Syntheses of Acetomycin-Related (2*R*,3*S*,4*R*)- and (2*S*,3*R*,4*R*)-2-Acetoxy-4-acetyl-3,4-dimethyltetrahydrofuran and Their Growth Inhibition Activity against Tumor Cells

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The syntheses of two tetrahydrofuran derivatives structurally related to the antitumor agent acetomycin are described. These compounds were synthesized starting from known D-glucose-derived functionalized tetrahydrofuran derivatives.

(−)-Acetomycin (**1**) is an antibiotic which was isolated from *Streptomyces ramulosus* sp. nov. by Prelog and co-workers in 1958.[1,2] The relative and absolute structures of **1** were determined by X-ray crystallography in 1985.[3] This antibiotic is a tetrasubstituted γ-lactone. It was recently found that compound **1** possesses potent antitumor activity against HCT-8 human colon adenocarcinoma cells, L1210 murine leukemia cells and human tumor stem cells.[4]

We have reported on the total synthesis of **1** and its three C-4/C-5 stereocongeners (**2**—**4**) (Fig. 1), as well as their growth inhibition activities against several types of tumor cells.[5,6] Concerning growth inhibition against tumor cells, compounds **1** and **3** exhibit 10-times the active potency against P388 and colon 26 than compounds **2** and **4**.[6] These results have led to the conclusion that although the stereochemistry at C-4 of compounds **1**—**4** does not play any important role regarding the growth inhibition activity, the stereochemistry at C-5 substantially affects the activity. Furthermore, it was recognized that the acetoxyl group at C-5 in **1** possibly contributes to the enzymatic mechanism regarding the biological effect of **1**[7] and that the antimicrobial activity disappears upon the reduction of the methyl ketone function at C-3 in **1**.[3] Considering these results, we then studied the necessity of the lactone functionality (which has remained unexplored) for antitumor activity. In this paper we described the syntheses of two tetrahydrofuran derivatives, such as **5** and **6**, which are lacking the lactone carbonyl functionality of **2** and **3**, in order to elucidate the biological importance of the lactone functionality.

Results and Discussion

Syntheses of (2*R*,3*S*,4*R*)- and (2*S*,3*R*,4*R*)-2-Acetoxy-4-acetyl-3,4-dimethyltetrahydrofurans (5 and 6). The syntheses of **5** and **6** were started from known tetrahydrofuran derivatives **8** and **9**, which were readily prepared from D-glucose featuring a stereoselective Claisen rearrangement of the allylic alcohol **7** with triethyl orthopropionate[8,9] (Scheme 1). The reduction of **8** with lithium aluminum hydride ($LiAlH_4$) gave a known alcohol **10**[8] (Scheme 2), of which the hydroxyl group was protected as a pivaloyl ester, providing **12** quantitatively. A selective removal of the isopropylidene group in the side chain at C-5 in **12** by acid hydrolysis afforded diol **14** in 93% yield. Sequential reactions from **14** by ozonolysis, a sodium periodate ($NaIO_4$) mediated glycol cleavage, followed by a reaction of the thus-formed dialdehyde with EtSH in the presence of $BF_3{\cdot}OEt_2$, provided the bis (dithioacetal) derivative **16** in 87% overall yield. Both dithioacetal groups in **16** were smoothly desulfurized by refluxing in EtOH in the presence of Raney Ni to provide trimethyl derivative **18** in 69% yield. Removal of the isopropylidene group in **18** was affected by 60% aqueous trifluoroacetic acid, affording hemiacetal **20** in 88% yield. Glycol cleavage of **20**, followed by sodium borohydride ($NaBH_4$) reduction of the thus-formed aldehyde function, provided diol **22** in 80% overall yield. The selective protection of the primary alcohol in **22** as a *t*-butyldimethylsilyl (TBDMS) ether afforded **24**. The secondary hydroxyl group in **24** was protected as a methoxymethyl (MOM) ether, giving **26** in 87% yield (Scheme 3). After standard four-step transformations, compound **26** was readily converted into a tetrasubstituted tetrahydrofuran derivative **34**. Unfortunately, deprotection of the MOM group did not proceed cleanly under our previous conditions, TMSBr/MS-4A/CH_2Cl_2/−30 °C,[10] applied to the total synthesis of **1**.[6,7] We have no reasonable explanation for this difficulty; furthermore, all of the other conditions examined[11] gave a complex mixture. Consequently, we had to seek an alternative route to the desired compounds **5** and **6**.

We envisioned a simultaneous oxidation of two hydroxyl groups in such as **37** to a methyl ketone and an aldehyde functionality (Scheme 4). Compound **37** was prepared by a DIBAL-H reduction of the aforementioned compound **24** in 90% yield. Both hydroxyl groups in **37** were smoothly oxidized by Swern's method,[12] thus providing the desired keto aldehyde **39**. The TBDMS group in **39** was then removed with tetrabutylammonium fluoride (*n*-Bu_4NF). However, a partial epimerization of the α-carbon adjacent to the aldehyde functionality was detected in this case. This epimerization was suppressed by the treatment of **39** with 60% aqueous acetic acid, which gave a nearly 2 : 1 hemiacetal mixture **41**, in a combined yield of 54%.

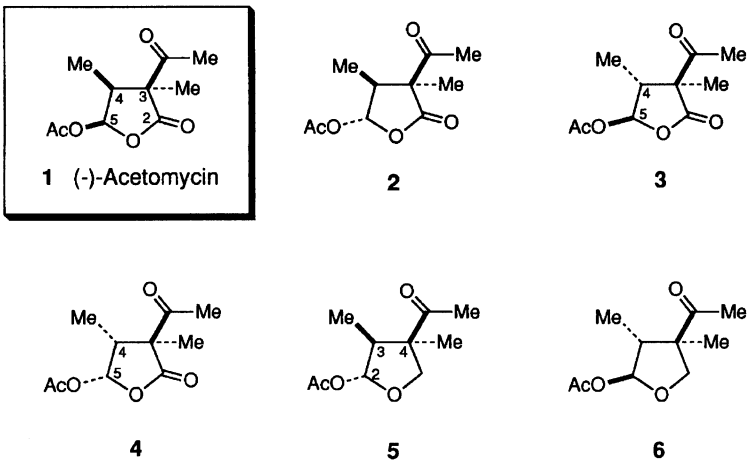
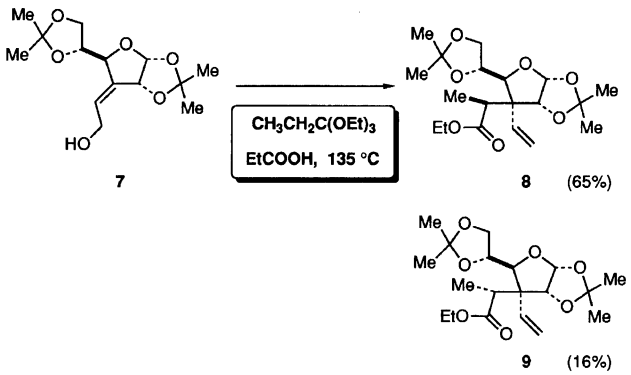


Fig. 1.



Scheme 1.

Finally, acetylation of this epimeric mixture **41** with acetic anhydride in pyridine provided **5** in 69% yield, which was contaminated with less than 5% of the C-2 epimer (^{1}H NMR analysis). Unfortunately, we could not remove the C-2 epimer by repeated chromatography. A biological assay was performed using this sample.

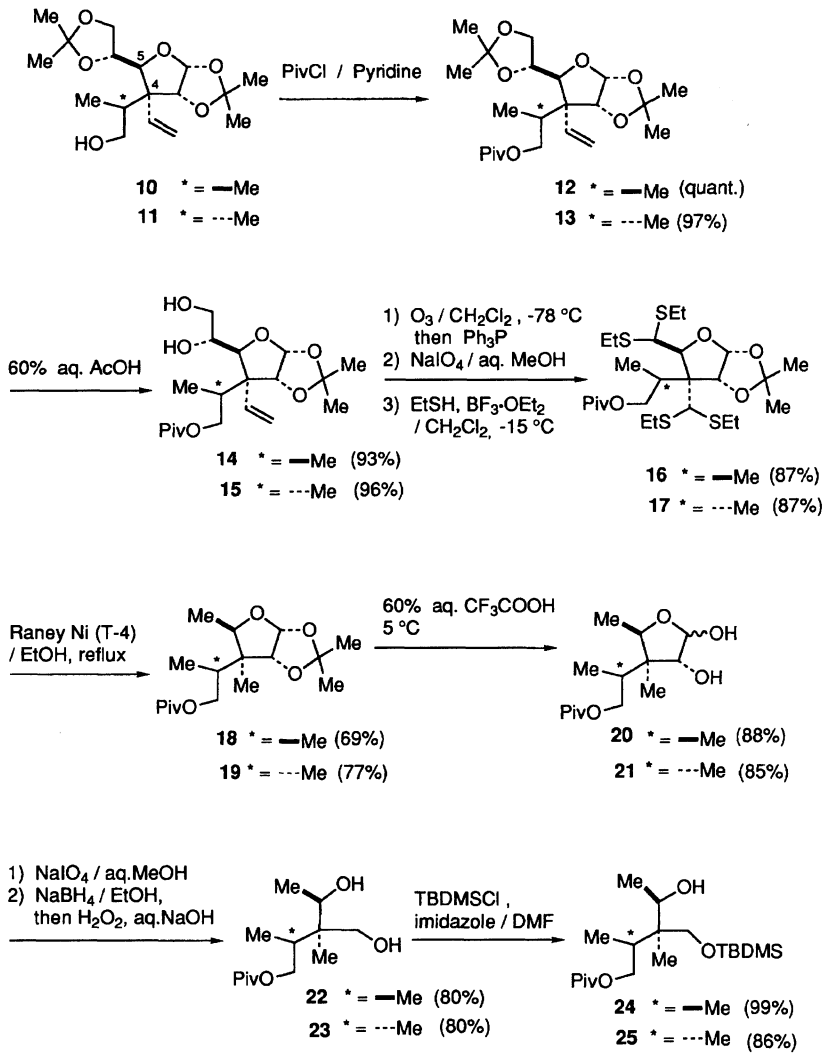
Another desired compound **6** was synthesized from a minor Claisen rearrangement product **9**[8] by an analogous route from **8** to **5** (Schemes 2, 3, and 4). Compound **9** was converted into hemiacetal intermediate **42** in 25% overall yield by the same reaction sequence applied to compound **8**. Acetylation of the epimeric mixture **42** with acetic anhydride in pyridine afforded a nearly 10:1 inseparable mixture of **6** and its C-2 epimer. A treatment of mixture **42** with sodium acetate in acetic anhydride, however, provided **6** in 75% yield, which was contaminated by the C-2 epimer in the ratio of 30 to 1 (^{1}H NMR analysis). A trace amount of the C-2 epimer in the mixture could not be completely removed by repeated chromatography.

The stereochemistry at C-2 of **5** or **6** was established by a ^{1}H NMR analysis which included NOE experiments (Fig. 2). In the ^{1}H NMR spectrum of **5**, H-2 appeared as a doublet at δ=5.95 having a coupling constant of $J_{2,3}$= 2.4 Hz. This rather small coupling constant suggested a *trans* relationship between H-2 and H-3. Furthermore, an 8% enhancement of the H-2 signal was observed when a doublet due to Me-3 (δ=1.02) was irradiated; a 5% enhancement of the Me-3 signal and a 1% enhancement of H-3 signal were also observed upon irradiation of the H-2 signal. Consequently, the acetoxyl group at C-2 of **5** was confirmed to be α-oriented. In the ^{1}H NMR of **6**, H-2 appeared at δ=5.87 as a doublet with $J_{2,3}$=2.9 Hz. In addition, a 9% enhancement of the H-2 signal was observed upon irradiation of a signal due to Me-3; a 6% enhancement of the Me-3 signal and a 1% enhancement of the H-3 signal were also observed upon irradiation of H-2 signal. Thus, the acetoxyl group at C-2 of **6** was confirmed to be β-oriented.[13]

Growth Inhibition Activity of 5 and 6. Growth inhibition activity assays of **5** and **6** were preliminarily performed using two tumor cells, such as P388 and colon 26, in comparison with an antitumor agent, adriamycin (Table 1). Compound **5** seems to be marginally active against P388 at a dosage of 10 μg ml^{-1}, but not against colon 26. Up to a concentration of 10 μg ml^{-1}, compound **6** barely showed any activity against P388 and colon 26. We could not directly compare their antitumor activity to that of **1**. However, compare with adriamycin, compounds **5** and **6** were estimated to be 10—20 and 20—40 times less active than (−)-acetomycin, respectively. It has been reported that the methyl ketone at C-3 in **1** is essential to the biological assay.[3] It should eventually be concluded that the oxygen functionalities in acetomycin play an important role regarding the biological activity of (−)-acetomycin

Experimental

General Procedures. Reactions were carried out at room temperature (r.t.) unless otherwise specified. The melting points were determined with a Mitamura Riken micromelting point apparatus and are uncorrected. Specific rotations were measured with a JASCO DIP-370 digital polarimeter in a 10 mm cell. Column chromatography was performed on silica gel 60 (Katayama Chemicals), and thin-layer chromatography (TLC) was performed on Kieselgel 60



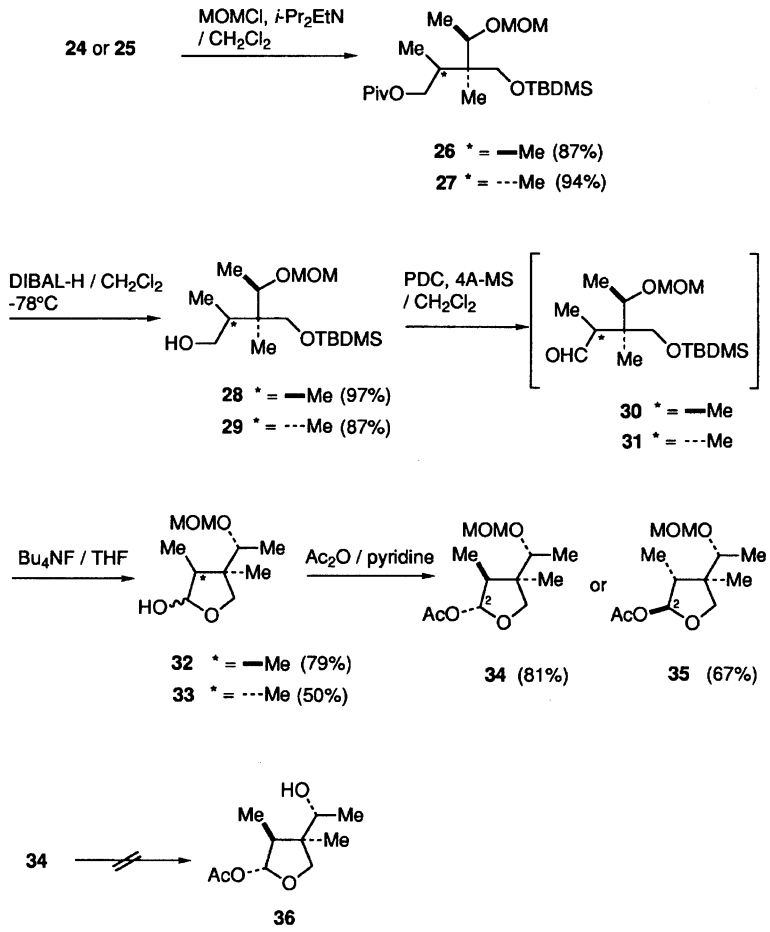
Scheme 2.

F_{254} (Merck) followed by detection using UV light and/or charring with H_2SO_4. Infrared (IR) spectra were recorded with a BIO-RAD DEGILAB FTS-65 ($CHCl_3$) or with a JASCO IR-810 (neat) spectrometer. ^1H NMR spectra were recorded with a JEOL EX-90 spectrometer (90 MHz) or with a JEOL GSX-270 spectrometer (270 MHz), and ^{13}C NMR spectra at 100 MHz were recorded with a JEOL GX 400 spectrometer. All NMR spectra were taken in a $CDCl_3$ solution.

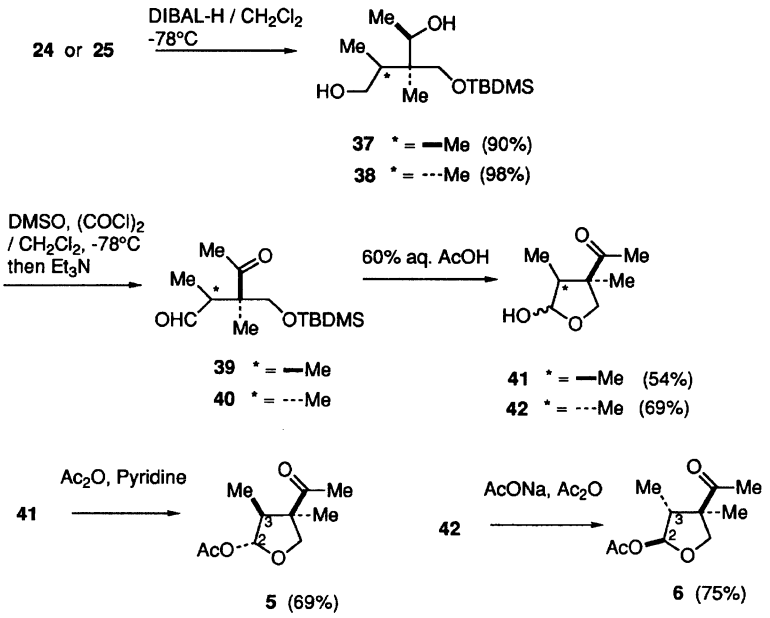
Dichloromethane (CH_2Cl_2), *N,N*-dimethylformamide (DMF) were dried over CaH_2 and then distilled. Pyridine was distilled over NaOH. Tetrahydrofuran (THF) was distilled over $LiAlH_4$ and then over Na/benzophenone.

(2*R*, 3*R*, 4*S*, 5*S*)-2, 3-(Isopropylidenedioxy)-5-[*R*-1, 2-(isopropylidenedioxy)ethyl]-4-[(*S*)-1-methyl-2-(pivaloyloxy)ethyl]-4-vinyltetrahydrofuran (12). To a stirred solution of **10**[8] (1.77 g, 5.40 mmol) in pyridine (36 ml) was added pivaloyl chloride (1.13 ml, 9.18 mmol). After being stirred for 3 h, the solution was poured into saturated aqueous $NaHCO_3$ (20 ml). The whole was extracted with CH_2Cl_2 (20 ml×3). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (45 g; EtOAc/hexane, 1:7) to give **12** (2.23 g, quant.) as a colorless oil: TLC R_f 0.47 (EtOAc/hexane, 1:5); $[\alpha]_D^{28}$ +50.7° (*c* 1.13, $CHCl_3$); IR (neat) ν_{max} 2980, 1725, 1635, 1280, 1150 cm^{-1}; ^1H NMR (270 MHz) δ=1.10 (3H, d, J=7.0 Hz, $CHCH_3$ of the side chain at C-4), 1.21 (9H, S, $C(CH_3)_3$), 1.32, 1.35, 1.42, 1.50 (each 3H, each s, $C(CH_3)_2$), 2.12—2.23 (1H, m, $CHCH_3$ of the side chain at C-4), 3.85—4.35 (6H, m, H-5, CH_2OPiv, H-1,2,2′ of the side chain at C-5), 4.76 (1H, d, J=3.3 Hz, H-3), 5.28 (1H, dd, J=1.5 and 11.4 Hz, CH=CH*H*), 5.40 (1H, dd, J=1.5 and 18.0 Hz, CH=CH*H*), 5.69 (1H, d, J=3.3 Hz, H-2), 5.92 (1H, dd, J=11.4 and 18.0 Hz, CH=CH_2). Found: C, 64.12; H, 8.74%. Calcd for $C_{22}H_{36}O_7$: 64.06; H, 8.80%.

(2*R*,3*R*,4*S*,5*S*)-2,3-(Isopropylidenedioxy)-5-[(*R*)-1, 2-(isopropylidenedioxy)ethyl]-4-[(*R*)-1-methyl-2-(pivaloyloxy)ethyl]-4-vinyltetrahydrofuran (13). Analogous to the preparation of **12**, 1.74 g (5.29 mmol) of **11** was converted into 2.12 g (97%) of **13**, a colorless oil: TLC R_f 0.16 (EtOAc/hexane, 1:15) ; $[\alpha]_D^{28}$ +18.0° (*c* 1.54, $CHCl_3$); IR (neat) ν_{max} 2990, 1730, 1640, 1280, 1150 cm^{-1}; ^1H NMR (270 MHz) δ=1.08 (3H, d, J=7.0 Hz, $CHCH_3$ of the side chain at C-4), 1.22 (9H, s, $C(CH_3)_3$), 1.31, 1.36, 1.42, 1.50 (each 3H, each s, $C(CH_3)_2$), 2.16—2.23



Scheme 3.



Scheme 4.

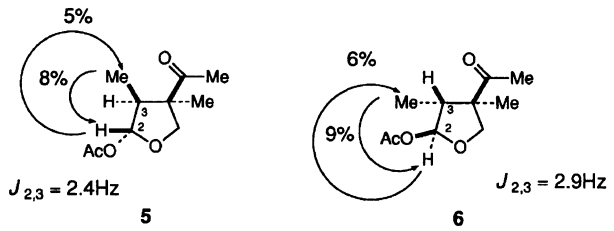


Fig. 2. NOE experiments of **5** and **6**.

Table 1. The Growth Inhibition of Murine Tumor Cell *in vitro* by **5** and **6**; Comparison with Adriamycin

Compd	Dosage / μg ml^{-1}	Inhibition rate [a] / % P388	Inhibition rate [a] / % Colon 26
	10	97	45
5	1	16	8
	0.1	−2	−5
	10	43	23
6	1	7	−3
	0.1	7	−12
	1	105	100
Adriamycin	0.1	100	71
	0.01	51	3
	0.001	6	−15

a) The calculation of the growth inhibiton rate (IR) (%); see Ref. 6.

(1H, m, C*H*CH$_3$ of the side chain at C-4), 3.84—4.36 (6H, m, H-5, CH$_2$OPiv, H-1,2,2′ of the side chain at C-5), 4.64 (1H, d, J=3.3 Hz, H-3), 5.30 (1H, dd, J=1.4 and 11.4 Hz, CH=CH*H*), 5.38 (1H, dd, J=1.4 and 18.0 Hz, CH=CH*H*), 5.71 (1H, d, J=3.3 Hz, H-2), 5.93 (1H, dd, J=11.4 and 18.0 Hz, C*H*=CH$_2$). Found: C, 64.05 ; H, 8.64%. Calcd for $C_{22}H_{36}O_7$: C, 64.06; H, 8.80%.

(2*R*,3*R*,4*S*,5*S*)-5-[(*R*)-1,2-Dihydroxyethyl]-2,3-(isopropylidenedioxy)-4-[(*S*)-1-methyl-2-(pivaloyloxy)ethyl]-4-vinyltetrahydrofuran (14). After compound **12** (2.23 g, 5.40 mmol) was dissolved in 60% aqueous acetic acid (45 ml), the solution was stirred for 1 d. The solvent was removed by concentration in vacuo. The residue was purified by column chromatography on silica gel (45 g; EtOAc/hexane, 1: 2) to give **14** (1.86 g, 93%) as white crystals, mp 85.5—86.2°C: TLC R_f 0.42 (EtOH/toluene, 1:8); $[\alpha]_D^{27}$ +31.5° (c 1.00, CHCl$_3$); IR (CHCl$_3$) ν_{max} 3506, 2980, 1721, 1639, 1286, 1168 cm^{-1}; ^{1}H NMR (270 MHz) δ=1.09 (3H, d, J=7.0 Hz, CHC*H*$_3$ of the side chain at C-4), 1.21 (9H, s, C(CH$_3$)$_3$), 1.32, 1.50 (each 3H, each s, C(CH$_3$)$_2$), 2.27 —2.33 (1H, m, C*H*CH$_3$ of the side chain at C-4), 2.92 (2H, d, J=5.5 Hz, OH), 3.67—4.00 (3H, m, H-1,2,2′ of the side chain at C-5), 3.97 (1H, dd, J=7.9 and 11.2 Hz, C*H*HOPiv), 4.13 (1H, d, J=9.2 Hz, H-5), 4.38 (1H, dd, J=3.1 and 11.2 Hz, CH*H*OPiv), 4.71 (1H, d, J=3.5 Hz, H-3), 5.31 (1H, dd, J=1.1 and 11.6 Hz, CH=CH*H*), 5.39 (1H, dd, J=1.1 and 18.1 Hz, CH=CH*H*), 5.71 (1H, d, J=3.5 Hz, H-2), 6.01 (1H, dd, J=11.6 and 18.1 Hz, C*H*=CH$_2$). Found: C, 61.24; H, 8.50%. Calcd for $C_{19}H_{32}O_7$: C, 61.27; H, 8.66%.

(2*R*,3*R*,4*S*,5*S*)-5-[(*R*)-1,2-Dihydroxyethyl]-2,3-(isopropylidenedioxy)-4-[(*R*)-1-methyl-2-(pivaloyloxy)ethyl]-4-vinyltetrahydrofuran (15). Analogous to the preparation of **14**, 2.07 g (5.03 mmol) of **13** was converted into 1.79 g (96%) of **15**, a colorless oil: TLC R_f 0.22 (EtOAc/hexane, 1:2); $[\alpha]_D^{28}$ +11.1 ° (c 0.95, CHCl$_3$); IR (neat) ν_{max} 3450, 2990, 1730, 1650, 1290, 1170 cm^{-1}; ^{1}H NMR (270 MHz) δ=1.11 (3H, d, J=7.0 Hz, CHC*H*$_3$ of the side chain at C-4), 1.22 (9H, s, C(CH$_3$)$_3$), 1.32, 1.52 (each 3H, each s, C(CH$_3$)$_2$), 2.28 (2H, s, OH), 2.31—2.39 (1H, m, C*H*CH$_3$ of the side chain at C-4), 3.68—4.15 (5H, m, H-5, C*H*HOPiv, H-1,2,2′ of the side chain at C-5), 4.42 (1H, dd, J=4.0 and 11.0 Hz, CH*H*OPiv), 4.59 (1H, d, J=3.7 Hz, H-3), 5.33 (1H, dd, J=1.3 and 11.5 Hz, CH=CH*H*), 5.36 (1H, dd, J=1.3 and 18.1 Hz, CH=CH*H*), 5.73 (1H, d, J=3.7 Hz, H-2), 6.03 (1H, dd, J=11.5 and 18.1 Hz, C*H*=CH$_2$). Found: C, 61.51; H, 8.40%. Calcd for $C_{19}H_{32}O_7$: C, 61.27; H, 8.66%.

(2*R*, 3*R*, 4*S*, 5*S*)- 4, 5- Bis[bis(ethylthio)methyl]-2,3-(isopropylidenedioxy)-4-[(*S*)-1-methyl-2-(pivaloyloxy)ethyl]tetrahydrofuran (16). To a solution of **14** (1.70 g, 4.56 mmol) in CH$_2$Cl$_2$ (100 ml) was bubbled ozone (ca. 3% in O$_2$) for 2 h at −78 °C. To the mixture was added a solution of Ph$_3$P (1.32 g, 5.02 mmol) in CH$_2$Cl$_2$ (5 ml). After being stirred for 1 h, the mixture was warmed slowly to r.t. This was concentrated in vacuo to give crude hydroxy aldehyde: TLC R_f 0.29 (EtOAc/hexane, 1:1); IR (neat) ν_{max} 3415, 2975, 1720, 1280, 1160 cm^{-1}; ^{1}H NMR (90 MHz) δ=1.10 (3H, d, J=7.2 Hz, CHC*H*$_3$ of the side chain at C-4), 1.20 (9H, s, C(CH$_3$)$_3$), 1.34, 1.47 (each 3H, each s, C(CH$_3$)$_2$), 2.40—2.70 (2H, m, OH, C*H*CH$_3$ of the side chain at C-4), 3.76—4.31 (7H, m, OH, H-5, CH$_2$OPiv, H-1,2,2′ of the side chain at C-5), 5.03 (1H, d, J=3.6 Hz, H-3), 5.80 (1H, d, J=3.6 Hz, H-2), 9.70 (1H, s, CHO).

To a stirred solution of the above mentioned aldehyde in MeOH (60 ml) was added an aqueous solution (40 ml) of NaIO$_4$ (4.88 g, 22.8 mmol) at 0 °C. After being stirred for 1.5 h, an aqueous solution (8 ml) of NaIO$_4$ (0.98 g, 4.56 mmol) and MeOH (12 ml) was added. Further, an aqueous solution (16 ml) of NaIO$_4$ (1.95 g, 9.12 mmol) and MeOH (24 ml) was added after 1 h; the mixture was then stirred for an additional 1 h. The resulting solids were filtered off and the filtrate was concentrated in vacuo. The residue was partitioned between H$_2$O (25 ml) and CH$_2$Cl$_2$ (100 ml). The aqueous layer was extracted with CH$_2$Cl$_2$ (100 ml×2). The combined organic layer and extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo to give crude dialdehyde: TLC R_f 0.38 (EtOAc/hexane, 1:2); IR (neat) ν_{max} 2980, 1730, 1280, 1160, cm^{-1}; ^{1}H NMR (90 MHz) δ=0.97 (3H, d, J=7.2 Hz, CHC*H*$_3$ of the side chain at C-4), 1.21 (9H, s, C(CH$_3$)$_3$), 1.34, 1.47 (each 3H, each s, C(CH$_3$)$_2$), 2.20—2.42 (1H, m, C*H*CH$_3$ of the side chain at C-4), 3.92—4.34 (2H, m, CH$_2$OPiv), 4.93 (1H, s, H-5), 5.20 (1H, d, J=3.6 Hz, H-3), 5.96 (1H, d, J=3.6 Hz, H-2), 9.80, 9.86 (each 1H, each s, CHO).

To a stirred solution of crude dialdehyde in CH$_2$Cl$_2$ (50 ml) were added EtSH (6.76 ml, 91.3 mmol) and BF$_3$·OEt$_2$–Et$_2$O complex (1.68 ml, 13.7 mmol). The mixture was stirred for 1.5 h at −15 °C. After aqueous ammonia (5 ml) was added for neutralization, the solution was poured into H$_2$O (100 ml). The whole was extracted with CH$_2$Cl$_2$ (100 ml×3). The combined extracts were dried (Na$_2$SO$_4$)

and concentrated in vacuo. The residue was purified by column chromatography on silica gel (100 g; EtOAc/hexane, 1:20) to give **16** (2.21 g, 87%), a colorless oil: TLC R_f 0.70 (EtOAc/hexane, 1:3); $[\alpha]_D^{26}$ −4.3° (*c* 1.16, $CHCl_3$); IR (neat) ν_{max} 2970, 1725, 1280, 1160 cm^{-1}; ^1H NMR (270 MHz) δ=1.18—1.33 (18H, m, $SCH_2CH_3\times4$, one of $C(CH_3)_2$, $CHCH_3$ of the side chain at C-4), 1.21 (9H, s, $C(CH_3)_3$), 1.56 (3H, s, one of $C(CH_3)_2$), 2.45—2.55 (1H, m, $CHCH_3$ of the side chain at C-4), 2.70—2.89 (9H, m, $SCH_2CH_3\times4$, $CH(SEt)_2$ of the side chain at C-4), 4.23—4.34 (3H, m, H-5, CH_2OPiv), 4.69—4.71 (1H, m, $CH(SEt)_2$ of the side chain at C-5), 4.75 (1H, d, J=3.7 Hz, H-3), 5.72 (1H, d, J=3.7 Hz, H-2). Found: C, 54.25; H, 8.14%. Calcd for $C_{25}H_{46}O_5S_4$: C, 54.12: H, 8.36%.

(2*R*,3*R*,4*S*,5*S*)-4,5-Bis[bis(ethylthio)methyl]-2,3-(isopropylidenedioxy)-4-[(*R*)-1-methyl-2-(pivaloyloxy)ethyl]tetrahydrofuran (17). Analogous to the preparation of **16**, 1.73 g (4.65 mmol) of **15** was converted into 2.24 g (87%) of **17**, a colorless oil.

The Ozonolysis Product: TLC R_f 0.30 (EtOAc/hexane, 1:1); IR (neat) ν_{max} 3420, 2970, 1730, 1280, 1170 cm^{-1}; ^1H NMR (90 MHz) δ=1.16—1.22 (12H, m, $C(CH_3)_3$, $CHCH_3$ of the side chain at C-4), 1.33, 1.49 (each 3H, each s, $C(CH_3)_2$), 2.40—2.75 (3H, m, OH×2, $CHCH_3$ of the side chain at C-4), 3.57—4.40 (6H, m, H-5, CH_2OPiv, H-1,2,2′ of the side chain at C-5), 4.98 (1H, d, J=4.0 Hz, H-3), 5.78 (1H, d, J=4.0 Hz, H-2), 9.78 (1H, s, CHO).

The Glycol Cleavage Product : TLC R_f 0.68 (EtOAc/hexane, 1:1); IR (neat) ν_{max} 2980, 1720, 1280, 1160 cm^{-1}; ^1H NMR (90 MHz) δ=1.10 (3H, d, J=6.0 Hz, $CHCH_3$ of the side chain at C-4), 1.20 (9H, s, $C(CH_3)_3$), 1.35, 1.50 (each 3H, each s, $C(CH_3)_2$, 2.30—2.52 (1H, m, $CHCH_3$ of the side chain at C-4), 3.95—4.07 (2H, m, CH_2OPiv), 4.98 (1H, s, H-5), 5.00 (1H, d, J=4.0 Hz, H-3), 5.97 (1H, d, J=4.0 Hz, H-2), 9.76—9.80 (2H, m, CHO).

Compound 17: TLC R_f 0.37 (EtOAc/hexane, 1:10); $[\alpha]_D^{24}$ +17.7° (*c* 0.75, $CHCl_3$); IR (neat) ν_{max} 2970, 1730, 1280, 1170 cm^{-1}; ^1H NMR (270 MHz) δ=1.21 (9H, s, $C(CH_3)_3$), 1.23—1.32 (18H, m, $SCH_2CH_3\times4$, one of $C(CH_3)_2$, $CHCH_3$ of the side chain at C-4), 1.55 (3H, s, one of $C(CH_3)_2$), 2.58—2.90 (10H, m, $SCH_2CH_3\times4$, $CHCH_3$ of the side chain at C-4, $CH(SEt)_2$ of the side chain at C-4), 4.13—4.70 (4H, m, CH_2OPiv, H-5, $CH(SEt)_2$ of the side chain at C-5), 4.70 (1H, d, J=3.3 Hz, H-3), 5.73 (1H, d, J=3.3 Hz, H-2). Found: C, 54.31; H, 8.05%. Calcd for $C_{25}H_{46}O_5S_4$: C, 54.12; H, 8.36%.

(2*R*,3*R*,4*S*,5*R*)-2,3-(Isopropylidenedioxy)-4,5-dimethyl-4-[(*S*)-1-methyl-2-(pivaloyloxy)ethyl]tetrahydrofuran (18). To a suspension of Raney nickel (T-4) (30 g) in EtOH) (20 ml) was added a solution of **16** (2.21 g, 3.98 mmol) in EtOH (30 ml). After the mixture was refluxed for 3 h, the catalyst was filtered off through a pad of Celite. The combined filtrate and washing (EtOH) were concentrated in vacuo. The residue was purified by column chromatography on silica gel (38 g; EtOAc/hexane, 1:20) to give **18** (860 mg, 69%), a colorless oil: TLC R_f 0.47 (EtOAc)/hexane, 1:5); $[\alpha]_D^{27}$ +12.6° (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 2980, 1725, 1280, 1160 cm^{-1}; ^1H NMR (270 MHz) δ=1.02 (3H, d, J=5.9 Hz, $CHCH_3$ of the side chain at C-4), 1.03 (3H, s, CH_3-4), 1.22 (9H, s, $C(CH_3)_3$), 1.23 (3H, d, J=6.6 Hz, CH_3-5), 1.31, 1.51 (each 3H, each s, $C(CH_3)_2$), 1.84—1.91 (1H, m, $CHCH_3$ of the side chain at C-4), 3.98—4.06 (2H, m, H-5, $CHHOPiv$), 4.18 (1H, dd, J=3.9 and 11.2 Hz, $CHHOPiv$), 4.56 (1H, d, J=4.0 Hz, H-3), 5.72 (1H, d, J=4.0 Hz, H-2). Found: C, 64.90; H, 9.45%. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62%.

(2*R*,3*R*,4*S*,5*R*)-2,3-(Isopropylidenedioxy)-4,5-dimethyl-4-[(*R*)-1-methyl-2-(pivaloyloxy)ethyl]tetrahydrofuran (19). As analogous to the preparation of **18**, 1.99 g (3.59 mmol) of **17** was converted into 872 mg (77%) of **19**, a colorless oil: TLC R_f 0.46 (EtOAc/hexane, 1:5); $[\alpha]_D^{24}$ −20.4° (*c* 0.94, $CHCl_3$); IR (neat) ν_{max} 2980, 1730, 1280, 1160 cm^{-1}; ^1H NMR (270 MHz) δ=1.01 (3H, s, CH_3-4), 1.02 (3H, d, J=6.6 Hz, $CHCH_3$ of the side chain at C-4), 1.21 (9H, s, $C(CH_3)_3$), 1.27 (3H, d, J=7.0 Hz, CH_3-5), 1.32, 1.51 (each 3H, each s, $C(CH_3)_2$), 1.91—1.95 (1H, m, $CHCH_3$ of the side chain at C-4), 3.72 (1H, dd, J=8.1 and 11.0 Hz, $CHHOPiv$), 4.02 (1H, q, J=6.6 Hz, H-5), 4.42 (1H, dd, J=4.0 and 11.0 Hz, $CHHOPiv$), 4.48 (1H, d, J=4.0 Hz, H-3), 5.71 (1H, d, J=4.0 Hz, H-2). Found: C, 64.98; H, 9.45%. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62%.

(2*RS*,3*R*,4*S*,5*R*)-2,3-Dihydroxy-4,5-dimethyl-4-[(*S*)-1-methyl-2-(pivaloyloxy)ethyl]tetrahydrofuran (20). After compound **18** (879 mg, 2.79 mmol) was dissolved in 60% aqueous trifluoroacetic acid (18 ml), the solution was stirred for 7.5 h at 5 °C. This was neutralized by adding 10 M aqueous NaOH (1 M=1 mol dm^{-3}). The whole was diluted with H_2O (70 ml), and extracted with CH_2Cl_2 (100 ml×3). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (31 g; EtOAc/hexane, 1:1) to give **20** as a 2:1 anomeric mixture (678 mg, 88%), a colorless oil: TLC R_f 0.25 (EtOAc/hexane, 1:1); IR (neat) ν_{max} 3430, 2970, 1725, 1280, 1160 cm^{-1}; ^1H NMR (270 MHz) δ=1.03 (3H×2/3, s, CH_3-4), 1.04 (3H×1/3, s, CH_3-4), 1.07 (3H, d, J=6.8 Hz, $CHCH_3$ of the side chain at C-4), 1.21—1.26 (3H×2/3, 9H, m, CH_3-5, $C(CH_3)_3$), 1.33 (3H×1/3, d, J=6.8 Hz, CH_3-5), 1.92—2.18 (1H, m, $CHCH_3$ of the side chain at C-4), 3.75—4.15 (4H, m, H-3, 5, CH_2OPiv), 5.21 (1H×1/3, d, J=3.9 Hz, H-2), 5.38 (1H×2/3, d, J=5.4 Hz, H-2). Found: C, 61.22; H, 9.48%. Calcd for $C_{14}H_{26}O_5$: C, 61.29; H, 9.55%.

(2*RS*,3*R*,4*S*,5*R*)-2,3-Dihydroxy-4,5-dimethyl-4-[(*R*)-1-methyl-2-(pivaloyloxy)ethyl]tetrahydrofuran (21). Analogously, as described regarding the preparation of **20**, 834 mg (2.65 mmol) of **19** was converted into 619 mg (85%) of **21** as a 1:1 anomeric mixture. Compound **19** was also recovered (68 mg, 8%). **21** as a colorless oil: TLC R_f 0.16 (EtOAc/hexane, 1:2); IR (neat) ν_{max} 3440, 2970, 1720, 1280, 1160 cm^{-1}; ^1H NMR (270 MHz) δ=0.91, 0.95 (each 3H×1/2, each d, J=6.6 Hz, $CHCH_3$ of the side chain at C-4), 1.05, 1.06 (each 3H×1/2, each s, CH_3-4), 1.17 (3H×1/2, d, J=6.6 Hz, CH_3-5), 1.205, 1.212 (each 9H×1/2, each s, $C(CH_3)_3$), 1.28 (3H×1/2, d, J=7.0 Hz, CH_3-5), 1.91—2.02 (1H, m, $CHCH_3$ of the side chain at C-4), 3.80—4.05 (2H, m, H-5, CH_2OPiv), 4.09 (1H×1/2, d, J=4.4 Hz, H-3), 4.12 (1H×1/2, d, J=5.9 Hz, H-3), 4.40 (1H×1/2, dd, J=5.1 and 11.2 Hz, $CHHOPiv$), 4.49 (1H×1/2, dd, J=4.0 and 11.2 Hz, $CHHOPiv$), 5.24 (1H×1/2, d, J=4.4 Hz, H-2), 5.39 (1H×1/2, d, J=5.9 Hz, H-2). Found: 61.07 ; H, 9.28%. Calcd for $C_{14}H_{26}O_5$: C, 61.29; H, 9.55%.

(2*R*,3*R*)-2-Methyl-2-[(*S*)-1-methyl-2-(pivaloyloxy)-ethyl]-1,3-butanediol (22). To a stirred solution of **20** (539 mg, 1.96 mmol) in MeOH (14 ml) was added an aque-

ous solution (9 ml) of $NaIO_4$ (1.05 g, 4.91 mmol). While the mixture was being stirred at rt for 2.5 h, aqueous solutions (2 ml) of $NaIO_4$ (210 mg, 0.98 mmol) and MeOH (2 ml) were added after 1.5 and 2.0 h. The resulting solids were filtered off and washed with MeOH. The combined filtrate and washing were concentrated in vacuo. The residue was partitioned with H_2O (90 ml) and CH_2Cl_2 (100 ml). The aqueous layer was extracted with CH_2Cl_2 (100 ml×2). The combined organic layer and extracts were dried (Na_2SO_4) and concentrated in vacuo to give crude aldehyde as a colorless oil: TLC R_f 0.47 (EtOAc/hexane, 1:4); IR (neat) ν_{max} 2970, 1725, 1710, 1280, 1150 cm^{-1}; ^1H NMR (90 MHz) δ=0.96—1.37 (9H, m, CH_3-1,3,4), 1.21 (9H, s, $C(CH_3)_3$), 2.10, 2.50 (1H, m, H-4), 3.96 (1H, dd, J=5.0 and 11.5 Hz, H-5), 4.21 (1H, dd, J=5.0 and 11.5 Hz, H-5′), 5.47 (1H, dq, J=1.0 and 6.5 Hz, H-2), 8.05 (1H, br, OCHO), 9.62 (1H, s, CHO).

To a stirred solution of the crude aldehyde in EtOH (11 ml) was added $NaBH_4$ (223 mg, 5.89 mmol) at 0 °C. After being stirred for 30 min, 35% aqueous H_2O_2 (5 ml) was added. After being stirred for 1 h, 1M aqueous NaOH (1 ml) was added and the mixture was stirred for 10 min. This solution was neutralized with 1M aqueous HCl. The resulting solids were filtered off, and the filtrate was concentrated in vacuo. The residue was partitioned between 1 M aqueous NaOH (100 ml) and CH_2Cl_2 (100 ml). The aqueous layer was extracted with CH_2Cl_2 (100 ml×3). The combined organic layer and extracts were dried (Na_2SO_4) are concentrated in vacuo. The residue was purified by column chromatography on silica gel (20 g; acetone/toluene, 1:7) to give **22** (385 mg; 80%) as white crystals, mp 89.0—89.5°C: TLC R_f 0.40 (EtOAc/hexane, 1:1); $[\alpha]_D^{26}$ +37.6° (c 1.07, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3478, 2978, 1719, 1288, 1167 cm^{-1}; ^1H NMR (270 MHz) δ=0.97 (3H, s, CH_3-2), 1.00 (3H, d, J=7.0 Hz, CHCH_3 of the side chain at C-2), 1.20 (9H, s, $C(CH_3)_3$), 1.31 (3H, d, J=6.3 Hz, CH_3-4), 1.86—1.98 (1H, m, CHCH$_3$ of the side chain at C-2), 3.56, 3.73 (each, 1H, ABq, J=11.0 Hz, H-1,1′), 3.83 (1H, dd, J=8.4 and 11.0 Hz, CHHOPiv). 3.93 (1H, q, J=6.3 Hz, H-3), 4.29 (1H, dd, J=4.0 and 11.0 Hz, CHHOPiv). Found: C, 63.21; H, 10.64%. Calcd for $C_{13}H_{26}O_4$: C, 63.38; H, 10. 64%.

(2*R*,3*R*)-2-Methyl-2-[(*R*)-1-methyl-2-(pivaloyloxy)ethyl]-1,3-butanediol (23). Analogously as describe in the preparation of **22**, 471 mg (1.72 mmol) of **21** was converted into 340 mg (80%) of **23**, a colorless oil.

The Glycol Cleavage Product: TLC R_f 0.69 (EtOAc/hexane, 1:2); IR (neat) ν_{max} 2980, 1725, 1280, 1150 cm^{-1}; ^1H NMR (90 MHz) δ=1.01 (3H, d, J=7.0 Hz, CH_3-4), 1.14 (3H, s, CH_3-3), 1.18 (9H, s $C(CH_3)_3$), 1.35 (3H, d, J=7.0 Hz, CH_3-1), 2.22—2.60 (1H, m, H-4), 3.88, 4.04 (each 1H, each dd, J=6.0 and 11.5 Hz, H-5,5′), 5.31 (1H, dd, J=1.0 and 7.0 Hz, H-2), 8.06 (1H, br, OCHO), 9.69 (1H, s, CHO).

Compound 23: TLC R_f 0.23 (EtOAc/hexane, 1:2); IR (neat) ν_{max} 3420, 2970, 1720, 1285, 1160 cm^{-1}; ^1H NMR (270 MHz) δ=0.88 (3H, s, CH_3-2), 0.99 (3H, d, J=6.8 Hz, CHCH_3 of the side chain at C-2), 1.21 (9H, s, $C(CH_3)_3$), 1.27 (3H, d, J=6.4 Hz, CH_3-4), 1.89—1.96 (1H, m, CHCH$_3$ of the side chain at C-2), 2.60 (2H, br, OH), 3.58, 3.76 (each 1H, ABq, J=11.2 Hz, H-1,1′), 3.88 (1H, dd, J=8.3 and 11.2 Hz, CHHOPiv), 3.94 (1H, q, J=6.4 Hz, H-3), 4.47 (1H, dd, J=3.7 and 11.2 Hz, CHHOPiv). Found: C, 63.49; H, 10.34%. Calcd for $C_{13}H_{26}O_4$: C, 63.38; H, 10.64%.

(2*R*,3*R*,4*S*)-3,4-Dimethyl-5-(pivaloyloxy)-3-[(*t*-butyldimethylsiloxy)methyl]-2-pentanol (24). To a stirred solution of **22** (385 mg, 1.56 mmol) in DMF (8 ml) were added imidazole (213 mg, 3.12 mmol) and TBDMSCl (282 mg, 1.87 mmol). After being stirred for 2 h, imidazole (53.2 mg, 0.78 mmol) and TBDMSCl (70.6 mg, 0.47 mmol) were added to the mixture. The mixture was stirred for an additional 1 h. This was diluted with saturated aqueous $NaHCO_3$ (25 ml) and extracted with CH_2Cl_2 (25 ml×3). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (23 g; acetone/toluene, 1:12) to give **24** (555 mg; 99%), a colorless oil: TLC R_f 0.58 (EtOAc/hexane, 1:4); $[\alpha]_D^{23}$ +17.6° (c 0.93, $CHCl_3$); IR (neat) ν_{max} 3520, 2960, 1725, 1280, 1255, 1155, 1085 cm^{-1}; ^1H NMR (270 MHz) δ=0.07, 0.08 (each 3H, each s, Si $(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.93 (3H, s, CH_3-3), 0.96 (3H, d, J=7.0 Hz, CH_3-4), 1.20 (9H, s, $C(CH_3)_3$), 1.25 (3H, d, J=6.6 Hz, CH_3-1), 1.91—1.98 (1H, m, H-4), 3.48, 3.66 (each 1H, ABq, J=9.9 Hz, CH_2OTBDMS), 3.85 (1H, q, J=6.6 Hz, H-2), 3.86 (1H, dd, J=8.4 and 11.0 Hz, H-5), 4.24 (1H, dd, J=4.4 and 11.0 Hz, H-5′). Found: C, 63.46; 10.90%. Calcd for $C_{19}H_{40}O_4Si$: C, 63.28; H, 11.18%.

(2*R*,3*R*,4*R*)-3,4-Dimethyl-5-(pivaloyloxy)-3-[(*t*-butyldimethylsiloxy)methyl]-2-pentanol (25). Analogously, as described for **24**, 321 mg (1.30 mmol) of **23** was converted into 402 mg (86%) of **25**, a colorless oil: TLC R_f 0.74 (EtOAc/hexane, 1:2); $[\alpha]_D^{21}$ −32.5° (c 1.09, $CHCl_3$); IR (neat) ν_{max} 3520, 2950, 1720, 1280, 1250, 1160, 1080, cm^{-1}; ^1H NMR (270 MHz) δ=0.07, 0.08 (each 3H, s, Si $(CH_3)_2$), 0.86 (3H, s, CH_3-3), 0.90 (9H, s, $SiC(CH_3)_3$), 0.97 (3H, d, J=7.0 Hz, CH_3-4), 1.20 (9H, s, $C(CH_3)_3$), 1.21 (3H, d, J=6.4 Hz, CH_3-1), 1.85—1.92 (1H, m, H-4), 3.47, 3.69 (each 1H, ABq, J=10.3 Hz, CH_2OTBDMS), 3.82 (1H, dd, J=8.8 and 11.0 Hz, H-5), 3.94 (1H, q, J=6.4 Hz, H-2), 4.41 (1H, dd, J=3.3 and 11.0 Hz, H-5′). Found: C, 63.28; H, 10.88%. Calcd for $C_{19}H_{40}O_4Si$: C, 63.28; H, 11.18 %.

(2*S*, 3*R*, 4*R*)-4-(Methoxymethoxy)-2,3-dimethyl-1-(pivaloyloxy)-3-[(*t*-butyldimethylsiloxy)methyl]pentane (26). To a stirred solution of **24** (466 mg, 1.29 mmol) in CH_2Cl_2 (10 ml) were added *N*,*N*-diisopropylethylamine (2.25 ml, 12.9 mmol) and chloromethyl methyl ether (0.49ml, 6.46 mmol) at 0 °C. After being stirred for 1 d, the mixture was diluted with 0.2 M aqueous HCl (20 ml). The whole was extracted with CH_2Cl_2 (20 ml×3). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20 g; EtOAc/hexane, 1:40) to give **26** (455 mg, 87%), a colorless oil: TLC R_f 0.68 (EtOAc/hexane, 1:7); IR (neat) ν_{max} 2960, 1730, 1280, 1260, 1150, 1090, cm^{-1}; ^1H NMR (270 MHz) δ=0.07 (6H, s, $Si(CH_3)_2$), 0.82 (3H, s, CH_3-3), 0.89 (9H, s, $SiC(CH_3)_3$), 1.02 (3H, d, J=6.8 Hz, CH_3-2), 1.19 (3H, d, J=6.4 Hz, CH_3-5), 1.20 (9H, s, $C(CH_3)_3$), 2.10—2.17 (1H, m, H-2), 3.36 (3H, s, OCH_3), 3.38, 3.57 (each 1H, ABq, J=9.8 Hz, CH_2OTBDMS), 3.71 (1H, q, J=6.4 Hz, H-4), 3.90 (1H, dd, J=8.5 and 10.7 Hz, H-1), 4.25 (1H, dd, J=3.9 and 10.7 Hz, H-1′), 4.59, 4.70 (each 1H, ABq, J=6.8 Hz, CH_2OCH$_3$).

(2*R*,3*R*,4*R*)-4-(Methoxymethoxy)-2,3-dimethyl-1-(pivaloyloxy)-3-[(*t*-butyldimethylsiloxy)methyl]pentane (27). Analogously as described for **26**, 355 mg (0.99

mmol) of **25** was converted into 375 mg (94%) of **27**, a colorless oil: TLC R_f 0.73 (EtOAc/hexane, 1:5); IR (neat) ν_{max} 2960, 1725, 1280, 1250, 1160, 1080 cm^{-1}; ^1H NMR (270 MHz) δ=0.04 (6H, s, $Si(CH_3)_2$), 0.80 (3H, s, CH_3-3), 0.89 (9H, s, $SiC(CH_3)_3$), 0.95 (3H, d, J=7.0 Hz, CH_3-2), 1.19 (3H, d, J=7.0 Hz, CH_3-5), 1.20 (9H, s, $C(CH_3)_3$), 2.13—2.21 (1H, m, H-2), 3.35 (3H, s, OCH_3), 3.47, 3.52 (each 1H, ABq, J=10.1 Hz, CH_2OTBDMS), 3.77 (1H, q, J=7.0 Hz, H-4), 3.93 (1H, dd, J=9.7 and 10.8 Hz, H-1), 4.33 (1H, dd, J=3.1 and 10.8 Hz, H-1'), 4.61, 4.69 (each 1H, ABq, J=7.0 Hz, CH_2OCH_3).

(2*S*,3*R*,4*R*)-4-(Methoxymethoxy)-2,3-dimethyl-3-[(*t*-butyldimethylsiloxy)methyl]-1-pentanol (28). The reacton was carried out under an argon atmosphere. To a stirred solution of **26** (415 mg, 1.03 mmol) in CH_2Cl_2 (9 ml) was added DIBAL-H (2.39 ml, 1.5 M solution in toluene, 3.59 mmol) at −78 °C. The mixture was stirred for 30 min, and quenched by adding H_2O (0.5 ml). After being stirred for 10 min at 0 °C, the resulting solids were filtered off and washed with CH_2Cl_2. The combined filtrate and washings were concentrated in vacuo. The residue was partitioned between 0.1 M aqueous HCl (20 ml) and CH_2Cl_2 (20 ml). The aqueous layer was extracted with CH_2Cl_2 (20 ml×3). The combined organic layer and extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (13 g; EtOAc/hexane, 1:7) to give **28** (319 mg, 97%), a colorless oil: TLC R_f 0.28 (EtOAc/hexane, 1:4); IR (neat) ν_{max} 3430, 2960, 1255, 1090 cm^{-1}; ^1H NMR (270 MHz) δ=0.08 (6H, s, $Si(CH_3)_2$), 0.89 (3H, s, CH_3-3), 0.91 (9H, s, $SiC(CH_3)_3$), 1.10 (3H, d, J=7.0 Hz, CH_3-2), 1.17 (3H, d, J=6.2 Hz, CH_3-5), 1.87—1.94 (1H, m, H-2), 3.32, 3.63 (each 1H, ABq, J=9.9 Hz, CH_2OTBDMS), 3.37 (3H, s, OCH_3), 3.54 (1H, dd, J=4.0 and 11.4 Hz, H-1), 3.62 (1H, q, J=6.2 Hz, H-4), 3.70 (1H, dd, J=4.0 and 11.4 Hz, H-1'), 4.57, 4.69 (each 1H, ABq, J=7.0 Hz, OCH_2OCH_3).

(2*R*,3*R*,4*R*)-4-(Methoxymethoxy)-2,3-dimethyl-3-[(*t*-butyldimethylsiloxy)methyl]-1-pentanol (29). Analogously, as described regarding the preparation of **28**, 375 mg (0.93 mmol) of **27** was converted into 259 mg (87%) of **29**, a colorless oil: TLC R_f 0.30 (EtOAc/hexane, 1:5); IR (neat) ν_{max} 3440, 2960, 1250, 1090 cm^{-1}; ^1H NMR (270 MHz) δ=0.08 (6H, s, $Si(CH_3)_2$), 0.82 (3H, s, CH_3-3), 0.91 (9H, s, $SiC(CH_3)_3$), 0.93 (3H, d, J=6.8 Hz, CH_3-2), 1.19 (3H, d, J=6.4 Hz, CH_3-5), 1.95—2.02 (1H, m, H-2), 3.37 (3H, s, OCH_3), 3.47, 3.62 (each 1H, ABq, J=10.5 Hz, CH_2-OTBDMS), 3.59 (2H, d, J=4.9 Hz, H-1,1'), 3.83 (1H, q, J=6.4 Hz, H-4), 4.65, 4.71 (each 1H, ABq, J=6.6 Hz, OCH_2OCH_3).

(2*RS*,3*S*,4*R*)-4-[(*R*)-1-(Methoxymethoxy)ethyl]-3,4-dimethyltetrahydro-2-furanol (32). To a stirred solution of **28** (266 mg, 0.83 mmol) in CH_2Cl_2 (6 ml) were added molecular sieves (4A powder) (624 mg) and PDC (1.25 g, 3.32 mmol). The mixture was stirred for 3 h, while molecular sieves (300 mg) and PDC (413 mg) were added after 2 h. The insoluble materials were removed by passage through silica gel (12 g, ether elution) to give **30**: TLC R_f 0.62 (EtOAc/hexane, 1:4); IR (neat) ν_{max} 2950, 1715, 1250, 1140, cm^{-1}; ^1H NMR (270 MHz) δ=0.029, 0.034 (each 3H, each s, $Si(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.97 (3H, s, CH_3-3), 1.07 (3H, d, J=7.1 Hz, CH_3-2), 1.16 (3H, d, J=6.3 Hz, CH_3-4), 2.52 (1H, dq, J=3.9 Hz, J=7.1 Hz, H-2), 3.34 (3H, s, OCH_3), 3.34, 3.44 (each 1H, ABq, J=10.3 Hz, CH_2OTBDMS), 4.51, 4.59 (each 1H, ABq, J=6.8 Hz, OCH_2OCH_3), 9.71 (1H, d, J=3.9 Hz, CHO).

To a stirred solution of **30** in THF (5 ml) was added *n*-Bu_4NF (2.49 ml, 1.0 M solution in THF, 2.49 mmol) at 0 °C. After being stirred for 40 min, the mixture was diluted with saturated aqueous $NaHCO_3$ (20 ml). The whole was extracted with EtOAc (20 ml×3). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (7 g; EtOAc/hexane, 1:2) to give **32** as a 1:1 anomeric mixture (134 mg, 79%), a colorless oil: TLC R_f 0.41 (EtOAc/hexane, 1:1); IR (neat) ν_{max} 3430, 2970, 1450, 1375 cm^{-1}; ^1H NMR (270 MHz) δ=1.08 (3H×1/2, d, J=7.8 Hz, CH_3-3), 1.09—1.16 (6H×1/2, m, CH_3-3, CH_3 of the side chain at C-4), 1.11, 1.20 (each 3H×1/2, each s, CH_3-4), 1.25 (3H×1/2, d, J=6.8 Hz, CH_3 of the side chain at C-4), 1.93—2.16 (1H, m, H-3), 3.38, 3.45 (each 3H×1/2, each s, OCH_3), 3.57—3.93 (3H, m, H-5,5', H-1 of the side chain at C-4), 4.59, 4.72 (each 1H×1/2, ABq, J=7.1 Hz, OCH_2OCH_3), 4.64, 4.82 (each 1H×1/2, ABq, J=7.3 Hz, OCH_2OCH_3), 5.13 (1H×1/2, t, J=3.4 Hz, H-2), 5.22 (1H×1/2, dd, J=5.4 and 11.5 Hz, H-2).

(2*RS*,3*S*,4*R*)-4-[(*S*)-1-(Methoxymethoxy)ethyl]-3,4-dimethyltetrahydro-2-furanol (33). Analogously, as described regarding the preparation of **32**, 17.4 mg (0.054 mmol) of **29** was converted into 5.5 mg (50%) of **33** (3:1 anomeric mixture) as a colorless oil via **31**.

Compound 31: TLC R_f 0.57 (EtOAc/hexane, 1:5); IR (neat) ν_{max} 2970, 1720, 1260, 1160, cm^{-1}; ^1H NMR (270 MHz) δ=0.04 (6H, s, $Si(CH_3)_2$), 0.79—1.27 (9H, m, CH_3-2,3,5), 0.88 (9H, s, $SiC(CH_3)_3$), 2.56—2.69 (1H, m, H-2), 3.34 (3H, s, CH_3O), 3.45 (2H, s, CH_2OTBDMS), 3.82 (1H, q, J=6.3 Hz, H-4), 4.57, 4.64 (each 1H, ABq, J=6.8 Hz, OCH_2OCH_3), 9.86 (1H, d, J=1.5 Hz, CHO).

Compound 33: TLC R_f 0.34 (EtOAc/hexane 1:1); IR (neat) ν_{max} 3420, 2960, 1450, 1380 cm^{-1}; ^1H NMR (270 MHz) δ=0.99 (3H, s, CH_3-4), 1.08 (3H×3/4, d, J=7.3 Hz, CH_3-3), 1.13—1.15 (6H×1/4, m, CH_3-3, CH_3 of the side chain at C-4), 1.13 (3H×3/4, d, J=6.4 Hz, CH_3 of the side chain at C-4), 2.09—2.13 (1H, m, H-3), 3.35 (1H, m, H-1 of the side chain at C-4), 3.39 (3H×1/4, s, CH_3O), 3.41 (3H×3/4, s, CH_3O), 3.57, 3.94 (each 1H×3/4, ABq, J=8.3 Hz, H-5,5'), 3.71, 3.83 (each 1H×1/4, ABq, J=8.8 Hz, H-5, 5'), 4.59, 4.73 (each 1H×1/4, ABq, J=6.8 Hz, OCH_2OCH_3), 4.62, 4.76 (each 1H×3/4, ABq, J=6.8 Hz, OCH_2OCH_3), 5.02 (1H×3/4, d, J=2.9 Hz, H-2), 5.37 (1H×1/4, d, J=5.4 Hz, H-2).

Diastereomeric Mixture of (2*R*,3*S*,4*R*)-2-Acetoxy-4-[(*R*)-1-(methoxymethoxy)ethyl]-3,4-dimethyltetrahydrofuran (34) and the 2*S* Isomer. Compound **32** (21.1 mg, 0.10 mmol) was acetylated with acetic anhydride (0.5 ml) in pyridine (0.5 ml) for 2 h. The mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (1 g; EtOAc/hexane, 1:8) to give an inseparable mixture of **34** and the 2*S* isomer (ca. 10:1) (20.5 mg, 81%), a colorless oil: TLC R_f 0.40 (EtOAc/hexane, 1:4); IR (neat) ν_{max} 2980, 1740, 1460, 1380, 1360 cm^{-1}; ^1H NMR(270 MHz) of **34** δ=1.10 (3H, d, J=7.3 Hz, CH_3-3), 1.15 (3H, d, J=6.2 Hz, CH_3 of the side chain at C-4), 1.23 (3H, s, CH_3-4), 2.07 (3H, s, CH_3CO), 2.13—2.22 (1H, m, H-3), 3.38 (3H, s, OCH_3), 3.63 (1H, q,

J=6.2 Hz, H-1 of the side chain at C-4), 3.68, 3.87 (each 1H, ABq, J=8.8 Hz, H-5,5′), 4.59, 4.72 (each 1H, ABq, J=7.0 Hz, OCH_2OCH_3), 5.88 (1H, d, J=2.9 Hz, H-2).

Diastereomeric Mixture of (2*S*,3*R*,4*R*)-2-Acetoxy-4-[(*R*)-1-(methoxymethoxy)ethyl]-3,4-dimethyltetrahydrofuran (35) and the 2*R* Isomer. Analogously, as described regarding **34**, 6.0 mg (0.029 mmol) of **33** was converted into 4.8 mg (67%) of inseparable mixture of **35** and the 2*R* isomer (5:3), a colorless oil: TLC R_f 0.75 (EtOAc/hexane, 1:1); IR (neat) ν_{max} 2970, 1740, 1460, 1380, cm^{-1}; ^1H NMR (270 MHz) δ=0.99 (3H×3/8, s, CH_3-4), 1.02 (3H×5/8, s, CH_3-4), 1.12 (3H×5/8, d, J=8.1 Hz, CH_3-3), 1.13 (3H×5/8, d, J=8.4 Hz, CH_3 of the side chain at C-4), 1.07—1.14 (6H×3/8, m, CH_3-3, CH_3 of the side chain at C-4), 2.01—2.31 (1H, m, H-3), 2.08 (3H×5/8, s, CH_3CO), 2.10 (3H×3/8, s, CH_3CO), 3.38 (3H×5/8, s, OCH_3), 3.41 (3H×3/8, s, OCH_3), 3.54—3.68 (2H, m, H-5, H-1 of the side chain at C-4), 3.84 (1H×5/8, d, J=8.1 Hz, H-5′), 3.94 (1H×3/8, d, J=8.4 Hz, H-5′) 4.58, 4.72 (each 1H×5/8, ABq, J=7.0 Hz, OCH_2OCH_3), 4.62, 4.76 (each 1H×3/8, ABq, J=7.0 Hz, OCH_2OCH_3), 5.02 (1H×3/8, d, J=3.3 Hz, H-2), 5.85 (1H×3/8, d, J=4.4 Hz, H-2).

(2*S*,3*R*,4*R*)-2,3-Dimethyl-3-[(*t*-butyldimethylsiloxy)methyl]-1,4-pentanediol (37). The reaction was carried out under an argon atmosphere. To a solution of **24** (555 mg, 1.54 mmol) in CH_2Cl_2 (11 ml) was added DIBAL-H (4.62 ml, 1.5 M solution in toluene, 6.93 mmol) at −78 °C. The mixture was stirred for 20 min, and quenched by adding H_2O (1 ml). After being stirred for 10 min at 0 °C, the resulting solids were filtered and washed with CH_2Cl_2. The filtrate and washing were combined and concentrated in vacuo. The residue was partitioned between 0.1 M aqueous HCl (25 ml) and CH_2Cl_2 (25 ml). The aqueous layer was extracted with CH_2Cl_2 (25 ml×3). The combined organic layer and extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (17 g; EtOAc/hexane, 1:2) to give **37** (384 mg, 1.39 mmol; 90%), a colorless oil: TLC R_f 0.44 (AcOEt/hexane, 1:1); $[\alpha]_D^{23}$ +12.5° (c 1.23, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3389, 2958, 1257, 1088 cm^{-1}; ^1H NMR (270 MHz) δ=0.08 (6H, s, $Si(CH_3)_2$), 0.81 (3H, s, CH_3-3), 0.90 (9H, s, $SiC(CH_3)_3$), 0.98 (3H, d, J=7.3 Hz, CH_3-2), 1.25 (3H, d, J=6.6 Hz, CH_3-5), 1.89—1.96 (1H, m, H-2), 2.56 (1H, s, OH), 3.44, 3.55 (each 1H, ABq, J=9.9 Hz, $CH_2OTBDMS$), 3.57 (1H, dd, J=4.6 and 11.0 Hz, H-1), 3.69 (1H, dd, J=5.5 and 11.0 Hz, H-1′), 3.88 (1H, q, J=6.6 Hz, H-4).

(2*R*,3*R*,4*R*)-2,3-Dimethyl-3-[(*t*-butyldimethylsiloxy)methyl]-1,4-pentanediol (38). Analogously, as described for **37**, 402 mg (1.11 mmol) of **25** was converted into 301 mg (98%) of **38**, a colorless oil: TLC R_f 0.18 (EtOAc/hexane, 1:2); $[\alpha]_D^{22}$ +1.9° (c 1.17, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3399, 2958, 1257, 1068 cm^{-1}; ^1H NMR (270 MHz) δ=0.08 (6H, s, $Si(CH_3)_2$), 0.81 (3H, s, CH_3-3), 0.90 (9H,s, $SiC(CH_3)_3$), 0.96 (3H, d, J=7.3 Hz, CH_3-2), 1.19 (3H, d, J=6.5 Hz, CH_3-5), 1.87—1.93 (1H, m, H-2), 3.43, 3.64 (each 1H, ABq, J=10.5 Hz, $CH_2OTBDMS$), 3.59 (1H, dd, J=3.4 and 11.2 Hz, H-1), 3.70—3.77 (3H, m, 2 OH, H-1′), 3.96 (1H, q, J=6.5 Hz, H-4). Found: C, 61.12; H, 11.37%. Calcd for $C_{14}H_{32}O_3Si$: C, 60.81; H, 11.67%.

(2*RS*,3*S*,4*R*)-4-Acetyl-3,4-dimethyltetrahydro-2-furanol (41). The reacton was carried out under an argon atmosphere. To a solution of oxalyl dichloride (0.90 ml, 10.3 mmol) in CH_2Cl_2 (1.7 ml) was added DMSO (1.10 ml, 15.5 mmol) at −78 °C over a period of 5 min. After 5 min, a solution of **37** (143 mg, 0.049 mmol) in CH_2Cl_2 (1.3 ml) was added over a period of 15 min. After being stirred for 1 h, Et_3N (2.89 ml, 20.6 mmol) was added to the mixture. This was stirred for an additional 10 min at 0 °C, diluted with H_2O (25 ml) and extracted with CH_2Cl_2 (25 ml×3). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give **39**: TLC R_f 0.55 (EtOAc/hexane, 1:4); IR (neat) ν_{max} 2950, 1700, 1250, 1150 cm^{-1}; ^1H NMR (270 MHz) δ=0.03 (6H, s, $Si(CH_3)_2$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.08 (3H, d, J=7.3 Hz, CH_3-2), 1.22 (3H, s, CH_3-3), 2.21 (3H, s, CH_3-5), 2.90 (1H, dq, J=1.3 and 7.3 Hz, H-2), 3.61, 3.68, (each, 1H, ABq, J=10.1 Hz, $CH_2OTBDMS$), 9.68 (1H, d, J=1.3 Hz, CHO).

Crude **39** was dissolved in 60% aqueous AcOH (3 ml). The solution was stirred for 3 h, then neutralized by adding $NaHCO_3$ (solid). This was diluted with H_2O (15 ml), and extracted with CH_2Cl_2 (15 ml×3). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatograhy on silica gel (3.3 g; EtOAc/hexane, 1:2) to give **41** as a 2:1 anomeric mixture (44.2 mg, 54%), a colorless oil: TLC R_f 0.29 (EtOAc/hexane, 1:1); IR ($CHCl_3$) ν_{max} 3406, 2973, 1701 cm^{-1}; ^1H NMR (270 MHz) δ=0.99 (3H×1/3, d, J=7.3 Hz, CH_3-3), 1.01 (3H×2/3, d, J=7.3 Hz, CH_3-3), 1.40 (3H×1/3, s, CH_3-4), 1.44 (3H×2/3, s, CH_3-4), 2.03—2.14 (1H, m, H-3), 2.19 (3H×1/3, s, CH_3CO), 2.26 (3H×2/3, s, CH_3CO), 3.56, 4.21 (each 1H×2/3, ABq, J=9.3 Hz, H-5,5′), 3.88, 4.27 (each 1H×1/3, ABq, J=8.8 Hz, H-5,5′), 4.90—4.94 (1H×1/3, br, OH), 5.21 (1H×2/3, d, J=3.9 Hz, H-2), 5.23 (1H×1/3, d, J=5.4 Hz, H-2).

(2*RS*,3*R*,4*R*)-4-Acetyl-3,4-dimethyltetrahydro-2-furanol (42). Analogously, as described for **41**, 59.5 mg (0.215 mmol) of **38** was converted into 23.6 mg (69%) of **42** as a 5:2 anomeric mixture, a colorless oil: TLC R_f 0.18 (EtOAc/hexane, 1:2); IR (neat) ν_{max} 3400, 2980, 1700, cm^{-1}; ^1H NMR (270 MHz) δ=0.98 (3H×2/7, d, J=6.8 Hz, CH_3-3), 1.06 (3H×5/7, d, J=7.2 Hz, CH_3-3), 1.20 (3H×5/7, s, CH_3-4), 1.33 (3H×2/7, s, CH_3-4), 2.18 (3H×2/7, s, CH_3CO), 2.23 (3H×5/7, s, CH_3CO), 2.45—2.54 (1H, m, H-3), 3.63, 4.44 (each 1H×5/7, ABq, J=8.7 Hz, H-5,5′), 3.85, 4.22 (each 1H×2/7, ABq, J=9.0 Hz, H-5,5′), 5.07 (1H×5/7, d, J=1.8 Hz, H-2), 5.43 (1H×2/7, d, J=4.7 Hz, H-2).

(2*R*,3*S*,4*R*)-2-Acetoxy-4-acetyl-3,4-dimethyltetrahydrofuran (5). Compound **41** (9.3 mg, 0.059 mmol) was acetylated with acetic anhydride (0.5 ml) in pyridine (0.5 ml) for 2 h. The mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (1 g; EtOAc/hexane, 1:4) to give **5** (8.1 mg, 69%), a colorless oil, and **41** (1.8 mg, 19%) was recovered: TLC R_f 0.47 (EtOAc/hexane, 1:2); $[\alpha]_D^{22}$ +30.3° (c 0.47, EtOH); IR (neat) ν_{max} 2980, 1740, 1700 cm^{-1}; ^1H NMR (270 MHz) δ=1.02 (3H, d, J=7.3 Hz, CH_3-3), 1.43 (3H, s, CH_3-4), 2.09, 2.20 (each 3H, each s, CH_3CO), 2.29 (1H, dq, J=2.4 and 7.3 Hz, H-3), 3.84, 4.41 (each 1H, ABq, J=9.3 Hz, H-5,5′), 5.95 (1H, d, J=2.4 Hz, H-2); ^{13}C NMR (100 MHz) δ=12.91, 21.32, 21.93, 27.55, 49.11, 57.64, 75.55, 104.93, 170.31, 208.45. Found: C, 59.84; H, 8.39%. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06%.

(2*S*,3*R*,4*R*)-2-Acetoxyl-4-acetyl-3,4-dimethyltetrahydrofuran (6). To a stirred solution of **42** (21.0 mg,

0.13 mmol) in acetic anhydride (2 ml) was added sodium acetate (21.8 mg, 0.27 mol). The mixture was stirred for 20 h, while sodium acetate (21.8 mg) was added after periods of 4 and 6.5 h. The mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (1 g; EtOAc/hexane, 1:4) to give **6** (20.0 mg, 75%) as a colorless oil: TLC R_f 0.26 (EtOAc/hexane, 1:2); $[\alpha]_D^{22}$ −73.8° (*c* 1.00, EtOH); IR (neat) ν_{max} 2980, 1705 cm^{-1}; ^1H NMR (270 MHz) δ=1.10 (3H, d, J=7.3 Hz, CH_3-3), 1.22 (3H, s, CH_3-4), 2.03, 2.21 (each 3H, each s, CH_3CO), 2.70 (1H, dq, J=2.9 and 7.3 Hz, H-3), 3.72, 4.44 (each 1H, ABq, J=8.8 Hz, H-5,5′), 5.87 (1H, d, J=2.9 Hz, H-2); ^{13}C NMR (100 MHz) δ=11.84, 16.87, 21.22, 26.12, 44.45, 57.45, 75.17, 104.19, 170.38, 208.73. Found: C, 59.84; H, 7.78%. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06%.

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13) ^1H NMR analysis including NOE experiments of **3** was observed as analogous to that of **5** and **6**. H-5 appeared at δ=6.15 as a doublet with $J_{4,5}$=2.9 Hz. In addition, a 7% enhancement of H-5 signal was observed when a doublet due to Me-4 was irradiated, and also a 4% enhancement of Me-4 signal and a 2% enhancement of H-4 signal were observed upon irradiation of H-5 signal. However in the ^1H NMR of **4**, H-5 appeared at δ=6.59 as a doublet with $J_{4,5}$=5.9 Hz. In addition, a 8% enhancement of H-4 signal was observed when a doublet due to H-5 was irradiated but no enhancement was observed at Me-4 signal, and also 3% enhancement of H-5 signal was observed upon irradiation of Me-4 signal.