

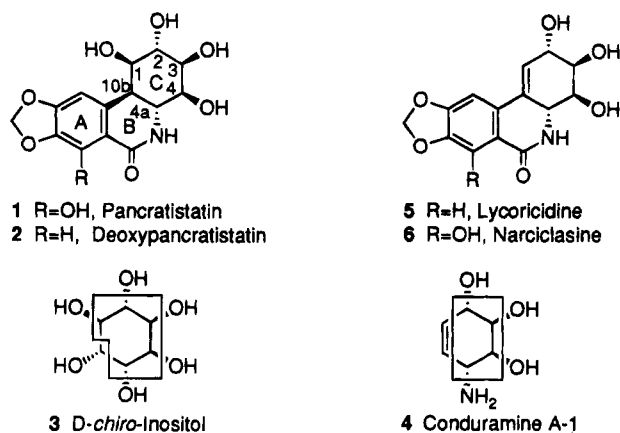
First Enantioselective Total Synthesis of (+)-Pancratistatin: An Unusual Set of Problems

Xinrong Tian, Tomas Hudlicky,* and Kurt Königsberger

Department of Chemistry
Virginia Polytechnic Institute and
State University, Blacksburg, Virginia 24061

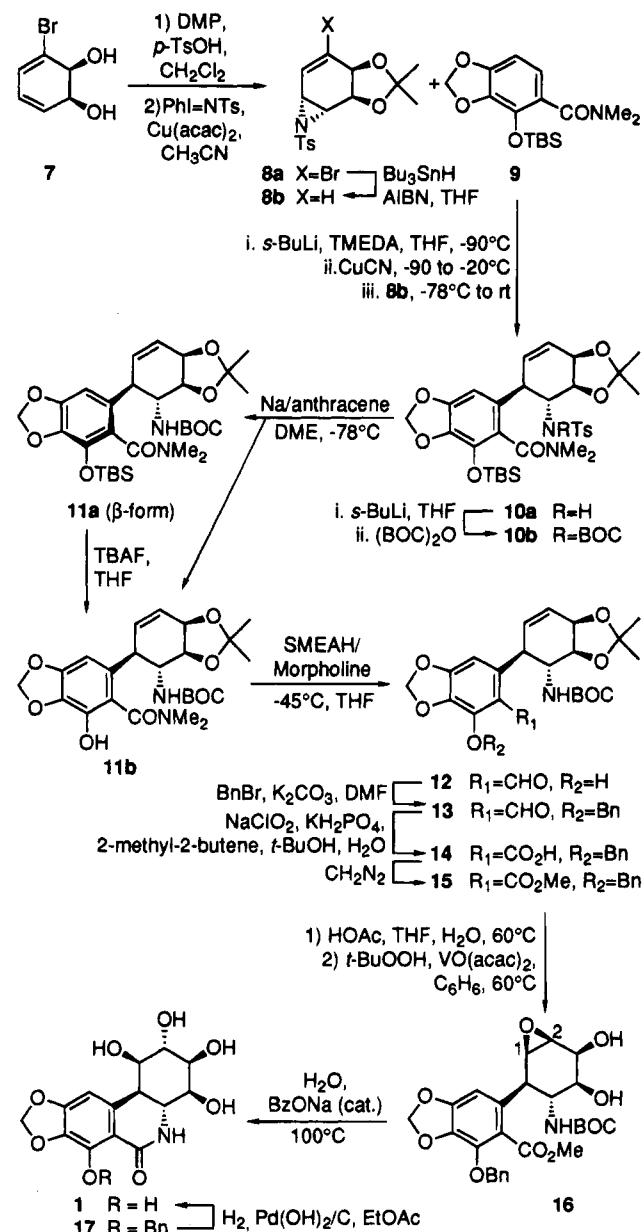
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Pancratistatin **1**, a member of the *Amaryllidaceae* group of alkaloids that have been used in herbal folk medicine since ancient Greek times,¹ was isolated by Pettit and co-workers from the root of the Hawaiian plant *Pancreatium littorale*.² To date only one synthesis of racemic pancratistatin, by Danishefsky, has been achieved,³ although a number of syntheses of lycoricidine, a congener of pancratistatin, have been reported.⁴ Approaches to pancratistatin abound in the literature,⁵ driven no doubt by the promising antimetabolic activities associated with the title alkaloid.^{2c} The established spectrum of biological activity of pancratistatin includes inhibition of protein synthesis and antineoplastic activities in ovarian sarcoma and lymphocytic leukemia.^{2c} Its natural abundance is low (0.039% of the dry weight of ground roots of *P. littorale*),^{2c} and completion of the biological screening would benefit from an efficient synthesis of this compound.



We approached the challenge by recognizing the configura-

Scheme 1



tional similarity between **1** and both D-chiro-inositol (**3**)⁶ and conduramine A-1 (**4**),⁷ as well as lycoricidine (**5**).⁸ All three compounds yielded to efficient syntheses in our laboratories starting with the protected diene diol **7**, which contains the *cis*-diol unit common to all of the compounds. The *trans*-diol unit in **1** could be reliably introduced via epoxide hydrolysis as demonstrated in the synthesis of D-chiro-inositol,⁶ and the *anti*-disposition of hydroxyl and amino groups in pancratistatin, lycoricidine, and conduramine A-1 would be expected to result from the directing effect imposed by the protected *cis*-diol in **7**. Diol **7**, now also commercially available,^{9a} is prepared by whole-cell oxidation of bromobenzene with *Pseudomonas putida* 39/D.^{9b,c} The pivotal issue of synthetic design for the title compound therefore reduced to the attachment of the aryl moiety to C-10b in a stereocontrolled fashion.

* To whom correspondence should be addressed at the Department of Chemistry, University of Florida, Gainesville, FL 32611-7200.

(1) Hartwell, J. L. *Lloydia* **1967**, *30*, 379.
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To this end we chose to examine the receptiveness of vinylaziridines **8** toward organometallic reagents derived from amide **9**, Scheme 1. Tosylaziridine **8a** was generated according to the procedure of Evans¹⁰ and was subsequently reduced to **8b** ($\text{Bu}_3\text{SnH/AIBN}$, THF, 78%). A preliminary study of the general tendencies of such a system toward $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}2'$ opening with organometallic reagents was undertaken for the parallel series of aziridines **8a** and **8b**, and the results were compared to those for the corresponding oxiranes.¹¹ Conditions have been developed to furnish either $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}2'$ opening. We found that higher-order phenyl cyanocuprate¹² afforded exclusively the desired $\text{S}_{\text{N}}2$ opening of **8b** in spite of the shielding of the β -face by the acetamide.

Amide **9** was subjected to ortho-metalation below -90°C by means of Snieckus's protocol¹³ and converted *in situ* into the lithium cyanocuprate species $\text{Ar}_2\text{Cu}(\text{CN})\text{Li}_2$,¹² whose addition to **8b** produced cleanly the tosylamide **10a** (75%). This compound was formed almost exclusively as one atropisomer (*vide* NMR and TLC), which slowly equilibrated at room temperature to its more stable form (presumably the α -form of the atropisomer as shown for **11a**). The synthesis took a difficult turn at this point. First, the transamidation procedure reported by Heathcock for a model system^{5c} and applied to amide **10c**¹⁴ did not yield positive results because of the greatly enhanced acidity of the C-10b proton and concomitant epimerization resulting from the treatment of **10c** with *s*-BuLi at low temperature. Second, attempts to functionalize the olefin in **10a** failed as a consequence of the hindrance imposed on the α -face by the dimethylamide moiety. Third, the ortho-disubstituted dimethylamide did not yield to hydrolysis even under conditions detrimental to the oxygenation of the C-ring. Fourth, reduction of the dimethylamide moiety in **10a** to the aldehyde¹⁵ and Jones oxidation gave the tosylactam **10d**.¹⁶ Unfortunately, all attempts to reductively remove the tosyl group resulted in the reduction of the benzamide to **10e**.¹⁶ The above problems were circumvented, albeit at the expense of reduced efficiency. Tosylamide **10a** was first converted to BOC derivative **10b** (68%), and reductive desotylation was then performed at this stage ($\text{Na}/\text{anthracene}/\text{DME}$, 82%).¹⁷ With this particular reagent, the α -atropisomer underwent smooth desotylation and desilylation to furnish **11b**, whereas the β -atropisomer gave only desotylation product **11a**, which was isolated and subjected to TBAF treatment to afford **11b** (93%). Reduction of the dimethylamide with modified sodium bis(methoxyethoxy)-

(9) (a) Available from Eastman Fine Chemical, Rochester, NY, and Genencor International, Inc., South San Francisco, CA. (b) For laboratory scale fermentation, see: Hudlicky, T.; Boros, E. E.; Boros, C. H. *Synthesis* **1992**, 174. (c) Gibson, D. T.; Hensley, M.; Yosioka, H.; Mabry, T. J. *Biochemistry* **1970**, 9, 1626.

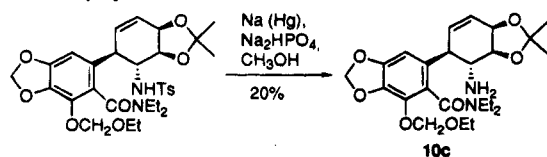
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(14) Treatment of **10c** (prepared in a similar fashion to **10a**) with *s*-BuLi resulted in only epimerization at C-10b.



(15) Kanazawa, R.; Tokoroyama, T. *Synthesis* **1976**, 526.

aluminum hydride to aldehyde **12** (72%)¹⁵ and protection of the phenol afforded **13** (83%), which was oxidized (NaClO_2 , KH_2PO_4 , 2-methyl-2-butene, *t*-BuOH, H_2O)¹⁸ to acid **14** and converted to methyl ester **15** in 98% yield. Attempts to epoxidize this substance to furnish the α -epoxide failed under a variety of conditions, again as a result of the atropisomerism and the effective blocking of the α -face of the molecule by the methyl ester and BOC groups. Deprotection ($\text{HOAc}/\text{THF}/\text{H}_2\text{O}$, 2:1:1, 73%) and $\text{VO}(\text{acac})_2$ -catalyzed *t*-BuOOH epoxidation¹⁹ on the β -face, directed by the free hydroxyl, afforded the β -epoxide **16** (53%). In this epoxide, only the C-2 site is available to diaxial opening by nucleophiles. The nearly neutral conditions (H_2O , sodium benzoate (catalyst), 100°C , 6 days) adapted from the *D*-chiro-inositol preparation^{6a} accomplished, in addition to the stereospecific epoxide opening, a quite remarkable series of events: thermal cleavage of the BOC group and cyclization to the lactam, as well as debenzoylation to the title compound in 51% yield. Alternatively, when stopped after 48 h, this reaction led to benzyl-protected pancratistatin **17** (80%), which was then quantitatively hydrogenated to **1**. Thus the total synthesis of (+)-pancratistatin, found identical to the natural material (^1H NMR, $R_f = 0.40$, $\text{CHCl}_3/\text{CH}_3\text{OH}$, 4:1), $[\alpha]_D^{25} = +41^\circ$ ($c = 1.0$, DMSO) [lit.^{2b} $[\alpha]_D^{34} = +48^\circ$ ($c = 1.0$, DMSO)], has been achieved in 13 steps and with an overall yield of 2%.

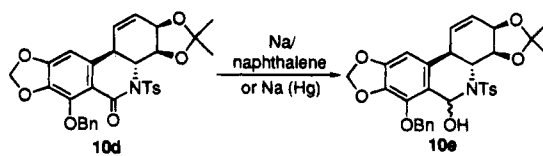
In summary, this synthesis demonstrated several anomalies of modern synthetic chemistry. More than half of the effort has been expended on the manipulation of the benzamide and the tosylamide moieties required for the coupling. Although eminently useful in ortho-metalation, the benzamide and the methods of its subsequent transformations have been found incompatible with the use of sensitive functional groups. Efforts are now under way to eliminate the use of both of these functionalities and to furnish a shorter synthesis of pancratistatin in a more practical fashion. These endeavors will be reported in the near future.

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Supplementary Material Available: Experimental procedures and spectral data for compounds **9**, **10a-c**, **11a,b**, **12**, **13**, **15-17**, and **1** (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(16) Reduction of the lactam carbonyl group in **10d** apparently relieves the ring strain, rendering **10d** more reactive toward formation of the stabilized radical anion at the benzamide site.



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