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First Total Synthesis of Dragmacidin A via Indolylglycines

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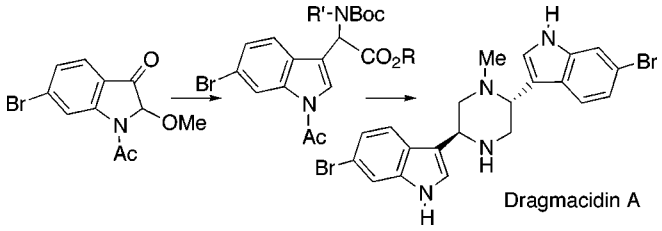
ABSTRACT



The first total synthesis of dragmacidin A has been accomplished using condensation of two indolylglycines followed by cyclization and reduction. The general and practical method for synthesis of indolylglycines via Wittig reaction, azide addition, and reduction from indolin-3-ones is also described.

The family of naturally occurring 2,5-bis(3′-indolyl)piperazine, dragmacidins **1**,[1−6] isolated from the deep-water sponges *Dragmacidon*, *Halicortex*, *Hexadella*, *Spongosorites*, and the tunicate *Didemnum candidum*, has become larger each year. Although these compounds have been shown to possess a wide array of biological activities, anticancerous, antifungal, antiviral, and antiinflammatory,[1−6] few general synthetic routes to dragmacidins **1** have been reported. The only known examples are the syntheses of dragmacidin **1a**[7] and dragmacidin B **1c** (Figure 1).[8] In view of the potential of these natural products as a lead compound to a new and more biologically active agent, formulation of a general synthesis of dragmacidins **1** and analogues is essential. In

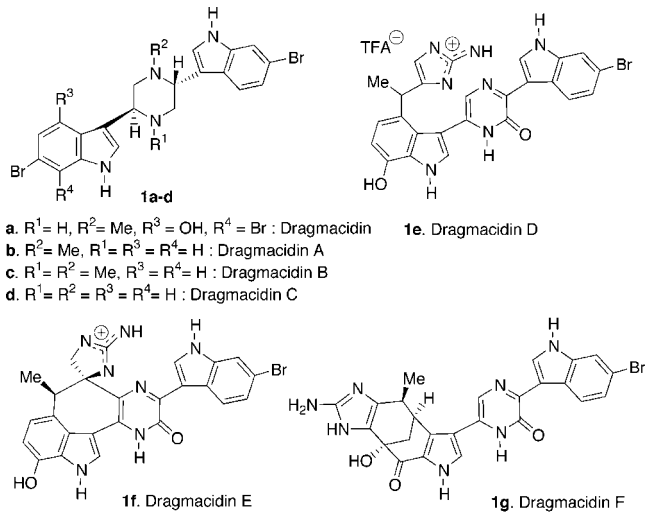


Figure 1.

(1) Dragmacidin (**1a**): Kohmoto, S.; Kashmann, Y.; McConnell, O. J.; Rinehart, K. L. Jr.; Wright, A.; Koehn, F. *J. Org. Chem.* **1988**, *53*, 3116−3118.

(2) Dragmacidin A (**1b**) and dragmacidin B (**1c**): Morris S. A.; Andersen, R. J. *Tetrahedron* **1990**, *46*, 715−720.

(3) Dragmacidin C (**1d**): Fahy, E.; Potts, B. C. M.; Faulkner, D. J.; Smith, K. *J. Nat. Prod.* **1991**, *54*, 564−569.

(4) Dragmacidin D (**1e**): Wright, A. E.; Pomponi, S. A.; Cross, S. S.; McCarthy, P. *J. Org. Chem.* **1992**, *57*, 4772−4775.

(5) Dragmacidin E (**1f**): 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.

(6) Dragmacidin F (**1g**): (a) Cutignano, A.; Bifulco, G.; Bruno, I.; Casapullo, A.; Gomez-Paloma, L.; Riccio, R. *Tetrahedron* **2000**, *56*, 3743−3748. (b) Write, A. E.; Pomponi, S. A.; Jacobs, R. S. U. S. Pat. US 3655, 1999.

(7) Jiang, B.; Smallheer, J. M.; Amaral-Ly, A.; Wuonola, M. A. *J. Org. Chem*. **1994**, *59*, 6823−6827.

(8) Whitlock, C. R.; Cava, M. P. *Tetrahedron Lett*. **1994**, *35*, 371−374.

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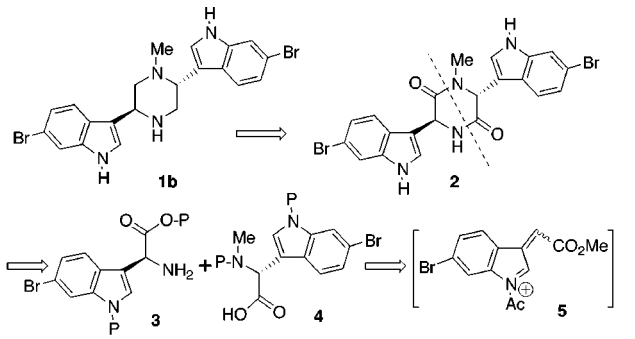
this Letter, we describe the first total synthesis of dragmacidin A **1b** as a typical example of a novel and general method for synthesis of 2,5-bis(3′-indolyl)piperazine derivatives.

Our synthetic strategy toward **1b** is illustrated in Scheme 1; the piperazine structure can be derived from reduction of

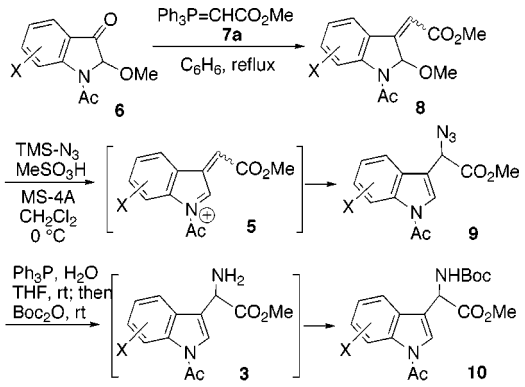
Scheme 1



piperazine-2,5-dione **2**, which would be obtained from condensation of indolylglycine **3** and its *N*-methyl derivative **4** followed by cyclization. To our knowledge, however, no efficient method for synthesis of indolylglycines having the electron-withdrawing group such as bromine has been reported in the literature.[9] Our project requires a practical and general method for synthesis of indolylglycines **3**. To begin with, we synthesized **3** from readily available indolin-3-ones **6**[10] through generation and azide addition of indolenium intermediate **5**.

Wittig olefination of 6-bromoindolin-3-one **6a** with phosphonium ylide **7a** in boiling benzene proceeded stereoselectively to give a *Z*,*E*-mixture (7:1) of 3-alkylideneindoline **8a** in 98% yield (Scheme 2). Reaction of **8a** with TMS azide

Scheme 2



in the presence of MsOH and molecular sieves (MS-4A) took place with elimination of methanol to generate an indolenium intermediate **5a**, which reacted with the azide species to produce indolyl-α-azidoacetate **9a** in excellent yield. The azide **9a** was reacted with triphenylphosphine in the presence of water followed by treatment with Boc_2O to afford *N*-Boc-indolylglycine **10a** in 93% yield. To test the scope of the procedure, a variety of substituted indolin-3-ones **6b**−**f**[10] were screened. As is evident from Table 1 , all the reactions

Table 1. Preparation of *N*-Boc-indolylglycines **10**

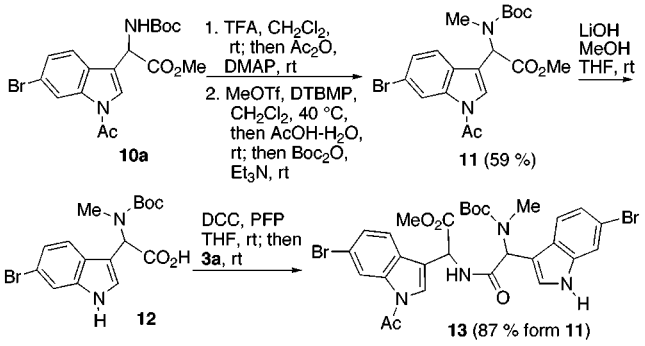
			yield (%)		
entry	X	R	**8** (Z : E)[a]	**9**	**10**
a	6-Br	Ac	98 (7 : 1)	96	93
b	5-Br	Ac	97 (9 : 1)	99	83
c	4-Br	CO_2Me	94 (13 : 1)	74	74
d	6-Cl	Ac	90 (5 : 1)	83	76
e	5-OMe	Ac	97 (6 : 1)	75	96
f	H	Ac	99 (11 : 1)	99	97

[a] The ratio was obtained from the 270 MHz ^{1}H NMR spectrum, and the stereochemistry was confirmed by NOE experiments.

gave various *N*-Boc-indolylglycines **10b**−**f** in good overall yields.

N-Boc-*N*-methylindolylglycine **11** was derived from indolylglycine **3a** according to the reported procedure[11] for monomethylation of primary amine; acetylation of **3a** obtained by treatment of **10a** with TFA and successive reactions, methylation with methyl triflate and DTBMP[12] followed by hydrolysis with AcOH−H_2O, and then Boc-protection gave **11** in 59% overall yield (Scheme 3). Ester

Scheme 3



11 was hydrolyzed with LiOH to produce deacetylated carboxylic acid **12**, which was condensed with amino ester **3a** using DCC and PFP[12] to afford dipeptide **13** in 87% yield.

(9) (a) Droste, H.; Wieland, T. *Liebigs Ann. Chem.* **1987**, 901−910. (b) O'Donnell, M. J.; Bennett, W. D. *Tetrahedron* **1988**, *44*, 5389−5401. (c) Bergman, J.; Bergman, S.; Lindström, J.-O. *Tetrahedron Lett.* **1989**, *30*, 5337−5340. (d) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1997**, *53*, 2941−2958. (e) Clark, B. P.; Harris, J. R. *Synth. Commun.* **1997**, *27*, 4223−4234. (f) Recently *N*-tosyl indolylglycines were prepared by the copper(I)-catalyzed addition of *N*-tosylimino ester to indoles with electron-withdrawing substituents: Johannsen, M. *Chem. Commun.* **1999**, 2233−2234.

(10) Kawasaki, T.; Nonaka, Y.; Matsumura, K.; Monai, M.; Sakamoto, M. *Synth. Commun.* **1999**, *29*, 3251−3261.

(11) Arnarp, J.; Lönngren, J. *Acta Chem. Scand. B* **1978**, *32*, 465−467.

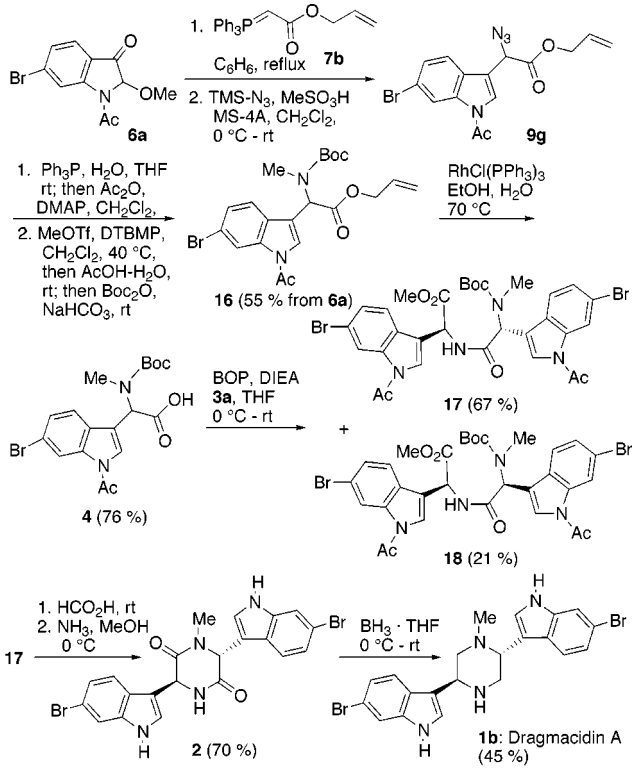
(12) DTBMP, 2,6-di-*tert*-butyl-4-methylpyridine; PFP, pentafluorophenol; BOP, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

Removal of the Boc group from **13** using ordinary reagents[13] was unsuccessful and gave a complex mixture. This could be caused by lack of acetyl group on one of the indole nitrogen atoms (N_1) of **13**.[14] Then we attempted acetylation of **13** for protection of the free indole nitrogen atom (N_1); however, the desired protection was not achieved at all.

To seek a useful carboxyl-protecting group of *N*-Boc-N_1-acetylindolylglycine, instead of the methyl group, which is easily removed to afford the corresponding acid without the undesired reaction such as deacetylation, we next tried deprotection of allyl indolylglycine esters **16**.[15] In a manner similar to that used above, ester **16** was prepared by a sequence of the following reactions: Wittig reaction of **6a** with ylide **7b**, azide addition, reduction of azide ester **9g** with Ph_3P-H_2O, acetylation with Ac_2O-DMAP, methylation with methyl triflate and DTBMP, hydrolysis with $AcOH-H_2O$, and Boc protection provided the indolylglycine ester **16** in 55% overall yield from **6a** (Scheme 4). Allyl deprotection of **16** with $RhCl(Ph_3P)_3$ in $EtOH-H_2O$ gave the desired acid **4** in 76% yield. Condensation of **3a** and **4** using BOP[12] and DIEA proceeded diastereoselectively to give dipeptide **17**[16] and its diastereomer **18** in 67% and 21% yields, respectively. Successive treatment of **17** with HCO_2H[17] and with NH_3[18] at 0 °C took place with deprotection of *N*-Boc and *N*-acetyl groups of **17** followed by spontaneous cyclization to afford the *trans*-piperazine-2,5-dione **2** in 70% overall yield. The final reduction of **2** with an excess amount of BH_3·THF produced dragmacidin A **1b** in 45% yield. The spectral data of the synthetic final product **1b** were identical to those of the natural material, and its stereochemistry was confirmed by NOE experiments.

In summary, we have described a novel and general method for synthesis of indolylglycines **3** and the first synthesis of dragmacidin A **1b** derived from 6-bromoindolylglycine **3a**. With minor modifications, the approach to **1b** should be readily applicable to the syntheses of other members of the dragmacidin family and analogues.

Scheme 4



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Supporting Information Available: Experimental procedures for preparation of **10a**, **9g**, **16**, **4**, **17**, **2**, and **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; pp 518−525.

(14) In some cases, deamination was observed as an undesired reaction.

(15) We also attempted to use benzyl ester; however, the hydrogenatic deprotection of the benzyl group led to debromination.

(16) The stereochemistry was confirmed by transformation to **1b** and its NOE experiments.

(17) King, R. R. *Can. J. Chem.* **1997**, *75*, 1172−1173.

(18) Treatment at temperatures higher than 10 °C resulted in epimerization to give a mixture of *trans*- and *cis*-isomers of **2**.