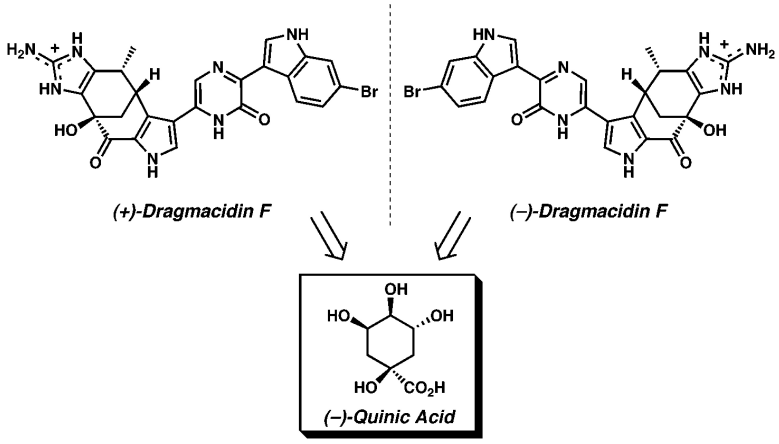
Article

Development of an Enantiodivergent Strategy for the Total Synthesis of (+)- and (–)-Dragmacidin F from a Single Enantiomer of Quinic Acid

Neil K. Garg, Daniel D. Caspi, and Brian M. Stoltz

J. Am. Chem. Soc., **2005**, 127 (16), 5970-5978• DOI: 10.1021/ja050586v • Publication Date (Web): 02 April 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 9 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 04/02/2005

Development of an Enantiodivergent Strategy for the Total Synthesis of (+)- and (−)-Dragmacidin F from a Single Enantiomer of Quinic Acid

Neil K. Garg, Daniel D. Caspi, and Brian M. Stoltz*

Contribution from The Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 East California Boulevard, MC 164-30, Pasadena, California 91125

Received January 28, 2005; E-mail: stoltz@caltech.edu

Abstract: An enantiodivergent strategy for the total chemical synthesis of both (+)- and (−)-dragmacidin F beginning from a single enantiomer of quinic acid has been developed and successfully implemented. Although unique, the synthetic routes to these antipodes share a number of key features, including novel reductive isomerization reactions, Pd(II)-mediated oxidative carbocyclization reactions, halogen-selective Suzuki couplings, and high-yielding late-stage Neber rearrangements.

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 analogues, 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 (**1**−**7**, Figure 1).[3,4] As part of a research program geared toward the synthesis of complex heterocyclic natural products, we initiated an effort to synthesize those dragmacidins that possess a pyrazinone core, namely, dragmacidins D, E, and F (**5**−**7**). In 2002, we reported the first total synthesis of any of these three unique alkaloids with our preparation of (±)-dragmacidin D (**5**).[5] Our highly convergent approach to **5** relied on a series of halogen-selective Suzuki cross-couplings of **8**, **9**, and **10** (Scheme 1) to build the bis(indole)pyrazine skeleton (**11**) of the natural product. We hypothesized that this general synthetic strategy could also be applied to the other pyrazinone-containing members of the dragmacidin family.

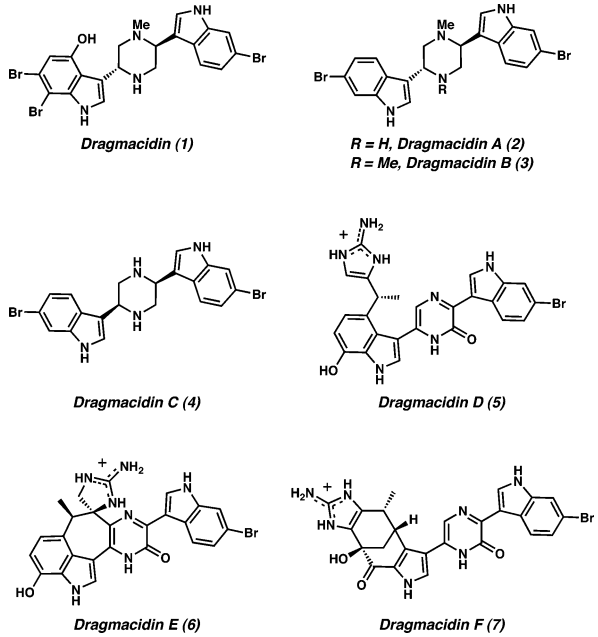


Figure 1. Dragmacidin alkaloids.

Perhaps the most daunting target of the dragmacidin natural products is dragmacidin F (**7**), which was isolated in 2000 from the ethanol extracts of the Mediterranean sponge *Halicortex* sp. Although **7** does not contain a bis(indole) framework, it is presumed to be derived biosynthetically from dragmacidin D (**5**) via an oxidative de-aromatization/cyclization process.[3f,5] Dragmacidin F (**7**) exhibits in vitro antiviral activity against herpes simplex virus (HSV-I; $EC_{50} = 95.8\ \mu M$) and human immunodeficiency virus (HIV-I; $EC_{50} = 0.91\ \mu M$)[3f] and thus is an attractive target from a biological standpoint. Given the limited supply of dragmacidin F (**7**) available from natural sources, a successful synthetic approach to **7** could facilitate

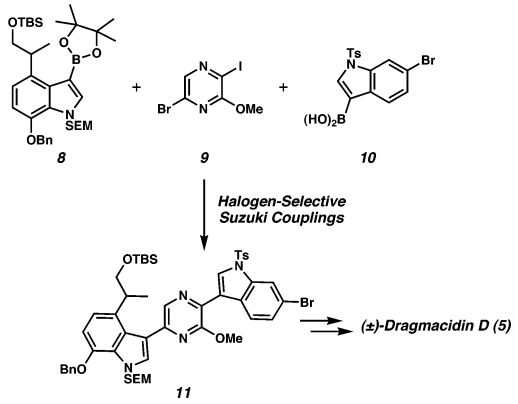
(1) (a) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2004**, *21*, 1−49. (b) Aygün, A.; Pindur, U. *Curr. Med. Chem.* **2003**, *10*, 1113−1127. (c) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1−48. (d) Pindur, U.; Lemster, T. *Curr. Med. Chem.* **2001**, *8*, 1681−1698.

(2) (a) Yang, C.-G.; Huang, H.; Jiang, B. *Curr. Org. Chem.* **2004**, *8*, 1691−1720. (b) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 584−605. (c) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2002**, *19*, 148−180. (d) Sasaki, S.; Ehara, T.; Sakata, I.; Fujino, Y.; Harada, N.; Kimura, J.; Nakamura, H.; Maeda, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 583−585.

(3) For the isolation of the piperazine-containing dragmacidins, see: (a) Kohmoto, S.; Kashman, Y.; McConnell, O. J.; Rinehart, K. L., Jr.; Wright, A.; Koehn, F. *J. Org. Chem.* **1988**, *53*, 3116−3118. (b) Morris, S. A.; Andersen, R. J. *Tetrahedron* **1990**, *46*, 715−720. (c) Fahy, E.; Potts, B. C. M.; Faulkner, D. J.; Smith, K. *J. Nat. Prod.* **1991**, *54*, 564−569. For the isolation of the pyrazinone-containing dragmacidins, see: (d) Wright, A. E.; Pomponi, S. A.; Cross, S. S.; McCarthy, P. *J. Org. Chem.* **1992**, *57*, 4772−4775. (e) Capon, R. J.; Rooney, F.; Murray, L. M.; Collins, E.; Sim, A. T. R.; Rostas, J. A. P.; Butler, M. S.; Carroll, A. R. *J. Nat. Prod.* **1998**, *61*, 660−662. (f) Cutignano, A.; Bifulco, G.; Bruno, I.; Casapullo, A.; Gomez-Paloma, L.; Riccio, R. *Tetrahedron* **2000**, *56*, 3743−3748. (g) Wright, A. E.; Pomponi, S. A.; Jacobs, R. S. PCT Int. Appl. WO 9942092, Aug. 26, 1999.

10.1021/ja050586v CCC: $30.25

Scheme 1



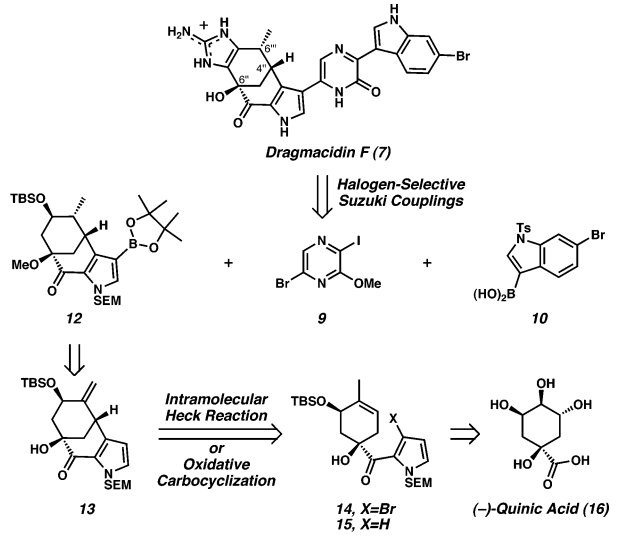
the production of sufficient quantities of material needed for advanced biological studies. Herein, we describe the development of an enantiodivergent strategy to access both enantiomers of dragmacidin F, beginning from a single enantiomer of a chiral starting material.

Results and Discussion

Retrosynthesis of Dragmacidin F.[6] The antiviral agent dragmacidin F (**7**) 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.

Our retrosynthetic analysis for dragmacidin F is shown in Scheme 2. On the basis of our experience with dragmacidin D (**5**), we reasoned that the aminoimidazole moiety would best be incorporated at a late stage in the synthesis.[5] The carbon skeleton of the natural product would then arise via a series of halogen-selective Suzuki cross-coupling reactions (**12** + **9** + **10**). Pyrazine **9** and indoloboronic acid **10** were both readily accessible,[5] while pyrroloboronic ester **12** perhaps could be derived from pyrrole-fused bicycle **13**, our key retrosynthetic intermediate. We then targeted bicycle **13** from two related directions: a Pd(0)-mediated intramolecular Heck reaction[7] of bromopyrrole **14** and a Pd(II)-promoted oxidative carbocyclization[8] involving *des*-bromopyrrole **15**. The successful implementation of the latter method was particularly attractive since it is closely aligned with our interest in Pd(II)-catalyzed dehydrogenation reactions.[9] Both of the cyclization substrates (**14** and **15**) could be prepared from commercially available (−)-quinic acid (**16**).[10] At the time of this synthetic effort, the absolute stereochemistry of natural dragmacidin F was not known; thus, the absolute stereochemistry of our target (**7**) was chosen arbitrarily.

Scheme 2



Synthesis of Cyclization Substrates. Our synthesis of **7** began with a known two-step protocol involving lactonization and silylation of **16** to afford bicyclic lactone **17** (Scheme 3).[11] Subsequent oxidation and Wittig olefination of **17** produced *exo*-methylene lactone **18** in good yield. Initially, we envisioned the direct conversion of lactone **18** to unsaturated carboxylic acid **19** by executing a homogeneous Pd(0)-catalyzed π-allyl hydride addition reaction.[12] Despite considerable experimentation, however, exposure of lactone **18** to a variety of Pd and hydride sources under standard conditions[12] led to the formation of complex product mixtures. As a result, a more stepwise approach was tried. Methanolysis of lactone **18** followed by acetylation of the resulting 2° alcohol[13] gave rise to allylic acetate **20**, another potential substrate for π-allyl reduction chemistry. Although **20** did react under most literature protocols, undesired exocyclic olefin **22** was typically the major product observed. After substantial optimization, we were able to access **21** as the major product by employing stoichiometric Pd(P(*t*-

(4) For synthetic work aimed toward the piperazine-containing dragmacidins, see: (a) Jiang, B.; Smallheer, J. M.; Amaral-Ly, C.; Wuonola, M. A. *J. Org. Chem.* **1994**, *59*, 6823−6827. (b) Whitlock, C. R.; Cava, M. P. *Tetrahedron Lett.* **1994**, *35*, 371−374. (c) Kawasaki, T.; Enoki, H.; Matsumura, K.; Ohyama, M.; Inagawa, M.; Sakamoto, M. *Org. Lett.* **2000**, *2*, 3027−3029. (d) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 3185−3187. (e) Yang, C.-G.; Wang, J.; Tang, X.-X.; Jiang, B. *Tetrahedron: Asymmetry* **2002**, *13*, 383−394. (f) Kawasaki, T.; Ohno, K.; Enoki, H.; Umemoto, Y.; Sakamoto, M. *Tetrahedron Lett.* **2002**, *43*, 4245−4248. For studies targeting dragmacidins D, E, or F, see: (g) Jiang, B.; Gu, X.-H. *Bioorg. Med. Chem.* **2000**, *8*, 363−371. (h) Jiang, B.; Gu, X.-H. *Heterocycles* **2000**, *53*, 1559−1568. (i) Yang, C.-G.; Wang, J.; Jiang, B. *Tetrahedron Lett.* **2002**, *43*, 1063−1066. (j) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2002**, *4*, 941−943. (k) Yang, C.-G.; Liu, G.; Jiang, B. *J. Org. Chem.* **2002**, *67*, 9392−9396.

(5) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179−13184.

(6) Recently, we reported the first total synthesis of (+)-dragmacidin F as a communication, see: Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552−9553.

(7) For recent reviews of the Heck reaction, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2963. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (c) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254−278.

(8) For related examples of Pd-mediated carbocyclizations in natural product synthesis, see: (a) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904−7905. (b) Williams, R. M.; Cao, J.; Tsujishima, H.; Cox, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 12172−12178.

(9) (a) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362−367. (b) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892−2895. (c) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578−9579. (d) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144−6148.

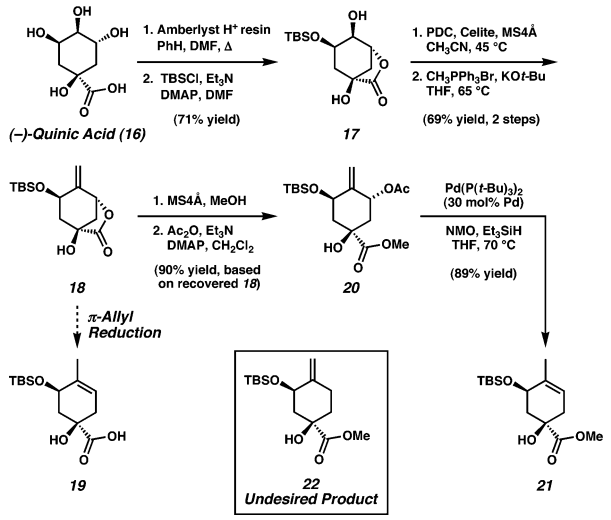
(10) For reviews and examples regarding the use of (−)-quinic acid in natural product synthesis, see: (a) Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3515−3545. (b) Huang, P.-Q. *Youji Huaxue* **1999**, *19*, 364−373. (c) Hanessian, S.; Pan, J.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997**, *62*, 465−473. (d) Hanessian, S. In *Total Synthesis of Natural Products: The "Chiron" Approach*; Baldwin, E. J., Ed.; Pergamon Press: Oxford, U.K., 1983; pp 206−208.

(11) (a) Philippe, M.; Sepulchre, A. M.; Gero, S. D.; Loibner, H.; Streicher, W.; Stutz, P. *J. Antibiot.* **1982**, *35*, 1507−1512. (b) Manthey, M. K.; González-Bello, C.; Abell, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 625−628.

(12) For a review, see: Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1−24.

(13) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.

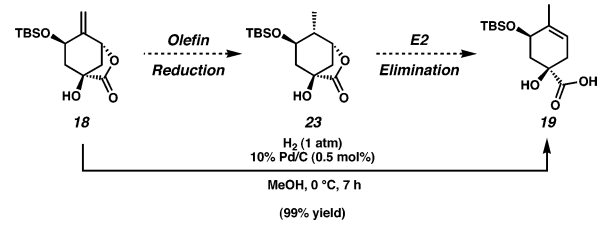
Scheme 3



Bu)$_3$)$_2$[14] 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.[15] Under these conditions, cyclohexene **21** 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 **21** or a closely related derivative thereof (i.e., **19**) in a more facile and preparative manner.

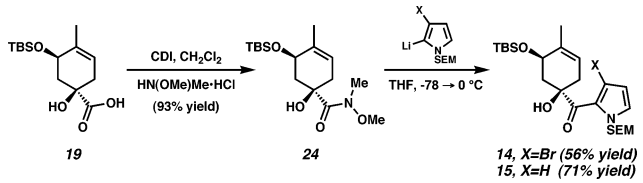
In our revised plan, we conceived a two-step route to obtain carboxylic acid **19** via diastereoselective reduction of olefin **18** followed by base-promoted elimination of the carboxylate functionality of **23** (Scheme 4). The first part of this sequence was attempted by exposing olefin **18** to 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., **23**). To our delight, the product was identified as unsaturated carboxylic acid **19**. Under our optimized reaction conditions (0.5 mol % Pd/C, 1 atm H_2, MeOH, 0 °C), essentially quantitative reductive isomerization to **19** was observed. Although the mechanism of this transformation has not been studied extensively, simple control experiments suggest that stepwise reduction/elimination[16] or π-allyl reduction processes are not operative.[17]

Scheme 4



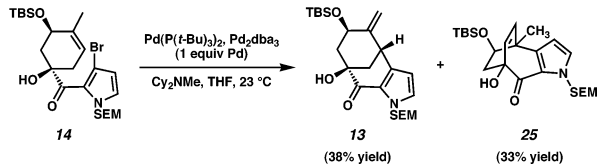
With facile access to cyclohexene carboxylic acid **19**, preparation of the key cyclization precursors proceeded without difficulty. Activation of acid **19** with CDI followed by the addition of HN(OMe)Me·HCl afforded Weinreb amide **24** (Scheme 5). The Weinreb amide functionality was then displaced with the appropriate lithiopyrrole[18] reagent to produce Heck cyclization substrate **14**[19] and oxidative cyclization substrate **15**.

Scheme 5



Constructing the [3.3.1] Bicycle. Extensive studies were carried out in order to achieve the intramolecular Heck cyclization of bromopyrrole **14**. Attempts to utilize standard procedures were unsuccessful,[7] likely due to the thermal instability of the bromopyrrole moiety. However, implementation of the room-temperature conditions developed by Fu[20] provided the desired [3.3.1] bicyclic product (**13**), albeit in low yield (Scheme 6). Unfortunately, the formation of **13** was hampered by competitive production of [3.2.2] bicycle **25**. 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 (**13**) to the undesired [3.2.2] bicycle (**25**). In addition, the ratio of **13** to **25** decreased over time,[21] 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 6



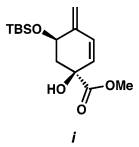
Although the Heck reaction was useful for preparing reasonable quantities of bicycle **13**, an alternative and potentially more selective route to **13** was desired. In conjunction with ongoing research in our group,[9] we turned to the Pd(II)-mediated C−C

(14) Despite its widespread use in modern cross-coupling chemistry, to the best of our knowledge, this is the first report of Pd(P(*t*-Bu)$_3$)$_2$ being used for a π-allylpalladium substitution reaction. For recent examples of Pd(P(*t*-Bu)$_3$)$_2$ in cross-coupling reactions, see: Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178−13179, and references therein.

(15) For the use of NMO as an additive in Stille couplings, see: Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc*. **1999**, *121*, 7600−7605.

(16) Under certain conditions, we were able to produce **23** as a mixture of diastereomers. However, upon exposure of **23** to Pd/C and H_2 in MeOH, no reaction took place.

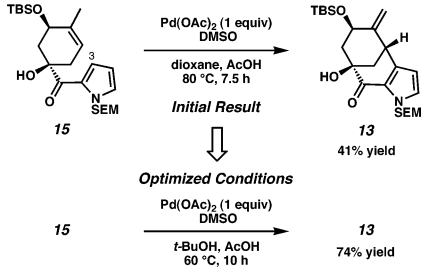
(17) Treatment of **20** under a variety of standard homogeneous π-allyl reduction conditions[12] led to the formation of **21**, **22**, and **i**, all of which presumably arise from loss of OAc^-. In stark contrast, exposure of **20** to heterogeneous reductive isomerization conditions did not produce any of these compounds (see Scheme 16).



i

(18) For the discovery and use of SEM pyrrole, see: (a) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630−633. (b) Muchowski, J. M.; Solas, D. R. *J. Org. Chem*. **1984**, *49*, 203−205. (c) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J. *J. Org. Chem.* **1984**, *49*, 3503−3516. (d) Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723−3729.

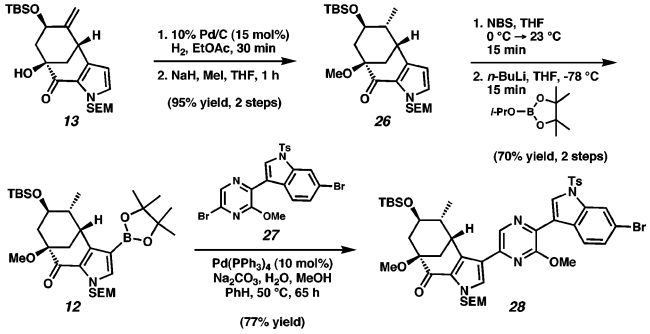
Scheme 7



bond forming approach. In this scenario, C(3)-unsubstituted pyrrole **15** would undergo intramolecular carbocyclization to afford **13** (Scheme 7). Initial experimentation revealed that pyridine and ethyl nicotinate were not effective ligands for promoting cyclization in the presence of $Pd(OAc)_2$.[9c,d] However, by using dimethyl sulfoxide (DMSO) as a ligand[22] the desired cyclization product could be obtained in modest yield. Subsequent optimization of solvent, temperature, and reaction time led to a set of improved conditions whereby the desired pyrrole-fused bicycle **13** was formed as a single stereo- and regioisomer in 74% yield. Interestingly, these conditions take advantage of a similar solvent mixture employed in Pd cyclization methodology from our laboratory.[9c,d] This transformation (**15** → **13**) is particularly noteworthy since it results in functionalization of the electronically deactivated and sterically congested C(3) position of acyl pyrrole **15**.[23,24] Despite our best efforts, we were unable to effect catalytic turnover of Pd with a stoichiometric oxidant in this reaction, presumably due to extensive oxidative decomposition of both the starting material and the desired product.[25] Nonetheless, the Pd(II)-mediated strategy provided bicycle **13** in nearly twice the isolated yield as the Heck route using equivalent amounts of Pd and obviated the need for polybrominated pyrroles.[19,26]

Assembling the Carbon Skeleton of Dragmacidin F. With the [3.3.1] bicyclic framework in hand (i.e., **13**), we focused our attention on constructing the full carbon skeleton of dragmacidin F (**28**, Scheme 8). The final stereocenter present in the natural product was installed via catalytic hydrogenation

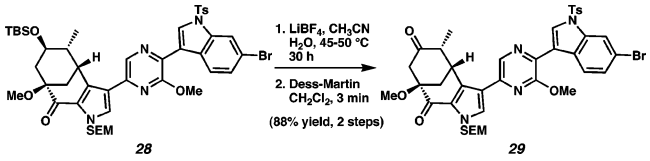
Scheme 8



of olefin **13** and was followed by methylation of the 3° alcohol to produce bis(ether) **26**. The methyl protecting group was selected initially for its robustness[13] and would presumably allow for the exploration of late-stage chemistry in the form of a model system.[27] Methyl ether **26** was then elaborated via regioselective bromination of the pyrrole and metalation to boronic ester **12**. In the critical halogen-selective Suzuki fragment coupling, pyrroloboronic ester **12** was reacted with dibromide **27** (prepared from **9** + **10**)[5] under Pd(0) catalysis. By analogy to our dragmacidin D studies,[5] we were pleased to find that, at 50 °C, the desired C−C bond forming reaction took place to afford the fully coupled product **28** in 77% yield. Importantly, the indolylbromide moiety was maintained under these reaction conditions.

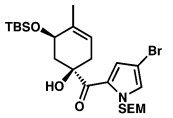
Completion of the Total Synthesis of (+)-Dragmacidin F. With the carbon framework completed, few tasks remained in order to finish the total synthesis of dragmacidin F, namely, removal of all protecting groups and installation of the aminoimidazole unit. Of particular note is the similarity of these synthetic challenges to those encountered in our total synthesis of dragmacidin D.[5] Not surprisingly, we decided to utilize the methods that were already familiar to us in order to elaborate **28** to the desired natural product (**7**). 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 deprotection of silyl ether **28**, followed by oxidation with Dess−Martin periodinane produced ketone **29** (Scheme 9).

Scheme 9



Our first effort to functionalize the ketone α-position involved a nitration strategy to access a compound analogous to an intermediate employed in the dragmacidin D synthesis (Scheme 10). Both lithium enolate **30** and trimethylsilyl (TMS) enol ether **31** were exposed to electrophilic NO_2 sources.[28] Unfortunately, in all of these cases, formation of the desired nitroketone product (**32**) was not observed.

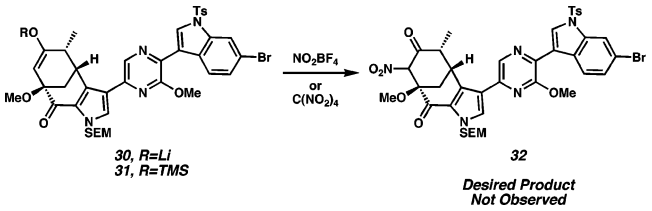
(19) During the conversion of **24** to **14**, 2,4-disubstituted pyrrole **ii** was formed as a byproduct.



ii

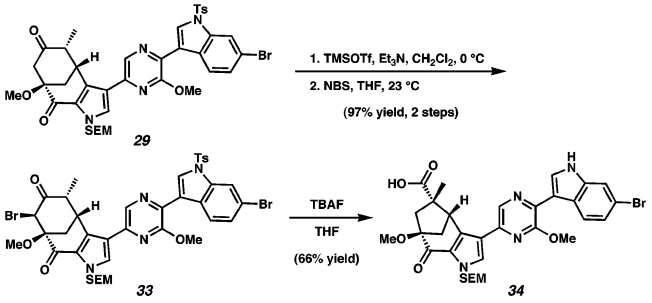
(20) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc*. **2001**, *123*, 6989−7000.
(21) By conducting reactions in THF-d_8, it was possible to monitor Heck reactions by ^{1}H NMR.
(22) DMSO has commonly been employed in oxidative Pd(II) chemistry. See: (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298−5300. (b) Van Benthem, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun*. **1994**, 357−359. (c) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett*. **1995**, *36*, 7749−7752. (d) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346−1347. (e) Stahl, S. S. *Angew. Chem., Int. Ed*. **2004**, *43*, 3400−3420. See also references therein.
(23) Gilow, H. M.; Hong, Y. H.; Millirons, P. L.; Snyder, R. C.; Casteel, W. J., Jr. *J. Heterocycl. Chem.* **1986**, *23*, 1475−1480.
(24) Reactions conducted in the presence of acetic acid-*d* led to deuterium incorporation in the pyrrole ring of both the starting material (**15**) and the product (**13**), mostly at C(4).
(25) The instability of pyrroles to oxidants is well-known. See: (a) Ciamician, G.; Silber, P. *Chem. Ber*. **1912**, *45*, 1842−1845. (b) Bernheim, F.; Morgan, J. E. *Nature* **1939**, *144*, 290. (c) Chierici, L.; Gardini, G. P. *Tetrahedron* **1966**, *22*, 53−56.
(26) 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. *Synth. Met.* **1986**, *15*, 9−22.
(27) In preliminary investigations, late-stage chemistry in the presence of a reactive 3° alcohol was unsuccessful.
(28) (a) Rathore, R.; Kochi, J. K. *J. Org. Chem*. **1996**, *61*, 627−639. (b) Elfehail, F. E.; Zajac, W. W., Jr. *J. Org. Chem*. **1981**, *46*, 5151−5155. (c) Elfehail, F.; Dampawan, P.; Zajac, W. *Synth. Commun*. **1980**, *10*, 929−932. (d) Fischer, R. H.; Weitz, H. M. *Synthesis* **1980**, 261−282.

Scheme 10



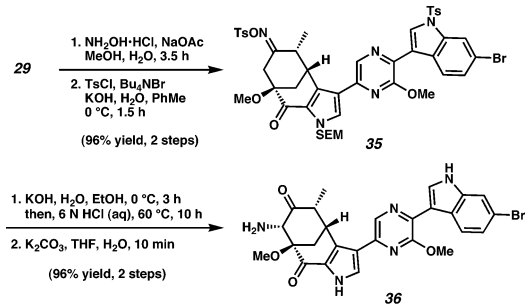
We then turned to an alternative strategy that would involve installation of an α-amino substituent via nucleophilic displacement of an alkylbromide. Therefore, ketone **29** was treated with TMSOTf and then exposed to *N*-bromosuccinimide (NBS) to afford bromoketone **33** as a single diastereomer (Scheme 11).[29] Interestingly, when bromoketone **33** was treated with various nitrogenous nucleophiles, base-promoted rearrangements were observed.[30] In fact, reaction of bromide **33** with a basic fluoride anion source (tetrabutylammonium fluoride (TBAF) in THF) gave [3.2.1] bicycle **34** as the major product via a Favorskii rearrangement.[31] The utilization of amine bases also led to the formation of related Favorskii products.

Scheme 11



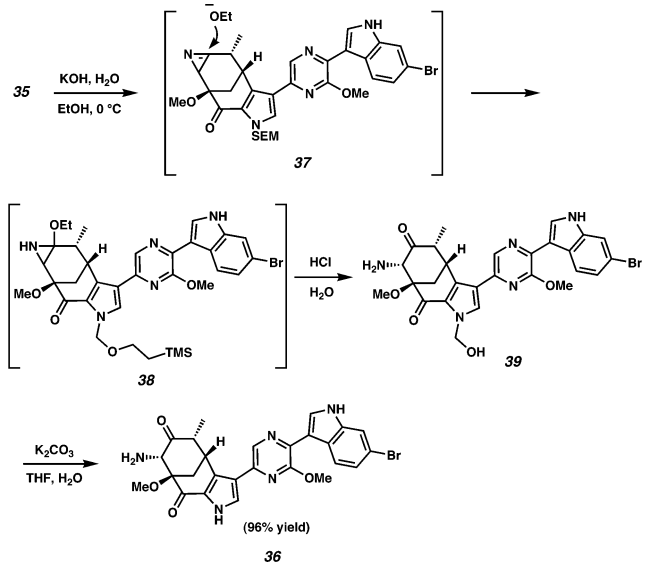
With limited options remaining, we became interested in the use of a Neber rearrangement in order to install the necessary α-amino substituent.[32,33] In this scenario, an activated oxime derivative would undergo alkoxide-promoted rearrangement to furnish an α-amino ketone. Thus, ketone **29** was converted to tosyloxime **35** via standard conditions (Scheme 12). Gratifyingly, exposure of substrate **35** to aqueous KOH in ethanol led to Neber rearrangement. After optimization, we found that simply exposing tosyloxime **35** to (i) KOH, (ii) HCl, and (iii) K_2CO_3 produced α-amino ketone **36** as a single regio- and stereochemical isomer in excellent yield.[34−36] Furthermore, under these reaction conditions, both the tosyl and 2-(trimethylsilyl)ethoxymethyl (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.[6,37]

Scheme 12



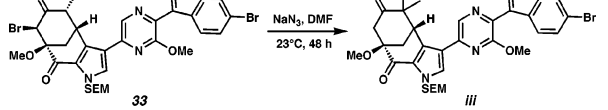
A more detailed look at the possible mechanism of the Neber rearrangement/deprotection sequence is shown in Scheme 13. Exposure of tosyloxime **35** to KOH in ethanol likely leads to the formation of detosylated azirine **37**, which is attacked by ethoxide to afford ethoxyaziridine **38**.[33a,38] Following acid-mediated hydrolysis, the amino ketone moiety is installed with concomitant partial cleavage of the SEM protective group (**38** → **39**).[34b,39] Finally, treatment of hemiaminal **39** with K_2CO_3 removes the remaining portion of the SEM group, thus giving rise to the deprotected amino ketone (**36**).

Scheme 13



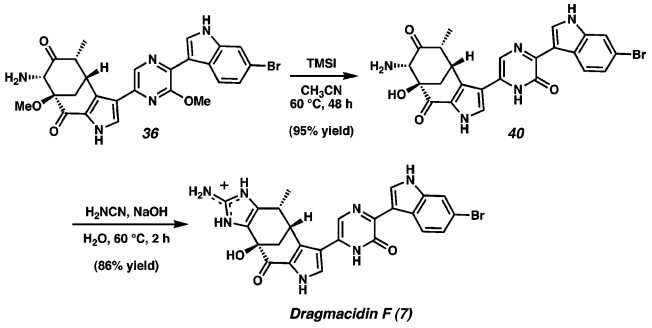
To unveil the masked pyrazinone functionality, Neber rearrangement product **36** was treated with trimethylsilyl iodide (TMSI) at 60 °C (Scheme 14).[13] Fortuitously, both the pyrazinone and the 3° alcohol functionalities were revealed simultaneously (**36** → **40**). In the final step of the synthesis, the penultimate amino ketone (**40**) was subjected to cyanamide and aqueous NaOH to produce enantiopure dragmacidin F.[5,40] Our efficient and enantiospecific route allows access to **7** in 7.8% overall yield in just 21 steps from (−)-quinic acid.

(29) Kreiser, W.; Körner, F. *Helv. Chim. Acta* **1999**, *82*, 1610−1629.
(30) For example, upon treatment of bromoketone **33** with NaN_3, α-azidoketone **iii** formed as the major product.



(31) (a) Favorskii, A. E. *J. Russ. Phys. Chem. Soc.* **1894**, *26*, 559−603. (b) Chenier, P. J. *J. Chem. Educ.* **1978**, *55*, 286−291.
(32) Neber, P. W.; Friedolsheim, A. V. *Justus Liebigs Ann. Chem.* **1926**, *449*, 109−134.
(33) (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.
(34) (a) Purified by reversed-phase chromatography using trifluoroacetic acid in the eluent. (b) See Supporting Information for details.
(35) Derivatives of **35** bearing a free 3° alcohol or a TMS-protected 3° alcohol afforded complex mixtures of products when subjected to Neber rearrangement conditions.
(36) Acid-promoted dimerization of the amino ketone functionalities was not observed.

Scheme 14



Absolute Stereochemistry of the Pyrazinone-Containing Dragmacidins. Synthetic **7** 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 **16** established, for the first time, the absolute configuration of natural **7** to be (4″*S*, 6″*S*, 6‴*S*) as shown in Figure 2.[41] 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 **5** and **6** are (6‴*S*) and (5‴*R*, 6‴*S*), respectively. Having developed a route to the unnatural antipode of (+)-**7**, we set out to extend our approach to the total synthesis of (−)-**7**.

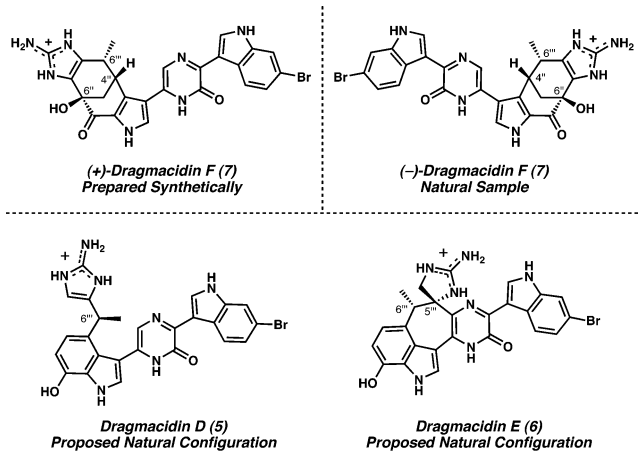
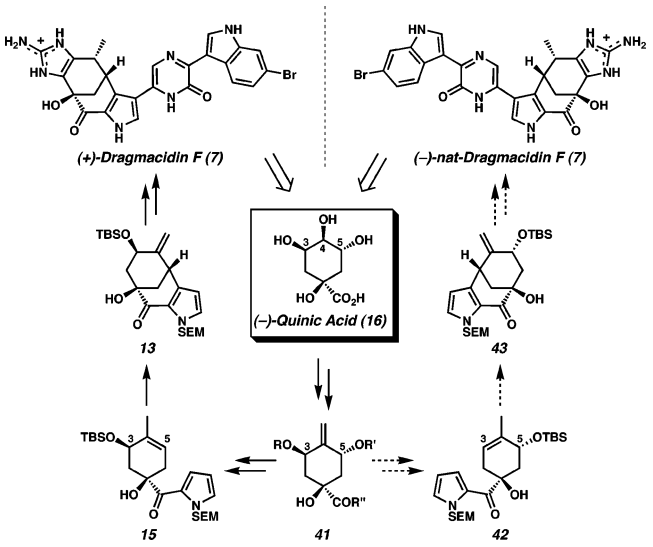


Figure 2. Absolute stereochemical configurations of dragmacidins D, E, and F.

Enantiodivergent Strategy for the Preparation of (−)-Dragmacidin F. As described above, naturally occurring and readily available **16**[10] had served as the starting material for our synthetic approach to (+)-**7**. Unfortunately, the (+)-enantiomer of **16** is not easily accessible,[42] and we were confronted with the possibility that our synthesis would not be amenable to the preparation of our new target molecule, (−)-**7**.

Scheme 15



We reasoned, however, that it might be possible to exploit **16** in an enantiodivergent manner that would allow access to both (+)- and (−)-**7** (Scheme 15).[43] For such an approach to succeed, **16** would be elaborated via selective manipulation of the C(3), C(4), and C(5) hydroxyl groups to a pseudo-C_2-symmetric[44] derivative (**41**) en route to pyrrolocyclohexene **42**, the diastereomer of which (i.e., **15**) was employed in our synthesis of (+)-**7**. Analogous to our approach to (+)-**7** (i.e., **15** → **13**), we anticipated that **42** could undergo oxidative carbocyclization to afford annulated pyrrole **43**. Bicycle **43** would then be elaborated to (−)-**7**. Of the key transformations outlined in Scheme 15, we were familiar with the Pd-mediated oxidative carbocyclizations and the late-stage manipulations of related compounds; however, the successful preparation of (−)-**7** would rely heavily on the identification of a suitable quinic acid derivative (**41**), the facile synthesis of that compound, and the rapid conversion of **41** to the requisite cyclization substrate (**42**).

Development and Investigation 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 (+)-**7**. Two critical results are shown in Scheme 16. In the first experiment, treatment of lactone **18** with Pd/C and H_2 in

(37) (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.

(38) 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.

(39) Hemiaminal **39** has been isolated and characterized by ^{1}H NMR.

(40) 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.

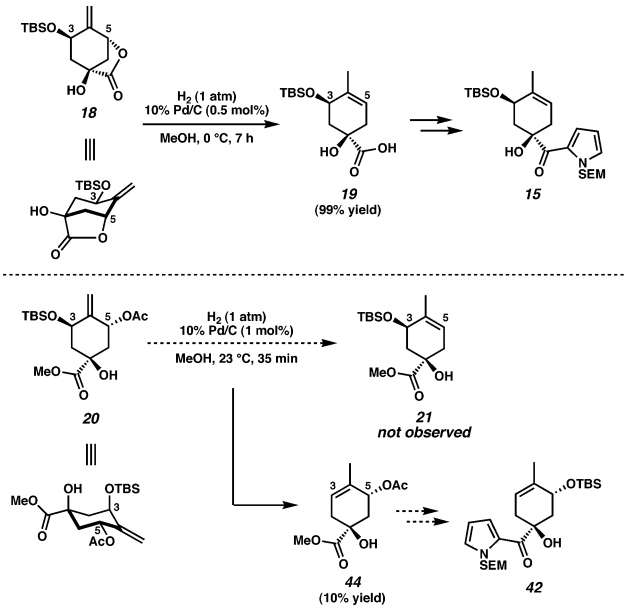
(41) Dragmacidin numbering convention, see ref 3f.

(42) (a) (+)-Quinic acid ((+)-**16**) is commercially available in limited quantities from Interbioscreen Ltd. (50 mg/$305 USD). (b) (+)-Quinic acid ((+)-**16**) potentially could be prepared via multistep synthesis by applying methods used for the preparation of (−)-quinic acid (**16**). See: Rapado, L. P.; Bulugahapitiya, V.; Renaud, P. *Helv. Chim. Acta* **2000**, *83*, 1625−1632, and references therein.

(43) Surprisingly, despite its widespread use in natural product synthesis and its near symmetry, (−)-quinic acid (**16**) 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.

(44) If R = R′, **41** 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.

Scheme 16



methanol at 0 °C furnished carboxylic acid **19** 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 (**20**) was exposed to similar reaction conditions.[45] 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 **44** instead of the anticipated product (**21**).[46] The observation that (*t*-Bu)Me_2SiO^- was preferentially ejected from compound **20** 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.[47] This preferred conformation of **20** represents a cyclohexane ring-flip with respect to lactone **18** and thus gives rise to the reductive isomerization product (**44**) possessing a $\Delta_{3,4}$ olefin. Importantly, the possibility existed that the unexpected product obtained from this reaction (i.e., **44**) could be converted to cyclization substrate **42** (diastereomeric to **15**).

Our efforts to optimize the reductive isomerization of **20** to **44** were hampered by competitive hydrogenation of the olefin moiety of **20**, a complication not observed in the high-yielding conversion of **18** to **19**. Although both processes presumably involve the elimination of an axially disposed leaving group,[47] we reasoned that the successful conversion of **18** to **19** was due to the carboxylate being conformationally restricted to an axial orientation, while substrate **20** possessed a poorer leaving group (*t*-Bu)Me_2SiO^-) and was free to adopt alternate conformations (Figure 3).[48] We hypothesized that derivatives of **20** containing an axially locked leaving group at C(3) (e.g., **45**) would be more suitable substrates for the reductive isomerization reaction. Thus, carbonate **46** was identified as the key (−)-quinic acid derived intermediate en route to the desired cyclization substrate (**42**) and became the focus of our efforts.

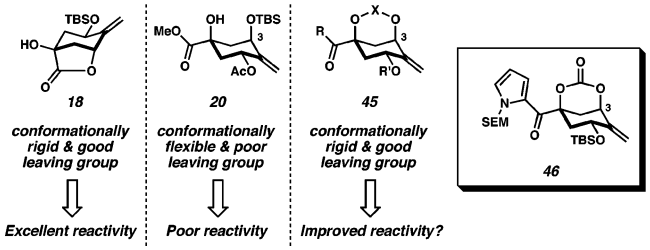
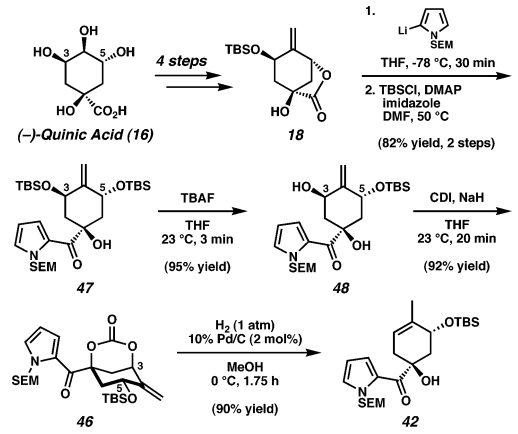


Figure 3. Rational design of an optimal substrate for the key reductive isomerization reaction.

Our synthesis of carbonate **46** began with bicyclic lactone **18**, a derivative of **16** that was used in our total synthesis of (+)-**7** (Scheme 17). Addition of 2-lithio-SEM-pyrrole[18] followed by TBS protection afforded bis(silyl ether) **47** 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 **48**.[49] 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 **48** was smoothly converted to bicyclic carbonate **46** in the presence of CDI, effectively restricting the C(3) substituent to an axial disposition. Gratifyingly, exposure of carbonate **46** to our reductive isomerization conditions (2 mol % Pd/C, H_2, MeOH, 0 °C) led to the selective formation of the desired cyclization substrate (**42**) in 90% yield.[50]

Scheme 17



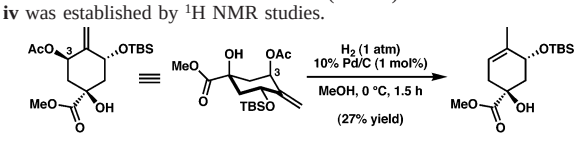
Constructing the [3.3.1] Bicycle en Route to (−)-Dragmacidin F. After assembling target substrate **42**, we turned our attention to the key Pd(II)-mediated cyclization reaction (Scheme 18). Substrate **42** was treated with 1.2 equiv of $Pd(OAc)_2$ under conditions similar to those described earlier, upon which, the

(45) Olefin **20** was also exposed to the reaction conditions used for the reductive isomerization of **18** to **19**. Only trace quantities of **44** were produced under those conditions.[34b,46b]

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

(47) The favored conformation of **20** depicted in Scheme 16 is consistent with ^{1}H NMR studies.[34b]

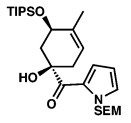
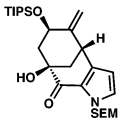
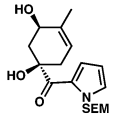
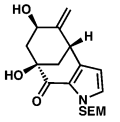
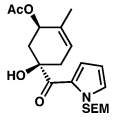
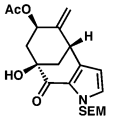
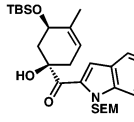
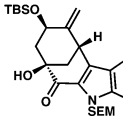
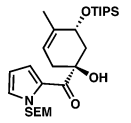
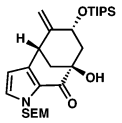
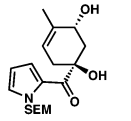
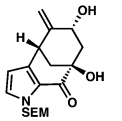
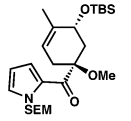
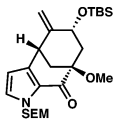
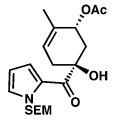
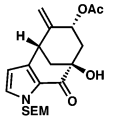
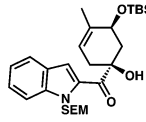
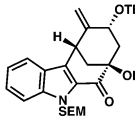
(48) Derivatives of **20** bearing C(3)-acetoxy groups (conformationally flexible and good leaving groups) were also poor substrates in the reductive isomerization reaction as shown below (**iv** → **v**).[46a] The conformation of **iv** was established by ^{1}H NMR studies.



(49) ^{1}H NMR experiments show that the C(3) silyl ether of **47** is axially disposed.[34b] 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.

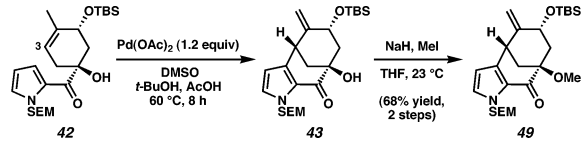
(50) For a classic example involving the use of conformational analysis to solve stereochemical problems in total synthesis, see: Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1−57.

Table 1. Pd(II)-Mediated Oxidative Carbocyclization[a]

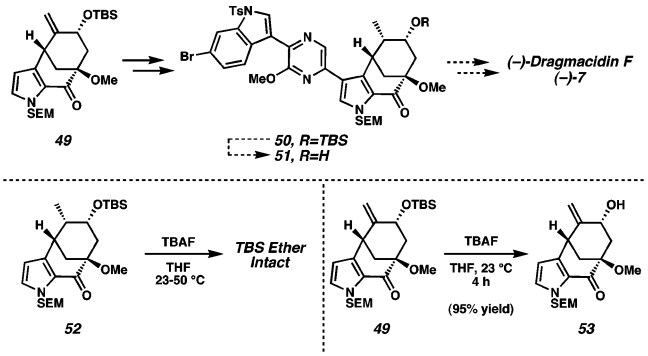
entry	substrate	product	temp (°C)	time	yield[b]
1			60	13.5 h	51% (63%)
2			80	*complex mixture*	
3			80	*no reaction*	
4			80	1.8 h	53% (66%)
5			80[d]	6.5 h	37% (55%)
6			80	2.5 h	49%
7			80	2.3 h	51% (70%)
8			80	*complex mixture*[c]	
9			80	*no reaction*	
10			60[e]	11 h	10%[f]
11			80	2.3 h	34%

[a] Standard Conditions: 1 equiv of $Pd(OAc)_2$, 2 equiv of 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] 20 mol % $Pd(OAc)_2$, 40 mol % DMSO, *t*-BuOH:AcOH (4:1, 0.01 M), O_2 (1 atm). [e] At 80 °C, trace product formation and substantial decomposition were observed. [f] Yield based on ^1H NMR with internal standard.

Scheme 18



Scheme 19



desired pyrrole-fused bicycle (**43**) formed as a single regio- and stereoisomer. Notably, bond formation between the pyrrole functionality and C(3) of **42** 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 **49** was obtained in 68% yield for the two-step process.

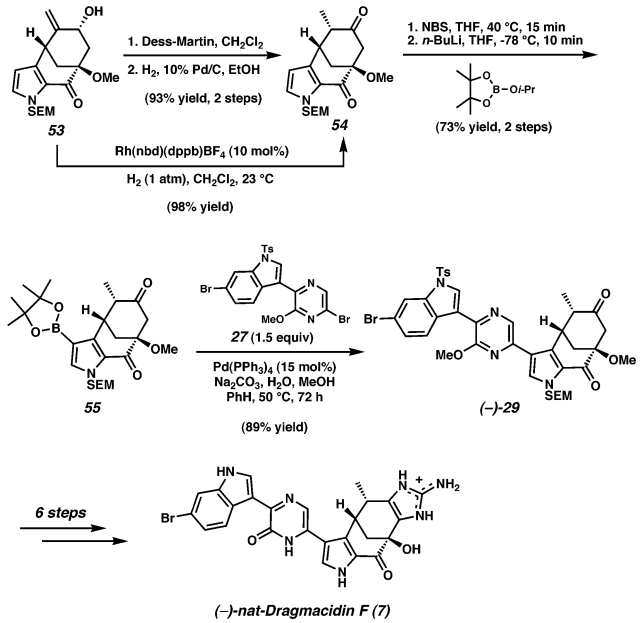
We also explored the Pd(II)-mediated carbocyclization of a number of substrates related to TBS ether **42** and its diastereomeric counterpart **15**. For instance, both TIPS ether analogues underwent cyclization (Table 1, entries 1 and 7), although in lower yield with respect to the parent TBS compounds. However, if the 2° alcohol was left unprotected altogether (entries 2 and 8)[51] or the substrates possessed 3° methyl ethers (entries 3 and 9), formation of the desired bicyclic products was not observed. Interestingly, the diastereomeric acetate derivatives displayed markedly different reactivity. While the substrate possessing an anti relationship between the acetate and acylpyrrole functionalities readily participated in the cyclization reaction (entry 4), the *syn*-isomer was much less reactive (entry 10). Exposure of the *anti*-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 turnover number (TON) of 1.9 (entry 5). It was also possible to annulate C(3) of related indole substrates under our standard conditions (entries 6 and 11).

Total Synthesis of (−)-Dragmacidin F. En route to (−)-dragmacidin F, cyclization product **49** was converted to pyrazine **50** (Scheme 19) by methods similar to those described above.[34b] Despite the similarity of **50** to its diastereomeric counterpart employed in the synthesis of (+)-**7** (**28**, Scheme 9), selective desilylation of **50** to afford **51** proved to be difficult. We reasoned that the steric congestion of the axial TBS ether, positioned syn to the methyl stereocenter, was the cause of these problems. In fact, attempted desilylation of parent bicycle **52** was also challenging even at elevated temperatures.[52] However, in a critical reaction, the sterically less crowded TBS ether of olefinic substrate **49** underwent smooth and selective cleavage upon treatment with TBAF in THF to afford allylic alcohol **53**. With this result in hand, we conceived of a modified route that would ultimately deliver (−)-**7** in a more convergent manner.

Since allylic alcohol **53** was readily accessible, we chose to employ it as an intermediate in our synthesis. Oxidation of allylic

(51) In both cases (entries 2 and 8), direct oxidation of the starting materials to the corresponding enone was observed.

Scheme 20



alcohol **53** followed by olefin reduction afforded ketone **54** in good overall yield (Scheme 20). However, because alcohol **53** and ketone **54** are in the same overall oxidation state, we imagined that a tandem olefin isomerization/tautomerization process would be more efficient. Upon exposure of alcohol **53** to Brown's cationic rhodium catalyst Rh(nbd)(dppb)BF_4[53] and H_2, ketone **54** formed directly as a single diastereomer in 98% yield.[54] Elaboration of ketone **54** to (−)-**7** proceeded with little difficulty. Position-selective bromination and low-temperature metalation of the pyrrole in the presence of two ketones gave rise to boronic ester **55**. Subsequent halogen-selective cross-coupling of **55** with dibromide **27** afforded the desired Suzuki adduct (−)-**29** (89% yield), the enantiomer of which had been employed in the synthesis of (+)-dragmacidin F. Finally, Suzuki adduct (−)-**29** was converted to (−)-**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**, $[\alpha]^{25}_D$ −159° (*c* 0.4, MeOH); synthetic (−)-**7**, $[\alpha]^{23}_D$ −148° (*c* 0.2, MeOH)).[34b]

(52) Heating reactions above 50 °C led to mixtures of products involving partial and complete cleavage of the SEM and TBS groups.
(53) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190−203.
(54) Bergens, S. H.; Bosnich, B. *J. Am. Chem. Soc.* **1991**, *113*, 958−967.

Conclusion

In summary, we have developed an enantiodivergent strategy to access both antipodes of dragmacidin F (**7**) from a single enantiomer of readily available (−)-quinic acid (**16**). Our highly efficient syntheses provide (+)-**7** in 7.8% overall yield and (−)-**7** in 9.3% overall yield beginning from **16**. The routes that we have developed to (+)- and (−)-**7** are concise and feature a number of key transformations, namely, (a) highly efficient functionalizations of (−)-**16** 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.

Acknowledgment. The authors thank the NIH-NIGMS (Grant R01 GM65961-01), the NDSEG (predoctoral fellowship to N.K.G.), Eli Lilly (predoctoral fellowship to D.D.C.), AstraZeneca, Boehringer Ingelheim, Johnson & Johnson, Pfizer, Merck, Amgen, Research Corp., Roche, and GlaxoSmithKline for generous funding. Drs. R. Riccio and A. Casapullo are acknowledged for an authentic sample of (−)-dragmacidin F. We also thank the Dervan and MacMillan laboratories for helpful discussions and the use of instrumentation.

Supporting Information Available: Full experimental details, characterization data for all new compounds, and spectral comparison for synthetic and natural (−)-dragmacidin F (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA050586V