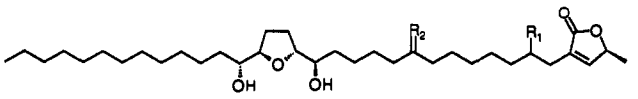
A Concise Convergent Strategy to Acetogenins. (+)-Solamin and Analogues

Barry M. Trost* and Zhongping Shi

Department of Chemistry
Stanford University
Stanford, California 94305-5080

Received May 17, 1994

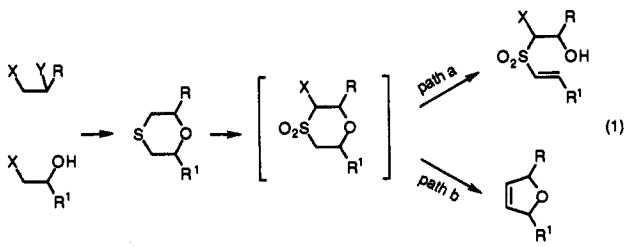
A search for the therapeutic agents from Annonaceae which had long been used in folk remedies revealed the presence of a class of compounds referred to as acetogenins.[1,2] The breadth of biological activity of these compounds spanning from cytotoxicity to antimalarial, immunosuppressant, and pesticidal activity stimulates a great interest in establishing their stereochemistry and in their synthesis.[3,4] The compounds consist of a very long aliphatic chain bearing a butenolide at one terminus with the chain adorned with additional oxygen substituents, some in the form of tetrahydrofuran rings. Illustrative of the monotetrahydrofuranoid members are the C_{35} series solamin (**1**: R_1 = H; R_2 = H, H),[4,5] murisoline (**2**: R_1 = OH; R_2 = H, H),[6] corossolone (**3**: R_1 = H; R_2 = O),[7] corossoline (**4**: R_1 = H; R_2 = H, OH),[7] annonacinone (**5**: R_1 = OH; R_2 = O),[8] and annonacin (**6**: R_1 = OH; R_2 = H, OH).[9] In developing a general synthetic strategy,



1-6

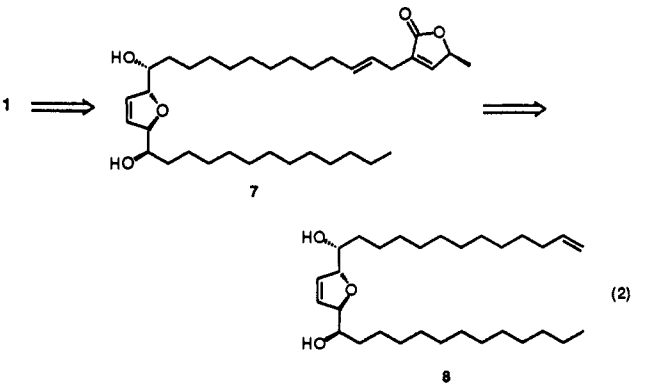
we focused on a convergent approach in which two nearly equal halves would be joined via a Ramberg–Backlund olefination[10] (eq 1); however, such a sequence for the synthesis of heterocycles like 2,5-dihydrofurans had no precedent. The absence of any previous examples stems from the anticipation that β-elimination (eq 1, path a) may preclude γ-elimination leading to olefination (eq 1, path b).

In order to explore the feasibility of such a strategy, we chose to synthesize (+)-solamin because the nearly C_2 symmetric nature of a potential intermediate **8**, which relies on a ruthenium-



(1)

catalyzed butenolide annulation to form the immediate precursor **7**, simplifies the synthetic strategy. Scheme 1 summarizes the



(2)

synthesis of the two halves from the known 12-bromo-1-dodecene[12] prepared in two steps from commercially available 11-bromo-1-undecanol.

The asymmetric epoxidation[13] of allyl alcohol **9**[14] produced (2*S*,3*R*)-epoxide **10**[14] of only 82% ee as determined by ^{1}H NMR analysis of the *O*-methylmandelate ester.[15] Fortunately, recrystallization from 4:1 hexane–methylene chloride gave epoxide **10** of >99% ee. The scheme bifurcates at this point to form the two different halves. Simple conversion of the hydroxy group to an iodide completes one of the halves, **11**.[14] Hydrogenation and thiolate substitution[16] of the Payne rearranged[17] hydroxy epoxide produces the other half, **13**.[14] Of various thiolates examined, 1,1-dimethylethanethiolate proved optimum in precluding premature epoxide ring opening and allowing the alkyl group to be easily removed.[18]

Coupling of the two halves to form the 1,4-oxathiane **14**[14] is achieved under basic conditions (see Scheme 2). Concerns regarding the suitability of the Ramberg–Backlund process immediately heightened by the failure to chlorinate either **14** or its corresponding sulfoxide. Furthermore, the bis TBDMS ether of **14** also fails to undergo α-chlorination. Chlorination of the bis-acetate of **14** with NCS succeeded only in 2:1 benzene–hexane. The best protocol invokes *in situ* chlorination–rearrangement of the corresponding sulfone **15**,[14] which required protection of the hydroxy groups as their silyl ethers to form the key intermediate **8**.[14,19]

(1) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237. Fang, X.-P.; Rieser, M. J.; Gu, Z.-M.; Zhao, G.-X.; McLaughlin, J. L. *Phytochem. Anal.* **1993**, *4*, 27.

(2) For determination of the absolute configuration of this series, see: Reiser, M. J.; Hui, Y.-H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203.

(3) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369. Harmange, J.-C.; Figadère, B.; Hocquemiller, R. *Tetrahedron: Asymmetry* **1991**, *2*, 347. Figadère, B.; Harmange, J.-C.; Hai, L. X.; Cavé, A. *Tetrahedron Lett.* **1992**, *33*, 5189. Bertrand, P.; Gesson, J.-P. *Tetrahedron Lett.* **1992**, *33*, 5177. Harmange, J. C.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1992**, *33*, 5749. Figadère, B.; Chaboche, C.; Peyrat, J.-F.; Cavé, A. *Tetrahedron Lett.* **1993**, *34*, 8093. Yao, Z. J.; Wu, Y.-L. *Tetrahedron Lett.* **1994**, *35*, 157. Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517.

(4) Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1993**, *115*, 4891.

(5) Myint, S. H.; Cortes, D.; Laurens, A.; Hocquemiller, R.; Leboeuf, M.; Cavé, A.; Cotte, J.; Quero, A.-M. *Phytochemistry* **1991**, *30*, 3335.

(6) Myint, S. H.; Laurens, A.; Hocquemiller, R.; Cavé, A.; Davoust, D.; Cortes, D. *Heterocycles* **1990**, *31*, 861. Also see: Figadère, B.; Harmange, J. C.; Hai, L. X.; Cavè, A. *Tetrahedron Lett.* **1992**, *33*, 5189.

(7) Cortes, D.; Myint, S. H.; Laurens, A.; Hocquemiller, R.; Leboeuf, M.; Cavé, A. *Can. J. Chem.* **1991**, *69*, 8.

(8) McCloud, T. G.; Smith, D. L.; Chang, C.-J.; Cassady, J. M. *Experentia* **1987**, *43*, 947.

(9) Xu, L. Z.; Chang, C.-J.; Yu, J.; Cassady, J. M. *J. Org. Chem.* **1989**, *54*, 5418.

(10) Paquette, L. A. *Org. React. (N.Y.)* **1977**, *25*, 1. Clough, J. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: Oxford; Vol. 3, Chapter 3.8, pp 861–886.

(11) This footnote was deleted on revision.

(12) Kato, M.; Mori, K. *Agric. Biol. Chem.* **1985**, *49*, 2479.

(13) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(14) This compound has been fully characterized spectroscopically and elemental composition established by combustion analysis and, in some cases, high-resolution mass spectroscopy.

(15) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370.

(16) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687.

(17) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

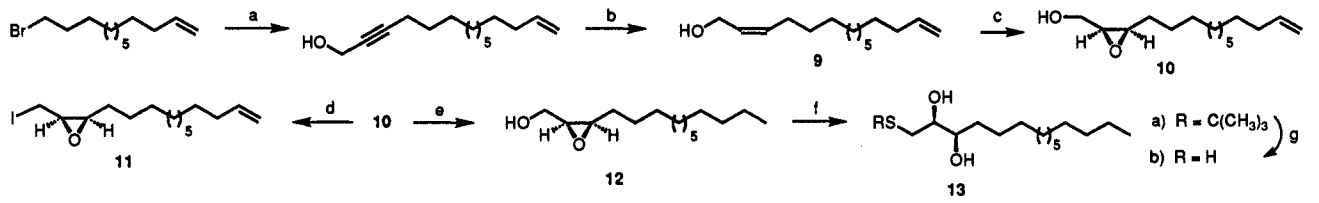
(18) Nishimura, O.; Kitada, C.; Fujino, M. *Chem. Pharm. Bull.* **1978**, *26*, 1576.

(19) Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510.

(20) We are grateful to Professor E. Keinan for an authentic sample of (+)-solamin.

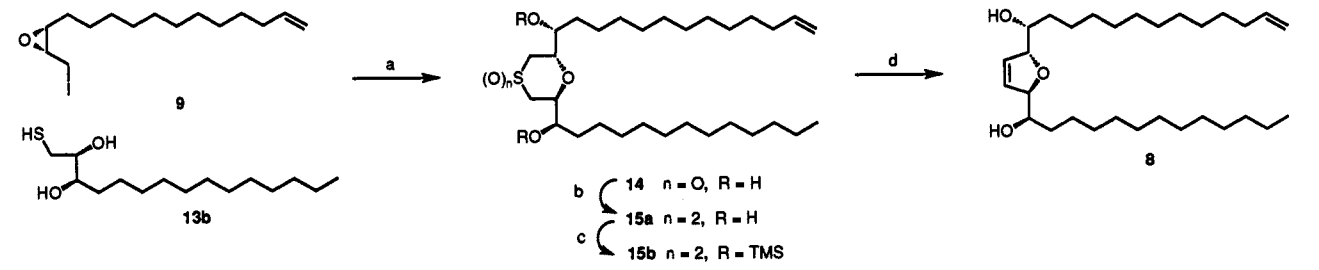
0002-7863/94/1516-7459$04.50/0

Scheme 1. Synthesis of Two Halves[a]



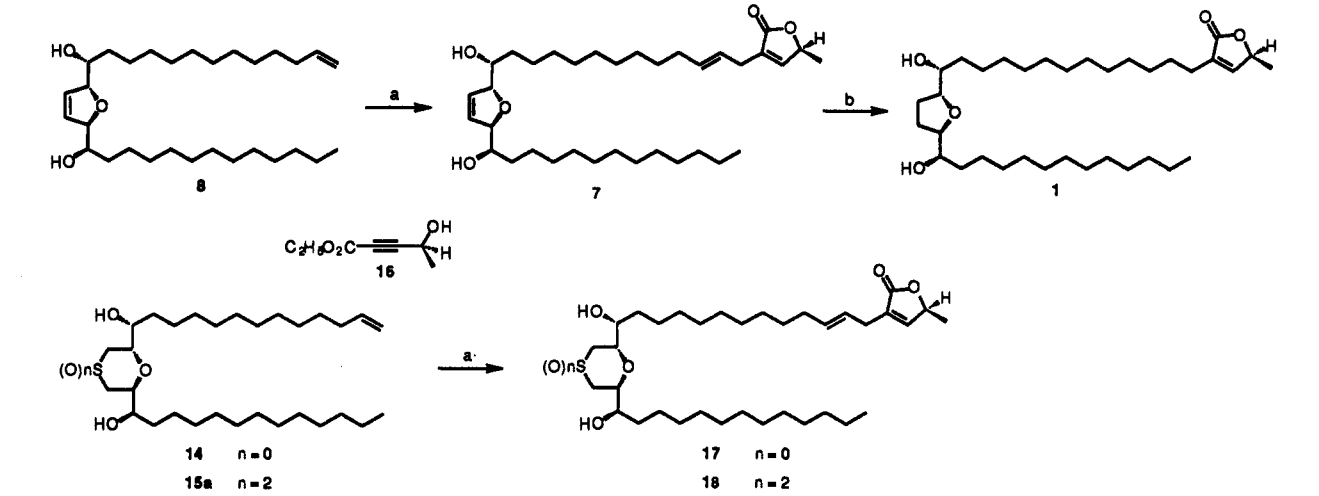
[a] (a) $HC{\equiv}CCH_2OH$, n-C_4H_9Li, THF, HMPA, −78 °C → room temperature, 76%. (b) H_2, Lindlar catalyst, hexane, room temperature. (c) t-C_4H_9OOH, 12% $Ti(OC_3H_7i)_4$, L-(+)-DET, 4-Å molecular sieves, CH_2Cl_2, −20 °C, 90%. (d) I_2, Ph_3P, $C_3H_4N_2$, $(C_2H_5)_3N$, THF, 0 °C, 93%. (e) 5% Pd/C, H_2 (1 atm), 9:1 hexane–ethyl acetate, 98%. (f) t-C_4H_9SH, NaOH, t-C_4H_9OH, H_2O, 81%. (g) $Hg(OAc)_2$, $PhOCH_3$, CF_3CO_2H, 0 °C, 92%.

Scheme 2. Coupling[a]



[a] (a) (i) Cs_2CO_3, DMF, room temperature, 92%; (ii) KOH, H_2O, t-C_4H_9OH, 65%. (b) MCPBA, PhH–hexane, 0 °C, 95%. (c) TMSCl, $(C_2H_5)_3N$, CH_2Cl_2, 0 °C room temperature, 94%. (d) (i) t-C_4H_9OK, t-C_4H_9OH, CCl_4, room temperature, 65%; (ii) TsOH, H_2O, C_2H_5OH, room temperature, 95%.

Scheme 3. Butenolide Annulation. (+)-Solamin and Analogues[a]



[a] (a) 5% CpRu(COD)Cl, CH_3OH, reflux, 75% (from **8**), 65% (from **14**), 88% (from **15**). (b) 8% $(Ph_3P)_3RhCl$, 1 atom of H_2, 1.2:1 PhH, C_2H_5OH, room temperature, 95%.

Ruthenium-catalyzed butenolide annulation of diol **8** with ynoate **16**[11] occurs chemoselectively at the sterically more accessible terminal olefin to give bis-dehydrosolamin **17**[14] (see Scheme 3). The two additional differentiated olefins of this solamin analogue provide opportunities for structural variations. Chemoselective hydrogenation of these two double bonds[21] completes a synthesis of (+)-solamin, mp 78.0–79.0 °C, $[\alpha]^{25}_D$ +22.2° (c 0.30, CH_3OH), identical to an authentic sample.[4,20] Interestingly, the same butenolide annulation protocol proceeds successfully with sulfide **14** and sulfone **15a** to give the two analogues **17**[14] and **18**.[14] Thus, the ruthenium-catalyzed reaction is not deterred by divalent sulfur (although the rate is depressed) nor by the propensity of β-alkoxy sulfones to undergo elimination. In summary, the Ramberg–Backlund protocol combined with the newly developed ruthenium-catalyzed butenolide annulation serves as an effective strategy for the synthesis of (+)-solamin and analogues and should prove useful to many other acetogenins and their analogues,

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences Institute, and the National Science Foundation for their generous support of our programs.

Supplementary Material Available: Characterization data for **1**, **7–15**, **17**, and **18** and experimental procedure for **8** to **7** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(21) Ireland, R. E.; Bey, P. *Org. Synth.* **1974**, *53*, 63.