Pergamon

Tetrahedron Letters, Vol. 35, No. 3, pp. 371-374, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0234-B

A TOTAL SYNTHESIS OF DRAGMACIDIN B

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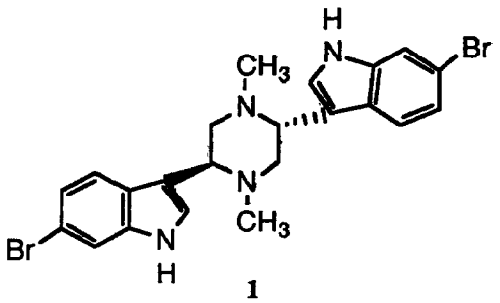
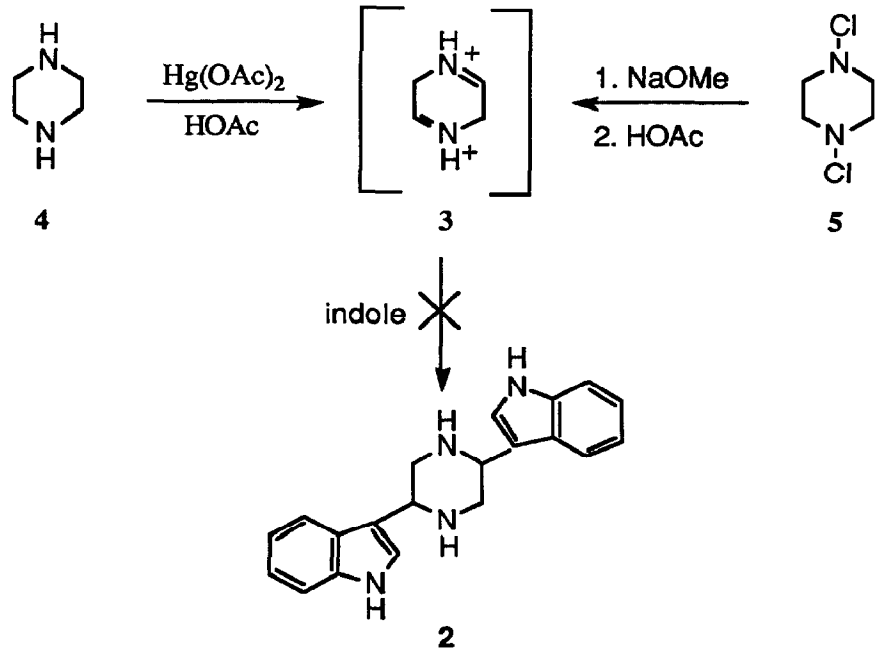
Abstract: A simple total synthesis of dragmacidin B is described. This constitutes the first synthesis of a member of the 2,5-bis(3'-indolyl)piperazine family of marine alkaloids. The didebromo analog of dragmacidin B was also prepared.

Dragmacidin B (**1**), which was isolated from the Pacific sponge *Hexadella sp.*,[1] is one of the small group of 2,5-bis(3'-indolyl)piperazine marine alkaloids which have been found in the sponge genera *Dragmacidon, Hexadella, and Spongosorites*,[1-3] as well as in the tunicate *Didemnum candidum*.[4] Although several of these compounds show anticancer, antifungal, and antiviral activity, no synthetic route to any bisindolyl piperazine has as yet been reported. We now describe a short synthesis of dragmacidin B (**1**), one of the simpler members of this family.



1

Our first target molecule was the unsubstituted diindolylpiperazine (**2**), which might be expected to form in a Mannich reaction between indole and the protonated form (**3**) of the unknown 2,5-dihydropiperazine. However, addition of indole to solutions prepared by the mercuric acetate oxidation of piperazine (**4**), or by the dehydrochlorination of N,N'-dichloropiperazine (**5**)[5] followed by acidification, yielded no isolable product other than recovered indole (Scheme 1).



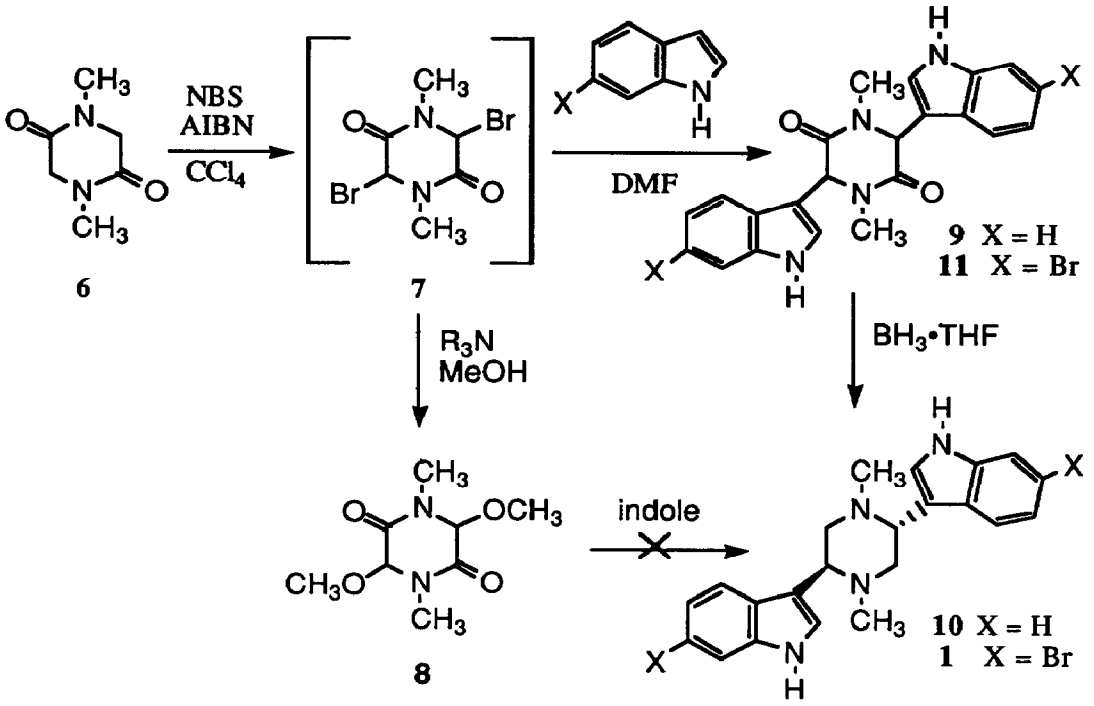
4 3 5 2

Scheme 1

It has been reported that 1,4-dimethylpiperazine-2,5-dione (**6**) may be brominated to give a labile dibromo derivative (**7**), which reacts readily with methanol in the presence of triethylamine to give the 3,6-dimethoxy analog (**8**) as a diastereomer mixture.[6] Our attempts to react indole with **7** in the presence of a tertiary amine, or with **8** in an acidic medium, failed. However, bromination of **6** and reaction of the resulting crude **7** with indole in DMF solution in the *absence* of added acid or base gave the desired diindolyl piperazinedione (**9**) in 43% overall yield. Reduction of **9** with borane•THF gave didebromodragmacidin B (**10**) in 39% yield.

Repetition of the above sequence starting with 6-bromoindole[7,8] afforded dione **11** and dragmacidin B (**1**) in yields of 57% and 25%, respectively (Scheme 2). The spectroscopic properties of synthetic **1**[9] were in accord with those reported for the natural product, which has been assigned the trans diindolyl configuration.[1]

Studies are in progress to optimize yields in this sequence and to adapt it to the synthesis of other members of the dragmacidin series.



Scheme 2

Acknowledgment. This work was supported by a grant from the National Institutes of Health (5-R01 GM44713).

References and Notes

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9. Compound **1**:

IR (KBr): 3150, 2950, 2830, 1620 and 1520 cm^{-1}.

^1H NMR (360 MHz, d_6-acetone): δ 2.06 (s), 2.64 (dd), 2.93 (dd), 3.57 (dd), 7.17 (dd), 7.36 (d), 7.60 (d), 7.92 (d) and 10.28 (bs).

^{13}C NMR (360 MHz, d_6-acetone): δ 43.5, 62.8, 64.1, 115.1, 115.3, 117.0, 122.5, 122.7, 125.0, 126.6 and 139.1.

LRMS m/z (rel. intensity) 500/502/504 (12/20/12), 305/307 (27/27), 250/252 (37/37), 237/239 (94/94), 221/223 (100/100) and 195/197 (50/50).

HRMS: exact mass calcd. for $C_{22}H_{22}N_4Br_2$ 500.0211/502.0199/504.0170, found 500.0238/502.0226/504.0200.

Satisfactory spectral data were obtained also for compounds **9**, **10**, and **11**. The stereochemistry of **10** is assumed to be the same as that of **1** on the basis of the similarity of synthesis and NMR spectra.

(*Received in USA* 22 *September* 1993; *revised* 2 *November* 1993; *accepted* 10 *November* 1993)