Approach to the Synthesis of Chlorothricolide: Synthesis of (±)-19,20-Dihydro-24-O-methylchlorotricolide, methyl ester, ethyl carbonate

Thesis by

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To my parents

ACKNOWLEDGEMENTS

I wish to thank Professor Robert E. Ireland for his encouragement and scientific guidance. I also wish to thank the members of the Ireland group, past and present, for their advice. I am grateful to Linda Cusimano and Jennifer Ball for their time, patience and skill in preparing this manuscript. Finally, I thank the Atlantic Richfield Foundation and the California Institute of Technology for financial support.

ABSTRACT

An approach to the total synthesis of the 14-membered macrolide antibiotic aglycon chlorothricolide is presented. Key steps from the two halves to (±)-19,20-Dihydro-24-O-methylchlorothricolide, methyl ester, ethyl carbonate include initial esterification across the C1 and C25 carbons followed by macrodilactonization across the C17 and C14 carbons. Ester enolate Claisen rearrangement and subsequent decarboxylation afforded the intact lactone. Functionalization of the top half is explored.

The ester enolate Claisen rearrangement of propionate derivatives of resolved 1-(t-butyldimethylsilyl)-trans-2-butene-1-ol is reported. Subsequent protiodesilation of the reduced and protected Claisen products resulted in the formation of 2,3-dimethyl-4-pentenyl ethers. Thus, the secondary α-silyl alcohol has functioned as a chiral primary alcohol equivalent.

The Claisen rearrangement of vinyl ethyl derivatives of 5-**tert**-butyl-1-(hydroxymethyl)-1-cyclohexene is reported. The standard allyl vinyl ether conditions as well as the triethyl orthoacetate and ester enolate variants of the Claisen rearrangement all resulted in the formation of **cis**(axial)-4-**tert**-butylcyclohexyl-substituted systems. Thus, in sterically unbiased cases, this [3.3] sigmatropic process results in the axial attachment of the side chain in a cyclohexyl system.

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PASCAL COVICI

Dear Pat,

You came upon me carving some kind of little figure out of wood and you said, "Why don't you make something for me?"

I asked you what you wanted, and you said, "A box."

"What for?"

"To put things in."

"What things?"

"Whatever you have," you said.

Well, here's your box. Nearly everything I have is in it, and it is not full. Pain and excitement are in it, and feeling good or bad and evil thoughts and good thoughts—the pleasure of design and some despair and the indescribable joy of creation.

And on top of these are all the gratitude and love I have for you.

And still the box is not full.

JOHN

CHAPTER 1

Approach to the Synthesis of Chlorothricolide

Approach to the Total Synthesis of Chlorothricolide: Synthesis of (±)-19,20-Dihydro-24-0-methylchlorothricolide, methyl ester, ethyl carbonate.[1]

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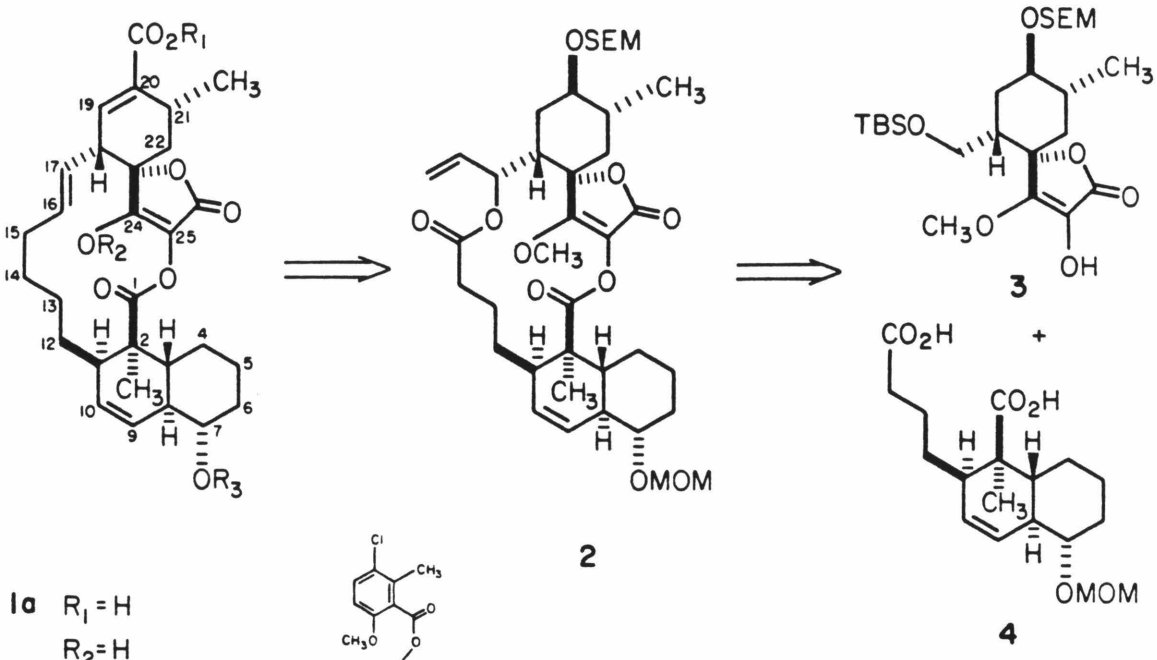
Abstract: An approach to the total synthesis of the macrolide antibiotic aglycon chlorothricolide (**1b**) is presented. Herein is described the synthesis of the advanced intermediate (±)-19,20-Dihydro-24-0-methylchlorothricolide, methyl ester, ethyl carbonate (**34**) from the "bottom half" acid **4** 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 antiobiotics,[3] was isolated in 1969 by W. Keller-Schierlein.[4] Active against gram-positive bacteria, it functions as a non-competitive 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-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 decarbonyation of the aldehyde **5a** with Wilkinson's catalyst. In this case, cyclopropane and isomerized olefin products were obtained (for details see Reference 6b . The second, as shown in Chart I, was the radical decomposition[8] of the selenoester **5b**. In this

Scheme I



2

3

4

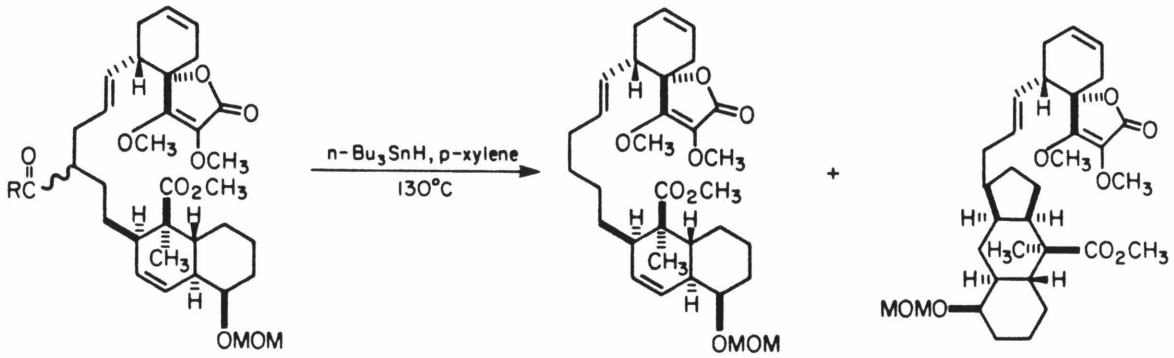
Ia $R_1 = H$
$R_2 = H$
$R_3 =$

Ib $R_1 = CH_3$
$R_2 = H$
$R_3 = H$

Ic $R_1 = CH_3$
$R_2 = CH_3$
$R_3 = H$

Id $R_1 = CH_3$
$R_2 = CH_3$
$R_3 = CO_2C_2H_5$

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



5a R=H
5b R=SePh

6

7

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 selenoester, allow for trapping of the intermediate radical before it could cyclize onto the C10 olefin. Results in this report bear this hypothesis as correct.

The current effort can be divided into four distinct parts. First, a synthesis of the diacid **4** from the

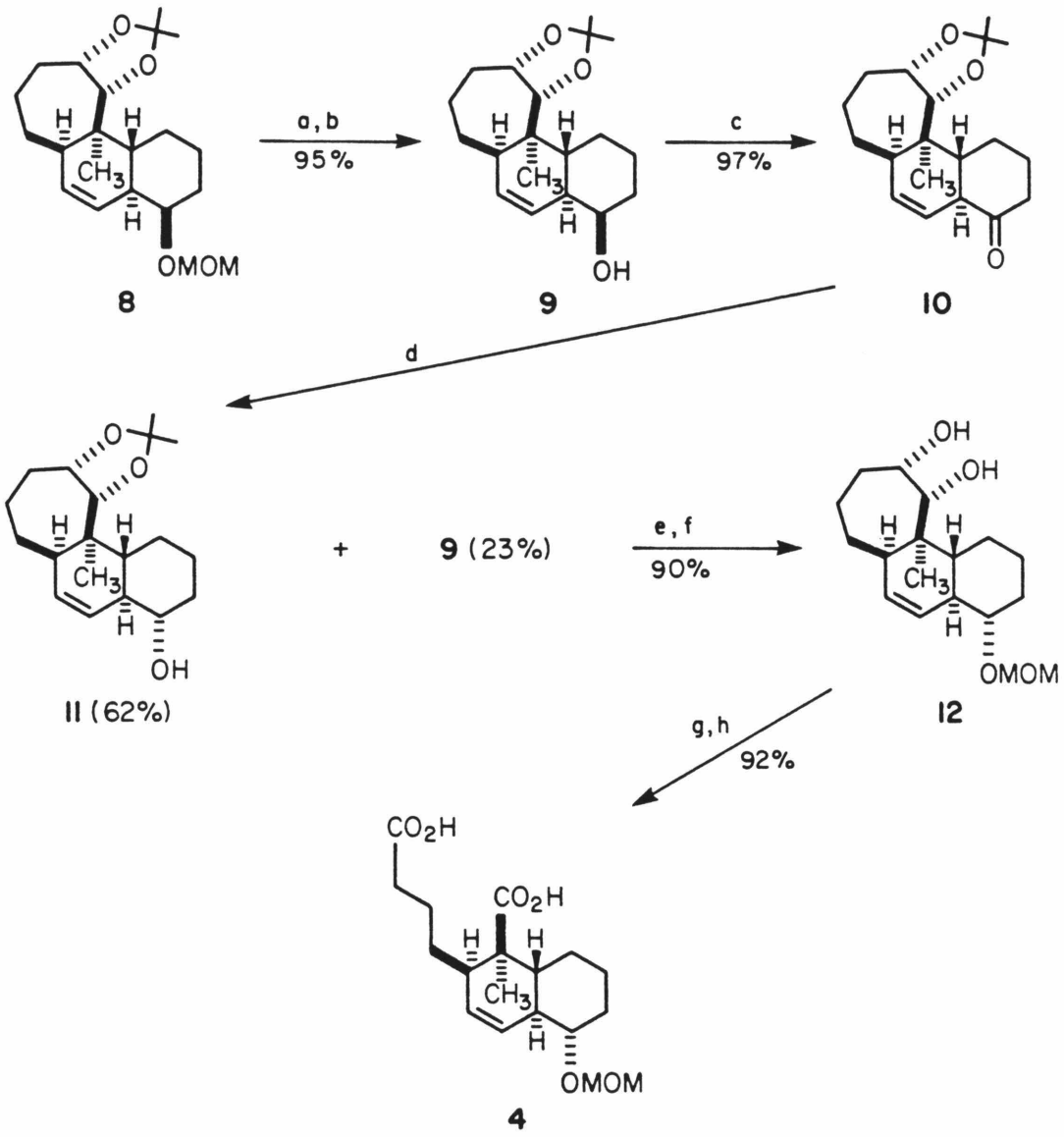
previously reported intermediate **8** was developed. Second, with some modifications, construction of the appropriately protected "top half" alcohol **3** was completed by a route similar to that developed earlier.[6a] Third, a successful scheme for the synthesis of the lactone **29** was realized through 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 isopropanol yielded a separable mixture of the α and β-alcohols **11** and **9** in a

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



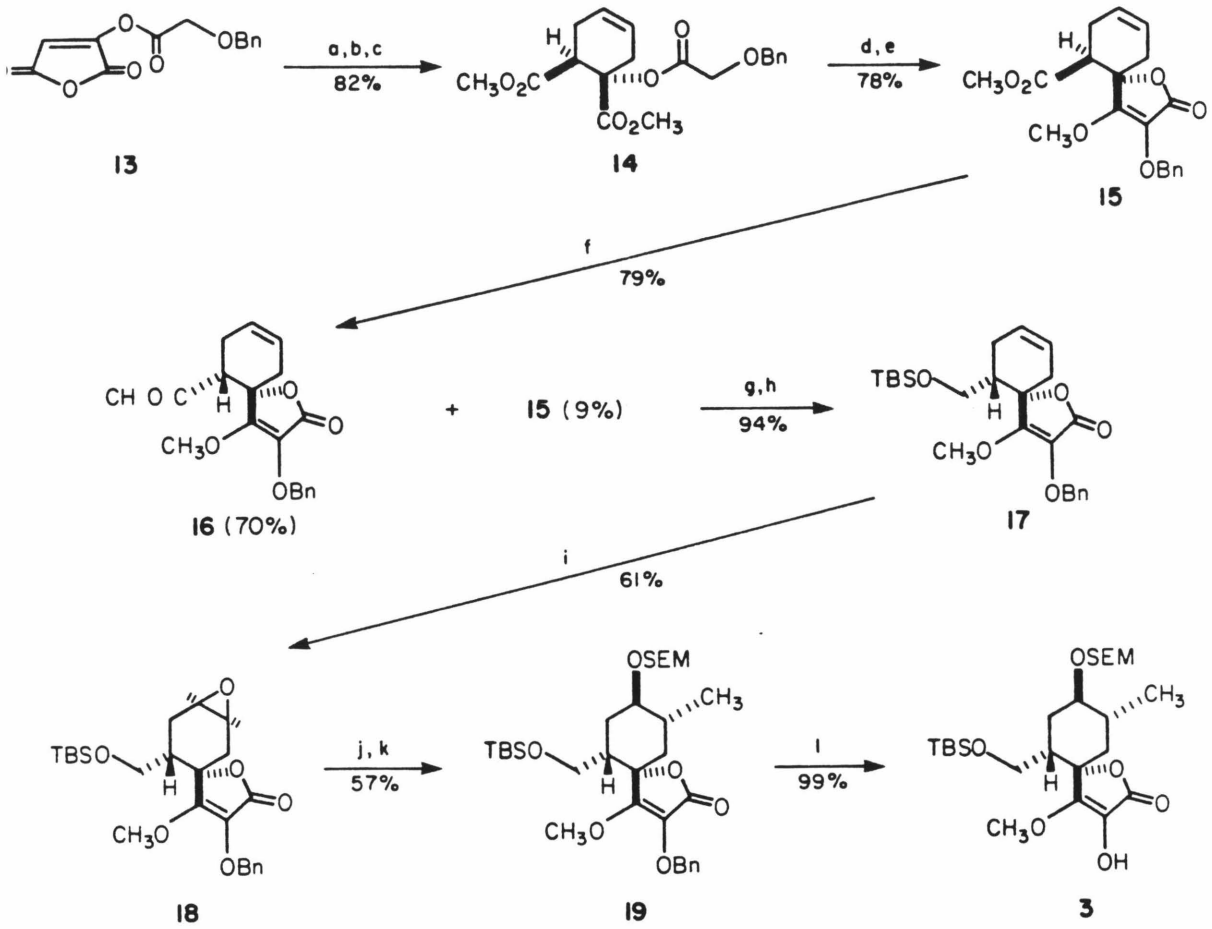
[a] a] p-TsOH, CH_3OH, H_2O, 85°C b] $CH_3C(OCH_3)_2CH_3$, p-TsOH, CH_2Cl_2 c] DMSO, ClCOCOCl, Et_3N, CH_2Cl_2 d] $NaBH_4$, $CH_3CH(OH)CH_3$, 0°C e] CH_3OCH_2Cl, $(i\text{-}C_3H_7)_2C_2H_5N$, CH_2Cl_2 f] CH_3OH, H_2O, PyOTs g] DMSO, PhH, $(i\text{-}C_3H_7N)_2C$, Cl_2CHCO_2H h] THF, H_2O, 10% aqueous KOH, 30% H_2O_2.

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 ^{1}HNMR 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-benzyloxyacetoxy)maleic anhydride (**13**), was prepared by acylation of the pyridine salt of hydroxymaleic anhydride with benzyloxyacetyl 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.

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] TBDMSCl, 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.

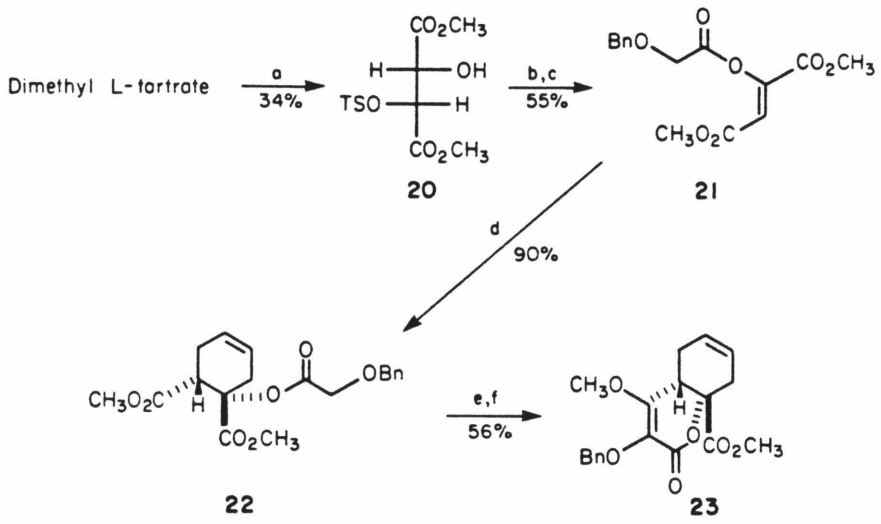
After extensive experimentation, improved conditions for the cyclization of the triester **14** to the spirobutenolide **15** were found. In the case of lithium diisopropylamide (LDA), β-elimination was the major reaction pathway. The use of a weaker base, lithium hexamethyldisilazide (LiHMDA), along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

and long reaction times allowed for both improved yield and reproducibility. Thus, inverse addition of 2 equivalents of LiHMDA in tetrahdyrofuran (THF) at -78°C to the triester **14** in THF at -78°C and warming to -30°C for 5 hours 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 eq $LiEt_3BH$, THF, 0°C) followed by protection with t-butyldimethylsilyl chloride[18] (TBDMSCl) 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 equivalent 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 equivalents 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 benzyoxyacetyl chloride followed by elimination of the

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



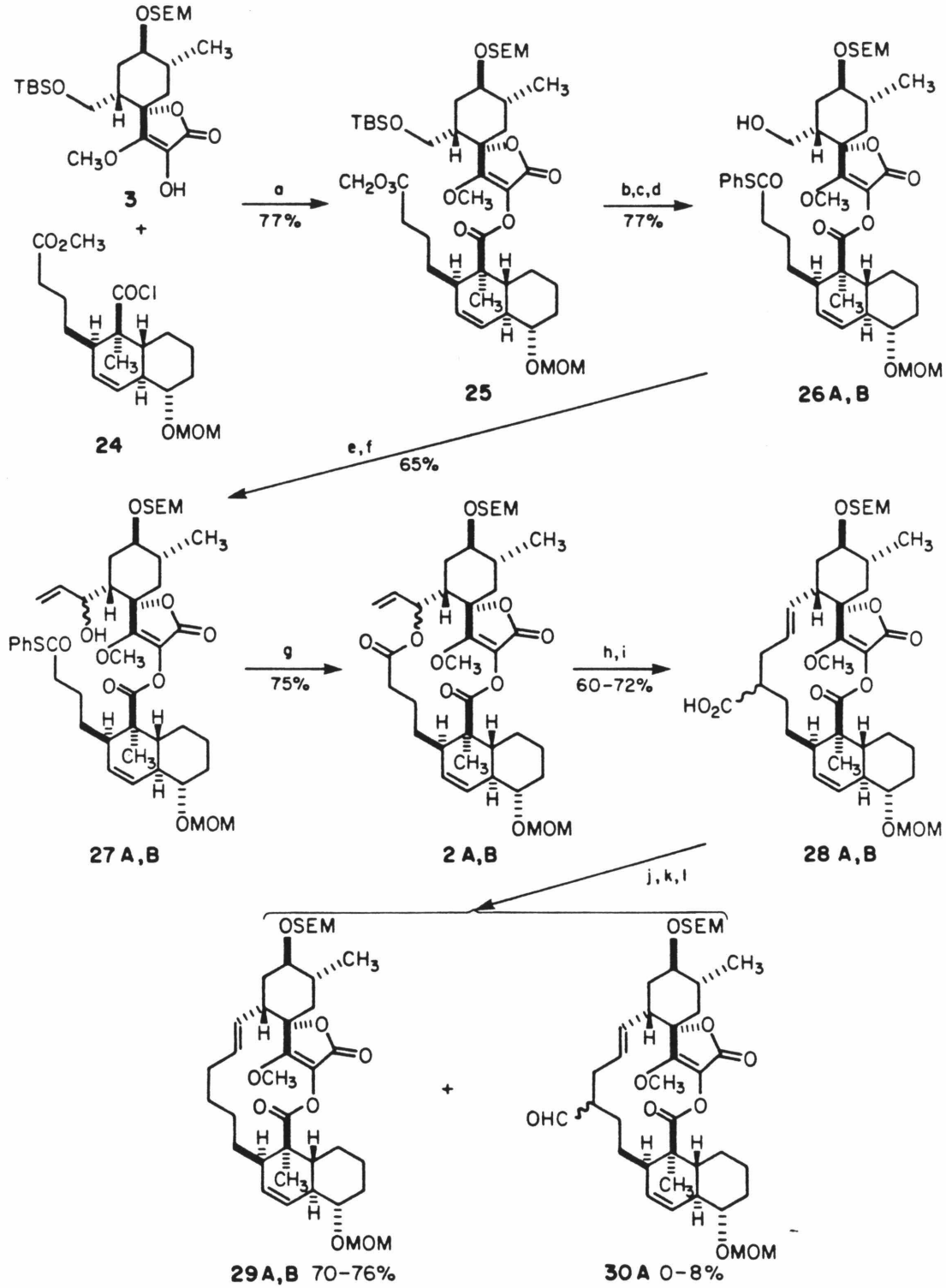
[a] a] p-TsCl, pyridine, DMAP, CH_2Cl_2 b] $BnOCH_2COCl$, pyridine, DMAP, CH_2Cl_2 c] THF, $(C_2H_5)_3N$, DBU d] $CH_2=CHCH=CH_2$, PhH, pyrogallol, Δ e] Li HMDA, THF, 0°C f] CH_2N_2

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 equivalents 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 methylfluorosulfonate 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**

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] HFx·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.

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-dimethylaminaopyridine[25] in CH_2Cl_2 to the "bottom half" acid chloride **24** in CH_2Cl_2 at 0^oC and then allowing the mixture to warm to room temperature. 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 thiophenol of the diacid chloride of **4** was not successful.[28] Introduction of the vinyl group required removal of the TBDMS protecting group (HFx·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 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 thioester **27** in 70-80% yield with diethyl chlorophosphate[34] and thiophenol.

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

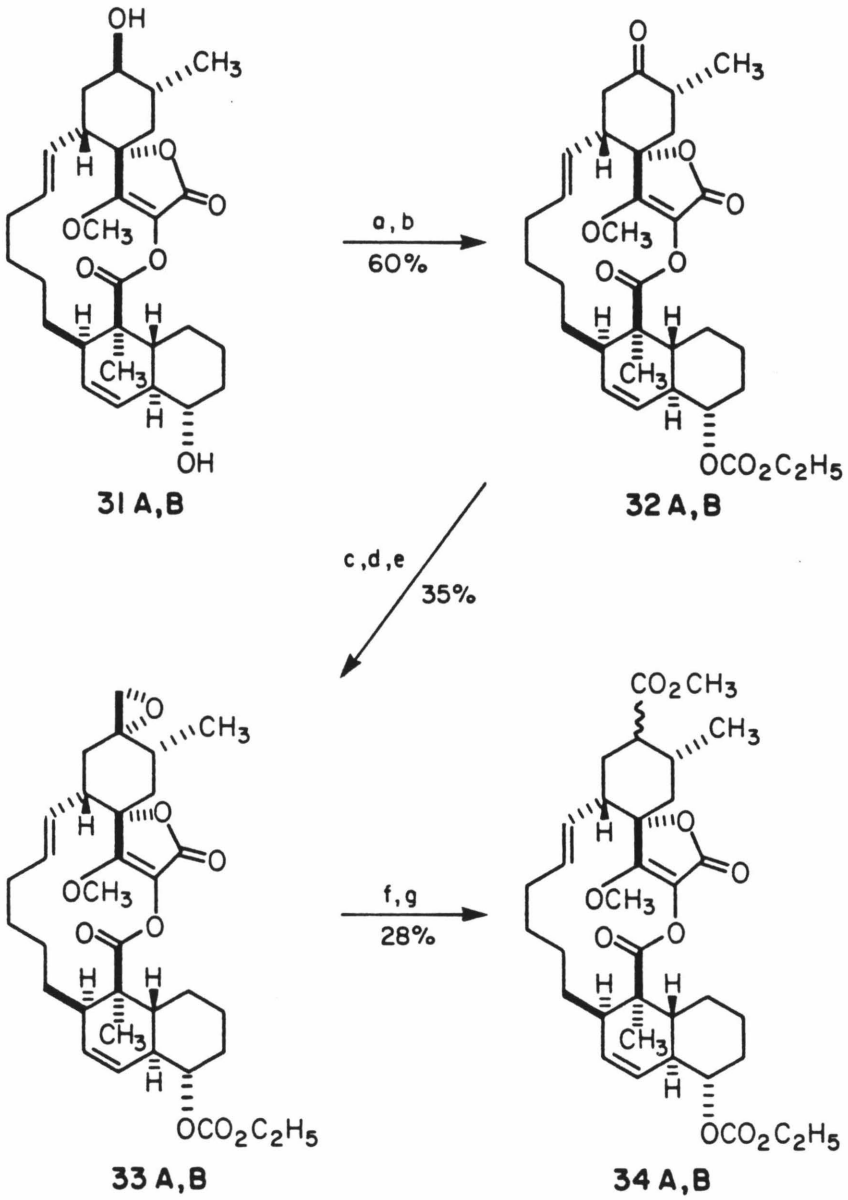
The hypothesis, as put forth earlier, concerning the restricted motion of the carboxylate containing side-chain could now be readily tested. The selenoester of the acid

28 was prepared, in 80% yield, using the method described previously.[35] Radical decomposition[8] was performed by preheating the selenoester 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 by-product from one of the diastereomer 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

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] TMSTrf,
2,6-Lutidine, DBU, $PhCH_3$ g] PDC, DMF

step[38] ($LiBH_4$, 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 towards 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 tributyltin-(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 trifluoromethane-sulfonate 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 oxidaton of the aldehyde to the carboxylic acid and treatment with diazomethane, the protected dihydro chlorothricolide **34** was obtained in moderate yield.

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}HNMR 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 oxidation of a silyl ketene acetal,[46b] both required initial enolate formation. Attempted enolization with up to 5 equivalents of LDA, KHMDS, and KDA[47] followed by trapping with diphenyldiselenide, phenylselenyl chloride, and t-butyldimethylsilyl trifluoromethanesulfonate gave only starting material and decomposition products. Hydrogenation of the natural carbonate **1d** to the hexahydro derivative[2] 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^{o}C) and cooled in a dessicator over anhydrous $CaSO_4$ prior to use. If feasible, reaction flasks were also flame-dried in vacuo.

1α,2α-(Isoprpylidenedioxy)-8β-hydroxy-11bα-methyl-5aα, 7aα, 8, 9, 10, 11, 11aβ, 11b-octahydronaptho[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^{o}C

for 36 h. The mixture was then poured into 300 ml saturated aqueous sodium bicarbonate solution and the mixture was extracted with ethyl acetate (3 x 400 ml) and the combined organic layers dried (Na_2SO_4). After removal of the solvent at reduced pressure, the crude residue was pumped at 0.1 mm Hg 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 saturated bicarbonate and extracted with ether (3 x 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}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 3H), 1.32 (s, 3H) 1.54 (s, 3H), 4.10 (d, 1H, J=7 Hz), 4.30 (m, 1H), 5.31 (d, 1H, J=10 Hz), 5.85 (m, 1H).

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(9H)-one

(10). To a rapidly stirred solution of 1.92 ml (22.0 mmol) of distilled oxaly l 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 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 x 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 silca 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}; ^1H NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.33 (s, 3H), 1.52 (s, 3H), 2.90 (d, 1H, J=10.5 Hz), 4.13 (d, 1H, J=6 Hz) 4.24 (m, 1H), 5.77 (m, 2H).

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 isopropanol 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 isopropanol at 0°C. After 15 min, 200 ml of water was added and the aqueous layer was extracted with 3 x 200 ml ether. The combined organic layers were washed with 200 ml of 2 N HCl, 200 ml saturate 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; ^1H NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.35 (s, 3H), 1.52 (s, 3H), 3.33 (m, 1H), 4.10 (d, 1H, J=7 Hz), 4.25 (m, 1H), 5.74 (m, 2H).

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 was 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 x 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 (250 g) with ether-petroleum ether (1:4). In this manner, there was obtained 3.4 g (99%) of methoxylmethyl ether as a colorless oil: IR ($CHCl_3$) 2940, 1385, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 3H), 1.32 (s, 3H), 1.50 (s, 3H), 3.38 (s, 3H), 4.10 (d, 1H, J=7 Hz), 4.25 (m, 1H), 4.58 and 4.72 (AB system, J=6 Hz, 2H), 5.70 (m, 2H).

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) pyridinium p-toluenesulfonate for 2.5 h. Saturated sodium bicarbonate (200 ml) was added, and the mixture was extracted with ether (3 x 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 (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}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 3H), 3.40 (s, 3H), 3.81 (brs, 1H), 4.00 (m, 1H), 4.64 and 4.79 (AB system, J=7 Hz, 2H), 4.52 (dm, 1H, J=9 Hz), 4.84 (brd, 1H, 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 1 N HCl and extracted with ether (3 x 60 ml). The combined organic layers were washed 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 THF. To this mixture at room temperature was 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

10% HCl,was extracted with ether (3 x 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, 3H), 3.38 (s, 3H), 4.61 and 4.75 (AB system, J=7 Hz, 2H), 5.69 (dd, 1H, J=10 and 3 Hz), 5.92 (d, 1H, J=10 Hz), 10.28 (brs, 2H). 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-Benzyloxyacetoxy)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 benzyloxyacetyl chloride in 50 ml benzene. After stirring for 1 h, the slightly pink supernatant liquid was decanted

off and filtered through 100 g of activity III alumina with 1 liter 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}; ^{1}H-NMR δ 4.40 (s, 2H), 4.67 (s, 2H), 6.88 (s, 1H), 7.35 (s, 5H). Due to its hygroscopic nature, this material was analyzed as its butadiene methanolysis product **14**.

Dimethyl-4-(2-benzyloxyacetoxy)cyclohexene-Cis-4,5-dicarboxylate (14). A teflon-lined autoclave was charged with a solution of 10.0 g (38.1 mmol) of 2-benzyloxyacetoxymaleic 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, 2H), 2.69 (brs, H) 2.95 (brs, 1H), 3.32 (m, 1H), 3.64 (s, 3H), 3.76 (s, 3H), 4.07 (s, 2H), 4.58 (s, 2H), 5.63 (brs, 2H), 7.34 (s, 5H).

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-oxospiro[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 hr, 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 x 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, 4H), 2.87 (t, 1H, J=7 Hz), 3.60 (s, 3H), 3.88 (s, 3H), 4.92 and 5.08 (AB system, J=11 Hz, 2H), 5.64 (brs, 2H), 7.34 (s, 5H).

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 x 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 (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, 5H), 3.60 (s, 3H), 3.95 (s, 3H), 5.00 and 5.17 (AB system, J=12 Hz, 2H), 5.67 (m, 2H), 7.37 (s, 5H).

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 x 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 (500 g) with ethylacetate/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};

^{1}H NMR ($CDCl_3$) δ 1.50-2.80 (m, 6H), 3.24 (m, 2H), 3.88 (s, 3H), 5.00 and 5.28 (AB system, J=12 Hz, 2H), 5.60 (m, 2H), 7.34 (s, 5H).

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-dimethylaminopyridine. After 18 h, 50 ml of saturated sodium bicarbonate was added and the aqueous layer was extracted with ether (3 x 150 ml) and dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was flash chromatographed on silica (150 g) with ethyl acetate/petroleum ether (1:10). In this manner, there was obtained 2.21 g (94%) of the silylether 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}; ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 6H), 0.85 (s, 9H), 1.8-2.8 (m, 5H), 3.36 (m, 2H), 3.89 (s, 3H), 5.12 (s, 2H), 5.68 (m, 2H), 7.36 (s, 5H).

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 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 x 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 (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, 6H), 0.89 (s, 9H), 1.65-2.50 (m, 5H), 3.10-3.60 (m, 4H), 3.90 (s, 3H), 5.10 (s, 2H), 7.34 (s, 5H).

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 10 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 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 methylithium 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 hr, 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 hr, 40 ml of saturated ammonium chloride was added and the aqueous layer was extracted with ether (3 x 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 (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, 6H), 0.80 (s, 9H), 3.33 (m, 2H), 3.88 (s, 3H), 5.10 (s, 2H), 7.36 (s, 5H).

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, 6H), 0.83 (s, 9H), 1.10 (d, 3H, J=7H), 3.25 and 3.45 (dAB system, J=10, 6 Hz, 2H), 3.86 (s, 3H), 5.08 (s, 2H), 7.35 (s, 5H).

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)ethoxymethoxy]-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 CH_2Cl_2 at room temperature was added 0.22 ml (1.38 mmol) of β-(trimethylsilyl)ethoxymethyl chloride and 0.36 ml (2.07 mmol) of N,N-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 x 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 (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, 15H), 0.84 (s, 9H), 1.10 (d, 3H, J=7 Hz), 3.21 and 3.44 (dAB

system, J=6, 10 Hz, 2H), 3.55 (t, 2H, J=7.5 Hz), 3.87 (s, 3H), 4.68 (s, 2H), 5.09 (brs, 2H), 7.36 (s, 5H).

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)ethoxymethoxy]-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 atmosphere of hydrogen gas. After 1 h, the mixture was filtered through a pad of celite and 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, 15H), 0.86 (s, 9H), 1.10 (d, 3H, J=7.5 Hz), 3.34 and 3.49 (dAB system, J=6, 10 Hz), 3.62 (t, 2H, J=8 Hz), 4.10 (s, 3H), 4.68 (s, 2H), 5.58 (brs, 1H).

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-toluenesulfonate)-3-hydroxy-butanedioate (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-dimethylaminopyridine, and 100 ml (1.20 mol) of pyridine in 1 liter 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 (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, 3H), 3.08 (d, 1H, J=7.5 Hz), 3.69 (s, 3H), 3.74 (s, 3H), 4.74 (m, 1H), 5.31 (d, 1H, J=1 Hz), 7.32 (d, 2H, J=9 Hz), 7.92 (d, 2H, 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-(benzyloxyacetoxy)-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 was added 6.0 ml (74 mmol) of pyridine, 0.70 g (5.7 mmol) of 4-

dimethylaminopyridine, and 11.6 g (63 mmol) of benzyloxyacetyl chloride. After 2 h, 100 ml of water and 50 ml 10% HCl were added and the aqueous layer was extracted with CH_2Cl_2 (3 x 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 was 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 x 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 (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, 3H), 3.83 (s, 3H), 4.35 (s, 2H), 4.69 (s, 2H), 6.70 (s, 1H), 7.35 (m, 5H).

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-benzyloxyacetoxy)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 silca (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, 5H), 3.65 (s, 3H), 3.77 (s, 3H), 4.10 (s, 2H), 4.63 (s, 2H), 5.64 (m, 2H), 7.35 (m, 5H).

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 x 150 ml) and the combined organic layers were dried (Na_2SO_2). After removal of the solvent at reduced pressure, the crude

residue was treated with ethereal diazomethane, and the chromatographed on silica (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 to 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, 4H), 3.06 (dd, 1H, J=6,10 Hz), 3.69 (s, 3H), 3.84 (s, 3H), 4.67 and 4.93 (AB system, 2H, J=12 Hz), 5.68 (m, 2H), 7.35 (m, 5H).

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 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-dimethylaminopyridine in 1.5 ml 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 X 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 (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}; ^{1}HNMR ($CDCl_3$) δ 0.02 (s, 15H), 0.88 (s, 9H), 1.28 (s, 3H), 3.36 (s, 3H), 3.62(s, 3H), 3.62 (t, 2H, J=7Hz), 3.95 (brs, 3H), 4.69 (m, 4H), 5.88 (m, 2H).

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*),2α4aβ,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 X 100 ml). The combined organic layers were dried ($MgSO_4$) and after removal of the solvent at reduced pressure, the crude residue was chromatographed of CC-4 silica (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}; ^{1}HNMR ($CDCl_3$) δ 0.02 (s, 15H), 0.88 (s, 9H), 1.27 (s, 3H), 3.36 (s, 3H), 3.60 (t, 2H, J=7Hz), 3.94 (s, 3H), 4.68 (m, 4H), 5.75 (m, 2H), 7.75 (brs, 1H).

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 was added 0.32 ml (3.12 mmol) of thiophenol, 10.0 mg (0.08 mmol) of 4-dimethylaminopyridine, 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 X 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 (50 g) with ethyl acetate-petroleum ether (1:5). In this manner, there was obtained 662 mg (92%) of the desired thioester as a colorless oil: IR ($CHCl_3$) 2960, 1765, 1690, 1350, 1120, 1040, 840 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.03 (s, 15H), 0.87 (s, 9H), 1.36 (s, 3H), 2.70 (m, 2H), 3.36 (s, 3H), 3.62 (t, 2H, J=7Hz), 3.94 (s, 3H), 4.68 (m, 4H), 5.87 (m, 2H), 7.37 (s, 5H).

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)ethoxyl]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 (26 A and B). 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 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 X 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 column with ethyl acetate-petroleum ether (28:72). In this manner, there was obtained 289mg (43%) of the "Fast" alcohol **26A** as a colorless oil: IR ($CHCl_3$) 3540, 2940, 1760, 1672, 1450, 1340, 1100, 1030, 835 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.00 (s, 9H), 0.89 (t, 2H, J=8Hz), 1.07 (d, 3H, J=7.5Hz), 1.24 (s, 3H), 3.33 (s, 3H), 3.58 (t, 2H, J=8Hz), 3.62 (m, 1H), 3.90 (s, 3H), 4.65 (m, 4H), 5.84 (m, 2H), 7.34 (s, 5H).

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}; ^{1}HNMR ($CDCl_3$) δ 0.02 (s, 9H), 0.90 (t, 2H, J=8Hz), 1.08 (d, 3H, J=7Hz), 1.28 (s, 3H), 3.35 (s, 3H), 3.61 (t, 2H, J=8Hz), 3.67 (m, 1H), 3.90 (s, 3H), 4.68 (m, 4H), 5.72 (dd, 1H, J=4,10Hz), 5.93 (d, 1H, J=10Hz), 7.35 (s, 5H).

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-oxospiro[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 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}; ^{1}HNMR ($CDCl_3$) δ 0.03 (s, 9H), 0.92 (t, 2H, J=7.5Hz), 1.15 (d, 3H, J=7Hz), 1.28 (s, 3H), 3.37 (s, 3H), 3.50 (t, 2H, J=7.5 Hz), 3.74 (m, 1H), 4.02 (s, 3H), 4.68 (m, 4H), 5.85 (m, 2H), 7.36 (s, 5H), 9.59 (brs, 1H). 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 X 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 (20 g) with ethyl acetate-petroleum ether (1:3). In this manner, there was obtianed 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}; ^{1}HNMR ($CDCl_3$) δ 0.02 (s, 9H), 0.90 (t, 2H, J=7.5Hz), 1.12 (d, 3H, J=7Hz), 1.28 (s, 3H), 3.27 (m, 1H), 3.36 (s, 3H), 3.58 (t, 2H, J=7.5Hz), 3.72 (m, 1H), 3.95 (s, 3H), 4.28 (m, 1H), 4.68 (m, 4H), 5.17 (m, 2H), 5.85 (m, 3H), 7.36 (s, 5H).

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]methyoxy]-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 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}; ^{1}HNMR ($CDCl_3$) δ 0.03 (s, 9H), 0.90 (t, 2H, J=7.5Hz), 1.15 (d, 3H, J=7Hz), 1.29 (s, 3H), 3.28 (m, 1H), 3.37 (s, 3H), 3.60 (t, 2H, J=7.5Hz), 3.75 (m, 1H), 4.00 (s, 3H), 4.67 (m, 4H), 5.85 (m, 2H), 7.36 (s, 5H), 9.55 (brs, 1H). 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 (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}; ^{1}HNMR ($CDCl_3$) δ 0.02 (s, 9H), 0.90 (t, 2H, J=7.5Hz), 1.14 (d, 3H, J=7Hz), 1.29 (s, 3H), 3.23 (m, 1H), 3.36 (s, 3H), 3.58 (t, 2H, J=7.5Hz), 3.71 (m, 1H), 3.95 (brs, 3H), 4.15 (m, 1H), 4.67 (m, 4H), 5.15 (m, 2H), 5.78 (m, 3H), 7.36 (s, 5H).

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]-18H-16a,19-metheno-2H,16aH-benzo[e]napththo[2,1-m][1,4,8]trioxacyclopentadecin-10,18,21(1H,3H)-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 X 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}; ^{1}HNMR ($CDCl_3$) δ 0.00 (s, 9H), 0.90 (t, 2H, J=8Hz), 1.30 (s, 3H), 3.28 (m, 1H), 3.33 (s, 3H), 3.58 (t, 2H, J=8Hz), 3.71 (m, 1H), 4.04 (s, 3H), 4.65 (m, 4H), 5.14 (m, 3H), 5.72 (m, 3H).

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}; ^{1}HNMR ($CDCl_3$) δ 0.00 (s, 9H), 1.10 (d, 3H, J=7Hz), 1.25 (s, 3H), 3.36 (s, 3H), 3.57 (t, 2H, J=8Hz), 3.74 (m, 1H), 3.95 (brs, 3H), 4.68 (m, 4H), 4.80-5.90 (m, 5H). 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 X 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]-18H-16a,19-metheno-2H-benzo[e]naphtho[2,1-m][1,4,8]trioxacyclopentadecin-10,18,21(1H,3H)-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}; ^{1}HNMR ($CDCl_3$) δ 0.00 (s, 9H), 0.89 (t, 2H, J=8Hz), 1.10 (d, 3H, J=7Hz), 1.27 (s, 3H), 3.16 (m, 1H), 3,57 (t, 2H, J=8Hz), 3.69 (m, 1H), 4.14 (brs, 3H), 4.64 (m, 4H), 5.11 (m, 3H), 5.71 (m, 3H).

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}; ^1HNMR ($CDCl_3$) δ 0.00 (s, 9H), 1.08 (d, 3H, J=7Hz), 1.28 (s, 3H), 3.36 (s, 3H), 3.58 (t, 2H, J=8Hz), 3.96 (brs, 3H), 4.68 (m, 4H), 4.85-5.90 (m, 5H). This hydroxy acid was recycled back to the allylic alcohol **27B** as described below.

Recycle of the hydroxy acid B to the allyliic 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 hexamehtyldisilazide 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 mixutre 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, triehtylamine 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 X 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}; ^{1}HNMR ($CDCl_3$) δ 0.03 (s, 9H), 3.22 (m, 1H), 3.37 (s, 3H), 3.60 (t, 2H, J=8Hz), 3.69 (m, 1H), 3.97 (brs, 3H), 4.69 (m, 4H), 5.32 (m, 2H), 5.69 (m, 2H).

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-Q-(methoxymethyl)-24-Q-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 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}; ^{1}HNMR ($CDCl_3$) δ 0.02 (s, 9H), 3.29 (m, 1H), 3.35 (s, 3H), 3.57 (t, 2H, J=8Hz), 3.67 (m, 1H), 4.09 (brs, 3H), 4.68 (m, 4H), 5.34 (m, 2H), 5.52 (brd, 1H, J=10Hz), 5.83 (brd, 1H, J=10Hz), 8.10 (brs, 1H).

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-Q-(methoxymethyl)-24-Q-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

was added 0.30 ml (2.10 mmol) of triethylamine and 0.15 ml (1.41 mmol) of freshly distilled phenyl selenol. After an additional 20 min, the mixture was poured into 30 ml of water and extracted with ether (2 X 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 selenoester as a colorless foam: IR ($CHCl_3$) 2940, 1755, 1710, 1670, 1420, 1050 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.02 (s, 9H), 0.89 (t, 2H, J=8Hz), 1.14 (d, 3H, J=7Hz), 1.27 (s, 3H), 2.80 (m, 2H), 3.24 (m, 1H), 3.37 (s, 3H), 3.60 (t, 2H, J=8Hz), 3.96 (s, 3H), 4.68 (m, 4H), 5.34 (m, 2H), 5.59 (dd, 1H, J=4 and 10Hz), 5.87 (d, 1H, J=10Hz), 7.37 (m, 5H). As decomposition occurred upon standing, the selenomester was immediately decarbonylated.

A solution of 96 mg (0.112 mmol) of the above selenoester in 6 ml of dry p-xylene[8] was heated with stirring to 130°C and to this was 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 $NaHCO_3$ and the aqueous layer was extracted with ether (3 X 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 decabonylated lactone **29A** as a colorless foam: IR ($CHCl_3$) 2940, 1760, 1680, 1455, 1340, 860, 840 cm^{-1}; 500 MHz ^{1}HNMR ($CDCl_3$) δ 0.00 (s, 9H, $-Si(CH_3)_3$), 0.91 (t, 2H, J=8Hz, $-CH_2C\underline{H}_2Si-$), 1.13 (d, 3H, J=7Hz, $CHC\underline{H}_3$), 1.30 (s, 3H, $CC\underline{H}_3$), 2.76 (ddd, 1H, J=13, 7.5, 4Hz, C-18H), 3.22 (dt, 1H, J=10, 4Hz, C-7H), 3.38 (s, 3H, $OC\underline{H}_3$), 3.62 (t, 2H, J=8Hz, $OC\underline{H}_2CH_2$), 3.72 (brs, 1H, C-20H), 3.98 (s, 3H, $OC\underline{H}_3$), 4.63 and 4.76 (AB, 2H, J=7Hz, $OC\underline{H}_2OCH_3$), 4.71 (brs, 2H, $OC\underline{H}_2OCH_2$), 5.26 (dd, 1H, J=16 and 7.5Hz, C-17H), 5.38 (ddd, 1H, J=16, 6, 6Hz, C-16H), 5.61 (ddd, 1H, J=10, 5, 2Hz, C-9 or C-10H), 5.78 (d, 1H, J=10Hz, C-9 or C-10H). The signal at 5.26 ppm collapses to a doublet (J=16Hz) 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}; ^{1}HNMR ($CDCl_3$) δ 0.00 (s, 9H), 0.91 (t, 2H, J=8Hz), 1.13 (d, 3H, J=7Hz), 1.30 (s, 3H), 2.79 (m, 1H), 3.20 (m, 1H), 3.38 (s, 3H), 3.62 (t, 2H, J=8Hz), 3.71 (m, 1H), 3.98 (s, 3H), 4.62 and 4.75 (AB, 2H, J=6Hz), 4.70 (brs, 2H), 5.35 (m, 2H), 5.62 (m, 1H), 5.82 (d, 1H, J=10Hz), 9.62 (brs, 1H).

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

(±)-Decarboxy-19,20-dihydro-7-Q-(methoxymethyl)-24-Q-methyl-20-[[2-(trimethylsilyl)ethoxy]methoxy]chlorothricolide (29B). By the procedure described for the selenoester A, 60 mg (83.5 *mol) of the Claisen acid **28B**, 50 μl (0.33 mmol) of phenyl dichlorophosphate, 90 μl (0.84 mmol) of phenyl selenol, 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 selenoester as a colorless foam: IR ($CHCl_3$) 2960, 1765, 1740, 1680, 1505, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.86 (t, 2H, J=8 Hz), 1.24 (s, 3H), 3.36 (s, 3H), 3.60 (t, 2H, J=8 Hz), 4.07 (brs, 3H), 4.67 (m, 4H), 5.34 (m, 2H), 5.62 (brd, 1H, J=10 Hz), 5.84 (d, 1H, J=10 Hz), 7.37 (m, 5H). As decomposition occurred upon standing, the selenoester was immediately decarbonylated.

By the procedure described for the lactone **29A**, 55 mg (64 μmol) of the above selenoester, 34 μl (0.13 mmol) of tributyltin hydride, and 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°; IR ($CHCl_3$) 2940, 1765, 1680, 1450, 1335 cm^{-1}; 500 MHz ^1H NMR ($CDCl_3$) δ0.00. (s, 9H, $Si(C\underline{H}_3)_3$), 0.92 (t, 2H, J=8 Hz, $OCH_2C\underline{H}_2Si$), 1.15 (d, 3H, J=7 Hz, $CHC\underline{H}_3$), 1.22 (s, 3H, $CC\underline{H}_3$), 2.68 (ddd, 1H, J=13,9,3.5 Hz, C-18H), 3.21 (ddd, 1H, J=10,10,4 Hz, C-7,H), 3.38 (s, 3H, $O\underline{C}H_3$), 3.61 (dd, 2H, J=17,8 Hz, $O\underline{C}H_2CH_2Si$), 3.67 (brs, 1H, C-20H), 4.08 (s, 3H, $OC\underline{H}_3$), 4.63 and 4.76 (AB, 2H, J=7 Hz, $OC\underline{H}_2OCH_3$), 4.71 (brs, 2H, $OC\underline{H}_2OCH_2$), 5.23 (ddd, 1H, J=15,6.5,6.5 Hz, C-16H), 5.31 (dd, 1H, J=15,9 Hz, C-17H), 5.57 (dd, 1H, J=10,2.5 Hz, C-9 or C-10H), 5.81 (d, 1H, J=10 Hz, C-9 or C-10H). 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 to that obtained by decomposition of the selenoester **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 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 and the aqueous layer was extracted with ether (3 x 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, 3H), 2.78 (m, 1H), 3.25 (m, 1H), 3.84 (m, 1H), 3.93 (s, 3H), 5.24 (m, 2H), 5.54 (dd, 1H, J=10,4 Hz), 5.71 (d, 1H, 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 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, 1H), 3.82 (m, 1H), 4.05 (s, 3H), 5.26 (m, 2H), 5.52 (brd, 1H, J=10 Hz), 5.88 (d, 1H, 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-24-0-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 x 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, 3H), 2.46 (dd, 1H, J=13,6 Hz), 2.84 (m, 1H), 3.89 (m, 1H), 3.96 (s, 3H), 4.15 (q, 2H, J=7 Hz), 4.31 (m, 1H), 5.28 (m, 2H), 5.57 (m, 2H).

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, 3H,), 2.35 (dd, 1H, J=13,6 Hz), 2.82 (m, 1H), 3.84 (m, 1H), 4.05 (s, 3H), 4.11 (dq, 2H, J=12,7 Hz), 4.34 (m, 1H), 5.24 (m, 2H), 5.66 (brs, 2H).

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-Q-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, 3H,), 4.13 (dq, 2H, J=12,7 Hz), 4.37 (m, 1H), 4.28 (m, 2H), 4.66 (brs, 2H).

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

(±)-20-Decarboxy-19,20-dihydro-24-Q-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 ($CDCl_3$) δ4.10 (s, 3H), 4.16 (q, 2H, J=7 Hz), 4.32 (m, 1H), 5.28 (m, 2H), 5.57 (brs, 2H).

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

(±)-(20S)-20-Decarboxy-19,20-dihydro-24-Q-methyl-20,20-(methyleneoxy)chlorotricolide, ethyl carbonate (33A). To a rapidly stirred solution of 79 mg (0.2 mmol) of tributyltin-(2-methoxy-isopropoxy)methane[42] in 0.5 ml 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 x 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: ^{1}H NMR ($CDCl_3$) δ3.20 (s, 3H, $OC\underline{H}_3$), 3.43 (AB, 2H, J=18,9 Hz), 3.96 (s, 3H), 4.19 (q, 2H, J=7 Hz), 4.35 (m, 1H), 5.26 (m, 2H), 5.68 (brs, 2H). 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 x 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-toluenesulfonyl 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 and the aqueous layer was extracted with ether (3 x 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}; ^{1}H NMR ($CDCl_3$) δ2.64 (brs, 2H),

3.95 (s, 3H), 4.15 (q, 2H, J=7 Hz), 4.44 (m, 1H), 5.34 (m, 2H), 5.58 (brs, 2H).

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

(±)-(20S)-20-Decarboxy-19,20-dihydro-24-Q-methyl-20,20-(methyleneoxy)chlorothricolide, ethyl carbonate (33B). By the procedure described for epoxide **33A**, 91 mg (0.23 mmol) of tributyltin-(2-methoxyisopropoxy)methane, 85 μl (0.19 mmol) of a 2.24 M solution of n-butyllithium in hexane, 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, 6H), 3.20 (s, 3H), 3.50 (m, 2H), 4.09 (s, 3H), 4.19 (q, 2H, J=7 Hz), 4.38 (m, 1H), 5.14 (m, 1H), 5.30 (m, 1H), 5.59 (brs, 2H). 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-toluenesulfonyl 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 (brs, 2H), 4.09 (s, 3H), 4.17 (q, 2H, J=7 Hz), 4.34 (m, 1H), 5.25 (m, 2H), 5.59 (brs, 2H).

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 was added 6 μl (51.4 μmol) of 2,6-lutidine and 9 μl (47.0 μmol) of trimethysilyl 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 hr, 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 x 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 ($CDCl_3$) δ3.92 (s, 3H), 4.19 (q, 2H, J=7 Hz), 4.37 (m, 1H), 5.30 (m, 2H), 5.57 (brs, 2H), 9.74 (s, 1H). 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 (brs, 3H), 4.00 (s, 3H), 4.18 (q, 2H, J=7 Hz), 5.38 (m, 2H), 5.59 (brs, 2H).

(±)-19,20-Dihydro-24-O-methylchlorothricolide-20-carboxadehyde, 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 and 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, 3H), 4.18 (q, 2H), 4.34 (m, 1H), 5.24 (m, 2H), 5.56 (brs, 2H), 9.72 (s, 1H). 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:

^{1}H NMR ($CDCl_3$) 1.75 (brs, 3H), 4.11 (s, 3H), 4.18 (q, 2H, J=7 Hz), 4.38 (m, 1H), 5.24 (m, 2H), 5.58 (brs, 2H).

(±)-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 N,N-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 and the aqueous layer was extracted with ether (3 x 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 ^{1}H NMR ($CDCl_3$) δ 1.20 (d, 3H, J=7.5 Hz, $CHC\underline{H}_3$), 1.30 (s, 3H, $CC\underline{H}_3$), 1.30 (t, 3H, J=7.5 Hz), $OCH_2C\underline{H}_3$), 3.69 (s, 3H, $OC\underline{H}_3$), 3.97 (s, 3H, $OC\underline{H}_3$), 4.18 (q, 2H, J=7.5 Hz, $OC\underline{H}_2CH_3$), 4.37 (ddd, 1H, J=10,10,4.5 Hz, C-7H), 5.21 (dd, 1H, J=16,7.5 Hz, C-17H), 5.37 (ddd, 1H, J=16,6,6 Hz, C-16H), 5.56 (d, 1H, J=10 Hz, C-9 or C-10 H), 5.62 (ddd, 1H, 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 N,N-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, 3H, CCH_3), 1.22 (d, 3H, J=7.5 Hz, $CHCH_3$), 1.29 (t, 3H, J=7 Hz, OCH_2CH_3), 2.27 (dd, 1H, J=14,6 Hz), 2.35 (ddd, 1H, J=13,9,4 Hz), 3.69 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 4.17 (q, 2H, J=7H, OCH_2CH_3), 4.36 (ddd, 1H, J=10.5,10.5,4.5 Hz, C-7H), 5.19 (ddd, 1H, J=15,5.5,5.5 Hz, C-16H), 5.26 (dd, 1H, J=15,9 Hz, C-17H), 5.58 (brs, 2H, 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 x 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, 3H, J=7.5 Hz, $OCH_2C\underline{H}_3$), 1.31 (d, 3H, J=7 Hz, $CHC\underline{H}_3$), 1.32 (s, 3H, $CC\underline{H}_3$), 2.28 (dd, 1H, J=15,7 Hz), 2.94 (brddd, 1H, J=11,7,7 Hz, C-21 H), 3.22 (brd, 1H, J=8.5 Hz, C-18 H), 3.73 (s, 3H, $OC\underline{H}_3$), 4.00 (s, 3H, $OC\underline{H}_3$), 4.18 (q, 2H, J=7.5 Hz, $OC\underline{H}_2CH_3$), 4.38 (ddd, 1H, J=10,10,4.5 Hz, C-7 H), 5.14 (dd, 1H, J=15.5,8.5 Hz, C-17 H), 5.42 (ddd, 1H, J=15.5, 8.5,4 Hz, C-16 H), 5.55 (d, 1H, J=10 Hz,, C-9 or C-10 H), 5.61 (ddd, 1H, J=10,5,2 Hz, C-9 or C-10 H), 6.71 (brs, 1H, 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 .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 x 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 to that reported by Keller-Schierlein.[4].

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CHAPTER 2

A Chiral Primary Alcohol Equivalent

A Chiral Primary Alcohol Equivalent: Silyl-Assisted Asymmetric Induction in the Ester Enolate Claisen Rearrangement[1]

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In an earlier publication[2] from these laboratories, a scheme for the total synthesis of the prostanoids was presented, and the construction of a racemic derivative of PGA_1 was delineated. This work was an initial example of the power of the ester enolate Claisen rearrangement for the convergent synthesis of complex molecules. The observation[2] that ester enolate geometry could be controlled by choice of reaction conditions led to the use of this Claisen variant for selective production of diastereomeric disubstituted γ,δ-unsaturated acids. When the allylic system is enantiomerically pure, the use of this feature for stereochemical control in the synthesis of acyclic systems with large numbers of contiguous asymmetric centers has led to the construction of ionophores,[3] macrolides,[4] terepenoids,[5] and other natural products.[6]

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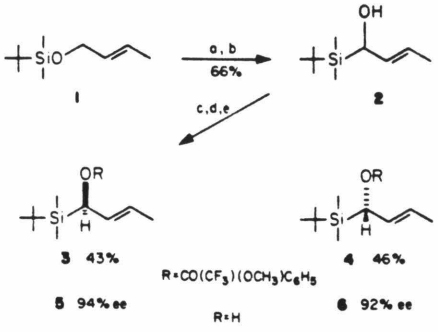
Scheme I. Synthesis of (*R*)- and (*S*)-1-(*tert*-Butyldimethylsilyl)-*trans*-2-butene-1-ols (**5** and **6**)[a]



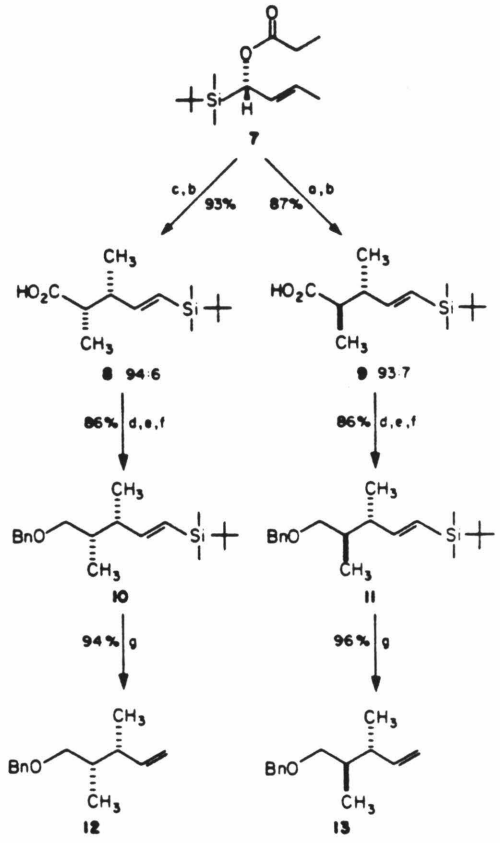
[a] a] 1.5 eq sec-BuLi, TMEDA, THF, −45°C, 30 min b] CH_3CO_2H, THF, −78°C c] (−)$C_6H_6(CF_3)(OCH_3)COCl$, CH_2Cl_2, CCl_4, OMAP, pyr., 0°C → RT, 2.5 hr d] LAH, Et_2O, THF, 0°C, 1 hr e] NaOH, $NaBH_4$, MeOH, R.T. 18 hr

Inherent in this process, however, is the requirement that the allylic system be derived from an *Enantiomerically pure secondary or tertiary alcohol*—i.e., primary allylic alcohols, such as that used in the prostanoid work,[2] can only lead to *racemic* diastereoisomeric products. Therefore, to take the fullest advantage of the stereochemical control that is possible in the Claisen rearrangement, there is a necessity for a *chiral primary alcohol equivalent*. Such methodology requires the generation of a "temporary" chiral secondary allylic alcohol, the rearrangement product of which can be converted to the system that would have resulted from the corresponding achiral primary allylic alcohol. An example of such a chiral primary alcohol equivalent is the α-silylcrotyl alcohol **2**, the synthesis and resolution of which is outlined in Scheme I.

Brook[7] rearrangement of *tert*-butyldimethylsilyl crotyl ether (**1**) under the conditions of Still[8] afforded racemic α-silyl alcohol **2** in 66% yield. Resolution of this racemic mixture was accomplished through formation of the diastereoisomeric MTPA[9,10] esters. The esters **3** and **4**, separable by medium-pressure liquid chromatography, were obtained in 43% and 46% yield, respectively. The ^{19}F NMR of these two esters confirmed that complete diastereoisomeric separation had occurred.

The conditions necessary for removal of the MTPA group were found to be different for each diastereomer, and ultimate analysis through reformation of the MTPA ester indicates a slight amount of racemization had occurred in one of these two procedures. For ester **3**, simple LAH reduction afforded the (*R*)-α-silyl alcohol **5**[11,12] in quantitative yield with a 94% enantiomeric excess (^{19}F NMR). In the case of ester **4**, the LAH reduction proceeded only to the hemiacetal stage. Subsequent treatment of this hemiacetal with $NaBH_4$ in basic methanol at room temperature for 18 h was required to remove completely the MTPA group. The (*S*)-α-silyl alcohol **6**[11,12] was obtained in 92% overall yield with a 92% enantiomeric excess. The stability of this *C*-silyl alcohol toward these basic conditions is rather remarkable in view of the reported[13] C → O migration of silicon. The alcohols (*R*)-**5** and (*S*)-**6** were found to be slightly unstable toward air oxidation but were quite stable as their propionate esters.

Scheme II. Ester Enolate Claisen Rearrangement with (*S*)-1-(*tert*-Butyldimethylsilyl)-*trans*-2-buten-1-yl Propionate (**7**)[a]



[a] a] LDA, THF, −78°C b] TBSCl, HMPA, −78°C → RT, 14 hr c] LHMDS, THF, −78°C d] CH_2N_2, Et_2O e] LAH, THF Et_2O, 0°C f] BnBr, KH, THF, 0°C → RT, 1 hr g] 50% HBF_4, CH_3CN, 55°C, 1.5 hr

The ester enolate Claisen rearrangement[2] of the propionate (*S*)-**7** and its enantiomer[14] offered the opportunity to test the utility of the α-silyl alcohols (*R*)-**5** and (*S*)-**6** as chiral primary alcohol equivalents, for the products will have two new asymmetric centers of predictable relative stereochemistry. Chirality transfer from the optically active α-silyl alcohols should then result in enantiomerically enriched vinylsilane acids **8** and **9** (Scheme II), and removal of the silicon would complete the process.

In the event, conversion of the ester (*S*)-**7** to its respective silyl ketene acetal with LDA/THF and *tert*-butyldimethylsilyl chloride (*t*-BuSiCl), warming for rearrangement and then hydrolysis afforded the acid **9** in the ratio indicated (^1H NMR). On the other hand, when the ester (*S*)-**7** was enolized with lithium hexa-

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(14) This sequence of reactions was performed on the enantiomeric *R* propionate as well, although this is not shown in Scheme II.

methyldisilyl azide in THF and then treated in the same manner, the acid **8** resulted. This high stereoselectivity in the enolization step is responsible for the efficiency of the process and has been observed before in these laboratories.[4a]

Conversion of these acids[15] individually to their corresponding benzyl ethers **10** and **11** followed standard procedures and then protiodesilylation of these ethers **10** and **11** was efficiently accomplished in high yield by treatment with aqueous HBF_4 in hot CH_3CN. Other more standard conditions for desilylation (CsF, KF, I_2, and $ArSO_2H$)[16] either failed to react or destroyed the starting material. This is a useful new method for the non-oxygen-assisted desilylation of vinylsilanes.

These results demonstrate the utility of α-silylallylic alcohols as chiral primary alcohol equivalents, and the value of such a concept for the previous prostanoid synthesis[2] is under investigation. In addition to their use in the ester enolate Claisen rearrangement, chiral α-silylallylic alcohols hold great potential as chiral substrates for other synthetic processes (S_N2', Wittig rearrangements, olefin additions, etc.) and selected of these are currently under investigation. In essence, as a result of this work, the α-silyl group can be envisaged as a "chirality inducing grouping".

Supplementary Material Available: Analytical data (IR, NMR, R_f, rotation) on all compounds, elemental analysis on compounds **1–4** and **7–13**, and experimental procedures for compounds **8** and **9** (8 pages). Ordering information is given on any current masthead page.

(15) The fluorboric acid desilation was attempted on the acid **9**, and a 54% yield of the desired product was obtained. Subsequent experiments indicated the remainder of material consisted of the five-membered lactone with the *tert*-butyldimethylsilyl group still attached to the molecule. Under forcing conditions (HBF_4, CH_3CN, °C, 12 h), this lactone gave the desired product. In order to avoid such cyclizations and possible epimerization, the acid was reduced and the resultant alcohol protected as shown.

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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 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^{o}C) and cooled in a dessicator over anhydrous $CaSO_4$ prior to use. If feasible, reaction flasks were also flame-dried in vacuo.

trans-2-Butene-1-O-(t-butyldimethylsilyl)ether (1). To a rapidly stirred solution of 1.0 g. (13.8 mmol) of crotyl alcohol in 30 ml CH_2Cl_2 at room temperature under an argon atmosphere was added 2.5 g (16.6 mmol) of TBSCl, 1.8 ml (22.1 mmol) of pyridine, and 0.17 g (1.4 mmol) of

DMAP in 5 ml CH_2Cl_2. After 15 h , the reaction mixture was poured into 100 ml saturated $NaHCO_3$, extracted with pentane (3 x 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 silica gel (100 g) with 1:400 ether/petroleum ether. In this manner, there was obtained 2.21 g (86%) of the desired ether as a colorless oil: IR ($CHCl_3$) 2960, 2860, 1460, 1250, 1090, 1040, 970, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.59 (m, 2H), 4.08 (m, 2H), 1.68 (d, 3H, J=5 Hz), 0.93 (s, 9H), 0.10 (s, 6H).

R_f=0.12 (pentane) Dist. 160°, 760 mm Hg.

Anal. Calcd for $C_{10}H_{22}OSi$: C, 64.45; H, 11.90 Found: C, 64.50; H, 11.84.

Racemic 1-(t-butyldimethylsilyl)-trans-2-butene-1-ol (2). To a rapidly stirred solution of 10 g (53.6 mmol) of the TBS ether **1** in 200 ml THF at -78°C under an argon atmosphere was added 16 ml (107 mmol) of TMEDA. To this mixture there was added 67 ml (80.4 mmol) of a 1.2 M solution of sec-Butyllithium in hexane over a 10 min period. After allowing the solution to warm to -45°C for 30 min, the solution was again cooled to -78°C. The reaction was quenched with 31 ml (536 mmol) of glacial acetic acid and allowed to warm to room temp. After pouring the reaction mixture into 500 ml of saturated

$NaHCO_3$, the aqueous layer was extracted with ether (3 x 300 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 (500 g) with 1:20 ether/petroleum ether. In this manner, there was obtained 3.3 g of the starting ether and 4.4 g (44%) of the desired alcohol as a colorless oil: IR ($CHCl_3$) 3590, 3430, 2830, 1460, 1250, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.55 (m, 2H), 4.03 (d, 1H, J=7 Hz), 1.73 (d, 3H, J=5 Hz, CH_3), 0.95 (s, 9H), 0.02 (s, 3H), -0.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 133.3, 122.2, 66.9, 27.0, 17.8, 16.9, -7.51, -8.68.

R_f=0.20 (1:20 ether/petroleum ether) Evap. dist. 40°C, 0.1 mm Hg.

Anal. Calcd for $C_{10}H_{22}OSi$: C, 64.45; H, 11.90. Found: C, 64.55; H, 11.55.

(R) and (S)-[1-(t-butyldimethylsilyl)-trans-2-butene]-1-(-)-α-methoxy-α-(trifluoromethyl) phenylacetate (3) and (4). To a rapidly stirred solution of 1.08 g (4.27 mmol) of MTPA-Cl (prepared by heating the acid 1 g (4.27 mmol) and triphenylphosphine 2.35 g (8.97 mmol) in a mixture of 5 ml CH_2Cl_2 and 5 ml CCl_4 at 45°C. for 70 min) at 0°C under an argon atmosphere was added 0.88 g (4.70 mmol) of allylic alcohol **2** in 4 ml CH_2Cl_2 containing 1.03 ml (12.8 mmol) pyridine and 0.10 g (0.85 mmol) DMAP. The

reaction mixture was allowed to warm to room temperature and after 2 h was poured into 100 ml of saturated $NaHCO_3$, and the aqueous layer was extracted with ether (3 x 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 silca gel (100 g) with 1:33 ether/petroleum ether. This chromatographed material was separated using a size C Lobar silica column with 1:134 ether/petroleum ether. In this manner, there was obtained 0.745 g (43%) of ester **3** as a colorless oil: R_f=0.38 (1:20 ether/petroleum ether) evap. dist. 80°C 0.01 mm Hg: $[\alpha]_D^{25}$=+3.6° (c=0.99, $CHCl_3$): IR ($CHCl_3$) 2860, 1738, 1460, 1170, 1120, 1010, 970, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43 (m, 5H), 5.48 (m, 2H), 3.54 (s, 3H), 1.71 (d, 3H, J=5 Hz), 0.95 (s, 9H), 0.05 (s, 6H).

Anal. Calcd for $C_{20}H_{29}O_3F_3Si$: C, 59.68; H, 7.26. Found: C, 59.83; H, 7.32.

In this manner, there was also obtained 0.795 g (46%) of ester **4** as a colorless oil: R_f=0.43 (1:20 ether/petroleum ether) evap. dist. 80°C, 0.01 mm Hg $[\alpha]_D^{25}$=-50.4° (c=0.55, $CHCl_3$): IR ($CHCl_3$) 2860, 1735, 1450, 1170, 1120 1015, 970, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (m, 5H), 5.55 (m, 2H) 3.56 (s, 3H), 1.75 (d, 3H J=5 Hz), 0.87 (s, 9H), -0.02 (s, 6H).

Anal. Calcd for $C_{20}H_{29}O_3F_3Si$: C, 59.68; H, 7.26. Found: C, 59.72; H, 7.24.

(R)-1-(t-butyldimethylsilyl)-trans-2-butene-1-ol (5). To a rapidly stirred solution of 0.716 g (1.78 mmol) of ester **3** in 10 ml ether at 0°C under an argon atmosphere was added 1.78 ml (1.78 mmol) of a 1 M solution of LAH in THF over a 5 min period. After 1 h , the reaction was quenched with 3 ml of saturated NH_4Cl and diluted with 20 ml of water. After extracting the aqueous layer with ether (3 x 60 ml), the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure the crude residue was chromatographed on silica gel (50 g) with 1:20 ether/petroleum ether. In this manner, there was obtained 0.348 g (100%) of the desired alcohol as a colorless oil: IR ($CHCl_3$) 3590, 3430, 2830, 1460, 1250, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ5.55 (m,2H), 4.03 (d, 1H, J=7 Hz), 1.73 (d, 3H, J=5 Hz), 0.95 (s, 9H), 0.02 (s, 3H), -0.03 (s, 3H).

R_f=0.20 (1:20 ether/petroleum ether) $[\alpha]_D^{25}$=+39.8° (c=2.98, $CHCl_3$).

A portion of this material was resubjected to the described MTPA ester formation conditions. Analysis using ^{19}F NMR shows two peaks at 4.98 and 5.23 ppm (relative to CF_3CO_2H) in a ratio of 97:3 indicating an enantiomeric excess of 94%.

(S)-1-(t-butyldimethylsilyl)-trans-2-butene-1-01 (6).

To a rapidly stirred solution of 0.776 g (1 93 mmol) of ester **4** in 10 ml ether at 0°C under an argon atmosphere was added 1.93 ml (1.93 mmol) of a 1 M solution of LAH in THF over a 5 min period. After 1.5 h , the reaction was quenched with 3 ml of saturated NH_4Cl and diluted with 20 ml of water. After extracting the aqueous layer with ether (3 x 60 ml), the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (50 g) with 1:20 ether/petroleum ether. In this manner there was obtained 0.760 g of the corresponding hemiacetal: IR ($CHCl_3$) 3600 3560, 2960, 2860, 1450, 1250, 1160, 1060, 970, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (m, 5H), 5.28 (m, 3H), 4.15 (d, 1H J=9 Hz), 3.45 (s, 3H), 2.68 (d, 1H, J=10 Hz), 1.68 (d, 3H, J=5 Hz), 0.93 (s, 9H), 0.00 (s, 3H), -0.07 (s, 3H). The above hemiacetal was dissolved in 25 ml of CH_3OH and to this mixture was added 10 ml (1.0 mmol) of a 0.1 N solution of NaOH and 0.25 g (6.57 mmol) of $NaBH_4$. After stirring at room temperature under argon for 18 hr, the reaction mixture was poured into 50 ml water and the aqueous layer was extracted with petroleum ether (3 x 120 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 (50 g) with 1:20 ether/petroleum ether. In this manner there was obtained 0.330 g (92%) of the desired

alcohol as a colorless oil: IR ($CHCl_3$) 3590, 3430, 2830, 1460 1250, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.55 (m, 2H), 4.03 (d, 1H, J=7 Hz), 1.73 (d, 3H, J=5 Hz), 0.95 (s, 9H), 0.02 (s, 3H), -0.03 (s, 3H).

R_f=0.20 (1:20 ether petroleum ether) $[\alpha]_D^{25}$=-37.0° (c=2.38 $CHCl_3$). A portion of this material was resubjected to the described MTPA ester formation conditions. Analysis using ^{19}F NMR shows the two peaks at 4.98 and 5.23 ppm (relative to CF_3CO_2H) in a ratio of 4:96 indicating an enantiomeric excess of 92%.

(S)-1-(t-butyldimethylsilyl)-trans-2-butene-1-propionate (7). To a rapidly stirred solution of 0.32 g (1 72 mmol) of allylic alcohol **6** in 10 ml CH_2Cl_2 at 0°C under an argon atmosphere was added 0.35 ml (4.30 mmol) of pyridine, 0.042 g (0.34 mmol) of DMAP, and 0.22 ml (2.58 mmol) of propionyl chloride. After 15 min, the reaction was allowed to warm to room temperature. After an additional 15 min the reaction mixture was poured into 50 ml saturated $NaHCO_3$, and the aqueous layer was extracted with ether (3 x 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 silca (30 g) with 1:55 ether/petroleum ether. In this manner, there was obtained 0.384 g (92%) of the desired ester as a colorless oil: IR ($CHCl_3$) 2920, 2860, 1720,

1460, 1360, 1190, 970, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.45 (m, 2H), 5.32 (s, 1H), 2.35 (q, 2H, J=7.5 Hz), 1.70 (d, 3H, 5 Hz), 1.16 (t, 3H, J=7.5 Hz), 0.95 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).

R_f=0.38 (1:20 ether/petroleum ether) $[\alpha]_D^{25}$=-47.1° C=1.32, $CHCl_3$) evap. dist. 40°C, 0.1 mm Hg.

Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81 Found: C, 64.25; H, 10.80.

(R)-1-(t-butyldimethylsilyl)-trans-2-butene-1-Propionate (7R), yield 92%. Identical in all respects to ester **7**.

$[\alpha]_D^{25}$=+50.5° (c=1.51, $CHCl_3$).

2(R)-3(R)-Dimethyl-5-(t-butyldimethylsilyl)-trans-4-pentenoic Acid (8RR). According to the procedure of Ireland and Daub[4], a solution of 200 mg (0.82 mmol) of the propionate **7** in 2 ml THF was added dropwise via a cannula to 3 ml (1.07 mmol) of a 0.35 M solution of LiHMDS in THF at -78°C under an argon atmosphere. After the mixture was stirred for 10 min, a solution of 224 mg (1.48 mmol) of tert-butyldimethylsilyl chloride, and 1.5 ml HMPA in 2 ml THF was added all at once After 10 min, the reaction mixture was allowed to warm to room temperature for 12 h. After addition of 1 ml (1.0 mmol) of 1 N HCl the reaction mixture was stirred for 1 h. The resulting mixture was poured into 50 ml of water and the aqueous layer was

extracted with ether (3 x 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 a 60:40 mixture of silicar CC-4 and silca gel (20 g) with 1:12 ether/petroleum ether. In this manner, there was obtained 165 mg (83%) of the acid as a colorless oil: IR ($CHCl_3$) 2960, 2940, 2860, 1705, 1610, 1460, 1250, 990, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ6.00 (dd 1H, J=6, 18 Hz) 5.64 (d, 1H, J=18 Hz), 2.53 (m, 2H), 1.16 (d, 3H, J=6 Hz), 0.98 (d, 3H, J=6 Hz), 0.88 (s, 9H), 0.05 (s, 6H). R_f=0.09 (1:9 ether/petroleum ether), evap. dist. 80°C 0.01 mm Hg.

Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H 10.81. Found: C, 64.49; H, 10.72. $[\alpha]_D^{25}$=-35.9° (c=1.49 $CHCl_3$).

A portion of this material was treated with etheral diazomethane and then a 500 MHz ^1H NMR was taken of the resultant methylesters. There were two methoxy peaks at 3.66 and 3.63 ppm in a ratio of 9:91.

2(S)-3(S)-Dimethyl-5-(t-butyldimethylsilyl)-trans-4-pentenoic Acid (8), yield 93%.

Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.44; H, 10.79. $[\alpha]_D^{25}$=+37.8° (c=1.02 $CHCl_3$)

A portion of this material was treated with ethereal dizaomethane and then a 500 MHz ^1H NMR was taken of the resultant methylesters. There were two methoxy peaks at 3.66 and 3.63 ppm in a ratio of 6:94.

2(S)-3(R)-Dimethyl-5-(t-butyldimethylsilyl)-trans-4-pentenoic Acid (9 S,R). According to the procedure of Ireland and Williard[2], a solution of 200 mg (0.82 mmol) of the propionate **7** in 2 ml THF was added dropwise via a cannula to 3 ml (1.07 mmol) of a 0.35 M solution of LDA in THF at -78°C under an argon atmosphere. After the mixture was stirred for 10 min, a solution of 224 mg (1.48 mmol) of tert-butyldimethylsilyl chloride, and 1.5 ml HMPA in 2 ml THF was added at once. After 10 min, the reaction mixture was allowed to warm to room temperature for 12 h. After addition of 1 ml (1.0 mmol) of 1 N HCl, the reaction mixture was stirred for 1 h. The resulting mixture was poured into 50 ml of water and the aqueous layer was extracted with ether (3 x 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 a 60:40 mixture of silcar CC-4 and silica gel (20 g) with 1:12 ether/petroleum ether. In this manner, there was obtained 166 mg (83%) of the acid as white crystals: IR ($CHCl_3$) 2960, 2860, 1700, 1610, 1460, 1250, 990, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.92 (dd, 1H, J=6, 18 Hz), 5.65 (d, 1H, J=18 Hz), 2.48 (m, 2H), 1.23 (d, 3H, J=6 Hz), 1.08 (d, 3H, J=6 Hz), 0.92 (s, 9H), 0.07 (s, 6H).
Recrystallization of the acid from petroleum ether yielded crystals suitable for analysis. Melting point 114.5-115°C.

Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.32; H, 10.72. $[\alpha]_D^{25}=-42.1^o$ (c=1.28, $CCHCl_3$) R_f=0.09 (1:9 ether/petroleum ether).

A portion of the nonrecrystallized material was treated with ethereal diazomethane and then a 500 MHz ^1H NMR was taken of the resultant methylesters. There were two methoxy peaks at 3.66 and 3.63 ppm in a ratio of 95:5.

2(R)-3(S)-Dimethyl-5-(t-butyldimethylsilyl)-trans-4-pentenoic Acid (9), yield 87%, Mp 114-114.5°C.

Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.53; H, 10.78. $[\alpha]_D^{25}=+41.2^o$ (c=1.66, $CHCl_3$).

A portion of the nonrecrystallized material was treated with ethereal diazomethane and then a 500 MHz ^1H NMR was taken of the resultant methylesters. There were two methoxy peaks at 3.66 and 3.63 ppm in a ratio of 93:7.

2(S)-3(S)-Dimethyl-5-(t-butyldimethylsilyl)-trans-4-pentene-1-ol. To a rapidly stirred solution of 87.8 mg (0.36 mmol) of acid **8** in 3 ml of ether was added excess ethereal diazomethane. After gas evolution had stopped, the solvent was removed at reduced pressure. To this methyl ester in 3 ml ether at 0°C under an argon atmosphere was added 0.54 ml (0.54 mmol) of a 1 M solution of LAH in THF over a 5 min period. After 1 h , the reaction was quenched with 0.1 ml H_2O 0.1 ml 10% NaOH, and 0.3 ml H_2O. After 30 min, $MgSO_4$ was added and the

solution was filtered. After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (10 g) with 1:4 ether/petroleum ether. In this manner, there was obtained 77.1 mg (93%) of the desired alcohol as a colorless oil: IR ($CHCl_3$) 3620, 2960, 2940, 2890,2860, 1615, 1465, 1250, 1010, 1000, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ5.96 (dd, 1H, J=7, 18 Hz), 5.56 (d, 1H, J=18), 3.50 (m, 2H), 2.23 (m, 1H), 1.60 (m, 1H), 1.00 (d, 3H, J=7 Hz), 0.86 (s, 12 H), 0.02 (s, 6H); R_f=0.16 (1:4 ether/petroleum ether), $[\alpha]_D^{25}$=+43.41 (c=1.71, $CHCl_3$), evap. dist. 60°C, 0.1 mm Hg.

Anal. Calcd for $C_{13}H_{28}OSi$: C, 68.35; H, 12.35. Found: C, 68.44; H, 12.32.

2(R)-3(R)-Dimethyl-5-(t-butyldimethylsilyl)-trans-4-pentene-1-ol: yield 100%, identical in all respects to its enantiomer. $[\alpha]_D^{25}$=-42.7° (c=1.15,$CHCl_3$).

2(R)-3(S)-Dimethyl-5-(t-butyldimethlysilyl)-trans-4-pentenè-1-ol. To a rapidly stirred solution of 115 mg (0.47 mmol) of acid (recrystallized twice from petroleum ether) **9** in 3 ml of ether was added excess ethereal diazomethane. After gas evolution had stopped, the solvent was removed at reduced pressure. To this methyl ester in 3 ml ether at 0°C under an argon atmosphere was added 0.7 ml (0.70 mmol) of a 1 M solution of LAH in THF over a 5 min period. After 1 h , the reaction was

quenched with 0.1 ml H_2O , 0.1 ml 10 % NaOH, and 0.2 ml H_2O. After 30 min, $MgSO_4$ was added and the solution was filtered. After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (10 g) with 1:4 ether/petroleum ether. In this manner, there was obtained 109 mg (100%) of the desired alcohol as a colorless oil: IR ($CHCl_3$) 3620, 3500, 2960, 2860, 1610, 1460, 1250, 1010, 830 cm^{-1}, ^1H NMR ($CDCl_3$) δ 5.95 (dd, 1H, J=7, 18 Hz), 5.58 (d, 1H, J=18 Hz), 3.50 (m, 2H), 2.32 (m, 1H), 1.60 (m, 1H), 1.05 (d, 3H, J=7 Hz), 0.89 (s, 12 H), 0.02 (s, 6H). R_f=0.16 (1:4 ether/petroleum ether). $[\alpha]_D^{25}$=+31.0° (c=1.58, $CHCl_3$); evap. dist. 60°C, 0.1 mm Hg.

Anal. Calcd for $C_{13}H_{28}OSi$: C, 68.35; H, 12.35. Found: C, 68.25; H, 12.30.

2(S)-3(R)-Dimethyl-5-(t-butyldimethylsilyl)-trans-4-pentene-1-ol; yield 94%, identical in all respects to its enantiomer. $[\alpha]_D^{25}$=-34.5° (c=1.31, $CHCl_3$).

Benzyl-2(S)-3(S)-dimethyl-5-(t-butyldimethylsilyl)-trans-4-pentenyl Ether (10). To a rapidly stirred suspension of 18.7 mg (0.47 mmol) of oil free KH in 1 ml THF at 0°C under an argon atmosphere was added a solution of 68 mg (0.30 mmol) of the corresponding alcohol and 0.055 ml (0.47 mmol) of benzyl bromide in 1 ml THF. After allowing to warm to room temperature over a 1 h period

the reaction mixture was poured into 50 ml of saturated $NaHCO_3$ and the aqueous layer was extracted with ether (3 x 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 (10 g) with 1:50 ether/petroleum ether In this manner, there was obtained 87.9 mg (93%) of the desired ether as a colorless oil: IR ($CHCl_3$) 2960, 2940, 1860, 1610, 1460, 1360, 1250, 1100, 1000, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 5H), 6.02 (dd, 1H, J=6, 18 Hz), 5.56 (d, 1H, J=18 Hz), 4.50 (s, 2H), 3.38 (m, 2H), 2.35 (m, 1H), 1.85 (m, 1H), 1.01 (d, 3H, J=6 Hz) 0.90 (s, 12H), 0.05 (s, 6H). R_f=0.33 (1:50 ether/petroleum ether), $[\alpha]_D^{25}$=+36.3° (c=1.75 $CHCl_3$), evap. dist. 100°C, 0.1 mm Hg.

Anal. Calcd for $C_{20}H_{34}OSi$: C, 75.40; H, 10.76. Found: C, 75.49; H, 10.81.

Benzyl-2(R)-3(R)-dimethyl-5-(t-butyldimethylsilyl)-trans-4-pentenyl Ether (10 R,R); yield 92%, identical in all respects to ether **10**. $[\alpha]_D^{25}$=-36.6° (c=2.12, $CHCl_3$).

Benzyl-2(R)-3(S)-dimethyl-5-(t-butyldimethylsilyl)-trans-4-pentenyl Ether (11). To a rapidly stirred suspension of 28.4 mg (0.71 mmol) of oil-free KH in 1 ml THF at 0°C under an argon atmosphere was added a solution of 108 mg (0.47 mmol) of the corresponding alcohol and

0.084 ml (0.71 mmol) of benzyl bromide in 1 ml THF. After allowing to warm to room temperature over a 1 hr period, the reaction mixture was poured into 50 ml of saturated $NaHCO_3$ and the aqueous layer was extracted with ether (3 x 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 (10 g) with 1:50 ether/petroleum ether. In this manner, there was obtained 129 mg (86%) of the desired ether as a colorless oil: IR ($CHCl_3$) 2960, 2940, 2860, 1615, 1460, 1370, 1250, 1095, 1000, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.93 (dd, 1H, J=7, 18 Hz), 5.55 (d, 1H, J=18 Hz), 4.50 (s, 2H), 3.35 (m, 2H), 2.40 (m, 1H), 1.83 (m, 1H), 1.05 (d, 3H, J=7Hz), 0.95 (d, 3H, J=7 Hz), 0.90 (s, 9H), 0.05 (s, 6H). R_f=0.33 (1:50 ether/petroleum ether), $[\alpha]_D^{25}$=+34.2° (c=2.56, $CHCl_3$), evap. dist. 100°C, 0.1 mm Hg.

Anal. Calcd for $C_{20}H_{34}OSi$: C, 75.40; H, 10.76. Found: C, 75.42; H, 10.71.

Benzyl-2(S)-3(R)-dimethyl-5-(t-butyldimethylsilyl)-trans-4-pen-tenyl Ether (11S,R); yield 97%, identical in all respects to ether **11**. $[\alpha]_D^{25}$=-35.9° (c=1.59, $CHCl_3$).

Benzyl-2(S)-3(S)-dimethyl-4-pentenyl Ether (12). To a rapidly stirred solution of 76 mg (0.24 mmol) of ether **10** in 2 ml CH_3CN at 55°C under an argon atmosphere was added

0.2 ml of 48-50% aqueous HBF_4. After heating for 1.5 h, the reaction mixture was poured into 40 ml of saturated $NaHCO_3$ and the aqueous layer was extracted with ether (3 x 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 (10 g) with 1:66 ether/petroleum ether. In this manner, there was obtained 46 mg (94%) of the desired olefin as a colorless oil: IR ($CHCl_3$) 2960, 1640, 1460, 1380, 1370, 1100, 1000, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (s, 5H), 5.78 (ddd, 1H, J=7, 7, 18 Hz), 5.07 (m, 1H), 4.91 (m, 1H), 4.50 (s, 2H), 3.38 (m, 2H), 2.23 (m, 1H), 1.85 (m, 1H), 1.02 (d, 3H, J=7 Hz), 0.96 (d, 3H, J=7 Hz). R_f=0.29 (1:50 ether/petroleum ether), $[\alpha]_D^{25}$=+26.5° (c=0.83°, $CHCl_3$), evap. dist. 60°C, 0.1 mm Hg.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.30; H, 9.89.

Benzyl-2(R)-3(R)-dimethyl-4-pentenyl Ether (12 R,R); yield 84%, identical in all respects to ether **12**. $[\alpha]_D^{25}$=-25.5° (c=0.90, $CHCl_3$).

Benzyl-2(R)-3(S)-dimethyl-4-pentenyl Ether (13 R,S). To a rapidly stirred solution of 115 mg (0.36 mmol) of ether **11 S,R** in 2 ml CH_3CN at 55°C under an argon atmosphere was added 0.3 ml of 48-50% aqueous HBF_4. After heating for 1.5 h , the reaction mixture was poured into

40 ml of saturated $NaHCO_3$ and the aqueous layer was extracted with ether (3 x 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 (10 g) with 1:66 ether/petroleum ether. In this manner, there was obtained 71 mg (96%) of the desired olefin as a colorless oil: IR ($CHCl_3$) 2960, 2880, 1640, 1460, 1370, 1100, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ7.35 (s, 5H), 5.73 (ddd, 1H, J=7, 7, 18 Hz), 5.07 (m, 1H), 4.91 (m, 1H), 4.50 (s, 2H), 3.33 (m, 2H), 2.36 (m, 1H), 1.79 (m, 1H), 1.04 (d, 3H, J=7 Hz), 0.92 (d, 3H, J=7 Hz). R_f=0.29 (1:50 ether/petroleum ether), $[\alpha]_D^{25}$=+18.3° (c=1.26, $CHCl_3$), evap. dist. 60°C, 0.1 mm Hg.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.34; H, 9.82.

Benzyl-2(S)-3(R)-dimethyl-4-pentenyl Ether. (13); yield 90%, identical in all respects to ether (13 R,S). $[\alpha]_D^{25}$=-19.1° (c=0.85, $CHCl_3$).

2(S), 3(S)-Dimethyl-4-pentenoic Acid. To a rapidly stirred solution of 152 mg (0.63 mmol) of acid **9,S,R** in 3 ml CH_3CH at 60°C under and argon atmosphere was added 0.5 ml of 48-50% aqueous HBF_4. After heating for 4 h, the reaction mixture was poured into 50 ml of 2 N NaOH and the aqueous layer was extracted with ether (50 ml) and the extracts were discarded. The aqueous layer was then

acidified with 6 N HCl to pH 2 and then extracted with ether (3 x 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 using 1:4 ether/petroleum ether. In this manner, there was obtained 43.2 mg (54%) of the desired acid as a colorless oil: IR ($CHCl_3$) 3500-2400, 1705, 1460, 1420, 1380, 1290, 1000, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.66 (ddd, 1H, J=7, 7, 18 Hz), 5.12 (m, 1H), 4.95 (m, 1H), 2.45 (m, 2H), 1.18 (d, 3H, J=7 Hz), 1.12 (d, 3H, J=7 Hz). R_f=0.17 (3:7 ether/petroleum ether), $[\alpha]_D^{25}$=-41.2° (c=1.25, $CHCl_3$), evap. dist. 50°C, 0.1 mm Hg.

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.60; H, 9.38.

Ozonization of Threo acid 8. A solution of 50 mg (0.21 mmol) of the acid in 1 ml of ethyl acetate and 1 ml acetic acid was cooled to -10°C. Ozone was passed through the solution for 1 min. The reaction was then purged with nitrogen and was treated with 0.35 ml of 15% aqueous hydrogen peroxide solution. After 16 h, the solvents were removed at reduced pressure and the crude residue was dissolved in 10 ml of 3% NaOH. This basic solution was extracted with ether (2 x 40 ml) and the extracts were discarded. The solution was acidified with 10% H_2SO_4 and the aqueous layer was extracted with ether (10 x 50 ml),

and the combined organic extracts were dried (Na_2SO_4). After removal of the solvent at reduced pressure, the crude residue was treated with excess ethereal diazomethane. After gas evolution had stopped, the solvent was removed at reduced pressure and the methyl ester was dissolved in 1 ml ether at 0°C under an argon atmosphere. To this solution was added 0.4 ml (0.4 mmol) of a 1 M solution of LAH in THF. After 30 min, the reaction mixture was poured into 10 ml of saturated NH_4Cl and aqueous layer was extracted with ether (4 x 50 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 (2 g) with ethyl acetate. In this manner there was obtained 16.3 mg of the desired diol as a colorless oil: NMR ($CDCl_3$) δ 3.63 (m, 4H), 2.97 (bs, 2H), 1.75 (m, 2H), 1.23 (d, 1.5H, J=7 Hz), 0.95 (d, 4.5H, J=7 Hz). By NMR this is a 3.4:1 ratio of the *l* and meso diol. $[\alpha]_D^{25}=-4.4^o$ (c=0.81, ether). The literature value for this diol is $[\alpha]_D^{25}=-5.42^o$ (c=5, dry ether)[3]. In References 3, 4, 5 this diol is the 2(S), 3(S)-dimethyl butane-1,4-diol.

CHAPTER 3

Stereochemistry of the Claisen Rearrangement

Stereochemistry of the Claisen Rearrangement of Derivatives of 5-*tert*-Butyl-1-(hydroxymethyl)-1-cyclohexene: Preferred Axial Attachment of the Side Chain[1]

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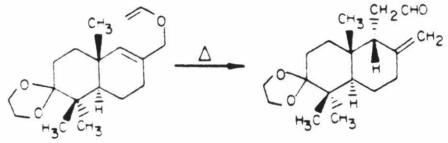
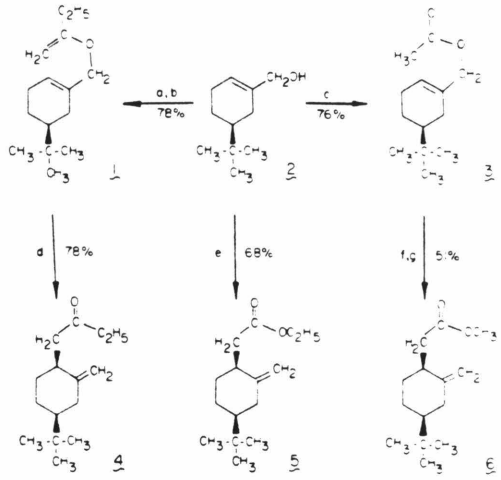
The Claisen rearrangement of vinyl ethyl derivatives of 5-*tert*-butyl-1-(hydroxymethyl)-1-cyclohexene is reported. The standard allyl vinyl ether conditions as well as the triethyl orthoacetate and ester enolate variants of the Claisen rearrangement all resulted in the formation of *cis*(axial)-4-*tert*-butylcyclohexyl-substituted systems. Thus, in sterically unbiased cases, this [3,3] sigmatropic process results in the axial attachment of the side chain in a cyclohexyl system.

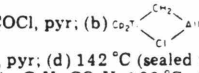
The Claisen rearrangement is a synthetically useful transformation,[2] and most of its stereochemical aspects are now well understood.[3] One stereochemical point that has not been addressed directly in the public literature[4,5] is whether there is a preference for axial or equatorial attachment of the side chain that results from such a rearrangement in certain cyclohexene series. In an earlier sterically biased case reported from these laboratories,[6] only the axially oriented product was observed (see below).



Since it was not clear if this result was the consequence of the steric congestion on the top face of this dicyclic molecule or a preferred stereoelectronically controlled quasi-axial approach of the vinyl ether to the cyclohexene ring system, it was decided to investigate the rearrangement in a stereochemically defined but sterically unbiased situation. The substrate chosen for this work was 5-*tert*-butyl-1-(hydroxymethyl)-1-cyclohexene (**2**),[7] and several variations of the Claisen rearrangement were explored (Scheme I).

Scheme I. Claisen Rearrangements with 5-*tert*-Butyl-1-(hydroxymethyl)-1-cyclohexene (2)[a]



[a] (a) C_2H_5COCl, pyr; (b)  , $C_6H_5CH_3$; (c) CH_3COCl, pyr; (d) 142 °C (sealed tube), 6 h; (e) $CH_3C(OC_2H_5)_3$, $C_5H_{11}CO_2H$, 166 °C, 44 h; (f) LDA, THF, HMPA; *t*-BuMe$_2$SiCl; 60 °C; H_3O^+; (g) CH_2N_2, Et_2O.

In one instance, the ketone **4** was prepared through the standard[6,13] allyl vinyl ether type rearrangement of the vinyl ether **1**. Alternately, direct formation of the ethyl ester **5** was accomplished through application of the Johnson[8] triethyl orthoacetate variant of the rearrange-

(1) Contribution No. 6697. Grateful acknowledgement is made for the support of this investigation through National Science Foundation Grant CHE-78-21066.

(2) (a) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1. (b) Bennett, G. B. *Synthesis* **1977**, 589. (c) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (d) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 1–72.

(3) (a) Gill, G. B. *Q. Rev., Chem. Soc.* **1968**, *22*, 338. (b) Hansen, H. J. Schmidt, H. *Tetrahedron* **1974**, *30*, 1959. (c) Takahashi, H.; Oshima, K.; Yamamoto, H.; Nazaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 5803. (d) Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67. (e) Vittovelli, P.; Winkler, T.; Hansen, H. J.; Schmidt, H. *Helv. Chim. Acta* **1968**, *51*, 1457. (f) Sucrow, W.; Richter, W. *Chem. Ber.* **1971**, *104*, 3679. (g) Faulkner, D. J.; Peterson, M. R. *Tetrahedron Lett.* **1969**, 3243. (h) Bartlett, P. A.; Hahne, W. F. *J. Org. Chem.* **1979**, *44*, 882.

(4) Dr. A. A. Panaras has informed us that his research group is investigating similar systems. See also ref 2c and 5.

(5) House, H. O.; Lubinkowski, J.; Good, J. J. *J. Org. Chem.* **1975**, *40*, 86.

(6) Ireland, R. E.; Marshall, J. A.; Church, R. F. *J. Org. Chem.* **1962**, *27*, 1118.

(7) Gream, G. E.; Serelis, A. K. *Aust. J. Chem.* **1978**, *31*, 863–91.

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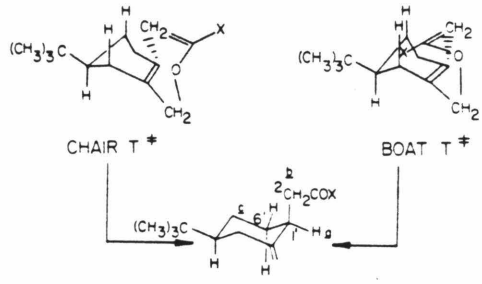
ment to the allylic alcohol **2**. Finally, the methyl ester **6** was formed after diazomethane esterification of the acid from the ester enolate Claisen rearrangement[9] of the acetate **3**. In each instance, the steric congestion associated with the addition of the CH_2COX side chain to the ring system should be minimal, and on the assumption[10] that the C5 *tert*-butyl grouping is sufficiently bulky to maintain a rigid cyclohexene conformation, the stereochemistry of these products should reflect the preferred mode of orientation for the rearrangement transition state.

The required stereochemical determination of the rearrangement products was accomplished through 500-MHz ^1H NMR analysis[11] of the individual diastereomers. In each instance, the two possible products (axial and equatorial side-chain attachment) were detected through the appearance of multiplet resonances for the C1′ allylic methine hydrogen at 2.89 and 2.46 ppm. That one isomer was by far the predominant product of the rearrangements was apparent from the ≥87:13 ratio observed on integration of the two peaks in the analytical VPC trace in each of the three products. After decoupling the C1′-methine hydrogen (a) from the C2 methylene hydrogens (b) of the side chain, it was possible to determine the stereochemistry at the C1′ center by analysis of the coupling between the C1′ methine hydrogen (a) and the adjacent C6′ methylene hydrogens (c). These coupling constants for the resonance at 2.89 ppm of the major product were 0 and 5 Hz. The resonance at 2.46 ppm of the minor product was a large multiplet and was determined to be both the C1′ and the C3′ equatorial hydrogens. That the C1′ hydrogen was in fact axial in the minor product was determined from its 12-Hz coupling constant to the C6′ axial hydrogen at 0.95 ppm. For the expected chair conformation of the cyclohexene ring system, these coupling constants indicate that the C1′ methine hydrogen of the major product is equatorial (dihedral angles: $H_aH_c(ax) = 38°$; $H_aH_c(eq) = 75°$) and that of the minor product is axial (dihedral angles: $H_aH_c(ax) = 170°$). Therefore, in each case, the Claisen rearrangement has resulted in the attachment of the CH_2COX side chain predominately on the β face of the cyclohexene ring in the *axial orientation*, as shown in structure **7**. Apparently, stereoelectronically controlled



7

axial approach during rearrangement is favored, and the steric bias of the earlier observed[6] system served only to augment this effect.

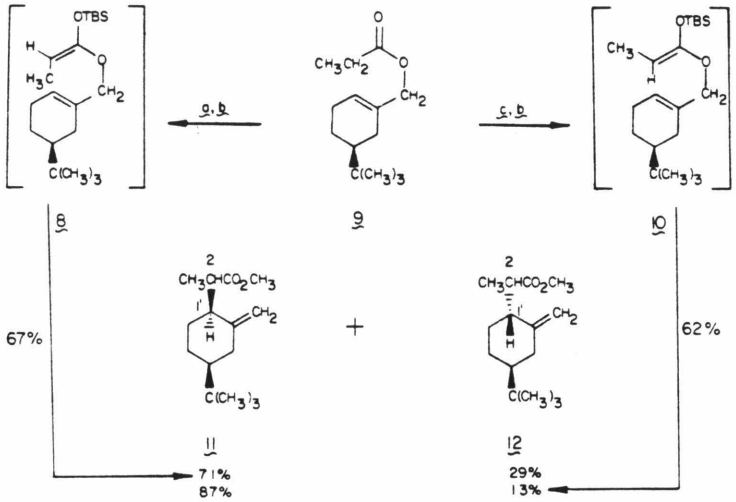
Ziegler's suggestion[2c] that this preference for axial approach is a result of the $A^{(1,3)}$ strain experienced in the trans (equatorial) products does not seem likely. Literature values for this interaction (~1.3 kcal/mol)[15] indicate that the product resulting from equatorial approach is still thermodynamically more stable than the product resulting from axial approach whose 1,3-diaxial interactions are on the order of 1.8 kcal/mol.[10]

Two limiting transition states (CHAIR T‡ and BOAT T‡) can be envisaged to account for this result. Molecular models, as reflected in the drawings above, make it apparent that in these cases where the vinyl ether portion of the allyl vinyl ether system terminates in a CH_2 grouping, the CHAIR T‡ arrangement is less hindered. In order to ascertain the effect of a substituent at this position on the preferred chair conformation of the transition state and hence the stereochemical effect that results, we prepared the corresponding allylic propionate **9** (Scheme II).

After enolization of this propionate **9**, the derived silyl ketene was rearranged at 50 °C, and the resulting silyl ester was hydrolyzed. Esterification with diazomethane then produced a stereoisomeric mixture of the esters **11** and **12**. Even though these esters are isomeric at both C2 and C1′, it was possible to analyze this mixture for the cis (axial side chain) and trans (equatorial side chain) components in the same fashion described above for the acetates. Again, the predominate component was assigned the structure **11** with an axial side chain by virtue of the equatorial C1′ hydrogen doublet of doublets at 2.36 ppm (J = 11, 5 Hz). This C1′ hydrogen appears at 2.05 ppm (J = 7.5, 11, 3.5 Hz) in the ^1H NMR spectrum of the minor isomers **12**.

(8) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.; Faulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
(9) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(10) Allinger, N. L.; Eliel, E. L. *Top. Stereochem.* **1967**, *1*, 199.
(11) Southern California Regional NMR Facility, NSF Grant CHE-79-16324.
(12) Infrared (IR) spectra were determined on a Perkin-Elmer 727B or 1310 infrared spectrometer. Proton nuclear magnetic resonance spectra were recorded on a Varian EM-390 (^1H NMR) or a Bruker WM500 (500-MHz ^1H NMR) spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Data are reported as follows: chemical shift (multiplicity, integrated intensity, coupling constants, assigned protons).
Silica gel columns for chromatography utilized E. Merck silica gel 60, 70–230-mesh ASTM, or for flash chromatography silica gel 60, 230–400-mesh ASTM, was used.
Analytical vapor-phase chromatographic (VPC) analyses were performed on a Hewlett-Parkard 5750 gas chromatograph, equipped with a flame-ionization detector (335 °C) and using helium carrier gas at a flow rate of 60 mL/min. The column size was 6 ft × $^1/_8$ in. and was packed with 10% SE-30 absorbed on 60–80-mesh Chromosorb W AW DMCS. Injector temperature was 330 °C. The column temperature and retention times are as indicated in each experimental.
Preparative vapor-phase chromatographic separations were performed on a Varian 920 gas chromatograph, equipped with a thermal-conductivity detector (230 °C) and using helium carrier gas at a flow rate of 60 mL/min. The column size was 6 ft × 0.25 in. and was packed with 10% SE-30 absorbed on 60–80-mesh Chromosorb W AW DMCS. The injector temperature was 230 °C. The column temperature and retention times are as indicated for each experiment.
"Dry" solvents were distilled shortly before use from an appropriate drying agent. Ether and tetrahydrofuran (THF) were distilled under argon from sodium metal in the presence of benzophenone. Benzene and pyridine were distilled from powdered calcium hydride. Dichloromethane was distilled from phosphorus pentoxide. Hexamethylphosphoramide (HMPA) was distilled at 1.0 mmHg from powdered calcium hydride and stored over 4-Å molecular sieves. Diisopropylamine was distilled under argon from sodium metal.
Lithium diisopropylamide (LDA) was prepared by adding a titrated hexane solution of *n*-butyllithium to a mixture of diisopropylamine in THF at 0 °C under argon and stirring the mixture for 5 min.
All other reactants and solvents were "reagent grade" unless described otherwise. "Ether" refers to anhydrous diethyl ether which is supplied by Mallinckrodt. "Petroleum ether" refers to the "analyzed reagent" grade hydrocarbon fraction, bp 35–60 °C, which is supplied by J. T. Baker Co., Phillipsburg, NJ, and was not further purified.
Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.
(13) (a) Tebbe, F. N.; Parshall, G. W.; Ready, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.
(14) Prepared as described in ref 7. The data (IR, NMR) for alcohol **2** was identical in all respects to those given.
(15) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

Scheme II. Ester Enolate Claisen Rearrangement of (5-*tert*-Butyl-1-cyclohexenyl)methyl Propionate (9)[a]



[a] (a), LDA, THF, −78 °C; TBSCl, HMPA; 50 °C; H_3O^+; (b) CH_2N_2, Et_2O; (c) LDA, 23% HMPA/THF, −78 °C; TBSCl; 50 °C; H_3O^+.

While rearrangement still occurs so as to attach the side chain predominately in the axial orientation, there is an interesting effect that results from the terminal methyl substituent on the vinyl ether portion of the molecule. Now, two geometrically isomeric enolates are possible. On the basis of prior results from these laboratories,[9] it is expected that enolization of the ester **9** in pure THF and then silylation would lead to the ketene acetal **8** (predominately), while the use of 23% HMPA–THF as the solvent for enolization will ultimately result in the ketene acetal **10** (predominately). For the *Z* form **10** of the ketene acetal, the CHAIR (axial) T* orientation seems to be favored, as the product ratio favors the ester **11** quite significantly. For the *E* form **8** of the ketene acetal, the steric congestion in the transition states is not nearly as obvious, and now equatorial attachment of the side chain competes significantly. For *either* the CHAIR T* or the BOAT T* conformation for the axial approach, this (*E*)-ketene acetal isomer **8** will require that a bulky vinyl substituent be buried in the cyclohexene ring (C2 CH_3 in the CHAIR T* and C1 OTBS in the BOAT T*). While similar destabilization is apparent in both the chair and boat transition states for equatorial attack, the overall effect must result in the narrowing of the energy difference between axial and equatorial attack so that more trans (equatorial) product is formed. The steric effects are also manifest in the ratio of the isomers at C2 in the cis (axial) products **11**. Independent ^1H NMR analysis indicates a virtual 1:1 ratio of the *R** and *S** isomers at C2 of the esters **11**; this is apparent from the two methyl doublets at 1.03 and 1.13 ppm and probably reflects a lack of preference for the energetically nearly equal CHAIR T* and BOAT T* conformations.

Thus, while axial attachment of the side chain by Claisen rearrangement is preferred in these cyclohexenylmethanol systems, relatively minor substitution of the vinyl ether portion of the molecule can significantly alter this generalization.

Experimental Section[12]

(5′-*tert*-Butyl-1′-cyclohexenyl)methyl Propionate (9). To a rapidly stirred solution of 1.53 g (9.1 mmol) of allylic alcohol **2**[7,14] in 50 mL of dry dichloromethane at 0 °C under an argon atmosphere was added 0.81 mL (10.0 mmol) of pyridine and 0.87 mL (10.0 mmol) of propionyl chloride. After 2 h, the reaction mixture was allowed to warm to room temperature. After an additional hour, the reaction mixture was poured into 200 mL of saturated $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL portions), 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 (200 g) with 1:50 ether/petroleum ether. In this manner, there was obtained 1.85 g (91%) of the desired ester as a colorless oil: IR ($CHCl_3$) 2970, 1750 (C=O), 1375, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.70 (br s, 1 H), 4.44 (br s, 2 H, OCH_2), 2.35 (q, 2 H, J = 8 Hz, O=$CHCH_2$), 1.3–2.2 (m, 7 H), 1.13 (t, 3 H, J = 8 Hz, CH_3), 0.88 (s, 9 H, $C(CH_3)_3$). Distillation [Kugelrohr, 70 °C (0.1 mmHg)] of this oil provided an analytical sample. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.04; H, 10.69.

(5′-*tert*-Butyl-1′-cyclohexyl)methyl Buten-2-yl Ether (1). According to the procedure of Grubbs et al.,[13b] 303 mg (1.34 mmol) of the above propionate ester **9** in 3 mL of THF was cooled to −40 °C under an argon atmosphere. To this mixture there was added 4.5 mL (1.48 mmol) of a 0.33 M solution of the "Tebbe"[13a] reagent in toluene over a 3-min period. After 1 h, the reaction mixture was allowed to warm to room temperature and stirred an additional 1.5 h. The reaction was quenched with 0.5 mL of 10% NaOH. After dilution with 100 mL of ether, the mixture was dried (Na_2SO_4) and then filtered through a pad of Celite. After removal of the solvent at reduced pressure, the crude residue was filtered through alumina (activity III, 30 g) with hexane. In this manner, there was obtained 257 mg (86%) of the desired enol ether as a colorless oil: IR ($CHCl_3$) 2975, 1650, 1610, 1470, 1365 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.72 (br s, 1 H, C=CHC), 4.05 (br s, 2 H, H_2C=C), 3.82 (br s, 2 H, CH_2O), 1.0–2.35 (m, 12 H), 0.88 (s, 9 H, $(CH_3)_3C$). Distillation [Kugelrohr, 60 °C (0.1 mmHg)] of this oil provided an analytical sample. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.16; H, 11.61.

2-Methylene-1-(2-oxobutyl)-4-*tert*-butylcyclohexane (4). According to the procedure of Ireland and Marshall,[6] 102 mg (0.46 mmol) of the enol ether **1** was sealed in a glass tube coated with dry KOH and heated at 142 °C for 6 h. After cooling, the crude product was diluted with ether and then dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (10 g) with 12:1 petroleum ether/ether. In this manner, there was obtained 79.2 mg (78%) of a mixture of the two diastereomeric ketones in a ratio of 87:13 (by analytical VPC) with retention times of 9.21 and 11.83 min.,

respectively, at a column temperature of 142 °C. Distillation [Kugelrohr, 70 °C (0.1 mmHg)] of this mixture provided an analytical sample. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.95; H, 11.68.

A portion of this mixture was separated via preparative VPC (column temperature 160 °C) to give pure samples of the two diastereomeric ketones for 500-MHz ^1H NMR analysis. For the major diastereomer **4** (retention time 24 min): IR ($CHCl_3$) 2980, 1715 (C=O), 1654 (C=C) cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.86 (s, 9 H, $(CH_3)_3$), 1.02 (t, 3 H, J = 7 Hz, CH_3), 1.09 (dddd, 1 H, J = 12, 12, 3.5, 5.0 Hz, H-6_{ax}), 1.21 (dddd, 1 H, J = 12, 12, 12, 3.5 Hz, H-5_{ax}), 1.54 (dddd, 1 H, J = 12, 12, 3.5, 3.5 Hz, H-4), 1.60 (ddd, 1 H, J = 12, 3.5, 3.5 Hz, H-6_{eq}), 1.69 (dddd, 1 H, J = 12, 3.5, 3.5, 3.5 Hz, H-5_{eq}), 1.85 (dd, 1 H, J = 12, 12 Hz, H-3_{ax}), 2.9 (ddd, 1 H, J = 12, 3, 3 Hz, H-3_{eq}), 2.40 (dq, 2 H, J = 2, 7 Hz, CH_2CH_3), 2.47 (dd, 1 H, J = 7.5, 15 Hz, HCHC=O), 2.54 (dd, 1 H, J = 7.5, 15 Hz, HCHC=O), 2.89 (dt, J = 5, 7.5 Hz, H-1_{eq}), 4.61 (s, 1 H, C=CH), 4.68 (s, 1 H, C=CH). For the minor diastereomer (retention time 27 min): IR ($CHCl_3$) 2980, 1730 (C=O), 1654 (C=C) cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.86 (s, 9 H, $(CH_3)_3C$), 0.95 (dddd, 1 H, J = 12, 12, 12, 3.5 Hz, H-6_{ax}), 1.06 (t, 3 H, J = 7.5 Hz, CH_3), 1.10 (dddd, 1 H, J = 12, 12, 3.5, 3.5 Hz, H-4_{ax}), 1.23 (dddd, 1 H, J = 12, 12, 12, 3.5 H-5_{ax}), 1.79 (m, 2 H, H-3_{ax}, H-5_{eq}), 1.85 (dddd, 1 H, J = 12, 3.5, 3.5, 3.5 Hz, H-6_{eq}), 2.34 (dd, 1 H, J = 7.5, 16 Hz, HCHC=O), 2.38 (m, 2 H, CH_2C=O), 2.46 (m, 2 H, H-3_{eq}, H-1_{ax}), 2.70 (dd, 1 H, J = 16, 5.5 Hz, HCHC=O), 4.39 (s, 1 H, C=CH), 4.66 (s, 1 H, C=CH).

As a control experiment, pure cis (axial) **4** was resubjected to the reaction conditions, and the material was recovered unchanged (analytical VPC).

(5′-*tert*-Butyl-1′-cyclohexenyl)methyl Acetate (3). To a rapidly stirred solution of 508 mg (3.0 mmol) of the allylic alcohol **2** in 20 mL of dry dichloromethane at 0 °C under an argon atmosphere was added 0.3 mL (3.6 mmol) of dry pyridine and 0.25 mL (3.6 mmol) of acetyl chloride. After 1 h, the reaction mixture was allowed to warm to room temperature, and after an additional hour, the reaction mixture was poured into 100 mL of saturated $NaHCO_3$, and the aqueous layer was extracted with ether (2 × 100 mL portions). 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 (50 g) with 99:1 petroleum ether/ether. In this manner, there was obtained 447 mg (76%) of the desired ester as a colorless oil: IR ($CHCl_3$) 2950, 1720, 1360, 945 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.70 (br s, 1 H, HC=CC), 4.44 (br s, 2 H, CH_2O), 2.04 (s, 3 H, CH_3C=O), 1.0–1.9 (m, 7 H), 0.88 (s, 9 H). Distillation [Kugelrohr, 55 °C (0.1 mmHg)] of this oil provided an analytical sample. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.01; H, 10.41.

Ethyl (4-*tert*-Butyl-2-methylenecyclohexyl)acetate (5). According to the procedure of Johnson and Faulkner,[8] a solution of 56.8 mg (0.33 mmol) of the allylic alcohol **2**[7] and triethyl orthoacetate containing 20 mg (0.16 mmol) of hexanoic acid was heated at 166 °C under an argon atmosphere. After 44 h, the excess orthoacetate was removed at reduced pressure. The crude residue was chromatographed on silica gel (10 g) with 99:1 petroleum ether/ether. In this manner, there was obtained 55 mg (68%) of a mixture of the two diastereomeric esters in a ratio of 91:9 (by analytical VPC) with retention times of 10.19 and 12.58 min, respectively, at a column temperature of 150 °C. Distillation [Kugelrohr, 70 °C (0.1 mmHg)] of this mixture provided an analytical sample. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.79; H, 10.88.

A portion of this mixture was separated via preparative VPC (column temperature 160 °C) to give pure samples of each diastereomeric ester suitable for 500-MHz ^1H NMR analysis. For the major diastereomer **5** (retention time 16 min): IR ($CHCl_3$) 2960, 1725 (C=O), 1648 (C=C) cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.87 (s, 9 H, $(CH_3)_3C$), 1.09 (dddd, 1 H, J = 12, 12, 3.5, 5.0 Hz, H-6_{ax}), 1.24 (t, 3 H, J = 7.5 Hz, CH_3), 1.23 (m, 1 H, H-5_{ax}), 1.56 (dddd, 1 H, J = 12, 12, 3.5, 5 Hz, H-4_{ax}), 1.60 (m, 1 H, H-6_{eq}), 1.74 (dm, 1 H, J = 12 Hz, H-5_{eq}), 1.87 (dd, 1 H, J = 12, 12 Hz, H-3_{ax}), 2.19 (dd, 1 H, J = 12, 3.5 Hz, H-3_{eq}), 2.40 (dd, 1 H, J = 7, 14 Hz, HCHC=O), 2.45 (dd, 1 H, J = 7, 14 Hz, HCHC=O), 2.86 (dt, 1 H, J = 5, 7 Hz, H-1_{eq}), 4.11 (q, 2 H, J = 7 Hz, OCH_2), 4.64 (s, 1 H, C=CH), 4.71 (s, 1 H, C=CH). For the minor diastereomer (retention time 19 min): IR ($CHCl_3$) 2970, 1730 (C=O), 1645 (C=C) cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.86 (s, 9 H, $(CH_3)_3C$), 1.01 (dddd, 1 H, J = 12, 12, 12, 3.5 Hz, H-6_{ax}), 1.11 (dddd, 1 H, J = 12, 12, 3.5, 3.5 Hz, H-4_{ax}), 1.23 (dddd, 1 H, J = 12, 12, 3.5, 3.5 Hz, H-5_{ax}), 1.26 (t, 3 H, J = 7 Hz, CH_3), 1.78 (dd, 1 H, J = 12, 12 Hz, H-3_{ax}), 1.82 (dddd, 1 H, J = 12, 3.5, 3.5, 3.5 Hz, H-5_{eq}), 1.91 (dddd, 1 H, J = 12, 3.5, 3.5, 3.5 Hz, H-6_{eq}), 2.24 (dd, 1 H, J = 15, 7.5 Hz, HCHC=O), 2.38 (m, 2 H, H-1, H-3_{eq}), 2.60 (dd, 1 H, J = 15, 6 Hz, HCHC=O), 4.14 (dq, 2 H, J = 7, 2.5 Hz, OCH_2CH_3), 4.47 (s, 1 H, C=CH), 4.68 (s, 1 H, C=CH).

Methyl (4-*tert*-Butyl-2-methylenecyclohexyl)acetate (6). According to the procedure of Ireland and Willard,[9] a solution of 100 mg (0.47 mmol) of the acetate **3** and 1 mL of THF was added dropwise via a cannula to 3.5 mL (0.79 mmol) of a 0.23 M solution of LDA in THF at −78 °C under an argon atmosphere. After the mixture was stirred for 5 min, a solution of 127 mg (0.84 mmol) of *tert*-butyldimethylsilyl chloride in 1 mL of THF was added all at once. The solution was allowed to warm to room temperature and was then heated at 60 °C for 4 h. After dilution with 50 mL of water, the mixture was separated, the aqueous layer was extracted with pentane (3 × 75 mL portions), and then the combined organic extracts were dried (Na_2SO_4). After removal of the solvent at reduced pressure, the crude residue was dissolved in 3 mL of THF, and to this solution there was added 0.5 mL of 5% HCl. The resulting mixture was stirred at room temperature for 45 min and then diluted with 200 mL of 10% NaOH. After extraction with 50 mL of ether, the aqueous layer was acidified with concentrated HCl and then extracted with ether (3 × 100 mL portions). The combined organic layers were dried ($MgSO_4$) and filtered. After removal of the solvent at reduced pressure, the crude residue was esterified with excess ethereal diazomethane. The esters were chromatographed on silica gel (10 g) with 99:1 petroleum ether/ether. In this manner, there was obtained 54 mg (51%) of a mixture of the two diastereomeric esters in a ratio of 91:9 (by analytical VPC) with retention times of 8.28 and 10.40 min, respectively, at a column temperature of 140 °C. Distillation [Kugelrohr, 60 °C (0.1 mmHg)] of this mixture provided an analytical sample. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.96; H, 10.73.

A portion of this mixture was separated via preparative VPC (column temperature 149 °C) to give pure samples of each diastereomeric ester suitable for 500-MHz ^1H NMR analysis. For the major diastereomer **6** (retention time 16 min): IR ($CHCl_3$) 2960, 1730 (C=O), 1645 (C=C), 910 cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.87 (s, 9 H, $(CH_3)_3C$), 1.09 (dddd, 1 H, J = 12, 12, 3.5, 3.5 Hz, H-6_{ax}), 1.23 (dddd, 1 H, J = 12, 12, 12, 4 Hz, H-5_{ax}), 1.57 (dddd, 1 H, J = 12, 12, 5, 5 Hz, H-4_{ax}), 1.60 (m, 1 H, H-6_{eq}), 1.73 (dm, 1 H, J = 12 Hz, H-5_{eq}), 1.86 (dd, 1 H, J = 12, 12 Hz, H-3_{ax}), 2.19 (dd, 1 H, J = 12, 3.5 Hz, H-3_{eq}), 2.42 (dd, 1 H, J = 7.5, 14 Hz, HCHC=O), 2.46 (dd, 1 H, J = 7.5, 14 Hz, HCHC=O), 2.85 (dt, 1 H, J = 5, 7.5 Hz, H-1_{eq}), 3.65 (s, 3 H, OCH_3), 4.64 (s, 1 H, C=CH_2), 4.71 (s, 1 H, C=CH_2). For the minor diastereomer (retention time 18 min): IR ($CHCl_3$) 2980, 1730 (C=O), 1645 (C=D), 930 cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.86 (s, 9 H, $(CH_3)_3C$), 1.01 (dddd, 1 H, J = 12, 12, 3.5, 3.5 Hz, H-6_{ax}), 1.11 (dddd, 1 H, J = 12, 12, 3.5, 3.5 Hz, H-4_{ax}), 1.23 (dddd, 1 H, J = 12, 12, 3.5, 3.5 Hz, H-5_{ax}), 1.78 (dd, 1 H, J = 12, 12 Hz, H-3_{ax}), 1.82 (m, 1 H, H-5_{eq}), 1.91 (dddd, 1 H, J = 12, 3.5, 3.5, 3.5 Hz, H-6_{eq}), 2.26 (dd, 1 H, J = 7.5, 15 Hz, HCHC=O), 2.39 (m, 2 H, H-6_{eq}, H-3_{eq}), 2.62 (dd, 1 H, J = 5.5, 15 Hz, HCHC=O), 3.67 (s, 3 H, OCH_3), 4.47 (s, 1 H, C=CH), 4.68 (s, 1 H, C=CH).

Methyl Methyl(4-*tert*-butyl-2-methylenecyclohexyl)-acetates (11 and 12). According to the procedure of Ireland and Willard,[9] a solution of 250 mg (1.1 mmol) of the propionate ester **9** and 2 mL of THF was added dropwise via a cannula to 4.7 mL (1.3 mmol) of a 0.28 M solution of LDA in 4:1 THF/HMPA at −78 °C under an argon atmosphere. After the mixture was stirred for 10 min, a solution of 202 mg (1.3 mmol) of *tert*-butyldimethylsilyl chloride in 2 mL of THF was added all at once. After the solution was stirred for an additional 5 min, it was allowed to warm to room temperature and then heated at 50 °C for 2 h. The mixture was then diluted with 200 mL of pentane and washed once with ice water (50 mL). After removal of the solvent at reduced pressure, the crude residue was dissolved in 5 mL of THF, and to this solution there was added 1 mL of 1 N HCl. The resulting mixture was stirred at room temperature for 45 min and then diluted with 50 mL of 1 N NaOH. After extraction with

pentane (50 mL), the aqueous layer was acidified with 6 N HCl and then extracted with ether (3 × 100 mL portions). The combined organic layers were dried ($MgSO_4$) and filtered. After removal of the solvent at reduced pressure, the crude residue was esterified with excess ethereal diazomethane. The esters were chromatographed on silica gel (20 g) with 98:2 petroleum ether/ether. In this manner, there was obtained 164 mg (62%) of a mixture of the diastereomeric esters **11** and **12** in a ratio of 87:13 (by analytical VPC) with retention times of 7.65 and 10.64 min, respectively, at a column temperature of 150 °C. Distillation [Kugelrohr, 70 °C (0.1 mmHg)] of this mixture provided an analytical sample. Anal. Calcd for $C_{15}H_{28}O_2$: C, 75.58; H, 10.99. Found: C, 75.41; H, 10.89.

A portion of this mixture was separated via preparative VPC (column temperature 156 °C) to give pure samples of the esters **11** and **12** suitable for 500-MHz ^1H NMR analysis. For the major diastereomer **11** (retention time 17 min): IR ($CHCl_3$) 2970, 1730 (C═O), 1650 (C═C) cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.86 (s, 9 H, $(CH_3)_3C$), 1.09 (m, 2 H, H-5 and H-6_{ax}), 1.13 (d, 3 H, J = 7.5 Hz, CH_3), 1.44 (dddd, 1 H, J = 12, 12, 3.5, 3.5 Hz, H-4_{ax}), 1.58 (m, 1 H, H-5_{eq}), 1.92 (m, 2 H, H-6_{eq} and H-3_{ax}), 2.18 (dd, 1 H, J = 12, 3.5 Hz, H-3_{eq}), 2.36 (dd, 1 H, J = 11, 5 Hz, H-1_{eq}), 2.73 (dq, 1 H, J = 11, 7.5 Hz), 3.58 (s, 3 H, OCH_3), 4.59 (t, 1 H, J = 1 Hz, C═CH_2), 4.62 (t, 1 H, J = 1 Hz, C═CH_2). For the minor diastereomer **12** (retention time 21 min): IR ($CHCl_3$) 2960, 1730 (C═O), 1645 (C═C) cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.86 (s, 9 H, $(CH_3)_3C$), 0.99 (dddd, 1 H, J = 12, 12, 12, 3.5 Hz, H-6_{ax}), 1.11 (dddd, 1 H, J = 12, 12, 3.5, 3.5 Hz, H-4_{ax}), 1.18 (d, 3 H, J = 7 Hz, CH_3), 1.78 (dd, 1 H, J = 12, 12 Hz, H-3_{ax}), 1.86 (dm, 1 H, J = 12 Hz, H-5_{eq}), 1.94 (dddd, 1 H, J = 12, 3.5, 3.5, 3.5 Hz, H-6_{eq}), 2.28 (m, 1 H, H-6_{eq}), 2.35 (ddd, 1 H, J = 12, 3.5, 3 Hz, H-3_{eq}), 2.70 (dq, 1 H, J = 7.5, 7.5 Hz, HCC═O), 3.67 (s, 3 H, OCH_3), 4.53 (s, 1 H, C═CH_2), 4.54 (s, 0.25 H, C═CH_2), 4.70 (s, 1 H, C═CH_2), 4.77 (s, 0.25 H, C═CH_2). This is a 4:1 mixture (determined by NMR) of the R^* and S^* isomers at the C-2 methyl center.

Methyl Methyl(4-*tert*-butyl-2-methylenecyclohexyl)-acetates (11 and 12). Enolization without HMPA. According to the procedure of Ireland and Willard,[9] a solution of 250 mg (1.1 mmol) of the propionate ester **9** and 2 mL of THF was added dropwise via a cannula to 4.7 mL (1.3 mmol) of a 0.28 M solution of LDA in THF at −78 °C under an argon atmosphere. After the mixture was stirred for 10 min, a solution of 202 mg (1.3 mmol) of *tert*-butyldimethylsilyl chloride in 3 mL THF containing 1.0 mL of HMPA was added all at once. After the solution was stirred for an additional 5 min, it was allowed to warm to room temperature and then heated at 50 °C for 2 h. The mixture was then diluted with 200 mL of pentane and washed once with ice–water (50 mL). After removal of the solvent at reduced pressure, the crude residue was dissolved in 5 mL of THF, and to this solution there was added 1 mL of 1 N HCl. The resulting mixture was stirred at room temperature for 45 min and then diluted with 50 mL of 1 N NaOH. After extraction with pentane (50 mL), the aqueous layer was acidified with 6 N HCl and then extracted with ether (3 × 100 mL portions). The combined organic layers were dried ($MgSO_4$) and filtered. After removal of the solvent at reduced pressure, the crude residue was esterified with excess ethereal diazomethane. The esters were chromatographed on silica gel (20 g) with 98:2 petroleum ether/ether. In this manner, there was obtained 177 mg (67%) of a mixture of the diastereomeric esters **11** and **12** in a ratio of 71:29 (by analytical VPC) with retention times of 7.68 and 10.01 min, respectively, at a column temperature of 150 °C.

A portion of this mixture was separated via preparative VPC (column temperature 156 °C) to give pure samples of the esters **11** and **12** suitable for 500-MHz ^1H NMR analysis. For the major diastereomers **11** (retention time 17 min): IR ($CHCl_3$) 2970, 1730 (C═O), 1650 (C═C) cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.86 (s, 9 H, $(CH_3)_3C$), 1.03 (d, 3 H, J = 7.5 Hz, CH_3), 1.11 (m, 2 H, H-5 and H-6_{ax}), 1.13 (d, 3 H, J = 7.5 Hz, CH_3), 1.30 (dddd, 1 H, J = 12, 12, 12, 3.5 Hz, H-5_{ax}), 1.47 (m, 2 H, H-4_{ax}), 1.66 (m, 2 H, H-3_{ax}), 1.96 (m, 2 H, H-6_{eq}), 2.18 (dd, 2 H, J = 12, 3.5 Hz, H-3_{eq}), 2.36 (dd, 1 H, J = 11, 5 Hz, H-1_{eq}), 2.39 (dd, 1 H, J = 11, 5 Hz, H-1_{eq}), 2.67 (dq, 1 H, J = 11, 7.5 Hz, CHC═O), 2.73 (dq, 1 H, J = 11, 7.5 Hz, CHC═O), 3.59 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 4.59 (s, 1 H, C═CH_2), 4.62 (s, 1 H, C═CH_2), 4.71 (s, 1 H, C═CH_2), 4.75 (s, 1 H, C═CH_2). This is a 1:1 mixture (determined by NMR) of the R^* and S^* epimers at the C-2 center adjacent to the ester function. For the minor diastereomer **12** (retention time 21 min): IR ($CHCl_3$) 2970, 1730 (C═O), 1645 (C═C) cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.86 (s, 9 H, $(CH_3)_3C$), 1.15 (m, 2 H, H-5, H-6_{ax}), 1.24 (d, 3 H, J = 7.5 Hz, CH_3), 1.73 (dd, 1 H, J = 12, 12 Hz, H-3_{ax}), 1.76 (m, 1 H, H-6_{eq}), 1.81 (m, 1 H, H-5_{eq}), 2.05 (ddd, 1 H, J = 7.5, 11, 3.5 Hz, H-1_{ax}), 2.36 (dd, 1 H, J = 12, 3.5 Hz, H-3_{eq}), 2.69 (dq, 1 H, J = 7.5, 7.5 Hz, CHC═O), 3.67 (s, 3 H, OCH_3), 4.54 (s, 1 H, C═CH_2), 4.77 (s, 1 H, C═CH_2).

Registry No. **1**, 85304-90-1; **2**, 62222-99-5; **3**, 85304-91-2; *cis*-**4**, 85304-92-3; *trans*-**4**, 85304-93-4; *cis*-**5**, 85304-94-5; *trans*-**5**, 85304-95-6; *cis*-**6**, 85304-96-7; *trans*-**6**, 85304-97-8; **8**, 85304-98-9; **9**, 85304-99-0; **10**, 85305-00-6; **11** (isomer 1), 85305-01-7; **11** (isomer 2), 85353-64-6; **12** (isomer 1), 85353-65-7; **12** (isomer 2), 85353-66-8; *t*-$BuMe_2SiCl$, 18162-48-6.

APPENDIX

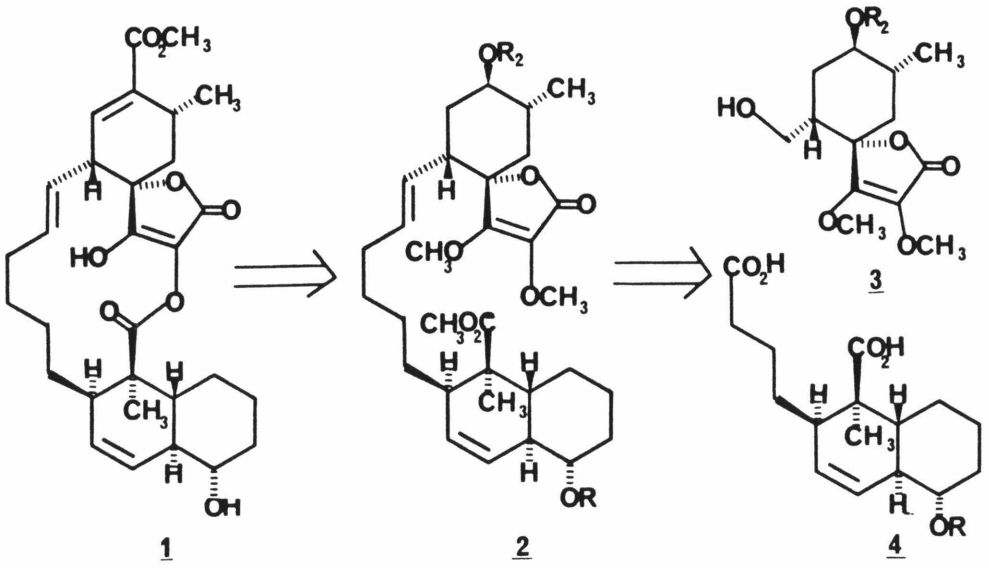
Keto Phosphonate Approach to Chlorothricolide

Appendix

Attempted connection of the two halves of chlorothricolide (1) via a Keto-phosphonate olefination.

In previous reports,[1] a strategy for the synthesis of chlorotricolide (**1**) was presented (Scheme I). Central to this scheme was the joining of two nearly equal halves along the C12-C17 side-chain followed finally by lactone formation. Herein are described the results of an investigation in which connection of the two halves was studied via condensation of the keto-phosphonate **6** and the aldehyde **9** followed by attempted deoxygenation.

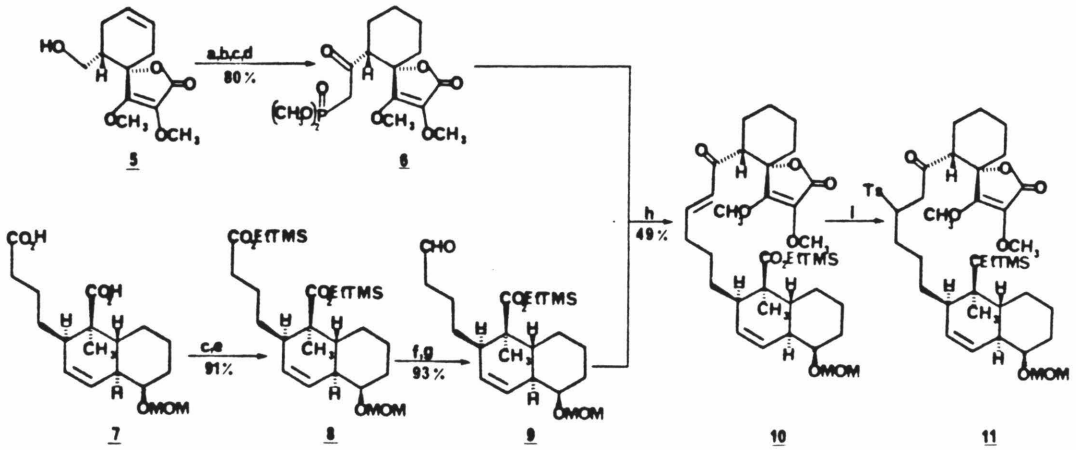
Scheme I Retrosynthetic Analysis



The keto-phosphonate **6** was prepared from the previously reported[1a] alcohol **5** by palladium catalyzed hydrogenation of the double bond followed by oxidation, acid chloride formation, and addition of the lithium anion of dimethyl methylphosphonate.[2]

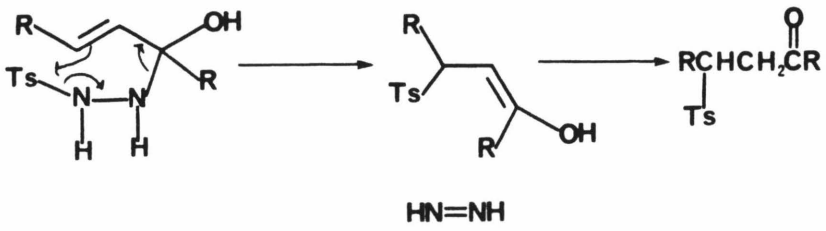
Appropriate functionalization of the previously[1b] "bottom half" diacid **7** was accomplished by acid chloride formation followed by addition of lithium 2-trimethylsilyl ethanoate to yield the diester **8** in 91% yield. Selective lithium triethylborohydride[3] reduction of the side-chain ester and subsequent oxidation afforded the aldehyde **9** in 93% yield.

Scheme II Condensation of 8 and 9



(a) H_2 1 atm, 5% Pd/ C, CH_3OH; (b) Jones Reagent acetone; (c) $ClCOCOCl$, PhH, DMF; (d) $(CH_3O)_2POCH_2Li$, THF, -78°C; (e) $LiOCH_2CH_2Si(CH_3)_3$, THF, 0°C; (f) $Li(C_2H_5)_3BH$, THF; (g) PCC, CH_2Cl_2; (h) K_2CO_3, $PhCH_3$, 18-Crown-6, 70°C; (i) CH_3OH, $TsNHNH_2$, 25°C.

Condensation of the Keto-phosphonate **6** and the aldehyde **9** was performed as described by Aristoff[4] to provide the α,β-unsaturated Ketone **10** in 49% yield. Deoxygenation of the ketone with concomitant double bond migration was to proceed as described by Kabalka[5] through the intermediate tosylhydrazone. However, as shown in Scheme II, attempted tosylhydrazoneformation led instead to formation of the Keto-tosylate **11**. Such reaction pathways are rare for α,β-unsaturated ketones but nonetheless are precedented[6] and are believed to proceed by the mechanism shown below. Because of this result, the route was abandoned.



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.

2-Oxo-3,4-dimethoxy-10α-(hydroxymethyl)-1α-oxaspiro[4.5]deca-3-ene. A solution of 491 mg (2.04 mmol) of 2-Oxo-3,4-dimethoxy-10α-(hydroxymethyl)-1α-spiro[4.5]deca-3,7-diene[1a] and 15 mg of 5% palladium on carbon in 30 ml of dry methanol was stirred under 1 atmosphere of hydrogen at room temperature for 2 h. The mixture was then filtered through celite and after removal

of the solvent at reduced pressure, the product crystallized: mp 123-123.5°C; IR ($CHCl_3$) 3660, 3510, 2970, 1760, 1680, 1470, 1355, 1150, 1110, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.34 (m, 2H), 3.73 (s, 3H), 4.05 (s, 3H).

Anal. Calcd for $C_{12}H_{15}O_5$: C, 59.49; H, 7.49. Found: C, 59.43; H, 7.39.

2-Oxo-3,4-dimethoxy-10α-(dimethyl phosphonoacetyl)-1α-oxaspiro[4.5]deca-3-ene (6). To a solution of 230 mg (0.95 mmol) of the above alcohol in 5 ml of dry acetone at room temperature was added 0.95 ml (1.89 mmol) of Jones reagent over a 30 min period. The mixture was then poured into 50 ml of 10% sodium acetate solution and extracted once with 30 ml of ether. The aqeuous layer was then acidified to pH 2 with concentrated HCl and extracted with ethyl acetate (3 x 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 (20 g) with acetone-petroleum ether (2:3). In this manner there was obtained 232 mg (95%) of the desired carboxylic acid as white crystals: mp 134-135°C; IR 3500-2500, 3020, 2970, 1770, 1720, 1690, 1470, 1350, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.73 (t, 1H, J=8 Hz), 3.75 (s, 3H), 4.12 (s, 3H), 6.14 (brs, 1H). This material was used directly in the next step.

To a solution of 136 mg (0.53 mmol) of the above acid

in 7 ml of benzene was added 0.3 ml of a 0.1 M solution of N,N-dimethylformamide in benezene and 115 μl (1.32 mmol) of oxalyl chloride. After 2 h, the solvent was removed at reduced pressure. In a separate flask, to a solution of 197 mg (1.59 mmol) of dimethyl methylphosphonate in 10 ml of THF at -78°C was added 0.95 ml (1.43 mmol) of a 1.50 M solution of n-butyllithium in hexane. After 5 min, a solution of the above acid chloride in 5 ml of THF was added via a cannula over 3 min period. After 4 min, 0.2 ml of acetic acid was added and the mixture was poured into 50 ml of water and the aqueous layer was extracted with ethyl acetate (3 x 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-acetone (2:4:4). In this manner, there was obtained 164 mg (86%) of the Ketophosphonate **6** as a colorless oil: IR ($CHCl_3$) 3450, 3030, 2980, 1770, 1725, 1685, 1470, 1350, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.05 (dd, 2H, J=22,8 Hz), 3.68 (s, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 4.11 (s, 3H).

Anal. Calcd for $C_{15}H_{23}O_3P$: C, 49.73; H, 6.40. Found: C, 49.65; H, 6.40.

2-(Trimethylsilyl)ethyl-[4-[1α-methyl-1β-(carbotrimethylsilylethyloxy)-5β-(methoxymethoxy)-1,2,4aα,5,6,7,8,8aβ-octahydronaphththyl]]butyrate (8). To

a solution of 200 mg (0.59 mmol) of the acid 7[1b] in 8 ml of benzene at room temperature was added 0.1 ml of a 0.1 M solution of N,N-dimethylformamide in benzene and 0.26 ml (2.94 mmol) of oxalyl chloride. After 4 h, the solvent was removed at reduced pressure and 2 ml of benzene was added and again removed under reduced pressure. The crude residue was put under vacuum (2 mmHg) for 30 min. In a separate flask, to a solution of 416 mg (3.52 mmol) of 2-(trimethylsilyl)ethanol in 5 ml of THF at -78°C was added 1.3 ml (2.94 mmol) of a 2.24 M solution of n-butyllithium in hexane. After 1 min, to this solution was added the above diacid chloride in 4 ml of THF. After 30 min, the solution was allowed to warm to 0°C and after 45 min was quenched with 2 ml of saturated $NaHCO_3$ and the mixture was poured into 30 ml of water. The aqueous layer was extracted with ether (3 x 100 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 (30 g) with ether-petroleum ether (15:85). In this manner there was obtained 290 mg (91%) of the diester as a colorless oil. This material was identical to that prepared earlier by Rolf Etter.

4-[1α-Methyl-1β-(carbotrimethylsilylethoxy)-5β-(methoxymethoxy)-1,2,4aα,5,6,7,8,8aβ-octahydronaphthyl]-butanol. To a solution of 50 mg (92.4 mol) of the

diester **8** in 0.6 ml of 1,2-dimethoxyethane at -50°C was added 0.23 ml (0.23 mmol) of a 1 M solution of lithium triethylborohydride in THF over a 3 min period. After 5 min, the mixture was allowed to warm to room temperature. After 1 h, the reaction was quenched with 0.5 ml of a pH 8 NH_3/NH_4Cl buffer and the reaction mixture was poured into 20 ml of water. The aqueous layer was extracted with ether (3 x 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 (10 g) with ethyl acetate-petroleum ether (35:65). In this manner, there was obtained 39 mg (99%) of the desired alcohol as a colorless oil: IR ($CHCl_3$) 3620, 3500, 2960, 1720, 1260, 1050, 870, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H), 1.14 (s, 3H), 3.33 (s, 3H), 3.60 (m, 2H), 3.89 (m, 1H), 4.24 (t, 2H, J=8 Hz), 4.52 and 4.65 (AB system, 2H, J=7 Hz), 5.47 (d, 1H, J=10 Hz), 5.70 (dm, 1H, J=10 Hz).

Anal. Calcd for $C_{23}H_{42}O_5Si$: C, 64.75; H, 9.92. Found: C, 64.86; H, 9.88.

4-[1α-Methyl-1β-(carbotrimethylsilylethoxy)-5β-(methoxymethoxy)-1,2,4aα,5,6,7,8,8aβ-octahydronaphthyl]butyraldehyde (9). To a solution of 43 mg (0.10 mmol) of the above alcohol in 1 ml of CH_2Cl_2 at room temperature was added 55 mg (0.25 mmol) of pyridinium chlorochromate. After 1.5 h, the mixture was

diluted with 10 ml of ether and decanted. The black precipitate was washed with three additional 10 ml portions of ether. After the solvent was removed at reduced pressure, the crude residue was chromatographed on silica gel (10 g) with ether. In this manner, there was obtained 40 mg (94%) of the desired aldehyde as a slightly yellow oil: IR ($CHCl_3$) 2980, 1725, 1465, 1260, 1050, 870, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H), 1.12 (s, 3H), 3.33 (s, 3H), 3.92 (m, 1H), 4.14 (t, 2H, J=8 Hz), 4.54 and 4.65 (AB system, 2H, J=7 Hz), 5.49 (d, 1H, J=10 Hz), 5.68 (dm, 1H, J=10 Hz), 9.74 (t, 1H, J=1.5 Hz).

Anal. Calcd for $C_{23}H_{40}O_5Si$; C, 65.05; H, 9.49. Found: C, 64.96; H, 9.51.

Condensation of the phosphonate 6 with the aldehyde 9 to form the enone 10. A solution containing 50 mg (118 μmol) of the aldehyde **9**, 47 mg (129 μmol) of the phosphonate **6**, 187 mg (706 μmol) of 18-crown-6 and 65 mg 471 μmol) of K_2CO_3 in 1.4 ml of toluene was heated at 70°C for 2.5 h. After cooling, the mixture was poured into 20 ml of brine and the aqueous layer was extracted with ether (3 x 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 6.7 mg (13%) of the

starting aldehyde and 38 mg (49%) of the trans enone **10** as a colorless oil: IR ($CHCl_3$) 2960, 1765, 1718, 1680, 1465, 1350, 1260, 1050, 870, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.05 (s, 9H), 1.10 (s, 3H), 2.80 (dd, 1H, J=11,4 Hz), 3.32 (s, 9H), 3.69 (s, 3H), 3.90 (m, 1H), 4.05 (s, 3H), 4.54 and 4.65 (AB system, 2H, J=7 Hz), 5.43(d, 1H, J=10 Hz), 5.64 (dm, 1H, J=10 Hz), 6.17 (d, 1H, J=16 Hz), 6.76 (ddd, 1H, J=16,7,7 Hz).

Formation of Ketotosylate 11. To a solution of 10 mg (15 μmol) of the enone **10** in 0.25 ml of dry methanol at room temperature was added 3.4 mg (18 μmol) of p-toluenesulfonyl hydrazine. After 16 h, the solvent was removed at reduced pressure and the crude residue was chromatographed on silica gel (10 g) with ethyl acetate-petroleum ether (3:7). In this manner, there was obtained 3.5 mg (28%) of the ketotosylate **11** as a colorless oil: IR ($CHCl_3$) 2960, 1765, 1720, 1680, 1350, 1260, 1160, 1050, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.06 (s, 9H), 2.43 (brs, 3H), 3.31 (s, 3H), 3.75 (s, 3H), 3.87 (m, 1H), 4.12 (s, 3H), 4.58 (m, 2H), 5.44 (m, 2H), 7.29 (d, 2H, J=9 Hz), 7.78 (d, 2H, J=9 Hz).

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