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Concise Formal Synthesis of Porothramycins A and B via Zincke Pyridinium Ring-Opening/Ring-Closing Cascade

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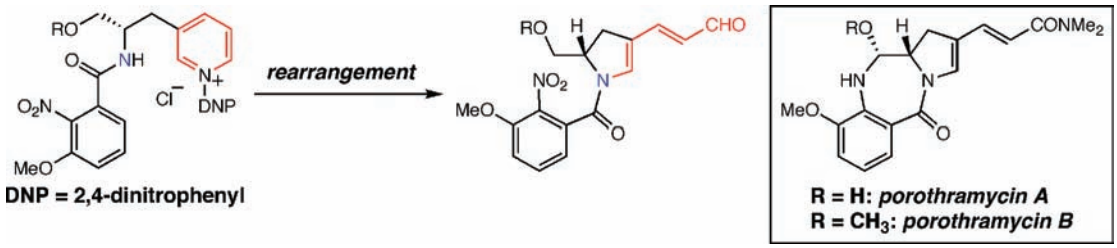
ABSTRACT



Short formal syntheses of the antitumor antibiotics porothramycins A and B from a commercially available ester of the unnatural amino acid 3-(3-pyridyl)alanine are presented. A rearrangement cascade that presumably involves a Zincke-type pyridinium ring-opening followed by cyclization of a pendant nucleophilic amide generates the salient pyrroline ring of the alkaloids.

Discovered in 1963, anthramycin (**1**, Figure 1) is the prototypical member of the large class of pyrrolobenzodiazepinone antitumor antibiotics that includes close relatives porothramycins A and B (**2** and **3**).[1−5] Their mechanism of action is thought to involve covalent modification of DNA via transiently generated C11 imine electrophiles within the minor groove; many members of the family display potent antitumor and antibiotic activity.[5] Within this alkaloid group, there is substantial variation with respect to functionalization

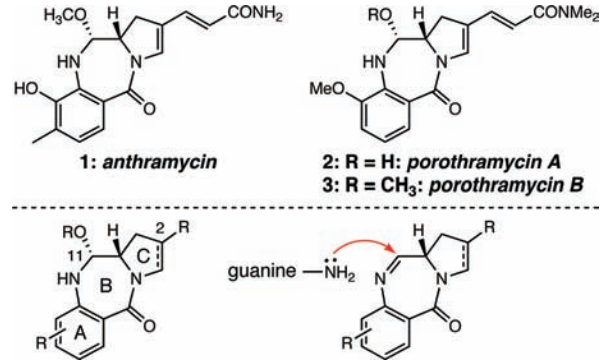


Figure 1. Structures of anthramycin and the porothramycins and the general scaffold of the pyrrolobenzodiazepinone antitumor antibiotics.

(1) Anthramycin isolation and structure elucidation: (a) Leimgruber, W.; Stefanovic, V.; Schenker, F.; Karr, A.; Berger, J. *J. Am. Chem. Soc.* **1965**, *87*, 5791–5793. (b) Leimgruber, W.; Batcho, A. D.; Schenker, F. *J. Am. Chem. Soc.* **1965**, *87*, 5793–5795.

(2) Syntheses of anthramycin: (a) Leimgruber, W.; Batcho, A. D.; Czajkowski, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 5641–5643. (b) Ishikura, M.; Mori, M.; Terashima, M.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1982**, *13*, 741–742. (c) Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1984**, *25*, 5505–5508. (d) Pena, M. R.; Stille, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 5417–5424.

(3) Isolation and structure elucidation of porothramycins A and B: Tsunakawa, M.; Kamei, H.; Konishi, M.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1988**, *41*, 1366–1373.

(4) Syntheses of the porothramycins: (a) Fukuyama, T.; Liu, G.; Linton, S. D.; Lin, S. C.; Nishino, H. *Tetrahedron Lett.* **1993**, *34*, 2577–2580. (b) Langlois, N.; Favre, F.; Rojas, A. *Tetrahedron Lett.* **1993**, *34*, 4635–4638.

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of the aromatic A ring and the presence/nature of the C2 appendage on the C-ring; the C11 hemiaminal or its corresponding imine is conserved throughout. While many of these natural products exhibit general toxicity and are therefore not clinically useful, interest remains in analogues of these alkaloids that might have improved therapeutic windows.[5,6] Extensive studies have demonstrated that the presence of a C2 side chain is meritorious with respect to antitumor activity, and removal of the ortho phenol reduces cardiotoxicity resulting from presumed in vivo generation of *o*-quinone imines.[5b] Efficient approaches that could readily afford A-ring and C2 side chain analogues are therefore valuable.

Our attention was drawn to the anthramycin alkaloids because of the opportunities that they presented for us to evaluate our recently described methodology for heterocycle synthesis using pyridine ring-opening reactions.[7] The 5-amino-2,4-pentadienamide motifs present in anthramycin and the porothramycins (see **1**−**3**) are close relatives of Zincke aldehydes (5-amino-2,4-pentadienals), which are readily available from the ring-opening of pyridinium salts (**4** → **5**, Figure 2).[8−10] In a previous report, we extended these ring-opening reactions to include pyridines bearing tethered nucleophiles; aniline nucleophiles led to indoles (**6** → **7**), and an amide derived from 3-(2-aminoethyl)pyridine (**8**) delivered *N*-acylpyrroline **9**.[7] While previous syntheses of the porothramycins by Fukuyama[4a] and Langlois[4b] have wisely used glutamate-type chiral pool precursors, we sought to develop a nonobvious approach beginning with a derivative of the commercially available unnatural amino acid 3-pyridylalanine that takes advantage of this pyridine to pyrroline rearrangement that simultaneously introduces the C2 side chain. Our expedient enantiospecific formal syntheses of porothramycins A and B using a Zincke ring-opening of 3-pyridylalanine derivative **10** is detailed in this paper.

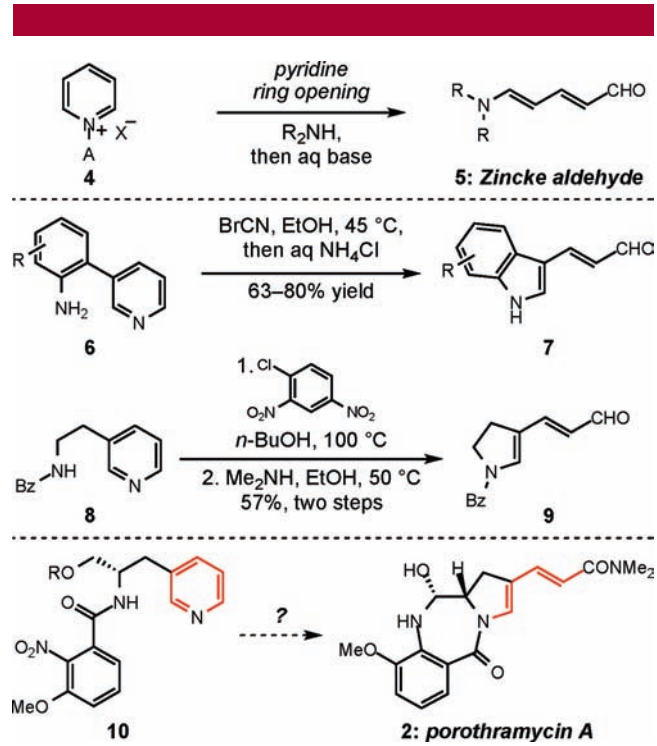


Figure 2. Pyridinium ring-openings to form acyclic Zincke aldehydes, indoles, and dihydropyrroles relevant to the porothramycins. A = activating group.

(*S*)-3-Pyridylalanine methyl ester bis(hydrochloride) (**11**) was acylated with 3-methoxy-2-nitrobenzoyl chloride (**12**); both substances are commercially available.[11] The ester group of **13** was selectively reduced with sodium borohydride. Activation of the pyridine with 2,4-dinitrochlorobenzene proceeded in moderate yield to afford salt **14**. Ring-opening of this pyridinium salt bearing the free hydroxyl group yielded only traces of the desired dihydropyrrole product, in spite of the success of model reactions (see **8** → **9**, Figure 2) in alcoholic solvents. A one-pot hydroxyl group silylation/rearrangement proceeded uneventfully to afford dihydropyrrole **15** in 55% yield; dry ethanol was required for rearrangement without hydrolysis to the acyclic Zincke aldehyde. Oxidation of the resulting unsaturated aldehyde to the corresponding dimethyl amide (**16**) could be accomplished in a single step according to the underutilized procedure of Gilman.[12,13] Cleavage of the silyl ether completed a formal synthesis of both porothramycins A and B because **17** is an intermediate in the Langlois syntheses;[4b] simple redox manipulations as prescribed would deliver porothramycins A (**2**) and B (**3**) in two and three more steps, respectively.

(5) For reviews of the pyrrolobenzodiazepinone antitumor antibiotics, see: (a) Cipolla, L.; Araujo, A. C.; Airoldi, C.; Bini, D. *Anti-Cancer Agents Med. Chem.* **2009**, *9*, 1–31. (b) Baraldi, P. G.; Bovero, A.; Fruttarolo, F.; Preti, D.; Tabrizi, M. A.; Pavani, M. G.; Romagnoli, R. *Med. Res. Rev.* **2004**, *4*, 475–528. (c) Kamal, A.; Rao, M. V.; Laxman, N.; Ramesh, G.; Reddy, G. S. K. *Curr. Med. Chem. Anti-Cancer Agents* **2002**, *2*, 215–254. (d) Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433–465. (e) Hurley, L. H.; Thurston, D. E. *Pharm. Res.* **1984**, 52–59. For more general reviews on small molecules that alkylate the minor groove of DNA, see: (f) Denny, W. A. *Curr. Med. Chem.* **2001**, *8*, 533–544. (g) Reddy, B. S. P.; Sondhi, S. M.; Lown, J. W. *Pharmacol. Ther.* **1999**, *84*, 1–111.

(6) For selected reports of analogue synthesis, see: (a) Langlois, N.; Andriamialisoa, R. Z. *Heterocycles* **1989**, *29*, 1529–1536. (b) Rojas-Rousseau, A.; Langlois, N. *Tetrahedron* **2001**, *57*, 3389–3395. (c) Hadjivassilenva, T.; Thurston, D. E.; Taylor, P. W. *J. Antimicrob. Chemother.* **2005**, *56*, 513–516.

(7) Kearney, A. M.; Vanderwal, C. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7803–7806.

(8) (a) Zincke, T. *Liebigs Ann. Chem.* **1903**, *330*, 361–374. (b) Zincke, T. *Liebigs Ann. Chem.* **1904**, *333*, 296–345. (c) Zincke, T.; Wurker, W. *Liebigs Ann. Chem.* **1905**, *338*, 107–141. (d) König, W. *J. Prakt. Chem.* **1904**, *69*, 105–137.

(9) For reviews, see: (a) Becher, J. *Synthesis* **1980**, 589–612. (b) Becher, J.; Finsen, L.; Winckelmann, I. *Tetrahedron* **1981**, *37*, 2375–2378. (c) Cheng, W.-C.; Kurth, M. J. *Org. Prep. Proced. Int.* **2002**, *34*, 587–608.

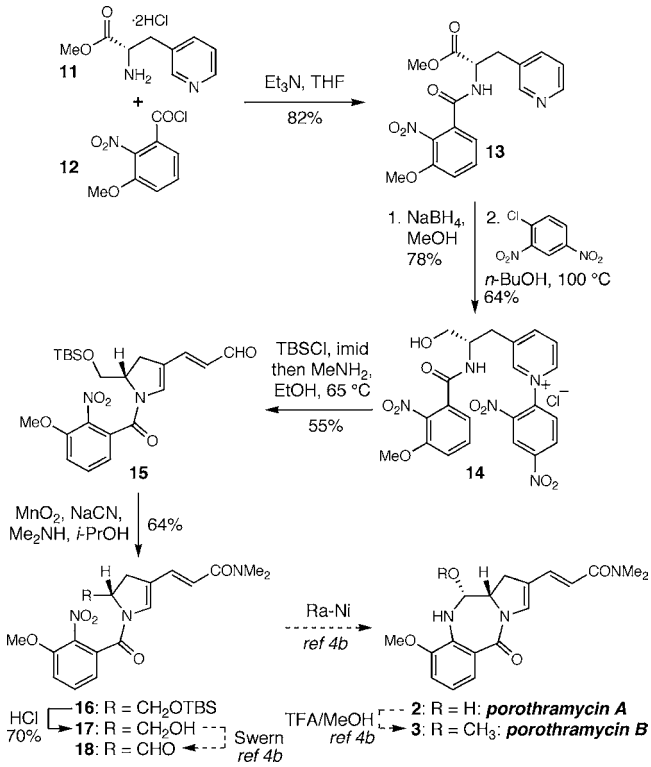
(10) For our other work inspired by the Zincke ring-opening of pyridines, see: (a) Steinhardt, S. E.; Silverston, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 7560–7561. (b) Michels, T. D.; Rhee, J. U.; Vanderwal, C. D. *Org. Lett.* **2008**, *10*, 4787–4790. (c) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473. (d) Steinhardt, S. E.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 7546–7547.

(11) Because of a temporary shortage of the amino acid ester **11** from Aapptech, we purchased the corresponding amino acid and performed a Fischer esterification to provide **11**. Similarly, while acid chloride **12** is commercially available from Aldlab Chemicals in 5 g quantities, a more economical approach was to convert the inexpensive carboxylic acid to **12** ourselves.

(12) Gilman, N. W. *Chem. Commum.* **1971**, 733–734.

(13) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616–5617.

Scheme 1. Formal Syntheses of Porothramycins A and B



The six step enantiospecific route to **17** requires only three chromatographic purifications and results in a route to porothramycins A and B of only eight and nine steps from commercially available starting materials, respectively, which is considerably more step economical than those syntheses reported previously. While some of the reactions are only moderately efficient and might be further optimized, we believe that the unusual rearrangement of a pyridinium salt into the salient pyrroline of the pyrrolobenzodiazepinone alkaloids—the cornerstone of our concise approach—is noteworthy. Finally, the potential to begin this short sequence with differentially substituted A rings and the ready manipulability of the C2 α,β-unsaturated aldehyde side chain that results from the rearrangement reaction indicate that analogue production via this strategy should be facile.

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Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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