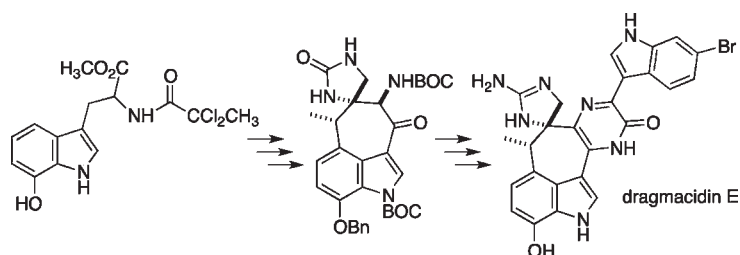


Total Synthesis of (\pm)-Dragmacidin EKen S. Feldman^{*†} and Paiboon Ngermeesri[‡]Chemistry Department, The Pennsylvania State University, University Park,
Pennsylvania 16802, United States, and Chemistry Department, Kasetsart University,
Bangkok, Thailand 10900

ksf@chem.psu.edu

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ABSTRACT



The bis indole sponge alkaloid dragmacidin E was synthesized in racemic form over 25 steps starting from 7-benzhydroxyindole. Key steps include (a) a Witkop cyclization to facilitate construction of the indole-spanning seven-membered ring and (b) a cyclodehydrative pyrazinone synthesis that unites the two indole-containing sectors.

The bis indole alkaloid dragmacidin E (**1**) along with its congener dragmacidin D was isolated from a *Spongosortes* sp. collected in Australian waters (Figure 1).¹ Both of these species are described as exhibiting potent serine-threonine protein phosphatase inhibitory activity. The challenges inherent in the unique molecular architecture of **1** and related species dragmacidins D and F have fueled much synthesis effort,^{2,3} culminating in total syntheses of dragmacidins D and F by Stoltz and colleagues.² Our own efforts have focused on dragmacidin E and, in particular, the assembly of the cycloheptannelated indole core via application of diradical cyclization chemistry to forge the key C(4'')–C(6''') bond.⁴ Additionally, successful preparation of **1** will have to utilize chemistry that is not derailed by

(1) severe steric congestion along the upper rim of the cycloheptanoid unit, (2) ring strain resulting from installation of five contiguous sp² carbons in a seven-membered ring, and (3) the sensitive guanidine unit. Preliminary studies that probed these issues resulted in the preparation of the model system **2**, lacking both the C(7'') hydroxyl and the C(6'') bromide.^{4b} In this report, the application and extension of this chemistry to the total synthesis of the intact (\pm)-dragmacidin E target is described. The key transformative step involves Witkop cyclization⁵ of a tryptophan derivative to deliver the C(3'')–C(4'') bridged indole core of the target.

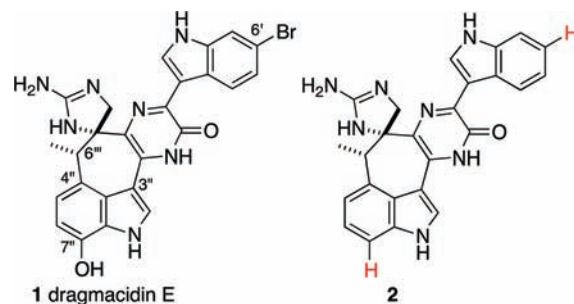


Figure 1. Dragmacidin E (**1**) and a simpler model compound **2**.

[†] The Pennsylvania State University.

[‡] Kasetsart University.

(1) Capon, R. J.; Rooney, F.; Murray, L. M.; Collins, E.; Sim, A. T. R.; Rostas, J. A. P.; Butler, M. S.; Carrol, A. R. *J. Nat. Prod.* **1998**, *61*, 660–662.

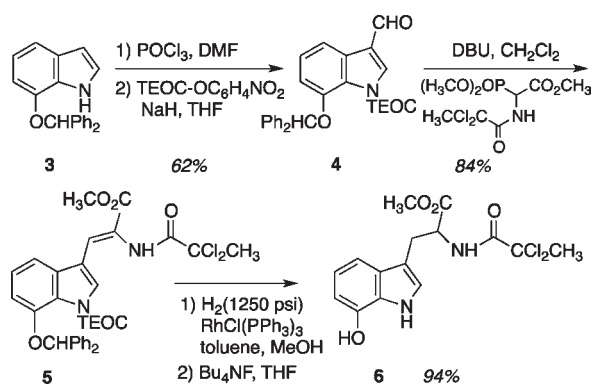
(2) (a) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179–13184. (b) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552–9553. (c) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5970–5978. (d) Garg, N. K.; Stoltz, B. M. *J. Chem. Soc., Chem. Commun.* **2006**, 3769–3779. (e) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *Synlett* **2006**, 3081–3087.

(3) (a) Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 4775–4778. (b) Huntley, R. J. Ph.D. Thesis, Pennsylvania State University, 2008.

(4) (a) Feldman, K. S.; Ngermeesri, P. *Org. Lett.* **2005**, *7*, 5449–5452. (b) Feldman, K. S.; Ngermeesri, P. *Org. Lett.* **2010**, *12*, 4502–4505.

The synthesis plan commenced with preparation of the Witkop cyclization precursor **6** from the known 7-diphenylmethyl ether of indole, **3**, itself available via Bartoli indole synthesis in two steps,⁶ Scheme 1. Installation of the tryptophan side chain proceeded via initial formylation of **3** at C(3) and then Emmons–Horner alkene extension with the anion of methyl (2,2-dichloropropionylamino)-(dimethylphosphoryl)acetate to furnish the (*Z*)-dehydrotryptophan derivative **5**. Exposure of **5** to catalytic Wilkinson’s catalyst and high pressure hydrogen gas served to both saturate the side chain and cleave the diphenylmethyl ether function at C(7'') to deliver the Witkop substrate **6** following deprotection of the indole nitrogen.

Scheme 1. Synthesis of the Witkop Cyclization Precursor



The key Witkop cyclization proceeded smoothly upon irradiation of dilute solutions of **6** in acetonitrile in a quartz vessel with 254 nm light, Scheme 2. The isolated product, **13**, represents one of the highest

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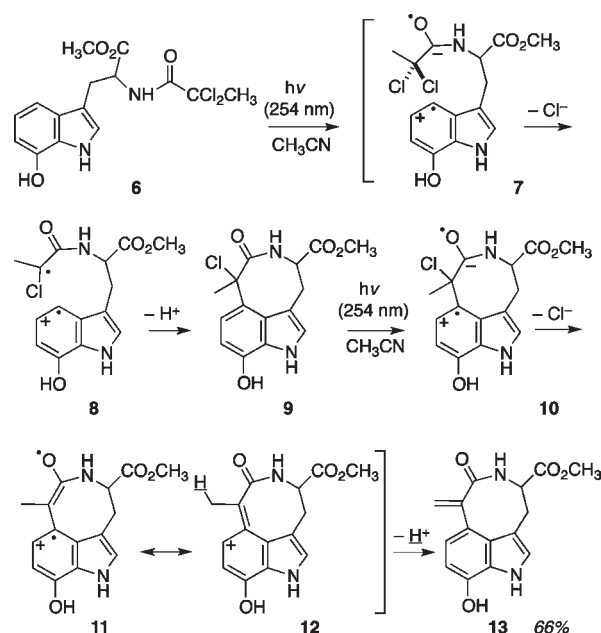
(6) Dobson, D.; Todd, A.; Gilmore, J. *Synth. Commun.* **1991**, *21*, 611–617.

(7) (a) McCall, M. T.; Hammond, G. S.; Yonemitsu, O.; Witkop, B. *J. Am. Chem. Soc.* **1970**, *92*, 6991–6993. (b) Naruto, S.; Yonemitsu, O. *Tetrahedron Lett.* **1975**, *16*, 3399–3402. (c) Hamada, T.; Ohmori, M.; Yonemitsu, O. *Tetrahedron Lett.* **1977**, *18*, 1519–1522. (d) Naruto, S.; Yonemitsu, O. *Chem. Pharm. Bull.* **1980**, *28*, 900–909.

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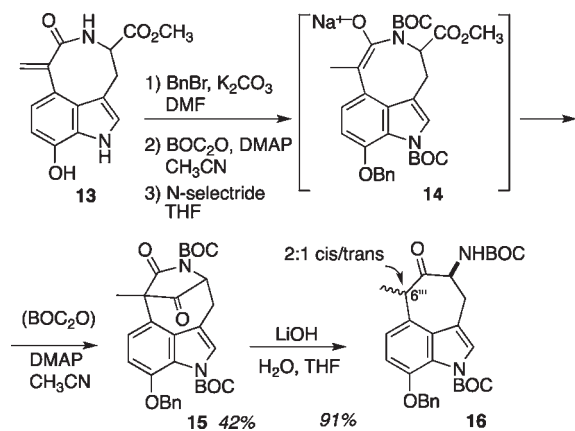
yielding Witkop cyclizations reported to date.⁸ The Witkop cyclization has been subject to numerous mechanistic studies⁷ and has been utilized as a pivotal step in many total syntheses of cognate indole alkaloids.⁸ Application of the consensus Witkop mechanistic paradigm to the chemistry of **6** is detailed below. This speculation features two consecutive photochemically mediated electron transfers that labilize both C–Cl bonds for further chemistry. In the first sequence, chloride loss promotes diradical **8** generation, and regioselective closure within **8** then constitutes the key C–C bond forming step of this Witkop cyclization. A subsequent photoelectron transfer within **9** provides a low-energy pathway for Cl[−], and then H⁺, loss to deliver the enone product **13**, although it is not unreasonable to imagine that HCl loss may proceed from **9** without intervention of excited state chemistry.

Scheme 2. Witkop Cyclization of **6**, with Mechanistic Speculation



Conversion of the eight-membered bridging lactam into a cycloheptanoid structure constituted the next synthesis objective, Scheme 3. This formal one-atom ring contraction could be effected by initial conjugate addition of hydride to the enone unit, which promoted a Dieckmann cyclization of the first-formed enolate **14**. The strained tetracyclic product **15** was readily hydrolyzed to deliver the desired cycloheptane-bridged indole substructure of dramacidin E, **16**. Tricycle **16** was formed as an inconsequential mixture of stereoisomers at C(6'''); both diastereomers later converged to the same product.

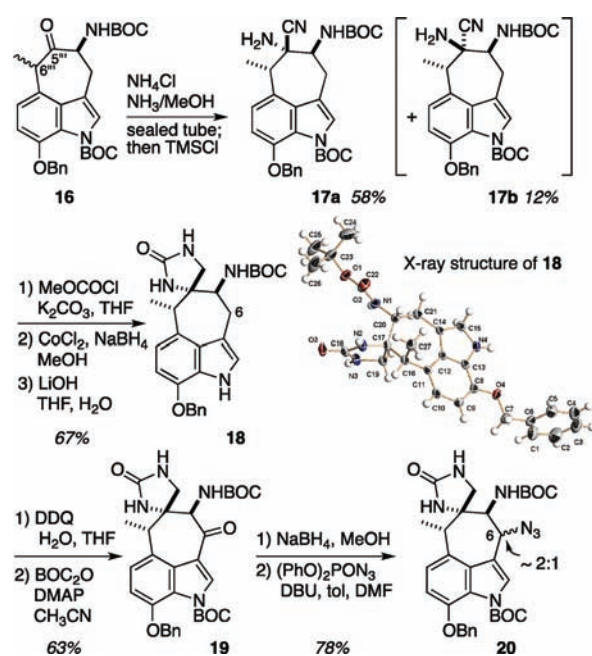
Conversion of the C(5''') carbonyl into the spiroimida-zolone unit with correct relative stereochemistry defined the next task, Scheme 4. Functionalizing this ketone proved quite challenging, and curiously, related difficulties

Scheme 3. Synthesis of the Cycloheptannelated Indole Core

did not plague the similar des- $C(7'')$ -oxy model system preceding **2**; the long-range reactivity-altering effects of the $C(7'')$ OBn unit on the chemistry of the $C(5''')$ carbonyl were not anticipated. Through much trial-and-error, an effective and reproducible Strecker reaction-based experimental procedure utilizing methanolic ammonia at elevated temperature ($75\text{ }^\circ\text{C}$) in a sealed tube, followed by rapid TMSCN addition to the crude reaction mixture, was developed. Diastereomeric cyanoamines **17a** and **17b** were formed in an $\sim 5:1$ ratio favoring the desired isomer **17a**; in the model system preceding **2**, only the desired diastereomer was produced. Epimerization at $C(6''')$ during the reaction ensured that only the most thermodynamically favorable cis methyl/NHBOC stereochemical arrangement emerged from these Strecker reaction conditions. Diastereomers **17a** and **17b** could be separated by chromatography, and the free amine of major isomer **17a** was immediately protected as its methyl carbamate. Without this protection, attempted transformations on **17a/17b** tended to promote retro-Strecker reaction and deliver either an imine of **16** or **16** itself following imine hydrolysis. This methyl carbamate was subjected to the nitrile reduction conditions of Satoh.⁹ The crude amino carbamate product was cyclized to furnish the imidazolone unit within **18** under base mediation, which removed the indole N -BOC group as well. The relative stereochemistry of **18** was established by single crystal X-ray analysis, as indicated in Scheme 4.¹⁰ Functionalization of **18** at $C(6)$ was required to install the pyrazinone ring of dragmacidin E, and that operation was accomplished by DDQ-mediated oxidation of this indolic position. Subsequent reduction of the $C(6)$ carbonyl to a pair of labile alcohols, and then conversion of those alcohols to the diastereomeric azides **20**,

(9) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, *10*, 4555–4588.

(10) Cambridge Crystallographic Data Centre deposition number for **18**: CCDC 826169. The data can be obtained free from Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

Scheme 4. Installation of the Spiro 2-Imidazolone; Structural Determination by X-ray Analysis

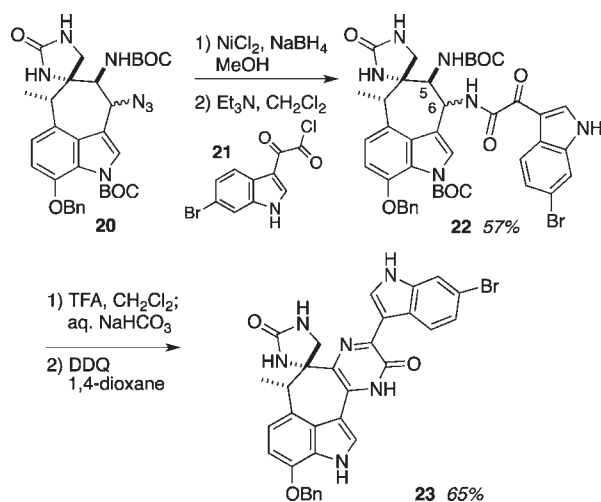
proceeded through standard transformations. The relative stereochemistry at $C(6)$ was not germane to the synthesis effort.

Coupling the tetracyclic indole core unit **20** with the second indole component, in the form of acid chloride **21**,¹¹ was preceded by azide reduction to the primary amines, Scheme 5. The product amide **22** was formed as an $\sim 2:1$ mixture of diastereomers at $C(6)$; both species were useful. Pyrazinone formation proceeded through a two-stage protocol involving first cyclization of the primary amine liberated by TFA-mediated deprotection of the $C(5)$ NHBOC moiety with the indolic ketone of **22** to give a dihydropyrazinone product. This pale yellow species immediately was subjected to DDQ-based oxidation to deliver the stable pyrazinone-containing product **23** as a bright yellow solid.

Completion of the dragmacidin E synthesis required successful execution of two transformations: (1) conversion of the spiroimidazolone's urea unit into a guanidine, and (2) removal of the $C(7''')$ benzyl protecting group. A priori, it was not clear which maneuver should be approached first. As it turned out, initial work on the imidazolone unit proved satisfactory, Scheme 6. O -Methylation of the nucleophilic carbonyl oxygen within the urea appeared to be slightly more facile than methylation at other potentially nucleophilic sites in **23**, and so moderate yields of the 2-methoxyamidine analogue of **23** could be isolated under carefully controlled reaction conditions.

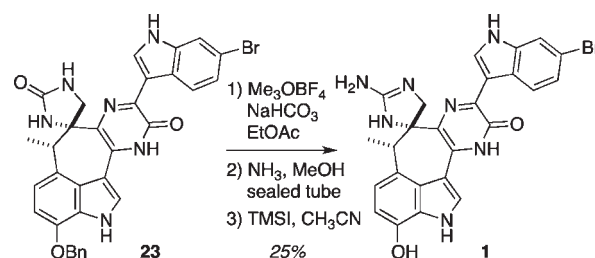
(11) Guinchard, X.; Vallee, Y.; Denis, J.-N. *J. Org. Chem.* **2007**, *72*, 3972–3975.

Scheme 5. Merging the Two Indole Cores; Synthesis of the Pyrazinone **23**



Replacement of the MeO function with NH_2 was accomplished by heating a methanolic solution of this 2-methoxyamidine with ammonia in a sealed tube, and the sensitive guanidine-containing product was subjected to the benzyl ether deprotection conditions reported by Stoltz in his dragmacidin D synthesis^{2a} to give, following SiO_2 chromatography, (\pm)-dragmacidin E (**1**) in modest yield. The final structural identity of synthetic **1** was derived from a comparison of the ^1H and ^{13}C NMR spectral data with those described by Capon and by coinjection HPLC with an authentic sample of natural dragmacidin E (see Supporting Information for details).

Scheme 6. Completion of Dragmacidin E Synthesis via Guanidine Introduction



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Supporting Information Available. General experimental and detailed experimental descriptions along with copies of ^1H and ^{13}C NMR spectra for **4–6**, **13**, **15–23**, and **1**; X-ray data for **18**; HPLC and UV traces of synthetic and authentic dragmacidin E. This material is available free of charge via the Internet at <http://pubs.acs.org>.