Enantioselective Synthesis of (+)-Brefeldin A

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A new enantioselective synthesis of (+)-brefeldin A is described. The five chiral centers are created by the following methodology: asymmetric Diels–Alder reaction to prepare the cyclopentanone 13, stereocontrolled reduction of the carbonyl in the ketone 14, stereocontrolled creation of the chiral centers C-4 and C-15 by a chiral sulfoxide group.

(+)-Brefeldin A, first isolated in 1958 from *Penecillium decumbens*[1] has been shown to have both antifungal and antiviral activity.[2] More recently, it has been shown that the antiviral activity of the molecule is due to inhibition of the intracellular transport of secretory proteins.[3] The finding that brefeldin A specifically blocks the movement of proteins from the endoplasmic reticulum to the Golgi apparatus[4] has made this molecule a powerful tool for biochemical investigation.[5]

The complete structure of (+)-brefeldin A was established in 1971 by X-ray analysis.[6] Five years later, Corey and Wollenberg reported the first synthesis of racemic brefeldin A.[7] The first enantioselective synthesis was reported in 1979.[8] In the years since Corey's initial report, there have been numerous partial,[9] formal,[10] and total[11] syntheses described.

We report in this paper an enantioselective total synthesis of (+)-brefeldin A following the retrosynthetic Scheme I with a complete control of the stereochemistry of the five chiral centers.

Synthesis of the Chiral Hydroxy Sulfone (+)-(5*S*)-2. (+)-Methyl (5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]hexanoate (3) was already prepared in the synthesis of zearalenone that we recently reported.[12] The chiral hydroxyl group was created by asymmetric reduction of a β-keto sulfoxide.

Reduction of the ester group of 3 with $LiAlH_4$, followed by bromination and reaction with sodium sulfinate, afforded the sulfone 2 in 71% overall yield (Scheme II).

Synthesis of the Cyclopentanone (−)-(3*R*,4*R*)-13. The cyclopentanone 13 was prepared using an asymmetric Diels–Alder reaction. Yamamoto[13] has previously shown that the addition of (−)-menthyl fumarate to butadiene in the presence of a Lewis acid, diisobutylaluminum chloride, at low temperature, afforded (*S*,*S*)-dimenthyl cyclohex-4-ene-1,2-dicarboxylate in 56% yield and 95% de. We repeated this experiment using (+)-dimenthyl fumarate [obtained from unnatural (+)-menthol] and diethylaluminum chloride as Lewis acid and we got the adduct 7 in the *R*,*R* configuration in 98% yield and a de higher than 90% (about 5% of the *S*,*S* isomer was detected by ^{13}C NMR). After reduction of the two esters (Scheme III), the two hydroxyl groups were protected (benzaldehyde acetonide 9) and DIBAL reduction gave the monobenzyl ether 10 (only one product can be obtained during this reduction step because of the *C*-2 symmetry of the molecule). Finally the second hydroxyl group was protected as a *tert*-butyldiphenylsilyl ether. The cyclohexene ring was cleaved into the diacid 12 by hydroxylation of the double bond with catalytic osmium tetroxide, followed by sodium periodate oxidation to the dialdehyde, which was subsequently oxidized to the diacid with sodium chlorite. Finally cyclization and decarboxylation was carried out in refluxing acetic anhydride to afford the cyclopentanone 13 in 72% overall yield.

Stereoselective Reduction of the Ketone 13 to Compound (−)-(1*S*,3*R*,4*R*)-6. We, first of all, tried several hydrides to reduce the ketone 13, but all these attempts gave a poor stereoselectivity (20–30% de with REDAL, DIBAL, L-Selectride, and $LiAl(OtBu)_3$). We, then, investigated the possibility to link by a covalent bond one of the hydroxyls and the reducing agent in order to have an intramolecular hydride transfer which must occur on

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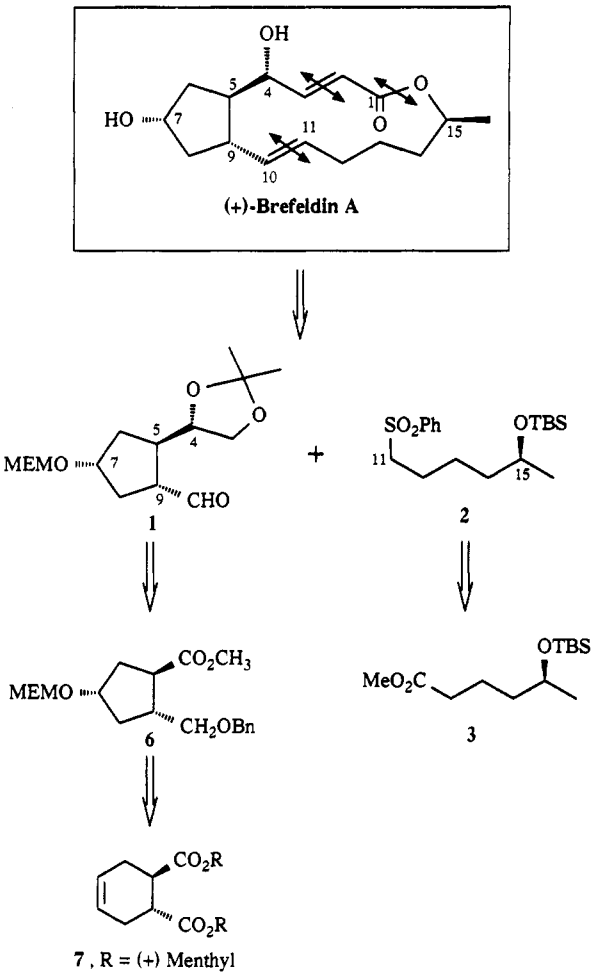
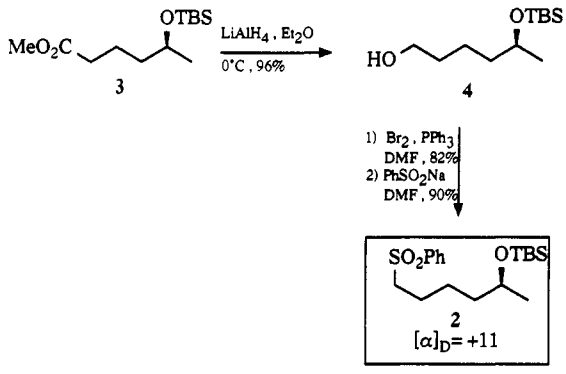
Scheme I



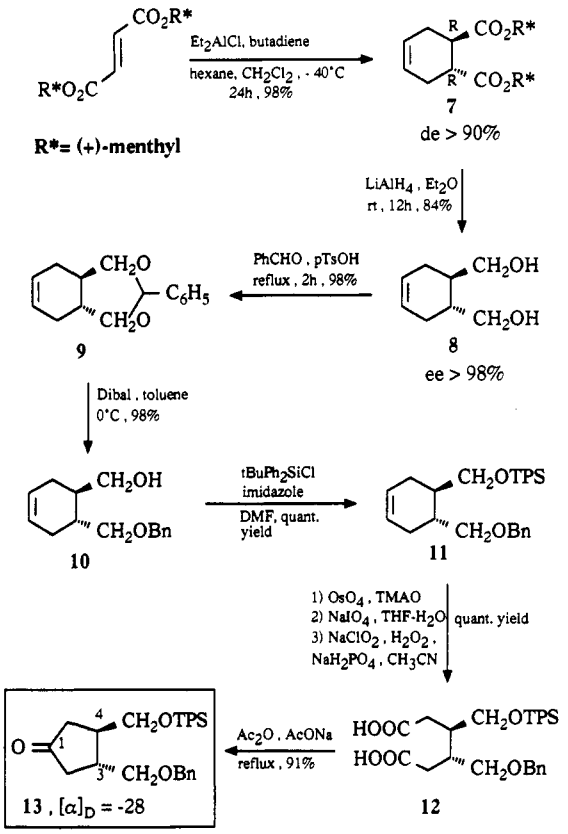
Scheme II



the side of the (*tert*-butyldiphenylsilyl)oxy group to give the desired configuration for the hydroxyl group.

Therefore, we removed the TBDPS protecting group in order to link by a true covalent bond the primary hydroxyl oxygen and the reducing agent before the intramolecular hydride transfer. When the ketone **14** was reduced with Red-Al [$NaH_2Al(OCH_2CH_2OCH_3)_2$] in THF, **15** was obtained in 70% de. In sharp contrast, Red-Al in toluene showed no diastereoselectivity at all. Finally the best result was obtained with Evan's reagent:[18] tetramethylammonium triacetoxyborohydride, which reduced ketone **14** into **15** at room temperature in 3 days with 98% de (determined by ^1H and ^{13}C NMR showing only one stereoisomer; the benzylic CH_2 gives a signal at 4.57 ppm; in the epimer on C-1, this benzylic signal is at 4.53 ppm). The absolute configuration of **15** will indeed be confirmed later by correlation with natural brefeldin. A possible explanation for the very high diastereoselection observed with the Evan's reagent is shown in Scheme IV: exchange of one acetoxy group on boron by **14**, and intramolecular hydride transfer to the carbonyl, under acid catalysis, giving the expected configuration for the resulting OH. Finally the primary OH group in compound **15** was acetylated and the secondary hydroxyl group protected with MEM. After deacetylation, the primary group was oxidized in two steps (Swern oxidation followed by sodium chlorite oxidation[19] of the resulting aldehyde) to the corresponding carboxylic acid which was then esterified with diazomethane. COSY and NOESY experiments confirmed the relative stereochemistry in compound **6**.

Scheme III



Enantioselective Synthesis of Compound 1 from 6. In order to create the chiral center C-4, we decided to use a chiral sulfoxide group which was introduced by reaction of the anion of (+)-(*R*)-methyl *p*-tolyl sulfoxide with the ester group of molecule **6**, in very high yield (Scheme V). Then following our procedure to reduce β-keto sulfoxides,[12,14] we obtained by using DIBAL the β-hydroxy sulfoxide (4*S*)-**18a** in 94% de while the (4*R*)-**18b** diastereomer was obtained with $ZnCl_2$/DIBAL with the same stereoselectivity (determined by ^1H NMR from the signal

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of proton H_X on C-4). The absolute configuration of C-4 was deduced from our preceeding results[14] and will be confirmed in the final product. The hydroxy sulfoxide **18a** was then submitted to a Pummerer rearrangement in acetic anhydride and the product **19** reduced with lithium borohydride (lithium aluminum hydride or DIBAL gave lower yields for the reduction). By silica gel chromatography, the diol **20** was obtained optically pure. Finally the acetonide **1** was made in standard conditions in 95% yield.

The acetonide **1** was first debenzylated and the resulting hydroxyl group oxidized by the Swern procedure. The aldehyde **21** (Scheme VI) was then reacted with the carbanion of sulfone **2** and the adduct acetylated. The acetate **22** was finally submitted to a reductive elimination with sodium amalgam in Julia's conditions[15] giving in 92% yield a mixture of (1″-*Z*) and (1″-*E*) isomers in the ratio cis/trans = 15/85 which could not be separated at this stage.

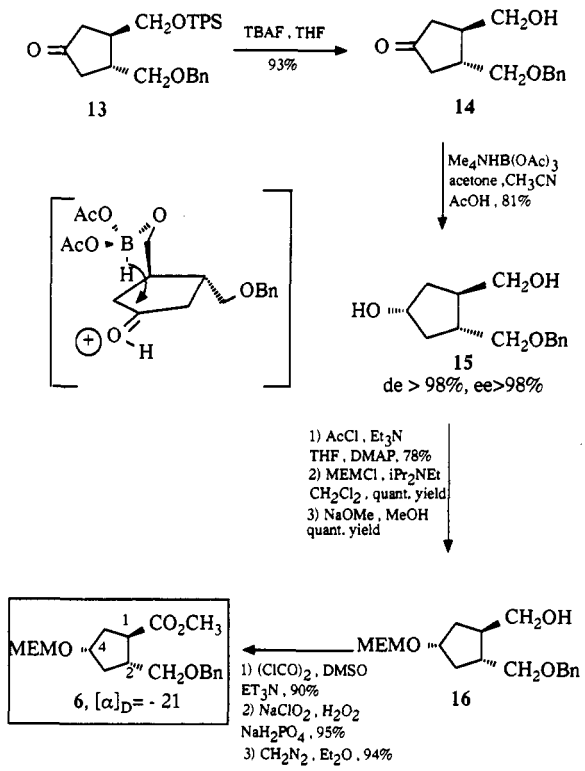
In order to protect selectively the OH on C-4, the acetonide **23** was hydrolyzed and transformed into the corresponding acetal **24**, with *p*-methoxybenzaldehyde dimethyl acetal, which was regiospecifically opened with DIBAL to **25**, the regioselectivity being probably controlled by steric hindrance (Scheme VII). Swern oxidation and Wittig reaction with methyl phosphonoacetate gave the α,β-unsaturated ester **26** as a 17/83 (2*Z*)/(2*E*) mixture of stereoisomers which were separated by chromatography. After deprotection of the C-15 hydroxyl and ester hydrolysis (Scheme VII), the seco-acid **27** was cyclized following Yamaguchi's procedure[16] to give the lactone **28**. Silica gel chromatography of **28** allowed the separation of the (10*Z*) and (10*E*) isomers. Lactone **28** was identical to the product already obtained by Takano.[11n] Finally deprotection of the C-4 and C-7 hydroxyls gave (+)-brefeldin showing all the literature characteristics.[11j]

Experimental Section

(+)-(5*S*)-[(*tert*-Butyldimethylsilyl)oxy]hexan-1-ol (4). To a solution of the ester **3** (2.2 g, 8.45 mmol) in ether (50 mL) at 0 °C was slowly added lithium aluminum hydride (260 mg, 6.76 mmol). The ice bath was removed, and the solution was stirred for 1 h. The mixture was cooled to 0 °C and then quenched by slow addition of saturated aqueous Na_2SO_4 (1.8 mL). The solution was dried ($MgSO_4$), concentrated, and chromatographed to yield **4** as an oil (1.89 g, 96%): R_f (40% Et_2O/hexane) = 0.5; $[\alpha]_D$ +14° (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.80 (m, 1H, H-5), 3.65 (t, J = 6.4 Hz, 2H, H-1), 1.63–1.26 (m, 6H, 3 × CH_2), 1.13 (d, J = 6 Hz, 3H, CH_3), 0.89 (s, 9H, t-Bu), 0.05 (s, 6H, SiMe_2); ^{13}C NMR ($CDCl_3$) δ 68.4 (C-5), 62.3 (C-1), 39.3 (C-4), 32.5 (C-2), 25.8 (tBuSi), 23.6 (C-6), 21.8 (C-3), 17.9 (C-Si), −4.6 and −4.9 (Me_2Si); IR (neat) 3320, 2930 cm^{-1} Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 62.01; H, 12.14. Found: C, 61.97; H, 12.20.

(+)-1-(Phenylsulfonyl)-(5*S*)-[(*tert*-butyldimethylsilyl)-oxy]hexane (2). (1) Bromination of Carbinol 4. Bromine (1.35 g, 8.45 mmol) was added dropwise to a solution of the alcohol **4** (1.87 g, 8.05 mmol) and triphenylphosphine (2.22 g, 8.45 mmol) in anhydrous DMF (35 mL) at 0 °C. The mixture was stirred for 1 h at room temperature, diluted with ether (50 mL), and then washed successively with water (15 mL) and brine (15 mL). The organic phase was dried ($MgSO_4$), concentrated, and chromatographed (2% Et_2O/hexane) to yield **5** as an oil (1.95 g, 82%): $[\alpha]_D$ +11° (*c* 1.06, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.80 (m, 1H, H-5), 3.41 (t, J = 6.9 Hz, 2H, H-1), 1.86 (m, 2H, H-2), 1.44 (m, 4H, H-3, H-4), 1.13 (d, J = 6 Hz, 3H, H-6), 0.89 (s, 9H, t-Bu), 0.05 (s, 6H, Me_2Si); ^{13}C NMR ($CDCl_3$) δ 68.2 (C-5), 38.7 (C-1), 33.6 (C-4), 32.8 (C-2), 25.8 (tBuSi), 24.3 (C-3), 23.8 (C-6), 18.0 (C-Si), −4.4 and −4.8 (Me_2Si); IR (neat) 2950, 1285 cm^{-1}. Anal. Calcd for $C_{12}H_{27}O_5SiBr$: C, 48.80; H, 9.21. Found: C, 48.92; H, 9.17.

Scheme IV

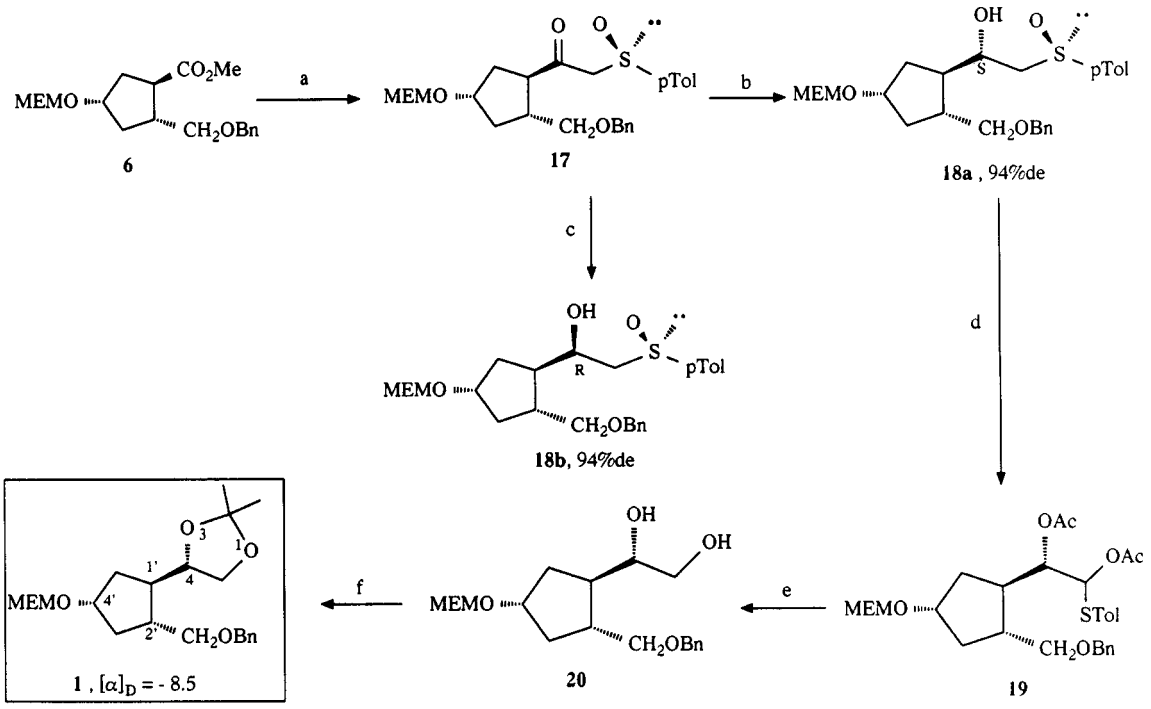


(2) Sulfonylation of the Preceding Bromide. Bromine **5** (0.93 g, 3.13 mmol) and the sodium salt of phenylsulfinic acid (575 mg, 3.44 mmol) in anhydrous DMF (20 mL) were stirred for 24 h at room temperature. After dilution with Et_2O (50 mL), the mixture was washed with water (20 mL) and brine (20 mL). The solution was dried ($MgSO_4$), concentrated, and chromatographed to afford **2** as a colorless oil (1 g, 90%): R_f (15% acetone/hexane) = 0.38; $[\alpha]_D$ +11° (*c* 0.51 EtOH) (lit.[11o] $[\alpha]_D$ +9°); ^1H NMR ($CDCl_3$) δ 7.91 (m, 2H arom.), 7.67–7.53 (m, 3H arom.), 3.70 (m, 1H, H-5), 3.09 (t, J = 7.9 Hz, 2H, H-1), 1.74–1.60 (m, 2H, H-2), 1.45–1.30 (m, 4H, H-3, H-4), 1.08 (d, J = 6 Hz, 3H, H-6), 0.85 (s, 9H, tBuSi), 0.02 and −0.01 (2s, 6H, Me_2Si); ^{13}C NMR ($CDCl_3$) δ 138.9, 133.2, 128.9, and 127.6 (arom C), 67.5 (C-5), 55.8 (C-1), 38.5 (C-2), 25.5 (tBuSi), 24.0 (C-4), 23.4 (C-6), 22.4 (C-3), 17.6 (CSi), −4.7 and −5.1 (Me_2Si); IR (neat) 2950, 1440, 1150 cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_3SSi$: C, 60.63; H, 9.04. Found: C, 60.80; H, 8.82.

(+)-(1*R*,2*R*)-Di-(+)-menthyl Cyclohex-4-ene-1,2-dicarboxylate (7). Chlorodiethylaluminum (100 mL of a 1 M solution in hexane, 0.1 mol) was added dropwise to a solution of (+)-menthyl fumarate (18.6 g, 0.047 mol) in anhydrous CH_2Cl_2 (400 mL) at −78 °C. The complex was stirred for 0.5 h (orange color), and then liquid butadiene (25 g, 0.47 mol) was added all at once under a stream of argon. The reaction was quenched after 24 h at −40 °C by slow addition of aqueous HCl (1250 mL) of a 0.16 N solution) and extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were washed with 5% aqueous $NaHCO_3$ (100 mL) and brine (100 mL) and then dried ($MgSO_4$). The solution was concentrated and filtered through silica gel (9% ether/hexane) to give **7a** (20.75 g, 98%) as an oil which crystallized on standing: mp 56–58 °C; $[\alpha]_D$ +29° (*c* 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.67 (m, 2H, H-4, H-5), 4.66 (td, J = 10.8, 4.3 Hz, 2H, CO_2CH), 2.85 (m, 2H, H-1, H-2), 2.55–2.07 (m, 4H, H-3, H-6), 2.07–0.78 (m, 18H, menthyl), 0.89 (d, J = 6.4 Hz, 6H, Me), 0.88 (d, J = 7 Hz, 6H, Me), 0.73 (d, J = 7 Hz, 6H, Me). ^{13}C NMR ($CDCl_3$) δ 173.8 (C=O), 124.6 (C-4,C-5), 73.7 (C—O), 46.6 (CH), 40.8 (CH), 40.3 (C-3, C-6), 33.9 (CH_2), 31.0 (CH), 27.6 (CH_2), 25.6 (CH), 22.8 (CH_2), 21.7 (CH_3), 20.5 (CH_3), 15.6 (CH_3); IR ($CHCl_3$) 2940, 1730 cm^{-1}. Anal. Calcd for $C_{28}H_{46}O_4$: C, 75.30; H, 10.40. Found: C, 75.20; H, 10.45.

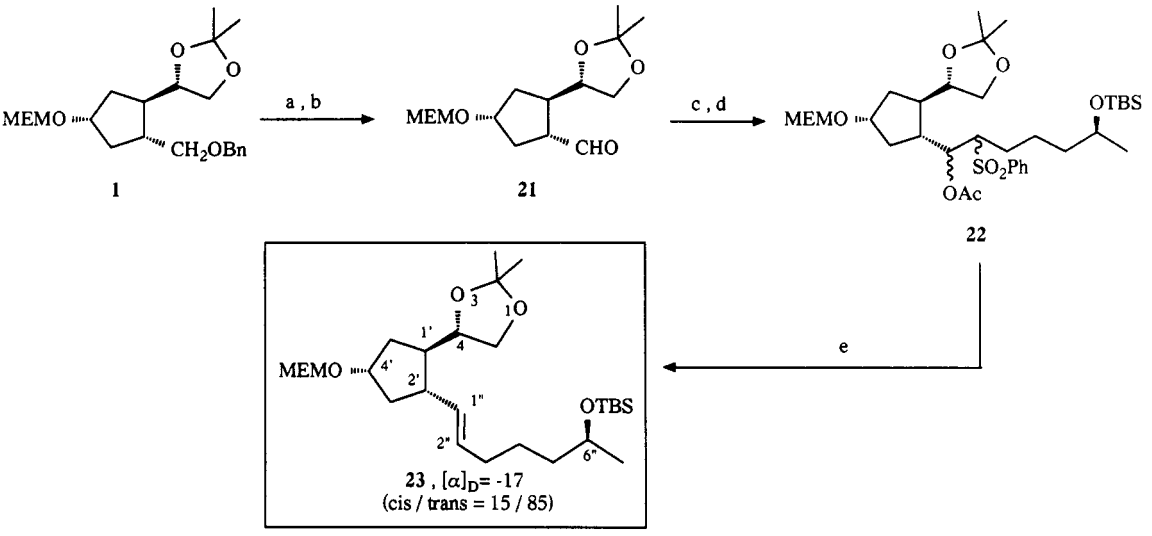
(−)-(1*R*,2*R*)-Cyclohex-4-ene-1,2-dimethanol (8). The diester **7a** (42.45 g, 0.095 mmol) in ether (250 mL) was added dropwise to lithium aluminum hydride (6.28 g, 0.166 mol) in ether (400 mL) at −78 °C. The mixture was stirred for 12 h at

Scheme V[a]



[a] (a) (*R*)-Methyl *p*-tolyl sulfoxide (2 equiv), LDA, THF, −78 °C, 99%; (b) DIBAL, THF, −78 °C, quant yield; (c) $ZnCl_2$, DIBAL, THF, −78 °C, 86%; (d) Ac_2O, AcONa, refux, 91%; (e) $LiBH_4$, THF, rt, 87%; (f) $Me_2C(OMe)_2$, acetone, TsOH, 95%.

Scheme VI[a]



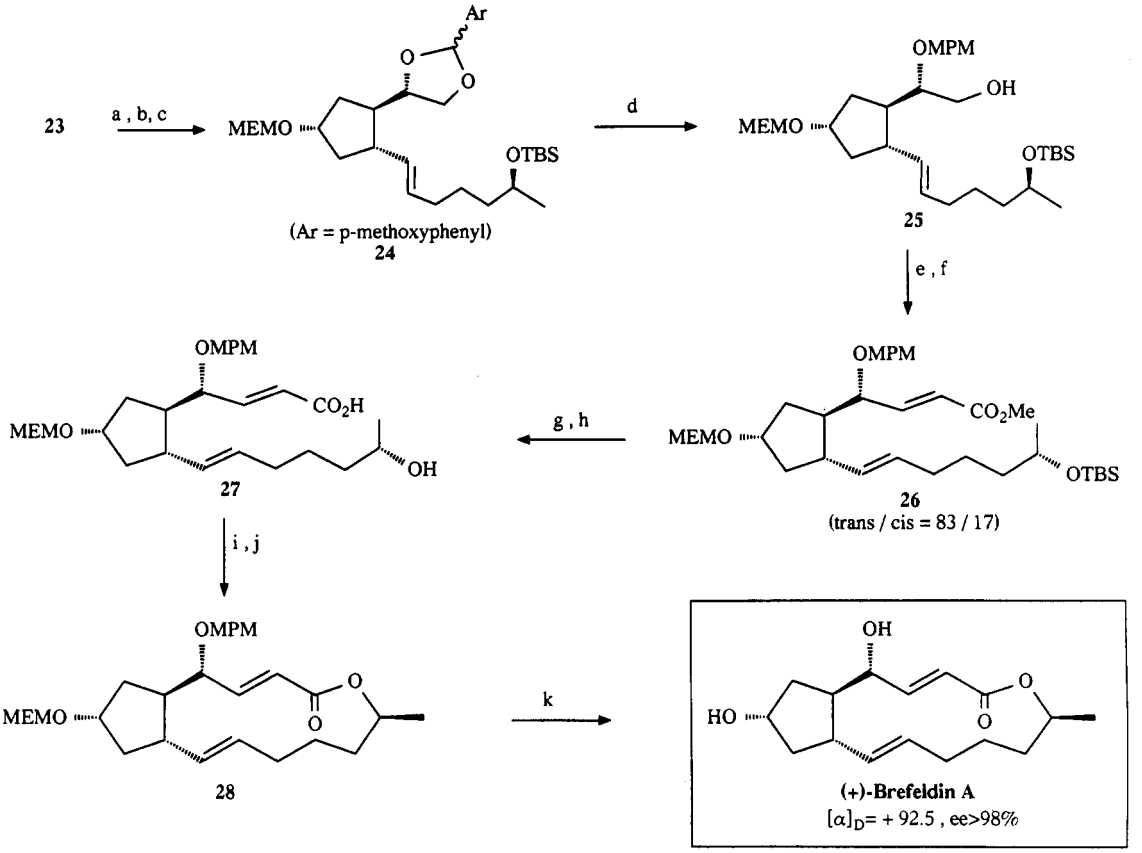
[a] (a) Pd/C, cyclohexane, H_2 (15 atm), 98%; (b) $(ClCO)_2$, DMSO, Et_3N, 83%; (c) sulfone **2**, nBuLi, THF, −78 °C; (d) Ac_2O, pyridine; 83% yield for the two steps; (e) Na(Hg), Na_2HPO_4, CH_3OH, AcOEt, −35 °C, 92%.

room temperature before cooling to −20 °C. Workup was achieved by successive addition of water (6.3 mL), 3 M aqueous NaOH (6.3 mL), and water (18.9 mL). The precipitate was filtered and the solution evaporated. Menthol (28 g, 94%) was separated from **8** by gradient chromatography (50% Et_2O in hexane to Et_2O). Recrystallization of diol **8** (ether/hexane) afforded 11.36 g of white crystals (84%, 98% ee): mp 62–63 °C; $[\alpha]_D$ −72° (*c* 1.4, $CHCl_3$) ($[\alpha]_D$ +73° for the antipode[17]); ^1H NMR ($CDCl_3$) δ 5.65 (m, 2H, H-4, H-5), 3.76–3.53 (m, 4H, CH_2O), 3.18 (s, 2H, OH), 2.18–1.63 (m, 6H, H-3, H-6, H-1, H-2); ^{13}C NMR ($CDCl_3$) δ 125.8 (C-4, C-5), 65.8 (CH_2OH), 39.3 (C-1, C-2), 28.1 (C-3, C-6); IR ($CHCl_3$) 3360, 2940 cm^{-1}. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.06; H, 9.79.

(−)-(1*R*,2*R*)-1,2-*O*-Benzylidenecyclohex-4-ene-1,2-dimethanol (9). A mixture of the diol **8** (11.36 g, 0.08 mol), benzaldehyde (25.4 g, 0.24 mol), and pyridinium *p*-toluenesulfonate (4 g, 16 mmol) in benzene (670 mL) was refluxed (Dean–Stark) for 2 h. Benzene was evaporated and the crude product was dissolved in ether (300 mL) before being decolorized with activated carbon. The solution was filtered through Celite, concentrated, and chromatographed to yield **9** as a white solid (18 g, 98%): mp 73–74°C; $[\alpha]_D$ −209° (*c* 1.77, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.55–7.30 (m, 5H, arom), 5.82 (s, 1H, OCHO), 5.71 (m, 2H, H-4, H-5), 4.03–3.95 (m, 1H, CH_2O), 3.80–3.70 (m, 1H, CH_2O), 3.55 (m, 2H, CH_2O), 2.09–1.90 (m, 2H, H-1, H-2), 1.77–1.59 (m, 4H, H-3, H-6); ^{13}C NMR ($CDCl_3$) δ 139.8, 128.0, 126.3, and 126.2 (arom C), 126.1 (C-4, C-5), 99.8 (OCHO), 70.9 (CH_2O), 65.6 (CH_2O), 41.45 and 41.3 (C-1, C-2), 28.0 and 27.9 (C-3, C-6); IR ($CHCl_3$) 2880, 1115 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.43; H, 8.10.

(−)-(1*R*,2*R*)-1-(Hydroxymethyl)-2-[(benzyloxy)methyl]-cyclohex-4-ene (10). Diisobutylaluminum hydride (DIBAL) (292 mL of a 1 M solution in toluene, 0.292 mol) was dropwise added to the acetal **9** (26.88 g, 0.117 mol) in anhydrous toluene (330 mL) at 0 °C. After 2 h, methanol was added (15 mL) followed by aqueous 3 M NaOH (110 mL, slow addition). The mixture

Scheme VII[a]



[a] (a) 1 N HCl, THF, rt, 93%; (b) *p*-methoxybenzaldehyde dimethyl acetal, CH_2Cl_2, camphorsulfonic acid, rt, 88%; (c) TBSCl, imidazole, DMAP, DMF, 91%; (d) DIBAL, toluene, −10 °C, 3 h, 91%; (e) $(ClCO)_2$, DMSO, and then Et_3N, 95%; (f) $(MeO)_2P(O)CH_2CO_2Me$, tBuOK, THF, 1 h, −78 °C, 99%; (g) 1 N HCl, THF, rt, 2.5 h; (h) LiOH, CH_3OH-H_2O, 60 °C, 4h; 93% yield for the 2 steps; (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 24 h, rt; (j) DMAP, toluene, refux, 12 h; 50% yield for the two steps; (k) $TiCl_4$, CH_2Cl_2, 0 °C, 30 min., quant yield.

was diluted with ether (300 mL) and the aqueous phase was extracted with ether (2 × 100 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (150 mL), dried ($MgSO_4$), concentrated, and filtered through silica gel (30% AcOEt in hexane) to afford **10** (26.7 g, 99%) as a pale yellow oil: R_f (30% AcOEt in hexane = 0.37; $[\alpha]_D$ −62° (*c* 4, EtOH); ^1H NMR ($CDCl_3$ + CD_3OD) δ 7.29 (m, 5H, arom), 5.58 (m, 2H, H-4, H-5), 4.48 (s, 2H, OCH_2Ph), 3.67–3.59 (m, 2H, CH_2O), 3.50–3.43 (m, 2H, CH_2O), 2.06–1.58 (m, 6H, H-1, H-2, H-3, H-6); ^{13}C NMR ($CDCl_3$) δ 137.6, 128.1, 127.5, 127.4 and 126.1 (arom), 125.2 (C-4, C-5), 73.7 (OCH_2Ph), 73.0 (CH_2O), 64.7 (CH_2O), 39.2 and 35.3 (C-1, C-2), 27.9 and 27.8 (C-3, C-6); IR (neat) 3400, 2895, 1695, 1080 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_2$: C, 78.23; H, 7.88. Found C, 78.57; H, 7.50.

(−)-(1*R*,2*R*)-1-[(Benzyloxy)methyl]-2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]cyclohex-4-ene (11). Chloro-*tert*-butyldiphenylsilane (33.2 g, 0.121 mol) was slowly added to a solution of **10** (26.5 g, 0.115 mol) and imidazole (19.6 g, 0.287 mol) in DMF (250 mL) at 0 °C. After 12 h at room temperature, the mixture was partitioned between ether (300 mL) and saturated aqueous NH_4Cl (150 mL). The organic phase was washed with brine (100 mL), dried ($MgSO_4$), concentrated, and filtered through silica gel to afford a quantitative yield of **11** (54 g): R_f (5% AcOEt in hexane) = 0.48; $[\alpha]_D$ −37° (*c* 2.85, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.71–7.66 (m, 4H arom), 7.45–7.27 (m, 11H arom), 5.65 (s, 2H, H-4, H-5), 4.44 (s, 2H, OCH_2Ph), 3.68 (AB of an ABX, J = 10, 6.1, 5.2 Hz, $\Delta\nu$ = 11 Hz, 2H, CH_2O), 3.46 (AB of an ABX, J = 9.2, 5.9, 4.4 Hz, $\Delta\nu$ = 22 Hz, 2H, CH_2O), 2.22–1.87 (m, 6H, H-1, H-2, H-3, H-6), 1.08 (s, 9H, tBuSi); ^{13}C NMR ($CDCl_3$) δ 138.6, 135.5, 133.8, 129.5, 128.2, 127.5, 127.3 and 127.2 (arom), 125.8 and 125.7 (C-4, C-5), 72.8 (OCH_2Ph), 72.7 (CH_2O), 65.7 (CH_2O), 37.3 and 34.6 (C-1, C-3), 27.6 and 27.2 (C-3, C-6), 26.9 (tBuSi), 19.2 (CSi); IR (neat) 2900, 2860, 1590, 1110 cm^{-1}. Anal. Calcd for $C_{31}H_{38}O_2Si$: C, 79.10; H, 8.14. Found: C, 79.10; H, 8.24.

(+)-(3*R*,4*R*)-3-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4-[(benzyloxy)methyl]hexane-1,6-dicarboxylic Acid (12). (1) Hydroxylation of the Double Bond. OsO_4 (3.3 mL of a 0.1 M solution in CCl_4, 0.33 mmol) was slowly added to **11** (14.29 g, 0.03 mol) and $Me_3N(O)$ (3.60 g, 0.032 mol) in CH_2Cl_2 (600 mL). After 6 h at room temperature, saturated aqueous $Na_2S_2O_5$ (150 mL) was added. The aqueous phase was extracted with AcOEt (2 × 50 mL), and the combined organic extracts were washed with saturated aqueous NH_4Cl (300 mL), dried ($MgSO_4$), and concentrated to yield the crude diol (15.4 g).

(2) Oxidation of the Diol to the Dialdehyde. $NaIO_4$ (80 mL of a 0.75 M aqueous solution, 0.06 mol) was added to the preceeding diol (15.32 g, 0.03 mol) in THF (130 mL) at 0 °C. After 2 h, the mixture was diluted with 1% aqueous $NaHCO_3$ (400 mL) and extracted with ether (4 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated, and the crude dialdehyde was used immediately (slow decomposition on standing).

(3) Oxidation to the Diacid 12. To the above aldehyde in CH_3CN (70 mL) at 0 °C were successively added NaH_2PO_4 (150 mL of a 0.95 M aqueous solution, 0.142 mol), H_2O_2 (11 mL of a 30% aqueous solution, 0.097 mol), and $NaClO_2$ (85 mL of a 1.0 M aqueous solution, 0.085 mol). The mixture was diluted with CH_3CN (500 mL) and vigorously stirred for 12 h at room temperature. After addition of ether (300 mL), the phases were separated. The aqueous phase was acidified with 1 N aqueous HCl (pH 2–3) and extracted with ether (4 × 100 mL). The combined organic solution was washed with brine (200 mL), dried ($MgSO_4$), and concentrated to give a quantitative yield (16.25 g) of diacid **12**. The product was pure enough to be used in the next sequence. An analytical sample was obtained from recrystallization in ether/chloroform: R_f (AcOEt) = 0.72; $[\alpha]_D$ +5.5° (*c* 2.24, CH_3OH); mp 113–114 °C; ^1H NMR ($CDCl_3$) δ 7.75–7.68 (m, 3H arom), 7.46–7.26 (m, 12H arom), 4.44 (s, 2H, OCH_2Ph), 3.78–3.76 (m, 2H, CH_2O), 3.57–3.53 (m, 2H, CH_2O), 2.60–2.41 (m, 6H, H-2, H-3, H-4, H-5), 1.07 (s, 9H, tBuSi); ^{13}C NMR (CD_3OD) δ 167.7 and 167.6 (C-1 and C-6), 130.6, 127.7, 127.6, 125.5, 125.4, 121.8, 120.3, 119.8, 119.7, 119.6 and 119.4 (arom), 64.9 (OCH_2-

Ph), 62.9 and 56.5 (CH_2O), 30.9 and 28.7 (C-3, C-4), 25.8 and 25.5 (C-5, C-2), 18.4 (tBu), 10.9 (C-Si); IR (KBr) 3200, 2865, 1750 cm^{-1}. Anal. Calcd for $C_{31}H_{38}O_6Si$: C, 69.63; H, 7.16. Found: C, 69.45; H, 7.22.

(−)-(3*R*,4*R*)-3-[(Benzyloxy)methyl]-4-[[(*tert*-butyldiphenylsilyl)oxy]methyl]cyclopentan-1-one (13). The diacid **12** (16.23 g, 0.03 mol) in acetic anhydride (170 mL) in the presence of sodium acetate (1.46 g) was rapidly heated to reflux for 1 h. The cooled mixture was diluted with toluene (400 mL) and evaporated (distillation of toluene–Ac_2O azeotrope). The residue was taken up in Et_2O and filtered through silica gel (Et_2O). The product was then purified by chromatography to afford **13** (12.98 g, 91%) as a pale yellow oil: R_f (30% AcOEt in hexane) = 0.64; $[\alpha]_D$ −28° (*c* 4.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.68–7.63 (m, 4H, arom), 7.46–7.27 (m, 11H, arom), 4.49 (s, 2H, OCH_2Ph), 3.73–3.71 (m, 2H, CH_2O), 3.56–3.39 (m, 2H, CH_2O), 2.55–2.16 (m, 6H, H-2, H-3, H-4, H-5), 1.07 (s, 9H, tBuSi); ^{13}C NMR ($CDCl_3$) δ 184.3 (C-1), 138.1, 135.4, 133.2, 133.1, 129.6, 128.2, 127.6, 127.5 and 127.3 (arom), 72.9 (OCH_2Ph), 72.1 (CH_2O), 65.3 (CH_2O), 41.9 and 41.4 (C-2, C-5), 40.8 and 38.3 (C-3, C-6), 26.7 (tBuSi), 19.1 (C-Si); IR (CCl_4) 2920, 2850, 1740, 1110 cm^{-1}. Anal. Calcd for $C_{30}H_{36}O_3Si$: C, 76.23; H, 7.67. Found: C, 76.18; H, 7.85.

(−)-(3*R*,4*R*)-3-(Hydroxymethyl)-4-[(benzyloxy)methyl]cyclopentan-1-one (14). Tetrabutylammonium fluoride (32.5 mL of a 1.0 M solution in THF, 0.0325 mol) was slowly added to **13** (12.8 g, 0.027 mol) in THF (200 mL) at 0 °C. The mixture was stirred 0.5 h at 0 °C and 1.5 h at room temperature, and the reaction was quenched at 0 °C by addition of half-saturated aqueous NH_4Cl (150 mL). The aqueous phase was extracted with AcOEt (3 × 30 mL), and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), concentrated, and chromatographed (20% acetone/60% CH_2Cl_2/20% hexane) to yield **14** (5.94 g, 94%) as a colorless oil: R_f (2% CH_3OH in CH_2Cl_2) = 0.24; $[\alpha]_D$ −64° (*c* 2.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.35 (m, 5H arom), 4.58 (s, 2H, OCH_2Ph), 3.72–3.44 (m, 4H, CH_2O), 2.51–2.39 (m, 2H, H-2, H-5), 2.09–1.98 (m, 2H, H-2, H-5), 2.42–2.25 (m, 2H, H-3, H-4); ^{13}C NMR ($CDCl_3$) δ 184.5 (C-1), 137.2, 128.0, 127.4 and 127.2 (arom), 72.8 (OCH_2Ph), 72.1 (CH_2O), 64.1 (CH_2O), 41.9 and 39.1 (C-3, C-4), 41.5 and 41.2 (C-2, C-5); IR (CCl_4) 3650, 3450, 2860, 1745, 1085 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.18; H, 7.60.

(+)-(1*R*,3*R*,4*R*)-1-Hydroxy-3-(hydroxymethyl)-4-[(benzyloxy)methyl]cyclopentane (15). Anhydrous acetic acid (24.3 mL, 0.383 mol) was slowly added to **14** (1.624 g, 6.39 mmol) in a 1/1 mixture of acetone and CH_3CN (190 mL). Solid $Me_4NHB(OAc)_3$ (27.28 g, 0.096 mol) was then added all at once under a stream of argon. The mixture was stirred for 3 d at room temperature before cooling to 0 °C. The workup was effected by successive addition of saturated aqueous NH_4Cl (250 mL), saturated aqueous sodium tartrate (300 mL), saturated aqueous $NaHCO_3$ (420 mL), and ethyl acetate (250 mL). The solution was stirred for 1 h and decanted. The aqueous phase was extracted with AcOEt (3 × 100 mL), and the combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed giving 235 mg (14%) of **14** and 1.326 g (81%) of diol **15**. The title compound was recrystallized (hexane in CH_2Cl_2) to afford 1.23 g (75%) of colorless crystals: R_f (10% EtOH in CH_2Cl_2) = 0.46; mp 79–80 °C; $[\alpha]_D$ +7° (*c* 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.28 (m, 5H arom), 4.51 (s, 2H, OCH_2Ph), 4.17 (m, 1H, H-1), 3.60–3.49 (m, 2H, CH_2O), 3.42–3.32 (m, 2H, CH_2O), 2.15–1.85 (m, 2H, H-2, H-5), 2.30–2.09 (m, 2H, H-3, H-4), 1.84–1.67 (m, 1H, H-3, H-4), 1.48–1.27 (m, 2H, H-2, H-5); ^{13}C NMR ($CDCl_3$) δ 137.3, 128.4, 127.8 and 127.7 (arom), 74.2 (OCH_2Ph), 73.4 (CH_2O), 72.0 (C-1), 66.4 (CH_2O), 44.5 and 42.4 (C-2, C-4), 39.5 and 38.7 (C-2, C-5); IR (CCl_4) 3650, 3480, 2920, 1085 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.19; 8.54.

(+)-(1*R*,3*R*,4*R*)-1-[(2-Methoxyethoxy)methoxy]-3-(hydroxymethyl)-4-[(benzyloxy)methyl]cyclopentane (16). (1) Acetylation of the Primary Hydroxyl Group. Diol **15** (2.324 g, 9.83 mmol) was solubilized in THF (170 mL) in the presence of triethylamine (4.1 mL, 29.5 mmol) and 4-(dimethylamino)-pyridine (240 mg, 1.97 mmol) and cooled to −78 °C. Acetyl chloride (0.775 mL, 10.81 mmol) was added dropwise and the mixture was slowly warmed to room temperature for 2 h. The mixture was then cooled to −78 °C and an additional 0.140 mL of acetyl chloride was added. After 3 h at room temperature, the reaction was quenched at 0 °C by addition of half-saturated aqueous NH_4Cl (140 mL) and AcOEt (150 mL). The aqueous phase was extracted with AcOEt (3 × 20 mL), and the combined organic solution was dried ($MgSO_4$) and chromatographed to yield a small quantity of diacetate (598 mg, 19%) and the expected primary monoacetate (2.135 g, 78%): R_f (60% AcOEt in hexane) = 0.49; $[\alpha]_D$ −30° (*c* 3.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.33 (m, 5H, arom), 4.56 (s, 2H, OCH_2Ph), 4.21 (m, 1H, H-1), 4.05 (d, *J* = 6.3 Hz, 2H, CH_2OAc), 3.48 (d, *J* = 3.5 Hz, 2H, CH_2OBn), 3.23 (s broad, 1H, OH), 2.49–2.37 (m, 1H, H-3), 2.19–2.11 (m, 1H, H-5β), 2.14–2.06 (m, 1H, H-4), 2.00 (s, 3H, CH_3CO_2), 1.94–1.84 (m, 1H, H-2α), 1.63–1.57 (m, 1H, H-5α), 1.51–1.37 (m, 1H, H-2β); ^{13}C NMR ($CDCl_3$) δ 170.8 (C=O), 137.5, 128.0, 127.4 and 127.3 (arom), 73.0 (CH_2OAc), 72.9 (OCH_2Ph), 72.1 (C-1), 67.3 (CH_2OBn), 40.4 and 38.6 (C-3, C-4), 39.5 and 38.5 (C-2, C-5), 20.5 (CH_3CO_2); IR (neat) 3420, 2925, 1730, 1250, 1100 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.43; H, 7.56.

(2) Protection of the Secondary Hydroxyl with a MEM Group. MEM chloride (2.5 mL, 21.7 mmol) was added dropwise to a solution of the preceeding monoacetate (2.414 g, 8.67 mmol) and diisopropylethylamine (4.52 mL, 26 mmol) in CH_2Cl_2 (90 mL) at 0 °C. After 24 h at room temperature, the reaction was quenched at 0 °C with half-saturated aqueous NH_4Cl (140 mL). The aqueous phase was extracted with AcOEt (3 × 30 mL) and the combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed to give a quantitative yield of (−)-(1*S*,3*R*,4*R*)-1-[(2-methoxyethoxy)methoxy]-3-(acetoxymethyl)-4-[(benzyloxy)methyl]cyclopentane (3.2 g) as a colorless oil: R_f (30% acetone in hexane) = 0.45; $[\alpha]_D$ −15.5° (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.32 (m, 5H arom), 4.69 (s, 2H, OCH_2O), 4.50 (s, 2H, OCH_2Ph), 4.19 (m, 1H, H-1), 4.16–4.07 (m, 1H, CH_2OAc), 4.03–3.94 (m, 1H, CH_2OAc), 3.72–3.64 (m, 2H, OCH_2CH_2O), 3.59–3.50 (m, 2H, OCH_2CH_2O), 3.48–3.38 (m, 2H, CH_2OBn), 3.39 (s, 3H, CH_3O), 2.21–1.86 (m, 4H, H-2, H-3, H-4, H-5), 1.66–1.53 (m, 2H, H-2, H-5), 2.01 (s, 3H, CH_3CO_2); ^{13}C NMR ($CDCl_3$) δ 170.7 (C=O), 138.2, 128.0 and 127.2 (arom), 93.7 (OCH_2O), 76.9 (C-1), 73.9 (CH_2O), 72.6 (CH_2O), 71.5 (CH_2O), 67.2 (CH_2O), 66.5 (CH_2O), 58.7 (CH_3O), 40.2 and 39.6 (C-3, C-4), 36.2 and 35.9 (C-2, C-5), 20.6 (CH_3CO_2); IR (neat) 3920, 1730, 1240, 1100 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.35; H, 8.38.

(3) Hydrolysis of the Acetate. CH_3ONa (162 mg, 2.99 mmol) was added to the preceeding compound (1.095 g, 2.99 mmol) in benzene (50 mL) and methanol (8.5 mL) at 0 °C. The mixture was stirred 1 h at 0 °C and 5 h at room temperature before addition of solid NH_4Cl (excess). The solution was filtered through silica gel (AcOEt) and concentrated to afford a quantitative yield of alcohol **16** (963 mg) as a pale yellow oil. The product was pure enough to be used in the next sequence. An analytical sample was obtained by chromatography: R_f (25% acetone in hexane) = 0.30; $[\alpha]_D$ +12° (*c* 3.61, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.33 (m, 5H, arom), 4.69 (s, 2H, OCH_2O), 4.56 (m, 2H, OCH_2Ph), 4.15 (m, 1H, H-1), 3.69–3.52 (m, 4H, OCH_2CH_2O), 3.62–3.58 (m, 2H, CH_2O), 3.39 (s, 3H, CH_3O), 3.36–3.30 (m, 2H, CH_2OBn), 2.19–1.85 (m, 4H, H-2, H-3, H-4, H-5), 1.51–1.37 (m, 2H, H-2, H-3, H-4, H-5); ^{13}C NMR ($CDCl_3$) δ 137.3, 128.1 and 127.4 (arom), 93.7 (OCH_2O), 76.5 (C-1), 74.3 (CH_2O), 72.9 (CH_2O), 71.4 (CH_2O), 66.4 (CH_2O), 66.1 (CH_2O), 58.6 (CH_2O), 45.1 and 42.3 (C-3, C-4), 36.0 and 35.9 (C-2, C-5); IR (neat) 3440, 2920, 2870 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.80; H, 8.66.

Methyl (−)-(1*R*,2*R*,4*S*)-2-[(Benzyloxy)methyl]-4-[(2-methoxyethoxy)methyl]-1-cyclopentanecarboxylate (6). (1) (−)-(1*R*,2*R*,4*S*)-2-[(Benzyloxy)methyl]-4-[(2-methoxyethoxy)-methoxy]-1-cyclopentanecarboxaldehyde by Swern Oxidation. Dimethyl sulfoxide (2.09 mL, 0.0295 mol) was added dropwise to oxalyl chloride (1.72 mL, 0.0197 mol) in CH_2Cl_2 (43 mL) at −78 °C. After 10 min, alcohol **16** (3.194 g, 9.846 mmol) in CH_2Cl_2 (38 mL) was added dropwise and the mixture was stirred 30 min at −78 °C before addition of triethylamine (8.25 mL, 0.059 mol). The solution was stirred at room temperature for 30 min and quenched at 0 °C by addition of saturated aqueous NH_4Cl (100 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed to yield the aldehyde (3.142 g, 90%) as a colorless oil: R_f (20% acetone in hexane) = 0.24; $[\alpha]_D$ −8.5° (*c* 2.77, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.70 (d, *J* = 2.2 Hz, 1H, CHO), 7.32 (m, 5H, arom), 4.69 (s, 2H, OCH_2O), 4.52 (s, 2H, OCH_2Ph), 4.20 (q, *J* = 5 Hz, 1H, H-4), 3.73–3.65 (m, 2H, OCH_2CH_2O), 3.59–3.52 (m, 2H, OCH_2CH_2O), 3.52–3.41 (m, 2H,

CH_2OBn), 3.39 (s, 3H, CH_3O), 2.81 (qd, J = 8.3, 2.2 Hz, 1H, H-1), 2.50 (sext, J = 7.3 Hz, 1H, H-2), 2.18–1.86 (m, 3H, H-3β, H-5), 1.54 (m, 1H, H-3α); ^{13}C NMR ($CDCl_3$) δ 199.7 (CHO), 137.8, 127.7, 126.9 and 126.8 (arom.), 93.5 (OCH_2O), 97.9 (C-4), 73.0 (CH_2O), 72.2 (CH_2O), 71.1 (CH_2O), 66.2 (CH_2O), 58.2 (CH_3O), 53.1 (C-1), 38.4 (C-2), 34.8 and 32.4 (C-3, C-5); IR (neat) 2920, 2860, 1710 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.90; H, 7.98.

(2) Oxidation to (−)-(1*R*,2*R*,4*S*)-2-[(benzyloxy)methyl]-4-[(2-methoxyethoxy)methoxy]-1-cyclopentanecarboxylic Acid. A solution of the preceeding aldehyde (3.142 g, 9.745 mmol) and NaH_2PO_4 (361 mg, 2.61 mmol) in water (20 mL)/CH_3CN (125 mL) was cooled to 0 °C. H_2O_2 (1.14 mL of a 30% aqueous solution, 11.2 mmol) was added, followed by $NaClO_2$ (1.720 g, 14.6 mmol). The mixture was stirred for 2 h at room temperature and partitioned between AcOEt (200 mL) and water (100 mL). The aqueous phase was extracted with AcOEt (3 × 30 mL), and the combined organic layers were washed with saturated aqueous NH_4Cl (100 mL), dried ($MgSO_4$), and concentrated to afford a quantitative yield (3.298 g) of acid as a colorless oil: R_f (20% Et_2O in CH_2Cl_2) = 0.2; $[\alpha]_D$ −4.5° (*c*, 1.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5H, arom), 4.68 (s, 2H, OCH_2O), 4.60 (s, 2H, OCH_2Ph), 4.24 (m, 1H, H-4), 3.67–3.51 (m, 4H, OCH_2CH_2O), 3.60–3.44 (m, 2H, CH_2OBn), 3.39 (s, 3H, CH_3O), 2.85 (qd, J = 8.5 Hz, 1H, H-1), 2.58–2.44 (m, 1H, H-2), 2.19–2.05 (m, 3H, H-3β, H-5), 1.49 (m, 1H, H-3α); ^{13}C NMR ($CDCl_3$) δ 179.4 (CO_2H), 137.7, 127.9, 127.2 and 127.1 (arom), 93.6 ($OC_{H2}O$), 77.0 (C-4), 73.3 (CH_2O), 72.6 (CH_2O), 71.3 (CH_2O), 66.4 (CH_2O), 58.5 (CH_3O), 45.2 (C-1), 40.9 (C-2), 36.2 and 35.3 (C-3, C-5); IR (CCl_4) 3200, 2900, 1705 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.79; H, 7.52.

(3) Esterification to Methyl (−)-(1*R*,2*R*,4*S*)-2-[(Benzyloxy)methyl]-4-[(2-methoxyethoxy)methoxy]-1-cyclopentanecarboxylate (6). The preceeding acid (2.993 g, 8.84 mmol) in ether (50 mL) was treated with an ethereal solution of diazomethane (1.02 g, 24.3 mmol). Excess CH_2N_2 was destroyed by addition of wet silica gel. After filtration and concentration, the ester was purified by chromatography to yield 2.921 g (94%) of pure **6** as a colorless oil: R_f (20% acetone in hexane) = 0.37; $[\alpha]_D$ −21° (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H, arom), 4.69 (s, 2H, OCH_2O); 4.51 (s, 2H, OCH_2Ph), 4.27 (q, J = 5 Hz, 1H, H-4), 3.69–3.65 (m, 2H, OCH_2CH_2O), 3.65 (s, 3H, CO_2CH_3), 3.57–3.52 (m, 2H, OCH_2CH_2O), 3.51–3.47 (m, 2H, CH_2OBn), 3.39 (s, 3H, OCH_3), 2.76 (q, J = 8.6 Hz, 1H, H-1), 2.54 (sext, J = 7.3 Hz, 1H, H-2), 2.18 (ddd, J = 14, 8.9, 6 Hz, 1H, H-3β), 2.07–1.99 (m, 2H, H-5), 1.56 (m, 1H, H-3α); ^{13}C NMR ($CDCl_3$) δ 176.0 (C=O), 138.4, 128.1, 127.3 and 127.2 (arom), 93.9 (OCH_2O), 77.2 (C-4), 73.3 (CH_2O), 72.7 (CH_2O), 71.6 (CH_2O), 66.7 (CH_2O), 58.8 (OCH_3), 51.6 (C-2), 45.2 (CO_2CH_3), 41.7 (C-1), 36.8 and 35.6 (C-3, C-5); IR (neat) 3005, 2960, 1715 cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.64; H, 8.21.

(+)-[1′*R*,2′*R*,4′*S*,(*S*)*R*]-1-[2′-[(Benzyloxy)methyl]-4′-[(2-methoxyethoxy)methoxy]-1′-cyclopentyl]-2-(*p*-tolylsulfinyl)-ethanone (17). n-Butyllithium (5.1 mL of a 1.6 M solution in hexane, 8.16 mmol) was dropwise added to diisopropylamine (1.2 mL, 8.56 mmol) in THF (8.5 mL) at −40 °C. After 30 min, (*R*)-Methyl *p*-tolyl sulfoxide (1.257 g, 8.16 mmol) in THF (17 mL) was added dropwise to the solution of LDA. The mixture was stirred 30 min at −40 °C and then cooled to −78 °C. This solution was slowly added to the ester **6** (1.436 g, 4.076 mmol) in THF (85 mL) at −78 °C. The reaction was kept for 1 h at −78 °C and then quenched with saturated aqueous NH_4Cl (100 mL) and ether (100 mL). The aqueous phase was extracted with ethyl acetate (3 × 40 mL), and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), concentrated, and chromatographed to yield **17** (1.911 g, 99%) as a pale yellow oil: R_f (60% AcOEt in Et_2O) = 0.51; $[\alpha]_D$ +77.5° (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.46 and 7.27 (d, AA′BB′, J = 8.2 Hz, 4H, arom.), 7.31 (m, 5H arom), 4.66 (s, 2H, OCH_2O), 4.50 (s, 2H, OCH_2Ph), 4.19 (m, 1H, H-4′), 3.96 (dd, AB, J = 14.1 Hz, $\Delta\nu$ = 17 Hz, 2H, H-2), 3.83–3.62 (m, 2H, OCH_2CH_2O), 3.56–3.48 (m, 2H, OCH_2CH_2O), 3.50–3.36 (m, 2H, CH_2OBn), 3.38 (s, 2H, OCH_3), 3.04 (q, J = 8 Hz, 1H, H-1′), 2.51 (m, 1H, H-2′), 2.40 (s, 3H, pTol CH_3), 2.05 (m, 1H, H-3′β), 1.92–1.83 (m, 2H, H-4′), 1.43 (m, 1H, H-3′α); ^{13}C NMR ($CDCl_3$) δ: 203.3 (C=O), 141.1, 139.8, 137.6, 129.4, 127.8, 127.1, 127.0 and 123.5 (arom), 93.5 (OCH_2O), 77.1 (C-4′), 73.5 (CH_2O), 72.4 (CH_2O), 71.1 (CH_2O), 67.6 (CH_2SO), 66.3 (OCH_2-Ph), 58.3 (OCH_3), 53.5 (C-2′), 40.5 (C-1′), 34.7 and 34.6 (C-3′, C-5′), 20.8 (pTol CH_3); IR (CCl_4) 2920, 2880, 1700, 1040 cm^{-1}. Anal. Calcd for $C_{26}H_{34}O_6S$: C, 65.80; H, 7.22. Found: C, 65.78; H, 6.97.

(+)-[1*S*,1′*R*,2′*R*,4′*S*,(*S*)*R*]-1-[2′-[(Benzyloxy)methyl]-4-[(2-methoxyethoxy)methoxy]-1′-cyclopentyl]-1-hydroxy-2-(*p*-tolylsulfinyl)ethane (18a). Diisobutylaluminum hydride (2.7 mL) of a 1.0 M solution in toluene, 2.7 mmol) was very slowly added to keto sulfoxide **17** (1.149 g, 2.422 mmol) in THF (70 mL) at −78 °C. The mixture was stirred 1 h at −78 °C before addition of saturated aqueous sodium tartrate (100 mL). The aqueous phase was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to give 1.146 g (quantitative) of **18a** as a white solid. The hydroxy sulfoxide was pure enough to be used in the next sequence. An analytical sample was obtained by chromatography: R_f (50% AcOEt in Et_2O) = 0.33; $[\alpha]_D$ +105.5° (*c* 0.78, $CHCl_3$); de = 94%; mp 124–125 °C; ^{1}H NMR ($CDCl_3$) δ 7.48 and 7.28 (d, AA′BB′, J = 8.2 Hz, 4H arom), 7.27 (m, 5H arom), 4.65 (s, 2H, OCH_2O), 4.47 (s, 2H, OCH_2Ph), 4.25 (m, X of an ABX, 1H, H-1), 4.13 (m, 1H, H-4′), 3.66–3.61 (m, 2H, OCH_2CH_2O), 3.55–3.50 (m, 2H, OCH_2CH_2O), 3.47–3.31 (m, 2H, CH_2OBn), 3.37 (s, 3H, CH_3O), 2.83 (ddd, AB of an ABX, J = 13.4, 10.3, 1.5 Hz, $\Delta\nu$ = 47 Hz, 2H, H-2), 2.41 (s, 3H, pTol CH_3), 2.12–1.67 (m, 6H, H-1′, H-2′, H-3′, H-5′); ^{13}C NMR ($CDCl_3$), δ 141.1, 140.0, 137.9, 129.7, 128.1, 127.4, 127.3 and 13.7 (arom), 93.7 (OCH_2O), 77.0 (C-4′), 74.1 (CH_2O), 72.8 (CH_2O), 71.5 (CH_2O), 66.5 (CH_2O), 66.4 (C-1), 62.3 (C-2), 58.7 (CH_3O), 46.8 and 38.9 (C-1′, C-2′), 35.8 and 33.5 (C-3′, C-5′), 21.15 (pTol CH_3); IR (CCl_4) 3420, 2930, 1045 cm^{-1}. Anal. Calcd for $C_{26}H_{36}O_6S$: C, 65.52; H, 7.61. Found: C, 65.76; H, 7.36.

(+)-[1*R*,1′*R*,2′*R*,4′*S*,(*S*)*R*]-1-[(2′-[(Benzyloxy)methyl]-4-[(2-methoxyethoxy)methoxy]-1′-cyclopentyl]-1-hydroxy-2-(*p*-tolylsulfinyl)ethane (18b). Anhydrous zinc chloride (30 mg, 0.215 mmol) in THF (2 mL) was added to keto sulfoxide **17** (51 mg, 0.107 mmol) in THF (2 mL) at 0 °C. The mixture was kept 10 min at 0 °C and 30 min at −78 °C. Diisobutylaluminum hydride (0.110 mL of a 1.0 M solution in toluene, 0.110 mmol) was added dropwise to the above solution at −78 °C. After 30 min, an additional 0.110 mL of DIBAL were added. After 1 h, the reaction was worked up as for **18a**. Purification by chromatography yielded 44 mg (86%) of hydroxy sulfoxide **18b** as a white solid (de = 94%): R_f (50% AcOEt in Et_2O) = 0.33; $[\alpha]_D$ +27.5° (*c* 0.75, $CHCl_3$); mp 79–80 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 and 7.31 (d, AA′BB′, J = 8.2 Hz, 4H, arom), 7.32 (m, 5H arom), 4.87 (s, 1H, OH), 4.64 (s, 2H, OCH_2O), 4.55 (dd, AB, J = 12.1 Hz, $\Delta\nu$ = 17 Hz, 2H, OCH_2Ph), 4.10 (m, 1H, H-4), 3.66–3.48 (m, 4H, OCH_2CH_2O), 3.56–3.50 (m, X of an ABX, 1H, H-1), 3.40–3.31 (m, 2H, CH_2OBn), 3.37 (s, 3H, OCH_3), 2.97 (ddd, AB of an ABX, J = 12.7, 8.5, 2.8 Hz, $\Delta\nu$ = 63 Hz, 2H, H-2), 2.41 (s, 3H, pTol CH_3), 2.17–1.91 (m, 4H, H-1′, H-2′, H-3′, H-4′), 1.43–1.22 (m, 2H, H-1′, H-2′, H-3′, H-4′); ^{13}C NMR ($CDCl_3$) δ 141.4, 140.7, 137.2, 129.8, 128.4, 127.9, 127.8 and 124.4 (arom), 93.8 (OCH_2O), 76.9 (C-4′), 74.6 (CH_2O), 73.3 (CH_2O), 71.7 (CH_2O), 71.8 (C-1), 66.8 (CH_2O), 64.1 (C-2), 58.9 (OCH_3), 49.2 and 41.8 (C-1′, C-2′), 36.8 and 35.9 (C-3′, C-5′), 21.4 (pTol CH_3); IR (CCl_4) 3420, 2940, 1055 cm^{-1}. Anal. Calcd for $C_{26}H_{36}O_6S$: C, 65.52; H, 7.61. Found: C, 65.70; H, 7.54.

(1*S*,1′*R*,2′*R*,4′*S*)-1-[(2′-[(Benzyloxy)methyl]-4′-[(2-methoxyethoxy)methoxy]-1′-cyclopentyl]-1,2-diacetoxy-2-(*p*-tolylthio)ethane (19). A solution of hydroxy sulfoxide **18a** (1.270 g, 2.664 mmol) in acetic anhydride (90 mL) in the presence of sodium acetate (2.54 g) was refluxed for 5 h. The cooled solution was diluted with toluene (300 mL) and evaporated. The residue taken up in ether (20 mL) and filtered through a pad of silica gel. Purification by chromatography afforded the Pummerer compound **19** (1.358 g, 91%) as a pale yellow oil: R_f (20% acetone in hexane) = 0.32; ^{1}H NMR ($CDCl_3$) δ 7.42–7.05 (m, 9H, arom), 6.23 and 5.96 [d, 1H (diaster), H-2], 5.30 (m, 1H, H-1), 4.68 (s, 2H, OCH_2O), 4.45 (s, 2H, OCH_2Ph), 4.15 (m, 2H, H-4′), 3.70–3.50 (m, 4H, OCH_2CH_2O), 3.49–3.32 (m, 2H, CH_2OBn), 3.40 (s, 3H, OCH_3), 2.68–1.58 (m, 3H, H-1′, H-2′, H-3′), 2.32 (s, 3H, pTol CH_3), 2.08, 2.04, and 2.03 [s, 6H, CH_3CO_2, (diaster)]; IR (neat) 2930, 1750 cm^{-1}. Anal. Calcd for $C_{30}H_{40}O_8S$: C, 64.26; H, 7.19. Found: C, 64.39; H, 7.20.

(+)-(2*S*,1′*R*,2′*R*,4′*S*)-1-[(2′-[(Benzyloxy)methyl]-4′-[(2-methoxyethoxy)methoxy]-1′-cyclopentyl]-2-hydroxyethanol (20).

Lithium borohydride (2.11 g, 0.097 mol) was added to the acetal **19** (1.358 g, 2.422 mmol) in THF (70 mL). After 12 h at room temperature, the mixture was cooled to −30 °C and diluted with ether (100 mL). Aqueous HCl (100 mL of a 1.0 M solution) was added with caution and the aqueous phase was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), concentrated, and chromatographed to afford diol **20** (742 mg, 87%) as a colorless oil: R_f (5% CH_3OH in CH_2Cl_2) = 0.26; $[\alpha]_D$ +5.5° (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.33 (m, 5H arom), 4.69 (m, 2H, OCH_2O), 4.53 (s, 2H, OCH_2Ph), 4.16 (m, 1H, H-4′), 3.69–3.40 (m, 9H, H-1, H-2, CH_2O), 3.39 (s, 3H, CH_3O), 2.70 (s, 1H, OH), 2.20–1.32 (m, 6H, H-1′, H-2′, H-3′, H-5′); ^{13}C NMR ($CDCl_3$) δ 137.7, 128.2, and 127.5 (arom), 93.7 (OCH_2O), 77.3 (C-4′), 74.7 (CH_2O), 73.6(C-2), 73.0 (CH_2O), 71.5 (CH_2O), 66.6 (CH_2O), 65.1 (CH_2O), 58.8 (CH_3O), 43.7 and 38.8 (C-1′, C-2′), 35.7 and 34.4 (C-3′, C-5′); IR (neat) 3400, 2940 cm^{-1}. Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.20; H, 8.58.

(−)-(4*S*,1′*R*,2′*R*,4′*S*)-2,2-Dimethyl-4-[2′-[(benzyloxy)methyl]-4′-[(2-methoxyethoxy)methoxy]-1′-cyclopentyl]-1,3-dioxolane (1). A solution of the diol **20** (742 mg, 2.093 mmol), dimethoxypropane (438 mg, 4.18 mmol), and *p*-toluenesulfonic acid (39 mg, 0.205 mmol) in acetone (25 mL) was stirred for 1.5 h before being concentrated and filtered through silica gel (20% AcOEt in hexane) to afford compound **1** (781 mg, 95%) as a yellow oil: R_f = 0.29 (AcOEt/hexane 30/70); $[\alpha]_D$ −8.5° (*c* 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.33 (m, 5H, arom), 4.69 (m, 2H, OCH_2O), 4.51 (s, 2H, OCH_2Ph), 4.21 (m, 1H, H-4′), 4.08 (m, 1H, H-4), 3.99 (dd, *J* = 7.5, 6.2 Hz, 1H, H-5), 3.69–3.53 (m, 4H, OCH_2CH_2O), 3.64 (m, 1H, H-5), 3.43 (m, 2H, CH_2OBn), 3.40 (s, 3H, OCH_3), 2.15–1.50 (m, 6H, H-1′, H-2′, H-3′, H-5′), 1.39 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.4, 128.2, 127.4, and 127.3 (arom), 108.4 (C-2), 93.8 (OCH_2O), 78.2 (C-4), 77.2 (C-4′), 74.2 (CH_2O), 72.8 (CH_2O), 71.6 (CH_2O), 68.1 (CH_2O), 66.6 (OCH_2Ph), 58.9 (OCH_3), 42.9 and 39.9 (C-1′, C-2′), 35.9 and 34.4 (C-3′, C-5′), 26.4 (CH_3), 25.4 (CH_3); IR (neat) 2920, 2870, 1450, 1365 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 67.18; H, 8.89.

(+)-(4*S*,1′*R*,2′*R*,4′*S*)-2,2-Dimethyl-4-[2′-formyl-4′-[(2-methoxyethoxy)methoxy]-1′-cyclopentyl]-1,3-dioxolane (21). (1) Debenzylation of Compound 1. Ether **1** (290 mg, 0.735 mmol) in cyclohexane (25 mL) containing a catalytic amount of palladium/C (10%) was hydrogenated (15 atm) for 6.5 h at room temperature. The solution was filtered over a pad of Celite and concentrated to yield the primary alcohol (219 mg, 98%) as a colorless oil. The product was pure enough to be used in the next sequence. An analytical sample was obtained by chromatography: R_f (40% acetone in hexane) = 0.46; $[\alpha]_D$ −8.5° (*c*, 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.72 (s, 2H, OCH_2O), 4.20 (m, 2H, H-4, H-4′), 4.01 (dd, *J* = 8, 6.3 Hz, 1H, H-5), 3.71–4.72 (s, 2H, OCH_2O), 4.20 (m, 2H, H-4, H-4′), 4.01 (dd, *J* = 8, 6.3 Hz, 1H, H-5), 3.71–3.53 (m, 7H, CH_2O, H-5), 3.39 (s, 3H, CH_3O), 2.30–1.90 (m, 4H, H-1′, H-2′, H-3′, H-5′), 1.69–1.55 (m, 2H, H-3′, H-5′), 1.41 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 108.5 (C-2), 93.8 (OCH_2O), 77.6 and 77.5 (C-4, C-4′), 71.5 (OCH_2), 67.4 (OCH_2), 66.6 (OCH_2), 65.9 (OCH_2), 58.7 (CH_3O), 41.9 and 41.5 (C-1′, C-2′), 35.9 and 34.8 (C-3′, C-5′), 26.2 (CH_3), 25.1 (CH_3); IR (neat) 3440, 2920 cm^{-1}. Anal. Calcd for $C_{15}H_{28}O_6$: C, 59.19; H, 9.27. Found: C, 59.31; H, 9.20.

(2) Oxidation of the Primary Hydroxyl. Dimethyl sulfoxide (215 mg, 2.763 mmol) was added dropwise to a solution of oxalyl chloride (233 mg, 1.842 mmol) in CH_2Cl_2 (3.5 mL) at −60 °C. After 10 min, the primary alcohol (187 mg, 0.614 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was stirred for 30 min at −78 °C before addition of triethylamine (559 mg, 5.526 mmol). After 30 min at 0 °C, the reaction was quenched by the addition of water (10 mL). The aqueous phase was extracted with ether (2 × 5 mL) and the combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed to yield **21** (171 mg, 92%) as a colorless oil: R_f (50% AcOEt in hexane) = 0.33; $[\alpha]_D$ +5° (c 2, $CHCl_3$); ^1H NMR ($CDCl_3$), δ: 9.43 (d, *J* = 1.7 Hz, 1H, CHO), 4.89 (s, 2H, OCH_2O), 4.00 (m, 1H, H-4′), 3.80 (q, *J* = 6.3 Hz, 1H, H-4), 3.67 (dd, *J* = 6.3, 7.9 Hz, 1H, H-5), 3.54–3.49 (m, 2H, OCH_2CH_2O), 3.38 (t, *J* = 7.5 Hz, 1H, H-5), 3.33–3.29 (m, 2H, OCH_2CH_2O), 3.11 (s, 3H, OCH_3), 2.57 (qd, *J* = 8, 6.3 Hz, 1H, H-1′), 2.20 (m, 1H, H-2′), 1.96–1.84 (m, 2H, H-3′α, H-5′α), 1.59 (m, 1H, H-3′β), 1.47 (m, 1H, H-5′β); ^{13}C NMR ($CDCl_3$) δ 202.8 (CHO), 108.7 (C-2), 93.5 (OCH_2O), 77.4 and 77.1 (C-4, C-4′), 71.4 (CH_2O), 67.3 (CH_2O), 66.7 (CH_2O), 58.7 (OCH_3), 51.9 (CH_3), 39.9 (CH_3), 34.1 and 33.4 (C-3′, C-5′), 26.1 and 25.0 (C-1′, C-2′); IR (neat) 2920, 1710 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67. Found: C, 59.47; H, 8.73.

(4*S*,1′*R*,2′*R*,4′*R*)-2,2-Dimethyl-4-[2′-[1″-acetoxy-2″-(phenylsulfonyl)-6″(*S*)-[(*tert*-butyldimethylsilyl)oxy]hept-1″-yl]-4′-[(2-methoxyethoxy)methoxy]cyclopent-1′-yl]-1,3-dioxolane (22). *n*-Butyllithium (0.50 mL of a 1.6 M solution in hexane, 0.805 mmol) was added dropwise to a solution of the sulfone **2** (313 mg, 0.878 mmol) in THF (4.5 mL) at −78 °C. This yellow solution was kept 20 min at −78 °C and added to the aldehyde **21** (147 mg, 0.488 mmol) in THF (2 mL) at −78 °C. The mixture was stirred 1 h at −78 °C, diluted with ether (10 mL), and hydrolyzed with saturated NH_4Cl (10 mL). The aqueous phase was extracted with EtOAc (3×5 mL), and the organic layers were washed with saturated NaCl (15 mL), dried ($MgSO_4$), concentrated, and chromatographed to yield **22** (280 mg, 83%) as a mixture of diastereoisomers: R_f (50% AcOEt in hexane) = 0.42 and 0.54 (2 spots). ^1H NMR ($CDCl_3$) δ 7.93–7.89 (m, 2H arom), 7.66–7.57 (m, 3H arom), 5.39–5.30 (m, 1H, H-1″), 4.70–4.47 (s, 2H, OCH_2O), 4.24–3.39 (m, 9H, OCH_2CH_2O, H-4, H-5, H-4′, H-6″), 3.39 (s, 3H, CH_3O), 3.12–2.75 (m, 1H, H-2″), 2.50–1.12 (m, 12H, CH_2), 2.03–1.90 (s, 3H, CH_3CO_2), 1.50–1.26 (s, 6H, CH_3), 1.14–1.03 (s, 3H, CH_3), 0.89–0.86 (s, 9H, tBu), 0.06–0.16 (s, 6H, Me_2Si); IR (CCl_4) 2920, 1740, 1370 cm^{-1}. Anal. Calcd for $C_{35}H_{60}O_{10}SSi$: C, 59.97; H, 8.63. Found: C, 59.88; H, 8.75.

(−)-(4*S*,1′*R*,2′*S*,4′*S*)-2,2-Dimethyl-4-[4′-[(2-methoxyethoxy)-methoxy]-2′-[(*E*)-6″(*S*)-[(*tert*-butyldimethylsilyl)oxy]hept-1″-en-1″-yl]cyclopent-1′-yl]-1,3-dioxolane (23). Disodium acid phosphate (139 mg, 0.98 mmol) was added to acetoxy sulfone **22** (114 mg, 0.163 mmol) in ethyl acetate (1.5 mL). The mixture was cooled to −35 °C and methanol was added (0.48 mL) followed by 6% sodium amalgam (374 mg, 0.98 mmol). The mixture was stirred for 2.5 h at −35 °C before dilution with ethyl acetate (10 mL). The solution was filtered through a pad of silica gel, concentrated, and chromatographed to yield alkene **23** (75 mg, 92%) as a colorless oil. By ^1H and ^{13}C NMR, the product was approximately 85:15 trans/cis: R_f (40% AcOEt in hexane) = 0.74; $[\alpha]_D$ −17° (*c* 0.48, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.41 (td, *J* = 15.2, 6.1 Hz, 1H, H-2″), 5.27 (dd, *J* = 15.2, 7.6 Hz, 1H, H-1″), 4.71 (s, 2H, OCH_2O), 4.20 (m, 1H, H-4′), 3.95 (m, 2H, H-5), 3.77 (m, 1H, H-6″), 3.75–3.65 (m, 2H, OCH_2CH_2O), 3.59–3.50 (m, 2H, OCH_2CH_2O), 3.52 (m, 1H, H-4), 2.23 (m, 1H, H-2′), 1.86 (m, 2H, H-3″), 2.27–1.71 (m, 5H, H-1′, H-5′, H-3′), 1.49–1.25 (m, 4H, H-4″, H-5″), 1.38 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.11 (d, *J* = 6.1 Hz, 3H, CH_3), 0.88 (s, 9H, tBu), 0.04 (s, 3H, Me_2Si); ^{13}C NMR ($CDCl_3$) δ 133.2 and 130.7 (C-1″, C-2″), 108.1 (C-2), 93.9 (OCH_2O), 77.7 (C-4′), 76.6 (C-4), 71.7 (CH_2O), 68.4 (CH_2O), 68.3 (C-6″), 66.7 (CH_2O), 58.9 (OCH_3), 46.4 and 44.4 C-1′, C-2′), 40.5 and 39.1 (C-5′, C-3′), 34.8 and 32.3 (C-3″, C-4″, C-5″), 26.5 (CH_3), 25.8 (tBu), 25.6 (C-7″), 23.7 (CH_3), 18.1 (CSi), −4.5 and −4.8 (Me_2Si); IR ($CHCl_3$) 2920, 1460, 1370 cm^{-1}. Anal. Calcd for $C_{27}H_{52}O_6Si$: C, 64.76; H, 10.47. Found: C, 64.50; H, 10.39.

(4*S*,1′*R*,2′*S*,4′*S*)-2-(*p*-Methoxyphenyl)-4-[4′-[(2-methoxyethoxy)methoxy]-2′-[(*E*)-6″(*S*)-[(*tert*-butyldimethylsilyl)-oxy]hept-1″-en-1″-yl]cyclopent-1′-yl]-1,3-dioxolane (24). (1) Hydrolysis of the Acetonide and TBS Group. Aqueous HCl (2.3 mL of a 1.0 N solution) was added to **23** (145.5 mg, 0.29 mmol) in THF (2.3 mL) at 0 °C. After 2.5h at room temperature, the mixture was basified with excess solid $NaHCO_3$, filtered and concentrated. Toluene was added (15 mL) and the solution was dried by azeotropic distillation (Dean–Stark). The cooled solution was filtered over a pad of $MgSO_4$ and concentrated to afford the crude triol (92.7 mg) as a viscous oil.

(2) Acetalization with *p*-Methoxybenzaldehyde Dimethyl Acetal. p-Methoxybenzaldehyde dimethyl acetal (139 mg, 0.762 mmol) was added to a solution of the above triol (92.7 mg, 0.267 mmol) in CH_2Cl_2 (6 mL), followed by *dl*-10-camphorsulfonic acid (3 mg). After 12 h, the mixture was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$), concentrated, and filtered over a pad of silica gel to afford the crude acetal (109.6 mg) as an oil.

(3) Protection of the Hydroxyl with TBS-Cl. *tert*-Butyldimethylsilyl chloride (79 mg, 0.53 mmol) was added to a solution of the above acetal (109.6 mg, 0.236 mmol) in DMF (0.5

mL) at 0 °C containing imidazole (62 mg, 0.91 mmol) and 4-(dimethylamino)pyridine (3 mg). After 12 h at room temperature, the mixture was partitioned between ether (5 mL) and half-saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with ether (2 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), concentrated, and chromatographed to yield 125 mg (91%) of acetal **24** as a mixture of diastereomers: R_f (80% Et_2O in hexane) = 0.73; ^1H NMR ($CDCl_3$) δ 7.42–7.38 (m, 2H, arom), 6.91 (m, 2H arom), 5.38 and 5.71 [s (2 diaster), 1H, H-2], 5.41–5.25 (m, 2H, H-1″, H-2″), 4.73 (s, 2H, OCH_2O), 4.24–4.00 (m, 3H, H-5, H-4′), 3.82 and 3.81 [s (2 diaster), 3H, p-OCH_3], 2.40–1.70 (m, 6H, CH_2), 1.60–1.20 (m, 6H, CH_2), 1.12 (d, J = 6.1 Hz, 3H, CH_3), 0.89 (s, 9H, tBu), 0.05 (s, 6H, Me_2Si); IR ($CHCl_3$) 2920, 1615, 1455 cm^{-1}. Anal. Calcd for $C_{32}H_{54}O_7Si$: C, 66.40; H, 9.41. Found: C, 66.38; H, 9.45.

(−)-(4*S*,1′*R*,2′*S*,4′*S*)-Methyl 4-[(*p*-Methoxybenzyl)oxy]-4-[4′-[(2-methoxyethoxy)methoxy]-2′-[(*E*)-6″(*S*)-[(*tert*-butyldimethylsilyl)oxy]-hept-1″-en-1″-yl]cyclopent-1′-yl]-(*E*)-but-2-enoate (26). (1) DIBAL Reduction of the Acetal. Diisobutylaluminum hydride (0.625 mL of a 1.0 M solution in toluene, 0.625 mmol) was added dropwise to a solution of **24** (125 mg, 0.216 mmol) in toluene (2.6 mL) at −30 °C. The mixture was stirred for 3h at −10 °C before addition of aqueous NaOH (0.45 mL of a 3M solution, 1.35 mmol). The aqueous phase was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$), concentrated and filtered through silica gel to afford 114.5 mg of the primary alcohol **25**.

(2) Swern Oxidation. Dimethyl sulfoxide (0.11 mL, 1.55 mmol) was added dropwise to oxalyl chloride (0.067 mL, 0.775 mmol) in CH_2Cl_2 (2 mL) at −60 °C. After 10 min, the above crude alcohol **25** (112.5 mg, 0.194 mmol) in CH_2Cl_2 (2 mL) was added to the Swern complex. The mixture was stirred at −60 °C for 0.5 h before addition of triethylamine (0.432 mL, 3.10 mmol). The solution was kept 5 min at −60 °C and 15 min at 0 °C before addition of ether (10 mL) and water (5 mL). The aqueous phase was extracted with ether (2 × 5 mL), and the combined organic layers were dried ($MgSO_4$), concentrated, and rapidly filtered through a small column of silica gel (50% Et_2O in hexane) to yield 107 mg of the aldehyde which was used immediately in the next step.

(3) Wittig Reaction. Potassium *tert*-butoxide (65.4 mg, 0.582 mmol) was added to a solution of trimethyl phosphonoacetate (135 mg, 0.647 mmol) in THF at 0 °C. The mixture was stirred 10 min at 0 °C and 50 min at −78 °C before slow addition of the above aldehyde (107 mg, 0.185 mmol) in THF (2 mL). After 15 h at −78 °C, water was added and the solution was extracted with ether (3 × 10 mL). The organic extracts were dried ($MgSO_4$), concentrated, and chromatographed (4% acetone in hexane) to afford **26** (96.6 mg, 71%, three steps) as a colorless oil: R_f (12% acetone in hexane) = 0.25; $[\alpha]_D$ −36 (c 1.5; $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.24 and 6.88 (d, AA′BB′, J = 8.6 Hz, 4H, arom), 6.86 (dd, J = 15.7, 5.8 Hz, 1H, H-3), 6.05 (dd, J = 15.7, 1.2 Hz, 1H, H-2), 5.20–5.11 (m, 2H, H-1″, H-2″), 4.69 (s, 2H, OCH_2O), 4.37 (dd, AB, J = 11.4 Hz, Δν = 64 Hz, 2H, OCH_2Ar), 4.16 (m, 1H, H-4′), 3.93 (m, 1H, H-4), 3.76–3.52 (m, 5H, OCH_2CH_2O, H-6″), 3.81 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 2.40–1.20 (m, 12H, CH_2), 1.11 (d, J = 6 Hz, 3H, CH_3), 0.89 (s, 9H, tBu), 0.05 (s, 6H, Me_2Si); ^{13}C NMR ($CDCl_3$) δ 166.6 (C-1), 159.2 (p-OCH_3), 148.8 (C-3), 133.1 and 131.2 (C-2″, C-2″), 130.1 (arom), 129.5 (arom), 120.9 (C-2), 113.7 (arom), 94.0 (OCH_2O), 76.6 (C-4′), 71.7 (CH_2O), 70.9 (CH_2O), 68.4 (C-6″), 66.7 (CH_2O), 58.9 (C-4), 55.2 (OCH_3), 51.5 (OCH_3), 48.2 (OCH_3), 43.1 (C-1′), 40.0 and 39.2 (C-3′, C-5′), 32.4 and 32.3 (C-4″, C-5″), 30.3 (C-2′), 25.9 (tBu), 25.6 (C-3″), 23.8 (C-7″), 18.1 (C-Si), −4.5 and −4.8 (Me_2Si); IR ($CHCl_3$) 2900, 1700, 1100, 1020 cm^{-1}. Anal. Calcd for $C_{35}H_{58}O_6Si$: C, 66.21; H, 9.21. Found: C, 66.15; H, 9.17.

(−)-(4*S*,1′*R*,2′*S*,4′*S*)-4-[(*p*-Methoxybenzyl)oxy]-4-[4′-[(2-methoxyethoxy)methoxy]-2′-[(*E*)-6″(*S*)-hydroxyhept-1″-en-1″-yl]cyclopent-1′-yl]-(*E*)-but-2-enoic Acid (27). (1) Deprotection of the Hydroxyl. Aqueous HCl (2 mL of a 1 N solution) was added to the ester **26** (96.6 mg, 0.152 mmol) in THF (2 mL). After 2.5h, excess solid $NaHCO_3$ was added. The mixture was partitioned between water and CH_2Cl_2, dried ($MgSO_4$) and concentrated.

(2) Ester Hydrolysis. To the crude product was added water (1 mL) and methanolic LiOH (5 mL of a 0.13 N solution). The mixture was heated to 60 °C for 4 h, acidified at 0 °C with aqueous HCl (0.7 mL of a 1 N solution), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and purified by preparative TLC (5% CH_3OH in CH_2Cl_2) to yield 71.5 mg (93%) of the hydroxy acid as a yellow oil: R_f (5% CH_3OH in CH_2Cl_2) = 0.14; $[\alpha]_D$ −47° (c, 0.89, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H, arom), 7.06 (d, J = 8.6 Hz, 2H, arom), 7.05–6.90 (m, 2H, H-3), 5.99 (d, J = 15.6 Hz, 1H, H-2), 5.40–5.00 (m, 2H, H-1″, H-2″), 4.70 (s, 2H, OCH_2O), 4.56 (d, J = 12 Hz, 1H, OCH_2Ar), 4.20 (d, J = 12 Hz, 1H, OCH_2Ar), 4.20–3.50 (m, 7H, OCH_2CH_2O, H-4, H-4′, H-6″), 3.81 (s, 3H, p-OCH_3), 3.38 (s, 3H, CH_3O), 2.31–0.85 (m, 12H, CH_2), 1.20 (d, J = 6.1 Hz, 3H, CH_3); IR ($CHCl_3$) 3360, 1700 cm^{-1}. Anal. Calcd for $C_{28}H_{42}O_8$: C, 66.38; H, 8.34. Found: C, 66.40; H, 8.25.

(−)-(2*E*,4*S*,5*R*,7*S*,9*S*,10*E*,15*S*)-4-[(*p*-Methoxybenzyl)oxy]-7-[(2-methoxyethoxy)methoxy]brefeldin (28). Triethylamine (5.9 mg, 0.058 mmol) and trichlorobenzoyl chloride (13.6 mg, 0.056 mmol) were added to the hydroxy acid **27** (27 mg, 0.053 mmol) in THF (0.54 mL). After 24 h, the mixture was diluted with anhydrous toluene (26.5 mL). This solution was added dropwise (0.2 mL/min) to 4-(dimethylamino)pyridine (39 mg, 0.32 mmol) in refluxing toluene (5.5 mL). After refluxing for 12 h, the solution was cooled, diluted with ether (100 mL), washed with aqueous HCl (10 mL of a 0.5 N solution) and 5% aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), concentrated, and chromatographed. The product was further purified by preparative TLC (40% Et_2O in hexane, eluted six times) to yield 13 mg (50%) of **28** as a colorless oil: R_f (50% Et_2O in hexane) = 0.23; $[\alpha]_D$ −38° (c 0.25, $CHCl_3$) (lit.[11n] $[\alpha]_D$ −38.2°); ^1H NMR ($CDCl_3$) δ 7.26 and 6.88 (d, AA′BB′, J = 8.6 Hz, 4H, arom), 7.12 (dd, J = 15.8, 3.7 Hz, 1H, H-3), 5.96 (dd, 1H, J = 15.8, 1.6 Hz, H-2), 5.63 (ddd, J = 14.8, 10.2, 4.9 Hz, 1H, H-11), 5.20 (dd, J = 14.8, 9 Hz, 1H, H-10), 4.95 (m, 1H, H-15), 4.70 (s, 2H, OCH_2O), 4.43 (dd, AB, J = 11.3 Hz, Δν = 66 Hz, 2H, OCH_2Ar), 4.10 (m, 1H, H-7), 3.81 (s, 3H, OCH_3) 3.73 (ddd, J = 9.8, 3.7, 1.6 Hz, 1H, H-4), 370–3.65 (m, 2H, OCH_2CH_2O), 3.58–3.52 (m, 2H, OCH_2CH_2O), 3.22 (s, 3H, CH_3O), 2.31–0.85 (m, 12H, CH_2), 1.28 (d, J = 6.5 Hz, 3H, CH_3); IR (CCl_4) 2930, 1715, 1250, 1040 cm^{-1}. Anal. Calcd for $C_{28}H_{40}O_7$: C, 68.83; H, 8.25. Found: C, 68.65; H, 8.40.

(+)-Brefeldin A. $TiCl_4$ (0.147 mL of a 1.0 M solution in CH_2Cl_2) was added dropwise to protected **28** (12 mg, 0.0246 mmol) in CH_2Cl_2 (2.2 mL). After 0.5 h, the mixture was partitioned between saturated aqueous $NaHCO_3$ (10 mL) and ethyl acetate (30 mL). The organic layer was dried ($MgSO_4$), concentrated, and chromatographed through a small column of silica gel to afford a quantitative yield (6.9 mg) of a white solid. Recrystallization in ethyl acetate (0.5 mL) gave synthetic brefeldin (4.2 mg) identical with the natural product: R_f (80% AcOEt in hexane) = 0.39; mp 204–205 °C (natural[11j]: 204–205 °C); $[\alpha]_D$ +92.5° (c 0.2, CH_3OH) (natural[11j]: +92.9°); ^1H NMR ($CDCl_3$ + CD_3OD) δ 7.32 (dd, J = 15.6, 3.1 Hz, 1H, H-3), 5.80 (ddd, J = 15.6, 1.5, 0.5 Hz, 1H, H-2), 5.63 (ddd, J = 14.9, 10, 4.8 Hz, 1H, H-11), 5.20 (dd, J = 14.9, 9.2 Hz, 1H, H-10) 4.76 (qdd, J = 10.7, 6.2, 1.6 Hz, 1H, H-15), 4.19 (m, 1H, H-7), 3.96 (td, J = 9.1, 2 Hz, 1H, H-4), 2.35–0.77 (m, 12H, CH_2), 1.19 (d, J = 6.2 Hz, 3H, CH_3); IR (KBr) 3365, 2855, 1710 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.50; H, 8.74.

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