The Pennsylvania State University

The Graduate School

Eberly College of Science

THE TOTAL SYNTHESIS OF COMPLEX MOLECULES VIA ELECTROCYCLIC RING CLOSURES OF DIVINYLPYRROLINES AND DIVINYLOXAZOLINES

A Dissertation in

Chemistry

by

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ABSTRACT

The total syntheses of the indole alkaloid natural products *cis*-trikentrin A and *cis*-trikentrin B, as well as the indolizidine natural product γ-lycorane are discussed in chapters 1 and 2. The key step in each of these syntheses is a thermal 6π-electrocyclic ring closure reaction of a divinylpyrroline. This chemistry extends our existing methodology for the synthesis of 3,4-annulated indoles to a much wider range of substitution patterns, particularly the preparation of indoles substituted at the 4, 5, 6 and 7 positions. The diastereoselective preparation of 2,4-dialkylated cyclopentanones was also examined as part of this work.

Chapters 3-5 describe our work towards the synthesis of the natural product dragmacidin E. Chemistry for the preparation of 3,4-annulated-7-hydroxyindoles, a key structural feature of dragmacidin E, was initially developed. This chemistry employed our earlier indole synthesis methodology, modified using lessons learned from our studies toward the trikentrin natural products. Pyrazine annulation chemistry was then examined, ultimately leading to the development of a 7-*exo*-Heck cyclization approach to the central 7-membered ring of dragmacidin E. This allowed for the preparation of the core ring system of the natural product.

The introduction of the remaining methyl and bromide substituents was then effected, requiring the development of conditions for a challenging halogen-selective Heck reaction. Finally, efforts were directed towards the spirocyclic guanidine ring of dragmacidin E, via either nitrile or aminonitrile intermediates.

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ACKNOWLEDGEMENTS

First and foremost I must acknowledge the love and support of my parents, Jeff and Elizabeth Huntley. I know it has been difficult for them seeing their son move so far away from home, and yet throughout they have been unquestioningly supportive of my career and life choices. That has meant more to me than I think they know.

I must also thank the many friends I have made during my time at Penn State, who have helped me maintain balance and perspective in my life through the ups and downs of graduate research. They have been a second family to me here in State College, and I could not have completed this work without them.

Finally, I would thank the many members of the Funk group I have worked with over the years for making the lab a fun and productive environment in which to work. It has truly been a privilege working with such a dedicated and talented group of people.

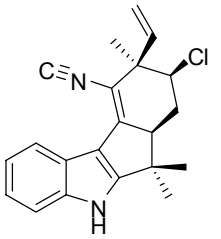
CHAPTER 1

Approaches to the Synthesis of Substituted Indoles

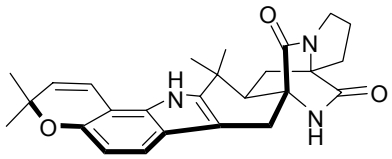
1.1 Introduction

The indole substructure is widely represented throughout both the fields of bioactive natural product chemistry[1] (Figure 1) and medicinal chemistry[2] (Figure 2). As a consequence, extensive efforts have been directed towards the development of syntheses of substituted indoles,[3] resulting in dozens of discrete approaches to this important heterocyclic system.

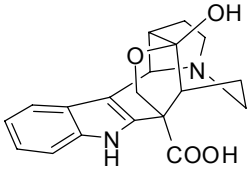
Figure 1. Examples of substituted indoles in natural product chemistry



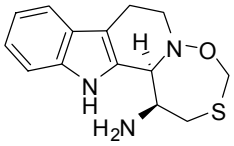
fischerindole I



stephacidin A

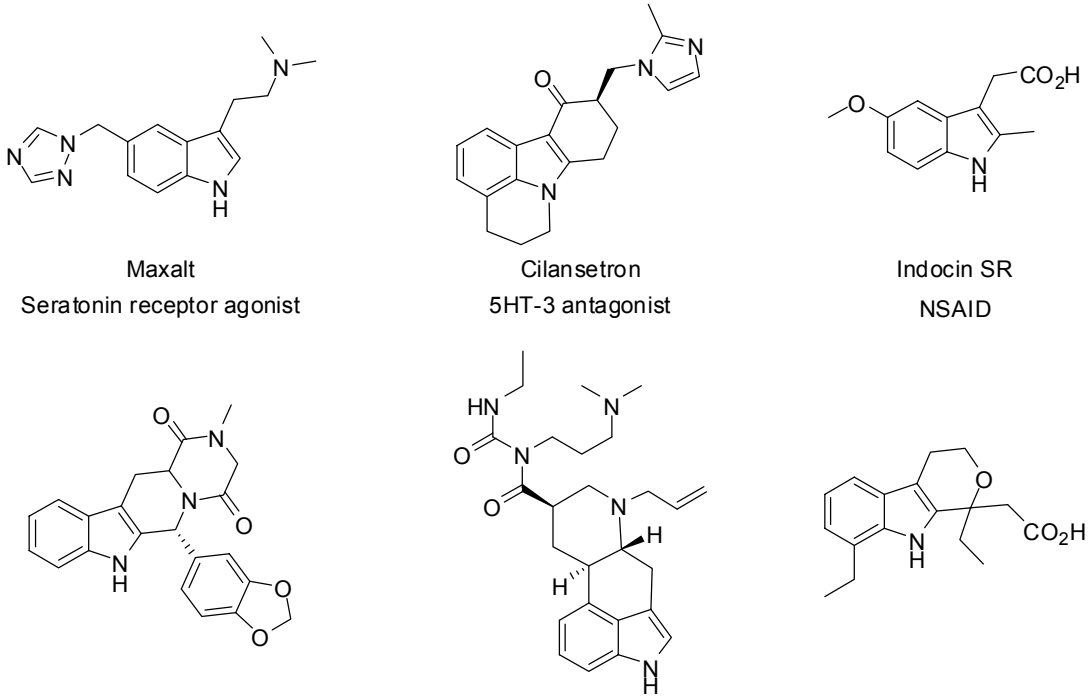


actinophyllic acid



eudistomin C

Figure 2. Examples of substituted indoles in pharmaceutical chemistry



1.2 Prior synthetic approaches to substituted indoles

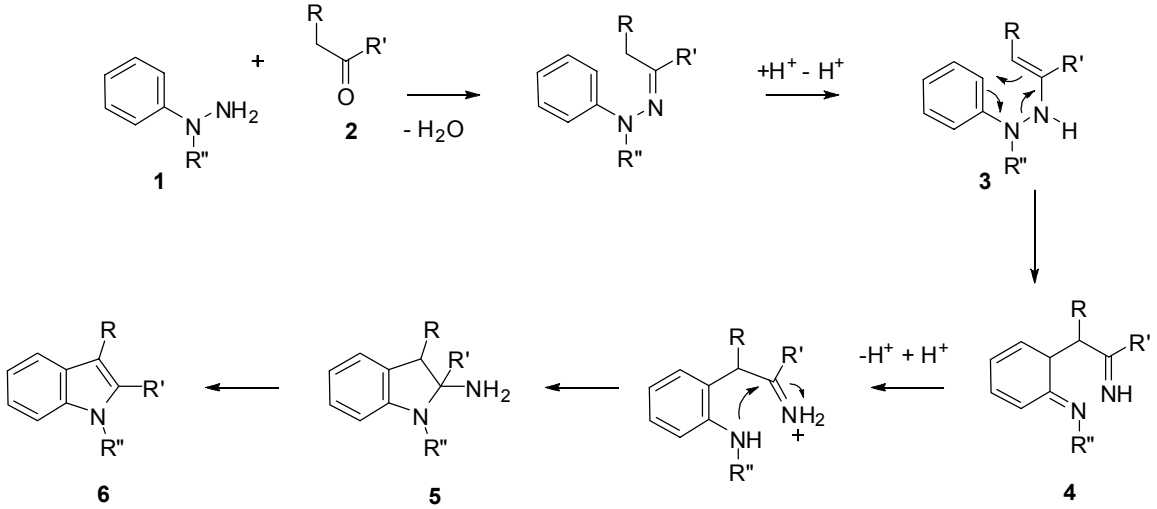
The majority of synthetic approaches to substituted indoles can broadly be classed into one of two categories, based upon the order of ring construction.

1.2.1 Indoles via annulation of an existing six-membered ring

The first and more prevalent category of indole synthetic approaches involves building the 5-membered ring onto an existing and appropriately substituted benzene ring. The classic Fischer indole synthesis[4] (Scheme 1) is an

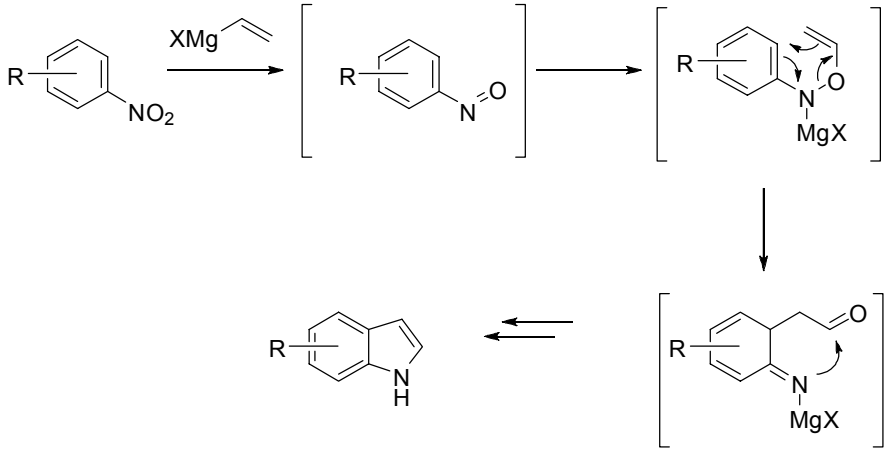
example of this general class, and utilizes the [3,3]-sigmatropic rearrangement of enamine **3** as the key carbon-carbon bond-forming step.

Scheme 1. The Fischer indole synthesis

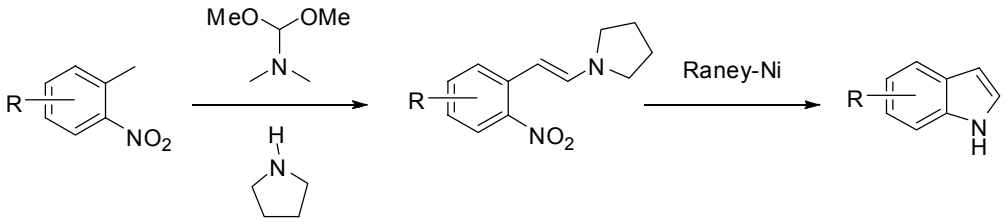


Other important examples of this class of indole synthesis include the Bartoli[5] (Scheme 2) and Leimgruber-Batcho[6] (Scheme 3) syntheses.

Scheme 2. The Bartoli indole synthesis



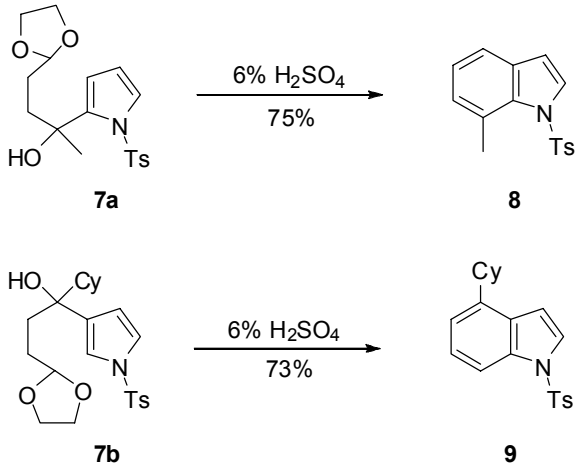
Scheme 3. The Leimgruber-Batcho indole synthesis



1.2.2 Indoles via annulation of an existing five-membered pyrrole ring

The other general class of indole syntheses involves construction of the 6-membered ring, often by making use of the inherent nucleophilicity of a pyrrole substrate. For example, under acidic conditions pyrroles **7** (Scheme 4) undergo intramolecular cationic cyclizations to indoles.[7,8]

Scheme 4. Cationic indole cyclizations



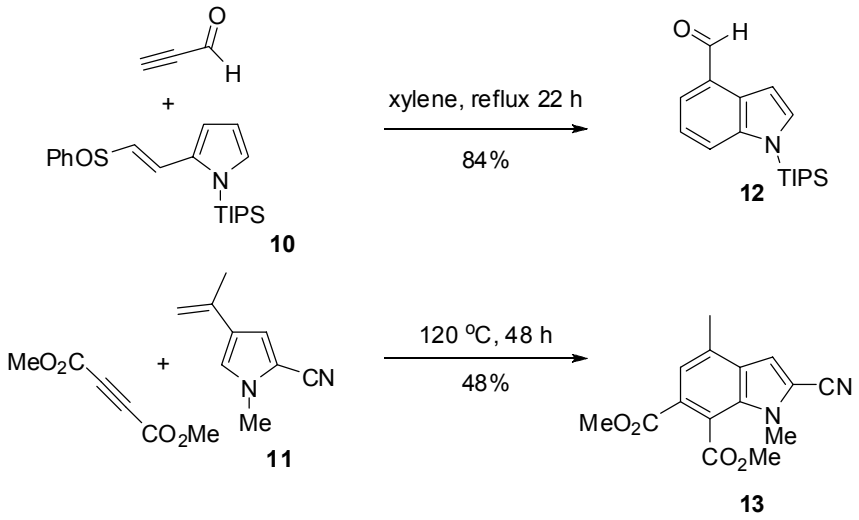
7a **8**

7b **9**

The six-membered ring has also been constructed through Diels-Alder cycloadditions (Scheme 5). Both 2-vinylpyrrole **10** and 3-vinylpyrrole **11**, for example, have been reacted with acetylene carboxylates to give rise to indoles

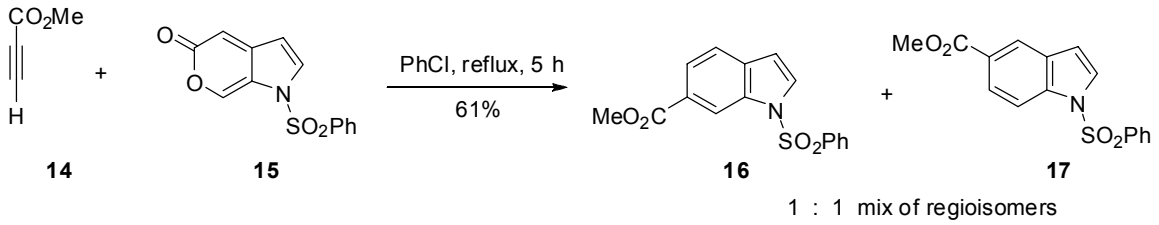
12 and **13**.[9,10] The scope of this method is extremely limited, however, since electron-withdrawing groups are often necessary on the pyrrole to prevent a competing Michael addition.

Scheme 5. Indole preparation via Diels-Alder cycloaddition



Likewise, the cycloaddition of pyrone-fused pyrroles **15** (Scheme 6)[11] is of limited usefulness due to poor regioselectivity, even with strongly polarized dienophile **14**.

Scheme 6. Preparation of indoles via pyrone cycloaddition



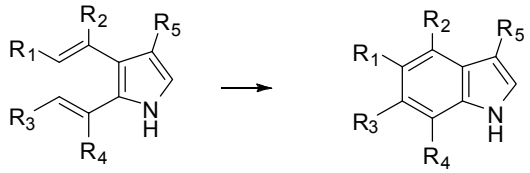
14 **15** **16** **17**

1 : 1 mix of regioisomers

A more intriguing approach to the indole heterocycle is the construction of the 6-membered ring via a 6π-electrocyclic ring closure of a divinylpyrrole substrate (Scheme 7). This methodology would allow for introduction of the

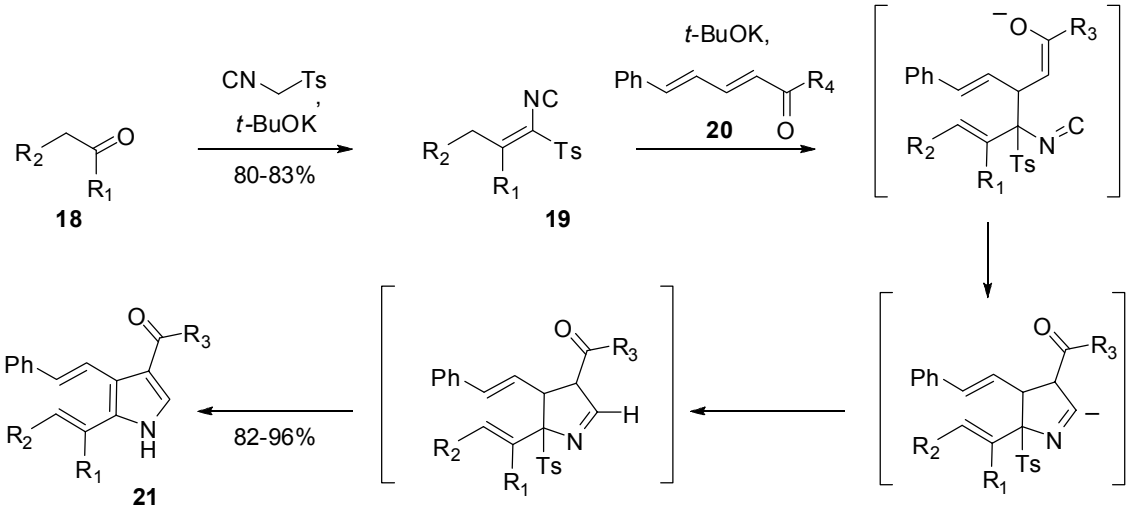
desired substituents in a regiocontrolled fashion prior to construction of the 6-membered ring.

Scheme 7. A 6π-electrocyclic ring closure approach to indoles



This approach was first investigated by the van Leusen group in 1986. Specifically, they investigated the preparation of 2,3-divinylpyrroles as potential substrates for 6π-electrocyclization to substituted indoles. To do so, they first had to develop a method for the synthesis of these substrates.

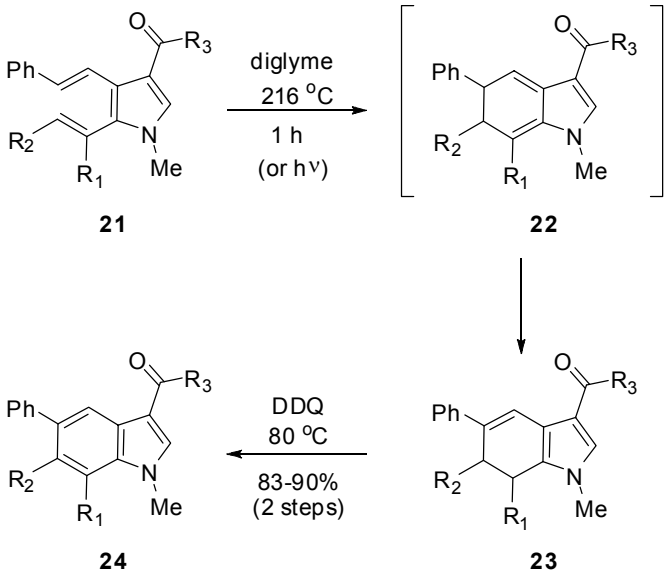
Scheme 8. Preparation of 2,3-divinylpyrroles



Beginning with an appropriate ketone or aldehyde **18** (Scheme 8), condensation with tosylmethyl isocyanide gave alkenyl isocyanides **19**.[12] Upon treatment with base and an appropriate Michael acceptor **20**, condensation to the pyrrole **21** was observed, presumably via the mechanistic sequence shown.

With these substrates in hand, electrocyclization conditions were examined. It was found that these divinylpyrroles **21** underwent a smooth, thermal electrocyclic ring closure in refluxing diglyme (216 ^{o}C), to give, after a 1,5-sigmatropic hydrogen shift, dihydroindoles **23**.[13] These were typically treated directly with DDQ without isolation to give indoles **24**.

Scheme 9. Preparation of indoles via electrocyclization of divinylpyrroles

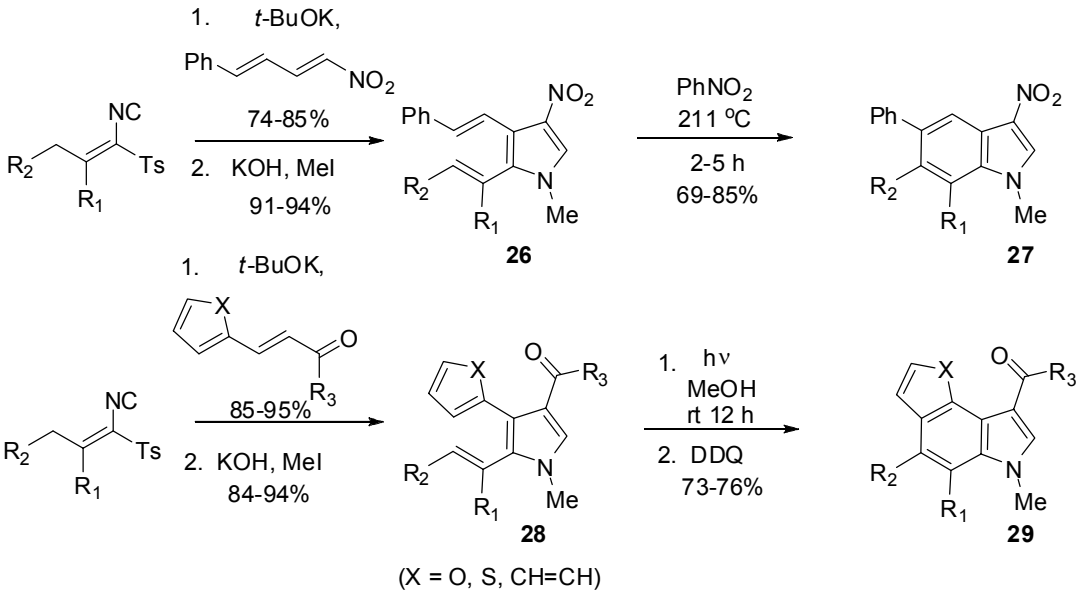


The conditions required for this thermal electrocyclization (216 ^{o}C) are relatively harsh. This is unsurprising, given the loss of aromaticity in the initial electrocyclization to intermediate **22**. It should be noted however, that 6π-electrocyclization of these same substrates was also accomplished in comparable yield under photochemical conditions with a UV immersion lamp at room temperature.

With these initial results in hand, attempts were made to expand the scope of the overall sequence. Nitropyrroles **26** were prepared[14] by an analogous

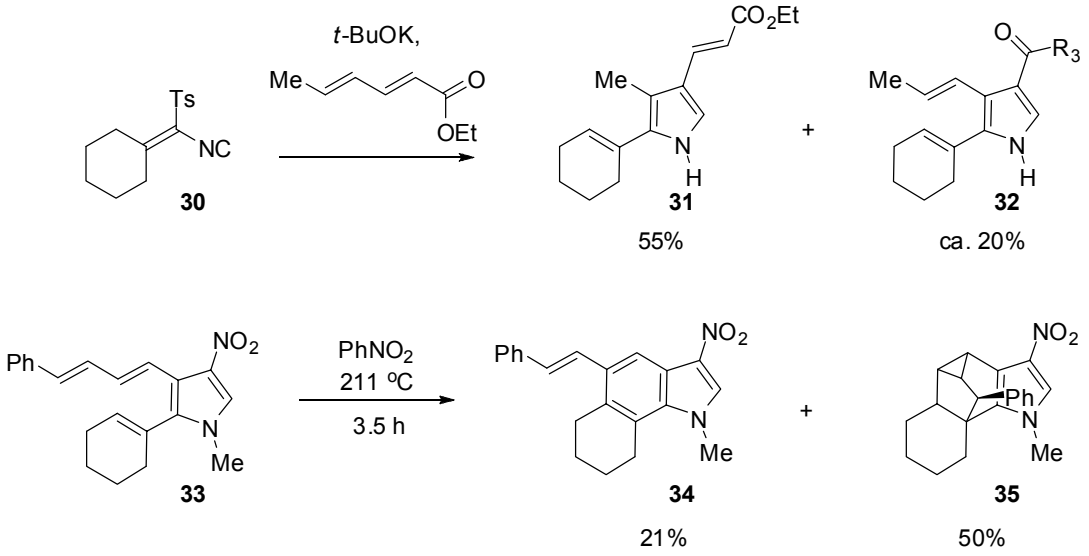
sequence to the earlier acylpyrroles, and were found to undergo electrocyclic ring closure and aromatization in refluxing nitrobenzene (Scheme 10). 2-Vinyl-3-*aryl*-pyrroles **28** were also prepared[13] and while they were unreactive under thermal conditions, did undergo electrocyclic ring closure under photochemical conditions.

Scheme 10. Preparation of nitro- and aryl-fused indoles



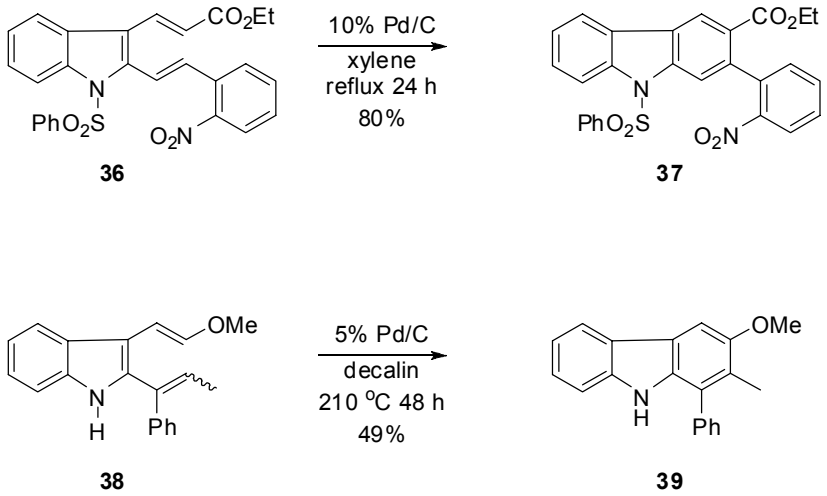
Besides these examples however, the scope of this methodology appears to be limited. Attempts to prepare 3-propenyl pyrrole **32** led instead to the preferential formation of isomeric pyrrole **31** (Scheme 11).[13] Preparation of 5-alkenyl indole **34** was also problematic, due to the competitive formation of tetracycle **35,** presumably via intramolecular trapping of the 5,6-dihydroindole intermediate. In addition to these concerns, this methodology requires the presence of an electron withdrawing substituent at the C(3) position (indole numbering). Every example shown to date also incorporates a substituent at C(7). The overall synthetic utility of the method is therefore limited.

Scheme 11. Attempted preparation of 5-alkyl and 5-alkenyl indoles



In addition to the electrocyclization of 2,3-divinylpyrroles, the corresponding cyclizations of 2,3-divinyl*indoles* has been employed in the preparation of carbazoles. Representative examples are shown in Scheme 12.[15,16]

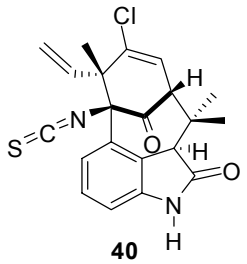
Scheme 12. 6π-electrocyclization of 2,3-divinylindoles



1.2.3 Indoles via the sequential construction of both 5- and 6-membered rings

An alternate approach to the synthesis of indoles via electrocyclic ring closure that avoids the use of pyrrole-based trienes was recently developed by Thomas Greshock of the Funk group.[17] This methodology was inspired by our interest in the complex alkaloid welwitindolinone C isothiocyanate (**40**)[18] (Figure 3), which incorporates an oxindole, bridged at the C(3) and C(4) positions.

Figure 3. Welwitindolinone C isothiocyanate

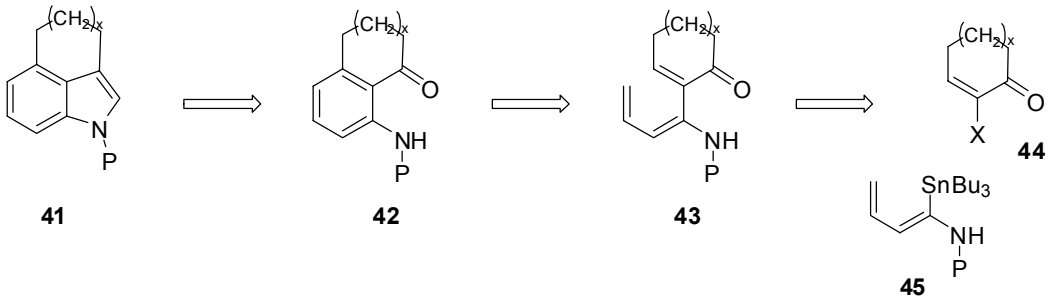


40

welwitindolinone C isothiocyanate (welwistatin)

A conceptual overview of our group's approach to indoles of this type is shown in Scheme 13. It was envisioned that 3,4-bridged indoles **41** could be formed from ketoaniline **42**. This aniline would in turn arise from the electrocyclization and oxidation of trienecarbamate **43**, which would result from the Stille coupling of α-halocycloalkanone **44** with dienamide stannane **45**.

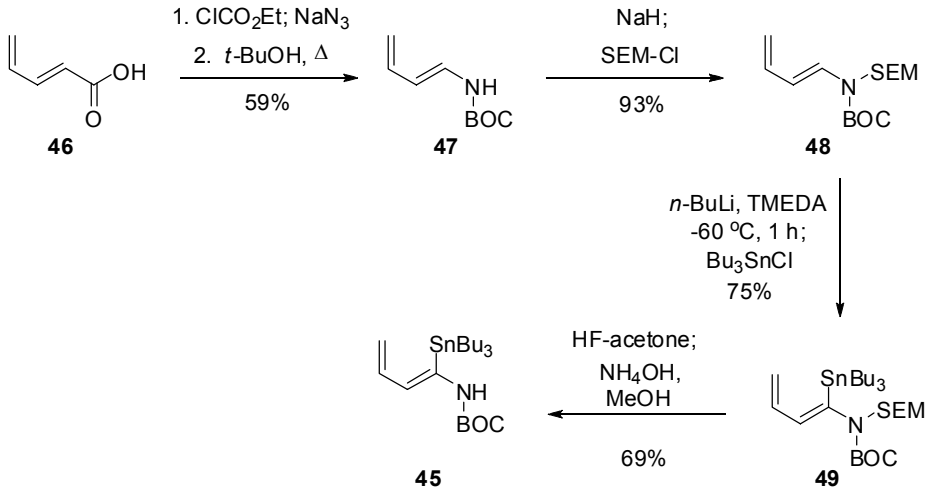
Scheme 13. An approach to 3,4-annulated indoles



41 **42** **43** **44** **45**

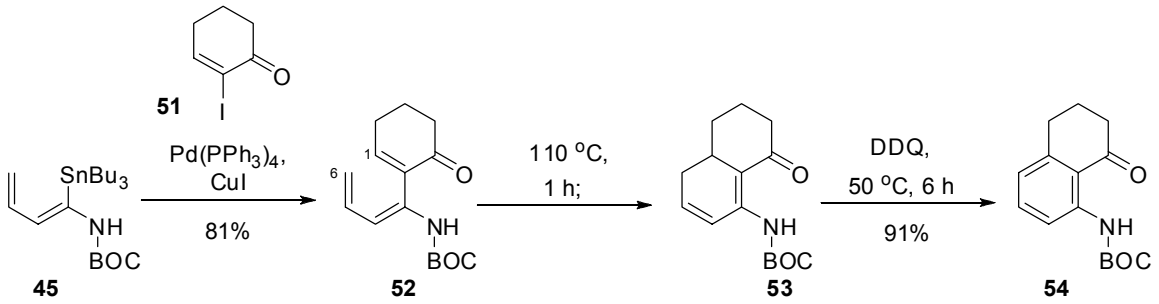
The initial synthetic challenge therefore was the preparation of dienamide stannane **45**. This synthesis was accomplished via the conditions shown in Scheme 14. Initially, the Overman diene **47**[19] was prepared from acid **46** under standard, Curtius rearrangement, conditions. SEM protection of the amide nitrogen, followed by lithiation of the diene, directed by the BOC-carbamate functionality, allowed for preparation of stannane **49**. Removal of the SEM-protecting group provided the desired stannane synthon **45**.

Scheme 14. Preparation of stannyl diene **45**



Stannane **45** was found to readily undergo Stille coupling with an α-haloenone such as 2-iodo-2-cyclohexen-1-one (**51**) in the presence of $Pd(PPh_3)_4$ and CuI to give triene **52**. In the key step of the overall sequence, triene **52** was then observed to undergo a remarkably facile, thermal electrocyclic ring closure reaction in refluxing toluene, giving dihydroaniline **53**. This dihydroaniline was oxidized without isolation, giving rise to ketoaniline **54**.

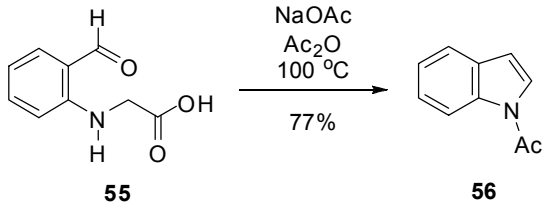
Scheme 15. Preparation and 6π-electrocyclization of a triene carbamate



The relatively mild conditions under which the electrocyclization of triene **52** proceeded led us to propose that a "push-pull" effect may be operative in this system. Specifically, we suggested that the electron-donating carbamate substituent, capable of donating electron density to the C(6) terminus of the π-system, combined with the electron-withdrawing ketone substituent which removes electron density from the C(1) terminus, act cooperatively to lower the activation energy and accelerate the reaction. A computational study, inspired in part by our results, supports this proposal (*vide infra.*).

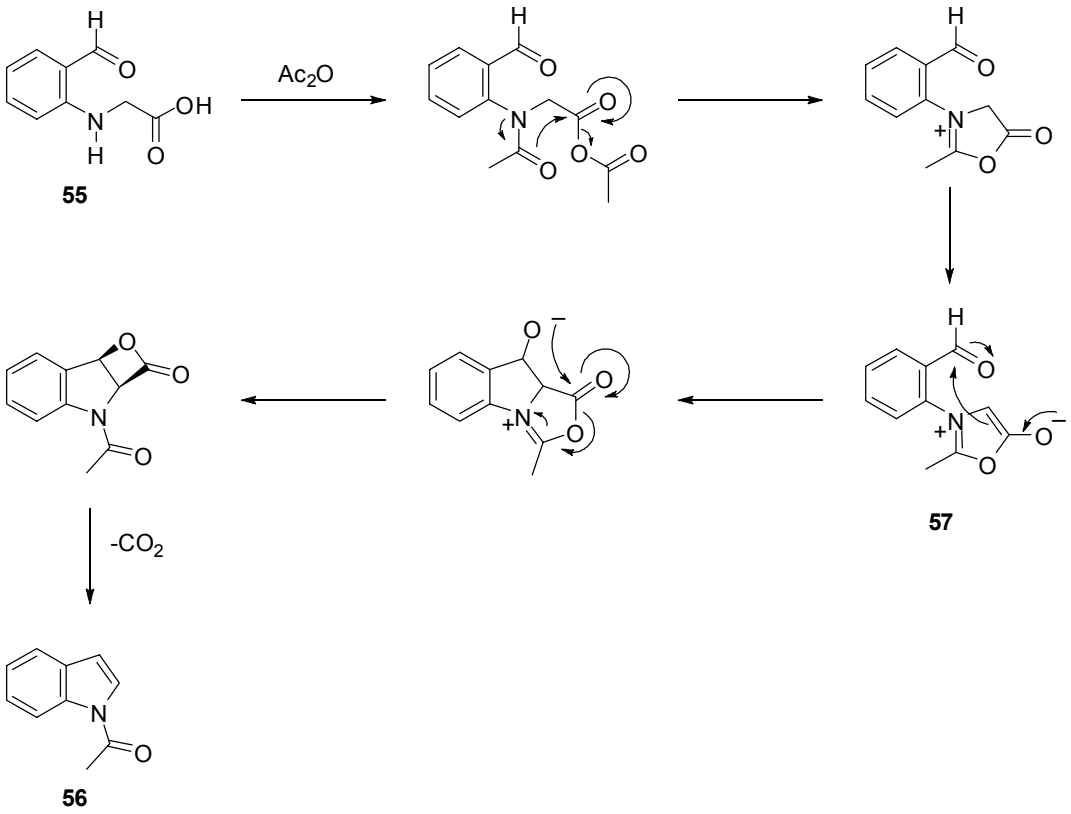
The last remaining problem in the overall indole synthesis was conversion of the *o*-substituted aniline **54** (or some derivative thereof) to the corresponding indole. A search of the literature revealed that this transformation had been effected for simple aryl glycines such as **55** by treatment with acetic anhydride as far back as 1915 (Scheme 16).[20]

Scheme 16. Acetic anhydride mediated indole cyclization



A possible mechanism for this transformation involving münchnone intermediate **57** is outlined in Scheme 17.

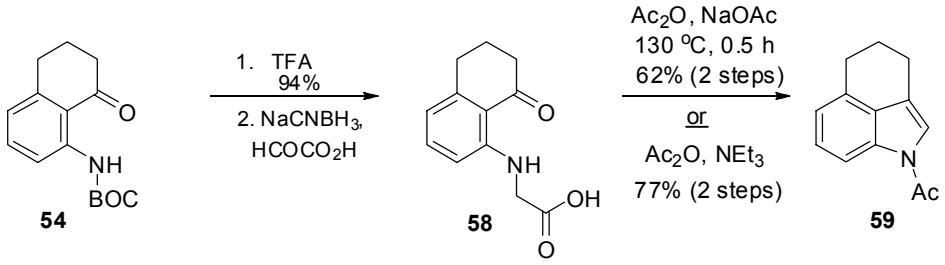
Scheme 17. Proposed münchnone cyclization mechanism



55 **57** **56**

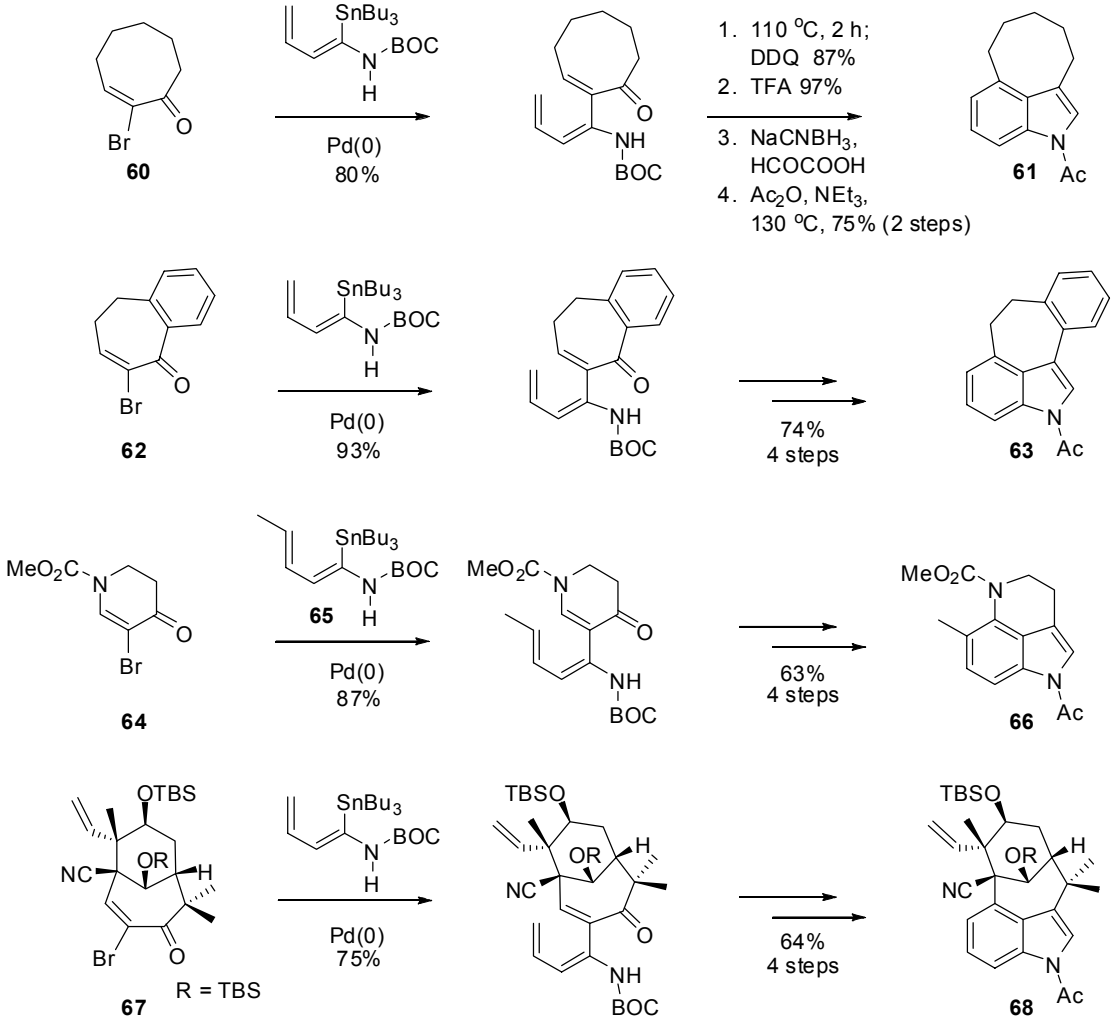
The direct application of this methodology to 3,4-annulated indole ring systems is shown in Scheme 18. Following deprotection of ketoaniline **54,** the acetic acid sidechain was introduced via reductive amination. The subsequent cyclization then proceeded in decent yield under conditions employed by Råileanu[21] (Ac_2O, NaOAc, 130 ^oC). Further studies showed that simple replacement of the acetate base with triethylamine, a modification that had previously been employed in a related pyrrole synthesis,[22] led to improved yields.

Scheme 18. Acetic anhydride mediated preparation of a 3,4-annulated indole



With this initial example in hand, the scope of the methodology for the more general synthesis of 3,4-substituted indoles was examined. Selected results from this investigation are shown in Scheme 19.

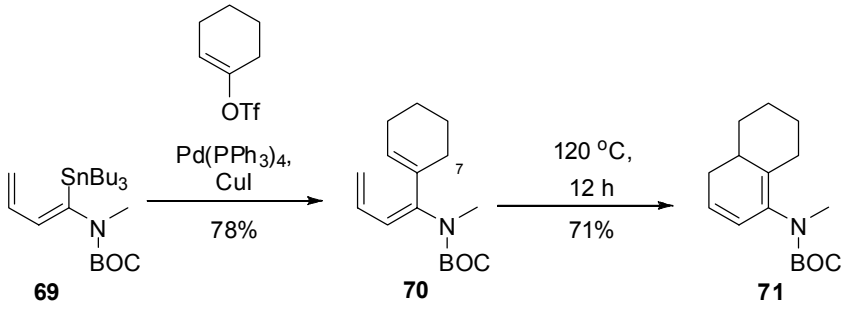
Scheme 19. Additional examples of 3,4-annulated indoles



As shown above, a variety of indole ring systems can be formed via this methodology. Various ring sizes are tolerated, (examples **61**, **63**), as is the incorporation of heteroatomic (**66**) and aryl-fused (**63**) bridging rings. Furthermore, additional substituents can be introduced by use of an appropriately substituted stannyl diene, as demonstrated by the preparation of indole **66**. The scope of such substitution is limited however by the availability of substituted dienecarbamates **65**. The penultimate example of this methodology is the preparation of indole **68**, synthesized as part of our group's studies towards the synthesis of welwistatin.[23]

One further electrocyclization was attempted with trienecarbamate **70**, in an attempt to probe the validity of our "push-pull" acceleration hypothesis.[24] This triene, which lacks the electron-withdrawing carbonyl substituent at C(7), was observed to require higher temperature and extended reaction time in order to undergo electrocyclization, in accordance with our predictions.

Scheme 20. 6π-electrocyclization of an electron rich trienecarbamate



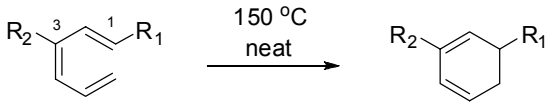
However, the 6π-electrocyclizations performed in this study were observed to proceed under significantly lower temperatures than most electrocyclic closures. It would appear that the donating carbamate functionality facilitates the electrocyclic closure.

1.3 Substituent effects in 6π-electrocyclization reactions

1.3.1 Experimental studies

Our group was not the first to consider substituent effects in thermal 6π-electrocyclization reactions. In 1973 Spangler and coworkers[25] systematically investigated the effect of alkyl substituents at the C(1) and C(3) positions of 1,3,5-hexatrienes (Scheme 21). Three conclusions were drawn from this study. Firstly, the rate of electrocyclization increased with the addition of alkyl substituents at either the C(1) or C(3) position. In addition, the rate increase was greater for substitution at the C(3) position than at C(1). Finally, the rate of electrocyclization increased as larger alkyl groups were introduced.

Scheme 21. Spangler's 6π-electrocyclization kinetic study

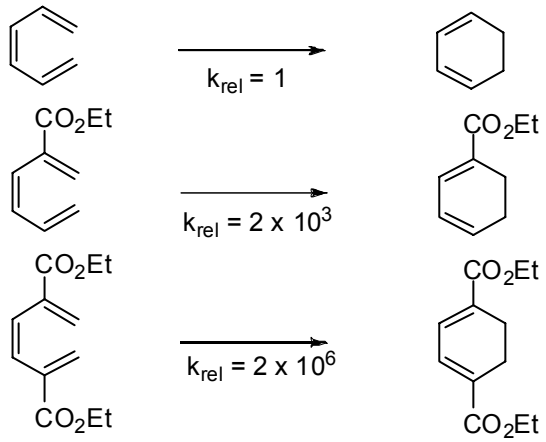


R_1	R_2	K ($\times 10^{-5}$ sec^{-1})	R_1	R_2	K ($\times 10^{-5}$ sec^{-1})
-H	-H	24.1	-H	-H	24.1
-Me	-H	28.3	-H	-Me	88.8
-Et	-H	66.9	-H	-Et	92.8

There were two possible explanations offered for these results. Firstly, the authors proposed that the increase in rate could be caused by an increase in electron density of the π-system by the donating alkyl substituents. The other explanation offered was that the presence of a C(3) substituent in particular may help to increase the equilibrium concentration of the reactive, all-*s*-*cis* conformation.

A second experimental study[26] on the effect of electron withdrawing groups on the cyclization of hexatrienes was conducted by Marvel and coworkers. They established that ester groups at C(2) and C(5) (Scheme 22) substantially increased the rate of reaction. In part they attributed this remarkable effect to the stabilization of π-orbitals at C(2) and C(5) in the transition state, as they are twisted out of conjugation.

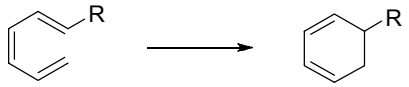
Scheme 22. Marvel's 6π-electrocyclization kinetic study



1.3.2 Theoretical studies

Substituent effects in 6π-electrocyclization reactions have also been the subject of several computational studies. Houk and co-workers performed[27] both semi-empirical (AM1) and *ab initio* calculations (MP2/6-31G*) on a range of substituted 1,3,5-hexatrienes in order to identify the effect of (predominantly withdrawing) substituent effects on the electrocyclization. At the highest level of theory, every C(1) substituent tested increased the activation energy. (Scheme 23) In part, this is attributed to stabilization of the triene that is largely lost in the transition state.

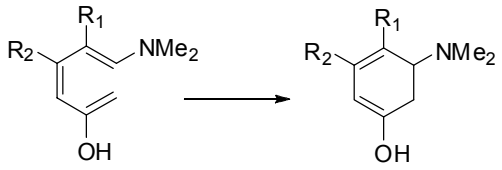
Scheme 23. Houk's computational study of 1-substituted hexatriene cyclization



R	$\Delta H^{\ddagger}$ (kcal mol^{-1})
-H	26.0
-F	26.4
$-CH_3$	30.3
-CN	29.1
-CHO	26.1
-NO	31.0
$-BH_2$	29.8

A later study (Scheme 24)[28] examined the effect of substituents at the C(2) and C(3) positions of 1-(dimethylamino)-1,3,5-hexatrienes using the B3LYP functional basis sets. This study showed dramatic (11-15 kcal mol^{-1}) lowering of activation energy by electron withdrawing ($-SO_2Ph$, $-NO_2$, $-C{=}NMe_2^+$) substituents at C(2) and a more modest decrease in activation energy by electron withdrawing substituents at C(3).

Scheme 24. Houk's computational study of 2- and 3-substituted hexatrienes

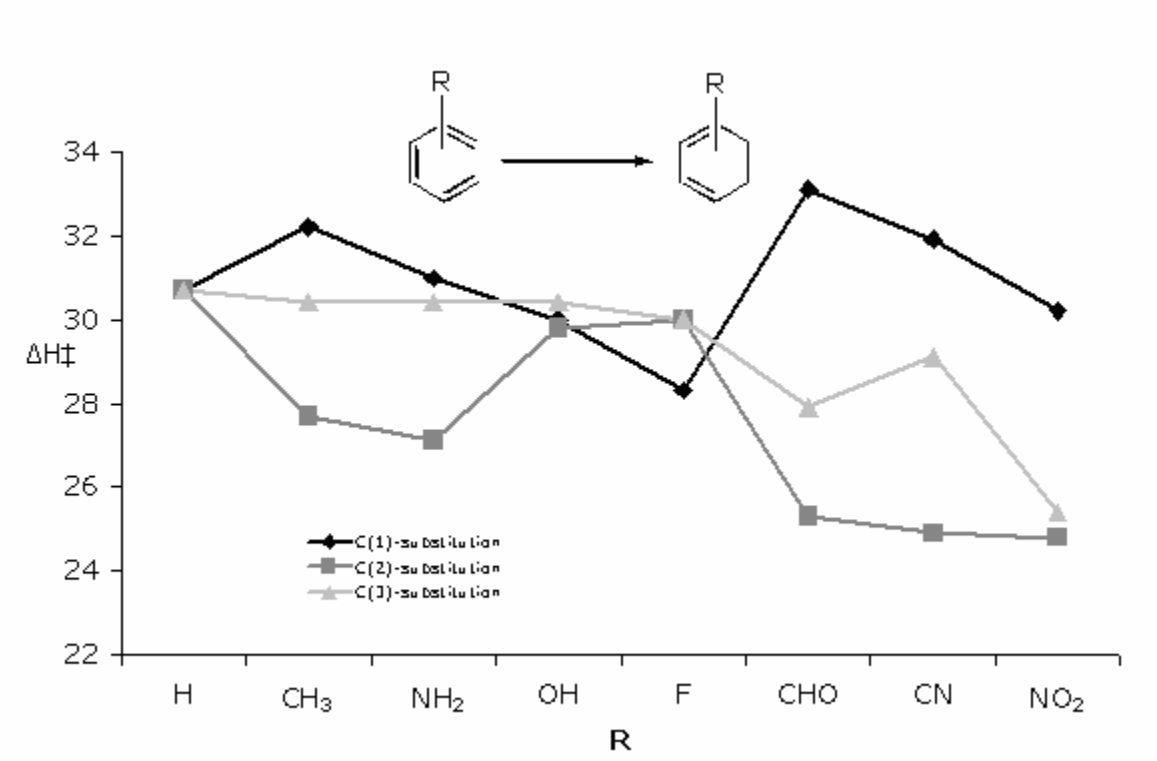


R_1	R_2	$\Delta H^{\ddagger}$ (kcal mol^{-1})
-H	-H	27.6
-H	$-CO_2Me$	23.2
$-NO_2$	$-CO_2Me$	12.5
$-C{=}NMe_2^+$	$-CO_2Me$	11.1
$-SO_2Ph$	$-CO_2Me$	7.5

The most comprehensive study, inspired in part by our own results, was performed Fu and Liu,[29] using the ONIOM method using QCISD(T) and B3LYP *ab initio* calculations. In this study, 6π-electrocyclization activation energies were calculated for 21 monosubstituted and 378 disubstituted 1,3,5-hexatrienes.

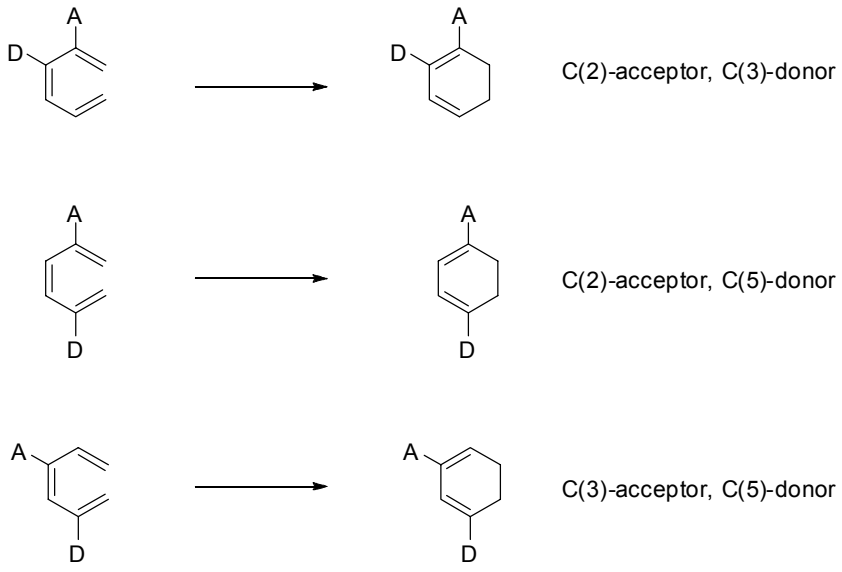
The calculated activation energies for monosubstituted hexatrienes, shown in Figure 4, indicate that substitution at C(2) or C(3) lowers the activation energy for cyclization for *both* electron donating and electron withdrawing substituents. Furthermore, the effect is greater at C(2) than at C(3), and is greater for withdrawing groups than for donating groups. At C(1), no clear effect is observed.

Figure 4. Fu and Liu's computational study of 6π-electrocyclization of monosubstituted hexatrienes



Following these results, the activation energies for every possible *disubstituted* 1,3,5-hexatriene with these same seven functional groups were calculated, in an effort to determine the best possible placement of donor and acceptor groups for the purposes of electrocyclization. They concluded that the arrangements shown in Scheme 25 should be extraordinarily rapid, as a result of what they call “captodative substitution”, or the matching of electron donating and withdrawing groups. This is essentially the “push-pull” argument we originally made with our indole syntheses, which fall under the C(2)-acceptor, C(3)-donor grouping.

Scheme 25. Preferred substitution patterns for “captodative substitution”



CHAPTER 2

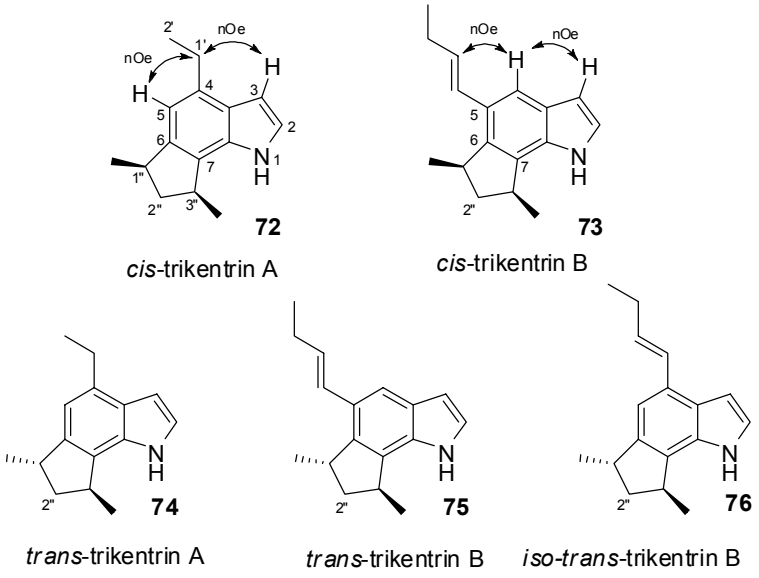
Total Syntheses of (±)-*cis*-Trikentrin A, (±)-*cis*-Trikentrin B and (±)-γ-Lycorane

2.1 The trikentrin family of natural products

2.1.1 Isolation and biological activity

The trikentrin series of polyalkylated indoles (Figure 5) were isolated by Capon *et al*. from the marine sponge *Trikentrion flabelliforme*, collected from coastal waters off Darwin, Australia.[30] A crude mixture of the trikentrins was shown to exhibit antimicrobial activity against the gram positive bacteria *Bacillus subtilus*, although the effect was not quantified. The least abundant components, *cis*-trikentrin B (**73**) and *iso*-*trans*-trikentrin B (**76**), were inseparable.

Figure 5. The trikentrin alkaloids

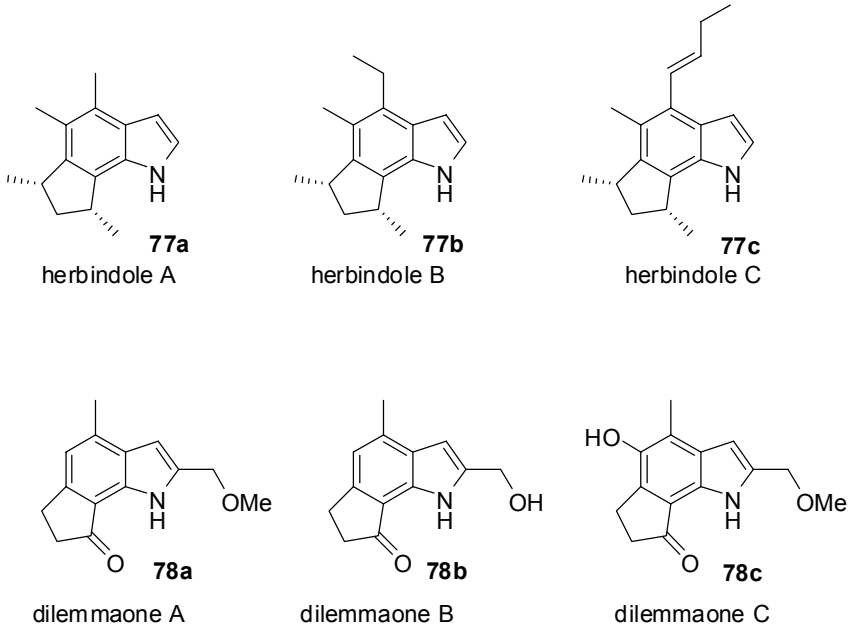


The structures and relative configurations of the trikentrin alkaloids, which were isolated as unstable oils, were determined by a combination of mass

spectrometry, IR as well as 1- and 2-D NMR experiments. In particular, the nOe experiments illustrated in Figure 5 demonstrated that the A series contained a 4,6,7-substituted indole core, as opposed to the B series, substituted at the 5,6 and 7-positions. The *cis*-relative stereochemistry of **72** and **73** was inferred by the presence of dramatically nonequivalent methylene protons at C(2”), as opposed to the near equivalence of the C(2”) methylene protons of alkaloids **74**, **75**, and **76**.

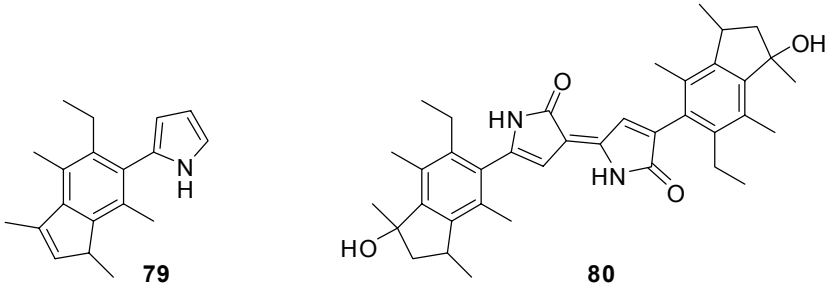
Other, related natural products include the herbindole **77**[31] and dilemmaone **78**[32] alkaloids (Figure 6). Herbindoles A, B and C, which were isolated from the sponge *Axinella sp.*, demonstrate cytotoxicity against KB cells at MIC values of 5 mg/mL, >10 mg/mL and 10 mg/mL respectively. No biological activity has been reported for the dilemmaones.

Figure 6. The herbindole and dilemmaone natural products



The route by which these indole alkaloids are formed in nature is unclear. However, the absence of substituents at the C(3) position suggests that tryptophan is likely not the precursor to these natural products. Further evidence supporting this hypothesis is provided by the isolation of indane natural products trikentramine (**79**)[33] and trikendiol (**80**)[34] from the closely related sponge *Trikentrion loeve* (Figure 7).

Figure 7. Related natural products trikentramine (**79**) and trikendiol (**80**)



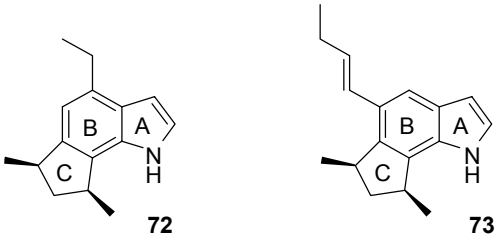
79 trikentramine

80 trikendiol

2.2. Prior approaches to the synthesis of the trikentrin natural products

The intriguing structures of the trikentrin alkaloids have led a number of groups to develop racemic[35] and enantioselective[36] synthetic approaches to the various members of the family. The synthetic strategy behind each approach can broadly be described in terms of the order of ring construction, as defined in Figure 8.

Figure 8. Ring labeling of the trikentrin natural products



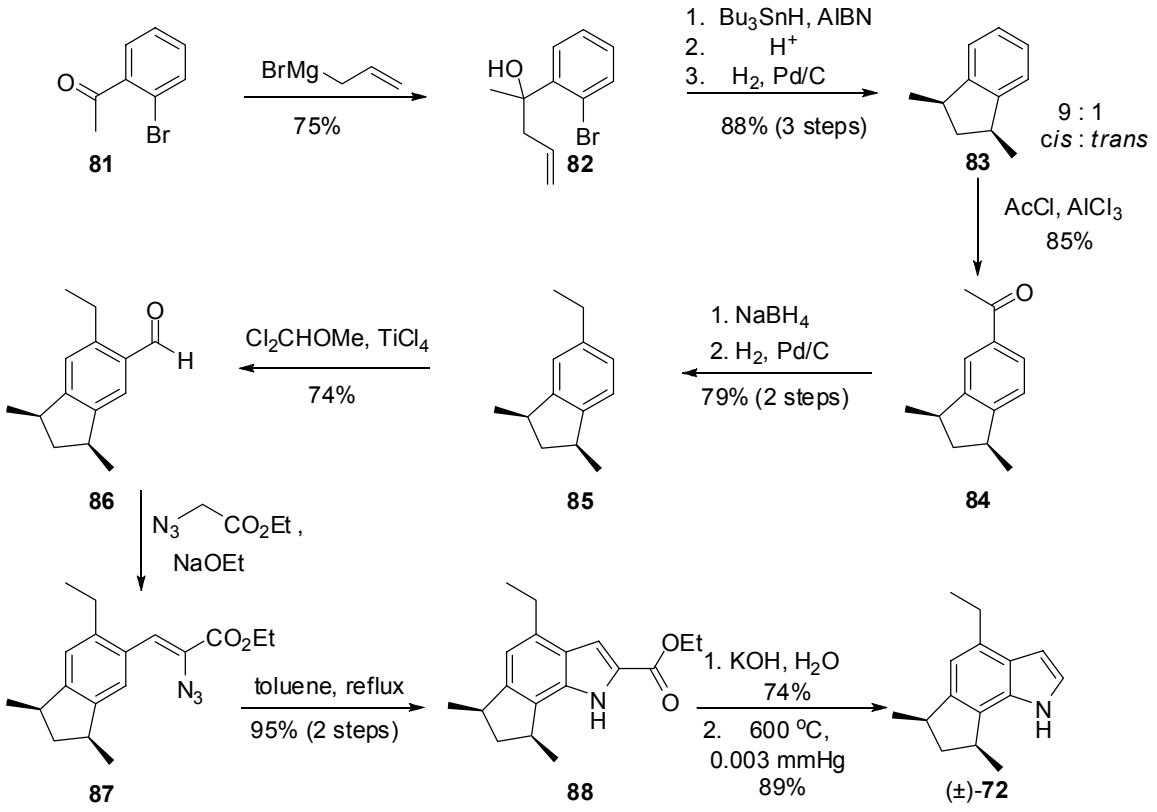
72 *cis*-trikentrin A

73 *cis*-trikentrin B

2.2.1 B → BC → BCA approaches

The Macleod group[35a] was the first to disclose a synthesis of a member of the trikentrin series, by the sequential elaboration of the C and A rings from an initial B ring core. Specifically, the addition of an allyl Grignard reagent to 2-bromoacetophenone (**81**) provided alcohol **82**. Radical ring closure effected formation of the C-ring, and was followed by facile elimination of the tertiary alcohol and hydrogenation to dimethylindane **83**.

Scheme 26. Macleod's synthesis of (±)-*cis*-trikentrin A (**72**)

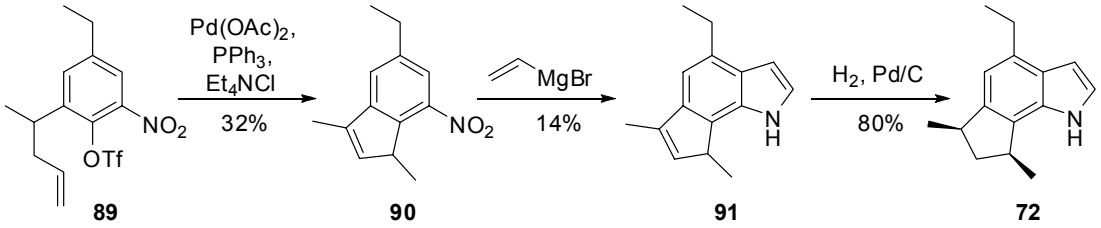


Regiospecific acylation of **83** under Friedel-Crafts conditions then furnished acetylindane **84**. Following deoxygenation, a second regiospecific

acylation was performed, giving formylindane **86** which was elaborated to the indole **88** via vinyl azide **87**. Saponification of this ester gave the corresponding acid, which was decarboxylated to the natural product by flash vacuum pyrolysis.

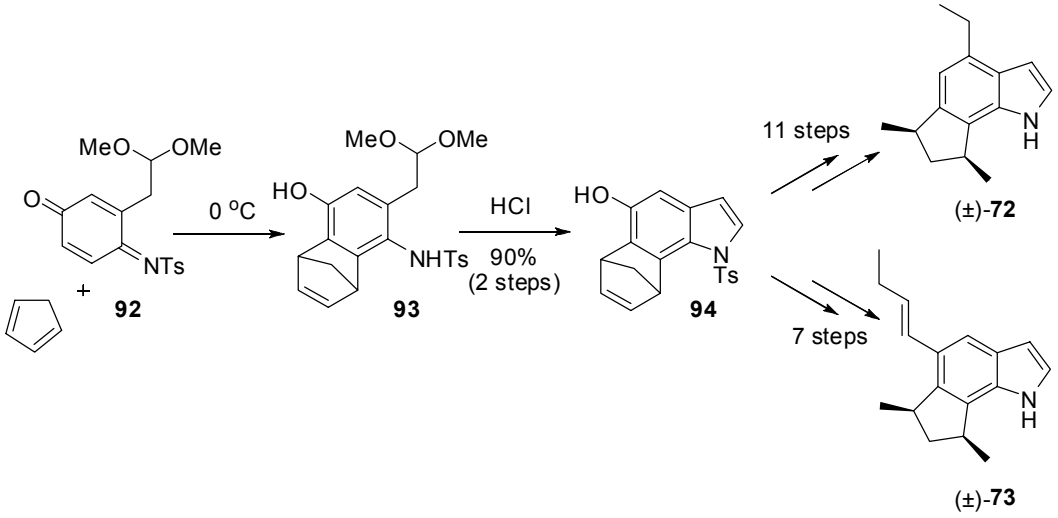
The Blechert group employed a similar approach,[35f] (Scheme 27) in which triflate **89** was subjected to Heck cyclization conditions to give, after double bond migration, nitroindene **90**. Subsequent Bartoli indole closure proceeded in poor yield to give tricycle **91**. Completion of the synthesis was effected by catalytic hydrogenation.

Scheme 27. Blechert's synthesis of (±)-*cis*-trikentrin A (**72**)



The third and most recent group to undertake a B → BC → BCA approach to the trikentrin ring system was the Kerr group, who utilized this strategy in racemic syntheses of both *cis*-trikentrin A and B.[35g,h] Beginning with quinone imine **92** (Scheme 28), cycloaddition with cyclopentadiene gave indane **93**. Upon hydrolysis of the acetal functionality, intramolecular condensation of the revealed aldehyde onto the tosylamide nitrogen effected formation of the indole A-ring. This common intermediate **94** was elaborated to both (±)-*cis*-trikentrin A (**72**), and (±)-*cis*-trikentrin B (**73**).

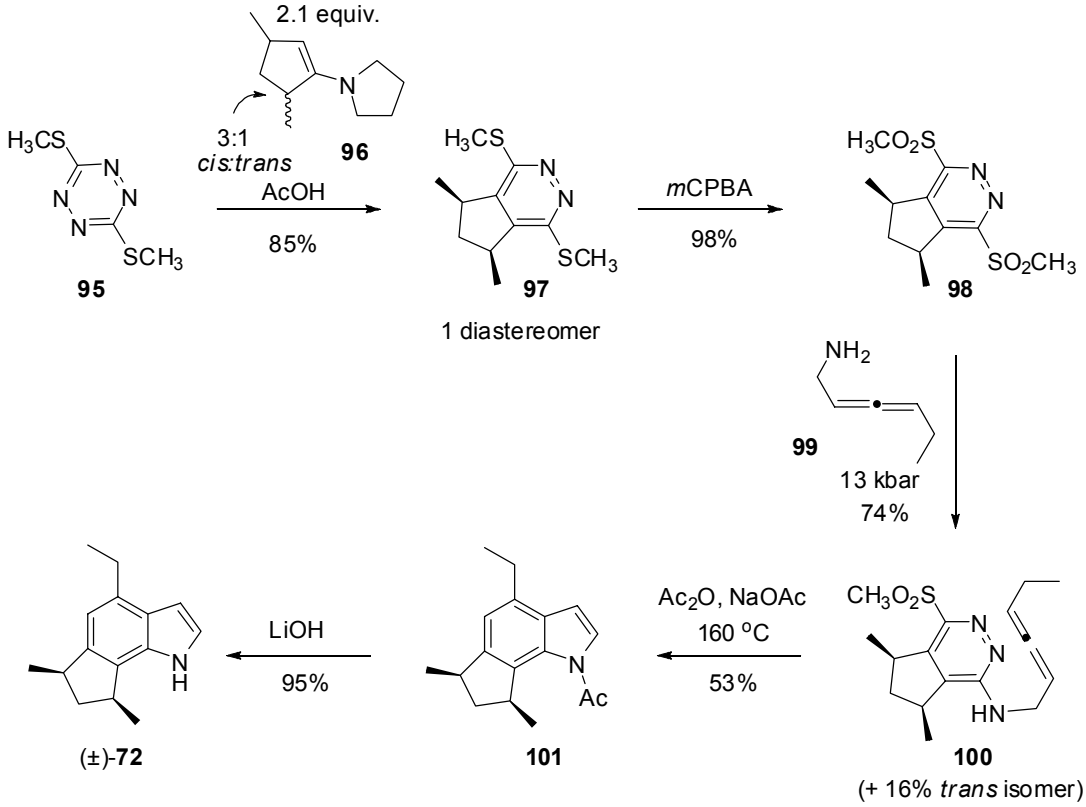
Scheme 28. Kerr's Synthesis of (±)-*cis*-trikentrin A (**72**) and B (**73**)



2.2.2 C → ABC approaches

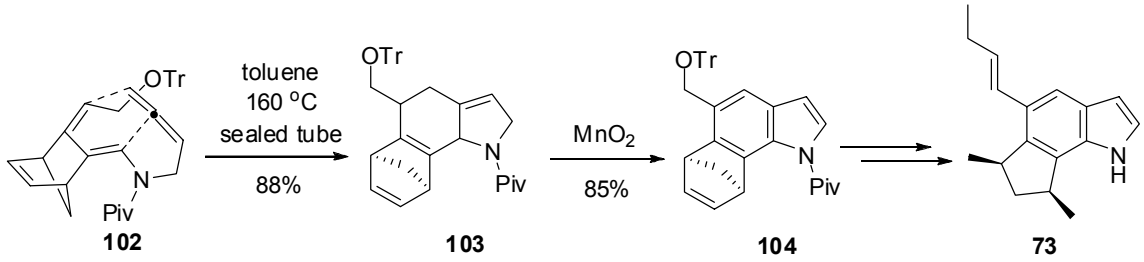
The Boger group undertook a conceptually distinct approach[35e] to the natural product that began with the cyclopentyl C-ring, from which the A and B rings were appended (Scheme 29). Specifically, heteroaromatic azadiene Diels-Alder reaction of tetrazine **95** with a two-fold excess of enamine **96** gave, after loss of dinitrogen and pyrrolidine, exclusively *cis*-dimethyl diazine **97**. After oxidation of **97** to bis-sulfone **98**, mono-displacement of sulfinate with allenylamine **99** (prepared in two steps and 22% yield from BOC-propargylamine) under high pressure conditions gave aminodiazine **100**, together with a small quantity of the *trans* epimer. Cycloaddition of the acetylated derivative, followed by elimination of both dinitrogen and methylsulfinate, gave *N*-acetyl-*cis*-trikentrin A (**101**), from which the racemic natural product **72** was readily obtained.

Scheme 29. Boger's synthesis of (±)-*cis*-trikentrin A (**72**)



Subsequent to Boger's synthesis of (±)-*cis*-trikentrin A, Kanematsu made use of similar allenyl cycloadditions in racemic[35b] and enantioselective[36b] syntheses of *cis*-trikentrin B (Scheme 30). In this sequence, alleneamide **102** underwent a thermal IMDA reaction to give tetrahydroindole **103**. Aromatization with MnO_2 then allowed for the isolation of indole **104**, which was elaborated to (+)-*cis*-trikentrin B (**73**).

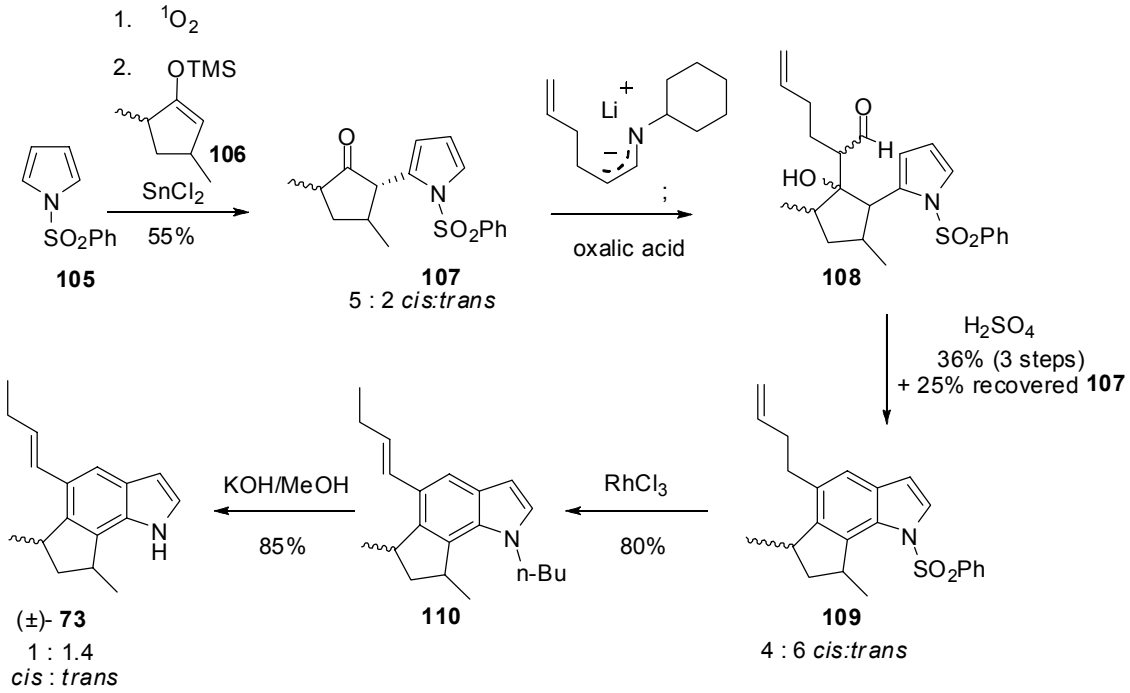
Scheme 30. Kanematsu's synthesis of (+)-*cis*-trikentrin B (**73**).



2.2.3 C → CA → CAB approaches

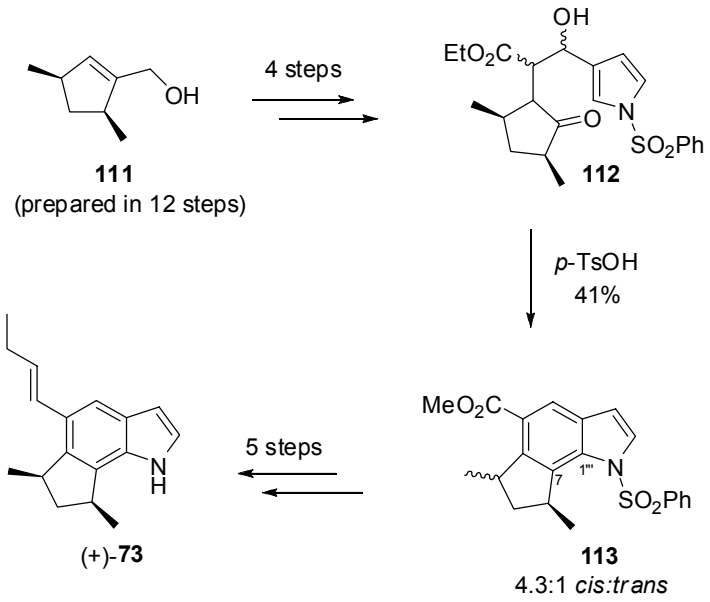
The final strategy that has been developed involves coupling of the C and A 5-membered rings, followed by later construction of the 6-membered B ring. Natsume made use of this strategy in both racemic[35d] and enantioselective[36a] syntheses of the trikentrin alkaloids. In his racemic route (Scheme 31), the singlet oxygen photocycloadduct of pyrrole **105** reacted with a mixture of silylenol ethers **106** and the resultant ketone **107** was then further elaborated to aldehyde **108**. Under strongly acidic conditions, condensation of the nucleophilic pyrrole onto the pendant aldehyde effected closure of the central B-ring, giving indole **109** as a mixture of diastereomers. This mixture was then transformed into a mixture of (±)-*cis*- and (±)-*trans*-trikentrin A.

Scheme 31. Natsume's synthesis of (±)-*cis*- and (±)-*trans*-trikentrin B



Natsume's enantioselective approach[36a] (Scheme 32) also employed the cationic cyclization of an AC precursor, in this case to form the C(7)-C(1'") bond.

Scheme 32. Natsume's synthesis of (+)-*cis*-trikentrin B (**73**)



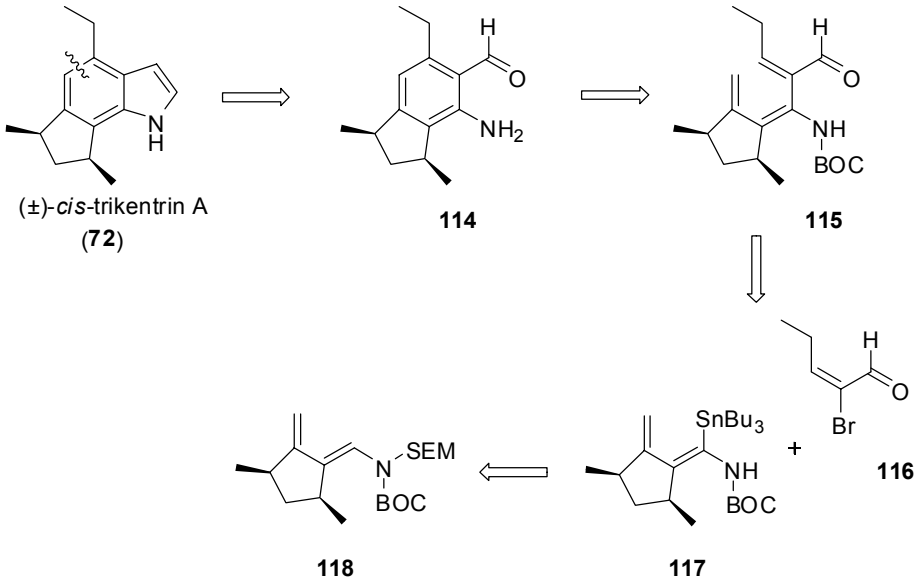
2.3 A 6π-electrocyclization approach to (±)-*cis*-trikentrin A and (±)-*cis*-trikentrin B

2.3.1 Retrosynthetic analyses

The demonstrated lack of a general and efficient route to the trikentrin series of natural products, combined with our interest in the synthesis of complexly substituted indoles via 6π-electrocyclization reactions, led us to consider our own approach to the trikentrin ring system.

Two related retrosynthetic strategies were initially considered. The first strategy, shown in Scheme 33 for (±)-*cis*-trikentrin A, can be classified as a C → CB → CBA approach and involves direct application of the Greshock indole synthesis methodology. Synthesis of (±)-*cis*-trikentrin A would be achieved by the "Råileanu-type" ring closure of formylaniline **114**. This aniline would be formed by the electrocyclization of trienecarbamate **115**. The triene would arise from the Stille coupling of haloenone **116** and C-ring precursor **117**, which would in turn be prepared via directed metalation of diene-carbamate **118**.

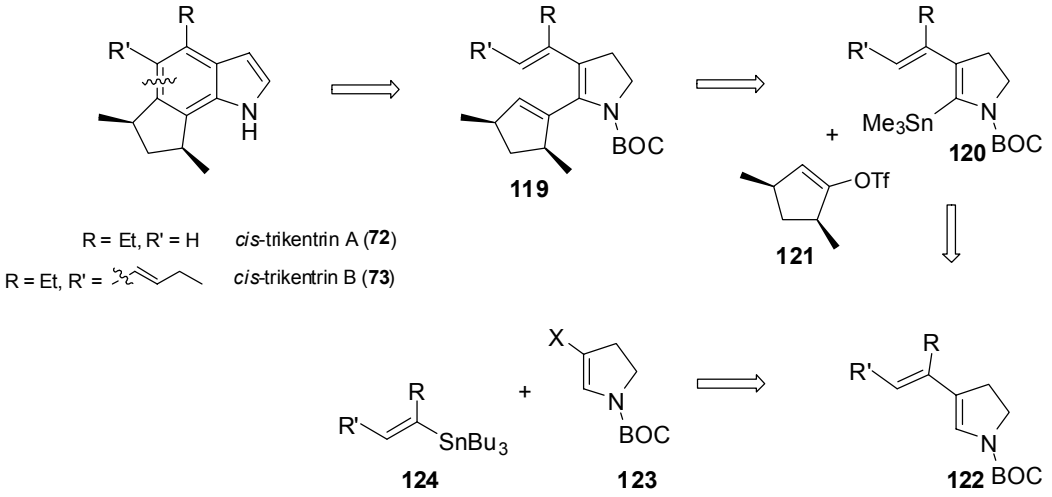
Scheme 33. A C→ CB → CBA approach to (±)-*cis*-trikentrin A



Several concerns immediately eliminated this approach from serious consideration. Preparation of dienecarbamate **118**, particularly with control of stereochemistry, appeared non-trivial. Secondly, the length of the sequence would not be competitive with existing methodology. Finally, extension of the method to (±)-*cis*-trikentrin B would require significant adjustments to the overall sequence.

We therefore turned to an alternate A → AC → ABC approach, shown in Scheme 34. In this approach, (±)-*cis*-trikentrin A (**72**) and B (**73**) could be prepared by the 6π-electrocyclization of trienecarbamates **119**. These trienecarbamates would be formed by Stille coupling of stannanes **120** and vinyltriflate **121**. The stannane would be formed by the directed lithiation of dienecarbamates **122** under the conditions developed in the Greshock methodology. These vinylpyrrolines would in turn arise from the coupling of the appropriate vinyl stannane **124** with the common precursor, β-halopyrroline **123**.

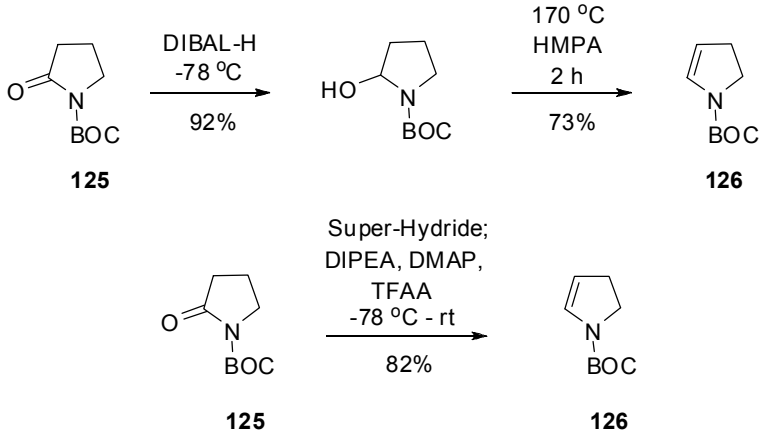
Scheme 34. An A→ AC → ABC approach to (±)-*cis*-trikentrin A and B



2.3.2 Preparation of the trialkylstannyl pyrroline

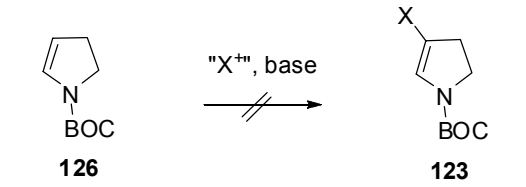
Our initial experiments towards the synthesis of the trikentrin natural products focused on the preparation of halopyrroline **123**. To that end, BOC-pyrroline **126** was prepared from commercially available BOC-2-pyrrolidinone (**125**) by either the two step procedure of Dieter,[37] or later in the project, via the one-pot procedure disclosed by Yu. [38]

Scheme 35. Preparation of BOC-pyrroline (**126**)



Our attention then turned to halogenation of enamide **126**. β-halogenation of enaminones and pyridinones[39] has substantial precedent in the literature. Examples of halogenation of simple enamide systems are less common,[40] however. Indeed, in our hands, treatment of pyrroline **126** with a variety of electrophilic halogen sources under the conditions shown in Scheme 36 resulted exclusively in decomposition of the substrate.

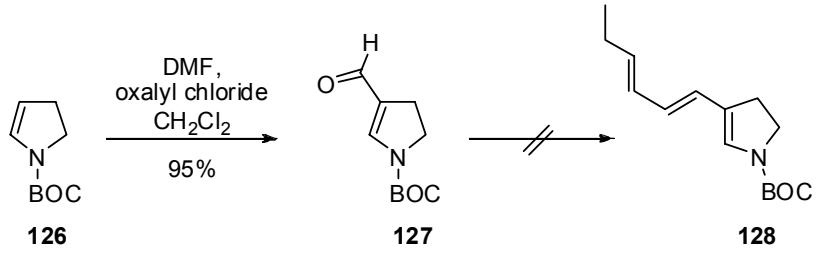
Scheme 36. Attempted formation of β-halopyrroline **123**



Our lack of success at introducing the desired halogen substituent led us to consider an alternate approach. We reasoned that aldehyde **127** (Scheme 37) might also allow us access to the desired vinylpyrroline substrates, via standard olefination protocols. A search of the literature showed that *N*-methoxycarbonyl-2-pyrroline had previously been formylated under Vilsmeier-Haack conditions.[41]

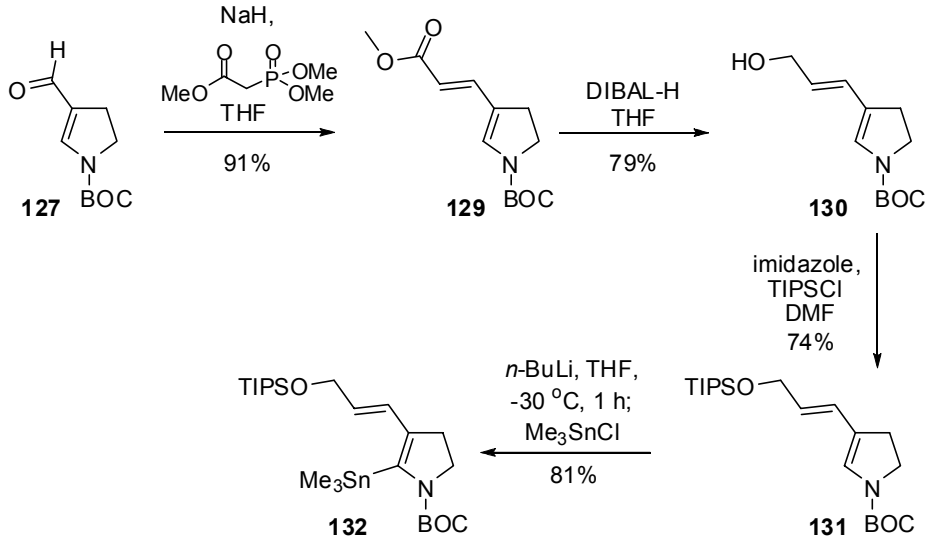
Application of this method to *N*-BOC pyrroline (**126**) was straightforward. Unfortunately, all attempts at direct conversion of this aldehyde to triene **128**, the desired precursor for *cis*-trikentrin B, proved unsuccessful via Wittig,[42] Julia,[43] or Koçieñski[44] protocols.

Scheme 37. Attempted preparation of triene **128**



In light of these results, we decided to attempt the synthesis of diene **131** (Scheme 38), which we believed would allow for later introduction of the butenyl sidechain of *cis*-trikentrin B. We were pleased to find that Horner-Wadsworth-Emmons olefination of aldehyde **127** proceeded smoothly to give ester **129**. Reduction and silyl protection were uneventful, providing the appropriately functionalized vinylpyrroline **131**.

Scheme 38. Preparation of stannane **132**

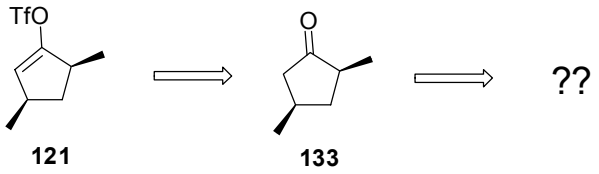


The key directed α-lithiation step was then attempted, under conditions analogous to those used in the Greshock indole annulation methodology (*vide supra*). This reaction proceeded in good yield, giving stannane **132**.

2.3.3 Diastereoselective synthesis of dialkylcyclopentanones

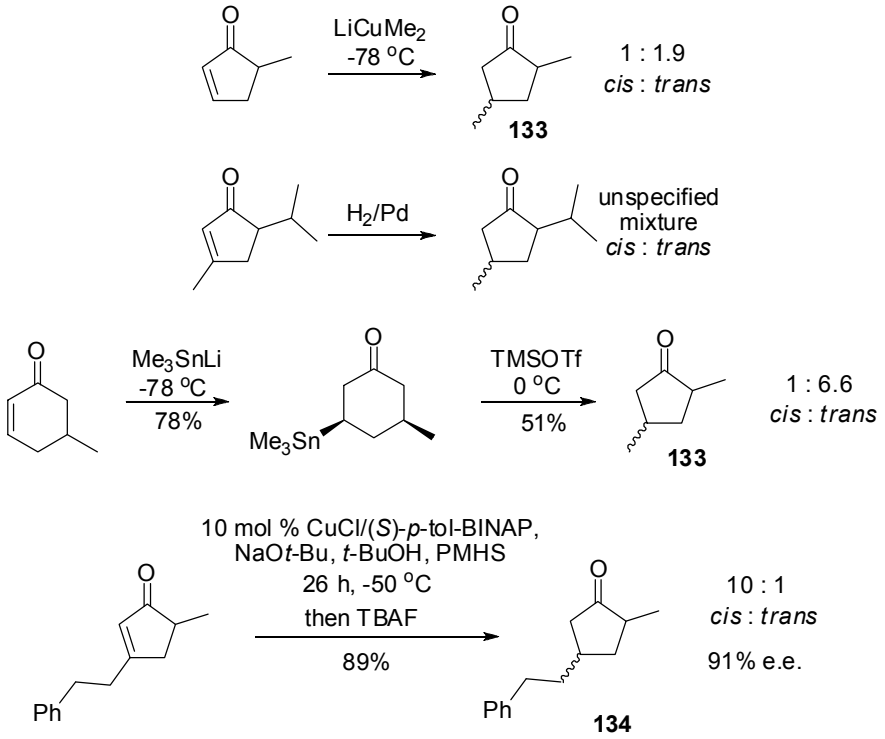
With this component in hand, our focus shifted to the preparation of vinyl triflate **121**, which we believed could be derived from ketone **133** (Scheme 39). To our surprise, however, diastereoselective preparation of 2,4-dialkylcyclopentanones is not a particularly well solved problem.

Scheme 39. Possible precursors to vinyl triflate **121**



Four strategies that have been previously employed for the synthesis of dialkylcyclopentanones are shown in Scheme 40. Simple cuprate addition[45] to cyclopentenones has been observed to occur with poor selectivity, as does simple heterogeneous hydrogenation.[46] Better selectivity was obtained by Sato,[47] who prepared *trans*-**133** via a diastereoselective ring contraction. Finally, Buchwald and co-workers have prepared *cis*-dialkylcyclopentanones **134** via a dynamic kinetic resolution process[48] with good enantio- and diastereoselectivity.

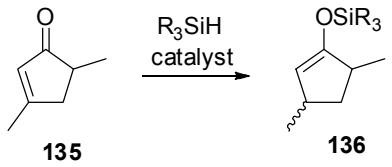
Scheme 40. Preparation of 2,4-dialkylcyclopentanones



The most promising avenue for our purposes appeared to be the cyclopentenone hydrosilylation protocol of Buchwald. However, the 10:1 diastereoselectivity concerned us, given the difficulties other groups have had in separating trikentrin diastereomers. Another concern was the relatively high catalyst loading required (greater than one wt. equiv. for dimethylcyclopentenone).

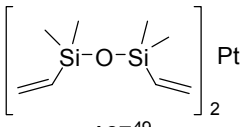
A brief screening of available hydrosilylation conditions using enone **135** was therefore conducted, with a goal of increasing the diastereoselectivity. Selected results from this screening are shown in Scheme 41.

Scheme 41. Hydrosilylation of ketone **135**



135 **136**

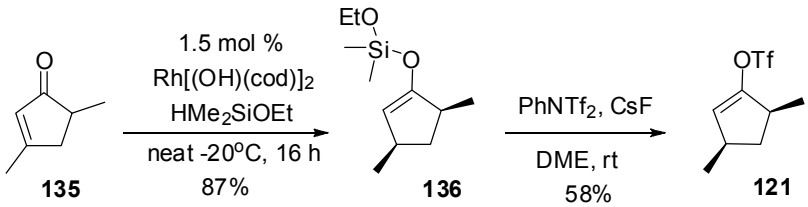
R_3	catalyst	temp	*cis:trans* selectivity
TBS	**137**	70 °C	2 : 1
TES	**137**	70 °C	6 : 1
TES	$RhClPPh_3$	70 °C	6 : 1
Me_2Ph	$[RhCl(cod)]_2$	rt	10 : 1
$Me_2(OEt)$	**137**	0 °C	10 : 1
$Me_2(OEt)$	$[Rh(OH)(cod)]_2$	-20 °C	20 : 1



137[49]

Ultimately, the key to good selectivity turned out to be the combination of a highly reactive catalyst, $[Rh(OH)(cod)]_2$,[50] and a highly reactive silane, ($Me_2(OEt)SiH$) which allowed for the reaction to be run at reduced temperatures. This in turn allowed for the preparation of silylenol ether **136** with excellent (20:1) diastereoselectivity. Subsequent conversion of this silylenol ether to the corresponding vinyl triflate **121** (Scheme 42) was effected in a single step by a protocol recently developed by Corey.[51]

Scheme 42. Preparation of vinyl triflate **121**



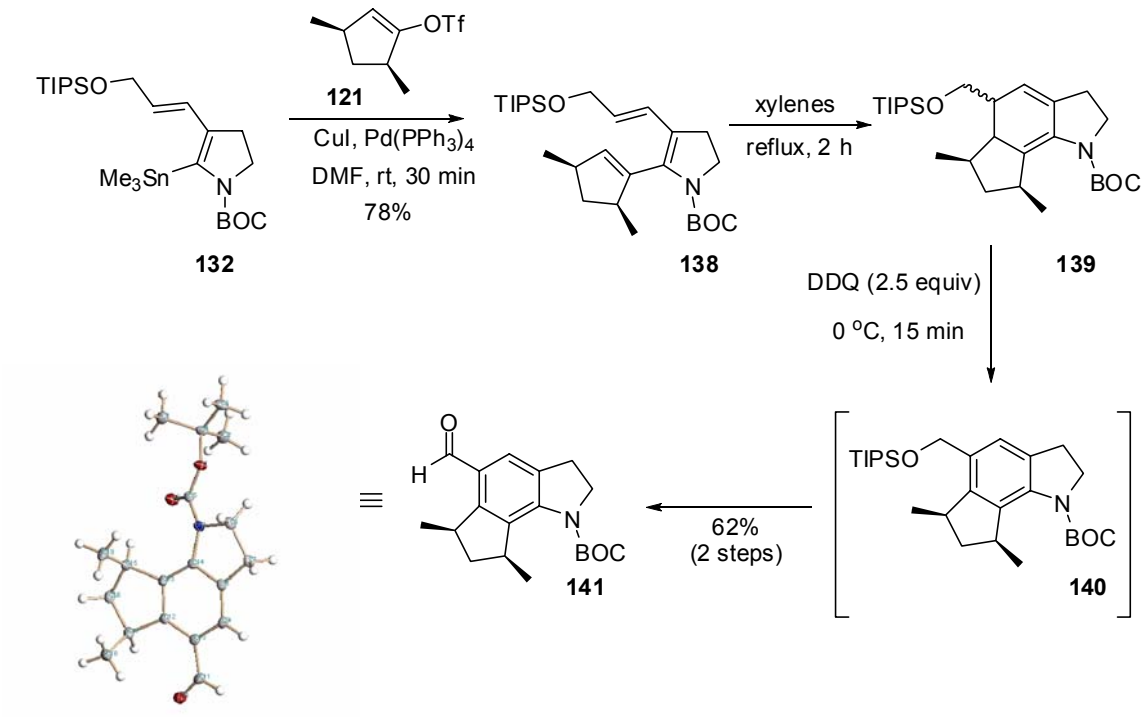
135 **136** **121**

2.3.4 Total synthesis of (±)-*cis*-trikentrin B

With both stannane **132** and triflate **121** in hand, copper (I) iodide assisted Stille coupling was performed (Scheme 43), giving us the desired divinylpyrroline **138**, ready for our key 6π-electrocyclization step.

We were extremely pleased to find that divinylpyrroline **138** underwent a smooth 6π-elecrocyclization over a period of 24 hours in refluxing toluene (110 ^{o}C) or two hours in refluxing xylenes (135 ^{o}C) to give a mixture of tetrahydroindoles **139**. Treatment, without isolation, of the resultant mixture with multiple equivalents of DDQ led, however, to an unexpected result, namely, the isolation of indoline aldehyde **141** as a crystalline solid.

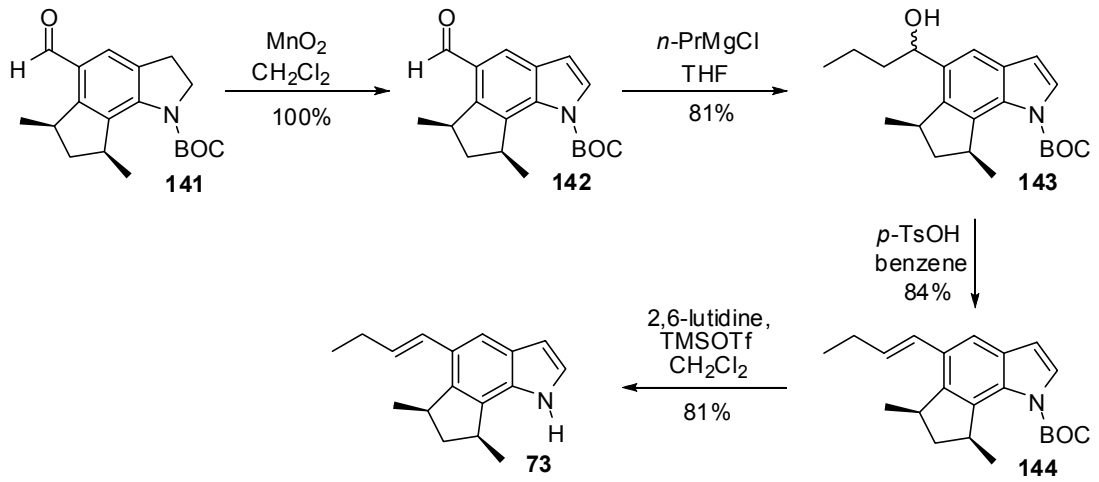
Scheme 43. 6π-Electrocyclization / oxidation of triene **138**



A control experiment in which DDQ was added in small portions with careful monitoring revealed that tetrahydroindoles **139** were undergoing an initial aromatization to indoline **140**, followed by subsequent oxidative desilylation. This second transformation, while unexpected, has been previously observed in related systems.[52]

We subsequently decided to take advantage of this fortuitous result. Indoline **141** was oxidized to indole **142** using MnO_2 (Scheme 44). The butenyl sidechain was then elaborated from the aldehyde via the same sequence employed by Natsume for his related *N*-phenylsulfonyl-protected system,[35d] namely, addition of propylmagnesium chloride and acid catalyzed dehydration. Finally, deprotection of the indole *N*-BOC protecting group was performed using TMSOTf/2,6-lutidine,[53] revealing the completed natural product, (±)-*cis*-trikentrin B (**73**), whose spectral data matched in all respects previously prepared material.

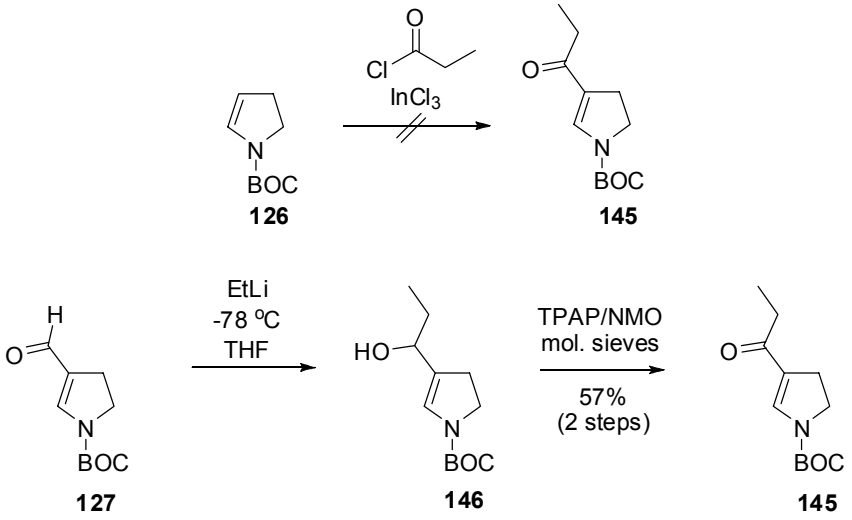
Scheme 44. Completion of the synthesis of (±)-*cis*-trikentrin B (**73**)



2.3.5 Total synthesis of (±)-*cis*-trikentrin A

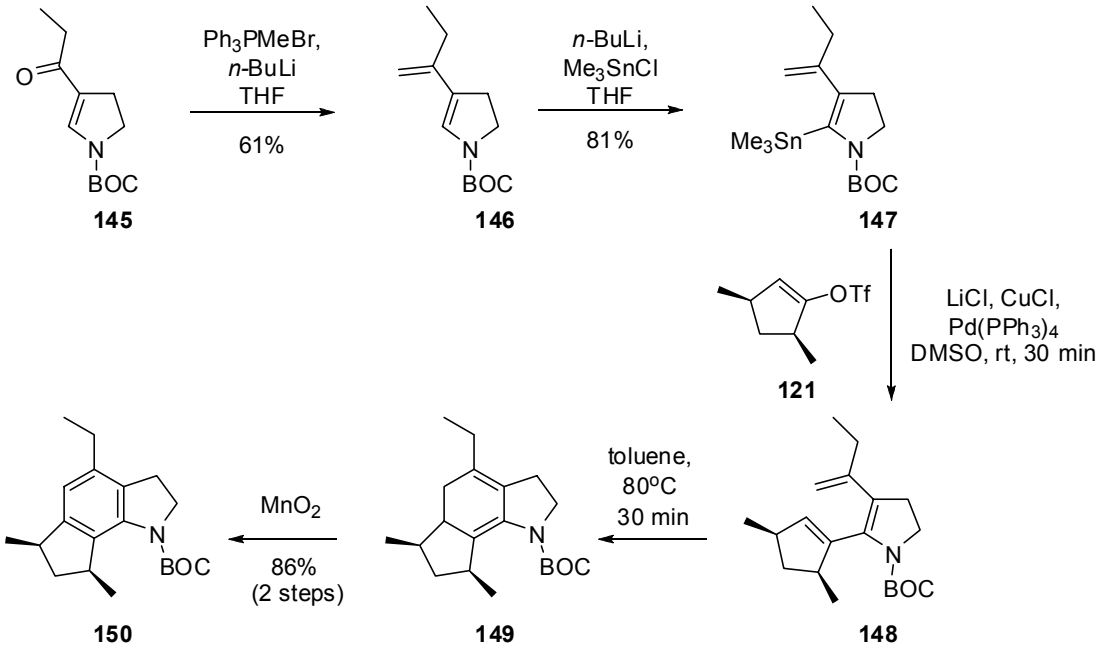
Our next goal was then to extend our approach to the synthesis of (±)-*cis*-trikentrin A, which as noted previously is substituted at the indole C(4) position. To that end, the direct acylation of pyrroline **126** with propionyl chloride was attempted, without success (Scheme 45). Ketone **145** could be prepared, however, by the addition of ethyllithium to aldehyde **127**, followed by oxidation.

Scheme 45. Preparation of propionylpyrroline **145**



Olefination of ketone **145** was accomplished via a Wittig reaction (Scheme 46). Directed metalation of the vinyl pyrroline followed by Stille coupling with triflate **121** then gave electrocyclization precursor **148**.

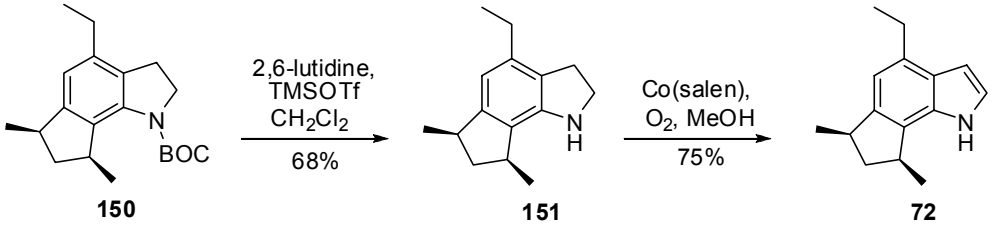
Scheme 46. Preparation and electrocyclization of divinylpyrroline **148**



We subsequently found that triene **148** underwent thermal 6π-electrocyclization under significantly milder conditions than the closely related triene **138**. Indeed, complete conversion to tetrahydroindole **149** was observed after only 30 minutes at 80 °C (compared to 24 hours at 110 °C for triene **138**). This observation serves as further experimental confirmation of the theoretical studies, outlined in Chapter 1, which show the presence of C(2) substituents and the absence of C(1) substituents to have a profoundly accelerative effect in 6π-electrocyclic ring closures.

Unexpectedly, all of our attempts at oxidative aromatization of BOC-indoline **150** (Scheme 47) in analogous fashion to our trikentrin B system proved unsuccessful, necessitating a small change to our endgame. Transformation to the natural product (±)-*cis*-trikentrin A was ultimately achieved[55] by removal of the protecting group and aromatization of indoline **151** under Co(salen) catalysis.[54]

Scheme 47. Completion of the synthesis of (±)-*cis*-trikentrin A (**72**)



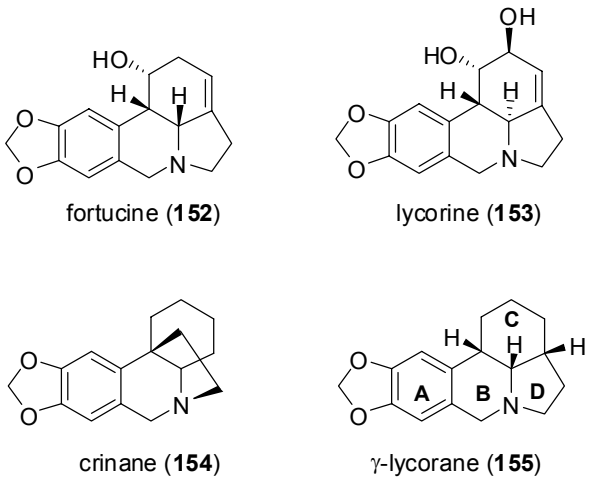
150 **151** **72**

2.4 (±)-γ-Lycorane

2.4.1 Introduction and previous synthetic approaches

The *Amaryllidaceae* family of natural products encompasses a structurally diverse range of compounds (Figure 9) with a host of biological activities,[56] and has seen extensive investigation by synthetic chemists. In particular, the lycorine sub-class[57] has for decades served as a test-ground for a range of synthetic methodologies. In fact, since its initial synthesis in 1966 one single member of this family, γ-lycorane (**155**), has been prepared in both racemic[58] and enantioenriched[59] form by over twenty different research groups using a multitude of synthetic approaches.

Figure 9. Selected *Amaryllidaceae* alkaloids



These approaches can broadly be grouped according to the order in which the remaining two rings can be constructed from an initial bicyclic compound. Without exception, all of the approaches to date conclude with construction of the B ring, often by Pictet-Spengler or Bischler-Napierelski cyclization. This allows the existing syntheses to be classed into three groups, based upon the order of

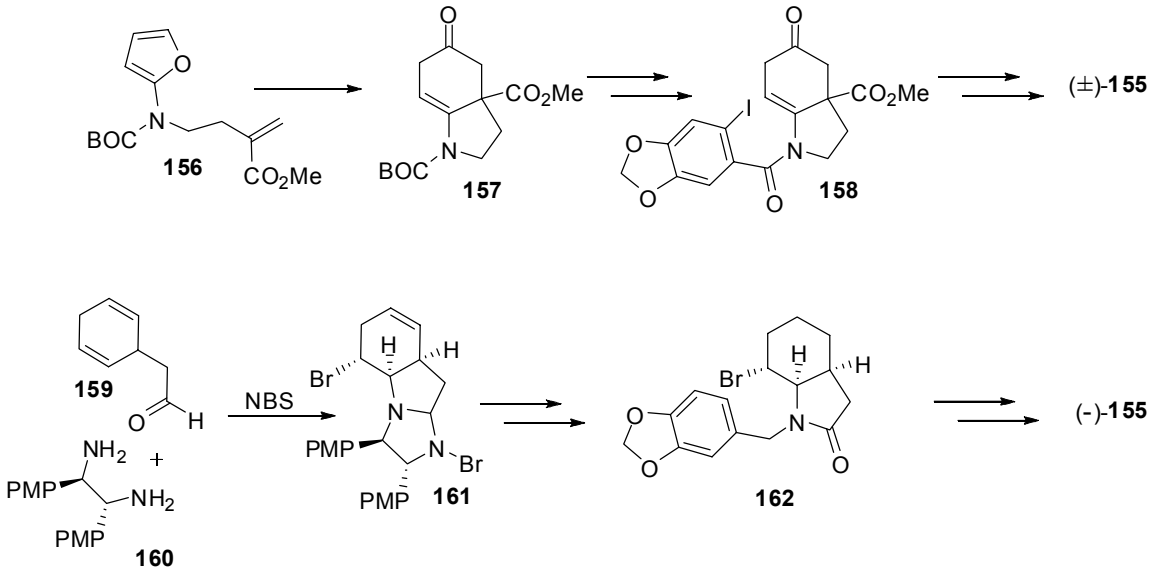
ring construction.

CD→ CDA→ CDAB approaches

Two examples of the CD→ CDA→ CDAB approach are shown in Scheme 48. In the first example, from the Padwa laboratory[58c], an intramolecular furan-acrylate cycloaddition is performed on amidofuran **156** to form the CD ring system **157**. The A ring is subsequently introduced by acylation, to give aryl amide **158**, which is subsequently transformed into the natural product (±)-**155**.

In the second example, Fujioka and Kita prepared the CD ring system by means of an intramolecular haloamination reaction.[59b] Condensation of aldehyde **159** with diamine **161** gave an aminal that was directly treated with NBS to give bromoaminal **161**. A subsequent four step sequence revealed a bromoindolizidinone, to which the piperonyl A ring was appended. A subsequent intramolecular Friedel-Crafts reaction and reduction of the resultant amide gave (-)-γ-lycorane (**155**).

Scheme 48. CD→ CDA→ CDAB approaches to γ-lycorane (**155**)

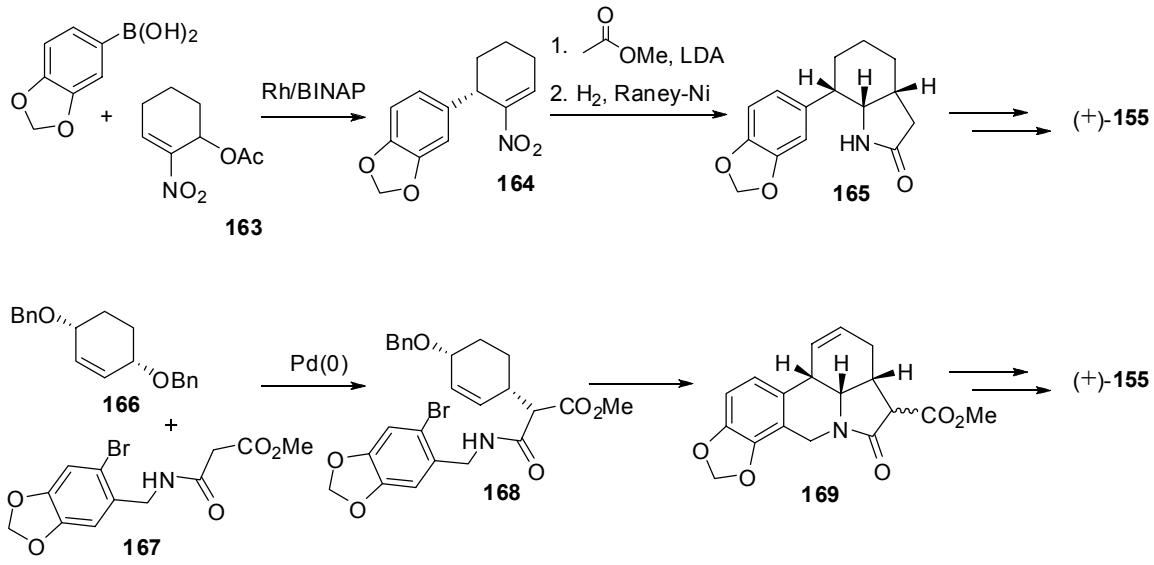


AC→ ACD→ ACDB Approaches

Gong and coworkers' concise synthesis of γ-lycorane[59c] began with the rhodium/BINAP displacement of acetate **163**, giving C-A ring congener **164**. Diastereoselective conjugate addition of methyl acetate enolate followed by reduction furnished indolizidinone **165**, which was subsequently converted to (+)-γ-lycorane (**155**).

In a second example of an AC→ACD→ACDB cyclization, Ojima and Chapsal[59a] have reported a recent synthesis, drawing heavily on earlier work by Mori,[59f] in which the A and C rings of γ-lycorane are coupled by means of an allylic alkylation reaction. Dibenzoate **166** was treated with the malonate half-amide **167** in the presence of a monodentate phosphoramidite palladium complex to give the desymmetrized benzoate **168**. A subsequent palladium catalyzed tandem allylic amination-intramolecular Heck reaction gave the completed ring system **169**, from which the natural product **155** was elaborated.

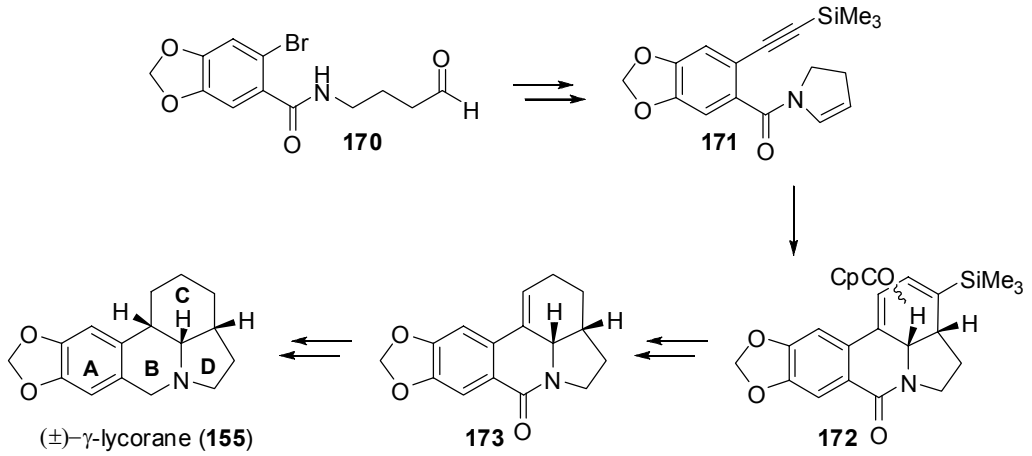
Scheme 49. AC→ ACD→ ACDB approaches to γ-lycorane (**155**)



AD→ ADC→ ADCB approaches

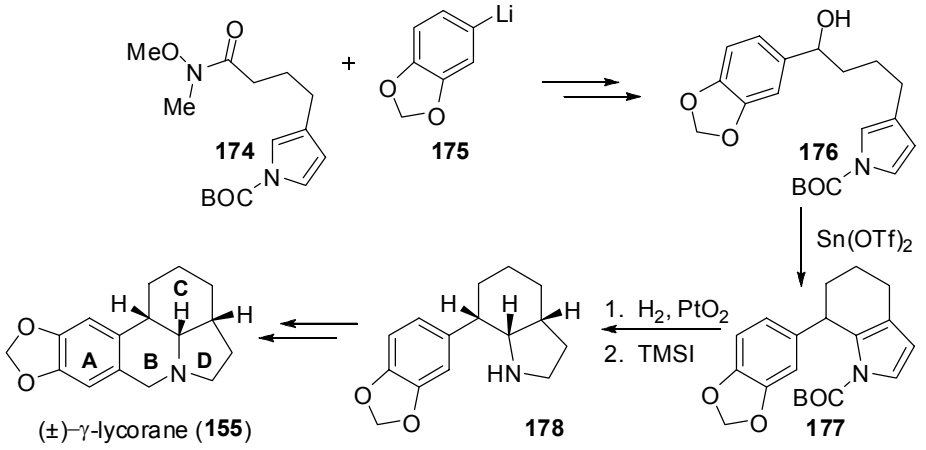
The final class of approaches, beginning with construction of an A-D ring congener, has seen little use with only two reported syntheses. In the first synthesis, from the Vollhardt laboratory, aldehyde **170** is elaborated to acyl pyrroline **171**[58i] (Scheme 50). Treatment with $CpCo(CO)_2$ and irradiation effected closure of the C and B rings to give cyclization product **172**. Subsequent demetalation and reduction steps gave (±)-γ-lycorane (**155**).

Scheme 50. An AD→ ADC→ ADCB approach to γ-lycorane (**155**)



The latter approach, by Angle and Boyce,[58h] begins with Weinreb amide **174**, available in six steps from TIPS-pyrrole. Addition of piperonyllithium to this amide and reduction of the resultant ketone gave benzylic alcohol **176** (Scheme 51). Upon treatment with $Sn(OTf)_2$ the alcohol undergoes a cationic cyclization, forming the C ring. Subsequent hydrogenation followed by BOC-deprotection afforded indolizidine **178**, which was subsequently cyclized in two steps to give (±)-γ-lycorane (**155**).

Scheme 51. Angle's AD→ ADC→ ADCB approach to (±)-γ-lycorane (**155**)



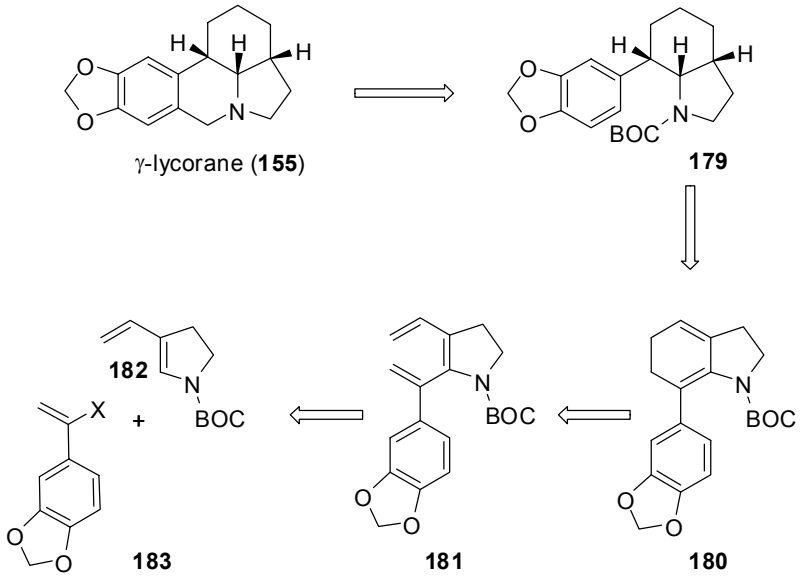
2.4.2 A 6π-electrocyclic ring closure approach to γ-lycorane

We felt that we could prepare γ-lycorane via the less common AD→ADC→ADBC approach using a modification of methodology employed for the synthesis of *cis*-trikentrin A and *cis*-trikentrin B. In doing so, we would demonstrate the utility of our method for the construction of indolizidine ring systems.

Our retrosynthetic analysis for the construction of γ-lycorane (**155**) is shown in Scheme 52. We envisaged that the natural product would be formed from indolizidine **179**, an intermediate in Angle's γ-lycorane synthesis (Scheme 51). This indolizidine, in turn, could be derived by sequential hydrogenations of tetrahydroindole **180**, expected to occur on the same face. In addition, it might be possible to effect asymmetric hydrogenation using one of the many catalysts developed for asymmetric reduction of enamides/enecarbamates.[60] In analogous fashion to our trikentrin syntheses, tetrahydroindole **180** would be formed from the electrocyclic ring closure of divinylpyrroline **181**, which would in

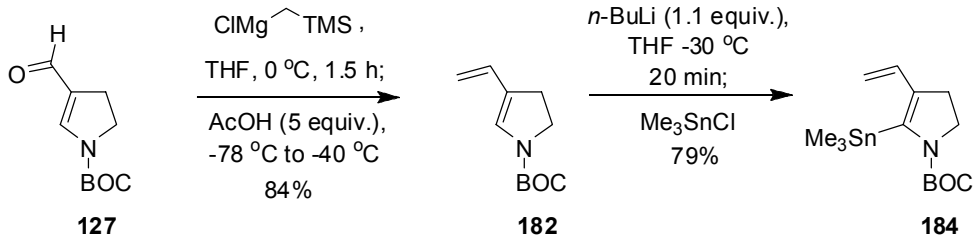
turn be derived from diene **182** by stannylation at C(2) and coupling with the appropriate vinyl halide **183**.

Scheme 52. Retrosynthetic analysis for (±)-γ-lycorane



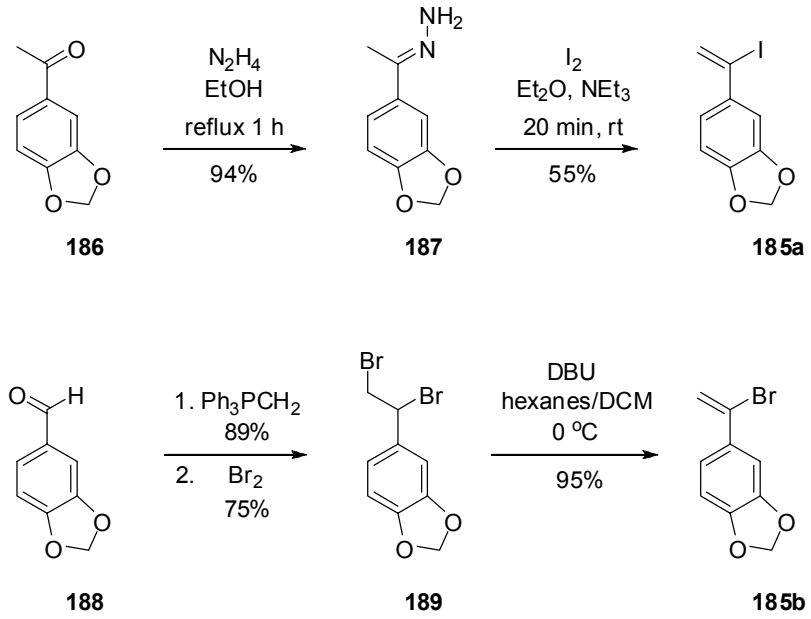
Our synthesis of γ-lycorane began with the preparation of diene **182** by Peterson olefination of aldehyde **127** (Scheme 53). Metalation at the pyrroline C(2) position, under our standard conditions, followed by treatment with trimethyltin chloride, gave stannane **184**.

Scheme 53. Preparation of stannane **184**



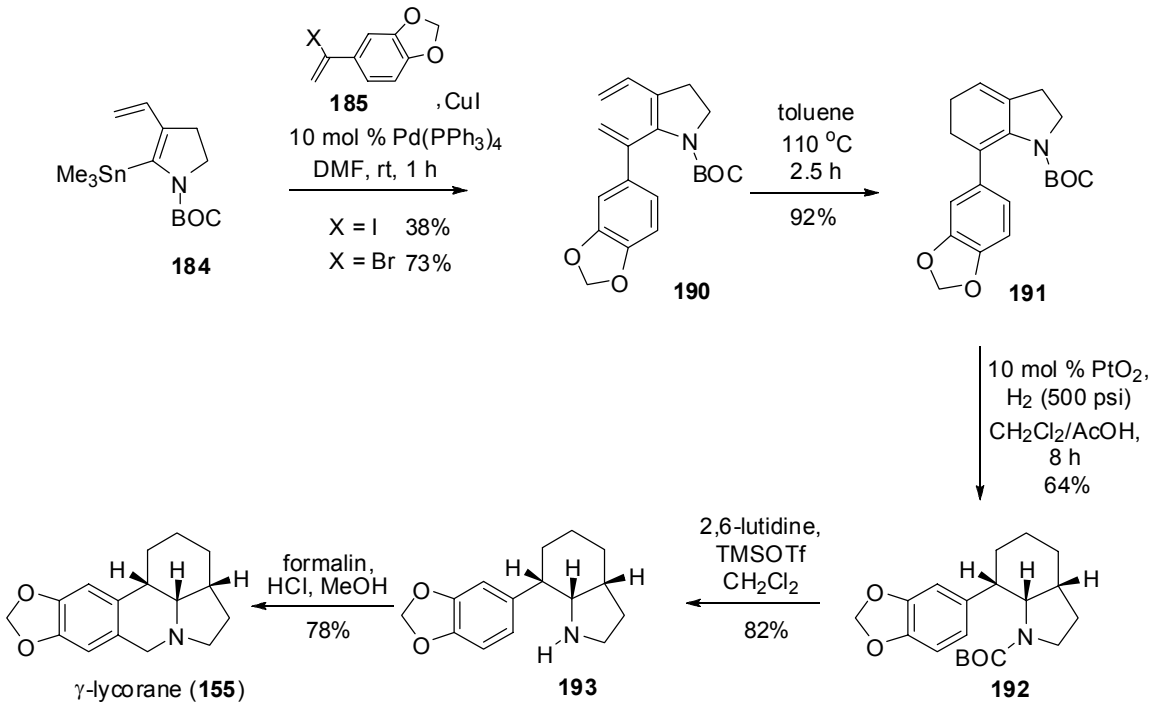
Two vinyl halide coupling partners, iodide **185a**[61] and bromide **185b**[62], were then prepared, as shown in Scheme 54. Conversion of ketone **186** to the corresponding hydrazone, followed by treatment with iodine, allowed for the isolation of vinyl iodide **185a** as an unstable oil, which was prone to violent decomposition if strictly basic conditions were not maintained. The significantly more stable vinyl bromide **185b** was prepared in a three-step procedure from piperonal (**188**).

Scheme 54. Synthesis of vinyl halides **185a** and **185b**



Stille coupling reactions between stannane **184** and vinyl halides **185** were then attempted (Scheme 55), with superior yields achieved by use of the more stable vinyl bromide.

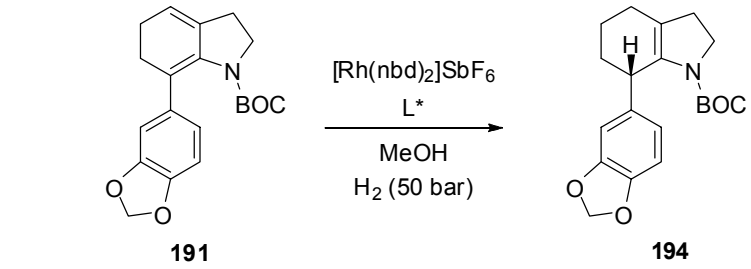
Scheme 55. Total synthesis of (±)-γ-lycorane (**155**)



Electrocyclic ring closure of trienecarbamate **190** proceeded smoothly and at relatively low temperature to afford tetrahydroindole **191** in excellent yield (Scheme 55). Catalytic hydrogenation then revealed indolizidine **192**. Removal of the BOC protecting group gave amine **193**, identical in all respects with published spectra.[58n] Pictet-Spengler ring closure provided (±)-γ-lycorane (**155**).

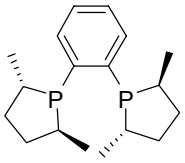
In an attempt to achieve the enantioselective synthesis of γ-lycorane, rhodium catalyzed asymmetric hydrogenations of tetrahydroindole **191** using DuPhos (**195**)[63], TangPhos (**196**)[64] and BINAP (**197**)[65] ligands were attempted, in a collaborative effort with the Zhang group. Unfortunately chiral HPLC analysis of the resultant monohydrogenated enecarbamate **194**, showed in each case negligible (< 5%) enantioselectivity, and these efforts were abandoned.

Scheme 56. Attempted asymmetric hydrogenations of tetrahydroindole **191**

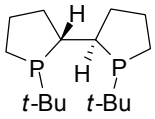


191 **194**

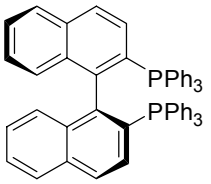
< 5% ee



195



196



197

2.5. Concluding Remarks

In conclusion, we have shown that complexly substituted indoles and indolizidines can be readily prepared by means of the facile electrocyclic ring closure of 2,3-divinylpyrrolines. The utility of this sequence has been shown by concise, diastereoselective syntheses of (±)-*cis*-trikentrin A, (±)-*cis*-trikentrin B and (±)-γ-lycorane, which were prepared in 10, 12 and 9 steps respectively, from commercially available *N*-BOC-2-pyrrolidinone.

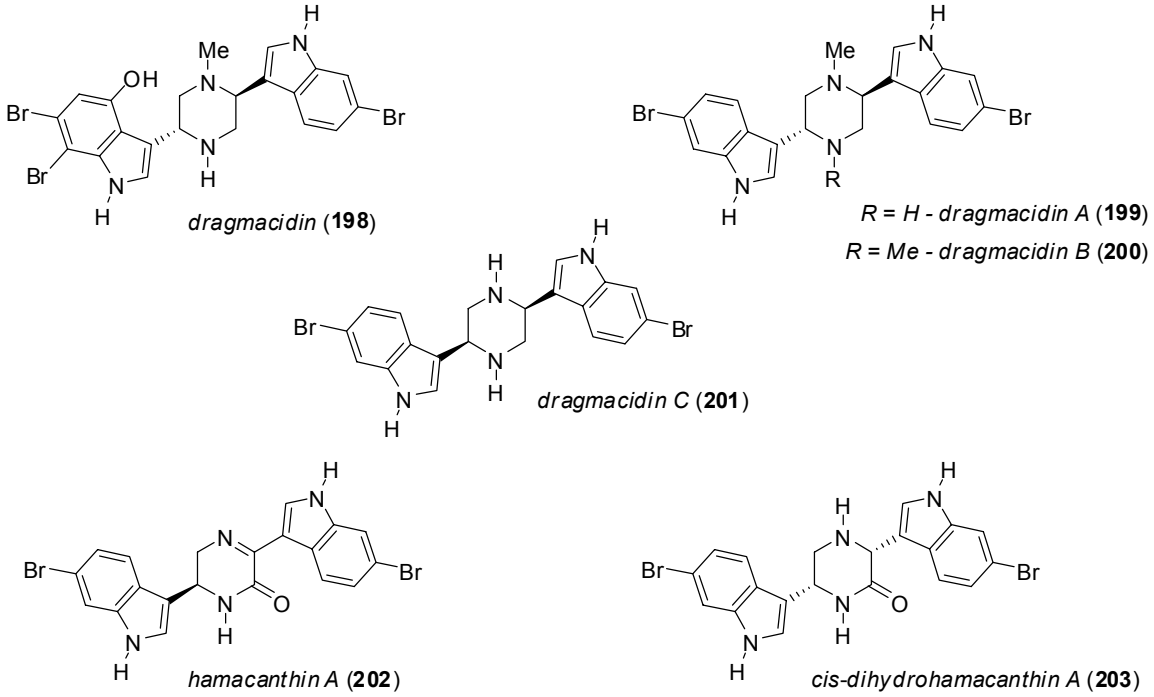
CHAPTER 3
The Dragmacidin Family of Natural Products

3.1 Bis-indolylpiperazine natural products

3.1.1 Structure and isolation

Over the past 20 years, a series of brominated bis-indolylpiperazine natural products have been isolated from a host of geographically remote marine organisms (primarily sponges).[66] Selected members of this class of natural products from the dragmacidin and hamacanthin families are shown in Figure 10.

Figure 10. Bis-indolylpiperazine natural products.

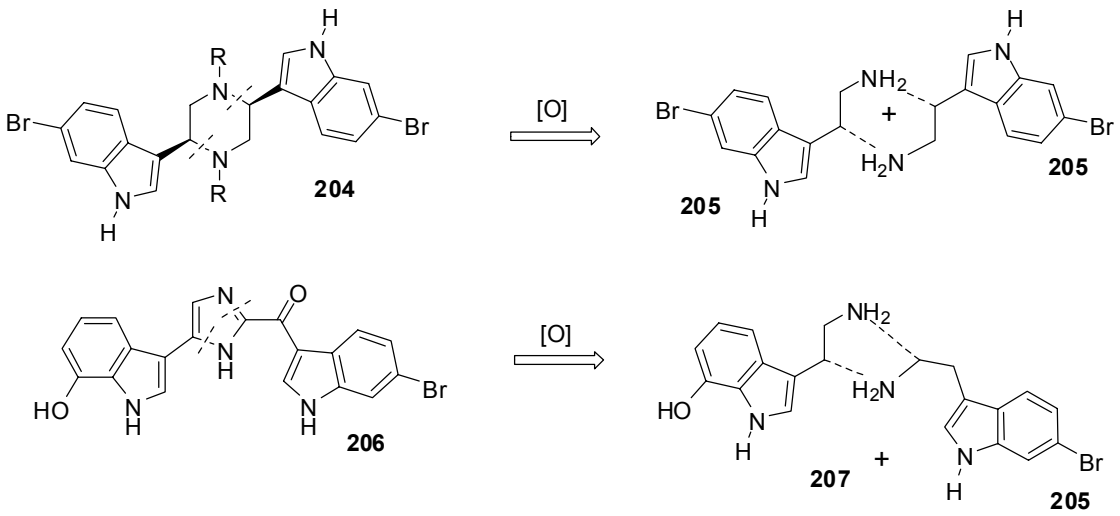


The key structural features shared by these natural products include the presence of a central piperazine core 2,5-disubstituted with bromoindolyl substituents. The various members can be largely distinguished by the oxidation state of the central piperazine ring, as well as by the degree of bromination and/or oxidation of the indolyl substituents.

3.1.2 Biosynthetic considerations

The dragmacidin and hamacanthin alkaloids are proposed to arise from the oxidative dimerization of bromotryptamine precursors (Scheme 57). Key evidence in support of this hypothesis is the co-isolation of 6-bromotryptamine (**205**) with dragmacidin C (**201**).[66c] Further evidence is provided by the co-isolation of the related natural product isobromotopsentin (**206**),[67] which could arise from similar precursors via slightly modified bond connections.

Scheme 57. Proposed biosyntheses of bis-indolyl piperazine natural products



3.1.3 Biological activity

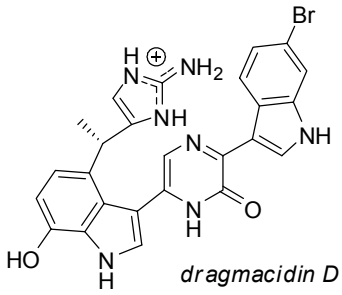
A range of biological assays have been performed on these piperazine natural products, revealing significant cytotoxicity[66a,b] and anti-microbial[66d] activity. As a consequence of this interesting biological activity, extensive synthetic studies have been performed, culminating in numerous total syntheses.[68]

3.2 Bis-indolylpyrazinone natural products

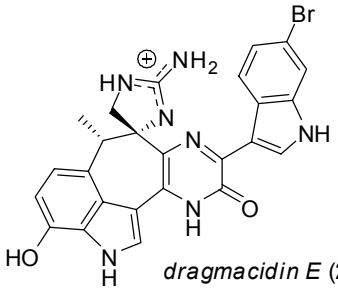
3.2.1 Structure and isolation

In addition to the relatively simple *piperazine* members of the dragmacidin family, three structurally complex *pyrazinone* natural products have been isolated from marine sponges *Dragmacidion sp.*,[69] *Spongosorites sp.*[70] and *Halicortex sp.*,[71] and have been assigned the names dragmacidin D (**208**), dragmacidin E (**209**) and dragmacidin F (**210**) (Figure 11).

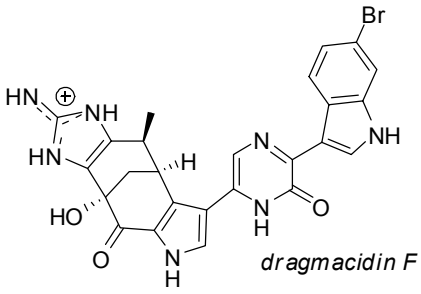
Figure 11. Bis-indolylpyrazinone natural products



dragmacidin D (**208**)



dragmacidin E (**209**)

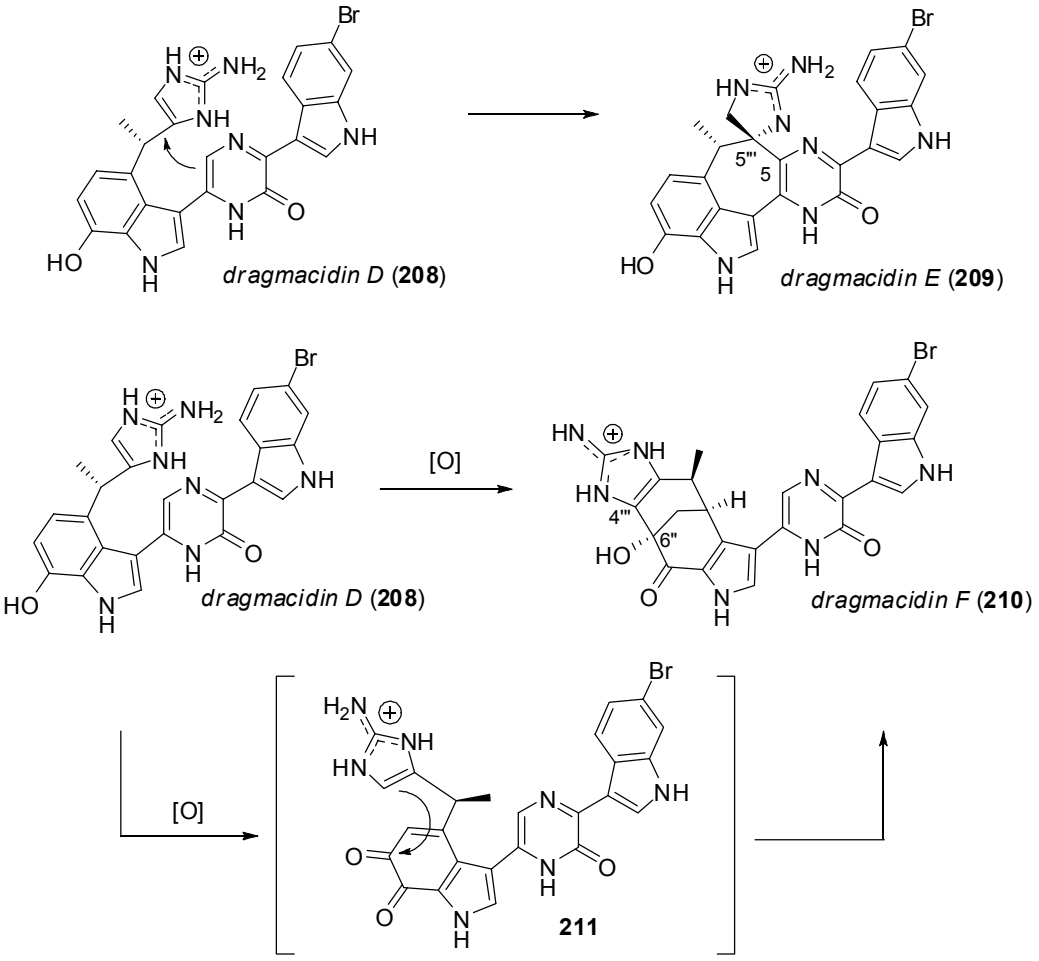


dragmacidin F (**210**)

3.2.2 Biosynthetic considerations

Biosynthetically, it has been proposed[70,71] that dragmacidin D may be a common precursor to both dragmacidin E and dragmacidin F. Specifically, it has been suggested that dragmacidin E (**209**) most likely arises from a simple Friedel-Crafts type of cyclization, effecting closure from C(5) to C(5"') (Scheme 58). The biosynthesis of dragmacidin F (**210**), in contrast, would require initial oxidative dearomatization of **208** to afford diketone **211** prior to formation of the C(4"') to C(6") bond. The biogenetic origin of the aminoimidazolium sidechain of dragmacidin D is unclear.

Scheme 58. Proposed biosyntheses of dragmacidin E (**209**) and F (**210**)



3.2.3 Biological Activity

The pyrazinone dragmacidins have been the subject of a number of biological assays. Dragmacidin D (**208**) has shown[69] anti-microbial activity against *Escherichia coli* (MIC 16 μg/mL), *Bacillus subtilus* (3.1 μg/mL), *Psuedomonas aeruginosa* (63 μg/mL), *Candida albicans* (16 μg/mL), and *Cryptococcus neoformans* (4 μg/mL). Dragmacidin E (**209**) exhibited similar activity when subsequently tested against *Escherichia coli* (MIC 22 μg/mL) and *Candida albicans* (36 μg/mL).[70]

Other biological activities exhibited by dragmacidin D (**208**) include inhibition of P388 murine and A549 human lung tumor cell lines, (IC_{50} values of 1.4 and 4.4 μg/mL respectively),[69] feline leukemia virus (MIC 6.3 μg/mL), as well as inhibition of neural nitric oxide synthase bNOS (IC_{50} 4 μM)[72], and resiniferitoxin-induced inflammation.[73] Dragmacidin F (**210**) has demonstrated antiviral activity[71] against HSV-1 (IC_{50} 95.8 μM) and HIV-1 (IC_{50} 0.91 μM). Dragmacidin E has not yet been assayed for these activities.

In addition to the above assays, dragmacidin D and E have been described as being inhibitors of serine-threonine protein phosphatases. The initial report[70] describing this activity did not provide quantitative data on the magnitude of the inhibition, simply labeling both compounds as “potent” and attributing subtype selectivity for PP1 over PP2A to dragmacidin D.

Subsequent to this report, a review[74] of serine-threonine protein phosphatase inhibitors was published that described the potency of both dragmacidin D and E to be quite low, with IC_{50} values in the “high micromolar to millimolar” range. Conflicting with this report, however, is an independent study[75] performed on synthetic (*vide infra.*) dragmacidin D, in which the activity

against protein phosphatases was given as IC_{50} 21.0 nM to PP1, IC_{50} 3.0 μM to PP2A1 and IC_{50} 3.9 μM to PP2A2.

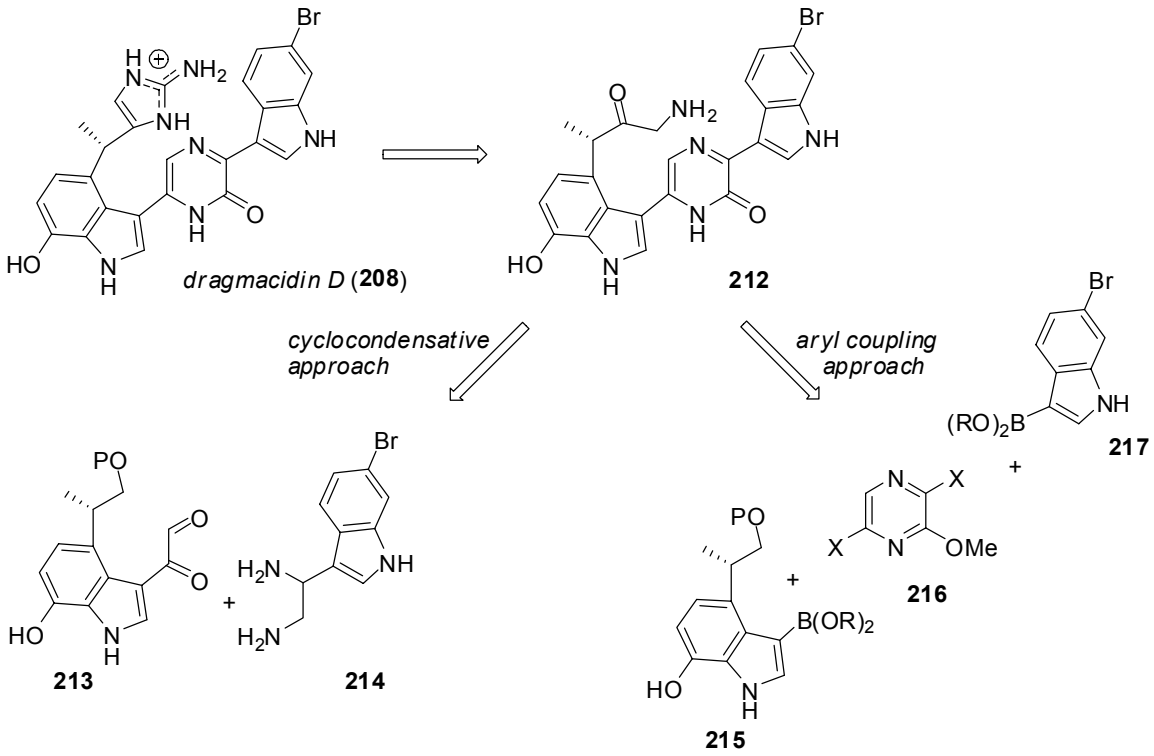
3.3 Prior synthetic efforts towards the pyrazinone dragmacidins

The intriguing biological activity, combined with the unprecedented and densely functionalized structures of the dragmacidins have led several groups to consider synthetic approaches to these unusual natural products. The leader in this area is the Stoltz group, which has described syntheses of both dragmacidin D[76] and dragmacidin F.[77]

3.3.1 Dragmacidin D

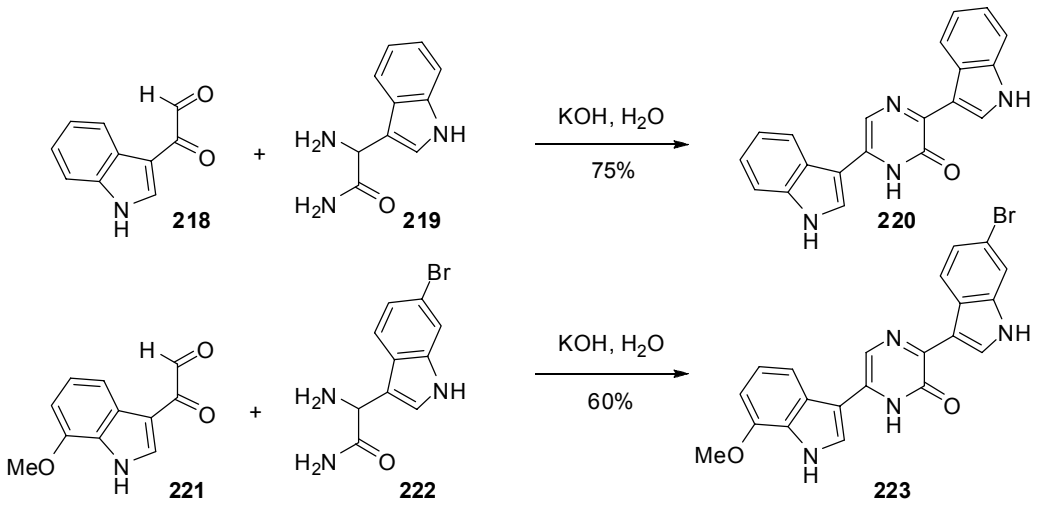
Retrosynthetic analysis of the natural product dragmacidin D reveals two distinct strategies, centered around the method used to construct the central pyrazinone ring. In both approaches, the aminoimidazole ring would be constructed at a late stage from aminoketone **212** (Scheme 59). In the first, biomimetic approach, the central pyrazinone ring would be constructed from the cyclocondensation of indole derivatives **213** and **214**. The second, an aryl coupling approach, would establish the bis-indolylpyrazinone functionality by sequential metal-mediated coupling reactions with a preexisting methoxypyrazine core.

Scheme 59. Approaches to the construction of the pyrazinone core



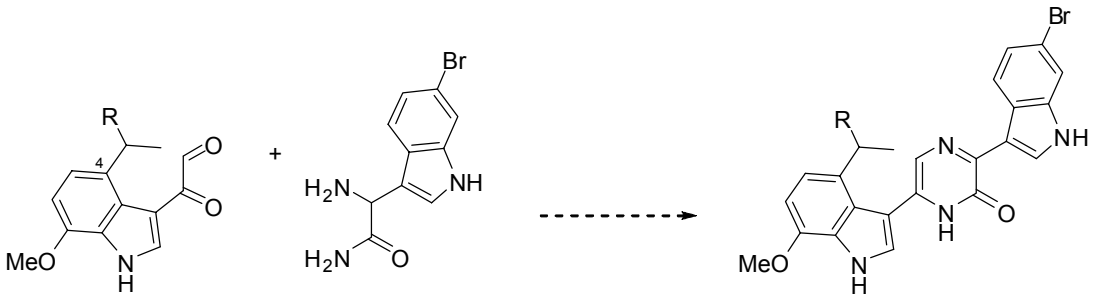
Results from Stoltz's initial model studies for the synthesis of dragmacidin D via the cyclocondensative approach are shown in Scheme 60. Aminoamides **219** and **222** were each found to undergo the desired cyclization with ketoaldehydes **218** and **221**, to give the desired bis-indolylpyrazinones.

Scheme 60. Cyclocondensation model systems



With the success of these model systems ketoaldehydes **224a** and **224b**, incorporating the requisite C(4) sidechain in different oxidation states, were prepared. Unfortunately, despite numerous attempts, the desired condensation to pyrazinones **225** could not be achieved (Scheme 61). This failure was attributed to the steric bulk of the C(4)-substituent.

Scheme 61. Stoltz's unsuccessful pyrazinone cyclocondensation



R = -CH_2OBn (**224a**)
R = -CO_2Me (**224b**)

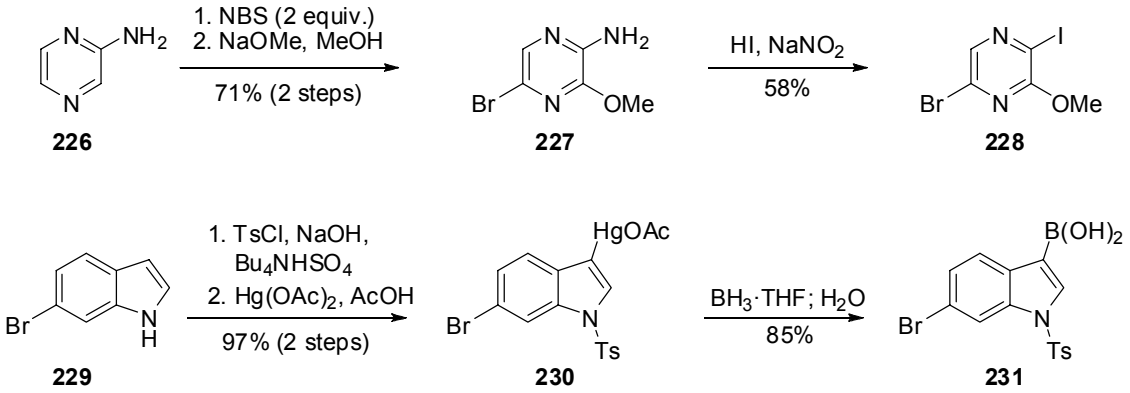
222

225

In light of these failures, Stoltz and coworkers abandoned the cyclocondensative method in favor of an aryl coupling approach. Efforts were therefore focused on the preparation of dihalopyrazine **228** and boronate **231**.

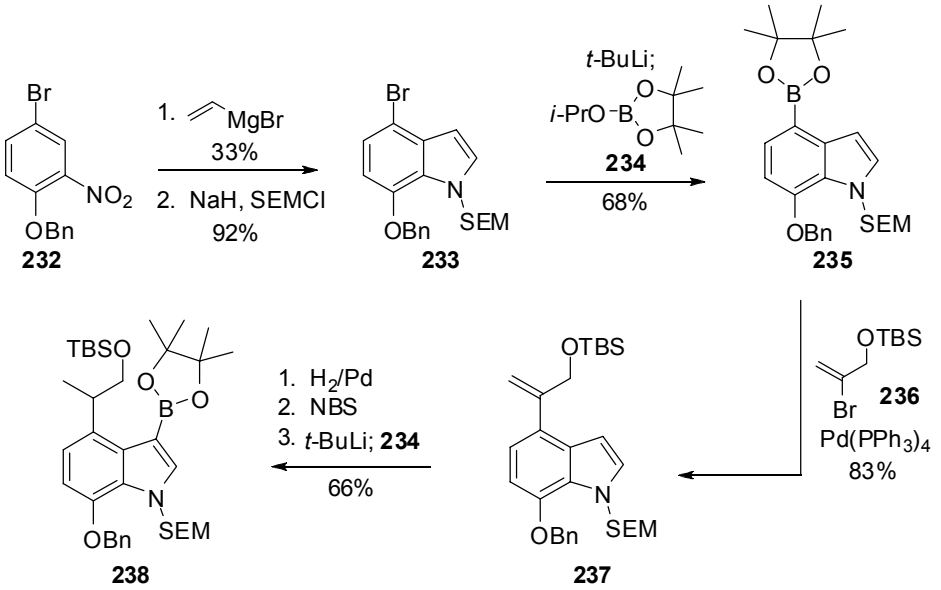
Bromination of commercially available aminopyrazine (**226**) gave rise to a dibromopyrazine, which underwent regioselective nucleophilic displacement with sodium methoxide to give methoxypyrazine **227**. This amine was subsequently converted to the corresponding iodide **228** under Sandmeyer reaction conditions. Boronic acid **231** was also straightforwardly prepared via the intermediate organomercurial **230**.

Scheme 62. Preparation of pyrazine and 6-bromoindole coupling partners



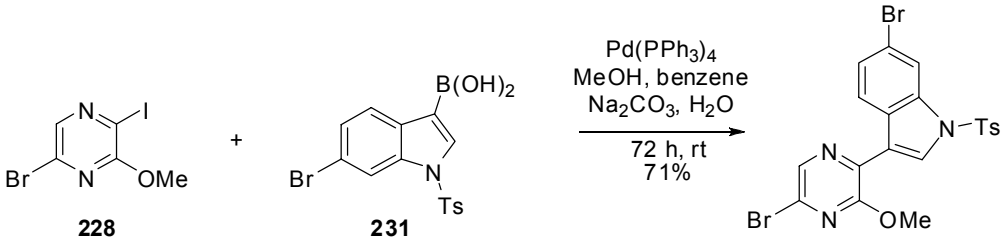
The preparation of boronate **238** is shown in Scheme 63. Indole **233** was prepared from nitroaromatic **232** via the Bartoli procedure. Nitrogen protection, halogen-metal exchange and treatment with dioxaborolane **234** gave boronate **235**. Suzuki coupling with vinyl bromide **236** furnished indole **237**. Reduction of the alkene followed by bromination gave a second aryl bromide species, which was straightforwardly converted to the desired boronate **238** via halogen-metal exchange.

Scheme 63. Preparation of 7-hydroxyindole coupling partner



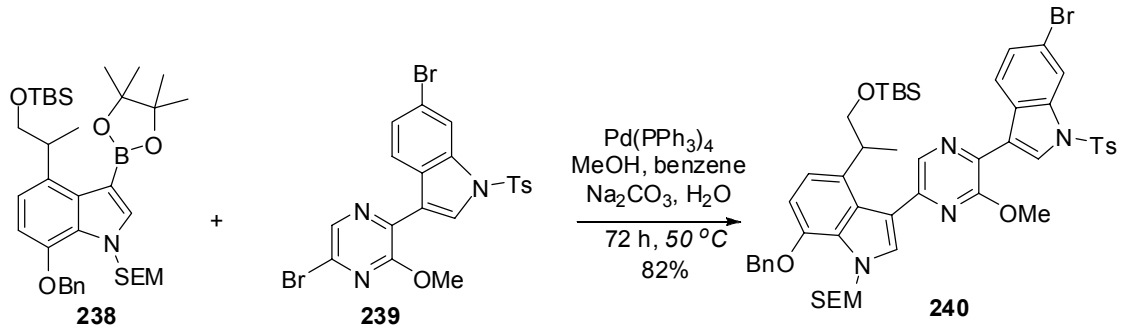
With all three components available, the stage was set for the proposed sequential halogen-selective metal-mediated couplings. The initial Suzuki coupling, shown in Scheme 64, called for regioselective oxidative addition at the aryl iodide center of pyrazine **228** over two potentially competing aryl bromide centers. This was achieved by performing the reaction over three days at room temperature.

Scheme 64. Iodopyrazine-selective Suzuki reaction



The subsequent Suzuki coupling between bromopyrazine **239** and boronate **238** (Scheme 65) was potentially more problematic. Unlike the previous case, this reaction would require the differentiation of two aryl bromide centers in the initial oxidative addition step.

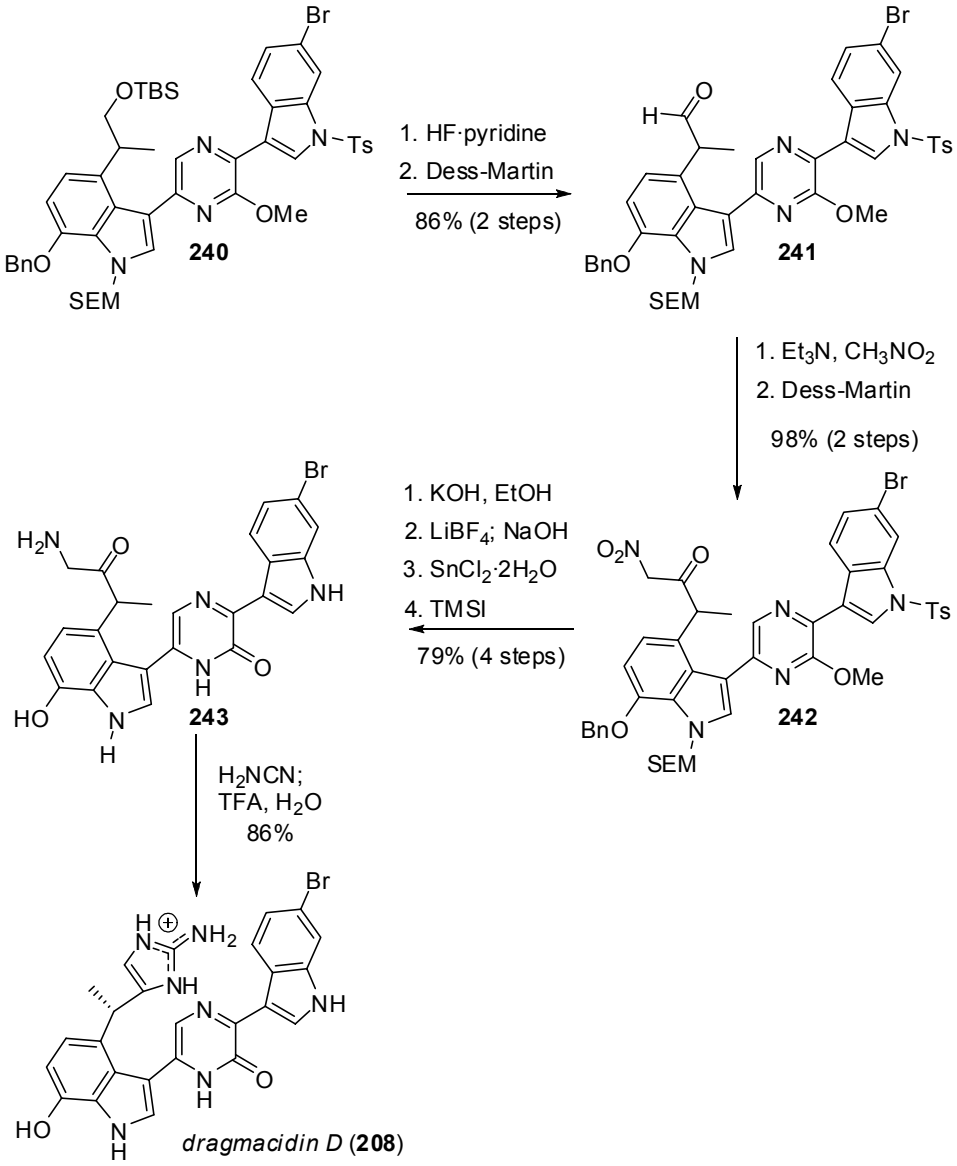
Scheme 65. Bromopyrazine-selective Suzuki coupling reaction



Fortunately, oxidative addition of palladium(0) species into aryl halides is known to favor electron deficient systems.[78] Furthermore, there are a number of precedents that indicate that halopyrazines are particularly reactive towards palladium coupling reactions.[79] Indeed, after a screen of available conditions it was determined that by carefully maintaining the temperature at 50 ^{o}C, selective coupling of bromopyrazine **239** with boronate **238** was achievable over three days to give bis-indolylpyrazine **240**.

With the core ring system established, elaboration to the natural product proved relatively straightforward. Silyl ether **240** was initially homologated to α-nitroketone **242** (Scheme 66). A series of deprotection steps and reduction of the nitro-substituent gave aminoketone **243**. The natural product **310** was then obtained via treatment with cyanamide.

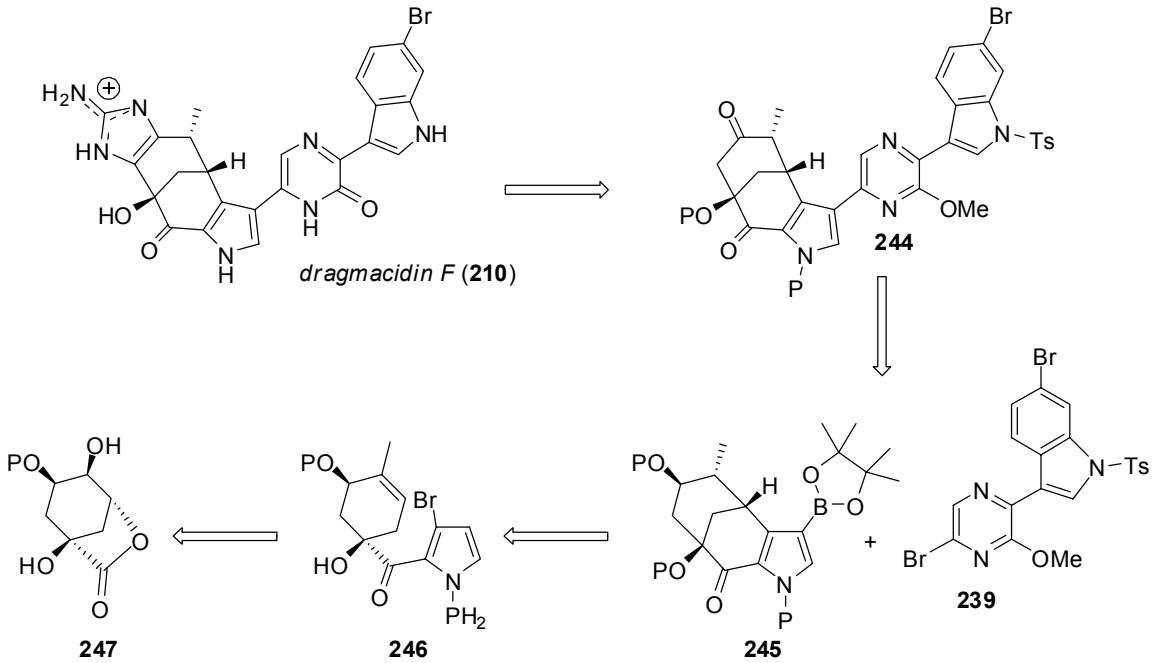
Scheme 66. Completion of the synthesis of dragmacidin D (**208**)



3.3.2 Dragmacidin F

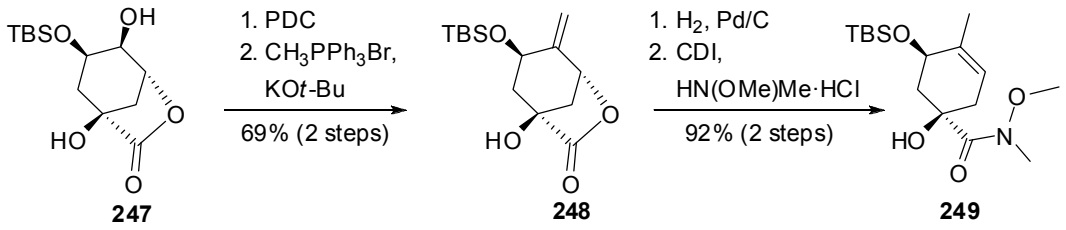
The Stoltz group has also developed a route to the synthesis of dragmacidin F (**210**), drawing upon many of the lessons learned in their original dragmacidin D synthesis. Retrosynthetically, they initially proposed to prepare dragmacidin F from ketone **244** (Scheme 67). This ketone would in turn arise from the halogen-selective coupling of bromopyrazine **239** and the pyrrolylboronate **245**. It was further imagined that this tricyclic system could be constructed by Heck cyclization of pyrrole **246**, which would arise from known[80] lactone **247**.

Scheme 67. Stoltz's retrosynthetic analysis for dragmacidin F (**210**)



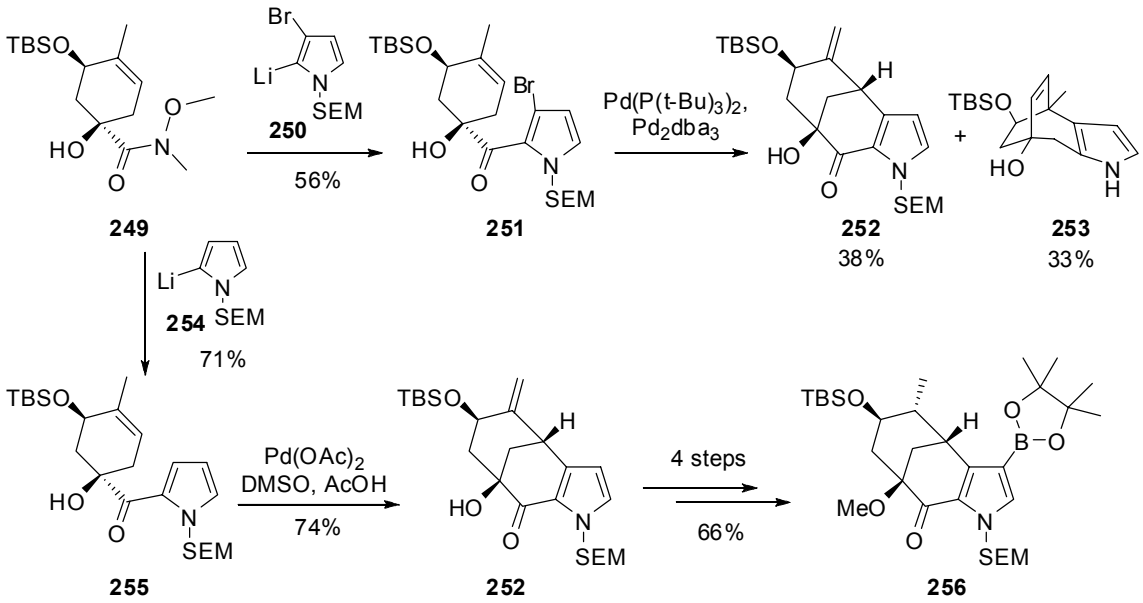
The synthetic sequence began with oxidation and olefination of diol **247** to give the allylic lactone **248** (Scheme 68). After some experimentation, ring opening was achieved under reductive conditions, giving rise to an acid, which was uneventfully converted to the corresponding Weinreb amide **249**.

Scheme 68. Preparation of Weinreb amide **249**



Amide **249** was then initially elaborated to bromopyrrole **251**, in preparation for Heck cyclization. Unfortunately, the desired 6-*exo*-Heck product **252** could only be achieved in poor yields, accompanied by significant amounts of 7-*endo*-cyclization product **253**.

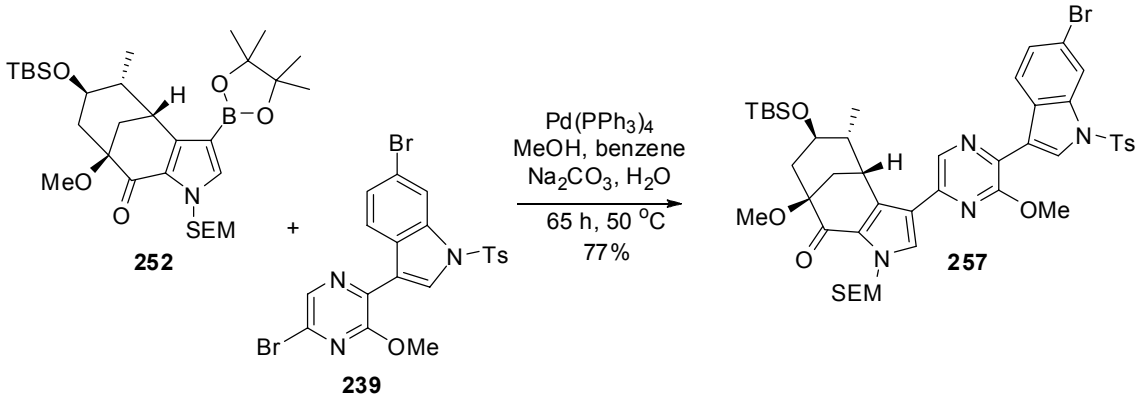
Scheme 69. Classical and oxidative Heck strategies to tricycle **252**



In an attempt to improve these disappointing results, des-bromopyrrole **255** was prepared in analogous fashion. This pyrrole was observed to undergo a palladium-catalyzed oxidative cyclization, giving tricycle **252** in good yield and as a single diastereomer. The improved regiochemistry was attributed to the smaller bulk of the ligand-free palladium intermediates. Elaboration of this tricycle to boronate **256** was straightforward.

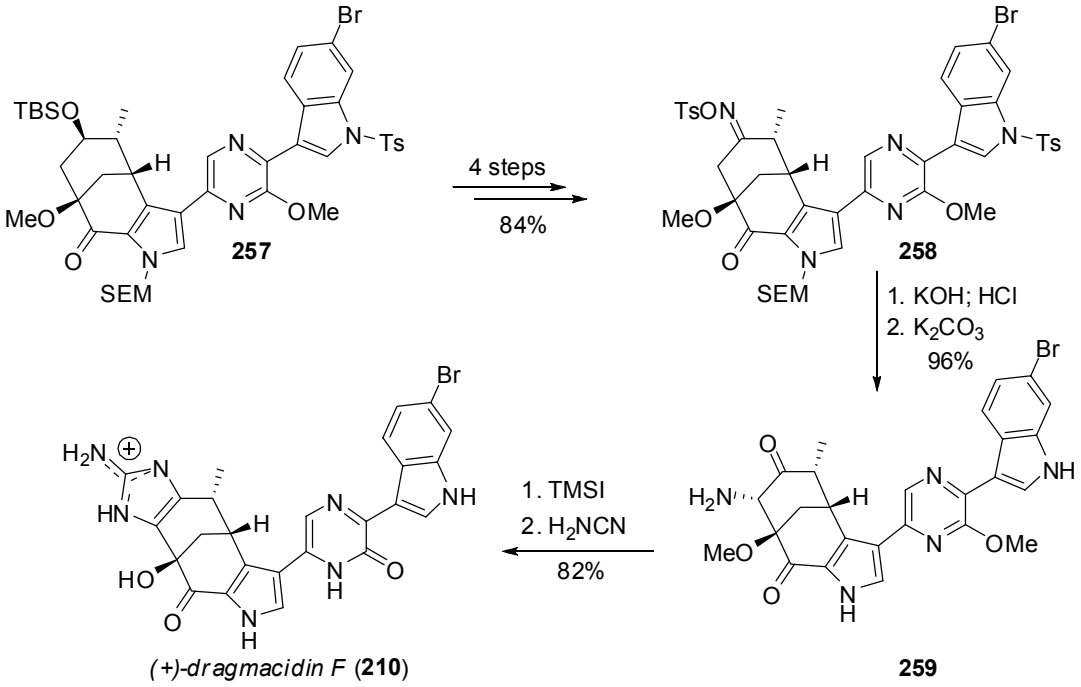
Utilizing the same conditions employed in the dragmacidin D synthesis, this borate underwent a halogen-selective Suzuki coupling with bromopyrazine **239** (Scheme 70), to give adduct **257**, having the full carbocyclic skeleton of dragmacidin F.

Scheme 70. Completion of the core ring system of dragmacidin F



The remaining synthetic challenge was introduction of the aminoimidazole ring. This was achieved by initial preparation of tosyloxime **258**, followed by Neber rearrangement to the α-amino derivative **259** (Scheme 71). Removal of the methyl ether protecting groups and treatment of the resultant pyrazinone with cyanamide in analogous fashion to **243**, (*vide supra*) gave rise to (+)-dragmacidin F (**210**).

Scheme 71. Completion of the total synthesis of (+)-dragmacidin F (**210**)

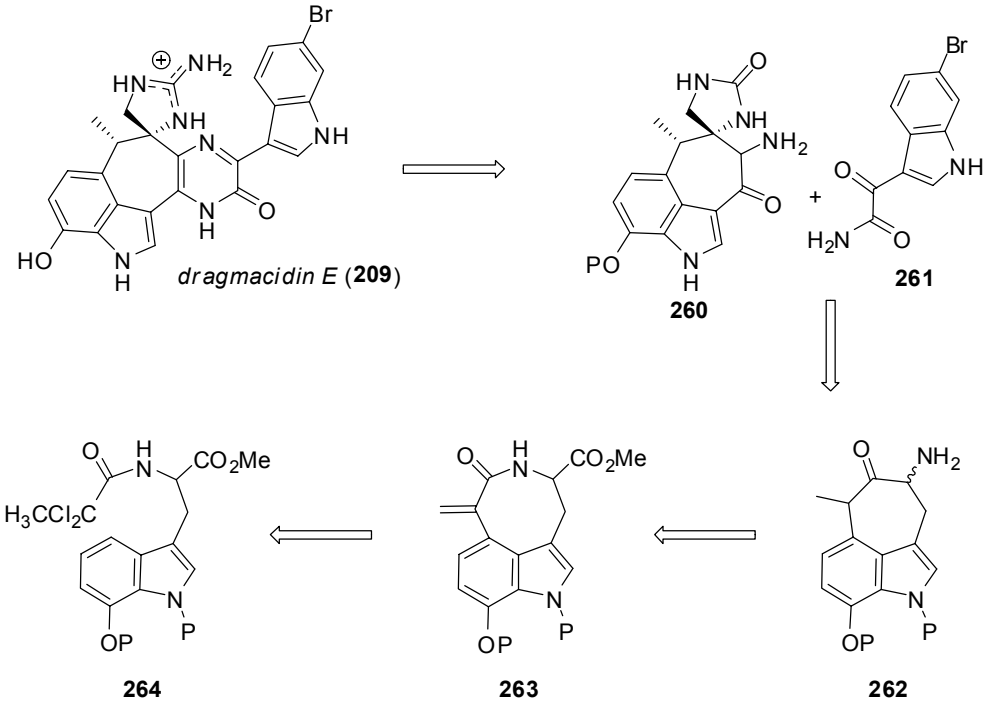


3.3.3 Dragmacidin E

Prior to our own work in this area, only one group had reported work towards a total synthesis of dragmacidin E (**209**). In this approach, the Feldman group proposed making the natural product by a cyclocondensative strategy.[81]

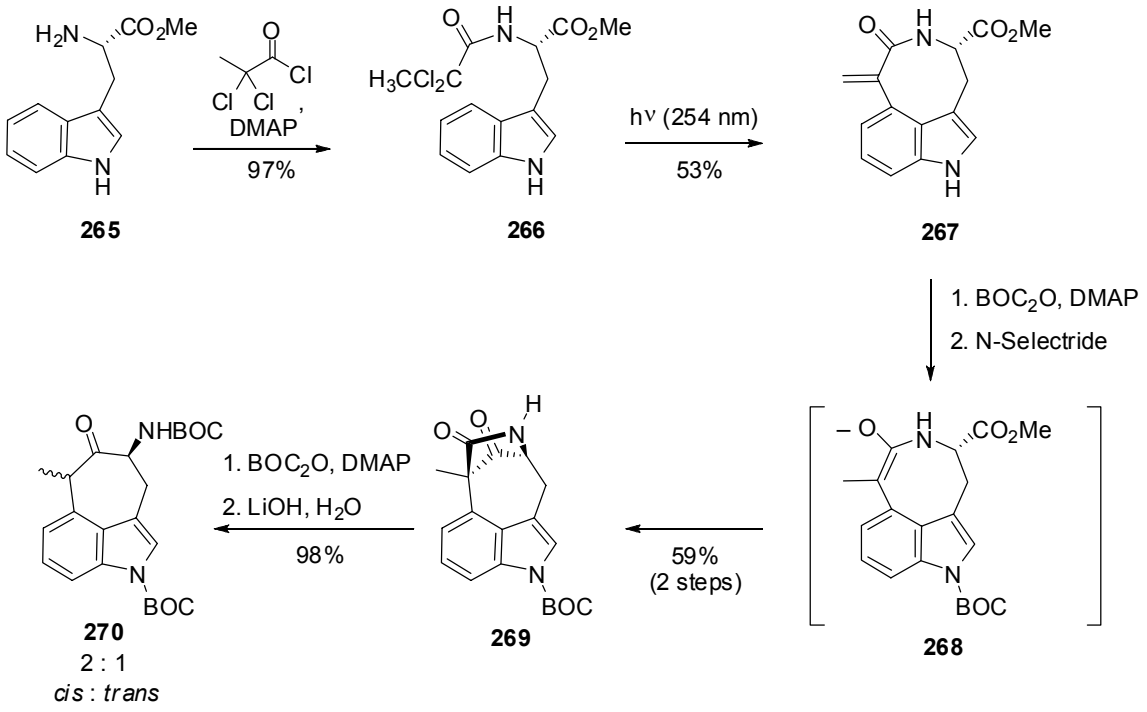
Specifically, they proposed that dragmacidin E could be prepared by the condensation of cyclic urea **260** with ketoamide **261** (Scheme 72). This urea would in turn arise from amino ketone **262** via Strecker chemistry and a benzylic oxidation. In the key step of the synthesis, aminoketone **262** would arise from the intramolecular Dieckmann cyclization of the regiospecific enolate derived from conjugate reduction of the unsaturated amide **263**. The central 7-membered ring of the natural product would be formed by a Witkop photocyclization[82] of dichloroamide **264**.

Scheme 72. Feldman's retrosynthetic analysis for dragmacidin E (**209**)



Experimentally, Witkop photocyclization precursor **266** was readily formed from tryptophan methyl ester (**265**) (Scheme 73). The subsequent photochemical cyclization proceeded in moderate yield to give the desired α,β-unsaturated lactam **267**.

Scheme 73. Preparation of cycloheptannelated indole **270**

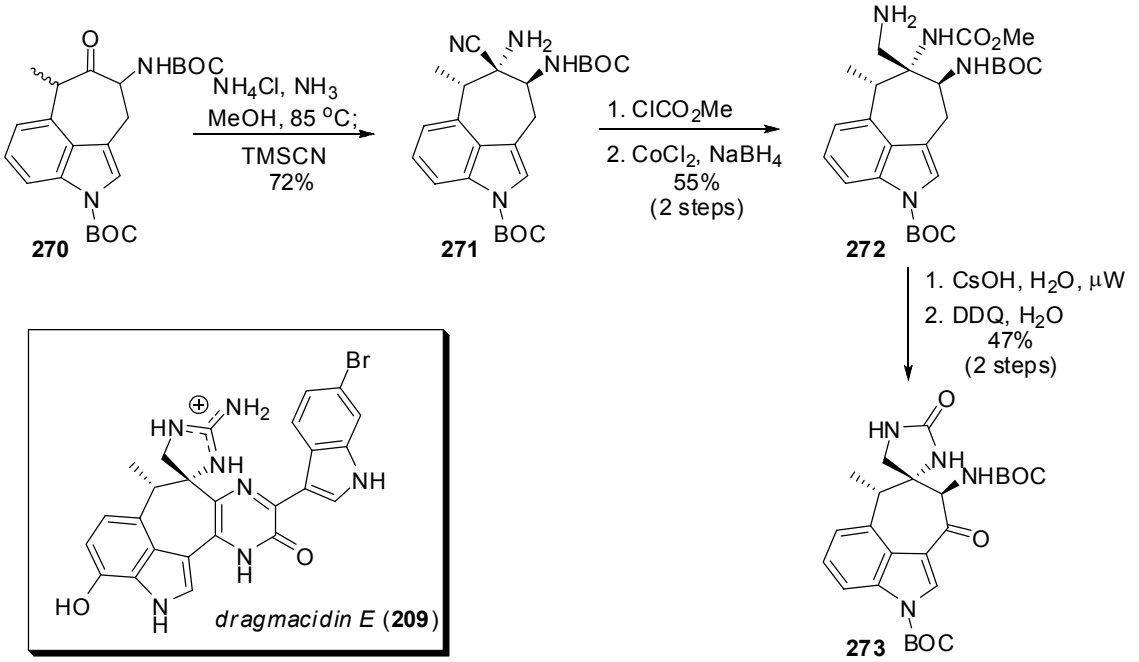


With this key intermediate in hand conditions were then investigated for the key intramolecular Dieckmann cyclization. After some experimentation, it was found that protection of indole **267** followed by treatment with N-Selectride allowed for the preparation of β-ketolactam **269**, presumably via intermediate enolate **268**. Imide formation followed by hydrolysis/decarboxylation gave aminoketone **270** as an inconsequential mixture of diastereomers.

Attention was then turned to the preparation of the imidazoline ring. When the mixture of diastereomeric ketones **270** was subjected to Strecker reaction conditions, aminonitrile **271** was obtained as a single diastereomer (Scheme 74). Presumably, under these conditions, epimerization at one or both chiral centers was occurring prior to attack by cyanide. Acylation of aminonitrile **271** and cobalt boride reduction allowed preparation of 1,2-diamine **272**. Cyclization to the corresponding urea followed by benzylic oxidation provided α-aminoketone **273**,

which is the key substrate for cyclocondensative formation of the pyrazinone ring. Efforts directed towards this closure, and towards introduction of the indole hydroxy substituent have not yet been disclosed.

Scheme 74. Preparation of spirocyclic urea **273**

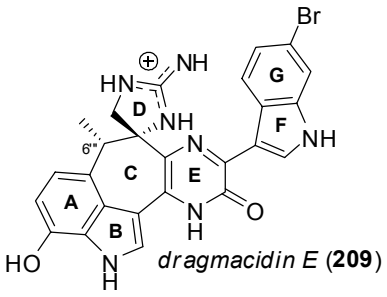


3.4 An electrocyclization approach to the synthesis of dragmacidin E

Of the three pyrazinone dragmacidin natural products, our interest was specifically drawn to dragmacidin E (**209**), since it embodies a complexly substituted indole (AB rings) that could potentially be addressed by application of our 6π-electrocyclization based methodology. In addition, the presence of additional heterocycles arrayed around the central 7-membered C ring (Figure 12) seemed to pose a significant synthetic challenge. This challenge was compounded by the presence of the spirocyclic guanidine D ring, which would

need to be constructed with control of stereochemistry, relative to the adjacent C(6''') center. In addition to the inherent challenge posed by this complex ring system, the conflicting reports of biological activity, combined with low natural availability, appeared to make the compound a prime target for total synthesis.

Figure 12. Ring labeling for dragmacidin E (**209**)



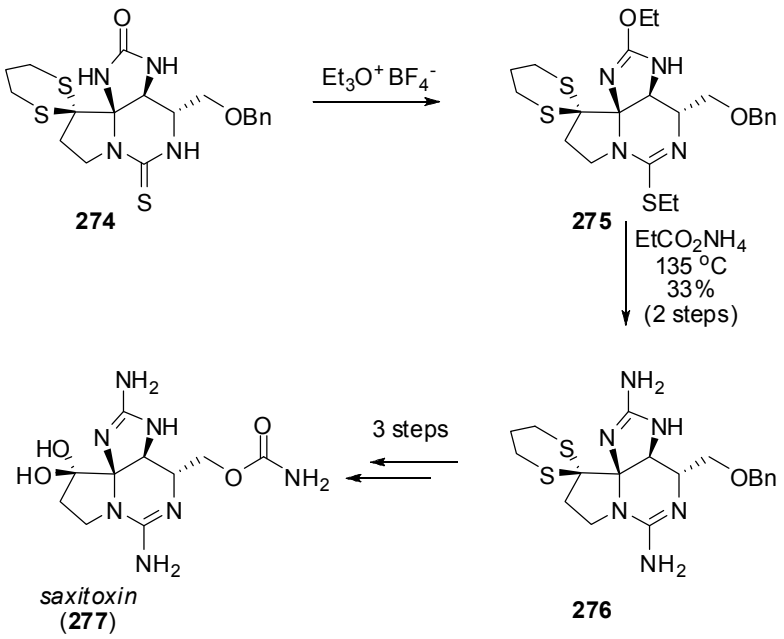
dragmacidin E (**209**)

3.4.1 Cyclic guanidine synthesis

Before a retrosynthetic analysis for the synthesis of dragmacidin E could even be contemplated however, we first had to consider possible means for construction of the challenging aminoimidazoline D ring.

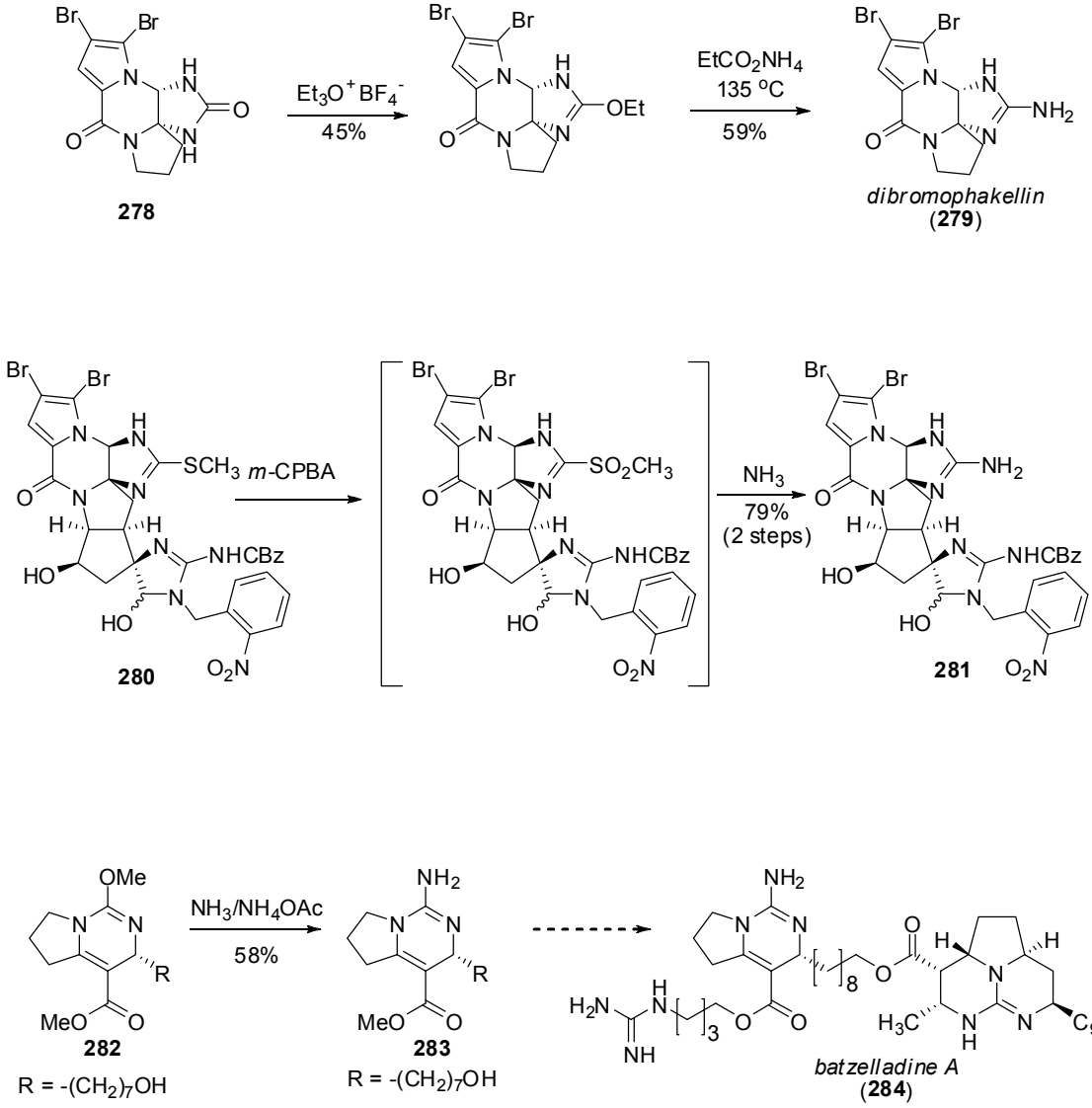
A key example of the synthesis of cyclic guanidines in the context of natural product synthesis is provided by Kishi's seminal total synthesis of (±)-saxitoxin (**277**).[83] In this paper tetracycle **274**, containing both cyclic urea and cyclic thiourea functionalities, was initially treated with Meerwein's reagent, effecting conversion to the corresponding dialkylated product **275** (Scheme 75). Upon stirring this bis-pseudourea in molten ammonium propionate at 135 ^{o}C, nucleophilic displacement at both pseudourea centers was observed, giving rise to bis-guanidine **276**.

Scheme 75. Synthesis of cyclic guanidine (±)-saxitoxin (**277**)



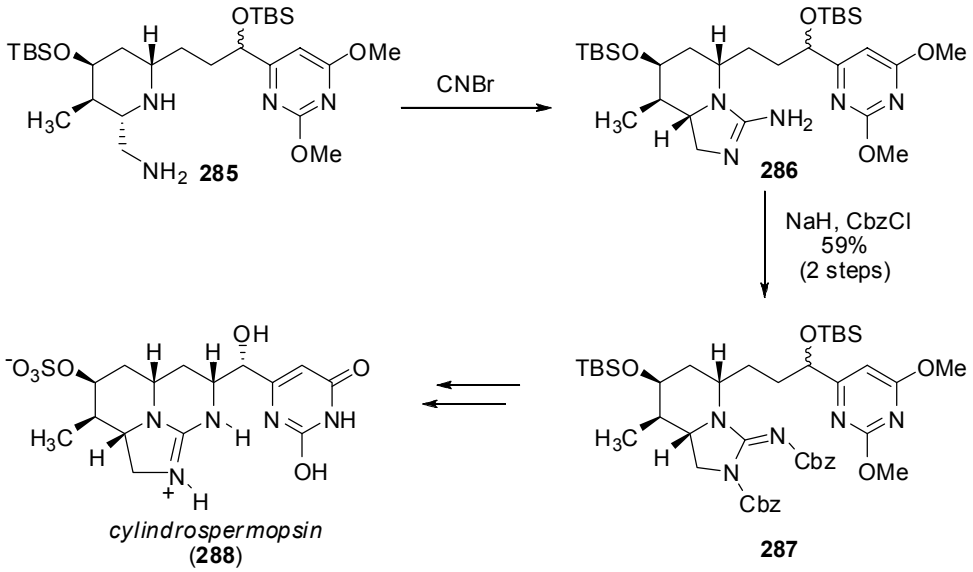
Other, related examples of pseudourea displacement in the course of natural product synthesis can be seen in Scheme 76, and include Feldman's synthesis of dibromophakellin (**279**),[84] Overman's synthesis of palau'amine derivative **281**[85] and Gin's approach to batzellidine A (**284**).[86]

Scheme 76. Cyclic guanidines via pseudourea displacement



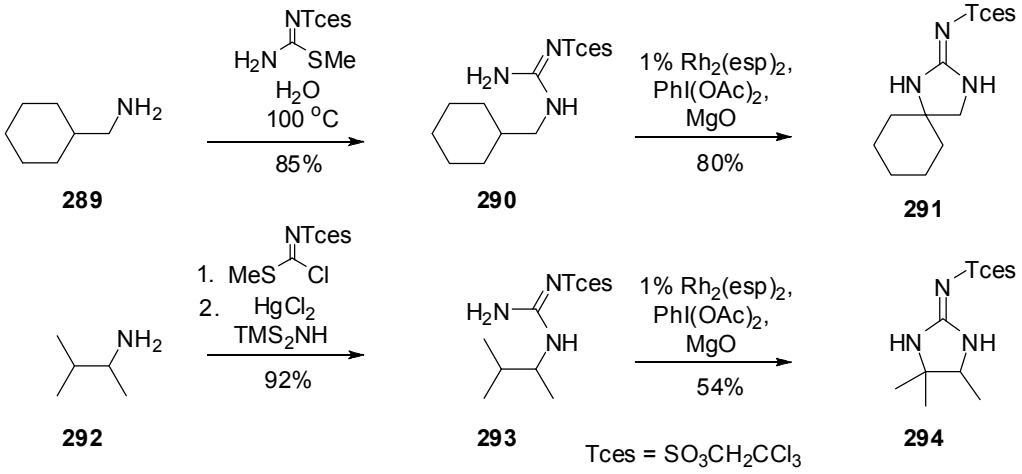
A more common approach to the preparation of cyclic guanidines involves treatment of a vicinal diamine with cyanogen bromide. One such example from Snider's synthesis of cylindrospermopsin (**288**)[87] is shown in Scheme 77. In this example, diamine **285** reacted with cyanogen bromide to give guanidine **286**.

Scheme 77. A cyclic guanidine via cyanogen bromide condensation



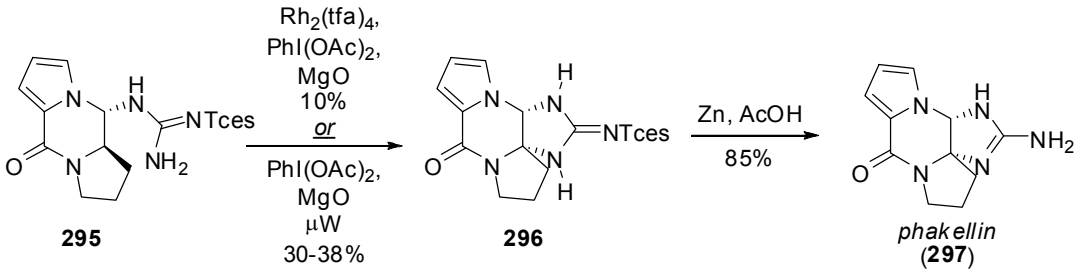
One other approach to the synthesis of this type of system was recently developed by the Du Bois laboratory.[88] They demonstrated that primary amines such as **289** and **292** could be transformed to acyclic sulfamoylguanidines **290** and **293** (Scheme 78). Upon treatment of these compounds with a rhodium catalyst under oxidative conditions, intramolecular C-H insertion occurred to give cyclic guanidines **291** and **294**. This reaction presumably proceeds via a nitrenoid intermediate.

Scheme 78. Cyclic guanidines via rhodium catalyzed C-H insertion



As yet, the sole application of this method to complex natural product synthesis has been the work of the Romo laboratory[89] directed towards the preparation of phakellin (**297**). In the course of this work, it was reported that cyclization of guanidine **295** via the Du Bois protocol provided cyclic guanidine **296** in a disappointing 10% yield (Scheme 79). It was subsequently found that the desired reaction proceeded in improved (albeit still poor) yield in the absence of the rhodium catalyst, suggesting that in this particular system an alternate, oxidative cyclization pathway was most likely operative.

Scheme 79. Romo's application of Du Bois' guanidinylation methodology

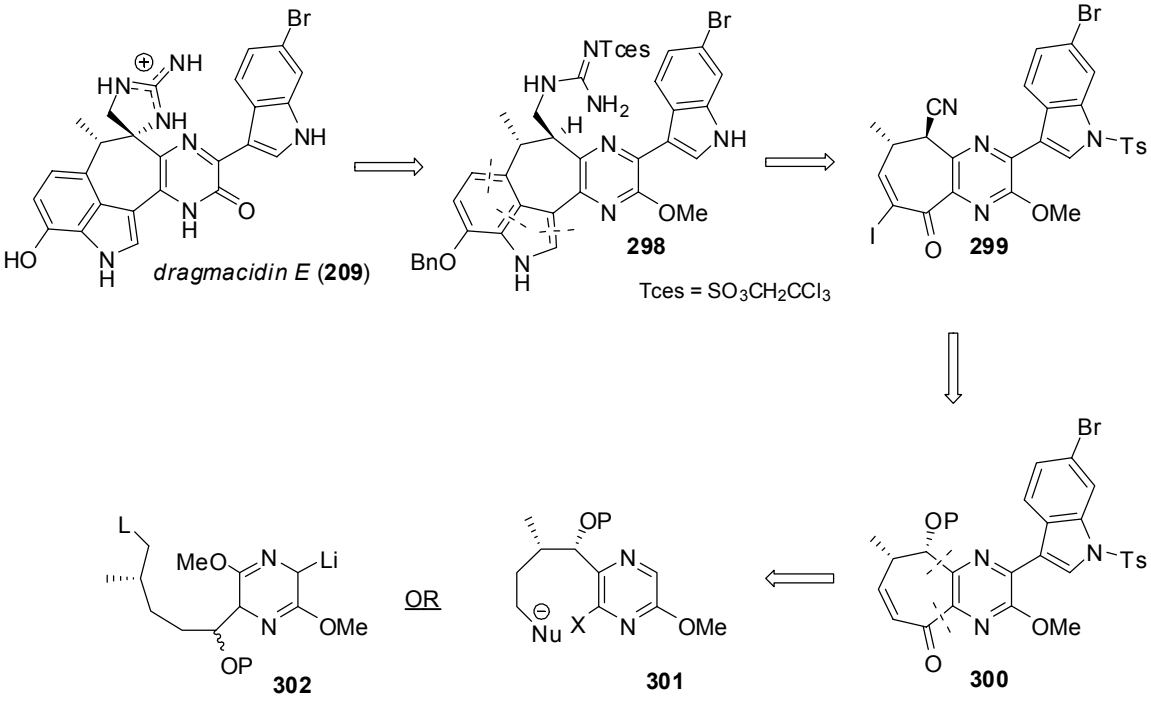


3.4.2 Retrosynthetic analyses

Armed with the above examples of cyclic guanidine formation, we began to develop a retrosynthetic plan for the synthesis of dragmacidin E (Scheme 80). We decided that the most elegant solution to the problem posed by the cyclic guanidine functionality was to employ the rhodium insertion chemistry of Du Bois at a late stage in the synthesis to cyclize acyclic guanidine **298**. The pendant guanidine, we imagined, could be elaborated from the corresponding nitrile, and the lower indole would be constructed from iodoenone **299** using our laboratory's existing methodology for the preparation of 3,4-annulated indoles. Nitrile **299** could be introduced by inversion of the corresponding alcohol **300**. Finally, the seven membered C-ring could be formed via the intramolecular displacement of

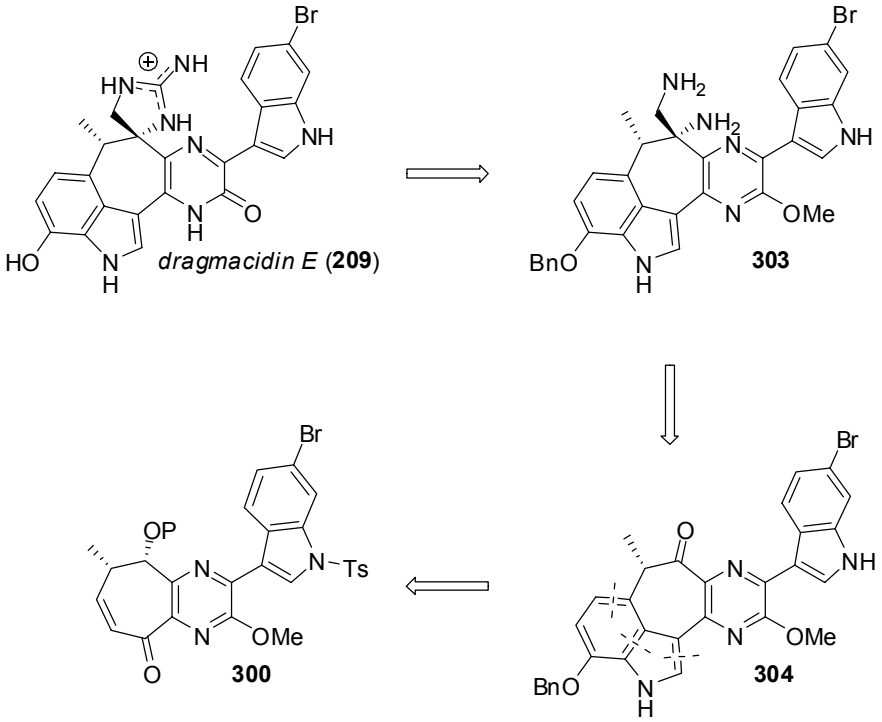
a pendant leaving group by allyl anion **302** or addition/elimination of pendant nucleophile **301**.

Scheme 80. A 6π-electrocyclization approach to dragmacidin E (**209**).



Given the relatively limited precedent for the Du Bois rhodium insertion chemistry, we also considered an alternate retrosynthetic analysis that would allow for preparation of the guanidine via a vicinal diamine (Scheme 81). In this retrosynthetic approach, dragmacidin E would be prepared from diamine **303** by either the cyanogen bromide or pseudourea displacement methods, outlined above. This diamine could arise from ketone **304** via a Strecker reaction, followed by reduction. Ketone **304** would in turn result from enone **300** via our 6π-electrocyclic ring closure methodology.

Scheme 81. An alternate approach to dragmacidin E (**209**).



CHAPTER 4

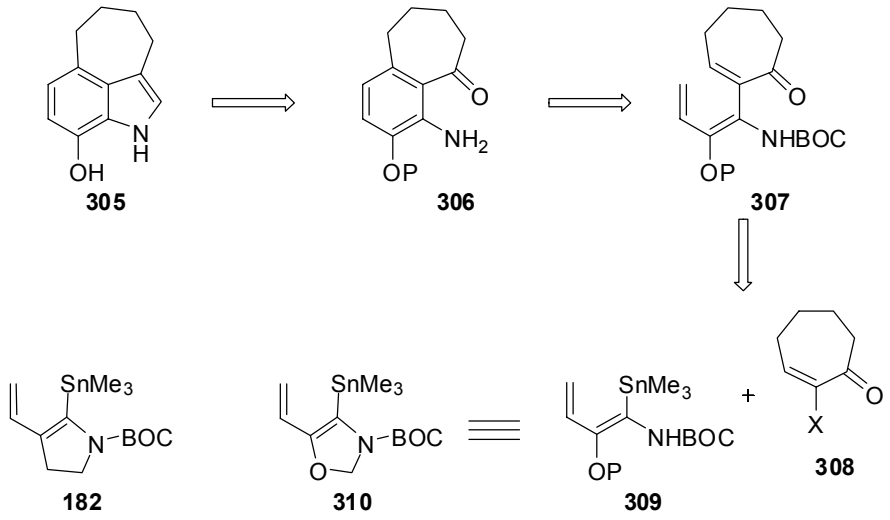
Construction of the core ring system of dragmacidin E

4.1 Development of a 7-hydroxyindole synthesis

Our retrosynthetic analysis for dragmacidin E, outlined in section 3.4.2, called for introduction of the lower indole substituent at a late stage in the synthesis via the Greshock 6π-electrocyclic ring closure methodology (Section 1.2.3). A key consideration in this proposal, however, was the presence of the hydroxy substituent at C(7”), which had not been introduced as part of the earlier work. Before commencing studies towards the synthesis of the pyrazine core of dragmacidin E, we decided to examine the feasibility of using our methodology for the preparation of 7-hydroxyindole substrates by preparing a simple model system.

The model system we initially decided to examine was the cycloheptannelated 7-hydroxyindole **305**. We believed this indole could be prepared from triene **307** via our standard 6π-electrocyclic and Råileanu ring closures (Scheme 82). Direct application of the Greshock methodology would then require the coupling of haloenone **308** and the potentially difficult to prepare stannane **309**.

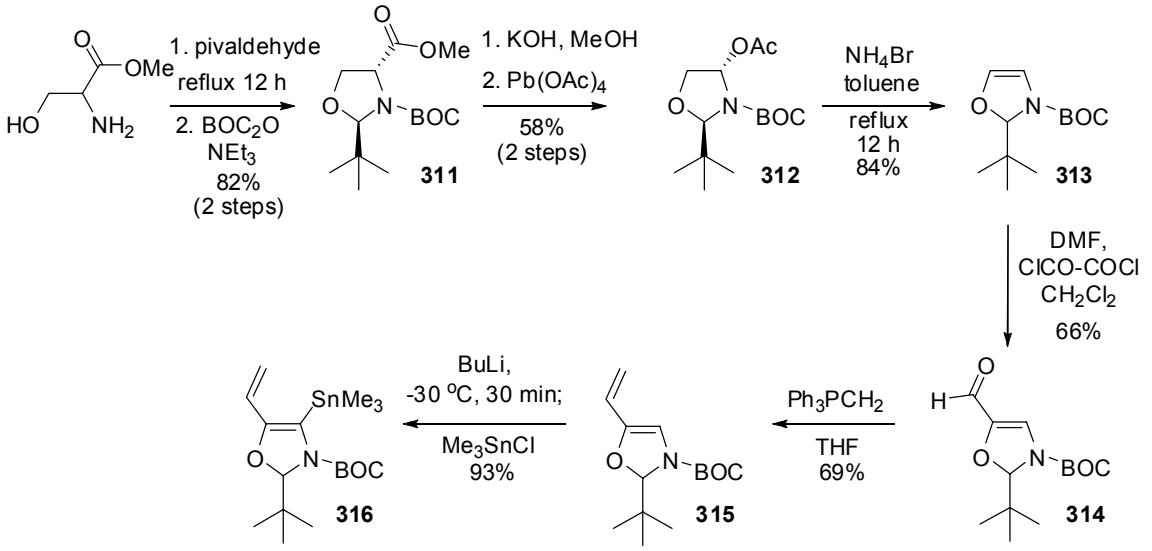
Scheme 82. A strategy for the synthesis of 7-hydroxyindoles



We soon realized, however, that the analogous stannane **310** would also provide access to the desired ring system. Furthermore, this stannane is simply the oxazoline variant of pyrroline **182**, which we had previously prepared as part of our γ-lycorane studies (Section 2.4.2).

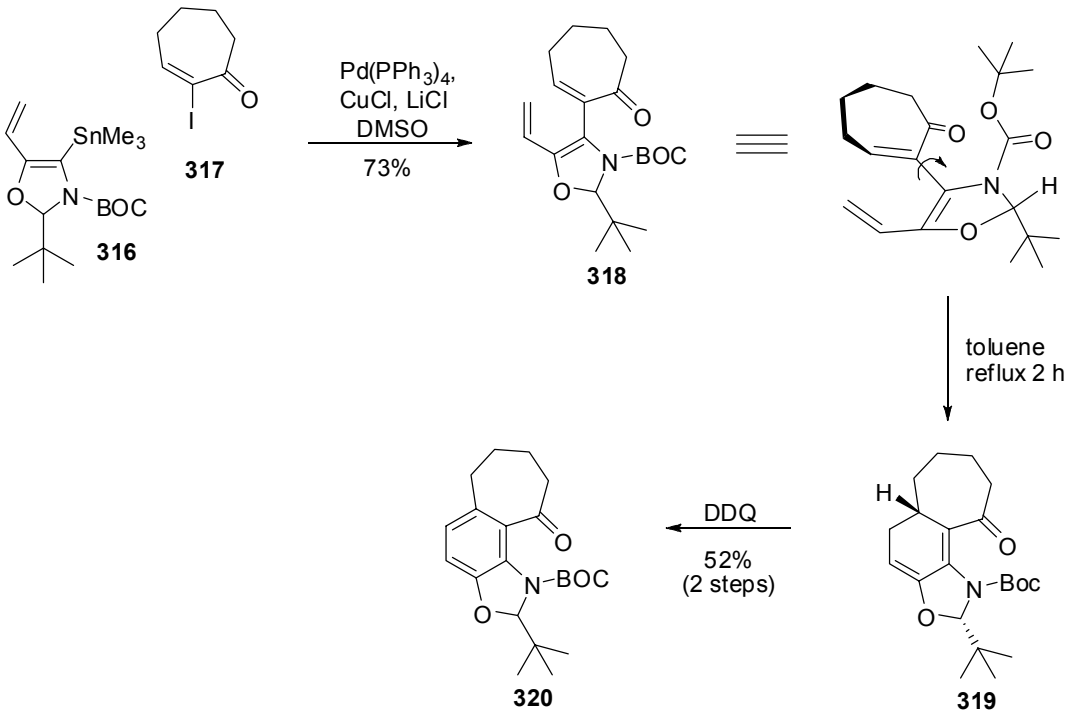
The preparation and use of functionalized oxazolines has been widely studied, most notably by Seebach,[90] in the context of amino acid synthesis. We were able to use this existing methodology, with slight modifications, to prepare vinylpyrroline **315**. Specifically, the N,O-acetal of serine methyl ester was prepared and protected to give ester **311**. Saponification of this ester followed by treatment with $Pb(OAc)_4$ gave acetate **312**. This acetate underwent elimination to give an oxazoline **313**. Formylation of oxazoline **313** occurred exclusively at the C(5) position to give aldehyde **314**. Elaboration of this aldehyde to stannane **316** was performed in analogous fashion to our earlier γ-lycorane work.

Scheme 83. Preparation of oxazolidine stannane **316**



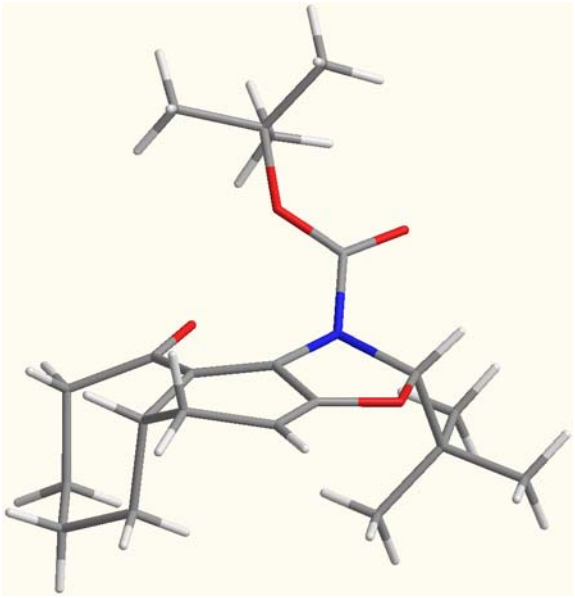
Coupling of stannane **316** with vinyl iodide **317** under the conditions employed by Greshock ($Pd(PPh_3)_4$, CuI, THF) was unsuccessful, necessitating a brief screening of potential coupling conditions. Ultimately, it proved necessary to employ the optimized conditions developed by Corey for the Stille coupling of hindered stannanes ($Pd(PPh_3)_4$, CuCl, LiCl, DMSO),[91] which gave the desired triene **318** in acceptable yield.

Scheme 84. Preparation and electrocyclization of a divinyloxazoline



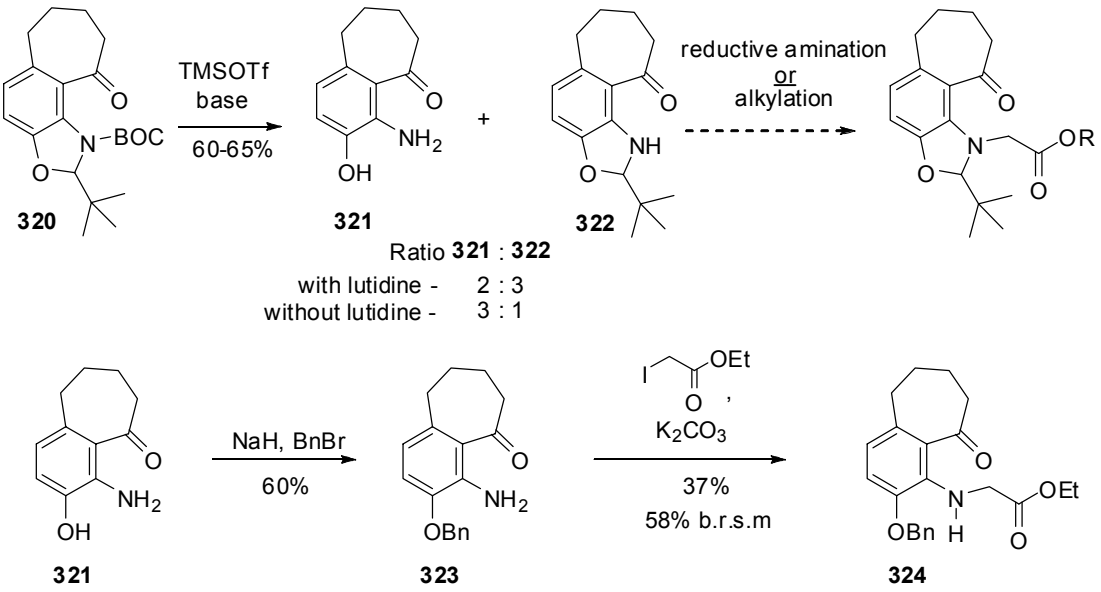
We were pleased to find that triene **318** underwent a facile electrocyclic ring closure to give dihydrobenzoxazoline **319**. Intriguingly, this diene was isolated as a single diastereomer, whose relative stereochemistry was identified by X-ray crystallography (Figure 13). This remote stereoinduction can be explained by the influence of the *tert*-butyl substituent forcing the BOC group out of plane, thereby influencing the torquoselectivity of the electrocyclic ring closure. While intriguing, however, this result was ultimately inconsequential as diene **319** was immediately aromatized to benzoxazoline **320**.

Figure 13. X-ray crystallographic structure determination of diene **319**



Treatment of BOC-carbamate **320** with TMSOTf provided a readily separable mixture of aminophenol **321** and benzoxazoline **322**. The composition of this mixture favored the aminophenol in the absence of added base, while the benzoxazoline product was favored in the presence of 2,6-lutidine (Scheme 85).

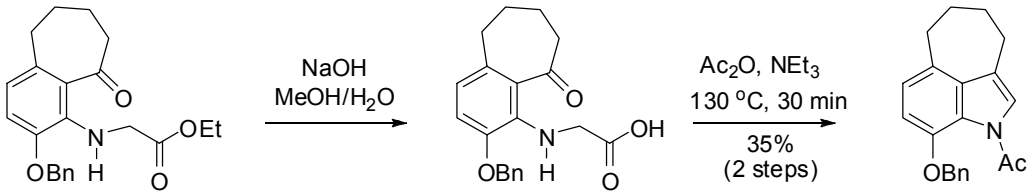
Scheme 85. Introduction of an acetic acid sidechain



We attempted to directly introduce an acetic acid sidechain to benzoxazoline **322**, in preparation for closure via our standard "Råileanu" protocol. Unfortunately, this hindered amine proved resistant to the reductive amination conditions employed by Greshock, as well as to alkylation with ethyl iodoacetate. We therefore elected to advance aminophenol **321** to the benzyl protected, primary aniline **323**. Whereas this less substituted amine was also unreactive towards reductive amination, the corresponding alkylation did provide ester **324** in modest yield.

Saponification of the ester (Scheme 86), followed by Råileanu closure under our standard conditions gave heptannelated indole **326** in modest yield (unoptimized).

Scheme 86. Completion of a 7-hydroxyindole synthesis



324 **325** **326**

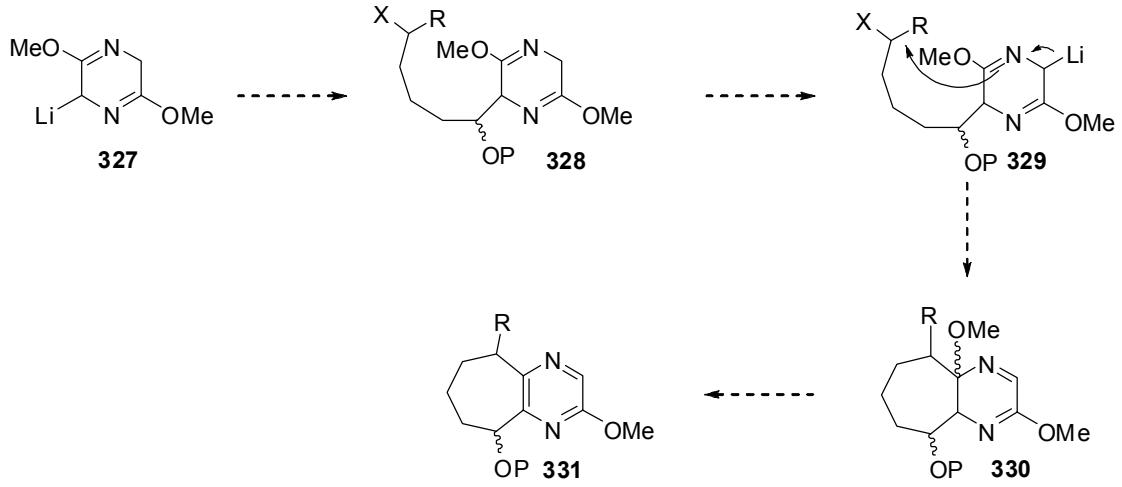
4.2 Strategies toward annulated pyrazines

4.2.1 Bis-imidate alkylation approach

Having demonstrated our ability to utilize a 6π-electrocyclization approach to prepare 7-hydroxyindoles from iodoenones, we shifted our focus to the preparation of an iodoenone incorporating the tetrasubstituted pyrazine embodied within dragmacidin E.[92]

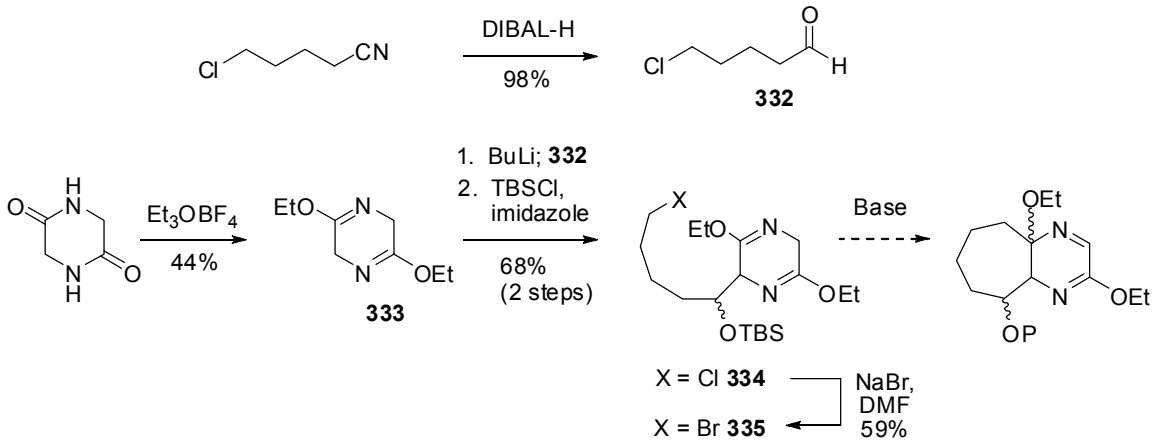
Our initial strategy for the preparation of pyrazine **331** is shown conceptually in Scheme 87. We imagined that treatment of the well-precedented[93] lithio-bis-imidate **327** with an appropriate aldehyde would allow preparation of alcohol **328**. A second metalation would then provide a second lithioimidate which could close to annulated pyrazine **331**.

Scheme 87. Bis-imidate strategy for the preparation of annulated pyrazine **331**



Experimentally, it was found that the lithio derivative of bis-imidate **333** could be readily added to aldehyde **332**[94] to give, after O-silyl protection, chloride **334**. Attempted lithiation of this chloride (or the corresponding bromide **335**) with *n*-butyllithium, *t*-butyllithium or LDA resulted only in recovery of starting material or decomposition.

Scheme 88. Attempted bis-imidate cyclization

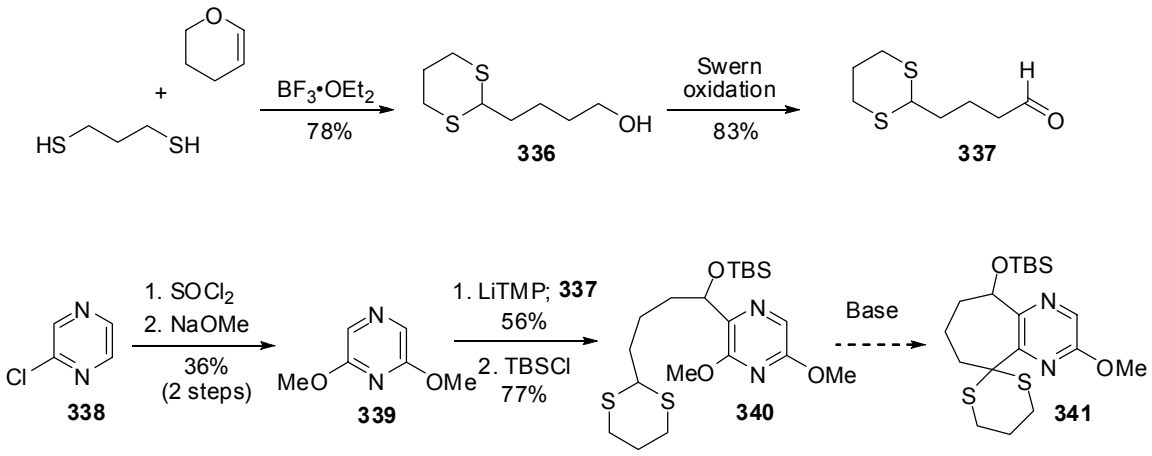


4.2.2 A pendant nucleophile approach to annulated pyrazines

Our second approach to an annulated pyrazine suitable for transformation to dragmacidin E (Scheme 89) would rely upon the intramolecular cyclization of a pendant nucleophile onto a bis-alkoxypyrazine substrate. Intermolecular nucleophilic addition/elimination reactions of *halo*pyrazines are well precedented for a variety of nucleophiles, including amines,[95] alkoxides,[96] cyanide[97] and enolates,[98] and we hoped that with a suitable pendant anion we could effect a similar substitution of methoxide.

To that end, pyrazine **339** was prepared in two steps from chloropyrazine (**338**). Deprotonation via a known[99] protocol and addition to the aldehyde derived from alcohol **336**[100] gave, after protection, dithiane **340**. Again, however, attempts at cyclization proved fruitless.

Scheme 89. Nucleophilic addition/elimination approach to annulated pyrazines

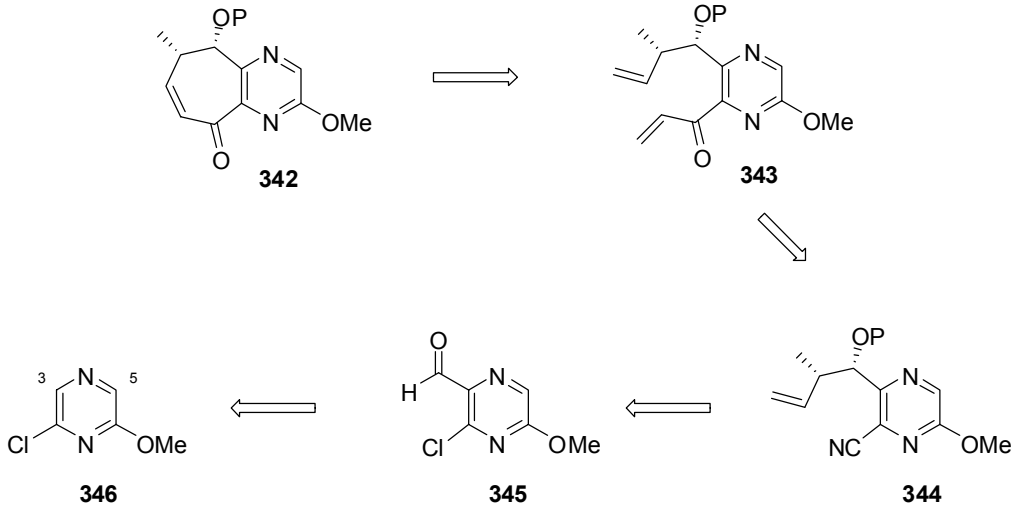


Metalation conditions attempted
LiTMP -78 °C to rt
n-BuLi, -78 °C
n-BuLi, -78 °C to -20 °C
n-BuLi, HMPA, -78 °C
t-BuLi, HMPA -78 °C

4.2.3 A ring-closing-metathesis approach to annulated pyrazines

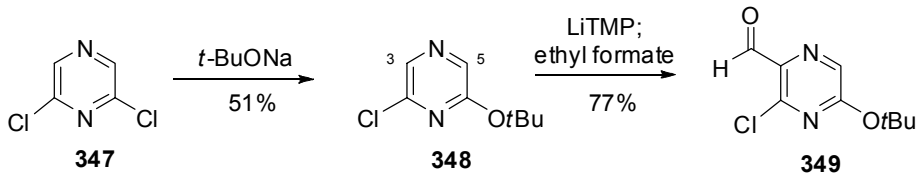
This brief exposure to pyrazine metalation chemistry led us to consider a third approach to the desired seven membered C-ring, represented retrosynthetically in Scheme 90. In this approach, we envisioned that cycloheptenone **342** would be prepared via a ring-closing-metathesis reaction of diene **343**. The necessary enone functionality could in turn be elaborated from nitrile **344**, which would arise from sequential additions of cyanide and a butenyl Grignard reagent to aldehyde **345**. This aldehyde would arise from metalation of pyrazine **346** at C(3).

Scheme 90. Metathesis approach to annulated pyrazines



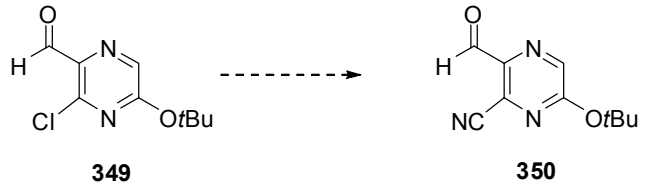
Experimentally, we found it necessary to employ *t*-butoxypyrazine **348** as our initial substrate, in order to prevent competitive deprotonation at C(5), and were able to prepare aldehyde **349** in good yield.

Scheme 91. Regiocontrolled preparation of a pyrazinyl aldehyde



We had hoped at this point we would be able to effect conversion of chloride **349** to the corresponding nitrile **350** (Scheme 92). We initially attempted to do so by simple nucleophilic addition/elimination of cyanide,[101] but were unsuccessful. We then identified protocols wherein chloropyrazines had been converted to the corresponding nitriles in the presence of palladium catalysts.[102] These conditions also proved unsuccessful for our system.

Scheme 92. Attempted pyrazinyl nitrile formation

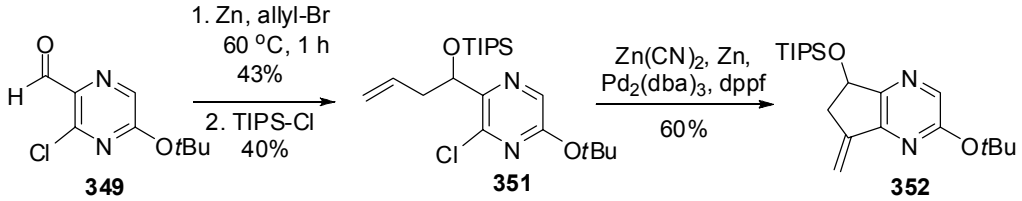


349 **350**

Cyanation conditions attempted
CuCN, DMF 80 ^{o}C
CuCN, DMF 120 ^{o}C
KCN, DMF, 80^{o}C
KCN, 18-crown-6, THF, reflux
KCN, $Pd(PPh_3)_4$, DMF, 100 ^{o}C
$Zn(CN)_2$, Zn, Pd_2dba_3, dppf, DMF, 80 ^{o}C 4 h

Rationalizing that the aldehyde functionality may not be compatible with these conditions, we decided to elaborate pyrazine **349** to protected alcohol **351** (Scheme 93). Unfortunately, subjection of this substrate to the palladium catalyzed cyanation conditions did not result in the desired product. Instead, 5-*exo*-Heck cyclization to cyclopentannelated pyrazine **352** was observed.

Scheme 93. An unexpected Heck reaction

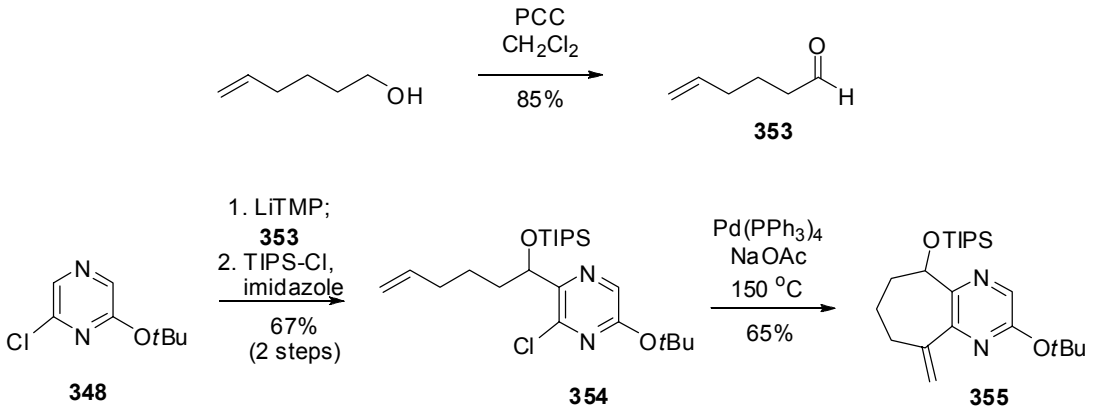


349 **351** **352**

4.2.4 7-*exo*-Heck cyclization approach to annulated pyrazines

Upon isolation of cyclopentannelated pyrazine **352**, we reasoned that the corresponding cycloheptannelated product might also be accessed by the cyclization of the appropriate substrate. Indeed, we were pleased to find that chloride **354** did undergo a facile 7-*exo*-trig cyclization, albeit under relatively forcing conditions, giving a product we felt was appropriately functionalized for introduction of both the cyclic guanidine ring and the lower 7-hydroxyindole substructure (Scheme 94).

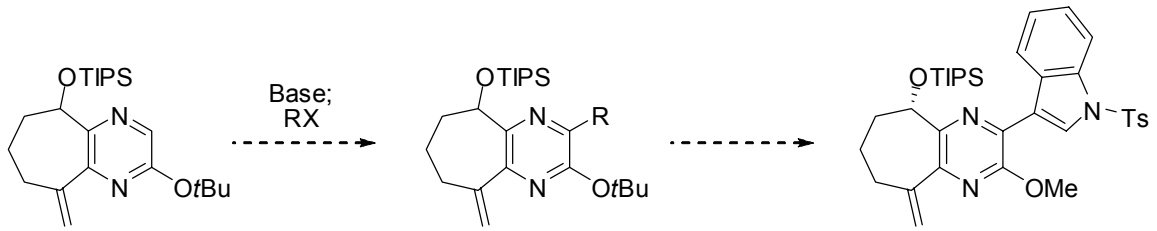
Scheme 94. A 7-*exo*-Heck cyclization approach to annulated pyrazines



4.3 Synthesis of the core ring system of dragmacidin E

With this functionalized ring in hand, our next goal became the introduction of the indolyl substituent at C(6). We had anticipated doing so via the two step procedure shown in Scheme 95, employing a second pyrazine metalation. Curiously, however, despite the formation of intensely blue/green anionic complexes upon addition of lithium bases to pyrazine **355**, quenching the resultant solutions with electrophiles returned only starting material (or decomposition) under any of the conditions tested.

Scheme 95. A 7-*exo*-Heck cyclization approach to annulated pyrazines

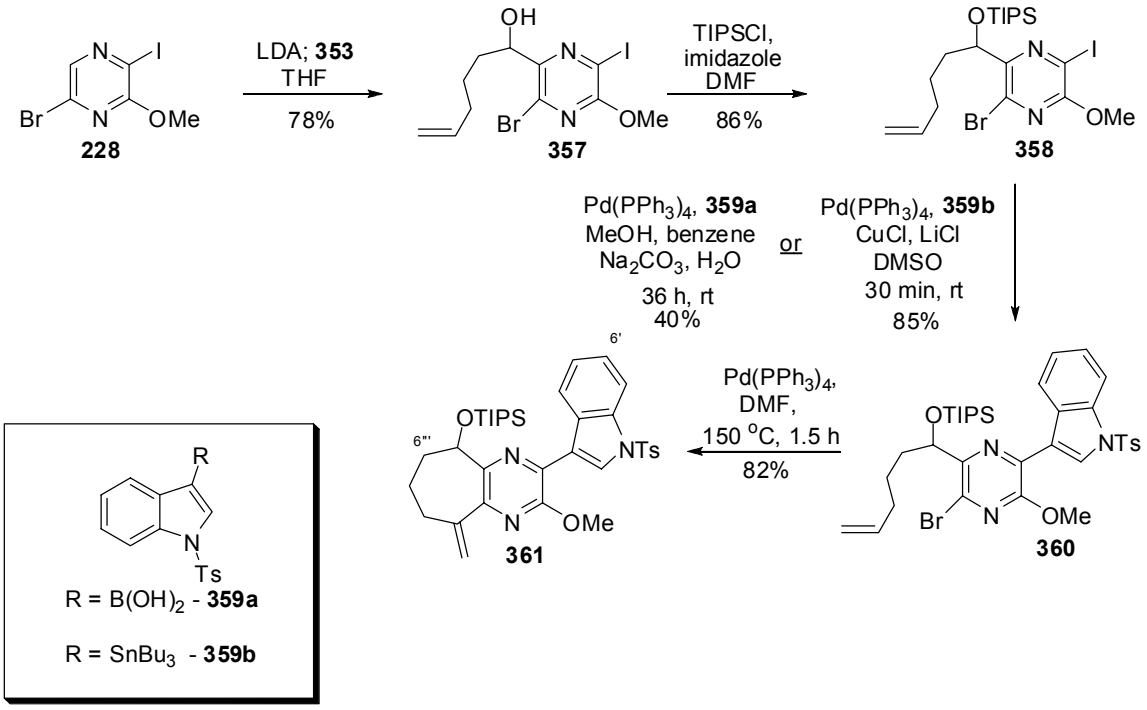


355 R = $SnBu_3$, I **356**

Metalation conditions attempted
LDA, -78 ^oC; I_2
LDA, -78 ^oC; MeI
LDA, HMPA (5 eq.), -30 ^oC to 0 ^oC; I_2
LDA, TMEDA, -30 ^oC; I_2
n-BuLi, -78 ^oC; MeI
t-BuLi, -78 ^oC; MeI
LDA (ether), -78 ^oC; I_2
$LiNEt_2$ (DME), -20 ^oC; I_2
t-BuLi (DME), -50 ^oC; I_2
n-BuLi, TMEDA (DME), -50 ^oC ; MeI
n-BuLi, TMEDA (ether), -50 ^oC; MeI

Reasoning that it might be better to introduce a C(6) substituent prior to cycloheptannelation, we then considered the possibility of metalating pyrazine **228** (Scheme 96). We were pleased to find this reaction proceeded smoothly to give, after protection, TIPS ether **358**. While coupling of this aryl iodide with boronic acid **359a** under the conditions employed by the Stoltz group proved problematic, coupling with stannane **359b**[103] proceeded efficiently. Finally, Heck cyclization of this substrate, again under relatively forcing conditions ($Pd(PPh_3)_4$, 150 ^oC) provided cycloheptannelated pyrazine **361**.

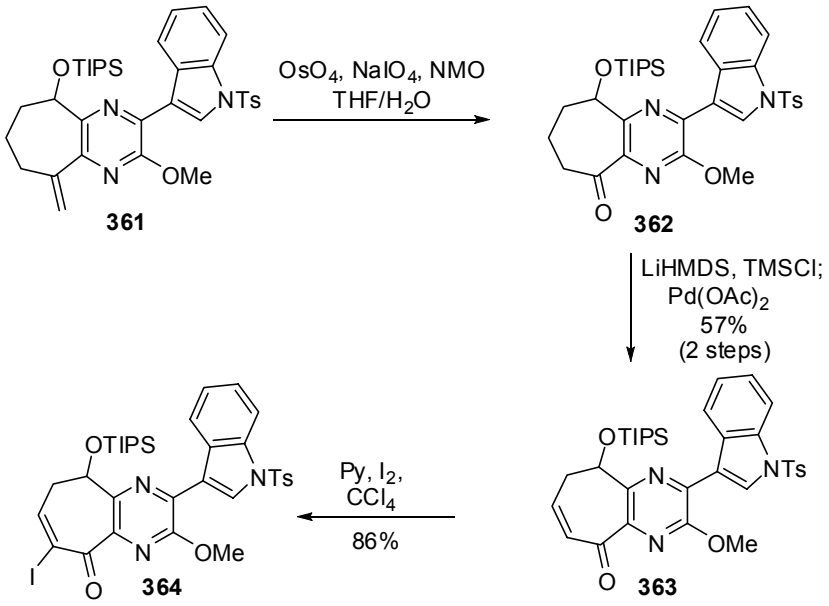
Scheme 96. Synthesis of a cycloheptannelated pyrazine



It should be noted at this point that pyrazine **361** lacked several key substituents that would be needed for the preparation of the complete natural product, namely, the methyl substituent at C(6’’’) and the bromo substituent at C(6’). We nonetheless decided to continue with this substrate as a model system for a later total synthesis.

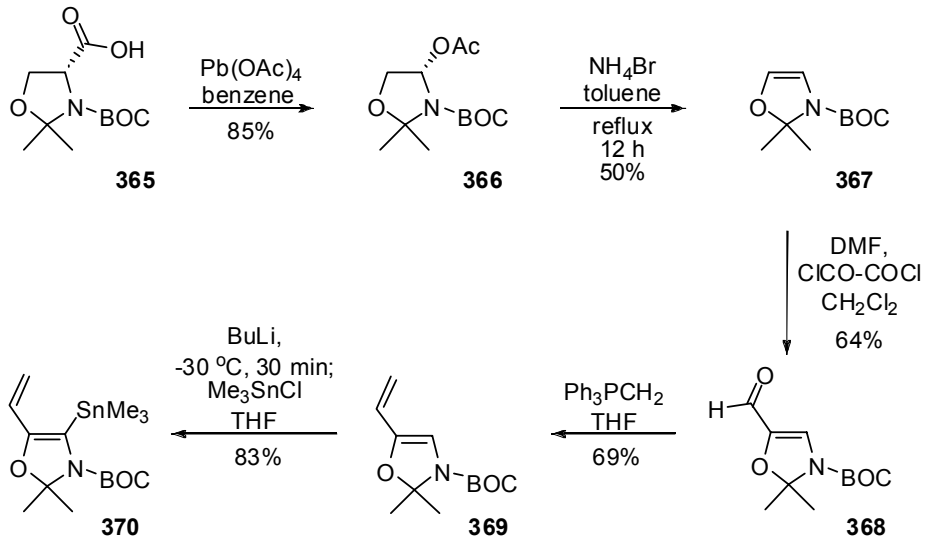
To that end, the exocyclic olefin of **361** was oxidatively cleaved with OsO_4 (Scheme 97). Installation of the desired unsaturation was effected via the Saegusa protocol,[104] and the resultant enone **363** halogenated under the conditions of Johnson,[105] to give α-iodoenone **364**.

Scheme 97. Elaboration of iodoenone coupling partner



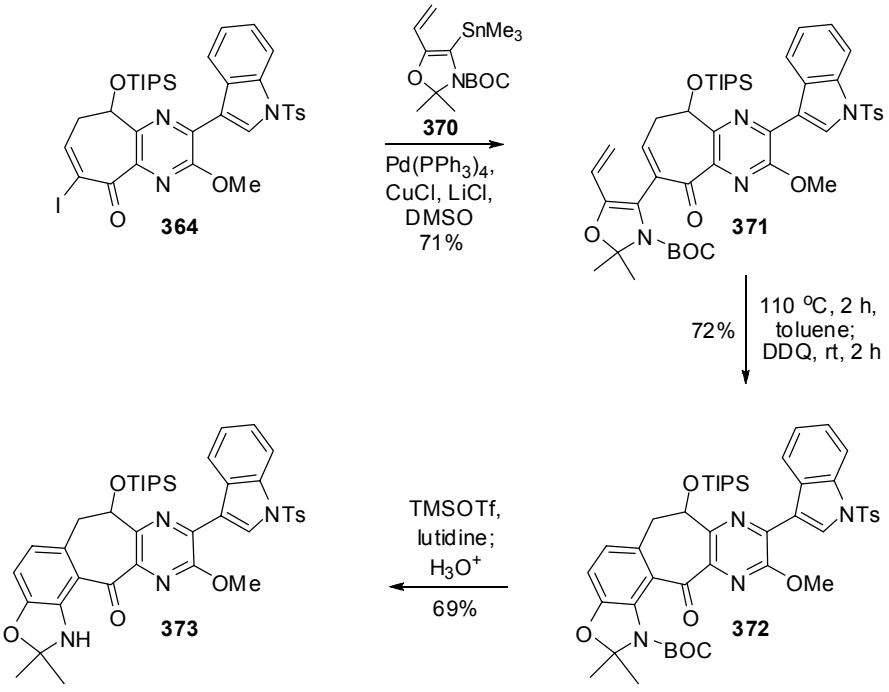
With this key component in hand, we were now ready to attempt our annulation methodology. Our earlier model system had employed racemic *t*-butyloxazoline **316** (Scheme 83) as a coupling partner. However, we elected at this point to switch to the achiral dimethyloxazoline **370**, in order to prevent the complication posed by the additional stereocenter. This stannane was prepared via a near identical protocol (Scheme 98).

Scheme 98. Preparation of dimethyloxazoline stannane **370**



Coupling under the Corey conditions then furnished the desired trienecarbamate **371**.

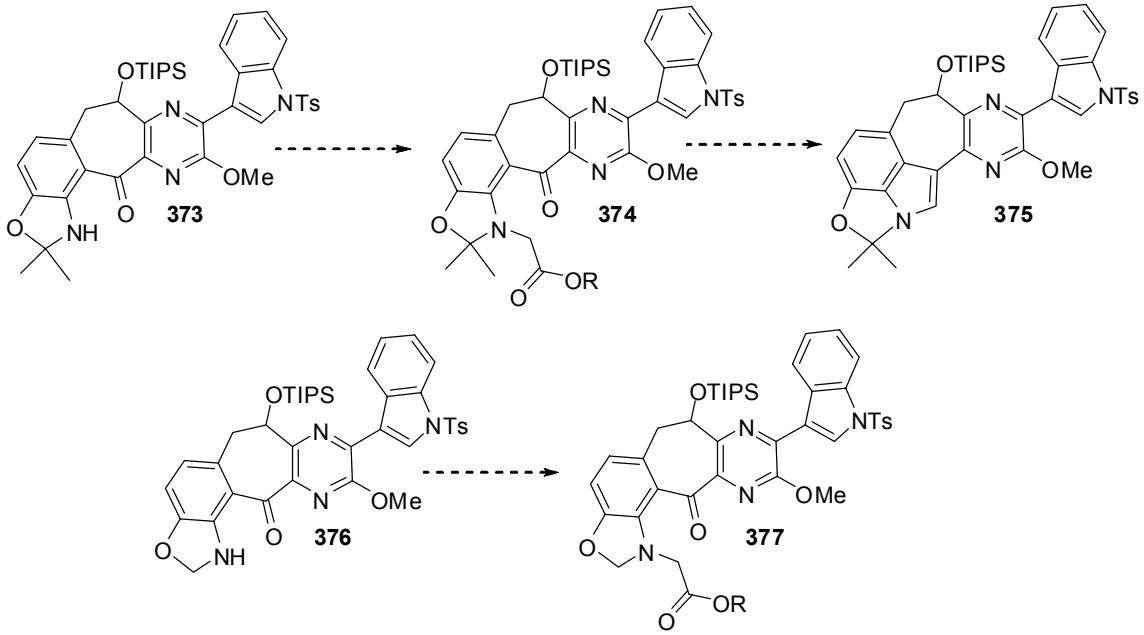
Scheme 99. Preparation and electrocyclic ring closure of trienecarbamate **371**



We were pleased to find that this highly substituted system underwent the expected facile thermal 6π-electrocyclization reaction in refluxing toluene, giving a diastereomeric mixture of dihydroanilines, which were typically oxidized without isolation to give BOC-benzoxazoline **372**. Removal of the BOC-protecting group gave benzoxazoline **373** as an intensely colored orange-red film.

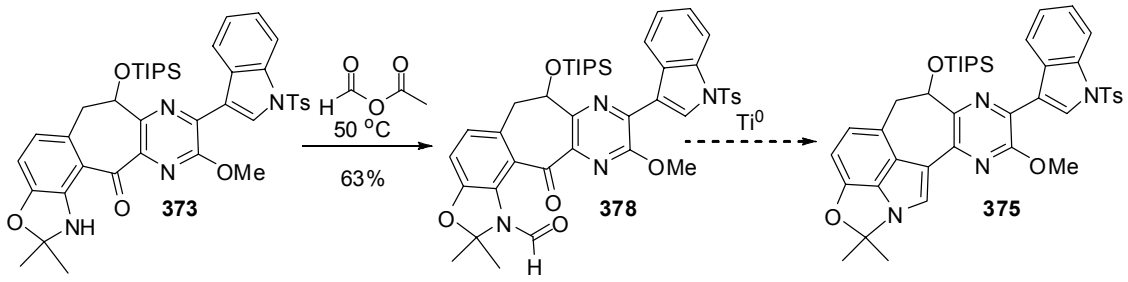
Extensive efforts were directed at this point towards the direct introduction of an acetic acid sidechain to benzoxazoline **373** in preparation for a Råileanu closure to indole **375** (Scheme 100). These efforts were uniformly unsuccessful. The less sterically demanding benzoxazoline **376** was also prepared, but did not provide any advantage.

Scheme 100. Attempted formation of oxazoline indoles



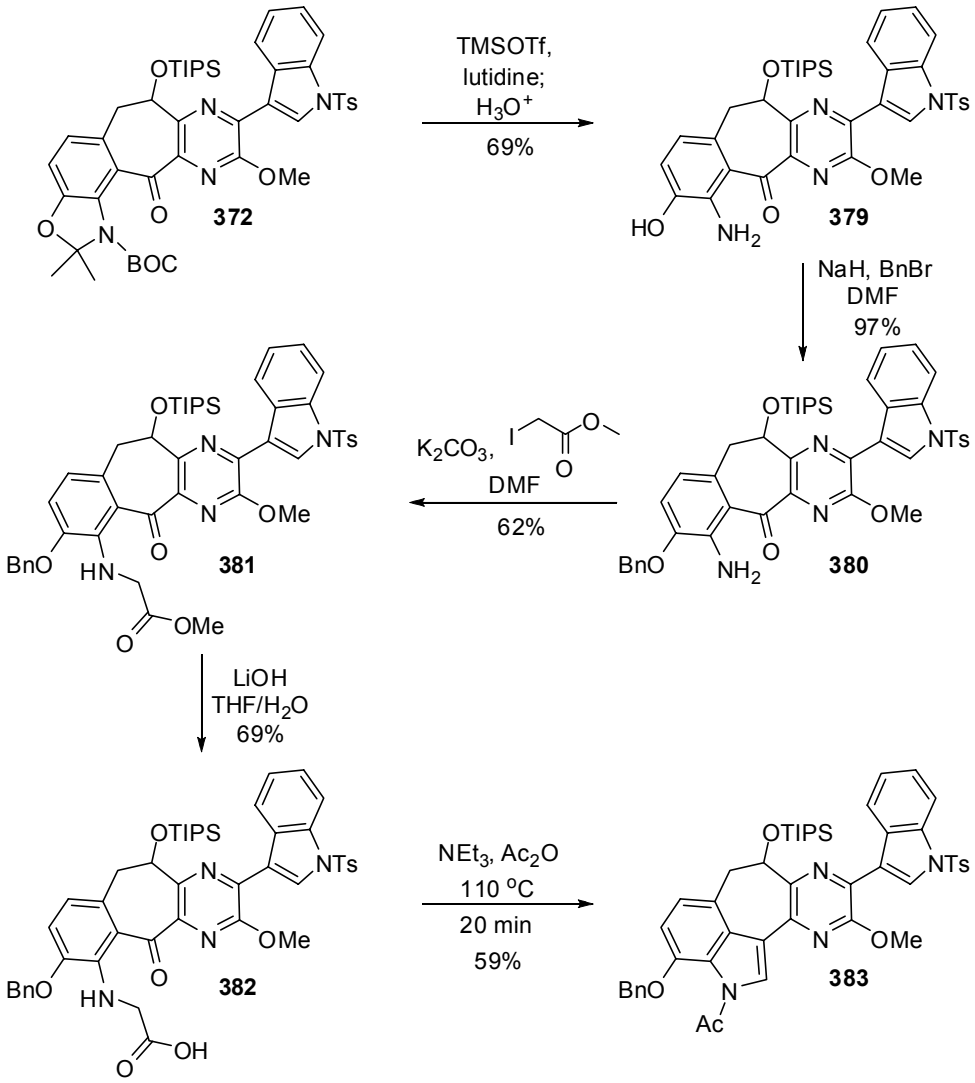
An alternate McMurray coupling approach[106] to indole **375** via formylbenzoxazoline **378** was also unsuccessfully explored (Scheme 101).

Scheme 101. Alternate McMurray indole closure



We ultimately elected to return to our original endgame, by first effecting a one-pot deprotection of benzoxazoline **372**, followed by reprotection of the phenol (Scheme 102). Careful monoalkylation of the resultant benzyl ether **380** with ethyl iodoacetate and saponification gave the desired acetic acid sidechain, which was cyclized to *N*-acetylindole **383** under optimized conditions in moderate yield.[107]

Scheme 102. Completion of the core ring system of dragmacidin E

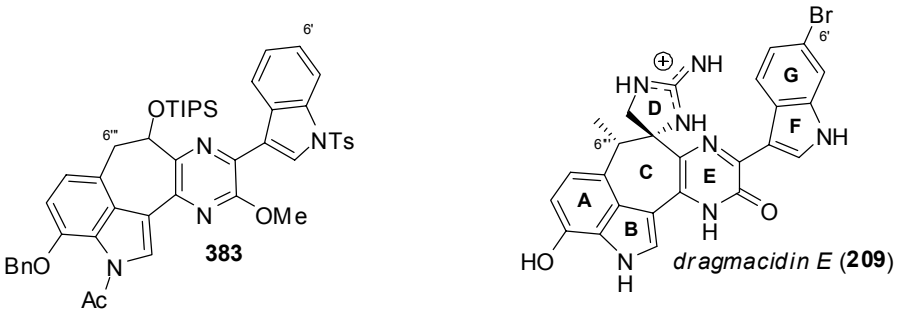


Chapter 5 -
Towards the synthesis of dragmacidin E

5.1 The fully substituted core ring system of dragmacidin E

Having demonstrated our ability to construct indole **383**, embodying the core ring system of dragmacidin E (Figure 14), we turned our attention to the total synthesis of the complete natural product. To do so, three major challenges remained to be solved, namely introduction of the C(6''') methyl substituent, introduction of the C(6') bromine and stereoselective construction of the spirocyclic aminoimidazoline D ring.

Figure 14. From model system **383** to dragmacidin E (**209**)

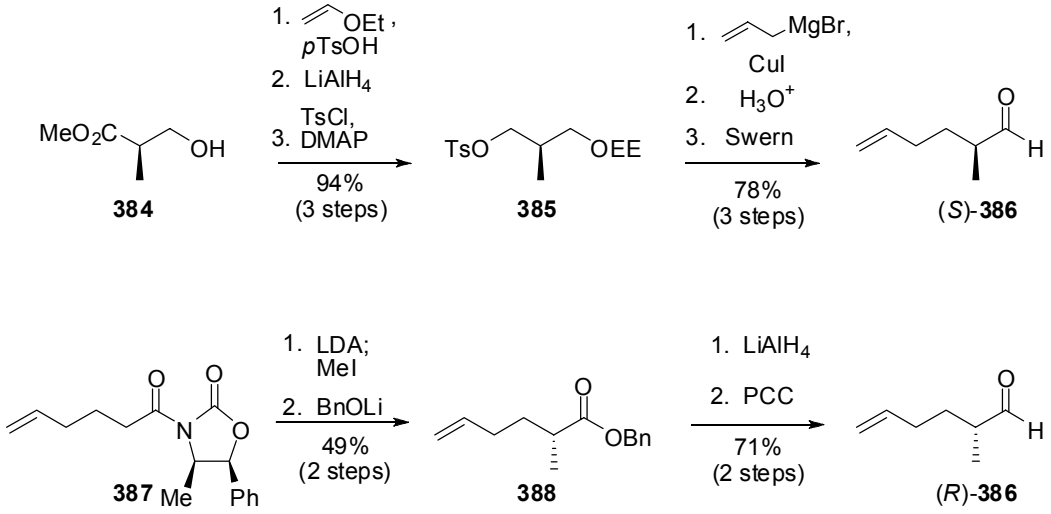


5.1.1 introduction of bromine and methyl substituents

Incorporation of the C(6''') methyl substituent into our synthetic sequence would require the preparation of aldehyde **386**. Ideally, this aldehyde would be prepared as a single enantiomer in order to render the overall synthesis enantioselective. Fortunately, both enantiomers of aldehyde **386** have been previously prepared, as shown in Scheme 103.

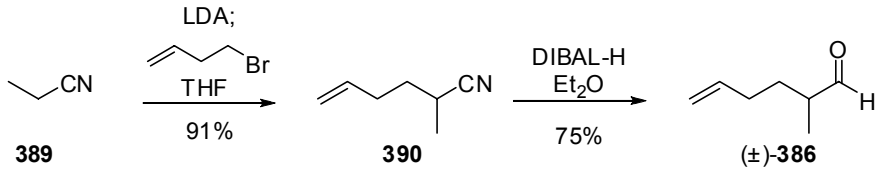
The first synthesis, developed in the Yoshii laboratory,[108] requires elaboration of commercially available ester **384** to the corresponding tosylate followed by allyl cuprate alkylation. The undesired enantiomer (*R*)-**386** was prepared by the Boeckman laboratory[109] by alkylation of *N*-acyl oxazolidinone **387** via the Evans protocol. This procedure is most likely easily adaptable to the desired enantiomer by use of the appropriate auxiliary.

Scheme 103. Prior syntheses of hexenal **386**



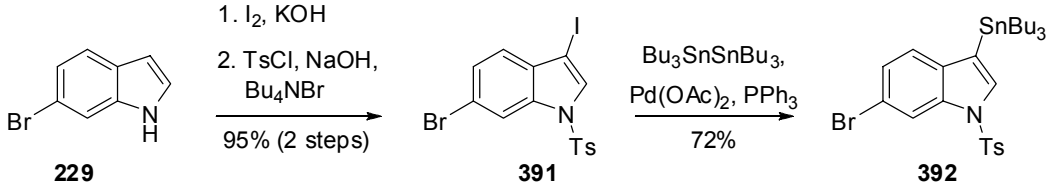
In the interests of both time and cost efficiency, we elected to prepare racemic aldehyde **386** for our initial studies, with the intent to revisit the chiral synthesis at a later stage. We found this was best accomplished by alkylation of propionitrile (**389**), followed by DIBAL-H reduction. This route allowed the ready preparation of racemic aldehyde **386** on 10-20 gram scale.

Scheme 104. Preparation of racemic hexenal **386**



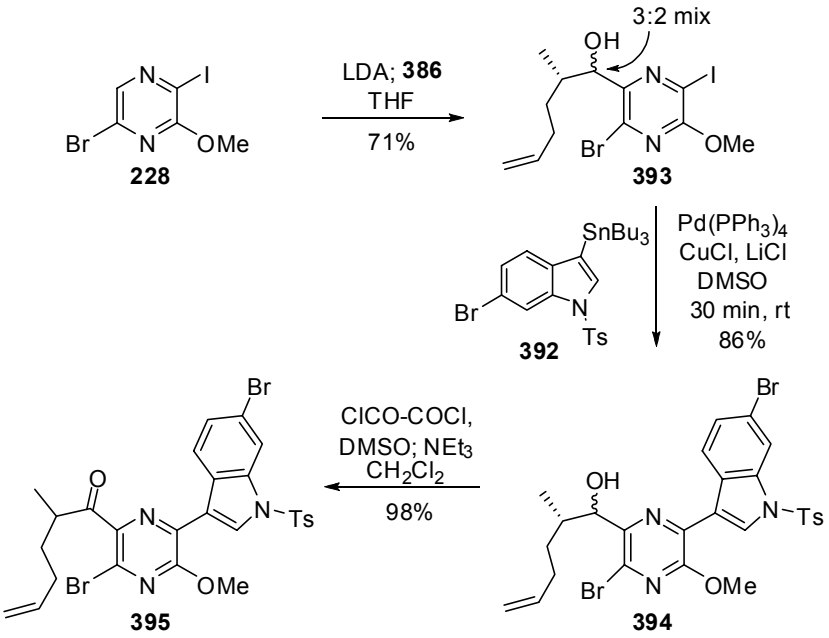
The next challenge was the introduction of the C(6') bromo substituent. Given our extensive use of palladium-coupling chemistry in our earlier model system, we were somewhat wary of attempting to carry an additional aryl bromo substituent through our existing sequence. Nonetheless, the halogen selective Suzuki coupling precedents established in Stoltz's earlier syntheses (Section 3.3.1) gave us reason to believe that early introduction of the C(6') bromo might be feasible. To that end, bromostannane **392** was prepared from 6-bromoindole (**229**) on greater than 20 gram scale via the halogen selective Stille coupling of iodoindole **391** with hexabutylditin[111] (Scheme 105).

Scheme 105. Preparation of indolyl stannane **392**



With indole **392** and aldehyde **386** in hand, we were then ready to assemble our fully functionalized pyrazine. Deprotonation of pyrazine **228** under our standard conditions, followed by addition of aldehyde **386**, furnished alcohols **393** as an inseparable (and inconsequential) 3:2 mixture of diastereomers. (Scheme 106). Halogen selective Stille coupling of iodopyrazine **393** with stannane **392** also proceeded uneventfully. Oxidation to ketone **395** was accomplished via the Swern protocol.

Scheme 106. Elaboration of second generation Heck precursor **395**

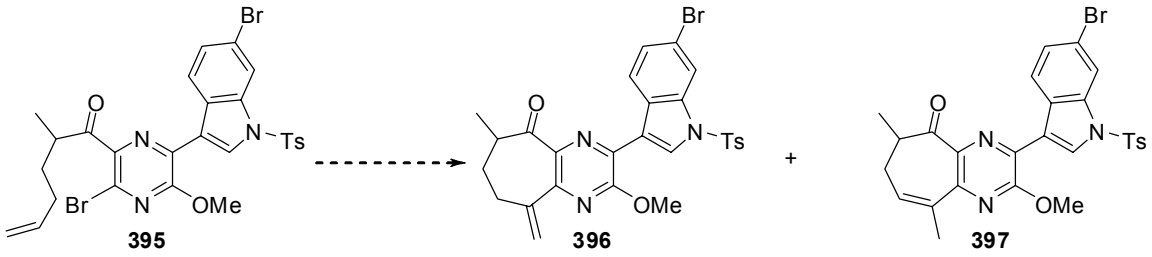


5.1.2 A challenging Heck cyclization

We now faced what was the potentially most problematic step of our revised approach to the full natural product, namely, the halogen selective 7-*exo*-Heck cyclization. Indeed, application of the conditions developed as part of our initial model system (entry 1 of Scheme 107), led to complete decomposition of the substrate. We subsequently investigated a broad screening of Heck cyclization conditions in order to identify an appropriate protocol.

We were very relieved to find that after even a brief screen (Scheme 107) of Heck cyclization conditions, we were able to identify a protocol (Entry 6) that did provide the desired 7-*exo*-Heck cyclization product **396**. Our relief was short lived, however, after discovering that this olefin was obtained as an inseparable mixture with endocyclic olefin **397**.

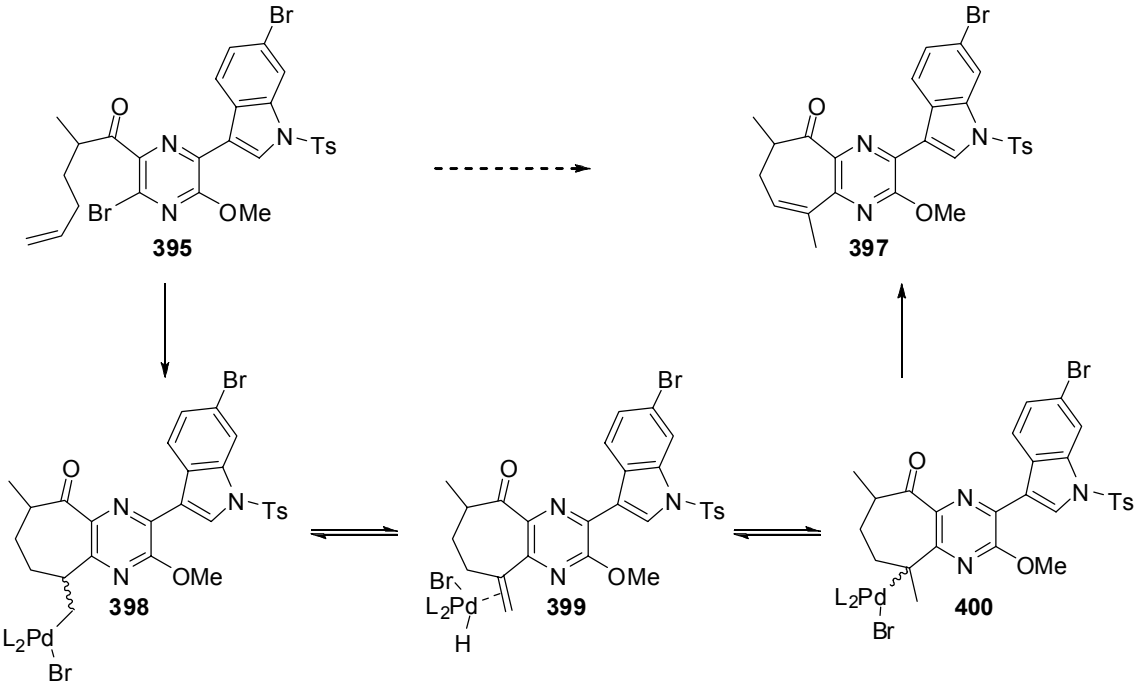
Scheme 107. Preliminary screening of halogen-selective Heck conditions



Entry	Pd	Ligand	Base	Solvent	Temp	Result
1	$Pd(PPh_3)_4$	none	NaOAc	DMF	150 °C	Decomposition
2	$Pd(PPh_3)_4$	none	NaOAc	DMF	85 °C	Decomposition
3	$Pd(OAc)_2$	dppf	Ag_2CO_3	MeCN	50 °C	no rxn
4	Pd_2dba_3	P(*t*-Bu)$_3$	Cy_2NMe	Dioxane	rt - 80 °C	Traces **396**
5	$Pd(OAc)_2$	PPh_3	Bu_4NOAc	DMF	80 °C	Traces **396**
6	$Pd(OAc)_2$	P(*o*-tol)$_3$	Cy_2NMe	DMF	80 °C	3 : 1 **396** : **397**

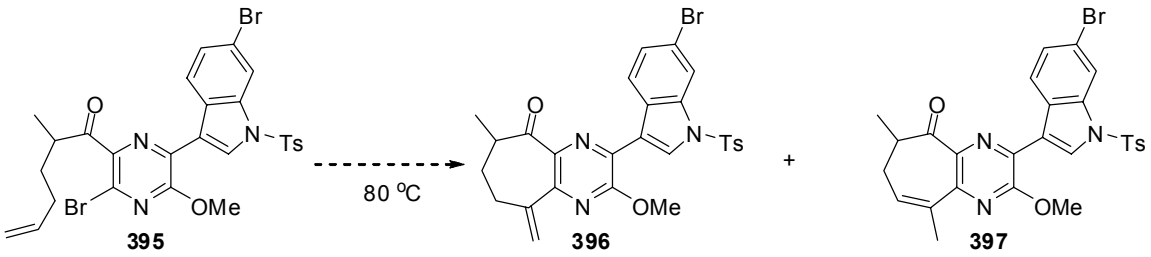
The formation of olefin isomerized products is well precedented for both 6-*exo*[112a] and 7-*exo*-Heck[112b] cyclizations. Mechanistically, the isolation of olefin **397** can be explained by an initial 7-*exo*-Heck ring closure to the palladated product **398** (Scheme 108). After β-hydride elimination to complex **399**, migratory insertion furnishes complex **400**, which undergoes a second, β-hydride elimination to olefin **397**.

Scheme 108. Olefin isomerization in the Heck reaction



Further optimization was then performed in an attempt to suppress olefin isomerization. Selected results from this study are shown in Scheme 109. The key conclusions drawn were: (1) isomerization decreased with increased solvent polarity (2) triphenylarsine ligands increased the total yield, but also increased olefin isomerization and (3) the presence of acetate salts appeared to reduce isomerization. Optimal results were obtained using DMSO, $AsPh_3$ and $Mg(OAc)_2$.

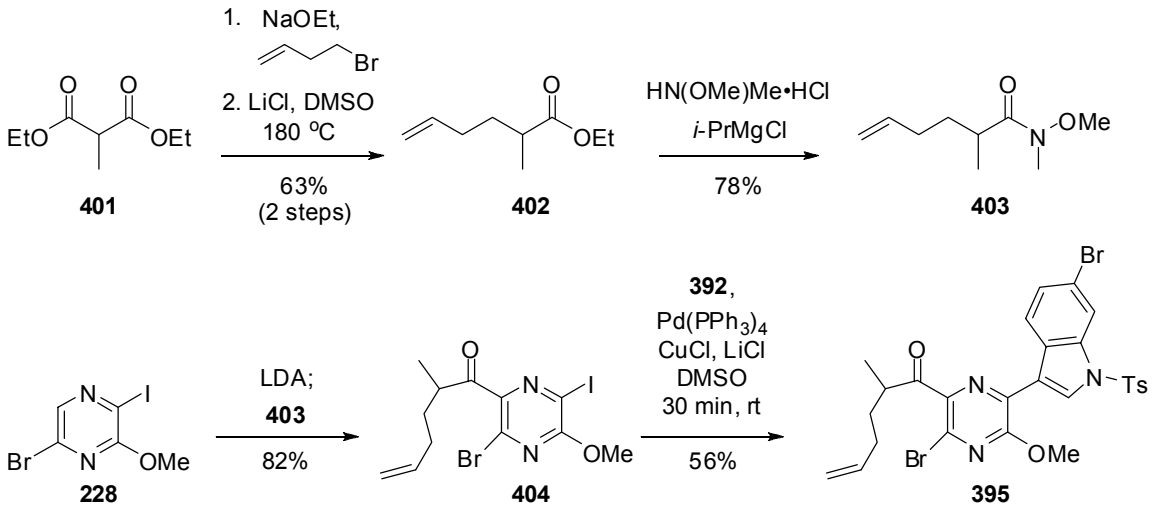
Scheme 109. Optimization of Heck reaction



	Pd	Ligand	Base	Solvent	Other	Selectivity **396** : **397**	Yield
	$Pd(OAc)_2$	$P(o\text{-tol})_3$	$N(i\text{-pr})_2Et$	**MeCN**		1 : 9	
Solvent:	$Pd(OAc)_2$	$P(o\text{-tol})_3$	$N(i\text{-pr})_2Et$	**DMF**		3 : 1	
	$Pd(OAc)_2$	$P(o\text{-tol})_3$	$N(i\text{-pr})_2Et$	**DMSO**		20 : 1	30-40%
	$Pd(OAc)_2$	**$P(o\text{-tol})_3$**	$N(i\text{-pr})_2Et$	DMF		3 : 1	
Ligand:	$Pd(OAc)_2$	**$AsPh_3$**	$N(i\text{-pr})_2Et$	DMF		1 : 2.5	
	$Pd(OAc)_2$	$P(o\text{-tol})_3$	$N(i\text{-pr})_2Et$	DMF		3 : 1	
Acetate:	$Pd(OAc)_2$	$P(o\text{-tol})_3$	$N(i\text{-pr})_2Et$	DMF	**+ $Mg(OAc)_2$**	20 : 1	30-40%
	$Pd(OAc)_2$	$AsPh_3$	$N(i\text{-pr})_2Et$	DMSO	**+ $Mg(OAc)_2$**	15 : 1	**65%**

It is worth noting at this point that the purity of the Heck precursor **395** is critical to the performance of this highly optimized cyclization reaction. Indeed, a slightly streamlined route to bromide **395** (Scheme 110) via addition to the readily prepared[113] Weinreb amide **403** had to be abandoned due to difficulties associated with the purification of the preceding Stille coupling product on a large scale.

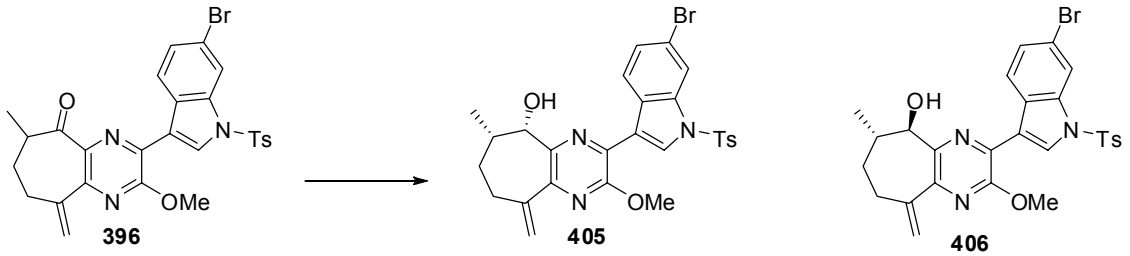
Scheme 110. Weinreb amide approach to Heck precursor **395**



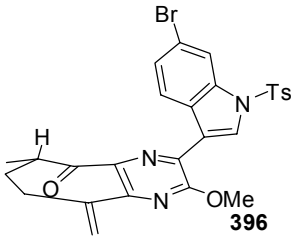
5.1.3 Completion of the fully substituted core ring system

The next step in our proposed sequence was reduction of ketone **396**. After observing conjugate 1,6-reduction with L-Selectride, we screened a series of other potential reductants (Scheme 111).

Scheme 111. Diastereoselective reduction of ketone **396**

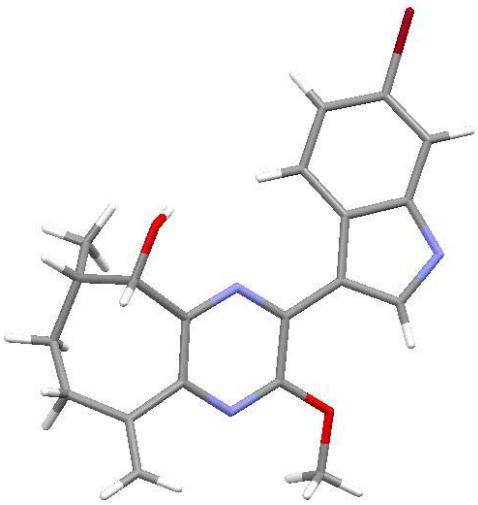


Conditions	Selectivity **405** : **406**
L-Selectride -78°C	see text
$LiAl(O\text{-}t\text{-}Bu)_3H$, -78 °C to rt	1 : 3
$NaBH_4$ -78 °C to rt	4 : 1
Super-Hydride -78 °C	5 : 1
Red-Al -78 °C	5.3 : 1
DIBAL-H -78 °C	1.1 : 1
$LiAlH_4$, -78 °C	>20 : 1



Alcohol **405** was ultimately cleanly prepared by addition of $LiAlH_4$ to ketone **393** at low temperature. The observed selectivity can be explained by attack of the hydride reagent from the less hindered, top face of conformer **393**. The structure and relative stereochemistry of alcohol **405** was confirmed by deprotection and X-ray crystallography (Figure 15).

Figure 15. Confirmation of reduction stereochemistry

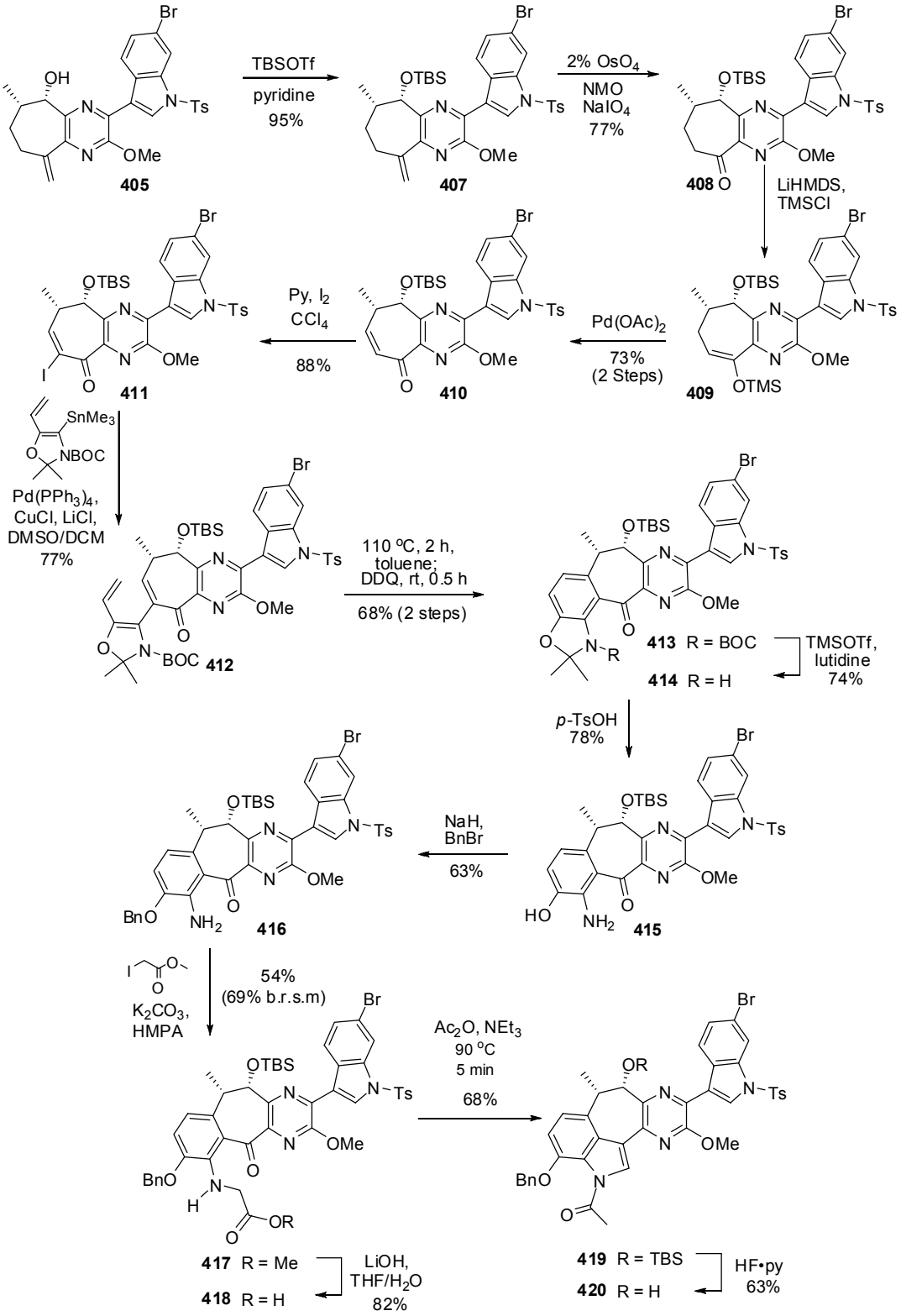


Our retrosynthetic analysis at this point called for conversion of alcohol **405** to the corresponding nitrile with inversion of stereochemistry. These efforts are outlined in Section 5.2. In parallel with these investigations, however, we elected to advance alcohol **405** through the remaining steps of our earlier model system work, in order to identify any potential problems and to provide ourselves the option of installing the desired nitrile at a late stage of the synthesis.

Elaboration of the fully 7-hydroxyindole ring system **420** (Scheme 112) from alcohol **405** could be accomplished with only minor modifications of our earlier methodology. Key differences between this system and the earlier model studies were: (1) The use of a silyl triflate in place of a silyl chloride to protect the hindered and less reactive alcohol **405**. (2) Employing a cosolvent for the Stille

coupling of poorly soluble iodide **411** and (3) The use of the solvent HMPA instead of DMF for the alkylation of aniline **416**. With these small changes, we were able to prepare the fully substituted core ring system **420** of dragmacidin E on greater than a 100 mg scale, in 23 linear steps from commercially available aminopyrazine (**226**).

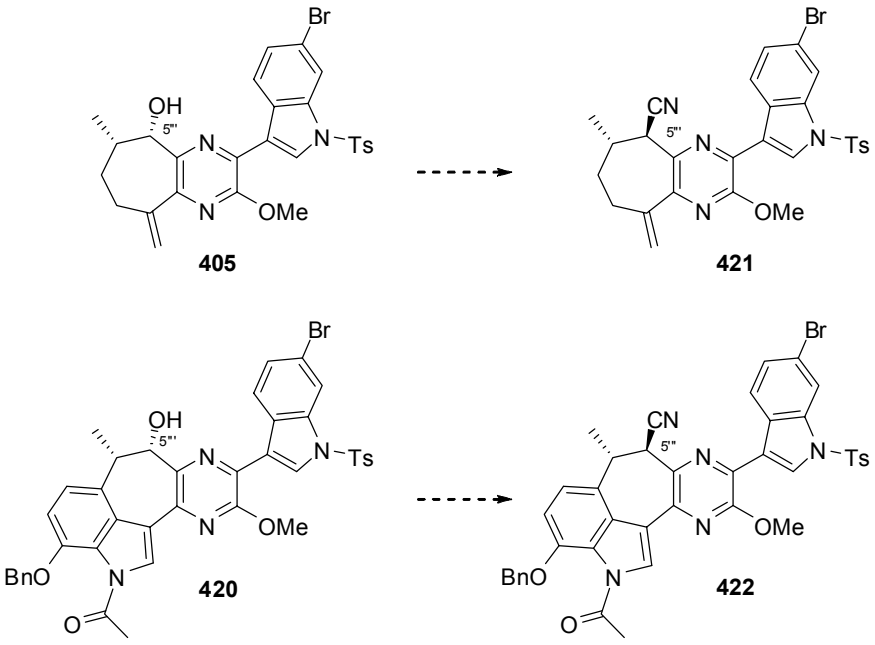
Scheme 112. Elaboration of fully substituted hydroxyindole **420**



5.2 Approaches to the formation of the imidazoline D ring

The final synthetic challenge was the construction of the spirocyclic aminoimidazoline ring at C(5’’’). The first step in preparing this ring, according to our retrosynthetic analysis, was conversion of alcohol **405** (or **420**) to the corresponding nitrile **421** (or **422**).

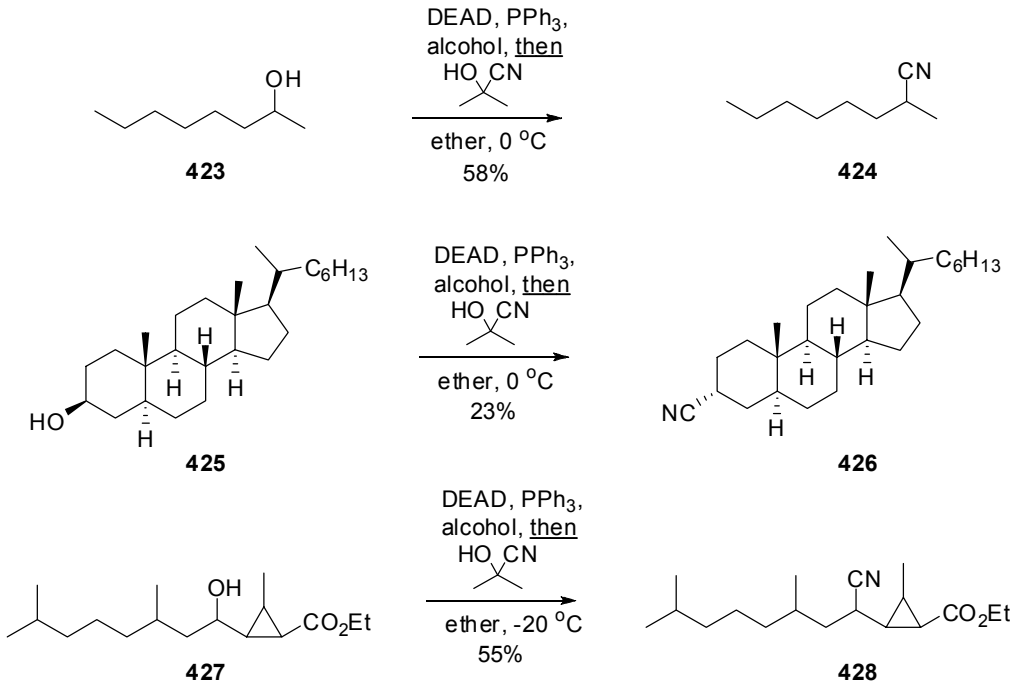
Scheme 113. Nitrile approaches to the C(5’’’) imidazoline ring



5.2.1 Nitrile introduction via the Mitsunobu reaction

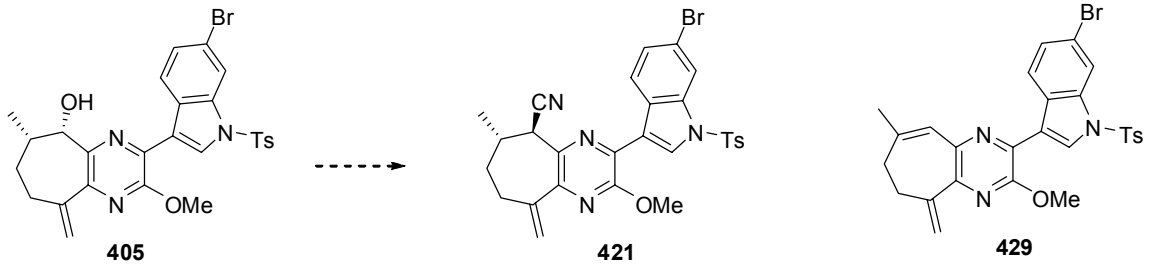
The most direct method of conversion of a secondary alcohol to the corresponding nitrile with inversion is to employ Mitsunobu chemistry. The most common such approach was developed by Wilk,[114] and employs acetone cyanohydrin as an HCN source. Several examples of the use of this methodology are shown in Scheme 114.

Scheme 114. Mitsunobu displacement of secondary alcohols with cyanide



We initially attempted this reaction on alcohol **405**. Initial screening indicated that the reaction proceeds in either ether or toluene, although a large number of equivalents of all three reagents were necessary to drive the reaction to completion. Competitive elimination to diene **429** was a major problem however. Beginning with our most promising lead (Entry 3), we systematically examined the effects of solvent, phosphine, azadicarboxylate and cyanohydrin, in order to obtain better results (Scheme 115). We were never able to improve on our initial results, however. We also examined order of addition, rate of addition and reagent stoichiometry to no avail.

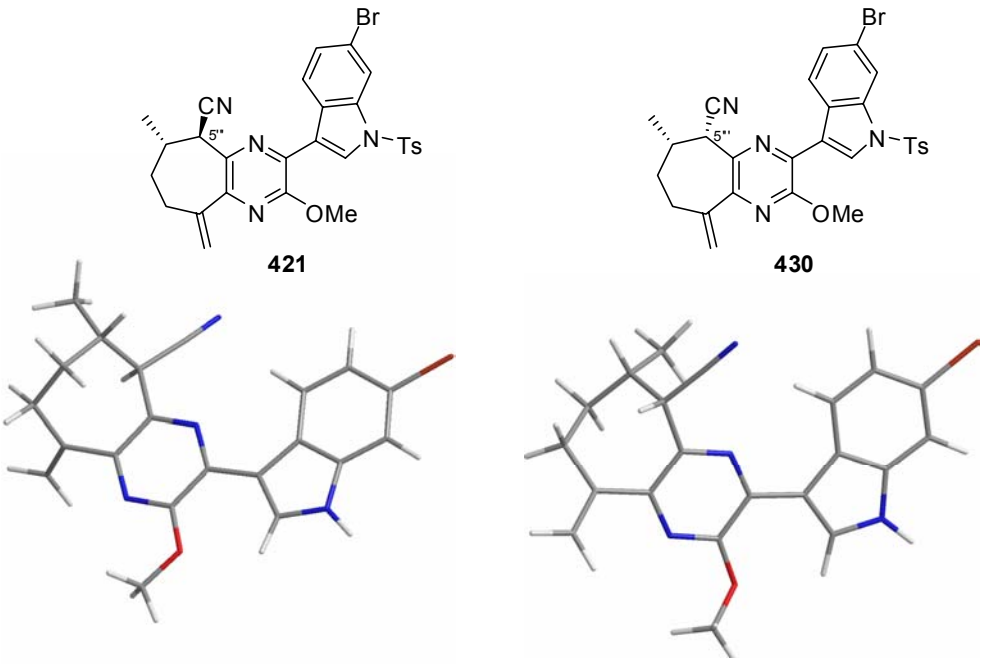
Scheme 115. Attempted formation of nitrile **421**



	Entry	Cyanohydrin (equiv.)	Phosphine (equiv.)	Dicarboxylate (equiv.)	Solvent	Temp	Selectivity **405** : **421** : **429**	Yield **421**
Initial Screening:	1	acetone (2)	PPh_3 (2)	DEAD (2)	ether	rt	1 : 1 : 1	20-30%
	2	acetone (2)	PPh_3 (2)	DEAD (2)	toluene	rt	1 : 1 : 1	20-30%
	3	**acetone (10)**	**PPh_3 (10)**	**DEAD (10)**	**toluene**	**rt**	**0 : 1 : 1**	**30-40%**
	4	acetone (10)	PPh_3 (10)	DEAD (10)	**hexanes/ toluene**	rt	0 : 1 : 4	
	5	acetone (10)	PPh_3 (10)	DEAD (10)	**CCl_4**	rt	0 : 2 : 3	
	6	acetone (10)	PPh_3 (10)	DEAD (10)	**ether**	rt	0 : 1 : 4	
	7	acetone (10)	PPh_3 (10)	DEAD (10)	**CH_2Cl_2**	rt	0 : 0 : 1	
	8	acetone (10)	PPh_3 (10)	DEAD (10)	**THF**	rt	0 : 0 : 1	
	9	acetone (10)	PPh_3 (10)	***t*-butyl (10)**	toluene	rt	0 : 1 : 1	
	10	acetone (10)	PPh_3 (10)	**benzyl (10)**	toluene	rt	1 : 1 : 1	
	11	acetone (10)	PPh_3 (10)	**DMF (10)**	toluene	rt	no rxn	
	12	acetone (10)	PPh_3 (10)	**polymer supported DEAD (10)**	toluene	rt	no rxn	
	13	acetone (10)	**P(*p*-Cl-Ph)$_3$ (10)**	DEAD (10)	toluene	rt	0 : 1 : 1	
	14	acetone (10)	**P(*o-tol*-Ph)$_3$ (10)**	DEAD (10)	toluene	rt	mostly SM	
	15	acetone (10)	**P(*p*-MeOPh)$_3$ (10)**	DEAD (10)	toluene	rt	5 : 1 : 5	
	16	acetone (10)	**$P(OPh)_3$**	DEAD (10)	toluene	rt	0 : 2 : 1	(multiple byproducts)
	17	acetone (10)	**Bu_3P (10)**	DEAD (10)	toluene	rt	3 : 1 : 3	
	18	acetone (10)	**$P(OPh)Ph_2$ (10)**	DEAD (10)	toluene	rt	0 : 1 : 3	
	19	**cyclohexyl (10)**	PPh_3 (10)	DEAD (10)	toluene	rt	0 : 1 : 5	
	20	acetone (**10**)	PPh_3 (**2**)	DEAD (**2**)	toluene	rt	no rxn	
	21	acetone (10)	PPh_3 (10)	DEAD (10)	toluene	**-20 °C**	no rxn	

The stereochemical assignment of the nitrile product was made primarily on the basis of ^{1}H NMR coupling constants. Molecular modeling suggested that the two potential products, **421** and **430,** would prefer to adopt the conformations shown in Figure 16. The calculated ^{3}J coupling constants for the proton at C(5'''), based upon the predicted conformations, were 9.7 Hz for nitrile **421** and 3.8 Hz for nitrile **430**. Our observed value of 9.1 Hz was therefore in close agreement with the calculated value for the desired *trans* epimer. Further confirmation was provided when the alternate epimer was later synthesized (*vide infra*), and shown to have a coupling constant of 2.7 Hz.

Figure 16. Conformational prediction for nitriles **421** and **430**



In addition, the cyanomethylene reagents **431** and **432** (Figure 17) recently developed by Tsunoda[115] for the cyanide Mitsunobu reaction were attempted, but returned only starting material.

Figure 17. Alternate reagents for Mitsunobu cyanide displacement

431 **432**

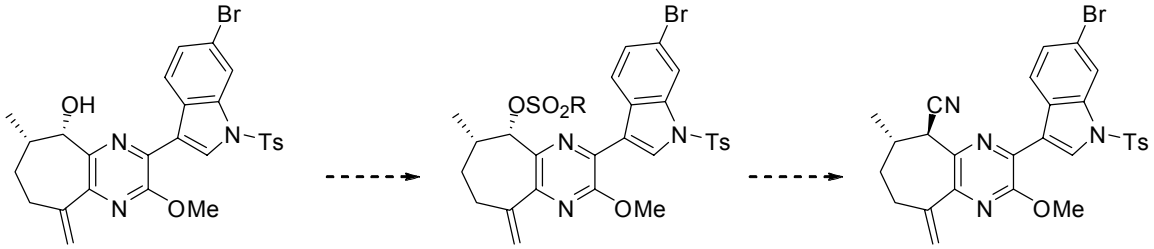
We then attempted to perform the Mitsunobu reaction on our advanced alcohol **420**, using our best conditions. Modeling suggested that the increased rigidity of this system would prevent the leaving group derived from alcohol **420** from adopting a true antiperiplanar conformation with respect to the adjacent proton, possibly suppressing elimination. Unfortunately our optimized conditions failed to provide any of the desired nitrile product.

5.2.2 Nitrile introduction via sulfonate displacement

Given these results, we elected to explore a more conventional approach to the desired nitrile, specifically, conversion of alcohol **405** to the corresponding sulfonate **433**, followed by displacement with cyanide. The results from these studies are shown in Scheme 116.

We were dismayed to find that all attempts at converting alcohol **405** to the corresponding tosylate or nosylate were unsuccessful, returning exclusively starting material. Attempts at generating mesylate **433** were more promising. However, product formation was consistently accompanied by elimination to alkene **429**. This alkene was the sole isolated product after chromatography. Attempted formation of the triflate or nonaflate of alcohol **405** led exclusively to decomposition.

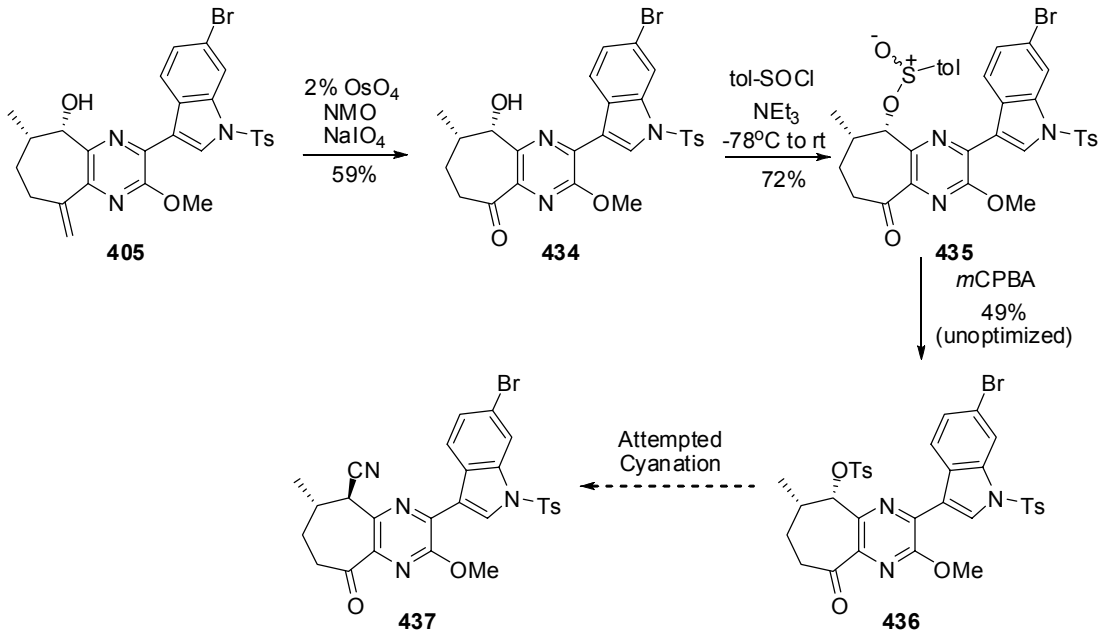
Scheme 116. Attempted sulfonylation of alcohol **405**



Entry	Sulfonylating reagent	Bases(s)	Solvent	Temp	Result
1	TsCl	NEt_3	CH_2Cl_2	rt	no rxn
2	TsCl	NaH	THF	0 °C	no rxn
3	TsCl	NaH	DMF	rt	no rxn
4	TsCl	DABCO	CH_2Cl_2	rt	no rxn
5	TsCl	$(CH_3)_2N(CH_2)_6N(CH_3)_2$	MeCN	rt	no rxn
6	Ts_2O	-	pyridine	rt	no rxn
7	NsCl	NEt_3, DMAP	pyridine	rt	no rxn
8	Ms_2O	NEt_3	CH_2Cl_2	rt	no rxn
9	MsCl	NEt_3	CH_2Cl_2	0 °C	chloride
10	Ms_2O	NEt_3	CH_2Cl_2	rt	mix of **405**, **433**? and **429**
11	Ms_2O	$N(i\text{-}pr)_2Et$	toluene	rt	**433**? (not isolated)
12	Tf_2O	-	pyridine	0 °C	decompostion
13	NfF	-	pyridine	0 °C	decompostion

Eventually, we were able to prepare a tosylate product suitable for potential displacement by the protocol shown in Scheme 117. Oxidative cleavage of exocyclic olefin **405**, gave ketone **434**, which was subjected to a two step sulfonylation procedure.[116] Attempted displacement of this sulfonate[117] proved fruitless, however.

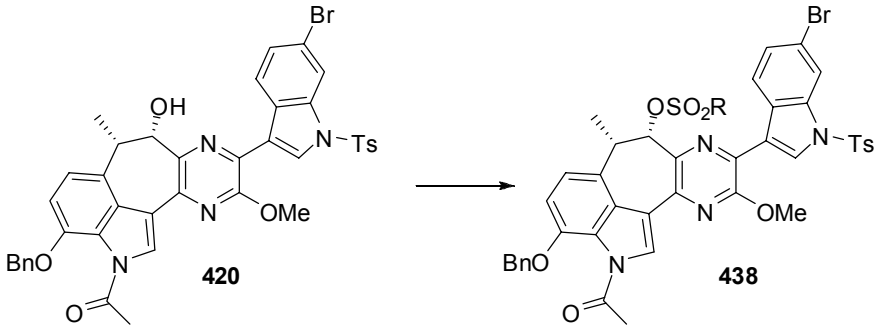
Scheme 117. Sulfonylation and attempted displacement of **434**



Entry	Cyanation reagent	Solvent	Temp	Result
1	KCN	DMF	rt	decomposition
2	LiOH, acetone cyanohydrin	THF/NMI	rt	decomposition
3	Bu_4NCN	DME	rt	mostly SM, some decomposition
4	Et_4NCN	DMSO	rt	complex mixture
5	Et_4NCN	HMPA	rt	complex mixture
6	LiCN	HMPA	rt	loss of N-Ts and elimination
7	Et_4NCN	THF/NMI	rt	decomposition
8	Li*O*tBu acetone cyanohydrin	DMSO	rt	decomposition

We also attempted selected sulfonylation procedures on our advanced alcohol **420**, as outlined in Scheme 118. After a fairly extensive survey, we found that we were able to prepare triflate **438** (R = CF_3) via an optimized protocol.

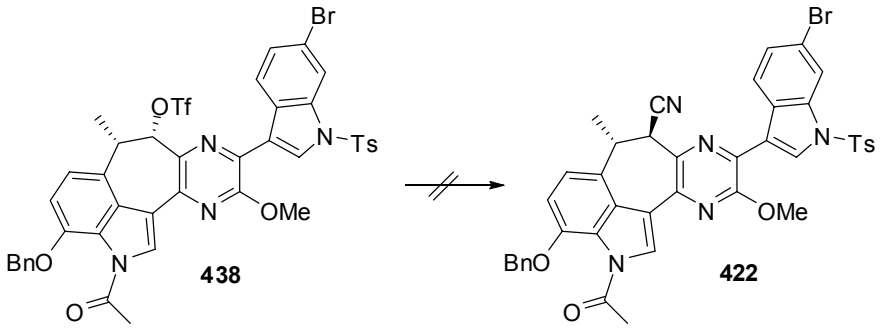
Scheme 118. Preparation of advanced sulfonate **438**



Entry	Sulfonylating reagent	Bases(s)	Solvent	Temp	Result
1	TsCl	NEt_3	CH_2Cl_2	rt	no rxn
2	TsCl	-	pyridine	rt	no rxn
3	Ts_2O	DMAP	pyridine	rt	no rxn
4	Ms_2O	NEt_3	CH_2Cl_2	rt	no rxn
5	Ms_2O	$N(i\text{-pr})_2Et$	toluene	rt	no rxn
6	MsCl	NEt_3	DCM	0 °C	decomposition
7	NsCl	NEt_3, DMAP	CH_2Cl_2	rt	chloride?
8	TfCl	NEt_3, DMAP	CH_2Cl_2	rt	no rxn
9	Tf_2O	2-Cl-py	CH_2Cl_2	0 °C	decomposition
10	Tf_2O	-	pyridine	0 °C	decomposition
11	Tf_2O (4 equiv.)	pyridine (8 equiv.)	$CDCl_3$	0 °C to rt	**438** 71%

After a quick aqueous workup we attempted to effect displacement of this chromatographically labile sulfonate with cyanide using the conditions shown in Scheme 119. These conditions invariably resulted in complex mixtures, from which the sole identifiable product by mass spectrometry corresponded to elimination of triflic acid.

Scheme 119. Attempted cyanide displacements of triflate **438**

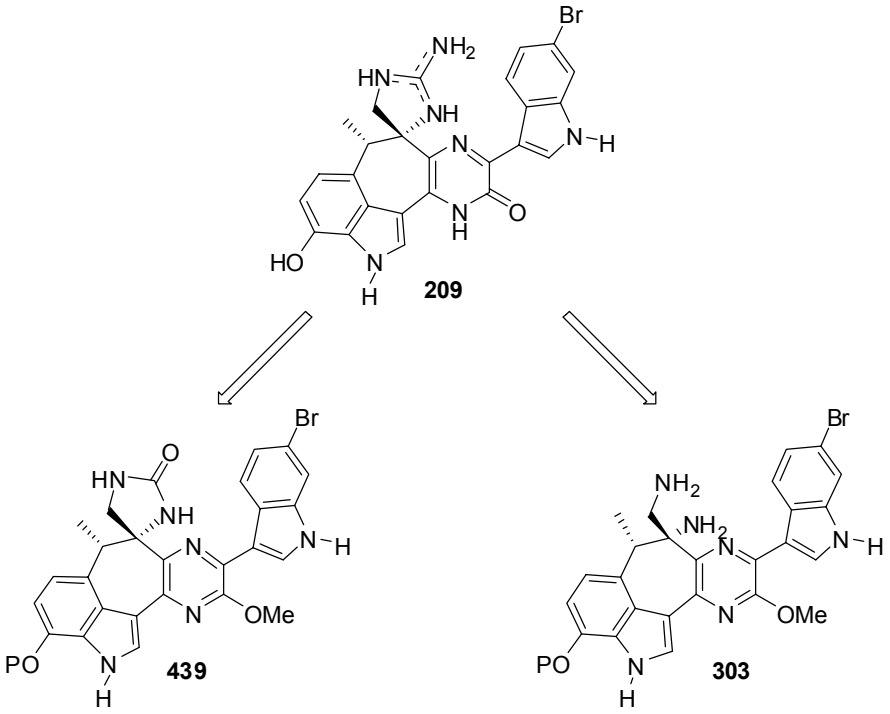


Entry	Cyanation reagent	Solvent	Temp
1	KCN, 18-crown-6	THF	rt
2	KCN, 18-crown-6	toluene	0 °C
3	KCN, 18-crown-6 mol sieves	DMF	rt
4	KCN	EtOH	0 °C
5	Bu_4NCN	toluene/$CDCl_3$	rt
6	Et_4NCN	MeCN	rt
7	LiOH, acetone cyanohydrin	THF/NMI	rt
8	Li*O*tBu acetone cyanohydrin	THF/NMI	rt

5.2.3 Aminonitrile introduction via a Strecker reaction

Given our lack of success to this point at obtaining the desired aminomethylated product needed for cyclization via the Du Bois methodology, we began examining our alternate approach to the desired spirocycle, which envisaged the preparation of urea **439** or vicinal diamine **303** (Scheme 120).

Scheme 120. Diamination approaches to the imidazoline D ring.

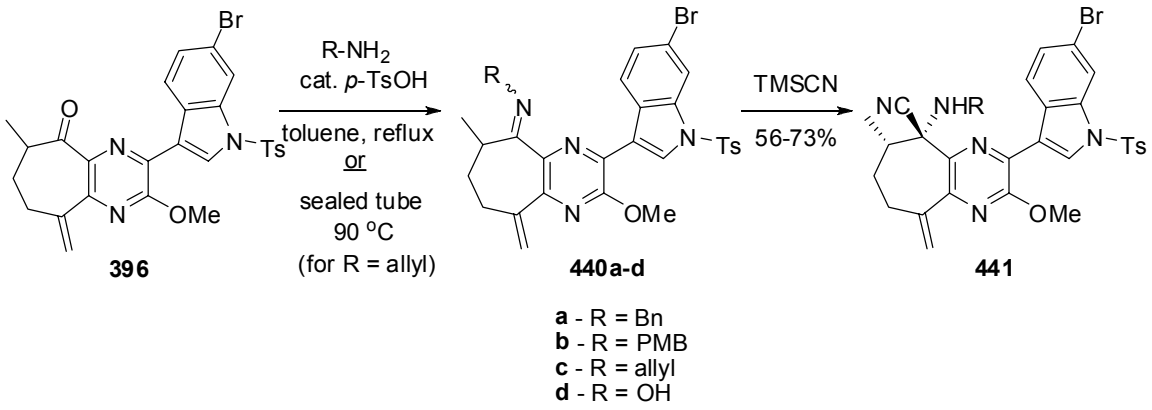


We directed our efforts initially to the introduction of the desired substituents into ketone **396**, with a view of either carrying the functionality through our existing sequence or (more likely) applying the lessons learned here to our advanced material at a later date.

We started by attempting to prepare primary aminonitrile **441** (R = H) via the conditions employed by the Feldman laboratory in their approach to dragmacidin E (NH_4Cl, NH_3, MeOH).[81] Unfortunately, these conditions were unsuccessful for our system, returning only starting material. Further exploration did, however, reveal conditions for the preparation of the chromatographically stable substituted imines **440** (Scheme 121). Further treatment of these imines with trimethylsilylcyanide effected transformation to the corresponding aminonitriles **441**, which were isolated as single diastereomers. The relative stereochemical assignment of the newly generated center could not be

definitively established at this stage, and could only be inferred from the previously demonstrated tendency for nucleophiles to attack ketone **396** from the face opposite to the methyl substituent. The reduction of aminonitrile **441a** was attempted with $LiAlH_4$, AlH_3 and $CoCl_2/NaBH_4$,[118] in an effort to obtain vicinal diamines, but these reductions were unsuccessful, however. Products of retro-Strecker reactions were commonly observed.

Scheme 121. Strecker aminonitrile synthesis



Attempts were made to acylate the aminonitriles, in order to provide a more stable substrate for reduction, and to provide a substrate that could be carried through our indole synthesis sequence. These acylations were again unsuccessful. Attempted deprotection of aminonitriles **441** resulted in isolation of ketone **396**, imines **440** or decomposition.

5.2.4 Imidazolone introduction via an intermediate hydantoin

We then considered an alternate intermediate for the preparation of spirocycle **439**, namely hydantoin **442**. This hydantoin could be prepared in small quantities (*vide infra*) via an optimized version of the classical Bucherer-Bergs reaction (Scheme 122).[119] Protection of the more acidic nitrogen gave

hydantoin **443**, which furnished crystals suitable for X-ray crystallography (Figure 18), confirming the correct relative stereochemistry was obtained.

Scheme 122. Hydantoin formation via a Bucherer-Bergs reaction

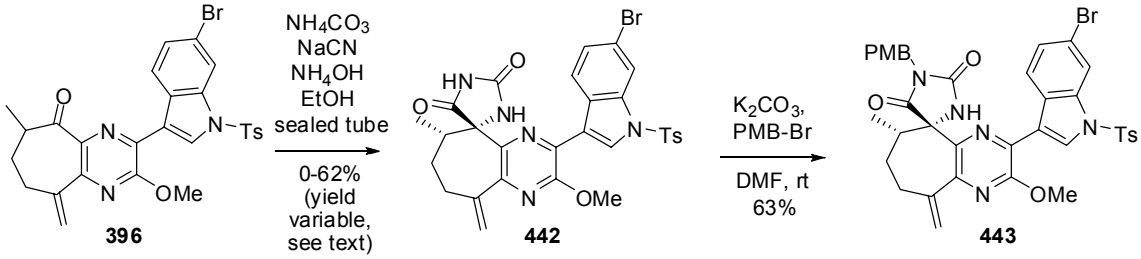
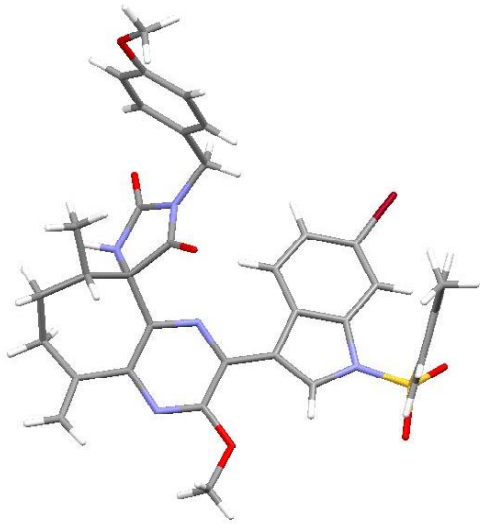


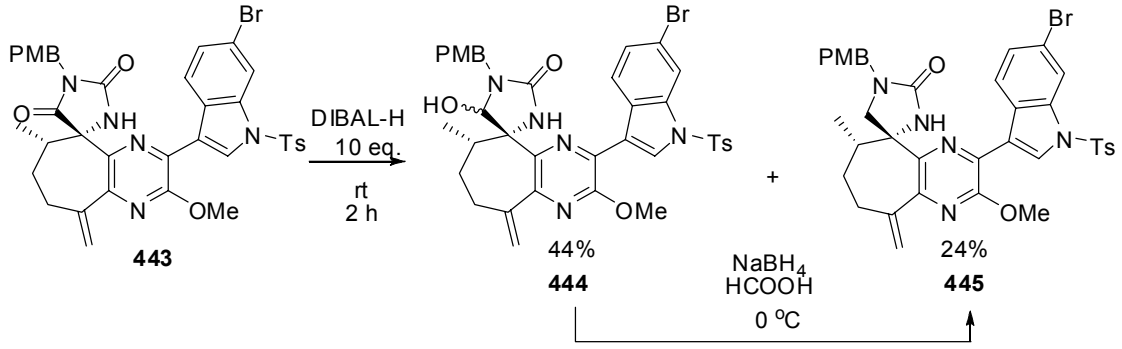
Figure 18. X-ray crystallographic structure confirmation of hydantoin **443**



The spirocyclic hydantoin ring system **443** incorporates all of the necessary atoms embodied within the desired cyclic guanidine. Reduction of the superfluous carbonyl group with a large excess of DIBAL-H gave a mixture of urea **445** and hemiaminal **444**, which was subsequently reduced with sodium borohydride to the corresponding cyclic urea **445** (Scheme 123). A preliminary attempt to covert urea **445** to the corresponding thiourea using Lawesson's reagent[120] was unsuccessful, as was conversion to the corresponding

pseudourea with Meerwein's reagent. A single attempt at O-alkylation of urea **445** with methyl triflate did appear to be successful however.

Scheme 123. Conversion of hydantoin to dihydroimidazolone **445**

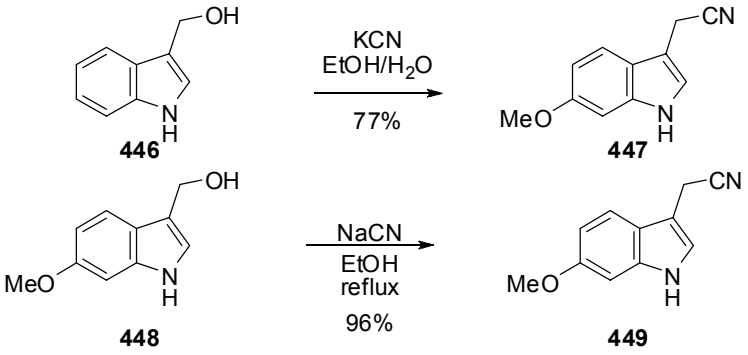


The key problem preventing us from developing this method further was our inability to perform the desired Bucherer-Bergs protocol on a synthetically useful scale. Ketone **396** is marginally soluble in the solvent system employed, requiring the use of large volumes in sealed vessels. A further possible problem arises from the ammonium carbonate reagent, which under the reaction conditions exists as an equilibrium mixture with ammonia and carbon dioxide. The actual head pressure of these active species appears to vary with vessel size and depth of immersion (since under most conditions it rapidly sublimes to the top of the vessel). Finally, a competing deprotection of the indole tosyl substituent by cyanide prevents the use of extended reaction times. All of these factors conspired to make the scalability and reproducibility of the Bucherer-Bergs reaction problematic. This approach was ultimately abandoned.

5.2.5 Miscellaneous approaches to the imidazoline D ring

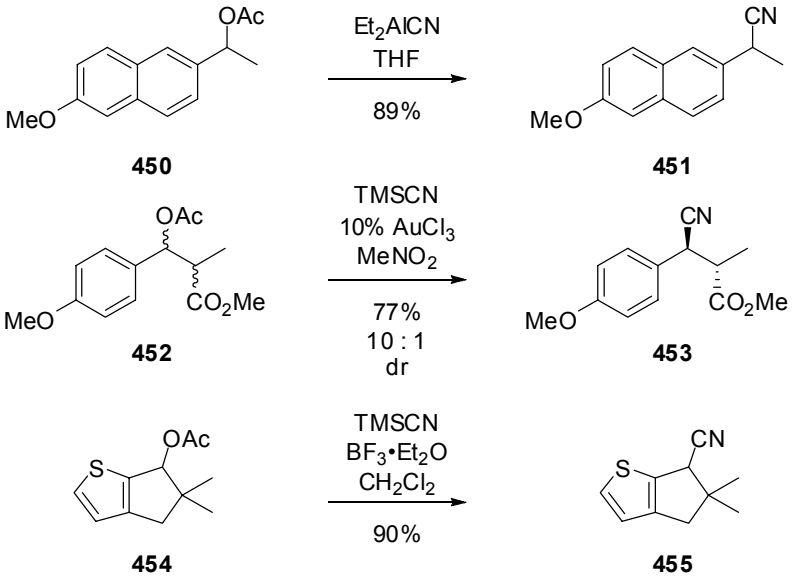
Having had little success with our original ideas for synthesis of nitrile **422** or diaminopyrazine **303**, we elected to explore some other, less common protocols. We noted that benzylic alcohols such as **446** and **448** (Scheme 124)[121] had been directly displaced with cyanide in refluxing ethanol, presumably by an S_N1 process. Attempts to perform this same reaction on alcohols **405** and **425** using these conditions led only to deprotection of the bromoindole.

Scheme 124. S_N1 alcohol displacement



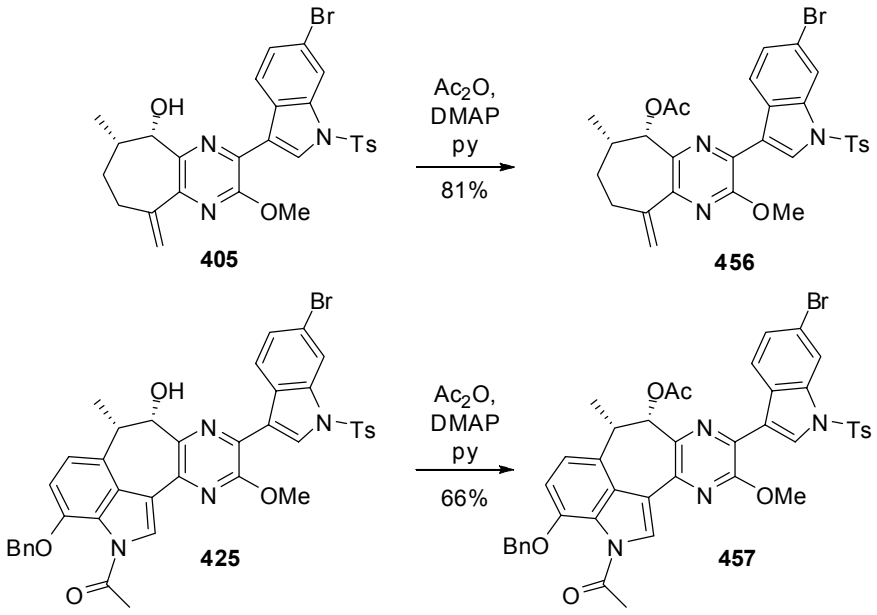
We further considered the possibility of effecting displacement of a benzylic acetate in the presence of a suitable Lewis acid. Key precedents for this transformation are shown in Scheme 125, and include displacements with Et_2AlCN[122], TMSCN/$AuCl_3$[123], and TMSCN/BF_3•Et_2O[124].

Scheme 125. Nitriles via acetate displacement



We subsequently prepared acetates **456** and **457** via standard procedures (Scheme 126).

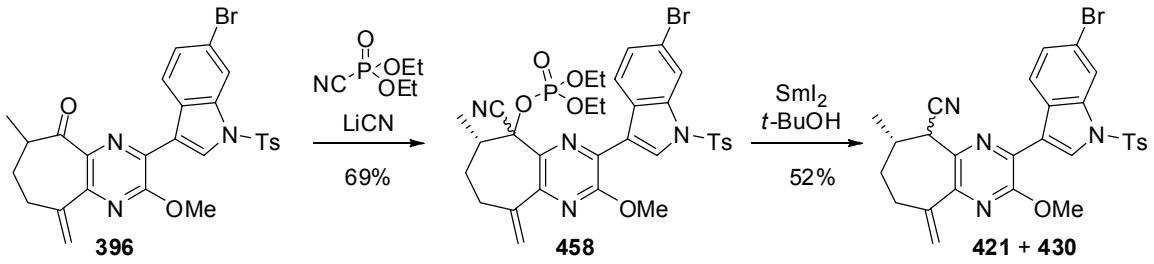
Scheme 126. Preparation of benzylic acetates



Attempts at displacement of either acetate **456** or **457** with Et_2AlCN led to the recovery of starting material, even under forcing conditions. Gold(III) catalyzed displacement led to starting material at room temperature, and complex mixtures at elevated temperature, from which a small amount of the undesired *cis*-nitrile **430** was recovered. The use of $BF_3•Et_2O$ led to decomposition.

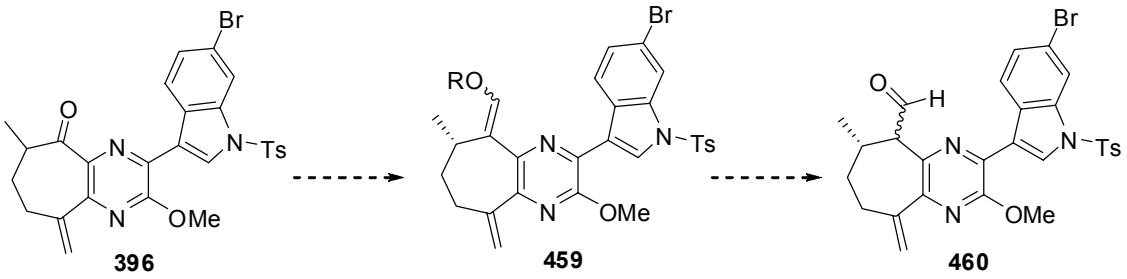
We were able to prepare nitriles **421** and **430** as an approximately 1:1 mixture of diastereomers (Scheme 127) by first conversion to cyanophosphate **458** followed by reductive cleavage of the phosphate group.[125] The resultant diastereomeric nitriles were separable only with great effort, however, and attempts at epimerization employing alkoxide bases led only to detosylation of the indole.

Scheme 127. Cyanophosphate approach to nitrile **421**



Exocyclic enol ether formation was attempted (Scheme 128) using a variety of protocols[126-129] in an attempt to isolate the (hopefully) separable and epimerizable aldehydes **460**. However, ketone **396** was either unreactive to the conditions tested, or underwent decomposition.

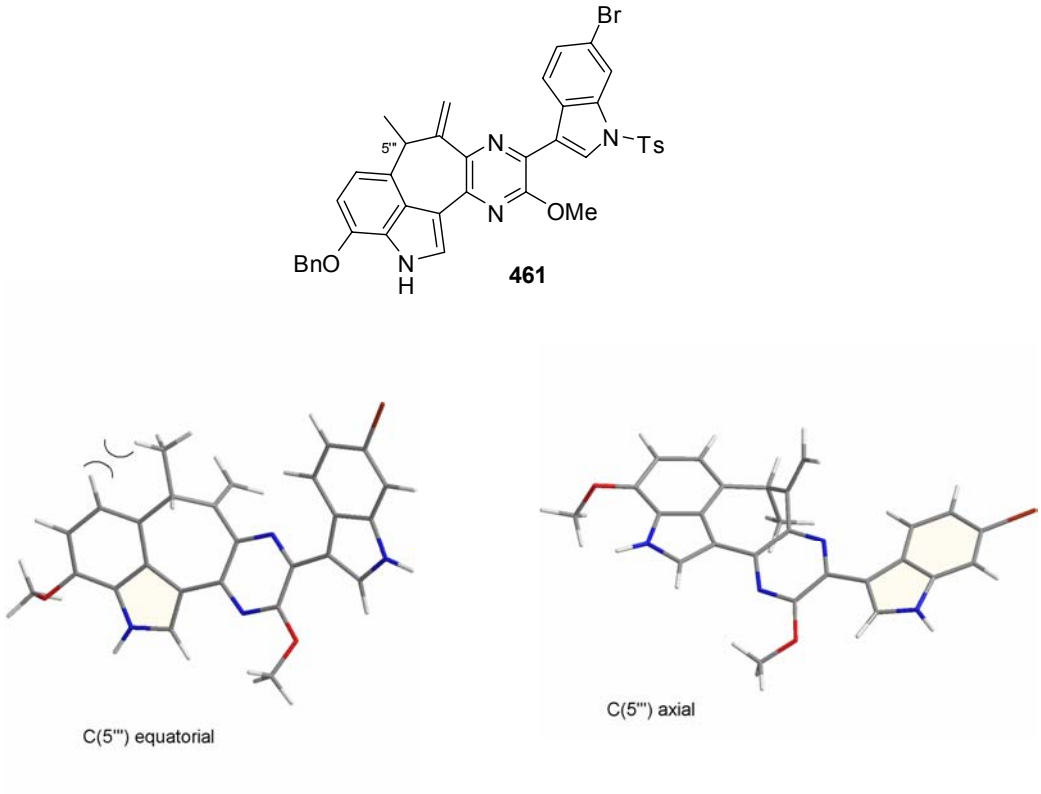
Scheme 128. Attempted homologation to aldehyde **460**



Entry	Olefination reagent	ref
1	TMS(MeO)CHLi	126
2	$Ph_2P(O)CH_2OMe$, LDA	127
3	$Ph_3P{=}CH(OMe)$	128
4	Cp_2TiCl, $P(OEt)_3$, Mg; BOM-Cl	129

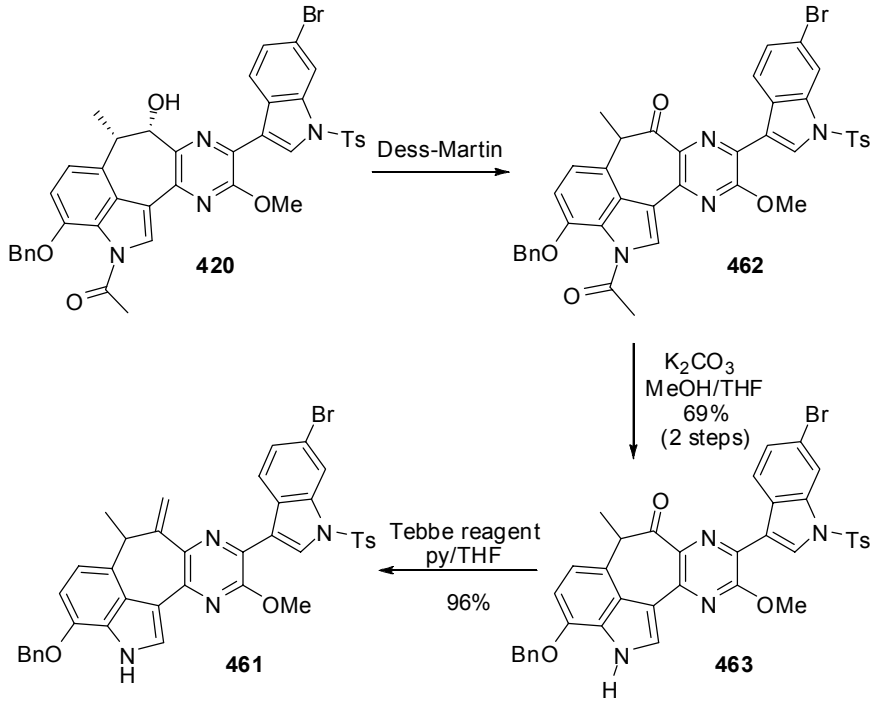
Finally, molecular modeling of our advanced intermediates opened up a potentially useful avenue for the synthesis of the cyclic guanidine (Figure 19). We noted that alkene **461** appeared to favor strongly a cup-shaped conformation wherein the C(5''') methyl substituent prefers to adopt a pseudoaxial conformation on the convex face of the cup, in order to avoid a destabilizing $A_{1,3}$ interaction. This modeling suggested that this convex face might be open to attack by electrophilic species.

Figure 19. Modeling of alkene **461**



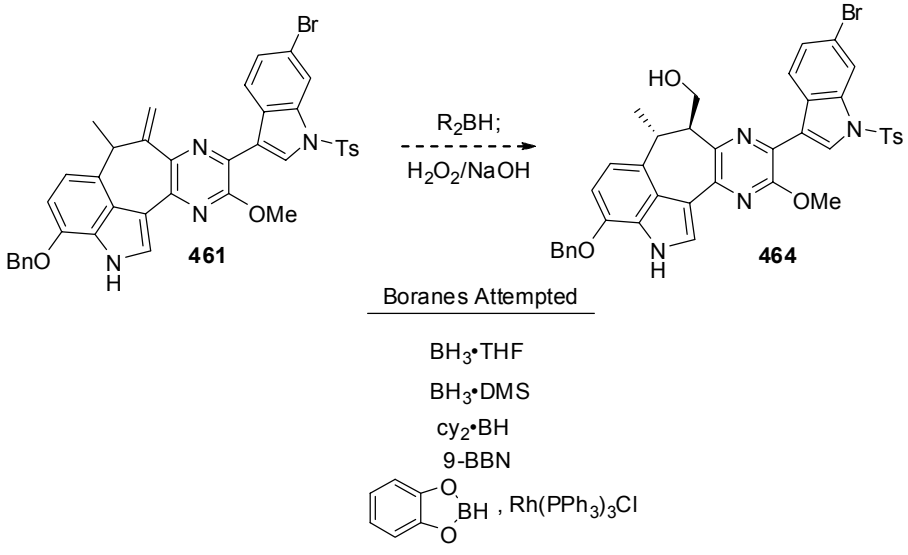
We decided to make use of this observation by preparing alkene **461** and subjecting it to hydroboration. This synthesis was accomplished by oxidation of alcohol **420** with Dess-Martin periodinane (Scheme 129), removal of the indole acetyl functionality and olefination with the Tebbe reagent.[130]

Scheme 129. Formation of advanced exocyclic alkene **461**



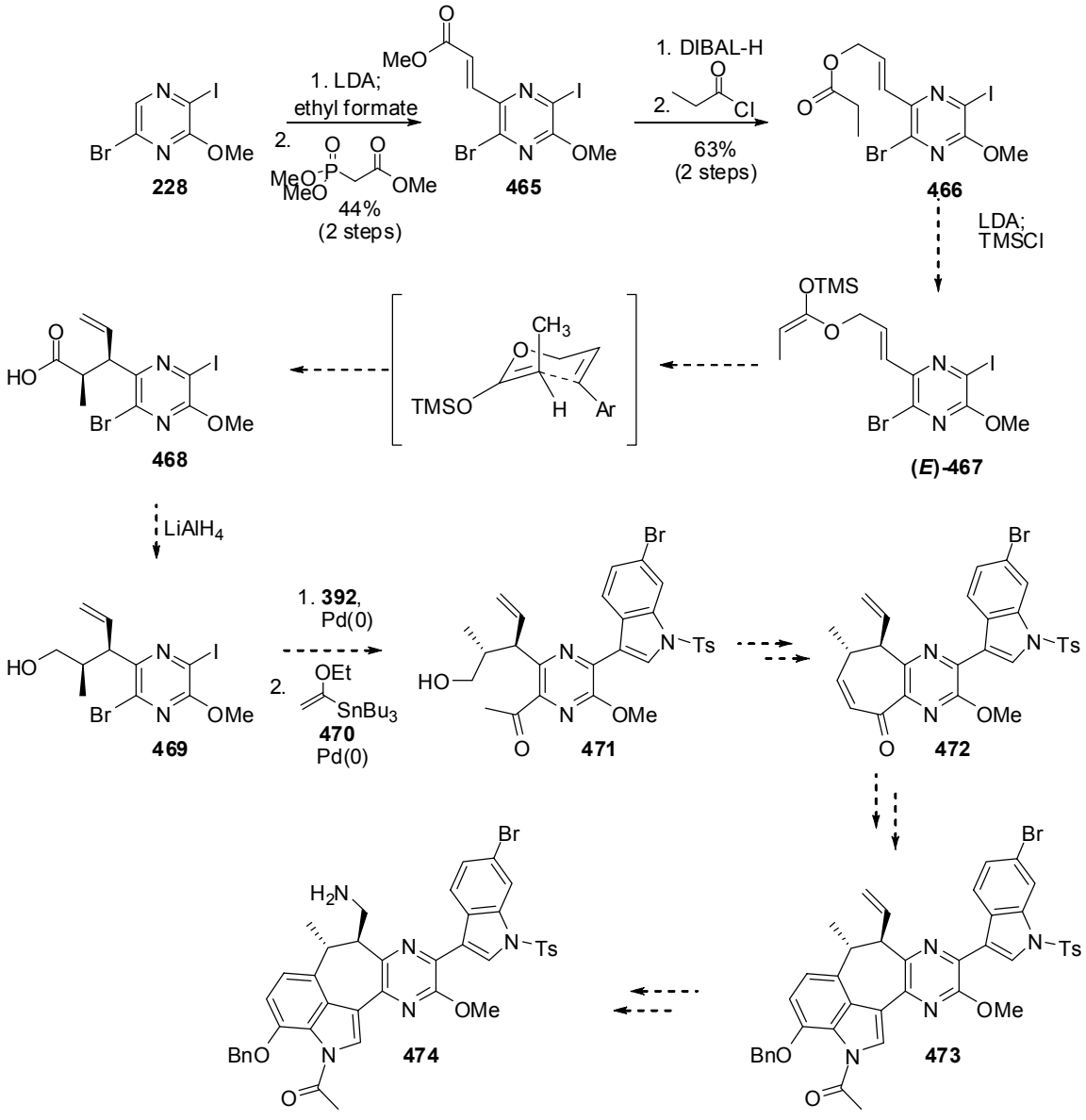
We then subjected olefin **461** to a series of hydroboration conditions,[131] in an attempt to prepare alcohol **464** (from which the corresponding primary amine could be elaborated). These attempts led only to partial or complete decomposition of the substrate.

Scheme 130. Hydroboration approach to hydroxymethyl intermediate **464**



One final approach that radically departs from our existing methodology is shown in Scheme 131. This sequence would employ a diastereoselective[133] Ireland-Claisen rearrangement of ester **466** via the (*E*)-silylenol ether **467** to give acid **468**. Reduction of the acid, followed by sequential Stille couplings of indole

Scheme 131. Cycloheptannelation reimagined



392 and commercially available stannane **470** would provide ketone **471**. Elaboration to bis-indole **473** and then amine **474** should be straightforward.

The preparation of ester **466** has been achieved as shown in the scheme. A single attempt at effecting the desired Claisen rearrangement was unsuccessful. However it is possible with more effort suitable conditions for rearrangement could be found.

5.3 Future directions and conclusions

The key remaining challenge for the total synthesis of dragmacidin E is the construction of the cyclic guanidine D-ring, a task that has proven more difficult than we imagined when we embarked on this endeavor. Exhaustive studies on the elaboration of alcohols **405** and **425** to their corresponding aminomethyl derivatives via Mitsunobu or sulfonate functionalization and displacement have been performed. However, no synthetically useful preparation has been found.

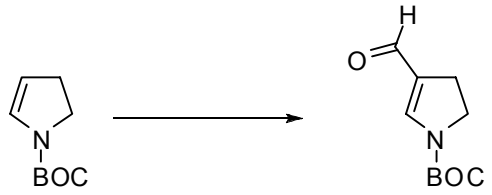
Alternative Strecker (Section 5.2.3) and Bucherer-Bergs (Section 5.2.4) approaches have allowed for introduction of the quaternary stereocenter, appropriately functionalized for preparation of the cyclic guanidine D ring. Effecting this latter transformation has not yet been achieved.

Finally, our existing route to our most advanced material, olefin **461**, may provide us access to a substrate suitable for preparation of the desired ring via the nitrene insertion chemistry of Du Bois. Critical questions that remain to be answered about this approach include not only whether this olefin can be functionalized appropriately, but also whether such functionalization will proceed with control of stereochemistry at C(5’’’).

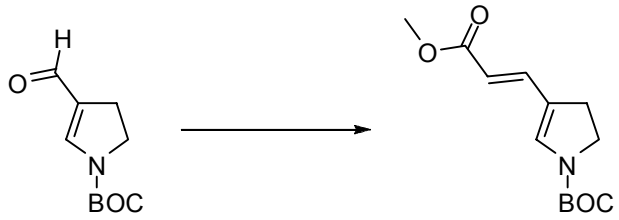
Nonetheless, we have succeeded in developing a 24 linear step route to the fully functionalized core ring system of dragmacidin E, employing key halogen-selective Stille and 7-*exo*-Heck cyclization reactions, as well as the mild, thermal 6π-electrocyclization reaction of a divinyloxazoline for the preparation of a 7-hydroxyindole.

Appendix

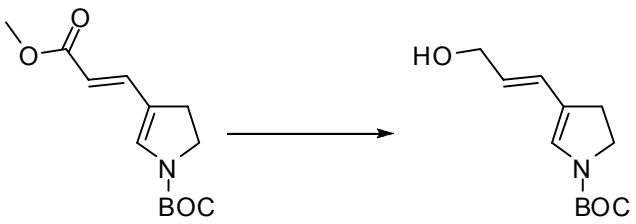
Experimental Procedures



***N*-BOC-3-formyl-4,5-dihydropyrrole (127).** To a solution of DMF (9.07 mL, 117 mmol) in dichloromethane (27 mL) at 0 °C was added dropwise oxalyl chloride (949 µL, 10.9 mmol). The solution was stirred at 0 °C for 10 min. To the resultant white suspension was then added enecarbamate **126**[37,38] (1.54 g, 9.07 mmol) in dichloromethane (9 mL). The solution was allowed to warm to rt and stirred for 1 h. Saturated aqueous Na_2CO_3 (40 mL) was then added and the mixture was stirred vigorously for 1 h. The organic layer was separated, and the aqueous layer washed with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave aldehyde **127** as a white solid (1.71 g, 95%); ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 1.49 (s, 9 H), 2.81 (t, *J* = 9.0 Hz, 2 H), 3.88 (t, *J* = 9.4 Hz, 2 H), 7.39 and 7.55 (br s, 1 H), 9.54 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.7, 28.0, 47.1, 82.5, 124.7, 147.5, 185.6; IR (neat) 2977, 1718, 1659, 1609 cm^{-1} ; HRMS ($M+H^+$) calcd for $C_{10}H_{16}NO_3$ 198.1125, found 198.1125.

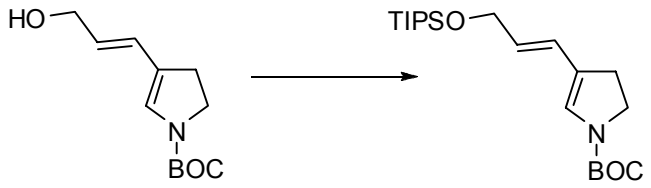


Methyl (*E*)-3-*N*-BOC(4,5-dihydropyrrol-3-yl)prop-2-enoate (129). To a suspension of NaH (60% w/w in mineral oil, 440 mg, 11.0 mmol) in THF (50 mL) at 0 ^{o}C was added dropwise trimethyl phosphonoacetate (1.94 mL, 12.0 mmol). The resultant suspension was then stirred for 30 min. Aldehyde **127** (1.95 g, 10.0 mmol) in THF (10 mL) was added dropwise. The mixture was then allowed to warm to rt and was stirred for 3 h. The solution was then quenched with saturated $NaHCO_3$, and extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated. Recrystallization of the resultant solid residue from hexanes gave ester **129** as a white solid (2.29 g, 91%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 2.68 (br t, *J* = 8.5 Hz, 2 H), 3.68 (s, 3 H), 3.82 (br t, *J* = 8.5 Hz, 2 H), 5.50 (d, *J* = 15.4 Hz, 1 H), 6.83 and 6.99 (br s, 1 H, rotamers), 7.43 (d, *J* = 15.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 45.8, 46.4, 51.2, 81.2, 113.9, 114.2, 135.9, 136.2, 138.7, 150.4, 151.3, 167.6; IR (neat) 2977, 1704, 1621 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{13}H_{20}NO_4$ 254.1387, found 254.1384.

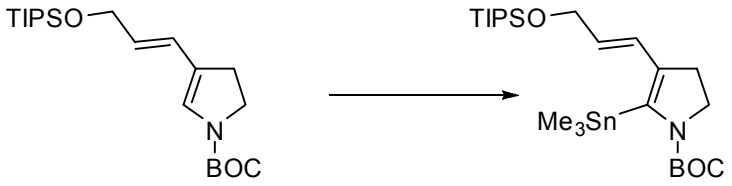


(*E*)-3-*N*-BOC(4,5-dihydropyrrol-3-yl)prop-2-en-1-ol (130). To a solution of ester **129** (2.29 g, 9.10 mmol) in dichloromethane (91 mL) at -60 °C was added dropwise DIBAL-H (1.5 M in toluene, 14.6 mL, 21.8 mmol). The solution

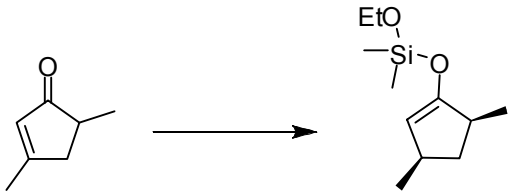
was then allowed to warm to 0 °C and was stirred for 1 h. The resultant solution was then poured onto saturated aqueous $NaHCO_3$ and diluted with ethyl acetate. The aqueous layer was removed and the organic layer filtered through layered sand and Celite. The resultant solution was dried (Na_2SO_4) and concentrated to give alcohol **130** as a yellow liquid (1.62 g, 79%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 2.38-2.48 (br m, 1 H, OH), 2.66 (app q, *J* = 9.3 Hz, 2 H), 3.73 (app q, *J* = 9.3 Hz, 2 H), 4.14 (br app t, *J* = 5.5 Hz, 2 H), 5.40-5.47 (br m, 1 H), 6.34 (app dd, *J* = 15.5, 6.0 Hz, 1 H), 6.44 and 6.58 (br s, 1 H, rotamers); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 27.7, 28.2, 28.7, 45.2, 45.8, 63.4, 80.5, 120.8, 125.3, 125.4, 126.3, 126.6, 128.1, 128.3, 151.3, 151.8; IR (neat) 3429, 2976, 1700, 1417 cm^{-1} ; HRMS (M^+) calcd for $C_{12}H_{19}NO_3$ 225.1365, found 225.1364.



(*E*)-3-*N*-BOC(4,5-dihydropyrrol-3-yl)-1-triisopropylsilyloxyprop-2-ene (131). To a solution of alcohol **130** (1.62 g, 7.18 mmol) in DMF (30 mL) at rt was added imidazole (977 mg, 14.4 mmol). Triisopropylchlorosilane (1.54 mL, 7.18 mmol) was then added dropwise. The solution was allowed to stir at rt for 12 h. The mixture was diluted with hexanes (100 mL) and washed (x3) with saturated $NaHCO_3$. The organic layer was then separated, dried (Na_2SO_4) and concentrated to give diene **131** as a colorless oil (2.03 g, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (m, 21 H), 1.45 (s, 9 H), 2.66 (m, 2 H), 3.74 (m, 2 H), 5.44 (m, 1 H), 6.43 and 6.59 (s, 1 H, rotamers); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 11.9, 17.9, 27.8 28.3, 28.8, 45.2, 45.7, 63.8, 63.9, 80.0, 80.2, 120.8, 121.0, 123.2, 123.7, 126.8, 127.2, 127.5, 127.8, 151.2, 151.8; IR (neat) 2942, 1705 cm^{-1}; HRMS (M^+) calcd for $C_{21}H_{39}NO_3Si$ 381.2699, found 381.2692.

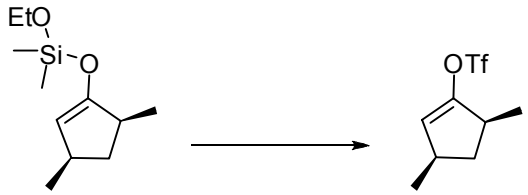


(*E*)-3-*N*-BOC(2-trimethylstannyl-4,5-dihydropyrrol-3-yl)-1-triisopropylsilyloxyprop-2-ene (132). To a solution of diene **131** (218 mg, 0.571 mmol) in THF (2.9 mL) at -30 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 366 μL, 0.914 mmol). The solution was stirred at -30 °C for 1 h. To the resultant solution was added dropwise trimethyltin chloride (1.0 M in THF, 0.914 mL, 0.914 mmol). The solution was allowed to warm to rt over 30 min. The mixture was quenched with saturated $NaHCO_3$ and extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated to give stannane **132** as a yellow oil (251 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.25 (t, *J* = 27.7 Hz, 9 H), 1.08 (m, 21 H), 1.46 (s, 9 H), 2.75 (t, *J* = 9.3 Hz, 2 H), 3.69 (t, *J* = 9.3 Hz, 2 H), 4.32 (d, *J* = 5.5 Hz, 2 H), 5.45 (dt, *J* = 15.3, 5.5 Hz, 1 H), 6.63 (d, *J* = 15.3 Hz,1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7 (t, *J* = 190 Hz, Sn-Me_3), 12.0, 18.0, 28.3, 30.8, 46.2, 64.5, 79.9, 126.1, 126.8, 132.2, 144.4, 153.4; IR (neat) 2942, 1683 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{24}H_{48}NO_3SiSn$ 546.2425, found 546.2448.

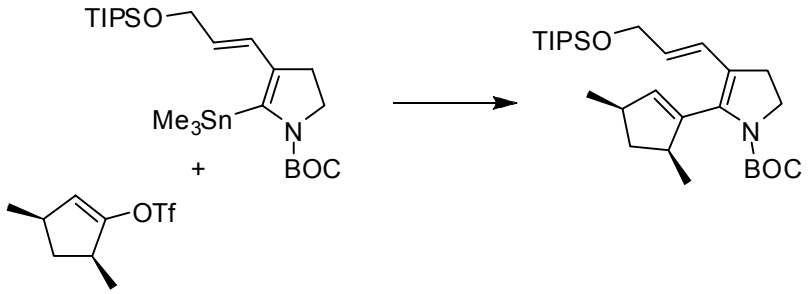


(*cis*-3,5-Dimethylcyclopent-1-enyloxy)ethoxydimethylsilane (136). To a solution of 3,5-dimethyl-2-cyclopentenone **135**[136] (1.10 g, 10.0 mmol) in dimethylethoxysilane (2.74 mL, 20.0 mmol) at –30 °C was added [Rh(OH)(cod)][50b] (68.0 mg, 0.150 mmol). The mixture was stirred for 16 h at –30 °C and concentrated. Purification of the resultant residue by chromatography

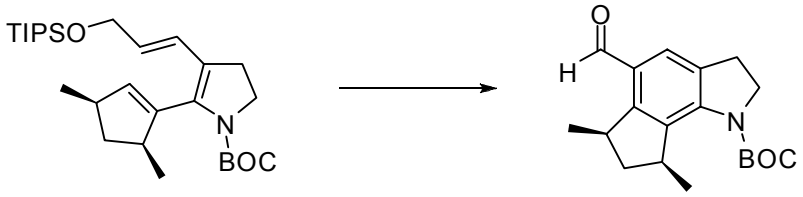
(triethylamine deactivated Florisil, hexanes) gave silylenolether **136** (1.87 g, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 6 H), 0.87 (dt, *J* = 12.5, 7.0 Hz, 1 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.19 (t, *J* = 7.0 Hz, 3 H), 2.26 (dt, *J* = 12.5, 8.1 Hz, 1 H), 2.42-2.61 (m, 2 H) 3.77 (q, *J* = 7.0 Hz, 3 H), 4.61 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -3.0, 18.2, 19.4, 34.6, 39.6, 39.9, 58.3, 108.4, 156.7; IR (neat) 2956, 2927, 2868, 1641 cm^{-1}; GCMS 214, 199, 103, 75. HRMS (M^+) calcd for $C_{11}H_{22}NO_2Si$ 214.1389, found 214.1371.



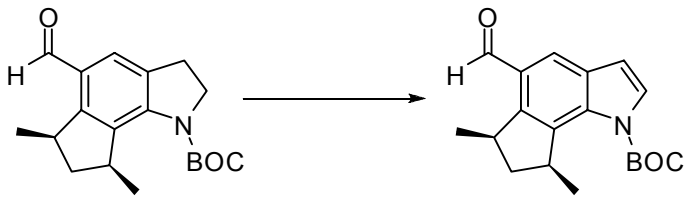
***cis*-3,5-Dimethylcyclopent-1-enyl trifluoromethanesulfonate (121).** Finely powdered cesium fluoride (3.65 g, 24.0 mmol) was dried under vacuum 16 h (170 ^{o}C). The flask was cooled to rt and a solution of silylenol ether **136** (1.75 g, 8.00 mmol) and *N*-phenyltrifluoromethanesulfonimide (7.15 g, 20.0 mmol) in DME (25 mL) was quickly added. The flask was quickly stoppered and sealed with Teflon tape. The mixture was stirred for 2 h at rt. The pressure was released carefully, and the mixture was diluted with pentane. The solution was washed (4 x 30 mL) with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated. Purification of the resultant residue by chromatography (triethylamine deactivated Florisil, pentane) gave triflate **121** (1.12 g, 58%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05-1.12 (m, 1 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 1.14 (d, *J* = 6.9 Hz, 3 H), 2.45 (dt, *J* = 12.8, 8.3 Hz, 1 H), 2.71-2.80 (m, 1 H) 2.85-2.96 (m, 1 H), 5.54 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.7, 21.7, 34.6, 38.3, 39.2, 118.6 (q, *J* = 321 Hz), 121.6, 152.4; IR (neat) 2967, 1653, 1424 cm^{-1} HRMS (M^+) calcd for $C_{12}H_{21}NO_3$ 244.0381, found 244.0385.



***N*-BOC-2-(*cis*-3,5-dimethylcyclopent-1-enyl)-3-[(*E*)-3-triisopropylsilyloxyprop-1-enyl)]-4,5-dihydropyrrole (138).** To a solution of stannane **132** (134 mg, 0.246 mmol) and enol triflate **121** (121 mg, 0.500 mmol) in DMF (1 mL) was added CuI (11.7 mg, 0.0615 mmol) and $Pd(PPh_3)_4$ (28.4 mg, 0.0246 mmol). The mixture was then stirred for 30 min at rt, diluted with hexanes (20 mL) and washed (x3) with saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave triene **138** (91 mg, 78%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 7.0 Hz, 3 H), 0.97 (dt, *J* = 12.3, 7.9 Hz, 1 H), 1.08 (m, 21 H), 1.12 (d, *J* = 7.2 Hz, 3 H), 1.26 (s, 9 H), 2.40 (dt, *J* = 12.4, 7.9 Hz, 1 H), 2.52 (ddd, *J* = 15.4,11.0, 4.3 Hz) 2.70-2.81 (m, 2 H) 2.95-3.02 (m, 1 H), 3.69 (td, *J* = 11.1, 9.6 Hz, 1 H), 3.96 (td *J* = 11.1, 4.3 Hz), 4.33 (dd, *J* = 5.2, 1.6 Hz, 2 H), 5.51 (dt, *J* = 15.6, 5.2 Hz, 1 H), 5.53 (m, 1 H), 6.53 (d, *J* = 15.6 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 12.0, 18.0, 20.0, 21.7, 28.3, 39.5, 42.0, 42.2, 47.1, 64.2, 79.9, 121.8, 124.5, 126.9, 136.4, 136.9, 139.9, 152.3; IR (neat) 2954, 1711, 1694 cm^{-1} ; HRMS ($M+H^+$) calcd for $C_{28}H_{50}NO_3Si$ 476.3555, found 476.3551.

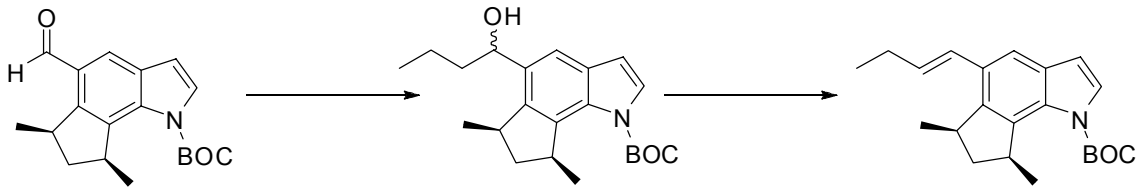


***N*-BOC-5-formyl-*cis*-6,8-dimethyl-2,3,6,7,8-pentahydrocyclopenta[g]indole (141).** A solution of triene **138** (215 mg, 0.452 mmol) in xylenes (18 mL) was refluxed for 2 h. The solution was cooled to 0 ^{o}C and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (308 mg, 1.36 mmol) was added. The solution was warmed to rt, stirred for 2 h, diluted with ether and washed with saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 20) gave indoline **141** (89 mg, 62%) as a white solid, mp 129-130 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 7.2 Hz, 3 H), 1.30 (d, *J* = 7.2 Hz, 3 H), 1.47 (dt, *J* = 13.1, 2.0 Hz. 1 H), 1.54 (s, 9 H), 2.66 (dt, *J* = 13.1, 9.5 Hz, 1 H), 2.86 (ddd, *J* = 15.6, 9.5, 2.0 Hz, 1 H) 3.18 (dt, *J* = 15.6,10.6 Hz, 1 H) 3.72-3.89 (m, 2 H), 3.91-4.01 (m, 1 H), 4.27 (td *J* = 10.7, 2.0 Hz, 1 H), 7.54 (s, 1 H), 10.09 (s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.5, 25.8, 27.8, 28.2, 37.1, 37.7, 40.6, 50.5, 81.2, 124.7, 127.8, 132.8, 136.2, 143.8, 151.8, 154.0, 190.4; IR (neat) 2961, 1715, 1681 cm^{-1} ; HRMS (M+H^{+}) calcd for $C_{19}H_{26}NO_3$ 316.1894, found 316.1907.



***N*-BOC-5-formyl-*cis*-6,8-dimethyl-6,7,8-trihydrocyclopenta[g]indole (142).** To a solution of indoline **141** (205 mg, 0.650 mmol) in dichloromethane (13 mL) was added γ-MnO_2 (3.08 g, 35.4 mmol). The resultant suspension was

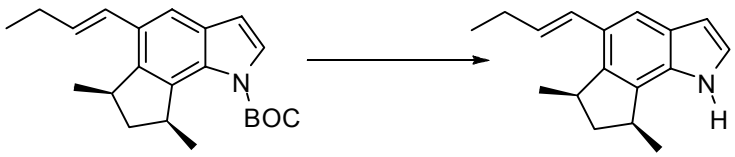
stirred at rt for 2 h, filtered and concentrated to give indole **142** (203 mg, 100%) as a white solid, mp 103-105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, *J* = 7.2 Hz, 3 H), 1.33 (d, *J* = 7.1 Hz, 3 H), 1.60 (d, *J* = 13.3 Hz, 1 H), 1.64 (s, 9 H), 2.69 (dt, *J* = 13.0, 9.4 Hz, 1 H), 4.19-4.30 (m, 1 H), 6.62 (d, *J* = 3.8 Hz, 1 H), 7.56 (d, *J* = 3.8 Hz, 1 H), 7.92 (s, 1 H), 10.19 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 25.4, 17.9, 37.5, 38.6, 40.4, 83.9, 107.9, 124.5, 127.9, 128.2, 130.8, 134.8, 135.3, 148.0, 148.4, 191.8; IR (neat) 2962, 1753, 1691 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{19}H_{24}NO_3$ 314.1751, found 314.1752.



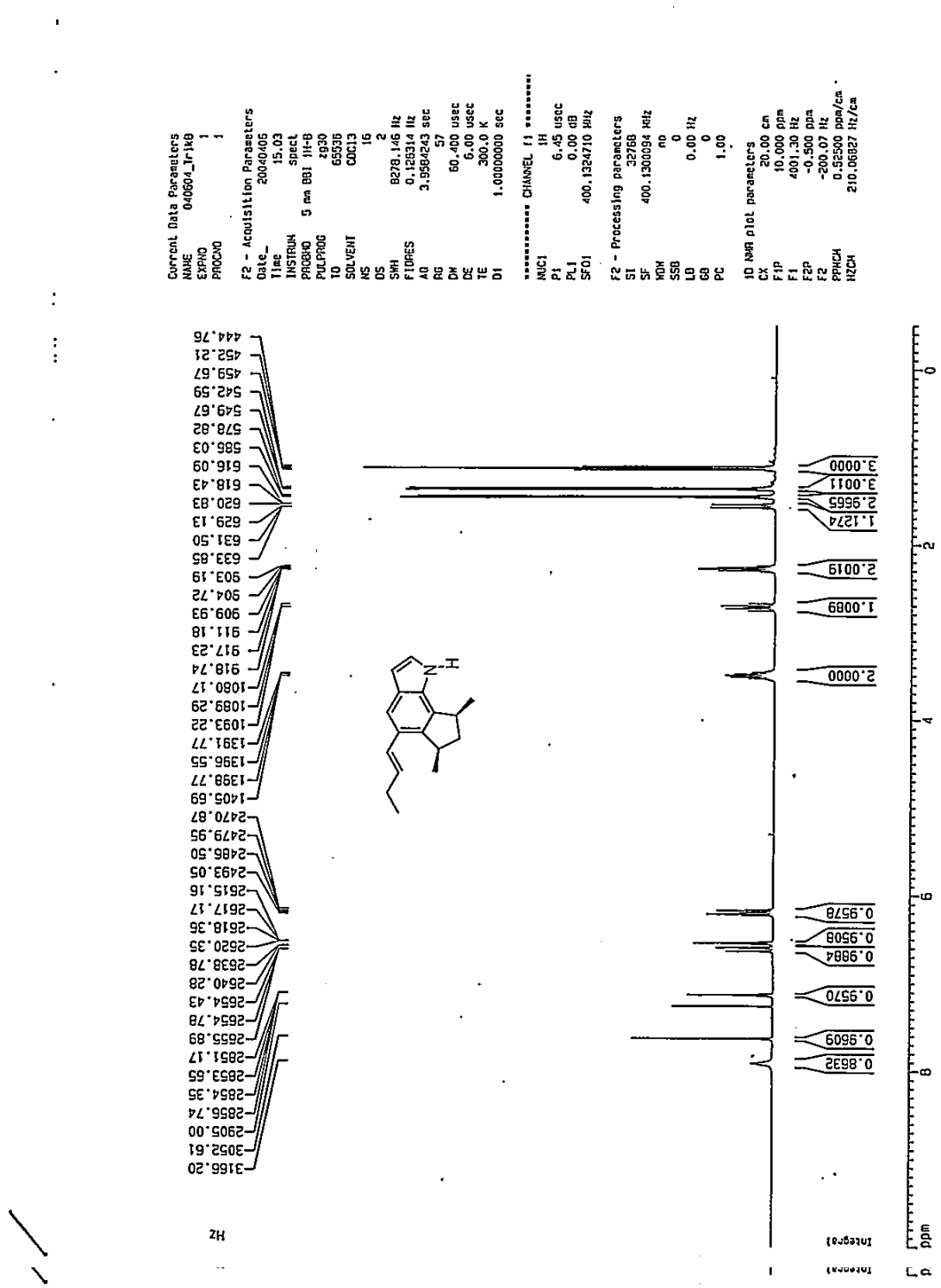
***N*-BOC-*cis*-trikentrin B (144).** To a solution of aldehyde **142** (125 mg, 0.400 mmol) in THF (13 mL) at –30 °C was added dropwise *n*-propylmagnesium chloride (2.0 M in ether, 400 μL, 0.800 mmol). The resultant solution was stirred at –30 °C for 10 min, quenched with saturated aqueous NH_4Cl and extracted with ether. The organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave an inseparable mixture of diastereomeric alcohols **143** (116 mg, 81%).

To a solution of diastereomeric alcohols **143** (101 mg, 0.283 mmol) in benzene (20 mL) was added *p*-TsOH (5.4 mg, 0.028 mmol). The solution was stirred at 50 °C for 2 h. The mixture was then poured onto saturated $NaHCO_3$, extracted with ether, dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 20) gave *N*-BOC-trikentrin B (**144**) (80.7 mg, 84%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.5 Hz, 3 H), 1.27 (d, *J* = 8.5 Hz, 3 H), 1.35 (d, *J* = 7.2 Hz, 3 H), 1.57 (d, *J* = 13.9 Hz, 1 H), 1.66 (s, 9 H), 2.30 (m, *J* = 7.5, 1.5 Hz 2 H),

2.70 (dt, *J* = 12.9, 9.4 Hz, 1 H), 3.47-3.56 (m, 1 H), 4.22-4.31 (m, 1 H), 6.26 (dt, *J* = 15.7, 6.6 Hz, 1 H), 6.54 (d, *J* = 3.8 Hz, 1 H), 6.62 (dt *J* = 15.7, 1.5 Hz, 1 H), 7.50 (d, *J* = 3.8 Hz, 1 H), 7.56 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 24.0, 24.3, 26.3, 28.1, 37.9, 39.3, 40.3, 82.9, 107.6, 115.8, 126.9, 127.0, 129.9, 130.9, 131.2, 132.0, 133.8, 143.7, 148.9; IR (neat) 2962, 1746 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{22}H_{30}NO_2$ 340.2271, found 340.2277.



***cis*-Trikentrin B (73).** To a solution of BOC-indole **144** (70.5 mg, 0.207 mmol) in dichloromethane (2 mL) was added 2,6-lutidine (240 μL, 2.07 mmol) and trimethylsilyltrifluoromethanesulfonate (280 μL, 1.55 mmol). The resultant solution was refluxed for 30 min, diluted with ether (20 mL) and poured onto saturated NH_4Cl (40 mL). The organic layer was washed (3 x 20 mL) with saturated aqueous NH_4Cl, dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 20) gave *cis*-trikentrin B (40.2 mg, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.5 Hz, 3 H), 1.37 (d, *J* = 7.2 Hz, 3 H), 1.46 (d, *J* = 7.2 Hz, 3 H), 1.56 (dt, *J* = 13.1, 1.4 Hz, 1 H), 2.28 (m, *J* = 7.5, 1.5 Hz 2 H), 2.72 (dt, *J* = 13.1, 9.1 Hz, 1 H), 3.42-3.59 (m, 2 H), 6.20 (dt, *J* = 15.6, 6.6 Hz, 1 H), 6.54 (dd, *J* = 3.2, 2.0 Hz, 1 H), 6.61 (d *J* = 15.7 Hz, 1 H), 7.14 (dd, *J* = 3.2, 2.5 Hz, 1 H), 7.63 (s, 1 H), 7.91 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 24.2, 26.3, 36.9, 38.4, 41.7, 103.1, 115.5, 123.7, 127.3, 127.4, 127.7, 129.0, 131.0, 131.9, 140.6; IR (neat) 3417, 2959 cm^{-1} ; HRMS (M+H$^+$) calcd for $C_{17}H_{22}N$ 240.1747, found 240.1737.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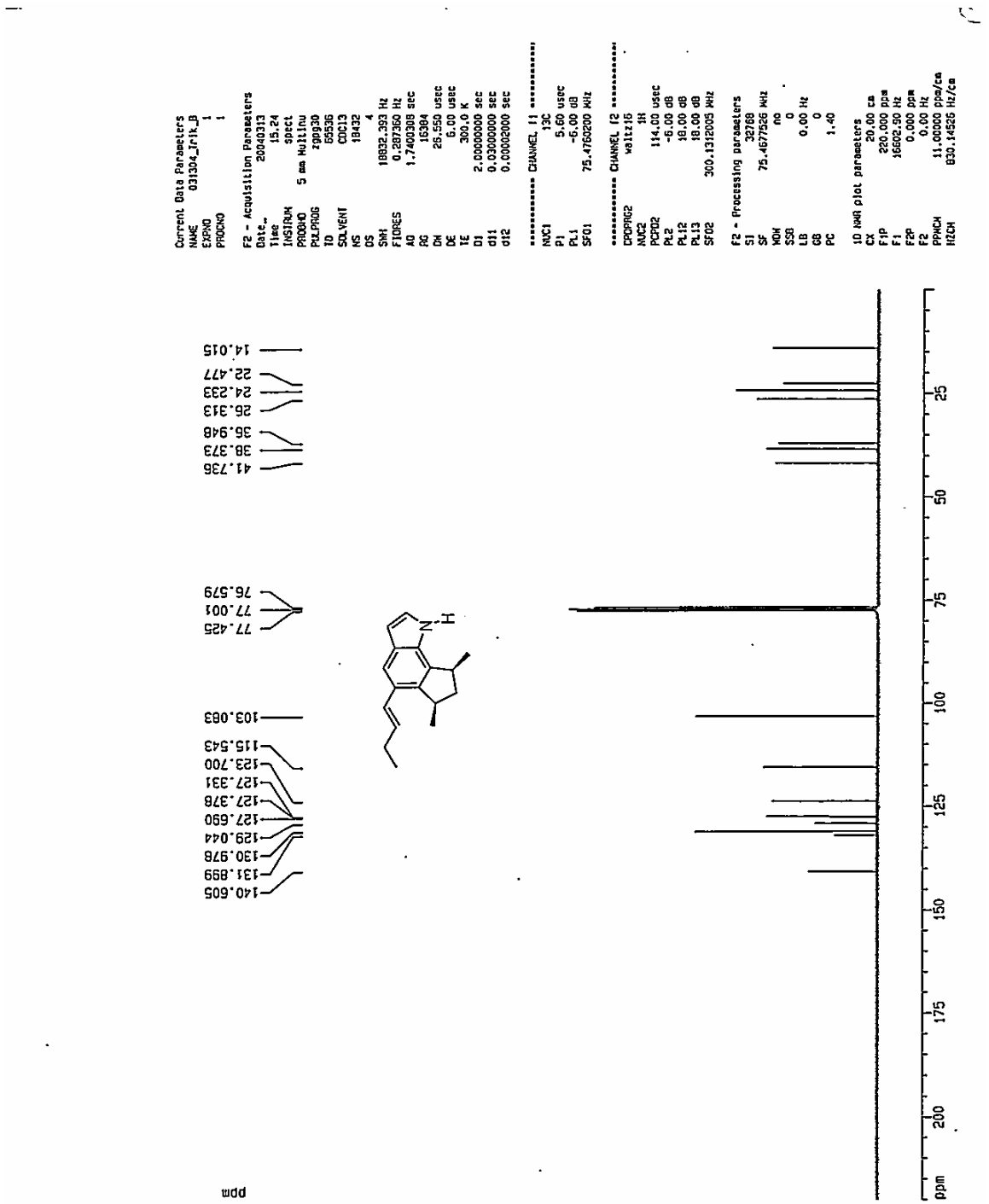
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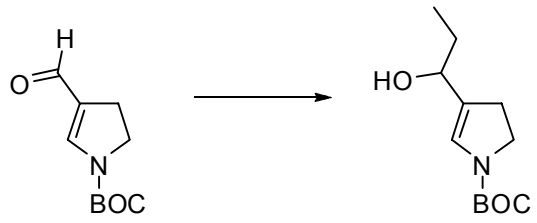
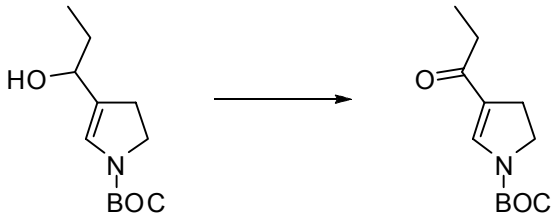
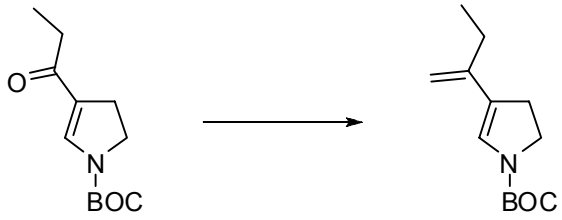


***N*-BOC-1-(4,5-dihydropyrrol-3-yl)propan-1-ol (146).** To a solution of aldehyde **127** (2.44 g, 12.5 mmol) in THF (50 mL) at -78 °C was added dropwise ethyllithium (0.5 M in 90/10 benzene/cyclohexane, 28.8 mL, 14.4 mmol). The resultant solution was stirred at -78 °C for 20 min and poured onto saturated aqueous $NaHCO_3$ (100 mL). The mixture was extracted (3 x 75 mL) with ether, dried (Na_2SO_4) and concentrated to give alcohol **146** (2.84 g, 100%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 0.78-0.86 (m, 3 H), 1.39 (s, 9 H), 1.53 (p, *J* = 7.4 Hz, 1 H), 2.42-2.62 (m, 2 H), 2.60 (app d, *J* = 4.0 Hz, 1 H), 3.59-3.72 (m, 2 H), 4.03-4.10 (m, 2 H), 6.31 and 6.44 (br s, 1 H, rotamers); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 9.8, 27.1, 28.1, 28.2, 45.1, 45.6, 79.9, 80.0, 124.5, 125.5, 151.5, 152.2; IR (neat) 3434, 2974, 1702 cm^{-1} ; HRMS (M^+) calcd for $C_{12}H_{21}NO_3$ 227.1521, found 227.1534.



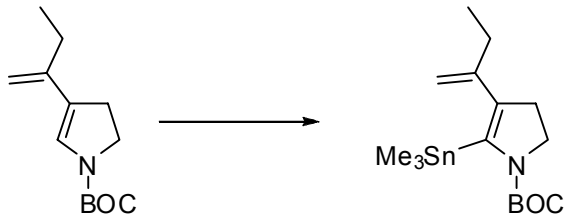
***N*-BOC-3-propionyl-4,5-dihydropyrrole (145).** To a solution of alcohol **146** (2.84 g, 12.5 mmol) in dichloromethane (50 mL) at 0 °C was added 4Å molecular sieves (powder, <5 micron, activated, 6.0 g), 4-methylmorpholine *N*-oxide (2.20 g, 18.8 mmol) and tetrapropylammonium perruthenate (439 mg, 1.25

mmol). The resultant suspension was stirred at 0 °C for 2 h. The solution was then poured onto saturated $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), filtered (Celite) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane-triethylamine, 20 : 100 : 1) gave ketone **145** (1.60 g, 57%) as a yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$, rotamers) δ 1.05 (t, *J* = 7.4 Hz, 3 H), 1.44 (s, 9 H), 2.52 (q, *J* = 7.4 Hz, 2 H), 2.76 (br t, *J* = 9.2 Hz, 2 H), 3.76 (br t, *J* = 9.2 Hz, 2 H), 7.28 and 7.48 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 8.9, 26.5, 27.5, 28.0, 31.4, 46.3, 46.7, 81.8, 122.2, 139.5, 140.2, 150.8, 151.6, 197.0; IR (neat) 2977, 1714, 1651 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{12}H_{20}NO_3$ 226.1443, found 226.1443.

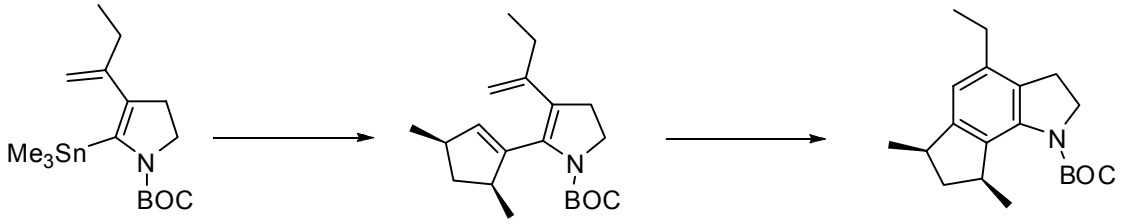


***N*-BOC-3-but-1-en-2-yl-4,5-dihydropyrrole (146).** To a suspension of methyltriphenylphosphonium bromide (385 mg, 1.08 mmol) in THF (2.6 mL) at –30 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 405 μL, 1.01 mmol). The solution was allowed to warm to 0° C over 30 min. Ketone **145** (163 mg, 0.723 mmol) in THF (1 mL) was added dropwise. The resultant mixture was stirred at 0 °C for 20 min and quenched with water (3 drops). The solution was then diluted with hexanes (5 mL) and filtered through a short plug of Celite. The resultant solution was concentrated, diluted again with hexanes and refiltered through Celite. Purification of the resultant residue by chromatography (ether-hexanes 1:10) through a very short column of Florisil gave diene **146** (98 mg, 61%) as a colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$, rotamers) δ 1.02-1.12 (m, 3 H), 1.46 (s, 9 H), 2.23 (q, *J* = 7.3 Hz, 2 H), 2.71 (br app q, *J* = 9.9 Hz, 2 H), 3.68-3.82 (m, 2 H), 4.65 and 4.69 (s, 1 H, rotamers), 4.80 and 4.82 (s, 1 H, rotamers)

6.49 and 6.70 (br s, 1 H, rotamers); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 13.0, 13.2, 16.1, 26.3, 28.9, 29.9, 45.2, 45.7, 80.1, 80.3, 107.8, 108.0, 122.4, 122.7, 125.1, 125.6, 143.9, 144.2, 151.4, 152.0; IR (neat) 2973.0, 1704.2, 1624.8 cm^{-1} ; HRMS (M^+) calcd for $C_{13}H_{21}NO_2$ 223.1572, found 223.1567.

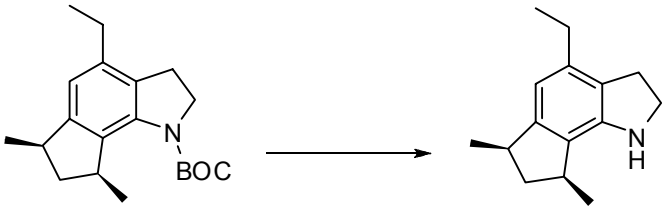


***N*-BOC-3-but-1-en-2-yl-2-trimethylstannyl-4,5-dihydropyrrole (147).** To a solution of diene **146** (266 mg, 1.19 mmol) in THF (5.5 mL) at -30 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 707 μL, 1.77 mmol). The solution was stirred at -30 °C for 30 min. To the resultant solution was added dropwise trimethyltin chloride (1.0 M in THF, 1.77 mL, 1.77 mmol). The solution was allowed to warm to rt over 30 min. The mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted (3 x 20 mL) with ether. The combined extracts were dried (Na_2SO_4) and concentrated to give stannane **147** as a yellow oil (374 mg, 81%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.17 (t, *J* = 28.6 Hz, 9 H), 1.01 (t, *J* = 7.4 Hz, 3 H), 1.46 (s, 9 H), 2.12 (t, *J* = 7.4 Hz, 2 H), 2.69 (t, *J* = 9.3 Hz, 2 H), 3.70 (t, *J* = 9.3 Hz, 2 H), 4.76-4.79 (m, 1 H), 4.87 (s, 1 H); IR (neat) 2968, 1684 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{15}H_{26}NO_2Sn$, 388.1299 found 388.1291.

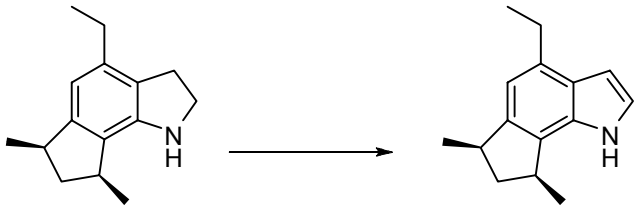


***N*-BOC-2,3-dihydro-*cis*-trikentrin A (150).** CuCl (198 mg, 2.00 mmol), LiCl (106 mg, 2.50 mmol) and $Pd(PPh_3)_4$ (53 mg, 0.050 mmol) were combined under N_2 in a round bottomed flask. This mixture was added in one portion to a solution of triflate **121** (157 mg, 0.650 mmol) and stannane **147** (193 mg, 0.50 mmol) in DMSO (10 mL). The reaction mixture was stirred at rt for 30 min, and poured carefully onto saturated $NaHCO_3$ (50 mL). The resultant slurry was diluted with ether (50 mL) and filtered through Celite, rinsing thoroughly with ether. The organic phase of the resultant filtrate was washed (x3) with saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated to give a crude oil that was immediately used in the next step without further purification.

The crude mixture above was dissolved in toluene (10 mL) and stirred at 80 ^oC for 30 minutes. The solution was cooled to 0 ^oC and γ-MnO_2 (1.93 g) was added. The suspension was stirred for 100 min at 0 ^oC, filtered (Celite) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane 90 : 10) gave BOC-indoline **150** (135 mg, 86% from **147**) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.04-1.18 (m, 1 H), 1.15 (d, *J* = 6.4 Hz, 3 H), 1.24 (t, *J* = 7.6 Hz, 3 H), 1.32 (d, *J* = 6.7 Hz, 3 H), 1.56, (s, 9 H), 2.52 (dt, *J* = 12.2, 7.5 Hz, 1 H), 2.76 (dd, *J* = 15.5, 9.1 Hz, 1 H), 3.04-3.15 (m, 2 H) 3.04-3.11 (m, 1 H), 3.49-3.60 (m, 1 H), 3.80 (td, *J* = 11.2, 9.2 Hz, 1 H), 4.39 (br t, *J* = 10.2 Hz, 1 H), 6.75 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 19.6, 26.1, 27.2, 28.4, 38.2, 38.4, 44.7, 50.1, 80.4, 117.7, 129.8, 133.8, 137.7, 138.5, 149.6, 153.5; IR (neat) 2959, 1711, 1421, 1367 cm^{-1} ; HRMS ($M+H^+$) calcd for $C_{20}H_{30}NO_2$ 316.2271, found 316.2297.

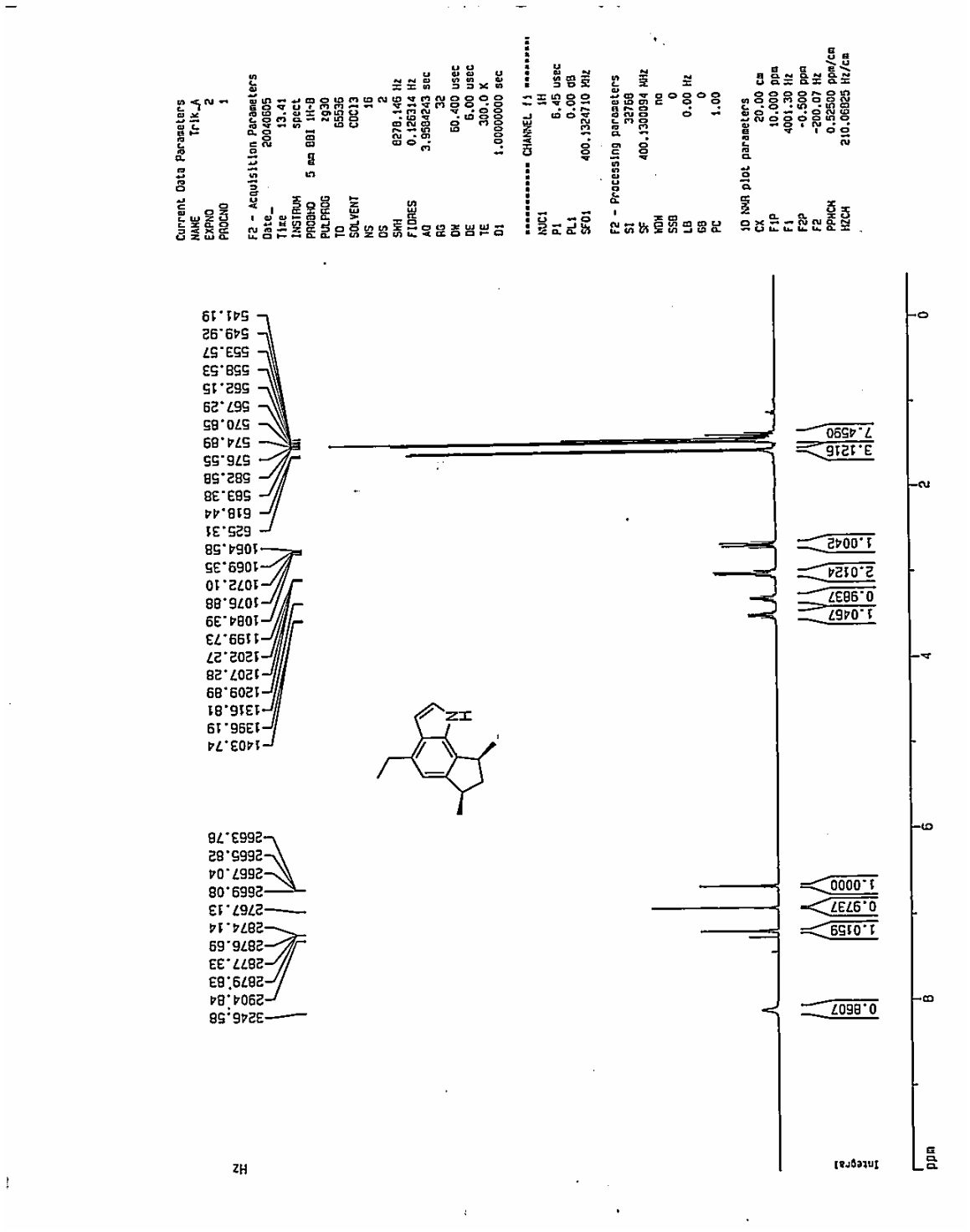


2,3-Dihydro-*cis*-trikentrin A (151). To a solution of BOC-indoline **150** (169 mg, 0.536 mmol) in dichloromethane (2.0 mL) was added 2,6-lutidine (187 μL, 1.61 mmol) and trimethylsilyltrifluoromethane sulfonate (194 μL, 1.07 mmol). The mixture was stirred for 15 min at rt, poured onto saturated $NaHCO_3$ (10 mL) and diluted with ether. The organic layer was separated, washed (x2) with saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (hexanes-ethyl acetate 10:1) gave indoline **151** (79 mg, 68%) as a colorless oil that darkened on standing. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-1.33 (m, 1 H), 1.29 (t, *J* = 7.6 Hz, 3 H), 1.37 (d, *J* = 6.8 Hz, 3 H), 1.40 (d, *J* = 6.8 Hz, 3 H), 2.55 (dt, *J* = 12.3, 7.5 Hz, 1 H), 2.63 (q, *J* = 7.6 Hz, 2 H) 3.02 (t, *J* = 8.4 Hz, 2 H) 3.04-3.11 (m, 1 H), 3.12-3.22 (m, 1 H), 3.59-3.71 (m, 2 H) 6.54 (s, 1 H; ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 19.8, 20.4, 26.4, 27.8, 36.6, 28.3, 44.7, 47.6, 113.0, 125.7, 126.3, 138.5, 147.1, 149.0; IR (neat) 3362, 2957, 2866, 1593 cm^{-1} ; HRMS ($M+H^+$) calcd for $C_{15}H_{22}N$ 216.1747, found 216.1760.



(±)-*cis*-Trikentrin A (72). To a solution of indoline **151** (21.5 mg, 0.100 mmol) in methanol (1.0 mL) was added *N, N'*-bis(salicylidene)ethylenediaminocobalt(II) (3.9 mg, 0.010 mmol). O_2 gas was

bubbled through the resultant suspension for 3 h. The solution was poured onto saturated $NaHCO_3$ (15 mL), and the aqueous layer was extracted (3 x 25 mL) with ether. The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (hexanes-ethyl acetate 20:1) gave *cis*-trikentrin A (**72**) (15.9 mg, 75%) as a pale pink oil that darkened on standing. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34-1.43 (m, 1 H), 1.44 (t, *J* = 7.6 Hz, 3 H), 1.45 (d, *J* = 6.8 Hz, 3 H), 1.55 (d, *J* = 6.9 Hz, 3 H), 2.68 (dt, *J* = 12.3, 7.5 Hz, 1 H), 2.96-3.06 (m, 2 H) 3.24-3.37 (m, 1 H), 3.44-3.56 (m, 1 H), 6.69 (dd, *J* = 3.3, 2.0 Hz, 1 H), 6.95 (s, 1 H), 7.20 (dd, *J* = 3.2, 2.5 Hz, 1 H), 8.12 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 20.7, 21.0, 26.5, 37.1, 38.9, 44.6, 101.3, 122.8, 126.3, 126.9, 132.4, 134.9, 142.9; IR (neat) 3362, 2957, 2866, 1593 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{15}H_{20}N$ 214.1590, found 216.1570.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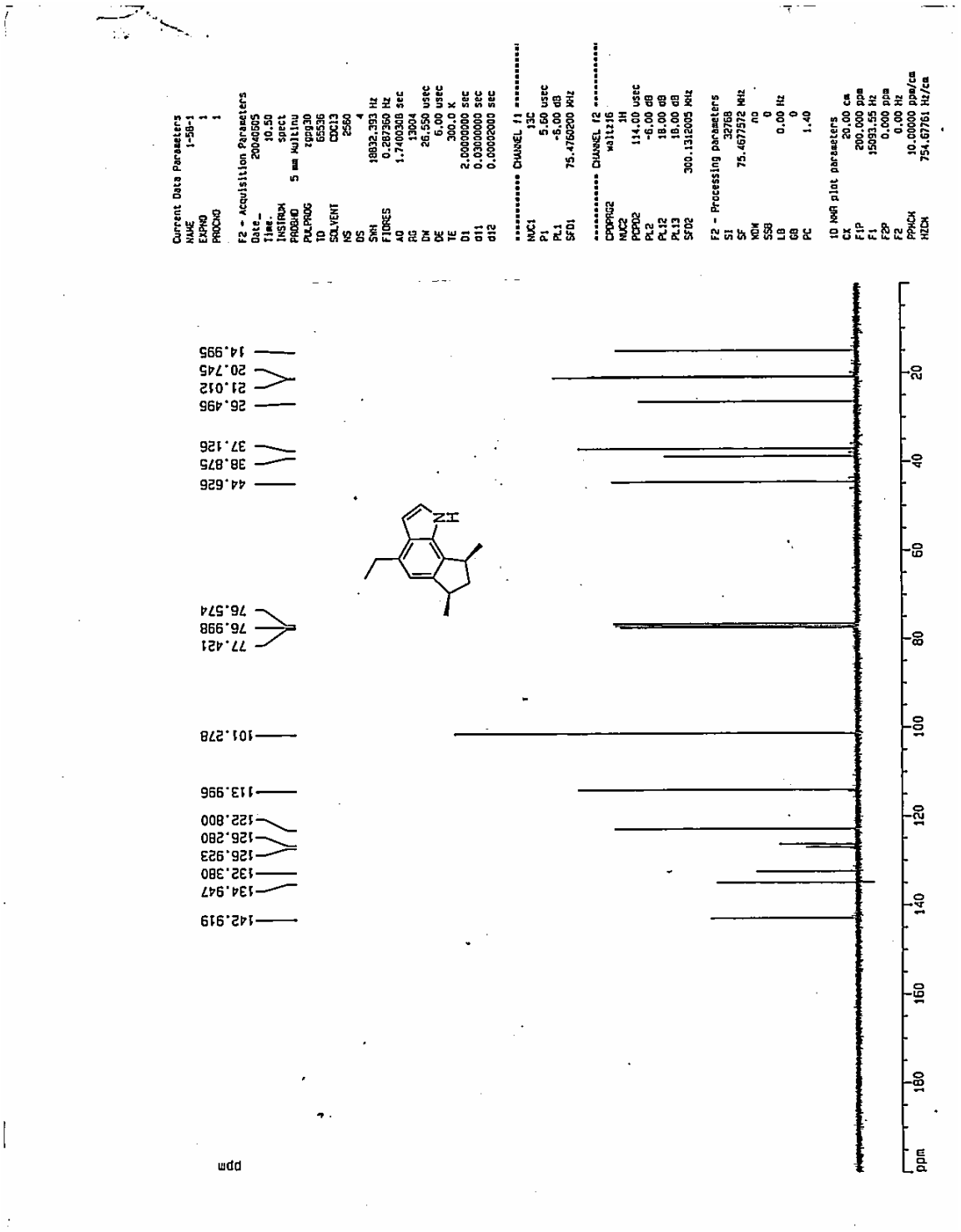
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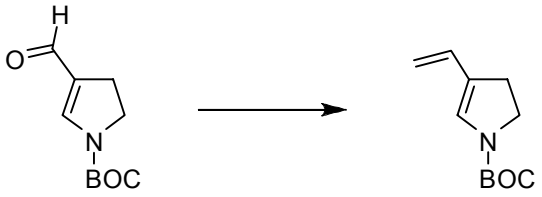
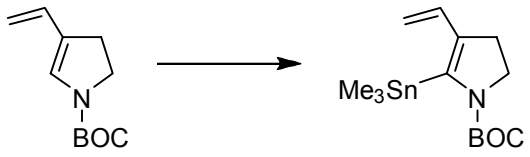
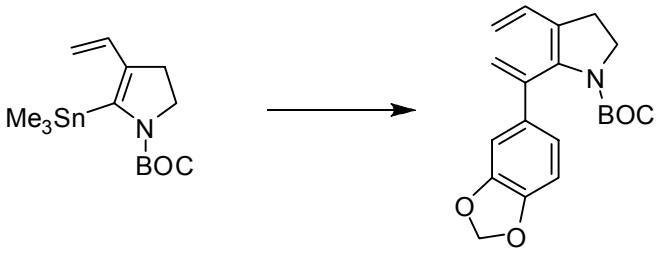


***N*-BOC-3-vinyl-4,5-dihydropyrrole (182)**. To a solution of aldehyde **127** (1.88 g, 9.53 mmol) in ether (38 mL) at 0 °C was added dropwise (trimethylsilyl)methylmagnesium chloride (1.0 M in THF, 14.3 mL, 14.3 mmol). The solution was stirred at 0 °C for 1.5 h. The solution was then cooled to –78 ^{o}C. Acetic acid (2.76 mL, 47.7 mmol) was then added dropwise. The solution was allowed to warm to –40 ^{o}C over 30 min. The mixture was quenched with saturated $NaHCO_3$ and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 40) gave diene **182** as a colorless oil (1.47 g, 79%); ^{1}H NMR (300 MHz, d_6-acetone) δ 1.45 (s, 9 H), 2.70 (m, 2 H), 3.73 (m, 2 H), 6.59 (m, 2 H); ^{13}C NMR (75 MHz, d_6-acetone) δ 27.7, 46.1, 46.5, 80.4, , 111.2, 111.4, 122.6, 129.6, 131.7, 151.6, 152.2; IR (neat) 2976, 1703, 1634 cm^{-1}; HRMS (M+H^{+}) calcd for $C_{11}H_{18}NO_2$ 196.1132, found 196.1137.

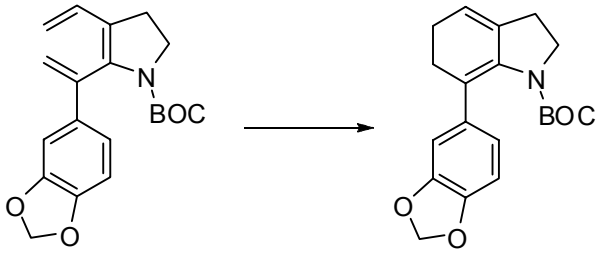


***N*-BOC-3-vinyl-2-trimethylstannyl-4,5-dihydropyrrole (184).** To a solution of diene **182** (1.19 g, 6.09 mmol) in THF (27 mL) at -30 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 2.68 mL, 6.70 mmol). The solution was stirred at -30 °C for 20 min. To the resulting solution was added dropwise trimethyltin chloride (1.0 M in THF, 6.70 mL, 6.70 mmol). The solution was

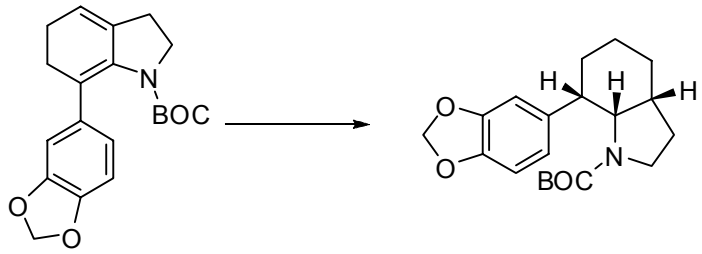
allowed to warm to rt over 30 min. The mixture was quenched with saturated $NaHCO_3$ and extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated to give stannane **184** as a yellow oil (1.84 g, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.25 (t, *J* = 27.9 Hz, 9 H), 1.46 (s, 9 H), 2.76 (t, *J* = 9.3 Hz, 2 H), 3.71 (t, *J* = 9.3 Hz, 2 H), 4.86 (d, *J* = 17.1 Hz, 1 H), 4.93 (d, *J* = 10.6 Hz,1 H), 6.75 (dd, *J* = 10.6, 17.1 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -4.5, 28.5, 30.6, 46.4, 80.2, 111.0, 133.0, 133.2, 145.6, 153.6; IR (neat) 2977, 1682 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{14}H_{26}NO_2Sn$ 360.0984, found 360.0974.



Trienamide 190. To a solution of stannane **184** (2.40 g, 6.70 mmol) and vinyl bromide **185b**[62] (1.67 g, 7.37 mmol) in DMF (25 mL) was added CuI (319 mg, 1.68 mmol) and $Pd(PPh_3)_4$ (774 mg, 0.67 mmol). The mixture was stirred at rt for 3 h. The solution was then quenched with saturated $NaHCO_3$, and extracted with ether. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave triene **190** (1.67 g, 73%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (s, 9 H), 2.76 (t, *J* = 9.1 Hz, 2 H), 3.93 (t, *J* = 9.1 Hz, 2 H), 4.98 (d, *J* = 10.6 Hz, 1 H), 5.00 (d, *J* = 17.3 Hz, 1 H), 5.14 (d, *J* = 1.0 Hz, 1 H), 5.71 (d, *J* = 1.0 Hz, 1 H), 5.95 (s, 2 H), 6.58 (dd, *J* = 17.3, 10.6 Hz, 1 H), 6.74 (d, *J* = 8.1 Hz, 1 H), 6.84 (dd, *J* = 8.1, 1.7 Hz, 1 H), 6.90 (d, *J* = 1.7 Hz, 1 H).

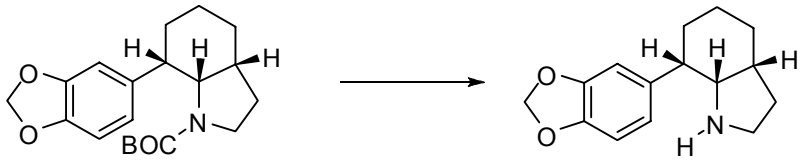


Tetrahydroindole 191. A solution of trienamide **190** (1.67 g, 4.89 mmol) in toluene (49 mL) was refluxed for 2.5 h. The solution was then concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave tetrahydroindole **191** (1.54 g, 92%) as a colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.16 (s, 9 H), 2.25–2.36 (m, 2 H), 2.44-2.51 (m, 2 H), 2.51-2.59 (m, 2 H), 3.74 (t, *J* = 7.2 Hz, 2 H), 5.57-5.62 (m, 1 H), 5.88 (s, 2 H), 6.72 (d, *J* = 8.2 Hz, 1 H), 6.84 (dd, *J* = 8.2, 1.7 Hz, 1 H), 6.89 (d, *J* = 1.7 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 23.6, 27.1, 27.8, 28.7, 47.4, 80.1, 100.6, 107.7, 107.9, 116.0, 116.9, 120.6, 131.7, 136.0, 145.5, 147.1, 152.3; IR (neat) 2975, 2889, 1688 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{20}H_{24}NO_4$ 342.1700, found 342.1675.

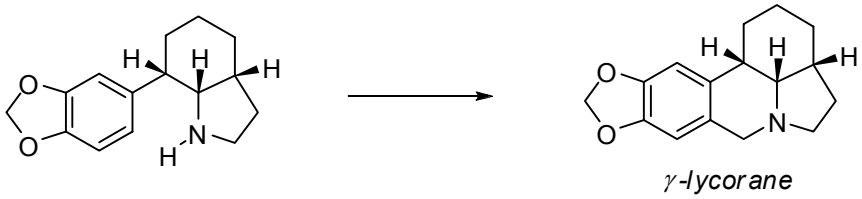


BOC-Indolizidine 192. To a solution of dieneamide **191** (504 mg, 1.48 mmol) in dichloromethane (15 mL) and AcOH (1.5 mL) was added PtO_2 (33.6 mg, 0.148 mmol). The mixture was stirred under 500 psi of hydrogen gas for 8 h. The solution was then carefully poured onto saturated $NaHCO_3$, and extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave BOC-indolizidine **192** (326 mg, 64%) as a

colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.35 (s, 9 H), 1.51-2.03 (m, 8 H), 2.30-2.43 (m, 1 H), 2.90 (br t, 1 H), 3.18 (br q, *J* = 5.9 Hz, 1 H), 3.35 (br q, *J* = 10.3 Hz, 1 H), 4.10 (t, *J* = 7.3 Hz, 1 H), 5.88 (dd, *J* = 10.6, 1.4 Hz, 2 H), 6.68 (d, *J* = 8.0 Hz, 1 H), 6.75 (dd, *J* = 8.0, 1.3 Hz, 1 H), 6.78 (d, *J* = 1.3 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.6, 24.7, 26.5, 28.3, 28.7, 37.2, 40.4, 46.0, 59.1, 78.8, 100.5, 107.6, 109.3, 121.6, 138.3, 145.4, 147.0, 154.9; IR (neat) 2931, 1688, 1489 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{20}H_{28}NO_4$ 346.2013, found 346.2042.

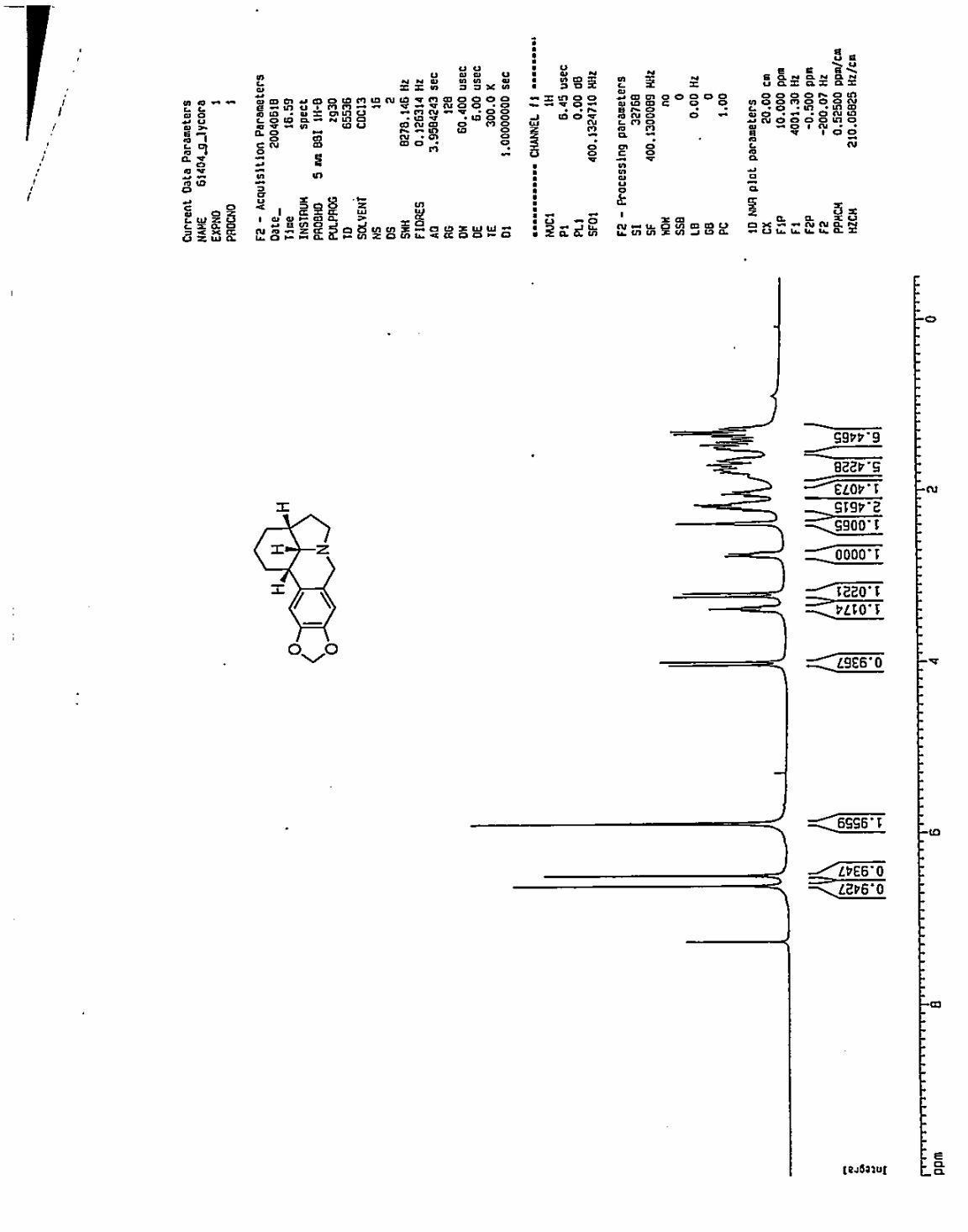


Indolizidine 193. To a solution of BOC-indolizidine **192** (326 mg, 0.943 mmol) in dichloromethane (5 mL) was added 2,6-lutidine (330 μL, 2.83 mmol) and trimethylsilyltrifluoromethane sulfonate (420 μL, 1.89 mmol). The solution was then refluxed for 2 h, carefully poured onto saturated $NaHCO_3$ and extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (NH_4OH-ethyl acetate 1 : 100) gave indolizidine **193** (189 mg, 82%) as a colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.20-1.41 (m, 2 H), 1.43-1.62 (m, 4 H), 1.79-1.94 (m, 3 H), 2.00-2.09 (m, 1 H), 2.81 (dd, *J* = 10.3, 3.9 Hz, 1 H), 2.84-2.88 (m, 1 H), 3.00-3.08 (m, 1 H), 3.20 (t, *J* = 4.0 Hz, 1 H), 5.90 (s, 2 H), 6.70 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 6.79 (d, *J* = 1.5 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.9, 25.8, 27.6, 31.5, 38.7, 43.2, 44.6, 63.2, 100.7, 108.0, 120.1, 139.1, 145.6, 147.5; IR (neat) 2928, 2855, 1488 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{15}H_{20}NO_2$ 246.1489 found 246.1481.



γ-lycorane

γ-Lycorane (155). To a solution of indolizidine **193** (36.4 mg, 0.148 mmol) in MeOH (1.2 mL) was added formalin (1.2 mL) and 6 M aqueous HCl (3.5 mL). The solution was stirred at rt overnight. The mixture was carefully poured onto 1 M NaOH and extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate) gave γ-lycorane **155** (29.7 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-1.53 (m, 4 H), 1.60-1.80 (m, 4 H), 1.98-2.07 (m, 1 H), 2.11-2.22 (m, 2 H), 2.37 (dd, *J* = 9.0, 9.0 Hz, 1 H), 2.74 (dt, *J* = 11.7, 4.6 Hz, 1 H), 3.21 (d, *J* = 14.3 Hz, 1 H), 3.37 (ddd, *J* = 9.0, 9.0, 3.7 Hz, 1 H), 4.01 (d, *J* = 14.3 Hz, 1 H), 5.89 (dd, *J* = 3.7, 1.2 Hz, 2 H), 6.49 (s, 1 H), 6.61 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.2, 29.3, 30.4, 31.7, 37.3, 39.4, 53.7, 57.1, 62.9, 100.6, 106.2, 108.3, 127.2, 133.1, 145.6, 146.0; IR (neat) 2925, 1482, 1230, 1040 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{16}H_{20}NO_2$ 258.1489 found 258.1477.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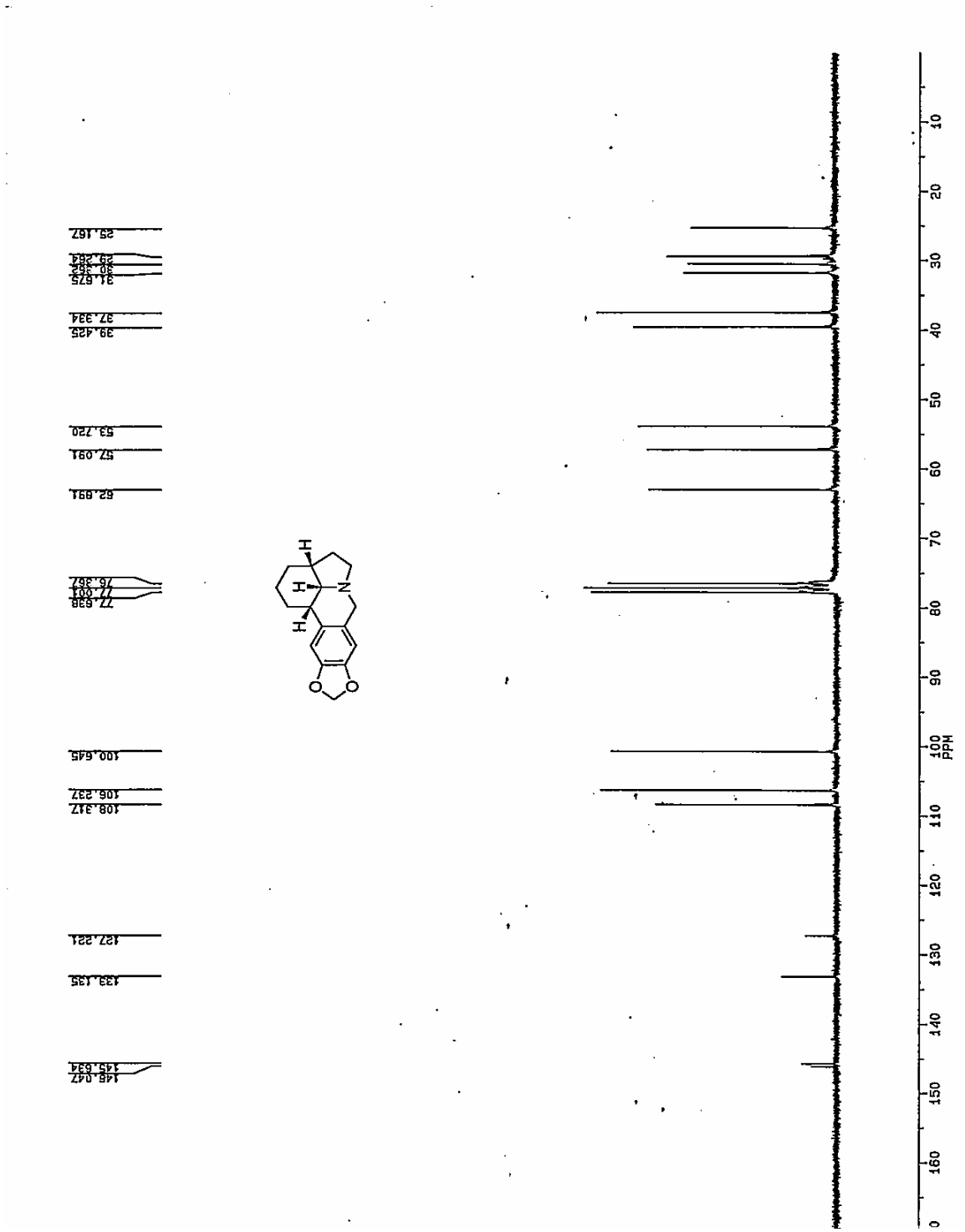
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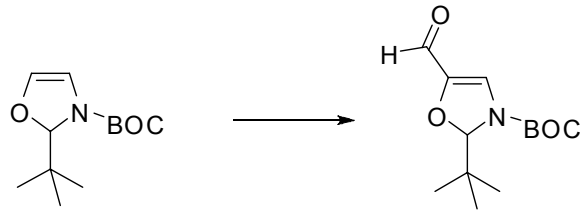
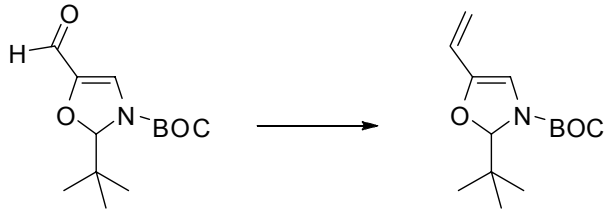
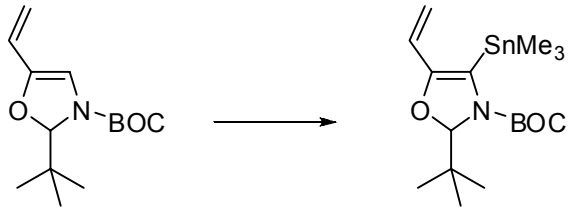


N-BOC-2-*tert*-butyl-5-formyl-2,3-dihydrooxazole (314). To a solution of DMF (4.41 mL, 57.0 mmol) in dichloromethane (46 mL) at 0 °C was added dropwise oxalyl chloride (1.15 mL, 13.2 mmol). The solution was stirred at 0 °C for 20 min. To the resultant white suspension was then added oxazoline **313**[90d] (2.60 g, 11.4 mmol) in dichloromethane (15 mL). The solution was allowed to warm to rt and stirred for 1 h. Saturated aqueous $NaHCO_3$ (150 mL) was then added and the mixture was stirred vigorously for 1 h. The organic layer was separated, and the aqueous layer extracted (3 x 100 mL) with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by deactivated silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave aldehyde **314** as a white solid (1.93 g, 66%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 9 H), 1.51 (s, 9 H), 5.74 (s, 1 H), 7.08 (s, 1 H), 9.18 (s, 1 H)

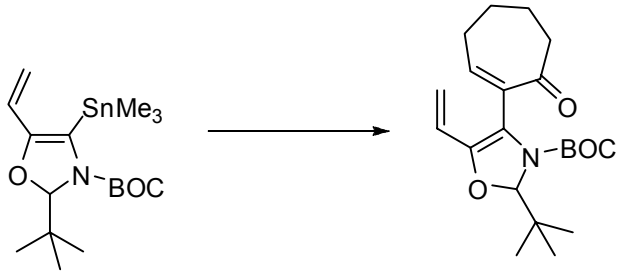


***N*-BOC-2-*tert*-butyl-5-vinyl-2,3-dihydrooxazole (315)**. To a suspension of methyltriphenylphosphonium bromide (3.24 g, 9.07 mmol) in THF (30 mL) at 0 ^{o}C was added dropwise *n*-butyllithium (2.5 M in hexanes, 3.33 mL, 8.32 mmol). The solution was stirred at 0^o C for 15 min. Aldehyde **314** (1.93 g, 7.56 mmol) in THF (30 mL) was added dropwise. The resultant mixture was stirred at 0 ^{o}C for 15 min and then poured onto saturated $NaHCO_3$. The solution was then diluted

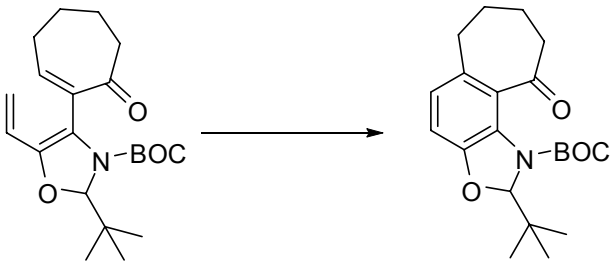
with hexanes (100 mL) and washed (3 x 50 mL) with saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (EtOAc-hexanes 1:20), gave diene **315** (1.32 g, 69%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 9 H), 1.43 (s, 9 H), 5.06 (d, *J* = 10.5 Hz, 1 H), 5.38 (d, *J* = 17.0 Hz, 1 H), 5.56 (s, 1 H), 6.05 (dd, *J* = 10.5, 17.0 Hz, 1 H), 6.07 (s, 1 H);



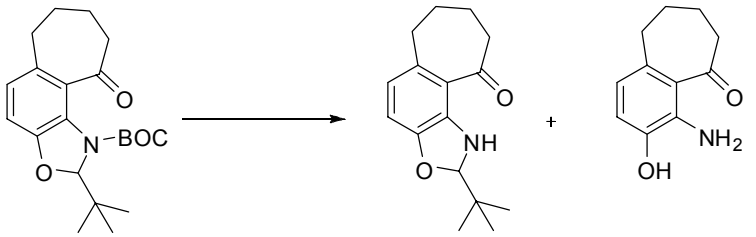
***N*-BOC-2-*tert*-butyl-5-vinyl-4-trimethylstannyl-2,3-dihydrooxazole (316)**. To a solution of diene **315** (2.39 g, 9.44 mmol) in THF (52 mL) at -20 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 5.66 mL, 14.2 mmol). The solution was stirred at -20 °C for 30 min. To the resultant solution was added dropwise trimethyltin chloride (1.0 M in THF, 14.2 mL, 14.2 mmol). The solution was allowed to stir at -20 ^{o}C for 30 min. The mixture was quenched with saturated $NaHCO_3$ (150 mL) and extracted (3 x 100 mL) with ether. The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by deactivated Florisil chromatography (EtOAc-hexanes 1:20), gave stannane **316** (3.15 g, 80%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.22 (t, *J* = 28 Hz, 9 H), 0.87 (s, 9 H), 1.46 (s, 9 H), 5.07 (d, *J* = 10.5 Hz, 1 H), 5.43 (d, *J* = 17.0 Hz,1 H), 5.51 (s, 1 H), 6.17 (dd, *J* = 10.5, 17.0 Hz, 1 H).



Trienecarbamate 318. CuCl (3.17 g, 32.0 mmol), LiCl (1.70 g, 40.0 mmol) and $Pd(PPh_3)_4$ (925 mg, 0.800 mmol) were combined under N_2 in a round bottomed flask. This mixture was added in one portion to a suspension of iodoenone **317**[105] (2.08 g, 8.80 mmol) and stannane **316** (3.32 g, 7.98 mmol) in dry, degassed DMSO (80 mL). The reaction mixture was stirred at rt for 2.5 h, and poured carefully onto saturated $NaHCO_3$ (150 mL). The resultant slurry was diluted with ether (150 mL) and filtered through Celite, rinsing thoroughly with ether. The organic phase of the resultant filtrate was separated, and the aqueous phase was extracted with ether (3 x 100 mL). The combined organic layers were then dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave trienecarbamate **318** (2.11 g, 73%) as a foamy yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 9 H), 1.39 (s, 9 H), 1.51-1.73 (m, 1 H), 1.75-2.01 (m, 3 H), 2.42-2.59 (m, 3 H), 2.84-3.02 (m, 1 H), 5.12 (dd, *J* = 10.6, 1.0 Hz, 1 H), 5.50 (dd, *J* = 17.2, 1.0 Hz, 1 H), 5.60 (s, 1 H), 6.17 (dd, *J* = 17.2, 10.6 Hz, 1 H), 6.51 (t, *J* = 6.3 Hz, 1 H)

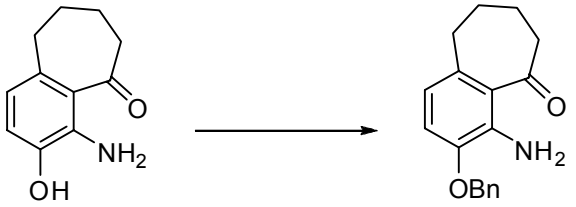


BOC-aniline 320. A solution of trienecarbamate **318** (163 mg, 0.451 mmol) in toluene (22 mL) was refluxed for 2 h. The solution was cooled to rt and DDQ (103 mg, 0.451 mmol) was added in one portion. The resultant red solution was stirred for 2 h, and then poured onto saturated $NaHCO_3$ (30 mL). The mixture was extracted (x2) with ether (10 mL), and the combined organic extracts dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave BOC-aniline **320** (85 mg, 52%) as a foamy yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 9 H), 1.48 (s, 9 H), 1.66-2.02 (m, 4 H), 2.39-2.57 (m, 1 H), 2.63-2.75 (m, 2 H), 2.95-3.11 (m, 1 H), 5.81 (s, 1 H), 6.68 (d, *J* = 9.0 Hz, 1 H), 6.74 (d, *J* = 9.0 Hz, 1 H)

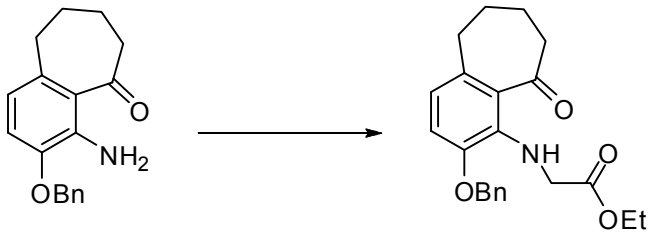


Benzoxazoline 322. To a solution of BOC-aniline **320** (282 mg, 0.784 mmol) in dichloromethane (7.8 mL) was added lutidine (550 μL, 4.70 mmol) and TMSOTf (568 μL, 3.14 mmol). The reaction mixture was refluxed for 2 h. The mixture was then poured onto saturated $NaHCO_3$ (30 mL) and extracted (x3) with ethyl acetate (20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 3) gave aminophenol **321** (39 mg, 26%) as a yellow oil

plus benzoxazoline **322** (74.4 mg, 37%) as a yellow film. ^{1}H NMR (200 MHz, $CDCl_3$) *benzoxazoline* δ 0.93 (s, 9 H), 1.70-2.02 (m, 4 H), 2.64-2.91 (m, 4 H), 5.57 (s, 1 H), 6.33 (d, *J* = 8.5 Hz, 1 H), 6.55 (d, *J* = 8.5 Hz, 1 H), 6.83 (br s, 1 H). *aminophenol* δ 1.63-1.87 (m, 4 H), H), 2.63-2.82 (m, 4 H), 6.18 (br s, 3 H), 6.30 (d, *J* = 9.0 Hz, 1 H), 6.73 (d, *J* = 9.0 Hz, 1 H).

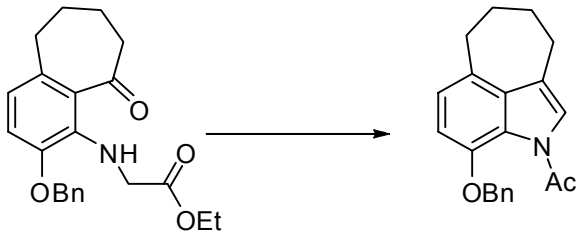


Benzyl ether 323. To a solution of phenol **321** (112 mg, 0.586 mmol) in DMF (5.9 mL) at 0 ^{o}C was added NaH (60 wt % in mineral oil, 23 mg, 0.59 mmol). The resultant mixture was stirred at 0 ^{o}C for 20 min. Benzyl bromide (84 μL, 0.70 mmol) was added, and the solution allowed to stir for 30 min. Saturated NH_4Cl (30 mL) was added, and the resultant mixture extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave benzyl ether **323** (99 mg, 60%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.69-1.83 (m, 4 H), 2.71 (t, *J* = 6.1 Hz, 2 H), 2.88 (t, *J* = 6.4 Hz, 2 H), 5.06 (s, 2 H), 6.37 (d, *J* = 8.4 Hz, 1 H), 6.76 (d, *J* = 8.4 Hz, 1 H), 7.28-7.40 (m, 5 H).

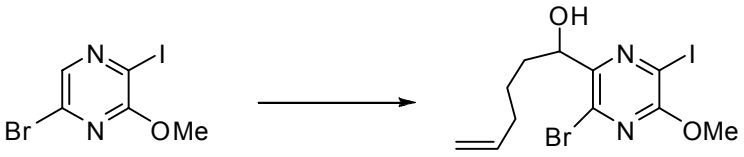


Ester 324. To a solution of benzyl ether **323** (29 mg, 0.10 mmol) in DMF (1.0 mL) was added K_2CO_3 (43 mg, 0.31 mmol) and ethyl iodoacetate (24 μL,

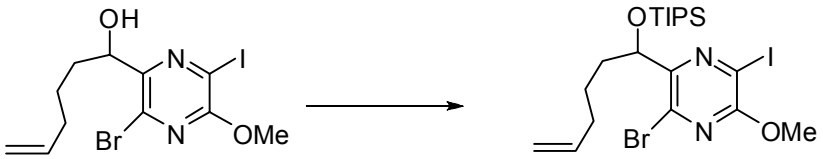
0.21 mmol). The solution was heated at 90 °C for 4.5 h, then cooled to rt. The solution was then diluted with ether (10 mL), poured onto saturated $NaHCO_3$ (20 mL) and extracted (x3) with ether (20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1:20 to 1 : 4 gradient elution) gave ester **324** (13.8 mg, 37%), as well as 10.5 mg recovered **323**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 6.9 Hz, 3 H), 1.68-1.89 (m, 4 H), 2.61-2.85 (m, 4 H), 4.02 (s, 2 H), 4.26 (t, *J* = 6.9 Hz, 2 H), 5.02 (s, 2 H), 6.11 (br s, 1 H), 6.53 (d, *J* = 8.5 Hz, 1 H), 6.83 (d, *J* = 8.5 Hz, 1 H), 7.32-7.45 (m, 5 H).



Indole 326. To a solution of ester **324** (19.6 mg, 0.053 mmol) in MeOH (3 mL) was added NaOH (4 M in H_2O, 1.5 mL, 6.0 mmol). The solution was stirred at rt for 2.5 h, poured onto saturated KH_2PO_4 (30 mL) and extracted (5 x 20 mL) with EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated. The resultant crude acid was then dissolved in acetic anhydride (1.0 mL). Triethylamine (74 μL, 0.53 mmol) was added and the solution heated at 130 °C for 30 min. The solution was then cooled to rt, diluted with ether (30 mL) and saturated $NaHCO_3$ (30 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 2) gave indole **326** (6.5 mg, 35%) as a yellow film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98-2.06 (m, 4 H), 2.52 (s, 3 H), 2.84 (t, *J* = 5.6 Hz, 2 H), 3.04 (t, *J* = 6.1 Hz, 2 H), 5.16 (s, 2 H), 6.78 (d, *J* = 7.9 Hz, 1 H), 6.93 (d, *J* = 7.9 Hz, 1 H), 7.30-7.51 (m, 5 H).

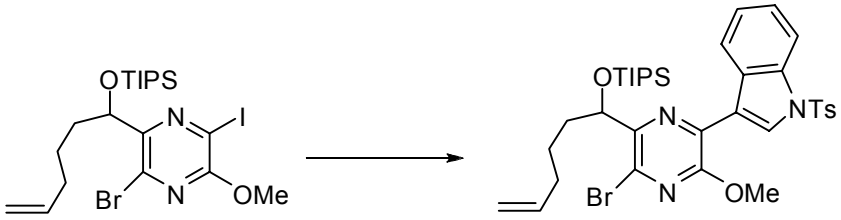


5-Bromo-2-iodo-3-methoxy-6-(1-hydroxyhex-5-en-1-yl)pyrazine (357). To a solution of diisopropylamine (8.86 mL, 63.3 mmol) in THF (300 mL) at -30 ^{o}C was added dropwise *n*-butyllithium (2.5 M in hexanes, 24.2 mL, 60.5 mmol). The solution was then stirred for 20 min at -30 ^{o}C and cooled to -78 ^{o}C. To this solution was added via cannula a -78 ^{o}C solution of pyrazine **228**[76] (8.67 g, 27.5 mmol) in THF (200 mL). The resultant dark red solution was stirred for 10 min. 5-hexenal (**353**)[137] (5.94 g, 60.5 mmol) in THF (25 mL) was added rapidly. The mixture was then stirred for 5 min at -78 ^{o}C, and then quenched with saturated $NaHCO_3$. The resultant slurry was then extracted with ether, the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave alcohol **357** (8.92 g, 78%) as a yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ 1.30-1.45 (m, 1 H), 1.46-1.63 (m, 1 H), 1.80 (q, *J* = 6.9 Hz, 2 H), 2.08 (q, *J* = 7.1 Hz, 2 H), 4.01 (s, 3 H), 4.85-5.02 (m, 3 H), 5.77 (ddt, *J* = 17.1, 10.3, 6.7 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 23.9, 32.4, 34.5, 54.5 69.2, 103.0, 113.2, 133.6, 137.4, 149.1, 156.8; IR (neat) 3439, 2943, 1640 cm^{-1}; HRMS (M+H^{+}) calcd for $C_{11}H_{15}N_2O_2BrI$ 412.9362, found 412.9377.



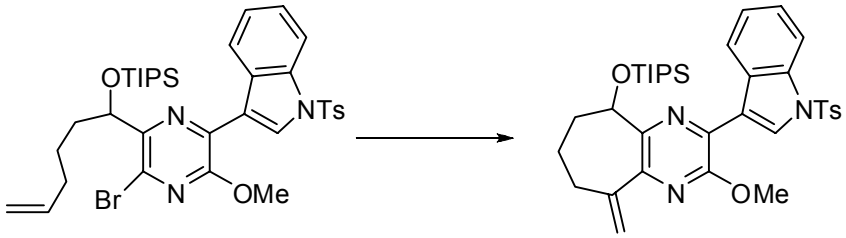
5-Bromo-2-iodo-3-methoxy-6-(1-triisopropylsilyloxyhex-5-en-1-yl)pyrazine (358). To a solution of alcohol **357** (7.29 g, 17.6 mmol) in DMF (35 mL) was added imidazole (3.00 g, 44.1 mmol) and chlorotriisopropylsilane (4.53 mL, 21.2 mmol). The solution was then heated at 40 ^{o}C and stirred for 16 h. The

reaction mixture was quenched with saturated $NaHCO_3$ (200 mL) and extracted with ether (3 x 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 30) gave TIPS alcohol **358** (8.62 g, 86%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.91-0.94 (m, 9 H), 0.97-1.03 (m, 12 H), 1.26-1.38 (m, 1 H), 1.42-1.58 (m, 1 H), 1.79-1.88 (m, 2 H), 2.05 (q, *J* = 7.1 Hz, 2 H), 4.01 (s, 3 H), 4.91 (ddt, *J* = 10.2, 2.0, 1.0 Hz, 1 H), 4.97 (ddt, *J* = 17.1, 2.0, 1.6 Hz, 1 H), 5.14 (t, *J* = 6.6 Hz, 1 H), 5.76 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 17.8, 17.9, 24.6, 33.5, 37.2, 55.8, 71.9, 104.1, 114.6, 133.9, 138.4, 150.6, 157.1; IR (neat) 2944, 2865, 1555, 1537 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{20}H_{35}N_2O_2BrISi$ 569.0696, found 569.0670.



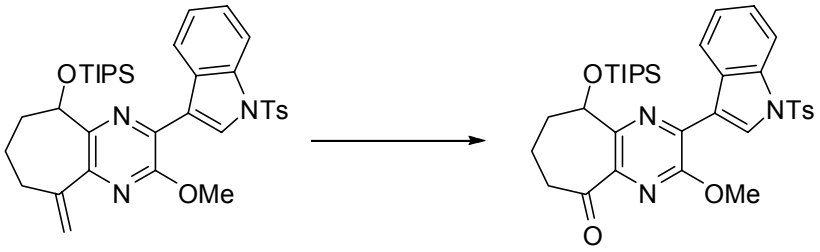
5-Bromo-2-(*N*-tosylindol-3-yl)-3-methoxy-6-(1-triisopropylsilyloxyhex-5-en-1-yl)pyrazine (360). CuCl (5.99 g, 16.7 mmol), LiCl (3.21 g, 75.7 mmol) and $Pd(PPh_3)_4$ (1.59 g, 1.51 mmol) were combined under N_2 in a round bottomed flask. This mixture was added in one portion to a solution of TIPS-alcohol **358** (8.62 g, 15.1 mmol) and stannane **359b** (8.71 g, 15.6 mmol) in dry, degassed DMSO (150 mL). The reaction mixture was stirred at rt for 30 min, and poured carefully onto saturated $NaHCO_3$ (300 mL). The resultant slurry was diluted with ether (300 mL) and filtered through Celite, rinsing thoroughly with ether. The organic phase of the resultant filtrate was separated, and the aqueous phase extracted with ether. The combined organic layers were then dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave bromide **360** (9.17 g, 85%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, *J* = 7.0 Hz, 9 H), 1.04 (d, *J* = 6.9 Hz, 9 H), 1.08-1.16 (m, 3 H), 1.27-1.39 (m, 1 H), 1.43-1.55 (m, 1 H), 1.92-2.01 (m, 2 H), 2.02-2.10 (m, 2 H), 2.34 (s, 3 H), 4.23 (s, 3 H), 4.89 (ddt, *J* = 10.2, 2.0, 1.0 Hz, 1 H), 4.96 (ddt, *J* = 17.1, 2.0, 1.6 Hz, 1 H), 5.40 (t, *J* = 7.1 Hz, 1 H), 5.75 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1 H), 7.25 (d, *J* = 7.4 Hz, 2 H), 7.33 (td, *J* = 8.1, 1.1 Hz, 1 H), 7.39 (td, *J* = 7.3, 1.3 Hz, 1 H), 7.87 (d, *J* = 7.4 Hz, 2 H), 8.02 (d, *J* = 7.3 Hz, 1 H), 8.57 (s, 1 H), 9.09 (d, *J* = 7.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 17.9, 18.0, 21.5, 24.2, 33.7, 37.9, 54.9, 71.7, 112.9, 114.5, 116.1, 123.9, 125.0, 125.2, 127.0, 128.8, 129.3, 130.0, 134.8, 135.1, 137.2, 138.6, 145.2, 147.6, 154.6; IR (neat) 2943, 2865, 1640, 1535 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{35}H_{47}N_3O_4SSiBr$ 712.2240, found 712.2249.

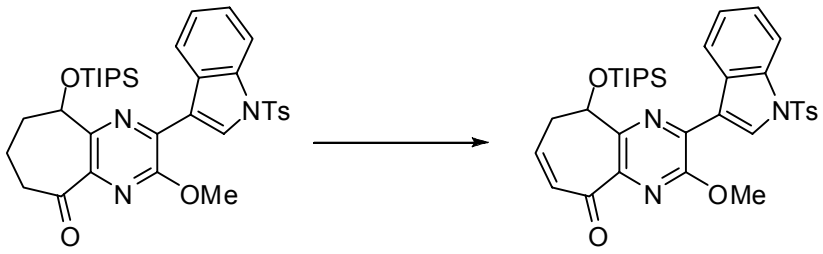


Olefin 361. To a solution of bromide **360** (1.70 g, 2.38 mmol) in DMF (36 mL) was added NaOAc (488 mg, 5.95 mmol) and $Pd(PPh_3)_4$ (251 mg, 0.238 mmol). The resultant mixture was thoroughly degassed and then heated at 150 ^{o}C for 2 h. The solution was then cooled to rt and poured onto saturated $NaHCO_3$ (150 mL). The mixture was then extracted with ether (3 x 100 mL), dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 5) gave olefin **361** (1.23 g, 82%) as a foamy oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 7.2 Hz, 9 H), 1.00 (d, *J* = 6.9 Hz, 9 H), 1.03-1.13 (m, 3 H), 1.72-1.82 (m, 1 H), 1.84-1.95 (m, 1 H), 2.20-2.31 (m, 2 H), 2.33 (s, 3 H), 2.38-2.46 (m, 1 H), 2.90-2.98 (m, 1 H), 4.19 (s, 3 H), 5.33-5.37 (m, 2 H), 5.71 (d, *J* = 2.1 Hz, 1 H), 7.23 (d, *J* = 8.2 Hz, 2 H), 7.30 (dd, *J* = 7.9, 7.2 Hz, 1 H), 7.36 (dd, *J* = 8.1, 7.2 Hz, 1 H), 7.83 (d, *J* = 8.2 Hz, 2 H), 8.02

(d, *J* = 8.1 Hz, 1 H), 8.54 (s, 1 H), 8.84 (d, *J* = 7.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 17.8, 18.0, 21.5, 23.6, 32.8, 35.0, 63.8, 75.6, 113.1, 116.7, 118.1, 123.5, 124.1, 124.9, 126.9, 128.6, 129.5, 129.9, 134.4, 134.9, 135.1, 145.1, 146.6, 147.2, 147.8, 154.8; IR (neat) 2942, 2865, 1445, 1173 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{35}H_{46}N_3O_4SSi$ 632.2978, found 632.2972.

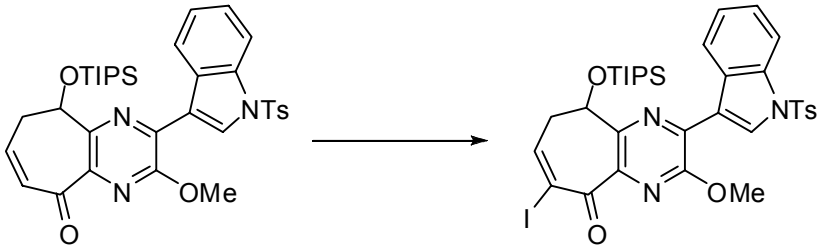


Ketone 362. To a solution of olefin **361** (1.60 g, 2.53 mmol) in THF (50 mL) and H_2O (25 mL) was added *N*-methylmorpholine-*N*-oxide (593 mg, 5.06 mmol) and OsO_4 (4 wt % in H_2O, 309 μL, 0.0506 mmol). The solution was stirred at rt for 3 h. $NaIO_4$ (2.71 g, 12.7 mmol) was subsequently added and the reaction mixture was stirred for a further 20 h at rt. The solution was then quenched with saturated $Na_2S_2O_3$, (200 mL), extracted with ether (3 x 100 mL), dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 5) gave ketone **362** (1.29 g, 80%) as a foamy oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, *J* = 7.1 Hz, 9 H), 0.97 (d, *J* = 7.0 Hz, 9 H), 0.99-1.10 (m, 3 H), 1.70-1.85 (m, 1 H), 2.15-2.32 (m, 3 H), 2.34 (s, 3 H), 2.75 (ddd, *J* = 17.4, 6.4, 2.3 Hz, 1 H), 3.24 (ddd, *J* = 17.6, 12.3, 2.5 Hz, 1 H), 4.26 (s, 3 H), 5.40 (t, *J* = 3.3 Hz, 1 H), 7.25 (d, *J* = 7.6 Hz, 2 H), 7.30 (td, *J* = 7.3, 1.2 Hz, 1 H), 7.39 (td, *J* = 7.3, 1.3 Hz, 1 H), 7.86 (d, *J* = 6.7 Hz, 2 H), 8.03 (d, *J* = 7.3 Hz, 1 H), 8.67 (s, 1 H), 8.84 (dd, *J* = 7.1, 1.1 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.0, 17.7, 17.8, 19.5, 21.5, 33.0, 40.6, 54.4, 75.0, 113.2, 115.9, 123.8, 123.9, 125.2, 127.0, 129.2, 130.0, 130.2, 134.8, 134.9, 138.8, 142.0, 145.3, 148.8, 156.2, 203.4; IR (neat) 2944, 2866, 1698, 1537 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{34}H_{44}N_3O_5SSi$ 634.2771, found 634.2767.

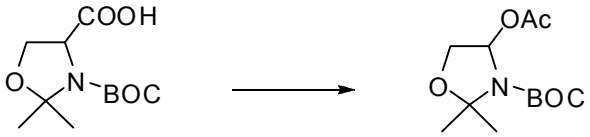


Enone 363. To a solution of ketone **362** (1.29 g, 2.03 mmol) in THF (12 mL) at -78 °C was added dropwise LiHMDS (1 M in THF, 2.44 mL, 2.44 mmol). The solution was then allowed to warm slowly over 30 min to -50 °C. The solution was then cooled to -78 °C, and chlorotrimethylsilane (310 μL, 2.44 mmol) was added dropwise, and the mixture was again allowed to warm to -50 °C over 30 min. Saturated $Na_2S_2O_3$ (30 mL) was added to quench the reaction. The resultant mixture warmed to rt, extracted with ether, dried (Na_2SO_4) and concentrated to give a crude oil that was immediately used in the next step without further purification.

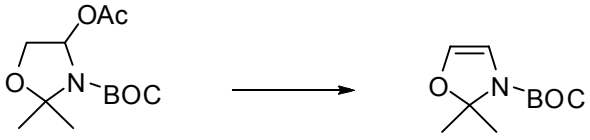
The crude oil generated above was dissolved in MeCN (14 mL). $Pd(OAc)_2$ (547 mg, 2.44 mmol) was added, and the mixture was allowed to stir at rt for 20 h. The reaction mixture was then diluted with ether (50 mL), washed (3 x 50 mL) with saturated NH_4Cl, dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 5) gave enone **363** (917 mg, 71% from **362**) as a foamy oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 7.1 Hz, 9 H), 0.96 (d, *J* = 6.9 Hz, 9 H), 0.98-1.08 (m, 3 H), 2.31 (s, 3 H), 2.85 (dm, *J* = 19.9 Hz, 1 H), 3.11 (dt, *J* = 19.9, 5.6 Hz, 1 H), 4.27 (s, 3 H), 5.38-5.42 (m, 1 H), 6.39-6.50 (m, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 7.34 (td, *J* = 7.4, 1.2 Hz, 1 H), 7.39 (td, *J* = 7.3, 1.2 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 2 H), 8.03 (d, *J* = 7.8 Hz, 1 H), 8.69 (s, 1 H), 8.82 (dd, *J* = 6.9, 1.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 17.7, 17.8, 21.5, 36.7, 54.4, 73.4, 113.1, 115.8, 123.7, 123.8, 125.2, 126.9, 129.0, 129.9, 130.3, 131.2, 134.7, 134.8, 139.0, 139.0, 142.4, 145.3, 148.3, 155.9, 191.2; IR (neat) 2944, 2866, 1664, 1537 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{34}H_{42}N_3O_5SSi$ 632.2614, found 632.2603.



Iodoenone 364. To a solution of enone **363** (1.62 g, 2.56 mmol) in CCl_4 (25 mL) was added pyridine (25 mL) and iodine (1.95 g, 7.69 mmol). The solution was then shielded from light and stirred at rt for 24 h. The solution was then diluted with ether (150 mL) and washed (x2) with saturated NH_4Cl (100 mL). The organic layer was then dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 5) gave iodoenone **364** (1.67 g, 86%) as an amorphous yellow solid, mp 204-206 ^oC (dec.). ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 7.1 Hz, 9 H), 0.95 (d, *J* = 6.9 Hz, 9 H), 0.98-1.08 (m, 3 H), 2.34 (s, 3 H), 2.86 (dt, *J* = 19.8, 2.2 Hz, 1 H), 3.11 (ddd, *J* = 19.8, 7.3, 5.1 Hz, 1 H), 4.25 (s, 3 H), 5.34-5.38 (m, 1 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.35 (t, *J* = 7.1 Hz, 1 H), 7.39 (td, *J* = 7.1 Hz, 1 H), 7.52 (dd, *J* = 7.3, 2.8 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 2 H), 8.02 (d, *J* = 8.1 Hz, 1 H), 8.67 (s, 1 H), 8.75 (d, *J* = 7.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 17.7, 17.8, 21.6, 40.5, 54.7, 72.6, 104.7, 113.2, 115.7, 123.7, 123.9, 125.3, 127.0, 129.0, 130.0, 130.5, 134.8, 134.8, 139.3, 139.4, 145.4, 147.7, 147.8, 155.9, 186.3; IR (neat) 2944, 2866, 1668, 1538 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{34}H_{41}N_3O_5SSiI$ 758.1581, found 758.1573.

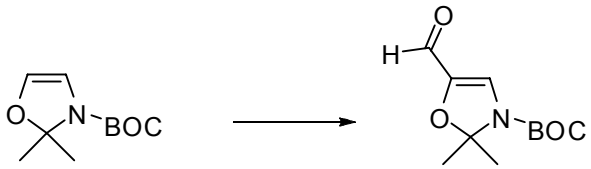


***N*-BOC-2,2-dimethyloxazolidin-4-ylacetate (366)**. To a solution of acid **365**[90] (9.58 g, 39.1 mmol) in benzene (156 mL) was added $Pb(OAc)_4$ (19.1 g, 43.0 mmol). The resultant slurry was refluxed for 12 h, cooled to rt and filtered through Celite. The filtrate was then poured onto saturated $NaHCO_3$ (300 mL) and the organic layer was separated. The aqueous layer was washed (3 x 150 mL) with ether, the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave acetate **366** (8.61 g, 85%) as a colorless oil that crystallized slowly on standing, mp 61-63 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9 H), 1.41 (s, 3 H), 1.97 (s, 3 H), 3.85 (d, *J* = 10.2 Hz, 1 H), 3.95 (dd, *J* = 10.2, 3.3 Hz), 6.30 (d, *J* = 3.3 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.8, 23.6, 26.1, 28.0, 69.2, 81.3, 94.9, 150.6, 170.2; IR (neat) 2891, 1739, 1714 cm^{-1}; HRMS ($M+Na^+$) calcd for $C_{12}H_{21}NO_5Na$ 282.1317, found 282.1313.

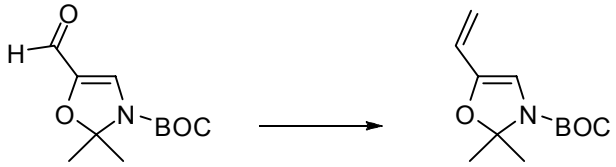


***N*-BOC-2,2-dimethyl-2,3-dihydrooxazole (367)**. To a solution of acetate **366** (5.12 g, 19.7 mmol) in toluene (59 mL) was added NH_4Br (5.12 g, 52.7 mmol). The flask was then equipped with a Dean-Stark trap, half filled with 3 M NaOH solution, and was refluxed for 12 h. The resultant slurry was poured onto saturated $NaHCO_3$ (150 mL) and the organic layer separated. The aqueous layer was washed (3 x 150 mL) with ether, the combined organic layers were

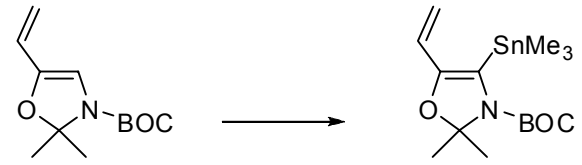
dried (Na_2SO_4) and concentrated. Purification of the resultant residue by deactivated silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave oxazoline **367** (1.97 g, 50%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers*) δ 1.05, 1.07* (s, 9 H), 1.17, 1.21* (s, 6 H), 4.41, 4.51* (br s, 1 H), 4.48, 4.63* (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers*) δ 24.1, 25.0*, 28.2, 80.1, 80.6*, 97.7, 98.2*, 108.6, 128.6, 129.3*, 149.1, 149.6*; IR (neat) 2933, 2872, 1695 cm^{-1}; HRMS (M-*t*-Bu + H$^+$) calcd for $C_6H_9NO_3$ 143.0582, found 143.0586.



***N*-BOC-2,2-dimethyl-5-formyl-2,3-dihydrooxazole (368)**. To a solution of DMF (3.15 mL, 40.7 mmol) in dichloromethane (24 mL) at 0 °C was added dropwise oxalyl chloride (815 µL, 9.35 mmol). The solution was stirred at 0 °C for 30 min. To the resultant white suspension was then added oxazoline **367** (1.62 g, 8.13 mmol) in dichloromethane (9 mL). The solution was allowed to warm to rt and stirred for 1 h. Saturated aqueous $NaHCO_3$ (50 mL) was then added and the mixture was stirred vigorously for 1 h. The organic layer was separated, and the aqueous layer extracted (3 x 30 mL) with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by deactivated silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave aldehyde **368** as a white solid (1.19 g, 64%), mp 92-93 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$, rotamers*) δ 1.41 (s, 9 H), 1.63 (s, 6 H), 6.96, 7.08* (br s, 1 H), 9.06 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers*) δ 24.7, 25.4*, 27.8, 82.9, 102.1, 126.3, 140.3, 148.2, 148.6*, 176.9; IR (neat) 2982, 1719, 1664, 1620 cm^{-1}; HRMS (M+Na$^+$) calcd for $C_{11}H_{17}NO_4Na$ 250.1055, found 250.1053.

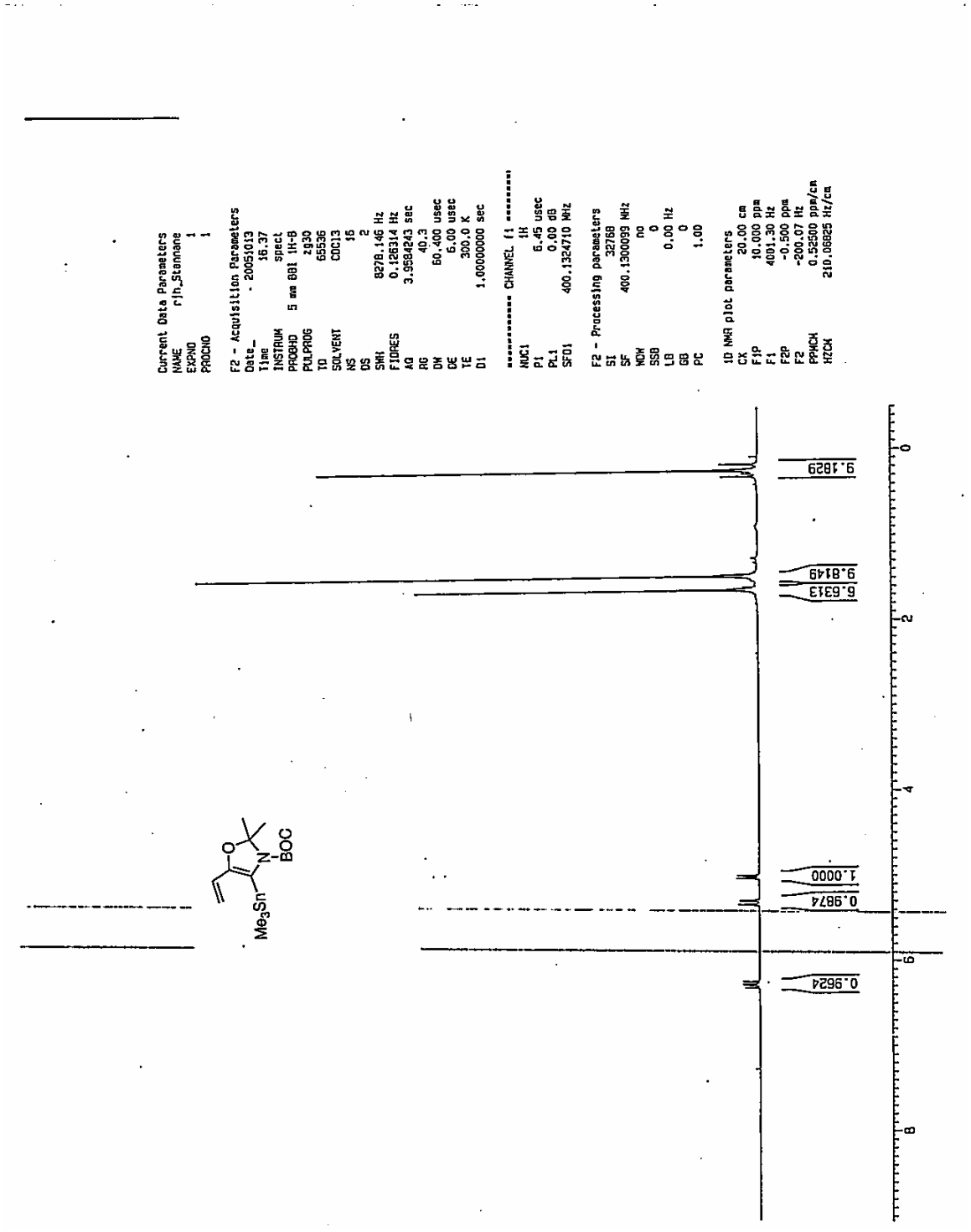


***N*-BOC-2,2-dimethyl-5-vinyl-2,3-dihydrooxazole (369)**. To a suspension of methyltriphenylphosphonium bromide (2.04 g, 5.73 mmol) in THF (18 mL) at –30 ^{o}C was added dropwise *n*-butyllithium (2.5 M in hexanes, 2.29 mL, 5.73 mmol). The solution was allowed to warm to 0^{o} C over 20 min. Aldehyde **368** (1.19 g, 5.21 mmol) in THF (5 mL) was added dropwise. The resultant mixture was stirred at 0 ^{o}C for 30 min and then poured onto saturated $NaHCO_3$. The solution was then extracted (3 x 40 mL) with ether. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by deactivated Florisil chromatography (EtOAc-hexanes 1:20), gave diene **369** (812 mg, 69%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers*) δ 1.45, 1.47* (s, 9 H), 1.64, 1.69* (s, 6 H), 5.03 (br d, *J* = 11.2 Hz, 1 H), 5.27, 5.30* (br d, *J* = 17.2 Hz, 1 H), 6.08, 6.11* (dd, *J* = 17.2, 11.2 Hz, 2 H), 6.07, 6.20* (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 24.7, 25.6*, 28.3, 80.6, 81.0*, 98.4, 98.8*, 107.4, 107.6*, 111.9, 112.1*, 123.2, 123.3*, 139.1, 139.6*, 149.0, 149.5*; IR (neat) 2981, 1705, 1657 cm^{-1} ; HRMS (M+H^{+}) calcd for $C_{12}H_{19}NO_3Sn$ 225.1365, found 225.1346.



***N*-BOC-2,2-dimethyl-5-vinyl-4-trimethylstannyl-2,3-dihydrooxazole (370)**. To a solution of diene **369** (398 mg, 1.77 mmol) in THF (7.9 mL) at -30 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 1.06 mL, 2.64 mmol). The solution was stirred at -30 °C for 30 min. To the resultant solution was added

dropwise trimethyltin chloride (1.0 M in THF, 2.64 mL, 2.64 mmol). The solution was allowed to warm to 0 ^{o}C over 20 min. The mixture was quenched with saturated $NaHCO_3$ (20 mL) and extracted (3 x 30 mL) with ether. The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by deactivated Florisil chromatography (EtOAc-hexanes 1:50), gave stannane **370** (570 mg, 83%) as a white solid, mp 75-77 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24 (t, *J* = 28.5 Hz, 9 H), 1.47 (s, 9 H), 1.64 (s, 6 H), 5.01 (dd, *J* = 11.0, 1.8 Hz, 1 H), 5.31 (dd, *J* = 17.1, 1.8 Hz, 1 H), 6.27 (dd, *J* = 17.1, 11.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.1 (t, *J* = 199 Hz, Sn*Me*$_3$), 25.8, 28.2, 80.8, 96.9, 111.7, 118.8, 125.2, 147.0, 151.2; IR (neat) 2979, 1679 cm^{-1}; HRMS (M+H^{+}) calc for $C_{15}H_{28}NO_3Sn$ 386.1087, found 386.1104.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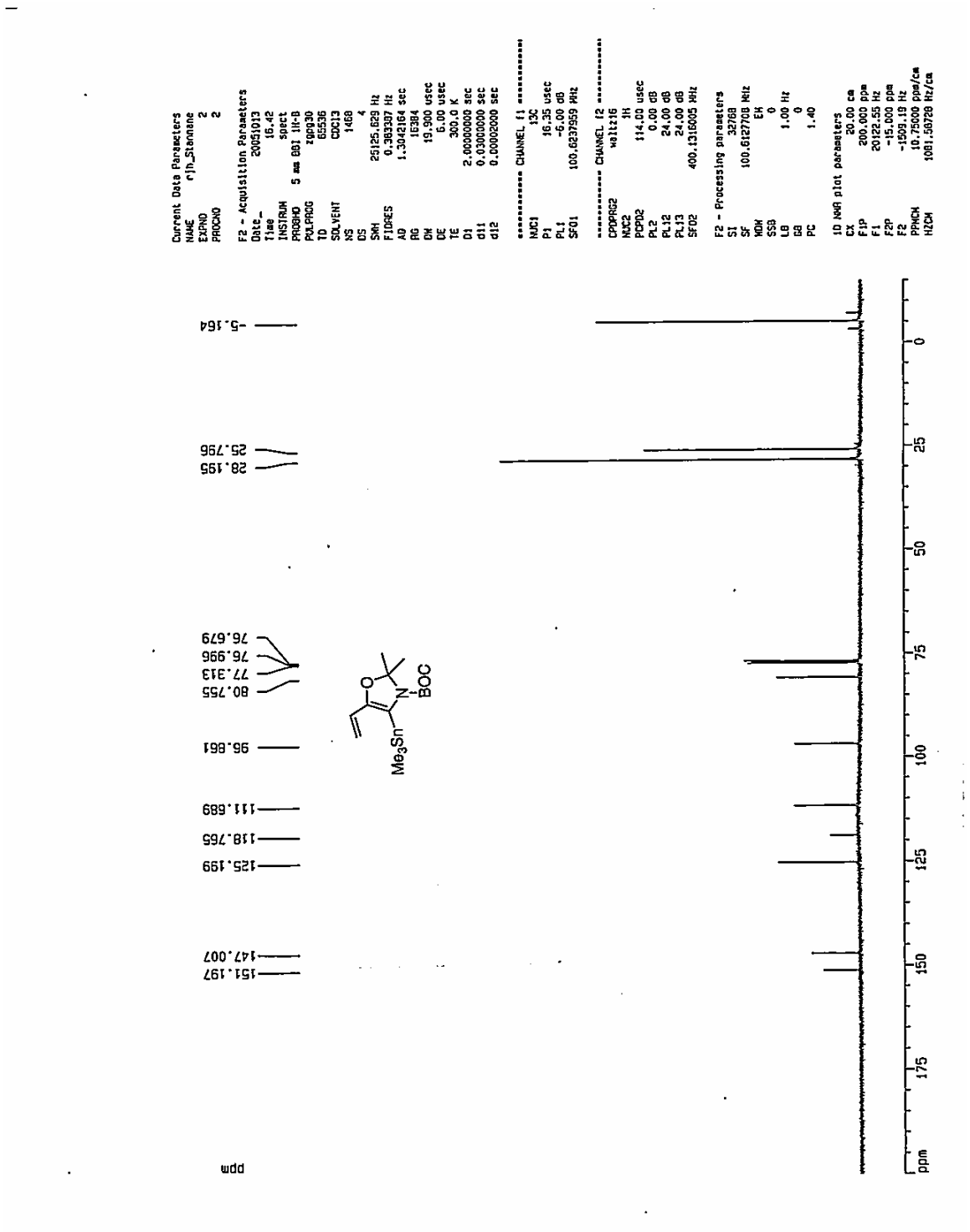
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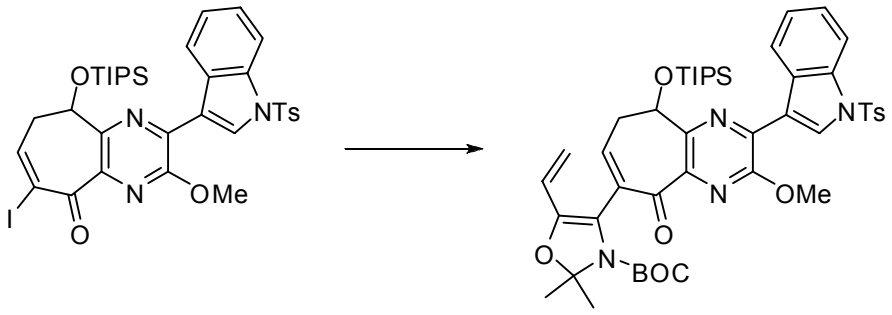
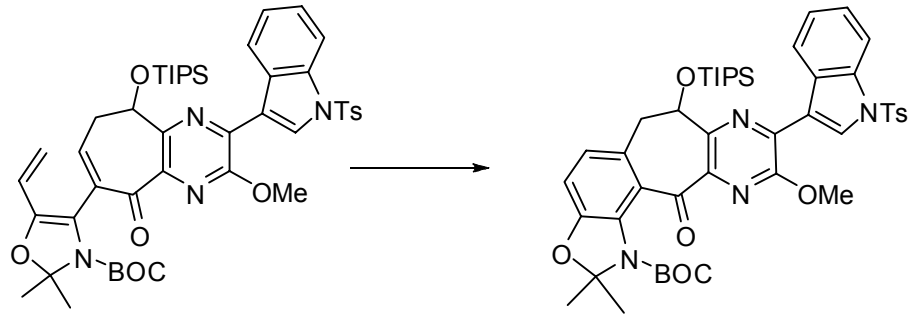
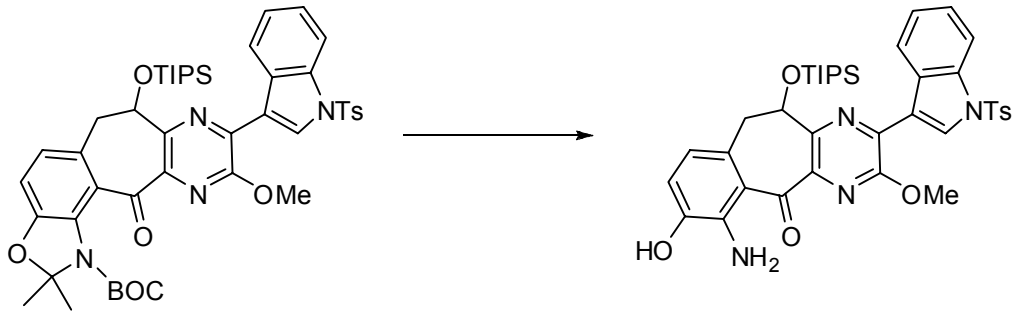


Trienecarbamate 371. CuCl (363 mg, 13.7 mmol), LiCl (194 mg, 4.59 mmol) and $Pd(PPh_3)_4$ (96.9 mg, 0.092 mmol) were combined under N_2 in a round bottomed flask. This mixture was added in one portion to a suspension of iodoenone **364** (694 mg, 0.918 mmol) and stannane **370** (536 mg, 1.38 mmol) in dry, degassed DMSO (18.4 mL). The reaction mixture was stirred at rt for 30 min, and poured carefully onto saturated NH_4Cl (60 mL). The resultant slurry was diluted with ether (100 mL) and filtered through Celite, rinsing thoroughly with ether. The organic phase of the resultant filtrate was separated, and the aqueous phase was extracted with ether (3 x 100 mL). The combined organic layers were then dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave trienecarbamate **371** (558 mg, 71%) as a foamy yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.8 Hz, 9 H), 0.96 (d, *J* = 6.4 Hz, 9 H), 0.96-1.10 (m, 3 H), 1.49 (br s, 9 H), 1.75 (br s, 3 H), 1.84 (br s, 3 H), 2.32 (s, 3 H), 3.00 (br d, *J* = 19.8, 1 H), 3.18 (br dt, *J* = 19.8, 5.6 Hz, 1 H), 4.22 (s, 3 H), 5.08 (br d, *J* = 12.4 Hz, 1 H), 5.37 (br s, 1 H), 5.41 (dd, *J* = 17.3, 1.5 Hz, 1 H), 6.38 (dd, *J* = 17.3, 11.2 Hz, 1 H), 6.41 (br s, 1 H), 7.24 (d, *J* = 8.3 Hz, 2 H), 7.34 (t, *J* = 6.8 Hz, 1 H), 7.39 (t, *J* = 6.8 Hz, 1 H), 7.84 (d, *J* = 8.1 Hz, 2 H), 8.03 (d, *J* = 7.9 Hz, 1 H), 8.65 (br s, 1 H), 8.77 (br d, *J* = 6.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 11.9, 17.6, 17.8, 21.4, 24.5, 26.3, 28.2, 37.1, 54.2, 73.1, 80.6, 99.0, 112.1, 113.1, 116.1, 120.3, 123.1, 123.7, 123.8, 125.1, 126.9, 129.2, 129.9, 130.1, 131.6, 134.4, 134.8, 134.8, 138.3, 140.4, 144.0, 145.2, 147.4, 149.4, 156.1, 189.6; IR

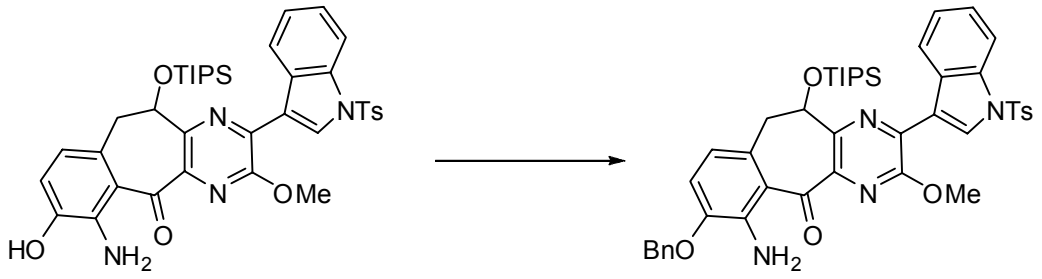
(neat) 2944, 2867, 1698, 1380 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{46}H_{59}N_4O_8SSi$ 855.3823, found 855.3846.



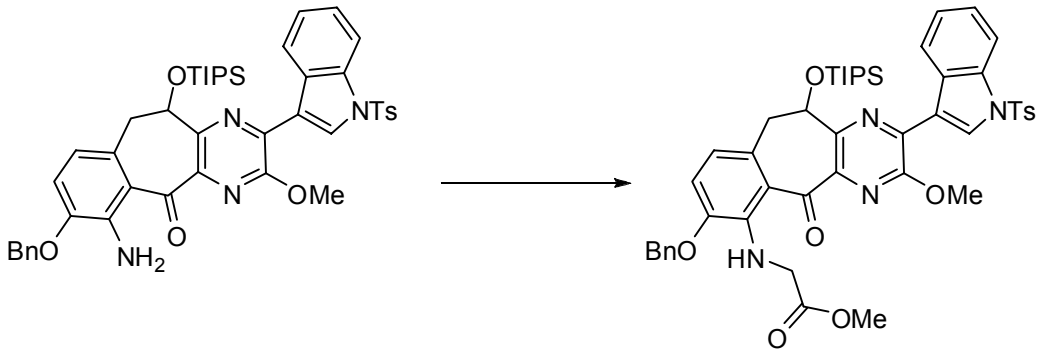
BOC-aniline 372. A solution of trienecarbamate **371** (41.0 mg, 0.0479 mmol) in d^8-toluene (1.0 mL) was refluxed for 2 h. The solution was cooled to rt and DDQ (22.5 mg, 0.0991 mmol) was added in one portion. The resultant red solution was stirred for 2 h, and then poured onto saturated $NaHCO_3$ (10 mL). The mixture was extracted (x2) with ether (10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave BOC-aniline **372** (29.5 mg, 72%) as a foamy yellow liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, *J* = 7.4 Hz, 9 H), 0.93 (d, *J* = 7.4 Hz, 9 H), 1.09 (septet, *J* = 7.4 Hz, 3 H), 1.51 (s, 9 H), 1.79, (s, 6 H), 2.34 (s, 3 H), 3.34 (dd, *J* = 15.0, 7.2 Hz, 1 H), 3.40 (dd, *J* = 15.0, 2.0 Hz, 1 H), 4.30 (s, 3 H), 5.44 (dd, *J* = 7.2, 2.0 Hz, 1 H), 6.71 (d, *J* = 7.9 Hz, 1 H), 6.79 (d, *J* = 7.9 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.30 (t, *J* = 7.4 Hz, 1 H), 7.36 (t, *J* = 7.7 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 2 H), 8.00 (d, *J* = 8.3 Hz, 1 H), 8.64 (s, 1 H), 8.74 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 17.9, 18.0, 21.6, 26.5, 26.7, 28.1, 41.0, 54.3, 73.5, 82.0, 102.3, 109.7, 113.1, 116.4, 123.5, 124.1, 125.0, 125.2, 126.0, 126.9, 127.0, 128.8, 129.2, 130.0, 130.3, 134.8, 134.9, 139.5, 140.9, 145.3, 148.4, 148.8, 150.3, 155.4, 191.1; IR (neat) 2944, 2865, 1716, 1681, 1549 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{46}H_{57}N_4O_8SSi$ 853.3666, found 853.3624.



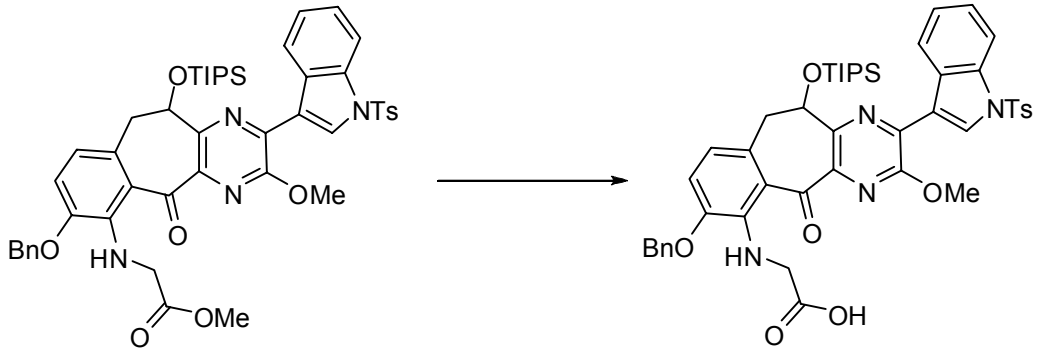
Aminophenol 379. To a solution of BOC-aniline **372** (22.5 mg, 0.0264 mmol) in dichloromethane (520 μL) was added 2,6-lutidine (15 μL, 0.13 mmol) and TMSOTf (19.0 μL, 0.106 mmol). The solution was refluxed for 1.5 h, then cooled to rt. THF (2 mL) was then added, followed by 1M aq. HCl (2 mL), and the resultant red solution was stirred for a further 2 h. The mixture was poured onto saturated $NaHCO_3$ (20 mL) and extracted (x3) with ethyl acetate (20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 3) gave phenol **379** (13.0 mg, 69%) as a red oil. ^{1}H NMR (300 MHz, d_6-acetone) δ 0.87 (d, *J* = 6.8 Hz, 9 H), 0.92 (d, *J* = 7.2 Hz, 9 H), 0.97-1.10 (m, 3 H), 2.31 (s, 3 H), 3.46 (d, *J* = 17.1 Hz, 1 H), 3.57 (dd, *J* = 17.1, 6.4 Hz, 1 H), 4.24 (s, 3 H), 5.46 (dd, *J* = 6.4, 1.5 Hz, 1 H), 6.36 (d, *J* = 7.8 Hz, 1 H), 6.84 (d, *J* = 7.8 Hz, 1 H), 6.91 (br s, 2 H), 7.32 – 7.39 (m, 3 H), 7.44 (td, *J* = 8.3, 1.4 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 2 H), 8.61 (br s, 1 H), 8.74 (s, 1 H), 8.93 (dm, *J* = 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, d_6-acetone) δ 12.9, 18.2, 18.2, 21.4, 43.9, 54.7, 73.4, 114.0, 117.0, 117.1, 118.7, 119.0, 124.7, 125.0, 126.2, 127.9, 129.2, 130.1, 130.8, 131.1, 135.6, 135.7, 138.8, 142.8, 143.8, 144.8, 146.8, 148.6, 157.0, 192.6; IR (neat) 3494, 3356, 3290 (br), 2943, 2865, 1614, 1538 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{38}H_{45}N_4O_6SSi$ 713.2829, found 713.2814.



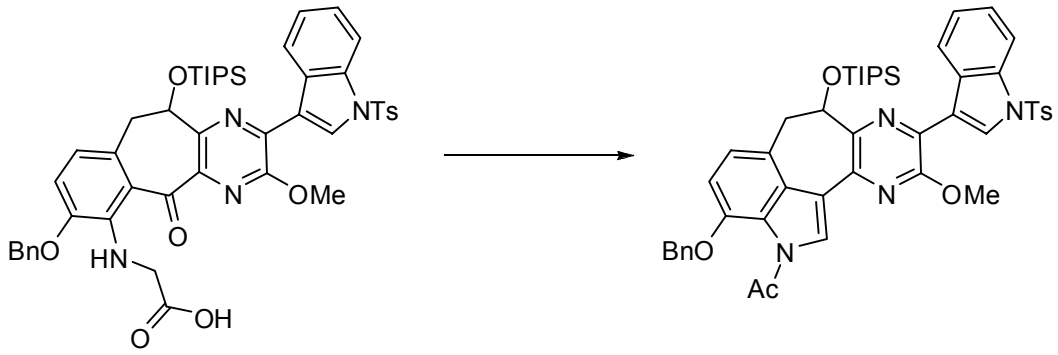
Benzyl ether 380. To a solution of phenol **379** (27.3 mg, 0.0383 mmol) in DMF (0.76 mL) at 0 ^{o}C was added NaH (60 wt % in mineral oil, 1.8 mg, 0.046 mmol). The resultant mixture was stirred at 0 ^{o}C for 20 min. Benzyl bromide (6.8 μL, 0.058 mmol) was added, and the solution allowed to stir for 30 min. Saturated NH_4Cl (10 mL) was added, and the resultant mixture extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave benzyl ether **380** (30 mg, 97%) as an orange solid, mp 210-212. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, *J* = 7.1 Hz, 9 H), 0.92 (d, *J* = 7.1 Hz, 9 H), 0.97-1.08 (m, 3 H), 2.34 (s, 3 H), 3.43 (d, *J* = 16.6 Hz, 1 H), 3.53 (dd, *J* = 16.6, 6.5 Hz, 1 H), 4.27 (s, 3 H), 5.09 (d, *J* = 11.8 Hz, 1 H), 5.14 (d, *J* = 11.8 Hz, 1 H), 5.40 (d, *J* = 4.9 Hz, 1 H), 6.40 (d, *J* = 8.0 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 7.00 (br s, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.30-7.47 (m, 7 H), 7.85 (d, *J* = 8.4 Hz, 2 H), 8.03 (d, *J* = 8.3 Hz, 1 H), 8.67 (s, 1 H), 8.85 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 17.8, 17.8, 21.6, 43.6, 54.4, 70.7, 72.2, 113.2, 114.0, 116.2, 117.8, 118.2, 123.8, 124.0, 125.2, 127.0, 127.5, 128.1, 128.6, 129.3, 129.8, 130.0, 130.1, 134.9, 134.9, 136.7, 138.6, 143.1, 143.2, 144.9, 145.3, 148.2, 156.2, 192.1; IR (neat) 3493, 3346, 2942, 2864, 1605, 1537 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{45}H_{51}N_4O_6SSi$ 803.3299, found 803.3298.



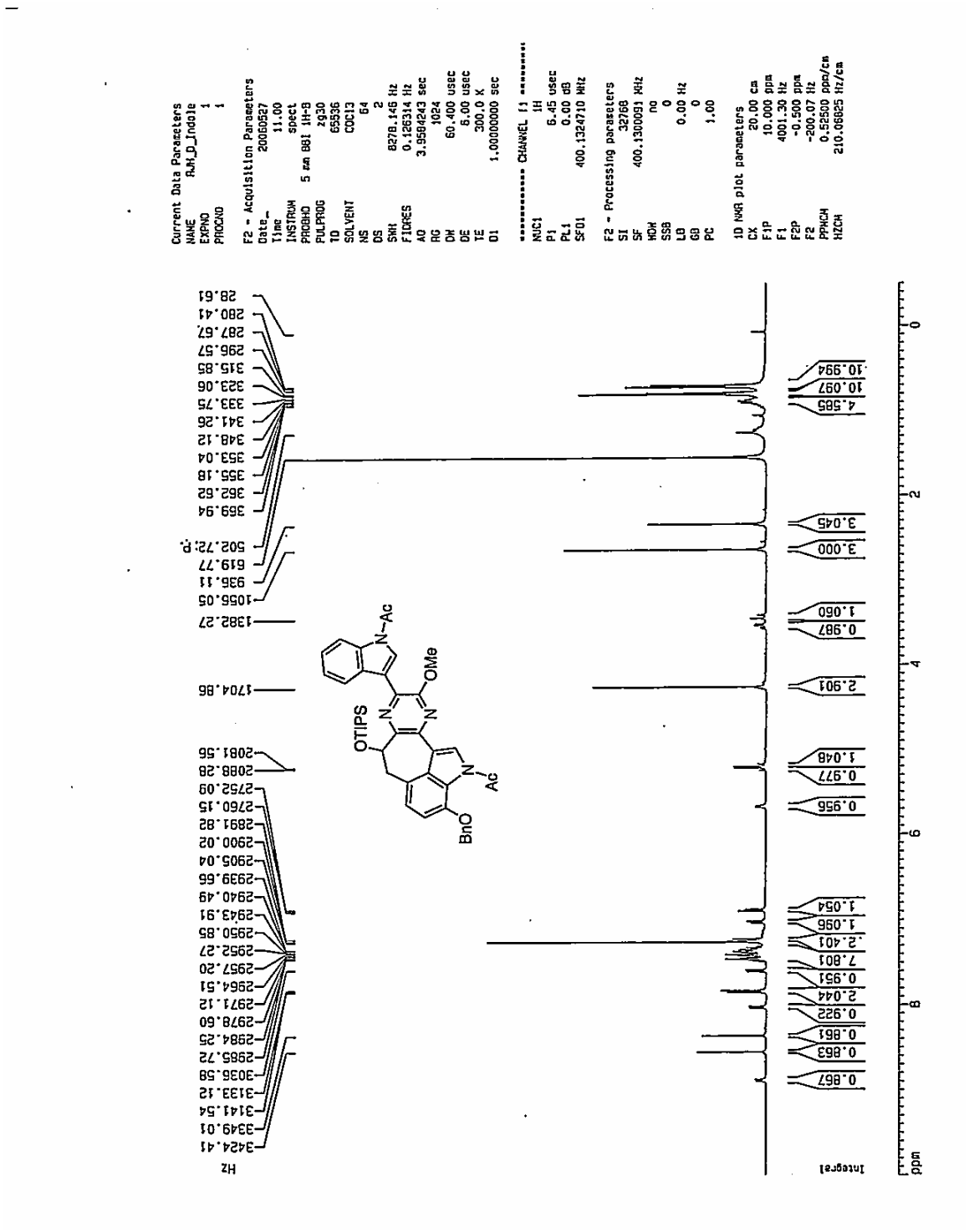
Ester 381. To a solution of benzyl ether **380** (57 mg, 0.071 mmol) in DMF (1.42 mL) was added K_2CO_3 (49 mg, 0.35 mmol) and methyl iodoacetate (141 μL, 1.42 mmol). The solution was heated at 100 ^oC for 2 h, and then cooled to rt. The solution was diluted with ether (10 mL), poured onto saturated $NaHCO_3$ (20 mL) and extracted (x3) with ethyl acetate (20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave ester **381** (33 mg, 53%), as well as 10 mg of recovered amine **380**. ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J* = 7.4 Hz, 9 H), 0.93 (d, *J* = 7.4 Hz, 9 H), 1.09 (septet, *J* = 7.4 Hz, 3 H), 2.34 (s, 3 H), 3.38-3.49 (m, 2 H), 3.59 (s, 2 H), 4.02 (s, 2 H), 4.27 (s, 3 H), 5.07 (d, *J* = 11.9 Hz, 1 H), 5.11 (d, *J* = 11.9 Hz, 1 H), 5.39 (dd, *J* = 6.2, 3.0 Hz, 1 H), 6.61 (d, *J* = 8.2 Hz, 1 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.28-7.47 (m, 7 H), 7.83 (d, *J* = 8.4 Hz, 2 H), 8.01 (d, *J* = 8.3 Hz, 1 H), 8.63 (s, 1 H), 8.74 (d, *J* = 7.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 17.9, 18.0, 21.6, 41.8, 48.7, 51.8, 54.4, 71.1, 72.6, 113.2, 115.4, 116.2, 122.2, 123.7, 123.9, 125.2, 125.7, 127.0, 127.4, 128.0, 128.4, 128.6, 129.1, 130.0, 130.2, 134.8, 134.9, 136.7, 139.4, 142.6, 145.3, 147.6, 147.7, 155.8, 172.0, 194.5; IR (neat) 3385, 2945, 2865, 1747, 1548 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{48}H_{55}N_4O_8SSi$ 875.3510, found 875.3541.



Acid 382. To a solution of ester **381** (31.5 mg, 0.0360 mmol) in THF (6 mL) and water (3 mL) at 0 ^{o}C was added LiOH (143 mg, 6.00 mmol). The solution was stirred at 0 ^{o}C for 2 h, poured onto saturated KH_2PO_4 (30 mL) and extracted (5 x 20 mL) with EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 2) gave acid **382** (21.4 mg, 69%) as a red film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J* = 7.4 Hz, 9 H), 0.92 (d, *J* = 7.4 Hz, 9 H), 1.01-1.11 (m, 3 H), 2.34 (s, 3 H), 3.42 (d, *J* = 15.9 Hz, 1 H), 3.48 (dd, *J* = 15.9, 6.7 Hz, 1 H), 3.92 (d, *J* = 18.4 Hz, 1 H), 3.99 (d, *J* = 18.4 Hz, 1 H), 4.24 (s, 3 H), 5.09 (d, *J* = 12.3 Hz, 1 H), 5.12 (d, *J* = 12.3 Hz, 1 H), 5.39 (dd, *J* = 6.5, 2.1 Hz, 1 H), 6.70 (d, *J* = 8.2 Hz, 1 H), 6.91 (d, *J* = 8.2 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.28-7.42 (m, 7 H), 7.83 (d, *J* = 8.4 Hz, 2 H), 8.01 (d, *J* = 8.2 Hz, 1 H), 8.63 (s, 1 H), 8.74 (d, *J* = 7.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 17.8, 17.9, 21.6, 42.0, 49.5, 54.5, 70.9, 72.5, 113.2, 115.9, 116.1, 123.0, 123.7, 123.9, 125.3, 126.5, 127.0, 127.5, 128.1, 128.6, 128.7, 129.1, 130.0, 130.3, 134.8, 134.9, 136.2, 139.2, 139.6, 142.3, 145.4, 147.8, 148.2, 155.9, 174.8, 194.5; IR (neat) 3377, 2943, 2865, 1720, 1547 cm^{-1}; HRMS (M+H^{+}) calcd for $C_{47}H_{53}N_4O_8SSi$ 861.3353, found 861.3372.



Indole 383. To a solution of acid **382** (19.0 mg, 0.0221 mmol) in Ac_2O (2 mL) was added triethylamine (300 μL). The solution was heated at 110 ^oC for 20 min. The resultant mixture was poured onto saturated $NaHCO_3$ (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave indole **383** (10.9 mg, 59%) as a yellow film. ^1H NMR (400 MHz, $CDCl_3$) δ 0.71 (d, *J* = 7.3 Hz, 9 H), 0.80 (d, *J* = 7.2 Hz, 9 H), 0.83-0.93 (m, 3 H), 2.34 (s, 3 H), 2.64 (s, 3 H), 3.44 (d, *J* = 15.6 Hz, 1 H), 3.55 (dd, *J* = 15.6, 7.0 Hz, 1 H), 4.26 (s, 3 H), 5.19 (d, *J* = 11.4 Hz, 1 H), 5.23 (d, *J* = 11.4 Hz, 1 H), 5.67 (d, *J* = 6.6 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 7.03 (d, *J* = 7.9 Hz, 1 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 7.31-7.48 (m, 7 H), 7.58-7.62 (m, 1 H), 7.84 (d, *J* = 8.4 Hz, 2 H), 8.03 (d, *J* = 8.5 Hz, 1 H), 8.37 (s, 1 H), 8.56 (s, 1 H), 8.89 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 17.6, 17.8, 21.6, 26.4, 54.0, 71.5, 74.2, 108.4, 113.2, 116.8, 120.0, 123.6, 124.1, 124.5, 125.0, 125.8, 127.0, 127.8, 128.2, 128.5, 128.6, 129.9, 133.8, 134.9, 135.1, 136.4, 145.1, 145.5, 146.1, 155.3, 170.8; IR (neat) 2942, 2864, 1713, 1597 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{48}H_{53}N_4O_6SSi$ 841.3455, found 841.3484.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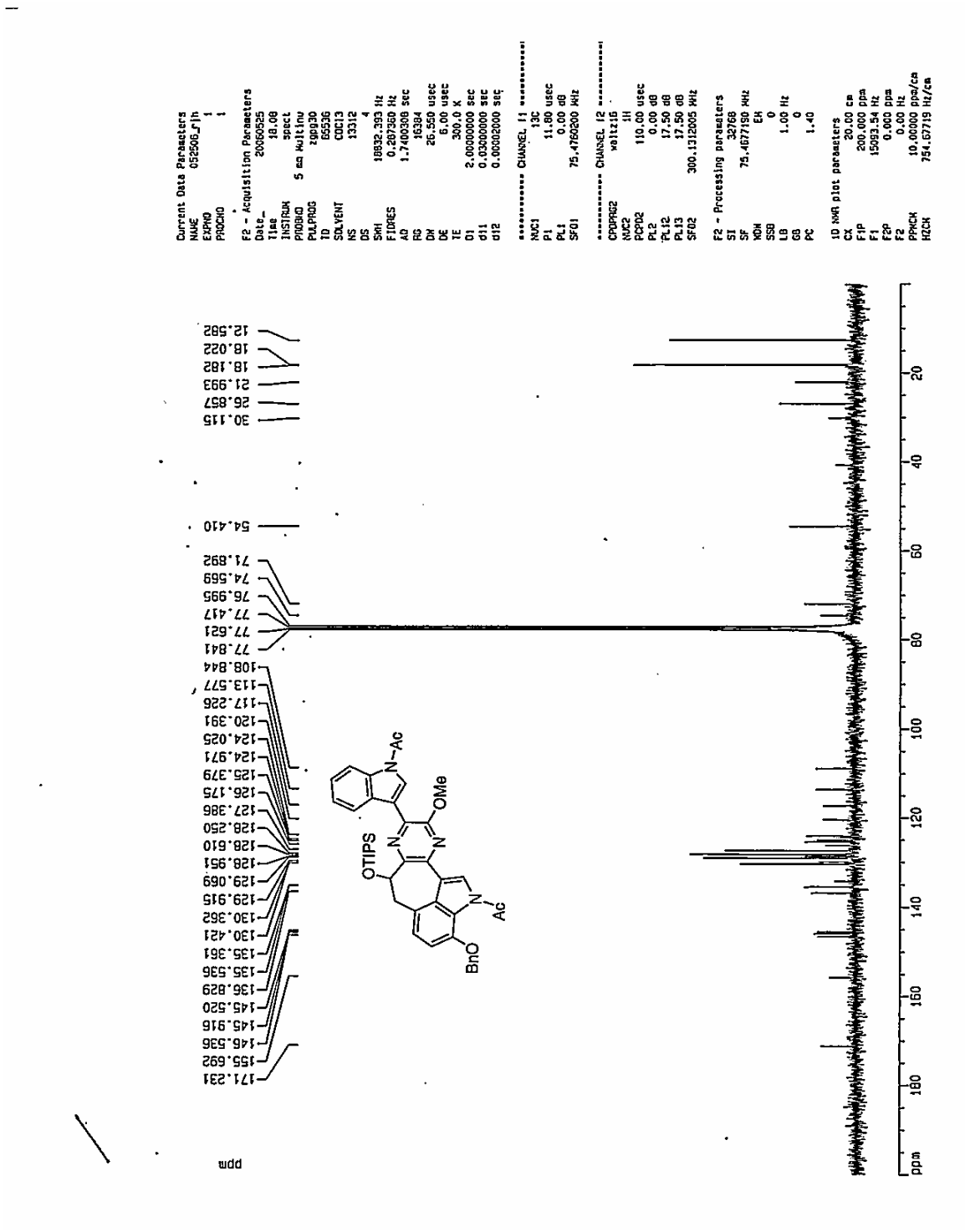
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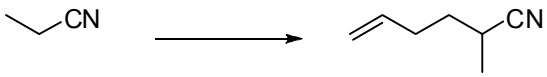
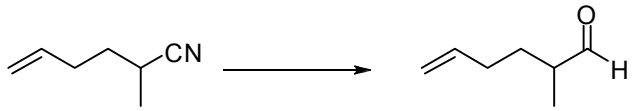
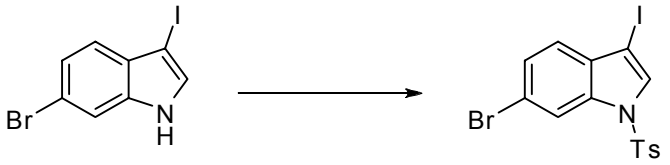


2-Methylhex-5-enitrile (390). To a solution of diisopropylamine (36.4 mL, 260 mmol) in THF (600 mL) at -78 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 100 mL, 250 mmol). The solution was then stirred for 30 min. To this solution was added via cannula a solution of propionitrile (19.3 mL, 270 mmol) in THF (60 mL). The solution was stirred at -78 °C for 1 h. A solution of 4-bromo-1-butene (22.8 mL, 225 mmol) in THF (60 mL) was then added rapidly. The mixture was stirred for 1 h at -78 °C, and then quenched with saturated $NaHCO_3$ (600 mL). The resultant solution was extracted (3 x 400 mL) with ether, the combined organic layers were washed with brine (1 x 200 mL), dried (Na_2SO_4) and carefully concentrated. Distillation of the resultant liquid at reduced pressure gave nitrile **390** (19.4 g, 60%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, *J* = 7.1 Hz, 3 H), 1.53-1.82 (m, 2 H), 2.18-2.35 (m, 2 H), 2.60-2.71 (m, 1 H), 5.06 (d, *J* = 10.3 Hz, 1 H), 5.12 (d, *J* = 17.0 Hz, 1 H), 5.79 (ddt, *J* = 17.0, 10.3, 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 24.8, 31.0, 33.1, 116.3, 122.8, 136.3. IR (neat) 3079, 2981, 2941, 2239, 1642, 1456 cm^{-1}.

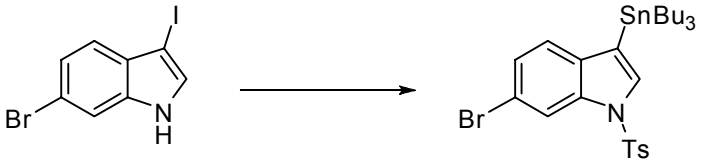


2-Methylhex-5-enal (386). To a solution of nitrile **390** (14.5 g, 133 mmol) in ether (440 mL) at -78 °C was added DIBAL-H (1.0 M in hexanes, 200 mL, 200 mmol). The resultant solution was stirred at -78 °C for 30 min, then quenched with 1M aqueous HCl (500 mL). The resultant slurry was allowed to warm to rt and stirred for 1 h. The organic layer was separated, dried (Na_2SO_4) and concentrated. Distillation of the resultant liquid under reduced pressure gave aldehyde **386** (9.17 g, 61%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12

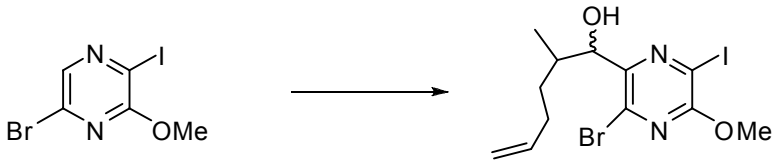
(d, *J* = 7.0 Hz, 3 H), 1.41-1.53 (m, 1 H), 2.04-2.20 (m, 2 H), 2.40 (sextet d, *J* = 7.0, 1.7, Hz, 1 H), 5.02 (dm, *J* = 10.4 Hz, 1 H), 5.06 (dm, *J* = 17.0 Hz, 1 H), 5.80 (ddt, *J* = 17.0, 10.4, 6.7 Hz), 9.65 (d, *J* = 1.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 29.5, 30.9, 45.5, 115.3, 137.6, 204.8. GCMS (M^+) calcd for $C_7H_{12}O$ 112, found 112.



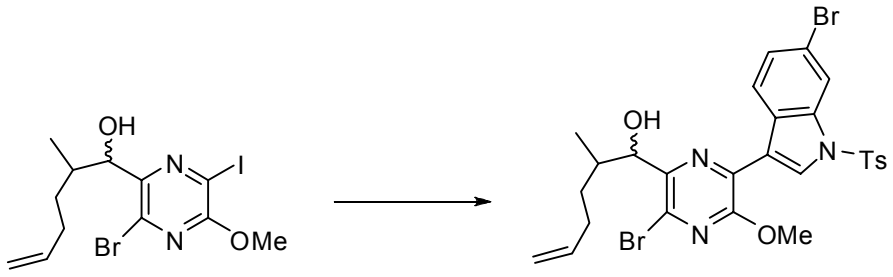
6-Bromo-3-iodo-1-tosylindole (391). To a solution of 6-bromo-3-iodoindole[134] (7.22 g, 22.4 mmol) in toluene (90 mL) at 0 ^{o}C was added sequentially water (56 mL), tetrabutylammonium bromide (722 mg, 2.24 mmol), toluenesulfonyl chloride (5.34 g, 28.0 mmol) and NaOH (56 g, 1.40 mol). The resultant biphasic mixture was stirred at 0 ^{o}C for 30 min, then warmed to rt and stirred for 3 h. The aqueous layer was removed, and the organic layer washed (3 x 200 mL) with water and with brine (1 x 200 mL). The organic layer was then dried (Na_2SO_4) and concentrated. Purification of the resultant residue by recrystallization from ether/hexanes (1:1) gave tosylindole **391** (9.69 g, 91%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 1 H), 7.25 (d, *J* = 8.4 Hz), 7.31 (d, *J* = 8.6 Hz, 2 H; 7.45 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.68 (s, 1 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 8.18 (d, *J* = 1.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 66.2, 116.4, 119.6, 123.2, 126.9, 127.3, 130.2,130.3, 132.1, 135.6, 135.8, 145.7; IR (neat) 3132, 1596, 1563, 1417; HRMS (M + NH_4^+) calcd for $C_{15}H_{15}N_2O_2SBrI$ 492.9082 found 492.9071.



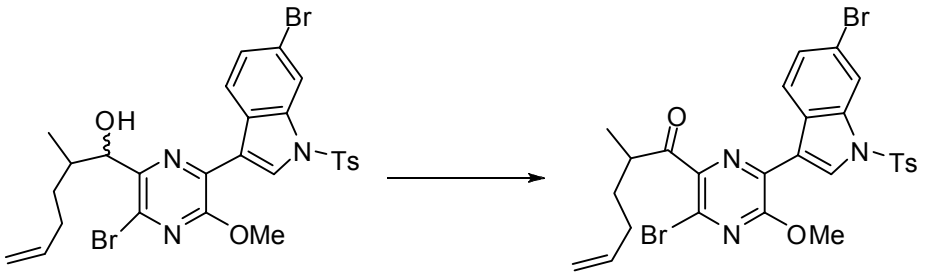
6-Bromo-1-tosyl-3-tributylstannylindole (392). To a solution of tosylindole **391** (18.7 g, 51.0 mmol) in DMF (102 mL) was added was added sequentially hexabutylditin (22.0 mL, 56.1 mmol), triphenylphosphine (803 mg, 3.06 mmol) and $Pd(OAc)_2$ (344 mg, 1.53 mmol). The resultant biphasic mixture was heated at 90 ^oC for 60 min. The heterogeneous solution was cooled to rt, and poured onto saturated $NaHCO_3$ (500 mL). The resultant mixture was extracted with ether (3 x 500 mL). The combined organic layers were washed (3 x 500 mL) with water and then with brine (1 x 200 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification of the resultant residue by deactivated silica gel chromatography (ethyl acetate-hexane, 1 : 20) gave stannane **392** (18.72 g, 64%) as a colorless viscous oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.3, 9 H), 1.05-1.23 (m, 6 H), 1.33 (sextet, *J* = 7.3, 6 H), 1.42-1.62 (m, 6 H), 2.34 (s, 3 H), 7.23 (d, *J* = 8.6, 2 H), 7.32 (s, 1 H), 7.32-7.34 (m, 1 H), 7.77 (d, *J* = 8.4 Hz, 2 H), 8.15-8.19 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.8 (t, *J* = 175 Hz, Sn-**CH_2**-), 13.6, 21.5, 27.1 (t, *J* = 30 Hz, Sn-CH_2-**CH_2**-), 29.0 (t, *J* = 10 Hz, Sn-CH_2-CH_2-**CH_2**-), 116.5, 116.7, 117.7, 123.8, 126.2, 126.7, 129.9, 132.0, 135.2, 135.8, 136.5, 144.9. ; IR (neat) 2955, 2925, 1596 cm^{-1}; HRMS ($M+Na^+$) calcd for $C_{27}H_{38}NO_2NaSBrSn$ 662.0726, found 662.0707.



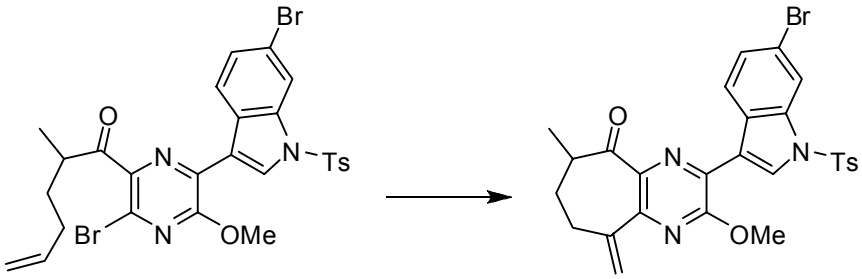
5-Bromo-2-iodo-3-methoxy-6-(1-hydroxy-2-methylhex-5-en-1-yl)pyrazine (393). To a solution of diisopropylamine (7.82 mL, 56.1 mmol) in THF (300 mL) at -78 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 21.4 mL, 53.6 mmol). The solution was then stirred for 30 min. To this solution was added via cannula a -78 °C solution of pyrazine **228** (8.03 g, 25.5 mmol) in THF (200 mL). The resultant dark red solution was stirred for 10 min. 2-Methyl-5-hexen-1-al (**386**) (4.00 g, 35.7 mmol) in THF (20 mL) was added rapidly. The mixture was stirred for 5 min at -78 °C, and quenched with saturated $NaHCO_3$. The resultant slurry was extracted with ether, the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 10) gave alcohols **393** (7.70 g, 71%) as a yellow oil. ^{1}H NMR (400 MHz, CD_3OD) (major isomer underlined, minor isomer italicized, where identifiable) δ *0.74* (d, *J* = 7.8 Hz, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H) 1.17-1.31 (m, 2 H), 1.82-2.23 (m, 3 H), 4.01 (s, 3 H), *4.68* (d, *J* = 7.0 Hz, 1 H), 4.73 (d, *J* = 7.0 Hz, 1 H), 4.81-5.04 (m, 2 H), 5.72 (ddt, *J* = 17.0, 10.4, 6.6 Hz) *5.82* (ddt, *J* = 17.0, 10.3, 6.5 Hz); ^{13}C NMR (75 MHz, CD_3OD) 15.0, *15.9*, 32.2, *33.6*, 38.6, *39.2*, 75.1, *75.7*, 104.8, *105.0*, *114.8*, 115.0 136.1, *136.4*, 139.7, *140.0*, 150.9, *151.0* 158.8, *158.9*; IR (neat) 3504 (br), 2930, 1460, 1374, 1330 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{12}H_{17}N_2O_2BrI$ 426.9518, found 426.9513.



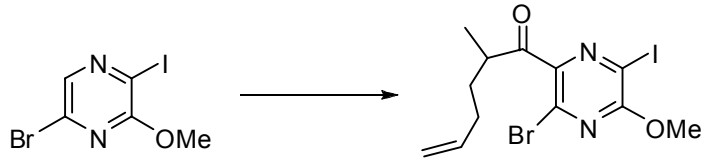
Bromide 394. To a solution of alcohols **393** (8.60 g, 20.1 mmol) and stannane **392** (14.13 g, 22.11 mmol) in degassed DMSO (201 mL) was added CuCl (7.96 g, 80.4 mmol), LiCl (4.26 g, 100.5 mmol) and $Pd(PPh_3)_4$ (2.32 g, 2.01 mmol) The reaction mixture was stirred at rt for 30 min, and poured carefully onto saturated $NaHCO_3$ (300 mL). The resultant slurry was diluted with ether (300 mL) and filtered through Celite, rinsing thoroughly with ether. The organic phase of the resultant filtrate was separated, and the aqueous phase extracted (x2) with ether. The combined organic layers were then washed (x2) with H_2O, once with brine, dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (dichloromethane : hexanes , 1 : 1) gave indolylpyrazine **394** (11.2 g, 86%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.8 Hz, 3 H), *1.02* (d, *J* = 6.8 Hz, 3 H), 1.35-1.54 (m, 1 H), 1.64-1.76 (m, 1 H), 1.92-2.30 (m, 2 H), 2.39 (s, 3 H), *3.00* (br d, *J* = 7.9 Hz, 1 H), 3.27 (br d, *J* = 7.6 Hz, 1 H), 4.23 (s, 3 H), 4.81-5.10 (m, 3 H), *5.77* (ddt, *J* = 16.5, 10.2, 6.9 Hz), 5.86 (ddt, *J* = 17.0, 10.3, 6.6 Hz), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.45-7.50 (m, 1 H), 7.85 (d, *J* = 8.4 Hz, 2 H), 8.22 (s, 1 H), 8.32 (d, *J* = 8.6 Hz, 1 H), *8.35* (d, *J* = 8.6 Hz, 1 H), 8.50 (d, *J* = 0.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, *16.3*, 21.6, *29.8*, *31.1*, 31.3, 33.1, 37.4, *38.5*, 55.3, 73.3, *75.1*, *114.5*, 114.6, 115.4, *115.4*, 116.5, 119.1, 124.0, *124.1*, 127.0, *127.5*, 127.6, 127.7, *127.7*, 129.5, 130.2, 130.8, *131.3*, 134.6, *135.4*, 135.5, *135.8*, 138.7, 145.8, 146.4, *146.6*, *155.1*, 155.1; IR (neat) 3509, 2932, 1537, 1372 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{27}H_{28}N_3O_4SBr_2$ 648.0167, found 648.0185.



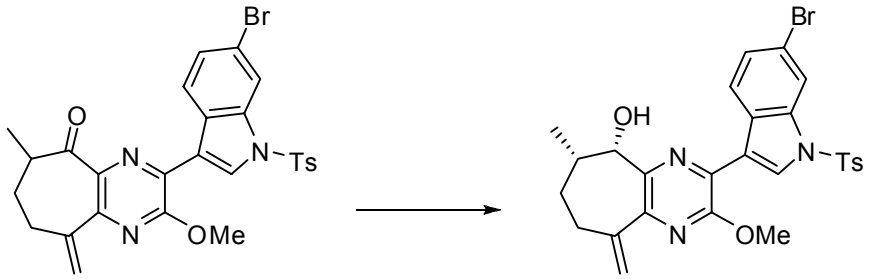
Ketone 395. To a solution of oxalyl chloride (3.01 mL, 34.6 mmol) in dichloromethane (130 mL) at -78 ^{o}C was added dropwise a solution of DMSO (3.07 mL, 43.2 mmol) in dichloromethane (20 mL). The resultant solution was stirred at -78 ^{o}C for 30 min. A solution of alcohols **394** (11.2 g, 17.3 mmol) in dichloromethane (20 mL) was added dropwise, and the mixture was then stirred at -78 ^{o}C for 25 min. Triethylamine (12.0 mL, 86.4 mmol) was added and the mixture was allowed to warm to rt over 1 h. The reaction mixture was then quenched with saturated $NaHCO_3$ (250 mL) and extracted (x3) with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (dichloromethane-hexane, 1 : 1) gave ketone **395** (11.0 g, 98%) as a white powder, mp 181-183 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, *J* = 7.0 Hz, 3 H), 1.51-1.62 (m, 1 H), 1.90-2.01 (m, 1 H), 2.10-2.19 (m, 2 H), 2.36 (s, 3 H), 3.83 (sextet, *J* = 6.9 Hz, 1 H), 4.28 (s, 3 H), 4.93 (d, *J* = 10.2 Hz, 1 H), 4.98 (d, *J* = 17.1 Hz), 5.77 (ddt, *J* = 17.1, 10.2, 6.9 Hz), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.44 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.83 (d, *J* = 8.3 Hz, 2 H), 8.18 (d, *J* = 1.7 Hz, 1 H), 8.42 (d, *J* = 8.6 Hz, 1 H), 8.52 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 21.6, 31.3, 31.6, 41.5, 55.7, 114.9, 115.1, 116.3, 119.2, 124.2, 126.9, 127.4, 127.5, 129.9, 130.2, 130.9, 134.5, 135.1, 135.3, 137.9, 140.2, 145.8, 155.9, 202.9; IR (neat) 2930, 1701, 1531, 1379, 1166 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{27}H_{26}N_3O_4SBr_2$ 646.0011, found 645.9992.



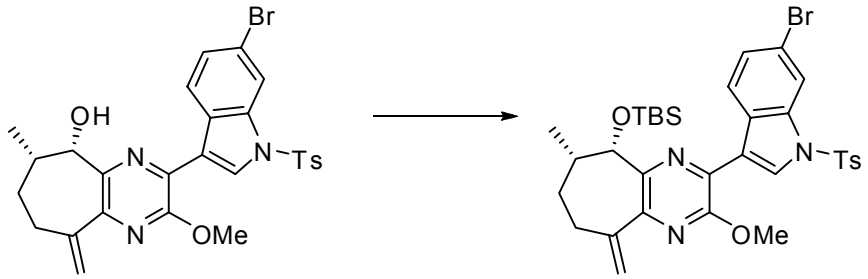
Olefin 396. To a solution of bromopyrazine **395** (13.7 g, 21.2 mmol) in degassed DMSO (424 mL) was added $Mg(OAc)_2.4H_2O$ (27.3 g, 127 mmol), $AsPh_3$ (1.30 g, 4.24 mmol), diisopropylethylamine (7.39 mL, 42.4 mmol) and $Pd(OAc)_2$ (476 mg, 2.12 mmol). The resultant mixture was heated at 85 ^oC and stirred for 2.5 h. The solution was then cooled to rt and poured onto saturated $NaHCO_3$ (500 mL). The mixture was extracted with ether (3 x 500 mL), washed with H_2O (3 x 500 mL) and brine (1 x 200 mL), dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (dichloromethane) gave olefin **396** (8.40 g, 70%) as a white powder. ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.5 Hz, 3 H), 1.67-1.79 (m, 1 H), 2.08–2.18 (m, 1 H), 2.32 (s, 3 H), 2.33-2.40 (m, 1 H), 2.80 (ddd, *J* = 13.9, 6.9, 1.9 Hz, 1 H), 3.01-3.11 (m, 1 H), 4.26 (s, 3 H), 5.51 (d, *J* = 1.7 Hz, 1 H), 6.25 (d, *J* = 1.7 Hz, 1 H), 7.23 (d, *J* = 8.3 Hz, 2 H), 7.47 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.77 (d, *J* = 8.3 Hz, 2 H), 8.16 (d, *J* = 1.7 Hz, 1 H), 8.48 (s, 1 H), 8.83 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 21.5, 33.7, 34.2, 44.4, 54.4, 116.0, 166.3, 119.1, 120.3, 125.6, 126.8, 127.8, 118.2, 129.4, 130.0, 134.6, 135.4, 136.7, 140.2, 144.1, 145.5, 149.0, 155.1, 202.7; IR (neat) 2933, 2865, 1697, 1597, 1168 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{27}H_{25}N_3O_4SBr$ 568.0729, found 568.0690.



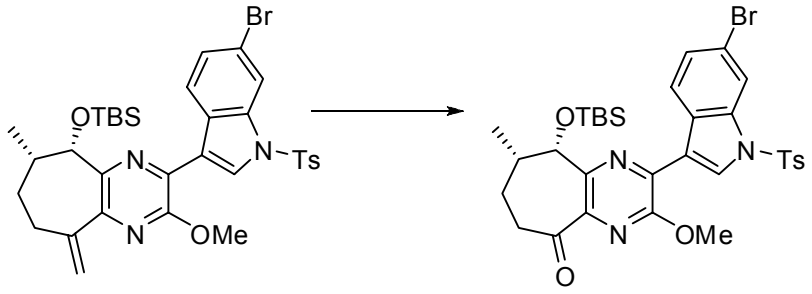
1-(3-Bromo-6-iodo-5-methoxypyrazin-2-yl)-2-methylhex-5-en-1-one (**404).** To a solution of diisopropylamine (4.78 mL, 34.3 mmol) in THF (110 mL) at -78 ^{o}C was added dropwise *n*-butyllithium (2.5 M in hexanes, 13.1 mL, 32.8 mmol). The solution was then stirred for 30 min. To this solution was added via cannula a -78 ^{o}C solution of pyrazine **228** (4.91 g, 15.6 mmol) in THF (50 mL). The resultant dark red solution was stirred for 10 min. Weinreb amide **403** (4.00 g, 23.4 mmol) in THF (50 mL) was added rapidly. The mixture was then stirred for 40 min at -78 ^{o}C, and then quenched with saturated $NaHCO_3$. The resultant slurry was then extracted with ether (2 x 300 mL), the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave iodoketone **404** (5.47 g, 82%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.9 Hz, 3 H), 1.50 (dq, *J* = 14.0, 7.1 Hz, 1 H), 1.86 (dq, *J* = 14.0, 6.9 Hz, 1 H), 2.10 (q, *J* = 7.2 Hz, 2 H), 3.76 (sextet, *J* = 6.8 Hz, 1 H), 4.13 (s, 3 H), 4.97 (dm, *J* = 10.3 Hz, 1 H), 5.01 (dq, *J* = 17.0, 1.6 Hz), 5.80 (ddt, *J* = 17.0, 10.3, 6.8 Hz, 1 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 31.3, 32.1, 14.0, 56.5, 102.0, 115.0, 134.6, 138.1, 142.0, 158.6, 201.8. IR (neat) 2973, 2932, 1703, 1524 cm^{-1}; HRMS (M+H^{+}) calcd for $C_{12}H_{15}N_2O_2BrI$ 424.9362, found 424.9373.



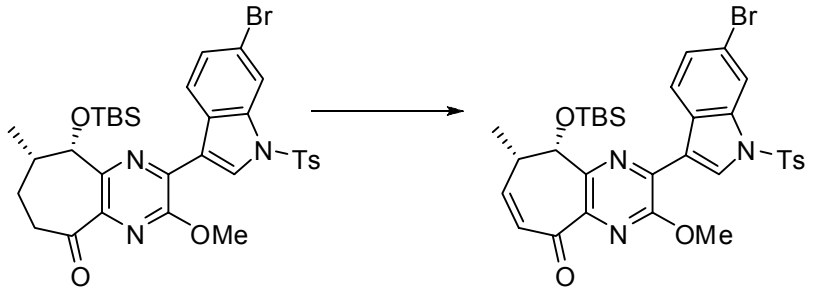
Alcohol 405. To a solution of ketone **396** (2.00 g, 3.53 mmol) in THF (140 mL) at -78 ^{o}C was added $LiAlH_4$ (1.0 M in THF, 5.30 mL, 5.30 mmol). The solution was then stirred at -78 ^{o}C for 40 min and poured onto saturated NH_4Cl (200 mL). The mixture was extracted with EtOAc (3 x 100 mL), dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (dichloromethane) gave alcohol **405** (1.65 g, 83%) as a viscous oil ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.9 Hz, 3 H), 1.64-1.77 (m, 1 H), 2.02–2.13 (m, 1 H), 2.35 (s, 3 H), 2.40-2.47 (m, 1 H), 2.55-2.63 (m, 2 H), 3.01-3.11 (m, 1 H), 4.21 (s, 3 H), 4.48 (d, *J* = 3.8 Hz, OH), 5.00 (d, *J* = 3.6 Hz, 1 H), 5.40 (s, 1 H), 5.78 (s, 1 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 7.43 (d, *J* = 8.6 Hz, 1 H), 7.83 (d, *J* = 8.2 Hz, 2 H), 8.22 (s, 1 H), 8.32 (d, *J* = 8.6 Hz, 1 H), 8.47 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 21.5, 30.7, 32.6, 35.5, 54.0, 74.1, 116.1, 116.3, 118.8, 119.2, 124.0, 126.8, 127.3, 127.9, 129.0, 130.1, 134.0, 134.6, 135.4, 142.5, 145.5, 145.7, 146.6, 155.3; IR (neat) 3436, 2930, 1597, 1545, 1377 cm^{-1}; HRMS (M+H^{+}) calcd for $C_{27}H_{25}N_3O_4SBr$ 568.0906, found 568.0931.



TBS Alcohol 407. To a solution of alcohol **405** (1.43 g, 2.52 mmol) in dichloromethane (25 mL) at 0 ^{o}C was added pyridine (408 μL, 5.04 mmol) and TBSOTf (868 μL, 3.78 mmol). The mixture was stirred at this temperature for 30 min, quenched with saturated $NaHCO_3$ (100 mL), and diluted with ether (100 mL). The organic layer was separated, and the aqueous layer extracted (2 x 50 mL) with ether. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (EtOAc-Hexanes 9:1) gave TBS alcohol **407** (1.64 g, 95%) as a viscous, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.32 (s, 3 H), 0.16 (s, 3 H), 0.85 (s, 9 H) 1.18 (d, *J* = 6.5 Hz, 3 H), 1.70-1.78 (m, 1 H), 1.92-2.11 (m, 2 H), 2.37 (s, 3 H), 2.42-2.51 (m, 1 H), 2.90 (ddd, *J* = 13.4, 8.4, 4.2 Hz, 1 H), 4.23 (s, 3 H), 5.37 (s, 1 H), 5.77 (s, 1 H), 7.29 (d, *J* = 8.1 Hz, 2 H), 7.50 (d, *J* = 8.6 Hz, 1 H), 7.87 (d, *J* = 8.1 Hz, 2 H), 8.25 (s, 1 H), 8.56 (s, 1 H), 8.83 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, -4.3, 18.2, 21.0, 25.7, 32.0, 34.4, 36.4, 53.8, 80.7, 116.1, 116.4, 118.0, 118.7, 125.4, 126.9, 126.9, 128.3, 128.8, 130.1, 134.2, 134.8, 135.6, 145.4, 146.1, 147.1, 147.4, 154.7; IR (neat) 2929, 1598, 1544, 1380 cm^{-1}; HRMS (M+H^{+}) calcd for $C_{33}H_{41}N_3O_4SSiBr$ 682.1770, found 682.1790.

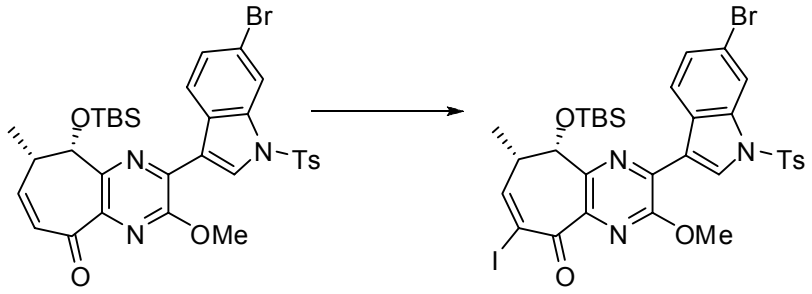


Ketone 408. To a solution of olefin **407** (7.91 g, 11.6 mmol) in THF (232 mL) and H_2O (116 mL) was added *N*-methylmorpholine-*N*-oxide (50 wt % in H_2O, 4.76 mL, 23.2 mmol) and OsO_4 (4 wt % in H_2O, 1.42 mL, 0.232 mmol). The solution was stirred at rt for 3 h. $NaIO_4$ (12.4 g, 58.0 mmol) was subsequently added and the reaction mixture was stirred for a further 40 h at rt. The solution was then quenched with saturated $Na_2S_2O_3$, (300 mL), extracted with ether (3 x 100 mL), dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 5) gave ketone **408** (6.11 g, 77%) as a white solid, mp 206-208 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.37 (s, 3 H), 0.07 (s, 3 H), 0.79 (s, 9 H), 1.22 (d, *J* = 6.9 Hz, 3 H), 1.90 (q, *J* = 6.6 Hz, 1 H), 2.28 (qd, *J* = 6.6, 2.4 Hz, 1 H), 2.36 (s, 3 H), 2.63-2.72 (m, 1 H), 3.16-3.27 (m, 1 H), 4.25 (s, 3 H), 4.98 (d, *J* = 2.6 Hz, 1 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.47 (dd, *J* = 8.6, 1.5 Hz, 1 H), 7.85 (d, *J* = 8.3 Hz, 2 H), 8.20 (d, *J* = 1.5 Hz, 1 H), 8.61 (s, 1 H), 8.71 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.5, -4.6, 18.0, 18.9, 21.6, 25.6, 27.3, 35.4, 39.9, 54.5, 79.1, 115.7, 116.2, 119.0, 125.1, 127.0, 127.3, 128.0, 130.2, 130.4, 134.6, 135.5, 138.2, 142.5, 145.7, 149.2, 156.0, 203.1; IR (neat) 2954, 2856, 1699, 1598, 1536, 1461, 1380 cm^{-1}; HRMS (M+H^{+}) calcd for $C_{32}H_{39}N_3O_5SSiBr$ 684.1563, found 684.1561.

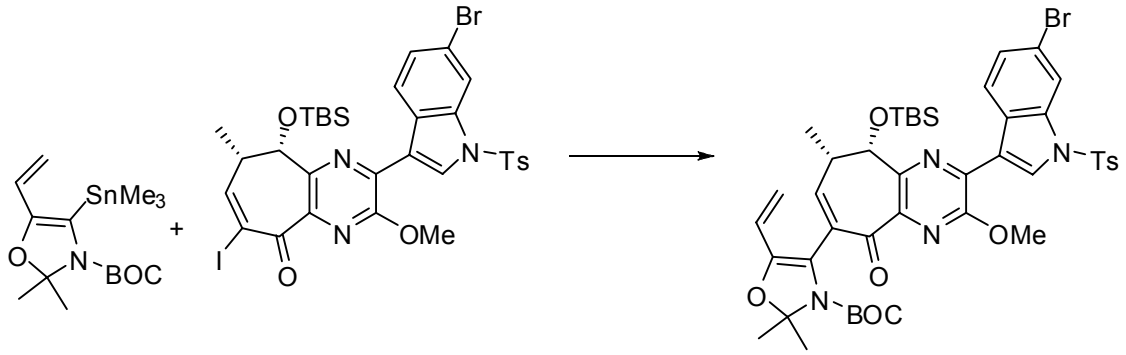


Enone 410. To a solution of ketone **408** (1.20 g, 1.75 mmol) in THF (10.6 mL) at -78 °C was added dropwise LiHMDS (1.0 M in THF, 2.10 mL, 2.10 mmol). The solution was stirred for 30 min at -78 °C. To the resultant solution chlorotrimethylsilane (265 μL, 2.10 mmol) was added dropwise, and the mixture was allowed to warm to -50 °C over 30 min. Saturated $NaHCO_3$ (30 mL) was added to quench the reaction. The resultant mixture warmed to rt, extracted with ether, dried (Na_2SO_4) and concentrated to give a crude oil that was immediately used in the next step without further purification.

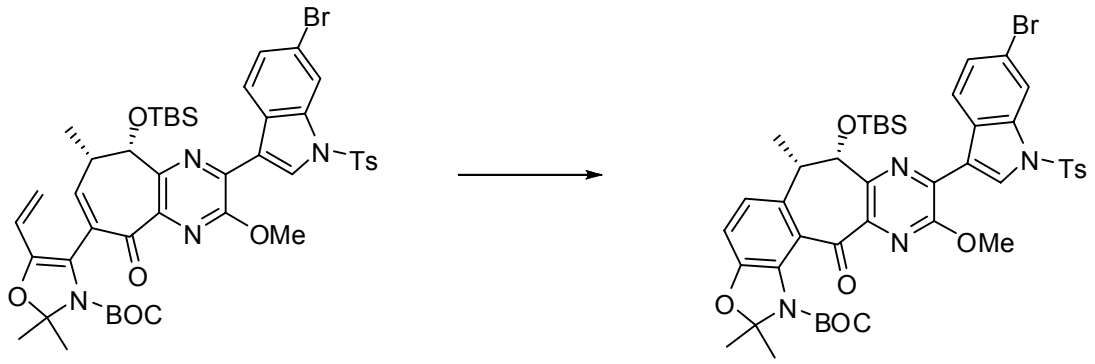
The crude oil generated above was dissolved in a 1:1 mixture of MeCN and dichloromethane (22 mL). $Pd(OAc)_2$ (590 mg, 2.63 mmol) was added, and the mixture was allowed to stir at rt for 20 h. The reaction mixture was then diluted with ether (50 mL), washed (3 x 50 mL) with saturated NH_4Cl, dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (dichloromethane, 3 : 1) gave enone **410** (870 mg, 73% from **408**) as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ. -0.45 (br s, 3 H), 0.09 (s, 3 H), 1.03 (s, 9 H), 1.43 (br s, 3 H), 2.34 (s, 3 H), 2.96-3.02 (m, 1 H), 4.29 (s, 3 H), 4.98 (br s, 1 H), 6.22 (br d, *J* = 12.3 Hz, 1 H), 6.64 (d, *J* = 12.3 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.51 (d, *J* = 8.6 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 2 H), 8.22 (s, 1 H), 8.65 (s, 1 H), 8.73 (d, *J* = 8.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, -4.7, 17.8, 21.5, 25.4, 39.6, 78.3, 115.6, 116.1, 118.9, 125.0, 126.9, 127.3, 127.9, 129.3, 130.1, 130.4, 134.5, 135.3, 138.6, 142.2, 145.7, 145.9, 148.2, 155.9, 190.6; IR (neat) 2954, 2856, 1661, 1537, 1461, 1380 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{32}H_{37}N_3O_5SSiBr$ 682.1407, found 682.1442.



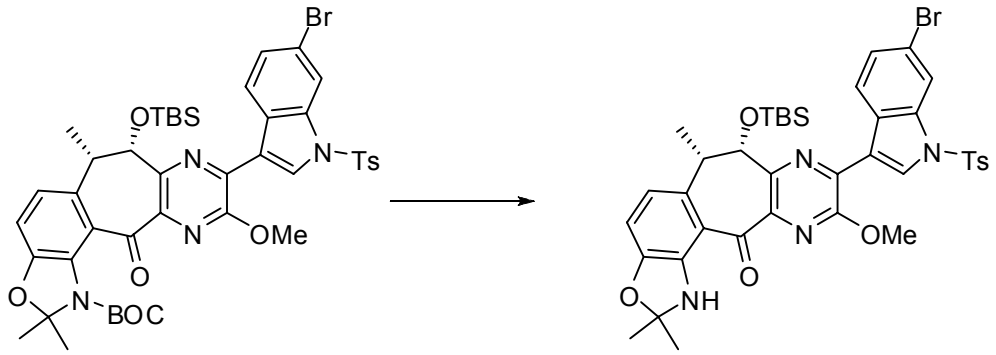
Iodoenone 411. To a solution of enone **410** (870 mg, 1.27 mmol) in CCl_4 (12.7 mL) was added pyridine (12.7 mL) and iodine (970 mg, 3.82 mmol). The solution was shielded from light and stirred at rt for 24 h. The solution was diluted with ether (150 mL), washed with saturated $Na_2S_2O_3$ (50 mL) and with saturated NH_4Cl (100 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (dichloromethane) gave iodoenone **411** (902 mg, 88%) as an amorphous yellow solid, mp 245-246 ^oC (dec.). ^1H NMR (300 MHz, $CDCl_3$) δ -0.32 (s, 3 H), 0.08 (s, 3 H), 0.81 (s, 9 H), 1.46 (d, *J* = 6.7 Hz, 3 H), 2.41 (s, 3 H), 3.03 (br q, *J* = 7.1 Hz, 1 H), 4.28 (s, 3 H), 4.94 (br s, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.34 (br s, 1 H), 7.51 (d, *J* = 8.5 Hz, 1 H), 7.88 (d, *J* = 8.1 Hz, 2 H), 8.23 (s, 1 H), 8.65 (s, 1 H), 8.68 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, -4.6, 17.9, 19.4, 21.6, 25.5, 44.0, 54.8, 103.0, 115.5, 116.3, 119.1, 124.9, 127.0, 127.5, 127.9, 130.3, 130.7, 134.6, 135.5, 139.0, 139.3, 145.8, 147.7, 154.4, 156.0 186.0; IR (neat) 2953, 2856, 1674, 1597, 1538, 1462, 1380 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{32}H_{36}N_3O_5SSiBrI$ 808.0373, found 808.0418.



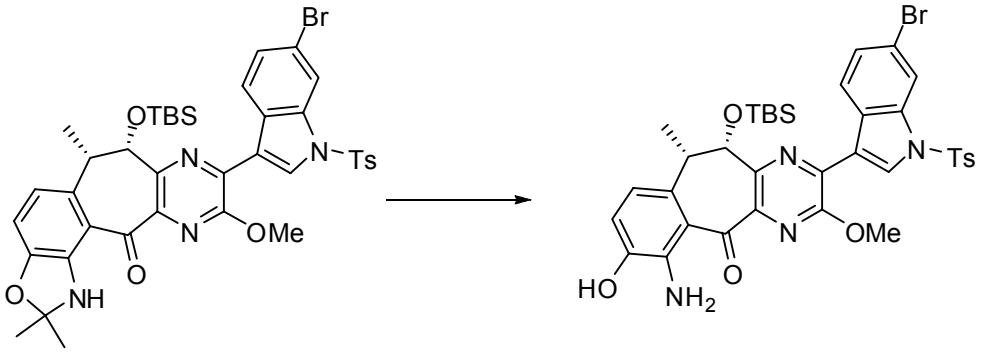
Trienecarbamate 412. CuCl (427 mg, 4.32 mmol), LiCl (229 mg, 5.40 mmol) and $Pd(PPh_3)_4$ (125 mg, 0.108 mmol) were combined under N_2 in a round bottomed flask. This mixture was added in one portion to a suspension of iodoenone **411** (871 mg, 1.02 mmol) and stannane **370** (838 mg, 2.16 mmol) in a dry, degassed solution of 4:1 DMSO:CH_2Cl_2 (27 mL). The reaction mixture was stirred at rt for 30 min, and poured carefully onto saturated NH_4Cl (60 mL). The resultant slurry was diluted with ether (100 mL) and filtered through Celite, rinsing thoroughly with ether. The organic phase of the resultant filtrate was separated, and the aqueous phase extracted with ether (3 x 100 mL). The combined organic layers were then dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave trienecarbamate **412** (753 mg, 77%) as a foamy yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.37 (br s, 3 H), 0.06 (s, 3 H), 0.76 (s, 9 H), 1.49 (br s, 12 H), 1.76 (br s, 3 H), 1.85 (br s, 3 H), 2.39 (s, 3 H), 3.10 (br q, *J* = 7.1 Hz, 1 H), 4.22 (br s, 3 H), 4.93 (br s, 1 H), 5.12 (d, *J* = 11.2 Hz, 1 H), 5.44 (d, *J* = 17.3 Hz, 1 H), 6.15 (br s, 1 H), 6.37 (dd, *J* = 17.2, 11.2 Hz, 1 H), 7.32 (d, *J* = 7.9 Hz, 2 H), 7.51 (d, *J* = 8.5 Hz, 1 H), 7.87 (d, *J* = 7.6 Hz, 2 H), 8.23 (s, 1 H), 8.61 (s, 1 H), 8.66 (br d, *J* = 8.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, -4.9, 17.8, 20.2, 21.5, 24.6, 25.4, 26.2, 28.1, 39.9, 54.3, 78.1, 80.7, 103.0, 112.4, 115.8, 116.2, 118.9, 120.2, 122.8, 124.8, 126.9, 127.3, 128.1, 129.5, 130.1, 133.8, 134.6, 135.4, 137.9, 140.4, 144.1, 145.6, 147.5, 149.3, 156.2, 189.2; IR (neat) 2955, 2931, 1698, 1538, 1462, 1381 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{44}H_{54}N_4O_8SSiBr$ 905.2615, found 905.2656.



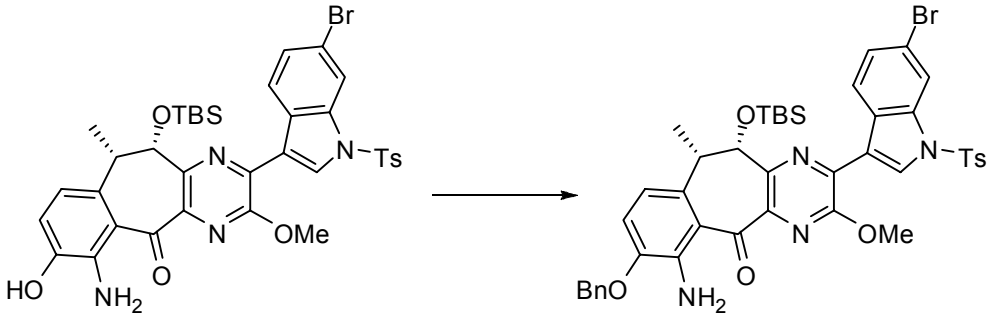
BOC-benzoxazoline 413. A solution of trienecarbamate **412** (753 mg, 0.830 mmol) in toluene (166 mL) was refluxed for 2 h. The solution was cooled to rt and concentrated. The resultant viscous oil was dissolved in dichloromethane (19 mL) and DDQ (279 mg, 1.25 mmol) was added in one portion. The resultant red solution was stirred for 2 h, and then poured onto saturated $NaHCO_3$ (100 mL). The mixture was extracted (x2) with ether (100 mL), and the combined organic extracts dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 3) gave benzoxazoline **413** (508 mg, 68%) as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.26 (s, 3 H), 0.21 (s, 3 H), 0.71 (s, 9 H), 1.53 (d, *J* = 7.3 Hz, 3 H), 1.55 (s, 9 H), 1.79 (s, 3 H), 1.83 (s, 3 H), 2.39 (s, 3 H), 3.54 (q, *J* = 6.9 Hz, 1 H), 4.34 (s, 3 H), 5.12 (s, 1 H), 6.78 (d, *J* = 8.1 Hz, 1 H), 6.87 (d, *J* = 8.1 Hz, 1 H), 7.31 (d, *J* = 7.9 Hz, 2 H), 7.47 (d, *J* = 8.6 Hz, 1 H), 7.87 (d, *J* = 7.6 Hz, 2 H), 8.22 (s, 1 H), 8.67 (s, 1 H), 8.77 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, -3.6, 17.6, 18.3, 21.6, 25.7, 26.4, 26.8, 28.1, 41.6, 54.3, 78.1, 82.0, 102.1, 116.0, 116.2, 119.0, 121.8, 125.5, 126.6, 126.9, 126.9, 128.0, 128.2, 130.2, 130.3, 130.6, 134.6, 135.5, 139.3, 140.8, 145.7, 147.5, 148.5, 150.3, 155.5, 191.7; IR (neat) 2931, 1715, 1679, 1543, 1470, 1381 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{44}H_{52}N_4O_8SSiBr$ 903.2459, found 903.2516.



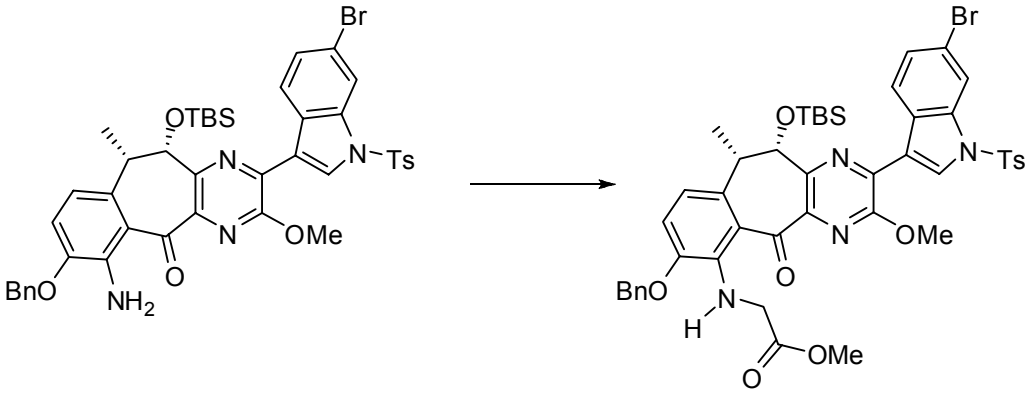
Benzoxazoline 414. To a solution of BOC-benzoxazoline **413** (212 mg, 0.235 mmol) in dichloromethane (4.7 mL) at 0 ^{o}C was added 2,4,6-collidine (155 μL, 1.18 mmol) and TMSOTf (170 μL, 0.94 mmol). The biphasic mixture was allowed to warm to rt and was stirred for 1 h. Saturated NH_4Cl (20 mL) was added and the solution was stirred for a further 30 min. The mixture was separated, and the aqueous layer extracted (x2) with ethyl acetate (10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 3) gave benzoxazoline **414** (139 mg, 74%) as a red film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3 H), 0.11 (s, 3 H), 0.88 (s, 9 H), 1.11 (br s, 3 H), 1.66 (s, 3 H), 1.72 (s, 3 H), 2.39 (s, 3 H), 3.38 (q, *J* = 6.9 Hz, 1 H), 4.32 (s, 3 H), 5.38 (br s, 1 H), 6.45 (d, *J* = 7.5 Hz, 1 H), 6.65 (d, *J* = 7.5 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.48 (d, *J* = 8.6 Hz, 1 H), 7.89 (d, *J* = 7.4 Hz, 2 H), 7.97 (br s, 1 H), 8.23 (s, 1 H), 8.68 (s, 1 H), 9.06 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.1, -4.1, 18.0, 18.4, 21.6, 25.9, 28.5, 28.6, 46.9, 54.3, 74.9, 100.4, 109.6, 114.7, 116.0, 116.4, 117.5, 119.1, 126.3, 127.0, 127.4, 128.3, 130.2, 130.4, 134.5, 134.7, 135.4, 139.4, 139.5, 144.2, 145.7, 146.6, 148.9, 155.9, 188.9; IR (neat) 3404, 2952, 2929, 1617, 1538, 1461 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{39}H_{44}N_4O_6SSiBr$ 803.1934, found 803.1918.



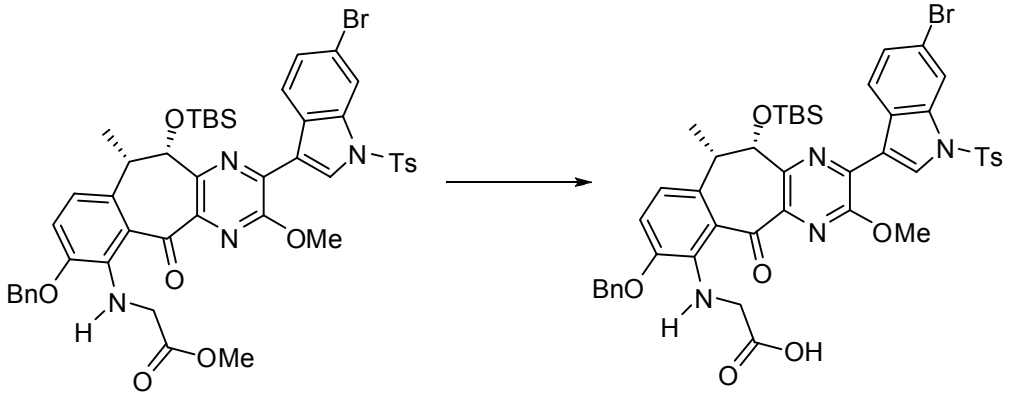
Aminophenol 415. To a solution of benzoxazoline **414** (139 mg, 0.173 mmol) in 2:1 MeOH:DCM (5.2 mL) was added *p*-TsOH·H_2O (39.5 mg, 0.208 mmol). The solution was stirred at rt for 1 h, then poured onto saturated $NaHCO_3$ (20 mL). The resultant mixture was extracted with ether (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 2) gave aminophenol **415** (103 mg, 78%) as a red film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.15 (s, 3 H), 0.86 (s, 9 H), 1.23 (br s, 3 H), 2.38 (s, 3 H), 3.46 (br s, 1 H), 4.28 (s, 3 H), 5.88 (s, 1 H), 6.47 (br s, 3 H), 6.86 (br s, 1 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 7.47 (dd, *J* = 8.6, 1.6 Hz, 1 H), 7.88 (d, *J* = 7.3 Hz, 2 H), 8.22 (d, *J* = 1.6 Hz, 1 H), 8.64 (s, 1 H), 8.92 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, -4.0, 18.4, 18.6, 21.6, 25.9, 45.6, 54.5, 75.1, 116.1, 116.2, 116.8, 117.1, 119.0, 125.9, 127.0, 127.2, 128.2, 130.2, 130.3, 134.6, 135.4, 135.7, 139.3, 141.1, 142.2, 145.7, 145.8, 156.0, 192.6; IR (neat) 3493, 3352, 2955, 1734, 1539, 1462 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{36}H_{40}N_4O_6SSiBr$ 763.1621, found 763.1650.



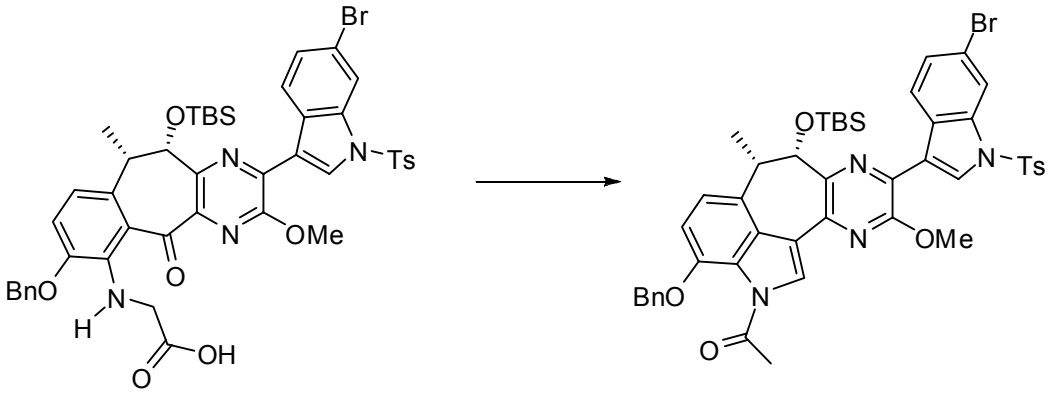
Benzyl ether 416. To a solution of phenol **415** (188 mg, 0.246 mmol) in DMF (5 mL) at 0 ^{o}C was added sodium hydride (60 wt % in mineral oil, 11.8 mg, 0.295 mmol). The resultant mixture was stirred at 0 ^{o}C for 5 min. Benzyl bromide (44 μL, 0.37 mmol) was added, and the solution allowed to stir for 30 min. Saturated NH_4Cl (30 mL) was added, and the resultant mixture extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave benzyl ether **416** (132 mg, 63%) as a red film ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.15 (s, 3 H), 0.87 (s, 9 H), 1.23 (d, *J* = 7.1 Hz, , 3 H), 2.40 (s, 3 H), 3.47 (q, *J* = 7.1 Hz, 1 H), 4.29 (s, 3 H), 5.13 (s, 2 H), 5.30 (d, *J* = 1.7 Hz, 1 H), 6.54 (d, *J* = 8.2 Hz, 1 H), 6.73 (br s, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.35-7.50 (m, 6 H), 7.88 (d, *J* = 8.4 Hz, 2 H), 8.23 (d, *J* = 1.7 Hz, 1 H), 8.64 (s, 1 H), 8.94 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, -4.0, 18.4, 18.6, 21.6, 25.9, 45.9, 54.4, 70.7, 74.9, 77.2, 113.9, 116.1, 116.3, 116.3, 118.2, 119.0, 126.0, 127.0, 127.2, 127.5, 128.2, 128.2, 128.6, 130.2, 134.7, 135.4, 135.7, 136.6, 139.0, 141.3, 142.0, 144.9, 145.5, 145.6, 156.0, 192.3; IR (neat) 3492, 3367, 2928, 1599, 1538, 1460 cm^{-1}; HRMS (M+H^{+}) calcd for $C_{43}H_{46}N_4O_6SSiBr$ 853.2091, found 853.2140.



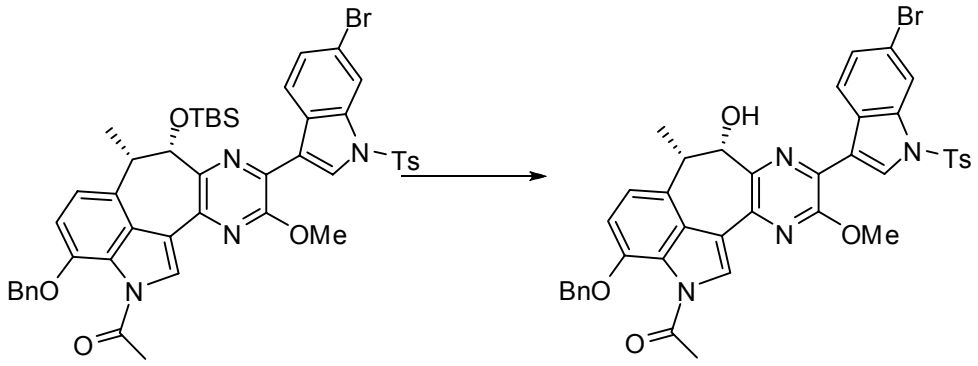
Ester 417. To a solution of benzyl ether **416** (185 mg, 0.217 mmol) in HMPA (4.3 mL) was added K_2CO_3 (149 mg, 1.08 mmol) and methyl iodoacetate (215 μL, 2.17 mmol). The solution was heated at 80 °C for 2 h, then cooled to rt. The solution was diluted with ether (20 mL), poured onto saturated $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave ester **417** (109 mg, 54%) as a red film, as well as 40 mg of recovered ether **416**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.26 (s, 3 H), 0.22 (s, 3 H), 0.73 (s, 9 H), 1.51 (d, *J* = 7.0 Hz, 3 H), 2.40 (s, 3 H), 3.56 (q, *J* = 7.3 Hz, 1 H), 3.59 (s, 3 H), 3.82 (d, *J* = 18.2 Hz, 1 H), 4.13 (d, *J* = 18.3 Hz, 1 H), 4.32 (s, 3 H), 5.10 (s, 1 H), 5.13 (s, 2 H), 6.74 (d, *J* = 8.4 Hz, 1 H), .93 (d, *J* = 8.4 Hz, 1 H), 7.32 (d, *J* = 8.3 Hz, 2 H), 7.34-7.50 (m, 6 H), 7.87 (d, *J* = 8.3 Hz, 2 H), 8.22 (d, *J* = 1.7 Hz, 1 H), 8.65 (s, 1 H), 8.75 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, -3.7, 18.1, 18.3, 21.6, 25.7, 41.6, 48.9, 51.8, 54.5, 71.0, 76.8, 114.6, 115.8, 116.2, 118.5, 119.1, 125.5, 126.2, 127.0, 127.1, 127.3, 127.9, 128.6, 130.2, 130.6, 132.4, 134.6, 135.5, 136.7, 137.7, 139.5, 141.6, 145.8, 146.8, 147.5, 155.7, 171.9, 195.3; IR (neat) 3386, 2952, 1747, 1699, 1541, 1460 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{46}H_{50}N_4O_8SSiBr$ 925.2302, found 925.2347.



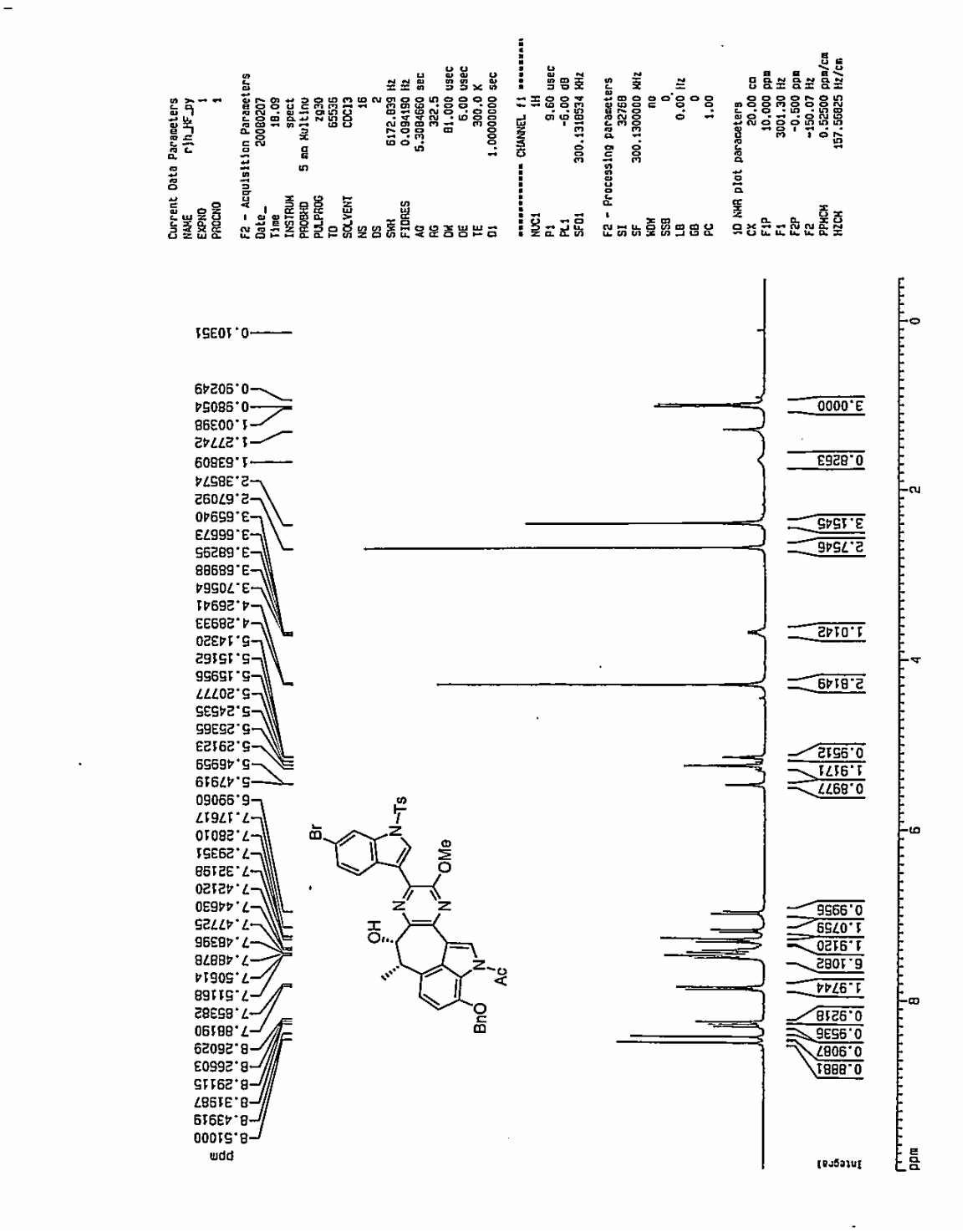
Acid 418. To a solution of ester **417** (120 mg, 0.130 mmol) in THF (3.9 mL) and water (1.3 mL) at 0 ^{o}C was added LiOH (62 mg, 2.6 mmol). The solution was stirred at 0 ^{o}C for 75 min, poured onto saturated KH_2PO_4 (30 mL) and extracted (5 x 20 mL) with EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane-AcOH, 1 : 2 : 0.02) gave acid **418** (97 mg, 82%) as a red film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.26 (s, 3 H), 0.21 (s, 3 H), 0.73 (s, 9 H), 1.51 (d, *J* = 7.1 Hz, 3 H), 2.38 (s, 3 H), 3.57 (q, *J* = 7.1 Hz, 1 H), 3.86 (d, *J* = 18.6 Hz, 1 H), 4.00 (d, *J* = 18.6 Hz, 1 H), 4.26 (s, 3 H), 5.10 (d, *J* = 1.3 Hz, 1 H), 5.12 (s, 2 H), 6.81 (d, *J* = 8.5 Hz, 1 H), 6.93 (d, *J* = 8.5 Hz, 1 H), 7.27-7.41 (m, 7 H), 7.47 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 2 H), 8.21 (d, *J* = 1.6 Hz, 1 H), 8.63 (s, 1 H), 8.73 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, -3.8, 18.3, 18.3, 21.6, 25.7, 41.8, 49.3, 54.5, 71.0, 76.7, 115.0, 115.7, 116.2, 119.1, 120.0, 125.4, 127.0, 127.0, 127.1, 127.4, 127.9, 128.1, 128.6, 130.2, 130.7; IR (neat) 3379, 2953, 1718, 1660, 1541, 1461 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{46}H_{48}N_4O_8SSiBr$ 911.2146, found 911.2162.



Indole 419. To a solution of acid **418** (97 mg, 0.106 mmol) in Ac_2O (3 mL) was added triethylamine (450 μL). The solution was heated at 80 °C for 6 min. The resultant mixture was poured onto saturated $NaHCO_3$ (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave indole **419** (65 mg, 68%) as a yellow film. ^{1}H NMR (400 MHz, $CDCl_3$, *rotamers*) δ -0.54, *0.05* (s, 3 H), 0.04, *0.08* (s, 3 H), 0.44, *0.95* (s, 9 H), 1.03, *1.74* (d, *J* = 7.1 Hz, 3 H), 2.39 (s, 3 H), 2.66, *2.68* (s, 3 H), 3.45-3.51 (m, 1 H), 4.29, *4.30* (s, 3 H), 5.20-5.35 (m, 3 H), 6.96, *6.97* (d, *J* = 8.2 Hz, 1 H), 7.12, *7.17* (d, *J* = 8.2 Hz, 1 H), 7.31 (d, *J* = 7.8 Hz, 2 H), 7.36-7.54 (m, 6 H), 7.89 (d, *J* = 8.3 Hz, 2 H), 8.22, *8.26* (d, *J* = 1.6 Hz, 1 H), 8.39, *8.42* (s, 1 H), 8.55, *8.56* (s, 1 H), 8.83, *9.20* (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, *rotamers*) δ -5.3, *-5.1*, -4.6, *-4.0*, 17.5, *17.7*, 18.7, *19.0*, 21.6, 25.2, 26.3, *26.5*, 40.6, *47.0*, 53.9, *54.0*, 71.4, 75.4, *81.3*, 108.2, 115.8, *116.3*, 116.5, *117.5*, 118.7, *118.8*, 118.8, *119.8*, 122.4, *123.7*, 124.8, 125.2, *125.4*, 127.0, 127.1, 127.8, *127.8*, 127.9, *128.2*, 128.3, *128.3*, 128.4, 128.7, 128.7, 129.6, 130.1, *130.1*, 131.0, 133.4, *134.6*, 134.9, *135.0*, 135.5, *135.6*, 136.2, *136.4*, 137.2, *140.2*, 142.8, *145.3*, 145.4, *145.5*, 145.6, *145.6*, 155.0, *155.4*, 170.5, *171.0* IR (neat) 2927, 1716, 1596, 1379, 1256 cm^{-1}; HRMS (M+H$^+$) calcd for $C_{46}H_{48}N_4O_6SSiBr$ 891.2261, found 891.2254.



Alcohol 420. To a solution of TBS alcohol **419** (58 mg, 0.065 mmol) in THF (4 mL) was added HF•Py (1 mL). The resultant solution was stirred for 3 h, then diluted with ether (15 mL) and poured carefully onto saturated $NaHCO_3$ (30 mL). The organic layer was separated, and the aqueous layer was extracted (x 3) with ether (30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane 1 : 3) gave alcohol **420** (32 mg, 63%) as a yellow solid, mp 145-147 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, *J* = 7.0 Hz, 3 H), 2.39 (s, 3 H), 2.67 (s, 3 H), 3.67 (qd, *J* = 7.0, 2.1 Hz, 1 H), 4.29 (s, 3 H), 5.15 (dd, *J* = 2.1, 2.9 Hz, 1 H), 5.23 (d, *J* = 11.3 Hz, 1 H), 5.27 (d, *J* = 11.3 Hz, 1 H), 5.48 (d, *J* = 2.9 Hz, 1 H), 6.98 (d, *J* = 8.2 Hz, 1 H), 7.19 (d, *J* = 8.2 Hz, 1 H), 7.31 (d, *J* = 8.5 Hz, 2 H), 7.39-7.52 (m, 6 H), 7.87 (d, *J* = 8.4 Hz, 2 H), 8.27 (d, *J* = 1.7 Hz, 1 H), 8.31 (d, *J* = 8.6 Hz, 1 H), 8.44 (s, 1 H), 8.51 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 21.6, 26.6, 44.4, 54.3, 71.4, 72.7, 108.3, 116.3, 116.6, 117.9, 118.9, 123.7, 124.4, 125.4, 126.9, 127.5, 127.9, 128.0, 128.0, 128.3, 128.5, 128.7, 129.0, 130.2, 130.5, 133.3, 134.7, 135.6, 136.1, 138.8, 140.6, 145.6, 145.7, 155.8, 170.7 IR (neat) 3426, 2925, 1715, 1595, 1378, 1254 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{40}H_{34}N_4O_6SBr$ 777.1382, found 777.1349.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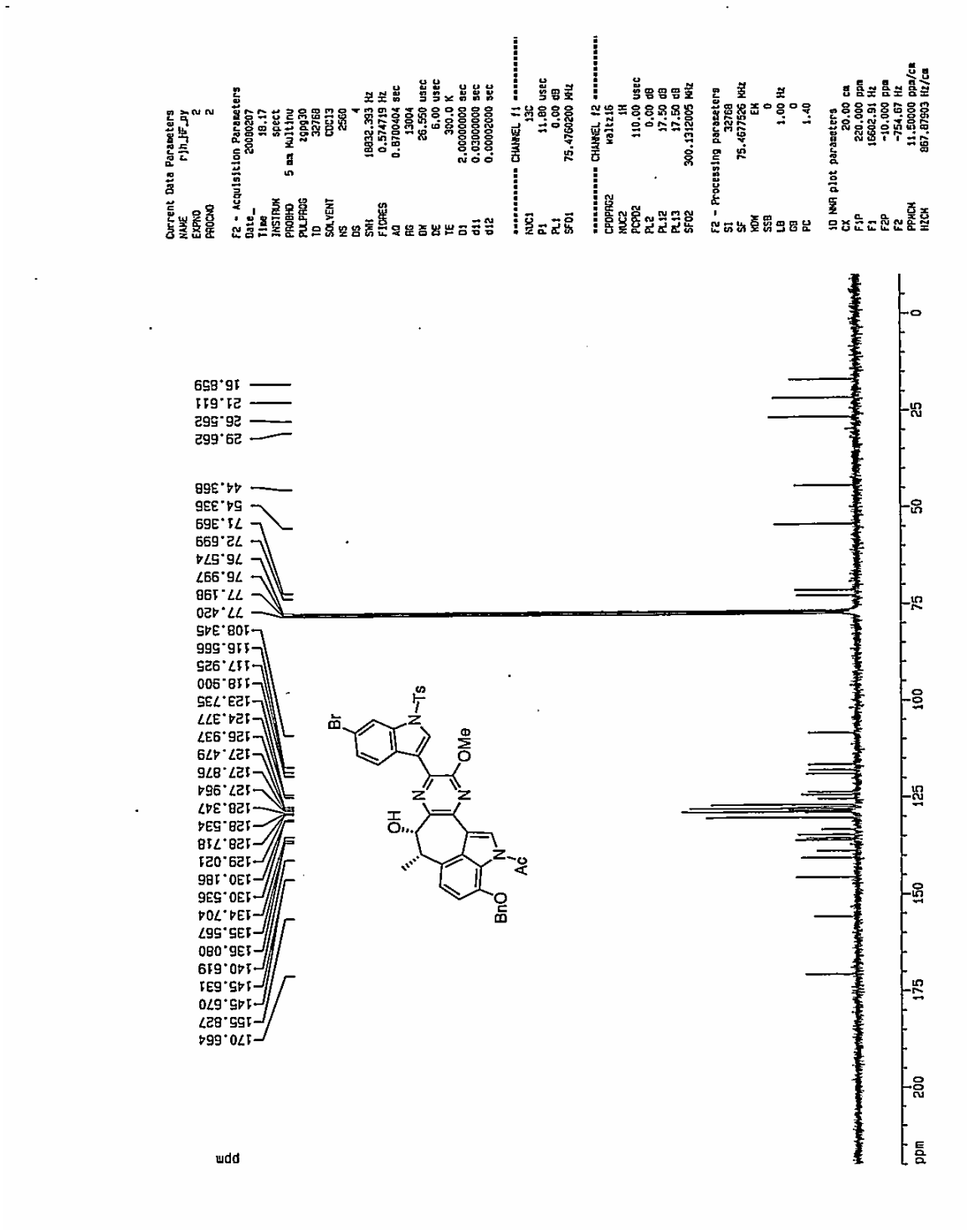
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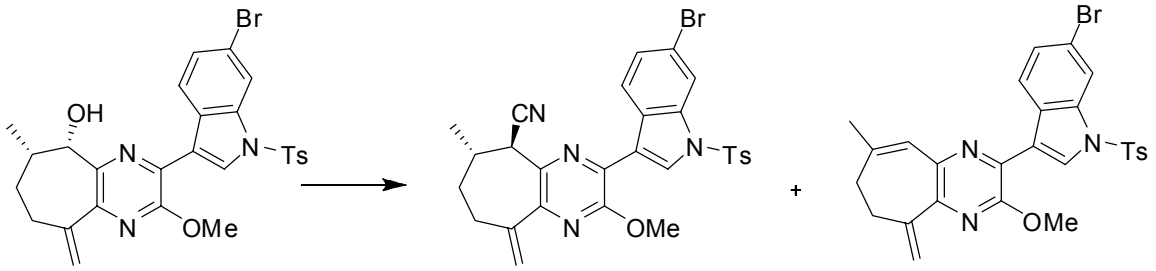
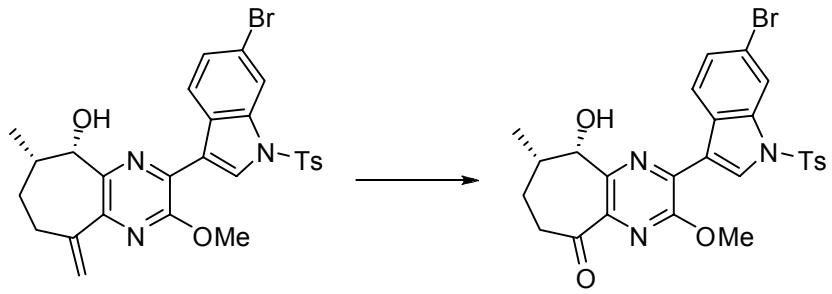
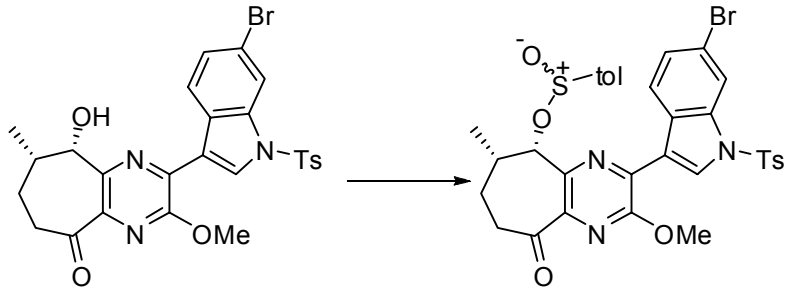


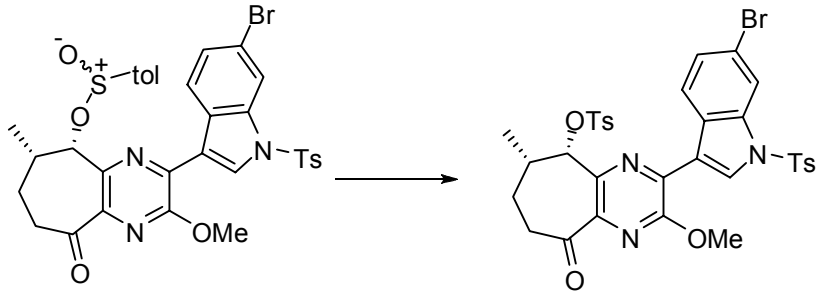
Nitrile 421. To a solution of alcohol **405** (100 mg, 0.176 mmol), PPh_3 (462 mg, 1.76 mmol), and acetone cyanohydrin (161 μL, 1.76 mmol) in toluene (10 mL) was added dropwise over 10 min diethyl azodicarboxylate (40 % solution in toluene, 798 μL, 1.76 mmol). The solution was stirred at rt for 1 h, then poured onto saturated $NaHCO_3$ (50 mL). The resultant mixture was extracted with EtOAc (3 x 50 mL), dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave nitrile **421** (27 mg, 27%) as a colorless film, plus diene **429** (24 mg, 27%) as a colorless film. *Nitrile:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, *J* = 6.8 Hz, 3 H), 1.68-1.78 (m, 1 H), 2.01-2.11 (m, 1 H), 2.38 (s, 3 H), 2.40-2.48 (m, 1 H), 2.58-2.73 (m, 2 H), 4.14 (d, *J* = 9.1 Hz, 1 H), 4.23 (s, 3 H), 5.46 (s, 1 H), 5.94 (s, 1 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 7.53 (d, *J* = 8.6 Hz, 1 H), 7.83 (d, *J* = 8.2 Hz, 2 H), 8.21 (d, *J* = 1.6 Hz, 1 H), 8.55 (s, 1 H), 8.97 (d, *J* = 8.5 Hz, 1 H). IR (neat) 2992, 2928, 2244, 1597 cm^{-1}. MS ($M+H^+$) calcd for $C_{28}H_{26}BrN_4O_3S$ 577/579 found 577/579. *Elimination product:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (s, 3 H), 2.37 (s, 3 H), 2.51 (t, *J* = 5.8 Hz, 2 H), 2.78 (t, *J* = 5.8 Hz, 2 H), 4.20 (s, 3 H), 5.28 (d, *J* = 2.3 Hz, 1 H), 6.11 (d, *J* = 2.3 Hz, 1 H), 6.55 (s, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.47 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 2 H), 8.22 (d, *J* = 1.7 Hz, 1 H), 8.49 (s, 1 H), 8.69 (d, *J* = 8.6 Hz, 1 H). IR (neat) 2925, 2854, 1597, 1542, 1455, 1378 cm^{-1}.



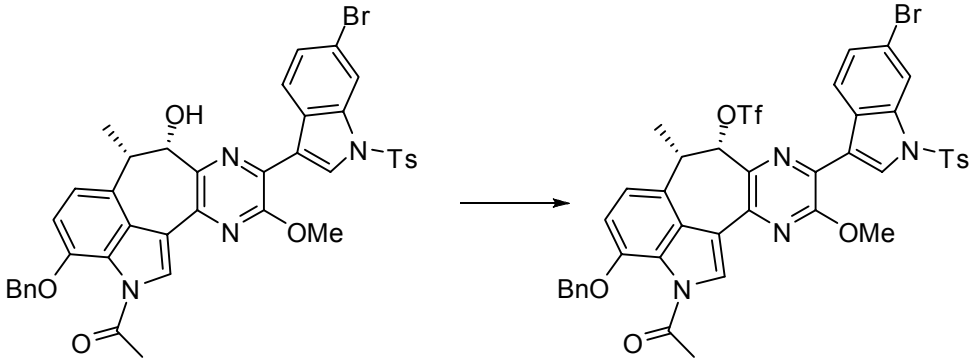
Hydroxyketone 434. To a solution of alcohol **405** (200 mg, 0.352 mmol) in THF (7.0 mL) and H_2O (3.5 mL) was added *N*-methylmorpholine-*N*-oxide (82.5 mg, 0.704 mmol) and OsO_4 (4 wt % in H_2O, 43 μL, 0.0070 mmol). The solution was stirred at rt for 3 h. $NaIO_4$ (376 mg, 1.76 mmol) was subsequently added and the reaction mixture was stirred for a further 20 h at rt. The solution was then quenched with saturated $Na_2S_2O_3$ (30 mL), extracted with ethyl acetate (3 x 40 mL), dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 5) gave hydroxyketone **434** (119 mg, 59%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.8 Hz, 3 H), 1.50-1.60 (m, 1 H), 2.18-2.29 (m, 1 H), 2.38 (s, 3 H), 2.50-2.60 (m, 1 H), 2.78-2.85 (m, 1 H), 2.99-3.05 (m, 1 H), 4.08 (d, *J* = 4.5 Hz, 1 H), 4.28 (s, 3 H), 5.17 (dd, *J* = 4.5, 4.0 Hz, 1 H), 7.31 (d, *J* = 8.3 Hz, 2 H), 7.48 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.85 (d, *J* = 8.3 Hz, 2 H), 8.21 (d, *J* = 1.7 Hz, 1 H), 8.37 (d, *J* = 8.6 Hz, 1 H), 8.61 (s, 1 H).



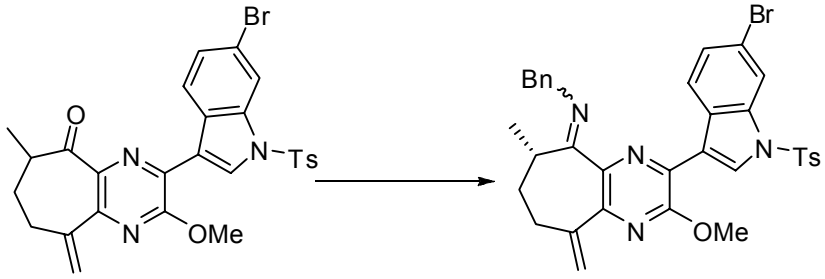
Sulfinates 435. To a solution of hydroxyketone **434** (185 mg, 0.324 mmol) in dichloromethane (3.24 mL) at -78 ^{o}C was added triethylamine (90 μL, 0.65 mmol) and toluenechlorosulfinate (0.2 M solution in dichloromethane, 2.43 mL, 0.487 mmol). The solution was allowed to warm to rt over 90 min. The resultant mixture was then poured onto saturated aqueous $NaHCO_3$, (20 mL), extracted with ethyl acetate (3 x 20 mL), dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave a mixture of diastereomeric sulfinates **435** (164 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 6.9 Hz, 3 H) 1.30 (d, *J* = 6.9 Hz, 3 H), 1.79-2.04 (m, 4 H), 2.39 (s, 12 H), 2.67-2.79 (m, 2 H), 3.01-3.09 (m, 1 H), 3.18 (ddd *J* = 16.8, 11.5, 3.5 Hz, 1 H), 4.23 (s, 1 H), 4.32 (s, 3 H), 5.58 (d, *J* = 3.5 Hz, 1 H), 5.63 (d, *J* = 3.7 Hz, 1 H), 6.60 (d, *J* = 7.9 Hz, 2 H), 7.19 (d, *J* = 8.1 Hz, 2 H), 7.24 (d, J = 7.9 Hz, 2 H), 7.34 (d, *J* = 8.1 Hz, 4 H), 7.46 (d, *J* = 8.1 Hz, 2 H), 7.46 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.52 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.88 (d, *J* = 8.1 Hz, 4 H), 8.22 (d, *J* = 1.8 Hz, 1 H), 8.24 (d, *J* = 1.8 Hz, 1 H), 8.45 (d, *J* = 8.6 Hz, 1 H), 8.55 (s, 1 H), 8.67 (s, 1 H), 8.73 (d, 1 H).



Tosylate 436. To the mixture of sulfinates **435** (164 mg, 0.232 mmol) in dichloromethane (4.6 mL) at rt was added 3-chloroperbenzoic acid (80.1 mg, 0.464 mmol). The solution was stirred at rt for 90 min. The resultant mixture was then poured onto saturated aqueous $NaHCO_3$, (20 mL), extracted with ethyl acetate (3 x 20 mL), dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave tosylate **436** (82.0 mg, 49%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, *J* = 6.8 Hz, 3 H), 2.01 (s, 3 H), 2.36-2.42 (m, 1 H), 2.41 (s, 3 H), 2.42- 2.53 (m, 2 H), 2.75-2.84 (m, 1 H), 3.07-3.17 (m, 1 H), 4.22 (s, 1 H), 5.79 (d, *J* = 3.0 Hz, 1 H), 6.74 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.5 Hz, 2 H), 7.40 (d, *J* = 8.2 Hz, 2 H), 7.56 (dd, *J* = 8.6, 1.6 Hz, 1 H), 7.88 (d, *J* = 8.3 Hz, 2 H), 8.26 (d, *J* = 1.6 Hz, 1 H), 8.57 (s, 1 H), 8.62 (d, *J* = 8.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 21.1, 21.3, 27.1, 30.0, 40.1, 54.7, 87.2, 115.2, 116.2, 119.4, 125.9, 127.0, 127.5, 127.7, 128.2, 128.8, 129.3, 130.3, 133.6, 134.6, 135.4, 139.9, 142.1, 142.4, 144.0, 146.0, 156.0, 201.0; IR (neat) 2954, 1700, 1597, 1545 cm^{-1}; HRMS (M + H^+) calcd for $C_{33}H_{31}N_3O_7S_2Br$ 724.0792 found 724.0840.

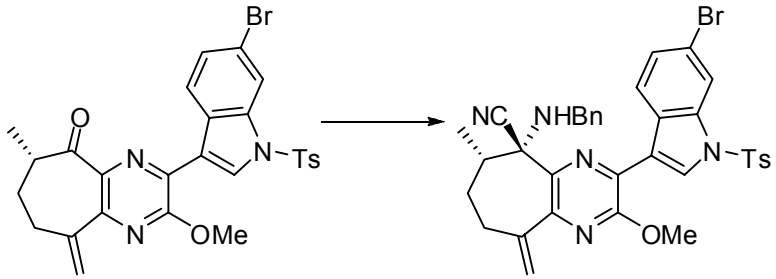


Triflate 438. To a solution of alcohol **420** (6.0 mg, 0.077 mmol) and pyridine (4.7 μL, 0.058 mmol), in $CDCl_3$ (250 μL) at 0 °C was added a trifluoromethanesulfonic anhydride (0.20 M solution in $CDCl_3$, 154 μL, 0.0309 mmol), during which time the solution turned red, and then yellow. The solution was stirred at rt for 1.5 h, then poured onto saturated NH_4Cl (10 mL). The resultant mixture was extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4) and concentrated to give triflate **438** (≈ 5 mg) as a crude yellow film, suitable for use in the following reactions. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, *J* = 6.9 Hz, 3 H), 2.37 (s, 3 H), 2.69 (s, 3 H), 4.39 (s, 3 H), 4.38- 4.43 (m, 1 H), 5.18 (s, 2 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 7.09 (d, *J* = 2.8 Hz, 1 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 7.28 (d, *J* = 8.5 Hz, 2 H), 7.39-7.52 (m, 6 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 8.58 (s, 1 H), 8.61 (s, 1 H), 8.69 (d, *J* = 8.6 Hz, 1 H), 9.01 (d, *J* = 5.8 Hz, 1 H).



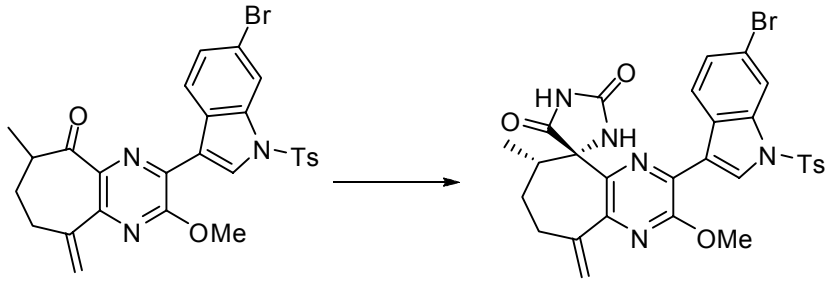
Benzyl imine 440a. A flask containing ketone **396** (100 mg, 0.177 mmol), benzylamine (500 mL, 4.58 mmol) and *p*-TsOH (2.0 mg, 0.011 mmol) in toluene

(2.5 mL) was equipped with a Dean-Stark trap the mixture was refluxed for 16 h. The solution was then cooled to rt, diluted with ether (20 mL), washed with saturated aqueous $NaHCO_3$ (2 x 20 mL) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane-triethylamine, 1 : 4 : 0.01) gave imine **440a** (90 mg, 77%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.5 Hz, 3 H), 2.11-2.25 (m, 2 H), 2.38 (s, 3 H), 2.55-2.63 (m, 2 H), 2.99-3.13 (m, 1 H), 4.30 (s, 3 H), 4.68 (s, 2 H), 5.39 (s, 1 H), 6.26 (s, 1 H), 7.20-7.45 (m, 8 H), 7.87 (d, *J* = 8.2 Hz, 2 H), 8.22 (s, 1 H), 8.49 (d, *J* = 8.6 Hz, 1 H), 8.63 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 21.5, 31.8, 33.5, 44.4, 53.9, 56.4, 116.0, 116.2, 118.8, 118.9, 125.1, 126.4, 126.9, 127,3, 127.6, 128.2, 129.5, 130.1, 134.7, 135.4, 136.3, 138.7, 140.4, 144.0, 144.6, 145.6, 154.9, 161.9, 172.4. IR (neat) 2929, 2866, 1731, 1643, 1597, 1542 cm^{-1}; HRMS ($M + H^+$) calcd for $C_{34}H_{32}N_4O_3SBr$ 655.1378 found 655.1396.



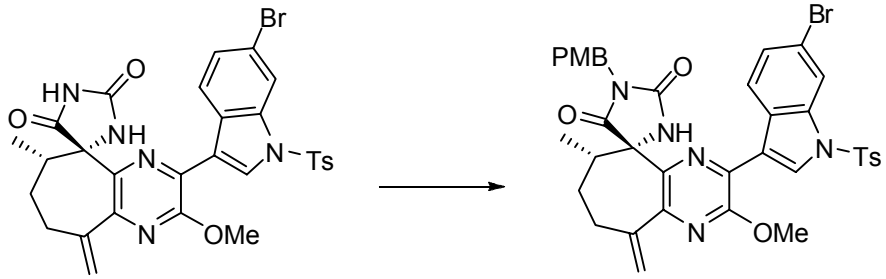
Benzylaminonitrile 441a. A flask containing ketone **396** (370 mg, 0.653 mmol), benzylamine (740 μL, 6.77 mmol) and *p*-TsOH (6.2 mg, 0.033 mmol) in toluene (13 mL) was equipped with a Dean-Stark trap and the mixture was refluxed for 16 h. The solution was then cooled to rt, washed with saturated aqueous $NaHCO_3$ (2 x 20 mL) and concentrated to give crude imine **440a**. This crude mixture was dissolved in dichloromethane (5 mL) and trimethylsilyl cyanide (1.00 mL, 7.99 mmol) was added. The solution was stirred at rt for 2 h, diluted with dichloromethane (20 mL), and washed (3 x 30 mL) with saturated aqueous $NaHCO_3$. The organic layer was then dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (benzene) gave

aminonitrile **441a** (320 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.9 Hz, 3 H), 2.00-2.20 (m, 2 H), 2.38 (s, 3 H), 2.51-2.69 (m, 2 H), 2.81-2.93 (m, 1 H), 3.62 (d, *J* = 11.7 Hz, 1 H), 3.95 (d, *J* = 11.7 Hz, 1 H), 4.23 (s, 3 H), 5.49 (d, *J* = 1.8 Hz, 1 H), 5.78 (d, *J* = 1.8 Hz, 1 H), 7.21-7.43 (m, 8 H), 7.83 (d, *J* = 8.4 Hz, 2 H), 8.20 (d, *J* = 1.8 Hz, 1 H), 8.55 (s, 1 H), 8.88 (d, *J* = 8.6 Hz, 1 H); IR (neat) 3332, 2928, 2250, 1597. MS ($M+H^+$) calcd for $C_{35}H_{33}BrN_5O_3S$ 682/684 found 682/684.

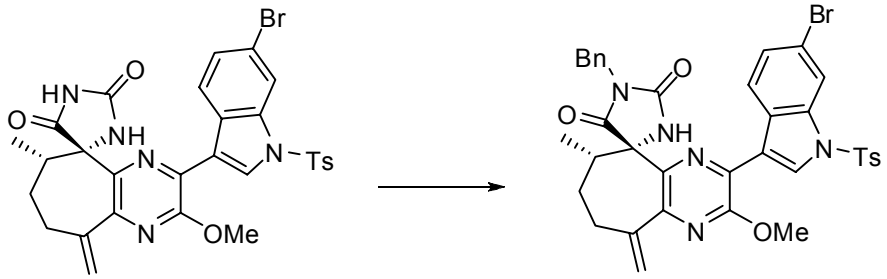


Hydantoin 442. To a suspension of ketone **396** (1.39 g, 2.45 mmol) in a 1:1 mixture of ethanol:NH_4OH (170 mL) in a heavy-walled vessel was added ammonium carbonate (13.9 g, 145 mmol) and sodium cyanide (2.78 g, 145 mmol). The vessel was then sealed and heated at 90 ^{o}C for 4 h (CAUTION: Cyanide, pressure). The vessel was then cooled to rt and carefully opened. The resultant solution was poured onto saturated $NaHCO_3$ (300 mL) and extracted (3 x 300 mL) with ethyl acetate. The combined organic layers were washed (3 x 400 mL) with water, and then with brine (1 x 200 mL). The solution was dried (Na_2SO_4), and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexanes 1:1) gave hydantoin **442** (970 mg, 62%) as an inseparable 5:1 mixture of epimers. *Major product:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 7.0 Hz, 3 H), 1.69-1.79 (m, 1 H), 1.94-2.11 (m, 1 H), 2.35 (s, 3 H), 2.34-2.41 (m, 1 H), 2.57-2.67 (m, 1 H), 2.72-2.80 (m, 1 H), 4.19 (s, 3 H),

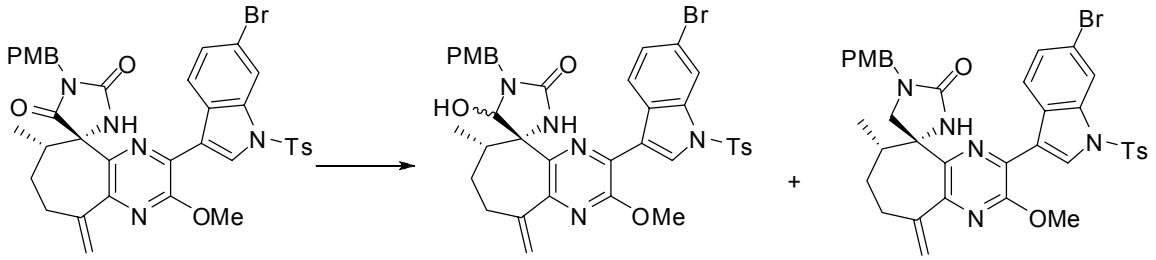
5.43 (d, *J* = 1.7 Hz, 1 H), 6.01 (d, *J* = 1.7 Hz, 1 H), 6.62 (br s, 1 H), 7.23 (dd, *J* = 8.7,1.7 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.78 (d, *J* = 8.4 Hz, 2 H), 8.05 (d, *J* = 1.7 Hz, 1 H), 8.09 (d, *J* = 8.7 Hz, 1 H), 8.39 (s, 1 H), 8.47 (br s, 1 H). MS ($M+H^+$) calcd for $C_{29}H_{27}N_5O_5BrS$ 636/638, found 636/638.



PMB Hydantoin 443a. To a solution of hydantoin **442** (272 mg, 0.427 mmol) in DMF (4.3 mL) was added potassium carbonate (71 mg, 0.51 mmol) and *p*-methoxybenzyl bromide (74 μL, 0.51 mmol). The reaction mixture was stirred for 3 h at rt. An additional portion of potassium carbonate (71 mg, 0.51 mmol) and *p*-methoxybenzyl bromide (74 μL, 0.51 mmol) was added and the reaction mixture was stirred for a further 4 h. The resultant mixture was then poured onto saturated aqueous NH_4Cl (50 mL) and extracted with ethyl acetate (3 x 50 mL). Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave PMB-hydantoin **443a** (205 mg, 63%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, *J* = 6.6 Hz, 3 H), 1.70-1.80 (m, 1 H), 1.91-2.01 (m, 1 H), 2.38 (s, 3 H), 2.38-2.47 (m, 1 H), 2.53-2.66 (m, 1 H), 2.74-2.83 (m, 1 H), 3.74 (s, 3 H), 4.16 (s, 3 H), 4.54 (d, *J* = 14.7 Hz, 1 H), 4.64 (d, *J* = 14.7 Hz, 1 H), 5.43 (d, *J* = 1.7 Hz, 1 H), 6.01 (d, *J* = 1.7 Hz, 1 H), 6.67 (d, *J* = 8.6 Hz, 2 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 7.09 (dd, *J* = 8.6, 1.6 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.82 (d, *J* = 8.4 Hz, 2 H), 7.93 (d, *J* = 8.6 Hz, 1 H), 8.13 (d, *J* = 1.6 Hz, 1 H), 8.36 (s, 1 H).

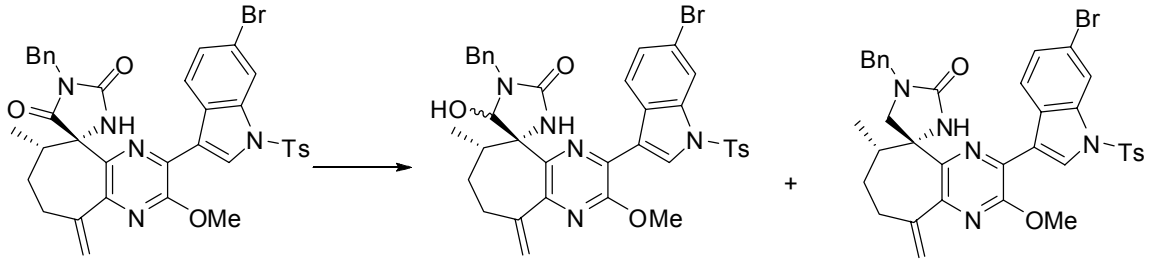


Benzylhydantoin 443b. To a solution of hydantoin **442** (185 mg, 0.290 mmol) in DMF (4 mL) was added potassium carbonate (185 mg, 1.34 mmol) and benzyl bromide (185 μL, 1.55 mmol). The reaction mixture was stirred for 2 h at rt. The resultant mixture was then poured onto saturated aqueous NH_4Cl (50 mL) and extracted with ethyl acetate (3 x 50 mL). Purification of the resultant residue by silica gel chromatography (dichloromethane) gave benzylhydantoin **443b** (130 mg, 62%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.5 Hz, 3 H), 155-1.82 (m, 1 H), 1.84-2.09 (m, 1 H), 2.38 (s, 3 H), 2.27-2.53 (m, 1 H), 2.54-2.68 (m, 1 H), 2.72-2.89 (m, 1 H), 4.15 (s, 3 H), 4.57 (d, *J* = 14.5 Hz, 1 H), 4.70 (d, *J* = 14.5 Hz, 1 H), 5.44 (d, *J* = 1.6 Hz, 1 H), 6.02 (d, *J* = 1.6 Hz, 1 H), 6.90-7.03 (m, 1 H), 7.05-7.10 (m, 3 H), 7.25-7.35 (m, 4 H), 7.84 (d, *J* = 8.3 Hz, 2 H), 7.88 (d, *J* = 8.8 Hz, 1 H), 8.13 (d, *J* = 1.5 Hz, 1 H), 8.34 (s, 1 H); IR (neat) 3234, 3166, 2930, 2859, 1770, 1710, 1547 cm^{-1}.



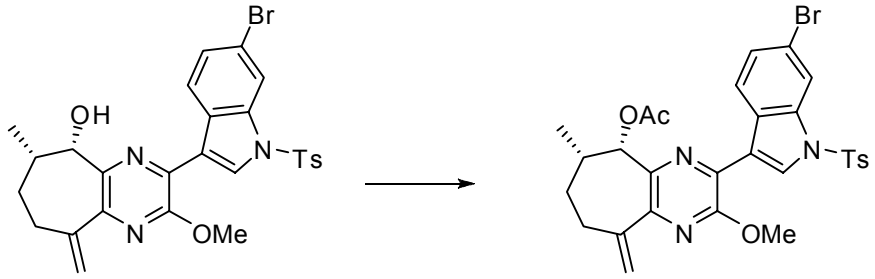
PMB-urea 445a To a solution of *p*-methoxybenzylhydantoin **443a** (123 mg, 0.162 mmol) in toluene (4 mL) was added at 0 °C in two portions DIBAL-H

(1.0 M in hexanes, 650 μL, 0.65 mmol). The reaction mixture was stirred for 2 h. The resultant mixture was then poured onto saturated aqueous NH_4Cl (25 mL) and extracted with ethyl acetate (3 x 25 mL). Purification of the resultant residue by silica gel chromatography (dichloromethane) gave hemiaminal **444a** (54 mg, 44%) and urea **445a** (30 mg, 24%) as white solids. ^{1}H NMR (300 MHz, $CDCl_3$) *urea:* δ 0.88 (d, *J* = 6.9 Hz, 3 H), 1.66-1.77 (m, 1 H), 1.93-2.09 (m, 2 H), 2.24-2.32 (m, 1 H), 2.39 (s, 3 H), 2.43-2.50 (m, 1 H), 3.47 (d, *J* = 9.1 Hz, 1 H), 3.54 (d, *J* = 9.1 Hz, 1 H), 3.77 (s, 3 H), 4.12 (d, *J* = 14.9 Hz, 1 H), 4.20, (s, 3 H), 4.31 (d, *J* = 14.9 Hz, 1 H), 5.38 (s, 1 H), 5.51 (d, *J* = 1.7 Hz, 1 H), 5.67 (s, 1 H), 6.70 (d, *J* = 9.6 Hz, 2 H), 6.97 (d, *J* = 9.6 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.61 (dd, *J* = 8.7, 1.7 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 2 H), 8.22 (d, *J* = 1.7 Hz, 1 H), 8.50 (s, 1 H), 8.60 (d, *J* = 8.7 Hz, 1 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 29.5, 29.6, 31.5, 39.6, 46.3, 54.1, 55.1, 55.1, 65.0, 113.7, 116.1, 116.5, 118.9, 119.1, 119.8, 125.0, 126.9, 127.8, 128.0, 128.7, 129.1, 130.1, 134.5, 134.7, 135.4, 143.5, 145.5, 146.1, 147.5, 155.6, 158.8, 161.8; IR (neat) 3260, 2930, 2246, 1698 cm^{-1}; HRMS calcd for $C_{37}H_{36}N_5O_5BrS$ 742.1699 found 742.1703.



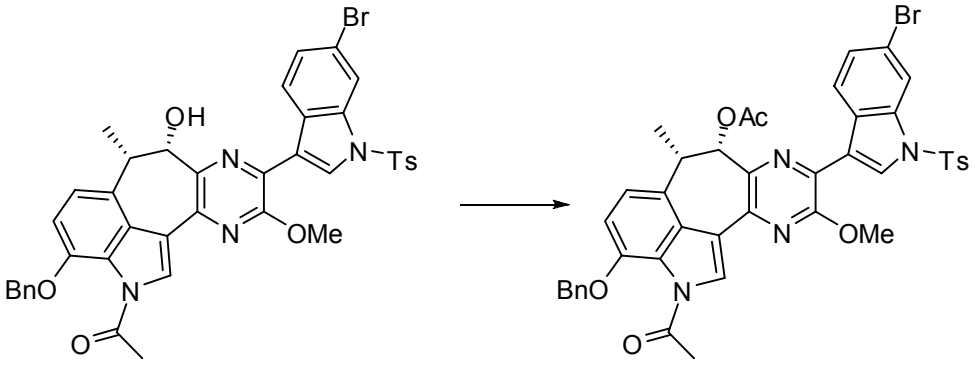
Benzyl urea 445b To a solution of benzylhydantoin **443b** (250 mg, 0.330 mmol) in toluene (10 mL) was added DIBAL-H (1.5 M in toluene, 2.20 mL, 3.30 mmol). The reaction mixture was stirred for 2 h at rt. The resultant mixture was

then poured onto saturated aqueous NH_4Cl (50 mL) and extracted with ethyl acetate (3 x 50 mL). Purification of the resultant residue by silica gel chromatography (dichloromethane) gave hemiaminal **444b** (99 mg, 40%) and urea **445b** (65 mg, 27%) white solids. ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.9 Hz, 3 H), 1.45-1.65 (m, 1 H), 2.38 (s, 1 H), 2.38-2.47 (m, 2 H), 2.56-2.70 (m, 2 H), 3.08 (br s, 1 H), 3.49 (d, *J* = 9.1 Hz, 1 H), 3.55 (d, *J* = 9.1 Hz, 1 H), 4.19 (s, 3 H), 4.22 (d, *J* = 15.0 Hz, 1 H), 4.34 (d, *J* = 15.0 Hz, 1 H), 5.37 (s, 1 H), 5.49 (s, 1 H), 5.87 (s, 1 H), 6.91-7.38 (m, 7 H), 7.60 (d, *J* = 8.7 Hz, 1 H), 7.85 (d, *J* = 8.2 Hz, 2 H), 8.21 (s, 1 H), 8.50 (s, 1 H), 8.62 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 21.5, 29.5, 29.6, 33.3, 39.5, 46.8, 54.1, 55.2, 65.1, 116.0, 116.5, 119.0, 120.0, 125.0, 126.8, 127.2, 127.6, 127.7, 128.3, 129.1, 130.1, 134.5, 134.7, 135.4, 136.6, 143.5, 145.5, 146.0, 146.9, 147.3, 155.5, 161.8; IR (neat) 3260, 2930, 2861, 2248, 1696, 1598 cm^{-1}; HRMS calcd for $C_{36}H_{35}N_5O_4BrS$ 712.1593 found 712.1577.



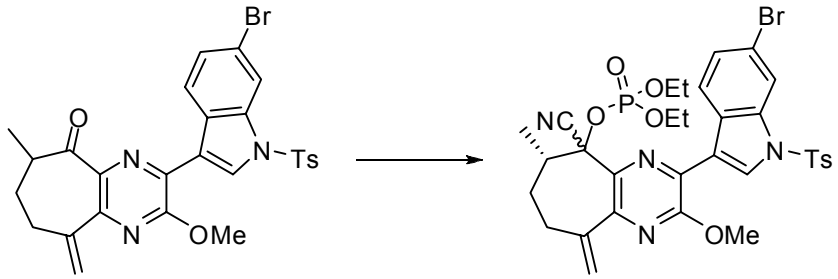
Acetate 456. To a solution of alcohol **405** (270 mg, 0.475 mmol) in pyridine (10.5 mL) was added acetic anhydride (550 μL, 5.82 mmol) and DMAP (135 mg, 1.11 mmol). The solution was then stirred at rt for 4 h. The resultant mixture was poured onto saturated aqueous NH_4Cl (200 mL), and extracted (3 x 100 mL) with ether. The combined organic layers were dried (Na_2SO_4) and

concentrated. Purification of the resultant residue by silica gel chromatography gave acetate **456** (235 mg, 81%) as a viscous colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.8 Hz, 3 H), 1.69-1.79 (m, 2 H), 1.90-2.02 (m, 1 H), 2.13 (s, 3 H), 2.37 (s, 3 H), 2.55-2.68 (m, 1 H), 2.71-2.81 (m, 1 H), 4.22 (s, 3 H), 5.41 (s, 1 H), 5.90 (d, *J* = 2.0 Hz, 1 H), 6.25 (d, *J* = 2.0 Hz, 1 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.51 (dd, *J* = 8.7 Hz, 1.7 Hz, 1 H), 7.83 (d, *J* = 8.3 Hz, 2 H), 8.21 (d, *J* = 1.7 Hz, 1 H), 8.80 (d, *J* = 8.7 Hz, 1 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 21.1, 21.5, 32.2, 32.6, 34.2, 53.8, 78.2, 116.0, 116.6, 118.8, 188.9, 125.5, 126.8, 127.4, 128.4, 128.8, 130.0, 134.7, 135.1, 135.5, 141.1, 145.4, 148.8, 146.3, 154.8, 170.2. IR (neat) 2948, 2873, 1738, 1597, 1546 cm^{-1}. HRMS (M + H^{+}) calcd for $C_{29}H_{28}N_3O_5SBr$ 610.1011 found 610.0999.



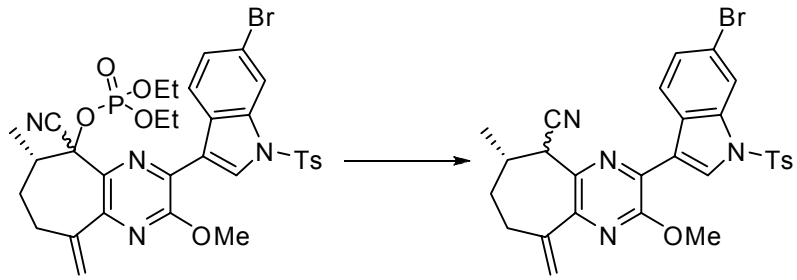
Acetate 457. To a solution of alcohol **425** (5.5 mg, 7.1 μmol) in pyridine (1.0 mL) was added acetic anhydride (100 μL, 1.06 mmol) and DMAP (20 mg, 0.16 mmol). The solution was then stirred at rt for 3 h. The resultant mixture was poured onto saturated aqueous NH_4Cl (10 mL), and extracted (3 x 10 mL) with ethyl acetate. The combined organic layers were then dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography gave acetate **457** (3.8 mg, 66%) as a yellow film. ^{1}H NMR (400 MHz, $CDCl_3$) δ

1.13 (d, *J* = 6.8 Hz, 3 H), 2.29 (s, 3 H), 2.39 (s, 3 H), 2.67 (s, 3 H), 3.58-3.67 (m, 1 H) 4.27 (s, 1 H), 5.23 (d, *J* = 11.2 Hz, 1 H), 5.28 (d, *J* = 11.2 Hz, 1 H), 6.21 (s, 1 H), 6.96 (d, *J* = 8.2 Hz, 1 H), 7.14 (d, *J* = 8.3 Hz, 1 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 7.32-7.60 (m, 6 H), 7.87 (d, *J* = 8.5 Hz, 2 H), 8.24 (d, *J* = 1.4 Hz, 1 H), 8.42 (s, 1 H), 8.50 (s, 1 H), 8.77 (d, *J* = 8.7 Hz, 1 H).



Cyanophosphates 458. To a solution of ketone **396** (500 mg, 0.882 mmol) in THF (10 mL) was added diethyl cyanophosphonate (234 μL, 1.50 mmol). LiCN[135] (49.4 mg, 1.50 mmol) was added in one portion, and the resultant solution stirred at rt for 15 min. The mixture was then poured onto $NaHCO_3$ (50 mL), and extracted (3 x 50 mL) with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated to give cyanophosphates **458** (442 mg, 69%) as an inseparable 1:3 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) *Major isomer* - δ 1.10-1.30 (m, 9 H), 1.72-1.83 (m, 1 H), 1.85-2.03 (m, 1 H), 2.39 (s, 1 H), 2.42-2.90 (m, 3 H), 3.95-4.16 (m, 4 H), 4.25 (s, 1 H), 5.46 (s, 1 H), 5.74 (s, 1 H), 7.30 (d, *J* = 8.3 Hz, 2 H), 7.54 (dd, *J* = 8.7, 1.7 Hz, 1 H), 7.84 (d, *J* = 8.3 Hz, 2 H), 8.20 (d, *J* = 1.7 Hz, 1 H), 8.57 (s, 1 H), 9.11 (d, *J* = 8.7 Hz, 1 H). *Minor isomer* δ 1.10-1.30 (m, 6 H), 1.51 (d, *J* = 6.8 Hz, 3 H), 1.72-1.83 (m, 1 H), 1.85-2.03 (m, 1 H), 2.39 (s, 1 H), 2.42-2.90 (m, 3 H), 3.95-4.16 (m, 4 H), 4.25 (s, 1 H), 5.45 (s, 1 H), 5.94 (s, 1 H), 7.30 (d, *J* = 8.3 Hz, 2 H), 7.53 (dd, *J* = 8.7, 1.7

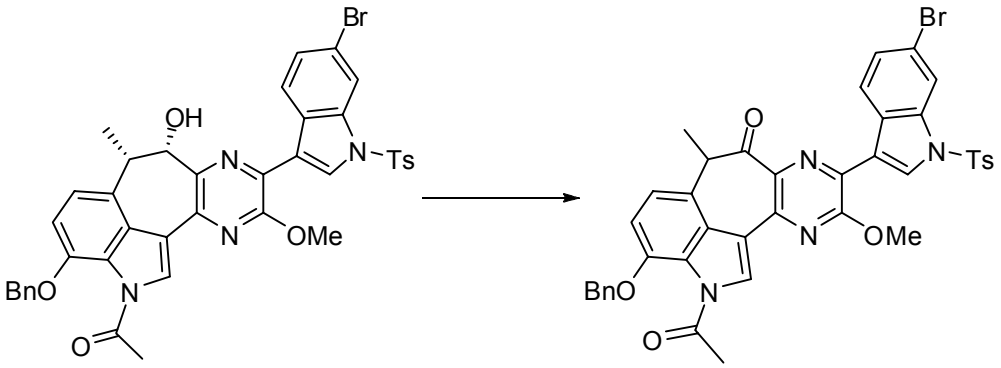
Hz, 1 H), 7.83 (d, *J* = 8.3 Hz, 2 H), 8.20 (d, *J* = 1.7 Hz, 1 H), 8.57 (s, 1 H), 9.18 (d, *J* = 8.7 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 16.2, 16.3, 16.3, 16.4, 22.0, 22.0, 30.1, 30.5, 40.1, 40.2, 40.6, 40.6, 54.8, 54.8, 64.9, 65.0, 86.1, 86.2, 116.4, 116.4, 119.0, 119.0, 119.6, 121.1, 126.4, 126.6, 127.3, 128.0, 128.1, 128.4, 130.0, 130.1, 130.6, 135.1, 135.9, 137.6, 137.6, 145.0, 145.9, 146.0, 147.6, 156.0, 156.3. IR (neat) 2983, 2946, 2245, 1598, 1545 cm^{-1}; HRMS (M + H$^+$) calcd for $C_{32}H_{34}N_4O_7PSBr$ 729.1147 found 729.1128.



Nitriles 421 and 430. *Preparation of* 0.1 M *SmI$_2$*: To a flask containing samarium powder (150 mg, 1.00 mmol) was added dropwise a solution of diiodomethane (67 μL, 0.833 mmol) in THF (8.33 mL). The resultant blue solution was stirred for 3 h at rt.

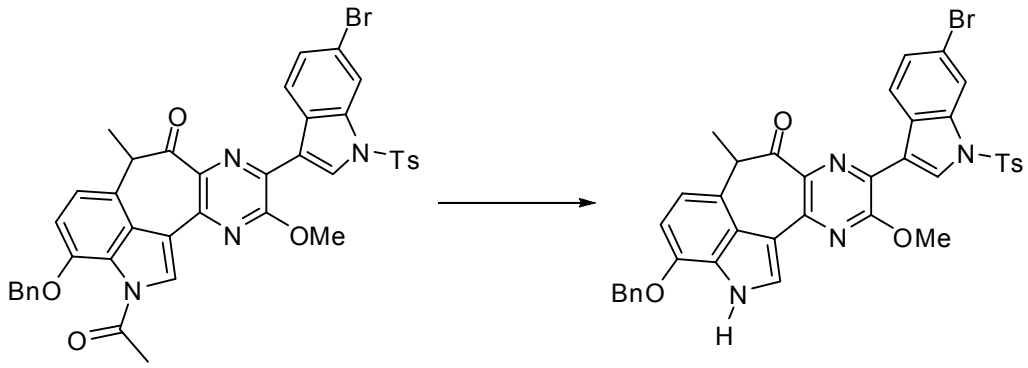
Reduction: To a flask containing a solution of cyanophosphate **458** (77 mg, 0.11 mmol) and 2-methyl-2-propanol (10 μL, 0.11 mmol) in THF (10 mL) was added SmI_2 (0.1 M in THF, 2.12 mL, 0.212 mmol). The solution was then stirred for 15 min, and additional SmI_2 (0.1 M in THF, 2.12 mmol, 0.212 mmol) was added. The solution was stirred for 15 min, poured onto saturated $NaHCO_3$, (40 mL) and extracted (3 x 40 mL) with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane, 1 : 4) gave nitriles **421** and **430**

(32 mg, 52%) as a 1:1 mixture of *cis* and *trans* epimers. *Trans epimer* **421** see pp.204. *Cis epimer* **430**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, *J* = 6.8 Hz, 3 H), 1.71-1.86 (m, 1 H), 2.01-2.11 (m, 1 H), 2.39 (s, 3 H), 2.54-2.72 (m, 1 H), 2.81 (ddd, *J* = 14.8, 9.0, 4.7 Hz, 1 H), 4.23 (s, 3 H), 4.33 (d, *J* = 2.7 Hz, 1 H), 5.46 (s, 1 H), 5.95 (s, 1 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.51 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.84 (d, *J* = 8.2 Hz, 2 H), 8.21 (d, *J* = 1.6 Hz, 1 H), 8.54 (s, 1 H), 8.74 (d, *J* = 8.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 21.6, 32.2, 33.5, 33.6, 43.6, 54.1, 116.0, 116.1, 118.6, 119.0, 119.7, 120.2, 125.2, 126.9, 127.5, 129.4, 130.1, 134.7, 135.5, 135.9, 137.3, 144.3, 145.6, 146.2, 155.3; IR (neat) 2947, 2250, 1597, 1547, 1455 cm^{-1}. HRMS (M + H^{+}) calcd for $C_{28}H_{26}N_4O_3SBr$ 577.0909 found 577.0919.



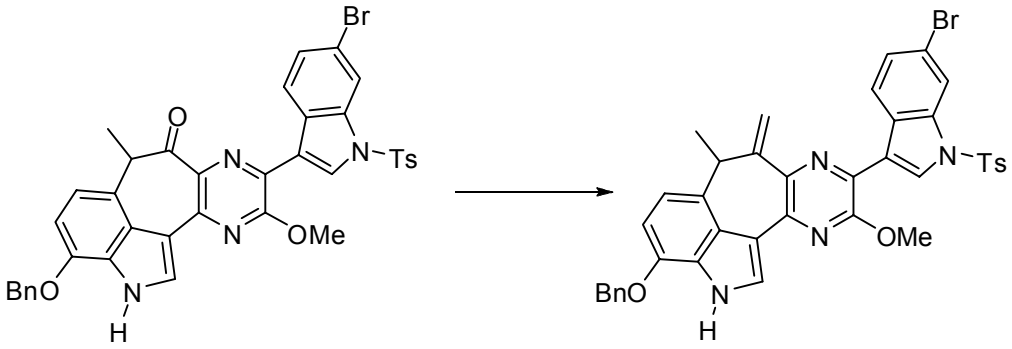
Ketone 462. To a solution of *N*-acetyl indole **420** (40 mg, 0.051 mmol) in dichloromethane (26 mL) at 0 ^{o}C was added Dess-Martin periodinane (80 mg, 0.19 mmol). The resultant solution was stirred for 1 h, then diluted with saturated NH_4Cl (25 mL) and $Na_2S_2O_3$ (20 mL). The resultant solution was extracted (x 3) with EtOAc (40 mL), dried (Na_2SO_4) and concentrated to give ketone **462** (40 mg, 100% crude) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, *J* = 7.1 Hz, 3 H), 2.38 (s, 3

H), 2.67 (s, 3 H), 4.34 (q, *J* = 7.2 Hz, 1 H), 4.36 (s, 3 H), 5.26 (s, 2 H), 7.04 (d, *J* = 8.2 Hz, 1 H), 7.21 (d, *J* = 8.2 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 7.38-7.53 (m, 6 H), 7.83 (d, *J* = 8.4 Hz, 2 H), 8.21 (d, *J* = 1.6 Hz, 1 H), 8.52 (s, 1 H), 8.54 (s, 1 H), 8.83 (d, *J* = 8.6 Hz, 1 H). MS calcd for $C_{40}H_{31}BrN_4O_6S$ 775/777 found 775/777.



Indole 463. To a solution of crude ketone **462** (40 mg, 0.051 mmol) in a 2:1 mixture of MeOH/THF (30 mL) was added K_2CO_3 (100 mg, 0.724 mmol). The solution was stirred for 6 min, then diluted with NH_4Cl (25 mL). The resultant mixture was extracted (x3) with EtOAc (25 mL), dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography gave indole **463** (26 mg, 69%) as a yellow film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, *J* = 7.1 Hz, 3 H), 2.37 (s, 3 H), 4.32 (s, 3 H), 4.34 (q, *J* = 7.2 Hz, 1 H), 5.24 (s, 2 H), 6.85 (d, *J* = 8.0 Hz, 1 H), 7.04 (d, *J* = 8.2 Hz, 1 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.38-7.54 (m, 6 H), 7.82 (d, *J* = 8.4 Hz, 2 H), 8.09 (d, *J* = 2.7 Hz, 1 H), 8.21 (d, *J* = 1.5 Hz, 1 H), 8.49 (s, 1 H), 8.84 (d, *J* = 8.6 Hz, 1 H), 8.97 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 21.5, 53.4, 54.1, 70.2, 105.1, 114.5, 116.0, 116.8, 118.9, 119.9, 123.1, 124.4, 125.8, 126.2, 126.8, 126.9, 127.2, 127.6, 128.2, 128.4, 128.6, 128.7, 130.0, 134.7, 134.9, 135.5, 136.5, 138.0, 141.8,

144.5, 145.5, 156.2, 198.6 IR (neat) 3322, 2925, 1683, 1545 cm^{-1}. HRMS (M + H^+) calcd for $C_{38}H_{30}N_4O_5SBr$ 733.1120 found 733.1097.



Indole 461. To a solution of *N*-H indole **463** (26 mg, 0.035 mmol) in THF (5 mL) at 0 °C was added pyridine (100 μL, 1.24 mmol), and Tebbe reagent (0.5 M in THF, 710 μL, 0.35 mmol). The resultant solution was stirred for 5 min, then diluted with saturated NH_4Cl (25 mL) and saturated Rochelle's salt (20 mL). The resultant solution was extracted (x 3) with EtOAc (25 mL), dried (Na_2SO_4) and concentrated. Purification of the resultant residue by silica gel chromatography (ethyl acetate-hexane 1 : 3) gave olefin **461** (25 mg, 96%) as a yellow film. ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, *J* = 7.1 Hz, 3 H), 2.37 (s, 3 H), 4.19 (q, *J* = 7.1 Hz, 1 H), 4.28 (s, 3 H), 5.24 (s, 2 H), 5.45 (d, *J* = 1.7 Hz, 1 H), 5.58 (d, *J* = 1.7 Hz, 1 H), 6.77 (d, *J* = 7.8 Hz, 1 H), 6.98 (d, *J* = 7.8 Hz, 1 H), 7.28 (d, *J* = 8.3 Hz, 2 H), 7.37-7.52 (m, 6 H), 7.85 (d, *J* = 8.3 Hz, 2 H), 8.02 (d, *J* = 2.6 Hz, 1 H), 8.24 (d, *J* = 1.5 Hz, 1 H), 8.50 (s, 1 H), 8.82 (d, *J* = 8.6 Hz, 1 H), 8.83 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 22.9, 46.7, 53.7, 70.5, 104.1, 116.1, 117.3, 117.8, 118.0, 118.7, 123.5, 125.2, 125.5, 126.9, 127.2, 127.3, 127.9, 128.1, 128.2, 128.6, 128.7, 129.6, 130.1, 132.0, 133.8, 134.9, 135.7, 136.9, 140.3, 141.0,

144.0, 145.3, 150.1, 155.4; IR (neat) 3418, 2923, 2854, 1539, 1520 cm^{-1}; HRMS ($M + H^+$) calcd for $C_{39}H_{31}N_4O_4SBr$ 731.1328 found 731.1320.

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