

A unified synthetic approach to the pyrazinone dragmacidins

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This review describes recent developments from our laboratory involving the synthesis of the structurally complex, pyrazinone-containing dragmacidin alkaloids.

Introduction

Over the past several decades, the search for natural products in marine and terrestrial 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. Although many bis(indole) alkaloids have been found in nature, relatively few have been discovered in marine environments.² Of those, a family of compounds isolated from *Dragmacidon* sp. (*i.e.*, the dragmacidins) have received considerable attention from the scientific community over the past decade because of their broad range of biological activity and complex and unique structures (1–7, Fig. 1).^{3,4} The four dragmacidins initially identified (1–4) contain a piperazine linker and display modest antifungal, antiviral and cytotoxic activities.^{3a–c} However, our interest in these natural products was piqued by the more complex pyrazinone-containing family members, dragmacidins D (5), E (6), and F (7).^{3d–g} The striking array of functionality in these stunning molecules (*i.e.*, the pyrazinone, aminoimidazole, aryl bromide, the free phenol in

5), in addition to the architectural arrangement of the polyheterocyclic core structures, posed a variety of synthetic challenges.

Preliminary studies suggest that the pyrazinone dragmacidins (*i.e.*, 5–7) are important compounds from a biological standpoint, thereby rendering them attractive targets for total synthesis. In particular, dragmacidins D (5) and F (7) have been studied most extensively. In addition to displaying anti-inflammatory activity, cytotoxicity and phosphatase inhibition,^{3d,3e} 5 has shown selectivity as an inhibitor of neural nitric oxide synthase.⁵ Molecules possessing this bioactivity are thought to be excellent leads for the discovery of novel drugs that target neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases.⁶ Furthermore, dragmacidin F (7) is reported to exhibit *in vitro* antiviral activity against herpes simplex virus (HSV-I; EC₅₀ = 95.8 μM) and human immunodeficiency virus (HIV-I; EC₅₀ = 0.91 μM).^{3f} Given the difficulty in obtaining dragmacidins from marine environments, as well as the low abundance of some of these compounds from natural sources, we reasoned that synthetic routes to the pyrazinone dragmacidins (5–7) and their analogs could facilitate advanced biological studies.

In this review, we highlight recent synthetic studies from our laboratory that has led to the development of a unified strategy

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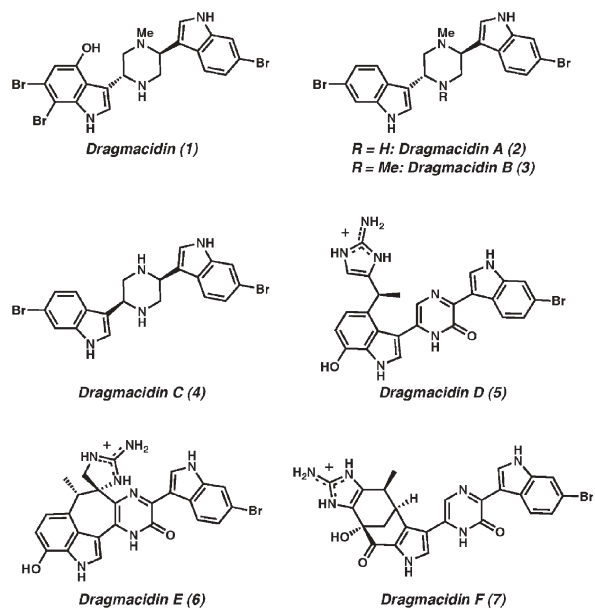


Fig. 1 The dragmacidin alkaloids.

for the preparation of several dragmacidin alkaloids. The success of these efforts can largely be attributed to the power of transition metal chemistry in modern organic synthesis.

The design of a unified strategy

While the biosynthesis of the dragmacidins has not been studied in detail, dragmacidins D, E and F are likely biosynthetically related. Of the possible biosynthetic scenarios, most probable is that dragmacidins E (6) and F (7) are derived by cyclization of either dragmacidin D (5) or a closely related congener (Fig. 2). For example, dragmacidins D and E are structural isomers that differ by a single C–C bond. In nature, it is likely that a Friedel–Crafts cyclization between the pyrazinone and aminoimidazole groups of dragmacidin D occurs in order to construct the seven-membered ring of dragmacidin E (*i.e.*, 5→6). Dragmacidins D (5) and F (7) also differ in connectivity by one C–C bond; however, in this case, there is also a difference in oxidation state between the two

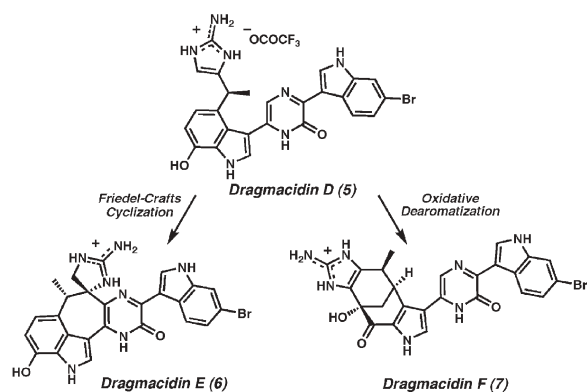


Fig. 2 Unified biosynthetic relationship.

natural products. Thus, oxidative dearomatization with concomitant cyclization could facilitate the formation of the unique polycyclic framework present in dragmacidin F (*i.e.*, 5→7). Related oxidation pathways for tryptophan derivatives have been observed in nature.⁷ Finally, it is plausible that dragmacidin D and hence the core of all the dragmacidins are derived by the biosynthetic dimerization of two functionalized tryptophan derivatives.

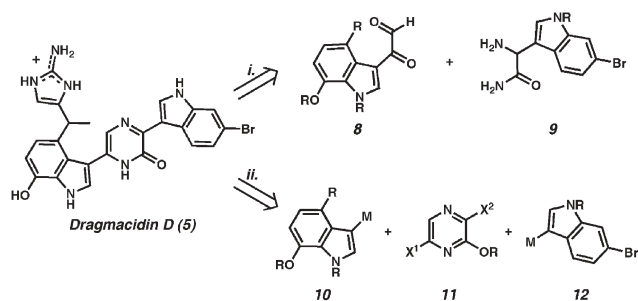
The identification that there was a clear biosynthetic relationship between the dragmacidins led us to consider the design of a unified synthetic strategy that would take advantage of the similar functionality groupings and connectivities of key skeletal components. While there were clear differences among the members of the pyrazinone family, the general feature that the molecules were constructed of a core pyrazinone flanked by two different heterocycles was of paramount importance in developing our strategy.

The total synthesis of dragmacidin D

Having selected the pyrazinone-containing dragmacidins, namely, dragmacidins D (5), E (6) and F (7), as formidable synthetic targets for our laboratory we first chose to pursue the total synthesis of dragmacidin D (5),^{3*d,e*,8} predominantly because it appeared to be the simplest of the pyrazinone-containing family members. Learning how to selectively build the skeleton of dragmacidin D, as well as construct and reveal all of the functionality present, was a major challenge to our laboratory. Moreover, we hoped to develop a strategy for the preparation of dragmacidin D (5) that would be amenable to the synthesis of the other complex dragmacidin natural products.

When considering the structure of dragmacidin D (5), several synthetic challenges become apparent. Dragmacidin D possesses a total of seven nitrogen atoms, three of which are incorporated in the aminoimidazole moiety, while two are within the pyrazinone core. The compound contains an unusual bis(indole) architecture featuring a 3,4,7-trisubstituted indole and a 3,6-disubstituted indole. Access to both of these indole substitution patterns is known to be synthetically challenging.⁹ It was predicted that dragmacidin D (5), as well as many of its synthetic precursors, would be highly polar, extremely reactive and perhaps difficult to handle in a laboratory setting.

Two retrosynthetic strategies for the synthesis of dragmacidin D (5) are presented in Scheme 1. We targeted 5 through



Scheme 1 Retrosynthesis of dragmacidin D (5).

two complementary routes: (i) a classical cyclocondensation approach¹⁰ and (ii) a more modern transition metal-mediated cross-coupling approach.¹¹ In approach *i*, the pyrazinone system would be constructed through the linkage of two functionalized indole units (**8** + **9**), while in route *ii*, the dragmacidin core was envisioned to arise by a stepwise three-component coupling sequence (**10** + **11** + **12**).

In 2000, our laboratory began working on the two approaches outlined above. Initially we investigated the viability of the cyclocondensation strategy (i). Although we were able to prepare simple bis(indole) pyrazinone model systems, attempts to utilize more advanced fragments were unsuccessful and we quickly redirected our attention to the transition metal-catalyzed cross-coupling route (ii). To carry out this plan successfully, it seemed that a more detailed strategy was needed, involving not only the exact order of the coupling reactions, but also the specific identity of each substrate involved. The judicious selection of halides, metals and protecting groups would be crucial. We thus carried out a series of experiments that would delineate suitable conditions for cross-coupling.

After examining a number of model systems, we began to identify appropriate substitution patterns for building blocks **10**, **11** and **12** (Fig. 3). It was immediately clear that the use of Pd(0)-catalyzed Suzuki couplings would be favorable given the abundant precedence for these cross-couplings in heterocycle chemistry.¹² Thus, boron substituents were employed as the nucleophilic component for both indole substrates (**10** \approx **13** and **12** \approx **15**). In addition, the protecting groups for the indoles were chosen in a manner that optimized orthogonality with respect to deprotection, thus facilitating control during late-stage manipulations. In particular, the N-protecting groups were carefully selected.¹³ The SEM group of **13** was considered ideal due to its marked stability and electron-donating nature,¹⁴ while the Ts group of **15** was preferred mainly because of its success in model system studies. Perhaps the most important decision was the selection of halogens X¹ and X² of generic pyrazine **11**. In order to keep **15** in tact through the cross-coupling sequence, both X¹ and X² would have to be more reactive to Pd(0) than the 6-bromoindole functionality. Ultimately, bromiodopyrazine **14** was chosen as the key synthetic fragment that would allow for this selectivity.¹⁵ We then developed rapid syntheses of the three

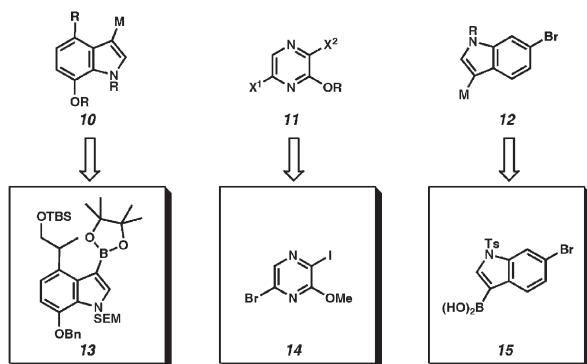
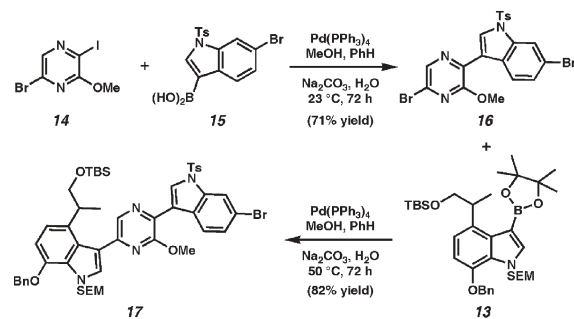


Fig. 3 Identification of cross-coupling fragments.

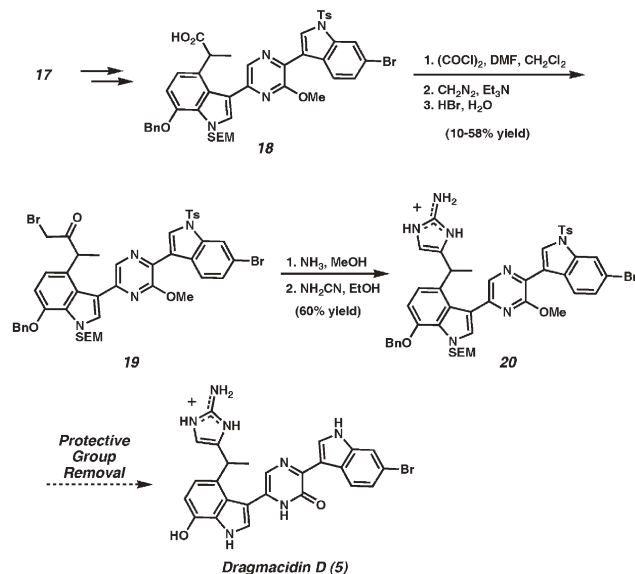


Scheme 2 Halogen-selective Suzuki couplings to access **17**.

essential pieces (**13**, **14** and **15**) in a relatively straightforward manner.

With the appropriate fragments in hand (**13**, **14** and **15**), the critical three-component coupling reaction sequence was explored. Suzuki coupling of dihalopyrazine **14** and indole **15** proceeded selectively to afford the coupled indolypyrazine **16** (Scheme 2). In the second Suzuki coupling of dibromide **16** with boronic ester **13**, we were delighted to find that the desired bis(indole)pyrazine **17** formed in good yield and with complete selectivity for coupling of the pyrazinyl bromide in the presence of the indolyl bromide. Precise temperature control was critical for the success of both coupling reactions (23 and 50 °C, respectively). Importantly, the selectivity of the second Suzuki reaction depended not only on temperature, but also on the exact identity of each coupling substrate. In fact, varying protective groups on the indole nitrogen in **15** had a dramatic effect on halide reactivity, as competitive coupling of the indolyl bromide occurred when electron-donating N-protective groups were employed.

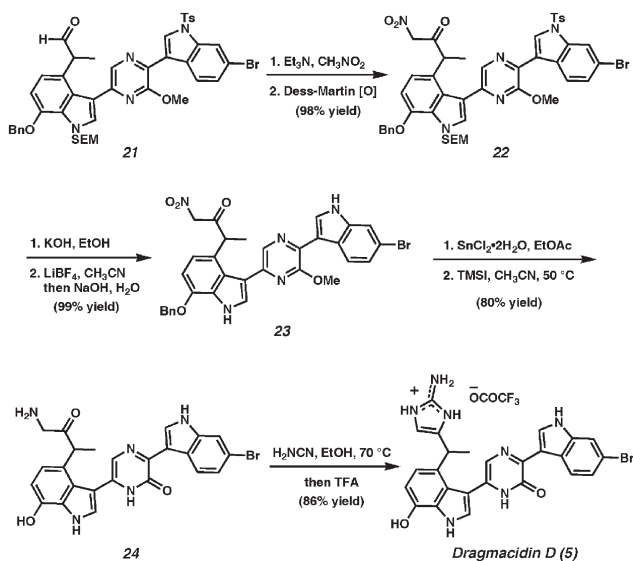
In our initial endgame approach, we chose to first attempt installation of the aminoimidazole unit and proceeded by elaborating **17** to carboxylic acid **18** (Scheme 3). Subsequent conversion of **18** to bromoketone **19** was accomplished by an



Scheme 3 End-game strategy 1.

Arndt–Eistert-type homologation, followed by treatment with aqueous HBr. The extreme sensitivity of the intermediate acid chloride was particularly troublesome and required that the diazomethane used in the reaction sequence be dried thoroughly over both potassium hydroxide and sodium metal immediately before use.¹⁶ In addition, chemical yields for this homologation varied to a large extent and caused substantial material throughput problems. Nonetheless, exposure of **19** to ammonia afforded an intermediate aminoketone which, in turn, underwent facile condensation with cyanamide to produce the desired aminoimidazole product (**20**).¹⁷ At this point, all that remained in order to complete the total synthesis of dragmacidin D (**5**) was the removal of the four protective groups from **20**. Despite several months of experimentation, our efforts to complete the total synthesis of **5** were accompanied by decomposition of the aminoimidazole moiety, which was exceptionally unstable to the conditions (acidic, basic or reductive) needed to remove the protective groups that we had strategically chosen (*vide supra*).

The possibility of installing the aminoimidazole as the last step of the total synthesis, after the full deprotection of a late-stage intermediate, was explored next. In addition, we sought an alternative one-carbon homologation reaction in place of the unreliable and experimentally tedious Arndt–Eistert sequence. After extensive experimentation, a solution to our problems was discovered. Namely, we found that nitromethane addition¹⁸ to aldehyde **21** and subsequent oxidation produced **22** in high yield (Scheme 4). Nitroketone **22**, in turn, was a suitable intermediate for the removal of the indole nitrogen protective groups. Deoxygenated ethanolic potassium hydroxide facilitated removal of the *N*-tosyl group,¹⁹ while lithium tetrafluoroborate followed by aqueous sodium hydroxide effected complete hydrolysis of the SEM group (**22** → **23**). Reduction of nitroketone **23** with stannous chloride,²⁰ then cleavage of the benzyl and methyl ethers with iodotrimethylsilane revealed fully deprotected aminoketone **24**.^{21,22} Final installation of the aminoimidazolium unit occurred by treatment of **24** with cyanamide followed by trifluoroacetic acid



Scheme 4 The total synthesis of dragmacidin D (**5**).

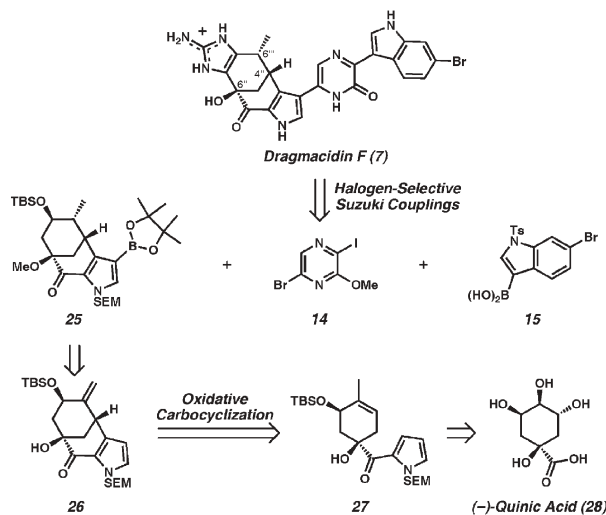
workup to produce dragmacidin D (**5**) in 86% yield. This effort stands as the only completed total synthesis of dragmacidin D to date.^{23–25}

The total synthesis of dragmacidin F

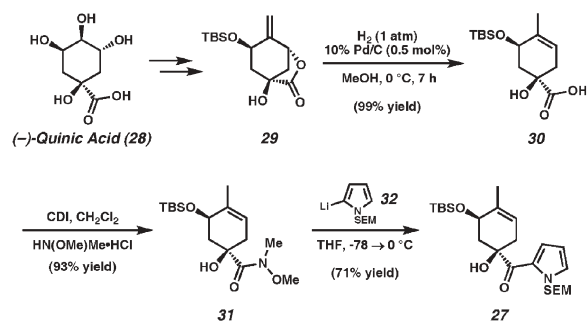
Having developed a strategy to construct the bis(indole)pyrazinone core of dragmacidin D (**5**), we set out to apply our Pd(0) halogen-selective Suzuki coupling methodology to the synthesis of related natural products. We hypothesized that our approach could be amenable to the preparation of the antiviral agent dragmacidin F,^{3f,g} which is perhaps the most challenging target of the dragmacidin natural products.

Dragmacidin F shares a number of structural features with dragmacidin D, namely, an aminoimidazolium fragment, a differentially substituted pyrazinone and a 6-bromoindole unit. However, rather than containing two indole functionalities, dragmacidin F possesses one indole, in addition to a pyrrole appended [3.3.1] bicycle. It is important to note that at the time of our synthetic effort, the absolute stereochemistry of natural dragmacidin F was not known; thus, the absolute stereochemistry of our target was chosen arbitrarily.

Our retrosynthetic analysis for dragmacidin F is shown in Scheme 5. We reasoned that the aminoimidazole would best be incorporated at a late stage in the synthesis. The carbon scaffold of **7**, could be assembled *via* a series of halogen-selective Suzuki cross coupling reactions of **25**, **14** and **15** in an analogous manner to the dragmacidin D sequence. Since pyrazine **14** and boronic acid **15** were readily accessible, our success would depend highly on the ability to prepare pyrroloboronic ester **25**. We envisioned deriving this key coupling fragment from parent bicycle **26** which, in turn, would arise *via* an intramolecular Pd-mediated oxidative carbocyclization reaction of acyl pyrrole **27**.²⁶ This latter transformation was extremely appealing to us given our laboratory's interest in Pd oxidation chemistry.²⁷ Although we had previously cyclized indoles and electron rich aromatics in the presence of Pd(II), examples of pyrroles undergoing the



Scheme 5 Retrosynthesis of dragmacidin F (**7**).



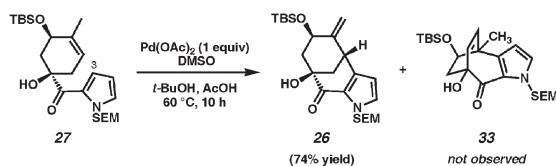
Scheme 6 Synthesis of cyclization substrate **27**.

analogous carbocyclization were not known in the literature or our own laboratory.²⁸ In the final retrosynthetic disconnection, pyrrole **27** would be accessible from (-)-quinic acid (**28**),²⁹ a commercially available enantiopure starting material.

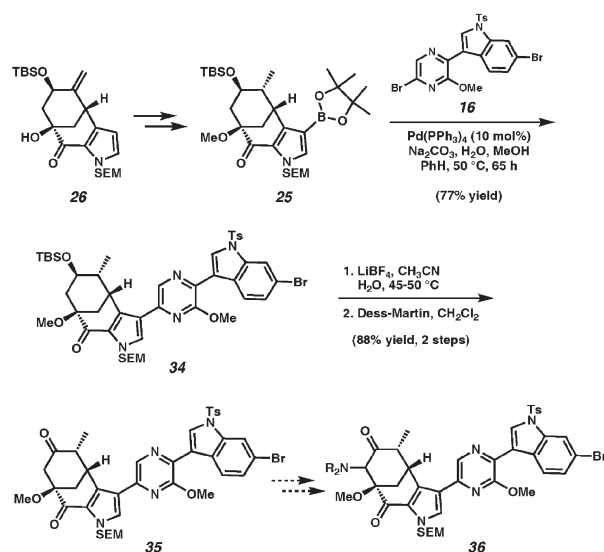
Our first task was to devise an efficient route to **27** beginning from (-)-quinic acid (**28**, Scheme 6). Lactone **29** could be obtained in four simple steps and then reductively isomerized to acid **30** upon treatment with Pd/C in MeOH at 0 °C in the presence of H₂.³⁰ Notably, this transformation proceeded in essentially quantitative yield and allowed for the preparation of multigram quantities of **30** in a facile manner. More importantly, acid **30** could be converted to cyclization substrate **27** via a two-step protocol involving Weinreb amide formation^{30,31} and displacement by 2-lithio-1-SEM-pyrrole (**32**).³¹

With acyl pyrrole **27** in hand, we turned our attention to the key Pd(II)-mediated cyclization reaction (Scheme 7). After substantial experimentation, we found that [3.3.1] bicycle **26** could be formed upon exposure of **27** to a Pd(OAc)₂/DMSO system.³² Under our optimized reaction protocol, bicycle **26** was isolated in 74% yield. Notably, this transformation (**27**→**26**) results in functionalization of the electronically deactivated and sterically congested C(3) position of acyl pyrrole **27**.^{33,34} Furthermore, undesired [3.2.2] bicycle **33** was not observed under these Pd(II) conditions, although **33** formed in substantial quantities in the analogous Heck reaction.^{35,36}

Our next goal was to construct the carbon skeleton of the natural product (Scheme 8). Following a straightforward four step sequence, bicycle **26** was elaborated to the crucial boronic ester fragment (**25**). By analogy to our dragmacidin D studies, we were pleased to find that upon treatment of **25** with bromopyrazine **16** under our standard Suzuki coupling conditions, the desired C–C bond formation took place to afford the fully coupled product (**34**) in 77% yield. Importantly, the indolyl bromide moiety was maintained under these reaction conditions. Following cleavage of the silyl ether and subsequent oxidation, we arrived at ketone **35**.



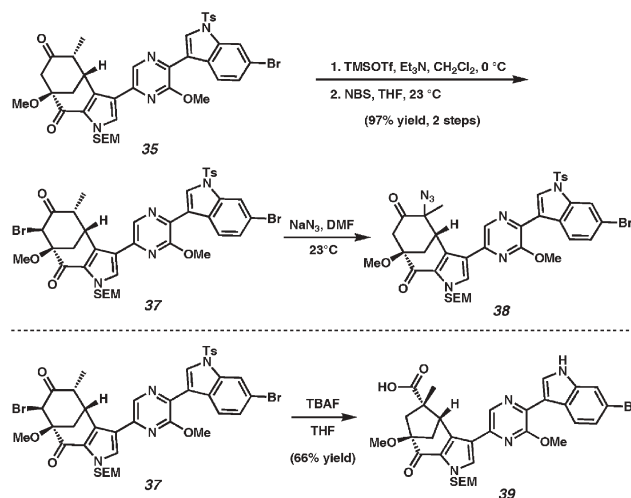
Scheme 7 Pd(II)-Mediated oxidative carbocyclization.



Scheme 8 Synthesis of the carbon scaffold of dragmacidin F.

We anticipated that the presence of an amino group α to the ketone would allow for eventual introduction of the aminoimidazole moiety, as was the case in our synthesis of dragmacidin D (**5**). Thus, we focused our efforts on preparing compounds related to **36**.

Our first efforts to functionalize the ketone α -position involved a nitration strategy to access a compound analogous to an intermediate employed in the dragmacidin D synthesis.³⁷ Unfortunately, in all of these cases, formation of the desired nitroketone product was not observed. We switched to a strategy whereby the α nitrogen substituent could be installed via nucleophilic displacement of an α bromide. Thus, bromoketone **37** was prepared from ketone **35** as a single diastereomer via a silyl enol ether intermediate (Scheme 9).³⁸ Much to our surprise, bromoketone **37** was extremely prone to base promoted rearrangements when treated with nitrogenous nucleophiles. For example, upon exposure of bromoketone **37** to NaN₃, azidoketone **38** formed as the major product. Furthermore, simply reacting bromide **37** with a basic fluoride

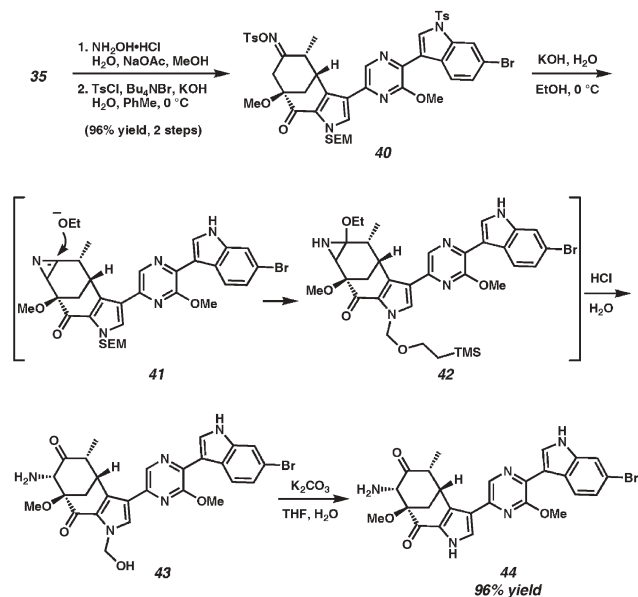


Scheme 9 End-game studies and unexpected rearrangements.

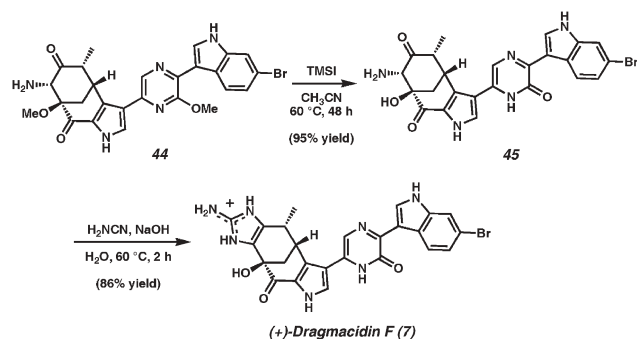
anion source (TBAF in THF) led to Favorskii rearrangement product **39**.³⁹ The use of basic amine nucleophiles also yielded related Favorskii products.

A number of other options for installing the α -aminoketone, including enol silane oxidative azide formation and aminohydroxylation, were attempted as well, but were met without success. As our options diminished, we considered an alternative plan that would rely on the use of a Neber rearrangement to install the necessary nitrogen substituent.^{40,41} In this scenario, an activated oxime derivative would undergo alkoxide-promoted rearrangement to furnish an α -aminoketone. Although this transformation is relatively uncommon and typically hampered by competitive Beckman rearrangement pathways, we elaborated ketone **35** to tosyl oxime **40** *via* known protocols (Scheme 10). In our initial experiments, exposure of substrate **40** to aqueous KOH in ethanol led to the formation of Neber rearrangement products. After optimization, we uncovered a simple two-pot protocol to access deprotected α -aminoketone **44** as a single regio- and stereochemical isomer in excellent yield, as follows: (i) reaction of tosyl oxime **40** with KOH in ethanol facilitates cleavage of the indole tosyl group and likely promotes formation of azirine **41** which, in turn, is attacked by ethoxide⁴² to afford ethoxyaziridine **42**; (ii) subsequent quenching with HCl results in hydrolysis of the ethoxyaziridine with concomitant partial cleavage of the SEM protective group to furnish aminoketone **43**;⁴³ (iii) treatment of hemiaminal **43** with K₂CO₃ removes the remaining portion of the SEM group, thus giving rise to the deprotected product (**44**).^{22,44} To the best of our knowledge, this is the first example of a successful Neber rearrangement in the context of natural product synthesis.^{45,46}

Having installed the α -aminoketone and removed the N-protective groups, completion of the total synthesis of dragmacidin F proceeded smoothly. In order to unveil the masked pyrazinone functionality, Neber rearrangement product **44** was treated with TMSI at 60 °C (Scheme 11).¹³



Scheme 10 Neber rearrangement/deprotection sequence.



Scheme 11 The total synthesis of (+)-dragmacidin F (7).

Fortuitously, both the pyrazinone and the tertiary alcohol functionalities were revealed simultaneously (**44** \rightarrow **45**). In the final step of the synthesis, the penultimate aminoketone (**45**) was subjected to cyanamide and aqueous NaOH to produce enantiopure dragmacidin F (**7**).⁴⁷ Our efficient and enantio-specific route allows access to **7** in 7.8% overall yield in just 21 steps from (–)-quinic acid (**28**).⁴⁸

As mentioned earlier, the absolute stereochemistry of natural dragmacidin F was not known when we began our total synthesis. Although our synthetic sample was identical to natural dragmacidin F^{3f} by most analytical techniques (¹H NMR, ¹³C NMR, IR, UV, HPLC), the sign of optical rotation differed. Thus, we had prepared the unnatural (+) enantiomer of dragmacidin F. However, our synthesis beginning from (–)-quinic acid (**28**) established, for the first time, the absolute configuration of natural dragmacidin F (**7**) to be (4''*S*, 6''*S*, 6'''*S*) as shown in Fig. 4.⁴⁹ In addition, it has been proposed that dragmacidins D, E and F are biosynthetically related. Based on this notion, it is likely that the absolute stereochemical configurations of natural dragmacidins D (**5**) and E (**6**) are (6'''*S*) and (5'''*R*, 6'''*S*), respectively.

The total synthesis of nat-(–)-dragmacidin F

We next pursued the total synthesis of the natural (–) enantiomer of dragmacidin F (**7**). Having developed a route to (+)-dragmacidin F (**7**) from (–)-quinic acid (**28**), we reasoned that the simplest solution to accessing the natural

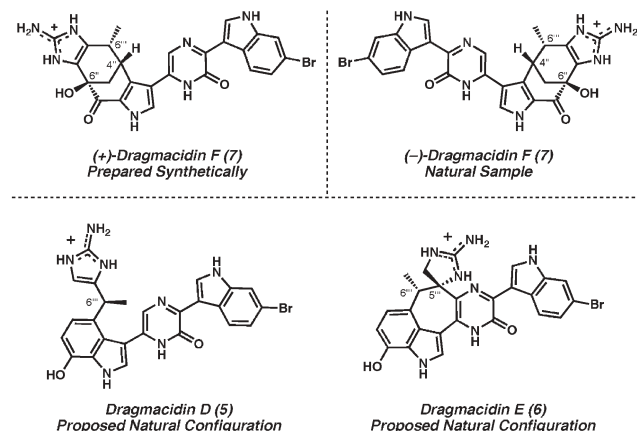


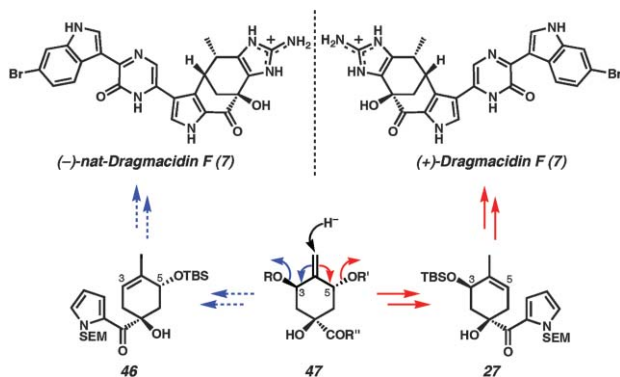
Fig. 4 The absolute stereochemistry of pyrazinone dragmacidins.

enantiomer of dragmacidin F (**7**) would be to employ (+)-quinic acid (**28**) as a starting material. Unfortunately, the (+)-enantiomer of **28** is not easily accessible either commercially or *via* synthetic means.⁵⁰ It seemed plausible, however, that the readily available (–) enantiomer of quinic acid (**28**) could be used to access both enantiomers of dragmacidin F (**7**).⁵¹ Despite its widespread use in natural product synthesis, (–)-quinic acid (**28**) has rarely been used in an enantiodivergent sense.

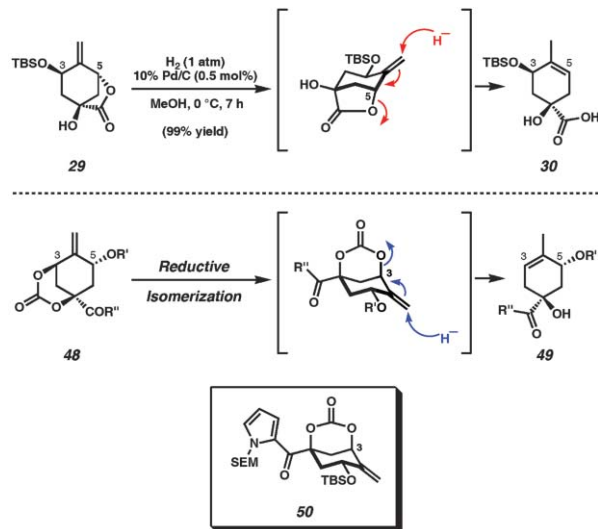
Our enantiodivergent strategy to prepare both enantiomers of dragmacidin F from a single enantiomer of quinic acid is shown in Scheme 12. In order to complete the total synthesis of (+)-dragmacidin F (**7**), a (–)-quinic acid derivative (*e.g.*, **47**) had been subjected to a reductive isomerization reaction that proceeded with loss of the C(5) leaving group. The product of this reaction was elaborated to acyl pyrrole **27** which, in turn, was used to prepare (+)-**7**. We reasoned that a similar reduction of **47** that occurred with removal of the C(3) substituent could be used to access cyclohexene **46** *en route* to (–)-nat-dragmacidin F (**7**). Since acyl pyrrole species **46** and **27** are diastereomeric, it was also possible that transformations that were used to convert **27** to (+)-**7** would not be applicable to the conversion of **46** to (–)-**7**. Nonetheless, we focused our attention on developing a reductive isomerization substrate of type **47** that would lead to cyclohexene **46**.

In order to select the appropriate reductive isomerization substrate needed to access (–)-**7**, a close examination of the analogous reaction used in our (+)-dragmacidin F (**7**) synthesis was necessary. It seemed that the success of the reductive isomerization of lactone **29** to cyclohexene **30** was largely the result of the excellent carboxylate leaving group at C(5) of **29** being restricted to an axial orientation, thereby facilitating its elimination (Scheme 13). Therefore, in designing our new substrate, we envisioned that the tertiary alcohol could be used to lock the C(3) oxygen substituent in an axial disposition in the form of a carbonate leaving group in order to facilitate its elimination (*i.e.*, **48** → **49**).³⁰ Thus, pyrrolocarbonate **50** was chosen as a suitable (–)-quinic acid derivative needed for our reductive isomerization studies and became our target of interest.

Developing a synthesis of carbonate **50** was relatively straightforward. (–)-Quinic acid derivative **29**, which was used in our total synthesis of (+)-**7**, was first treated with



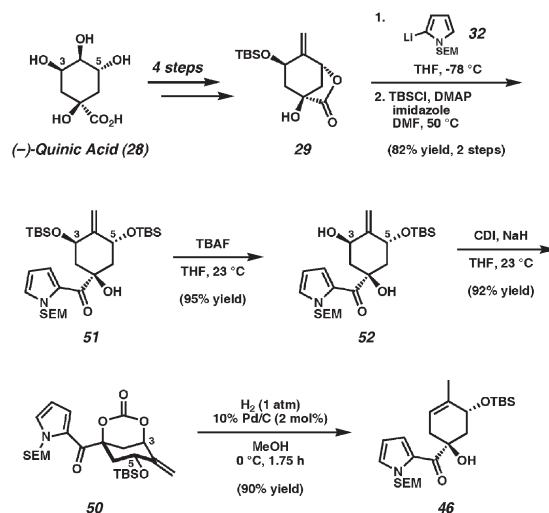
Scheme 12 An enantiodivergent strategy for the preparation of (+)- and (–)-dragmacidin F (**7**).



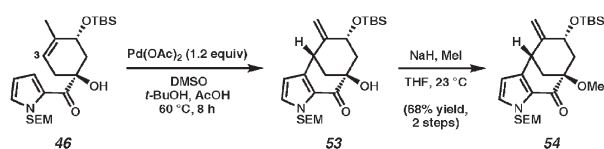
Scheme 13 Rational design of reductive isomerization substrate **50**.

2-lithio-SEM-pyrrole (**32**, Scheme 14). Subsequent TBS protection afforded bis(silyl ether) **51** in good yield. This pseudo-*C*₂-symmetric⁵² compound then underwent rapid diastereoselective mono-desilylation upon treatment with TBAF in THF to produce the *syn* 1,3-diol **52**.⁵³ 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 **52** was smoothly converted to bicyclic carbonate **50** in the presence of CDI, effectively restricting the C(3) substituent to an axial disposition. In the key reductive isomerization reaction, exposure of carbonate **50** to our optimal reaction conditions (2 mol% Pd/C, H₂, MeOH, 0 °C) led to the selective formation of the desired cyclization substrate (**46**) in 90% yield.⁵⁴

With cyclization substrate **46** in hand, we focused our attention on the key Pd(II)-mediated carbocyclization to construct the [3.3.1] bicycle of the natural product (Scheme 15). Despite the degree of steric hindrance imposed upon the C(3) α face by the bulky C(5) silyl ether group



Scheme 14 Elaboration of (–)-quinic acid to **46**.

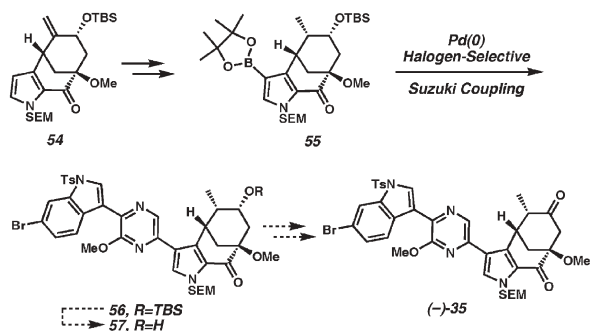


Scheme 15 Construction of [3.3.1] bicycle **54**.

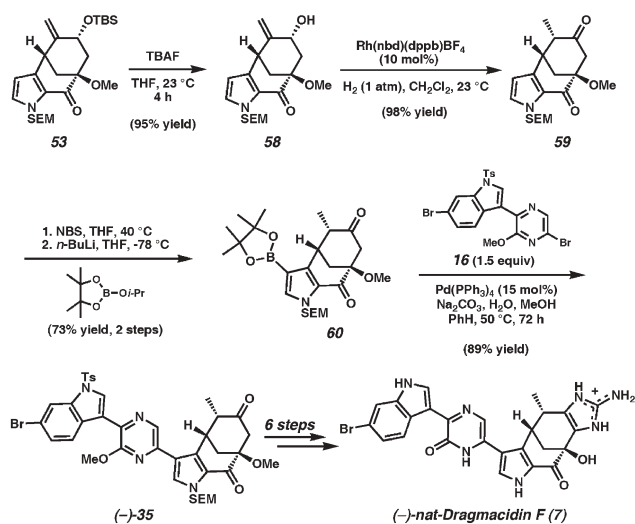
positioned syn to the acyl pyrrole, exposure of **46** to our optimal cyclization conditions resulted in formation of the desired product (**53**). Following protection of the tertiary alcohol, [3.3.1] bicycle **54** was obtained in 68% yield for the two-step process.

After elaboration of bicycle **54** to boronic ester **55**, we were able to assemble the carbon skeleton of (–)-dragmacidin F (**56**) using our halogen-selective Suzuki coupling methods (Scheme 16). We hoped to convert silyl ether **56** to ketone **35**, the enantiomer of which was employed in our synthesis of (+)-**7**. Unfortunately, the selective desilylation of **56** to afford **57** proved to be difficult. This was surprising, since the diastereomer of **56** employed in the synthesis of (+)-**7** participated in the analogous deprotection reaction.

To overcome this roadblock, we pursued strategies whereby the TBS ether could be cleaved at an earlier stage in the synthesis. In a critical reaction, the sterically less crowded TBS ether of olefinic substrate **53** underwent smooth and selective cleavage upon treatment with TBAF in THF to afford allylic alcohol **58** (Scheme 17). Upon exposure of alcohol **58** to Brown's cationic rhodium catalyst Rh(nbd)(dppb)BF₄⁵⁵ and H₂, ketone **59** formed directly as a single diastereomer in 98% yield. Regioselective bromination and low-temperature metalation of the pyrrole in the presence of two ketones gave rise to boronic ester **60**. Subsequent halogen-selective cross-coupling of **60** with dibromide **16** afforded the desired Suzuki adduct (–)-**35** (89% yield). Finally, Suzuki product (–)-**35** was converted to (–)-dragmacidin F ((–)-**7**) via our previously described six-step protocol (*vide supra*). Synthetic and natural (–)-**7**^{3f} were spectroscopically identical, including the sign of optical rotation (natural (–)-**7**: [α]_D²⁵ –159° (c 0.4, MeOH); synthetic (–)-**7**: [α]_D²³ –148° (c 0.2, MeOH)). Our highly efficient syntheses provide (+)-**7** in 7.8% overall yield and (–)-**7** in 9.3% overall yield beginning from **28**. Moreover, this work represents the first and, to date, only total synthesis of the antiviral agent dragmacidin F.⁵⁶



Scheme 16 End-game strategy 1.

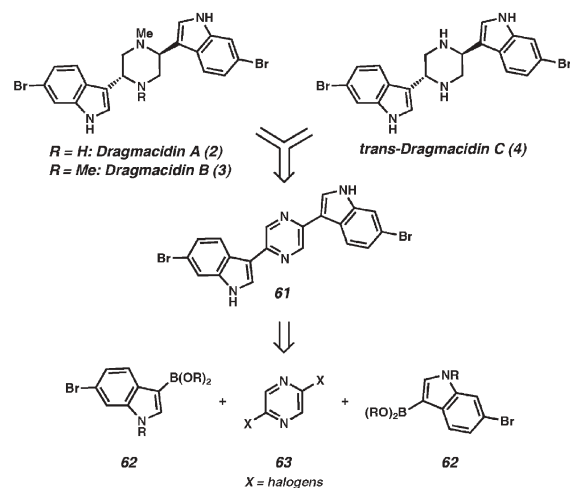


Scheme 17 The total synthesis of (–)-dragmacidin F (**7**).

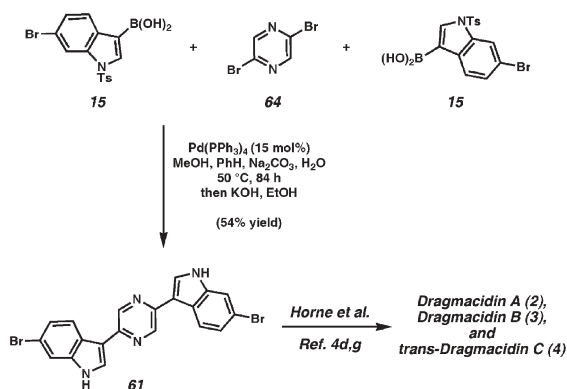
The pyrazine dragmacidins: the formal total synthesis of dragmacidins A, B and *trans*-dragmacidin C

Having established that halogen-selective Suzuki couplings are a powerful method for constructing the carbon skeleton of the pyrazinone-containing dragmacidins, we hypothesized that a similar strategy could be used to access the piperazine dragmacidins. More specifically, our retrosynthesis for dragmacidins A (**2**), B (**3**)^{3b} and *trans*-dragmacidin C (**4**)^{3c} is shown in Scheme 18. Based on the work of Horne and co-workers,^{4d,g} we envisioned that each of the bis(indole) alkaloids could be accessed from unsaturated pyrazine **61** in a single step. Pyrazine **61**, in turn, would be obtained from two halogen-selective Suzuki cross-coupling reactions of boronate **62** with a dihalogenated pyrazine (**63**).

In order to probe the limits of our halogen-selective Suzuki cross-coupling methodology, we chose to use known dibromide **64**⁵⁷ as the critical pyrazine fragment (Scheme 19).



Scheme 18 Retrosynthesis of piperazine dragmacidins.



Scheme 19 The formal total synthesis of dragmacidins A (2), B (3) and *trans*-dragmacidin C (4).

In a one-pot, four-step transformation, an excess of 6-bromoindolylboronic acid (**15**) was exposed to dibromopyrazine **64** under our standard cross-coupling conditions. Following quenching with KOH/ethanol, the deprotected pyrazine product (**61**) was obtained in 54% yield. Notably, although four bromides were introduced in the reaction mixture, only the two pyrazinyl bromides were reactive in the presence of Pd(0) at 50 °C. This rapid synthesis of bis(indole)pyrazine **61** constitutes a formal total synthesis of dragmacidins A (2), B (3) and *trans*-dragmacidin C (4).^{4d,4g,58,59} We have also used a similar approach to prepare members of a related family of natural products, the dihydrohamacanthins.⁶⁰

Conclusion

In summary, we have developed a highly convergent strategy to assemble the dragmacidin natural products. Our approach involves the use of sequential Pd(0)-catalyzed halogen-selective Suzuki couplings to construct the carbon skeletons of these important molecules. Ultimately, this method has been used to achieve the total syntheses of dragmacidins A, B, C and D, in addition to both enantiomers of dragmacidin F. Our work involving dragmacidin D (5) and (+)- and (–)-dragmacidin F (7) remain the only completed total syntheses of the pyrazinone-containing dragmacidins, to date. The success of this work can largely be attributed to the utility of transition metal chemistry in modern organic synthesis, where we have used Pd-mediated cross-couplings, reductive isomerizations and oxidative carbocyclizations as key steps in our total syntheses. Biological evaluation of synthetic dragmacidins and their analogs is currently in progress.

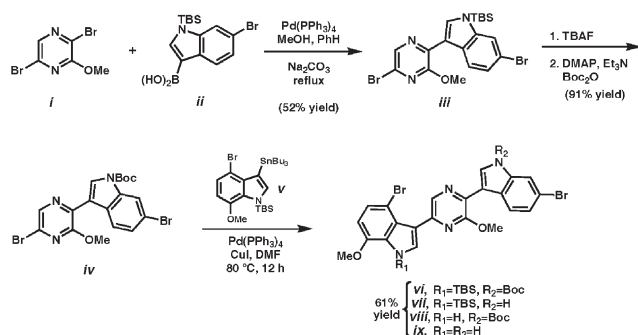
Acknowledgements

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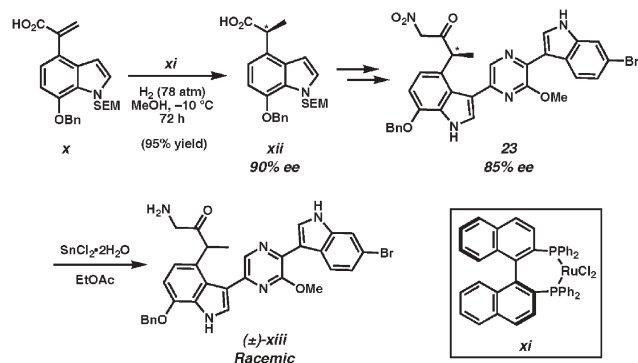
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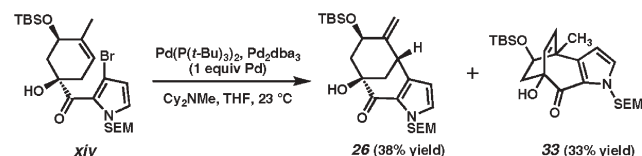


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