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# The Total Synthesis of (+)-Dragmacidin F

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The dragmacidins represent a small but growing family of marine alkaloids that possess a variety of interesting structural and biological features.<sup>1</sup> These novel alkaloids have attracted considerable attention from the synthetic community over the past decade.<sup>2</sup> Our interest in the dragmacidins was piqued by the structurally complex, pyrazinone-containing members, dragmacidins D, E, and F (Scheme 1, 1–3).<sup>1</sup> We recently completed the first and, to date, only total synthesis of any of these three unique alkaloids with our preparation of  $(\pm)$ -dragmacidin D (1).<sup>3</sup> 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<sub>50</sub> = 95.8  $\mu$ M) and HIV-1 (EC<sub>50</sub> = 0.91  $\mu$ M).<sup>1c</sup> 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.<sup>3</sup> The core of dragmacidin F (3)



could then arise via a halogen-selective Suzuki coupling sequence (Scheme 1,  $3 \Rightarrow 4 + 5 + 6$ ). While 5 and 6 were readily available from our established routes,<sup>3</sup> 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,<sup>4</sup> 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.<sup>4c</sup> The desired cyclization substrate (8) could be derived from commercially available (-)-quinic acid (9).

Our synthesis commenced with bicyclic lactone 10, a compound available by known lactonization and selective silvlation of (-)quinic acid (9).<sup>5</sup> 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  $\pi$ -allyl hydride addition to allylic lactone 11, we discovered that an exceedingly simple and selective reduction  $(11 \rightarrow 12)$  occurs via heterogeneous catalysis. Under our reaction conditions (0.5 mol % Pd/C, 1 atm H<sub>2</sub>, MeOH, 0 °C) essentially quantitative reductive isomerization to the desired unsaturated carboxylic acid 12 was observed.<sup>6</sup> With 12 now readily available, oxidative cyclization substrate 8 was prepared via Weinreb amide formation  $(12 \rightarrow 13)$  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<sup>'''</sup>) 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,<sup>3</sup> at 50 °C, an exquisitely selective bond formation



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 silvl ether 17 and oxidation with Dess-Martin periodinane produced ketone 18 (Scheme 4). We anticipated that the introduction of an amino group  $\alpha$  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.<sup>9</sup> Thus, conversion of ketone 18 to tosyloxime 19, followed by sequential treatment with (i) KOH, (ii) HCl, and (iii) K<sub>2</sub>CO<sub>3</sub> produced amino ketone 20 as a single regio- and stereochemical isomer in excellent yield.<sup>10</sup> 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).<sup>10</sup>

## Scheme 4



Synthetic dragmacidin F was spectroscopically identical (1H NMR, <sup>13</sup>C NMR, IR, UV, HPLC) to the natural product<sup>1c</sup> with the exception of the sign of rotation (natural:  $[\alpha]^{25}_{D} - 159^{\circ}$  (c 0.4, MeOH); synthetic:  $[\alpha]^{23}_{D}$  +146° (*c* 0.45, MeOH)).<sup>10b</sup> 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,<sup>1,3</sup> 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  $(8 \rightarrow 7)$ , a highly selective Suzuki coupling reaction (4+16) $\rightarrow$  17), and an unprecedented late-stage Neber rearrangement sequence  $(19 \rightarrow 20)^{9c}$  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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- (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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