50 mL) and stirred for 1 h, warming to room temperature. The solids were filtered under reduced pressure and washed with ethyl acetate until the washings ran was clear. The filtrate was concentrated *in vacuo* to provide the amine **291** as a pure orange oil (476 mg, 99%) which was taken on without further purification: R_f = 0.10 (EtOAc); IR (neat) 3286, 2968, 2935, 2835, 1583, 1469, 1250, 1083 cm^{-1}; ^1H NMR δ 7.01 (t, *J* = 8.1 Hz, 1H), 6.69 (d, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 3.83 (s, 2H), 3.78 (t, *J* = 6.7 Hz, 2H), 2.86 (t, *J* = 6.8 Hz, 2H), 2.62 (q, *J* = 7.3 Hz, 4H), 1.13 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR δ 158.0, 142.6, 128.5, 125.1, 121.9, 107.9, 62.9, 45.7, 44.9, 42.7, 35.6, 10.2; HRMS for $C_{13}H_{22}NO_2$ [MH+] *m/z* calc. 224.1651 Da, found 224.1654 Da.

3-(2-hydroxyethyl)-2-methylphenol (292):



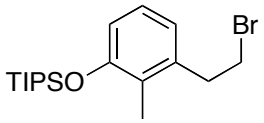
To a stirred solution of amine **291** (338 mg, 1.51 mmol) in methanol (15 mL), saturated with H_2 (g) by bubbling through for 30 min, was added 20% $Pd(OH)_2$ on carbon (60 mg). To the reaction mixture was attached a balloon of H_2 (g) through a septum and the reaction was allowed to stir under a balloon of H_2 (g). After 2 days of stirring under an atmosphere of H_2 (g), the balloon was removed, and the mixture filtered through a Celite plug under reduced pressure. After repeated methanol washings, the filtrates were combined and concentrated to give a crude brown oil. The residue was dissolved in ethyl acetate (20 mL) and the organic layer washed with 1M aq. H_3PO_4 (20 mL), H_2O (20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to provide alcohol **292** as a spectroscopically pure, pale brown oil (205 mg, 89%) which was taken on without further purification. Chromatographic purification of the product for the purpose of characterization (SiO_2, 20% ethyl acetate in hexanes) gave a brown powder: mp = 87 - 90 °C, R_f = 0.26 (30% EtOAc in Hexanes); IR (neat) 3336, 3286, 2928, 1584, 1464, 1257, 1104 cm^{-1}; ^1H NMR δ 7.02 (t, J = 7.8 Hz, 1H), 6.79 (d, J = 7.4 Hz 1H), 6.67 (d, J = 7.8 Hz, 1H), 3.83 (q, J = 5.1 Hz, 2H), 2.92 (t, J = 6.7 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR δ 154.5, 137.8, 125.9, 123.1, 121.6, 113.2, 62.5, 36.5, 11.2; HRMS for $C_9H_{13}O_2$ [MH+] m/z calc. 153.0916 Da, found 153.0914 Da.

3-(2-bromoethyl)-2-methylphenol (293):



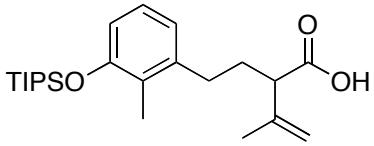
A solution of alcohol **292** (7.68 g, 55.6 mmol) in 48% aq. HBr (60 mL) was heated to 100 °C and stirred 16 h. The solution was cooled to 23 °C, poured into H_2O (60 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to provide a spectroscopically pure black oil which was taken on without further purification. Column chromatographic purification for the purpose of characterization (SiO_2, 20% ethyl acetate in hexanes) gave the bromophenol **293** as a white powder: mp = 108 – 109 °C; R_f = 0.55 (20% EtOAc in Hexanes); IR (neat) 3286, 2962, 2932, 1456, 1252, 1212 cm^{-1}; ^1H NMR δ 7.13 (t, J = 7.8 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 7.8 Hz, 1H), 3.54 (t, J = 8.5 Hz, 2H), 3.21 (t, J = 8.4 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR δ 153.9, 138.7, 126.3, 122.5, 121.8, 113.7, 37.1, 31.6, 11.2; HRMS for $C_9H_{12}OBr$ [MH+] *m/z* calc. 215.0072 Da, found 215.0072 Da.

3-(2-bromoethyl)-2-methylphenoxytris(propan-2-yl)silane (294):



To a solution of crude bromophenol **293** in CH_2Cl_2 (50 mL) was added imidazole (3.92 g, 61.16 mmol) and triisopropylsilyl choride (11.80 g, 61.16 mmol) and the reaction was stirred 16 h. The solution was poured into sat. aq. NH_4Cl (50 mL), extracted with CH_2Cl_2 (2 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatographic purification of the the crude oil (SiO_2, 6% ethyl acetate in hexanes) gave the bromide **294** as a colorless oil (16.65 g, 84% from **292**): R_f = 0.8 (2% EtOAc in Hexanes); IR (neat) 2944, 2866, 1583, 1463, 1273, 1066, 940, 882, 776 cm^{-1}; ^1H NMR δ 7.00 (t, *J* = 7.8 Hz, 1H), 6.76 (t, *J* = 7.8 Hz, 2H), 3.51 (t, *J* = 8.5 Hz, 2H), 3.18 (t, *J* = 8.5 Hz, 2H), 2.24 (s, 3H), 1.25 – 1.35 (m, 3H), 1.14 (d, *J* = 7.2 Hz, 18H); ^{13}C NMR δ 154.5, 138.7, 126.8, 125.9, 121.9, 116.7, 37.6, 31.7, 18.0, 13.0, 12.3; HRMS for $C_{18}H_{32}OBrSi$ [MH+] *m/z* calc. 371.1406 Da, found 371.1404 Da.

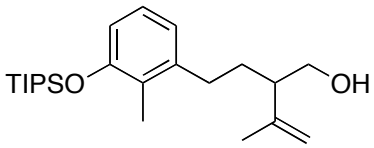
3-methyl-2-[2-(2-methyl-3-{[tris(propan-2-yl)silyl]oxy}phenyl)ethyl]but-3-enoic acid (295):



A flame-dried, three-necked 50 mL flask under Ar (g) and equipped with stirbar was charged with diisopropylamine (167 μL, 1.181 mmol) and THF (10 mL). The solution was cooled to –78 °C and *n*-BuLi (0.513 mL, 1.181 mmol, 2.4 M in hexanes) was added *via* syringe. The cold bath was removed and the solution was stirred for 15 min and then re-cooled to –78 °C. A solution of 3,3-dimethylacrylic acid **247** (54 mg, 0.537 mmol) in a minimal amount of THF (5 mL) was added to the reaction flask *via* cannula and the reaction mixture was stirred at rt for 2 h, until a white precipitate formed throughout the reaction vessel. The suspension was then re-cooled to –78 °C and bromide **294** (200 mg, 0.537 mmol) in a minimal amount of THF (5 mL) was added *via* cannula. The reaction was allowed to stir at –78 °C for 2 h and overnight at room temperature. The reaction was quenched by the addition of water (15 mL) and then diluted with ether and transferred to a separatory funnel. The organic layer was removed and the aqueous layer extracted with ether (10 mL). The aqueous layer was acidified with conc. aq. H_3PO_4 and extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to give acid **295** as a gummy, yellow oil of sufficient purity (83 mg, 40%): R_f = 0.24 (30% EtOAc in Hexanes); IR (neat) 3077, 2945, 2867, 1706, 1464, 1272 cm^{-1}; ^1H NMR δ 6.97 (dd, J = 7.8, 8.2 Hz, 1H), 6.74 (d, J = 7.4 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 5.0 (s, 1H), 4.99 (s,

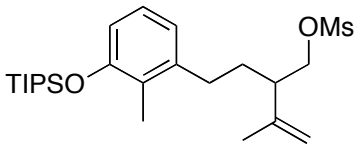
1H), 3.13 (t, *J* = 7.4 Hz, 1H), 2.6 (t, *J* = 8.1 Hz, 2H), 2.21 (s, 3H), 1.82 (s, 3H), 1.84 – 2.19 (m, 2H), 1.25 – 1.35 (m, 3H), 1.12 (d, *J* = 7.2 Hz, 18H); ^{13}C NMR δ 179.4, 154.3, 141.8, 141.1, 126.5, 125.6, 125.3, 121.6, 115.9, 114.6, 52.6, 31.6, 30.5, 18.0, 13.0, 12.1; HRMS for $C_{23}H_{39}O_3Si$ [MH+] *m/z* calc. 391.2688 Da, found 391.2654 Da.

3-methyl-2-[2-(2-methyl-3-{[tris(propan-2-yl)silyl]oxy}phenyl)ethyl]but-3-en-1-ol:



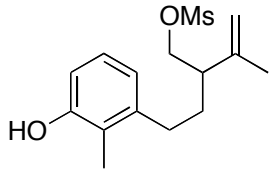
To a stirred solution of acid **295** (181 mg, 0.46 mmol) in dry ether (25 mL) at 0 °C was added LAH (s) (190 mg, 5.15 mmol). After stirring for four hours, the reaction was quenched with the dropwise addition of sat. aq. Na_2SO_4 until bubbling ceased. The suspension was filtered over celite, the filtrate dried (Na_2SO_4) and concentrated to give the alcohol as a pure, colorless oil (173 mg, 99%): IR (neat) 3344, 2943, 2866, 1463, 1272, 1051 cm^{-1}; ^{1}H NMR δ 6.95 (dd, *J* = 7.8, 7.5 Hz, 1H), 6.72 (d, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 7.9 Hz, 1H), 5.01 (s, 1H), 4.90 (s, 1H), 3.54 (dd, *J* = 8.2, 5.7 Hz, 2H), 2.45 – 2.61 (m, 2H), 2.36 (t, *J* = 6.3 Hz, 1H), 2.19 (s, 3H), 1.74 (s, 3H), 1.64 – 1.78 (m, 2H), 1.24 – 1.35 (m, 3H), 1.08 (d, *J* = 7.1 Hz, 18H); ^{13}C NMR δ 154.2, 126.4, 125.6, 125.5, 121.4, 115.7, 115.6, 114.1, 49.9, 31.5, 29.6, 28.9, 18.04, 17.6, 12.9, 12.1; HRMS for $C_{23}H_{41}O_2Si$ [MH+] *m/z* calc. 377.2876 Da, found 377.2881 Da.

3-methyl-2-[2-(2-methyl-3-{[tris(propan-2-yl)silyl]oxy}phenyl)ethyl]but-3-en-1-yl methanesulfonate (296):



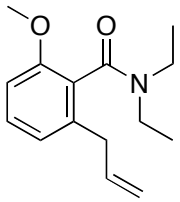
To a stirred solution of alcohol (216 mg, 0.573 mmol) in DCM (6 mL) with NEt_3 (1 mL) was added methansulfonyl chloride (0.10 mL, 12.36 mmol). After stirring for 3 h, the reaction was poured into sat. aq. NH_4Cl (10 mL) and extracted with DCM (3 x 20 mL). The combined organic extracts were washed with sat. aq. NH_4Cl, brine, dried (Na_2SO_4) and concentrated to give mesylate as a crude oil, which was taken on without further purification (254 mg, 97%): R_f = 0.40 (20% EtOAc in Hexanes); IR (neat) 3363, 2943, 2866, 1463, 1273 cm^{-1}; ^1H NMR δ 6.94 (dd, J = 7.8, 7.7 Hz, 1H), 6.69 (d, J = 7.5 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 4.98 (s, 1H), 4.88 (s, 1H), 4.14 (septet, J = 7.5, 6.2 Hz, 2H), 2.97 (s, 3H), 2.48 – 2.62 (m, 3H), 2.16(s, 3H), 1.74 (s, 3H), 1.59 – 1.72 (m, 2H), 1.24 – 1.35 (m, 3H), 1.08 (d, J = 7.1 Hz, 18H); ^{13}C NMR δ 154.2, 144.7, 141.9, 125.6, 121.5, 115.7, 114.3, 112.7, 63.9, 49.9, 31.6, 31.1, 29.9, 18.0, 13.0, 12.1, 11.0; HRMS for $C_{24}H_{42}O_4SSi$ [MH+] m/z calc. 455.2676 Da, found 455.2681 Da.

2-[2-(3-hydroxy-2-methylphenyl)ethyl]-3-methylbut-3-en-1-yl methanesulfonate (296):



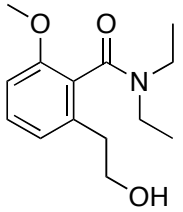
To a stirred solution of triisopropylsilyl ether (209 mg, 0.460 mmol) in THF (4 mL) was added TBAF (2 mL, 1.0M in THF) and the reaction stirred 3h. The solution was poured into sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organics were washed with water (20 mL), and the organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatographic purification (SiO_2, 30% EtOAc in hexanes) gave the phenol **296** as a brownish oil (62 mg, 45%): R_f = 0.25 (30% EtOAc in Hexanes); IR (neat) 3481, 2938, 1465, 1351, 1174, 950 cm^{-1}; ^1H NMR δ 6.99 (dd, *J* = 8.1, 7.7 Hz, 1H), 6.72 (d, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 5.01 (s, 1H), 4.91 (s, 1H), 4.20 (septet, *J* = 7.5, 6.2 Hz, 2H), 2.99 (s, 3H), 2.50 – 2.64 (m, 3H), 2.17(s, 3H), 1.77 (s, 3H), 1.64 – 1.78 (m, 2H); ^{13}C NMR δ 142.7, 141.6, 126.2, 121.9, 121.4, 114.5, 112.8, 106.2, 71.2, 46.2, 37.4, 30.8, 29.8, 19.5, 11.1; HRMS for $C_{15}H_{22}O_4S$ [MH+] *m/z* calc. 298.1239 Da, found 298.1235 Da.

***N,N*-Diethyl-2-methoxy-6-(prop-2-en-1-yl)benzamide (302):**



To a stirred solution of benzamide[5, 6] **301** (20.7 g, 0.100 mol) in THF (500 mL) at –78 °C was added *t*-butyllithium (80.00 mL, 1.5 M solution in pentane) *via* cannula over 30 min and the solution stirred an additional 1 h at –78 °C. $CuBr•SMe_2$ (24.60 g, 0.120 mol) was added and the reaction was stirred for 30 min. at –78 °C, 1 h at 23 °C, and then recooled to –78 °C. To this stirred suspension was added allyl bromide (9.0 mL, 10.4 mmol) and the reaction was stirred 4 h at 23 °C. The reaction was quenched by the addition of sat. aq. NH_4Cl (200 mL) and 1N HCl (aq.) (50 mL) and then diluted in ether (300 mL). After washing of the organic layer with sat. aq. NH_4Cl (2 x 500 mL) and brine (300 mL), concentration *in vacuo* provided the allyl product[7] **302** as a spectroscopically pure orange oil (24.3 g, 98%): R_f = 0.26 (30% EtOAc in hexanes); IR (neat) 2975, 2935, 1629, 1597, 1582, 1468, 1427, 1072, 762 cm^{-1}; ^1H NMR δ 7.20 (t, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 5.89 (m, 1H), 5.02 (m, 2H), 3.74 (s, 3H), 3.32 – 3.40 (quintet, *J* = 6.7 Hz, 2H), 3.27 (t, *J* = 6.8 Hz, 2H), 3.00 – 3.1 (quintet, *J* = 6.7 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 167.8, 155.1, 137.5, 136.3, 129.0, 125.9, 121.4, 116. 0, 108.3, 55.2, 42.5, 38.2, 36.8, 13.7, 12.6; HRMS for $C_{15}H_{22}NO_2$ [MH+] *m/z* calc. 248.1651 Da, found 248.1654 Da.

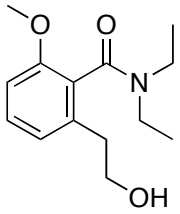
***N*,*N*-diethyl-2-(2-hydroxyethyl)-6-methoxybenzamide (303):**



To a stirred solution of benzamide **301** (15.55 g, 75.00 mmol) in THF (300 mL) at -78 °C was added *t*-butyllithium (100 mL, 1.5 M solution in pentane) *via* cannula over 30 min and the solution stirred an additional 1 h at -78 °C. To the reaction was added CuBr•SMe_2 (30.80 g, 150 mmol) and after stirring for 30 min., the reaction was allowed to warm to room temperature and stirred an additional 1 h. Meanwhile, ethylene oxide (g) was passed through a cold finger and the liquid collected in a flame dried, double neck round bottom until approximately 50 mL had been collected. To the room temperature, black reaction mixture was added the cold ethylene oxide (l) *via* cannula. After stirring for 30 min, the direct, dropwise addition of the cold-finger condensed ethylene oxide (l) was begun and maintained until the starting material was completely consumed (TLC monitoring). The reaction was quenched by the addition of sat. aq. NH_4Cl (100 mL) and diluted in ether (300 mL). After washing of the organic layer with sat. aq. NH_4Cl (2 x 500 mL) and brine (300 mL), concentration *in vacuo* provided a crude red oil which, upon trituration with cold ether, provided phenethylalcohol **302** as a pure, white powder (17.93 g, 95%): mp = 89 – 91 °C, R_f = 0.35 (EtOAc); IR (neat) 3392, 2972, 2936, 1610, 1596, 1469, 1436, 1260, 1083 cm^{-1}; ^1H NMR δ 7.26 (t, J = 8.1 Hz, 1H), 6.86

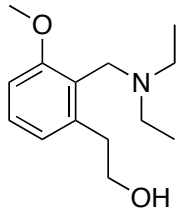
(d, J = 7.4 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 3.86 – 3.91 (quintet, J = 5.2 Hz, 1H), 3.77 (s, 3H), 3.68 – 3.75 (quintet, J = 5.2 Hz, 1H), 3.51 – 3.69 (m, 2H), 3.08 – 3.16 (d of quartets, J = 3.0, 7.4 Hz, 2H), 2.74 – 2.81 (m, 1H), 2.60 – 2.69 (m, 1H), 1.24 (t, J = 7.4 Hz, 3H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 168.8, 154.9, 137.7, 129.7, 126.3, 121.9, 108.4, 63.0, 55.3, 42.7, 38.8, 36.0, 13.7, 12.6; HRMS for $C_{14}H_{21}NO_3$ [MH+] m/z calc. 252.1525 Da, found 252.1545 Da.

***N,N*-diethyl-2-(2-hydroxyethyl)-6-methoxybenzamide (303):**



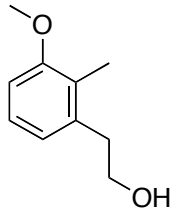
A solution of allyl **302** (2.63 g, 10.64 mmol) in DCM (50 mL) at –78 °C was treated with O_3, continuously bubbling it through the solution until the solution became a persistent pale blue (2 hours). The solution was warmed to 0 °C, and then to this was added dropwise a stirred solution of $NaBH_4$ (3.00 g, 79.30 mmol) in EtOH/H_2O (1 : 1, 50 mL). The reaction was stirred 3 h at 0 °C, then quenched by pouring it into aq. 3M HCl (25 mL) and further acidifying it to ph ~ 1. The solution was extracted with DCM (3 x 50 mL) and the combined organics were washed with brine (50 mL), and concentrated *in vacuo* to yield the alcohol **303** (3.88 g, 95%) as a colorless oil, which solidified on standing (1.96 g, 73%): characterized as above.

2-{2-[(diethylamino)methyl]-3-methoxyphenyl}ethanol (304):



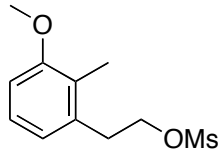
To a stirred suspension of lithium aluminum hydride (s) (LAH, 16.0 g) in THF (600 mL) at 0 °C was added the amide **303** (23.90 g, 95.10 mmol) as a solution in THF (100 mL) *via* addition funnel over 15 min. The mixture was heated to reflux and stirred 2 days. After cooling to room temperature, the reaction mixture was quenched by dropwise addition to sat. aq. Na_2SO_4 (400 mL) at 0 °C *via* cannula. Upon complete addition, the mixture was diluted in ethyl acetate (500 mL) and stirred for 1 h, warming to room temperature. The solids were filtered under reduced pressure and washed with ethyl acetate until the washings ran was clear. The filtrate was concentrated *in vacuo* to provide the amine **304** as a spectroscopically pure brown oil (22.24 g, 99%) which was taken on without further purification: R_f = 0.15 (EtOAc); IR (neat) 3392, 2969, 2937, 2835, 1584, 1468, 1250, 1082 cm^{-1}; ^1H NMR δ 7.24 (t, J = 8.1 Hz, 1H), 6.89 (d, J = 7.4 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 3.85 (t, J = 5.1 Hz, 2H), 3.81 (s, 3H), 3.63 (s, 2H), 2.89 (t, J = 5.1 Hz, 2H), 2.56 (q, J = 6.6 Hz, 4H), 1.09 (t, J = 6.6 Hz, 6H); ^{13}C NMR δ 158.0, 142.6, 128.5, 125.1, 121.9, 107.9, 62.9, 55.3, 45.7, 44.9, 42.7, 35.6, 10.2; HRMS for $C_{14}H_{24}NO_2$ [MH+] m/z calc. 238.1807 Da, found 238.1807 Da.

2-(3-methoxy-2-methylphenyl)ethanol (305):



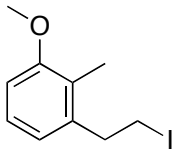
To a stirred solution of amine **304** (21.40 g, 0.0902 mol) in methanol (300 mL), saturated with H_2 (g) by bubbling through for 30 min, was added 20% $Pd(OH)_2$ on carbon (2.40 g). To the reaction mixture was attached a balloon of H_2 (g) through a septum and the reaction was allowed to stir overnight under a balloon of H_2. After 4 days of stirring under an atmosphere of H_2 (g), the balloon was removed, and the mixture filtered through a Celite plug under reduced pressure. After repeated methanol washings, the filtrates were combined and concentrated to give a crude brown oil. The residue was dissolved in ethyl acetate (200 mL) and the organic layer washed with 1M aq. H_3PO_4 (100 mL), H_2O (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to provide alcohol[8,9] **305** as a spectroscopically pure, pale brown oil (14.86 g, 99%) which was taken on without further purification. Chromatographic purification of the product for the purpose of characterization (SiO_2, 20% ethyl acetate in hexanes) gave a white solid: mp = 54 - 56 °C (lit.[9] 57 °C), R_f = 0.46 (30% EtOAc in Hexanes); IR (neat) 3336, 2928, 1584, 1464, 1257, 1104 cm^{-1}; ^1H NMR δ 7.13 (t, J = 8.0 Hz, 1H), 6.81 (d, J = 7.8, Hz 1H), 6.76 (d, J = 8.1 Hz, 1H), 3.82 (s, 3H), 3.80 (t, J = 7.0 Hz, 2H), 2.92 (t, J = 7.0 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR δ 157.7, 247.6, 126.0, 125.0, 122.0, 108.4, 62.5, 55.4, 36.6, 29.6; HRMS for $C_{10}H_{15}O_2$ [MH+] m/z calc. 167.1072 Da, found 167.1069 Da.

3-methoxy-2-methylphenethyl methanesulfonate (306):



To a stirred solution of alcohol **305** (5.74 g, 34.5 mmol) in CH_2Cl_2 (100 mL) at 0°C with triethylamine (6.0 mL) was added methanesulfonyl chloride (3.00 mL, 38.0 mmol) dropwise over 15 min. The reaction was allowed to stir overnight, after which, the solution was poured into sat. aq. NH_4Cl (100 mL), extracted with CH_2Cl_2 (2 x 100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatographic purification of the the crude oil (SiO_2, 20% ethyl acetate in hexanes) gave the mesylate **306** as a yellow oil (8.35 g, 99%): R_f = 0.22 (20% EtOAc in Hexanes); IR (neat) 2955, 2918, 2849, 1575, 1557, 1455 cm^{-1}; ^1H NMR δ 7.13 (t, J = 8.1 Hz, 1H), 6.80 (t, J = 8.1 Hz, 2H), 4.37 (t, J = 7.4 Hz, 2H), 3.82 (s, 3H), 3.09 (t, J = 7.3 Hz, 2H), 2.87 (s, 3H), 2.21 (s, 3H); ^{13}C NMR δ 157.8, 135.4, 126.3, 125.1, 122.0, 108.9, 69.4, 55.4, 37.2, 33.2, 11.3; HRMS for $C_{11}H_{16}O_4S$ [MH+] m/z calc. 244.0769 Da, found 244.0771 Da.

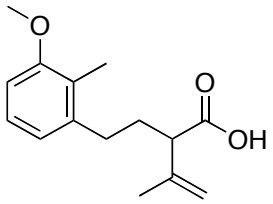
1-(2-iodoethyl)-3-methoxy-2-methylbenzene (307):



To a stirred solution of triphenylphosphine (1.12 g, 4.93 mmol) in CH_2Cl_2 (40 mL) was added imidazole (1.12 mg, 17.49 mmol), iodine (1.22 gg, 4.80 mmol) and alcohol **305** (600 mg, 3.60 mmol). After stirring overnight, the suspension was

concentrated and the residue chromatographed (SiO_2, 5% EtOAc in hexanes) to provide iodide[9] **307** as a yellow oil (626 mg, 63%): R_f = 0.82 (5% EtOAc in hexanes); IR (neat) 2954, 1259, 1096, 668 cm^{-1}; ^1H NMR δ 7.13 (t, J = 8.1 Hz, 1H), 6.80 (d, J = 8.1 Hz, 2H), 3.83 (s, 3H), 3.17 – 3.32 (m, 4H), 2.21 (s, 3H); ^{13}C NMR δ 157.9, 140.3, 126.4, 1245, 121.4, 108.8, 55.5, 38.5, 11.4, 3.9; HRMS for $C_{10}H_{14}OI$ [MH+] m/z calc. 277.0089 Da, found 277.0091 Da.

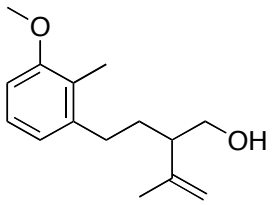
2-(3-methoxy-2-methylphenethyl)-3-methylbut-3-enoic acid (307):



A flame-dried, three-necked 500 mL flask under Ar (g) and equipped with stirbar was charged with diisopropylamine (12.60 mL, 89.65 mmol) and THF (150 mL). The solution was cooled to –78 °C and *n*-BuLi (37.4 mL, 89.65 mmol, 2.4 M in hexanes) was added *via* syringe. The cold bath was removed and the solution was stirred for 30 min and then re-cooled to –78 °C. A solution of 3,3-dimethylacrylic acid **247** (4.09 g, 40.82 mmol) in a minimal amount of THF (50 mL) was added to the reaction flask *via* cannula and the reaction mixture was stirred at –78 °C for 1 h and at rt for an additional 1 h, until a white precipitate formed throughout the reaction vessel. The suspension was then re-cooled to –78 °C and mesylate **306** (8.31 g, 34.02 mmol) in a minimal amount of THF (50 mL) was added *via* cannula. The alkylation reaction was allowed to stir at –78 °C for 2 h and overnight at room temperature. The reaction was quenched by the addition of water (150 mL) and then diluted with ether and transferred to a separatory funnel. The organic layer was removed and the aqueous layer extracted with ether (100 mL). The aqueous layer was acidified with H_3PO_4 (conc.) and extracted with ether (3 x 200 mL). The combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4) and concentrated to give acid **307** as a gummy, orange oil of sufficient purity (6.63 g, 78%): R_f = 0.24 (30% EtOAc in Hexanes); IR (neat) 2952, 2835, 1705, 1585, 1464, 1258, 1104

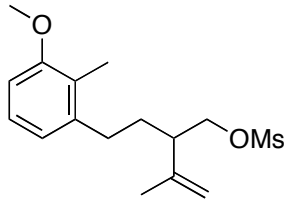
cm^{-1}; ^{1}H NMR δ 7.10 (t, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 5.0 (s, 1H), 4.98 (s, 1H), 3.82 (s, 3H), 3.13 (t, *J* = 7.4 Hz, 1H), 2.61 (t, *J* = 8.1 Hz, 2H), 2.17 (s, 3H), 1.82 (s, 3H), 1.79 – 2.10 (m, 2H); ^{13}C NMR δ 179.6, 157.7, 141.8, 140.9, 126.0, 124.6, 121.5, 114.7, 108.1, 55.5, 52.7, 31.3, 30.5, 20.2, 11.1; HRMS for $C_{15}H_{21}O_3$ [MH+] *m/z* calc. 249.1491 Da, found 249.1487 Da.

2-(3-methoxy-2-methylphenethyl)-3-methylbut-3-en-1-ol (309):



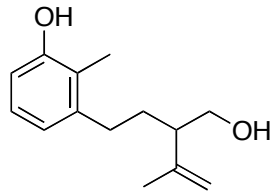
To a stirred suspension of LAH (3.0 g, 79.1 mmol) in ether (100 mL) at 0 °C was slowly added acid **307** (5.49 g, 22.1 mmol) as a solution in ether (50 mL) and the suspension was stirred at 23 °C for 16 h. The reaction was quenched at 0 °C, by the dropwise addition of sat. aq. Na_2SO_4 until bubbling ceased. The mixture was diluted in EtOAc, filtered, and concentrated *in vacuo* to yield alcohol **307** as a colorless oil (4.48 g, 87%): R_f = 0.29 (20% EtOAc in Hexanes); IR (neat) 3371, 2931, 1585, 1465, 1258, 1105, 1044 cm^{-1}; ^{1}H NMR δ 7.08 (t, *J* = 8.1 Hz 1H), 6.76 (d, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 5.0 (s, 1H), 4.89 (s, 1H), 3.80 (s, 3H), 3.53 (d, *J* = 5.9 Hz, 2H), 2.46 – 2.64 (m, 2H), 2.2 – 2.4 (m, 1H), 2.16 (s, 3H), 1.74 (s, 3H), 1.56 – 1.70 (m, 2H); ^{13}C NMR δ 144.7, 141.8, 126.0, 124.4, 123.6, 121.4, 114.2, 107.9, 64.0, 55.5, 49.9, 31.3, 30.1, 18.8, 11.2; HRMS for $C_{15}H_{23}O_2$ [MH+] *m/z* calc. 235.1698 Da, found 235.1703 Da.

2-(3-methoxy-2-methylphenethyl)-3-methylbut-3-en-1-yl methanesulfonate (310):



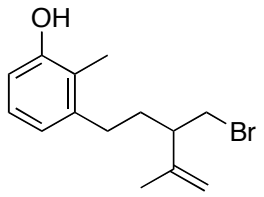
To a stirred solution of alcohol **309** (520 mg, 2.22 mmol) in DCM (10 mL) with diisopropylethylamine (2.00 mL) at 0 °C was added methansulfonyl chloride (2.0 mL, 25.8 mmol). After stirring 16 h at 23 °C, the reaction was poured into sat. aq. NH_4Cl (20 mL) and extracted with DCM (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to give a crude oil, which was chromatographed (SiO_2, 20% EtOAc in hexanes) to give mesylate **310** as a pure, pale-yellow oil (445 mg, 64%): R_f = 0.40 (20% EtOAc in Hexanes); IR (neat) 2940, 1584, 1465, 1355, 1258, 1176, 1098, 954, 528 cm^{-1}; ^1H NMR δ 7.10 (d of d, J = 8.1, 7.4 Hz, 1H), 6.75 (d, J = 7.4 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 5.01 (s, 1H), 4.91 (s, 1H), 4.16 (septet, J = 6.6, 9.5 Hz, 2H), 3.82 (s, 3H), 2.99 (s, 3H), 2.43 – 2.71 (m, 3H), 2.16 (s, 3H), 1.77 (s, 3H), 1.61 – 1.75 (m, 2H); ^{13}C NMR δ 157.7, 142.8, 0126.1, 124.3, 121.3, 114.4, 113.8, 107.9, 71.2, 55.5, 46.3, 37.4, 30.9, 29.9, 19.5, 11.1; HRMS for $C_{16}H_{24}O_4S$ [MH+] m/z calc. 312.1395 Da, found 312.1398 Da.

3-[4-hydroxy-3-(prop-1-en-2-yl)butyl]-2-methylphenol (312):



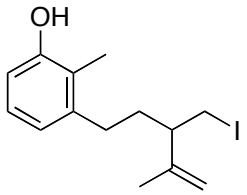
NaH (60% dispersion in mineral oil) was added portionwise to a solution of anisole **309** (2.4 g, 10.2 mmol) and ethanethiol (10 mL) in DMF (100 mL) at 0 °C. The suspension was stirred at reflux for 12 h, cooled, and poured into 1M H_3PO_4 (100 ml). The aqueous layer was extracted with MTBE (3 x 100 mL) and the combined organics were washed with brine (2 x 100 mL), dried (Na_2SO_4), and concentrated. The crude residue was purified by column chromatography (SiO_2, 20% EtOAc in hexanes) to provide phenol **312** as a brownish oil (1.84 g, 82%): R_f = 0.11 (20% EtOAc in Hexanes); IR (neat) 3350, 2936, 1585, 1465, 1275, 1036 cm^{-1}; ^1H NMR δ 6.98 (t, J = 8.1 Hz, 1H), 6.72 (d, J = 7.4 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 5.03 (s, 2H), 3.54 – 3.63 (quintet, J = 5.1, 8.1 Hz, 2H), 2.46 – 2.67 (m, 2H), 2.33 – 2.43 (m, 1H), 2.18 (s, 3H), 1.75 (s, 3H), 1.56 – 1.70 (m, 2H); ^{13}C NMR δ 163.6, 154.0, 144.5, 142.0, 126.0, 121.2, 63.9, 49.7, 31.2, 29.9, 18.7, 11.0; HRMS for $C_{14}H_{21}O_2$ [MH+] m/z calc. 221.1542 Da, found 221.1544 Da.

3-(3-(bromomethyl)-4-methylpent-4-enyl)-2-methylphenol (314):



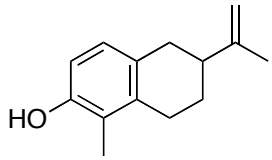
To a stirred solution of triphenylphosphine (1.82 g, 8.00 mmol) in CH_2Cl_2 (35 mL) in a 25 °C water bath was added bromine (1.20 g, 7.28 mmol) in CH_2Cl_2 (10 mL) dropwise over 10 min. To this solution, imidazole (1.0 g, 14.68 mmol) and alcohol **312** (400 mg, 1.82 mmol) were added and the reaction was stirred overnight. After pouring the solution into sat. aq. NH_4Cl (50 mL) and extracting with CH_2Cl_2 (2 x 50 mL), the combined organic extracts were concentrated and the residue chromatographed (SiO_2, 5% ethyl acetate in hexanes) to provide bromide **314** as a yellow oil (450 mg, 87%): R_f = 0.6 (20% EtOAc in Hexanes); IR (neat) 3446, 2937, 1584, 1464, 1457, 1273, 1063, 667 cm^{-1}; ^1H NMR δ 7.00 (t, J = 8.1 Hz, 1H), 6.74 (d, J = 7.4 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 5.0 (s, 1H), 4.89 (s, 1H), 3.42 (d, J = 7.4 Hz, 2H), 2.46 – 2.66 (m, 3H), 2.19 (s, 3H), 1.78 – 1.88 (m, 1H), 1.75 (s, 3H), 1.61 – 1.71 (m, 1H); ^{13}C NMR δ 153.8, 144.2, 141.9, 126.2, 121.7, 121.5, 113.9, 112.7, 49.2, 36.3, 32.3, 31.3, 18.9, 11.1; HRMS for $C_{14}H_{20}OBr$ [MH+] m/z calc. 283.0698 Da, found 283.0702 Da.

3-(3-(iodomethyl)-4-methylpent-4-enyl)-2-methylphenol (313):



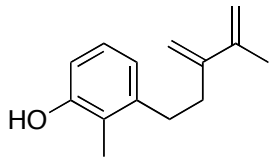
To a stirred solution of triphenylphosphine (420 mg, 1.60 mmol) in CH_2Cl_2 (10 mL) was added imidazole (220 mg, 3.20 mmol), iodine (370 mg, 2.45 mmol) and alcohol **313** (160 mg, 0.73 mmol). After stirring overnight, the suspension was concentrated and the residue chromatographed (SiO_2, 10% ethyl acetate in hexanes) to provide iodide **314** as a yellow oil (198 mg, 83%): R_f = 0.23 (10% EtOAc in Hexanes); IR (neat) 3446, 2934, 2867, 1584, 1465, 1273, 1182, 1063, 897, 783, 718 cm^{-1}; ^1H NMR δ 7.00 (t, J = 8.1 Hz, 1H), 6.74 (d, J = 7.4 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 5.0 (s, 1H), 4.86 (s, 1H), 3.24 (dd, J = 6.6 Hz, 2H), 2.37 – 2.61 (m, 3H), 2.19 (s, 3H), 1.75 – 1.85 (m, 1H), 1.72 (s, 3H), 1.61 – 1.71 (m, 1H); ^{13}C NMR δ 153.8, 144.7, 141.9, 126.2, 121.5, 113.9, 113.8, 112.8, 49.4, 36.6, 31.6, 18.6, 11.2, 11.1; HRMS for $C_{14}H_{20}OI$ [MH+] m/z calc. 331.0559 Da, found 331.0562 Da.

1-methyl-6-(prop-1-en-2-yl)-5,6,7,8-tetrahydro-naphthalen-2-ol (298):



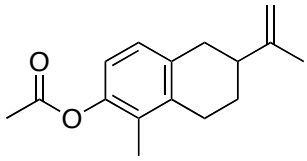
To a stirred solution of bromide **314** (0.549 g, 1.94 mmol) in *tert*-butanol (550 mL) at rapid reflux was added Cs_2CO_3 (1.50 g, 4.61 mmol). The reaction was stirred at reflux for 48h after which, the *tert*-butanol was removed by distillation. The remaining residue was taken up in sat. aq. NH_4Cl (100 mL), neutralized with 0.5 N HCl (aq.), and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine and concentrated *in vacuo* to give a yellow oil which was taken on without further purification. Column chromatographic purification (SiO_2, 40% CH_2Cl_2 in hexanes), carried out for the purposes of characterization, provided phenol **298** as an off-white powder: R_f = 0.25 (40% CH_2Cl_2 in hexanes); mp = 93 - 95 °C, IR (neat) 3319, 2917, 885, 795 cm^{-1}; ^1H NMR δ 6.82 (d, J = 8.1 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 4.79 (s, 2H), 2.77 – 2.89 (m, 2H), 2.61 – 2.70 (d of t, J = 5.2, 6.6 Hz, 2H), 2.22 – 2.32 (m, 1H), 2.14 (s, 3H), 2.03 – 2.12 (m, 1H), 1.82 (s, 3H), 1.59 – 1.69 (d of q, J = 5.9, 6.1 Hz, 1H); ^{13}C NMR δ 151.5, 149.7, 136.1, 128.7, 126.7, 121.9, 112.5, 108.7, 41.2, 35.0, 28.2, 27.5, 20.8, 15.1; HRMS for $C_{14}H_{19}O$ [MH+] *m/z* calc. 203.1436 Da, found 203.1438 Da.

2-methyl-3-(4-methyl-3-methylidenepent-4-en-1-yl)phenol) (299):



Diene **299** was obtained from the elimination of bromide **314** as a side product in the phenolate cyclization as a yellow oil: R_f = 0.20 (40% CH_2Cl_2 in hexanes); IR (neat) 3392, 2927, 1595, 1464, 1274, 1063, 890 cm^{-1}; ^1H NMR δ 7.01 (t, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 8.1 Hz 1H), 5.16 (d, *J* = 8.9 Hz, 2H), 5.02 (d, *J* = 11.0 Hz, 2H), 2.80 (t, *J* = 8.2 Hz, 2H), 2.52 (t, *J* = 7.3 Hz, 2H), 2.22 (s, 3H), 1.96 (s, 3H); ^{13}C NMR δ 153.7, 147.4, 142.5, 142.3, 126.2, 121.5, 112.6, 112.4, 110.6, 108.8, 34.5, 33.1, 21.1, 11.1; HRMS for $C_{14}H_{19}O$ [MH+] *m/z* calc. 203.1436 Da, found 203.1438 Da.

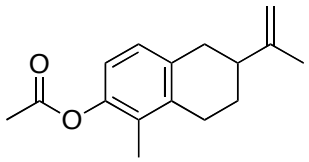
1-methyl-6-(prop-1-en-2-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl acetate (315):



To a stirred solution of phenol **298** (0.549 g, 2.71 mmol) in pyridine (10 mL) at room temperature was added acetic anhyride (5 mL). The reaction was stirred at room temperature for 30 min and was concentrated *in vacuo*. The remaining residue was purified *via* column chromatography (SiO_2, 40% CH_2Cl_2 in hexanes) to provide the phenolic acetate **315** as a pale yellow oil (0.663 g, 100%): R_f = 0.33 (40% CH_2Cl_2 in hexanes); IR (neat) 2924, 1761, 1222, 1196, 667 cm^{-1}; ^1H NMR δ 6.96 (d, *J* = 8.1 Hz,

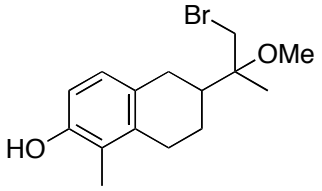
1H), 6.79 (d, *J* = 8.1 Hz, 1H), 4.79 (s, 1H), 4.77 (s, 1H), 2.79 – 2.87 (m. 2H), 2.63 – 2.74 (m, 2H), 2.33 (s, 3H), 2.26 – 2.31 (m, 1H), 2.06 – 2.13 (m, 1H), 2.03 (s, 3H), 1.81 (s, 3H), 1.59 – 1.69 (d of q, *J* = 5.9, 6.1 Hz, 1H); ^{13}C NMR δ 169.7, 149.3, 146.9, 136.4, 134.6, 127.9, 127.2, 118.8, 109.0, 40.9, 35.2, 27.9, 27.5, 20.8, 11.9; HRMS for $C_{16}H_{21}O_2$ [MH+] *m/z* calc. 245.1542 Da, found 245.1545 Da.

1-methyl-6-(prop-1-en-2-yl)-5,6,7,8-tetrahydro-naphthalen-2-yl acetate (315):



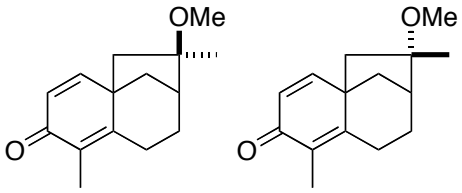
To a stirred solution of bromide **314** (2.61, 9.22 mmol) in *tert*-butanol (1.8 L) at rapid reflux was added Cs_2CO_3 (12.00 g, 36.88 mmol). The reaction was stirred at reflux for 36 h after which, the *tert*-butanol was removed by distillation. The remaining residue was taken up in acetic anhydride (150 mL) and stirred for 6 h at room temperature, after which, the mixture was concentrated *in vacuo*. The remaining residue was dissolved in sat. aq. NH_4Cl (100 mL), and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine and concentrated *in vacuo* to give phenol acetate **315** as a pale yellow oil (2.18 g, 96%): characterized as above.

6-(1-bromo-2-methoxypropan-2-yl)-1-methyl-5,6,7,8-tetrahydro-naphthalen-2-yl (316):



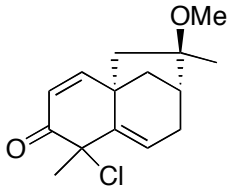
To a room temperature, stirred solution of olefin **315** (220 mg, 0.900 mmol) in CH_2Cl_2 (10 mL) was added freshly recrystallized *N*-bromosuccinimide (NBS) (176 mg, 0.990 mmol). After stirring for 15 min (or until complete dissolution of the NBS was achieved), distilled methanol (10 mL) was added and the reaction stirred overnight. To the reaction mixture was added K_2CO_3 (s) (500 mg) and stirring was continued for 4h. The mixture was poured into H_2O (30 mL) and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to provide a yellow oil which was chromatographed (SiO_2, 20% ethyl acetate in hexanes) to give bromohydrin **316** as a mixture of inseparable diastereomers (1:1) as a pale yellow oil which foamed *in vacuo* (278 mg, 99%): R_f = 0.45 (20% EtOAc in Hexanes); IR (neat) 3369, 2933, 1488, 1457, 1278, 1065, 731 cm^{-1}; ^1H NMR δ 6.84 (d, *J* = 8.1 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 2H), 3.60 (d of d, *J* = 11.0, 6.1 Hz, 4H), 3.28 (s, 6H), 2.78 – 2.91 (d of t, *J* = 13.2, 4.4 Hz, 4H), 2.59 (t, *J* = 6.0 Hz, 4H), 2.06 – 2.21 (m, 4H), 2.13 (s, 6H), 1.91 – 1.97 (m, 2H), 1.35 – 1.47 (m, 2H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (some resonances are overlapping) δ 151.4, 136.5, 136.1, 128.9, 127.2, 121.7, 121.6, 112.6, 49.3, 49.2, 39.8, 39.6, 38.3, 37.8, 30.7, 30.2, 27.9, 27.8, 24.7, 23.6, 18.3, 17.5, 11.0; HRMS for $C_{15}H_{22}O_2Br$ [MH+] *m/z* calc. 313.0803 Da, found 313.0800 Da.

10-methoxy-5,10-dimethyltricyclo[7.2.1.01,6]dodeca-2,5-dien-4-one (317 & 318):



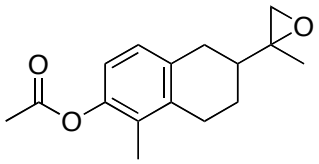
To a stirred solution of bromides **316** (0.868 g, 2.77 mmol) in *tert*-butanol (600 mL) was added Cs_2CO_3 (8.68 g). The reaction was stirred at reflux for 48h after which, the *tert*-butanol was removed by distillation. The remaining residue was taken up in brine (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, concentrated, and purified (SiO_2, 30% EtOAc in hexanes) to provide dienones **317** and **318** as yellow oils (1:1, 0.423g, 66%): R_f = 0.20, 0.18 (20% ethyl acetate in hexanes); **317**: IR (neat) 2935, 1653, 1066, 667 cm^{-1}; ^1H NMR δ 6.61 (d, *J* = 9.5 Hz, 1H), 6.23 (d, *J* = 10.3 Hz, 1H), 3.31 (s, 3H), 2.73 – 2.81 (dd, *J* = 9.9, 7.3 Hz, 1H), 2.63 – 2.70 (m, 1H), 2.08 – 2.45 (m, 3H), 1.87 (s, 3H), 1.75 – 1.94 (m, 2H), 1.45 (s, 3H), 1.40 – 1.59 (m, 2H); ^{13}C NMR δ 186.5, 160.5, 153.9, 127.9, 126.7, 84.5, 55.5, 51.8, 48.3, 45.0, 43.5, 27.4, 26.3, 25.9, 10.4; HRMS for $C_{15}H_{21}O_2$ [MH+] *m/z* calc. 233.1536 Da, found 233.15361 Da; **318**: IR (neat) 2935, 1657, 1627, 1066 cm^{-1}; ^1H NMR δ 6.76 (d, *J* = 10.3 Hz, 1H), 6.24 (d, *J* = 9.6 Hz, 1H), 3.22 (s, 3H), 2.77 – 2.86 (dd, *J* = 16.9, 7.3 Hz, 1H), 2.46 (dt, *J* = 16.3, 2.9 Hz, 1H), 2.06 – 2.37 (m, 3H), 1.86 (s, 3H), 1.54 – 1.70 (m, 2H), 1.41 (s, 3H), 1.20 – 1.33 (m, 2H); ^{13}C NMR δ 186.5, 159.5, 154.4, 128.6, 127.2, 86.0, 52.5, 49.6, 48.9, 43.2, 40.6, 26.4, 24.8, 18.6, 10.4; HRMS for $C_{15}H_{21}O_2$ [MH+] *m/z* calc. 233.1536 Da, found 233.15361 Da.

5-chloro-10-methoxy-5,10-dimethyltricyclo[7.2.1.0^{1,6}]dodeca-2,6-dien-4-one (320):



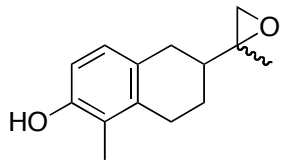
To a stirred solution of dienone **317** (0.009 g, 0.039 mmol) in THF (6 mL) was added LDA (2 mL, 1.0M in THF). The reaction was stirred at reflux for 2h, cooled to room temperature and stirred 1h. To this reaction was added NCS (25 mg, 0.187 mmol) and stirred 2h. The reaction was quenched by the addition of sat. aq. NH_4Cl (5 mL) and poured into ether (10 mL). The organic layer was separated and washed with sat. aq. NH_4Cl (5 mL), brine (5 mL) and the solvent was evaporated. The remaining residue was purified (SiO_2, 30% EtOAc in hexanes) to provide α-Cl dienone **320** as a yellow oil (0.006g, 58%): R_f = 0.68 (30% EtOAc in hexanes); IR (neat) 2930, 1662, 1446, 1071 cm^{-1}; ^{1}H NMR δ 6.48 (d, *J* = 10.3 Hz, 1H), 5.50 (d, *J* = 9.6 Hz, 1H), 5.40 (t, *J* = 7.3 Hz, 1H), 3.28 (s, 3H), 2.70 (dd, *J* = 14.5, 6.6 Hz, 1H), 2.23 (m, 1H), 1.88 – 2.15 (m, 4H), 1.80 (s, 3H), 1.58 (s, 3H), 1.40 – 1.50 (m, 1H); ^{13}C NMR δ 155.9, 140.2, 135.8, 132.0, 123.7, 121.4, 51.6, 50.7, 46.7, 45.7, 29.6, 28.2, 26.3, 23.3, 14.0.

1-methyl-6-(2-methyloxiran-2-yl)-5,6,7,8-tetrahydronaphthalen-2-yl acetate (326):



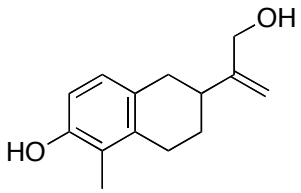
To a stirred solution of olefin **315** (445 mg, 1.82 mmol) in CH_2Cl_2/acetone (1:1, 20 mL) with sat. aq. $NaHCO_3$ (10 mL) was added sat. aq. Oxone dropwise until the olefin was consumed (TLC monitoring). The resulting suspension was diluted in ether (20 mL) and washed with H_2O (2 x 20 mL), brine (20 mL) and concentrated *in vacuo* to yield the epoxides **326** as an otherwise pure, inseparable mixture of diastereomers (1:1) as a pale yellow oil (469 mg, 99%): R_f = 0.24 (10% EtOAc in Hexanes); IR (neat) 2928, 1761, 1480, 1368, 1223, 1196 cm^{-1}; ^1H NMR δ 6.96 (t, J = 7.3 Hz, 2H), 6.80 (d, J = 8.1 Hz, 2H), 2.81 – 2.89 (m, 3H), 2.55 – 2.76 (m, 11H), 2.32 (s, 6H), 2.05 – 2.16 (m, 2H), 2.02 (s, 6H), 1.55 – 1.71 (m, 2H), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR δ 169.7, 147.0, 136.4, 136.4, 133.8, 133.7, 128.2, 127.4, 127.2, 119.1, 59.2, 59.1, 53.4, 52.7, 40.2, 39.7, 32.0, 27.3, 27.1, 25.2, 25.0, 20.8, 18.6, 18.0, 12.0; HRMS for $C_{16}H_{21}O_3$ [MH+] m/z calc. 261.1491 Da, found 261.1494 Da.

1-methyl-6-(2-methyloxiran-2-yl)-5,6,7,8-tetrahydronaphthalen-2-ol:



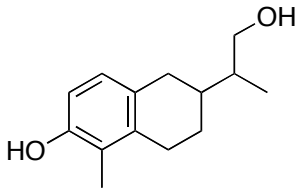
A solution of acetate epoxide **326** (34 mg, 0.13 mmol) in MeOH (5 mL) with K_2CO_3 (s) (100 mg) was stirred for 4 h. The reaction was diluted in H_2O (10 mL) and extracted with DCM (2 x 20 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated to give an inconsequential mixture of phenolic diastereomeric epoxides as a purplish waxy solid (28 mg, 99%): IR (neat) 2928, 1650, 1588, 1465 cm^{-1}; ^1H NMR δ 6.83 (dd, *J* = 7.4, 6.6 Hz, 2H), 6.61 (d, *J* = 8.1 Hz, 2H), 2.54 – 2.89 (m, 12H), 2.06 – 2.19 (m, 2H), 2.12 (s, 6H), 2.05 – 2.16 (m, 2H), 1.26 – 1.63 (m, 4H), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR δ 151.5, 136.1, 136.0, 128.1, 127.8, 127.0, 126.9, 126.8, 121.8, 121.7, 112.7, 60.7, 60.5, 59.4, 59.3, 53.5, 52.8, 47.9, 41.6, 40.5, 39.9, 37.1, 31.7, 29.6, 27.9, 27.3, 27.1, 25.4, 25.2, 23.5, 18.6, 17.8, 14.2, 14.1, 11.0; HRMS for $C_{14}H_{19}O_2$ [MH+] *m/z* calc. 219.1385 Da, found 219.1385 Da.

6-(3-hydroxyprop-1-en-2-yl)-1-methyl-5,6,7,8-tetrahydro-naphthalen-2-ol (327):



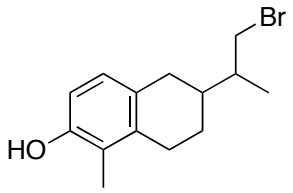
A solution of epoxides **326** (170 mg, 0.691 mmol) in THF (4 mL) at 23 °C under an atmosphere of Ar, was treated with lithium diethylamide (6 mL, 0.5 M solution in THF) and stirred for 2h. The reaction mixture was poured into sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organics were washed with brine, concentrated and the crude residue purified by column chromatography (SiO_2, 30% EtOAc in hexanes) to provide the allylic alcohol **327** as a white powder (132 mg, 94%): mp = 112.3 - 113.8 °C; R_f = 0.36 (30% EtOAc in Hexanes); IR (neat) 3350, 2922, 2853, 1455, 1279, 1074, 906, 802 cm^{-1}; ^1H NMR δ 6.79 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 5.10 (s, 1H), 4.95 (s, 1H), 4.20 (s, 2H), 2.77 – 2.86 (m, 2H), 2.55 – 2.70 (m, 2H), 2.29 – 2.37 (m, 1H), 2.10 (s, 3H), 1.58 – 1.70 (m, 2H), 1.23 (s, 3H); ^{13}C NMR δ 51.3, 139.8, 135.9, 128.7, 126.8, 121.8, 60.5, 39.9, 39.7, 35.5, 33.9, 31.9, 27.6, 27.4, 25.7, 21.0, 14.1, 13.6, 13.3, 7.8; HRMS for $C_{14}H_{19}O_2$ [MH+] m/z calc. 219.1385 Da, found 219.1385 Da.

6-(1-hydroxypropan-2-yl)-1-methyl-5,6,7,8-tetrahydro-naphthalen-1-ol (328):



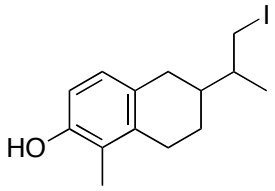
A solution of epoxides **326** (420 mg, 1.61 mmol) in toluene (30 mL) was treated with Al(O*i*-Pr)$_3$ (1.20 g, 5.87 mmol) and the resulting suspension stirred at reflux for 16h. The solvent was evaporated and the crude residue was partitioned between EtOAc (20 mL) and sat. aq. sodium potassium tartrate (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield an inseparable mixture (1:1) of the saturated alcohols **328** and the allylic alcohol **327** as an otherwise pure, pale yellow powder (326 mg, 93%): R_f = 0.36 (30% EtOAc in hexanes); IR (neat) 3383, 2962, 2918, 1260, 1089, 1018, 802 cm^{-1}; ^{1}H NMR δ 6.79 (d, *J* = 8.1 Hz, 2H), 6.60 (d, *J* = 8.1 Hz, 2H), 3.73 (dd, *J* = 5.2, 4.4 Hz, 4H), 3.58 (dd, *J* = 5.2, 6.6 Hz, 4H), 2.36 – 2.88 (m, 8H), 1.69 – 2.21 (m, 2H), 2.12 (s, 6H), 1.38 – 1.66 (m, 4H), 1.27 (d, *J* = 7.3 Hz, 3H), 1.25 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (some resonances are overlapping) δ 153.0, 151.4, 136.0, 129.5, 128.8, 126.9, 112.6, 108.5, 65.2, 35.6, 29.7, 28.6, 27.5, 11.0; HRMS for $C_{14}H_{21}O_2$ [MH+] *m/z* calc. 221.2268 Da, found 221.2270 Da.

6-(1-bromopropan-2-yl)-1-methyl-5,6,7,8-tetrahydro-naphthalen-1-ol (329):



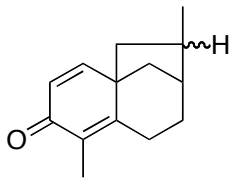
To a stirred solution of alcohol **329** (78 mg, 0.35 mmol) in DCM (10 mL) was added triphenylphosphine (126 mg, 0.56 mmol) and carbon tetrabromide (186 mg, 0.56 mmol). After stirring for 2h, the solution was diluted in ether (20 mL), washed with sat. aq. $NaHCO_3$ (20 mL), brine, and concentrated. Column chromatographic purfication of the crude oil (SiO_2, 20% EtOAc in hexanes) provided inseparable bromides **329** as a yellow oil: R_f = 0.27 (10% EtOAc in hexanes); IR (neat) 3404, 2921, 1486, 1455, 1275, 802 cm^{-1}; ^1H NMR δ 6.81 (d, J = 8.1 Hz, 2H), 6.60 (d, J = 8.1 Hz, 2H), 3.52 (m, 4H), 2.47 – 2.88 (m, 8H), 2.12 (s, 6H), 1.95 – 2.06 (m, 2H), 1.73 – 1.85 (m, 4H), 1.29 – 1.48 (m, 2H), 1.11 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 5.2 Hz, 3H); ^{13}C NMR (some resonances are overlapping) δ 151.4, 136.3, 128.5, 127.1, 121.7, 112.6, 40.1, 39.8, 39.3, 38.9, 36.9, 36.8, 33.7, 31.9, 30.9, 27.3, 27.2, 25.8, 16.1, 15.6, 10.9; HRMS for $C_{14}H_{20}OBr$ [MH+] m/z calc. 283.0698 Da, found 283.0699 Da.

6-(1-iodopropan-2-yl)-1-methyl-5,6,7,8-tetrahydro-naphthalen-1-ol:



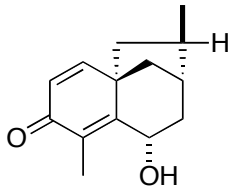
To a stirred solution of alcohol **328** (159 mg, 0.723 mmol) in benzene (10 mL) was added triphenylphosphine (224 mg, 0.987 mmol), imidazole (119 mg, 1.85 mmol), and I_2 (217 mg, 0.856 mmol). The suspension was heated to reflux and stirred for 16 h, after which it was diluted in ether (20 mL), washed with sat. aq. NH_4Cl (20 mL), H_2O (20 mL), and brine (20 mL) and concentrated *in vacuo*. The crude residue was chromatographed (SiO_2, 10% EtOAc in hexanes) to give the title compound as a brownish oil (82 mg, 33%): R_f = 0.40 (10% EtOAc in Hexanes); IR (neat) 3420, 2926, 1559, 1155, 667 cm^{-1}; ^1H NMR δ 6.82 (d, J = 8.1 Hz, 2H), 6.60 (d, J = 8.1 Hz, 2H), 3.35 (dq, J = 9.6, 4.4 Hz, 4H), 2.45 – 2.8 (m, 10H), 1.69 – 2.21 (m, 6H), 2.12 (s, 6H), 1.38 – 1.66 (m, 4H), 1.08 (d, J = 4.6 Hz, 3H), 1.07 (d, J = 5.2 Hz, 3H); ^{13}C NMR δ 159.1, 151.1, 136.0, 128.1, 127.1, 127.0, 126.9, 126.8, 121.8, 121.7, 112.7, 53.5, 52.8, 41.2, 41.6, 38.6, 33.9, 31.7, 29.6, 27.2, 27.0, 25.6, 17.4, 15.9, 10.7; HRMS for $C_{14}H_{20}OI$ [MH+] m/z calc. 331.0559 Da, found 331.0563 Da.

5,10-dimethyltricyco[7.2.1.0^{1,6}]dodeca-2,5-dien-4-one (330):



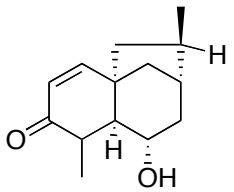
To a solution of bromide **329** (14 mg, 0.050 mmol) in *t*-BuOH (12 mL) was added Cs_2CO_3 (30 mg, 0.092 mmol) and the reaction was stirred at reflux for 16 h. After allowing the reaction to cool to room temperature, it was diluted in brine (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (20 mL) and concentrated *in vacuo* to provide a mixture (1:1) of diastereomeric dienones **330** as a brownish oil (8 mg, 80%): R_f = 0.64, 0.57 (20% EtOAc in Hexanes); IR (neat) 2929, 2865, 1656, 1652, 1626, 1622, 829 cm^{-1}; ^{1}H NMR δ 6.72 (d, *J* = 9.6 Hz, 1H), 6.67 (d, *J* = 10.3 Hz, 1H), 6.24 (d, *J* = 10.3 Hz, 1H), 6.23 (d, *J* = 9.6 Hz, 1H), 2.80 (dd, *J* = 16.2, 10.3 Hz, 4H), 1.20 – 2.27 (m, 16H), 1.87 (s, 6H), 1.15 (d, *J* = 7.4 Hz, 3H), 1.14 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 186.6, 160.6, 159.6, 154.8, 154.7, 127.7, 127.3, 126.9, 60.3, 49.4, 46.3, 45.3, 43.2, 42.9, 42.6, 39.9, 37.0, 31.9, 31.1, 26.8, 25.5, 25.1, 23.3, 20.9, 15.9, 14.1, 14.0; HRMS for $C_{14}H_{19}O$ [MH+] *m/z* calc. 203.1436 Da, found 203.1440 Da.

7-hydroxy-5,10-dimethyltricyco[7.2.1.0^{1,6}]dodeca-2,5-dien-4-one (331):



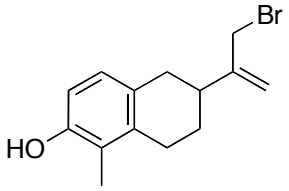
A solution of dienone **330** (16 mg, 0.0792 mmol) in DMF (10 mL) was treated with Cs_2CO_3 (150 mg, 0.448 mmol) and the resulting suspension stirred at 90 °C open to air, for 16h. The solvent was removed *in vacuo* and the residue taken up in brine (20 mL) and extracted with ether (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to provide autoxidation product **331** as a colorless oil (8 mg, 46%): R_f = 0.21 (20% EtOAc in Hexanes); IR (neat) 2921, 1653, 1558, 668 cm^{-1}; ^{1}H NMR δ 6.72 (d, *J* = 9.6 Hz, 1H), 6.27 (d, *J* = 10.3 Hz, 1H), 4.94 (d, *J* = 5.9 Hz, 1H), 2.65 (m, 1H), 2.32 (ddd, *J* = 8.1, 5.2, 3.0 Hz, 1H), 2.04 – 2.19 (m, 2H), 1.97 (s, 3H), 1.85 – 1.91 (m, 1H), 1.18 – 1.46 (m, 2H), 1.08 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 173.7, 158.7, 152.4, 133.5, 131.2, 66.0, 45.4, 43.2, 42.3, 39.9, 29.7, 28.5, 23.8, 10.4; HRMS for $C_{14}H_{19}O_2$ [MH+] *m/z* calc. 219.1385 Da, found 219.1389 Da.

7-hydroxy-5,10-dimethyltricyclo[7.2.1.0^{1,6}]dodec-2-en-4-one (333):



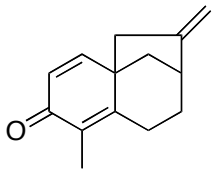
To a stirred solution of hydroxydienone **331** (2 mg, 0.0092 mmol) in THF (2 mL) at 0 °C was added LAH (0.1 mL, 1.0M in toluene) dropwise. After 5 min., the reaction was quenched by the dropwise addition of MeOH (1 mL). The solvent was evaporated and the residue washed with DCM (10 mL). The organic washings were dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatographic purification (SiO_2, 30% EtOAc in hexanes) yielded enone **333** as a yellow oil (1 mg, 48%): R_f = 0.18 (30% EtOAc in Hexanes); IR (neat) 3446, 2922, 1668, 1260 cm^{-1}; ^{1}H NMR δ 6.69 (d, *J* = 10.4 Hz, 1H), 5.91 (d, *J* = 9.6 Hz, 1H), 4.80 (d, *J* = 5.2 Hz, 1H), 1.82 (d, *J* = 9.6 Hz, 3H), 1.62 – 1.81 (m, 4H), 1.02 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR δ 168.2, 127.5, 107.8, 47.6, 41.4, 41.3, 37.5, 35.9, 34.8, 29.7, 23.9, 23.7, 13.1; HRMS for $C_{14}H_{21}O_2$ [MH+] *m/z* calc. 221.1540 Da, found 221.1542 Da.

6-(3-bromoprop-1-en-2-yl)-1-methyl-5,6,7,8-tetrahydronaphthalen-2-ol (336):



To a stirred solution of alcohol **XXX** (25 mg, 0.115 mmol) in DCM (6 mL) was added triphenylphosphine (75 mg, 0.330 mmol) and carbon tetrabromide (110 mg, 0.330 mmol). After stirring for 2h, the solution was diluted in ether (20 mL), washed with sat. aq. $NaHCO_3$ (20 mL), brine, and concentrated. Column chromatographic purfication of the crude oil (SiO_2, 5% EtOAc in hexanes) provided bromide **XXX** (12 mg, 37%) as a yellow oil: $R_f = 0.54$ (10% EtOAc in hexanes); IR (neat) 2920, 2849, 1260 cm^{-1}; ^1H NMR δ 6.83 (d, J = 8.1 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 5.27 (s, 1H), 5.07 (s, 1H), 4.10 (s, 2H), 2.80 – 2.95 (m, 2H), 2.60 – 2.74 (m, 3H), 2.13 (s, 3H), 1.52 – 1.70 (m, 2H), 1.26 (s, 3H); HRMS for $C_{14}H_{18}OBr$ [MH+] m/z calc. 281.0541 Da, found 281.0546 Da.

5-methyl-10-methylidenetricyclo[7.2.1.0^{1,6}]dodeca-2,5-dien-4-one (330):



To a solution of bromide **336** (40 mg, 0.143 mmol) in *t*-BuOH (40 mL) was added Cs_2CO_3 (600 mg, 1.84 mmol) and the reaction was stirred at reflux for 16 h. After allowing the reaction to cool to room temperature, it was diluted in brine (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (20 mL) and concentrated *in vacuo*. Column chromatography of the crude residue (SiO_2, 20% EtOAc in hexanes) provided dienone **337** as a colorless oil (22 mg, 76%): R_f = 0.64 (20% EtOAc in Hexanes); IR (neat) 2928, 1658, 1628 cm^{-1}; ^{1}H NMR δ 6.70 (d, *J* = 10.3 Hz, 1H), 6.29 (d, *J* = 9.6 Hz, 1H), 5.05 (s, 1H), 4.96 (s, 1H), 2.93 (bs, 1H), 2.80 (dd, *J* = 15.4, 5.8 Hz, 1H), 2.58 (ddd, *J* = 17.6, 2.9, 2.2 Hz, 1H), 2.32 (m, 1H), 2.18 (s, 3H), 2.08 (m, 1H), 1.86 (m, 1H), 1.65 (m, 1H), 1.47 (dd, 11.1, 2.2 (H, 1H), 1.26 (m, 1H); ^{13}C NMR δ 186.6, 153.5, 152.5, 128.3, 127.8, 106.3, 102.8, 44.9, 43.5, 42.8, 33.5, 29.7, 24.9, 10.5; HRMS for $C_{14}H_{17}O$ [MH+] *m/z* calc. 201.1279 Da, found 201.1282 Da.

6.3. REFERENCES

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2) Methyl 2-(3-hydroxyphenyl)acetate is commercially available from Aldrich.

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6) Amide **301** can be prepared as in reference 5 and is commercially available from Aldrich.

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List of Abbreviations

1,2-DCE	1,2-dichloroethane
1,2-DME	1,2-dimethoxyethane
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
atm	atmosphere
BHT	butylated hydroxytoluene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
BOPCl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
br	broad
Bu	butyl
CAN	ammonium cerium(IV) nitrate
cat.	catalytic
Cbz	benzyloxycarbonyl
CI	chemical ionization
cod	cyclooctodiene
m-CPBA	*m*-chloroperoxybenzoic acid
CSA	camphorsulfonic acid
d	doublet
DABCO	1,3-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	double doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIOP	(4*R*,5*R*)-(-)-*O*-isopropylidine-2,3-dihydroxy-1,4-bis (diphenylphosphino)butane
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIBALH	diisobutylaluminium hydride
DMAP	4-*N*,*N*-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide

DMTS	dimethylthexylsilyl
equiv.	equivalents
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
HRMS	high resolution mass spectrometry
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphorphoramide
imid.	imidazole
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide
LHMDS	lithium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
m	multiplet
m	meta
M	molar
Me	methyl
mol	mole
MEM	methoxyethoxymethyl
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
NBA	*N*-bromoacetamide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic tesonance
Ns	*p*-nitrobenzenesulfonyl
o	ortho
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
Pht	phthalimidyl
PIFA	[bis(trifluoroacetoxy)iodo]benzene
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl
pyr.	pyridine
PyBOP®	benzotriazolyloxy-tris[pyrrolidino]-phosphonium hexafluorophosphate
ORTEP	Oak Ridge thermal ellipsoid program
oxid.	oxidation
R	alkyl

q	quartet
qu	quintet
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBDMS or TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
tert	tertiary
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Trt	trityl
Ts	toluenesulfonyl
TsOH or *p*TSA	toluenesulfonic acid

Vita

Evan Adam Hecker was born on February 5, 1980, the son of Linda and David Hecker. He was raised in East Windsor, NJ, with his sister Dara. After graduating from Hightstown High School in June, 1997, Evan attended The College of New Jersey where he earned his B.S. in Chemistry in May of 2001. He then spent two years working as a Research Associate at Pharmacopeia, Inc. on the development of a chemokine antagonist for the treatment of COPD and is an author of several patents, both domestic and abroad. In the fall of 2003, Evan matriculated to the University of Texas, at Austin, where he undertook graduate study under the supervision of Prof. Philip D. Magnus. He currently resides in Boston, MA with his wife, Cara, and child.

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This dissertation was typed by the author.