Communication

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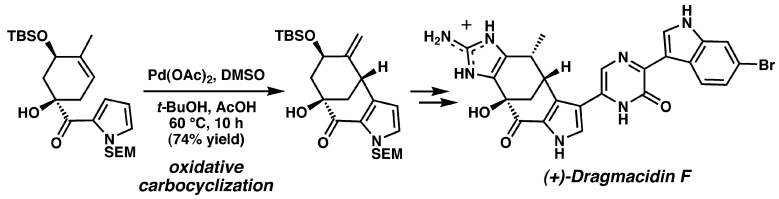

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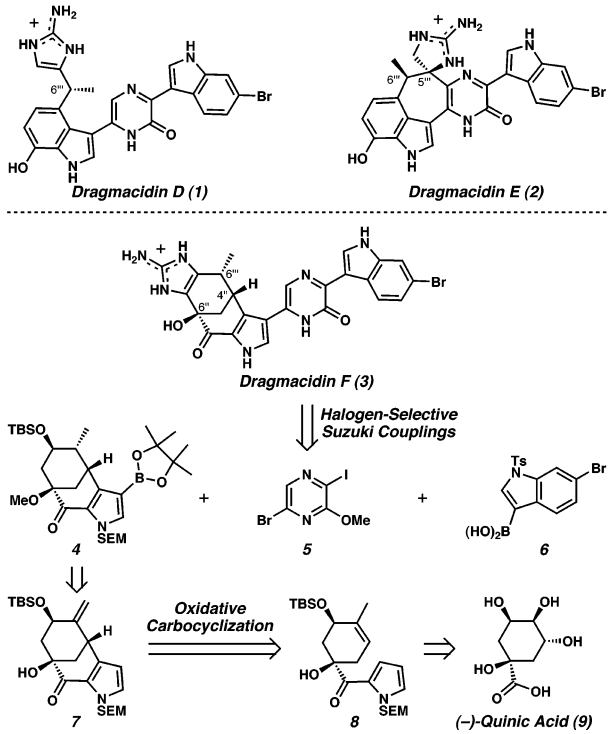
The Total Synthesis of (+)-Dragmacidin F

Neil K. Garg, Daniel D. Caspi, and Brian M. Stoltz*
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125
Received June 4, 2004; E-mail: stoltz@caltech.edu

The dragmacidins represent a small but growing family of marine alkaloids that possess a variety of interesting structural and biological features.[1] These novel alkaloids have attracted considerable attention from the synthetic community over the past decade.[2] Our interest in the dragmacidins was piqued by the structurally complex, pyrazinone-containing members, dragmacidins D, E, and F (Scheme 1, **1**−**3**).[1] We recently completed the first and, to date, only total synthesis of any of these three unique alkaloids with our preparation of (±)-dragmacidin D (1).[3] In this communication, we detail the enantiospecific total synthesis of (+)-dragmacidin F (**3**), which features a palladium-mediated intramolecular oxidative carbocyclization, a halogen-selective Suzuki cross-coupling reaction, and a high-yielding late-stage Neber rearrangement.

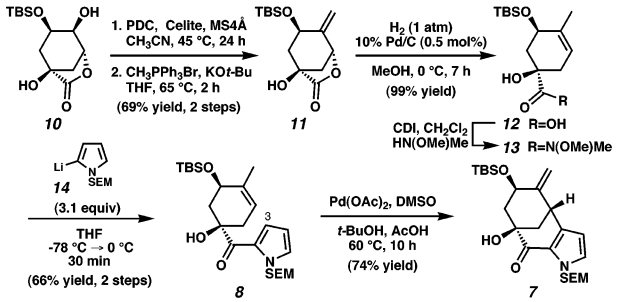
Dragmacidin F (**3**) is an antiviral bromoindole alkaloid isolated from the ethanol extracts of the Mediterranean sponge *Halicortex* sp. and exhibits in vitro activity against HSV-1 ($EC_{50} = 95.8\ \mu M$) and HIV-1 ($EC_{50} = 0.91\ \mu M$).[1c] This structurally interesting natural product poses a variety of synthetic challenges, namely, 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.

Scheme 1



On the basis of our total synthesis of dragmacidin D, we recognized that the aminoimidazole would best be incorporated at a late stage in the synthesis and that the pyrazinone subunit could be masked as an alkoxypyrazine.[3] The core of dragmacidin F (**3**) could then arise via a halogen-selective Suzuki coupling sequence (Scheme 1, **3** ⇒ **4** + **5** + **6**). While **5** and **6** were readily available from our established routes,[3] boronic ester **4** could originate from pyrrole-appended bicycle **7**, the key retrosynthetic intermediate. In conjunction with our research program focused on palladium(II)-catalyzed dehydrogenation reactions,[4] bicycle **7** was further disconnected to acyl pyrrole **8** by applying a heteroarene/olefin oxidative C−C coupling transform. This key step could serve to illustrate some of the methodology developed in these laboratories in the context of a complex total synthesis.[4c] The desired cyclization substrate (**8**) could be derived from commercially available (−)-quinic acid (**9**).

Scheme 2



Our synthesis commenced with bicyclic lactone **10**, a compound available by known lactonization and selective silylation of (−)-quinic acid (**9**).[5] Oxidation of bicycle **10** followed by Wittig olefination of the resultant ketone produced *exo*-methylene lactone **11** in 69% overall yield (Scheme 2). Following considerable effort to execute a homogeneous Pd-catalyzed π-allyl hydride addition to allylic lactone **11**, we discovered that an exceedingly simple and selective reduction (**11** → **12**) occurs via heterogeneous catalysis. Under our reaction conditions (0.5 mol % Pd/C, 1 atm H_2, MeOH, 0 °C) essentially quantitative reductive isomerization to the desired unsaturated carboxylic acid **12** was observed.[6] With **12** now readily available, oxidative cyclization substrate **8** was prepared via Weinreb amide formation (**12** → **13**) followed by the addition of lithiopyrrole **14**. To our delight, exposure of **8** to $Pd(OAc)_2$ under a variety of conditions led to carbocyclization, and under optimized conditions, produced the desired pyrrole-fused bicycle **7** as a single stereo- and regioisomer in 74% yield (Scheme 2).[7] This transformation is particularly remarkable since it results in functionalization of the deactivated C(3) position of acyl pyrrole **8**.[8]

With the [3.3.1] bicyclic framework in hand, we set out to construct the full carbon skeleton of dragmacidin F (Scheme 3). The final stereocenter present in the natural product (i.e., **3**, 6‴) was installed via catalytic hydrogenation of olefin **7** followed by methylation to produce 3° ether **15**. To advance **15** for fragment coupling, regioselective bromination of the pyrrole followed by metalation to boronic ester **4** proceeded smoothly. In the critical halogen-selective Suzuki fragment-coupling reaction, pyrroloboronic ester **4** and dibromide **16** (prepared from **5** + **6**)[3] were reacted under Pd(0) catalysis. As we observed in our total synthesis of dragmacidin D,[3] at 50 °C, an exquisitely selective bond formation

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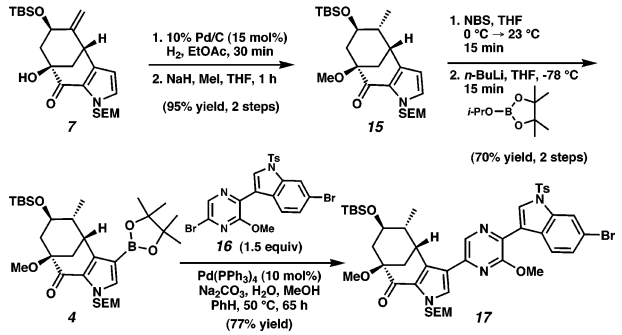
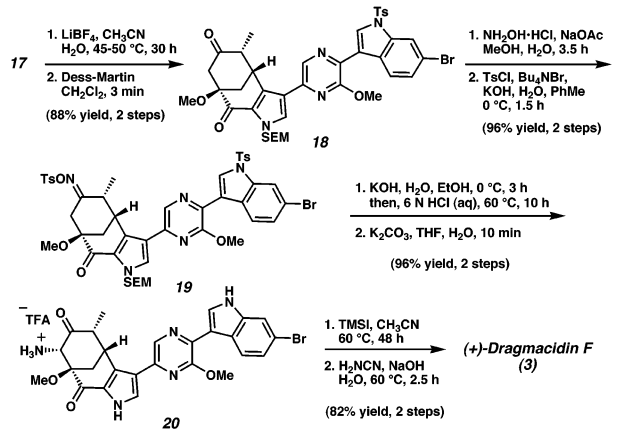
Scheme 3



constructed the dragmacidin F framework (i.e., **17**) by fusion of the pyrrole and alkoxypyrazine subunits of **4** and **16**, while leaving the indolyl bromide of **16** and, in turn, **17** intact.

Having successfully prepared the desired carbon skeleton of dragmacidin F, we began the final stages of the synthesis. Selective deprotection of silyl ether **17** and oxidation with Dess−Martin periodinane produced ketone **18** (Scheme 4). We anticipated that the introduction of an amino group α to the ketone would allow for eventual elaboration to the aminoimidazole moiety. To this end, a number of transformations involving enolate or enol ether derivatives of **18** were attempted, none of which were successful. With limited options remaining, we became interested in the potential application of a Neber rearrangement as a solution to this obstacle.[9] Thus, conversion of ketone **18** to tosyloxime **19**, followed by sequential treatment with (i) KOH, (ii) HCl, and (iii) K_2CO_3 produced amino ketone **20** as a single regio- and stereochemical isomer in excellent yield.[10] Moreover, under our optimized reaction conditions, both the tosyl and SEM protecting groups were quantitatively removed from the corresponding heterocycles. Finally, liberation of the 3° hydroxyl and pyrazinone functionalities by exposure of bis-ether **20** to TMSI, followed by treatment of the penultimate amino ketone with cyanamide and aqueous NaOH produced (+)-dragmacidin F (**3**).[10]

Scheme 4



Synthetic dragmacidin F was spectroscopically identical (^{1}H NMR, ^{13}C NMR, IR, UV, HPLC) to the natural product[1c] 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)).[10b] Thus, our synthesis from (−)-quinic acid (**9**) establishes that the absolute configuration of natural dragmacidin F is (4″*S*, 6″*S*, 6‴*S*).[11] On the basis of the hypothesis that dragmacidins D, E, and F are biosynthetically related,[1,3] we propose that the absolute stereochemical configurations of natural dragmacidins D and E are (6‴*S*) and (5‴*R*, 6‴*S*), respectively (enantiomeric to the structures depicted in Scheme 1).

In summary, we have completed the first total synthesis of (+)-dragmacidin F (**3**), establishing the absolute configuration of this biologically important marine alkaloid and suggesting the absolute configuration of the related dragmacidins D and E (**1** and **2**). Our efficient and enantiospecific approach (19 steps from **10**) relies on a number of key steps. Specifically, a novel catalytic reductive isomerization of lactone **11**, an oxidative heteroarene/olefin cyclization (**8** → **7**), a highly selective Suzuki coupling reaction (**4**+**16** → **17**), and an unprecedented late−stage Neber rearrangement sequence (**19** → **20**)[9c] provide access to this interesting natural product.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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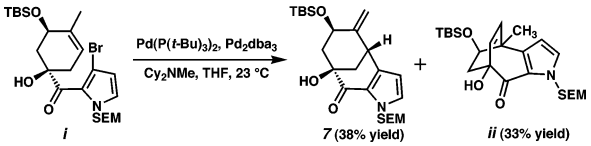
(6) Preliminary mechanistic studies suggest that a Pd-catalyzed π-allyl reduction is not operative.

(7) (a) Under optimized conditions,[7b] intramolecular Heck cyclization of related 3-bromopyrrole derivative **i** resulted in competitive production of undesired product **ii**.[10b] (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000.



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(10) (a) Purified by reversed-phase chromatography using trifluoroacetic acid in the eluent. (b) See Supporting Information for details.

(11) Dragmacidin numbering convention, see ref 1.

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