

characterized by analytical and spectral data.

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Registry No. 1, 35618-58-7; 2, 82248-46-2; 3, 82309-70-4; 4, 82248-47-3; 5, 82309-71-5; 6, 82248-48-4; 7, 82248-49-5; 8, 35438-35-8; cyclooctatetraene, 629-20-9.

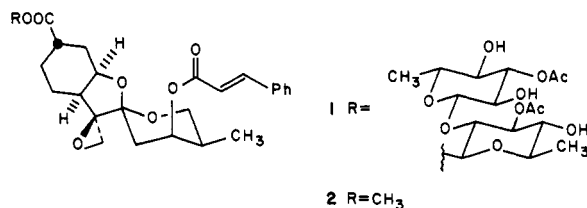
Total Synthesis of (+)-Phyllanthocin

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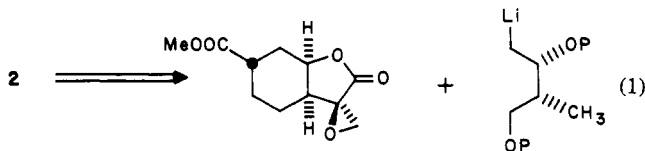
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The crude ethanol extract obtained from the root of *Phyllanthus acuminatus* Vahl^{1,2} was found to inhibit growth in the P388 leukemia system in mice. Kupchan and co-workers traced the interesting pharmacological properties to a bisabolane sesquiterpene glycoside, (+)-phyllanthoside (1).¹ Although the structure



of the corresponding aglycone, (+)-phyllanthocin (2), was elucidated by single-crystal X-ray diffraction, the exact nature of the sugar moiety in 1 and the absolute configurations of 1 and 2 remained unknown. Recently Pettit and co-workers determined the structure of phyllanthose, the novel disaccharide portion of 1, as well as the structures of several closely related tumor inhibitory sesquiterpene glycosides.³ Studies pertaining to phyllanthoside's pronounced activity against the NCI murine B16 melanoma have reached the level of advanced preclinical trials.⁴ We report herein the first synthesis and the absolute configuration of (+)-phyllanthocin (2).

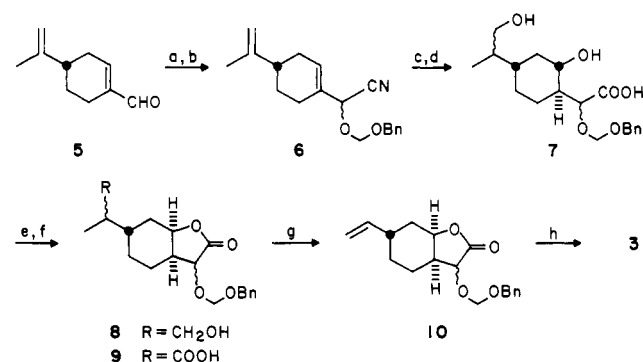
The spiroketal moiety of 2 readily lent itself to the retrosynthetic dissection illustrated in eq 1. Although the convergency of such



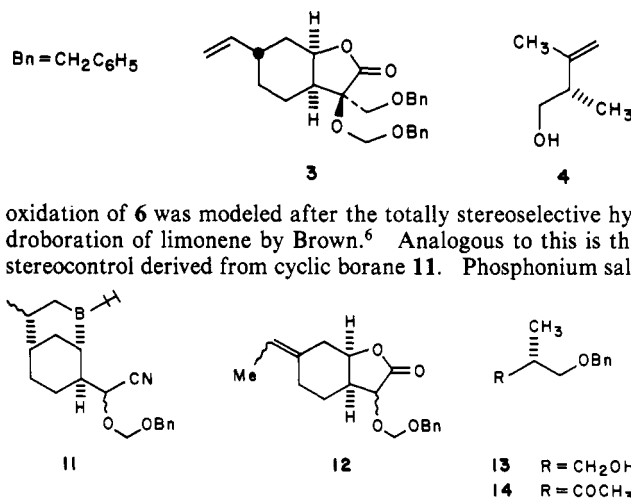
an approach seemed attractive, several problems pertaining to stereocontrol remained. Notably, since the absolute configuration of 2 was unknown, entry into either enantiomeric series was essential. We settled on 3 and 4 as our two pivotal intermediates.

We prepared lactone 3 starting with (*S*)-(-)-perilla aldehyde (5) in eight steps as illustrated in Scheme I. Several features warrant comment. The thexylborane-mediated hydroboration-

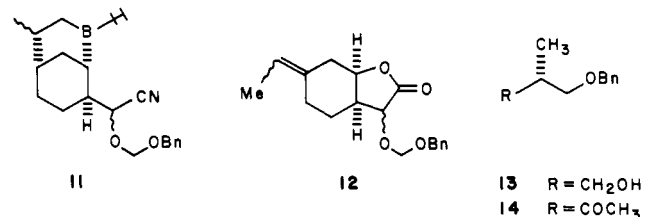
Scheme I



a, KCN/HOAc/diethyl ether/25 °C (95% yield);
b, PhCH₂OCH₂Cl/C₅H₅N/60 °C (51% yield); c, thexylborane/THF/-40 °C H₂O/NaOAc (83% yield); d, KOH/ethanol/100 °C (95% yield); e, EtOOCN=NCOEt/PPH₃/THF/-20 °C; f, Jones' reagent/acetone 0 °C (81% yield from 7); g, Ph(OAc)₄/Cu(OAc)₂/C₅H₅N/benzene/80 °C (82% yield); h, LDA/THF/-78 °C PhCH₂OCH₂Cl/THF/HMPA/-60 °C (71% yield)



oxidation of 6 was modeled after the totally stereoselective hydroboration of limonene by Brown.⁶ Analogous to this is the stereocontrol derived from cyclic borane 11. Phosphonium salt



induced lactonization proceeded with the anticipated⁷ complete inversion of configuration at the alcohol center as shown by comparison of 8 with a sample of the corresponding trans-fused lactone prepared by acid-catalyzed closure. Oxidative decarboxylation of 9 by the method of Kochi⁸ produced 10 as a readily separable mixture of epimers free of regioisomeric impurities corresponding to 12. Although a preference for the formation of the desired terminal alkene was expected,⁹ this exclusive Hofmann orientation was not. Highly stereoselective (≥95%) benzyloxymethylation¹⁰ of the lithium enolate derived from 10 afforded 3 as a white, crystalline solid (mp 50-51 °C). High stereoselectivities in the alkylations of similar systems have been observed.¹¹

Throughout the sequence depicted in Scheme I there are a variety of intermediates that contain one or two random asymmetric centers. Although the eventual destruction of these centers made them inconsequential to the final outcome, they made product analyses in the developmental stages problematic. However, through exhaustive searches for isomeric products and

(1) Kupchan, S. M.; LaVoie, E. J.; Branfman, A. R.; Fei, B. Y.; Bright, W. M.; Bryan, R. F. *J. Am. Chem. Soc.* 1977, 99, 3199.

(2) The plant collection providing the original sample of phyllanthoside was incorrectly believed to be *P. brasiliensis*. Subsequently, this was shown to be an error (ref 3).

(3) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P. *Can. J. Chem.* 1982, 60, 544.

(4) We thank Dr. Matthew Suffness of the National Cancer Institute for this information. Phyllanthocin (2) has been shown to exhibit no antitumor activity (ref 1, 3).

(5) Either antipode of perilla aldehyde can be purchased from Research Organics Inc., Belleville, NJ.

(6) Brown, H. C.; Pfaffenberger, C. D. *J. Am. Chem. Soc.* 1967, 89, 5475. For excellent leading references to cyclic hydroborations see: Still, W. C.; Darst, K. P. *J. Am. Chem. Soc.* 1980, 102, 7385.

(7) For a comprehensive review, see: Mitsunobu, O. *Synthesis* 1981, 1.

(8) Bacha, J. D.; Kochi, J. K. *Tetrahedron* 1968, 24, 2215.

(9) Review: Sheldon, R. A.; Kochi, J. K. *Org. React.* 1972, 19, 279.

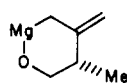
(10) McQuillan, F. J.; Simpson, P. L. *J. Chem. Soc.* 1963, 4726. Caine, D.; Smith, T. L., Jr. *J. Am. Chem. Soc.* 1980, 102, 7568.

(11) Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem.* 1981, 46, 3896. Smith, A. B., Jr.; Richmond, R. E. *Ibid.* 1981, 46, 4816. Welch, S. C.; Gruber, J. M.; Chou, C.-Y.; Willcott, M. R. *Ibid.* 1981, 46, 4816. Grieco, P. A.; Miyashita, M. *Ibid.* 1974, 39, 120. Greene, A. E.; Muller, J.-C.; Ourisson, G. *Ibid.* 1974, 39, 186.

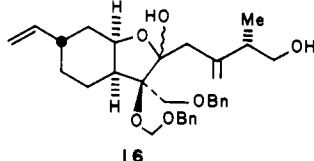
characterizations of the individual components of these mixtures (when possible), combined with compelling literature precedents, we conclude that the stereo- and regioselectivities implicit in Scheme I are very high. In any event, we obtained analytically pure (+)-3 in 16–20% overall yield from (*S*)-(-)-perilla aldehyde (5).¹²⁻¹⁴

Key intermediate 4 was prepared enantiomerically pure from known alcohol 13¹⁵ as follows. Oxidation of 13 (Jones reagent/acetone) followed by methyl ketone formation [(1) 1.5 equiv of (COCl)₂/benzene, (2) 3 equiv of Me₂CuLi/Et₂O, -78 °C] afforded 14 in 75–80% yield. Wittig olefination (Ph₃P=CH₂/THF) and reductive debenzoylation (Li/NH₃) provided 4 (55–60% yield from 14).

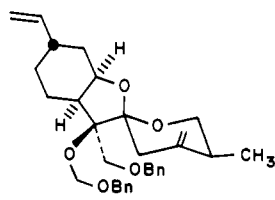
With 3 and 4 in hand we were ready to effect the critical connection. Treatment of alkenol 4 with 2.0 equiv of Schlosser's base (*t*-BuOK/*n*-BuLi/hexane, 0 °C)¹⁶ followed by MgBr₂/THF afforded a milky solution of a dianion that we are tempted to formulate as 15. Addition of "15" (3.5 equiv) to 3 (Et₂O/-60



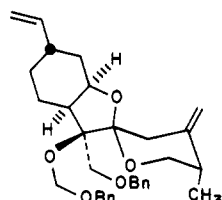
15



16



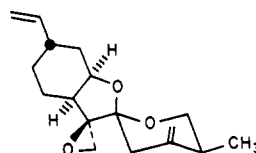
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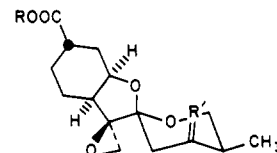
18

°C) provided 16. Crude 16 was induced to spiroketalize (3.0 equiv of ZnCl₂/CH₂Cl₂, -20 °C), producing 17 and 18 (48:1) in 69% combined yield from lactone 3.¹⁷

Completion of the synthesis proceeded uneventfully as follows. The epoxide moiety could be prepared in 82% yield by sequential treatment of 17 with (1) Li/NH₃, (2) MsCl/NEt₃, and (3) DBU/benzene.¹⁸ The two latent carbonyl moieties in resulting diene 19 were unmasked oxidatively by using the method of Sharpless (RuCl₃·3H₂O/NaIO₄/H₂O/CH₃CN/CCl₄).¹⁹ Acid 20 was esterified (CH₂N₂), and the resulting keto ester 21 was reduced with high axial selectivity (KS-Selectride/THF, 0 °C; axial/equatorial = 450:1)²⁰ to provide alcohol 22 in 42% yield overall from 19. Cinnamoylation (*trans*-PhCH=CHCOCl/CH₂Cl₂/C₅H₅N/DMAP) afforded material that was indistin-



19



- 20 R = H; R' = O
21 R = CH₃; R' = O
22 R = CH₃; R' = H, axial OH

guishable from natural (+)-phyllanthocin (2) by routine spectroscopic and analytical techniques.¹²⁻¹⁴

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Registry No. 2, 62948-37-2; 3, 82167-72-4; 4, 82189-55-7; 5, 18031-40-8; 6, 82167-73-5; 7, 82167-74-6; 8, 82167-75-7; 9, 82167-76-8; (3*R*)-10, 82167-77-9; (3*S*)-10, 82167-78-0; 11, 82182-03-4; 13, 63930-46-1; 14, 82167-79-1; 16, 82167-80-4; 17, 82167-81-5; 18, 82189-56-8; 19, 82167-82-6; 20, 82167-83-7; 21, 82167-84-8; 22, 82167-85-9; *trans*-PhCH=CHCOCl, 17082-09-6; (*S*)-(+)-3-hydroxy-2-methylpropanoic acid, 26543-05-5.

Supplementary Material Available: IR, ¹³C NMR, and 300-MHz ¹H NMR data for key intermediates (3 pages). Ordering information is given on any current masthead page.

Delessierine, a New Metabolite of Mixed Biogenesis from the Red Marine Alga *Delesseria sanguinea* (Lamouroux)

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In the past decade, the number of newly discovered metabolites from marine organisms has rapidly increased; however, very few are derived from the secondary sugar metabolism. We now report on the isolation and structure elucidation of such a new metabolite, delessierine (1), without any equivalent from other marine sources

(12) All compounds were purified by flash chromatography [Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, 43, 2923]. Compounds depicted as mixtures were characterized by IR, 90-MHz ¹H NMR, and low-resolution mass spectroscopy. The two epimeric lactones depicted by formula 10 and all subsequent intermediates were characterized by IR, 300-MHz ¹H NMR, and carbon-13 NMR spectroscopy, high-resolution MS or C, H analysis, optical rotation, and melting point (ref 13).

(13) Detailed experimental procedures and spectroscopic data will be reported in a forthcoming publication. Selected spectroscopic data are provided as supplementary material.

(14) The optical purities of 3, 4, and synthetic and natural 2 were checked by a standard literature procedure [see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* 1969, 34, 2543].

(15) Alcohol 13 has been prepared from (*S*)-(+)-3-hydroxy-2-methylpropanoic acid by standard procedures: Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* 1980, 102, 2118 (see ref 13).

(16) Schlosser, M.; Hartmann, J. *Angew. Chem., Int. Ed. Engl.* 1973, 12, 508.

(17) This is a thermodynamically controlled ketalization; identical product distributions can be obtained by equilibration of 17 or 18 under the reaction conditions.

(18) Grieco, P. A.; Oguri, T.; Burke, S. *J. Org. Chem.* 1978, 43, 4552.

(19) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* 1981, 46, 3936.

(20) Determined by digitally integrated gas chromatographic comparison with an authentic sample of the equatorial isomer.

(1) Supported by a CNRS grant (bourse Ingénieur-Docteur) from ICSN.