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Enantioselective synthesis of the aminoimidazole segment of dragmacidin D

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Abstract—A facile enantioselective synthesis of the 2-aminoimidazole side-chain of dragmacidin D has been developed, which involved the regio- and stereoselective opening of the chiral epoxide **9** by a diindolylcuprate reagent, followed by further steps to give 5-substituted *N*-(1*H*-imidazol-2-yl)acetamide **2**.

Dragmacidin D (**1**, Fig. 1), a novel secondary metabolite, was first isolated from a deep-water marine sponge of the genus *Spongosorites* by Wright and co-workers in 1992.[1] In 1995, Capon and co-workers also reported the isolation and structure determination of **1** from a *Spongosorites* collected during a trawling operation off the southern coast of Australia.[2] It inhibited the growth of the feline leukemia virus, the opportunistic fungal pathogens *Cryptococcus neoformans* and *Candida albicans*, and the P388 and A549 tumor cell lines. Further biological studies indicated that dragmacidin D, and its co-metabolite dragmacidin E, have been identified as potent inhibitors of serine–threonine protein phosphatases, and dragmacidin D was a selective inhibitor of PP1.[3] The structure of **1** was exclusively determined by NMR methods, including one- and two-dimensional NMR spectroscopy. Structurally, it varied from the previously reported dragmacidins[4] in the further oxidation of the piperazine ring to a 1(2*H*)-pyrazinone and the addition of a 2-aminoimidazole-containing side-chain on one of the indole rings. However, the absolute configuration remains unknown at the present time. Its unique structure and wide range of biological and pharmacological activities attracted our attention and prompted us to undertake the total synthetic study. We previously reported the synthesis of the bis(indol-3-yl)-

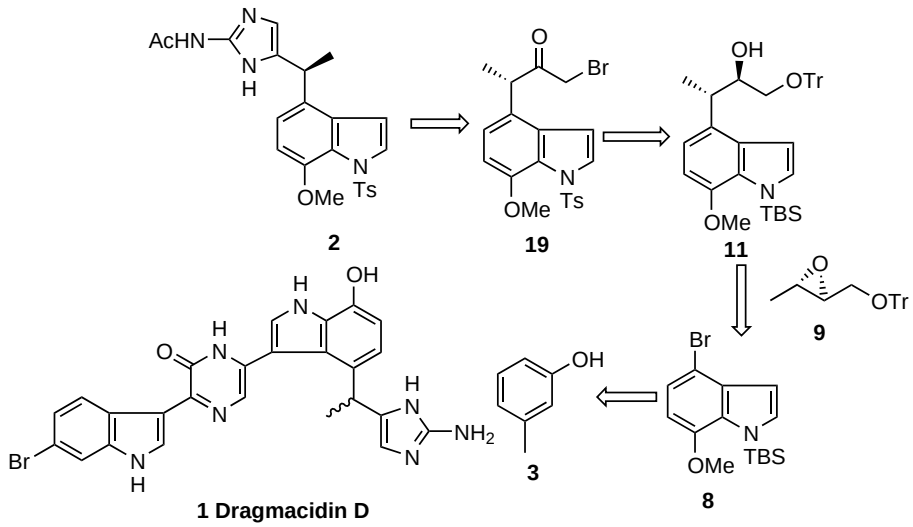

Figure 1.

Keywords: enantioselective; 2-aminoimidazole; dragmacidin D.

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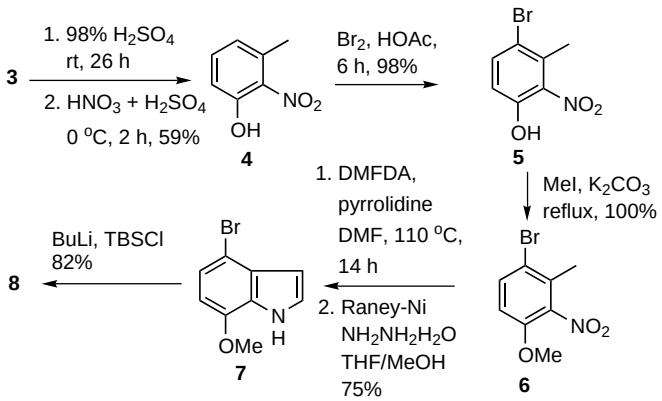


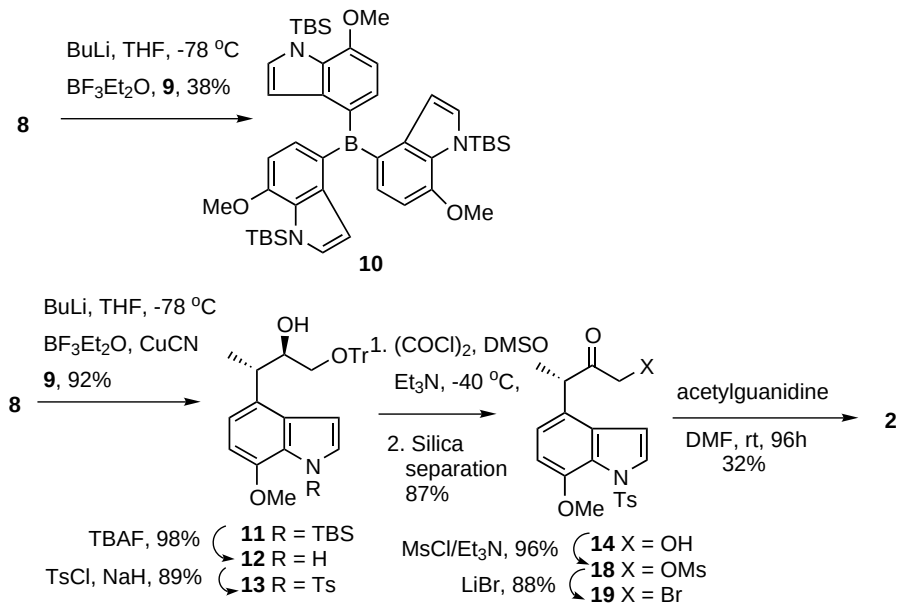
Scheme 1.

2(1*H*) pyrazinone core of **1** through the condensation of *N*-Boc-indolyl glycine with indol-3-yl-*N*-methyl-*O*-methoxyglycinamide, followed by selective reduction and intramolecular cyclization.[5] In this letter, we wish to report the enantioselective synthesis of the 2-aminoimidazole segment of dragmacidin D.

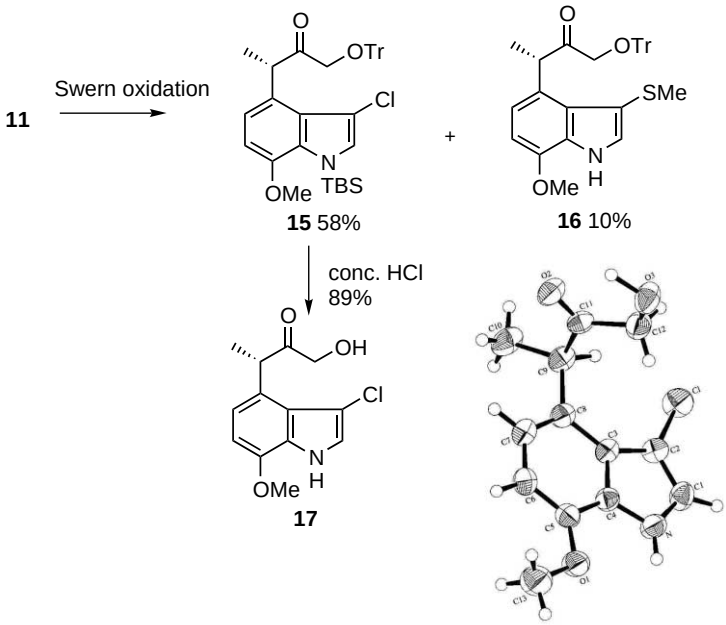
Several classes of marine natural products possessing the 2-aminoimidazole structure have been discovered and identified over recent years.[6] However, only a limited number of the methods described the direct synthesis of the corresponding 2-aminoimidazole derivatives.[7] As shown in Fig. 1, our strategy for assembling the 2-aminoimidazole system of dragmacidin D relied on the cyclization reaction of α-bromo ketone **19** and *N*-acetylguanidine as a guanidine equivalent in dimethylformamide at room temperature to give 5-substituted *N*-(1*H*-imidazol-2-yl)acetamide **2**.[8] α-Bromo ketone **19** would be derived from **11** as a result of regioselective protection, Swern oxidation,[9] and nucleophilic substitution. Compound **11** was expected to arise from a regio- and stereoselective opening of epoxide **9** using the higher order cuprate reagent prepared from the 4,7-disubstituted indole **8**, which in turn could be obtained using Leimgruber–Batcho indole synthetic methodology.[10]

On the basis of the synthetic plan, we initially prepared disubstituted indole **8** as follows (Scheme 1). The starting material **3** was converted to the known nitro compound **4** by selective sulfonation, nitration and acid-induced desulfonation in 59% yield.[11] Treatment of **4** with bromine in the presence of acetic acid gave *p*-bromophenol **5** in high yield, which in turn could be protected by methylation to give intermediate **6** quantitatively.[12] The 4,7-disubstituted indole **7** was prepared in 75% yield via Batcho–Leimgruber indole synthesis from nitrotoluene **6** by reaction with dimethylformamide dimethyl acetal, followed by reduction of the intermediate enamine with hydrazine hydrate in the presence of Raney-Ni as the catalyst.[13] The indole **7** was protected with *tert*-butyldimethylsilyl chloride (TBSCl) using *n*-butyllithium as the base in THF to provide compound **8**[14] in 82% yield along with the unconverted starting material.[15]

The epoxide **9** was prepared according to an established method as a single enantiomer.[16] The initial attempt to realize the epoxide opening with the indolyllithium reagent from **8** was unsuccessful. Reaction of compound **9** with TBS-protected indole **8**, *n*-butyllithium and BF_3 etherate produced the tris(indol-4-yl) borane **10**[14] in 38% yield, but none of the expected epoxide-opened product.[17] However, as shown in Scheme 2, reaction of bromoindole **8** sequentially with *n*-butyllithium, copper(I) cyanide, BF_3 etherate, and epoxide **9** proceeded regio- and stereoselectively to give **11**[14] as a single isomer in 92% yield.[18] This procedure establishes the desired stereochemistry as either the *R*- or *S*-



Scheme 2.



Scheme 3.

configuration at the 3-position of the newly produced compound **11**.

Swern oxidation of the secondary alcohol **11** to the ketone was carried out by treatment with oxalyl chloride, dimethyl sulfoxide and triethylamine at −40°C to room temperature. On the basis of NMR spectroscopy, the resulting major product was shown to be 3-chloroindole **15** in 58% yield, while the minor product was 3-methylthio indole **16** in 10% yield.[19] In order to determine the structure of **15**, we deprotected **15** with conc. HCl in methanol to give **17**[14] in 89% yield and 99% ee,[20] the structure of which was confirmed by X-ray analysis (Scheme 3). The reason for the chlorination of the indole at the 3-position is that the electron-donating property of the TBS-protection makes the indole ring electron-rich, and electrophilic substitution occurs more easily. The known facile tetrabutylammonium fluoride induced cleavage of the TBS protecting group from **11** gave **12** in 98% yield, which was regioselectively protected as the tosylamide using sodium hydride as base to provide **13** in 89% yield. Oxidation of **13** under Swern conditions directly gave the desired α-hydroxy ketone **14** in 87% yield (Scheme 2).

Considerable effort was devoted to convert the α-hydroxy ketone **14** directly to the corresponding α-bromo ketone **19**, but without success. These halogenation systems included chlorodiphenylphosphine/bromine/imidazole,[21] *N*-bromosuccinimide/triphenylphosphine/dichloromethane/0°C[22] and *N*-bromosuccinimide/triphenylphosphine/DMF/50°C.[23] Finally, treatment of **14** with mesyl chloride and triethylamine in dichloromethane afforded mesylate **18** in 96% isolated yield, which in turn was reacted with lithium bromide in acetone to give the α-bromo ketone **19** in 88% yield. The cyclization reaction of ketone **19** and *N*-acetylguanidine in dimethylformamide at room temperature for 4 days gave 5-substituted *N*-(1*H*-imidazol-2-yl)-acetamide **2**[14] in 32% yield as a single enantiomer[24] (Scheme 2).

Acknowledgements

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14. For compound **8**: IR (KBr) 2956, 2932, 1569, 1483, 1288 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.23 (d, $J=3.2$ Hz, 1H), 7.16 (d, $J=8.3$ Hz, 1H), 6.60 (d, $J=3.2$ Hz, 1H), 6.47 (d, $J=8.3$ Hz, 1H), 3.85 (s, 3H), 0.85 (s, 9H), 0.53 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.8, 133.5, 132.5, 131.0, 122.9, 105.4, 105.1, 102.9, 54.2, 26.7, 19.5, −1.8; EIMS m/z: 339/341; anal. calcd for $C_{15}H_{22}BrNOSi$: C, 52.94; H, 6.47; N, 4.12. Found: C, 53.15; H, 6.51; N, 3.94.
    For compound **10**: Mp 158–159°C; IR (KBr) 2932, 1590, 1561, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, $J=7.8$ Hz, 3H), 7.30 (d, $J=3.1$ Hz, 3H), 7.00 (d, $J=3.1$ Hz, 3H), 6.67 (d, $J=7.8$ Hz, 3H), 3.94 (s, 9H), 0.91 (s, 27H), 0.56 (s, 18H); EIMS m/z: 792. HREIMS calcd for $C_{45}H_{66}BN_3O_3Si_3$: 791.4533, found: 791.4519.
    For compound **11**: Mp 59–61°C; $[\alpha]_D^{20}$ −3 (c 1.22, $CHCl_3$); IR (KBr) 2931, 1583, 1493, 1287 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (dd, $J=8.3$ and 1.3 Hz, 6H), 7.20 (m, 10H), 6.79 (d, $J=8.0$ Hz, 1H), 6.58 (d, $J=3.3$ Hz, 1H), 6.50 (d, $J=8.0$ Hz, 1H), 4.07 (m, 1H), 3.86 (s, 3H), 3.31 (m, 1H), 3.13 (dd, $J=9.4$ and 6.6 Hz, 1H), 3.05 (dd, $J=9.4$ and 4.5 Hz, 1H), 1.33 (d, $J=7.0$ Hz, 3H), 0.88 (s, 9H), 0.54 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.8, 144.0, 132.3, 131.6, 130.7, 128.7, 128.3, 127.7, 126.9, 118.0, 103.2, 101.7, 86.7, 74.5, 66.0, 53.9, 39.1, 26.9, 19.6, 15.6, -3.2; EIMS m/z: 591; anal. calcd for $C_{38}H_{45}NO_3Si$: C, 77.16; H, 7.61; N, 2.37. Found: C, 77.08; H, 7.82; N, 2.55.
    For compound **17**: Mp 120°C (dec.); $[\alpha]_D^{20}$ +270 (c 0.44, $CHCl_3$); IR (KBr) 3461, 3216, 2944, 1679 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.60 (br s, 1H), 7.41 (d, $J=2.5$ Hz, 1H), 6.67 (s, 2H), 4.91 (q, $J=7.0$ Hz, 1H), 4.14 (d, $J=18.3$ Hz, 1H), 4.01 (d, $J=18.3$ Hz, 1H), 3.90 (s, 3H), 1.36 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 210.5, 145.3, 125.8, 124.1, 123.2, 123.0, 122.2, 118.6, 102.6, 66.1, 55.3, 41.6, 17.6; EIMS m/z: 267; anal. calcd for $C_{13}H_{14}ClNO_3$: C, 58.43; H, 5.24; N, 5.24. Found: C, 58.25; H, 5.50; N, 4.95.
    For compound **2**: $[\alpha]_D^{20}$ −18 (c 0.50, $CHCl_3$); IR (KBr) 3374, 1679, 1607, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, $J=4.0$ Hz, 1H), 7.73 (d, $J=8.4$ Hz, 2H), 7.27 (d, $J=8.4$ Hz, 2H), 6.87 (d, $J=8.0$ Hz, 1H), 6.63 (d, $J=4.0$ Hz, 1H), 6.59 (d, $J=8.0$ Hz, 1H), 6.50 (br s, 1H), 4.33 (q, $J=7.2$ Hz, 1H), 3.65 (s, 3H), 2.39 (s, 3H), 2.15 (s, 3H), 1.62 (d, $J=7.2$ Hz, 3H); EIMS m/z: 452.
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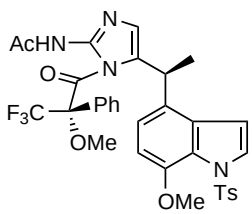
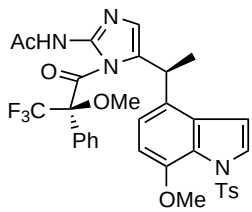
24. The enantiomeric excess of compound **2** was determined by converting **2** into the (*S*)-MTPA derivative **20** and (*R*)-MTPA derivative **21**, respectively. In the ^{19}F NMR ($CDCl_3$, 282 MHz) spectra of compounds **20** and **21** only one peak was observed at 1318.52 and 1338.10 Hz, respectively. It was thus revealed that compound **2** was obtained as a single enantiomer.



20 (*S*)-MTPA derivative
single peak at 1318.52 Hz



21 (*R*)-MTPA derivative
single peak at 1338.10 Hz