Research Fund, administered by the American Chemical Society, for partial support of this work. This work also received partial support through the University of California Committee on Research.

Supplementary Material Available: Tables of coordinates, bond distances and angles, best least-squares planes, and torsion angles for **1** (12 pages); listing of structure factors (18 pages). Ordering information is given on any current masthead page.

Phyllanthoside–Phyllanthostatin Synthetic Studies. 7. Total Synthesis of (+)-Phyllanthocin and (+)-Phyllanthocindiol†

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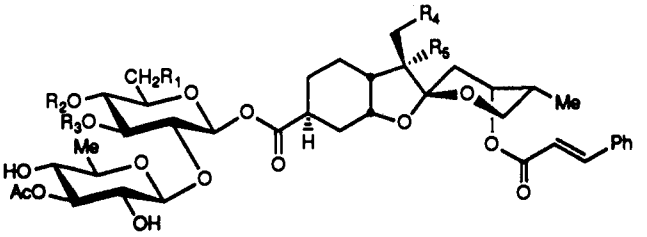
Abstract: A stereochemically linear total synthesis of (+)-phyllanthocin (**5a**), the aglycon methyl ester of the antineoplastic glycoside (+)-phyllanthoside (**1**), is described. The synthesis proceeds in 23 steps (4.5% overall yield) and affords (+)-phyllanthocin in high enantiomeric purity. The central features of the strategy include: (a) construction of aldehyde **8** via a stereoselective, intramolecular ene reaction; (b) elaboration of the spiroketal unit by a two-step tactic involving addition of a functionalized dihydropyran anion (i.e., **9**) to **8**, followed by a highly stereoselective spiroketalization; and (c) chemo- and stereoselective methylenation of the C(7) carbonyl group. In addition, a second-generation approach is presented, wherein an augmented spiroketalization maneuver not only establishes the C(8) spirocenter but also permits the regio- and stereocontrolled introduction of the C(11) methyl group. The latter sequence furnishes (+)-phyllanthocin in 21 steps (5.6% overall yield). Finally, the advanced phyllanthocin intermediate (+)-**49** is converted in five steps (42% overall yield) to (+)-phyllanthocindiol (**5b**), the aglycon of phyllanthostatin 3.

While searching for antitumor agents from the *Euphorbiaceae* family of plants, Kupchan and colleagues isolated (+)-phyllanthoside (**1**), a novel bisabolane glycoside derived from the roots of the Central American tree *Phyllanthus acuminatus* Vahl.[1] Methanolysis of **1** furnished (+)-phyllanthocin (**5a**), a crystalline aglycon methyl ester, whose structure was elucidated in 1977 via single-crystal X-ray analysis.[2] Formulation of the parent glycoside, however, remained unknown until 1982, when Pettit announced the complete characterization of phyllanthoside (**1**) and the closely related phyllanthostatins (**2–4**).[3] The structure of phyllanthocindiol (**5b**), the aglycon of phyllanthostatin 3 (**4**), likewise emerged from X-ray analysis of the derived methyl ester.

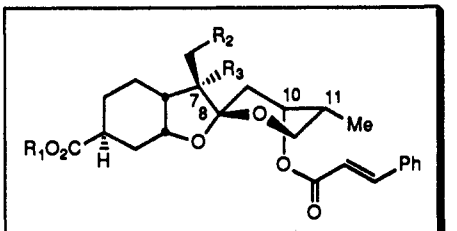
Medicinal interest in these glycosides stems principally from the discovery that phyllanthoside (**1**) and phyllanthostatin 1 (**2**) are potent inhibitors of several NCI tumor cell lines, including human breast cancer and B16 carcinomas.[4] As such both **1** and **2** are currently in phase I clinical trials in the U.K.[4b] Although the aglycon derivative phyllanthocin (**6**) proved to be biologically inactive, it nonetheless has attracted considerable synthetic effort, primarily focused upon the spiroketal architecture.[5-7]

Intrigued with the phyllanthoside–phyllanthostatin class of antitumor agents,[3] we initiated a synthetic program in this area in 1982. Our goals were 4-fold: (a) to develop an efficient synthetic approach to the two aglycons, phyllanthocin (**5a**) and phyllanthocindiol (**5b**); (b) to complete total syntheses of the parent glycoside (+)-phyllanthoside and the closely related phyllanthostatins 1–3; (c) to explore in-depth the chemical reactivity of the [4.5]spiroketal functionality central to the aglycon skeleton; and (d) to prepare a number of structurally related analogues for biological screening.

In this, a full account, we record the realization of the first of these goals, namely an efficient (5.6% and 2.4% overall yields, respectively), stereochemically linear route to (+)-phyllanthocin (**5a**) and (+)-phyllanthocindiol (**5b**) of high enantiomeric purity. From the outset, this venture was seen as prelude to the con-



1 Phyllanthoside: $R_1 = R_2 = H$, $R_3 = Ac$, $R_4, R_5 = O$ (epoxide)
2 Phyllanthostatin 1: 1, $R_2 = Ac$, $R_3 = H$
3 Phyllanthostatin 2: 1, $R_1 = OH$
4 Phyllanthostatin 3: 1, $R_4 = R_5 = OH$



5a Phyllanthocin: $R_1 = Me$, $R_2, R_3 = O$ (epoxide)
5b Phyllanthocindiol: $R_1 = H$, $R_2 = R_3 = OH$

† This paper is dedicated to the memory of Dr. Mineo Fukui.
‡ Deceased, Aug 14, 1990.

(1) Watt, J. M.; Breyer-Brandwijk, M. G. *The Medicinal and Poisonous Plants of Southern and Eastern Africa*; E. S. Livingstone Ltd: London, 1962; p 426. Morton, J. F. *Major Medicinal Plants*; C. C. Thomas: Springfield, IL, 1977; pp 193, 366.

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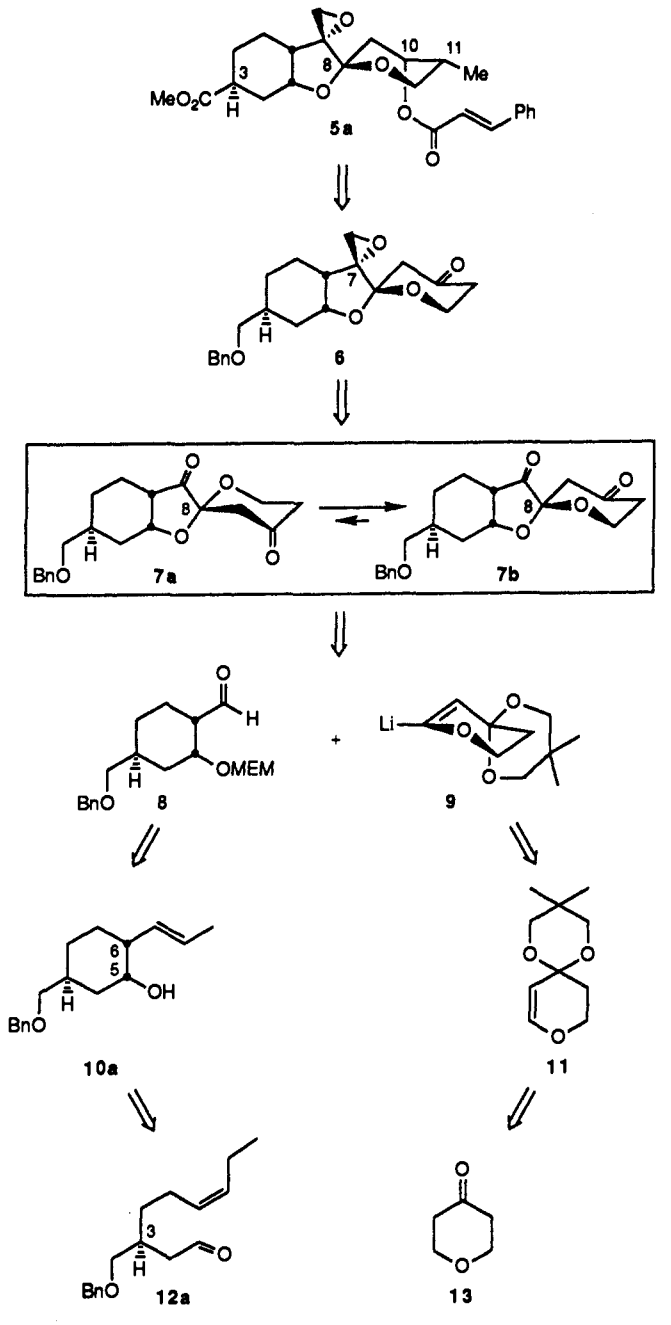
Scheme I



struction of the biologically active glycosides. In the following papers in this issue (contributions 8 and 9 in this series), we describe the first total synthesis of (+)-phyllanthoside as well as (−)-phyllanthostatin 1, (+)-phyllanthostatin 2, and (+)-phyllanthostatin 3.[8,9] Significant improvements in our first-generation phyllanthocin strategy, devised since we first announced the completion of (+)-phyllanthocin in 1984,[8a] will also be presented.

A Stereochemically Linear Synthetic Strategy for Phyllanthocin. The cornerstone of our phyllanthocin strategy (Scheme I) was based on the conjecture that spiroketal **7b**, possessing the requisite configuration at the spirocenter [i.e., C(8)], would prove to be more stable than diastereomer **7a**. Specifically, the anomeric interactions of the furanone and pyranone oxygens,[10] in conjunction with the rigidity of the perhydrobenzofuranone system, would blend together to stabilize **7b** relative to the C(8) epimer. Assuming the validity of this proposition, construction of the spiroketal skeleton was envisioned to involve addition of anion **9**,[11] derived from a suitably functionalized dihydropyran (**11**), to aldehyde **8**, followed by a spiroketalization–equilibration protocol.[12,13] Methylenation at C(7), and introduction of the C(10) and C(11) substituents required for phyllanthocin, would then take advantage of the predictable stereochemical biases of the perhydrobenzofuranone and pyranone ring systems.

Aldehyde **8** in turn was expected to arise via a stereoselective, intramolecular ene reaction (**12a** → **10a**),[14] followed by ozonolysis. Given the preferred chair transition state for the ene process,[15]

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

(3) The structures of these complex glycosides as well as the parent disaccharide phyllanthose were based on a detailed analysis of their 400-MHz ^{1}H NMR, 100-MHz ^{13}C NMR, and mass spectra, see: (a) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P. *Can. J. Chem.* **1982**, *60*, 544. Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P.; Schmidt, J. M. *Can. J. Chem.* **1982**, *60*, 939. Pettit, G. R.; Cragg, G. M.; Niven, M. L.; Nassimbeni, L. R. *Can. J. Chem.* **1983**, *61*, 2630. Further evidence for phyllanthose derived from the X-ray structures of phyllanthose peracetate, see: (b) Pettit, G. R.; Cragg, G. M.; Suffness, M. I.; Gust, D.; Boettner, F. E.; Williams, M.; Saenz-Renauld, J. A.; Brown, P.; Schmidt, J. M.; Ellis, P. D. *J. Org. Chem.* **1984**, *49*, 4258. (c) Pettit, G. R.; Cragg, G. M.; Suffness, M. I. *J. Org. Chem.* **1985**, *50*, 5060. (d) Pettit, G. R.; Schautelberger, D. E.; Nieman, R. A.; Dufresne, C.; Saenz-Renauld, J. A. *J. Nat. Prod.* **1990**, *53*, 1406.

(4) (a) See, for example: Powis, G.; Moore, D. J. *Proc. Assoc. Cancer Res.* **1985**, *26*, 354. Also, see: ref 2. (b) Personal communication from Dr. Charles K. Grieshaber, Chief, Toxicology Branch, Developmental Therapeutics Program, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.

(5) For recent syntheses of **5a**, see: (a) McGuirk, P. R.; Collum, D. B. *J. Am. Chem. Soc.* **1982**, *104*, 4496. (b) Williams, D. R.; Sit, S.-Y. *J. Am. Chem. Soc.* **1984**, *106*, 2949. (c) Burke, S. D.; Cobb, J. E.; Takeuchi, K. J. *J. Org. Chem.* **1985**, *50*, 3420. Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237. (d) Martin, S. F.; Dapper, M. S.; Dupré, B.; Murphy, C. J. *J. Org. Chem.* **1987**, *52*, 3760. Martin, S. F.; Dapper, M. S.; Dupré, B.; Murphy, C. J.; Colapret, J. A. *J. Org. Chem.* **1989**, *54*, 2209. For synthesis of **5b**, see: (e) McGuirk, P. R.; Collum, D. B. *J. Org. Chem.* **1984**, *49*, 843.

(6) For leading references on the synthesis and chemistry of spiroketals, see: Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789. Martinez, G. R.; Grieco, P. A.; Williams, E.; Kanai, K.; Srinivanasan, C. V. *J. Am. Chem. Soc.* **1982**, *104*, 1436. Baker, R.; Herbert, R. H.; Parton, A. H. *J. Chem. Soc., Chem. Commun.* **1982**, 601. Williams, D. R.; Barner, B. A. *Tetrahedron Lett.* **1983**, *24*, 427. Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303, and references cited therein. Evans, D. A.; Sacks, C. E.; Whitney, R. A.; Mandel, N. G. *Tetrahedron Lett.* **1978**, 727. Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.

(7) For related work from our laboratory on the synthesis of spiroketal systems, see: Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015. Smith, A. B., III; Thompson, A. S. *J. Org. Chem.* **1984**, *49*, 1469. Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N.; Smith, A. B., III *J. Am. Chem. Soc.* **1986**, *108*, 2662.

(8) For the preceding papers in this series, see: (a) (+)-Phyllanthocin (**5a**): Smith, A. B., III; Fukui, M. *Abstracts of Papers*, 187th National Meeting of the American Chemical Society, St. Louis, MO; American Chemical Society: Washington, DC, 1984; ORGN 6. Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. (b) (+)-Phyllanthoside (**1**): Smith, A. B., III; Fukui, M.; Rivero, R. A. *Abstracts of Papers*, 189th National Meeting of the American Chemical Society, Miami Beach, FL; American Chemical Society: Washington, DC, 1985; ORGN 82. Smith, A. B., III; Rivero, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 1272. (c) (−)-Phyllanthostatin 1 (**2**): Smith, A. B., III; Hale, K. J.; Vaccaro, H. A. *J. Chem. Soc., Chem. Commun.* **1987**, 1026. (d) (+)-Phyllanthostatin 2 (**3**): Smith, A. B., III; Hale, K. J.; Vaccaro, H. A. *Tetrahedron Lett.* **1987**, *28*, 5591. (e) (+)-Phyllanthostatin 3 (**4**) and (+)-phyllanthocindiol methyl ester (**5b**): Vaccaro, H. A.; Rivero, R. A.; Smith, A. B., III *Tetrahedron Lett.* **1989**, *30*, 1465. (f) Smith, A. B., III; Empfield, J. R.; Vaccaro, H. A. *Tetrahedron Lett.* **1989**, 7325.

(9) For contributions 8 and 9 in this series, see: Smith, A. B., III; Rivero, R. A.; Hale, K. J.; Vaccaro, H. A. *J. Am. Chem. Soc.*, following paper in this issue. Smith, A. B., III; Hale, K. J.; Vaccaro, H. A.; Rivero, R. A. *J. Am. Chem. Soc.*, paper following contribution no. 8 in this issue. Also, see: ref 30.

(10) For excellent reviews of the anomeric effect, see: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon: New York, 1983. Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Hafner, K., Ed.; Springer-Verlag: Berlin, 1983.

(11) For examples of unfunctionalized anions related to **9**, see: Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997.

(12) At the time of our original disclosure of the phyllanthocin synthesis (1984), such a construction of the [4.5]spiroketal framework was unknown. Thereafter Kurth independently reported a similar approach: Kurth, M. J.; Brown, E. G.; Hendra, E.; Hope, H. J. *J. Org. Chem.* **1985**, *50*, 1115.

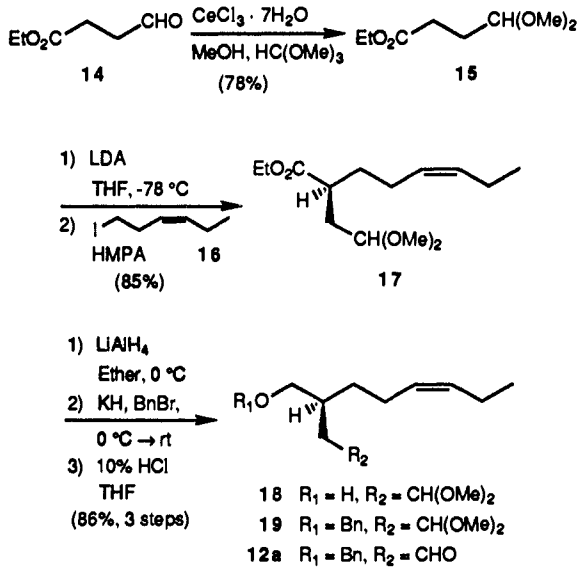
(13) For related examples of acid-promoted spiroketalization of 2-(ω-hydroxyalkyl)dihydropyran derivatives, see: Danishefsky, S. J.; Pearson, W. H. *J. Org. Chem.* **1983**, *48*, 3865. Also, see: ref 6.

(14) For a review of the ene reaction, see: Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476.

the relative stereochemistry at C(5) and C(6) would follow directly. Thus, the entire stereochemical problem of (+)-phyllanthocin (**5a**) reduces, due to the linearity of the strategy, to the preparation of **12a** possessing the correct absolute stereochemistry at C(3). We have termed such an approach a stereochemically linear strategy.[16]

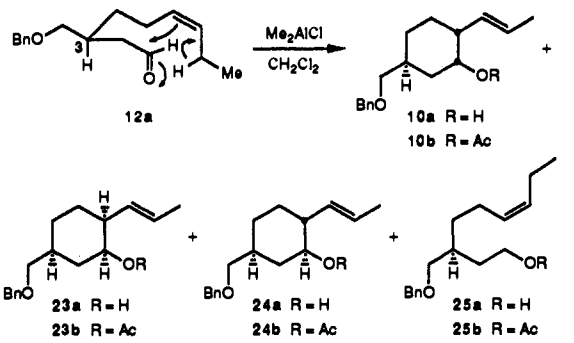
Synthesis of Racemic Phyllanthocin: An Important Initial Objective. At the outset we planned to prepare (±)-phyllanthocin in order to explore the feasibility of key synthetic transformations, including the intramolecular ene reaction, the spiroketalization–equilibration maneuver, and the regioselective methylation at C(11). Initial efforts therefore addressed the development of an efficient route to aldehyde (±)-**12a**.

Our point of departure was dimethyl acetal **15**,[17] readily prepared in 78% yield from ethyl 4-oxobutyrate (**14**).[18,19] Alkylation with homoallylic iodide **16**[20] afforded ester **17** (85% yield), which was reduced to alcohol **18** in 91% yield. Benzylation followed by acetal hydrolysis then furnished **12a** (92% yield). In preparative experiments it was found most convenient to convert **17** to **12a** without chromatographic purification of the intermediates. In this fashion **12a** could be obtained in 86% yield for the three steps.

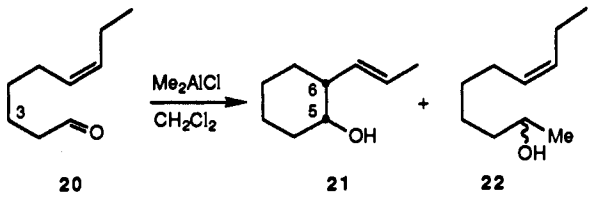


The Intramolecular Ene Reaction: Establishment of the A-Ring Relative Stereochemistry. In 1982 Snider[15] demonstrated that the intramolecular ene reaction comprises an effective method for the stereoselective preparation of *cis*-alkenyl cyclohexanols. For example, the Me_2AlCl-promoted cyclization of (*Z*)-6-nonenal (**20**) furnished exclusively *cis*-2-((*E*)-1-propenyl)cyclohexan-1-ol (**21**), along with minor amounts of (*Z*)-7-decen-2-ol (**22**).[15] The ene process is thought to involve a synchronous, unimolecular reaction of the aldehyde–Me_2AlCl complex, affording the major product (**21**) via a chair-like transition state.[15] Alcohol **22**, on the other hand, is believed to arise from the same complex by addition of a second equivalent of Me_2AlCl.[21]

Table I. The Intramolecular Ene Reaction of Aldehyde (±)-**12a**



entry	substrate concn (mM)	reaction conditions	yields (%) 10a	23a	24a	25a
1	20	0 °C, 2.0 h	69	5	trace	3
2	20	room temp, 1.5 h	79	6	trace	2
3	20	0 °C → room temp, 45 min	81	8	1	2
4	20	room temp, 30 min	83	4	1	1



We anticipated that a benzyloxymethyl substituent at C(3) would occupy an equatorial position in the preferred transition state,[14] generating a functionalized cyclohexanol with the correct relative stereochemistry for ring A of phyllanthocin. Indeed, treatment of (±)-**12a** with Me_2AlCl did furnish the requisite alcohol (**10a**) as the major product under a variety of conditions (Table I). Yields ranged from good to excellent. Minor amounts of cis and trans alcohols **23a** and **24a** as well as reduced alcohol **25a** were also formed.[22] The major products (**10a** and **24a**) were readily purified by flash chromatography. Alcohols **23a** and **25a** proved separable only after conversion to the corresponding acetates (**23b** and **25b**) or alternatively after oxidation to ketone **26** and aldehyde **12a**, respectively.

Structural assignments for the ene products were based on a combination of spectroscopic analyses and chemical transformations. The ^1H NMR resonances of the C(5) protons served to establish the C(5,6) vicinal stereochemistry in the derived acetates (**10b**, **23b**, and **24b**). For **10b** this hydrogen appeared as a quartet centered at δ 5.08, with a coupling constant of 2.8 Hz and a peak width at half-height of 8.7 Hz. Acetate **23b**, in contrast, presented the C(5) hydrogen as a doublet of triplets centered at δ 4.82, with coupling constants of 11.4 and 4.4 Hz and a peak width at half-height of 21.3 Hz. Finally, acetate **24b** displayed the C(5) hydrogen as a triplet of doublets centered at δ 4.61, with coupling constants of 10.8 and 4.2 Hz and a peak width at half-height of 27.5 Hz. These observations are indicative of an equatorial–axial C(5,6) coupling in **10a**, an axial–equatorial C(5,6) coupling in **23b**, and an axial–axial C(5,6) couling in **24b**.[23]

Chemical evidence for the structures and stereochemistry of

(15) Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* **1982**, *47*, 4538, and references cited therein. Also, see: ref 51.

(16) In contrast with convergent syntheses, a stereochemically linear strategy exploits the stereogenicity of the starting material by inducing the relative and absolute stereochemistry of all remaining centers. Although the latter approach may in some cases entail an increase in the total number of steps, compared with a stereochemically convergent strategy, overall efficiency may nonetheless be enhanced in that only one resolution, asymmetric induction, or resort to the pool of chiral substrates is required.

(17) Luche, J.-L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976.

(18) Aldehyde **14** was prepared in three steps (48% yield) from succinic anhydride via conversion to the monoethyl ester (absolute EtOH, Δ), followed by formation of the acid chloride ($SOCl_2$, Δ) and subsequent Rosenmund reduction (H_2, $Pd/BaSO_4$, quinoline-S, xylene, Δ). See: Cason, J. *Organic Syntheses*; Wiley: New York, Collect. Vol. III, p 169. For a review of the Rosenmund reduction, see: Mossettig, E.; Mozingo, R. *Org. Reactions* **1948**, *4*, 362.

(19) Originally the ethylene acetal of **14** was employed in this sequence. However, hydrolysis of this moiety was problematic.

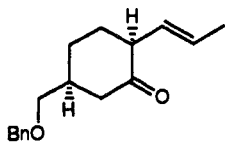
(20) Iodide **16** was prepared in two steps (83% overall yield) from commercially available (*Z*)-3-hexen-1-ol, via formation of the mesylate (MesCl, py, 0 °C → rt) followed by a Finkelstein reaction (NaI, acetone, Δ).

(21) The ene product (**21**) is favored at low concentration, whereas addition predominates at low temperatures. The latter pathway is also favored by an excess of Me_2AlCl.[14]

(22) Presumably, alcohol **23a** is formed via an unfavorable chair-like transition state in which the benzyloxymethyl substituent is axial. Isomer **24a** arises via a chair-like cyclization of trans aldehyde **12b**; the cis-trans ratio of commercially available (Aldrich) *cis*-3-hexen-1-ol is 98:2. In the latter transition state, the benzyloxymethyl substituent is axial.

(23) Such multiplicities and, in particular, half-height peak widths are diagnostic of axial and equatorial orientations: Jackman, M. L.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon: Oxford, 1969; pp 238–241; and references cited therein.

10a and **23a** was obtained via independent Collins oxidation[24] to ketones **27** and **26**, respectively. Sodium borohydride reduction of **27** then produced **24a** and **10a** in a 3:1 ratio. However, similar reduction of **26**, possessing the axial α-propenyl group, produced a 4.8:1 mixture of **23a** and **24a**! In the latter case, equilibration of the α-substituent presumably competed with ketone reduction. Finally, the structure of **25a** was secured via reduction of aldehyde **12a**.



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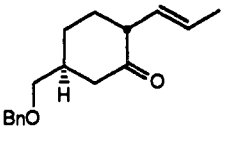
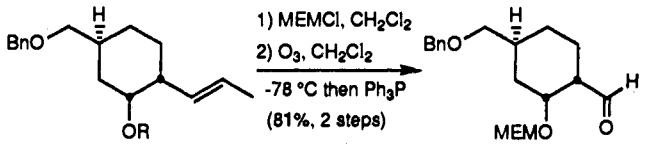


27

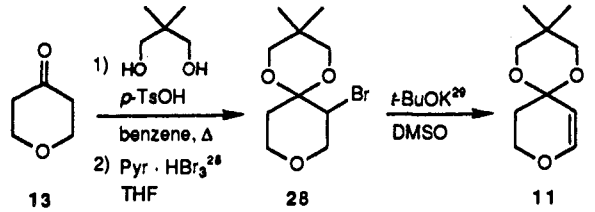
Continuing with the synthesis, protection of the hydroxyl in **10a** as its MEM ether[25,26] and ozonolysis of the olefin furnished aldehyde **8**. Here overoxidation was a significant problem; crucial for success were rigorous temperature control during the addition of 1 equiv of ozone at −78 °C and then the immediate destruction of the ozonide with triphenylphosphine. These optimized conditions afforded aldehyde **8** in 38% overall yield for the eight steps from **14**.



10a R = H
10c R = MEM

8

Generation of Lithiated Dihydropyran 9: A Useful Building Block. After developing a viable synthesis of aldehyde **8**, we turned to the preparation of dihydropyran **11**, required for construction of the spiroketal unit. This was accomplished in three steps from commercially available tetrahydropyran-4-one (**13**).[27]



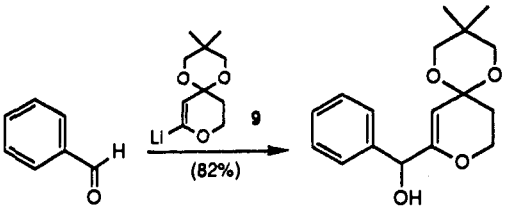
13 **28** **11**

(70% overall yield)

The generation and stability of the derived vinyl anion (i.e., **9**) were next investigated in a model reaction with benzaldehyde.[11] As expected, treatment of dihydropyran **11** with *t*-BuLi (−78 °C → 0 °C), followed by addition of benzaldehyde, furnished **29** in good yield.

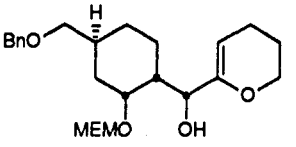
A Highly Stereoselective Spiroketalization Maneuver: Cornerstone of the Synthetic Strategy. To explore the feasibility of the proposed spiroketalization–equilibration tactic, we undertook a model study utilizing the 2-lithio derivative of dihydropyran in place of **9**. Addition to aldehyde **8** resulted in a 3:2 mixture of alcohols **30** and **31** in 82% yield.[11]

Spiroketalization was then attempted by treating **30** and **31** individually with excess trifluoroacetic acid; the resulting trifluoroacetates were hydrolyzed with base. Under these conditions, **30** furnished epimeric alcohols **32a** and **33a** in 73% yield (ratio



29

1.4:1), whereas **31** gave epimers **34a** and **35a** in 79% yield (ratio 7.4:1).[30]



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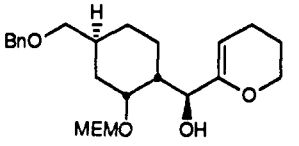
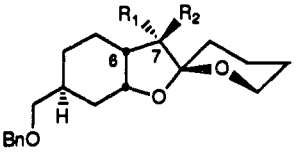
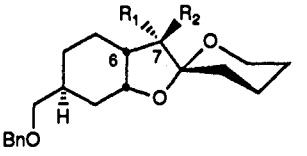


31

Structural assignments for the spiroketals were again based on a combination of spectroscopic and chemical observations. The ^{1}H NMR characteristics of the C(7) protons in the derived acetates (i.e., **32b–35b**) established the C(6,7) vicinal stereo-





32a R_1 = H, R_2 = OH
32b R_1 = H, R_2 = OAc
34a R_1 = OH, R_2 = H
34b R_1 = OAc, R_2 = H

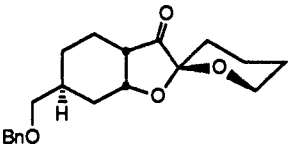
33a R_1 = H, R_2 = OH
33b R_1 = H, R_2 = OAc
35a R_1 = OH, R_2 = H
35b R_1 = OAc, R_2 = H

chemistry. For example, in the spectrum of **32b** the C(7) proton appeared as a doublet centered at δ 4.60 with a coupling constant of 1.5 Hz, and for **33b** this proton gave a singlet at δ 4.85; these coupling constants are indicative of trans relationships between the C(6) and C(7) hydrogens.[31] NMR analysis likewise revealed cis orientations of the C(6) and C(7) protons in **34b** and **35b**.[31] Infrared experiments were next employed to establish the relative configurations of the spiroketal stereocenters vis-à-vis the hydroxyl substituents at C(7). At high dilution alcohols **32a** and **35a** were capable of significant intramolecular hydrogen bonding, as evidenced by the O–H stretching vibrations at 3500 and 3540 cm^{-1}, respectively.[32] Alcohols **33a** and **34a**, in contrast, displayed bands attributable to both free and intermolecularly hydrogen-bonded hydroxyls.

Chemical evidence for the structures of **32a** and **34a** derived from Swern oxidations[33] which furnished the same ketone (i.e., **36**); the structure of the latter was secured via single-crystal X-ray analysis.[34] Similarly, Swern oxidations[33] of **33a** and **35a** furnished ketone **37**.[35]

Upon completion of the model study, we turned to the preparation of spiroketal **7b** required for phyllanthocin. Generation of anion **9**[11] and rapid addition of aldehyde **8** led to a 3:2 mixture of alcohols **38** and **39** in 83% yield. Assignments of these structures were based upon spectroscopic comparisons with al-

(24) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363.
(25) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.
(26) Both the 1-ethoxyethyl ether and the methoxymethyl ether derivatives of **10a** were also studied. However, the MEM ether gave superior results in the subsequent transformations.
(27) Although **13** was available from Aldrich, we prepared the material from commercially available 3-chloropropionyl chloride via the procedure of Reese: Arentzen, R.; Yan Kui, Y. T.; Reese, C. B. *Synthesis* **1975**, 509. Friedel-Crafts acylation of ethylene with 3-chloropropionyl chloride ($AlCl_3$, CH_2Cl_2) afforded 1,5-dichloropentan-3-one; acid hydrolysis (NaH_2PO_4, *o*-phosphoric acid, H_2O, 100 °C) then provided **13** in 33% overall yield.
(28) Djerassi, C.; Scholz, C. R. *J. Am. Chem. Soc.* **1948**, *70*, 1911.
(29) Garbisch, E. W., Jr. *J. Org. Chem.* **1965**, *30*, 2109.
(30) A detailed investigation of the spiroketalization process will be reported in the tenth paper in this series: Vaccaro, H. A.; Sprengeler, P. A.; Smith, A. B., III, manuscript in preparation.
(31) Karplus, M. J. *J. Am. Chem. Soc.* **1963**, *85*, 2870.
(32) The intramolecular hydrogen bonding presumably involves the C(7) hydroxyl group and the C(11) spiroketal oxygen.
(33) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. Also, see: Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.
(34) Carroll, P. University of Pennsylvania X-ray Crystallographic Facility, unpublished results.
(35) Ketones **36** and **37** were subsequently obtained via spiroketalization (trifluoroacetic acid, CH_2Cl_2) of the enone derived from oxidation of alcohol **30** or **31**. Also, see: ref 30.



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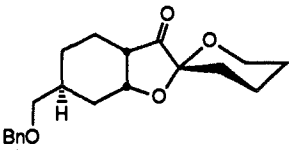
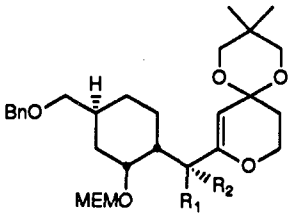
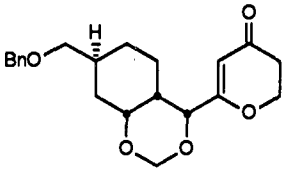


37

cohols **30** and **31** as well as correlations of their chromatographic mobilities.[36]



38 R_1 = H, R_2 = OH
39 R_1 = OH, R_2 = H



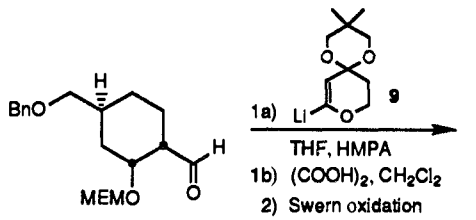
40

To effect the spiroketalization–equilibration maneuver, **38** was treated with trifluoroacetic acid in methylene chloride, followed by base to hydrolyze the expected acetates. However, this sequence merely removed the ketal moiety in **38**. Attempted spiroketalization of deketalized **38** invariably furnished only the very unreactive methylene ketal **40**.[37,38]

Undaunted, we envisioned diketone **41** as another suitable substrate for the spiroketalization–equilibration sequence. Toward this end, hydrolysis of ketal **39** with aqueous oxalic acid in methylene chloride, followed by Collins oxidation,[24] afforded **41** in 72% overall yield. A more expedient route involved addition of lithio dihydropyran **9** to aldehyde **8**; ketal hydrolysis then gave a mixture of diastereomeric alcohols which without separation was subjected to Swern oxidation,[33] to afford **41** in 71% yield for the three steps.

Removal of the MEM moiety and spiroketalization were then attempted as a single operation mediated by trifluoroacetic acid. Although the desired spiroketal **7b** was in fact formed, the yield was only 38%. To circumvent the low yield, we devised a two-step procedure involving removal of the MEM moiety with zinc bromide,[25] followed by treatment of the resultant alcohol with a catalytic amount of camphorsulfonic acid in dry benzene. Under these conditions **41** was converted into **7b** in 71% yield, along with a small amount of **7a** (26:1 ratio). The structure of **7b** was confirmed by single-crystal X-ray analysis.[34]

Although this remarkable stereoselectivity will be the subject of a forthcoming paper,[30] we note here that the observed product distribution did not arise via equilibration, as we had envisioned a priori, but instead was a kinetic result.[39] This finding is consistent with the intervention of a kinetic anomeric effect, in conjunction with steric interactions involving the nascent spiroketal ring system.



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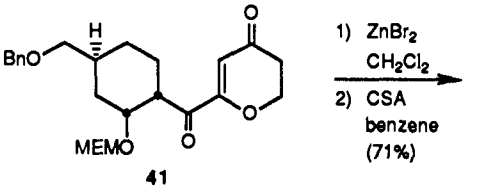
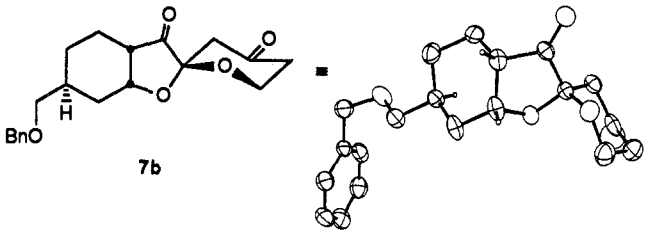


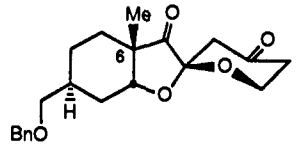
41



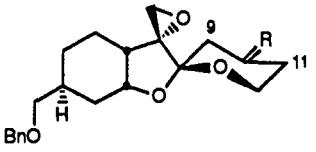
7b

Elaboration of Racemic Phyllanthocin. With the tricyclic skeleton in hand, the synthesis of (±)-phyllanthocin (**1**) still required the execution of three stereochemically demanding operations: methylenation at C(7), methylation at C(11), and reduction of the C(10) carbonyl. Attempted methylation at C(11) of **7b**, employing a variety of kinetic alkylation protcols, proved unsuccessful. For example, treatment with LDA (1.1 equiv) at −78 °C followed by addition of methyl iodide in HMPA (−78 °C → 23 °C) resulted in preferential alkylation at C(6) to afford **42** as the major product!

Consequently, we sought to differentiate the C(7) and C(10) carbonyls of **7b** by chemoselective methylenation. We anticipated that enhanced electrophilicity of the former, attributable to the



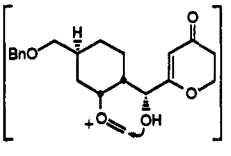
42



6 R = O
43 R = H, H

(36) Both major alcohols (**30** and **38**) were more mobile on TLC than the respective diastereomers **31** and **39**; in addition **30** and **38** predominated in the same ratio (1.5:1). Comparisons of the 250-MHz ^{1}H NMR spectra of the diastereomers were inconclusive, although pairwise chemical shift similarities were noted in the δ 4.0–6.0 region.

(37) Presumably, the C(7) hydroxyl group traps the oxonium ion (i) resulting from scission of the MEM ether in **38**.



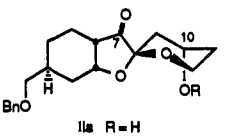
i

(38) All attempts to effect hydrolysis of the acetal resulted in recovery of **40** or total destruction.

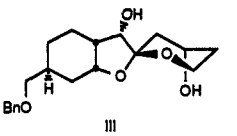
(39) The ratio of spiroketals isolated earlier in a preparative experiment was 35:1.[8a] However, subsequent analysis by preparative HPLC revealed the ratio to be 26:1. The discrepancy can be traced to loss of the minor isomer during purification. A similar kinetically controlled spiroketalization has subsequently been employed by Martin and co-workers in their synthesis of phyllanthocin (ref 5d).

(40) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(41) The C(7) carbonyl is both more electrophilic and more sterically encumbered than the C(10) carbonyl. Treatment of diketone **7b** with L-Selectride (1 equiv) at −78 °C provided ketone **iia** as the major product (62% yield) along with diol **iii** (25% yield). The absence of C(7) monoreduction product suggested that diol **iii** resulted from overly rapid addition of L-Selectride. Indeed, addition of a 0.05 M THF solution of L-Selectride to **7b** over a period of 5.5 h afforded **iia** in 96% yield. With ketone **iia** in hand, a variety of phyllanthocin analogues can be prepared. The assignment of structure **iia** was based on the propensity of L-Selectride to afford axial alcohols (Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159), in conjunction with the multiplicity of the C(10) proton resonance for the derived acetate **iib**. This resonance appeared as a dddd centered at δ 5.23 with coupling constants of 6.0, 6.0, 4.0, and 4.0 Hz, indicative of an equatorial hydrogen. In addition, the IR spectrum of **iia** revealed the presence of the C(7) carbonyl group (1770 cm^{-1}).

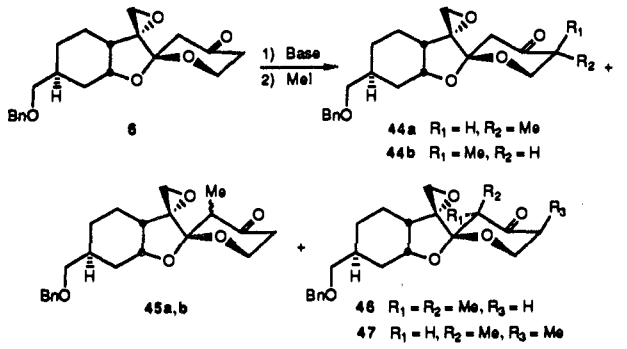


iia R = H
iib R = Ac



iii

Table II. Direct Methylation of Ketone (±)-6



entry	conditions	yields (%) 6	44a,b	45a,b	46	47
1	(1) LDA, THF, −78 °C (2) MeI, HMPA −78 °C → rt	48	5	5		
2	(1) $(Me_3Si)_2NK$, THF, −78 °C (2) MeI, HMPA −78 °C → 0 °C			12	12	14
3	(1) LiTMP, DME, −78 °C (2) MeI, HMPA −78 °C → rt	51	9	13		
4	(1) $(Me_2PhSi)_2NLi$, THF, 0 °C (2) MeI, HMPA 0 °C → rt	19	12	29	6	
5	(1) $(Me_2PhSi)_2NK$, THF 18-C-6, −78 °C (2) MeI, HMPA, −78 °C	12		trace	41	10
6	(1) $(Me_3Si)_2NK$, THF, −78 °C (2) Et_3B, rt (3) MeI, HMPA	31	5	34		

two α-alkoxy substituents, would facilitate this transformation. Support for this conjecture derived from the unusually high IR frequency (1770 cm^{-1}) of the C(7) carbonyl. That the correct stereochemical outcome would pertain appeared reasonable in view of the concave–convex nature of the substrate. In the event, treatment of **7b** with sodium dimethylsulfoxonium methylide[40] afforded the requisite epoxide **6** exclusively.[41] The structure of **6** was assigned via spectroscopic comparisons with epoxide **43**, obtained by methylenation of ketone **36**,[42] together with the IR spectrum which confirmed the presence of the C(10) carbonyl group (1725 cm^{-1}).

Continuing with the synthesis, regiocontrolled C(11) methylation of **6** likewise proved troublesome, presumably because the proximate ether moiety further enhanced the acidity of the C(9) methylene protons. As shown in Table II, execution of standard kinetic alkylation protocols (entries 1–3) led only to small amounts of C(11)-methylated products (**44a** and **44b**), along with varying mixtures of unreacted **6**[43] and the undesired products of C(9) mono- and dialkylation (**45**, **46**, and **47**).

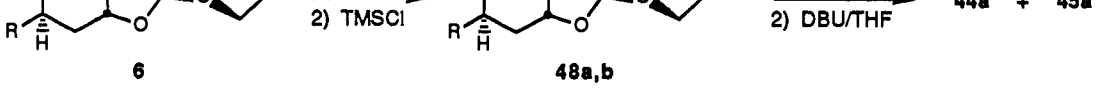
Assuming that the requisite C(11) enolate could be generated and trapped by increasing the steric bulk of the base and/or the reactivity of the electrophile, we next explored the more highly encumbered amide bases introduced by Masamune (Table II, entries 4–6).[44] Again, substantial quantities of C(9)-alkylated products were formed. These results suggested that efficient capture of the putative C(11) enolate with MeI was not feasible. However, the use of trimethylsilyl chloride as electrophile did result in more effective trapping of the kinetic enolate, as outlined in Table III. Optimal results (entry 4) were obtained via deprotonation of **6** with potassium diphenyltetramethyldisilazide (−78 °C, 5 min), followed by addition of excess trimethylsilyl chloride, to furnish an 83:17 mixture of silyl enol ethers **48a** and **48b**. Regioselective alkylation then was best achieved by employing the method of Kuwajima.[45] Specifically, regeneration of the enolate with anhydrous *N*-benzyltrimethylammonium fluoride, in the presence of excess methyl iodide, afforded **44a** and **44b** in a 1:5 ratio, along with a small amount of starting ketone. Without separation, this mixture was subjected to equilibrating conditions (DBU, THF) to convert the axial isomer (**44b**) to the desired, more stable equatorial compound (**44a**). Purification by flash chromatography gave **44a** in 53% yield for the three steps (62% based on recovered starting material). Minor amounts of **45a** (11%) and **6** (15%) were also obtained.[46]

The C(3) benzyloxymethyl substituent was next converted to a carbomethoxy group in three steps: (a) debenzylation via hydrogenolysis, (b) oxidation with RuO_4 to the corresponding acid (**49**),[47] and (c) esterification with diazomethane. This sequence led to **50** in 68% yield. At this point, completion of the synthesis of (±)-phyllanthocin entailed stereoselective reduction of the C(10) carbonyl group and esterification of the resultant axial alcohol. Following the precedent of Collum,[48] treatment of **50** with sodium borohydride afforded predominantly (ca. 6.3:1) the axial epimer (**51**). Cinnamoylation then gave (±)-phyllanthocin (**5a**), identical with a sample of natural phyllanthocin in all respects, except for chiroptical properties.[49]

Total Synthesis of (+)-Phyllanthocin. Given a viable route leading to the racemate, the synthesis of (+)-phyllanthocin reduced to the preparation of aldehyde **12a** with the correct absolute stereochemistry at C(3). For this endeavor we selected the asymmetric alkylation methodology of Evans (Scheme II).[50]

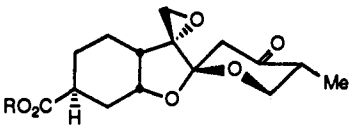
The synthesis began with imide (+)-**56**, available in 98% yield via acylation of (+)-oxazolidone **55**[51] with acid chloride **54**.[52]

Table III. Methylation of Ketone (±)-6 via the Intermediate Trimethylsilyl Enol Ether

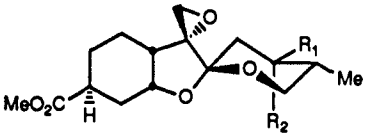


entry	R	base	ratio[a] $\Delta^{10,11}:\Delta^{9,10}$	methylation yield[b] (%)	isolated ratio 44a:45a	recovered 6 (%)
1	$BnOCH_2^-$	$(Me_3Si)_2NK$ −78 °C, 30 min	65:35			
2	$BnOCH_2^-$	$(Me_2PhSi)_2NK$ −78 °C → −40 °C	50:50			
3	$BnOCH_2^-$	$(Me_2PhSi)_2NK$ −78 °C, 1.5 h	77:23	51	77:23	26
4	$BnOCH_2^-$	$(Me_2PhSi)_2NK$ −78 °C, 5 min	83:17	64	83:17	15
5	MeO_2C^-	$(Me_2PhSi)_2NK$ −78 °C, 45 min	58:42	54	59:41	16
6	MeO_2C^-	$(Me_2PhSi)_2NK$ −78 °C, 5 min	75:25	52	70:30	16

[a] Determined by 250-MHz ^1H NMR. [b] Combined yield (**44a** and **45a**).



49 R = H
50 R = Me



51 R_1 = H, R_2 = OH
52 R_1 = OH, R_2 = H

Alkylation with allyl bromide then afforded mixtures of diastereomers **57a,b**. The alkylation experiments are outlined in Table IV. Best results (entry 4) were obtained by generation of the lithium enolate of (+)-**56** with $LiN(SiMe_3)_2$ in THF at −78 °C, followed by addition of allyl bromide and gradual warming to 0 °C, to provide an inseparable 94:6 mixture of (−)-**57a** and **57b** in 92% yield.[50]

Removal of the chiral auxiliary proved more troublesome than expected.[53] Ultimately $LiAlH_4$ reduction[50] of **57a,b** provided the corresponding alcohol (+)-**58** (Scheme II), admixed with a small amount of amino alcohol **59a**. Benzylation of this mixture permitted facile separation of **59b** from (−)-**60**. Selective ozonolysis[54] of the olefinic bond in (−)-**60** led to aldehyde (−)-**61** in 62% yield overall from **57**. As before, successful ozonlysis required rigorous temperature control (i.e., −78 °C) during the addition of 1 equiv

Scheme II

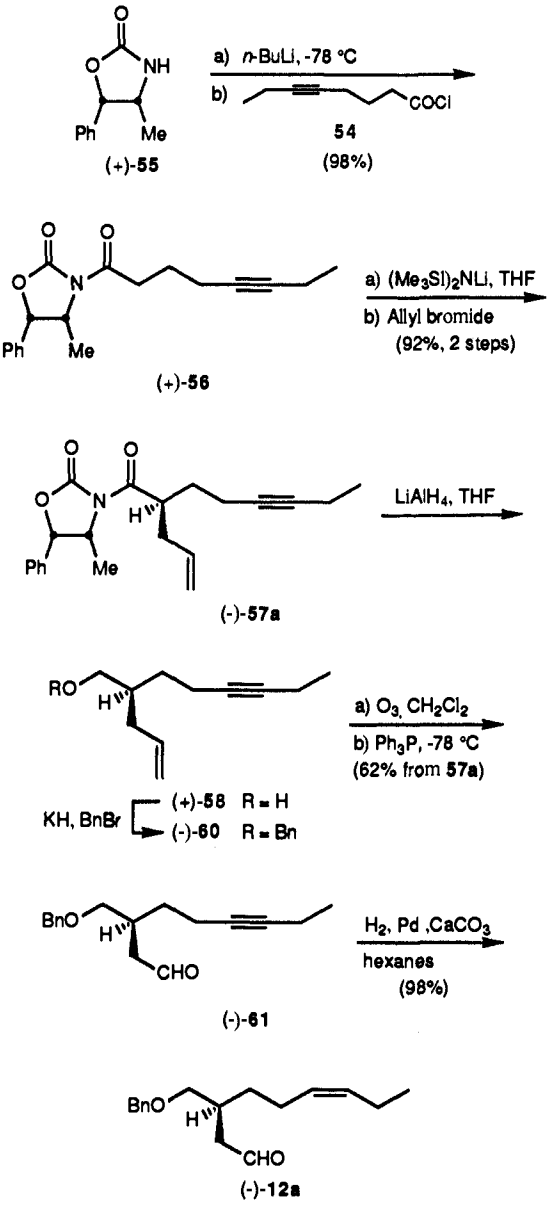
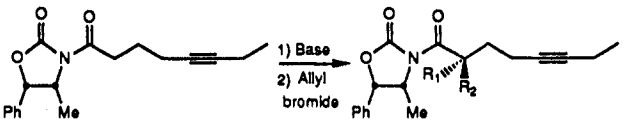
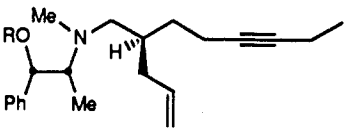


Table IV. Alkylation of Imide (+)-56 with Allyl Bromide



entry	base	allyl bromide (equiv)	alkylation conditions	combined yield (%)	ratio[a] **57a:57b**
1	$(Me_3Si)_2NNa$	5	−78 °C, 10 h	72	92:8
2	$(Me_3Si)_2NNa$	4	−78 °C, 15 min then −40 °C, 1 h	76	90:10
3	$(Me_3Si)_2NLi$	3	−78 °C, 30 min then 0 °C, 4 h	58	95:5
4	$(Me_3Si)_2NLi$	6	−78 °C → 0 °C (2.5 h) then 0 °C, 2.5 h	92	96:4

[a] Determined by 250-MHz ^1H NMR.



59a R = H
59b R = Bn

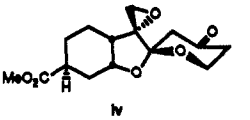
(42) Obtained in 88% yield via treatment of ketone **36** with sodium dimethylsulfoxonium methylide.

(43) This observation, in conjunction with related work in our laboratory, suggests that coordination of the lithium counterion with substrate oxygen atoms can suppress deprotonation in highly oxygenated systems: Smith, A. B., III; Richmond, R. E. *J. Am. Chem. Soc.* **1983**, *105*, 575. Also, see: ref 7.

(44) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.

(45) Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025, and references cited therein.

(46) Application of this sequence to methyl ester iv (Table III, entries 5 and 6) furnished **50** in 56% overall yield. However, the ratio of silyl enol ethers (ca. 75:25) and the overall yield for the preparation of **iv** (59%) rendered this procedure relatively unattractive. Ester **iv** was generated from 6 via reductive removal of the benzyl group (H_2, Pd/C, MeOH), followed by oxidation with RuO_4 (RuO_2–$NaIO_4$) and esterification (CH_2N_2).



iv

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

(48) Ester **50** was reduced with high stereoselectivity as reported by Collum, see: ref 5a.

(49) We thank Dr. Matthew Suffness (National Institutes of Health, National Cancer Institute) for providing a generous sample of (+)-phyllanthocin.

(50) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(51) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(52) Acid chloride **54** was generated by oxalyl chloride treatment of the corresponding acid **53**. The latter was prepared in 59% overall yield via alkylation of the dianion of commercially available 5-hexyn-1-ol with ethyl iodide [$LiNH_2$, NH_3(l), −78 °C], followed by Jones oxidation of the resultant alcohol.

of ozone and immediate reduction with Ph_3P. Finally, the requisite cis olefin [i.e., (−)-**12a**], substrate for the intramolecular ene reaction, was obtained via semihydrogenation of the triple bond with Lindlar catalyst.[55,56]

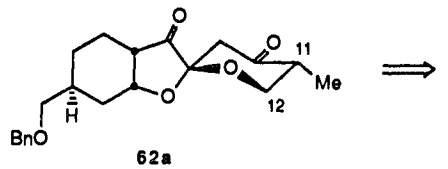
As anticipated, treatment of (−)-**12a** with 1 equiv of Me_2AlCl provided (−)-**10a** in 83% yield, accompanied by minor amounts (<8%) of diastereomeric alcohols **23a** and **24a**. The enantiomeric purity of (−)-**10a** (ca. 88% ee) was determined by NMR analysis of the corresponding Mosher esters.[57,58] The synthesis of aldehyde (−)-**8** then proceeded uneventfully as in the racemic series (see Experimental Section).

Following the generation of homochiral **8**, diketone (−)-**41** was prepared and subjected to spiroketalization. Chemoselective methylenation[40] of (+)-**7b** then afforded epoxide (+)-**6**. Problems however were encountered in the regiocontrolled C(11) methylation of (+)-**6** when the scale of the reaction exceeded 0.5 mmol. Fortunately, this difficulty could be circumvented by employing the "in situ trapping" method of Corey,[59] whereby the kinetic enolate of (+)-**6** was formed via addition of the ketone to a THF solution of LDA and trimethylsilyl chloride at −78 °C, followed after 3 min by the addition of triethylamine. The result was an 85:15 mixture of silyl enol ethers (i.e., **48a** and **48b**). Regeneration of the enolate with *N*-benzyltrimethylammonium fluoride (4.2 equiv),[45] alkylation with MeI, and equilibration with DBU afforded (+)-**44a** in 60% yield for the three steps (71% based on recovered **6**). Small amounts of **45a** (12%) and **6** (17%) were also obtained.

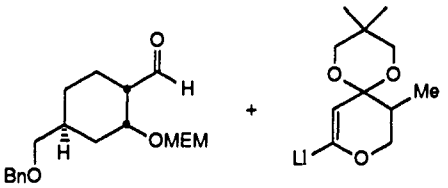
Conversion of the C(3) benzyloxymethyl substituent to a carboxyl group gave (+)-**49**. Esterification,[60] reduction of the C(10) ketone,[5a] and cinnamoylation then proceeded smoothly to afford (+)-phyllanthocin (**5a**), identical in all respects (250-MHz ^{1}H NMR, IR, TLC, mp, and mmp) with an authentic sample of (+)-phyllanthocin {$[\alpha]^{24}_D$ +28.0° (*c* 2.04, $CHCl_3$);[61] lit.[2] $[\alpha]^{24}_D$ +25.2° (*c* 2.00, $CHCl_3$); lit.[5b] $[\alpha]^{20}_D$ +24.9° (*c* 1.86, $CHCl_3$)}.

An Augmented Spiroketalization Tactic. Although regio- and stereoselective methylation at C(11) of spiroketal **6** was eventually achieved (vide supra), we became intrigued by the possibility of incorporating the methyl group prior to execution of the spiroketalization maneuver. However, we also were committed to the stereochemically linear nature of the synthetic strategy. These considerations prompted us to explore the possibility of controlling (i.e., by equilibration) the C(11) stereocenter via the spiroketalization process. To this end, we envisioned use of the lithio derivative of methyl dihydropyran (±)-**63** for addition to aldehyde **8**. Importantly, this tactic would ensure the regiocontrolled introduction of the methyl group. Acid-mediated spiroketalization might then effect equilibration at C(11) together with a stereocontrolled spirocyclization to furnish **62a**. It should be emphasized that such a strategy contrasts markedly with the other syntheses of (+)-phyllanthocin, wherein the correct absolute configuration of the C(11) methyl center was secured prior to spiroketal construction (i.e., via stereochemically convergent synthetic strategies).[5]

The requisite methylated dihydropyran (±)-**63** was prepared in four steps from tetrahydropyran-4-one (**13**) as outlined in Scheme III.[27]

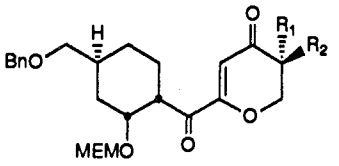


62a



8

Diketones **66a** and **66b**, substrates for the augmented spiroketalization maneuver, were then readily prepared in the racemic series via addition of the anion derived from (±)-**63** to (±)-**8**, followed by deketalization and Swern oxidation.[33] The overall yield for this three-step operation was 68%. After separation by preparative HPLC, the epimers were independently subjected to the spiroketalization protocol devised earlier. Diketone **66a** afforded a 115:2:1 mixture of spiroketals **62a–c**, as determined by



66a R_1 = Me, R_2 = H
66b R_1 = H, R_2 = Me

preparative HPLC, in 61% yield (Table V, entry 1). Similar treatment of **66b** (entry 2) led to the same spiroketals (**62a–c**) in 57% yield; the ratio in this case was 1:14:2. Thus, camphorsulfonic acid proved ineffective for the requisite axial–equatorial equilibration of the C(11) methyl group. The stereochemistry of the major product in each case (i.e., **62a** and **62b**, respectively) suggested that the configurations of the diastereomeric diketones (**66a** and **66b**) were as indicated. The axial methyl epimer related to **62c** was not detected in any of the spiroketalizations.

In the next series of experiments (entries 3 and 4), the MEM group of **66a,b** was removed with Me_2BBr.[63] Exposure of the resultant mixture of alcohols to *p*-toluenesulfonic acid in place of CSA furnished an ca. 25:1 mixture of desired (**62a,b**) and undesired (**62c**) spiroketals in 63–72% yields. These results essentially reproduced the ratio of **7b** and **7a** (ca. 26:1) obtained earlier in the kinetically controlled spiroketalization of **41**. We next explored treatment of the alcohol mixture derived from **66a,b** with DBU in dry benzene (entry 5); DBU was previously employed for epimerization of the C(11) methyl center. This base-mediated spirocyclization afforded a 32:1 mixture of spiroketals **62a,b** and **62c**; however, the yield was only 49%.

Best results vis-ă-vis phyllanthocin (entry 6) were obtained by exposure of the alcohol mixture to *p*-toluenesulfonic acid in benzene, followed by equilibration with DBU. Under these conditions, a 51:1 mixture of desired (**62a,b**) and undesired (**62c**) spiroketals was obtained in 64% yield. DBU treatment enhanced the stereoselectivity at the C(8) spirocenter (cf., entries 3 and 4), presumably via an elimination–recyclization pathway for equilibration. In contrast, the proportions of equatorial and axial methyl epimers (**62a**:**62b**) remained unaffected, suggesting that the C(11) stereocenter was in fact equilibrated during the acid-mediated spiroketalization, as envisioned a priori. The incomplete conversion of **62b** to **62a** contrasts with the behavior of the corresponding C(7) epoxide **44b**, which was efficiently isomerized to **44a** upon exposure to DBU. Thus, methylenation significantly

(53) A number of methods for removal of the chiral auxiliary (e.g., $PhCH_2OLi$, THF; MeONa, THF) were explored with limited success.

(54) Because alkenes are more nucleophilic than alkynes, chemoselective ozonolysis of **60** could be effected via addition of 1 equiv of O_3 at −78 °C.

(55) Lindlar, H.; Dubois, R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 880.

(56) The semihydrogenation led to the cis isomer with >99:1 stereoselectivity (GLC).

(57) The enantiomeric purity was established by comparison of the 250-MHz ^{1}H NMR spectra of the Mosher esters derived from (−)-**10a** and (±)-**10a**.

(58) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(59) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

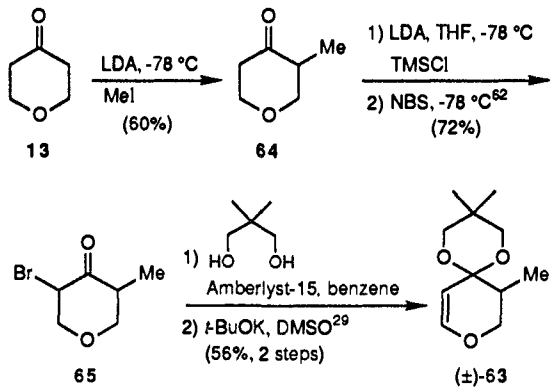
(60) Ester **50** was spectroscopically indistinguishable from material prepared by Collum. We thank Professor Collum (Cornell University) for providing the NMR and IR spectra of **50**.

(61) The optical rotation was measured with a recrystallized sample of synthetic (+)-**5a**.

(62) Blanco, L.; Amice, P.; Conia, J. M. *Synthesis* **1976**, 194. Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785.

(63) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912.

Scheme III

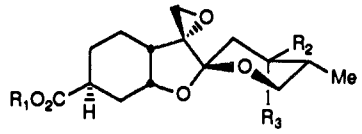


13 64 65 (±)-63

enhances the relative stability of the requisite equatorial epimer **44a**, perhaps by strengthening the anomeric stabilization which anchors the conformation of the spirocyclic rings.

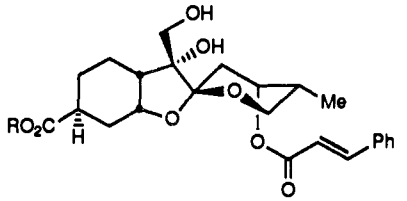
Structural assignments for spiroketals **62a–c** were initially based upon spectroscopic observations. The ^{1}H NMR multiplicities of the C(12) axial and equatorial protons and the chemical shifts of the C(11) methyl groups were particularly diagnostic.[64] Unambiguous determinations of structure and stereochemistry for **62a** and **62b** were obtained by independent conversion of the diketones to the previously prepared epoxides **44a** and **44b**, respectively.

Total Synthesis of (+)-Phyllanthocindiol, the Aglycon of Phyllanthostatin 3. Phyllanthocindiol methyl ester (**73**) differs formally from phyllanthocin (**5a**) by hydration of the 7,14-epoxide in the latter to a vicinal diol unit. For the synthesis of phyllanthocindiol (**5b**) we utilized acid (+)-**49**, an advanced phyllanthocin intermediate. To this end, (+)-**49** was protected as its trimethylsilylethyl ester (+)-**67**.[65] Reduction of the C(10) keto group then provided a 5:1 epimeric mixture favoring axial alcohol (+)-**68**.[66] Acylation of (+)-**68** with *trans*-cinnamoyl chloride furnished (+)-**70**, whereupon removal of the silyl group with anhydrous tetra-*N*-butylammonium fluoride[65] led to (+)-**71** in 57% yield for the four steps. As described in contribution 8 in this series, we have employed this more highly endowed aglycon in the first total syntheses of phyllanthostatin 1 (**2**) and phyllanthostatin 2 (**3**).[8c,d]



(+)-**67** R_1 = CH_2CH_2TMS, R_2, R_3 = O (ketone)
(+)-**68** R_1 = CH_2CH_2TMS, R_2 = H, R_3 = OH
69 R_1 = CH_2CH_2TMS, R_2 = OH, R_3 = H
(+)-**70** R_1 = CH_2CH_2TMS, R_2 = H, R_3 = O-cinnamoyl
(+)-**71** R_1 = H, R_2 = H, R_3 = O-cinnamoyl

For the synthesis of phyllanthocindiol (**5b**), hydration of the epoxide moiety[67] in (+)-**70** with 15% H_2O in *N*-methylpyrrolidinone at 130 °C generated diol (+)-**72**, which on desilylation with anhydrous tetra-*N*-butylammonium fluoride[65] gave (+)-**5b** in 67% overall yield. The identity of synthetic phyllanthocindiol was established via diazomethane esterification; the resultant phyllanthocindiol methyl ester [(+)-**73**], a white crystalline solid {mp 126–127 °C; lit.[3c] mp 127–128 °C; $[\alpha]^{20}_D$ +3.7° (*c* 0.88, $CHCl_3$); lit.[5e] $[\alpha]^{22.5}_D$ +3.4° (*c* 1.67, $CHCl_3$)}, was identical in all respects [500-MHz ^{1}H NMR, ^{13}C NMR, IR, MS, and TLC (two solvent systems)] with an authentic sample provided by Professor David Collum (Cornell University).



(+)-**72** R = $TMSCH_2CH_2$
(+)-**5b** R = H
(+)-**73** R = CH_3

Summary. A stereochemically linear, reasonably efficient (21 steps, 5.6% overall yield) total synthesis of (+)-phyllanthocin has been achieved. Noteworthy features of the scheme include a highly stereoselective intramolecular ene reaction and a novel spiroketalization maneuver which effectively controls the configuration at the C(8) spirocenter. Importantly, an augmented spiroketalization tactic ensures regiocontrolled introduction of the C(11) methyl substituent and establishes the correct stereochemistry at C(11) as well. Finally, acid (+)-**49**, an advanced phyllanthocin intermediate, has been converted to phyllanthocindiol in five steps (42% overall yield). The syntheses of phyllanthocin and phyllanthocindiol set the stage for construction of phyllanthoside and the phyllanthostatins. The latter endeavors, entailing the preparation and coupling of suitably protected disaccharides, are described in the contributions which follow.

Experimental Section[68]

Ethyl 4-Oxobutyrate (14).[18] Under argon, a solution of succinic anhydride (50 g, 0.50 mol) in absolute ethanol (35 mL) was heated to reflux for 1 h. Excess ethanol was distilled off, and the residual oil crystallized on cooling to room temperature, affording 69.07 g (95% yield) of monoethyl succinate.

The half ester (69.07 g, 0.473 mol) was dissolved in thionyl chloride (60 mL, 1.4 equiv), and the solution was heated to 50 °C under argon. After 2 h, excess thionyl chloride was distilled off, and the residue was distilled to give 70.0 g (90% yield) of ethyl succinyl chloride as an oil, bp 87–92 °C (11 mmHg).

Hydrogen was bubbled into a mixture of ethyl succinyl chloride (44 g, 0.267 mol), 5% Pd on $BaSO_4$ (6.0 g), sulfur-poisoned quinoline (0.30

(64) For example, in the spectrum of **62a** the C(12) axial hydrogen appeared as an apparent triplet centered at δ 3.79 with a coupling constant of 11.2 Hz, whereas the C(12) equatorial hydrogen appeared as a doublet of doublets centered at δ 3.98 with coupling constants of 11.2 and 7.0 Hz. Furthermore, the chemical shift of the C(11) methyl resonance was δ 1.00. These observations are indicative of an equatorial methyl group.[23] Comparison with the spectrum of ketone **44a** reinforced this conclusion. In the latter case the C(12) axial hydrogen similarly gave rise to an apparent triplet centered at δ 3.73 with a coupling constant of 11.2 Hz; the C(12) equatorial hydrogen appeared as a doublet of doublets centered at δ 3.86 with coupling constants of 11.2 and 7.1 Hz, and the chemical shift of the C(11) methyl resonance was δ 0.96. Further NMR analysis indicated that the methyl substituents in **62b** and **62c** were axial and equatorial, respectively (see Experimental Section).[23]

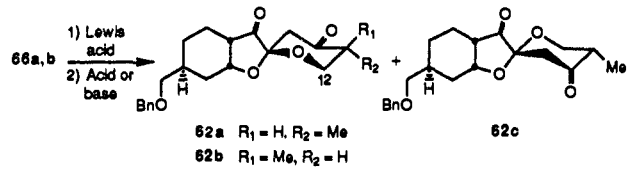
(65) Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711.

(66) This level of selectivity was first observed by Collum and McGuirk, see: ref 5a.

(67) Hutchins, R. O.; Taffer, I. M. *J. Org. Chem.* **1983**, *48*, 1360.

(68) **Materials and Methods.** Reactions were carried out under an argon atmosphere, with freshly distilled solvents in vacuum-flamed glassware, unless otherwise noted. All solvents were reagent grade. Ether and THF were distilled from sodium and benzophenone. Precoated silica gel plates (250 μm) with a fluorescent indicator (E. Merck) were used for analytical thin-layer chromatography. *n*-Butyllithium was standardized by titration with diphenylacetic acid. ^{1}H and ^{13}C NMR spectra were recorded in deuteriochloroform solutions with a Bruker WP250, AM250 (250 MHz), or AM500 (500 MHz) spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane. All infrared spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Melting points were determined on either a Thomas-Hoover instrument or a Bristoline micro hot stage apparatus and are corrected. Microanalyses were performed by the Rockefeller University Microanalytical Laboratories under the direction of S. T. Bella or by Robertson Labs, Madison, NJ. High-resolution mass spectra were measured by the University of Pennsylvania Mass Spectrometry Service Center on a Hitachi-Perkin-Elmer RMH-2 or VG 70-70 Micromass spectrometer interfaced with a Kratos DS-50-s data system. Gas–liquid chromatography (GLC) analyses were performed on a Hewlett-Packard 5790A chromatograph equipped with a Hewlett Packard 25 m × 0.2 mm × 0.33 μm Ultra 1 (cross-linked methylsilicone) column. Chromatograms were recorded on a Hewlett-Packard 3390a integrator. High-pressure liquid chromatography (HPLC) was performed on a Waters analytical chromatograph equipped with a Model 6000A solvent delivery system, a U6K injector, and a R-400 refractive index detector or a Model 440 absorbance detector. A 4.6 mm × 25 cm column packed with 5 μm Ultrasphere-Si was employed. Chromatograms were recorded on a Hewlett-Packard 3390a integrator.

Table V. Spiroketalization–Equilibration of 11-Methyl Diketone (±)-66a,b



entry	starting material	reaction conditions	yld (%)	ratio 62a:b:c	ratio (a + b):c
1	66a	(1) $ZnBr_2/CH_2Cl_2$ (2) CSA/benzene, 4 days	61	115:2:1	117:1
2	66b	(1) $ZnBr_2/CH_2Cl_2$ (2) CSA/benzene, 4 days	57	1:14:2	8:1
3	66a,b	(1) Me_2BBr/CH_2Cl_2, −78 °C (2) *p*-TsOH/benzene, 17 h	72	20:5:1	25:1
4	66a,b	(1) Me_2BBr/CH_2Cl_2, −78 °C (2) *p*-TsOH/benzene, 6 days	63	21:3:1	24:1
5	66a,b	(1) Me_2BBr/CH_2Cl_2, −78 °C (2) DBU/benzene, 24 h	49	27:5:1	32:1
6	66a,b	(1) Me_2BBr/CH_2Cl_2, −78 °C (2) *p*-TsOH/benzene, 2 h (3) DBU/benzene, 24 h	64	44:7:1	51:1

mL), and xylene (200 mL) at room temperature. After 10 min, the mixture was heated to reflux (140–150 °C). The top of the reflux condensor was then connected to a flask containing an aqueous solution of phenolphthalein (300 mL), and the evolved hydrogen chloride was titrated with 5 N NaOH. After 4 h at reflux, gas evolution ceased; the mixture was cooled to room temperature, and argon was bubbled into the solution. The mixture was then filtered through a Celite pad, and the precipitates were washed with ether. The solvent was removed in vacuo, and the residue was distilled to give 19.42 g (56% yield) of ethyl 4-oxobutyrate (**14**) as a colorless oil: bp 73–75 °C (11 mmHg): IR ($CHCl_3$) 3000 (s), 2980 (s, br), 2930 (s), 2900 (s), 2820 (m), 2720 (m), 1710–1750 (s, br), 1445 (s), 1370–1420 (s, br), 1350 (s), 1150–1310 (s, br), 1050 (s, br), 1025 (s, br), 950 (m), 900 (m), 845 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.28 (t, J = 7.5 Hz, 3 H), 2.64 (t, J = 7.0 Hz, 2 H), 2.82 (t, J = 7.0 Hz, 2 H), 4.17 (q, J = 7.5 Hz, 2 H), 9.84 (s, 1 H).

Dimethyl Acetal 15. Freshly distilled trimethylorthoformate (134 mL, 9 equiv) was added to a solution of ethyl 4-oxobutyrate (**14**) (20.75 g, 159.4 mmol) and $CeCl_3 \cdot 7H_2O$ (1.04 equiv) in methanol (415 mL, 0.4 M solution) at room temperature. After 10 min, the reaction was quenched with saturated $NaHCO_3$. The mixture was extracted twice with ether, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Distillation afforded 21.9 g (78% yield) of dimethyl acetal **15** as an oil, bp 75–78 °C (2 mmHg): IR ($CHCl_3$) 3005 (m), 2980 (m), 2930 (m), 2900 (m), 2830 (m), 1725 (s), 1440 (m, br), 1370 (m, br), 1350 (m), 1300 (m), 1150–1290 (s, br), 1125 (s), 1025–1100 (s, br), 990 (w), 965 (w), 910 (m), 855 (w), 770–790 (w, br), 710 (w), 655 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3 H), 1.93 (dd, J = 7.5 and 5.6 Hz, 2 H), 2.37 (t, J = 7.5 Hz, 2 H), 3.33 (s, 6 H), 4.14 (q, J = 7.1 Hz, 2 H), 4.41 (t, J = 5.6 Hz, 1 H); high-resolution mass spectrum (Cl, NH_3) m/z 145.0855 [$(M - OMe)^+$, calcd for $C_7H_{13}O_3$ 145.0861].

Iodide 16. A solution of *cis*-3-hexen-1-ol (10 g, 97.84 mmol) in pyridine (80 mL) was cooled to 0 °C under argon, and methanesulfonyl chloride (8.33 mL, 1.1 equiv) was added dropwise. After 1 h at 0 °C, the solution was warmed to room temperature for 5 h. The mixture was then diluted with ether and filtered, and the filtrate was concentrated in vacuo. The residual oil was dissolved in ether, washed with 10% HCl, saturated $NaHCO_3$, and brine, and dried over Na_2SO_4. Removal of solvent in vacuo gave 15.92 g (91% yield) of the mesylate as a pale yellow oil.

To a solution of the mesylate (23.85 g, 134 mmol) in acetone (300 mL) was added sodium iodide (30.13 g, 1.5 equiv). The resultant solution was heated to reflux (70–75 °C) for 15 h. After cooling to room temperature, the solution was diluted with pentane, washed three times with water, washed with brine, and dried over Na_2SO_4. Following evaporation of solvent, distillation under reduced pressure furnished a red oil which was then passed through a short column of neutral alumina, eluting with pentane. The solvent was removed in vacuo, and the product was distilled to give 25.75 g (91% yield) of iodide **16** as an orange oil, bp 59–62 °C (12 mmHg): IR ($CHCl_3$) 2997 (s), 2960 (s), 2930 (s), 2865 (s), 1645 (w), 1455 (m, br), 1420 (m), 1400 (w), 1370 (w), 1295 (w), 1235 (s), 1166 (s), 1010–1050 (m, br), 960 (w), 903 (s), 857 (w), 690 (m, br) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (t, J = 7.5 Hz, 3 H), 2.04 (quintet of d, J = 7.5 and 1.3 Hz. 2 H), 2.60 (br q, J = 7.2 Hz, 2 H), 3.14 (t, J = 7.2 Hz, 2 H), 5.26–5.34 (m, 1 H), 5.49–5.59 (m, 1 H).

Ester 17. A solution of LDA (1.1 equiv) in THF (50 mL) was cooled to −78 °C under argon, and a solution of ester **15** (5.0 g, 28.4 mmol) in THF (25 mL) was added slowly (ca. 20 min). After 30 min at −78 °C, a mixture of HMPA (7.4 mL, 1.5 equiv) and iodide **16** (7.8 g, 1.3 equiv) was added rapidly (ca, 5 min). After 2 h at −78 °C, the solution was warmed gradually to 0 °C (ca. 3 h) and quenched with saturated NH_4Cl. The mixture was extracted twice with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:9, then 1:8, then 1:7, then 1:6) as eluant, gave 6.24 g (85% yield) of ester **17** as an oil: IR ($CHCl_3$) 3000 (m), 2980 (s), 2920 (s), 2860 (m), 2820 (m), 1720 (s), 1440–1460 (m, br), 1375 (m), 1160–1190 (s, br), 1120 (s), 1040–1090 (s, br), 955 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.46–1.77 (comp m, 3 H), 2.01 (comp m, 5 H), 2.48 (m, 1 H), 3.31 (s, 3 H), 3.31 (s, 3 H), 4.15 (q, J = 7.1 Hz, 2 H), 4.37 (dd, $J_1 = J_2$ = 5.7 Hz, 1 H), 5.26–5.44 (m, 2 H); high-resolution mass spectrum (Cl, NH_3) m/z 227.1670 [$(M - OMe)^+$, calcd for $C_{13}H_{23}O_3$ 227.1640].

Alcohol 18. Under argon, a suspension of $LiAlH_4$ (900 mg, 1 equiv) in ether (75 mL) was cooled to 0 °C, and a solution of ester **17** (6.06 g, 23.45 mmol) in ether (15 mL) was added slowly (ca. 20 min). The mixture was warmed to room temperature for 1 h and carefully quenched with water (0.9 mL), 5 N NaOH (0.9 mL), and water (3.0 mL). The resultant white precipitate was filtered off and washed with ether. After removal of solvent in vacuo, the product was purified by flash chromatography, using ethyl acetate–hexane (1:2) as eluant, to give 4.62 g (91% yield) of alcohol **18** as a colorless oil: IR ($CHCl_3$) 3610 (w), 3220–3560 (m, br), 3000 (s), 2960 (s), 2935 (s, br), 2830 (m), 1430–1470 (m, br), 1365–1390 (m, br), 1210–1250 (m, br), 1190 (m), 1120 (s), 1030–1070 (s, br), 980 (m), 950 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.96 (t, J = 7.5 Hz, 3 H), 1.29–1.47 (m, 2 H), 1.69 (br d, J = 3.2 Hz, 3 H), 1.98–2.11 (m, 4 H), 2.67 (br s, 1 H), 3.33 (s, 3 H), 3.35 (s, 3 H), 3.41–3.63 (br m, 2 H), 4.50 (t, J = 5.0 Hz, 1 H), 5.28–5.43 (m, 2 H); high-resolution mass spectrum (Cl, NH_3) m/z 185.1550 [$(M - OMe)^+$, calcd for $C_{11}H_{21}O_2$ 185.1536].

Aldehyde 12a. A suspension of KH (3.1 g, 1.2 equiv) in THF (30 mL) was cooled to 0 °C under argon, and a solution of alcohol **18** (4.62 g, 21.3 mmol) and benzyl bromide (3.1 mL, 1.2 equiv) in THF (12 mL) was added slowly (10 min). After 5 min, the mixture was warmed to room temperature for 2 h, then cooled to 0 °C, and carefully quenched with water. The mixture was extracted twice with ether, and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the residual yellow oil was dissolved in THF (85 mL) and treated with 25% HCl (35 mL). After 1 h at room temperature, the reaction mixture was diluted with brine and extracted twice with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ether–hexane (1:20, then 1:15, then 1:12) as eluant, furnished 5.11 g (92% yield) of aldehyde **12a** as an oil.

19: IR ($CHCl_3$) 3000 (s), 2830–2980 (s, br), 1495 (m), 1455 (s, br), 1385 (m, br), 1360 (s, br), 1170–1260 (m, br), 1030–1150 (s, br), 1020 (s), 960 (s, br), 905 (m), 690 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3 H), 1.33–1.52 (m, 2 H), 1.55–1.83 (m, 3 H), 2.02 (m, 4 H), 3.29 (s, 3 H), 3.30 (s, 3 H), 3.39 (d, J = 5.1 Hz, 2 H), 4.47 (t, J = 5.8 Hz, 1 H), 4.50 (s, 2 H), 5.25–5.41 (m, 2 H), 7.23–7.34 (comp m, 5 H); high-resolution mass spectrum (Cl, NH_3) m/z 275.2020 [$(M - OMe)^+$, calcd for $C_{18}H_{27}O_2$ 275.2011].

12a: IR ($CHCl_3$) 3020 (w), 3000 (m), 2960 (s), 2930 (s), 2860 (s), 1725 (s), 1495 (w), 1480 (w), 1455 (m), 1365 (m, br), 1230 (w), 1040–1140 (s, br), 1025 (m), 990 (w, br), 695 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3 H), 1.31–1.55 (m, 2 H), 2.02 (m, 4 H), 2.31 (m, 1 H), 2.41–2.55 (m, 2 H), 3.31 (dd, J = 9.1 and 7.1 Hz, 1 H), 3.50 (dd, J = 9.1 and 4.4 Hz, 1 H), 4.47 (s, 2 H), 5.25–5.43 (m, 2 H), 7.27–7.38 (comp m, 5 H), 9.76 (t, J = 2.1 Hz, 1 H); high-resolution mass spectrum (Cl, NH_3) m/z 260.1788 (M^+, calcd for $C_{17}H_{24}O_2$ 260.1770).

Aldehyde 12a. A suspension of $LiAlH_4$ (805 mg, 1 equiv) in ether (80 mL) was cooled to 0 °C under argon, and a solution of ester **17** (5.47 g, 21.17 mmol) in ether (40 mL) was added slowly (ca, 20 min). The mixture was warmed to room temperature for 2 h and carefully quenched with water (0.9 mL), 5 N NaOH (0.9 mL), and water (3.0 mL). The resultant white precipitate was filtered off and washed with ether, and the solvent was removed in vacuo to give crude alcohol **18** as an oil.

A suspension of KH (2.92 g, 1.2 equiv) in THF (80 mL) was cooled to 0 °C under argon, and a solution of alcohol **18** and benzyl bromide (3.02 mL, 1.2 equiv) in THF (20 mL) was added slowly (ca. 20 min). After 5 min at 0 °C, the reaction mixture was warmed to room temperature for 2 h, then cooled to 0 °C, and carefully quenched with water. The mixture was extracted twice with ether, and the combined extracts

were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo to give a yellow oil, which was dissolved in THF (100 mL) and treated with 10% HCl (25 mL). After stirring for 1 day, the mixture was diluted with brine and extracted twice with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ether–hexane (1:15) as eluant, gave 4.72 g (86% yield) of aldehyde **12a** as an oil.

Intramolecular Ene Reaction of Aldehyde 12a. Under argon, a 1.926 M solution of Me_2AlCl in hexane (2.54 mL, 1 equiv) was added dropwise to a solution of aldehyde **12a** (1.27 g, 4.90 mmol) in methylene chloride (245 mL) at room temperature. After 30 min, 25% aqueous KOH (49 mL) was added. The mixture was extracted twice with methylene chloride, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography, with ethyl acetate-hexane (1:4) as eluant, afforded 1.06 g (83% yield) of **10a**, 19 mg (1% yield) of **24a**, and 67.1 mg (ca. 5% yield) of a 4:1 mixture of **23a** and **25a**, as determined by 250-MHz ^1H NMR. The acetates (**10b**, **23b**, **24b**, and **25b**) were individually prepared by addition of acetic anhydride to a solution of the corresponding alcohol and DMAP in pyridine. After stirring for 2 h the mixture was quenched with water and extracted three times with ether. The combined extracts were washed twice with 10% HCl, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed in vacuo, and the product was purified by flash chromatography, using ethyl acetate–hexane (1:2) as eluant.

10a: IR ($CHCl_3$) 3610 (w), 3570 (w), 3470 (w, br), 2870–3010 (s), 1500 (w), 1460 (s), 1370 (m), 1245 (w, br), 1095 (s, br), 1030 (s), 980 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.04 (qd, J = 12.3 and 4.4 Hz, 1 H), 1.24 (m, 1 H), 1.48 (br s, 1 H), 1.49–1.62 (m, 2 H), 1.70 (dd, J = 4.5 and 1.1 Hz, 3 H), 1.84–2.12 (comp m, 4 H), 3.30 (ABX, J_{AB} = 9.1 Hz, J_{AX} = 6.4 Hz, J_{BX} = 5.9 Hz, $\Delta\nu_{AB}$ = 15.5 Hz, 2 H), 3.94 (br s, 1 H), 4.50 (s, 2 H), 5.50 (m, 2 H), 7.23–7.37 (comp m, 5 H); high-resolution mass spectrum (CI, isobutane) m/z 261.1849 [$(M + H)^+$, calcd for $C_{17}H_{25}O_2$ 261.1848], 260.1780 (M^+, calcd for $C_{17}H_{24}O_2$ 260.1770).

10b: IR ($CHCl_3$) 3075 (w), 3050 (w), 3000 (s), 2920 (s, br), 2845 (s), 2780 (w), 1720 (s, br), 1490 (m), 1450 (s, br), 1355–1380 (s, br), 1190–1290 (s, br), 1175 (w), 1085 (s, br), 1020 (s), 965 (s), 888 (m), 810 (w), 688 (m), 600 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.05–1.27 (m, 2 H), 1.54–1.68 (m, 1 H), 1.63 (d, J = 5.5 Hz, 3 H), 1.86–2.11 (comp m, 5 H), 2.03 (s, 3 H), 3.27 (d, J = 5.8 Hz, 2 H), 4.49 (s, 2 H), 5.08 (q, J = 2.8 Hz, 1 H), 5.39 (m, 2 H), 7.25–7.38 (comp m, 5 H); high-resolution mass spectrum (CI, NH_3) m/z 320.2220 [$(M + NH_4)^+$, calcd for $C_{19}H_{30}NO_3$ 320.2226].

23a: IR ($CHCl_3$) 3540 (m), 3340–3600 (m, br), 3000 (s), 2920 (s), 2850 (s), 1490 (m), 1450 (s), 1380 (m), 1360 (m), 1200–1260 (m, br), 1070–1110 (s, br), 1050 (s), 1020 (s), 970 (s), 690 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.08–1.28 (m, 2 H), 1.50–1.87 (comp m, 6 H), 1.73 (d, J = 4.7 Hz, 3 H), 2.52 (br s, 1 H), 3.35 (d, J = 6.0 Hz, 2 H), 3.63 (br m, 1 H), 4.51 (s, 2 H), 5.54–5.72 (m, 2 H), 7.26–7.35 (comp m, 5 H); high-resolution mass spectrum (CI, NH_3) m/z 261.1836 [$(M + H)^+$, calcd for $C_{17}H_{25}O_2$ 261.1854].

23b: IR ($CHCl_3$) 3000 (m), 2930 (s, br), 2860 (s), 2790 (w), 1720 (s, br), 1490 (m), 1450 (s, br), 1360–1380 (s, br), 1200–1280 (s, br), 1175 (w), 1070–1120 (s, br), 1025 (s), 965 (s, br), 805 (w), 690 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18–1.88 (comp m, 7 H), 1.69 (d, J = 5.9 Hz, 3 H), 2.00 (s, 3 H), 2.69 (br m, 1 H), 3.34 (ABX, J_{AB} = 9.0 Hz, J_{AX} = 6.6 Hz, J_{BX} = 5.6 Hz, $\Delta\nu_{AB}$ = 16.6 Hz, 2 H), 4.50 (s, 2 H), 4.82 (dt, J = 11.4 and 4.4 Hz, 1 H), 5.46 (dq, J = 15.0 and 5.9 Hz, 1 H), 5.61 (ddd, J = 15.0, 7.5, and 1.5 Hz, 1 H), 7.27–7.38 (comp m, 5 H); high-resolution mass spectrum (CI, isobutane) m/z 303.1974 [$(M + H)^+$, calcd for $C_{19}H_{27}O_3$ 303.1960], 302.1869 (M^+, calcd for $C_{19}H_{26}O_3$ 302.1882).

24a: IR ($CHCl_3$) 3560 (m), 3300–3600 (m, br), 3080 (m), 3060 (m), 3000 (s), 2920 (s, br), 2850 (s), 1490 (m), 1450 (s), 1390 (m), 1360 (s), 1200–1290 (m, br), 1050–1130 (s, br), 1040 (s), 1025 (s), 970 (s), 930 (m), 690 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.89–1.25 (comp m, 4 H), 1.70 (dd, J = 6.4 and 1.4 Hz, 3 H), 1.73–1.83 (m, 3 H), 1.94 (s, 1 H), 2.11 (br d, J = 7.5 Hz, 1 H), 3.23 (td, J = 5.8 and 2.8 Hz, 1 H), 3.32 (d, J = 6.2 Hz, 2 H), 4.50 (s, 2 H), 5.26 (ddd, J = 15.0, 8.7 and 1.5 Hz, 1 H), 5.61 (dq, J = 15.0 and 6.4 Hz, 1 H), 7.27–7.34 (comp m, 5 H); high-resolution mass spectrum (CI, NH_3) n/z 261.1828 [$(M + H)^+$, calcd for $C_{17}H_{25}O_2$ 261.1854].

24b: IR ($CHCl_3$) 3000 (m), 2920 (s, br), 2860 (s), 2790 (w), 1720 (s, br), 1490 (w), 1450 (m, br), 1370 (s, br), 1200–1280 (s, br), 1070–1130 (s, br), 1025 (s), 965 (m), 940 (w), 905 (w), 840 (w), 690 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.98–1.43 (comp m, 3 H), 1.62 (dd, J = 6.2 and 1.2 Hz, 3 H), 1.72–1.82 (m, 3 H), 1.94–2.13 (m, 2 H), 1.99 (s, 3 H), 3.31 (d, J = 5.9 Hz, 2 H), 4.48 (s, 2 H), 4.61 (td, J = 10.8 and 4.3 Hz, 1 H), 5.24 (ddd, J = 15.0, 7.5 and 1.2 Hz, 1 H), 5.45 (dq, J = 15.2 and 6.3 Hz, 1 H), 7.26–7.38 (comp m, 5 H); high-resolution mass spectrum (CI, isobutane) m/z 303.1973 [$(M + H)^+$, calcd for $C_{19}H_{27}O_3$ 303.1960], 302.1863 (M^+, calcd for $C_{19}H_{26}O_3$ 302.1882).

25a: IR ($CHCl_3$) 3600 (w), 3200–3560 (m, br), 2990 (s), 2955 (s), 2920 (s), 2860 (s), 1490 (m), 1450 (s), 1360 (m), 1200–1260 (m, br), 1050–1100 (s, br), 1030 (m), 990 (m), 685 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3 H), 1.37 (m, 2 H), 1.54–1.83 (m, 3 H), 1.95–2.08 (m, 4 H), 2.41 (br s, 1 H), 3.36 (dd, J = 9.1 and 7.1 Hz, 1 H), 3.48 (dd, J = 9.1 and 3.9 Hz, 1 H), 3.58–3.76 (m, 2 H), 4.52 (s, 2 H), 5.33 (m, 2 H), 7.29–7.39 (comp m, 5 H); high-resolution mass spectrum (CI, NH_3) m/z 263.2027 [$(M + H)^+$, calcd for $C_{17}H_{27}O_2$ 263.2004].

25b: IR ($CHCl_3$) 3000 (s), 2960 (s), 2920 (s), 2880 (s, br), 1720–1740 (s, br), 1490 (m), 1450 (s), 1390 (m), 1365 (s), 1210–1270 (s, br), 1025–1110 (s, br), 690 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3 H), 1.35–1.48 (m, 2 H), 1.72 (m, 2 H), 1.96–2.08 (m, 5 H), 2.03 (s, 3 H), 3.38 (m, 2 H), 4.14 (dd, J = 6.8 and 6.2 Hz, 2 H), 4.49 (s, 2 H), 5.32 (m, 2 H), 7.30–7.36 (comp m, 5 H); high-resolution mass spectrum (CI, NH_3) m/z 305.2081 [$(M + H)^+$, calcd for $C_{19}H_{29}O_3$ 305.2111].

Alcohol (−)-10a. Under argon, a 1.926 M solution of Me_2AlCl in hexane (20.16 mL, 1 equiv) was added dropwise over 15 min to a solution of aldehyde (−)-**12a** (10.11 g, 38.8 mmol) in methylene chloride (1.2 L) at room temperature. After 30 min, the reaction was quenched with 25% aqueous KOH (400 mL), and the mixture was extracted twice with methylene chloride. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography, with ether–hexane (1:2) as eluant, furnished 8.35 g (83% yield) of **10a**, 92 mg (0.9% yield) of **24a**, and 666 mg (6.6% yield) of **23a**, all as colorless oils.

(−)-**10a**: $[\alpha]^{24}_D$ −23.4° (*c* 0.83, $CHCl_3$). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.54; H, 9.38.

Determination of Enantiomeric Purity of 10a. Under argon, (−)-α-methoxy-α-trifluoromethylphenylacetyl chloride [(−)-MTPA-Cl, 19 mg, 1.5 equiv][58] was added to a solution of alcohol (−)-**10a** (13 mg, 0.0499 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 2 mg) in pyridine (0.5 mL) at room temperature, and the resultant solution was stirred for 18 h. *unsym-N,N*-Dimethylethylenediamine (3 drops) was then added, and after 15 min the mixture was diluted with ether, washed with 10% HCl and saturated $NaHCO_3$, and dried over $MgSO_4$. The solvent was removed in vacuo, and the product was purified by preparative TLC [0.5 mm × 20 cm × 20 cm, ether-hexane (1:4), 2 developments] to afford 21.5 mg (90% yield) of a colorless oil. The products comprised a 94:6 mixture of diastereomers (88% ee), as determined by integration of the benzyl singlets at δ 4.48 and 4.44 in the 250-MHz ^1H NMR spectrum: ^1H NMR (250 MHz, $CDCl_3$) δ 1.11 (qd, J = 10.3 and 4.0 Hz, 1 H), 1.27–1.68 (comp m, 3 H), 1.57 (dd, J = 6.2 and 1.5 Hz, 3 H), 1.87 (br d, J = 12.6 Hz, 1 H), 1.90 (m, 1 H), 2.15 (m, 2 H), 3.29 (ABX, J_{AB} = 9.2 Hz, J_{AX} = 6.1 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 15.7 Hz, 2 H), 3.53 (d, J = 1.1 Hz, 3 H), 4.48 (s, 2 H), 5.17 (ddd, J = 15.4, 6.9 and 1.5 Hz, 1 H), 5.34–5.49 (m, 2 H), 7.27–7.39 (comp m, 8 H), 7.50–7.56 (m, 2 H).

Oxidation of Alcohols 23a and 25a. Under argon, chromium trioxide (428 mg, 6 equiv) was added to a solution of pyridine (0.69 mL, 12 equiv) in methylene chloride (20 mL) at room temperature. The mixture was stirred for 10 min, and a solution of **23a** and **25a** (185.5 mg, 0.713 mmol) in methylene chloride (5.0 mL) was added. After 30 min at room temperature, the reaction mixture was diluted with ether, washed twice with saturated $NaHCO_3$, washed with brine, and dried over $MgSO_4$. The solvent was removed in vacuo, and the product was purified by flash chromatography, with ether–hexane (1:2) as eluant, to give 24.7 mg (13% yield) of the less polar aldehyde **12a** and 92.4 mg (50% yield) of the more polar ketone **26**, both as colorless oils.

26: IR ($CHCl_3$) 3000 (m), 2930 (s, br), 2855 (s, br), 1705 (s), 1490 (w), 1450 (s), 1360 (br, m), 1200–1240 (m, br), 1070–1120 (s, br), 960 (m), 690 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.69 (d, J = 4.7 Hz, 3 H), 1.73–1.91 (comp m, 4 H), 2.20–2.39 (m, 3 H), 3.03 (br d, J = 5.0 Hz, 1 H), 3.36 (d, J = 5.5 Hz, 2 H), 4.50 (s, 2 H), 5.43–5.61 (m, 2 H), 7.28–7.34 (comp m, 5 H); high-resolution mass spectrum (CI, isobutane) m/z 258.1618 (M^+, calcd for $C_{17}H_{22}O_2$ 258.1620).

Ketone 27. Under argon, chromium trioxide (270 mg, 6 equiv) was added to a solution of pyridine (0.44 mL, 12 equiv) in methylene chloride (14 mL) at room temperature. The mixture was stirred for 10 min, and a solution of **10a** (117 mg, 0.45 mmol) in methylene chloride (2.0 mL) was added. After 30 min, the reaction mixture was diluted with ether, washed twice with saturated $NaHCO_3$, washed with brine, and dried over $MgSO_4$. After removal of solvent in vacuo, the product was purified by flash chromatography, with ethyl acetate–hexane (1:4) as eluant, to give 102 mg (88% yield) of ketone **27** as a pale yellow oil: IR ($CHCl_3$) 3000 (m), 2930 (s, br), 2850 (s), 1705 (s), 1495 (m), 1450 (s), 1360 (br, m), 1310 (m), 1270 (m), 1200–1230 (m, br), 1175 (m), 1070–1125 (s, br), 1040 (m), 1025 (m), 960 (s), 690 (m) cm^{-1}; ^1H NMR (250 MHz,

$CDCl_3$) δ 1.54 (br d, J = 8.5 Hz, 2 H), 1.71 (d, J = 6.7 Hz, 3 H), 1.96–2.24 (m, 4 H), 2.48 (dt, J = 12.5 and 2.6 Hz, 1 H), 2.93 (m, 1 H), 3.37 (d, J = 5.5 Hz, 2 H), 4.49 (s, 2 H), 5.38–5.51 (dq, J = 15.5 and 6.7 Hz, 1 H), 5.57–5.67 (ddd, J = 15.5, 8.3, and 2.0 Hz, 1 H), 7.27–7.38 (comp m, 5 H); high-resolution mass spectrum (CI, isobutane) m/z 258.1643 (M^+, calcd for $C_{17}H_{22}O_2$ 258.1620).

Reduction of Ketone 27. A solution of ketone **27** (90.7 mg, 0.351 mmol) in methanol (2.0 mL) was cooled to 0 °C under argon and sodium borohydride (20 mg, 1.5 equiv) was added. After 30 min, the reaction was quenched with brine. The mixture was extracted three times with methylene chloride, and the combined extracts were dried over $MgSO_4$, and concentrated in vacuo. Preparative TLC [0.5 mm × 20 cm × 20 cm, ethyl acetate–hexane (1:6), three developments] furnished 18.7 mg (20.5% yield) of the less polar alcohol **10a** and 57.7 mg (63.1% yield) of the more polar alcohol **24a**, both as colorless oils.

Reduction of Ketone 26. A solution of ketone **26** (67.2 mg, 0.26 mmol) in methanol (2.0 mL) was cooled to 0 °C, and sodium borohydride (15 mg, 1.5 equiv) was added. After 30 min, the mixture was diluted with brine and extracted three times with methylene chloride. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Preparative TLC [0.5 mm × 20 cm × 20 cm, ethyl acetate–hexane (1:4), six developments] gave 10 mg (15% yield) of the less polar alcohol **24a** and 48.2 mg (71% yield) of the more polar alcohol **23a**, both as colorless oils.

Reduction of Aldehyde 12a. A solution of aldehyde **12a** (70.1 mg, 0.269 mmol) in methanol (2.0 mL) and THF (0.5 mL) was cooled to 0 °C and sodium borohydride (40 mg, 4 equiv) was added. After 30 min, the reaction mixture was quenched with water and extracted twice with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:4) as eluant, gave 65.4 mg (93% yield) of alcohol **25a** as a colorless oil.

MEM Ether 10c. Under argon, MEM chloride (13.16 mL, 1.5 equiv) was added dropwise to a solution of alcohol (−)-**10a** (20.01 g, 76.8 mmol) (vide infra), diisopropylethylamine (26.8 mL, 2 equiv), and DMAP (150 mg) in methylene chloride (100 mL) at room temperature. The reaction was stirred for 48 h and diluted with ether. The ether extracts were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ether–hexane (1:2) as eluant, gave 24.9 g (93% yield) of (−)-**10c** as a colorless oil: $[\alpha]^{24}_D$ −29.7° (c 1.34, $CHCl_3$); IR ($CHCl_3$) 2870–3010 (s, br), 1455 (m), 1365 (w), 1130 (s), 1100 (s, br), 1045 (s, br), 975 (m), 850 (w, br) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.11–1.16 (m, 2 H), 1.51–1.64 (m, 2 H), 1.65 (d, J = 5.3 Hz, 3 H), 1.83 (br d, J = 12.5 Hz, 1 H), 1.93–2.07 (m, 3 H), 3.28 (d, J = 6.0 Hz, 2 H), 3.36 (s, 3 H), 3.51 (t, J = 4.6 Hz, 2 H), 3.69 (m, 2 H), 3.83 (br s, 1 H), 4.49 (s, 2 H), 4.72 (ABq, J_{AB} = 7.1 Hz, $\Delta\nu_{AB}$ = 27.2 Hz, 2 H), 5.36–5.56 (m, 2 H), 7.27–7.36 (comp m, 5 H). Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.52; H, 9.21.

Aldehyde 8. A solution of olefin (−)-**10c** (25.48 g, 73.12 mmol) in methylene chloride (250 mL) was cooled to −78 °C, and ozone was bubbled into the solution for 70 min. A solution of triphenylphosphine (29 g, 1.5 equiv) in methylene chloride (40 mL) then was added at −78 °C, and the resultant mixture warmed to room temperature for 4 h. After removal of solvent in vacuo, the residual oil was purified by flash chromatography, using ethyl acetate–hexane (1:2) as eluant, to give 20.66 g (84% yield) of (−)-**8** as a colorless oil: $[\alpha]^{24}_D$ −20.0° (c 1.34, $CHCl_3$); IR ($CHCl_3$) 2860–3000 (s, br), 2720 (w), 1725 (s), 1450 (m), 1360 (m), 1235 (m, br), 1165 (m), 1130 (s), 1095 (s), 1040 (s), 840 (w), 690 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.96–1.22 (m, 2 H), 1.68–2.05 (comp m, 4 H), 2.15–2.28 (m, 2 H), 3.31 (d, J = 6.1 Hz, 2 H), 3.36 (s, 3 H), 3.50 (t, J = 4.4 Hz, 2 H), 3.63 (q, J = 4.6 Hz, 2 H), 4.49 (s, 2 H + 1 H), 4.72 (ABq, J_{AB} = 7.3 Hz, $\Delta\nu_{AB}$ = 34.2 Hz, 2 H), 7.27–7.36 (comp m, 5 H), 9.70 (s, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 354.2294 [$(M + NH_4)^+$, calcd for $C_{19}H_{32}NO_5$ 354.2280]. Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.77; H, 8.48.

Similar transformations of (±)-**10a** furnished (±)-**8** in 81% yield (two steps).

Tetrahydro-4*H*-pyran-4-one (13).[27] A mechanically stirred suspension of aluminum chloride (750 g, 1.4 equiv) in methylene chloride (550 mL) was cooled to 0 °C under argon, and 3-chloropropionyl chloride (365 mL, 3.82 mol) was added slowly. Ethylene gas was then bubbled into the reaction mixture, which was allowed to warm to room temperature. After 3 h at room temperature, the addition of ethylene was terminated. Excess aluminum chloride was then destroyed by slow addition of the reaction mixture to a biphasic mixture of methylene chloride (500 mL) and 1 M HCl (ca. 2 L) cooled to 0 °C. The temperature was carefully maintained below 20 °C. The methylene chloride layer was separated, washed three times with water, and dried over $MgSO_4$. The solvent was removed in vacuo to give 557 g (94% yield) of 1,5-dichloropentan-3-one as an oil which was used without purification.

A mechanically stirred aqueous (1.2 L) solution of NaH_2PO_4 (624 g, 2 equiv) and *o*-phosphoric acid (196 g, 1 equiv) was heated to reflux (100 °C), and 1,5-dichloropentan-3-one (310 g, 2 mol) was added over a period of 75 min. The reaction mixture was stirred for 3 h at 100 °C, cooled to 0 °C, and neutralized with 10 M aqueous NaOH (650 mL). The supernatant was decanted from the solid residue and extracted twice with methylene chloride. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Distillation furnished 69.5 g (35% yield) of tetrahydro-4*H*-pyran-4-one (**13**) as a colorless oil, bp 77–78 °C (37 mmHg): IR ($CHCl_3$) 3000 (s), 2970 (s), 2920 (s), 2880 (s), 1710–1730 (s, br), 1470 (m), 1410 (s), 1380 (s), 1360 (s), 1320 (s), 1310 (s), 1285 (s), 1205–1240 (s, br), 1160 (s), 1087 (s), 980 (s, br), 850 (s), 680 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.53 (t, J = 7.0 Hz, 2 H), 3.99 (t, J = 7.0 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 118.0871 [$(M + NH_4)^+$, calcd for $C_5H_{12}NO_2$ 118.0868].

Bromide 28. A mixture of tetrahydro-4*H*-pyran-4-one (**13**) (9.79 g, 96.8 mmol), 2,2-dimethyl-1,3-propanediol (12.47 g, 1.2 equiv), *p*-TsOH-H_2O (200 mg), and benzene (200 mL) was heated at reflux with azeotropic removal of water (Dean-Stark trap) for 1 h. After cooling to room temperature, the reaction mixture was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed in vacuo to give 18.2 (quantitative) of the ketal as a white solid, mp 57–62 °C.

Under argon, a solution of pyridinium bromide perbromide (38.7 g, 1 equiv) in THF (50 mL) was added dropwise to a solution of the ketal (18.2 g) in THF (200 mL) with cooling via a water bath. The mixture was stirred for 15 min at room temperature and then diluted with ether. Pyridinium bromide was filtered off, and the filtrate was washed with saturated $NaHCO_3$, 20% aqueous $Na_2S_2O_3$, and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography, with ether–petroleum ether (1:4) as eluant, gave 23.4 g (91% yield) of bromide **28** as a pale yellow oil. Treatment with cold ether–hexane resulted in the crystallization of **28** as colorless prisms, mp 77–78 °C: IR ($CHCl_3$) 2970 (s), 2870 (s), 1470 (m), 1300 (s), 1160 (s), 1125 (s), 1100 (s), 1020 (s), 1000 (m), 980 (m), 965 (m), 920 (w), 905 (w), 840 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.87 (s, 3 H), 1.18 (s, 3 H), 1.70 (m, 1 H), 2.64 (m, 1 H), 3.44–3.85 (m, 7 H), 3.97 (dd, J = 11.5 and 3.8 Hz, 1 H), 4.21 (dd, J = 8.5 and 3.8 Hz, 1 H); high-resolution mass spectrum (CI, isobutane) m/z 266.0330 [$(M + H)^+$, calcd for $C_{10}H_{18}O_3Br$ 266.0341], 264.0360 [$(M - H)^+$, calcd for $C_{10}H_{16}O_3Br$ 264.0360]. Anal. Calcd for $C_{10}H_{17}O_3Br$: C, 45.30; H, 6.46; Br, 30.14. Found: C, 45.32; H, 6.46; Br, 30.32.

Dihydropyran Ketal 11. Under argon, *t*-BuOK (40 g, 4.0 equiv) was added to a solution of bromide **28** (23.4 g, 88.3 mmol) in DMSO (100 mL) at room temperature. After 15 min, the resulting black solution was poured onto crushed ice. The mixture was extracted three times with ether, and the combined extracts were washed twice with water and dried over Na_2SO_4. Following solvent evaporation in vacuo, the brown residue was purified by flash chromatography, with ether–petroleum ether (1:3) as eluant, to give an oil. Distillation furnished 12.6 g (77% yield) of dihydropyran **11** as a colorless oil, bp 76–78 °C (3.5 mmHg), which solidified upon refrigeration: IR ($CHCl_3$) 2960 (s), 2870 (s), 1640 (s), 1470 (m), 1410 (m), 1370 (m), 1275 (m), 1255 (s), 1120 (s, br), 1080 (s), 1020 (m), 985 (s), 970 (s), 915 (s), 860 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (s, 3 H), 1.09 (s, 3 H), 2.08 (t, J = 5.8 Hz, 2 H), 3.45 (d, J = 11.6 Hz, 2 H), 3.67 (d, J = 11.6 Hz, 2 H), 4.11 (t, J = 5.8 Hz, 2 H), 5.31 (d, J = 6.6 Hz, 1 H), 6.42 (d, J = 6.6 Hz, 1 H). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.04; H, 8.87.

Alcohol 29. A solution of dihydropyran ketal **11** (210 mg, 1.14 mmol) in THF (0.5 mL) was cooled to −78 °C under argon, and a solution of *t*-BuLi (1 equiv) in pentane (0.57 mL, 2.0 M) was added dropwise. The reaction was warmed to 0 °C for 30 min and then cooled to −78 °C. A solution of benzaldehyde (0.17 mL, 1.5 equiv) in THF (0.3 mL) was added dropwise, and the resultant mixture was stirred for 15 min at −78 °C and quenched with saturated NH_4Cl. The mixture was extracted three times with ether, and the combined extracts were washed twice with water, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:2) as eluant, gave 272 mg (82% yield) of alcohol **29** as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (s, 3 H), 1.08 (s, 3 H), 2.05 (m, 2 H), 2.47 (br d, J = 5.1 Hz, 1 H), 3.44 (d, J = 11.6 Hz, 2 H), 3.68 (d, J = 11.6 Hz, 2 H), 4.11 (m, 2 H), 5.06 (d, J = 5.0 Hz, 1 H), 5.54 (s, 1 H), 7.30–7.44 (comp m, 5 H).

Alcohols 30 and 31. Under argon, a solution of dihydropyran (0.253 mL, 2 equiv) in THF (1.0 mL) was cooled to −78 °C, and a solution of *t*-BuLi (2 equiv) in pentane (1.73 mL, 1.6 M) was added dropwise. The reaction was warmed to 0 °C for 1 h and cooled to −78 °C. A solution of aldehyde **8** (446.4 mg, 1.39 mmol) in THF (1.5 mL) and HMPA (0.362 mL, 1.5 equiv) was then added over 5 min. The resulting dark red-brown mixture was stirred for 40 min at −78 °C and quenched with saturated NH_4Cl. The mixture was extracted three times with ether, and

the combined extracts were washed twice with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:1) as eluant, afforded 269.4 mg (46% yield) of the less polar alcohol **30** and 211.3 mg (36% yield) of the more polar alcohol **31**, both as yellow oils.

30: IR ($CHCl_3$) 3460–3620 (m, br), 3000 (m), 2940 (s), 2860 (s), 1680 (m), 1500 (w), 1455 (m, br), 1370 (m), 1300 (w), 1280 (w), 1200–1260 (m, br), 1160 (m), 1000–1150 (s, br), 920 (m), 850 (w), 695 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.04 (m, 2 H), 1.56–2.23 (comp m, 10 H), 2.85 (d, J = 3.5 Hz, 1 H), 3.30 (dd, J = 5.5 and 2.5 Hz, 2 H), 3.35 (s, 3 H), 3.50 (dd, J = 5.0 and 4.0 Hz, 2 H), 3.72 (dd, J = 7.5 and 4.0 Hz, 2 H), 3.80–4.06 (m, 4 H), 4.49 (s, 2 H), 4.78 (ABq, J_{AB} = 6.0 Hz, $\Delta\nu_{AB}$ = 23.2 Hz, 2 H), 4.81 (m, 1 H), 7.26–7.36 (comp m, 5 H); high-resolution mass spectrum (CI, NH_3) m/z 421.2606 [$(M + H)^+$, calcd for $C_{24}H_{37}O_6$ 421.2590], 420.2533 (M^+, calcd for $C_{24}H_{36}O_6$ 420.2512).

31: IR ($CHCl_3$) 3260–3680 (m, br), 3005 (s), 2820–2980 (s, br), 1680 (m), 1500 (w), 1455 (m, br), 1370 (m), 1350 (m), 1280 (m), 1200–1270 (s, br), 1170 (m), 990–1150 (s, br), 920 (m), 850 (m), 700–800 (s, br), 695 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.03 (m, 1 H), 1.41 (m, 2 H), 1.58–2.19 (comp m, 9 H), 3.28 (d, J = 1.5 Hz, 1 H), 3.30 (d, J = 1.5 Hz, 1 H), 3.37 (br s, 3 H + 1 H), 3.54 (t, J = 5.1 Hz, 2 H), 3.63–3.85 (m, 3 H), 4.01 (t, J = 5.1 Hz, 2 H), 4.20 (br d, J = 1.4 Hz, 1 H), 4.49 (s, 2 H), 4.75 (m, 1 H), 4.76 (ABq, J_{AB} = 6.8 Hz, $\Delta\nu_{AB}$ = 18.3 Hz, 2 H), 7.28–7.34 (m, 5 H); high-resolution mass spectrum (CI, isobutane) m/z 421.2632 [$(M + H)^+$, calcd for $C_{24}H_{37}O_6$ 421.2590], 420.2539 (M^+, calcd for $C_{24}H_{36}O_6$ 420.2512).

Spiroketal Alcohols 32a and 33a. A solution of MEM ether **30** (185.9 mg, 0.422 mmol) in methylene chloride (4.0 mL) was cooled to 0 °C under argon, and trifluoroacetic acid (1.0 mL, 29 equiv) was introduced dropwise. After 30 min at 0 °C, the solvent was removed in vacuo to give a yellow residue which was dissolved in methanol (4.0 mL) and treated with anhydrous K_2CO_3 (500 mg). The reaction mixture was stirred for 30 min at room temperature, quenched with brine, and extracted three times with ether. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:2) as eluant, gave 63.6 mg (43% yield) of the less polar spiroketal **32a** and 44.3 mg (30% yield) of the more polar spiroketal **33a**, both as colorless oils. The acetates (**32b** and **33b**) were individually prepared by addition of acetic anhydride to a solution of the corresponding alcohol and DMAP in pyridine. After stirring for 2 h the reaction was quenched with water. The mixture was extracted three times with ether, and the combined extracts were washed twice with 10% HCl, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed in vacuo, and the product was purified by flash chromatography, using ethyl acetate–hexane (1:2) as eluant.

32a: IR ($CHCl_3$) 3500 (m, br), 3000 (m), 2950 (s), 2860 (s), 1455 (m), 1360 (m), 1300 (w), 1270 (w), 1030–1150 (s, br), 980 (s), 960 (m), 920 (m), 695 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (qd, J = 12.0 and 3.3 Hz, 1 H), 1.19 (qd, J = 12.0 and 3.4 Hz, 1 H), 1.30 (m, 1 H), 1.52 (m, 1 H), 1.58–1.78 (comp m, 5 H), 1.77 (dd, superimposed on a comp m, J = 12.9 and 3.9 Hz, 1 H), 1.83–1.92 (m, 3 H), 2.02 (br d, J = 14.4 Hz, 1 H), 3.29 (ABX, J_{AB} = 9.1 Hz, J_{AX} = 6.7 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 24.2 Hz, 2 H), 3.32 (d, superimposed on an ABX, J = 4.9 Hz, 1 H), 3.57 (d, J = 4.9 Hz, 1 H), 3.76 (ddd, J = 11.2, 4.5, and 2.9 Hz, 1 H), 3.97 (td, J = 11.2 and 2.7 Hz, 1 H), 4.28 (dd, J = 7.5 and 3.6 Hz, 1 H), 4.50 (s, 2 H), 7.26–7.38 (comp m, 5 H); high-resolution mass spectrum (CI, isobutane) m/z 333.2062 [$(M + H)^+$, calcd for $C_{20}H_{29}O_4$ 333.2066], 332.1991 (M^+, calcd for $C_{20}H_{28}O_4$ 332.1988). Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.22; H, 8.32.

32b: ^1H NMR (250 MHz, $CDCl_3$) δ 0.92–1.08 (m, 1 H), 1.20–2.05 (comp m, 13 H), 2.07 (s, 3 H), 3.30 (ABX, J_{AB} = 9.0 Hz, J_{AX} = 6.5 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 13.1 Hz, 2 H), 3.68 (m, 1 H), 3.91 (td, J = 11.3 and 3.8 Hz, 1 H), 4.32 (q, J = 3.5 Hz, 1 H), 4.49 (s, 2 H), 4.60 (d, J = 1.5 Hz, 1 H), 7.24–7.38 (comp m, 5 H).

33a: IR ($CHCl_3$) 3600 (w), 3200–3500 (w, br), 3000 (m), 2940 (s), 2860 (s), 1600 (w), 1500 (w), 1450 (m), 1360 (m), 1290 (w), 1230 (m), 1030–1160 (s, br), 990 (s), 950 (m), 900 (m), 890 (m), 690 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (qd, J = 12.4 and 3.2 Hz, 1 H), 1.28 (m, 1 H), 1.49–1.63 (m, 3 H), 1.71–1.87 (comp m, 8 H), 1.95 (m, 1 H), 2.10 (br d, J = 14.1 Hz, 1 H), 3.32 (ABX, J_{AB} = 9.1 Hz, J_{AX} = 6.9 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 30.9 Hz, 2 H), 3.60 (dt, J = 11.3 and 2.2 Hz, 1 H), 3.83 (s, 1 H), 3.96 (td, J = 11.3 and 2.8 Hz, 1 H), 4.40 (q, J = 3.5 Hz, 1 H), 4.50 (s, 2 H), 7.27–7.38 (m, 5 H); high-resolution mass spectrum (CI, isobutane) m/z 333.2071 [$(M + H)^+$, calcd for $C_{20}H_{29}O_4$ 333.2066], 332.2004 (M^+, calcd for $C_{20}H_{28}O_4$ 332.1988). Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 71.87; H, 8.58.

33b: ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (m, 1 H), 1.26 (td, J = 12.5 and 4.5 Hz, 1 H), 1.43–1.98 (comp m, 11 H), 2.04 (s, 3 H), 2.13 (br d, J = 14.5 Hz, 1 H), 3.31 (ABX, J_{AB} = 9.2 Hz, J_{AX} = 6.3 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 18.3 Hz, 2 H), 3.62 (br d, J = 11.3 Hz, 1 H), 3.95 (td, J = 11.3 and 3.3 Hz, 1 H), 4.32 (br d, J = 3.0 Hz, 1 H), 4.49 (s, 2 H), 4.85 (s, 1 H), 7.25–7.37 (comp m, 5 H).

Spiroketals 34a and 35a. Under argon, a solution of MEM ether **31** (452.8 mg, 1.08 mmol) in methylene chloride (7.2 mL) was cooled to 0 °C, and trifluoroacetic acid (2.2 mL, 27 equiv) was added dropwise. After 30 min at 0 °C, the solvent was removed in vacuo to furnish a yellow residue which was dissolved in methanol (8.6 mL) and treated with anhydrous K_2CO_3 (1.08 g). The mixture was stirred for 30 min at room temperature, quenched with brine, and extracted three times with ether. The ether extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:3) as eluant, gave 33.7 mg (9.4% yield) of the less polar spiroketal **35a** as an oil and 250.5 mg (70% yield) of the more polar spiroketal **34a** as a white solid. Recrystallization of **34a** from ether–hexane gave colorless prisms, mp 91.5–92.5 °C. The acetates (**34b** and **35b**) were individually prepared by addition of acetic anhydride to a solution of the corresponding alcohol and DMAP in pyridine. After stirring for 2 h the mixture was quenched with water and extracted three times with ether. The combined extracts were washed twice with 10% HCl, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash chromatography, using ethyl acetate–hexane (1:2) as eluant.

34a: IR ($CHCl_3$) 3600 (w), 3200–3500 (w, br), 3000 (s), 2950 (s), 2860 (s), 1450 (m), 1360 (m), 1240 (m, br), 1100 (s), 1080 (s), 1065 (s), 980 (s), 950 (s), 910 (m), 895 (m), 880 (m), 690 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (qd, J = 13.2 and 3.1 Hz, 1 H), 1.26–1.35 (m, 2 H), 1.49 (br d, J = 12.9 Hz, 1 H), 1.56–1.75 (comp m, 5 H), 1.82–1.88 (m, 3 H), 1.95 (m, 1 H), 2.06 (m, 1 H), 2.15 (m, 1 H), 3.31 (ABX, J_{AB} = 9.1 Hz, J_{AX} = 6.6 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 24.2 Hz, 2 H), 3.60 (dd, J = 11.2 and 4.7 Hz, 1 H), 3.91 (td, J = 11.2 and 2.6 Hz, 1 H), 4.08 (q, J = 3.3 Hz, 1 H), 4.16 (dd, $J_1 = J_2$ = 6.6 Hz, 1 H), 4.50 (s, 2 H), 7.26–7.36 (comp m, 5 H); high-resolution mass spectrum (CI, isobutane) m/z 333.2021 [$(M + H)^+$, calcd for $C_{20}H_{29}O_4$ 333.2066], 332.1998 (M^+, calcd for $C_{20}H_{28}O_4$ 332.1988). Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.31; H, 8.51.

34b: IR ($CHCl_3$) 2920 (s), 2860 (s), 1720 (s, br), 1450 (m, br), 1360 (m, br), 1205–1280 (s, br), 1050–1120 (s, br), 980 (s, br), 895 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.81 (qd, J = 13.5 and 5.0 Hz, 1 H), 1.19–1.36 (m, 4 H), 1.45–2.13 (comp m, 8 H), 2.05 (s, 3 H), 2.37 (m, 1 H), 3.30 (ABX, J_{AB} = 9.5 Hz, J_{AX} = 6.0 Hz, J_{BX} = 5.6 Hz, $\Delta\nu_{AB}$ = 12.9 Hz, 2 H), 3.61 (br dd, J = 11.5 and 2.5 Hz, 1 H), 3.80 (td, J = 11.5 and 3.5 Hz, 1 H), 4.16 (q, J = 3.5 Hz, 1 H), 4.49 (s, 2 H), 4.98 (d, J = 6.5 Hz, 1 H), 7.26–7.38 (comp m, 5 H).

35a: IR ($CHCl_3$) 3540 (w, br), 3030 (m), 2950 (s), 2860 (s), 1455 (m), 1415 (w), 1360 (m), 1330 (m, br), 1115 (s), 1070 (s), 1040 (s), 985 (s), 960 (s), 900 (m), 695 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (qd, J = 13.1 and 3.3 Hz, 1 H), 1.25 (ddd, J = 14.4, 12.3 and 3.6 Hz, 1 H), 1.49 (br m, 2 H), 1.53–1.60 (m, 2 H), 1.65–1.71 (m, 2 H), 1.73 (dd, J = 13.0 and 4.2 Hz, 1 H), 1.80–1.87 (m, 2 H), 1.89 (m, 1 H), 2.02–2.08 (m, 2 H), 2.71 (d, J = 9.9 Hz, 1 H), 3.31 (ABX, J_{AB} = 9.0 Hz, J_{AX} = 6.7 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 27.3 Hz, 2 H), 3.71 (br dd, J = 11.2 and 4.6 Hz, 1 H), 3.87 (dd, J = 9.9 and 6.6 Hz, 1 H), 3.95 (br m, 1 H), 3.97 (td, superimposed on a m, J = 11.2 and 2.6 Hz, 1 H), 4.51 (s, 2 H), 7.26–7.36 (m, 5 H); high-resolution mass spectrum (CI, NH_3) m/z 332.1988 (M^+, calcd for $C_{20}H_{28}O_4$ 332.1988). Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.23; H, 8.31.

35b: ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (m, 1 H), 1.29 (m, 1 H), 1.40–2.02 (comp m, 10 H), 2.11 (br d, J = 16.0 Hz, 1 H), 2.16 (s, 3 H), 2.29 (m, 1 H), 3.31 (dd, J = 6.2 and 1.3 Hz, 2 H), 3.73 (br dd, J = 11.4 and 4.2 Hz, 1 H), 3.98 (td, J = 11.4 and 2.7 Hz, 1 H), 4.06 (br dd, J = 6.6 and 3.0 Hz, 1 H), 4.51 (s, 2 H), 4.86 (d, J = 6.5 Hz, 1 H), 7.26–7.36 (comp m, 5 H).

Ketone 36. A solution of oxalyl chloride (0.09 mL, 2 equiv) in methylene chloride (4.0 mL) was cooled to −78 °C under argon, and a solution of DMSO (0.11 mL, 3 equiv) in methylene chloride (2.0 mL) was added dropwise. After 5 min, a solution of alcohol **34a** (171.6 mg, 0.516 mmol) in methylene chloride (6.0 mL) was introduced dropwise over 10 min. The resultant milky solution was stirred for 20 min at −78 °C, and then triethylamine (0.5 mL, 6.8 equiv) was added. The reaction mixture was stirred for 5 min at −78 °C, warmed to room temperature, quenched with water, and extracted twice with methylene chloride. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:3) as eluant, gave 164.1 mg (96% yield) of spiroketal **36** as a white solid, mp 89–90 °C: IR ($CHCl_3$) 3050 (m), 2950 (s), 2860 (s), 1768 (s), 1455 (m), 1450 (w), 1360 (w), 1225 (w), 1175 (m), 1160 (m), 1115 (m), 1080 (m), 1060 (m), 1050 (s), 1040 (s), 1020 (m), 975 (m), 955 (m), 910 (w), 890 (w), 695 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (m, 1 H), 1.29 (m, 1 H), 1.43 (ddd, J = 15.0, 12.5 and 3.9 Hz, 1 H),

1.50 (br d, J = 12.2 Hz, 1 H), 1.52 (m, 1 H), 1.68–1.93 (comp m, 6 H), 1.96 (m, 1 H), 2.16 (br dd, J = 14.8 and 1.7 Hz, 1 H), 2.37 (ddd, J = 11.6, 6.7 and 4.3 Hz, 1 H), 3.34 (ABX, J_{AB} = 9.1 Hz, J_{AX} = 6.4 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 27.0 Hz, 2 H), 3.70 (br d, J = 11.2 Hz, 1 H), 3.88 (td, J = 11.2 and 2.6 Hz, 1 H), 4.51 (br s, 2 H + 1 H), 7.26–7.36 (comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.70, 138.54, 128.34, 127.53, 99.31, 75.24, 73.10, 71.66, 61.88, 44.10, 31.58, 30.41, 29.91, 27.17, 24.92, 23.48, 18.76; high-resolution mass spectrum (Cl, NH_3) m/z 331.1897 [(M + H)$^+$, calcd for $C_{20}H_{27}O_4$ 331.1909]. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.90; H, 7.92.

Ketone 37. Under argon, a solution of oxalyl chloride (0.105 mL, 2 equiv) in methylene chloride (5.0 mL) was cooled to −78 °C, and a solution of DMSO (0.13 mL, 3 equiv) in methylene chloride (2.4 mL) was added dropwise. After 5 min at −78 °C, a solution of alcohol **33a** (201 mg, 0.605 mmol) in methylene chloride (7.0 mL) was added dropwise over 10 min. The resultant milky solution was stirred for 20 min at −78 °C, and then triethylamine (0.5 mL, 6.8 equiv) was added. After 5 min at −78 °C, the reaction was warmed to room temperature and quenched with water. The mixture was extracted twice with methylene chloride, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:2) as eluant, furnished 151.1 mg (76% yield) of spiroketal **37** as a white amorphous solid, mp 50.5–51.5 °C: IR ($CHCl_3$) 3010 (m), 2965 (s), 2860 (s), 1765 (s), 1495 (w), 1452 (m), 1360 (m), 1230 (m, br), 1180 (m), 1085 (s, br), 1070 (m), 1050 (s, br), 1020 (m), 985 (s), 955 (m), 906 (s), 695 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (m, 1 H), 1.48–1.62 (m, 3 H), 1.68–1.86 (comp m, 7 H), 2.09 (br m, 2 H), 2.40 (m, 1 H), 3.36 (ABX, J_{AB} = 9.1 Hz, J_{AX} = J_{BX} = 3.0 Hz, $\Delta\nu_{AB}$ = 15.6 Hz, 2 H), 3.78 (br d, J = 11.2 Hz, 1 H), 3.95 (td, J = 11.2 and 2.4 Hz, 1 H), 4.27 (dd, J = 9.3 and 4.5 Hz, 1 H), 4.51 (s, 2 H), 7.26–7.36 (comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.20, 138.55, 128.36, 127.51, 99.61, 74.24, 73.06, 71.46, 63.07, 44.95, 31.62, 31.09, 28.52, 26.09, 24.67, 21.56, 18.30; high-resolution mass spectrum (Cl, NH_3) m/z 330.1858 (M$^+$, calcd for $C_{20}H_{26}O_4$ 330.1831). Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.80; H, 7.93.

Alcohols 38 and 39. A solution of dihydropyran ketal **11** (232.8 mg, 1.5 equiv) in THF (0.6 mL) was cooled to −78 °C under argon, and a solution of t-BuLi (1.5 equiv) in pentane (0.74 mL, 1.7 M) was added dropwise. The resultant orange solution was stirred for 1 h at 0 °C and cooled to −78 °C, and a solution of aldehyde **25** (277.2 mg, 0.824 mmol) in THF (1.0 mL) and HMPA (0.215 mL, 1.5 equiv) was added dropwise over 5 min. The reaction mixture was stirred for 30 min at −78 °C, quenched with saturated $NaHCO_3$, and extracted three times with ether. The combined extracts were washed twice with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:1) as eluant, gave 216 mg (50% yield) of the less polar alcohol **38** and 140.6 mg (33% yield) of the more polar alcohol **39**, both as yellow oils.

Alcohol 38: IR ($CHCL_3$) 3270–3670 (m, br), 3000 (s), 2940 (s, br), 2880 (s, br), 1665 (s), 1450 (s), 1430 (m), 1395 (s), 1360 (s), 1340 (s), 1200–1300 (s, br), 1170 (m), 1160 (w), 900–1060 (s, br), 985 (s), 950 (m), 910 (s), 875 (m), 850 (m), 690 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (s, 3 H), 1.08 (m, 2 H), 1.15 (s, 3 H), 1.63–1.98 (comp m, 5 H), 2.03 (br t, J = 5.6 Hz, 2 H), 2.19 (br d, J = 14.5 Hz, 1 H), 3.28 (dd, J = 5.9 and 3.1 Hz, 2 H), 3.35 (s, 3 H), 3.34–3.41 (m, 3 H), 3.51 (m, 2 H), 3.73 (m, 4 H), 4.06–4.17 (comp m, 4 H), 4.48 (s, 2 H), 4.80 (ABq, J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 31.0 Hz, 2 H), 5.55 (s, 1 H), 7.26–7.34 (comp m, 5 H); high-resolution mass spectrum (Cl, NH_3) m/z 521.3120 [(M + H)$^+$, calcd for $C_{29}H_{45}O_8$ 521.3114].

Alcohol 39: IR ($CHCl_3$) 3230–3630 (m, br), 3000 (s), 2930 (s), 2870 (s), 1660 (m), 1450 (m), 1390 (m), 1360 (m), 1340 (m), 1300 (w), 1200–1290 (m, br), 1155 (m), 1000–1140 (s, br), 965 (m), 950 (m), 910 (m), 895 (m), 855 (w), 845 (m), 695 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (s, 3 H), 1.02–1.25 (m, 3 H), 1.09 (s, 3 H), 1.40–2.17 (comp m, 8 H), 3.28 (dd, J = 6.2 and 2.8 Hz, 2 H), 3.36 (s, 3 H), 3.38–3.54 (comp m, 5 H), 3.66–3.90 (m, 4 H), 3.92 (m, 1 H), 4.14 (dd, J_1 = J_2 = 5.5 Hz, 1 H), 4.16 (br s, 1 H), 4.48 (s, 2 H), 4.76 (ABq, J_{AB} = 6.9 Hz, $\Delta\nu_{AB}$ = 20.4 Hz, 2 H), 5.43 (s, 1 H), 7.25–7.37 (comp m, 5 H); high-resolution mass spectrum (Cl, isobutane) m/z 521.3122 [(M + H)$^+$, calcd for $C_{29}H_{45}O_8$ 521.3114].

Methylene Acetal 40. A solution of alcohol **38** (105 mg, 0.202 mmol) in methylene chloride (2.0 mL) was cooled to 0 °C under argon, and trifluoroacetic acid (0.5 mL, 17 equiv) was added dropwise. After 30 min at 0 °C, the reaction mixture was added dropwise by syringe to a suspension of K_2CO_3 (1.5 g) in methanol (5.0 mL). After stirring for 30 min at room temperature, brine was added, and the mixture was extracted twice with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (2:1–1:0) as eluant, furnished 64 mg (73% yield) of deketalized **38** as an oil.

Under argon, a solution of deketalized **38** (60 mg, 0.138 mmol) in methylene chloride (2.0 mL) was cooled to 0 °C, and trifluoroacetic acid (0.5 mL, 26 equiv) was added dropwise. After 30 min at 0 °C, the reaction mixture was warmed to room temperature for 1.5 h and then concentrated in vacuo. The residue was diluted with ether, and the resultant solution was washed with saturated $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed in vacuo, and the product was purified by flash chromatography, with ethyl acetate–hexane (1:1) as eluant, to give 47.8 mg (97% yield) of acetal **40** as an oil.

Deketalized 38: IR ($CHCl_3$) 3650 (w), 3220–3600 (m, br), 2995 (s), 2850–2950 (s, br), 1670 (s, br), 1610 (s, br), 1450 (s), 1390–1460 (m, br), 1360 (s), 1280 (m), 1200–1260 (s, br), 1070–1140 (s, br), 1010–1040 (s, br), 980 (s), 870 (m), 840 (m), 690 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.00–1.16 (m, 2 H), 1.48 (m, 1 H), 1.63–1.92 (comp m, 4 H), 2.20 (br d, J = 14.5 Hz, 1 H), 2.45–2.67 (m, 2 H), 3.29 (dd, J = 6.3 and 3.0 Hz, 2 H), 3.36 (s, 3 H), 3.51 (t, J = 4.5 Hz, 2 H), 3.65–3.81 (m, 2 H), 3.87 (s, 1 H), 4.17 (br s, 1 H), 4.39 br s, 1 H), 4.41–4.56 (m, 2 H), 4.48 (s, 2 H), 4.81 (ABq, J_{AB} = 7.0 Hz, $\Delta\nu_{AB}$ = 34.8 Hz, 2 H), 5.71 (s, 1 H), 7.26–7.37 (comp m, 5 H); high-resolution mass spectrum (Cl, isobutane) m/z 435.2399 [(M + H)$^+$, calcd for $C_{24}H_{35}O_7$ 435.2382], 434.2338 (M$^+$, calcd for $C_{24}H_{34}O_7$ 434.2304).

40: IR ($CHCl_3$) 2990 (s), 2930 (s, br), 2830 (s), 2770 (m), 1665 (s, br), 1615 (s), 1465 (m), 1450 (m), 1400 (m), 1365 (m), 1330 (s), 1315 (s), 1195–1250 (s, br), 1165 (s), 1135 (s), 1100 (s, br), 1070 (s), 1025 (s, br), 980 (s), 880 (m), 865 (m), 835 (m), 690 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.05 (m, 1 H), 1.25–1.37 (m, 2 H), 1.69–1.89 (m, 4 H), 2.04 (br d, J = 14.0 Hz, 1 H), 2.57 (s, 2 H), 3.30 (d, J = 6.0 Hz, 2 H), 3.92 (br s, 1 H), 4.34 (s, 1 H), 4.35–4.57 (m, 2 H), 4.49 (s, 2 H), 4.78 (d, J = 6.0 Hz, 1 H), 5.27 (d, J = 6.0 Hz, 1 H), 5.61 (s, 1 H), 7.24–7.34 (comp m, 5 H); high-resolution mass spectrum (Cl, isobutane), m/z 359.1817 [(M + H)$^+$, calcd for $C_{21}H_{27}O_5$ 359.1852], 358.1783 (M$^+$, calcd for $C_{21}H_{26}O_5$ 358.1773).

Diketone 41. Under argon, a solution of dihydropyran ketal **11** (10.46 g, 1.4 equiv) in THF (20 mL) was cooled to −78 °C, and a solution of t-BuLi (1.4 equiv) in pentane (28.4 mL, 2.0 M) was added dropwise. The resultant orange solution was stirred for 1 h at 0° and cooled to −78 °C, and a solution of aldehyde (−)-**8** (13.65 g, 40.6 mmol) in THF (15 mL) and HMPA (10.6 mL, 1.5 equiv) was introduced dropwise over 10 min. After 30 min at −78 °C, the reaction mixture was quenched with saturated $NaHCO_3$ and extracted twice with ether. The combined extracts were washed twice with water, washed with brine, and dried over $MgSO_4$. Following removal of solvent in vacuo, the residue was dissolved in methylene chloride (200 mL) and treated with a saturated solution of oxalic acid (20 mL). After 2 h at room temperature, the reaction was quenched with saturated $NaHCO_3$. The methylene chloride layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (4:1, then 1:0) as eluant, furnished 14.19 g (80%, two steps) of a mixture of alcohols.

A solution of oxalyl chloride (4.51 mL, 1.5 equiv) in methylene chloride (100 mL) was cooled to −78 °C under argon, and DMSO (7.35 mL, 3 equiv) was introduced dropwise over 5 min. After 5 min at −78 °C, a solution of the alcohols (14.98 g, 34.5 mmol) in methylene chloride (50 mL) was added dropwise over 15 min. The resultant milky solution was stirred 30 min further at −78 °C, and then triethylamine (32.7 mL, 6.8 equiv) was added. After 10 min at −78 °C, the reaction was warmed gradually to room temperature and quenched with water. The methylene chloride layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (2:1) as eluant, gave 13.0 g [70% yield from (−)-**8**, two steps] of (−)-**41** as a pale yellow solid. Recrystallization from ethyl acetate–hexane gave colorless needles, mp 71–72 °C; $[\alpha]^{24}_D$ −32.5° (c 1.34, $CHCl_3$): IR ($CHCl_3$) 2860–3000 (s, br), 1710 (s), 1680 (s), 1600 (s), 1455 (m), 1355 (s), 1230 (m, br), 1155 (s), 1100 (s, br), 1040 (s, br), 985 (s, br), 960 (w), 875 (w), 845 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.08 (qd, J = 12.8 and 3.5 Hz, 1 H), 1.24 (m, 1 H), 1.61 (m, 1 H), 1.88–2.07 (m, 3 H), 2.16 (br d, J = 13.5 Hz, 1 H), 2.65 (td, J = 7.0 and 2.1 Hz, 2 H), 3.07 (dt, J = 12.3 and 3.0 Hz, 1 H), 3.30 (s, 3 H), 3.32 (d, J = 1.8 Hz, 2 H), 3.36–3.55 (comp m, 4 H), 4.46 (br s, 1 H), 4.50 (s, 2 H), 4.57–4.68 (m, 2 H), 4.63 (ABq, J_{AB} = 7.0 Hz, $\Delta\nu_{AB}$ = 48.5 Hz, 2 H), 6.07 (s, 1 H), 7.24–7.36 (comp m, 5 H); high-resolution mass spectrum (Cl, isobutane) m/z 433.2222 [(M + H)$^+$, calcd for $C_{24}H_{33}O_7$ 433.2227], 432.2160 (M$^+$, calcd for $C_{24}H_{32}O_7$ 432.2148). Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.57; H, 7.44.

Similar transformations of (±)-**8** furnished (±)-**41** in 71% yield as colorless needles, mp 86–87 °C (ether).

Spiroketals 7a and 7b. Under argon, $ZnBr_2$ (17.04 g, 10 equiv) was added to a solution of MEM ether (−)-**41** (3.28 g, 7.58 mmol) in methylene chloride (30 mL), and the mixture was stirred for 23 h at room temperature. After dilution with ether, saturated $NaHCO_3$ was added. The resultant mixture was stirred for 30 min at room temperature, and

the ether layer was separated, washed with brine, and dried over $MgSO_4$. The solvent was removed in vacuo, and the residual yellow oil was dissolved in 140 mL of benzene. Camphorsulfonic acid (340 mg) was then added, and the resultant solution was stirred for 18 h at room temperature. The mixture was diluted with ether, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:4 then 1:0) as eluant, gave 1.92 g (73.5% yield) of the spiroketals as a viscous oil along with a small amount of starting material. The products comprised a 26:1 mixture of **7b** and **7a**, as determined by preparative HPLC. The recovered starting material was dissolved in benzene (40 mL) and treated with a catalytic amount of camphorsulfonic acid (ca. 20 mg). The resultant solution was stirred for 18 h at room temperature, then diluted with ether, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. After removal of solvent in vacuo, purification by flash chromatography, with ethyl acetate–hexane (1:4) as eluant, afforded an additional 100 mg of the spiroketals as a colorless oil [total yield 2.02 g (77%)]. Treatment of the mixture with cold hexane resulted in the crystallization of **7b**; recrystallization from ether–hexane gave colorless prisms, mp 71–72 °C.

7b: $[\alpha]^{24}_D$ +72.9° (*c* 0.68, $CHCl_3$); IR ($CHCl_3$) 2860–3010 (s), 1770 (s), 1730 (s), 1450 (w), 1365 (w), 1315 (w), 1230 (s, br), 1165 (s), 1140 (m), 1100 (s), 1055 (s), 1010 (m), 980 (m), 955 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (ddd, J = 15.9, 13.1 and 3.1 Hz, 1 H), 1.24 (ddd, J = 15.7, 13.2 and 3.3 Hz, 1 H), 1.46 (ddd, J = 15.3, 12.5 and 3.8 Hz, 1 H), 1.82 (br d, J = 12.9 Hz, 1 H), 1.86–1.94 (comp m, 2 H), 2.14 (br d, J = 15.1 Hz, 1 H), 2.35 (dd, J = 15.0 and 1.5 Hz, 1 H), 2.42 (br d, J = 15.1 Hz, 1 H), 2.45 (ddd, J = 11.6, 7.1 and 4.3 Hz, 1 H), 2.69 (ddd, J = 15.1, 11.5 and 7.2 Hz, 1 H), 2.91 (d, J = 15.0 Hz, 1 H), 3.33 (ABX, J_{AB} = 9.1 Hz, J_{AX} = 6.2 Hz, J_{BX} = 5.7 Hz, and $\Delta\nu_{AB}$ = 19.5 Hz, 2 H), 4.07 (ddd, J = 11.3, 7.2 and 1.9 Hz, 1 H), 4.17 (td, J = 11.3 and 3.2 Hz, 1 H), 4.50 (s, 2 H), 4.54 (dd, J = 6.3 and 3.8 Hz, 1 H), 7.26–7.37 (comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.97, 203.20, 138.43, 128.35, 127.53, 127.48, 101.56, 74.85, 73.01, 72.73, 60.17, 46.29, 42.99, 41.19, 31.31, 30.05, 26.89, 23.55: high-resolution mass spectrum (Cl isobutane) m/z 345.1717 [$(M + H)^+$, calcd for $C_{20}H_{25}O_5$: 345.1702], 344.1599 (M^+, calcd for $C_{20}H_{24}O_5$ 344.1624). Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.91; H, 7.06.

Similar transformations of (±)-**41** furnished (±)-**7b** in 71% yield as colorless prisms, mp 88–89 °C (ether–hexane).

7a: IR ($CHCl_3$) 2870–3000 (s), 1770 (s), 1725 (s), 1455 (w), 1405 (w), 1365 (m), 1320 (m), 1240 (s, br), 1165 (s), 1100 (s, br), 1050 (s), 1015 (s), 990 (s), 960 (m), 900 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (ddd, J = 9.7, 5.8, and 2.4 Hz, 1 H), 1.59 (comp m, 1 H), 1.78 (dt, J = 13.4 and 4.4 Hz, 1 H), 1.81–1.85 (comp m, 2 H), 2.01–2.08 (comp m, 2 H), 2.34 (dd, J = 14.5 and 1.7 Hz, 1 H), 2.41–2.47 (comp m, 2 H), 2.70 (ddd, J = 15.0, 11.2, and 7.2 Hz, 1 H), 2.79 (d, J = 14.5 Hz, 1 H), 3.35 (ABX, J_{AB} = 8.8 Hz, J_{AX} = 6.4 Hz, J_{BX} = 6.1 Hz and $\Delta\nu_{AB}$ = 18.8 Hz, 2 H), 4.15 (ddd, J = 11.2, 7.2, and 2.3 Hz, 1 H), 4.25 (td, J = 11.2 and 3.4 Hz, 1 H), 4.33 (dd, J = 8.9 and 4.7 Hz, 1 H), 4.51 (s, 2 H), 7.26–7.37 (comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.26, 203.58, 138.38, 128.38, 127.59, 127.51, 101.74, 74.10, 73.11, 72.32, 61.73, 45.47, 44.22, 41.13, 31.54, 30.75, 26.04, 21.71; high-resolution mass spectrum (Cl, isobutane) m/z 345.1635 [$(M + H)^+$, calcd for $C_{20}H_{25}O_5$ 345.1702], 344.1618 (M^+, calcd for $C_{20}H_{24}O_5$ 344.1624).

Diketone 42. A solution of LDA (0.22 mmol, 1.2 equiv) in THF (0.5 mL) was cooled to −78 °C under argon, and a solution of diketone **7b** (63 mg, 0.183 mmol) in THF (0.5 mL) was introduced dropwise. The reaction was stirred for 30 min at −78 °C and then treated with methyl iodide (0.014 mL, 1.2 equiv). After an additional 90 min, HMPA (0.4 mL) was added, and the resultant mixture was warmed gradually to room temperature (ca. 1 h). Saturated NH_4Cl was added, and the mixture was extracted twice with ether. The combined extracts were washed twice with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:3) as eluant, gave 21 mg (32% yield) of methylated diketone **42** and 10.1 mg (16% yield) of recovered **7b**, both as colorless oils.

42: IR ($CHCl_3$) 3000 (m), 2920 (s), 2840 (s), 1765 (s), 1725 (s), 1450 (m), 1370 (m), 1355 (m), 1310 (m), 1205–1240 (s, br), 1150 (s), 1125 (s), 1100 (s), 1075 (s), 1045 (s), 985 (s), 950 (s), 690 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.17 (s, 3 H), 1.25–1.48 (comp m, 4 H), 1.71 (br d, J = 12.5 Hz, 1 H), 1.95 (m, 1 H), 2.09 (br d, J = 15.0 Hz, 1 H), 2.38 (dd, J = 15.0 and 1.5 Hz, 1 H), 2.42 (m, 1 H), 2.71 (m, 1 H), 2.95 (d, J = 15.0 Hz, 1 H), 3.33 (ABX, J_{AB} = 9.0 Hz, J_{AX} = 6.5 Hz, J_{BX} = 5.5 Hz, $\Delta\nu_{AB}$ = 14.4 Hz, 2 H), 4.01–4.23 (m, 3 H), 4.50 (s, 2 H), 7.26–7.39 (comp m, 5 H); high-resolution mass spectrum (Cl, isobutane) m/z 359.1853 [$(M + H)^+$, calcd for $C_{21}H_{27}O_5$ 359.1858].

Epoxy Ketone 6. A solution of diketone (+)-**7b** (860 mg, 2.50 mmol) in DMSO–THF (1:1, 20 mL) was cooled to 0 °C under argon, and a 0.5 M solution of dimethylsulfoxonium methylide in DMSO (6.0 mL, 1.2 equiv)[40] was added dropwise. The mixture was stirred for 1 h at 0 °C and for 45 min at room temperature, quenched with saturated NH_4Cl, and extracted twice with ether. The combined extracts then were washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:4) as eluant, furnished 704 mg (79% yield) of (+)-**6** as a colorless solid. Recrystallization from ether–hexane afforded white needles, mp 107–108 °C: $[\alpha]^{24}_D$ +106.5° (*c* 0.765, $CHCl_3$); IR (Cl_3) 2860–3010 (s, br), 1725 (s), 1455 (m), 1405 (w), 1365 (m), 1325 (s), 1315 (s), 1245 (s), 1165 (s), 1150 (s), 1135 (s), 1095 (s), 1065 (s), 985 (s), 950 (s), 895 (m), 835 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (qd, J = 13.0 and 3.0 Hz, 1 H), 1.26–1.44 (m, 2 H), 1.57–1.68 (m, 1 H), 1.79 (br d, J = 12.8 Hz, 1 H), 1.87–2.04 (m, 2 H), 2.11 (br d, J = 14.6 Hz, 1 H), 2.32 (dt, J = 15.0 and 1.5 Hz, 1 H), 2.39 (d, J = 1.3 Hz, 1 H), 2.41 (s, 1 H), 2.45–2.60 (m, 1 H), 3.05 (ABq, J_{AB} = 5.2 Hz, $\Delta\nu_{AB}$ = 20.4 Hz, 2 H), 3.31 (d, J = 6.0 Hz, 2 H), 3.94 (ddd, J = 11.4, 7.7, and 1.1 Hz, 1 H), 4.12 (td, J = 11.4 and 3.1 Hz, 1 H), 4.35 (dd, J = 6.4 and 3.6 Hz, 1 H), 4.49 (s, 2 H), 7.26–7.38 (comp m, 5 H); high-resolution mass spectrum (Cl, isobutane) m/z 359.1865 [$(M + H)^+$, calcd for $C_{21}H_{27}O_5$ 359.1858], 358.1798 (M^+, calcd for $C_{21}H_{26}O_5$ 358.1780). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.52; H, 7.48.

Similar methylenation of (±)-**7b** afforded (±)-**6** in 79% yield as white crystals: mp 83–85 °C (ether–hexane).

Reduction of Diketone 7b. Under argon, a solution of diketone **7b** (30.0 mg, 0.088 mmol) in THF (1.0 mL) was cooled to −78 °C, and a 1.0 M THF solution of L-Selectride (0.01 mL, 1.1 equiv) was added dropwise. After 40 min at −78 °C, the mixture was neutralized with acetic acid (2 drops), diluted with water, and extracted twice with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:2, then 1:1, then 2:1) as eluant, furnished 18.8 mg (62% yield) of the less polar alcohol **iia** and 7.8 mg (25% yield) of the more polar diol **iii**, both as oils. The acetate **iib** was prepared by addition of acetic anhydride to a solution of the corresponding alcohol (**iia**) and DMAP in pyridine. After stirring for 2 h the reaction was quenched with water, and the mixture extracted three times with ether. The combined extracts were washed twice with 10% HCl, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed in vacuo, and the product was purified by flash chromatography, using ethyl acetate–hexane (1:2) as eluant.

iia: IR ($CHCl_3$) 3540 (m, br), 3060 (w), 3005 (s), 2925 (s, br), 2855 (s), 1770 (s), 1600 (w), 1498 (w), 1460 (w), 1448 (m), 1435 (m), 1407 (m), 1380 (m), 1360 (m), 1330 (w), 1302 (w), 1275 (w), 1190–1250 (m, br), 1174 (m), 1030–1150 (s, br), 1000 (w), 980 (m), 940 (m, br), 910 (m), 890 (w), 875 (m), 825 (w), 785 (w, br), 695 (m, br), 659 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (m, 1 H), 1.29 (m, 1 H), 1.47 (ddd, J = 15.2, 12.5, and 3.9 Hz, 1 H), 1.67–1.72 (m, 2 H), 1.81–1.97 (comp m, 4 H), 2.17 (ABq, J_{AB} = 3.5 Hz, $\Delta\nu_{AB}$ = 13.7 Hz, 2 H), 2.39 (ddd, J = 11.5, 6.9, and 4.4 Hz, 1 H), 3.14 (br d, J = 9.2 Hz, 1 H), 3.34 (ABX, J_{AB} = 9.1 Hz, J_{AX} = 6.3 Hz, J_{BX} = 5.9 Hz, $\Delta\nu_{AB}$ = 18.2 Hz, 2 H), 3.69 (ddd, J = 11.8, 5.0, and 2.4 Hz, 1 H), 4.15 (td, J = 11.8 and 2.6 Hz, 1 H), 4.19 (m, 1 H), 4.51 (s, 2 H), 4.59 (dd, J = 6.2 and 3.7 Hz, 1 H), 7.26–7.37 (comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.23, 138.41, 128.35, 127.55, 127.50, 99.64, 74.99, 73.22, 73.11, 63.36, 56.71, 43.29, 35.88, 32.07, 31.45, 30.27, 26.95, 23.47; high-resolution mass spectrum (Cl, NH_3) m/z 364.2125 [$(M + NH_4)^+$, calcd for $C_{20}H_{30}NO_5$ 364.2121]. Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.33; H, 7.58. Found: C, 69.25; H, 7.96.

iib: IR ($CHCl_3$) 3000 (s), 2920 (m, br), 2840 (m), 1760 (s, br), 1720 (s), 1360 (m), 1200–1250 (s, br), 1040 (s, br), 590–600 (m, br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (m, 1 H), 1.27 (m, 1 H), 1.43 (ddd, J = 15.5, 12.4, and 3.9 Hz, 1 H), 1.68 (m, 1 H), 1.79–1.95 (m, 3 H), 1.85 (dd, J = 14.1 and 6.6 Hz, 1 H), 2.00 (ddd, J = 12.5, 7.9, and 3.8 Hz, 1 H), 2.06 (s, 3 H), 2.10 (dd, J = 14.1 and 4.1 Hz, 1 H), 2.15 (br d, J = 14.9 Hz, 1 H), 2.38 (m, 1 H), 3.33 (ABX, J_{AB} = 9.1 Hz, J_{AX} = 6.3 Hz, J_{BX} = 5.9 Hz, $\Delta\nu_{AB}$ = 24.4 Hz, 2 H), 3.72 (ddd, J = 11.5, 6.1, and 4.0 Hz, 1 H), 4.08 (ddd, J = 11.5, 8.4, and 3.4 Hz, 1 H), 4.50 (s, 2 H), 4.58 (dd, J = 6.5 and 3.9 Hz, 1 H), 5.23 (dddd, $J_1 = J_2$ = 6.5 and $J_3 = J_4$ = 4.0 Hz, 1 H), 7.28–7.38 (comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.19, 170.53, 138.49, 128.33, 127.52, 127.43, 98.56, 75.09, 72.99, 72.58, 66.08, 58.40, 43.61, 34.06, 31.39, 30.34, 29.81, 26.94, 23.54, 21.29; high-resolution mass spectrum (Cl, NH_3) m/z 406.2240 [$(M + NH_4)^+$, calcd for $C_{22}H_{32}NO_6$ 406.2230].

iii: IR ($CHCl_3$) 3600 (w, br), 3500 (m, br), 2998 (s), 2923 (s, br), 2880 (m), 2842 (m), 1600 (w), 1480 (w), 1450 (m), 1430 (w), 1410 (m), 1380 (w), 1360 (m), 1170–1250 (s, br), 1030–1120 (s, br), 1020 (w), 1000 (m), 973 (m), 950 (m), 920 (m), 865 (m), 825 (w), 715 (s), 690 (m), 655 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (qd, J = 13.0 and 2.9 Hz, 1 H), 1.28–1.39 (m, 2 H), 1.60–1.64 (m, 2 H), 1.67 (br d, J = 13.8 Hz, 1 H), 1.81–1.96 (comp m, 5 H), 1.97 (dd, J = 14.2 and 3.3 Hz, 1 H), 2.07 (br d, J = 15.6 Hz, 1 H), 2.16 (m, 1 H), 3.31 (d, J

= 6.1 Hz, 2 H), 3.61 (dd, J = 11.4 and 5.0 Hz, 1 H), 4.14–4.22 (comp m, 4 H), 4.50 (s, 2 H), 7.26–7.36 (comp m, 5 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 138.61, 128.33, 127.48, 106.86, 82.43, 75.39, 74.18, 73.03, 64.26, 57.00, 42.07, 36.56, 32.38, 32.11, 30.73, 27.41, 20.38; high-resolution mass spectrum (Cl, NH_3) m/z 349.2018 [$(M + H)^+$, calcd for $C_{20}H_{29}O_5$ 349.2017].

Alcohol iia. Under argon, a solution of diketone **7b** (114.3 mg, 0.332 mmol) in THF (1.5 mL) was cooled to −78 °C, and a 0.05 M THF solution of L-Selectride (11 mL, 1.66 equiv) was added dropwise over 5.5 h. After 40 min at −78 °C, the mixture was neutralized with acetic acid (5 drops), diluted with water, and extracted twice with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (2:3) as eluant, gave 110.1 mg (96% yield) of alcohol iia as an oil.

Epoxide 43. Under argon, a solution of diketone **27** (32.6 mg, 0.0987 mmol) in DMSO–THF (1:1, 1.0 mL) was cooled to 0 °C, and a 0.5 M solution of dimethylsulfoxonium methylide in DMSO (0.236 mL, 1.2 equiv)[40] was added dropwise. The mixture was stirred for 1 h at 0 °C, then quenched with saturated NH_4Cl, and extracted twice with ether. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo. Preparative TLC [0.5 mm × 20 cm × 20 cm, ethyl acetate–hexane (1:2)] afforded 30 mg (88% yield) of epoxide **43** as a colorless oil: IR ($CHCl_3$) 3000 (s), 2940 (s, br), 2860 (s, br), 1455 (m), 1360 (m), 1200–1270 (m, br), 1180 (m), 1160 (m), 1100 (s), 1080 (s, br), 1045 (s), 980 (s), 950 (s), 920 (m), 905 (m), 890 (s), 695 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.90 (qd, J = 14.0 and 4.0 Hz, 1 H), 1.26–1.67 (comp m, 8 H), 1.76–2.02 (m, 4 H), 2.15 (br d, J = 14.0 Hz, 1 H), 2.94 (ABq, J_{AB} = 5.5 Hz, $\Delta\nu_{AB}$ = 10.7 Hz, 2 H), 3.33 (ABX, J_{AB} = 9.1 Hz, J_{AX} = 6.5 Hz, J_{BX} = 5.5 Hz, $\Delta\nu_{AB}$ = 15.5 Hz, 2 H), 3.58 (br dd, J = 11.0 and 3.0 Hz, 1 H), 3.90 (td, J = 11.0 and 4.5 Hz, 1 H), 4.34 (dd, J = 7.5 and 5.0 Hz, 1 H), 4.50 (s, 2 H), 7.26–7.37 (comp m, 5 H); high-resolution mass spectrum (CI, isobutane) m/z 345.2065 [$(M + H)^+$, calcd for $C_{21}H_{29}O_4$ 345.2066], 344.1994 (M^+, calcd for $C_{21}H_{28}O_4$ 344.1988).

Attempted Methylation of Epoxy Ketone 6 (Table II, Entry 4). A solution of lithium tetramethyldiphenyldisilazide[44] (1.2 equiv) in THF (0.5 mL, 0.324 M) was cooled to −78 °C under argon, and a solution of ketone **6** (61.8 mg, 0.172 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C, and then HMPA (0.06 mL, 2 equiv) and methyl iodide 12.9 μL, 1.2 equiv) were added. The solution was warmed to 0 °C for 3 h and then to room temperature. After 15 h, saturated $NaHCO_3$ was added, the mixture was extracted twice with ether, and the combined extracts were washed twice with water, dried over $MgSO_4$, and concentrated in vacuo. Preparative TLC [1 mm × 20 cm × 20 cm, ethyl acetate–hexane (1:3), four developments] furnished 12.3 mg (ca. 18% yield) of a mixture (ca. 1.9:1) of ketone **44** and dimethylated ketone **46**, 18.6 mg (29% yield) of methylated ketone **45**, and 11.6 mg (19% yield) of recovered **6**.

(±)-**44a**: white needles, mp 81–82 °C (hexane); IR ($CHCl_3$) 2860–2940 (s, br), 1720 (s), 1450 (m), 1385 (m), 1325 (s), 1225 (s, br), 1170 (s), 1100 (s, br), 1060 (s), 980 (s), 950 (s), 900 (m, br), 830 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90–1.01 (qd, J = 13.2 and 2.9 Hz, 1 H). 0.96 (d, superimposed on a qd, J = 6.6 Hz, 3 H). 1.32–1.40 (m, 2 H), 1.61 (ddd, J = 13.8, 6.5, and 3.3 Hz, 1 H), 1.78 (br d, J = 12.8 Hz, 1 H), 1.91–1.99 (m, 2 H), 2.09 (br d, J = 14.7 Hz, 1 H), 2.42 (ABq, J_{AB} = 14.7 Hz, $\Delta\nu_{AB}$ = 27.6 Hz, 2 H), 2.55 (m, 1 H), 3.05 (ABq, J_{AB} = 5.2 Hz, $\Delta\nu_{AB}$ = 50.9 Hz, 2 H), 3.30 (d, J = 6.0 Hz, 2 H), 3.73 (dd, $J_1 = J_2$ = 11.2 Hz, 1 H), 3.86 (dd, J = 11.2 and 7.1 Hz, 1 H), 4.33 (br d, J = 2.8 Hz, 1 H), 4.49 (s, 2 H), 7.26–7.36 comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.24, 138.67, 128.31, 127.47, 127.43, 106.83. 75.27. 73.96, 72.94, 70.57, 66.25, 50.27, 47.71, 44.58, 39.11, 31.72, 30.50, 27.08, 22.66, 8.90; high-resolution mass spectrum (CI, isobutane) m/z 373.2017 [$(M + H)^+$, calcd for $C_{22}H_{29}O_5$ 373.2015], 372.1935 (M^+, calcd for $C_{22}H_{28}O_5$ 372.1937).

45a: IR ($CHCl_3$) 2920 (s, br), 2840 (s), 1715 (s), 1445 (m), 1435 (m, br), 1415 (m), 1390 (m, br), 1340 (m, br), 1270 (m), 1060–1110 (s, br), 1045 (s), 970 (s), 895 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.93 (qd, J = 12.5 and 5.0 Hz, 1 H), 1.18 (d, J = 6.5 Hz, 3 H), 1.38 (m, 1 H), 1.50–1.56 (m, 2 H), 1.80–1.90 (m, 2 H), 1.98–2.08 (m, 1 H), 2.14 (br d, J = 14.5 Hz, 1 H), 2.29 (br q, J = 6.5 Hz, 1 H), 2.36 (br d, J = 3.5 Hz, 1 H). 2.58 (m, 1 H), 3.04 (ABq, J_{AB} = 5.2 Hz, $\Delta\nu_{AB}$ = 18.4 Hz, 2 H), 3.30 (ABX, J_{AB} = 9.0 Hz. J_{AX} = 5.8 Hz, J_{BX} = 5.7 Hz, $\Delta\nu_{AB}$ = 14.0 Hz, 2 H), 3.89 (ddd, J = 11.1, 7.6, and 0.9 Hz, 1 H), 4.04 (dt, J = 11.1 and 2.9 Hz, 1 H), 4.32 (br dd, J = 6.3 and 4.2 Hz, 1 H), 4.50 (s, 2 H), 7.26–7.39 (comp m, 5 H); high-resolution mass spectrum (Cl isobutane) m/z 373.2025 [$(M + H)^+$, calcd for $C_{22}H_{29}O_5$ 373.2015], 372.1958 (M^+, calcd for $C_{22}H_{28}O_5$ 372.1937).

46: IR ($CHCl_3$) 2920 (s, br), 2840 (s), 1710 (s, br), 1450 (m), 1380 (m), 1360 (m), 1310 (m), 1210–1280 (m, br), 1125 (m), 1080 (s), 1050 (s), 975 (s), 960 (m), 880 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.82 (m, 1 H), 1.13 (s, 3 H), 1.23 (s, 3 H), 1.34 (m, 1 H), 1.47–1.57 (m, 2 H), 1.79–2.01 (m, 3 H), 2.11 (br d, J = 17.0 Hz, 1 H), 2.22 (dd, J = 15.0 and 8.5 Hz, 1 H), 2.82 (m, 1 H), 2.96 (ABq, J_{AB} = 6.0 Hz, $\Delta\nu_{AB}$ = 20.6 Hz, 2 H), 3.29 (dd, J = 5.5 and 1.5 Hz, 2 H), 3.88 (dd, $J_1 = J_2$ = 9.5 Hz, 1 H), 3.98 (td, J = 11.5 and 4.0 Hz, 1 H), 4.23 (br dd, J = 6.0 and 4.0 Hz, 1 H), 4.50 (s, 2 H), 7.26–7.36 (comp m, 5 H); high-resolution mass spectrum (Cl, NH_3) m/z 387.2203 [$(M + H)^+$, calcd for $C_{23}H_{31}O_5$ 387.2093], 386.2153 (M^+, calcd for $C_{23}H_{30}O_5$ 386.2171).

Attempted Methylation of Epoxy Ketone 6 (Table II, Entry 5). Under argon, a solution of potassium tetramethyldiphenyldisilazide[44] (3 equiv) in THF (1.2 mL, 0.324 M) was cooled to −78 °C, and a solution of ketone **6** (45 mg, 0.125 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture as stirred for 30 min at −78 °C, and then HMPA (0.11 mL, 5 equiv) and methyl iodide (23 μL, 3 equiv) were added. After 8 h, saturated $NaHCO_3$ was added, the mixture was extracted twice with ether, and the combined extracts were washed twice with water, dried over $MgSO_4$, and concentrated in vacuo. Preparative TLC [1 mm × 20 cm × 20 cm, ethyl acetate–hexane (1:3), four developments] gave 5.0 mg (10% yield) of dimethylated ketone **47**, 20.1 mg (41% yield) of dimethylated ketone **46**, and 5.2 mg (12% yield) of recovered **6**.

47: IR ($CHCl_3$) 2920 (s, br), 2840 (s), 1710 (s, br), 1450 (m), 1360–1385 (s, br), 1250–1300 (m, br), 1050–1130 (s, br), 950–995 (s, br), 900 (m), 885 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.93 (m, 2 H), 1.12 (d, J = 6.5 Hz, 3 H), 1.25 (d, J = 7.0 Hz, 3 H), 1.38 (m, 1 H), 1.51 (m, 2 H), 1.83 (br d, J = 14.0 Hz, 1 H), 1.83 (m, 1 H), 2.04 (m, 1 H), 2.14 (br d, J = 14.0 Hz, 1 H), 2.48 (br q, J = 7.0 Hz, 1 H), 3.06 (ABq, J_{AB} = 5.0 Hz, $\Delta\nu_{AB}$ = 15.7 Hz, 2 H), 3.30 (dd, J = 6.0 and 1.5 Hz, 2 H), 3.55 (d, J = 11.0 Hz, 1 H), 4.17 (dd, J = 11.0 and 4.0 Hz, 1 H), 4.34 (br dd, J = 6.0 and 4.0 Hz, 1 H), 4.50 (s, 2 H), 7.26–7.39 (comp m, 5 H); high-resolution mass spectrum (Cl, isobutane) m/z 387.2182 [$(M + H)^+$, calcd for $C_{23}H_{31}O_5$ 387.2171], 386.2128 (M^+, calcd for $C_{23}H_{30}O_5$ 386.2093).

Methylation of Epoxy Ketone 6. Under argon, a solution of LDA (1.96 mmol, 1.15 equiv) in THF (3.0 mL) was cooled to −78 °C, and trimethylchlorosilane (2.16 mL, 10 equiv) was added dropwise. A solution of ketone (+)-**6** (610 mg, 1.70 mmol) in THF (3.0 mL) was cooled to −78 °C and then added dropwise over 10 min. After 3 min, triethylamine (3.56 mL, 15 equiv) was added, and the reaction was quenched with saturated $NaHCO_3$. The mixture was extracted twice with ether, and the combined extracts were washed with brine and dried over Na_2SO_4. Removal of solvent in vacuo gave 760 mg of a yellow viscous oil which comprised an 85:15 mixture of enol silyl ethers **48a** and **48b**, as determined by preparative GLC.

Under argon, a solution of **48a,b** (760 mg) in methyl iodide (4.0 mL) was added to a suspension of *N*-benzyltrimethylammonium fluoride (1.20 g, 4.17 equiv, finely powdered and dried at 0.1 mmHg, 90 °C, 15 h) and 4 Å molecular sieves (3.0 g, powdered and flame-dried at 0.1 mmHg) in methyl iodide (10 mL). After 1 h, the reaction mixture was diluted with dry ether, filtered through a Celite pad, and concentrated in vacuo. The crude products were dissolved in THF (10 mL) and treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (1.0 mL). After 3 days at room temperature, the reaction mixture was diluted with ether, washed with 10% HCl and saturated $NaHCO_3$, and dried over $MgSO_4$. The solvent was removed in vacuo, and the product was purified by flash chromatography, using ethyl acetate–hexane (1:3) as eluant, to give 382.9 mg of (+)-**44a** [60% yield from **6** (three steps), 71% based on recovered **6**], 77.8 mg (12.3% yield) of **45a**, and 101.9 mg (16.7% yield) of **6**, respectively. Ketone (+)-**44a** solidified on treatment with hexane; recrystallization from hexane gave white crystals, mp 69.5–70.5 °C: $[\alpha]^{24}_D$ +102.6° (c 1.31, $CHCl_3$). Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.95; H, 7.58. Found: C, 71.14; H, 7.57.

Similar transformations of (±)-**6** furnished (±)-**44a** in 53% yield as white needles, mp 81–82 °C (hexane).

Methyl Ester iv. Benzyl ether **6** (274 mg, 0.795 mmol) was dissolved in methanol (15 mL), and 10% Pd/C (100 mg) was added. The flask was flushed three times with hydrogen, and the mixture was stirred for 45 min at room temperature under an atmosphere of hydrogen. The reaction was then diluted with ether, filtered through a Celite pad, and concentrated in vacuo to give 217 mg of a colorless, viscous oil, which was used for the next reaction without purification.

A biphasic mixture of the alcohol (217 mg), $NaIO_4$ (680 mg, 4 equiv), CCl_4 (4.0 mL), CH_3CN (4.0 mL), and H_2O (6.0 mL) was cooled to 0 °C, and $RuO_2{\cdot}H_2O$ (4.0 mg, 2.8 mol%) was added. The reaction mixture was warmed to room temperature for 1.5 h and then diluted with water (10 mL). The mixture was extracted three times with methylene chloride, and the combined extracts were dried over $MgSO_4$. After evaporation of solvent in vacuo, the residue was dissolved in hot ether, and the resultant solution was filtered through a Celite pad and concentrated in vacuo. The acid thus obtained was suspended in ether (2.0 mL) and treated with ethereal diazomethane at 0 °C until a yellow color persisted.

The reaction was then quenched with a few drops of acetic acid, and the mixture was diluted with ether, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:2) as eluant, gave 132.0 mg (59% yield, three steps from **6**) of iv as an oil: ^1H NMR (250 MHz, $CDCl_3$) δ 1.22–1.47 (m, 2 H), 1.66 (m, 1 H), 1.80 (ddd, J = 14.5, 12.0, and 4.0 Hz, 1 H), 2.03 (m, 2 H), 2.25–2.67 (comp m, 6 H), 3.07 (ABq, J_{AB} = 5.5 Hz, $\Delta\nu_{AB}$ = 19.2 Hz, 2 H), 3.70 (s, 3 H), 3.97 (dd, J = 12.5 and 7.0 Hz, 1 H), 4.12 (td, J = 12.5 and 3.8 Hz, 1 H), 4.40 (q, J = 3.5 Hz, 1 H).

Acid 49. Benzyl ether (+)-**44a** (291.6 mg, 0.783 mmol) was dissolved in ethyl acetate (4.0 mL), and 10% $Pd(OH)_2$ on carbon (153.2 mg) was added. The flask was flushed three times with hydrogen, and the mixture was stirred for 40 min at room temperature under an atmosphere of hydrogen. The reaction mixture was diluted with ether, filtered through a Celite pad, and concentrated in vacuo to give 229.4 mg of a viscous oil, which was used for the next reaction without purification.

To a biphasic mixture of the alcohol (229.4 mg), $NaIO_4$ (670 mg, 4 equiv), CCl_4 (3.0 mL), CH_3CN (3.0 mL), and H_2O (4.5 mL) at room temperature was added $RuCl_3$ (catalytic amount). After 3 h at room temperature, the mixture was diluted with water and extracted three times with methylene chloride. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography, using ethyl acetate–hexane (2:1, then 1:0) as eluant, afforded 190.2 mg (82% yield) of acid (+)-**49** as a white solid, mp 173–175 °C: $[\alpha]^{20}_D$ +90.3° (c 0.75, $CHCl_3$); IR ($CHCl_3$) 2390–3600 (w, br), 3000–3020 (m, br), 2920 (s, br), 2860 (m), 1705–1730 (s, br), 1435 (m, br), 1430 (w), 1405 (w), 1380 (m), 1320 (m), 1305 (m), 1280 (m, br), 1200–1240 (s, br), 1180 (m), 1160 (s), 1140 (m), 1110 (m), 1096 (s), 1080 (m), 1050 (m), 987 (s), 968 (s), 940 (s), 917 (m), 900 (w), 887 (w), 860 (w), 832 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 3 H), 1.22–1.48 (m, 2 H), 1.65–1.83 (m, 2 H), 2.03 (m, 2 H), 2.31 (br d, J = 15.0 Hz, 1 H), 2.42 (ABq, J_{AB} = 14.7 Hz, $\Delta\nu_{AB}$ = 16.9 Hz, 2 H), 2.55–2.66 (m, 2 H), 3.07 (ABq, J_{AB} = 5.1 Hz, $\Delta\nu_{AB}$ = 21.5 Hz, 2 H), 3.73 (dd, $J_1 = J_2$ = 11.1 Hz, 1 H), 3.89 (dd, J = 11.1 and 7.2 Hz, 1 H), 4.38 (q, J = 3.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.17, 181.12, 106.90, 73.13, 70.25, 66.39, 50.10, 47.59, 44.60, 38.19, 36.84, 29.12, 26.14, 22.08, 8.88; high-resolution mass spectrum (Cl, NH_3) m/z 297.1369 [$(M + H)^+$, calcd for $C_{15}H_{21}O_6$ 297.1338]. Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.79; H, 6.82. Found: C, 60.57; H, 6.63.

Methyl Ester 50. Benzyl ether (+)-**44a** (213 mg, 0.572 mmol) was dissolved in methanol (10 mL), and 10% Pd/C (100 mg) was added. The flask was flushed three times with hydrogen, and the mixture was stirred for 30 min at room temperature under an atmosphere of hydrogen. The mixture was then diluted with ether, filtered through a Celite pad, and concentrated in vacuo to give 182 mg of a colorless, viscous oil, which was used for the next reaction without purification.

A biphasic mixture of the alcohol (182 mg), $NaIO_4$ (367 mg, 3 equiv), CCl_4 (3.0 mL), CH_3CN (3.0 mL), and H_2O (4.5 mL) was cooled to 0 °C, and $RuO_2{\cdot}H_2O$ (3.0 mg, 2.8 mol%) was added. The reaction mixture was warmed to room temperature for 2 h, then diluted with water (10 mL), and extracted three times with methylene chloride. The combined extracts were dried over $MgSO_4$, and the solvent was evaporated in vacuo. The residue was dissolved in hot ether, filtered through a Celite pad, and concentrated in vacuo. The acid thus obtained was suspended in ether (2.0 mL) and treated with ethereal diazomethane at 0 °C until a yellow color persisted. The reaction was then quenched with a few drops of acetic acid, and the mixture was diluted with ether, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:2) as eluant, gave 134.6 mg (76% yield, three steps from **44a**) of (+)-**50** as a white solid. Recrystallization from ether–hexane gave long, colorless needles, mp 121.5–122.5 °C: $[\alpha]^{24}_D$ +123.2° (c 1.78, $CHCl_3$); IR ($CHCl_3$) 2880–3030 (s, br), 1730 (s), 1450 (m), 1440 (m), 1385 (m), 1320 (m), 1310 (s), 1235 (s), 1170 (s), 1120 (m), 1100 (s), 1055 (m), 1030 (m), 995 (s), 980 (s), 945 (s), 920 (w), 910 (w), 895 (w), 830 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 3 H), 1.33 (m, 2 H), 1.64–1.82 (m, 2 H), 1.96–2.05 (m, 2 H), 2.27 (br d, J = 14.8 Hz, 1 H), 2.41 (ABq, J_{AB} = 14.7 Hz, $\Delta\nu_{AB}$ = 18.3 Hz, 2 H), 2.54–2.61 (m, 2 H), 3.06 (ABq, J_{AB} = 5.1 Hz, $\Delta\nu_{AB}$ = 21.9 Hz, 2 H), 3.67 (s, 3 H), 3.72 (dd, $J_1 = J_2$ = 11.0 Hz, 1 H), 3.88 (dd, J = 11.0 and 7.2 Hz, 1 H), 4.37 (br dd, J = 7.4 and 4.4 Hz, 1 H). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.14. Found: C, 61.91; H, 7.16.

Similar transformations of (±)-**44a** furnished (±)-**50** in 68% yield as long, colorless needles, mp 134.5–135.5 °C (ether–hexane).

Reduction of Ketone 50. Under argon, a solution of ketone (+)-**50** (82 mg, 0.264 mmol) in methanol (10 mL) and THF (1.0 mL) was cooled to −20 °C, and sodium borohydride (50 mg, 5 equiv) was added. After 30 min at −20 °C, the reaction was quenched with saturated NH_4Cl. The mixture was extracted three times with ether, and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:2) as eluant, gave 66.8 mg (81% yield) of the less polar axial alcohol (+)-**51** as a white solid and 12 mg (15% yield) of the more polar equatorial alcohol **52** as a colorless, viscous oil. Recrystallization of (+)-**51** from ether–hexane afforded white needles, mp 129–130 °C: $[\alpha]^{24}_D$ +128.1° (c 0.86, $CHCl_3$); IR ($CHCl_3$) 3520 (w), 2880–3000 (m), 1730 (s), 1435 (w), 1305 (w), 1225 (w), 1165 (m), 1160 (m), 1120 (m), 1105 (m), 1075 (m), 1045 (m), 1010 (w), 990 (m), 945 (s), 915 (m), 890 (w), 855 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.89 (d, J = 6.9 Hz, 3 H), 1.25–1.51 (m, 2 H), 1.59 (dd, J = 14.7 and 3.2 Hz, 1 H), 1.64–1.78 (m, 3 H), 1.85 (ddd, J = 14.7, 6.6, and 3.0 Hz, 1 H), 1.97–2.04 (m, 2 H), 2.30 (br d, J = 15.0 Hz, 1 H), 2.63 (m, 1 H), 2.93 (s, 2 H), 3.19 (d, J = 9.0 Hz, 1 H), 3.41 (dd, J = 11.6 and 4.8 Hz, 1 H), 3.69 (s, 3 H), 3.73 (dd, $J_1 = J_2$ = 11.6 Hz, 1 H), 3.81 (br d, J = 9.0 Hz, 1 H), 4.44 (dd, J = 7.3 and 4.0 Hz, 1 H).

Equatorial alcohol 52: IR ($CHCl_3$) 3590 (w), 3490 (w, br), 2880–3000 (s, br), 1730 (s), 1455 (m), 1445 (m), 1435 (m), 1375 (m), 1340 (w), 1305 (m), 1265 (m, br), 1220 (m, br), 1195 (m), 1170 (s), 1110 (m), 1075 (m), 1040 (s), 990 (s), 950 (s), 925 (w), 900 (m, br), 830 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (d, J = 6.5 Hz, 3 H), 1.25–2.07 (comp m, 10 H), 2.28 (br d, J = 15.0 Hz, 1 H), 2.62 (tt, J = 11.8 and 3.5 Hz, 1 H), 2.95 (ABq, J_{AB} = 5.2 Hz, $\Delta\nu_{AB}$ = 7.5 Hz, 2 H), 3.45 (dd, $J_1 = J_2$ = 11.3 Hz, 1 H), 3.52 (dd, J = 11.3 and 5.3 Hz, 1 H), 3.65 (m, 1 H), 3.69 (s, 3 H), 4.34 (dd, J = 6.9 and 3.9 Hz, 1 H).

Similar reduction of (±)-**50** afforded (±)-**51** in 82% yield as a colorless solid, mp 126.5–127.5 °C (ether–hexane), accompanied by (±)-**52** (13% yield) as an oil.

Determination of Enantiomeric Purity of 51. Under argon, (−)-α-methoxy-α-trifluoromethylphenylacetyl chloride [(−)-MTPACl, 50 mg, 8 equiv][58] was added to a solution of (+)-**51** (7.5 mg, 0.024 mmol) and 4-(*N,N*-dimethylamino)pyridine (DMAP, 5 mg) in pyridine (0.5 mL) at room temperature. The reaction mixture was stirred for 14 h at room temperature and *unsym*-*N,N*-dimethylethylenediamine (3 drops) was added. After 15 min, the mixture was diluted with ether, washed with 10% HCl and saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Preparative TLC [0.5 mm × 20 cm × 20 cm, ether–hexane (1:4), two developments] afforded 10.8 mg (85% yield) of a colorless oil. The products comprised a 97.5:2.5 mixture of diastereomers (95% ee), as determined by integration of the methyl doublets centered at δ 0.83 and 0.58 in the 250-MHz ^1H NMR spectrum: ^1H NMR (250 MHz, $CDCl_3$) δ 0.83 (d, J = 7.0 Hz, 3 H), 1.19–1.35 (m, 2 H), 1.56–1.71 (m, 1 H), 1.72 (dd, J = 14.3 and 3.3 Hz, 1 H), 1.85–2.15 (comp m, 6 H), 2.04 (dd, J = 14.3 and 2.3 Hz, 1 H), 2.93 (ABq, J_{AB} = 5.2 Hz, $\Delta\nu_{AB}$ = 4.3 Hz, 2 H), 3.39 (dd, J = 11.4 and 4.1 Hz, 1 H), 3.57 (d, J = 0.65 Hz, 3 H), 3.63 (s, 3 H), 3.84 (dd, $J_1 = J_2$ = 11.4 Hz, 1 H), 4.31 (dd, J = 6.2 and 3.7 Hz, 1 H), 5.22 (br d, J = 2.7, 1 H), 7.40–7.43 (m, 3 H), 7.56–7.59 (m, 2 H). In similar fashion, the (−)-MTPA ester of (−)-**51** was obtained by treatment of (±)-**51** (6.8 mg, 0.0217 mmol) with (−)-MTPACl. Preparative TLC [0.5 mm × 20 cm × 20 cm, ethyl acetate–hexane (1:3), six developments] afforded 5.2 mg of the less polar (−)-MTPA ester of (−)-**51** and 3.7 mg of the more polar (−)-MTPA ester of (+)-**51** (77% combined yield), both as colorless oils. (−)-MTPA ester of (−)-**51**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.58 (d, J = 7.0 Hz, 3 H), 1.25–1.44 (m, 2 H), 1.65–1.97 (comp m, 5 H), 1.74 (dd, J = 15.8 and 3.7 Hz, 1 H), 2.05 (dd, J = 15.8 and 2.5 Hz, 1 H), 2.20 (br d, J = 14.0 Hz, 1 H), 2.39 (tt, J = 11.0 and 3.5 Hz, 1 H), 2.93 (ABq, J_{AB} = 5.2 Hz, $\Delta\nu_{AB}$ = 8.0 Hz, 2 H), 3.32 (dd, J = 11.4 and 4.4 Hz, 1 H), 3.65 (s, 3 H), 3.70 (d, J = 1.2 Hz, 3 H), 3.81 (dd, $J_1 = J_2$ = 11.4 Hz, 1 H), 4.37 (dd, J = 6.7 and 3.7 Hz, 1 H), 5.18 (br d, J = 2.6 Hz, 1 H), 7.38–7.42 (m, 3 H), 7.59–7.63 (m, 2 H).

Phyllanthocin (5a). To a solution of (+)-**51** (42 mg, 0.134 mmol) and DMAP (33 mg, 2 equiv) in pyridine (1.0 mL) at room temperature under argon was added *trans*-cinnamoyl chloride (112 mg, 5 equiv). After 26 h at room temperature, *unsym*-*N,N*-dimethylethylenediamine (1.5 mL) was added. The resultant mixture was then diluted with ether, washed with 10% HCl and saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Preparative TLC [0.5 mm × 20 cm × 20 cm; two plates, ethyl acetate–hexane (2:3), three developments] afforded 48 mg (81% yield, 90% based on recovered **51**) of (+)-phyllanthocin (**5a**) and 4.2 mg (10% yield) of unreacted (+)-**51**, both as white solids. Recrystallization of (+)-**5a** from ether–hexane gave white needles, mp 128–129 °C: $[\alpha]^{24}_D$ +28.0° (c 2.04, $CHCl_3$); IR ($CHCl_3$) 2950 (s), 2880 (m), 1735 (s), 1710 (s), 1640 (m), 1450 (m), 1435 (w), 1380 (w), 1305 (s), 1270 (s), 1250 (m), 1200 (s), 1170 (s, br), 1125 (s), 1075 (m), 1050 (s), 1020 (m), 990 (m), 980 (m), 950 (m), 900 (w), 860 (w), 700 (w), 680 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (d, J = 6.9 Hz, 3 H), 1.14–1.44 (m, 2 H), 1.56–1.79 (m, 3 H), 1.63 (dd, J = 15.3 and 3.1 Hz, 1 H), 1.85–1.98 (m, 2 H), 2.04 (dd, J = 15.3 and 2.7 Hz, 1 H), 2.23 (br d, J = 15.0 Hz, 1 H), 2.42 (tt, J = 12.0 and 3.3 Hz, 1 H), 2.95 (ABq, J_{AB} = 5.3 Hz, $\Delta\nu_{AB}$ = 12.4 Hz, 2 H), 3.28 (s, 3 H), 3.45 (dd, J = 11.4 and 4.7 Hz, 1 H), 4.02 (dd, $J_1 = J_2$ = 11.4 Hz, 1 H), 4.39 (dd, J = 6.5

and 3.5 Hz, 1 H), 5.09 (dd, J = 6.0 and 3.0 Hz, 1 H), 6.48 (d, J = 16.0 Hz, 1 H), 7.36–7.39 (m, 3 H), 7.51–7.56 (m, 2 H), 7.76 (d, J = 16.0 Hz, 1 H). Anal. Calcd for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83. Found: C, 68.13; H, 6.91.

Similar acylation of (±)-**51** furnished (±)-**5a** in 74% yield as colorless prisms, mp 116.5–117.5 °C (ether–hexane).

5-Octynolic Acid (53). Under argon, 5-hexyn-1-ol (30 g, 306 mmol) was added dropwise via a cannula, over 15 min, to a solution of $LiNH_2$ (2.2 equiv) in NH_3 (l, 650 mL) at −78 °C. After 2 h at −78 °C, ethyl iodide (30 mL, 1.2 equiv) was added dropwise over a period of 15 min. The mixture was stirred for 2 h at −78 °C and then warmed to room temperature overnight to distill off the excess NH_3. After dilution with ether, the reaction was quenched with NH_4Cl and crushed ice. The mixture was extracted twice with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Distillation gave 37.1 g (96% yield) of 5-octyn-1-ol as a colorless oil, bp 120–125 °C (25 mmHg).

A solution of 5-octyn-1-ol (35.2 g, 0.279 mol) in acetone (800 mL) was cooled to 0 °C, and Jones reagent (2.67 M solution, 260 mL, 2.5 equiv) was added dropwise. After 1 h at 0 °C, excess Jones reagent was quenched with isopropyl alcohol (40 mL). Following the addition of brine, the mixture was extracted twice with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Distillation afforded 24.22 g (62% yield) of acid **53** as a colorless oil, bp 100–105 °C (0.95 mmHg): IR ($CHCl_3$) 2400–3600 (m, br), 3000 (s), 2970 (s), 2930 (s), 2870 (s), 2840 (m), 1710 (s, br), 1410–1450 (m, br), 1320 (m), 1200–1250 (s, br), 1160 (m), 900–960 (m, br) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (t, J = 7.5 Hz, 3 H), 1.81 (quintet, J = 7.5 Hz, 2 H), 2.14 (m, 2 H), 2.24 (m, 2 H), 2.51 (t, J = 7.5 Hz, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 158.1177 [$(M + NH_4)^+$, calcd for $C_8H_{16}NO_2$ 158.1181].

5-Octynoyl Chloride (54). Under argon, oxalyl chloride (0.93 mL, 1.5 equiv) was added dropwise to a solution of 5-octynoic acid (1.0 g, 7.13 mmol) in dry benzene (10 mL) at room temperature. The reaction mixture was stirred for 1 h at room temperature and then treated with *N,N*-dimethylformamide (1 drop). After an additional 1 h, the resulting yellow solution was concentrated in vacuo; removal of the final traces of solvent at reduced pressure (2.0 h, 2 mmHg) furnished 1.06 g of a yellow oil, which was used for the next reaction without purification.

Imide 56. A solution of oxazolidone (+)-**55**[51] (1.15 g, 6.48 mmol) in THF (15 mL) was cooled to −78 °C under argon, and a solution of *n*-BuLi (1.1 equiv) in hexane (2.85 mL, 2.5 M) was added dropwise. After 15 min at −78 °C, a solution of 5-octynoyl chloride (**54**) (ca. 7.13 mmol) in THF (2.0 mL) was introduced dropwise. The resultant mixture was then stirred for 15 min at −78 °C, warmed to 0 °C for 30 min, quenched with saturated $NaHCO_3$, and extracted twice with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ether–hexane (1:2) as eluant, gave 1.90 g (98% yield) of imide (+)-**56** as a colorless, viscous oil. Treatment with cold hexane resulted in crystallization; recrystallization from ether–hexane gave white crystals, mp 57–58 °C: $[\alpha]^{24}_D$ 37.3° (c 2.46, $CHCl_3$); IR ($CHCl_3$) 2850–3010 (w), 1780 (s), 1700 (s), 1455 (w), 1385 (m), 1370 (w), 1350 (s), 1250 (m), 1195 (s), 1120 (m), 1065 (w), 1040 (w), 995 (w, br), 960 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 3 H), 1.12 (t, J = 7.5 Hz, 3 H), 1.87 (quintet, J = 7.5 Hz, 2 H), 2.12–2.31 (comp m, 4 H), 3.07 (td, J = 7.3 and 3.0 Hz, 2 H), 4.76 (quintet, J = 6.8 Hz, 1 H), 5.68 (d, J = 6.8 Hz, 1 H), 7.29–7.46 (comp m, 5 H). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.36; H, 6.96; N, 4.64.

Alkylated Imide 57. Under argon, a solution of hexamethyldisilazane (21.1 mL, 1.2 equiv) in THF (120 mL) was cooled to −78 °C, and a solution of *n*-BuLi (1.05 equiv) in hexane (35.1 mL, 2.5 M) was added dropwise. The mixture was warmed to 0 °C for 10 min, then cooled to −78 °C, treated with a solution of imide (+)-**56** (25.0 g, 83.5 mmol) in THF (40 mL), and added dropwise over 30 min. After 30 min further at −78 °C, allyl bromide (43.4 mL, 6 equiv) was added, and the resultant solution was allowed to warm to 0 °C over a period of 2.5 h. The reaction mixture was stirred an additional 2.5 h at 0 °C, then quenched with saturated NH_4Cl, and extracted three times with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ether–hexane (1:4) as eluant, gave 26.11 g (92% yield) of imide **57** as a colorless oil. The products comprised a 94:6 mixture of diastereomers **57a** and **57b**, as determined by the peak heights of the methyl doublets at δ 0.86 and 0.92 in the 250-MHz ^1H NMR spectrum: $[\alpha]^{24}_D$ −3.01° (c 1.03, $CHCl_3$); IR ($CHCl_3$) 2850–3070 (w), 1780 (s), 1695 (s), 1640 (sh, w), 1450 (w), 1385 (m), 1370 (sh, m), 1345 (s), 1225 (m, br), 1145 (w), 1120 (m), 1065 (w), 1030 (w), 990 (w), 920 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (d, J = 6.8 Hz, 3 H), 1.12 (t, J = 7.5 Hz, 3 H), 1.72 (m, 1 H), 1.94 (m, 1 H), 2.12–2.26 (comp m, 4 H), 2.28–2.52 (m, 2 H), 4.09 (m, 1 H), 4.79 (quintet, J = 6.8 Hz, 1 H), 5.01–5.08 (m, 2 H), 5.66 (d, J = 6.8 Hz, 1 H), 5.74–5.91 (m, 1 H), 7.27–7.47 (comp m, 5 H). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.12; H, 7.46; N, 4.02.

Alcohol 58. A mechanically stirred suspension of $LiAlH_4$ (17.4 g, 3 equiv) in THF (250 mL) was cooled to −20 °C under argon, and a solution of imide **57a,b** (51.85 g, 0.153 mol) in THF (100 mL) was added dropwise over 30 min. The mixture was stirred for 30 min at −20 °C, warmed to 0 °C for 1.5 h, and then quenched with water (17.4 mL), 15% aqueous NaOH (17.4 mL), and water (52.2 mL). The resultant white precipitate was filtered off and washed with ether, and the filtrate was concentrated in vacuo. The colorless residue was treated with ether–hexane (1:3), and the resultant white precipitate was removed by filtration. Concentration in vacuo and distillation furnished 17.27 g of alcohol (+)-**58** as a colorless oil, bp 84–87 °C (0.35 mmHg). The distillation residue was then treated with ether–hexane (1:3), the resultant white precipitate filtered off, and the filtrate was concentrated in vacuo. Flash chromatography, using ethyl acetate–hexane (1:3) as eluant, afforded an additional 2.77 g of alcohol (+)-**58** [total yield 20.04 g (79%)] along with a small amount of **59a**, both as oils.

58: $[\alpha]^{24}_D$ +7.6° (c 0.81, $CHCl_3$); IR ($CHCl_3$) 3620 (m), 3460 (m, br), 3070 (w), 2850–3000 (s), 1640 (m), 1440 (m, br), 1320 (m), 1220 (m, br), 1030 (s), 995 (m), 915 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.11 (t, J = 7.4 Hz, 3 H), 1.49–1.61 (m, 3 H), 1.73 (m, 1 H), 2.11–2.26 (comp m, 6 H), 3.59 (br s, 2 H), 5.02–5.11 (m, 2 H), 5.73–5.91 (m, 1 H). Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.58; H, 11.03.

59a: IR ($CHCl_3$) 3595 (w), 3240–3540 (w, br), 3060 (m), 3000 (s), 2975 (s), 2920 (s), 2840 (s), 2800 (m), 1635 (m), 1490 (m), 1450 (s), 1375 (m), 1320 (m), 1200–1230 (s, br), 1100 (m), 1060 (m), 1040 (m), 1020 (m), 995 (s), 910 (s), 785 (m), 695 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (d, J = 7.0 Hz, 3 H), 1.13 (t, J = 7.5 Hz, 3 H), 1.35–1.58 (m, 2 H), 1.79 (quintet, J = 6.5 Hz, 1 H), 2.00–2.22 (comp m, 7 H), 2.22 (s, 3 H), 2.35 (d, J = 7.5 Hz, 2 H), 2.77 (m, 1 H), 4.92 (d, J = 5.0 Hz, 1 H), 5.02 (s, 1 H), 5.58 (m, 1 H), 5.67–5.84 (m, 1 H), 7.20–7.35 (comp m, 5 H).

Aldehyde 61. Under argon, potassium hydride (35% dispersion in mineral oil, 16.6 g, 1.2 equiv) was washed three times with dry hexane, and the residual hexane was removed under reduced pressure. A suspension of the grey powder in THF (150 mL) was cooled to 0 °C under argon, and a solution of alcohol (+)-**58** (20.04 g, 0.120 mol) and benzyl bromide (15.8 mL, 1.1 equiv) in THF (50 mL) was added dropwise over a 30-min period. The mixture was stirred for 30 min at 0 °C, then quenched with NH_4Cl, and extracted twice with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 33.46 g of (−)-**60** along with a small amount of **59b**, both as oils.

60: $[\alpha]^{24}_D$ −9.9° (c 1.046, $CHCl_3$); IR ($CHCl_3$) 3060 (m), 3030 (w), 2970 (s), 2915 (s), 2840 (s), 2780 (w), 1635 (m), 1490 (m), 1450 (s), 1360 (m), 1315 (m), 1200–1230 (m, br), 1060–1125 (s, br), 1035 (m), 990 (m), 910 (s), 690 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.10 (t, J = 7.5 Hz, 3 H), 1.47–1.63 (m, 2 H), 1.87 (quintet, J = 6.2 Hz, 1 H), 2.05–2.25 (comp m, 6 H), 3.37 (d, J = 5.6 Hz, 2 H), 4.49 (s, 2 H), 4.98–5.07 (m, 2 H), 5.69–5.85 (m, 1 H), 7.25–7.39 (comp m, 5 H); high-resolution mass spectrum (CI, NH_3) m/z 257.1889 [$(M + H)^+$, calcd for $C_{18}H_{25}O$ 257.1905].

59b: IR ($CHCl_3$) 3060 (m), 3000 (s), 2920 (s), 2850 (s), 2800 (m), 1635 (w), 1490 (m), 1450 (s), 1365 (m), 1320 (m), 1225 (m), 1085 (s, br), 1060 (s, br), 1025 (m), 990 (m), 910 (m), 692 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (t, J = 7.5 Hz, 3 H), 1.12 (d, J = 7.0 Hz, 3 H), 1.25 (q, J = 7.5 Hz, 2 H), 1.52 (m, 1 H), 1.69–1.93 (m, 2 H), 2.01 (m, 2 H), 2.11–2.33 (comp m, 4 H), 2.20 (s, 3 H), 2.85 (quintet, J = 7.0 Hz, 1 H), 4.36 (ABq, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 37.6 Hz, 2 H), 4.38 (d, J = 7.0 Hz, 1 H), 4.89 (br d, J = 7.0 Hz, 1 H), 4.94 (s, 1 H), 5.53–5.70 (m, 1 H), 7.26–7.38 (comp m, 10 H).

A solution of (−)-**60** (33.46 g) in methylene chloride (400 mL) was cooled to −78 °C. Ozone was bubbled into the solution for 85 min, and the reaction mixture then was treated with a solution of triphenylphosphine (25 g, 1 equiv) in methylene chloride (30 mL). After removal of ca. one-half of the solvent in vacuo, additional triphenylphosphine (12.5 g, 0.5 equiv) was added, and the resultant mixture was stirred overnight. Following concentration in vacuo, the residue was treated with ether–hexane (1:3), and the resulting precipitate was removed by filtration. The solid was washed with ether–hexane (1:3) repeatedly. Concentration in vacuo and flash chromatography, with ether–hexane (1:4) as eluant, furnished 24.48 g of aldehyde (−)-**61** (62% overall yield from imide **57**, three steps) as a colorless oil: $[\alpha]^{24}_D$ −22.5° (c 1.046, $CHCl_3$); IR ($CHCl_3$) 2860–3005 (m), 2720 (w), 1700 (w), 1450 (m), 1365 (m), 1320 (w), 1225 (m, br), 1110 (m), 1090 (s, br), 690 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.10 (d, J = 7.5 Hz, 3 H), 1.46–1.71 (m, 2 H),

2.10–2.24 (comp m, 4 H), 2.40–2.54 (m, 3 H), 3.33 (m, 1 H), 3.51 (dd, J = 9.5 and 4.3 Hz, 1 H), 4.48 (s, 2 H), 7.25–7.39 (comp m, 5 H), 9.76 (t, J = 1.0 Hz, 1 H). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.95; H, 8.63.

Aldehyde (−)-12a. To a solution of alkyne (−)-**61** (20.0 g, 77.4 mmol) in hexane (380 mL) were added 5% Pd on $CaCO_3$ (1.90 g, lead-poisoned) and synthetic quinoline (3.80 mL). After flushing three times with hydrogen, the mixture was stirred for 1.75 h under an atmosphere of hydrogen and then filtered through a Celite pad. Removal of solvent in vacuo and flash chromatography, with ether–hexane (1:4) as eluant, furnished 19.7 g (98% yield) of aldehyde (−)-**12a** as a colorless oil: $[\alpha]^{24}_D$ −23.7° (c 1.344, $CHCl_3$).

2-Methyltetrahydropyran-4-one (64). Under argon, a solution of LDA (1.2 equiv) in THF (42 mL) was cooled to −78 °C, and a solution of tetrahydropyran-4-one (**13**) (1.1 g, 11 mmol) and HMPA (2.0 mL, 1 equiv) in THF (30 mL) was introduced dropwise. After stirring for 5 min at −78 °C, methyl iodide (3.4 mL, 5 equiv) in THF (30 mL) was added, and the resultant mixture was warmed gradually to 0 °C. After 2 h at 0 °C, the reaction was warmed to room temperature for 5 min, then cooled to 0 °C, quenched with saturated NH_4Cl, and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ether–pentane (1:4, then 2:3) as eluant, gave 755 mg (60%) of **64** as a colorless oil: IR ($CHCl_3$) 3000 (m), 2970 (m), 2940 (m), 2860 (m), 1717 (s), 1460 (m), 1415 (w), 1380 (s), 1370 (m), 1310 (w), 1270 (m), 1200–1230 (m, br), 1155 (s), 1095 (s), 970 (s), 887 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 3 H), 2.29 (dt, J = 14.2 and 2.7 Hz, 1 H), 2.50–2.61 (comp m, 2 H), 3.23 (dd, $J_1 = J_2$ = 11.0 Hz, 1 H), 3.62 (dd, J = 11.0 and 3.1 Hz, 1 H), 4.07 (m, 1 H), 4.14 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.13, 73.88, 68.44, 45.87, 42.14, 9.53; high-resolution mass spectrum (CI NH_3) m/z 132.1040 [$(M + NH_4)^+$, calcd for $C_6H_{14}NO_2$ 132.1024].

Bromide 65. A solution of LDA (1.3 equiv) in THF (300 mL) was cooled to −78 °C under argon, and chlorotrimethylsilane (72 mL, 5 equiv) was added dropwise. After 5 min, a solution of ketone **64** (12.92 g, 113 mmol) in THF (120 mL) was added dropwise. The mixture was then stirred for 1 min at −78 °C, triethylamine (210 mL, 15 equiv) was added, and the reaction was quenched with saturated $NaHCO_3$. The resultant mixture was extracted twice with ether, and the combined extracts were washed with 0.1 N citric acid and dried over K_2CO_3. Removal of solvent in vacuo gave a yellow viscous oil, which was used without purification.

Under argon, a solution of the enol silyl ethers in THF (90 mL) was cooled to 0 °C and treated with NBS (5.1 g, 1.1 equiv). After 5 min, the reaction was warmed to room temperature, stirred for 30 min, quenched with saturated $NaHCO_3$, and extracted twice with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography, with ether–pentane (1:5) as eluant, furnished 15.75 g (72% yield) of **65** as a mixture of diastereomers: IR ($CHCl_3$) 3010 (w), 2970 (w), 2930 (w), 2840 (w), 1725 (s), 1460 (w), 1385 (w), 1300 (w), 1188 (m), 1170 (w), 1130 (w), 1100 (m), 980 (w), 965 (w), 935 (w), 905 (s), 715 (s, br), 660 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05, 1.06 (diastereomers, d, J = 6.8 Hz, J = 7.7 Hz, 3 H), δ 2.83–4.68 {[2.88 (m), 3.32 (dd, $J_1 = J_2$ = 11.3 Hz), 3.36 (dd, $J_1 = J_2$ = 10.7 Hz), 3.42–3.48 (m), 3.65 (dd, $J_1 = J_2$ = 11.3 Hz), 4.03 (d, J = 2.9 Hz), 4.06 (d, J = 2.6 Hz), 4.13–4.22 (comp m), 4.25 (dd, $J_1 = J_2$ = 2.7 Hz), 4.44 (ddd, J = 11.1, 6.7, and 1.8 Hz), 4.66 (ddd, J = 11.6, 6.7, and 1.2 Hz)], 6 H}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.11, 199.14, 74.82, 74.47, 74.23, 73.69, 52.46, 48.60, 46.96, 41.33, 9.87, 9.52; high-resolution mass spectrum (CI, NH_3) m/z 210.0139 [$(M + NH_4)^+$, calcd for $C_6H_{13}NO_2Br$ 210.0130].

Dihydropyran 63. A solution of bromide **65** (15.75 g, 81.6 mmol), 2,2-dimethyl-1,3-propanediol (10.2 g, 1.2 equiv), and Amberlyst 15 (catalytic amount, 100 mg) in benzene (210 mL) was heated to reflux (ca. 85 °C) with azeotropic removal of water (Dean-Stark trap) for 5 h. The mixture was then cooled to room temperature, filtered, and concentrated in vacuo. Flash chromatography, with ether–pentane (1:5) as eluant, gave 15.9 g (70% yield) of a mixture of diastereomeric bromoketals as an oil.

Under argon, a solution of the bromoketals (15.9 g, 57 mmol) in DMSO (470 mL) was cooled to 0 °C, and t-BuOK (31.9 g) was added in two portions. The mixture was then warmed to room temperature. After 5 h, the solution was poured onto ice and extracted twice with ether, and the combined extracts were washed with brine, dried over K_2CO_3, and concentrated in vacuo. Flash chromatography, with ether–pentane (1:10) as eluant, gave 9.01 g (56% yield, two steps) of **63** as an oil which solidified in the freezer: IR ($CHCl_3$) 3000 (m), 2960 (s, br), 2870 (s), 1740 (s), 1460 (m, br), 1405 (m), 1395 (m), 1375 (m), 1300 (m), 1260 (m), 1245 (s), 1200–1240 (s, br), 1125 (s), 1110 (s, br), 1090 (s), 1060 (s), 1035 (m), 1005 (s), 955 (s), 920 (m), 910 (s), 720–790 (s, br), 600 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (s, 3 H), 1.02 (d, J = 7.0 Hz, 3 H), 1.30 (s, 3 H), 2.37 (m, 1 H), 3.35 (dd, J = 11.3 and 2.3 Hz, 1 H), 3.40 (dd, J = 11.3 and 2.3 Hz, 1 H), 3.68 (d, J = 11.3 Hz, 1 H), 3.72 (d, J = 11.3 Hz, 1 H), 3.84 (dd, J = 10.9 and 8.8 Hz, 1 H), 4.00 (dd, J = 10.9 and 3.4 Hz, 1 H), 5.32 (d, J = 6.5 Hz, 1 H), 6.36 (d, J = 6.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.66, 97.50, 93.98, 70.26, 68.90, 36.57, 30.04, 22.90, 22.18, 9.77; high-resolution mass spectrum (CI, NH_3) m/z 199.1316 [$(M + H)^+$, calcd for $C_{11}H_{19}O_3$ 199.1334].

Diketones 66a,b. A solution of dihydropyran ketal **63** (375 mg, 1.5 equiv) in THF (1.5 mL) was cooled to −78 °C, and t-BuLi (1.5 equiv) in pentane (1.23 mL, 1.5 M) was added dropwise. The mixture was warmed to 0 °C for 1 h and then cooled to −78 °C. A solution of aldehyde **8** (432.9 mg, 1.26 mmol) in THF (2.5 mL) and HMPA (0.33 mL, 1.5 equiv) was added dropwise over 5 min. After 15 min further at −78 °C, the reaction was quenched with saturated $NaHCO_3$. The mixture was extracted twice with ether, and the combined extracts were washed twice with water, washed with brine, and dried over $MgSO_4$. Following concentration in vacuo, the residue was dissolved in methylene chloride (10 mL) and treated with saturated oxalic acid (3.0 mL). The resultant mixture was stirred vigorously for 4 h and quenched with $NaHCO_3$. The methylene chloride layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (2:1 then 5:1) as eluant, gave 452.1 mg (80.0% yield, two steps) of a mixture of alcohols.

Under argon, a solution of oxalyl chloride (0.18 mL, 2 equiv) in methylene chloride (1.0 mL) was cooled to −78 °C, and DMSO (0.286 mL, 4 equiv) was added dropwise. After 5 min, a solution of the alcohols (452.1 mg, 1.01 mmol) in methylene chloride (3.0 mL) was added dropwise, and the resultant milky solution was stirred for 30 min at −78 °C. Triethylamine (1.26 mL, 9 equiv) was added, and after 10 min the reaction mixture was gradually warmed to room temperature and then partitioned between water and methylene chloride. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:2, then 1:1) as eluant, gave 382.3 mg (68% yield from aldehyde **8**, three steps) of enones **66a,b**. Separation by preparative HPLC [ether–hexane (3:1)] then furnished equal amounts of **66a** and **66b**, both as colorless solids.

66a: mp 76–77 °C; IR ($CHCl_3$) 3000 (s), 2940 (s), 2880 (s), 2855 (s), 1710 (s), 1680 (s), 1600 (s), 1480 (w), 1450 (s), 1390 (m), 1375 (m), 1352 (s), 1320 (m), 1310 (m), 1272 (m), 1235 (m), 1190 (m), 1150 (s), 1130 (s), 1090 (s), 1070 (s), 1035 (s), 985 (m), 960 (m), 840 (m), 810 (m), 690 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (m, 1 H), 1.16 (d, J = 7.0 Hz, 3 H), 1.26 (m, 2 H), 1.58 (s, 1 H), 1.63 (m, 1 H), 1.91 (br d, J = 13.2 Hz, 1 H), 1.95–2.04 (m, 2 H), 2.15 (br d, J = 14.0 Hz, 1 H), 2.65 (m, 1 H), 3.05 (dt, J = 12.5 and 2.9 Hz, 1 H), 3.28–3.45 (m, 2 H), 3.30 (s, 3 H), 3.49–3.56 (m, 2 H), 4.23 (dd, $J_1 = J_2$ = 11.3 Hz, 1 H), 4.41 (d, J = 1.9 Hz, 1 H), 4.49 (s, 2 H), 4.57 (dd, J = 11.3 and 5.2 Hz, 1 H), 4.62 (ABq, J_{AB} = 7.4 Hz, $\Delta\nu_{AB}$ = 84.3 Hz, 2 H), 6.03 (s, 1 H), 7.27–7.36 (comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.90, 195.91, 162.91, 138.62, 128.33, 127.49, 105.18, 94.02, 75.32, 73.67, 73.02, 71.92, 71.59, 67.34, 58.95, 49.89, 39.30, 33.38, 31.60, 28.00, 20.64, 10.81; high-resolution mass spectrum (CI, NH_3) m/z 447.2376 [$(M + H)^+$, calcd for $C_{25}H_{35}O_7$ 447.2383].

66b: mp 74–76 °C; IR ($CHCl_3$) 3000 (m), 2920 (m), 2870 (m), 2840 (m), 1710 (s), 1680 (s), 1600 (m), 1490 (w), 1450 (m), 1390 (m), 1375 (m), 1352 (s), 1310 (m), 1275 (m), 1235 (m), 1190 (m), 1150 (s), 1090 (s), 1035 (s), 985 (m), 960 (m), 840 (m), 690 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (m, 1 H), 1.14 (d, J = 7.0 Hz, 3 H), 1.23 (m, 2 H), 1.63 (m, 2 H), 1.91 (br d, J = 6.9 Hz, 1 H), 1.95–2.04 (m, 2 H), 2.15 (br d, J = 14.0 Hz, 1 H), 2.68 (m, 1 H), 3.06 (dt, J = 12.4 and 2.9 Hz, 1 H), 3.29–3.44 (m, 2 H), 3.30 (s, 3 H), 3.47–3.56 (m, 2 H), 4.15 (dd, $J_1 = J_2$ = 11.4 Hz, 1 H), 4.48 (m, 1 H), 4.49 (s, 2 H), 4.60 (dd, J = 11.4 and 5.3 Hz, 1 H), 4.62 (ABq, J_{AB} = 7.4 Hz, $\Delta\nu_{AB}$ = 88.3 Hz, 2 H), 6.04 (s, 1 H), 7.27–7.36 (comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.89, 195.84, 163.14, 138.61, 128.33, 127.48, 105.16, 93.87, 75.33, 73.51, 73.02, 71.57, 67.36, 58.93, 49.67, 39.27, 33.18, 31.57, 27.99, 20.57, 10.58; high-resolution mass spectrum (CI NH_3) m/z 447.2390 [$(M + H)^+$, calcd for $C_{25}H_{35}O_7$ 447.2383].

Spiroketalization of Diketones 66a,b. Under argon, a solution of diketones **66a,b** (26.3 mg, 0.0589 mmol) in methylene chloride (2.0 mL) was cooled to −78 °C, and a solution of Me_2BBr (3 equiv) in methylene chloride (0.29 mL, 0.615 M) was introduced dropwise. After 10 min at −78 °C, the reaction was poured onto a biphasic mixture of THF and saturated $NaHCO_3$ at 0 °C. The resultant mixture was extracted twice with ether, and the combined extracts were washed with brine and dried over $MgSO_4$. Following concentration in vacuo, the residual oil was dissolved in benzene (2.0 mL). A catalytic amount of p-toluenesulfonic acid (ca. 5 mg) was then added, and the solution was stirred for 2 h at

room temperature. After addition of water, the mixture was extracted twice with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was dissolved in THF (2.0 mL), and DBU (1 drop) was added. After 4 days, the mixture was cooled to 0 °C, and ice water was added dropwise. The mixture was extracted twice with ether, and the combined extracts were washed with brine and dried over $MgSO_4$. Solvent evaporation in vacuo and flash chromatography, with ethyl acetate–hexane (1:2) as eluant, then gave 13.6 mg (64% yield) of a mixture of spiroketals. The products comprised a 44:7:1 mixture of **62a–c**, as determined by preparative HPLC [ether–hexane (7:13)].

62a: mp 103–105 °C; IR ($CHCl_3$) 3010 (m), 3000 (m), 2920 (s), 2880 (m), 2850 (m), 1765 (s), 1720 (s), 1600 (w), 1491 (w), 1450 (m), 1380 (m), 1360 (m), 1320 (m), 1230 (m), 1220 (s), 1160 (s), 1135 (m), 1090 (s), 1041 (m), 970 (m), 937 (m), 690 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (d, J = 6.7 Hz, 3 H), 1.09 (m, 1 H), 1.24 (m, 1 H), 1.45 (ddd, J = 15.1, 12.5 and 3.8 Hz, 1 H), 1.81 (m, 1 H), 1.85–1.95 (m, 2 H), 2.13 (dt, J = 14.9 and 1.7 Hz, 1 H), 2.32 (d, J = 14.4 Hz, 1 H), 2.43 (ddd, J = 11.6, 7.1 and 4.3 Hz, 1 H), 2.74 (m, 1 H), 2.96 (dd, J = 14.4 and 0.7 Hz, 1 H), 3.32 (ABX, J_{AB} = 9.2 Hz, J_{AX} = 6.2 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 18.5 Hz, 2 H), 3.79 (dd, $J_1 = J_2$ = 11.1 Hz, 1 H), 3.98 (dd, J = 11.1 and 7.1 Hz, 1 H), 4.50 (s, 2 H), 4.50 (m, 1 H), 7.27–7.36 (comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.76, 205.07, 138.49, 128.36, 127.54, 127.50, 102.73, 74.89, 73.04, 72.64, 66.45, 46.13, 44.81, 43.05, 31.30, 30.04, 26.92, 23.54, 9.05; high-resolution mass spectrum (Cl, NH_3) m/z 376.2094 [$(M + NH_4)^+$, calcd for $C_{21}H_{30}NO_5$ 376.2124]. Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.35; H, 7.33. Found: C, 70.00; H, 7.40.

62b: IR ($CHCl_3$) 3020 (m), 3000 (m), 2920 (s), 2880 (m), 2850 (s), 1768 (s, br), 1728 (s), 1490 (w), 1450 (m), 1383 (m), 1360 (m), 1270–1290 (m, br), 1190–1250 (m, br), 1172 (m), 1130 (s, br), 1089 (s, br), 1045 (s, br), 1030 (m), 980 (m), 690 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (qd, J = 13.0 and 3.2 Hz, 1 H), 1.19 (d, J = 7.0 Hz, 3 H), 1.26 (m, 1 H), 1.46 (ddd, J = 15.2, 12.5 and 3.9 Hz, 1 H), 1.82 (br d, J = 12.8 Hz, 1 H), 1.86–1.93 (m, 2 H), 2.14 (dt, J = 15.0 and 1.8 Hz, 1 H), 2.44 (dd, superimposed on a m, J = 15.3 and 0.8 Hz, 1 H), 2.44 (m, 1 H), 2.58 (m, 1 H), 2.85 (d, J = 15.3 Hz, 1 H), 3.33 (ABX, J_{AB} = 9.2 Hz, J_{AX} = 6.2 Hz, J_{BX} = 5.7 Hz, $\Delta\nu_{AB}$ = 21.7 Hz, 2 H), 3.67 (dd, J = 11.4 and 5.9 Hz, 1 H), 4.18 (dd, J = 11.4 and 5.1 Hz, 1 H), 4.50 (s, 2 H), 4.62 (dd, J = 6.4 and 4.0 Hz, 1 H), 7.27–7.36 (comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.45, 206.02, 138.45, 128.36, 127.55, 127.49, 100.98, 74.88, 73.05, 66.06, 44.31, 44.24, 43.10, 31.33, 30.12, 26.86, 23.68, 12.82; high-resolution mass spectrum (Cl, NH_3) m/z 376.2094 [$(M + NH_4)^+$, calcd for $C_{21}H_{30}NO_5$ 376.2124].

62c: IR ($CHCl_3$) 3020 (w), 3000 (w), 2920 (s), 2880 (m), 2845 (m), 1767 (s), 1720 (s), 1490 (w), 1440 (m, br), 1380 (m), 1325 (m), 1280 (m), 1230 (m, br), 1160 (s), 1100 (s, br), 1042 (m), 990 (m), 805 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (d, J = 6.6 Hz, 3 H), 1.17 (m, 1 H), 1.57 (ddd, J = 14.0, 9.7 and 4.2 Hz, 1 H), 1.75–1.84 (m, 3 H), 1.99–2.07 (m, 2 H). 2.32 (d, J = 13.9 Hz, 1 H), 2.44 (m, 1 H), 2.78 (m, 1 H), 2.82 (dd, J = 13.9 and 0.9 Hz, 1 H), 3.34 (ABX, J_{AB} = 9.1 Hz, J_{AX} = 6.3 Hz, J_{BX} = 6.0 Hz, $\Delta\nu_{AB}$ = 16.9 Hz, 2 H), 3.88 (dd, $J_1 = J_2$ = 11.1 Hz, 1 H), 4.06 (dd, J = 11.1 and 7.1 Hz, 1 H), 4.32 (dd, J = 9.1 and 4.1 Hz, 1 H), 4.50 (s, 2 H), 7.27–7.37 (comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.91, 205.40, 138.40, 128.39, 127.60, 127.53, 102.88, 74.14, 73.15, 72.31, 68.11, 45.13, 44.80, 44.25, 31.58, 30.78, 26.04, 21.68, 9.03; high-resolution mass spectrum (Cl, NH_3) m/z 359.1852 [$(M + H)^+$, calcd for $C_{21}H_{27}O_5$ 359.1858].

Methylenation of 62a. A solution of diketone **62a** (11.9 mg, 0.0332 mmol) in DMSO–THF (1:1, 1.0 mL) was cooled to 0 °C under argon, and a 0.2 M solution of dimethylsulfoxonium methylide in DMSO (0.2 mL, 1.2 equiv) was added dropwise. The mixture was stirred for 1 h at 0 °C, then diluted with saturated NH_4Cl, and extracted twice with ether. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:4) as eluant, gave 9.0 mg (73% yield) of **44a** as a colorless solid.

Methylenation of 62b. Under argon, a solution of diketone **62b** (9.6 mg, 0.0268 mmol) in DMSO–THF (1:1, 1.0 mL) was cooled to 0 °C, and a 0.2 M solution of dimethylsulfoxonium methylide in DMSO (0.16 mL, 1.2 equiv) was added dropwise. The mixture was stirred for 1 h at 0 °C, diluted with saturated NH_4Cl, and extracted twice with ether. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:4) as eluant, gave 7.0 mg (70% yield) of a mixture of epoxides. The products comprised a 9:1 mixture of **44b** and **44a**, as determined by 500-MHz ^1H NMR.

44b: ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (qd, J = 13.1 and 2.9 Hz, 1 H), 1.21 (d, J = 7.3 Hz, 3 H), 1.30–1.40 (m, 2 H), 1.62 (m, 1 H), 1.78 (br d, J = 12.9 Hz, 1 H), 1.93 (m, 1 H), 1.99 (m, 1 H), 2.10 (br d, J = 14.8 Hz, 1 H), 2.28 (d, J = 15.8 Hz, 1 H), 2.46 (m, 1 H), 2.62 (d, J = 15.8 Hz, 1 H), 3.05 (ABq, J_{AB} = 5.1 Hz, $\Delta\nu_{AB}$ = 40.7 Hz, 2 H), 3.30 (d, J = 6.0 Hz, 2 H), 3.59 (dd, J = 11.3 and 1.8 Hz, 1 H), 4.23 (dd, J = 11.3 and 3.6 Hz, 1 H), 4.36 (br d, J = 2.7 Hz, 1 H), 4.49 (s, 2 H), 7.26–7.36 (comp m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.59, 138.67, 128.32, 127.47, 105.91, 75.28, 73.94, 72.95, 70.76, 65.47, 50.29, 44.55, 44.48, 39.10, 31.79, 30.56, 27.08, 22.69, 15.83.

TMS Ethyl Ester 67. Under argon, 1,3-dicyclohexylcarbodiimide (278 mg, 2 equiv) was added to a solution of acid (+)-**49** (337.2 mg, 1.14 mmol), TMS ethanol (0.211 mL, 1.3 equiv), and 4-pyrrolidinopyridine (catalytic amount) in methylene chloride (4.5 mL) at room temperature. After 1 h, the resultant precipitate was filtered off and washed with ether. Concentration in vacuo and flash chromatography, with ethyl acetate–hexane (1:3) as eluant, afforded 376.0 mg (83% yield) of ester (+)-**67** as a white solid, mp 123.5–125.5 °C: $[\alpha]^{24}_D$ +93.1° (c 0.13, $CHCl_3$); IR ($CHCl_3$) 3005 (m), 2950 (s), 2880 (m), 1720 (s, br), 1600 (w), 1450 (w), 1445 (m), 1405 (m), 1380 (m), 1317 (m), 1305 (m, br), 1250 (s), 1200–1270 (m, br), 1162 (s), 1090 (m), 1052 (m, br), 987 (m), 970 (m), 940 (m), 917 (m), 900 (w), 887 (w), 855 (s), 835 (s), 690 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 9 H), 0.97 (d, superimposed on a m, J = 6.6 Hz, 3 H), 0.98 (m, 2 H), 1.21–1.46 (m, 2 H), 1.62–1.82 (m, 2 H), 2.00 (m, 2 H), 2.27 (br d, J = 15 Hz, 1 H), 2.41 (ABq, J_{AB} = 14.5 Hz, $\Delta\nu_{AB}$ = 17.3 Hz, 2 H), 2.57 (m, 2 H), 3.06 (ABq, J_{AB} = 5.1 Hz, $\Delta\nu_{AB}$ = 21.7 Hz, 2 H), 3.72 (dd, $J_1 = J_2$ = 11.1 Hz, 1 H), 3.88 (dd, J = 11.1 and 7.2 Hz, 1 H), 4.15 (m, 2 H), 4.37 (q, J = 3.2 Hz, 1 H); high-resolution mass spectrum (Cl, NH_3) m/z 396.1967 (M^+, calcd for $C_{20}H_{32}O_6Si$ 396.1968). Anal. Calcd for $C_{20}H_{32}O_6Si$: C, 60.56; H, 8.15. Found: C, 60.82; H, 8.27.

Reduction of Ketone 67. Under argon, a solution of ketone (+)-**67** (348.6 mg, 0.879 mmol) in methanol (5.0 mL) and THF (1.0 mL) was cooled to −30 °C and sodium borohydride (166.3 mg, 5 equiv) was added. After 40 min at −30 °C, the reaction was quenched with saturated $NaHCO_3$ and extracted twice with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:4, then 1:2) as eluant, afforded 279.1 mg (80% yield) of the less polar axial alcohol (+)-**68** and 50.4 mg (14% yield) of the more polar equatorial alcohol **69**, both as colorless solids.

Axial alcohol (+)-68: mp 65–67 °C; $[\alpha]^{24}_D$ +99.4° (c 0.51, $CHCl_3$); IR ($CHCl_3$) 3522 (m), 3002 (m), 2952 (s), 2920 (s), 2980 (m), 1720 (s), 1460 (m), 1440 (m), 1380–1440 (m, br), 1360 (w), 1345 (w), 1300 (m), 1248 (s), 1210–1260 (m, br), 1160 (s, br), 1115 (m), 1070 (m), 1050 (m), 1040 (s), 1010 (m), 985 (m), 945 (s), 910 (m), 890 (m), 865 (s), 830 (s), 685 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.05 (s, 9 H), 0.89 (d, J = 6.9 Hz, 3 H), 0.99 (m, 2 H), 1.25–1.50 (m, 2 H), 1.55–1.89 (comp m, 5 H), 2.00 (m, 2 H), 2.28 (m, 1 H), 2.58 (m, 1 H), 2.93 (s, 2 H), 3.18 (br d, J = 10.3 Hz, 1 H), 3.41 (dd, J = 11.6 and 4.8 Hz, 1 H), 3.73 (dd, $J_1 = J_2$ = 11.6 Hz, 1 H), 3.83 (m, 1 H), 4.16 (m, 2 H), 4.44 (q, J = 3.6 Hz, 1 H); high-resolution mass spectrum (Cl NH_3) m/z 398.2124 (M^+, calcd for $C_{20}H_{34}O_6Si$ 398.2125). Anal. Calcd for $C_{20}H_{34}O_6Si$: C, 60.26; H, 8.61. Found: C, 60.08; H, 8.54.

Equatorial alcohol 69: mp 91.5–92 °C; IR ($CHCl_3$) 3590 (w), 3220–3640 (w, br), 2997 (m), 2950 (s), 2920 (s), 2890 (m), 1717 (s, br), 1440–1470 (m, br), 1427 (m), 1370–1400 (s, br), 1335 (m), 1300 (m), 1250 (s), 1200–1260 (m, br), 1162 (s, br), 1100 (m), 1070 (m), 1035 (s, br), 983 (s), 941 (s), 930 (m), 902 (s), 845 (s), 832 (s), 685 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 9 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.99 (m, 2 H), 1.24–1.46 (m, 3 H), 1.27 (dd, superimposed on a m, J = 13.0 and 7.2 Hz, 1 H), 1.52 (m, 1 H), 1.65 (m, 1 H), 1.78 (m, 1 H), 1.90 (dd, J = 13.0 and 4.6 Hz, 1 H), 1.97 (br d, J = 12.0 Hz, 1 H), 2.02 (m, 1 H), 2.26 (br d, J = 14.6 Hz, 1 H), 2.58 (m, 1 H), 2.49 (ABq, J_{AB} = 5.3 Hz, $\Delta\nu_{AB}$ = 16.6 Hz, 2 H), 3.45 (dd, superimposed on a dd, $J_1 = J_2$ = 11.3 Hz, 1 H), 3.51 (dd, J = 11.3 and 5.1 Hz, 1 H), 3.66 (br m, 1 H), 4.17 (m, 2 H), 4.34 (br d, J = 3.4 Hz, 1 H); high-resolution mass spectrum (Cl, NH_3) m/z 398.2113 (M^+, calcd for $C_{20}H_{34}O_6Si$ 398.2125).

Ester 70. To a solution of alcohol (+)-**68** (138.7 mg, 0.348 mmol) and 4-pyrrolidinopyridine (109.8 mg, 2.1 equiv) in triethylamine (1.5 mL) and pyridine (1.5 mL) at room temperature under argon was added *trans*-cinnamoyl chloride (594.1 mg, 10.3 equiv). After 48 h at room temperature, *unsym-N,N*-dimethylethylenediamine (1.0 mL) was added. The resultant mixture was then diluted with ether, washed twice with 10% HCl, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:4) as eluant, gave 173.1 mg (94% yield) of ester (+)-**70** as an oil: $[\alpha]^{24}_D$ +28.9° (c 0.11, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 3000 (m), 2950 (s), 2890 (m), 2870 (m), 1700–1730 (s, br), 1635 (m), 1445 (s), 1435 (w), 1385 (m), 1370 (m), 1340 (m), 1325 (m), 1305 (s), 1275 (s), 1250 (s), 1200 (m), 1165 (s, br), 1120 (m), 1060 (m), 1050 (s), 1015 (m), 987 (m), 975 (m), 945 (m, br), 900 (m), 855 (s), 835 (s), 675 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ −0.05 (s, 9 H), 0.53–0.75 (comp

m, 2 H), 0.85 (d, J = 6.9 Hz, 3 H), 1.00–1.42 (m, 2 H), 1.54–2.05 (comp m, 7 H), 2.21 (br d, J = 14.5 Hz, 1 H), 2.37 (m, 1 H), 2.93 (ABq, J_{AB} = 5.3 Hz, $\Delta\nu_{AB}$ = 11.4 Hz, 2 H), 3.42 (dd, J = 11.2 and 4.3 Hz, 1 H), 3.70–3.92 (comp m, 2 H), 4.00 (dd, $J_1 = J_2$ = 11.2 Hz, 1 H), 4.38 (q, J = 3.3 Hz, 1 H), 5.08 (d, J = 2.6 Hz, 1 H), 6.46 (d, J = 16.0 Hz, 1 H), 7.36 (m, 3 H), 7.51 (m, 2 H), 7.74 (d, J = 16.0 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 528.2535 (M^+, calcd for $C_{29}H_{40}O_7Si$ 528.2543).

Acid 71. Under argon, a solution of ester (+)-**70** (173.1 mg, 0.327 mmol) and anhydrous tetra-*N*-butylammonium fluoride (3.5 equiv) in DMSO (1.5 mL, 0.76 M) was warmed to 50 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with methylene chloride, and then quenched with aqueous pH 7.0 buffer. The mixture was extracted three times with methylene chloride, and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (2:1) as eluant, afforded 127.4 mg (91% yield) of acid (+)-**71** as a white solid, mp 170–171 °C: $[\alpha]^{24}_D$ +58.3° (c 0.42, $CHCl_3$); IR ($CHCl_3$) 2400–3600 (w, br), 3020 (m), 2997 (m), 2950 (s), 2920 (s), 2860 (m), 1690–1750 (s, br), 1630 (m), 1460 (m), 1445 (m), 1380 (m), 1370 (m), 1340 (m), 1303 (s), 1270 (s, br), 1250 (s, br), 1195 (m), 1150–1190 (s, br), 1115 (s), 1065 (m), 1017 (s), 1010 (m, br), 985 (m), 970 (m), 943 (m), 900 (m), 885 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (d, J = 6.9 Hz, 3 H), 1.15–1.47 (m, 2 H), 1.60–1.78 (m, 3 H), 1.92–2.07 (m, 4 H), 2.27 (br d, J = 14.7 Hz, 1 H), 2.45 (m, 1 H), 2.95 (ABq, J_{AB} = 5.3 Hz, $\Delta\nu_{AB}$ = 8.8 Hz, 2 H), 3.45 (dd, J = 11.3 and 4.5 Hz, 1 H), 4.02 (dd, $J_1 = J_2$ = 11.3 Hz, 1 H), 4.41 (q, J = 3.4 Hz, 1 H), 5.12 (d, J = 2.5 Hz, 1 H), 6.48 (d, J = 16.0 Hz, 1 H), 7.30 (m, 3 H), 7.49 (m, 2 H), 7.76 (d, J = 16.0 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 181.40, 166.75, 144.72, 134.31, 130.00, 128.65, 127.98, 118.61, 101.97, 72.46, 71.00, 69.64, 62.85, 50.06, 38.35, 36.77, 34.22, 33.01, 26.46, 26.20, 22.07, 12.69; high-resolution mass spectrum (CI, NH_3) m/z 428.1853 (M^+, calcd for $C_{24}H_{28}O_7$ 428.1835). Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.26; H, 6.60. Found: C, 67.46; H, 6.72.

Diol 72. A solution of epoxide **71** (78.1 mg, 0.148 mmol) and $NaHCO_3$ (40 mg, 3.2 equiv), in *N*-methylpyrrolidinone (1.0 mL) and H_2O (0.15 mL) was heated to 130 °C for 24 h. After cooling to room temperature, the reaction was quenched with water and extracted twice with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (2:3) as eluant, gave 61.8 mg (77% yield) of diol (+)-**72** as an oil: $[\alpha]^{24}_D$ +5.6° (c 0.32, $CHCl_3$); IR ($CHCl_3$) 3530 (w, br), 3000 (m), 2942 (m), 2922 (m), 2824 (m), 1700 (s, br), 1630 (w), 1302 (m), 1270 (m), 1248 (m), 1200 (s), 1170 (m), 1110 (w), 1060 (m), 1040 (m), 985 (s), 850 (m), 830 (w), 720 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.03 (s, 9 H), 0.59–0.72 (comp m, 2 H), 0.89 (d, J = 6.9 Hz, 3 H), 1.21 (qd, J = 13.0 and 2.8 Hz, 1 H), 1.44 (qd, J = 13.2 and 3.4 Hz, 1 H), 1.64–1.75 (m, 3 H), 1.89 (dd, superimposed on a m, J = 15.2 and 3.2 Hz, 1 H), 1.90–1.92 (m, 1 H), 1.98 (m, 1 H), 2.08 (br d, J = 6.9 Hz, 1 H), 2.26 (dd, J = 15.2 and 2.9 Hz, 1 H), 2.34 (m, 1 H), 2.67 (dd, J = 10.1 and 3.6 Hz, 1 H), 2.72 (s, 1 H), 3.43 (dd, J = 10.9 and 10.5 Hz, 1 H), 3.53 (dd, J = 11.3 and 4.7 Hz, 1 H), 3.71–3.76 (m, 1 H), 3.81–3.87 (m, 1 H), 4.04 (dd, superimposed on a dd, J = 10.5 and 3.2 Hz, 1 H), 4.09 (dd, $J_1 = J_2$ = 11.3 Hz, 1 H), 4.15 (dd, J = 7.2 and 3.5 Hz, 1 H), 5.12 (br d, J = 2.6 Hz, 1 H), 6.47 (d, J = 15.9 Hz, 1 H), 7.36 (m, 3 H), 7.51 (m, 2 H), 7.73 (d, J = 15.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.89, 166.64, 144.45, 134.68, 130.05, 128.78, 128.01, 118.92, 106.65, 85.29, 72.97, 69.83, 66.79, 63.17, 62.25, 43.87, 37.07, 35.96, 33.32, 29.77, 26.91, 20.87, 17.10, 12.66, −1.55; high-resolution mass spectrum (CI, NH_3) m/z 547.2714 [(M + H)$^+$, calcd for $C_{29}H_{43}O_8Si$ 547.2731].

Phyllanthocindiol (5b). Under argon, a solution of TMS ethyl ester (+)-**72** (57.4 mg, 0.105 mmol) and anhydrous tetra-*N*-butylammonium fluoride (330 mg, 7 equiv) in DMSO (2.0 mL) was warmed to 55 °C for 4 h. The reaction was cooled to room temperature, diluted with methylene chloride, quenched with aqueous pH 7.0 buffer, and extracted three times with ether. The combined extracts were washed twice with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (5:1, 1–20% MeOH) as eluant, gave 41.5 mg (88% yield) of (+)-phyllanthocindiol (**5b**) as an oil: $[\alpha]^{24}_D$ +29.2° (c 0.80, $CHCl_3$); IR ($CHCl_3$) 3520 (w), 2400–3600 (w, br), 3000 (m), 2950 (m), 2920 (s), 2860 (m), 1700 (s), 1635 (w), 1445 (m), 1305 (m), 1272 (m), 1250 (m), 1200 (s, br), 1176 (s, br), 1120 (m, br), 1060 (m), 1040 (m), 985 (m), 720 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, J = 6.9 Hz, 3 H), 1.25 (m, 2 H), 1.46 (m, 1 H), 1.68 (m, 2 H), 1.75 (ddd, J = 11.0, 6.2 and 4.4 Hz, 1 H), 1.90 (dd, J = 15.2 and 3.3 Hz, 1 H), 1.94–2.01 (m, 2 H), 2.12 (br dd, J = 11.1 and 2.4 Hz, 1 H), 2.27 (dd, J = 15.2 and 3.0 Hz, 1 H), 2.41 (m, 1 H), 2.91 (br s, 1 H), 3.45 (d, J = 11.5 Hz, 1 H), 3.53 (dd, J = 11.2 and 4.5 Hz, 1 H), 4.04 (d, J = 11.5 Hz, 1 H), 4.08 (dd, $J_1 = J_2$ = 11.2 Hz, 1 H), 4.15 (dd, J = 7.7 and 3.7 Hz, 1 H), 5.14 (d, J = 2.7 Hz, 1 H), 6.46 (d, J = 16.0 Hz, 1 H), 7.31 (m, 3 H), 7.48 (m, 2 H), 7.72 (d, J = 16.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.65, 166.76, 144.74, 134.47, 130.05, 128.72, 128.08, 118.77, 106.66, 85.18, 72.82, 69.81, 66.72, 63.14, 43.70, 36.70, 35.77, 33.31, 29.65, 26.38, 20.72, 12.65; high-resolution mass spectrum (CI, NH_3) m/z 447.2053 [(M + H)$^+$, calcd for $C_{24}H_{31}O_8$ 447.2027].

Phyllanthocindiol Methyl Ester (73). A solution of (+)-phyllanthocindiol (**5b**) (10.8 mg, 0.0242 mmol) in ether (2.0 mL) was cooled to 0 °C and treated with ethereal diazomethane until a yellow color persisted. The reaction was then quenched with a few drops of acetic acid, and the mixture was diluted with ether, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:1) as eluant, gave 9.3 mg (83% yield) of phyllanthocindiol methyl ester (**73**) as a colorless solid, mp 126–127 °C: $[\alpha]^{24}_D$ + 3.7° (c 0.88, $CHCl_3$); IR ($CHCl_3$) 3530 (w, br), 3020 (w), 2996 (w), 2940 (s), 2920 (s), 2842 (m), 1721 (s, br), 1700 (s, br), 1635 (m), 1575 (w), 1490 (w), 1445 (m, br), 1430 (m), 1375 (m, br), 1350 (m), 1302 (s), 1270 (s, br), 1250 (m), 1170 (s, br), 1080–1120 (m, br), 1060 (s), 1010 (m), 985 (s), 690–730 (m, br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, J = 6.9 Hz, 3 H), 1.21 (qd, J = 13.2 and 2.7 Hz, 1 H), 1.43 (qd, J = 13.7 and 3.5 Hz, 1 H), 1.63–1.73 (m, 3 H), 1.88 (dd, superimposed on a m, J = 15.2 and 3.2 Hz, 1 H), 1.89–1.91 (m, 1 H), 1.99 (m, 1 H), 2.10 (br d, J = 14.4 Hz, 1 H), 2.28 (dd, J = 15.2 and 3.0 Hz, 1 H), 2.36 (m, 1 H), 2.73 (br s, 2 H), 3.23 (s, 3 H), 3.42 (br d, J = 11.4 Hz, 1 H), 3.54 (dd, J = 11.3 and 4.7 Hz, 1 H), 4.05 (d, superimposed on a dd, J = 11.4 Hz, 1 H), 4.09 (dd, $J_1 = J_2$ = 11.3 Hz, 1 H), 4.14 (q, J = 3.4 Hz, 1 H), 5.11 (d, J = 2.7 Hz, 1 H), 6.47 (d, J = 16.0 Hz, 1 H), 7.34–7.40 (m, 3 H), 7.52 (m, 2 H), 7.73 (d, J = 16.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.17, 166.62, 144.44, 134.66, 130.01, 128.77, 128.00, 118.91, 106.68, 85.30, 72.89, 69.90, 66.79, 63.23, 51.14, 43.87, 36.82, 35.94, 33.30, 29.96, 26.74, 20.83, 12.67; high-resolution mass spectrum (CI, NH_3) m/z 478.2401 [(M + NH_4)$^+$, calcd for $C_{25}H_{36}NO_8$ 478.2445]. Anal. Calcd for $C_{25}H_{32}O_8$: C, 65.19; H, 7.02. Found: C, 65.34; H, 6.90.

Acknowledgment. We are pleased to acknowledge support of this investigation by the National Institutes of Health (National Cancer Institute) through Grant CA 19033. In addition, we thank Drs. George Furst, Patrick J. Carroll, and John Dykins of the University of Pennsylvania Spectroscopic Service Centers for assistance in securing and interpreting high-field NMR spectra, X-ray crystal structures, and mass spectra. Finally, we thank Dr. Christopher S. Shiner for helpful suggestions and critical comments.

Registry No. (+)-**5a**, 62948-37-2; (±)-**5a**, 131102-87-9; (+)-**5b**, 87925-07-3; (+)-**6**, 106569-73-7; (±)-**6**, 131102-88-0; (+)-**7a**, 106624-58-2; (+)-**7b**, 106569-72-6; (±)-**7b**, 131176-66-4; (−)-**8**, 106569-69-1; (±)-**8**, 129261-10-5; **9**, 131067-41-9; (−)-**10a**, 131102-89-1; (±)-**10a**, 131102-90-4; (−)-**10a** (−)-MTPA ester, 131067-42-0; (+)-**10a** (−)-MTPA ester, 131067-43-1; (±)-**10b**, 131067-44-2; (−)-**10c**, 131067-45-3; **11**, 106569-79-3; (−)-**12a**, 131102-91-5; (±)-**12a**, 131102-92-6; **13**, 29943-42-8; **13** ketal, 131067-46-4; **14**, 10138-10-0; **15**, 76367-43-6; **16**, 21676-03-9; **16** mesylate, 79503-95-0; (±)-**17**, 131067-47-5; (±)-**18**, 131067-48-6; (±)-**19**, 131067-49-7; **23a**, 131102-93-7; (±)-**23a**, 131102-94-8; (±)-**23b**, 131067-50-0; **24a**, 131102-95-9; (±)-**24a**, 131102-96-0; (±)-**24b**, 131067-51-1; (±)-**25a**, 131067-52-2; (±)-**25b**, 131067-53-3; (±)-**26**, 131067-54-4; (±)-**27**, 131102-97-1; (±)-**28**, 131067-55-5; (±)-**29**, 131067-56-6; (±)-**30**, 131067-57-7; (±)-**31**, 131067-58-8; (±)-**32a**, 131067-59-9; (±)-**32b**, 131067-60-2; (±)-**33a**, 131102-98-2; (±)-**33b**, 131102-99-3; (±)-**34a**, 131103-00-9; (±)-**34b**, 131103-01-0; (±)-**35a**, 131103-02-1; (±)-**35b**, 131103-03-2; (±)-**36**, 131067-61-3; (±)-**37**, 131103-04-3; (±)-**38**, 131067-62-4; (±)-**39**, 131067-63-5; (±)-**40**, 131067-64-6; (−)-**41**, 106569-71-5; (±)-**41**, 131103-05-4; (−)-**41** (alcohol, isomer 1), 131067-65-7; (−)-**41** (alcohol, isomer 2), 131067-66-8; (±)-**42**, 131067-67-9; (±)-**43**, 131067-68-0; (+)-**44a**, 106569-76-0; (±)-**44a**, 131103-06-5; (+)-**44a** (debenzyl derivative), 131067-69-1; **44b**, 106624-59-3; (±)-**44b**, 131103-07-6; **45a**, 106569-77-1; (±)-**45a**, 131103-08-7; **45b**, 131103-09-8; **46**, 131067-70-4; **47**, 131067-71-5; **48a**, 106569-74-8; **48b**, 106569-75-9; (+)-**49**, 82167-83-7; (+)-**50**, 82167-84-8; (±)-**50**, 131103-10-1; (+)-**51**, 82167-85-9; (±)-**51**, 131103-11-2; (+)-**51** (−)-MTPA ester, 88729-03-7; (−)-**51** (−)-MTPA ester, 131103-12-3; **52**, 88729-02-6; (±)-**52**, 131103-13-4; **53**, 76469-08-4; **54**, 106569-63-5; (+)-**55**, 77943-39-6; (+)-**56**, 106569-64-6; (−)-**57a**, 106569-65-7; **57b**, 131067-72-6; (+)-**58**, 131067-73-7; **59a**, 131067-74-8; **59b**, 131067-75-9; (−)-**60**, 106588-22-1; (−)-**61**, 106569-66-8; (±)-**62a**, 129144-85-0; (±)-**62b**, 129213-17-8; (±)-**62c**, 129213-18-9; (±)-**63**, 129144-81-6; (±)-**63** (lithio derivative), 129144-82-7; (±)-**64**, 131067-76-0; (±)-*trans*-**65**, 131067-77-1; (±)-*cis*-**65**, 131067-78-2; (±)-*trans*-**65** (ketal), 131067-79-3; (±)-*cis*-**65** (ketal), 131067-80-6; (±)-**66a**, 129144-83-8; (±)-**66b**, 129144-84-9; (+)-**67**, 131067-81-7;

(+)-68, 114828-02-3; 69, 131103-14-5; (+)-70, 124516-70-7; (+)-71, 114828-03-4; (+)-72, 124516-71-8; (+)-73, 87925-07-3; (±)-iia, 131067-82-8; (±)-iii, 131067-83-9; (±)-iv, 131067-84-0; (±)-iv alcohol, 131067-85-1; $EtO_2C(CH_2)_2CO_2H$, 131067-86-2; $EtO_2C(CH_2)_2COCl$, 1070-34-4; (Z)-$HO(CH_2)_2CH{=}CHC_2H_5$, 14794-31-1; $Cl(CH_2)_2COCl$, 928-96-1; $CH_2{=}CH_2$, 625-36-5; $Cl(CH_2)_2CO(CH_2)_2Cl$, 74-85-1; $HC{\equiv}C(CH_2)_4OH$, 3592-25-4; $C_2H_5C{\equiv}C(CH_2)_4OH$, 928-90-5; succinic anhydride, 41547-21-1, 108-30-5.

Phyllanthoside–Phyllanthostatin Synthetic Studies. 8. Total Synthesis of (+)-Phyllanthoside. Development of the Mitsunobu Glycosyl Ester Protocol

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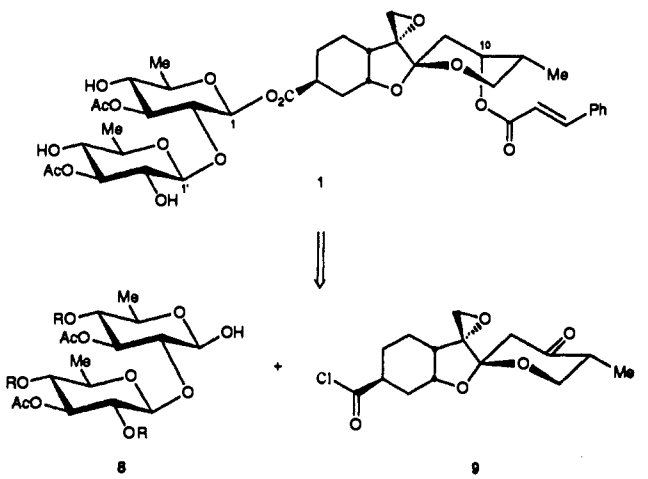
Abstract: The first total syntheses of the antineoplastic glycoside (+)-phyllanthoside (**1**) and the parent disaccharide (−)-phyllanthose (**5**) have been achieved. Stereoselective Koenigs–Knorr coupling of two 6-deoxyglucose derivatives, bromide **54** and alcohol **55**, generated the uncommon $1' \rightarrow 2\beta$ glycosidic linkage of (−)-phyllanthose. A stereochemically convergent Mitsunobu reaction of protected disaccharide **87** with aglycon carboxylic acid **80**, prepared via asymmetric synthesis, then led to **1** of high enantiomeric purity. The Mitsunobu procedure comprises an efficient general method for stereospecific assembly of β-glycosyl esters.

Phyllanthoside (**1**)[1] and phyllanthostatins 1–3 (**2–4**)[1,2] comprise an architecturally novel family of antineoplastic glycosides,[3,4] isolated and characterized by Kupchan, Pettit, and their coworkers. The preceding paper in this issue details our syntheses of the aglycons in this series: phyllanthocin (**6a**), the aglycon methyl ester of **1–3** and phyllanthocindiol (**6b**), derived from phyllanthostatin 3 (**4**).[5,6] Novel features of the four glycoside structures likewise present notable synthetic challenges. The disaccharide units, derived in each case from (−)-phyllanthose (**5**), are coupled to the aglycons by an unusual β-glycosyl ester moiety. Phyllanthose in turn is a dehydro dimer of 6-deoxyglucose, linked via a $1' \rightarrow 2\beta$ glycosidic bond.

Scheme I



Herein we record the completion of the first total syntheses of (−)-phyllanthose (**5**), (+)-phyllanthoside (**1**), and the α-glycosyl ester analogue of **1**; crucial to success was the development of the Mitsunobu glycosyl ester protocol.[7] This venture marked the culmination of our phyllanthocin synthetic studies; it also served as a prelude to the now complete constructions of phyllanthostatins 1–3. A full account of the phyllanthostatin efforts appears in the following paper in this issue.[8]

Phyllanthoside: An Initial Retrosynthetic Analysis. With a viable, stereocontrolled route to (+)-phyllanthocin in hand,[6a] the central issues in the synthesis of phyllanthoside (**1**) became the preparation of the disaccharide and its coupling to the aglycon.

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

(2) The structures of these complex glycosides as well as the parent disaccharide phyllanthose (**5**) were based on detailed analysis of their 400-MHz ^1H NMR, 100-MHz ^{13}C NMR, and mass spectra, see: (a) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P. *Can. J. Chem.* **1982**, *60*, 544. Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P.; Schmidt, J. M. *Can. J. Chem.* **1982**, *60*, 939. Pettit, G. R.; Cragg, G. M.; Niven, M. L.; Nassimbeni, L. R. *Can. J. Chem.* **1983**, *61*, 2630. Further evidence for phyllanthose (**5**) derived from the X-ray crystal structure of phyllanthose peracetate (**7**), see: (b) Pettit, G. R.; Cragg, G. M.; Suffness, M. I.; Gust, D.; Boettner, F. E.; Williams, M.; Saenz-Renauld, J. A.; Brown, P.; Schmidt, J. M.; Ellis, P. D. *J. Org. Chem.* **1984**, *49*, 4258. (c) Pettit, G. R.; Cragg, G. M.; Suffness, M. I. *J. Org. Chem.* **1985**, *50*, 5060.

(3) See, for example: Powis, G.; Moore, D. J. *Proc. Assoc. Cancer Res.* **1985**, *26*, 354. Also, see: refs 1 and 2.

(4) Phyllanthoside (**1**) and phyllanthostatin 1 (**2**) are in phase 1 clinical trials under the auspices of the NCI-EORTC. Both compounds inhibit human breast cancer cell lines with ED50s (μg/mL) against P388 of 0.27 and 0.19, respectively. Against P388 in vivo, the respective T/C values are 152% and 162–190% at doses of 6.68 and 4–16 mg/kg. Personal communication from Dr. Charles K. Grieshaber, Chief, Toxicology Branch, Developmental Therapeutics Program, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.

(5) Smith, A. B., III; Fukui, M.; Vaccaro, H. A.; Empfield, J. R. *J. Am. Chem. Soc.*, preceding paper in this issue.

(6) For the preceding papers in this series, see: (a) (+)-Phyllanthocin (**6a**): Smith, A. B., III; Fukui, M. *Abstracts of Papers*, 187th National Meeting of the American Chemical Society, St. Louis, MO; American Chemical Society: Washington, DC, 1984; ORGN 6. Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. Smith, A. B., III; Empfield, J. R.; Vaccaro, H. A. *Tetrahedron Lett.* **1989**, *30*, 7325. (b) (+)-Phyllanthoside (**1**): Smith, A. B., III; Fukui, M., Rivero, R. A. *Abstracts of Papers*, 189th National Meeting of the American Chemical Society, Miami Beach, FL; American Chemical Society: Washington, DC, 1985; ORGN 82. Smith, A. B., III; Rivero, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 1272. (c) (−)-Phyllanthostatin 1 (**2**): Smith, A. B., III; Hale, K. J.; Vaccaro, H. A. *J. Chem. Soc., Chem. Commun.* **1987**, 1026. (d) (+)-Phyllanthostatin 2 (**3**): Smith, A. B., III; Hale, K. J.; Vaccaro, H. A. *Tetrahedron Lett.* **1987**, *28*, 5591. (e) (+)-Phyllanthostatin 3 (**4**) and (+)-phyllanthocindiol methyl ester (**6b**): Vaccaro, H. A.; Rivero, R. A.; Smith, A. B., III *Tetrahedron Lett.* **1989**, *30*, 1465.

(7) Smith, A. B., III; Hale, K. J.; Rivero, R. A. *Tetrahedron Lett.* **1986**, *27*, 5813.

(8) Smith, A. B., III; Hale, K. J.; Vaccaro, H. A.; Rivero, R. A. *J. Am. Chem. Soc.*, following paper in this issue.

0002-7863/91/1513-2092$02.50/0