# Total Synthesis of (+)-Phyllanthocin. Introduction of Intramolecular Hydroformylation for Complex Molecule Functionalization

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A 17-step total synthesis of (+)-phyllanthocin (**1a**) is described. Application of Sharpless' asymmetric epoxidation reaction provided access to the diastereo- and enantiomerically pure epoxy ketone **9**, a partner in a crossed aldol construction. A notably rapid and high-yielding spiroketal equilibration leading to the tetracyclic intermediate **2** was effected with HF in acetonitrile. A Rh(I)-catalyzed hydroformylation was used to introduce the C3 functionality. Studies of intramolecular delivery of the rhodium nucleus to the concave face of the C3–C4 olefin led to a substantial improvement in yield and regioselectivity over the intermolecular version.

The isolation and structural assignment of (+)-phyllanthocin (**1a**), a methanolysis product of the bisabolane glycoside phyllanthoside (**1b**), was reported by Kupchan in 1977.[1] The genus *Phyllanthus* has a history of human medicinal usage, including the primitive treatment of cancer.[2] Although the original plant source of phyllanthoside was believed to be *Phyllanthus brasiliensis* Muell., this was revised by Pettit[3] to *P. accuminatus* Vahl. Root extracts of this Central American plant yielded phyllanthoside (**1b**) and three related antineoplastic glycosides, phyllanthostatins 1, 2, and 3, the first two of which have in common with phyllanthoside the phyllanthocin sesquiterpene aglycon.[3] Pettit further devised a large-scale isolation protocol by which 1.56 metric tons of chipped stems of *P. accuminatus* yielded 215.6 g (0.014%) of phyllanthoside (**1b**). Recent studies by the U.S. National Cancer Institute have focused on the differential cytotoxicity of phyllanthoside toward breast tumors in the human tumor colony forming assay (50% response rate at 1 $\mu$g/mL).[4] The aglycon phyllanthocin (**1a**) retains none of the biological activity of phyllanthoside (**1b**), which itself suffers from rapid metabolic degradation.[4] To date, five different synthetic routes to this class of natural products have been devised.[5] We report herein the full details of our synthesis of (+)-phyllanthocin (**1a**).[6]

Several structural features are apparent upon inspection of the phyllanthocin structure **1a** (Scheme I). Seven asymmetric centers are broadly distributed about the tetracyclic nucleus. The central tetrahydrofuran ring has one vicinal and two spiro fusions, and all the carbon atoms of this heterocyclic subunit are stereogenic. Noteworthy is the fact that the C7-spiro epoxide moiety has an endo-oriented oxygen relative to the cis-fused C1–C8 bicyclic subunit, thus indicating a poor prognosis for a standard C7 olefin epoxidation tactic.[7] The C8 spiroketal moiety, prevalent in many molecules of current synthetic and biological interest, is an obvious focal point as well.

The antithetic outline presented in Scheme I reveals the overall strategy of our successful approach. Two key features are illustrated in the functionally simplified tetracyclic structure **2**. First, an operating assumption was that the desired C8 spiroketal configuration would prevail under thermodynamic control. The alternative C8 epimer would not enjoy the favorable combination of anomeric stabilization,[8] the indicated intramolecular hydrogen bond and the equatorially oriented C11 methyl group as in **2**. Secondly, we sought to avoid the complication of accommodating the stereofunctional presence of the C3 carbomethoxy group until the end stages of the synthesis. Attending this decision was the need to develop a regioselective means of functionalizing the C3 site in **2** with oxidized carbon. The exo, equatorial orientation[9] of the C3 carbomethoxy group in **1a** would ultimately be of importance (vide infra) to the success of this gambit. The convergency via directed aldol coupling[10] between the enolate of epoxy ketone **3** and aldehyde **4** required high enantiomeric purity for both coupling partners to avoid diastereomeric complexity in the product. Also of concern was the compatibility of the sensitive 1,1-disubstituted C7 epoxide in **3** with the generation and reactivity of the C8–C9 enolate. Since a primary element of our approach was based upon the production of optically active epoxide **3** from racemic allylic alcohol **5** via Sharpless' asymmetric epoxidation[11] and homologation, the survival of the epoxide

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(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) (a) Usher, G. *A Dictionary of Plants Used by Man*; Constable and Co.: Great Britain, 1974; p 455. (b) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P. *Can. J. Chem.* **1982**, *60*, 544.

(3) 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 and references cited therein.

(4) These data were provided to us in January 1987 by Dr. Gordon M. Cragg, Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, NIH, Bethesda, MD. We thank him for his encouragement and assistance.

(5) (a) McGuirk, P. R.; Collum, D. B. *J. Am. Chem. Soc.* **1982**, *104*, 4496. (b) Williams, D. R.; Sit, S.-Y. *Ibid.* **1984**, *106*, 2949. (c) McGuirk, P. R.; Collum, D. B. *J. Org. Chem.* **1984**, *49*, 843. (d) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *Ibid.* **1985**, *50*, 3420. (e) Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237. (f) Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. (g) Smith, A. B., III; Rivero, R. *Ibid.* **1987**, *109*, 1272. See also Smith, A. B., III; Hale, K. J.; Vaccaro, H. A. *Tetrahedron Lett.* **1987**, *28*, 5591. Vaccaro, H. A.; Rivero, R. A.; Smith, A. B., III *Tetrahedron Lett.* **1989**, *30*, 1465. (h) Martin, S. F.; Dappen, M. S.; Dupre, B.; Murphy, C. J. *J. Org. Chem.* **1987**, *52*, 3706.

(6) For preliminary communications of our efforts in this area, see refs 5d,e.

(7) In fact, all of the syntheses of this class of compounds have avoided such a tactic, with all (5b,f,g,h) but two (5a,d) invoking epoxidation via a methylene transfer to the exo face of a C7 ketone.

(8) For an excellent discussion of the anomeric effect, see: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; Chapter 2.

(9) Although attached to a cis-fused bicyclic subunit with potential conformational mobility, the equatorial orientation of the C3 carbomethoxyl group is reflected in the crystal structure.[1] Also, a conformational flip of the cyclohexane would cause a loss of favorable conformational features about the tetrahydropyran nucleus.

(10) For recent reviews of stereoselective aldol reactions, see: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Mukaiyama, T. *Org. React. (N.Y.)* **1982**, *28*, 203. (c) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Durst, T., Buncel, E., Eds.; Elsevier: Amsterdam, 1984; Vol. II, Part B, p 177. (d) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 111.

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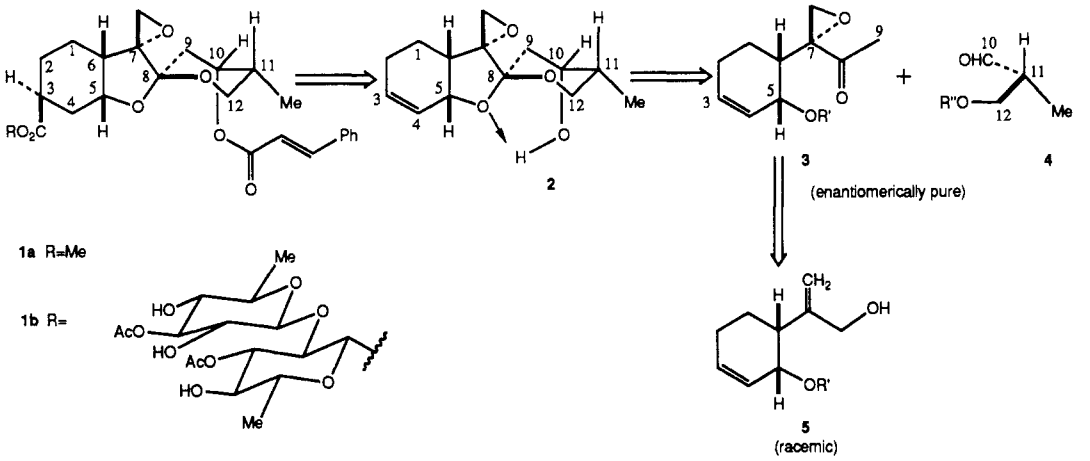
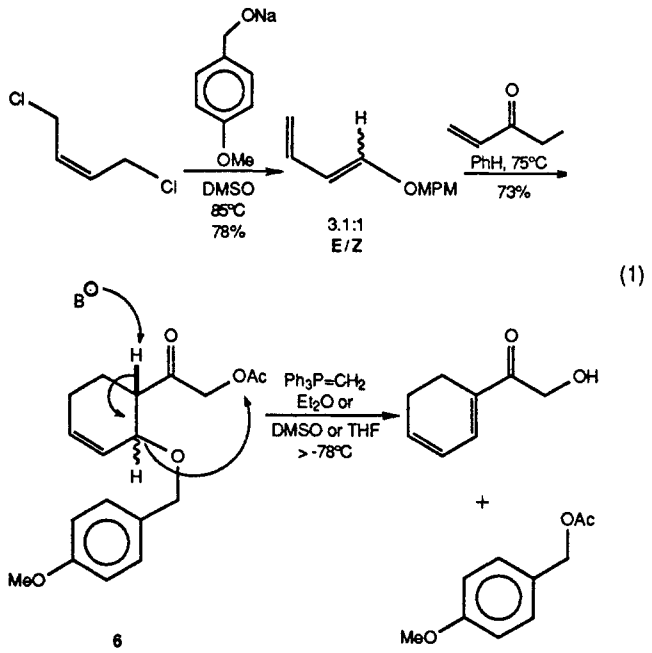
**Scheme I**




moiety to numerous subsequent functional manipulations was critical.

The initial need for a functionalized cyclohexene such as **5** suggested a Diels–Alder construction, in which a dienyl ether and acetoxymethyl vinyl ketone[12] would combine. The resultant ether (OR′ in **5**) ultimately would have to be cleaved to an alcohol in a molecule intolerant of reducing agents, acids, bases, and nucleophiles. The *p*-methoxybenzyl [or *p*-*m*ethoxy*p*henyl*m*ethyl (MPM)] ether[13] promised to be removable under neutral oxidative conditions and was thus incorporated in the Diels–Alder diene by a modification of a procedure developed by Everhardus (eq 1).[14] Attempted conversion of *cis*-1,4-dichloro-2-butene to the bis-ether with either lithium or sodium *p*-methoxybenzyl oxide in THF gave no product, but reaction in DMSO at room temperature gave the pure *E*-dienyl ether in 25% yield. A higher yield (78%) is available at the expense of stereoselectivity (*E*:*Z* 3.1:1) by conducting the reaction at 85 °C. Separation of these was unnecessary in that only the *E* isomer reacted with acetoxymethyl vinyl ketone at 75 °C in benzene; the minor *Z*-dienyl ether was recovered unchanged. The cycloadduct was obtained as a 3.7:1 mixture of cis and trans racemates **6** (eq 1) arising via competing endo and exo transition states.




As illustrated in eq 1, the Wittig methylenation of ketone **6** was initially plagued by a β-elimination/transacylation process. Fortunately, this problem was minimized by conducting the Wittig reaction in THF at −100 °C, with an enhancement of the cis/trans ratio to 5.9:1, possibly by selective eliminative destruction of *trans*-**6**. After cleavage of the acetate with methanolic $K_2CO_3$, the racemic alcohol **7** (Scheme II) was obtained in 61% overall yield from **6**, free of diastereomeric content.

Application of the tartrate-mediated Ti(IV)-catalyzed asymmetric epoxidation procedure of Sharpless[11] to the racemic allylic alcohol **7** was attempted in two modes. Kinetic resolution[15] of this substance failed in that the rate differential for the epoxidation of the enantiomers of **7** was insufficient for synthetic utility. However, epoxidation to complete consumption of **7** with L-(+)-diethyl tartrate/Ti(O-*t*-Bu)$_4$/*t*-BuOOH in methylene chloride at −23 °C gave the diastereomeric, optically active epoxy alcohols, which were separable by chromatography on silical gel. Under these conditions[16] the combined yield of diastereomeric epoxides was 95%, with a 4% yield of *tert*-butoxide-opened epoxide. The desired epoxy alcohol (mp 73–73.5 °C) was determined to have an enantiomeric excess of ≥95% based on 400-MHz $^1$H NMR analysis of the Mosher's ester derivative.[17] Swern oxidation[18] of the desired epoxy alcohol diastereomer gave the aldehyde **8**, which was converted in two standard steps (71% overall) to the crystalline, homochiral epoxy ketone **9** (mp 86–86.5 °C).

The aldehyde partner **4** (R′ = $SiMe_2$-*t*-Bu) for the crossed aldol coupling was readily obtained in 85% yield

(11) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p 193.

(12) Hennion, G. F.; Kupiecki, F. P. *J. Org. Chem.* **1953**, *18*, 1601.

(13) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(14) Everhardus, R. H.; Peterse, A.; Vermeer, P.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 90.

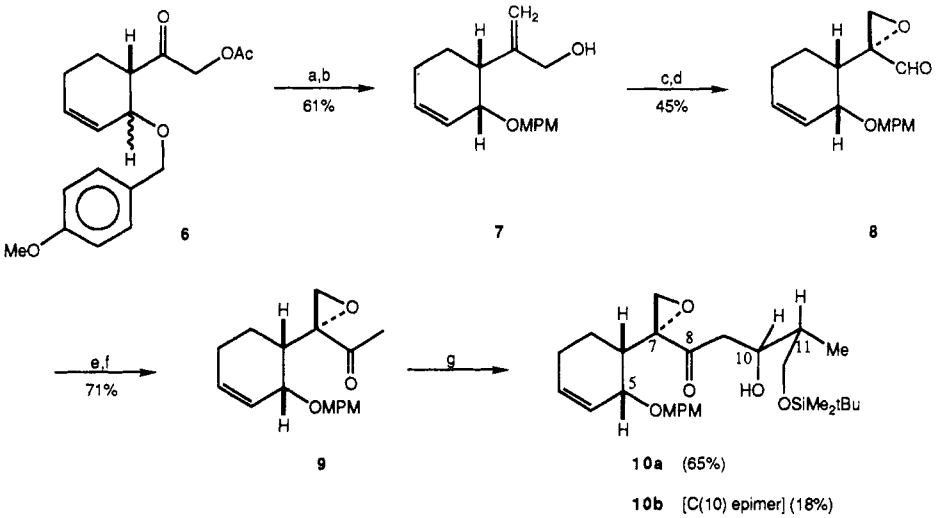
(15) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(16) Lu, L. D.-L.; Johnson, R. A.; Finn, M. G.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 728.

(17) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732. X-ray crystallographic analysis of a derivative of the undesired diastereomer and chemical correlation confirmed the structure of the desired epoxy alcohol. We thank Dr. Lukasz Lebioda (University of South Carolina, Department of Chemistry) for this X-ray structure determination.

(18) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

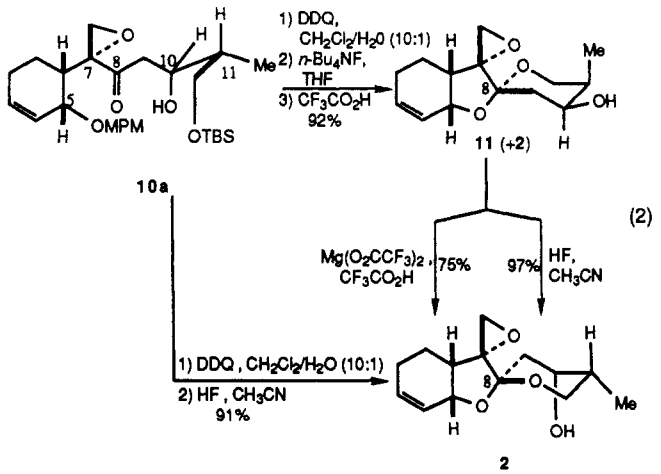
**Scheme II**[a]




[a] (a) $Ph_3P{=}CH_2$, THF, −100 → 25 °C; (b) $K_2CO_3$, MeOH, 25 °C, 90 min; (c) *t*-BuOOH, L-(+)-DET, $Ti(O\text{-}t\text{-}Bu)_4$, $CH_2Cl_2$, −23 °C, 5.5 h; chromatographic separation of diastereomers; (d) $(COCl)_2$, DMSO, $CH_2Cl_2$, −60 °C; $Et_3N$, −60 → 25 °C; (e) 5 equiv of MeLi, $Et_2O$–THF, −78 °C, 7 min; (f) $(COCl)_2$, DMSO, $CH_2Cl_2$, −55 °C; $Et_3N$, −55 → 25 °C; (g) 1.1 equiv of LDA, THF, −78 °C, 50 min; 4 (R″ = $SiMe_2$-*t*-Bu), THF, −78 °C, 10 min.

from commercially available (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate. Generation of the enolate of **9** with LDA in THF at −78 °C followed by the addition of the C10–C12 aldehyde **4** gave an easily separable 3.6:1 mixture of aldol products **10** in 83% yield, plus 11% recovery of ketone **9**. Our concerns about the ability of the 1,1-disubstituted epoxide moiety to withstand the conditions for this coupling were thus unfounded. The major aldol product **10a** proved to have the correct C10 configuration for direct elaboration to phyllanthocin.[19] The minor C10 diastereomer **10b** was also usable for the production of phyllanthocin (vide infra).

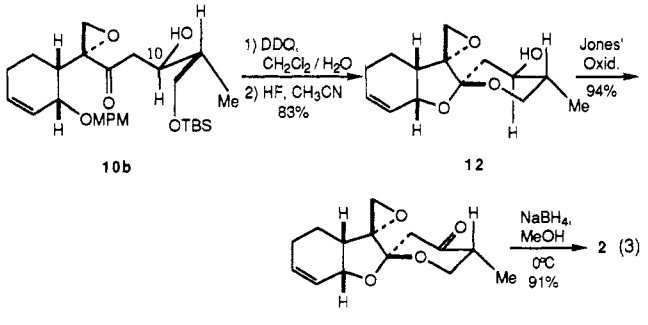
The establishment of the C8 spiro ketal moiety was initiated by oxidative cleavage of the MPM ether with DDQ in $CH_2Cl_2/H_2O$ (eq 2).[13] The resulting mixture of




(2)

five-membered hemiacetals was treated directly with *n*-$Bu_4NF$ to cleave the TBS ether, and cyclization with trifluoroacetic acid gave a 3.8:1 mixture of spiro ketals **11** and **2** in 92% overall yield from **10a**. The $^1H$ NMR and IR spectra for these products clearly indicated that the unwanted diastereomer **11** was the major product. Especially characteristic in these and model compounds is the intramolecular hydrogen bond between the axial C10 hydroxyl group in **2** and the axial spiro ketal oxygen. Applying a variant of Williams' procedure[5b] for isomerizing a closely related spiro ketal effected the conversion of **11** to **2** in 75% yield. However, a more direct and satisfying spiroketalization procedure was discovered. If, after cleaving the MPM ether in **10a** as before, the hydrolysis of the C12 TBS ether was done with 5% aqueous HF in acetonitrile, the desired spiroketal **2** was obtained in 91% overall yield from **10a**. That this spiroketalization occurred directly under equilibrium control is supported by the observation by TLC of diastereomer **11** at short reaction times (~3 min), but within 10 min at 25 °C only the epimer **2** could be detected. Moreover, subjection of purified, undesired epimer **11** to the $HF/CH_3CN$ conditions led in 1 min to complete conversion to **2** in 97% yield.

A sequence by which the minor isomer **10b** resulting from the crossed aldol coupling was converted in high yield to **2** is summarized in eq 3. Sequential cleavage of the MPM and TBS ethers gave directly the spiroketal **12** in 83% yield. Inversion of the C10 equatorial alcohol was accomplished in a straightforward manner by Jones' oxidation (94%) and sodium borohydride reduction to give a 10.5:1 ratio of **2** (91%) and **11** (9%), separable by flash chromatography[20] on silica gel.

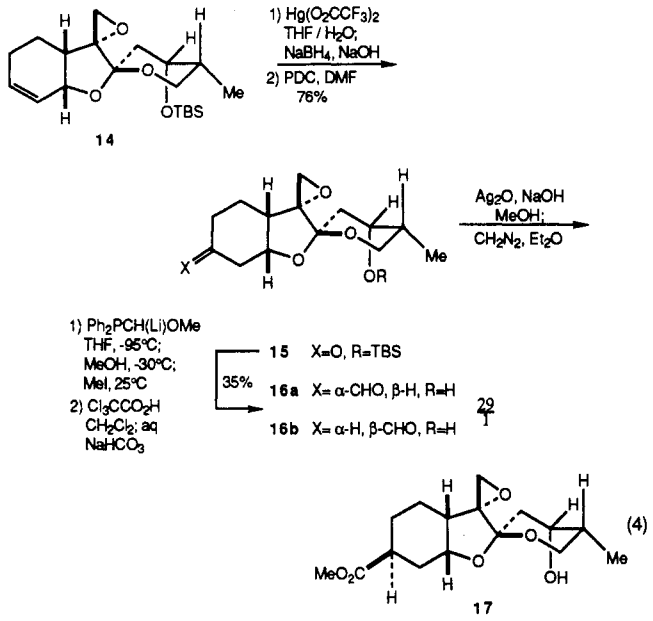



Having developed a sequence that provided gram quantitities of the tetracyclic spiroketal **2**, it remained to put in place the C3 carbomethoxy group. After protection

(19) This diastereoselectivity is similar in degree and direction to a related aldol condensation reported by Masamune: Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

of the C10 axial alcohol as the *tert*-butyldimethylsilyl ether (**14**, eq 4), regioselective functionalization of the cyclo-

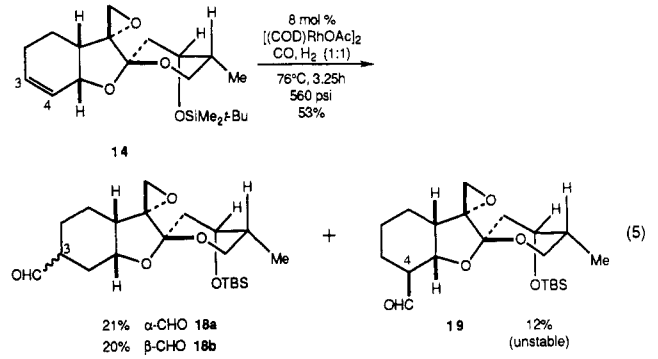



hexene subunit was attempted. Hopeful that a steric preference for C3 metalation would outweigh the olefin polarization imparted by the allylic oxygen, we looked first at methods for hydrometalation/carbonylation. Upon subjection to the usual conditions developed by Schwartz[21] for hydrozirconation [$(Cp)_2Zr(H)Cl$, PhH, alkene, 25 °C], the substrate **14** was simply unreactive. More forcing conditions (65 °C) led to extensive degradation of the substrate. Likewise, no reaction could be effected between **14** and 9-BBN, attempted within the framework of a hydroboration/carbonylation tactic. This apparent lack of reactivity may be due to the presence of multiple Lewis basic sites in **14** competing effectively but unproductively for the electrophilic reagents, or the conflicting steric and electronic features of the allylic ether moiety in **14** may be muting its reactivity.

Limited success was achieved via conversion of **14** to the corresponding C3 ketone **15** (eq 4) and homologation. Oxymercuration/demercuration of **14** gave a 1.7:1 mixture of epimeric C3 alcohols that converged to a single ketone **15** in 76% overall yield upon oxidation with pyridinium dichromate[24] in DMF. After failing to homologate this ketone via numerous methods,[25] we found that the Corey–Tius procedure for converting **14** to the homologous methyl enol ether mixture followed by hydrolysis afforded the C3$\alpha$- and C3$\beta$-formyl compounds **16a** and **16b** (29:1) in yields peaking at 35%. Oxidation of the axial aldehyde **16a** with $Ag_2O$ in alkaline MeOH[27] was accompanied by partial epimerization to give, after esterification, a 2:1 mixture of descinnamoylphyllanthocin (**17**) and its C3 epimer. Although this formally completed a synthetic route to (+)-phyllanthocin, this method for C3 functionalization of **14** was unreliable and unesthetic. A more direct olefin functionalization method was sought.

Catalytic hydroformylation[28] offered, at least in principle, a most attractive solution to this problem. Typically involving a rhodium- or cobalt-catalyzed addition of hydrogen and carbon monoxide to a linear terminal olefin, the hydroformylation process leads to a mixture of linear (usually desired) and branched saturated aldehydes. The linear/branched isomer ratio is influenced by a number of factors, including catalyst, temperature, pressure, concentration, and solvent. The presence of excess phosphine ligand is notably effective for increasing the linear/branched aldehyde ratio.

The hydroformylation substrate **14** (eq 5) represented an unusually complicated test of this process in terms of functionality and stereochemistry. Much experimentation led to the partially satisfying result in eq 5, whereby a usable mixture of C3$\alpha$- and C3$\beta$-formyl products **18a,b** was obtained in a combined yield of 41%, in addition to a 12% yield of the unstable C4$\beta$-aldehyde **19**. The fact that **18a** could be equilibrated with NaOMe/MeOH at 25 °C to give a 2.3:1 mixture (80%) favoring **18b** allowed both C3 epimers to be used for the production of (+)-phyllanthocin, as described in our initial report.[5d]




Efforts to improve the yield, regioselectivity, and stereoselectivity of this hydroformylation step were discouraging. Most modifications led to increased amounts of the unwanted regioisomer **19**, to the extent that this could be made in predominance. After approximately 50 attempts to improve upon the result in eq 5 by varying the catalysts,[29] conditions (temperature, pressure, time, presence of excess phosphine or phosphite ligands, and solvent), the most striking conclusion was that the presence of excess phosphine or phosphite ligands greatly enhanced the rate and cleanliness of the reaction, although favoring production of the unwanted regioisomer **19**. For example, use of 160 mol % of tris(*o-tert*-butylphenyl)phosphite with 8 mol % $[(COD)RhOAc]_2$ at 660 psi with **14** gave a 54% yield of **19** and 20% of **18a** and **18b**. We sought to exploit the positive aspects of this "added phosphine effect" by finding a way to override the inherent tendency of the substrate to undergo C4-functionalization.

Illustrated in eq 6 is the notion of incorporating the phosphine ligand into the hydroformylation substrate. Intramolecular delivery and bidentate coordination of the

(21) (a) Bertelo, C. A.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 228. (b) Carr, D. B.; Schwartz, J. *Ibid.* **1979**, *101*, 3521.

(22) (a) Brown, H. C.; Hubbard, J. L.; Smith, K. *Synthesis* **1979**, 701. (b) Kabalka, G. W.; Delgado, M. C.; Kunda, U. S.; Kunda, S. A. *J. Org. Chem.* **1984**, *49*, 174.

(23) Brown, H. C.; Geoghegan, P. J., Jr.; Kurek, J. T. *J. Org. Chem.* **1981**, *46*, 3810.

(24) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(25) (a) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150. Wittig, G.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 1373. (b) Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1977**, *99*, 4536. (c) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.

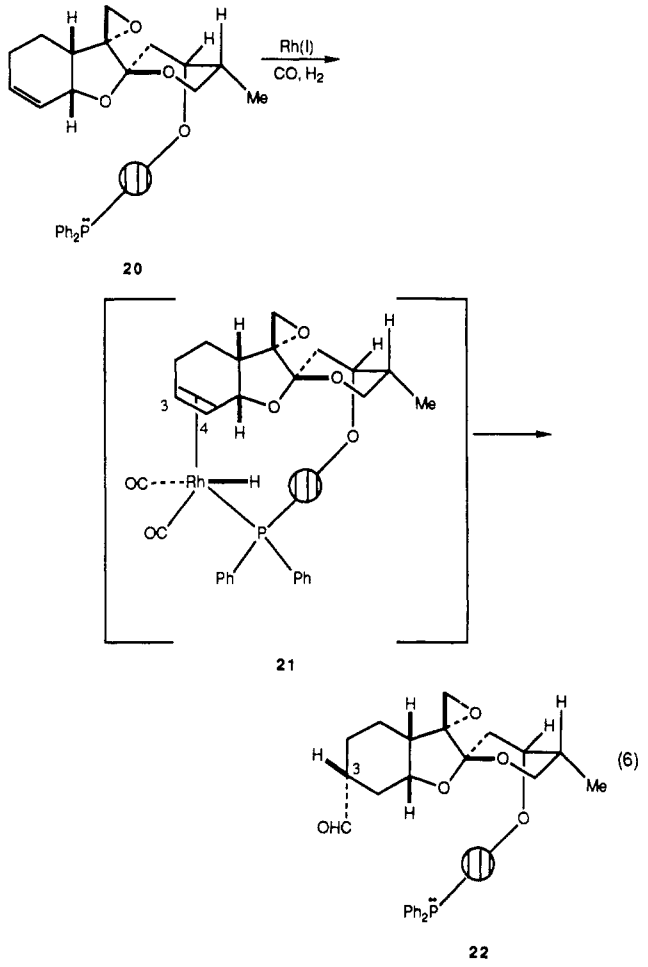
(26) Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980**, *21*, 3535.

(27) Campaigne, E.; LeSuer, W. M. In *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 919.

(28) Pino, P.; Piacenti, F.; Bianchi, M. In *Organic Syntheses Via Metal Carbonyls*; Wender, I., Pino, P., Eds.; John Wiley and Sons: New York, 1977; Vol. II.

(29) The following catalysts were all screened for effectiveness in this transformation: $[(COD)RhCl]_2$, $Rh_6(CO)_{16}$, $Rh_4(CO)_{12}$, $Rh_2O_3$, $(Ph_3P)_3RhCl$, $(CO)(Ph_3P)_2RhCl$, $[Rh(OAc)_2]_2$, $[(CO)_2RhCl]_2$, $(Ph_3P)_2Rh(CO)(H)$, $[(Ph_3P)_2Rh(CO)_3]^+ClO_4^-$, $Ru_3(CO)_{12}$, $Co_2(CO)_8$, and $(Ph_3P)_3Ir(CO)(H)$.

rhodium catalyst would result in the bracketed intermediate, wherein the metal is complexed on the more hindered concave face of the C3–C4 olefin. We envisioned a rigid spacer attaching the C10 axial oxygen to the phosphine with a length and geometry conductive to our needs. Specifically, the bracketed $\pi$-complex would have to proceed to the C3 rhodium acyl, leading, after reductive elimination, to the C3$\alpha$-formyl product (eq 6). A further



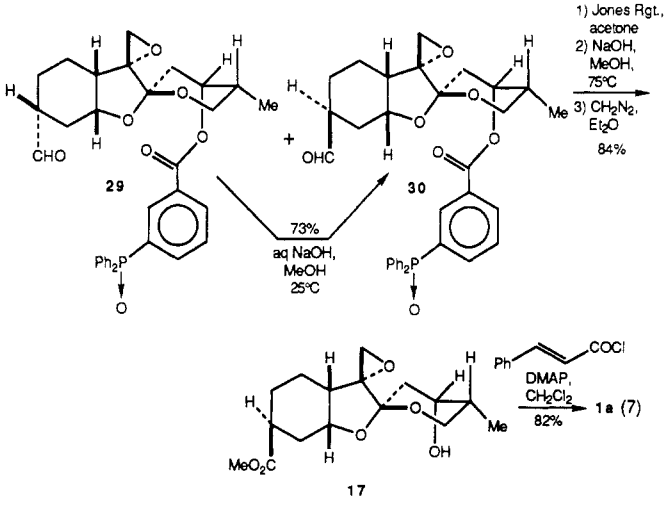

requirement was that the product phosphine then give up the substoichiometric Rh(I) catalyst to another substrate phosphine. Note that, although this "intramolecular hydroformylation" would lead to the C3 epi configuration vis-ă-vis phyllanthocin, we had already succeeded in epimerizing a related endo-oriented C3$\alpha$-formyl (**18a**, vide supra).

Scheme III details our first attempt at reducing this concept to practice. Molecular models suggested that the *p*-(diphenylphosphino)benzoate auxiliary had approximately the needed spatial characteristics for the intramolecular delivery to the concave face of the C3–C4 linkage. Coupling of the known[30] *p*-(diphenylphosphino)benzoic acid to the C10 axial alcohol in **2** via the DCC/4-pyrrolidinopyridine procedure[31] gave in 77% yield the requisite ester **23**. Subjection of this substrate to the hydroformylation conditions led to an 84% recovery of unchanged **23** and an 8% yield of C4$\beta$-formyl product **24** as the only observable hydroformylation product. Not only had the initially chosen auxiliary failed to direct the C–C bond formation to C3, it had failed to serve in any intramolecular delivery mode.

An enlightening set of experiments involved oxidation of **23** to the corresponding phosphine oxide **25** (1% $H_2O_2$ in $Et_2O$).[32] No longer having an internal ligand, this substrate exhibited hydroformylation characteristics reminiscent of **14**; all substrate was consumed, the reaction gave numerous products, and the undesired C4$\beta$-formyl product **26** was obtained in 49% yield. The products **24** and **26** were correlated by oxidation of the former to give the latter. These observations suggested that the phosphine moiety in **23** was indeed serving as a ligand for the Rh(I) catalyst, but that this association was inhibiting hydroformylation. It was concluded that the ligand/spacer combination in **23** was too long, serving only to force the complexed Rh(I) nucleus beyond the olefin locale.

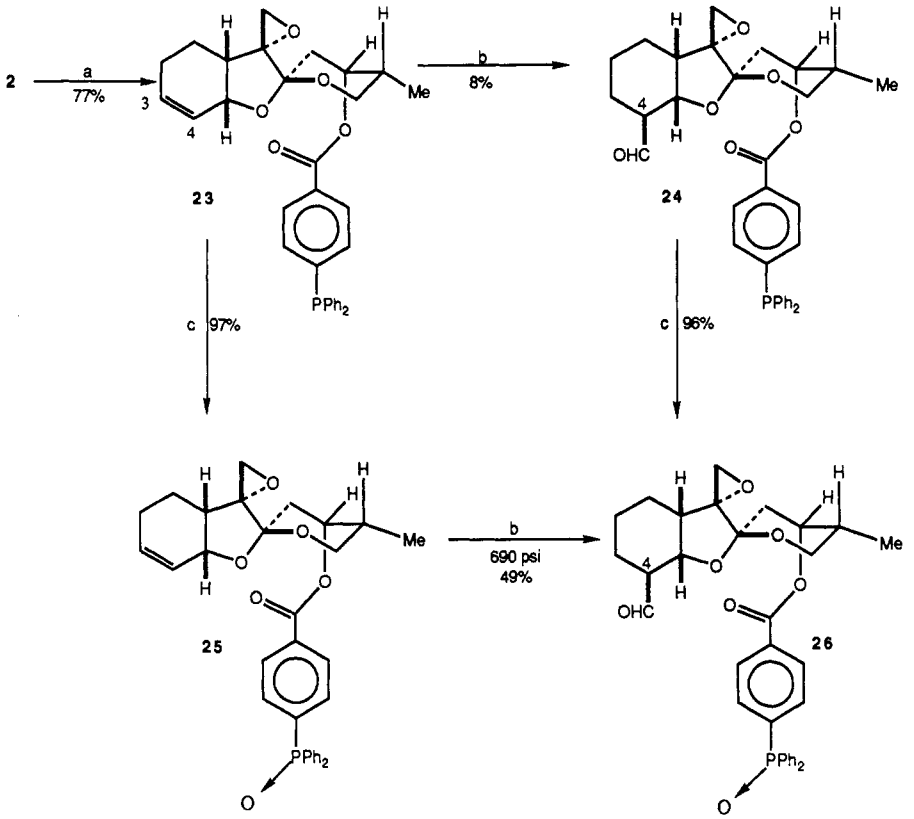
A shortened phosphine/tether combination was examined as shown in Scheme IV. Coupling of *m*-(diphenylphosphino)benzoic acid[33] to the alcohol **2** as before gave in 88% yield the substrate **27**. Subjection of this material to the indicated hydroformylation conditions led, presumably via the bracketed intermediate, to a mixture of aldehydes **28a–d** in a ratio of 7.7:1:1:0.3. In the crude product mixture, the eight resonances due to the C3 or C4 methines and the associated formyl protons were distinguishable in the 400-MHz $^1$H NMR spectrum. This provided a reliable means of relative quantitation of these four isomeric aldehydes. Chromatographic separation of the four aldehydes followed a workup procedure involving sequential treatment with bis(1,3-diphenylphosphino)propane and then *t*-BuOOH to (1) remove the rhodium catalyst and (2) produce the phosphine oxides.[34] The combined yield of desired C3-formyl isomers **28a** and **28d** was 72%.

The final steps of the total synthesis are shown in eq 7. Equilibration of **29** with aqueous NaOH/MeOH at 25 °C gave in 73% yield the epimeric aldehyde **30**, plus an 18% recovery of **29**. Oxidation to the carboxylic acid with Jones' reagent, cleavage of the C10 benzoate with aqueous NaOH in MeOH at 75 °C, and esterification with diazomethane accomplished the conversion of **30** to the crystalline hydroxy ester **17** (mp 130–130.5 °C) in 84% overall yield. Cinnamoylation of the C10 hydroxyl group gave (+)-phyllanthocin [**1a**, mp 129–129.5 °C, $[\alpha]^{25}_D$ +27.2° (*c* 2.04, $CHCl_3$)][35] in 82% yield.




(30) Baldwin, R. A.; Cheng, M. T.; Homer, G. D. *J. Org. Chem.* **1967**, *32*, 2176.
(31) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(32) Buckler, S. A. *J. Am. Chem. Soc.* **1962**, *84*, 3093.
(33) Gilman, H.; Brown, G. E. *J. Am. Chem. Soc.* **1945**, *67*, 824.
(34) This oxidation step was employed to avoid problems encountered by partial air-oxidation of the phosphine-containing products during isolation.

**Scheme III**[a]




[a] (a) $p$-$Ph_2PC_6H_4CO_2H$, DCC, 4-pyrrolidinopyridine, $CH_2Cl_2$, 25 °C (1 h) → 60 °C (21 h); (b) 8 mol % $[(COD)RhOAc]_2$, PhH, $CO:H_2$ (1:1), 85 °C, 680–690 psi, 3 h; (c) 1% aqueous $H_2O_2$, $Et_2O$, 25 °C, 1 h.

The synthetic objective was thus attained via a sequence of 17 steps. Key elements included the establishment of absolute and relative stereochemistry in **9** via an application of Sharpless' asymmetric epoxidation and a novel intramolecularly guided hydroformylation process.[36] Early concessions to imperfect distereoselectivity in the first five steps were compensated by an overall yield exceeding 13% for the final 12 steps of the synthesis.

## Experimental Section

All melting points were determined with a Büchi capillary melting point apparatus. All melting and boiling points are uncorrected. The infrared (IR) spectra were recorded on a Perkin-Elmer Model 682 or 727B or a Beckman IR 4210 spectrometer. Proton nuclear magnetic resonance ($^1H$ NMR) spectra were recorded on either a 90-MHz (Varian EM 390), a 200-MHz (Bruker WP-200), or a 400-MHz (Bruker WH-400) spectrometer as indicated. Carbon nuclear magnetic resonance ($^{13}C$ NMR) spectra were recorded at 20 MHz on an IBM NR-80 spectrometer. Chemical shift data for the proton and carbon resonances are reported in parts per million ($\delta$) relative to $Me_4Si$ ($\delta$ 0.0). Mass spectral data were obtained on a Finnegan 4021 spectrometer. Optical rotations were measured on a Perkin-Elmer 243B digital polarimeter. Analytical glass capillary gas chromatographic analyses were done on a Hewlett-Packard 5790A GC utilizing 25 m capillary columns coated with SE-54 or SUPEROX-4 (Alltech Associates, Inc., Deerfield, IL).

Analytical thin-layer chromatography (TLC) was carried out with Analtech TLC plates precoated with silica gel GHLF (250-$\mu$m thickness). TLC visualization was accomplished with either a UV lamp, $I_2$ staining, or a charring solution (2 g of $CoCl_2$, 10 mL of concentrated $H_2SO_4$, and 100 mL of $H_2O$ or 25 g of phosphomolybdic acid in 1 pint of absolute ethanol). Gravity column chromatography was done with Baker silica gel, 60–200 mesh. Flash chromatography was performed as described by Still.[20]

Tetrahydrofuran (THF) was distilled just prior to its use from sodium benzophenone ketyl. Dimethyl sulfoxide (DMSO) was distilled from BaO and stored over 3-Å molecular sieves. Methylene chloride ($CH_2Cl_2$) was distilled from $CaH_2$ just prior to use. Benzene was stored over sodium ribbon. Triethylamine, diisopropylamine, and pyridine were distilled from $CaH_2$ and stored over KOH.

Moisture-sensitive reactions were performed in flame-dried glassware under a positive pressure of Ar maintained by a balloon.

Solvents described as deoxygenated had Ar bubbled through them for 5 min followed by 5 min of ultrasound sonication under a positive pressure of Ar and finally 5 more minutes of bubbling Ar just prior to their use.

The hydroformylation experiments were carried out in a 45 mL capacity Parr bomb.

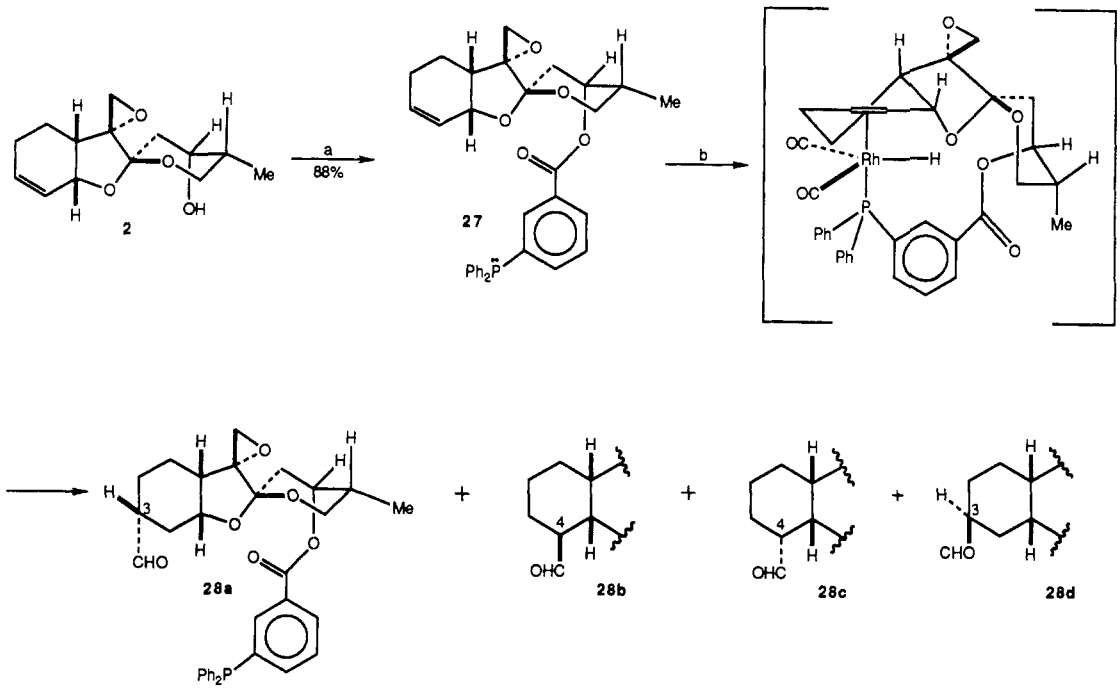
Elemental analyses were performed by Robertson Laboratory, Madison, NJ.

***cis*- and *trans*-2-(Acetyloxy)-1-[2-[(4-methoxybenzyl)oxy]-3-cyclohexen-1-yl]ethanone (6c,t).** To a suspension of 9.22 g (384 mmol) of NaH in 800 mL of DMSO (freshly distilled from BaO) was added 49.8 mL (400 mmol) of $p$-methoxybenzyl alcohol over a 10-min period with the generated $H_2$ being vented through a bubbler. The solution became homogeneous while stirring for 1 h, at which time 16.8 mL (160 mmol) of *cis*-1,4-dichloro-2-butene was added. This solution was warmed to 85 °C and stirred for 4 h. The solution was cooled to 25 °C and quenched with the addition of 10 g of $NH_4Cl$. The solution was diluted with 300 mL of $H_2O$ and extracted with 3 × 1 L of ether.

(35) Our synthetic sample of (+)-phyllanthocin proved to be identical by standard spectroscopic and chromatographic criteria to an authentic sample of **1a** provided by Professor D. R. Williams (Indiana University), whom we thank. The literature values for the melting point and $[\alpha]_D$ of (+)-phyllanthocin are as follows: mp 126–127 °C, $[\alpha]^{24}_D$ +25.2° (*c* 2.00, $CHCl_3$);[1] mp 120–121 °C, $[\alpha]^{33}_D$ +23.81° (*c* 1.26, $CHCl_3$);[3] mp 118–120 °C, $[\alpha]^{24}_D$ +24.9° (*c* 1.86, $CHCl_3$).[5b]

(36) For a recent report of additional cases of chelation-controlled hydroformylation of alkenes, see: Jackson, W. R.; Perlmutter, P.; Suh, G.-H. *J. Chem. Soc., Chem. Commun.* **1987**, 724.

Scheme IV[a]




[a] (a) $m$-$Ph_2PC_6H_4CO_2H$, DCC, 4-pyrrolidinopyridine, 60 °C, 10 h; (b) 8 mol % $[(COD)RhOAc]_2$, PhH, $CO:H_2$ (1:1), 85 °C, 710 psi, 3 h.

These extracts were washed with 750 mL of $H_2O$, dried over $MgSO_4$, and concentrated. Chromatography on 1 kg of 60–200-mesh silica gel (elution with 1:19 ether–hexanes) afforded 23.7 g (78%) of the (*E*)- and (*Z*)-1-[(*p*-methoxybenzyl)oxy]butadienes as a yellow slush. The *E*/*Z* ratio was found to be 3.1:1.0 (by glass capillary GLC). A pure sample of the *E*-diene was obtained by recrystallization from MeOH to give colorless platelike crystals melting at 42.0–42.5 °C.

Data for the *E*-diene: $R_f$ 0.70 (1:1 ether–hexanes); IR ($CHCl_3$) 3010, 2940, 2840, 1642, 1613, 1515, 1465, 1378, 1332, 1303, 1250, 1190, 1154, 1035, 996, 921, 914, 888, 824, 625 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.08 (AB q, 4 H, $J_{AB}$ = 8.2 Hz, $\Delta\nu_{AB}$ = 49.1 Hz), 6.64 (d, 1 H, $J$ = 12.6 Hz), 6.21 (dt, 1 H, $J$ = 10.4, 17.0 Hz), 5.66 (t, 1 H, $J$ = 11.5 Hz), 5.00 (d, 1 H, $J$ = 17.0 Hz), 4.82 (d, 1 H, $J$ = 10.5 Hz), 4.73 (s, 2 H), 3.80 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 159.50, 150.53, 133.29, 129.19, 128.64, 113.91, 111.67, 107.95, 71.47, 55.14; MS (15 eV) parent 190, base peak 138. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.49; H, 7.27.

To a solution of 23.3 g (122 mmol) of the diene mixture from above (3.1:1.0 *E*:*Z*) and 350 mg of hydroquinone in 300 mL of benzene was added 17.3 g (135 mmol) of acetoxymethyl vinyl ketone.[12] This solution was warmed to 75 °C and stirred for 14 h. Concentration gave 41 g of a yellow oil, which was flash chromatographed on 525 g of 230–400-mesh silica gel (eluting with 13:7 hexanes–ether) to give 5.4 g (95%) of the *Z*-diene followed by 28.3 g (73%) of the cyclohexene **6** as a yellow oil (3.7:1.0 cis:trans by glass capillary GLC). Careful monitoring of the chromatographic fractions gave pure samples of **6c** and **6t**.

Data for the *Z*-diene: $R_f$ 0.68 (1:1 ether–hexanes); IR ($CHCl_3$) 3010, 2939, 2840, 1648, 1613, 1513, 1464, 1442, 1380, 1358, 1302, 1248, 1174, 1078, 1037, 1000, 898, 827 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.07 (AB q, 4 H, $J_{AB}$ = 8.8 Hz, $\Delta\nu_{AB}$ = 150.2 Hz), 6.77–6.67 (m, 1 H), 6.04 (br d, 1 H, $J$ = 6.2 Hz), 5.12–5.03 (m, 2 H), 4.91–4.87 (m, 1 H), 4.78 (s, 2 H), 3.79 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 159.32, 145.76, 129.79, 129.05, 128.88, 113.72, 113.21, 107.66, 73.73, 54.88; MS (15 eV) parent peak 190, base peak 138. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.53; H, 7.28.

Data for **6t**: $R_f$ 0.39 (1:1 ether–hexanes); IR ($CHCl_3$) 3030, 2940, 2840, 1750, 1730, 1613, 1512, 1415, 1372, 1302, 1240, 1173, 1068, 1037, 909, 803 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.03 (AB q, 4 H, $J_{AB}$ = 8.7 Hz, $\Delta\nu_{AB}$ = 149.6 Hz), 5.78 (br s, 2 H), 4.76 (AB q, 2 H, $J_{AB}$ = 17.1 Hz, $\Delta\nu_{AB}$ = 33.7 Hz), 4.45 (AB q, 2 H, $J_{AB}$ = 10.9 Hz, $\Delta\nu_{AB}$ = 39.4 Hz), 4.24 (d, 1 H, $J$ = 8.9 Hz), 3.77 (s, 3 H), 2.75–2.67 (m, 1 H), 2.16 (s, 3 H), 2.10–1.73 (m, 4 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 205.18, 169.28, 158.74, 129.82, 128.94, 128.18, 126.62, 113.22, 74.51, 70.32, 67.86, 54.54, 48.35, 23.95, 23.29, 19.73; MS (14 eV) parent peak 318, base peak 137.

Data for **6c**: recrystallization from ether/hexane gave long crystalline needles melting at 80–82 °C; $R_f$ 0.38 (1:1 ether–hexanes); IR ($CHCl_3$) 3025, 2960, 2875, 1748, 1731, 1614, 1514, 1372, 1244, 1173, 1058, 1037, 824 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.02 (AB q, 4 H, $J_{AB}$ = 8.7 Hz, $\Delta\nu_{AB}$ = 142.0 Hz), 5.97–5.93 (m, 2 H), 4.73 (AB q, 2 H, $J_{AB}$ = 16.6 Hz, $\Delta\nu_{AB}$ = 9.3 Hz), 4.46 (AB q, 2 H, $J_{AB}$ = 11.5 Hz, $\Delta\nu_{AB}$ = 54.4 Hz), 4.18 (t, 1 H, $J$ = 3.9 Hz), 3.78 (s, 3 H), 2.66–2.62 (m, 1 H), 2.22–1.88 (m, 4 H), 2.14 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 202.84, 169.54, 158.74, 132.10, 129.72, 128.81, 124.16, 113.23, 69.32, 69.09, 66.94, 54.60, 48.86, 24.22, 19.86, 17.66; MS (14 eV) parent peak 318, base peak 137. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.96. Found: C, 67.65; H, 7.00.

***cis*- and *trans*-2-[2-[(4-Methoxybenzyl)oxy]-3-cyclohexen-1-yl]-2-propen-1-ol 1-Acetate.** To a suspension of 40.8 g (114 mmol) of methyltriphenylphosphonium bromide in 500 mL of THF at −78 °C was added 68.5 mL (106 mmol) of 1.55 M nBuLi in hexanes. After 15 min, the bright yellow solution was cooled to −100 °C. A solution of 26.0 g (81.7 mmol) of the ketone **6** in 100 mL of THF was added to the ylide over a 30-min period. This solution was kept at −100 °C for 1 h and then allowed to warm slowly to 25 °C while stirring for 12 h. This solution was concentrated to a yellow slush, which was filtered through a pad of 100 g of 60–200-mesh silica gel (elution with ether) and concentrated to 23 g of the crude product. This material was determined to be a 5.9:1.0 mixture of the cis and trans products by glass capillary GLC. This material was flash chromatographed on 750 g of 230–400 mesh silica gel (elution with 9:1 hexanes–ether) to afford 15.7 g (61%) of the cis allylic acetate as a yellow oil, homogeneous by glass capillary GLC: $R_f$ 0.68 (1:1 ether–hexanes); IR ($CCl_4$) 3014, 2935, 2839, 1742, 1612, 1509, 1464, 1372, 1303, 1240, 1172, 1100, 1041, 913, 822 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.02 (AB q, 4 H, $J_{AB}$ = 8.8 Hz, $\Delta\nu_{AB}$ = 149.8 Hz), 5.89 (br s, 2 H), 5.18 (br s, 1 H), 5.10 (br s, 1 H), 4.59 (AB q, 2 H, $J_{AB}$ = 13.4 Hz, $\Delta\nu_{AB}$ = 19.9 Hz), 4.45 (AB q, 2 H, $J_{AB}$ = 11.6 Hz, $\Delta\nu_{AB}$ = 21.3 Hz), 3.86 (br s, 1 H), 3.77 (s, 3 H), 2.33–1.60 (m, 5 H), 2.06 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 169.58, 158.51, 144.36, 130.59, 130.53, 128.41, 126.01, 113.03, 112.67, 70.65, 69.93, 65.80, 54.40, 41.79, 25.37, 20.96, 20.09; MS (14 eV) parent peak 316, base peak 137. Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.19; H, 7.77.

Further elution provided a sample of the pure trans diastereomer: $R_f$ 0.64 (1:1 ether–hexanes); IR ($CHCl_3$) 3010, 2935, 2835, 1732, 1612, 1512, 1302, 1245, 1172, 1068, 1035, 910, 822 $cm^{-1}$; $^1H$

NMR (400 MHz, $CDCl_3$) $\delta$ 7.03 (AB q, 4 H, $J_{AB}$ = 8.8 Hz, $\Delta\nu_{AB}$ = 156.8 Hz), 5.79 (br s, 2 H), 5.10 (br s, 1 H), 4.98 (br s, , 1 H), 4.58 (AB q, 2 H, $J_{AB}$ = 13.6 Hz, $\Delta\nu_{AB}$ = 27.5 Hz), 4.47 (AB q, 2 H, $J_{AB}$ = 11.3 Hz, $\Delta\nu_{AB}$ = 29.8 Hz), 3.96 (dd, $J$ = 3.0, 8.3 Hz), 3.77 (s, 3 H), 2.37–1.57 (m, 5 H), 2.06 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.32, 158.99, 146.20, 130.65, 129.44, 129.19, 127.62, 113.55, 111.95, 77.19, 75.42, 70.16, 66.45, 55.05, 43.03, 26.72, 24.93, 20.76; MS (13 eV) parent peak 316, base peak 137.

***cis*-2-[2-[(4-Methoxybenzyl)oxy]-3-cyclohexen-1-yl]-2-propenol (7).** To a solution of 15.6 g (49.3 mmol) of the preceding cis allylic acetate in 200 mL of MeOH was added 13.6 g (98.6 mmol) of $K_2CO_3$. The resulting suspension was stirred for 90 min. The solution was diluted with 200 mL of $H_2O$ and extracted with 2 × 500 mL of ether. These extracts were dried over $MgSO_4$ and concentrated to a yellow oil, which was chromatographed on 100 g of 70–200-mesh silica gel to afford 13.4 g (99%) of the allylic alcohol **7** as a yellow oil: $R_f$ 0.36 (1:1 ether–hexanes); IR ($CHCl_3$) 3610, 3390, 3010, 2938, 2875, 2836, 1612, 1512, 1465, 1303, 1248, 1173, 1033, 912, 822 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.02 (AB q, 4 H, $J_{AB}$ = 8.7 Hz, $\Delta\nu_{AB}$ = 151.0 Hz), 5.93 (m, 2 H), 5.14 (br s, 1 H), 5.00 (br s, 1 H), 4.47 (AB q, 2 H, $J_{AB}$ = 11.3 Hz, $\Delta\nu_{AB}$ = 53.4 Hz), 4.12–3.97 (m, 2 H), 3.86 (br s, 1 H), 3.76 (s, 3 H), 2.87 (t, 1 H, $J$ = 5.4 Hz), 2.48–2.44 (m, 1 H), 2.24–2.17 (m, 1 H), 2.08–1.88 (m, 2 H), 1.64–1.60 (m, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 159.00, 149.66, 131.71, 130.30, 129.19, 125.83, 113.53, 112.94, 72.10, 70.28, 64.82, 54.99, 43.18, 25.83, 21.16; MS (15 eV) parent peak 274, base peak 137. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.21; H, 7.93.

**2(*S*)-[2(*R*)-[(4-Methoxybenzyl)oxy]-3-cyclohexen-1(*S*)-yl]oxiranemethanol and 2(*S*)-[2(*S*)-[(4-Methoxybenzyl)-oxy]-3-cyclohexen-1(*R*)-yl]oxiranemethanol.** To a solution of 8.16 g (39.6 mmol) of (+)-diethyl L-tartrate in 170 mL of $CH_2Cl_2$ was added 12.7 mL (33 mmol) of titanium(IV) *tert*-butoxide. After stirring for 1 h at 25 °C, the now yellow solution was cooled to −23 °C. To this solution was added a solution of 9.05 g (33.0 mmol) of the allylic alcohol **7** in 40 mL of $CH_2Cl_2$. This was followed by the addition of 18.2 mL (66.0 mmol) of anhydrous 3.63 M *tert*-butyl hydroperoxide. The reaction was quenched after stirring for 5.5 h at −23 °C with the addition of 200 mL of 10% aqueous L-tartaric acid. This solution was warmed to 25 °C after 30 min and stirred vigorously until the solution cleared (ca. 1 h). The solution was diluted with 600 mL of ether, and the organic layer was washed with 2 × 200 mL of 1.0 M $Na_2S_2O_3$ and 2 × 200 mL of $H_2O$ (these washes were extracted with 500 mL of ether). The organic solutions were concentrated, and the residual oil was dissolved in 250 mL of ether and cooled to 0 °C. To this solution was added 120 mL (120 mmol) of 1.0 M NaOH (precooled to 0 °C). After stirring for 30 min, the ethereal layer was washed with 2 × 100 mL of $H_2O$ (these washes were extracted with 300 mL of ether). The ethereal solutions were dried over $MgSO_4$ and concentrated to a colorless oil. Flash chromatography on 550 g of 230–400-mesh-silica gel (elution with 45:55 ether–hexanes) afforded 530 mg (4%) of an epoxide-opened diol, 1.8 g of the pure undesired epoxide, and 7.3 g (95% for the epoxides overall) of a mixture of the diastereomeric epoxides. Repetitive flash chromatography was necessary to obtain substantial quantitities of the pure epoxides. For example, 3.4 g of the pure desired epoxide was obtained after four such columns.

Data for the epoxide-opened diol: $R_f$ 0.43 (3:1 ether–hexanes); $[\alpha]^{25}_D$ +162° (*c* 1.87, $CH_2Cl_2$); IR ($CHCl_3$) 3480, 3000, 2975, 2940, 2880, 2840, 1613, 1512, 1463, 1392, 1368, 1306, 1248, 1178, 1074, 1038, 940, 882, 828 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 7.04 (AB q, 4 H, $J_{AB}$ = 9.2 Hz, $\Delta\nu_{AB}$ = 152.5 Hz), 6.03 (m, 2 H), 4.49 (AB q, 2 H, $J_{AB}$ = 11.0 Hz, $\Delta\nu_{AB}$ = 102.7 Hz), 4.10–4.09 (m, 1 H), 4.01 (s, 1 H), 3.77 (s, 3 H), 3.66–3.57 (m, 2 H), 3.44–3.38 (m, 2 H), 3.00 (dd, 1 H, $J$ = 3.6, 8.7 Hz), 2.27–1.73 (m, 5 H), 1.11 (s, 9 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 159.21, 133.01, 129.90, 124.74, 113.69, 73.99, 72.83, 70.67, 69.16, 66.37, 65.92, 54.83, 39.84, 27.04, 26.37, 17.06; MS (14 eV) parent peak + 1 365, base peak 121.

Data for undesired epoxide: recrystallization from ether–hexanes gave colorless prisms, mp 50.0–51.5 °C; $R_f$ 0.41 (3:1 ether–hexanes); $[\alpha]^{26}_D$ +183° (*c* 2.19, $CH_2Cl_2$); IR ($CCl_4$) 3450, 3030, 2940, 2845, 1642, 1617, 1514, 1417, 1395, 1306, 1284, 1250, 1177, 1108, 1043, 937, 827 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.04 (AB q, 4 H, $J_{AB}$ = 8.6 Hz, $\Delta\nu_{AB}$ = 146.9 Hz), 6.00–5.93 (m, 2 H), 4.51 (AB q, 2 H, $J_{AB}$ = 11.2 Hz, $\Delta\nu_{AB}$ = 69.9 Hz), 3.96 (t, 1 H, $J$ = 3.6 Hz), 3.87 (dd, 1 H, $J$ = 4.7, 12.2 Hz), 3.78 (s, 3 H), 3.48 (dd, 1 H, $J$ = 7.9, 12.2 Hz), 2.79 (AB q, 2 H, $J_{AB}$ = 4.7 Hz, $\Delta\nu_{AB}$ = 8.1 Hz), 2.40–2.50 (m, 1 H), 2.20–2.15 (m, 1 H), 2.03–1.90 (m, 2 H), 1.66–1.54 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 158.68, 131.74, 130.39, 128.49, 125.24, 113.27, 69.56, 69.48, 62.98, 60.05, 54.56, 48.49, 39.93, 25.47, 16.95; MS (15 eV) base peak 137. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.26; H, 7.73.

Data for desired epoxide: recrystallization from ether–hexanes gave crystalline rods, mp 73.0–73.5 °C; $R_f$ 0.38 (3:1 ether–hexanes); $[\alpha]^{25}_D$ −243° (*c* 1.54, $CH_2Cl_2$); IR ($CHCl_3$) 3470, 2990, 2930, 2860, 1606, 1502, 1452, 1298, 1242, 1169, 1104, 1030, 902, 822 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.04 (AB q, 4 H, $J_{AB}$ = 8.7 Hz, $\Delta\nu_{AB}$ = 151.5 Hz), 6.0–5.9 (m, 2 H), 4.50 (AB q, 2 H, $J_{AB}$ = 11.1 Hz, $\Delta\nu_{AB}$ = 87.6 Hz), 3.99 (dd, 1 H, $J$ = 6.1, 12.1 Hz), 3.85 (br s, 1 H), 3.77 (s, 1 H), 3.40 (dd, 1 H, $J$ = 6.5, 12.1 Hz), 3.00 (t, 1 H, $J$ = 6.3 Hz), 2.75 (AB q, 2 H, $J_{AB}$ = 4.7 Hz, $\Delta\nu_{AB}$ = 83.4 Hz), 2.25–1.47 (m, 5 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 159.13, 132.00, 129.97, 129.21, 125.10, 113.63, 70.57, 69.77, 62.06, 60.61, 54.88, 49.64, 44.72, 25.87, 19.20; MS (15 eV) parent peak 290, base peak 137. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.55; H, 7.39.

**2(*R*)-[2(*R*)-[(4-Methoxybenzyl)oxy]-3-cyclohexen-1(*S*)-yl]oxiranecarboxaldehyde (8).** To a solution of 1.05 mL (12.1 mmol) of oxalyl chloride in 70 mL of $CH_2Cl_2$ at −60 °C was added dropwise 1.72 mL (24.2 mmol) of DMSO. This was followed 5 min later by 3.19 g (11.0 mmol) of the desired epoxy alcohol from above in 10 mL of $CH_2Cl_2$. The resulting suspension was stirred for 30 min. Triethylamine (7.66 mL, 54.9 mmol) was then added. The solution was warmed to room temperature after 5 min, diluted with 250 mL of $CH_2Cl_2$, and washed with 150 mL of saturated $NaHCO_3$ and $H_2O$. These washes were back-extracted with 200 mL of $CH_2Cl_2$. The organic layers were combined, dried over $MgSO_4$, and concentrated to a yellow oil, which was chromatographed on 100 g of 60–200-mesh silica gel (elution with 1:4 ether–hexanes) to afford 3.02 g (95%) of the aldehyde **8** as a pale yellow oil: $R_f$ 0.53 (1:1 ether–hexanes); $[\alpha]^{25}_D$ −184.0° (*c* 2.09, $CH_2Cl_2$); IR ($CHCl_3$) 3030, 2940, 2840, 1728, 1615, 1304, 1252, 1178, 1106, 1072, 1040, 828 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.13 (s, 1 H), 7.01 (AB q, 4 H, $J_{AB}$ = 8.7 Hz, $\Delta\nu_{AB}$ = 147.6 Hz), 5.93–5.90 (m, 2 H), 4.44 (AB q, 2 H, $J_{AB}$ = 11.2 Hz, $\Delta\nu_{AB}$ = 74.1 Hz), 4.01 (br s, 1 H), 3.78 (s, 3 H), 3.00 (AB q, 2 H, $J_{AB}$ = 5.1 Hz, $\Delta\nu_{AB}$ = 122.4 Hz), 2.33–1.54 (m, 5 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 199.04, 158.90, 131.48, 130.51, 129.01, 125.28, 113.46, 69.98, 69.40, 61.67, 54.94, 47.15, 37.30, 25.23, 18.74; MS (15 eV) parent peak 288, base peak 137. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.68; H, 7.06.

**1-[2(*R*)-[2(*R*)-[(4-Methoxybenzyl)oxy]-3-cyclohexen-1-(*S*)-yl]oxiranyl]ethanone (9).** To a solution of 67 mL (93.5 mmol) of 1.40 M MeLi in ether in 400 mL of THF at −78 °C was added a solution of 5.39 g (18.7 mmol) of the aldehyde **8** in 20 mL of THF. The reaction was quenched after 7 min with the addition of 10 g of dry ice. The resulting cloudy solution was poured into 500 mL of Fisher pH 7 buffer at 0 °C. The aqueous layer was extracted with 2 × 500 mL of ether. These extracts were washed with 150 mL of $H_2O$, dried over $MgSO_4$, and concentrated to a yellow oil, which was flash chromatographed on 250 g of 230–400-mesh silica gel (elution with 9:11 ether–hexanes) affording 3.67 g (65%) of an inseparable mixture of alcohols (1.3:1.0 by $^{13}C$ NMR) as a colorless oil. This material has been obtained in a 77% yield on a 500 mg scale: $R_f$ 0.26 (1:1 ether–hexanes). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.82; H, 8.08.

To a cooled (−55 °C) solution of 1.25 mL (14.3 mmol) of oxalyl chloride in 100 mL of $CH_2Cl_2$ was added 2.03 mL (28.6 mmol) of DMSO. This was followed by the addition of 3.63 g (11.9 mmol) of the above alcohols in 20 mL of $CH_2Cl_2$. The resulting suspension was stirred for 1 h. Triethylamine (8.31 mL, 59.6 mmol) was added. The solution was warmed to room temperature 5 min later and diluted with 500 mL of ether. This solution was washed with 100 mL of saturated aqueous $NaHCO_3$ and 150 mL of water. These washes were extracted with 500 mL of ether. The ethereal solutions were dried over $MgSO_4$, concentrated to a yellow oil, and flash chromatographed on 100 g of 230–400-mesh silica gel (elution with 1:4 ether–hexanes); to afford 3.31 g (92%) of methyl ketone **9** as white, crystalline needles. An analytical sample was obtained by recrystallization from ether–hexanes giving colorless rods melting at 86.0–86.5 °C: $R_f$ 0.47 (1:1 ether–hexanes); $[\alpha]^{25}_D$

-202° (c 1.84, $CH_2Cl_2$); IR ($CHCl_3$) 3005, 2940, 2840, 1703, 1612, 1511, 1359, 1303, 1248, 1172, 1118, 1072, 1036, 822 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.03 (AB q, 4 H, $J_{AB}$ = 8.7 Hz, $\Delta\nu_{AB}$ = 161.3 Hz), 5.95–5.87 (m, 2 H), 4.41 (AB q, 2 H, $J_{AB}$ = 11.2 Hz, $\Delta\nu_{AB}$ = 94.0 Hz), 4.08–4.06 (m, 1 H), 3.77 (s, 3 H), 2.82 (AB q, 2 H, $J_{AB}$ = 4.7 Hz, $\Delta\nu_{AB}$ = 145.3 Hz), 2.70 (dt, 1 H, J = 3.8, 12.5 Hz), 2.19–1.86 (m, 2 H), 1.92 (s, 3 H), 1.56 (dq, 1 H, J = 5.4, 12.5 Hz), 1.35–1.31 (m, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 208.15, 158.76, 131.47, 128.75, 125.34, 113.38, 69.62 (2 C), 62.88, 54.93, 45.80, 36.88, 25.11, 23.88, 17.72; MS (20 eV) parent peak 302, base peak 137. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.25; H, 7.44.

**(*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropanal.** To a solution of 10.0 g (84.6 mmol) of (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate and 9.2 g (135 mmol) of imidazole in 350 mL of THF was added 19.0 g (126 mmol) of *tert*-butyldimethylsilyl chloride. This solution was stirred at room temperature for 16 h. The precipitate-filled solution was filtered and concentrated. The residual oil was dissolved in 300 mL of ether and washed with 150 mL each of $H_2O$, 0.5 M HCl (2×), and $H_2O$. The ethereal solution was dried over $MgSO_4$ and concentrated. The residual oil was vacuum distilled to afford 18.01 g (92%) of the silyl ether as a colorless oil: bp 68 °C/1.0 mm; $R_f$ 0.86 (1:1 ether–hexanes); $[\alpha]^{25}_D$ −20.5° (c 3.21, $CH_2Cl_2$); IR ($CHCl_3$) 2955, 2930, 2558, 1732, 1469, 1462, 1388, 1361, 1258, 1200, 1178, 1102, 1061, 838 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 4.83–4.48 (m, 5 H), 3.81–3.41 (m, 1 H), 1.07 (d, 3 H, J = 7 Hz), 0.82 (s, 9 H), −0.02 (s, 6 H); $^{13}C$ NMR ($CDCl_3$) δ 175.03, 65.10, 51.15, 42.37, 25.61, 18.02, 13.25, −5.70; MS (19 eV) base peak 175. Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 57.12; H, 10.50.

To a solution of 13.9 g (59.8 mmol) of the TBS-protected ester in 150 mL of $CH_2Cl_2$ at −23 °C was added 126 mL of 20% (wt/wt, ca. 126 mmol) diisobutylaluminum hydride in hexane. This solution was stirred for 90 min at −23 °C and then quenched with 120 mL of 10% NaOH. The solution was warmed to room temperature and stirred vigorously until the emulsion cleared (25 min). The aqueous layer was extracted with 2 × 200 mL of ether. The organic layers were washed with 150 mL of $H_2O$, dried over $MgSO_4$, filtered through a pad of silica gel, and concentrated to yield 11.7 g (96%) of the alcohol as a colorless oil: $R_f$ 0.56 (1:1 ether–hexanes); $[\alpha]^{25}_D$ −10.0° (c 2.06, $CH_2Cl_2$); IR ($CHCl_3$) 3630, 3500, 2958, 2935, 2860, 1472, 1466, 1392, 1362, 1260, 1088, 1028, 838 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 4.83–4.42 (m, 4 H), 2.72 (t, 1 H, J = 6 Hz), 2.17–1.80 (m, 1 H), 1.0–0.8 (m, 12 H), 0.09 (s, 6 H); $^{13}C$ NMR ($CDCl_3$) δ 68.17, 67.63, 37.17, 25.77, 18.09, 13.05, −5.63, −5.68; MS (19 eV) base peak 75. Anal. Calcd for $C_{10}H_{24}O_2Si$: C, 58.77; H, 11.84. Found: C, 58.75; H, 11.91.

To a solution of 1.90 mL (21.8 mmol) of oxalyl chloride in 90 mL of $CH_2Cl_2$ at −55 °C was added 3.09 mL (43.6 mmol) of DMSO. This was followed 5 min later with the addition of a solution of 3.71 g (18.2 mmol) of the alcohol from above in 10 mL of $CH_2Cl_2$. The resulting slurry was stirred for 1 h. Triethylamine (12.7 mL, 90.9 mmol) was added at this point. The solution was warmed to room temperature 5 min later. The solution was diluted with 100 mL of $CH_2Cl_2$ and was washed with 182 mL of ice-cold 0.5 M HCl and 200 mL of $H_2O$. These washes were extracted with 200 mL of $CH_2Cl_2$. The organic layers were combined, dried over $MgSO_4$, and concentrated to afford 3.58 g (97%) of the aldehyde as a pale yellow oil (97% pure by glass capillary GLC): $R_f$ 0.81 (1:1 ether–hexanes); $[\alpha]^{25}_D$ −37.8° (c 2.24, $CH_2Cl_2$): IR ($CHCl_3$) 2955, 2930, 2855, 1723, 1462, 1389, 1362, 1258, 1100, 1032, 1008, 938, 910, 838 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 9.75 (d, 1 H, J = 2 Hz), 4.82 (d, 2 H, J = 5 Hz), 2.7–2.4 (m, 1 H), 1.07 (d, 3 H, J = 7 Hz), 0.89 (s, 9 H), 0.07 (s, 6 H); $^{13}C$ NMR ($CDCl_3$) δ 204.08, 63.33, 48.67, 25.66, 18.07, 10.12, −5.69; MS (15 eV) parent peak + 1 203, base peak 145. Anal. Calcd for $C_{10}H_{22}O_2Si$: C, 59.35; H, 10.96. Found: C, 59.25; H, 11.12.

**(3*S*,4*S*)- and (3*R*,4*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-1-[2(*R*)-[2(*R*)-[(4-methoxybenzyl)oxy]-3-cyclohexen-1(*S*)-yl]oxiranyl]-4-methyl-1-pentanone (10a,b).** A solution of 2.01 g (6.65 mmol) of the methyl ketone **9** in 12 mL of THF was added slowly to 7.31 mmol of LDA in 80 mL of THF maintained at −78 °C; 50 min later, 1.61 g (7.98 mmol) of (*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropanal (generated just prior to this use) in 5 mL of THF was added dropwise to the yellow enolate solution. The reaction was quenched 10 min later with the addition of 0.6 mL of acetic acid. The solution was diluted with 200 mL of ether and washed with 100 mL each of saturated aqueous $NaHCO_3$ and $H_2O$ (back-extracted with 200 mL of ether). The ethereal extracts were dried over $MgSO_4$ and concentrated to a yellow oil, which was flash chromatographed on 175 g of 230–400-mesh silica gel (elution with 3:1 hexanes–ether) to afford a mixture of **9** and **10b** as well as 2.175 g (65%) of **10a** as a pale yellow oil. The **9,10b** mixture was flash chromatographed on 175 g of 230–400 mesh silica gel (elution with 1:6 EtOAc–hexanes) to afford 595 mg (18%) of **10b** and 228 mg (11%) of recovered **9**.

Data for **10b**: $R_f$ 0.52 (1:1 ether–hexanes); $[\alpha]^{25}_D$ −109° (c 1.60, $CH_2Cl_2$); IR ($CHCl_3$) 3470, 3000, 2955, 2930, 2855, 1698, 1610, 1508, 1460, 1388, 1300, 1246, 1223, 1092, 1070, 1032, 834 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.04 (AB q, 4 H, $J_{AB}$ = 8.7 Hz, $\Delta\nu_{AB}$ = 172.9 Hz), 5.94–5.85 (m, 2 H), 4.42 (AB q, 2 H, $J_{AB}$ = 11.2 Hz, $\Delta\nu_{AB}$ = 69.8 Hz), 4.15–4.11 (m, 1 H), 4.05–4.03 (m, 1 H), 3.76 (s, 3 H), 3.58–3.53 (m, 2 H), 3.11 (d, 1 H, J = 3.0 Hz), 2.81 (AB q, 2 H, $J_{AB}$ = 4.7 Hz, $\Delta\nu_{AB}$ = 164.2 Hz), 2.72–2.60 (m, 1 H), 2.55 (dd, 1 H, J = 9.5, 18.1 Hz), 2.38 (dd, 1 H, J = 3.1, 18.1 Hz), 2.19–1.92 (m, 2 H), 1.65–1.34 (m, 3 H), 0.85 (s, 9 H), 0.76 (d, 3 H, J = 7.0 Hz), 0.02 (s, 6 H); $^{13}C$ NMR ($CDCl_3$) δ 210.88, 158.91, 131.66, 130.99, 128.99, 125.53, 113.59, 69.77, 69.69, 68.40, 66.28, 63.30, 55.11, 46.14, 40.70, 39.83, 37.25, 25.82, 25.30, 18.15, 17.92, 10.43, −5.58; MS (16 eV) base peak 121. Anal. Calcd for $C_{28}H_{44}O_6Si$: C, 66.63; H, 8.79. Found: C, 66.68; H, 8.76.

Data for **10a**: $R_f$ 0.40 (1:1 ether–hexanes); $[\alpha]^{25}_D$ −140° (c 1.42, $CH_2Cl_2$); IR ($CHCl_3$) 3460, 3010, 2955, 2930, 2855, 1705, 1613, 1514, 1464, 1388, 1302, 1248, 1173, 1102, 1072, 1038, 837 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.02 (AB q, 4 H, $J_{AB}$ = 8.7 Hz, $\Delta\nu_{AB}$ = 163.9 Hz), 5.95–5.89 (m, 2 H), 4.40 (AB q, 2 H, $J_{AB}$ = 11.2 Hz, $\Delta\nu_{AB}$ = 103.7 Hz), 4.13–4.10 (m, 1 H), 3.91–3.87 (m, 1 H), 3.76 (s, 3 H), 3.66 (d, 1 H, J = 3.1 Hz), 3.58 (dd, 1 H, J = 4.8, 10.0 Hz), 3.50 (dd, 1 H, J = 6.6, 10.0 Hz), 2.88 (AB q, 2 H, $J_{AB}$ = 4.8 Hz, $\Delta\nu_{AB}$ = 75.8 Hz), 2.77–2.75 (m, 1 H), 2.52 (dd, 1 H, J = 10.2, 17.2 Hz), 2.20 (app dd, 1 H, J = 2.1, 17.2 Hz), 2.13–2.12 (m, 1 H), 2.01–1.98 (m, 1 H), 1.60–1.35 (m, 3 H), 0.85 (s, 9 H), 0.66 (d, 3 H, J = 7.0 Hz), 0.02 (s, 6 H); $^{13}C$ NMR ($CDCl_3$) δ 210.03, 158.85, 131.72, 131.02, 128.63, 125.51, 113.56, 70.99, 69.96, 69.53, 66.67, 63.18, 55.08, 45.27, 40.83, 39.87, 36.84, 25.77, 25.16, 18.05(2), 13.34, −5.67; MS (15 eV) parent peak + 1 505, base peak 121. Anal. Calcd for $C_{28}H_{44}O_6Si$: C, 66.63; H, 8.79. Found: C, 66.83; H, 9.01.

**(2*R*,2′*R*,3′a*R*,7′a*R*,4″*S*,5″*S*)-4″-Hydroxy-5″-methyl-3′a,6′,7′,7′a,3″,4″,5″,6″-octahydrodispiro[oxirane-2,3′(2′*H*)-benzofuran-2′,2″-[2*H*]pyran] (11).** To a solution of 1.50 g (3.90 mmol) of the DDQ deprotection product of **10a** (see below) in 25 mL of THF was added 3.9 mL (3.9 mmol) of 1.0 M tetrabutylammonium fluoride in THF. After 10 min the solvent was removed in vacuo, and the residual viscous oil was chromatographed on 60 g of 60–200-mesh silica gel (elution with 3:7 acetone–hexane) to afford 1.04 g (99%) of the triol.

To a solution of 998 mg (3.69 mmol) of the triol in 20 mL of $CH_2Cl_2$ was added 0.114 mL (1.48 mmol) of trifluoroacetic acid. Spiroketalization was virtually instantaneous. All volatiles were removed in vacuo after 10 min. The residual brown oil was flash chromatographed on 35 g of 230–400-mesh silica gel (elution with 3:1 ether–hexanes) to yield 172.8 mg (19%) of the spiroketal **2** and 679.1 mg (73%) of the epimeric spiroketal **11**.

Data for **11**: mp 123–125 °C; $R_f$ 0.21 (4:1 ether–hexanes); $[\alpha]^{25}_D$ −171° (c 2.74, $CH_2Cl_2$); IR ($CHCl_3$) 3610, 3490, 3008, 2968, 2937, 2883, 1464, 1437, 1395, 1365, 1340, 1235, 1152, 1142, 1110, 1099, 1086, 1028, 995, 957, 931, 907, 898, 878, 869, 848, 677 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.96–5.92 (m, 1 H), 5.85–5.80 (m, 1 H), 4.50–4.47 (m, 1 H), 4.24–4.20 (m, 1 H), 3.98 (dd, 1 H, J = 2.7, 11.5 Hz), 3.50 (dd, 1 H, J = 1.8, 11.6 Hz), 2.90 (AB q, 2 H, $J_{AB}$ = 5.0 Hz, $\Delta\nu_{AB}$ = 94.8 Hz), 2.36–2.30 (m, 1 H), 2.19–2.12 (m, 1 H), 1.91–1.66 (m, 5 H), 1.57 (dd, 1 H, J = 4.6, 12.2 Hz), 1.44 (t, 1 H, J = 11.8 Hz), 0.97 (d, 3 H, J = 7.0 Hz); MS (70 eV) parent peak + 1 253, base peak 80.

**(2*R*,2′*S*,3′a*R*,7′a*R*,4″*S*,5″*S*)-4″-Hydroxy-5″-methyl-3′a,6′,7′,7′a,3″,4″,5″,6″-octahydrodispiro[oxirane-2,3′(2′*H*)-benzofuran-2′,2″-[2*H*]pyran] (2).** To a solution of 3.66 g (7.25 mmol) of the major aldol product **10a** in 150 mL of $CH_2Cl_2/H_2O$ (10/1) was added 1.65 g (7.25 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The resulting dark green solution was stirred vigorously for 90 min. The now dark brown precipitate-filled solution was washed with 75 mL of saturated aqueous

$NaHCO_3$. The aqueous layer was extracted with 2 × 150 mL of ether. The organic layers, in turn, were washed with 75 mL of $H_2O$, dried over $MgSO_4$, and concentrated to a yellow oil, which was flash chromatographed on 100 g of 230–400-mesh silica gel (elution with 2:3 ether–hexanes); to give 2.64 g (95%) of a hemiketal as a pale yellow oil: $R_f$ 0.56 (1:1 ether–hexanes); IR ($CHCl_3$) 3500, 3008, 2960, 2935, 2890, 1452, 1432, 1396, 1231, 1176, 1096, 1064, 998, 973, 950, 922, 902, 885, 849, 661, 605 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.12 (s, 1 H), 6.08–5.95 (m, 2 H), 4.88 (m, 1 H), 4.66 (br s, 1 H), 4.25–4.20 (m, 1 H), 3.78 (dd, 1 H, $J$ = 3.6, 10.1 Hz), 3.56 (dd, 1 H, $J$ = 8.1, 10.1 Hz), 2.96 (AB q, 2 H, $J_{AB}$ = 5.1 Hz, $\Delta\nu_{AB}$ = 18.8 Hz), 2.31–1.23 (m , 8 H), 0.85 (s, 9 H), 0.80 (d, 2 H, $J$ = 7.0 Hz), 0.04 (s, 6 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 132.84, 124.69, 103.40, 74.39, 70.04 (2), 68.48, 49.71, 39.84, 38.59, 37.74, 25.61, 23.76, 19.12, 17.85, 13.02, -5.86; MS (15 eV) parent peak 384, base peak 145. Anal. Calcd for $C_{20}H_{36}O_5Si$: C, 62.46; H, 9.43. Found: C, 62.72; H, 9.66.

To a solution of 2.439 g (6.34 mmol) of the hemiketal in 100 mL of acetonitrile was added 9.5 mL of 5% HF in acetonitrile (v/v). The resulting pink solution was quenched after 10 min with the addition of 100 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 2 × 300 mL of ether. These extracts were washed with 150 mL of $H_2O$, dried over $MgSO_4$, and concentrated to a yellow oil, which was flash chromatographed on 80 g of 230–400-mesh silica gel (elution with 1:2 ether–hexanes) to afford 1.540 g (96%) of the spiroketal **2** as a pale yellow oil, homogeneous by glass capillary GLC: $R_f$ 0.66 (1:1 EtOAc–hexanes); $[\alpha]^{24}_D$ +45.2° ($c$ 1.05, $CH_2Cl_2$); IR ($CHCl_3$) 3535, 3010, 2965, 2935, 2880, 1465, 1428, 1248, 1232, 1161, 1127, 1111, 1071, 1046, 1009, 997, 978, 951, 922, 887, 862 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.07–6.03 (m, 1 H), 5.87–5.83 (m, 1 H), 4.47–4.44 (m, 1 H), 3.77–3.72 (m, 1 H), 3.71 (t, 1 H, $J$ = 11.8 Hz), 3.37 (dd, 1 H, $J$ = 4.9, 11.5 Hz), 3.14 (br s, 1 H), 2.86 (AB q, 2 H, $J_{AB}$ = 4.9 Hz, $\Delta\nu_{AB}$ = 16.7 Hz), 2.26–2.20 (m, 1 H), 2.12–2.06 (m, 1 H), 1.86–1.67 (m, 2 H), 1.76 (dd, 1 H, $J$ = 2.9, 14.5 Hz), 1.53–1.46 (m, 1 H), 1.45 (dd, 1 H, $J$ = 3.3, 14.6 Hz), 1.29 (dq, $J$ = 4.7, 12.5 Hz), 0.84 (d, 3 H, $J$ = 6.9 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 133.06, 123.81, 103.39, 71.35, 68.93, 67.47, 61.69, 48.06, 36.79, 35.50, 34.32, 23.47, 18.88, 12.71; MS (70 eV) parent peak + 1 253, base peak 80. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.71; H, 8.15.

To a solution of 25.2 mg (0.100 mmol) of the spiroketal **11** in 3 mL of acetonitrile was added 0.10 mL of 5% HF in acetonitrile. A TLC taken after 1 min showed complete epimerization. The reaction was quenched by the addition of 15 mg of $NaHCO_3$. The solution was filtered through 1.0 g of silica gel and concentrated to 24.4 mg (97%) of the epimeric spiroketal **2**. This material is 99% pure by glass capillary GLC with no trace of **11**.

To a solution of 276.3 mg (1.10 mmol) of the ketone **13** (see below) in 10 mL of MeOH maintained at 0 °C was added 21 mg (0.55 mmol) of $NaBH_4$. The reaction was quenched after 15 min with the addition of 1.0 mL of acetone. The MeOH was removed in vacuo, and the residual tan oil was dissolved in 10 mL of $H_2O$ and extracted with 2 × 50 mL of ether. These extracts were dried over $MgSO_4$, filtered through a pad of silica gel, concentrated to a yellow oil, and flash chromatographed on 20 g of 230–400-mesh silica gel (elution with 4:1 ether–hexanes) to afford 251 mg (91%) of the axial alcohol **2** and 24.0 mg (9%) of the equatorial alcohol **12**.

**(2*R*,2′*S*,3′a*R*,7′a*R*,4″*R*,5″*S*)-4″-Hydroxy-5″-methyl-3′a,6′,7′,7′a,3″,4″,5″,6″-octahydrodispiro[oxirane-2,3′(2′*H*)-benzofuran-2′,2″-[2*H*]pyran] (12).** To a vigorously stirred solution of 781 mg (1.55 mmol) of the minor aldol product **10b** in 50 mL of 10:1 $CH_2Cl_2$–$H_2O$ was added 352 mg (1.55 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. After 70 min, 30 mL of saturated aqueous $NaHCO_3$ was added to the now dark brown solution. The aqueous layer was extracted with 2 × 50 mL of $CH_2Cl_2$. These extracts in turn were washed with 50 mL of $H_2O$, dried over $MgSO_4$, and concentrated to a yellow oil, which was flash chromatographed on 75 g of 230–400-mesh silica gel (elution with 2:3 ether–hexanes) to give 543 mg (91%) of a hemiketal: $R_f$ 0.25 (1:1 ether–hexanes). Anal. Calcd for $C_{20}H_{36}O_5Si$: C, 62.46; H, 9.43. Found: C, 62.76; H, 9.70.

A solution of 538 mg (1.40 mmol) of the hemiketal in 20 mL of acetonitrile was treated with 2.0 mL of 5% HF in acetonitrile (v/v). The resulting pink solution was stirred for 10 min, and then the reaction was quenched with 20 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 2 × 50 mL of ether. These extracts were washed with 25 mL of $H_2O$, dried over $MgSO_4$, and concentrated to a yellow oil. Flash chromatography on 50 g of 230–400-mesh silica gel (elution with 4:1 ether–hexanes) afforded 322.8 mg (91%) of the spiroketal **12** as a white solid. Recrystallization from ether–hexanes gave thin crystalline rods melting at 109 °C: $R_f$ 0.46 (4:1 ether–hexanes); $[\alpha]^{24}_D$ -0.2° ($c$ 2.54, $CH_2Cl_2$); IR ($CHCl_3$) 3620, 3500, 3010, 2965, 2935, 2880, 1462, 1434, 1396, 1378, 1303, 1170, 1108, 1088, 1040, 995, 950, 927, 907, 898, 839, 670, 613 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.12–6.08 (m, 1 H), 5.92–5.88 (m, 1 H), 4.42–4.40 (m, 1 H), 3.68 (dt, 1 H, $J$ = 4.6, 10.8 Hz), 3.54–3.45 (m, 2 H), 2.92 (AB q, 2 H, $J_{AB}$ = 5.0 Hz, $\Delta\nu_{AB}$ = 6.3 Hz), 2.26 (dt, 1 H, $J$ = 12.7, 5.6 Hz), 2.16–2.09 (m, 1 H), 1.90–1.81 (m, 1 H), 1.86 (dd, 1 H, $J$ = 4.7, 13.0 Hz), 1.60–1.48 (m, 3 H), 1.33 (dq, 1 H, $J$ = 4.7, 12.6 Hz), 1.17 (dd, 1 H, $J$ = 11.4, 13.0 Hz), 0.92 (d, 2 H, $J$ = 6.6 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 133.38, 124.12, 105.11, 70.50, 70.33, 69.00, 65.55, 48.36, 38.73(2), 37.25, 23.74, 19.18, 12.75; MS (15 eV), base peak 80. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.38; H, 8.04.

**(2*R*,2′*S*,3′a*R*,7′a*R*,5″*S*)-5″-Methyl-4-oxo-3′a,6′,7′,7′a,-3″,4″,5″,6″-octahydrodispiro[oxirane-2,3′(2′*H*)-benzofuran-2′,2″-[2*H*]pyran] (13).** To a solution of 109.7 mg (0.435 mmol) of the alcohol **12** in 10 mL of acetone maintained at 0 °C was added 0.163 mL (0.435 mmol) of 2.67 M Jones reagent. The reaction was quenched after 40 min with the addition of a few drops of 2-propanol. The reaction mixture was filtered through a pad of silica gel (ether rinse) and concentrated. Chromatography on 15 g of 60–200-mesh silica gel (elution with 1:1 ether–hexanes) afforded 102.6 mg (94%) of the ketone **13** as white crystals: mp 99–99.5 °C; $R_f$ 0.71 (4:1 ether–hexanes; $[\alpha]^{24}_D$ +14.7° ($c$ 1.05, $CH_2Cl_2$); IR ($CHCl_3$) 3035, 3015, 2975, 2960, 2895, 1730, 1468, 1454, 1402, 1389, 1333, 1320, 1309, 1242, 1157, 1121, 1111, 1102, 1090, 1065, 1003, 989, 957, 929, 909, 891, 844, 684, 660 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.09–6.05 (m, 1 H), 5.87–5.84 (m, 1 H), 4.43 (m, 1 H), 3.87 (dd, 1 H, $J$ = 7.3, 11.0 Hz), 3.76 (t, 1 H, $J$ = 11.2 Hz), 3.02 (AB q, 2 H, $J_{AB}$ = 4.8 Hz, $\Delta\nu_{AB}$ = 11.0 Hz), 2.58–2.52 (m, 1 H), 2.32 (AB q, 1 H, $J_{AB}$ = 14.8 Hz, $\Delta\nu_{AB}$ = 12.1 Hz), 2.29–2.25 (m, 1 H), 2.15–2.11 (m, 1 H), 1.90–1.81 (m, 1 H), 1.58–1.52 (m, 1 H), 1.32 (dq, 1 H, $J$ = 4.7, 12.5 Hz), 0.96 (d, 3 H, $J$ = 6.7 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 205.63, 133.27, 123.68, 106.92, 70.88, 68.75, 65.76, 48.44, 46.32, 44.39, 37.06, 23.56, 18.98, 8.71; MS (15 eV) parent peak 250, base peak 80. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.91; H, 7.42.

**(2*R*,2′*S*,3′a*R*,7′a*R*,4″*S*,5″*S*)-4″-[(*tert*-Butyldimethylsilyl)oxy]-5″-methyl-3′a,6′,7′,7′a,3″,4″,5″,6″-octahydrodispiro[oxirane-2,3′(2′*H*)-benzofuran-2′,2″-[2*H*]pyran] (14).** To a solution of 1.63 mL (14.0 mmol) of 2,6-lutidine and 1.72 g (7.02 mmol) of the alcohol **2** in 50 mL of $CH_2Cl_2$ maintained at 0 °C was added 2.42 mL (10.5 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. The reaction was quenched after 10 min with the addition of 50 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 2 × 150 mL of ether. These extracts, in turn, were washed with 50 mL each of $H_2O$, saturated aqueous $CuSO_4$, and $H_2O$, dried over $MgSO_4$, and concentrated to a yellow oil. Flash chromatography on 80 g of 230–400-mesh silica gel (elution with 3:1 hexanes–ether) gave 2.53 g (98%) of **14** as a yellow oil: $R_f$ 0.72 (1:1 ether–hexanes); $[\alpha]^{25}_D$ +42.2° ($c$ 1.10, $CH_2Cl_2$); IR ($CDCl_3$) 3015, 2970, 2940, 2895, 2870, 1466, 1395, 1359, 1318, 1256, 1165, 1140, 1115, 1099, 1077, 1064, 1005, 988, 959, 935, 913, 900, 842, 680 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.99–5.96 (m, 1 H), 5.88–5.84 (m, 1 H), 4.41–4.38 (m, 1 H), 3.93 (t, 1 H, $J$ = 11.1 Hz), 3.85–3.83 (m, 1 H), 3.21 (dd, 1 H, $J$ = 4.2, 10.8 Hz), 2.87 (AB q, 2 H, $J_{AB}$ = 5.0 Hz, $\Delta\nu_{AB}$ = 9.9 Hz), 2.19 (dt, 1 H, $J$ = 12.8, 5.6 Hz), 2.10–2.04 (m, 1 H), 1.86–1.76 (m, 1 H), 1.70–1.64 (m, 1 H), 1.61 (dd, 1 H, $J$ = 2.9, 14.6 Hz), 1.51–1.45 (m, 1 H), 1.33 (dd, 1 H, $J$ = 3.2, 14.5 Hz), 1.26 (dq, 1 H, $J$ = 4.6, 12.5 Hz), 0.88 (s, 9 H), 0.76 (d, 3 H, $J$ = 6.9 Hz), 0.01 (s, 3 H), -0.03 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 131.55, 125.31, 102.44, 70.51, 69.93, 67.58, 62.09, 48.50, 37.44, 36.65, 35.33, 25.80, 23.86, 19.40, 18.16, 13.41, -4.37, -5.12; MS (15 eV) parent peak 366, base peak 189. Anal. Calcd for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35. Found: C, 65.43; H, 9.42.

**(2*R*,2′*S*,3′a*R*,7′a*R*,4″*S*,5″*R*)-4″-[(*tert*-Butyldimethylsilyl)oxy]decahydro-5″-methyl-6′-oxodispiro[oxirane-2,3′-(2′*H*)-benzofuran-2′,2″-[2*H*]pyran] (15).** A solution of 423.4 mg (1.16 mmol) of the unsaturated spiroketal **14** and 492.8 mg

(1.16 mmol) of mercuric trifluoroacetate in 6 mL of 1:1 THF–$H_2O$ was stirred vigorously for 2 h. This solution was made alkaline by the slow addition (1 drop/10 s) of 1.16 mL of 3.0 M NaOH. This was followed by the slow addition (1 drop/10 s) of 1.16 mL of 0.5 M $NaBH_4$ in 3.0 M NaOH. After 5 min the solution was diluted with 75 mL of ether and washed with 2 × 20 mL of $H_2O$ (back-extracted with 50 mL of ether). The ethereal solutions were dried over $MgSO_4$ and concentrated to a pale oil. Flash chromatography on 30 g of 230–400-mesh silica gel (elution with 2:1 ether–hexanes) afforded 44.7 mg (11%) of recovered **14** and 365.4 mg (82%) of a mixture (1.7:1) of alcohols.

To a solution of 354.6 mg (0.922 mmol) of the alcohols in 15 mL of DMF was added 1.04 g of PDC (2.77 mmol). The resulting brown solution was stirred for 18 h. This solution was diluted with 200 mL of saturated aqueous $NaHCO_3$ and extracted with 2 × 250 mL of ether. These extracts were then washed with 100 mL each of $H_2O$, saturated aqueous $CuSO_4$ and $H_2O$. The ethereal solutions were dried over $MgSO_4$ and concentrated to a light yellow oil. Flash chromatography on 30 g of 230–400-mesh silica gel (elution with 1:1 ether–hexanes) afforded 328.8 mg (93%) of the ketone **15** as a puffy white solid: mp 106.5–108 °C; $R_f$ 0.32 (1:1 ether–hexanes); $[\alpha]^{25}_D$ +160° (*c* 1.39, $CH_2Cl_2$); IR ($CHCl_3$) 2960, 2930, 2860, 1716, 1463, 1406, 1363, 1311, 1250, 1234, 1163, 1131, 1071, 1057, 998, 984, 953, 912, 876, 834, 828 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.62–4.58 (m, 1 H), 3.83 (m, 1 H), 3.83 (t, 1 H, $J$ = 11.1 Hz), 3.20 (dd, 1 H, $J$ = 3.7, 10.5 Hz), 2.80 (AB q, 2 H, $J_{AB}$ = 4.6 Hz, $\Delta\nu_{AB}$ = 4.5 Hz), 2.72–2.68 (m, 1 H), 2.69 (dd, 1 H, $J$ = 3.3, 16.7 Hz), 2.53 (dd, 1 H, $J$ = 3.8, 17.0 Hz), 2.23–2.19 (m, 2 H), 1.71–1.64 (m, 3 H), 1.59 (dd, 1 H, $J$ = 2.8, 14.7 Hz), 1.23 (dd, 1 H, $J$ = 3.2, 14.6 Hz), 0.84 (s, 9 H), 0.75 (d, 3 H, $J$ = 6.9 Hz), −0.06 (s, 3 H); irradiation at $\delta$ 4.60 reduces an apparent pair of dd to an AB q at $\delta$ 2.61: 2 H, $J_{AB}$ = 17.0 Hz, $\Delta\nu_{AB}$ = 59.2 Hz; $^{13}C$ NMR ($CDCl_3$) $\delta$ 209.82, 103.22, 73.43, 68.27, 67.11, 61.94, 46.81, 41.74, 36.59, 35.23, 34.89(2), 25.70, 19.25, 18.07, 13.37, −4.40, −5.21; MS (15 eV) base peak 325.

**(2*R*,2′*S*,3′a*R*,6′*S*,7′a*R*,4″*S*,5″*S*)- and (2*R*,2′*S*,3′a*R*,6′*R*,7′a*R*,4″*S*,5″*S*)-Decahydro-4″-hydroxy-5″-methyldispiro[oxirane-2,3′(2′*H*)-benzofuran-2′,2″-[2*H*]pyran]-6′-carboxaldehyde (16b,a).** To a solution of 0.128 mL (0.166 mmol) of 1.30 M *sec*-butyllithium in cyclohexane in 1 mL of THF maintained at −95 °C was added 0.400 mL (0.194 mmol) of 0.49 M diphenyl(methoxymethyl)phosphine in THF over a 20-min period. The resulting orange solution was stirred for 15 min. A solution of 10.6 mg (0.0277 mmol) of the ketone **15** in 0.500 mL of THF was added over a 15-min period. This solution was stirred at −95 °C for 15 min and was then warmed slowly to −30 °C. This reaction was quenched with the addition of 15 $\mu$L of MeOH. Methyl iodide (100 $\mu$L) was added, and this solution was stirred at ambient temperature for 2 h. This solution was diluted with 30 mL of ether and washed with 2 × 10 mL of $H_2O$ (back-extracted with 20 mL of ether). The ethereal solutions were dried over $MgSO_4$ and concentrated to a clear oil. Flash chromatography on 6 g of 230–400-mesh silica gel (elution with 2:1 hexanes–ether) afforded 4.4 mg (42%) of recovered **15** and 4.0 mg (35%) of a mixture of enol ethers.

Trichloroacetic acid (6 mg) was added to a solution of 4.0 mg of the enol ether mixture in 0.5 mL of $CH_2Cl_2$. The reaction was stirred for 30 min at room temperature and then quenched with the addition of several drops of saturated aqueous $NaHCO_3$. This solution was diluted with 30 mL of ether and washed with 2 × 10 mL of $H_2O$ (back-extracted with 30 mL of ether). The ethereal solutions were dried over $MgSO_4$ and concentrated to a clear oil. Flash chromatography on 6 g of 230–400-mesh silica gel (elution with 2:1 ether–hexanes) afforded 0.1 mg of the aldehyde **16b** and 2.9 mg of the aldehyde **16a**.

Data for **16b**: $R_f$ 0.17 (1:1 ether–hexanes); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.68 (s, 1 H), 4.48–4.45 (m, 1 H), 3.80–3.78 (m, 1 H), 3.71 (t, 1 H, $J$ = 11.8 Hz), 3.40 (dd, 1 H, $J$ = 4.9, 11.5 Hz), 3.10 (d, 1 H, $J$ = 10.4 Hz), 2.92 (s, 2 H), 2.63–2.57 (m, 1 H), 2.29–2.25 (m, 1 H), 2.07–2.01 (m, 2 H), 1.84 (dd, 1 H, $J$ = 3.1, 14.6 Hz) 1.77–1.12 (m, 5 H), 1.58 (dd, 1 H, $J$ = 3.2, 14.6 Hz), 0.87 (d, 3 H, $J$ = 6.9 Hz).

Data for **16a**: $R_f$ 0.12 (1:1 ether–hexanes); IR ($CHCl_3$) 3535, 3015, 2960, 2935, 2875, 1725, 1459, 1233, 1158, 1121, 1064, 1041, 863 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.66 (s, 1 H), 4.41–4.37 (m, 1 H), 3.79 (br s, 1 H), 3.74 (t, 1 H, $J$ = 11.7 Hz), 3.39 (dd, 1 H, $J$ = 4.2, 10.9 Hz), 2.83 (AB q, 2 H, $J_{AB}$ = 4.6 Hz, $\Delta\nu_{AB}$ = 11.2 Hz), 2.45–1.41 (m, 9 H), 1.74 (dd, 1 H, $J$ = 3.0, 14.4 Hz), 1.47 (dd, 1 H, $J$ = 3.3, 14.5 Hz), 0.87 (d, 3 H, $J$ = 6.9 Hz).

**(2*R*,2′*S*,3′a*R*,7′*S*,7′a*R*,4″*S*,5″*R*)-4″-[(*tert*-Butyldimethylsilyl)oxy]decahydro-5″-methyldispiro[oxirane-2,3′(2′*H*)-benzofuran-2′,2″-[2*H*]pyran]-7′-carboxaldehyde (19) and (2*R*,2′*S*,3′a*R*,6′*S*,7′a*R*,4″*S*,5″*R*)- and (2*R*,2′*S*,3′a*R*,6′*R*,7′a*R*,4″*S*,5″*R*)-4″-[(*tert*-Butyldimethylsilyl)oxy]decahydro-5″-methyldispiro[oxirane-2,3′(2′*H*)-benzofuran-2′,2″-[2*H*]pyran-6′-carboxaldehyde (18b,a).** To a solution of 341.5 mg (0.932 mmol) of **14** in 10 mL of benzene in a 45 mL capacity Parr bomb was added 40.3 mg (75 mmol) of $[(COD)RhOAc]_2$. The bomb was sealed, evacuated under aspirator pressure, filled with 400 psi of CO, vented, and filled to 280 psi with CO and then to 555 psi with $H_2$. The bomb was then placed in a 76 °C oil bath, and its contents were stirred for 3.25 h.

This reaction was repeated on 284.3 mg of **14** in an exactly analogous manner. The two reactions were combined and filtered through 50 g of silica gel and concentrated to a brown oil. Flash chromatography on 60 g of 230–400-mesh silica gel (elution with 1:5 ether–hexanes) afforded 83.1 mg (12%) of **19**, 135.6 mg (20%) of **18b**, and 139.9 mg (21%) of **18a**.

Data for **19**: $R_f$ 0.56 (2:3 ether–hexanes); $[\alpha]^{25}_D$ +101° (*c* 3.06, $CH_2Cl_2$); IR ($CHCl_3$) 2960, 2935, 2890, 2865, 1726, 1465, 1390, 1355, 1312, 1252, 1238, 1161, 1135, 1095, 1078, 1060, 1009, 992, 975, 930, 909, 893, 881, 838, 812 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.73 (s, 1 H), 4.56 (t, 1 H, $J$ = 4.9 Hz), 3.89 (t, 1 H, $J$ = 11.2 Hz), 3.85–3.84 (m, 1 H), 3.20 (dd, 1 H, $J$ = 4.2, 10.8 Hz), 2.85 (AB q, 2 H, $J_{AB}$ = 4.9 Hz, $\Delta\nu_{AB}$ = 20.1 Hz), 2.75 (q, 1 H, $J$ = 5.0 Hz), 2.23 (dq, 1 H, $J$ = 9.4, 5.9 Hz), 1.77–1.16 (m, 7 H), 1.74 (dd, 1 H, $J$ = 4.7, 8.8 Hz), 1.65 (dd, 1 H, $J$ = 2.6, 9.2 Hz), 0.89 (s, 9 H), 0.75 (d, 3 H, $J$ = 6.9 Hz), 0.03 (s, 3 H), −0.01 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 202.69, 102.27, 72.48, 70.12, 67.37, 62.12, 50.56, 48.32, 36.92, 36.39, 35.08, 25.72, 21.74, 20.75, 20.31, 18.06, 13.36, −4.33, −5.21; MS (15 eV) parent peak 396, base peak 145. Anal. Calcd for $C_{21}H_{36}O_5Si$: C, 63.60; H, 9.15. Found: C, 63.86; H, 9.02.

Data for **18b**: $R_f$ 0.41 (2:3 ether–hexanes); $[\alpha]^{25}_D$ +99.6° (*c* 2.85, $CH_2Cl_2$); IR ($CHCl_3$) 2958, 2930, 2858, 1725, 1463, 1388, 1366, 1357, 1251, 1238, 1161, 1137, 1059, 981, 964, 900, 836 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.63 (s, 1 H), 4.35 (q, 1 H, $J$ = 3.6 Hz), 3.89 (t, 1 H, $J$ = 11.1 Hz), 3.83–3.82 (m, 1 H), 3.18 (dd, 1 H, $J$ = 4.1, 10.8 Hz), 2.87 (AB q, 2 H, $J_{AB}$ = 5.2 Hz, $\Delta\nu_{AB}$ = 9.5 Hz), 2.54 (tt, 1 H, $J$ = 3.9, 11.9 Hz), 2.28–2.22 (m, 1 H), 1.98–1.92 (m, 2 H), 1.69–1.07 (m, 5 H), 1.62 (dd, 1 H, $J$ = 2.9, 14.6 Hz), 1.45 (dd, 1 H, $J$ = 3.2, 14.6 Hz), 0.89 (s, 9 H), 0.74 (d, 3 H, $J$ = 6.9 Hz), 0.02 (s, 3 H), −0.02 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 203.77, 102.34, 71.94, 71.04, 67.43, 62.21, 49.70, 44.75, 38.38, 37.29, 35.08, 26.69, 25.65, 23.13, 21.87, 18.04, 13.38, −4.37, −5.16; MS (15 eV) parent peak 396, base peak 145. Anal. Calcd for $C_{21}H_{36}O_5Si$: C, 63.60; H, 9.15. Found: C, 63.34; H, 9.45.

Data for **18a** (this material is contaminated with ca. 20% of an isomeric aldehyde which could not be removed by chromatography): $R_f$ 0.36 (2:3 ether–hexanes); IR ($CHCl_3$) 2955, 2930, 2855, 1723, 1463, 1389, 1360, 1353, 1251, 1236, 1161, 1132, 1057, 889, 837 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.61 (s, 1 H), 4.30 (q, 1 H, $J$ = 6.4 Hz), 3.88–3.77 (m, 1 H), 3.87 (t, 1 H, $J$ = 11.2 Hz), 3.17 (dd, 1 H, $J$ = 4.1, 10.8 Hz), 2.74 (AB q, 2 H, $J_{AB}$ = 4.5 Hz, $\Delta\nu_{AB}$ = 34.4 Hz), 2.48–1.14 (m, 11 H), 0.88 (s, 9 H), 0.74 (d, 3 H, $J$ = 6.9 Hz), 0.03 (s, 3 H), −0.03 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 203.45, 103.01, 74.36, 68.75, 67.09, 61.92, 50.14, 44.81, 36.25, 35.56, 35.11, 28.50, 25.79, 22.49, 18.82, 18.04, 13.32, −4.37, −5.30.

To a solution of 43.7 mg (0.110 mmol) of the impure aldehyde **18a** in 0.80 mL of MeOH was added 5 mg of 60% NaH. This solution was stirred at room temperature for 22 h and then filtered through 500 mg of silica gel. The filtrate was concentrated to a yellow oil, which was flash chromatographed on 30 g of 230–400-mesh silica gel (elution with 1:5 ether–hexanes) to afford 24.5 mg (56%) of pure **18b** as well as 10.3 mg (24%) of recovered (but still somewhat impure) **18a**.

To a solution of 59.2 mg (0.161 mmol) of **14** and 7.0 mg (0.0129 mmol) of $[(COD)RhOAc]_2$ in 3.0 mL of benzene in a 45 mL capacity Parr bomb was added 124 mg (0.258 mmol) of tris(*o*-*tert*-butylphenyl) phosphite. The bomb was sealed, evacuated

under aspirator pressure, filled to 400 psi with CO, vented, and filled to 330 psi with CO and then to 660 psi with $H_2$. The bomb was then placed in a 77 °C oil bath (final pressure: 730 psi), and its contents were stirred for 75 min. The yellow solution was then loaded directly on a column of 50 g of 230–400-mesh silica gel (elution with 1:4 ether–hexanes) to afford 34.5 mg (54%) of **19**, 9.3 mg (15%) of **18b**, and 3.2 mg (5%) of a mixture of aldehydes which was predominantly **18a**.

**Methyl (2*R*,2′*S*,3′a*R*,6′*S*,7′a*R*,4″*S*,5″*S*)-Decahydro-4″-hydroxy-5″-methyl-3′a,6′,7′,7′a,3″,4″,5″,6″-octahydrodispiro[oxirane-2,3′(2′*H*)-benzofuran-2′,2″-[2*H*]pyran]-6′-carboxylate (17).** To a solution of 110.8 mg (0.189 mmol) of the aldehyde **30** in 5 mL of acetone was added 0.071 mL (0.189 mmol) of 2.67 M Jones' reagent. The resulting dark green solution was quenched after 10 min with the addition of 1 mL of 2-propanol. The acetone was removed in vacuo and replaced with 5 mL of MeOH. This solution was treated with 0.63 mL (1.89 mmol) of 3.0 M NaOH in $H_2O$. The resulting aquamarine suspension was warmed to 75 °C and stirred for 30 min. The suspension was cooled to room temperature, neutralized with 1.5 N $H_2SO_4$, and concentrated. The residual slush was dissolved in 15 mL of $H_2O$ and extracted with 3 × 30 mL of ether. These extracts were concentrated to 10 mL, cooled to 0 °C, and treated with an excess of ethereal $CH_2N_2$. This solution was stirred at 0 °C for 5 min and then at room temperature for 25 min, dried over $MgSO_4$, and concentrated to a yellow oil, which was flash chromatographed on 20 g of 230–400-mesh silica gel (elution with 4:1 hexanes–acetone) to afford 49.5 mg (84%) of **17** as thin crystalline rods. An analytical sample was obtained by recrystallization from ether–hexanes: mp 130–130.5 °C; $R_f$ 0.49 (2:1 ether–hexanes); $[\alpha]^{25}_D$ +126° (*c* 1.23, $CHCl_3$); IR ($CHCl_3$) 3535, 3012, 2960, 2940, 2880, 1730, 1458, 1449, 1439, 1428, 1414, 1388, 1363, 1355, 1309, 1249, 1198, 1173, 1161, 1124, 1111, 1086, 1076, 1059, 1048, 1033, 1019, 992, 950, 921, 895, 860, 847 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 4.41 (q, 1 H, *J* = 3.6 Hz), 3.83–3.75 (m, 1 H), 3.69 (t, 1 H, *J* = 11.8 Hz), 3.65 (s, 3 H), 3.37 (dd, 1 H, *J* = 4.7, 11.6 Hz), 3.12 (d, 1 H, *J* = 10.3 Hz), 2.90 (s, 2 H), 2.59 (tt, 1 H, *J* = 3.9, 11.8 Hz), 2.28–2.23 (m, 1 H), 2.01–1.92 (m, 2 H), 1.82 (dd, 1 H, *J* = 3.1, 14.6 Hz), 1.82–1.58 (m, 3 H), 1.56 (dd, 1 H, *J* = 3.3, 14.6 Hz), 1.44–1.24 (m, 2 H), 0.85 (d, 3 H, *J* = 6.9 Hz); $^{13}C$ NMR ($CDCl_3$) δ 175.91, 103.53, 73.80, 70.37, 67.98, 62.32, 51.59, 49.73, 38.12, 37.10, 36.67, 34.47, 29.58, 26.26, 21.95, 12.94; MS (70 eV) parent peak 312, base peak 71. Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.73; H, 7.82.

To a solution of 54.2 mg (0.137 mmol) of the aldehyde **18b** in 5.0 mL of acetone maintained at 0 °C was added 46 μL of 2.67 M Jones' reagent. The reaction was quenched after 10 min with the addition of 5 drops of 2-propanol. The solution was diluted with 5.0 mL of $H_2O$, acidified to pH 3 with 1% $H_2SO_4$, and extracted with 2 × 50 mL of ether. These extracts were concentrated to 5 mL, cooled to 0 °C, and treated with an excess of ethereal diazomethane. This solution was stirred for 5 min at 0 °C and then for 10 min at room temperature. This solution was concentrated to a colorless oil, which was flash chromatographed on 6 g of 230–400-mesh silica gel (elution with 1:1 ether–hexanes) to afford 54.3 mg (93%) of the TBS protected ester as white crystals: mp 89.5–91 °C; $R_f$ 0.57 (1:1 ether–hexanes); $[\alpha]^{25}_D$ +101° (*c* 1.95, $CH_2Cl_2$); IR ($CHCl_3$) 2955, 2930, 2855, 1728, 1472, 1463, 1448, 1437, 1388, 1352, 1309, 1251, 1238, 1167, 1136, 1111, 1089, 1075, 1059, 1043, 994, 980, 956, 948, 931, 901, 888, 838 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.31 (q, 1 H, *J* = 3.5 Hz), 3.90 (t, 1 H, *J* = 11.2 Hz), 3.84–3.83 (m, 1 H), 3.65 (s, 3 H), 3.18 (dd, 1 H, *J* = 4.2, 10.8 Hz), 2.88 (AB q, 2 H, $J_{AB}$ = 5.3 Hz, $\Delta\nu_{AB}$ = 10.1 Hz), 2.59 (tt, 1 H, *J* = 3.6, 11.9 Hz), 2.28–2.22 (m, 1 H), 1.94–1.90 (m, 2 H), 1.75–1.55 (m, 3 H), 1.63 (dd, 1 H, *J* = 2.9, 14.6 Hz), 1.45 (dd, 1 H, *J* = 3.2, 14.6 Hz), 1.38–1.17 (m, 2 H), 0.91 (s, 9 H), 0.74 (d, 3 H, *J* = 6.9 Hz), 0.05 (s, 3 H) –0.01 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 176.24, 102.20, 72.20, 71.13, 67.42, 62.17, 51.37, 49.79, 38.18, 37.34 (2), 35.07, 29.66, 26.34, 25.60, 22.18, 17.97, 13.35, –4.43, –5.19; MS (13 eV) parent peak + 1 427, base peak 145. Anal. Calcd for $C_{22}H_{38}O_6Si$: C, 61.94; H, 8.98. Found: C, 61.87; H, 8.97.

To a solution of 192.8 mg (0.452 mmol) of the TBS-protected ester in 10 mL of acetonitrile at 0 °C was added 0.452 mL of 5% HF in acetonitrile (v/v). This solution was quenched after 2 h with the addition of 15 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 2 × 60 mL of ether. The organic layers were dried over $MgSO_4$ and concentrated to a yellow oil, which was chromatographed on 55 g of 230–400-mesh silica gel (elution with 1:1 ether–hexanes) to afford 134.9 mg (96%) of **17** as a powdery white solid.

To a solution of 2.8 mg (9.9 μmol) of the aldehyde **16a** and 6.9 mg (30 μmol) of $Ag_2O$ in 0.5 mL of MeOH was added 30 μL of 2.0 M NaOH. The resulting gray suspension was warmed to 50 °C and stirred for 2 h. This gave none of the desired acid, but the majority of the aldehyde appeared (by TLC) to have been epimerized. This solution was further warmed to 75 °C and stirred for 3 h. This solution was diluted with $H_2O$ and acidified to pH 3 with 10% $H_2SO_4$. This solution was extracted with 2 × 50 mL of ether. These extracts were concentrated to 1 mL and cooled to 0 °C. This solution was treated with an excess of ethereal $CH_2N_2$. This solution was stirred for 10 min, dried over $MgSO_4$, and concentrated to a clear oil. Flash chromatography on 6 g of 230–400-mesh silica gel (elution with 3:1 ether–hexanes) afforded 3.1 mg of an impure mixture (ca. 2:1 by 400-MHz NMR) of the ester **17** and its C3 epimer.

**(2*R*,2′*S*,3′a*R*,7′a*R*,4″*S*,5″*R*)-4″-[[4-(Diphenylphosphino)benzoyl]oxy]-5″-methyl-3′a,6′,7′,7′a,3″,4″,5″,6″-octahydrodispiro[oxirane-2,3′(2′*H*)-benzofuran-2′,2″-[2*H*]pyran] (23).** To a solution of 64.7 mg (0.256 mmol) of the alcohol **2** and 102 mg (0.333 mmol) of *p*-(diphenylphosphino)benzoic acid[30] (chromatographed under Ar just prior to use) and 15 mg (0.101 mmol) of 4-pyrrolidinopyridine in 1.5 mL of degassed $CH_2Cl_2$ was added 63.5 mg (0.308 mmol) of DCC. The resulting suspension was stirred at room temperature for 1 h and then at 57 °C for 8 h. An additional 51 mg (0.167 mmol) of the acid and 31.7 mg (0.156 mmol) of DCC was added to this solution. This mixture was further warmed to 60 °C and stirred for 13 h. This solution was concentrated to a white solid. Flash chromatography under Ar on 25 g of 230–400-mesh silica gel (elution with 6:1 hexanes–EtOAc) afforded the impure ester. Further flash chromatography on 25 g of 230–400-mesh silica gel (elution with 1:2 ether–hexanes) afforded 106.9 mg (77%) of the ester **23** as a white foam: $R_f$ 0.62 (2:1 hexanes–EtOAc); $[\alpha]^{24}_D$ –51.9° (*c* 1.76, $CH_2Cl_2$); IR ($CHCl_3$) 3010, 2975, 2935, 2875, 1714, 1598, 1433, 1393, 1283, 1258, 1162, 1119, 1110, 1069, 1048, 1018, 1008, 953, 697 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.06 (br d, 2 H, *J* = 8.5 Hz), 7.40–7.25 (m, 12 H), 5.96–5.92 (m, 1 H), 5.81–5.77 (m, 1 H), 5.29–5.28 (m, 1 H), 4.45 (m, 1 H), 4.01 (t, 1 H, *J* = 11.5 Hz), 3.42 (dd, 1 H, *J* = 4.5, 11.0 Hz), 2.90 (AB q, 2 H, $J_{AB}$ = 4.9 Hz, $\Delta\nu_{AB}$ = 16.6 Hz), 2.29–2.23 (m, 1 H), 2.07–1.76 (m, 3 H), 1.89 (dd, 1 H, *J* = 2.8, 15.3 Hz), 1.53 (dd, 1 H, *J* = 3.4, 15.2 Hz), 1.47–1.41 (m, 1 H), 1.28–1.17 (m, 1 H), 0.82 (d, 3 H, *J* = 6.9 Hz); $^{13}C$ NMR ($CDCl_3$) δ 166.04, 143.79, 143.11, 136.64, 136.11, 134.37, 133.54, 133.39, 132.59, 132.54, 130.99, 129.80, 129.48, 129.00, 128.76, 128.41, 124.58, 102.32, 70.74, 69.74, 69.60, 62.40, 48.36, 37.21, 33.59, 33.37, 23.71, 19.13, 12.73; MS (15 eV) parent peak 540, base peak 262. Anal. Calcd for $C_{33}H_{33}O_5P$: C, 73.32; H, 6.15. Found: 73.06; H, 6.23.

**(2*R*,2′*S*,3′a*R*,7′*S*,7′a*R*,4″*S*,5″*R*)-Decahydro-4″-[[4-(diphenylphosphinyl)benzoyl]oxy]-5″-methyldispiro[oxirane-2,3′(2′*H*)-benzofuran-2′,2″-[2*H*]pyran]-7′-carboxaldehyde (26).** To a solution of 51.2 mg (94.7 μmol) of the phosphine **23** in 4 mL of deoxygenated benzene in a 45 mL capacity Parr bomb in an Ar-filled glovebag was added 4.1 mg (7.6 μmol) of $[(CO\text{-}D)RhOAc]_2$. The bomb was sealed while still in the glovebag and then evacuated under aspirator pressure. The bomb was then filled to 400 psi with CO, vented, and filled to 310 psi with CO and then to 620 psi with $H_2$. The bomb was then placed in a 85 °C oil bath, and its contents were stirred for 3 h (final pressure: 680 psi). The bomb was then cooled to room temperature and vented. Bis(1,3-diphenylphosphino)propane (18.8 mg, 45.6 μmol) was added, the bomb was again placed in a 85 °C oil bath, and its contents were stirred for 30 min. The contents of the bomb were filtered through a pad of silica gel and concentrated to a yellow oil. Flash chromatography under Ar on 12 g of 230–400-mesh silica gel (elution with 4:1 hexanes–ether) afforded 42.8 mg (84%) of recovered **23** and 4.3 mg (8%) of the aldehyde **24**.

Repeating this reaction with the recovered **23** gave essentially the same results (72% recovered **23** and 9% of **24**).

Data for **24**: $R_f$ 0.40 (4:1 hexanes–acetone); $^1H$ NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1 H), 8.02 (d, 2 H, *J* = 8.3 Hz), 7.36–7.29 (m, 12 H), 5.21 (m, 1 H), 4.52 (t, 1 H, *J* = 5.7 Hz), 4.01 (t, 1 H, *J* = 11.5 Hz), 3.45 (dd, 1 H, *J* = 4.7, 11.2 Hz), 2.88 (s, 2 H), 2.50 (q,

1 H, $J$ = 5.6 Hz), 2.34 (dt, 1 H, $J$ = 8.3, 6.0 Hz), 2.04 (dd, 1 H, $J$ = 2.9, 14.9 Hz), 2.00–1.94 (m, 1 H), 1.58 (dd, 1 H, $J$ = 3.3, 15.2 Hz), 1.50–1.13 (m, 6 H), 0.85 (d, 3 H, $J$ = 6.9 Hz). Irradiation at $\delta$ 4.52 produced: $\delta$ 2.50 (br t, 1 H, $J$ = 5.2 Hz), 2.35 (br t, 1 H, $J$ = 6.8 Hz).

This material was further characterized as the phosphine oxide **26**. To a solution of 8.7 mg (15.2 $\mu$mol) of **24** in 5 mL of ether was added 1 mL of 1% aqueous $H_2O_2$. This solution was stirred vigorously for 45 min. The solution was diluted to 50 mL with ether and washed with 15 mL of $H_2O$. The ethereal solution was dried over $MgSO_4$ and concentrated to 8.6 mg (96%) of **26** as a yellow oil: $R_f$ 0.55 (1:1 acetone–hexanes); IR ($CHCl_3$) 2975, 2940, 1722, 1438, 1397, 1358, 1315, 1287, 1277, 1259, 1180, 1122, 1108, 1092, 1077, 1059, 1021, 1006, 993, 912, 855, 697 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.47 (s, 1 H), 8.17–8.14 (m, 2 H), 7.79–7.44 (m, 12 H), 5.24 (m, 1 H), 4.53 (t, 1 H, $J$ = 5.7 Hz), 4.01 (t, 1 H, $J$ = 11.5 Hz), 3.46 (dd, 1 H, $J$ = 4.7, 11.4 Hz), 2.87 (AB q, 2 H, $J_{AB}$ = 4.7 Hz, $\Delta\nu_{AB}$ = 5.9 Hz), 2.50 (q, 1 H, $J$ = 5.6 Hz), 2.38 (m, 1 H), 2.03 (dd, 1 H, $J$ = 2.8, 15.3 Hz), 1.99–1.98 (m, 1 H), 1.59 (dd, 1 H, $J$ = 3.3, 15.2 Hz), 1.48–1.16 (m, 6 H), 0.85 (d, 3 H, $J$ = 7.0 Hz); MS (70 eV) base peak 321.

A solution of 30.9 mg (57.2 $\mu$mol) of the phosphine **23** and 1 mL of 1% $H_2O_2$ in 20 mL of ether was stirred vigorously for 1 h. This solution was diluted to 50 mL with ether and washed with 15 mL of $H_2O$ (back-extracted with 20 mL of ether). These ethereal solutions were dried over $MgSO_4$ and concentrated to 30.9 mg (97%) of **25** as a colorless oil: $R_f$ 0.52 (1:1 acetone–hexanes); $[\alpha]^{25}_D$ –29.0° ($c$ 1.87, $CH_2Cl_2$); IR ($CHCl_3$) 2975, 2935, 1718, 1438, 1396, 1357, 1316, 1287, 1278, 1260, 1179, 1122, 1108, 1071, 1049, 1021, 1008, 999, 955, 915, 887, 859, 697 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.22–8.18 (m, 2 H), 7.78–7.44 (m, 12 H), 5.98–5.94 (m, 1 H), 5.82–5.79 (m, 1 H), 5.30 (m, 1 H), 4.47 (m, 1 H), 4.02 (t, 1 H, $J$ = 11.5 Hz), 3.44 (d, 1 H, $J$ = 4.8, 11.4 Hz), 2.91 (AB q, 2 H, $J_{AB}$ = 4.9 Hz, $\Delta\nu_{AB}$ = 16.8 Hz), 2.29–2.23 (m, 1 H), 2.02–1.98 (m, 2 H), 1.89 (dd, 1 H, $J$ = 2.8, 15.3 Hz), 1.83–1.80 (m, 1 H), 1.54 (dd, 1 H, $J$ = 3.3, 15.3 Hz), 1.48–1.44 (m, 1 H), 1.27–1.20 (m, 1 H), 0.82 (d, 3 H, $J$ = 6.9 Hz); MS (70 eV) parent peak 556, base peak 80.

To a solution of 30.7 mg (55.2 $\mu$mol) of the phosphine oxide **25** in 3 mL of benzene in a 45 mL capacity Parr bomb was added 2.4 mg (4.4 $\mu$mol) of $[(COD)RhOAc]_2$. The bomb was sealed, evacuated under aspirator pressure, filled with 400 psi of CO, vented, refilled to 320 psi with CO and then to 640 psi with $H_2$. The bomb was placed in a 85 °C oil bath, and its contents were stirred for 3 h (final pressure: 690 psi). After cooling to room temperature, the reaction solution was filtered through a pad of silica gel and concentrated to a brown oil. Flash chromatography on 15 g of 230–400-mesh silica gel (elution with 45:55 acetone–hexane) afforded 16.0 mg (49%) of a mixture of aldehydes of which **26** was predominant (by 400-MHz NMR).

**(2*R*,2′*S*,3′a*R*,7′a*R*,4″*S*,5″*R*)-4″-[[3-(Diphenylphosphino)benzoyl]oxy]-5″-methyl-3′a,6′,7′,7′a,3″,4″,5″,6″-octahydrodispiro[oxirane-2,3′(2′*H*)-benzofuran-2′,2″-[2*H*]pyran] (27).** To a solution of 168.2 mg (0.667 mmol) of the alcohol **2**, 306 mg (1.00 mmol) of *m*-(diphenylphosphino)benzoic acid[33] (chromatographed just prior to use under Ar), and 49 mg (0.333 mmol) of 4-pyrrolidinopyridine in 0.80 mL of deoxygenated $CH_2Cl_2$ was added 192.6 mg (0.933 mmol) of *N*,*N*′-dicyclohexylcarbodiimide in 1.92 mL of $CH_2Cl_2$. A precipitate appeared within 30 s. This suspension was placed in a 60 °C oil bath and stirred for 10 h. The solvent was removed in vacuo, and the residual sludge was flash chromatographed on 50 g of 230–400-mesh silica gel (elution with 7:1 hexane–EtOAc under Ar) to afford 315.5 mg (88%) of the ester **27** as a colorless oil: $R_f$ 0.62 (2:1 hexanes–EtOAc); $[\alpha]^{25}_D$ –25.0° ($c$ 1.03, $CH_2Cl_2$); IR ($CHCl_3$) 3075, 3060, 3030, 3015, 1713, 1479, 1463, 1434, 1426, 1389, 1357, 1317, 1280, 1268, 1258, 1234, 1168, 1138, 1124, 1071, 1050, 1011, 999, 956, 910, 886, 865, 698 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.10–8.06 (m, 2 H), 7.49–7.25 (m, 12 H), 5.84–5.80 (m, 1 H), 5.68–5.64 (m, 1 H), 5.19–5.18 (m, 1 H) 4.37–4.35 (m, 1 H), 3.83 (t, 1 H, $J$ = 11.4 Hz), 3.35 (dd, 1 H, $J$ = 4.7, 11.1 Hz), 2.88 (AB q, 2 H, $J_{AB}$ = 4.9 Hz, $\Delta\nu_{AB}$ = 18.3 Hz), 2.26–2.20 (m, 1 H), 2.03–1.40 (m, 4 H), 1.90 (dd, 1 H, $J$ = 2.8, 15.2 Hz), 1.47 (dd, 1 H, $J$ = 3.4, 15.2 Hz), 1.18 (dq, 1 H, $J$ = 5.4, 12.9 Hz), 0.75 (s, 3 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 165.78, 138.23, 138.00, 137.35, 137.31, 136.96, 136.91, 136.41, 136.36, 135.49, 134.44, 134.21, 134.03, 133.24, 133.06, 132.19, 131.39, 131.04, 130.15, 128.80, 128.67, 128.41, 128.32, 128.11, 124.74, 102.19, 70.64, 69.79, 69.48, 62.32, 48.22, 37.06, 33.26(2), 23.60, 19.07, 12.66; MS (15 eV) parent peak 540, base peak 307. Anal. Calcd for $C_{33}H_{33}O_5P$: C, 73.32; H, 6.15. Found: C, 73.31; H, 6.16.

**(2*R*,2′*S*,3′a*R*,6′*S*,7′a*R*,4″*S*,5″*R*)- and (2*R*,2′*S*,3′a*R*,-6′*R*,7′a*R*,4″*S*,5″*R*)-Decahydro-4″-[[3-(diphenylphosphinyl)benzoyl]oxy]-5″-methyldispiro[oxirane-2,3′-(2′*H*)-benzofuran-2′,2″-[2*H*]pyran]-6′-carboxaldehyde (29, 30).** To a solution of 159.1 mg (0.294 mmol) of the phosphine **27** in 5.0 mL of deoxygenated benzene in a 45 mL capacity Parr bomb in an Ar-filled glovebag was added 12.7 mg (0.024 mmol) of $[(COD)RhOAc]_2$. The initially yellow-orange solution became caramel colored while standing for 5 min. The bomb was sealed in the glovebag, evacuated under aspirator pressure, filled to 400 psi with CO, vented, and refilled to 330 psi with CO and then to 660 psi with $H_2$. The bomb was placed in a 85 °C oil bath (final pressure: 710 psi), and its contents were stirred for 3 h. The bomb was cooled to room temperature, and 58 mg (0.141 mmol) of bis(1,3-diphenylphosphino)propane was added to it. The bomb was again placed in the 85 °C oil bath, and its contents were stirred for 30 min. After cooling to room temperature, the reaction solution was loaded directly on a column of 30 g of 230–400-mesh silica gel, and the products were eluted under Ar with 5:1 hexanes–acetone for the phosphines and later with 1:1 hexane–acetone for the phosphine oxides. This afforded 123.8 mg of a mixture of phosphine aldehydes which were predominantly **28a** and 18.4 mg of the phosphine oxide **29** as white crystals. The phosphine mixture was dissolved in 5 mL of benzene and treated with 69 $\mu$L (0.250 mmol) of 3.63 M anhydrous *tert*-butyl hydroperoxide in toluene. The solution was stirred for 10 min and then loaded on a column of 15 g of 230–400-mesh silica gel (elution with 1:1 hexanes–acetone) to afford 127.1 mg (100% for the oxidation) of the phosphine oxides. The cumulative yield of phosphine oxide (145.5 g) was 84%. According to 90-MHz NMR this material was 86% regiochemically pure. Thus the revised yield of usable material is 72%.

Data for **29**: mp 73–76 °C; $R_f$ 0.43 (1:1 acetone–hexanes); $[\alpha]^{26}_D$ –8.79° ($c$ 1.16, $CH_2Cl_2$); IR ($CHCl_3$) 3065, 3030, 3015, 2975, 2940, 2885, 1723, 1596, 1487, 1439, 1297, 1269, 1260, 1178, 1143, 1123, 1072, 1052, 1009, 1001, 978, 956, 910, 868, 819, 697, 663 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.87 (s, 1 H), 8.38–8.29 (m, 2 H), 7.97–7.91 (m, 1 H), 7.71–7.42 (m, 11 H), 5.17–5.16 (m, 1 H), 4.24 (q, 1 H, $J$ = 4.8 Hz), 3.85 (t, 1 H, $J$ = 11.5 Hz), 3.36 (dd, 1 H, $J$ = 4.1, 11.3 Hz), 2.83 (s, 2 H), 2.19 (q, 1 H, $J$ = 6.6 Hz), 2.02–1.77 (m, 5 H), 1.84 (dd, 1 H, $J$ = 2.8, 15.3 Hz), 1.51 (dd, 1 H, $J$ = 3.4, 15.3 Hz), 1.38–1.23 (m, 3 H), 0.75 (d, 1 H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 202.27, 164.35, 164.28, 135.87, 135.34, 134.41, 132.99, 132.79, 132.68, 132.43, 131.83, 131.66, 131.35, 131.09, 130.48, 130.20, 129.23, 129.18, 128.51, 127.90, 102.04, 73.05, 69.85, 69.24, 62.17, 47.69, 42.99, 36.44, 33.02, 32.68, 26.73, 20.31, 17.96, 12.34; MS (70 eV) parent peak 586, base peak 323. Anal. Calcd for $C_{34}H_{35}O_7P$: C, 69.61; H, 6.01. Found: C, 69.80; H, 6.03.

To a solution of 175.8 mg (0.300 mmol) of the aldehyde **29** in 10 mL of MeOH was added 0.25 mL (0.75 mmol) of 3.0 M NaOH in $H_2O$. The reaction was quenched after 30 min with the addition of 10 mL of a pH 7 buffer. The MeOH was removed in vacuo, and the resulting aqueous solution was diluted to 15 mL with $H_2O$ and extracted with 3 × 30 mL of $CH_2Cl_2$. These extracts were dried over $MgSO_4$ and concentrated to yellow oil. This material was flash chromatographed on 45 g of 230–400-mesh silica gel (elution with 2:3 acetone–hexanes) to afford 129.1 mg (73%) of **30** as white crystals and 32.5 mg (18%) of recovered **29**.

Data for **30**: mp 71–73 °C; $R_f$ 0.50 (1:1 acetone–hexanes); $[\alpha]^{26}_D$ +46.0° ($c$ 1.20, $CH_2Cl_2$); IR ($CHCl_3$) 3065, 3030, 3015, 2975, 2940, 2885, 1722, 1599, 1439, 1311, 1295, 1272, 1260, 1180, 1144, 1124, 1079, 1053, 1009, 718, 698, 665 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.28 (s, 1 H), 8.35–8.29 (m, 2 H), 7.89–7.84 (m, 1 H), 7.68–7.43 (m, 11 H), 5.12–5.11 (m, 2 H), 4.32 (q, 1 H, $J$ = 3.5 Hz), 3.88 (t, 1 H, $J$ = 11.5 Hz), 3.40 (dd, 1 H, $J$ = 4.3, 11.3 Hz), 2.91 (AB q, 2 H, $J_{AB}$ = 5.2 Hz, $\Delta\nu_{AB}$ = 19.4 Hz), 2.05 (dd, 1 H, $J$ = 3.0, 15.3 Hz), 2.01–0.97 (m, 8 H), 1.61 (dd, 1 H, $J$ = 3.1, 15.2 Hz), 0.79 (d, 3 H, $J$ = 6.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 203.43, 165.14, 164.98, 136.26, 135.97, 135.78, 134.46, 133.28, 132.87, 132.74, 132.06, 131.91, 131.58, 131.46, 130.86, 129.29, 129.25, 128.76, 128.67, 128.15, 101.85, 72.26, 70.84, 70.69, 62.79, 49.83, 44.02, 38.51, 33.91, 32.96, 26.63, 22.92, 21.65, 12.64; MS (70 eV) parent peak 586, base peak 323. Anal.

Calcd for $C_{34}H_{35}O_7P$: C, 69.61; H, 6.01. Found: C, 69.87; H, 6.03.

**Methyl (2*R*,2′*S*,3′a*R*,6′*S*,7′a*R*,4″*S*,5″*S*)-4″-[(*E*)-cinnamoyloxy]decahydro-5″-methyldispiro[oxirane-2,3′-(2′*H*)-benzofuran-2′,2″-[2*H*]pyran]-6′-carboxylate [(+)-Phyllanthocin, 1a].** To a solution of 32.6 mg (0.104 mmol) of the alcohol **17** and 63.8 mg (0.522 mmol) of 4-(dimethylamino)-pyridine in 1.0 mL of $CH_2Cl_2$ was added 50 μL of freshly distilled *trans*-cinnamoyl chloride. The resulting suspension was heated at reflux (bath temperature: 54 °C) for 19 h. The reaction was quenched with the addition of 10 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 2 × 60 mL of ether. These extracts were then washed with 15 mL each of $H_2O$, saturated $CuSO_4$, and $H_2O$, dried over $MgSO_4$, and concentrated to a brown oil. Flash chromatography on 30 g of 230–400-mesh silica gel (elution with 1:1 ether–hexanes) afforded 37.8 mg (82%) of (+)-phyllanthocin (**1a**) as pale yellow crystals. Recrystallization from ether–hexanes afforded colorless prisms: mp 129–129.5 °C; $R_f$ 0.39 (2:1 ether–hexanes); $[\alpha]^{25}_D$ +27.2° (*c* 2.04, $CHCl_3$); IR ($CHCl_3$) 3012, 2955, 2940, 2885, 1728, 1704, 1640, 1579, 1498, 1450, 1437, 1387, 1372, 1344, 1328, 1308, 1278, 1254, 1232, 1201, 1173, 1126, 1111, 1085, 1073, 1051, 1021, 1009, 993, 979, 950, 908, 868, 710, 683 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.74 (d, 1 H, *J* = 15.9 Hz), 7.52–7.50 (m, 2 H), 7.39–7.33 (m, 3 H), 6.46 (d, 1 H, *J* = 15.9 Hz), 5.06 (br q, 1 H, *J* = 2.8 Hz), 4.36 (q, 1 H, *J* = 3.4 Hz), 3.99 (t, 1 H, *J* = 11.5 Hz), 3.42 (dd, 1 H, *J* = 4.0, 11.2 Hz), 3.25 (s, 3 H), 2.92 (AB q, 2 H, $J_{AB}$ = 5.4 Hz, $\Delta\nu_{AB}$ = 19.8 Hz), 2.39 (tt, 1 H, *J* = 3.5, 12.0 Hz), 2.20 (br d, 1 H, *J* = 14.8 Hz), 2.02 (dd, 1 H, *J* = 2.9, 15.2 Hz), 1.95–1.83 (m, 3 H), 1.73–1.55 (m, 2 H), 1.61 (dd, 1 H, *J* = 3.2, 15.2 Hz), 1.40–1.16 (m, 2 H), 0.85 (d, 3 H, *J* = 7 Hz); $^{13}C$ NMR ($CDCl_3$) δ 176.02, 166.58, 144.38, 134.65, 129.92, 128.71, 127.96, 118.93, 101.96, 72.61, 71.05, 69.79, 62.95, 51.12, 50.13, 38.58, 36.81, 34.32, 33.06, 29.90, 26.47, 22.16, 12.71; MS (14 eV) parent peak 442, base peak 182.[35] Anal. Calcd for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83. Found: C, 67.72; H, 6.90.

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**Registry No.** **1a**, 62948-37-2; **2**, 97860-62-3; **4** (R″ = TBS), 97826-89-6; (±)-**6c**, 97826-90-9; (±)-**6t**, 97826-97-6; (±)-**7**, 97826-91-0; (±)-**7** (acetate), 124603-86-7; (±)-*trans*-**7** (acetate), 124603-87-8; **8**, 97826-92-1; **8** (alcohol), 97826-98-7; **8** (*t*-BuO⁻ ring-opened diol), 124603-88-9; **9**, 97826-88-5; **9** (alcohol, isomer 1), 124603-89-0; **9** (alcohol, isomer 2), 124649-52-1; **10a**, 97905-63-0; **10a** (5,10-diol), 124603-90-3; **10a** (5,10,12-triol), 124603-91-4; **10b**, 97826-93-2; **10b** (5,10-diol), 124649-54-3; **11**, 124649-53-2; **12**, 124649-55-4; **13**, 124603-92-5; **14**, 97827-00-4; **15**, 124603-94-7; **15** (X = α-OH, β-H), 124649-56-5; **15** (X = α-H, β-OH), 124603-93-6; **15** (X = (*E*)-CHOMe), 124603-95-8; **15** (X = (*Z*)-CHOMe), 124649-57-6; **16a**, 124649-58-7; **16b**, 124603-96-9; **17**, 82167-85-9; **17** (TBS ether), 97827-01-5; **18a**, 97826-95-4; **18b**, 97905-64-1; **19**, 124603-97-0; **23**, 111692-59-2; **24**, 124603-99-2; **25**, 111675-18-4; **26**, 111767-82-9; **27**, 111692-60-5; **28a**, 111675-15-1; **28d**, 111767-81-8; **29**, 124649-59-8; **30**, 124603-98-1; *p*-$MeOC_6H_4CH_2OH$, 105-13-5; (*Z*)-$ClCH_2CH{=}CHCH_2Cl$, 1476-11-5; (*E*)-$CH_2{=}CHCH{=}CHOMPM$, 124603-84-5; (*Z*)-$CH_2{=}CHCH{=}CHOMPM$, 124603-85-6; $CH_2{=}CHCOCH_2OAc$, 38982-28-4; $Ph_3PMe^+Br^-$, 1779-49-3; (*R*)-$HOCH_2CH(Me)CO_2Me$, 72657-23-9; (*R*)-$TBSOCH_2CH(Me)CO_2Me$, 105859-44-7; (*S*)-$TBSOCH_2CH(Me)CH_2OH$, 105859-45-8; $Ph_2PCH_2OMe$, 43139-94-2; *p*-$Ph_2PC_6H_4CO_2H$, 2129-31-9; (*E*)-PhCH=CHCOCl, 17082-09-6; *m*-$Ph_2PC_6H_4CO_2H$, 2129-30-8.

# Conformation Dynamics of 1,2-Dimethylenecyclohexane: A Model for Ring-A Mobility in Vitamins D

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The conformation dynamics of 1,2-dimethylenecyclohexane was examined by means of ab initio MO theory employing the STO-3G and 3-21G basis sets. The calculations show that the most economic mode of chair–chair interconversion begins with inversion of twist angles in the diene part of the chairlike minimum conformation and proceeds via pseudorotation and reinversion to the alternate chair. The results are discussed in relation to the ring A structure and mobility of vitamins D.

## Introduction

The combination of a cyclohexane ring with an exocyclic diene system in the 1,2-dimethylenecyclohexane molecule **1** leads to questions about the conformational structure of this compound. On the one hand, the cyclohexane ring prefers the chair conformation, and on the other hand, the *s-cis*-diene tends to a planar orientation with most conjugation. Thus, competition between these two contrary structure aspects could be expected. Whereas the introduction of one exocyclic double bond into the cyclohexane ring leaves the chair conformation principally unchanged, e.g. exomethylenecyclohexane,[1,2] cyclohexanone,[2–5] the formation on an endocyclic double bond transforms the chair into a half-chair as minimum conformation, e.g. cyclohexene.[1–4,6]

Experimental structure data available from indirect methods (PE, UV, NMR spectroscopy) support the maintenance of the chair conformation in **1**.[7] Thus, tor-

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