Macrolide Total Synthesis. The Synthesis of Spiro Ketal Intermediates and Their Cleavage into Open-Chain Derivatives

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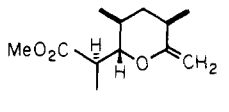
A convergent method for the preparation of spiro ketals by hetero-Diels–Alder condensation of the keto–enol ether **14** with α,β-unsaturated carbonyl compounds is developed which is applicable with the poor heterodienes methacrolein and 2-methyl-1-penten-3-one. Additionally, the cleavage of spiro ketals to open-chain derivatives for macrolide total synthesis is realized by thioketal exchange with 1,2-ethanedithiol.

The macrolide antibiotics[2,3] are a class of fascinating, stereochemically complex organic molecules which have been under intense investigation for 30 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 aglycons have recently yielded to chemical total synthesis.[4]

For the current work,[5,6] the long-standing relationship between the macrolide antibiotics and their spiro ketals[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 spiro ketals *and* subsequently their cleavage to open-chain systems suitable for macrolactonization. A similar basic plan is independently under investigation by 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 spiro ketal key intermediate **6** was envisioned. The present report describes a successful convergent approach to the construction and characterization of such spiro ketals (see Scheme I) 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



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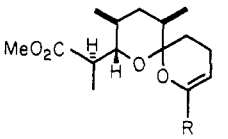

8, R = H
9, R = CH_2CH_3

provide a spiro ketal that would possess the necessary carbon skeleton. Subsequent hydrogenation or hydroboration of the resultant enol ether would afford the spiro ketals **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 spiro ketal **9** in only 6% yield (by ^1H 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 un-

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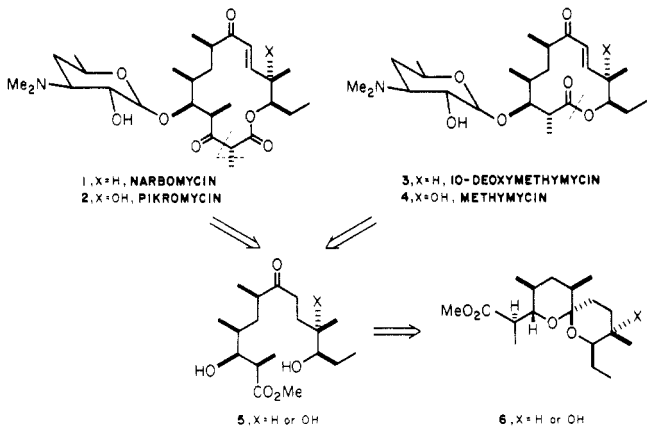
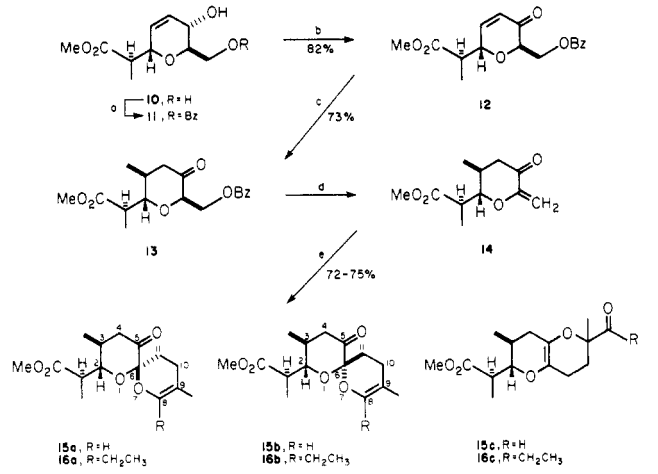
Scheme I. Synthetic Strategy for Macrolide Synthesis



Scheme II. Hetero-Diels-Alder Synthesis of Spiro Ketals[a]

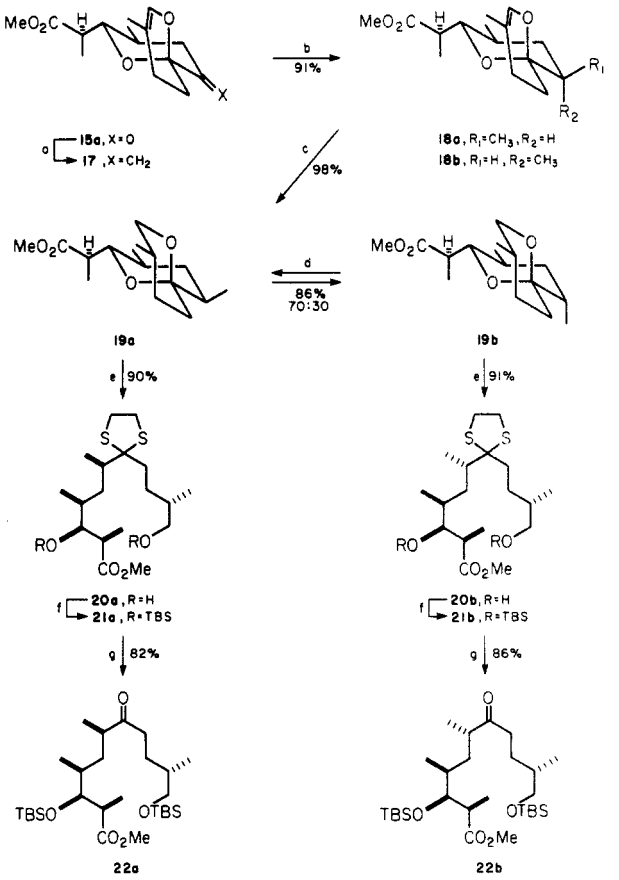


[a] (a) BzCl, C_5H_5N, CH_2Cl_2, −78 °C → room temperature; (b) $[C_5H_5N{\cdot}H]_2Cr_2O_7$ (PDC), DMF, 0 °C; (c) $LiCu(CH_3)_2$, Et_2O, 0 °C; (d) Et_3N; (e) methacrolein or 2-methyl-1-penten-3-one.

favorable reactivity of the *exo*-methylene 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 regionselectivity and/or role-selectivity question, however, as the keto–enol ether **14**, which is held in an s-cis conformation, can participate as either a 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.

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 oxobenzoates **13** and 3-*epi*-**13** as a 77:23 mixture (by ^1H NMR) in 78% overall yield. This moderate stereoselectivity in the cuprate addition is to be contrasted

Scheme III. Elaboration of Spiro Ketal 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 of H_2, MeOH, 5 days; (d) *p*-TsOH·H_2O, CH_2Cl_2, 48 h; (e) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, −40 °C; (f) TBSCl, imidazole, DMF, 80 °C, 18–20 h; (g) $HgCl_2$, $CaCO_3$, MeCN, H_2O.
[b] TBS = *t*-$Bu(CH_3)_2Si$.

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. For avoidance of this dimerization, the elimination reaction was performed at 60 °C 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–c** and **16a–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 spiro ketals from 3-oxo-2-methylenetetrahydropyran 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 spiro ketals **15a** and **15b** by isolation was 83:17; the major component of this spiro ketal mixture is **15a**, which enjoys the stabilization of the anomeric effect.[17] This stereoselectivity indicates a small

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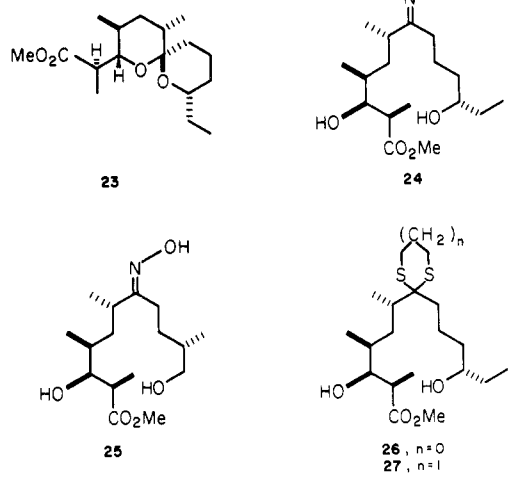
(17) (a) Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789–6791. (b) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105–1121.

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 spiro ketal **15a** in accord with a deshielding effect by the axial O(7), while in spiro ketal **15b** this hydrogen appears at 3.87 ppm. Similarly, a 69:31 ratio between the spiro ketals **16a** and **16b** was observed.

Further elaboration of the spiro ketal **15a** through Wittig methylenation and subsequent hydrogenation (Scheme III) afforded the spiro ketals **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 spiro ketal **19b** afforded a 70:30 equilibrium mixture of the spiro ketals **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, 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 spiro ketals **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).

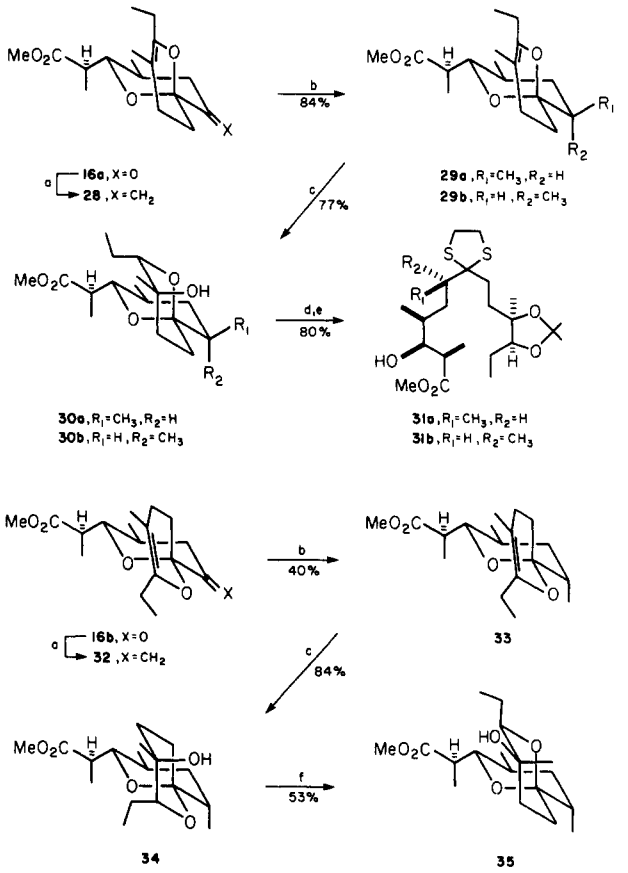
With suitable model spiro ketals in hand, methods for spiro ketal cleavage to the open-chain derivatives were investigated.[18] Initial investigations focused on the thermodynamically less stable[19] spiro ketal **23**,[5] and it was



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 spiro ketal **19b**, 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 spiro ketal **23** with boronitrifluoride etherate in 1,2-ethanedithiol at −40 °C afforded the thioketal–diol **26** in 90% yield. Substitution of 1,3-propanedithiol in 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 °C) products were obtained in which an internal oxidation–reduction had occurred[15] as observed by Djerassi[21] with sapogenins. Similar results have been independently observed by Deslongchamps.[22] Application of this low-temperature 1,2-ethanedithiol procedure to the spiro ketals **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 spiro ketals **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 spiro ketal **16a** in 84% yield. It should be noted that the enol ether **29a**

Scheme IV. Elaboration of the Spiro Ketals 16a,b



[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) *p*-TsOH·H_2O, acetone; (f) *p*-TsOH·H_2O, CH_2Cl_2, 10 min.

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

(19) In the conformation of spiro ketal **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. Alleviation of this steric effect requires the molecular to adopt a conformation in which an electronically favorable anomeric effect has been lost. The spiro kettals **19a** and **19b** possess no such destablizing effects.

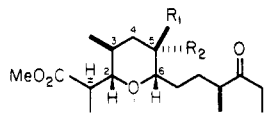
(20) This method has been applied by Professor E. J. Corey to the spiro ketal derived from erythronolide A.[12d]

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

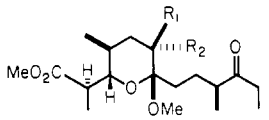
(22) Deslongchamps, P.; Rowan, D. D.; Pothier, N. *Can. J. Chem.* **1981**, *59*, 2787–2791.

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 of H_2, 10 days) of enol ethers **29a,b** afforded, in addition to 25% starting material and trace quantities of hydrogenation products, a 37:63 (by 500-MHz ^1H NMR) mixture of the inseparable hydrogenolysis products **36a** and **36b** in 22%



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, $R_1 = H, R_2 = CH_3$

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 in the pyran **36a** and the 4-Hz couplings 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 ^1H 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 ^1H NMR. This high stereoselectivity of this spirocyclic system even toward protonation is quite remarkable.

Hydrogenation 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 illustrate the compatibility of this methodology with a tertiary alcohol. This same sequence of reactions with the spiro ketal **16b** led to the spiro ketal **34** in 34% overall yield. This spiro ketal 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 spiro ketal **34** rearranges the spirocenter to the more stable spiro ketal **35** in 53% yield; in addition, the corresponding 1,6-dioxaspiro[4.5]decane ring-contracted spiro ketals were formed in 47% yield.

Although the spiro ketals **30a,b** after a double-inversion sequence and/or the spiro ketal **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 (^1H 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, the numbering in the assignments employs the numbering system implicit in the *Chemical Abstracts* name at the heading for each experiment. 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 × 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 a published procedure.[23] 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 powder calcium hydride. Hexamethyldisilazane and diisopropylamine were distilled under argon from powdered calcium hydride. Dimethyl sulfoxide (Me_2SO), 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 open 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 [2*S*-[2α(*S),5α,6β]]-6-[(Benzoyloxy)methyl]-5,6-dihydro-5-hydroxy-α-methyl-2*H*-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 were 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 being stirred at −78 °C for 3 h, the mixture was allowed to warm to room temperature 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 × 10 mL) followed by chromatography of the residue on 15 g of silica gel with 2:1 ether/petroleum ether afforded 276 mg

(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(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), 1615 cm^{-1} (phenyl); ^1H NMR ($CDCl_3$) δ 1.27 (d, 3 H, J = 7 Hz, α-CH_3), 2.42 (br, 1 H, OH), 2.75 (dq, 1 H, $J = J'$ = 7 Hz, α-H), 3.63 (s, 3 H, OCH_3), 3.82 (ddd, 1 H, $J = J'$ = 6 Hz, J'' = 3 Hz, C(6) H), 3.98 (br m, 1 H, C(5) H), 4.35 (d plus allylic couplings, 1 H, J = 7 Hz, C(2) H), 4.44 and 4.60 (AB q plus different couplings with C(6) H, 2 H, J_{AB} = 12 Hz, J = 3 Hz, J' = 6 Hz, CH_2OBz), 5.87 (AB q plus allylic couplings, 2 H, J_{AB} = 11 Hz, CH=CH), 7.48 (br m, 3 H, Ar H), 8.03 (dd, 2 H, J = 2 Hz, J' = 7 Hz, Ar H); $[\alpha]^{24}_D$ -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 [2*S*-[2α(*S),6β]]-6-[(Benzoyloxy)methyl]-5,6-dihydro-α-methyl-5-oxo-2*H*-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 × 20 mL) afforded 251 mg (98%) of the enone 12 as as 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), 1615 cm^{-1} (phenyl); ^1H NMR ($CDCl_3$) δ 1.27 (d, 3 H, J = 7 Hz, α-CH_3), 2.82 (dq, 1 H, $J = J'$ = 7 Hz, α-H), 3.62 (s, 3 H, OCH_3), 4.55 (br m, 3 H, CH_2OBz and C(6) H), 4.85 (ddd, 1 H, $J = J'$ = 2 Hz, J'' = 7 Hz, C(2) H), 6.18 (dd, 1 H, J = 2 Hz, J' = 11 Hz, C(4) H), 7.03 (dd, 1 H, J = 2 Hz, J' = 11 Hz, C(3) H), 7.47 (br m, 3 H, Ar H), 7.96 (dd, 2 H, J = 2 Hz, J' = 8 Hz, Ar H); $[\alpha]^{24}_D$ -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 [2*S*-[2α(*S),3β,6β]]-6-[(Benzoyloxy)methyl]-α,3-dimethyl-5-oxotetrahydro-2*H*-pyran-2-acetate (13) and Methyl [2*S*-[2α(*S**),3α,6β]]-6-[(Benzoyloxy)methyl]-α,3-dimethyl-5-oxotetrahydro-2*H*-pyran-2-acetate (3-*epi*-13).** To a stirred slurry of 220 mg (1.07 mmol) of cuprous bromide–dimethyl sulfide 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 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: mp 57–57.5 °C; R_f 0.23 (silica gel, 1:1 ether/petroleum ether); IR ($CHCl_3$) 1720 (C=O), 1615 cm^{-1} (phenyl); ^1H NMR ($CDCl_3$) δ 1.03 (d, 3 H, J = 6 Hz, C(3) CH_3), 1.22 (d, 3 H, J = 7 Hz, α-CH_3), 2.13–2.62 (br m, 3 H, C(3) H, C(4) H_2), 2.78 (dq, 1 H, J = 6 Hz, J' = 7 Hz, α-H), 3.58 (s, 3 H, OCH_3), 4.08 (dd, 1 H, J = 6 Hz, J' = 8 Hz, C(2) H), 4.33 (t, 1 H, J = 5 Hz, C(6) H), 4.56 (d, 2 H, J = 5 Hz, CH_2OBz), 7.48 (br m, 3 H, Ar H), 7.99 (dd, 2 H, J = 2 Hz, J' = 7 Hz, Ar H); $[\alpha]^{24}_D$ +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 [2*S*-[2α(*S),3β,6β]]-α,3,9-Trimethyl-5-oxo-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (15a), Methyl [2*S*-[2α(*S**),3β,6α]]-α,3,9-Trimethyl-5-oxo-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (15b), and Methyl [2*S*-[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 7g (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 the 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 spiro ketal 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), 1690 cm^{-1} (O—C=C); ^1H NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 7 Hz, C(3) CH_3), 1.19 (d, 3 H, J = 7 Hz, α-CH_3), 1.57 (br s, 3 H, C(9) CH_3), 1.70–2.43 (br m, 6 H, C(3) H, equatorial C(4) H, C(10) H_2, C(11) H_2), 2.59 (dq, 1 H, J = 10 Hz, J' = 7 Hz, α-H), 3.08 (dd, 1 H, J = 5 Hz, J' = 13 Hz, axial C(4) H), 3.67 (s, 3 H, OCH_3), 4.28 (dd, 1 H, J = 2 Hz, J' = 10 Hz, C(2) H), 6.04 (br s, 1 H, C(8) H); $[\alpha]^{24}_D$ +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 spiro ketal 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: mp 76.5–77 °C; R_f 0.20 (silica gel, 1:8:1 ether/petroleum ether/dichloromethane); IR ($CHCl_3$) 1735 (C=O), 1685 cm^{-1} (O—C=C); 500 MHz ^1H NMR δ 0.98 (d, 3 H, J = 7 Hz, C(3) CH_3), 1.12 (d, 3 H, J = 7 Hz, α-CH_3), 1.56 (br s, 3 H, C(9) CH_3), 1.75 (br m, 2 H), 1.93 (ddd, 1 H, $J = J'$ = 13 Hz, J'' = 6 Hz), 2.01 (br m, 1 H), 2.18 (br m, 1 H), 2.41 (dd, 1 H, J = 4 Hz, J' = 14 Hz, equatorial C(4) H), 2.63 (dd, 1 H, J = 12.5 Hz, J' = 14 Hz, axial C(4) H), 2.74 (dq, 1 H, J = 3.5 Hz, J' = 7 Hz, α-H), 3.62 (s, 3 H, OCH_3), 4.36 (dd, 1 H, J = 3.5 Hz, J' = 10 Hz, C(2) H), 6.03 (s, 1 H, C(8) H); $[\alpha]^{24}_D$ +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 spiro ketal 15b and the Diels–Alder regioisomers 15c as a colorless oil: R_f 0.16 (silica gel, 1:8:1 ether/petroleum ethr/dichloromethane); IR ($CHCl_3$) 1730 (C=O), 1685 cm^{-1} (O—C=C); ^1H NMR ($CDCl_3$; for spiro ketal 15b) δ 0.98 (d, 3 H, J = 6 Hz, C(3) CH_3), 1.19 (d, 3 H, J = 7 Hz, α-CH_3), 1.58 (br s, 3 H, C(9) CH_3), 1.67–2.82 (br m, 7 H), 2.87 (dq, 1 H, $J = J'$ = 7 Hz, α-H), 3.67 (s, 3 H, OCH_3), 3.87 (dd, 1 H, J = 7 Hz, J' = 8 Hz, C(2) H), 6.03 (br s, 1 H, C(8) H); ^1H NMR (regioisomers 15c) δ 1.14 (d, 3 H, J = 7 Hz, α-CH_3), 1.24 (s, 3 H, C(6) CH_3), 9.50 and 9.53 (2 s, 1 H, CHO). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.92; H, 7.82.

Methyl [2*S*-[2α(*S),3β,6β]]-8-Ethyl-α,3,9-trimethyl-5-oxo-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (16a), Methyl [2*S*-[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 [2*S*-[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.

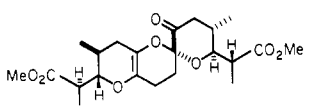
Chromatography of 330 mg of the Diels–Alder adducts on 35 g of silica gel with 1:6 ether/petroleum ether afforded (after recycling of the mixed fractions) first 40 mg of the spiro ketal 3-*epi*-16a as a colorless oil: R_f 0.24 (silica gel, 1:6 ether/petroleum ether); IR ($CHCl_3$) 1725 (C=O), 1695 cm^{-1} (O—C=C); ^1H NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 7 Hz, C(3) CH_3), 1.08 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.17 (d, 3 H, J = 7 Hz, α-CH_3), 1.60 (br s, 3 H, C(9) CH_3), 1.73–2.42 (br m, 8 H), 2.58 (dq, 1 H, J = 11 Hz, J' = 7 Hz, α-H), 3.12 (dd, 1 H, J = 5 Hz, J' = 13 Hz, axial C(4) H), 3.67 (s, 3 H, OCH_3), 4.32 (dd, 1 H, J = 2 Hz, J' = 11 Hz, C(2) H); $[\alpha]^{25}_D$ +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.

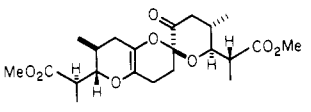
There was then eluted 160 mg of the spiro ketal **16a** as a very low melting white solid: R_f 0.20 (silica gel, 1:6 ether/petroleum ether); IR ($CHCl_3$) 1730 (C=O), 1695 cm^{-1} (O—C=C); ^1H NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 6 Hz, C(3) CH_3), 1.07 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.10 (d, 3 H, J = 7 Hz, α-CH_3), 1.58 (br s, 3 H, C(9) CH_3), 1.70–2.84 (br m, 10 H), 3.57 (s, 3 H, OCH_3), 4.31 (dd, 1 H, J = 3 Hz, J' = 11 Hz, C(2) H); $[\alpha]^{25}_D$ +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 spiro ketal **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); ^1H NMR ($CDCl_3$; for spiro ketal **16b**) δ 1.60 (br s, 3 H, C(9) CH_3), 3.67 (s, 3 H, OCH_3), 3.83 (dd, 1 H, J = J' = 7 Hz, C(2) H); ^1H NMR ($CDCl_3$; for regioisomers **16c**) δ 1.27 (s, 3 H, C(6) CH_3) 3.67 (s, 3 H, 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 [2*S*-[2α(*S),3β]]-α,3-Dimethyl-6-methylene-5-oxotetrahydro-2*H*-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



i



ii

of a 51 mg portion of this solid from n-pentane provided 27 mg of analytically pure dimer i as large colorless prisims: mp 103–104 °C; R_f 0.21 (silica gel, 1:2 ether/petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.96 and 0.98 (2 d, 6 H, J = 6 Hz, C(3) CH_3), 1.10 and 1.14 (2 d, 6 H, J = 7 Hz, α-CH_3), 1.67–2.90 (br m, 12 H), 3.64 and 3.68 (2 s, 6 H, OCH_3), 3.79 (dd, 1 H, J = 4 Hz, J' = Hz, C(2) H in fused ring portion), 4.29 (dd, 1 H, J = 4 Hz, J' = 10 Hz, C(2) H in spiro ketal portion); $[\alpha]^{25}_D$ +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: mp 97–97.2 °C; R_f 0.15 (silica gel, 1:2 ether/petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.98 (d, 6 H, J = 6 Hz, C(3) CH_3), 1.16 and 1.24 (2 d, 6 H, J = 7 Hz, α-CH_3), 1.73–2.97 (br m, 12 H), 3.68 (s, 6 H, OCH_3), 3.77 (m, 1 H, C(2) H in fused ring portion), 3.83 (dd, 1 H, J = J' = 7 Hz, C(2) H in spiro ketal portion); $[\alpha]^{25}_D$ +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 [2*S*-[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 methyltriphenylphosphonium bromide in 1.5 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 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 room temperature, 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: mp 50–50.5 °C; R_f 0.22 (silica gel, 1:10 ether/petroleum ether); IR ($CHCl_3$) 1735 (C=O), 1690 cm^{-1} (O—C=C); ^1H NMR ($CDCl_3$) δ 0.88 (d, 3 H, J = 7 Hz, C(3) CH_3), 1.07 (d, 3 H, J = 7 Hz, α-CH_3), 1.54 (br s, 3 H, C(9) CH_3), 1.67–2.37 (br m, 7 H), 2.63 (dq, 1 H, J = 3 Hz, J' = 7 Hz, α-H), 3.57 (s, 3 H, OCH_3), 3.97 (dd, 1 H, J = 3 Hz, J' = 10 Hz, C(2) H), 4.80 and 4.88 (2 br s, 2 H, C=CH_2), 5.98 (br s, 1 H, C(8) H); $[\alpha]^{23}_D$ +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 [2*S*-[2α(*S),3β,5β,6β]]-α,3,5,9-Tetramethyl-1,7-dioxaspiro[5.5]undec-8-ene-2-acetate (18a) and Methyl [2*S*-[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 room temperature 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 o8.5 mg (98%) of a 55:45 (by NMR) mixture of the enol ethers **18a** and **18b** as a white solid: mp 79–93 °C; R_f 0.13 (silica gel, 1:20 ether/petroleum ether); IR ($CHCl_3$) 1735 (C=O), 1685 cm^{-1} (C—C=C); ^1H NMR ($CDCl_3$) δ 0.79–1.04 (br m, 6 H, C(3) CH_3 and C(5) CH_3), 1.08 and 1.11 (2 d, 3 H, J = 7 Hz, α-CH_3 of β and α isomers, respectively), 1.52 (br s, 3 H, C(9) CH_3), 1.30–2.20 (br m, 8 H), 2.64 (dq, 1 H, J = 3 Hz, J' = 7 Hz, α-H), 3.56 (s, 3 H, OCH_3), 3.77 and 3.80 (2 dd, 1 H, J = 3 Hz, J' = 10 Hz, C(2) H), 5.97 (br s, 1 H, 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 [2*S*-[2α(*S),3β,5β,6β(*R**)]]-α,3,5,9-Tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (19a) and Methyl [2*S*-[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 ether **18a** and **18b** in 4 mL of methanol was hydrogenated under a hydrogen atmosphere (50 psi; Parr apparatus) at room temperature 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 spiro ketal **19a** as a white solid: mp 71–72 °C; R_f 0.16 (silica gel, 1:20 ether/petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); 500-MHz ^1H NMR ($CDCl_3$) δ 0.75 (d, 3 H, J = 7 Hz, C(9) CH_3), 0.83 (d, 3 H, J = 7 Hz, C(3) CH_3), 0.88 (d, 3 H, J = 7 Hz, C(5) CH_3), 1.13 (d, 3 H, J = 7 Hz, α-CH_3), 1.34–1.75 (br m, 9 H), 2.71 (dq, 1 H, J = 3.5 Hz, J' = 7 Hz, α-H), 3.10 (dd, 1 H, J = J' = 11 Hz, axial C(8) H), 3.42 (ddd, 1 H, J = 2 Hz, J' = 4.5 Hz, J'' = 11 Hz, equatorial C(8) H), 3.69 (s, 3 H, OCH_3), 3.74 (dd, 1 H, J = 3.5 Hz, J' = 10.5 Hz, C(2) H); $[\alpha]^{25}_D$ +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 spiro ketal **19b** as a white solid: mp 89–90 °C; R_f 0.10 (silica gel, 1:20 ether/petroleum ether); IR ($CHCl_3$) 1735 cm^{-1} (C=O); 500-MHz ^1H NMR ($CDCl_3$) δ 0.76 (d, 3 H, J = 7 Hz, C(9) CH_3), 0.81 (d, 3 H, J = 7 Hz, C(3) CH_3), 0.97 (d, 3 H, J = 7 Hz, C(5) CH_3), 1.16 (d, 3 H, J = 7 Hz, α-CH_3), 1.24–1.74 (br m, 8 H), 1.89 (ddd, 1 H, J = 5 Hz, J' = J'' = 13 Hz, axial C(11) H), 2.72 (dq, 1 H, J = 3.5 Hz, J' = 7 Hz, α-H), 3.11 (dd, 1 H, J = J' = 11 Hz, axial C(8) H), 3.45 (ddd, 1 H, J = 2 Hz, J' = 4.5 Hz, J'' = 11 Hz, equatorial C(8) H), 3.69 (s, 3 H, OCH_3), 3.77 (dd, 1 H, J = 3.5 Hz, J' = 10.5 Hz, C(2) H); $[\alpha]^{25}_D$ +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 Spiro Ketal 19b. The spiro ketal **19b** (5.8 mg, 0.025 mmol) was treated with 2 mL of dry dichloromethane saturated with p-toluenesulfonic acid monohydrate under an argon atmosphere for 2 days at room temperature. 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 spiro ketals **19a** and **19b** in a 70:30 ratio, respectively. These spiro ketals were identical (^1H NMR, TLC) to those prepared above by hydrogenation.

Methyl [2*R*-(2*R,3*S**,4*S**,6*S**,11*S**)]-3,11-Dihydroxy-7-(hydroxyimino)-2,4,6-trimethyltridecanoate (24).** A solution of 8.5 mg (0.0285 mmol) of the spiro ketal **23**, 128 mg (1.85 mmol) of NH_2OH·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 of 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 ^1H 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), 0.25 (minor isomer) (silica gel, 4:1 ether/ethyl acetate); IR ($CHCl_3$) 3340 (OH), 1725 (C=O), 1650 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 0.80–1.02 (br m, 6 H, C(4) CH_3 and C(13) H_3), 1.06 (d, 3 H, J = 7 Hz, C(6) CH_3), 1.15 (d, 3 H, J = 7 Hz, C(2) CH_3), 1.33–1.83 (br m, 10 H), 2.12–2.53 (br m, 4 H, C(6) H, C(8) H_2 and OH), 2.64 (dq, 1 H, J = 3 Hz, J' = 7 Hz, C(2) H), 3.39–3.64 (br m, 2 H, C(3) H and C(11) H), 3.64 (s, 3 H, 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 [2*R*-(2*R,3*S**,4*S**,6*S**,10*S**)]-3,11-Dihydroxy-7-(hydroxyimino)-2,4,6,10-tetramethylundecanoate (25).** A solution of 8.2 mg (0.0288 mmol) of the spiro ketal **19b**, 128 mg (1.85 mmol) of NH_2OH·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 spiro ketal **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 ^1H 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), 0.17 (minor isomer) (silica gel, 4:1 ether/ethyl acetate); IR ($CHCl_3$) 3340 (OH), 1725 (C=O), 1650 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 0.85 and 0.97 (2 d, 6 H, J = 6 Hz, C(4) CH_3 and C(10) CH_3), 1.07 (d, 3 H, J = 7 Hz, C(6) CH_3), 1.16 (d, 3 H, J = 7 Hz, C(2) CH_3), 1.33–1.87 (br m, 7 H), 2.13–2.60 (br m, 4 H, C(6) H, C(8) H_2, and OH), 2.65 (dq, 1 H, J = 4 Hz, J' = 7 Hz, C(2) H), 3.46–3.66 (br m, 3 H, C(3) H and C(11) H_2), 3.66 (s, 3 H, 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 [2*R*-(2*R,3*S**,4*S**,6*S**,11*S**)]-3,11-Dihydroxy-2,4,6-trimethyl-7-oxotridecanoate, 1,2-Ethanediyl Dithioketal Derivative (26).** To a vigorously stirred solution of 12.6 mg (0.0422 mmol) of the spiro ketal **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 boron trifluoride 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 room temperature. 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), 1725 cm^{-1} (C=O); 500-MHz ^1H NMR ($CDCl_3$) δ 0.86 (d, 3 H, J = 6 Hz, C(4) CH_3), 0.95 (t, 3 H, J = 7 Hz, C(13) H_3), 1.08 (d, 3 H, J = 6.5 Hz, C(6) CH_3), 1.19 (d, 3 H, J = 7 Hz, C(2) CH_3), 1.40–1.75 (br m, 10 H), 1.87–2.03 (br m, 3 H, C(6) H and C(8) H_2), 2.51 (br d, 1 H, J = 4 Hz, OH), 2.71 (dq, 1 H, J = 3.5 Hz, J' = 7 Hz, C(2) H), 3.23 (br m, 4 H, thioketal), 3.55 and 3.64 (2 br m, 2 H, C(3) H and C(11) H), 3.71 (s, 3 H, OCH_3); $[\alpha]^{25}_D$ −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 [2*R*-(2*R,3*S**,4*S**,6*S**,11*S**)]-3,11-Dihydroxy-2,4,6-trimethyl-7-oxotridecanoate, 1,3-Propanediyl Dithioketal Derivative (27).** To a vigorously stirred solution of 11.3 mg (0.0379 mmol) of the sipro ketal **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 boron trifluoride 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 room temperature. 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 spiro ketals 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), 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.88 (d, 3 H, J = 6 Hz, C(4) CH_3), 0.94 (t, 3 H, J = 7 Hz, C(13) H_3), 1.07 (d, 3 H, J = 7 Hz, C(6) CH_3), 1.19 (d, 3 H, J = 7 Hz, C(2) CH_3), 1.37–2.03 (br m, 15 H), 2.42 (br m, 1 H, OH), 2.57–2.85 (br m, 5 H, C(2) H and SCH_2), 3.61 (br m, 2 H, C(3) H and C(11) H), 3.67 (s, 3 H, OCH_3); $[\alpha]^{25}_D$ −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 [2*R*-(2*R,3*S**,4*S**,6*R**,10*S**)]-3,11-Dihydroxy-2,4,6,10-tetramethyl-7-oxoundecanoate, 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 spiro ketal **19a** in 0.30 mL (340 mg, 3.6 mmol) of 1,2-ethanedithiol and 0.037 mL (42 mg, 0.30 mmol) of boron trifluoride etherate afforded, after 4 h at −40 °C, a 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), 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.89 and 0.93 (2 d, 6 H, J = 6 Hz, C(4) CH_3 and C(10) CH_3), 1.13 (d, 3 H, J = 6 Hz, C(6) CH_3), 1.15 (d, 3 H, J = 7 Hz, C(2) CH_3), 1.37–2.20 (br m, 10 H), 2.65 (dq, 1 H, J = 3 Hz, J' = 7 Hz, C(2) H), 2.76 (br m, 1 H, OH), 3.21 (s, 4 H, thioketal), 3.46 (br d, 2 H, J = 5 Hz, C(11) H_2), 3.67 (s, 3 H, OCH_3), 3.72 (br m, 1 H, C(3) H); $[\alpha]^{25}_D$ +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 [2*R*-(2*R,3*S**,4*S**,6*S**,10*S**)]-3,11-Dihydroxy-2,4,6,10-tetramethyl-7-oxoundecanoate, 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 spiro ketal **19b** in 0.29 mL (320 mg, 3.4 mmol) of 1,2-ethanedithiol and 0.036 mL (40 mg, 0.28 mmol) of boron trifluoride etherate afforded, after 3 h at −40 °C, a 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), 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.86 and 0.92 (2 d, 6 H, J = 6 Hz, C(4) CH_3, and C(10) CH_3), 1.07 (d, 3 H, J = 6 Hz, C(6) CH_3), 1.18 (d, 3 H, J = 7 Hz, C(2) CH_3), 1.42–2.05 (br m, 10 H), 2.53 (br m, 1 H, OH), 2.68 (dq, 1 H, J = 4 Hz, J' = 7 Hz, C(2) H), 3.20 (s, 4 H, thioketal), 3.46 (br d, 2 H, J = 5 Hz, C(11) H_2), 3.58 (br m, 1 H, C(3) H), 3.67 (s, 3 H, OCH_3); $[\alpha]^{25}_D$ −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 [2*R*-(2*R,3*S**,4*S**,6*R**,10*S**)]-3,11-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6,10-tetramethyl-7-oxoundecanoate, 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 di-

methylformamide (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); ^1H NMR ($CDCl_3$) δ 0.03 (s, 12 H, $Si(CH_3)_2$), 0.91 (s, 18 H, $SiC(CH_3)_3$), 0.87–1.00 (2 d, 6 H, C(4) CH_3 and C(10) CH_3), 1.09 (d, 3 H, J = 7 Hz, C(6) CH_3), 1.15 (d, 3 H, J = 7 Hz, C(2) CH_3), 1.40–2.05 (br m, 9 H), 2.68 (dq, 1 H, J = 4.5 Hz, J' = 7 Hz, C(2) H), 3.19 (s, 4 H, thioketal), 3.38 and 3.41 (2 d, 2 H, J = 6 Hz, C(11) H_2), 3.63 (s, 3 H, OCH_3), 3.99 (dd, 1 H, $J = J'$ = 4.5 Hz, C(3) H); $[\alpha]^{24}_D$ +13.3° ($CHCl_3$, c 1.16); mass spectrum, calcd for $C_{30}H_{62}O_4S_2Si_2$ ($M^+ - CH_3$) m/e 591.3393, found ($M^+ - CH_3$) m/e 591.3379.

Methyl [2*R*-(2*R,3*S**,4*S**,6*S**,10*S**)]-3,11-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6,10-tetramethyl-7-oxoundecanoate, 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 for 18 h at 80 °C afforded, after the 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); ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$), 0.90 (br m, 24 H, C(4) CH_3, C(10) CH_3, and $SiC(CH_3)_3$), 1.02 (d, 3 H, J = 7 Hz, C(6) CH_3), 1.14 (d, 3 H, J = 7 Hz, C(2) CH_3), 1.33–2.00 (br m, 9 H), 2.63 (dq, 1 H, J = 6 Hz, J' = 7 Hz, C(2) H), 3.18 (s, 4 H, thioketal), 3.39 (d, 2 H, J = 5 Hz, C(11) H_2), 3.63 (s, 3 H, OCH_3), 3.80 (dd, 1 H, J = 4 Hz, J' = 6 Hz, C(3) H); $[\alpha]^{24}_D$ -23.7° ($CHCl_3$, c 1.14); mass spectrum, calcd for $C_{30}H_{62}O_4S_2Si_2$: ($M^+ - CH_3$) m/e 591.3393, found ($M^+ - CH_3$) m/e 591.3379.

Methyl [2*R*-(2*R,3*S**,4*S**,6*R**,10*S**)]-3,11-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6,10-tetramethyl-7-oxoundecanoate (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 atmosphere were 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 room temperature, 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), 1710 cm^{-1} (ketone C=O); ^1H NMR ($CDCl_3$) δ 0.03 (s, 12 H, $Si(CH_3)_2$), 0.89 (br m, 24 H, C(4) CH_3, C(10) CH_3, and $SiC(CH_3)_3$), 1.06 (d, 3 H, J = 7 Hz, C(6) CH_3), 1.12 (d, 3 H, J = 7 Hz, C(2) CH_3), 1.37–1.93 (br m, 6 H), 2.33–2.73 (br m, 4 H, C(2) H, C(6) H, and C(8) H_2), 3.38 (d, 2 H, J = 5 Hz, C(11) H_2), 3.62 (s, 3 H, OCH_3), 3.81 (dd, 1 H, J = 4 Hz, J' = 6 Hz, C(3) H); $[\alpha]^{25}_D$ +2.4° ($CHCl_3$, c 1.22); mass spectrum, calcd for $C_{28}H_{58}O_5Si_2$ ($M^+ - CH_3$) m/e 515.3588, found ($M^+ - CH_3$) m/e 515.3530.

Methyl [2*R*-(2*R,3*S**,4*S**,6*S**,10*S**)]-3,11-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6,10-tetramethyl-7-oxoundecanoate (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 room temperature, a 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), 1710 cm^{-1} (ketone (C=O); ^1H NMR ($CDCl_3$) δ 0.03 (s, 12 H, $Si(CH_3)_2$), 0.90 (br m, 24 H, C(4) CH_3, C(10) CH_3, and $SiC(CH_3)_3$), 1.00 (d, 3 H, J = 7 Hz, C(6) CH_3), 1.13 (d, 3 H, J = 7 Hz, C(2) CH_3), 1.30–1.72 (br m, 6 H), 2.36–2.72 (br m, 4 H, C(2) H, C(6) H, C(8) H_2), 3.37 (d, 2 H, J = 5 Hz, C(11) H_2), 3.62 (s, 3 H, OCH_3), 3.81 (dd, 1 H, J = 4 Hz, J' = 6 Hz, C(3) H); $[\alpha]^{25}_D$ -1.7° ($CHCl_3$, c 1.65); mass spectrum, calcd for $C_{28}H_{58}O_5Si_2$ ($M^+ - CH_3$) m/e 515.3588, found ($M^+ - CH_3$) m/e 515.3582.

Methyl [2*S*-[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: mp 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), 1665 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.88 (d, 3 H, J = 7 Hz, C(3) CH_3), 1.06 (d, 3 H, J = 7 Hz, α-CH_3), 1.07 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.58 (br s, 3 Hz, C(9) CH_3), 1.65–2.45 (br m, 9 H), 2.62 (dq, 1 H, J = 4 Hz, J' = 7 Hz, α-H), 3.55 (s, 3 H, OCH_3), 3.99 (dd, 1 H, J = 4 Hz, J' = 10 Hz, C(2) H), 4.78 and 4.86 (2 br s, 2 H, $C=CH_2$); $[\alpha]^{20}_D$ +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 [2*S*-[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 [2*S*-[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 atomsphere (H_2-filled balloon) in the presence of a catalytic amount of powdered platinum oxide at room temperature for 1 h. 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), 1695 cm^{-1} (C—C=C); ^1H NMR ($CDCl_3$) δ 0.78–1.13 (br m, 9 H, overlapping C(3) CH_3, C(5) CH_3, and CH_2CH_3), 1.07 and 1.10 (2 d, 3 H, J = 7 Hz, α-CH_3 of β and α isomers, respectively), 1.55 (br s, 3 H, C(9) CH_3), 1.41–2.12 (br m, 8 H), 2.12 (q, 2 H, J = 7 Hz, CH_2CH_3), 2.61 (dq, 1 H, J = 4 Hz, J' = 7 Hz, α-H), 3.52 (s, 3 H, OCH_3), 3.79 and 3.83 (2 dd, 1 H, 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 [2*S*-[2α(*S),3β,5β,6α(*R**)]]-α,3,5-Trimethyl-6-(3-methyl-4-oxohexyl)tetrahydro-2*H*-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 room temperature 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 ^1H 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), 1710 cm^{-1} (ketone C=O); 500-MHz ^1H NMR ($CDCl_3$) (5β isomer **36a**) δ 0.76 (d, 3 H, J = 6.5 Hz, C(5) CH_3), 0.80 (d, 3 H, J = 6.5 Hz, C(3) CH_3), 1.03 (d, 3 H, J = 7 Hz, C(6)–(C(3)–CH_3)), 1.04 (t, 3 Hz, J = 7 Hz, CH_2CH_3), 1.11 (d, 3 H, J = 7 Hz, α-CH_3), 1.28–1.73 (br m, 8 H), 2.40–2.55 (br m, 3 H), 2.68 (dq, 1 H, 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, 3 H, OCH_3); 500-MHz ^1H NMR ($CDCl_3$) (5α isomer **36b**) δ 0.77 (d, 3 H, J = 6.5 Hz, C(3) CH_3), 0.87 (d, 3 H, J = 7 Hz, C(5) CH_3), 1.03 (d, 3 H, J = 7 Hz, C(6)–(C(3)–CH_3)), 1.04 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.14 (d, 3 H, J = 7 Hz, α-CH_3), 1.28–1.73 (br m, 8 H), 2.40–2.55 (br m, 3 H), 2.68 (dq, 1 H, J = 3 Hz, J' = 7 Hz, α-H), 3.25 (ddd, 1 H, 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, 3 H, 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 ^1H NMR, and these products were identical (TLC, 500-MHz ^1H NMR) with those obtained below by methanolysis of the enol ethers **29a** and **29b**.

Methyl [2*S*-[2α(*S),3β,5β,6β,6(*R**)]]-6-Methoxy-α,3,5-trimethyl-6-(3-methyl-4-oxohexyl)tetrahydro-2*H*-pyran-2-acetate (37a) and Methyl [2*S*-[2α(*S**),3β,5α,6β,6(*R**)]]-6-Methoxy-α,3,5-trimethyl-6-(3-methyl-4-oxohexyl)tetrahydro-2*H*-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 room temperature for 40 min. The reaction was then quenched by the addition of 1 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), 1710 cm^{-1} (ketone C=O); 500-MHz ^1H NMR ($CDCl_3$) δ 0.82 (2 d, 6 H, J = 7 Hz, C(3) CH_3 and C(5) CH_3), 1.05 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.07 (d, 3 H, J = 7 Hz, C(6)-(C-(3)-CH_3)), 1.11 (d, 3 H, J = 7 Hz, α-CH_3), 1.30–1.75 (br m, 8 H), 2.47 (q, 2 H, J = 7 Hz, CH_2CH_3), 2.50 (br m, 1 H, C(6)-(C(3)-H)), 2.68 (dq, 1 H, J = 3 Hz, J' = 7 Hz, α-H), 3.08 (s, 3 H, OCH_3), 3.66 (s, 3 H, CO_2CH_3), 3.73 (dd, 1 H, J = 3 Hz, J' = 10 Hz, C(2) H); $[\alpha]^{24}_D$ +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), 1710 cm^{-1} (ketone C=O); 500-MHz ^1H NMR ($CDCl_3$) δ 0.79 (d, 3 Hz, J = 6.5 Hz, C(3) CH_3), 0.97 (d, 3 H, J = 7 Hz, C(5) CH_3), 1.04 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.08 (d, 3 H, J = 7 Hz, C(6)-(C(3)-CH_3)), 1.13 (d, 3 H, J = 7 Hz, α-CH_3), 1.25–1.85 (br m, 8 H), 2.38–2.54 (br m, 3 H), 2.68 (dq, 1 H, J = 3 Hz, J' = 7 Hz, α-H), 3.07 (s, 3 H, OCH_3), 3.67 (s, 3 H, CO_2CH_3), 3.73 (dd, 1 H, J = 3 Hz, J' = 10 Hz, C(2) H); $[\alpha]^{24}_D$ +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 [2*S*-[2α(*S),3β,5β,6β(8*R**,9*S**)]]-8-Ethyl-9-hydroxy-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (30a) and Methyl [2*S*-[2α(*S**),3β,5α,6β(8*R**,9*S**)]]-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 2.b 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 room temperature for 40 min, was diluted wiith 5 mL of water, and was 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), 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.76–1.13 (br m, 15 H, 5 overlapping CH_3 groups), 1.2702.20 (br m, 11 H), 2.63 (dq, 1 H, 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 (2 s, 3 H, OCH_3 of 5α and 5β isomers, respectively), 3.88 and 4.07 (2 dd, 1 H, 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 [2*R*-(2*R,3*S**,4*S**,6*R**,10*R**,11*S**)]-3,10,11-Trihydroxy-2,4,6,10-tetramethyl-7-oxotridecanoate, Acetonide and 1,2-Ethanediyl Dithioketal Derivative (31a), and Methyl [2*R*-(2*R**,3*S**,4*S**,6*S**,10*R**,11*S**)]-3,10,11-Trihydroxy-2,4,6,10-tetramethyl-7-oxotridecanoate, 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 spiro ketals **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 boron trifluoride etherate afforded, after 4 h at −40 °C and a 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), 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.76–1.13 (br m, 9 Hz, C(4) CH_3, C(6) CH_3, and C(13) H_3), 1.14 (s, 3 H, C(10) CH_3), 1.15 and 1.18 (2 d, 3 H, J = 7 Hz, C(2) CH_3 of the 6*R** and 6*S** isomers, respectively), 1.42–2.83 (br m, 14 H), 3.21 (s, 4 H, thioketal), 3.30 (br m, 1 H, C(11) H), 3.64 (br m, 1 H, C(3) H), 3.68 (s, 3 H, 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 room temperature 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 ^1H NMR) mixture of the acetonides **31a** and **31b** as a colorless oil. Distillation [Kugelrohr, 160 °C (0.001 mmGh)] of this oil provided the analytical sample: R_f 0.15 (6*R** isomer), 0.11 (6*S** isomer) (silica gel, 1:2 ether/petroleum ether); IR ($CHCl_3$) 3500 (OH), 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.85–1.18 (br m, 12 H, C(2) CH_3, C(4) CH_3, C(6) CH_3, and C(13) H_3), 1.20 (s, 3 H, C(10) CH_3), 1.33 and 1.44 (2 s, 6 H, acetonide), 1.44–2.37 (br m, 10 H), 2.64 (br m, 2 H, C(2) H and OH), 3.18 (s, 4 H, thioketal), 3.61 (br m, 2 H, C(3) H and C(11) H), 3.67 (s, 3 H, 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 [2*S*-[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 mixutre of the spiro ketal **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 etther/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), 1660 cm^{-1} (C=CH_2); ^1H NMR ($CDCl_3$) δ 0.89 (d, 3 H, J = 6 Hz, C(3) CH_3), 1.02 (t, 3 H, J = 7 Hz, CH_2CH_3) 1.13 (d, 3 H, J = 7 Hz, α-CH_3), 1.57 (br s, 3 H, C(9) CH_3), 1.47–2.57 (br m, 9 H), 2.71 (dq, 1 H, J = 5 Hz, J' = 7 Hz, α-H), 3.62 (s, 3 H, OCH_3), 3.73 (dd, J = 5 Hz, J' = 8 Hz, C(2) H), 4.79 and 5.07 (2 br s, 2 H, C=CH_2); $[\alpha]^{20}_D$ −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); ^1H NMR ($CDCl_3$) δ 0.98 (d, 3 H, J = 7 Hz, C(3) CH_3), 1.02 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.15 (d, 3 H, J = 7 Hz, α-CH_3), 1.27 (s, 3 H, C(6) CH_3), 1.53–2.90 (br m, 10 H), 3.66 (s, 3 H, OCH_3), 3.75 (m, 1 H, 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 [2*S*-[2α(3*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 [2*S*-[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 atmosphere (H_2-filled balloon) in the presence of a catalytic amount of powdered platinum oxide at room temperature 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. Concentration 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.

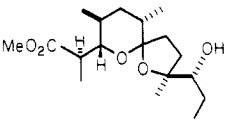
Chromatography, with significant decomposition of the enol ethers, on 10 g of silica gel with 1:30 ethyl acetate/petroleum ether afforded first 21.6 mg (65%) of the enol ether **33** as a colorless oil. Distillation [Kugelrohr, 80 °C (0.003 mmHg)] of a portion

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), 1700 cm^{-1} (O—C=C); ^1H NMR ($CDCl_3$) δ 0.96 (2 d, 6 H, J = 7 Hz, C(3) CH_3 and C(5) CH_3), 1.08 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.12 (d, 3 H, J = 7 Hz, α-CH_3), 1.57 (br s, 3 H, C(9) CH_3), 1.40–2.27 (br m, 10 H), 2.88 (dq, 1 H, $J = J'$ = 7 Hz, α-H), 3.60 (dd, 1 H, $J = J'$ = 7 Hz, C(2) H), 3.63 (s, 3 H, OCH_3); $[\alpha]^{23}_D$ -46.1° ($CHCl_3$, c 1.29); mass spectrum, calcd for $C_{18}H_{30}O_4$ (M^+) m/e 310.2144; found (M^+) m/e 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), 1700 cm^{-1} (O—C=C); ^1H NMR ($CDCl_3$) δ 0.81 (d, 3 H, J = 6 Hz, C(5) CH_3), 0.85 (d, 3 H, J = 6.5 Hz, C(3) CH_3), 0.97 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.12 (d, 3 H, J = 7 Hz, α-CH_3), 1.54 (br s, 3 H, C(9) CH_3), 1.43–2.14 (br m, 10 H), 2.61 (dq, 1 H, J = 3.5 Hz, J' = 7 Hz, α-H), 3.59 (dd, 1 H, J = 3.5 Hz, J' = 9.5 Hz, C(2) H), 3.62 (s, 3 H, OCH_3); $[\alpha]^{23}_D$ -24.8° ($CHCl_3$, c 0.33).

Methyl [2*S*-[2α(*S),3β,5α,6α(8*S**,9*R**)]]-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 with 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 room temperature and chromatography on 7 g of silica gel with 1:1 ether/petroleum ether, 12.0 mg (84%) of the alcohol **3** as a colorless oil: R_f 0.12 (silica gel, 1:1 ether/petroleum ether); IR ($CHCl_3$) 3600 ($CDCl_3$) δ 0.79 (d, 3 H, J = 6 Hz, C(3) CH_3), 1.01 (t, 3 H, J = M Hz, CH_2CH_3), 1.05 (d, 3 H, J = 7 Hz, C(5) CH_3), 1.10 (s, 3 H, C(9) CH_3), 1.18 (d, 3 H, J = 7 Hz, α-CH_3), 1.35–2.17 (br m, 11 H), 2.61 (dq, 1 H, J = 3 Hz, J' = 7 Hz, α-H), 3.32 (dd, 1 H, J = 4 Hz, J' = 11 Hz, C(6) H), 3.67 (s, 3 H, OCH_3), 3.71 (dd, 1 H, J = 3 Hz, J' = 10 Hz, C(2) H); $[\alpha]^{23}_D$ +69.3° ($CHCl_3$, c 1.16); mass spectrum, calcd for $C_{18}H_{32}O_5$ (M^+) m/e 328.2250, found (M^+) m/e 328.2280.

Methyl [2*S*-[2α(*S),3β,5α,6β(8*S**,9*R**)]]-8-Ethyl-9-hydroxy-α,3,5,9-tetramethyl-1,7-dioxaspiro[5.5]undecane-2-acetate (35) and Methyl [5*R*-[5α[2*S**(*R**)],7β(*R**),8α,10β]]- and [5*S*-[5α[2*R**(*S**)],7α(*S**),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 room temperature, 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 spiro ketals iii as a 71:29 (by ^1H NMR) mixture of spiro



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isomers: R_f 0.39 (minor isomer), 0.30 (major isomer) (silica gel, 1:1 ether/petroleum ether); IR ($CHCl_3$) 3500 (OH), 1735 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.75–1.18 (br m, 15 H, 5 overlapping CH_3 groups), 1.27–2.08 (br m, 11 H), 2.67 (br m, 1 H, α-H), 3.31 (br m, 1 H, >CHOH), 3.61 and 3.71 (2 s, 3 H, OCH_3 of major and minor isomers, respectively), 3.93 (br m, 1 H, C(7) H); mass spectrum, calcd for $C_{18}H_{32}O_5$ (M^+) m/e 328.2250, found (M^+) m/e 328.2224.

There was then eluted 3.7 mg (53%) of the spiro ketal **35** as a white solid: mp 91–93 °C; R_f 0.13 (silica gel, 1:1 ether/petroleum ether); IR ($CHCl_3$) 3620 (free OH), 3500 (H-bonded OH), 1735 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.80 (d, 3 H, J = 6 Hz, C(3) CH_3), 0.95 (d, 3 H, J = 7 Hz, C(5) CH_3), 1.10 (s, 3 H, C(9) CH_3), 1.11 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.14 (d, 3 H, J = 7 Hz, α-CH_3), 1.26–1.97 (br m, 11 H), 2.69 (dq, 1 H, J = 3 Hz, J' = 7 Hz, α-H), 3.18 (dd, 1 H, J = 2 Hz, J' = 10 Hz, C(8) H), 3.67 (s, 3 H, OCH_3), 3.77 (dd, 1 H, J = 3 Hz, J' = 10 Hz, C(2) H); $[\alpha]^{24}_D$ +77.8° ($CHCl_3$, c 0.36); mass spectrum, calcd for $C_{18}H_{32}O_5$ (M^+) m/e 328.2250, found (M^+) m/e 328.2261.

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

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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 spiro ketal derivatives prepared by hetero-Diels–Alder condensation to the key intermediate spiro ketals **14** and **15** which possess all of the stereochemistry for the natural products. Thioketal exchange then provided the desired open-chain seco-acid derivatives.

In the preceding report,[2] new methods were presented for the synthesis of spiro ketals through hetero-Diels–Alder condensation and the cleavage of these spiro ketals to open-chain derivatives that are potentially useful for the synthesis of macrolide antibiotics. This report covers the

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