Communications to the Editor

Total Synthesis of (+)-Narciclasine

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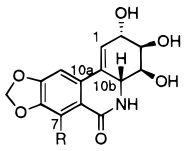
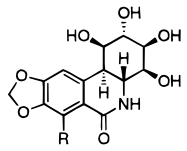
The *Amaryllidaceae* alkaloids have long been a source of structurally intriguing target molecules that continue to challenge the capabilities of contemporary organic synthesis.[1] Within this group, the phenanthridone alkaloids of the narciclasine family have recently become the subject of intense synthetic study due in large measure to their important antitumor activity.[2] Indeed, numerous syntheses of lycoricidine (**1a**)[3] have been reported in recent years, as have several approaches into 7-deoxypancratistatin (**2a**).[4] In contrast, synthetic successes into the closely related congeners narciclasine (**1b**) and pancratistatin (**2b**) are



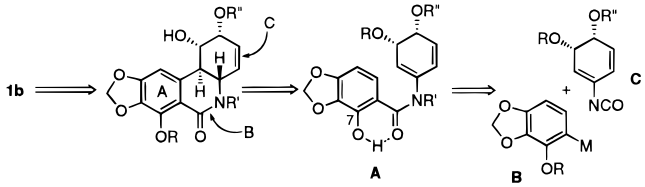
1a, R=H; lycoricidine
1b, R=OH; narciclasine



2a, R=H; 7-deoxypancratistatin
2b, R=OH; pancratistatin

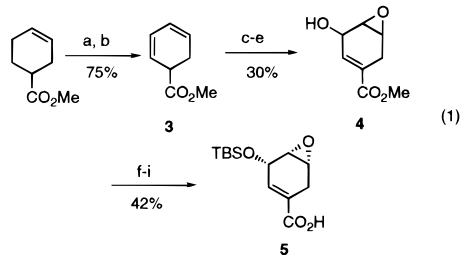
considerably fewer in number, perhaps reflecting the additional level of preparative difficulty introduced by the presence of the phenolic hydroxyl group at C7. The first synthesis of racemic pancratistatin was completed by Danishefsky and Lee in 1989,[5a] while asymmetric approaches into the compound have been recorded by Hudlicky[5b] and Trost.[5c] Recently, a formal synthesis of this compound was disclosed by Haseltine.[5d] To date there has been no synthesis of narciclasine reported despite several attempts.[6] We now present the first total synthesis of (+)-narciclasine in enantiomerically pure form.

The synthesis strategy reported in this document features a late-stage construction of the critical C10a−C10b bond with concomitant control of the relative stereochemistry of the incipient trans-BC ring fusion. The key transformation for achieving this objective is a hydrogen-bond-directed aryl enamide photocyclization of a chiral, nonracemic seco precursor (**A**) possessing intact A and C ring units. Critical to the success



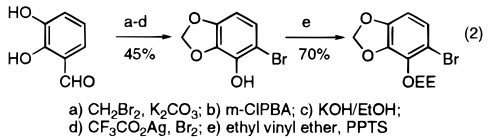
of this endeavor was the ability to overcome the normal propensity for *o*-alkoxy substituents on the arene moiety to promote ipso bond formation during the photocyclization event.[7a] This would be accomplished by exploiting possible intramolecular hydrogen bonding between the C7 hydroxyl group and the proximate enamide carbonyl oxygen to exert conformational control during the cyclization as suggested in intermediate **A**.[7b]

The synthesis began by preparing the *syn*-epoxy alcohol **5**[8] in optically pure form from commercially available 3-cyclohexene-1-carboxylic acid employing a modification of the Berchtold sequence used previously for the synthesis of chorismate derivatives (eq 1).[9] In this instance, compound **5** serves

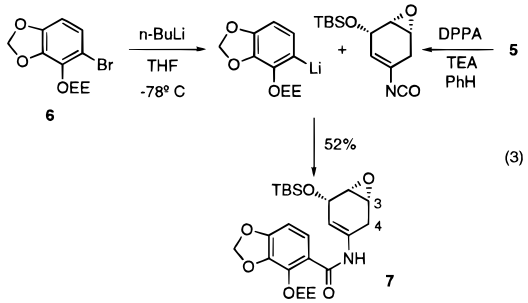


a) NBS, AIBN, PhH, reflux; b) AIBN, Bu_3SnH, PhH; c) $^1O_2$, hν, rose bengal; d) $(Ph_3P)_2RuCl_2$, CH_2Cl_2; e) NaOMe, MeOH; f) butyryl chloride, TEA; g) cholesterol esterase; h) TBSCl, imidazole; i) LiOH, MeOH, H_2O

as a masked form of diene **C**, since it has been previously observed in our laboratory that unsaturation present at C3−C4 in these systems (narciclasine numbering) was incompatible with the projected photocyclization conditions. The A ring fragment was prepared in four steps from commercial 2,3-dihydroxybenzaldehyde employing known chemistry.[10] Protection as the ethoxyethyl ether afforded **6**,[8] which sets the stage for coupling of the A and C ring fragments prior to cyclization.



a) CH_2Br_2, K_2CO_3; b) m-ClPBA; c) KOH/EtOH; d) CF_3CO_2Ag, Br_2; e) ethyl vinyl ether, PPTS



Metalation of **6** (*n*-BuLi, −78 °C) followed by addition of the isocyanate derived from **5** at −78 °C afforded the enamide

(1) For an overview of the *Amarylliclaceae* alkaloids, see: Martin, S. F. In *The Alkaloids*; Brossi, A. A., Ed.; Academic Press: New York, 1987; Vol. 30, p 251.

(2) For a review of synthetic studies in this area, see: Polt, R. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, 1996; Vol. 3, p 109.

(3) (a) Ohta, S.; Kimoto, S. *Chem. Pharm. Bull.* **1976**, *24*, 2977. (b) Paulsen, H.; Stubbe, M. *Liebigs Ann. Chem.* **1983**, 535. (c) Chida, N.; Ohtsuka, M.; Ogawa, S. *Ibid.* **1991**, *32*, 4525. (d) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694. (e) Chida, N.; Ohtsuka, M.; Ogawa, S. *J. Org. Chem.* **1993**, *58*, 4441. (f) Martin, S. F.; Tso, H.-H. *Heterocycles* **1993**, *35*, 85. (g) Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108.

(4) (a) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289. (b) Tian, X.; Maurya, R.; Königsberger, K.; Hudlicky, T. *Synlett* **1995**, 1125. (c) Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Roudan, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752.

(5) (a) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829. (b) Tian, X.; Hudlicky, T.; Königsberger, K. *Ibid.* **1995**, *117*, 3643. (c) Trost, B. M.; Pulley, S. R. *Ibid.* **1995**, *117*, 10143. (d) Doyle, T. J.; Hendrix, M.; Vanderveer, D.; Javanmard, S.; Haseltine, J. *Tetrahedron* **1997**, *53*, 11153. (e) Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1997**, *38*, 5933.

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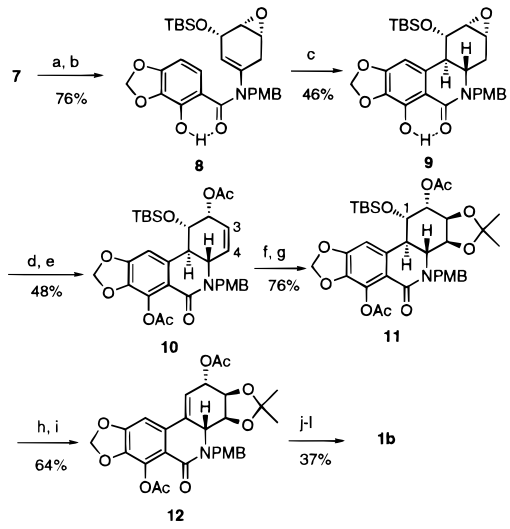
Scheme 1



7[8] in 52% yield. A *p*-methoxybenzyl group was then installed in virtually quantitative yield, and careful hydrolysis of the ethoxyethyl group under mildly acidic conditions afforded the free phenol **8** (Scheme 1).[8] Irradiation of this material at 254 nm in benzene (Rayonet photochemical reactor) produced the desired trans-fused phenanthridone **9**[8] as a single diastereomer in 46% yield based on recovered starting material along with several minor products. A number of other solvents were examined in this reaction, including cyclohexane, 1,2-dichloroethane, and several mixed solvent systems. Unfortunately, no yield improvement was observed under these conditions. The regioisomeric cyclization product was obtained when methanol was used as the solvent for this transformation, reinforcing the notion that intramolecular hydrogen bonding is controlling the course of reaction in compound **8**.[11]

The requisite C3−C4 unsaturation was then revealed by processing the epoxide in **9** using the Sharpless protocol[12] followed by acylation of the resulting free hydroxyl functions to give **10**.[8] Stereocontrolled, cis-dihydroxylation and protection of the resultant diol as the acetonide proceeded without incident to give **11**[8] in 76% yield. The double bond required at C1 was introduced by selective deprotection of the hydroxyl group at this location followed by dehydration with the Burgess reagent[13] in refluxing benzene to afford advanced intermediate **12**[8] in good yield.

The synthesis end-game involved a series of deprotection steps, one of which was the removal of the lactam PMB group, an operation that was viewed as being particularly challenging. Several of the usual oxidative methods for PMB group removal were explored for this purpose to no avail; however, an interesting procedure for selective removal of amide *N*-benzyl protection developed by Williams proved more successful.[14] In the event, routine saponification of the acetate groups in **12** followed by execution of the Williams protocol (*n*-BuLi/O_2) on the resultant diol provided the free amide, and acid-mediated removal of the remaining acetonide function afforded (+)-narciclasine ($[\alpha]^{25}_D$ 141.8°, lit.[15] $[\alpha]^{22}_D$ 142.8°; mp: 248 °C dec, lit.[15] 250−2 °C dec) in 37% overall yield. 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.

In summary, the application of a hydrogen-bond-directed aryl enamide photocyclization provides access to the *Amaryllidacene* alkaloid (+)-narciclasine in enantiomerically pure form. Minor modification of the current synthetic sequence could permit the preparation of pancratistatin, which will be reported in due time.

Acknowledgment. The authors thank the National Science Foundation for their generous support of this work, as well as the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, DCTDC, National Cancer Institute, for providing a sample of authentic (+)-narciclasine.

Supporting Information Available: Experimental details and full characterization data for key synthetic intermediates (8 pages). See any current masthead page for ordering and Internet access instructions.

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(6) (a) Krohn, K.; Mondon, A. *Chem. Ber.* **1976**, *109*, 855. (b) Banwell, M. G.; Cowden, C. J.; MacKay, M. F. *J. Chem. Soc., Chem. Commun.* **1994**, 61. (c) Khaldi, M.; Chretien, F.; Chapleur, Y. *Tetrahedron Lett.* **1995**, *36*, 3003. (d) Park, T. K.; Danishefsky, S. J. *Ibid.* **1995**, *36*, 195.

(7) (a) 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. (b) Rigby, J. H.; Gupta, V. *Synlett* **1995**, 547.

(8) This compound exhibited spectral (^{1}H NMR, ^{13}C NMR, and IR) and analytical (HRMS and/or elemental analysis) data consistent with the assigned structure.

(9) Pawlak, J. C.; Berchtold, G. A. *J. Org. Chem.* **1987**, *52*, 1765 and references therein. Improved yields of **4** could be obtained using chromatographic purification rather than crystallization.

(10) Brown, E.; Loriot, M.; Robin, J.-P. *Tetrahedron Lett.* **1982**, *23*, 949.

(11) Unfortunately, efforts to apply this strategy to the synthesis of pancratistatin via the corresponding *trans*-epoxy alcohol afforded the wrong BC ring fusion stereochemistry.

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

(13) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(14) Williams, R. M.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 451.

(15) Ghosal, S.; Lochan, R.; Ashitosh; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1985**, *24*, 1825.