Total Synthesis of (+)-7-Deoxypancratistatin: A Radical Cyclization Approach

Gary E. Keck,* Stanton F. McHardy, and Jerry A. Murry

Department of Chemistry, University of Utah
Salt Lake City, Utah 84112

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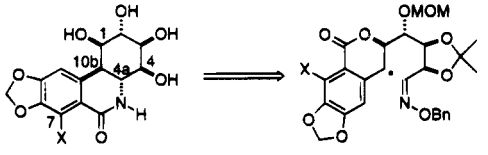
The use of *Amaryllidaceous* plant extracts for medicinal purposes dates back to at least the fourth century;[1] in recent times a large number of alkaloids which possess a wide spectrum of biological activities have been isolated from these species. Pancratistatin (**1**), isolated by Pettit and co-workers,[2] displays promising antineoplastic and antiviral activity. The 7-deoxy structure **2**, isolated by Ghosal and co-workers,[3] has been shown in *in vitro* antiviral assays to exhibit a better therapeutic index than **1** due to decreased toxicity.[4] We describe herein a total synthesis of **2** in which the key strategic element is the use of a 6-*exo* cyclization between a benzylic radical and an oxime ether (note structure **3**) to construct the highly functionalized cyclohexane nucleus found in **1**,[5,6] **2**, and related substances.[7] Although radical cyclizations involving oxime acceptors are known,[8] none have been described in such a complex setting.



1 X = OH
2 X = H

The synthesis began with diol **4** derived[9] from D-gulonolactone, which furnishes carbons **4a**–**10b** with the desired absolute configurations at C_1–C_4. Conversion of **4** to the bis-TBS derivative, followed by DIBAL reduction and *O*-benzyl oxime formation afforded the hydroxy oxime **5** in 90% overall yield (Scheme 1). Protection of the hydroxyl moiety as a MOM ether and selective removal of the primary TBS group using HF–pyridine gave the primary alcohol, from which incorporation of the aromatic moiety commenced. Although oxidation of the primary alcohol to the corresponding aldehyde **6** *via* the method of Ley[10] (TPAP–NMO) was straightforward, additions of various lithiated aromatic subunits to **6** were problematic. Further oxidation[11] to acid **7** (84%) also occurred readily, but attempts to add lithiated aromatic subunits to the corresponding Weinreb amide[12] again failed, yielding only recovered starting material. In view of the difficulties associated with these intermolecular reactions, use of an intramolecular rearrangement approach was adopted.[13] Mitsunobu esterification[14] of acid **7** with alcohol **8** cleanly afforded ester **9**. Treatment of **9** with *n*-butyllithium, initially at −98 °C with warming to −78 °C, gave the desired rearranged alcohol which unexpectedly proved to be quite unstable. Immediate oxidation (TPAP, NMO), however, afforded the stable aldehyde **10** in 72% overall yield from **9**.

Aldehyde **10** was converted to ketolactone **11** *via* TBS deprotection (HF–pyridine) and Dess–Martin oxidation.[15] Ketone reduction ($NaBH_4$) and acylation with TCDI[16] (1,1′-(thiocarbonyl)diimidazole) provided the desired radical precursor **12**. Radical cyclization of **12** (Bu_3SnH, AIBN, toluene, 90 °C) was complicated by competing reduction of the lactone moiety, and afforded **13** in only 25% isolated yield. However, **13** was obtained as a *single* diastereomer in which the desired stereochemical relationships had been established at both C_{10b} and C_{4a}, thus establishing the viability of this aspect of the radical cyclization approach.

In order to circumvent the unanticipated lactone reduction, ketoaldehyde **10** was converted to the TBS-protected lactol **14**. Ketone reduction and acylation with TCDI as previously described afforded radical precursor **15**, which yielded **16** as a single stereoisomer (ignoring lactol stereoisomers) upon radical cyclization (Bu_3SnH, AIBN, toluene, 90 °C) in 70% isolated yield.[17]

The remaining steps to **2** required oxidation of protected lactol to lactone, lactone to lactam isomerization, and protecting group removal, and were accomplished as follows.[18] Acylation of **16** (TFAA) followed by TBS removal (TBAF) and oxidation (TPAP–NMO) gave lactone **17**. Reductive cleavage of the N–O bond was effected at this stage using SmI_2.[19] Removal of the acetonide and cleavage of the MOM ether were accomplished very cleanly (Dowex H^+ resin in methanol, 65 °C) to give the desired triol in 88% yield. Finally, cleavage of the trifluoracetamide with concomitant lactone to lactam reorganization[20] proceeded efficiently with K_2CO_3 in dry methanol, yielding **2**.[21]

The approach described above clearly demonstrates the potential of radical–oxime cyclizations in the construction of *Amaryllidaceae* alkaloids, and affords **2** in 7% yield from **4**.

(1) Hartwell, J. L. *Lloydia* **1967**, *30*, 379.
(2) (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.
(3) Ghosal, S.; Singh, S.; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1989**, *28*, 611.
(4) Gabrielsen, B.; Monath, T. P.; Huggins, J. W.; Kefauver, D. F.; Pettit, G. R.; Groszek, G.; Hollingshead, M.; Kirsi, J. J.; Shannon, W. M.; Schubert, E. M.; Dare, J.; Ugarkar, B.; Ussery, M. A.; Phelan, M. J. *J. Nat. Prod.* **1992**, *55*, 1569.
(5) For previous syntheses of **1**, see: (a) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829. (b) Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643. (c) For a previous synthesis of **2**, see: Paulsen, H.; Stubbe, M. *Liebigs Ann. Chem.* **1983**, 535.
(6) For previous synthetic studies on **1** and **2** see: (a) Lopes, R. S. C.; Lopes, C. C.; Heathcock, C. H. *Tetrahedron Lett.* **1992**, *33*, 6775. (b) Angle, S. R.; Louie, M. S. *Tetrahedron Lett.* **1993**, *34*, 4751. (c) Park, T. K.; Danishefsky, S. J. *Tetrahedron Lett.* **1995**, *36*, 195. (d) Doyle, T. J., Hendrix, M.; Haseltine, J. *Tetrahedron Lett.* **1994**, *35*, 8295.
(7) For total syntheses of (and leading references to) lycoricidine, see: (a) Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108. (b) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823. (c) Martin, S. F.; Tso, H. *Heterocycles* **1993**, *35*, 85. (d) Chida, N.; Ohtsuka, M.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 4525.
(8) (a) Naito, T.; Tajiri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**, *35*, 2205. (b) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martinez, L.; Martinez-Grau, A. *J. Org. Chem.* **1992**, *57*, 2625. (c) Marco-Contelles, J.; Ruiz, P.; Sanchez, B.; Jimeno, M. L. *Tetrahedron Lett.* **1992**, *33*, 5261. (d) Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688. (e) Marco-Contelles, J.; Martinez, L.; Martinez-Grau, A.; Pozuelo, C.; Jimeno, M. L. *Tetrahedron Lett.* **1991**, *32*, 6437. (f) Marco-Contelles, J.; Martinez, L.; Martinez-Grau, A. *Tetrahedron: Asymmetry* **1991**, *2*, 961. (g) Enholm, E. J.; Burnoff, J. A.; Jaramillo, L. M. *Tetrahedron Lett.* **1990**, *31*, 3727. (h) Parker, K. A.; Spero, D. M.; Van Epp, J. *J. Org. Chem.* **1988**, *53*, 4628. (i) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633. (j) Hart, D. J.; Seely, F. *J. Am. Chem. Soc.* **1988**, *110*, 1631. (k) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821.
(9) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 319.
(10) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(11) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175.
(12) (a) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. (c) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (d) Aidhen, I. S.; Ahuja, J. *Tetrahedron Lett.* **1992**, *33*, 5431. (e) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.
(13) (a) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300. (b) Horne, S.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1992**, 164. (c) Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402. (d) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1994**, *59*, 5147.
(14) Mitsunobu, O. *Synthesis* **1981**, 1.
(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(16) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574.

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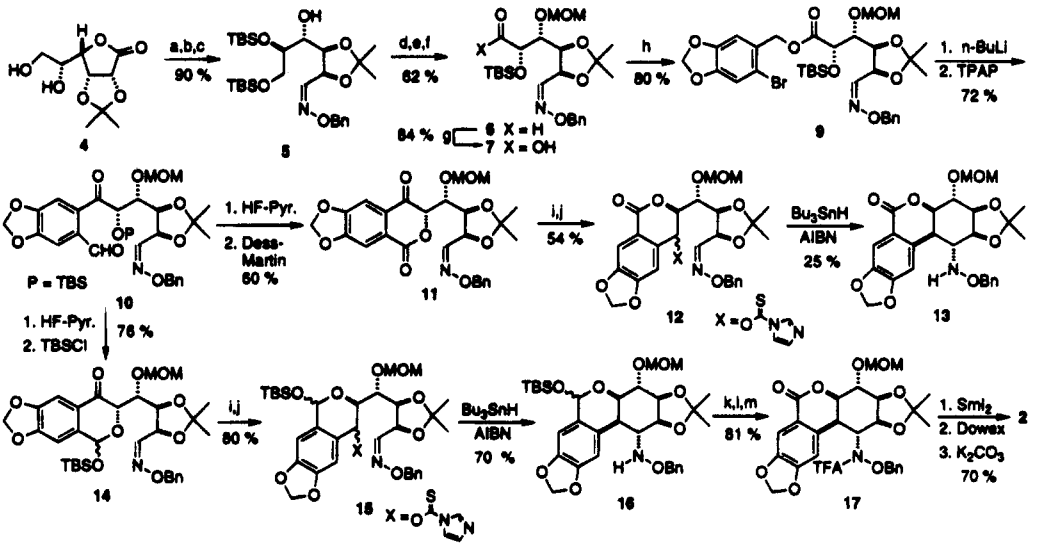
Scheme 1



[a] Reagents: (a) TBSCl, imidazole. (b) DIBAL, −78 °C. (c) $BnONH_2$−HCl. (d) MOMCl, DIEA. (e) HF−Pyridine. (f) TPAP, NMO. (g) $NaClO_2$, KH_2PO_4. (h) Ph_3P, DEAD, 4-bromo-5-(hydroxymethyl)-1,2-(methylenedioxy)benzene (**8**). (i) $NaBH_4$, MeOH. (j) TCDI, DMAP, 1,2-dichloroethane. (k) TFAA, pyridine, DMAP. (l) TBAF, THF. (m) TPAP, NMO.

Now that the viability and stereochemistry of the critical cyclization have been established, efforts toward shorter and more convergent approaches to radical precursors such as **15** are in progress and will be reported in due course.

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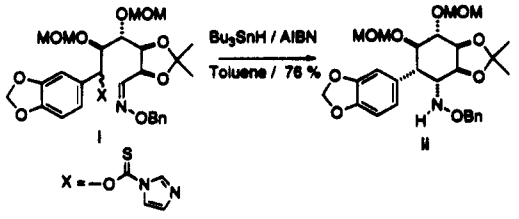
(17) Use of the lactone or protected lactol linkage between the aromatic subunit and acyclic tether terminating in the *O*-benzyl oxime is essential in order to obtain the required stereochemical result in the radical cyclization event. The problem is largely one of conformation: the oxygen substituents at C_1 and C_2 are *axially* disposed in **1** and **2**, dispositions which correspond to unfavorable conformations in purely *acyclic* radical precursors. Thus, intermediate **i** below yields **ii** as the major product upon free radical cyclization as described for **13** and **16**. A complete discussion will be given in our full paper.



(18) The timing of these operations proved critical. For example, it was not possible to effect lactone to lactam rearrangement prior to removal of the acetonide and MOM ether protecting groups. Another alternative sequence (from **13**) involving initial deprotection of the acetonide followed by rearrangement of the resulting dihydroxy *O*-benzylhydroxylamine also failed.

(19) (a) We have found this N−O bond cleavage using SmI_2 to be a convenient and high-yielding reaction for cleavage of N−O bonds in a variety of structures, including *O*-alkylhydroxylamines and *O*-alkylhydroxamic acids; these studies will be reported separately. (b) With this particular substrate, attempts at reductive cleavage of the N−O bond by hydrogenolysis[19c] or by reaction with aluminum[19d] or sodium[19d] amalgam all failed. (c) Nikam, S. S.; Komberg, B. E.; Johnson, D. R.; Doherty, J. A. *Tetrahedron Lett.* **1995**, *36*, 197. (d) Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281.

(20) (a) For a closely related transformation, see ref 5c. (b) For a different outcome in a similar transformation using the same reagents, see ref 5a.

(21) This material was best characterized after peracetylation with Ac_2O−pyridine. The resulting tetraacetate was spectroscopically indistinguishable from that described by Paulsen,[5c] and had $[\alpha]_D$ +68.4° (*c* 0.5, $CHCl_3$), in excellent agreement with the literature[5c] value ($[\alpha]_D$ +68.4° (*c* 1.0, $CHCl_3$)).