Studies on the Narciclasine Alkaloids: Total Synthesis of (+)-Narciclasine and (+)-Pancratistatin

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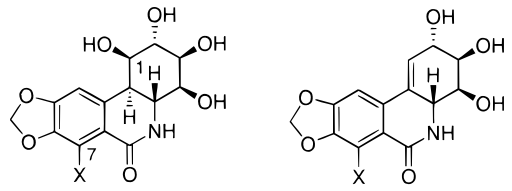
Received March 15, 2000. Revised Manuscript Received May 17, 2000

Abstract: Enantioselective total syntheses of the antitumor alkaloids, (+)-narciclasine and (+)-pancratistatin, are reported. These syntheses feature a stereo- and regiocontrolled aryl enamide photocyclization to construct a common, advanced intermediate possessing a trans-fused BC substructure. Differential functional group interchange in the C-ring of this phenanthridone core structure allows for the production of the two target natural products in enantiomerically pure form.

The Amaryllidaceae alkaloid (+)-pancratistatin (**1a**) was first isolated from the roots of *Pancratium littorale* by Pettit and co-workers in 1984 as part of a systematic search for natural products that exhibit anticancer activity.[1] Recent studies have shown that this substance exhibits a range of antineoplastic properties, including activity against murine P-5076 ovarian sarcoma and P-388 lymphocytic leukemia.[2] No detailed examination of the molecular basis of this activity has been conducted, but work on structurally related narciclasine (**2a**) has suggested that these compounds could act by disrupting protein biosynthesis in eukaryotic organisms.[3]



1a, X=OH
1b, X=H

2a, X=OH
2b, X=H

The promising biological activity and limited availability of this series of highly oxygenated phenanthridone alkaloids has stimulated considerable synthetic work in which the first total synthesis of (±)-pancratistatin was recorded by Danishefsky and Lee in 1989,[4] and the first asymmetric synthesis of the natural enantiomer of this material was reported in 1995 by Hudlicky,[5] followed in the same year by work by Trost and Pulley.[6] More recently, Haseltine[7] and Magnus[8] have successfully achieved syntheses of this alkaloid, as well. The pancratistatin congeners 7-deoxypancratistatin (**1b**),[9] narciclasine (**2a**),[10] and lycoricidine (**2b**)[11] have also garnered considerable attention from the synthetic community. Despite the successes cataloged above, it is clear from the considerable effort expended by numerous research groups over many years that members of this family of alkaloids remain particularly formidable targets for organic synthesis.[12] Indeed, they possess deceptively simple molecular structures that present a number of challenges to the capabilities of contemporary synthesis. The principal hurdles to synthesis include elaboration of the fused BC ring system and the stereocontrolled installation of the hydroxyl functions located around the perimeter of the C-ring moiety. We now wish to report on the successful synthesis of both (+)-pancratistatin (**1a**) and (+)-narciclasine (**2a**) from a common advanced phenanthridone intermediate.[13] Our strategy into these interesting target molecules is depicted in Scheme 1.

The key transformation upon which our entry into both compounds is predicated is the hydrogen bond controlled aryl enamide photocyclization (**3** → **4**), which should result in the desired trans-locked advanced intermediate **4**.[14] The requisite enamide precursor for this crucial reaction would be assembled by addition of a metalated arene to the protected, enantiomeri-

(1) (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.

(2) 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.

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(6) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143.

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(8) (a) Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341. (b) Magnus, P.; Sebhat, I. K. *Tetrahedron* **1998**, *54*, 15509.

(9) (a) Tian, X.; Maurya, R.; Königsberger, K.; Hudlicky, T. *Synlett* **1995**, 1125. (b) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289. (c) Chida, N.; Sitsuoka, M.; Yamamoto, Y.; Ohtsuka, M.; Ogawa, S. *Heterocycles* **1996**, *43*, 1385. (d) Keck, G. E.; Water, T. T.; McHardy, S. F. *J. Org. Chem.* **1998**, *63*, 9164.

(10) (a) Gonzalez, D.; Martinot, T.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3077. (b) Reference 13.

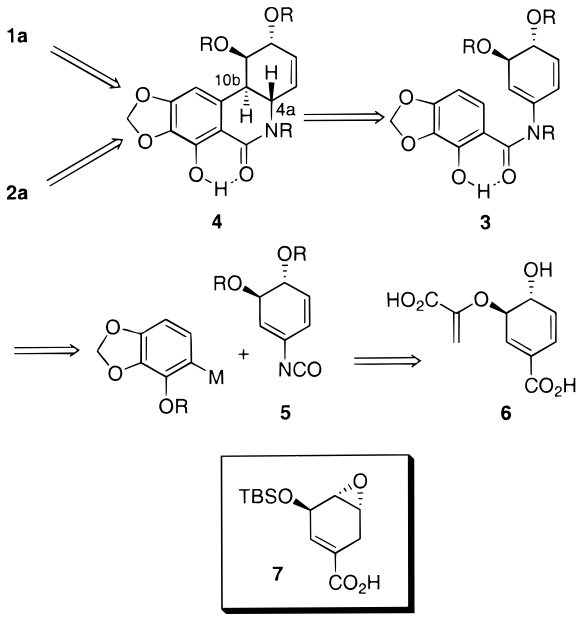
(11) (a) Paulsen, H.; Stubbe, M. *Justus Liebigs Ann. Chem.* **1983**, 535. (b) Chida, N.; Ohtsuka, M.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 4525. (c) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694. (d) Martin, S. F.; Tso, H.-H. *Heterocycles* **1993**, *35*, 85. (e) Chida, N.; Ohtsuka, M.; Ogawa, S. *J. Org. Chem.* **1993**, *58*, 4441. (f) Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108. (g) Keck, G. E.; Wage, T. T. *J. Org. Chem.* **1996**, *61*, 8366.

(12) For an informative discussion of the synthetic problems presented by pancratistatin and its congeners, see: Polt, R. In *Organic Synthesis Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 3, p 109.

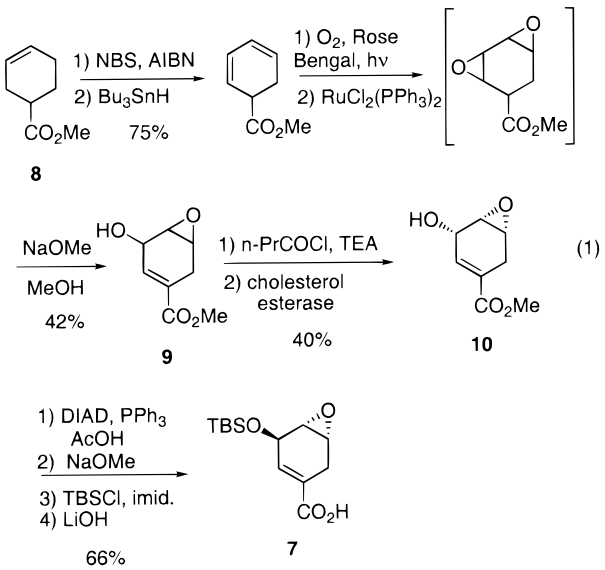
(13) For a preliminary account of the first synthesis of (+)-narciclasine, see: Rigby, J. H.; Mateo, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 12655.

10.1021/ja000930i CCC: $19.00
Published on Web 06/29/2000

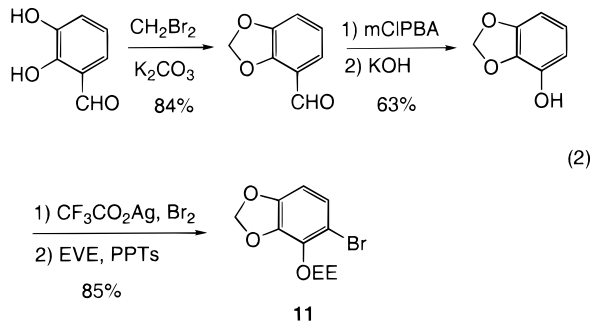
Scheme 1



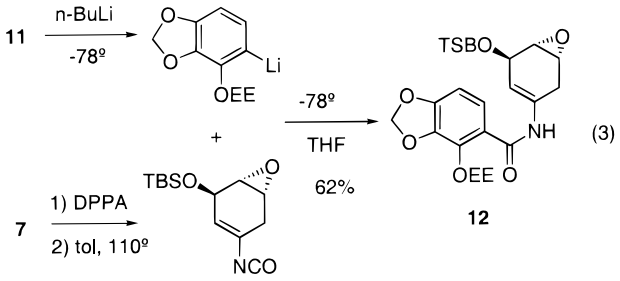
cally pure vinyl isocyanate **5**,[15] which in turn would be derived from (−)-chorismic acid (**6**) or one of its derivatives. The production of the correct relative stereochemistry at $C_{4a}-C_{10b}$ during the photocyclization was anticipated based on several observations made by Haslam and co-workers indicating that external reagents often attack the α,β-unsaturated acid moiety of chorismate from the β-direction.[16] This assumption was destined not to be tested directly during our investigations since it was quickly established in early model studies that the diene unit of chorismate was not compatible with the photocyclization conditions required for the B-ring assembly.[17] Instead, a surrogate for chorismate, epoxy acid **7**, in which the diene functionality was present in masked form, was selected for this purpose. This material was expected to participate in the key B-ring forming event without incident and then be amenable to tetraol elaboration at a later point in the synthesis. Indeed, **7** was a key intermediate used by Berchtold in his excellent synthesis of (−)-chorismic acid itself.[18]



Following a sequence essentially as described by Berchtold,[18] the commercially available ene ester **8** was transformed into the racemic *syn*-epoxy alcohol **9** in serviceable overall yield. Esterification followed by enzymatic resolution of the resultant butyryl ester with cholesterol esterase gave the corresponding enantiomerically pure *syn*-epoxy alcohol **10** in 40% isolated yield. Inversion of the alcohol under Mitsunobu conditions provided the protected trans-epoxy alcohol **7** after ester saponification.



The A-ring building block common to both pancratistatin and narciclasine was prepared in straightforward fashion from commercial 2,3-dihydroxybenzaldehyde using a literature procedure.[19] The choice of phenol protection was particularly critical at this stage of the synthesis, since it had to be robust enough to survive the subsequent metalation-addition steps and yet be removed under conditions sufficiently mild to not jeopardize the relatively fragile enamide function prior to photocyclization. After some experimentation it was found that the ethoxy ethyl group satisfied both of these criteria. With each of the segments of the cyclization precursor now in hand, coupling was achieved in the following fashion. Compound **11** was metalated with n-BuLi at −78 °C and then combined with a solution of the preformed vinyl isocyanate derived from acid **7** to afford enamide **12** in 62% yield (eq 3).



At this juncture in the synthesis, several significant features of the projected photocyclization step had to be addressed. Of paramount importance to the success of our endeavor was the notion of controlling the regiochemical course of the ring forming event by exploiting a hydrogen bond between the phenolic alcohol and the amide carbonyl oxygen that would restrict rotation around the aryl-amide carbonyl bond as depicted

(14) For a review of aryl enamide photocyclizations, see: Ninomiya, I.; Naito, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. XXII, p 189.

(15) For an overview of vinyl isocyanate chemistry, see: Rigby, J. H. *Synlett* **2000**, 1.

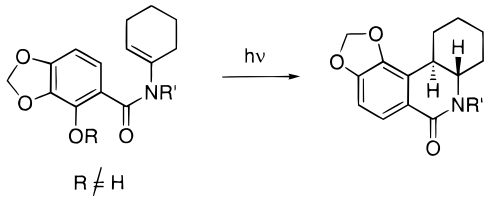
(16) Ife, R. J.; Ball, L. F.; Lowe, P.; Haslam, E. *J. Chem. Soc., Perkin Trans 1* **1976**, 1776.

(17) Gupta, V., WSU. Unpublished results.

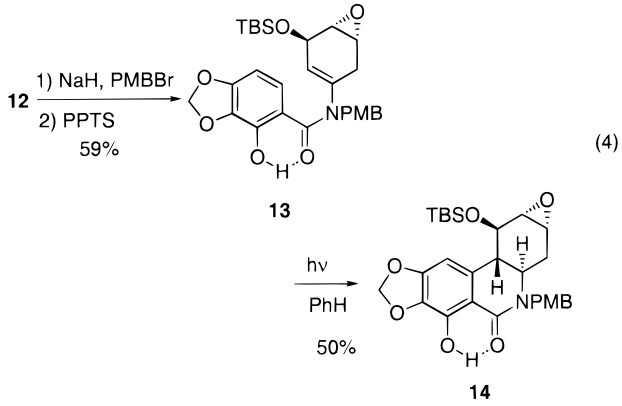
(18) (a) McGowen, D. A.; Berchtold, G. A. *J. Org. Chem.* **1981**, *46*, 2381. (b) Hoare, J. H.; Policastro, P. P.; Berchtold, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 6264. (c) Pawlak, J. L.; Berchtold, G. A. *J. Org. Chem.* **1987**, *52*, 1765.

(19) Brown, E.; Loriot, M.; Robin, J. P. *Tetrahedron Lett.* **1982**, *32*, 949.

Scheme 2



in Scheme 1. This type of conformational control was necessary because ample literature precedent indicated that photocyclization of related *o-alkoxy*-substituted enamides resulted in a bond formation that occurred at the *ipso* arene carbon (Scheme 2).[14] Indeed, early model studies in our own laboratory confirmed that this reaction pathway prevailed in phenanthridone precursors possessing *o-alkoxy*-substituents on the arene moiety.[20] In addition to these concerns, model studies from our laboratory also revealed that it was necessary for the amide nitrogen to exhibit a non-hydrogen substituent for successful photocyclization to occur, presumably due to unfavorable rotamer populations in the secondary amide.[20] It is also possible that N-alkyl substitution also serves to stabilize putative intermediates in the photocyclization process. In light of these observations, compound **12** was processed to give cyclization precursor **13** as shown in eq 4. Although a number of candidates for this



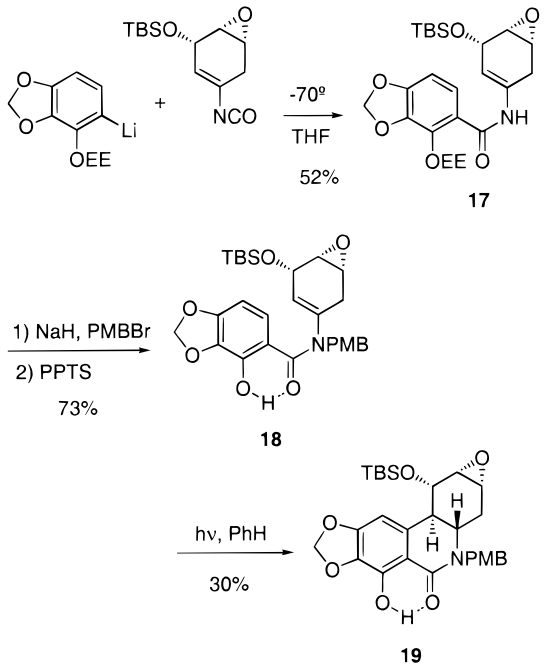
(4)

N-protection was considered, PMB protection was ultimately selected so as to provide for maximum flexibility during the removal process in the eventual "end-game" of the synthesis. The crucial B-ring formation was now at hand.

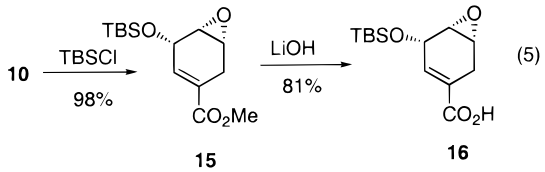
Irradiation of a dilute (0.2 M) solution (benzene) of **13** (Rayonet reactor at 254 nm; 5 °C) afforded a cyclized product **14** in which the incorrect trans ring fusion had been formed exclusively. This disappointing result indicated that the notion of extending the chorismate conformational behavior to the very different trans-epoxy alcohol system of compound **13** was, in fact, faulty, and a new plan of attack had to be devised.

This problem was quite easily remedied since it was anticipated that the corresponding *syn*-epoxy alcohol would lead to the correct ring fusion stereochemistry during the photolysis. Furthermore, it was expected that the α-oriented hydroxyl group present at C_1 in the resulting phenanthridone product could be inverted to provide the correct *β*-configuration at that center. A related inversion was performed in the Trost/Pulley synthesis of pancratistatin.[6] It was also reasoned that a syn relationship between the C_1 hydroxyl and the proton at C_{10b} would facilitate dehydration to give the corresponding unsaturated intermediate from which narciclasine could be prepared. Thus, protection and saponification of **10** gave the requisite enantiomerically pure

Scheme 3



C-ring precursor **16** and the stage was set for a second attempt at the key photocyclization.



(5)

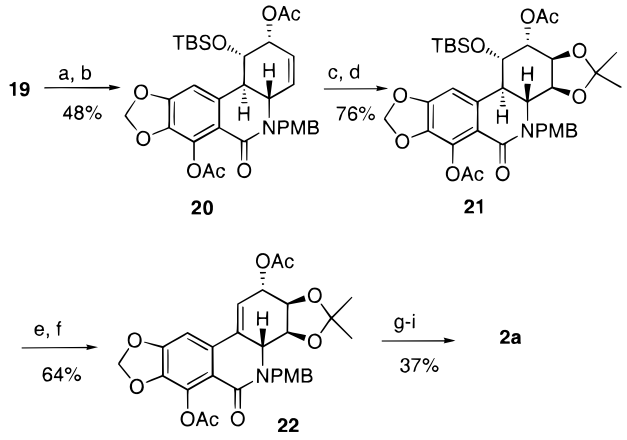
Conversion of carboxylic acid **16** into the corresponding isocyanate via Curtius rearrangement of the corresponding acyl azide as before followed by addition of the aryllithium derivative of bromide **11** gave enamide **17** in 52% yield, and further conversion into the requisite photosubstrate **18** proceeded without incident (Scheme 3). Irradiation of **18** followed under standard conditions to give phenanthridone **19** in 30% yield (60% based on recovered starting material), which possessed the desired trans relationship between the C_{4a} and C_{10b} centers. High-field ^{1}H NMR analysis revealed that the proton at C_{10b} exhibited the expected trans diaxial coupling with both C_1 and C_{4a} (13 and 9 Hz), confirming that the necessary ring junction had been obtained. It should be noted that considerable effort was expended to identify an alternative solvent system in which to conduct this reaction, since it was believed that the low conversions observed above were due to preferential light absorption by benzene. Unfortunately, no other satisfactory solvent surfaced during this study and attempts to improve conversion efficiency using other wavelengths of light also failed. Consequently, the recovered starting material had to be recycled. With the successful production of **19**, the stage was now set to effect separate conversions from this common intermediate into the (+)-pancratistatin and (+)-narciclasine targets.

The preparation of narciclasine was pursued first (Scheme 4). Thus, treatment of phenanthridone **19** with diphenyldiselenide/$NaBH_4$ and then H_2O_2[21] installed the requisite C_3-C_4 unsaturation, and acylation of the free hydroxyl groups in this material furnished compound **20**. Stereoselective cis-dihydroxy-

(20) Rigby, J. H.; Gupta, V. *Synlett* **1995**, 547 and references therein.

(21) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

Scheme 4



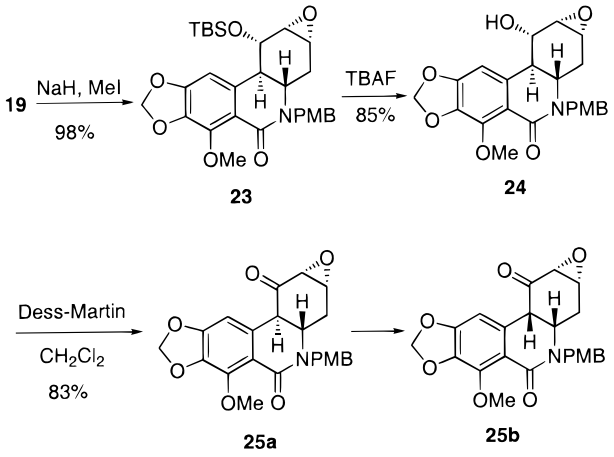
a) $(PhSe)_2$, $NaBH_4$, Ox; b) NaH, AcCl; c) OsO_4, TMNO, t-BuOH; d) TsOH, $(Me)_2C(OMe)_2$; e) F^-, THF; f) Burgess Rgnt; g) K_2CO_3 MeOH; h) n-BuLi, THF, O_2; i) TsOH

lation and protection of the resultant diol as the acetonide followed to give **21** in 75% yield. The alkene function required at C_1 was then introduced by selective deprotection of the hydroxyl group at C_1 with fluoride followed by dehydration mediated by the Burgess reagent[22] in refluxing benzene. This set of transformations afforded compound **22** in good yield.

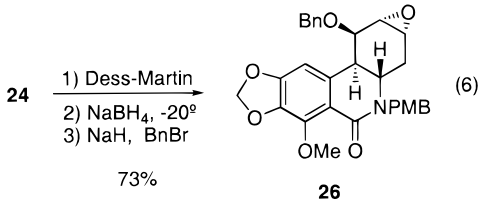
The synthesis end-game consisted of a series of deprotection steps, the most difficult of which proved to be the removal of the PMB group from the lactam nitrogen. Several of the usual oxidative methods for this purpose failed; however, an intriguing procedure for selective removal of amide *N*-benzyl protection devised by Williams[23] proved to be more successful. Thus, saponification of the acetates in **21** followed by treatment of the resultant product with excess BuLi and dry oxygen provided the free amide after workup. Routine acid hydrolysis of the acetonide gave (+)-narciclasine ($[\alpha]^{25}_D$ 141.8°, lit.[24] $[\alpha]^{25}_D$ 142.8°; mp 248 °C dec, lit.[24] mp 250−252 °C dec) in 37% overall yield. In addition, the synthetic material was identical (^{1}H NMR and ^{13}C NMR) to a sample of the natural product provided by the National Cancer Institute.

With narciclasine in hand, our attention then turned to completing the synthesis of pancratistatin. Each of the anticipated methods for addressing the projected inversion of the C_1 alcohol in phenanthridone **19** would require prior protection of the phenolic hydroxyl group and deprotection of the C_1 hydroxyl group. These two objectives were easily achieved in straightforward fashion on **19** to yield **24** as shown in Scheme 5, and a detailed examination of the alcohol inversion process was then initiated. Unfortunately, exposing compound **24** to the classic Mitsunobu conditions (DEAD, PPh_3, $PhCO_2H$) provided only starting material. However, an alternative approach was envisioned that would involve initial oxidation to the corresponding ketone followed by reduction to the desired inverted alcohol. While potentially attractive, this approach was somewhat dangerous in that the presence of a ketone directly adjacent to the ring fusion could potentially compromise the relatively strained trans-BC ring stereochemistry. Indeed, Kallmerten had observed a decided preference for the cis-fusion in a related phenanthridone intermediate.[25] Furthermore, elimination of the

Scheme 5



oxygen at C_1 could also be an unwanted outcome of this oxidation−reduction approach.[26] In the event, **24** was treated with the Dess−Martin reagent to give the ketone **25a**, which slowly, but inexorably, epimerized to the more stable cis-isomer **25b** on standing for a few hours as expected. In an effort to prevent this isomerization the sequence of events was modified slightly. Thus, the alcohol in **24** was again oxidized as before, but now it was *immediately* treated with $NaBH_4$ at −20 °C. This action proved successful and provided the desired axial alcohol in good yield, and the newly installed hydroxyl group was protected as a benzyl ether to give compound **26**. The structural assignment made for this compound was supported by relevant ^{1}H NMR coupling patterns.



The final C-ring functional group processing of **26** proceeded as follows. Epoxide **26** was treated with $(PhSe)_2$, $NaBH_4$, and then H_2O_2 at reflux as before to afford allylic alcohol **27** via selective axial opening of the epoxide with phenylselenide anion followed by facile selenoxide elimination. Routine cis-dihydroxylation gave **28** in good yield. All that remained at this juncture were several deprotection steps, one of which caused some initial difficulties. The principal goal at this stage of the synthesis was to identify conditions that could cleanly remove the PMB group from the lactam nitrogen. From the very outset of the synthetic planning, this projected operation was a source of considerable concern since nitrogen deprotections of this type can be problematic. Unfortunately, the usual set of oxidative conditions (i.e., DDQ or CAN) failed to deliver any of the desired product as was the case with the narciclasine series described previously. Furthermore, the Williams protocol, which was so effective earlier, also failed in the current situation. Finally, after considerable experimentation it was found that exposure of **28** to $Pd(OH)_2/C-H_2$ in EtOH resulted in the smooth removal of both the benzyl ether at C_1 and the *N*-*p*-methoxybenzyl group to give the penultimate intermediate **29** in good yield.[27] The synthesis of (+)-pancratistatin was

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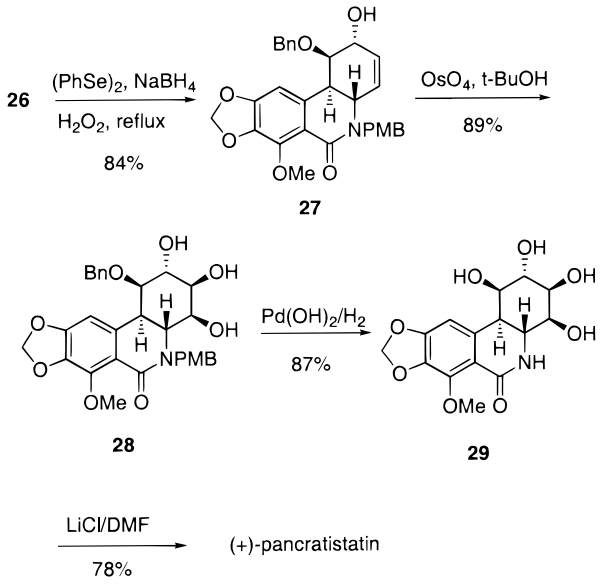
(23) Williams, R. M.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 451.
(24) Ghosal, S.; Luchan, R.; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1985**, *24*, 1825.
(25) Thompson, R. C.; Kallmerten, J. *J. Org. Chem.* **1990**, *55*, 6076.
(26) Khaldi, M.; Chretien, F.; Chapleur, Y. *Tetrahedron Lett.* **1995**, *36*, 3003.

Scheme 6



completed by treatment of **29** with LiCl/DMF under reflux to remove the C_7 methyl group protection, a reaction patterned after a similar step in the Trost/Pulley synthesis.[6] The resultant product was shown to be identical in all respects with authentic (+)-pancratistatin. In summary, the syntheses of (+)-pancratistatin and (+)-narciclasine have been achieved from a common phenanthridone intermediate starting from commercial 3-cyclohexene-1-carboxylic acid.

Acknowledgment. The authors wish to thank the National Science Foundation for their generous support of this research. They also wish to thank Professor G. R. Pettit for providing a generous sample of authentic (+)-pancratistatin and the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, DCTDC, National Cancer Institutes, for providing a sample of narciclasine for comparison purposes.

Supporting Information Available: Experimental details and full characterization data for key synthetic intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA000930I

(27) Bernotas, R. C.; Cue, R. U. *Synth. Commun*. **1990**, *20*, 1209. (b) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.