An Annulative, Carbohydrate-Based Approach to Pancratistatin and Structurally Related Phenanthridone Alkaloids. Synthesis of (+)-Tetrabenzyllycoricidine

Richard C. Thompson and James Kallmerten*

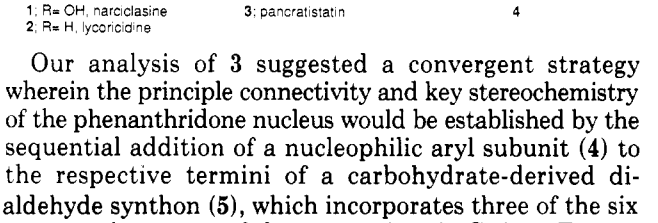
Department of Chemistry, Syracuse University, Syracuse, New York 13244-4100

Received September 17, 1990

Summary: A convergent, asymmetric approach to the antitumor alkaloid pancratistatin, based on a novel annulative construction of the highly oxygenated phenanthridone system is described.

The *Amaryllidaceae* alkaloids narciclasine[1] (**1**) and lycoricidine[2] (7-deoxynarciclasine) (**2**) are powerful antimitotic agents that effectively inhibit eukaryotic protein synthesis at the ribosomal level.[3,4] Recently, Pettit and co-workers reported the isolation and characterization of the structurally related phenanthridone alkaloid, pancratistatin (**3**), from cytotoxic extracts of two *Amaryllidaceae* species.[5] Pancratistatin exhibits pronounced in vivo antitumor activity[5c] in animal models and demonstrates significantly higher therapeutic indices than the isocarbostyril congeners **1** and **2**; however, preclinical development of pancratistatin has been impeded by the limited quantities of the natural product that are available from the producing species and by practical difficulties encountered in the preparative separation of **3** from other alkaloidal constituents. The limited availability of **3** for further biological evaluation and interest in analogues with which to evaluate structure–activity parameters[6] have contributed to recent efforts aimed at the development of a preparatively useful synthetic route to pancratistatin.[7,8]

Herein we report an expedient synthetic approach to pancratistatin and related phenanthridones based on an annulative construction of the C ring of these alkaloids.



1: R= OH, narciclasine
2: R= H, lycoricidine

3: pancratistatin

4

Our analysis of **3** suggested a convergent strategy wherein the principle connectivity and key stereochemistry of the phenanthridone nucleus would be established by the sequential addition of a nucleophilic aryl subunit (**4**) to the respective termini of a carbohydrate-derived dialdehyde synthon (**5**), which incorporates three of the six stereogenic centers of the pancratistatin C ring. For examination of this scheme, aldehyde **8** was prepared from the L-(+)-arabinose derivative **6**[9] and treated with the lithium dianion of *o*-toluic acid to afford, after esterification, alcohol **9** as a mixture of C_1 epimers (Scheme I).[10] Oxidation of **9** yielded the corresponding ketone, which was smoothly transformed to keto aldehyde **10** by acid-catalyzed hydrolysis. We next examined the intramolecular aldol reaction of **10**, anticipating that the enone obtained from such a condensation would present an attractive stage for stereocontrolled introduction of a C_{4a} nitrogen substituent. Treatment of **10** with Na_2CO_3 in THF afforded a mixture of diastereomeric aldol adducts **11**; however, attempted dehydraton of **11** by prolonged exposure to these reaction conditions resulted in enolization/lactonization to yield isocoumarin **12** *as a single stereoisomer*. Alternatively, isocoumarin **12** is obtained directly from **10** by treatment of the latter with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF. The exclusive formation of an axial C_1 alcohol[11] from the aldol condensation–lactonization of **10** and related substrates (vide infra) presumably derives from a thermodynamic partitioning of C_1-epimeric isocoumarins via reversible lactonization and equilibration of the initially formed aldol products **11**, and as such, may constitute a unique mani-

(1) Narciclasine: (a) Ceriotti, G. *Nature* **1967**, *213*, 595. (b) Piozzi, F.; Fuganti, C.; Mondelli, R.; Ceriotti, G. *Tetrahedron* **1968**, *24*, 1119. (c) The structure of narciclasine has been subject to several revisions; an X-ray structure has been published and the absolute configuration determined. See: Fuganti, C.; Mazza, M. *J. Chem. Soc., Chem. Commun.* **1972**, 239. Immirzi, A.; Fuganti, C. *J. Chem. Soc., Chem. Commun.* **1972**, 240. Mondon, A.; Krohn, K. *Tetrahedron Lett.* **1972**, 2085. (d) Dihydronarciclasine: Pettit, G. R.; Cragg, G. M.; Singh, S. B.; Duke, J. A.; Doubek, D. L. *J. Nat. Prod.* **1990**, *53*, 176.

(2) Lycoricidine: Okamoto, T.; Torii, Y.; Isogai, Y. *Chem. Pharm. Bull.* **1968**, *16*, 1860.

(3) (a) Barbacid, M.; Vazquez, D. *J. Mol. Biol.* **1974**, *84*, 603. (b) Carrasco, L.; Fresno, M.; Vazquez, D. *FEBS Lett.* **1975**, *52*, 236. (c) Baez, A.; Angoso, M.; Alonso, G.; Vazquez, D. *Biochimie* **1977**, *59*, 751.

(4) Competitive binding studies suggest that narciclasine inhibits protein elongation by binding to intact 80S ribosomes at or near the peptidyl transferase center, a site that appears to be accessible to structurally diverse elongation inhibitors including anisomycin, nonmacrocyclic trichothecanes, homoharringtonine, and the biogenetically related *Amaryllidaceae* alkaloids haemanthamine and pretazettine: (a) Jimenez, A.; Sanchez, L.; Vazquez, D. *FEBS Lett.* **1975**, *60*, 66. (b) Jimenez, A.; Santos, A.; Alonso, G.; Vazquez, D. *Biochim. Biophys. Acta* **1976**, *425*, 342. (c) Baez, A.; Vazquez, D. *Biochim. Biophys. Acta* **1978**, *518*, 95. (d) Rivera, G., Gosalbez, M.; Ballesta, J. P. G. *Biochem. Biophys. Res. Commun.* **1980**, *94*, 800.

(5) (a) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 1018. (b) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693. (c) Pettit, G. R., Gaddamidi, V.; Herald, D. L.; Cragg, G. M.; Singh, S. B.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.* **1986**, *49*, 995. (d) The isolation of 7-deoxypancratistatin and the 2-*O*-β-D-glucoside of pancratistatin (pancratiside) has recently been reported: Ghosal, S.; Singh, S.; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1989**, *28*, 611.

(6) (a) For structure–activity studies in the narciclasine series, see: Mondon, A.; Krohn, K. *Chem. Ber.* **1975**, *108*, 445. (b) See also: Evidente, A.; Arrigoni, O.; Liso, R.; Calabrese, G.; Randazzo, G. *Phytochemistry* **1986**, *25*, 2739.

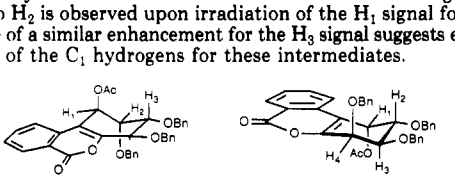
(7) Synthesis of lycoricidine: (a) Ohta, S.; Kimoto, S. *Chem. Pharm. Bull.* **1976**, *24*, 2969. Ohta, S.; Kimoto, S. *Chem. Pharm. Bull.* **1976**, *24*, 2977. (b) Paulsen, H.; Stubbe, M. *Tetrahedron Lett.* **1982**, 3171. Paulsen, H.; Stubbe, M. *Liebigs. Ann. Chem.* **1983**, 535. (c) A modified scheme based on the Ohta synthesis has recently been reported: Ugarkar, B. G.; DaRe, J.; Schubert, E. M. *Synthesis* **1987**, 715.

(8) Synthesis of (±)-pancratistatin: Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829. For a recent synthetic approach to **3**, see: Clark, R. D.; Souchet, M. *Tetrahedron Lett.* **1990**, *31*, 193.

(9) Tejima, S.; Fletcher, H. G. *J. Org. Chem.* **1963**, *28*, 2999.

(10) All compounds reported herein were fully characterized by IR and ^1H and ^{13}C NMR spectroscopy. Satisfactory combustion analyses were obtained for all new compounds.

(11) Assignment of C_1 stereochemistry for alcohols **12** and **15** is based on NOE and ^1H decoupling studies of the derived acetates i and ii. The decoupling series for i and ii reveal a small H_1–H_2 coupling (3.7 Hz and 4.0 Hz, respectively), an observation consistent with axial orientation of the C_1 hydroxyl substituent. An NOE enhancement of the signal corresponding to H_2 is observed upon irradiation of the H_1 signal for i and ii; the absence of a similar enhancement for the H_3 signal suggests equatorial disposition of the C_1 hydrogens for these intermediates.



I

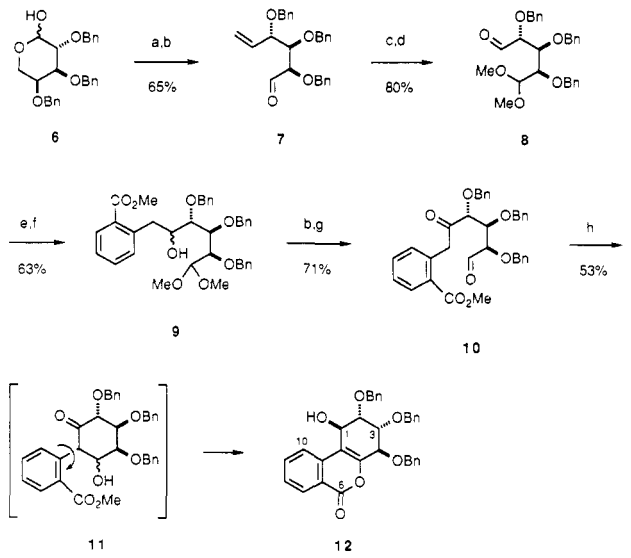
$J_{1,2}$= 3.7 Hz
$J_{2,3}$= 2.3 Hz
$J_{3,4}$= 7.6 Hz

II

$J_{1,2}$= 4.0 Hz
$J_{2,3}$= 10.6 Hz
$J_{3,4}$= 3.9 Hz

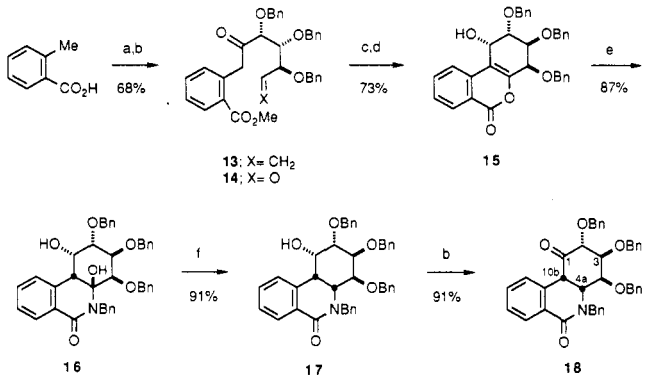
0022-3263/90/1955-6076$02.50/0

Scheme I[a]



[a] Reagents: (a) $Ph_3P{=}CH_2$, THF; (b) $(COCl)_2$, NEt_3, DMSO, CH_2Cl_2; (c) TsOH, MeOH; (d) O_3, MeOH, −78 °C, then Me_2S; (e) *o*-toluic acid, LiTMP (2 equiv), THF, −78 °C; (f) CH_2N_2, Et_2O; (g) 2 N aqueous HCl, MeCN; (h) Na_2CO_3, THF *or* DBU, THF.

Scheme II[a]



[a] Reagents: (a) LiTMP, **7**, THF, −78 → 0 °C, then CH_2N_2, Et_2O; (b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (c) O_3, MeOH, −78 °C, then Me_2S; (d) DBU, THF, 25 °C; (e) $PhCH_2NH_2$, PPTs; (f) $NaCNBH_3$, 10% aqueous HCl–MeOH.

festation of the recently described "vinylogous anomeric effect".[12,13]

While the formation of an isocoumarin product from the intramolecular condensation of **10** afforded unanticipated opportunities for further development of a pancratistatin-type phenanthridone system, the 180° rotation of the C ring that necessarily precedes lactonization of aldol intermediates **11** results in an effective "inversion" of stereochemistry at C_3. A consideration of the intrinsic symmetry of the pancratistatin C ring suggested that the problem of C_3 stereochemistry could be effectively circumvented by reversing the reactivity order of our dialdehyde synthon (Scheme II). Thus, addition of the dianion derived from *o*-toluic acid to aldehyde **7** and oxidation of the resulting epimeric alcohol adducts afforded ketone **13**. Ozonolysis furnished keto aldehyde **14**, which underwent clean aldol condensation and lactonization to give isocoumarin **15**; as in the previous example, alcohol **15** was obtained as a single stereoisomer in which the C_1 hydroxyl substituent adopts an axial orientation.[11] With the desired C_2–C_4 stereochemistry in place, development of the phenanthridone nucleus was accomplished by the reaction of **15** with benzylamine to afford hemiamidal **16**.[14] Subsequent reduction with sodium cyanoborohydride under acidic conditions yielded, as the only isolated product, phenanthridone **17**, possessing the desired configuration at C_{4a}. Direct stereochemical assignment at the B–C ring junction of **17** was hampered by line broadening in the ^1H NMR spectrum of this intermediate, an observation that, while consistent with severe steric compression across the concave face of the cis-fused phenanthridone system of **17**, precludes an unequivocal evaluation of intraannular coupling constants. By contrast, the stereochemistry of ketone **18**, obtained from **17** by Swern oxidation, was evident from an examination of decoupled ^1H NMR spectra; particularly significant was a modest (5.1 Hz) H_{4a}–H_{10b} coupling[15] indicative of a cis-fused C ring. Reduction of **18** with sodium borohydride resulted in the regeneration of alcohol **17**, confirming the stereochemical relationship between these intermediates and eliminating the possibility that epimerization had occurred during oxidation of **17**.

Further support for these stereochemical assignments was provided by the preparation of lycoricidine derivative **26** (Scheme III). In contrast to our earlier results, addition of the dianion derived from acid **19** to **7** gave low yields of the desired adducts, an observation we attribute to competitive metalation of the aryl system of **19**. The toluide anion derived from amide **21** proved markedly superior as a nucleophilic component and added smoothly to aldehyde **7**, affording adduct **22** as a complex mixture of diastereomeric atropisomers.[16] Cleavage of the amide moiety of **22** was accomplished under mild conditions by desilylation and acid-catalyzed transformation[17] to the epimeric lactones **23**. Careful hydrolysis of the lactone system, followed by immediate esterification and oxidation, afforded ketone **24**.

Oxidative cleavage of the olefinic moiety of **24** and direct treatment of the resulting keto aldehyde with DBU resulted in a smooth intramolecular aldol event and isocoumarin formation; addition of benzylamine to the isocoumarin product and treatment of the resulting hemiamidal with cyanoborohydride gave phenanthridone **25**, again as a single stereoisomer. The C_{4a} stereochemistry of **25** was unequivocally established by dehydration, via the intermediacy of the corresponding iodide,[18] to afford tetrabenzyllycoricidine ((+)**26**), identical in all respects to

(12) (a) Denmark, S. E.; Dappen, M. S. *J. Org. Chem.* **1984**, *49*, 798. (b) Curran, D. P.; Suh, Y.-G. *J. Am. Chem. Soc.* **1984**, *106*, 5002. (c) Lessard, J.; Tan, P. V. M.; Martino, R.; Saunders, J. K. *Can. J. Chem.* **1977**, *55*, 1015.

(13) Alternatively, the formation of axial alcohol **12** may reflect kinetic lactonization of a stereoelectronically favored enolate, in conjunction with equilibration of the initially formed aldol products **11**. Under the essentially anhydrous conditions employed for intramolecular aldol condensation, equilibration of isocoumarin **12** by direct substitution at C_1 would be expected to yield the corresponding *O*-methyl ether; our failure to observe this product implies that epimerization proceeds via lactone opening.

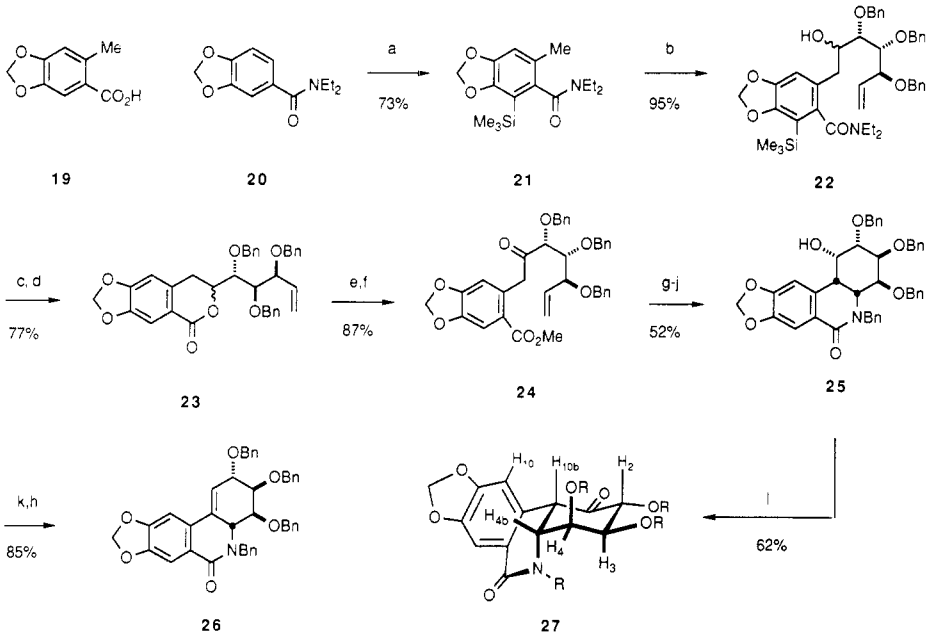
(14) Optimized yields for hemiamidal formation were obtained by concentration of a THF solution of the isocoumarin, benzylamine (5 equiv), and pyridinium *p*-toluenesulfonate (10 mol %) and allowing the resulting residue to stand for 12 h at room temperature, at which time the viscous reaction mixture was taken up in Et_2O, washed with brine, and purified by flash chromatography. Assigned stereochemistry for **16** is based on a comparison of chemical shifts and intraannular ^1H coupling constants with those of **17** and **18**.

(15) The analogous H_{4a}–H_{10b} coupling constants for *cis*- and *trans*-dihydronarciclasine[1d,6a] are 3.5 Hz and 12.0 Hz, respectively.

(16) Addition of **21** to aldehyde substrates affords products that exhibit atropisomerism due to hindered rotation of the carboxamide group. For example, addition of the anion derived from **21** to cyclohexanecarboxaldehyde affords two diastereomeric adducts, which are separable by chromatography; in ether solution, the individual diastereomers slowly interconvert at 25 °C.

(17) Lee, D.; Still, W. C. *J. Org. Chem.* **1989**, *54*, 4715.

Scheme III[a]



[a] Reagents: (a) *s*-BuLi, Me_3SiCl, THF, TMEDA, -78 °C; *s*-BuLi, THF, TMEDA, MeI; (b) *s*-BuLi, THF, -78 °C, 7; (c) Bu_4NF, THF, 0 → 25 °C; (d) CSA, PhH, 90 °C; (e) LiOH, THF-MeOH, then CH_2N_2, Et_2O; (f) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (g) O_3, MeOH, -78 °C, then Me_2S; (h) DBU, THF; (i) $PhCh_2NH_2$, PPTs; (j) $NaCNBH_3$, MeOH-10% aqueous HCl; (k) $MeP(OPh_3)I$, HMPA, 100 °C; (l) $(nPr)_4NRuO_4$, NMO, CH_2Cl_2.

a sample prepared from authentic (+)-**2**.[19] Finally, NOE studies of the derived ketone **27** have confirmed the spatial proximity of the methine proton at C_{10b} to those at C_2, C_{4b}, and C_{10}, an observation uniquely consistent with cis fusion of the C ring and equatorial disposition of the C_2 benzyloxy substituent.

The sequence described above constitutes a highly efficient, asymmetric route to the phenanthridone systems of pancratistatin and structurally related alkaloids of biological interest and provides a viable preparative entry to C-ring analogues of pancratistatin and the narciclasines from which specific structure-activity relationships can be elucidated. Our scheme effectively defines four of the six stereogenic centers of the pancratistatin C ring and presents several options for final elaboration of the desired trans-fused phenanthridone system. Interestingly, preliminary attempts to directly establish a trans-fused phenanthridone by epimerization of ketones **18** and **27** have revealed an unexpected kinetic preference for deprotonation of both substrates at the undesired C_2 position. The nature of the protecting groups used to mask the C-ring hydroxyl substituents may profoundly effect the regiochemistry of deprotonation for these intermediates; efforts to define an alternative strategy for elaboration of the requisite trans-fused phenanthridones and to extend our scheme to the synthesis of pancratistatin are in progress.

Acknowledgment. The generous support of this work by the American Cancer Society (CH-401) is gratefully acknowledged.

Supplementary Material Available: Experimental procedures for the preparation of all new compounds and full characterization data (14 pages). Ordering information is given on any current masthead page.

(18) Hutchins, R. O.; Hutchins, M. G.; Milewski, C. A. *J. Org. Chem.* **1972**, *37*, 4190. (b) Spangler, C. W.; Hartford, T. W. *J. Chem. Soc., Perkin Trans. I* **1976**, 1792.

(19) An authentic sample of **26** was prepared by treatment of (+)-lycoricidine (**2**), kindly provided by Professor G. Pettit, with sodium hydride and excess benzyl bromide in DMF.

Effects on Anions and Radicals of α-Quaternary Ammonium Substituents

Frederick G. Bordwell* and Xianman Zhang

Department of Chemistry, Northwestern University, Evanston, Illinois 60208-3113

Received September 4, 1990

Summary: α-Pyridinium groups increase the acidities of acetophenone, acetonitrile, and ethyl acetate much more than do α-Me_3N^+ groups; they decrease the BDEs of the acidic C-H bonds, whereas α-Me_3N^+ groups increase them.

The $\sigma_\alpha^\bullet$ scale of Wayner and Arnold indicates that meta substituents in benzylic radicals are generally destabilizing.[1] Similarly, in our laboratory, recent estimates of the homolytic bond dissociation energies (BDEs) in DMSO of the O-H bonds in phenols has led to the conclusion that all meta substituents possess an inherent bond strengthening (i.e., radical destabilizing) factor, and that the bond-strengthening effects of para electron-withdrawing

(1) Wayner, D. D. M.; Arnold, D. R. *Can. J. Chem.* **1984**, *62*, 1164-1168.

0022-3263/90/1955-6078$02.50/0