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Total Synthesis of 7-Deoxypancratistatin-1-carboxaldehyde and Carboxylic Acid via Solvent-Free Intramolecular Aziridine Opening: Phenanthrene to Phenanthridone Cyclization Strategy

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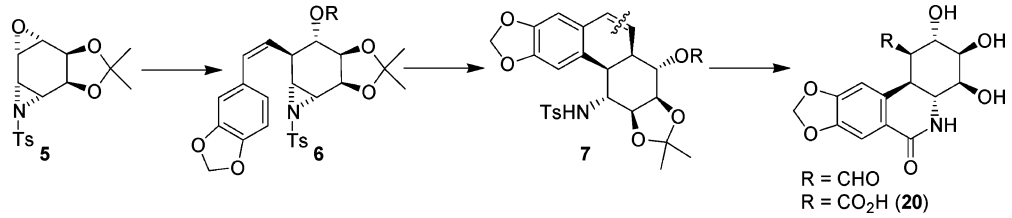
ABSTRACT



Solid-state silica-gel-catalyzed opening of aziridine 6 provided phenanthrene 7, whose oxidative cleavage, recyclization, and further elaboration furnished the C-1 aldehyde and carboxylic acid derivatives of 7-deoxypancratistatin for potential analogue synthesis.

Since the first asymmetric synthesis of pancratistatin that we published in 1995,[1] we have devoted considerable effort to multigenerational design of and improvements[2] in approaches to the total synthesis of Amaryllidaceae constituents[3] and their unnatural derivatives.[4] In collaboration with Pettit's group at Arizona State University, we have focused on designs to produce a variety of derivatives[5] containing the minimum pharmacophore but with better bioavailability or solubility than the otherwise very potent natural products such as pancratistatin (**1**), narciclasine (**2**), or their 7-deoxy analogues 7-deoxypancratistatin (**3**) and lycoricidine (**4**). These constituents are shown in Figure 1 along with an indication of the structural requirements for activity as elucidated through the efforts of Pettit and others.[6]

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(1) (a) Tian, X.; Hudlicky, T.; Koenigsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643. (b) Hudlicky, T.; Tian, X.; Koenigsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752.

(2) For improved preparations see: (a) Tian, X.; Maurya, R.; Konigsberger, K.; Hudlicky, T. *Synlett* **1995**, 1125 (7-deoxypancratistatin). (b) Akgun, H.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3081 (*ent*-7-deoxypancratistatin). (c) Gonzalez, D.; Martinot, T.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3077 (narciclasine). (d) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694 (lycoricidine). (e) Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108 (lycoricidine). (f) Rinner, U.; Siengalewicz, P.; Hudlicky, T. *Org. Lett.* **2002**, *4*, 115 (epi-7-deoxypancratistatin).

(3) For reviews on synthesis of Amaryllidaceae constituents see: (a) Chapleur, Y.; Chretien, F.; Ahmed, S. I.; Khaldi, M. *Curr. Org. Syn.* **2006**, *3*, 341. (b) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365. (c) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 606. (d) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, pp 323−424. (e) Polt, R. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed; JAI Press: Greenwich, CT, 1997; Vol. 3, p 109. (f) Martin, S. F. In *The Alkaloids*; Brossi, A. R., Ed.; Academic Press: New York, 1987; Vol. 40, p 251. (g) Fuganti, C. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. 10, Chapter 3, pp 83−164. (h) Wildman, W. C. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1968; Chapter 10, pp 307−406. (i) Cook, J. W.; Loudon, J. D. In *Alkaloids of the Amaryllidaceae*, *The Alkaloids*; Manske, R. H. F., Holmes, H. L., Eds.; Academic Press: New York, 1952; Vol. II, Chapter XI, pp 331.

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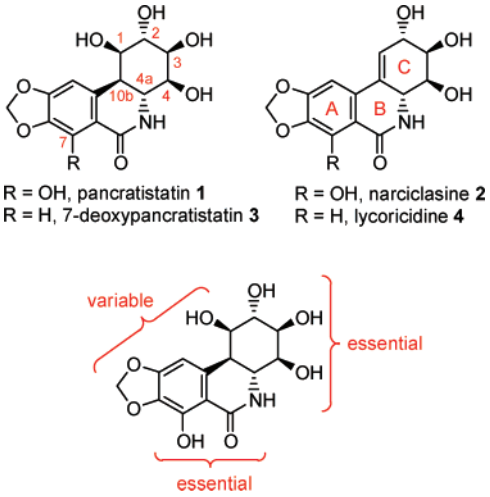


Figure 1. Pancratistatin and congeners; the structural and functional requirements for a minimum pharmacophore.

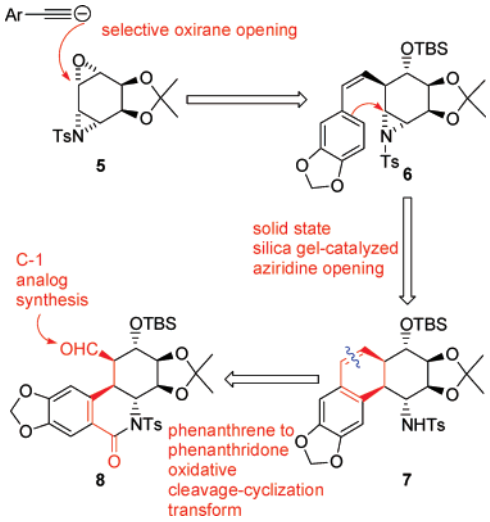


Figure 2. Design strategy toward 7-deoxypancratistatin and its C-1 analogues based on oxidative cleavage of the phenanthrene core and recyclization to the phenanthridone.

Pancratistatin and narciclasine are highly active against many cancer cell lines: murine P388 lymphocytic leukemia; human cancer cells: pancreas BXPC-3, breast MCF-7, CNS SF-268, lung NCI-H460, colon KM20L2, and prostate DU-145. Although the exact mode of action remains unknown for pancratistatin, narciclasine is believed to inhibit peptide bond formation in eukaryotic ribosomes.[7] Lycoricidine and 7-deoxypancratistatin are significantly less active, probably because of the absence of the hydrogen-bonded donor−acceptor pair in the phenanthridone functionality.

As C-1 substitution does not appear to be detrimental to biological activity,[8] we considered preparation of compounds with varied functionality at this position. To this end we envisioned a new approach that would provide an aldehyde functionality at C-1, well suited for further derivatization. The new strategy, portrayed in Figure 2, is based on the recently discovered solid-state silica-gel-catalyzed opening of aziridines with carbon nucleophiles.[4c] The approach relies on the regioselective opening of epoxy aziridine **5**[9,2f] with aluminum acetylide, reduction of the alkyne to the cis olefin in **6**, solid-state cyclization to the complete phenanthrene core **7**, and oxidative cleavage with concomitant recyclization and selective oxidation to the phenathridone **8**, which possesses the complete nucleus of pancratistatin-type compounds. The recyclization strategy not only provides the C-1 aldehyde for further functionalization and production of analogues but also allows the conversion of this compound to 7-deoxypanacratistatin by a more efficient protocol than used in our previous syntheses. In this manuscript we report the total synthesis of the C-1 carboxylic acid analogue of 7-deoxypancratistatin and outline the potential of a library-type approach to C-1 derivatives from aldehyde **8**.

The synthesis began with the preparation of homochiral epoxy aziridine **5**[9] from bromobenzene by previously established protocols.[10] Selective opening of the oxirane ring was accomplished with the aluminum acetylide derived from **11**, generated *in situ*, providing after protection the silyl ether **12**. Borane reduction furnished the cis alkene **6**, which was adsorbed on silica[4c] and heated without solvent at 120 °C for 24 h to provide a 52% yield of phenanthrene **7**, as shown in Scheme 1.

Phenanthrene **7** was converted to the phenanthridol skeleton **15** either by direct ozonolysis of **7** or by a three-step procedure consisting of OsO_4-mediated oxidation to the stage of over-oxidized keto alcohol **13** (OsO_4/NMO, 89%), followed by reduction and periodate cleavage to dialdehyde **14**, which immediately cyclized to the hemiaminal **15**. The three-step procedure produced **15** in an overall yield of 82% from **7**. Oxidation with IBX provided the complete phen-

(4) See for example: (a) Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726 (truncated derivatives). (b) Rinner, U.; Hudlicky, T.; Gordon, H.; Pettit, G. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 5342 (indole-containing mimic). (c) Hudlicky, T.; Rinner, U.; Finn, K. J.; Ghiviriga, I. *J. Org. Chem.* **2005**, *70*, 3490 (indole-containing mimic). (d) Rinner, U.; Hillebrenner, H. L.; Adams, D. R.; Hudlicky, T.; Pettit, G. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2911 (truncated derivatives). (e) Ibn-Ahmed, S.; Khaldi, M.; Chretien, F.; Chapleur, Y. *J. Org. Chem.* **2004**, *69*, 6722 (lactone mimics of lycoricidine and pancratistatin).

(5) For recent library type approaches to pancratistatin derivatives by cyclotrimerization strategy see: (a) Moser, M.; Sun, X.; Hudlicky, T. *Org. Lett.* **2005**, *7*, 5669. (b) Hudlicky, T.; Moser, M.; Banfield, S. C.; Rinner, U.; Chapuis, J.-C.; Pettit, G. R. *Can. J. Chem.* **2006**, *84*, 1313.

(6) (a) Pettit, G. R.; Freeman, S.; Simpson, M. J.; Thompson, M. A.; Boyd, M. R.; Williams, M. D.; Pettit, G. R., III; Doubek, D. L. *Anti-Cancer Drug Design* **1995**, *10*, 243. (b) McNulty, J.; Larichev, V.; Pandey, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5315.

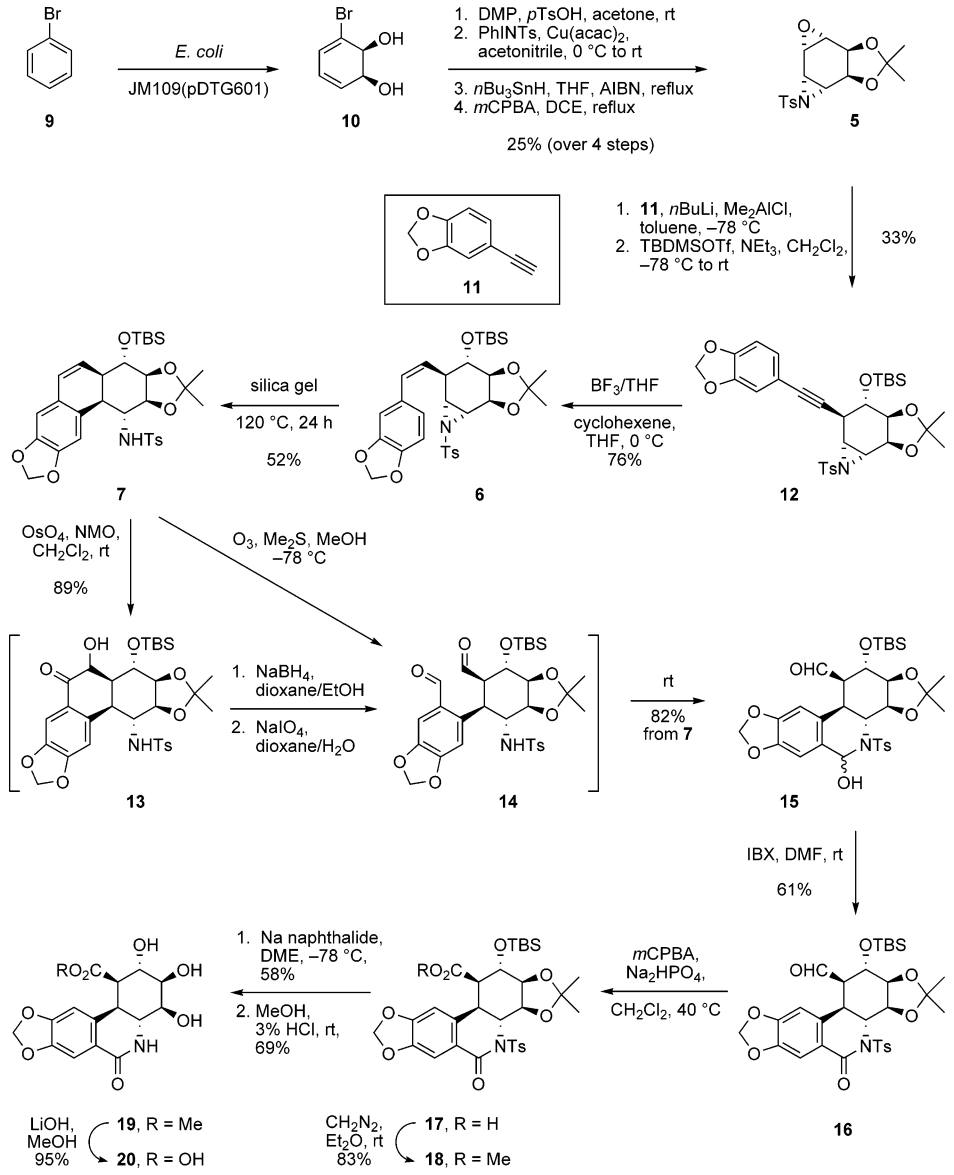
(7) Baez, A.; Vazquez, D. *Biochim. Biophys. Acta* **1978**, *518*, 95.

(8) (a) Pettit, G. R.; Melody, N.; Herald, D. L. *J. Nat. Prod.* **2004**, *67*, 322. (b) McNulty, J.; Mao, J.; Gibe, R.; Mo, R.; Wolf, S.; Pettit, G.; Herald, D.; Boyd, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 169. (c) McNulty, J.; Larichev, V.; Pandey, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5315.

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

(10) For large-scale preparation of diene diol **10** by fermentation with *Escherichia coli* JM109(pDTG601) see: Endoma, M. A.; Bui, V. P.; Hansen, J.; Hudlicky, T. *Org. Process Res. Dev.* **2002**, *6*, 525.

Scheme 1



athridone skeleton **16** in six steps from epoxy aziridine **5** or ten steps from bromobenzene. Further oxidation of the aldehyde with *m*-CPBA furnished in 85% yield the C-1 carboxylic acid **17**, which was then elaborated to the fully hydroxylated stage of **20**. Because of the polarity of the final product, subsequent preparation proceeded to the methyl ester **18**, obtained in 83% yield from acid **17** by treatment with diazomethane. Ester **18** was then converted to the fully hydroxylated species **19** by reductive detosylation and deprotection prior to the final hydrolysis with LiOH in MeOH. The synthesis of the C-1 acid proceeded in 15 steps from bromobenzene.

Future efforts will focus on the conversion of **19** by oxidative decarboxylation[11] to the conduramine derivative **21**, a compound whose *N*-methoxybenzyl derivative has been converted to 7-deoxypancratistatin,[12] Figure 3. Aldehyde **16**

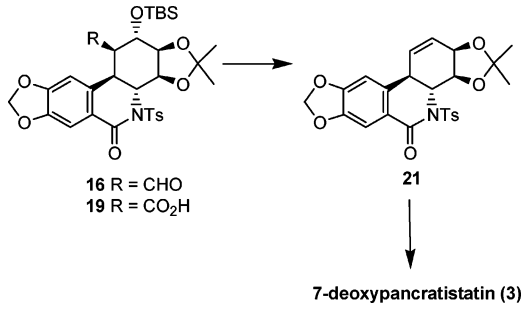


Figure 3. Conversion of C-1 carboxylic acid to 7-deoxypancratistatin.

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(12) Padwa, A.; Zhang, H. *J. Org. Chem.* **2007**, *72*, 2570.

will be subjected to reductive amination protocols, and the acquired derivatives will be tested for biological activities and improved solubility. We will report on these endeavors in due course.

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Supporting Information Available: Experimental procedures and spectral data for key compounds **12**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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