CHAPTER THREE

The Total Syntheses of (+)- and (–)-Dragmacidin F[†]

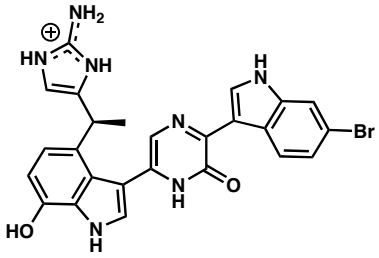
3.1 Background

3.1.1 Introduction

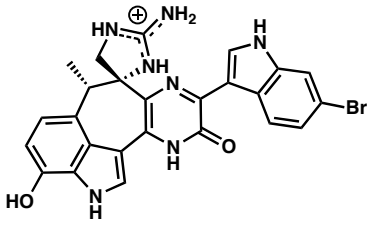
Over the past several decades, the search for natural products in marine environments has led to the discovery of a number of biologically active bis(indole) alkaloids.[1] These compounds, as well as their unnatural analogs, have shown promise as leads for the development of novel therapeutics, particularly in the area of cancer.[2] Of the many bis(indole) alkaloids found in nature, the dragmacidins have received considerable attention from the scientific community over the past decade due to their broad range of biological activity and complex structures.[3,4,5] This structurally elaborate class of bromoindole marine alkaloids was isolated from a variety of deep-water sponges including *Dragmacidon*, *Halicortex*, *Spongosorites*, and *Hexadella,* and the tunicate *Didemnum candidum.* As part of a research program geared toward the synthesis of complex heterocyclic natural products, our laboratory initiated an effort in the fall of 2000 to synthesize those dragmacidins that possess a pyrazinone core, namely, dragmacidins D, E, and F (Figure 3.1.1, **82**–**84**).[4]

[†] This work was performed in collaboration with Neil K. Garg, a graduate student in the Stoltz group (Ph.D. 2005).

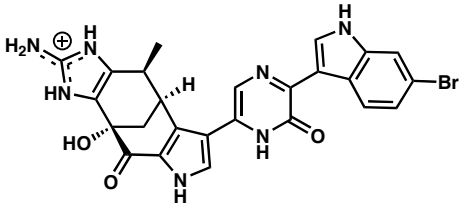
Figure 3.1.1



Dragmacidin D (82)



Dragmacidin E (83)

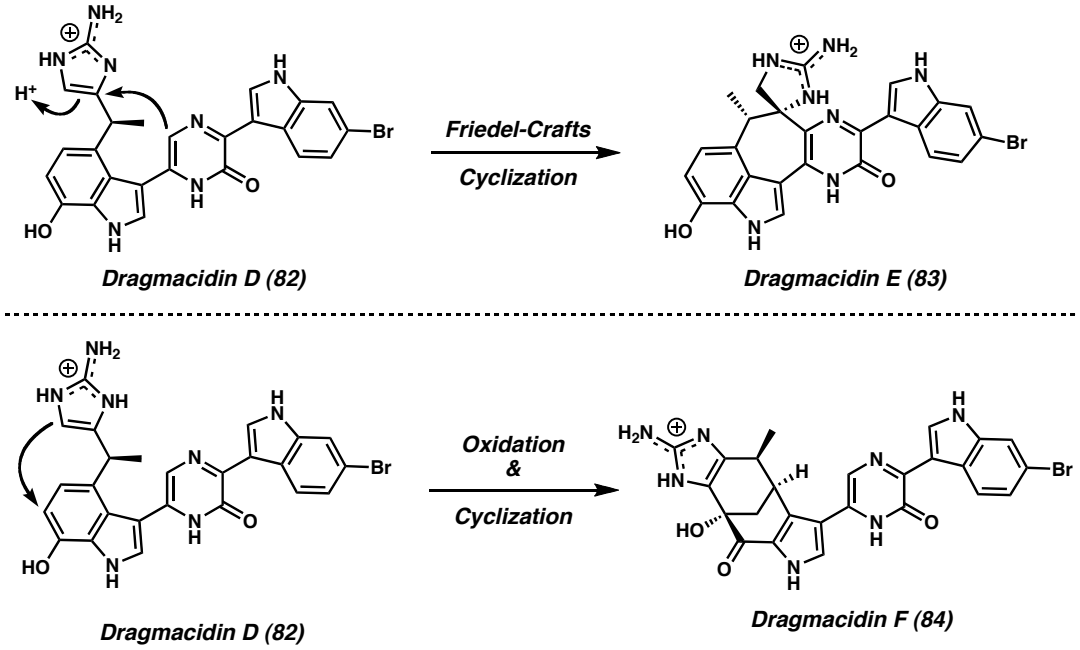


Dragmacidin F (84)

3.1.2 Biosynthesis

Dragmacidin D (**82**),[4a,b] was selected as a primary target predominantly because it was believed to be the biosynthetic precursor to dragmacidins E (**83**) and F (**84**).[4c] (Scheme 3.1.1). Dragmacidins D (**82**) and E (**83**) are related via a Friedel-Crafts cyclization between the pyrazinone and aminoimidazole groups of dragmacidin D, which occurs in order to construct the seven-membered ring of dragmacidin E (i.e., **82** → **83**). Although **84** does not contain a bis(indole) framework, it is presumed to be derived biosynthetically from dragmacidin D (**82**) via an oxidative de-aromatization/cyclization process (i.e., **82** → **84**). Related oxidation pathways for tryptophan derivatives have been observed in nature.[6] Furthermore, dragmacidin D (**82**) seemed to be the least structurally complex of the pyrazinone-containing dragmacidin family members, and therefore a suitable entry point into this class.

Scheme 3.1.1

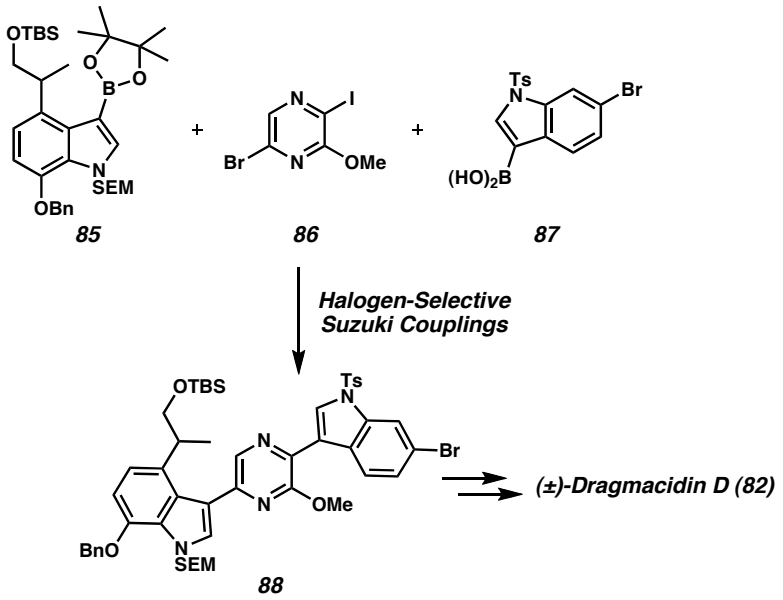


3.1.3 Previous Synthetic Studies

In 2002, our laboratory reported the total synthesis of (±)-dragmacidin D (**82**), the first of any of these three unique dragmacidin alkaloids to be prepared.[7] The highly convergent approach to **82** relied on a series of halogen-selective Suzuki cross-couplings of **85**, **86**, and **87** to build the bis(indole)pyrazine skeleton (**88**) of the natural product (Scheme 3.1.2). In addition, the appropriate selection and cleavage sequence of protecting groups proved to be of critical importance, as only highly specific arrangements permitted successful late-stage manipulations. We hypothesized that this general synthetic strategy could also be applied to the other pyrazinone-containing members of the dragmacidin family. Having developed a strategy to construct the bis(indole)pyrazinone core of dragmacidin D (**82**), we set out to extend the scope of our halogen-selective Suzuki coupling methodology to the synthesis of related natural

products. We reasoned that our approach could be amenable to the preparation of the antiviral agent dragmacidin F (**84**),[4c] which is perhaps the most daunting target of the dragmacidin natural products.[8,9]

Scheme 3.1.2



3.1.4 Isolation and Bioactivity of Dragmacidin F

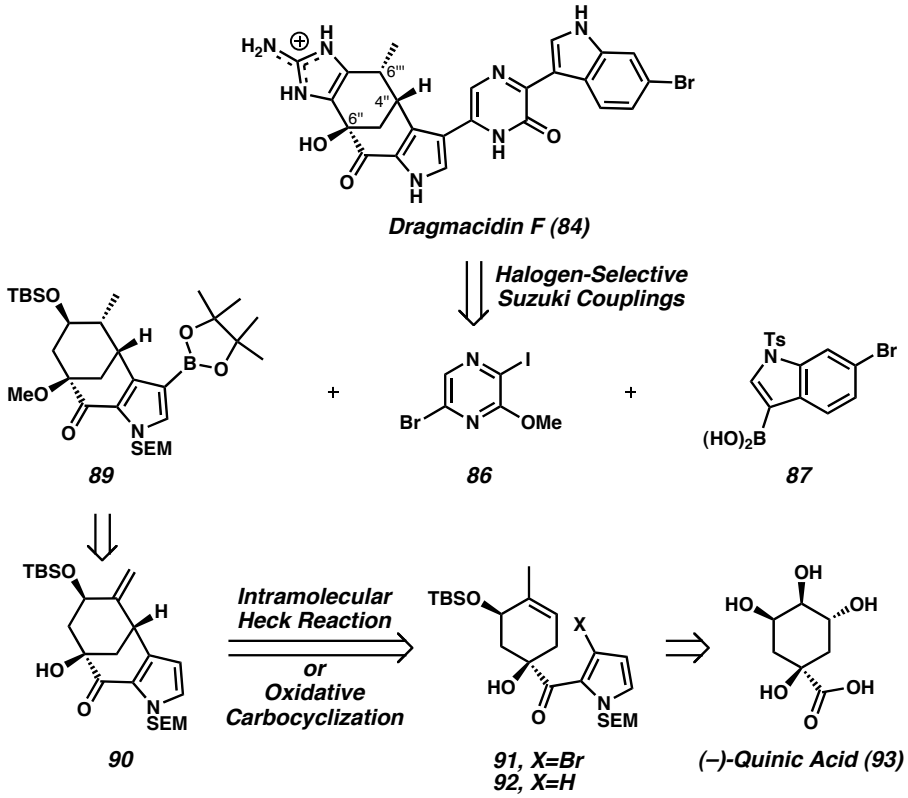
Dragmacidin F (**84**) was isolated in 2000 from the ethanol extracts of the Mediterranean sponge *Halicortex* sp. This marine natural product exhibits in vitro antiviral activity against herpes simplex virus (HSV-I; EC_{50} = 95.8 μM) and human immunodeficiency virus (HIV-I; EC_{50} = 0.91 μM),[4c] and thus is an attractive target from a biological perspective. In addition, dragmacidin F (**84**) possesses a variety of structural features that make it an attractive target for total synthesis. These synthetic challenges include the differentially substituted pyrazinone, the bridged [3.3.1] bicyclic ring system, which is fused to both the trisubstituted pyrrole and aminoimidazole heterocycles, and the

installation and maintenance of the 6-bromoindole fragment. Given the limited supply of dragmacidin F (**84**) available from natural sources, a successful synthetic approach to **84** could also facilitate the production of sufficient quantities of material needed for advanced biological studies.

3.1.5 Retrosynthetic Analysis of Dragmacidin F

Our retrosynthetic analysis for dragmacidin F (**84**) is shown in Scheme 3.1.3. On the basis of our experience with dragmacidin D (**82**), we reasoned that the aminoimidazole moiety would best be incorporated at a late stage in the synthesis.[7] The carbon skeleton of the natural product would then arise via a series of halogen-selective Suzuki cross-coupling reactions (**89** + **86** + **87**). Pyrazine **86** and indoloboronic acid **87** were both readily accessible,[7] while pyrroloboronic ester **89** perhaps could be derived from pyrrole-fused bicycle **90**, our key retrosynthetic intermediate. We then targeted bicycle **90** from two related directions: a Pd(0)-mediated intramolecular Heck reaction[10] of bromopyrrole **91**, and a Pd(II)-promoted oxidative carbocyclization[11] involving *des*-bromopyrrole **92**. The successful implementation of the latter method was particularly attractive since it is closely aligned with our interest in Pd(II)-catalyzed dehydrogenation reactions.[12] Both of the cyclization substrates (**91** and **92**) could be prepared from commercially available (–)-quinic acid (**93**).[13] At the time of this synthetic effort, the absolute stereochemistry of natural dragmacidin F (**84**) was not known; thus, the absolute stereochemistry of our target (**84**) was chosen arbitrarily.

Scheme 3.1.3



3.2 The Total Synthesis of (+)-Dragmacidin F

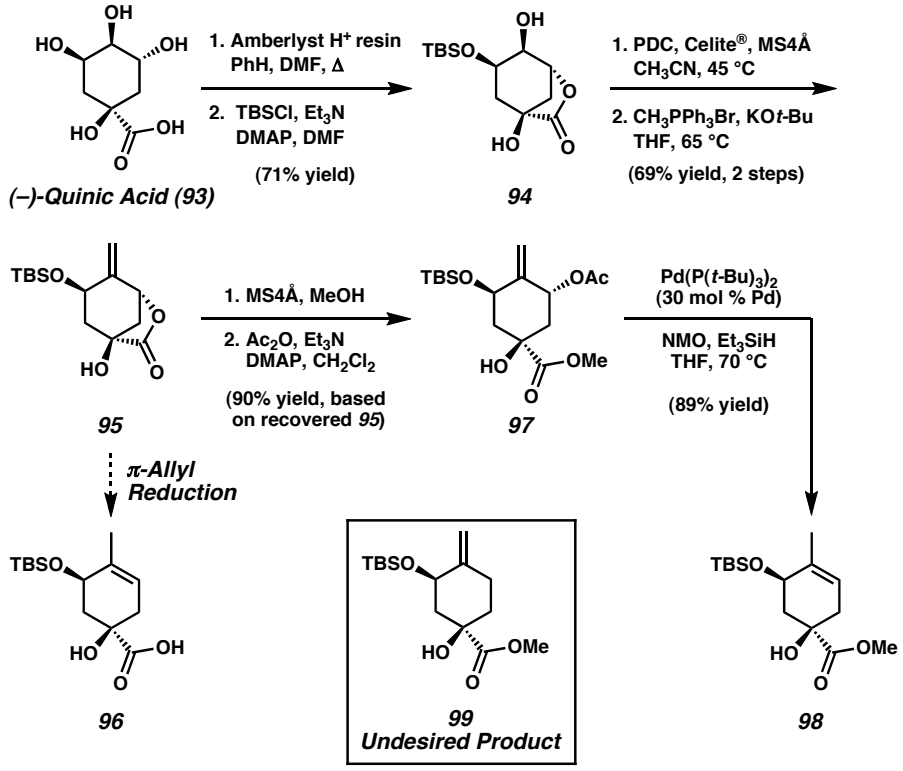
3.2.1 Synthesis of Cyclization Substrates

Our synthesis of dragmacidin F (**84**) began with a known two-step protocol involving lactonization and silylation of (–)-quinic acid (**93**) to afford bicyclic lactone **94** (Scheme 3.2.1).[14] Subsequent oxidation and Wittig olefination of **94** produced exo-methylene lactone **95** in good yield. Initially, we envisioned the direct conversion of lactone **95** to unsaturated carboxylic acid **96** by executing a homogeneous Pd(0)-catalyzed π-allyl hydride addition reaction.[15] Despite considerable experimentation, however, exposure of lactone **95** to a variety of Pd and hydride sources under standard conditions[15] led to the formation of complex product mixtures. As a result, a more

stepwise approach was tried. Methanolysis of lactone **95** followed by acetylation of the resulting 2° alcohol[16] gave rise to allylic acetate **97**, another potential substrate for π-allyl reduction chemistry. Although **97** did react under most literature protocols, undesired exocyclic olefin **99** was typically the major product observed, and **98** could not be isolated by conventional purification techniques. This was not an altogether unexpected outcome; in fact, overcoming the practical problem of regioselectivity (e.g., **98** vs. **99**) in nucleophilic addition to π-allylpalladium complexes has been the subject of intense study.[17]

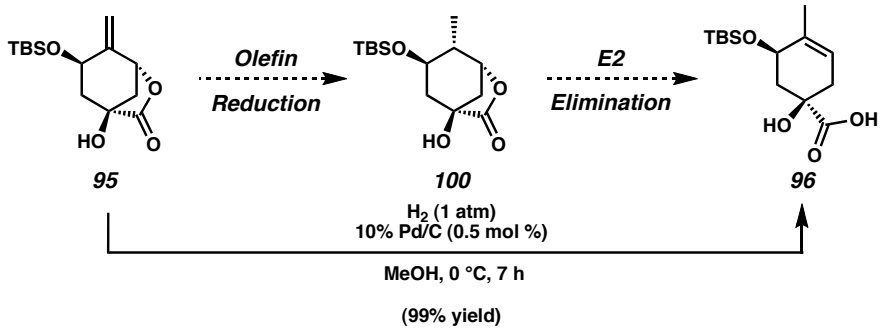
After substantial optimization, we were able to access **98** as the major product by employing stoichiometric $Pd(P(t\text{-}Bu)_3)_2$[18] in the presence of triethylsilane as a reductant. Further refinements designed to facilitate catalysis led to a reduced Pd loading (30 mol %) when *N*-methylmorpholine-*N*-oxide (NMO) was used as an additive.[19] Under these conditions, cyclohexene **98** was obtained in 89% yield as a single olefin regioisomer. Unfortunately, this transformation often gave inconsistent results and was particularly sensitive to oxygen, water, and the quality of Et_3SiH. These difficulties coupled with the high catalyst loading resulted in substantial material throughput problems. We therefore sought yet another method to prepare cyclohexene **98**, or a closely related derivative thereof (i.e., **96**), in a more facile and preparative manner.

Scheme 3.2.1



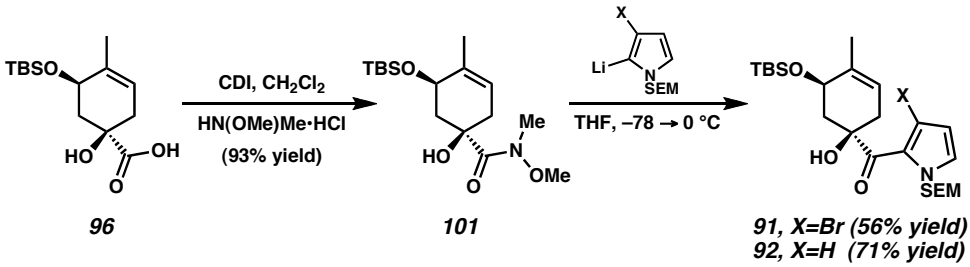
In our revised plan, we conceived a two-step route to obtain carboxylic acid **96** via diastereoselective reduction of olefin **95** followed by base-promoted elimination of the carboxylate functionality of **100** (Scheme 3.2.2). The first part of this sequence was attempted by exposing olefin **95** to standard catalytic hydrogenation conditions (Pd/C, 1 atm H_2). Surprisingly, these conditions led to the production of a compound that was more polar than we expected for simple olefin hydrogenation (i.e., **100**). To our delight, the product was identified as unsaturated carboxylic acid **96**. Under our optimized reaction conditions (0.5 mol % Pd/C, 1 atm H_2, MeOH, 0 °C), essentially quantitative reductive isomerization to **96** was observed.[20,21]

Scheme 3.2.2



With facile access to cyclohexene carboxylic acid **96**, preparation of the key cyclization precursors proceeded without difficulty. Activation of acid **96** with CDI followed by the addition of HN(OMe)Me•HCl afforded Weinreb amide **101** (Scheme 3.2.3). The Weinreb amide functionality was then displaced with the appropriate lithiopyrrole[22] reagent to produce Heck cyclization substrate **91**[23] and oxidative cyclization substrate **92**.

Scheme 3.2.3

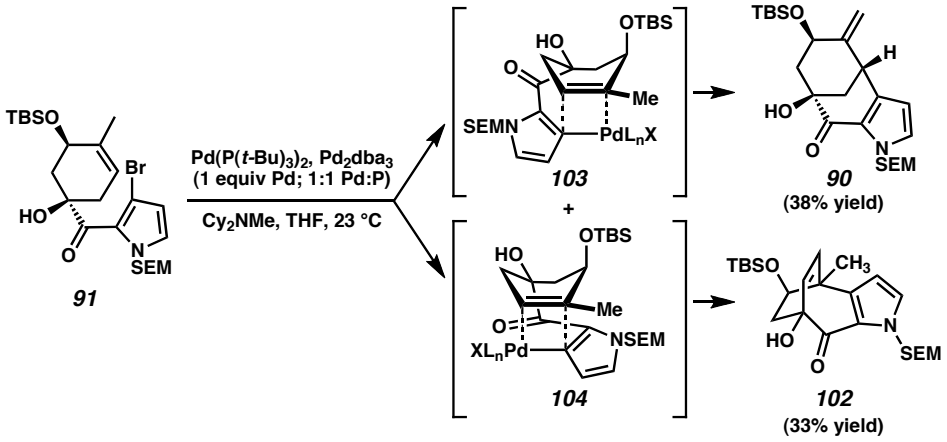


3.2.2 Intramolecular Heck Cyclization

With the pyrrole-fused cyclohexene substrates in hand, Neil Garg carried out extensive studies in order to achieve the intramolecular Heck cyclization of bromopyrrole

91. Attempts to utilize standard procedures were unsuccessful,[10] likely due to the thermal instability of the bromopyrrole moiety. However, implementation of the room-temperature conditions developed by Fu[24] provided the desired [3.3.1] bicyclic product (**90**), albeit in low yield (Scheme 3.2.4). Unfortunately, the formation of **90** was hampered by competitive production of [3.2.2] bicycle **102**. Although efforts to optimize temperature, solvent, base, and concentration were not met with success, it was found that increased quantities of Pd improved the ratio of the desired [3.3.1] bicycle (**90**) to the undesired [3.2.2] bicycle (**102**). In addition, the ratio of **90** to **102** decreased over time,[25] suggesting that the active catalytic species varied during the course of the reaction or that selectivity changed as the concentration of $R_3NH^+Br^-$ increased.

Scheme 3.2.4

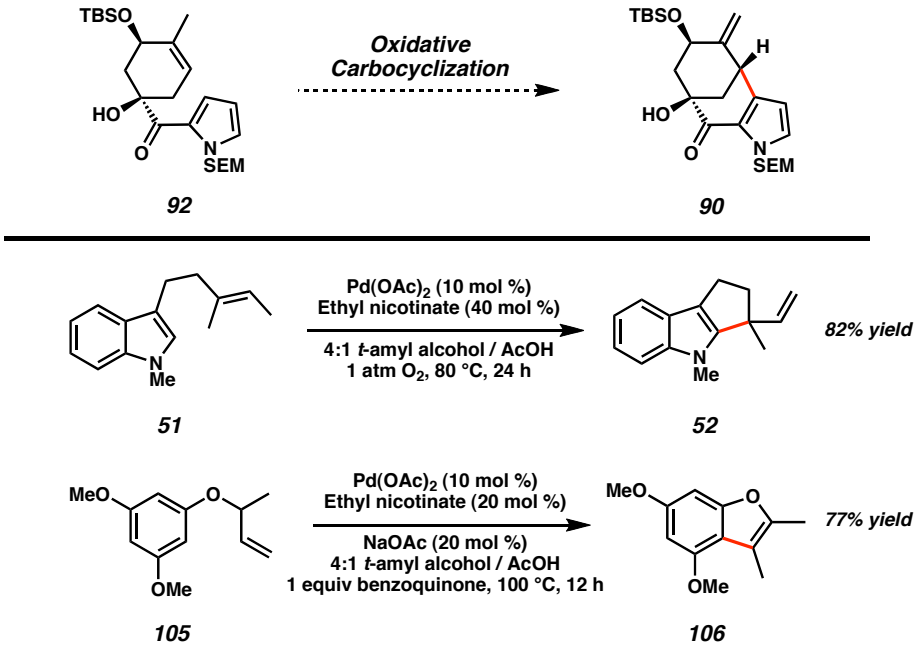


3.2.3 Intramolecular Oxidative Cyclization

Although the Heck reaction was useful for preparing reasonable quantities of bicycle **90**, an alternative and potentially more selective route to **90** was desired. In conjunction with ongoing research in our group,[12] we turned to the Pd(II)-mediated C–C

bond forming approach. In this scenario, C(3)-unsubstituted pyrrole **92** would undergo intramolecular carbocyclization to afford **90** (Scheme 3.2.5). Previously in our laboratories, indoles (e.g., **51**) and electron-rich aryl ethers (e.g., **105**) had been shown to be competent cyclization substrates. However, pyrrole heterocycles had never been tested in this regard, especially not to form bridged bicycles.

Scheme 3.2.5

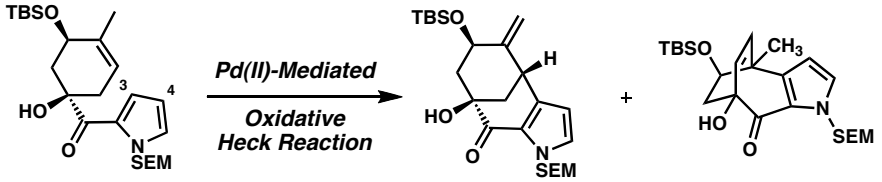


As a starting point, stoichiometric Pd(II) was employed for the oxidative cyclization reaction to eliminate the need for a co-oxidant, which could complicate preliminary studies. Catalytic methods could, in theory, be devised once these stoichiometric conditions were optimized. Protocols reported by our group were initially tried, however, these conditions did not afford any of desired bicycle **90** (Table 3.2.1, entry 1). Indeed, initial experimentation revealed that neither pyridine, ethyl nicotinate,

nor triphenylphosphine were effective ligands for promoting cyclization in the presence of $Pd(OAc)_2$.[12c,d]

Although these initial conditions failed, a control experiment omitting the ligand did produce a trace amount of desired bicycle **90** (entry 2). Interestingly, a number of byproducts were also discovered in the reaction pot of entry 2, which appeared to be caused by *t*-amyl alcohol incorporation into the starting material and product.[26] Thus, substituting *t*-butyl alcohol for *t*-amyl alcohol as solvent (entry 3) and conducting the reaction under an atmosphere of dioxygen led to the consumption of all starting material and production of desired bicycle **90** as the major product by crude ^{1}H NMR in 15% isolated yield.[27]

Table 3.2.1



92 ***90*** ***102***

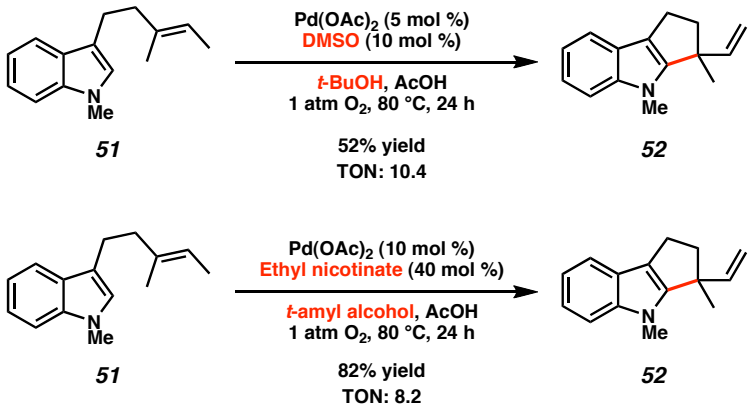
entry	conditions	result	
1	$Pd(OAc)_2$ (stoichiometric or cat w/ O_2) ethyl nicotinate, pyridine or PPh_3 *t*-amyl OH, AcOH, 80 °C	no reaction, starting material recovered	
2	$Pd(OAc)_2$ (1 equiv) *t*-amyl OH, AcOH, 80 °C	***90*** *trace*	***102*** *not observed*
3	$Pd(OAc)_2$ (1 equiv) *t*-BuOH, AcOH, 80 °C, O_2	***90*** 15% yield	***102*** *not observed*
4	$Pd(OAc)_2$ (stoichiometric or cat w/ O_2) ethyl nicotinate, pyridine or PPh_3 *t*-BuOH, AcOH, 80 °C	no reaction, starting material recovered	
5	$Pd(OAc)_2$ (1 equiv), DMSO *t*-BuOH, AcOH, 80 °C, 2 h	***90*** 56% yield	***102*** *not observed*
6	$Pd(OAc)_2$ (1 equiv), DMSO dioxane, AcOH, 80 °C, 7.5 h	***90*** 41% yield	***102*** *not observed*
7	$Pd(OAc)_2$ (1 equiv), DMSO *t*-BuOH, AcOH, 60 °C, 10 h	***90*** 74% yield	***102*** *not observed*

Upon learning that the use of *t*-amyl alcohol was deleterious to this cyclization, both pyridine and phosphine-based ligands were reinvestigated with *t*-butanol (entry 4). Unfortunately, however, the desired transformation was rendered inactive under these conditions. On the basis of these results, we hypothesized that an ideal ligand would be sufficient to stabilize the palladium complex without being overly coordinating as to halt the reactivity in the cyclization.[28] Thus, a focused investigation of possible ligands was undertaken. A marked improvement was realized when DMSO was employed;[29] the desired cyclization product could be obtained in 56% yield (entry 5). Dioxane was also competent as a *t*-butanol substitute, though a diminished yield of product was obtained (entry 6). Subsequent optimization of temperature, solvent, and reaction time led to an ideal set of conditions whereby the desired [3.3.1] bicycle (**90**) was isolated as the sole product in 74% yield (entry 7). This transformation is particularly noteworthy since it results in functionalization of the electronically deactivated and sterically congested C(3) position of acyl pyrrole **92**.[30,31] Importantly, the undesired [3.2.2] bicycle (**102**) seen as a byproduct in the classical Heck reaction has never been observed as a product of the oxidative Heck cyclization of substrate **92**.

Despite considerable experimentation, we were unable to render the conversion of acyl pyrrole **92** to bicycle **90** catalytic in Pd in the presence of a stoichiometric oxidant (e.g., O_2 or benzoquinone). This difficulty has been attributed to the extreme sensitivity of both the starting material and desired product to oxidative decomposition.[32,33] This hypothesis is corroborated by related catalytic pyrrole cyclizations that were described after the report of this work, [34] as well as an unoptimized study that we conducted in the conversion of **51** → **52** (Scheme 3.2.6). Applying our DMSO-based conditions in the

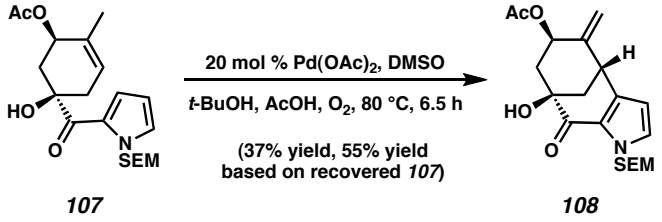
same cyclization yields a similar turnover number (10.4) to the one initially reported (8.2).[12c] These collective results suggest that palladium is capable of reoxidation under these conditions, and thus in principle, is also able to function in a catalytic manner.

Scheme 3.2.6



Notably, we have observed some catalysis in the cyclization of a closely related substrate, acetate **107** (Scheme 3.2.7). In this case, oxidative Heck cyclization using 20 mol % $Pd(OAc)_2$, under 1 atm of O_2, afforded [3.3.1] bicycle **108** in 37% yield (55% based on recovered **107**). As isolated yields and catalyst turnover for this process were low, and bicycle **108** was not directly useful for our total synthesis goals, we elected to utilize the stoichiometric Pd-mediated oxidative Heck reaction (**92** → **90**) as a means to advance material en route to dragmacidin F.

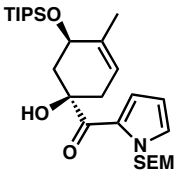
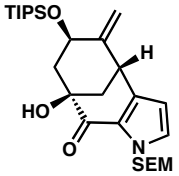
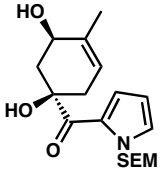
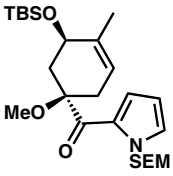
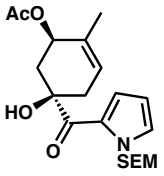
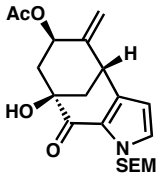
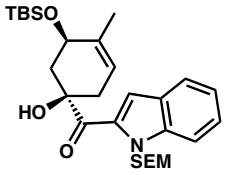
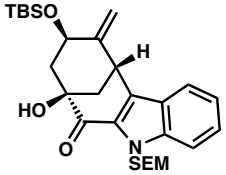
Scheme 3.2.7



107 ***108***

We also explored the Pd(II)-mediated carbocyclization of a number of substrates related to TBS ether **92** (Table 3.2.2, entry 1). For instance, the TIPS ether analog (entry 2) underwent cyclization, albeit in lower yield with respect to the parent TBS compound. However, if the 2° alcohol was left unprotected altogether (entry 3)[35] or the substrate possessed a 3° methyl ether (entry 4)[36], formation of the desired bicyclic products was not observed. Interestingly, the acetate derivative readily participated in the cyclization reaction (entry 5). As previously described, exposure of the acetate substrate to catalytic conditions (20 mol % Pd, 1 atm O_2) also led to the formation of the desired product, although in modest yield with a TON of 1.9 (entry 6). It was also possible to annulate C(3) of related indole substrates under our standard conditions (entry 7).

Table 3.2.2[a]

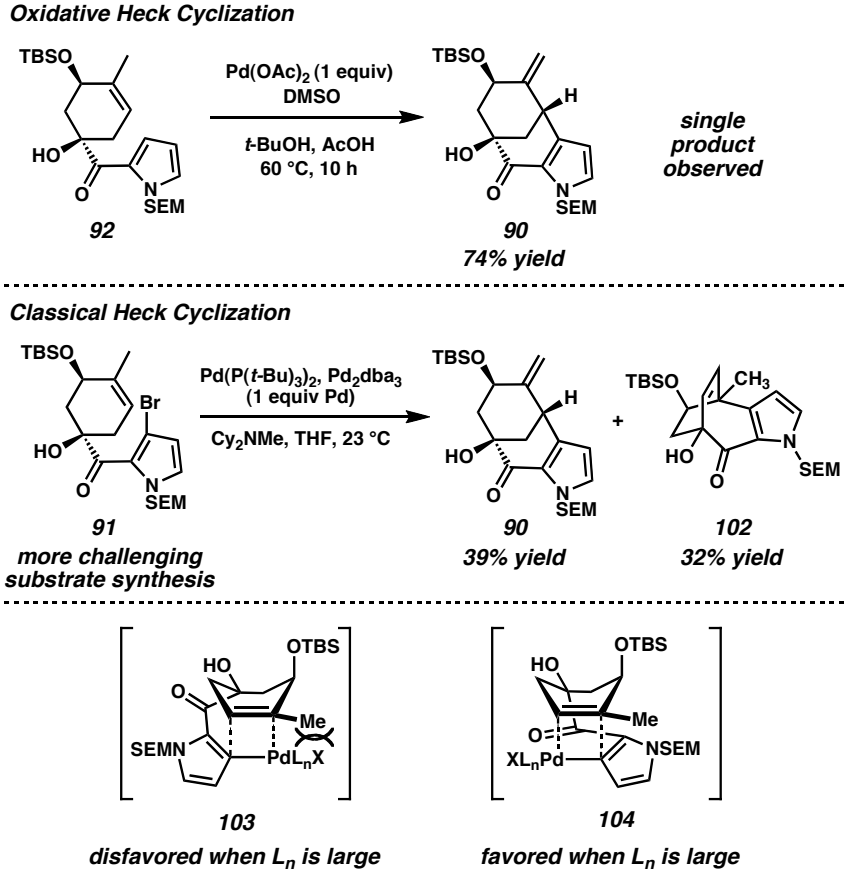
entry	substrate	product	temp (°C)	time	yield[b]
1	 ***92***	 ***90***	60	10 h	74%
2	 ***109***	 ***110***	60	13.5 h	51% (63%)
3	 ***111***	—	80	*complex mixture*	
4	 ***112***	—	80	*no reaction*	
5	 ***107***	 ***108***	80	1.8 h	53% (66%)
6			80[c]	6.5 h	37% (55%)
7	 ***113***	 ***114***	80	2.5 h	49%

[a] Standard Conditions: 1 equiv $Pd(OAc)_2$, 2 equiv DMSO, *t*-BuOH:AcOH (4:1, 0.01 M). [b] Isolated Yield. Number in parentheses represents the yield based on recovered starting material. [c] 20 mol % $Pd(OAc)_2$, 40 mol % DMSO, *t*-BuOH:AcOH (4:1, 0.01 M), O_2 (1 atm)

In the context of our total synthesis objective, the oxidative Heck reaction strategy is advantageous compared to the classical Heck route for preparing [3.3.1] bicycle **90** on

the basis of several factors (Scheme 3.2.8): a) the oxidative Heck approach does not require the synthesis of a halogenated starting material (i.e., **91**), which can sometimes be significantly challenging;[23,37] b) using identical palladium loadings, the oxidative Heck cyclization provides bicycle **90** in nearly twice the chemical yield as the classical Heck reaction; c) the oxidative Heck reaction furnishes bicycle **90** as a single product, whereas the classical Heck reaction requires a more tedious chromatographic separation of the undesired [3.2.2] bicycle (**102**). Although more detailed mechanistic studies are pending, we partially attribute the differences in product distribution between the two strategies to the effects of ligands. More specifically, the use of bulky P(*t*-Bu)$_3$ ligands in the classical Heck cyclization could favor olefin insertion transition state **104** over **103**, as it would place the large PdL_nX away from the more substituted position of the olefin undergoing insertion.

Scheme 3.2.8

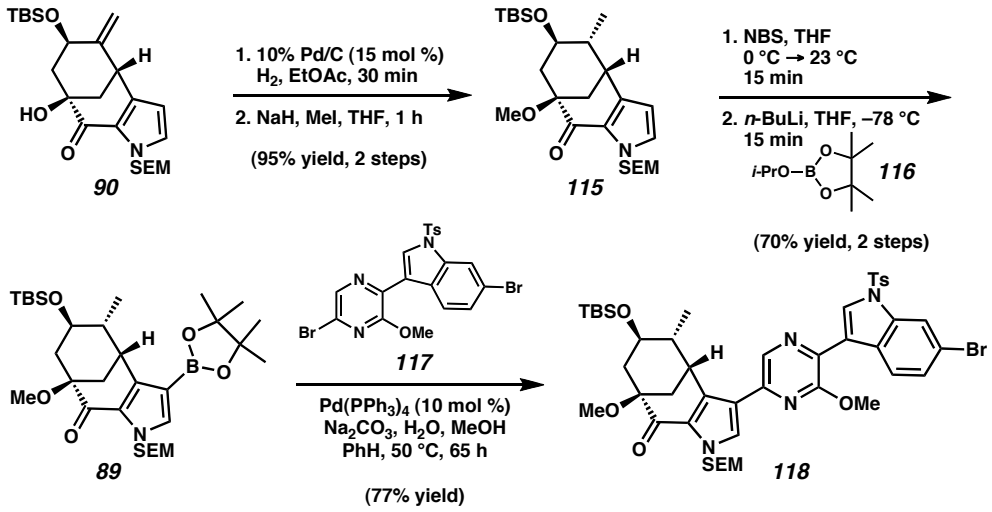


3.2.4 Assembling the Carbon Skeleton of Dragmacidin F

With the [3.3.1] bicyclic framework in hand (i.e., **90**), we focused our attention on constructing the full carbon skeleton of dragmacidin F (**118**, Scheme 3.2.9). The final stereocenter present in the natural product was installed via catalytic hydrogenation of olefin **90**, and was followed by methylation of the 3° alcohol to produce bis(ether) **115**. The methyl protecting group was selected initially for its robustness[16] and would presumably allow for the exploration of late-stage chemistry in the form of a model system.[38] Methyl ether **115** was then elaborated via regioselective bromination of the pyrrole and metalation to boronic ester **89**. In the critical halogen-selective Suzuki

fragment coupling, pyrroloboronic ester **89** was reacted with dibromide **117** (prepared from **86** + **87**)[7] under Pd(0) catalysis. By analogy to our dragmacidin D studies,[7] we were pleased to find that at 50 °C, the desired C–C bond forming reaction took place to afford the fully coupled product (**118**) in 77% yield. Importantly, the indolylbromide moiety was maintained under these reaction conditions.

Scheme 3.2.9

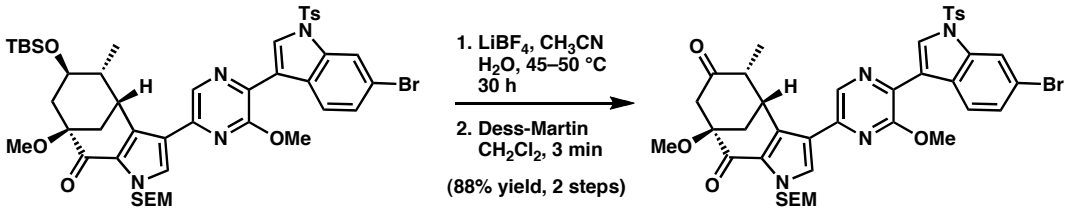


3.2.5 End-Game: Total Synthesis of (+)-Dragmacidin F

With the carbon framework completed, few tasks remained in order to finish the total synthesis of dragmacidin F (**84**), namely, removal of all protecting groups and installation of the aminoimidazole unit. Of particular note is the similarity of these synthetic challenges to those encountered in our total synthesis of dragmacidin D (**82**).[7] Not surprisingly, we decided to utilize the methods that were already familiar to us in order to elaborate **118** to the desired natural product (**84**). To this end, we anticipated that the presence of an amino group α to the ketone would allow for eventual introduction of

the aminoimidazole moiety. Therefore, selective cleavage of silyl ether **118**, followed by oxidation with Dess-Martin periodinane, produced ketone **119** (Scheme 3.2.10).

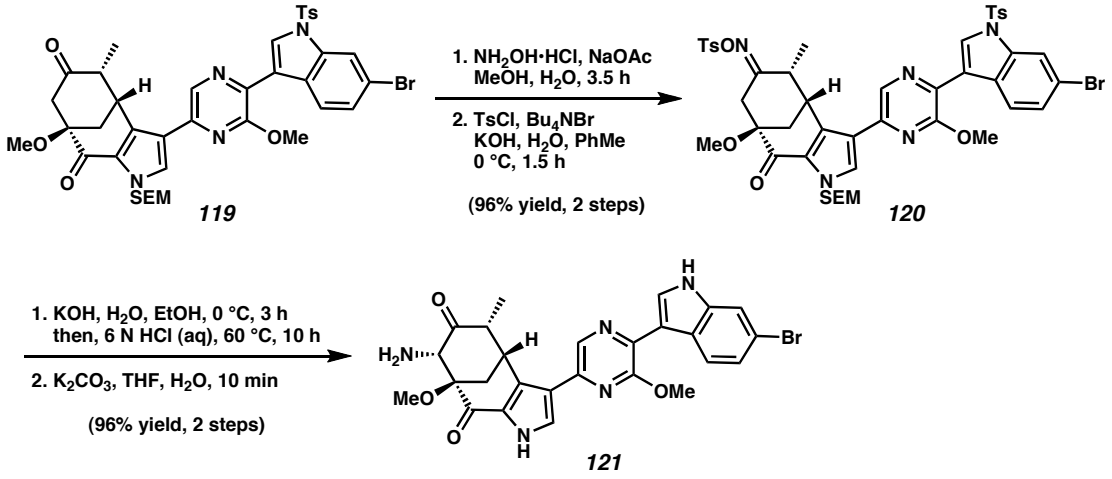
Scheme 3.2.10



118 ***119***

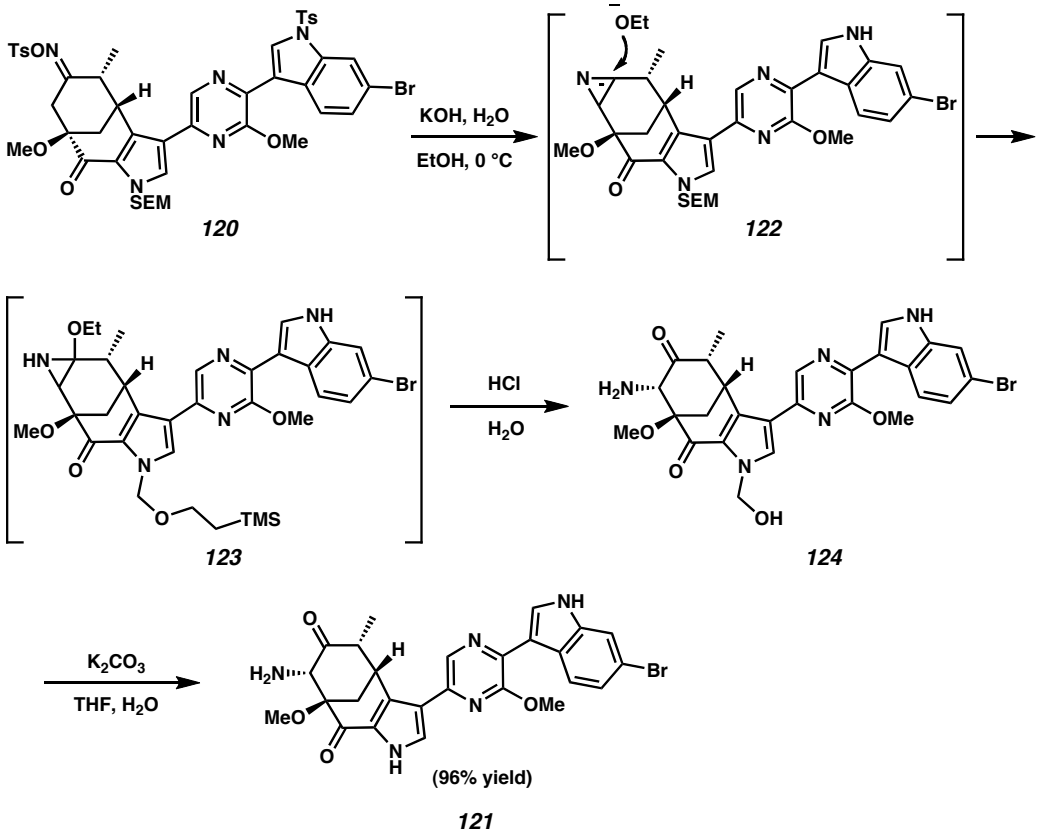
Although attempts to introduce the necessary α-amino group failed under numerous literature protocols,[8b] Neil Garg skillfully managed the installation of this substituent using a Neber rearrangement.[39,40] In this scenario, an activated oxime derivative would undergo alkoxide-promoted rearrangement to furnish an α-amino ketone. Thus, ketone **119** was converted to tosyloxime **120** via standard conditions (Scheme 3.2.11). Gratifyingly, exposure of substrate **120** to aqueous KOH in ethanol led to Neber rearrangement. After optimization, we found that simply exposing tosyloxime **120** to i) KOH, ii) HCl, and iii) K_2CO_3 produced α-amino ketone **121** as a single regio- and stereochemical isomer in excellent yield.[41,42,43] Furthermore, under these reaction conditions, both the tosyl and SEM protective groups were quantitatively removed from their corresponding heterocycles. To the best of our knowledge, this is the first example of a successful Neber rearrangement in the context of natural product synthesis.[44]

Scheme 3.2.11



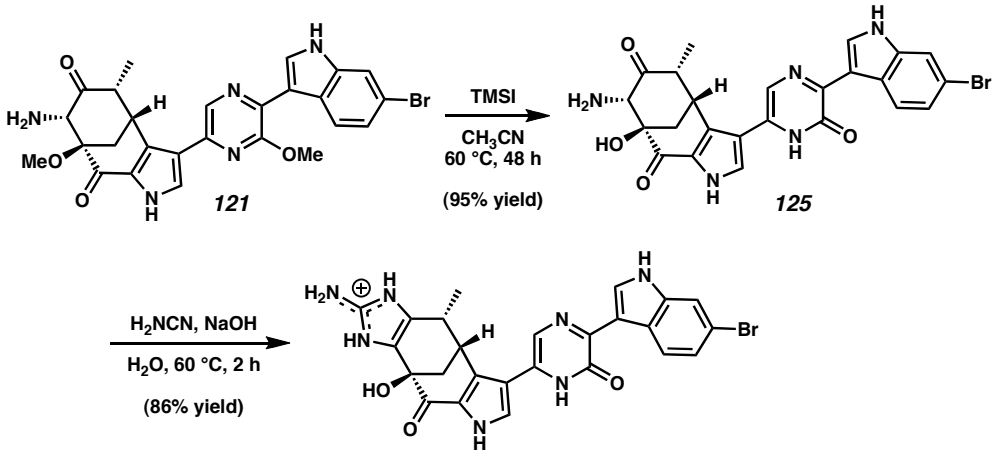
A more detailed look at the possible mechanism of the Neber rearrangement/deprotection sequence is shown in Scheme 3.2.12. Exposure of tosyloxime **120** to KOH in ethanol likely leads to the formation of detosylated azirine **122**, which is attacked by ethoxide to afford ethoxyaziridine **123**.[40a,45] Following acid-mediated hydrolysis, the amino ketone moiety is installed with concomitant partial cleavage of the SEM protective group (**123** → **124**).[41b,46] Finally, treatment of hemiaminal **124** with K_2CO_3 removes the remaining portion of the SEM group, thus giving rise to the deprotected amino ketone (**121**).

Scheme 3.2.12



In order to unveil the masked pyrazinone functionality, Neber rearrangement product **121** was treated with TMSI at 60 °C (Scheme 3.2.13).[16] Fortuitously, both the pyrazinone and the 3° alcohol functionalities were revealed simultaneously (**121** → **125**). In the final step of the synthesis, the penultimate amino ketone (**125**) was subjected to cyanamide and aqueous NaOH to produce enantiopure dragmacidin F (**84**).[7,47] Our efficient and enantiospecific route allows access to **84** in 7.8% overall yield in just 21 steps from (–)-quinic acid (**93**).

Scheme 3.2.13

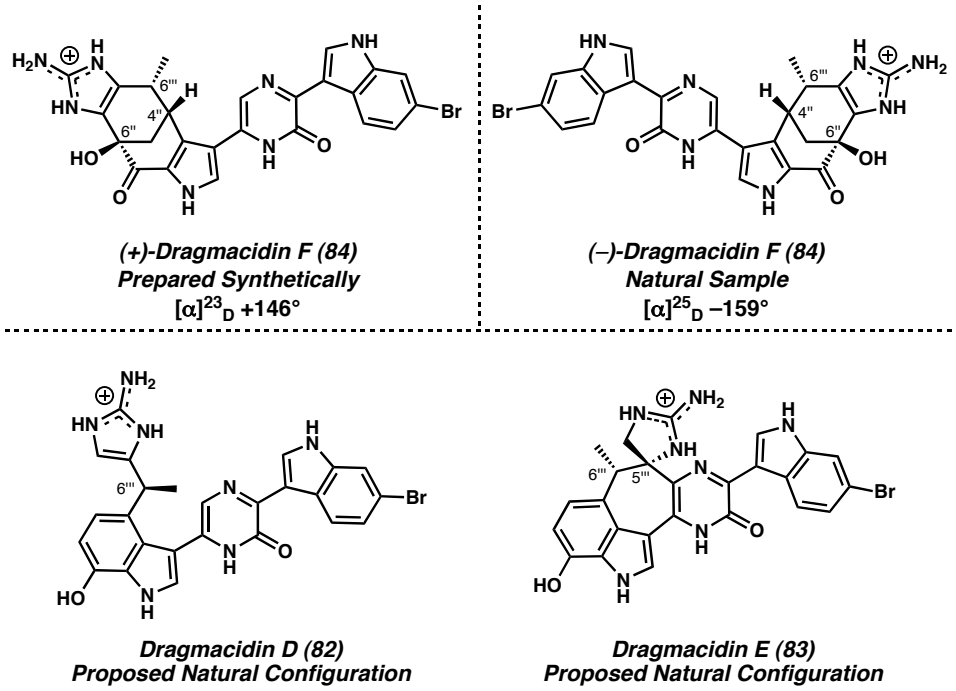


121 *125* ***(+)-Dragmacidin F (84)***

3.3 The Absolute Stereochemistry of the Pyrazinone-Containing Dragmacidins.

Synthetic dragmacidin F (**84**) was spectroscopically identical (^{1}H NMR, ^{13}C NMR, IR, UV, HPLC) to a sample obtained from natural sources,[3f] with the exception of the sign of rotation (natural: $[\alpha]^{25}_{D}$ –159° (*c* 0.4, MeOH); synthetic: $[\alpha]^{23}_{D}$ +146° (*c* 0.45, MeOH)). Thus, our synthesis from (–)-quinic acid (**93**) established, for the first time, the absolute configuration of natural dragmacidin F (**84**) to be (4"*S*, 6"*S*, 6"'*S*) as shown in Figure 3.3.1.[48] On the basis of the hypothesis that dragmacidins D, E, and F are biosynthetically related, it is likely that the absolute stereochemical configurations of natural dragmacidins D (**82**) and E (**83**) are (6"'*S*) and (5"'*R*, 6"'*S*), respectively. Having developed a route to the unnatural antipode of dragmacidin F ((+)-**84**), we set out to extend our approach to the total synthesis of (–)-**84**.

Figure 3.3.1



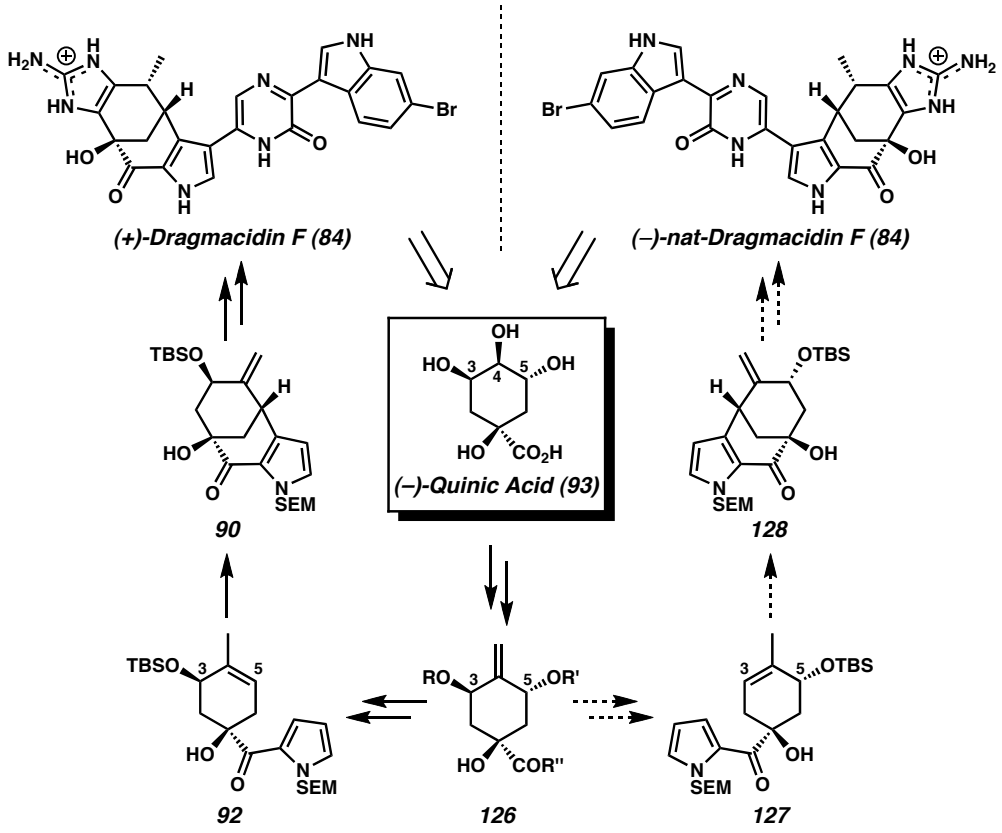
3.4 The Total Synthesis of (–)-Dragmacidin F

3.4.1 An Enantiodivergent Strategy for the Preparation of (–)-Dragmacidin F

As described above, naturally occurring and readily available (–)-quinic acid (**84**)[13] had served as the starting material for our synthetic approach to (+)-**84**. Unfortunately, the (+)-enantiomer of **93** is not easily accessible,[49] and we were confronted with the possibility that our synthesis would not be amenable to the preparation of our new target molecule, (–)-dragmacidin F ((–)-**84**). We reasoned, however, that it might be possible to exploit (–)-quinic acid (**93**) in an enantiodivergent manner that would allow access to both (+)- and (–)-**84** (Scheme 3.4.1).[50] For such an approach to succeed, (–)-quinic acid (**93**) would be elaborated via selective manipulation of the C(3), C(4), and C(5) hydroxyl groups to a pseudo-C_2-symmetric[51] derivative (**126**) en route to pyrrolocyclohexene **127**, the diastereomer of which (i.e., **92**) was employed in our

synthesis of (+)-**84**. Analogous to our approach to (+)-**84** (i.e., **92** → **90**), we anticipated that **127** could undergo oxidative carbocyclization to afford annulated pyrrole **128**. Bicycle **128** would then be elaborated to (–)-dragmacidin F ((–)-**84**). Of the key transformations outlined in Scheme 3.4.1, we were familiar with the Pd-mediated oxidative carbocyclizations and the late-stage manipulations of related compounds; however, the successful preparation of (–)-dragmacidin F ((–)-**84**) would rely heavily on the identification of a suitable quinic acid derivative (**126**), the facile synthesis of that compound, and the rapid conversion of **126** to the requisite cyclization substrate (**92**).

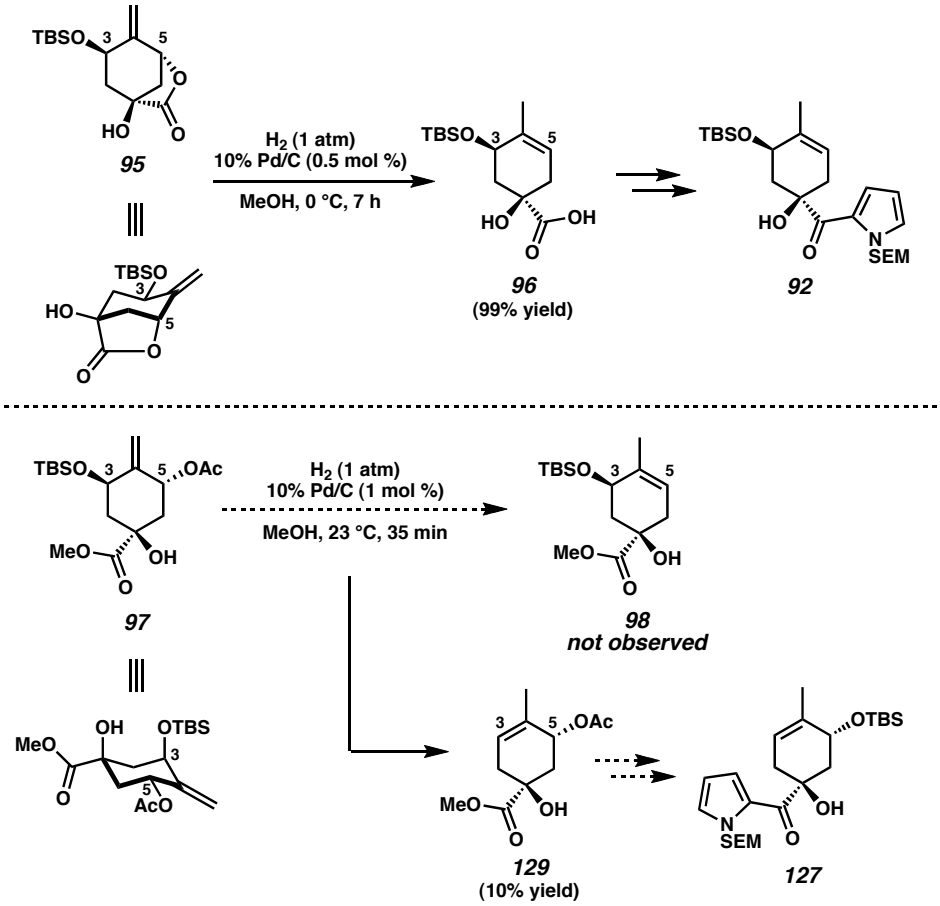
Scheme 3.4.1



3.4.2 The Development of a Reductive Isomerization Reaction

Fortunately, potential solutions to these problems had become apparent during our studies of a novel reductive isomerization reaction discovered in our synthesis of (+)-dragmacidin F ((+)-**84**). Two critical results are shown in Scheme 3.4.2. In the first experiment, treatment of lactone **95** with Pd/C and H_2 in methanol at 0 °C furnished carboxylic acid **96** in essentially quantitative yield via reductive loss of the C(5) carboxylate with concomitant olefin migration (i.e., net S_N2' reduction). In the second experiment, a closely related derivative (**97**) was exposed to similar reaction conditions.[52] Surprisingly, the reductive isomerization reaction proceeded with loss of the C(3) silyl ether rather than the C(5) acetate, thus producing small quantities of allylic acetate **129** instead of the anticipated product (**98**).[53] The observation that (*t*-Bu)Me_2SiO^- was preferentially ejected from compound **97** despite the clear superiority of AcO^- as a leaving group led us to consider that the C(3) silyl ether moiety was positioned in an axial orientation, thereby facilitating its elimination.[54] This preferred conformation of **97** represents a cyclohexane ring-flip with respect to lactone **95**, and thus gives rise to the reductive isomerization product (**129**) possessing a $\Delta_{3,4}$ olefin. Importantly, the possibility existed that the unexpected product obtained from this reaction (i.e., **129**) could be converted to cyclization substrate **127** (diastereomeric to **92**).

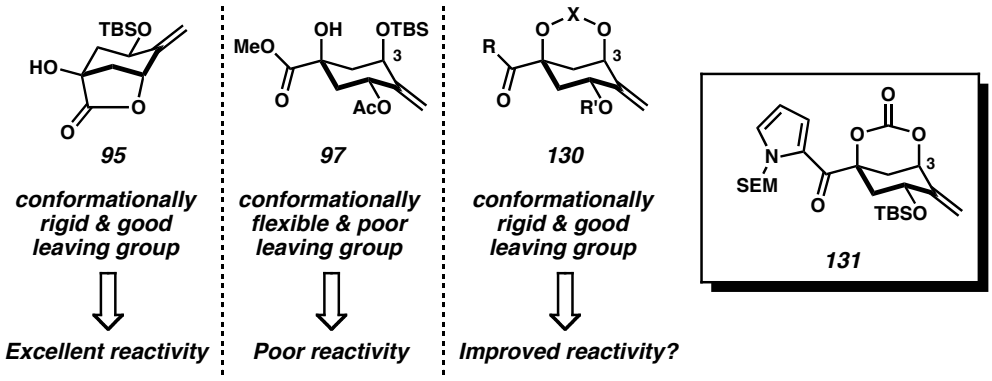
Scheme 3.4.2



Our efforts to optimize the reductive isomerization of **97** to **129** were hampered by competitive hydrogenation of the olefin moiety of **97**, a complication not observed in the high-yielding conversion of **95** to **96**. Although both processes presumably involve the elimination of an axially disposed leaving group,[54] we reasoned that the successful conversion of **95** to **96** was due to the carboxylate being conformationally restricted to an axial orientation, while substrate **97** possessed a poorer leaving group (*t*-Bu)Me_2SiO^-) and was free to adopt alternate conformations (Figure 3.4.1). We hypothesized that derivatives of **97** containing an axially-locked leaving group at C(3) (e.g., **130**) would be more suitable substrates for the reductive isomerization reaction. Thus, carbonate **131**

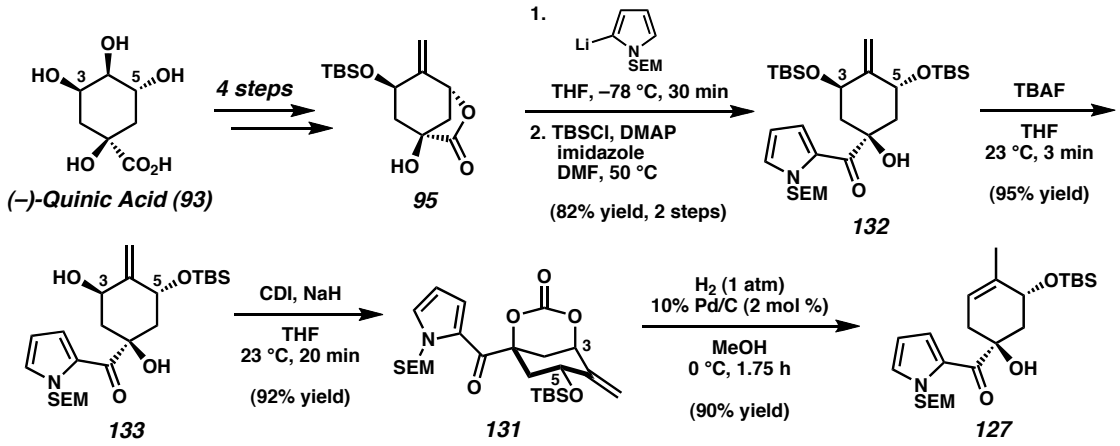
was identified as the key (–)-quinic acid derived intermediate en route to the desired cyclization substrate (**127**), and became the focus of our efforts.

Figure 3.4.1



Our synthesis of carbonate **131** began with bicyclic lactone **95**, a derivative of (–)-quinic acid (**93**) that was used in our total synthesis of (+)-**84** (Scheme 3.4.3). Addition of 2-lithio-SEM-pyrrole[22] followed by TBS protection afforded bis(silylether) **132** in good yield. This pseudo-C_2-symmetric compound then underwent rapid diastereoselective mono-desilylation upon treatment with TBAF in THF to produce the *syn* 1,3-diol **133**.[55] Importantly, this desymmetrization proceeded with complete selectivity and allowed us to efficiently differentiate the C(3) and C(5) positions of the cyclohexyl moiety. Diol **133** was smoothly converted to bicyclic carbonate **131** in the presence of CDI, effectively restricting the C(3) substituent to an axial disposition. Gratifyingly, exposure of carbonate **131** to our reductive isomerization conditions (2 mol % Pd/C, H_2, MeOH, 0 °C) led to the selective formation of the desired cyclization substrate (**127**) in 90% yield.[56]

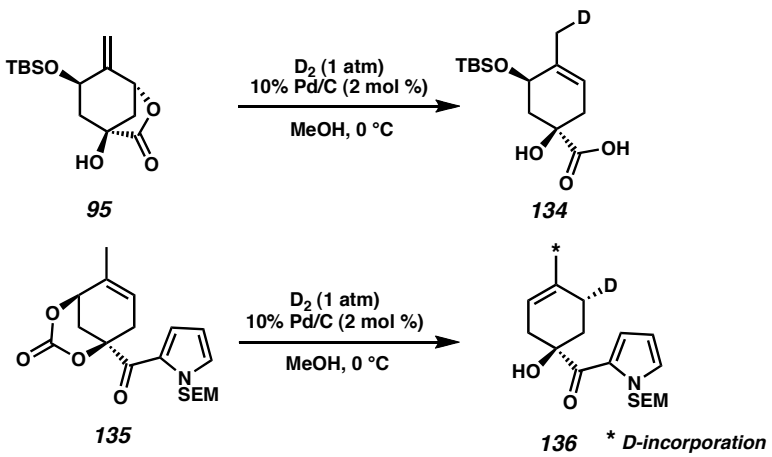
Scheme 3.4.3



3.4.3 The Scope and Mechanism of the Reductive Isomerization Reaction

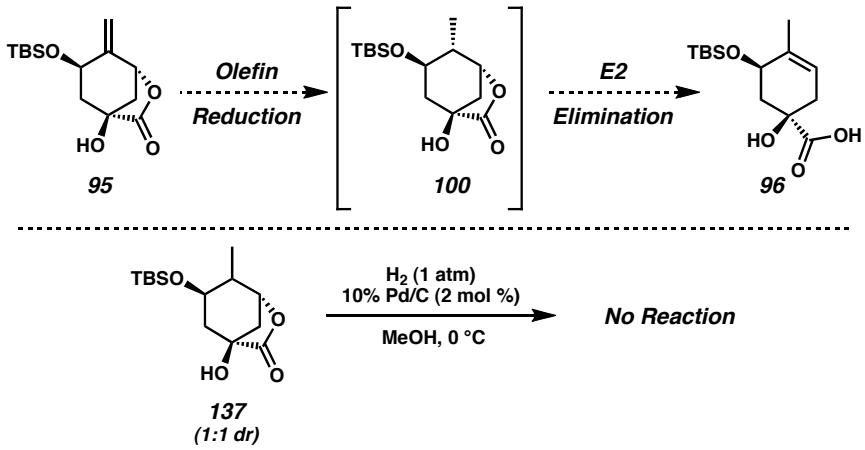
On the basis of these results, we set out to examine the unusual reactivity of the heterogeneous palladium system.[57] Intrigued by our initial results (**95** → **96** and **131** → **127**), we began a more detailed study of this reductive isomerization by examining the origin of the hydrogen atom in the newly formed C-H bond. Experiments employing D_2 indicate that the deuterium delivered at the allylic positions of **134** and **136** originates from D_2, whereas no C-D incorporation was observed by using CD_3OD (Scheme 3.4.4).[58] Furthermore, deuterium incorporation occurs with complete stereoselectivity (**135** → **136**), with additional incorporation at the exocyclic methyl group.[59]

Scheme 3.4.4



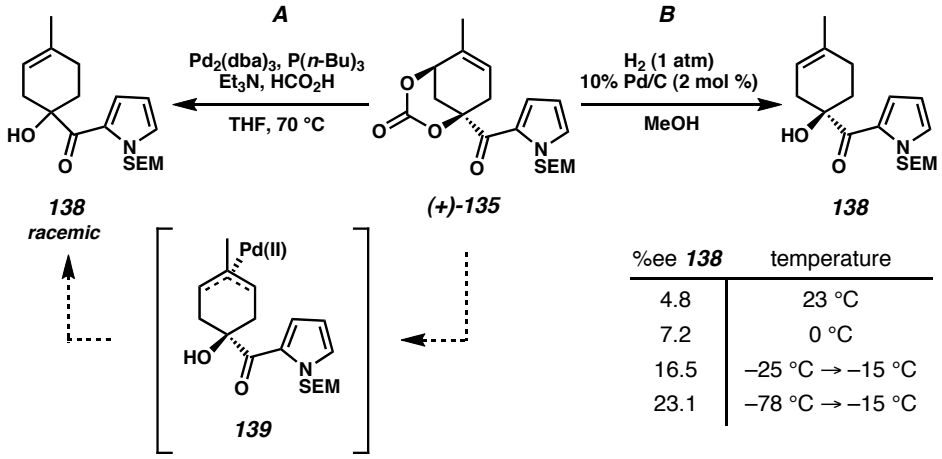
In terms of mechanism, we considered the simple possibility that our transformation could be proceeding in a tandem fashion via hydrogenation of the olefin followed by E2 elimination (e.g., **95** → **100** → **96**, Scheme 3.4.5). However, subjection of an independently prepared sample of saturated lactone **137** (1:1 dr) to the identical reaction conditions (10% Pd/C, H_2, MeOH, 0 °C) led to no reaction, allowing us to dismiss its potential as a viable intermediate.[60]

Scheme 3.4.5



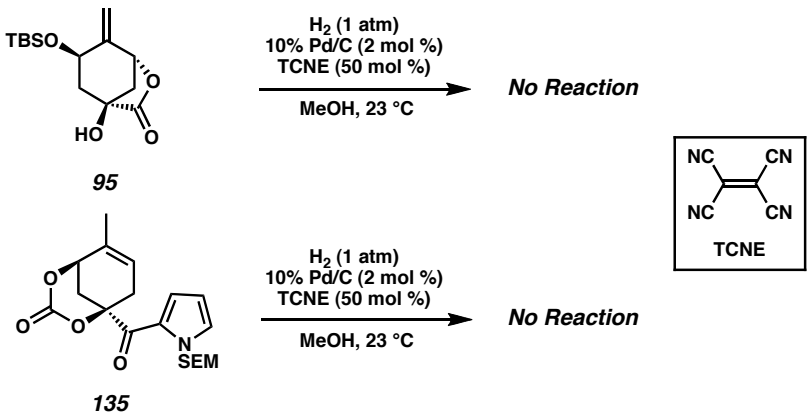
A π-allyl mechanism could be probed by using carbonate-bearing trisubstituted olefin **135**. Under π-allyl hydrogenolysis conditions, racemic **138** was obtained (Scheme 3.4.6A).[41b] Interestingly, analysis by chiral HPLC revealed that, under our reductive isomerization conditions at 0 °C, cyclohexene **138** was produced in 7.2% ee (Scheme 3.4.6B). In fact, by lowering the reaction temperature, up to 23.1% ee could be achieved.[41b] Although complete optical purity was not maintained in the product, this result suggests a reaction pathway that does not solely involve a meso-π-allylpalladium complex (e.g., **139**).[61]

Scheme 3.4.6



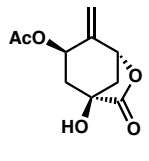
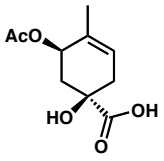
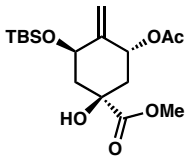
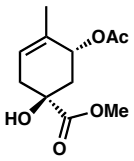
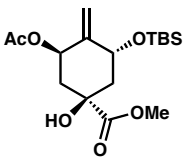
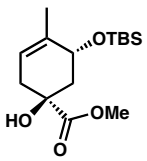
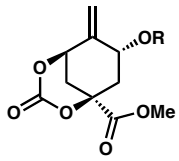
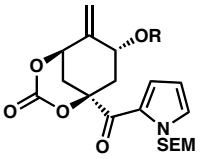
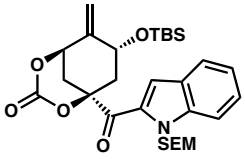
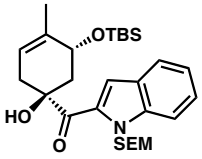
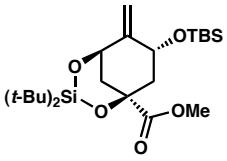
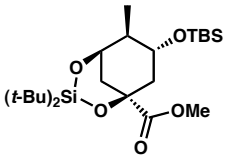
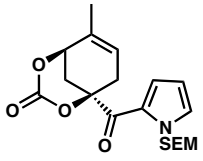
Recently, both Sajiki and Hara have invoked a single-electron transfer (SET) mechanism for other transformations involving the use of 10% Pd/C and MeOH.[62] In accordance with this hypothesis, exposing either lactone **95** or carbonate **135** to our standard conditions in the presence of tetracyanoethylene (TCNE) as a SET inhibitor completely halts all reactivity, even at 23 °C (Scheme 3.4.7).[63]

Scheme 3.4.7



We prepared a number of substrates to assess the generality of this reaction (Table 3.4.1).[64] As a starting point, a simple variant of lactone **95** bearing an acetate on the secondary allylic alcohol was synthesized (i.e., **140**). We were pleased to see that **140** could be converted to carboxylic acid **141** in good yield (entry 1). The use of allylic acetate **97** as a substrate (entry 2), on the other hand, led to an unexpected result. We anticipated that methyl ester **98** would be the observed product because acetate is a superior leaving group to silanolate (see Scheme 3.4.2, vide supra). However, the compound obtained (i.e., **129**) resulted from a net loss of the OTBS group.[65] Notably, none of the byproducts formed under homogeneous π-allyl protocols were observed under these heterogeneous conditions (**98**, **99**, **iv**[20], see Scheme 3.2.1, vide supra). In order to probe this result further, a version of **97** with exchanged protecting groups on the secondary alcohols was prepared (**142**, entry 3). In this case, elimination of acetate occurred.[65]

Table 3.4.1[a]

entry	substrate	product		time	yield[b]
1				15 min	71%
	140	***141***			
2[c]				1 h 35 min	3%[d] 10%[e,f]
	97	***129***			
3[c,e]				1.5 h	27%
	142	***143***			
4		***144***	***129*** **R = Ac**	1 h	81%
5		***145***	***143*** **R = TBS**	8 min	94%
6		***146***	***147*** **R = Ac**	20 min	94%
7		***148***	***149*** **R = H**	15 min	80%
8				4 h	90%
	150	***151***			
9				1 h	68%
	152	***153***			
10[g]				1.3 h	91%
	135	***138***			

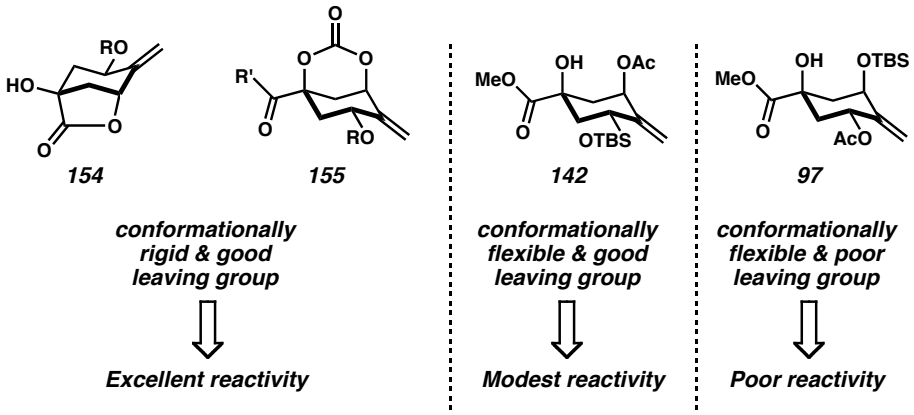
[a] Standard conditions: H_2 (balloon, 1 atm), 10% Pd/C (2 mol % Pd), MeOH, 0 °C. [b] Isolated yield. [c] Yield based on ^{1}H NMR integration. [d] 10% Pd/C (0.5 mol % Pd). [e] 10% Pd/C (1 mol % Pd). [f] Reaction performed at 23 °C. [g] Product formed in 7.2% ee.

Due to the success of the rigid bicyclic lactone framework in this reaction, we reasoned that the reactivity of **97** and **142** might be improved by restricting them as bicyclic carbonates (**144** and **145**). These carbonate-containing substrates were well tolerated and led to competent production of the corresponding methyl esters (entries 4 and 5). Additionally, carbonates with adjacent heterocyclic moieties such as pyrrole (**146** and **148**) and indole (**150**) could be converted into their reductively isomerized counterparts in excellent yields (entries 6–8 and 10). The use of an acetate protecting group on the secondary allylic alcohol (entries 1, 4, and 6), or an unprotected alcohol altogether (entry 7), did not significantly influence the overall reaction efficiency. Interestingly, replacement of the carbonate moiety with a dioxasilyl linkage led solely to diastereoselective hydrogenation of the olefin (entry 9).[66] Somewhat surprisingly, reductive isomerization using a trisubstituted olefin was also quite facile (entry 10, cf. Scheme 3.4.6).[67]

A model to rationalize some of these anomalous differences in reactivity is presented in Figure 3.4.2, which is an extended version of the model conceived in our initial hypothesis (see Figure 3.4.1, vide supra). An examination of the three-dimensional structures of the starting materials in Table 3.4.1 reveals that the leaving group is positioned preferentially in an axial orientation with respect to the six-membered ring.[68] Furthermore, structurally rigid bicyclic lactones and carbonates with locked axial leaving groups (e.g., **154** and **155**) exhibited enhanced yields relative to their more flexible monocyclic counterparts (**142** and **97**). The difference in yield between substrates **142** and **97** can be attributed to leaving group ability (i.e. $AcO^- > Me_2(t\text{-Bu})SiO^-$). This leaving group effect was also observed when the carbonate functionality was replaced

with a dioxasilyl moiety (entry 9), in which case only direct olefin hydrogenation occurred.

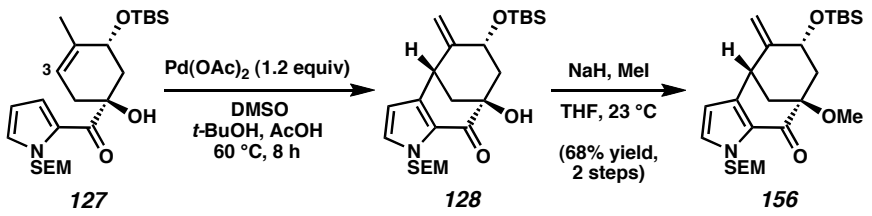
Figure 3.4.2



3.4.4 Constructing the [3.3.1] Bicycle En Route to (–)-Dragmacidin F

After assembling target substrate **127**, we turned our attention to the key Pd(II)-mediated cyclization reaction (Scheme 3.4.8). Substrate **127** was treated with 1.2 equiv of $Pd(OAc)_2$ under conditions similar to those described earlier, at which point, the desired pyrrole-fused bicycle (**128**) formed as a single regio- and stereoisomer. Notably, bond formation between the pyrrole functionality and C(3) of **127** occurred even in the presence of the bulky C(5) silyl ether group positioned syn to the acyl pyrrole subunit. Following protection of the 3° alcohol, [3.3.1] bicycle **156** was obtained in 68% yield for the two-step process.

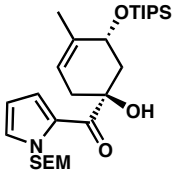
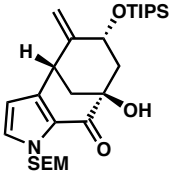
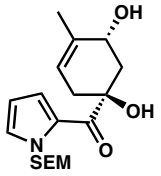
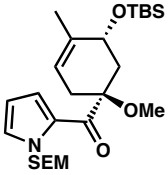
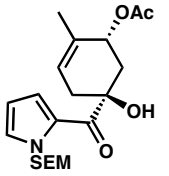
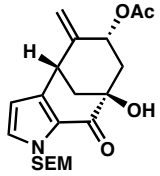
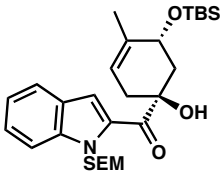
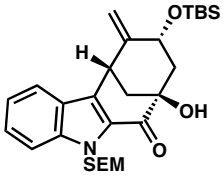
Scheme 3.4.8



127 ***128*** ***156***

We also explored the Pd(II)-mediated carbocyclization of a number of substrates related to the diastereomeric counterpart (**127**) of TBS ether **92** (cf. Table 3.2.2, vide supra). The TIPS ether analog underwent smooth cyclization (Table 3.4.2, entry 1), while the use of the hydroxy derivative[35] (entry 2) or the 3° methyl ether derivative[36] (entry 3) did not lead to any product formation. Additionally, the substrates bearing acetate (entry 4) and indole (entry 5) moieties participated in the cyclization reaction. In general, the results of this study (Table 3.4.2) mirrored the results of their diastereomeric counterparts in Table 3.2.2, albeit in lower yields. This decrease in reactivity could be attributed, at least in part, to the steric repulsion between the newly forming bond at C(3) and the protected alcohol at C(5).

Table 3.4.2[a]

entry	substrate	product	temp (°C)	time	yield[b]
1	 **157**	 **158**	80	2.3 h	51% (70%)
2	 **149**	—	80	*complex mixture*[c]	
3	 **159**	—	80	*no reaction*	
4	 **147**	 **160**	60[d]	11 h	10%[e]
5	 **151**	 **161**	80	2.3 h	34%

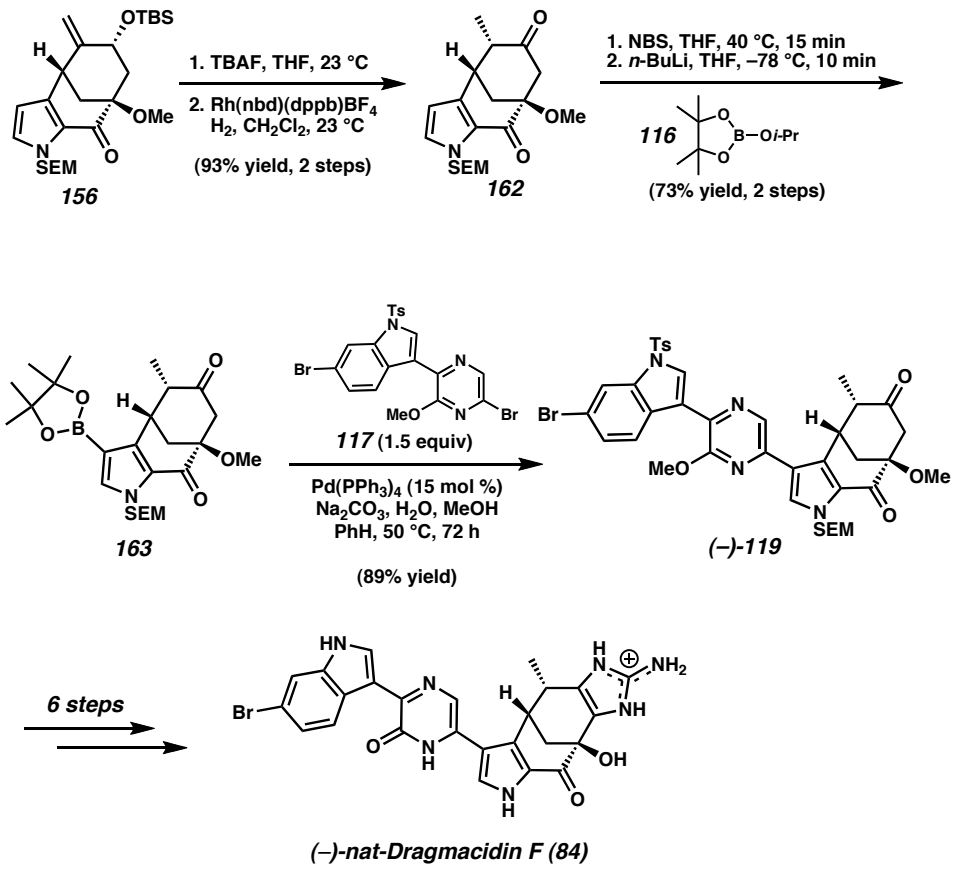
[a] Standard Conditions: 1 equiv $Pd(OAc)_2$, 2 equiv DMSO, *t*-BuOH:AcOH (4:1, 0.01 M). [b] Isolated Yield. Number in parentheses represents the yield based on recovered starting material. [c] Trace product may have formed in this reaction, but could not be isolated. [d] At 80 °C, trace product formation and substantial decomposition were observed.

3.4.5 End-Game: Total Synthesis of (–)-Dragmacidin F

Despite the similarity of **156** to its diastereomeric counterpart (**115**, Scheme 3.2.9) employed in the synthesis of (+)-dragmacidin F (**84**), attempts to carry out similar elaborations using previously developed protocols were unsuccessful. Thus, a slightly

modified end-game route was conceived and carried out by Neil Garg. Cleavage of the TBS ether of **156** using TBAF in THF, followed by a tandem olefin isomerization/tautomerization process using Brown's cationic rhodium catalyst[69] Rh(nbd)(dppb)BF_4 and H_2, formed ketone **162** as a single diastereomer in 93% yield over two steps (Scheme 3.4.9).[70] Position-selective bromination and low-temperature metalation of the pyrrole in the presence of two ketones gave rise to boronic ester **163**. Subsequent halogen-selective cross-coupling of **163** with dibromide **117** afforded the desired Suzuki adduct (–)-**119** (89% yield), the enantiomer of which had been employed in the synthesis of (+)-dragmacidin F. Finally, Suzuki adduct (–)-**119** was converted to (–)-dragmacidin F ((–)-**84**) via our previously described six-step protocol (vide supra). Synthetic and natural (–)-**84**[3f] were spectroscopically identical, including the sign of optical rotation (natural (–)-**84**: $[\alpha]^{25}_D$ –159° (*c* 0.4, MeOH); synthetic (–)-**84**: $[\alpha]^{23}_D$ –148° (*c* 0.2, MeOH)).[41b]

Scheme 3.4.9



3.5 Conclusion

In summary, we have developed an enantiodivergent strategy to access both antipodes of dragmacidin F (**84**) from a single enantiomer of readily available (–)-quinic acid (**93**). Our highly efficient syntheses provide (+)-**84** in 7.8% overall yield and (–)-**84** in 9.3% overall yield beginning from **93**. The routes that we have developed to (+)- and (–)-**84** are concise and feature a number of key transformations, namely: a) highly efficient functionalizations of (–)-**93** to differentiate C(3) and C(5), b) novel reductive isomerization reactions, c) sterically demanding Pd(II)-mediated oxidative carbocyclizations, d) halogen-selective Suzuki cross-coupling reactions, and e) high-

yielding late-stage Neber rearrangements. Advanced biological testing of both synthetic antipodes of dragmacidin F is currently underway.

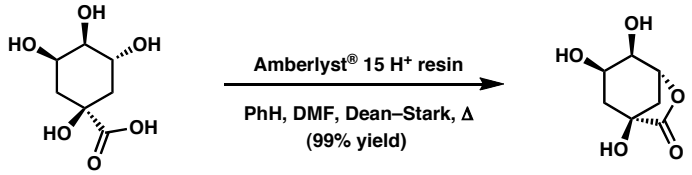
3.6 Experimental Section

3.6.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). 10% Pd/C was purchased from Aldrich Chemical Company, Inc. (20,569-9). All commercially obtained reagents were used as received. Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash column chromatography. Disposable Sep-Pak C_{18} Vac Cartridges were purchased from Waters and used for all reversed-phase filtrations. HPLC analysis was performed on a Beckman Gold system using a Rainin C_{18}, Microsorb MV, 5 μm, 300 x 4.6 mm reversed-phased column in 0.1% (*w*/*v*) TFA with acetonitrile/H_2O as eluent and a flow rate of 1.0 mL/min, gradient elution of 1.25% acetonitrile/min. Preparatory reversed-phase HPLC was performed on a Beckman HPLC with a Waters DeltaPak 25 x 100 mm, 100 μm C_{18} column equipped with a guard, 0.1% (*w*/*v*) TFA with acetonitrile/H_2O as eluent, and gradient elution of 0.50% acetonitrile/min. For all reversed-phase purifications, H_2O (18MΩ) was obtained from a Millipore MiliQ water purification system and TFA from Halocarbon, Inc. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz), a Varian Inova 500 (at 500 MHz), or a Varian Inova 600 (at 600 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity,

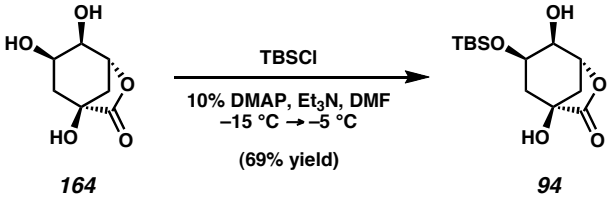
coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz), or a Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer or a Perkin Elmer Spectrum BXII spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter. High-resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Analytical chiral HPLC was performed on a Chiralpak® AD column (4.6 mm x 250 mm) obtained from Daicel Chemical Industries, Ltd.

3.6.2 Preparative Procedures



(–)-Quinic Acid (93) *164*

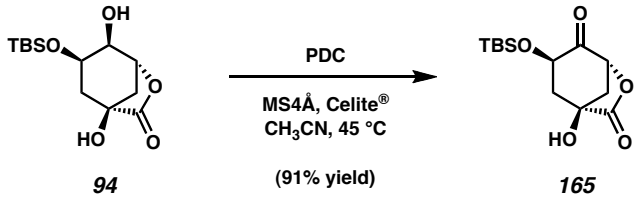
Lactone 164. A mixture of D-(–)-quinic acid (**93**) (50.0 g, 260.2 mmol), Amberlyst® 15 ion-exchange resin (7 g, 35 mmol), benzene (500 mL), and DMF (125 mL) was refluxed under a Dean-Stark trap for 16 h. The reaction mixture was cooled to 23 °C and filtered over a pad of Celite®. The filtrate was then evaporated under reduced pressure to afford a thick oil, which was diluted with CH_2Cl_2 (150 mL). Hexanes (250 mL) was added and the resulting mixture was allowed to sit at 23 °C for 2 h. The product was collected by vacuum filtration and was further dried in vacuo to afford lactone **164** (44.9 g, 99% yield) as a white powder. R_f 0.40 (3:1 EtOAc:acetone); characterization data for this compound have been previously reported.[14a]



164 *94*

TBS Lactone 94. To a mixture of lactone **164** (90.0 g, 517 mmol), DMAP (6.31 g, 51.7 mmol), triethylamine (90 mL, 646 mmol), and DMF (345 mL) at –15 °C was added TBSCl (84.9 g, 563 mmol) in 3 equal portions over 30 min. The temperature was maintained between –20 °C and –15 °C during the addition. The reaction mixture was allowed to warm to –5 °C over 3 h, quenched by the addition of 5% aq. citric acid (120 mL), and then warmed to 23 °C. The solvent was removed in vacuo, and the crude

product was diluted with 5% aq. citric acid (350 mL) and extracted with Et_2O (1 x 500 mL, 2 x 400 mL). The combined organic layers were washed with H_2O (2 x 400 mL) and brine (400 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The product was triturated with hexanes (750 mL) and collected by vacuum filtration. It was further dried under vacuum to afford TBS lactone **94** (102.8 g, 69% yield) as a dry white solid. R_f 0.48 (1:1 hexanes:EtOAc); R_f 0.28 (2:1 Et_2O:hexanes); characterization data for this compound have been previously reported.[14b]

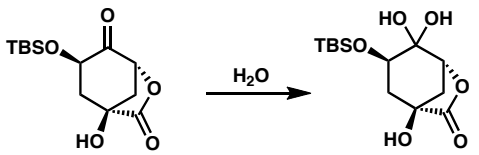


Keto Lactone 165. A mixture of TBS lactone **94** (3.72 g, 12.90 mmol), powdered 4Å activated molecular sieves (2.79 g), Celite® (2.79 g), pyridinium dichromate (12.13 g, 32.2 mmol), and acetonitrile (185 mL) was heated to 45 °C for 24 h. The reaction was allowed to cool to 23 °C, and then was filtered over a plug of silica gel topped with Celite® (EtOAc eluent). The solvent was removed under reduced pressure to afford a brown oil, which was further purified by passage over a plug of silica gel (1:1 hexanes:EtOAc eluent). Evaporating the solvent in vacuo afforded keto lactone **165** (3.35 g, 91% yield) as a pale yellow oil.

Alternate Procedure. Powdered 4Å activated molecular sieves (184.6 g) were agitated and flame-dried under vacuum for approximately 30 min until a fine, powder-like consistency was obtained. Upon cooling to 23 °C, CH_2Cl_2 (540 mL) was introduced, and the slurry was cooled to 0 °C. Freshly prepared pyridinium dichromate[71] (148.7 g,

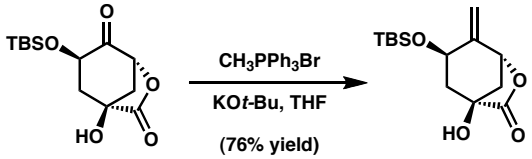
395.3 mmol) was added, and the resulting heterogeneous orange mixture was treated with TBS lactone **94** (70.04 g, 242.8 mmol) portionwise over 4 min. After the addition was complete, the reaction was stirred for 5 min and then freshly distilled AcOH (49.0 mL, 856.0 mmol) was added dropwise over a 20-min period. The reaction temperature was maintained at 0 °C for 15 min after the addition was complete, and the mixture was then stirred at 23 °C. After 10 h, the reaction was judged complete by ^{1}H NMR. The dark mixture was evenly divided into 3 portions, each of which was filtered over a pad of silica gel (10 cm diameter x 7.5 cm height, EtOAc eluent). The filtrates were combined and evaporated in vacuo to afford a dark liquid, and this residue was further coevaporated with toluene (3 x 150 mL). The crude product was diluted in a mixture of hexanes:EtOAc (10:1; 250 mL) and filtered over a pad of powdered Na_2SO_4 to remove insoluble impurities. The filtrate was evaporated, and dried in vacuo, to afford keto lactone **165** (55.27 g, 80% yield) as a brown, waxy solid. This material was used immediately in the next step without further purification. *Unstable to TLC conditions*; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.71 (d, *J* = 6.6 Hz, 1H), 4.52 (dd, *J* = 10.3, 8.9 Hz, 1H), 2.95 (s, 1H), 2.88–2.79 (m, 1H), 2.57–2.47 (m, 1H), 2.39 (d, *J* = 12.4 Hz, 1H), 2.13 (dd, *J* = 12.4 Hz, 10.5 Hz, 1H), 0.88 (s, 9H), 0.11 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.6, 177.4, 79.0, 72.0, 70.6, 43.2, 42.6, 25.8 (3C), 18.5, –4.6, –5.3; IR (film): 3444 (br), 2931, 2858, 1799, 1753, 1254, 1144, 1111 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^{+}$ calc'd for $C_{13}H_{23}O_5Si$, 287.1315; found, 287.1316; $[\alpha]^{19}_{D}$ –96.47° (*c* 1.0, C_6H_6).

*NOTE: Exposure of keto lactone **165** to water (e.g., aqueous workup, or prolonged exposure to silica gel) led to the formation of hydrate **166**, as a white powder.*



165 *166*

Hydrate 166. *Unstable to TLC conditions*; mp 104–6 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 4.46 (d, *J* = 5.8 Hz, 1H), 3.75 (dd, *J* = 10.7, 7.0 Hz, 1H), 2.48–2.31 (comp. m, 2H), 2.10–2.00 (m, 1H), 1.76 (app. t, *J* = 11.4 Hz, 1H), 0.93 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ 179.4, 93.2, 81.8, 73.0, 72.3, 41.5, 40.9, 26.5 (3C), 19.1, –4.3, –4.7; IR (KBr): 3440 (br), 3374 (br), 2929, 2858, 1782, 1256, 1108, 1070 cm^{-1}; HRMS-CI (*m/z*): $[M + H]^+$ calc'd for $C_{13}H_{24}O_6Si$, 304.1342; found, 304.1336; $[\alpha]^{19}_D$ –54.29° (*c* 1.0, MeOH).



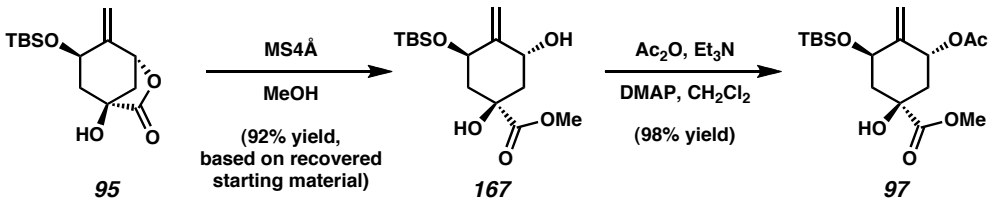
165 *95*

Methylene Lactone 95. To CH_3PPh_3Br (105 mg, 0.293 mmol) in THF (2.8 mL) at 0 °C was added potassium *t*-butoxide (31.3 mg, 0.279 mmol). The mixture was warmed to 23 °C and stirred for an additional 10 min. Keto lactone **165** (40 mg, 0.140 mmol) in THF (1 mL) was added and stirring was continued at 23 °C for 15 min. The reaction mixture was then refluxed for 2 h and cooled to 23 °C. The solvent was removed under reduced pressure, and the residue was partitioned between Et_2O (3 mL) and brine (1.5 mL). The layers were separated, and the aqueous layer was further extracted with Et_2O (3 x 1 mL). The combined organic layers were washed with brine (1.5 mL), dried by passage over a plug of silica gel (Et_2O eluent, then 2:1 hexanes:EtOAc eluent), and

evaporated under reduced pressure. The crude product was purified by flash chromatography (2:1 hexanes:EtOAc eluent) to afford methylene lactone **95** (30 mg, 76% yield) as a white solid.

Alternate Procedure. To CH_3PPh_3Br (82.9 g, 232.1 mmol) in THF (1.10 L) at 23 °C was added potassium *t*-butoxide (23.8 g, 212.1 mmol) in one portion. The mixture was stirred for 2 h, then cooled to 0 °C. Keto lactone **165** (54.5 g, 190.3 mmol) in THF (240 mL) was added dropwise over a 30 min period. The reaction was allowed to warm slowly to 23 °C over 9 h, then quenched by the addition of ice-cold 15% aq. NH_4Cl (500 mL). The solvent was evaporated under reduced pressure, and the residue was partitioned between Et_2O (500 mL) and H_2O (100 mL). The aqueous phase was extracted with Et_2O (3 x 250 mL), and the combined organics were washed with H_2O (100 mL) and brine (100 mL) and dried over $MgSO_4$. Evaporation of the solvent afforded a crude yellow oil, which was filtered over a plug of silica gel (4:1 pentane:Et_2O → 3:2 pentane:Et_2O eluent). After evaporating the solvent in vacuo, the residue was triturated with ice-cold pentane (40 mL). The white solid was filtered and washed with ice-cold pentane (2 x 2 mL). A second crop was collected from the filtrate after concentrating its volume to 15 mL. Drying the collected material in vacuo afforded methylene lactone **95** (22.1 g, 41% yield) as a white solid. R_f 0.59 (1:1 hexanes:EtOAc); mp 87–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.25–5.23 (m, 1H), 5.13–5.10 (m, 1H), 5.07 (d, J = 6.0 Hz, 1H), 4.38–4.29 (m, 1H), 2.85 (s, 1H), 2.67–2.59 (m, 1H), 2.31–2.21 (m, 1H), 2.09 (d, J = 11.5 Hz, 1H), 1.86 (app. t, J = 11.3 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.1, 144.8, 111.0, 79.4, 73.1, 67.1, 44.7, 44.7, 26.0 (3C), 18.5, –4.5, –4.7; IR (film): 3426 (br),

2956, 2931, 2858, 1791, 1254, 1120, 1071 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{14}H_{25}O_4Si$, 285.1522; found, 285.1519; $[\alpha]^{19}_D$ –101.71° (*c* 1.0, $CHCl_3$).

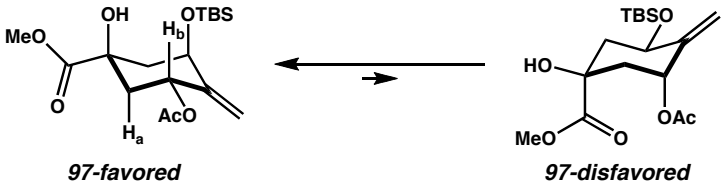


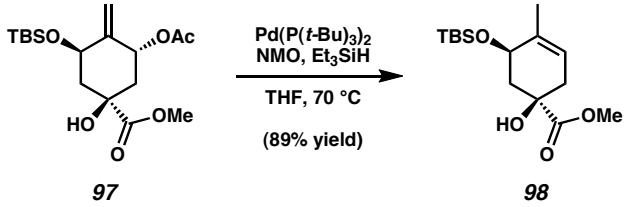
Methyl Ester 97. To lactone **95** (420 mg, 1.477 mmol) and activated oven-dried 4Å molecular sieves (100 mg) was added MeOH (15 mL). The reaction mixture was stirred at 23 °C for 5.5 h, then filtered over a short plug of Celite® (EtOAc eluent). After evaporation of the reaction mixture under reduced pressure, the residue was purified by flash column chromatography (2:1 hexanes:EtOAc eluent) to afford starting material lactone **95** (82 mg, 20% yield) and siloxy diol **167** (345 mg, 74% yield, 92% yield based on recovered starting material), which was used directly in the subsequent reaction.

To siloxy diol **167** (80.0 mg, 0.253 mmol) in CH_2Cl_2 (1.5 mL) was added Et_3N (71 μL, 0.506 mmol), DMAP (3 mg, 0.0253 mmol), followed by Ac_2O (31 μL, 0.329 mmol). The reaction mixture was stirred at 23 °C for 10 min, quenched with saturated aq. $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were filtered over a plug of silica gel (CH_2Cl_2 eluent, then EtOAc eluent) and evaporated under reduced pressure. The crude product was purified by flash chromatography (3:1 hexanes:EtOAc eluent) to afford methyl ester **97** (89.0 mg, 98% yield) as a colorless oil. R_f 0.50 (1:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 5.90–5.81 (m, 1H), 4.96 (br s, 1H), 4.94 (br s, 1H), 4.91–4.89 (m, 1H), 4.67 (app. t, *J* = 3.2 Hz, 1H), 3.74 (s, 3H), 2.38 (ddd, *J* = 12.7, 5.2, 2.2 Hz, 1H), 2.19–2.03 (comp. m, 2H), 2.09 (s, 3H), 1.93 (app. t,

J = 12.1 Hz, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 169.6, 146.3, 108.5, 76.5, 75.1, 68.0, 52.9, 42.7, 41.2, 25.8 (3C), 21.1, 18.1, –4.6, –5.2; IR (film) 3464 (br), 2954, 2932, 2858, 2888, 1739 (br), 1369, 1233 (br), 1124, 1098, 1072, 1036 cm^{-1}; HRMS-FAB (m/z): $[M + H]^+$ calc'd for $C_{17}H_{31}O_6Si$, 359.1890; found, 359.1900; $[\alpha]^{26}_D$ –26.61° (*c* 1.0, C_6H_6).

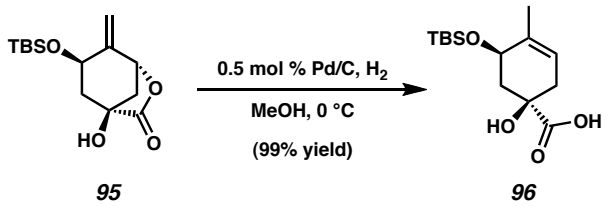
The stable chair conformer of methyl ester **97** was determined using homodecoupling NMR experiments. The coupling constant between H_a and H_b was measured as J_{ab} = 10.7 Hz.





Siloxycyclohexene 98. Methyl ester **97** (94 mg, 0.262 mmol), Pd(P(t-Bu_3)$_2$) (40.2 mg, 0.0786 mmol), anhydrous *N*-methylmorpholine *N*-oxide (307 mg, 2.52 mmol), THF (5.2 mL), and freshly distilled Et_3SiH (1.67 mL, 10.5 mmol) were combined under a glovebox atmosphere. The reaction mixture was immediately removed from the glovebox and placed in a 70 °C oil bath. After 3.5 h, the reaction mixture was cooled to 0 °C, and the volatiles were removed under reduced pressure. Saturated aq. NH_4Cl (15 mL) was added, and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic

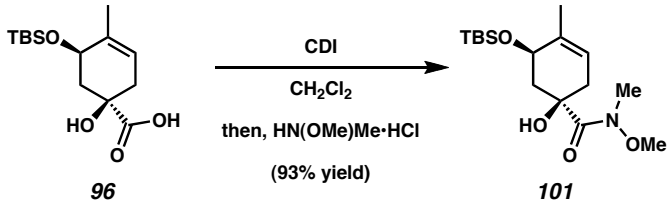
layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes:EtOAc eluent) to afford siloxycyclohexene **98** (70 mg, 89% yield) as a pale yellow oil. R_f 0.55 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.49–5.42 (m, 1H), 4.62 (s, 1H), 4.18–4.12 (m, 1H), 3.76 (s, 3H), 2.45–2.38 (comp. m, 2H), 2.16–2.10 (comp. m, 2H), 1.79–1.74 (m, 3H), 0.88 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 133.7, 120.9, 73.0, 68.7, 52.6, 38.4, 36.9, 25.9 (3C), 21.4, 18.0, –4.3, –4.7; IR (film) 3478 (br), 2955, 2858, 1740, 1451, 1253, 1217, 1111, 1065, 1037 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{15}H_{19}O_4Si$, 301.1835; found, 301.1835; $[\alpha]^{24}_D$ +77.62° (*c* 0.47, $CHCl_3$).



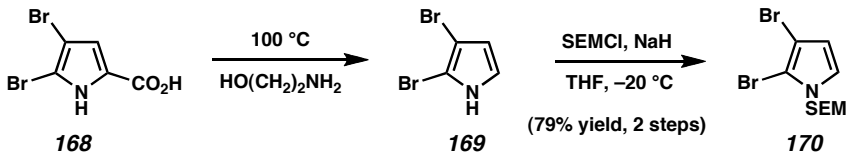
95 *96*

Acid 96. A mixture of methylene lactone **95** (4.0 g, 14.1 mmol) and 10% Pd/C (80 mg, 0.075 mmol) in methanol (120 mL) was cooled to 0 °C. The reaction vessel was evacuated and back-filled with H_2 (3x). After 7 h at 0 °C, the mixture was filtered over a pad of Celite® (MeOH eluent), and the solvent was evaporated under reduced pressure to afford a colorless oil. Residual solvent was removed by holding the crude product under vacuum for 10 h, providing acid **96** (4.0 g, 99% yield), which was used immediately without further purification. R_f 0.28 (1:1 hexanes:EtOAc; 1% acetic acid); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (s, 1H), 5.53–5.48 (m, 1H), 4.16–4.11 (m, 1H), 2.71–2.60 (m, 1H), 2.36–2.22 (m, 1H), 2.18 (dd, *J* = 14.3, 3.9 Hz, 1H), 2.08–2.01 (m, 1H), 1.79–1.76 (m,

3H), 0.89 (s, 9H), 0.15–0.13 (comp. m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 133.2, 121.1, 73.6, 68.6, 37.9, 35.9, 25.8 (3C), 21.4, 18.0, –4.5, –4.7; IR (film): 3356 (br), 2956, 2931, 2858, 1768 (br), 1718 (br), 1255, 1063 cm^{-1}; HRMS-FAB (*m/z*): [M + H]$^+$ calc'd for $C_{14}H_{27}O_4Si$, 287.1679; found, 287.1675; $[\alpha]^{19}_D$ +37.58° (*c* 1.0, C_6H_6).



Weinreb Amide 101. To acid **96** (4.0 g, 14.1 mmol) in CH_2Cl_2 (70 mL) at 23 °C was added 1,1'-carbonyldiimidazole (3.65 g, 22.5 mmol) in equal portions over 15 min. After the final addition, stirring was continued for 10 min, then *N,O*-dimethylhydroxylamine • HCl (3.43 g, 35.16 mmol) was added in one portion. The reaction was allowed to stir at 23 °C for 3 h. Et_2O was added (50 mL), and the reaction mixture was filtered. The filtrate was evaporated, diluted with Et_2O (125 mL), washed with 5% aq. citric acid (2 x 50 mL) and brine (50 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography (3:1 hexanes:EtOAc eluent) to afford Weinreb amide **101** (4.29 g, 93% yield) as a colorless oil. R_f 0.42 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.43 (m, 1H), 4.72 (s, 1H), 4.17–4.11 (m, 1H), 3.71 (s, 3H), 3.22 (s, 3H), 2.59–2.24 (comp. m, 3H), 2.03 (dd, *J* = 14.6, 4.1 Hz, 1H), 1.75–1.71 (m, 3H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 15/16 C): δ 133.5, 121.5, 74.3, 69.4, 61.2, 38.1, 35.9, 26.0, 25.9 (3C), 21.3, 18.1, –4.3, –4.7; IR (film): 3463 (br), 2956, 2932, 2858, 1655, 1362, 1254 cm^{-1}; HRMS-EI (*m/z*): [M + H]$^+$ calc'd for $C_{16}H_{32}NO_4Si$, 330.2101; found, 330.2085; $[\alpha]^{19}_D$ +41.13° (*c* 1.0, $CHCl_3$).

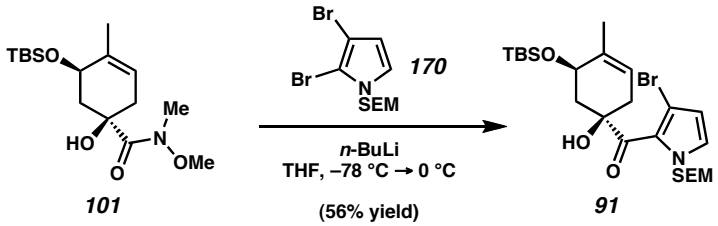


Dibromopyrrole 170. A solution of 4,5-dibromopyrrole carboxylic acid (**168**)[72] (6.05 g, 22.5 mmol) in ethanolamine (36 mL) was heated to 100 °C for 2 h, cooled to 23 °C, and poured into a mixture of Et_2O (200 mL) and 0.5 N aq. HCl (300 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 250 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and concentrated to 100 mL. The solution was diluted with hexanes (100 mL), filtered over a plug of silica gel (2:1 hexanes:Et_2O eluent), and concentrated to 150 mL. THF (100 mL) was added, and the solution was concentrated to 100 mL. This solvent exchange procedure was repeated 2 additional times (2 x 100 mL THF) to afford 2,3-dibromopyrrole (**169**) as a solution in THF, which was used immediately in the subsequent reaction.

*CAUTION: Concentrating the above described solutions to dryness or near-dryness leads to rapid decomposition of 2,3-dibromopyrrole (***169***).*[37]

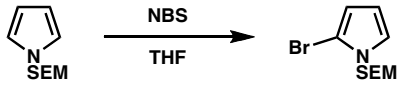
To 2,3-dibromopyrrole (**169**) in THF at –20 °C was added NaH (60% dispersion in mineral oil, 1.51 g, 37.8 mmol) in 3 equal portions over 3 min. After 10 min at –20 °C, SEMCl (4.8 mL, 27.1 mmol) was added dropwise over 1 min. The reaction mixture was allowed to warm to –8 °C over 40 min and was then quenched with saturated aq. NH_4Cl (30 mL). After warming to 23 °C, the reaction mixture was diluted with Et_2O (75 mL) and H_2O (20 mL), and the layers were separated. The aqueous layer was further extracted

with Et_2O (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (6:1 hexanes:CH_2Cl_2, then 4:1 hexanes:CH_2Cl_2 eluent) to afford dibromopyrrole **170** (6.25 g, 79% yield) as a yellow oil. R_f 0.17 (6:1 hexanes:CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (d, *J* = 3.6 Hz, 1H), 6.25 (d, *J* = 3.3 Hz, 1H), 5.21 (s, 2H), 3.48 (t, *J* = 8.1 Hz, 2H), 0.88 (t, *J* = 8.1 Hz, 2H), –0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.1, 112.3, 103.7, 99.8, 77.8, 66.2, 17.9, –1.2 (3C); IR (film): 2953, 2896, 1514, 1470, 1279, 1250, 1109, 1084 cm^{-1}; HRMS-EI (*m*/*z*): $[M + H]^+$ calc'd for $C_{10}H_{17}NOSiBr_2$, 352.9446; found, 352.9435.



Bromo Acyl Pyrrole 91. To dibromopyrrole **170** (6.02 g, 17.06 mmol) in THF (114 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 6.7 mL, 16.8 mmol) dropwise over 1 min. After 10 min at –78 °C, Weinreb amide **101** (1.58 g, 4.80 mmol) in THF (15 mL) was added dropwise over 30 seconds. The reaction vessel was immediately warmed to 0 °C, stirred for 90 min, and cooled to –78 °C. The reaction was quenched with saturated aq. NH_4Cl (15 mL), then warmed to 23 °C. The volatiles were removed in vacuo, and the residue was partitioned between Et_2O (75 mL) and H_2O (30 mL). The layers were separated, and the aqueous layer was further extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash

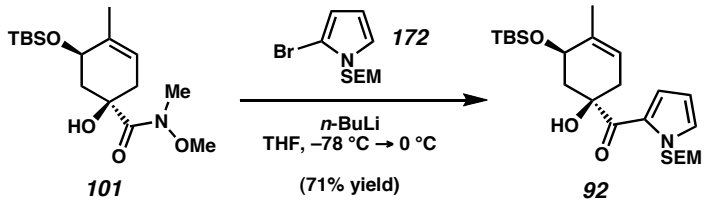
chromatography (11:9 CH_2Cl_2:hexanes eluent) to afford bromo acyl pyrrole **91** (1.47 g, 56% yield) as a colorless oil. R_f 0.29 (11:9 hexanes:CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (d, *J* = 2.9 Hz, 1H), 6.20 (d, J= 2.7 Hz, 1H), 5.53–5.47 (m, 1H), 5.35 (d, *J* = 10.4 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 4.72 (s, 1H), 4.18–4.14 (m, 1H), 3.31 (t, *J* = 8.2 Hz, 2H), 2.65–2.53 (m, 1H), 2.53–2.41 (m, 1H), 2.32 (dt, *J* = 14.3, 1.7 Hz, 1H), 2.15 (dd, *J* = 14.2 Hz, 4 Hz, 1H), 1.79–1.76 (m, 3H), 0.87 (s, 9H), 0.81 (t, *J* = 8.2 Hz, 2H), 0.12 (s, 6H), –0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.9, 133.2, 129.6, 125.0, 121.6, 112.5, 101.8, 78.9, 78.6, 68.9, 66.2, 38.6, 37.4, 26.0 (3C), 21.5, 18.1, 17.8, –1.2 (3C), –4.1, –4.7; IR (film): 3477 (br), 2953, 1664 (br), 1400, 1253, 1101 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+$ calc'd for $C_{24}H_{43}NO_4Si_2Br$, 544.1914; found, 544.1903; $[\alpha]^{19}_D$ +1.64° (*c* 1.0, $CHCl_3$).



171 *172*

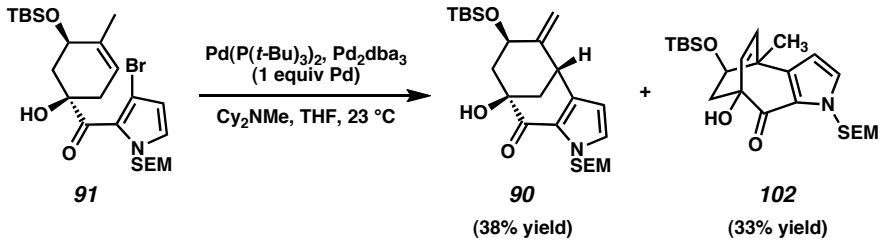
Bromopyrrole 172. To SEM pyrrole **171**[22] (1.25 g, 6.33 mmol) in THF (125 mL) at 23 °C was added freshly recrystallized NBS (1.127 g, 6.33 mmol) in one portion. After stirring for 5 min, additional NBS was added (15 mg, 0.084 mmol), and the reaction was immediately judged complete by TLC. The reaction mixture was poured into saturated aq. $NaHCO_3$ (100 mL) and extracted with Et_2O (1 x 100 mL, 2 x 50 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by passage over a plug of silica gel (CH_2Cl_2 eluent) to afford bromopyrrole **172** (1.73 g, 99% yield) as a pale yellow oil. R_f 0.53 (1:1 CH_2Cl_2:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (app. t, *J* = 2.5 Hz, 1H),

6.18–6.16 (comp. m, 2H), 5.22 (s, 2H), 3.53–3.46 (m, 2H), 0.92–0.85 (m, 2H), –0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.9, 111.9, 110.1, 102.0, 76.7, 66.0, 17.9, –1.2 (3C); IR (film): 2953, 2895, 1264, 1249, 1108, 1085 cm^{-1}; HRMS-EI (*m*/*z*): [M + H]$^+$ calc'd for $C_{10}H_{18}NOSiBr$, 275.0341; found, 275.0331.



Acyl Pyrrole 92. To bromopyrrole **172** (1.73 g, 6.26 mmol) in THF (42 mL) at –78 °C was added *n*-BuLi (2.25 M in hexanes, 2.7 mL, 6.16 mmol) dropwise over 1 min. After 10 min at –78 °C, Weinreb amide **101** (655 mg, 1.99 mmol) in THF (5 mL) was added dropwise over 1 min. The reaction vessel was immediately warmed to 0 °C, stirred for 25 min, and cooled to –78 °C. The reaction mixture was quenched with saturated aq. NH_4Cl (10 mL), then warmed to 23 °C. The volatiles were removed under reduced pressure. The residue was partitioned between Et_2O (75 mL) and H_2O (50 mL), and the layers were separated. The aqueous layer was further extracted with Et_2O (2 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (23:1 hexanes:EtOAc, then 15:1 hexanes:EtOAc eluent) to afford acyl pyrrole **92** (656 mg, 71% yield) as a colorless oil. R_f 0.30 (9:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 4.0, 1.7 Hz, 1H), 7.06 (dd, *J* = 2.5, 1.7 Hz, 1H), 6.19 (dd, *J* = 4.0, 2.5 Hz, 1H), 5.71 (d, *J* = 10.4 Hz, 1H), 5.67 (d, *J* = 10.0 Hz, 1H), 5.52–5.47 (m, 1H), 4.90 (s, 1H), 4.19 (app. t, *J* = 3.1 Hz, 1H), 3.51 (t, *J* = 8.3 Hz, 2H), 2.52–2.46

(comp. m, 2H), 2.19–2.16 (comp. m, 2H), 1.80–1.78 (m, 3H), 0.92–0.88 (comp. m, 11H), 0.13 (s, 6H), –0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 22/24 C): δ 193.7, 133.5, 129.9, 128.0, 123.8, 121.7, 109.0, 78.2, 69.4, 66.3, 38.6, 38.3, 26.0 (3C), 21.5, 18.1, –1.2 (3C), –4.2, –4.7; IR (film): 3476, 2954, 2931, 2859, 1639, 1412, 1310, 1251, 1085 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+$ calc'd for $C_{24}H_{44}NO_4Si_2$, 466.2809; found, 466.2822; $[\alpha]^{19}_D$ +34.25° (*c* 1.0, C_6H_6).



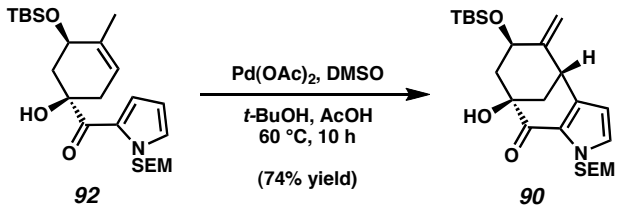
[3.3.1] Bicycle 90. Bromo acyl pyrrole **91** (52.0 mg, 0.0955 mmol), Pd_2dba_3 (21.9 mg, 0.0239 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (24.4 mg, 0.0477 mmol), THF (1.2 mL), and Cy_2NMe (24.3 μL, 0.115 mmol) were combined under a glovebox atmosphere and stirred at 23 °C for 10 h. The reaction vessel was removed from the glovebox, diluted with 3:1 hexanes:EtOAc (2 mL), and filtered over a plug of silica gel topped with Celite® (3:1 hexanes:EtOAc eluent). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (CH_2Cl_2, then 3:1 hexanes:EtOAc eluent). The crude product was further purified by flash chromatography (6:1 hexanes:EtOAc eluent) to afford [3.3.1] bicycle **90** (16.7 mg, 38% yield) and [3.2.2] bicycle **102** (14.4 mg, 33% yield), both as pale yellow oils.

[3.3.1] Bicycle 90: R_f 0.20 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07 (d, *J* = 2.7 Hz, 1H), 6.05 (d, *J* = 2.7 Hz, 1H), 5.71 (d, *J* = 9.9 Hz, 1H), 5.58 (d, *J* = 9.9 Hz,

1H), 5.09–5.05 (m, 2H), 4.00 (s, 1H), 3.99–3.90 (m, 1H), 3.84 (app. t, *J* = 3.0 Hz, 1H), 3.55–3.47 (m, 2H), 2.39 (app. dt, *J* = 7.4, 3.8 Hz, 1H), 2.13–2.03 (comp. m, 2H), 1.73 (app. t, *J* = 11.8 Hz, 1H), 0.98–0.76 (comp. m, 11H), –0.04 (s, 9H), –0.11 (s, 6H); ^{1}H NMR (300 MHz, C_6D_6): δ 6.53 (d, *J* = 2.5 Hz, 1H), 5.77 (d, *J* = 2.8 Hz, 1H), 5.55 (d, *J* = 10.2 Hz, 1H), 5.32 (app. t, *J* = 1.9 Hz, 1H), 5.26 (d, *J* = 10.2 Hz, 1H), 5.01–4.97 (m, 1H), 4.29 (s, 1H), 4.27–4.19 (m, 1H), 3.59–3.47 (comp. m, 3H), 2.45–2.31 (comp. m, 2H), 2.16 (dd, *J* = 12.1, 3.0 Hz, 1H), 2.07 (app. t, *J* = 11.8 Hz, 1H), 0.92–0.89 (comp. m, 11H), 0.01 (s, 9H), –0.06 (s, 3H), –0.07 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 191.5, 149.4, 141.8, 132.0, 125.5, 108.5, 107.4, 76.8, 75.8, 68.4, 66.3, 48.9, 45.5, 40.7, 26.3 (3C), 18.8, 18.2, –0.8 (3C), –4.4, –4.7; IR (film): 3480, 2953, 2858, 1651, 1420, 1318, 1251, 1100, 1077 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calc'd for $C_{24}H_{41}NO_4Si_2$, 463.2574; found, 463.2577; $[\alpha]^{23}_D$ –275.07° (*c* 1.0, $CHCl_3$).

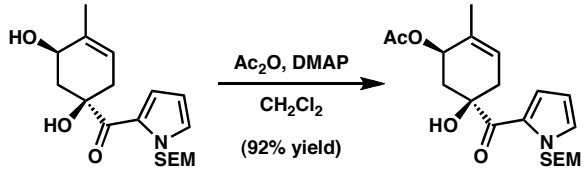
[3.2.2] Bicycle 102: R_f 0.42 (5:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.55 (d, *J* = 2.7 Hz, 1H), 6.23 (d, *J* = 8.8 Hz, 1H), 5.96 (d, *J* = 3.3 Hz, 1H), 5.94 (d, *J* = 9.2 Hz, 1H), 5.59 (d, *J* = 10.4 Hz, 1H), 5.40 (d, *J* = 9.9 Hz, 1H), 5.32 (s, 1H), 3.82–3.75 (m, 1H), 3.46 (t, *J* = 7.7 Hz, 2H), 2.46 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.25 (dd, *J* = 13.7, 1.6 Hz, 1H), 1.52 (s, 3H), 0.92 (s, 9H), 0.82 (t, *J* = 8.0 Hz, 2H), –0.03 (s, 3H), –0.08 (s, 3H), –0.09 (s, 9H); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (d, *J* = 2.7 Hz, 1H), 6.15 (d, *J* = 2.7 Hz, 1H), 6.02 (d, *J* = 9.3 Hz, 1H), 5.98 (d, *J* = 8.8 Hz, 1H), 5.69 (d, *J* = 9.9 Hz, 1H), 5.62 (d, *J* = 9.9 Hz, 1H), 4.93 (s, 1H), 3.81 (d, *J* = 7.7 Hz, 1H), 3.50 (t, *J* = 8.0 Hz, 2H), 2.36 (dd, *J* = 14.3, 7.7 Hz, 1H), 1.94 (dd, *J* = 14.3, 1.6 Hz, 1H), 1.55 (s, 3H), 0.91–0.83 (comp. m, 11H), 0.02 (s, 3H), 0.01 (s, 3H), –0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.7,

144.1, 139.4, 134.5, 129.1, 121.8, 107.7, 78.2, 77.8, 73.3, 66.4, 45.7, 45.0, 26.0 (3C), 22.2, 18.2, 18.0, –1.25 (3C), –4.1, –4.6; IR (film): 3432, 2955, 2858, 1645, 1250, 1081 cm^{-1}; HRMS-EI (*m*/*z*): $[M + H]^+$ calc'd for $C_{24}H_{42}NO_4Si_2$, 464.2652; found, 464.2665; $[\alpha]^{19}_D$ +19.22° (*c* 1.0, C_6H_6).



92 *90*

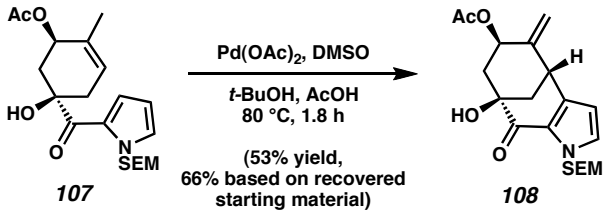
Alternate Procedure. To acyl pyrrole **92** (106.0 mg, 0.227 mmol) was added $Pd(OAc)_2$ (51.1 mg, 0.227 mmol), DMSO (32.3 μL, 0.455 mmol), *t*-BuOH (18.2 mL), and AcOH (4.5 mL). The mixture was heated to 60 °C for 10 h, cooled to 23 °C, and filtered over a plug of silica gel (3:1 hexanes:EtOAc eluent). The solvent was evaporated, and the residue was again filtered over a plug of silica gel (3:1 hexanes:EtOAc eluent). After removal of solvent in vacuo, the product was purified by flash chromatography on silica gel (6:1 hexanes:EtOAc eluent) to afford [3.3.1] bicycle **90** (78.4 mg, 74% yield) as a pale yellow oil.



111 *107*

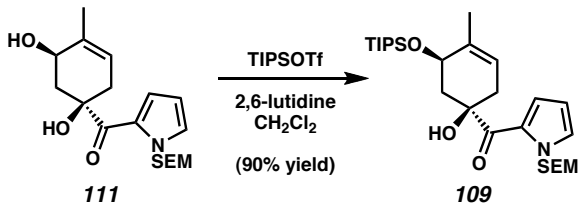
Allylic Acetate 107. To allylic alcohol **111**[73] (131.0 mg, 0.37 mmol) in CH_2Cl_2 (7.5 mL) at 23 °C was added DMAP (68.1 mg, 0.56 mmol) followed by Ac_2O (53 μL, 0.56 mmol). After stirring for 50 min, the reaction was quenched by the addition of

saturated aq. $NaHCO_3$ (10 mL). Et_2O (30 mL) was added, the phases were partitioned, and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organics were washed successively with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated in vacuo. Flash chromatography of the crude product (7:3 hexanes:Et_2O eluent) provided allylic acetate **107** (134.4 mg, 92%) as a colorless oil. R_f 0.21 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.71 (dd, *J* = 3.9, 1.7 Hz, 1H), 6.76 (dd, *J* = 2.6, 1.8 Hz, 1H), 6.10 (dd, *J* = 4.0, 2.6 Hz, 1H), 5.63 (d, *J* = 10.2 Hz, 1H), 5.57 (d, *J* = 9.9 Hz, 1H), 5.50–5.45 (m, 1H), 5.32–5.26 (m, 1H), 3.45 (t, *J* = 7.8 Hz, 2H), 3.39 (s, 1H), 2.69–2.58 (m, 1H), 2.51–2.35 (comp. m, 2H), 2.28 (app. dt, *J* = 8.6, 5.0 Hz, 1H), 1.60–1.57 (comp. m, 6H), 0.84 (t, *J* = 7.8 Hz, 2H), –0.07 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 193.4, 169.9, 131.2, 130.6, 128.3, 124.6, 124.0, 109.2, 78.5, 77.6, 69.7, 66.4, 38.4, 38.3, 20.9, 20.8, 18.3, –1.0 (3C); IR (film) 3458 (br), 2924, 1734, 1641, 1314, 1372, 1247, 1085 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{20}H_{32}NO_5Si$, 394.2050; found, 394.2030; $[\alpha]^{27}_D$ +22.38° (*c* 1.0, C_6H_6).



Allylic Acetate 108. For representative procedures, see oxidative cyclization of **92** → **90** or **113** → **114**. Purified by preparative thin-layer chromatography (4:1 CH_2Cl_2:Et_2O eluent). *Note:* Table 3.2.2, Entry 5 was performed in a round-bottom flask fitted with reflux condenser and an O_2 balloon. R_f 0.56 (4:1 CH_2Cl_2:Et_2O); ^{1}H NMR (300 MHz, C_6D_6): δ 6.52 (d, *J* = 2.7 Hz, 1H), 5.76 (d, *J* = 2.7 Hz, 1H), 5.51–5.41 (m, 1H), 5.46

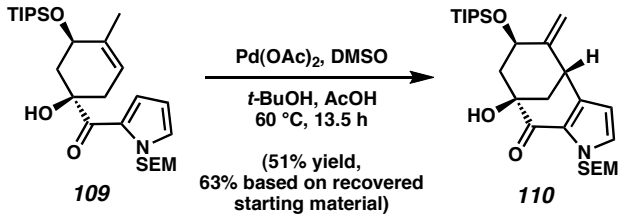
(d, *J* = 10.4 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 4.93 (app. t, *J* = 1.7 Hz, 1H), 4.91–4.88 (m, 1H), 4.35 (s, 1H), 3.56 (t, *J* = 7.7 Hz, 2H), 3.47 (app. t, *J* = 3.1 Hz, 1H), 2.49–2.36 (comp. m, 2H), 2.17–2.09 (m, 1H), 1.94 (app. t, *J* = 12.0 Hz, 1H), 1.55 (s, 3H), 0.96–0.86 (m, 2H), –0.01 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 190.6, 169.2, 145.5, 141.0, 132.4, 125.4, 108.6, 106.8, 76.8, 75.4, 69.0, 66.5, 45.3, 44.5, 40.9, 20.6, 18.2, –0.9 (3C); IR (film) 3469 (br), 2952, 1743, 1651, 1237, 1093, 1037 cm^{-1}; HRMS-FAB (*m*/*z*): [M+H]$^+$ calc'd for $C_{20}H_{30}NO_5Si$, 392.1893; found, 392.1886; $[\alpha]^{27}_D$ –389.72° (*c* 0.6, C_6H_6).



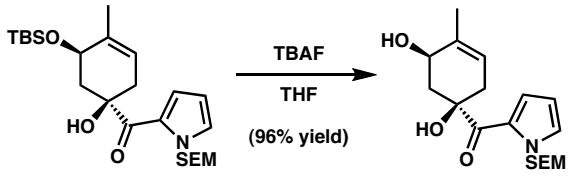
111 *109*

TIPS Ether 109. To allylic alcohol **111**[73] (50.7 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) at 23 °C was added 2,6-lutidine (34 μL, 0.29 mmol), followed by TIPSOTf (44 μL, 0.16 mmol). After stirring 5 min, saturated aq. NH_4Cl (5 mL) was added to quench the reaction. The phases were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (5 mL), and dried over $MgSO_4$. Following evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to provide TIPS ether **109** (65.8 mg, 90%) as a colorless oil. R_f 0.58 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 8.12 (dd, *J* = 3.9, 1.6 Hz, 1H), 6.77 (dd, *J* = 2.5, 1.6 Hz, 1H), 6.15 (dd, *J* = 3.9, 2.5 Hz, 1H), 5.69 (d, *J* = 10.1 Hz, 1H), 5.65 (d, *J* = 9.6 Hz, 1H), 5.34–5.29 (m, 1H), 5.00 (s, 1H), 4.24–4.19 (m, 1H), 3.49 (t, *J* = 7.8 Hz, 2H), 2.69–2.63 (comp. m, 2H), 2.50–2.42 (m, 1H), 2.40–2.32 (m, 1H), 1.78–1.74 (m, 3H), 1.09–0.97 (comp. m, 21H), 0.85 (t, *J* =

7.8 Hz, 2H), –0.06 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 194.1, 133.8, 130.3, 129.0, 124.7, 122.8, 109.2, 78.9, 78.5, 70.5, 66.3, 39.6, 39.4, 22.0, 18.7 (3C), 18.7 (3C), 18.4, 13.3 (3C), –0.9 (3C); IR (film) 3472 (br), 2947, 2868, 1639, 1413, 1310, 1249, 1084 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{27}H_{50}NO_4Si_2$, 508.3278; found, 508.3273; $[\alpha]^{27}_D$ +29.49° (*c* 1.0, C_6H_6).



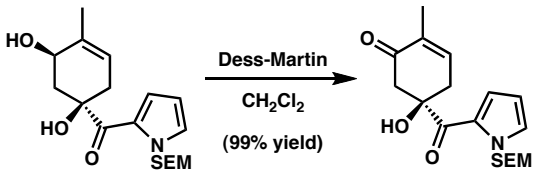
TIPS Ether 110. For representative procedures, see oxidative cyclization of **92 → 90** or **113 → 114**. Purified by preparative thin-layer chromatography (4:1 hexanes:EtOAc eluent). R_f 0.29 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.54 (d, *J* = 2.7 Hz, 1H), 5.78 (d, *J* = 2.7 Hz, 1H), 5.52 (d, *J* = 10.1 Hz, 1H), 5.41 (app. t, *J* = 2.1 Hz, 1H), 5.32 (d, *J* = 10.1 Hz, 1H), 5.02 (app. t, *J* = 2.3 Hz, 1H), 4.38–4.29 (m, 1H), 4.25 (s, 1H), 3.59–3.45 (comp. m, 3H), 2.50–2.38 (comp. m, 2H), 2.21–2.04 (comp. m, 2H), 1.09–0.78 (comp. m, 23H), –0.01 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 191.5, 149.6, 141.7, 131.8, 125.6, 108.5, 107.5, 76.9, 75.9, 68.6, 66.5, 49.2, 40.7, 18.6 (3C) 18.6 (3C), 18.2, 13.1 (3C), –0.9 (3C); IR (film) 3478 (br), 2946, 2867, 1650, 1100, 1080 cm^{-1}; HRMS-EI (*m*/*z*): [M]$^+$ calc'd for $C_{27}H_{47}NO_4Si_2$, 505.3044; found, 505.3041; $[\alpha]^{27}_D$ –207.44° (*c* 0.6, C_6H_6).



92 *111*

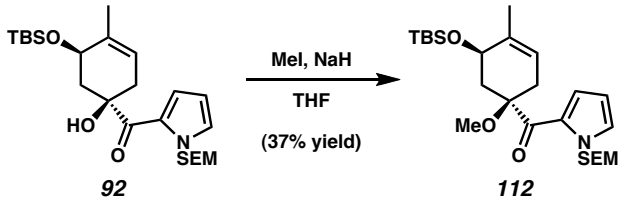
Allylic Alcohol 111. To allylic silyl ether **92** (100.0 mg, 0.21 mmol) in THF (5 mL) at 23 °C was added TBAF (1.0 M in THF, 250 μL, 0.25 mmol). After stirring 5 min, the reaction mixture was quenched by the addition of saturated aq. NH_4Cl (5 mL). The reaction was poured into Et_2O (5 mL) and H_2O (5 mL), and the phases were partitioned. The aqueous phase was extracted with Et_2O (4 x 3 mL), and the combined organic extracts were dried by passage over a plug of SiO_2 gel (Et_2O eluent). The solvent was evaporated in vacuo, and the residue was passed over another plug of SiO_2 gel (Et_2O eluent) to afford allylic alcohol **111** (72.8 mg, 96% yield) as a colorless oil. R_f 0.38 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.01 (dd, *J* = 4.1, 1.7 Hz, 1H), 6.70 (dd, *J* = 2.5, 1.7 Hz, 1H), 5.99 (dd, *J* = 4.1, 2.8 Hz, 1H), 5.52 (d, *J* = 10.0 Hz, 1H), 5.49 (d, *J* = 10.2 Hz, 1H), 5.31–5.25 (m, 1H), 4.95 (s, 1H), 3.93–3.84 (m, 1H), 3.60 (app. d, *J* = 9.6 Hz, 1H), 3.41 (t, *J* = 7.8 Hz, 2H), 2.77–2.65 (m, 1H), 2.27–2.16 (comp. m, 3H), 1.93–1.89 (m, 3H), 0.82 (t, *J* = 7.7 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 194.0, 136.2, 131.0, 126.9, 123.5, 120.0, 109.5, 78.8, 77.8, 68.1, 66.6, 41.0, 38.7, 21.7, 18.3, –1.0 (3C); IR (film) 3388 (br), 2953, 1632, 1412, 1309, 1249, 1086 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{18}H_{30}NO_4Si$, 352.1944; found, 352.1941; $[\alpha]^{27}_D$ +31.11° (*c* 1.0, C_6H_6).

*For entry 2 (Table 3.2.2) and entry 8 (Table 3.4.2), small quantities of enone **173** were observed. An authentic sample was prepared as follows:*

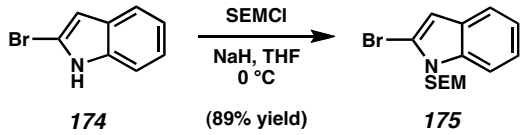


111 ***173***

Enone 173. To allylic alcohol **111** (11.4 mg, 0.032 mmol) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (31.4 mg, 0.074 mmol). After stirring for 20 min, a solution of saturated $Na_2S_2O_3$: saturated $NaHCO_3$ (1:1, 1 mL) was added to quench the reaction. The phases were partitioned, and the aqueous phase was extracted with Et_2O (1 x 4 mL). The combined organics were dried by passage over a plug of SiO_2, and the solvent was evaporated in vacuo. The residue was purified by preparative thin layer chromatography (1:1 hexanes:EtOAc eluent) to furnish enone **173** (11.4 mg, 99% yield) as a pale yellow oil. R_f 0.40 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.03 (dd, *J* = 4.1, 1.4 Hz, 1H), 6.68 (dd, *J* = 2.5, 1.6 Hz, 1H), 5.97 (dd, *J* = 4.1, 2.7 Hz, 1H), 5.92–5.87 (m, 1H), 5.48 (d, *J* = 9.6 Hz, 1H), 5.43 (d, *J* = 9.6 Hz, 1H), 3.40 (t, *J* = 7.8 Hz, 2H), 3.25 (s, 1H), 2.98 (d, *J* = 16.0 Hz, 1H), 2.83–2.73 (m, 1H), 2.66 (dd, *J* = 16.3, 1.6 Hz, 1H), 2.25–2.14 (m, 1H), 1.84–1.81 (m, 3H), 0.82 (t, *J* = 7.8 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 195.2, 191.4, 138.9, 135.8, 131.1, 126.7, 123.5, 109.5, 80.3, 78.7, 66.6, 49.5, 38.4, 18.3, 16.4, –1.0 (3C); IR (film) 3424 (br), 2953, 1677, 1639, 1412, 1249, 1085 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{18}H_{28}NO_4Si$, 350.1788; found, 350.1784; $[\alpha]^{27}_D$ –21.94° (*c* 1.0, C_6H_6).

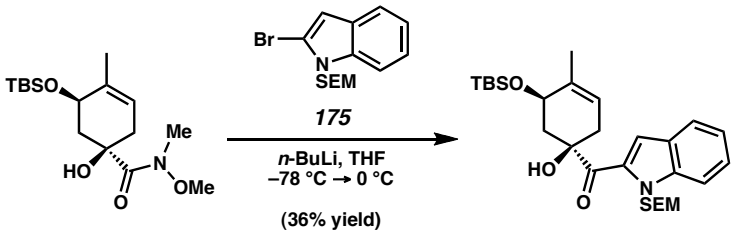


Methyl Ether 112. To allylic silyl ether **92** (55.0 mg, 0.12 mmol) in THF (2 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 95.5 mg, 2.39 mmol). After stirring for 5 min, MeI (200 μL, 3.21 mmol) was added. After stirring for 30 min, saturated aq. NH_4Cl (2 mL) was added dropwise over 1 min to quench the reaction. EtOAc (1 mL) was added, and the phases were partitioned. The aqueous phase was extracted with EtOAc (2 x 1 mL), and the combined organic extracts were washed with brine (1 mL) and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to afford methyl ether **112** (21.1 mg, 37% yield). R_f 0.53 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.76 (dd, *J* = 3.9, 1.6 Hz, 1H), 6.69 (dd, *J* = 2.5, 1.5 Hz, 1H), 6.08 (dd, *J* = 3.9, 2.5 Hz, 1H), 5.64 (d, *J* = 9.6 Hz, 1H), 5.45 (d, *J* = 10.1 Hz, 1H), 5.35–5.30 (m, 1H), 4.52–4.43 (m, 1H), 3.45 (t, *J* = 7.8 Hz, 2H), 3.10 (s, 3H), 2.99–2.85 (comp. m, 2H), 2.36–2.25 (m, 1H), 2.22 (dd, *J* = 12.4, 9.2 Hz, 1H), 1.82–1.79 (m, 3H), 0.98 (s, 9H), 0.88–0.82 (m, 2H), 0.09 (s, 3H), 0.07 (s, 3H), –0.05 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6, 24/25 C): δ 193.2, 136.5, 130.0, 122.2, 120.7, 109.2, 84.6, 78.2, 70.1, 66.4, 51.7, 42.4, 35.0, 26.4 (3C), 20.3, 18.6, 18.4, –1.0 (3C), –3.7, –4.4; IR (film) 2954, 1645, 1412, 1250, 1079 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{25}H_{46}NO_4Si_2$, 480.2965; found, 480.2958; $[\alpha]^{27}_D$ +43.57° (*c* 1.0, C_6H_6).



174 (89% yield) *175*

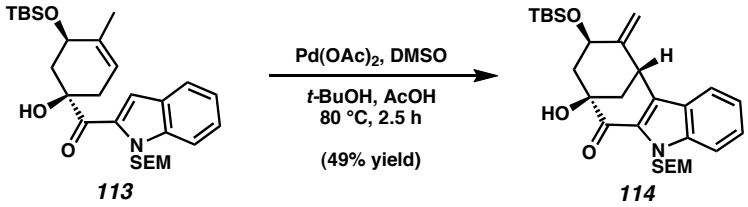
2-Bromo SEM Indole (175). To a solution of 2-bromoindole[74] (**174**, 500.0 mg, 2.55 mmol) in THF (25 mL) cooled to 0 °C was added NaH (60% dispersion in mineral oil, 145.2 mg, 3.63 mmol). After H_2 evolution ceased (3 min), SEMCl (500.0 μL, 2.82 mmol) was added dropwise over 1 min. The reaction was stirred for 10 min, and was quenched by the addition of saturated aq. NH_4Cl (20 mL). Et_2O (50 mL) was added, the phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 75 mL). The combined organic extracts were washed with brine (15 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography (9:1 hexanes:Et_2O eluent) to afford 2-bromo SEM indole (**175**, 741.3 mg, 89% yield) as a colorless oil. R_f 0.60 (4:1 hexanes:EtOAc).



101 (36% yield) *113*

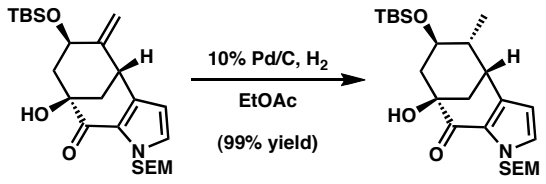
Indole 113. To 2-bromo SEM indole (**175**, 482.6 mg, 1.48 mmol) in THF (7 mL) cooled to –78 °C was added *n*-BuLi (2.5 M in hexanes, 590 μL, 1.48 mmol). The solution was stirred for 10 min, and was then treated dropwise over 1 min with a solution of Weinreb amide **101** (161.5 mg, 0.49 mmol) in THF (2 mL). The solution was immediately warmed to 0 °C and stirred for 30 min. The reaction was quenched at –78 °C with saturated aq. NH_4Cl (10 mL), and was allowed to thaw slowly to 23 °C. Et_2O (50

mL) was added, the phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 75 mL). The combined organic extracts were washed successively with H_2O (15 mL) and brine (15 mL), and dried over $MgSO_4$. Following evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (19:1 hexanes:EtOAc eluent) to furnish indole **113** (92.2 mg, 36% yield) as a colorless oil. R_f 0.48 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 8.41 (s, 1H), 7.64–7.60 (m, 1H), 7.50–7.46 (m, 1H), 7.28–7.21 (m, 1H), 7.10–7.04 (m, 1H), 6.03–5.95 (m, 2H), 5.35–5.30 (m, 1H), 5.23 (s, 1H), 3.96–3.92 (m, 1H), 3.58 (t, *J* = 7.8 Hz, 2H), 2.77–2.57 (comp. m, 2H), 2.42–2.35 (m, 1H), 2.35–2.28 (m, 1H), 1.70–1.67 (m, 3H), 0.93–0.81 (m, 2H), 0.89 (s, 9H), 0.00 (s, 3H), –0.02 (s, 3H), –0.10 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 196.9, 141.0, 133.7, 132.8, 127.5, 126.8, 124.1, 122.3, 121.9, 117.8, 112.2, 79.3, 74.1, 69.9, 66.0, 39.3, 39.3, 26.2 (3C), 21.6, 18.4, 18.3, –0.9 (3C), –4.3, –4.6; IR (film) 3466 (br), 2954, 1655, 1250, 1072 cm^{-1}; HRMS-EI (*m/z*): [M]$^+$ calc'd for $C_{28}H_{45}NO_4Si_2$, 515.2887; found, 515.2893; $[\alpha]^{27}_D$ –12.17° (*c* 1.0, C_6H_6).



Indole 114. To indole **113** (23.5 mg, 0.05 mmol) was added $Pd(OAc)_2$ (10.2 mg, 0.05 mmol), DMSO (6.5 μL, 0.09 mmol), *t*-BuOH (3.6 mL), and AcOH (0.9 mL). The mixture was heated at 80 °C for 2.5 h, cooled to 23 °C, and filtered over a plug of silica gel (EtOAc eluent). The solvent was evaporated, and the crude product was purified by flash chromatography on silica gel (19:1 hexanes:EtOAc eluent) to afford pure [3.3.1]

bicycle. R_f 0.33 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.52–7.46 (m, 1H), 7.37–7.32 (m, 1H), 7.20–7.14 (m, 1H), 7.05–6.97 (m, 1H), 5.97 (d, *J* = 10.9 Hz, 1H), 5.73 (d, *J* = 10.9 Hz, 1H), 5.39 (app. t, *J* = 2.1 Hz, 1H), 5.11 (app. t, *J* = 2.0 Hz, 1H), 4.24–4.15 (m, 1H), 4.18 (s, 1H), 3.85 (app. t, *J* = 3.2 Hz, 1H), 3.69–3.52 (m, 2H), 2.47 (app. dt, *J* = 7.5, 3.9 Hz, 1H), 2.40–2.31 (m, 1H), 2.29–2.22 (m, 1H), 2.11 (app. t, *J* = 11.8 Hz, 1H), 1.01–0.77 (m, 2H), 0.83 (s, 9H), –0.05 (s, 9H), –0.17 (s, 3H), –0.24 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6, 27/28 C): δ 194.9, 148.1, 141.6, 133.8, 129.1, 125.0, 122.2, 122.1, 112.6, 108.3, 76.5, 73.6, 68.3, 66.1, 48.6, 45.4, 38.7, 26.2 (3C), 18.7, 18.2, –0.9 (3C), –4.5, –4.8; IR (film) 3485, 2953, 1657, 1250, 1106, 1073 cm^{-1}; HRMS-FAB (*m/z*): [M]$^+$ calc'd for $C_{28}H_{43}NO_4Si_2$, 513.2731; found, 513.2719; $[\alpha]^{27}_D$ –281.78° (*c* 0.3, C_6H_6).

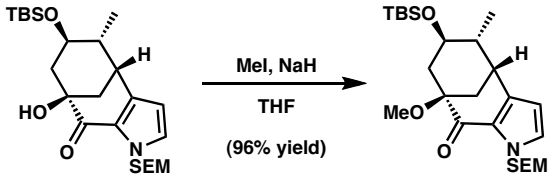


90 *176*

Reduced [3.3.1] Bicycle 176. [3.3.1] Bicycle **90** (360 mg, 0.78 mmol), 10% Pd/C (130 mg, 0.12 mmol), and EtOAc (8 mL) were combined, and the reaction vessel was evacuated and back-filled with H_2 (1 atm). The reaction mixture was stirred under H_2 for 30 min, then filtered over a plug of silica gel topped with Celite® (EtOAc eluent) to afford reduced [3.3.1] bicycle **176** as a colorless oil (358 mg, 99% yield). R_f 0.28 (5:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.55 (d, *J* = 2.5 Hz, 1H), 5.74 (d, *J* = 2.5 Hz, 1H), 5.56 (d, *J* = 10.2 Hz, 1H), 5.30 (d, *J* = 10.2 Hz, 1H), 4.27 (s, 1H), 3.59–3.45 (m, 2H), 3.19 (ddd, *J* = 12.9, 7.7, 3.3 Hz, 1H), 2.58 (dd, *J* = 6.5, 3.2 Hz, 1H), 2.37–2.20

(comp. m, 2H), 2.06–1.90 (comp. m, 2H), 1.63–1.50 (m, 1H), 1.00 (d, J = 6.6 Hz, 3H), 0.94–0.89 (comp. m, 11H), –0.02 (s, 9H), –0.06 (s, 3H), –0.09 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 190.8, 140.4, 131.3, 125.2, 110.1, 76.6, 75.6, 71.8, 66.1, 46.8, 44.3, 40.0, 37.3, 25.9 (3C), 18.1, 17.9, 16.5, –1.2 (3C), –4.0, –4.6; IR (film): 3473 (br), 2953, 2931, 2857, 1651, 1420, 1249, 1079 cm^{-1}; HRMS-EI (m/z): [M + H]$^+$ calc'd for $C_{24}H_{44}NO_4Si_2$, 466.2809; found, 466.2804; $[\alpha]^{19}_D$ –166.30° (*c* 1.0, C_6H_6).

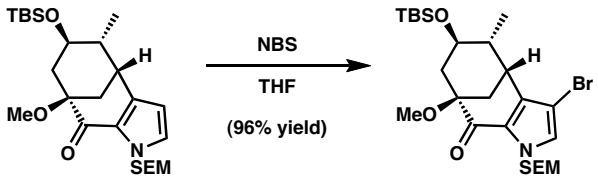
NOTE: In some instances, trace phosphine contaminants from the Heck reaction (i.e., ***91 → 90****) prevented the reduction from occurring. Simply working up the reaction and re-exposing it to the identical reaction conditions (as described above) allowed the reduction to proceed.*



176 ***115***

Methyl Ether 115. To reduced [3.3.1] bicycle **176** (358 mg, 0.77 mmol) in THF (7.7 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 123 mg, 3.08 mmol). After stirring for 2 min at 23 °C, MeI was added (335 μL, 5.38 mmol). The resulting mixture was stirred for 1 h, cooled to 0 °C, and quenched with saturated aq. NH_4Cl (4 mL), then warmed to 23 °C. Et_2O (10 mL) and H_2O (5 mL) were added, and the layers were separated. The aqueous layer was further extracted with Et_2O (2 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash

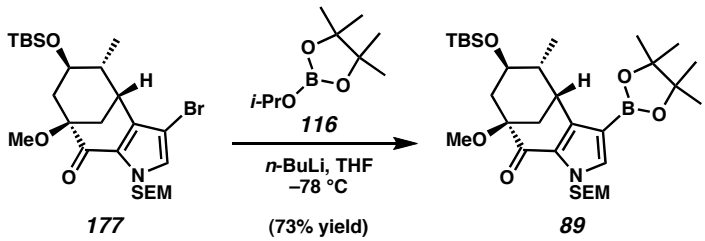
chromatography (4:1 hexanes:EtOAc eluent) to afford methyl ether **115** (354 mg, 96% yield) as a colorless oil. R_f 0.34 (5:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.58 (d, *J* = 2.8 Hz, 1H), 5.78 (d, *J* = 2.5 Hz, 1H), 5.57 (d, *J* = 10.2 Hz, 1H), 5.54 (d, *J* = 10.2 Hz, 1H), 3.65–3.50 (m, 2H), 3.37 (s, 3H), 3.22 (ddd, *J* = 12.9, 7.9, 3.1 Hz, 1H), 2.68 (dd, *J* = 6.5, 3.2 Hz, 1H), 2.59–2.49 (comp. m, 2H), 1.86 (dd, *J* = 12.4 Hz, 11.3 Hz, 1H), 1.72–1.56 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.93–0.85 (comp. m, 11H), –0.02 (s, 9H), –0.07 (s, 3H), –0.10 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6, 24/25 C): δ 189.4, 138.3, 130.4, 109.7, 81.9, 76.9, 72.4, 66.2, 51.8, 45.9, 41.3, 41.2, 37.6, 26.4 (3C), 18.5, 18.3, 17.0, –0.9 (3C), –3.6, –4.4; IR (film): 2954, 1657, 1421, 1250, 1085 cm^{-1}; HRMS-EI (*m*/*z*): [M + H]$^+$ calc'd for $C_{25}H_{46}NO_4Si_2$, 480.2965; found, 480.2970; $[\alpha]^{19}_D$ –172.9° (*c* 1.0, C_6H_6).



115 *177*

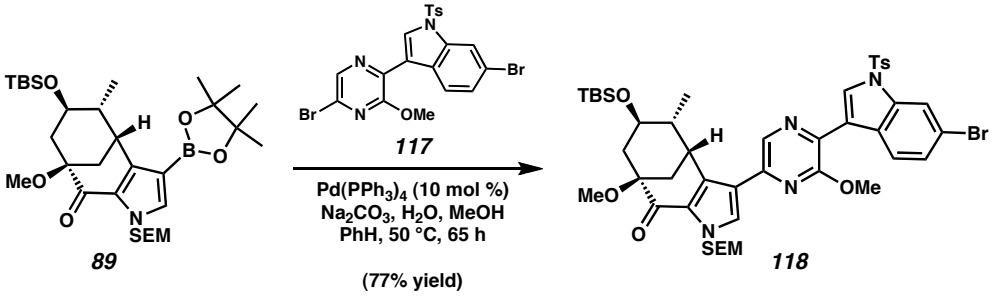
Bromide 177. To methyl ether **115** (305 mg, 0.64 mmol) in THF (6 mL) at 0 °C was added freshly recrystallized NBS (147 mg, 0.83 mmol). After stirring for 10 min at 0 °C, the reaction mixture was warmed to 23 °C, and additional NBS (30 mg, 0.17 mmol) was added. After 5 min, the reaction was quenched with saturated aq. $Na_2S_2O_3$, diluted with H_2O (15 mL), and extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes:EtOAc eluent) to afford bromide **177** (340 mg, 96% yield) as a colorless oil. R_f 0.55 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.57 (s, 1H), 5.46 (d, *J* = 10.2 Hz, 1H),

5.34 (d, *J* = 10.2 Hz, 1H), 3.57–3.41 (m, 2H), 3.32–3.20 (m, 4H), 2.88 (dd, *J* = 6.5, 3.2 Hz, 1H), 2.46 (ddd, *J* = 12.2, 5.1, 2.5 Hz, 1H), 2.28 (app. dt, *J* = 7.4, 4.0 Hz, 1H), 1.78 (app. t, *J* = 11.8 Hz, 1H), 1.69–1.57 (m, 1H), 1.52 (dd, *J* = 11.8, 3.0 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.91–0.80 (comp. m, 11H), –0.05 (s, 9H), –0.09 (s, 3H), –0.12 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 189.6, 147.2, 137.2, 130.1, 98.4, 81.8, 77.0, 72.1, 66.6, 51.8, 45.8, 42.4, 41.0, 35.9, 26.3 (3C), 18.5, 18.3, 17.8, –0.9 (3C), –3.7, –4.3; IR (film): 2954, 2930, 1664, 1249, 1089 cm^{-1}; HRMS-EI (*m*/*z*): [M + H]$^+$ - H_2 calc'd for $C_{25}H_{43}NO_4Si_2Br$, 556.1914; found, 556.1928; $[\alpha]^{19}_D$ –98.22° (*c* 1.0, C_6H_6).



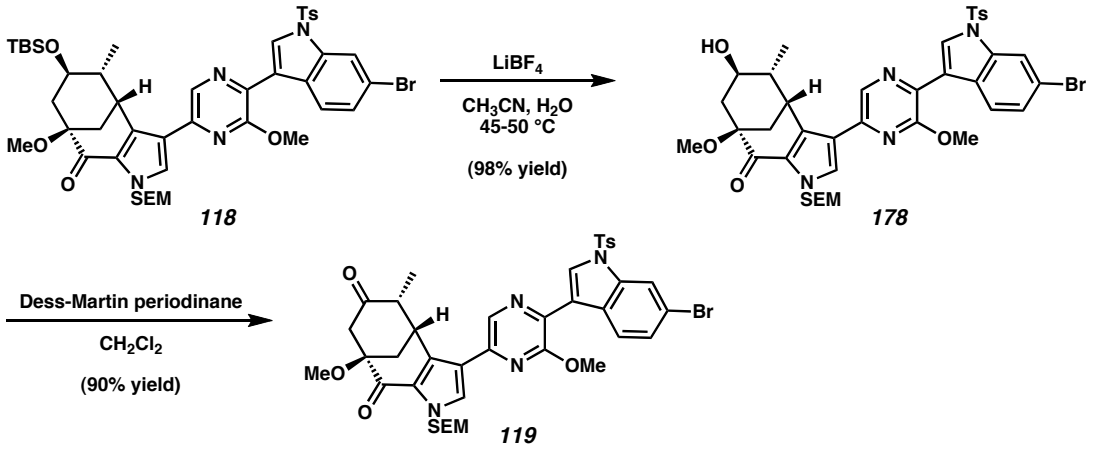
Boronic Ester 89. To bromide **177** (116 mg, 0.21 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**116**) (847 μL, 4.15 mmol) in THF (10.4 mL) at –78 °C was added *n*-BuLi (2.3 M in hexanes, 1.35 mL, 3.11 mmol) dropwise over 2 min. After stirring for 15 min at –78 °C, the reaction mixture was quenched with saturated aq. NH_4Cl, warmed to 23 °C, and diluted with H_2O (10 mL). The mixture was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (4:1 hexanes:EtOAc with 0.5% Et_3N eluent) to afford boronic ester **89** (92 mg, 73% yield) as a white powder, which was used immediately in the next step. R_f 0.50 (3:1 hexanes:EtOAc); mp 143–145 °C; ^{1}H NMR (300 MHz, C_6D_6): δ 7.42 (s, 1H), 5.55 (d, *J* = 10.1 Hz, 1H), 5.51 (d, *J* = 9.8 Hz, 1H), 3.74–3.68 (m, 1H), 3.60–3.50 (m,

2H), 3.43–3.36 (m, 1H), 3.33 (s, 3H), 2.65–2.53 (comp. m, 2H), 1.91 (app. t, J = 11.8 Hz, 1H), 1.89–1.80 (m, 1H), 1.68 (dd, J = 11.8, 2.8 Hz, 1H), 1.34 (d, J = 6.6 Hz, 3H), 1.15 (s, 6H), 1.14 (s, 6H), 0.94–0.81 (comp. m, 11H), –0.04 (s, 3H), –0.05 (s, 9H), –0.07 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6, 30/31 C): δ 190.1, 145.1, 139.3, 130.2, 83.5 (2C), 82.0, 77.2, 72.6, 66.5, 51.7, 46.1, 42.0, 41.6, 36.8, 26.4 (3C), 25.4 (2C), 25.2 (2C), 18.5, 18.3, 16.9, –0.9 (3C), –3.6, –4.3; IR (film): 2953, 2931, 2858, 1658, 1543, 1249, 1141, 1085 cm^{-1}; HRMS-FAB (m/z): [M + H]$^+$ calc'd for $C_{31}H_{57}BNO_6Si_2$, 606.3818; found, 606.3805; $[\alpha]^{19}_D$ –98.84° (c 1.0, C_6H_6).



Suzuki Adduct 118. Bromopyrazine **117** (46.5 mg, 0.087 mmol), boronic ester **89** (35 mg, 0.058 mmol), benzene (1.15 mL), methanol (231 μL), 2 M aq. Na_2CO_3 (96 μL), and tetrakis(triphenylphosphine)palladium(0) (6.7 mg, 0.0058 mmol) were combined and deoxygenated by sparging with argon for 5 min. The reaction vessel was evacuated, purged with N_2, sealed, heated to 50 °C for 65 h, cooled to 23 °C, then quenched by the addition of Na_2SO_4 (200 mg). Following filtration over a pad of silica gel (2:1 hexanes:EtOAc eluent) and evaporation to dryness under reduced pressure, the remaining residue was purified by flash chromatography (3:1 hexanes:EtOAc eluent) to afford Suzuki adduct **118** (41.5 mg, 77% yield) as a yellow oil. R_f 0.43 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (d, J = 8.5 Hz, 1H), 8.45 (s, 1H),

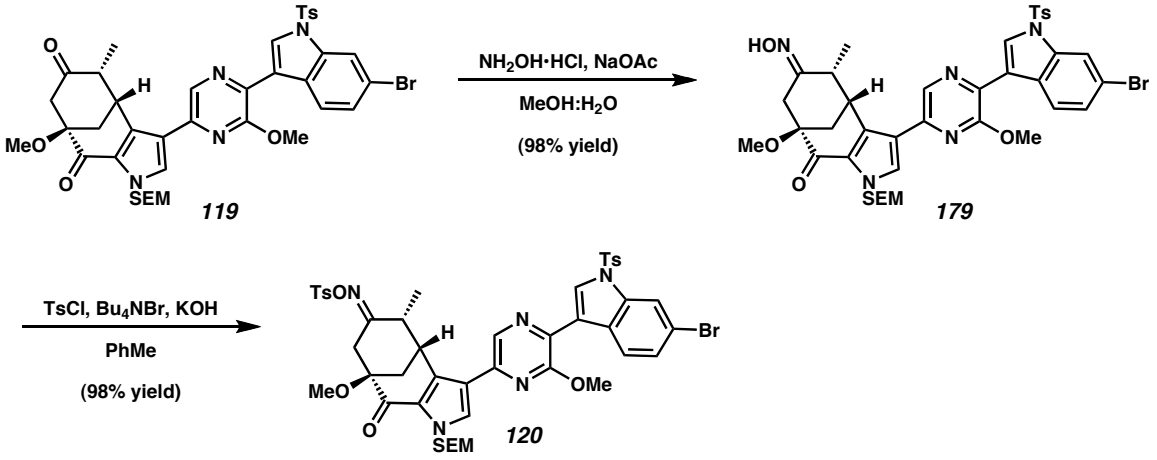
8.44 (s, 1H), 8.16 (d, *J* = 1.5 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.59 (s, 1H), 7.40 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 5.85 (d, *J* = 10.0 Hz, 1H), 5.78 (d, *J* = 10.0 Hz, 1H), 4.27–4.21 (m, 1H), 4.19 (s, 3H), 3.72–3.59 (m, 2H), 3.34 (s, 3H), 3.13–3.02 (m, 1H), 2.87–2.77 (m, 1H), 2.32 (s, 3H), 2.22–2.12 (m, 1H), 1.98–1.89 (m, 1H), 1.82–1.72 (m, 1H), 1.67 (app. t, *J* = 11.7 Hz, 1H), 1.04–0.83 (m, 2H), 0.78 (s, 9H), 0.72 (d, *J* = 6.7 Hz, 3H), –0.02 (s, 9H), –0.09 (s, 3H), –0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 44/45 C): δ 190.0, 156.2, 145.7, 143.6, 136.9, 135.7, 135.5, 135.0, 132.7, 130.3 (2C), 130.2, 129.3, 128.8, 128.5, 127.3, 127.1 (2C), 125.3, 120.5, 119.0, 116.9, 116.4, 81.3, 77.2, 71.4, 66.7, 54.3, 51.6, 44.8, 41.8, 40.2, 34.8, 25.9 (3C), 21.8, 18.1, 16.1, –1.1 (3C), –4.0, –4.7; IR (film): 2952, 1660, 1555, 1372, 1372, 1190, 1140, 1089 cm^{-1}; HRMS-FAB (*m*/*z*): [M]$^+$ calc'd for $C_{45}H_{59}N_4O_7Si_2SBr$, 934.2826; found, 934.2829; $[\alpha]^{21}_D$ +51.73° (*c* 1.0, $CHCl_3$).



Ketone 119. Suzuki adduct **118** (113 mg, 0.121 mmol), $LiBF_4$ (113 mg, 1.21 mmol), acetonitrile (6 mL), and water (600 μL) were heated to 45–50 °C. After 9 h, additional $LiBF_4$ (30 mg, 0.32 mmol) was introduced, and heating was continued. After 6 h, additional $LiBF_4$ (35 mg, 0.32 mmol) was introduced, and heating was continued for 16 h. The reaction mixture was cooled to 23 °C, quenched with 10% aq. citric acid (10

mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography (3:1 EtOAc:hexanes eluent) to yield alcohol **178** (96.9 mg, 98% yield) as a yellow oil, which was used in the subsequent step without further purification. R_f 0.44 (3:1 EtOAc:hexanes).

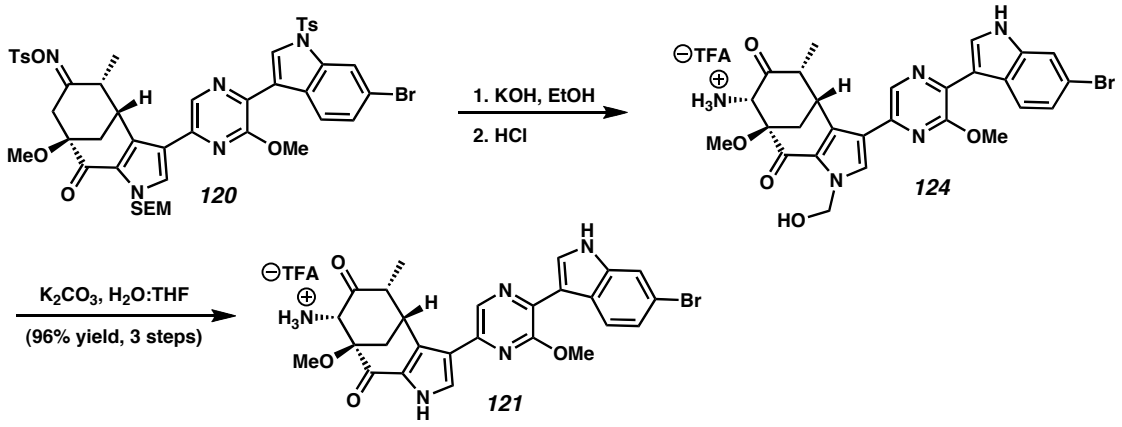
To alcohol **178** (96 mg, 0.117 mmol) in CH_2Cl_2 (2.0 mL) at 23 °C was added Dess-Martin periodinane (74.3 mg, 0.175 mmol). The mixture was stirred for 3 min, quenched with a solution of saturated aq. $NaHCO_3$ and saturated aq. $Na_2S_2O_3$ (1:1, 5 mL), stirred for 5 min, and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (1:1 hexanes:EtOAc eluent) to yield ketone **119** (86 mg, 90% yield) as a yellow foam. R_f 0.48 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (d, *J* = 8.5 Hz, 1H), 8.45 (s, 1H), 8.42 (s, 1H), 8.18 (d, *J* = 1.7 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.56 (s, 1H), 7.42 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 2H), 5.77 (d, *J* = 10.5 Hz, 1H), 5.72 (d, *J* = 10.2 Hz, 1H), 4.62–4.56 (m, 1H), 4.20 (s, 3H), 3.57 (app. dt, *J* = 8.2, 1.8 Hz, 2H), 3.43 (s, 3H), 3.14–3.06 (m, 1H), 2.91–2.81 (m, 1H), 2.74 (s, 2H), 2.40 (dd, *J* = 12.5, 2.9 Hz, 1H), 2.34 (s, 3H), 0.96–0.88 (m, 2H), 0.78 (d, *J* = 6.6 Hz, 3H), –0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 37/39 C): δ 207.2, 188.0, 156.1, 145.7, 143.2, 136.3, 135.7, 134.9, 132.6, 130.7, 130.3 (2C), 128.8, 128.4, 127.3, 127.1 (2C), 125.4, 120.5, 119.0, 116.8, 116.3, 82.4, 77.1, 66.9, 54.3, 52.2, 52.0, 49.2, 40.2, 35.2, 21.8, 18.1, 12.2, –1.2 (3C); IR (film): 2950, 1716, 1664, 1557, 1373, 1190, 1178, 1090 cm^{-1}; HRMS-FAB (*m*/*z*): $[M]^+$ calc'd for $C_{39}H_{43}N_4O_7SiSBr$, 818.1805; found, 818.1836; $[\alpha]^{21}_D$ +71.61° (*c* 1.0, $CHCl_3$).



Tosyl Oxime 120. To ketone **119** (50.0 mg, 0.061 mmol), NH_2OH•HCl (85 mg, 1.22 mmol), and NaOAc•$3H_2O$ (125 mg, 0.915 mmol) was added methanol (2.5 mL), followed by H_2O (350 μL), then additional methanol (5 mL). The homogeneous solution was stirred at 23 °C for 8 h, and the solvent was removed under reduced pressure. H_2O (15 mL) was added, and the resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was further purified by filtration over a plug of silica gel (EtOAc eluent) to yield oxime **179** (50.1 mg, 98% yield) as a yellow foam, which was used without purification in the subsequent reaction. R_f 0.46 (1:1 hexanes:EtOAc).

To a solution of oxime **179** (20.0 mg, 0.0240 mmol), TsCl (14.0 mg, 0.0734 mmol), and Bu_4NBr (1.0 mg, 0.0031 mmol) in toluene (2.0 mL) at 0 °C was added 50% aq. KOH (310 μL). The reaction mixture was stirred at 0 °C for 2 h, quenched with ice-cold H_2O (1.5 mL) and extracted with ice-cold EtOAc (5 x 1 mL). The combined organic layers were washed with brine (1 mL), dried by passage over a plug of silica gel (EtOAc eluent), and evaporated under reduced pressure. The crude product was purified by flash

chromatography (1:1 hexanes:EtOAc eluent) to yield tosyl oxime **120** (23.3 mg, 98% yield) as a yellow foam. R_f 0.48 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, *J* = 8.5 Hz, 1H), 8.46 (s, 1H), 8.41 (s, 1H), 8.19 (d, *J* = 1.4 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.51 (s, 1H), 7.44 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.28–7.19 (comp. m, 4H), 5.87 (d, *J* = 10.2 Hz, 1H), 5.42 (d, *J* = 10.2 Hz, 1H), 4.45–4.43 (m, 1H), 4.20 (s, 3H), 3.67–3.53 (comp. m, 3H), 3.38 (s, 3H), 2.98–2.89 (m, 1H), 2.87–2.77 (m, 1H), 2.42 (s, 3H), 2.35 (s, 3H), 2.12 (d, *J* = 14.0 Hz, 2H), 1.05–0.85 (m, 2H), 0.78 (d, *J* = 6.6 Hz, 3H), –0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.2, 165.8, 156.3, 145.8, 144.8, 143.5, 135.8, 135.7, 135.3, 135.0, 132.9, 132.6, 130.4 (2C), 129.9, 129.4 (2C), 129.1 (2C), 128.9, 128.4, 128.0, 127.5, 127.2 (2C), 125.3, 120.3, 119.2, 116.8, 116.5, 80.8, 77.4, 67.2, 54.4, 52.2, 42.5, 40.3, 36.5, 36.2, 21.9, 21.9, 18.1, 13.7, –1.1 (3C); IR (film): 2946, 1665, 1555, 1373, 1191, 1178, 1140 cm^{-1}; HRMS-FAB (*m*/*z*): $[M]^+$ calc'd for $C_{46}H_{50}N_5O_9SiS_2Br$, 987.2002; found, 987.2038; $[\alpha]^{20}_D$ +139.01° (*c* 1.0, $CHCl_3$).

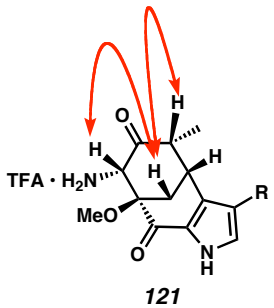


Aminoketone 121. To a stirred solution of tosyl oxime **120** (23.3 mg, 0.0236 mmol) in EtOH (3.5 mL) at 0 °C was added 50% aq. KOH (450 μL) dropwise over 1 min. The reaction mixture was stirred at 0 °C for 3 h, then 6 N aq. HCl (5 mL) was added. The reaction mixture was heated to 60 °C for 10 h, cooled to 23 °C, and purified by reversed-phase filtration through a Sep-Pak column: loaded with water containing 0.1% (*w*/*v*) TFA, washed with 15% acetonitrile:water containing 0.1% (*w*/*v*) TFA to remove salts, then 70% acetonitrile:water containing 0.1% (*w*/*v*) TFA to collect the crude product. The solvents were removed under reduced pressure to afford hemiaminal **124**, which was used immediately in the subsequent reaction. Although hemiaminal **124** is typically used in crude form, it has been observed by ^{1}H NMR. ^{1}H NMR (600 MHz, CD_3OD): δ 8.61 (d, *J* = 8.2 Hz, 1H), 8.52 (s, 1H), 8.24 (s, 1H), 7.94 (s, 1H), 7.60 (s, 1H), 7.25 (d, *J* = 9.2 Hz, 1H), 5.72 (d, *J* = 10.1 Hz, 1H), 5.65 (d, *J* = 10.1 Hz, 1H), 4.85–4.82 (m, 1H), 4.49 (s, 1H), 4.21 (s, 3H), 3.47 (s, 3H), 3.36–3.30 (m, 1H), 3.26 (dd, *J* = 12.8, 2.7 Hz, 1H), 2.61 (dd, *J* = 12.8, 2.7 Hz, 1H), 0.85 (d, *J* = 7.3 Hz, 3H).

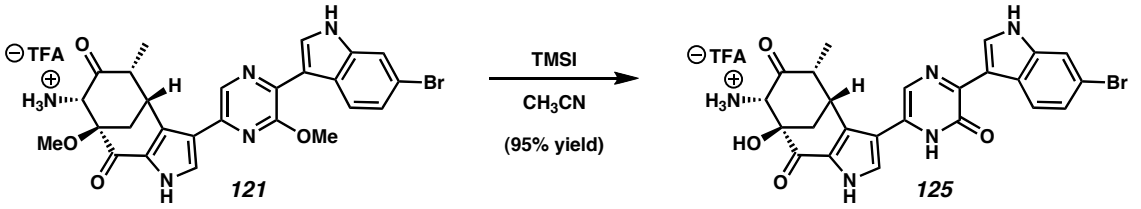
To hemiaminal **124** and K_2CO_3 (60 mg, 0.434 mmol) in THF (2 mL) at 23 °C was added H_2O (200 μL). The reaction mixture was stirred for 10 min, then purified by reversed-phase filtration through a Sep-Pak column: loaded with water containing 0.1%

(*w*/*v*) TFA, washed with 10% acetonitrile:water containing 0.1% (*w*/*v*) TFA to remove salts, then 70% acetonitrile:water containing 0.1% (*w*/*v*) TFA to collect the crude product. After removal of solvents under reduced pressure, the crude material was further purified by reversed-phased HPLC. Concentration under reduced pressure provided aminoketone **121** (15.0 mg, 96% yield) as an orange/red oil. ^{1}H NMR (300 MHz, CD_3OD): δ 8.60 (d, *J* = 8.5 Hz, 1H), 8.53 (s, 1H), 8.23 (s, 1H), 7.81 (s, 1H), 7.61 (d, *J* = 1.4 Hz, 1H), 7.25 (dd, *J* = 8.7, 1.8 Hz, 1H), 4.82–4.78 (m, 1H), 4.46 (s, 1H), 4.21 (s, 3H), 3.47 (s, 3H), 3.41–3.30 (m, 1H), 3.26 (dd, *J* = 12.9, 3.9 Hz, 1H), 2.61 (dd, *J* = 12.9, 3.0 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD, 25/26 C): δ 203.5, 183.3, 156.8, 142.4, 139.9, 139.1, 136.3, 133.4, 130.7, 129.9, 129.6, 126.9, 125.5, 124.5, 123.1, 116.9, 115.4, 112.6, 84.3, 66.0, 54.5, 52.9, 40.4, 36.6, 12.2; IR (film): 3156 (br), 2935, 1674, 1531, 1447, 1409, 1203, 1135 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{26}H_{25}N_5O_4Br$, 550.1090; found, 550.1071; $[\alpha]^{20}_D$ +99.19° (*c* 0.87, MeOH).

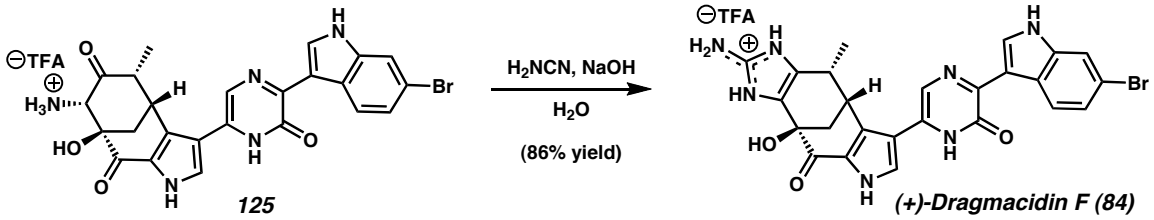
The relative stereochemistry of deprotected aminoketone **121** was determined by NOE experiments. Medium-strength NOE interactions were observed as indicated below.[75] Analogous NOE interactions were observed for hemiaminal **124** and deprotected aminoketone **125**.



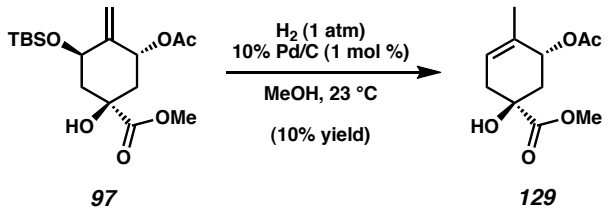
121



Deprotected Aminoketone 125. To a stirred solution of aminoketone **121** (7.5 mg, 0.0113 mmol) in MeCN (1 mL) at 0 °C was added TMSI (500 μL, 3.51 mmol) dropwise over 30 sec. The reaction mixture was heated to 60 °C for 48 h, cooled to 0 °C, then transferred dropwise into a chilled solution (0 °C) of saturated aqueous sodium metabisulfite (5 mL). The mixture was diluted with 6 N HCl (15 mL), stirred at 0 °C for 20 min, then purified by reversed-phase filtration through a Sep-Pak column: loaded with water containing 0.1% (*w*/*v*) TFA, washed with 1 N HCl, 10% acetonitrile:water containing 0.1% (*w*/*v*) TFA to remove salts, then 60% acetonitrile:water containing 0.1% (*w*/*v*) TFA to collect the crude product. After removal of solvents under reduced pressure, the crude material was further purified by reversed-phase HPLC. Concentration under reduced pressure provided deprotected aminoketone **125** (6.8 mg, 95% yield) as an orange/red oil. ^{1}H NMR (300 MHz, CD_3OD): δ 8.69 (s, 1H), 8.59 (d, *J* = 8.5 Hz, 1H), 7.69 (s, 1H), 7.61 (d, *J* = 1.7 Hz, 1H), 7.57 (s, 1H), 7.27 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.40 (s, 1H), 4.06–3.98 (m, 1H), 3.31–3.21 (m, 1H), 2.87 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.79 (dd, *J* = 13.1, 2.9 Hz, 1H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD, 23/24 C): δ 203.4, 186.0, 157.4, 139.1, 136.3, 132.5, 132.4, 130.2, 130.1, 128.2, 126.7, 126.7, 125.6, 124.9, 117.1, 115.4, 113.6, 79.3, 67.1, 49.6, 45.5, 36.7, 12.3; IR (film): 3164 (br), 2927, 1674, 1451, 1207, 1143 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{24}H_{21}N_5O_4Br$, 522.0777; found, 522.0783; $[\alpha]^{22}_D$ +86.88° (*c* 0.33, MeOH).



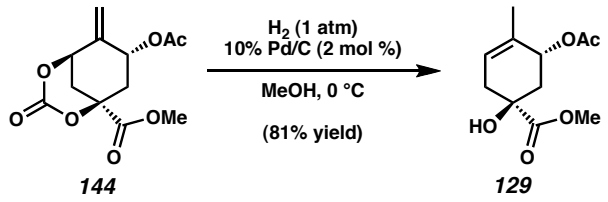
(+)-Dragmacidin F (84). To deprotected aminoketone **125** (3.6 mg, 0.0056 mmol) and cyanamide (120 mg, 2.86 mmol) in H_2O (2 mL, degassed by sparging with argon) at 23 °C was added 10% aq. NaOH (80 μL). The reaction mixture was heated to 60 °C for 2 h, cooled to 23 °C, then purified by reversed-phase filtration through a Sep-Pak column: loaded with water containing 0.1% (*w*/*v*) TFA, washed with 10% acetonitrile:water containing 0.1% (*w*/*v*) TFA to remove salts, then 60% acetonitrile:water containing 0.1% (*w*/*v*) TFA to collect the crude product. After removal of solvents under reduced pressure, the product was further purified by reversed-phase HPLC. Concentration under reduced pressure afforded (+)-dragmacidin F (**84**, 3.2 mg, 86% yield) as an orange/red oil. ^{1}H NMR (600 MHz, CD_3OD): δ 8.69 (s, 1H), 8.59 (d, *J* = 8.7 Hz, 1H), 7.68 (s, 1H), 7.60 (s, 1H), 7.47 (s, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 4.12 (br s, 1H), 3.40–3.34 (m, 1H), 2.73 (dd, *J* = 12.0, 2.9 Hz, 1H), 2.45 (d, *J* = 11.6 Hz, 1H), 0.92 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD, 22/25 C): δ 188.5, 157.5, 149.6, 139.1, 132.6, 132.4, 128.5, 128.4, 126.7, 126.2, 125.6, 124.9, 124.8, 123.3, 117.1, 115.4, 113.7, 72.8, 45.3, 36.9, 33.3, 15.9; IR (film): 3175 (br), 2925, 1679, 1637, 1205, 1141 cm^{-1}; UV (MeOH) λ_{max} 283, 389 nm; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{25}H_{21}N_7O_3Br$, 546.0889; found, 546.0883; $[\alpha]^{23}_D$ +146.21° (*c* 0.45, MeOH).



97 *129*

Acetoxycyclohexene 129. A mixture of methyl ester **97** (50.0 mg, 0.140 mmol) and 10% Pd/C (1.5 mg, 0.0014 mmol) in MeOH (1.3 mL) was stirred under an H_2 atmosphere at 23 °C. After 35 min, the reaction mixture was filtered over a Celite® plug (MeOH eluent), and the solvent was evaporated in vacuo. ^{1}H NMR integration showed that acetoxycyclohexene **129** was formed in approximately 10% yield.

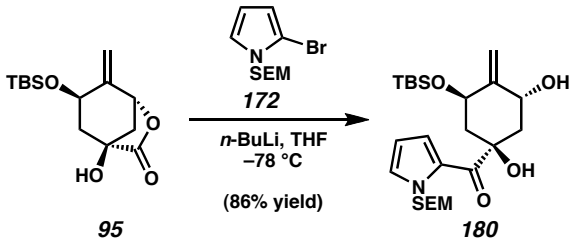
Alternate Procedure. A mixture of methyl ester **97** (21.4 mg, 0.06 mmol) and 10% Pd/C (0.3 mg, 0.0003 mmol) in MeOH (1.5 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (4x). After 1 h, the reaction mixture was filtered over a Celite® plug (MeOH eluent), and the solvent was evaporated in vacuo. ^{1}H NMR integration showed that acetoxycyclohexene **129** was formed in approximately 3% yield. An analytical sample of **129** was prepared via an alternate route as follows:



144 *129*

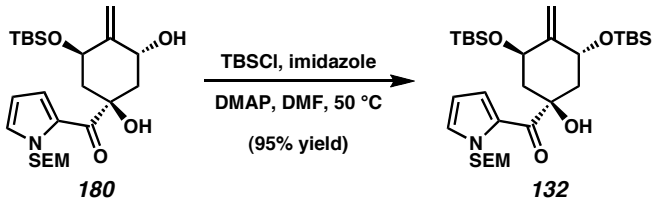
A mixture of acetoxycarbonate **144**[76] (18.5 mg, 0.07 mmol) and 10% Pd/C (1.4 mg, 0.001 mmol) in MeOH (1.3 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (3x). After 1 h at 0 °C, the reaction mixture was filtered over a Celite® plug (MeOH eluent), and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (1:1 EtOAc:hexanes eluent) to afford

acetoxycyclohexene **129** (12.6 mg, 81% yield) as a colorless oil. R_f 0.46 (2:1 EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.57–5.48 (comp. m, 2H), 3.77 (s, 3H), 3.06 (br s, 1H), 2.69–2.58 (m, 1H), 2.29–2.20 (m, 1H), 2.16–1.91 (comp. m, 2H), 2.05 (s, 3H), 1.69–1.66 (m, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 170.9, 132.7, 122.0, 73.8, 70.7, 53.2, 37.1, 35.3, 21.3, 19.2; IR (film) 3477 (br), 2953, 1736, 1239 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{11}H_{17}O_5$, 229.1076; found 229.1066; $[\alpha]^{25}_D$ –3.31° (*c* 0.6, $CHCl_3$).



***Anti*-diol 180.** To 2-bromo SEM pyrrole (**172**, 4.66 g, 16.87 mmol) in THF (112 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 6.04 mL, 15.09 mmol) dropwise over 1 min. After 7 min at –78 °C, lactone **95** (1.26 g, 4.44 mmol) in THF (10 mL) was added dropwise over 1 min. The reaction vessel was immediately warmed to –42 °C, stirred for 30 min, and cooled to –78 °C. The reaction mixture was quenched with saturated aq. NH_4Cl (50 mL), then warmed to 23 °C. The volatiles were removed under reduced pressure. The residue was partitioned between Et_2O (125 mL) and H_2O (100 mL), and the layers were separated. The aqueous layer was further extracted with Et_2O (2 x 125 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (4:1 hexanes:EtOAc eluent) to afford *anti*-diol **180** (1.84 g, 86% yield) as a pale yellow foam. R_f 0.48 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 8.11

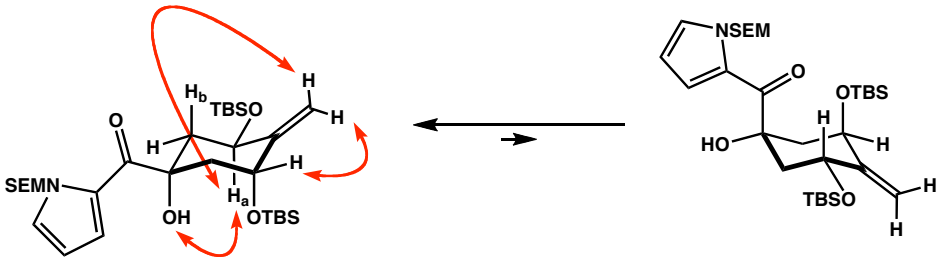
(dd, *J* = 4.1, 1.7 Hz, 1H), 6.78 (app. t, *J* = 2.1 Hz, 1H), 6.15 (dd, *J* = 4.0, 2.6 Hz, 1H), 5.71 (d, *J* = 9.9 Hz, 1H), 5.58 (d, *J* = 10.2 Hz, 1H), 5.26 (s, 1H), 5.17 (app. t, *J* = 1.8 Hz, 1H), 4.92–4.82 (m, 1H), 4.76–4.73 (m, 1H), 4.45 (app. t, *J* = 3.0 Hz, 1H), 3.47 (t, *J* = 7.7 Hz, 2H), 2.66 (ddd, *J* = 12.4, 5.2, 2.5 Hz, 1H), 2.39 (dd, *J* = 14.4, 2.9 Hz, 1H), 2.20 (app. dt, *J* = 8.7, 4.8 Hz, 1H), 1.92 (app. t, *J* = 12.0 Hz, 1H), 0.88–0.80 (comp. m, 12H), –0.04 (s, 3H), –0.06 (s, 3H), –0.06 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 192.8, 151.6, 130.5, 128.6, 124.8, 109.3, 108.3, 83.0, 78.5, 76.7, 66.4, 66.2, 48.5, 42.1, 26.1 (3C), 18.4, 18.4, –0.9 (3C), –4.4, –5.1; IR (film): 3456 (br), 2953, 1637, 1406, 1250, 1091 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{24}H_{44}NO_5Si_2$, 482.2758; found, 482.2751; $[\alpha]^{28}_D$ –21.18° (*c* 1.0, C_6H_6).



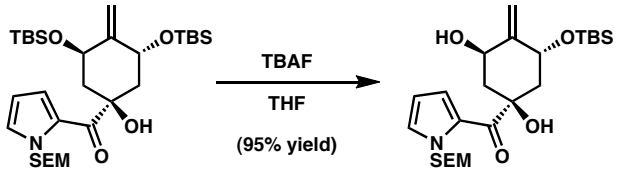
Bis(silylether) 132. To a solution of *anti*-diol **180** (253.1 mg, 0.53 mmol), imidazole (147.1 mg, 2.16 mmol), and DMAP (23.5 mg, 0.19 mmol) in DMF (5.0 mL), was added TBSCl (152.5 mg, 1.01 mmol). The solution was warmed to 50 °C for 70 min, cooled to 0 °C, then quenched by the addition of 10% (*w*/*v*) aq. citric acid (10 mL). Et_2O (40 mL) was added, and the layers were partitioned. The aqueous phase was further extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to provide bis(silylether) **132** (296.0 mg, 95% yield) as a colorless oil that solidified under reduced

pressure. R_f 0.61 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 8.17 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.76 (dd, *J* = 2.5, 1.7 Hz, 1H), 6.14 (dd, *J* = 4.0, 2.6 Hz, 1H), 5.68 (d, *J* = 9.9 Hz, 1H), 5.62 (d, *J* = 10.2 Hz, 1H), 5.37 (s, 1H), 5.32 (app. t, *J* = 2.1 Hz, 1H), 5.22–5.14 (m, 1H), 4.77 (app. t, *J* = 1.9 Hz, 1H), 4.50 (app. t, *J* = 3.0 Hz, 1H), 3.47 (t, *J* = 7.8 Hz, 2H), 2.82 (ddd, *J* = 12.7, 5.1, 2.6 Hz, 1H), 2.45 (dd, *J* = 14.6, 2.8 Hz, 1H), 2.27–2.18 (comp. m, 2H), 0.99 (s, 9H), 0.88 (s, 9H), 0.82 (t, *J* = 7.8 Hz, 2H), 0.17 (s, 3H), 0.14 (s, 3H), 0.00 (s, 3H), –0.04 (s, 3H), –0.07 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6, 29/30 C): δ 192.6, 151.6, 130.4, 124.5, 109.3, 108.6, 83.2, 78.5, 76.8, 67.4, 66.3, 49.3, 42.1, 26.4 (3C), 26.1 (3C), 18.9, 18.4, 18.3, –0.9 (3C), –4.3, –4.4, –4.5, –5.1; IR (film): 3464 (br), 1953, 2929, 1640, 1405, 1309, 1251, 1094 cm^{-1}; HRMS-FAB (*m/z*): [M + H]$^+$ calc'd for $C_{30}H_{58}NO_5Si_3$, 596.3623; found, 596.3594; $[\alpha]^{27}_D$ –7.16° (*c* 1.0, C_6H_6).

The stable chair conformer of bis(silylether) **132** was determined using a combination of NOESY-1D, gCOSY, and homodecoupling NMR experiments. Medium-strength NOE interactions were observed as indicated below.[75] The coupling constant between H_a and H_b was measured as J_{ab} = 11.0 Hz.

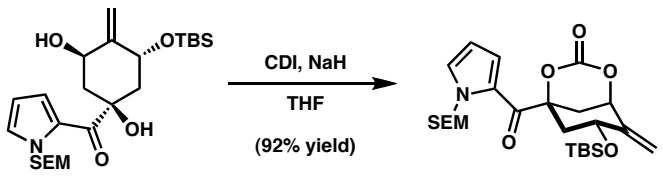


132-favored *132-disfavored*



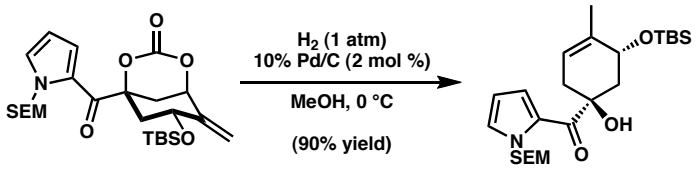
132 *133*

***Syn*-diol 133.** To bis(silylether) **132** (113.9 mg, 0.19 mmol) in THF (10.0 mL) was added TBAF (1.0 M in THF, 195 μL, 0.20 mmol) in a dropwise fashion over 1 min. The reaction mixture was stirred for 2 min, quenched with saturated aq. NH_4Cl (15 mL), then poured into EtOAc (40 mL). The layers were partitioned, and the aqueous layer was further extracted with EtOAc (2 x 40 mL). The combined organic extracts were successively washed with H_2O (15 mL) and brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (7:1 hexanes:EtOAc eluent) to furnish *syn*-diol **133** (87.5 mg, 95% yield) as a pale yellow oil. R_f 0.29 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.09 (dd, *J* = 4.1, 1.4 Hz, 1H), 6.63 (dd, *J* = 2.3, 1.5 Hz, 1H), 5.89 (dd, *J* = 4.1, 2.5 Hz, 1H), 5.51–5.39 (comp. m, 4H), 5.27–5.19 (m, 1H), 5.01 (app. t, *J* = 2.1 Hz, 1H), 4.52–4.46 (m, 1H), 3.86 (d, *J* = 8.0 Hz, 1H), 3.37 (t, *J* = 7.7 Hz, 2H), 2.45–2.23 (comp. m, 3H), 2.04 (app. dt, *J* = 8.4, 4.9 Hz, 1H), 0.99 (s, 9H), 0.79 (t, *J* = 7.8 Hz, 2H), 0.14 (s, 3H), 0.11 (s, 3H), –0.09 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 191.6, 152.9, 131.4, 126.4, 124.0, 109.8, 108.5, 81.2, 78.8, 74.7, 67.4, 66.6, 49.0, 43.3, 26.4 (3C), 18.9, 18.3, –1.0 (3C), –4.5, –4.5; IR (film): 3363 (br), 2954, 1631, 1410, 1314, 1250, 1101 (br) cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{24}H_{44}NO_5Si_2$, 482.2758; found, 482.2780; $[\alpha]^{27}_D$ –27.06° (*c* 1.0, C_6H_6).



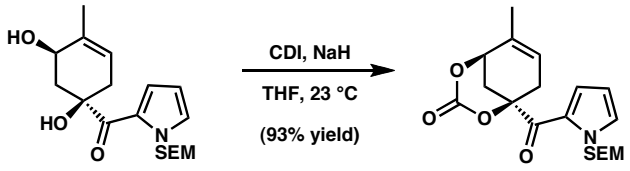
133 *131*

Carbonate 131. To *syn*-diol **133** (68.2 mg, 0.14 mmol) and 1,1'-carbonyldiimidazole (37.0 mg, 0.23 mmol) in THF (2.6 mL) was added NaH (60% dispersion in mineral oil, 21.9 mg, 0.55 mmol) in one portion. The reaction was stirred for 20 min at 23 °C, then quenched by addition of saturated aq. NH_4Cl (20 mL). The reaction mixture was poured into EtOAc (30 mL), the layers were partitioned, and the aqueous layer was further extracted with EtOAc (2 x 30 mL). The combined organic extracts were successively washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure. Purification of the residue by flash chromatography (6:1 hexanes:EtOAc eluent) afforded carbonate **131** (65.8 mg, 92% yield) as a colorless oil. R_f 0.29 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.91 (dd, *J* = 4.1, 1.7 Hz, 1H), 6.68 (dd, *J* = 2.8, 1.7 Hz, 1H), 6.02 (dd, *J* = 4.3, 2.6 Hz, 1H), 5.51 (d, *J* = 9.9 Hz, 1H), 5.43 (d, *J* = 9.9 Hz, 1H), 5.24 (app. t, *J* = 1.9 Hz, 1H), 4.84–4.75 (m, 1H), 4.69 (app. t, *J* = 1.8 Hz, 1H), 4.46 (dd, *J* = 3.9, 1.9 Hz, 1H), 3.39 (t, *J* = 7.7 Hz, 2H), 2.78 (ddd, *J* = 13.5, 6.1, 2.5 Hz, 1H), 2.12–1.98 (comp. m, 2H), 1.92–1.85 (m, 1H), 0.86 (s, 9H), 0.81 (t, *J* = 7.8 Hz, 2H), –0.07 to –0.08 (comp. m, 12H), –0.10 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 185.9, 147.2, 146.4, 132.1, 126.7, 125.0, 112.2, 110.3, 87.9, 80.3, 78.8, 66.8, 66.5, 46.1, 33.7, 26.2 (3C), 18.6, 18.3, –1.0 (3C), –4.7, –5.0; IR (film): 2954, 1764, 1641, 1413, 1354, 1251, 1173, 1089 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{25}H_{42}NO_6Si_2$, 508.2551; found, 508.2560; $[\alpha]^{27}_D$ –54.78° (*c* 1.0, C_6H_6).



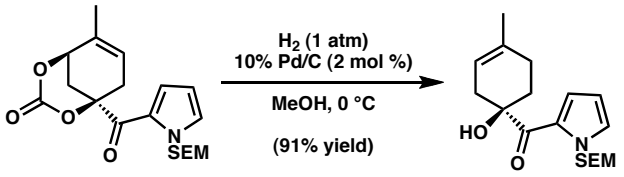
131 *127*

Pyrrolocyclohexene 127. A mixture of carbonate **131** (40.0 mg, 0.08 mmol) and 10% Pd/C (1.7 mg, 0.002 mmol) in MeOH (1.0 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (3x). After 1.75 h at 0 °C, the reaction mixture was filtered over a Celite® plug (MeOH eluent), and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to afford pyrrolocyclohexene **127** (33.1 mg, 90% yield) as a colorless oil. R_f 0.53 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.94 (dd, *J* = 4.1, 1.4 Hz, 1H), 6.64 (dd, *J* = 2.6, 1.5 Hz, 1H), 5.89 (dd, *J* = 4.0, 2.6 Hz, 1H), 5.54 (d, *J* = 10.2 Hz, 1H), 5.45 (d, *J* = 10.2 Hz, 1H), 5.39–5.33 (m, 1H), 4.87–4.78 (m, 1H), 4.78 (s, 1H), 3.40 (t, *J* = 7.8 Hz, 2H), 2.97–2.85 (m, 1H), 2.48 (dd, *J* = 12.5, 9.8 Hz, 1H), 2.34–2.26 (m, 1H), 2.21–2.08 (m, 1H), 1.95–1.90 (m, 3H), 0.96 (s, 9H), 0.81 (t, *J* = 7.8 Hz, 2H), 0.06 (s, 3H), 0.03 (s, 3H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 193.8, 138.5, 131.0, 126.4, 123.1, 120.1, 109.7, 78.8, 78.2, 69.6, 66.5, 44.7, 38.9, 26.4 (3C), 20.6, 18.6, 18.3, –1.0 (3C), –3.8, –4.5; IR (film): 3431 (br), 2954, 1634, 1414, 1250, 1089 (br) cm^{-1}; HRMS-FAB (*m/z*): [M + H]$^+$ calc'd for $C_{24}H_{44}NO_4Si_2$, 466.2809; found, 466.2804; $[\alpha]^{28}_D$ +26.19° (*c* 1.0, C_6H_6).



111 *135*

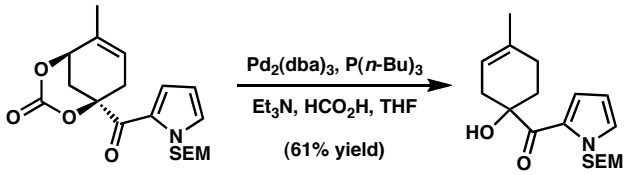
Pyrrolocarbonate 135. To diol **111** (114.5 mg, 0.33 mmol) in THF (6 mL) at 23 °C was added 1,1'-carbonyldiimidazole (86.9 mg, 0.54 mmol) followed by NaH (60% dispersion in mineral oil, 55.2 mg, 1.38 mmol). After stirring for 40 min at 23 °C, saturated aq. NH_4Cl (10 mL) was added to quench the reaction and EtOAc (50 mL) was added. The phases were partitioned, and the aqueous layer was further extracted with EtOAc (2 x 75 mL). The combined organic layers were successively washed with H_2O (15 mL) and brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (4:1 hexanes:EtOAc eluent) to provide pyrrolocarbonate **135** (114.3 mg, 93% yield) as a pale yellow oil. R_f 0.53 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.85 (dd, *J* = 4.1, 1.4 Hz, 1H), 6.70 (dd, *J* = 2.7, 1.8 Hz, 1H), 6.04 (dd, *J* = 4.1, 2.7 Hz, 1H), 5.52 (d, *J* = 9.9 Hz, 1H), 5.48 (d, *J* = 10.0 Hz, 1H), 4.91–4.86 (m, 1H), 3.78 (app. t, *J* = 3.0 Hz, 1H), 3.41 (t, *J* = 7.8 Hz, 2H), 2.42–2.37 (comp. m, 2H), 1.97 (ddd, *J* = 14.1, 3.3, 1.0 Hz, 1H), 1.83 (dd, *J* = 14.2, 2.3 Hz, 1H), 1.40 (app. q, *J* = 2.0 Hz, 3H), 0.83 (t, *J* = 7.8 Hz, 2H), –0.07 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 187.6, 147.5, 132.6, 131.9, 127.1, 125.1, 122.6, 110.2, 85.9, 78.7, 73.8, 66.5, 37.9, 30.4, 21.0, 18.3, –1.0 (3C); IR (film) 2952, 1751, 1643, 1413, 1178, 1093 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{19}H_{27}NO_5Si$, 377.1658; found, 377.1655; $[\alpha]^{24}_D$ +2.72° (*c* 1.0, C_6H_6).



135 *138*

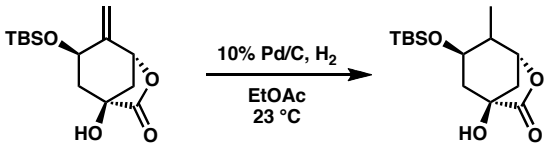
Trisubstituted Olefin 138. A mixture of pyrrolocarbonate **135** (41.6 mg, 0.11 mmol) and 10% Pd/C (2.3 mg, 0.002 mmol) in MeOH (2.0 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (3x). After 1.3 h at 0 °C, the reaction mixture was filtered over a Celite® plug (MeOH eluent) and the solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (13:4:3 hexanes:EtOAc:CH_2Cl_2 eluent) to afford pyrrolocyclohexene **138** (33.5 mg, 91% yield) as a colorless oil. R_f 0.64 (13:7 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.16 (dd, *J* = 4.0, 1.5 Hz, 1H), 6.72 (dd, *J* = 2.7, 1.6 Hz, 1H), 6.02 (dd, *J* = 4.0, 2.7 Hz, 1H), 5.56 (s, 2H), 5.35–5.28 (m, 1H), 3.98 (s, 1H), 3.43 (t, *J* = 7.8 Hz, 2H), 2.98–2.85 (m, 1H), 2.51–2.33 (m, 1H), 2.24–2.10 (comp. m, 2H), 1.88–1.73 (comp. m, 2H), 1.67–1.63 (m, 3H), 0.82 (t, *J* = 7.8 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 195.5, 134.0, 130.6, 127.3, 123.1, 118.5, 109.3, 78.7, 76.8, 66.5, 38.4, 34.2, 27.2, 24.1, 18.3, –1.0 (3C); IR (film) 3441 (br), 2957, 1727, 1632, 1413, 1084 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{18}H_{30}NO_3Si$, 336.1995; found, 336.1993; $[\alpha]^{24}_D$ –0.02° (*c* 1.0, C_6H_6); 7.2% ee as measured by chiral HPLC (2% EtOH:hexanes eluent). Retention times: 13.9 min, 15.6 min.

A racemic sample was prepared as follows:



135 ***138 racemic***

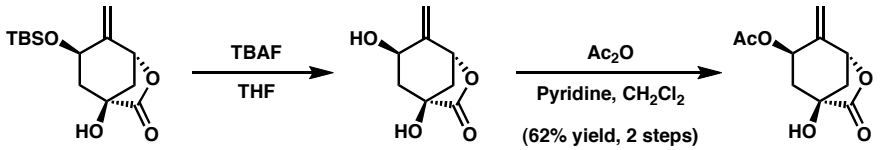
To carbonate **135** (9.9 mg, 0.03 mmol) and $Pd_2(dba)_3$ (2.7 mg, 0.003 mmol) was added THF (800 μL) followed by P(*n*-Bu)$_3$ (2.8 μL, 0.011 mmol), Et_3N (5.2 μL, 0.04 mmol) and formic acid (1.6 μL, 0.04 mmol).[77] The solution was stirred at 23 °C for 3 h, and was then heated to 70 °C for 70 min. The reaction was cooled to 23 °C and purified directly by preparative thin-layer chromatography (4:1 hexanes:EtOAc eluent). The crude product was then re-purified by preparative thin-layer chromatography (13:4:3 hexanes:EtOAc:CH_2Cl_2 eluent) to provide an a racemic, analytical sample of **138** (5.4 mg, 61% yield).



95 ***137 1:1 dr***

Reduced Lactone 137. A mixture of methylene lactone **95** (63.1 mg, 0.22 mmol) and 10% Pd/C (39.8 mg, 0.04 mmol) in EtOAc (2 mL) was evacuated and back-filled with H_2 (3x). After 7 min at 23 °C, the mixture was filtered over a pad of Celite® (EtOAc eluent) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (2:1 hexanes:EtOAc eluent) to provide reduced lactone **137** (8.7 mg, 14% yield) as a white amorphous solid and a 1:1 mixture of diastereomers. R_f 0.59 (1:1

hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of diastereomers): δ 4.68–4.63 (m, 1H), 4.51 (d, *J* = 6.4 Hz, 1H), 4.04–3.94 (m, 1H), 3.45 (ddd, *J* = 12.9, 6.2, 4.1 Hz, 1H), 2.63 (app. d, *J* = 10.1 Hz, 1H), 2.49 (ddd, *J* = 11.2, 6.4, 3.2 Hz, 1H), 2.44–2.33 (m, 1H), 2.29–2.22 (comp. m, 2H), 2.14 (ddd, *J* = 12.1, 6.6, 2.9 Hz, 1H), 2.08 (app. d, *J* = 11.2 Hz, 1H), 2.00–1.82 (comp. m, 3H), 1.65–1.54 (comp. m, 2H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 7.4 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.03–0.02 (comp. m, 6H), 0.02–0.01 (comp. m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of diastereomers): δ 178.5, 178.2, 80.4, 80.0, 73.5, 72.8, 71.4, 67.0, 44.8, 43.6, 41.9, 41.4, 37.4, 35.9, 25.9 (6C), 18.2, 18.1, 16.1, 10.7, –4.0, –4.6, –4.6, –4.8; IR (film) 3424 (br), 2930, 1787, 1099 cm^{-1}; HRMS-EI (*m*/*z*): [M]$^+$ calc'd for $C_{14}H_{26}O_4Si$, 286.1600; found, 286.1612; $[\alpha]^{25}_D$ –64.48° (*c* 1.0, C_6H_6).

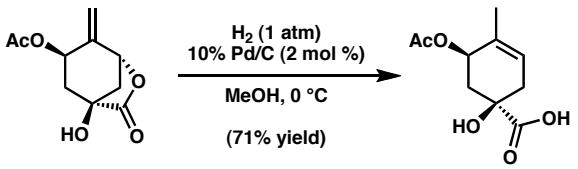


95 ***181*** ***140***

Acetoxylactone 140. To lactone **95** (510.1 mg, 1.80 mmol) in THF (25 mL) and freshly distilled AcOH (300 μL, 5.24 mmol) was added TBAF (1.0 M in THF, 4.0 mL, 4.0 mmol) in a dropwise fashion over 3 min. The reaction was stirred for 16 h, and then the solvent was evaporated in vacuo to afford hydroxylactone **181**, which was used immediately in the subsequent reaction. Although hydroxylactone **181** is typically used in crude form, it has been observed by ^{1}H NMR. R_f 0.25 (3:1 EtOAc:hexanes). ^{1}H NMR (300 MHz, CD_3OD): δ 5.27 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.20–5.17 (m, 1H), 5.11 (d, *J* = 6.1

Hz, 1H), 4.26 (app ddt, *J* = 10.7, 7.5, 2.4 Hz, 1H), 2.63 (ddd, *J* = 11.3, 6.1, 3.1 Hz, 1H), 2.34 (ddd, *J* = 11.4, 7.4, 3.3 Hz, 1H), 1.98 (d, *J* = 11.4 Hz, 1H), 1.72 (t, *J* = 11.3, 1H).

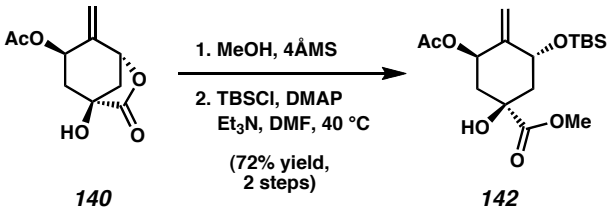
Hydroxylactone **181** was dissolved in CH_2Cl_2 (17 mL) and pyridine (1.02 mL, 12.6 mmol) was added. A solution of Ac_2O (355 μL, 3.76 mmol) in CH_2Cl_2 (355 μL) was added via syringe pump at a rate of 170 μL/h. After the addition was complete, the reaction was quenched by the addition of 10% *(w/v)* aq. citric acid (35 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (3:2 hexanes:EtOAc eluent) to provide acetoxylactone **140** (235 mg, 62% yield, 2 steps) as a white crystalline solid. R_f 0.52 (3:1 EtOAc:hexanes); mp 87–89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.54–5.44 (m, 1H), 5.16 (d, *J* = 2.4 Hz, 1H), 5.09–5.04 (comp. m, 2H), 3.26 (br s, 1H), 2.70 (ddd, *J* = 11.4, 6.1, 2.9 Hz, 1H), 2.52–2.42 (m, 1H), 2.14–2.08 (m, 1H), 2.12 (s, 3H), 1.87 (dd, *J* = 12.0, 10.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7, 169.9, 140.4, 111.6, 79.2, 72.9, 67.4, 44.2, 40.3, 21.0; IR (film) 3441 (br), 1790, 1743, 1240, 1128, 1042 cm^{-1}; HRMS-EI (*m/z*): $[M + H]^+$ calc'd for $C_{10}H_{13}O_5$, 213.0763; found, 213.0769; $[\alpha]^{25}_D$ –229.70° (*c* 1.0, C_6H_6).



140 ***141***

Acid 141. For representative procedures, see reductive isomerization of **131** → **127** or **135** → **138**. Purified by preparative thin-layer chromatography (19:1:1

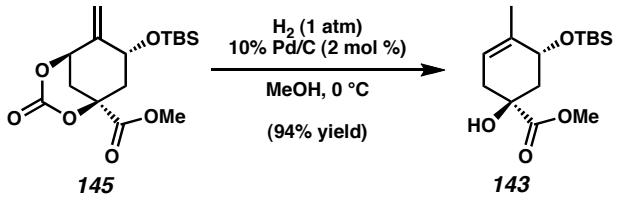
EtOAc:MeOH:AcOH eluent). R_f 0.53 (19:1:1 EtOAc:MeOH:AcOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (br s, 1H), 5.66–5.60 (m, 1H), 5.39–5.32 (m, 1H), 2.68–2.54 (m, 1H), 2.39–2.23 (comp. m, 2H), 2.14–2.00 (m, 1H), 2.06 (s, 3H), 1.74–1.69 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.9, 170.7, 130.8, 123.7, 72.5, 68.9, 36.6, 35.7, 21.4, 20.6; IR (film) 3440 (br), 2938, 1728, 1242 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + Na]^+$ calc'd for $C_{10}H_{14}O_5Na$, 237.0739; found, 237.0744; $[\alpha]^{25}_D$ +83.74° (*c* 1.0, $CHCl_3$).



140 *142*

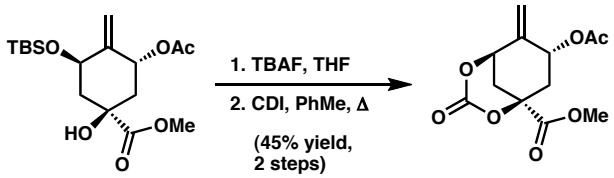
Methyl Ester 142. To acetoxylactone **140** (310 mg, 1.46 mmol) and oven-dried powdered 4ÅMS (220 mg) was added MeOH (20 mL). The suspension was stirred for 1 h, and then filtered over Celite® (EtOAc eluent). The filtrate was evaporated in vacuo, and was subsequently passed over a plug of SiO_2 gel (EtOAc eluent). Following evaporation of the solvent under reduced pressure, this material was used in the next step without further purification. R_f 0.33 (3:1 EtOAc:hexanes). To this crude material in DMF (7.3 mL) was added Et_3N (1.63 mL, 11.7 mmol) and DMAP (17.8 mg, 0.15 mmol). TBSCl (880 mg, 5.84 mmol) was added, and the solution was warmed to 40 °C. After stirring for 1 h, the solution was allowed to cool to 23 °C and quenched by the addition of 10% (*w*/*v*) aq. citric acid (10 mL). The reaction mixture was poured over H_2O (10 mL) and Et_2O (40 mL), and the phases were partitioned. The aqueous phase was extracted with Et_2O (2 x 30 mL), and the combined organic extracts were washed with brine (15 mL) and dried over $MgSO_4$. Following evaporation of the solvent in vacuo, the crude

product was purified by flash chromatography (2:1 hexanes:EtOAc eluent) to afford methyl ester **142** (376 mg, 72% yield, 2 steps) as a white solid. R_f 0.53 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.62 (app. t, *J* = 3.7 Hz, 1H), 5.24 (app. t, *J* = 1.9 Hz, 1H), 5.10 (app. t, *J* = 1.7 Hz, 1H), 4.73–4.63 (m, 1H), 3.74 (s, 3H), 3.16 (br s, 1H), 2.14 (dd, *J* = 14.9, 4.3 Hz, 1H), 2.09–2.00 (comp. m, 2H), 2.03 (s, 3H), 1.90 (dd, *J* = 12.5, 10.6 Hz, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 170.2, 146.6, 111.7, 75.3, 74.0, 66.8, 53.2, 45.7, 38.8, 26.0 (3C), 21.5, 18.4, –4.8, –4.9; IR (film) 3481 (br), 2955, 2930, 2858, 1734 (br), 1372, 1251, 1237, 1124, 1108, 1069, 1016 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{17}H_{31}O_6Si$, 359.1890; found, 359.1894; $[\alpha]^{26}_D$ –7.32° (*c* 1.0, $CHCl_3$).



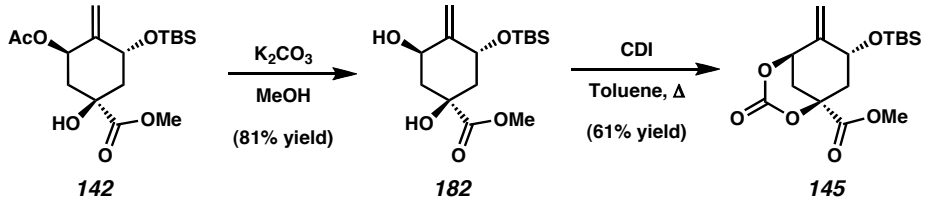
145 *143*

Methyl Ester 143. For representative procedures, see reductive isomerization of **131 → 127** or **135 → 138**. Purified by flash chromatography (7:3 hexanes:EtOAc eluent). R_f 0.62 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38–5.31 (m, 1H), 4.44–4.34 (m, 1H), 3.78 (s, 3H), 3.10 (br s, 1H), 2.65–2.53 (m, 1H), 2.08–1.89 (comp. m, 3H), 1.74–1.70 (m, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.9, 137.2, 119.0, 74.5, 68.2, 53.2, 40.8, 35.8, 26.1 (3C), 20.1, 18.3, –4.1, –4.6; IR (film) 3492 (br), 2954, 2857, 1730, 1249, 1095 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{15}H_{29}O_4Si$, 301.1835; found, 301.1841; $[\alpha]^{24}_D$ +29.49° (*c* 1.0, C_6H_6).



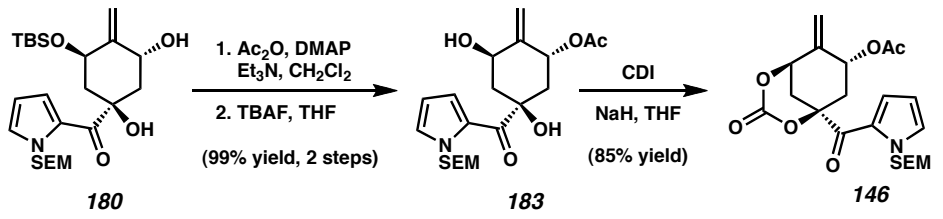
97 *144*

Acetoxycarbonate 144. To a solution of methyl ester **97** (44.8 mg, 0.12 mmol) in THF (2 mL) was added TBAF (1.0 M in THF, 140 μL, 0.14 mmol). After 3 min of stirring, the reaction was quenched by the addition of saturated aq. NH_4Cl (2 mL). EtOAc (4 mL) was added, and the phases were partitioned. The aqueous phase was further extracted with EtOAc (2 x 2 mL). The combined organic layers were successively washed with H_2O (1 mL) and brine (1 mL), and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the residue was dissolved in toluene (4 mL). 1,1'-carbonyldiimidazole (82.1 mg, 0.51 mmol) was added, and the mixture was heated at reflux for 2 h. After cooling to 23 °C, the crude reaction mixture was directly purified by flash column chromatography (3:2 hexanes:EtOAc eluent) to afford pure acetoxycarbonate **144** (16.9 mg, 45% yield, 2 steps). R_f 0.15 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.70–5.62 (m, 1H), 5.25 (app. d, *J* = 2.5 Hz, 1H), 5.19 (app. d, *J* = 2.5 Hz, 1H), 5.16 (dd, *J* = 4.1, 1.9 Hz, 1H), 3.81 (s, 3H), 2.84 (ddd, *J* = 13.4, 6.4, 2.7 Hz, 1H), 2.55–2.48 (m, 1H), 2.32–2.26 (m, 1H), 2.12 (s, 3H), 1.96 (dd, *J* = 13.3, 11.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 168.3, 146.6, 140.2, 113.7, 81.6, 79.5, 66.4, 53.7, 39.3, 32.7, 20.9; IR (film) 1763 (br), 1230, 1180, 1120 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{12}H_{15}O_7$, 271.0818; found, 271.0810; $[\alpha]^{25}_D$ –154.53° (*c* 1.0, C_6H_6).



TBS Carbonate 145. To methyl ester **142** (201 mg, 0.56 mmol) in MeOH (5 mL) was added powdered K_2CO_3 (150 mg, 1.09 mmol). After stirring 10 min, the MeOH was evaporated in vacuo and the residue was diluted in Et_2O (50 mL) and saturated aq. NH_4Cl (25 mL). The layers were partitioned, and the aqueous phase was extracted with Et_2O (25 mL). The combined organics were successively washed with H_2O (15 mL) and brine (15 mL), and dried over $MgSO_4$. The solvent was evaporated in vacuo, and *syn*-diol **182** (143.9 mg, 81% yield) was carried on to the next step without further purification. R_f 0.38 (1:1 hexanes:EtOAc).

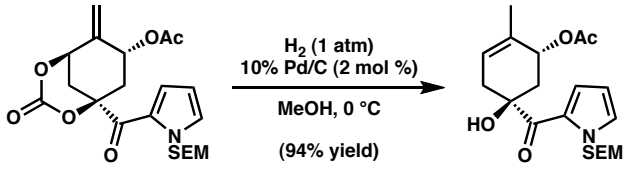
To *syn*-diol **182** (48.9 mg, 0.15 mmol) in toluene (3 mL) was added 1,1'-carbonyldiimidazole (80 mg, 0.50 mmol), and the reaction mixture was heated to reflux for 2.5 h. After cooling to 23 °C, the residue was chromatographed directly (7:3 hexanes:EtOAc eluent) to afford TBS carbonate **145** (32.2 mg, 61% yield). R_f 0.47 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.34 (dd, J = 2.2, 1.1 Hz, 1H), 5.21–5.19 (m, 1H), 5.15 (dd, J = 4.0, 1.8 Hz, 1H), 4.55–4.47 (m, 1H), 3.82 (s, 3H), 2.62 (ddd, J = 13.6, 6.2, 2.6 Hz, 1H), 2.45 (ddd, J = 14.2, 4.1, 2.7 Hz, 1H), 2.26 (dd, J = 14.2, 1.8 Hz, 1H), 1.92 (dd, J = 13.5, 10.7 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 147.2, 144.9, 113.4, 82.1, 79.9, 65.7, 53.6, 43.5, 33.0, 25.9 (3C), 18.3, –4.7, –4.9; IR (film) 2957, 2930, 2857, 1748 (br), 1254, 1178, 1103, 1054 cm^{-1}; HRMS-FAB (m/z): [M + H]$^+$ calc'd for $C_{16}H_{27}O_6Si$, 343.1577; found, 343.1592; $[\alpha]^{26}_D$ –81.11° (*c* 1.0, C_6H_6).



Acetoxycarbonate 146. To *anti*-diol **180** (1.77 g, 3.68 mmol) in CH_2Cl_2 (25 mL) at 23 °C was added Et_3N (1.28 mL, 9.19 mmol) and DMAP (45 mg, 0.368 mmol), followed by Ac_2O (451 μL, 4.78 mmol). The reaction mixture was stirred for 5 min, and then additional Ac_2O (125 μL, 1.32 mmol) was added. Stirring was continued for 5 min, and then another portion of Ac_2O (100 μL, 1.06 mmol) was added. After 5 min, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (15 mL). The volatile solvents were removed under reduced pressure. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 70 mL). The combined organic layers were dried over $MgSO_4$, and evaporated under reduced pressure. Subsequent filtration over a short plug of silica gel afforded the crude product, which was used immediately in the following reaction. R_f 0.63 (2:1 hexanes:EtOAc).

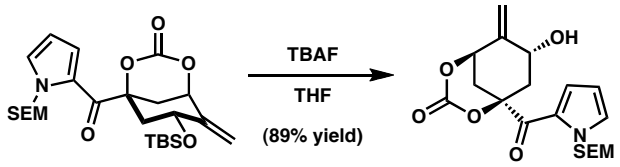
To the crude product in THF (25 mL) was added TBAF (1.0 M in THF, 3.85 mL, 3.85 mmol). After 2 min of stirring, the reaction was quenched by the addition of saturated aq. NH_4Cl (30 mL) and the volatile solvents were removed under reduced pressure. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (3:2 hexanes:EtOAc eluent) to afford acetoxycyclohexene **183** (1.49 g, 99% yield, 2 steps) as a colorless oil. R_f 0.23 (2:1 hexanes:EtOAc).

To acetoxycyclohexene **183** (222 mg, 0.542 mmol) and 1,1'-carbonyldiimidazole (132 mg, 0.813 mmol) in THF (10.8 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 54 mg, 1.35 mmol). After 2 min of stirring, the reaction was quenched by the addition of saturated aq. NH_4Cl (10 mL) and the volatile solvents were removed under reduced pressure. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (2:1 hexanes:EtOAc eluent) to afford acetoxycarbonate **146** (200.1 mg, 85% yield) as a colorless oil. R_f 0.25 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.75 (dd, *J* = 4.3, 1.5 Hz, 1H), 6.74 (dd, *J* = 2.5, 1.7 Hz, 1H), 6.03 (dd, *J* = 4.3, 2.6 Hz, 1H), 5.89–5.79 (m, 1H), 5.47 (s, 2H), 4.90 (d, *J* = 2.2 Hz, 1H), 4.73 (d, *J* = 1.9 Hz, 1H), 4.54 (dd, *J* = 3.9, 1.9 Hz, 1H), 3.40 (t, *J* = 7.8 Hz, 2H), 2.82 (ddd, *J* = 13.4, 6.3, 2.3 Hz, 1H), 2.03 (dd, *J* = 14.6, 1.9 Hz, 1H), 1.95 (ddd, *J* = 14.6, 3.8, 2.4 Hz, 1H), 1.81 (dd, *J* = 13.2, 11.3 Hz, 1H), 1.63 (s, 3H), 0.81 (t, *J* = 7.8 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 185.4, 168.9, 146.8, 141.6, 132.3, 126.4, 125.4, 112.6, 110.4, 87.4, 80.0, 78.7, 67.3, 66.5, 41.7, 33.3, 20.5, 18.3, –1.0 (3C); IR (film) 2953, 1764, 1643, 1413, 1356, 1234, 1177, 1129, 1106, 1086, 1048 cm^{-1}; HRMS-FAB (*m*/*z*): $[M + H]^+$ calc'd for $C_{21}H_{30}NO_7Si$, 436.1792; found, 436.1807; $[\alpha]^{27}_D$ –112.57° (*c* 1.0, C_6H_6).



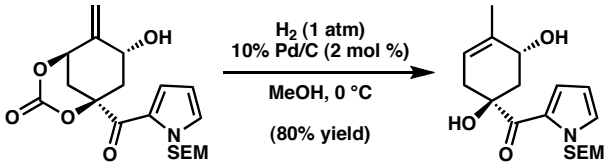
146 *147*

Allylic Acetate 147. A mixture of acetoxycarbonate **146** (734 mg, 1.69 mmol) and 10% Pd/C (36 mg, 0.03 mmol) in MeOH (17 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (3x). After 20 min at 0 °C, the reaction mixture was filtered over a Celite® plug (MeOH eluent) and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (3:1 hexanes:EtOAc eluent) to afford allylic acetate **147** (625 mg, 94% yield). R_f 0.56 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.05 (dd, *J* = 4.1, 1.7 Hz, 1H), 6.69 (dd, *J* = 2.2, 1.4 Hz, 1H), 6.07–5.98 (m, 1H), 5.95 (dd, *J* = 3.9, 2.8 Hz, 1H), 5.53 (d, *J* = 9.9 Hz, 1H), 5.47 (d, *J* = 9.9 Hz, 1H), 5.36–5.30 (m, 1H), 4.09 (br s, 1H), 3.42 (t, *J* = 7.8 Hz, 2H), 2.80 (ddd, *J* = 18.0, 5.2, 2.6 Hz, 1H), 2.43 (ddd, *J* = 12.6, 6.1, 1.7 Hz, 1H), 2.34 (dd, *J* = 12.4, 9.6 Hz, 1H), 2.17–2.06 (m, 1H), 1.72–1.69 (m, 3H), 1.68 (s, 3H), 0.82 (t, *J* = 7.8 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 193.3, 170.4, 133.8, 130.9, 126.9, 123.1, 122.7, 109.5, 78.7, 78.3, 71.9, 66.6, 39.6, 38.2, 21.0, 19.4, 18.3, –1.0 (3C); IR (film) 3438 (br), 2951, 1735, 1717, 1636, 1413, 1370, 1241, 1082, 1024 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{20}H_{32}NO_5Si$, 394.2050; found, 394.2031; $[\alpha]^{27}_D$ –9.91° (*c* 1.0, C_6H_6).



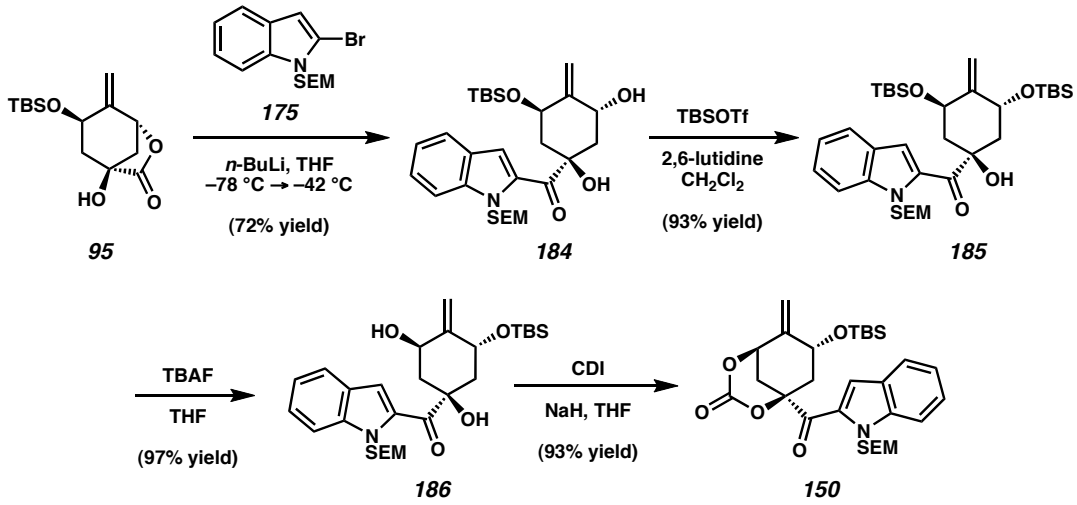
131 *148*

Hydroxycarbonate 148. To carbonate **131** (41.8 mg, 0.08 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 85 μL, 0.085 mmol) at 23 °C. After stirring 3 min, the reaction was quenched by the addition of saturated aq. NH_4Cl (1 mL). EtOAc (1 mL) was added, the phases were partitioned, and the aqueous phase was extracted with EtOAc (3 x 1 mL). The combined organics were washed successively with H_2O (1 mL) and brine (1 mL), and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the crude product was purified by flash chromatography (1:1 hexanes:EtOAc eluent) to provide hydroxycarbonate **148** (28.7 mg, 89% yield) as a colorless oil. R_f 0.29 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.77 (dd, *J* = 4.1, 1.4 Hz, 1H), 6.72 (app. t, *J* = 2.1 Hz, 1H), 6.08 (dd, *J* = 4.1, 2.3 Hz, 1H), 5.48 (d, *J* = 10.1 Hz, 1H), 5.42 (d, *J* = 10.1 Hz, 1H), 5.29 (app. t, *J* = 1.6 Hz, 1H), 4.78–4.75 (m, 1H), 4.52–4.42 (comp. m, 2H), 3.40 (t, *J* = 8.0 Hz, 2H), 2.67 (ddd, *J* = 13.4, 6.1, 2.6 Hz, 1H), 2.47 (app. d, *J* = 5.5 Hz, 1H), 2.00 (dd, *J* = 14.4, 1.6 Hz, 1H), 1.91–1.81 (comp. m, 2H), 0.83 (t, *J* = 7.8 Hz, 2H), –0.07 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 185.8, 147.9, 145.9, 132.0, 126.6, 125.1, 112.2, 110.2, 88.1, 80.6, 78.7, 66.6, 65.4, 45.2, 33.4, 18.2, –1.0 (3C); IR (film) 3455 (br), 2953, 2895, 1756, 1644, 1414, 1360, 1250, 1179, 1082 (br) cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{19}H_{28}NO_6Si$, 394.1686; found, 394.1690; $[\alpha]^{26}_D$ –77.69° (*c* 1.0, C_6H_6).



148 *149*

Allylic alcohol 149. A mixture of hydroxycarbonate **148** (34.2 mg, 0.09 mmol) and 10% Pd/C (1.5 mg, 0.001 mmol) in MeOH (1.4 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (3x). After 15 min at 0 °C, the reaction mixture was filtered over a Celite® plug (MeOH eluent) and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (3:1 hexanes:EtOAc eluent) to afford allylic alcohol **149** (24.3 mg, 80% yield) as a colorless oil. R_f 0.33 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.19 (dd, *J* = 4.0, 1.6 Hz, 1H), 6.69 (dd, *J* = 2.4, 1.6 Hz, 1H), 5.98 (dd, *J* = 4.1, 2.5 Hz, 1H), 5.50 (d, *J* = 10.1 Hz, 1H), 5.46 (d, *J* = 9.8 Hz, 1H), 5.27–5.21 (m, 1H), 4.45–4.34 (m, 1H), 3.99 (s, 1H), 3.41 (t, *J* = 7.8 Hz, 2H), 2.91–2.79 (m, 1H), 2.26 (dd, *J* = 12.9, 8.1 Hz, 1H), 2.20–2.03 (comp. m, 3H), 1.87–1.83 (m, 3H), 0.82 (t, *J* = 7.8 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 194.3, 137.9, 130.9, 126.9, 123.5, 119.9, 109.5, 78.7, 78.4, 68.4, 66.6, 43.9, 38.8, 19.9, 18.3, –1.0 (3C); IR (film) 3407 (br), 2953, 2920, 1629, 1412, 1309, 1250, 1081 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{18}H_{30}NO_4Si$, 352.1944; found, 352.1931; $[\alpha]^{25}_D$ +21.44° (*c* 1.0, C_6H_6).



Indolocarbonate 150. To 2-bromo SEM indole (**175**, 345.0 mg, 1.06 mmol) in THF (7 mL) cooled to –78 °C was added *n*-BuLi (2.5 M in hexanes, 380 μL, 0.95 mmol) dropwise over 1 min. The reaction was stirred for 7 min, and then a solution of lactone **95** (80.8 mg, 0.28 mmol) in THF (1 mL) was added dropwise over 2 min. The solution was warmed to –42 °C, and stirred for 1 h. The reaction was quenched at –78 °C by the addition of saturated aq. NH_4Cl (3 mL), and was allowed to thaw slowly to 23 °C. Et_2O (50 mL) and H_2O (10 mL) were added, the phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (15 mL) and dried over $MgSO_4$. Following evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to afford *anti*-diol **184** (108.9 mg, 72% yield) as a pale yellow foam. R_f 0.40 (4:1 hexanes:EtOAc).

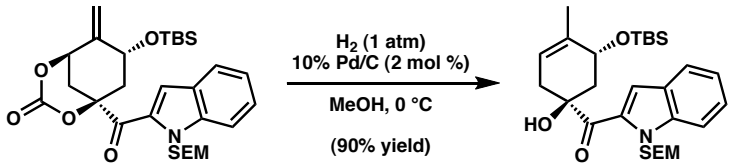
To *anti*-diol **184** (762.8 mg, 1.43 mmol) in CH_2Cl_2 (20 mL) at 23 °C was added 2,6-lutidine (360 μL, 3.09 mmol). The solution was treated with TBSOTf (480 μL, 2.09 mmol), and was stirred for 10 min. The reaction was quenched by the addition of saturated aq. NH_4Cl (50 mL). The phases were partitioned, and the aqueous phase was

extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were washed with brine (15 mL) and dried over $MgSO_4$. Following evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to afford bis(silylether) **185** (859.6 mg, 93% yield) as a white solid. R_f 0.48 (4:1 hexanes:EtOAc).

To bis(silylether) **185** (859.6 mg, 1.33 mmol) in THF (34 mL) at 23 °C was added TBAF (1.0 M in THF, 1.40 mL, 1.40 mmol) in a dropwise fashion over 1 min. After stirring 5 min, the reaction was quenched by the addition of saturated aq. NH_4Cl (50 mL). Et_2O (50 mL) was added, the phases were partitioned, and the aqueous phase was extracted with Et_2O (75 mL x 2). The combined organics were washed with brine (25 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (9:1 hexanes:EtOAc → 4:1 hexanes:EtOAc eluent) to afford *syn*-diol **186** (687.1 mg, 97% yield) as a pale yellow foam. R_f 0.28 (4:1 hexanes:EtOAc).

To *syn*-diol **186** (687.1 mg, 1.29 mmol) in THF (30 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 167.0 mg, 4.18 mmol). When H_2 evolution ceased (3 min), 1,1'-carbonyldiimidazole (331.3 mg, 2.04 mmol) was added in one portion. The reaction was quenched after 30 min of stirring with saturated aq. NH_4Cl (50 mL). Et_2O (50 mL) was added, the phases were partitioned, and the aqueous phase was extracted with Et_2O (75 mL x 2). The combined organics were washed with brine (25 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to furnish indolocarbonate **150** (668.9 mg, 93% yield) as a white foam. R_f 0.37 (4:1 hexanes:EtOAc); ^1H NMR (300 MHz, C_6D_6): δ

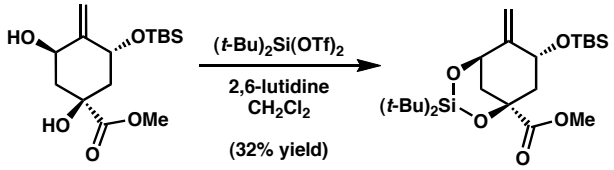
8.24 (d, *J* = 0.8 Hz, 1H), 7.45 (app. dt, *J* = 4.5, 2.8 Hz, 1H), 7.38–7.34 (m, 1H), 7.24–7.18 (m, 1H), 7.03–6.97 (m, 1H), 5.86 (d, *J* = 10.6 Hz, 1H), 5.77 (d, *J* = 10.4 Hz, 1H), 5.26 (dd, *J* = 2.0, 1.5 Hz, 1H), 4.88–4.79 (m, 1H), 4.74 (app. t, *J* = 1.7 Hz, 1H), 4.54 (dd, *J* = 3.9, 2.0 Hz, 1H), 3.51–3.44 (m, 2H), 2.86 (ddd, *J* = 13.5, 6.0, 2.3 Hz, 1H), 2.11–1.92 (comp. m, 3H), 0.87 (s, 9H), 0.80 (t, *J* = 7.7 Hz, 2H), –0.05 (s, 3H), –0.07 (s, 3H), –0.12 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 188.9, 147.0, 146.2, 141.5, 130.7, 127.9, 127.3, 124.7, 122.4, 118.2, 112.5, 111.9, 88.3, 80.2, 74.1, 66.7, 66.2, 46.1, 33.6, 26.2 (3C), 18.6, 18.3, –1.0 (3C), –4.7, –4.9; IR (film) 2954, 1765, 1656, 1355, 1170, 1086 cm^{-1}; HRMS-EI (*m*/*z*): [M]$^+$ calc'd for $C_{29}H_{43}NO_6Si_2$, 557.2629; found, 557.2632; $[\alpha]^{23}_D$ –34.29 (*c* 1.0, C_6H_6).



150 ***151***

Acyl Indole 151. A mixture of indolocarbonate **150** (230.2 mg, 0.41 mmol) and 10% Pd/C (8.8 mg, 0.008 mmol) in MeOH (10 mL) was cooled to 0 °C. The reaction vessel was then evacuated and back-filled with H_2 (3x). After 4 h at 0 °C, the reaction mixture was filtered over a Celite® plug (MeOH eluent) and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (9:1 hexanes:EtOAc eluent) to afford acyl indole **151** (192.2 mg, 90% yield) as a pale yellow oil. R_f 0.48 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.43–7.42 (m, 1H), 7.42–7.39 (m, 1H), 7.39–7.37 (m, 1H), 7.24–7.17 (m, 1H), 7.07–7.01 (m, 1H), 5.90 (d, *J* = 10.6 Hz, 1H), 5.82 (d, *J* = 10.6 Hz, 1H), 5.41–5.35 (m, 1H), 4.87–4.77 (m, 1H), 4.29 (s, 1H), 3.51 (t, *J*

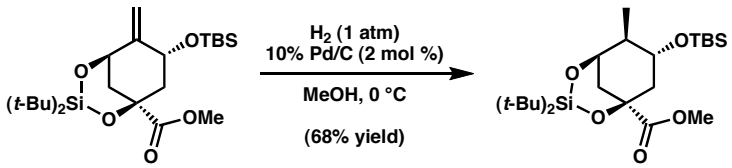
= 7.8 Hz, 2H), 3.03–2.92 (m, 1H), 2.66–2.57 (m, 1H), 2.43–2.35 (m, 1H), 2.23–2.11 (m, 1H), 1.95–1.92 (m, 3H), 0.96 (s, 9H), 0.82 (t, *J* = 7.8 Hz, 2H), 0.08 (s, 3H), 0.06 (s, 3H), –0.12 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 197.1, 141.0, 138.7, 130.7, 127.4, 127.0, 124.0, 122.3, 119.9, 116.1, 112.2, 79.3, 74.2, 69.5, 66.2, 44.4, 38.8, 26.4 (3C), 20.6, 18.6, 18.3, –1.0 (3C), –3.8, –4.5; IR (film) 3449 (br), 2954, 1643, 1249, 1092 cm^{-1}; HRMS-EI (*m*/*z*): [M]$^+$ calc'd for $C_{28}H_{45}NO_4Si_2$, 515.2887; found, 515.2875; $[\alpha]^{27}_D$ –27.67° (*c* 1.0, C_6H_6).



182 ***152***

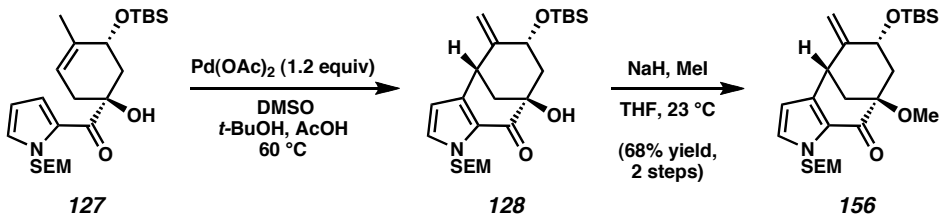
Dioxasilylcyclohexane 152. To *syn*-diol **182** (19.3 mg, 0.06 mmol) in CH_2Cl_2 (1.2 mL) was added 2,6-lutidine (30 μL, 0.26 mmol) followed by rapid dropwise addition of $(t\text{-Bu})_2Si(OTf)_2$ (30 μL, 0.08 mmol) over 1 min. The reaction was stirred for 16 h at 23 °C, and then quenched by the addition of saturated aq. NH_4Cl (1 mL). The phases were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. Purification by preparative thin-layer chromatography (11:2 hexanes:EtOAc eluent) afforded dioxasilylcyclohexane **152** (9.0 mg, 32% yield) as a colorless oil. R_f 0.50 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (app. t, *J* = 1.9 Hz, 1H), 5.14–5.06 (comp. m, 2H), 4.78 (dd, *J* = 3.8, 2.1 Hz, 1H), 3.73 (s, 3H), 2.71 (app. dt, *J* = 9.1, 4.9 Hz, 1H), 2.42 (ddd, *J* = 13.1, 7.2, 2.9 Hz, 1H), 2.00–1.80 (comp. m, 2H), 1.08 (s, 9H), 1.07 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 150.2, 110.6,

76.8, 74.9, 66.6, 52.6, 45.4, 39.1, 29.2 (3C), 28.7 (3C), 26.0 (3C), 21.7, 21.6, 18.3, –4.3, –4.5; IR (film) 2937, 2860, 1758, 1739, 1473, 1243, 1112 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{23}H_{44}O_5Si_2$, 456.2727; found, 456.2740; $[\alpha]^{21}_D$ –47.35° (*c* 1.0, C_6H_6).



152 *153*

Reduced Dioxasilylcyclohexane 153. For representative procedures, see reductive isomerization of **131 → 127** or **135 → 138**. Purified by preparative thin-layer chromatography (4:1 hexanes:EtOAc eluent). R_f 0.82 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.30–4.19 (comp. m, 2H), 3.73 (s, 3H), 2.64 (ddd, *J* = 14.5, 4.0, 3.1 Hz, 1H), 2.29 (ddd, *J* = 13.4, 5.9, 2.9 Hz, 1H), 1.88–1.72 (comp. m, 2H), 1.53–1.43 (m, 1H), 1.15 (d, *J* = 6.6 Hz, 3H), 1.09 (s, 9H), 1.06 (s, 9H), 0.86 (s, 9H), 0.02 (s, 3H), 0.02 (s, 3H); ^{1}H NMR (300 MHz, C_6D_6): δ 4.47 (app. dt, *J* = 9.9, 5.6 Hz, 1H), 3.97–3.92 (m, 1H), 3.32 (s, 3H), 2.71–2.58 (comp. m, 2H), 1.99 (dd, *J* = 13.3, 10.3 Hz, 1H), 1.63 (dd, *J* = 14.4, 1.7 Hz, 1H), 1.44–1.31 (m, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.20 (s, 9H), 1.19 (s, 9H), 1.00 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 173.7, 77.6, 74.1, 70.1, 52.1, 45.9, 44.8, 38.6, 29.8 (3C), 29.4 (3C), 26.4 (3C), 22.2, 22.1, 18.5, 15.9, –3.2, –3.8; IR (film) 2954, 2936, 2895, 2860, 1757, 1739, 1258, 1146, 1100, 1081 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{23}H_{46}O_5Si_2$, 458.2884; found, 458.2886; $[\alpha]^{25}_D$ –52.92° (*c* 1.0, $CHCl_3$).

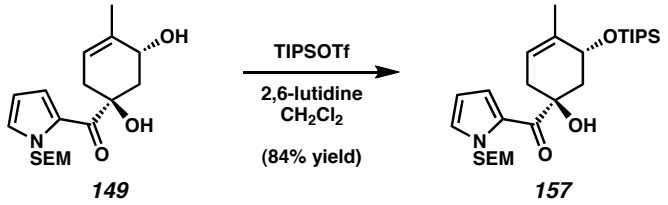


127 *128* *156*

[3.3.1] Bicycle 128. To pyrrolocyclohexene **127** (40.0 mg, 0.0859 mmol) was added $Pd(OAc)_2$ (23.0 mg, 0.103 mmol), DMSO (14.6 μL, 0.206 mmol), *t*-BuOH (6.9 mL), and AcOH (1.7 mL). The mixture was heated to 60 °C for 8 h, cooled to 23 °C, and filtered over a plug of silica gel (2:1 hexanes:EtOAc eluent). The solvent was evaporated, and the product was purified by flash chromatography on silica gel (8:1 hexanes:EtOAc eluent) to afford [3.3.1] bicycle **128** contaminated with a trace amount of pyrrolocyclohexene **127**. Although this material was carried on to the subsequent step without further purification, an analytical sample of **128** was obtained by flash chromatography on silica gel (12:1 hexanes:EtOAc eluent) as a colorless oil. R_f 0.64 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.64 (d, *J* = 2.5 Hz, 1H), 6.25 (d, *J* = 10.2 Hz, 1H), 5.84 (d, *J* = 2.8 Hz, 1H), 5.07 (d, *J* = 9.9 Hz, 1H), 4.79 (br s, 1H), 4.66 (br s, 1H), 4.24–4.19 (m, 1H), 4.19 (s, 1H), 3.68–3.51 (m, 2H), 3.43–3.38 (m, 1H), 2.61 (app. dt, *J* = 7.3, 3.9 Hz, 1H), 2.21–2.10 (m, 2H), 2.06–1.98 (m, 1H), 0.99–0.77 (m, 2H), 0.72 (s, 9H), –0.04 (s, 9H), –0.11 (s, 3H), –0.24 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 192.0, 148.6, 142.7, 130.5, 126.3, 113.2, 108.3, 77.0, 73.4, 73.0, 66.6, 48.5, 45.5, 40.2, 26.1 (3C), 18.4, 18.3, –1.0 (3C), –4.4, –5.1; IR (film): 3468 (br), 2951, 1648, 1422, 1250, 1094, 1062 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{24}H_{42}NO_4Si_2$, 464.2652; found, 464.2661; $[\alpha]^{27}_D$ +319.22° (*c* 1.0, C_6H_6).

Methyl Ether 156. The crude mixture of **127** and **128** obtained from the previous step was dissolved in THF (1.5 mL) at 23 °C, and NaH (60% dispersion in mineral oil, 17

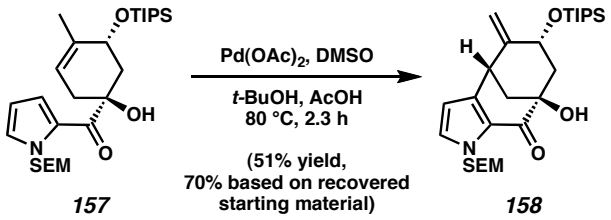
mg, 0.429 mmol) was added. After stirring for 1 min at 23 °C, MeI was added (53 μL, 0.859 mmol). The resulting mixture was stirred for 1.5 h, quenched with saturated aq. NH_4Cl (1.5 mL), and extracted with Et_2O (4 x 1 mL). The combined organic layers were washed with brine (1 mL), dried by passage over a plug of silica gel (EtOAc eluent), and evaporated under reduced pressure. The crude product was purified by flash chromatography (10:1 hexanes:EtOAc eluent) to afford methyl ether **156** (28.2 mg, 68% yield, 2 steps) as a colorless oil. R_f 0.43 (5:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.62 (d, *J* = 2.6 Hz, 1H), 6.43 (d, *J* = 10.3 Hz, 1H), 5.86 (d, *J* = 2.6 Hz, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.84 (d, *J* = 1.5 Hz, 1H), 4.69 (d, *J* = 1.5 Hz, 1H), 4.29–4.22 (m, 1H), 3.42–3.52 (m, 2H), 3.45 (app. t, *J* = 2.8 Hz, 1H), 3.39 (s, 3H), 2.79 (app. dt, *J* = 7.4, 3.8 Hz, 1H), 2.49 (app. dt, *J* = 8.1, 4.4 Hz, 1H), 1.96 (dd, *J* = 13.8, 4.7 Hz, 1H), 1.70 (dd, *J* = 11.7, 3.2 Hz, 1H), 0.96–0.82 (m, 2H), 0.73 (s, 9H), –0.06 (s, 9H), –0.11 (s, 3H), –0.23 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 189.2, 149.2, 140.9, 129.6, 128.9, 112.9, 107.6, 79.0, 77.3, 72.7, 66.6, 51.5, 46.3, 41.7, 39.9, 26.1 (3C), 18.4, 18.4, –1.0 (3C), –4.4, –5.1; IR (film): 2951, 1661, 1426, 1250, 1113, 1066; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{25}H_{44}NO_4Si_2$, 478.2809; found, 478.2815; $[\alpha]^{27}_D$ +312.37° (*c* 1.0, C_6H_6).



149 *157*

TIPS Ether 157. To allylic alcohol **149** (48.5 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) at 23 °C was added 2,6-lutidine (32 μL, 0.27 mmol), followed by TIPSOTf (42 μL, 0.16 mmol). After stirring 5 min, saturated aq. NH_4Cl (5 mL) was added to quench the

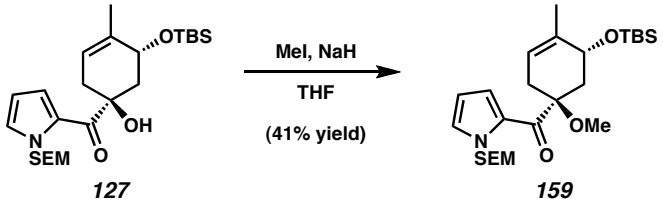
reaction. The phases were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (5 mL), and dried over $MgSO_4$. Following evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (19:1 hexanes:EtOAc → 9:1 hexanes:EtOAc eluent) to provide TIPS ether **157** (58.5 mg, 84%) as a colorless oil. R_f 0.48 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.98 (dd, *J* = 4.1, 1.4 Hz, 1H), 6.64 (dd, *J* = 2.5, 1.6 Hz, 1H), 5.91 (dd, *J* = 4.1, 2.7 Hz, 1H), 5.50 (d, *J* = 10.0 Hz, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 5.39–5.33 (m, 1H), 5.07–4.98 (m, 1H), 4.79 (s, 1H), 3.39 (t, *J* = 7.8 Hz, 2H), 2.97–2.85 (m, 1H), 2.55–2.46 (m, 1H), 2.44–2.36 (m, 1H), 2.20–2.08 (m, 1H), 2.05–2.00 (m, 3H), 1.16–1.02 (comp. m, 21H), 0.80 (t, *J* = 7.8 Hz, 2H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 193.9, 139.1, 131.0, 126.3, 123.0, 119.9, 109.7, 78.8, 78.2, 70.1, 66.6, 44.9, 38.9, 20.8, 18.9 (3C), 18.8 (3C), 18.3, 13.5 (3C), –1.0 (3C); IR (film) 3431 (br), 2946, 2866, 1631, 1413, 1382, 1250, 1094 cm^{-1}; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{27}H_{50}NO_4Si_2$, 508.3278; found, 508.3264; $[\alpha]^{27}_D$ +14.46° (*c* 1.0, C_6H_6).



157 *158*

TIPS Ether 158. For representative procedures, see oxidative cyclization of **92 → 90** or **113 → 114**. Purified by preparative thin-layer chromatography (9:1 CH_2Cl_2:Et_2O eluent). R_f 0.48 (4:1 hexanes:EtOAc); R_f 0.65 (4:1 Et_2O:CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6): δ 6.62 (d, *J* = 2.7 Hz, 1H), 6.26 (d, *J* = 10.1 Hz, 1H), 5.86 (d, *J* = 2.7 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H), 4.84 (app. d, *J* = 1.6 Hz, 1H), 4.73 (app. d, *J* = 1.6 Hz, 1H),

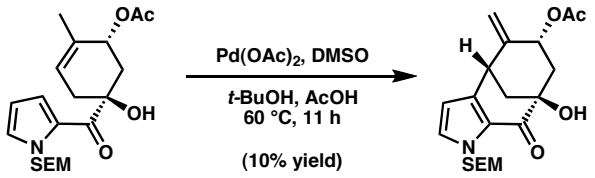
4.39–4.33 (m, 1H), 4.24 (s, 1H), 3.67–3.50 (m, 2H), 3.42 (app. t, *J* = 3.1 Hz, 1H), 2.62 (app. dt, *J* = 7.4, 4.1 Hz, 1H), 2.30 (app. dt, *J* = 8.1, 4.7 Hz, 1H), 2.15 (dd, *J* = 11.8, 3.1 Hz, 1H), 2.06 (dd, *J* = 14.0, 4.9 Hz, 1H), 0.98–0.71 (comp. m, 23H), –0.04 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 192.0, 148.3, 142.6, 130.6, 126.1, 113.8, 108.6, 77.0, 73.5, 72.9, 66.6, 48.6, 45.9, 40.3, 18.6 (3C), 18.6 (3C), 18.2, 12.8 (3C), –1.0 (3C); IR (film) 3475 (br), 2945, 1648, 1094, 1057 cm^{-1}; HRMS-EI (*m*/*z*): [M]$^+$ calc'd for $C_{27}H_{47}NO_4Si_2$, 505.3044; found, 505.3040; $[\alpha]^{23}_D$ +253.79° (*c* 0.7, C_6H_6).



127 ***159***

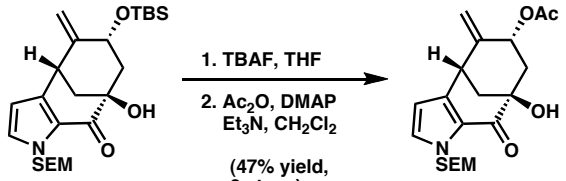
Methyl Ether 159. To allylic silyl ether **127** (10 mg, 0.02 mmol) in THF (1 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 17 mg, 0.43 mmol). After stirring for 5 min, MeI (37 μL, 0.59 mmol) was added, and the reaction was stirred for 30 min. Saturated aq. NH_4Cl (2 mL) was added slowly to quench the reaction mixture, and Et_2O (1 mL) was added. The phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 1 mL). The combined organic extracts were dried over $MgSO_4$, evaporated in vacuo, and purified by flash chromatography (19:1 hexanes:EtOAc eluent) to afford methyl ether **159** (4.2 mg, 41% yield). R_f 0.51 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.78 (dd, *J* = 4.1, 1.7 Hz, 1H), 6.73 (dd, *J* = 2.5, 1.7 Hz, 1H), 6.10 (dd, *J* = 4.0, 2.6 Hz, 1H), 5.64 (d, *J* = 9.9 Hz, 1H), 5.59 (d, *J* = 9.9 Hz, 1H), 5.29–5.23 (m, 1H), 4.62–4.53 (m, 1H), 3.47 (t, *J* = 2.8 Hz, 2H), 3.14 (s, 3H), 2.77 (ddd, *J* = 13.7, 5.4, 2.4 Hz, 1H), 2.70–2.58 (m, 1H), 2.53–2.41 (m, 1H), 2.32 (dd, *J* = 13.8, 9.9 Hz, 1H),

1.84–1.80 (m, 3H), 0.97 (s, 9H), 0.84 (t, J = 7.8 Hz, 2H), 0.09 (s, 6H), –0.08 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6): δ 193.7, 137.6, 130.4, 129.2, 122.4, 119.8, 109.5, 85.8, 78.3, 69.6, 66.4, 52.6, 38.8, 34.9, 26.4 (3C), 20.3, 18.6, 18.3, –1.0 (3C), –3.8, –4.4; IR (film) 2953, 2930, 2857, 1644, 1412, 1250, 1078 cm^{-1}; HRMS-EI (*m*/*z*): [M]$^+$ calc'd for $C_{25}H_{45}NO_4Si_2$, 479.2887; found, 479.2887; $[\alpha]^{27}_D$ +7.38° (*c* 0.6, C_6H_6).



147 *160*

[3.3.1] Bicycle 160. For representative procedures, see oxidative cyclization of **92** → **90** or **113** → **114**. A 10% yield of **160** was obtained based on ^{1}H NMR integration relative to benzothiazole as an internal standard. An analytical sample of **160** was prepared as follows:

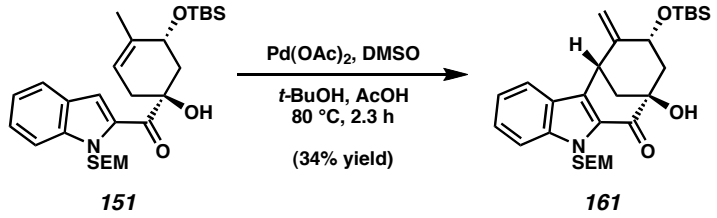


128 *160*

To silyl ether **128** (10.4 mg, 0.02 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 75 μL, 0.075 mmol) dropwise over 1 min at 23 °C. After 23 h, the reaction was quenched by the addition of saturated aq. NH_4Cl (1 mL). The aqueous layer was extracted with EtOAc (4 x 1 mL), and the combined organics were dried over $MgSO_4$ and evaporated in vacuo. Purification of the crude product by preparative thin-layer

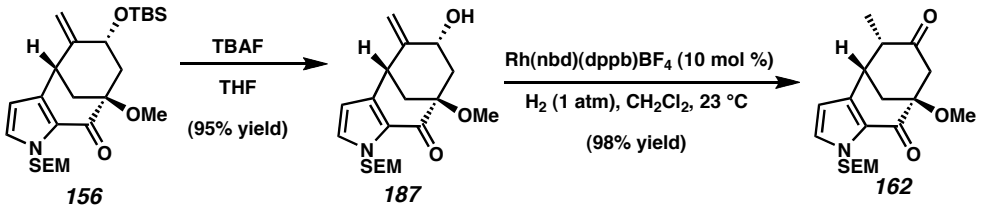
chromatography (1:1 hexanes:EtOAc eluent) afforded the crude diol, which was used in the subsequent reaction. R_f 0.09 (7:3 hexanes:EtOAc).

To a vial containing the crude diol in CH_2Cl_2 (1.1 mL) was added DMAP (2.2 mg, 0.02 mmol) and Et_3N (31 μL, 0.22 mmol), followed by Ac_2O (31 μL, 0.33 mmol). The vial was sealed and heated at 50 °C for 40 min. The reaction was allowed to cool to 23 °C, and saturated aq. $NaHCO_3$ (1 mL) was added. The aqueous layer was extracted with EtOAc (4 x 1 mL), and the combined organics were dried over $MgSO_4$ and evaporated in vacuo. Purification of the residue by preparative thin-layer chromatography (7:3 hexanes:EtOAc) afforded [3.3.1] bicycle **160** (4.1 mg, 47% yield, 2 steps) as a colorless oil. R_f 0.22 (7:3 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.53 (d, *J* = 2.3 Hz, 1H), 5.73 (d, *J* = 2.3 Hz, 1H), 5.53 (d, *J* = 10.1 Hz, 1H), 5.49–5.45 (m, 1H), 5.39 (d, *J* = 10.1 Hz, 1H), 5.12 (d, *J* = 1.4 Hz, 1H), 4.92 (d, *J* = 1.8 Hz, 1H), 4.20 (s, 1H), 3.67–3.52 (m, 2H), 3.33–3.29 (m, 1H), 2.50 (app. dt, *J* = 7.7, 4.0 Hz, 1H), 2.12 (ddd, *J* = 14.7, 2.7, 1.8 Hz, 1H), 2.04 (dd, *J* = 12.1, 3.0 Hz, 1H), 1.96 (dd, *J* = 14.7, 5.5 Hz, 1H), 1.35 (s, 3H), 0.91–0.85 (m, 2H), –0.04 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): δ 191.4, 169.0, 143.6, 142.3, 131.2, 126.1, 117.5, 108.2, 76.8, 73.1, 72.9, 66.7, 44.5, 44.0, 40.0, 20.8, 18.3, –1.0 (3C); IR (film) 3471 (br), 2951, 1738, 1650, 1231, 1094 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_{20}H_{29}NO_5Si$, 391.1815; found, 391.1800; $[\alpha]^{24}_D$ +396.32° (*c* 0.5, C_6H_6).



151 *161*

[3.3.1] Bicycle 161. For representative procedures, see oxidative cyclization of **92** → **90** or **113** → **114**. Purified by preparative thin-layer chromatography (4:1 hexanes:EtOAc eluent). R_f 0.55 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.51–7.48 (m, 1H), 7.48–7.46 (m, 1H), 7.27–7.21 (m, 1H), 7.08–7.02 (m, 1H), 6.63 (d, *J* = 10.7 Hz, 1H), 5.59 (d, *J* = 10.7 Hz, 1H), 4.89 (app. d, *J* = 1.4 Hz, 1H), 4.68 (app. d, *J* = 1.7 Hz, 1H), 4.20–4.15 (m, 1H), 4.13 (s, 1H), 3.79–3.58 (comp. m, 3H), 2.69 (app. dt, *J* = 7.6, 4.0 Hz, 1H), 2.23 (dd, *J* = 11.8, 3.0 Hz, 1H), 2.20–2.12 (m, 1H), 2.09–2.01 (m, 1H), 1.03–0.79 (m, 2H), 0.51 (s, 9H), –0.07 (s, 9H), –0.25 (s, 3H), –0.69 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6, 27/28 C): δ 195.3, 147.4, 141.4, 134.7, 129.8, 127.8, 121.8, 121.6, 113.8, 112.4, 74.1, 73.7, 72.9, 66.2, 48.6, 45.2, 38.1, 25.7 (3C), 18.2, 18.1, –1.0 (3C), –5.0, –5.3; IR (film) 3475 (br), 2951, 1656, 1250, 1061 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calc'd for $C_{28}H_{43}NO_4Si_2$, 513.2731; found, 513.2730; $[\alpha]^{24}_D$ +216.18° (*c* 0.25, C_6H_6).



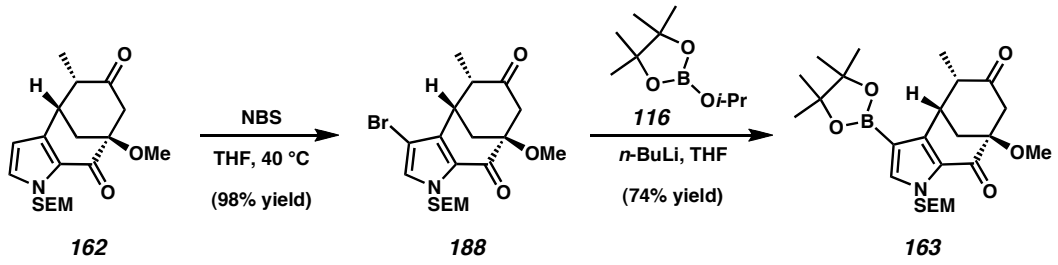
156 *187* *162*

Ketone 162. To methyl ether **156** (120 mg, 0.25 mmol) in THF (12.5 mL) was added TBAF (1.0 M in THF, 750 μL, 0.75 mmol). The reaction mixture was stirred for 4 h, quenched with saturated aq. NH_4Cl (10 mL), diluted with H_2O (5 mL), and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (15

mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash chromatography (1:1 hexanes:EtOAc eluent) to furnish allylic alcohol **187** (86 mg, 95% yield) as a pale yellow oil. R_f 0.12 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.60 (d, *J* = 2.8 Hz, 1H), 5.81 (d, *J* = 2.8 Hz, 1H), 5.64 (d, *J* = 10.2 Hz, 1H), 5.58 (d, *J* = 10.2 Hz, 1H), 4.80 (d, *J* = 1.7 Hz, 1H), 4.64 (d, *J* = 1.7 Hz, 1H), 4.15–4.09 (m, 1H), 3.68–3.59 (m, 2H), 3.42 (t, *J* = 3.2 Hz, 1H), 3.36 (s, 3H), 2.72 (app. dt, *J* = 7.4, 3.9 Hz, 1H), 2.58 (app. dt, *J* = 8.1, 4.9 Hz, 1H), 1.89 (dd, *J* = 14.2, 5.1 Hz, 1H), 1.65 (dd, *J* = 11.6, 3.0 Hz, 1H), 0.97–0.88 (m, 2H), 0.59 (d, *J* = 3.9 Hz, 1H), –0.03 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6, 18/19 C): δ 189.4, 149.4, 140.6, 130.4, 113.8, 107.4, 78.9, 76.7, 72.0, 66.2, 51.6, 44.3, 41.1, 39.5, 18.4, –0.9 (3C); IR (film): 3460 (br), 2951, 1659, 1424, 1248, 1111, 1023 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{19}H_{30}NO_4Si$, 364.1944; found, 364.1942; $[\alpha]^{24}_D$ +330.71° (*c* 1.0, C_6H_6).

Allylic alcohol **187** (44.0 mg, 0.121 mmol) and freshly prepared Rh(nbd)(dppb)BF_4 (8.6 mg, 0.0121 mmol)[69] were combined under a glovebox atmosphere. The reaction vessel was carefully sealed and removed from the glovebox. CH_2Cl_2 (12.0 mL) was added, and a balloon of H_2 (1 atm) was applied without purging. After 3 h of stirring, the reaction mixture was filtered over a plug of silica gel (CH_2Cl_2, then 2:1 hexanes:EtOAc eluent) to afford ketone **162** (43.0 mg, 98% yield) as a colorless oil. R_f 0.30 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 6.53 (d, *J* = 2.5 Hz, 1H), 5.66 (d, *J* = 2.5 Hz, 1H), 5.50 (d, *J* = 10.5 Hz, 1H), 5.36 (d, *J* = 10.2 Hz, 1H), 3.57–3.38 (m, 2H), 3.34 (s, 3H), 2.98 (dd, *J* = 14.3, 2.5 Hz, 1H), 2.70–2.64 (m, 1H), 2.57–2.47 (m, 1H), 2.43 (d, *J* = 14.3 Hz, 1H), 2.11–1.99 (m, 1H), 1.69 (dd, *J* = 12.2, 2.6 Hz, 1H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.84 (t, *J* = 8.0 Hz, 2H), –0.03 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): δ

205.7, 187.9, 137.5, 131.1, 126.6, 109.7, 82.9, 76.8, 66.4, 52.7, 52.3, 48.1, 41.0, 37.7, 18.3, 13.0, –1.0 (3C); IR (film): 2952, 2931, 1716, 1660, 1421, 1123, 1097, 1076 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+ - H_2$ calc'd for $C_{19}H_{28}NO_4Si$, 362.1788; found, 362.1778; $[\alpha]^{27}_D$ +163.23° (*c* 1.0, C_6H_6).

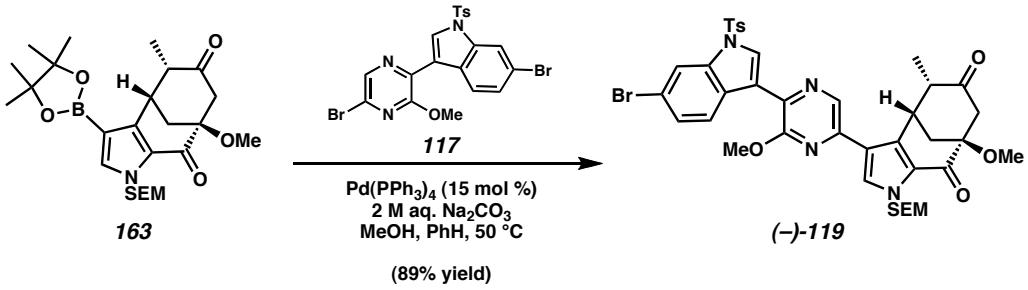


162 *188* *163*

Boronic Ester 163. A flask wrapped in aluminum foil at 23 °C was charged with ketone **162** (25 mg, 0.0689 mmol), THF (5 mL), and freshly recrystallized NBS (37.5 mg, 0.211 mmol). The reaction vessel was placed in a 40 °C oil bath, stirred for 15 min, then cooled to 0 °C. The reaction was quenched with saturated aq. $Na_2S_2O_3$ (10 mL), diluted with H_2O (5 mL), and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product. Further purification by flash column chromatography (3:1 hexanes:EtOAc eluent) afforded bromide **188** (29.9 mg, 98% yield) as a colorless oil. R_f 0.45 (2:1 hexanes:EtOAc).

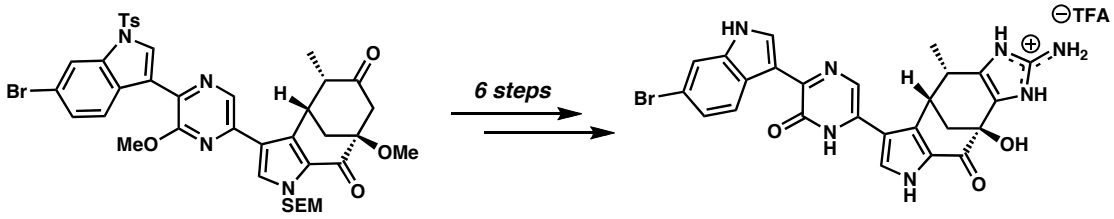
To bromide **188** (27 mg, 0.061 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**116**, 510 μL, 2.5 mmol) in THF (7 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 730 μL, 0.183 mmol) dropwise over 3 min. After stirring for an additional 10 min at –78 °C, the reaction mixture was quenched with saturated aq. NH_4Cl (7 mL), warmed to 23 °C, diluted with H_2O (10 mL), and extracted with EtOAc (3 x 20

mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and evaporated under reduced pressure to afford the crude product. Further purification by flash column chromatography (3:1 hexanes:EtOAc eluent) afforded boronic ester **163** (22 mg, 74% yield) as a colorless oil. R_f 0.42 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6): δ 7.37 (s, 1H), 5.46 (d, *J* = 10.2 Hz, 1H), 5.33 (d, *J* = 10.2 Hz, 1H), 3.77–3.72 (m, 1H), 3.49–3.38 (m, 2H), 3.31 (s, 3H), 3.03 (dd, *J* = 14.0, 2.8 Hz, 1H), 2.61–2.53 (m, 1H), 2.47 (d, *J* = 13.8 Hz, 1H), 2.36–2.25 (m, 1H), 1.78 (dd, *J* = 12.4, 3.0 Hz, 1H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.12 (s, 12H), 0.84–0.77 (m, 2H), –0.05 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6, 23/25 C): δ 206.4, 188.3, 144.6, 140.0, 83.6 (2C), 83.1, 77.1, 66.5, 52.9, 52.3, 49.0, 41.4, 37.1, 25.3 (2C), 25.2 (2C), 18.3, 13.0, –0.9 (3C); IR (film) 2977, 2951, 1718, 1664, 1543, 1399, 1322, 1263, 1145, 1092, 1074; HRMS-FAB (*m*/*z*): [M + H]$^+$ calc'd for $C_{25}H_{41}NO_6SiB$, 490.2796; found, 490.2800; $[\alpha]^{29}_D$ +50.77° (*c* 0.4, C_6H_6).



Pyrazine (–)-119. A vial charged with bromopyrazine **117** (29.6 mg, 0.055 mmol), boronic ester **163** (18 mg, 0.0368 mmol), and tetrakis(triphenylphosphine)palladium(0) (6.4 mg, 0.0055 mmol) was evacuated and purged with N_2. Deoxygenated benzene (735 μL), deoxygenated methanol (150 μL), and deoxygenated 2 M aq. Na_2CO_3 (61 μL) were then added. The reaction vessel was sealed, heated to 50 °C for 72 h, cooled to 23 °C, then quenched by the addition of Na_2SO_4 (200

mg). Following filtration over a pad of silica gel (3:1 EtOAc:hexanes eluent) and evaporation to dryness under reduced pressure, the residue was purified by flash column chromatography (2:1 → 1:1 hexanes:EtOAc eluent) to afford pyrazine (–)-**119** (26.8 mg, 89% yield) as a yellow foam. R_f, ^{1}H NMR, ^{13}C NMR, HRMS, and IR characterization data for (+)-**119** are reported earlier in this section. $[\alpha]^{27}_D$ –72.92° (*c* 1.0, $CHCl_3$).



(–)-119 *(–)-nat-Dragmacidin F (84)*

(–)-Dragmacidin F (84). Pyrazine (–)-**119** was converted to (–)-dragmacidin F (**84**) by methods described earlier in this section. ^{1}H NMR, ^{13}C NMR, HRMS, and IR characterization data for (+)-**84** are also reported above. $[\alpha]^{29}_D$ –148.33° (*c* 0.20, MeOH). For comparison, natural (–)-dragmacidin F (**84**): $[\alpha]^{25}_D$ –159° (*c* 0.40, MeOH).[4c]

3.7 Notes and References

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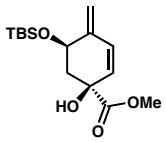
from loss of $^{-}$OAc. In stark contrast, exposure of **97** to heterogeneous reductive isomerization conditions did not produce any of these compounds (see Scheme 3.4.2).



iv

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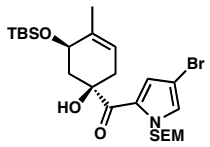

v

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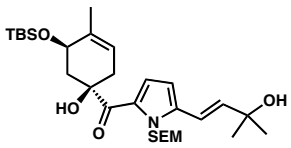
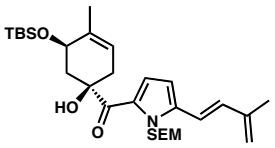
(25) By conducting reactions in THF-d_8, it was possible to monitor Heck reactions by ^{1}H NMR.

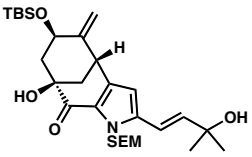
(26) The use of *t*-amyl alcohol in the cyclization of **92** → **90** led to the formation of byproducts such as **vi**, **vii**, and **viii**. Additionally, simply re-exposing **90** to the *t*-amyl alcohol-based reaction conditions, led to the formation of **viii**.



vi



vii



viii

(27) This reaction was performed using stoichiometric $Pd(OAc)_2$. The atmosphere of dioxygen seemed to enhance the overall conversion, but this reaction also proceeded under an inert atmosphere. In either case, the formation of Pd black was observed.

(28) Although pyridine and ethyl nicotinate failed to perform in this cyclization, employing more electron-deficient pyridines (such as 3,4,5–trihalogenated pyridines) led to production of desired bicycle **90**.

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(31) Reactions conducted in the presence of acetic acid-*d* led to deuterium incorporation in the pyrrole ring of both the starting material (**92**) and the product (**90**), mostly at C(4).

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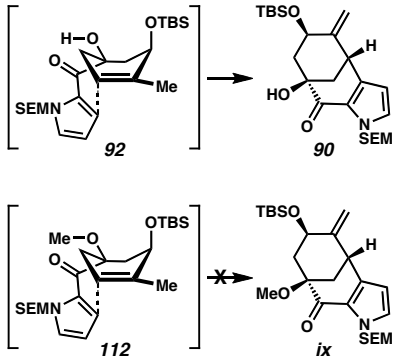
(34) Recently, related oxidative cyclizations of pyrrole substrates have been reported. See: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Paladino, G. *Tetrahedron* **2005**, *61*, 1077–1082. (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc*. **2006**, *128*, 2528–2529.

(35) Direct oxidation of starting material to the corresponding enone was observed.

(36) The lack of reactivity of the 3° methyl ether substrate (**112**) vs. **92** may be due to the transition state. In order to form bicycle **90**, a nearly coplanar arrangement between the tertiary alcohol and the carbonyl of **92** is required, which may also be facilitated via an intramolecular hydrogen bond. In the case of the tertiary methyl ether (**112**), the additional steric bulk of the methyl group may disfavor this orientation.



(37) The Heck route required the use of 2,3-dibromopyrrole, an extremely unstable compound. For a discussion regarding the instability of bromopyrroles, see: Audebert, P.; Bidan, G. *Synthetic Metals* **1986**, *15*, 9–22.

(38) In preliminary investigations, late-stage chemistry in the presence of a reactive 3° alcohol was unsuccessful.

(39) Neber, P. W.; Friedolsheim, A. V. *Justus Liebigs Ann. Chem.* **1926**, *449*, 109–134.

(40) (a) For a review, see: O'Brien, C. *Chem. Rev.* **1964**, *64*, 81–89. (b) For a recent study involving the Neber rearrangement, see: Ooi, T.; Takahashi, M.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *124*, 7640–7641.

(41) (a) Purified by reversed-phase chromatography using trifluoroacetic acid in the eluent. (b) See *3.6 Experimental Section* for details.

(42) Derivatives of **120** bearing a free 3° alcohol or a TMS-protected 3° alcohol produced complex mixtures of products when subjected to Neber rearrangement conditions.

(43) Acid-promoted dimerization of the amino ketone functionalities was not observed.

(44) (a) Woodward reported a Neber rearrangement during synthetic studies involving lysergic acid. Unfortunately, the Neber rearrangement product could not be further utilized in the synthesis. See: Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087–3114. (b) For the use of the Neber rearrangement in drug discovery, see: Chung, J. Y. L.; Ho, G.-J.; Chartrain, M.; Roberge, C.; Zhao, D.; Leazer, J.; Farr, R.; Robbins, M.; Emerson, K.; Mathre, D. J.; McNamara, J. M.; Hughes, D. L.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 6739–6743.

(45) The intermediacy of azirines in Neber rearrangements is well accepted. These azirines presumably arise from transient nitrenes. See: (a) House, H. O.; Berkowitz, W. F. *J. Org. Chem.* **1963**, *28*, 307–311. (b) House, H. O.; Berkowitz, W. F. *J. Org. Chem.* **1963**, *28*, 2271–2276.

(46) Hemiaminal **124** has been isolated and characterized by ^{1}H NMR.

(47) Boehm, J. C.; Gleason, J. G.; Pendrak, I.; Sarau, H. M.; Schmidt, D. B.; Foley, J. J.; Kingsbury, W. D. *J. Med. Chem.* **1993**, *36*, 3333–3340.

(48) Dragmacidin numbering convention, see reference 4c.

(49) (a) (+)-Quinic acid ((+)-**93**) is commercially available in limited quantities from Interbioscreen Ltd. (50 mg/$305 USD). (b) (+)-Quinic acid ((+)-**93**) potentially

could be prepared via multistep synthesis by applying methods used for the preparation of (–)-quinic acid (**93**). See: Rapado, L. P.; Bulugahapitiya, V.; Renaud, P. *Helv. Chim. Acta* **2000**, *83*, 1625–1632 and references therein. (c) Enantiopure (–)-quinic acid (**93**) can also be racemized. See: Grewe, R.; Lorenzen, W.; Vining, L. *Chem. Ber.* **1954**, *87*, 793–802.

(50) Surprisingly, despite its widespread use in natural product synthesis and its near symmetry, (–)-quinic acid (**93**) has rarely been used in an enantiodivergent manner. For examples, see: (a) Ulibarri, G.; Nadler, W.; Skrydstrup, T.; Audrain, H.; Chiaroni, A.; Riche, C.; Grierson, D. S. *J. Org. Chem.* **1995**, *60*, 2753–2761. (b) Ulibarri, G.; Audrain, H.; Nadler, W.; Lhermitte, H.; Grierson, D. S. *Pure Appl. Chem.* **1996**, *68*, 601–604. (c) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 166–173.

(51) If R = R', **126** is considered to be pseudo-C_2-symmetric. Pseudo-C_2-symmetric molecules are those that would be C_2-symmetric if they did not contain a central chirotopic, nonstereogenic center. For discussions, see: (a) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563–566. (b) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9–17. (c) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167–2213. (d) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994.

(52) Olefin **97** was also exposed to the reaction conditions used for the reductive isomerization of **95** to **96**. Only trace quantities of **129** were produced under those conditions.[41b,53b]

(53) (a) Yield determined based on ^{1}H NMR integration. (b) The material isolated was predominantly a mixture of diastereomeric olefin hydrogenation products.

(54) The favored conformation of **97** depicted in Scheme 3.4.2 is consistent with ^{1}H NMR studies.[41b]

(55) ^{1}H NMR experiments show that the C(3) silyl ether of **132** is axially disposed.[41b] For similar examples of axial-selective TBS cleavage promoted by TBAF, see: (a) Craig, B. N.; Janssen, M. U.; Wickersham, B. M.; Rabb, D. M.; Chang, P. S.; O'Leary, D. J. *J. Org. Chem.* **1996**, *61*, 9610–9613. (b) Meier, R.-M.; Tamm, C. *Helv. Chim. Acta*, **1991**, *74*, 807–818.

(56) For a classic example involving the use of conformational analysis to solve stereochemical problems in total synthesis, see: Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1–57.

(57) Isolated examples of similar reactivity using Pd/C, H_2 and a protic solvent have been reported in the literature, see: (a) Paulson, D. R.; Gilliam, L. S.; Terry, V. O.; Farr, S. M.; Parker, E. J.; Tang, F. Y. N.; Ullman, R.; Ribar, G. *J. Org. Chem.* **1978**,

43, 1783–1787. (b) Dauben, W. G.; Hance, P. D. *J. Am. Chem. Soc*. **1955**, *77*, 2451–2453. (c) Dauben, W. G.; Hayes, W. K.; Schwarz, J. S. P.; McFarland, J. W. *J. Am. Chem. Soc*. **1960**, *82*, 2232–2238.

(58) Complete deuterium incorporation was observed at the internal allylic positions by ^{1}H and ^{2}H NMR (See Scheme 3.4.4). Although nearly complete deuterium incorporation was observed at the exocyclic methyl group, this may only be occurring after initial reductive isomerization. See reference 59.

(59) Control experiments demonstrate that the deuterium incorporation at the exocyclic methyl group can happen after the reductive isomerization has occurred. The stereochemistry of the deuterium in **136** was elucidated by ^{1}H NMR homonuclear decoupling and NOESY-1D experiments.

(60) Conducting this experiment in the presence of **95** did not lead to consumption of **137**.

(61) Few examples of heterogeneous Pd/C-mediated allylic substitution have been reported, see: (a) Bergbreiter, D. E.; Chen, B. *J. Chem. Soc, Chem. Commun*. **1983** 1238–1239. (b) Felpin, F.-X.; Landais, Y. *J. Org. Chem*. **2005**, *70*, 6441–6446.

(62) (a) Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* **2002**, *43*, 7247–7250. (b) Ishizaki, M.; Yamada, M.; Watanabe, S.-i.; Hoshino, O.; Nishitani, K.; Hayashida, M.; Tanaka, A.; Hara, H. *Tetrahedron* **2004**, *60*, 7973–7981.

(63) Simple control experiments suggest that the presence of TCNE does not prevent the direct reduction of olefins from occurring.

(64) With the exception of **138** (entry 10), all of the compounds in Table 3.4.1 are enantiopure.

(65) The major product in this reaction resulted from direct hydrogenation of the olefin moiety and was formed as a mixture of diastereomers.

(66) No reductive isomerization product could be isolated from this reaction.

(67) The absolute stereochemistry of **138** (entry 10) depicted is shown by analogy to the other products in Table 3.4.1.

(68) The three-dimensional conformations of **97** and **142** were ascertained by ^{1}H NMR homonuclear decoupling and NOESY-1D experiments.

(69) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190–203.

(70) Bergens, S. H.; Bosnich, B. *J. Am. Chem. Soc.* **1991**, *113*, 958–967.

(71) Xiao, W. *Huaxue Shiji* **1992**, *14*, 363–366.

(72) Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300–1302.

(73) The synthesis of allylic alcohol **111** is described on p. 96.

(74) (a) Liu, Y.; Gribble, G. W. *J. Nat. Prod.* **2002**, *65*, 748–749. (b) Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495–2497.

(75) Claridge, T. D. W. in *High-Resolution NMR Techniques in Organic Chemistry*; Pergamon: Amsterdam, 1999; pp. 320–326.

(76) The synthesis of acetoxycarbonate **144** is described on p. 96.

(77) Tsuji, J; Minami, I; Shimizu, I. *Synthesis* **1986**, 623–627.