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A Concise Synthesis of Topsentin A and Nortopsentins B and D

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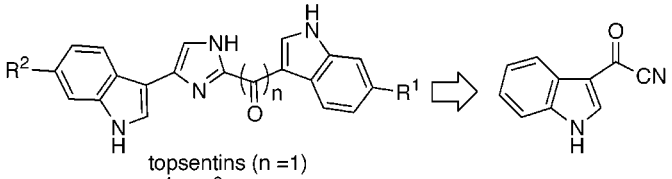
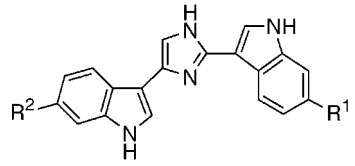
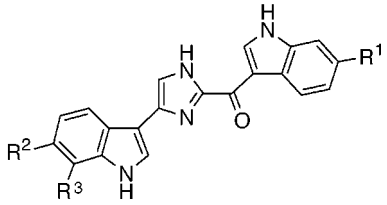
ABSTRACT



A concise synthesis of topsentin A ($R^1 = R^2 = H$) and nortopsentins B ($R^1 = Br$, $R^2 = H$) and D ($R^1 = R^2 = H$) is described from oxotryptamine 5 via reduction of acyl cyanide 4. Regiospecific bromination of 3-cyanoindole afforded 6-bromo-3-cyanoindole (10) as the major product.

The bisindole alkaloids nortopsentin (**1**)[1] and topsentin (**2**)[2] represent a class of deep-sea sponge metabolites that has received much attention due to their potent biological activities as antitumor, antiviral, and antiinflammatory agents. Previous syntheses of these bis(indolyl)imidazoles have been accomplished via palladium-catalyzed cross coupling of 3-indolylboronic acids or 3-stannylindoles with halogenoimidazoles,[3] rearrangement and dimerization of hydrazinium bromide prepared from 3-bromoacetylindole,[4] and oxidative dimerization of 3-hydroxyacetylindoles using $Cu(OAc)_2$ and NH_4OH.[2b] We felt that a direct preparation of 3-aminoacetylindole (**5**) would offer a facile entry to this bisindole series. Moreover, this tryptamine synthon is found in a number of indole-related natural products,[5] and its efficient preparation should find many useful applications. Herein, we report a concise synthesis of nortopsentins B (**1**, $R^1 = Br$, $R^2 = H$) and D (**1**, $R^1 = R^2 = H$) and topsentin A (**2**, $R^1 = R^2 = H$) using acyl cyanide **4** as an α-amino ketone equivalent for the efficient preparation of key intermediate **5**.





To date, the best method reported for the preparation of **5**[5b] is based on the Yonemitsu oxidation of *N*-Boc-protected

(1) Sakemi, S.; Sun, H. H. *J. Org. Chem.* **1991**, *56*, 4304.

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(4) (a) Braekman, J. C.; Daloze, D.; Stoller, C. *Bull. Soc. Chim. Belg.* **1987**, *96*, 809. (b) Braekman, J. C.; Daloze, D.; Moussiaux, B.; Stoller, C.; Deneubourg, F. *Pure Appl. Chem.* **1989**, *61*, 509.

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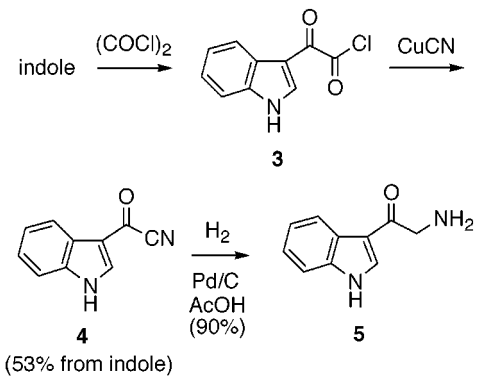
tryptamine with DDQ.[6] While the method is applicable to *N*-acyltryptamine derivatives, the direct conversion of tryptamine to **5** has not been reported. As an alternative to DDQ oxidation, we chose to investigate the reduction of indole-3-carbonyl nitrile (**4**), which would allow a practical preparation of oxotryptamine **5**.

Starting with indole, acyl cyanide **4**[7] was readily prepared in two steps as a colorless crystalline solid (Scheme 1). The

Scheme 1



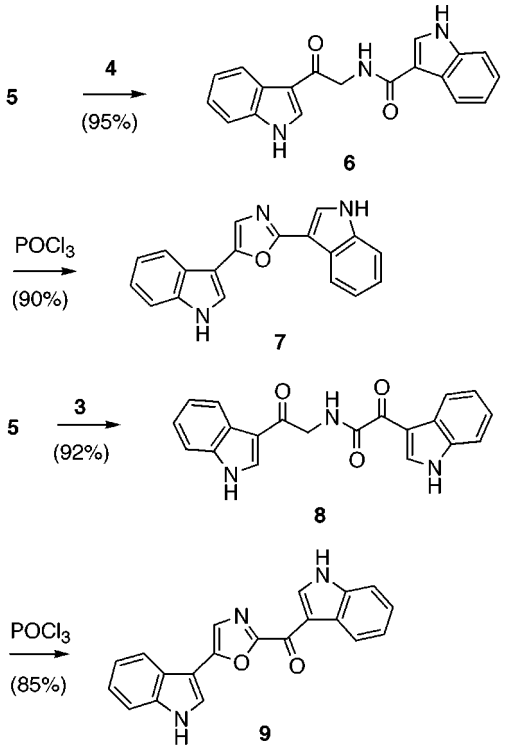
ensuing key step is the hydrogenation of acyl cyanide **4** using 10% Pd/C in acetic acid (23 °C, 16 h). This produced oxotryptamine **5** in 90% yield as the acetate salt.

To our knowledge, the direct formation of α-amino ketones by hydrogenation of acyl cyanides over Pd/C has not been reported[8] and only one report describes the direct conversion of acyl cyanides to α-amino ketones using $SnCl_2$ in saturated Et_2O/HCl and H_2S workup.[9]

With oxotryptamine **5** in hand, the versatility of this intermediate was investigated. Acylation of amine **5** with acyl cyanide **4** gave amide **6** in excellent yield (Scheme 2).[10] Cyclodehydration of **6** with phosphorus oxychloride (23 °C, 12 h) produced bis(3-indolyl)oxazole **7**. Similarly, acylation of amine **5** with acid chloride **3** produced amide **8**. Cylcodehydration of **8** afforded the oxazole topsentin analogue, **9**. Attempts to convert oxazoles **7** and **9** to imidazoles[11] by treatment with formamide or NH_4OH were unsuccessful.

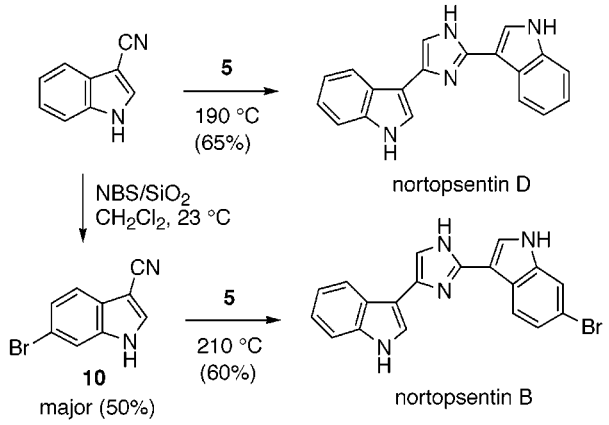
The synthesis of nortopsentins B and D is outlined in Scheme 3. Condensation under neat conditions of commercially available 3-cyanoindole with oxotryptamine **5** produced nortopsentin D. Extension of this strategy to the synthesis of nortopsentin B, which possesses a 6-bromoindole unit, requires the use of 6-bromocyanoindole (**10**).[12] Rather

Scheme 2



than synthesize this precursor using Batcho-Leimgruber indole methodology,[13] the direct bromination of readily available 3-cyanoindole was pursued. The electron withdrawing cyano group was anticipated to direct the bromination meta to the indole nitrogen. Upon treatment of 3-cyanoindole with NBS over silica[14] in CH_2Cl_2, a 50% yield of bromoindole **10** was obtained as the major product. Small amounts (20%) of the 5-substituted regioisomer were also observed. Although the yield is modest at this time, the preparation of **10** requires only one step from commercially available 3-cyanoindole and is easily separated from the minor regioisomer. HMQC correlations confirmed the position of substitution. Condensation of oxotryptamine **5** with nitrile **10** produced nortopsentin B.

Scheme 3



(5) For recent examples, see: (a) Kobayashi, Y.; Fujimoto, T.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 6501. (b) Barret, R.; Roue, N. *Tetrahedron Lett.* **1999**, *40*, 3889.

(6) Oikawa, Y.; Yoshioka, T.; Mohri, K.; Yonemitsu, O. *Heterocycles* **1979**, *12*, 1457.

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(8) For review, see: Hünig, S.; Schaller, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 36.

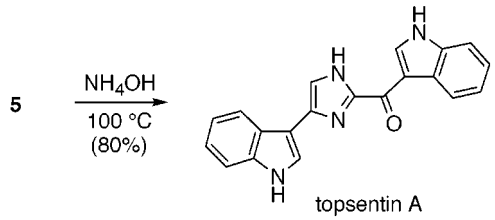
(9) Stuckwisch, C. G. *J. Org. Chem.* **1972**, *37*, 318.

(10) All new compounds gave satisfactory spectral data (^1H and ^{13}C NMR and HRMS).

(11) Potts, K. T. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 5, p 156.

Several attempts were made to synthesize topsentin A by condensing acyl nitrile **4** with amine **5**; however, none afforded the desired product. Finally, a successful preparation of topsentin A was achieved through oxidative dimerization of **5** in NH_4OH and air (Scheme 4).[15]

Scheme 4



All spectral data for synthetic nortopsentin B[1] and topsentin A[2a] were identical to those reported for the natural material. While imidazole tautomerism was not detected by NMR for nortopsentins B and D, or the hydrochloride salt of topsentin A, mixtures of slowly interconverting tautomers were seen with the free base of topsentin A in neutral solution. These results are consistent with previous observations.

In summary, a short synthesis of topsentin A and nortopsentins B and D has been accomplished from readily available starting materials. The synthesis is highly symmetrical in nature, and to date, represents the most efficient entry to this bioactive class of bis(indolyl)imidazole metabolites. The acyl cyanide synthon approach should find further applications to other latent α-amino ketone derived natural products.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **5**−**10**, topsentin A, and nortopsentins B and D. This material is free of charge via the Internet at http://pubs.acs.org.

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(14) Mistry, A. G.; Smith, K.; Bye, M. R. *Tetrahedron Lett.* **1986**, *27*, 1051.
(15) A full account of this dimerization will be described elsewhere.