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# Total Synthesis of *epi*-7-Deoxypancratistatin via Aza-Payne Rearrangement and Intramolecular Cyclization

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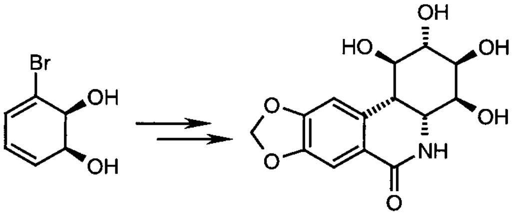
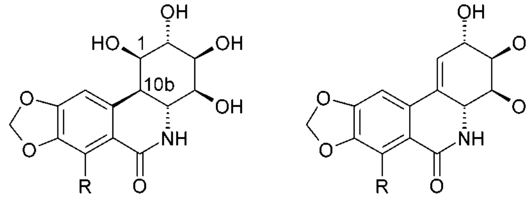
## ABSTRACT



***epi*-7-Deoxypancratistatin containing the *cis*-fused phenanthridone core was synthesized in 12 steps from bromobenzene. Key features of this synthesis include the enzymatic oxidation of bromobenzene with toluene dioxygenase, selective opening of a cyclic sulfate over an aziridine with oxygen nucleophiles, and an intramolecular Lewis acid-catalyzed cyclization onto an epoxy conduramine derived via aza-Payne rearrangement.**

The Amaryllidaceae alkaloids, most notably those related to pancratistatin (**1**, Figure 1) and narciclasine (**2**), have attracted much attention because of their known cytotoxic properties.[1] Following the publication of their biological activities by Pettit,[2] many synthetic approaches to these alkaloids have been pursued.[3,4] Following our disclosure of the first asymmetric synthesis of (+)-pancratistatin in 1995,[4b] which at 14 steps remains the shortest preparation on record, we focused our attention on practical improvements in the preparation of **1** and its congeners. For potential scale-up, the synthesis should be reduced to fewer than 10 steps. The past few generations of our effort have focused on the use of vinylaziridines such as **6**[5] as electrophilic partners in approaches to fully hydroxylated alkaloids in the pancratistatin series while conduramines **7**[4v,6] were utilized in direct coupling as synthons for the narciclasine series (Scheme 1).[4o] Both are rapidly derived from the corresponding *cis*-dihydrocatechols of type **5**[4o,7] produced by enzymatic



**1** R = OH pancratistatin
**3** R = H 7-deoxypancratistatin

**2** R = OH narciclasine
**4** R = H lycoricidine

**Figure 1.** Amaryllidaceae Alkaloids.

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[1] For applications in ancient folk medicine, see: Hartwell, J. L. *Lloydia* **1967**, *30*, 379.

[2] (a) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693. (b) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 1018. (c) Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.* **1986**, *49*, 995.

[3] For a review of total syntheses, see: Polt, R. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 3, p 109.

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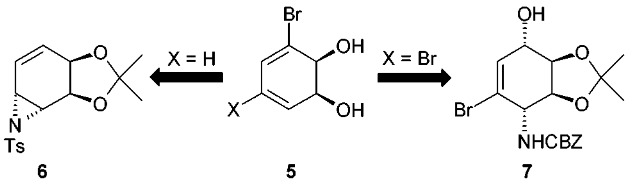
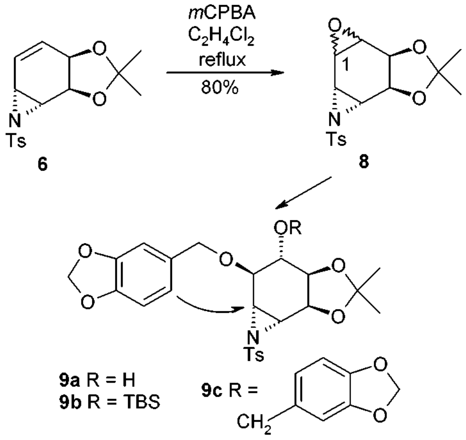
**Scheme 1.** *cis*-Diols as Starting Material for Alkaloid Synthesis



oxidation of the corresponding arenes with *Escherichia coli* JM109 (pDTG601).[8]

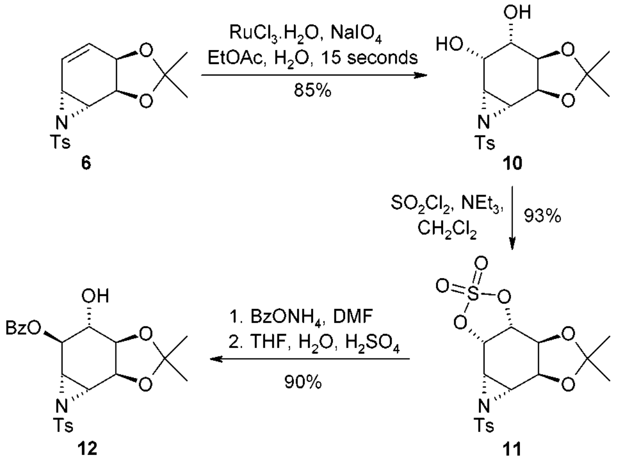
We investigated the possibility of an intramolecular aziridine opening in **9** similar to the epoxide opening reported by Bender (Scheme 2).[9] Ether **9** was envisioned as originating from selective opening of epoxyaziridine **8** at the epoxide site corresponding to C-1 of the phenanthridone skeleton. Both α- and β-oxiranes in **8** would yield the same trans-diol, if opened with identical oxygen nucleophiles, as anticipated from *trans*-diaxial requirements for such an opening. Despite intense efforts to achieve selectivity in these openings, we failed to produce **9**[10] by either acid- or base-catalyzed openings. Under all conditions the aziridine was opened preferentially to the epoxide. We therefore considered the investigation of selectivity in the opening of cyclic sulfites or sulfates versus aziridines and turned our attention to cyclic sulfate **11** instead.[11]

**Scheme 2.** Approach to Amaryllidaceae Alkaloids via Intramolecular Aziridine Opening



Aziridine **6**, prepared in four steps from bromobenzene, was dihydroxylated and converted to the cyclic sulfate **11** with sulfuryl chloride and Et$_3$N in 85% yield (Scheme 3).

**Scheme 3.** Preparation of Benzoate **12**



In contrast to previous experience with epoxyaziridine **9**, benzoate **12** was selectively generated on treatment of sulfate **11** with PhCO$_2$NH$_4$ in DMF followed by hydrolysis of the sulfate with dilute H$_2$SO$_4$ in 90% yield.[12] Protection of the free alcohol, hydrolysis of the benzoate, and alkylation of **13** with piperonyl bromide did not furnish ether **9** as expected but rather the *N*-alkylated amino oxirane **14**, a product of aza-Payne rearrangement of the alkoxide in **13**. We were subsequently able to generate bis-piperonyl compound **9c**

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(4) Total synthesis efforts. Pancratistatin: (a) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829. (b) Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643. (c) Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752. (d) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143. (e) Doyle, T. J.; Hendrix, M.; VanDerveer, D.; Javanmard, S.; Haseltine, J. *Tetrahedron* **1997**, *53*, 11153. (f) Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341. (g) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624. 7-Deoxypancratistatin: (h) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289. (i) Tian, X.; Maurya, R.; Königsberger, K.; Hudlicky, T. *Synlett* **1995**, 1125. (j) Chida, N.; Jitsuoka, M.; Yamamoto, Y. *Heterocycles* **1996**, *43*, 1385. (k) Keck, G. E.; Wager, T. T.; McHardy, S. F. *J. Org. Chem.* **1998**, *63*, 9164. (l) Keck, G. E.; McHardy, S. F. *J. Org. Chem.* **1999**, *64*, 4465. (m) Acena, J. L.; Arjona, O.; Leon, M. L.; Plumet, J. *Org. Lett.* **2000**, *2*, 3683. Narciclasine: (n) Rigby, J. H.; Mateo, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 12655. (o) Gonzalez, D.; Martinot, T.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3077. (p) Keck, G. E.; Wager, T. T. Rodriguez, J. F. D. *J. Am. Chem. Soc* **1999**, *121*, 5176. Lycoricidine: (q) Ohta, S.; Kimoto, S. *Tetrahedron Lett.* **1975**, *23*, 2279. (r) Ohta, S.; Kimoto, S.; *Chem. Pharm. Bull.* **1976**, *24*, 2977. (s) Paulsen, H.; Stubbe, M. *Tetrahedron Lett.* **1982**, *23*, 3171. (t) Paulsen, H.; Stubbe, M. *Liebigs Ann. Chem.* **1983**, 535. (u) Ogawa, S.; Ohtsuka, M.; Chida, N *Tetrahedron Lett.* **1991**, *32*, 4525. (v) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694. (w) Martin, S. F.; Tso, H. H. *Heterocycles* **1993**, *35*, 85. (x) Ogawa, S.; Chida, N. *J. Org. Chem.* **1993**, *58*, 4441. (y) Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108.

(5) For aziridinations using Yamamoto's reagent, see: (a) Evans, D. E.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (b) Knight, J. G.; Muldowney, M. P. *Synlett* **1995**, 949.

(6) Hudlicky, T.; Olivo, H. F. *Tetrahedron Lett.* **1991**, *32*, 6077.

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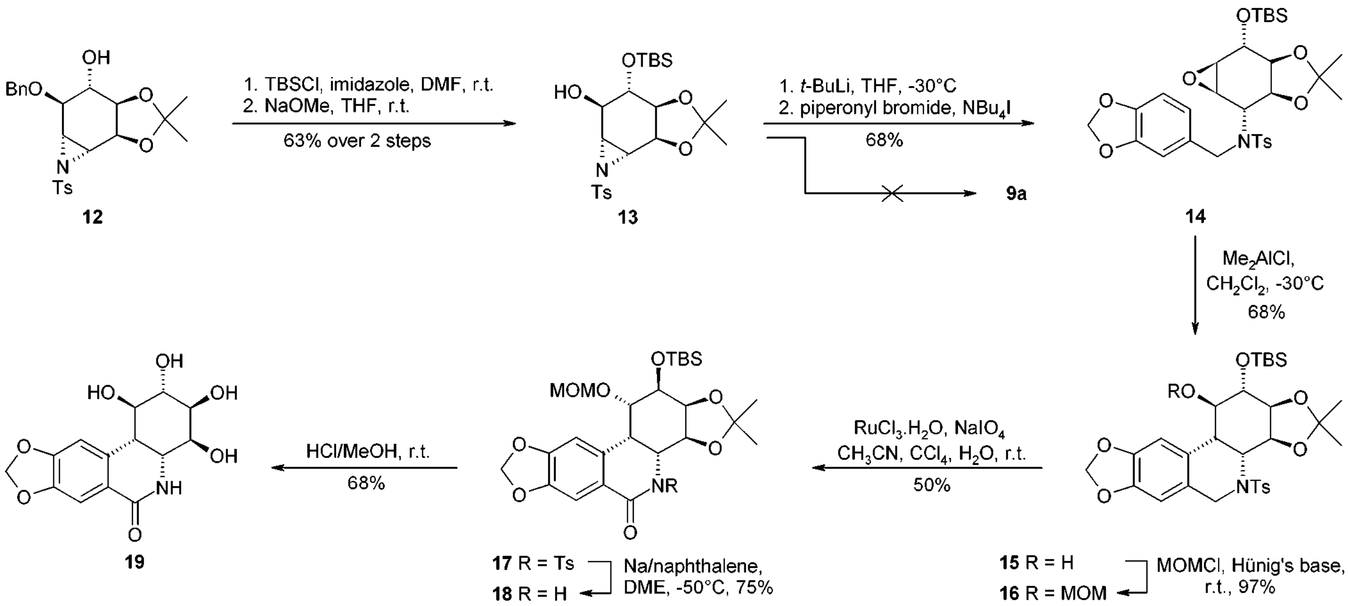
(9) Gauthier, D. R.; Bender, S. L. *Tetrahedron Lett.* **1996**, *37*, 13.

(10) Schilling, S.; Rinner, U.; Chan, C.; Ghiviriga, I.; Hudlicky, T. *Can. J. Chem.* **2001**, *79*, 1659.

(11) (a) Lohray, B. B. *Synthesis* **1992**, 1035. (b) Byun, H. S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.

(12) (a) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655. (b) For application of cyclic sulfates in the synthesis of pancratistatin, see ref 4d. (c) To our knowledge this is the first example of chemoselective opening of cyclic sulfate (or sulfite) over aziridine.

**Scheme 4.** Preparation of *epi*-7-Deoxypancratistatin



and tested the acid-catalyzed opening of the azirdine, but all attempts resulted in the cleavage of the piperonyl group only. On the other hand, epoxyconduramine **14** underwent a smooth cyclization with $Me_2AlCl$ to furnish the phenanthridone core of the alkaloid in **15** with α-stereochemistry at 10b. This observation suggests that the tosylamide is less prone to protonation and ejection by the *p*-situated oxygen in the piperonyl unit than the ether moiety in **9**. The successful cyclization of **14** also validates, in principle, the original strategy of Haseltine who designed an approach to *cis*-phenanthridone by the cationic aromatic cyclization of a piperonyl unit—in his case an unexpected migration occurred.[13] This material (**15**) was protected prior to $RuCl_3$/$NaIO_4$ oxidation, reductive detosylation, and final hydrolysis to furnish the *cis*-epimer of 7-deoxypancratistatin (**19**) in ∼4% overall yield over 12 steps.

The fully deprotected product **19** had an $R_f$ value of 0.1 (chloroform/methanol 4:1), less than that of 7-deoxypancratistatin ($R_f$ value of 0.30 in the same solvent mixture). This compound, previously unknown, has been submitted for testing with the cell lines used for pancratistatin and its congeners. Last, the fact that H-10b is disposed γ to a crotyl amide moiety extends the possibility of epimerization at this center either at the fully protected stage of **17** or at the stage of the fully hydroxylated **19**. Should this prove feasible, the route described above could be adopted for the synthesis of the natural trans-series, especially in view of the fact that **14** is available in only six steps via acylnitroso Diels—Alder addition strategy and epoxidation of the resulting conduramine as previously described.[6,14] Finally, the interesting chemoselectivity of opening of cyclic sulfates over aziridines may be extrapolated to similar systems containing oxiranes. Such endeavors will be reported in due course.

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[13] Doyle, T. J.; Hendrix, M.; Haseltine, J. *Tetrahedron Lett.* **1994**, *35*, 8295.

[14] Tian, X.; Hudlicky, T. Unpublished results.