Pergamon

Tetrahedron, Vol. 53, No. 9, pp. 3057-3072, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00071-9

Synthetic Study of Ciguatoxin. Absolute Configuration of the C2 Hydroxy Group

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Abstract: The absolute stereochemistry of the secondary alcohol of the 1,2-dihydroxybutenyl substituent of ciguatoxin (**1**) was shown to be *S* by comparing the split CD curve of ciguatoxin tetra-*p*-bromobenzoate (**2**) with those of di- and tri-*p*-bromobenzoates of AB ring fragments that were synthesized enantioselectively.

INTRODUCTION

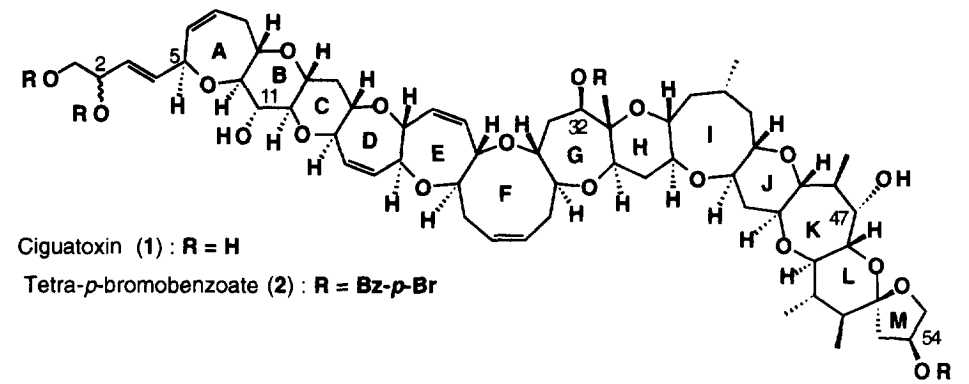
Ciguatera is one of the most common forms of poisoning in the tropical and subtropical regions.[1,2] Although the extremely low availability of the causative agent, ciguatoxin (CTX1B, **1**), has hampered structural studies, the structure of **1**, except for the absolute configuration and the stereochemistry at C2, has been determined.[3] We previously suggested that the absolute configuration of the polycyclic core of **1** was 5*R* using synthetic AB ring models (**3**-**7**), which lack the C11 hydroxy group, and CD studies.[4,5] In this paper, we report the enantio-controlled synthesis of AB ring fragments (**8**-**11**) which possess the C11 hydroxy group[6,7] and the absolute configuration of the C2 hydroxy of **1** based on the CD exciton chirality method.[8,9]

RESULTS AND DISCUSSION

Ciguatoxin Tetra-p-bromobenzoate (2)

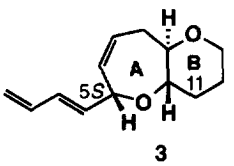
The CD exciton chirality method has recently proved to be very useful for determining the absolute configuration of acyclic chiral *vic*-dibenzoates.[8b,c] To elucidate the configuration of the C2 secondary alcohol in **1**, we used this method. A *p*-bromobenzoylation reaction of 30 μg of **1** was carried out with excess *p*-bromobenzoyl chloride/Et_3N/4-dimethylaminopyridine (DMAP). Tetra-*p*-bromobenzoate (**2**) (~7 μg based on the UV absorption) was isolated as the major product from the reaction mixture by HPLC. This tetra-*p*-bromobenzoate (**2**) showed a positive split CD curve with extrema at 253 nm (Δε +8.9) and 234 nm (Δε -5.8), as shown in Figure 1, which is characteristic of acyclic *vic*-di-*p*-bromobenzoates.[8b,c] In fact, the 1,2*S*-di-*p*-

bromobenzoate (**5**) of the previously synthesized AB ring fragment which lacks the C11 hydroxy group[5] exhibited a split curve very similar to that of **2**, while the diastereomeric 1,2*R*-dibenzoate (**7**) showed an opposite negative split Cotton effect. This marked resemblance of the CD split curves between **2** and **5** strongly suggests that the split Cotton effect of **2** essentially arises from the bichromophores at C1 and C2, and accordingly that **2** has a 2*S* configuration.



Ciguatoxin (**1**) : **R = H**

Tetra-*p*-bromobenzoate (**2**) : **R = Bz-*p*-Br**



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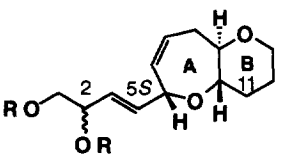
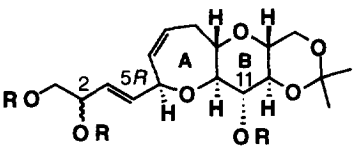


4 (2*S*): R = H
5 (2*S*): R = Bz-*p*-Br
6 (2*R*): R = H
7 (2*R*): R = Bz-*p*-Br



8 (2*S*): R = H
9 (2*S*): R = Bz-*p*-Br
10 (2*R*): R = H
11 (2*R*): R = Bz-*p*-Br

By considering steric hindrance, it is reasonable to assume that the hydroxy groups at C1, C2, C32, and C54 would be *p*-bromobenzoylated more readily than those at C11 and C47 in **1**; these four benzoylated hydroxy groups were not assigned spectroscopically due to the very limited amount of **2**. The C47 pseudoaxial hydroxy seems to be the most hindered. *p*-Bromobenzoylation of the C11 hydroxy would be hindered by the close proximity of the dihydroxybutenyl substituent on the neighboring A ring, particularly when the hydroxy groups at both C1 and C2 of the substituent are benzoylated. In fact, these presumed reactivities have been supported by model experiments. *p*-Bromobenzoylation (*p*-BrBzCl, Et_3N, DMAP, CH_2Cl_2, room temperature, 2 h) of synthetic AB ring fragments (**8**, **10**) gave the corresponding C1,C2-di-*p*-bromobenzoates as major product in ca. 70% yield. The third benzoylation of the C11 hydroxy group proceeded slowly. Tachibana and coworkers observed that *p*-bromobenzoylation of the C54 hydroxy in the synthetic JKLM ring fragment occurred quickly and then was followed by the slow reaction at C47.[10] The pseudoequatorial benzoate at C32 should have little effect on either the split Cotton effect of the dibenzoates at C1 and C2 or the C54 chromophore of **2** because of the long interchromophoric distances.[8a] However, if the C11 equatorial hydroxy is benzoylated, the split curve of the C1,C2-di-*p*-bromobenzoates might be appreciably affected. Therefore, we

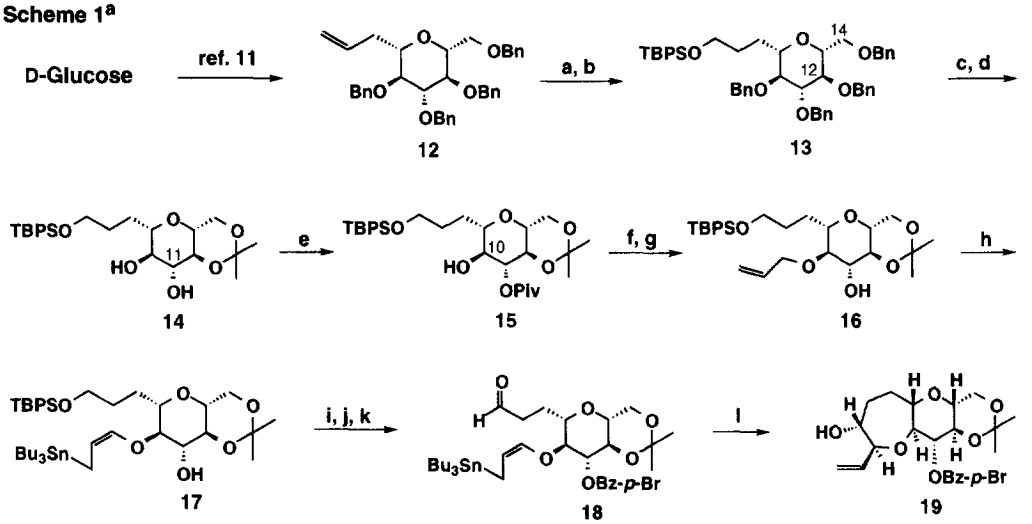
synthesized tri-*p*-bromobenzoylated AB ring fragments (**9**, **11**)[6] and examined their CD spectra to answer this question.

Tri-p-bromobenzoylated AB Ring fragments (9, 11)

In the present synthetic study,[6] we paid special attention to the two points : (1) an enantio-controlled method for synthesizing both enantiomers, **8** and **10**, is desirable, since the absolute configuration of **1** has not yet been determined decisively,[4] and (2) the highly acid-sensitive and highly functionalized structure of C1 to C7 requires an efficient and mild method for constructing the A ring and its side chain.

We chose a chiral compound (**12**) as a versatile starting material to synthesize the B ring, since the relevant chemical manipulation of either the benzyloxymethyl or the allyl group of **12** would lead to each enantiomer of the target **8** (**10**). This compound (**12**) was prepared readily and stereoselectively from methyl α-*D*-glucoside according to Kishi's method.[11] Thus, our synthesis started with **12**, assuming that **1** has a 5*R*-configuration (Scheme 1).[4]

Scheme 1[a]



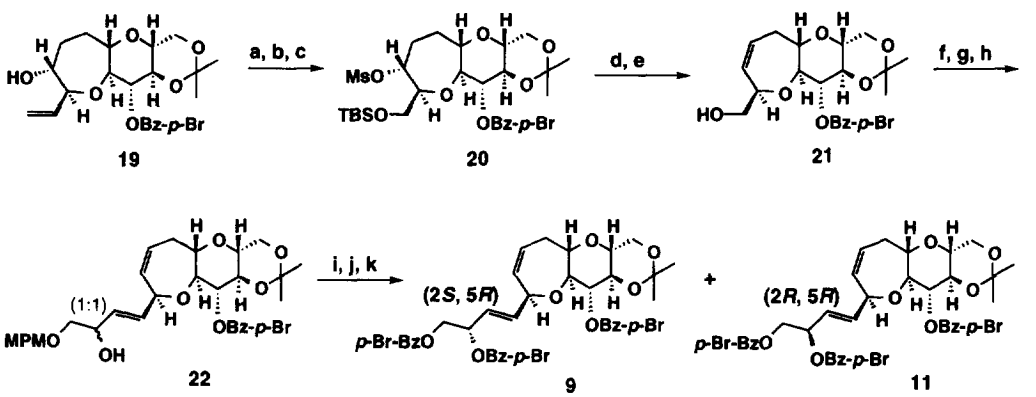
[a]Reagents and conditions: (a) 9-BBN, sonication, THF, then H_2O_2, NaOH, 84%; (b) TBPSCl, Imidazole, DMF, 90%; (c) H_2, $Pd(OH)_2$, EtOAc:EtOH (1:1), 88%; (d) 2,2-Dimethoxypropane, PPTS, DMF, 77%; (e) PivCl, DMAP, Py, 0 °C, 80%; (f) Allyl methyl carbonate, $Pd(dba)_2$, dppb, THF, 65 °C, 95%; (g) DIBAL, CH_2Cl_2, -78°C, 85%; (h) *n*-BuLi, Bu_3SnCl, HMPA, THF, -78 °C, 63%; (i) *p*-Br-BzCl, Et_3N, DMAP, CH_2Cl_2, 99%; (j) TBAF, THF, 95%; (k) SO_3·Py, Et_3N, DMSO, CH_2Cl_2, 87%; (l) BF_3·Et_2O, CH_2Cl_2, -90 °C, 94%.

Hydroboration of **12** with 9-BBN was sluggish under the standard conditions. However, ultrasonic irradiation remarkably accelerated the reaction;[12] the alcohol was obtained in good yield after oxidation, and was protected as the TBPS ether (**13**). All of the benzyl groups in **13** were removed and the resulting C12[7] and C14 alcohols were selectively protected as an acetonide (**14**). Further selective protection of the C11 hydroxy in **14** was achieved with pivaloyl chloride and DMAP in pyridine at 0 °C to give **15**. Palladium-catalyzed

allylation[13] of the C10 hydroxy of **15** followed by reduction of the pivalate gave allyl ether (**16**), which was then converted to allylstannane (**17**). Presence of a protecting group at the C11 hydroxy substantially retarded this stannylation reaction. Protection of the C11 hydroxy in **17** as a p-bromobenzoate and subsequent removal of the TBPS group followed by oxidation of the resulting alcohol with SO_3·pyridine complex gave aldehyde (**18**). BF_3·OEt_2-promoted cyclization reaction[14] of **18** provided the AB ring skeleton (**19**) stereoselectively.

The remaining task was an efficient introduction of the internal double bond and the dihydroxybutenyl side chain of the A ring. Construction of the acid-sensitive, doubly allylic ether is the most crucial step in this synthesis. Ozonolysis of **19** followed by reduction, selective protection of the resulting primary alcohol as the TBS ether, and mesylation yielded **20** (Scheme 2).

Scheme 2[a]



[a]Reagents and conditions: (a) O_3, CH_2Cl_2:MeOH (3:1), -78 °C, then $NaBH_4$, -78 °C to r.t., 97%; (b) TBSCl, Et_3N, DMAP, CH_2Cl_2, 92%; (c) MsCl, Et_3N, CH_2Cl_2; (d) DBU, toluene, 100-110 °C, 60% (2 steps); (e) TBAF, THF, 92%; (f) Dess-Martin periodinane, CH_2Cl_2; (g) $Ph_3PCHCOCH_2OMPM$, Benzene, r.t.; (h) $NaBH_4$, $CeCl_3$, MeOH, -70 to -35 °C, 53% (3 steps); (i) *p*-Br-BzCl, Et_3N, DMAP, CH_2Cl_2, 93%; (j) DDQ, CH_2Cl_2:H_2O (20:1), 89%; (k) *p*-Br-BzCl, Et_3N, DMAP, CH_2Cl_2, 93%.

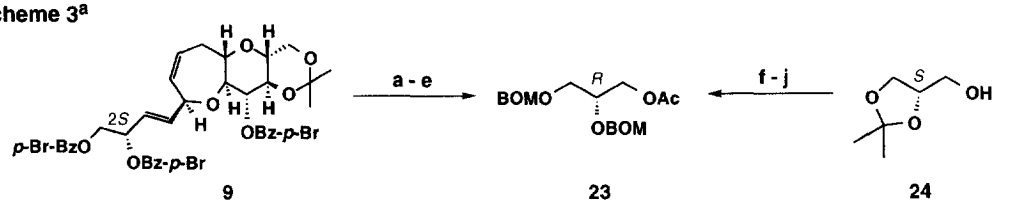
Mesylate (**20**) underwent regioselective elimination[4,6] with DBU at 100-110 °C and removal of the TBS group gave alcohol **21**. Since the double bond of the β,γ-unsaturated aldehyde prepared from **21** was prone to migrate to a position of conjugation, several conditions for oxidation to the aldehyde were examined, and Dess-Martin periodinane[15] was found to give the best result. The crude aldehyde was immediately subjected to a Wittig-type olefination without purification at room temperature. The resulting enone was reduced with $NaBH_4$-$CeCl_3$ to give **22** as a 1:1 diastereomeric mixture. Conversion of **22** to the tri-*p*-bromobenzoates (**9**, **11**) was achieved by stepwise procedures, since deprotection of the MPM group of **22** with DDQ without protection of the C2 allylic alcohol caused decomposition. The diastereomeric 1:1 mixture of **9** and **11** was separated by HPLC [DAICEL-CHIRALPAK AS, eluent: hexane/*i*PrOH 30/1] and their C2 configurations were determined by the CD exciton chirality method for the acyclic 1,2-dibenzoates.[8b,c] Since **9** and **11** exhibited positive [CD (EtOH) 237 nm (Δε -11.0), 242 nm (Δε 0), 252 nm (Δε +26.2); UV (EtOH) λmax 245 nm (logε 4.8)] and

negative split Cotton CD spectra [CD (EtOH) 241 nm (Δε +12.7), 249 nm (Δε 0), 254 nm (Δε -6.5); UV (EtOH) λmax 244 nm (logε 4.8)], respectively, as shown in Figure 2, their configurations were assigned to be 2*S* for **9** and 2*R* for **11**. However, there should exist some exciton coupling between C1,C2-dibenzoates and C11-benzoate, since their CD spectra are not as symmetrical as those of dibenzoates **4** and **6**. Therefore, the assignments for **9** and **11** needed to be confirmed.

C2 Absolute Configuration of Synthetic Fragments

Methanolysis of **9** showed that C1,C2-dibenzoates reacted much faster than C11-benzoate and finally gave triol **8** (Scheme 3), which was then protected with benzyloxymethyl (BOM) chloride. The resulting tri-BOM ether was subjected to Lemieux oxidation[16] followed by $NaBH_4$ reduction and acetylation to yield (*R*)-1-acetoxy-2,3-di(benzyloxymethyloxy)propane (**23**). This glycerol derivative was identical to the authentic material prepared from (*S*)-1,2-isopropylideneglycerol (**24**) on HPLC [DAICEL-CHIRALCEL OD, eluent: hexane/*i*PrOH 10/1] (Scheme 3). Thus, the absolute configurations of **9** and **11** were unambiguously determined by chemical transformations and the assignments based on the exciton chirality method were confirmed to be correct.

Scheme 3[a]



9 **23** **24**

[a]Reagents and conditions: (a) K_2CO_3, MeOH, r.t., 27 h; (b) BOMCl, $(i\text{Pr})_2\text{NEt}$, Bu_4NI, CH_2Cl_2; (c) OsO_4, $NaIO_4$, H_2O, CH_3CN, pH 7 Phosphate buffer; (d) $NaBH_4$, MeOH; (e) Ac_2O, Pyridine; (f) NaH, MPMCl, THF, DMF; (g) 1N HCl, MeOH, 87% (2 steps); (h) BOMCl, $(i\text{Pr})_2\text{NEt}$, Bu_4NI, CH_2Cl_2, 90%; (i)DDQ, H_2O, CH_2Cl_2, 96%; (j) Ac_2O, Pyridine, 95%.

C2 Absolute Configuration of Ciguatoxin (1)

These results clearly show that the exciton chirality of C1,C2-di-*p*-bromobenzoates is appreciably affected by the C11-benzoate if it is present, while the sign of the split Cotton of the C1,C2-dibenzoates remains unchanged. Thus, C2 chirality is a dominant factor in determining the sign of the split CD curves of C1,C2,C11-tribenzoates. Ciguatoxin tetra-*p*-bromobenzoate (**2**) should possess a 2*S* configuration, since **2** exhibited a positive split CD.

Conclusion

A comparison of the CD spectra of the ciguatoxin tetra-*p*-bromobenzoate (**2**) with those of the synthetic AB ring fragments indicated that the C2 configuration of **1** is *S*. Further synthetic studies and unambiguous determination of the absolute configuration of ciguatoxin (**1**) will be reported in due course.

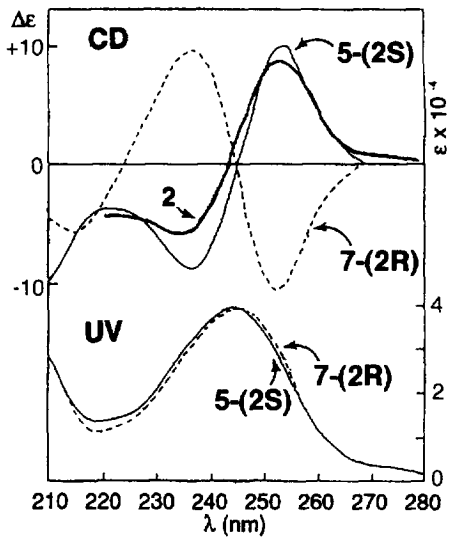


Figure 1. CD and UV spectra of **5**, **7**, and **2**.

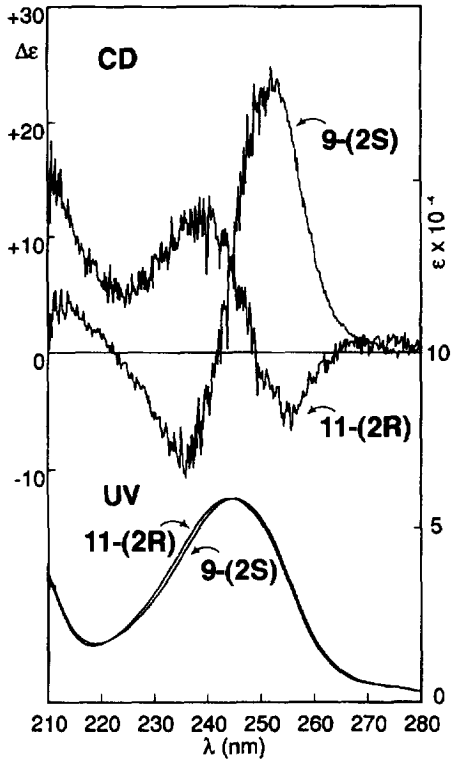


Figure 2. CD and UV spectra of **9** and **11**.

EXPERIMENTAL

General methods ^{1}H-NMR spectra were recorded on a Varian Gemini 200, a JEOL GX-400, or a Brucker AM-600 spectrometer. Chemical shifts are reported in δ (ppm) using chloroform as an internal standard of δ 7.26. IR spectra were recorded on a JASCO FT/IR-7000 spectrometer. Low- and high-resolution mass spectra (MS, HRMS) were recorded on a JEOL HX-110, a JEOL JMS-DX303, a JEOL JMS-AX500, or a HITACHI M-2500-S instrument. UV spectra were recorded on a JASCO Ubest-50 spectrophotometer. CD spectra were obtained on a JASCO J-400X spectrometer. Optical rotations were recorded on a JASCO DIP-370 polarimeter. Elemental analysis was conducted with a Yanaco CHN corder MT-5. THF was distilled from benzophenone ketyl just prior to use. Dichlorometane was distilled from calcium hydride. Flash column chromatography was performed using Merck Kiesegel 60 (230-400 mesh).

Preparation of Ciguatoxin Tetra-*p*-bromobenzoate 2. Ciguatoxin (**1**, 30 μg, 27 nmol) was dissolved in 100 μl of CH_2Cl_2 containing 10 μl of Et_3N, and *p*-bromobenzoyl chloride (4.0 μmol) and DMAP (0.2 μmol) were added. The reaction mixture was standing at room temperature for 28 h. After removal of solvent under a nitrogen stream, the residue was purified by HPLC (Inertsil ODS, 8.4 x 250 mm; linear gradient of EtOH (0 % to 100 %) in CH_3CN by 2%/min; monitored at 254 nm). Tetra-*p*-bromobenzoate (**2**) was isolated as a major product and its amount was estimated to be 7 μg (ca. 14% yield) on the basis of the

absorbance of UV absorption. FAB-MS (JEOL-DX303HF) of the benzoate revealed $(M+Na)^+$ ion peaks at *m/z* 1861/1863/1865/1867/1869, which correspond to tetra-*p*-bromobenzoylated ciguatoxin (**2**).

Regeneration of the toxicity after alkaline hydrolysis of **2** indicated that ciguatoxin remained intact during the acylation reaction. The benzoate (**2**) was hydrolyzed in 0.5 N NaOH in MeOH-H_2O (9:1) at 40 °C for 2 h, and then neutralized, and the mixture was injected intraperitoneally into a mouse. This caused typical symptoms of ciguatoxin poisoning and the mouse died within several hours, which implied that more than 3 μg of **1** was recovered by the hydrolysis.

(4a*S*,6*S*,9a*R*,3'*S*)-6-[(*E*)-3',4'-Bis(*p*-bromobenzoyloxy)-1'-butenyl]-3,4,4a,6,9,9a-hexahydro-2*H*-pyrano[3,2-*b*]oxepin (5).[5] ^{1}H-NMR (400 Hz, CD_3CN) δ 1.32-1.48 (1H, m), 1.55-1.70 (2H, m), 1.94-2.03 (1H, m), 2.29-2.46 (2H, m), 2.93 (1H, td, *J* = 9.2, 4.2 Hz), 3.26 (1H, m), 3.34 (1H, ddd, *J* = 11.0, 8.7, 4.7 Hz), 3.77 (1H, m), 4.49 (1H, dd, *J* = 11.9, 6.8 Hz), 4.57 (1H, dd, *J* = 11.9, 3.6 Hz), 4.61 (1H, br.), 5.74 (1H, ddd, *J* = 11.0, 4.1, 2.6 Hz), 5.82-5.88 (2H, m), 5.91 (1H, ddd, *J* = 14.7, 6.1, 1.3 Hz), 6.01 (1H, br. dd, *J* = 14.7, 4.9 Hz), 7.64 (2H, d, *J* = 8.8 Hz), 7.66 (2H, d, *J* = 8.8 Hz), 7.85 (2H, d, *J* = 8.8 Hz), 7.91 (2H, d, *J* = 8.8 Hz); IR (film) ν_{max} 2926, 2856, 1727, 1593, 1400, 1263, 1176, 1098, 1013, 756 cm^{-1}; MS (EI) *m/z* (relative intensity) 608 (M^+, 0.2), 606 (M^+, 0.4), 604 (M^+, 0.2), 406 (11), 404 (13), 221 (8), 204 (12), 185 (76), 183 (78), 105 (28), 97 (24), 71 (100); UV (EtOH) λ_{max} 245 nm (ε 39000); CD (EtOH) λ_{ext} 238 nm (Δε -8.4), 246 (0.0), 253 (+10.1).

(4a*S*,6*S*,9a*R*,3'*R*)-6-[(*E*)-3',4'-Bis(*p*-bromobenzoyloxy)-1'-butenyl]-3,4,4a,6,9,9a-hexahydro-2*H*-pyrano[3,2-*b*]oxepin (7).[5] ^{1}H-NMR (400 Hz, CD_3CN) δ 1.32-1.56 (1H, m), 1.57-1.67 (2H, m), 1.95-2.05 (1H, m), 2.31-2.39 (2H, m), 2.38-2.46 (1H, m), 2.93 (1H, td, *J* = 9.2, 4.2 Hz), 3.26 (1H, m), 3.33 (1H, ddd, *J* = 11.0, 8.7, 4.7 Hz), 3.77 (1H, m), 4.50 (1H, dd, *J* = 11.9, 6.8 Hz), 4.56 (1H, dd, *J* = 11.9, 3.6 Hz), 4.62 (1H, br), 5.74 (1H, ddd, *J* = 11.0, 4.1, 2.6 Hz), 5.82-5.88 (2H, m), 5.91 (1H, ddd, *J* = 14.7, 6.1, 1.3 Hz), 6.01 (1H, br. dd, *J* = 14.7, 4.9 Hz), 7.64 (2H, d, *J* = 8.8 Hz), 7.66 (2H, d, *J* = 8.8 Hz), 7.85 (2H, d, *J* = 8.8 Hz), 7.91 (2H, d, *J* = 8.8 Hz); IR (film) ν_{max} 2928, 2858, 1729, 1593, 1400, 1263, 1176, 1098, 1033, 103, 756 cm^{-1}; MS (EI) *m/z* (relative intensity) 608 (M^+, 0.2), 606 (M^+, 0.4), 604 (M^+, 0.2), 406 (9), 404 (10), 221 (8), 204 (10), 185 (84), 183 (88), 105 (37), 97 (23), 71 (100); UV (EtOH) λ_{max} 245 nm (ε 39000); CD (EtOH) λ_{ext} 238 nm (Δε +9.9), 246 (0.0), 253 (-10.2).

2,6-Anhydro-1,3,4,5-tetrabenzyl-9-*O*-(*tert*-butyldiphenylsilyl)-7,8-dideoxy-D-*gluco*-L-*glycero*-nonitol (13). Under an argon atmosphere, to a solution of **12** (7.69 g, 13.6 mmol) in THF (50 ml) was added 9-BBN (80 mL of a 0.5 M solution in THF, 40 mmol), and then the mixture was sonicated for 2 h at room temperature. The mixture was treated with 2N NaOH (8 ml) and 30% hydrogen peroxide (8 ml) at 0 °C and stirred at room temperature for 17 h. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, concentrated, and subjected to flash column chromatography (silica, hexane/EtOAc 3/1) to give the primary alcohol (6.68 g, 11.4 mmol, 84%) as a colorless solid: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.54 (1H, m), 1.71 (2H, m), 1.98 (1H, m), 2.32 (1H, br, OH), 3.29 (2H, m), 3.44 (1H, ddd, *J* = 9.6, 4.9, 2.0 Hz), 3.59 (1H, dd, *J* = 9.6, 9.3 Hz), 3.62 (1H, dd, *J* = 10.7, 4.9 Hz), 3.64 (2H, m), 3.68 (1H, dd, *J* = 10.7, 4.9 Hz), 3.69 (1H, m), 4.53 (1H, d, *J* = 12.2 Hz), 4.54 (1H, d, *J* = 10.8 Hz), 4.59 (1H, d, *J* = 12.2 Hz), 4.64 (1H, d, *J* = 10.9 Hz), 4.81 (1H, d, *J* = 10.8 Hz), 4.89 (3H, m), 7.15 (2H, m), 7.25-7.35 (18H, m); IR (film) ν_{max} 3298, 3032, 2910, 2864, 1456, 1361, 1214, 1093, 1065, 1029, 750, 698 cm^{-1}.

To a stirred solution of this alcohol (29.7 g, 51.0 mmol) and imidazole (7.00 g, 103 mmol) in DMF (100 ml) was added TBPSCl (16 ml, 61 mmol) at room temperature. After 12 h, the mixture was concentrated, diluted with ether, washed with aqueous saturated NH_4Cl, aqueous saturated $NaHCO_3$, and brine, and dried over $MgSO_4$. Filtration, concentration, and flash column chromatography (silica, hexane/EtOAc 6/1) gave the ether **13** (37.7 g, 45.9 mmol, 90%): colorless solid; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.03 (9H, s), 1.45-2.10 (4H, m), 3.15-3.40 (3H, m), 3.55-3.74 (6H, m), 4.48-4.68 (8H, m), 7.23-7.75 (30H, m); IR (neat) ν_{max} 3418, 3066, 3032, 2866, 2364, 1497, 1456, 1361, 1094, 1029, 737, 698 cm^{-1}; $[\alpha]_D^{24}$ +3.40 (c 1.04, $CHCl_3$); Anal. Calcd for $C_{53}H_{60}O_6Si$: C, 77.52, H, 7.36. Found: C, 77.58, H, 7.24.

2,6-Anhydro-9-*O*-(*tert*-butyldiphenylsilyl)-7,8-dideoxy-1,3-*O*-isopropylidene-D-*gluco*-L-*glycero*-nonitol (14). A solution of **13** (4.90 g, 6.18 mmol) in EtOAc (40 ml) and EtOH (40 ml) was stirred with $Pd(OH)_2$ (20% on carbon, Aldrich, 862 mg, 1.24 mmol) under an H_2 atmosphere (4.2 kg/cm^2) for 18 h. The mixture was filtered through Celite. The filtrate was concentrated and the residue was azeotropically dried with toluene to give the crude tetraol as a colorless oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.03 (9H, s), 1.15-2.00 (4H, m), 2.99 (1H, m), 3.09-3.15 (2H, m), 3.35-3.82 (6H, m), 4.02 (1H, br), 4.68 (1H, br), 4.95 (1H, br), 7.35 (6H, m), 7.64 (4H, m); IR (film) ν_{max} 3384, 2934, 2862, 1429, 1089, 1009, 702 cm^{-1}; $[\alpha]_D^{26}$ -10.0 (c 1.00, $CHCl_3$).

A solution of the crude tetraol and 2,2-dimethoxypropane (3.02 ml, 24.6 mmol) in DMF (10 ml) was stirred with PPTS (309 mg, 1.23 mmol) at room temperature for 24 h. The mixture was treated with aqueous saturated $NaHCO_3$ (5 ml) and extracted with EtOAc (x 3). The combined organic layer was dried over $MgSO_4$, concentrated, and subjected to flash column chromatography (silica, CH_2Cl_2/MeOH 10/1) to give the diol **14** (2.06 g, 4.11 mmol, 67% from **13**): colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.43 (3H, s), 1.50 (3H, s), 1.45-2.02 (4H, m), 2.43 (1H, br), 2.67 (1H, br), 3.12-3.83 (8H, m), 3.87 (1H, dd, J = 10.4, 5.3 Hz), 7.35 (6H, m), 7.64 (4H, m); IR (film) ν_{max} 3424, 2998, 2934, 2862, 1429, 1383, 1267, 1201, 1106, 855, 704 cm^{-1}; $[\alpha]_D^{25}$ -20.5 (c 1.05, $CHCl_3$); HRMS (EI) Calcd for $C_{27}H_{37}O_6Si$ (M - CH_3)$^+$: 485.2357, Found: 485.2341; Calcd for $C_{24}H_{31}O_6Si$ (M - C_4H_9)$^+$: 443.1888, Found: 443.1873.

2,6-Anhydro-9-*O*-(*tert*-butyldiphenylsilyl)-7,8-dideoxy-1,3-*O*-isopropylidene-4-*O*-(2,2-dimethylpropionyl)-D-*gluco*-L-*glycero*-nonitol (15). A solution of **14** (4.32 g, 8.62 mmol) and DMAP (96 mg 0.86 mmol) in pyridine (20 ml) was treated with trimethylacetyl chloride (1.27 ml, 10.3 mmol) at 0 °C and the mixture was stirred for 16 h. Additional DMAP (96 mg 0.86 mmol) and trimethylacetyl chloride (0.42 ml, 3.4 mmol) were added and the mixture was stirred for 5 h, and then diluted with water, and extracted with ether (x 2). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (silica, hexane/EtOAc 4/1) gave the pivalate **15** (4.92 g, 8.41 mmol, 98%): colorless solid; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.23 (9H, s), 1.36 (3H, s), 1.46 (3H, s), 1.45-2.08 (4H, m), 2.78 (1H, br), 3.15-3.75 (7H, m), 3.89 (1H, dd, J = 10.4, 5.3 Hz), 4.78 (1H, t, J = 9.6 Hz), 7.35 (6H, m), 7.67 (4H, m); IR (film) ν_{max} 3506, 2962, 2934, 2862, 1717, 1429, 1383, 1288, 1203, 1180, 1112, 859, 704 cm^{-1}; $[\alpha]_D^{23}$ -36.7 (c 1.05, $CHCl_3$). Anal. Calcd for $C_{33}H_{48}O_7Si$: C, 67.77, H, 8.27. Found: C, 67.47, H, 8.25.

2,6-Anhydro-9-*O*-(*tert*-butyldiphenylsilyl)-7,8-dideoxy-1,3-*O*-isopropylidene-7-*O*-(2'-propenyl)-D-*gluco*-L-*glycero*-nonitol (16). Under an argon atmosphere, to a stirred solution of $Pd(dba)_2$ (174 mg, 0.303 mmol) and dppb (324 mg, 0.750 mmol) in THF (5 ml) were added a solution of **15** (1.11g, 1.90 mmol) and allyl methyl carbonate (2.16 ml, 19.0 mmol) in THF (7 ml). After stirring at 65 °C for 2.5 h, the mixture was concentrated and subjected to flash column chromatography (silica, hexane/EtOAc 8/1) to

give the corresponding allyl ether (1.13 g, 1.81 mmol, 95%) as a colorless oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.03 (9H, s), 1.21 (9H, s), 1.34 (3H, s), 1.41 (3H, s), 1.47 (1H, m), 1.62 (1H, m), 1.76 (1H, m), 1.99 (1H, m), 3.19 (1H, t, *J* = 9.2 Hz), 3.23 (1H, ddd, *J* = 10.4, 9.6, 5.3 Hz), 3.34 (1H, td, *J* = 9.2, 2.6 Hz), 3.51 (1H, t, *J* = 9.6 Hz), 3.62 (1H, t, *J* = 10.4 Hz), 3.66 (2H, m), 3.87 (1H, dd, *J* = 10.4, 5.3 Hz), 4.04 (1H, ddt, *J* = 12.2, 5.9, 1.5 Hz), 4.08 (1H, ddt, *J* = 12.2, 5.4, 1.5 Hz), 5.11 (1H, m), 5.12 (1H, dd, *J* = 9.6, 9.2 Hz), 5.19 (1H, ddd, *J* = 17.2, 3.1, 1.5 Hz), 5.81 (1H, m), 7.35 (6H, m), 7.67 (4H, m); IR (neat) ν_{max} 2962, 2934, 2862, 1742, 1481, 1462, 1431, 1383, 1371, 1282, 1203, 1178, 1112, 884, 859 cm^{-1}; $[\alpha]_D^{23}$ -22.7° (c 1.05, $CHCl_3$); MS (EI) *m/z* (relative intensity) 624 (M^+, 0.2), 609 (3), 567 (20), 268 (30), 199 (22), 131 (24), 69 (26), 57 (100).

To a solution of this allylether (2.60 g, 4.18 mmol) in CH_2Cl_2 (30 ml) was added DIBAL (5.9 ml of 1.76 M hexane solution, 10 mmol) at -78 °C under an argon atmosphere and the mixture was stirred at the same temperature for 1 h. An additional DIBAL (2.0 ml of 1.76 M hexane solution, 1.1 mmol) was added, and the reaction mixure was stirred for 30 min at -78 °C and treated with aqueous saturated NH_4Cl (3 ml), diluted with ether (30 ml) and EtOAc (30 ml). Aqueous saturated solution of Rochelle salt (3 ml) was then added and the mixture was vigorously stirred at room temperature for 2 h, extracted with EtOAc (x 3). The combined organic layer was washed with brine and dried over Na_2SO_4. Filtration, concentration, and column chromatography (silica, hexane/EtOAc 4/1) afforded the alcohol **16** (2.03 g, 3.75 mmol, 90%): colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.43 (3H, s), 1.50 (3H, s), 1.42-2.06 (4H, m), 2.46 (1H, br), 3.01-3.32 (3H, m), 3.45 (1H, t, *J* = 9.6 Hz), 3.6-3.75 (4H, m), 3.85 (1H, dd, *J* = 10.4, 5.3 Hz), 4.18 (1H, ddt, *J* = 12.0, 6.0, 1.5 Hz), 4.32 (1H, ddt, *J* = 12.0, 5.5, 1.5 Hz), 5.18 (1H, m), 5.28 (1H, m), 5.81 (1H, m), 7.35 (6H, m), 7.67 (4H, m); IR (neat) ν_{max} 3462, 2934, 2862, 1475, 1429, 1381, 1267, 1201, 1172, 1108, 855, 704 cm^{-1}; $[\alpha]_D^{25}$ -27.9 (c 1.01, $CHCl_3$); HRMS (EI) Calcd for $C_{30}H_{41}O_6Si$ (M - CH_3)$^+$: 525.2670, Found: 525.2664; Calcd for $C_{27}H_{35}O_6Si$ (M - C_4H_9)$^+$: 483.2200, Found: 483.2214.

2,6-Anhydro-9-*O*-(*tert*-butyldiphenylsilyl)-7,8-dideoxy-1,3-*O*-isopropylidene-5-*O*-[(*Z*)-3'-tributylstannyl-1'-propenyl]-D-*gluco*-L-*glycero*-nonitol (17). A solution of **16** (2.00 g, 3.70 mmol) and HMPA (3ml) in THF (25 ml) was treated with *n*-BuLi (3.00 ml of 1.56 M hexane solution, 11.1 mmol) at -78° C and the mixture was stirred at -78 °C for 1 h under an argon atmosphere. To this solution was added dropwise a solution of Bu_3SnCl (3.00 ml, 11.1 mmol) in THF (10 ml) over a period of 20 min. After stirring at -78 °C for 30 min, the reaction mixture was treated with aqueous saturated $NaHCO_3$ (5 ml) and extracted with ether. The organic layer was dried over Na_2SO_4. Filtration, concentration, and column chromatography (silica, hexane/EtOAc/Et_3N 100/20/1) gave the allylstannane **17** (1.91 g, 2.30 mmol, 62%): colorless oil : ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.68-1.97 (33H, m), 1.04 (9H, s), 1.45 (3H, s), 1.51 (3H, s), 2.43 (1H, br), 3.11-3.40 (3H, m), 3.50 (1H, t, *J* = 9.6 Hz), 3.61-3.77 (4H, m), 3.86 (1H, dd, *J* = 10.4, 5.3 Hz), 4.51 (1H, td, *J* = 9.0, 6.0 Hz), 5.92 (1H, m), 7.35 (6H, m), 7.67 (4H, m) ; IR (neat) ν_{max} 3480, 2960, 2930, 2860, 1653, 1464, 1431, 1377, 1267, 1201, 1162, 1106, 702 cm^{-1}; $[\alpha]_D^{28}$ -41.2 (c 1.00, $CHCl_3$). Electrospray MS *m/z* 852 (M+Na)$^+$.

(4a*R*,5a*S*,8*R*,9*S*,10a*S*,11*R*,11a*R*)-11-(*p*-Bromobenzoyloxy)-4,4a,5a,6,7,8,9,10a,11,11a-decahydro-oxepino[2',3':5,6]pyrano[3,2-*d*]-1,3-dioxin-8-ol (19). To a solution of **17** (145 mg, 0.177 mmol) in CH_2Cl_2 (2 ml) were added Et_3N (146 ml, 1.05 mmol), *p*-BrBzCl (96.0 mg, 0.438 mmol) and DMAP (5.0 mg, 0.035 mmol). After stirring at room temperature for 12 h, additional Et_3N (146 ml, 1.05 mmol), *p*-BrBzCl (96.0 mg, 0.438 mmol), and DMAP (5.0 mg, 0.035 mmol) were added, and the mixture was stirred for 7 h. The resulting solution was concentrated and directly subjected to column chromatography

(silica, hexane/EtOAc/Et_3N 100/10/1) to give the benzoate (180 mg, 0.177 mmol, 99%) as a pale yellow oil : ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.68-1.98 (33H, m), 1.05 (9H, s), 1.35 (3H, s), 1.42 (3H, s), 3.25-3.55 (3H, m), 3.61-3.75 (4H, m), 3.90 (1H, dd, J = 10.4, 5.3 Hz), 4.31 (1H, td, J = 9.0, 6.0 Hz), 5.38 (1H, m), 5.73 (1H, m), 7.36 (6H, m), 7.58 (2H, m), 7.67 (4H, m), 7.88 (2H, m); IR (neat) ν_{max} 2960, 2930, 2860, 1736, 1593, 1267, 1098, 1013, 702 cm^{-1}; $[\alpha]_D^{25}$ +51.6 (c 1.03 , $CHCl_3$).

A solution of the resulting benzoate (176 mg, 0.174 mmol) in THF (3 ml) was treated with TBAF (434 ml of 1.0 M THF solution, 0.434 mmol) and stirred for 10 h. Concentration and flash column chromatography (silica, hexane/EtOAc/Et_3N 100/30/1) gave the corresponding alcohol (127 mg, 0.164 mmol, 95%) as a colorless oil : ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.60-2.00 (33H, m), 1.35 (3H, s), 1.42 (3H, s), 3.30-3.55 (3H, m), 3.60-3.80 (4H, m), 3.96 (1H, dd, J = 10.4, 5.3 Hz), 4.31 (1H, ddd, J = 9.5, 8.5, 6.0 Hz), 5.41 (1H, m), 5.72 (1H, m), 7.58 (2H, m), 7.88 (2H, m); IR (neat) ν_{max} 3452, 2958, 2926, 2874, 1736, 1653, 1593, 1267, 1203, 1176, 1100, 1013, 861, 845, 779, 752 cm^{-1}; $[\alpha]_D^{25}$ +98.8 (c 0.746, $CHCl_3$).

A solution of the alcohol (127 mg, 0.163 mmol) and Et_3N (230 µl, 1.64 mmol) in DMSO (1 ml) and CH_2Cl_2 (3 ml) was treated with SO_3·pyridine (131 mg, 0.820 mmol) at 0 °C and allowed to stand at room temperature for 1 h. The mixture was quenched with H_2O (2 ml) and extracted with EtOAc. The separated organic layer was washed with brine and dried over Na_2SO_4. The filtrate was concentrated and subjected to flash column chromatography (silica, hexane/EtOAc/Et_3N 100/25/1) to give the crude aldehyde **18** (110 mg, 0.143 mmol, ca 87%), that was immediately used for the next step, because **18** was not stable.

To a stirred solution of **18** (110 mg, 0.143 mmol) in CH_2Cl_2 (12 ml), BF_3·Et_2O (1.71 ml of 0.1 M CH_2Cl_2 solution, 0.171 mmol) was added dropwise over a period of 30 min at -90 °C. After 20 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 ml) and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Filtration, concentration, and flash column chromatography (silica, hexane/EtOAc 3/1) afforded the oxepane **19** (65.3 mg, 0.135 mmol, 94%): colorless oil; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.45 (3H, s), 1.85-1.92 (2H, m), 1.93-1.99 (2H, m), 3.41 (1H, ddd, J = 10.6, 9.6, 5.2 Hz), 3.46 (1H, m), 3.53 (1H, dd, J = 9.5, 9.3 Hz), 3.73 (1H, dd, J = 10.8, 10.6 Hz), 3.74 (1H, m), 3.76 (1H, dd, J = 9.6, 9.3 Hz), 3.81 (1H, m), 3.95 (1H, dd, J = 10.8, 5.2 Hz), 4.93 (1H, dt, J = 10.6, 1.5 Hz), 5.07 (1H, dt, J = 17.2, 1.5 Hz), 5.32 (1H, t, J = 9.3 Hz), 5.70 (1H, ddd, J = 17.2, 10.6, 5.3 Hz), 7.58 (2H, m), 7.89 (2H, m); IR (film) ν_{max} 3506, 2996, 2942, 2878, 2364, 1731, 1593, 1270, 1104, 1073, 754 cm^{-1}; MS (EI) *m/z* (relative intensity) 484 (M^+, 8), 482 (M^+, 8), 469 (5), 467 (6), 427 (8), 425 (9), 185 (97), 183 (100); $[\alpha]_D^{25}$ -29.4 (c 1.06, $CHCl_3$).

(4a*R*,5a*S*,8*R*,9*S*,10a*S*,11*R*,11a*R*)-11-(*p*-Bromobenzoyloxy)-9-(*tert*-butyldimethylsilyloxymethyl)-4,4a,5a,6,7,8,9,10a,11,11a-decahydro-8-methanesulfonyloxy-oxepino[2',3':5,6]pyrano[3,2-*d*]-1,3-dioxin (20). A solution of **19** (356 mg, 0.736 mmol) in MeOH (6.7 ml) and CH_2Cl_2 (20 ml) was treated with ozone at -80 °C for 15 min. Excess ozone was purged with N_2 gas for 5 min. The mixture was treated with $NaBH_4$ (140 mg, 3.70 mmol) and allowed to stand at 0 °C. After stirring for 4 h, the mixture was quenched with aqueous saturated NH_4Cl (3 ml) and extracted with EtOAc (x 3). The extracts were washed with aqueous saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The filtrate was concentrated and subjected to flash column chromatography (silica, hexane/EtOAc 1/2) to give the diol (348 mg, 0.715 mmol, 97%) as a colorless oil : ^{1}H-NMR (200 MHz, $CDCl_3$) 1.36 (3H, s), 1.47 (3H, s), 1.75-2.0 (4H, m), 3.30-3.55 (6H, m), 3.60-3.85 (3H, m), 3.97 (1H, dd, J = 10.5, 5.5 Hz), 5.31 (1H, t, J = 9.5 Hz), 7.58 (2H, m), 7.88 (2H, m); IR (film) ν_{max} 3496, 2998, 2920, 2886, 1723, 1593, 1487, 1270, 1203, 1176, 1104, 1069, 1040, 1013, 857, 739 cm^{-1}; $[\alpha]_D^{27}$ -50.8 (c 0.992, $CHCl_3$).

A solution of this diol (930 mg, 1.91 mmol) and Et_3N (800 µl, 5.73 mmol) in CH_2Cl_2 (20 ml) was treated with TBSCl (431 mg, 2.86 mmol) and DMAP (23 mg, 0.19 mmol) at 0 °C. After 5 min, an ice bath was removed and the mixture was stirred for 10 h at room temperature. Additional Et_3N (400 µl, 2.87 mmol), TBSCl (288 mg, 1.91 mmol), and DMAP (12 mg, 0.096 mmol) were added and the mixture was stirred at room temperature for 10 h. Concentration and flash column chromatography (silica, hexane/EtOAc 3/1) gave the mono-TBS ether (1.13 g, 1.88 mmol, 98%) as a colorless oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ -0.13 (3H, s), -0.10 (3H, s), 0.78 (9H, s), 1.36 (3H, s), 1.46 (3H, s), 1.81-2.00 (4H, m), 3.28-3.52 (6H, m), 3.65-3.80 (3H, m), 3.95 (1H, dd, J = 10.5, 5.5 Hz), 5.26 (1H, t, J = 9.5 Hz), 7.60 (2H, m), 7.91 (2H, m); IR (film) ν_{max} 3510, 2956, 2932, 2886, 2862, 1734, 1593, 1270, 1203, 1176, 1102, 1013, 839, 754 cm^{-1}; $[\alpha]_D^{26}$ +3.36 (c 0.990, $CHCl_3$).

A stirred solution of this ether (1.13 g, 1.88 mmol) and Et_3N (786 µl, 5.64 mmol) in CH_2Cl_2 (10 ml) was treated with methanesulfonyl chloride (218 µl, 2.82 mmol) at 0 °C. After 30 min, an ice bath was removed and the mixture was stirred at room temperature for 1.5 h. The mixture was quenched with water (2 ml) at 0 °C and extracted with EtOAc. The organic layer was washed with aqueous saturated NH_4Cl, aqueous saturated $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, concentrated, and subjected to flash column chromatography (silica, hexane/EtOAc 2/1) to give the mesylate **20** (1.25 g, 1.84 mmol. 98%): a pale yellow oil ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ -0.09 (3H, s), -0.07 (3H, s), 0.78 (9H, s), 1.35 (3H, s), 1.45 (3H, s), 1.75-2.24 (4H, m), 3.02 (3H, s), 3.25-3.80 (8H, m), 3.95 (1H, dd, J = 10.5, 5.5 Hz), 5.08 (1H, m, CHOMs), 5.27 (1H, t, J = 9.5 Hz), 7.60 (2H, m), 7.92 (2H, m) ; IR (film) ν_{max} 2958, 1729, 1357, 1330, 1270, 1178, 1102, 924, 841, 734 cm^{-1}; HRMS (EI) Calcd for $C_{27}H_{40}O_{10}{}^{79}BrSSi$ (M - CH_3)$^+$: 663.1293, Found: 663.1306; Calcd for $C_{27}H_{40}O_{10}{}^{79}BrSSi$ (M - C_4H_9)$^+$: 621.0823, Found: 621.0859.

(4a*R*,5a*S*,9*R*,10a*S*,11*R*,11a*R*)-11-(*p*-Bromobenzoyloxy)-4,4a,5a,6,9,10a,11,11a-octahydro-oxepino[2',3':5,6]pyrano[3,2-*d*]-1,3-dioxin-9-methanol (21). A solution of **20** (1.29 g, 1.89 mmol) and DBU (2.0 ml) in toluene (10 ml) was heated at 100 °C for 58 h. Water (2 ml) was added and the mixture was extracted with ether. The organic layer was washed with aqueous saturated NH_4Cl, aqueous saturated $NaHCO_3$, and brine, and dried over Na_2SO_4. Filtration, concentration, and flash column chromatography (silica, hexane/EtOAc 5/1) gave the TBS ether as a colorless solid (702 mg, 1.21 mmol, 64%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ -0.15 (3H, s), -0.09 (3H, s), 0.76 (9H, s), 1.35 (3H, s), 1.45 (3H, s), 2.40 (1H, m), 2.66 (1H, m), 3.33-4.00 (9H, m), 5.33 (1H, t, J = 9.5 Hz), 5.78-5.92 (2H, m), 7.60 (2H, m), 7.91 (2H, m); IR (film) ν_{max} 2958, 2932, 2862, 1734, 1593, 1267, 1114, 839, 781, 754 cm^{-1}; $[\alpha]_D^{25}$ +2.91 (c 0.638, $CHCl_3$)

The resulting solid (702 mg, 1.21 mmol) was dissolved in THF (20 ml) and stirred with *n*-Bu_4NF (1.8 ml of 1.0 M THF solution, 1.8 mmol) for 3 h at room temperature. Concentration and flash column chromatography (silica, hexane/EtOAc 3/1) afforded **21** (536 mg, 1.14 mmol, 94%): colorless solid; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.37 (3H, s), 1.48 (3H, s), 2.38 (1H, m), 2.70 (1H, m), 3.35-3.60 (5H, m), 3.74 (1H, t, J = 10.5 Hz), 3.84 (1H, t, J = 9.5 Hz), 3.92-4.40 (2H, m), 5.34 (2H, m), 5.52 (1H, dt, J = 11.5, 3.0 Hz), 5.80 (1H, m), 7.60 (2H, m), 7.91 (2H, m); IR (film) ν_{max} 3542, 2996, 2958, 2878, 1725, 1593, 1270, 1203, 1178, 1110, 1071, 1013, 857, 754 cm^{-1}; $[\alpha]_D^{26}$ -58.4 (c 0.928, $CHCl_3$); MS (EI) *m/z* (relative intensity) 470 (M^+, 0.2), 468 (M^+, 0.2), 455 (0.7), 453 (0.7), 440 (25), 438 (26), 185 (95), 183 (100); Anal. Calcd for $C_{21}H_{25}BrO_7$: C, 53.74, H, 5.37. Found: C, 54.36, H, 5.25.

(*E*)-4-[(4a'*R*,5a'*S*,9'*R*,10a'*S*,11'*R*,11a'*R*)-11-(*p*-Bromobenzoyloxy)-4',4a',5a',6',9',10a',11',11a'-octahydro-oxepino[2',3':5,6]pyrano[3,2-*d*]-1,3-dioxinyl]-1-(*p*-methoxybenzoyloxy)-3-buten-2-ol (22). A solution of **21** (23.0 mg, 48.9 μmol) in CH_2Cl_2 (1.5 ml) was treated with Dess-Martin periodinane[14] (106 mg, 250 μmol) and the mixture was stirred at room temperature for 1.5 h. The mixture was quenched with aqueous saturated $Na_2S_2O_3$ (1 ml) at 0 °C, diluted with ether (5 ml), and stirred at room temperature for 20 min. The organic layer was separated, washed with aqueous saturated $NaHCO_3$, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and treated immediately with $Ph_3PCHCOCH_2OMPM$ (1.5 ml of 0.25 M in benzene solution, 375 μmol) in benzene (2 ml) at room temperature. After stirred for 1.5 h, the mixture was concentrated and subjected to Florisil column chromatography (hexane/EtOAc 2/1) to give an enone. The enone and $CeCl_3 \cdot 7H_2O$ (372 mg, 1.00 mmol) were dissolved in MeOH (2 ml), and immediately treated with $NaBH_4$ (38.0 mg, 1.99 mmol) at -60 °C. After stirring at -60 °C for 1 h, the mixture was quenched with aqueous saturated NH_4Cl (1 ml) and diluted with EtOAc. The organic layer was concentrated, diluted with EtOAc and washed with water and aqueous saturated $NaHCO_3$, and dried over $MgSO_4$. Filtration, concentration, and flash column chromatography (silica, hexane/EtOAc 2/1) afforded the allylic alcohol **22** as a 1:1 diastereomeric mixture (17.0 mg, 26.3 μmol, 53% from **21**): colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.36 (3H, s), 1.46 (3H, s), 2.41 (1H, m, H8), 2.66 (1H, m, H8), 2.82 (0.5H, dd, *J* = 9.5, 8.6 Hz), 2.82 (0.5H, dd, *J* = 9.5, 8.8 Hz), 3.06 (0.5H, dd, *J* = 9.5, 3.0 Hz), 3.20 (0.5H, dd, *J* = 9.5, 3.3 Hz), 3.42 (1H, m, H13), 3.44 (1H, m, H9), 3.57 (1H, t, *J* = 9.0 Hz), 3.73 (1H, dd, *J* = 10.9, 10.5 Hz), 3.80 (1H, m), 3.82 (3H, s), 3.94 (1H, dd, *J* = 10.9, 5.3 Hz), 4.08 (0.5H, m), 4.17 (0.5H, m), 4.31 (0.5H, d, *J* = 11.6 Hz), 4.36 (0.5H, d, *J* = 11.6 Hz), 4.40 (1H, d, *J* = 11.6 Hz), 4.43 (1H, m), 5.40 (1H, dd, *J* = 9.3, 9.0 Hz), 5.47 (0.5H, 1H, ddd, *J* = 15.5, 5.3, 1.9 Hz), 5.49 (0.5H, 1H, ddd, *J* = 15.5, 5.6, 1.9 Hz), 5.71 (1H, m), 5.79 (2H, m), 6.89 (2H, m), 7.23 (2H, m), 7.56 (2H, m), 7.89 (2H, m); IR (film) ν_{max} 3474, 2998, 2896, 1729, 1613, 1591, 1516, 1270, 1203, 1178, 1106, 859, 754, 735 cm^{-1}; HRMS (EI) Calcd for $C_{32}H_{37}O_9{}^{81}Br$ (M^+): 646.1598, Found: 646.1608; Calcd for $C_{32}H_{37}O_9{}^{79}Br$ (M^+): 644.1619, Found: 644.1621.

(4a*R*,5a*S*,9*R*,10a*S*,11*R*,11a*R*,3'*S*)-11-(*p*-Bromobenzoyloxy)-9-[(*E*)-3',4'-di(*p*-bromobenzoyloxy)-1'-butenyl]-4,4a,5a,6,9,10a,11,11a-octahydro-oxepino[2',3':5,6]pyrano[3,2-*d*]-1,3-dioxin (9) and (4a*R*,5a*S*,9*R*,10a*S*,11*R*,11a*R*,3'*R*)-11-(*p*-Bromobenzoyloxy)-9-[(*E*)-3',4'-di(*p*-bromobenzoyloxy)-1'-butenyl]-4,4a,5a,6,9,10a,11,11a-octahydro-oxepino[2',3':5,6]pyrano[3,2-*d*]-1,3-dioxin (11). A solution of **22** (9.6 mg, 15 μmol), *p*-BrBzCl (13.1 mg, 59.5 μmol), Et_3N (20 μl, 0.15 mmol) and DMAP (0.5 mg, 3 μmol) in CH_2Cl_2 (0.5 ml) was stirred at room temperature for 1.5 h. The reaction mixture was concentrated and subjected to flash column chromatography (silica, hexane/EtOAc 3/1) to give the di-*p*-bromobenzoate (11.5 mg, 13.9 μmol, 93%) as a pale yellow solid: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.36 (3H, s), 1.46 (3H, s), 2.42 (1H, m), 2.65 (1H, m), 3.1-3.9 (7H, m), 3.80 (3H, s), 3.95 (1H, dd, *J* = 10.5, 5.5 Hz), 4.36 (2H, m), 4.46 (1H, m), 5.40 (1H, t, *J* = 9.5 Hz), 5.5-5.9 (5H, m), 6.84 (2H, m), 7.17 (2H, m), 7.38-7.92 (10H, m); IR (film) ν_{max} 2930, 1725, 1591, 1516, 1270, 1104, 1013, 754 cm^{-1}.

A mixture of the dibenzoate (6.2 mg, 7.5 μmol) and water (30 μl) in CH_2Cl_2 (600 μl) was treated with DDQ (3.4 mg, 15 μmol), and stirred at room temperature for 1.5 h. Additional DDQ (2.0 mg, 8.8 μmol) was added and the mixture was stirred for 1.5 h. The reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$ (0.5 ml), and the mixture was diluted with ether, washed with water, brine, and dried over $MgSO_4$. Filtration, concentration, and flash column chromatography (silica, hexane/EtOAc 2/1) gave the alcohol (4.7 mg, 6.6 μmol, 89%) as a pale yellow oil : ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.36 (3H, s), 1.46 (3H, s), 2.42

(1H, m), 2.68 (1H, m), 3.3-3.9 (7H, m), 3.95 (1H, dd, J = 10.5, 5.5 Hz), 4.47 (1H, m), 5.34-5.50 (2H, m), 5.58-5.90 (4H, m), 7.4-8.0 (8H, m); IR (film) ν_{max} 3480, 2928, 2882, 1725, 1593, 1270, 1106, 1071, 1013, 756, 735 cm^{-1}.

A solution of the alcohol (4.7 mg, 6.6 μmol), *p*-BrBzCl (5.8 mg, 26.5 μmol), Et_3N (40 μl, 260 μmol), and DMAP (0.3 mg, 3 μmol) in CH_2Cl_2 (0.5 ml) was stirred at room temperature for 2 h. The reaction mixture was concentrated and subjected to flash column chromatography (silica, hexane/EtOAc 3/1) to give a diastereomeric 1:1 mixture of **9** and **11** (5.3 mg, 6.0 μmol, 90%). The mixture was separated by HPLC [DAICEL-CHIRALPAK AS, eluent: hexane/*i*PrOH 30/1] and their C2 configurations were determined by CD exciton chirality method. (2*S*,5*R*)-**9**: colorless solid; ^{1}H-NMR (600MHz, $CDCl_3$) δ 1.36 (3H, s), 1.47 (3H, s), 2.41 (1H, m), 2.66 (1H, m), 3.42 (1H, m), 3.46 (1H, m), 3.58 (1H, t, J = 9.1 Hz), 3.78 (1H, t, J = 10.5 Hz), 3.81 (1H, t, J = 9.6 Hz), 3.95 (1H, dd, J = 10.9, 5.3 Hz), 4.15 (1H, dd, J = 11.8, 7.5 Hz), 4.18 (1H, dd, J = 11.8, 3.8 Hz), 4.48 (1H, m), 5.42 (1H, dd, J = 9.6, 9.1 Hz), 5.66-5.89 (5H, m), 7.38-8.06 (12H, m); IR (film) ν_{max} 2926, 1731, 1593, 1400, 1270, 1176, 1104, 1013, 847, 754 cm^{-1}; $[\alpha]_D^{26}$ 46 (c 0.45, $CHCl_3$); UV (EtOH) λ_{max} 245 nm (logε 4.8); CD (EtOH) λ_{ext} 237 nm (Δε -11.0), 242 (0.0), 252 (+26.2); MS (EI) *m/z* (relative intensity) 692 (0.2), 690 (0.4), 688 (0.2), 507 (4), 505 (4), 490 (3), 488 (2), 185 (97), 183 (100); Electrospray MS *m/z* 917 $(M+Na)^+$, 915 $(M+Na)^+$, 913 $(M+Na)^+$, 911 $(M+Na)^+$. (2*R*,5*R*)-**11**: colorless solid; ^{1}H-NMR (600MHz, $CDCl_3$) δ 1.36 (3H, s), 1.47 (3H, s), 2.41 (1H, m), 2.66 (1H, m), 3.42 (1H, m), 3.46 (1H, m), 3.58 (1H, t, J = 9.1 Hz), 3.78 (1H, t, J = 10.5 Hz), 3.81 (1H, t, J = 9.6 Hz), 3.95 (1H, dd, J = 10.9, 5.3 Hz), 4.26 (1H, dd, J = 12.0, 7.5 Hz), 4.35 (1H, dd, J = 12.0, 3.0 Hz), 4.52 (1H, m), 5.42 (1H, dd, J = 9.6, 9.1 Hz), 5.70-5.88 (5H, m), 7.38-8.06 (12H, m); IR (film) ν_{max} 2926, 1729, 1593, 1400, 1267, 1176, 1104, 1071, 1013, 847, 756 cm^{-1}; $[\alpha]_D^{32}$ 29 (c 0.20, $CHCl_3$); UV (EtOH) λ_{max} 244 nm (logε 4.8); CD (EtOH) λ_{ext} 241 nm (Δε +12.7), 249(0), 254 (-6.5); MS (EI) *m/z* (relative intensity) 879 (0.1), 877 (0.4), 875 (0.4), 873 (0.1), 692 (2), 690 (4), 688 (2), 507 (5), 505 (5), 490 (1), 488 (1), 185 (97), 183 (100); Electrospray MS *m/z* 917 $(M+Na)^+$, 915 $(M+Na)^+$, 913 $(M+Na)^+$, 911 $(M+Na)^+$.

Transformation of 9 to (*R*)-1-Acetoxy-2,3-di(benzyloxymethoxy)propane (23). A solution of **9** (0.8 mg, 0.9 μmol) and anhydrous K_2CO_3 (1.5 mg, 10 μmol) in absolute MeOH (500 μl) was stirred at room temperature for 27 h. The mixture was concentrated and subjected to flash column chromatography (silica, CH_2Cl_2/MeOH 5/1) to give the triol (0.3 mg, 0.9 μmol, quant.) as a colorless solid; ^{1}H-NMR (600 MHz, Pyridine-d_5) δ 1.48 (3H, s), 1.49 (3H, s), 2.53 (1H, m), 2.70 (1H, ddd, J = 16.0, 8.0, 4.1 Hz), 3.48 (1H, ddd, J = 10.5, 9.8, 5.3 Hz), 3.50 (1H, m), 3.75 (1H, t, J = 8.9 Hz), 3.85 (1H, t, J = 10.5 Hz), 3.93 (1H, t, J = 9.8 Hz), 3.94 (2H, m), 4.03 (1H, dd, J = 10.5, 5.3 Hz), 4.08 (1H, dd, J = 10.5, 8.9 Hz), 4.65 (1H, m), 4.85 (1H, m), 5.74 (1H, m), 5.88 (1H, dt, J = 11.5, 3.2 Hz), 6.33 (2H, m).

To a solution of the triol (0.9 mg, 2.8 μmol), $(iPr)_2NEt$ (48 μl, 0.28 mmol), and Bu_4NI (11 mg, 28 μmol) in CH_2Cl_2 (0.5 ml), benzyloxymethyl chloride (13 μl, 84 μmol) were added at 0 °C. The mixture was stirred for 10 min and allowed to stand at room temperature for 5 h. An additional benzyloxymethyl chloride (13 μl, 84 μmol) was then added and the mixture was stirred for 10 h, concentrated, and subjected to flash column chromatography (silica, hexane/EtOAc 3/1) to give the tribenzyloxymethyl ether (0.9 mg, 1.3 μmol, 46%) as a colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.35 (3H, s) 1.50 (3H, s), 2.34 (3H, m), 2.63 (1H, m), 3.29 (1H, m), 3.34 (1H, m), 3.46 (1H, t, J = 8.8 Hz), 3.58 (2H, m), 3.62 (1H, t, J = 9.4 Hz), 3.69 (1H, t, J = 10.5 Hz), 3.81 (1H, dd, J = 9.4, 8.8 Hz), 3.90 (1H, dd, J = 10.5, 5.3 Hz), 4.28 (1H, m), 4.50 - 4.62 (4H, m), 4.56 (1H, m), 4.66 - 4.77 (6H, m), 4.89 - 4.99 (2H, m), 5.68 (1H, ddd, J = 15.7, 7.1, 1.4 Hz), 5.72 - 5.76 (2H, m), 5.85 (1H, ddd, J = 15.7, 5.7, 1.0 Hz), 7.32 (15H, m).

A suspension of the tribenzyloxymethyl ether (0.9 mg, 1.3 μmol) and $NaIO_4$ (14 mg, 65 μmol) in phosphate buffer (pH 7, 200 μl), H_2O (200 μl), and CH_3CN (500 μl) was stirred with OsO_4 (100 μl of 0.02 M solution of *t*-BuOH, 2 μmol) at room temperature for 1.5 h. The mixture was diluted with ether and the organic layer was decanted and concentrated. The residue was dissolved in absolute MeOH (1 ml), and treated with $NaBH_4$ (9.0 mg, 240 μmol) at 0 °C. After 40 min, the reaction mixture was quenched with aqueous saturated NH_4Cl (500 μl) and extracted with EtOAc (x 3). The extracts were washed with aqueous saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in pyridine (800 μl) and treated with Ac_2O (400 μl) at room temperature for 10 h. The mixture was concentrated and subjected to column chromatography (silica, hexane/EtOAc 3/1) to give the crude acetate **23**. Further purification was performed by HPLC [Merck LiChospher Si60 (5 μm) eluent: hexane/*i*PrOH 10/1]. This glycerol derivative (*R*)-(**23**) was identical with the authentic material (Rt = 26.0 min) prepared from D-mannitol on HPLC [DAICEL-CHIRALCEL OD (25 cm x 4.6 mmø, eluent: hexane/*i*PrOH 10/1 (0.5 ml/min)]; Rt = 27.4 min for (*S*)-enantiomer.

Preparation of authentic 23. To a stirred mixture of NaH (453 mg, 60% dispersion in mineral oil, 11.3 mmol) in dry DMF (40 ml) and dry THF (20 ml), a solution of **24** (1.00 g, 7.56 mmol) in dry THF (20 ml) was added at room temperature. After stirring for 50 min, the mixture was treated with MPMCl 1.33 ml (9.83 mmol) and stirred at room temperature for 11 h. The reaction mixture was carefully quenched with water and extracted with ether (x 2). The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in MeOH (40 ml) and treated with 1N HCl (30 ml, 30 mmol) at room temperature for 3 h. The mixture was neutralized with aqueous saturated $NaHCO_3$ (30 ml) and extracted with EtOAc (x 3). Concentration and column chromatography (silica, $CHCl_3$/MeOH 20/1) afforded the diol (1.40 g, 6.60 mmol, 87 % from **24**) as a pale yellow oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.53 (2H, m), 3.63 (1H, dd, *J* = 11.0, 5.5 Hz), 3.70 (1H, dd, *J* = 11.0, 4.0 Hz), 3.81 (3H, s), 3.87 (1H, m), 4.48 (2H, s), 6.88 (2H, m), 7.27 (2H, m); IR (film) ν_{max} 3406, 2936, 2872, 1613, 1516, 1464, 1303, 1251, 1178, 1077, 1035, 820 cm^{-1}; $[\alpha]_D^{27}$ -0.8 (c 1.07, MeOH).

To a solution of the diol (100 mg, 0.471 mmol), $(i\text{Pr})_2\text{NEt}$ (806 μl, 4.71 mmol), and Bu_4NI (521 mg, 1.41 mmol) in CH_2Cl_2 (3 ml), was added benzyloxymethyl chloride (13 μl, 84 μmol) at room temperature. The mixture was stirred for 12 h, and then quenched with water, and extracted with ether. The separated organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (silica, hexane/EtOAc 3/1) gave the dibenzyloxymethyl ether (191 mg, 0.422 mmol, 90 %) as a pale yellow oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.60 (2H, m), 3.74 (2H, m), 3.79 (3H, s), 4.48 (2H, s), 4.59 (2H, s), 4.65 (2H, s), 4.77 (2H, s), 4.89 (2H, s), 6.85 (2H, m), 7.25 (2H, m), 7.32 (10H, m); IR (film) ν_{max} 3034, 2936, 2888, 1613, 1586, 1514, 1499, 1456, 1381, 1303, 1249, 1210, 1174, 1042, 907, 822, 739, 700 cm^{-1}; $[\alpha]_D^{26}$ +5.23 (c 1.00, $CHCl_3$).

A mixture of the dibenzyloxymethyl ether (169 mg, 0.372 mmol) and water (100 μl) in CH_2Cl_2 (2 ml) was treated with DDQ (127 mg, 0.559 mmol) and stirred at room temperature for 1.5 h. The reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$ (1 ml) and extracted with ether. The separated organic layer was washed with brine, concentrated, and subjected to flash column chromatography (silica, hexane/EtOAc 2/1) to give the alcohol (119 mg, 0.358 mmol, 96%) as a colorless oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.55 (1H, br), 3.72 (4H, m), 3.86 (1H, m), 4.61 (2H, s), 4.64 (1H, d, *J* = 11.5 Hz), 4.72 (1H, d, *J* = 11.5 Hz), 4.78 (2H, s), 4.88 (1H, d, *J* = 11.5 Hz), 4.91 (1H, d, *J* = 11.5 Hz), 7.34 (10H, m); IR (film) ν_{max} 3450, 2888, 1611, 1516, 1497, 1458, 1383, 1251, 1212, 1168, 1035, 907, 822, 745, 700 cm^{-1}; $[\alpha]_D^{25}$ -28.1 (c 0.936, $CHCl_3$).

A solution of the alcohol (19 mg, 57 μmol) and Ac_2O (200 μl) in pyridine (800 μl) was stirred at room temperature for 12 h. The reaction mixture was concentrated and subjected to flash column chromatography (silica, hexane/EtOAc 3/1) to give the authentic **23** (20 mg, 54 μmol, 95%). **23**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.04 (3H, s), 3.73 (2H, m), 4.07 (1H, m), 4.20 (1H, dd, *J* = 16.0, 6.5 Hz), 4.30 (1H, dd, *J* = 16.0, 4.5 Hz), 4.60 (2H, s), 4.67 (2H, s), 4.78 (2H, s), 4.88 (2H, s), 7.35 (10H, m); IR (film) ν_{max} 2956, 2890, 1744, 1456, 1381, 1241, 1170, 1110, 1038, 739, 700cm^{-1}; MS (EI) *m/z* (relative intensity) 268 (1), 253 (1), 237 (1), 225 (1), 192 (3), 181 (5), 146 (38), 91 (100); $[\alpha]_D^{30}$ -8.06 (c 0.56, $CHCl_3$).

ACKNOWLEDGMENTS

We thank Dr. Masayuki Satake for his helpful discussions and measurement of Electrospray MS spectra. NMR (500 MHz and 600 MHz), MS, and elemental analyses were performed by the Instrumental Analysis Center for Chemistry, Faculty of Science, Tohoku University. A fellowship to H. O. from the Japanese Society for the Promotion of Science for Young Japanese Scientists is gratefully acknowledged. This work was supported in part by the Ministry of Education, Science, Sports, and Culture of Japan.

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(*Received in Japan* 9 *December* 1996; *accepted* 16 *January* 1997)