Total Synthesis of (±)-Breynolide: An Aglycon Derivative of a Potent, Orally Active Hypocholesterolemic Agent

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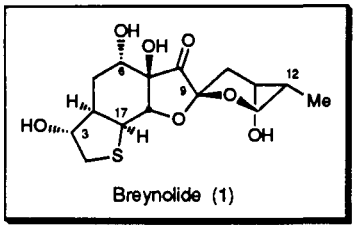
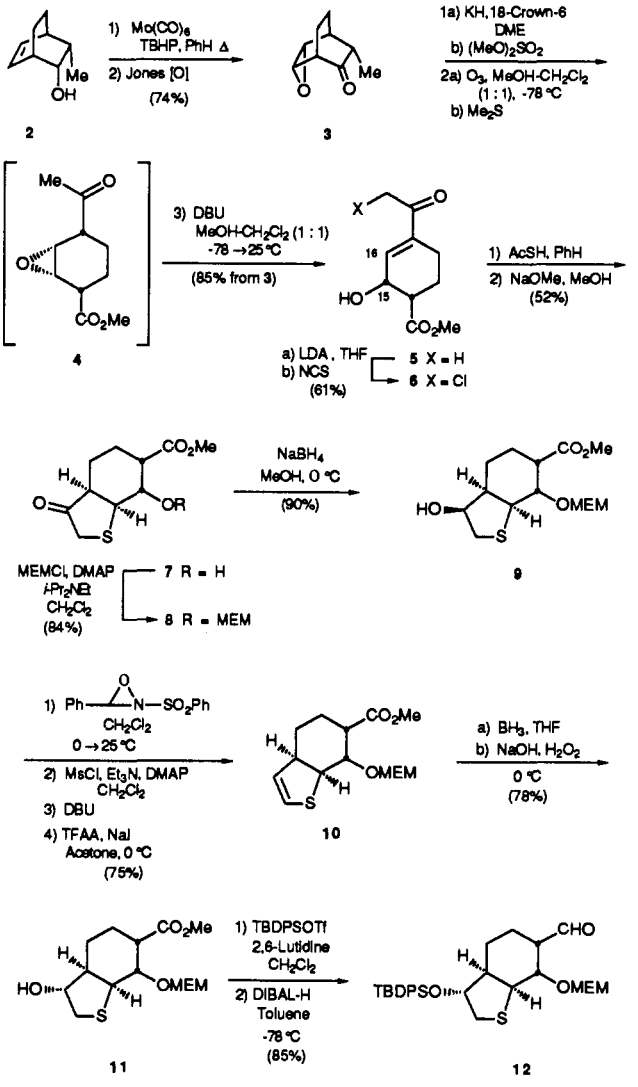
Breynins A and B, novel sulfur-containing glycosides isolated from the Taiwanese woody shrub *Breynia officinalis* Hemsl, possess significant oral hypocholesterolemic activity.[1] Although the complete structures of the breynins remain unknown, exhaustive hydrolysis of breynin A afforded breynolide (**1**), along with D-glucose, L-rhamnose, and *p*-hydroxybenzoic acid.[1b] The structure of **1** was then secured via single-crystal X-ray analysis.[1c] Our interest in the breynins stems from their potent pharmacological properties and the remarkable structural similarity of **1** with phyllanthocin,[2a] the aglycon methyl ester of the phyllanthoside family of antitumor agents.[2b] Not surprisingly, others in the synthetic community have also been attracted to this arena,[3] and in 1990 Williams et al. reported the first total synthesis of (+)-**1**.[3b] Herein we disclose an alternate, stereochemically linear[4] approach which recently culminated in the construction of racemic breynolide. Highlights include (1) anomerically driven spiroketalization–equilibration of enedione **14b**, via a protocol utilized to great advantage in our phyllanthocin synthesis;[5] (2) a chemoselective elimination effecting regiocontrolled epoxide ring opening (**4** → **5**); (3) expeditious three-step elaboration of the perhydrobenzothiophene ring system; and (4) an end game exploiting the strain in enone **19** to permit Michael addition of allyl alcohol, followed by the generation and hydroxylation of an enolate bearing two β-alkoxy groups.



Breynolide (1)

As our point of departure, the directed epoxidation[6] of **2**[7] followed by Jones oxidation[8] afforded **3**[9a] (Scheme I). Enol ether

Scheme I



formation, ozonolysis, and DBU-promoted epoxide ring opening then provided **5**[9a] in excellent overall yield (85% from **3**). Subsequent generation of the dianion (LDA, THF) and chlorination with NCS furnished **6**,[9] the substrate for sulfur incorporation. As anticipated, addition of thiolacetic acid followed by treatment with NaOMe in MeOH (4 h, 23 °C) led to **7**;[9,10] unequivocal proof of the latter structure derived from single-crystal X-ray analysis.[11] Protection of the secondary hydroxyl (MEMCl) and reduction of ketone **8**[9a] ($NaBH_4$, MeOH) then generated endo alcohol **9**[9a] as the exclusive product (>99:1). Unfortunately, a variety of tactics including Mitsunobu inversion[12] of **9** and dissolving metal reduction[13] of **8** gave only trace amounts of the desired exo isomer. Accordingly, we prepared vinyl sulfide **10**[9a,14] and reintroduced

(1) (a) Sasaki, K.; Hirata, Y. *Tetrahedron Lett.* **1973**, 2439. (b) Sakai, F.; Ohkuma, H.; Koshiyama, H.; Naito, T.; Koshiyama, H. *Chem. Pharm. Bull.* **1976**, *24*, 114. (c) Sasaki, K.; Hirata, Y. *Acta Crystallogr.* **1974**, *B30*, 1347. (d) Koshiyama, H.; Hatori, M.; Ohkuma, H.; Sakai, F.; Imanishi, H.; Ohbayashi, M.; Kawaguchi, H. *Chem. Pharm. Bull.* **1976**, *24*, 169. (e) Trost, W. *IRCS Med. Sci.* **1986**, *14*, 905.

(2) (a) Kupchan, S. M.; La Voie, E.; Branfman, A.; Fei, B.; Bright, W.; Bryan, R. *J. Am. Chem. Soc.* **1977**, *99*, 3199. (b) Pettit, G. R.; Cragg, G. M.; Niven, M. L.; Nassimbeni, L. R. *Can. J. Chem.* **1983**, *61*, 2630 and references cited therein.

(3) (a) Nishiyama, S.; Ikeda, Y.; Yoshida, S.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 105. (b) Williams, D. R.; Jass, P.; Tse, H.-L.; Gaston, R. *J. Am. Chem. Soc.* **1990**, *112*, 4552.

(4) (a) As we have noted earlier,[4b,5a] a stereochemically linear strategy employs a single enantiomerically pure starting material, inducing the relative and absolute configurations of all remaining centers. Although such an approach may entail an increase in the total number of steps, compared with a stereochemically convergent strategy, overall efficiency may nonetheless be enhanced because only one resolution, asymmetric reaction, or naturally occurring chiral substrate is required. (b) Smith, A. B., III; Fukui, M.; Vaccaro, H. A.; Empfield, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 2071.

(5) (a) Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. (b) Smith, A. B., III; Empfield, J. R.; Vaccaro, H. A. *Tetrahedron Lett.* **1989**, *30*, 7325.

(6) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(7) Willcott, M. R., III; Davis, R. E.; Holder, R. W. *J. Org. Chem.* **1975**, *40*, 1952.

(8) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

(9) (a) The structure assigned to each new compound is in accord with its infrared, 500-MHz ^1H NMR, and 125- or 62.5-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry. (b) In addition, an analytical sample of this new compound gave satisfactory C and H combustion analysis.

(10) NMR analyses established that (i) 1,4-addition initially occurred anti to the C(15) hydroxyl group; (ii) base treatment of the resultant adduct induced acetyl migration to the vicinal hydroxyl, generating a thiolate anion which cyclized via displacement of chloride; and (iii) equilibration at C(4) of the bicyclic system then provided the more stable cis-fused isomer.

(11) Unpublished results of Dr. P. Carroll, University of Pennsylvania X-Ray Crystallographic Facility.

(12) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

(13) Review: Pradhan, S. K. *Tetrahedron* **1986**, *42*, 6351.

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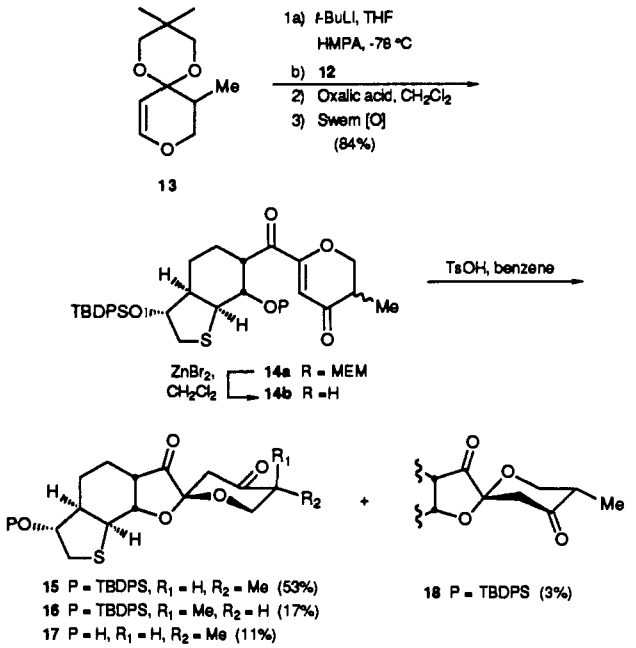
Scheme II

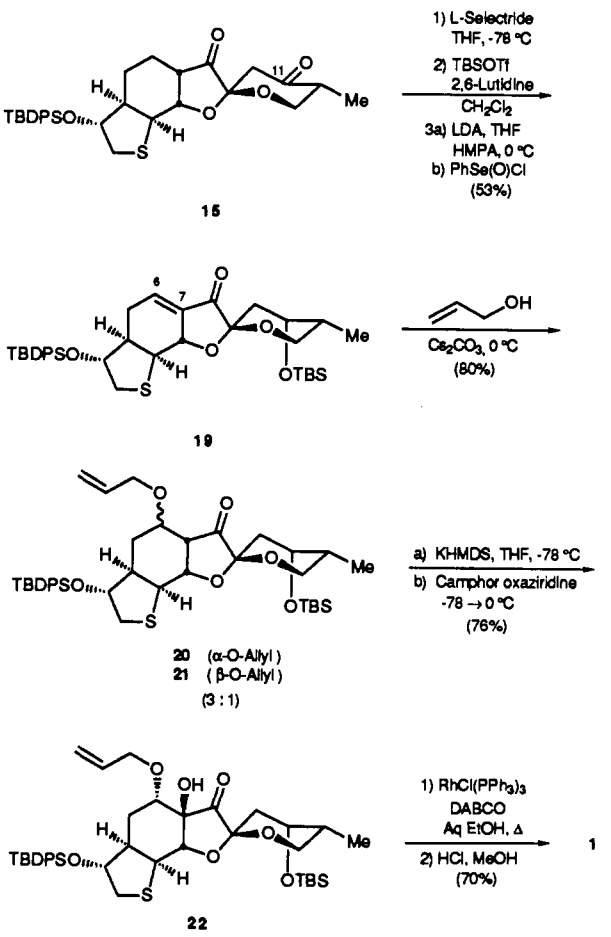


the hydroxyl via hydroboration, exploiting the convex bias of the bicyclic skeleton to set the exo stereochemistry; the overall yield for this five-step operation was 59%. Protection of alcohol **11**[9,15] [TBDPSOTf (TBDPS = *tert*-butyldiphenylsilyl), 2,6-lutidine] and ester reduction (DIBAL-H, toluene) then afforded aldehyde **12**.[9a]

Union of the vinyl anion derived from **13**[5] with aldehyde **12**, ketal hydrolysis (aqueous oxalic acid, CH_2Cl_2), and Swern oxidation[16] furnished enedione **14a**,[9a] poised for the spiroketalization maneuver (Scheme II). In the event, removal of the MEM group ($ZnBr_2$, CH_2Cl_2) and treatment of alcohol **14b** with acid (TsOH, PhH)[7] produced spiroketal **15**[9] in 53% yield, accompanied by **16**,[9a] **17**,[9a] and **18**.[9a] The stereochemistry of **15**, initially deduced from ^1H NMR data, was confirmed by single-crystal X-ray analysis of alcohol **17**;[11] resilylation of the latter afforded additional **15** (TBDPSOTf, 2,6-lutidine, CH_2Cl_2, 90%). Moreover, equilibration of minor spiroketals **16** and **18** (TsOH, PhH) generated **15** as the major product; treatment of the remaining **16** with DBU (PhH, 24 h, room temperature) then furnished **15** in 70% yield. In this fashion, spiroketal **15** could be prepared from **14a** in 77% overall yield.

At this juncture, completion of the synthesis of **1** entailed reduction of the C(11) ketone, installation of the trans vicinal diol at C(6,7),[17] and deprotection. We reasoned that the ring strain inherent in enone **19** would facilitate both 1,4-addition of a suitable oxygen nucleophile and C(7) hydroxylation via the corresponding enolate, without elimination of the β-alkoxy groups. To this end, diketone **15** was reduced chemo- and stereoselectively with L-Selectride (Scheme III) and the resultant axial alcohol protected as the TBS ether (76% yield, two steps). Unsaturation at C(6,7) was introduced via treatment of the derived enolate (LDA, HMPA, THF, 0 °C) with benzeneseleninyl chloride;[18] this method

Scheme III



circumvented the potential problem of sulfur oxidation. Enone **19**[9a] was then exposed to allyl alcohol and Cs_2CO_3 catalyst; a readily separable mixture of **20**[9a] and **21**[9a] (ca. 3:1, 80%) resulted. Davis hydroxylation[19] of **20** [(a) KHMDS, THF; (b) camphor oxaziridine], isomerization of allyl ether **22** to an enol ether [$RhCl(PPh_3)_3$, aqueous EtOH, DABCO, at reflux],[20] and hydrolysis with methanolic HCl (10% concentrated HCl in anhydrous MeOH, 16 h) then furnished synthetic (±)-breynolide (**1**), identical in all respects (500-MHz ^1H NMR, 125-MHz ^{13}C NMR, IR, MS) except optical rotation with an authentic sample provided by Professor Williams.[21]

In summary, a reasonably concise, stereochemically linear total synthesis of breynolide has been achieved. Importantly, the three secondary hydroxyl groups in penultimate intermediate **22** are differentially protected; this substance therefore holds considerable promise as a precursor to the biologically active glycosides. Progress toward the structure elucidation and total synthesis of the breynins will be reported in due course.

Acknowledgment. Support for this investigation was provided by the National Institutes of Health (National Cancer Institute) through Grant CA19033. In addition, we thank Ms. Michelle Sulikowski and Mr. James J.-W. Duan for preparation of early intermediates.

Supplementary Material Available: Spectroscopic and analytical data for **3**, **5–12**, **14–22** (9 pages). Ordering information is given on any current masthead page.

(14) To facilitate dehydration, **9** was oxidized to a mixture of diastereomeric sulfoxides, employed without separation (see: Davis, F. A.; Jenkins, R. H.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, 5171). Reduction of the vinylic sulfoxides then gave **10**.

(15) The structure of **11** was confirmed via single-crystal X-ray analysis.[11]

(16) Mancuso, A.; Brownfain, D.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

(17) In preliminary experiments, oxidation of 19 with 1 equiv of OsO_4 (Schröder, M. *Chem. Rev.* **1980**, *80*, 187) followed by removal of the protecting groups (HCl, MeOH) gave 6-epibreynolide. Attempted Mitsunobu inversion of this substrate proved fruitless, whereas Williams et al. successfully employed this tactic with a C(7)-OMEM intermediate. In fact, *cis*-1,2-cyclohexanediols generally are poor substrates in this reaction: Mitsunobu, O.; Kimura, J.; Iiizumi, K.; Yanagida, N. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 510.

(18) (a) Ayrey, G.; Barnard, D.; Woodbridge, D. T. *J. Chem. Soc.* **1962**, 2089. (b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(19) Davis, F. A.; Hague, M. S. *J. Org. Chem.* **1986**, *51*, 4083.

(20) (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224. (b) Gent, P. A.; Gigg, R. *J. Chem. Soc., Chem. Commun.* **1974**, 277.

(21) We thank Prof. David R. Williams (University of Indiana) for a generous sample of synthetic (+)-**1**.