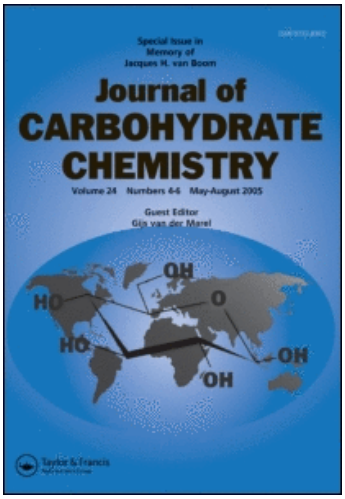


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# Intramolecular Radical, Knoevenagel, or $S_N2'$ Cyclization of Carbohydrate Derivatives for Access to Enantiomerically Pure 2-Oxospiroalkanes

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# INTRAMOLECULAR RADICAL, KNOEVENAGEL, OR $S_N2'$ CYCLIZATION OF CARBOHYDRATE DERIVATIVES FOR ACCESS TO ENANTIOMERICALLY PURE 2-OXOSPIROALKANES

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## ABSTRACT

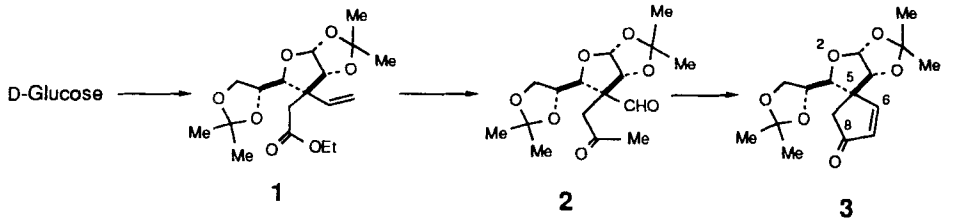
Intramolecular radical cyclization of D-glucose-derived substrate, (2*R*,3*R*,4*R*,5*S*)-2, 3-(isopropylidenedioxy)-5-[(1*R*)-1, 2-(isopropylidenedioxy)ethyl]-4-[3-bromo-3, 3-bis(methoxycarbonyl)propyl]-4-vinyltetrahydrofuran, **7** proceeded in a 6-*endo-trig* mode to give a derivative of 2-oxaspiro[4.5]decane **8** exclusively. Intramolecular Knoevenagel-like reaction of substrate **9** afforded derivatives of 2-oxaspiro-[4.4]nonane **10** as a 3:1 diastereomeric mixture. Intramolecular $S_N2'$ displacement of substrate **22** proceeded highly stereoselectively giving a derivative of 2-oxaspiro-[4.4]decane **23**.

## INTRODUCTION

Construction of carbocycles possessing a spiro carbon is one of the formidable subjects in current organic synthesis. As solutions for this particular requirement, a number of methodologies have been developed so far,[1] especially in the context of the sesquiterpenes synthesis.[2] Several years ago, we reported a concise synthetic approach to the enantiomerically pure 2-oxaspiro[4.4]nonane skeleton from D-glucose. Our approach[3] is summarized in Scheme 1. The versatile building block **1**,[4] which was readily obtained from D-glucose,[5] was efficiently converted into **2**, the substrate

for an intramolecular aldol condensation. The base-catalyzed intramolecular aldol condensation of **2** proceeded smoothly to give a derivative of 2-oxaspiro[4.4]non-6-en-8-one **3**, in which C-5 is a spiro carbon having four differentially functionalizable carbon substituents.

As part of our ongoing interest in these areas, we describe herein other enantiospecific approaches to derivatives of 2-oxaspiro[4.4]nonane and 2-oxaspiro-[4.5]decane. The present approaches also utilize **1** as a starting material.




**1** **2** **3**

**Scheme 1**

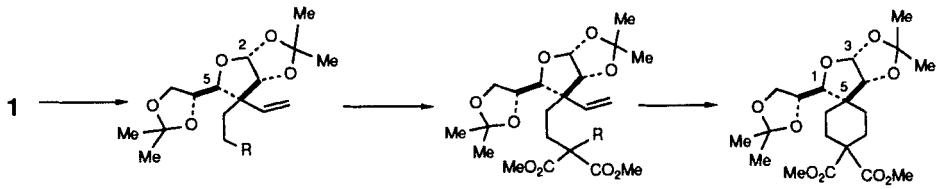


## RESULTS AND DISCUSSION

An extensively studied subject in current organic synthesis is free-radical intiated carbon-carbon bond forming reactions. Numerous examples, including stereoselective carbocyclizations, have been reported and are reviewed.[6] The carbohydrate-derived compounds also served as promising substrates for stereo-selective radical-mediated carbocyclizations.[7]

As our first approach, we investigated an intramolecular carbocyclization of a bromo-olefin **7** by means of the radical-mediated trapping process (Scheme 2). Two bond forming modes can be possible for the cyclization of **7**. When a radical generated at the carbon bearing two carbomethoxy groups attacks the double bond, five-membered carbocycle(s) can be formed in a 5-*exo-trig* cyclization mode[8] or a six-membered carbocycle can be formed in a 6-*endo-trig* mode.[8] Owing to that the reaction sites in **7** are disposed in a sterically crowded surrounding, we were interested in the possibility and regioselectivity of the cyclization.[9] The preparation of the substrate **7** was achieved from **1** as follows. $LiAlH_4$-reduction of **1** and subsequent displacement of the thus formed hydroxyl group in **4** with an iodo atom[10] provided the iodide **5**. Alkylation of **5** with dimethyl sodiomalonate in refluxing THF gave a diester **6** (96% yield for 3 steps). Substitution of the malonyl methine hydrogen in **6** by a bromo atom using *N*-bromosuccinimide (NBS) afforded the substrate **7** (86% yield). The cyclization of **7** was executed under standard radical-initiated conditions

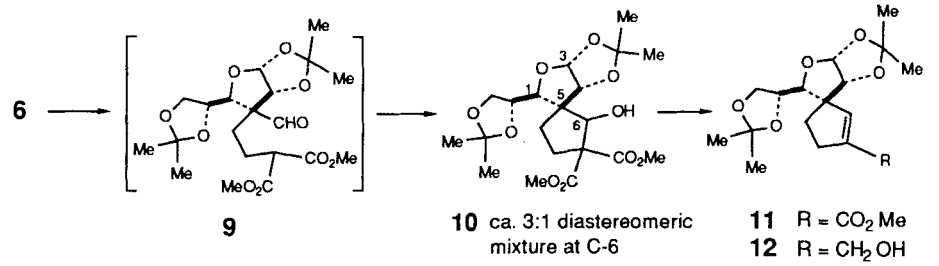
[$Bu_3SnH$ in refluxing benzene in the presence of 1,1'-azobis(isobutyronitrile) (AIBN) as a radical initiator]. As a result, a derivative of 2-oxaspiro[4.5]decane **8** was obtained as a single product in 72% yield. Neither the five-membered carbocycle(s) nor uncyclized reduction product **6** were detected. $^1H$ NMR analysis verified the structure of **8**, in which no doublet(s), due to a methyl substituent in an alternative five-membered carbocycle(s), appeared. The cyclization proceeded in the 6-*endo-trig* mode exclusively. Although we have no reasonable account for this exclusive formation of **8**, the cyclization product **8** may serve as an enantiomerically pure building block which possesses differentially functionalizable geminal *C*-substituents at the spiro position.




**Scheme 2**

We investigated next the intramolecular Knoevenagel-like cyclization of the substrate **9**, which was prepared by ozonolysis of **6** (Scheme 3). When the ozonolysis product was subjected to reductive workup with $Ph_3P$, cyclization of aldehyde **9** thus formed was observed to some extent. After this crude mixture was passed through a column of silica gel, the cyclization occurred completely giving two derivatives of 2-oxaspiro[4.4]nonanes **10** as an inseparable mixture in a combined yield of 85% from **6**.[11] The ratio of the diastereomers was estimated to be 3:1 based on $^1H$ NMR (270 MHz) analysis. Unfortunately, we could not determine unequivocally the configurations of the newly introduced stereogenic centers (C-6) in the mixture **10** by means of NOE experiments. The C-6 bearing a hydroxyl group is adjacent to two quaternary carbons (C-5 and 7). This structural characteristic made the unequivocal establishment of the configuration at C-6 quite difficult. We planned next introduction of a carbon functionality onto C-6 of **10**. Oxidation of **10** with DMSO-$Ac_2O$[12] afforded the corresponding cyclopentanone derivative smoothly. Unfortunately, Wittig olefination of the ketone carbonyl function with $Ph_3P$=CHCOOEt resulted in complete recovery of the starting material. Thermal

demethoxycarbonylation of **10** was then carried out. By heating **10** in an aqueous DMSO solution at 160 °C in the presence of NaCl,[13] α,β-unsaturated ester **11** was obtained in 80% yield. Under these conditions, β-elimination of the hydroxyl group also took place. To our disappointment, carbon nucleophiles (MeMgBr or $^-CH_2COOEt$) did not react with the β-carbon (C-6) of the unsaturated ester **11**, which was recovered entirely. Furthermore, hydroboration of allylic alcohol derivative **12**, prepared by diisobutylaluminum hydride (DIBAL-H) reduction of **11** in 96% yield, did not proceed. From these observations, it was concluded that carbon functionalization at C-6 was required prior to carbocyclic ring formation.

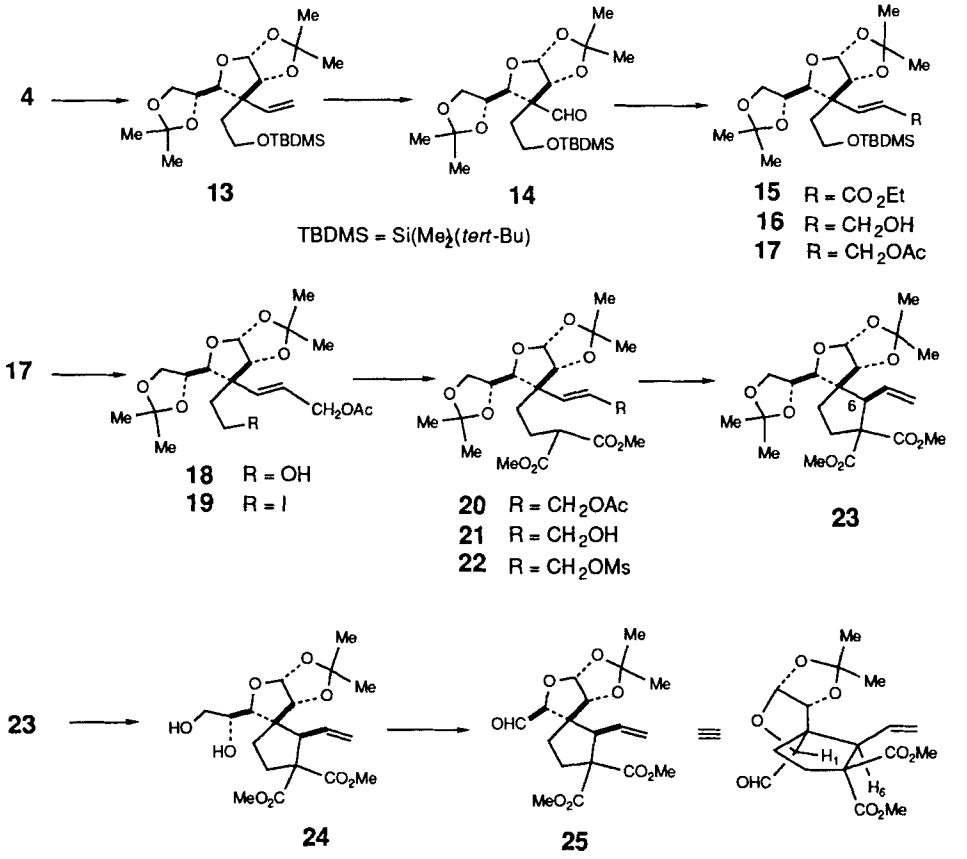



**Scheme 3**

To meet this requirement, we next investigated the intramolecular $S_N2'$ reaction of allylic mesylate **22** (Scheme 4). We anticipated that the anion generated at the malonyl methine carbon in **22** would attack the β-carbon of the activated allylic double bond with removal of the mesyloxy group and migration of the double bond, the product **23** possessing a vinyl group at C-6. The vinyl group could then be variously transformed for further functionalization. Diastereoselectivity at C-6 of the cyclization product was also a concern. First, we searched for an efficient preparation of the substrate **22** and, after some experimentations, found a reproducible route to **22**. Protection of the hydroxyl group in **4** with a silyl (TBDMS) group afforded **13** (96% yield). Ozonolysis of **13** followed by reductive workup with $Ph_3P$ gave aldehyde **14**. Wittig olefination of **14** with the anion generated from $(EtO)_2P(O)CH_2COOEt$ proceeded smoothly to give (*E*)-α,β-unsaturated ester **15**[14] exclusively (90% from **13**). DIBAL-H reduction of **15** gave allylic alcohol **16**. The allylic alcohol was converted to the acetate **17** and then the silyl protecting group was removed using tetrabutylammonium fluoride (TBAF) to give **18** (94 % yield from **15**). Substitution of the liberated hydroxyl group in **18** by a malonate anion was achieved *via* iodide **19**, similar to the conversion of **4** to **6** (41% yield from **18**). The

acetyl group in resulting malonate ester **20** was then removed with sodium methoxide to give allylic alcohol **21** (88% yield). Introduction of a leaving group was best achieved by brief exposure of **21** to mesyl chloride affording the allylic mesylate **22** (64% yield). With the substrate **22** in hand, we executed the intramolecular $S_N2'$ cyclization of **22** using sodium hydride as a base. To our delight, the desired cyclization proceeded smoothly. An inseparable mixture of 2-oxaspiro[4.4]nonane **23** and its 6-epimer was obtained in a combined yield of 88%. As anticipated, formation of a seven-membered carbocycle as a result of an $S_N2$ reaction of **22** did not occur. It was determined that the diastereomeric ratio of the cyclization product **23** and the 6-epimer was 10:1 based on $^1H$ NMR analysis (270 MHz) of the mixture. The configuration at C-6 of the major product **23** as depicted in Scheme 4 was established as follows. Selective removal of the isopropylidene group in **23** by acid (60% AcOH) hydrolysis gave diol **24**, from which the glycol was cleaved by $NaIO_4$






**Scheme 4**

oxidation affording aldehyde **25**. An NOE experiment on **25** was employed to verify the configuration of C-6 in the major product. Irradiation of the H-1 doublet at δ 4.38 resulted in 5.3% enhancement of H-6 at δ 3.46. Inspection of molecular models indicates that both H-1 and H-6 in **25** are on the same side of the molecule as illustrated in Scheme 4. This NOE experiment ensured that the configuration of C-6 in the major product **23** is *R* .

In conclusion, the present work constitutes enantiospecific access to five- and six-membered carbocycles which possess an asymmetric spiro carbon center. The 2-oxaspiroalkanes **8**, **10**, and **23** may serve as versatile building blocks for the syntheses of spiro[4.4]nonanes and spiro[4.5]decanes, the skeletal characteristics of a number of spiro-type sesquiterpenes.

## EXPERIMENTAL



**General Procedures.** Melting points are uncorrected. All specific rotations were measured in $CHCl_3$ solution using a JASCO Model DIP-370 polarimeter in a 10 mm cell. IR spectra (neat) were recorded using a JASCO Model IR-810 spectrometer. $^1H$ NMR spectra were recorded using a JEOL EX-90 (90 MHz) or a JEOL GX-270 (270 MHz) FT NMR spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. High resolution mass spectra (HRMS) were obtained with a Hitachi M-80 mass spectrometer. Microanalyses were carried out by the staff of the Analytical Center in our university. Thin-layer chromatography (TLC) was performed with glass plates coated with Kieselgel 60 $GF_{254}$ (Merck). Column chromatography was performed using silica gel 60 K070 (Katayama Chemicals). Unless otherwise specified, reactions were carried out at room temperature (rt). Combined extracts were dried over anhydrous $Na_2SO_4$. Reagents and solvents were removed by concentration *in vacuo*, using an evaporator with the bath at 35-45 °C. Sodium hydride (NaH) was used as a commercially available 60% emulsion in mineral oil. Solvents were dried (desiccants are shown in parenthesis) and distilled prior to use: tetrahydrofuran=THF ($LiAlH_4$, then Na/benzophenone ketyl), *N*,*N*-dimethylformamide=DMF ($MgSO_4$), $CH_2Cl_2$ ($CaH_2$), dimethyl sulfoxide= DMSO ($CaH_2$), benzene ($CaH_2$), and pyridine (NaOH).

**(2*R*, 3*R*, 4*R*, 5*S*)-4-(2-Hydroxyethyl)-2, 3-(isopropylidenedioxy)-5-[(1*R*)-1, 2-(isopropylidenedioxy)ethyl]-4-vinyltetrahydrofuran (4)**. To a cold (0 °C) stirred suspension of $LiAlH_4$ (233 mg, 6.14 mmol) in THF (7 mL) was added a solution of **1**

(1.05 g, 2.95 mmol) in THF (9 mL) dropwise. After stirring at rt for 30 min, the mixture was quenched with $H_2O$ (0.2 mL), diluted with 15 wt% aqueous NaOH (0.2 mL), and $H_2O$ (0.6 mL). The resulting white solids were removed by filtration, and washed with EtOAc (50 mL). The combined filtrate and washing were washed with $H_2O$ (60 mL). The aqueous layer was extracted with EtOAc (60 mL x 3). The organic layers were combined, dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give 892 mg (96% yield) of **4** as a colorless oil: TLC, $R_f$ 0.39 (EtOAc/hexane, 1:1); $[\alpha]^{29}_D$ +41.4° (*c* 1.70); IR 3460, 2990, 2940, 2890, 1640, 1460, 1380, 1250, 1220, 1160 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 1.32, 1.39 (2 s, 9H, 3H), 1.66-2.12 (m, 2H), 3.75-3.89, 3.96-4.16 (2 m, total 6H), 4.64 (d, *J* =3.8 Hz, 1H), 5.27 (dd, *J* =1.9 and 10.4 Hz, 1H), 5.28 (dd, *J* =1.9 and 18.0 Hz, 1H), 5.76 (d, *J* =3.8 Hz, 1H), 6.01 (dd, *J* =10.4 and 18.0 Hz, 1H).

Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.21; H, 8.24.

**(2*R*, 3*R*, 4*R*, 5*S*)-4-(2-Iodoethyl)- 2,3 -(Isopropylidenedioxy)-5-[(1*R*)-1, 2-(isopropylidenedioxy)ethyl]-4-vinyltetrahydrofuran (5).** The following reaction was carried out under Ar. To a cold (0 °C) stirred solution of **4** (892 mg, 2.84 mmol) and $Ph_3P$ (1.50 g, 6.10 mmol) in THF (10 mL) was added diethyl azodicarboxylate (DEAD) (0.90 mL, 5.72 mmol). After the solution was stirred for 10 min, MeI (0.35 mL, 5.62 mmol) was added. The mixture was stirred at rt for 1 h and concentrated. The residue was diluted with EtOAc (60 mL), and washed with $H_2O$ (50 mL x 3). The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to give 1.20 g (quantitatively) of **5** as white crystals, mp 49.5-51.0 °C: TLC, $R_f$ 0.58 (EtOAc/hexane, 1:5); $[\alpha]^{28}_D$ +10.4° (*c* 1.02); IR 2990, 2940, 2880, 1450, 1380, 1250, 1165 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 1.32, 1.34, 1.39, 1.52 (4 s, 3H x 4), 2.02 (ddd, *J* =5.5, 12.3, 14.1 Hz, 1H), 2.34 (ddd, *J* =4.9, 12.1, 14.1 Hz, 1H), 3.18 (ddd, *J* =5.5, 9.7, 12.1 Hz, 1H), 3.28 (ddd, *J* =4.9, 9.7, 12.3 Hz, 1H), 3.89-4.16 (m, 4H), 4.46 (d, *J* =3.3 Hz, 1H), 5.30 (dd, *J* =0.9, 17.8 Hz, 1H), 5.34 (dd, *J* =0.9, 11.4 Hz, 1H), 5.75 (d, *J* =3.3 Hz, 1H), 5.90 (dd, *J* =11.4, 17.8 Hz, 1H).

Anal. Calcd for $C_{16}H_{25}O_5I$: C, 45.30; H, 5.94. Found: C, 45.65; H, 5.68.

**(2*R*, 3*R*, 4*R*, 5*S*)-2, 3-(Isopropylidenedioxy)-5-[(1*R*)-1, 2-(isopropylidenedioxy)-ethyl]-4-[3,3-bis(methoxycarbonyl)propyl]-4-vinyltetrahydrofuran (6).** The following reaction was carried out under Ar. To a stirred suspension of NaH (682 mg, 17.1 mmol) in THF (9 mL) was added $CH_2(COOMe)_2$ (2.0 mL, 17.5 mmol). After stirring for 15 min, a solution of **5** (1.21 g, 2.85 mmol) in THF (9 mL) was added to the mixture dropwise for 10 min at 0 °C. Then the resulting solution was

refluxed for 13 h. After being cooled to rt, the solution was quenched with saturated aqueous $NH_4Cl$ (1 mL), diluted with $H_2O$ (90 mL), and the liquid mixture extracted with EtOAc (90 mL x 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give 1.28 g (quantitatively) of **6** as a pale yellow oil: TLC, $R_f$ 0.34 (EtOAc/hexane, 1:3); $[\alpha]^{28}_D$ +17.3° (*c* 0.89); IR 2990, 2950, 2890, 1750, 1745, 1455, 1435, 1380, 1240, 1210, 1160 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 1.33, 1.39, 1.53 (3 s, 6H, 3H, 3H), 1.60-1.68, 1.95-2.05 (2 m, total 4H), 3.34 (t, *J* =7.3 Hz, 1H), 3.75, 3.76 (2 s, 3H x 2), 3.90-3.95, 4.01-4.19 (2 m, total 4H), 4.53 (d, *J* =3.3 Hz, 1H), 5.28 (dd, *J* =1.5, 18.3 Hz, 1H), 5.29 (dd, *J* =1.5, 11.0 Hz, 1H), 5.73 (d, *J* =3.3 Hz, 1H), 5.93 (dd, *J* =11.0, 18.3 Hz, 1H).

Anal. Calcd for $C_{21}H_{32}O_9$: C, 58.87; H, 7.53. Found: C, 58.88; H, 7.34.

**(2*R*, 3*R*, 4*R*, 5*S*)-2,3-(Isopropylidenedioxy)-5-[(1*R*)-1,2-(isopropylidenedioxy)-ethyl]-4-[3-bromo-3,3-bis-(methoxycarbonyl)propyl]-4-vinyltetrahydrofuran (7).** To a cold (0 °C) stirred solution of **6** (94.7 mg, 0.22 mmol) in THF (2.5 mL) were added NaH (13.5 mg, 0.34 mmol) and NBS (78.1 mg, 0.44 mmol). After stirring for 30 min at 0 °C, the mixture was quenched by adding EtOH (1 mL) and diluted with $H_2O$ (25 mL). The liquid mixture was extracted with EtOAc (25 mL x 3) and the combined extracts were dried and concentrated. The residue was purified by column chromato-graphy on silica gel (EtOAc/hexane, 1:5) to give **7** (96.6 mg, 86% yield) as a colorless oil: TLC, $R_f$ 0.56 (EtOAc/hexane, 1:2); $[\alpha]^{23}_D$ +27.9° (*c* 1.45); IR 2980, 2950, 2930, 1740, 1450, 1430, 1380, 1370, 1250, 1210 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 1.33, 1.39, 1.53 (3 s, 6H, 3H, 3H), 1.40-1.51, 1.73-1.85, 2.28-2.49 (3 m, 1H, 1H, 2H), 3.83, 3.84 (2 s, 3H x 2), 3.86-3.93, 4.02-4.13 (2m, 1H and 3H), 4.47 (d, *J* =3.3 Hz, 1H), 5.29 (dd, *J* =1.5, 18.3 Hz, 1H), 5.30 (dd, *J* =1.5, 11.0 Hz, 1H), 5.74 (d, *J* =3.3 Hz, 1H), 5.92 (dd, *J* =11.0, 18.3 Hz, 1H). HRMS. Calcd for $C_{21}H_{31}O_9Br$ ($M^+$): *m/z* 506.1150. Found: *m/z* 506.1163.

**(1*S*,3*R*,4*R*)-3,4-(Isopropylidenedioxy)-1-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-8,8-bis(methoxycarbonyl)-2-oxaspiro[4.5]decane (8).** The following reaction was carried out under Ar. To a refluxing solution of **7** (43.8 mg, 0.086 mmol) in benzene (3 mL) was added dropwise a solution of AIBN (7.3 mg, 0.045 mmol) and $Bu_3SnH$ (0.07 mL, 0.26 mmol) in benzene (6 mL) over 2 h. The mixture was refluxed for an additional 2 h and the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to give **8** (26.6 mg, 72% yield) as a colorless oil: TLC, $R_f$ 0.53 (EtOAc/hexane, 1:2); $[\alpha]^{22}_D$ +32.5 ° (*c* 1.31); IR 2980, 2950, 2875, 1730, 1450, 1380, 1370, 1310, 1250, 1230 $cm^{-1}$; $^1H$ NMR (270

MHz) δ 1.31, 1.33, 1.37, 1.52 (4 s, 3H x 4), 1.71-1.93, 2.30-2.45 (2m, total 8H), 3.62 (d, *J* =8.8 Hz, 1H), 3.72, 3.77 (2 s, 3H x 2), 3.85 (dd, *J* =5.6, 8.1 Hz, 1H), 3.97 (dt, *J* =5.6, 8.6 Hz, 1H), 4.09 (dd, *J* =5.6, 8.1 Hz, 1H), 4.50 (d, *J* =3.7 Hz, 1H), 5.74 (d, *J* =3.7 Hz, 1H).

Anal. Calcd for $C_{21}H_{32}O_9$: C, 58.87; H, 7.52. Found: C, 58.86; H, 7.24.

**Mixture of (1*S*, 3*R*, 4*R*, 5*R*, 6*R* and *S*)-6-Hydroxy-3,4-(isopropylidenedioxy)-1-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-7,7-bis(methoxycarbonyl)-2-oxaspiro[4.4]nonane (10).** Through a cold (-78 °C) solution of **6** (867 mg, 2.02 mmol) in $CH_2Cl_2$ (10 mL) was bubbled ozone (*ca.* 3% in $O_2$) for 25 min. To the solution was added $Ph_3P$ (1.31 g, 4.99 mmol) and the mixture was stirred at -78 °C for 3 h, then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give a 3:1 inseparable mixture of **10** (736 mg, 85% yield) as white crystals: TLC, $R_f$ 0.42 (EtOAc/hexane, 1:2); IR 3390, 2980, 2960, 2900, 1730, 1460, 1430, 1370, 1280, 1210 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 1.25, 1.31, 1.32, 1.45 (4 s, each 1/4 x 3H), 1.35, 1.42, 1.55 (3 s, 3/4 x 3H, 3/4 x 6H, 3/4 x 3H), 1.64-1.70 (m, 1H), 1.72-1.92 (m, 1/4 x 2H), 1.98-2.12 (3/4 x 2H), 2.14-2.25 (m, 1/4 x 2H), 2.58-2.70 (m, 3/4 x 2H), 3.74, 3.75 (2 s, each 3/4 x 3H), 3.77 (s, 1/4 x 6H), 4.34 (d, *J* =3.4 Hz, 3/4 x 1H), 3.95-4.36 (m, 4H), 4.65 (d, *J* =3.4 Hz, 1/4 x 1H), 5.05 (d, *J* =11.2 Hz, 3/4 x 1H), 5.12 (d, *J* =4.9 Hz, 1/4 x 1H), 5.64 (d, *J* =3.4 Hz, 3/4 x 1H), 5.70 (d, *J* =3.4 Hz, 1/4 x 1H).

Anal. Calcd for $C_{20}H_{30}O_{10}$: C, 55.81; H, 7.02. Found: C, 56.11; H, 6.84.

**(1*S*, 3*R*, 4*R*, 5*R*)-3,4-(Isopropylidenedioxy)-1-[(1*R*)-1,2-(isopropylidenedioxy)-ethyl]-7-(methoxycarbonyl)-2-oxaspiro[4.4]non-6-ene (11).** To a solution of the mixture **10** (39.0 mg, 0.091 mmol) in DMSO (4 mL) were added $H_2O$ (0.4 mL) and NaCl (17 mg). The mixture was heated with stirring at 160 °C for 4 h, cooled to rt, and diluted with EtOAc (40 mL). The liquid mixture was washed with $H_2O$ (30 mL x 3) and the organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:9) to give **11** (25.6 mg, 80% yield) as white crystals, mp 85.0-86.5 °C: TLC, $R_f$ 0.41 (EtOAc/hexane, 1:3); $[\alpha]^{23}_D$ +108.9 ° (*c* 1.28); IR 2980, 2930, 2870, 1715, 1630, 1455, 1430, 1380, 1370, 1350, 1310, 1270, 1250 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 1.28, 1.29, 1.33, 1.56 (4 s, 3H x 4), 2.00-2.32 (m, 2H), 2.60-2.79 (m, 2H), 3.75 (s, 3H), 3.98-4.18 (m, 4H), 4.33 (d, *J* =3.7 Hz, 1H), 5.74 (d, *J* =3.7 Hz, 1H), 6.64 (t, *J* =1.8 Hz, 1H).

Anal. Calcd for $C_{18}H_{26}O_7$: C, 61.00; H, 7.39. Found: C, 61.04; H, 7.14.

**(1*S*, 3*R*, 4*R*, 5*R*)-7-(Hydroxymethyl)-3,4-(isopropylidenedioxy)-1-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-2-oxaspiro[4.4]non-6-ene (12).** The following reaction

was carried out under Ar. To a cold (-78 °C) stirred solution of **11** (29.7 mg, 0.084 mmol) in $CH_2Cl_2$ (1 mL) was added DIBAL-H (0.23 mL of 1.5 M solution in toluene, 0.35 mmol). After stirring at rt for 30 min, the mixture was quenched by adding $H_2O$ (0.1 mL). The resulting solids were removed by filtration, washed well with $CH_2Cl_2$ and the combined filtrate and washing were diluted with $H_2O$ (25 mL), and then extracted with $CH_2Cl_2$ (25 ml x 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to give **12** (26.2 mg, 96% yield) as a colorless oil: TLC, $R_f$ 0.34 (EtOAc/hexane, 1:1); $[\alpha]^{24}_D$ +83.6 °(*c* 0.54); IR 3450, 2995, 2930, 1650, 1460, 1380, 1370, 1310, 1250, 1215 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 1.30, 1.38, 1.56 (3 s, 6H, 3H, 3H), 1.93-2.23 (m, 2H), 2.37-2.56 (m, 2H), 3.98-4.22 (m, 7H), 4.27 (d, *J* =3.6 Hz, 1H), 5.59 (t, *J* =1.7 Hz, 1H), 5.72 (d, *J* =3.6 Hz, 1H).

Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.24; H, 7.86.

**(2*R*, 3*R*, 4*R*, 5*S*)-2,3-(Isopropylidenedioxy)-5-[(1*R*)-1,2-(isopropylidenedioxy)-ethyl]-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-4-vinyltetrahydrofuran (13).** To a stirred solution of **4** (941 mg, 2.99 mmol) in DMF (9 mL) was added imidazole (418 mg, 6.14 mmol). After the solution was stirred for 15 min, *tert*-butylchlorodimethylsilane (681 mg, 4.52 mmol) was added. The reaction mixture was stirred for 1.5 h, diluted with EtOAc (100 mL) and then washed with $H_2O$ (100 mL x 3). The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to give **13** (1.232 g, 96% yield) as a colorless oil: TLC, $R_f$ 0.37 (EtOAc/hexane, 1:10); $[\alpha]^{22}_D$ +41.5° (*c* 1.32), IR 2980, 2960, 2930, 2880, 2860, 1640, 1470, 1460, 1380, 1250, 1215 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 0.04 (s, 6H), 0.87 (s, 9H), 1.29, 1.33, 1.46 (3 s, 6H, 3H, 3H), 1.59-1.95 (m, 2H), 3.65-4.19 (m, 6H), 4.79 (d, *J* =3.6 Hz, 1H), 5.22 (dd, *J* =1.9, 18.6 Hz, 1H), 5.23 (dd, *J* =1.9, 9.8 Hz, 1H), 5.70 (d, *J* =3.6 Hz, 1H), 5.95 (dd, *J* =9.8, 18.6 Hz, 1H). HRMS. Calcd for $C_{21}H_{37}O_6Si$ ($M^+$- $CH_3$): *m/z* 413.2357. Found: *m/z* 413.2357

**(2*R*, 3*R*, 4*S*, 5*S*)-4-Formyl-2,3-(isopropylidenedioxy)-5-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]tetrahydrofuran (14).** Through a cold (-78 °C) solution of **13** (1.232 g, 2.87 mmol) in $CH_2Cl_2$ (10 mL) was bubbled ozone (*ca.* 3% in $O_2$) for 1 h. To the solution was added $Ph_3P$ (1.51 g, 5.76 mmol) and the mixture was gradually warmed to rt. After stirring for 2 h, the mixture was concentrated and the residue purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to give **14** (1.236 g), contaminated with a small amount of $Ph_3P$ but used in the next step without further purification. A sample for spectral analysis was obtained by repeated chromatography but was too unstable at rt to give a satisfactory microanalysis: Compound **14** as white crystals had mp 51-53 °C: TLC,

$R_f$ 0.30 (EtOAc/hexane, 1:10); $[\alpha]^{23}_D$ +1.1° (*c* 1.83); IR 2980, 2960, 2930, 2880, 2860, 1725, 1470, 1460, 1430, 1380, 1370, 1300, 1250, 1215 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 0.06 (s, 6H), 0.89 (s, 9H), 1.28, 1.36, 1.57 (3 s, 6H, 3H, 3H), 1.46-1.83, 2.02-2.30 (2 m, 1H x 2), 3.86 (t, *J* =5.6 Hz, 2H), 3.97-4.18 (m, 2H), 4.16 (d, *J* =2.0 Hz, 1H), 4.51 (dt, *J* =3.0, 12.0 Hz, 1H), 5.06 (d, *J* =3.2 Hz, 1H), 5.83 (d, *J* =3.2 Hz, 1H), 9.72 (s, 1H).

**(2*R*, 3*R*, 4*R*, 5*S*)-4-[(*E*)-2-(Ethoxycarbonyl)ethenyl]-2,3 -(isopropylidenedioxy)-5-[(1*R*)-1, 2- (isopropylidenedioxy)ethyl]-4-[2-(*tert* - butyldimethylsilyloxy)ethyl]-tetrahydrofuran (15).** The following reaction was carried out under Ar. To a cold (0 °C) stirred suspension of NaH (456 mg, 11.4 mmol) in THF (5 mL) was added $(EtO)_2P(O)CH_2COOEt$ (2.40 mL, 12.1 mmol). The mixture was stirred at rt for 1 h, then **14** (1.236 g), obtained above, in THF (15 mL) solution was added at 0 °C. The mixture was stirred at rt for 1.5 h, quenched by addition of $H_2O$ (0.1 mL), diluted with $H_2O$ (100 mL), and then extracted with $CH_2Cl_2$ (100 mL x 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to give **15** (1.298 g, 90% yield from **13**) as a colorless oil: TLC, $R_f$ 0.55 (EtOAc/hexane, 1:5); $[\alpha]^{23}_D$ +57.8° (*c* 0.99); IR 2980, 2955, 2930, 2880, 2860, 1715, 1650, 1470, 1460, 1375, 1365, 1305, 1250, 1210 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.22 (t, *J* =7.0 Hz, 3H), 1.30, 1.38, 1.52 (3 s, 6H, 3H, 3H), 1.47-2.13 (m, 2H), 3.70 (t, *J* =5.7 Hz, 2H), 3.91-4.05 (m, 4H), 4.17 (q, *J* =7.0 Hz, 2H), 4.90 (d, *J* =3.3 Hz, 1H), 5.76 (d, *J* =3.3 Hz, 1H), 6.02 (d, *J* =16.4 Hz, 1H), 7.05 (d, *J* =16.4 Hz, 1H).

Anal. Calcd for $C_{25}H_{44}O_8Si$: C, 59.97; H, 8.86. Found: C, 60.21; H, 8.77.

**(2*R*, 3*R*, 4 *R*, 5*S*)-4-[(*E*)-3-Hydroxy-1-propenyl]-2,3-(isopropylidenedioxy)-5-[(1*R*)- 1,2-(isopropylidenedioxy)ethyl]-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]tetrahydrofuran (16).** The following reaction was carried out under Ar. To a cold (-78 °C) stirred solution of **15** (1.279 g, 2.55 mmol) in $CH_2Cl_2$ (5 mL) was added DIBAL-H (5.30 mL of 1.5 M solution in toluene, 7.91 mmol). After stirring at -78 °C for 45 min, the mixture was quenched by adding $H_2O$ (1 mL). The resulting solids were removed by filtration, and washed with $CH_2Cl_2$. The combined filtrate and washing were diluted with $H_2O$ (100 mL) and the liquid mixture was extracted with $CH_2Cl_2$ (100 mL x 3). The combined extracts were dried and concentrated and the residue purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give **16** (1.155 g, 99% yield) as a colorless oil: TLC, $R_f$ 0.64 (EtOAc/hexane, 1:1); $[\alpha]^{21}_D$ +48.2° (*c* 0.94); IR 3480, 2980, 2955, 2930, 2880, 2860, 1470, 1460, 1380, 1370, 1310, 1250, 1215 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.26,

1.34, 1.46 (3 s, 6H, 3H, 3H), 1.64-2.07 (m, 2H), 3.70-4.08 (m, 7H), 4.14-4.19 (m, 2H), 4.83 (d, $J$ =3.5 Hz, 1H), 5.75 (d, $J$ =3.5 Hz, 1H), 5.82-5.88 (m, 2H).

Anal. Calcd for $C_{23}H_{42}O_7Si$: C, 60.23; H, 9.23. Found: C, 60.30; H, 9.02.

**(2*R*, 3*R*, 4*R*, 5*S*)-4-[(*E*)-3-Acetoxy-1-propenyl]-2, 3-(isopropylidenedioxy)-5-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-4-[2-(*tert*-butyldimethylsilyloxy)ethyl]tetrahydrofuran (17).** To a stirred solution of **16** (1.155 g, 2.52 mmol) in pyridine (4 mL) was added $Ac_2O$ (4 mL). The solution was stirred for 3h and then co-evaporated with toluene. The residue was purified by column chromatography (EtOAc/hexane, 2:19) to give **17** (1.250 g, 99% yield) as a colorless oil: TLC, $R_f$ 0.63 (EtOAc/hexane, 1:3); $[\alpha]^{24}_D$ +53.4 ° (*c* 0.82); IR 2980, 2960, 2930, 2880, 2860, 1740, 1470, 1460, 1380, 1370, 1310, 1250, 1230 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.31, 1.37, 1.52 (3 s, 6H, 3H, 3H), 1.56-1.90 (m, 2H), 2.06 (s, 3H), 3.70-4.18 (m, 6H), 4.58 (d, $J$ =5.8 Hz, 2H), 4.85 (d, $J$ =3.3 Hz, 1H), 5.75 (d, $J$ =3.3 Hz, 1H), 5.83-5.87 (m, 2H). HRMS. Calcd for $C_{25}H_{45}O_8Si$ ($M^+$+H): *m/z* 501.2881. Found: *m/z* 501.2874.

**(2*R*, 3*R*, 4*R*, 5*S*)-4-[(*E*)-3-Acetoxy-1-propenyl]-4-(2-hydroxyethyl)-2, 3-(isopropylidenedioxy)-5-[(1*R*)-1, 2-(isopropylidenedioxy)ethyl]tetrahydrofuran (18).** To a cold (0 °C) stirred solution of **17** (1.250 g, 2.50 mmol) in THF (6 mL) was added TBAF (3.75 ml of 1.0 M solution in THF, 3.75 mmol). The mixture was stirred at rt for 1 h, diluted with $H_2O$ (100 mL) and the liquid mixture was extracted with EtOAc (100 mL x 3). The combined extracts were dried and concentrated and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:3) to give **18** (930 mg, 96% yield) as a colorless oil: TLC, $R_f$ 0.20 (EtOAc/hexane, 1:1); $[\alpha]^{22}_D$ +39.2° (*c* 2.21); IR 3500, 2980, 2940, 2880, 1740, 1450, 1380, 1370, 1250, 1235 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 1.32, 1.37, 1.52 (3 s, 6H, 3H, 3H), 1.75-2.02 (m, 3H), 2.07 (s, 3H), 3.74-4.18 (m, 6H), 4.56-4.66 (m, 3H), 5.76 (d, $J$ =3.4 Hz, 1H), 5.82-5.91 (m, 2H).

Anal. Calcd for $C_{19}H_{30}O_8$: C, 59.05; H, 7.82. Found: C, 58.68; H, 8.13.

**(2*R*, 3*R*, 4*R*, 5*S*)-4-[(*E*)-3-Acetoxy-1-propenyl]-4-(2-iodoethyl)-2, 3-(isopropylidenedioxy)-5-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]tetrahydrofuran (19).** The following reaction was carried out under Ar. To a cold (0 °C) stirred solution of **18** (923 mg, 2.38 mmol) in THF (8 mL) were added $Ph_3P$ (1.88 g, 7.17 mmol) and DEAD (1.20 mL, 7.62 mmol). After stirring at rt for 30 min, MeI (0.50 mL, 8.03 mmol) was added to the mixture. The mixture was stirred at rt in dark for 2.5 h, and then diluted with $H_2O$ (100 mL). The liquid mixture was extracted with EtOAc (100 mL x 3) and the combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:9) to give **19** (954 mg), which, although contaminated by a small amount of $Ph_3P$, was used in the next

step without further purification. In a small scale experiment, an analytical sample of **19** was obtained by repeated column chromatography. Compound **19** was obtained as a colorless oil: TLC, $R_f$ 0.66 (EtOAc/hexane, 1:2); $[\alpha]^{24}_D$ +7.0° (*c* 1.57); IR 2980, 2930, 2880, 1740, 1450, 1380, 1370, 1230, 1165 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 1.33, 1.38, 1.51 (3 s, 6H, 3H, 3H), 2.08 (s, 3H), 1.83-2.60 (m, 2H), 3.05-3.35 (m, 2H), 3.84-4.20 (m, 4H), 4.46 (d, *J* =3.5 Hz, 1H), 4.55-4.61 (m, 2H), 5.75 (d, *J* =3.5 Hz, 1H), 5.80-5.88 (m, 2H).

Anal. Calcd for $C_{19}H_{29}O_7I$: C, 45.98; H, 5.89. Found: C, 46.10; H, 5.78.

**(2*R*, 3*R*, 4*R*, 5*S*)-4-[(*E*)-3-Acetoxy-1-propenyl]-2, 3-(isopropylidenedioxy) -5-[(1*R*) -1, 2-(isopropylidenedioxy)ethyl]-4-[3, 3-bis(methoxycarbonyl)propyl]tetrahydrohydrofuran (20).** The following reaction was carried out under Ar. To a cold (0 °C) stirred suspension of NaH (474 mg, 11.9 mmol) in THF (9 mL) was added $CH_2(COOMe)_2$ (1.45 mL, 12.6 mmol). After stirring at rt for 3 h, a solution of **19** obtained above (954 mg) in THF (5 mL) was added to the mixture. The mixture was refluxed for 6 h, and then diluted with $H_2O$ (90 mL). The liquid mixture was extracted with EtOAc (100 mL x 3) and the combined extracts dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give **20** (487 mg, 41% yield from **18**) as a pale yellow oil: TLC, $R_f$ 0.34 (EtOAc/hexane, 1:2); $[\alpha]^{22}_D$ +23.7° (*c* 0.98); IR 2980, 2960, 2930, 2860, 1735, 1455, 1435, 1380, 1370, 1240, 1225 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 1.32, 1.38, 1.52 (3 s, 6H, 3H, 3H), 2.06 (s, 3H), 1.45-2.32 (m, 4H), 3.26-3.42 (m, 1H), 3.76 (s, 6H), 3.83-4.16 (m, 4H), 4.49-4.60 (m, 3H), 5.72 (d, *J* =3.5 Hz, 1H), 5.79-5.87 (m, 2H).

Anal. Calcd for $C_{24}H_{36}O_{11}$: C, 57.59; H, 7.25. Found: C, 57.62; H, 7.00.

**(2*R*, 3*R*, 4*R*, 5*S*)-4-[(*E*)-3-Hydroxy-1-propenyl]-2, 3-(isopropylidenedioxy)-5-[(1*R*)-1, 2-(isopropylidenedioxy)ethyl]-4-[3, 3-bis(methoxycarbonyl)propyl]tetrahydrofuran (21).** To a cold (0 °C) stirred solution of **20** (294 mg, 0.59 mmol) in MeOH (4 mL) was added MeONa (0.30 mL of 1.0 M solution in MeOH, 0.30 mmol). After stirring at rt for 1 h, the solution was neutralized by adding Amberlite IR-120 ($H^+$). The resin was removed by filtration and washed with $CH_2Cl_2$. The combined filtrate and washing were concentrated and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:3) to give **21** (235.5 mg, 88% yield) as a colorless oil: TLC, $R_f$ 0.24 (EtOAc/hexane, 1:1); $[\alpha]^{22}_D$ +25.6° (*c* 1.03); IR 3480, 2980, 2960, 2930, 2880, 1750, 1735, 1460, 1435, 1380, 1370, 1240, 1215 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 1.32, 1.37, 1.52 (3 s, 6H, 3H, 3H), 1.46-2.15 (m, 5H), 3.26-3.46 (m, 1H), 3.75 (s, 6H), 3.87-4.23 (m, 6H), 4.51 (d, *J* =3.3 Hz, 1H), 5.72 (d, *J* =3.3 Hz, 1H), 5.83-5.91 (m, 2H).

Anal. Calcd for $C_{22}H_{34}O_{10}$: C, 57.63; H, 7.47. Found: C, 57.54; H, 7.47.

**(2*R*, 3*R*, 4*R*, 5*S*)-2, 3-(Isopropylidenedioxy)-5-[(1*R*)-1, 2-(isopropylidenedioxy)-ethyl]-4-[(*E*)-3-(mesyloxy)-1-propenyl]-4-[3, 3-bis(methoxycarbonyl)propyl]tetrahydrofuran (22).** To a cold (0 °C) stirred solution of **21** (217 mg, 0.47 mmol) in $CH_2Cl_2$ (4 mL) were added DMAP (233.5 mg, 1.91 mmol) and MsCl (0.092 mL, 1.19 mmol). After stirring at rt for 20 min, the mixture was diluted with $CH_2Cl_2$ (70 mL). The liquid mixture was washed with 0.1 M aqueous HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), then $H_2O$ (50 mL) successively. The organic layer was dried and concentrated and the residue purified by column chromatography on silica gel (EtOAc/hexane, 2:5) to give **22** (161 mg, 64% yield) as a colorless oil. This product was somewhat unstable at rt and satisfactory microanalysis could not obtained: TLC, $R_f$ 0.30 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ +41.3° (*c* 0.54); IR 2990, 2960, 2930, 2860, 1750, 1735, 1670, 1460, 1440, 1370, 1240, 1215 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 1.32, 1.38, 1.50 (3 s, 6H, 3H, 3H), 1.20-1.75, 1.90-2.05 (2m, total 4H), 3.03 (s, 3H), 3.38 (t, *J* =7.1 Hz, 1H), 3.75, 3.76 (2 s, 3H x 2), 3.87-4.14 (m, 4H), 4.54 (d, *J* =3.2 Hz, 1H), 4.75 (d, *J* =5.9 Hz, 2H), 5.73 (d, *J* =3.2 Hz, 1H), 5.84-6.05 (m, 2H).

**Mixture of (1*S*, 3*R*, 4*R*, 5*R*, 6*R* and *S*)-3, 4-(Isopropylidenedioxy)-1-[(1*R*)-(1,2-isopropylidenedioxy)ethyl]-7,7-bis(methoxycarbonyl)-6-vinyl -2-oxaspiro[4.4] nonane (23).** To a cold (0 °C) stirred solution of **22** (151 mg, 0.281 mmol) in THF (2.5 mL) was added NaH (26 mg, 0.65 mmol). After stirring at rt for 3.5 h, the mixture was quenched by adding EtOH (0.2 mL), and then diluted with $H_2O$ (30 mL). The liquid mixture was extracted with EtOAc (40 mL x 3) and the combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to give an inseparable mixture **23** (109 mg, 88% yield) as a colorless oil (the diastereomeric ratio was deteremined to be 10:1 by $^1H$ NMR analysis): TLC, $R_f$ 0.53 (EtOAc/hexane, 1:2); IR 2980, 2960, 2930, 2850, 1730, 1640, 1460, 1440, 1380, 1370, 1250, 1220 $cm^{-1}$; $^1H$ NMR (270 MHz) for the major 6*R* isomer δ 1.28, 1.35, 1.43, 1.45 (4 s, 10/11 x 3H x 4), 1.40-1.55 (m, 1H), 1.82-2.05 (m, 1H), 2.14-2.25 (m, 1H), 2.65-2.76 (m, 1H), 3.72, 3.74 (2 s, 10/11 x 3H x 2), 3.78 (d, *J* =10.6 Hz, 1H), 3.85-4.19 (m, 4H), 4.52 (d, *J* =3.3 Hz, 10/11 x 1H), 5.07 (dd, J=2.6, 10.0 Hz, 10/11 x 1H), 5.15 (dd, *J* =2.6, 17.3 Hz, 10/11 x 1H), 5.62 (d, *J* =3.3 Hz, 1H), 6.05 (dt, *J* =10.0, 17.3 Hz, 10/11 x 1H); for the minor 6*S* isomer: δ 1.32, 1.38, 1.41, 1.47 (4 s, 1/11 x 3H x 4), 3.66 (s, 1/11 x 6H), 4.27 (d, *J* =3.7 Hz, 1/11 x 1H), 5.09 (dd, *J* =2.2, 10.0 Hz, 1/11 x 1H), 5.23 (dd, *J* =2.2, 17.3 Hz, 1/11 x 1H), 5.89 (dt, *J* =10.0, 17.3 Hz, 1/11 x 1H).

Anal. Calcd for $C_{22}H_{32}O_9$: C, 59.99; H, 7.32. Found: C, 59.68; H, 7.30.

**Mixture of (1*S*, 3*R*, 4*R*, 5*R*, 6*R* and *S*)-1-[(1*R*)-1, 2-(Dihydroxy)ethyl]-3,4-(isopropylidenedioxy) -7, 7-bis(methoxycarbonyl)-6-vinyl-2-oxaspiro[4. 4]nonane**

**(24).** The mixture **23** (15.7 mg, 0.036 mmol) was dissolved in 60% aqueous AcOH (2 mL). The solution was stirred for 21 h, and the solvents were removed by co-evaporation with toluene and EtOH. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:1) to give an inseparable mixture **24** (14.3 mg, quantitatively) as a colorless oil: TLC, $R_f$ 0.18 (EtOAc/hexane, 1:1); IR 3480, 2980, 2955, 2880, 1730, 1635, 1455, 1435, 1380, 1370, 1270 $cm^{-1}$; $^1H$ NMR (90 MHz) δ 1.28, 1.45 (2 s, 3H x 2), 1.36-2.91 (m, 6H), 3.70 (s, 1/11 x 6H), 3.72, 3.73 (2 s, 10/11 x 3H x 2), 3.66-4.10 (m, 5H), 4.21 (d, *J* =3.2 Hz, 1/11 x 1H), 4.50 (d, *J* =3.2 Hz, 10/11 x 1H), 5.06 (dd, J =2.9, 10.3 Hz, 1H), 5.14 (dd, J =2.9, 17.2 Hz, 10/11 x 1H), 5.20-5.38 (m, 1/11 x 1H), 5.62 (d, *J* =3.2 Hz, 1H), 6.05 (dt, *J* =10.3, 17.2 Hz, 10/11 x 1H).

**Mixture of (1*S*, 3*R*, 4*R*, 5*R*, 6*R* and *S*)-1-Formyl-3, 4-(isopropylidenedioxy)-7,7-bis(methoxycarbonyl)-6-vinyl-2-oxaspiro[4.4]nonane (25).** To a cold (0 °C) stirred solution of the mixture **24** (14.3 mg, 0.036 mmol) in MeOH (1 mL) was added a solution of $NaIO_4$ (17.6 mg, 0.082 mmol) in $H_2O$ (0.5 mL). After stirring for 4 h, the mixture was diluted with $H_2O$ (15 mL). The liquid mixture was extracted with EtOAc (20 mL x 3) and the combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give an inseparable mixture **25** (11.0 mg, 83% yield) as a colorless oil: TLC, $R_f$ 0.70 (EtOAc/hexane, 1:1); IR 2980, 2955, 2880, 1730, 1635, 1455, 1430, 1380, 1370 $cm^{-1}$; $^1H$ NMR (270 MHz) for the major 6*R* isomer δ 1.30, 1.45 (2 s, 10/11 x 3H x 2), 1.51-1.70 (m, 2H), 2.00-2.11 (m, 10/11 x 1H), 2.63-2.74 (m, 10/11 x 1H), 3.46 (d, *J* =10.1 Hz, 10/11 x 1H), 3.72, 3.76 (2 s, 10/11 x 3H), 4.38 (d, *J* =2.0 Hz, 10/11 x 1H), 4.56 (d, *J* =2.9 Hz, 10/11 x 1H), 5.15 (dd, *J* =2.1, 10.1 Hz, 10/11 x 1H), 5.26 (dd, *J* =2.0, 16.8 Hz, 10/11 x 1H), 5.86 (d, *J* =2.9 Hz, 10/11 x 1H), 6.02 (dt, *J* =16.8, 10.1 Hz, 10/11 x 1H), 9.80 (d, *J* =2.0 Hz, 10/11 x 1H).



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