Total Synthesis and Stereochemistry of (+)-Phyllanthocindiol

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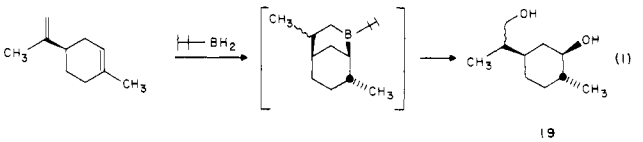
The total synthesis of (+)-phyllanthocindiol starting with (*S*)-(+)-3-hydroxy-2-methylpropanoic acid and (*S*)-(−)-perilla aldehyde is reported. The totally enantioselective sequence elucidated the relative and absolute stereochemistry of (+)-phyllanthocindiol.

The crude ethanol extract obtained from the root of *Phyllanthus acuminatus* Vahl was found to inhibit growth in the P388 leukemia system in mice. Kupchan and co-workers traced the significant pharmacological properties to a bisabolane sesquiterpene glycoside, (+)-phyllanthoside (**1**).[1] Although the structure of the corresponding aglycon (+)-phyllanthocin (**2**) was elucidated by single-crystal X-ray diffraction, the exact nature of the sugar moiety in **1** and the absolute configuration of **1** and **2** remained unknown. Recently, Pettit and co-workers determined the structure of phyllanthose, the novel disaccharide portion of **1** (Chart I), as well as the structure of phyllanthostatins I (**3**) and II (**4**) and the partial structure of phyllanthostatin III (**5**).[2,3] Although the total synthesis of **2** allowed us to determine the absolute configuration of this series,[4a] the relative stereochemistry of the vicinal diol moiety in **5** remained undetermined. We report herein the details of a total synthesis of (+)-phyllanthocindiol (**6**), the hitherto unreported aglycon portion of phyllanthostatin III (**5**), demonstrating that the absolute and relative stereochemistries of **5** and **6** are as drawn.[4b]

Results and Discussion

Synthesis of Lactone 15 (Scheme I). Treatment of (*S*)-(−)-perilla aldehyde (**7**)[5,6] with potassium cyanide and acetic acid[7] at room temperature in diethyl ether for 48 h provided cyanohydrin **8** in 90–95% yield after flash chromatography. The (benzyloxy)methyl ether protecting group seemed ideally suited to protect cyanohydrin **8** due to the absence of an additional unwanted asymmetric center, the presence of a UV-active chromophore for analytical and preparative separations, its base and acid stability, and anticipated economies enjoyed in the deprotection step (vide infra). However, benzyloxymethylation of cyanohydrin **8** proved to be surprisingly problematic. In the presence of a wide variety of tertiary amine bases **8** rapidly decomposed back to aldehyde **7**. In the absence of base, HCl-mediated olefin isomerization at the isopropenyl side chain became competitive.[8] Under fully maximized conditions, reaction of cyanohydrin **8** with chloromethyl benzyl ether in the presence of a *deficiency* of pyridine (50 mol %) at reflux in methylene chloride provided a 54% yield of **9** (NMR integration), contaminated by the relatively innocuous dibenzyl formal.

On the basis of Brown's hydroboration of limonene (eq 1)[9,10] we felt that the requisite 1,4-trans stereochemical relationship in the cyclohexane system could be generated stereospecifically with concomitant introduction of the proper oxygenation pattern. After treatment of diene **9** with thexylborane at −40 °C in anhydrous tetrahydrofuran, oxidative workup produced diol **10** in 83% yield along with minor amounts of monohydroboration product **16** (10–15%). The stereochemistry assigned to **10** was based strictly on literature precedent; the presence of two randomized asymmetric centers made stereochemical studies difficult at best.



(1)

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Hydrolysis of nitrile **10** with 40% potassium hydroxide in absolute ethanol at reflux for 1–2 h gave a 95% yield of a readily separable mixture of acids **11a** and **11b**.[11] By independent conversion of the two acids to **14a** and **14b**, respectively, the relative configurations of the alkoxy acid moieties in **11a** and **11b** (and all subsequent intermediates) could be determined.[11] Lactonization of the mixture of diol acids **11a,b** with diethyl azodicarboxylate/triphenylphosphine[12] in tetrahydrofuran at −20 °C provided chromatographically separable lactones **12a** and **12b** in 87% yield. The lactonization proceeded with the anticipated[13] complete inversion of configuration at the alcohol

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

(2) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P. *Can. J. Chem.* **1982**, *60*, 544, 939.

(3) Phyllanthoside and phyllanthostatins I–III exhibit significant cytotoxicity and antileukemic activity (ref 1 and 2). Studies pertaining to phyllanthoside's pronounced activity against the NCI murine B16 melanoma are still at the level of advanced preclinical trials. Phyllanthocin exhibits no antitumor activity (ref 1 and 2), and phyllanthocindiol appears not to have been tested yet. We thank Dr. Matthew Suffness of the National Cancer Institute for this information.

(4) (a) For a preliminary report of the total synthesis of (+)-phyllanthocin (**2**), see: McGuirk, P. R.; Collum, D. B. *J. Am. Chem. Soc.* **1982**, *104*, 4496. (b) Full experimental details for the conversion of **40** to (+)-phyllanthocin (**2**; ref 4a) and the optical purity proofs described herein are included as supplementary material.

(5) For other examples of perilla aldehyde in organic syntheses, see: Hortmann, A. G.; Ong, A. Q. *J. Org. Chem.* **1970**, *35*, 4290. Parker, K. A.; Kallmerten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5881. Mounden, A.; Surburg, H. *Chem Ber.* **1981**, *114*, 118. Joshi, G. D.; Kulkarni, S. N. *Indian J. Chem.* **1968**, *25*, 155. Banerjee, R. C. *J. Sci. Ind. Res., Sect. B* **1962**, *B21*, 285.

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

(7) Rambaud, R. *Bull. Soc. Chim. Fr.* **1934**, 1318.

(8) A number of other methods also failed. For example, see: Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 2527. Corey, E. J.; Gras, J.-L.; Ulrich, P. *Ibid.* **1976**, 809. Various silver salt- and iodide-catalyzed procedures effected no improvements.

(9) Brown, H. C.; Pfaffenberger, C. D. *J. Am. Chem. Soc.* **1967**, *89*, 5475. Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *Ibid* **1971**, *93*, 1491.

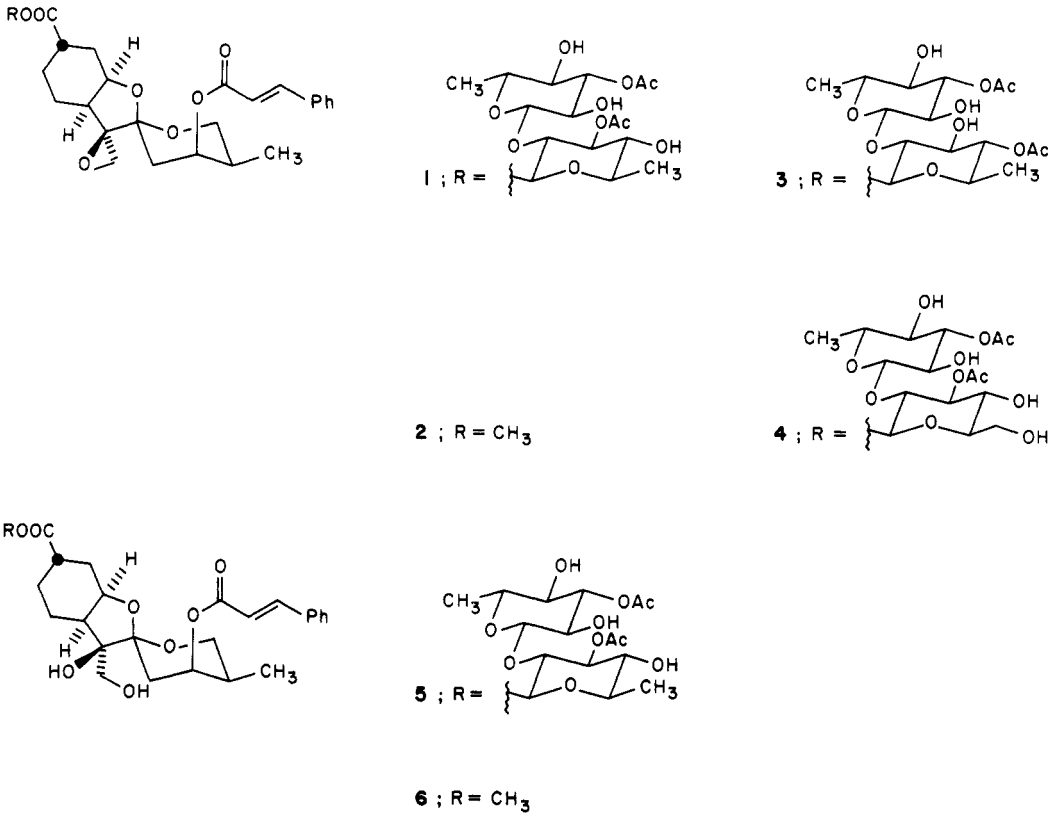
(10) For excellent leading references to cyclic hydroborations, see: Still, W. C.; Darst, K. P. *J. Am. Chem. Soc.* **1980**, *102*, 7385.

(11) The stereochemistries of lactones **14a** and **14b** were assigned on the basis coupling constants measured in their 300-Mhz ^{1}H NMR spectra. Furthermore, quantitative conversion of **14a** to **14b** was observed by kinetic protonation of the corresponding lithium enolate (presumably from the convex face). The independent conversion of **11a** → **12a** → **13a** → **14a** and **11b** → **12b** → **13b** → **14b** allowed the same stereochemical assignment as above to be made throughout the sequence. The epimers at the hydroxypropyl side chain were never separable.

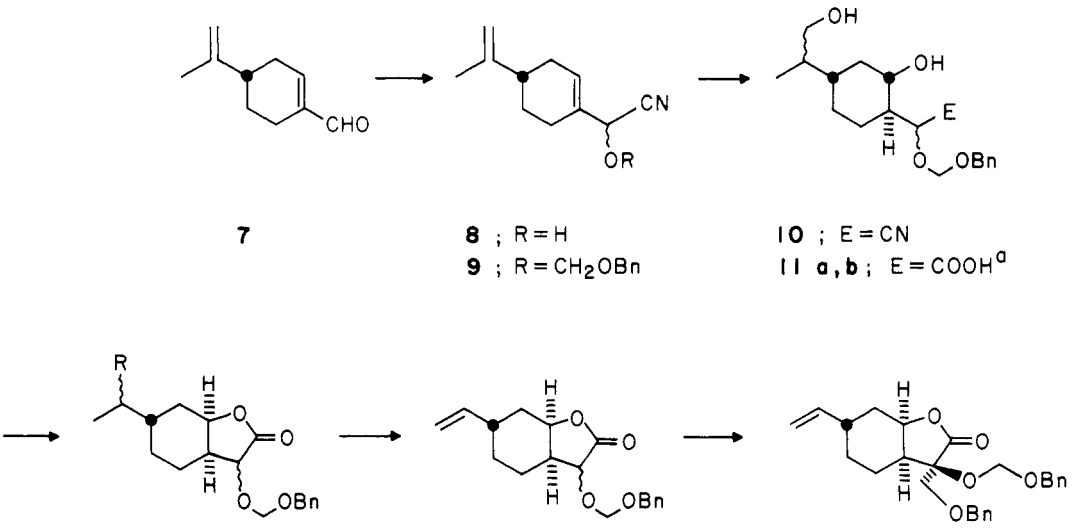
(12) For a comprehensive review, see: Mitsunobu, O. *Synthesis* **1981**, 1.

0022-3263/84/1949-0843$01.50/0

Chart I

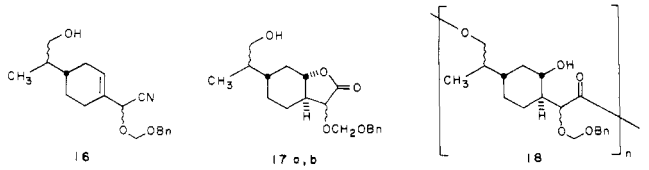


Scheme I[a]



[a] Isomers 11a, 12a, 13a, and 14a are those with the OCH_2OBn group on the α face.

center as shown by comparison with the corresponding trans-fused lactones **17a,b** prepared by protic acid-cata-



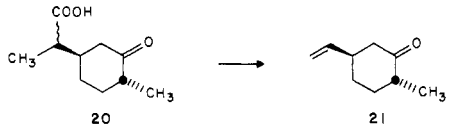
lyzed closure. High dilution conditions during lactonization were employed to suppress the formation of significant amounts (up to 50%) of material believed to be head-to-tail oligomer **18**.[14]

Using limonene-derived diol **19** as a model system, we explored what proved to be a highly efficient degradation of the propanol side chain in **12a,b** to the terminal vinyl

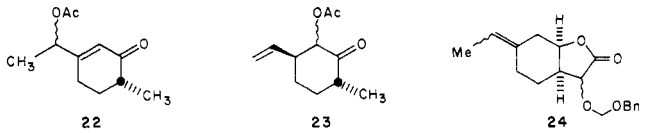
(13) Melillo, D. G.; Liu, T.; Ryan, K.; Sletzinger, M.; Shinkai, I. *Tetrahedron Lett.* **1981**, *22*, 913. Kurihara, T.; Nakajima, Y.; Mitsunobo, O. *Tetrahedron Lett.* **1976**, 2455. Trost, B. M.; Shuey, C. D.; DiNinno, F., Jr.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1284. Takano, S.; Yonaga, M.; Ogasawara, K. *Synthesis* **1981**, 265. Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119. Meyers, A. I.; Amos, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 870.

(14) Compound **18** exhibited all of the anticipated spectral properties: IR (neat) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (s, 5 H), 4.83 (s, 2 H), 4.75 (m, 1 H), 4.63 (s, 2 H), 4.30–3.30 (br m, 5 H), 2.10–1.05 (br m, 8 H), 0.86 (t, 3 H); high molecular weight (>800 amu). Furthermore, hydrolysis ($K_2CO_3/CH_3OH/H_2O$) afforded **11a,b**.

group in key intermediate **15**. Following oxidation of diol **19** (Jones reagent), exposure of the resulting keto acid **20**



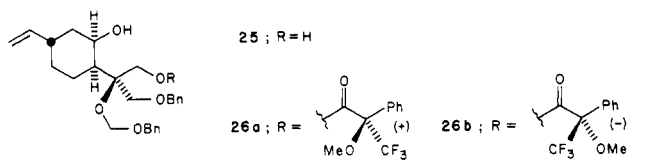
20 **21**



22 **23** **24**

to Kochi oxidative decarboxylation conditions (lead tetraacetate/cupric acetate/pyridine in benzene/80 °C)[15] produced terminal alkene **21** in 60% yield.[16] Minor products **22** and **23** were isolated[16] in 1.9 and 9.5% yield, respectively, along with several more polar materials (<-10% combined yield). However, none of the internal double-bond isomer could be detected. Although a preference for the formation of the terminal alkene was expected,[15,17] this *exclusive* Hofmann orientation was not. Oxidation of the alcohol moiety of **12a,b** with 8 N Jones reagent in acetone at 0 °C gave separable acids **13a** and **13b** in 81% yield from **11a,b**. Analogous oxidative decarboxylation of the **13a,b** mixture cleanly produced **14a,b** as a readily separable mixture of epimers free of regioisomeric impurities corresponding to **24**.[18] After separation by flash chromatography, lactones **14a** and **14b** were each shown to be homogeneous by the gamut of analytical and spectroscopic techniques.[11]

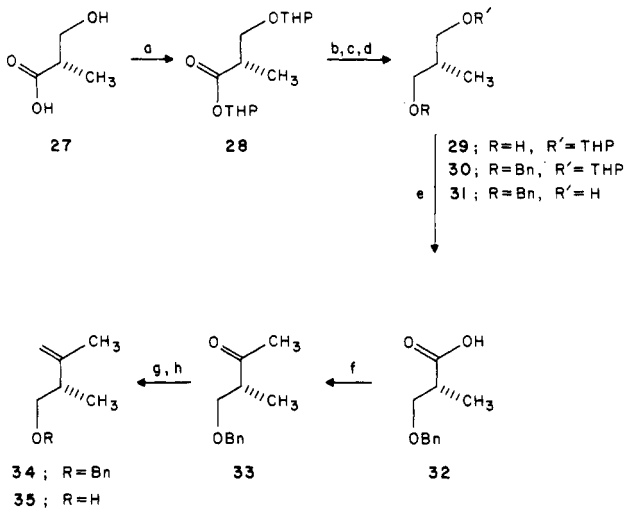
Treatment of **14a,b** with lithium diisopropylamide in tetrahydrofuran at −78 °C followed by addition of benzyl chloromethyl ether[19] in hexamethylphosphoric triamide provided lactone **15** (mp 50–51 °C, 62–71% yield), with highly stereoselective alkylation occurring from the convex α face; high stereoselectivities (≥95%) have been observed in alkylations of similar systems.[20] The optical purity of lactone **15** was determined by LAH reduction to diol **25**



25; R = H

26a; R = **26b**; R =

Scheme II[a]



27 **28**

29; R = H, R′ = THP
30; R = Bn, R′ = THP
31; R = Bn, R′ = H

34; R = Bn
35; R = H

33 **32**

[a] (a) Dihydropyran/CH_2Cl_2/*p*-TsOH/0 °C; (b) $LiAlH_4$/THF/0 °C; (c) KH/$PhCH_2Br$/THF/23 °C; (d) *p*-TsOH/95% ethanol/reflux (65% yield from **10**); (e) $CrO_3 \cdot H_2SO_4$/acetone/23 °C (85% yield); (f) $(COCl)_2$/benzene/50 °C followed by $(CH_3)_2CuLi$/THF/−78 °C → 0 °C (80% yield; (g) $Ph_3P{=}CH_2$/THF/0 °C (69% yield); (h) Li/NH_3/−78 °C/2.0 min (79% yield).

(THF/0 °C; 86% yield) with subsequent conversion to diasteromeric MTPA esters **26a** (83% yield) and **26b** (81% yield) by the method of Dale.[21] Esters **26a** and **26b** were shown to be isomerically pure (>98%).[4b]

Throughout the synthesis of key fragment **15** several intermediates contained one or two random asymmetric centers. Although the eventual destruction of these centers made them inconsequential to the final outcome, product analyses in the developmental stages were often difficult. However, through rigorous searches for isomeric products and characterization of individual components of epimeric mixtures (when separation was possible),[11] combined with strong literature precedents, we concluded that the stereo- and regioselectivities in the synthesis of lactone **15** were high. In any event, analytically pure (+)-**15** was obtained in 16–20% overall yield from enantiomerically pure (*S*)-(−)-perilla aldehyde (**7**).

Synthesis of Alkenol 35. Preparation of key fragment **35** from readily available (*S*)-(+)-3-hydroxy-2-methylpropanoic acid (**27**) was effected uneventfully in 24–28% overall yield by the sequence of reactions depicted in Scheme II. Full experimental details are reported in the Experimental Section. The optical purity of **35** was determined by conversion[21] to diastereomeric MTPA esters **36a** and **36b**. Although esters **36a** and **36b** were indistinguishable by ^{13}C NMR and ^{19}F NMR spectroscopy, as well

36a **36b**

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

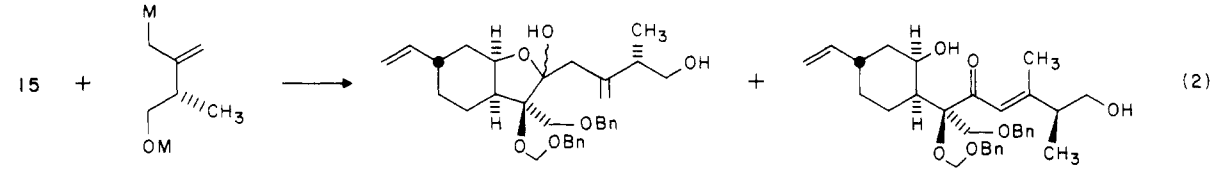
(16) **21**: $[\alpha]^{22}_D$ +21.0° (*c* 7.05, $CHCl_3$); IR (neat) 3100, 2950, 2890, 1720, 1650, 1460, 1428, 1380, 1366, 1320, 1246, 1222, 1197, 1000, 920, 890, 732, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (ddd, J = 16.8, 10.4, 6.2 Hz, 1 H), 5.00 (ddd, J = 16.8, 1.4, 1.4 Hz, 1 H), 4.96 (ddd, J = 10.4, 1.2, 1.2 Hz, 1 H), 2.47–2.20 (m, 3 H), 2.17–2.05 (m, 2 H), 1.94–1.87 (m, 1 H), 1.62–1.48 (m, 1 H), 1.37 (ddd, J = 16.0, 12.7, 3.1 Hz, 1 H), 1.01 (d, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.19, 140.82, 112.46, 46.43, 43.69, 43.03, 33.98, 30.88, 13.66; exact mass calcd for $C_9H_{14}O$ 138.1045, found 138.1046. **22**: IR (neat) 2950, 1750, 1695, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.65 (s, 1 H), 5.61 (m, 1 H), 2.90 (sextet, 1 H), 2.60 (m, 1 H), 2.20 (m, 1 H), 2.10 (s, 3 H), 1.80–1.10 (m, 5 H), 1.10 (d, 3 H); MS, *m/e* 197 (M + H, isobutane). **23**: IR (neat) 3100, 2950, 1750, 1725, 1650, 1460, 1370, 1227 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (m, 1 H), 5.20–4.85 (m, 3 H), 2.65 (sextet, 1 H), 2.50–1.20 (m, 5 H), 2.10 (s, 3 H), 1.10 (d, J = 7.0 Hz, 3 H); MS, *m/e* 197 (M + H, isobutane).

(17) Beckwith , A. J. L.; Cross, R. T.; Gream, G. E. *Aust. J. Chem.* **1974**, *27*, 1673. Barton, *J. Chem. Soc. C.* **1969**, *1047*.

(18) If the reaction was run unshielded from laboratory light, significant amounts (up to 5% yield) of the corresponding 2° acetate were formed: ^1H NMR ($CDCl_3$) δ 7.26 (s, 5 H), 5.20–4.60 (m, 4 H), 4.60 (s, 2 H), 3.95 (br s, 1 H), 2.30–1.10 (m, 8 H), 2.00 (s, 3 H), 1.25 (d, 3 H).

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

(20) Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem.* **1981**, *46*, 3896. Welch, S. C.; Gruber, J. M.; Chow, C.-Y; Willcott, M. R. *Ibid.* **1981**, *46*, 4816. Greene, A. E.; Muller, J.-C.; Ourisson, G. *Ibid.* **1974**, *39*, 186. Grieco, P. A.; Miyashita, M. *Ibid.* **1974**, *39*, 120. Shibasaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* **1980**, *21*, 3587. Welch, S. C.; Chayabunjonglerd, S. *J. Am. Chem. Soc.* **1979**, *101*, 6768. Whitesell, J. K.; Matthews, R. S.; Helbling, A. M. *J. Org. Chem.* **1978**, *43*, 784. Nozoe, S. *Tetrahedron Lett.* **1976**, 195. Han, Y.-K.; Paquette, L. A. *J. Org. Chem.* **1979**, *44*, 3731. Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1979**, *101*, 6765.



37a; M = Li
37b; M = K
37c; M = MgBr

as HPLC, their 300-MHz ^{1}H NMR spectra showed them to be at least 98% isomerically pure.[4b,22]

Synthesis of (+)-Phyllanthocindiol (6). With successful syntheses of lactone **15** and alkenol **35** behind us we were ready to effect the last and most crucial carbon–carbon bond forming step of the synthesis (eq 2). Initial attempts to generate dianion **37a** from alkenol **35** by using *n*-butyllithium or *sec*-butyllithium and *N,N,N′,N′*-tetramethylethylenediamine in hexanes were disappointing.[23] The yields of **37a** were low and its generation required prolonged reactions times, typically 1–2 days at 0 °C, as shown by quenching with benzaldehyde. However, by employing 2 equiv of Schlosser's base (potassium *tert*-butoxide/*n*-butyllithium)[24] in hexanes at 0 °C, the formation of dianion **37b** was rapid (1–2 h). Unfortunately, reaction of the potassium dianion **37b** with lactone **15** caused extensive enolization of the resulting ketone moiety. Using a variety of quenching conditions, we isolated **38**, along with 25–30% of the isomerized product **39**. Upon conversion of **37b** to the less dissociated[25] magnesium species (**37c**) using magnesium dibromide, adduct **38** could be obtained cleanly by adding 3.5 equiv of **37c** to lactone **15** in diethyl ether at −60 °C. Only a trace of the conjugated enone system was visible by thin-layer chromatography.

We were moderately concerned about the stereochemical outcome of the impending spiroketalization of **38**. It seemed reasonable to assume that the spiroketal function in this series of sesquiterpenes arose from a biosynthetic precursor *prior to cinnamoylation*, with the preference for the observed stereochemistry at the ketal ring fusion resultant of the very favorable[26] intramolecular hydrogen bonding indicated in Figure 1. Stereocontrol in the ketalization of **38** would have to depend on less dramatic conformational energy contributions. However, we felt that ketalization would provide the desired ketal **40**. The exocyclic protected vicinal diol moiety, by virtue of its size, should maintain an equatorial disposition with respect to both cyclohexanoid ring systems. Thus, we needed to consider stereoisomeric spiroketals **40** and **41** only in the conformations depicted. The two six-atom (van der Waals)

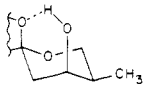
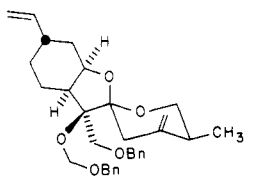


Figure 1.

interactions in ketal **41** (and absent in **40**) were noted.[27,28]



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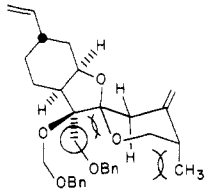
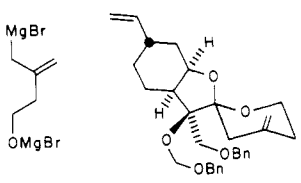
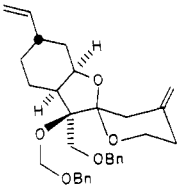


41

In the event, ketalization of **38** using excess $ZnCl_2$ (CH_2Cl_2/−20 °C) afforded a 48:1 mixture of ketals **40** and **41**. Equilibration of either ketal under the reaction conditions provided the same product distribution, indicating the process to be under thermodynamic control.[29] By subjecting crude **38** to the ketalization conditions we were able to obtain ketal **40** in 72% overall yield from lactone **15**. Out of curiosity we sought additional information on the source of the apparent 1.8–2.0-kcal preference for ketal **40**. Treatment of lactone **15** with desmethyl anion **42**[23]



42 43



44

followed by ketalization under similar conditions provided a 1:1.5 mixture of ketals **43** and **44**, respectively (70% overall yield).[30] Thus axial placement of the methyl group

(21) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. The absolute configurations of (−)- and (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride have been determined: Kalyanam, N.; Lightner, D. A. *Tetrahedron Lett.* **1979**, 415.

(22) Addition of *racemic* **37c** to lactone **15** demonstrated that the other enantiomer of **37c** was not present in our chiral sample; the resulting stereoisomer would have been detected.

(23) The dianion of 3-methyl-3-buten-1-ol has been reported [Cardillo, G.; Contento, M.; Sandri, S. *Tetrahedron Lett.* **1974**, 2215]. However, we have found Schlosser's base (*t*-BuOK/*n*-BuLi/hexane; ref 24) to be far superior to the organolithium–TMEDA complexes for difficult deprotonations.

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

(25) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737.

(26) Aaron, H. S. *Top. Stereochem.* **1979**, *11*, 1.

(27) The *A* value for 3-methyltetrahydropyran has been reported to be 1.44 kcal/mol: Eliel, E. L.; Hargrave, K. D.; Pietrusiewicz, K. M.; Manoharan, M. *J. Am. Chem. Soc.* **1982**, *104*, 3635.

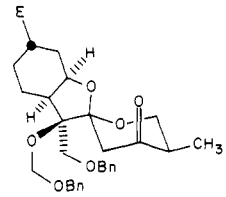
(28) For a detailed review on the kinetics and thermodynamics of cyclic ketal and acetal formation, see: Clode, D. M. *Chem. Rev.* **1979**, *79*, 491.

(29) Protic acid-mediated cyclization of **38** under exlusively kinetic conditions (HCl/CH_2Cl_2/0 °C) afforded a 5:1 ratio of spiroketals **40** and **41** (49% yield from lactone **15**).

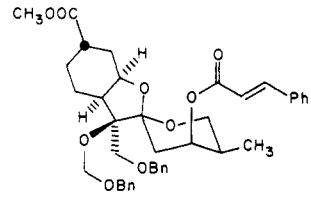
(30) **43**: IR (film) 3050, 2900, 2880, 1660, 1640, 1500, 1450, 1410, 1380, 1370, 1282, 1250, 1150, 1120, 1070, 1025, 988, 910, 890, 735, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (m, 10 H), 5.75 (ddd, *J* = 17.1, 10.4, 6.4 Hz, 1 H), 5.02 (AB q, J_{AB} = 6.0 Hz, 2 H), 4.97 (ddd, *J* = 17.1, 1.6, 1.6 Hz, 1 H), 4.90 (ddd, *J* = 10.4, 1.6, 1.6 Hz, 1 H), 4.79 (dt, *J* = 4.5, 1.9 Hz, 2 H), 4.68 (AB q, J_{AB} = 11.9 Hz, 2 H), 4.50 (AB q, J_{AB} = 11.9 Hz, 2 H), 4.08 (dd, *J* = 8.2, 4.0 Hz, 1 H), 3.83 (AB q, J_{AB} = 11.3 Hz, 2 H), 3.82 (dt, *J* = 10.5, 3.0 Hz, 1 H), 3.69 (dd, *J* = 10.5, 5.5 Hz, 1 H), 2.49 (AB q, J_{AB} = 14.1 Hz, 2 H), 2.50–2.42 (m, 1 H), 2.34–2.23 (m, 2 H), 2.16–2.02 (m, 2 H), 1.77 (br d, *J* = 13.0 Hz, 1 H), 1.63–1.55 (m, 2 H), 1.35 (ddd, *J* = 14.5, 10.8, 3.7 Hz, 1 H), 1.10–0.98 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 143.70, 142.09, 138.58, 138,29, 128.19, 127.66, 127.46, 127.37, 112.30, 109.86, 108.06, 91.72, 89.68, 73.39, 70.76, 69.93, 61.98, 43.12, 41.90, 34.83, 33.95, 33.22, 29.76, 22.00; exact mass calcd for $C_{31}H_{38}O_5$ 490.2719, found 490.2701. **44**: IR (neat) 3090, 2920, 1660, 1640, 1500, 1450, 1408, 1370, 1350, 1275, 1240, 1185, 1140, 1100, 1070, 1060, 1025, 1010, 990, 910, 890, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37–7.26 (m, 10 H), 5.76 (ddd, *J* = 17.0, 10.4, 6.1 Hz, 1 H), 5.10 (AB q, J_{AB} = 7.1 Hz, 2 H), 4.97 (ddd, *J* = 17.0, 1.5, 1.5 Hz, 1 H), 4.90 (ddd, *J* = 10.4, 1.5, 1.5 Hz, 1 H), 4.74 (dd, *J* = 20.6, 1.9 Hz, 2 H), 4.76 (AB q, J_{AB} = 12.0 Hz, 2 H), 4.49 (AB q, J_{AB} = 11.9 Hz, 2 H), 4.15 (br quintet, 1 H), 3.95 (dt, *J* = 10.8, 2.8 Hz, 1 H), 3.84 (dd, *J* = 10.8, 5.2 Hz, 1 H), 3.70 (AB q, J_{AB} = 10.4 Hz, 2 H), 2.64 (quintet, 1 H), 2.50 (br d, *J* = 13.6 Hz, 1 H), 2.35–2.21 (m, 2 H), 2.15–2.03 (m, 4 H), 1.74 (br d, *J* = 12.6 Hz, 1 H), 1.61–1.55 (7, 1 H), 1.32–1.21 (m, 1 H), 1.10–0.92 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 143.99, 141.70, 138.48, 137.86, 128.39, 127.95, 127.71, 127.51, 127.37, 112.20, 110,15, 104.65, 91.87, 88.02, 75.44, 73.54, 70.17, 69.98, 60.76, 39.41, 35.61, 35.36, 33.70, 29.95, 22.15; exact mass calcd for $C_{31}H_{38}O_5$ 490.2719, found 490.2700.

in **41** occurred at a significant cost.

Although ruthenium-catalyzed olefin cleavage[31] of **40** to keto acid **45** failed completely, a slightly less efficient se-



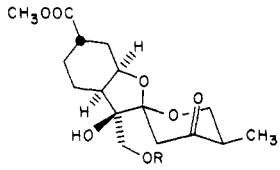
45 ; E = COOH
46 ; E = CHO
47 ; E = $COOCH_3$



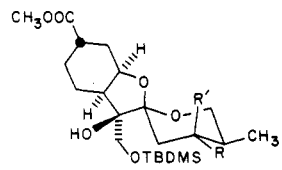
48

quence proceeded uneventfully. Thus, ozonolysis of **40** in methylene chloride at −78 °C followed by reduction with dimethyl sulfide[32] (23 °C/26 h) furnished ketoaldehyde **46** in 70% yield. Rigorous temperature control and immediate quenching at −78 °C upon saturation with ozone was crucial. Aldehyde **46** was oxidized to keto acid **45** with 8 N Jones reagent in acetone at −10 °C, and the crude acid was esterified directly with ethereal diazomethane at 0 °C to provide keto ester **47** in 80% purified yield from **46**.

Initially we attempted to complete the synthesis of **6** from **47** by a reduction–cinnamoylation sequence proceeding through penultimate intermediate **48**. However, all attempts to selectively remove the benzyl ether functions in the presence of the cinnamate group failed. Therefore, the following slightly less efficient sequence was employed. Hydrogenolysis of keto ester **47** (10% palladium-on-carbon/H_2) furnished diol **49** in 96% yield. Protection of the primary alcohol function of **49** with *tert*-butyldimethylsilyl chloride provided protected diol **50** in 77% yield.



49 ; R = H
50 ; R = $Si(CH_3)_2(t\text{-}Bu)$



51 ; R = H, R′ = OH
52 ; R = OH, R′ = H
53 ; R = H, R′ = trans-C(O)CH=CHPh

Addition of hydride from the equatorial face of ketone **50** to provide the desired axial alcohol **51** was favored by both the equatorially disposed methyl group[33] and the axially disposed β-alkoxy function.[34] Reduction of the ketone moiety with sodium borohydride at 0 °C produced a 12:1 (axial/equatorial) mixture of separable alcohols **51** and **52** (91% combined yield). Alternatively, KS-Selectride[35] (Aldrich) reduction of **50** in tetrahydrofuran at 0 °C gave the axial alcohol **51** exclusively (>450:1) in 54% yield after alkaline hydrogen peroxide workup. The resulting monoprotected triol **51** was cinnamoylated to provide silyl-protected (+)-phyllanthocindiol **53** in 83% yield. Deprotection with tetra-*n*-butylammonium fluoride in tetrahydrofuran furnished (+)-phyllanthocindiol (**6**). The synthetic sample of **6** was indistinguishable from an authentic sample by using the gamut of chromatographic, spectroscopic, and analytical techniques. The optical rotation of our synthetic sample [$[\alpha]^{22.5}_D$ +3.4°, (*c* 1.67, $CHCl_3$)] was slightly high compared to that of the naturally derived sample [$[\alpha]^{23}_D$ +2.45°, (*c* 1.66, $CHCl_3$)].[36]

Experimental Section[37]

(4*S*)-7-Hydroxy-*p*-mentha-1,8-diene-7-carbonitrile (8). A solution of (*S*)-(−)-perilla aldehyde (**7**; 3.0 g, 20.0 mmol) in anhydrous diethyl ether (20 mL) at 0 °C is treated with glacial acetic acid (1.6 mL, 28.0 mmol) and finely pulverized potassium cyanide (1.8 g, 28.8 mmol). The reaction pot is warmed to room temperature under a dry ice condenser. After a 3-h period, the reaction is stirred at room temperature for an additional 48 h. The resulting white suspension is partitioned between ether (100 mL) and water (50 mL). The aqueous layer is extracted with additional ether (3 × 100 mL), and the combined organic layers are dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (25% ethyl acetate/75% hexanes) affords 3.36 g (95%) of **8** as a light yellow oil: IR (neat) 3450, 3050, 2900, 2250, 1675, 1650, 1435, 1150, 1035, 895, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.10 (br s, 1 H), 4.87 (br s, 1 H), 4.70 (m, 2 H), 2.99 (d, 1 H, OH), 2.45–1.60 (m, 7 H), 1.72 (s, 3 H); exact mass calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1153.

(4*S*)-7-[(Benzyloxy)methoxy]-*p*-mentha-1,8-diene-7-carbonitrile (9). Benzyl chloromethyl ether (26.5 mL, 193 mmol) is added to a magnetically stirred solution of cyanohydrin **8** (14.56 g, 82.3 mmol) in methylene chloride (200 mL) and pyridine (6.9 mL, 85.0 mmol) at 0 °C under nitrogen. The clear, colorless solution is allowed to warm to 23 °C and then refluxed at 60 °C for 22 h. The resulting yellow solution is partitioned between methylene chloride (200 mL) and water (100 mL), and the organic layer is washed with water (2 × 100 mL), saturated aqueous sodium bicarbonate (2 × 100 mL), and saturated aqueous sodium chloride (100 mL). The organic layer is dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (10% ethyl acetate/90% hexanes) provides 18.02 g of a mixture consisting of 13.2 g of **9** (54%, NMR integration) and 4.82 g of a reagent related byproduct, dibenzylformal. This material is used without further purification. A small analytical sample of **9** is obtained by HPLC [μ-Porasil (30 cm), 2% ethyl acetate/98% hexanes]: IR (neat) 3050, 2900, 1675, 1640, 1500, 1450, 1430, 1375, 1210, 1160, 1150, 1100, 1025, 900, 735, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (s, 5 H), 6.09 (br s, 1 H), 5.00–4.60 (m, 5 H), 4.70 (s, 2 H), 2.50–1.50 (br m, 7 H), 1.70 (br s, 3 H); exact mass calcd for $C_{19}H_{23}NO_2$ 297.1729, found 297.1730.

(1*S*,2*S*,4*S*)-7-[(Benzyloxy)methoxy]-2,9-dihydroxy-*p*-menthane-8-carbonitrile (10). A 0.5 M solution of thexylborane (15 mL, 7.5 mmol) in tetrahydrofuran is added rapidly to a solution of diene **9** (1.5 g, 5.05 mmol) in tetrahydrofuran (15 mL) at −40 °C under nitrogen. The clear, colorless solution is warmed to 23 °C over a period of 3 h, cooled to 0 °C, and quenched with

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(32) Pappas, J.; Keaveney, W. P.; Gaucher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273.

(33) For highly stereoselective reductions of 2-alkylcycloalkanones, see: Brown, H. C.; Dickason, W. C. *J. Am. Chem. Soc.* **1970**, *92*, 709. Yamamoto, Y.; Toi, H.; Sonoda, A.; Murashi, S.-I. *Ibid.* **1976**, *98*, 1965. Kretchmer, R. A.; Thompson, W. J. *Ibid.* **1976**, *98*, 3379. Caine, D.; Hasenhuettl, G. *J. Org. Chem.* **1980**, *45*, 3278.

(34) Axially disposed β-alkoxy groups exert strong influences on the stereochemistry of dissolving metal- and complex metal hydride-mediated ketone reductions: Jaisli, F.; Sternbach, M.; Shibuya, M.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1978**, *18*, 637.

(35) Krishnamurthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 3383.

(36) We thank Dr. G. R. Pettit and Dr. G. M. Cragg for providing an authentic sample of **6**, as well as effecting the mixture melting point determination on **6**.

(37) Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Optical rotations were taken on a Perkin-Elmer Model 141 polarimeter. ^1H NMR were taken on a 300-MHz Bruker WM-300 or a 90 MHz Varian EM-390 instrument and ^{13}C NMR were performed with a JEOL FX-90Q operating at 22.7 MHz. Gas chromatography was performed on a Varian 3700 chromatograph with digital integration. Solvents and reagents were purified and dried by using standard procedures.

water (500 μL). To the mixture at 0 °C is added a solution of 3 M sodium acetate and 30% hydrogen peroxide [1:1 (v/v), 5 mL]. The resulting two-phase mixture is heated to 50 °C for 1 h, cooled to room temperature, and diluted with diethyl ether (100 mL). After saturation of the aqueous layer with sodium chloride, the organic layer is separated and washed with water (50 mL) and saturated aqueous sodium chloride (50 mL). The combined aqueous layers are extracted with additional ether (4 × 50 mL), and the combined organic layers are dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (ethyl acetate) affords 1.4 g (83%) of **10** as a clear, colorless oil: IR (neat) 3350, 2900, 2250, 1500, 1450, 1375, 1200, 1175, 1140, 1100, 1050, 950, 905, 740, 695, cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (s, 5 H), 4.90–4.78 (m, 3 H), 4.62 (s, 2 H), 3.50 (br d, 3 H), 2.20–0.80 (m, 9 H), 0.90 (d, J = 7.0 Hz, 3 H); exact mass calcd for $C_{19}H_{27}NO_4$ 333.1940, found 333.1949.

(1*S*,2*S*,4*S*)-7-[(Benzyloxy)methoxy]-2,9-dihydroxy-*p*-menthane-7-carboxylic Acid (11a,b). A solution of nitrile **10** (395 mg, 1.19 mmol) in absolute ethanol (6 mL) and 40% aqueous potassium hydroxide (5 mL) is heated to 120 °C under nitrogen for 2 h. The resulting yellow solution is cooled to room temperature and extracted with diethyl ether (2 × 5 mL). The aqueous layer is cooled to 0 °C, acidified to pH 1 with 8 N hydrochloric acid, and extracted with diethyl ether (5 × 20 mL). The resulting organic phase is dried ($MgSO_4$) and filtered, and the solvents are removed in vacuo to yield 398.5 mg (95%) of an off-white solid, which is two spots by TLC. The epimeric mixture of four compounds is routinely carried on to the next step without purification. However, the epimers adjacent to the carboxyl group can be separated for analytical purposes (flash chromatography; 99% acetone/1% acetic acid). **11a** (elutes first): white crystals; mp 118–119 °C (recrystallized from chloroform); IR (KBr) 3500–2500, 2900, 1700, 1500, 1450, 1400, 1390, 1300, 1225, 1175, 1150, 1110, 1090, 1040, 955, 905, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3/Me_2SO$-d_6) δ 7.20 (s, 5 H), 5.10 (br s, 3 H, OH), 4.70 (s, 2 H), 4.60 (s, 2 H), 4.55 (m, 1 H), 3.50 (m, 3 H), 2.10–1.00 (m, 9 H), 0.89 (d, J = 6.4 Hz, 3 H); MS, m/e 335 (M − 17). **11b**: white crystals; mp 152–153 °C (recrystallized from chloroform/acetone); IR (KBr) 3500–2500, 2900, 1720, 1450, 1380, 1210, 1165, 1100, 1050, 930, 905, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3/Me_2SO$-d_6) δ 7.20 (s, 5 H), 5.50–4.90 (br s, 3 H, OH), 4.72 (s, 2 H), 4.52 (s, 2 H), 4.13 (d, J = 3.1 Hz, 1 H), 3.59–3.57 (m, 1 H), 3.40–3.28 (m, 2 H), 1.87–1.00 (m, 9 H), 0.74 (d, J = 6.3 Hz, 3 H); MS, m/e 335 (M − 17).

(3a*S*,6*S*,7a*R*)-3-[(Benzyloxy)methoxy]hexahydro-6-(2-hydroxy-1-methylethyl)-2(3*H*)-benzofuranone (12a,b). A magnetically stirred solution of tetrahydrofuran (310 mL) and triphenylphosphine (5.2 g, 19.8 mmol) at −20 °C under nitrogen is treated with diethyl azodicarboxylate (2.3 mL, 14.8 mmol) in tetrahydrofuran (10 mL). After 30 min at −20 °C diols **11a,b** (2.6 g, 7.39 mmol) in tetrahydrofuran (50 mL) are added via syringe pump over a 4.5-h period while carefully maintaining the reaction temperature at −20 °C. The reaction mixture is quenched at −20 °C with saturated aqueous sodium chloride (100 mL and 30% hydrogen peroxide. After dilution with diethyl ether (500 mL) the layers are separated and the aqueous is layer extracted with additional diethyl ether (3 × 200 mL). The combined organic layers are dried ($MgSO_4$) and filtered, and the solvents are removed in vacuo. Flash chromatography (70% ethyl acetate/30% hexanes) affords a mixture of epimeric lactones **12a** and **12b** contaminated with diethyl hydrazodicarboxylate. This mixture is carried on to the next step without further purification. Analytical samples of **12a** (elutes first) and **12b** can be obtained by medium-pressure liquid chromatography (75% ethyl acetate/hexanes). **12a**: white crystals; mp 83–84 °C; IR (thin crystalline film) 3500, 2900, 1780, 1500, 1450, 1380, 1340, 1275, 1200, 1160, 1060, 1025, 960, 900, 855, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (s, 5 H), 4.85, (ABq, J_{AB} = 8.0 Hz, 2 H), 4.85 (br m, 1 H), 4.6 (s, 2 H), 3.90 (br s, 1 H), 3.55 (m, 2 H), 2.20 (br d, 2 H), 1.90–1.00 (m, 7 H), 0.95 (d, J = 6.6 Hz, 3 H); MS, m/e 335 (M + H, isobutane). **12b**: white crystals; mp 73–74 °C; IR (thin crystalline film) 3500, 2950, 1780, 1500, 1450, 1390, 1340, 1295, 1220, 1175, 1140, 1060, 1040, 965, 900, 885, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (s, 5 H), 4.90 (ABq, J_{AB} = 5.0 Hz, 2 H), 4.65 (ABq, J_{AB} = 8.25 Hz, 2 H), 4.55 (m, 1 H), 4.45 (br q, 1 H), 3.52 (m, 2 H), 2.45 (sextet, 1 H), 2.20 (br d, 1 H), 2.00–1.00 (br m, 7 H), 0.92 (d, J = 6.6 Hz, 3 H); MS, m/e 335 (M + H, isobutane).

Trans Lactone 17a,b. Diol acids **11a,b** (50 mg, 0.14 mmol) are dissolved in tetrahydrofuran (1 mL) and benzene (1.5 mL) and treated with p-toluenesulfonic acid monohydrate (2 mg, 0.01 mmol). The clear solution is allowed to stir for 25 h at 23 °C. The solvents are then evaporated and the crude residue is purified by flash chromatography (50% ethyl acetate/50% hexanes) to give epimers **17a** (elutes first; 10 mg, 21%) and **17b** (10 mg; 21%) as white crystalline solids. **17a**: IR (thin crystalline film) 3450, 2950, 2890, 1780, 1500, 1450, 1375, 1200, 1170, 1107, 1080, 1025, 930, 890, 850, 740, 700 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.33 (s, 5 H), 4.89 (ABq, J_{AB} = 6.8 Hz, 2 H), 4.61 (s, 2 H), 4.23 (br d, 2 H), 3.56 (br d, J = 5.7 Hz, 2 H), 2.20 (br d, 1 H), 1.80–1.10 (m, 8 H), 0.91 (d, J = 6.4 Hz, 3 H); MS, m/e 335 (M + H, isobutane). **17b**: IR (thin crystalline film) 3450, 2890, 1780, 1500, 1450, 1375, 1220, 1170, 1130, 1070, 1040, 1005, 982, 900, 840, 740, 700 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.33 (s, 5 H), 4.99 (ABq, J_{AB} = 7.1 Hz, 2 H), 4.67 (s, 2 H), 4.26 (d, J = 11.3 Hz, 1 H), 3.80 (dt, J = 10.0, 4.0 Hz, 1 H), 3.55 (br d, 5.7 Hz, 2 H), 2.30–1.10 (m, 9 H), 0.90 (d, J = 6.4 Hz, 3 H); MS, m/e 335 (M + H, isobutane). HPLC analysis [μ-Porasil (30 cm), 35% ethyl acetate/65% hexanes] of the crude reaction mixture from diethyl azodicarboxylate mediated lactonization shows exclusively cis lactones **12a,b** (see text) when compared with authentic samples of the trans lactones.

(3a*S*,6*S*,7a*R*)-α^3-[(Benzyloxy)methoxy]-2-hydroxy-α^4-methylcyclohexane-1,4-diacetic Acid γ-Lactone (13a,b). The crude alcohols **12a,b** in acetone (10 mL) are added dropwise to a solution of 8 N Jones reagent (5.5 mL, 11.1 mmol) in acetone (30 mL) at 0 °C. After the resulting blue green suspension is stirred at 0 °C for 0.5 h, the excess Jones reagent is quenched with 2-propanol (500 μL). The mixture is partioned between diethyl ether (250 mL) and water (250 mL), and the organic layer is washed with additional water (50 mL). The combined aqueous layers are extracted with ether (3 × 100 mL) and the combined organic layers washed with saturated aqueous sodium chloride (100 mL), dried ($MgSO_4$), and filtered. Removal of the solvents in vacuo provides a yellow oil, which is taken up in saturated aqueous sodium bircarbonate. The resulting aqueous solution is extracted with diethyl ether (2 × 50 mL) and acidified at 0 °C with 6 N hydrochloric acid. The aqueous phase is extracted with ether (5 × 100 mL), and the resulting organic phase is dried ($MgSO_4$) and filtered, and the solvent is removed in vacuo to provide 2.09 g (81% from **11a,b**) of a clear, yellow oil as a mixture of **13a** and **13b**. This material is used for the next step without further purification. Due to the difficulties encountered in the separation of **13a** (elutes first) and **13b**, the previously purified corresponding alcohols **12a** and **12b** are oxidized to acids **13a** and **13b**, respectively. **13a**: white crystals; mp 72–73 °C; IR (neat) 3600–2500, 2900, 1780, 1730, 1710, 1500, 1450, 1380, 1260, 1210, 1160, 1110, 1040, 945, 890, 830, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (s, 5 H), 4.89 (ABq, J_{AB} = 6.9 Hz, 2 H), 4.89 (m, 1 H), 4.64 (s, 2 H), 3.95 (br s, 1 H), 2.45–2.10 (br m, 3 H), 2.00–1.50 (br m, 4 H), 1.50–1.00 (m, 2 H), 1.19 (d, J = 7.0 Hz, 3 H); MS, m/e 349 (M + H, isobutane). **13b**: white crystals; mp 95–96 °C; IR (neat) 3600–2500, 2900, 1780, 1730, 1710, 1500, 1450, 1380, 1275, 1210, 1160, 1060, 1025, 960, 885, 830, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (s, 5 H), 4.92 (ABq, J_{AB} = 8.0 Hz, 2 H), 4.65 (br s, 2 H), 4.55 (m, 1 H), 4.45 (m, 1 H), 2.60–2.10 (br m, 3 H), 2.00–1.30 (m, 4 H), 1.20–1.00 (m, 2 H), 1.19 (d, J = 7.0 Hz, 3 H); MS, m/e 349 (M + H, isobutane).

(3a*S*,6*S*,7a*R*)-3-[(Benzyloxy)methoxy]hexahydro-6-vinyl-2(3*H*)-benzofuranone (14a,b). To a solution of the lactones **13a,b** (668 mg, 1.92 mmol) in dry benzene (12 mL) is added cupric acetate monohydrate (19 mg, 0.10 mmol) and pyridine (192 μL, 0.02 mmol, 1.24 M in benzene). The blue-green reaction mixture is stirred at room temperature for 0.5 h under nitrogen. The flask is then covered with aluminum foil and lead tetraacetate (1.6 g, 3.5 mmol) is added. The mixture is stirred for 1 h at 23 °C, heated to 80 °C for 2 h, cooled to room temperature, and poured into diethyl ether (100 mL). The resulting brown suspension is filtered through silica gel with ether rinsings (500 mL), and the filtrate is concentrated to a yellow oil. Flash chromatography (25% ethyl acetate/75% hexanes) affords 242 mg (42%) of **14a** (elutes first) and 234 mg (40%) of **14b**. **14a**: mp 47–48 °C (recrystallized from ether–petroleum ether); $[\alpha]^{23}_D$ +106.2° (c 2.11, $CHCl_3$); IR (thin crystalline film) 3050, 2900, 1780,

1640, 1500, 1450, 1375, 1260, 1210, 1160, 1120, 1040, 950, 740, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5 H), 5.72 (dd, J = 17.0, 10.4, 6.3 Hz, 1 H), 5.01 (ddd, J = 17.0, 1.4, 1.4 Hz, 1 H), 4.98 (ddd, J = 10.4, 1.4, 1.4, Hz, 1 H), 5.00 (d, J = 6.9 Hz, 1 H), 4.87 (dd, J = 7.1, 3.5 Hz, 1 H), 4.80 (d, J = 6.9 Hz, 1 H), 4.64 (ABq, J_{AB} = 11.9 Hz, 2 H), 3.98 (br s, 1 H), 2.23 (br d, 3 H), 1.74 (m, 2 H), 1.43 (m, 1 H), 1.14 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 174.28, 141.87, 137.43, 128.37, 127.83, 113.50, 93.52, 77.93, 77.59, 70.23, 40.21, 34.41, 33.04, 29.00, 22.90; MS, m/e 303 (M + H, isobutane). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33; O, 21.17. Found: C, 71.48; H, 7.53; O, 20.68. **14b**: mp 63–64.5 °C (recrystallized from ether–petroleum ether); $[\alpha]^{23}_D$ +32.2° (c 2.28, $CHCl_3$); IR (thin crystalline film) 3050, 2900, 1780, 1640, 1500, 1450, 1375, 1270, 1210, 1160, 1130, 1060, 1030, 1010, 965, 920, 740, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5 H), 5.73 (ddd, J = 17.1, 10.4, 6.4 Hz, 1 H), 5.03 (d, J = 7.0 Hz, 1 H), 5.01 (ddd, J = 17.1, 1.4, 1.4 Hz, 1 H), 4.97 (ddd, J = 10.4, 1.4, 1.4 Hz, 1 H), 4.85 (d, J = 7.0 Hz, 1 H), 4.69 (ABq, J_{AB} = 11.7 Hz, 2 H), 4.64 (d, J = 6.5 Hz, 1 H), 4.46 (dd, J = 6.0, 3.3 Hz, 1 H), 2.42 (m, 1 H), 2.24 (m, 2 H), 1.79 (m, 2 H), 1.34 (m, 2 H), 1.04 (br q, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.97, 142.11, 137.33, 128.36, 127.87, 113.29, 94.08, 76.09, 74.63, 70.09, 38.60, 34.74, 33.14, 28.75, 21.34; MS m/e 303 (M + H, isobutane). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33; O, 21.17. Found: C, 71.53; H, 7.43; O, 20.92.

(3*R*,3a*S*,6*S*,7a*R*)-3-[(Benzyloxy)methoxy]-3-[(benzyloxy)methyl]hexahydro-6-vinyl-2(3*H*)-benzofuranone (15). To a solution of freshly distilled diisopropylamine (100 μL, 0.72 mmol) in anhydrous tetrahydrofuran (1 mL) at 0 °C under nitrogen is added a 2.4 M solution of n-butyllithium in hexane (300 μL, 0.72 mmol). After 20 min the reaction vessel is cooled to −78 °C and lactones **14a,b** (115 mg, 0.38 mmol) in tetrahydrofuran (500 μL) are added dropwise over a 25-min period. The reaction mixture is stirred at −78 °C for 0.5 h and treated with benzyl chloromethyl ether (112 μL, 0.82 mmol) as a solution in hexamethylphosphoric triamide (125 μL, 0.72 mmol) and tetrahydrofuran (250 μL). After being stirred at −78 °C for 1 h, the resulting yellow solution is warmed to −40 °C for 2 h, at which time the reaction is quenched with saturated aqueous ammonium chloride and partitioned between ether (5 mL) and water (2 mL). The aqueous layer is extracted with diethyl ether (3 × 5 mL), and the combined organic layers are dried ($MgSO_4$), filtered, and concentrated in vacuo to give a clear, colorless oil. Flash chromatography (18% ethyl acetate/82% hexanes) affords 113 mg (71%) of **15** as a clear, colorless oil. Crystallization from ether/petroleum ether at −15 °C gives white needles; mp 50–51 °C; $[\alpha]^{23}_D$ +8.2° (c 2.13, $CHCl_3$); IR (thin crystalline film) 3050, 2950, 1780, 1640, 1500, 1450, 1360, 1300, 1275, 1210, 1150, 1100, 1025, 970, 910, 735, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (m, 10 H), 5.73 (ddd, J = 17.3, 10.3, 5.9 Hz, 1 H), 5.32 (d, J = 7.0 Hz, 1 H), 5.01 (ddd, J = 17.3 1.5, 1.5, Hz, 1 H), 4.98 (d, J = 7.0 Hz, 1 H), 4.96 (ddd, J = 10.3, 1.5, 1.5, Hz, 1 H), 4.69 (s, 2 H), 4.58 (br d, J = 2.6 Hz, 1 H), 4.50 (ABq, J_{AB} = 12.1 Hz, 2 H), 3.85 (ABq, J_{AB} = 10.7 Hz, 2 H), 2.63 (quintet, J = 5.5 Hz, 1 H), 2.21 (br d, 2 H), 1.85–1.77 (m, 2 H), 1.46–1.33 (m, 2 H), 1.1–1.0 (br q, 1 H); ^{13}C NMR ($CDCl_3$) δ 175.09, 142.22, 137.74, 137.20, 128.38, 128.28, 127.99, 127.84, 127.69, 127.50, 113.31, 91.03, 84.01, 75.23, 73.57, 70.02, 69.48, 41.15, 34.81, 33.40, 29.01, 21.89; exact mass calcd for $C_{26}H_{30}O_5$ 422.2093, found 422.2111. Anal. Calcd for $C_{26}H_{30}O_5$: C, 73.90; H, 7.16; O, 18.94. Found: C, 73.99; H, 7.14; O, 18.69.

Tetrahydropyranyl (*S*)-2-Methyl-3-[(tetrahydropyranyl)oxy]propanoate (28). Acid **27** (13.5 g, 153 mmol) in dichloromethane (80 mL) at 0 °C is treated with dihydropyran (80 mL, 878 mmol) and p-toluenesulfonic acid monohydrate (10 mg, 0.053 mmol). After being stirred at 0 °C for 2 h, the reaction mixture is quenched with saturated aqueous sodium bicarbonate (50 mL) and partitioned between diethyl ether (400 mL) and water (200 mL). The aqueous layer is extracted with additional diethyl ether (3 × 200 mL), and the combined organic layers are dried ($MgSO_4$), filtered, and concentrated in vacuo to give 30 g of **28** as a clear, yellow oil. This material is sufficiently pure to use for the next step. An analytical sample can be obtained by flash chromatography (20% ethyl acetate/80% hexanes): IR (neat) 2900, 2850, 1740, 1450, 1438, 1380, 1351, 1318, 1282, 1250, 1205, 1176, 1117, 1078, 1064, 1031, 1020, 976, 948, 901, 870, 823 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.0 (br s, 1 H), 4.60 (br s, 1 H), 4.10–3.35 (m, 6 H), 2.80 (sextet, 1 H), 2.00–1.30 (br m, 12 H), 1.23 (d, J = 7.0 Hz, 3 H); MS, m/e 187 (M − C_5H_9O).

(*R*)-3-[(Tetrahydropyranyl)oxy]-2-methyl-1-propanol (29). A magnetically stirred suspension of lithium aluminum hydride (12.0 g, 317 mmol) in anhydrous tetrahydrofuran (600 mL) cooled to 0 °C under nitrogen is treated with a solution of **28** (30 g, 110 mmol) in tetrahydrofuran (50 mL) dropwise. The gray suspension is stirred at 0 °C for 1.5 h and quenched sequentially with saturated aqueous ammonium chloride (12 mL), 3 M sodium hydroxide (12 mL), and water (36 mL). The resulting white suspension is suction filtered, and the aluminum salts are washed with diethyl ether (4 × 200 mL). The filtrate is then washed with saturated aqueous sodium chloride (200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give **29** as a clear, colorless oil, which can be carried on to the next step without purification. An analytical sample is obtained by flash chromatography (40% ethyl acetate/hexanes): IR (neat) 3450, 2900, 1450, 1387, 1350, 1315, 1258, 1200, 1183, 1170, 1136, 1117, 1075, 1062, 1030, 975, 905, 888, 870, 816 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.60 (br d, 1 H), 4.00–3.20 (m, 6 H), 2.57 (br s, 1 H), 2.25–1.10 (m, 7 H), 0.90 (d, J = 7.0 Hz, 3 H); MS, m/e 174 (M^+).

(*R*)-1-(Benzyloxy)-2-methyl-3-[(tetrahydropyranyl)oxy]propane (30). To a 1000-mL, nitrogen flushed round-bottomed flask charged with hexane-washed potassium hydride (6.60 g, 0.165 mol) and anhydrous tetrahydrofuran (400 mL) is added monoprotected diol **29** (19.2 g, 110 mmol) in tetrahydrofuran (100 mL). After stirring at 0 °C for 0.5 h, benzyl bromide (16.5 mL, 143 mmol) is added neat, and the reaction mixture is warmed to 23 °C over a period of 1 h. After being stirred at 23 °C for 1 h and quenched by the dropwise addition of saturated aqueous ammonium chloride (100 mL), the reaction contents are partitioned between diethyl ether (200 mL) and water (100 mL). The aqueous layer is extracted with diethyl ether (3 × 200 mL), and the combined organic layers are dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 32.9 g of **30** as a clear, yellow oil. This material is carried on to the next step without further purification. However, an analytical sample is obtained by flash chromatography (10% ethyl acetate/hexanes), which provides a clear, colorless oil: IR (neat) 2900, 2850, 1470, 1450, 1350, 1253, 1200, 1111, 1093, 1075, 1058, 1030, 975, 900, 870, 816, 735, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (s, 5 H), 4.48 (m, 1 H), 4.40 (s, 2 H), 3.90–3.10 (m, 6 H), 2.05 (sextet, 1 H), 1.80–1.20 (br m, 6 H), 0.98 (d, J = 7.0 Hz, 3 H); MS, m/e 179 (M − C_5H_9O).

(*S*)-3-(Benzyloxy)-2-methyl-1-propanol (31). A solution of **30** (32.9 g, 125 mmol), 95% ethanol (350 mL) and p-toluenesulfonic acid monohydrate (60 mg, 0.32 mmol) are heated to reflux for 3 h. After being cooled to 23 °C, the reaction mixture is quenched with saturated aqueous sodium bicarbonate (50 mL) and partitioned between diethyl ether (300 mL) and water (150 mL). Following saturation of the aqueous layer with sodium chloride and extraction with additional diethyl ether (2 × 250 mL), the combined organic layers are dried ($MgSO_4$), filtered, and concentrated in vacuo at 35 °C. The crude oil is distilled to give 17.8 g (65% from **27**) of **31** as a clear, colorless oil: bp 100 °C (0.25 mmHg); $[\alpha]^{25}_D$ −18.5° (c 1.94, $CHCl_3$); IR (neat) 3400, 3050, 2900, 1500, 1475, 1360, 1200, 1099, 1042, 990, 740, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (s, 5 H), 4.48 (s, 2 H), 3.70–3.40 (m, 4 H), 2.80 (t, 1 H, OH), 2.1 (sextet, 1 H), 0.95 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.95, 127.95, 127.12, 73.83, 72.76, 65.88, 35.51, 13.38; exact mass calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1152.

(*R*)-3-(Benzyloxy)-2-methylpropanoic Acid (32). To a solution of 8 N Jones reagent (60 mL, 120 mmol) in acetone (200 mL) at 23 °C is added a solution of **31** (17.8 g, 99 mmol) in acetone (50 mL) dropwise over a 2-h period. The reaction mixture is maintained at 23 °C (by occasional application of an ice bath) for the entire 2-h period. The excess Jones reagent is quenched with 2-propanol and the mixture diluted with ether (500 mL) and water (200 mL). The aqueous layer is extracted with additional ether (3 × 250 mL), the combined organic layers are dried ($MgSO_4$) and filtered, and the solvents are removed in vacuo to give a yellow oil. The crude oil is dissolved in saturated aqueous sodium bicarbonate, and the aqueous solution is extracted with diethyl ether (2 × 100 mL). After discarding the first ether washings, the aqueous layer is acidified to pH 1 at 0 °C with 6 N hydrochloric acid and extracted with diethyl ether (4 × 150 mL). The ether layer is dried ($MgSO_4$), filtered, and concentrated in vacuo to

afford 16.3 g (85%) of **32** as a pale yellow oil. The product is homogenous by TLC and used without further purification: $[\alpha]^{25}_D$ −8.5° (*c* 3.65, $CHCl_3$); IR (neat) 3500–2500, 2900, 1715, 1500, 1475, 1425, 1360, 1282, 1227, 1096, 1030, 935, 735, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.8 (br s, 1 H), 7.20 (s, 5 H), 4.46 (s, 2 H), 3.55 (m, 2 H), 2.78 (sextet, 1 H), 1.20 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 180.75, 137.75, 128.10, 127.37, 72.86, 71.34, 39.95, 13.47; exact mass calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0948.

(*R*)-4-(Benzyloxy)-3-methyl-2-butanone (33). Oxalyl chloride (11.0 mL, 126 mmol) is added neat to a solution of acid **32** (16.3 g, 84 mmol) in dry benzene (440 mL). The clear, colorless solution is stirred at room temperature for 0.5 h and at 50 °C for an additional 2 h. The benzene and excess oxalyl chloride are removed by distillation (18 mmHg) to leave a yellow oil. The crude acid chloride is further concentrated under high vacuum (0.25 mmHg) and used immediately for the next step: IR (neat) 2900, 1750, 1500, 1475, 1360, 1250, 1210, 1100, 940, 875, 740, 695 cm^{-1}.

Methyllithium (208 mL, 504 mmol, 1.8 M in ether) is added to a suspension of cuprous iodide (51.6 g, 271 mmol) in diethyl ether (1000 mL) at 0 °C under nitrogen. After being stirred at 0 °C for 0.5 h, the bright yellow suspension is chilled to −78 °C and the crude acid chloride (19.2 g, 84 mmol) is added in diethyl ether (100 mL). The resulting yellow-orange solution is stirred at −78 °C for 0.5 h, quenched at −78 °C by addition of a solution of glacial acetic acid (23 mL) and saturated aqueous ammonium chloride (80 mL), warmed to 0 °C, washed with saturated aqueous ammonium chloride (adjusted to pH 8 with ammonia) until basic, and partitioned into two layers. The aqueous layer is extracted with diethyl ether (3 × 200 mL), and the combined organic layers are washed with additional aqueous ammonium chloride (2 × 300 mL), water (1 × 200 mL), and saturated aqueous sodium chloride (1 × 300 mL). The combined organic layers are then dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 12.95 g (80%) of **33** as clear, yellow oil. This material is used in the next step without purification. An analytical sample can be obtained by flash chromatography (20% ethyl acetate/80% hexanes): $[\alpha]^{25}_D$ −16.7° (*c* 3.91, $CHCl_3$); IR (neat) 3000, 2900, 1725, 1500, 1475, 1350, 1180, 1090, 1030, 950, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (s, 5 H), 4.40 (s, 2 H), 3.50 (m, 2 H), 2.78 (sextet, *J* = 7.0 Hz, 1 H), 2.05 (s, 3 H), 1.01 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.01, 137.72, 127.89, 127.06, 72.65, 71.64, 46.66, 28.43, 12.88; exact mass calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1149.

(*S*)-4-(Benzyloxy)-2,3-dimethyl-1-butene (34). *n*-Butyllithium (41.6 mL, 100 mmol, 2.4 M in hexane) is added to a suspension of methyltriphenylphosphonium bromide (36 g, 100 mmol) in anhydrous tetrahydrofuran (600 mL) at −78 °C under nitrogen. After stirring the bright yellow suspension at −78 °C for 0.5 h and warming to 0 °C, ketone **33** (12.95 g, 6.80 mmol) is added dropwise as a solution in tetrahydrofuran (50 mL). The reaction mixture is stirred at 0 °C for 1 h, quenched sequentially with 30% hydrogen peroxide (25 mL) and saturated aqueous ammonium chloride (100 mL), and partitioned between diethyl ether (300 mL) and water (100 mL). The aqueous layer is extracted with additional ether (2 × 200 mL) and the combined organic layers are dried ($MgSO_4$), filtered, and concentrated in vacuo. Triphenylphosphine oxide is precipitated by addition of hexane/ether (2.5:1 (v/v); 300 mL), and the mixture is suction filtered. The solid is washed with the hexanes/ether solution (3 × 100 mL), and the filtrate is concentrated in vacuo to afford 12.7 g of a crude oil. Flash chromatography (5% ethyl acetate/hexanes) gives 8.8 g (69%) of **34** as a pale green oil: $[\alpha]^{25}_D$ +10.1° (*c* 2.23, $CHCl_3$); IR (neat) 3100, 3000, 2900, 1660, 1512, 1468, 1385, 1258, 1212, 1100, 1036, 896, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (s, 5 H), 4.70 (s, 2 H), 4.44 (s, 2 H), 3.40 (seven-line multiplet, 2 H), 2.50 (sextet, *J* = 7.0 Hz, 1 H), 1.67 (br s, 3 H), 1.07 (d, *J* = 8.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.60, 138.63, 128.24, 127.51, 127.37, 110.35, 74.03, 72.90, 40.97, 20.15, 16.54; exact mass calcd for $C_{13}H_{18}O$ 190.1358, found 190.1354.

(*S*)-2,3-Dimethyl-3-buten-1-ol (35). To a dark blue solution of lithium (1.37 g, 199 mmol) in liquid ammonia (500 mL) at −78 °C under nitrogen is added **34** (8.8 g, 46.3 mmol) as a solution in diethyl ether (10 mL) all at once. The reaction mixture is stirred at −78 °C for 2 min and quenched at −78 °C by rapid addition of methanol (50 mL). As the clear, colorless solution warms slowly to room temperature, saturated aqueous ammonium chloride (50 mL) and diethyl ether (100 mL) are added. The aqueous and organic layers are separated and the aqueous layer extracted with diethyl ether (3 × 100 mL). The combined organic layers are dried ($MgSO_4$) and filtered, and the solvent is removed by distillation at 1 atm. Flash chromatography [*n*-pentane followed by 1:1 *n*-pentane/ether (v/v)] affords a pale green oil after removal of solvents by fractional distillation at 1 atm. The oil is distilled to provide 3.64 g (79%) of **35** as a clear, colorless liquid bp 65–68 °C (42 mmHg). The distilled product is homogenous by gas chromatography [5% OV-101 (10 ft)/50 °C]: $[\alpha]^{25}_D$ −10.3° (*c* 8.63, $CHCl_3$); IR (neat) 3450, 3090, 2950, 1650, 1450, 1375, 1042, 1030, 985, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.84 (q, *J* = 1.6 Hz, 1 H), 4.77 (d, *J* = 0.7 Hz, 1 H), 3.47 (t, *J* = 6.0 Hz, 2 H), 2.35 (sextet, *J* = 6.8 Hz, 1 H), 1.68 (br s, 3 H), 1.59 (br t, *J* = 5.4 Hz, 1 H, OH), 1.00 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.69, 110.45, 65.10, 43.00, 19.33, 15.32; exact mass calcd for $C_6H_{12}O$ 100.0888, found, 100.0887.

(2*S*,3*R*,3a*S*,5′*S*,6*S*,7a*R*)-3-[(Benzyloxy)methoxy]-3-[(benzyloxy)methyl]decahydro-5′-methyl-4′-methylene-6-vinylspiro[benzofuran-2(3*H*),2′-[2*H*]pyran] (40). To a suspension of potassium *tert*-butoxide (750 mg, 6.7 mmol) and **37** (321 mg, 3.21 mmol) in hexanes[24] (7 mL) at −20 °C under nitrogen is added a 2.4 M solution (3.25 mL, 7.8 mmol) of *n*-butyllithium in hexane. The resulting yellow suspension is warmed to 0 °C, stirred at 0 °C for 1 h, and added to a slurry of $MgBr_2$ (8.5 mmol) in anhydrous tetrahydrofuran (15 mL) at −60 °C via gas-tight syringe. The resulting milky white suspension is warmed to −40 °C and immediately added dropwise to lactone **15** (380 mg, 0.9 mmol) in diethyl ether (10 mL) at −60 °C. The reaction mixture is stirred at precisely −60 °C for an additional 0.5 h, quenched at −60 °C with glacial acetic acid (2 mL) in tetrahydrofuran (10 mL), warmed to 0 °C, and diluted with diethyl ether (150 mL) and saturated aqueous ammonium chloride (25 mL). The biphasic solution is separated, and the organic phase is washed with saturated aqueous sodium bicarbonate (until basic). The combined aqueous layers are basified with solid sodium bicarbonate and extracted with additional diethyl ether (3 × 50 mL). The combined organic layers are dried ($MgSO_4$), filtered, and concentrated in vacuo to give 485 mg of **38** as a pale green oil, which was used without further purification.

To a suspension of anhydrous zinc chloride (589 mg, 4.36 mmol) in dichloromethane (50 mL) at 0 °C under nitrogen is added **38** (485 mg) in dichloromethane (10 mL). After being stirred at 0 °C for 1.5 h, the reaction mixture is quenched with saturated aqueous sodium bicarbonate (50 mL) and partitioned between diethyl ether (150 mL) and water (50 mL). The aqueous phase is extracted with additional ether (3 × 50 mL), and the combined organic layers are dried ($MgSO_4$) and filtered, and the solvents are removed in vacuo. Flash chromatography (8% ethyl acetate/92% hexanes) affords 324.6 mg (72%) of **40** as a clear, colorless oil. The ratio of **40** to **41** is determined to be 25:1 [HPLC μ-Porasil (30 cm), 2% ethyl acetate/98% hexanes, 2 mL/min; with t_R of 5.9 min and 18.5 min, respectively]. Alternatively, when the spiroketalization is run at −20 °C (6 h, 72% yield), the ratio of **40** to **41** is 48:1. **40**: $[\alpha]^{25}_D$ +44.7° (*c* 2.39, $CHCl_3$); IR (neat) 3050, 2950, 1660, 1650, 1500, 1450, 1375, 1280, 1210, 1160, 1080, 1030, 995, 735, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (m, 10 H), 5.76 (ddd, *J* = 17.1, 10.3, 6.3 Hz, 1 H), 5.09 (d, *J* = 6.1 Hz, 1 H), 4.97 (ddd, *J* = 17.1, 1.6, 1.6 Hz, 1 H), 4.95 (d, *J* = 6.1 Hz, 1 H), 4.90 (ddd, *J* = 10.3, 1.6, 1.6 Hz, 1 H), 4.81 (d, *J* = 1.6 Hz, 1 H), 4.74 (d, *J* = 1.6 Hz, 1 H), 4.68 (ABq, J_{AB} = 12.1 Hz, 2 H), 4.50 (ABq, J_{AB} = 12.1 Hz, 2 H), 4.07 (dd, *J* = 8.1, 4.04 Hz, 1 H), 3.84 (ABq, J_{AB} = 11.4 Hz, 2 H), 3.56 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.40 (dd, *J* = 10.5 Hz, 1 H), 2.60 (br d, *J* = 14.0 Hz, 1 H), 2.49–2.42 (br m, 2 H), 2.30–2.26 (br m, 2 H), 2.05 (br d, *J* = 14.0 Hz, 1 H), 1.77 (br d, *J* = 12.9 Hz, 1 H), 1.62–1.57 (m, 2 H), 1.39–1.26 (m, 1 H), 1.09–0.95 (m, 1 H), 0.96 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.48, 143.60, 138.48, 138.24, 128.10, 127.66, 127.51, 127.37, 127.22, 112.20, 108.30, 107.08, 91.63, 89.58, 73.20, 70.71, 69.78, 68.08, 43.02, 42.58, 35.95, 34.73, 33.17, 29.71, 21.91, 12.30; exact mass calcd from $C_{32}H_{40}O_5$ 504.2876, found 504.2873. **41**: IR (neat) 3050, 2900, 1650, 1640, 1500, 1450, 1375, 1350, 1290, 1210, 1160, 1090, 1075, 1040, 1030, 980, 935, 915, 885, 735, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 10 H), 5.76 (ddd, *J* = 16.9, 10.3, 5.9 Hz, 1 H), 5.12 (s, 2 H), 4.97 (d, *J* = 16.9 Hz, 1 H), 4.90 (d, *J* = 10.3 Hz, 1 H), 4.80 (br s, 1 H), 4.74 (ABq, J_{AB} = 12.1 Hz, 2 H), 4.66 (br s, 1 H), 4.51 (ABq, J_{AB} = 12.1 Hz, 2 H),

4.14 (br d, J = 2.9 Hz, 1 H), 4.10 (br d, J = 2.9 Hz, 1 H), 3.71 (ABq, J_{AB} = 10.3 Hz, 2 H), 3.59 (d, J = 10.3 Hz, 1 H), 2.67–2.58 (m, 2 H), 2.36 (br d, J = 6.6 Hz, 1 H), 2.32–2.17 (m, 1 H), 2.02 (ABq, J_{AB} = 13.2 Hz, 2 H), 1.75 (br d, J = 12.8 Hz, 1 H), 1.64–1.56 (m, 1 H), 1.32–1.17 (m, 1 H), 1.18 (d, J = 6.99 Hz, 3 H), 1.02–0.86 (br m, 2 H); ^{13}C NMR ($CDCl_3$) δ 146.09, 143.99, 138.39, 138.00, 128.39, 128.29, 127.71, 127.41, 112.20, 109.62, 104.69, 91.68, 88.07, 75.24, 73.54, 70.13, 70.03, 65.98, 39.70, 37.17, 36.09, 35.41, 30.00, 29.71, 22.25, 18.44; exact mass calcd for $C_{32}H_{40}O_5$ 504.2876, found 504.2905.

(2*S*,3*R*,3a*S*,5′*R*,6*S*,7a*R*)-3-[(Benzyloxy)methoxy]-3-[(benzyloxy)methyl]decahydro-5′-methyl-4′-oxospiro[benzofuran-2(3*H*),2′-[2*H*]pyran]-6-carboxaldehyde (46). Diene **40** (113 mg, 0.224 mmol) in dichloromethane (3 mL) is purged with ozone at −78 °C until a blue color persists. The reaction mixture is quenched immediately with dimethyl sulfide (3 mL, 41.0 mmol) at −78 °C and warmed to 23 °C. After the mixture is stirred at 23 °C for 26 h, the solvents are removed in vacuo. Flash chromatography (25% ethyl acetate/75% hexanes) affords 80 mg (70%) of **46** as a clear, colorless oil: $[\alpha]^{25}_D$ +63.0° (*c* 7.84, $CHCl_3$); IR (neat) 2950, 1740, 1500, 1450, 1380, 1307, 1150, 1100, 1025, 910, 740, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1 H), 7.35–7.27 (m, 10 H), 5.01 (ABq, J_{AB} = 6.3 Hz, 2 H), 4.63 (ABq, J_{AB} = 11.9 Hz, 2 H), 4.51 (ABq, J_{AB} = 11.8 Hz, 2 H), 4.09 (br dd, J = 9.3, 4.9 Hz, 1 H), 3.88 (ABq, J_{AB} = 11.3 Hz, 2 H), 3.85 (dd, J = 11.2, 7.3 Hz, 1 H), 3.65 (dd, J = 11.2 Hz, 1 H), 2.88 (dd, J = 14.2, 0.94 Hz, 1 H), 2.60 (d, J = 14.2 Hz, 1 H), 2.61–2.41 (m, 3 H), 2.11–1.96 (m, 2 H), 1.71–1.59 (m, 3 H), 1.31–1.16 (m, 1 H), 0.94 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.49, 203.33, 137.78, 137.66, 127.89, 127.18, 110.31, 91.36, 88.68, 73.07, 72.95, 69.85, 69.73, 65.62, 48.52, 43.87, 43.63, 42.50, 26.17, 22.24, 20.51, 8.53; MS, *m/e* 509 (M + H, isobutane). Anal. Calcd for $C_{30}H_{36}O_7$: C, 70.84; H, 7.13, O, 22.03. Found: 70.83; H, 7.22; O, 22.13.

Methyl (2*S*,3*R*,3a*S*,5′*R*,6*S*,7a*R*)-3-[(Benzyloxy)methoxy]-3-[(benzyloxy)methyl]decahydro-5′-methyl-4′-oxospiro[benzofuran-2(3*H*),2′-[2*H*]pyran]-6-carboxylate (47). A solution of keto aldehyde **46** (154 mg, 0.303 mmol) in acetone (2 mL) is added dropwise to a solution of 8 N Jones reagent (200 μL, 0.8 mmol) in acetone (10 mL) at −10 °C. The red solution is stirred for 20 min at −10 °C, warmed slowly to −5 °C, quenched with 2-propanol (10 μL), and partitioned between ether (50 mL) and water (20 mL). The aqueous layer is extracted with additional ether (3 × 50 mL), and the combined organic layers are washed with water (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude keto acid **45** (160 mg; homogeneous by TLC) is dissolved in diethyl ether (2 mL) at 0 °C and treated with ethereal diazomethane until a yellow color persists. The excess diazomethane is quenched with glacial acetic acid (20 μL), and the organic phase is washed with saturated aqueous sodium bicarbonate (2 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (25% ethyl acetate/75% hexanes) provides 131 mg of **47** (80% from **46**) as a clear colorless oil: $[\alpha]^{25}_D$ +66.7° (*c* 3.90, $CHCl_3$); IR (neat) 2900, 1725, 1500, 1450, 1375, 1307, 1282, 1242, 1170, 1093, 1050, 1020, 900, 735, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (m, 10 H), 5.00 (ABq, J_{AB} = 6.3 Hz, 2 H), 4.63 (ABq, J_{AB} = 11.9 Hz, 2 H), 4.51 (ABq, J_{AB} = 11.9 Hz, 2 H), 4.12 (dd, J = 8.9, 4.5 Hz, 1 H), 3.86 (ABq, J_{AB} = 11.2 Hz, 2 H), 3.84 (dd, J = 11.1, 7.5 Hz, 1 H), 3.66 (dd, J = 11.1 Hz, 1 H), 3.65 (s, 3 H), 2.87 (d, J = 14.6 Hz, 1 H), 2.64–2.43 (m, 3 H), 2.58 (d, J = 14.6 Hz, 1 H), 2.12–2.05 (m, 1 H), 2.00–1.93 (m, 1 H), 1.77–1.67 (m, 1 H), 1.62–1.49 (m, 2 H), 1.40–1.30 (m, 1 H), 0.94 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.79, 175.86, 137.96, 137.78, 128.07, 127.36, 110.49, 91.54, 89.04, 73.25, 69.91, 65.80, 51.26, 48.93, 44.05, 42.38, 36.48, 29.33, 25.93, 20.93, 8.65 MS *m/e* 539 (M + H, isobutane). Anal. Calcd for $C_{31}H_{38}O_8$: C, 69.12; H, 7.11; O, 23.77. Found: C, 68.90; H, 6.88; O, 23.90.

Methyl (2*S*,3*R*,3a*S*,5′*R*,6*S*,7a*R*)-Decahydro-3-hydroxy-3-(hydroxymethyl)-5′-methyl-4′-oxospiro[benzofuran-2-(3*H*),2′-[2*H*]pyran]-6-carboxylate (49). To a solution of keto ester **47** (101 mg, 0.19 mmol) in ethyl acetate (2 mL) and hexanes (5 mL) is added 10% palladium on carbon (100 mg, 0.094 mmol). The black suspension is purged with hydrogen and placed under 20 psi of hydrogen pressure for 15 min. Filtration through Florisil with ethyl acetate (40 mL) affords 60.9 mg (99%) of crude diol, which is homogeneous by TLC. Flash chromatography (70% ethyl acetate/30% hexanes) gives 59 mg (96%) of **49** as pure white crystals: mp 133–134 °C; $[\alpha]^{22}_D$ +84.6° (*c* 2.95, $CHCl_3$); IR ($CHCl_3$) 3600, 2950, 2895, 1730, 1450, 1440, 1385, 1307, 1280, 1220, 1160, 1105, 1095, 1070, 1053, 1012, 990, 950, 925, 900, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (dd, J = 7.9, 3.8 Hz, 1 H); 4.09 (dd, J = 11.3, 4.1 Hz, 1 H), 3.93 (dd, J = 11.3, 7.3 Hz, 1 H), 3.77 (dd, J = 11.3 Hz, 1 H), 3.65 (s, 3 H), 3.51 (dd, J = 11.3, 9.7 Hz, 1 H), 2.86 (s, 1 H, OH), 2.70 (dd, J = 14.3, 0.90 Hz, 1 H), 2.62–2.56 (m, 2 H), 2.56 (d, J = 14.3 Hz, 1 H), 2.49 (dd, J = 9.7, 4.1 Hz, 1 H), 2.16–2.11 (br d, J = 14.7 Hz, 1 H), 2.01–1.96 (m, 1 H), 1.85–1.66 (m, 3 H), 1.54–1.40 (m, 1 H), 1.38–1.24 (m, 1 H), 0.97 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.21, 176.10, 110.79, 84.03, 73.13, 65.86, 65.38, 51.44, 48.57, 44.17, 42.97, 36.66, 29.15, 25.87, 20.39, 8.59; exact mass calcd for $C_{16}H_{25}O_7$ 329.1600, found 329.1621. Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.52; H, 7.36; O, 34.12. Found: C, 57.98; H, 7.54; O, 33.91.

Methyl (2*S*,3*R*,3a*S*,5′*R*,6*S*,7a*R*)-3-[(*tert*-Butyldimethylsiloxy)methyl]decahydro-3-hydroxy-5′-methyl-4′-oxospiro[benzofuran-2(3*H*),2′-[2*H*]pyran]-6-carboxylate (50). Diol **49** (56 mg, 0.17 mmol) in dimethylformamide (10 mL) at room temperature is treated with imidazole (289 mg, 4.25 mmol) and *tert*-butyldimethylsilyl chloride (127 mg, 0.84 mmol). After being stirred at 23 °C for 2 h, the clear, colorless solution is poured into a mixture of diethyl ether (60 mL) and water (20 mL). The layers are separated, and the organic layer is washed with additional water (2 × 20 mL). The combined aqueous layers are back-extracted with ether (3 × 50 mL), and the combined organic layers are dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (20% ethyl acetate/80% hexanes) affords 57 mg (76%) of **50** as a clear, colorless oil: $[\alpha]^{22}_D$ +69.0° (*c* 3.72, $CHCl_3$); IR (neat) 3650, 2950, 2900, 1750, 1730, 1475, 1380, 1310, 1275, 1200, 1170, 1110, 1090, 1005, 975, 892, 842, 785 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (dd, J = 9.8, 4.8 Hz, 1 H), 3.89 (d, J = 9.9 Hz, 1 H), 3.83 (dd, J = 10.9, 7.3 Hz, 1 H), 3.66 (dd, J = 10.9 Hz, 1 H), 3.65 (s, 3 H), 3.57 (d, J = 9.9 Hz, 1 H), 2.94 (s, 1 H, OH), 2.65 (ABq, J_{AB} = 14.2 Hz, 2 H), 2.72–2.62 (m, 1 H), 2.58–2.45 (m, 1 H), 2.10–1.80 (m, 4 H), 1.60–1.40 (m, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.89 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 206.85, 176.22, 110.00, 83.08, 73.19, 65.50, 64.55, 51.38, 47.32, 44.40, 41.96, 36.48, 29.33, 25.69, 25.10, 20.03, 18.06, 8.77, −5.65; MS, *m/e* 443 (M + H, isobutane). Anal. Calcd for $C_{22}H_{38}O_7Si$: C, 59.69, H, 8.65; Si, 6.35. Found: C, 59.49; H, 8.76; Si, 6.30.

Methyl (2*S*,3*R*,3a*S*,4′*S*,5′*R*,6*S*,7a*R*)-3-[(*tert*-Butyldimethylsiloxy)methyl]decahydro-3,4′-dihydroxy-5′-methylspiro[benzofuran-2(3*H*),2′-[2*H*]pyran]-6-carboxylate (51). Keto ester **50** (49.0 mg, 0.11 mmol) is dissolved in absolute methanol (10 mL), cooled to 0 °C, and treated with sodium borohydride (10 mg, 0.27 mmol). After 30 min at 0 °C the reaction mixture is quenched with saturated aqueous ammonium chloride (2 mL) and partitioned between ether (50 mL) and water (10 mL). The aqueous layer is extracted with ether (3 × 20 mL), and the combined layers are dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (20% ethyl acetate/80% hexanes) provides 40.7 mg (83%) of **51** (elutes first) and 3.3 mg (6.7%) of **52** as a readily separable mixture of colorless oil. **51**: $[\alpha]^{22.5}_D$ +69.8° (C 2.35, $CHCl_3$); IR (neat) 3600, 2950, 2890, 1730, 1460, 1430, 1410, 1390, 1360, 1250, 1200, 1160, 1120, 1080, 1030, 1000, 965, 955, 940, 920, 890, 865, 840, 780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (dd, J = 11.4, 6.6 Hz, 1 H), 3.81 (br d, J = 3.3 Hz, 1 H), 3.77 (d, J = 9.6 Hz, 1 H), 3.67 (s, 3 H), 3.65 (dd, J = 11.4 Hz, 1 H), 3.50 (d, J = 9.6 Hz, 1 H), 3.37 (dd, J = 11.4, 5.2 Hz, 1 H), 3.35 (d, J = 10.2 Hz, 1 H, OH), 2.91 (s, 1 H, OH), 2.71 (m, 1 H), 2.11–1.84 (m, 5 H), 1.76–1.40 (m, 5 H), 0.89 (s, 9 H), 0.87 (d, J = 6.9 Hz, 3 H), 0.07 (s, 6 H); ^{13} C NMR ($CDCl_3$) δ 176.34, 106.68, 83.32, 73.78, 68.12, 64.66, 61.75, 51.49, 41.87, 36.54, 36.00, 34.57, 29.45, 25.75, 24.92, 19.79, 18.12, 12.94, −5.59; exact mass calcd for $C_{22}H_{40}O_7Si$ 444.2543, found 444.2545. **52**: IR (neat) 3550, 2940, 2860, 1730, 1450, 1430, 1380, 1250, 1197, 1160, 1111, 1080, 1040, 990, 950, 940, 900, 840, 780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (dd, J = 11.4, 6.6 Hz, 1 H), 3.78 (d, J = 9.6 Hz, 1 H), 3.66 (s, 3 *H*), 3.64 (dt, J = 11.0, 4.8 Hz, 1 H), 3.52 (d, J = 9.6 Hz, 1 H), 3.46 (dd, J = 11.4, 6.3 Hz, 1 H), 3.40 (dd, J = 11.4 Hz, 1 H), 2.70 (m, 1 H), 2.15–1.86 (m, 5 H), 1.65–1.39 (m, 5 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); MS, *m/e* 445 (M + H, isobutane).

Alternatively, a 1.0 M solution of KS-Selectride (97 μL, 0.097 mmol) in tetrahydrofuran is added to keto ester **50** (20.4 mg, 0.046

mmol) in anhydrous tetrahydrofuran (5 mL) at 0 °C under nitrogen. After being stirred at 0 °C for 10 h, the clear, colorless solution is quenched sequentially with water (50 μL), 30% aqueous hydrogen peroxide (1 mL), and 3 M sodium acetate (1 mL) and diluted with ether (50 mL) and water (10 mL). Following extraction of the aqueous layer with ether (3 × 20 mL), the combined organic layers are dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (20% ethyl acetate/80% hexanes) provides 11 mg (54%) of **51** as a single isomer, which is spectroscopically identical with **51** obtained from sodium borohydride reduction of **50** described previously. Gas chromatographic analysis of the crude reaction product [5% Carbowax 20M (10 ft)/240 °C] shows exclusive selectivity for the axial alcohol.

Methyl (2*S*,3*R*,3a*S*,4′*S*,5′*R*,6*S*,7a*R*)-3-[(*tert*-Butyldimethylsiloxy)methyl]-4′-[(*E*)-cinnamoyloxy]decahydro-3-hydroxy-5′-methylspiro[benzofuran-2(3*H*),2′-[2*H*]pyran]-6-carboxylate (53). A solution of alcohol **51** (51 mg, 0.115 mmol), 4-(dimethylamino)pyridine (20 mg, 0.16 mmol), dichloromethane (2.5 mL), pyridine (2.5 mL) and *trans*-cinnamoyl chloride (100 mg, 0.60 mmol) is stirred at 23 °C for 18 h. Following the addition of *unsym*-dimethylethylenediamine, the reaction mixture is partitioned between ether (10 mL) and water (2 mL), and the organic layer is washed sequentially with 10% hydrochloric acid (until acidic) and saturated aqueous sodium bicarbonate (until basic). The organic phase is dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (15% ethyl acetate/85% hexanes) affords 54.4 mg (83%) of **53** as a clear, colorless oil: $[\alpha]^{22.5}_D$ +27.3° (*c* 2.67, $CHCl_3$); IR (neat) 3600, 2950, 2890, 1730, 1700, 1640, 1500, 1450, 1440, 1390, 1350, 1300, 1265, 1250, 1200, 1175, 1120, 1075, 1050, 1025, 955, 930, 900, 840, 775, 710, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 16.0 Hz, 1 H), 7.54–7.41 (m, 2 H), 7.39–7.35 (m, 3 H), 6.47 (d, *J* = 16.0 Hz, 1 H), 5.13 (br d, *J* = 2.6 Hz, 1 H), 4.15 (br dd, *J* = 10.3, 5.9 Hz, 1 H), 3.94 (dd, *J* = 11.4 Hz, 1 H), 3.77 (d, *J* = 9.9 Hz, 1 H), 3.53 (d, *J* = 9.9 Hz, 1 H), 3.39 (dd, *J* = 11.4, 4.0 Hz, 1 H), 3.39 (s, 3 H), 2.82 (br s, 1 H, OH), 2.57–2.48 (seven-line multiplet, 1 H), 2.18 (dd, *J* = 15.1, 2.6 Hz, 1 H), 2.02–1.76 (m, 5 H), 1.54–1.29 (m, 4 H), 0.89 (s, 9 H), 0.85 (d, *J* = 6.9 Hz, 3 H), 0.074 (s, 3 H), 0.069 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.46, 166.69, 144.28, 134.69, 129.86, 128.67, 127.95, 119.01, 105.07, 84.15, 72.65, 69.91, 64.84, 62.28, 51.20, 42.56, 36.54, 34.10, 33.08, 29.81, 25.75, 25.63, 20.51, 18.12, 12.70, −5.53; exact mass calcd for $C_{22}H_{39}O_6Si$ (M − $C_9H_7O_2$) 427.2516, found 427.2522.

Synthesis of Phyllanthocindiol 6, Methyl (2*S*,3*R*,3a*S*,4′*S*,5′*R*,6*S*,7a*R*)-4′-[(*E*)-cinnamoyloxy]decahydro-3-hydroxy-3-(hydroxymethyl)-5′-methylspiro[benzofuran-2(3*H*),2′-[2*H*]pyran]-6-carboxylate. Protected diol **53** (53.5 mg, 0.93 mmol) in anhydrous tetrahydrofuran (10 mL) at 23 °C under nitrogen is treated with a 1.0 M solution of *tetra-n*-butylammonium fluoride (110 μL, 0.110 mmol) in tetrahydrofuran. After being stirred at 23 °C for 10 min, the resulting clear, yellow solution is quenched with water (1.0 mL) and partitioned between ether (50 mL) and water (20 mL). The aqueous layer is extracted with diethyl ether (3 × 25 mL), and the combined organic layers are dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (60% ethyl acetate/40% hexanes) gives 41.2 mg (96%) of **6** as a clear, colorless oil, which crystallized on standing: mp 122–123 °C (recrystallized; acetone–hexanes); $[\alpha]^{22.5}_D$ +3.4° (*c* 1.67, $CHCl_3$); IR (thin crystalline film) 3600, 2950, 1740, 1710, 1640, 1500, 1450, 1390, 1355, 1312, 1280, 1260, 1206, 1180, 1124, 1075, 1055, 1025, 995, 930, 910, 870, 847, 825, 775, 714, 687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 16.0 Hz, 1 H), 7.53–7.49 (m, 2 H), 7.37–7.35 (m, 3 H), 6.46 (d, *J* = 16.0 Hz, 1 H), 5.10 (dd, *J* = 5.4, 2.9 Hz, 1 H), 4.12 (dd, *J* = 6.1, 3.6 Hz, 1 H), 4.06 (two overlapping doublet of doublets, six lines, 2 H), 3.53 (dd, *J* = 11.2, 4.7 Hz, 1 H), 3.40 (dd, *J* = 11.0 Hz, 1 H), 3.21 (s, 3 H), 2.72 (s, 1 H), 2.66 (dd, *J* = 10.4, 3.6 Hz, 1 H), 2.35 (tt, *J* = 11.8, 3.7 Hz, 1 H), 2.27 (dd, *J* = 15.1, 3.0 Hz, 1 H), 2.09 (br d, *J* = 15.1 Hz, 1 H), 2.02–1.95 (m, 1 H), 1.91–1.85 (m, 1 H), 1.86 (dd, *J* = 15.1, 3.0 Hz, 1 H), 1.72–1.60 (m, 3 H), 1.46–1.35 (m, 1 H), 1.28–1.17 (m, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.16, 166.63, 144.40, 134.57, 129.98, 128.73, 127.95, 118.83, 106.56, 85.22, 72.83, 69.91, 66.57, 63.06, 51.08, 43.75, 36.72, 35.70, 33.20, 29.86, 26.64, 20.80, 12.64; exact mass calcd for $C_{25}H_{32}O_8$ 460.2097, found 460.2116. Anal. Calcd for $C_{25}H_{32}O_8$: C, 65.20; H, 7.00. Found: C, 65.28; H, 7.09.

An authentic sample of **6** exhibits a slightly depressed optical rotation $[[\alpha]^{23}_D$ +2.45° (*c* 1.66, $CHCl_3$)] compared to our synthetic sample. However, mixture melting point determination and a 300-MHz ^1H NMR analysis of the natural material shows synthetic and natural **6** to be identical.[36]

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Supplementary Material Available: Procedures for the preparation of (+)-phyllanthocin and determination of optical purities of key intermediates en route to (+)-phyllanthocindiol (17 pages). Ordering information is given on any current masthead page.