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Asymmetric Synthesis of the Polyol Subunit of the Polyene Macrolide Antibiotic RK-397

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A total asymmetric synthesis of the polyol subunit of the polyene macrolide antibiotic RK-397 has been developed by the stereoselective functionalization of (1*R*,1′*S*,6*S*,6′*R*)-3,3′-methylenebis(cyclohept-3-ene-1,6-diol). The pathway generates a large variety of stereoisomeric intermediates and thus can be applied to the preparation of analogues of this natural antibiotic.

Introduction

A great variety of natural products of biological interest include polyketides (1,3-polyoxo, 1,3-polyols, aldols), in particular the large family of polyene macrolides.[1] Representative members of this family are amphotericins, nystatin, and mycoticins. In 1993, RK-397 was isolated from streptomyces from a Japanese soil sample and its structure was elucidated by Osada et al.[2] This macrolide exhibits antifungal and antibacterial activity as well as promising anticancer activity (Scheme 1). Two total syntheses of this antibiotic macrolide have been reported by the groups of McDonald[3] and Denmark,[4] and some approaches to the preparation of the polyol subunit have also been presented.[5] We have recently developed a new, noniterative asymmetric synthesis of C_{15} 1,3-polyols based on the sequential stereoselective functionalization of dialkenes of type *meso*-**5**,[6] which are readily obtained from the *meso*-bicycloadduct resulting from the double [4+3] cycloaddition of 2,2′-methylenebis(furan) to the 1,1,3-trichloro-2-oxyallyl cation.[7] The *threo* compound **4** has been converted efficiently into long-chain polyketides[8] and 6,6-spiroketal derivatives[9] by a double elongation strategy. Applying these methodologies, we report here our studies toward the asymmetric synthesis of a protected form of the C^{11}–C^{28} polyol subunit of RK-397.

Our initial retrosynthetic plan envisaged the assembly of the polyol fragment **9** by an enantioselective allylation to introduce the C_{25}–C_{28} skeleton and to perform the kinetic resolution of the corresponding dialdehyde **10** (Scheme 2). This derivative was expected to be obtained by the double oxidative cleavage of dialkene *meso*-**11** followed by a diastereoselective reduction process. The starting diolefin can be derived from *meso*-**3** by a Merweein–Pondorf–Verley reduction.[10]

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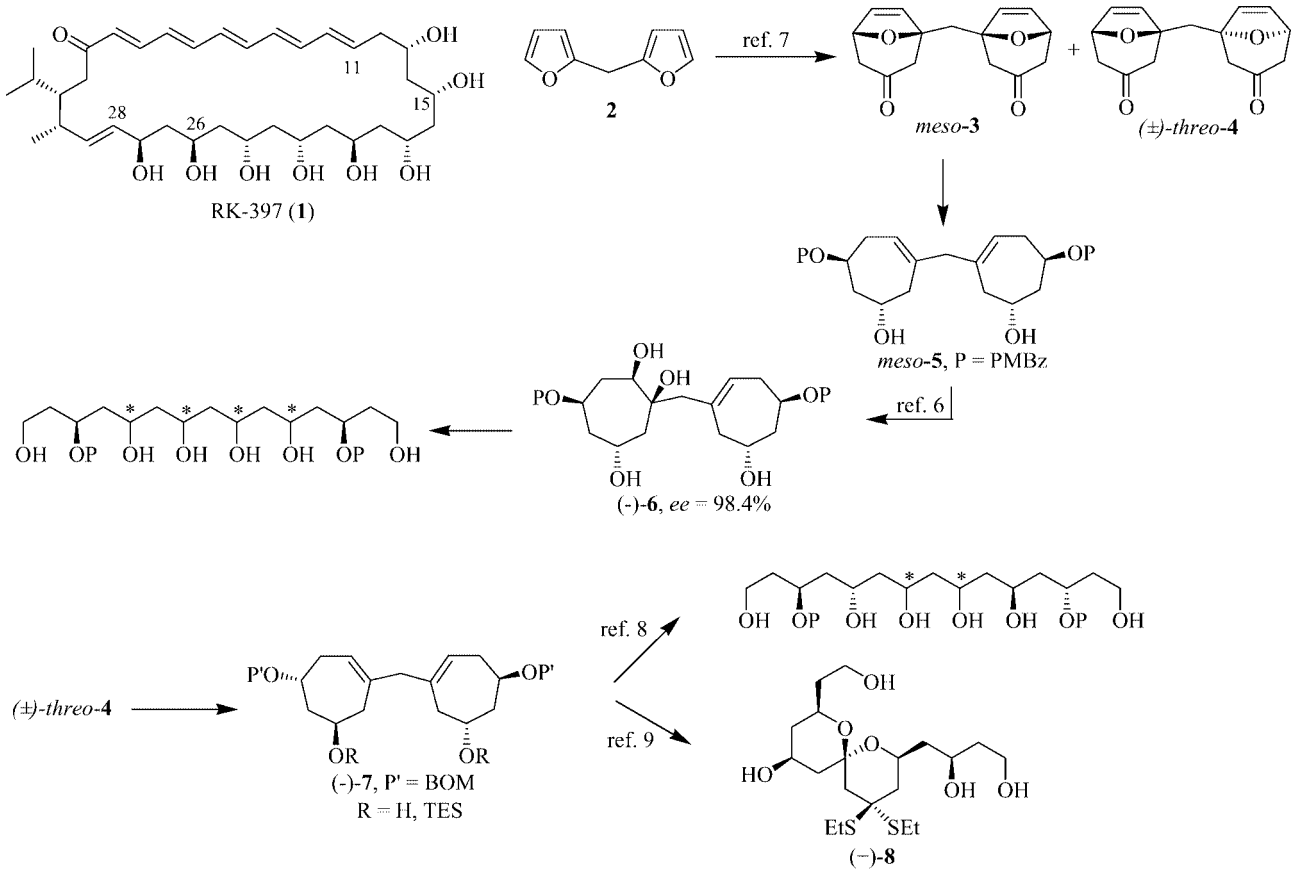
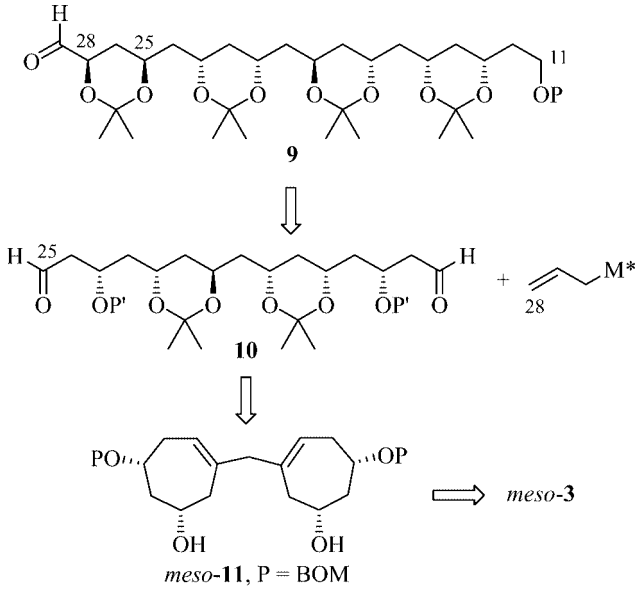
Results and Discussion

The previously reported diacetate *meso*-**12**[10] was treated with Bu_3SnH and AIBN (toluene, 80 °C), followed by methanolysis under classical conditions, to provide *meso*-**11** (66% yield). Then, we submitted dialkene *meso*-**11** to double oxidative cleavage. This was followed by a diastereoselective reduction of the ozonide intermediate to provide a mixture of hemiacetals **13**, which was treated with $NaBH_4$ to provide the targeted polyol fragment (±)-**14** (Scheme 3). In the presence of an excess of $Me_4NBH(OAc)_3$[11] in a mixture of MeCN and acetic acid at 0 °C, the reduction led to a mixture of desired (±)-**14** and unwanted *meso*-**15** in a 3:1 ratio (65% yield). These products could be separated by flash chromatography. Unfortunately, (±)-**14** was contaminated with traces of a polyol presenting the *anti*/*anti* configuration of the diol moieties at C(5)/C(7) and C(9)/C(11). All our attempts to purify (±)-**14** were unsuccessful. The relative configuration of the newly formed stereogenic centers was assigned by analysis of the ^{13}C NMR spectra of the corresponding bis-acetonides (±)-**16** and **17**.[12] The use of different solvents, as well as variation of the temperature (–20 to 25 °C), did not improve the diastereoselectivity of the reduction. Other reducing agents such as K- and L-selectride, led to decomposition of the intermediate product obtained after ozonolysis. Despite this lack of selectivity, we continued our explorations and submitted the major polyol (±)-**16** to the Swern oxidation. This provided the corresponding dialdehyde (80% yield), a very unstable compound that was not isolated but directly submitted to various allylation procedures. In particular, Brown's [(+)-Ipc_2BCl, allylmagnesium bromide][13] and Keck's [$Ti(OiPr)_4$,



Scheme 1.

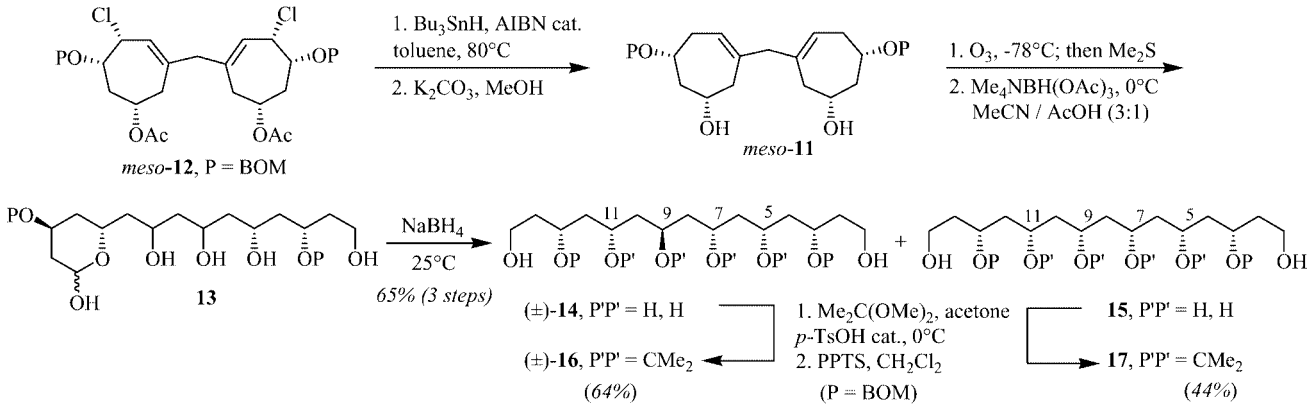


Scheme 2. Retrosynthetic plan.

(*S*)-BINOL, allyltributylstannane][14] conditions were applied. Unfortunately, only mixtures of allylated compounds were formed and we were unable to perform the expected kinetic resolution.

Attempts to desymmetrize the diol *meso*-**11** by a transacylation catalyzed by lipases (from *Candida cylindracea*, *Pseudomonas fluorescens*, pig pancreas, *Pseudomonas cepacia*, and *Candida antartica*) were also performed, but only very low conversion into the corresponding monoacetate was observed.

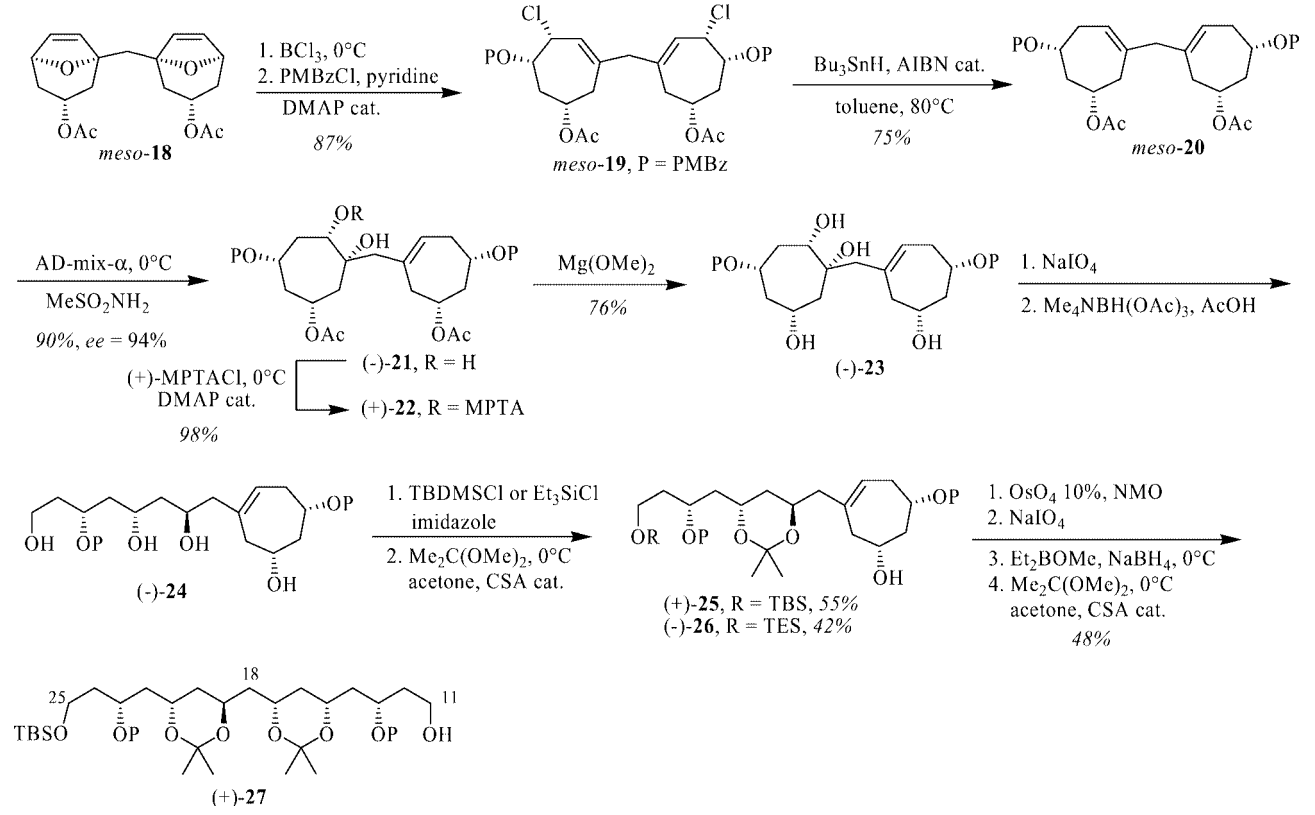
In view of these unsatisfactory results, another approach based on the sequential functionalization of dialkene *meso*-**20** was developed. For that purpose, the previously reported *exo*-diacetate *meso*-**18**[10] was treated with BCl_3 to afford the corresponding dichlorodiol intermediate, which was subsequently converted into the bis(*p*-methoxybenzoate) *meso*-**19** in 87% yield (two steps). Dechlorination with Bu_3SnH and AIBN (toluene, 80 °C) afforded *meso*-**20** (75% yield). This compound was desymmetrized into diol (–)-**21** by Sharpless asymmetric dihydroxylation[15] with an enantiomeric excess of 94% (90% yield), as measured for the corresponding Mosher ester (+)-**22** (Scheme 4). Because of the poor solubility of the starting dialkene *meso*-**20** in the reaction mixture, it was necessary to introduce an enriched AD-mix-α portionwise, over a period of 24 hours. Moreover, the presence of *p*-methoxybenzoyl groups was necessary to reach good enantioselectivities. The acetyl groups were then selectively removed in the presence of an excess of $Mg(OMe)_2$ to afford tetraol (–)-**23** in 76%yield. Cleavage of the cycloheptadiol unit was performed with $NaIO_4$. With-



Scheme 3. Double elongation strategy for the synthesis of the polyol subunit of RK-397.

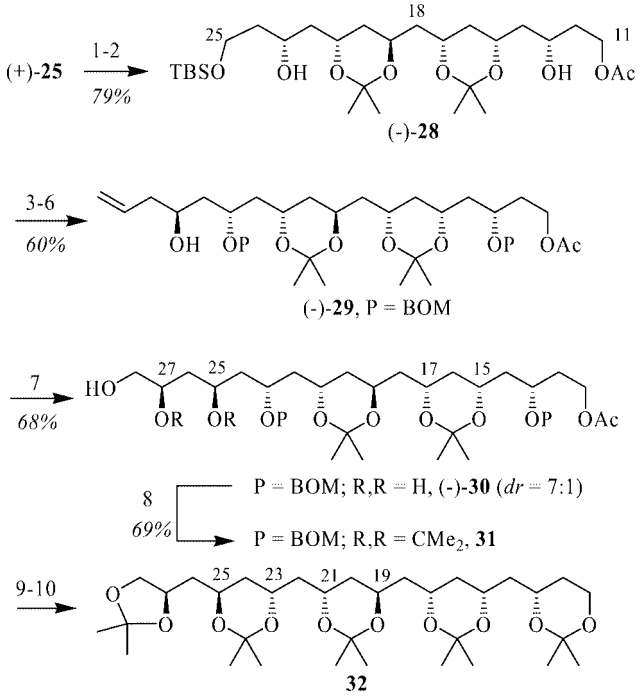
out isolating it, the intermediate oxoaldehyde was treated with an excess of $Me_4NBH(OAc)_3$ to afford the corresponding 1,3-*anti* diol (–)-**24** with a diastereoselectivity higher than 15:1. The primary alcohol was selectively silylated (*t*BuSiMe$_2$Cl or Et$_3$SiCl, 1 M, imidazole) and the remaining diol was protected as an acetonide to give compounds (+)-**25** and (–)-**26** in 55 and 42% yield, respectively, over four steps. This sequence could be efficiently carried out without intermediate purification. In the following steps, the triethylsilyl protecting group proved to be too labile and the synthesis was thus continued with derivative (+)-**25**. Its cycloheptene moiety was submitted to a similar cleavage process using dihydroxylation of the double bond, followed by oxidative cleavage with $NaIO_4$ and reduction under Narasaka conditions (Et_2BOMe, $NaBH_4$).[16] This gave the corresponding 1,3-*syn* diol (only one isomer detected by NMR spectroscopy). The latter compound was not purified but was directly protected as the acetonide to afford (+)-**27** [48% overall yield based on (+)-**25**]. As we previously reported for related compounds,[6a] the absolute configuration of (–)-**21** was established by circular dichroism (CD) of derivative (+)-**25**, the CD spectrum of which displays a positive Cotton effect.

At this stage, it was necessary to oxidize the alcohol moiety at C(25) to perform a diastereoselective allylation, in order to complete the polyol skeleton of RK-397. Preliminary assays of oxidation of the other terminal alcohol led to elimination of the corresponding β-*para*-methoxybenzo-



Scheme 4. Synthesis of the C^{11}–C^{25} skeleton of the polyol subunit of RK-397.

yloxy aldehyde and prompted us to change the protecting groups of the alcohol moieties at C(13) and C(23) (Scheme 5). Methanolysis of the *p*-methoxybenzoates with KOMe, followed by selective transacetylation of the primary alcohol catalyzed by *Candida cylindracea* lipase, provided (–)-**28** with 79% yield. Benzyloxymethyl ethers were introduced at C(13) and C(23) and the C(25) silyl ether was cleaved (HF·pyridine, –20 °C) to afford the corresponding primary alcohol. Oxidation in the presence of a catalytic amount of Pr_4NRuO_4 and NMO[17] gave an intermediate aldehyde that was directly submitted to an allylation reaction under Keck's conditions.[13] This sequence afforded the homoallylic alcohol (–)-**29** as a single diastereoisomer in 60% yield. In order to get the C^{11}–C^{28} fragment of RK-397, a last asymmetric dihydroxylation step in the presence of an enriched AD-mix-β was performed and gave the expected polyol (–)-**30** as the major diastereoisomer (*dr* = 7:1), in 68% yield. A comparable diastereoselectivity was observed with $(DHQD)_2PYR$ but the yield was lower.



Scheme 5. Completion of the polyol synthesis. 1. MeOK, MeOH; 2. vinyl acetate, *Candida cylindracea* lipase; 3. BOMCl, $(iPr)_2NEt$, Bu_4NI cat., 40 °C; 4. HF·pyridine, –20 °C; 5. Pr_4NRuO_4 0.2 equiv., NMO, molecular sieves; 6. $Ti(OiPr)_4$ (0.1 equiv.), (*S*)-BINOL (0.2 equiv.), (allyl)$SnBu_3$, 0 °C; 7. AD-mix-β, $MeSO_2NH_2$; 8. acetone/$Me_2C(OMe)_2$, CSA cat., –10 °C; 9. (a) K_2CO_3, MeOH; (b) H_2, $Pd(OH)_2$/C; 10. acetone/$Me_2C(OMe)_2$, CSA cat.

The relative configurations at C(25) and C(27) were confirmed by Rychnovsky's ^{13}C NMR method.[12] Methanolysis (K_2CO_3, MeOH) of the polyol (–)-**30**, followed by hydrogenolysis of the benzyloxymethyl ethers and treatment with a mixture of acetone/$Me_2C(OMe)_2$ in the presence of a catalytic amount of camphorsulfonic acid, provided pentaacetonide **32**. The ^{13}C NMR spectrum of **32** exhibits signals at δ = 25.8, 25.6, 24.8 (doubled peak), 24.4, and 24.3 ppm that are typical for an *anti*/*anti* relative configuration of the diols at C(19)/C(21) and C(23)/C(25) and for the 1,2-diol at C(27)/C(28). Moreover, polyol (–)-**30** was protected at –10 °C as the corresponding triacetonide **31**, the ^{13}C NMR spectrum of which displays two different sets of signals at δ = 30.5 ppm (doubled peak) and δ = 20.3, 20.2 ppm typical of *syn* relative configurations of the diols at C(15)/C(17) and C(25)/C(27).

Conclusions

The complete polyol subunit of the polyene macrolide antibiotic RK-397 has been derived from dialkene *meso*-**20** in 17 steps, with the need to isolate only seven intermediates. In theory, our strategy can be used to generate a high diversity of stereoisomers by varying the conditions of reduction of oxoaldehyde intermediates resulting from the oxidative cleavage of our starting material.

Experimental Section

General: Commercial reagents (Fluka, Aldrich) were used without purification. Solvents were filtered prior to use (Innovative Technology). Light petroleum ether refers to the fraction with the boiling range 40–60 °C. Solutions after reactions and extractions were evaporated on a rotary evaporator under reduced pressure. Liquid/solid flash chromatography (FC): columns of silica gel (0.040–0.63 mm, Merck no. 9385 silica gel 60, 240–400 mesh). TLC for reaction monitoring: Merck silica gel $60F_{254}$ plates; detection by UV light; Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O] or $KMnO_4$. IR spectra: Perkin–Elmer 1420 spectrometer. ^1H NMR spectra: Bruker-ARX-400 spectrometer (400 MHz); δ in ppm relative to the solvent's residual ^1H signal ($CHCl_3$: δ = 7.27 ppm; CH_3OD: δ = 3.34 ppm; C_6H_6: δ = 7.3 ppm) as internal reference; all ^1H assignments were confirmed by 2D-COSY-45 spectra. ^{13}C NMR spectra: same instrument as above (100.6 MHz); δ in ppm relative to solvent's C signal ($CDCl_3$: δ = 77.0 ppm; CD_3OD: δ = 48.5 ppm; C_6D_6: δ = 128.5 ppm) as internal reference. MS: Nermag R-10-10C, chemical ionization (NH_3) mode. MALDI-TOF mass spectra were obtained at the Swiss Institute of Technology Mass Spectral Facility. Elemental analyses: Ilse Beetz, 96301 Kronach, Germany.

(1*R*,1′S,6*R*,6′*S*)-3,3′-Methylenebis{6-[(benzyloxy)methoxy]cyclohept-3-en-1-ol} (*meso*-11): Bu_3SnH (7.8 mL, 29.6 mmol) and AIBN (280 mg) were added to a solution of *meso*-**12**[10] (4.90 g, 7.41 mmol) in toluene (30 mL). The mixture was stirred at 80 °C for 3 h. The solvent was then evaporated, the residue taken up in MeCN (90 mL), and the solution washed with pentane (20 mL, 4 times) and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/light petroleum ether, 1:3) afforded a colorless oil that was taken up in MeOH containing K_2CO_3 (1.03 g, 7.41 mmol). This mixture was vigorously stirred at 25 °C for 4 h. The solution was then poured into water (100 mL) and extracted with $CHCl_3$ (100 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (CH_2Cl_2/MeOH, 97:3) afforded *meso*-**11** as a white solid (2.48 g, 66%).

Intermediate (1*R*,1′*S*,6*R*,6′*S*)-3,3′-Methylenebis{6-[(benzyloxy)methoxy]cyclohept-3-en-1-yl} Diacetate: IR (film): $\tilde{\nu}$ = 3090, 3065, 3030, 2940, 1740, 1610, 1495, 1455, 1370, 1240, 1165, 1100, 1080, 1045, 975, 735, 700, 645 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C):

δ = 7.39–7.29 (m, 10 H arom.), 5.54 (t, $^3J_{4,5a} = {}^3J_{4,5b}$ = 6.8 Hz, 2 H, 4-H, 4′-H), 4.79, 4.77 [2 d, $^2J_{H,H}$ = 14.2 Hz, 4 H, 2 CH_2(BOM)], 4.63, 4.60 (2 d, $^2J_{H,H}$ = 12.6 Hz, 4 H, 2 CH_2Ph), 4.52 (m, 2 H, 1-H, 1′-H), 3.56 (m, 2 H, 6-H, 6′-H), 2.73 (d, $^2J_{H,H}$ = 13.9 Hz, 1 H, 8-H), 2.64 (d, $^2J_{H,H}$ = 13.9 Hz, 1 H, 8-H), 2.42–2.36 (m, 6 H, 2-H, 2′-H, 5-H, 5′-H, 7-H, 7′-H), 2.26 (m, 2 H, 5-H, 5′-H), 2.09 (br. d, $^2J_{H,H}$ = 12.6 Hz, 2 H, 2-H, 2′-H), 2.03 [s, 6 H, 2 CH_3(OAc)], 1.82 (m, $^2J_{H,H}$ = 11.4 Hz, 2 H, 7-H, 7-H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 170.0 (s, 2 C=O), 137.8 (s, 2 C arom.), 137.1 [s, C(3), C(3′)], 128.4, 127.9, 127.8 (3 d, 10 C arom.), 124.5 [d, $^1J_{C,H}$ = 156 Hz, C(4), C(4′)], 92.7 [t, $^1J_{C,H}$ = 163 Hz, 2 CH_2(BOM)], 72.2 [d, $^1J_{C,H}$ = 144 Hz, C(6), C(6′)], 69.5 (t, $^1J_{C,H}$ = 143 Hz, 2 CH_2Ph), 69.2 [d, $^1J_{C,H}$ = 149 Hz, C(1), C(1′)], 49.8 [t, C(8)], 44.7 [t, $^1J_{C,H}$ = 129.6, C(7), C(7′)], 36.8 [t, $^1J_{C,H}$ = 126 Hz, C(2), C(2′)], 34.0 [t, $^1J_{C,H}$ = 128 Hz, C(5), C(5′)], 21.4 [q, $^1J_{C,H}$ = 129 Hz, 2 CH_3(OAc)] ppm. MALDI-MS: *m*/*z* (%) = 615 (100) [M + Na^+].

***meso*-11:** IR (film): $\tilde{\nu}$ = 3426, 2932, 2890, 1599, 1454, 1377, 1163, 1109, 1032, 945, 743, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.37–7.29 (m, 10 H arom.), 5.53 (t, $^3J_{4,5a} = {}^3J_{4,5b}$ = 6.8 Hz, 2 H, 4-H, 4′-H), 4.80, 4.78 [2 d, $^2J_{H,H}$ = 10.2 Hz, 4 H, 2 CH_2(BOM)], 4.65, 4.61 (2 d, $^2J_{H,H}$ = 12.0 Hz, 4 H, 2 CH_2Ph), 3.70–3.55 (m, 4 H, 1-H, 1′-H, 6-H, 6′-H), 2.73–2.69 (2 d, $^2J_{H,H}$ = 15.1 Hz, 2 H, 8-H_2), 2.39–2.28 (m, 8 H, 2-H, 2′-H, 5-H_2, 5′-H_2, 7-H, 7′-H), 2.18 (br. d, $^2J_{H,H}$ = 14.2 Hz, 2 H, 2-H, 2′-H), 1.88 (m, 2 H, 7-H, 7′-H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 138.0 [s, 2 C arom, C(3), C(3′)], 128.6, 128.0, 127.8 (3 d, 10 C arom.), 123.9 [d, $^1J_{C,H}$ = 156 Hz, C(4), C(4′)], 92.8 [t, $^1J_{C,H}$ = 163 Hz, 2 CH_2(BOM)], 72.5 [d, $^1J_{C,H}$ = 143 Hz, C(6), C(6′)], 69.7 (t, $^1J_{C,H}$ = 142 Hz, 2 CH_2Ph), 67.5 [d, $^1J_{C,H}$ = 153 Hz, C(1), C(1′)], 50.7 [t, $^1J_{C,H}$ = 125 Hz, C(8)], 47.2 [t, $^1J_{C,H}$ = 126 Hz, C(7), C(7′)], 40.1 [t, $^1J_{C,H}$ = 127 Hz, C(2), C(2′)], 33.7 [t, $^1J_{C,H}$ = 121 Hz, C(5), C(5′)] ppm. CI-MS: *m*/*z* (%) = 509 (100) [M + H^+]. MALDI-MS: *m*/*z* = 531 [M + Na^+]. $C_{31}H_{40}O_6$ (508.651): calcd. C 73.20, H 7.93; found C 72.48, H 7.79.

(3*S*,5*R*,7*R*,9*R*,11*S*,13*R*)-3,13-Bis[(benzyloxy)methoxy]pentadecane-1,5,7,9,11,15-hexaol [(±)-14] and (3*S*,5*R*,7*R*,3′*S*,5′*S*,7′*R*)-3,13-Bis[(benzyloxy)methoxy]pentadecane-1,5,7,9,11,15-hexaol (15): A solution of *meso*-**11** (0.30 g, 0.59 mmol) in anhydrous CH_2Cl_2 (15 mL) was ozonolyzed at –78 °C for 5 min. A stream of dry O_2 was then passed through the solution for 2 min, and Me_2S (175 μL, 2.36 mmol) was added dropwise. After stirring at –78 °C for 15 min, the solvent was evaporated at –20 °C. The residue was taken up in MeCN/AcOH (3:1, 10 mL) at 0 °C, and $(Me_4N)BH(OAc)_3$ (2.75 g, 10.6 mmol) was added portionwise. After the mixture had been stirred at 0 °C for 4 h, the solvents were evaporated. The residue was diluted with EtOAc (30 mL) and poured onto ice (20 mL). The mixture was neutralized with solid $NaHCO_3$ and extracted with EtOAc (10 mL, 4 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude hemiacetals were dissolved in MeOH (8 mL) and treated with $NaBH_4$ (180 mg, 4.72 mmol) at 25 °C for 30 min. AcOH was then added (500 μL), and after stirring at 25 °C for 5 min, the solution was poured into a sat. aq. solution of $NaHCO_3$ (15 mL) and extracted with EtOAc (15 mL, 5 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (CH_2Cl_2/MeOH, 14:1, 1% NEt_3) afforded **15** (55 mg) and (±)-**14** (166 mg; 65% combined yield), both as colorless oils.

(±)-14: IR (film): $\tilde{\nu}$ = 3385, 3065, 3030, 2940, 1560, 1460, 1380, 1210, 1165, 1035, 825, 740, 700, 670 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz, 25 °C): δ = 7.39–7.27 (m, 10 H arom.), 4.83 [d, $^2J_{H,H}$ = 11.9 Hz, 2 H, CH_2(BOM)], 4.81 [d, $^2J_{H,H}$ = 11.9 Hz, 2 H, CH_2(BOM)], 4.65 (s, 4 H, 2 CH_2Ph), 4.13–3.93 (m, 6 H, 3-H, 5-H, 7-H, 9-H, 11-H, 13-H), 3.72 (t, $^3J_{H,H}$ = 6.7 Hz, 4 H, 1-H_2, 15-H_2), 1.97–1.47 (m, 14 H, 2-H_2, 4-H_2, 6-H_2, 8-H_2, 10-H_2, 12-H_2, 14-H_2) ppm. ^{13}C NMR (CD_3OD, 100.6 MHz, 25 °C): δ = 139.3 (s, 2 C arom.), 129.4, 128.9, 128.7 (3 d, 10 C arom.), 94.7 [t, 2 CH_2(BOM)], 74.5, 74.4 [2 d, C(3), C(13)], 70.7 (t, 2 CH_2Ph), 68.3, 68.1, 66.6, 66.5 [4 d, C(5), C(7), C(9), C(11)], 46.5, 46.2, 46.0, 45.9, 44.1, 44.0, 43.6 [7 t, C(2), C(4), C(6), C(8), C(10), C(12), C(14)] ppm. MALDI-MS: *m*/*z* (%) = 604 (100) [M + Na^+]. $C_{31}H_{48}O_{10}$ (580.71): calcd. C 64.12, H 8.33; found C 64.37, H 8.30.

15: IR (film): $\tilde{\nu}$ = 3380, 3030, 2940, 1495, 1455, 1435, 1385, 1165, 1045, 850, 740, 700, 665 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz, 25 °C): δ = 7.38–7.27 (m, 10 H arom.), 4.82 [d, $^2J_{H,H}$ = 9.2 Hz, 2 H, CH_2(BOM)], 4.81 [d, $^2J_{H,H}$ = 9.2 Hz, 2 H, CH_2(BOM)], 4.65 [s, 4 H, 2 CH_2Ph], 4.02–3.92 [m, 6 H, 3-H, 5-H, 7-H, 9-H, 11-H, 13-H], 3.73–3.68 [m, 4 H, 1-H_2, 15-H_2], 1.93–1.54 [2 m, 14 H, 2-H_2, 4-H_2, 6-H_2, 8-H_2, 10-H_2, 12-H_2, 14-H_2] ppm. ^{13}C NMR [CD_3OD, 100.6 MHz]: δ = 139.3 [s, 2 C arom.], 129.4, 128.9, 128.7 [3 d, 10 C arom.], 94.7 [t, $^1J_{C,H}$ = 161 Hz, 2 CH_2(BOM)], 74.5 [d, $^1J_{C,H}$ = 142 Hz, C(3), C(13)], 70.7 [t, $^1J_{C,H}$ = 141 Hz, 2 CH_2Ph], 70.3, 68.7 [2 d, $^1J_{C,H}$ = 140, 161 Hz, C(5), C(7), C(9), C(11)], 59.6 [t, $^1J_{C,H}$ = 142 Hz, C(1), C(15)], 47.1, 45.4, 45.3, 43.7 [4 t, C(2), C(4), C(6), C(8), C(10), C(12), C(14)] ppm. MALDI-MS: *m*/*z* (%) = 604 (100) [M + Na^+].

(3*S*)-3-[(Benzyloxy)methoxy]-4-[{(4*R*,6*R*)-6-[(4*R*,6*S*)-6-{(2*R*)-2-[(benzyloxy)methoxy]-4-hydroxybutyl}-2,2-dimethyl-1,3-dioxan-4-yl]methyl}-2,2-dimethyl-1,3-dioxan-4-yl]butan-1-ol [(±)-16]: A solution of (±)-**14** (260 mg, 0.448 mmol) in 2,2-dimethoxypropane/acetone (20 mL/2 mL) was stirred in the presence of *p*TsOH (35 mg) at 0 °C for 45 min. The mixture was then neutralized with solid Na_2CO_3, filtered, and concentrated. The residue was taken up in CH_2Cl_2 (15 mL), PPTS (30 mg) was added, and the mixture was stirred for 15 min at 25 °C. After neutralization with solid Na_2CO_3, filtration and evaporation, the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 97:3) to afford (±)-**16** (190 mg, 64%) as a pale-yellow oil. IR (film): $\tilde{\nu}$ = 3455, 2985, 2940, 1450, 1380, 1220, 1165, 1110, 1040, 740, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.36–7.28 (m, 10 H arom.), 4.79 [s, 4 H, 2 CH_2(BOM)], 4.67, 4.61 (2 d, $^2J_{H,H}$ = 11.8 Hz, 4 H, 2 CH_2Ph), 4.04–3.90 (m, 6 H, 3-H, 4′-H, 6′-H, 4‴-H, 6‴-H, 2^{IV}-H), 3.80–3.72 (m, 4 H, 1-H_2, 4^{IV}-H_2), 2.48 (t, $J_{H,OH}$ = 5.9 Hz, 2 H, 2 OH), 1.92–1.86 (m, 4 H, 4-H, 5′-H, 5‴-H, 1^{IV}-H), 1.75–1.72 (m, 3 H, 4-H, 1″-H, 1^{IV}-H), 1.67–1.55 (m, 4 H, 2-H, 5′-H, 5‴-H, 3^{IV}-H), 1.52–1.41 (m, 3 H, 2-H, 1″-H, 3^{IV}-H), 1.39, 1.35, 1.33, 1.30 [4 s, 12 H, 2 CH_3-C(2′), 2 CH_3C(2‴)] ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 137.6 (s, 2 C arom.), 128.5, 127.8, 127.7 (3 d, 10 C arom.), 100.4 [s, C(2′)], 98.5 [s, C(2‴)], 93.7 [t, 2 CH_2(BOM)], 73.9, 73.6 [2 d, C(3), C(2^{IV})], 69.9 (t, 2 CH_2Ph), 66.0, 64.9, 63.5, 62.2 [4 d, C(4′), C(6′), C(4‴), C(6‴)], 59.8 [t, C(1), C(4^{IV})], 42.1, 41.0, 40.6, 39.1, 37.6 [5 t, C(4), C(5′), C(1″), C(5‴), C(1^{IV})], 36.5, 36.4 [2 t, C(2), C(3^{IV})], 30.2, 19.8 [2 q, 2 CH_3C(5‴)], 24.6 [q, 2 CH_3C(5′)] ppm. MALDI-MS: *m*/*z* (%) = 683 (100) [M + Na^+]. $C_{37}H_{56}O_{10}$ (660.84): calcd. C 67.25, H 8.54; found C 67.13, H 8.49.

(3*S*,5*R*,7*R*,3′*S*,5′*S*,7′*R*)-3,13-Bis[(benzyloxy)methoxy]-5,7;9,11-di-*O*-isopropylidenepentadecane-1,5,7,9,11,15-hexaol (17): A solution of **15** (20 mg, 0.034 mmol) in 2,2-dimethoxypropane/acetone (1.5 mL/0.15 mL) was stirred in the presence of *p*TsOH (3 mg) at 0 °C for 45 min. The mixture was then neutralized with solid Na_2CO_3, filtered, and concentrated. The residue was taken up in CH_2Cl_2 (2 mL), PPTS (3 mg) was added, and the mixture was stirred for 15 min at 25 °C. After neutralization with solid Na_2CO_3,

filtration, and evaporation, the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 97:3) to afford **17** (10 mg, 44%) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.39–7.28 (m, 10 H arom.), 4.82, 4.80 [2 d, $^2J_{H,H}$ = 8.6 Hz, 4 H, 2 CH_2(BOM)], 4.70, 4.64 (2 d, $^2J_{H,H}$ = 11.9 Hz, 4 H, 2 CH_2Ph), 4.07–3.95 (m, 6 H, 3-H, 5-H, 7-H, 9-H, 11-H, 13-H), 3.87–3.74 (m, 4 H, 1-H_2, 15-H_2), 2.44 (t, $^3J_{OH,H}$ = 5.5 Hz, 2 H, 2×OH), 1.96–1.87 (m, 4 H, 4-H, 6-H, 10-H, 12-H), 1.82–1.74 (m, 3 H, 4-H, 8-H, 12-H), 1.67–1.61 (m, 2 H, 6-H, 10-H), 1.48 (dt, $^2J_{H,H}$ = 12.8, $^3J_{H,H}$ = 2.3 Hz, 2 H, 2-H, 14-H), 1.42 (m, 1 H, 8-H), 1.41, 1.37 (2 s, 6 H, 4 CH_3), 1.19 (m, 2 H, 2-H, 14-H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 137.7 (s, 2 C arom.), 128.7, 128.0, 127.8 (3 d, 10 C arom.), 98.5 [s, 2 C$(CH_3)_2$], 93.8 [t, $^1J_{C,H}$ = 159 Hz, 2 CH_2(BOM)], 73.8 [d, $^1J_{C,H}$ = 141 Hz, C(3), C(13)], 70.1 (t, $^1J_{C,H}$ = 143 Hz, 2 CH_2Ph), 66.0, 65.3 [2 d, $^1J_{C,H}$ = 137, 141 Hz, C(5), C(7), C(9), C(11)], 60.0 [t, $^1J_{C,H}$ = 143 Hz, C(1), C(15)], 42.8 [t, $^1J_{C,H}$ = 125 Hz, C(8)], 41.2, [t, $^1J_{C,H}$ = 126 Hz, C(6), C(10)], 37.1 [t, $^1J_{C,H}$ = 126 Hz, C(2), C(14)], 36.6 [t, $^1J_{C,H}$ = 126 Hz, C(4), C(12)], 30.3, 19.9 (2 q, $^1J_{C,H}$ = 130, 126 Hz, 2 CH_3), 19.9 (q, $^1J_{C,H}$ = 126 Hz, CH_3) ppm. MALDI-MS: *m*/*z* (%) = 684 (100) [M + H + Na$^+$], 700 (60) [M + H+ K$^+$].

4,4′-Methylenebis[(1*R*,1′*S*,2*S*,2′*R*,6*R*,6′*S*)-6-acetoxy-2-chlorocyclohept-3-en-1-yl]bis(4-methoxybenzoate) (*meso*-19): BCl_3 (1 M in CH_2Cl_2, 168 mmol, 168 mL) was added dropwise to a solution of *meso*-**18** (13 g, 37.71 mmol) in CH_2Cl_2 (650 mL) at 0 °C. After 30 min at 0 °C, the mixture was poured into a sat. aq. solution of $NaHCO_3$ (800 mL) and extracted with CH_2Cl_2 (600 mL, twice). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was taken up in pyridine (220 mL) and treated with PMBzCl (15.2 mL, 112 mmol) and DMAP (400 mg) at 0 °C. After 30 min the reaction was allowed to reach 25 °C and stirred for 12 h. The solvent was evaporated in vacuo. The residue was taken up in EtOAc (500 mL) and washed with 1 M HCl (80 mL) and a sat. aq. solution of $NaHCO_3$ (60 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (Et_2O/pentane, 1:1) afforded *meso*-**19** as a pale-yellow foam (22.6 g, 87%). IR (KBr): $\tilde{\nu}$ = 3450, 2925, 2855, 1740, 1715, 1605, 1510, 1460, 1370, 1255, 1170, 1105, 1030, 965, 850, 770, 695 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 8.01, 6.92 (2 d, $^3J_{H,H}$ = 8.6 Hz, 8 H arom.), 5.89 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 3-H, 3′-H), 5.28 (dt, $^3J_{H,H}$ = 10.5, 3.1 Hz, 2 H, 1-H, 1′-H), 4.77 (br. d, $^3J_{H,H}$ = 8.0 Hz, 2-H, 2′-H), 4.75 (tt, $^3J_{H,H}$ = 10.5, 2.5 Hz, 2 H, 6-H, 6′-H), 3.87 (s, 6 H, 2 OCH_3), 2.80 (m, 4 H, 5-H, 8-H_2, 5′-H), 2.72 (q, $^2J_{H,H}$ = $^3J_{H,H}$ = 10.5 Hz, 7-H, 7′-H), 2.31 (br. d, $^2J_{H,H}$ = 10.5 Hz, 2 H, 7-H, 7′-H), 2.19 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 2.5 Hz, 5-H, 5′-H), 2.05 [s, 6 H, 2 CH_3(OAc)] ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 169.9 (s, 2 C=O), 165.3 (s, 2 C arom.), 163.6 (s, 2 C=O), 141.7 (s, 2 C arom.), 131.8 (d, $^1J_{C,H}$ = 162 Hz, 4 C arom.), 125.3 [d, $^1J_{C,H}$ = 162 Hz, C(3), C(3′)], 122.0 [s, C(4), C(4′)], 113.6 (d, $^1J_{C,H}$ = 157 Hz, 4 C arom.), 70.0 [d, $^1J_{C,H}$ = 143 Hz, C(1), C(1′)], 68.6 [d, $^1J_{C,H}$ = 137 Hz, C(6), C(6′)], 59.2 [d, $^1J_{C,H}$ = 150 Hz, C(2), C(2′)], 55.3 (q, $^1J_{C,H}$ = 144 Hz, 2 OCH_3), 51.4 [t, $^1J_{C,H}$ = 128 Hz, C(8)], 36.5 [t, $^1J_{C,H}$ = 128 Hz, C(7), C(7′)], 36.0 [t, $^1J_{C,H}$ = 128 Hz, C(5), C(5′)], 21.1 [q, $^1J_{C,H}$ = 129 Hz, 2 CH_3(OAc)]. CI-MS: *m*/*z* (%) = 706 (88) [M + NH_4^+], 689 (4) [M]$^+$, 670 (44), 170 (100), 135 (85). $C_{35}H_{38}Cl_2O_{10}$ (689.58): calcd. C 60.96, H 5.55; found C 61.05, H 5.72.

4,4′-Methylenebis[(1*R*,1′*S*,6*S*,6′*R*)-6-acetoxycyclohept-3-en-1-yl]bis(4-methoxybenzoate) (*meso*-20): Bu_3SnH (12.7 mL, 47.85 mmol) and AIBN (500 mg) were added to a solution of *meso*-**19** (11 g, 15.95 mmol) in toluene (80 mL) and the mixture was stirred at 80 °C for 8 h. The solvent was then evaporated and the residue taken up in MeCN (300 mL). The solution was washed with pentane (50 mL, 4 times) and concentrated in vacuo. Flash chromatography on silica gel (Et_2O/pentane, 2:1) afforded *meso*-**20** (7.4 g, 75%) as a white solid. M.p. 94–95 °C. IR (KBr): $\tilde{\nu}$ = 3060, 2955, 2850, 1735, 1705, 1605, 1515, 1465, 1440, 1370, 1345, 1245, 1175, 1105, 1025, 985, 950, 905 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 8.07, 6.62 (2 d, $^3J_{H,H}$ = 8.8 Hz, 8 H arom.), 5.42 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, 3-H, 3′-H), 4.96 (dddd, $^3J_{H,H}$ = 10.5, 10.5, 3.1, 3.1 Hz, 2 H, 1-H, 1′-H), 4.67 (dddd, $^3J_{H,H}$ = 10.6, 10.6, 2.1, 2.1 Hz, 2 H, 6-H, 6′-H), 3.21 (s, 6 H, 2 OCH_3), 2.72, 2.51 (2 d, $^3J_{H,H}$ = 13.2 Hz, 2 H, 8-H), 2.46 (m, 2 H, 7-H, 7′-H), 2.39 (m, 4 H, 2-H_2, 2′-H_2), 2.38 (m, 2 H, 5-H, 5′-H), 2.27 (d, $^2J_{H,H}$ = 13.2 Hz, 5-H, 5′-H), 1.98 (m, 2 H, 7-H, 7′-H), 1.64 [s, 6 H, 2 CH_3(OAc)] ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 169.8 (s, 2 C=O), 165.2 (s, 2 C arom.), 163.2 (s, 2 C=O), 137.3 [s, C(4), C(4′)], 131.5 (d, $^1J_{C,H}$ = 163 Hz, 4 C arom.), 124.0 [d, $^1J_{C,H}$ = 156 Hz, C(3), C(3′)], 122.7 (s, 2 C arom.), 113.4 (d, $^1J_{C,H}$ = 160 Hz, 4 C arom.), 69.3 [d, $^1J_{C,H}$ = 151 Hz, C(6), C(6′)], 68.7 [d, $^1J_{C,H}$ = 150 Hz, C(1), C(1′)], 55.3 (q, $^1J_{C,H}$ = 144 Hz, 2 OCH_3), 49.8 [t, $^1J_{C,H}$ = 132 Hz, C(8)], 43.3 [t, $^1J_{C,H}$ = 124 Hz, C(5), C(5′)], 36.5 [t, $^1J_{C,H}$ = 131 Hz, C(7), C(7′)], 33.3 [t, $^1J_{C,H}$ = 130 Hz, C(2), C(2′)], 21.1 [q, $^1J_{C,H}$ = 125 Hz, 2 CH_3(OAc)]. CI-MS: *m*/*z* (%) = 638 (100) [M + NH_4^+], 256 (6), 196 (16), 135 (21). $C_{35}H_{40}O_{10}$ (620.69): calcd. C 67.73, H 6.50; found C 67.60, H 6.47.

(1*S*,6*R*)-6-Acetoxy-4-[{(1′*R*,2′*S*,4′*R*,6′*S*)-6-acetoxy-1,2-dihydroxy-4-[(4-methoxybenzoyl)oxy]cyclohept-1-yl}methyl]cyclohept-3-en-1-yl 4-Methoxybenzoate [(–)-21]: A suspension of *meso*-**20** (14 g, 22.56 mmol) in a mixture of *t*BuOH, H_2O, and MeCN (140/140/28 mL) was heated at 80 °C for 30 min. The solution was then cooled to 0 °C and $Me_2SO_2NH_2$ (4.3 g, 45.12 mmol) was added. An enriched AD-mix-α [70 g; $K_3Fe(CN)_6$ (47.7 g), K_2CO_3 (20.05 g), $(DHQ)_2PHAL$ (1.88 g), $K_2OsO_2(OH)_4$ (370 mg)] was added in four equivalent portions every 6 h. After stirring for 24 h at 0 °C, the mixture was diluted with EtOAc (100 mL) and H_2O (100 mL). Na_2SO_3 (5.7 g, 45.12 mmol) was then added and the solution was stirred at 25 °C for 45 min. The solution was poured into H_2O (200 mL) and extracted with EtOAc (200 mL, 3 times). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) afforded (–)-**21** (13.3 g, 90%) as a white foam. $[\alpha]_D^{20}$ = –1, $[\alpha]_{577}^{20}$ = –13, $[\alpha]_{546}^{20}$ = –53, $[\alpha]_{435}^{20}$ = –314, $[\alpha]_{405}^{20}$ = –370 (*c* = 0.90, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3495, 2930, 2850, 1720, 1605, 1510, 1460, 1370, 1255, 1170, 1105, 1025, 985, 950, 905, 850, 815, 770 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.96, 6.90 (2 d, $^3J_{H,H}$ = 8.8 Hz, 8 H arom.), 5.71 (t, $^3J_{H,H}$ = 6.2 Hz, 1 H, 3-H), 5.18 (tt, $^3J_{H,H}$ = 10.6, 4.4 Hz, 1 H, 1-H), 4.92 (m, 1 H, 6-H), 4.90 (m, 1 H, 6′-H), 4,83 (m, 1 H, 4′-H), 3.86 (s, 6 H, 2 OCH_3), 3.50 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, 2′-H), 2.59 (d, $^2J_{H,H}$ = 13.2 Hz, 1 H, 5-H), 2.56 (m, 2 H, 5′-H, 8-H), 2.51 (m, 1 H, 5′-H), 2.44, 2.41 (2 m, 2 H, 2-H_2), 2.35 (m, 1 H, 5-H), 2.33 (m, 2 H, 3-H), 2.30 (m, 1 H, 8-H), 2.21 (d, $^2J_{H,H}$ = 14.1, 1 H, 7′-H), 2.06, 2.04 [2 s, 6 H, 2 CH_3(OAc)], 2.04 (m, 1 H, 7′-H), 2.02 (m, 2 H, 3′-H), 1.97 (d, $^2J_{H,H}$ = 12.4 Hz, 1 H, 7-H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 171.2, 169.9 (2 s, 2 C=O), 165.5, 165.2 (2 s, 2 C arom.), 163.4 (s, 2 C=O), 136.9 [s, C(4)], 131.6, 131.5 (2 d, $^1J_{C,H}$ = 163 Hz, 4 C arom.), 127.3 [d, $^1J_{C,H}$ = 161 Hz, C(3)], 122.7, 122.5 (s, 2 C arom.), 113.6 (d, $^1J_{C,H}$ = 160 Hz, 4 C arom.), 74.2 [s, C(1′)], 72.7 [d, $^1J_{C,H}$ = 141 Hz, C(2′)], 69.5 [d, $^1J_{C,H}$ = 144 Hz, C(1)], 69.3 [d, $^1J_{C,H}$ = 142 Hz, C(6)], 69.2 [d, $^1J_{C,H}$ = 142 Hz, C(6′)], 66.2 [d, $^1J_{C,H}$ = 141 Hz, C(4′)], 55.4 (q, $^1J_{C,H}$ = 144 Hz, 2 OCH_3), 47.9 [t, $^1J_{C,H}$ = 125 Hz, C(8)], 43.3, 42.6, 40.7, 39.4, 33.7 [4 t, $^1J_{C,H}$ = 131, 128, 134, 128 Hz, C(2), C(7), C(3′), C(5′), C(7′)], 37.6 [t, $^1J_{C,H}$ = 131 Hz, C(5)], 21.3, 21.2 [2 q, $^1J_{C,H}$ = 131 Hz, 2 CH_3(OAc)] ppm. CI-MS: *m*/*z* (%) = 672 (74) [M

+ NH_4^+], 613 (9), 595 (32), 170 (100), 135 (52). $C_{35}H_{42}O_{12}$ (654.70): calcd. C 64.21, H 6.47; found C 64.35, H 6.41.

(α*S*,1*S*,3*S*,5*R*,7*R*)-5-Acetoxy-7-[{(4*S*,6*R*)-6-acetoxy-4-[(4-methoxybenzoyl)oxy]cyclohept-1-en-1-yl}methyl]-3-[(4-methoxybenzoyl)oxy-7-hydroxycyclohept-1-yl] α-Methoxy-α-(trifluoromethylphenyl)acetate [(+)-22]: (*S*)-(+)-MPTACl (20 μL) and DMAP (3 mg) were added to a solution of (–)-**21** (20 mg, 0.03 mmol) in pyridine (500 μL) at 0 °C and the mixture stirred at 0 °C for 1 h. It was then poured into a sat. aq. solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (10 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (CH_2Cl_2/MeOH, 99:1) afforded (+)-**22** (25 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$ = +0.4, $[\alpha]_{546}^{20}$ = +9, $[\alpha]_{435}^{20}$ = +21, $[\alpha]_{405}^{20}$ = +24 (*c* = 0.5, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3415, 2955, 2845, 1730, 1715, 1605, 1580, 1510, 1460, 1420, 1370, 1315, 1255, 1170, 1100, 1025, 955, 850, 830, 770, 735, 720 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.96, 6.91 [2 m, 8 H arom(PMBz)], 7.56, 7.38 [2 m, 5 H arom(MPTA)], 5.62 (t, $^3J_{H,H}$ = 6.2 Hz, 1 H, 2′-H), 5.30 (dddd, $^3J_{H,H}$ = 10.5, 10.5, 4.9, 4.9 Hz, 1 H, 4′-H), 4.83 (m, 2 H, 6′-H, 5-H), 4.79 (dd, $^3J_{H,H}$ = 9.2, 1.2 Hz, 1 H, 1-H), 4.76 (m, 1 H, 3-H), 3.87 (s, 6 H, 2 OCH_3), 3.63 (s, 3 H, OCH_3), 2.61–1.83 (m, 16 H, 2-H_2, 4-H_2, 6-H_2, 8-H_2, 3′-H_2, 5′-H_2, 7′-H_2), 2.05, 2.01 [2 s, 6 H, 2 CH_3(OAc)] ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 170.4, 170.0 (2 s, 2 C=O), 165.6 (s, C=O), 165.2, 165.0 (2 s, 2 C arom.), 163.5, 163.4 (s, 2 C=O), 135.6 (s, C arom.), 132.3 [s, C(1′)], 131.6, 131.5 (2 d, $^1J_{C,H}$ = 162 Hz, 4 C arom.), 129.6, 128.4 (2 d, $^1J_{C,H}$ = 162, 158 Hz, 4 C arom.), 127.5 [d, $^1J_{C,H}$ = 159 Hz, C(2′)], 127.1 (d, $^1J_{C,H}$ = 162 Hz, 2 C arom.), 122.7, 122.4 (2 s, 2 C arom.), 113.6, 113.5 (2 d, $^1J_{C,H}$ = 161 Hz, 4 C arom.), 78.5 [d, C(5)], 73.8 [s, C(7)], 69.2 [d, $^1J_{C,H}$ = 142 Hz, C(6′)], 68.8 [d, $^1J_{C,H}$ = 140 Hz, C(3)], 68.5 [d, $^1J_{C,H}$ = 141 Hz, C(4′)], 66.1 [d, $^1J_{C,H}$ = 148 Hz, C(1)], 55.8 (q, $^1J_{C,H}$ = 143 Hz, OCH_3), 55.4 (q, $^1J_{C,H}$ = 142 Hz, 2 OCH_3), 46.6 [t, $^1J_{C,H}$ = 128 Hz, C(8)], 41.5 [t, $^1J_{C,H}$ = 131 Hz, C(6)], 40.8 [t, $^1J_{C,H}$ = 130 Hz, C(4)], 40.1 [t, $^1J_{C,H}$ = 129 Hz, C(5′)], 39.5 [t, $^1J_{C,H}$ = 133 Hz, C(7′)], 34.0 [t, $^1J_{C,H}$ = 132 Hz, C(3′)], 33.7 [t, $^1J_{C,H}$ = 130 Hz, C(2)], 21.2, 20.7 [2 q, $^1J_{C,H}$ = 131, 127 Hz, 2 CH_3(OAc)] ppm. ^{19}FNMR (377 MHz, $CDCl_3$/$CFCl_3$, 25 °C): δ = –71.78 (s, 3 F, CF_3) ppm. CI-MS: *m*/*z* (%) = 888 (30) [M + NH_4^+], 672 (23), 657 (58), 642 (15), 570 (100). $C_{45}H_{49}F_3O_{14}$ (654.70): calcd. C 62.06, H 5.67; found C 61.86, H 5.72.

(1*S*,6*R*)-6-Hydroxy-4-[{(1*R*,2*S*,4*S*,6*R*)-1,2,6-trihydroxy-4-[(4-methoxybenzoyl)oxy]cyclohept-1-yl}methyl]cyclohept-3-en-1-yl 4-Methoxybenzoate [(–)-23]: $Mg(OMe)_2$ (0.8 M in MeOH, 122 mmol, 153 mL) was added dropwise to a solution of (–)-**21** (10 g, 15.27 mmol) in MeOH (500 mL), and the mixture was stirred at 25 °C for 7 h. Oxalic acid (122 mmol, 11 g) was then added and the mixture was stirred at 0 °C for 1 h. The solution was filtered through a pad of silica gel and concentrated in vacuo. Flash chromatography on silica gel (CH_2Cl_2/MeOH, 96:4) afforded (–)-**23** (6.62 g, 76%) as a white solid. M.p. 146–148 °C. $[\alpha]_D^{20}$ = –6, $[\alpha]_{577}^{20}$ = –13 (*c* = 0.2, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3430, 2935, 2850, 1735, 1715, 1710, 1685, 1610, 1585, 1510, 1460, 1420, 1355, 1320, 1285, 1165, 1115, 1085, 1060, 1030, 990, 840, 770, 695 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.91, 6.90 (2 m, 8 H arom.), 5.62 (t, $^3J_{H,H}$ = 6.2 Hz, 1 H, 3-H), 5.03 (t, $^3J_{H,H}$ = 9.2 Hz, 1 H, 4′-H), 4.93 (t, $^3J_{H,H}$ = 9.8 Hz, 1 H, 1-H), 4.12 (m, 1 H, 6-H), 3.91 (m, 1 H, 6′-H), 3.84 (s, 6 H, 2 OCH_3), 3.57 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, 2′-H), 2.61, 2.18 (2 m, 2 H, 3′H_2), 2.61–2.18, 2.49–2.00, 2.26–1.75 (3m, 8 H, 5-H_2, 7-H_2, 5′-H_2, 7′-H_2), 2.47 (m, 2 H, 8-H_2), 2.39 (dd, $^2J_{H,H}$ = 14.7, $^3J_{H,H}$ = 6.2 Hz, 1 H, 2-H), 2.15 (d, $^2J_{H,H}$ = 14.7 Hz, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 165.7, 163.5 (2 s, 2 C arom.), 158.7, 157.6 (2 s, 2 C arom.), 137.9 [s, C(4)], 131.6 (d, $^1J_{C,H}$ = 169 Hz, 4 C arom.), 126.7 [d, $^1J_{C,H}$ = 158 Hz, C(3)], 122.6, 122.5 (2 s, 2 C arom.), 113.6 (d, $^1J_{C,H}$ = 169 Hz, 4 C arom.), 77.8 [s, C(1′)], 73.3 [d, $^1J_{C,H}$ = 147 Hz, C(2′)], 69.9 [d, $^1J_{C,H}$ = 147 Hz, C(4′)], 69.1 [d, $^1J_{C,H}$ = 142 Hz, C(1)], 66.5 [d, $^1J_{C,H}$ = 141 Hz, C(6′)], 65.6 [d, $^1J_{C,H}$ = 145 Hz, C(6)], 55.4 (q, $^1J_{C,H}$ = 145 Hz, 2 OCH_3), 49.4, 42.7, 42.4, 40.0 [4 t, $^1J_{C,H}$ = 128, 128, 135, 136 Hz, C(5), C(7), C(5′), C(7′)], 46.0 [t, $^1J_{C,H}$ = 132 Hz, C(3′)], 33.5 [t, $^1J_{C,H}$ = 133 Hz, C(8)] ppm. CI-MS: *m*/*z* (%) = 571 (10) [M + H], 152 (57), 135 (100). $C_{31}H_{38}O_{10}\cdot H_2O$ (588.64): calcd. C 63.25, H 6.84; found C 63.03, H 6.59.

(1*S*,6*R*)-6-Hydroxy-4-{(2*R*,4*S*,6*R*)-2,4,8-trihydroxy-6-[(4-methoxybenzoyl)oxy]octyl}cyclohept-3-en-1-yl 4-Methoxybenzoate [(–)-24]: $NaIO_4$ (1.42 g, 6.66 mmol) was added to a solution of (–)-**23** (1.9 g, 3.33 mmol) in dioxane/H_2O (68 mL/11 mL). The mixture was stirred at 25 °C for 13 h and then poured into brine (200 mL). The aqueous layer was extracted with $CHCl_3$ (100 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residual solid was taken up in acetic acid (40 mL) and treated with $Me_4NBH(OAc)_3$ (11.1 g, 42.20 mmol) at 25 °C for 14 h. The solvent was then evaporated and the residue taken up into EtOAc/ice (50 mL/100 mL). The mixture was vigorously stirred for 10 min and solid $NaHCO_3$ was added to reach pH 7. The mixture was then extracted with EtOAc (80 mL, 4 times). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford a pale-yellow foam that was either used directly for the next steps. An analytical sample was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 12:1) to afford (–)-**24** as a white foam. $[\alpha]_D^{20}$ = –8, $[\alpha]_{577}^{20}$ = –12, $[\alpha]_{546}^{20}$ = –13, $[\alpha]_{435}^{20}$ = –17, $[\alpha]_{405}^{20}$ = –20 (*c* = 0.2, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3420, 2935, 1705, 1605, 1510, 1460, 1420, 1320, 1260, 1170, 1100, 1025, 950, 915, 845, 770, 730 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.91, 6.85 (2 m, 8 H arom.), 5.56 (t, $^3J_{H,H}$ = 6.2 Hz, 3-H), 5.42 (m, 1 H, 6′-H), 4.85 (m, 1 H, 1-H), 4.14 (m, 1 H, 4′-H), 4.11 (m, 1 H, 2′-H), 3.83, 3.80 (2 s, 6 H, 2 OCH_3), 3.79 (m, 1 H, 6-H), 3.71 (t, $^3J_{H,H}$ = 4.9 Hz, 8′-H2), 2.49 (dt, $^2J_{H,H}$ = 11.7, $^3J_{H,H}$ = 9.8 Hz, 1 H, 7-H), 2.46 (m, 1 H, 5-H), 2.38 (m, 2 H, 2-H_2), 2.35 (m, 1 H, 5-H), 2.16 (m, 2 H, 1′-H_2), 2.06 (dt, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 4.9 Hz, 1 H, 5′-H), 2.04 (m, 1 H, 5′-H), 1.93 (m, 1 H, 7-H), 1.83 (m, 1 H, 7′-H), 1.81 (m, 1 H, 5′-H), 1.53 (m, 2 H, 3′-H_2) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 166.8, 165.5 (2 s, 2 C arom.), 163.5, 163.3 (2 s, 2 C=O), 138.0 [s, C(4)], 131.7, 131.6 (2 d, $^1J_{C,H}$ = 162 Hz, 4 C arom.), 124.1 [d, $^1J_{C,H}$ = 157 Hz, C(3)], 122.8, 122.3 (2 s, 2 C arom.), 113.6, 113.5 (2 d, $^1J_{C,H}$ = 167 Hz, 4 C arom.), 69.9 [d, $^1J_{C,H}$ = 138 Hz, C(2′)], 69.8 [d, $^1J_{C,H}$ = 135 Hz, C(6′)], 66.8 [d, $^1J_{C,H}$ = 146 Hz, C(1)], 66.1 [d, $^1J_{C,H}$ = 139 Hz, C(6)], 65.7 [d, $^1J_{C,H}$ = 144 Hz, C(4′)], 58.4 [t, $^1J_{C,H}$ = 142 Hz, C(8′)], 55.4 (q, $^1J_{C,H}$ = 145 Hz, 2 OCH_3), 48.5 [t, $^1J_{C,H}$ = 125 Hz, C(1′)], 46.3 [t, $^1J_{C,H}$ = 129 Hz, C(7)], 43.5 [t, $^1J_{C,H}$ = 127 Hz, C(3′)], 42.1 [t, $^1J_{C,H}$ = 127 Hz, C(5′)], 41.1 [t, $^1J_{C,H}$ = 129 Hz, C(5)], 36.9 [t, $^1J_{C,H}$ = 127 Hz, C(7′)], 33.4 [t, $^1J_{C,H}$ = 129 Hz, C(2)] ppm. CI-MS: *m*/*z* (%) = 573 (100) [M + H], 555 (8), 403 (2), 135 (2). $C_{31}H_{40}O_{10}$ (572.65): calcd. C 65.02, H 7.04; found C 65.16, H 7.13.

(1*S*,6*R*)-6-Hydroxy-4-{[(4*R*,6*S*)-6-{(2*R*)-2-(4-methoxybenzoyl)oxy}-4-{[*tert*-butyldimethylsilyloxy]butyl}-2,2-dimethyl-1,3-dioxan-4-yl]methyl}cyclohept-3-en-1-yl 4-Methoxybenzoate [(+)-25]: Imidazole (190 mg, 2.974 mmol) and TBDMSCl (1 M in DMF, 1.538 mmol, 1.54 mL) were added dropwise to a solution of crude (–)-**24** (400 mg, 0.699 mmol) in DMF (7 mL) at 0 °C. After 30 min the reaction was warmed to 25 °C and stirred for 15 min. The solution was poured into H_2O (20 mL) and extracted with Et_2O (20 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford a pale-yellow oil that was taken up in acetone/$Me_2C(OMe)_2$ (11 mL/3 mL) at 0 °C. Cam-

phorsulfonic acid (10 mg) was then added and the solution was stirred at 0 °C for 20 min. The mixture was poured into a sat. aq. solution of $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/pentane, 1:2) afforded (+)-**25** [432 mg, 55% from (–)-**23**, 4 steps] as a colorless oil. $[\alpha]_D^{20}$ = +8, $[\alpha]_{435}^{20}$ = +8, $[\alpha]_{405}^{20}$ = +12 (*c* = 0.5, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3500, 2930, 2855, 1700, 1605, 1580, 1510, 1460, 1370, 1250, 1165, 1095, 1030, 955, 845, 770, 695 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.99, 7.98 (2 d, $^3J_{H,H}$ = 8.9 Hz, 4 H arom.), 6.92, 6.91 (2 d, $^3J_{H,H}$ = 8.9 Hz, 4 H arom.), 5.57 (t, $^3J_{H,H}$ = 6.9 Hz, 1 H, 3-H), 5.36 (m, 1 H, 2‴-H), 4.88 (m, 1 H, 1-H), 3.95 (m, 2 H, 4″-H, 6″-H), 3.86 (s, 6 H, 2 OC*H*$_3$), 3.74 (tm, $^3J_{H,H}$ = 9.0 Hz, 1 H, 6-H), 3.70 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, 4‴-H2), 2.47 (m, 2 H, 5-H, 3‴-H), 2.41 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, 2-H2), 2.30 (d, $^2J_{H,H}$ = 15.8 Hz, 1 H, 5-H), 2.27 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 7.2 Hz, 1 H, 1′-H), 2.12 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 5.5 Hz, 1 H, 1′-H), 2.02 (dd, $^2J_{H,H}$ = 10.2, $^3J_{H,H}$ = 6.9 Hz, 1 H, 3‴-H), 1.98–1.89 (m, 3 H, 7-H$_2$, 1‴-H), 1.82 (dt, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 9.1 Hz, 1 H, 1‴-H), 1.71–1.54 (m, 2 H, 5′-H$_2$), 1.29, 1.28 [2 s, 6 H, 2 C*H*$_3$–C(2″)], 0.89 [s, 9 H, C(C*H*$_3$)$_3$], 0.01 [s, 6 H, Si(C*H*$_3$)$_2$] ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 165.7, 165.4 (2 s, 2 C arom.), 163.3, 163.2 (2 s, 2 C=O), 137.3 [s, C(4)], 131.5 (d, 4 C arom.), 123.3 [d, C(3)], 113.5 (d, 4 C arom.), 100.3 [s, C(2″)], 69.6 [d, C(1)], 69.3 [d, C(2″)], 66.6 [d, C(6)], 65.2 [d, C(6″)], 63.9 [d, C(4″)], 59.5 [t, C(4‴)], 55.4 (q, 2 O*C*H$_3$), 46.8 [t, C(3‴)], 45.8 [t, C(1′)], 41.3 [t, C(5)], 40.4 [t, C(1‴)], 38.1 [t, C(5‴)], 37.5 [t, C(7)], 33.4 [t, C(2)], 25.9 [q, C(*C*H$_3$)$_3$], 24.9, 24,7 [2 q, 2 *C*H$_3$–C(2″)], 18.2 [s, *C*(CH$_3$)$_3$], –5.4 [q, Si(*C*H$_3$)$_2$]. MALDI-TOF: *m*/*z* (%) = 749 (100) [M + Na]$^+$, 765 (40) [M + K]$^+$. $C_{40}H_{58}O_{10}Si$ (726.97): calcd. C 66.09, H 8.04, Si 3.86; found C 66.15, H 7.96, Si 3.89.

(1*S*,6*R*)-6-Hydroxy-4-{[{(4*R*,6*S*)-6-[(2*R*)-2-(4-methoxybenzoyl)oxy]-4-[(triethylsilyl)oxy]butyl}-2,2-dimethyl-1,3-dioxan-4-yl]methyl}cyclohept-3-en-1-yl 4-Methoxybenzoate [(–)-26]: The same procedure as above was applied with crude (–)-**24** and Et_3SiCl, at 0 °C, to afford (–)-**26** as a colorless oil [42% from (–)-**23**, 4 steps]. $[\alpha]_D^{20}$ = –6, $[\alpha]_{435}^{20}$ = –11, $[\alpha]_{405}^{20}$ = –13 (*c* = 0.5, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3520, 2955, 2870, 1710, 1605, 1515, 1455, 1415, 1380, 1260, 1170, 1100, 845, 730, 695, 665 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.99, 7.98 (2 d, $^3J_{H,H}$ = 8.9 Hz, 4 H arom.), 6.92, 6.91 (2 d, $^3J_{H,H}$ = 8.9 Hz, 4 H arom.), 5.54 (t, $^3J_{H,H}$ = 6.6 Hz, 1 H, 3-H), 5.34 (m, 1 H, 2‴-H), 4.80 (m, 1 H, 1-H), 3.98 (m, 1 H, 4″-H), 3.90 (dd, $^3J_{H,H}$ = 6.4, 6.3 Hz, 6″-H), 3.87, 3.86 (2 s, 6 H, 2 OC*H*$_3$), 3.71 (t, $^3J_{H,H}$ = 7.1 Hz, 2 H, 4‴-H$_2$), 3.61 (ddm, $^3J_{H,H}$ = 12.0, 11.9 Hz, 1 H, 6-H), 2.36 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 11.9 Hz, 1 H, 5-H), 2.29 (m, 1 H, 3‴-H), 2.29 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, 2-H$_2$), 2.30 (dd, $^2J_{H,H}$ = 14.1, $^3J_{H,H}$ = 6.4 Hz, 1′-H), 2.19 (d, $^2J_{H,H}$ = 14.0 Hz, 5-H), 2.05 (dd, $^2J_{H,H}$ = 14.1, $^3J_{H,H}$ = 6.3 Hz, 1 H, 1′-H), 2.05 (dd, $^2J_{H,H}$ = 14.1, $^3J_{H,H}$ = 6.3 Hz, 1 H, 1′-H), 2.02–1.89 (m, 4 H, 7-H$_2$, 1‴-H, 3‴-H), 1.82 (dt, $^2J_{H,H}$ = 14.3, $^3J_{H,H}$ = 5.2 Hz, 1‴-H), 1.60 (m, 2 H, 5″-H$_2$), 1.29, 1.28 [2 s, 6 H, 2 CH$_3$C(2″)], 0.95 [t, $^3J_{H,H}$ = 8.1 Hz, 9 H, 3 CH$_3$(TES)], 0.58 [q, $^3J_{H,H}$ = 8.1 Hz, 6 H, 3 CH$_2$(TES)] ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 165.7, 165.4 (2 s, 2 C arom.), 163.3, 163.2 (2 s, 2 C=O), 137.6 [s, C(4)], 131.5 (d, 4 C arom.), 123.1 [d, C(4)], 122.7 (s, 2 C arom.), 113.5 (d, 4 C arom.), 100.2 [s, C(2″)], 69.7 [d, C(1)], 69.4 [d, C(2‴)], 67.3 [d, C(6)], 65.0 [d, C(6″)], 63.9 [d, C(4″)], 59.3 [t, C(4‴)], 55.4 (q, 2 O*C*H$_3$), 47.9 [t, C(3‴)], 45.9 [t, C(1′)], 42.3 [t, C(5)], 40.4 [t, C(1‴)], 38.5 [t, C(5′)], 37.5 [t, C(7)], 33.5 [t, C(2)], 24.8, 24.7 [2 q, 2 *C*H$_3$C(2″)], 6.73 [q, 3 *C*H$_3$(TES)], 4.74 [t, 3 CH$_2$(TES)] ppm. $C_{40}H_{58}O_{10}Si$ (726.97): calcd. C 66.09, H 8.04 Si 3.86; found C 66.16, H 8.08 Si 3.87.

(1*R*)-3-[(*tert*-Butyl)dimethyl]silyl)oxy)-1-(((4*S*,6*R*)-6-[{(4*R*,6*R*)-6-[(2*S*)-4-hydroxy-2-{[4-methoxybenzoyl)oxy]butyl}-2,2-dimethyl-1,3-dioxan-4-yl]methyl-2,2-dimethyl-1,3-dioxan-4-yl}methyl]propyl 4-Methoxybenzoate [(+)-27]: NMO·H_2O (372 mg, 2.751 mmol) and OsO_4 (0.1 M in H_2O, 1.38 mL, 0.138 mmol) were added to a solution of (+)-**25** (1 g, 1.376 mmol) in acetone/H_2O (24 mL/3 mL) and the mixture was stirred at 25 °C for 1 h. $Na_2S_2O_5$ (785 mg, 4.128 mmol) was then added and the solution was stirred at 25 °C for 15 min. The mixture was poured into H_2O (60 mL) and extracted with EtOAc (60 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford a pale-yellow oil that was taken up in dioxane/H_2O (28 mL/5.2 mL). $NaIO_4$ (589 mg, 2.752 mmol) was added and the mixture was stirred at 25 °C for 12 h. The solution was poured into brine (60 mL) and extracted with $CHCl_3$ (3×60 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford an intermediate hemiacetal that was taken up in THF (28 mL). Et_2BOMe (1 M in THF, 3.9 mL, 3.90 mmol) was added dropwise and the mixture was stirred at 25 °C for 1 h. The solution was cooled to 0 °C and MeOH (3.2 mL) and $NaBH_4$ (197 mg, 5.2 mmol) were added. The mixture was stirred at 0 °C for 30 min. The solution was poured into a sat. aq. solution of $NaHCO_3$ (80 mL) and extracted with EtOAc (60 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was taken up in MeOH (10 mL) and concentrated in vacuo (twice). The residual yellow oil was dissolved in acetone/$Me_2C(OMe)_2$ (12 mL/4 mL) at 0 °C. Camphorsulfonic acid (15 mg) was added and the solution was stirred at 0 °C for 20 min. The mixture was poured into a sat. aq. solution of $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (25 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/pentane, 1:1) afforded (+)-**27** (530 mg, 48%, 4 steps) as a colorless oil. $[\alpha]_D^{20}$ = +18, $[\alpha]_{435}^{20}$ = +30, $[\alpha]_{405}^{20}$ = +37 (*c* = 0.5, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3520, 2955, 2870, 1710, 1605, 1515, 1455, 1415, 1380, 1260, 1170, 1100, 845, 730, 695, 665 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.99, 7.98 (2 d, $^3J_{H,H}$ = 9.1 Hz, 4 H arom.), 6.94, 6.91 (2 d, $^3J_{H,H}$ = 9.1 Hz, 4 H arom.), 5.51–5.44 (m, 1 H, 2^{VI}-H), 5.37–5.31 (m, 1 H, 1-H), 4.06–3.89 (m, 4 H, 4″-H, 6″-H, 4^{IV}-H, 6^{IV}-H), 3.87, 3.86 (2 s, 6 H, 2 OC*H*$_3$), 3.70 (t, $^3J_{H,H}$ = 6.7 Hz, 3-H$_2$), 3.68 (dm, $^2J_{H,H}$ = 9.7 Hz, 1 H, 2^{IV}-H), 3.59 (m, 1 H, 2^{IV}-H), 2.05–1.73 (m, 10 H, 1′-H$_2$, 5″-H$_2$, 1‴-H$_2$, 5^{IV}-H$_2$, 1^{V}-H$_2$), 1.57–1.40 (m, 4 H, 2-H$_2$, 3^{VI}-H$_2$), 1.33, 1.24, 1.21, 1.18 [4 s, 12 H, 2 C*H*$_3$C(2″), 2 C*H*$_3$C(2^{IV})], 0.87 [s, 9 H, C(C*H*$_3$)$_3$], 0.02, 0.01 [2 s, 6 H, Si(CH$_3$)$_3$] ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 166.9, 165.6 (2 s, 2 C arom.), 163.5, 163.2 (2 s, 2 C=O), 131.6, 131.4 (2 d, $^1J_{C,H}$ = 162, 160 Hz, 4 C arom.), 123.0, 122.2 (2 s, 2 C arom.), 133.7, 133.5 (2 d, $^1J_{C,H}$ = 161, 162 Hz, 4 C arom.), 100.5 [s, C(2″)], 98.6 [s, C(2^{IV})], 69.2, 68.3 [2 d, $^1J_{C,H}$ = 147 Hz, C(1), C(2^{VI})], 65.7, 64.9, 63.3, 62.1 [4 d, $^1J_{C,H}$ = 146, 148, 145, 147 Hz, C(4″), C(6″), C(4^{IV}), C(6^{IV})], 59.6 [t, $^1J_{C,H}$ = 140 Hz, C(3)], 58.3 [t, $^1J_{C,H}$ = 142 Hz, C(4^{VI})], 55.4, 55.3 (2q, $^1J_{C,H}$ = 145 Hz, 2 O*C*H$_3$), 42.0, 41.6 [2 t, $^1J_{C,H}$ = 126 Hz, C(2), C(3^{VI})], 40.9, 39.0, 38.1, 37.6 [4 t, $^1J_{C,H}$ = 125 Hz, C(1′), C(5″), C(5^{IV}), C(1^{V})], 38.0 [t, $^1J_{C,H}$ = 123 Hz, C(1‴)], 30.1, 19.5 [2 q, $^1J_{C,H}$ = 125, 124 Hz, 2 *C*H$_3$C(2^{IV})], 25.8 [q, $^1J_{C,H}$ = 126 Hz, C(*C*H$_3$)$_3$], 24.3, 24.0 [2 q, $^1J_{C,H}$ = 124 Hz, 2 *C*H$_3$C(2″)], 18.1 [s, *C*(CH$_3$)$_3$], –5.5 [q, $^1J_{C,H}$ = 118 Hz, Si(*C*H$_3$)$_2$] ppm. MALDI-TOF: *m*/*z* (%) = 826 (100) [M + Na]$^+$. $C_{43}H_{66}O_{12}Si$ (803.07): calcd. C 64.31, H 8.28; found C 64.31, H 8.28.

(3*S*)-4-{(4*S*,6*S*)-6-[{(4*S*,6*R*)-6-[(2*R*)-4-{[(*tert*-Butyl)dimethyl]-silyl}oxy-2-hydrobutyl]-2,2-dimethyl-1,3-dioxan-4-yl}methyl]-2,2-dimethyl-1,3-dioxan-4-yl}-3-hydroxybutyl Acetate [(–)-28]: KOMe (665 mg, 9.480 mmol) was added to a solution of (+)-**27** (190 mg,

0.237 mmol) in MeOH (7 mL) at 0 °C. After 30 min the solution was warmed to 25 °C and stirred for 15 h. The mixture was poured into a sat. aq. solution of NH_4Cl (15 mL) and extracted with EtOAc (15 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford a pale-yellow oil (114 mg, 90% crude), which was taken up in vinyl acetate (4 mL) and treated with *Candida cylindracea* lipase (4800 U per mmol, 3.86 U per mg, 265 mg). The mixture was stirred at 25 °C for 1 h, then filtered and concentrated in vacuo. Flash chromatography on silica gel (CH_2Cl_2/MeOH, 97:3) afforded (–)-**28** (108 mg, 79%, 2 steps). $[\alpha]_D^{20} = -9$, $[\alpha]_{577}^{20} = -48$ ($c = 0.18$, MeOH). IR (film): $\tilde{\nu}$ = 3415, 2985, 2935, 2870, 1735, 1645, 1440, 1380, 1255, 1165, 1100, 1055, 940, 835, 775 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz, 25 °C): δ = 4.15–4.04 (m, 4 H, 4′-H, 6′-H, 4‴-H, 6‴-H), 3.95–3.81 (m, 2 H, 3-H, 2^{IV}-H), 3.80 (dd, $^3J_{H,H}$ = 6.0, 5.5 Hz, 2 H, 1-H_2), 3.71 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, 4^{IV}-H_2), 2.08 [s, 3 H, CH_3(OAc)], 1.78–1.53 (m, 14 H, 2-H_2, 4-H_2, 5′-H_2, 1″-H_2, 5‴-H_2, 1^{IV}-H_2, 3^{IV}-H_2), 1.48, 1.37 [2 s, 6 H, 2 CH_3C(2′)], 1.36, 1.34 [2 s, 6 H, 2 CH_3C(2‴)], 0.94 [s, 9 H, C(CH_3)$_3$], 0.11 [s, 6 H, Si(CH_3)$_3$] ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 171.2 (s, C=O), 100.5 [s, C(2‴)], 98.7 [s, C(2′)], 68.2, 67.2 [2 d, $^1J_{C,H}$ = 146, 142 Hz, C(3), $C(2^{IV})$], 65.5, 65.3, 65.0, 64.0 [4 d, $^1J_{C,H}$ = 143, 142, 140 Hz, C(4′), C(6′), C(4‴), C(6‴)], 62.2 [t, $^1J_{C,H}$ = 140 Hz, C(1)], 61.6 [t, $^1J_{C,H}$ = 141 Hz, $C(4^{IV})$], 42.8, 42.0 [2 t, $^1J_{C,H}$ = 126, 125 Hz, C(2), $C(3^{IV})$], 38.9, 38.7 [2 t, $^1J_{C,H}$ = 124 Hz, C(5′), C(5‴)], 36.7 [t, $^1J_{C,H}$ = 122 Hz, C(1″)], 36.2 [t, $^1J_{C,H}$ = 125 Hz, C(4), $C(1^{IV})$], 30.2, 19.6 [2 q, $^1J_{C,H}$ = 125 Hz, 124, 2 CH_3C(2′)], 25.8 [q, $^1J_{C,H}$ = 126 Hz, C(CH_3)$_3$], 24.7, 24.6 [2 q, $^1J_{C,H}$ = 122, 125 Hz, 2 CH_3C(2‴)], 21.0 [q, $^1J_{C,H}$ = 124 Hz, CH_3(OAc)], 18.1 [s, C(CH$_3$)$_3$], –5.5 [q, $^1J_{C,H}$ = 119 Hz, Si(CH_3)$_3$] ppm. MALDI-TOF: *m*/*z* (%) = 599 (100) $[M + Na]^+$. $C_{29}H_{56}O_9Si$ (576.84): calcd. C 60.38, H 9.78; found C 60.16, H 9.60.

(3*S*)-4-[(4*R*,6*R*)-6-{[(4*R*,6*S*)-6-{(2*R*,4*S*)-4-Hydroxy-2-[{[(phenylmethyl)oxy]methyl}oxy]-6-hepten-1-yl}-2,2-dimethyl-1,3-dioxan-4-yl]methyl}-2,2-dimethyl-1,3-dioxan-4-yl]-3-[{[(phenylmethyl)oxy]methyl}oxy]butyl Acetate [(–)-29]: (iPr)$_2$NEt (251 μL, 1.464 mmol), $BnOCH_2Cl$ (136 μL, 0.976 mmol), and Bu_4NI (5 mg) were added to a solution of (–)-**28** (100 mg, 0.122 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 30 min the mixture was heated to 40 °C for 3 h. The solution was poured into a sat. aq. solution of $NaHCO_3$ (12 mL) and extracted with CH_2Cl_2 (12 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford a yellow oil that was taken up in THF (6 mL) and treated with HF·pyridine (400 mL) at –20 °C. After stirring for 20 min at –20 °C, the mixture was poured into a sat. aq. solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Filtration over a pad of silica gel (10 cm, CH_2Cl_2/MeOH, 95:5) afforded a pale-yellow oil. This crude alcohol (69 mg, 0.098 mmol) was dissolved in CH_2Cl_2 (1.2 mL) and treated with activated 4-Å molecular sieves (30 mg), NMO·H_2O (27 mg, 0.196 mmol), and Pr_4NRuO_4 (7 mg, 0.020 mmol). After stirring for 30 min at 25 °C the solution was directly filtered through a pad of silica gel and concentrated in vacuo. Ti(OiPr)$_4$ (0.1 M in CH_2Cl_2, 98 mL) was added to a solution of (*S*)-BINOL (6 mg, 0.020 mmol) in CH_2Cl_2 (300 μL) and the solution was stirred at 25 °C for 45 min. The mixture was cooled to –78 °C. A solution of the crude aldehyde (67 mg, 0.098 mmol) in CH_2Cl_2 (700 μL) and allyltributylstannane (45 μL, 0.147 mmol) were added. After 10 min the solution was warmed to 0 °C and stirred for 50 min. EtOAc (2 mL) and a sat. aq. solution of $NaHCO_3$ (1 mL) were added and the mixture was stirred for 30 min at 0 °C, then filtered and concentrated in vacuo. Flash chromatography on silica gel (CH_2Cl_2/MeOH, 97:3) afforded (–)-**29** (54 mg, 60%, 4 steps) as a pale-yellow oil. $[\alpha]_D^{20} = -57$, $[\alpha]_{435}^{20} = -102$, $[\alpha]_{435}^{20} = -122$ ($c = 0.4$, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3495, 2985, 2920, 1735, 1645, 1450, 1380, 1240, 1165, 1105, 1035, 740, 700 cm^{-1}. ^1H NMR (C_6D_6, 400 MHz, 25 °C): δ = 7.35, 7.20 (2 m, 10 H arom.), 5.83 (m, 1 H, 6^{IV}-H), 5.11 (d, $^3J_{H,H}$ = 17.1 Hz, 1 H, 7^{IV}-H), 5.09 (m, 1 H, 7^{IV}-H), 4.82 [s, 2 H, CH_2(BOM)], 4.80, 4.78 [2 d, $^2J_{H,H}$ = 8.2 Hz, 2 H, CH_2(BOM)], 6.68, 4.65 (2 d, $^2J_{H,H}$ = 9.1 Hz, 2 H, CH_2Ph), 4.62 (s, 2 H, CH_2Ph), 4.20 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, 1-H_2), 4.09–3.96 (m, 5 H, 3-H, 4′-H, 6′-H, 4‴-H, 6‴-H), 3.94 (m, 1 H, 2^{IV}-H), 3.87 (m, 1 H, 4^{IV}-H), 2.25 (dd, $^3J_{H,H}$ = 6.2, 5.9 Hz, 5^{IV}-H), 2.04 [s, 3 H, CH_3(OAc)], 1.99–1.82 (m, 2 H, 2-H_2), 1.80 (m, 1 H, 1″-H), 1.73–1.60 (m, 8 H, 5′-H_2, 5‴-H_2, 1^{IV}-H_2, 3^{IV}-H_2), 1.46 (m, 1 H, 1″-H), 1.44 (m, 1 H, 4-H), 1.35, 1.34, 1.31, 1.26 [4 s, 2 CH_3C(2′), 2 CH_3C(2‴)], 1.17 (m, 1 H, 4-H) ppm. ^{13}C NMR (C_6D_6, 100.6 MHz, 25 °C): δ = 169.9 (s, C=O), 137.6 (s, 2 C arom.), 135.0 [d, $C(6^{IV})$], 128.5, 127.8, 127.7 (3 d, 8 C arom.), 128.4 (s, 2 C arom.), 117.3 [t, $C(7^{IV})$], 100.5 [s, C(2‴)], 98.5 [s, C(2′)], 94.7, 94.2 [2 t, 2 CH_2(BOM)], 72.1 [d, $C(4^{IV})$], 70.1 [d, C(3), $C(2^{IV})$], 69.5 (t, 2 CH_2Ph), 67.2, 65.5, 65.2 [3 d, C(4′), C(6′), C(4‴), C(6‴)], 61.1 [t, C(1)], 44.0, 42.9, 42.5 [3 t, C(4), C(5′), C(5‴), $C(1^{IV})$], 38.5 [t, C(1″)], 34.5 [t, C(2), $C(3^{IV})$], 30.2, 19.8 [2 q, 2 CH_3C(2‴)], 24.9 [q, 2 CH_3C(2‴)], 21.0 [q, CH_3(OAc)] ppm. MALDI-TOF: *m*/*z* (%) = 765 (100) $[M + Na]^+$. $C_{42}H_{62}O_{11}$ (742.94): calcd. C 67.90, H 8.41; found C 68.01, H 8.47.

(3*S*)-4-[(4*R*,6*R*)-6-{[(4*R*,6*S*)-6-{(2*R*,4*S*)-4,6-Dihydroxy-2-[{[(phenylmethyl)oxy]methyl}oxy]heptan-1-yl}-2,2-dimethyl-1,3-dioxan-4-yl]methyl}-2,2-dimethyl-1,3-dioxan-4-yl]-3-[{[(phenylmethyl)oxy]methyl}oxy]butyl Acetate [(–)-30]: $Me_2SO_2NH_2$ (17 mg, 0.128 mmol) and AD-mix-β (1486 mg per mmol, 95 mg) were added to a solution of (–)-**29** (50 mg, 0.064 mmol) in a mixture of *t*BuOH and H_2O (700 μL/700 μL) cooled to 0 °C. AD-mix-β (70 g) was prepared from $K_3Fe(CN)_6$ (47.7 g), K_2CO_3 (20 g), $(DHQD)_2$-PHAL (1.88 g), and $K_2OsO_2(OH)_4$ (370 mg). The mixture was stirred at 0 °C for 13 h. EtOAc (2 mL), H_2O (1 mL), and Na_2SO_3 (24 mg, 0.256 mmol) were added. After stirring for 30 min at 25 °C, the mixture was poured into H_2O (5 mL) and extracted with EtOAc (4 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (CH_2Cl_2/MeOH, 16:1) afforded (–)-**30** (34 mg, 68%, major diastereoisomer) as a colorless oil. $[\alpha]_D^{20} = -11$ ($c = 0.2$, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3440, 3090, 3030, 2960, 1730, 1606, 1495, 1480, 1455, 1400, 1285, 1160, 970, 865 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz, 25 °C): δ = 7.38–7.31 (m, 10 H arom.), 4.87, 4.85, 4.84, 4.83 [4 d, $^2J_{H,H}$ = 5.6 Hz, 4 H, 2 CH_2(BOM)], 4.67, 4.64 (2 d, $^2J_{H,H}$ = 7.1 Hz, 2 H, CH_2Ph), 4.64 (s, 2 H, CH_2Ph), 4.21 (m, 2 H, 3-H, 2^{IV}-H), 4.19–4.00 (m, 5 H, 4′-H, 6′-H, 4‴-H, 6‴-H, 6^{IV}-H), 3.85 (m, 1 H, 4^{IV}-H), 3.69 (t, $^3J_{H,H}$ = 6.7 Hz, 2 H, 2 H, 1-H_2), 3.49 (t, $^3J_{H,H}$ = 6.1 Hz, 2 H, 2 H, 7^{IV}-H_2), 2.03 [s, 3 H, CH_3(OAc)], 1.95–1.40 (m, 16 H, 2-H_2, 4-H_2, 5′-H_2, 1″-H_2, 5‴-H_2, 1^{IV}-H_2, 3_{IV}-H_2, 5^{IV}-H_2), 1.36, 1.33, 1.32, 1.31 [4 s, 12 H, 2 CH_3C(2′), 2 CH_2C(2‴)] ppm. ^{13}CNMR (CD_3OD, 100.6 MHz, 25 °C): δ = 170.1 (s, C=O), 138.8 (s, 2 C arom.), 128.9, 128.4, 128.2 (3 d, 10 C arom.), 101.0 [s, C(2‴)], 99.4 [s, C(2′)], 95.3, 95.2 [2 t, 2 CH_2(BOM)], 74.3, 73.5 [2 d, C(3), $C(2^{IV})$], 71.3, 69.7 [2 d, $C(4^{IV})$, $C(6^{IV})$], 70.3 (t, 2 CH_2Ph), 67.4, 66.5, 64.3 [3 d, C(4′), C(6′), C(4″), C(6″)], 63.8 [t, C(1)], 58.9 [t, $C(7^{IV})$], 44.5, 44.0, 42.9, 40.5, 40.2, 39.4, 38.9, 38.1 [8 t, C(2), C(4), C(5′), C(1″), C(5‴), $C(1^{IV})$, $C(3^{IV})$, $C(5^{IV})$], 30.0, 19.7 [2 q, 2 CH_3C(2′)], 24.9, 24.8 [2 q, 2 CH_3C(2‴)], 20.8 [q, CH_3(OAc)] ppm. MALDI-TOF: *m*/*z* (%) = 758 (100) $[M - H_2O]^+$. $C_{42}H_{64}O_{13}$ (776.956): calcd. C 64.93, H 8.30; found C 64.12, H 8.12.

NMR Spectroscopic Data for Triacetonide 31: Numbering according to RK-397. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 7.27–7.30

(m, 10 H arom.), 4.85 [m, 4 H, 2 CH_2(BOM)], 4.73, 4.58 (2 d, $^2J_{H,H}$ = 11.9 Hz, 2 H, CH_2Ph), 4.68, 4.57 (2 d, $^2J_{H,H}$ = 11.8 Hz, 2 H, CH_2Ph), 4.20 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, 11-H_2), 4.15, 4.07–3.94 (2 m, 8 H, 13-H, 15-H, 17-H, 19-H, 21-H, 23-H, 25-H, 27-H), 3.85, 3.73 (2 m, 2 H, 28-H_2), 2.03 [s, 3 H, CH_3(OAc)], 1.95–1.80, 1.78–1.35 (2 m, 16 H, 12-H_2, 14-H_2, 16-H_2, 18-H_2, 20-H_2, 22-H_2, 24-H_2, 26-H_2), 1.39, 1.36, 1.35, 1.32, 1.30 [5 s, 18 H, 6CH_3(acetonide)] ppm. ^{13}C NMR (CD_3OD, 100.6 MHz, 25 °C): δ = 172.9 (s, C=O), 133.6 (s, 2 C arom.), 129.4, 128.9, 128.7 (3 d, 10 C arom.), 101.5 [s, C_{quat}(acetonide *anti*)], 99.8 [s, 2 C_{quat}(acetonide *syn*)], 95.7, 95.6 [2 d, 2 *C*H_2(BOM)], 73.9, 73.8 [2 d, C(13), C(23)], 70.7 (t, 2 CH_2Ph), 70.6, 67.0, 66.9, 66.3, 64.8, 64.2 [6 d, C(15), C(17), C(19), C(21), C(25), C(27)], 62.4 [t, C(1)], 59.4 [t, C(28)], 43.9, 43.3, 43.1, 39.6, 39.5, 38.5, 35.5, 35.4 [8 t, C(12), C(14), C(16), C(18), C(20), C(22), C(24), C(26)], 30.5 (doubled peak), 20.3, 20.2 [3 q, 4 *C*H_3(acetonide *syn*)], 25.4, 25.3 [2 q, 2 CH_3(acetonide *anti*)], 20.9 [s, CH_3(OAc)] ppm.

NMR Spectroscopic Data for Pentaacetonide 32: Numbering according to RK-397. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 4.12–3.92 (m, 8 H, 13-H, 15-H, 17-H, 19-H, 21-H, 23-H, 25-H, 27-H), 3.82 (m, 4 H, 11-H_2, 28-H_2), 1.82, 1.65–1.48 (2 m, 16 H, 12-H_2, 14-H_2, 16-H_2, 18-H_2, 20-H_2, 22-H_2, 24-H_2, 26-H_2), 1.46, 1.45, 1.37, 1.36, 1.33 [5 s, 30 H, 10 CH_3(acetonide)] ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz, 25 °C): δ = 104.0, 100.4, 100.2, 98.4, 98.3 [5 s, 5 C_{quat}(acetonide)], 65.5, 64.8, 63.2 (doubled peak), 63.0, 62.8, 62.1, 61.2 [7 d, C(13), C(15), C(17), C(19), C(21), C(23), C(25), C(27)], 60.0, 59.9 [2 t, C(11), C(28)], 42.4, 41.8, 38.6, 38.3, 37.1 (doubled peak), 31.8, 30.7 [7 t, C(12), C(14), C(16), C(18), C(20), C(22), C(24), C(26)], 29.9, 29.8, 19.2, 19.1 [4 q, 4 *C*H_3(acetonide *syn*)], 25.8, 25.6 [2 q, 2 *C*H_3 [acetonide C(27),C(28)], 24.8 (doubled peak), 24.4, 24.3 [3 q, 2 *C*H_3 (acetonide *anti*)] ppm. MALDI-TOF: *m*/*z* (%) = 637 [100] $[M + Na]^+$.

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