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

Robert E. Ireland* and John P. Daub[2]

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

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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]

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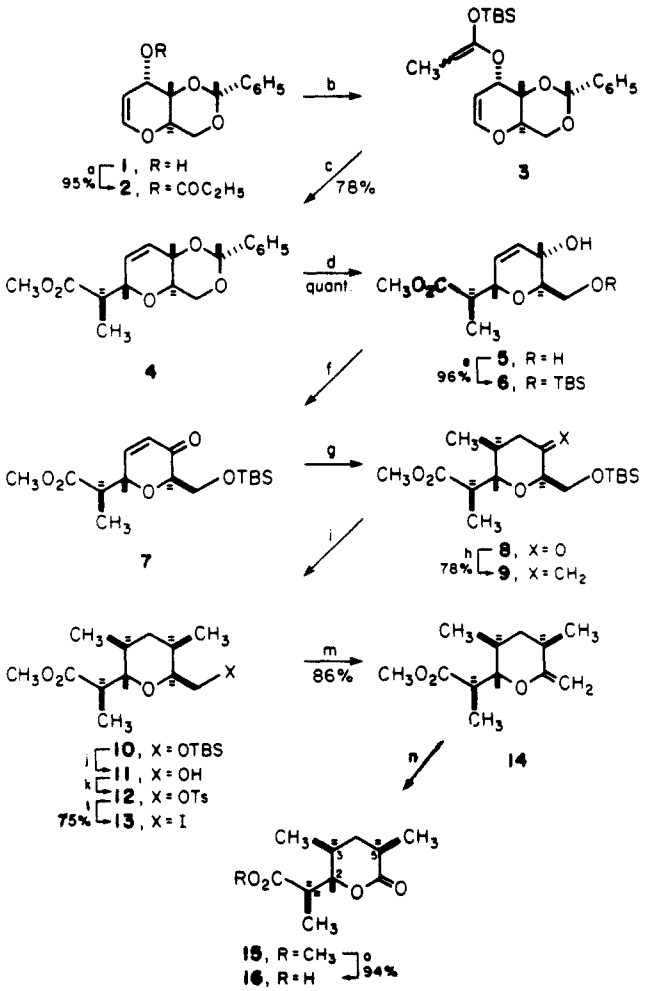
Scheme I. Synthesis of the Prelog-Djerassi Lactone[a,b]

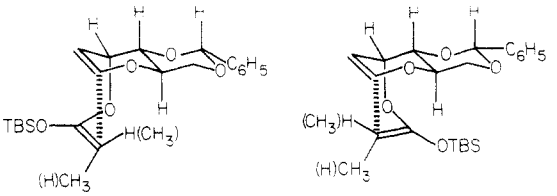


[a] a, $(CH_3CH_2CO)_2O$, pyridine, (dimethylamino)pyridine (cat.), CH_2Cl_2; b, LiHMDS, THF, −100 °C; t-Bu$(CH_3)_2$SiCl, HMPA, −100 °C ⟶ room temp; c, C_6H_6, 80 °C, 19 h; H_3O^+, THF, room temp; CH_2N_2, Et_2O; d, H_3O^+, THF, 60 °C; e, t-Bu$(CH_3)_2$SiCl, pyridine, 0 °C; f, PDC, CH_2Cl_2; g, $LiCu(CH_3)_2$, Et_2O, 0 °C; h, $(C_6H_5)_3PCH_2$, THF; i, PtO_2, H_2, pentane; j, $(n$-Bu$)_4$NF, 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 predominantely 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 ^{1}H 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 ^{1}H 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).

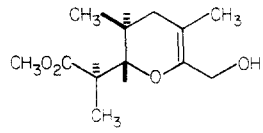
Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.58; H, 9.67.

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.



i

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)[9g] 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.