Total Synthesis of *ent*-Lycoricidine *via* a Thiyl Radical Addition−Cyclization Sequence†

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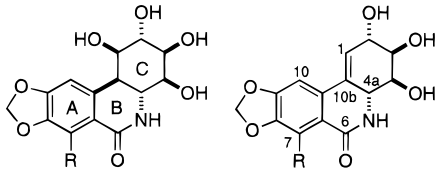
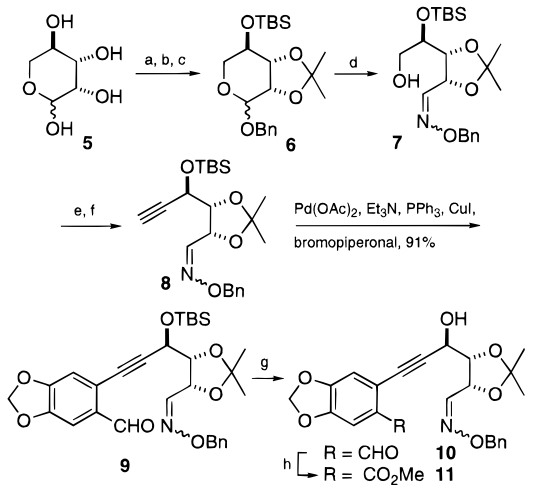
Pancratistatin (**1**) and structurally related naturally occurring materials such as 7-deoxypancratistatin (**2**), narciclasine (**3**), and lycoricidine (**4**) have attracted considerable synthetic attention because of interest in the biological activity of these compounds and their novel structural aspects.[1] In particular, three recent total syntheses of **1** have been recorded[2] as have five total syntheses of **4**.[3] Our own efforts in this area have led to a recently reported synthesis of **2** *via* a radical cyclization-based strategy.[4] We now report the development of a rather different radical based approach to **4**. Although the approach is capable of providing either enantiomer of **4**, we chose to pursue the synthesis of *ent*-**4** to allow for biological assay of this material.



The strategy chosen for experimental scrutiny was based on establishing the $C_{4a}-C_{10b}$ bond late in the synthesis, *via* radical cyclization using an *O*-benzyloxime as the radical acceptor.[5] The synthesis of potential substrates for this reaction is outlined in Scheme 1. The route began with D-lyxose (**5**), which was converted to the *O*-benzyl-3,4-isopropylidenelyxopyranoside *via* known[6] procedures; silyation of the remaining hydroxyl afforded **6**. Reduction of **6** with lithium in liquid ammonia

Scheme 1[a]



[a] *Key*: (a) BnOH, *p*-TsOH, 81%; (b) DMP, acetone, *p*-TsOH, 90%; (c) TBS-Cl, imidazole, 95%; (d) (i) Li, NH_3, (ii) $BnONH_2$·HCl, pyridine, 93% over two steps; (e) (i) TPAP, NMO, 4 Å MS, (ii) CBr_4, PPh_3, NEt_3, 55% over two steps; (f) *n*-BuLi, 91%; (g) HF·pyridine, 88%; (h) MnO_2, NaCN, HOAc, MeOH, 81%.

followed by reaction of the crude lactol with *O*-benzylhydroxylamine hydrochloride in pyridine gave a 93% isolated yield of the *O*-benzyloxime **7** as a 2.5:1 mixture of *E*/*Z* oxime isomers.[7] This material was then converted to the terminal alkyne **8** *via* oxidation using the general procedure of Ley[8] followed by application of the Corey−Fuchs protocol[9] to the resulting aldehyde. Coupling with the aromatic subunit was achieved in excellent yield by reaction of the terminal alkyne **8** with bromopiperonal[10] using the palladium-catalyzed process developed by Sonogashira and co-workers,[11] affording the alkynealdehyde **9**. This material was also processed (*vide supra*) to afford two additional radical cyclization substrates: removal of the TBS group afforded hydroxy aldehyde **10**, which was converted (81% isolated yield) to the hydroxy ester **11** using the Corey−Gilman−Ganem oxidation.[12]

The critical reaction envisioned for establishing the functionalized cyclohexene moiety present in **4** was addition of a radical X• to the alkyne moiety in a substrate such as **12**, followed by cyclization of the resulting vinyl radical onto the pendant oxime moiety. Although the relative amounts of the potential products of this reaction are a function of a fairly complex kinetic scheme, clearly regiochemistry in the addition of X• to the alkyne is an issue here. We anticipated that the regiochemical issue should be dominated by benzylic stabilization[13] of the vinyl radical intermediate, thus leading to the vinyl radical desired for our purposes. As candidates for X•, we focused our attention on tri-n-butylstannyl and phenyl thiyl radicals.

† The synthesis described herein has been previously disclosed: Keck, G. E.; Wager, T. T. *Abstracts of Papers*; 212th National Meeting of the American Chemical Society, Orlando, FL, Aug 1996; American Chemical Society: Washington, DC, 1996; ORGN 317.

(1) Polt, R. L. In *Amaryllidaceae Alkaloids with Antitumor Activity*; Hudlicky, T., Ed.; Organic Synthesis: Theory and Application: JAI Press, Inc.: Greenwich, 1996; Vol. 3, pp 109−148.

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

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

(4) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289.

(5) For additional earlier examples see ref 4 and references cited therein. (a) Marco-Contelles, J.; Destabel, C.; Chiara, J. L.; Bernabe, M. *Tetrahedron Asymmetry* **1995**, *6*, 1547. (b) Naito, T.; Ninomiya, I.; Tajiri, K.; Kiguchi, T.; Hiramatsu, H. *Tetrahedron Lett.* **1995**, *36*, 253. (c) Marco-Contelles, J.; Chiara, J. L.; Khiar, N.; Gallego, P.; Destabel, C.; Bernabe, M. *J. Org. Chem.* **1995**, *60*, 6010. (d) Parker, K. A.; Fokas, D. *J. Org. Chem.* **1994**, *59*, 3927. (e) Booth, S. E.; Jenkins, P. R.; Swain, C. J.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3499. (f) Parker, K. A.; Fokas, D. *J. Org. Chem.* **1994**, *59*, 3933. (g) Grissom, J. W.; Klingberg, D. *J. Org. Chem.* **1993**, *58*, 6559. (h) Pattenden, G.; Schulz, D. J. *Tetrahedron Lett.* **1993**, *34*, 6787.

(6) Keck, G. E.; Kachensky, D. F.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 4317.

(7) For purposes of characterization, the major oxime isomer of all synthetic intermediates en route to *ent*-**4** was isolated and characterized; for preparative purposes the mixture of oxime isomers was carried through the sequence.

(8) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(9) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(10) Dallacker, F. *Liebigs Ann. Chem.* **1960**, 14.

(11) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(12) Corey, E. J.; Gilman, N .W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5618.

(13) Aryl-substituted vinyl radicals appear to be linear: (a) Dolbier, W. R., Jr.; Bartberger, M. D. *J. Org. Chem.* **1995**, *60*, 4984. (b) Bennett, J. E.; Howard, J. A. *Chem. Phys. Lett.* **1971**, *9*, 460.

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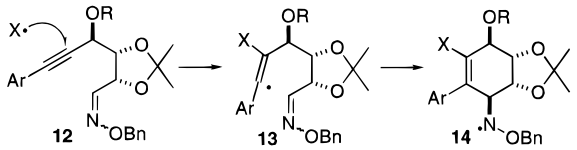
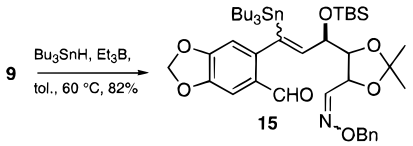
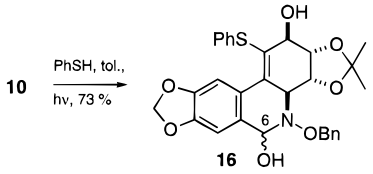


Initial experiments with **9** and Bu_3SnH provided an unexpected result: *addition of stannyl radical and trapping by Bu_3SnH occurred without radical cyclization and exclusively with the "wrong" regiochemistry,*[14] *yielding vinyl stannane **15***. Since the observed regiochemistry

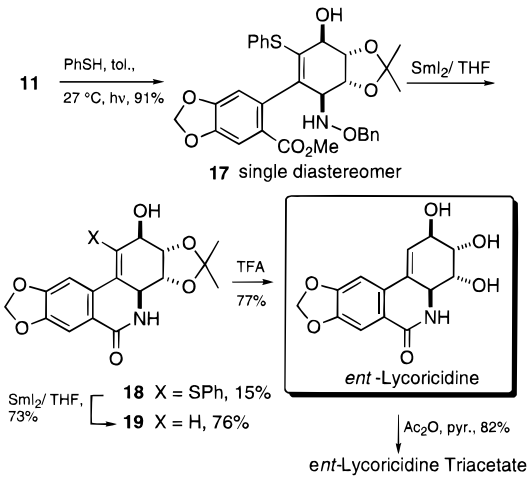


could have resulted from the influence of steric factors on the initial addition of stannyl radicals to alkyne **9**, the reaction was also investigated with hydroxy aldehyde **10**, but with essentially the same outcome. Much better results were achieved with thiyl radicals. Reaction of hydroxy aldehyde **10** with thiophenol in toluene solution, under irradiation from a sunlamp, afforded cyclized product **16** (73% isolated yield) as a 4:1 mixture of isomers at the hemiaminal carbon C_6. Thus, the entire framework necessary for lycoricidine was constructed in a single operation by sequential one-electron and two-electron cyclization processes. However, attempts to perform the requisite oxidation at C_6 (on the C_2 acetate derived from **16**) were low yielding.



In contrast, reaction of hydroxy ester **11** with thiophenol (toluene solution, 27 °C, sunlamp, 2 h) afforded amino ester **17** in 91% isolated yield;[15] none of the other possible diastereomer was detected (Scheme 2). Although **17** showed no tendency to cyclize spontaneously

Scheme 2



(no reaction in refluxing toluene), subjection of **17** to the SmI_2 procedure[16] developed during the course of our work of 7-deoxypancratistatin effected three operations: reductive cleavage of the N−O bond, cyclization of the resulting amino ester, and removal of the thiophenyl group, affording **19** in 76% isolated yield.

Also isolated from this reaction was 15% of **18**, which still contained the phenylthio moiety; thus, the yield of tricyclic material is actually 91%. Intermediate **18** could be resubjected to the SmI_2 reduction to give **19** in 73% isolated yield.[17] Completion of the synthesis required only the known removal of the acetonide moiety to give (−)-lycoricidine (mp 221−224 °C dec; (lit.[3b] mp 224−226 °C dec), which gave ^1H and ^{13}C NMR data indistinguishable from those previously reported for the (+) enantiomer. Further characterization was achieved by conversion to the known triacetate, whose spectral data were also in excellent agreement with those previously reported.

The route described herein thus affords lycoricidine in optically pure form and 11.1% overall yield in 14 steps from lyxose.

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Supporting Information Available: Experimental procedures for all synthetic intermediates and final products (15 pages).

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(14) This result is in contrast to the finding of Marco-Contelles and co-workers,[5a] who observed very high yielding 5-*exo* cyclization upon stannyl radical additions to closely related terminal alkynes; undoubtedly, steric effects slow the rate of 5-*exo* cyclization in the present system.

(15) This reaction has been extensively optimized and was found qualitatively to proceed better (faster reaction, higher isolated yields) at lower temperature rather than at elevated temperatures, a result that clearly seems related to the reversibility of the initial thiyl radical addition. For example, conducting the same reaction thermally (65 °C) gave a 76% yield after 48 h.

(16) Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995**, *36*, 7419.

(17) This is not an isolated result. Small amounts of **18** were always detected in the reduction of **17**, even with excess SmI_2 and long reaction times. Curiously, however, isolation and resubjection of **18** to these conditions affords **19**.