THE TOTAL SYNTHESIS OF MACROLIDE ANTIBIOTICS

Thesis by

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To my parents, my teachers and my wife, Shelley

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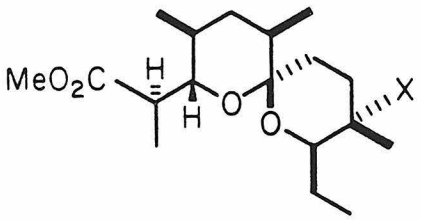
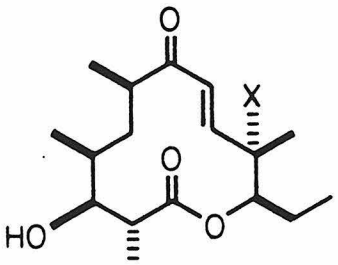
I wish to thank Professor Robert E. Ireland for his support and scientific guidance. I also wish to thank those members of the Ireland Group and the Evans Group who have contributed to my education. I am very grateful to Kathleen Flanagan and Gwen Anastasi for their time, patience, and skill in preparing this manuscript. Finally, I thank the National Science Foundation and the California Institute of Technology for financial support.

Abstract

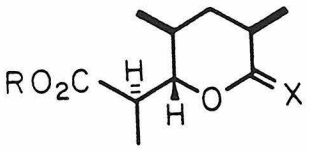
An approach to the total synthesis of macrolide antibiotics via the key spiroketal intermediates i and ii, which possess all of the stereochemistry for the macrolides 10-deoxymethynolide (iii) and methynolide (iv), is described. Initially, the exocyclic enol ether v, which through hetero-Diels-Alder condensation with an α,β-unsaturated carbonyl compound would lead to these spiroketals i and ii, was prepared stereoselectively in optically pure form from 4,6-O-benzylidene-D-allal and was converted into the Prelog-Djerassi lactone (vi) by way of stereochemical confirmation. The low reactivity of this sensitive enol ether v toward hetero-Diels-Alder condensation led to the development of a new, high yield spiroketal synthesis through hetero-Diels-Alder condensation of the keto-enol ether vii with hetero-dienes; and, in this manner, the spiroketals i and ii were prepared stereoselectively. Cleavage of these spiroketals i and ii by thioketal exchange with 1,2-ethanedithiol led to seco-acid derivatives for the synthesis of the macrolides iii and iv. Additionally, a formal total synthesis of the antibiotic methymycin is achieved.



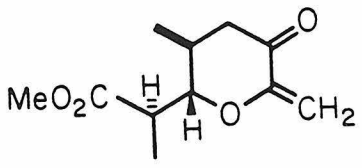
i, X=H
ii, X=OH



iii, X=H, 10-DEOXYMETHYNOLIDE
iv, X=OH, METHYNOLIDE



v, X=CH2, R=Me
vi, X=O, R=H



vii

TABLE OF CONTENTS

Chapter 1

The Prelog-Djerassi Lactone and Derivatives

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Synthesis of Chiral Subunits for Macrolide Synthesis: The Prelog–Djerassi Lactone and Derivatives[1]

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An approach to the total synthesis of macrolide antibiotics is described which involves hetero-Diels–Alder condensation between an exocyclic enol ether and an α,β-unsaturated carbonyl compound. Herein is described the synthesis of the desired exocyclic enol ether **14** in optically pure form from 4,6-*O*-benzylidene-D-allal (**1**). Verification of the assigned stereochemistry was achieved by conversion of this key intermediate into the Prelog–Djerassi lactone (**16**).

The Prelog–Djerassi lactone (**16**) was first isolated independently by Prelog[3] and Djerassi[4] as a degradation product of narbomycin and methymycin, respectively, and later isolated as a degradation product of neomethymycin[5] and picromycin.[6,7] The stereochemistry of this important degradation product was not completely elucidated until 1970 by Rickards and Smith.[8]

This lactone **16** has been a key feature of both the degradative work[3-8] that led to the structure elucidation of these macrolide antibiotics and subsequent synthetic efforts[9] that have culminated in the total synthesis of methymycin. As a result of the latter synthetic efforts several chiral, stereoselective syntheses of the Prelog–Djerassi lactone (**16**) are available and this molecule has become the stereochemical touchstone for syntheses in this field. As part of a similar synthetic effort recently initiated in these laboratories, the enol ether **14** (see Scheme I) was envisaged as a key intermediate for the synthesis of both macrolide antibiotics and subunits for ionophore antibiotics[10] wherein subsequent hetero-Diels–Alder condensations would lead to spiroketals[11] that possess the desired antibiotic carbon skeleton. An efficient procedure for the generation of such enol ethers is available in the carbohydrate literature,[12] which also provides an attractive chiral starting material for this synthesis in the glycal 4,6-*O*-benzylidene-D-allal (**1**).[13] Thus utilization of the stereoselection provided by the enolate Claisen rearrangement[14] allows the introduction of the C2-acid side chain. In addition the result of such a rearrangement is the incorporation in the pyran ring of the functionality necessary for the introduction of the two methyl groups. In the ultimate then, a chiral carbohydrate-based synthesis of the key synthetic intermediate enol ether **14** was planned. By way of stereochemical confirmation, as well as to present an alternate chiral synthesis, ozonolytic cleavage of the enol ether **17** can readily be seen as a means to prepare the Prelog–Djerassi lactone (**16**).

After conversion of the glycal **1** to its propionate ester, enolization of this ester with lithium hexamethyldisilazide (LiHMDS) in THF at −100 °C afforded a mixture of enolates in which the (*E*)-enolate was presumed to be vastly predominant on the basis of previous experience.[15]

(1) Contribution no. 6291. Grateful acknowledgement is made for the support of this investigation through National Science Foundation Grant CHE 74-19858.

(2) National Science Foundation Research Fellow, 1977–1980.

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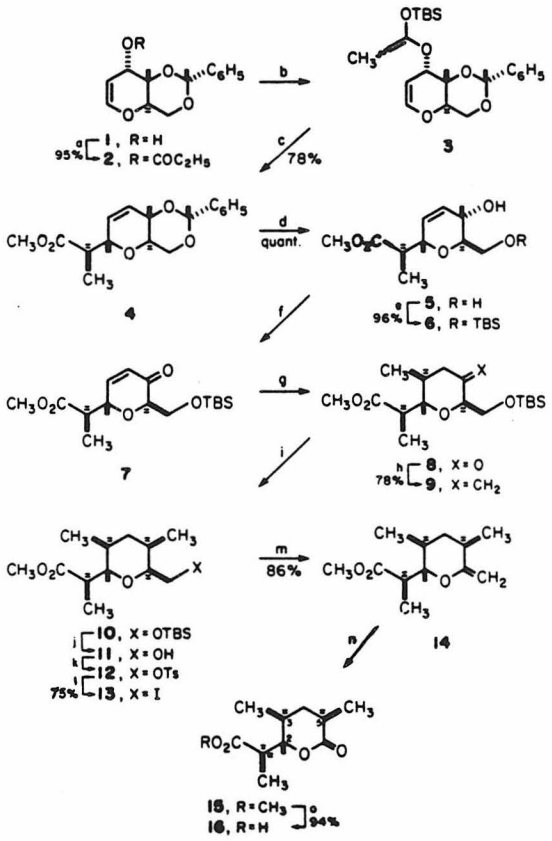
(15) LiHMDS in THF give comparable stereochemical results to LDA in 23% HMPA/THF for ester–enolate Claisen reactions on propionates, unpublished results, these laboratories.

Scheme I. Synthesis of the Prelog–Djerassi Lactone[a,b]

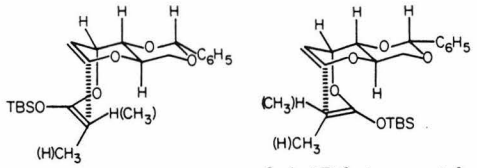


[a] a, $(CH_3CH_2CO)_2O$, pyridine, (dimethylamino)pyridine (cat.), CH_2Cl_2; b, LiHMDS, THF, −100 °C; *t*-Bu$(CH_3)_2$SiCl, HMPA, −100 °C ⟶ room temp; c, C_6H_6, 80 °C, 19 h; H_3O^+, THF, room temp; CH_2N_2, Et_2O; d, H_3O^+, THF, 60 °C; e, *t*-Bu$(CH_3)_2$SiCl, pyridine, 0 °C; f, PDC, CH_2Cl_2; g, $LiCu(CH_3)_2$, Et_2O, 0 °C; h, $(C_6H_5)_3PCH_2$, THF; i, PtO_2, H_2, pentane; j, $(n\text{-Bu})_4NF$, THF; k, *p*-TsCl, pyridine; l, NaI, 2-butanone, 80 °C; m, AgF, pyridine; n, O_3, CH_2Cl_2, −78 °C; $(CH_3)_2S$; o, LiOH, H_2O, MeOH. [b] TBS = *t*-Bu$(CH_3)_2$SiCl.

When these enolates were trapped with *tert*-butyldimethylchlorosilane, the mixture of silyl ketene acetals **3** was isolated, although neither individual isomer could be purified exclusive of the other. Rearrangement of this silyl ketene acetal mixture **3** required heating the mixture at 80 °C for 19 h in contrast to the previously investigated acyclic series. After conversion of the rearrangement product to its methyl ester, a chromatographically separable 90:10 mixture of ester isomers was obtained in 87% yield. That the major component of this isomeric mixture was the desired ester **4** was ultimately confirmed by its subsequent conversion to the Prelog–Djerassi lactone (**16**). In concert with recent results[10,16] with such a rearrangement in the furanoid ring system, the predominant formation of the ester **4** implies that a boat-like transition state was followed with the (*Z*)-silyl ketene acetal.

The use of lithium diisopropylamide (LDA) in THF can be presumed to form predominantly the (*Z*)-enolate of the glycal ester **2** and rearrangement of the derived (*E*)-silyl ketene acetal would be expected to generate the C_α epimer of the ester **4**. In point of fact, however, such a complete stereochemical reversal did not take place, and the ratio of isomeric esters formed from the silyl ketene acetals again at 80 °C was 65:35 in which the ester **4** was still predominant. Since the stereochemical outcome of the ester enolization seems on firm ground,[14] the lack of correspondence between this dicyclic system and the earlier acyclic compounds[14] would appear to be found in the character of the Claisen rearrangement transition state.

As can be seen from the drawings below, the chair



boat (*Z*)-ketene acetal
boat [(*E*)-ketene acetal]

chair (*Z*)-ketene acetal
chair [(*E*)-ketene acetal]

transition state for either ketene acetal isomer should be destabilized relative to the boat arrangement by virtue of the placement of the OTBS-bearing carbon underneath the ring system. However, the boat form of the (*E*)-ketene acetal will also suffer a similar steric congestion due to the location of the methyl group underneath the ring system. Thus, while there is a clear preference for the boat-like transition state when the (*Z*)-ketene acetal is used and only a hydrogen projects under the ring system, little preference would be expected between the boat and chair forms of the (*E*)-ketene acetal transition state, as in both forms significant steric congestion exists. The product ratios from the rearrangement of these isomeric systems bear out this analysis.

Further transformations of the ester **4** led through the enone **7** to the ketone **8** in which the first of the two ring methyl groups was added. The major isomer from the lithium dimethylcuprate addition represented 94% of the isomer mixture and, after separation, was shown to have the desired configuration by the 8-Hz coupling in the ^1H NMR between the C2 and C3 hydrogens. The minor isomer (3-epi-**8**) shows a 2-Hz coupling between these hydrogens.

After Wittig methylenation and catalytic hydrogenation, the second of the two required ring methyl groups was added and again the preponderant isomer from the reduction mixture was shown to have the desired β configuration by ^1H NMR decoupling experiments on the silyl ether **10** in C_6D_6. The coupling between the hydrogens at C2 and C3 is 9 Hz and that between the hydrogens at C5 and C6 is 3 Hz in agreement with the trans diaxial and cis relationships, respectively. The respective coupling constants for the C5 epimer of the silyl ether **10** are 4.5 and 7.5 Hz, which is in agreement with equilibrium values for the two trans relationships.

At this stage all four chiral centers have been defined in a relative as well as absolute sense; it remains to generate the desired enol ether **14** by elimination. After conversion of the C6-oxygen function through the tosylate **12** to the iodide **13**, silver fluoride–pyridine[12] promoted elimination led to the enol ether **14** in 65% overall yield. This key intermediate is currently under investigation as a substrate for spiroketal formation.[11]

By way of stereochemical confirmation as well as the completion of a carbohydrate-based chiral synthesis, the enol ether **14** was converted in excellent yield to the Pre-

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log–Djerassi lactone (16) by ozonolysis and then saponification. The specific optical rotation of material prepared by this route was $[\alpha]^{21}_D$ +47.7° ($CHCl_3$, c 1.93), the highest yet recorded;[3-5,9d,9g] the spectral data (IR, ^1H NMR, and ^{13}C NMR) for this sample are identical with those kindly provided by Professor S. Masamune and NMR data reported by Bartlett.[9e]

For additional stereochemical confirmation, the same latter reaction sequence was performed on the C5-epimeric silyl ether 10 (the minor isomer from hydrogenation). This process afforded a 48% overall yield of the C5-epimeric Prelog–Djerassi lactone (16), the spectral data (^1H NMR and ^{13}C NMR) of which are identical with those previously reported.[9e]

Experimental Section

Melting points were determined by using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 727B infrared spectrometer. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Varian EM-390 or JEOL FX-90Q 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, assignment). Spectra in C_6D_6 were often used to aid in the analysis of overlapping signals in the reported spectra in $CDCl_3$. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL FX-90Q 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 (assignment). For all spectra, numbering in the assignments employs the numbering system implicit in the *Chemical Abstracts* name at the heading of each experimental. Optical rotations were measured in 1-dm cells of 1-mL capacity by using a Perkin-Elmer Model 141 polarimeter. Chloroform, when used as a solvent for optical rotations, was filtered through neutral alumina (activity I) immediately prior to use.

Analytical thin-layer chromatography (TLC) was conducted on 2.5 × 10 cm precoated TLC plates, silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Company, Darmstadt, Germany.

Silica gel columns for chromatography utilized E. Merck "Silica Gel 60", 70–230-mesh ASTM. Acidic silica gel refers to Silicar CC-4 special "for column chromatography", sold by Mallinckrodt Chemical Works, St. Louis, MO. "Alumina" refers to the grade I neutral variety manufactured by M. Woelm, Eschwege, Germany, which was neutralized to the indicated grade by the addition of water.

"Dry" solvents were distilled shortly before use from an appropriate drying agent. Ether and tetrahydrofuran (THF) were distilled under dry argon from sodium metal in the presence of benzophenone. Benzene and pyridine were distilled from powdered calcium hydride. Dichloromethane was distilled from phosphorus pentoxide. *n*-Pentane was distilled under dry argon from sodium metal. Hexamethylphosphoramide (HMPA) was distilled at 1.0 mmHg from powdered calcium hydride. Hexamethyldisilazane was distilled under dry argon from powdered calcium hydride.

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.

1,5-Anhydro-3-deoxy-4,6-*O*-phenylmethylene-3-*O*-propanoyl-D-*ribo*-hex-1-enitol (2). To a stirred solution of 26.6 g (113 mmol) of 4,6-*O*-benzyliden-D-allal (1)[13] in 625 mL of dry dichloromethane cooled to 0 °C (ice bath) under an argon atmosphere was added first 36 g (456 mmol) of dry pyridine followed by 29.5 g (227 mmol) of propanoyl anhydride. The solution was allowed to warm to room temperature and 0.4 g (3.3 mmol) of *p*-(dimethylamino)pyridine (DMAP) was added to catalyze the reaction. After 6 h, the mixture was washed with three 150-mL portions of water and one 100-mL portion of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Azeotropic removal of the pyridine with *n*-heptane followed by recrystallizing the solid residue twice from hot *n*-hexane afforded 30.6 g (93%) of analytically pure propanoate 2 as a white crystalline solid melting at 78–79 °C: R_f 0.18 (silica gel, 1:5 ether–petroleum ether); IR ($CHCl_3$) 1730 (C=O), 1640 cm^{-1} (O—C=C); ^1H NMR ($CDCl_3$) δ 1.12 (t, 3 H, J = 7.5 Hz, $O_2CCH_2CH_3$), 2.37 (q, 2 H, J = 7.5 Hz, $O_2CH_2CH_3$), 3.69–4.35 (br m, 3 H), 4.43 (dd, 1 H, J = 9 Hz, J' = 4 Hz, C(4)-H), 4.97 (dd, 1 H, J = J' = 6 Hz, C(2)-H), 5.44 (dd, 1 H, J = 4 Hz, J' = 6 Hz, C(3)-H), 5.56 (s, 1 H, acetal H), 6.47 (d, 1 H, J = 6 Hz, C(1)-H), 7.36 (br m, 5 H, Ar H); $[\alpha]^{25}_D$ +248° ($CHCl_3$, c 1.00).

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25. Found: C, 66.33; H, 6.17.

Methyl [2*R*-[2α,4aα,6α(*R),8aβ]]-4,4a,6,8a-Tetrahydro-α-methyl-2-phenylpyrano[3,2-*d*]-1,3-dioxin-6-acetate (4) and Methyl [2*R*-[2α,4aα,6α(*S**),8aβ]]-4,4a,6,8a-Tetrahydro-α-methyl-2-phenylpyrano[3,2-*d*]-1,3-dioxin-6-acetate (α-epi-4) A. Deprotonation with LiHMDS in THF.** To a stirred solution of 93.2 mmol of lithium hexamethyldisilazide [from 16.8 g (104 mmol) of hexamethyldisilazane and 93.2 mmol of *n*-butyllithium in hexane] in 175 mL of dry THF cooled to −100 °C (liquid N_2/methanol slush) was added dropwise 13.40 g (46.2 mmol) of the propanoate 2 in 55 mL of dry THF over 10 min. After 10 min, 15.8 g (105 mmol) of *tert*-butyldimethylchlorosilane in 76 mL of dry HMPA was added rapidly with vigorous stirring. After being stirred for 10 min at −100 °C, the resulting mixture was allowed to warm to 0 °C for 30 min and then allowed to warm to room temperature for 30 min. The reaction mixture was diluted with 1400 mL of *n*-pentane and washed with three 250-mL portions of water. The aqueous washings were extracted once with 250 mL of *n*-pentane. After being dried ($MgSO_4$), the combined organic layers were concentrated under reduced pressure followed by further concentration under vacuum (0.5 mmHg). The crude silyl ketene acetals 3 were taken up in 100 mL of dry benzene, dried briefly over $MgSO_4$, and diluted with 740 mL of dry benzene. This solution was refluxed for 19 h under an argon atmosphere and then concentrated under reduced pressure. The crude epimeric silyl esters (yellow solid) were hydrolyzed by stirring with 270 mL of THF and 110 mL of water for 2 h. This mixture was diluted with 400 mL of saturated $NaHCO_3$ followed by 900 mL of water, washed with two 100-mL portions of ether, carefully acidified at 0 °C to pH 3.0–3.5 with 10% aqueous HCl at which point the epimeric carboxylic acids separated as a white solid, and finally extracted with four 250-mL portions of ether. The dried ($MgSO_4$) ether extracts were treated at 0 °C with excess alcohol-free diazomethane [generated from 21.5 g (100 mmol) of Aldrich Diazald] in ether, and concentration under reduced pressure afforded the crude methyl esters as a yellow solid. This solid was rapidly column filtered through 50 g of silica gel and medium-pressure liquid chromatography (Lobar prepacked column, size C, LiChroprep Si60, EM Reagents) of the resulting solid with 1:5 ether–petroleum ether eluant afforded (afte recycle of mixed fractions) first 10.92 g (78%) of the ester 4 as a white solid melting at 62–62.5 °C. Recrystallization of a portion of this solid from hot *n*-hexane provided the analytical sample of the ester 4 as a white solid melting at 62–62.5 °C: R_f 0.13 (silica gel, 1:5 ether–petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.30 (d, 3 H, J = 7 Hz, α-CH_3), 2.77 (dq, 1 H, J = J' = 7 Hz, α-H), 3.43–3.87 (br m, 2 H, C(4)-H_2), 3.70 (s, 3 H, OCH_3), 4.07–4.50 (br m, 3 H), 5.57 (s, 1 H, C(2)-H), 5.73 and 6.09 (AB q plus allylic couplings, 2 H, J_{AB} = 11 Hz, CH=CH), 7.33–7.60 (br m, 5 H, Ar H); $[\alpha]^{21}_D$ −11° ($CHCl_3$, c 1.00).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.89; H, 6.59.

There was then eluted 1.29 g (9%) of the isomeric ester α-epi-4 as a white solid melting at 80.5–81.5 °C. Recrystallization of a portion of this solid from hot *n*-hexane provided the analytical sample of the ester α-epi-4 as fine white needles melting at 81–82 °C: R_f 0.084 (silica gel, 1:5 ether–petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.18 (d, 3 H, J = 7 Hz, α-CH_3), 2.89 (dq, 1 H, J = 7 Hz, J' = 9 Hz, α-H), 3.57–3,83 (br m, 2 H, C(4)-H_2), 3.70 (s, 3 H, OCH_3), 4.07–4.47 (br m, 3 H), 5.57

(s, 1 H, C(2)-H), 5.85 and 6.10 (AB q plus allylic couplings, 2 H, J_{AB} = 11 Hz, CH=CH), 7.32–7.58 (br m, 5 H, Ar H); $[\alpha]^{21}_D$ +99° ($CHCl_3$, c 1.00).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.29; H, 6.67.

B. Deprotonation with LDA in THF. To a stirred solution of 0.668 mmol of lithium diisopropylamide [from 101 mg (1.00 mmol) of diisopropylamine in 0.14 mL of dry *n*-hexane and 0.668 mmol (0.28 mL) of *n*-butyllithium (2.38 M in hexane) at 0 °C followed by removal of solvents under high vacuum at 0 °C] in 3 mL of dry THF cooled to −78 °C (dry ice/*i*-PrOH) was added dropwise 97 mg (0.334 mmol) of the propanoate **2** in 0.4 mL of dry THF over 4 min. After 5 min, 117 mg (0.776 mmol) of *tert*-butyldimethylchlorosilane in 0.6 mL of dry HMPA was added rapidly with vigorous stirring. The resulting mixture was allowed to warm to room temperature over 1 h. The reaction mixture was diluted with 50 mL of *n*-pentane and washed with four 15-mL portions of water. After being dried ($MgSO_4$), the organic layer was concentrated under reduced pressure. The crude silyl ketene acetals **3** were taken up in 6 mL of dry benzene and dried briefly over K_2CO_3, and the resulting solution was refluxed for 15 h under an argon atmosphere. After concentration under reduced pressure, the residue was treated with 98 mg (1.04 mmol) of $KF{\cdot}2H_2O$ and 106 mg (1.06 mmol) of $KHCO_3$ in 2 mL of dry HMPA under an argon atmosphere for 19 h followed by the additon of 0.083 mL (190 mg, 1.34 mmol) of methyl iodide. This mixture was stirred for 3 h at room temperature followed by dilution with 30 mL of *n*-pentane and washing with three 10-mL portions of water. After the organic layer was dried ($MgSO_4$), concentration under reduced pressure and chromatographic separation of the epimeric esters afforded 28.5 mg (28%) of the ester **4** and 14.5 mg (14%) of its C_α epimer. This represents a 66:34 ratio of epimers with the same isomer predominating as in the experiment using LiHMDS.

Methyl [2*S*-[2α(*S),5α,6β]]-5,6-Dihydro-5-hydroxy-6-(hydroxymethyl)-α-methyl-2*H*-pyran-2-acetate (5).** A mixture of 1.00 g (3.29 mmol) of the benzylidene acetal **4**, 21 mL of tetrahydrofuran, and 75 mL of 0.01 N sulfuric acid was heated at 60 °C under an argon atmosphere for 3 h. The tetrahydrofuran and benzaldehyde were removed under reduced pressure, and the remaining aqueous solution was saturated with sodium chloride and extracted with six 25-mL portions of tetrahydrofuran. The combined extracts were dried ($MgSO_4$) and removal of the solvent under reduced pressure afforded 711 mg (100%) of **5** as a white solid melting at 49.5–50.5 °C. This material was used without further purification.

Chromatography of a portion of this solid (99 mg) on 10 g of silica gel with 40:1 ether–methanol afforded 63 mg of **5**. Distillation [kugelrohr, 150 °C (0.005 mmHg)] of this material provided the analytical sample: R_f 0.23 (silica gel, 40:1 ether–methanol); IR ($CHCl_3$) 3470 (OH), 1735 (C=O), 1630 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 1.26 (d, 3 H, *J* = 7 Hz, α-CH_3), 2.33 (br s, 2 H, OH), 2.73 (dq, 1 H, *J* = *J*′ = 7 Hz, α-H), 3.49 (dt, 1 H, *J* = 7 Hz, *J*′ = 5 Hz, C(6)-H), 3.68 (s, 3 H, OCH_3), 3.70 (m, 2 H, CH_2OH), 4.03 (m, 1 H, C(5)-H), 4.29 (d plus allylic couplings, 1 H, *J* = 7 Hz, C(2)-H), 5.77 and 5.89 (AB q plus allylic couplings, 2 H, J_{AB} = 11 Hz, CH=CH); $[\alpha]^{21}_D$ −48° ($CHCl_3$, c 1.00).

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.34; H, 7.35.

Methyl [2*S*-[2α(*S),5α,6β]]-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-5,6-dihydro-5-hydroxy-α-methyl-2*H*-pyran-2-acetate (6).** To a stirred solution of 2.473 g (11.44 mmol) of the diol **5** in 35 mL of dry pyridine cooled to 0 °C (ice bath) under an argon atmosphere was added 1.83 g (12.14 mmol) of *tert*-butyldimethylchlorosilane (TBSCl) in four portions over 1 h. Two hours after the last addition, three 180-mg portions of TBSCl were added with 1 h between additions. One hour after the last addition, TLC analysis (silica gel, ether) showed the absence of starting material. The reaction mixture was poured into 250 mL of water and extracted with three 80-mL portions of ether. After the combined extracts were dried ($MgSO_4$), the solvent was removed under reduced pressure, and the pyridine was azeotroped off by the addition of *n*-heptane followed by removal under reduced pressure four successive times. Chromatography of the residue on 110 g of silica gel using 1:1 ether–petroleum ether afforded 3.65 g (96.5%) of the monosilated product **6** as a colorless oil. Distillation of a portion of this oil [kugelrohr, 140 °C (0.005 mmHg)] provided the analytical sample: R_f 0.28 (silica gel, 1:1 ether–petroleum ether); IR ($CHCl_3$) 3520 (OH), 1735 (C=O), 1630 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $Si(CH_3)_2$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 1.24 (d, 3 H, *J* = 7.5 Hz, α-CH_3), 2.72 (dq, 1 H, *J* = *J*′ = 7.5 Hz, α-H), 2.77 (d, 1 H, *J* = 5 Hz, OH), 3.45 (dt, 1 H, *J* = *J*′ = 6 Hz, C(6)-H), 3.67 (s, 3 H, OCH_3), 3.80 (AB portion of ABX system, 2 H, J_{AB} = 9 Hz, CH_2OSi), 4.05 (m, 1 H, C(5)-H), 4.24 (d plus allylic couplings, 1 H, *J* = 7.5 Hz, C(2)-H), 5.76 and 5.88 (AB q plus allylic couplings, 2 H, J_{AB} = 11 Hz, CH=CH); $[\alpha]^{23}_D$ −63° ($CHCl_3$, c 1.1).

Anal. Calcd for $C_{16}H_{30}O_5Si$: C, 58.15; H, 9.15. Found: C, 58.09; H, 9.21.

Methyl [2*S*-[2α(*S),6β]]-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-5,6-dihydro-α-methyl-5-oxo-2*H*-pyran-2-acetate (7).** To a vigorously stirred solution of 1.30 g (3.93 mmol) of the allylic alcohol **6** in 17 mL of dry dichoromethane under an argon atmosphere was added 2.22 g (5.90 mmol) of pyridinium dichromate (PDC). After 15 h at room temperature, 450 mg (1.20 mmol) of PDC was added and stirring continued. Three more 450-mg portions of PDC were added after 4 h, 6 h, and 14 h, respectively. Twelve hours after the last addition, TLC analysis (silica gel, 1:2 ether–petroleum ether) showed the absence of starting material. The reaction mixture was diluted with 150 mL of ether and then filtered through a 3-cm pad of packed anhydrous $MgSO_4$ with the aid of suction. The filter cake was washed with an additional 150 mL of ether, and then the filtrate was concentrated under reduced pressure. Azeotropic removal of pyridine from this residue under reduced pressure with *n*-heptane afforded 1.29 g (100%) of the enone **7**. This material was used without further purification. Chromatography of a portion of this oil (180 mg) on 5 g of silica gel with 1:4 ether–petroleum ether afforded 173 mg (96%) of the enone **7** as a colorless oil. Distillation [kugelrohr, 110 °C (0.005 torr)] provided the analytical sample: R_f 0.20 (silica gel, 1:4 ether–petroleum ether); IR ($CHCl_3$) 1735 (ester C=O), 1685 (enone C=O), 1635 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H, $Si(CH_3)_2$), 0.83 (s, 9 H, $SiC(CH_3)_3$), 1.25 (d, 3 H, *J* = 7 Hz, α-CH_3), 2.77 (dq, 1 H, *J* = *J*′ = 7 Hz, α-H), 3.70 (s, 3 H, OCH_3), 3.95 (d, 2 H, *J* = 3 Hz, CH_2OSi), 4.16 (t, 1 H, *J* = 3 Hz, C(6)-H), 5.00 (ddd, 1 H, *J* = *J*′ = 2 Hz, *J*″ = 7 Hz, C(2)-H), 6.14 (dd, 1 H, *J* = 11 Hz, *J*′ = 2 Hz, C(4)-H), 6.95 (dd, 1 H, *J* = 11 Hz, *J*′ = 2 Hz, C(3)-H); $[\alpha]^{25}_D$ −46° ($CHCl_3$ c 0.96).

Anal. Calcd for $C_{16}H_{28}O_5Si$: C, 58.50; H, 8.59. Found: C, 58.37; H, 8.47.

Methyl [2*S*-[2α(*S),3β,6β]]-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-α,3-dimethyl-5-oxo-2*H*-pyran-2-acetate (8) and Methyl [2*S*-[2α(*S**),3α,6β]]-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-α,3-dimethyl-5-oxo-2*H*-pyran-2-acetate (3-epi-8).** To a stirred slurry of 1.70 g (8.27 mmol) of cuprous bromide–dimethyl sulfide complex in 80 mL of dry ether cooled to 0 °C (ice bath) under an argon atmosphere was added 1.58 M methyllithium (low halide in ether) until a small amount of yellow precipitate (methylcopper) remained (9.0 mL of methyllithium solution added). After 30 min, a solution of 1.051 g (3.20 mmol) of the enone **7** in 12 mL of dry ether was added dropwise over 10 min to this rapidly stirred solution of lithium dimethylcuprate at 0 °C. The reaction was quenched after 10 min by the addition of a saturated aqueous NH_4Cl solution (150 mL) and then poured into 150 mL of water. The layers were separated and the aqueous layer (blue) was extracted with two 100-mL portions of ether. After the organic layers were dried ($MgSO_4$), concentration under reduced pressured afforded 1.10 g (100%) of the labile isomeric ketones as a light yellow oil. This oil was promptly subjected to Wittig olefination as described below. The ^1H NMR spectrum of this material showed only a trace of the 3α isomer.

The analytical samples were prepared by following the above procedure with 133 mg (0.405 mmol) of the enone **7** in 1 mL of dry *n*-pentane and lithium dimethyl cuprate from 166 mg (0.872 mmol) of cuprous iodide and 0.774 mL of 2.17 M methyllithium in 8 mL of dry *n*-pentane. Workup as described, followed by chromatography of the crude product on 25 g of silica gel with 1:6 ether–petroleum ether, provided, after distillation [kugelrohr, 90–100 °C (0.004 torr)], the following analytically pure products. Ketone 3-epi-8: 16.3 mg(12%) as a colorless oil; R_f 0.20 (silica gel, 1:6 ether–petroleum ether); IR ($CHCl_3$) 1725 cm^{-1} (C=O);

^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 1.00 (d, 3 H, J = 7 Hz, C(3)-CH_3), 1.35 (d, 3 H, J = 7 Hz, α-CH_3), 2.20 (m, 1 H, C(3)-H), 2.57 (m, 3 H, α-H and C(4)-H_2), 3.63 (s, 3 H, OCH_3), 3.95 (m, 3 H, C(6)-H and CH_2OSi), 4.46 (dd, 1 H, J = 11 Hz, J' = 2 Hz, C(2)-H); $[\alpha]^{24}_D$ +107° ($CHCl_3$, c 0.86).

Anal. Calcd for $C_{17}H_{32}O_5Si$: C, 59.27; H, 9.36. Found: C, 59.15; H, 9.32.

Ketone 8: 93 mg (67%) of a white solid melting at 32–33 °C; R_f 0.14 (silica gel, 1:6 ether–petroleum ether); IR ($CHCl_3$) 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.95 (d, 3 H, J = 6 Hz, C(3)-CH_3), 1.18 (d, 3 H, J = 7 Hz, α-CH_3), 2.12–2.65 (m, 3 H, C(3)-H and C(4)-H_2), 2.74 (dq, 1 H, J = 5 Hz, J' = 7 Hz, α-H), 3.70 (s, 3 H, OCH_3), 3.92 (m, 3 H, C(6)-H and CH_2OSi), 4.35 (dd, 1 H, J = 5 Hz, J' = 8 Hz, C(2)-H); $[\alpha]^{24}_D$ +64° ($CHCl_3$, c 1.06).

Anal. Calcd for $C_{17}H_{32}O_5Si$: C, 59.27; H, 9.36. Found: C, 59.16; H, 9.44.

Methyl [2*S*-[2α(*S),3β,6β]]-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-α,3-dimethyl-5-methylene-2*H*-pyran-2-acetate (9) and Methyl [2*S*-[2α(*S**),3α,6β]]-6-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-α,3-dimethyl-5-methylene-2*H*-pyran-2-acetate (3-epi-9).** To a stirred solution of 6.0 mmol of methylenetriphenylphosphorane [prepared by addition of 2.55 mL (6.0 mmol) of 2.36 M n-butyllithium in hexane to a stirred slurry of 2.30 g (6.44 mmol) of (methyl)triphenylphosphonium bromide (dried in vacuo in 80 °C) in 50 mL of dry THF at −78 °C, followed by stirring at room temperature for 2 h] cooled to −78 °C (dry ice/2-propanol) under an argon atmosphere was added the mixture of ketone 8 and its C3 epimer, described above, in 12 mL of dry THF over 8 min. The reaction mixture was stirred at −78 °C for 5 min and then allowed to warm to room temperature. After 2 h at room temperature, the reaction mixture was quenched with 10 mL of saturated aqueous $NaHCO_3$, poured into 750 mL of ether, and washed with two 140-mL portions of saturated aqueous $NaHCO_3$ and one 140-mL portion of saturated aqueous NaCl. The aqueous washings were extracted twice with 100-mL portions of ether. The combined organic layers were dried ($MgSO_4$) and then concentrated to afford an oily solid which was applied in 25 mL of carbon tetrachloride to 25 g of silica gel and rapidly eluted with 1:10 ether–petroleum ether. Separation of the resulting mixture of olefins by medium-pressure liquid chromatography (Lobar prepacked column, size B, LiChroprep Si60, EM Reagents) with 1:15 ether–petroleum ether eluant afforded the pure isomers of olefin 3-epi-9, 54.5 mg (5.0%). Distillation [kugelrohr, 85 °C (0.005 mmHg)] provided the analytical sample of the olefin 3-epi-9: R_f 0.21 (silica gel, 1:15 ether–petroleum ether); IR ($CHCl_3$) 1730 (C=O), 1665 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.89 (d, 3 H, J = 7 Hz, C(3)-CH_3), 1.25 (d, 3 H, J = 7 Hz, α-CH_3), 1.60–1.94 (m, 2 H, C(4)-H_2), 2.55 (dq, 1 H, J = 10 Hz, J' = 7 Hz, α-H), 2.60 (br m, 1 H, C(3)-H), 3.64 (s, 3 H, OCH_3), 3.76 (AB portion of ABX system, 2 H, J_{AB} = 10 Hz, CH_2OSi), 3.79 (dd, 1 H, J = 2 Hz, J' = 10 Hz, C(2)-H), 4.16 (t, 1 H, J = 6 Hz, C(6)-H), 4.81 (m, 2 H, C=CH_2); $[\alpha]^{22}_D$ +61° ($CHCl_3$, c 1.16).

Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00. Found: C, 63.23; H, 10.12.

Olefin 9, 853 mg (78%), was also eluted. Distillation [kugelrohr, 85 °C (0.005 mmHg)] of a portion provided the analytical sample of the olefin 9: R_f 0.15 (silica gel, 1:15 ether–petroleum ether); IR ($CHCl_3$) 1735 (C=O), 1665 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.87 (d, 3 H, J = 7 Hz, C(3)-CH_3), 1.11 (d, 3 H, J = 7 Hz, α-CH_3), 1.65 (br m, 1 H, C(3)-H), 2.06 and 2.30 (AB q plus couplings with C(3)-H, 2 H, J_{AB} = 14 Hz, C(4)-H_2), 2.69 (dq, 1 H, J = 4 Hz, J' = 7 Hz, α-H), 3.68 (s, 3 H, OCH_3), 3.72 (d, 1 H, J = 6 Hz, SiOCHH), 3.75 (d, 1 H, J = 6 Hz, SiOCHH), 3.87 (dd, 1 H, J = 4 Hz, J' = 9 Hz, C(2)-H), 4.08 (dd, 1 H, J = J' = 6 Hz, C(6)-H), 4.78 (br s, 2 H, C=CH_2); $[\alpha]^{25}_D$ +38° ($CHCl_3$, c 0.94).

Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00. Found: C, 63.24; H, 10.06.

Methyl [2*S*-[2α(*S),3β,5β,6β]]-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-α,3,5-trimethyl-2*H*-pyran-2-acetate (10) and Methyl [2*S*-[2α(*S**),3β,5α,6β]]-6-[[[(1,1-Dimethylethyl]dimethylsilyl]oxy]methyl]tetrahydro-α,3,5-trimethyl-2*H*-pyran-2-acetate (5-epi-10).** A solution of 400 mg (1.17 mmol) of the olefin 9 in 30 mL of dry n-pentane was hydrogenated under a hydrogen atmosphere (H_2-filled balloon) at room temperature in the presence of 4 mg of powdered platinum oxide for 8 h followed by filtration of the mixture through a pad of $MgSO_4$. The filter cake was washed with 100 mL of ether, and concentration of the filtrate under reduced pressure followed by medium-pressure liquid chromatography (Lobar prepacked column, size B, LiChroprep Si 60, EM Reagents) with 1:15 ether–petroleum ether eluant afforded first the minor isomer 5-epi-10, 42.5 mg (10.6%) of a colorless oil. Distillation [kugelrohr, 85 °C (0.005 mmHg)]provided the analytical sample of the ester 5-epi-10: R_f 0.18 (silica gel, 1:15 ether–petroleum ether); IR ($CHCl_3$) 1730 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.91 (d, 3 H, J = 6 Hz, CH_3), 0.99 (d, 3 H, J = 6 Hz, CH_3), 1.18 (d, 3 H, J = 7 Hz, α-CH_3), 1.40–1.93 (m, 4 H, C(3)-H, C(4)-H_2, and C(5)-H), 2.88 (dq, 1 H, J = 8 Hz, J' = 7 Hz, α-H), 3.13 (dt, 1 H, J = 7.5 Hz, J' = 4.5 Hz, C(6)-H), 3.48–3.82 (m, 3 H, C(2)-H and CH_2OSi), 3.65 (s, 3 H, OCH_3); ^{1}H NMR (C_6D_6) δ 0.10 (s, 6 H, $Si(CH_3)_2$), 0.78 (d, 3 H, J = 6 Hz, CH_3), 0.93 (d, 3 H, J = 6 Hz, CH_3), 0.97 (s, 9 H, $SiC(CH_3)_3$), 1.27 (d, 3 H, J = 7 Hz, α-CH_3), 1.24–1.94 (m, 4 H, C(3)-H, C(4)-H_2, and C(5)-H), 2.83 (dq, 1 H, J = 8 Hz, J' = 7 Hz, α-H), 3.07 (dt, 1 H, J = 7.5 Hz, J' = 4.5 Hz, C(6)-H), 3.34 (s, 3 H, OCH_3), 3.63 (d, 1 H, J = 4.5 Hz, SiOCHH), 3.66 (d, 1 H, J = 4.5 Hz, SiOCHH), 3.76 (dd, 1 H, J = 4.5 Hz, J' = 8 Hz, C(2)-H), plus a small singlet (8%) at β 3.42 believed to be the OCH_3 of the TBS ether of structure i (see preparation of alcohol 5-epi-11); $[\alpha]^{19}_D$ +11° ($CHCl_3$, c 1.06).

Anal. Calcd for $C_{18}H_{36}O_4Si$: C, 62.74; H, 10.53. Found: C, 62.82; H, 10.43.

After a few mixed fractions, there was eluted the major isomer 10, 357.5 mg (89%) of a colorless oil. Distillation [kugelrohr, 85 °C (0.005 mmHg)] provided the analytical sample of the ester 10: R_f 0.12 (silica gel, 1:15 ether–petroleum ether); IR ($CHCl_3$) 1730 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6 H, $Si(CH_3)_2$), 0.80 (d, 3 H, J = 6 Hz, CH_3), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.90 (d, 3 H, J = 7 Hz, CH_3), 1.09 (d, 3 H, J = 7 Hz, α-CH_3), 1.20–2.00 (m, 4 H, C(3)-H, C(4)-H_2, and C(5)-H), 2.64 (dq, 1 H, J = 3 Hz, J' = 7 Hz, α-H), 3.67 (s, 1 H, OCH_3), 3.56–3.89 (m, 4 H, C(2)-H, C(6)-H, and CH_2OSi); ^{1}H NMR (C_6D_6) δ 0.07 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.64 (d, 3 H, J = 6 Hz, CH_3), 0.82 (d, 3 H, J = 7 Hz, CH_3), 0.95 (s, 9 H, $SiC(CH_3)_3$), 1.23 (d, 3 H, J = 7 Hz, α-CH_3), 1.13–2.00 (m, 4 H, C(3)-H, C(4)-H_2, and C(5)-H, 2.51 (dq, 1 H, J = 3 Hz, J' = 7 Hz, α-H), 3.47 (s, 3 H, OCH_3), 3.66 (dt, 1 H, J = J' = 3 Hz, C(6)-H), 3.77 (m, 2 H, CH_2OSi), 3.93 (dd, 1 H, J = 3 Hz, J' = 9 Hz, C(2)-H); $[\alpha]^{19}_D$ +22° ($CHCl_3$, c 1.13).

Anal. Calcd for $C_{18}H_{36}O_4Si$: C, 62.74; H, 10.53. Found: C, 62.81; H, 10.51.

Methyl [2*S*-[2α(*S),3β,5β,6β]]-Tetrahydro-6-(hydroxymethyl)-α,3,5-trimethyl-2*H*-pyran-2-acetate (11).** To a stirred solution of 425 mg (1.23 mmol) of the silyl ether 10 in 10 mL of dry THF under an argon atmosphere was added 0.97 g (3.7 mmol) of tetrabutyl ammonium fluoride in 5 mL of dry THF. After 2.5 h at room temperature, filtration of the reaction mixture through 25 g of silica gel with ether eluant followed by chromatography of the residue on 25 g of silica gel with 1:1 ether–petroleum ether afforded 275 mg (97%) of the alcohol 11 as a colorless oil.

Distillation [kugelrohr, 85 °C (0.005 mmHg)] provided the analytical sample: R_f 0.17 (silica gel, 1:1 ether–petroleum ether); IR ($CHCl_3$) 3480 (OH), 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.81 (d, 3 H, J = 8 Hz, CH_3), 0.82 (d, 3 H, J = 6 Hz, CH_3), 1.20 (d, 3 H, J = 7 Hz, α-CH_3), 1.27 (m, 1 H), 1.58 (br m, 2 H), 2.07 (br m, 1 H, methine H), 2.70 (dq, 1 H, J = 3 Hz, J' = 7 Hz, α-H), 3.00 (d, 1 H, J = 11 Hz, OH), 3.38 (m, 1 H, OCHH), 3.68 (s, 3 H, OCH_3), 3.80 (dd, 1 H, J = 3 Hz, J' = 9 Hz, C(2)-H), 3.95 (br m, 2 H, OCHH and C(6)-H); $[\alpha]^{22}_D$ +97° ($CHCl_3$, c 1.20).

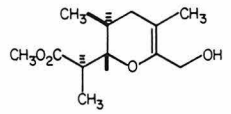
Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.58; H, 9.67.

Methyl [2*S*-[2α(*S),3β,5α,6β]]-Tetrahydro-6-(hydroxymethyl)-α,3,5-trimethyl-2*H*-pyran-2-acetate (5-epi-11).** In the manner described for the preparation of alcohol 11 from silyl ether 10, 144 mg (0.418 mmol) of silyl ether 5-epi-10 in 2 mL of dry THF was treated with 352 mg (1.35 mmol) of tetrabutylammonium fluoride in 2 mL of dry THF. After 40 min, filtration as described through 10 g of silica gel followed by chromatography

on 25 g of silica gel with 1:1 ether–petroleum ether afforded first the alcohol 5-epi-11, 87 mg (90%) of a colorless oil. Distillation [kugelrohr, 75 °C (0.003 mmHg)] provided the analytical sample: R_f 0.15 (silica gel, 1:1 ether–petroleum ether); IR ($CHCl_3$) 3500 (OH), 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.93 (d, 3 H, J = 7 Hz, CH_3), 0.98 (d, 3 H, J = 6 Hz, CH_3), 1.21 (d, 3 H, J = 7 Hz, α-CH_3), 1.30–1.80 (br m, 4 H, C(3)-H, C(4)-H_2, and C(5)-H), 2.57 (dd, 1 H, J = 4 Hz, J' = 9 Hz, OH), 2.83 (dq, 1 H, J = J' = 7 Hz, α-H), 3.30–3.93 (br m, 4 H, C(2)-H, C(6)-H, and CH_2O), 3.67 (s, 3 H, OCH_3); $[\alpha]^{21}D$ +43° ($CHCl_3$, c 0.98).

Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.61; H, 9.64.

After a few mixed fractions, there was eluted 8 mg of a colorless oil whose NMR and IR are consistent with structure i below. This product presumably arises from a small amount of double bond isomerization in the hydrogenation step.



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Methyl [2*S*-[2α(*S),3β,5β,6β]]-Tetrahydro-α,3,5-trimethyl-6-[[[(4-methylphenyl)sulfonyl]oxy]methyl]-2*H*-pyran-2-acetate (12).** To a stirred solution of 185 mg (0.803 mmol) of the alcohol 11 in 1.5 mL of dry pyridine under an argon atmosphere cooled to 0 °C (ice bath) was added 310 mg (1.63 mmol) of p-toluenesulfonyl chloride. The flask was stoppered and kept in the refrigerator (3 °C) for 24 h. The reaction mixture was poured into 40 mL of cold water and extracted with three 15-mL portions of ether. After the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure, azeotropic removal of pyridine under reduced pressure with n-heptane afforded 310 mg (100%) of the crude tosylate 12 as a white solid melting at 104–107 °C. This material was used in subsequent experiments without further purification.

Recrystalization of a portion (51 mg) of this solid twice by dissolving it in 10 mL of 2:1 n-pentane–ether at room temperature, cooling to −78 °C (dry ice/2-propanol), and filtering afforded the analytical sample (40 mg) as a white solid melting at 108–108.5 °C: R_f 0.14 (silica gel, 1:2 ether–petroleum ether); IR ($CHCl_3$) 1735 (C=O), 1610 (phenyl), 1365 (assym S(=O)$_2$), 1180 cm^{-1} (sym S(=O)$_2$); ^1H NMR ($CDCl_3$) δ 0.77 (d, 3 H, J = 7 Hz, CH_3), 0.80 (d, 3 H, J = 6 Hz, CH_3), 1.07 (d, 3 H, J = 7 Hz, α-CH_3), 1.17 (m, 1 H), 1.56 (br m, 2 H), 1.96 (br m, 1 H, methine H), 2.41 (s, 3 H, $ArCH_3$), 2.64 (dq, 1 H, J = 3 Hz, J' = 7 Hz, α-H), 3.62 (dd, 1 H, J = 3 Hz, J' = 10 Hz, C(2)-H), C(2)-H, 3.64 (s, 3 H, OCH_3), 3.86 (br m, 1 H, C(6)-H), 4.04 and 4.23 (AB q plus unequal couplings with C(6)-H, 2 H, J_{AB} = 10 Hz, CH_2OTs), 7.33 (d, 2 H, J = 9 Hz, Ar H), 7.79 (d, 2 H, J = 9 Hz, Ar H); $[\alpha]^{22}_D$ +27° ($CHCl_3$, c 0.97).

Anal. Calcd for $C_{19}H_{28}O_6S$: C, 59.35; H, 7.34; S, 8.34. Found: C, 59.38; H, 7.22; S, 8.29.

Methyl [2*S*-[2α(*S),3β,5α,6β]]-Tetrahydro-α,3,5-trimethyl-6-[[[(4-methylphenyl)sulfonyl]oxy]methyl]-2*H*-pyran-2-acetate (5-epi-12).** The procedure for the tosylation of alcohol 11 with 76 mg (0.33 mmol) of the alcohol 5-epi-11, 131 mg (0.687 mmol) of tosyl chloride, and 1 mL of dry pyridine followed by chromatography of the crude tosylate on 10 g of silica gel with 1:2 ether–petroleum ether afforded 117 mg (92%) of analytically pure tosylate 5-epi-12 as a colorless oil: R_f 0.17 (silica gel, 1:2 ether–petroleum ether); IR ($CHCl_3$) 1730 (C=O), 1605 (phenyl), 1360 (assym S(=O)$_2$), 1175 cm^{-1} (sym S(=O)$_2$); ^1H NMR ($CDCl_3$) δ 0.90 (d, 3 H, J = 6 Hz, CH_3), 0.95 (d, 3 H, J = 6 Hz, CH_3), 1.12 (d, 3 H, J = 7 Hz, α-CH_3), 1.32–1.86 (br m, 4 H, C(3)-H, C(4)-H_2, and C(5)-H), 2.42 (s, 3 H, $ArCH_3$), 2.82 (dq, 1 H, J = J' = 7 Hz, α-H), 3.36 (dt, 1 H, J = 6 Hz, J' = 5 Hz, C(6)-H), 3.56 (dd, 1 H, J = 7 Hz, J' = 5 Hz, C(2)-H), 3.65 (s, 3 H, OCH_3), 4.09 (d, 2 H, J = 5 Hz, CH_2OTs), 7.34 (d, 2 H, J = 9 Hz, Ar H), 7.80 (d, 2 H, J = 9 Hz, Ar H); $[\alpha]^{22}_D$ +12.5° ($CHCl_3$, c 0.86).

Anal. Calcd for $C_{19}H_{28}O_6S$: C, 59.35; H, 7.34; S, 8.34. Found: C, 59.50; H, 7.36; S, 8.28.

Methyl [2*S*-[2α(*S),3β,5β,6β]]-Tetrahydro-6-(iodomethyl)-α,3,5-trimethyl-2*H*-pyran-2-acetate (13).** A mixture of 288 mg (0.749 mmol) of the tosylate 12 and 375 mg (2.50 mmol) of sodium iodide in 4 mL of 2-butanone under an argon atmosphere was heated under gentle reflux for 33 h at which point, based on chromatography of the product, there was still 3% of the tosylate remaining plus 3% of byproducts arising from elimination and hydration. The reaction mixture was diluted with 25 mL of water and 15 mL of 10% aqueous $NaHSO_3$ and extracted with three 15-mL portions of ether. After the combined extracts were dried ($MgSO_4$), concentration under reduced pressure followed by chromatography of the residue on 13 g of silica gel with 1:10 ether–petroleum ether afforded 220 mg (86.4%) of the iodide 13 as a colorless oil.

Distillation [kugelrohr, 85 °C (0.003 mmHg)] of a portion of this oil afforded the analytical sample of the iodide 13: R_f 0.13 (silica gel, 1:10 ether–petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.84 (d, 3 H, J = 7 Hz, CH_3), 0.86 (d, 3 H, J = 7 Hz, CH_3), 1.13 (d, 3 H, J = 7 Hz, α-CH_3), 1.20 (br m, 1 H), 1.52 (br m, 2 H), 1.97 (br m, 1 H, methine H), 2.69 (dq, 1 H, J = 3 Hz, J = 7 Hz, α-H), 3.31 (AB portion of an ABX pattern, 2 H, J_{AB} = 11 Hz, CH_2I), 3.53 (dd, 1 H, J = 3 Hz, J' = 10 Hz, C(2)-H), 3.73 (s, 3 H, OCH_3), 3.93 (m, 1 H, C(6)-H); $[\alpha]^{23}_D$ +97° ($CHCl_3$, c 1.20).

Anal. Calcd for $C_{12}H_{21}O_3I$: C, 42.37; H, 6.22. Found: C, 42.35; H, 6.07.

Methyl [2*S*-[2α(*S),3β,5α,6β]]-Tetrahydro-6-(iodomethyl)-α,3,5-trimethyl-2*H*-pyran-2-acetate (5-epi-13).** The procedure for the preparation of the iodide 13 with 105 mg (0.273 mmol) of the tosylate 5-epi-12 and 128 mg (0.854 mmol) of sodium iodide in 1.5 mL of 2-butanone and only 7 h of reflux afforded, after chromatography on 11 g of silica gel with 1:10 ether–petroleum ether, 88.4 mg (95%) of the iodide 5-epi-13 as a colorless oil.

Distillation [kugelrohr, 85 °C (0.003 mmHg)] of a portion of this oil provided the analytical sample of the iodide 5-epi-13: R_f 0.19 (silica gel, 1:10 ether–petroleum ether); IR ($CHCl_3$) 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.93 (d, 3 H, J = 6 Hz, CH_3), 1.00 (d, 3 H, J = 6 Hz, CH_3), 1.22 (d, 3 H, J = 7 Hz, α-CH_3), 1.38–1.95 (br m, 4 H, C(3)-H, C(4)-H_2, and C(5)-H), 2.85 (dq, 1 H, J = J' = 7 Hz, α-H), 3.05–3.42 (br m, 3 H, C(6)-H and CH_2I), 3.62 (dd, 1 H, J = 5 Hz, J' = 7 Hz, C(2)-H), 3.67 (s, 3 H, OCH_3); $[\alpha]^{23}_D$ +38° ($CHCl_3$, c 1.20).

Anal. Calcd for $C_{12}H_{21}O_3I$: C, 42.37; H, 6.22. Found: C, 42.48; H, 6.06.

Methyl [2*S*-[2α(*S),3β,5β]]-Tetrahydro-α,3,5-trimethyl-6-oxo-2*H*-pyran-2-acetate (15).** To a stirred slurry of 289 mg (2.28 mmol) of silver fluoride (anhydrous, supplied by ROC-RIC) in 0.5 mL of dry pyridine under an argon atmosphere was added 209 mg (0.614 mmol) of the iodide 13 in 1.5 mL of dry pyridine and the dark mixture was stirred in the dark at room temperature for 21 h. The mixture was diluted with 3 mL of dry ether, stirred 15 min, and filtered through a 1-cm pad of Celite with the aid of 10 mL of dry ether. The filter cake was washed with 20 mL of ether and concentration of the filtrate under reduced pressure afforded the acid-sensitive enol ether 14 as a solution in approximately 1 mL of pyridine which was directly ozonized as described below.

A spectral sample was prepared from a portion of the above pyridine solution as follows: azeotropic removal of the pyridine under reduced pressure with n-heptane followed by chromatography on 1 g of alumina (activity III) with 1:10 ether–petroleum ether afforded a spectral sample of the enol ether 14: R_f 0.22 (silica gel, 1:10 ether–petroleum ether, streaks much due to decomposition); IR ($CHCl_3$) 1750 (C=O), 1660 cm^{-1} (O—C=C); ^1H NMR ($CDCl_3$) δ 0.84 (d, 3 H, J = 6 Hz, C(3)-CH_3), 1.03 (d, 3 H, J = 6 Hz, C(5)-CH_3), 1.17 (d, 3 H, J = 7 Hz, α-CH_3), 1.53–1.93 (br m, 3 H, C(3)-H and C(4)-H_2), 2.17 (br m, 1 H, C(5)-H), 2.70 (dq, 1 H, J = 3 Hz, J Hz, α-H), 3.63 (dd, 1 H, J = 3 Hz, J' = 10 Hz, C(2)-H), 3.70 (s, 3 H, OCH_3), 4.12 (d, 1 H, J = 2 Hz, *trans*-O—C=CH), 4.32 (d, 1 H, J = 2 Hz, *cis*-O—C=CH).

The above pyridine solution of the enol ether 14 in 12 mL of dry dichloromethane was cooled to −78 °C (dry ice/2-propanol) and treated with a stream of ozone in oxygen until the light blue color persisted (5 min). After the mixture was stirred at −78 °C for 10 min, 2 mL of dimethyl sulfide was added and the mixture was allowed to warm to room temperature for 3 h. Concentration under reduced pressure followed by azeotropic removal of pyridine under reduced pressure with n-heptane afforded, after chroma-

tography of the solid residue on 25 g of silica gel with 1:1 ether–petroleum ether, 113 mg (86%) of the lactonic ester **15** as a white solid melting at 77–78 °C.

Recrystalization of a portion of this solid from hot *n*-pentane afforded the analytical sample (84% recovery) as long colorless needles melting at 78–78.5 °C (lit. 75.5–76.5 °C,[3] 79–81 °C[4]): R_f 0.16 (silica gel, 1:1 ether–petroleum ether); IR ($CHCl_3$) 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.99 (d, 3 H, J = 6 Hz, C(3)-CH_3), 1.18 (d, 3 H, J = 7 Hz, α-CH_3), 1.26 (d, 3 H, J = 6 Hz, C(5)-CH_3), 1.45 (dd, 1 H, $J = J'$ = 12 Hz, C(4)-H**H**), 1.63–2.07 (br m, 2 H, C(4)-H**H** and C(3)-H), 2.49 (ddq, 1 H, J = 12 Hz, $J' = J''$ = 6 Hz, C(5)-H), 2.71 (dq, 1 H, J = 2.5 Hz, J' = 7 Hz, α-H), 3.70 (s, 3 H, OCH_3), 4.51 (dd, 1 H, J = 2.5 Hz, J' = 10 Hz, C(2)-H); $[\alpha]^{25}_D$ +38° ($CHCl_3$, *c* 1.03); $[\alpha]^{25}_D$ +42° (CH_3OH, *c* 3.30) [lit.[3] $[\alpha]^{25}_D$ +42° (CH_3OH, *c* 3.29)].

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.51; H, 8.22.

Methyl [2*S*-[2α(*S),3β,5α]]-Tetrahydro-α,3,5-trimethyl-6-oxo-2*H*-pyran-2-acetate (5-epi-15).** The procedure for the preparation of the lactonic ester **15** with 98 mg (0.772 mmol) of anhydrous siliver fluoride and 80 mg (0.235 mmol) of the iodide 5-epi-**13** in 0.70 mL of dry pyridine afforded after workup the enol ether 5-epi-**14** in pyridine (approximately 0.3 mL): R_f 0.23 (silica gel, 1:10 ether–petroleum ether, streaks much due to decomposition); IR (neat) 1730 (C=O), 1640 cm^{-1} (O—C=C); ^1H NMR ($CDCl_3$) δ 0.92 (d, 3 H, J = 6 Hz, C(3)-CH_3), 1.09 (d, 3 H, J = 7 Hz, C(5)-H), 1.20 (d, 3 H, J = 7 Hz, α-CH_3), 1.42–2.06 (br m, 3 H), 2.46 (br m, 1 H, C(5)-H), 2.71 (dq, 1 H, J = 5 Hz, J' = 7 Hz, α-H), 3.66 (s, 3 H, OCH_3), 3.74 (dd, 1 H, J = 5 Hz, J' = 8 Hz, C(2)-H), 4.06 (s, 1 H, *trans*-O—C=CH), 4.23 (s, 1 *H*, *cis*-O—C=CH).

This pyridine solution was ozonized as in the above procedure in 5 mL of dry dichloromethane and quenched with 0.8 mL of dimethyl sulfide. After concentration of the reaction mixture under reduced pressure, chromatography of the residue on 12 g of silica gel with 2:3 ether–petroleum ether afforded 34 mg (69%) of the lactonic ester 5-epi-**15** with minor contaminents. Rechromatography on 10 g of silica gel with 1:2:1 ether–petroleum ether–dichloromethane afforded 30.7 mg (61%) of pure lactonic ester 5-epi-**15** as a colorless oil.

Distillation [kugelrohr, 85 °C (0.005 mmHg)] of a portion of this oil provided the analytical sample: R_f 0.12 (silica gel, 2:3 ether–petroleum ether), R_f 0.25 (silica gel, 1:2:1 ether–petroleum ether–dichloromethane); IR ($CHCl_3$) 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.01 (d, 3 H, J = 6 Hz, C(3)-CH_3), 1.21 (d, 3 H, J = 7 Hz, CH_3), 1.23 (d, 3 H, J = 7 Hz, CH_3), 1.63–2.13 (br m, 3 H), 2.69 (overlapping dq and m, 2 H, J = 3 Hz, J' = 7 Hz, α-H and C(5)-H), 3.70 (s, 3 H, OCH_3), 4.49 (dd, 1 H, J = 3 Hz, J' = 10 Hz, C(2)-H); $[\alpha]^{24}_D$ +104° ($CHCl_3$, *c* 1.03).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.49; H, 8.35.

[2*S*-[2α(*S),3β,5β]]-Tetrahydro-α,3,5-trimethyl-6-oxo-2*H*-pyran-2-acetic Acid (16).** To a stirred solution of 107 mg (0.50 mmol) of the lactonic ester **15** in 5 mL of methanol was added 5 mL of 0.5 M aqueous lithium hydroxide and after 1 h the methanol was removed under reduced pressure. The resulting aqueous solution was poured into 25 mL of water, acidified to pH 1 with 10% aqueous hydrochloric acid, saturated with sodium chloride, and extracted with four 15-mL portions of ether. After being dried ($MgSO_4$), the extracts were concentrated under reduced pressure and chromatography of the residue on 12 g of acidic silica gel with 2:1 ether–petroleum ether afforded 94 mg (94%) of the Prelog–Djerassi lactonic acid (**16**) as a white solid melting at 120–123 °C.

Recrystallization of this solid from hot *n*-pentane/ether afforded 70 mg of pure Prelog–Djerassi lactone as white crystals melting at 123.5–125 °C (lit. 124–125 °C[3], 126–128 °C[4]): R_f 0.18 (silica gel, 2:1 ether–petroleum ether plus 2% acetic acid); IR ($CHCl_3$) 2500–3500 (CO_2H), 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) (see ref 9e) δ 1.02 (d, 3 H, J = 6.2 Hz, C(3)-CH_3), 1.20 (d, 3 H, J = 7.3 Hz, α-CH_3), 1.28 (d, 3 H, J = 7.3 Hz, C(5)-CH_3), 1.48 (t, 1 H, J = 13 Hz, C(4)-H**H**), 1.88–2.07 (br m, 2 H, C(3)-H and C(4)-H**H**), 2.54 (ddq, 1 H, J = 13 Hz, J' = 7 Hz, J'' = 7 Hz, C(5)-H), 2.76 (dq, 1 H, J = 2.3 Hz, J' = 7.3 Hz, α-H), 4.59 (dd, 1 H, J = 2.3 Hz, J' = 10.1 Hz, C(2)-H), 10.91 (br s, 1 H, CO_2H); ^{13}C NMR[9e] ($CDCl_3$) δ 8.4 (α-CH_3), 16.8 and 17.2 (C(3)-CH_3 and C(5)-CH_3), 30.8 (C(4)), 36.2 and 37.1 (C(3) and C(5)), 41.0 (C(α)), 86.4 (C(2)), 174.7 and 177.6 (HO_2C and C(6)); $[\alpha]^{21}_D$ +47.7° ($CHCl_3$, *c* 1.93) (lit. $[\alpha]_D$ +33° ($CHCl_3$, *c* 0.797),[3] $[\alpha]_D$ +38° ($CHCl_3$),[4] and $[\alpha]_D$ +43° ($CHCl_3$)[5] from degradation studies; $[\alpha]^{25}_D$ +38.7° ($CHCl_3$, *c* 1.90)[9d] and $[\alpha]^{25}_D$ +43.3° ($CHCl_3$, *c* 2.40)[9e] from resolution of synthetic intermediates].

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.01; H, 7.96.

Recrystallization of a portion (54 mg) of the analytical sample from hot *n*-pentane/ether afforded 42 mg of the Prelog–Djerassi lactone as a white solid melting at 124–125 °C with little change in the optical rotation [$[\alpha]^{21}_D$ +47.4° ($CHCl_3$, *c* 1.85)].

[2*S*-[2α(*S),3β,5α]]-Tetrahydro-α,3,5-trimethyl-6-oxo-2*H*-pyran-2-acetic Acid (5-epi-16).** The procedure for the preparation of the Prelog–Djerassi lactone (**16**) with 22.5 mg (0.105 mmol) of the lactonic ester 5-epi-**15** in 1 mL of methanol and 1 mL of 0.5 M aqueous LiOH afforded, after workup and chromatography on 10 g of acidic silica gel with 1:1 ether–petroleum ether, 20.9 mg (99%) of the lactonic acid 5-epi-**16** as a white solid melting at 70–85 °C.

Recrystallization of this solid from hot *n*-hexane/ether afforded 15 mg of analytically pure lactonic acid 5-epi-**16** melting at 92–93 °C: R_f 0.18 (silica gel, 2:1 ether–petroleum ether plus 2% acetic acid); IR ($CHCl_3$) 2500–3600 (CO_2H), 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) (see ref 9e) δ 1.03 (d, 3 H, J = 6.3 Hz, C(3)-CH_3), 1.21 (d, 3 H, J = 6 Hz, CH_3, 1.23 (d, 3 H, J = 7 Hz, CH_3), 1.54–2.14 (br m, 3 H), 2.68 (br m, 2 H, α-H and C(5)-H), 4.54 (dd, 1 H, J = 2.7 Hz, J' = 9.6 Hz, C(2)-H), 8.51 (br s, 1 H, CO_2H); ^{13}C NMR ($CDCl_3$) (see ref 9e) δ 8.8 (α-CH_3), 16.5 and 17.4 (C(3)-CH_3 and C(5)-CH_3), 28.7 (C(4)), 32.5 and 34.8 (C(3) and C(5)), 40.9 (C(α)), 82.8 (C(2)), 175.8 and 178.3 (CO_2H and C(6)); $[\alpha]^{21}_D$ +117° ($CHCl_3$, *c* 1.03).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.85; H, 7.99.

Registry No. **1**, 63598-38-9; **2**, 72233-95-5; **4**, 75830-55-6; α-*epi*-**4**, 75879-59-3; **5**, 75830-56-7; **6**, 75830-57-8; **7**, 75830-58-9; **8**, 75830-59-0; 3-*epi*-**8**, 75830-60-3; **9**, 75830-61-4; 3-*epi*-**9**, 75830-62-5; **10**, 75830-63-6; 5-*epi*-**10**, 75879-60-6; **11**, 75830-64-7; 5-*epi*-**11**, 75879-61-7; **12**, 75830-65-8; 5-*epi*-**12**, 75879-62-8; **13**, 75830-66-9; 5-*epi*-**13**, 75879-63-9; **14**, 75830-67-0; 5-*epi*-**14**, 75830-69-2; **15**, 72367-05-6; 5-*epi*-**15**, 75879-64-0; **16**, 26539-81-1; 5-*epi*-**16**, 75879-65-1; i, 75830-68-1; *tert*-butyldimethylchlorosilane, 18162-48-6; methylenetriphenylphosphorane, 3487-44-3.

CHAPTER ONE

LARGE-SCALE EXPERIMENTALS FOR INTERMEDIATES 5, 6 and 7

Methyl [2S-[2α(S*),5α,6β]]-5,6-dihydro-5-hydroxy-6-(hydroxymethyl)-α-methyl-2H-pyran-2-acetate (5). A vigorously stirred mixture of 15.5 g (50.9 mmol) of the benzylidene acetal 4, 305 mL of tetrahydrofuran, and 1145 mL of 0.01 N sulfuric acid was heated at 70°C under an argon atmosphere for 3 hours. The tetrahydrofuran and benzaldehyde were removed under reduced pressure, and the remaining aqueous solution was saturated with sodium chloride and extracted with eleven 250 mL portions of ethyl acetate. The combined extracts were dried ($MgSO_4$) and removal of the solvent under reduced pressure afforded 11.0 g (100%) of the diol 5 as a white solid melting at 49.5-50.5°C. This material was used without further purification.

Methyl [2S-[2α(S*),5α,6β]]-6-[[[(1,1-dimethylethyl)-dimethylsilyl]oxy]methyl]-5,6-dihydro-5-hydroxy-α-methyl-2H-pyran-2-acetate (6). To a stirred solution of 11.0 g (50.9 mmol) of the crude diol 5 in 100 mL of dry pyridine cooled to 0°C (ice bath) under an argon atmosphere was added 9.60 g (63.5 mmol) of tert-butyldimethylchlorosilane (TBSCl) in five equal portions allowing 30 min to elapse

between additions. The reaction mixture was allowed to stir for 90 min after the last addition and then was poured into 1000 mL of water and extracted with three 100 mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Azeotropic removal of pyridine by the addition of 100 mL of n-heptane followed by removal under reduced pressure six successive times afforded 16.8 g (100%) of the monosilylated product 6 as a clear oil. This material was used without further purification.

Methyl [2S-[2α(S*),6β]]-6-[[[(1,1-dimethylethyl)-dimethylsilyl]oxy]methyl]-5,6-dihydro-α-methyl-5-oxo-2H-pyran-2-acetate (7). To a mechanically stirred mixture of 22.0 g (102 mmol) of pyridinium chlorochromate (PCC), 1.67 g (20.4 mmol) of anhydrous sodium acetate, 22.0 g of Celite (dried at 170°C), and 130 mL of dry dichloromethane under an argon atmosphere was added 16.8 g (50.9 mmol) of the crude allylic alcohol 6 in 33 mL of dry dichlormethane over 10 min. After 4.3 h at room temperature, the reaction mixture was diluted with 300 mL of ether, stirred for 20 min, and finally filtered. The filter cake was washed liberally with ether (700 mL) and then the filtrate was filtered through an 80 g Fluorisil column using ether as eluent. The resulting eluent was concentrated under reduced pressure followed by azeotropic removal of pyridine

under reduced pressure with 200 mL of n-heptane. Chromatography of the residue on 600 g of silica gel with 1:4 ether:petroleum ether afforded 15.6 g (93% over 3 steps) of the enone 7 as a colorless oil.

Chapter 2

The Synthesis of Spiroketal Intermediates and Their Cleavage into Open-Chain Derivatives

Macrolide Total Synthesis: The Synthesis of Spiroketal Intermediates and Their Cleavage into Open-Chain Derivatives

Robert E. Ireland* and John P. Daub[1]

Contribution No. 6690 from the Chemical Laboratories
California Institute of Technology
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Abstract: A convergent method for the preparation of spiroketals by hetero-Diels-Alder condensation of the keto-enol ether 14 with α,β-unsaturated carbonyl compounds is developed which is applicable with the poor heterodienes methacrolein and 2-methyl-1-penten-3-one. Additionally, the cleavage of spiroketals to open-chain derivatives for macrolide total synthesis is realized by thioketal exchange with 1,2-ethanedithiol.

Macrolide Total Synthesis: The Synthesis of Spiroketal Intermediates and Their Cleavage into Open-Chain Derivatives

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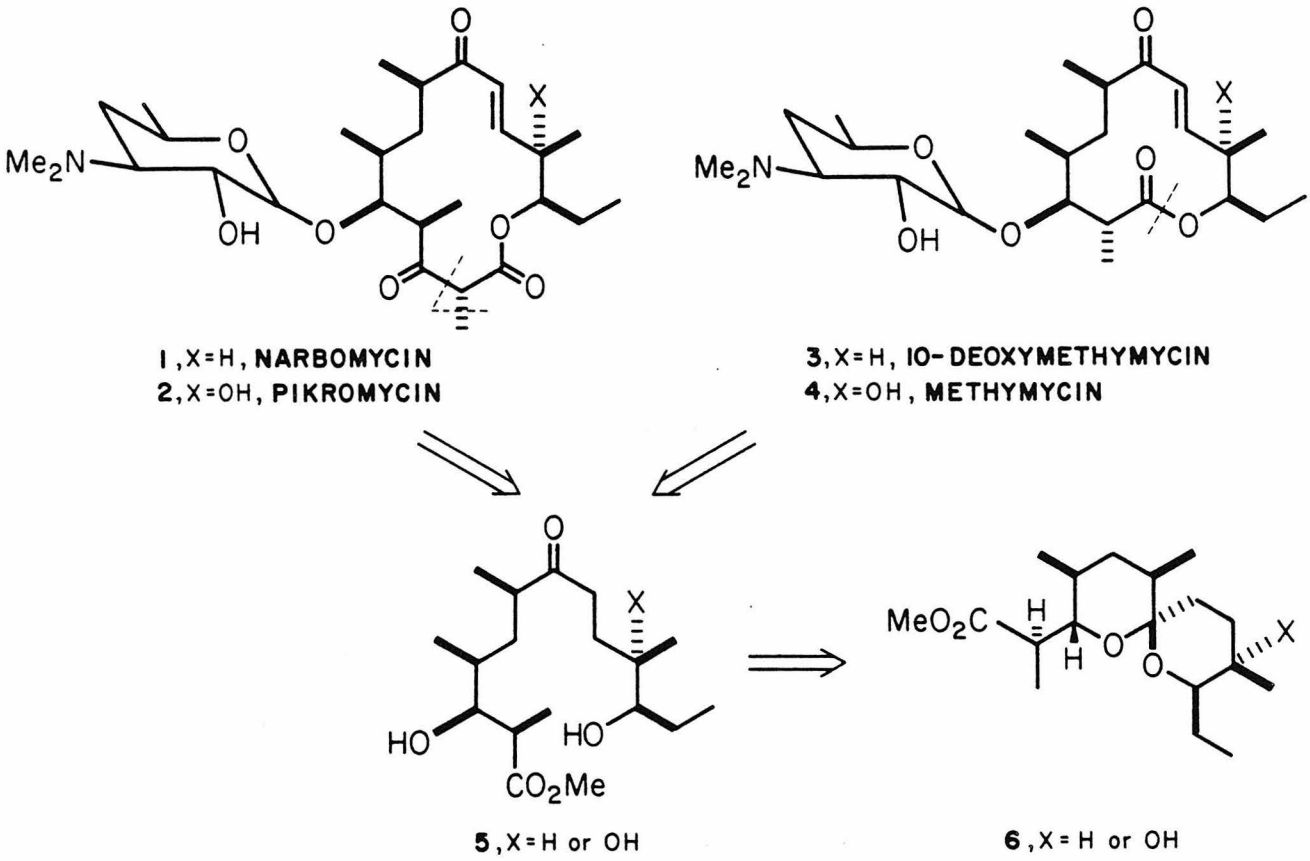
The macrolide antibiotics[2,3] are a class of fascinating, stereochemically complex organic molecules which have been under intense investigation for thirty years. Initial work focused on the elucidation of their macrolactone structure and stereochemistry and, more recently, on their total synthesis. Several macrolide antibiotics and their aglycones have recently yielded to chemical total synthesis.[4]

For the current work,[5,6] the long standing relationship between the macrolide antibiotics and their spiroketals[7,8] suggested that the latter stereochemically rigid systems might be useful key intermediates for the construction of these antibiotics. The success of such a plan then depends on the development of efficient means for first the generation of the appropriate spiroketals and subsequently their cleavage to open-chain systems suitable for macrolactonization. A similar basic plan is independently

SCHEME I: Synthetic Strategy for Macrolide Synthesis



1, X=H, **NARBOMYCIN**
2, X=OH, **PIKROMYCIN**

3, X=H, **10-DEOXYMETHYMYCIN**
4, X=OH, **METHYMYCIN**

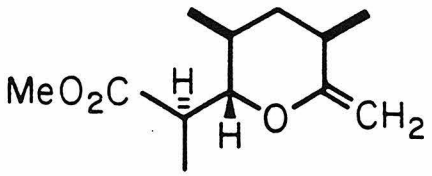
5, X=H or OH

6, X=H or OH

under investigation by Professor P. Deslongchamps,[9] and his results will be reported elsewhere.

For the synthesis of the macrolide antibiotics--narbomycin (1)[10], pikromycin (2)[11], 10-deoxymethymycin (3)[12] and methmycin (4)[7]--a common spiroketal key intermediate 6 was envisioned. The present report describes a successful convergent approach to the construction and characterization of such spiroketals, and the development of efficient methodology for their cleavage to representative open-chain systems.

In addressing this first problem, the exocyclic enol ether 7 was prepared stereoselectively from D-glucose and was converted into the Prelog-Djerassi lactone as a stereochemical proof.[6b] Hetero-Diels-Alder condensation[13] of this enol ether 7 with 2-methyl-1-penten-3-one would provide a spiroketal that would possess the necessary



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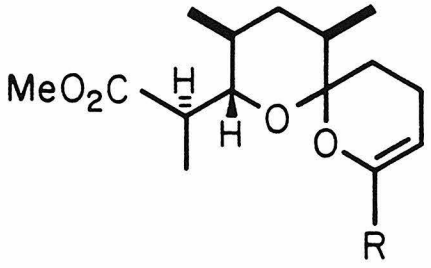
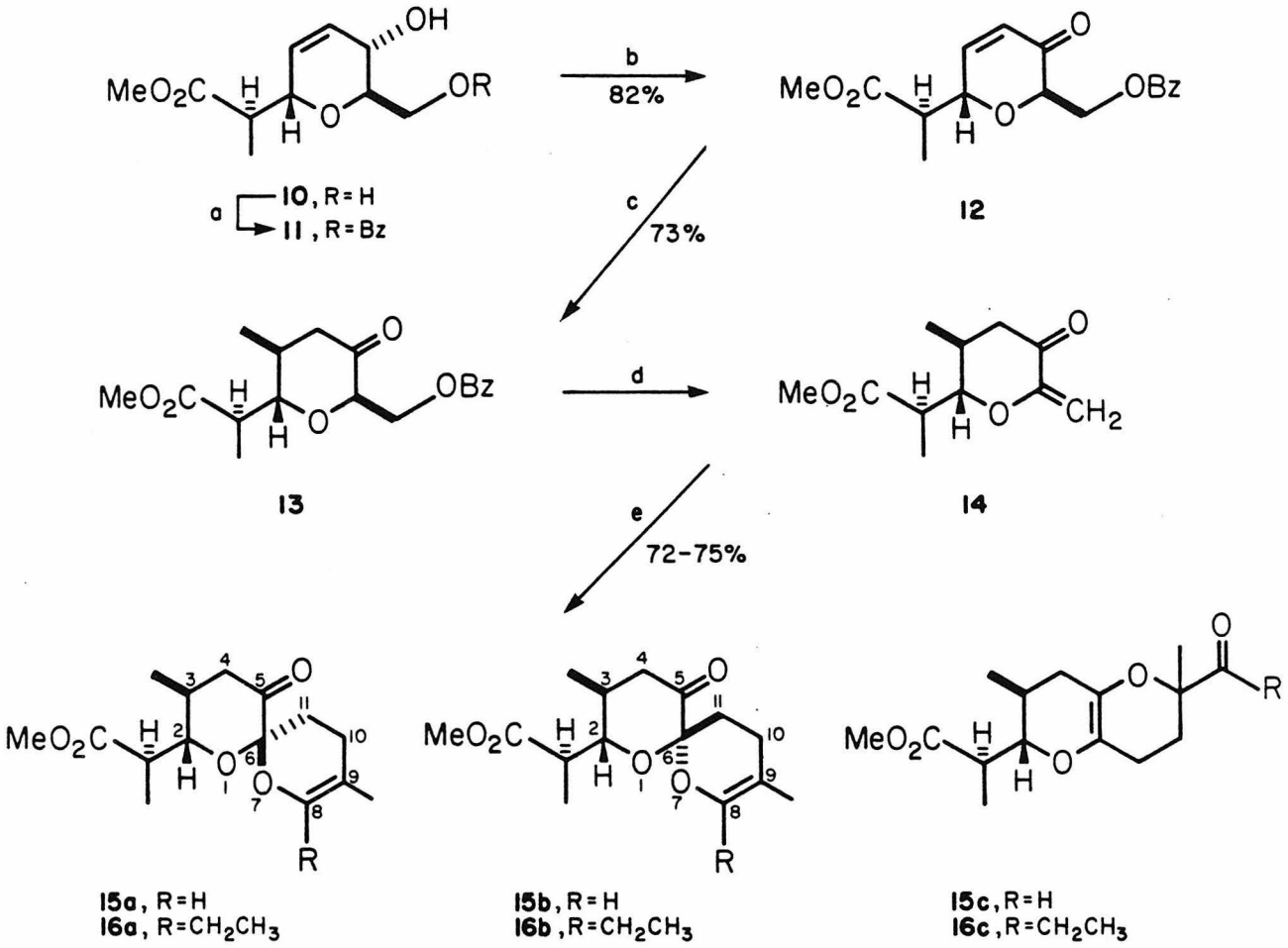


8, R=H
9, R=CH_2CH_3

carbon-skeleton. Subsequent hydrogenation or hydroboration of the resultant enol ether would afford the spiroketals 6 and a diastereomer from attack on the two faces of the double bond. It was, however, found that the exocyclic enol ether 7 was quite unreactive as a dienophile and was very unstable toward rearrangement of the double bond into the endocyclic position. For example, condensation of the enol ether 7 with the very reactive hetero-diene acrolein afforded the Diels-Alder adduct 8 in only 19% yield, while condensation with ethyl vinyl ketone afforded the spiroketal 9 in only 6% yield (by ^{1}H-NMR). Due to the inverse electron demand nature of this hetero-Diels-Alder reaction[14], it was clear that the more electron rich hetero-diene 2-methyl-1-penten-3-one was certain to meet with failure. Thus, in order to overcome the unfavorable reactivity of the exomethylene enol ether 7, the keto-enol ether 14 (see Scheme II) was chosen as an alternative hetero-Diels-Alder substrate, since double bond migration is precluded. This presents a regio- and/or role-selectivity question, however, as the keto-enol ether 14, which is held in an s-cis conformation, can participate as either diene or dienophile. Due to the inverse electron demand character of this hetero-Diels-Alder reaction[14], it was proposed that the electron rich enol ether double bond of the keto-enol ether 14 would participate as the dienophile.

SCHEME II: Hetero-Diels-Alder Synthesis of Spiroketals[a]



[a] a, BzCl, C_5H_5N, CH_2Cl_2, -78°C → RT; b, $[C_5H_5N{\cdot}H]_2Cr_2O_7$ (PDC), DMF, 0°C; c, $LiCu(CH_3)_2$, Et_2O, 0°C; d, Et_3N; e, methacrolein or 2-methyl-1-penten-3-one.

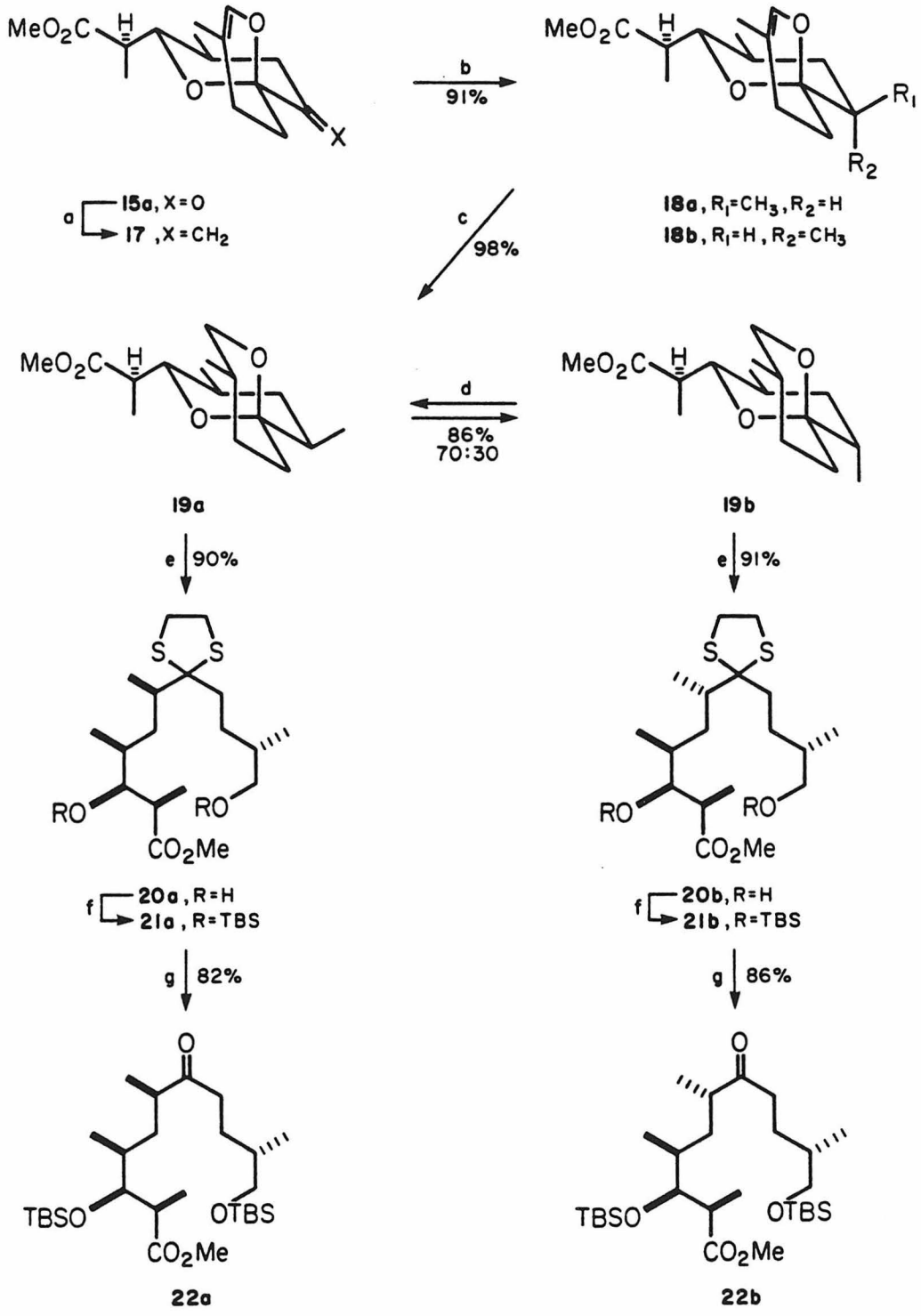
After initial investigation of a tosylate leaving group for the generation of the enol ether 14[15], the sequence in Scheme II with a benzoate leaving group was found to be very successful. The diol 10[6b] was converted through the enone 12 into the keto-benzoates 13 and 3-epi-13 as a 77:23 mixture (by ^{1}H-NMR) in 78% overall yield. This moderate stereoselectivity in the cuprate addition is to be contrasted with the very high stereoselectivity (94:6) observed with the corresponding tert-butyldimethylsilyl derivative.[6b] Triethylamine then readily effects elimination of benzoic acid. The resulting keto-enol ether 14 is, however, unstable and dimerizes very rapidly at room temperature even in dilute solution. To avoid this dimerization, the elimination reaction was performed at 60° in the presence of a large excess of the hetero-dienes methacrolein and 2-methyl-1-penten-3-one and the desired Diels-Alder adducts 15a,b,c and 16a,b,c were realized in 72% and 75% yields, respectively. These high yields with such unreactive α,β-unsaturated carbonyl compounds illustrates the high hetero-Diels-Alder reactivity of this keto-enol ether 14 and provides a new general method for the synthesis of spiroketals from 3-keto-2-methylene-tetrahydro-pyran intermediates.[16]

Chromatographic separation and NMR analysis showed that the undesired regioisomers 15c and 16c represented

only 5% and 15%, respectively, of the mixture of the adducts. The ratio between the spiroketals 15a and 15b by isolation was 83:17; the major component of this spiroketal mixture is 15a which enjoys the stabilization of the anomeric effect.[17] This stereoselectivity indicates a small electronic effect in the transition state for the hetero-Diels-Alder reaction. The assignment of the spirocenter stereochemistry is based on the chemical shift of the C(2) hydrogen plus other spectroscopic and chemical data (vide infra). The hydrogen at C(2) appears at 4.36 ppm in spiroketal 15a in accord with a deshielding effect by the axial O(7), while in spiroketal 15b this hydrogen appears at 3.87 ppm. Similarly, a 69:31 ratio between the spiroketals 16a and 16b was observed.

Further elaboration of the spiroketal 15a through Wittig methylenation and subsequent hydrogenation (Scheme III) afforded the spiroketals 19a and 19b as a separable 55:45 mixture in 89% overall yield. The low stereoselectivity of the first hydrogenation is of little consequence since acid catalyzed equilibration of spiroketal 19b afforded a 70:30 equilibrium mixture of the spiroketals 19a and 19b in 86% yield. This result verifies both the stereochemistry at C(5), and that at the spirocenter for the more stable configuration is expected to be that which manifests the anomeric effect. More significant, however,

SCHEME III: Elaboration of Spiroketal 15a and Cleavage to Seco-Acid Derivatives[a,b]

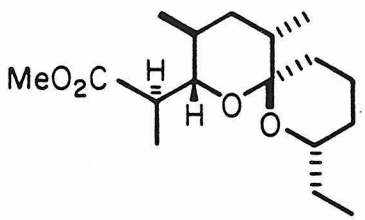


[a] a, $(C_6H_5)_3PCH_2$, THF; b, PtO_2, H_2, pentane; c, Pd, 50 psi H_2, MeOH, 5 days; d, pTsOH·H_2O, CH_2Cl_2, 48 h; e, $HSCH_2CH_2SH$, BF_3·Et_2O, -40°C; f, TBSCl, imidazole, DMF, 80°C, 18-20 h; g, $HgCl_2$, $CaCO_3$, MeCN, H_2O.

[b] TBS = t-Bu$(CH_3)_2$Si-.

is the stereoselectivity of the second hydrogenation of the enol ether double bond which occurred completely from the slightly convex surface of this spirocyclic system. The stereochemistry at C(9) was assigned from the coupling constants observed for the hydrogens at C(8) in these spiroketals 19a,b. The axial hydrogen at C(8) shows, in addition to a geminal coupling of 11 Hz, a vicinal coupling of 11 Hz with the axial hydrogen at C(9). The equatorial hydrogen at C(8) shows, in addition to a geminal coupling of 11 Hz and a zigzag coupling of 2 Hz with the equatorial hydrogen at C(10), a vicinal coupling of 4.5 Hz with the axial hydrogen at C(9).

With suitable model spiroketals in hand, methods for spiroketal cleavage to the open-chain derivatives were investigated.[18] Initial investigation focused on the thermodynamically less stable[19] spiroketal 23[5], and it was found that this substance could be converted by oxime formation as described earlier by Corey[20] to the oxime-diol 24 in 85% yield. However, this method was not totally satisfactory for the spiroketal 15b, which formed the oxime-diol 25 in 74% yield with only 57% conversion. As a result, attention was turned to ketal exchange with 1,2-ethanedithiol. Treatment of the spiroketal 23 with borontrifluoride etherate in 1,2-ethanedithiol at -40°C afforded the thioketal-diol 26 in 90% yield. Substitution



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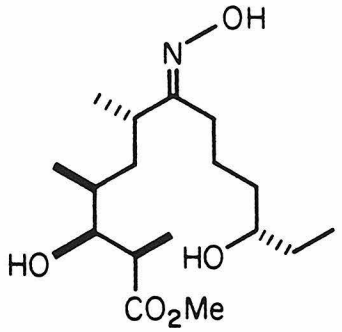

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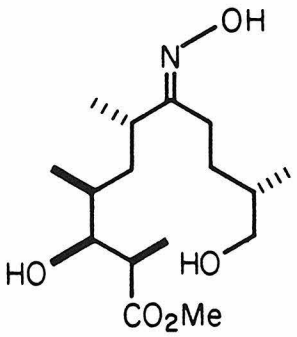

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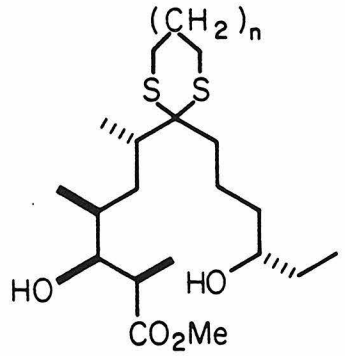


26, n=0
27, n=1

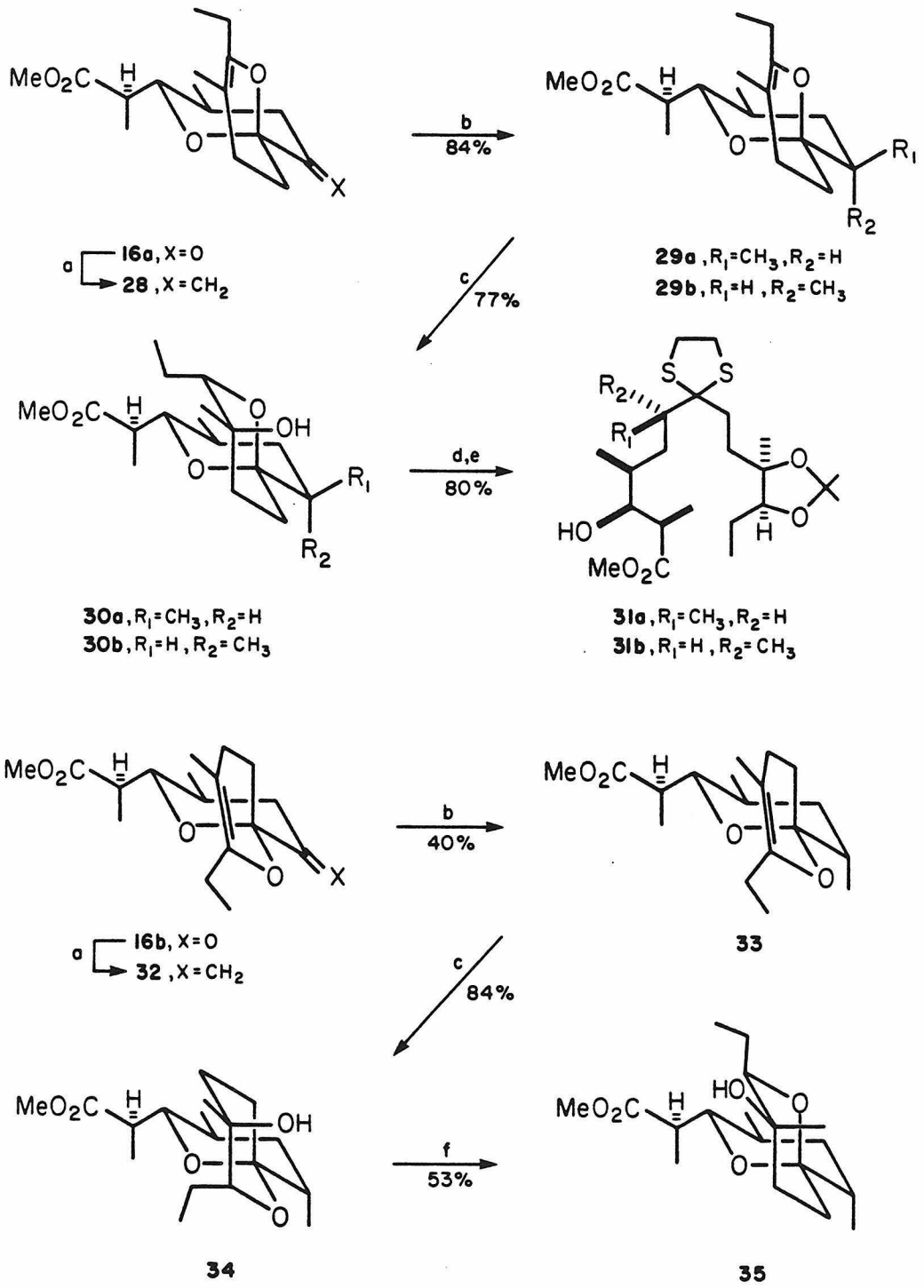
of 1,3-propanedithiol for this reaction provided the analogous dithiane 27; however, in this case, only a 70% conversion was observed. These reactions were performed at low temperature, since at higher reaction temperatures (25°) products were obtained in which an internal oxidation-reduction had occurred[15] as observed by C. Djerassi[21] with sapogenins. Similar results have been independently observed by Professor Deslongchamps[22]. Application of this low temperature 1,2-ethanedithiol procedure to the

spiroketals 19a and 19b afforded the thioketal-diols 20a and 20b, respectively, in 90% yields without any apparent epimerization of the methyl group adjacent to the ketal grouping. This remarkable preservation of the stereochemistry of this methyl group is very important for the synthesis of the natural products. These thioketal-diols 20a and 20b were then readily converted into the open chain ketones 22a and 22b in yields of 82% and 86%, respectively.

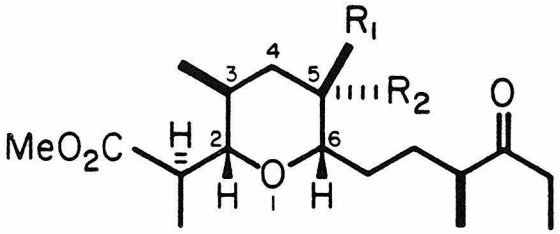
With an efficient method for the conversion of spiroketals into open chain ketones in hand, the further elaboration of the spiroketals 16a and 16b was continued (Scheme IV). The enol ethers 29a and 29b were prepared as a 60:40 mixture (by ^{1}H-NMR) from the spiroketal 16a in 84% yield. It should be noted that the enol ether 29a is the product expected from the Diels-Alder condensation of the enol ether 7 with 2-methyl-1-penten-3-one.

Attempted hydrogenation (Pd, CH_3OH, 50 psi H_2, 10 days) of these enol ethers 29a,b afforded, in addition to 25% starting material and trace quantities of hydrogenation products, a 37:63 (by 500 MHz ^{1}H-NMR) mixture of the inseparable hydrogenolysis products 36a and 36b in 22% yield. The stereochemistry of the side chain stereocenter was assigned from previously observed convex hydrogenation of this system. The stereochemistry at C(6) was assigned from the 9 Hz coupling between the C(5) and C(6) hydrogens

SCHEME IV: Elaboration of the Spiroketals 16a,b[a]

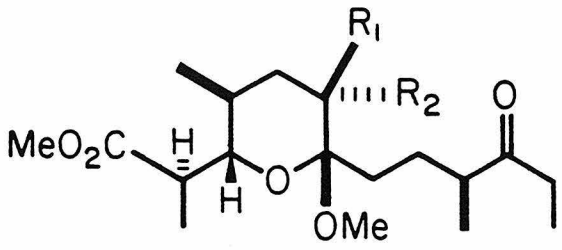


[a] a, $(C_6H_5)_3PCH_2$, THF; b, PtO_2, H_2, pentane; c, BH_3, THF, 0°C, 1 N NaOH, 30% H_2O_2; d, $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$, -40°C; e, $pTsOH \cdot H_2O$, acetone; f, $pTsOH \cdot H_2O$, CH_2Cl_2, 10 min.



36a, $R_1 = CH_3, R_2 = H$

36b, $R_1 = H, R_2 = CH_3$



37a, $R_1 = CH_3, R_2 = H$

37b, $R_1 = H, R_2 = CH_3$

in the pyran 36a and the 4 Hz coupling between these hydrogens in the pyran 36b. These pyrans 36a,b arise by either a hydrogenolysis mechanism or by hydrogenation, and then an acid catalyzed internal hydride transfer reaction which is known to proceed by axial entry of the hydride.[15,22] In fact, independent synthesis of the expected cis-hydrogenation product afforded upon acid treatment these same pyrans 36a,b (by 500 MHz ^{1}H-NMR) consistent with this latter mechanistic possibility.[15] Additionally, a 48% yield was obtained of the methanolysis products 37a,b, apparently due to traces of acid present in the hydrogenation mixture. These same methanolysis products 37a,b could also be prepared in 96% yield by treatment of the enol ethers 29a,b with 0.01 M HCl in methanol and possessed a single configuration at the exocyclic stereocenter by 500 MHz ^{1}H-NMR. This high

stereoselectivity of this spirocyclic system even toward protonation is quite remarkable.

Hydroboration of these enol ethers 29a,b afforded the alcohols 30a,b with the expected high stereoselectivity. It should be noted that this is the incorrect chirality for the natural products (see Scheme I), but that a stereospecific double inversion of the open-chain vicinal diol should be possible through epoxide formation and subsequent hydrolysis. Thioketal exchange followed by acetonide formation afforded the open chain thioketal-acetonides 31a,b in 80% overall yield and illustrated the compatibility of this methodology with a tertiary alcohol. This same sequence of reactions with the spiroketal 16b led to the spiroketal 34 in 34% overall yield. This spiroketal possesses the correct chirality for the natural products since reversal of the spirocenter stereochemistry exposes the opposite face of the enol ether double bond. Very brief acid treatment of this spiroketal 34 rearranges the spirocenter to the more stable spiroketal 35 in 53% yield; in addition, the corresponding 1,6-dioxaspiro[4.5]decane ring contracted spiroketals were formed in 47% yield.

Although the spiroketals 30a,b after a double-inversion sequence and/or the spiroketal 35 after equilibration of the C(5) methyl group could be utilized for the preparation of the seco-acid derivative 5 (X=OH), the

low yields and stereoselectivity of this route left much to be desired. Thus, rather than pursue the synthesis with the present materials, the basic tenets of this approach and the technological experience gained were used in an alternate more selective scheme that is reported in the following paper.[5]

Experimental Section

Melting points were determined by using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 727B or 1310 infrared spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM-390 or a JEOL FX-90Q spectrometer, except where "500 MHz" denotes spectra recorded on a Bruker WM-500 (Southern California Regional NMR Facility, Caltech, Pasadena, CA). 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, assignment). Spectra in C_6D_6 were often used to aid in the analysis of overlapping signals in the reported spectra in $CDCl_3$. Carbon nuclear magnetic resonance ^{13}C-NMR) spectra were recorded on a JEOL FX-90Q 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 (assignment). For all spectra, numbering in the assignments employs the numbering system implicit in the Chemical Abstracts name at the heading of each experimental. Optical rotations were measured in 1 dm

cells of 1 mL capacity by using a JASCO Model DIP-181 polarimeter. Chloroform, when used as a solvent for optical rotations, was filtered through neutral alumina (activity I) immediately prior to use.

Analytical thin layer chromatography (TLC) was conducted on 2.5 x 10 cm precoated TLC plates, silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co. Darmstadt, Germany.

Silica gel columns for chromatography utilized E. Merck "Silica Gel 60", 70-230 mesh ASTM. Flash chromatography was performed on E. Merck "Silica Gel 60", 230-400 mesh ASTM, according to published procedure (Still, W.C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923-2925). Acidic silica gel refers to Silicar CC-4 Special "for column chromatography", sold by Mallinckrodt Chemical Works, St. Louis, MO. "Alumina" refers to the grade I neutral variety manufactured by M. Woelm, Eschwege, Germany, which was neutralized to the indicated grade by the addition of water.

"Dry" solvents were distilled shortly before use from an appropriate drying agent. Benzene, pyridine, and n-hexane were distilled from powdered calcium hydride. Hexamethyldisilazane and diisopropylamine were distilled under argon from powdered calcium hydride. Dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and hexamethylphosphoramide (HMPA) were distilled under reduced pressure

from powdered calcium hydride. Tetrahydrofuran (THF) and triethylamine were distilled under argon from sodium metal with sodium benzophenone ketyl as an indicator. Ether was distilled under argon from sodium metal with sodium benzophenone ketyl as an indicator or was used directly from freshly opened cans. Dichloromethane was distilled from phosphorus pentoxide.

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. Mass spectral analyses were performed by the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE.

Methyl [2S-[2α(S*),5α,6β]]-6-[(benzoyloxy)methyl]-5,6-dihydro-5-hydroxy-α-methyl-2H-pyran-2-acetate (11). To a stirred solution of 223 mg (1.03 mmol) of the diol 10 in 6 mL of dry dichloromethane cooled to -78°C (dry ice/2-propanol) under an argon atmosphere was added first 95 mg (97 μl, 1.20 mmol) of dry pyridine and then 154 mg (127 μl, 1.09 mmol) of benzoyl chloride. After stirring at -78°C for 3h, the mixture was allowed to warm to RT over

30 min. The reaction mixture was then diluted with 20 mL of water and extracted with three 5 mL portions of dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Azeotropic removal of pyridine with n-heptane (2 x 10 mL) followed by chromatography of the residue on 15 g of silica gel with 2:1 ether:petroleum ether afforded 276 mg (84%) of the monobenzoate 11 as a white solid.

Recrystallization of a portion (145 mg) of this solid from hot n-pentane/ether afforded the analytical sample (100 mg) as colorless needles: R_f = 0.18 (silica gel, 2:1 ether:petroleum ether); IR ($CHCl_3$) 3500 (OH), 1725 (C=O), and 1615 cm^{-1} (phenyl); ^{1}H-NMR ($CDCl_3$) δ 1.27 (d, 3H, J = 7 Hz, α-CH_3), 2.42 (br, 1H, OH), 2.75 (dq, 1H, J = J' = 7 Hz, α-H), 3.63 (s, 3H, OCH_3), 3.82 (ddd, 1H, J = J' = 6 Hz, J'' = 3 Hz, C(6)-H), 3.98 (br m, 1H, C(5)-H), 4.35 (d plus allylic couplings, 1H, J = 7 Hz, C(2)-H), 4.44 and 4.60 (ABq plus different couplings with C(6)-H, 2H, J_{AB} = 12 Hz, J = 3 Hz, J' = 6 Hz, CH_2OBz), 5.87 (ABq plus allylic couplings, 2H, J_{AB} = 11 Hz, CH=CH), 7.48 (br m, 3H, ArH), 8.03 (dd, 2H, J = 2 Hz, J' = 7 Hz, ArH); $[\alpha]_D^{24}$ = -60.2° ($CHCl_3$, c 1.02).

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.82; H, 6.36.

Methyl [2S-[2α(S*),6β]]-6-[(benzoyloxy)methyl]-5,6-dihydro-α-methyl-5-oxo-2H-pyran-2-acetate (12). To a vigorously stirred solution of 257 mg (0.802 mmol) of the allylic alcohol 11 in 2 mL of dry DMF cooled to 0°C (ice bath) under an argon atmosphere was added 950 mg (2.53 mmol) of pyridinium dichromate (PDC). After 24 h at 0°C, the reaction mixture was diluted with 70 mL of water and extracted with four 20 mL portions of ether. After the combined extracts were dried, concentration under reduced pressure followed by azeotropic removal of pyridine with n-heptane (2 x 20 mL) afforded 251 mg (98%) of the enone 12 as a clear oil. This material was used without further purification.

Chromatography of a portion (70 mg) of this oil on 15 g of silica gel with 1:1 ether:petroleum ether followed by distillation [kugelrohr, 150°C (0.003 mmHg)] provided the analytical sample as a colorless oil: R_f = 0.19 (silica gel, 1:1 ether:petroleum ether); IR ($CHCl_3$) 1725 (ester C=O), 1690 (enone C=O), and 1615 cm^{-1} (phenyl); ^{1}H-NMR ($CDCl_3$) δ 1.27 (d, 3H, J = 7 Hz, α-CH_3), 2.82 (dq, 1 H, J = J' = 7 Hz, α-H), 3.62 (s, 3H, OCH_3), 4.55 (br m, 3H, CH_2OBz and C(6)-H), 4.85 (ddd, 1H, J = J' = 2 Hz, J'' = 7 Hz, C(2)-H), 6.18 (dd, 1H, J = 2 Hz, J' = 11 Hz, C(4)-H), 7.03 (dd, 1H, J = 2 Hz, J' = 11 Hz, C(3)-H), 7.47 (br m, 3H, ArH), 7.96 (dd, 2H, J = 2 Hz,

J' = 8 Hz, ArH); $[\alpha]_D^{24}$ = -87.6° ($CHCl_3$, c 1.24).

Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.23; H, 5.71.

Methyl [2S-[2α(S*),3β,6β]]-6-[(benzoyloxy)methyl]-tetrahydro-α,3-dimethyl-5-oxo-2H-pyran-2-acetate (13) and Methyl [2S-[2α(S*),3α,6β]]-6-[(benzoyloxy)methyl]-tetrahydro-α,3-dimethyl-5-oxo-2H-pyran-2-acetate (3-epi-13). To a stirred slurry of 220 mg (1.07 mmol) of cuprous bromide-dimethylsulfide complex in 11 mL of dry ether cooled to 0°C (ice bath) under an argon atmosphere was added 1.60 M methyllithium (low halide in ether) until a small amount of yellow precipitate (methylcopper) remained. After 30 min, 137 mg (0.429 mmol) of the enone 12 in 1.2 mL of dry ether was added over 5 min to this rapidly stirred solution of lithium dimethylcuprate at 0°C. The reaction was quenched after 10 min by the addition of 45 mL of saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer (blue) was extracted with three 15 mL portions of ether. After the combined organic layers were dried ($MgSO_4$), concentration under reduced pressure afforded 136 mg (95%) of the labile isomeric ketones 13 and 3-epi-13 as a colorless oil. This material was promptly subjected to subsequent reactions without further purification. Spectral analysis showed this oil to be a 77:23 mixture of ketone 13 (methyl ester at 3.58 ppm) and ketone 3-epi-13 (methyl

ester at 3.65 ppm).

Repeated crystallization of a portion of this oil from hot n-pentane provided the analytical sample of the major ketone 13 as a white solid melting at 57-57.5°C: R_f = 0.23 (silica gel, 1:1 ether:petroleum ether); IR ($CHCl_3$) 1720 (C=O) and 1615 cm^{-1} (phenyl); ^{1}H-NMR ($CDCl_3$) δ 1.03 (d, 3H, J = 6 Hz, C(3)-CH_3), 1.22 (d, 3H, J = 7 Hz, α-CH_3), 2.13-2.62 (br m, 3H, C(3)-H, C(4)-H_2), 2.78 (dq, 1H, J = 6 Hz, J' = 7 Hz, α-H), 3.58 (s, 3H, OCH_3), 4.08 (dd, 1H, J = 6 Hz, J' = 8 Hz, C(2)-H), 4.33 (t, 1H, J = 5 Hz, C(6)-H), 4.56 (d, 2H, J = 5 Hz, CH_2OBz), 7.48 (br m, 3H, ArH), 7.99 (dd, 2H, J = 2 Hz, J' = 7 Hz, ArH); $[\alpha]_D^{24}$ = +63.7° ($CHCl_3$, c 0.51).

Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.76; H, 6.70.

Methyl [2S-[2α(S*),3β,6β]]-α,3,9-trimethyl-5-oxo-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (15a), Methyl [2S-[2α(S*),3β,6α]]-α,3,9-trimethyl-5-oxo-1,7-dioxaspiro-[5.5]undec-8-ene-2-acetate (15b), and Methyl [2S-[2α(S*),3β,6α and 6β]]-6-formyl-2,3,4,6,7,8-hexahydro-α,3,6-trimethylpyrano[3,2-b]pyran-2-acetate (15c). To a stirred solution of 56.5 mg (0.169 mmol) of the benzoates 13 and 3-epi-13 in 4 mL (48 mmol) of methacrolein (distilled from hydroquinone, stabilized with 1% hydroquinone) heated to 60°C under an argon atmosphere was added 73 mg (100 μL,

0.72 mmol) of dry triethylamine. After 5 h at 60°C, concentration of the reaction mixture under reduced pressure followed by chromatography of the residue on 16 g of silica gel with 1:4 ether:petroleum ether afforded 34.2 mg (72%) of the Diels-Alder adducts as a mixture of isomers.

Chromatography of 252 mg of Diels-Alder adducts on 35 g of silica gel with 1:8:1 ether:petroleum ether:dichloromethane afforded (after recycle of mixed fractions) first 33 mg of the spiroketal 3-epi-15a as a colorless oil: R_f = 0.24 (silica gel, 1:8:1 ether:petroleum ether:dichloromethane); IR ($CHCl_3$) 1730 (C=O) and 1690 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.97 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.19 (d, 3H, J = 7 Hz, α-CH_3), 1.57 (br s, 3H, C(9)-CH_3), 1.70-2.43 (br m, 6 H, C(3)-H, eq C(4)-H, C(10)-H_2, C(11)-H_2), 2.59 (dq, 1H, J = 10 Hz, J' = 7 Hz, α-H), 3.08 (dd, 1H, J = 5 Hz, J' = 13 Hz, ax C(4)-H), 3.67 (s, 3H, OCH_3), 4.28 (dd,1H, J = 2 Hz, J' = 10 Hz, C(2)-H), 6.04 (br s, 1H, C(8)-H); $[\alpha]_D^{24}$ = +77.2° ($CHCl_3$, c 0.53).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.06; H, 7.93.

There was then eluted 169 mg of the spiroketal 15a as a white solid melting at 70-76°C. Recrystallization of a portion of this solid from hot n-pentane provided the analytical sample as colorless needles melting at 76.5-77°C:

R_f = 0.20 (silica gel, 1:8:1 ether:petroleum ether: dichloromethane); IR ($CHCl_3$) 1735 (C=O) and 1685 cm^{-1} (O-C=C); 500 MHz ^{1}H-NMR δ 0.98 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.12 (d, 3H, J = 7 Hz, α-CH_3), 1.56 (br s, 3H, C(9)-CH_3), 1.75 (br m, 2H), 1.93 (ddd, 1H, J = J' = 13 Hz, J" = 6 Hz), 2.01 (br m, 1H), 2.18 (br m, 1H), 2.41 (dd, 1H, J = 4 Hz, J' = 14 Hz, eq C(4)-H), 2.63 (dd, 1H, J = 12.5 Hz, J' = 14 Hz, ax C(4)-H), 2.74 (dq, 1H, J = 3.5 Hz, J' = 7 Hz, α-H), 3.62 (s, 3H, OCH_3), 4.36 (dd, 1H, J = 3.5 Hz, J' = 10 Hz, C(2)-H), 6.03 (s, 1H, C(8)-H); $[\alpha]_D^{24}$ = +46.4° ($CHCl_3$, c 0.98).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.92; H, 7.81.

Finally there was eluted 47 mg of a 75:25 (by NMR) mixture of the spiroketal 15b and the Diels-Alder regioisomers 15c as a colorless oil: R_f = 0.16 (silica gel, 1:8:1 ether:petroleum ether:dichloromethane); IR ($CHCl_3$) 1730 (C=O) and 1685 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) (spiroketal 15b) δ 0.98 (d, 3H, J = 6 Hz, C(3)-CH_3), 1.19 (d, 3H, J = 7 Hz, α-CH_3), 1.58 (br s, 3H, C(9)-CH_3), 1.67-2.82 (br m, 7H), 2.87 (dq, 1H, J = J' = 7 Hz, α-H), 3.67 (s, 3H, OCH_3), 3.87 (dd, 1H, J = 7 Hz, J' = 8 Hz, C(2)-H), 6.03 (br s, 1H, C(8)-H); ^{1}H-NMR (regioisomers 15c) δ 1.14 (d, 3H, J = 7 Hz, α-CH_3),

1.24 (s, 3H, C(6)-CH_3), 9.50 and 9.53 (2s, 1H, CHO).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.92; H, 7.82.

Methyl [2S-[2α(S*),3β,6β]]-8-ethyl-α,3,9-trimethyl-5-oxo-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (16a), Methyl [2S-[2α(S*),3β,6α]]-8-ethyl-α,3,9-trimethyl-5-oxo-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (16b), and Methyl [2S-[2α(S*),3β,6α and 6β]]-2,3,4,6,7,8-hexahydro-α,3,6-trimethyl-6-(1-oxopropyl)-pyrano[3,2-b]pyran-2-acetate (16c). To a stirred solution of 68 mg (0.203 mmol) of the benzoates 13 and 3-epi-13 in 4 mL (34 mmol) of 2-methylpent-1-en-3-one (distilled from hydroquinone at 70 mmHg, stabilized with 1% hydroquinone) heated to 60°C under an argon atmosphere was added 84 mg (115 μL, 0.827 mmol) of dry triethylamine. After 5 h at 60°C, concentration of the reaction mixture under reduced pressure followed by chromatography of the residue on 16 g of silica gel with 1:4 ether:petroleum ether afforded 47 mg (75%) of the Diels-Alder adducts as a mixture of isomers.

Chromatography of 330 mg of Diels-Alder adducts on 35 g of silica gel with 1:6 ether:petroleum ether afforded (after recyle of mixed fractions) first 40 mg of the spiroketal 3-epi-16a as a colorless oil: R_f = 0.24 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1725 (C=O) and 1695 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.97 (d, 3H,

J = 7 Hz, C(3)-CH_3), 1.08 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.17 (d, 3H, J = 7 Hz, α-CH_3), 1.60 (br s, 3H, C(9)-CH_3), 1.73-2.42 (br m, 8H), 2.58 (dq, 1H, J = 11 Hz, J' = 7 Hz, α-H), 3.12 (dd, 1H, J = 5 Hz, J' = 13 Hz, ax C(4)-H), 3.67 (s, 3H, OCH_3), 4.32 (dd, 1H, J = 2 Hz, J' = 11 Hz, C(2)-H); $[\alpha]_D^{25}$ = +60.9° ($CHCl_3$, c 0.64).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78, H, 8.44. Found: C, 65.95; H, 8.31.

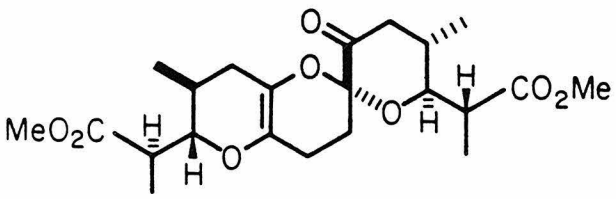
There was then eluted 160 mg of the spiroketal 16a as a very low melting white solid: R_f = 0.20 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1730 (C=O) and 1695 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.97 (d, 3H, J = 6 Hz, C(3)-CH_3), 1.07 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.10 (d, 3H, J = 7 Hz, α-CH_3), 1.58 (br s, 3H, C(9)-CH_3), 1.70-2.84 (br m, 10H), 3.57 (s, 3H, OCH_3), 4.31 (dd, 1H, J = 3 Hz, J' = 11 Hz, C(2)-H); $[\alpha]_D^{25}$ = +39.1° ($CHCl_3$, c 1.13).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.84; H, 8.38.

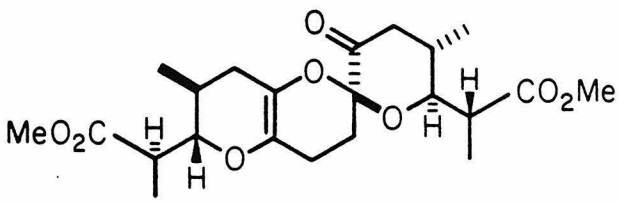
Finally, there was eluted 120 mg of a 60:40 (by NMR) mixture of the spiroketal 16b and the Diels-Alder regioisomers 16c as a colorless oil: R_f = 0.16 (silica gel, 1:6 ether: petroleum ether); IR ($CHCl_3$) 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) (spiroketal 16b) δ 1.60 (br s, 3H, C(9)-CH_3), 3.67 (s, 3H, OCH_3), 3.83 (dd, 1H, J = J' = 7 Hz, C(2)-H); ^{1}H-NMR ($CDCl_3$) (regioisomers 16c) δ 1.27 (s, 3H, C(6)-CH_3), 3.67 (s, 3H, OCH_3).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.86; H, 8.39.

Dimers of Methyl [2S-[2α(S*),3β]]-tetrahydro-α,3-dimethyl-6-methylene-5-oxo-2H-pyran-2-acetate (14). In the above Diels-Alder reactions, variable amounts of dimers of the enone 14 were isolated by further elution of the chromatography columns. Chromatography of 320 mg of crude enone dimers on 50 g of silica gel with 1:2 ether:petroleum ether afforded first 160 mg of the major enone dimer i as a white solid. Recrystallization of a 51 mg portion of this



i



ii

solid from n-pentane provided 27 mg of analytically pure dimer i as large colorless prisms melting at 103-104°C: R_f = 0.21 (silica gel, 1:2 ether:petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.96 and 0.98 (2d, 6H, J = 6 Hz, C(3)-CH_3), 1.10 and 1.14 (2d, 6H, J = 7 Hz, α-CH_3), 1.67-2.90 (br m, 12H), 3.64 and 3.68

(2s, 6H, OCH_3), 3.79 (dd, 1H, J = 4 Hz, J' = 8 Hz, C(2)-H in fused ring portion), 4.29 (dd, 1H, J = 4 Hz, J' = 10 Hz, C(2)-H in spiroketal portion); $[\alpha]_D^{25}$ = +61.9° ($CHCl_3$, c 1.02).

Anal. Calcd for $C_{22}H_{32}O_8$: C, 62,25; H, 7.60. Found: C, 62.34, H, 7.63.

There was then eluted 60 mg of the minor enone dimer ii as a white solid. Recrystallization of a 14 mg portion of this solid from hot n-pentane provided 8.3 mg of analytically pure dimer ii as clumps of small colorless prisms melting at 97-97.2°C: R_f = 0.15 (silica gel, 1:2 ether:petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.98 (d, 6H, J = 6 Hz, C(3)-CH_3), 1.16 and 1.24 (2d, 6H, J = 7 Hz, α-CH_3), 1.73-2.97 (br m, 12H), 3.68 (s, 6H, OCH_3), 3.77 (m, 1H, C(2)-H in fused ring portion), 3.83 (dd, 1H, J = J' = 7 Hz, C(2)-H in spiroketal portion); $[\alpha]_D^{25}$ = +56.2° ($CHCl_3$, C = 0.53).

Anal. Calcd for $C_{22}H_{32}O_8$: C, 62.25; H, 7.60. Found: C, 62.17; H, 7.56.

Methyl [2S-[2α(S*),3β,6β]]-α,3,9-trimethyl-5-methylene-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (17). To a stirred solution of 0.276 mmol of methylenetriphenylphosphorane [prepared by addition of 120 μL (0.28 mmol) of 2.36 M n-butyllithium in hexane to a stirred slurry of 98.6 mg (0.276 mmol) of (methyl)triphenylphosphonium bromide in

1.5 mL of dry THF at -78°C, followed by stirring at RT for 2 h] cooled to -78°C (dry ice/2-propanol) under an argon atmosphere was added 50 mg (0.177 mmol) of the ketone 15a in 1 mL of dry THF over 5 min. After being stirred for 5 min at -78°C, the reaction mixture was allowed to warm to room temperature. After 2 h at RT, the reaction mixture was quenched by the addition of 1 mL of saturated aqueous $NaHCO_3$ and poured into 20 mL of ether. This ether solution was washed with two 3 mL portions of saturated aqueous $NaHCO_3$ and one 3 mL portion of saturated aqueous NaCl. The aqueous washings were extracted twice with 5 mL portions of ether. After being dried ($MgSO_4$), the combined organic layers were concentrated under reduced pressure followed by chromatography of the residue on 10 g of silica gel with 1:10 ether:petroleum ether afforded 46.1 mg (93%) of the olefin 17 as a white solid melting at 50-50.5°C: R_f = 0.22 (silica gel, 1:10 ether:petroleum ether); IR ($CHCl_3$) 1735 (C=O) and 1690 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.88 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.07 (d, 3H, J = 7 Hz, α-CH_3), 1.54 (br s, 3H, C(9)-CH_3), 1.67-2.37 (br m, 7 H), 2.63 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.57 (s, 3H, OCH_3), 3.97 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H), 4.80 and 4.88 (2br s, 2H, C=CH_2), 5.98 (br s, 1H, C(8)-H); $[\alpha]_D^{23}$ = +47.7° ($CHCl_3$, c 0.93).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.60; H, 8.63.

Methyl [2S-[2α(S*),3β,5β,6β]]-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (18a) and Methyl [2S-[2α(S*),3β,5α,6β]]-α,3,5,9-tetramethyl-1,7-dioxaspiro-[5.5]undec-8-ene-2-acetate (18b). A vigorously stirred solution of 39 mg (0.139 mmol) of the olefin 17 in 2.5 mL of n-pentane was hydrogenated under a hydrogen atmosphere (H_2 filled balloon) at RT in the presence of a catalytic amount of powdered platinum oxide for 1 h. The reaction mixture was filtered through a pad of $MgSO_4$ and the filter cake washed liberally with ether (30 mL). The filtrate was concentrated under reduced pressure and chromatography of the residue on 1 g of silica gel with 1:20 ether:petroleum ether afforded 38.5 mg (98%) fo a 55:45 (by NMR) mixture of the enol ethers 18a and 18b as a white solid melting at 79-93°C: R_f = 0.13 (silica gel, 1:20 ether:petroleum ether); IR ($CHCl_3$) 1735 (C=O) and 1685 cm^{-1} (C-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.79-1.04 (br m, 6H, C(3)-CH_3 and C(5)-CH_3), 1.08 and 1.11 (2d, 3H, J = 7 Hz, α-CH_3 of β- and α-isomers, respectively), 1.52 (br s, 3H, C(9)-CH_3), 1.30-2.20 (br m, 8H), 2.64 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.56 (s, 3H, OCH_3), 3.77 and 3.80 (2dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H), 5.97 (br s, 1H, C(8)-H).

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.12; H, 9.30.

Methyl [2S-[2α(S*),3β,5β,6β(R*)]]-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (19a) and Methyl [2S-[2α(S*),3β,5α,6β(R*)]]-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (19b). A. Hydrogenation of enol ethers 18a and 18b. A vigorously stirred solution of 82 mg (0.290 mmol) of the enol ethers 18a and 18b in 4 mL of methanol was hydrogenated under a hydrogen atmosphere (50 psi; Parr apparatus) at RT in the presence of 3 mg of palladium black for 5 days. The reaction mixture was filtered through a pad of Celite and the filter cake was washed liberally with 20 mL of ether. Concentration of the filtrate under reduced pressure followed by chromatography on 10 g of silica gel with 1:20 ether: petroleum ether afforded first 44 mg (53%) of the spiroketal 19a as a white solid melting at 71-72°C: R_f = 0.16 (silica gel, 1:20 ether:petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.75 (d, 3H, J = 7 Hz, C(9)-CH_3), 0.83 (d, 3H, J = 7 Hz, C(3)-CH_3), 0.88 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.13 (d, 3H, J = 7 Hz, α-CH_3), 1.34-1.75 (br m, 9H), 2.71 (dq, 1H, J = 3.5 Hz, J' = 7 Hz, α-H), 3.10 (dd, 1H, J = J' = 11 Hz, ax C(8)-H), 3.42 (ddd, 1H, J = 2 Hz, J' = 4.5 Hz, J'' = 11 Hz, eq C(8)-H), 3.69 (s, 3H, OCH_3), 3.74 (dd,

1H, J = 3.5 Hz, J' = 10.5 Hz, C(2)-H); $[\alpha]_D^{25}$ = +72.6° ($CHCl_3$, c 0.53).

Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.45; H, 10.00.

There was then eluted 37 mg (45%) of the spiroketal 19b as a white solid melting at 89-90°C: R_f = 0.10 (silica gel, 1:20 ether:petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.76 (d, 3H, J = 7 Hz, C(9)-CH_3), 0.81 (d, 3H, J = 7 Hz, C(3)-CH_3), 0.97 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.16 (d, 3H, J = 7 Hz, α-CH_3), 1.24-1.74 (br m, 8H), 1.89 (ddd, 1H, J = 5 Hz, J' = J'' = 13 Hz, ax C(11)-H), 2.72 (dq, 1H, J = 3.5 Hz, J' = 7 Hz, α-H), 3.11 (dd, 1H, J = J' = 11 Hz, ax C(8)-H), 3.45 (ddd, 1H, J = 2 Hz, J' = 4.5 Hz, J'' = 11 Hz, eq C(8)-H), 3.69 (s, 3H, OCH_3), 3.77 (dd, 1H, J = 3.5 Hz, J' = 10.5 Hz, C(2)-H); $[\alpha]_D^{25}$ = +73.8° ($CHCl_3$, c 0.52).

Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.61; H, 10.08.

B. Equilibration of spiroketal 19b. 5.8 mg (0.025 mmol) of the spiroketal 19b were treated with 2 mL of dry dichloromethane saturated with p-toluenesulfonic acid-monohydrate under an argon atmosphere for 2 days at RT. The reaction mixture was then diluted with 7 mL of ether and washed with two 2 mL portions of saturated

aqueous $NaHCO_3$. The aqueous washings were extracted with two 2 mL portions of ether. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on 7 g of silica gel with 1:15 ether:petroleum ether afforded 5.0 mg (86%) of the spiroketals 19a and 19b in a 70:30 ratio, respectively. These spiroketals were identical (^{1}H-NMR, TLC) to those prepared above by hydrogenation.

Methyl [2R-(2R*,3S*,4S*,6S*,11S*)]-3,11-dihydroxy-7-(hydroxyimino)-2,4,6-trimethyltridecanoate (24). A solution of 8.5 mg (0.0285 mmol) of the spiroketal 23, 128 mg (1.85 mmol) of $NH_2OH \cdot HCl$, and 134 mg (1.63 mmol) of NaOAc (anhydrous) in 1 mL of methanol and 0.5 mL of water was heated to 65°C under an argon atmosphere for 4.5 h. The reaction mixture was then diluted with 10 mL of saturated aqueous NaCl and extracted with two 5 mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure followed by azeotropic removal of acetic acid with n-heptane. Chromatography of the residue on 7 g of silica gel with 4:1 ether:ethyl acetate afforded 8.0 mg (85%) of the diol-oxime 24 as a 70:30 (by ^{1}H-NMR) mixture of geometrical isomers. Distillation [kugelrohr, 170°C (0.003 mmHg)] provided the analytical sample as a colorless oil: R_f = 0.31 (major isomer) and 0.25 (minor isomer) (silica gel, 4:1 ether: ethyl acetate); IR ($CHCl_3$) 3340 (OH),

1725 (C=O), and 1650 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ 0.80-1.02 (br m, 6H, C(4)-CH_3 and C(13)-H_3), 1.06 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.15 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.33-1.83 (br m, 10H), 2.12-2.53 (br m, 4H, C(6)-H, C(8)-H_2 and OH), 2.64 (dq, 1H, J = 3 Hz, J' = 7 Hz, C(2)-H), 3.39-3.64 (br m, 2H, C(3)-H and C(11)-H), 3.64 (s, 3H, OCH_3).

Anal. Calcd for $C_{17}H_{33}NO_5$: C, 61.60; H, 10.04; N, 4.23. Found: C, 61.52; H, 9.93; N, 4.25.

Methyl [2R-(2R*,3S*,4S*,6S*,10S*)]-3,11-dihydroxy-7-(hydroxyimino)-2,4,6,10-tetramethylundecanoate (25).
A solution of 8.2 mg (0.0288 mmol) of the spiroketal 19b, 128 mg (1.85 mmol) of $NH_2OH \cdot HCl$, and 135 mg (1.65 mmol) of NaOAc (anhydrous) in 1 mL of methanol and 0.5 mL of water was heated to 65°C under an argon atmosphere for 9 days. The reaction mixture was then diluted with 10 mL of saturated aqueous $NaHCO_3$ and 2 mL of water and extracted with three 5 mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on 7 g of silica gel with 4:1 ether:ethyl acetate afforded first 3.5 mg (43%) of unreacted spiroketal 19b containing only a trace of its C-5 epimer. There was then eluted 3.9 mg (42%) of the diol-oxime 25 as a 75:25 (by ^{1}H-NMR) mixture of geometrical isomers containing only a trace of its C-6 epimer. Distillation [kugelrohr, 165°C (0.005 mmHg)] provided the

analytical sample as a colorless oil: R_f = 0.24 (major isomer) and 0.17 (minor isomer)(silica gel, 4:1 ether: ethyl acetate); IR ($CHCl_3$) 3340 (OH), 1725 (C=O), and 1650 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ 0.85 and 0.97 (2d, 6H, J = 6 Hz, C(4)-CH_3 and C(10)-CH_3), 1.07 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.16 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.33-1.87 (br m, 7H), 2.13-2.60 (br m, 4H, C(6)-H, C(8)-H_2, and OH), 2.65 (dq, 1H, J = 4 Hz, J' = 7 Hz, C(2)-H), 3.46-3.66 (br m, 3H, C(3)-H and C(11)-H_2), 3.66 (s, 3H, OCH_3).

Anal. Calcd for $C_{16}H_{31}NO_5$: C, 60.54; H, 9.84; N, 4.41. Found: C, 60.50; H, 9.84; N, 4.48.

Methyl [2R-(2R*,3S*,4S*,6S*,11S*)]-3,11-dihydroxy-2,4,6-trimethyl-7-oxo-tridecanoate, 1,2-ethanediyl dithioketal derivative (26). To a vigorously stirred solution of 12.6 mg (0.0422 mmol) of the spiroketal 23 in 0.38 mL (430 mg, 4.5 mmol) of 1,2-ethanedithiol cooled to -40°C (dry ice/acetonitrile slush) under an argon atmosphere was added dropwise 0.047 mL (53 mg, 0.37 mmol) of borontrifluoride etherate. After 1 h at -40°C with vigorous stirring, the reaction was quenched by the cautious addition of 0.25 mL of saturated aqueous $NaHCO_3$ while the reaction mixture was allowed to slowly warm to RT. This mixture was then diluted with 8 mL of saturated aqueous $NaHCO_3$ and extracted with three 8 mL portions of ether.

After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure followed by removal of the 1,2-ethanedithiol under high vacuum (0.5 mmHg). Chromatography of the residue immediately on 7 g of silica gel with 3:1 ether:petroleum ether afforded 15.0 mg (90%) of the diol-thioketal 26 as a colorless oil. Distillation [kugelrohr, 175°C (0.005 mmHg)] of this oil provided the analytical sample: R_f = 0.21 (silica gel, 3:1 ether:petroleum ether); IR ($CHCl_3$) 3610 (free OH), 3500 (H-bonded OH), and 1725 cm^{-1} (C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.86 (d, 3H, J = 6 Hz, C(4)-CH_3), 0.95 (t, 3H, J = 7 Hz, C(13)-H_3), 1.08 (d, 3H, J = 6.5 Hz, C(6)-CH_3), 1.19 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.40-1.75 (br m, 10H), 1.87-2.03 (br m, 3H, C(6)-H and C(8)-H_2), 2.51 (br d, 1H, J = 4 Hz, OH), 2.71 (dq, 1H, J = 3.5 Hz, J' = 7 Hz, C(2)-H), 3.23 (br m, 4H, thioketal), 3.55 and 3.64 (2br m, 2H, C(3)-H and C(11)-H), 3.71 (s, 3H, OCH_3); $[\alpha]_D^{25}$ = -30.9° ($CHCl_3$, c 0.93).

Anal. Calcd. for $C_{19}H_{36}O_4S_2$: C, 58.12; H, 9.24; S, 16.33. Found: C, 58.21; H, 9.35; S, 16.34.

Methyl [2R-(2R*,3S*,4S*,6S*,11S*)]-3,11-dihydroxy-2,4,6-trimethyl-7-oxo-tridecanoate,1,3-propanediyl dithioketal derivative (27). To a vigorously stirred solution of 11.3 mg (0.0379 mmol) of the spiroketal 23 in 0.38 mL (410 mg, 3.8 mmol) of 1,3-propanedithiol cooled to -60°C

(dry ice/chloroform slush) under an argon atmosphere was added dropwise 0.040 mL (45 mg, 0.32 mmol) of borontrifluoride etherate. After 5 h at -60°C with vigorous stirring, the reaction was quenched by the cautious addition of 0.25 mL of saturated aqueous $NaHCO_3$ while the reaction mixture was allowed to slowly warm to RT. The resulting mixture was diluted with 10 mL of saturated aqueous $NaHCO_3$ and extracted with three 7 mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure followed by removal of the 1,3-propanedithiol under high vacuum (0.5 mmHg). Chromatography of the residue immediately on 7 g of silica gel with 3:1 ether:petroleum ether afforded, after approximately 3 mg (27%) of epimerized spiroketals eluted, 10 mg (65%) of the diol-thioketal 27 as a colorless oil. Distillation [kugelrohr, 185°C (0.005 mmHg)] of this oil provided the analytical sample: R_f = 0.16 (silica gel, 3:1 ether:petroleum ether); IR ($CHCl_3$) 3610 (free OH), 3500 (H-bonded OH), and 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.88 (d, 3H, J = 6 Hz, C(4)-CH_3), 0.94 (t, 3H, J = 7 Hz, C(13)-H_3), 1.07 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.19 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.37-2.03 (br m, 15H), 2.42 (br m, 1H, OH), 2.57-2.85 (br m, 5H, C(2)-H and -SCH_2-), 3.61 (br m, 2H, C(3)-H and C(11)-H), 3.67 (s, 3H, OCH_3); $[\alpha]_D^{25}$ = -38.1° ($CHCl_3$, c 0.69).

Anal. Calcd for $C_{20}H_{38}O_4S_2$: C, 59.07; H, 9.42; S, 15.77. Found: C, 59.19; H, 9.40; S, 15.88.

Methyl [2R-(2R*,3S*,4S*,6R*,10S*)]-3,11-dihydroxy-2,4,6,10-tetramethyl-7-oxo-undecanoate,1,2-ethanediyl dithioketal derivative (20a). The procedure for the preparation of the diol-thioketal 26 with 9.9 mg (0.035 mmol) of the spiroketal 19a in 0.30 mL (340 mg, 3.6 mmol) of 1,2-ethanedithiol and 0.037 mL (42 mg, 0.30 mmol) of borontrifluoride etherate afforded, after 4 h at -40°C, workup as described, and chromatography on 1 g of silica gel with 3:1 ether:petroleum ether, 11.9 mg (90%) of the diol-thioketal 20a as a colorless oil. Distillation [kugelrohr, 175°C (0.003 mmHg)] of this oil provided the analytical sample: R_f = 0.16 (silica gel, 3:1 ether: petroleum ether); IR ($CHCl_3$ 3490 (OH) and 1725 cm^{-1} (C=O); ^1H-NMR ($CDCl_3$) δ 0.89 and 0.93 (2d, 6H, J = 6 Hz, C(4)-CH_3 and C(10)-CH_3), 1.13 (d, 3H, J = 6 Hz, C(6)-CH_3), 1.15 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.37-2.20 (br m, 10H), 2.65 (dq, 1H, J = 3 Hz, J' = 7 Hz, C(2)-H), 2.76 (br m, 1H, OH), 3.21 (s, 4H, thioketal), 3.46 (br d, 2H, J = 5 Hz, C(11)-H_2), 3.67 (s, 3H, OCH_3), 3.72 (br m, 1H, C(3)-H); $[\alpha]_D^{25}$ = +15.2° ($CHCl_3$, c 0.75).

Anal. Calcd for $C_{18}H_{34}O_4S_2$: C, 57.11; H, 9.05; S, 16.94. Found: C, 56.98; H, 8.96; S, 17.03.

Methyl [2R-(2R*,3S*,4S*,6S*,10S*)]-3,11-dihydroxy-2,4,6,10-tetramethyl-7-oxo-undecanoate,1,2-ethanediyl dithioketal derivative (20b). The procedure for the preparation of the diol-thioketal 26 with 8.7 mg (0.031 mmol) of the spiroketal 19b in 0.29 mL (320 mg, 3.4 mmol) of 1,2-ethanedithiol and 0.036 mL (40 mg, 0.28 mmol) of borontrifluoride etherate afforded, after 3 h at -40°C, workup as described, and chromatography on 7 g of silica gel with 4:1 ether:petroleum ether, 10.5 mg (91%) of the diol-thioketal 20b as a colorless oil. Distillation [kugelrohr, 175°C (0.003 mmHg)] of this oil provided the analytical sample: R_f = 0.15 (silica gel, 3:1 ether: petroleum ether); IR ($CHCl_3$) 3640 (free OH), 3490 (H-bonded OH), and 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.86 and 0.92 (2d, 6H, J = 6 Hz, C(4)-CH_3, and C(10)-CH_3), 1.07 (d, 3H, J = 6 Hz, C(6)-CH_3), 1.18 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.42-2.05 (br m, 10H), 2.53 (br m, 1H, OH), 2.68 (dq, 1H, J = 4 Hz, J' = 7 Hz, C(2)-H), 3.20 (s, 4H, thioketal), 3.46 (br d, 2H, J = 5 Hz, C(11)-H_2), 3.58 (br m, 1H, C(3)-H), 3.67 (s, 3H, OCH_3); $[\alpha]_D^{25}$ = -42.7° ($CHCl_3$, c 0.79).

Anal. Calcd for $C_{18}H_{34}O_4S_2$: C, 57.11; H, 9.05; S, 16.94. Found: C, 57.18; H, 9.04; S, 16.85.

Methyl [2R-(2R*,3S*,4S*,6R*,10S*)]-3,11-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6,10-tetramethyl-7-oxo-undecanoate,1,2-ethanediyl dithioketal derivative (21a). A stirred solution of 11.7 mg (0.0309 mmol) of the diol-thioketal 20a, 139 mg (2.04 mmol) of imidazole, and 149 mg (0.99 mmol) of tert-butyldimethylchlorosilane (TBSCl) in 1 mL of dry dimethylformamide (DMF) under an argon atmosphere was heated at 80°C for 20 h. The reaction mixture was then diluted with 20 mL of water and extracted with three 5 mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on 7 g of silica gel with 1:30 ether:petroleum ether afforded 17.4 mg (93%) of the thioketal 21a as a colorless oil: R_f = 0.13 (silica gel, 1:30 ether:petroleum ether); IR ($CHCl_3$) 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.03 (s, 12H, $Si(CH_3)_2$), 0.91 (s, 18H, $SiC(CH_3)_3$), 0.87-1.00 (2d, 6H, C(4)-CH_3 and C(10)-CH_3), 1.09 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.15 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.40-2.05 (br m, 9H), 2.68 (dq, 1H, J = 4.5 Hz, J' = 7 Hz, C(2)-H), 3.19 (s, 4H, thioketal), 3.38 and 3.41 (2d, 2H, J = 6 Hz, C(11)-H_2), 3.63 (s, 3H, OCH_3), 3.99 (dd, 1H, J = J' = 4.5 Hz, C(3)-H); $[\alpha]_D^{24}$ = +13.3° ($CHCl_3$, c 1.16).

Anal. Calcd for $C_{30}H_{62}O_4S_2Si_2$: M^+-CH_3, 591.3393. Found: M^+-CH_3, 591.3379.

Methyl [2R-(2R*,3S*,4S*,6S*,10S*)]-3,11-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6,10-tetramethyl-7-oxo-undecanoate,1,2-ethanediyl dithioketal derivative (21b). The procedure for the preparation of the thioketal 21a with 21.0 mg (0.0555 mmol) of the diol-thioketal 20b, 149 mg (2.19 mmol) of imidazole, and 161 mg (1.07 mmol) of TBSCl in 1 mL of dry DMF and 18 h at 80°C afforded, after workup and chromatography on 7 g of silica gel with 1:30 ether:petroleum ether, 31.2 mg (93%) of the thioketal 21b as a colorless oil: R_f = 0.12 (silica gel, 1:30 ether:petroleum ether); IR ($CHCl_3$) 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.03 (s, 9H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.90 (br m, 24H, C(4)-CH_3, C(10)-CH_3, and $SiC(CH_3)_3$), 1.02 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.14 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.33-2.00 (br m, 9H), 2.63 (dq, 1H, J = 6 Hz, J' = 7 Hz, C(2)-H), 3.18 (s, 4H, thioketal), 3.39 (d, 2H, J = 5 Hz, C(11)-H_2), 3.63 (s, 3H, OCH_3), 3.80 (dd, 1H, J = 4 Hz, J' = 6 Hz, C(3)-H); $[\alpha]_D^{24}$ = -23.7° ($CHCl_3$, c 1.14).

Anal. Calcd for $C_{30}H_{62}O_4S_2Si_2$: M^+-CH_3, 591.3393. Found: M^+-CH_3, 591.3379.

Methyl [2R-(2R*,3S*,4S*,6R*,10S*)]-3,11-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6,10-tetramethyl-7-oxo-undecanoate (22a). To a vigorously stirred solution of 16.0 mg (0.0264 mmol) of the thioketal 21a in 0.4 mL of acetonitrile and 0.1 mL of water under an argon atmos-

phere was added first 30 mg (0.30 mmol) of $CaCO_3$ (powder) and then 68 mg (0.25 mmol) of $HgCl_2$. After 11 h at RT, the reaction mixture was diluted with 10 mL of dichloromethane and filtered through a pad of Celite followed by washing the filter cake with 40 mL of dichloromethane. The filtrate was washed with one 15 mL portion of 5 M aqueous NH_4OAc, one 15 mL portion of water, and finally one 15 mL portion of saturated aqueous NaCl. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on 7 g of silica gel with 1:10 ether:petroleum ether afforded 12.3 mg (88%) of the ketone 22a as a colorless oil: R_f = 0.18 (silica gel, 1:10 ether:petroleum ether); IR ($CHCl_3$) 1725 (ester C=O) and 1710 cm^{-1} (ketone C=O); ^1H-NMR ($CDCl_3$) δ 0.03 (s, 12H, $Si(CH_3)_2$), 0.89 (br m, 24H, C(4)-CH_3, C(10)-CH_3, and $SiC(CH_3)_3$), 1.06 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.12 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.37-1.93 (br m, 6H), 2.33-2.73 (br m, 4H, C(2)-H, C(6)-H, and C(8)-H_2), 3.38 (d, 2H, J = 5 Hz, C(11)-H_2), 3.62 (s, 3H, OCH_3), 3.81 (dd, 1H, J = 4 Hz, J' = 6 Hz, C(3)-H); $[\alpha]_D^{25}$ = +2.4° ($CHCl_3$, c 1.22).

Anal. Calcd for $C_{28}H_{58}O_5Si_2$: M^+-CH_3, 515.3588. Found: M^+-CH_3, 515.3530.

Methyl [2R-(2R*,3S*,4S*,6S*,10S*)]-3,11-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6,10-tetramethyl-7-oxo-undecanoate (22b). The procedure for the preparation of the ketone 22a with 20.8 mg (0.0343 mmol) of the thioketal 21b, 30 mg (0.30 mmol) of $CaCO_3$ (powder), and 68 mg (0.25 mmol) of $HgCl_2$ in 0.4 mL of acetonitrile and 0.1 mL of water afforded, after 10 h at RT, workup as described, and chromatography on 7 g of silica gel with 1:10 ether:petroleum ether, 16.7 mg (92%) of the ketone 22b as a colorless oil: R_f = 0.17 (silica gel, 1:10 ether:petroleum ether); IR ($CHCl_3$) 1725 (ester C=O) and 1710 cm^{-1} (ketone (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.03 (s, 12H, $Si(CH_3)_2$), 0.90 (br m, 24H, C(4)-CH_3, C(10)-CH_3, and $SiC(CH_3)_3$), 1.00 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.13 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.30-1.72 (br m, 6H), 2.36-2.72 (br m, 4H, C(2)-H, C(6)-H, C(8)-H_2), 3.37 (d, 2H, J = 5 Hz, C(11)-H_2), 3.62 (s, 3H, OCH_3), 3.81 (dd, 1H, J = 4 Hz, J' = 6 Hz, C(3)-H); $[\alpha]_D^{25}$ = -1.7° ($CHCl_3$, c 1.65).

Anal. Calcd for $C_{28}H_{58}O_5Si_2$: M^+-CH_3, 515.3588. Found: M^+-CH_3 515.3582.

Methyl [2S-[2α(S*),3β,6β]]-8-ethyl-α,3,9-trimethyl-5-methylene-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (28). The procedure for the preparation of the olefin 17 with 51 mg (0.164 mmol) of the ketone 16a in 0.7 mL of dry

THF and 0.286 mmol of methylenetriphenylphosphorane in 1.5 mL of dry THF afforded, after chromatography on 12 g of silica gel with 1:20 ether:petroleum ether, 45.1 mg (89%) of the olefin 28 as a white solid melting at 27.5-28°C: R_f = 0.17 (silica gel, 1:20 ether:petroleum ether); IR ($CHCl_3$) 1735 (C=O), 1695 (O-C=C), and 1665 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 0.88 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.06 (d, 3H, J = 7Hz, α-CH_3), 1.07 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.58 (br s, 3H, C(9)-CH_3), 1.65-2.45 (br m, 9H), 2.62 (dq, 1H, J = 4 Hz, J' = 7 Hz, α-H), 3.55 (s, 3H, OCH_3), 3.99 (dd, 1H, J = 4 Hz, J' = 10 Hz, C(2)-H), 4.78 and 4.86 (2br s, 2H, C=CH_2); $[\alpha]_D^{20}$ = +34.0° ($CHCl_3$, c 1.17).

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.19; H, 9.12.

Methyl [2S-[2α(S*),3β,5β,6β]]-8-ethyl-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (29a) and Methyl [2S-[2α(S*),3β,5α,6β]]-8-ethyl-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (29b). A solution of 37 mg (0.120 mmol) of the olefin 28 in 2.5 mL of n-pentane was hydrogenated under a hydrogen atmosphere (H_2 filled balloon) in the presence of a catalytic amount of powdered platinum oxide at RT for 1 hour. The reaction mixture was filtered through a pad of $MgSO_4$ and the filter cake was washed with 30 mL of ether. The

filtrate was concentrated under reduced pressure and chromatography of the residue on 1 g of silica gel with 1:25 ether:petroleum ether afforded 35 mg (94%) of a mixture of the enol ethers 29a and 29b as a colorless oil: R_f = 0.17 (silica gel, 1:20 ether:petroleum ether); IR ($CHCl_3$) 1735 (C=O) and 1695 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.78-1.13 (br m, 9H, overlapping C(3)-CH_3, C(5)-CH_3, and $CH_2\underline{CH}_3$), 1.07 and 1.10 (2d, 3H, J = 7 Hz, α-CH_3 of β- and α-isomers, respectively), 1.55 (br s, 3H, C(9)-CH_3), 1.41-2.12 (br m, 8H), 2.12 (q, 2H, J = 7 Hz, $\underline{CH}_2CH_3$), 2.61 (dq, 1H, J = 4 Hz, J' = 7 Hz, α-H), 3.52 (s, 3H, OCH_3), 3.79 and 3.83 (2dd, 1H, J = 4 Hz, J' = 10 Hz, C(2)-H).

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.50; H, 9.69.

Methyl [2S-[2α(S*),3β,5β,6α(R*)]]-tetrahydro-α,3,5-trimethyl-6-(3-methyl-4-oxohexyl)-2H-pyran-2-acetate (36a) and Methyl [2S-[2α(S*),3β,5α,6α(R*)]]-tetrahydro-α,3,5,-trimethyl-6-(3-methyl-4-oxohexyl)-2H-pyran-2-acetate (36b). A vigorously stirred solution of 28 mg (0.0902 mmol) of the enol ethers 29a and 29b in 3 mL of methanol was hydrogenated under a hydrogen atmosphere (50 psi; Parr apparatus) at RT in the presence of 2 mg of palladium black for 10 days. The reaction mixture was filtered through a pad of Celite and the filter cake

was washed with 30 mL of ether. The filtrate was concentrated under reduced pressure and chromatography of the residue on 10 g of silica gel with 1:4 ether:petroleum ether afforded first 6.9 mg (25%) of starting material containing only traces of hydrogenation products. Further elution afforded 6.1 mg (22%) of a 37:63 (by 500 MHz ^{1}H-NMR) mixture of the hydrogenolysis products 36a and 36b, respectively, as a colorless oil. Distillation [kugelrohr, 95°C (0.005 mmHg)] of a portion of this oil provided the analytical sample: R_f = 0.22 (silica gel, 1:4 ether: petroleum ether); IR ($CHCl_3$) 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) (5β-isomer 36a) δ 0.76 (d, 3H, J = 6.5 Hz, C(5)-CH_3), 0.80 (d, 3H, J = 6.5 Hz, C(3)-CH_3), 1.03 (d, 3H, J = 7 Hz, C(6)-(C(3)-CH_3)), 1.04 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.11 (d, 3H, J = 7 Hz, α-CH_3), 1.28-1.73 (br m, 8H), 2.40-2.55 (br m, 3H), 2.68 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 2.79 (ddd, J = 2 Hz, J' = J'' = 9.5 Hz, C(6)-H), 3.39 (dd, J = 3 Hz, J' = 10 Hz, C(2)-H), 3.67 (s, 3H, OCH_3); 500 MHz ^{1}H-NMR ($CDCl_3$) (5α-isomer 36b) δ 0.77 (d, 3H, J = 6.5 Hz, C(3)-CH_3), 0.87 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.03 (d, 3H, J = 7 Hz, C(6)-(C(3)-CH_3)), 1.04 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.14 (d, 3H, J = 7 Hz, α-CH_3), 1.28-1.73 (br m, 8H), 2.40-2.55 (br m, 3H), 2.68 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.25 (ddd, 1H,

J = 2 Hz, J' = 4 Hz, J'' = 9 Hz, C(6)-H), 3.40 (dd, J = 3 Hz, J' = 10 Hz, C(2)-H), 3.68 (s, 3H, OCH_3).

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.17; H, 10.33.

There was then eluted 8.9 mg (29%) of the methanolysis product 37a followed by 5.7 mg (19%) of the isomeric methanolysis product 37b. Each of these products was isomerically pure by 500 MHz ^{1}H-NMR and these products were identical (TLC, 500 MHz ^{1}H-NMR) to those obtained below by methanolysis of the enol ethers 29a and 29b.

Methyl [2S-[2α(S*),3β,5β,6β,6(R*)]]-tetrahydro-6-methoxy-α,3,5,-trimethyl-6-(3-methyl-4-oxohexyl)-2H-pyran-2-acetate (37a) and Methyl [2S-[2α(S*),3β,5α,6β,6(R*)]]-tetrahydro-6-methoxy-α,3,5-trimethyl-6-(3-methyl-4-oxohexyl)-2H-pyran-2-acetate (37b). The enol ethers 29a and 29b (6.8 mg, 0.22 mmol) were treated with 1 mL of 0.01 M HCl in methanol [prepared by the addition of 7.1 μL of acetyl chloride to 10 mL of dry methanol] under an argon atmosphere at RT for 40 min. The reaction was then quenched by the addition of one drop of dry pyridine and concentrated under reduced pressure. Chromatography of the residue on 7 g of silica gel with 1:4 ether:petroleum ether afforded first 4.3 mg (57%) of the methanolysis product 37a as a colorless oil. Distillation [kugelrohr, 105°C (0.005 mmHg)] provided the analytical

sample: R_f = 0.17 (silica gel, 1:4 ether:petroleum ether); IR ($CHCl_3$) 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.82 (2d, 6H, J = 7 Hz, C(3)-CH_3 and C(5)-CH_3), 1.05 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.07 (d, 3H, J = 7 Hz, C(6)-(C(3)-CH_3)), 1.11 (d, 3H, J = 7 Hz, α-CH_3), 1.30-1.75 (br m, 8H), 2.47 (q, 2H, J = 7 Hz, $\underline{CH}_2CH_3$), 2.50 (br m, 1H, C(6)-(C(3)-H)), 2.68 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.08 (s, 3H, OCH_3), 3.66 (s, 3H, CO_2CH_3), 3.73 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H); $[\alpha]_D^{24}$ = +94.0° ($CHCl_3$, c 0.68).

Anal. Calcd for $C_{19}H_{34}O_5$: C, 66.64; H, 10.01. Found: C, 66.77; H, 10.09.

There was then eluted 2.9 mg (39%) of the isomeric methanolysis product 37b as a colorless oil. Distillation [kugelrohr, 105°C (0.005 mmHg)] provided the analytical sample: R_f = 0.14 (silica gel, 1:4 ether:petroleum ether); IR ($CHCl_3$) 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.79 (d, 3H, J = 6.5 Hz, C(3)-CH_3), 0.97 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.04 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.08 (d, 3H, J = 7 Hz, C(6)-(C(3)-CH_3)), 1.13 (d, 3H, J = 7 Hz, α-CH_3), 1.25-1.85 (br m, 8H), 2.38-2.54 (br m, 3H), 2.68 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.07 (s, 3H, OCH_3), 3.67 (s, 3H, CO_2CH_3), 3.73 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H); $[\alpha]_D^{24}$ = +64.9° ($CHCl_3$, c 0.39).

Anal. Calcd for $C_{19}H_{34}O_5$: C, 66.64; H, 10.01. Found: C, 66.45; H, 10.00.

Methyl [2S-[2α(S*),3β,5β,6β(8R*,9S*)]]-8-ethyl-9-hydroxy-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (30a) and Methyl [2S-[2α(S*),3β,5α,6β(8R*,9S*)]]-8-ethyl-9-hydroxy-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]-undecane-2-acetate (30b). To a stirred solution of 64 mg (0.206 mmol) of the enol ethers 29a and 29b in 0.7 mL of dry THF cooled to 0°C (ice bath) under an argon atmosphere was added 0.62 mL (0.62 mmol) of 1 M borane in THF over 2 min. After 18 min at 0°C, the reaction mixture was quenched at 0°C by the slow cautious concurrent addition of 0.370 mL of 1 N aqueous NaOH solution and 0.062 mL of 30% aqueous H_2O_2 solution. The reaction mixture was allowed to warm to RT for 40 min and was then diluted with 5 mL of water and extracted with one 15 mL portion of ether and two 5 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure and chromatography of the residue on 10 g of silica gel with 1:1 ether:petroleum ether afforded 51.8 mg (77%) of a 60:40 (by NMR) mixture of the alcohols 30a and 30b as a colorless oil. Distillation [kugelrohr, 105°C (0.005 mmHg)] of a portion of this oil provided the analytical sample: R_f = 0.17 (silica gel, 1:1 ether:petroleum ether); IR ($CHCl_3$) 3610

(free OH), 3480 (H-bonded OH), and 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.76-1.13 (br m, 15H, 5 overlapping CH_3 groups), 1.27-2.20 (br m, 11H), 2.63 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.12 (dd, J = 3 Hz, J' = 9 Hz, C(8)-H), 3.27 (dd, J = J' = 6 Hz, C(8)-H), 3.62 and 3.64 (2s, 3H; OCH_3 of 5α- and 5β-isomers, respectively), 3.88 and 4.07 (2dd, 1H, J = 3 Hz, J' = 9 Hz, C(2)-H).

Anal. Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.95; H, 9.83.

Methyl [2R-(2R*,3S*,4S*,6R*,10R*,11S*)]-3,10,11-trihydroxy-2,4,6,10-tetramethyl-7-oxo-tridecanoate, acetonide and 1,2-ethanediyl dithioketal derivative (31a) and Methyl [2R-(2R*,3S*,4S*,6S*,10R*,11S*)]-3,10,11-trihydroxy-2,4,6,10-tetramethyl-7-oxo-tridecanoate, acetonide and 1,2-ethanediyl dithioketal derivative (31b). The procedure for the preparation of the diol-thioketal 26 with 5.9 mg (0.018 mmol) of the spiroketals 30a and 30b in 0.30 mL (340 mg, 3.6 mmol) of 1,2-ethanedithiol and 0.090 mL (102 mg, 0.72 mmol) of borontrifluoride etherate afforded, after 4 h at -40°C and workup as described, 7.6 mg (100%) of crude triol-thioketals as a light yellow oil. This material was subjected immediately to subsequent reactions without further purification.

Chromatography of a portion of this oil on 1 g of silica gel with ether provided, with substantial (50-60%)

loss of material, a clean spectral sample of a 50:50 (by NMR) mixture of the triol-thioketals as a colorless oil: R_f = 0.19 (silica gel, ether); IR ($CHCl_3$) 3500 (OH) and 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.76-1.13 (br m, 9H, C(4)-CH_3, C(6)-CH_3, and C(13)-H_3), 1.14 (s, 3H, C(10)-CH_3), 1.15 and 1.18 (2d, 3H, J = 7 Hz, C(2)-CH_3 of the 6R* and 6S* isomers, respectively), 1.42-2.83 (br m, 14H), 3.21 (s, 4H, thioketal), 3.30 (br m, 1 H, C(11)-H), 3.64 (br m, 1H, C(3)-H), 3.68 (s, 3H, OCH_3).

A solution of the 7.6 mg (0.018 mmol) of crude triol-thioketals, described above, and approximately 3 mg of p-toluenesulfonic acid-monohydrate in 3 mL of dry acetone under an argon atmosphere was stirred at RT for 4.5 h. The reaction mixture was then diluted with 20 mL of saturated aqueous $NaHCO_3$ and extracted with three 10 mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on 1 g of silica gel with 1:2 ether:petroleum ether afforded 6.6 mg (80% over two steps) of a 50:50 (by ^{1}H-NMR) mixture of the acetonides 31a and 31b as a colorless oil. Distillation [kugelrohr, 160°C (0.001 mmHg)] of this oil provided the analytical sample: R_f = 0.15 (6R* isomer) and 0.11 (6S* isomer) (silica gel, 1:2 ether:petroleum ether); IR ($CHCl_3$) 3500

(OH) and 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.85-1.18 (br m, 12H, C(2)-CH_3, C(4)-CH_3, C(6)-CH_3, and C(13)-H_3), 1.20 (s, 3H, C(10)-CH_3), 1.33 and 1.44 (2s, 6H, acetonide), 1.44-2.37 (br m, 10H), 2.64 (br m, 2H, C(2)-H and OH), 3.18 (s, 4H, thioketal), 3.61 (br m, 2H, C(3)-H and C(11)-H), 3.67 (s, 3H, OCH_3).

Anal. Calcd for $C_{23}H_{42}O_5S_2$: C, 59.70; H, 9.15; S, 13.86. Found: C, 59.85; H, 9.15; S, 13.74.

Methyl [2S-[2α(S*),3β,6α]]-8-ethyl-α,3,9-trimethyl-5-methylene-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (32). The procedure for the preparation of the olefin 17 with 107 mg (0.345 mmol) of the mixture of the spiroketal 16b and the Diels-Alder regioisomers 16c, described above, in 1 mL of dry THF and 0.633 mmol of methylenetriphenylphosphorane in 3 mL of dry THF afforded, after chromatography on 15 g of silica gel with 1:20 ether:petroleum ether, first 39.6 mg (37%) of the olefin 32 as a colorless oil: R_f = 0.14 (silica gel, 1:20 ether:petroleum ether); IR 1735 (C=O), 1700 (O-C=C), and 1660 cm^{-1} (C=CH_2); ^{1}H-NMR ($CDCl_3$) δ 0.89 (d, 3H, J = 6 Hz, C(3)-CH_3), 1.02 (t, 3H, J = 7 Hz, CH_2CH_3) 1.13 (d, 3H, J = 7 Hz, α-CH_3), 1.57 (br s, 3H, C(9)-CH_3), 1.47-2.57 (br m, 9H), 2.71 (dq, 1H, J = 5 Hz, J' = 7 Hz, α-H), 3.62 (s, 3H, OCH_3), 3.73 (dd, J = 5 Hz, J' = 8 Hz, C(2)-H), 4.79 and 5.07 (2br s, 2H, C=CH_2); $[\alpha]_D^{20}$ = -69.7° ($CHCl_3$, c 1.03).

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.96; H, 9.10.

Further elution with 1:6 ether:petroleum ether afforded 34.6 mg (32%) of a 50:50 (by NMR) mixture of the stereoisomeric Diels-Alder regioisomers 16c unchanged by the reaction conditions. Distillation [kugelrohr, 85°C (0.003 mmHg)] of a portion of this oil provided the analytical sample: R_f = 0.16 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.98 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.02 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.15 (d, 3H, J = 7 Hz, α-CH_3), 1.27 (s, 3H, C(6)-CH_3), 1.53-2.90 (br m, 10H), 3.66 (s, 3H, OCH_3), 3.75 (m, 1H, C(2)-H).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.87; H, 8.35.

Methyl [2S-[2α(S*),3β,5β,6α]]-8-ethyl-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (5-epi-33) and Methyl [2S-[2α(S*),3β,5α,6α]]-8-ethyl-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (33). A solution of 33 mg (0.107 mmol) of the olefin 32 in 3 mL of n-pentane was hydrogenated under a hydrogen atomosphere (H_2 filled balloon) in the presence of a catalytic amount of powdered platinum oxide at RT for 2 h. The reaction mixture was filtered through a pad of $MgSO_4$ and the filter cake was washed with 30 mL of ether. Concen-

tration of the filtrate under reduced pressure afforded 33.2 mg (100%) of a 16:84 mixture of the enol ethers 5-epi-33 and 33 as a colorless oil.

Chromatography, with significant decomposition of the enol ethers, on 10 g of silica gel with 1:30 ethyl acetate:petroleum ether afforded first 21.6 mg (65%) of the enol ether 33 as a colorless oil. Distillation [kugelrohr, 80°C (0.003 mmHg)] of a portion of this oil provided the analytical sample: R_f = 0.18 (silica gel, 1:30 ethyl acetate:petroleum ether); IR ($CHCl_3$) 1730 (C=O) and 1700 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.96 (2d, 6H, J = 7 Hz, C(3)-CH_3 and C(5)-CH_3), 1.08 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$), 1.12 (d, 3H, J = 7 Hz, α-CH_3), 1.57 (br s, 3H, C(9)-CH_3), 1.40-2.27 (br m, 10H), 2.88 (dq, 1H, J = J' = 7 Hz, α-H), 3.60 (dd, 1H, J = J' = 7 Hz, C(2)-H), 3.63 (s, 3H, OCH_3); $[\alpha]_D^{23}$ = -46.1° ($CHCl_3$, c 1.29).

Anal. Calcd for $C_{18}H_{30}O_4$: M^+ 310.2144. Found: M^+ 310.2148.

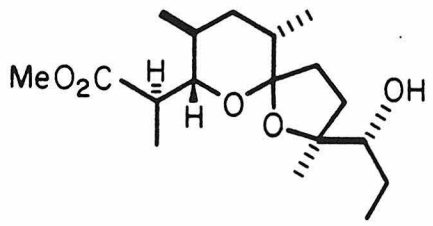
There was then eluted 4.1 mg (12%) of the enol ether 5-epi-33 as a colorless oil: R_f = 0.15 (silica gel, 1:30 ethyl acetate:petroleum ether); IR ($CHCl_3$) 1730 (C=O) and 1700 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, 3H, J = 6 Hz, C(5)-CH_3), 0.85 (d, 3H, J = 6.5 Hz, C(3)-CH_3), 0.97 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$), 1.12 (d, 3H,

J = 7 Hz, α-CH_3), 1.54 (br s, 3H, C(9)-CH_3), 1.43-2.14 (br m, 10H), 2.61 (dq, 1H, J = 3.5 Hz, J' = 7 Hz, α-H), 3.59 (dd, 1H, J = 3.5 Hz, J' = 9.5 Hz, C(2)-H), 3.62 (s, 3H, OCH_3); $[\alpha]_D^{23}$ = -24.8°($CHCl_3$, c 0.33).

Methyl [2S-[2α(S*),3β,5α,6α(8S*,9R*)]]-8-ethyl-9-hydroxy-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (34). The procedure for the preparation of the alcohols 30a and 30b with 13.5 mg (0.0435 mmol) of the enol ether 33 in 0.13 mL of dry THF and 0.13 mL (0.13 mmol) of 1 M borane in THF quenching with 0.078 mL of 1 N aqueous NaOH solution and 0.013 mL of 30% aqueous H_2O_2 afforded, after 25 min at RT and chromatography on 7 g of silica gel with 1:1 ether:petroleum ether, 12.0 mg (84%) of the alcohol 34 as a colorless oil: R_f = 0.12 (silica gel, 1:1 ether:petroleum ether); IR ($CHCl_3$) 3600 (free OH), 3490 (H-bonded OH), and 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.79 (d, 3H, J = 6 Hz, C(3)-CH_3), 1.01 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.05 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.10 (s, 3H, C(9)-CH_3), 1.18 (d, 3H, J = 7 Hz, α-CH_3), 1.35-2.17 (br m, 11H), 2.61 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.32 (dd, 1H, J = 4 Hz, J' = 11 Hz, C(6)-H), 3.67 (s, 3H, OCH_3), 3.71 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H); $[\alpha]_D^{23}$ = +69.3° ($CHCl_3$, c 1.16).

Anal. Calcd for $C_{18}H_{32}O_5$: M^+ 328.2250. Found: M^+ 328.2280.

Methyl [2S-[2α(S*),3β,5α,6β(8S*,9R*)]]-8-ethyl-9-hydroxy-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (35), and Methyl [5R-[5α[2S*(R*)],7β,8α,10β]]- and [5S-[5α[2R*(S*)],7α,8β,10α]]-2-(1-hydroxypropyl)-α,2,8,10-tetramethyl-1,6-dioxaspiro[4.5]decane-7-acetate (iii). A stirred solution of 7.0 mg (0.0213 mmol) of the alcohol 34 in 0.1 mL of dry dichloromethane was treated with one crystal (less than 1 mg) of p-toluenesulfonic acid-monohydrate. After 10 min at RT, the reaction mixture was applied directly to a 1 g silica gel column. Elution with 1:1 ether:petroleum ether afforded first 3.3 mg (47%) of the ring contracted spiroketals iii as a 71:29



iii

(by ^{1}H-NMR) mixture of spiroisomers: R_f = 0.39 (minor isomer) and 0.30 (major isomer) (silica gel, 1:1 ether: petroleum ether); IR ($CHCl_3$) 3500 (OH) and 1735 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.75-1.18 (br m, 15H, 5 overlapping

CH_3 groups), 1.27-2.08 (br m, 11H), 2.67 (br m, 1H, α-H), 3.31 (br m, 1H, >C<u>H</u>-OH), 3.61 and 3.71 (2s, 3H, OCH_3 of major and minor isomers, respectively), 3.93 (br m, 1H, C(7)-H).

Anal. Calcd for $C_{18}H_{32}O_5$: M^+ 328.2250. Found: M^+ 328.2224.

There was then eluted 3.7 mg (53%) of the spiroketal <u>35</u> as a white solid melting at 91-93°C: R_f = 0.13 (silica gel, 1:1 ether:petroleum ether); IR ($CHCl_3$) 3620 (free OH), 3500 (H-bonded OH), and 1735 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.80 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.95 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.10 (s, 3H, C(9)-CH_3), 1.11 (t, 3H, J = 7 Hz, $CH_2C\underline{H}_3$), 1.14 (d, 3H, J = 7 Hz, α-CH_3), 1.26-1.97 (br m, 11H), 2.69 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.18 (dd, 1H, J = 2 Hz, J' = 10 Hz, C(8)-H), 3.67 (s, 3H, OCH_3), 3.77 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H); $[\alpha]_D^{24}$ = +77.8° ($CHCl_3$, <u>c</u> 0.36).

Anal. Calcd for $C_{18}H_{32}O_5$: M^+ 328.2250. Found: M^+ 328.2261.

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(18) These results have been reported in preliminary form.[6a]

(19) In the conformation of spiroketal 23 which enjoys stabilization by the anomeric effect[17], there is a destabilizing 1,3-diaxial interaction between the ethyl group and the pyran oxygen. To alleviate this steric effect requires the molecule to adopt a

conformation in which an electronically favorable anomeric effect has been lost. The spiroketals 19a and 19b possess no such destabilizing effects.

(20) This method has been applied by Professor E. J. Corey to the spiroketal derived from erythronolide A.[12d]

(21) Djerassi, C.; Halpern, O.; Pettit, G. R.; Thomas, G. H. J. Org. Chem. 1959, 24, 1-6.

(22) Deslongchamps, P.; Rowan, D. D.; Pothier, N. Can. J. Chem. 1981, 59, 2787-2791.

Chapter 3

The Synthesis of Seco-Acid Derivatives for the Synthesis of Methymycin and 10-Deoxymethymycin

Macrolide Total Synthesis: The Synthesis of Seco-Acid Derivatives for the Synthesis of Methymycin and 10-Deoxymethymycin

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Contribution No. 6686 from the Chemical Laboratories
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Abstract: A stereoselective synthesis of the chiral seco-acid derivatives for the synthesis of methymycin and 10-deoxymethymycin from carbohydrate precursors is described. Additionally, a formal total synthesis of methymycin is achieved. The synthetic scheme proceeds through spiroketal derivatives prepared by hetero-Diels-Alder condensation to the key intermediate spiroketals 14 and 15 which possess all of the stereochemistry for the natural products. Thioketal exchange then provided the desired open-chain seco-acid derivatives.

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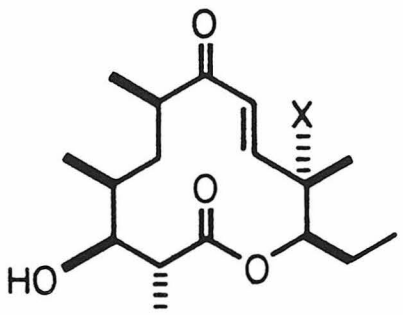
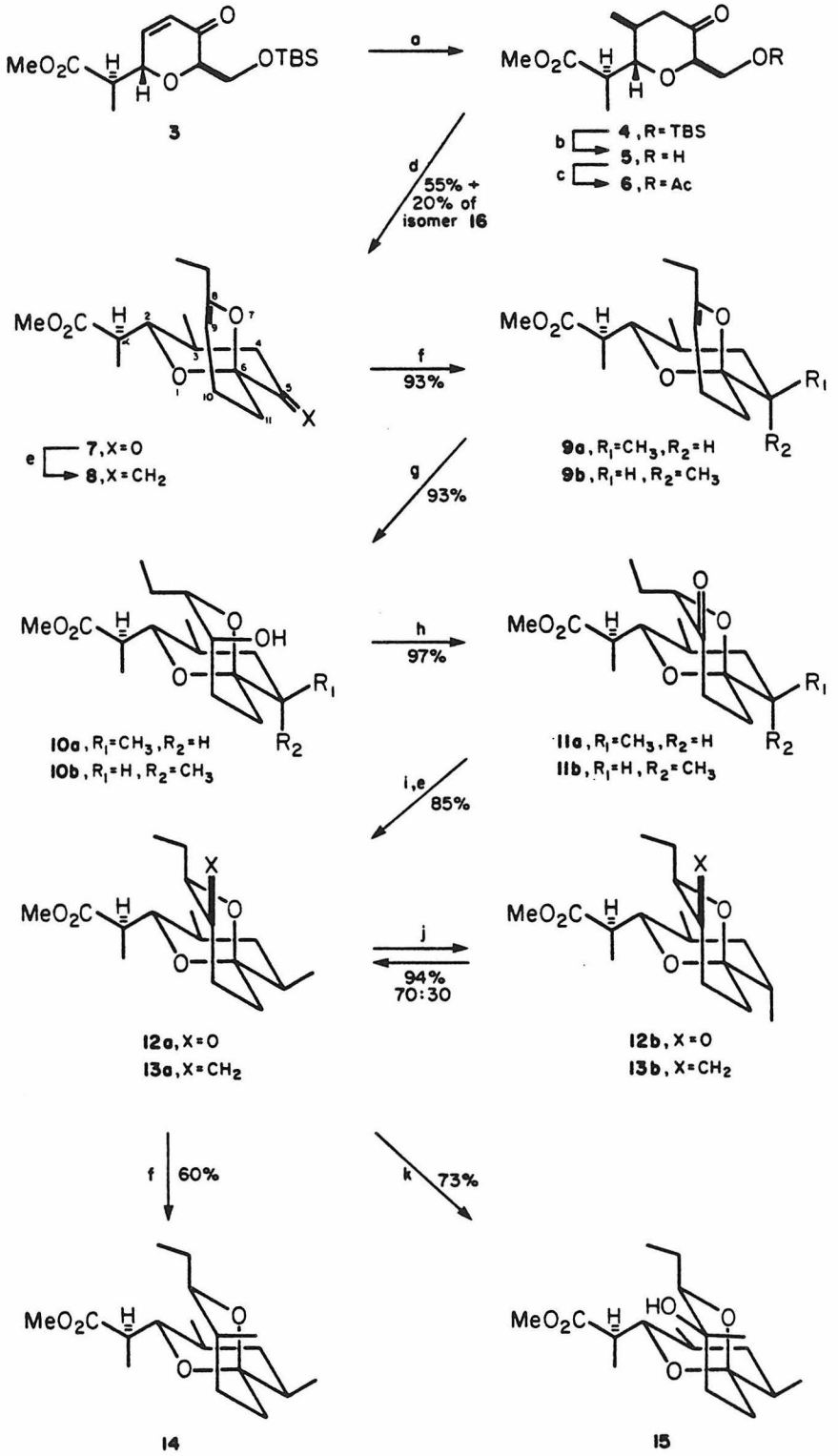
In the preceding report[2], new methods were presented for the synthesis of spiroketals through hetero-Diels-Alder condensation and the cleavage of these spiroketals to open-chain derivatives that are potentially useful for the synthesis of macrolide antibiotics. This report covers the application of this methodology to the synthesis of the seco-acid derivatives 30 and 37 in optically pure form for the synthesis of 10-deoxymethynolide (1)[3] and methynolide (2)[4], respectively. By virtue of the conversion of the seco-acid 37 (see Scheme IV) into methymycin on a previous occasion by Professor Masamune[4a], the current synthesis constitutes a formal total synthesis of this antibiotic.



1, X=H, 10-DEOXYMETHYNOLIDE
2, X=OH, METHYNOLIDE

The optically pure enone 3[5] (Scheme I) was utilized, as opposed to the corresponding benzoate derivative[2] used in the preceeding report, to take advantage of its known[5] high stereoselectivity toward lithium dimethylcuprate addition. Removal of the t-butyldimethylsilyl (TBS) group and acetylation of the resulting alcohol provided the keto-acetate 6 which was used as the progenitor of the desired keto-enol ether dienophile.[2] In order to minimize the dimerization of this intermediate keto-enol ether without resort to a vast excess of the hetero-diene in the hetero-Diels-Alder condensation, the keto-acetate 6 in benzene was added slowly over 5 hours to a mixture of 10 equivalents of ethyl vinyl ketone and 1.5 equivalents of triethylamine in benzene at 80°. This procedure afforded, in 75% overall yield from the enone 3, the desired spiroketals 7 (Scheme I) and 16 (Scheme II) in a 74:26 ratio, respectively.

SCHEME I: Synthesis of Key Intermediates: Spiroketals 14 and 15[a,b]



[a] a, $LiCu(CH_3)_2$, Et_2O, 0°C; b, d,l-10-camphorsulfonic acid, THF, H_2O; c, CH_3COCl, C_5H_5N, CH_2Cl_2, 0°C; d, Et_3N, ethyl vinyl ketone, C_6H_6, 80°C; e, $(C_6H_5)_3PCH_2$, THF; f, PtO_2, H_2, pentane; g, BH_3, THF, 0°C, 1 N NaOH, 30% H_2O_2; h, $(COCl)_2$, Me_2SO, CH_2Cl_2, -60°C, Et_3N; i, DBU, MeOH; j, $BF_3 \cdot Et_2O$, CH_2Cl_2; k, $Hg(OAc)_2$, H_2O, THF, $NaBH_4$.

[b] TBS = t-Bu$(CH_3)_2$Si-.

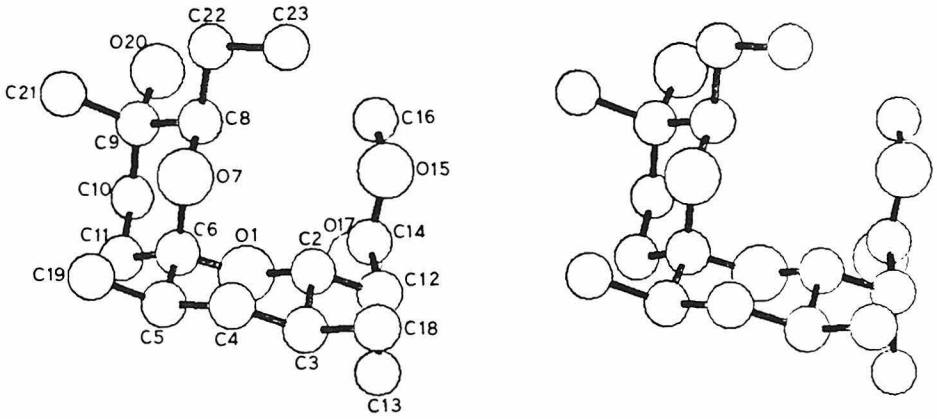
Further elaboration of the spiroketal 7 proceeded through the enol ethers 9a,b which were hydroborated with the expected high stereoselectivity.[2] Swern oxidation[6] of the resultant alcohols 10a,b afforded the ketones 11a,b in 84% overall yield from the spiroketal 7. The indicated conformation of the ketones 11a,b possesses a 1,3-diaxial interaction between the ethyl group and the axial O(1). This steric strain can only be relieved if the ring adopts a twist-boat conformation or the alternate chair conformation in which an electronically favorable anomeric effect[7] is lost. Therefore, there is a large driving force for the epimerization of this ethyl group to the equatorial position and, in fact, treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded in 91% yield the ketones 12a,b accompanied by only trace epimerization of the ester side chain. Wittig methylenation of the mixture of ketones 12a,b afforded, after chromatographic separation, the olefins 13a and 13b in 93% combined yield. Equilibration of the olefin 13b with borontrifluoride etherate in dichloromethane afforded a 70:30 equilibrium mixture of the olefins 13a and 13b, respectively, in 94% combined yield after chromatographic separation. This represents an overall yield of 68% from the Diels-Alder adduct 7 to the olefin 13a in which only one stereocenter for the natural products remains to be incorporated.

While the spherical nature of these spiroketals prevents attack of an endocyclic C(8,9) double bond[2] on the desired concave face, the exocyclic double bond of the olefin 13a allows the ring to adopt a puckered chair conformation which more effectively exposes the concave surface of the molecule. Thus, it was gratifying to find that this exocyclic olefin 13a could be predominately functionalized from the less hindered equatorial direction by both hydrogenation and oxymercuration.

Hydrogenation of the olefin 13a afforded the spiroketal 14, which possesses all of the stereochemistry for the macrolide 10-deoxymethynolide (1), in 60% yield. In addition, the isomeric spiroketal 9-epi-14 was formed in 32% yield. The stereochemical assignment was confirmed by the 9 Hz coupling between the trans diaxial hydrogens at C(8) and C(9) in spiroketal 9-epi-14.

Oxymercuration-demercuration[8] of the olefin 13a afforded a chromatographically separable 86:14 mixture of the tertiary alcohol 15, which possesses all of the stereochemistry for the macrolide methynolide (2), and its C(9) epimer, respectively, in 85% yield. The initial stereochemical assignment was based again on equatorial attack by the reagent; however, the central stereochemical importance of this spiroketal 15, which is the first as well as last crystalline synthetic intermediate, commanded

FIGURE 1: X-Ray Crystal Structure of Spiroketal 15



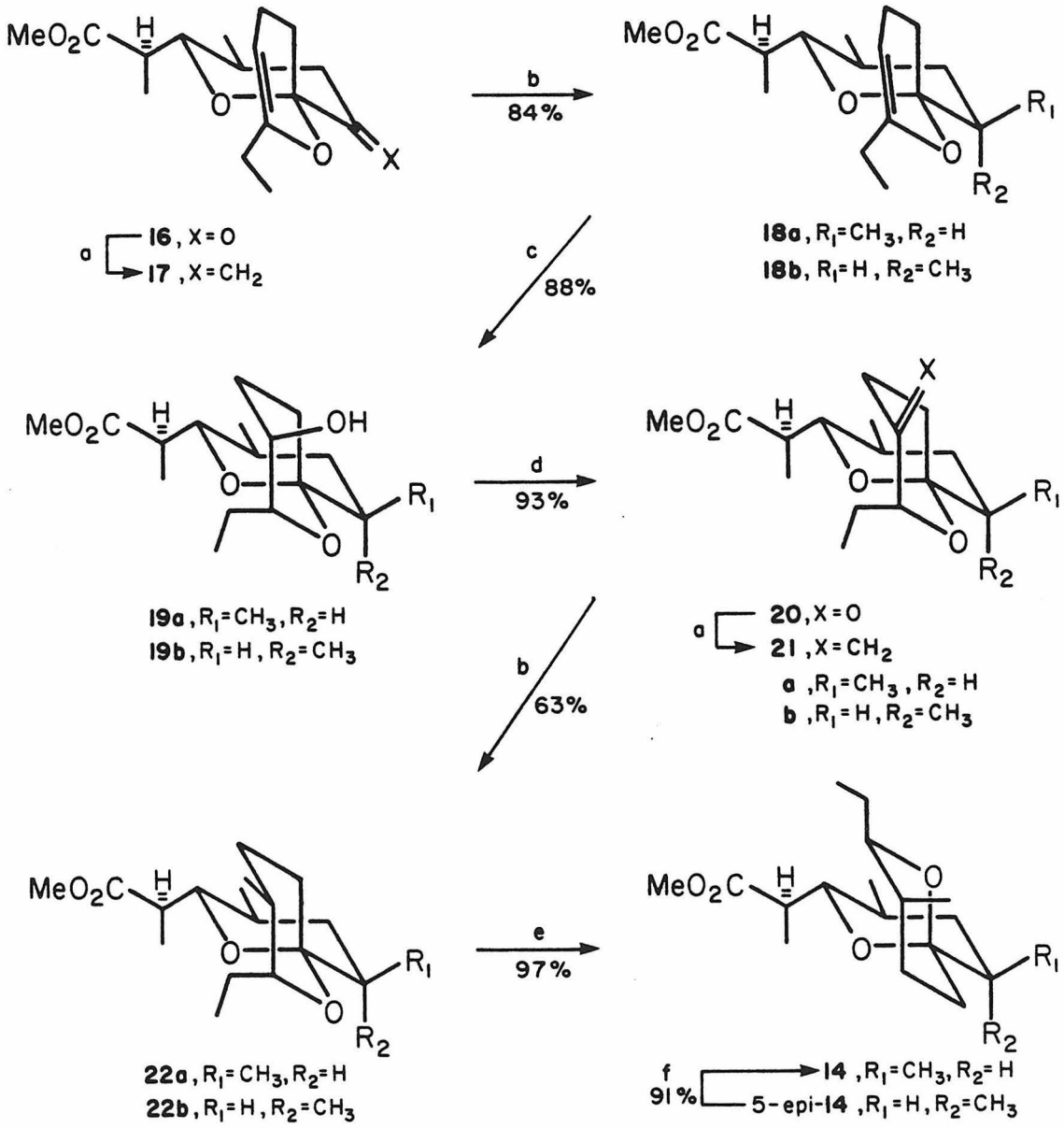
an x-ray crystallographic investigation. Figure 1 illustrates the result of the crystal structure analysis that completely confirms the foregoing stereochemical assignments. An interesting feature of this analysis is that this spiroketal 15 crystallized as hydrogen bonded dimers between the hydroxyl groups and the ester carbonyls. An alternate synthesis of this spiroketal 15 and its C(5) epimer was through axial addition of methylmagnesium bromide to the mixture of ketones 12a,b. The inseparability of both the starting ketones 12a,b and the product alcohols

15 and 5-epi-15 prevented, for practical reasons, the application of this Grignard addition sequence, however.

An exactly analogous sequence using the minor Diels-Alder adduct 16 in which only the epimerization of the C(8) ethyl group is omitted is shown in Scheme II. This process afforded the spiroketals 22a and 22b in 7% and 37% overall yields, respectively, and their C(9) epimers in 3% and 13% yields, respectively. These spiroketals 22a,b and their accompanying C(9) epimers are quite novel. In the indicated conformations, these systems are highly destabilized by the lack of an anomeric stabilizing effect[7] and the incorporation of a 1,3-diaxial steric interaction between the C(8) ethyl group and O(1)[9]. Clearly, such thermodynamically unstable spiroketals could not be prepared by the standard acid-catalyzed cyclization methods.[7,10] Access to the desired, previously prepared spiroketal 14 for 10-deoxymethynolide (1) was achieved by acid-catalyzed isomerization of spiroketal 22a in 100% yield and by sequential isomerization of spiroketal 22b, through the spiroketal 5-epi-14, in 91% yield (56% conversion).

The thioketal exchange methodology[2] with the spiroketal 14 afforded in 92% yield (87% conversion) the diol-thioketal 23 without any apparent epimerization (Scheme III). After selective protection of the alcohol groups, thioketal removal[11] afforded the ketone 26 in 77% overall yield. The regioselective enolization of the ketone 26 in the

SCHEME II: Synthesis of Spiroketal 14 from the Minor Diels-Alder Adduct 16[a]

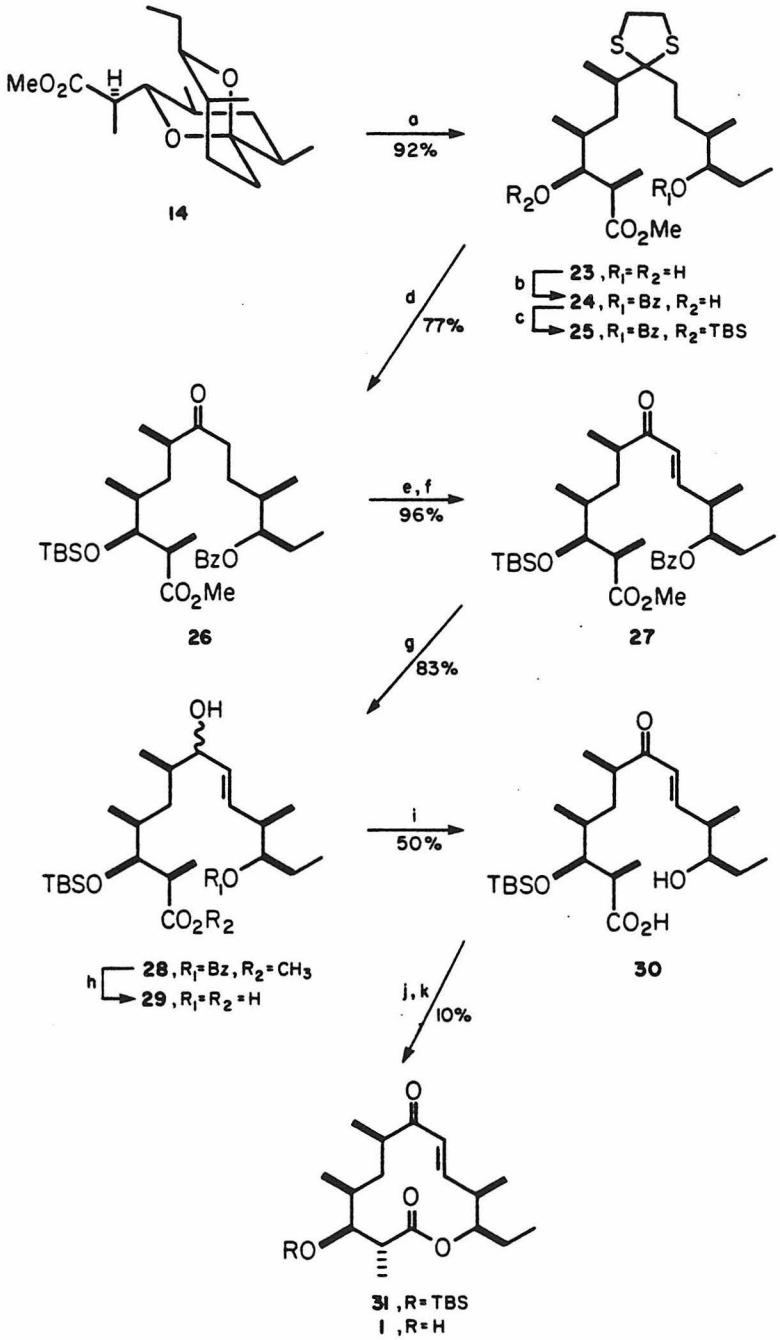


[a] a, $(C_6H_5)_3PCH_2$, THF; b, PtO_2, H_2, pentane; c, BH_3, THF, 0°C, 1 N NaOH, 30% H_2O_2; d, $(COCl)_2$, Me_2SO, CH_2Cl_2, -60°C, Et_3N; e, pTsOH·H_2O, CH_2Cl_2, 10 min; f, pTsOH·H_2O, CH_2Cl_2, 50 h.

presence of an ester group required an inverse addition procedure in which one equivalent of lithium diisopropylamide (LDA) in THF was added to a mixture of the ketone 26 and the trimethylchlorosilane (TMSCl) trapping reagent in 13% HMPA/THF at -78°C. Palladium (II) acetate oxidation[12] in acetonitrile of the resultant silyl enol ether provided the desired trans enone 27 in 96% overall yield. Final preparation of the seco-acid derivative 30 of 10-deoxymethynolide (1) was accomplished by zinc borohydride[13] reduction, saponification, and reoxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 42% overall yield. Macrolactonization of this seco-acid 30 was accomplished by the new procedure of Professor Masamune[14] through a phosphoric acid mixed anhydride intermediate and afforded in 10% yield a lactone believed to be the 10-deoxymethynolide derivative 31 in addition to an isomeric lactone in 3% yield. Proof, however, that the major monolactone is indeed the 10-deoxymethynolide derivative 31 through its deprotection to 10-deoxymethynolide (1) could not be accomplished with a variety of conditions ($HF/H_2O/CH_3CN$[15], $LiBF_4/CH_3CN$[16], $(HF)_\chi \cdot C_5H_5N/THF$[17], trifluoroacetic acid/H_2O/CH_3CN, and nBu_4NF/THF).

In a similar manner, the spiroketal 15 was elaborated for the synthesis of methynolide (2) (Scheme IV). In this case, however, the thioketal exchange was not as efficient and resulted in a low conversion with substantial epimeri-

SCHEME III: Synthesis of Seco-Acid Derivative 30 for the Synthesis of 10-Deoxymethymycin[a,b]



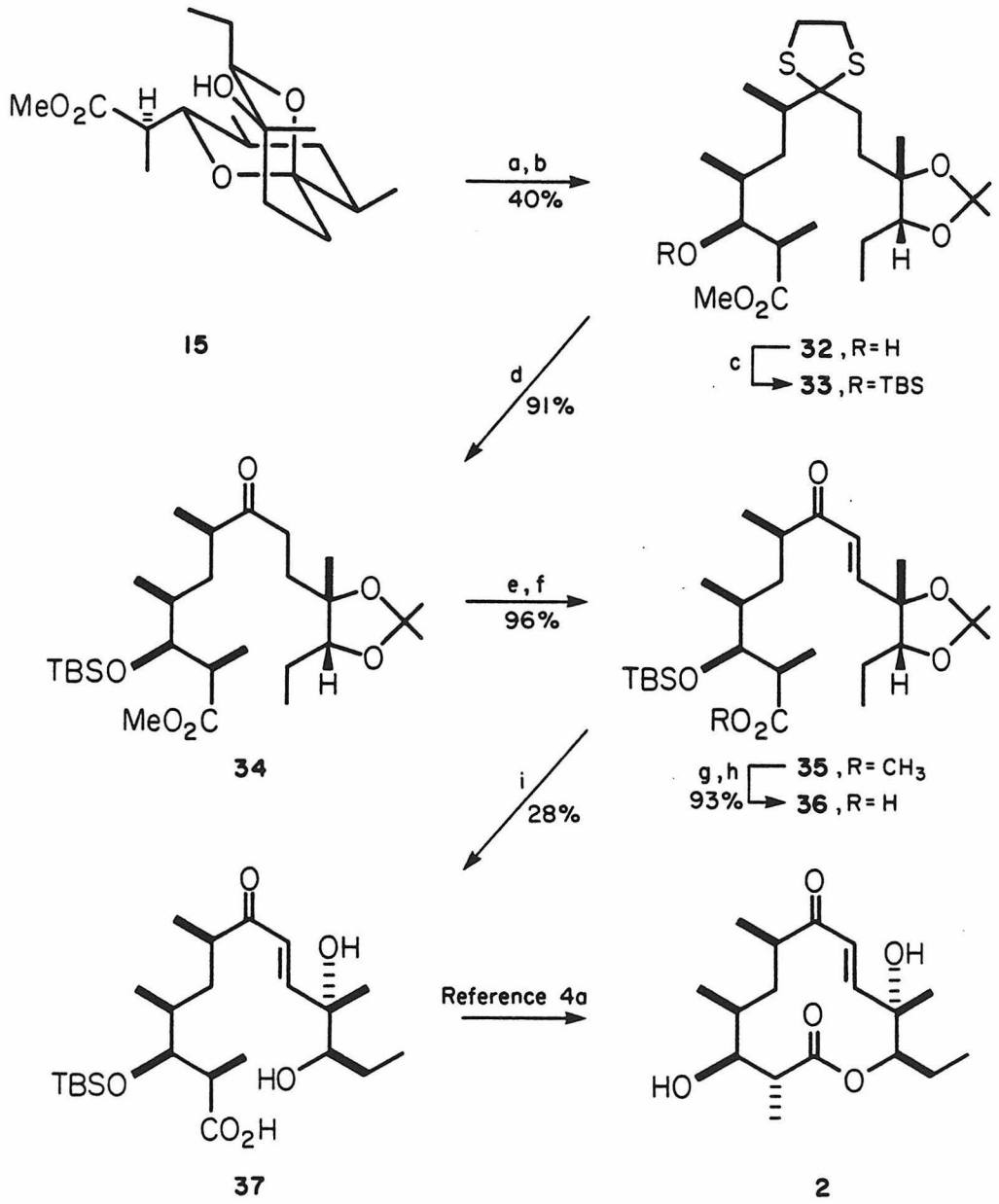
[a] a, $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$, -40°C; b, BzCl, C_5H_5N, CH_2Cl_2; c, TBSCl, imidazole, DMF, 85°C, 21 h; d, $HgCl_2$, $CaCO_3$, MeCN, H_2O; e, LDA, TMSCl, Et_3N, THF, HMPA, -78°C; f, Pd (II)$(OAc)_2$, MeCN; g, $Zn(BH_4)_2$, DME, 0°C → RT; h, 1 N KOH, DME, 75°C, 24 h; i, DDQ, C_6H_6; j, $(C_6H_5O)_2POCl$, Et_3N, THF, 0°C; k, DMAP, C_6H_6, 75°C.

[b] TBS = t-Bu$(CH_3)_2$Si-.

zation. After acetonide formation, the desired thioketal 32 could, however, be obtained in 23% overall yield; a 10% yield of its C(6) epimer was also formed in the process. If the recovery of partially epimerized starting spiroketal 15 and its ring contracted isomers in 52% yield is taken into consideration the effective overall yield of this cleavage is approximately 40%. Solutions to the low conversion and yield caused by the tertiary alcohol group are currently under further investigation.[18]

Further elaboration of the thioketal 32 proceeded very smoothly through the enone-ester 35 which, by reduction with diisobutylaluminum hydride (DIBAH) and reoxidation of the resulting diol with Jones reagent, afforded the enone-acid 36 in 81% overall yield. This indirect reduction-reoxidation procedure was necessary because saponification of the methyl ester 35 afforded a 37:63 mixture (by 500 MHz ^{1}H-NMR) of the desired carboxylic acid 36 and its C(6) epimer, respectively. Finally, treatment of this carboxylic acid 36 with 1:1 1 N aqueous HCl: acetonitrile[4b] afforded the desired seco-acid 37. The IR and ^{1}H-NMR spectra of the acetonide derivative 36 and the ^{1}H-NMR spectrum of the seco-acid 37 were in excellent agreement with those kindly provided by Professor Grieco of the acetonide derivative 36 (a 1:1 mixture of diastereomers)[4b] and of the seco-acid 37.[4b] By virtue of the previous

SCHEME IV: Synthesis of Seco-Acid Derivative 37 for the Synthesis of Methymycin[a,b]



[a] a, $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$, -20°C; b, $pTsOH \cdot H_2O$, acetone; c, TBSCl, imidazole, DMF, 85°C, 17 h; d, $HgCl_2$, $CaCO_3$, MeCN, H_2O; e, LDA, TMSCl, Et_3N, THF, HMPA, -78°C; f, Pd (II)$(OAc)_2$, MeCN; g, DIBAH, hexane, -78°C → 0°C → -78°C; h, 8 N Jones reagent, acetone, -20°C; i, 1 N aq. HCl, MeCN (1:1).

[b] TBS = t-Bu$(CH_3)_2$Si-.

conversion of this seco-acid 37 into methynolide (2) and methymycin by Professor Masamune,[4a] the current work constitutes a formal total synthesis of this macrolide antibiotic.

Further studies directed toward the total synthesis of the related fourteen-membered ring macrolide antibiotics narbomycin and pikromycin[2] from the current intermediates and the application of the Eschenmoser sulfide contraction[19] are currently under investigation in these laboratories.

EXPERIMENTAL SECTION

Melting points were determined by using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 727B or 1310 infrared spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM-390 or a JEOL FX-90Q spectrometer, except where "500 MHz" denotes spectra recorded on a Bruker WM-500 (Southern California Regional NMR Facility, Caltech, Pasadena, California). 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, assignment). Spectra in C_6D_6 were often used to aid in the analysis of overlapping signals in the reported spectra in $CDCl_3$. Carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on a JEOL FX-90Q 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). For all spectra, numbering in the assignments employs the numbering system implicit in the Chemical Abstracts name at the heading of each experimental. Optical rotations were measured in 1 dm cells of 1 mL capacity by using a JASCO Model DIP-181

polarimeter. Chloroform, when used as a solvent for optical rotations, was filtered through neutral alumina (activity I) immediately prior to use.

Analytical thin layer chromatography (TLC) was conducted on 2.5 x 10 cm precoated TLC plates, silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co., Darmstadt, Germany.

Silica gel columns for chromatography utilized E. Merck "Silica Gel 60", 70-230 mesh ASTM. Flash chromatography was performed on E. Merck "Silica Gel 60", 230-400 mesh ASTM, according to published procedure (Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem., 1978, 43, 2923-2925). Acidic silica gel refers to Silicar CC-4 Special "for column chromatography", sold by Mallinckrodt Chemical Works, St. Louis, Missouri. "Alumina" refers to the grade I neutral variety manufactured by M. Woelm, Eschwege, Germany, which was neutralized to the indicated grade by the addition of water.

"Dry" solvents were distilled shortly before use from an appropriate drying agent. Benzene, pyridine, n-hexane and acetonitrile were distilled from powdered calcium hydride. Hexamethyldisilazane and diisopropylamine were distilled under argon from powdered calcium hydride. Dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and hexamethylphosphoramide (HMPA) were distilled under

reduced pressure from powdered calcium hydride. Tetrahydrofuran (THF), dimethoxyethane (DME), and triethylamine were distilled under argon from sodium metal with sodium benzophenone ketyl as an indicator. Ether was distilled under argon from sodium metal with sodium benzophenone ketyl as an indicator or was used directly from freshly opened cans. Dichloromethane was distilled from phosphorus pentoxide.

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, New Jersey and was not further purified.

Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan. Mass spectral analyses were performed by the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, Nebraska.

Methyl [2S-[2α(S*),3β,6β]]-6-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-α,3-dimethyl-5-oxo-2H-pyran-2-acetate (4) and Methyl [2S-[2α(S*),3α,6β]]-6-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-α,3-dimethyl-5-oxo-2H-pyran-2-acetate(3-epi-4). To a

stirred slurry of 21.7 g (105.6 mmol) of cuprous bromide-dimethylsulfide complex in 1000 mL of dry ether cooled to 0°C (ice bath) under an argon atmosphere was added 1.8 M methyllithium (low halide in ether) until a small amount of yellow precipitate (methylcopper) remained (105 ml of methyllithium solution added). After 45 min, a solution of 17.3 g (52.7 mmol) of the enone 3 in 150 mL of dry ether was added dropwise over 10 minutes to this rapidly stirred solution of lithium dimethylcuprate at 0°C. The reaction mixture was quenched after 10 min by the addition of 500 mL of saturated aqueous NH_4Cl solution and was then poured into 500 mL of saturated aqueous NH_4Cl solution and 200 mL of water. The layers were separated and the aqueous layer (blue) was extracted twice with 100 mL of ether. After the combined organic layers were dried ($MgSO_4$), concentration under reduced pressure afforded 18.1 g (100%) of the labile isomeric ketones 4 and 3-epi-4 as a clear oil. This oil was promptly subjected to subsequent reactions without further purification.

Chromatography of a portion of this oil on 25 g of silica gel with 1:6 ether:petroleum ether afforded first the minor ketone 3-epi-4 as a colorless oil. Distillation [kugelrohr, 100°C (0.004 mm Hg)] provided the analytical sample of the ketone 3-epi-4: R_f = 0.20 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1725 cm^{-1} (C=O);

^{1}H-NMR ($CDCl_3$) δ 0.05 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.00 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.35 (d, 3H, J = 7 Hz, α-CH_3), 2.20 (m, 1H, C(3)-H), 2.57 (m, 3H, α-H and C(4)-H_2), 3.63 (s, 3H, OCH_3), 3.95 (m, 3H, C(6)-H and CH_2OSi), 4.46 (dd, 1H, J = 11 Hz, J' = 2 Hz, C(2)-H); $[\alpha]_D^{24}$ = +107.1°($CHCl_3$, c 0.86).

Anal. Calcd for $C_{17}H_{32}O_5Si$: C, 59.27; H, 9.36. Found: C, 59.15; H, 9.32.

There was then eluted the major ketone 4 as a white solid. Distillation [kugelrohr, 100°C (0.004 mm Hg)] provided the analytical sample of the ketone 4 as a white solid melting at 32-33°C: R_f = 0.14 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.04 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.95 (d, 3H, J = 6 Hz, C(3)-CH_3), 1.18 (d, 3H, J = 7 Hz, α-CH_3), 2.12-2.65 (m, 3H, C(3)-H and C(4)-H_2), 2.74 (dq, 1H, J = 5 Hz, J' = 7 Hz, α-H), 3.70 (s, 3H, OCH_3), 3.92 (m, 3H, C(6)-H and CH_2OSi), 4.35 (dd, 1H, J = 5 Hz, J' = 8 Hz, C(2)-H); $[\alpha]_D^{24}$ = +64.4° ($CHCl_3$, c 1.06).

Anal. Calcd for $C_{17}H_{32}O_5Si$: C, 59.27; H, 9.36. Found: C, 59.16; H, 9.44.

Methyl [2S-[2α(S*),3β,6β]]-tetrahydro-6-(hydroxymethyl)-α,3-dimethyl-5-oxo-2H-pyran-2-acetate (5) and Methyl [2S-[2α(S*),3α,6β]]-tetrahydro-6-(hydroxymethyl)-α,3-dimethyl-5-oxo-2H-pyran-2-acetate (3-epi-5). To a stirred

solution of 18.1 g (52.7 mmol) of the mixture of the silyl ethers 4 and 3-epi-4, described above, in 415 mL of THF and 208 mL of water under an argon atmosphere was added 1.38 g (5.94 mmol) of d,ℓ-10-camphorsulfonic acid and the resulting mixture stirred at RT for 3 days and 19 h. The THF was removed under reduced pressure and the remaining aqueous mixture was diluted with 250 mL of water. The aqueous mixture was extracted with two 50 mL portions of petroleum ether to remove silicon containing byproducts and these petroleum ether extracts were extracted with two 25 mL portions of water. The 50 mL of aqueous extracts and the main aqueous solution were combined and saturated with NaCl. The resulting NaCl solution was extracted with eight 50 mL portions of ethyl acetate and the combined ethyl acetate extracts were dried ($MgSO_4$). Concentration of this dried solution under reduced pressure afforded 12.1 g (100%) of a 94:6 (by NMR) mixture of the labile ketols 5 and 3-epi-5 as a white solid. This solid was promptly subjected to subsequent reactions without further purification.

Recrystallization of a 63 mg portion of this solid from hot n-pentane/ether provided the analytical sample (50 mg) of the major ketol 5 as fine white needles melting at 51-52°C; R_f = 0.27 (silica gel, ether); IR ($CHCl_3$) 3450 (OH) and 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.97 (d,

3H, J = 6 Hz, C(3)-CH_3), 1.27 (d, 3H, J = 7 Hz, α-CH_3), 2.00-2.70 (br m, 3H, C(3)-H and C(4)-H_2), 2.80 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 2.90 (br s, 1H, OH), 3.73 (s, 3H, OCH_3), 3.62-4.17 (br m, 4H, C(2)-H, C(6)-H, and CH_2O); $[\alpha]_D^{24}$ = +166.0° ($CHCl_3$, c 0.95).

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.31; H, 7.82.

Methyl [2S-[2α(S*),3β,6β]]-6-[(acetyloxy)methyl]-tetrahydro-α,3-dimethyl-5-oxo-2H-pyran-2-acetate (6) and Methyl [2S-[2α(S*),3α,6β]]-6-[(acetyloxy)methyl]-tetrahydro-α,3-dimethyl-5-oxo-2H-pyran-2-acetate (3-epi-6).

To a stirred solution of 12.1 g (52.7 mmol) of the mixture of the isomeric ketols 5 and 3-epi-5, described above, in 260 mL of dry dichloromethane cooled to 0°C (ice bath) under an argon atmosphere was added first 12.7 mL (12.5 g, 158 mmol) of dry pyridine and then 5.6 mL (6.2 g, 78.8 mmol) of acetyl chloride over 5 min. After 30 min at 0°C, the reaction mixture was poured into 400 mL of saturated aqueous $NaHCO_3$ and 400 mL of water. This mixture was extracted with three 400 mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Azeotropic removal of pyridine with three 100 mL portions of n-heptane afforded 14.3 g (100%) of a 94:6 (by NMR) mixture of the labile isomeric acetates 6 and 3-epi-6 as a white solid: R_f = 0.17

(3β-isomer) and 0.22 (3α-isomer) (silica gel, 1:1 ether: petroleum ether); IR ($CHCl_3$) 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) (3β-isomer) δ 1.01 (d, 3H, J = 6 Hz, C(3)-CH_3), 1.22 (d, 3H, J = 7 Hz, α-CH_3), 2.07 (s, 3H, CH_3CO_2), 2.13-2.63 (br m, 3H, C(3)-H and C(4)-H_2), 2.78 (dq, 1H, J = 6 Hz, J' = 7 Hz, α-H), 3.69 (s, 3H, OCH_3), 4.00 (dd, 1H, J = 6 Hz, J' = 8 Hz, C(2)-H), 4.13-4.35 (br m, 3H, C(6)-H and CH_2O). This solid was promptly subjected to subsequent reactions without further purification.

Methyl [2S-[2α(S*),3β,6β]]-8-ethyl-α,3-dimethyl-5-oxo-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (7), Methyl [2S-[2α(S*),3β,6α]]-8-ethyl-α,3-dimethyl-5-oxo-1,7-dioxaspiro-[5.5]undec-8-ene-2-acetate (16), and Methyl [2S-[2α(S*),3β,-6α and 6β]]-2,3,4,6,7,8-hexahydro-α,3-dimethyl-6-(1-oxo-propyl)-pyrano[3,2-b]pyran-2-acetate (i). To a stirred solution of 52 mL (44 g, 523 mmol) of ethyl vinyl ketone (distilled from hydroquinone at 60 mm Hg, stabilized with 1% hydroquinone), 52 mL of dry benzene, and 11 mL (8.0 g, 79 mmol) of dry triethylamine heated to 85°C under an argon atmosphere was added a solution of 14.3 g (52.7 mmol) of the mixture of the isomeric acetates 6 and 3-epi-6, described above, in 48 mL of dry benzene slowly over 5 h. After an additional 2 h at 85°C, the reaction mixture was concentrated under reduced pressure and chromatography of the residue on 600 g of silica gel with 1:4 ether:petroleum ether afforded 13.8 g of the Diels-Alder adducts as a light yellow oil. Medium pressure liquid chromatography (Lobar pre-packed column, size C, LiChroprep Si 60, EM Reagents) of this oil with 1:6 or 1:8 ether:petroleum ether afforded (after recycle of mixed fractions) first 0.70 g (4.5%) of the spiroketal 3-epi-7 as colorless oil. Distillation [kugelrohr, 85°C (0.001 mm Hg)] of a portion of this oil provided the analytical sample of the spiroketal 3-epi-7: R_f = 0.25 (silica gel, 1:6 ether:petroleum ether); IR

($CHCl_3$) 1730 (C=O) and 1680 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.97 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.07 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.21 (d, 3H, J = 7 Hz, α-CH_3), 1.60-2.40 (br m, 8H), 2.60 (dq, 1H, J = 10 Hz, J' = 7 Hz, α-H), 3.13 (dd, 1H, J = 5 Hz, J' = 13 Hz, ax C(4)-H), 3.67 (s, 3H, OCH_3), 4.33 (dd, 1H, J = 2 Hz, J' = 10 Hz, C(2)-H), 4.63 (br d, 1H, J = 3 Hz, C(9)-H); $[\alpha]_D^{24}$ = +73.5° ($CHCl_3$, $\underline{c}$ 0.85).

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 65.09; H, 8.22.

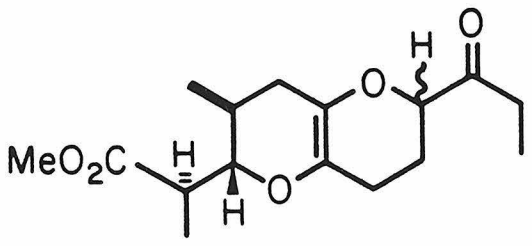
There was then eluted 8.59 g (55.1%) of the spiroketal $\underset{\sim}{7}$ as a colorless oil. Distillation [kugelrohr, 85° C (0.001 mm Hg)] of a portion of this oil provided the analytical sample of the spiroketal $\underset{\sim}{7}$: $R_{\underline{f}}$ = 0.21 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1730 (C=O) and 1680 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.98 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.07 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.11 (d, 3H, J = 7 Hz, α-CH_3), 1.60-2.86 (br m, 10H), 3.63 (s, 3H, OCH_3), 4.36 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H), 4.60 (br d, 1H, J = 3 Hz, C(9)-H); ^{13}C-NMR ($CDCl_3$) δ 8.4 (q), 11.3 (q), 16.0 (t), 17.3 (q), 24.2 (t), 26.6 (t), 36.7 (d), 40.2 (d), 43.4 (t), 51.4 (q), 75.0 (d), 96.0 (d), 96.6 (s), 151.0 (s), 174.1 (s), 202.2 (s); $[\alpha]_D^{24}$ = +45.6° ($CHCl_3$, $\underline{c}$ 0.85).

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.71; H, 8.06.

Further elution afforded 3.04 g (19.5%) of the spiroketal 16 as a colorless oil. Distillation [kugelrohr, 85°C (0.001 mm Hg)] of a portion of this oil provided the analytical sample of the spiroketal 16: R_f = 0.17 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1730 (C=O) and 1680 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 1.00 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.01 (t, 3H, J = 7 Hz, CH_2CH_3), 1.19 (d, 3H, J = 7 Hz, α-CH_3), 1.67-3.03 (br m, 10H), 3.67 (s, 3H, OCH_3), 3.87 (dd, 1H, J=J'=7 Hz, C(2)-H), 4.63 (br d, 1H, J = 3 Hz, C(9)-H); ^{13}C-NMR ($CDCl_3$) δ 11.2 (q), 11.9 (q), 16.1 (t), 18.5 (q), 25.5 (t), 26.8 (t), 31.6 (d), 41.5 (t), 43.5 (d), 51.7 (q), 80.3 (d), 95.5 (d), 96.8 (s), 152.1 (s), 175.0 (s), 202.5 (s); $[\alpha]_D^{24}$ = +46.7° ($CHCl_3$, c 0.92).

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.73; H, 8.03.

Finally, there was eluted 0.89 g (5.7%) of a 50:50 mixture (by ^{1}H-NMR) of the regioisomers i as a colorless oil.



i

Distillation [kugelrohr, 95°C (0.001 mm Hg)] of a portion of this oil provided the analytical sample of the regioisomers i: R_f = 0.12 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1725 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.00 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.04 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.16 (d, 3H, J = 7 Hz, α-CH_3), 1.75-2.33 (br m, 7H), 2.61 (br q, 2H, J = 7 Hz, $\underline{CH}_2CH_3$), 2.74 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.67 (s, 3H, OCH_3), 3.77 (m, 1H, C(2)-H), 4.12 (br m, 1H, C(6)-H).

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.76; H, 8.01.

Methyl [2S-[2α(S*),3β,6β]]-8-ethyl-α,3-dimethyl-5-methylene-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (8). To a stirred solution of 0.553 mmol of methylenetriphenylphosphorane in 4 mL of dry THF [prepared by addition of 0.24 mL (0.55 mmol) of 2.28 M n-butyllithium in hexane to a stirred slurry of 198 mg (0.553 mmol) of (methyl)triphenylphosphonium bromide in 4 mL of dry THF at 0°C, followed by stirring at RT for 30 min] cooled to -78°C (dry ice/2-propanol) under an argon atmosphere was added 102 mg (0.343 mmol) of the ketone 7 in 1 mL of THF over 5 min. After being stirred for 5 min at -78°C, the reaction mixture was allowed to warm to room temperature. After 2h at RT, the reaction mixture was quenched by the addition of a few drops of saturated aqueous $NaHCO_3$ and was then poured into

40 mL of ether. This ether solution was washed with two 10 mL portions of saturated aqueous $NaHCO_3$ and one 10 mL portion of saturated aqueous NaCl. The combined aqueous washings were extracted with two 10 mL portions of ether. After being dried ($MgSO_4$), the combined organic layers were concentrated under reduced pressure and chromatography of the residue on 10 g of alumina (activity III) with 1:20 ether:petroleum ether afforded 94 mg (93%) of the olefin 8 as a colorless oil. Distillation [kugelrohr, 80°C (0.002 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.15 (silica gel, 1:20 ether: petroleum ether); IR ($CHCl_3$) 1735 (C=O) and 1680 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 0.88 (d, 3H, J = 6 Hz, C(3)-CH_3), 1.05 (t, 3H, J = 7 Hz, CH_2CH_3), 1.07 (d, 3H, J = 7 Hz, α-CH_3), 1.67-2.45 (br m, 9H), 2.63 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.59 (s, 3H, OCH_3), 4.01 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H), 4.50 (br d, 1H, J = 4 Hz, C(9)-H), 4.81 and 4.90 (2br s, 2H, $C=CH_2$); $[\alpha]_D^{24}$ = +53.8° ($CHCl_3$, c 0.90).

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.45; H, 8.84.

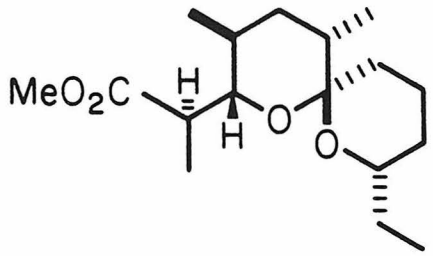
Methyl [2S-[2α(S*),3β,5β,6β]]-8-ethyl-α,3,5-trimethyl-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (9a) and Methyl [2S-[2α(S*),3β,5α,6β]]-8-ethyl-α,3,5-trimethyl-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (9b). A vigorously

stirred solution of 150 mg (0.510 mmol) of the olefin 8 in 5 mL of n-pentane was hydrogenated under a hydrogen atmosphere (H_2 filled balloon) at RT in the presence of a catalytic amount of powdered platinum oxide for 0.5 h. The reaction mixture was filtered through a pad of $MgSO_4$, and the filter cake was washed liberally with ether (15 mL). Concentration of the filtrate under reduced pressure afforded 151 mg (100%) of an inseparable 55:45 (by ^{1}H-NMR) mixture of the enol ethers 9a and 9b, respectively, as a colorless oil. This material was used for subsequent reactions without further purification.

Chromatography of a portion of this oil on 10 g of silica gel with 1:15 ether:petroleum ether followed by distillation [kugelrohr, 80°C (0.002 mm Hg)] provided the analytical sample of the mixture of enol ethers 9a and 9b as a colorless oil: R_f = 0.22 (silica gel, 1:15 ether: petroleum ether); IR ($CHCl_3$) 1730 (C=O) and 1680 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.78-1.00 (br m, 6H, C(3)-CH_3 and C(5)-CH_3), 1.03 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.07 and 1.10 (2d, 3H, J = 7 Hz, α-CH_3 for 5β- and 5α-isomers, respectively), 1.40-2.13 (br m, 10H), 2.61 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.54 (s, 3H, OCH_3), 3.80 (br m, 1H, C(2)-H), 4.41 (br d, 1H, J = 4 Hz, C(9)-H).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 69.04; H, 9.58.

Allowing the reaction to proceed after hydrogenation of the exo-methylene produced variable quantities of the fully reduced spiroketal ii along with its C(5) epimer and much hydrogenolysis product.



ii

Distillation [kugelrohr, 85°C (0.005 mm Hg)] of a portion of spiroketal ii provided the analytical sample as a colorless oil: R_f = 0.11 (silica gel, 1:15 ether: petroleum ether); IR ($CHCl_3$) 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.78 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.91 (t, 3H, J = 7 Hz, CH_2CH_3), 0.94 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.12 (d, 3H, J = 7 Hz, α-CH_3), 1.27-2.13 (br m, 12H), 2.62 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.37 (br m, 1H, C(8)-H), 3.64 (s, 3H, OCH_3), 4.08 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H); $[\alpha]_D^{25}$ = +6.5° ($CHCl_3$, c 1.28).

Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.23; H, 9.91.

Methyl [2S-[2α(S*),3β,5β,6β(8R*,9S*)]]-8-ethyl-9-hydroxy-α,3,5-trimethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (10a) and Methyl [2S-[2α(S*),3β,5α,6β(8R*,9S*)]]-8-ethyl-9-hydroxy-α,3,5-trimethyl-1,7-dioxaspiro[5.5]-undecane-2-acetate (10b). To a stirred solution of 92.8 mg (0.313 mmol) of the mixture of enol ethers 9a and 9b, described above, in 1 mL of dry THF cooled to 0°C (ice bath) under an argon atmosphere was added 0.94 mL (0.94 mmol) of 1 M borane in THF over 1 min. After 15 min at 0°C, the reaction mixture was quenched at 0°C by the slow cautious concurrent addition of 0.58 mL of 1 N aqueous NaOH solution and 0.094 mL of 30% aqueous H_2O_2 solution. The reaction mixture was allowed to warm to RT for 30 min and was then diluted with 3 mL of water and extracted with one 20 mL portion of ether and two 2 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure and chromatography of the residue on 11 g of silica gel with 2:1 ether:petroleum ether afforded 91.1 mg (93%) of a mixture of the alcohols 10a and 10b as a colorless oil. Distillation [kugelrohr, 100°C (0.002 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.25 (silica gel, 2:1 ether:petroleum ether); IR ($CHCl_3$) 3600

(free OH), 3480 (H-bonded OH), and 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.79-1.04 (br m, 9H, C(3)-CH_3, C(5)-CH_3, and $CH_2\underline{CH}_3$), 1.06 and 1.11 (2d, 3H, J = 7 Hz, α-CH_3 of 5β- and 5α-isomers, respectively), 1.27-2.17 (br m, 11H), 2.65 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.18-3.64 (br m, 2H, C(8)-H and C(9)-H), 3.80-4.11 (br m, 1H, C(2)-H).

Anal. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 65.02; H, 9.51.

Methyl [2S-[2α(S*),3β,5β,6β(R*)]]-8-ethyl-α,3,5-trimethyl-9-oxo-1,7-dioxaspiro[5.5]undecane-2-acetate (11a) and Methyl [2S-[2α(S*),3β,5α,6β(R*)]]-8-ethyl-α,3,5-trimethyl-9-oxo-1,7-dioxaspiro[5.5]undecane-2-acetate (11b). To a stirred solution of 0.092 mL (136 mg, 1.07 mmol) of oxalyl chloride (distilled from CaH_2) in 2.5 mL of dry dichloromethane cooled to -60°C (dry ice/chloroform slush) under an argon atmosphere was added 0.166 mL (183 mg, 2.34 mmol) of dry DMSO in 0.5 mL of dry dichloromethane over 5 min. After 5 min, 307 mg (0.976 mmol) of the mixture of the alcohols 10a and 10b, described above, in 1 mL of dry dichloromethane was added to the resulting solution over 5 min. After 15 min at -60°C, 0.68 mL (494 mg, 4.88 mmol) of dry triethylamine was added over 5 min and, after 5 min, the reaction mixture was allowed to warm slowly to RT over 15 min. To the resulting mixture was then added 3 mL of water and, after stirring

for 10 min, the layers were separated. The aqueous layer was extracted with two 4 mL portions of dichloromethane. After being dried ($MgSO_4$), the combined organic layers were concentrated under reduced pressure and chromatography of the residue on 25 g of silica gel with 1:4 ether:petroleum ether afforded 296 mg (97%) of the inseparable ketones 11a and 11b as a colorless oil. Distillation [kugelrohr, 95°C (0.004 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.14 (silica gel, 1:4 ether: petroleum ether); IR ($CHCl_3$) 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.80-1.15 (br m, 12H, four CH_3 groups), 1.32-2.53 (br m, 10H), 2.65 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.57 and 3.59 (2s, 3H, OCH_3 of 5β- and 5α-isomers, respectively), 3.73-4.08 (br m, 2H, C(2)-H and C(8)-H).

Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.43; H, 8.99.

Methyl [2S-[2α(S*),3β,5β,6β(S*)]]-8-ethyl-α,3,5-trimethyl-9-oxo-1,7-dioxaspiro[5.5]undecane-2-acetate (12a) and Methyl [2S-[2α(S*),3β,5α,6β(S*)]]-8-ethyl-α,3,5-trimethyl-9-oxo-1,7-dioxaspiro[5.5]undecane-2-acetate (12b). To a solution of 39.1 mg (0.125 mmol) of the mixture of ketones 11a and 11b in 0.16 mL of dry methanol under an argon atmosphere was added 0.040 mL (41 mg, 0.27 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). After 28 h at RT, the reaction mixture was

diluted with 10 mL of water and extracted with four 5 mL portions of ether. After being dried ($MgSO_4$), the combined organic extracts were concentrated under reduced pressure and chromatography of the residue on 12 g of silica gel with 1:5 ether:petroleum ether afforded first 33.6 mg (86%) of the inseparable epimerized ketones 12a and 12b as a colorless oil. Distillation [kugelrohr, 90°C (0.001 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.20 (silica gel, 1:4 ether: petroleum ether); IR ($CHCl_3$) 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.80-1.05 (br m, 9H, C(3)-CH_3, C(5)-CH_3, and CH_2CH_3), 1.11 and 1.17 (2d, 3H, α-CH_3 of 5β- and 5α-isomers, respectively), 1.33-2.80 (br m, 11H), 3.59 (s, 3H, OCH_3), 3.72-3.95 (br m, 2H, C(2)-H and C(8)-H).

Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.39; H, 8.95.

There was then eluted a small amount (1.3 mg, 3%) of material also epimerized at the alpha carbon (α-epi-12a,b) followed by 2.3 mg (6%) of the starting ketones 11a,b.

Methyl [2S-[2α(S*),3β,5β,6β(S*)]]-8-ethyl-α,3,5-trimethyl-9-methylene-1,7-dioxaspiro[5.5]undecane-2-acetate (13a) and Methyl [2S-[2α(S*),3β,5α,6β(S*)]]-8-ethyl-α,3,5-trimethyl-9-methylene-1,7-dioxaspiro[5.5]-undecane-2-acetate (13b).

A. Wittig Olefination of the Ketones 12a and 12b.

The procedure for the preparation of the olefin 8 with 54.4 mg (0.174 mmol) of the mixture of ketones 12a and 12b, described above, in 0.5 mL of dry THF and 0.302 mmol of methylenetriphenylphosphorane in 2.5 mL of dry THF afforded, after chromatography on 10 g of silica gel with 1:30 ether:petroleum ether and recycle of mixed fractions, first 27 mg (50%) of the olefin 13a as a colorless oil. Distillation [kugelrohr, 85°C (0.003 mm Hg)] of a portion of this oil provided the analytical sample of the olefin 13a: R_f = 0.15 (silica gel, 1:30 ether:petroleum ether); IR ($CHCl_3$) 1735 (C=O) and 1650 cm^{-1} ($C=CH_2$); ^1H-NMR ($CDCl_3$) δ 0.83 and 0.85 (2d, 6H, J = 6 Hz, C(3)-CH_3 and C(5)-CH_3), 1.04 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.13 (d, 3H, J = 7 Hz, α-CH_3), 1.38-2.53 (br m, 10H), 2.71 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.61 (s, 3H, OCH_3), 3.74-3.85 (br m, 2H, C(2)-H and C(8)-H), 4.68 (br s, 2H, $C=CH_2$); $[\alpha]_D^{25}$ = +71.6° ($CHCl_3$, c 1.09).

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.70; H, 9.73.

There was then eluted 23 mg (43%) of the olefin 13b as a colorless oil. Distillation [kugelrohr, 85°C (0.003 mm Hg)] of a portion of this oil provided the analytical sample of the olefin 13b: R_f = 0.13 (silica gel, 1:30 ether:petroleum ether); IR ($CHCl_3$) 1735 (C=O)

and 1650 cm^{-1} ($C=CH_2$); ^1H-NMR ($CDCl_3$) δ 0.81 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.96 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.08 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$), 1.17 (d, 3H, J = 7 Hz, α-CH_3), 1.32-2.43 (br m, 10H), 2.71 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.61 (s, 3H, OCH_3), 3.81 (br m, 2H, C(2)-H and C(8)-H), 4.69 (br s, 2H, $C=CH_2$); $[\alpha]_D^{25}$ = +73.4° ($CHCl_3$, c 0.93).

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.58; H, 9.70.

B. Equilibrium of Olefin 13b. To a stirred solution of 40.0 mg (0.129 mmol) of the olefin 13b in 2 mL of dry dichloromethane under an argon atmosphere was added 5.0 μL (5.6 mg, 0.040 mmol) of borontrifluoride etherate. After 15 min at RT, the reaction mixture was poured into 15 mL of saturated aqueous $NaHCO_3$ and extracted with three 7 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure and chromatography of the residue on 12 g of silica gel with 1:30 ether:petroleum ether afforded first 26.3 mg (66%) of the olefin 13a and then 11.2 mg (28%) of the olefin 13b. This represents a 70:30 equilibrium ratio between the olefins 13a and 13b.

Methyl [2S-[2α(S*),3β,5β,6β(8S*,9S*)]]-8-ethyl-α,-3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (14) and Methyl [2S-[2α(S*),3β,5β,6β(8S*,9R*)]]-8-ethyl-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (9-epi-14).

A. Hydrogenation of the Olefin 13a. The procedure for the preparation of the enol ethers 9a and 9b with 15.0 mg (0.0483 mmol) of the olefin 13a in 3 mL of n-pentane afforded, after chromatography on 1 g of silica gel with 1:30 ether:petroleum ether, 14.5 mg (96%) of a 63:37 (by 500 MHz ^{1}H-NMR) mixture of the spiroketals 14 and 9-epi-14, respectively, as a colorless oil. Medium pressure liquid chromatography (Lobar pre-packed column, size A, LiChroprep Si60, EM Reagents) of this oil with 1:50 ether:petroleum ether afforded (after recycle of mixed fractions) first 4.8 mg (32%) of the spiroketal 9-epi-14 as a colorless oil. Distillation [kugelrohr, 80°C (0.005 mm Hg)] of this oil provided the analytical sample of the spiroketal 9-epi-14: R_f = 0.17 (silica gel, 1:30 ether:petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); 500 MHz ^{1}H-NMR δ 0.77 and 0.81 (2d, 6H, J = 7 Hz, C(3)-CH_3 and C(9)-CH_3), 0.87 (d, 3H, J = 7 Hz, C(5)-CH_3), 0.97 (t, 3H, J = 7 Hz, CH_2CH_3), 1.11 (d, 3H, J = 7 Hz, α-CH_3), 1.26-1.70 (br m, 11H), 2.69 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 2.96 (ddd, 1H, J = 2.5 Hz, J'=J''= 9 Hz, C(8)-H), 3.67 (s, 3H, OCH_3), 3.71 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H); $[\alpha]_D^{23}$ = +66.5° ($CHCl_3$, c 0.75).

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.22; H, 10.25.

There was then eluted 9.0 mg (60%) of the spiroketal 14

as a colorless oil. Distillation [kugelrohr, 75°C (0.003 mm Hg)] of this oil provided the analytical sample of the spiroketal 14: R_f = 0.16 (silica gel, 1:30 ether: petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, 3H, J = 6.5 Hz, C(3)-CH_3), 0.83 (d, 3H, J = 6.5 Hz, C(5)-CH_3), 0.89 (d, 3H, J = 7 Hz, C(9)-CH_3), 0.95 (t, 3H, J = 7 Hz; CH_2CH_3), 1.11 (d, 3H, J = 7 Hz, α-CH_3), 1.21-1.55 (br m, 9H), 1.81 (ddd, 1H, J = 4.5 Hz, J'=J''= 13.5 Hz, ax C(11)-H), 1.93 (dddd, 1H, J=J'= 4.5 Hz, J''=J'''= 13.5 Hz, ax C(10)-H), 2.69 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.42 (ddd, 1H, J = 2.5 Hz, J' = 4.5 Hz, J'' = 9 Hz, C(8)-H), 3.66 (s, 3H, OCH_3), 3.72 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H); $[\alpha]_D^{23}$ = +60.3° ($CHCl_3$, c 1.09).

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32 Found: C, 69.30; H, 10.38.

B. Isomerization of the Spiroketal 22a. The spiroketal 22a (2.6 mg, 0.0083 mmol) was treated with 0.10 mL of dry dichloromethane saturated with p-toluenesulfonic acid-monohydrate for 10 min at RT. Chromatography of the reaction mixture on 1 g of silica gel with 1:30 ether: petroleum ether afforded 2.6 mg (100%) of the spiroketal 14 identical (500 MHz ^{1}H-NMR, TLC) to that prepared above.

C. Isomerization of the Spiroketal 22b. The spiroketal 22b (49.0 mg, 0.157 mmol) was treated with 0.5 mL of dry

dichloromethane saturated with p-toluenesulfonic acid-monohydrate for 10 min. Chromatography of the reaction mixture on 7 g of silica gel with 1:30 ether:petroleum ether afforded 47.7 mg (97%) of the spiroketal 5-epi-14 as a colorless oil. Distillation [kugelrohr, 90°C (0.003 mm Hg)] of a portion of this oil provided the analytical sample of the spiroketal 5-epi-14: R_f = 0.13 (silica gel, 1:30 ether:petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.80 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.85 (d, 3H, J = 7 Hz, C(9)-CH_3), 0.95 (d, 3H, J = 7 Hz, C(5)-CH_3), 0.99 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.15 (d, 3H, J = 7 Hz, α-CH_3), 1.26-1.56 (br m, 7H), 1.66 (br m, 1H), 1.73 (br m, 1H), 1.87 (br m, 1H), 1.95 (ddd, 1H, J = 4.5 Hz, J'=J''= 12.5 Hz, ax C(11)-H), 2.70 (dq, 1H, J = 3 Hz, J' = 7Hz, α-H), 3.47 (ddd, 1H, J = 2.5 Hz, J' = 4.5 Hz, J'' = 9.5 Hz, C(8)-H), 3.67 (s, 3H, OCH_3), 3.76 (dd, 1H, J = 3 Hz, J' = 10.5 Hz, C(2)-H); $[\alpha]_D^{25}$ = +69.4° ($CHCl_3$, c 0.68).

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.16; H, 10.23.

This spiroketal 5-epi-14 (24.3 mg, 0.0778 mmol) was treated under an argon atmosphere with 0.3 mL of dry dichloromethane saturated with p-toluenesulfonic acid-monohydrate for 50 h. The reaction mixture was then diluted with 1 mL of saturated aqueous $NaHCO_3$ and extracted

with three 1 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure and chromatography of the residue on 10 g of silica gel with 1:50 ether:petroleum ether afforded first 13.0 mg (53%) of the spiroketal 14 identical (500 MHz ^{1}H-NMR, $[\alpha]_D$, and TLC) to that prepared above. There was then eluted 10.7 mg (44%) of the starting spiroketal 5-epi-14.

Methyl [2S-[2α(S*),3β,5β,6β(8S*,9R*)]]-8-ethyl-9-hydroxy-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (15) and Methyl [2S-[2α(S*),3β,5β,6β(8S*,9S*)]]-8-ethyl-9-hydroxy-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]-undecane-2-acetate (9-epi-15).

A. Oxymercuration of the olefin 13a. To a stirred solution of 104 mg (0.335 mmol) of the olefin 13a in 0.8 mL of dry THF under an argon atmosphere was added 220 mg (0.690 mmol) of $Hg(OAc)_2$ in 0.8 mL of H_2O. After 30 min at RT, the reaction mixture was cooled to 0°C followed by the very cautious addition of 158 mg (4.17 mmol) of $NaBH_4$ in small portions. The reaction mixture was then allowed to warm to RT and, after all baseline material by TLC had disappeared, the reaction mixture was poured into 15 mL of water and extracted with three 5 mL portions of ether. After being dried ($MgSO_4$), the combined organic extracts were concentrated under reduced pressure and chromatography

of the residue on 10 g of silica gel with 1:1 ether: petroleum ether afforded first 12.9 mg (12% of the alcohol 9-epi- 15 as a colorless oil. Distillation [kugelrohr, 95°C (0.003 mm Hg)] of this oil provided the analytical sample of the alcohol 9-epi-15: R_f = 0.34 (silica gel, 1:1 ether:petroleum ether); IR ($CHCl_3$) 3590 (free OH), 3480 (H-bonded OH), and 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.92 (d, 3H, J = 6 Hz, C(5)-CH_3), 1.01 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.04 (s, 3H, C(9)-CH_3), 1.11 (d, 3H, J = 7 Hz, α-CH_3), 1.30-1.96 (br m, 11H), 2.68 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.25 (dd, 1H, J = 4 Hz, J' = 9 Hz, C(8)-H), 3.64 (s, 3H, OCH_3), 3.71 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H); $[\alpha]_D^{25}$ = +62.6° ($CHCl_3$, c 1.26).

Anal. Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.75; H, 9.73.

There was then eluted 80.7 mg (73%) of the alcohol 15 as a white solid. Recrystallization of a portion (21 mg) of this solid from 0.5 mL of a n-pentane provided the analytical sample (13 mg) as long prisms melting at 109.5-110.0°C: R_f = 0.14 (silica gel, 1:1 ether:petroleum ether); IR ($CHCl_3$) 3610 (free OH), 3500 (H-bonded OH), and 1735 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.88 (d, 3H, J = 6 Hz, C(5)-CH_3), 1.08 (s, 3H, C(9)-CH_3), 1.09 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.11 (d, 3H, J = 7 Hz,

α-CH_3), 1.23-1.83 (br m, 11H), 2.68 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.13 (dd, 1H, J = 2 Hz, J' = 10 Hz, C(8)-H), 3.67 (s, 3H, OCH_3), 3.71 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H); $[\alpha]_D^{24}$ = +69.1° ($CHCl_3$, c 0.95).

Anal. Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.86; H, 9.82.

B. Grignard Addition to the Ketones 12a and 12b. To a stirred solution of 15.6 mg (0.0499 mmol) of the mixture of ketones 12a and 12b in 1 mL of dry ether cooled to -40°C (dry ice/acetonitrile slush) under an argon atmosphere was added 21 μL (0.058 mmol) of 2.8 M methylmagnesium bromide in ether (Aldrich). The reaction mixture was allowed to stir at -40°C for 1 h and then at 0°C for 0.5 h. The reaction mixture was then diluted with 1 mL of saturated aqueous $NaHCO_3$ and extracted with three 1 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure and chromatography of the residue on 7 g of silica gel with 1:1 ether:petroleum ether afforded first 0.9 mg (6%) of the starting ketones 12a and 12b. There was then eluted 1.0 mg (6%) of the alcohol 9-epi-15 identical (^{1}H-NMR, TLC) to that prepared above.

Further elution afforded 1.0 mg (6%) of the alcohol 5-epi-9-epi-15 as a white solid melting at 97-100°C. Rechromatography on 1 g of silica gel with 1:2 ether: petroleum ether and distillation [kugelrohr, 105°C

(0.003 mm Hg)] of this solid provided the analytical sample of the alcohol 5-epi-9-epi-15 as a white solid melting at 102-104°C: R_f = 0.23 (silica gel, 1:1 ether:petroleum ether); IR ($CHCl_3$) 3590 (free OH), 3500 (H-bonded OH), and 1735 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.80 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.97 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.07 (s, 3H, C(9)-CH_3), 1.07 (t, 3H, $CH_2\underline{CH}_3$), 1.14 (d, 3H, J = 7 Hz, α-CH_3), 1.25-1.98 (br m, 11H), 2.68 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.26 (dd, 1H, J = 4 Hz, J' = 8 Hz, C(8)-H), 3.63 (s, 3H, OCH_3), 3.75 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H); $[\alpha]_D^{24}$ = +72.4° ($CHCl_3$, c 0.21).

Anal. Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.95; H, 9.72.

Finally, there was eluted 13.8 mg (84%) of an inseparable mixture of the alcohols 15 and 5-epi-15 as a white solid. The ^{1}H-NMR was consistent with a mixture of the previously prepared alcohol 15 (see above) and the alcohol 5-epi-15.[2]

X-ray Crystallography of the Spiroketal 15. $C_{18}O_5H_{32}$, crystallized by slow evaporation of n-hexane in the orthorhombic space group $P2_12_12_1$. Crystal data are a = 13.200(6), b = 31.949(14), c = 9.102(4) A, Z = 8, D_c = 1.133 gm·cm^{-3}, Mol Wt = 328.5, F(000) = 1431, μ(MoKα) = 0.88 cm^{-1}.

Diffraction data were collected on a Nicolet $P2_1$ automated diffractometer by the θ-2θ scan technique at room temperature with graphite monochromated MoKα radiation.

The scan rate varied from 2.0°/min to 15°/min dependent on the intensity of the diffraction maxima. The base width was 1.8° and the sum of the background times was equal to one-half of the total scan time. No decay was noted in the three check reflections monitored every 50 reflections. A total of 4667 reflections were collected out to a maximum 2θ of 55°, with 2295 being considered observed with intensities > 2.3 $\sigma(I)$.

The structure was solved by direct methods using the program MULTAN.[20] The best statistical set indicated all 46 nonhydrogen atoms in the first E-map.[21] Hydrogen atoms were located in difference maps and their bond geometries idealized. Block diagonal least square minimizing $\Sigma w(|F_o|-|F_c|)^2$ and refining the scale factor, nonhydrogen atom coordinates and anisotropic temperature factors converged at R = 0.068 and a goodness-of-fit of 2.78.

The two molecules of the spiroketal 15 in the asymmetric unit have the same configuration and conformation within experimental error. The molecules form hydrogen bonded dimers between O(20)-H(20)---O(17') and O(20')-H(20')---O(17). The details of the hydrogen bonds are: O(20)---O(17') = 2.910(6) A, O(20)-H(20)---O(17') = 116°, O(20')---O(17) = 2.896 A, and O(20')-H(20')---O(17) = 81°. The differences in the strength of the two hydrogen bonds

cause small, but significant differences in the carbonyl bond distances: C(14)-O(17) = 1.235(7) and C(14')-O(17') = 1.184(8). The only significant difference in bond angles was the C(2)-C(12)-C(14) angle of 106.5(5)° and 110.2(5)° for the non-primed and primed molecules, respectively. There were no significant differences in the ring torsion angles.

An ORTEP[22] drawing of the non-primed molecule is given in Figure 1. The relative rather than the absolute stereochemistry was determined in this structural determination.

Methyl [2S-[2α(S*),3β,6α]]-8-ethyl-α,3-dimethyl-5-methylene-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (17). The procedure for the preparation of the olefin 8 with 365 mg (1.23 mmol) of the ketone 16 in 2 mL of dry THF and 1.91 mmol of methylenetriphenylphosphorane in 16 mL of dry THF afforded, after chromatography on 36 g of alumina (activity III) with 1:15 ether:petroleum ether, 319 mg (88%) of the olefin 17 as a colorless oil. Distillation [kugelrohr, 80°C (0.002 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.17 (silica gel, 1:15 ether:petroleum ether); IR ($CHCl_3$) 1730 (C=O) and 1685 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.93 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.03 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.15 (d, 3H, J = 7 Hz, α-CH_3), 1.43-2.60 (br m, 9H),

2.75 (dq, 1H, J = 6 Hz, J' = 7 Hz, α-H), 3.64 (s, 3H, OCH_3), 3.74 (dd, 1H, J = 6 Hz, J' = 8 Hz, C(2)-H), 4.50 (br d, 1H, J = 4 Hz, C(9)-H), 4.83 and 5.07 (2br s, 2H, $C=CH_2$); $[\alpha]_D^{24}$ = -78.2° ($CHCl_3$, c 1.35).

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.09; H, 8.71.

Methyl [2S-[2α(S*),3β,5β,6α]]-8-ethyl-α,3,5-trimethyl-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (18a) and Methyl [2S-[2α(S*),3β,5α,6α]]-8-ethyl-α,3,5-trimethyl-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (18b). The procedure for the preparation of the enol ethers 9a and 9b with 78 mg (0.265 mmol) of the olefin 17 afforded 78.5 mg (100%) of the enol ethers 18a and 18b as a colorless oil. Chromatography on 12 g of silica gel with 1:15 ether:petroleum ether containing 0.5% pyridine (omission of pyridine results in extensive decomposition of the enol ethers) afforded first 61.9 mg (79%) of the enol ether 18b as a colorless oil. Distillation [kugelrohr, 80°C (0.002 mm Hg)] of a portion of this oil provided the analytical sample of the enol ether 18b: R_f = 0.20 (silica gel, 1:15 ether:petroleum ether); IR ($CHCl_3$) 1730 (C=O) and 1680 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.95 and 0.99 (2d, 6H, J = 6 Hz, C(3)-CH_3 and C(5)-CH_3), 1.01 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.15 (d, 3H, J = 7 Hz, α-CH_3), 1.33-2.18 (br m, 10H), 2.92 (dq, 1H, J = J' = 7 Hz, α-H), 3.63 (s, 3H, OCH_3), 3.63 (dd, 1H,

J = 6 Hz, J' = 7 Hz, C(2)-H), 4.48 (br m, 1H, C(9)-H); $[\alpha]_D^{26}$ = -63.0° ($CHCl_3$, c 1.14).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.72; H, 9.39.

There was then eluted 12.7 mg (16%) of the enol ether 18a as a colorless oil. Distillation [kugelrohr, 80°C (0.002 mm Hg)] of a portion of this oil provided the analytical sample of the enol ether 18a: R_f = 0.14 (silica gel, 1:15 ether:petroleum ether); IR ($CHCl_3$) 1730 (C=O) and 1680 cm^{-1} (O-C=C); ^{1}H-NMR ($CDCl_3$) δ 0.81 and 0.86 (2d, 6H, J = 6 Hz, C(3)-CH_3 and C(5)-CH_3), 0.99 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.14 (d, 3H, J = 7 Hz, α-CH_3), 1.33-2.10 (br m, 10H), 2.62 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.61 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H), 3.63 (s, 3H OCH_3), 4.42 (br d, 1H, J = 4 Hz, C(9)-H); $[\alpha]_D^{25}$ = -33.8° ($CHCl_3$, c 1.27).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 69.11; H, 9.55.

Methyl [2S-[2α(S*),3β,5β,6α(8S*,9R*)]]-8-ethyl-9-hydroxy-α,3,5-trimethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (19a). The procedure for the preparation of the alcohols 10a and 10b with 44.2 mg (0.149 mmol) of the enol ether 18a in 1 mL of dry THF and 0.45 mL (0.45 mmol) of 1 M borane in THF quenching with 0.27 mL of 1 N aqueous NaOH solution and 0.045 mL of 30% aqueous H_2O_2 afforded, after 40 min at RT and chromatography on 10 g of silica gel with 3:2 ether:petroleum ether, 41.4 mg (88%) of the alcohol 19a as a colorless oil: R_f = 0.15 (silica gel, 3:2 ether:petroleum ether); IR ($CHCl_3$) 3620 (free OH), 3500 (H-bonded OH), and 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.80 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.90 (d, 3H, J = 7 Hz, C(5)-CH_3), 0.97 (t, 3H, J = 7 Hz, CH_2CH_3), 1.14 (d, 3H, J = 7 Hz, α-CH_3), 1.30-1.90 (br m, 11H), 2.63 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.47-3.70 (br m, 3H, C(2)-H, C(8)-H, and C(9)-H), 3.67 (s, 3H, OCH_3); $[\alpha]_D^{25}$ = +30.5° ($CHCl_3$, c = 1.13).

Anal. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 65.08; H, 9.57.

Methyl [2S-[2α(S*),3β,5α,6α(8S*,9R*)]]-8-ethyl-9-hydroxy-α,3,5-trimethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (19b). The procedure for the preparation of the alcohols 10a and 10b with 95 mg (0.321 mmol) of the enol ether 18b in 1 mL of dry THF and 1.16 mL (1.16 mmol) of

1 M borane in THF quenching with 0.69 mL of 1 N aqueous NaOH solution and 0.116 mL of 30% aqueous H_2O_2 afforded, after 40 min at RT and chromatography on 13 g of silica gel with 5:2 ether:petroleum ether, 89 mg (88%) of the alcohol 19b as a colorless oil. Distillation [kugelrohr, 120°C (0.002 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.16 (silica gel, 5:2 ether: petroleum ether); IR ($CHCl_3$) 3610 (free OH), 3500 (H-bonded OH), and 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.79 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.98 (t, 3H, J = 7 Hz, CH_2CH_3), 1.02 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.19 (d, 3H, J = 7 Hz, α-CH_3), 1.38-2.03 (br m, 11H), 2.62 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.27-3.63 (br m, 2H, C(8)-H and C(9)-H), 3.66 (s, 3H, OCH_3), 3.69 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H); $[\alpha]_D^{25}$ = +70.6° ($CHCl_3$, c 0.95).

Anal. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C. 64.99; H, 9.75.

Methyl [2S-[2α(S*),3β,5β,6α(S*)]]-8-ethyl-α,3,5-trimethyl-9-oxo-1,7-dioxaspiro[5.5]undecane-2-acetate (20a). The procedure for the preparation of the ketones 11a and 11b with 7.0 μL (10 mg, 0.082 mmol) of oxalyl chloride in 0.3 mL of dry dichloromethane, 12.6 μL (13.9 mg, 0.178 mmol) of dry DMSO in 0.04 mL of dry dichloromethane, 23.3 mg (0.074 mmol) of the alcohol 19a in 0.2 mL of dry dichloromethane, and 51.5 μL (37.4 mg, 0.37 mmol) of dry triethyl-

amine afforded, after workup as described and chromatography on 10 g of silica gel with 1:3 ether:petroleum ether, 21.3 mg (92%) of the ketone 20a as a colorless oil. Distillation [kugelrohr, 100°C (0.003 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.14 (silica gel, 1:3 ether:petroleum ether); IR ($CHCl_3$) 1715 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.83 (d, 3H, J = 7 Hz, C(3)-CH_3), 0.92 (d, 3H, J = 7 Hz, C(5)-CH_3), 0.96 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.13 (d, 3H, J = 7 Hz, α-CH_3), 1.57-2.52 (br m, 10H), 2.63 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.59 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H), 3.93 (t, 1H, J = 7 Hz, C(8)-H); $[\alpha]_D^{25}$ = +92.6° ($CHCl_3$, c 0.90).

Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.51; H, 9.18.

Methyl [2S-[2α(S*),3β,5α,6α(S*)]]-8-ethyl-α,3,5-trimethyl-9-oxo-1,7-dioxaspiro[5.5]undecane-2-acetate (20b). The procedure for the preparation of the ketones 11a and 11b with 17.4 μL (25.8 mg, 0.203 mmol) of oxalyl chloride in 0.5 mL of dry dichloromethane, 31.4 μL (34.6 mg, 0.443 mmol) of dry DMSO in 0.1 mL of dry dichloromethane, 58.0 mg (0.184 mmol) of the alcohol 19b in 0.2 mL of dry dichloromethane, and 130 μL (93 mg, 0.92 mmol) of dry triethylamine afforded, after workup as described and chromatography on 10 g of silica gel with 1:2 ether: petroleum ether, 54.2 mg (94%) of the ketone 20b as a

colorless oil. Distillation [kugelrohr, 100°C (0.004 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.18 (silica gel, 1:2 ether: petroleum ether); IR ($CHCl_3$) 1715 cm^{-1} (C=0); ^{1}H-NMR ($CDCl_3$) δ 0.85 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.97 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$), 1.10 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.17 (d, 3H, J = 7 Hz, α-CH_3), 1.50-2.17 (br m, 7H), 2.30-2.69 (br m, 3H), 2.69 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.64 (s, 3H, OCH_3), 3.65 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H), 3.88 (dd, 1H, J = 6 Hz, J' = 8 Hz, C(8)-H); $[\alpha]_D^{27}$ = +110.4° ($CHCl_3$, c 1.01).

Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.49; H, 9.10.

Methyl [2S-[2α(S*),3β,5β,6α(S*)]]-8-ethyl-α,3,5-trimethyl-9-methylene-1,7-dioxaspiro[5.5]undecane-2-acetate (21a). The procedure for the preparation of the olefin 8 with 16.5 mg (0.053 mmol) of the ketone 20a in 0.3 mL of dry THF and 0.099 mmol of methylenetriphenylphosphorane in 1 mL of dry THF afforded, after chromatography on 7 g of silica gel with 1:20 ether:petroleum ether, 14.4 mg (88%) of the olefin 21a as a colorless oil. Distillation [kugelrohr, 90°C (0.003 mm Hg)] of this oil provided the analytical sample: R_f = 0.15 (silica gel, 1:20 ether:petroleum ether); IR ($CHCl_3$) 1735 (C=0) and 1650 cm^{-1} (C=CH_2); ^{1}H-NMR ($CDCl_3$) δ 0.80 and 0.83 (2d, 6H,

J = 6 Hz, C(3)-CH_3 and C(5)-CH_3), 0.87 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$), 1.14 (d, 3H, J = 7 Hz, α-CH_3), 1.40-2.42 (br m, 10H), 2.63 (dq, 1H, J = 2 Hz, J' = 7 Hz, α-H), 3.64 (dd, 1H, J = 2 Hz, J' = 10 Hz, C(2)-H), 3.65 (s, 3H, OCH_3), 3.97 (t, 1H, J = 7 Hz, C(8)-H), 4.61 and 4.67 (2br s, 2H $C=CH_2$); $[\alpha]_D^{28}$ = +24.2° ($CHCl_3$, c 0.86).

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.75; H, 9.78.

Methyl [2S-[2α(S*),3β,5α,6α(S*)]]-8-ethyl-α,3,5-trimethyl-9-methylene-1,7-dioxaspiro[5.5]undecane-2-acetate (21b). The procedure for the preparation of the olefin 8 with 48.0 mg (0.154 mmol) of the ketone 20b in 0.5 mL of dry THF and 0.263 mmol of methylenetriphenylphosphorane in 2 mL of dry THF afforded, after chromatography on 10 g of silica gel with 1:25 ether:petroleum ether, 43.6 mg (91%) of the olefin 21b as a colorless oil. Distillation [kugelrohr, 80°C (0.003 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.13 (silica gel, 1:25 ether:petroleum ether); IR ($CHCl_3$) 1735 (C=O) and 1650 cm^{-1} ($C=CH_2$); ^{1}H-NMR ($CDCl_3$) δ 0.80 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.91 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$), 1.04 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.19 (d, 3H, J = 7 Hz, α-CH_3), 1.32-2.53 (br m, 10H), 2.64 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.66 (s, 3H, OCH_3), 3.68 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H), 3.97 (dd, 1H, J = 6 Hz, J' = 9 Hz, C(8)-H), 4.67

and 4.70 (2br s, 2H, C=CH_2); $[\alpha]_D^{27}$ = +49.2° ($CHCl_3$, c 1.09).

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.71; H, 9.70.

Methyl [2S-[2α(S*),3β,5β,6α(8S*,9S*)]]-8-ethyl-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (22a) and Methyl [2S-[2α(S*),3β,5β,6α(8S*,9R*)]]-8-ethyl-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (9-epi-22a). The procedure for the preparation of the enol ethers 9a and 9b with 10 mg (0.32 mmol) of the olefin 21a in 3 mL of n-pentane afforded, after filtration of the reaction mixture through a pad of Celite (filtration through $MgSO_4$ results in substantial isomerization at the spirocenter), 10 mg (100%) of the spiroketals 22a and 9-epi-22a as a colorless oil. Chromatography of this oil on 7 g of silica gel with 1:20 ether:petroleum ether afforded first 6.6 mg (65%) of the spiroketal 22a as a colorless oil: R_f = 0.17 (silica gel, 1:20 ether:petroleum ether); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.82 and 0.83 (2d, 6H, J = 6.5 Hz, C(3)-CH_3 and C(5)-CH_3), 0.89 (d, 3H, J = 7 Hz, C(9)-CH_3), 1.03 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.17 (d, 3H, J = 7 Hz, α-CH_3), 1.28-1.43 (br m, 4H), 1.55-1.73 (br m, 4H), 1.89 (br m, 1H), 1.98 (br m, 1H), 2.65 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.61 (ddd, 1H, J = 3.5 Hz, J' = 6 Hz, J'' = 12 Hz, C(8)-H), 3.65 (dd, 1H, J = 3 Hz, J' = 10.5 Hz, C(2)-H), 3.70 (s, 3H, OCH_3).

There was then eluted 3.4 mg (34%) of the spiroketal

9-epi-22a as a colorless oil: R_f = 0.12 (silica gel, 1:20 ether:petroleum ether); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.80 (d, 3H, J = 6.5 Hz, C(3)-CH_3), 0.88 (d, 3H, J = 6.5 Hz, C(5)-CH_3), 0.94 (t, 3H, J = 7 Hz, CH_2CH_3), 0.98 (d, 3H, J = 6.5 Hz, C(9)-CH_3), 1.16 (d, 3H, J = 7 Hz, α-CH_3), 1.40-1.80 (br m, 10H), 2.64 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.31 (ddd, 1H, J=J' = 4.5 Hz, J'' = 9 Hz, C(8)-H), 3.62 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H), 3.68 (s, 3H, OCH_3).

Methyl [2S-[2α(S*),3β,5α,6α(8S*,9S*)]]-8-ethyl-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (22b) and Methyl [2S-[2α(S*),3β,5α,6α(8S*,9R*)]]-8-ethyl-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (9-epi-22b). The procedure for the preparation of the enol ethers 9a and 9b with 69.7 mg (0.225 mmol) of the olefin 21b in 3 mL of n-pentane afforded, after filtration of the reaction mixture through a pad of Celite (filtration through $MgSO_4$ results in substantial isomerization at the spirocenter), 70.1 mg (100%) of the spiroketals 22b and 9-epi-22b as a colorless oil. Chromatography of this oil on 7 g of silica gel with 1:6 ether:petroleum ether afforded first 49.0 mg (70%) of the spiroketal 22b as a colorless oil. Distillation [kugelrohr, 90°C (0.003 mm Hg)] of a portion of this oil provided the analytical sample of the spiroketal 22b: R_f = 0.28 (silica gel, 1:6 ether:petroleum

ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.78 (d, 3H, J = 6.5 Hz, C(3)-CH_3), 0.85 (d, 3H, J = 7 Hz, C(5)-CH_3), 0.95 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.02 (d, 3H, J = 7 Hz, C(9)-CH_3), 1.19 (d, 3H, J = 7 Hz, α-CH_3), 1.24 (br m, 1H), 1.45-1.65 (br m, 6H), 1.79 (br m, 2H), 1.92 (br m, 1H), 2.03 (br m, 1H), 2.62 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.52 (ddd, 1H, J=J' = 4.5 Hz, J'' = 10 Hz, C(8)-H), 3.69 (s, 3H, OCH_3), 3.74 (dd, 1H, J = 3 Hz, J' = 10.5 Hz, C(2)-H); $[\alpha]_D^{25}$ = +71.6° ($CHCl_3$, c 0.86).

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.31; H, 10.24.

There was then eluted 17.7 mg (25%) of the spiroketal 9-epi-22b as a colorless oil. Distillation [kugelrohr, 90°C (0.003 mm Hg)] of a portion of this oil provided the analytical sample of the spiroketal 9-epi-22b: R_f = 0.14 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1730 cm^{-1} (C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.78 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.84 (d, 3H, J = 6.5 Hz, C(5)-CH_3), 0.96 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 0.99 (d, 3H, J = 7 Hz, C(9)-CH_3), 1.17 (br m, 1H), 1.22 (d, 3H, J = 7 Hz, α-CH_3), 1.41-1.62 (br m, 6H), 1.70-1.82 (br m, 2H), 2.10 (br m, 1H), 2.16 (ddd, 1H, J=J' = 5 Hz, J'' = 13 Hz), 2.63 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.03 (ddd, 1H, J = 3 Hz, J'=J'' = 8.5 Hz, C(8)-H), 3.68 (s, 3H, OCH_3), 3.80 (dd, 1H, J = 3 Hz, J' = 10.5 Hz, C(2)-H); $[\alpha]_D^{25}$ = +83.6° ($CHCl_3$, c 0.66).

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 68.94; H, 10.13.

Methyl [2R-(2R*,3S*,4S*,6R*,10R*,11R*)]-3,11-dihydroxy-2,4,6,10-tetramethyl-7-oxo-tridecanoate,1,2-ethanediyl dithioketal derivative (23). To a vigorously stirred solution of 23.0 mg (0.0736 mmol) of the spiroketal 14 in 0.617 mL (693 mg, 7.36 mmol) of 1,2-ethanedithiol cooled to -40°C (dry ice/acetonitrile slush) under an argon atmosphere was added dropwise 0.186 mL (209 mg, 1.47 mmol) of borontrifluoride etherate. After 6 h at -40°C with vigorous stirring, the cold reaction mixture was poured into 15 mL of saturated aqueous Na_2CO_3 and the resulting mixture was extracted with three 7 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure followed by removal of the 1,2-ethanedithiol under high vacuum (0.5 mm Hg). Chromatography of the residue immediately on 1 g of silica gel with 2:1 ether:petroleum ether afforded, after 3 mg (13%) of the starting spiroketal 14, 24.0 mg (80%) of the diol-thioketal 23 as a colorless oil. Distillation [kugelrohr, 180°C (0.001 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.21 (silica gel, 2:1 ether: petroleum ether); IR ($CHCl_3$) 3500 (OH) and 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.86-1.10 (br m, 9H, C(4)-CH_3, C(10)-CH_3, and C(13)-H_3), 1.12 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.16 (d,

3H, J = 7 Hz, C(2)-CH_3), 1.32-2.22 (br m, 12H), 2.63 (d, 1H, J = 4 Hz, OH), 2.67 (dq, 1H, J = 3 Hz, J' = 7 Hz, C(2)-H), 3.22 (s, 4H, thioketal), 3.43 (br m, 1H, C(11)-H), 3.68 (s, 3H, OCH_3), 3.73 (br m, 1H, C(3)-H); $[\alpha]_D^{24}$ = +26.0° ($CHCl_3$, c 1.11).

Anal. Calcd for $C_{20}H_{38}O_4S_2$: C, 59.07; H, 9.42; S, 15.77. Found: C, 59.14; H, 9.34; S, 15.75.

Methyl [2R-(2R*,3S*,4S*,6R*,10R*,11R*)]-11-(benzoyloxy)-3-hydroxy-2,4,6,10-tetramethyl-7-oxo-tridecanoate,1,2-ethanediyl dithioketal derivative (24). To a stirred solution of 33.3 mg (0.0819 mmol) of the diol-thioketal 23 in 0.86 mL of dry dichloromethane under an argon atmosphere was added first 0.044 mL (43 mg, 0.55 mmol) of dry pyridine followed by 0.030 mL (36 mg, 0.26 mmol) of benzoyl chloride. After 3 h at RT, the reaction mixture was diluted with 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of water and extracted with three 5 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure followed by azeotropic removal of pyridine with n-heptane (2x2 mL). Chromatography of the resulting oil on 7 g of silica gel with 1:2 ether:petroleum ether afforded 38.7 mg (93%) of the benzoate 24 as a colorless oil. Distillation [kugelrohr, 220°C (0.001 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.14 (silica gel, 1:2 ether:

petroleum ether); IR ($CHCl_3$) 3520 (OH) and 1710 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.86 and 1.01 (2d, 6H, J = 7 Hz, C(4)-CH_3 and C(10)-CH_3), 0.93 (t, 3H, J = 7 Hz, C(13)-H_3), 1.07 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.14 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.43-2.17 (br m, 11H), 2.65 (dq, 1H, J = 3 Hz, J' = 7 Hz, C(2)-H), 3.17 (s, 4H, thioketal), 3.67 (s, 3H, OCH_3), 3.70 (dd, 1H, J = 3 Hz, J' = 8 Hz, C(3)-H), 5.04 (br m, 1H, C(11)-H), 7.32-7.58 (br m, 3H, ArH), 7.97-8.12 (br m, 2H, ArH); $[\alpha]_D^{25}$ = +17.3° ($CHCl_3$, c 1.23).

Anal. Calcd for $C_{27}H_{42}O_5S_2$: C, 63.49; H, 8.29; S, 12.56. Found: C, 63.60; H, 8.32; S, 12.45.

Methyl [2R-(2R*,3S*,4S*,6R*,10R*,11R*)]-11-(benzoyloxy)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6,10-tetramethyl-7-oxo-tridecanoate,1,2-ethanediyl dithioketal derivative (25). A stirred solution of 38.7 mg (0.0758 mmol) of the benzoate 24, 71.9 mg (1.06 mmol) of imidazole, and 77.3 mg (0.51 mmol) of tert-butyldimethylchlorosilane (TBSCl) in 0.5 mL of dry DMF under an argon atmosphere was heated at 85°C for 21 h. The reaction mixture was diluted with 10 mL of saturated aqueous $NaHCO_3$ and extracted with three 5 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure and chromatography of the residue on 7 g of silica gel with 1:10 ether:petroleum ether afforded 42.0 mg (89%) of the silyl ether 25 as a colorless oil. Distillation [kugelrohr,

220°C (0.001 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.14 (silica gel, 1:10 ether: petroleum ether); IR ($CHCl_3$) 1710 cm^{-1} (C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) δ -0.01 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.88 (s, 9H, t-BuSi), 0.94 (t, 3H, J = 7 Hz, C(13)-H_3), 0.94 and 1.02 (2d, 6H, J = 7 Hz, C(4)-CH_3 and C(10)-CH_3), 1.06 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.13 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.45-2.01 (br m, 11H), 2.67 (dq, 1H, J = 4.5 Hz, J' = 7 Hz, C(2)-H), 3.18 (m, 4H, thioketal), 3.61 (s, 3H, OCH_3), 3.97 (dd, 1H, J=J' = 4.5 Hz, C(3)-H), 5.05 (ddd, 1H, J=J' = 4.5 Hz, J'' = 8 Hz, C(11)-H), 7.44 (dd, 2H, J=J' = 8 Hz, ArH), 7.55 (t, 1H, J = 8 Hz, ArH), 8.05 (d, 2H, J = 8 Hz, ArH); $[\alpha]_D^{25}$ = +13.3° ($CHCl_3$, c 0.77).

Anal. Calcd for $C_{33}H_{56}O_5S_2Si$: C, 63.42; H, 9.03; S, 10.26. Found: C, 63.33; H, 9.01; S, 10.30.

Methyl [2R-(2R*,3S*,4S*,6R*,10R*,11R*)]-11-(benzoyloxy)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6,10-tetramethyl-7-oxo-tridecanoate (26). To a vigorously stirred solution of 42.0 mg (0.0672 mmol) of the thioketal 25 in 0.55 mL of acetonitrile and 0.14 mL of water under an argon atmosphere was added first 48.9 mg (0.49 mmol) of $CaCO_3$ (powder) and then 93.8 mg (0.35 mmol) of $HgCl_2$. After 11 h at RT, the reaction mixture was diluted with 10 mL of dichloromethane and filtered through a pad of Celite followed by washing the filter cake with 35 mL of dichloro-

methane. The filtrate was washed with one 15 mL portion of 5 M aqueous NH_4OAc, one 15 mL portion of saturated aqueous $NaHCO_3$, and finally one 15 mL portion of saturated aqueous NaCl. After being dried ($MgSO_4$), the organic layer was concentrated under reduced pressure and chromatography of the residue on 7 g of silica gel with 1:6 ether: petroleum ether afforded 34.3 mg (93%) of the ketone 26 as a colorless oil. Distillation [kugelrohr, 175°C (0.001 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.14 (silica gel, 1:6 ether: petroleum ether); IR ($CHCl_3$) 1710 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.83-1.03 (br m, 18H), 1.06 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.11 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.29-1.94 (br m, 8H), 2.39-2.80 (br m, 4H), 3.59 (s, 3H, OCH_3), 3.80 (dd, 1H, J = 4 Hz, J' = 6 Hz, C(3)-H), 5.02 (br m, 1H, C(11)-H), 7.27-7.60 (br m, 3H, ArH), 7.93-8.04 (br m, 2H, ArH); $[\alpha]_D^{24}$ = +3.2° ($CHCl_3$, c = 1.00).

Anal. Calcd for $C_{31}H_{52}O_6Si$: C, 67.84; H, 9.55. Found: C, 67.69; H, 9.46.

Methyl [2R-(2R*,3S*,4S*,6R*,8E,10R*,11R*)]-11-(benzoyloxy)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6,10-tetramethyl-7-oxo-8-tridecenoate (27). To a stirred solution of 29.9 mg (0.0545 mmol) of the ketone 26 in 0.34 mL of dry THF and 0.051 mL of dry HMPA cooled to -78°C (dry ice/2-propanol) under an argon atmosphere was

added first rapidly 0.028 mL (0.17 mmol) of the supernatant centrifugate from a mixture of 2.1 mL of trimethylchlorosilane (TMSCl) and 0.7 mL of dry triethylamine followed immediately by the addition of 0.120 mL (0.060 mmol) of 0.50 M lithium diisopropylamide (LDA) in THF [prepared by the addition of 0.32 mL (0.50 mmol) of 1.56 M n-butyllithium in hexane to a stirred solution of 0.10 mL (72 mg, 0.71 mmol) of dry diisopropylamine in 0.3 mL of dry THF cooled to 0°C under an argon atmosphere followed by, after 30 min at 0°C, the dilution of the resulting mixture with dry THF to a total volume of 1.00 mL] dropwise over 2 min. After stirring for 10 min at -78°C, the reaction mixture was allowed to warm to 0°C for 5 min, diluted with 10 mL of saturated aqueous $NaHCO_3$, and then extracted with three 5 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure and chromatography of the residue on 1 g of Fluorisil with 1:15 ether:petroleum ether afforded first 28.7 mg (85%) of the desired silyl enol ether: R_f = 0.15 (silica gel, 1:15 ether:petroleum ether). Further elution with ether afforded (after repurification) 4.9 mg (16%) of pure starting ketone 26.

A solution of this silyl enol ether (28.7 mg, 0.0462 mmol) and 97 mg (0.432 mmol) of palladium(II) acetate in 1.8 mL of dry acetonitrile was stirred under an

argon atmosphere for 3.5 h. The reaction mixture was then diluted with 60 mL of ether and washed with two 15 mL portions of 10% aqueous $Na_2S_2O_3$, one 15 mL portion of saturated aqueous $NaHCO_3$, and one 15 mL portion of saturated aqueous NaCl. The combined aqueous washings were extracted with one 15 mL portion of ether. After being dried ($MgSO_4$), the combined ether solutions were concentrated under reduced pressure and chromatography of the residue on 1 g of silica gel with 1:6 ether:petroleum ether afforded 24.1 mg (95%) of the enone 27 as a colorless oil. Distillation [kugelrohr, 185°C (0.001 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.11 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1715 (ester C=O), 1665 (enone C=O), and 1625 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 0.87 (d, 3H, J = 6 Hz, C(4)-CH_3), 0.88 (s, 9H, t-BuSi), 0.93 (t, 3H, J = 7 Hz, C(13)-H_3), 1.06 and 1.11 (2d, 6H, J = 7 Hz, C(6)-CH_3 and C(10)-CH_3), 1.14 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.28-1.97 (br m, 5H), 2.40-2.93 (br m, 3H, C(2)-H, C(6)-H, and C(10)-H), 3.61 (s, 3H, OCH_3), 3.81 (dd, 1H, J = 4 Hz, J' = 6 Hz, C(3)-H), 5.07 (dt, 1H, J=J' = 6 Hz, C(11)-H), 6.16 (d, 1H, J = 16 Hz, C(8)-H), 6.84 (dd, 1H, J = 8 Hz, J' = 16 Hz, C(9)-H), 7.31-7.61 (br m, 3H, ArH), 7.95-8.06 (br m, 2H, ArH); $[\alpha]_D^{25}$ = +21.4° ($CHCl_3$, c 1.07).

Anal. Calcd for $C_{31}H_{50}O_6Si$: C, 68.09; H, 9.22. Found: C, 68.07; H, 9.27.

Methyl [2R-(2R*,3S*,4S*,6R*,7R* and 7S*,8E,10R*,11R*)]-11-(benzoyloxy)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-hydroxy-2,4,6,10-tetramethyl-8-tridecenoate (28). A mixture of 18.0 mg (0.0329 mmol) of the enone 27 and 0.5 mL of 0.5 M (0.25 mmol) of zinc borohydride in dry DME under an argon atmosphere was stirred at 0°C for 5 h and then, over 1 h, allowed to warm to RT for 2.5 h. The reaction mixture was then cooled to 0°C and quenched by the cautious addition of 0.020 mL of water followed by 0.050 mL of acetic acid. The resulting mixture was then diluted with 5 mL of water and 10 mL of saturated aqueous $NaHCO_3$ and extracted with three 5 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure and chromatography of the residue on 1 g of silica gel with 1:2 ether:petroleum ether afforded, after 2.5 mg (14%) of a 50:50 mixture of the starting enone 27 and the saturated ketone 26 eluted, 15.1 mg (83%) of the allylic alcohols 28 as a mixture of isomers contaminated with some of the corresponding saturated alcohols: R_f = 0.18 and 0.13 (silica gel, 1:2 ether:petroleum ether); IR ($CHCl_3$) 3520 (OH) and 1710 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.80-1.05 (br m, 9H, C(4)-CH_3, C(6)-CH_3, and C(13)-H_3), 0.90 (s, 9H, t-BuSi), 1.10 (d, 3H, J = 6 Hz, C(10)-CH_3), 1.16 (d, 3H, J = 7 Hz, C(2)-H), 1.27-1.87 (br m, 7H), 2.47-2.77 (br m, 2H, C(2)-H and OH),

3.63 and 3.65 (2s, 3H, OCH_3's of the 2 isomers), 3.82-4.03 (br m, 2H, C(3)-H and C(7)-H), 5.03 (dt, 1H, J=J' = 6H, C(11)-H), 5.53-5.63 (br m, 2H, C(8)-H and C(9)-H), 7.32-7.63 (br m, 3H, ArH), 8.01-8.11 (br m, 2H, ArH).

Anal. Calcd for $C_{31}H_{52}O_6Si$: $M^+-H_2O-C_4H_9$ 473.2723. Found: $M^+-H_2O-C_4H_9$ 473.2727.

[2R-(2R*,3S*,4S*,6R*,8E,10R*,11R*)]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-11-hydroxy-2,4,6,10-tetramethyl-7-oxo-8-tridecenoic acid (30). To a stirred solution of 15.0 mg (0.0273 mmol) of the allylic alcohols 28 in 0.80 mL of dry DME under an argon atmosphere was added 0.20 mL of 1 N aqueous KOH and the resulting mixture was heated to 75°C for 24 h. The reaction mixture was then diluted with 15 mL of water and acidified to pH 3 by the addition of 1 N aqueous HCl (0.22 mL added). The resulting mixture was extracted with three 5 mL portions of ether and the combined extracts were dried ($MgSO_4$). Concentration of this dried solution under reduced pressure afforded 13.4 mg of crude carboxylic acid as an oil. A stirred solution of this oil in 0.46 mL of dry benzene under an argon atmosphere was treated with 31.5 mg (0.14 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and the resulting stirred mixture was kept in the dark for 36 h. The reaction mixture was then diluted with 20 mL of ether

and was washed with two 5 mL portions of 10% aqueous $Na_2S_2O_3$. The combined aqueous washings were extracted with one 5 mL portion of ether and this extract was combined with the main ether layer. After being dried ($MgSO_4$), the ether layer was concentrated under reduced pressure and chromatography of the residue on 1 g of silica gel with 2:1 ether:petroleum ether containing 0.1% acetic acid afforded 8.6 mg of slightly impure seco-acid 30. Rechromatography of this material on 1 g of silica gel with 1:1 ether:petroleum ether containing 0.1% acetic acid afforded 5.8 mg (50%) of pure seco-acid 30 as a colorless oil: R_f = 0.14 (silica gel, 2:1 ether:petroleum ether containing 0.1% acetic acid); IR ($CHCl_3$) 3600-2500 (OH), 1705 (acid C=O), 1660 (enone C=O), and 1620 cm^{-1} (C=C); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.09 (s, 6H, $SiCH_3$), 0.91 (s, 9H, t-BuSi), 0.95 (d, 3H, J = 7 Hz, C(4)-CH_3), 0.98 (t, 3H, J = 7.5 Hz, C(13)-H_3), 1.08 (d, 3H, J = 7 Hz, C(10)-CH_3), 1.12 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.17 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.50-1.74 (br m), 1.77 (ddd, 1H, J = 6 Hz, J' = 9 Hz, J'' = 14 Hz, C(5)-H), 2.51 (br m, 1H, C(10)-H), 2.62 (dq, 1H, J=J' = 7 Hz, C(2)-H), 2.82 (ddq, J = 9 Hz, J'=J'' = 7 Hz, C(6)-H), 3.76 (br m, 1H, C(11)-H), 3.78 (dd, 1H, J = 2.5 Hz, J' = 7 Hz, C(3)-H), 6.25 (dd, 1H, J = 2 Hz, J' = 16 Hz, C(8)-H), 6.96 (dd, 1H, J = 6 Hz, J' = 16 Hz, C(9)-H); $[\alpha]_D^{25}$ = +16.6° ($CHCl_3$, c 0.58).

Anal. Calcd for $C_{23}H_{44}O_5Si$: $M^+-H_2O-C_4H_9$ 353.2148. Found: $M^+-H_2O-C_4H_9$ 353.2173.

[3R-(3R*,4S*,5S*,7R*,9E,11R*,12R*)]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-12-ethyl-3,5,7,11-tetramethyl-oxacyclododec-9-ene-2,8-dione (31). To a stirred solution of 3.8 mg (0.0089 mmol) of the seco-acid 30 in 0.080 mL of dry THF cooled to 0°C under an argon atmosphere was added first 0.010 mL (0.0098 mmol) of 0.98 M triethylamine in dry THF and then 0.010 mL (0.0098 mmol) of 0.98 M diphenyl chlorophosphate in dry THF. After 0.5 h at 0°C, the reaction mixture was diluted with 0.10 mL of dry THF and stirred an additional 0.5 h. The resulting solution of the mixed anhydride was diluted with 3.5 mL of dry benzene and maintained at 5°C. This cold solution was added by syringe pump over 8 h to a stirred solution of 4.8 mg (0.039 mmol) of 4-dimethylaminopyridine (DMAP) in 5.5 mL of dry benzene heated to 75°C under an argon atmosphere. Heating at 75°C was continued for an additional 33 h, and then the reaction mixture was allowed to cool to RT. Concentration of the reaction mixture under reduced pressure and chromatography of the residue on 1 g of silica gel with 1:6 ether:petroleum ether afforded first 0.3 mg (10%) of the lactone 31 as a colorless oil: R_f = 0.19 (silica gel, 1:6 ether:petroleum ether); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H,

$SiCH_3$), 0.87 (t, 3H, J = 7.5 Hz, $CH_2\underline{CH}_3$), 0.88 (s, 9H, t-BuSi), 0.93 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.08 (2d, 6H, J = 7 Hz, C(7)-CH_3 and C(11)-CH_3), 1.17 (d, 3H, J = 7 Hz, C(3)-CH_3), 2.62 (br m, 1H, C(11)-H), 2.65 (dq, 1H, J=J' = 7 Hz, C(3)-H), 2.81 (tq, 1H, J=J' = 7 Hz, C(7)-H), 3.91 (dd, 1H, J = 2 Hz, J' = 7 Hz, C(4)-H), 4.77 (ddd, 1H, J = 7 Hz, J'=J'' = 5 Hz, C(12)-H), 6.23 (d, 1H, J = 15.5 Hz, C(9)-H), 6.87 (dd, 1H, J = 7 Hz, J' = 15.5 Hz, C(10)-H).

Anal. Calcd for $C_{23}H_{42}O_4Si$: $M^+-C_4H_9$ 353.2148. Found: $M^+-C_4H_9$ 353.2156.

There was then eluted 0.1 mg (3%) of an isomeric lactone epi-31 as a colorless oil: R_f = 0.11 (silica gel, 1:6 ether:petroleum ether); 500 MHz ^{1}H-NMR δ 0.06 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.88 (t, 3H, J = 7.5 Hz, $CH_2\underline{CH}_3$), 0.90 (s, 9H, t-BuSi), 0.92 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.10 (d, 3H, J = 7 Hz, C(11)-CH_3), 1.20 (2d, 6H, J = 7 Hz, C(3)-CH_3 and C(7)-CH_3), 2.50 (br m, 1H, C(11)-H), 2.62 (dq, 1H, J = 10 Hz, J' = 7 Hz, C(3)-H), 2.66 (br m, 1H, C(7)-H), 3.61 (d, 1H, J = 10 Hz, C(4)-H), 4.95 (ddd, 1H, J = 2.3 Hz, J' = 5.5 Hz, J'' = 8.8 Hz, C(12)-H), 6.42 (dd, 1H, J = 1.5 Hz, J' = 16 Hz, C(9)-H), 6.74 (dd, 1H, J = 5.5 Hz, J' = 16 Hz, C(10)-H).

Anal. Calcd for $C_{23}H_{42}O_4Si$: $M^+-C_4H_9$ 353.2148. Found: $M^+-C_4H_9$ 353.2153.

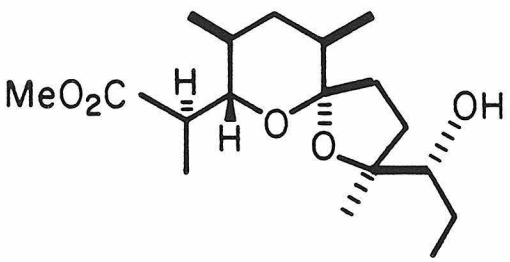
Further elution with 1:2 ether:petroleum ether afforded

0.3 mg (10%) of the corresponding diolide as a colorless oil: R_f = 0.05 (silica gel, 1:6 ether:petroleum ether); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.04 (s, 6H, $SiCH_3$), 0.05 (s, 6H, $SiCH_3$), 0.85 (t, 6H, J = 7 Hz, $CH_2\underline{CH}_3$), 0.88 (s, 18H, t-BuSi), 0.91 (d, 6H, J = 7 Hz, C(5)-CH_3), 1.06 and 1.07 (2d, 12H, J = 7 Hz, C(7)-CH_3 and C(11)-CH_3), 1.16 (d, 6H, J = 7 Hz, C(3)-CH_3), 2.62 (dq, 2H, J=J' = 7 Hz, C(3)-H), 2.63 (br m, 2H, C(11)-H), 2.83 (br m, 2H, C(7)-H), 3.86 (dd, 2H, J = 2.8 Hz, J' = 7 Hz, C(4)-H), 4.75 (ddd, 2H, J = 4 Hz, J' = 6 Hz, J'' = 8 Hz, C(12)-H), 6.18 (dd, 2H, J = 1 Hz, J' = 15.7 Hz, C(9)-H), 6.79 (dd, 2H, J = 8 Hz, J' = 15.7 Hz, C(10)-H).

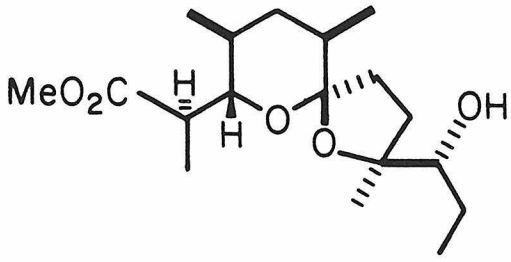
Methyl [2R-(2R*,3S*,4S*,6R*,10S*,11R*)]-3,10,11-trihydroxy-2,4,6,10-tetramethyl-7-oxo-tridecanoate, acetonide and 1,2-ethanediyl dithioketal derivative (32) and Methyl [2R-(2R*,3S*,4S*,6S*,10S*,11R*)]-3,10,11-trihydroxy-2,4,6,10-tetramethyl-7-oxo-tridecanoate, acetonide and 1,2-ethanediyl dithioketal derivative (6-epi-32). To a vigorously stirred solution of 81.5 mg (0.248 mmol) of the spiroketal 15 in 2.1 mL (2.3 g, 25 mmol) of 1,2-ethanedithiol cooled to -40°C (dry ice/acetonitrile slush) under an argon atmosphere was added dropwise 0.63 mL (700 mg, 4.96 mmol) of borontrifluoride etherate. The reaction mixture was allowed to slowly warm to -20°C over

20 min and was then maintained at -20°C (dry ice/carbon tetrachloride slush) for 5.5 h with vigorous stirring. The cold reaction mixture was then poured into 40 mL of saturated aqueous Na_2CO_3, and the resulting mixture was extracted with three 20 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure followed by removal of the 1,2-ethanedithiol under high vacuum (0.5 mm Hg). The residue was immediately dissolved in 5 mL of dry acetone under an argon atmosphere and 25 mg (0.13 mmol) of p-toluenesulfonic acid-monohydrate and some $MgSO_4$ (anhydrous) were added. After 2 h at RT with stirring, the reaction mixture was filtered into 40 mL of saturated aqueous $NaHCO_3$, and the filter cake was washed with 20 mL of ether. The layers were separated, and the aqueous layer was extracted with two 20 mL portions of ether. After being dried ($MgSO_4$), the combined organic layers were concentrated under reduced pressure and chromatography of the residue on 25 g of silica gel with 1:2 ether:petroleum ether afforded first 8.3 mg (10%) of the ring contracted spiroketal iii as a colorless oil: R_f = 0.23 (silica gel, 1:2 ether:petroleum ether). There was then eluted 48.5 mg (50%) of a mixture of the desired acetonide 32 (23%) and the ring contracted spiroketal iv (27%) in a 47:53 molar ratio by ^{1}H-NMR: R_f = 0.15 (silica gel, 1:2 ether:petroleum ether); ^{1}H-NMR ($CDCl_3$) (acetonide 32) δ 1.20 (s, 3H,

C(10)-CH_3), 1.33 and 1.43 (2s, 6H, acetonide), 3.19 (s, 4H, thioketal), 3.67 (s, 3H, OCH_3).



iii



iv

Further elution afforded 11.5 mg (10%) of the acetonide 6-epi-32 as a colorless oil. Distillation [kugelrohr, 175°C (0.001 mm Hg)] of this oil provided the analytical sample of the acetonide 6-epi-32: R_f = 0.10 (silica gel, 1:2 ether:petroleum ether); IR ($CHCl_3$) 3520 (OH) and 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.87 (d, 3H, J = 6 Hz, C(4)-CH_3), 1.04 (t, 3H, J = 7 Hz, C(13)-H_3), 1.08 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.18 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.20 (s, 3H, C(10)-CH_3), 1.34 and 1.44 (2s, 6H, acetonide), 1.38-2.39 (br m, 11H), 2.68 (dq, 1H, J = 3 Hz, J' = 7 Hz, C(2)-H), 3.19 (s, 4H, thioketal), 3.53-3.68 (br m, 2H, C(3)-H and C(11)-H), 3.68 (s, 3H, OCH_3); $[\alpha]_D^{25}$ = -43.9° ($CHCl_3$, c 1.13).

Anal. Calcd for $C_{23}H_{42}O_5S_2$: C, 59.70; H, 9.15; S, 13.86. Found: C, 59.85; H, 9.26; S, 13.82.

Finally, there was eluted 15.4 mg (19%) of the starting spiroketal 15 contaminated with a small amount (15-20%) of its C-5 epimer as a white solid: R_f = 0.06 (silica gel, 1:2 ether:petroleum ether).

Methyl [2R-(2R*,3S*,4S*,6R*,10S*,11R*)]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-10,11-dihydroxy-2,4,6,10-tetramethyl-7-oxo-tridecanoate, acetonide and 1,2-ethanediyl dithioketal derivative (33). The procedure for the preparation of the silyl ether 25 with 51.5 mg (0.132 mmol) of the mixture of the acetonide 32 (28.6 mg, 0.0618 mmol) and the spiroketal iv (22.9 mg, 0.0699 mmol), described above, 93 mg (1.37 mmol) of imidazole, and 100 mg (0.66 mmol) of TBSCl in 0.6 mL of dry DMF afforded, after 17 h at 85°C, workup as described, and chromatography on 7 g of silica gel with 1:8 ether:petroleum ether, first 30.0 mg (97% based on amount of spiroketal iv in starting material) of the TBS derivative of the spiroketal iv as a colorless oil: R_f = 0.42 (silica gel, 1:8 ether:petroleum ether).

There was then eluted 34.6 mg (97% based on amount of acetonide 32 in starting material) of the silyl ether 33 as a colorless oil. Distillation [kugelrohr, 175°C (0.001 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.18 (silica gel, 1:8 ether:petroleum ether); IR ($CHCl_3$) 1730 cm^{-1} (C=O); ^1H-NMR ($CDCl_3$) δ 0.05 (s, 6H, $SiCH_3$), 0.89 (s, 9H, t-BuSi), 0.97

(d, 3H, J = 6 Hz, C(4)-CH_3), 1.03 (t, 3H, J = 7 Hz, C(13)-H_3), 1.11 (d, 3H, J = 6 Hz, C(6)-CH_3), 1.14 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.20 (s, 3H, C(10)-CH_3), 1.33 and 1.44 (2s, 6H, acetonide), 1.37-2.25 (br m, 10H), 2.68 (dq, 1H, J = 4 Hz, J' = 7 Hz, C(2)-H), 3.17 (s, 4H, thioketal), 3.60 (dd, 1H, J = 4 Hz, J' = 9 Hz, C(3)-H), 3.62 (s, 3H, OCH_3), 3.99 (t, 1H, J = 4 Hz, C(11)-H); $[\alpha]_D^{25}$ = +4.9° ($CHCl_3$, c 1.31).

Anal. Calcd for $C_{29}H_{56}O_5S_2Si$: C, 60.37; H, 9.78; S, 11.11. Found: C, 60.42; H, 9.70; S, 11.12.

Methyl [2R-(2R*,3S*,4S*,6R*,10S*,11R*)]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-10,11-dihydroxy-2,4,6,10-tetramethyl-7-oxo-tridecanoate, acetonide derivative (34). The procedure for the preparation of the ketone 26 with 27.5 mg (0.0477 mmol) of the thioketal 33 in 0.4 mL of acetonitrile and 0.1 mL of water, 36 mg (0.36 mmol) of $CaCO_3$ (powder), and 68 mg (0.25 mmol) of $HgCl_2$ afforded, after workup as described and chromatography on 6 g of silica gel with 1:6 ether:petroleum ether, 22.5 mg (94%) of the ketone 34 as a colorless oil. Distillation [kugelrohr, 145°C (0.001 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.12 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.03 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, t-BuSi), 0.88-1.08 (br m, 6H, C(4)-CH_3 and C(13)-H_3),

1.08 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.12 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.16 (s, 3H, C(10)-CH_3), 1.33 and 1.35 (2d, 6H, acetonide), 1.27-1.97 (br m, 7H), 2.45-2.77 (br m, 4H), 3.60 (dd, 1H, J = 4 Hz, J' = 9 Hz, C(11)-H), 3.62 (s, 3H, OCH_3), 3.80 (dd, 1H, J = 4 Hz, J' = 6 Hz, C(3)-H); $[\alpha]_D^{24}$ = +2.9° ($CHCl_3$, c 0.97).

Anal. Calcd for $C_{27}H_{52}O_6Si$: C, 64.76; H, 10.47. Found: C, 64.86; H, 10.46.

Methyl [2R-(2R*,3S*,4S*,6R*,8E,10S*,11R*)]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-10,11-dihydroxy-2,4,6,10-tetramethyl-7-oxo-8-tridecenoate, acetonide derivative (35). The procedure for the preparation of the enone 27 with 18.1 mg (0.0361 mmol) of the ketone 34 in 0.22 mL of dry THF and 0.034 mL of dry HMPA, 0.019 mL (0.11 mmol) of the supernatant centrifugate from a mixture of 2.1 mL of TMSCl and 0.7 mL of dry triethylamine, and 0.079 mL (0.040 mmol) of 0.50 M LDA in THF afforded, after workup as described and chromatography on 1 g of Fluorisil with 1:15 ether:petroleum ether, first 14.8 mg (72%) of the intermediate silyl enol ether as a colorless oil: R_f = 0.18 (silica gel, 1:15 ether:petroleum ether). Further elution with ether afforded (after repurification) 4.7 mg (26%) of pure starting ketone 34.

In the manner described for the preparation of the enone 27, this silyl enol ether (14.8 mg, 0.0258) and 55 mg

(0.245 mmol) of palladium(II) acetate in 1 mL of dry acetonitrile afforded, after workup as described and chromatography on 1 g of silica gel with 1:6 ether:petroleum ether, 12.8 mg (99%) of the enone 35 as a colorless oil. Distillation [kugelrohr, 150°C (0.001 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.10 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1730 (ester C=O), 1690 (s-cis enone C=O), 1665 (s-trans enone C=O), and 1630 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 0.03 (s, 6H, $SiCH_3$), 0.88 (s, 9H, t-BuSi), 0.91 (d, 3H, J = 7 Hz, C(4)-CH_3), 1.01 (t, 3H, J = 7 Hz, C(13)-H_3), 1.10 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.12 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.37 (s, 3H, C(10)-CH_3), 1.41 and 1.50 (2s, 6H, acetonide), 1.43-2.23 (br m, 5H), 2.58 (dq, 1H, J=J' = 7 Hz, C(2)-H), 2.81 (br m, 1H, C(6)-H), 3.63 (s, 3H, OCH_3), 3.71-3.89 (br m, 2H, C(3)-H and C(11)-H), 6.39 (d, 1H, J = 15 Hz, C(8)-H), 6.75 (d, 1H, J = 15 Hz, C(9)-H); $[\alpha]_D^{25}$ = +14.8° ($CHCl_3$, c 0.95).

Anal. Calcd for $C_{27}H_{50}O_6Si$: C, 65.02; H, 10.10. Found: C, 65.03; H, 9.96.

[2R-(2R*,3S*,4S*,6R*,8E,10S*,11R*)]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-10,11-dihydroxy-2,4,6,10-tetramethyl-7-oxo-8-tridecenoic acid, acetonide derivative (36).

A. Reduction and Oxidation of the Ester 35. To a stirred solution of 2.0 mg (0.0040 mmol) of the ester 35 in 0.1 mL

of dry hexane cooled to -78°C (dry ice/2-propanol) under an argon atmosphere was added 0.024 mL (0.024 mmol) of 1 M diisobutylaluminum hydride in hexane over 2 min. After 40 min at -78°C, the reaction mixture was immersed in an ice bath for 5 min and then recooled to -78°C for 15 min. The reaction mixture was quenched at -78°C by the cautious addition of 0.010 mL of methanol and was then poured into 1 mL of 0.5 M aqueous sodium potassium tartrate and 1 mL of ether. This mixture was stirred vigorously at RT until all of the gelatinous precipitate had dissolved. The layers were then separated, and the aqueous layer was extracted with three 1 mL portions of ether. The combined organic layers were dried ($MgSO_4$) and concentration under reduced pressure afforded 1.9 mg (100%) of the desired diols as a colorless oil: R_f = 0.11 (silica gel, 2:1 ether:petroleum ether).

To a stirred solution of these diols (1.9 mg, 0.0040 mmol) in 0.080 mL of acetone cooled to -20°C (dry ice/carbon tetrachloride slush) under an argon atmosphere was added 5.7 μL (0.046 mmol) of 8 N Jones reagent over 1 h. After 0.5 h at -20°C, the reaction was quenched by the addition of 10 μL of 2-propanol and allowed to warm to RT. The resulting green mixture was decanted into 1 mL of saturated aqueous NaCl. The green solids were rinsed with ether and the ether rinsings added to the NaCl solution. The layers

were separated, and the aqueous layer was extracted with three 1 mL portions of ether. After being dried ($MgSO_4$), the combined organic layers were concentrated under reduced pressure and chromatography of the residue on 1 g of silica gel with 2:1 ether:petroleum ether afforded 1.8 mg (93%) of the carboxylic acid 36 as a colorless oil: R_f = 0.28 (2:1 ether:petroleum ether); IR ($CHCl_3$) 3520-2500 (OH), 1710 (acid C=O), 1670 (enone C=O), and 1630 cm^{-1} (C=C); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.08 (2s, 6H, $SiCH_3$), 0.91 (s, 9H, t-BuSi), 0.92 (d, 3H, J = 7 Hz, C(4)-CH_3), 1.03 (t, 3H, J = 7.5 Hz, C(13)-H_3), 1.12 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.18 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.42 (s, 3H, C(10)-CH_3), 1.43 and 1.53 (2q, 6H, J = 0.8 Hz, acetonide), 1.50 (dq, 1H, J = 8 Hz, J' = 7.5 Hz, C(12)-H), 1.51 (dq, 1H, J = 5.3 Hz, J' = 7.5 Hz, C(12)-H), 1.60 (br m, 2H, C(4)-H and C(5)-H), 1.87 (ddd, 1H, J = 3.8 Hz, J' = 10 Hz, J'' = 14 Hz, C(5)-H), 2.63 (dq, 1H, J=J' = 7 Hz, C(2)-H), 2.77 (ddq, 1H, J = 4.8 Hz, J' = 10 Hz, J'' = 7 Hz, C(6)-H), 3.80 (dd, 1H, J = 3.3 Hz, J' = 7 Hz, C(3)-H), 3.84 (dd, 1H, J = 5.3 Hz, J' = 8 Hz, C(11)-H), 6.46 (d, 1H, J = 15.5 Hz, C(8)-H), 6.77 (d, 1H, J = 15.5 Hz, C(9)-H); $[\alpha]_D^{25}$ = +8.6° ($CHCl_3$, c 0.39).

Anal. Calcd for $C_{26}H_{48}O_6Si$: M^+-CH_3 469.2985. Found: M^+-CH_3 469.2979.

B. Basic Hydrolysis of the Ester 35. A mixture of 1.0 mg (0.0020 mmol) of the ester 35, 0.12 mL of dry DME, and 0.040 mL of 1 N aqueous KOH under an argon atmosphere was stirred at RT for 24 h and then heated to 50°C for 36 h. The reaction mixture was then diluted with 1 mL of H_2O, acidified to pH 2.5 with 0.1 N aqueous H_2SO_4, and extracted with four 1 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure and chromatography of the residue on 1 g of silica gel with 3:2 ether:petroleum ether afforded an inseparable 37:63 mixture (by 500 MHz ^{1}H-NMR) of carboxylic acids in which the minor isomer is identical (500 MHz ^{1}H-NMR) to the carboxylic acid 36 prepared above, and the major isomer is the carboxylic acid 6-epi-36: 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.06 and 0.08 (2s, 6H, $SiCH_3$), 0.90 (s, 9H, t-BuSi), 0.92 (d, 3H, J = 7 Hz, C(4)-CH_3), 1.03 (t, 3H, J = 7.5 Hz, C(13)-H_3), 1.06 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.17 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.39 (s, 3H, C(10)-CH_3), 1.43 and 1.52 (2q, 6H, J = 0.8 Hz, acetonide), 3.82 (dd, 1H, J=J' = 7 Hz), 3.85 (dd, 1H, J = 4.4 Hz, J' = 5.5 Hz), 6.42 (d, 1H, J = 15.3 Hz, C(8)-H), 6.77 (d, 1H, J = 15.3 Hz, C(9)-H).

[2R-(2R*,3S*,4S*,6R*,8E,10S*,11R*)]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-10,11-dihydroxy-2,4,6,10-tetramethyl-7-oxo-8-tridecenoic acid (37). To a stirred solution of

1.2 mg (0.0025 mmol) of the acetonide 36 in 0.10 mL of acetonitrile under an argon atmosphere was added 0.10 mL of 1 N aqueous HCl. After 60 min at RT, the reaction mixture was diluted with 1.5 mL of water, and 0.090 mL of 1 N aqueous NaOH was added resulting in a pH 2 solution. This mixture was extracted with three 1 mL portions of ether, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was separated by preparative TLC (10 x 10 cm precoated TLC plate, silica gel 60 F-254, layer thickness 0.5 mm, manufactured by E. Merck and Co.) with ethyl acetate eluant (single elution, visualized by ultraviolet light) and afforded three major fractions:

Fraction 1: R_f = 0.55 (silica gel, ethyl acetate), 0.4 mg (30%) of recovered starting acetonide 36.

Fraction 2: R_f = 0.30 (silica gel, ethyl acetate), 0.2 mg (20%) of the desired diol 37 as a colorless oil: 500 MHz ^{1}H-NMR δ 0.11 (s, 6H, $SiCH_3$), 0.92 (s, 9H, t-BuSi), 0.97 (d, 3H, J = 6.8 Hz, C(4)-CH_3), 1.02 (t, 3H, J = 7.3 Hz, C(13)-H_3), 1.12 (d, 3H, J = 6.8 Hz, C(6)-CH_3), 1.16 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.37 (s, 3H, C(10)-CH_3), 2.61 (dq, 1H, J=J' = 7.3 Hz, C(2)-H), 2.76 (tq, 1H, J=J' = 6.9 Hz, C(6)-H), 3.49 (m, 1H, C(11)-H), 3.81 (dd, 1H, J = 2 Hz, J' = 7.5 Hz, C(3)-H), 6.49 (d, 1H, J = 15.6 Hz, C(8)-H), 6.88 (d, 1H, J = 15.6 Hz, C(9)-H).

Anal. Calcd for $C_{23}H_{44}O_6Si$: $M^+-H_2O-C_4H_9$ 369.2097. Found: $M^+-H_2O-C_4H_9$ 369.2105.

Fraction 3: R_f = 0.20 (silica gel, ethyl acetate), 0.1 mg (10%) of a compound lacking both the acetonide and the TBS.

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Supplementary Material Available: Atomic positional and thermal parameters (Table I); hydrogen atom positional and thermal parameters (Table II); bond distances (Table III); and bond angles (Table IV)(6 pages). Ordering information is given on any current masthead page.

References and Notes

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Table I. Final atomic positional and thermal parameters. The atomic coordinates have been multiplied by 10^4 and the thermal parameters by 10^3. The form of the temperature factor is $\exp\ [-2\pi^2(U_{11}ha^* + \ldots\ 2U_{12}hka^*b^* + \ldots)]$. Estimated standard deviations are given in parenthesis.

ATOM	X	Y	Z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	5520(3)	1131(1)	4266(4)	46(2)	50(2)	47(2)	3(2)	2(2)	3(2)
C(2)	5820(4)	1022(2)	5720(7)	46(4)	48(4)	56(4)	3(3)	-2(3)	1(3)
C(3)	6833(5)	1222(2)	6116(7)	63(4)	61(5)	74(5)	-9(4)	1(4)	-11(4)
C(4)	7591(5)	1102(2)	4930(8)	53(4)	74(5)	85(5)	-13(4)	-7(4)	-2(4)
C(5)	7246(5)	1190(2)	3402(7)	64(4)	61(4)	64(4)	-15(4)	0(4)	6(4)
C(6)	6194(4)	1009(4)	3135(7)	48(4)	43(4)	69(2)	2(3)	0(4)	3(3)
O(7)	6320(3)	566(1)	3129(4)	42(2)	59(3)	62(3)	0(2)	3(2)	-3(2)
C(8)	5425(4)	325(2)	2885(7)	44(4)	58(4)	69(4)	0(3)	9(4)	-3(4)
C(9)	4963(5)	433(2)	1397(8)	52(4)	49(4)	66(4)	-5(3)	5(4)	-1(4)
C(10)	4764(5)	889(2)	1376(7)	66(5)	64(4)	56(4)	3(4)	0(4)	2(4)
C(11)	5699(5)	1152(2)	1726(7)	60(4)	52(4)	55(4)	-6(3)	-1(4)	1(3)
C(12)	4935(5)	1152(2)	6746(7)	52(4)	61(4)	61(4)	-3(3)	-1(4)	6(4)
C(13)	4808(5)	1617(2)	6924(8)	83(5)	76(5)	85(5)	-5(4)	-12(5)	-32(5)
C(14)	3990(5)	955(2)	6119(7)	62(4)	54(4)	51(4)	2(4)	22(4)	4(3)
O(15)	3991(3)	547(1)	6232(5)	65(3)	46(3)	81(3)	2(2)	2(3)	3(2)
C(16)	3150(6)	324(2)	5620(9)	84(5)	53(5)	117(6)	-14(4)	16(6)	8(4)
O(17)	3278(3)	1151(1)	5574(5)	58(3)	61(3)	92(3)	-3(2)	-3(3)	7(3)
C(18)	7164(6)	1114(2)	7699(8)	82(5)	105(6)	77(5)	-34(5)	-29(5)	15(5)
C(19)	8024(5)	1039(3)	2255(8)	46(4)	135(7)	89(6)	-23(5)	28(4)	-9(5)
O(20)	4017(3)	213(1)	1235(5)	76(3)	75(3)	92(4)	-12(3)	-8(3)	0(3)
C(21)	5617(6)	288(2)	129(8)	93(5)	74(5)	76(5)	3(5)	6(5)	-2(4)
C(22)	5718(5)	-124(2)	3101(8)	81(5)	51(4)	90(5)	2(4)	0(5)	10(4)
C(23)	5992(6)	-232(2)	4666(10)	120(7)	52(5)	122(7)	6(5)	-15(6)	12(5)
O(1')	2281(3)	1634(1)	410(4)	48(2)	56(3)	60(3)	0(2)	-2(2)	-1(2)
C(2')	1322(5)	1504(2)	-146(7)	53(4)	73(5)	59(4)	-10(4)	3(4)	-1(4)
C(3')	1127(5)	1679(2)	-1673(8)	71(5)	102(6)	56(4)	10(4)	-5(4)	0(4)
C(4')	1230(5)	2149(2)	-1582(7)	83(5)	75(5)	57(4)	22(4)	0(4)	10(4)
C(5')	2236(5)	2295(2)	-943(7)	70(4)	80(5)	46(4)	10(4)	12(4)	8(4)
C(6')	2402(4)	2073(2)	514(7)	55(4)	55(4)	56(4)	-3(3)	0(4)	-10(3)
O(7')	1676(3)	2241(1)	1489(4)	50(2)	64(3)	52(2)	12(2)	3(2)	4(2)
C(8')	1704(5)	2092(2)	2971(7)	71(4)	58(4)	49(4)	8(4)	4(4)	5(3)
C(9')	2720(5)	2190(2)	3665(7)	82(5)	48(4)	54(4)	3(4)	-9(4)	6(3)

ATOM	X	Y	Z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(10')	3529(5)	1987(2)	2753(7)	59(4)	75(5)	65(4)	0(4)	-17(4)	9(4)
C(11')	3477(5)	2119(2)	1180(9)	54(4)	76(5)	99(6)	-1(4)	0(4)	-9(4)
C(12')	1323(5)	1026(2)	-67(8)	63(4)	63(4)	69(4)	-14(4)	-2(4)	-11(4)
C(13')	2081(6)	830(2)	-1109(8)	126(7)	58(5)	87(5)	-8(5)	32(6)	-27(4)
C(14')	1511(5)	881(2)	1507(7)	63(4)	56(4)	67(4)	-13(3)	10(4)	-2(4)
O(15')	765(3)	1011(2)	2393(5)	65(3)	114(4)	68(3)	3(3)	9(3)	13(3)
C(16')	850(6)	897(3)	3883(8)	82(6)	126(7)	69(5)	6(5)	9(5)	16(5)
O(17')	2206(3)	683(1)	1945(5)	69(3)	78(3)	92(3)	10(3)	5(3)	13(3)
C(18')	41(6)	1547(3)	-2229(9)	87(6)	172(9)	67(5)	-25(6)	-32(5)	-14(6)
C(19')	2337(6)	2775(2)	-866(9)	129(7)	55(5)	95(6)	18(5)	17(6)	18(5)
O(20')	2754(4)	2026(1)	5104(5)	112(4)	80(3)	78(3)	7(3)	-11(3)	-8(3)
C(21')	2857(6)	2663(2)	3857(9)	99(6)	48(4)	121(7)	-4(4)	-46(6)	-8(4)
C(22')	785(6)	2273(2)	3739(7)	106(6)	75(5)	54(4)	27(5)	17(5)	0(4)
C(23')	-217(6)	2145(3)	3056(9)	68(5)	166(9)	82(6)	0(6)	6(5)	-8(6)

Table II. Hydrogen atom positional and thermal parameters. Coordinates have been multiplied by 10^3. Temperature factors were derived by adding 1.0 to the B_{iso} of the bonded atom.

ATOM	X	Y	Z	B_{iso}
H(2)	588	73	579	5.3
H(3)	681	151	616	6.5
H(4A)	768	82	499	6.7
H(4B)	819	122	509	6.7
H(5)	720	148	334	6.3
H(8)	492	38	355	6.1
H(10A)	429	95	203	5.6
H(10B)	456	96	46	5.6
H(11A)	552	143	182	6.7
H(11B)	616	114	98	6.7
H(12)	509	106	770	5.5
H(13A)	418	168	730	6.8
H(13B)	528	173	747	6.8
H(13C)	482	174	600	6.8
H(16A)	288	59	536	7.6
H(16B)	270	20	612	7.6
H(16C)	323	20	470	7.6
H(18A)	785	119	780	7.2
H(18B)	680	122	834	7.2
H(18C)	718	82	774	7.2
H(19A)	861	117	244	7.7
H(19B)	782	111	132	7.7
H(19C)	810	76	228	7.7
H(20)	394	12	200	6.5
H(21A)	535	38	-74	6.6
H(21B)	568	1	7	6.6
H(21C)	628	40	14	6.6
H(22A)	625	-19	249	6.7
H(22B)	519	-30	278	6.7
H(23A)	654	-8	488	8.9
H(23B)	609	-50	484	8.9
H(23B)	548	-14	530	8.9
H(2')	84	161	44	6.2
H(3')	163	158	-237	7.4
H(4'A)	70	224	-97	5.9
H(4'B)	110	228	-248	5.9
H(5')	278	221	-154	6.2
H(8')	162	181	308	6.0
H(10'A)	343	170	280	5.5
H(10'B)	415	204	313	5.5
H(11'A)	391	198	61	6.0
H(11'B)	364	240	111	6.0
H(12')	67	94	-36	6.3
H(13'A)	224	54	-103	8.4
H(13'B)	271	97	-95	8.4
H(13'C)	192	88	-206	8.4

ATOM	X	Y	Z	B_{iso}
H(16'A)	143	100	433	7.7
H(16'B)	88	61	400	7.7
H(16'C)	32	100	443	7.7
H(18'A)	-2	158	-329	7.7
H(18'B)	-42	171	-186	7.7
H(18'C)	-7	128	-206	7.7
H(19'A)	182	287	-17	8.6
H(19'B)	212	289	-172	8.6
H(19'C)	290	286	-57	8.6
H(20')	242	185	520	6.8
H(21'A)	353	270	422	8.0
H(21'B)	245	276	452	8.0
H(21'C)	283	279	301	8.0
H(22'A)	86	256	377	6.4
H(22'B)	80	219	472	6.4
H(23'A)	-28	225	208	9.6
H(23'B)	-76	224	353	9.6
H(23'C)	-27	186	296	9.6

Table III. Bond distances and estimated standard deviations for both the non-primed and primed molecules.

	non-prime	prime
O(1) - C(2)	1.424(7) A	1.424(7) A
O(1) - C(6)	1.414(7)	1.416(7)
C(2) - C(12)	1.551(8)	1.532(9)
C(2) - C(3)	1.525(9)	1.520(10)
C(3) - C(18)	1.544(10)	1.578(11)
C(3) - C(4)	1.521(10)	1.509(10)
C(4) - C(5)	1.491(10)	1.522(10)
C(5) - C(19)	1.541(10)	1.544(10)
C(5) - C(6)	1.524(9)	1.519(9)
C(6) - O(7)	1.426(7)	1.413(7)
C(6) - C(11)	1.510(9)	1.550(9)
O(7) - C(8)	1.428(7)	1.431(7)
C(8) - C(22)	1.497(9)	1.514(10)
C(8) - C(9)	1.525(9)	1.516(9)
C(9) - O(20)	1.441(8)	1.411(8)
C(9) - C(21)	1.514(10)	1.532(9)
C(9) - C(10)	1.482(9)	1.500(9)
C(10)- C(11)	1.526(9)	1.494(10)
C(12)- C(13)	1.506(10)	1.514(10)
C(12)- C(14)	1.509(9)	1.526(10)
C(14)- O(15)	1.307(7)	1.338(8)
C(14)- O(17)	1.235(7)	1.184(8)
O(15)- C(16)	1.432(9)	1.408(9)
C(22)- C(23)	1.510(12)	1.518(11)

Table IV. Bond angles and standard deviations.

	non-prime	prime
C(2) - O(1) - C(6)	115.8(4)°	114.3(4)°
O(1) - C(2) - C(3)	111.2(5)	111.6(5)
O(1) - C(2) - C(12)	106.6(4)	105.8(5)
C(3) - C(2) - C(12)	114.0(5)	114.2(6)
C(2) - C(3) - C(4)	107.7(5)	107.4(6)
C(2) - C(3) - C(18)	112.1(5)	110.4(6)
C(4) - C(3) - C(18)	114.8(6)	111.5(6)
C(3) - C(4) - C(5)	114.4(5)	113.8(6)
C(4) - C(5) - C(6)	110.8(5)	108.5(5)
C(4) - C(5) - C(19)	111.7(6)	113.4(6)
C(6) - C(5) - C(19)	112.4(5)	114.3(5)
O(1) - C(6) - C(5)	110.7(5)	112.8(5)
O(1) - C(6) - O(7)	110.4(5)	110.0(5)
O(1) - C(6) - C(11)	105.3(4)	102.9(5)
C(5) - C(6) - O(7)	105.7(4)	105.9(5)
C(5) - C(6) - C(11)	114.6(5)	115.5(5)
O(7) - C(6) - C(11)	110.3(5)	109.9(5)
C(6) - O(7) - C(8)	116.1(4)	116.6(4)
O(7) - C(8) - C(9)	110.3(5)	110.3(5)
O(7) - C(8) - C(22)	106.4(5)	106.7(5)
C(9) - C(8) - C(22)	115.9(6)	116.0(5)
C(8) - C(9) - C(10)	107.8(5)	108.1(5)
C(8) - C(9) - O(20)	109.1(5)	109.8(5)
C(8) - C(9) - C(21)	112.3(5)	110.7(5)
C(10)- C(9) - O(20)	109.0(5)	109.4(5)
C(10)- C(9) - C(21)	113.1(6)	113.9(6)
O(20)- C(9) - C(21)	105.5(5)	104.8(5)
C(9) - C(10)- C(11)	113.2(5)	112.1(5)
C(6) - C(11)- C(10)	111.2(5)	113.0(6)
C(2) - C(12)- C(13)	114.3(5)	112.6(5)
C(2) - C(12)- C(14)	106.5(5)	110.2(5)
C(13)- C(12)- C(14)	111.2(5)	110.8(5)
C(12)- C(14)- O(15)	112.7(5)	110.7(5)
C(12)- C(14)- O(17)	124.6(5)	127.2(6)
O(15)- C(14)- O(17)	122.7(5)	122.2(6)
C(14)- O(15)- C(16)	117.7(5)	116.3(5)
C(8) - C(22)- C(23)	113.3(6)	113.9(6)

APPENDIX ONE

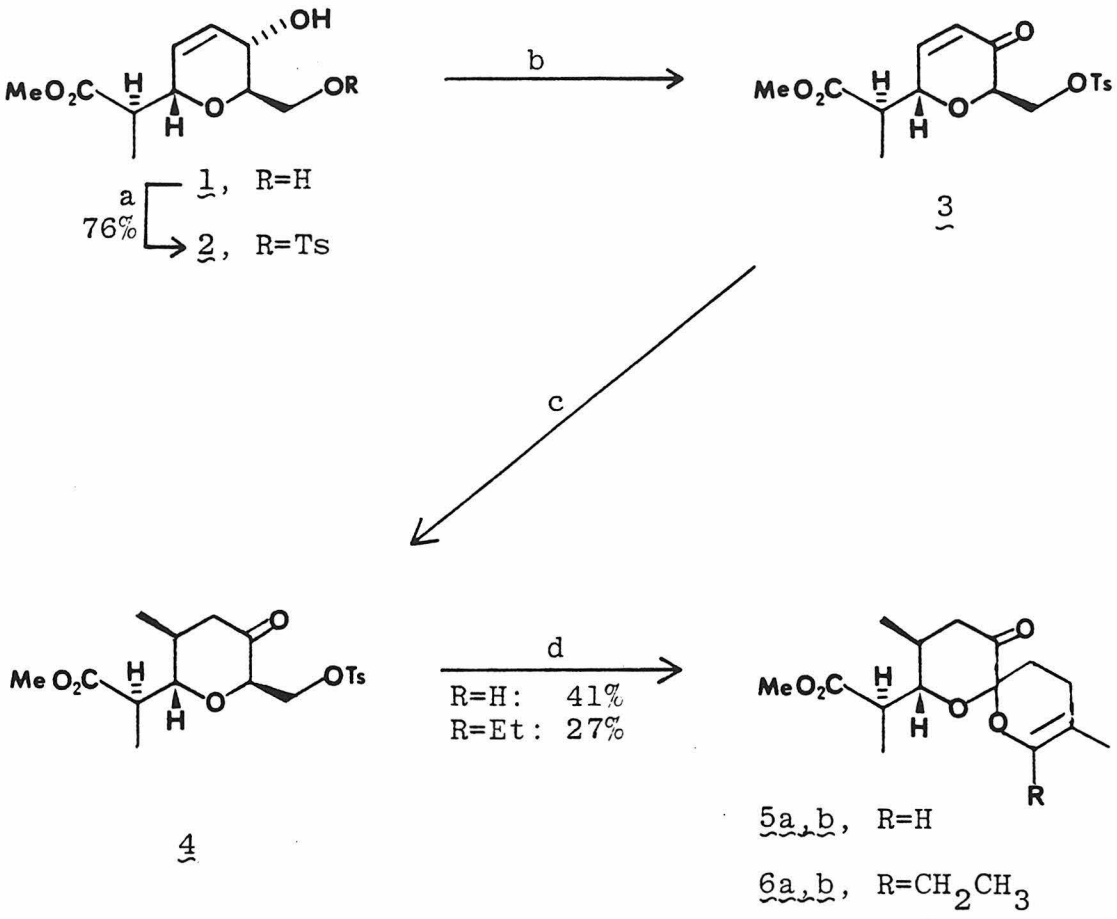
TOSYLATE LEAVING-GROUP FOR HETERO-DIELS-ALDER CONDENSATION

APPENDIX ONE

Tosylate Leaving-Group for Hetero-Diels-Alder Condensation

In Chapter 2, it was mentioned that a tosylate leaving-group was investigated for generating the desired keto-enol ether. Herein are described the results of this preliminary investigation. The primary alcohol group in the diol 1 was selectively tosylated in 76% yield. Oxidation of the allylic alcohol 2 with pyridinium dichromate proceeded quite well; however, the resulting enone 3 was slightly unstable, apparently tending to eliminate to a dienone on chromatography. Lithium dimethylcuprate addition to this enone 3 afforded an extremely labile mixture of the desired keto-tosylates 4 and 3-epi-4 in approximately an 83:17 ratio (by ^{1}H-NMR) along with undesired elimination products. Elimination was effected with triethylamine in the presence of the appropriate hetero-diene. This procedure afforded the Diels-Alder adducts 5a,b in 41% yield over 3 steps and the Diels-Alder adducts 6a,b in 27% yield over 3 steps. Clearly, this route was abandoned because of the low overall yield due to the lability of the intermediates.

Scheme[a]



[a] a, pTsCl, C_5H_5N, 0°C; b, $[C_5H_5N\cdot H]_2Cr_2O_7$(PDC), DMF, 0°C; c, $LiCu(CH_3)_2$, Et_2O, 0°C; d, Et_3N, methacrolein or 2-methyl-1-penten-3-one, 60°C.

EXPERIMENTAL SECTION

Methyl [2S-[2α(S*),5α,6β]]-5,6-dihydro-5-hydroxy-α-methyl-6-[[[(4-methylphenyl)sulfonyl]oxy]methyl]-2H-pyran-2-acetate (2). To a stirred solution of 302 mg (1.40 mmol) of the diol 1 in 2.2 mL of dry pyridine cooled to 0°C (ice bath) under an argon atmosphere was added 320 mg (1.68 mmol) of p-toluenesulfonyl chloride in 4 portions allowing 30 min to elapse between additions. The reaction mixture was allowed to stir at 0°C for 3 h. The mixture was then

diluted with 50 mL of water and extracted with four 15 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure followed by azeotropic removal of pyridine by the addition of 30 mL of n-heptane followed by removal under reduced pressure three successive times. Chromatography of this residue on 60 g of silica gel with 4:1 ether:petroleum ether afforded 391 mg (76%) of the monotosylate 2 as a colorless oil.

Chromatography of a portion (91 mg) of this oil on 12 g of silica gel with 4:1 ether:petroleum ether followed by drying under high vacuum afforded the analytical sample: R_f = 0.20 (silica gel, 4:1 ether:petroleum ether); IR ($CHCl_3$) 3550 (OH), 1730 (C=O), 1610 (phenyl), 1365 (assym $S(=O)_2$), and 1175 cm^{-1} (sym $S(=O)_2$); ^{1}H-NMR ($CDCl_3$) δ 1.20 (d, 3H, J = 7 Hz, α-CH_3), 2.30 (br, 1H, OH), 2.43 (s, 3H, $ArCH_3$), 2.67 (dq, 1H, J = J' = 7 Hz, α-H), 3.64 (m, 1H, C(6)-H), 3.66 (s, 3H, OCH_3), 3.92 (br m, 1H, C(5)-H), 4.18 (d, 2H, J = 4 Hz, CH_2OTs), 4.18 (br m, 1H, C(2)-H), 5.79 (AB q plus allylic couplings, 2H, J_{AB} = 11 Hz, CH=CH), 7.31 (d, 2H, J = 8 Hz, ArH), 7.76 (d, 2H, J = 8 Hz, ArH); $[\alpha]_D^{25}$ = -41.5° ($CHCl_3$, c 1.00).

Anal. Calcd for $C_{17}H_{22}O_7S$: C, 55.12; H, 5.99; S, 8.66. Found: C, 55.11; H, 6.01; S, 8.65.

Methyl [2S-[2α(S*),6β]]-5,6-dihydro-α-methyl-6-[[[(4-methylphenyl)sulfonyl]oxy]methyl]-5-oxo-2H-pyran-2-acetate (3). To a vigorously stirred solution of 383 mg (1.03 mmol) of the allylic alcohol 2 in 2 mL of dry DMF cooled to 0°C (ice bath) under an argon atmosphere was added 1.00 g (2.66 mmol) of pyridinium dichromate (PDC). After 28 h at 0°C, the reaction mixture was diluted with 60 mL of water and extracted with four 15 mL portions of ether. After being dried ($MgSO_4$), the combined extracts were concentrated under reduced pressure. Azeotropic removal of pyridine with n-heptane (2 x 30 mL) afforded 381 mg (100%) of the crude enone 3 as a clear oil. This material was used without further purification.

Flash chromatography of a portion (47 mg) of this oil on silica gel (10 mm diameter column) with 2:1 ether: petroleum ether followed by drying under high vacuum afforded the analytical sample as a colorless oil: R_f = 0.21 (silica gel, 2:1 ether:petroleum ether); IR ($CHCl_3$) 1730 (ester C=O), 1690 (enone C=O), 1600 (phenyl), 1365 (assym $S(=O)_2$), and 1175 (sym $S(=O)_2$); ^{1}H-NMR ($CDCl_3$) δ 1.27 (d, 3H, J = 7 Hz, α-CH_3), 2.42 (s, 3H, $ArCH_3$), 2.81 (dq, 1H, J = J' = 7 Hz, α-H), 3.70 (s, 3H, OCH_3), 4.30 (br m, 3H, CH_2OTs and C(6)-H), 4.72 (ddd, 1H, J = J' = 2 Hz, J'' = 7 Hz, C(2)-H), 6.10 (dd, 1H, J = 11 Hz, J' = 2 Hz, C(4)-H), 7.03 (dd, 1H, J = 11 Hz,

J' = 2 Hz, C(3)-H), 7.33 (d, 2H, J = 9 Hz, ArH), 7.77 (d, 2H, J = 9 Hz, ArH); $[\alpha]_D^{25}$ = -75.1° ($CHCl_3$, c 0.77).

Anal. Calcd for $C_{17}H_{20}O_7S$: C, 55.42; H, 5.47; S, 8.70. Found: C, 55.54; H, 5.40; S, 8.85.

Methyl [2S-[2α(S*),3β,6β]]-tetrahydro-α,3-dimethyl-6-[[[(4-methylphenyl)sulfonyl]oxy]methyl]-5-oxo-2H-pyran-2-acetate (4) and Methyl [2S-[2α(S*),3α,6β]]-tetrahydro-α,3-dimethyl-6-[[[(4-methylphenyl)sulfonyl]oxy]methyl]-5-oxo-2H-pyran-2-acetate (3-epi-4). To a stirred slurry of 408 mg (1.98 mmol) of cuprous bromide-dimethylsulfide complex in 20 mL of dry ether cooled to 0°C (ice bath) under an argon atmosphere was added 1.60 M methyllithium (low halide in ether) until a small amount of yellow precipitate (methylcopper) remained (2.2 ml of CH_3Li solution added). After 30 min, 298 mg (0.809 mmol) of the enone 3 in 4 mL of dry ether was added over 4 min to this stirred solution of lithium dimethylcuprate at 0°C. The reaction was quenched after 10 min by the addition of 50 mL of saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer (blue) was extracted with three 15 mL portions of ether. After the combined organic layers were dried ($MgSO_4$), concentration under reduced pressure afforded 311 mg (100%) of the extremely labile isomeric ketones 4 and 3-epi-4 as a yellow oil. This crude mixture was immediately subjected to subsequent reactions without further purification. Spectral analysis

showed this oil to be an 83:17 mixture of ketone 4 and ketone 3-epi-4: R_f = 0.13 (3β-isomer) and 0.17 (3α-isomer) (silica gel, 1:1 ether:petroleum ether); IR ($CHCl_3$) 1730 (C=O), 1610 (phenyl), 1370 (assym $S(=O)_2$), and 1180 cm^{-1} (sym $S(=O)_2$); ^{1}H-NMR ($CDCl_3$) (3β-isomer 4) δ 0.97 (d, 3H, J = 6 Hz, C(3)-CH_3), 1.19 (d, 3H, J = 7 Hz, α-CH_3), 2.43 (s, 3H, $ArCH_3$), 3.70 (s, 3H, OCH_3), 7.31 (d, 2H, J = 9 Hz, ArH), 7.73 (d, 2H, J = 9 Hz, ArH).

Methyl [2S-[2α(S*),3β,6β]]-α,3,9-trimethyl-5-oxo-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (5a), Methyl [2S-[2α(S*),3β,6α]]-α,3,9-trimethyl-5-oxo-1,7-dioxaspiro[5.5]-undec-8-ene-2-acetate (5b), and Methyl [2S-[2α(S*),3β, 6α and 6β]]-6-formyl-2,3,4,6,7,8-hexahydro-α,3,6-trimethyl-pyrano[3,2-b]pyran-2-acetate. To a stirred solution of 69.9 mg (0.182 mmol) of the crude tosylates 4 and 3-epi-4 in 4 mL (48 mmol) of methacrolein (distilled from hydroquinone, stabilized with 1% hydroquinone) heated to 60°C under an argon atmosphere was added 73 mg (100 μL, 0.72 mmol) of dry triethylamine. After 2.8 h at 60°C, concentration of the reaction mixture under reduced pressure followed by chromatography of the residue on 16 g of silica gel with 1:4 ether:petroleum ether afforded 21 mg (41% over three steps) of the Diels-Alder adducts as a mixture of isomers. See Chapter 2 for chromatographic separation and characterization of the Diels-Alder adducts.

Methyl [2S-[2α(S*),3β,6β]]-8-ethyl-α,3,9-trimethyl-5-oxo-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (6a), Methyl [2S-[2α(S*),3β,6α]]-8-ethyl-α,3,9-trimethyl-5-oxo-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (6b), and Methyl [2S-[2α(S*),3β,6α and 6β]]-2,3,4,6,7,8-hexahydro-α,3,6,-trimethyl-6-(1-oxopropyl)-pyrano[3,2-b]pyran-2-acetate. To a stirred solution of 311 mg (0.809 mmol) of the crude tosylates 4 and 3-epi-4 in 10 mL (86 mmol) of 2-methylpent-1-en-3-one (distilled from hydroquinone at 70 mmHg, stabilized with 1% hydroquinone) heated to 60°C under an argon atmosphere was added 255 mg (0.35 mL, 2.52 mmol) of dry triethylamine. After 4 h at 60°C, concentration of the reaction mixture under reduced pressure followed by chromatography of the residue on 28 g of silica gel with 1:6 ether:petroleum ether afforded 68 mg (27% over 3 steps) of the Diels-Alder adducts as a mixture of isomers. See Chapter 2 for chromatographic separation and characterization of the Diels-Alder adducts.

APPENDIX TWO

ATTEMPTED CYCLIC CARBONATE TRAPPING IN THIOKETAL EXCHANGE FOR SPIROKETALS WITH A C(9) ALCOHOL GROUP

APPENDIX TWO

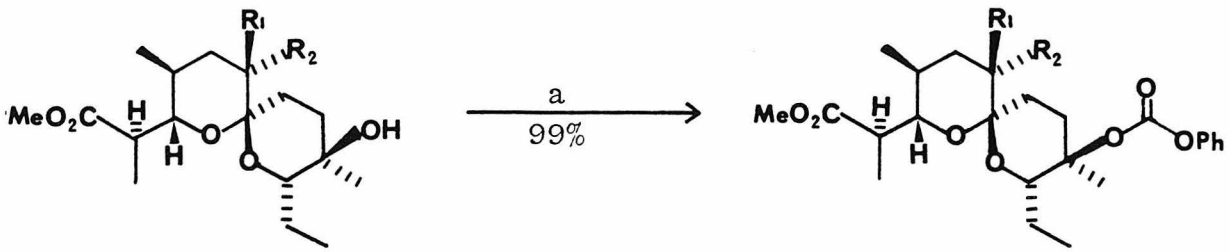
Attempted Cyclic Carbonate Trapping in Thioketal Exchange for Spiroketals with a C(9) Alcohol Group

In Chapter 3, it was found that the spiroketal 5a (see Scheme II) could be opened by thioketal exchange; however, only a very low conversion was realized accompanied by substantial epimerization. As a potential solution to this low conversion caused by this proximal C(9) alcohol group, it was planned to take advantage of the proximal disposition of this alcohol to trap the open-chain derivative as a cyclic carbonate, thereby driving the reaction to completion.

Initially, the more labile spiroketals 1a,b were investigated (Scheme I). These spiroketals were converted into the phenyl carbonates 2a,b which were then treated with 1,2-ethanedithiol and borontrifluoride etherate at -20°C. This operation delightfully afforded the desired cyclic carbonate thioketals 3a,b; however, only a 40% yield was realized. Additionally, a 17% yield of the bis-thioketals 4a,b was obtained through either a competing or subsequent pinacol-type rearrangement to the corresponding ketone.

Based on these encouraging results, attention was turned to the spiroketal for methymycin synthesis (Scheme II). These preliminary studies used a mixture of the actual

Scheme I[a]



1a, R_1=CH_3, R_2=H

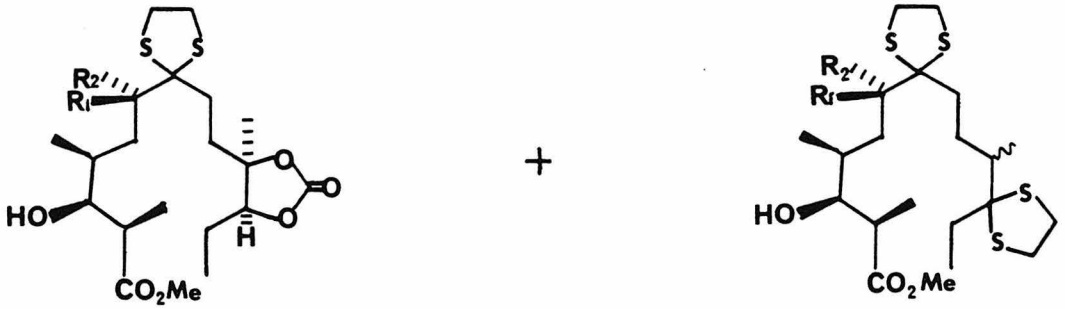
1b, R_1=H, R_2=CH_3

2a, R_1=CH_3, R_2=H

2b, R_1=H, R_2=CH_3

b

40% + 17%



3a, R_1=CH_3, R_2=H

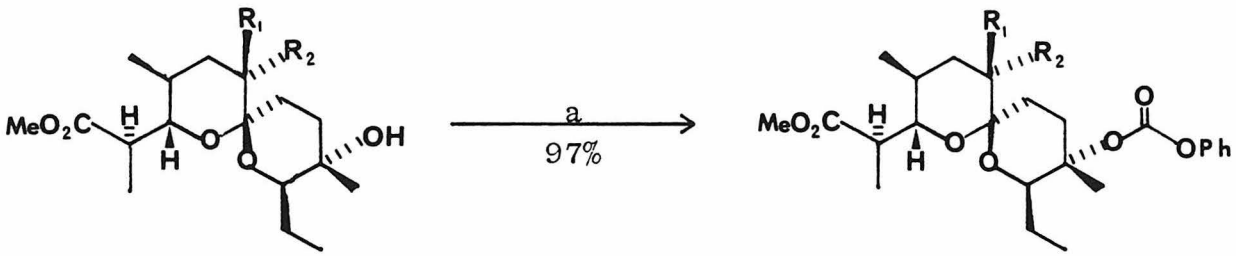
3b, R_1=H, R_2=CH_3

4a, R_1=CH_3, R_2=H

4b, R_1=H, R_2=CH_3

[a] a, C_6H_5OCOCl, C_5H_5N, CH_2Cl_2; b, $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$, -20 °C.

Scheme II[a]

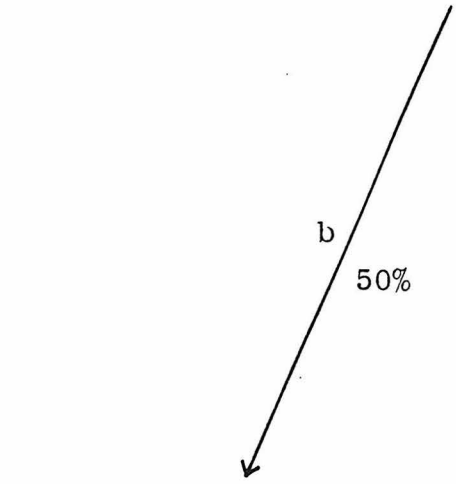


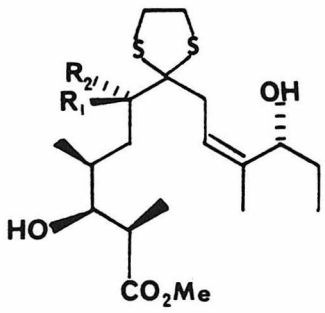
5a, $R_1=CH_3$, $R_2=H$

5b, $R_1=H$, $R_2=CH_3$

6a, $R_1=CH_3$, $R_2=H$

6b, $R_1=H$, $R_2=CH_3$





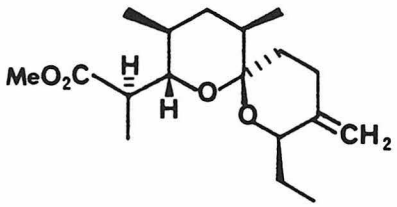
7a, $R_1=CH_3$, $R_2=H$

7b, $R_1=H$, $R_2=CH_3$

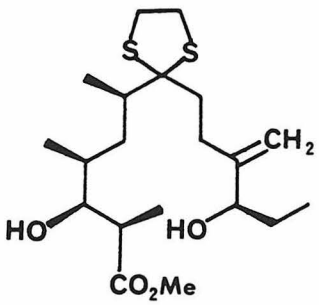
[a] a, C_6H_5OCOCl, C_5H_5N, CH_2Cl_2; b, $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$, 0°C.

methymycin spiroketal intermediate 5a and its C(5) epimer which were converted into the phenyl carbonates 6a,b. Treatment of these phenyl carbonates 6a,b with 1,2-ethanedithiol and borontrifluoride etherate at 0°C afforded the undesired thioketals 7a,b in 50% yield. The 500 MHz ^{1}H-NMR of these thioketals 7a,b was consistent with a single geometry about the double bond which is assigned the cis stereochemistry based on the presumption that the elimination of the phenyl carbonate occurs before thioketal exchange since products comparable to the cyclic carbonates 3a,b and bis-thioketals 4a,b were not observed. Therefore, investigation of this cyclic carbonate route was curtailed.

Another solution to the low conversion problem is to incorporate the guilty C(9) alcohol after thioketal exchange. Therefore, the immediate precursor, spiroketal 8,



8



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should provide, in concert with the thioketal exchange of its hydrogenation product (see Chapter 3), the diol-thioketal 9 in high yield and good conversion without epimerization. Subsequent stereoselective incorporation of the tertiary hydroxyl group would intersect with the desired open-chain triol-thioketal derivative for methymycin. This solution is still to be investigated.

A third solution to this problem would be through the C(8) epimer of spiroketal 5a which possesses a destabilizing 1,3-diaxial interaction between the ethyl group and the pyran oxygen. Therefore, thioketal exchange with this spiroketal 8-epi-5a should proceed with high conversion analogous to the thioketal exchange with spiroketals 1a,b which afforded, after acetonide formation, the desired open-chain thioketals in 80% yield (see Chapter 2). Then, at a later stage, the epimeric stereocenter would be inverted to the natural stereochemistry by the method of Mitsunobu.

APPENDIX TWO

EXPERIMENTAL SECTION

Methyl [2S-[2α(S*),3β,5β,6β(8R*,9S*)]]-8-ethyl-α,3,5,9-tetramethyl-9-[(phenoxycarbonyl)oxy]-1,7-dioxaspiro[5.5]-undecane-2-acetate (2a) and Methyl [2S-[2α(S*),3β,5α,6β-(8R*,9S*)]]-8-ethyl-α,3,5,9-tetramethyl-9-[(phenoxycarbonyl)oxy]-1,7-dioxaspiro[5.5]undecane-2-acetate (2b). To a stirred solution of 14.0 mg (0.0426 mmol) of the spiroketals 1a and 1b in 0.3 mL of dry dichloromethane under an argon atmosphere was added first 15 μL (15 mg, 0.19 mmol) of dry pyridine and then 11 μL (14 mg, 0.087 mmol) of phenyl chloroformate. After 6 h at RT, the reaction mixture was diluted with 1 mL of saturated aqueous $NaHCO_3$ and extracted with four 1 mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure followed by azeotropic removal of pyridine with n-heptane (2 x 3 mL) under reduced pressure. Chromatography of the residue on 1 g of silica gel with 1:8 ether:petroleum ether afforded 18.9 mg (99%) of a 55:45 (by ^{1}H-NMR) mixture of carbonates 2a and 2b as a colorless oil. Distillation [kugelrohr, 150°C (0.001 mmHg)] of a portion of this oil provided the analytical sample: R_f = 0.13 (silica gel, 1:8 ether:petroleum ether); IR($CHCl_3$) 1745 (C=O) and 1600 cm^{-1} (phenyl); ^{1}H-

NMR ($CDCl_3$) δ 0.77-1.13 (br m, 12H, four overlapping CH_3's), 1.41 and 1.46 (2s, 3H, C(9)-CH_3 for 5α- and 5β-isomers), 1.27-2.37 (br m, 10H), 2.63 (dq, 1H, J = 3Hz, J' = 7Hz, α-H), 3.60 and 3.63 (2s, 3H, OCH_3 for 5α- and 5β-isomers), 3.52-4.14 (br m, 2H, C(2)-H and C(8)-H), 7.07-7.42 (br m, 5H, ArH).

Anal. Calcd for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.00; H, 7.92.

Methyl [2R-(2R*,3S*,4S*,6R* and 6S*,10R*,11S*)]-3,10,11-trihydroxy-2,4,6,10-tetramethyl-7-oxo-tridecanoate, cyclic carbonate and 1,2-ethanediyl dithioketal derivative (3 a,b) and Methyl [2R-(2R*,3S*,4S*,6R* and 6S*,10R* and 10S*)]-3-hydroxy-2,4,6,10-tetramethyl-7,11-dioxo-tridecanoate, bis[1,2-ethanediyl dithioketal] derivative (4 a,b). To a vigorously stirred solution of 9.0 mg (0.020 mmol) of the mixture of the phenyl carbonates 2a and 2b, described above, in 0.30 mL (340 mg, 3.6 mmol) of 1,2-ethanedithiol cooled to -20°C (dry ice/carbon tetrachloride slush) under an argon atmosphere was added dropwise 90 μL (102 mg, 0.72 mmol) of borontrifluoride etherate. After 1.5 h at -20°C with vigorous stirring the reaction was quenched by the cautious addition of 0.25 mL of saturated aqueous $NaHCO_3$ while the reaction mixture was allowed to slowly warm to RT. This mixture was then diluted with 8 mL of saturated aqueous $NaHCO_3$ and extracted with three 8 mL portions of ether. After being dried ($MgSO_4$), the combined

extracts were concentrated under reduced pressure followed by removal of the 1,2-ethanedithiol under high vacuum (0.5 mmHg). Chromatography of the residue immediately on 1 g of silica gel with 2:1 ether:petroleum ether afforded first 2.8 mg (29%) of the bis-thioketals 4 a,b contaminated with some minor byproducts. Rechromatography of this material on 7 g of silica gel with 1:2 ether: petroleum ether afforded 1.7 mg of clean bis-thioketals 4 a,b as a colorless oil: R_f = 0.18 (silica gel, 1:2 ether:petroleum ether); IR ($CHCl_3$) 3500 (OH) and 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.86-1.20 (br m, 15H, five overlapping CH_3's), 1.42-2.24 (br m, 11H), 2.57-2.80 (br m, 2H, C(2)-H and OH), 3.22 (s, 8H, thioketals), 3.68 (s, 3H, OCH_3), 3.74 (br m, 1H, C(3)-H).

Anal. Calcd for $C_{22}H_{40}O_3S_4$: M^+ 480.1860. Found: M^+ 480.1761.

There was then eluted 3.6 mg (40%) of the stereoisomeric carbonate-thioketals 3a and 3b as a 42:58 (by ^{1}H-NMR) mixture, respectively. Distillation [kugelrohr, 220°C (0.003 mmHg)] of this material provided the analytical sample: R_f = 0.24 (6R* isomer) and 0.15 (6S* isomer) (silica gel, 2:1 ether:petroleum ether); IR ($CHCl_3$) 3540 (OH), 1790 (carbonate C=O), and 1725 cm^{-1} (ester C=O); ^{1}H-NMR ($CDCl_3$) δ 0.84-1.23 (br m, 12H, four overlapping CH_3's), 1.45 (s, 3H, C(10)-CH_3), 1.50-2.42 (br m, 11H), 2.65

(br m, 1H, C(2)-H), 3.20 (s, 4H, thioketal), 3.61 (s, 3H, OCH_3), 4.16 (dd, 1H, J = 5 Hz, J' = 9 Hz, C(11)-H).

Anal. Calcd for $C_{21}H_{36}O_6S_2$: C, 56.22; H, 8.09, S, 14.29. Found: C, 56.27; H, 7.97; S, 14.35.

Methyl [2S-[2α(S*),3β,5β,6β(8S*,9R*)]]-8-ethyl-α,3,5,9-tetramethyl-9-[(phenoxycarbonyl)oxy]-1,7-dioxaspiro[5.5]undecane-2-acetate (6a) and Methyl [2S-[2α(S*),3β,5α,6β(8S*,9R*)]]-8-ethyl-α,3,5,9-tetramethyl-9-[(phenoxycarbonyl)oxy]-1,7-dioxaspiro[5.5]undecane-2-acetate (6b). To a stirred solution of 15.0 mg (0.0457 mmol) of a mixture of spiroketals 5a and 5b in 0.5 mL of dry dichloromethane under an argon atmosphere was added first 30 μL (30 mg, 0.37 mmol) of dry pyridine and then 23 μL (29 mg, 0.18 mmol) of phenyl chloroformate. After 2 days at RT, the reaction mixture was diluted with 1 mL of saturated aqueous $NaHCO_3$ and extracted with three 1 mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure followed by azeotropic removal of pyridine with n-heptane (2 x 5 mL) under reduced pressure. Chromatography of the residue on 1 g of silica gel with 1:10 ether:petroleum ether afforded 19.8 mg (97%) of a mixture of the carbonates 6a and 6b as a white solid. Distillation [kugelrohr, 150°C (0.001 mmHg)] of a portion of this solid provided the analytical sample: R_f = 0.14 (silica gel, 1:10 ether:petroleum ether);

IR ($CHCl_3$) 1750 (carbonate C=O), 1735 (ester C=O), and 1600 cm^{-1} (phenyl); ^{1}H-NMR ($CDCl_3$) δ 0.80-1.19 (br m, 12H, four overlapping CH_3 groups), 1.48 (s, 3H, C(9)-CH_3), 1.33-2.47 (br m, 10H), 2.70 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.42 and 3.44 (2dd, 1H, J = 2 Hz, J' = 9 Hz, C(8)-H), 3.68 (s, 3H, OCH_3), 3.79 (br m, 1H, C(2)-H), 7.06-7.44 (br m, 5H, ArH).

Anal. Calcd for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.04; H, 7.94.

Methyl [2R-(2R*,3S*,4S*,6R*,9Z,11R*)]-3,11-dihydroxy-2,4,6,10-tetramethyl-7-oxo-9-tridecenoate,1,2-ethanediyl dithioketal derivative (7a) and Methyl [2R-(2R*,3S*,4S*,6S*,9Z,11R*)]-3,11-dihydroxy-2,4,6,10-tetramethyl-7-oxo-9-tridecenoate,1,2-ethanediyl dithioketal derivative (7b). To a vigorously stirred solution of 8.5 mg (0.019 mmol) of the phenyl carbonates 6a and 6b in 0.30 mL (340 mg, 3.6 mmol) of 1,2-ethanedithiol cooled to -20°C (dry ice/carbon tetrachloride slush) under an argon atmosphere was added dropwise 90 μL (102 mg, 0.72 mmol) of borontrifluoride etherate. After 0.5 h at -20°C, the reaction mixture was warmed to 0°C (ice bath) for 4.2 h. The reaction mixture was then quenched by the slow cautious addition of 0.7 mL of saturated aqueous $NaHCO_3$. The resulting mixture was diluted with 10 mL of saturated aqueous $NaHCO_3$ and extracted with three 5 mL portions of

ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure followed by removal of 1,2-ethanediol under high vacuum (0.5 mmHg). Chromatography of the residue immediately on 1 g of silica gel with 1:4 ether:petroleum ether afforded 3.8 mg (50%) of a 64:36 (by ^{1}H-NMR) mixture of the thioketals 7a and 7b, respectively, as a colorless oil: R_f = 0.11 (6R* isomer) and 0.09 (6S* isomer) (silica gel, 1:4 ether:petroleum ether); IR ($CHCl_3$) 3520 (OH) and 1725 cm^{-1} (C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) (6R* isomer) δ 0.90 (d, 3H, J = 7 Hz, C(4)-CH_3), 0.93 (t, 3H, J = 7 Hz, C(13)-H_3), 1.12 (d, 3H, J = 7 Hz, C(6)-CH_3), 1.17 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.61 (br s, 3H, C(10)-CH_3), 1.49-1.74 (br m, 2H, C(5)-Hz), 1.87-2.28 (br m, 7H), 2.64 (d, 1H, J = 4 Hz, OH), 2.68 (dq, 1H, J = 3.5 Hz, J' = 7 Hz, C(2)-H), 3.23 (br m, 4H, thioketal), 3.65 (br m, 1H, C(3)-H), 3.70 (s, 3H, OCH_3), 3.76 (ddd, 1H, J = J' = 4 Hz, J'' = 8 Hz, C(10)-H), 5.16 (t, 1H, J = 7 Hz, C(9)-H); 500 MHz ^{1}H-NMR ($CDCl_3$) (6S* isomer) δ 0.87 (d, 3H, J = 6 Hz, C(4)-CH_3), 0.93 (t, 3H, J = 7 Hz, C(13)-H_3), 1.09 (d, 3H, J = 6.5 Hz, C(6)-CH_3), 1.19 (d, 3H, J = 7 Hz, C(2)-CH_3), 1.56 (br s, 3H, C(10)-CH_3), 1.49-1.74 (br m, 2H, C(5)-H_2), 1.87-2.28 (br m, 7H), 2.46 (d, 1H, J = 4 Hz, OH), 2.71 (dq, 1H, J = 3.5 Hz, J' = 7 Hz, C(2)-H), 3.23 (br m, 4H, thioketal), 3.65 (br m, 1H, C(3)-H), 3.70 (s, 3H, OCH_3),

3.76 (ddd, 1H, J = J' = 4 Hz, J'' = 8 Hz, C(10)-H), 5.16 (t, 1H, J = 7 Hz, C(9)-H).

Anal. Calcd for $C_{20}H_{36}O_4S_2$: $M^+-CH_3O_2$ 357.1922. Found: $M^+-CH_3O_2$ 357.1934.

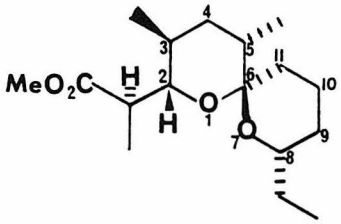
APPENDIX THREE

INTERNAL OXIDATION-REDUCTION CHEMISTRY OF SPIROKETALS

APPENDIX THREE

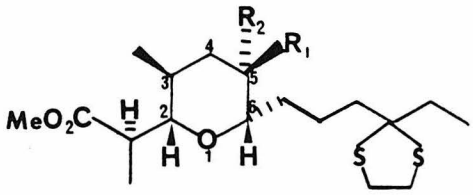
Internal Oxidation-Reduction Chemistry of Spiroketals

In the course of early studies on the conversion of spiroketals into open-chain derivatives through thioketal exchange, it was found that thioketal exchange at room temperature with the spiroketals 1 and 3 afforded in high yields the pyran-thioketals 2a,b and 4a,b, respectively,



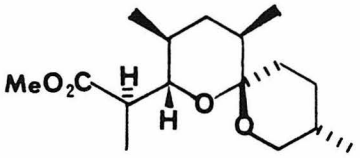
1

$HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$, 95%



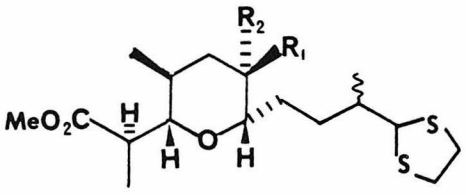
2a, $R_1=CH_3$, $R_2=H$

2b, $R_1=H$, $R_2=CH_3$



3

$HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$, 90%



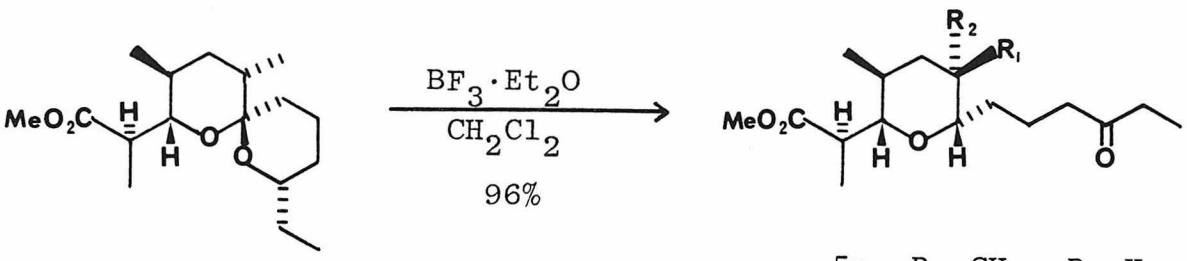
4a, $R_1=CH_3$, $R_2=H$

4b, $R_1=H$, $R_2=CH_3$

via an internal hydride transfer. These products are exactly analogous to those obtained by C. Djerassi[1] in his work with the sapogenins. This internal oxidation-reduction chemistry was first proposed by R. B. Woodward[2] as a mechanism for the acid catalyzed epimerization of a methyl group in the sapogenins which corresponds in position to the C(9) methyl group in spiroketal 3. Professor Woodward hypothesized that the spiroketal portion of the sapogenins was in equilibrium with a pyran-aldehyde, thereby allowing for epimerization of the methyl group. This hypothesis was supported through independent synthesis of the proposed pyran-aldehyde intermediate and its subsequent conversion upon acid treatment into the sapogenin system.[2] The stereochemistry at C(6) in the thioketals 2a,b corresponds to axial entry of the hydride through stereoelectronic control and was confirmed by the 9.5 Hz coupling between the hydrogens at C(5) and C(6) in the thioketal 2a and by the 4 Hz coupling between these hydrogens in the thioketal 2b.

In the course of studies toward the macrolide antibiotics, a method for epimerization of a C(8) ethyl group in spiroketal intermediates was needed, so it was envisioned that this ethyl group in the model spiroketal 1 could be epimerized through the pyran-ketones 5a,b in which this stereochemistry is destroyed. However, treatment of the spiroketal 1 with borontrifluoride etherate in dichloro-

methane afforded in 96% yield the pyran-ketones 5a,b.



1

5a, $R_1=CH_3$, $R_2=H$

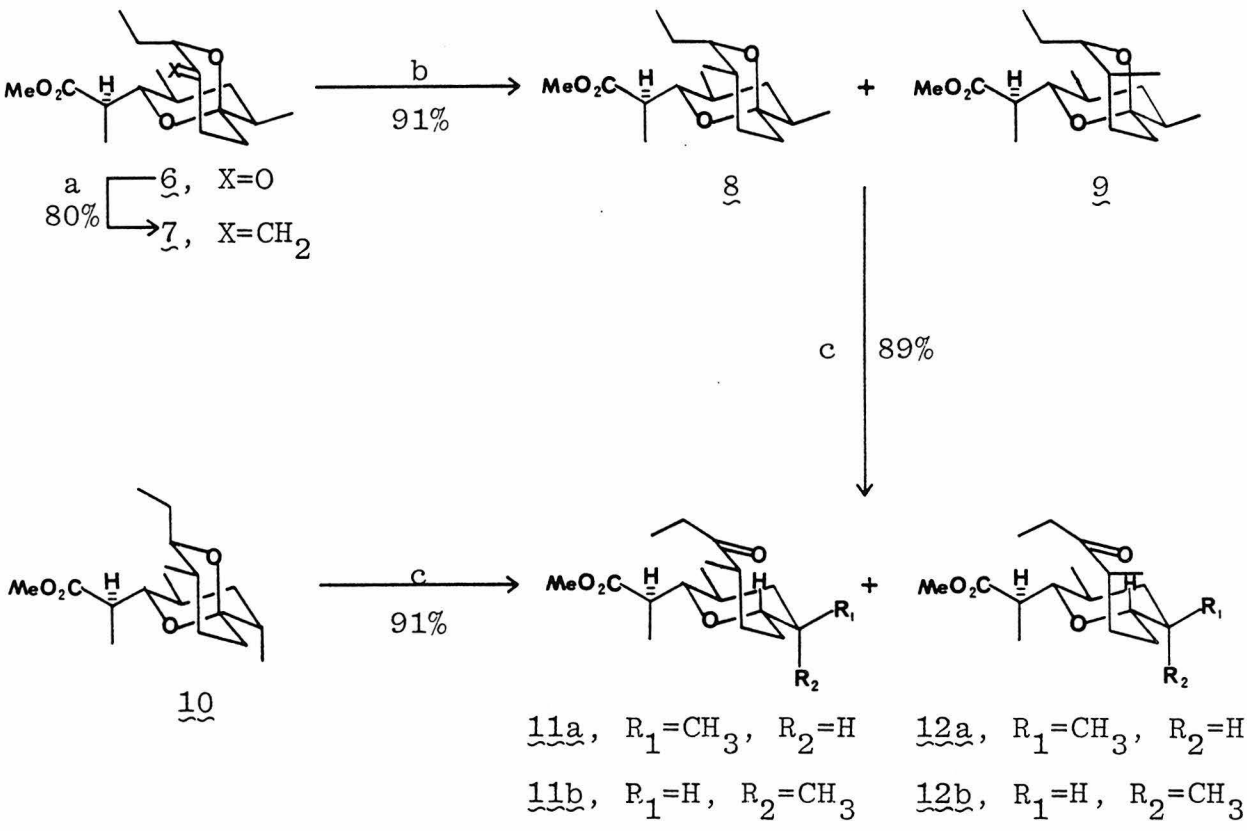
5b, $R_1=H$, $R_2=CH_3$

Therefore, while the equilibrium between the analogous pyran-aldehydes and spiroketals lies on the side of the spiroketals,[2] the equilibrium between pyran-ketones and spiroketals lies on the side of the pyran-ketones. Again, the stereochemistry corresponds to axial entry of the hydride as confirmed by the 9.5 Hz coupling between the hydrogens at C(5) and C(6) in the pyran-ketone 5a and the 3.5 Hz coupling between these hydrogens in the pyran-ketone 5b. Similarly, while this work was in progress, P. Deslongchamps[3] reported that spiroketals are converted into pyran-ketones with axial entry of the hydride through stereoelectronic control.

Due to this observation, it was realized that the hydrogenolysis products 11a,b (see Scheme) reported in Chapter 2 may actually arise through cis hydrogenation of

the spiroketal enol ethers (see Chapter 2, enol ethers 29a,b) to the spiroketal 8 and its C(5) epimer which, under acid catalysis, would afford the hydrogenolysis products 11a,b through this internal oxidation-reduction reaction. As support for this possibility, the ketone 6 and its C(5) epimer were converted into the olefin 7 and its C(5) epimer which were then separated by chromatography. Hydrogenation

Scheme[a]



[a] a, $(C_6H_5)_3PCH_2$, THF; b, PtO_2, H_2, pentane; c, $BF_3 \cdot Et_2O$, CH_2Cl_2.

of the olefin 7 afforded an inseparable 77:23 (by 500 MHz ^{1}H-NMR) mixture of the spiroketals 8 and 9, respectively. Treatment of this mixture with borontrifluoride etherate in dichloromethane for 30 min at RT afforded in 89% yield an inseparable 80:20 mixture of the pyran-ketones 11a,b and 12a,b, respectively. The major pyran-ketones 11a,b were identical (500 MHz ^{1}H-NMR and TLC) with those obtained in Chapter 2 in accord with this mechanistic possibility. In this very rapid oxidation-reduction reaction, the stereochemistry at C(9) is preserved on the ketone side chain. This retention of the C(9) stereochemistry of the spiroketal in the product pyran-ketone, along with the stereoelectronic control of the product's C(6) stereochemistry, is potentially a useful method for the synthesis of complex pyran derivatives from spiroketal derivatives.

Treatment of the much more stable spiroketal 10 with borontrifluoride etherate in dichloromethane afforded these same four pyran-ketones 11a,b and 12a,b, although at a vastly reduced rate where only a 70% conversion was observed after 4 days. The ratio between the ketones 11a,b and 12a,b is 55:45 (by 500 MHz ^{1}H-NMR) due to extensive epimerization of the ketone stereocenter in this very slow reaction. The ratios of 11a:11b and 12a:12b were both 92:8 which is approximately the expected equilibrium ratio at C(5).

APPENDIX THREE

EXPERIMENTAL SECTION

Methyl [2S-[2α(S*),3β,5β,6α]]-6-[3-(2-ethyl-1,3-dithiolan-2-yl)propyl]-tetrahydro-α,3,5-trimethyl-2H-pyran-2-acetate (2a) and Methyl [2S-[2α(S*),3β,5α,6α]]-6-[3-(2-ethyl-1,3-dithiolan-2-yl)propyl]-tetrahydro-α,3,5-trimethyl-2-H-pyran-2-acetate (2b). To a stirred solution of 16.0 mg (0.0536 mmol) of the spiroketal 1 in 0.45 mL (500 mg, 5.4 mmol) of 1,2-ethanedithiol under an argon atmosphere was added dropwise 56 μL (63 mg, 0.44 mmol) of borontrifluoride etherate. After 40 min at RT, the reaction mixture was diluted with 6 mL of saturated aqueous $NaHCO_3$ and extracted with three 6 mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure followed by removal of 1,2-ethanedithiol under high vacuum (0.5 mm Hg). Chromatography of the residue on 7 g of silica gel with 1:13 ether:petroleum ether afforded 19 mg (95%) of a 75:25 (by 500 MHz ^{1}H-NMR) mixture of the thioketals 2a and 2b as a colorless oil. Distillation [kugelrohr, 135°C (0.003 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.14 (silica gel, 1:13 ether:petroleum ether); IR($CHCl_3$) 1730 cm^{-1} (C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) (5β-isomer) δ 0.78 and 0.80 (2d, 6H, J = 6 Hz, C(3)-CH_3 and C(5)-CH_3), 1.04 (t, 3H, J = 7 Hz, $CH_2\underline{C}H_3$), 1.12 (d, 3H, J = 7 Hz,

α-CH_3), 1.25-1.74 (br m, 8 H), 1.82-1.95 (br m, 4H, α-to-thioketal), 2.66 (dq, 1H, J = 3.5 Hz, J' = 7 Hz, α-H), 2.82 (ddd, 1H, J = 2.5 Hz, J' = J'' = 9.5 Hz, C(6)-H), 3.25 (br m, 4H, thioketal), 3.38 (dd, 1H, J = 3.5 Hz, J' = 10 Hz, C(2)-H), 3.69 (s, 3H, OCH_3); 500 MHz ^{1}H-NMR ($CDCl_3$) (5α-isomer) δ 0.77 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.89 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.03 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.14 (d, 3H, J = 7 Hz, α-CH_3), 1.25-1.74 (br m, 8H), 1.82-1.95 (br m, 4H, α-to-thioketal), 2.67 (dq, 1H, J = 3.5 Hz, J' = 7 Hz, α-H), 3.25 (br m, 4H, thioketal), 3.29 (ddd, 1H, J = 2.5 Hz, J' = 4 Hz, J'' = 9 Hz, C(6)-H), 3.40 (dd, 1H, J = 3.5 Hz, J' = 10 Hz, C(2)-H), 3.70 (s, 3H, OCH_3).

Anal. Calcd for $C_{19}H_{34}O_3S_2$: C, 60.92; H, 9.15; S, 17.12. Found: C, 60.72; H, 9.08; S, 17.19.

Methyl [2S-[2α(S*), 3β,5β and 5α,6α(R* and S*)]]-6-[3-(1,3-dithiolan-2-yl)butyl]-tetrahydro-α,3,5-trimethyl-2H-pyran-2-acetate (4a and 4b). The procedure for the preparation of the thioketals 2a and 2b with 9.8 mg (0.0345 mmol) of the spiroketal 3 in 0.28 mL (320 mg, 3.4 mmol) of 1,2-ethanedithiol and 35 μL (39 mg, 0.28 mmol) of boron-trifluoride etherate afforded, after 10 h at RT, workup as described, and chromatography on 7 g of silica gel with 1:2 ether:petroleum ether, first the thioacetals 4a and 4b. Rechromatography of this material on 7 g of silica gel with

1:13 ether:petroleum ether afforded 6.3 mg (51%) of pure thioacetals 4a and 4b as a colorless oil.

There was then eluted 5.3 mg (44%) of the corresponding carboxylic acids. Treatment of this material at 0°C with excess alcohol-free etherial diazomethane (from Aldrich Diazald), removal of solvents under reduced pressure, and chromatography of the residue on 1 g of silica gel with 1:13 ether:petroleum ether afforded an additional 4.9 mg (40%) of the thioacetals 4a and 4b as a colorless oil. Therefore, a combined total yield of 11.2 mg (90%) was obtained.

Distillation [kugelrohr, 135°C (0.005 mm Hg)] provided the analytical sample: R_f = 0.11 (silica gel, 1:13 ether: petroleum ether); IR($CHCl_3$) 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.78 (d, 6H, J = 6 Hz, C(3)-CH_3 and C(5)-CH_3), 1.01 (d, 3H, J = 6 Hz, CH_3 α-to-thioketal), 1.11 (d, 3H, J = 7 Hz, α-CH_3), 1.24-1.80 (br m, 9H), 2.63 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 2.79 (m, 1H, C(6)-H of 5β-isomer), 3.14 (s, 4H, thioketal), 3.34 (dd, 1H, J = 3 Hz, J' = 9 Hz, C(2)-H), 3.67 (s, 3H, OCH_3), 4.47 (d, 1H, J = 6 Hz. $(-S)_2CH-$).

Anal. Calcd for $C_{18}H_{32}O_3S_2$: C, 59.96; H, 8.95; S, 17.78. Found: C, 60.07; H, 9.04; S, 17.76.

Methyl [2S-[2α(S*),3β,5β,6α]]-tetrahydro-α,3,5-trimethyl-6-(4-oxohexyl)-2H-pyran-2-acetate (5a) and Methyl [2S-[2α(S*),3β,5α,6α]]-tetrahydro-α,3,5-trimethyl-6-(4-oxohexyl)-2H-pyran-2-acetate (5b). To a stirred solution of 8.4 mg (0.028 mmol) of the spiroketal 1 in 0.30 mL of dry dichloromethane under an argon atmosphere was added 10 μL (11 mg, 0.079 mmol) of borontrifluoride etherate. After 30 min at RT, the reaction mixture was diluted with 1 mL of saturated aqueous $NaHCO_3$ and extracted with three 1 mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on 1 g of silica gel with 1:6 ether:petroleum ether afforded 8.1 mg (96%) of a 79:21 (by 500 MHz ^{1}H-NMR) mixture of the ketones 5a and 5b, respectively, as a colorless oil. Distillation [kugelrohr, 90°C (0.003 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.11 (silica gel, 1:6 ether:petroleum ether); IR ($CHCl_3$) 1730 (ester C=0) and 1710 cm^{-1} (ketone C=0); 500 MHz ^{1}H-NMR ($CDCl_3$) (5β-isomer) δ 0.77 and 0.80 (2d, 6H, J = 7 Hz, C(3)-CH_3 and C(5)-CH_3), 1.04 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$), 1.11 (d, 3H, J = 7 Hz, α-CH_3), 1.23-1.74 (br m, 8H), 2.37 and 2.41 (t and q, 4H, J = 7 Hz, α-to-ketone), 2.67 (dq, 1H, J = 3.5 Hz, J' = 7 Hz, α-H), 2.82 (ddd, 1H, J = 2.5 Hz, J' = J'' = 9.5 Hz; C(6)-H), 3.39 (dd, 1H, J = 3.5 Hz,

J' = 10 Hz, C(2)-H), 3.66 (s, 3H, OCH_3); 500 MHz ^{1}H-NMR ($CDCl_3$) (5α-isomer) δ 0.78 (d, 3H, J = 7 Hz, C(3)-CH_3), 0.88 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.04 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.13 (d, 3H, J = 7 Hz, α-CH_3), 1.23-1.74 (br m, 8H), 2.37 and 2.41 (t and q, 4H, J = 7 Hz, α-to-ketone), 2.67 (dq, 1H, J = 3.5 Hz, J' = 7 Hz, α-H), 3.29 (ddd, 1H, J = 2.5 Hz, J' = 3.5 Hz, J'' = 9 Hz, C(6)-H), 3.40 (dd, 1H, J = 3.5 Hz, J' = 10 Hz, C(2)-H), 3.67 (s, 3H, OCH_3).

Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.45; H, 10.14.

Methyl [2S-[2α(S*),3β,5β,6β(R*)]]-8-ethyl-α,3,5-trimethyl-9-methylene-1,7-dioxaspiro[5.5]undecane-2-acetate (7) and Methyl [2S-[2α(S*),3β,5α,6β(R*)]]-8-ethyl-α,3,5-trimethyl-9-methylene-1,7-dioxaspiro[5.5]-undecane-2-acetate (5-epi-7). To a stirred solution of 0.115 mmol of methylenetriphenylphosphorane [prepared by addition of 51 μL (0.115 mmol) of 2.28 M n-butyllithium in hexane to a stirred slurry of 41.2 mg (0.115 mmol) of (methyl)triphenylphosphonium bromide in 0.9 mL of dry THF at 0°C, followed by stirring at RT for 30 min] cooled to -78°C (dry ice/2-propanol) under an argon atmosphere was added 24.0 mg (0.0768 mmol) of the ketones 6 and 5-epi-6 in 0.25 mL of dry THF over 5 min. After being stirred for 5 min at -78°C, the reaction mixture was allowed to warm to room temperature. After 1.7 h at

RT, the reaction mixture was quenched by the addition of a few drops of saturated aqueous $NaHCO_3$. The reaction mixture was then diluted with 15 mL of ether and washed with two 3 mL portions of saturated aqueous $NaHCO_3$ and one 3 mL portion of saturated aqueous NaCl. The combined aqueous washings were extracted with two 3 mL portions of ether. The organic layers were combined and dried ($MgSO_4$). Concentration of the dried solution under reduced pressure followed by chromatography of the residue on 7 g of silica gel with 1:25 ether:petroleum ether afforded first 11.4 mg (48%) of the olefin 7 as a colorless oil. Distillation [kugelrohr, 90°C (0.005 mm Hg)] of this oil provided the analytical sample: R_f = 0.16 (silica gel, 1:25 ether:petroleum ether); IR ($CHCl_3$) 1730 (C=O) and 1645 cm^{-1} ($C=CH_2$); ^{1}H-NMR ($CDCl_3$) δ 0.77-0.93 (br m, 9H, three overlapping CH_3's), 1.08 (d, 3H, J = 7 Hz, α-CH_3), 1.33-2.13 (br m, 9H), 2.49 (br m, 1H), 2.65 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.60 (s, 3H, OCH_3), 3.79-3.98 (br m, 2H, C(2)-H and C(8)-H), 4.63 and 4.70 (2br s, 2H, $C=CH_2$); $[\alpha]_D^{25}$ = -23.1 ($CHCl_3$, c 1.09).

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.80; H, 9.85.

There was then eluted 7.5 mg (32%) of the olefin 5-epi-7 as a colorless oil. Distillation [kugelrohr, 90°C (0.005 mm Hg)] of this oil provided the analytical

sample: R_f = 0.13 (silica gel, 1:25 ether:petroleum ether); IR($CHCl_3$) 1730 (C=O) and 1650 cm^{-1} ($C=CH_2$); ^{1}H-NMR ($CDCl_3$) δ 0.83 (d, 3H, J = 6 Hz, C(3)-CH_3), 0.86 (t, 3H, J = 7 Hz, CH_2CH_3), 0.94 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.13 (d, 3H, J = 7 Hz, α-CH_3), 1.32-2.44 (br m, 10H), 2.66 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.61 (s, 3H, OCH_3), 3.80-3.98 (br m, 2H, C(2)-H and C(8)-H), 4.63 and 4.70 (2br s, 2H, $C=CH_2$); $[\alpha]_D^{25}$ = -14.2° ($CHCl_3$, c 0.71).

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.72; H, 9.62.

Methyl [2S-[2α(S*),3β,5β,6β(8R*,9R*)]]-8-ethyl-α,3,-5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (8) and Methyl [2S-[2α(S*),3β,5β,6β(8R*,9S*)]]-8-ethyl-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (9). A vigorously stirred solution of 8.0 mg (0.026 mmol) of the olefin 7 in 2 mL of n-pentane was hydrogenated under a hydrogen atmosphere (H_2 filled balloon) at RT in the presence of a catalytic amount of powdered platinum oxide for 1 h. The reaction mixture was filtered through a pad of celite and the filter cake was washed liberally with ether (15 mL). The filtrate was concentrated under reduced pressure and chromatography of the residue on 1 g of silica gel with 1:40 ether:petroleum ether afforded 7.3 mg (91%) of a 77:23 (by 500 MHz ^{1}H-NMR) mixture of

the spiroketals 8 and 9 as a colorless oil. Distillation [kugelrohr, 80°C (0.003 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.12 (silica gel, 1:30 ether:petroleum ether); IR ($CHCl_3$) 1730 cm^{-1} (C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) (major isomer (9R*) 8) δ 0.81 (d, 3H, J = 7 Hz, C(3)-CH_3), 0.84 (d, 3H, J = 7 Hz, C(5)-CH_3), 0.87 (d, 3H, J = 7 Hz, C(9)-CH_3), 0.99 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.08 (d, 3H, J = 7 Hz, α-CH_3), 1.25-1.90 (br m, 11H), 2.66 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.50 (ddd, 1H, J = 4 Hz, J' = 5 Hz, J'' = 9 Hz, C(8)-H), 3.66 (s, 3H, OCH_3), 3.88 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H); 500 MHz ^{1}H-NMR ($CDCl_3$) (minor isomer (9S*) 9) δ 0.82 and 0.83 (2d, 6H, J = 6 Hz), 0.96 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.08 (d, 3H, J = 7 Hz, α-CH_3), 3.15 (ddd, J = 4 Hz, J' = 8 Hz, J'' = 8.5 Hz, C(8)-H), 3.64 (s, 3H, OCH_3), 3.96 (dd, J = 3 Hz, J' = 10 Hz, C(2)-H).

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.27; H, 10.24.

Methyl [2S-[2α(S*),3β,5β and 5α,6α(R*)]]-tetrahydro-α,3,5-trimethyl-6-(3-methyl-4-oxohexyl)-2H-pyran-2-acetate (11a,b) and Methyl [2S-[2α(S*),3β,5β and 5α,6α-(S*)]]-tetrahydro-α,3,5-trimethyl-6-(3-methyl-4-oxohexyl)-2H-pyran-2-acetate (12a,b).

A. From Spiroketals 8 and 9. The procedure for the preparation of the ketones 5a,b with 3.5 mg (0.0112 mmol) of the 77:23 mixture of spiroketals 8 and 9, described above, afforded after chromatography on 1 g of silica gel with 1:8 ether:petroleum ether afforded 3.1 mg (89%) of a mixture of the ketones 11a,b and 12a,b in an 80:20 ratio by 500 MHz ^{1}H-NMR. The ketones 11a,b were identical by 500 MHz ^{1}H-NMR with those obtained in Chapter 2 (ketones 36a,b). Distillation [kugelrohr, 95°C (0.005 mm Hg)] of this oil provided the analytical sample: R_f = 0.11 (silica gel, 1:8 ether:petroleum ether); IR ($CHCl_3$) 1735 (ester C=0) and 1710 cm^{-1} (ketone C=0); 500 MHz ^{1}H-NMR ($CDCl_3$) (ketone 12a) δ 0.76 (d, 3H, J = 6.5 Hz, C(5)-CH_3), 0.80 (d, 3H, J = 6.5 Hz, C(3)-CH_3), 1.04 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.05 (d, 3H, J = 7 Hz, C(6)-(C(3)-CH_3)), 1.11 (d, 3H, J = 7 Hz, α-CH_3), 1.28-1.73 (br m, 8H), 2.40-2.55 (br m, 3H), 2.67 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 2.79 (ddd, J = 2 Hz, J' = J'' = 9.5 Hz, C(6)-H), 3.38 (dd, J = 3 Hz, J' = 10 Hz, C(2)-H), 3.66 (s, 3H, OCH_3); 500 MHz ^{1}H-NMR ($CDCl_3$) (ketone 12b) δ 0.77 (d, 3H, J = 6.5 Hz, C(3)-CH_3), 0.87 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.04 (t, 3H, J = 7 Hz, $CH_2\underline{CH}_3$), 1.05 (d, 3H, J = 7 Hz, C(6)-(C(3)-CH_3)), 1.14 (d, 3H, J = 7 Hz, α-CH_3), 1.28-1.73 (br m, 8H), 2.40-2.55 (br m, 3H), 2.68 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 3.25 (ddd, 1H, J = 2 Hz, J' = 4 Hz,

J'' = 9 Hz, C(6)-H), 3.40 (dd, J = 3 Hz, J' = 10 Hz, C(2)-H), 3.67 (s, 3H, OCH_3).

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.30; H, 10.22.

B. From Spiroketal 10. The procedure for the preparation of the ketones 5a,b with 6.6 mg (0.0211 mmol) of the spiroketal 10 afforded, after 4 days, workup as described, and chromatography on 1 g of silica gel with 1:8 ether:petroleum ether, first 2.0 mg (30%) of a mixture of the spiroketals 10 and 5-epi-10. There was then eluted 4.2 mg (64%) of a mixture of the ketones 11a,b and 12a,b, identical by 500 MHz ^{1}H-NMR with those prepared above, in a 55:45 ratio by 500 MHz ^{1}H-NMR. The ratios of 11a:11b and 12a:12b were 92:8 and is approximately the expected equilibrium ratio at C(5). Distillation [kugelrohr, 90°C (0.003 mm Hg)] of this oil provided the analytical sample.

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.26; H, 10.38.

Methyl [2S-[2α(S*),3β,5α,6β(8S*,9R*)]]-8-ethyl-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (10). The spiroketal 6-epi-10 (17.6 mg, 0.0563 mmol) was treated with 0.10 mL of dry dichloromethane saturated with p-toluenesulfonic acid-monohydrate for 10 min at RT.

Chromatography of the reaction mixture on 7 g of silica gel with 1:30 ether:petroleum ether afforded 17.6 mg (100%) of the spiroketal 10 as a colorless oil. Distillation [kugelrohr, 80°C (0.001 mm Hg)] of this oil provided the analytical sample as a white solid melting at 53.5-54.5°C: R_f = 0.14 (silica gel, 1:30 ether: petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); 500 MHz ^{1}H-NMR ($CDCl_3$) δ 0.78 and 0.80 (2d, 6H, J = 6.5 Hz, C(3)-CH_3 and C(9)-CH_3), 0.95 (d, 3H, J = 7 Hz, C(5)-CH_3), 1.02 (t, 3H, J = 7 Hz, CH_2CH_3), 1.15 (d, 3H, J = 7 Hz, α-CH_3), 1.18-1.45 (br m, 7H), 1.62-1.78 (br m, 3H), 1.95 (ddd, 1H, J = 4.5 Hz, J'=J'' = 13 Hz, ax C(11)-H), 2.70 (dq, 1H, J = 3 Hz, J' = 7 Hz, α-H), 2.97 (ddd, 1H, J = 2.5 Hz, J'=J'' = 10 Hz, C(8)-H), 3.68 (s, 3H, OCH_3), 3.76 (dd, J = 3 Hz, J' = 10.5 Hz, C(2)-H); $[\alpha]_D^{25}$ = +70.2° ($CHCl_3$, c 1.30).

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32
Found: C, 69.02; H, 10.15.

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APPENDIX FOUR

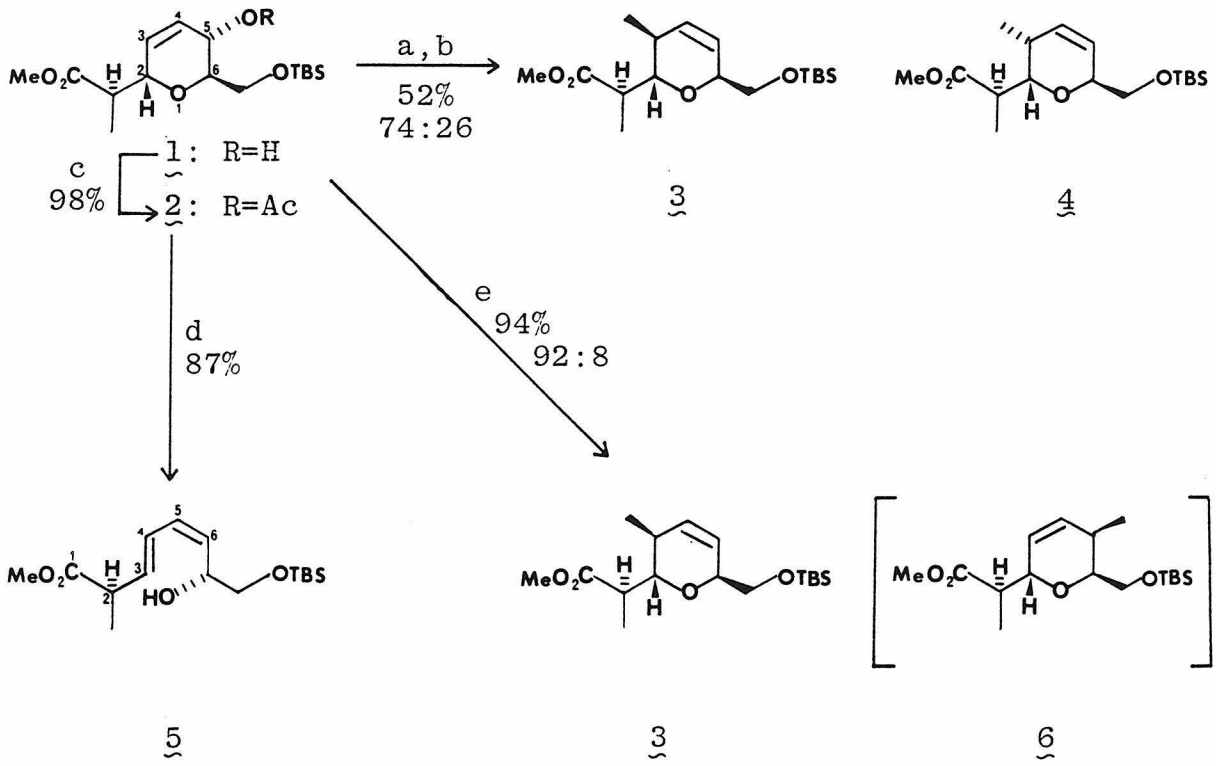
CUPRATE REACTIONS ON ALLYLIC DERIVATIVES OF 5,6-DIHYDRO-2H-PYRANS

APPENDIX FOUR

Cuprate Reactions on Allylic Derivatives of 5,6-Dihydro-2H-Pyrans

In the course of some early work directed toward the macrolide antibiotics, it was desired to incorporate the C(3) methyl group of the dihydropyran 3 through a coupling reaction with allylic rearrangement on the allylic alcohol 1. Initially, the method of Murahashi[1] was investigated since it shows very high regioselectivity for γ-substitution (Sn2') and high anti stereoselectivity on allylic alcohols. Therefore, treatment of the cuprous alkoxide of the allylic alcohol 1 with one equivalent each of methyllithium and N,N-methylphenylaminotributylphosphonium iodide [$nBu_3\overset{+}{P}N(CH_3)(C_6H_5)I^-$] afforded in 52% yield (81% conversion) the dihydropyrans 3 and 4 in a 74:26 ratio by isolation. The stereochemical assignments are verified by the 7 Hz coupling between the hydrogens at C(2) and C(3) in dihydropyran 3 and the 3 Hz coupling between these hydrogens in dihydropyran 4. The regiochemistry of this reaction was confirmed by ^{1}H-NMR decoupling experiments. There was no evidence (TLC, ^{1}H-NMR) for any of the coupling products without allylic rearrangement (e.g. dihydropyran 6). It should be noted that the anti stereoselectivity is much lower than that observed by Murahashi[1] on a cyclohexenyl system.

Scheme[a]



[a] a, CH_3Li, CuI, THF, -100°C → RT; b, CH_3Li, $(nBu)_3\overset{+}{P}N-(CH_3)(C_6H_5)$ I^-, DMF, -100°C → RT; c, CH_3COCl, C_5H_5N, CH_2Cl_2, 0°C; d, $LiCu(CH_3)_2$, Et_2O, -78°C; e, $LiCu(CH_3)_2$, Et_2O, 0°C, inverse addition.

Due to the low yield for the above reaction, lithium dimethylcuprate reactions on the allylic acetate 2 were investigated in spite of the 50:50 regioselectivity usually observed for these reactions.[2] It was hoped, however, that the C(6) substituent would disfavor coupling at the C(5) carbon in this cuprate reaction which proceeds with anti stereochemistry stereospecifically.[2] It fact, this cuprate reaction at 0°C under standard conditions afforded the dihydropyran 3, identical (IR, ^{1}H-NMR, TLC) with that prepared above by the Murahashi method except that it contains 8% of an inseparable impurity presumed to be the regioisomer 6. However, significant quantities (26%) of a reductive elimination product 5 were obtained. The trans-cis stereochemistry of the diene 5 was confirmed by the 15 Hz coupling between the hydrogens at C(3) and C(4) and the 11 Hz coupling between the hydrogens at C(5) and C(6).

When the reaction was performed at -78°C, an 87% yield of the diene 5 was obtained. Apparently, this product may arise from two sequential electron transfers and is favored over the coupling reaction at low temperature. Therefore, it was reasoned that a procedure that kept the concentration of lithium dimethylcuprate low might reduce these sequential electron transfers. In fact, an inverse addition procedure where a solution of lithium dimethyl-cuprate was added slowly to the allylic acetate 2 in ether

at 0°C afforded the dihydropyrans 3 and 6 in 94% yield accompanied by only 6% of the diene 5.

Therefore, one can obtain in high yield either the reductive elimination product 5 or the coupling products 3 and 6 simply by changing the reaction conditions. This regioselective and stereospecific coupling reaction on 5,6-dihydro-2H-pyrans with a C(2) or C(6) substituent trans to the departing acetate may be quite general and certainly useful. Additionally, this novel reductive elimination reaction on such 5,6-dihydro-2H-pyran derivatives may be a general and useful trans-cis diene synthesis.

APPENDIX FOUR

EXPERIMENTAL SECTION

Methyl [2S-[2α(S*),3β,6β]]-6-[[[(1,1-dimethylethyl)-dimethylsilyl]oxy]methyl]-3,6-dihydro-α,3-dimethyl-2H-pyran-2-acetate (3) and Methyl [2S-[2α(S*),3α,6β]]-6-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3,6-dihydro-α,3-dimethyl-2H-pyran-2-acetate (4). To a stirred slurry of 281 mg (0.850 mmol) of the allylic alcohol 1 and 164 mg (0.861 mmol) of CuI (purified by THF extraction) in 2.3 mL of dry THF cooled to -100°C (N_2/methanol slush) under an argon atmosphere was added dropwise 0.40 mL (0.87 mmol) of 2.17 M methyllithium (low halide in ether) over 2 min. After 5 min at -100°C, the mixture was allowed to warm to RT for 30 min, and the resulting brown suspension was recooled to -100°C. To this brown suspension at -100°C was added first 0.40 mL (0.87 mmol) of 2.17 M methyllithium (low halide in ether) over 2 min followed immediately by 381 mg (0.875 mmol) of N,N-methylphenylaminotributyl-phosphonium iodide in 3.5 mL of dry DMF in one portion. After 5 min at -100°C, the mixture was allowed to warm to RT for 4 h. The reaction mixture was then quenched by the addition of 17 mL of saturated aqueous NH_4Cl and then 7 mL of ether. The resulting mixture was filtered, and the

filter cake was washed with 17 mL of water and 20 mL of ether. The layers of the filtrate were separated, and the aqueous layer was extracted with two 20 mL portions of ether. After being dried ($MgSO_4$), the combined ether layers were concentrated under reduced pressure and chromatography of the residue on 21 g of silica gel with 1:10 ether: petroleum ether afforded 124 mg (44%) of a mixture of the dihydropyrans 3 and 4 as a yellow oil (separated and purified below). Further elution with ether afforded 52.7 mg (19%) of recovered allylic alcohol 1.

Chromatography of the mixture of the dihydropyrans 3 and 4, described above, on 21 g of silica gel with 1:20 ether:petroleum ether afforded first 30.3 mg (11%) of the dihydropyran 4 as a colorless oil. Distillation [kugelrohr, 95°C (0.005 mm Hg)] of this oil provided the analytical sample of the dihydropyran 4: R_f = 0.29 (silica gel, 1:10 ether:petroleum ether); IR ($CHCl_3$) 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.06 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, t-BuSi), 0.94 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.30 (d, 3H, J = 7 Hz, α-CH_3), 2.03 (br m, 1H, C(3)-H), 2.57 (dq, 1H, J = 10 Hz, J' = 7 Hz, α-H), 3.43-3.70 (br m, 2H, -CH_2OTBS), 3.63 (s, 3H, OCH_3), 3.75 (dd, 1H, J = 3 Hz, J' = 10 Hz, C(2)-H), 4.17 (br m, 1H, C(6)-H), 5.62 (dd, 1H, J = 3 Hz, J' = 11 Hz, C(5)-H), 5.89 (ddd, 1H, J = 2 Hz, J' = 6 Hz, J'' = 11 Hz, C(4)-H); $[\alpha]_D^{25}$ = -139.3° ($CHCl_3$, c 0.61).

Anal. Calcd for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 62.27; H, 10.00.

There was then eluted 86.4 mg (31%) of the dihydropyran 3 as a colorless oil. Distillation [kugelrohr, 95°C (0.005 mm Hg)] of a portion of this oil provided the analytical sample of the dihydropyran 3: R_f = 0.22 (silica gel, 1:10 ether:petroleum ether); IR ($CHCl_3$) 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.05 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, t-BuSi), 0.97 (d, 3H, J = 7 Hz, C(3)-CH_3), 1.18 (d, 3H, J = 7 Hz, α-CH_3), 2.07 (br dq, 1H, J=J' = 7 Hz, C(3)-H), 2.72 (dq, 1H, J=J' = 7 Hz, α-CH_3), 3.48-3.64 (br m, 2H, -CH_2OTBS), 3.64 (s, 3H, OCH_3), 3.72 (dd, 1H, J=J' = 7 Hz, C(2)-H), 4.04 (dt, 1H, J = 2 Hz, J' = 6 Hz, C(6)-H), 5.70 (s, 2H, C(4)-H and C(5)-H); $[\alpha]_D^{25}$ = -45.2° ($CHCl_3$, c 1.19).

Anal. Calcd for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 62.19; H, 9.96.

Methyl [2S-[2α(S*),5α,6β]]-5-(acetyloxy)-6-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-5,6-dihydro-α-methyl-2H-pyran-2-acetate (2). To a stirred solution of 151 mg (0.457 mmol) of the allylic alcohol 1 in 3 mL of dichloromethane cooled to 0°C (ice bath) under an argon atmosphere was added first 0.110 mL (108 mg, 1.37 mmol) of dry pyridine followed by 0.049 mL (54 mg, 0.68 mmol) of acetyl chloride. After 1 h at 0°C, the reaction mixture

was diluted with 30 mL of water and extracted with three 15 mL portions of ether. The combined extracts were washed with one 10 mL portion of saturated aqueous $NaHCO_3$, one 10 mL portion of water, and one 10 mL portion of saturated aqueous NaCl. After being dried ($MgSO_4$), the organic layer was concentrated under reduced pressure and chromatography of the residue on 8 g of silica gel with 1:3 ether:petroleum ether afforded 166 mg (98%) of the acetate 2 as a colorless oil. Distillation [kugelrohr, 115°C (0.003 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.26 (silica gel, 1:3 ether:petroleum ether); IR ($CHCl_3$) 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.06 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, t-BuSi), 1.27 (d, 3H, J = 7 Hz, α-CH_3), 2.03 (s, 3H, CH_3CO_2), 2.68 (dq, 1H, J=J' = 7 Hz, C(2)-H), 3.69 (br s, 6H, OCH_3, C(6)-H and -CH_2OTBS), 4.33 (dd, 1H, J = 2 Hz, J' = 7 Hz, C(2)-H), 5.07 (m, 1H, C(5)-H), 5.86 (m, 2H, C(3)-H and C(4)-H); $[\alpha]_D^{23}$ = +45.8° ($CHCl_3$, c 1.20).

Anal. Calcd for $C_{18}H_{32}O_6Si$: C, 58.03; H, 8.66. Found: C, 58.08; H, 8.52.

Methyl [2R-(2R*,3E,5Z,7R*)]-8-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-7-hydroxy-2-methyl-3,5-octadienoate (5). To a stirred slurry of 118 mg (0.620 mmol) of CuI (purified by THF extraction) in 6 mL of dry ether cooled to 0°C (ice bath) under an argon atmosphere was added 0.56 mL (1.22 mmol) of 2.17 M methyllithium (low halide in ether)

over 2 min. After 30 min at 0°C, this solution of lithium dimethylcuprate was cooled to -78°C (dry ice/2-propanol) and then 73 mg (0.196 mmol) of the allylic acetate 2 in 1 mL of dry ether was added over 2 min. After stirring at -78°C for 15 min, the reaction was quenched by the addition of 10 mL of saturated aqueous NH_4Cl and then allowed to warm to RT. The resulting mixture was diluted with 5 mL of water and the layers separated. The aqueous layer was extracted with two 10 mL portions of ether which were combined with the first organic layer. After being dried ($MgSO_4$), this organic solution was concentrated under reduced pressure and chromatography of the residue on 8 g of silica gel with 1:3 ether:petroleum ether afforded first 1.5 mg (2%) of the coupling product 3 and then 21.2 mg (29%) of the starting allylic acetate 2. Finally, there was eluted 37.9 mg (62%) of the diene 5 as a colorless oil. Distillation [kugelrohr, 120°C (0.005 mm Hg)] of a portion of this oil provided the analytical sample: R_f = 0.17 (silica gel, 1:3 ether:petroleum ether); IR ($CHCl_3$) 3580 (OH), 1730 (C=O), and 1665 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 0.09 (2, 6H, $Si(CH_3)_2$), 0.91 (s, 9H, t-BuSi), 1.28 (d, 3H, J = 7 Hz, C(2)-CH_3), 2.52 (d, 1H, J = 2 Hz, OH), 3.19 (dq, 1H, J = 8 Hz, J' = 7 Hz, C(2)-H), 3.46 (d, 1H, J = 7 Hz, C(8)-H), 3.54 (d, 1H, J = 4 Hz, C(8)-H), 3.66 (s, 3H, OCH_3), 4.55 (br m, 1H, C(7)-H), 5.31 (dd, 1H, J = 8 Hz, J' = 11 Hz, C(6)-H), 5.77 (dd, 1H, J = 8 Hz, J' = 15 Hz, C(3)-H),

6.07 (dd, 1H, J=J' = 11 Hz, C(5)-H), 6.43 (dd, 1H, J = 11 Hz, J' = 15 Hz, C(4)-H); $[\alpha]_D^{23}$ = -39.5° ($CHCl_3$, c 1.05).

Anal. Calcd for $C_{16}H_{30}O_4Si$: C, 61.11; H, 9.61. Found: C, 61.05; H, 9.49.

Methyl [2S-[2α(S*),3β,6β]]-6-[[[(1,1-dimethylethyl)-dimethylsilyl]oxy]methyl]-3,6-dihydro-α,3-dimethyl-2H-pyran-2-acetate (3) and Methyl [2S-[2α(S*),5β,6β]]-6-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-5,6-dihydro-α,5-dimethyl-2H-pyran-2-acetate (6). To a stirred solution of 73.0 mg (0.196 mmol) of the allylic acetate 2 in 4 mL of dry ether cooled to 0°C (ice bath) under an argon atmosphere was added slowly 0.62 mmol of a cold solution of lithium dimethylcuprate in 6 mL of dry ether [prepared by the addition of 0.57 mL (1.24 mmol) of 2.17 M methyllithium (low halide in ether) to a stirred slurry of 124 mg (0.65 mmol) of CuI cooled to 0°C under an argon atmosphere] over 20 min. After 10 min at 0°C, the reaction was quenched by the addition of 10 mL of saturated aqueous NH_4Cl and then 5 mL of water. The layers were separated, and the aqueous layer was extracted with two 10 mL portions of ether. After being dried ($MgSO_4$), the combined organic solutions were concentrated under reduced pressure and chromatography of the residue on 8 g of silica gel with 1:3 ether:petroleum ether afforded first 60.2 mg (94%) of the dihydropyran 3 identical (^{1}H-NMR, IR, and TLC) with

that prepared above except that in the ^{1}H-NMR there is a small doublet at 1.27 ppm amounting to 8% of the mixture. This minor impurity is believed to be the regioisomer 6 from the cuprate coupling and significantly alters the optical rotation. Distillation [kugelrohr, 100°C (0.005 mm Hg)] of a portion of this oil provided the analytical sample: $[\alpha]_D^{22} = -52.2°$ ($CHCl_3$, c 1.09).

Anal. Calcd for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 62.30; H, 9.70.

There was then eluted 3.8 mg (6%) of the diene 5 identical (^{1}H-NMR, TLC) to that prepared above.

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