Total Syntheses of (+)-Altholactone [(+)-Goniothalenol] and Three Stereocongeners and Their Cytotoxicity against Several Tumor Cell Lines[1)]

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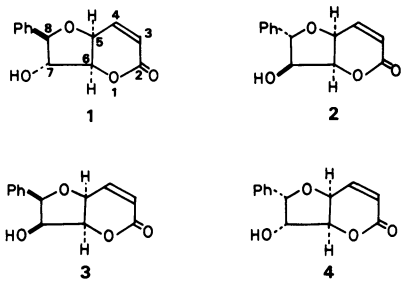
Enantiospecific total synthesis of (+)-altholactone [(+)-goniothalenol] (**1**), a novel tetrahydrofuropyran-5-one possessing significant cytotoxicity against several tumor cell lines, has been achieved by using L-arabinose as the redundant starting material. The pivotal tetrahydrofuran formation was realized by treatment of the diastereomeric mixture of (2*S*,3*R*)-4,5-epoxy-5-phenyl-1,2,3-pentanetriol 1,3-benzylidene acetals **8** and **8'** with silica gel. Simultaneous stereochemical inversion at C-4 and C-5 of the major cyclization product, *O*,*O'*-benzylidene derivative of (2*S*,3*R*,4*S*,5*S*)-2-(hydroxymethyl)-5-phenyltetrahydrofuran-3,4-diol (**11**), to the 2*S*,3*R*,4*R*,5*R* diastereomer **10** was achieved by hydroboration of (2*S*,3*S*)-3-hydroxy-2-(hydroxymethyl)-5-phenyl-2,3-dihydrofuran *O*,*O'*-benzylidene derivative (**18**) which derived from **11**. Pfitzner-Moffatt oxidation of **10** followed by $NaBH_4$ reduction gave the 2*S*,3*R*,4*S*,5*R* diastereomer **20** exclusively. Displacement of the triflate group in (2*S*,3*R*,4*S*,5*S*)-2-(hydroxymethyl)-5-phenyl-4-[(trifluoromethylsulfonyl)oxy]tetrahydrofuran-3-ol *O*,*O'*-benzylidene derivative (**21**) by acetate, which was prepared from **11**, furnished the 2*S*,3*R*,4*R*,5*S* diastereomer **22**. The total synthesis of **1** was completed by Collins oxidation of (2*S*,3*R*,4*R*,5*R*)-2-(hydroxymethyl)-3,4-bis(methoxymethoxy)-5-phenyltetrahydrofuran (**34**), which was prepared from **10**, and subsequent Witting olefination with (ethoxycarbonylmethylene)triphenylphosphorane followed by hydrolysis. By employing the analogous reaction sequence, compounds **11**, **20**, and **22** were efficiently converted into (+)-7,8-di-*epi*- (**2**), (+)-7-*epi*- (**3**), and (+)-8-*epi*-altholactone (**4**), respectively. The cytotoxicity of **1**—**4** against several tumor cell lines was examined.

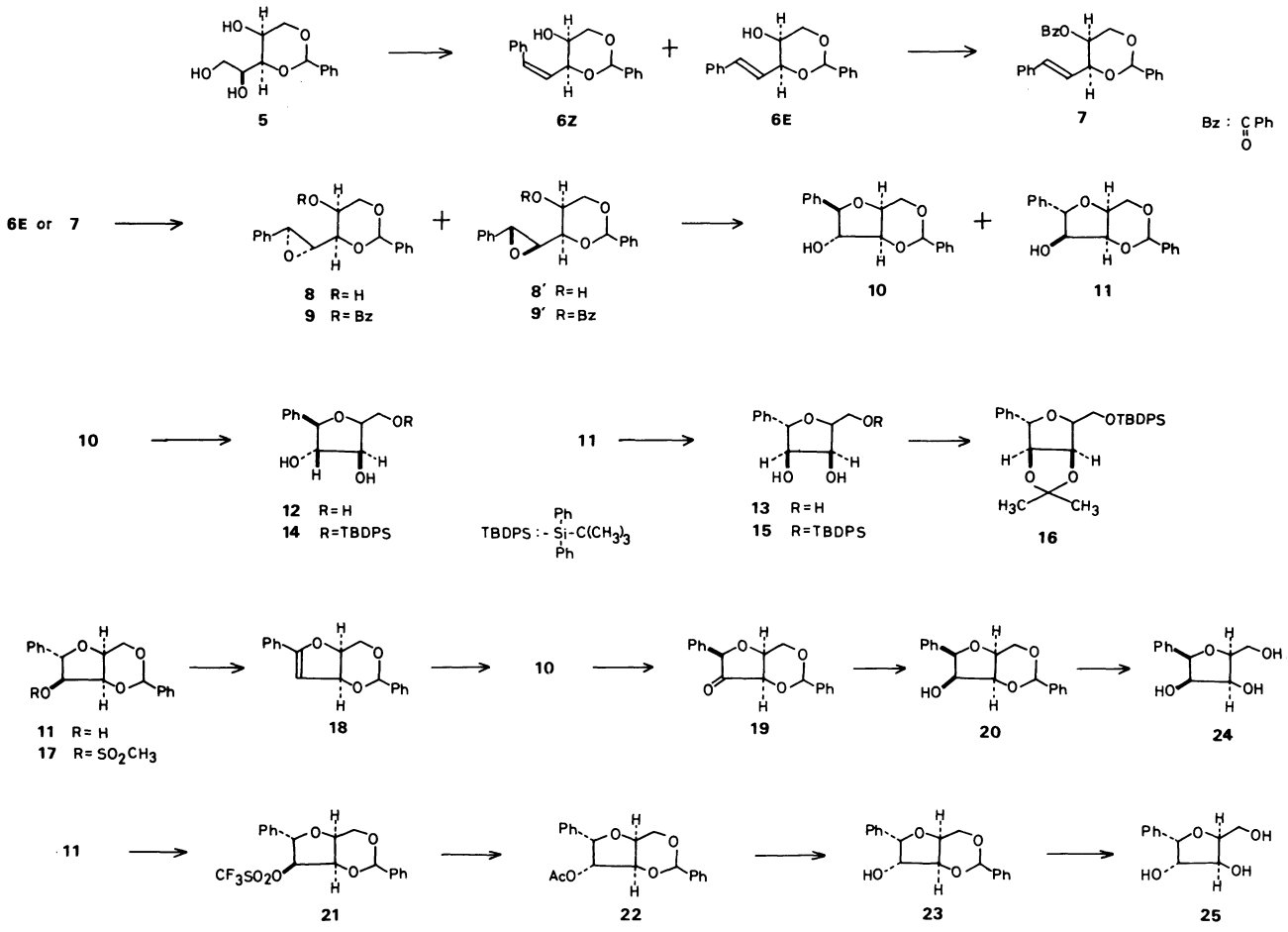
In 1977, Loder and Nearn reported the isolation of a novel tetrahydro-5*H*-furo[3,2-*b*]pyran-5-one derivative from the extracts of the bark of an unnamed *Polyathia* species (Annonaceae) and they named this natural product "altholactone".[2)] The relative configuration of altholactone was determined by means of spectral analyses of it and some derivatives, and the absolute configuration of natural (+)-enantiomer was tentatively assigned to be **1** based on correlation of the CD spectrum of it with those of the structurally defined natural α,β-unsaturated δ-lactones.[2)] Compound **1** was later isolated from the ethanolic extract of the stem bark of *Goniothalamus giganteus* (Annonaceae) by one of us (J. L. M.),[3)] and the proposed relative configuration was confirmed by the X-ray crystallographic analysis. This tetrahydrofuropyran-5-one **1** is known to possess bioactivities such as an antitumor activity against murine P388 leukemia in vivo at 45 mg/kg and shows lethality to brine shrimp (LC_{50} 234 μg ml^{-1}).[3)] As the structurally similar natural products to **1**, goniothalamin,[4)] goniodiol,[5)] goniotriol,[5)] dihydrokawain-5-ol,[6)] olguine,[7)] anamarine,[8)] and asperlin[9)] were isolated from some plants and a fungus. Some of them (goniothalamin, goniodiol, and goniotriol) were reported to have an asymmetric carbon atom with *S* configuration as δ-carbon of the α,β-unsaturated δ-lactone moiety. On the other hand, the same position of the other natural products was *R* configuration. These facts provoke much interest in the biosynthetic correlation of **1** to the other natural products. This structural uniqueness and biological importance of **1** prompted us to undertake the total synthesis of **1**. Very recently, two total syntheses of **1** and its (−)-enantiomer have been reported by Gesson and coworkers[10)] and by Gillhouley and Shing.[11)] In this article, we describe in detail our independent total syntheses of **1** and three stereocongeners, namely, (+)-7,8-di-*epi*- (**2**), (+)-7-*epi*- (**3**), and (+)-8-*epi*-altholactone (**4**).[12)] The cytotoxicity of **1**—**4** against several tumor cell lines was examined and the results are also described herein.



Results and Discussion

Syntheses of (+)-Altholactone (1) and Three Stereocongeners (2—4). As a starting material for the enantiospecific total synthesis of **1**, we chose the known 1,3-*O*-benzylidene-L-arabinitol (**5**) which was readily prepared from L-arabinose by a two-step reaction sequence.[13)] The C-2 and C-3 of **5** correspond to C-5 and C-6 (altholactone numbering) of **1**. Oxidative cleavage of the glycol in **5** with $NaIO_4$ in

aqueous MeOH and subsequent Wittig olefination with benzylidenetriphenylphosphorane, prepared by BuLi treatment of benzyltriphenylphosphonium chloride,[14] furnished a 1:3 mixture of **6Z** and **6E** in a combined yield of 84%. These geometrical isomers were cleanly separated by silica-gel chromatography. The *Z* isomer **6Z** was isomerized to **6E** in 81% yield by treatment wth thiophenol (PhSH) in refluxing benzene in the presence of 2,2′-azobis(2-methylpropanenitrile) (AIBN).[15] Epoxidation of **6E** with *m*-chloroperbenzoic acid (mCPBA) in refluxing CH_2Cl_2 provided an inseparable mixture of (*R*,*R*)- (**8**) and (*S*,*S*)-epoxides (**8′**). The ratio of **8** to **8′** could not be determined by its ^{1}H NMR spectral analysis. It was found that tetrahydrofuran formation took place partly during purification of the mixture of **8** and **8′** by silica-gel chromatography. Therefore, the mixture of **8** and **8′** in CH_2Cl_2 was kept standing with silica gel (30 to 40 multiple weight of **6E**) at room temperature for 25—35 h. As a result, the cyclization products **10** and **11** were obtained in 19% and 73% yields, respectively, after chromatographic separation on silica gel. From these results, the ratio of **8** to **8′** was estimated to be 1 to 3.8. The effect of the C-2 substituent on the epoxidation was next pursued. The benzoate **7** was prepared by the standard benzoylation of **6E**. Treatment of **7** with mCPBA in refluxing CH_2Cl_2 gave an inseparable mixture of **9** and **9′**. The benzoyl groups of this mixture were removed with sodium methoxide, and the resulting mixture of **8** and **8′** was treated with silica gel as described above. Compound **11** was obtained by crystallization of the reaction mixture in 83% yield. The other cyclization product **10** was obtained in 6% yield after silica-gel chromatography of the mother liquor. In consideration of the yields of **10** and **11**, the ratio of the epoxides **9** and **9′** was estimated to be 1 to 13.8.[16] By reason that the combined yield of **10** and **11** was sufficiently high, the silica-gel-promoted cyclization found in the present work is worthy to note.[17,18] The structures of **10** and **11** could not be determined unambiguously from their ^{1}H NMR spectra. However, these were established as follows. Hydrolysis of **10** and **11** with 1 M† HCl gave the debenzylidene derivatives **12** and **13**. The primary hydroxyl groups in **12** and **13** were silylated to give **14** and **15**. Treatment of **14** with 2,2-dimethoxypropane in the presence of 10-camphorsulfonic acid (CSA) resulted in a quantitative recovery of **14**. On the other hand, compound **15** was converted into the isopropylidene derivative **16** in 87% yield under the same reaction conditions. These results

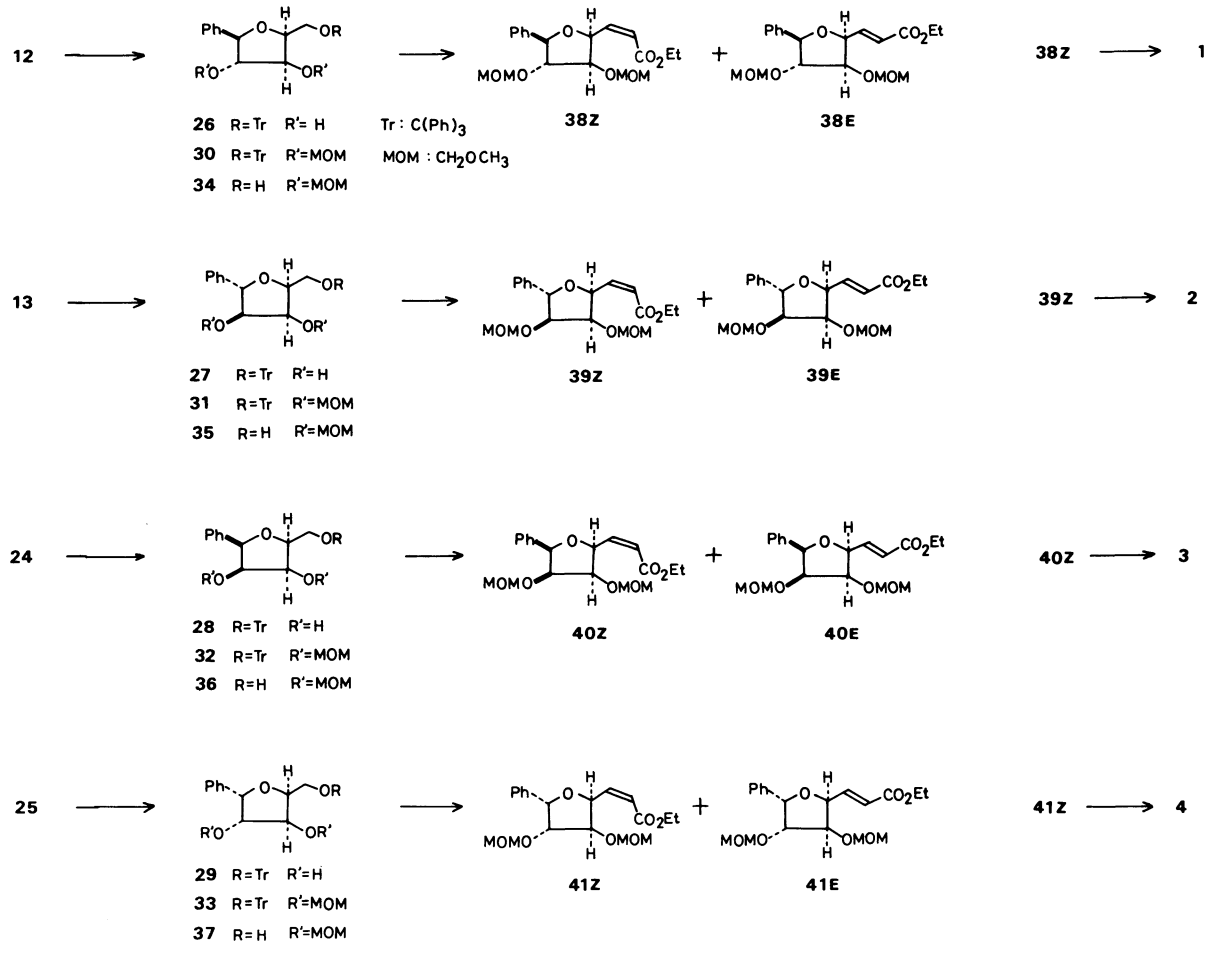


† 1 M=1 mol dm^{-3}.

reveal that relationship of the vicinal diols are trans for **14** and cis for **15**. The structures of **10** and **11** were established as depicted.

Unfortunately, the minor cyclization product **10** possesses all of the required asymmetric carbons. Therefore, the conversion of **11** into **10** was investigated. For this purpose, an introduction of a hydroxyl group at C-3 of a model such as **18** by hydroboration protocol was examined. The attack of borane to **18** was expected to proceed from the less hindered convex face. The dihydrofuran **18** was prepared as follows. Methanesulfonylation of **11** gave the mesylate **17**. Brief exposure of **17** to *t*-BuOK in refluxing THF resluted in the formation of **18** through elimination of methanesulfonic acid. As anticipated, the hydroboration of **18** with BH_3–THF complex in THF followed by oxidative work-up with H_2O_2 furnished **10** as a single product in 65% yield from **17**. Two other diastereomers **20** and **23**, the proper synthetic precursors for **3** and **4**, were prepared as follows. Pfitzner–Moffatt oxidation[19] of **10** gave **19** smoothly,[20] and $NaBH_4$ reduction of **19** gave **20** in 83% yield from **10**. The attack of the hydride occurred exclusively from the convex face of **19**. Trifluoromethanesulfonylation of **11** gave the triflate **21**. Displacement of the triflate group by acetate group in S_N2 fashion took place by heating of **21** in DMF with AcOK at 135 °C. The acetate **22** was obtained in 79% yield.[21] Deacetylation of **22** with sodium methoxide gave **23**. Direct displacement of the triflate group by hydroxyl group was achieved by treatment of **21** in DMF–DMSO with KO_2.[22] Compound **23** was obtained in 58% yield.

The remaining elaboration for the total synthesis of **1** from **12** was an introduction of 2-pyrone unit, and this was accomplished as follows. Selective tritylation of **12** gave the mono trityl ether **26** in 75% yield. The remaining hydroxyl groups were protected as methoxymethyl (MOM) ethers to provide **30** in 89% yield. Hydrolysis of **30** with *p*-TsOH provided the detritylated product **34**. Collins oxidation[23] of **34** followed by Wittig olefination of thus formed aldehyde[24] with (ethoxycarbonylmethylene)triphenylphosphorane in MeOH gave *Z* and *E* isomers of α,β-unsaturated esters **38Z** and **38E** in 62% and 9% yields, respectively. Finally, hydrolysis of **38Z** with 1 M HCl provided (+)-altholactone **1** as needles in 96% yield in consequence of deprotection of the MOM ethers followed by δ-lactonization. The ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra of synthetic **1** were identical with those of natural product. Mixed melting point of synthetic **1** (mp 113—114 °C) with natural **1** (mp 110 °C[3]) showed no depression (mmp 112—113 °C). Furthermore, the



specific rotation of synthetic **1** [$[\alpha]_D^{33}$ +180.8° (*c* 0.52, EtOH)] revealed that the absolute configuration of natural **1** [$[\alpha]_D^{20}$ +188°[2] and $[\alpha]_D^{25}$ +184.7°[3]] is 5*S*,6*R*, 7*R*,8*R*.

The syntheses of three stereocongeners **2**—**4** were accomplished by the virtually same reaction sequence described above. Debenzylidenation of **20** and **23** gave the triols **24** and **25**. By the sequence of tritylation, methoxymethylation, and detritylation, the triol **13** was converted into **35** in an overall yield of 51% via **27** (72%) and **31** (91%). Similarly, compound **24** was converted into **36** in an overall yield of 51% via **28** (79%) and **32** (90%). Also, compound **37** was obtained from **25** in an overall yield of 82% via **29** (93%) and **33** (94%). By the Collins oxidation followed by Wittig olefination, compounds **35**, **36**, and **37** were transformed to *Z* and *E* isomers of the α,β-unsaturated esters, **39Z** (58%) and **39E** (5%), **40Z** (72%) and **40E** (5%), and **41Z** (53%) and **41E** (4%). Hydrolysis of **39Z**, **40Z**, and **41Z** with 1 M HCl gave (+)-7,8-di-*epi*- (**2**), (+)-7-*epi*- (**3**), and (+)-8-*epi*-altholactone (**4**), in 78%, 79%, and 82% yields, respectively. The stereocongeners **2**—**4** were fully characterized by the spectral means. In addition, the synthesis of **3** has been reported very recently by Gillhouley and Shing.[11] The physical data of our synthetic **3** [mp 117—117.5 °C, $[\alpha]_D^{30}$ +23.0° (*c* 0.50, EtOH)] coincides well with those of the reported data [mp 121—123 °C, $[\alpha]_D^{22}$ +23.5° (*c* 0.4, EtOH)].

Cytotoxicity of (+)-Altholactone (1) and Three Stereocongeners (2—4). The cytotoxicity assays of **1**—**4** were carried out by using the following tumor cells: 9PS, a methylcholanthrene induced murine leukemia; 9KB, a human nasopharyngeal carcinoma; A-549, a human lung-cell cancer; MCF-7, a human breast cancer; HT-29, a human colon cancer. The ED_{50} values ($\mu g\ ml^{-1}$) of **1**—**4** are as follows. **1**: 9PS (2.01×10^{-1}), 9KB (3.03), A-549 (>10), MCF-7 (>10), HT-29 (2.49); **2**: 9PS (9.4×10^{-1}), 9KB (>10), A-549 (5.85), MCF-7 (4.7), HT-29 (4.7×10^{-1}); **3**: 9PS (1), 9KB (2.6), A-549 (4.6), MCF-7 (4.8), HT-29 (2.1); **4**: 9PS (9.5×10^{-1}), 9KB (>10), A-549 (>10), MCF-7 (>10), HT-29 (4.5). From these results, the level of cytotoxicity of **2**—**4** seems to be marginal. It appears that the 8-*epi* isomer **4** is less active than the other isomers, but **4** may be selectively active in the colon tumor. Meanwhile, the cytotoxicity of natural **1** was examined in detail at the National Cancer Institute. The cytotoxicity of **1** is quite potent (10^{-5} to 10^{-7} molar for IC_{50} values), and the results are listed in Table 1.

Table 1. The NCI Human Tumor Panel Cytotoxicity Results for **1**

Disease cell	log (IC_{50})
Fibroblast	
CCD-19Lu	−4.6
Leukemia	
MOLT-4	−6.1
K-562	−5.4
P388/ADR	−5.6
P388	−5.6
Non-small cell lung cancer	
H522	−5.8
H23	−5.6
H125	−6.0
H358	−5.5
H460	−5.5
A549(ATCC)	−5.1
H322	−5.2
EKVX	−5.0
Small cell lung cancer	
DMS114	−5.5
Colon cancer	
LoVo	−5.5
WIDR	−5.6
SW620	−5.5
DLD-1	−5.4
HT29	−5.3
Breast cancer	
MCF7	−5.5
MCF7/ADR	−5.6
CNS cancer	
TE671	−5.5
U251	−5.5
Melanoma	
SK-MEL-5	−5.9
LOX	−5.5
RPMI-7951	−5.5
Malme-3M	−5.3
SK-MEL-2	−5.6
Ave. log (IC_{50})	−5.5
Delta	0.6
Range	1.6

Experimental

General Procedures. Reactions were carried out at room temperature unless otherwise described. Melting points were determined with a Mitamura Riken micro melting points apparatus and are uncorrected. Specific rotations were measured with a Jasco DIP-4 polarimeter in a 10 mm cell. Column chromatography was performed on Silicagel 60 (Katayama Chemicals), flash column chromatography was performed on Wako C-300 (Wako Pure Chemicals), and thin-layer chromatography (TLC) was performed on a glass plate coated with Kieselgel 60 GF_{254} (Merck) followed by detection using UV light and/or charring with H_2SO_4. Preparative TLC (PTLC) was performed on a glass plate (20×20 cm) coated with Kieselgel PF_{254} (Merck), and compounds were extracted with CH_2Cl_2 or AcOEt. IR spectra were recorded with a Hitachi Model 225 (KBr) or with a Jasco Model A-202 (neat) spectrometer. ^1H NMR spectra at 90 MHz were recorded with a Varian EM-390 spectrometer, and ^1H NMR at 400 MHz and ^{13}C NMR at 100 MHz were recorded with a JEOL JNM-GX 400 FT NMR spectrometer with internal standard of Me_4Si. High-resolution mass spectra were obtained with a Hitachi Model M-80 spectrometer.

Benzene, dichloromethane (CH_2Cl_2), and *N*,*N*-dimethylformamide (DMF) were dried over CaH_2 and then distilled. Acetone was dried over $CaSO_4$ and then distilled. Pyridine was distilled over NaOH. Tetrahydrofuran (THF) was

distilled over $LiAlH_4$ and then over Na/benzophenone.

Glycol Cleavage of 5 and Successive Wittig Olefination with Benzylidenetriphenylphosphorane. (2*S*,3*S*,4*Z*)- and (2*S*,3*S*,4*E*)-1,3-*O*-Benzylidene-5-phenyl-4-pentene-1,2,3-triol (6Z and 6E). To a solution of **5** (15.0 g, 62.4 mmol) in methanol (350 ml) was added an aqueous solution (150 ml) of $NaIO_4$ (14.7 g, 68.6 mmol). This mixture was stirred for 30 min, and the resulting white solids were removed by filtration. The filtrate was concentrated in vacuo. The residue was partitioned between AcOEt (600 ml) and H_2O (150 ml). The aqueous phase was extracted with AcOEt (2×300 ml). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give an aldehyde, which was subjected to Wittig reaction directly. The Wittig reaction was carried out under an argon atmosphere. To a suspension of benzyltriphenylphosphonium chloride (48.2 g, 124 mmol) in THF (250 ml) was injected BuLi (1.60 M solution in hexane, 77.5 ml, 124 mmol). After being stirred for 1 h, a THF solution (50 ml) of the aldehyde above was added to the ylide solution. After being stirred for 1 h, 1% aqueous NH_4Cl solution (90 ml) and H_2O (300 ml) were added to the mixture. This aqueous mixture was extracted with AcOEt (3×450 ml). The organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was treated with a small amount of AcOEt, and insoluble materials were removed. The filtrate was concentrated in vacuo. Column chromatography of the residue (AcOEt/hexane 1:10) provided **6Z** (3.60 g, 21%) and **6E** (11.1 g, 63%). **6Z** as white crystals, mp 106—107 °C: R_f 0.73 (AcOEt/hexane 1:1): $[\alpha]_D^{23}$ −340° (*c* 1.05, $CHCl_3$); IR ν_{max}^{KBr} 3320, 1445, 1390, 1330, 1130, 1075 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.70—3.10 (br s, 1H), 3.37—3.67 (m, 1H), 4.12 (dq, 2H, *J*=1 and 11 Hz), 4.72 (d, 1H, *J*=9 Hz), 5.63 (s, 1H), 6.07 (dd, 1H, *J*=9 and 12 Hz), 6.79 (d, 1H, *J*=12 Hz), 7.25—7.65 (m, 10H). Found: C, 76.48; H, 6.56%. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43%. **6E** as white crystals, mp 109.5—110 °C: TLC R_f 0.65 (AcOEt/hexane 1:1); $[\alpha]_D^{22}$ +61.0° (*c* 1.51, $CHCl_3$); IR ν_{max}^{KBr} 3570, 2980, 1490, 1450, 1395, 1370, 1350, 1215, 1145, 1115, 1070 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.60—3.00 (br s, 1H), 3.43—3.73 (br s, 1H), 4.05, 4.19 (each dd, each 1H, *J*=1 and 12 Hz), 4.55 (d, 1H, *J*=6 Hz), 5.67 (s, 1H), 6.32 (dd, 1H, *J*=6 and 16.5 Hz), 6.75 (d, *J*=16.5 Hz, 1H), 7.17—7.67 (m, 10H). Found: C, 76.64; H, 6.42%. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43%.

Isomerization of 6Z to 6E. A mixture of **6Z** (3.60 g, 12.8 mmol), PhSH (0.66 ml, 6.4 mmol), and AIBN (420 mg, 2.56 mmol) in benzene (120 ml) was refluxed for 30 min. The mixture was then concentrated in vacuo. Pure **6E** (2.92 g, 81%) was obtained by flash column chromatography (AcOEt/hexane 1:10) of the residue.

Epoxidaion of 6E Followed by Treatment with Silica Gel. (2*S*,3*R*,4*R*,5*R*)- and (2*S*,3*R*,4*S*,5*S*)-2-(Hydroxymethyl)-5-phenyltetrahydrofuran-3,4-diol *O*,*O*′-Benzylidene Derivatives (10 and 11). A mixture of **6E** (1.62 g 5.74 mmol) and mCPBA (2.49 g, 14.4 mmol) in CH_2Cl_2 (30 ml) was refluxed for 30 min. The mixture was diluted with CH_2Cl_2 (120 ml) and washed with 20 wt% aqueous $Na_2S_2O_3$ (2×80 ml) and saturated aqueous $NaHCO_3$ (2×80 ml). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give an inseparable mixture of **8** and **8′** as amorphous solids, which was used in the next step without further purification. The mixture of **8** and **8′** was dissolved in CH_2Cl_2 (120 ml) and silica gel (60 g) was added. The mixture was kept standing for 36 h. Then the silica gel was removed by filtration, washed with CH_2Cl_2 (500 ml), AcOEt (500 ml), and EtOH (250 ml). The combined filtrate and washings were concentrated in vacuo. The residue was purified by flash column chromatography (AcOEt/$PhCH_3$ 1:40, 1:20, and 1:5 successively). From the fractions corresponding to R_f 0.46 (AcOEt/$PhCH_3$ 1:3), compound **11** (1.25 g, 73%) was obtained as crystals, mp 127—128 °C. From the fractions corresponding to R_f 0.21, compound **10** (124 mg) was obtained as crystals, mp 131—132 °C. The fractions corresponding to R_f 0.31 was also concentrated in vacuo to give uncyclized **8**. Thus obtained **8** was treated with silica gel (10 g) in CH_2Cl_2 (20 ml) for 6 days. Filtration and chromatographic purification as described above gave an additional **10** (208 mg, total 332 mg, 19%). **10**: $[\alpha]_D^{25}$ +28.4° (*c* 0.90, $CHCl_3$) IR ν_{max}^{KBr} 3430, 2910, 2880, 1450, 1390, 1335, 1245, 1210, 1125, 1080, 1055 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.30 (br s, 1H), 3.97—4.30 (m, 4H), 4.50 (d, 1H, *J*=12 Hz), 4.80 (d, 1H, *J*=2 Hz), 5.46 (s, 1H), 7.17—7.60 (m, 10H). Found: C, 72.62; H, 6.12%. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08%. **11**: $[\alpha]_D^{23}$ −11.3° (*c* 1.00, $CHCl_3$); IR ν_{max}^{KBr} 3420, 1450, 1390, 1360, 1215, 1150, 1095, 1050 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.50—2.75 (m, 1H), 3.97—4.60 (m, 5H), 5.01 (d, 1H, *J*=8 Hz), 5.59 (s, 1H), 7.23—7.67 (m, 10H). Found: C, 72.56; H, 6.11%. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08%.

(2*S*,3*S*,4*E*)-1,3-*O*-Benzylidene-2-*O*-benzoyl-5-phenyl-4-pentene-1,2,3-triol (7). To a stirred solution of **6E** (6.88 g, 24.4 mmol) in pyridine (180 ml) was added benzoyl chloride (9.26 ml, 78.1 mmol) at 0 °C. After being stirred for 20 h, the resulting crystals were removed by filtration. The filtrate was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (1500 ml) and saturated aqueous $NaHCO_3$ (500 ml). The organic phase was washed with saturated aqueous $NaHCO_3$ (500 ml) and H_2O (500 ml) successively. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The resulting crystals were recrystallized from AcOEt to give **7** (7.73 g). The mother liquor was concentrated and recrystallization of the residue gave an additional **7** (1.02 g, total 8.75 g, 93%), mp 164.5—165.5 °C: TLC R_f 0.69 (AcOEt/toluene 1:5), $[\alpha]_D^{22}$ +161° (*c* 1.19, $CHCl_3$); IR ν_{max}^{KBr} 2850, 1715, 1445, 1350, 1265, 1085 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=4.22, 4.51 (each d, each 1H, *J*=15 Hz), 4.75—4.90 (m, 1H), 5.07—5.20 (m, 1H), 5.75 (s, 1H), 6.26 (dd, 1H, *J*=6 and 16.5 Hz), 6.69 (d, 1H, *J*=16.5 Hz), 7.17—7.73, 8.07—8.30 (m, 15H). Found: C, 77.90; H, 5.86%. Calcd for $C_{25}H_{22}O_4$: C, 77.70; H, 5.74%.

Conversion of 7 into 10 and 11. Compound **7** (16.4 g, 42.2 mmol) in CH_2Cl_2 (200 ml) was oxidized with mCPBA (18.3 g, 106 mmol) under reflux for 2.5 h. After extractive workup as described in the case of **8** and **8′**, the mixture of **9** and **9′** was obtained. The mixture of **9** and **9′** was dissolved in MeOH (750 ml), and MeONa (1 M in MeOH, 63.6 ml, 63.6 mmol) was added. After being stirred for 2.5 h, the solution was neutralized with 1 M HCl and concentrated in vacuo. Extractive workup (AcOEt/H_2O) of the residue gave a mixture of **8** and **8′**, which was treated with silica gel (600 g, 32 h). Recrystallization of the concentrate of the reaction mixture from MeOH provided **11** (8.37 g). From the mother liquor, an additional **11** (2.13 g, total 10.5 g, 83%) and **10** (759 mg, 6%) were obtained by the similar chromatographic purification and retreatment with silica gel as described above. Compounds **10** and **11** from **6E** and those from **7** were identical in all respects.

Debenzylidenation of 10 and 11. (2*S*,3*R*,4*R*,5*R*)- and (2*S*,3*R*,4*S*,5*S*)-2-(Hydroxymethyl)-5-phenyltetrahydrofuran-3,4-diol (12 and 13). A solution of **10** (845 mg, 2.8 mmol) in a mixture of 1,4-dioxane (20 ml) and 1 M HCl (20 ml) was refluxed for 30 min. The mixture was neutralized with 4 M NaOH, then concentrated in vacuo. The residue was partitioned between AcOEt (40 ml) and water (50 ml). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by silica-gel chromatography (AcOEt/hexane 2:3) to give **12** (529 mg, 89%) as a colorless oil: TLC R_f 0.41 (EtOH/$PhCH_3$ 1:4); $[\alpha]_D^{25}$ +24.4° (*c* 0.76, MeOH); IR ν_{max}^{neat} 3380, 2880, 1495, 1455, 1100, 1085 cm^{-1}; ^1H NMR (90 MHz, CD_3OD) δ=3.81—4.41 (m, 5H), 4.52 (d, 1H, *J*=6 Hz), 7.15—7.51 (m, 5H).

Compound **11** (850 mg) was converted into **13** (489 mg, 82%) as described in the preparation of **12** after chromatographic purification, mp 81.5—82.5 °C: TLC R_f 0.17 (EtOH/$PhCH_3$ 1:10); $[\alpha]_D^{29}$ −41.3° (*c* 1.15, MeOH); IR ν_{max}^{KBr} 3400, 2885, 1450, 1340, 1280, 1150 cm^{-1}; ^1H NMR (90 MHz, CD_3OD) δ=3.80—4.12 (m, 3H), 4.19—4.48 (m, 2H), 4.80 (d, 1H, *J*=7.5 Hz), 7.25—7.59 (m, 5H). Found: C, 62.88; H, 6.69%. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71%.

***t*-Butyldiphenylsilylation of 12 and 13. (2*S*,3*R*,4*R*,5*R*)- and (2*S*,3*R*,4*S*,5*S*)-2-[(*t*-Butyldiphenylsilyloxy)methyl]-5-phenyltetrahydrofuran-3,4-diol (14 and 15).** To a solution of **12** (10 mg, 0.05 mmol) in DMF (0.5 ml) were added *t*-butylchlorodiphenylsilane (0.015 ml, 0.06 mmol) and imidazole (8 mg, 0.12 mmol). After being stirred for 3.5 h, the silylating reagent (0.03 ml) and imidazole (16 mg) were added, and the mixture was stirred more 2 h. The mixture was concentrated in vacuo, and AcOEt (4 ml) was added to the residue. The insoluble materials were removed by filtration, and the filtrate was concentrated. The residue was purified by PTLC (EtOH/$PhCH_3$ 1:10) to give **14** (17 mg, 79%) as a colorless oil: TLC R_f 0.73 (EtOH/$PhCH_3$ 1:5); ^1H NMR (90 MHz, $CDCl_3$) δ=1.02 (s, 9H), 1.52—1.80, 2.39—2.72 (m, each 1H), 3.55—4.45 (m, 5H), 4.57 (d, 1H, *J*=6 Hz), 7.15—7.85 (m, 15H).

Analogously as described above, compound **13** (20 mg) was converted into **15** (37 mg, 85%). **15** as a colorless oil: TLC R_f 0.66 (AcOEt/hexane 1:2); $[\alpha]_D^{29}$ −31.5° (*c* 1.56, $CHCl_3$); IR ν_{max}^{neat} 3400, 2940, 2860, 1430, 1110 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.10 (s, 9H), 3.40—3.85 (m, 2H), 3.90—4.53 (m, 5H), 4.92 (d, 1H, *J*=6 Hz), 7.30—7.55, 7.65—7.89 (m, 15H).

Isopropylidenation of 15. A mixture of **15** (21 mg, 0.05 mmol), 2,2-dimethoxypropane (0.008 ml), and CSA (3 mg) in acetone (0.5 ml) was stirred for 2 h, and neutralized with saturated aqueous $NaHCO_3$, then concentrated. The residue was purified by PTLC (AcOEt/hexane 1:10) to give **16** (20 mg, 87%) as a pale yellow oil. **16**: TLC R_f 0.85 (AcOEt/hexane 1:4); $[\alpha]_D^{28}$ −4.3° (*c* 1.00, $CHCl_3$); IR ν_{max}^{neat} 2940, 1430, 1385, 1375, 1215, 1120 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.08 (s, 9H), 1.32, 1.45 (each s, 3H×2), 4.05 (s, 3H), 4.62—4.98 (m, 2H), 5.12 (s, 1H), 7.30—7.52, 7.62—7.82 (m, 15H).

(2*S*,3*R*,4*S*,5*S*)-2-(Hydroxymethyl)-4-[(methylsulfonyl)oxy]-5-phenyltetrahydrofuran-3-ol *O*,*O*′-Benzylidene Derivative (17). To a stirred solution of **11** (1.67 g, 5.6 mmol) in pyridine (35 ml) were added methanesulfonyl chloride (0.65 ml, 8.4 mmol) and DMAP (137 mg, 1.12 mmol). After being stirred for 2.5 h, the mixture was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (600 ml) and H_2O (200 ml). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The resulting crystals were recrystallized from AcOEt to give **17** (1.35 g). The mother liquor was concentrated, and the residue was purified by a silica-gel column chromatography (AcOEt/$PhCH_3$ 1:5) to give an additional **17** (0.58 g, total 1.93 g, 93%), mp 186—186.5 °C. **17**: TLC R_f 0.48 (AcOEt/$PhCH_3$ 1:3); $[\alpha]_D^{22}$ −75.2° (*c* 1.24, $CHCl_3$);IR ν_{max}^{KBr} 2920, 1410, 1350, 1175 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.83 (s, 3H), 4.00—4.57 (m, 3H), 4.75—5.03 (m, 2H), 5.37 (d, 1H, *J*=6 Hz), 5.58 (s, 1H), 7.30—7.68 (m, 10H). Found: C, 60.75; H, 5.51%. Calcd for $C_{19}H_{20}O_6S$: C, 60.62; H, 5.36%.

Elimination of the Mesyloxy Group in 17, Successive Hydroboration of the Dihydrofuran Derivative 18 Followed by Oxidative Work-up. Conversion of 17 into 10. A mixture of **17** (1.96 g, 5.21 mmol) and *t*-BuOK (2.04 g, 18.2 mmol) in THF (140 ml) was refluxed for 20 min under argon atmosphere. The reaction mixture was mainly consisted of the dihydrofuran **18**, and used directly without purification [**18**: ^1H NMR (90 MHz, $CDCl_3$) δ=4.05—4.45 (m, 2H), 4.70 (d, 1H, *J*=12.5 Hz), 5.00 (t, 1H, *J*=3 Hz), 5.47 (s, 1H), 5.66 (d, 1H, *J*=2.5 Hz), 7.22—7.80 (m, 5H)]. The mixture in THF obtained above was cooled to 0 °C, and BH_3–THF complex (1 M in THF, 31.3 ml, 31.3 mmol) was added. After being stirred for 1.5 h, 2 M aqueous NaOH (26 ml) and H_2O (30 ml) were added successively to the mixture. After being warmed to room temperature, H_2O_2 (35 wt% in H_2O, 28 ml) was added to the mixture which was stirred more 1.5 h. To the mixture was added saturated aqueous Na_2SO_3 (30 ml), and the mixture was stirred for 1 h. This was diluted with AcOEt (500 ml), washed with 0.1 M HCl (100 ml) and saturated aqueous $NaHCO_3$ (100 ml). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by repeated flash column chromatography (AcOEt/$PhCH_3$ 1:5) to give **10** (1.09 g 65%), which was identical with an authentic sample described above in all respects.

Pfitzner-Moffatt Oxidation of 10 and Successive $NaBH_4$ Reduction. (2*S*,3*R*,4*S*,5*R*)-2-(Hydroxymethyl)-5-phenyltetrahydrofuran-3,4-diol *O*,*O*′-Benzylidene Derivative (20). To a stirred solution of **10** (913 mg, 3.06 mmol) in benzene (85 ml) were added DMSO (1.31 ml, 18.4 mmol), pyridine (0.37 ml, 4.6 mmol), CF_3COOH (0.35 ml, 4.6 mmol), and dicyclohexylcarbodiimide (1.89 g, 9.2 mmol). After being stirred for 30 min, the resulting white solids were filtered off. The filtrate was diluted with AcOEt (500 ml), and this was washed with H_2O (100 ml). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. To the residue was added a small amount of AcOEt, and the precipitates were filtered off. The filtrate was concentrated in vacuo to give crude tetrahydrofuranone **19**, which was reduced directly. The residue was dissolved in MeOH (20 ml), and $NaBH_4$ (174 mg, 4.6 mmol) was added. After being stirred for 1 h, the mixture was neutralized with Amberlite IR-120 (H^+). The resin was removed by filtration and washed with MeOH. The combined filtrate and washings were concentrated in vacuo. The residue was purified by flash column chromatography (AcOEt/$PhCH_3$ 1:20) to give **20** (758 mg, 83%) as white crystals, mp 121—122 °C. **20**: TLC R_f 0.43 (AcOEt/$PhCH_3$ 1:2); $[\alpha]_D^{27}$ +12.7° (*c* 1.42, $CHCl_3$); IR ν_{max}^{KBr} 3560, 2915, 1400, 1225, 1210, 1150, 1095, 1080, 1065 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.00 (br s, 1H), 3.92—4.01 (m, 1H), 4.18 (dd, 1H, *J*=2 and 13.5 Hz), 4.38 (dd, 1H, *J*=2 and

6 Hz), 4.55 (d, 1H, J=13.5 Hz), 4.54—4.96 (m, 1H), 5.20 (d, 1H, J=9 Hz), 5.53 (s, 1H), 7.25—7.77 (m, 10H). Found: C, 72.34; H, 6.06%. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08%.

Inversion of the Hydroxyl Group at C-4 in 11 via Triflate 21. (2*S*,3*R*,4*R*,5*S*)-4-Acetoxy-2-(hydroxymethyl)-5-phenyltetrahydrofuran-3-ol *O*,*O*′-Benzylidene Derivative (22). To a stirred solution of **11** (1.00 g, 3.35 mmol) in pyridine (20 ml) were added triethylamine (1.87 ml, 13.4 mmol) and trifluoromethanesulfonic anhydride (1.70 ml, 10.1 mmol) at −15 °C. After being stirred at −15 °C for 2 h, the mixture was concentrated in vacuo. The residue was partitioned between AcOEt (200 ml) and H_2O (100 ml). The organic phase was washed with saturated aqueous NaCl (2×100 ml), dried (Na_2SO_4), and concentrated in vacuo to give crude triflate **21**, which was rapidly passed through a silica-gel column by flash chromatography (AcOEt/hexane 1:10 then 1:5). The fractions having R_f 0.55 (AcOEt/hexane 1:2) were concentrated in vacuo to give **21** as a yellow solid (1.31 g). A mixture of **21** (1.31 g) and potassium acetate (1.49 g, 15.2 mmol) in DMF (26 ml) was heated at 135 °C for 1 h with stirring. After being cooled to room temperature, insoluble materials were removed by filtration. The filtrate was concentrated in vacuo. The residue was partitioned between AcOEt (200 ml) and H_2O (50 ml). The organic phase was washed with saturated aqueous NaCl (50 ml), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (AcOEt/hexane 1:10 then 1:5) to give **22** (902 mg, 79%) as white crystals, mp 123—124 °C. **22**: TLC R_f 0.69 (AcOEt/hexane 1:2); $[\alpha]_D^{21}$ +16.9° (c 1.57, $CHCl_3$); IR ν_{max}^{KBr} 3060, 2920, 2900, 1740, 1370, 1240, 1140 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.72 (s, 3H), 4.05—4.35, 4.49—4.70 (each m, each 2H), 5.55 (s, 1H), 5.57—5.77 (m, 2H), 7.30—7.69 (m, 10H). Found: C, 70.29; H, 5.94%. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92%.

(2*S*,3*R*,4*R*,5*S*)-2-(Hydroxymethyl)-5-phenyltetrahydrofuran-3,4-diol *O*,*O*-Benzylidene Deriative (23). A mixture of **22** (1.97 g, 5.79 mmol) and MeONa (1 M in MeOH, 8.7 ml, 8.7 mmol) in MeOH (40 ml) was stirred for 30 min. The mixture was neutralized with Amberlite IR-120 (H^+), the resin was removed by filtration, washed with MeOH. The combined filtrate and washings were concentrated in vacuo. The residual crystals were recrystallized from toluene to give **23** (1.53 g). By silica-gel column chromatography of the concentrate of the mother liquor (AcOEt/hexane 1:10 then 1:4), an additional **23** (0.10 g, total 1.63 g, 94%) was obtained. **23** as white crystals, mp 154—155 °C: TLC R_f 0.49 (AcOEt/hexane 1:2); $[\alpha]_D^{23}$ +76.1° (c 1.43, $CHCl_3$); IR ν_{max}^{KBr} 3330, 2920, 1490, 1445, 1390, 1300, 1210, 1125, 1110, 1080, 1065 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.85 (br s, 1H), 4.02—4.69 (m, 5H), 5.54 (s, 1H), 5.61 (d, 1H, J=3 Hz), 7.30—7.67 (m, 10H). Found: C, 72.22; H, 6.08%. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08%.

Direct Preparation of 23 from 21 with KO_2. Compound **21** (20.0 mg), which was prepared from 17.8 mg of **11** as described above, was dissolved in DMSO–DMF (v/v 1/1, 1 ml). To the solution were added a solution of 18-crown-6 (55 mg) and KO_2 (13 mg) in DMSO–DMF (v/v 1/1, 1 ml). After being stirred for 30 min, the mixture was quenched with 5% aqueous $Na_2S_2O_3$ (5 ml). This aqueous solution was extracted with CH_2Cl_2 (4×10 ml). The combined extracts were dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (AcOEt/hexane 2:3) to give **23** (10.2 mg, 58% from **11**), which was identical with an authentic sample in all respects.

Debenzylidenation of 20 and 23. (2*S*,3*R*,4*S*,5*R*)- and (2*S*,3*R*,4*R*,5*S*)-2-(Hydroxymethyl)-5-phenyltetrahydrofuran-3,4-diol (24 and 25). By the analogous reaction conditions and work-up as described in the preparation of **12**, 836 mg of **20** was converted into debenzylidene derivative **24** (503 mg, 85%) as white crystals, mp 100.5—101 °C. **24**: TLC R_f 0.22 (EtOH/$PhCH_3$ 1:4); $[\alpha]_D^{28}$ −89.4° (c 1.50, MeOH); IR ν_{max}^{KBr} 3280, 1450, 1315, 1280, 1200, 1145, 1125, 1100, 1050 cm^{-1}; ^1H NMR (90 MHz, CD_3OD) δ=3.77—3.92 (m, 2H), 4.00—4.22 (m, 2H), 4.58 (dd, 1H, J=4.5 and 7.5 Hz), 4.85 (d, 1H, J=3 Hz), 7.25—7.55 (m, 5H). Found: C, 62.68; H, 6.63%. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71%.

Analogously, compound **23** (1.57 g) was debenzylidenated to give **25** (1.02 g, 92%) as white crystals, mp 100—101 °C. **25**: TLC R_f 0.31 (EtOH/$PhCH_3$ 1:5); $[\alpha]_D^{23}$ +94.0° (c 2.13, MeOH); IR ν_{max}^{KBr} 3440, 2930, 2880, 1480, 1450, 1285, 1260, 1200, 1070 cm^{-1}; ^1H NMR (90 MHz, CD_3OD) δ=3.80—4.00 (m, 2H), 4.08—4.54 (m, 3H), 5.23 (d, 1H, J=3 Hz), 7.21—7.56 (m, 5H). Found: C, 62.83; H, 6.67%. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71%.

Selective Tritylation of the Primary Hydroxyl Groups in 12, 13, 24, and 25. (2*S*,3*R*,4*R*,5*R*)-, (2*S*,3*R*,4*S*,5*S*)-, (2*S*,3*R*,4*S*,5*R*)-, and (2*S*,3*R*,4*R*,5*S*)-5-Phenyl-2-[(triphenylmethoxy)-methyl]tetrahydrofuran-3,4-diol (26, 27, 28, and 29). To a solution of **12** (507 mg, 2.41 mmol) in pyridine (15 ml) were added triphenylmethyl chloride (1.01 g, 3.62 mmol) and DMAP (59 mg, 0.48 mmol). After being stirred at 90 °C for 8 h, the mixture was concentrated in vacuo. The residue was dissolved in AcOEt (400 ml) and washed with H_2O (2×100 ml). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica-gel column chromatography (AcOEt/hexane 1:2 containing 1% Et_3N, then EtOH/$PhCH_3$ 1:40) to give **26** (823 mg, 75%) as a pale yellow oil: TLC R_f 0.62 (EtOH/$PhCH_3$ 1:5 containing 1% Et_3N); $[\alpha]_D^{28}$ −26.9° (c 1.16, $CHCl_3$); IR ν_{max}^{neat} 3430, 3060, 3040, 2940, 2880, 1600, 1490, 1450, 1320, 1220, 1150, 1100 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.80—3.70 (m, 4H), 3.87—4.33 (m, 3H), 4.56 (d, 1H, J=6 Hz), 7.10—7.67 (m, 20H).

Analogously as described above, **13** (440 mg), **24** (500 mg), and **25** (967 mg) were converted into **27** (686 mg, 72%), **28** (851 mg, 79%), and **29** (1.94 g, 93%). **27** as a pale yellow oil: TLC R_f 0.70 (AcOEt/hexane 1:2); $[\alpha]_D^{29}$ −19.1° (c 1.10, $CHCl_3$); IR ν_{max}^{neat} 3410, 3100, 3070, 3045, 2870, 1600, 1495, 1450, 1400, 1325, 1220, 1155, 1080, 1045 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.57—3.29 (br s, 1H), 3.31—3.71 (m, 2H), 3.99 (dd, 1H, J=4.5 Hz and 7.5 Hz), 4.23—4.52 (m, 2H), 4.85 (d, 1H, J=7.5 Hz), 7.25—7.62 (m, 20H). **28** as a pale yellow oil: TLC R_f 0.37 (AcOEt/hexane 1:2 containing 1% Et_3N); $[\alpha]_D^{27}$ −71.1° (c 1.45, $CHCl_3$); IR ν_{max}^{neat} 3400, 3050, 3025, 2925, 2875, 1600, 1485, 1445, 1215, 1070 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.41—3.22 (br, 2H), 3.40, 3.72 (each dd, each 1H, J=4.5 and 10.5 Hz), 4.06—4.52 (m, 3H), 4.93 (d, 1H, J=4.5 Hz), 7.25—7.65 (m, 20H). **29** as a colorless foam: TLC R_f 0.66 (EtOH/$PhCH_3$ 1:5 containing 1% Et_3N); $[\alpha]_D^{23}$ +43.6° (c 2.05, $CHCl_3$); IR ν_{max}^{neat} 3450, 3055, 3025, 2930, 2875, 1600, 1490, 1445, 1220, 1180, 1150 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.45 (br s, 1H), 3.54 (d, 2H, J=6 Hz), 4.12—4.22 (m, 1H), 4.36—4.66 (m, 2H), 5.40 (d, 1H, J=3 Hz), 7.25—7.63 (m, 20H).

Methoxymethylation of Compounds 26, 27, 28, and 29. (2*S*,3*R*,4*R*,5*R*)-, (2*S*,3*R*,4*S*,5*S*)-, (2*S*,3*R*,4*S*,5*R*)-, and (2*S*,3*R*,4*R*,5*S*)-3,4-Bis(methoxymethoxy)-5-phenyl-2-[(triphenyl-

methoxy)methyl]tetrahydrofuran (30, 31, 32, and 33). To a solution of **26** (823 mg, 1.82 mmol) in THF (20 ml) were added *N,N*-diisopropylethylamine (19.0 ml, 109 mmol) and freshly distilled chloromethyl methyl ether (7.47 ml, 98.3 mmol). After being refluxed for 2 h under argon atmosphere, the mixture was diluted with AcOEt (500 ml). The solution was washed with H_2O (100 ml), saturated aqueous NaCl (100 ml), and then dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by siliica-gel chromatography (AcOEt/hexane 1:40 containing 1% Et_3N) to give **30** (875 mg, 89%) as a pale yellow oil: TLC R_f 0.72 (AcOEt/$PhCH_3$ 1:5 containing 1% Et_3N); $[\alpha]_D^{28}$ +48.4° (*c* 1.21,$CHCl_3$); IR ν_{max}^{neat} 3060, 3040, 2950, 2900, 1600, 1495, 1450, 1215, 1150, 1100, 1080 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=3.02, 3.33 (each s, each 3H), 3.14—3.43 (m, 1H), 3.68 (dd, 1H, *J*=6 and 9 Hz), 3.88—4.93 (m, 6H), 4.13 (dd, 1H, *J*=3 and 9 Hz), 4.85 (d, 1H, *J*=3 Hz), 7.01—7.86 (m, 20H). Found: C, 75.86; H, 6.90%. Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71%.

By the analogous procedure for the preparation of **30**, **27** (667 mg), **28** (822 mg), and **29** (1.88 g) were converted into **31** (726 mg, 91%), **32** (888 mg, 90%), and **33** (2.12 g, 94%). **31** as a pale yellow oil: TLC R_f 0.52 (AcOEt/hexane 1:5 containing 1% Et_3N); $[\alpha]_D^{29}$ −12.4° (*c* 1.58, $CHCl_3$); IR ν_{max}^{neat} 3075, 3050, 2960, 2910, 1600, 1500, 1460, 1225, 1160, 1080, 1060, 1035 cm^{-1}; ^1H NMR (90 MHz. $CDCl_3$) δ=3.06, 3.22 (each s, each 3H), 3.12—3.42, 3.50—3.72 (each m, 2H), 4.12 (dd, 1H, *J*=4.5 and 9 Hz, 1H), 4.30—4.78 (m, 6H), 4.83 (d, 1H. *J*=9 Hz), 7.15—7.69 (m, 20H). **32** as a pale yellow oil: TLC R_f 0.44 (AcOEt/hexane 1:3 containing 1% Et_3N); $[\alpha]_D^{26}$ + 11.6° (*c* 2.17, $CHCl_3$); IR ν_{max}^{neat} 3055, 3025, 2950, 2895, 1600, 1490, 1445, 1210, 1145, 1070, 1025 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.89, 3.20 (each s, each 3H), 3.30—3.85 (m, 2H), 4.02—4.60 (m, 6H), 5.00 (d, 1H, *J*=4.5 Hz), 7.18—7.70 (m, 20H). Found: C, 75.91; H, 6.74%. Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71%. **33** as a pale yellow oil: TLC R_f 0.68 (AcOEt/$PhCH_3$ 1:4 containing 1% Et_3N); $[\alpha]_D^{24}$ +82.8° (*c* 2.42, $CHCl_3$); IR ν_{max}^{neat} 3060, 3040, 2950, 2900, 1600, 1490, 1445, 1220, 1150, 1110, 1070, 1035 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.94, 3.25 (each s, each 3H), 3.60 (dd, 1H, *J*=6 and 9 Hz), 4.10—4.80 (m, 8H), 5.15 (d, 1H, *J*=3 Hz), 7.20—7.68 (m, 20H).

Detritylation of 30, 31, 32, and 33. (2*S*,3*R*,4*R*,5*R*)-, (2*S*,3*R*,4*S*,5*S*)-, (2*S*,3*R*,4*S*,5*R*)-, and (2*S*,3*R*,4*R*,5*S*)-2-(Hydroxymethyl)-3,4-bis(methoxymethoxy)-5-phenyltetrahydrofuran (34, 35, 36, and 37). A solution of **30** (853 mg, 1.58 mmol) in a mixture of AcOEt (30 ml) and MeOH (30 ml) containing *p*-TsOH (monohydrate, 601 mg, 3.16 mmol) was stirred for 45 min. The mixture was neutralized with Et_3N and concentrated in vacuo. The residue was purified by silica-gel chromatography (AcOEt/$PhCH_3$ 1:3) to give **34** (440 mg, 94%) as a colorless oil. **34**: TLC R_f 0.30 (EtOH/$PhCH_3$ 1:10); $[\alpha]_D^{27}$ +66.3° (*c* 1.13, $CHCl_3$); IR ν_{max}^{neat} 3460, 2950, 2900, 1600, 1500, 1450, 1400, 1365, 1210, 1150, 1100, 1040, 1030 cm^{-1}; ^1H NMR (90 MHz) δ=2.45 (br s, 1H), 3.24 (s, 6H), 3.66—4.39 (m, 5H), 4.39—4.85 (m, 5H), 7.07—7.49 (m, 5H); MS *m/z* calcd for $C_{15}H_{21}O_6$ (M^+−H) 297.1336, observed 297.1329.

Analogously as described above, **31** (712 mg), **32** (839 mg), and **33** (2.12 g) were converted into **35** (306 mg, 78%), **36** (332 mg, 72%), and **37** (1.10 g, 94%). **35** as a colorless oil: TLC R_f 0.20 (AcOEt/hexane 1:2) $[\alpha]_D^{28}$ +5.2° (*c* 1.63, $CHCl_3$); IR ν_{max}^{neat} 3450, 2950, 2900, 1600, 1490, 1450, 1400, 1360, 1300, 1220, 1150, 1080, 1050, 1020 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.85 (br s, 1H), 3.15, 3.42 (each s, each 3H), 3.82 (d, 2H, *J*=6 Hz), 4.05 (dd, 1H, *J*=4.5 and 7.5 Hz), 4.24—4.78 (m, 6H), 4.93 (d, 1H, *J*=7.5 Hz), 7.18—7.46 (m, 5H) MS *m/z* calcd for $C_{15}H_{23}O_6$ (M^++H), 299.1493, observed 299.1497. **36** as a colorless oil: TLC R_f 0.12 (AcOEt/hexane 1:2); $[\alpha]_D^{26}$ +2.4° (*c* 1.52, $CHCl_3$); IR ν_{max}^{neat} 3470, 2950, 2900, 1600, 1500, 1460, 1370, 1260, 1220, 1155, 1030 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.90, 3.45 (each s, each 3H), 3.92 (d, 2H, *J*=4.5 Hz), 4.05—4.50, 4.61—4.85 (m, 7H), 5.00 (d, 1H, *J*=3 Hz), 7.58—7.86 (m, 5H). Found: C, 60.63; H, 7.51%. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43%. **37** as a colorless oil: TLC R_f 0.18 (AcOEt/hexane 1:2); $[\alpha]_D^{24}$ +89.3° (*c* 1.24, $CHCl_3$); IR ν_{max}^{neat} 3450, 2950, 2890, 1600, 1495, 1455, 1400, 1360, 1215, 1150, 1105, 1045 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=2.40 (br s, 1H), 2.98, 3.48 (each s, each 3H), 3.90 (dd, 2H,*J*=3 and 6 Hz), 4.1—4.59 (m, 5H), 4.75 (s, 2H), 5.25 (d, 1H, *J*=3.5 Hz), 7.22—7.52 (m, 5H).

Collins Oxidation of 34, 35, 36, and 37, and Successive Wittig Olefination with (Ethoxycarbonylmethylene)triphenylphosphorane. (2*S*,3*R*,4*R*,5*R*)-, (2*S*,3*R*,4*S*,5*S*)-, (2*S*,3*R*,4*S*,5*R*)-, and (2*S*,3*R*,4*R*,5*S*)-2-[(*Z*)- and (*E*)-2-(Ethoxycarbonyl)-ethenyl]-3,4-bis(methoxymethoxy)-5-phenyltetrahydrofuran (38Z and 38E, 39Z and 39E, and 40Z and 40E, and 41Z and 41E). The oxidation was carried out under argon atmosphere. To a mixture of pyridine (3.40 ml, 42.0 mmol) and CH_2Cl_2 (30 ml) was added CrO_3 (2.10 g, 21.0 mmol) at 0 °C. After being stirred for 13 h, a solution of **34** (418 mg, 1.40 mmol) in CH_2Cl_2 (5 ml) was added to the mixture. The mixture was stirred for 15 min, and applied on a short silica-gel column (12 g). The column was eluted with ether to give an aldehyde [R_f 0.46 (AcOEt/$PhCH_3$ 1:2)], which was subjected to the Wittig reaction. A mixture of the aldehyde obtained and (ethoxycarbonylmethylene)triphenylphosphorane (975 mg, 2.80 mmol) in MeOH (10 ml) was stirred for 30 min, and concentrated in vacuo. The residue was purified by flash chromatography (AcOEt/hexane 1:10 then 1:5) to give **38Z** (320 mg, 62%) and **38E** (47 mg, 9%). **38Z** as a colorless oil: TLC R_f 0.71 (AcOEt/$PhCH_3$ 1:2); $[\alpha]_D^{29}$ +176° (*c* 1.13, $CHCl_3$); IR ν_{max}^{neat} 3000, 2950, 2900, 1720, 1655, 1600, 1500, 1450, 1200, 1155, 1110 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.30 (t, 3H, *J*=7.5 Hz), 3.18, 3.35 (each s, each 3H), 4.06—4.21 (m, 1H), 4.18 (q, 2H, *J*=7.5 Hz), 4.42—4.85 (m, 6H), 5.43—5.61 (m, 1H), 5.92 (dd, 1H, *J*=1.5 and 12 Hz), 6.53 (dd, 1H, *J*=7.5 and 12 Hz), 7.23—7.55 (m, 5H). Found: C, 62.47; H, 7.10%. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15%. **38E** as a colorless oil: TLC R_f 0.62 (AcOEt/$PhCH_3$ 1:2); $[\alpha]_D^{30}$ +15.7° (*c* 0.96, $CHCl_3$); IR ν_{max}^{neat} 3000, 2950, 2900, 1720, 1665, 1600, 1500, 1470, 1455, 1370, 1305, 1265, 1220, 1180, 1155, 1105 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.30 (t, 3H, *J*=7.5 Hz), 3.22, 3.34 (each s, each 3H), 4.06—4.22 (m, 2H), 4.21 (q, 2H, *J*=7.5 Hz), 4.44—4.79 (m, 5H), 4.82 (d, 1H, *J*=4.5 Hz), 6.23 (dd, 1H, *J*=1.5 and 16.5 Hz), 7.08 (dd, 1H, *J*=6 and 16.5 Hz), 7.22—7.51 (m, 5H). Found: C, 61.99; H, 6.99%. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15%.

By the analogous reaction conditions and work-up described for preparation of 38Z and **38E**, **35** (264 mg), **36** (345 mg), and **37** (944 mg) were converted into **39Z** (188 mg, 58%) and **39E** (16 mg, 5%), **40Z** (305 mg, 72%) and **40E** (23 mg, 5%), and **41Z** (614 mg, 53%) and **41E** (46 mg, 4%). **39Z** as a colorless oil: TLC R_f 0.46 (AcOEt/hexane 1:4); $[\alpha]_D^{29}$ +34.5° (*c* 1.56, $CHCl_3$); IR ν_{max}^{neat} 3000, 2960, 2950, 2900, 2850, 1720, 1655, 1600 1500, 1470, 1460, 1420, 1400, 1310, 1200, 1160 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.30 (t, 3H, *J*=7.5 Hz), 3.11, 3.39 (each s, each 3H), 4.10—4.30 (m, 1H),

4.20 (q, 2H, J=7.5 Hz), 4.40—4.82 (m, 5H), 5.08 (d, 1H, J=7.5 Hz), 5.78—5.98 (m, 1H), 5.95 (dd, 1H, J=1 and 12 Hz), 6.50 (dd, 1H, J=7.5 and 12 Hz), 7.20—7.55 (m, 5H). Found: C, 62.18; H, 7.06%. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15%. **39E** as a colorless oil: TLC R_f 0.28 (AcOEt/hexane 1:4); $[\alpha]_D^{29}$ −17.6° (*c* 1.48, $CHCl_3$); IR ν_{max}^{neat} 3000, 2950, 2900, 2835, 1720, 1660, 1600, 1500, 1470, 1460, 1400, 1370, 1300, 1270, 1220, 1180, 1155, 1130 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.28 (t, 3H, J=7.5 Hz), 3.15, 3.40 (each s, each 3H), 4.17 (q, 2H, J=7.5 Hz), 4.10—4.82 (m, 6H), 4.82—5.05 (m, 1H), 5.00 (d, 1H, J=7.5 Hz), 6.11 (dd, 1H, J=1 and 16.5 Hz), 7.03 (dd, 1H, J=6 and 16.5 Hz), 7.30—7.57 (m, 5H). Found: C, 61.96; H, 7.02%. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15%. **40Z** as a colorless oil: TLC R_f 0.49 (AcOEt/hexane 1:3); $[\alpha]_D^{25}$ +6.8° (*c* 1.33, $CHCl_3$); IR ν_{max}^{neat} 2950, 2900, 1710, 1645, 1600, 1500, 1450, 1410, 1380, 1360, 1260, 1185, 1150 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.31 (t, 3H, J=7.5 Hz), 2.90, 3.39 (each s, each 3H), 4.20 (q, 2H, J=7.5 Hz), 4.30—4.82 (m, 6H), 5.05 (d, 1H, J=3 Hz), 5.82 (t, 1H, J=4.5 HZ), 5.98 (d, 1H, J=12 Hz), 6.66 (dd, 1H, J=4.5 and 12 Hz), 7.26—7.58 (m, 5H); MS *m/z* calcd for $C_{19}H_{26}O_7$ (M^+), 366.1676, observed, 366.1662. **40E** as a colorless oil: TLC R_f 0.30 (AcOEt/hexane 1:3); $[\alpha]_D^{25}$ −79.8° (*c* 1.42, $CHCl_3$); IR ν_{max}^{neat} 3000, 2950, 2900, 1720, 1660, 1600, 1500, 1450, 1370, 1300, 1270, 1250, 1215, 1150 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.32 (t, 3H, J=7.5 Hz), 2.90, 3.40 (each s, each 3H), 4.22 (q, 2H, J=7.5 Hz), 4.21—4.86 (m, 7H), 5.05 (d, 1H, J=3 Hz), 6.09 (d, 1H, J=15 Hz), 7.25 (dd, 1H, J=6 and 15 Hz), 7.32—7.56 (m, 5H); MS *m/z* calcd for $C_{19}H_{26}O_7$ (M^+) 366.1676, observed 366.1669. **41Z** as a colorless oil: TLC R_f 0.60 (AcOEt/hexane 1:2); $[\alpha]_D^{23}$ +161.8° (*c* 1.66, $CHCl_3$); IR ν_{max}^{neat} 2980, 2950, 2890, 1715, 1640, 1600, 1490, 1450, 1410, 1380, 1360, 1300, 1190, 1150 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ= 1.31 (t, 3H, J=7.5 Hz), 2.97, 3.40 (each s, each 3H), 4.22 (q, 2H, J=7.5 Hz), 4.18—4.73 (m, 6H), 5.40 (d, 1H, J=3.5 Hz), 5.80—6.00 (m, 1H), 5.95 (dd, 1H, J=1.5 and 12 Hz), 6.50 (dd, 1H, J=7.5 and 12 Hz), 7.27—7.58 (m, 5H); MS *m/z* calcd for $C_{19}H_{26}O_7$ (M^+) 366.1677, observed 366.1688. **41E** as a colorless oil: TLC R_f 0.51 (AcOEt/hexane 1:2); $[\alpha]_D^{23}$ +116.2° (*c* 1.79, $CHCl_3$); IR ν_{max}^{neat} 2980, 2950, 1720, 1660, 1600, 1500, 1455, 1370, 1300, 1260, 1215, 1180, 1150 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=1.30 (t, 3H, J=7.5 Hz), 2.95, 3.43 (each s, each 3H), 4.22 (q, 2H, J=7.5 Hz), 4.11—4.52 (m, 4H), 4.71 (d, 2H, J=3 Hz), 4.98—5.18 (m, 1H), 5.31 (d, 1H, J=3 Hz), 6.23 (dd, 1H, J=2.5 and 16.5 Hz), 7.11 (dd, 1H, J=5.5 and 16.5 Hz), 7.29—7.55 (m, 5H); MS *m/z* calcd for $C_{19}H_{26}O_7$,(M^+) 366.1677, observed 366.1667.

Demethoxymethylation of 38Z, 39Z, 40Z, and 41Z Accompanied by γ-Lactonization. (+)-Altholactone (1), (+)-7,8-Di-*epi*- (2), (+)-7-*epi*- (3), and (+)-8-*epi*-Altholactone (4). A solution of **38Z** (320 mg, 0.87 mmol) in a mixture of 1 M HCl (8 ml) and 1,4-dioxane (8 ml) was refluxed for 1 h and concentrated in vacuo. The residue was partitioned between AcOEt (100 ml) and saturated aqueous $NaHCO_3$ (30 ml). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (AcOEt/hexane 1:2) to give **1** (195 mg, 96%) as needles, mp 113—114 °C: TLC R_f 0.40 (AcOEt/hexane 1:1); $[\alpha]_D^{33}$ +180.8° (*c* 0.52 EtOH); IR ν_{max}^{KBr} 3430, 3070, 3040, 2950, 2930, 2900, 1730, 1640, 1600, 1490, 1365, 1245, 1150, 1100, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=2.66 (d, 1H, J=4.4 Hz), 4.45 (dd, 1H, J=2.4 and 5.9 Hz, after irradiation of the doublet at δ=2.66), 4.65 (1H, t, J=5.4 Hz), 4.74 (d, 1H, J=5.9 Hz), 4.95 (dd, 1H, J=2.4 and 5.4 Hz), 6.22 (d, 1H, J=10.2 Hz), 6.99 (dd, 1H, J=5.4 and 10.2 Hz), 7.29—7.36 (m, 5H) ^{13}C NMR (100 MHz, $CDCl_3$) δ=68.15 (d), 83.56 (d), 86.03 (d), 86.63 (d), 123.59 (d), 126.12 (d), 128.34 (d), 128.63 (d), 138.12 (s), 140.56 (d), 161.70 (s). Found: C, 67.24; H, 5.18%. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21%.

By the analogous procedure described for the preparation of **1**, **39Z** (164 mg), **40Z** (305 mg), and **41Z** (271 mg) were converted into **2** (81.5 mg, 78%), **3** (153 mg, 79%), and **4** (140 mg, 82%), respectively. **2** as a needles, mp 99—100 °C; TLC R_f 0.52 (AcOEt/hexane 1:1); $[\alpha]_D^{30}$ +74.1° (*c* 0.54, EtOH); IR ν_{max}^{KBr} 3430, 3080, 3050, 2945, 1730, 1645, 1610, 1500, 1460, 1400, 1255, 1170, 1130 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=3.30 (d, 1H, J=6.4 Hz), 4.26 (dd, 1H, J=5.4 and 7.3 Hz, after irradiation of the doublet at δ=3.30), 4.78 (d, 1H, J=7.3 Hz), 4.88 (dd, 1H, J=4.4 and 5.9 Hz), 5.04 (dd, 1H, J=5.4 and 5.9 Hz), 6.20 (d, 1H, J=9.3 Hz), 6.87 (dd, 1H, J=4.4 and 9.3 Hz), 7.30—7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=67.73 (d), 78.32 (d), 78.51 (d), 83.30 (d), 122.95 (d), 125.69 (d), 128.27 (d), 128.62 (d), 138.47 (s), 141.77 (d), 161.23 (s). Found: C, 67.21; H, 5.20%. Calcd for $C_{13}H_{12}O_4$; C, 67.23; H, 5.21%. **3** as needles, mp 117—117.5 °C: TLC R_f 0.43 (AcOEt/hexane 1:1); $[\alpha]_D^{30}$ +23.0° (*c* 0.50, EtOH); IR ν_{max}^{KBr} 3380, 3050, 2940, 2880, 1710, 1635, 1600, 1480, 1400, 1345, 1280, 1245, 1200, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=2.24 (d, 1H, J=5.9 Hz), 4.52 (t, 1H, J=4.4 Hz, after irradiation of the doublet at δ=2.24), 4.78 (ddd, 1H, J=1.0, 3.4, and 7.8 Hz), 5.06 (d, 1H, J=4.4 Hz), 5.22 (dd, 1H, J=4.4 and 7.8 Hz), 6.11 (dd, 1H, J=1.0 and 10.3 Hz), 6.85 (dd, 1H, J=3.4 and 10.3 Hz), 7.29—7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=67.23 (d), 73.70 (d), 79.69 (d), 80.72 (d), 121.56 (d), 126.90 (d), 128.32 (d), 128.44 (d), 135.28 (s), 141.70 (d), 161.21 (s). Found: C, 67.23; H, 5.40%. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21%. **4** as needles, mp 193.5—194 °C: TLC R_f 0.46 (AcOEt/hexane 1:1); $[\alpha]_D^{26}$ +224° (*c* 0.5, EtOH); IR ν_{max}^{KBr} 3440, 3060, 2940, 2920, 2860, 1700, 1635, 1600, 1490, 1450, 1385, 1355, 1325, 1260, 1255, 1195, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.66 (d, 1H, J=2.4 Hz), 4.50 (d, 1H, J=2.0 Hz, after irradiation of the doublet at δ 1.16), 4.88 (t 1H, J=4.9 Hz), 5.08 (dd, 1H, J=2.0 and 4.9 Hz), 5.35 (d, 1H, J=2.0 Hz), 6.20 (d, 1H, J=9.8 Hz), 7.00 (dd, 1H, J=4.9 and 9.8 Hz), 7.33—7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=68.13 (d), 77.89 (d), 83.54 (d), 84.25 (d), 123.08 (d), 126.62 (d), 128.62 (d), 128.89 (d), 134.72 (s), 140.59 (d), 161.01 (s). Found: C, 67.09; H, 5.43%. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21%.

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