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Asymmetric Total Synthesis of (+)-Dragmacidin D Reveals Unexpected Stereocomplexity

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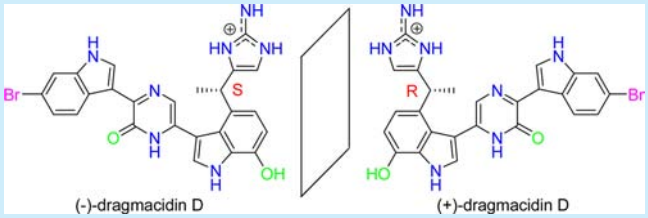
Supporting Information

ABSTRACT: The first asymmetric total synthesis of the bis-indole marine alkaloid (+)-dragmacidin D (**1**) has been achieved. This synthesis revises an earlier configurational assignment based on biosynthetic considerations and assigns an *R* absolute configuration to (+)-**1**. The current studies reveal that natural dragmacidin D is isolated as either a racemate or a scalemic mixture (39% ee).



(+)-Dragmacidin D (**1**), (−)-dragmacidin E (**2**), and (−)-dragmacidin F (**3**), the more structurally complex members of the dragmacidin family of bis-indole alkaloids, have been isolated from deep water Caribbean,[1] Australian,[2] and Mediterranean[3] sponges (Figure 1).[1−3] These marine alkaloids feature two

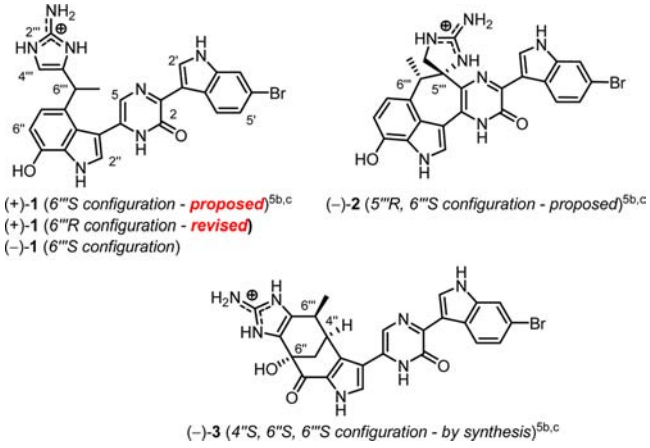


Figure 1. Sponge metabolites dragmacidins D−F (**1**−**3**).

unsymmetrically substituted indoles linked by a pyrazinone spacer, with one indole bearing either an aminoimidazole or a *spiro*-dihydro-aminoimidazole moiety. Early reports on biological activity describe (−)-**2** as a potent inhibitor of the serine-threonine protein phosphatases PP_1 and PP_2A, with (+)-**1** recognized as a selective inhibitor of PP_1 (IC_{50} 21 nM),[2,4a] with moderate antiviral (feline leukemia virus, MIC 6.25 μg/mL),[1] antibacterial (*E. coli*, *B. subtilis*, and *P. aeruginosa*, MIC 15.6, 3.1, and 62.5 μg/mL),[1] antifungal (*C. albicans* and *Cryptococcus neoformans*, MIC 15.6 and 3.9 μg/mL),[1] and cytotoxic (P388 and A549, IC_{50} 1.4 and 4.4 μg/mL)[1] activity. A sample of **1** (racemic, see below)[1] was also patented as a selective inhibitor of neural nitric oxide synthase (bNOS),[4b] for application in the treatment of CNS inflammation and neurodegenerative diseases (e.g., Alzheimer's, Parkinson's, and Huntington's disease). The closely related marine alkaloid (−)-**3** exhibited *in vitro* antiviral activity against HIV-1 (EC_{50} 0.91 μM).[3]

Not surprisingly, these remarkable marine scaffolds, with their diverse biological properties, have attracted considerable attention from the synthetic community.[5−8] For example, in 2002 Stoltz et al. achieved the first total synthesis of (±)-**1**, as well as (+)-**3** and (−)-**3**, by a series of Pd-catalyzed halogen-selective Suzuki−Miyaura cross-couplings.[5] In 2011 Yamaguchi and Itami et al. reported an elegant and efficient total synthesis of (±)-**1** via a similar strategy, using direct C−H coupling reactions,[6] while Feldman et al. reported the first and to date only synthesis of (±)-**2**, employing a Witkop photocyclization.[7]

Having successfully assigned an absolute configuration to (−)-**3**, Stoltz et al. invoked biosynthetic arguments to propose the absolute configurations for (+)-**1** and (−)-**2** (Figure 1),[5b,c] despite the fact that neither had been reported as a cometabolite with (−)-**3**. Intriguingly, dragmacidin D (**1**) isolated in 1992 by Wright[1] et al. did not exhibit an optical rotation, whereas a reisolation in 1998 by Capon[2] et al. returned (+)-**1** ($[\alpha]_D$ +12°), as a cometabolite with (−)-**2** ($[\alpha]_D$ −34°). Based on these observations we conclude that further effort is required to resolve the absolute configuration of (+)-**1** and (−)-**2**. As part of our program focusing on the total synthesis of 3,4-substituted indole alkaloids we elected to determine the absolute configuration of (+)-**1**.[9]

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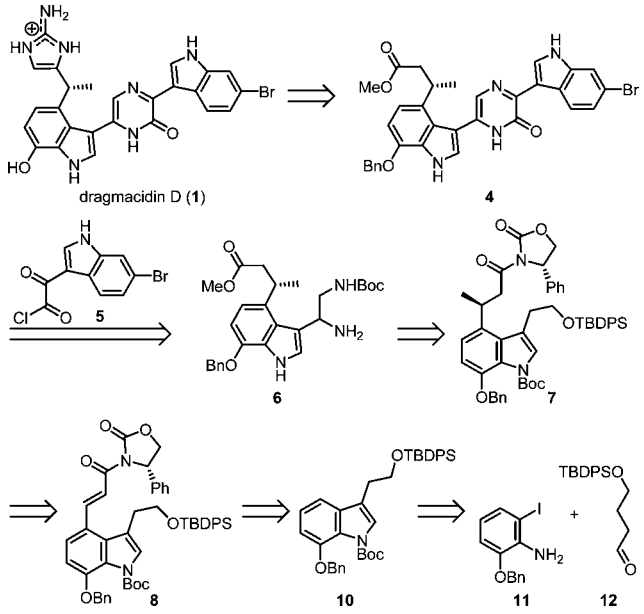
Herein, we report the first asymmetric total synthesis and assignment of an *R* absolute configuration to (+)-**1**. We also determined that the 1998 sample of (+)-**1** was not enantiopure (39% ee) and that a more recent reisolation from a duplicate sponge specimen yielded racemic (±)-**1**. This unexpected stereocomplexity revealed that the biosynthetic relationship with (−)-**2** and (−)-**3** is less obvious than previously supposed.

Our retrosynthetic analysis of (+)-**1** as illustrated in Scheme 1 seeks to install the aminoimidazole moiety at the end of the

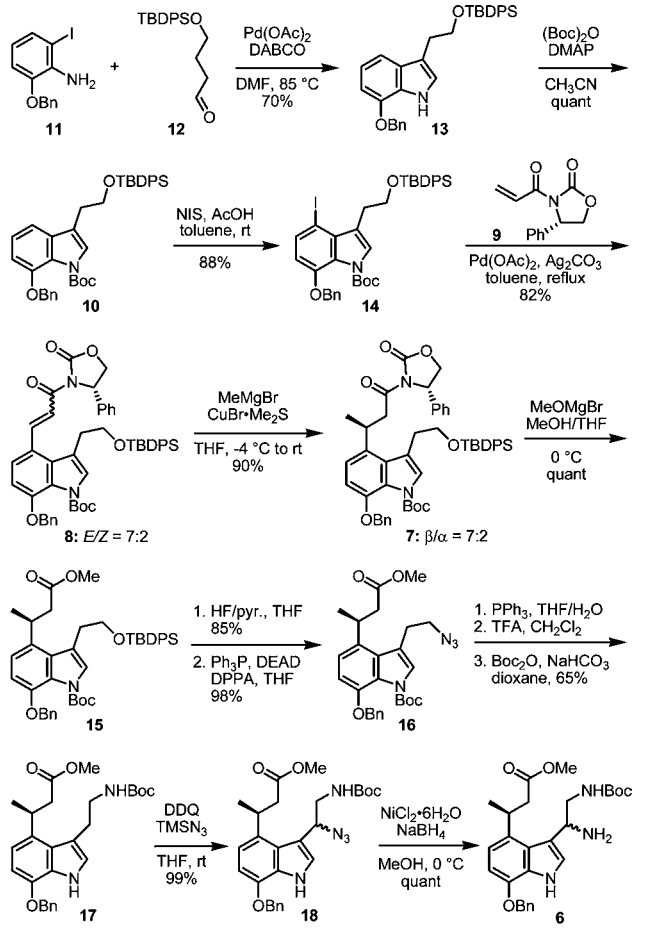
Scheme 1. Retrosynthetic Analysis of (+)-Dragmacidin D



synthesis via a modification to the Chen's method.[10] The central pyrazinone ring would be constructed via a classical sequence including coupling of the known 6-bromoindole acid chloride **5**[11] and indole diamine derivative **6**, intramolecular condensation, and oxidative aromatization.[7] Accordingly, the key 3,4,7-trisubstituted indole **6** could be derived from **7**. In turn, the stereogenic center bearing a methyl group within the C-4 branched chain of indole **7** could be realized by Evans' chiral auxiliary induced asymmetric conjugate addition.[12] The Michael acceptor **8** would be obtained via chemoselective iodination of 7-substituted tryptophol **10** followed by Heck reaction of the corresponding iodide with the known *N*-acryl-oxazolidinone **9**.[13] 7-Substituted indole **10** could be prepared via Pd-catalyzed annulations of *ortho*-iodoaniline **11** and butaldehyde **12**.[14]

Our synthesis of (+)-**1** commenced with the preparation of the key 3,4,7-trisubstituted indole intermediate **6** as shown in Scheme 2. Reaction of 2-iodo-6-benzoxyaniline **11** with the known butaldehyde **12** under standard Pd-catalyzed conditions afforded the indole **13** (70%). Boc-protection of the indole nitrogen gave **10** in quantitative yield. Chemoselective iodination of C-4 in **10** with NIS in the presence of AcOH provided the desired 4-iodoindole **14** (88%).[15] Heck reaction of **14** and **9** under ligand-free conditions ($Pd(OAc)_2$ Ag_2CO_3) provided the desired product **8** (82%), with an *E* to *Z* ratio of 7:2, which could not be separated by careful flash chromatography. Under classical Heck reaction conditions [($Pd(OAc)_2$ with phosphine ligands], the same *E*/*Z* ratio with a diminished yield was obtained. Treatment of **8** with methyl cuprate, prepared from MeMgBr and $CuBr_2$·SMe_2 at −4 °C, gave the 1,4-addition product **7** (70%),

Scheme 2. Synthesis of 3,4,7-Trisubstituted Indole 6



accompanied by its diastereoisomer **7a** (20%), which could be separated via careful column chromatography purification in small scale, but it was difficult to be completely separated in large-scale preparation. The absolute configuration of the newly formed stereogenic center in **7** was confirmed to be *S* (see Supporting Information).

Selective removal of the Evans' chiral auxiliary in **7** with MeOMgBr, prepared from MeMgBr and anhydrous MeOH, produced the desired methyl ester **15** in quantitative yield.[16] Removal of the TBDPS group in **15** with the HF·pyridine complex was followed by a Mitsunobu reaction to deliver the desired azide **16**. The azide **16** was converted to tryptamine **17** (65%) via a conventional three-step sequence involving (a) Staudinger reduction of the azide; (b) Boc deprotection with TFA, and (c) selective Boc protection of the primary amine. Treatment of **17** with $DDQ/TMSN_3$ smoothly yielded azide **18** (99%) as a mixture of diastereomers. Reduction of the azide **18** with $NaBH_4/NiCl_2$ provided the corresponding amine **6** in quantitative yield.[7]

With the key amine **6** in hand, completion of the synthesis of (+)-**1** was achieved as illustrated in Scheme 3. Pyrazinone formation proceeded smoothly through a three-stage protocol involving acylation of amine **6** with 6-bromoindole oxalyl chloride **5**, cyclization of the primary amine liberated by TFA-mediated deprotection with the indolic ketone, and subsequent DDQ-based oxidative aromatization of the resultant dihydropyrazinone to deliver the pyrazinone-containing product **4** (50%).[7] It is noteworthy that this five-step transformation starting from **18** required only a single chromatographic purification. With a

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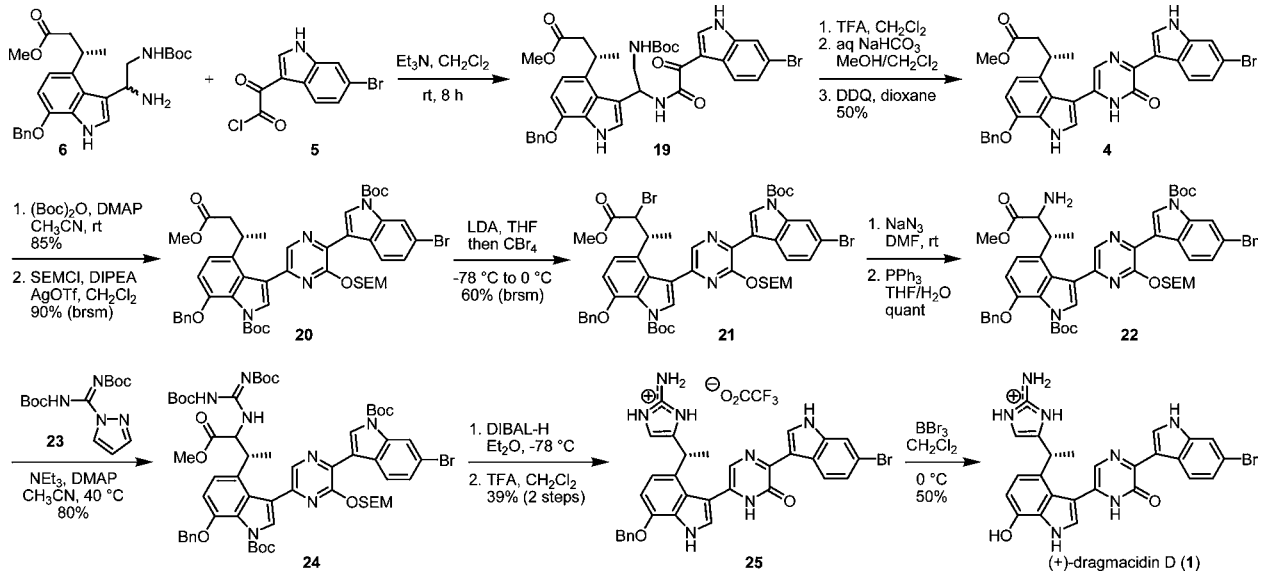
Scheme 3. Completing the Total Synthesis of (+)-Dragmacidin D



practical method in hand, we easily prepared 2.0 g of **4** and set about installing the pendant aminoimidazole moiety. As attempts to functionalize **4** by α-bromination or α-amination led to recovery of the starting materials, we reasoned that protection of **4** was critical. The choice of protecting group took into account the requirement that it should be not only stable to subsequent manipulations but also easily removed under mild conditions compatible with the aminoimidazole moiety and retention of chirality. Boc protection of both indole nitrogens followed by chemoselective *O*-alkylation with SEMCl and DIPEA in the presence of silver salt led to the *O*-alkylation product **20** (90%).[17] Bromination of the ester **20** with LDA and CBr_4 occurred smoothly to give the α-bromoester **21** (60%) as a single detectable diastereomer.[18] S_N2 displacement of α-bromoester **21** with NaN_3 followed by Staudinger reduction of the resultant azide with PPh_3 provided a near-quantitative yield of the desired α-amino ester **22**. Treatment of α-amino ester **22** with pyrazole-1-carboxamidine **23** and Et_3N in the presence of DMAP gave the guanidine-containing product **24** (80%).[10] To our delight, the subsequent reduction/cyclization strategy for construction of an aminoimidazole moiety proved to be realizable. Thus, reduction of the ester **24** with DIBAL-H followed by treatment of the resultant aza-hemiacetal with 10% TFA in CH_2Cl_2 provided **25** (39%) as a trifluoroacetate salt. Finally, removal of the benzyl protecting group in **25** with BBr_3 in CH_2Cl_2 yielded the desired natural product (+)-dragmacidin D (50%).[19] The spectroscopic properties (^1H and ^{13}C NMR, MS, CD) of synthetic (+)-**1** were identical to those of an authentic sample of the natural product.

To assist our assignment of the absolute configuration of natural (+)-dragmacidin D, we prepared racemic (±)-**1** from (±)-**15**, via the same synthetic route as detailed above. Chiral HPLC-DAD analysis confirmed the enantiopurity of synthetic (+)-**1** (Figure 2a). We next analyzed an archived sample of our sponge extract that yielded natural (+)-**1** (RJC-91-011)[2] and were surprised to observe low enantiopurity (39% ee) (Figure 2b).[20] Nevertheless, coelution of the dominant enantiomer in this extract with synthetic (+)-**1** unambiguously established a common *R* absolute configuration. Concerned that prolonged storage of RJC-91-011 had facilitated partial racemization, we searched our sponge extract library (>2500 specimens) to identify a younger duplicate specimen (RJC-98-305), which we

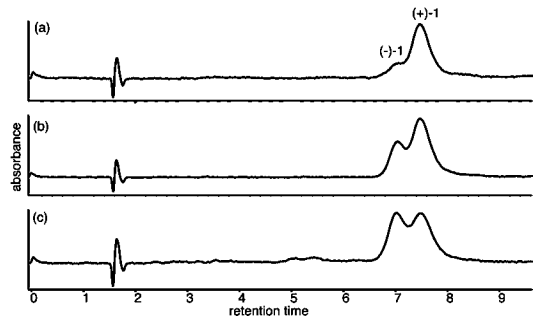


Figure 2. Chiral HPLC-DAD analyses. (a) Synthetic (+)-dragmacidin D, (b) (+)-dragmacidin D (39% ee) from RJC-91-011, and (c) (±)-dragmacidin D from RJC-98-305.

anticipated would yield (+)-**1** with a higher enantiopurity. To our surprise, chiral HPLC-DAD analysis of RJC-98-305 revealed racemic (±)-**1** (Figure 2c), although in hindsight the scientific literature foreshadowed just such a finding. The original 1992 report of dragmacidin D (**1**)[1] failed to detect a measurable optical rotation, attributing this to the intense yellow color of the natural product rather than it being racemic. However, as the subsequent 1998 report documented an optical rotation for (+)-**1**, a racemic (±)-**1** for the 1992 account would seem more plausible.

In summary, we achieved the first asymmetric total synthesis of (+)-dragmacidin D (**1**) via a process that features a Pd-catalyzed indole synthesis, an Evans' oxazolidinone chiral auxiliary induced asymmetric conjugate addition to introduce the stereogenic center, a classical three-step sequence to form the central pyrazinone ring, and a modified Chen's method to install the aminoimidazole moiety. This synthesis revises an earlier configurational assignment based on biosynthetic considerations and assigns an *R* absolute configuration to the marine alkaloid (+)-dragmacidin D. Chiral HPLC-DAD methodology developed during this study confirmed for the first time that dragmacidin D isolated from marine sponges either is of low enantiopurity [(+)-**1**, 39% ee] or is racemic [(±)-**1**], prompting questions regarding the biosynthetic and absolute configuration relationships between dragmacidins D−F, and the significance of reported biological activities.

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■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, and ^{1}H and ^{13}C NMR spectra of compounds **1**, **4**, **7**, **8**, **10**, **13**−**18**, **20**, **21**, **24**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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