above was treated with 0.5 N NaOH solution (80 mL) and extracted with three 50-mL portions of chloroform. The combined chloroform layer was washed with water (100 mL) and dried over Na_2SO_4. Evaporation of the solvent gave (*S*)-(−)-**5** (1.11 g, 36% based on the initially used (*S*)-(−)-**5**), mp 225–232 °C, $[\alpha]^{24}_D$ −107° (*c* 1.1, chloroform). (*S*)-(−)-**5**: ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 6 CH_3), 1.37 (s, 6 CH_3), 6.50 (d, 2 H, *J* = 7.9 Hz), 6.92 (t, 2 H, *J* = 7.0 Hz), 6.96–7.03 (m, 4 H), 7.06–7.14 (dd, 4 H, *J* = 7.6 and 12.5 Hz), 7.33–7.40 (m, 2 H), 7.44–7.53 (dd, 2 H, *J* = 8.6 and 13.1 Hz), 7.61–7.67 (m, 4 H), 7.75–7.84 (m, 6 H), 7.97 (d, 2 H, *J* = 7.0 Hz); ^{31}P NMR ($CDCl_3$) 29.5 ppm; IR (KBr) ν 3050 (m), 2950 (s), 2900 (m), 2870 (m), 1598 (m), 1553 (w), 1502 (m), 1462 (m), 1392 (m), 1363 (m), 1302 (w), 1265 (m), 1195 (s), 1133 (m), 1112 (w), 1018 (w), 869 (w), 815 (m), 810 (m), 751 (s), 740 (m), 693 (w), 683 (w), 650 (m), 607 (s), 581 (w), 568 (w), 557 (m), 522 (m), 489 (m) cm^{-1}; UV (ethanol) λ_{max} 233 (ε 130 000), 273 (sh, 12 000), 287 (12 000), 300 (sh, 10 000), 316 (sh, 3600), 332 (3500) nm.

The purification of the antipode (*R*)-(+)-**5**, which went to the mother liquor of recrystallization of the (*S*)-(−)-**5**–(−)-**7** complex was not carried out.

Reduction of (*S*)-(−)-5 into 2,2′-Bis[bis(*p*-*tert*-butylphenyl)phosphinyl]-1,1′-binaphthyl [*p*-*tert*-BuC$_6$H$_4$BINAP] [(*S*)-(−)-9]. To a mixture of (*S*)-(−)-**5** (1.50 g, 1.71 mmol) and triethylamine (1.65 mL, 1.20 g, 11.9 mmol) in xylene (25 mL) was added dropwise a solution of trichlorosilane (1.40 g, 10.3 mmol) in xylene (5 mL) at 20 °C. After the addition was completed, the mixture was heated with stirring at 100–110 °C for 3 h. Workup as described above gave 0.75 g (52%) of (*S*)-(−)-**9**, mp 263–265 °C, $[\alpha]^{24}_D$ −83° (*c* 1.0, benzene). (*S*)-(−)-**9**: ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 6 CH_3), 1.26 (s, 6 CH_3), 6.65 (d, 2 H, *J* = 8.5 Hz), 6.74 (t, with fine splitting, 2 H, *J* = 7.6 Hz), 6.92–6.98 (m, 4 H), 7.06 (d, 4 H, *J* = 7.9 Hz), 7.08–7.16 (m, 4 H), 7.20–7.32 (m, 6 H), 7.47 (d, with fine splitting, 2 H, *J* = 7.0 Hz), 7.78 (d, 2 H, *J* = 8.2 Hz), 7.87 (d, 2 H, *J* = 8.2 Hz); ^{31}P NMR ($CDCl_3$) −16.4 ppm; IR (KBr) ν 3050 (w), 2950 (s), 2895 (w), 2860 (w), 1596 (w), 1551 (w), 1495 (m), 1461 (m), 1392 (m), 1361 (m), 1307 (w), 1264 (s), 1200 (w), 1082 (s), 1015 (s), 946 (w), 865 (w), 825 (s), 815 (s), 776 (w), 745 (s), 697 (w), 645 (w), 581 (w), 556 (m), 515 (w), 456 (w), cm^{-1}; LRMS (70 eV), *m*/*z* (% intensity) 846 (M^+, 0.14), 552 (11), 551 (48), 550 (100), 549 (M^+ − (C_4H_9–C_6H_4)$_2$P, 1.3), 298 ((C_4H_9–C_6H_4)$_2$P, 2.3); HRMS (70 eV), *m*/*z* 846.4464, calcd for $C_{60}H_{64}P_2$ 846.4482. UV (ethanol) λ_{max} 221 (ε 125 000), 237 (sh, 100 000) nm. Anal. Calcd for $C_{60}H_{64}P_2$: C, 85.07; H, 7.62. Found: C, 84.95; H, 8.03.

X-ray Analysis of the Complex of (*S*)-(−)-3, (1*R*)-(−)-6, and Acetic Acid. Crystal data for the title complex are given in Table I. Single crystals were grown from a solution of the complex (0.25 g, 0.38 mmol) in a mixture of ethyl acetate (8.5 mL) and acetic acid (0.1 mL). A suitable crystal was sealed in a thin-walled glass capillary. Diffraction data were collected with graphite-monochromated Cu Kα radiation. Fifty accurately centered reflections in the range 40° < 2θ < 60° were used for determination and least-squares refinement of the unit cell parameters. A total of 8589 reflections were collected and 7842 reflections had $|F_o| > 3\sigma(F_o)$, in which 5062 are independent. Three standard reflections, measured after every 50 reflections, showed neither indication of any misalignment nor deterioration of the crystal. The intensities were empirically corrected for Lorents and polarization factors and used in the structure determination. The structure solution by the use of the direct method (MULTAN 78 program) for 5062 reflections revealed positions for 48 non-hydrogen atoms, containing two phosphorus atoms. Three cycles of blockdiagonal least-squares refinement converged to $R = 0.27$ and $R_w = 0.34$. The remaining non-hydrogen atoms and hydrogen atoms were located after carrying out a series of blockdiagonal least-squares refinement and Fourier and difference Fourier syntheses. Total 123 atoms were refined by use of anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms. Least-squares refinement based on 7842 observed reflections led to a final $R = 5.96\%$ and $R_w = 7.08\%$. The bond parameters in crystal solvent ethyl acetate have fairly large estimated standard deviations as is often observed for solvate molecules. Ten hydrogen atoms were not located from final difference Fourier maps. Selected bond lengths and angles appear in Table II. Coordinates and thermal parameters for 123 atoms, observed and calculated structure factor amplitudes, all bond lengths and angles, and best planes (14 pages) are included as supplementary material.

Acknowledgment. We thank Dr. C. Katayama, Nagoya University, for valuable contribution in X-ray crystal structure analysis. We gratefully acknowledge financial support from the Ministry of Education, Science, and Culture, Japan (No. 59540331 and 60219012).

Supplementary Material Available: Lists of atomic coordinates, thermal parameters, bond distances, bond angles, and best planes (14 pages). Ordering information is given on any current masthead page.

Approach to the Total Synthesis of Chlorothricolide: Synthesis of (±)-19,20-Dihydro-24-*O*-methylchlorothricolide, Methyl Ester, Ethyl Carbonate†[1]

Robert E. Ireland* and Michael D. Varney[2]

The Chemical Laboratories, California Institute of Technology, Pasadena, California 91125

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An approach to the total synthesis of the macrolide antibiotic aglycone chlorothricolide (**1b**) is presented. Herein is described the synthesis of the advanced intermediate (±)-19,20-dihydro-24-*O*-methylchlorothricolide, methyl ester, ethyl carbonate (**34**) from the "bottom half" acid **4** and the "top half" alcohol **3** by the sequence esterification, macrolactonization, ester enolate Claisen rearrangement, and decarboxylation.

Chlorothricin (**1a**), one of some 500 known macrolide antibiotics,[3] was isolated in 1969 by W. Keller-Schierlein.[4] Active against gram-positive bacteria, it functions as a noncompetitive inhibitor of pyruvate carboxylase.[5] The aglycone chlorothricolide methyl ester (**1b**) has been the subject of intense study by many synthetic chemists in recent years.[6] In previous reports[6a,b] from this group, a convergent synthetic strategy was presented for the construction of chlorothricolide (**1b**). Central to the proposal was the joining of two nearly equal halves along the C12–

† Contribution No. 7249.

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(2) Atlantic Richfield Foundation Research Fellow, 1984.

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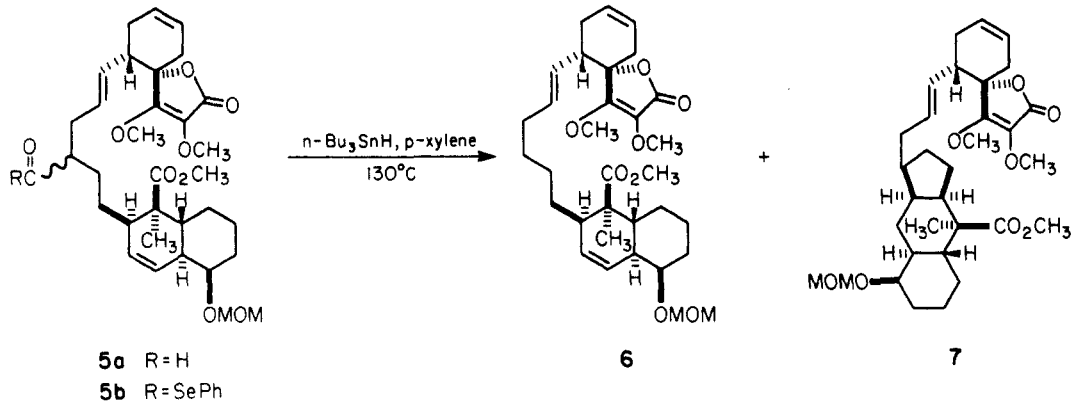
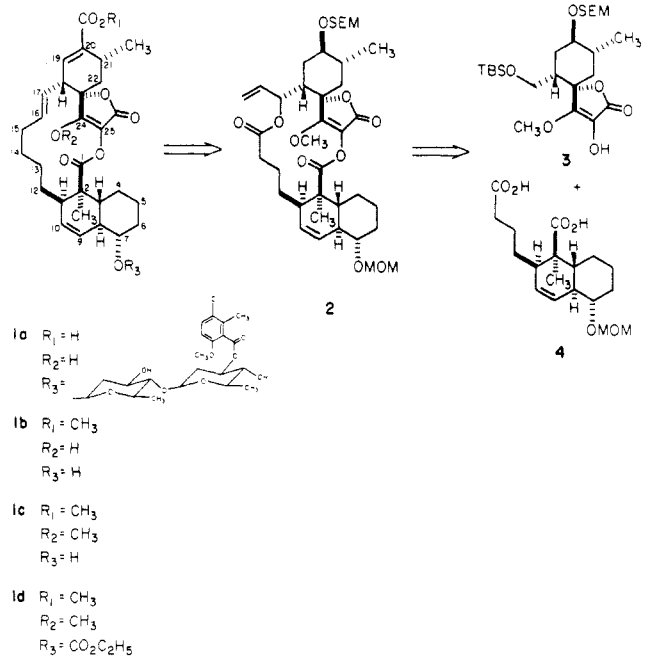
Chart I.[9] Attempted Decarboxylation of the Seleno Ester 5b



5a R = H
5b R = SePh

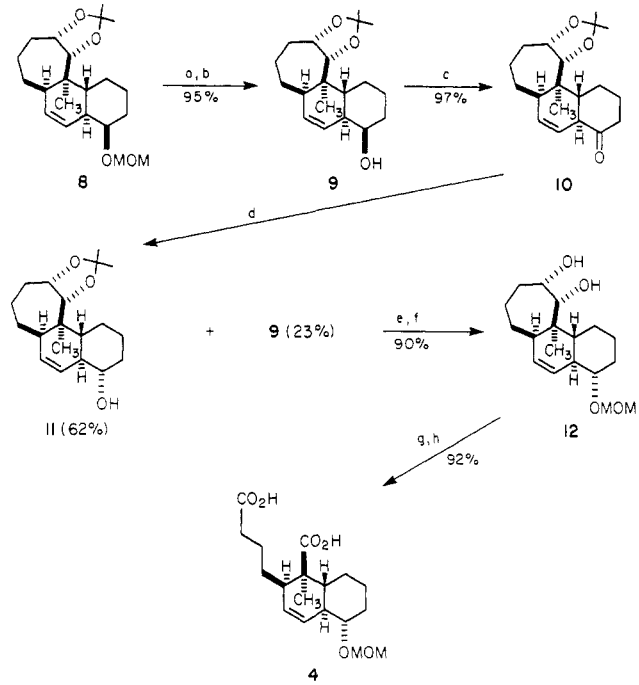
6 **7**

Scheme I



2 **3** **4**

Scheme II.[9] Inversion of the C-7 Alcohol and Synthesis of the Bottom Half 4[a]



8 **9** **10** **11** (62%) **12** **4**

[a] (a) *p*-TsOH, CH_3OH, H_2O, 85 °C; (b) $CH_3C(OCH_3)_2CH_3$, *p*-TsOH, CH_2Cl_2; (c) Me_2SO, ClCOCOCl, Et_3N, CH_2Cl_2; (d) $NaBH_4$, $CH_3CH(OH)CH_3$, 0 °C; (e) CH_3OCH_2Cl, $(i\text{-}C_3H_7)_2C_2H_5N$, CH_2Cl_2; (f) CH_3OH, H_2O, PyHOTs; (g) Me_2SO, PhH, $(i\text{-}C_3H_7N)_2C$, Cl_2CHCO_2H; (h) THF, H_2O, 10% aqueous KOH, 30% H_2O.

C17 side chain followed finally by lactone formation. An equally convergent, but alternate, approach to this macrocycle is presented herein (Scheme I). This plan hinges on the preparation of the dilactone **2** from the "top half" alcohol **3** and "bottom half" acid **4** by initial esterification across the C1 and C25 carbons followed by macrolactonization. Subsequent ester enolate Claisen rearrangement[7] and decarboxylation would then yield the intact monolactone.

Such a strategy change was deemed necessary as a result of two key experiments. The first, as reported previously,[6b] was attempted decarbonylation of the aldehyde **5a** with Wilkinson's catalyst. In this case, cyclopropane and isomerized olefin products were obtained (for details see ref 6b). The second, as shown in Chart I, was the radical decomposition[8] of the seleno ester **5b**. In this exploratory experiment, the pentacycle **7** and the aldehyde **5a** were obtained together with the desired decarboxylated product **6**. Modification of the reaction conditions never resulted in exclusive formation of compound **6**. It was felt that tying the side chain back, that is, making it part of a macrolactone, might restrict its motion enough to either reduce metal participation of the side-chain olefin to the point where no cyclopropanes were formed or, in the case of the seleno ester, allow for trapping of the intermediate radical before it could cyclize onto the C10 olefin. Results in this report bear this hypothesis as correct.

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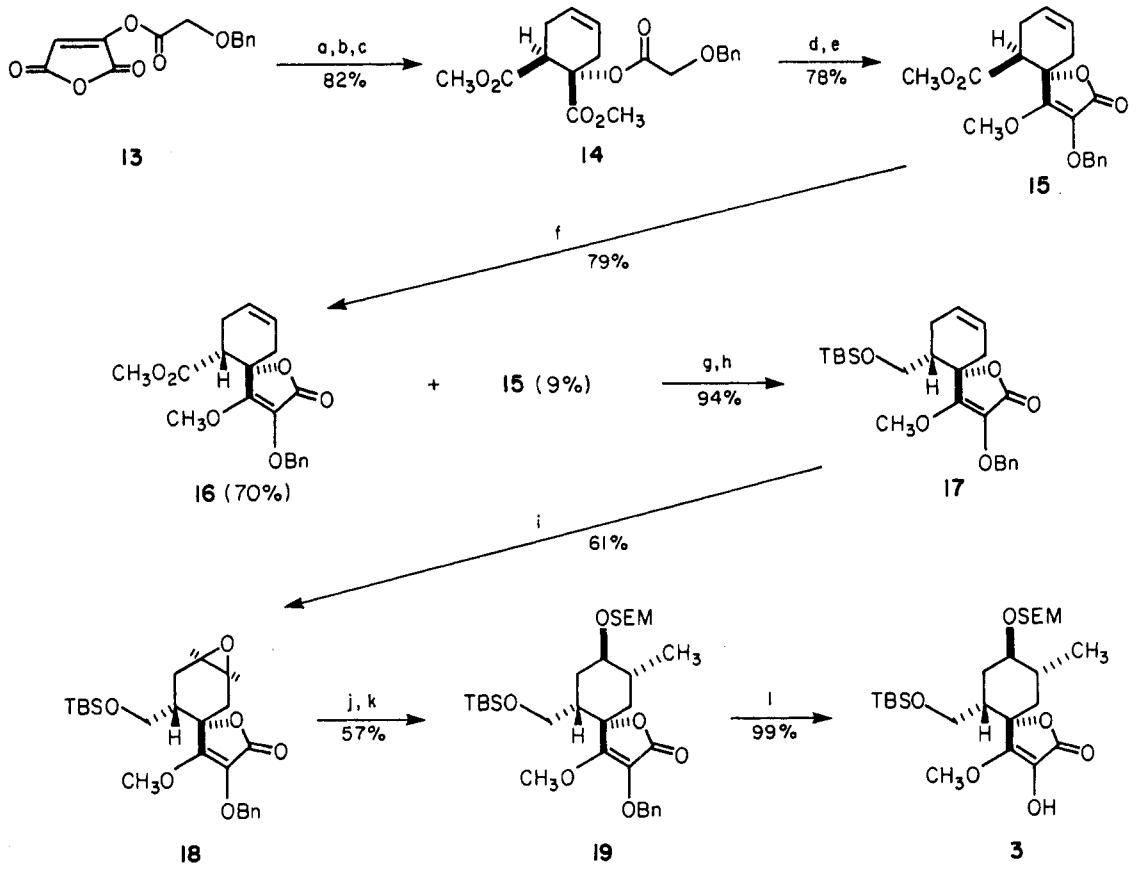
(9) The structures shown in these schemes depict one enantiomer of a racemic mixture for graphic simplicity, but in all cases only the racemate was obtained. No resolution of these racemates was affected.

Scheme III.[9] Synthesis of the Top Half 3[a]



[a] (a) CH_2=CHCH=CH_2, PhH, pyrogallol, Δ; (b) CH_3OH, Δ; (c) ether, CH_2N_2; (d) LiHMDA, THF, −30 °C; (e) HMPA, CH_3OSO_2F; (f) catalytic $NaOCH_3$, CH_3OH, Δ; (g) $LiEt_3BH$, THF, 0 °C; (h) *t*-$BuMe_2SiCl$, pyridine, DMAP, CH_2Cl_2; (i) MCPBA, $LiClO_4$, Et_2O, 0 °C; (j) $LiMe_2Cu$, Et_2O, hexane, 0 °C; (k) SEMCl, $(i\text{-}C_3H_7)_2C_2H_5N$,$CH_2Cl_2$; (l) 10% Pd/C, H_2, C_2H_5OH.

The current effort can be divided into four distinct parts. First, a synthesis of the diacid **4** from the previously reported intermediate **8** was developed. Second, with some modifications, construction of the appropriately protected top half alcohol **3** was completed by a route similar to that developed earlier.[6a] Third, a successful scheme for the synthesis of the lactone **29** was realized through decarboxylation of the ester enolate Claisen rearrangement product **28**. Fourth, functionalization of the top portion of the ketone **32** is explored.

I. Inversion of the C-7 Alcohol and Synthesis of the Bottom Half Diacid 4. In a previous paper,[6a] the synthesis of "7-epi-bottom half" was outlined. Epimerization of the C-7 center was delayed because, at the time, its configuration had no effect on the outcome of the studies presented. For the sake of convergency, we felt that inversion of this center to the natural configuration would best be completed as early as possible. In Scheme II the inversion of the C-7 alcohol is presented together with a more efficient method of converting the 1,2-diol **12** to the diacid **4**.

Aqueous acid treatment of the tricyclic acetal **8**[6b] followed by reketalization with 1,2-dimethoxypropane provided the alcohol **9** in 95% yield. Swern[10] oxidation afforded the ketone **10** (97%) which when treated with sodium borohydride[11] in dry isopropyl alcohol yielded a separable mixture of the α- and β-alcohols **11** and **9** in a 2.6:1 ratio. Protection of the C7-hydroxy as a methoxymethyl ether[12] followed by selective hydrolysis (pyridinium tosylate, CH_3OH, H_2O, 80 °C) of the acetonide gave the 1,2-diol **12** in 90% yield. Oxidation of the 1,2-diol to the corresponding 1,2-dione[13] followed by treatment with basic hydrogen peroxide[14] (KOH, H_2O_2, THF, H_2O) afforded the diacid **4** in excellent yield. The ^1H NMR spectrum of the dimethyl ester of the synthetic diacid **4** and that of the one-carbon homologue obtained from natural chlorothricin[6b] were superimposable.

II. Synthesis of the Top Half Alcohol 3. After deciding upon the alcohol **3** as our key intermediate, we investigated two approaches for its construction. The first, shown in Scheme III, is an extension of earlier work reported from this group.[6a] A benzyl-protecting group was chosen in place of the previously used methyl group to insure selective deprotection. The starting material (α-(benzyloxy)acetoxy)maleic anhydride (**13**), was prepared by acylation of the pyridine salt of hydroxymaleic anhydride with (benzyloxy)acetyl chloride.[16] Diels–Alder reaction of the anhydride **13** with 1,3-butadiene (autoclave, 90 °C, 5 days) gave, after methanolysis and diazomethane treatment, the triester **14** in 82% yield.

After extensive experimentation, improved conditions for the cyclization of the triester **14** to the spirobutenolide **15** were found. In the case of lithium diisopropylamide (LDA), β-elimination was the major reaction pathway. The use of a weaker base, lithium hexamethyldisilazide

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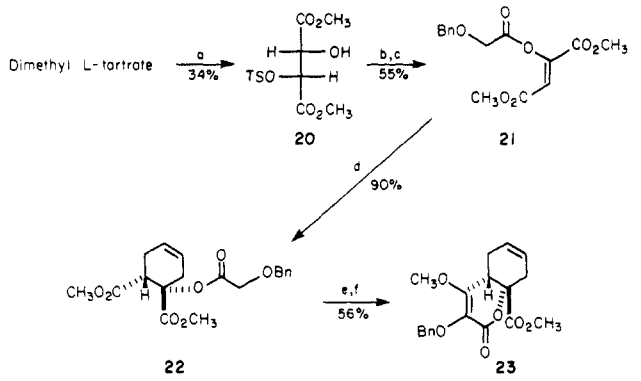
Scheme IV.[9] Tartrate Approach to the Top Half 3[a]



[a] (a) *p*-TsCl, pyridine, DMAP, CH_2Cl_2; (b) $BnOCH_2COCl$, pyridine, DMAP, CH_2Cl_2; (c) THF, $(C_2H_5)_3N$, DBU; (d) $CH_2{=}CHCH{=}CH_2$, PhH, pyrogallol, Δ; (e) LiHMDA, THF, 0 °C; (f) CH_2N_2.

(LiHMDA), along with low temperatures and long reaction times allowed for both improved yield and reproducibility. Thus, inverse addition of 2 equiv of LiHMDA in tetrahydrofuran (THF) at −78 °C to the triester **14** in THF at −78 °C and warming to −30 °C for 5 h afforded, after trapping with methyl fluorosulfonate, the desired spirobutenolide **15** in 78% yield. Equilibration of the pseudoaxial carbomethoxy group provided a 79% yield of **15** and **16** as an inseparable 1:7 mixture. Superhydride reduction (2 equiv of $LiEt_3BH$, THF, 0 °C) followed by protection with *tert*-butyldimethylsilyl chloride[18] (*t*-$BuMe_2SiCl$) afforded the protected alcohol **17** in 94% overall yield. Selective epoxidation of the cyclohexene double bond was accomplished in 61% yield with *m*-chloroperbenzoic acid (MCPBA) in ether containing 1 equiv of anhydrous lithium perchlorate.[6a] Treatment of the epoxide **18** with the higher order cuprates as described by Lipshutz[19] in various solvents failed to give any of the desired alcohol, giving instead starting material or decomposition products. Alternately, when the epoxide **18** was exposed to 10 equiv of lithium dimethylcuprate in hexane,[20] the alcohol was obtained in 62% yield, together with 17% of a ketonic product. Hexane was critical to the success of this reaction. Protection of the alcohol with β-(trimethylsilyl)ethoxymethyl chloride[21] (SEMCl) provided the ether **19** in 92% yield. Selective removal of the benzyl group (H_2 10% Pd/C, EtOH) gave the crystalline "top half" alcohol **3** in essentially quantitative yield.

Subsequent to the synthesis of the alcohol **3**, a shorter alternative route to the intermediate **16** was pursued (Scheme IV). This plan entailed the use of the relative stereochemistry of the hydroxy groups in natural tartaric acid to generate stereospecifically the trans dienophile **21**. Diels–Alder reaction and intramolecular Claisen condensation was to yield the spirolactone **16**. In the event, monotosylation[22] of dimethyl L-tartrate afforded the alcohol **20**. The moderate yield of this reaction was of no consequence since both starting materials were readily available. Treatment of this alcohol with (benzyoxy)acetyl chloride followed by elimination of the tosylate group provided the olefin **21** in 55% yield. The Diels–Alder reaction of olefin **21** with 1,3-butadiene gave adduct **22** in high yield (autoclave, 150 °C, 3 days). All that remained was the cyclization of the triester **22** to the spirobutenolide **16**. However, addition of the triester **22** to 2 equiv of LiHMDA in THF at −78 °C followed by warming afforded, after treatment with diazomethane, the δ-lactone **23** as the only cyclization product. The remainder of the material consisted of products resulting from β-elimination. Reversing the order of addition of the reagents and changing the trapping agent from diazomethane to methyl fluorosulfonate affected only the relative yields of **23** and β-eliminated products. This result, though unexpected, is not without precedent. In Dieckmann cyclizations of related triesters, small modifications in backbone structure resulted in drastic changes in product composition.[23] Inspection of molecule models of **14** and **22** was of little help, and it is possible that because of the kinetic nature of the reaction conditions, the proximity of the two reacting centers is the controlling factor. However, further studies are needed.

III. Formation of Macrolactone 29. With the two appropriately functionalized intermediates **3** and **4** in hand, the construction of the macrolactone **29** was pursued. The methyl ester acid chloride **24** was prepared in situ by selective esterification of the diacid chloride[24] of acid **4**. Connection of the two pieces was accomplished by adding a solution of the top half alcohol **3** and 4-(dimethylamino)pyridine[25] in CH_2Cl_2 to the bottom half acid chloride **24** in CH_2Cl_2 at 0 °C and then allowing the mixture to warm to room temperature (Scheme V). After aqueous workup, the ester **25** could be obtained in 77% overall yield.[26]

The methyl ester function of compound **25** was converted to the thiophenol ester by hydrolysis and reesterification.[27] This two-step sequence was necessary in light of the fact that selective esterification using the thiophenol of the diacid chloride of **4** was not successful.[28] Introduction of the vinyl group required removal of the *t*-$BuMe_2Si$ protecting group (HF_x·pyridine),[29] and it was at this stage that the two diastereomers, produced in the esterification step, became separable. A 1:1.26 ratio of the alcohols **26A,B** was obtained with the more mobile one (by chromatography) being the minor component **26A**. Since comparison with the natural product was impossible at this stage, all subsequent reactions were performed on both diastereomers individually. Oxidation of the alcohol **26** with pyridinium chlorochromate[30] (PCC) yielded the corresponding aldehyde which was immediately treated with vinyl-Grignard to provide the vinyl alcohol **27** in 65% overall yield.

The macrolactonization of the alcohol **27** and related compounds was studied in some detail. The "double

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(26) Since the alcohol **3** and the diacid **4** are racemates, the connection of the two compounds produces a diastereomeric mixture. For the sake of clarity only one diastereomeric racemate is shown, but up to alcohol **26** the materials prepared were indeed inseparable mixtures of diastereoisomeric racemates.
(27) Neises, B.; Steglich, W. *Agnew. Chem., Int. Ed. Engl.* **1978**, *17*, 522–524.
(28) Attempted selective esterification of the diacid chloride of acid **4** with thiolphenol and pyridine at −90 °C gave only a 2:1 mixture of the side-chain thio ester over the ring thio ester.
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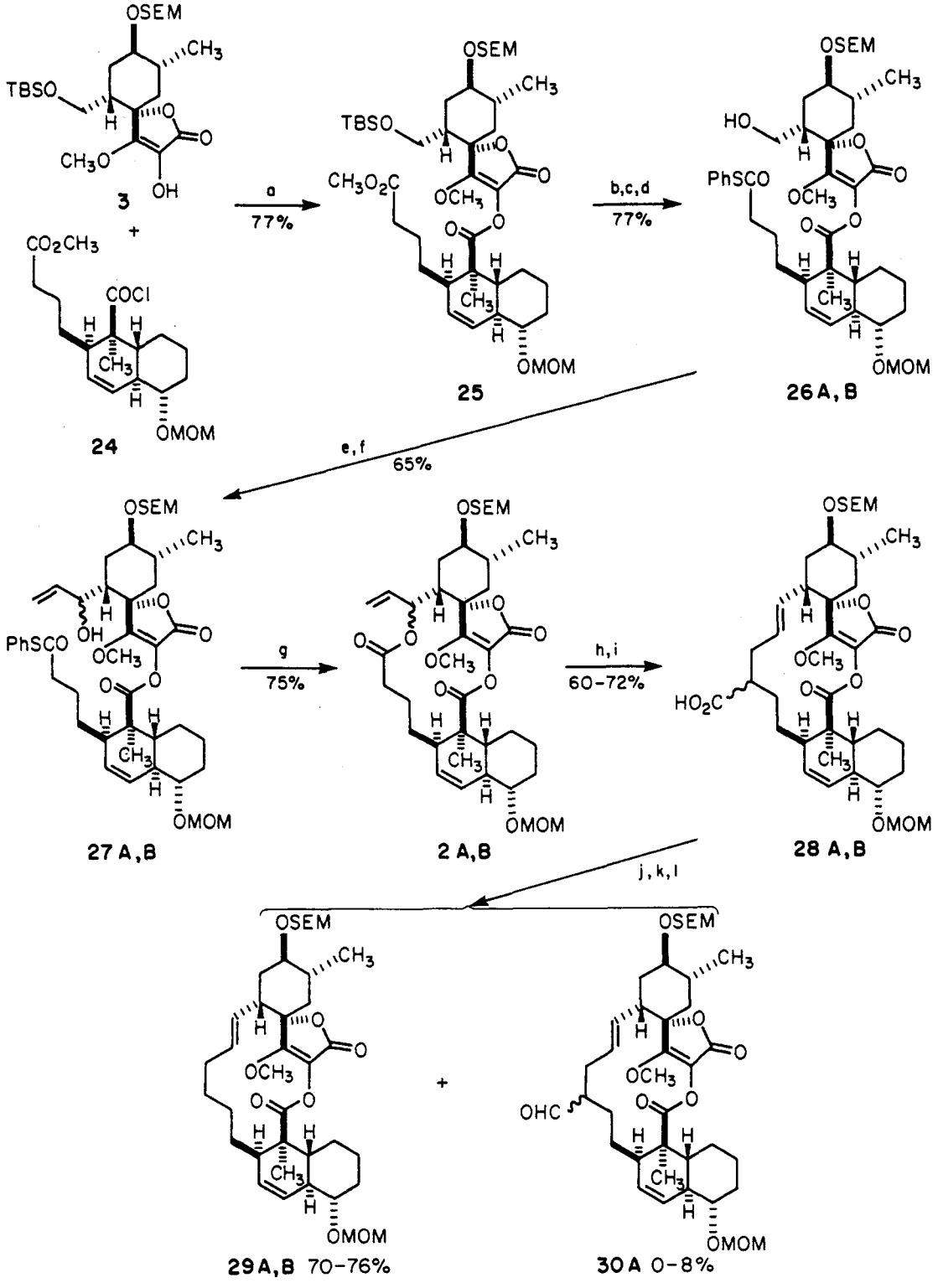
Scheme V.[9] Formation of Macrolactone 29[a]



[a] (a) DMAP, CH_2Cl_2; (b) LiOH, CH_3OH, H_2O; (c) PhSH, DCC, DMAP, CH_2Cl_2; (d) HF_x·pyridine, THF; (e) PCC, CH_2Cl_2; (f) CH_2=$CHMgBr$, THF, 0 °C; (g) $Ag(O_2CCF_3)$, Na_2HPO_4, PhH, 82 °C; (h) KHMDS, THF, HMPA, −78 °C; (i) HMPA, $(C_2H_5)_3SiCl$, $(C_2H_5)_3N$, THF; (j) Cl_2POOPh, $(C_2H_5)_3N$, THF, 0 °C; (k) PhSeH, $(C_2H_5)_3N$, THF, 0 °C; (l) $(n\text{-}C_4H_9)_3SnH$, AIBN, *p*-Xylene, 130 °C.

activation" methods of Corey[31] failed to produce any lactone as did Masamune's[32] mixed phosphate anhydride method. However, silver-promoted oxidation of the thiophenol ester **27**, as described by Masamune[33] under high dilution conditions, afforded the 14-membered macrodilactone **2** in 75% yield together with ~20% of the corresponding hydroxy acid hydrolysis product. This hydroxy acid could be recycled back to the thio ester **27** in 70–80% yield with diethyl chlorophosphate[34] and thiophenol.

(31) (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614–5616. (b) Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, 3409–3412.

(32) Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612–1614.

(33) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, B. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756–6758.

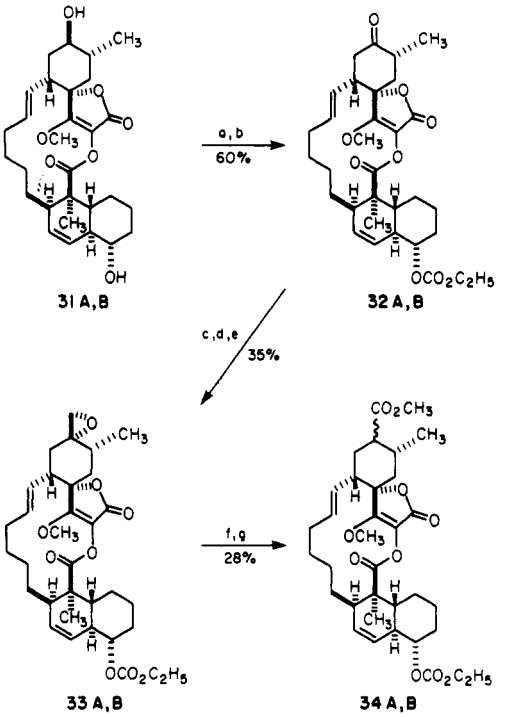
(34) Masamune, S.; Kamata, S.; Diakur, J.; Sugihara, Y.; Bates, G. S. *Can. J. Chem.* **1975**, *53*, 3693–3695.

Enolization of the dilactone **2** with potassium hexamethyldisilazide[6a,b] followed by trapping with triethylsilyl chloride gave, after being allowed to warm to room temperature for 2–4 h and aqueous workup, the 14-membered macrolactone Claisen acid **28** in 60–72% yield. When *t*-BuMe$_2$SiCl was employed as the trapping agent, yields of only 40–50% resulted. Analysis of the 400-MHz ^{1}H NMR spectrum of the acid **28** and its decarboxylation product **29** revealed that the newly formed C16–C17 double bond was exclusively the trans isomer (see Experimental Section).

The hypothesis, as put forth earlier, concerning the restricted motion of the carboxylate-containing side chain could now be readily tested. The seleno ester of the acid **28** was prepared, in 80% yield, by using the method described previously.[35] Radical decomposition[8] was performed by preheating the seleno ester in *p*-xylene at 130 °C and then adding the tributyltin hydride and AIBN. In this manner, the decarboxylated product **29** could be obtained in 88–95% yield with no evidence of radical cyclization on the C10 olefin. Produced as a byproduct from one of the diastereomers was the aldehyde **30A**, which when treated with Wilkinson's[36] catalyst also afforded the lactone **29**. In this case no evidence of cyclopropane formation or olefin isomerization was found. These results are in stark contrast to those obtained in both the previously discussed open-chain cases.[6b]

IV. Functionalization of the Top Half of Lactone 29. With the macrolactone now intact, functionalization of the top portion of the molecule was explored. The first requirement was distinction of the C7 and C20 hydroxy functions. As can be seen in compound **29** this problem had theoretically been solved by having two different protecting groups. However, attempted selective removal of the SEM group under the conditions described by Lipshutz[21] (TBAF, THF, or HMPA) and those developed in this group (CsF, HMPA)[37] led to concomitant removal of the tetronic methyl group and extensive decomposition. Both the SEM and the MOM group could, however, be removed in one step[38] ($LiBF_4$, CH_3CN, H_2O, 70 °C) to give the diol **31** (Scheme VI) in quantitative yield. Conditions for selective reprotection of the less hindered C7 hydroxy group were eventually found[39] (pyridine, C_2H_5OCOCl, 0 °C) and, after oxidation, the ketone **32** could be obtained in 60% yield. Model studies indicated that this ketone was not only very unreactive toward nucleophiles but also very susceptible to epimerization.[40] The only carbon nucleophile found that would add successfully, without epimerizing the adjacent methyl group, was the modified Still[41] reagent (tributylstannyl)(2-methoxyisopropoxy)-methane.[42] Unfortunately, treatment of the resultant 3° alcohol with thionyl chloride in pyridine gave the dehydrated product with the double bond exclusively in the undesired C20–C21 position. Dehydration using other known methods ($POCl_3$ or mesylchloride and base) on similar systems always occurred to the more substituted side. Available methods for converting epoxides to allylic alcohols are numerous[43] and, therefore, intermediate **33** was prepared. Treatment of the epoxide **33** with trimethylsilyl trifluoromethanesulfonate as described by Noyori[44] resulted unexpectedly in formation of the isomeric aldehyde. A trace of allylic alcohol could be found in the reaction, but it had the undesired C20–C21 olefin. Alternate attempts to convert the epoxide to the desired allylic alcohol[43] or to improve the yield of isomerization to the corresponding aldehyde[43] were uniformly unsuccessful. However, after oxidation of the aldehyde to the carboxylic acid and treatment with diazomethane, the protected dihydrochlorothricolide **34** was obtained in moderate yield.

Scheme VI.[9] Functionalization of the Top Half[a]



[a] (a) C_2H_5OCOCl, pyridine; (b) PCC, Celite, CH_2Cl_2; (c) $(n\text{-}C_4H_9)_3SnCH_2OC(OCH_3)(CH_3)_2$, *n*-BuLi, THF, −78 °C; (d) 10% HCl, THF; (e) TosIm, NaH, THF; (f) Me_3SiTrf, 2,6-lutidine, DBU, $PhCH_3$; (g) PDC, DMF.

For the purpose of comparison, chlorothricolide[6b] **1c** was treated with ethyl chloroformate[39] to provide the carbonate **1d**. Study of the 400-MHz ^{1}H NMR spectra of esters **34** and **1d** revealed that the minor diastereomer from the connection reaction (see Scheme V) corresponded to the natural product.[45]

The final transformation necessary to complete the total synthesis was the regioselective dehydrogenation of the ester **34**. The two preparative useful methods available for this reaction, decomposition of a selenoxide[46a] or oxi-

(35) Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285–3294.
(36) Tsuji, J.; Ohno, D. *Tetrahedron Lett.* **1965**, 3969–3971.
(37) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279–3285.
(38) Lipshutz, B. H.; Harvey, D. F. *Synth. Commun.* **1982**, *12*, 267–277.
(39) Fieser, L. F.; Herz, J. E.; Klohs, M. W.; Romero, M. A.; Utne, T. *J. Am. Chem. Soc.* **1952**, *74*, 3309–3313.
(40) The keto derivative of compound **19** was used as a model for functionalization studies. Acidic removal of the trimethylsilyl group from its corresponding trimethylsilyl cyanohydrin yielded the starting ketone. Attempted addition of numerous disubstituted one-carbon acyl anion equivalents gave no reaction. Addition of both trimethylsulfonium methylide and trimethylsulfoxonium methylide resulted in extensive epimerization of the methyl group.
(41) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481–1487.
(42) First prepared in this group by D. W. Norbeck from (tributylstannyl)methanol and 2-methoxypropene.
(43) Gorzynski-Smith, J. *Synthesis* **1984**, 629–656.
(44) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738–2739.
(45) This conclusion is based on the chemical shifts of the C16 and C17 protons. The natural material had the C16 proton at 5.42 ppm and the C17 proton at 5.14 ppm, and the minor component had the C16 proton at 5.37 ppm and the C17 proton at 5.21 ppm. In contrast, the major component had the C16 proton at 5.19 ppm and C17 proton at 5.26 ppm.
(46) (a) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697–1705. (b) Tsuji, J.; Takahashi, K.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1984**, *25*, 4783–4786.

dation of a silyl ketene acetal,[46b] both required initial enolate formation. Attempted enolization with up to 5 equiv of LDA, KHMDS, and KDA[47] followed by trapping with diphenyl diselenide, phenylselenyl chloride, and *tert*-butyldimethylsilyl trifluoromethanesulfonate gave only starting material and decomposition products. Hydrogenation of the natural carbonate **1d** to the hexahydro derivative[4] and subjection of this to numerous enolization conditions also were unsuccessful. Thus, while the construction of the macrolactone has been efficiently accomplished, modification of the strategy is necessary such that functionalization of the top half is performed prior to the connection of the two halves. The results of this effort, currently under way, will be the subject of a future report.

Experimental Section

Melting points are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 90 MHz except where designated "500 MHz". Data are reported as follows: chemical shift (multiplicity, integrated intensity, coupling constants, assignment). Optical rotations were measured in 1-dm cells of 1-mL capacity; chloroform, when used as a solvent for optical rotations, was filtered through neutral alumina (activity I) immediately prior to use. Reaction solvents and liquid reagents were purified by distillation or drying shortly before use. Reactions were run under an argon atmosphere arranged with a mercury bubbler so that the system could be alternately evacuated and filled with argon and left under a positive pressure. Reported temperatures were measured externally. Syringes and reaction flasks were dried at least 12 h in an oven (120–140 °C) and cooled in a dessicator over anhydrous $CaSO_4$ prior to use. If feasible, reaction flasks were also flame-dried in vacuo. Analytical samples of crystalline compounds were in all cases prepared by recrystallization from ether/petroleum.

1α,2α-(Isopropylidenedioxy)-8β-hydroxy-11bα-methyl-5aα,7aα,8,9,10,11,11aβ,11b-octahydronaphtho[*a*]cycloheptane (9). To a solution of 7.10 g (19.7 mmol) of ether **8** in 160 mL of methanol and 40 mL of water was added 0.28 g (1.47 mmol) of *p*-toluenesulfonic acid monohydrate, and the resulting mixture was heated at 85 °C for 36 h. The mixture was then poured into 300 mL of saturated aqueous sodium bicarbonate solution, the mixture was extracted with ethyl acetate (3 × 400 mL), and the combined organic layers were dried (Na_2SO_4). After removal of the solvent at reduced pressure, the crude residue was pumped at 0.1 mmHg for 30 min.

To a solution of this crude material in 200 mL of CH_2Cl_2 was added 2.2 g (21.1 mmol) of 2,2-dimethoxypropane and 0.1 g (0.53 mmol) of *p*-toluenesulfonic acid monohydrate. After being stirred at room temperature for 1 h, the reaction mixture was poured into 50 mL of saturated bicarbonate and extracted with ether (3 × 300 mL). The combined organic layers were dried ($MgSO_4$), and, after removal of the solvent at reduced pressure, the crude residue was flash chromatographed on silica gel (350 g) with ether–petroleum ether (2:3). In this manner, there was obtained 5.9 g (95%) of the alcohol **9** as white crystals: mp 112–114 °C; IR ($CHCl_3$) 3475 (OH), 2945, 1460, 1380, 1260, 1210, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 3 H), 1.32 (s, 3 H) 1.54 (s, 3 H), 4.10 (d, 1 H, *J* = 7 Hz), 4.30 (m, 1 H), 5.31 (d, 1 H, *J* = 10 Hz), 5.85 (m, 1 H).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.86. Found: C, 74.34; H, 9.75.

1α,2α-(Isopropylidenedioxy)-11bα-methyl-5aα,7aα,10,11,-11aβ,11b-hexahydronaphtho[*a*]cyclohepten-8(9*H*)-one (10). To a rapidly stirred solution of 1.92 mL (22.0 mmol) of distilled oxalyl chloride in 50 mL of CH_2Cl_2 at −78 °C was added 3.2 mL (45.8 mmol) of dimethyl sulfoxide over 3 min. After stirring for 15 min, 5.2 g (17.0 mmol) of alcohol **9** in 25 mL of CH_2Cl_2 was added over 5 min. After stirring for an additional 15 min, 11.8 mL (84.9 mmol) of triethylamine was added, and the reaction mixture was allowed to warm to room temperature over 30 min. Saturated aqueous sodium bicarbonate solution was added, and the mixture was extracted with 2 × 500 mL of ether. The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was flash chromatographed on silica gel (250 g) with ether–petroleum ether (1:3), and in this manner there was obtained 5.0 g (97%) of the desired ketone as a white solid; mp 143–145 °C; IR ($CHCl_3$) 2940, 1710, 1380, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.33 (s, 3 H), 1.52 (s, 3 H), 2.90 (d, 1 H, *J* = 10.5 Hz), 4.13 (d, 1 H, *J* = 6 Hz), 4.24 (m, 1 H), 5.77 (m, 2 H).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.93; H, 9.26.

1α,2α-(Isopropylidenedioxy)-8β-hydroxy-11bα-methyl-5aα,7aα,8,9,10,11,11aβ,11b-octahydronaphtho[*a*]cycloheptane (11). A solution of 5.35 g (17.6 mmol) of the ketone **10** in 125 mL of isopropyl alcohol was added over a 15-min period under argon to a rapidly stirred solution of 1.0 g (26.4 mmol) of sodium borohydride in 75 mL of isopropyl alcohol at 0 °C. After 15 min, 200 mL of water was added and the aqueous layer was extracted with 3 × 200 mL of ether. The combined organic layers were washed with 200 mL of 2 N HCl and 200 mL of saturated sodium bicarbonate and then dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (400 g) with benzene–ethyl acetate (16:1). In this manner, there was obtained 3.34 g (62%) of the desired α-alcohol as a white solid: mp 112–113 °C; IR ($CHCl_3$) 3560, 3000, 1350, 1005; ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.35 (s, 3 H), 1.52 (s, 3 H), 3.33 (m, 1 H), 4.10 (d, 1 H, *J* = 7 Hz), 4.25 (m, 1 H), 5.74 (m, 2 H).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.86. Found: C, 74.37; H, 9.71.

Further elution afforded 1.24 g (23%) of the β-alcohol **9** which was recycled through ketone **10**.

1α,2α-(Isopropylidenedioxy)-8α-(methoxymethoxy)-11bα-methyl-5aα,7aα,8,9,10,11,11aβ,11b-octahydronaphtho[*a*]-cycloheptane. To a rapidly stirred solution of 3.0 g (9.80 mmol) of alcohol **11** in 30 mL of CH_2Cl_2 at 0 °C were added 4.4 mL (25.4 mmol) of diisopropylethylamine and 1.7 mL (22.5 mmol) of chloromethyl methyl ether. After being stirred for 12 h at room temperature, the mixture was treated with 15 mL of saturated sodium bicarbonate and then stirred for another 15 min. The mixture was then poured into 60 mL of saturated sodium bicarbonate and extracted with ether (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and, after removal of the solvent at reduced pressure, the crude residue was flash chromatographed on silica gel (250 g) with ether–petroleum ether (1:4). In this manner, there was obtained 3.4 g (99%) of methoxymethyl ether as a colorless oil: IR ($CHCl_3$) 2940, 1385, 1135 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 3 H), 1.32 (s, 3 H), 1.50 (s, 3 H), 3.38 (s, 3 H), 4.10 (d, 1 H, *J* = 7 Hz), 4.25 (m, 1 H), 4.58 and 4.72 (AB system, *J* = 6 Hz, 2 H), 5.70 (m, 2 H).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.98; H, 9.67.

1α,2α-Dioxo-8α-(methoxymethoxy)-11bα-methyl-5aα,7aα,8,9,10,11,11aβ,11b-octahydronaphtho[*a*]cycloheptane (12). A solution of 3.4 g (9.70 mmol) of the above acetonide in 60 mL of methanol/water (4:1) was heated under reflux in the presence of 240 mg (0.96 mmol) of pyridinium *p*-toluenesulfonate for 2.5 h. Saturated sodium bicarbonate (200 mL) was added, and the mixture was extracted with ether (3 × 200 mL). The combined organic layers were dried (Na_2SO_4), and, after removal of the solvent at reduced pressure, the crude residue was flash chromatographed on silica gel (250 g) with ethyl acetate–petroleum ether (1:1). In this manner, there was obtained 2.7 g (90%) of the desired diol as a colorless oil: IR ($CHCl_3$) 3580, 3440, 2905, 1090, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 3 H), 3.40 (s, 3 H), 3.81 (br s, 1 H), 4.00 (m, 1 H), 4.64 and 4.79 (AB system, *J* = 7 Hz, 2 H), 4.52 (dm, 1 H, *J* = 9 Hz), 4.84 (br d, 1 H, *J* = 9 Hz).

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.63; H, 9.86.

4-[1α-Methyl-1β-carboxy-5α-(methoxymethoxy)-1,2,4aα,5,6,7,8,8aβ-octahydronaphthyl]butyric Acid (4). To a rapidly stirred solution of 100 mg (0.32 mmol) of the diol **12** in 2 mL of benzene/dimethyl sulfoxide (1:1) at room temperature was added 0.18 mL (1.13 mmol) of diisopropylcarbodiimide and 27 μL (0.32 mmol) of dichloroacetic acid. After 1 h, an additional 27 μL (0.32 mmol) of dichloroacetic acid was added. After 30 min, the mixture was poured into 30 mL of 1 N HCl and extracted with ether (3 × 60 mL). The combined organic layers were washed

(47) Raucher, S.; Koolpe, G. H. *J. Org. Chem.* **1978**, *43*, 3794–3796.

with 20 mL of saturated sodium bicarbonate and then dried (Na_2SO_4). After removal of the solvent at reduced pressure, the crude residue was dissolved in 2 mL of THF. To this mixture at room temperature were added 2 mL 10% KOH and 3 mL of 30% H_2O_2. After 1 h, the mixture was poured into 30 mL of 50% $NaHSO_3$, and, after the addition of 2 mL of 10% HCl, the mixture was extracted with ether (3 × 60 mL). The combined organic extracts were dried ($MgSO_4$), and, after removal of the solvent at reduced pressure, the crude residue was chromatographed on Silicar CC-4 silica gel (15 g) with ether–petroleum ether (6:4). In this manner, there was obtained 100 mg (92%) of the desired diacid as a colorless oil. This material was unstable and was used immediately in the next step: IR ($CHCl_3$) 3350–2300, 1690, 1040 cm^{-1}; ^1H NMR δ 1.20 (s, 3 H), 3.38 (s, 3 H), 4.61 and 4.75 (AB system, J = 7 Hz, 2 H), 5.69 (dd, 1 H, J = 10 and 3 Hz), 5.92 (d, 1 H, J = 10 Hz), 10.28 (br s, 2 H). Due to the instability of the diacid the elemental analysis was performed on the dimethyl ester prepared by diazomethane treatment.

Anal. Calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 65.16; H, 8.67.

[2-(Benzyloxy)acetoxy]maleic Anhydride (13). To a rapidly stirred suspension of 24.0 g (124 mmol) of the pyridine salt of hydroxymaleic anhydride in 250 mL of dry benzene at room temperature was added 27.5 g (149 mmol) of (benzyloxy)acetyl chloride in 50 mL of benzene. After being stirred for 1 h, the slightly pink supernatant liquid was decanted off and filtered through 100 g of activity III alumina with 1 L of benzene. The solvent was concentrated under reduced pressure to about 100 mL, and 300 mL of petroleum ether was added. After the resultant crystals were collected by vacuum filtration, they were redissolved in 800 mL of benzene and the solvent volume was again reduced to 100 mL under reduced pressure. After the addition of 300 mL of petroleum ether, the white crystals were collected by vacuum filtration and dried under vacuum. In this manner, there was obtained 26.9 g (83%) of the desired anhydride **13** as slightly pink crystals: mp 109–110 °C; IR ($CHCl_3$) 3180, 3045, 2890, 1780, 1645, 1210, 1180, 1100 cm^{-1}; ^1H NMR δ 4.40 (s, 2 H), 4.67 (s, 2 H), 6.88 (s, 1 H), 7.35 (s, 5 H). Due to its hygroscopic nature, this material was analyzed as its butadiene methanolysis product **14**.

Dimethyl 4-[2-(Benzyloxy)acetoxy]cyclohexene-*cis*-4,5-dicarboxylate (14). A Teflon-lined autoclave was charged with a solution of 10.0 g (38.1 mmol) of [2-(benzyloxy)acetoxy]maleic anhydride (**13**) in 250 mL of dry benzene, 50 mL (0.57 mol) of butadiene, and 50 mg (0.39 mmol) of pyrogallol. The sealed autoclave was heated at 85 °C for 5 days. After cooling, the solvent was removed at reduced pressure and the crude residue was dissolved in 200 mL of dry methanol and heated at 65 °C for 4 h. After cooling, the solvent was removed at reduced pressure and the crude residue was treated with excess ethereal diazomethane. After removal of the solvent at reduced pressure, the crude residue was flash chromatographed on silica gel (500 g) with ether/petroleum ether (2:3). In this manner, there was obtained 11.3 g (82%) of the desired triester as a colorless oil: IR ($CHCl_3$) 3040, 2970, 1745, 1440, 1290, 1200, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (m, 2 H), 2.69 (br s, H) 2.95 (br s, 1 H), 3.32 (m, 1 H), 3.64 (s, 3 H, 3.76 (s, 3 H), 4.07 (s, 2 H), 4.58 (s, 2 H), 5.63 (br s, 2 H), 7.34 (s, 5 H).

Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.98; H, 6.12. Found: C, 63.04; H, 6.02.

2-Oxo-3-(benzyloxy)-4-methoxy-10β-carbomethoxy-1α-oxaspiro[4.5]deca-3,7-diene (15). To a rapidly stirred solution of 100 mg (0.28 mmol) of the triester **14** in 3 mL of THF at −78 °C was added dropwise via a cannula over a 25-min period 3.5 mL (0.55 mmol) of a 0.16 M solution of lithium hexamethyldisilazide in THF at −78 °C. After 15 min, the reaction was allowed to warm to −30 °C, and, after an additional 4.5 h, 1 mL of HMPA was added followed immediately by 58 L (0.72 mmol) of methyl fluorosulfonate. After 3 min, the solution was diluted with 3 mL of 1 N HCl and the aqueous layer was extracted with ether (3 × 60 mL). The combined organic extracts were washed with saturated bicarbonate solution and then dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (20 g) with ether/petroleum ether (3:7). In this manner, there was obtained 74 mg (78%) of the spirolactone **15** as a colorless oil: IR ($CHCl_3$) 3040, 2970, 1760, 1680, 1460, 1440, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (m, 4 H), 2.87 (t, 1 H, J = 7 Hz), 3.60 (s, 3 H), 3.88 (s, 3 H), 4.92 and 5.08 (AB system, J = 11 Hz, 2 H), 5.64 (br s, 2 H), 7.34 (s, 5 H).

Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.31; H, 6.01.

2-Oxo-3-(benzyloxy)-4-methoxy-10α-carbomethoxy-1α-oxaspiro[4.5]deca-3,7-diene (16). To a rapidly stirred solution of 2.9 g (8.42 mmol) of spirobutenolide **15** in 200 mL of dry methanol was added 1.75 mL (1.26 mmol) of a freshly prepared 0.72 M solution of sodium methoxide in dry methanol, and the resulting mixture was warmed to 60 °C. After 5 days, 20 mL of saturated ammonium chloride solution was added and the reaction mixture was poured into 500 mL of water. The aqueous layer was extracted with ether (3 × 150 mL) and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was flash chromatographed on silica gel (200 g) with ethyl acetate–petroleum ether (1:4). In this manner, there was obtained 2.3 g (79%) of an inseparable mixture of the α- and β-esters in a 7:1 ratio: IR ($CDCl_3$) 3040, 2970, 1765, 1680, 1345, 1120, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8–3.0 (m, 5 H), 3.60 (s, 3 H), 3.95 (s, 3 H), 5.00 and 5.17 (AB system, J = 12 Hz, 2 H), 5.67 (m, 2 H), 7.37 (s, 5 H).

Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.36; H, 5.86.

The ratio of the two esters was determined by integration of the two methoxy peaks at 3.95 ppm for the α-ester and 3.88 ppm for the β-ester.

2-Oxo-3-methoxy-4-(benzyloxy)-10α-(hydroxymethyl)-1α-oxaspiro[4.5]deca-3,7-diene. To a rapidly stirred solution of 5.90 g (17.1 mmol) of the ester **16** in 100 mL of THF at −20 °C was added 37.6 mL of a 1.0 M solution of lithium triethylborohydride in THF dropwise over 5 min. The mixture was then allowed to warm to 0 °C in an ice bath. After 20 min, 100 mL of 10% HCl was added and the aqueous layer was extracted with ether (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$), and, after removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (500 g) with ethyl acetate–petroleum ether (2:3). In this manner, there was obtained 5.40 g (100%) of an inseparable mixture of the α- and β-alcohols in a 7:1 ratio: IR ($CHCl_3$) 3630, 3520, 3040, 2960, 1760, 1680, 1480, 1390, 1350, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–2.80 (m, 6 H), 3.24 (m, 2 H), 3.88 (s, 3 H), 5.00 and 5.28 (AB system, J = 12 Hz, 2 H), 5.60 (m, 2 H), 7.34 (s, 5 H).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.21; 6.36.

2-Oxo-3-(benzyloxy)-4-methoxy-10α-[(*tert*-butyldimethylsiloxy)methyl]-1α-oxaspiro[4.5]deca-3,7-diene (17). To a rapidly stirred solution of 1.73 g (5.47 mmol) of the above alcohol in 10 mL of CH_2Cl_2 at room temperature was added 1.80 mL (21.9 mmol) of pyridine, 1.0 g (6.6 mmol) of *tert*-butyldimethylsilyl chloride, and 200 mg (1.63 mmol) of 4-(dimethylamino)pyridine. After 18 h, 50 mL of saturated sodium bicarbonate was added and the aqueous layer was extracted with ether (3 × 150 ml) and dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was flash chromatographed on silica gel (150 g) with ethyl acetate–petroleum ether (1:10). In this manner, there was obtained 2.21 g (94%) of the silyl ether as a colorless oil. This is still a mixture of diastereomers from ester **16**: IR ($CHCl_3$) 2970, 2880, 1755, 1675, 1470, 1380, 1345, 1260, 1130, 915, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6 H), 0.85 (s, 9 H), 1.8–2.8 (m, 5 H), 3.36 (m, 2 H), 3.89 (s, 3 H), 5.12 (s, 2 H), 5.68 (m, 2 H), 7.36 (s, 5 H).

Anal. Calcd for $C_{24}H_{34}O_5Si$: C, 66.94; H, 7.96. Found: C, 67.05; H, 8.08.

2-Oxo-3-(benzyloxy)-4-methoxy-7β,8β-epoxy-10α-[(*tert*-butyldimethylsiloxy)methyl]-1α-oxaspiro[4.5]dec-3-ene (18). To a rapidly stirred solution of 2.17 g (5.04 mmol) of the silyl ether **17** in 25 mL of ether at 0 °C was added 1.07 g (10.0 mmol) of anhydrous lithium perchlorate and 3.04 g (17.6 mmol) of 85% *m*-chloroperbenzoic acid. After 20 h, 30 mL of 10% Na_2SO_3 was added, and the aqueous layer was extracted with ether (3 × 150 mL). The combined organic extracts were washed with 40 mL of saturated sodium bicarbonate and then dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (150 g) with ethyl acetate–petroleum ether (1:5). In this manner, there was obtained 1.36 g (61%) of the desired epoxide: mp 112.5–114 °C; IR ($CHCl_3$) 2970, 2870,

1755, 1675, 1465, 1340, 1260, 1165, 1120, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H), 0.89 (s, 9 H), 1.65–2.50 (m, 5 H), 3.10–3.60 (m, 4 H), 3.90 (s, 3 H), 5.10 (s, 2 H), 7.34 (s, 5 H).

Anal. Calcd for $C_{24}H_{34}O_6Si$: C, 64.54; H, 7.67. Found: C, 64.73; H, 7.73.

From this reaction mixture was also recovered 292 mg (14%) of the unreacted minor silyl ether having the 10β configuration.

2-Oxo-3-(benzyloxy)-4-methoxy-7α-methyl-8β-hydroxy-10α-[(*tert*-butyldimethylsiloxy)methyl]-1α-oxaspiro[4.5]-dec-3-ene. To a rapidly stirred solution of 500 mg (1.12 mmol) of the epoxide **18** in 30 mL of hexane at 0 °C was added 12 mL (5.04 mmol) of a 0.42 M solution of lithium dimethylcuprate in ether [prepared by adding 13.1 mL (20.2 mmol) of a 1.54 M solution of methyllithium in ether to a suspension of 2.3 g (11.2 mmol) of copper(I) bromide–dimethyl sulfide complex in 10.9 mL of ether at 0 °C] over a 5-min period. After 1.5 h, another 12 mL (5.04 mmol) of a 0.42 M solution of lithium dimethylcuprate in ether was added. After 30 min, the reaction mixture was allowed to warm to room temperature. After 3 h, 40 mL of saturated ammonium chloride was added and the aqueous layer was extracted with ether (3 × 150 mL). The combined organic layers were dried ($MgSO_4$), and, after removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (50 g) with ethyl acetate–petroleum ether (1:4). In this manner, there was obtained 87 mg (17%) of a ketone: mp 103–104 °C; IR ($CHCl_3$) 2970, 2880, 1765, 1720, 1680, 1470, 1350, 1260, 1130, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.05 (s, 6 H), 0.80 (s, 9 H), 3.33 (m, 2 H), 3.88 (s, 3 H), 5.10 (s, 2 H), 7.36 (s, 5 H).

Anal. Calcd for $C_{24}H_{34}O_6Si$: C, 64.54; H, 7.67. Found: C, 64.36; H, 7.56.

Further elution afforded 320 mg (62%) of the desired alcohol as white crystals: mp 113–114 °C; IR ($CHCl_3$) 3620, 3480, 2940, 2860, 1750, 1675, 1460, 1340, 1255, 1115, 1000, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.03 (s, 6 H), 0.83 (s, 9 H), 1.10 (d, 3 H, J = 7 Hz), 3.25 and 3.45 (d AB system, J = 10, 6 Hz, 2 H), 3.86 (s, 3 H), 5.08 (s, 2 H), 7.35 (s, 5 H).

Anal. Calcd for $C_{25}H_{38}O_6Si$: C, 64.90; H, 8.28. Found: C, 65.03; H, 8.25.

2-Oxo-3-(benzyloxy)-4-methoxy-7α-methyl-8β-[[2-(trimethylsilyl)ethoxy]methoxy]-10α-[(*tert*-butydimethylsiloxy)methyl]-1α-oxaspiro[4.5]dec-3-ene (19). To a rapidly stirred solution of 320 mg (0.69 mmol) of the above alcohol in 4 mL of CH_2Cl_2 at room temperature was added 0.22 mL (1.38 mmol) of [β-(trimethylsilyl)ethoxy]methyl chloride and 0.36 mL (2.07 mmol) of diisopropylethylamine. After 4 h, the reaction mixture was poured into 40 mL of saturated sodium bicarbonate solution and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), and, after removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (20 g) with ether–petroleum ether (1:6). In this manner there was obtained 378 mg (92%) of the desired ether as white crystals: mp 78–80 °C; IR ($CHCl_3$) 2970, 1755, 1678, 1470, 1345, 1255, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.02 (s, 15 H), 0.84 (s, 9 H), 1.10 (d, 3 H, J = 7 Hz), 3.21 and 3.44 (d AB system, J = 6, 10 Hz, 2 H), 3.55 (t, 2 H, J = 7.5 Hz), 3.87 (s, 3 H), 4.68 (s, 2 H), 5.09 (br s, 2 H), 7.36 (s, 5 H).

Anal. Calcd for $C_{31}H_{52}O_7Si_2$: C, 62.80; H, 8.84. Found: C, 63.08; H, 8.77.

2-Oxo-3-hydroxy-4-methoxy-7α-methyl-8β-[[2-(trimethylsilyl)ethoxy]methoxy]-10α-[(*tert*-butyldimethylsiloxy)methyl]-1α-oxaspiro[4.5]dec-3-ene (3). To a rapidly stirred solution of 61 mg (0.103 mmol) of the benzyl ether **19** in 3 mL of ethanol at room temperature was added 2 mg of 10% palladium on activated carbon, and the resulting reaction mixture was put under 1 atm of hydrogen gas. After 1 h, the mixture was filtered through a pad of Celite, the catalyst was washed with ether (50 mL), and the solvent was removed at reduced pressure. In this manner, there was obtained 53 mg (99%) of the desired alcohol as white crystals: mp 96–97 °C; IR ($CHCl_3$) 3520, 3310, 2960, 1750, 1690, 1465, 1345, 1255, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 15 H), 0.86 (s, 9 H), 1.10 (d, 3 H, J = 7.5 Hz), 3.34 and 3.49 (d AB system, J = 6, 10 Hz), 3.62 (t, 2 H, J = 8 Hz), 4.10 (s, 3 H), 4.68 (s, 2 H), 5.58 (br s, 1 H).

Anal. Calcd for $C_{24}H_{46}O_7Si_2$: C, 57.33; H, 9.22. Found: C, 57.35; H, 9.15.

Dimethyl 2-[(*p*-Tolylsulfonyl)oxy]-3-hydroxybutanedioate (20). To a rapidly stirred solution of 60.0 g (0.34 mol) of dimethyl L-tartrate, 2.05 g (16.8 mmol) of 4-(dimethylamino)pyridine, and 100 mL (1.20 mol) of pyridine in 1 L of CH_2Cl_2 at 0 °C was added 32.1 g (0.17 mol) of *p*-toluenesulfonyl chloride in 200 mL of CH_2Cl_2 over a 3-h period. The reaction mixture was allowed to warm to room temperature and after 15 h was poured into 500 mL of 10% HCl and extracted. The organic layer was dried (Na_2SO_4), and, after the solvent was removed at reduced pressure, the crude residue was flash chromatographed on silica gel (1000 g) with ethyl acetate–petroleum ether (1:1). In this manner, there was obtained 19.0 g (34%) of the monotosylate as white crystals: mp 86–89 °C; IR ($CHCl_3$) 3540, 3020, 2960, 1750, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3 H), 3.08 (d, 1 H, J = 7.5 Hz), 3.69 (s, 3 H), 3.74 (s, 3 H), 4.74 (m, 1 H), 5.31 (d, 1 H, J = 1 Hz), 7.32 (d, 2 H, J = 9 Hz), 7.92 (d, 2 H, J = 9 Hz).

Anal. Calcd for $C_{13}H_{16}O_8S$: C, 46.99; H, 4.85. Found: C, 47.07; H, 4.87.

(*E*)-Dimethyl 2-[2-(Benzyloxy)acetoxy]-2-butenedioate (21). To a rapidly stirred solution of 19.0 g (57 mmol) of the monotosylate **20** in 100 mL of CH_2Cl_2 at 0 °C were added 6.0 mL (74 mmol) of pyridine, 0.70 g (5.7 mmol) of 4-(dimethylamino)-pyridine, and 11.6 g (63 mmol) of (benzyloxy)acetyl chloride. After 2 h, 100 mL of water and 50 mL of 10% HCl were added and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried (Na_2SO_2), and the solvent was removed at reduced pressure. In this manner, there was obtained a yellow oil which was immediately taken up in 100 mL of THF at room temperature. To the resulting mixture were added 12.7 mL (91.2 mmol) of triethylamine and 0.86 mL (5.7 mmol) of DBU. After 3 h, the mixture was poured into 100 mL of water and acidified to pH 2 with 10% HCl. The aqueous layer was extracted with ether (3 × 250 mL) and the combined organic layers were dried (Na_2SO_4). After removal of the solvent at reduced pressure, the crude residue was flash chromatographed on silica gel (500 g) with ethyl acetate–petroleum ether (1:4). In this manner, there was obtained 9.6 g (55%) of the desired olefin as white crystals: mp 61–62 °C; IR ($CHCl_3$) 3010, 2960, 1790, 1730, 1660, 1285, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.74 (s, 3 H), 3.83 (s, 3 H), 4.35 (s, 2 H), 4.69 (s, 2 H), 6.70 (s, 1 H), 7.35 (m, 5 H).

Anal. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.40; H, 5.22.

Dimethyl 4-[2-(Benzyloxy)acetoxy]cyclohexene-*trans*-4,5-dicarboxylate (22). A Teflon-lined autoclave was charged with a solution of 25.9 g (84 mmol) of the butenedioate **21** in 100 mL of dry benzene, 100 mL (1.14 mol) of butadiene, and 100 mg (0.78 mmol) of pyrogallol. The sealed autoclave was heated at 150 °C for 3 days. After cooling, 500 mL of ether was added and the mixture was filtered through Celite. After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (400 g) with ether–petroleum ether (1:2). In this manner, there was obtained 27.5 g (90%) of the desired butadiene adduct as a colorless oil: IR ($CHCl_3$) 3010, 2960, 1745, 1435, 1190, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05–3.35 (m, 5 H), 3.65 (s, 3 H), 3.77 (s, 3 H), 4.10 (s, 2 H), 4.63 (s, 2 H), 5.64 (m, 2 H), 7.35 (m, 5 H).

Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.98; H, 6.12. Found: C, 63.01; H, 6.09.

2-Oxo-3-(benzyloxy)-4-methoxy-10β-carbomethoxy-*cis*-bicyclo[4.4.0]deca-3,7-diene (23). A solution of 226 mg (0.62 mmol) of the triester **22** in 4 mL of THF was added dropwise to 3.9 mL (1.30 mmol) of a 0.33 M solution of LiHMDS in THF at −78 °C under an argon atmosphere. After 10 min, the mixture was allowed to warm to 0 °C, and, after an additional 30 min, 3 mL of 10% HCl was added. The aqueous layer was extracted with ether (3 × 150 mL) and the combined organic layers were dried (Na_2SO_4). After removal of the solvent at reduced pressure, the crude residue was treated with ethereal diazomethane and then chromatographed on silica gel (20 g) with ether–petroleum ether (1:2). In this manner, there was obtained 120 mg (56%) of the cyclized product as a colorless oil that was found to be identical with the product obtained when the reaction was run using HMPA and methyl fluorosulfonate: IR ($CHCl_3$) 3010, 2960, 1725, 1640, 1455, 1170, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80–2.80 (m, 4 H), 3.06 (dd, 1 H, J = 6, 10 Hz), 3.69 (s, 3 H), 3.84 (s, 3 H), 4.67 and 4.93 (AB system, 2 H, J = 12 Hz), 5.68 (m, 2 H), 7.35 (m, 5 H).

Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.47; H, 6.00.

Methyl (±)-[1α(5S*,6S*,8R*,9R*),2α,4aβ,5β,8aα]-1-[[[6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-4-methoxy-9-methyl-2-oxo-8-[[2-(trimethylsilyl)ethoxy]methoxy]-1-oxaspiro[4.5]dec-3-en-3-yl]oxy]carbonyl]-1,2,4a,5,6,7,8,8a-octahydro-5-(methoxymethoxy)-1-methyl-2-naphthalenebutanoate (25). To a rapidly stirred solution of 100.4 mg (0.29 mmol) of diacid **4** in 2 mL of CH_2Cl_2 at room temperature was added 0.10 mL (0.71 mmol) of freshly prepared 1-chloro-N,N,2-trimethylpropenylamine. After 5 h, the mixture was cooled to 0 °C and to this was added 39 μL (0.48 mmol) of pyridine and 13 μL (0.32 mmol) of dry methanol. After 45 min, a solution of 135 mg (0.27 mmol) of the debenzylated butenolide **3** and 72 mg (0.59 mmol) of 4-(dimethylamino)pyridine in 1.5 mL of CH_2Cl_2 was added via a cannula and the reaction was allowed to warm to room temperature. After 1.5 h, the mixture was poured into 40 mL of saturated $NaHCO_3$ and the aqueous layer was extracted with ether (3 × 60 mL). The combined organic extracts were dried ($MgSO_4$), and, after removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (20 g) with ethyl acetate–petroleum ether (1:5). In this manner, there was obtained 173 mg (77%) of the desired ester as a mixture of diastereomers: IR ($CHCl_3$) 3960, 1760, 1730, 1685, 1460, 1350, 1255, 1120, 1040, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 15 H), 0.88 (s, 9 H), 1.28 (s, 3 H), 3.36 (s, 3 H), 3.62 (s, 3 H), 3.62 (t, 2 H, J = 7 Hz), 3.95 (br s, 3 H), 4.69 (m, 4 H), 5.88 (m, 2 H).

Anal. Calcd for $C_{43}H_{74}O_{12}Si_2$: C, 61.54; H, 8.89. Found: C, 61.49; H, 8.80.

(±)-[1α(5S*,6S*,8R*,9R*),2α,4aβ,5β,8aα]-1-[[[6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-4-methoxy-9-methyl-2-oxo-8-[[2-(trimethylsilyl)ethoxy]methoxy]-1-oxaspiro[4.5]dec-3-en-3-yl]oxy]carbonyl]-1,2,4a,5,6,7,8,8a-octahydro-5-(methoxymethoxy)-1-methyl-2-naphthalenebutyric Acid. To a rapidly stirred solution of 790 mg (0.94 mmol) of the ester **25** in 14 mL of a 4:1 mixture of methanol/H_2O at room temperature was added 1.88 mL (1.88 mmol) of a 1 N LiOH solution. After 24 h, the reaction mixture was poured into 100 mL of water and the aqueous phase was acidified to pH 2 with 10% H_2SO_4 and then extracted with ether (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), and, after removal of the solvent at reduced pressure, the crude residue was chromatographed on CC-4 silica gel (50 g) with ethyl acetate–petroleum ether (1:4). In this manner, there was obtained 651 mg (84%) of the desired acid as a colorless oil: IR ($CHCl_3$) 3400–2700, 1740, 1660, 1440, 1325, 1095, 1010, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 15 H), 0.88 (s, 9 H), 1.27 (s, 3 H), 3.36 (s, 3 H), 3.60 (t, 2 H, J = 7 Hz), 3.94 (s, 3 H), 4.68 (m, 4 H), 5.75 (m, 2 H), 7.75 (br s, 1 H).

Anal. Calcd for $C_{42}H_{72}O_{12}Si_2$: C, 61.13; H, 8.80. Found: C, 61.00; H, 8.68.

(±)-[1α(5S*,6S*,8R*,9R*),2α,4aβ,5β,8aα]-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-4-methoxy-9-methyl-2-oxo-8-[[2-(trimethylsilyl)ethoxy]methoxy]-1-oxaspiro[4.5]dec-3-en-3-yl 1,2,4a,5,6,7,8,8a-Octahydro-5-(methoxymethoxy)-1-methyl-2-[4-oxo-4-(phenylthio)butyl]-1-naphthalenecarboxylate. To a rapidly stirred solution of 651 mg (0.79 mmol) of the above acid in 10 mL of CH_2Cl_2 at room temperature were added 0.32 mL (3.12 mmol) of thiophenol, 10.0 mg (0.08 mmol) of 4-(dimethylamino)pyridine, and 200 mg (0.95 mmol) of 1,3-dicyclohexylcarbodiimide. After 4 h, the reaction mixture was poured into 75 mL of saturated $NaHCO_3$ and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic extracts were washed with 2 N H_2SO_4 (50 mL) and dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (50 g) with ethyl acetate–petroleum ether (1:5). In this manner, there was obtained 662 mg (92%) of the desired thio ester as a colorless oil: IR ($CHCl_3$) 2960, 1765, 1690, 1350, 1120, 1040, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 15 H), 0.87 (s, 9 H), 1.36 (s, 3 H), 2.70 (m, 2 H), 3.36 (s, 3 H), 3.62 (t, 2 H, J = 7 Hz), 3.94 (s, 3 H), 4.68 (m, 4 H), 5.87 (m, 2 H), 7.37 (s, 5 H).

Anal. Calcd for $C_{48}H_{76}O_{11}Si_2S$: C, 62.85; H, 8.35. Found: C, 62.93; H, 8.40.

(±)-[1α(5S*,6S*,8R*,9R*),2α,4aβ,5β,8aα]-6-(Hydroxymethyl)-4-methoxy-9-methyl-2-oxo-8-[[2-(trimethylsilyl)ethoxy]methoxy]-1-oxaspiro[4.5]dec-3-en-3-yl 1,2,4a,5,6,7,8,8a-Octahydro-5-(methoxymethoxy)-1-methyl-2-[4-oxo-4-(phenylthio)butyl]-1-naphthalenecarboxylate (26A and 26B). To a rapidly stirred solution of 762 mg (0.83 mmol) of the above thio ester in 10 mL of THF was added 5 mL of an HF_x·pyridine solution (prepared by diluting 13 g of Aldrich HF_x·pyridine with 31 mL of pyridine and 100 mL of THF), and the resulting mixture was stirred at room temperature for 2 h. After the reaction mixture was poured into 50 mL of saturated $NaHCO_3$, the aqueous layer was extracted with ether (3 × 100 mL) and the combined organic layers were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on a size C Lobar silica gel column with ethyl acetate–petroleum ether (28:72). In this manner, there was obtained 289 mg (43%) of the "fast" alcohol **26A** as a colorless oil: IR ($CHCl_3$) 3540, 2940, 1760, 1672, 1450, 1340, 1100, 1030, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 9 H), 0.89 (t, 2 H, J = 8 Hz), 1.07 (d, 3 H, J = 7.5 Hz), 1.24 (s, 3 H), 3.33 (s, 3 H), 3.58 (t, 2 H, J = 8 Hz), 3.62 (m, 1 H), 3.90 (s, 3 H), 4.65 (m, 4 H), 5.84 (m, 2 H), 7.34 (s, 5 H).

Anal. Calcd for $C_{42}H_{62}O_{11}SiS$: C, 62.82; H, 7.78. Found: C, 62.74; H, 7.74.

Further elution afforded 360 mg (54%) of the "slow" alcohol **26B** as a colorless oil: IR ($CHCl_3$) 3520, 3470, 2940, 1755, 1675, 1450, 1375, 1340, 1105, 1040, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 9 H), 0.90 (t, 2 H, J = 8 Hz), 1.08 (d, 3 H, J = 7 Hz), 1.28 (s, 3 H), 3.35 (s, 3 H), 3.61 (t, 2 H, J = 8 Hz), 3.67 (m, 1 H), 3.90 (s, 3 H), 4.68 (m, 4 H), 5.72 (dd, 1 H, J = 4, 10 Hz), 5.93 (d, 1 H, J = 10 Hz), 7.35 (s, 5 H).

Anal. Calcd for $C_{42}H_{62}O_{11}SiS$: C, 62.82; H, 7.78. Found: C, 63.02; H, 7.95.

6-(1-Hydroxy-2-propenyl)-4-methoxy-9-methyl-2-oxo-8-[[2-(trimethylsilyl)ethoxy]methoxy]-1-oxaspiro[4.5]dec-3-en-3-yl 1,2,4a,5,6,7,8,8a-Octahydro-5-(methoxymethoxy)-1-methyl-2-[4-oxo-4-(phenylthio)butyl]-1-naphthalenecarboxylate (27A). To a rapidly stirred solution of 200 mg (0.25 mmol) of the alcohol **26A** in 4 mL of CH_2Cl_2 was added 110 mg (0.49 mmol) of pyridinium chlorochromate and 110 mg of Celite. After 2 h, another 110 mg (0.49 mmol) of pyridinium chlorochromate and 110 mg of Celite were added, and the mixture was stirred for an additional 2 h. The mixture was diluted with 30 mL of ether and decanted. The brown powder was washed with four additional 30-mL portions of ether, and the combined organic extracts were filtered through 20 g of silica gel with ether. In this manner there was obtained 183 mg (92%) of the desired aldehyde as a white foam: IR ($CHCl_3$) 2940, 2890, 1765, 1715, 1670, 1455, 1340, 1250, 1110, 1030, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H), 0.92 (t, 2 H, J = 7.5 Hz), 1.15 (d, 3 H, J = 7 Hz), 1.28 (s, 3 H), 3.37 (s, 3 H), 3.50 (t, 2 H, J = 7.5 Hz), 3.74 (m, 1 H), 4.02 (s, 3 H), 4.68 (m, 4 H), 5.85 (m, 2 H), 7.36 (s, 5 H), 9.59 (br s, 1 H). This compound was immediately converted to the allylic alcohol **27A** to avoid decomposition.

To a rapidly stirred solution of 183 mg (0.228 mmol) of the above aldehyde in 1.5 mL of THF at −78 °C was added 0.30 mL (0.25 mmol) of a 0.84 M solution of vinylmagnesium bromide in THF. After 5 min, the solution was allowed to warm to 0 °C for 10 min and was then quenched with 0.5 mL of saturated aqueous NH_4Cl. The resulting mixture was poured into 30 mL of water and the aqueous layer was extracted with ether (3 × 50 mL), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (20 g) with ethyl acetate–petroleum ether (1:3). In this manner, there was obtained 140 mg (73%) of the desired allylic alcohol as a white foam: IR ($CHCl_3$) 3500, 2940, 1765, 1685, 1110, 1040, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 9 H), 0.90 (t, 2 H, J = 7.5 Hz), 1.12 (d, 3 H, J = 7 Hz), 1.28 (s, 3 H), 3.27 (m, 1 H), 3.36 (s, 3 H), 3.58 (t, 2 H, J = 7.5 Hz), 3.72 (m, 1 H), 3.95 (s, 3 H), 4.28 (m, 1 H), 4.68 (m, 4 H), 5.17 (m, 2 H), 5.85 (m, 3 H), 7.36 (s, 5 H).

Anal. Calcd for $C_{44}H_{64}O_{11}SSi$: C, 63.74; H, 7.78. Found: C, 63.68; H, 7.71.

6-(1-Hydroxy-2-propenyl)-4-methoxy-9-methyl-2-oxo-8-[[2-(trimethylsilyl)ethoxy]methoxy]-1-oxaspiro[4.5]dec-3-en-3-yl 1,2,4a,5,6,7,8,8a-Octahydro-5-(methoxymethoxy)-1-methyl-2-[4-oxo-4-(phenylthio)butyl]-1-naphthalenecarboxylate (27B). By the procedure described for the aldehyde

26A, 200 mg (0.25 mmol) of the alcohol **26B**, 110 mg (0.49 mmol) of pyridinium chlorochromate, and 110 mg of Celite in 4 mL of CH_2Cl_2 afforded, after filtration through silica gel (20 g) with ether, 187 mg (94%) of the aldehyde as a white foam: IR ($CHCl_3$) 2950, 1765, 1710, 1680, 1495, 1340, 1100, 1030, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H), 0.90 (t, 2 H, J = 7.5 Hz), 1.15 (d, 3 H, J = 7 Hz), 1.29 (s, 3 H), 3.28 (m, 1 H), 3.37 (s, 3 H), 3.60 (t, 2 H, J = 7.5 Hz), 3.75 (m, 1 H), 4.00 (s, 3 H), 4.67 (m, 4 H), 5.85 (m, 2 H), 7.36 (s, 5 H), 9.55 (br s, 1 H). This compound was immediately converted to the allylic alcohol **27B** to avoid decomposition.

By the procedure described for the allylic alcohol **27A**, 187 mg (0.23 mmol) of the above aldehyde and 0.31 mL of a 0.84 M solution of vinylmagnesium bromide in 1.5 mL of THF afforded, after chromatography on silica gel (20 g) with ethyl acetate–petroleum ether (1:3), 139 mg (71%) of the desired allylic alcohol as a white foam: IR ($CHCl_3$) 3400, 2940, 1760, 1680, 1450, 1345, 1250, 1110, 1035, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 9 H), 0.90 (t, 2 H, J = 7.5 Hz), 1.14 (d, 3 H, J = 7 Hz), 1.29 (s, 3 H), 3.23 (m, 1 H), 3.36 (s, 3 H), 3.58 (t, 2 H, J = 7.5 Hz), 3.71 (m, 1 H), 3.95 (br s, 3 H), 4.15 (m, 1 H), 4.67 (m, 4 H), 5.15 (m, 2 H), 5.78 (m, 3 H), 7.36 (s, 5 H).

Anal. Calcd for $C_{44}H_{64}O_{11}SSi$: C, 63.74; H, 7.78. Found: C, 63.56; H, 7.75.

12-Ethenyl-4,4a,6a,7,8,9,12,12a,13,14,15,16,21a,21b-tetradecahydro-22-methoxy-4-(methoxymethoxy)-15,21a-dimethyl-14-[[2-(trimethylsilyl)ethoxy]methoxy]-18*H*-16a,19-metheno-2*H*,16a*H*-benzo[*e*]naphththo[2,1-*m*][1,4,8]trioxacyclopentadecin-10,18,21(1*H*,3*H*)-trione (2A). To a rapidly stirred suspension of 148 mg (1.04 mmol) of anhydrous Na_2HPO_4 and 116 mg (0.52 mmol) of dry silver trifluoroacetate in 80 mL of dry benzene at 82 °C was added 40 mL of a benzene solution of 108 mg (0.13 mmol) of the vinyl alcohol **27A** over a 3-h period. After the addition was complete the mixture was held at 82 °C for an additional hour. After cooling, the reaction mixture was poured into 80 mL of water and acidified to pH 2 with 10% HCl. The aqueous layer was extracted with ether (3 × 150 mL) and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on Silicar CC-4 (15 g) with ethyl acetate–petroleum ether (1:3). In this manner there was obtained 71 mg (75%) of the macrolactone as a white foam: IR ($CHCl_3$) 2980, 1760, 1730, 1680, 1460, 1345, 1110, 1040, 870, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 9 H), 0.90 (t, 2 H, J = 8 Hz), 1.30 (s, 3 H), 3.28 (m, 1 H), 3.33 (s, 3 H), 3.58 (t, 2 H, J = 8 Hz), 3.71 (m, 1 H), 4.04 (s, 3 H), 4.65 (m, 4 H), 5.14 (m, 3 H), 5.72 (m, 3 H).

Anal. Calcd for $C_{38}H_{58}O_{11}Si$: C, 63.48; H, 8.13. Found: C, 63.44; H, 8.00.

Further elution afforded 19 mg (20%) of the corresponding hydroxy acid as a colorless oil: IR ($CHCl_3$) 3600–2400, 2960, 1765, 1710, 1685, 1420, 1345, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 9 H), 1.10 (d, 3 H, J = 7 Hz), 1.25 (s, 3 H), 3.36 (s, 3 H), 3.57 (t, 2 H, J = 8 Hz), 3.74 (m, 1 H), 3.95 (br s, 3 H), 4.68 (m, 4 H), 4.80–5.90 (m, 5 H). This material was recycled back to the allylic alcohol **27A** as described below.

Recycle of Hydroxy Acid A to Allylic Alcohol 27A. To a rapidly stirred solution of 257 mg (0.35 mmol) of the hydroxy acid A in 3 mL of THF at room temperature was added 0.15 mL (1.05 mmol) of triethylamine and 0.10 mL (0.73 mmol) of diethyl chlorophosphate. After 3 h, 0.15 mL (1.05 mmol) of triethylamine and 0.1 mL (1.05 mmol) of thiophenol was added, and the mixture was allowed to stir for an additional 16 h. After the mixture was poured into 50 mL of saturated $NaHCO_3$, the aqueous layer was extracted with ether (3 × 60 mL), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (20 g) with ethyl acetate–petroleum ether (1:3). In this manner, there was obtained 214 mg (74%) of allylic alcohol **27A** as a white foam.

12-Ethenyl-4,4a,6a,7,8,9,12,12a,13,14,15,16,21a,21b-tetradecahydro-22-methoxy-4-(methoxymethoxy)-15,21a-dimethyl-14-[[2-(trimethylsilyl)ethoxy]methoxy]-18*H*-16a,19-metheno-2*H*-benzo[*e*]naphtho[2,1-*m*][1,4,8]trioxacyclopentadecin-10,18,21(1*H*,3*H*)-trione (2B). By the procedure described for the lactone **2A**, 223 mg (1.57 mmol) of anhydrous Na_2HPO_4, 173 mg (0.78 mmol) of dry silver trifluoroacetate, and 162 mg (0.19 mmol) of the allylic alcohol **27B** in 140 mL of benzene afforded, after chromatography on Silicar CC-4 (20 g) with ethyl acetate–petroleum ether (1:2), 98 mg (70%) of the lactone **2B** as a colorless oil: IR ($CHCl_3$) 2960, 1775, 1720, 1685, 1460, 1345, 1235, 1145, 1110, 1040, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 9 H), 0.89 (t, 2 H, J = 8 Hz), 1.10 (d, 3 H, J = 7 Hz), 1.27 (s, 3 H), 3.16 (m, 1 H), 3.57 (t, 2 H, J = 8 Hz), 3.69 (m, 1 H), 4.14 (br s, 3 H), 4.64 (m, 4 H), 5.11 (m, 3 H), 5.71 (m, 3 H).

Anal. Calcd for $C_{38}H_{58}O_{11}Si$: C, 63.48; H, 8.13. Found: C, 63.40; H, 8.07.

Further elution afforded 31 mg (22%) of the hydroxy acid B as a colorless oil: IR ($CHCl_3$) 3600–2400, 2960, 1770, 1710, 1685, 1460, 1350, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 9 H), 1.08 (d, 3 H, J = 7 Hz), 1.28 (s, 3 H), 3.36 (s, 3 H), 3.58 (t, 2 H, J = 8 Hz), 3.96 (br s, 3 H), 4.68 (m, 4 H), 4.85–5.90 (m, 5 H). This hydroxy acid was recycled back to the allylic alcohol **27B** as described below.

Recycle of the Hydroxy Acid B to the Allylic Alcohol 27B. By the procedure described for the hydroxy acid A, 238 mg (0.32 mmol) of the hydroxy acid B, 0.10 mL (0.68 mmol) of diethyl chlorophosphate, 0.15 mL (0.97 mmol) of triethylamine, and 0.10 mL (0.97 mmol) of thiophenol in 3 mL of THF afforded, after chromatography on silica gel (20 g) with ethyl acetate–petroleum ether (1:3), 217 mg (81%) of the allylic alcohol **27B** as a white foam.

(±)-14-Carboxy-20-decarboxy-19,20-dihydro-7-*O*-(methoxymethyl)-24-*O*-methyl-20-[[2-(triethylsilyl)ethoxy]methoxy]chlorothricolide (28A). A 0.8 M solution of potassium hexamethyldisilazide was prepared by addition of 1.0 mL (4.74 mmol) of freshly distilled hexamethyldisilizane to a slurry of 161 mg (4.0 mmol) of potassium hydride (obtained from 460 mg of a 35% potassium hydride suspension in oil by three washings with ether) in 4.0 mL of THF at room temperature. The resulting slightly cloudy mixture was stirred for 1 h. To 1.04 mL (0.83 mmol) of this solution in 3 mL of THF at −78 °C was added 0.8 mL of hexamethylphosphoramide. To this solution was added dropwise over a 10-min period 195 mg (0.27 mmol) of the lactone **2A** in 1 mL of THF. After 15 min, 0.4 mL (1.40 mmol) of a 3:1:1 solution of chlorotriethylsilane, triethylamine, and THF was added. After 5 min, the mixture was allowed to warm to room temperature. After 4 h, 0.4 mL of 10% HCl and 0.2 mL of H_2O were added and stirring was continued for 10 min. The mixture was then poured into 50 mL of 5% HCl and extracted with ether (3 × 60 mL), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on Silicar CC-4 with ethyl acetate–petroleum ether (1:3). In this manner, there was obtained 38 mg (19%) of starting lactone and 114 mg (59%) of the Claisen acid as a white foam: IR ($CHCl_3$) 3550–2400, 2950, 1775, 1700, 1675, 1340, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H), 3.22 (m, 1 H), 3.37 (s, 3 H), 3.60 (t, 2 H, J = 8 Hz), 3.69 (m, 1 H), 3.97 (br s, 3 H), 4.69 (m, 4 H), 5.32 (m, 2 H), 5.69 (m, 2 H).

Anal. Calcd for $C_{38}H_{58}O_{11}Si$: C, 63.48; H, 8.13. Found: C, 63.16; H, 8.03.

(±)-14-Carboxy-20-decarboxy-19,20-dihydro-7-*O*-(methoxymethyl)-24-*O*-methyl-20-[[2-(trimethylsilyl)ethoxy]methoxy]chlorothricolide (28B). By the procedure described for the acid **28A**, 54 mg (69.5 mmol) of the lactone **27B**, 0.26 mL (0.21 mmol) of a 0.8 M solution of potassium hexamethyldisilazide in THF, 98 μL (0.35 mmol) of a 3:1:1 chlorotriethylsilane/triethylamine/THF solution, and 0.2 mL of hexamethylphosphoramide in 1 mL of dry THF afforded, after chromatography on Silicar CC-4 with ethyl acetate–petroleum ether (1:3), 39 mg (72%) of the desired Claisen acid as a colorless foam: IR ($CHCl_3$) 3550–2350, 3460, 2940, 1755, 1670, 1440, 1330, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 9 H), 3.29 (m, 1 H), 3.35 (s, 3 H), 3.57 (t, 2 H, J = 8 Hz), 3.67 (m, 1 H), 4.09 (br s, 3 H), 4.68 (m, 4 H), 5.34 (m, 2 H), 5.52 (br d, 1 H, J = 10 Hz), 5.83 (br d, 1 H, J = 10 Hz), 8.10 (br s, 1 H).

Anal. Calcd for $C_{38}H_{58}O_{11}Si$: C, 63.48; H, 8.13. Found: C, 63.29; H, 8.18.

(±)-20-Decarboxy-19,20-dihydro-7-*O*-(methoxymethyl)-24-*O*-methyl-20-[[2-(trimethylsilyl)ethoxy]methoxy]chlorothricolide (29A). To a rapidly stirred solution of 101 mg (0.14 mmol) of the Claisen acid **28A** in 2 mL of THF at 0 °C was

added 0.12 mL (0.84 mmol) of triethylamine and 84 μL (0.56 mmol) of phenyl dichlorophosphate. After 15 min, to the mixture were added 0.30 mL (2.10 mmol) of triethylamine and 0.15 mL (1.41 mmol) of freshly distilled phenylselenol. After an additional 20 min, the mixture was poured into 30 mL of water and extracted with ether (2 × 60 mL), and the combined organic extracts were dried (Na_2SO_4). After removal of the solvent at reduced pressure, the crude residue was chromatographed on neutral activity III alumina with ethyl acetate–petroleum ether (1:4). In this manner, there was obtained 96 mg (80%) of the desired seleno ester as a colorless foam: IR ($CHCl_3$) 2940, 1755, 1710, 1670, 1420, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 9 H), 0.89 (t, 2 H, J = 8 Hz), 1.14 (d, 3 H, J = 7 Hz), 1.27 (s, 3 H), 2.80 (m, 2 H), 3.24 (m, 1 H), 3.37 (s, 3 H), 3.60 (t, 2 H, J = 8 Hz), 3.96 (s, 3 H), 4.68 (m, 4 H), 5.34 (m, 2 H), 5.59 (dd, 1 H, J = 4 and 10 Hz), 5.87 (d, 1 H, J = 10 Hz), 7.37 (m, 5 H). As decomposition occurred upon standing, the seleno ester was immediately decarbonylated.

A solution of 96 mg (0.112 mmol) of the above seleno ester in 6 mL of dry p-xylene[8] was heated with stirring to 130 °C, and to this were added 60 μL (0.22 mmol) of tributyltin hydride and a small crystal of AIBN. After 10 min, the mixture was poured into 30 mL of saturated $NaHCO_3$, the aqueous layer was extracted with ether (3 × 60 mL), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (15 g) with ethyl acetate–petroleum ether (1:5). In this manner, there was obtained 66 mg (88%) of the decarbonylated lactone **29A** as a colorless foam: IR ($CHCl_3$) 2940, 1760, 1680, 1455, 1340, 860, 840 cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.00 (s, 9 H, $Si(CH_3)_3$), 0.91 (t, 2 H, J = 8 Hz, $-CH_2CH_2Si-$), 1.13 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.30 (s, 3 H, CCH_3), 2.76 (ddd, 1 H, J = 13, 7.5, 4 Hz, C-18 H), 3.22 (dt, 1 H, J = 10, 4 Hz, C-7 H), 3.38 (s, 3 H, OCH_3), 3.62 (t, 2 H, J = 8 Hz, OCH_2CH_2), 3.72 (br s, 1 H, C-20 H), 3.98 (s, 3 H, OCH_3), 4.63 and 4.76 (AB, 2 H, J = 7 Hz, OCH_2OCH_3), 4.71 (br s, 2 H, OCH_2OCH_2), 5.26 (dd, 1 H, J = 16 and 7.5 Hz, C-17 H), 5.38 (ddd, 1 H, J = 16, 6, 6 Hz, C-16 H), 5.61 (ddd, 1 H, J = 10, 5, 2 Hz, C-9 or C-10 H), 5.78 (d, 1 H, J = 10 Hz, C-9 or C-10 H). The signal at 5.26 ppm collapses to a doublet (J = 16 Hz) upon irradiation of the 2.76-ppm peak.

Anal. Calcd for $C_{37}H_{58}O_9Si$: $(M + H)^+$, 675.3928. Found: $(M + H)^+$, 675.3942.

Further elution afforded 6 mg (8%) of the aldehyde **30A** as a colorless oil: IR ($CHCl_3$) 2960, 1760, 1720, 1680, 1510, 1430, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 9 H), 0.91 (t, 2 H, J = 8 Hz), 1.13 (d, 3 H, J = 7 Hz), 1.30 (s, 3 H), 2.79 (m, 1 H), 3.20 (m, 1 H), 3.38 (s, 3 H), 3.62 (t, 2 H, J = 8 Hz), 3.71 (m, 1 H), 3.98 (s, 3 H), 4.62 and 4.75 (AB, 2 H, J = 6 Hz), 4.70 (br s, 2 H), 5.35 (m, 2 H), 5.62 (m, 1 H), 5.82 (d, 1 H, J = 10 Hz), 9.62 (br s, 1 H).

Anal. Calcd for $C_{38}H_{58}O_{10}Si$: $(M + H)^+$, 703.3878. Found: $(M + H)^+$, 703.3917.

(±)-Decarboxy-19,20-dihydro-7-*O*-(methoxymethyl)-24-*O*-methyl-20-[[2-(trimethylsilyl)ethoxy]methoxy]chlorothricolide (29B). By the procedure described for the seleno ester A, 60 mg (83.5 μmol) of the Claisen acid **28B**, 50 μL (0.33 mmol) of phenyl dichlorophosphate, 90 μL (0.84 mmol) of phenylselenol, and 0.27 mL (1.75 mmol) of triethylamine in 1.7 mL of THF afforded, after chromatography on neutral activity III alumina with ethyl acetate–petroleum ether (1:4), 55 mg (77%) of the desired seleno ester as a colorless foam: IR ($CHCl_3$) 2960, 1765, 1740, 1680, 1505, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 9 H), 0.86 (t, 2 H, J = 8 Hz), 1.24 (s, 3 H), 3.36 (s, 3 H), 3.60 (t, 2 H, J = 8 Hz), 4.07 (br s, 3 H), 4.67 (m, 4 H), 5.34 (m, 2 H), 5.62 (br d, 1 H, J = 10 Hz), 5.84 (d, 1 H, J = 10 Hz), 7.37 (m, 5 H). As decomposition occurred upon standing, the seleno ester was immediately decarbonylated.

By the procedure described for the lactone **29A**, 55 mg (64 μmol) of the above seleno ester, 34 μL (0.13 mmol) of tributyltin hydride, and a small crystal of AIBN in 5 mL of p-xylene afforded, after chromatography on silica gel (15 g) with ethyl acetate–petroleum ether (1:5), 41 mg (95%) of the desired lactone **29B** as white crystals: mp 132–133.5 °C; IR ($CHCl_3$) 2940, 1765, 1680, 1450, 1335 cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.00 (s, 9 H, $Si(CH_3)_3$), 0.92 (t, 2 H, J = 8 Hz, OCH_2CH_2Si), 1.15 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.22 (s, 3 H, CCH_3), 2.68 (ddd, 1 H, J = 13, 9, 3.5 Hz, C-18 H), 3.21 (ddd, 1 H, J = 10, 10, 4 Hz, C-7 H), 3.38 (s, 3 H, OCH_3), 3.61 (dd, 2 H, J = 17, 8 Hz, OCH_2CH_2Si), 3.67 (br s, 1 H, C-20 H), 4.08 (s, 3 H, OCH_3), 4.63 and 4.76 (AB, 2 H, J = 7 Hz, OCH_2OCH_3), 4.71 (br s, 2 H, OCH_2OCH_2), 5.23 (ddd, 1 H, J = 15, 6.5, 6.5 Hz, C-16 H), 5.31 (dd, 1 H, J = 15, 9 Hz, C-17 H), 5.57 (dd, 1 H, J = 10, 2.5 Hz, C-9 or C-10 H), 5.81 (d, 1 H, J = 10 Hz, C-9 or C-10 H). The signal at 5.31 ppm collapses to a doublet (J = 15 Hz) upon irradiation of the peak at 2.68 ppm.

Anal. Calcd for $C_{37}H_{58}O_9Si$: $(M + H)^+$, 675.3928. Found: $(M + H)^+$, 675.3922.

Decarbonylation of the Aldehyde 30A. A solution of 17 mg (24.2 μmol) of the aldehyde **30A** and 87 mg (91 μmol) of tris(triphenylphosphine)rhodium chloride in 1 mL of freshly distilled 1,2-dichloroethane was heated at 82 °C for 2 h. After dilution with 5 mL of ether, the mixture was filtered and the solvent was removed under reduced pressure. The crude residue was chromatographed on silica gel (2 g) with ethyl acetate–petroleum ether (1:5). In this manner, there was obtained 8 mg (50%) of the decarbonylated product **29A** which was identical in all respects with that obtained by decomposition of the seleno ester A.

(±)-20-Decarboxy-19,20-dihydro-24-*O*-methyl-20-hydroxychlorothricolide (31A). A solution of 152 mg (0.225 mmol) of the lactone **29A** and 151 mg (1.61 mmol) of lithium tetrafluoroborate in 5 mL of CH_3CN containing 0.2 mL of water was heated at 72 °C for 5 h. After the mixture was cooled to room temperature, it was poured into 30 mL of water, the aqueous layer was extracted with ether (3 × 60 mL), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (15 g) with ethyl acetate–petroleum ether (45:55). In this manner, there was obtained 112 mg (100%) of the diol **31A** as a glass: IR ($CHCl_3$) 3600, 3420, 2940, 1760, 1730, 1680, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H), 2.78 (m, 1 H), 3.25 (m, 1 H), 3.84 (m, 1 H), 3.93 (s, 3 H), 5.24 (m, 2 H), 5.54 (dd, 1 H, J = 10, 4 Hz), 5.71 (d, 1 H, J = 10 Hz).

Anal. Calcd for $C_{29}H_{40}O_7$: $(M + H)^+$, 501.2852. Found: $(M + H)^+$, 501.2882.

(±)-20-Decarboxy-19,20-dihydro-24-*O*-methyl-20-hydroxychlorothricolide (31B). By the procedure described for the diol **31A**, 227 mg (0.336 mmol) of the lactone **29B**, 252 mg (2.69 mmol) of lithium tetrafluoroborate in 9 mL CH_3CN, and 0.5 mL of water afforded, after chromatography on silica gel (20 g) with ethyl acetate–petroleum ether (1:1), 168 mg (100%) of the diol **31B** as an amorphous solid: IR ($CHCl_3$) 3550, 3500, 2940, 1775, 1760, 1685, 1510, 1430, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (m, 1 H), 3.82 (m, 1 H), 4.05 (s, 3 H), 5.26 (m, 2 H), 5.52 (br d, 1 H, J = 10 Hz), 5.88 (d, 1 H, J = 10 Hz).

Anal. Calcd for $C_{29}H_{40}O_7$: $(M + H)^+$, 501.2852. Found: $(M + H)^+$, 501.2866.

(±)-20-Decarboxy-19,20-dihydro-24-*O*-methyl-20-hydroxychlorothricolide, Ethyl Carbonate (A). To a rapidly stirred solution of 110 mg (0.23 mmol) of the diol **31A** in 3.1 mL of dry pyridine at 0 °C was added 20 μL (0.20 mmol) of ethyl chloroformate. After 30 min, another 20 μL (0.20 mmol) of ethyl chloroformate was added. Addition of 20-μL batches of ethyl chloroformate was continued every 30 min until a total of five had been added. The mixture was poured into 30 mL of 10% HCl and extracted with ether (3 × 60 mL), and the combined organic extracts were washed with 20 mL of saturated $NaHCO_3$ and then dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (15 g) with ethyl acetate–petroleum ether (35:65). In this manner there was obtained 78 mg (62%) of the desired monoprotected alcohol as white crystals: mp 244–247 °C; IR ($CHCl_3$) 3550, 3500, 2950, 1760, 1680, 1460, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 2.46 (dd, 1 H, J = 13, 6 Hz), 2.84 (m, 1 H), 3.89 (m, 1 H), 3.96 (s, 3 H), 4.15 (q, 2 H, J = 7 Hz), 4.31 (m, 1 H), 5.28 (m, 2 H), 5.57 (m, 2 H).

Anal. Calcd for $C_{32}H_{44}O_9$: $(M + H)^+$, 573.3064. Found: $(M + H)^+$, 573.3095.

Further elution afforded 8 mg (7%) of the starting diol. In addition, there was obtained 20 mg (15%) of the compound containing two ethyl carbonate groups. Subjection of this compound to the isolation conditions reported[4] yielded the original starting diol **31A**.

(±)-20-Decarboxy-19,20-dihydro-24-*O*-methyl-20-hydroxychlorothricolide, Ethyl Carbonate (B). By the procedure described for the alcohol **31A**, 168 mg (0.336 mmol) of the diol **31B** and five 32-μL (0.336 mmol) portions of ethyl chloroformate in 3 mL of dry pyridine afforded, after chromatography on silica gel (20 g) with ethyl acetate–petroleum ether (35:65), 139 mg (72%) of the desired monoprotected alcohol as a glass: IR ($CHCl_3$) 3550, 3500, 1775, 1735, 1690, 1430, 1380, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 3 H), 2.35 (dd, 1 H, J = 13, 6 Hz), 2.82 (m, 1 H), 3.84 (m, 1 H), 4.05 (s, 3 H), 4.11 (dq, 2 H, J = 12, 7 Hz), 4.34 (m, 1 H), 5.24 (m, 2 H), 5.66 (br s, 2 H).

Anal. Calcd for $C_{32}H_{44}O_9$: $(M + H)^+$, 573.3064. Found: $(M + H)^+$, 573.3029.

In addition there was obtained 10 mg (6%) of the starting material and 37 mg (17%) of the diprotected compound. Subjection of the diprotected material to the reported isolation conditions afforded the starting diol **31B**.

(±)-20-Decarboxy-19,20-dihydro-24-*O*-methyl-20-oxochlorothricolide, Ethyl Carbonate (32A). To a rapidly stirred solution of 35 mg (61.5 μmol) of the above alcohol A in 1 mL of CH_2Cl_2 at room temperature were added 26 mg (122 μmol) of pyridinium chlorochromate and 26 mg of Celite. After 2 h, the mixture was diluted with 5 mL of ether and decanted. The brown powder was washed with four additional 5-mL portions of ether. After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (10 g) with ethyl acetate–petroleum ether (28:72). In this manner, there was obtained 33 mg (94%) of the ketone **32A** as a colorless glass: IR ($CHCl_3$) 2950, 1765, 1715, 1680, 1455, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.02 (s, 3 H), 4.13 (dq, 2 H, J = 12, 7 Hz), 4.37 (m, 1 H), 4.28 (m, 2 H), 4.66 (br s, 2 H).

Anal. Calcd for $C_{32}H_{42}O_9$: $(M + H)^+$, 571.2907. Found: $(M + H)^+$, 571.2908.

(±)-20-Decarboxy-19,20-dihydro-24-*O*-methyl-20-oxochlorothricolide, Ethyl Carbonate (32B). By the procedure described for the ketone **32A**, 137 mg (0.239 mmol) of the above alcohol B, 103 mg (0.48 mmol) of pyridinium chlorochromate, and 103 mg of Celite in 3 mL of CH_2Cl_2 afforded, after chromatography on silica gel (15 g) with ethyl acetate–petroleum ether (3:7), 115 mg (84%) of the ketone **32B** as a glass: IR ($CHCl_3$) 2950, 1770, 1725, 1685, 1450, 1370, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (s, 3 H), 4.16 (q, 2 H, J = 7 Hz), 4.32 (m, 1 H), 5.28 (m, 2 H), 5.57 (br s, 2 H).

Anal. Calcd for $C_{32}H_{42}O_9$: $(M + H)^+$, 571.2907. Found: $(M + H)^+$, 571.2857.

(±)-(20*S*)-20-Decarboxy-19,20-dihydro-24-*O*-methyl-20,20-(methyleneoxy)chlorothricolide, Ethyl Carbonate (33A). To a rapidly stirred solution of 79 mg (0.2 mmol) of (tributylstannyl)(2-methoxyisopropoxy)methane[42] in 0.5 mL of THF at −78 °C was added 65 μL (0.145 mmol) of a 2.24 M solution of *n*-butyllithium in hexane. After 15 min, 46 mg (81 μmol) of the ketone **32A** in 0.5 mL of THF was added via a cannula over a 3-min period. After 15 min, 0.3 mL of saturated $NaHCO_3$ was added and the entire mixture was poured into 20 mL of saturated $NaHCO_3$. The aqueous layer was extracted with ether (3 × 30 mL) and the combined organic extracts were dried (Na_2SO_4). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (2 g) with ethyl acetate–petroleum ether (35:65) that contained 0.1% pyridine. In this manner, there was obtained 14 mg (30%) of the starting ketone and 35 mg (64%) of the very acid-sensitive addition product as a colorless glass: ^1H NMR ($CDCl_3$) δ 3.20 (s, 3 H, OCH_3), 3.43 (AB, 2 H, J = 18, 9 Hz), 3.96 (s, 3 H), 4.19 (q, 2 H, J = 7 Hz), 4.35 (m, 1 H), 5.26 (m, 2 H), 5.68 (br s, 2 H). This material was used directly in the next step.

To a stirred solution of 35 mg (51 μmol) of the above addition product in 1 mL of THF at room temperature was added 0.1 mL of 10% HCl. After 10 min, the mixture was poured into 20 mL of 5% HCl and the aqueous layer was extracted with ether (3 × 30 mL), and the combined organic extracts were dried (Na_2SO_4). After removal of the solvent at reduced pressure, the crude residue was dissolved in 1 mL of dry THF. To this solution was added 27 mg (0.16 mmol) of (*p*-tolylsulfonyl)imidazole and 9 mg (0.24 mmol) of a 60% dispersion of NaH in oil. After 30 min at room temperature, the mixture was poured into 20 mL of water, the aqueous layer was extracted with ether (3 × 30 mL), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (10 g) with ethyl acetate–petroleum ether (28:72). In this manner, there was obtained 16 mg (54%) of the desired epoxide **33A** as a colorless glass: IR ($CHCl_3$) 2940, 1760, 1680, 1460, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.64 (br s, 2 H), 3.95 (s, 3 H), 4.15 (q, 2 H, J = 7 Hz), 4.44 (m, 1 H), 5.34 (m, 2 H), 5.58 (br s, 2 H).

Anal. Calcd for $C_{33}H_{44}O_9$: $(M + H)^+$, 585.3064. Found: $(M + H)^+$, 585.3080.

(±)-(20*S*)-20-Decarboxy-19,20-dihydro-24-*O*-methyl-20,20-(methyleneoxy)chlorothricolide, Ethyl Carbonate (33B). By the procedure described for epoxide **33A**, 91 mg (0.23 mmol) of (tributylstannyl)(2-methoxyisopropoxy)methane, 85 μL (0.19 mmol) of a 2.24 M solution of *n*-butyllithium in hexane, and 60 mg (0.105 mmol) of the ketone **32B** in 1 mL of THF afforded, after chromatography on silica gel with ethyl acetate–petroleum ether (35:65) containing 0.1% pyridine, 13 mg (22%) of the starting ketone and 33 mg (48%) of the desired addition product as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.38 (s, 6 H), 3.20 (s, 3 H), 3.50 (m, 2 H), 4.09 (s, 3 H), 4.19 (q, 2 H, J = 7 Hz), 4.38 (m, 1 H), 5.14 (m, 1 H), 5.30 (m, 1 H), 5.59 (br s, 2 H). This material was used directly in the step.

By the procedure described for the epoxide **33A**, 33 mg (49 μmol) of the above addition product, 0.1 mL of 10% HCl, 27 mg (0.16 mmol) of (*p*-tolylsulfonyl)imidazole, and 9 mg (0.24 mmol) of a 60% dispersion of NaH in oil in 1.5 mL of THF afforded, after chromatography on silica gel (10 g) with ethyl acetate–petroleum ether (28:72), 20.6 mg (72%) of the desired epoxide **33B** as white crystals: mp 203–205 °C; IR ($CHCl_3$) 2950, 1780, 1755, 1680, 1460, 1350, 1265, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62 (br s, 2 H), 4.09 (s, 3 H), 4.17 (q, 2 H, J = 7 Hz), 4.34 (m, 1 H), 5.25 (m, 2 H), 5.59 (br s, 2 H).

Anal. Calcd for $C_{33}H_{44}O_9$: $(M + H)^+$, 585.3064. Found: $(M + H)^+$, 585.3047.

(±)-19,20-Dihydro-24-*O*-methylchlorothricolide-20-carboxaldehyde, Ethyl Carbonate (A). To a rapidly stirred solution of 25 mg (42.8 μmol) of the epoxide **33A** in 0.4 mL of toluene at 0 °C were added 6 μL (51.4 μmol) of 2,6-lutidine and 9 μL (47.0 μmol) of trimethylsilyl triflate. After 30 min, another 6 μL of 2,6-lutidine and 9 μL of trimethylsilyl triflate were added and again after an additional 30 min. After 1 h, 12 μL (77.0 μmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added and the reaction mixture was allowed to warm to room temperature. After 14 h, the mixture was poured into 20 mL of 10% HCl and 20 mL of ether. The separatory funnel was then shaken for 5 min. The aqueous layer was then extracted with ether (3 × 30 mL) and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (2 g) with ethyl acetate–petroleum ether (3:7). In this manner, there was obtained 6.0 mg (24%) of the desired aldehyde A as a colorless oil: IR ($CHCl_3$) 2950, 1760, 1680, 1380, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3 H), 4.19 (q, 2 H, J = 7 Hz), 4.37 (m, 1 H), 5.30 (m, 2 H), 5.57 (br s, 2 H), 9.74 (s, 1 H). This aldehyde was used directly in the next step.

Further elution afforded 9.4 mg (37%) of the starting epoxide and 2.9 mg (12%) of the undesired allylic alcohol having the double bond across the C-20 and C-21 carbons: ^1H NMR ($CDCl_3$) δ 1.74 (br s, 3 H), 4.00 (s, 3 H), 4.18 (q, 2 H, J = 7 Hz), 5.38 (m, 2 H), 5.59 (br s, 2 H).

(±)-19,20-Dihydro-24-*O*-methylchlorothricolide-20-carboxaldehyde, Ethyl Carbonate (B). By the procedure described for the aldehyde A, 19 mg (33 μmol) of the epoxide **33B**, three portions of 5 μL (39 μmol) of 2,6-lutidine, 7 μL (36 μmol) of trimethylsilyl triflate, and 18 μL (117 μmol) of DBU in 0.3 mL of toluene afforded, after chromatography on silica gel (2 g) with ethyl acetate–petroleum ether (3:7), 8 mg (42%) of the desired aldehyde B as a colorless oil: IR ($CHCl_3$) 2940, 1780, 1750, 1690, 1450, 1380, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.02 (s, 3 H), 4.18 (q, 2 H), 4.34 (m, 1 H), 5.24 (m, 2 H), 5.56 (br s, 2 H), 9.72 (s, 1 H). This aldehyde was used directly in the next step.

Further elution afforded 7 mg (37%) of the starting epoxide and 3 mg (16%) of the undesired allylic alcohol having the double bond across the C-20 and C-21 carbons: ^1H NMR ($CDCl_3$) δ 1.75 (br s, 3 H), 4.11 (s, 3 H), 4,18 (q, 2 H, J = 7 Hz), 4.38 (m, 1 H), 5.24 (m, 2 H), 5.58 (br s, 2 H).

(±)-19,20-Dihydro-24-*O*-methylchlorothricolide, Methyl Ester, Ethyl Carbonate (34A). To a rapidly stirred solution of 9 mg (15 μmol) of the aldehyde A in 0.15 mL of dimethylformamide at room temperature was added 46 mg (0.12 mmol) of pyridinium dichromate. After 36 h, the mixture was poured into 10 mL of 10% HCl, the aqueous layer was extracted with ether (3 × 30 mL), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was treated with excess ethereal diazomethane and chromatographed on silica gel (2 g) with ethyl acetate–petroleum ether (15:85). In this manner, there was obtained 7 mg (76%) of the methyl ester **34A** as a colorless oil: IR ($CHCl_3$) 2950, 1760, 1730, 1680, 1510, 1430 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H, J = 7.5 Hz, $CHCH_3$), 1.30 (s, 3 H, CCH_3), 1.30 (t, 3 H, J = 7.5 Hz, OCH_2CH_3), 3.69 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 4.18 (q, 2 H, J = 7.5 Hz, OCH_2CH_3), 4.37 (ddd, 1 H, J = 10, 10, 4.5 Hz, C-7 H), 5.21 (dd, 1 H, J = 16, 7.5 Hz, C-17 H), 5.37 (ddd, 1 H, J = 16, 6, 6 Hz, C-16 H), 5.56 (d, 1 H, J = 10 Hz, C-9 or C-10 H), 5.62 (ddd, 1 H, J = 10, 5, 2 Hz, C-9 or C-10 H).

Anal. Calcd for $C_{34}H_{46}O_{10}$: $(M + H)^+$, 615.3169. Found: $(M + H)^+$, 615.3177.

(±)-19,20-Dihydro-24-*O*-methylchlorothricolide, Methyl Ester, Ethyl Carbonate (34B). By the procedure described for the methyl ester **34A**, 11.5 mg (19 μmol) of the aldehyde B, 59 mg (0.16 mmol) of pyridinium dichromate, and 0.2 mL of dimethylformamide afforded, after chromatography on silica gel (2 g) with ethyl acetate–petroleum ether (15:85), 8.5 mg (70%) of the methyl ester **34B** as a colorless oil: IR ($CHCl_3$) 2940, 1780, 1750, 1690, 1520, 1480, 1430, 1350 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 1.21 (s, 3 H, CCH_3), 1.22 (d, 3 H, J = 7.5 Hz, $CHCH_3$), 1.29 (t, 3 H, J = 7 Hz, OCH_2CH_3), 2.27 (dd, 1 H, J = 14, 6 Hz), 2.35 (ddd, 1 H, J = 13, 9, 4 Hz), 3.69 (s, 3 H, OCH_3), 4.06 (s, 3 H, OCH_3), 4.17 (q, 2 H, J = 7 H, OCH_2CH_3), 4.36 (ddd, 1 H, J = 10.5, 10.5, 4.5 Hz, C-7 H), 5.19 (ddd, 1 H, J = 15, 5.5, 5.5 Hz, C-16 H), 5.26 (dd, 1 H, J = 15, 9 Hz, C-17 H), 5.58 (br s, 2 H, C-9 and C-10 H).

Anal. Calcd for $C_{34}H_{46}O_{10}$: $(M + H)^+$, 615.3169. Found: $(M + H)^+$, 615.3157.

24-*O*-Methylchlorothricolide, Methyl Ester, Ethyl Carbonate (1d). To a rapidly stirred solution of 40 mg (73 μmol) of *O*-methyl chlorothricolide, methyl ester[6b] **1c** in 0.5 mL of pyridine at room temperature was added 28 μL (0.29 mmol) of ethyl chloroformate. After 30 min, an additional 28 μL of ethyl chloroformate was added and the reaction was stirred for an additional 30 min. The reaction mixture was poured into 20 mL of 5% HCl and extracted with ether (3 × 60 mL), and the combined organic extracts were dried ($MgSO_4$).

After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (10 g) with ethyl acetate–petroleum ether (1:3). In this manner, there was obtained 43 mg (96%) of the carbonate protected chlorothricolide **1d** as a colorless glass: IR ($CHCl_3$) 2950, 1765, 1710, 1680, 1350 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7.5 Hz, OCH_2CH_3), 1.31 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.32 (s, 3 H, CCH_3), 2.28 (dd, 1 H, J = 15, 7 Hz), 2.94 (br ddd, 1 H, J = 11, 7, 7 Hz, C-21 H), 3.22 (br d, 1 H, J = 8.5 Hz, C-18 H), 3.73 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.18 (q, 2 H, J = 7.5 Hz, OCH_2CH_3), 4.38 (ddd, 1 H, J = 10, 10, 4.5 Hz, C-7 H), 5.14 (dd, 1 H, J = 15.5, 8.5 Hz, C-17 H), 5.42 (ddd, 1 H, J = 15.5, 8.5, 4 Hz, C-16 H), 5.55 (d, 1 H, J = 10 Hz, C-9 or C-10 H), 5.61 (ddd, 1 H, J = 10, 5, 2 Hz, C-9 or C-10 H), 6.71 (br s, 1 H, C-19 H).

Anal. Calcd for $C_{34}H_{44}O_{10}$: $(M + H)^+$, 613.3013. Found: $(M + H)^+$, 613.3018.

Generation of 24-*O*-Methylchlorothricolide, Methyl Ester (1c) from 24-*O*-Methylchlorothricolide, Methyl Ester, Ethyl Carbonate (1d). A solution containing 14 mg (23 μmol) of the carbonate **1d** and 0.05 mL of concentrated H_2SO_4 in 0.5 mL of dry methanol was heated at 72 °C. After 24 h, the mixture was poured into 20 mL of water and the aqueous layer was extracted with ether (3 × 30 mL), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (2 g) with ethyl acetate–petroleum ether (35:65). In this manner, there was obtained 9.6 mg (78%) of the deprotected material as a colorless oil. The spectra of this material was identical with that reported by Keller-Schierlein.[4]

Synthesis and Utilization of the Chiral Synthon Methyl 3-*O*-Benzyl-2,4,6-trideoxy-6-iodo-α-D-*erythro*-hexopyranoside in the Synthesis of a Potent HMG-CoA Reductase Inhibitor

John D. Prugh,* C. Stanley Rooney, Albert A. Deana, and Harri G. Ramjit

Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

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Synthesis of the potent HMG-CoA reductase inhibitor **1a** has been achieved by utilizing the chiral synthon **2**, which was prepared from methyl α-D-glucopyranoside in 12 steps (6 new). A key step in this sequence, which should have general applicability for the synthesis of 4-deoxy sugars, is the reductive scission of the 4-tosylate substituent of **9** with $NaBH_4$ in hot $(CH_3)_2SO$. Coupling of the aryl substituent to the synthon was accomplished via the anion of arylmethyl phenyl sulfoxide **13** followed by thermal elimination of benzenesulfinic acid to give cleanly the *all-trans* ene intermediate **16a**. Selective removal of the benzyl ether blocking group was achieved without effect on the olefin by a novel palladium-mediated oxidative procedure utilizing 20% $Pd(OH)_2/C$, Pd black, or 10% Pd/C in refluxing ethanol (or methanol). Anomeric hydrolysis conducted in 80% aqueous acetic acid followed by oxidation of the lactols **18** with *N*-iodosuccinimide and tetrabutylammonium iodide provided the target **1a** which was shown to be identical with the biologically active dextrorotatory isomer of **1a** prepared by resolution of the racemate. On the basis of model studies, the limitations of the palladium-catalyzed debenzylation procedure along with insights into the reaction mechanism provided by isolation of benzaldehyde and benzoic acid derivative byproducts are discussed.

The fungal-derived natural products compactin (**1c**)[1] and mevinolin (**1d**)[2] have been shown to be specific inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-limiting enzyme

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