

207. Stereoselective Synthesis of the C(19)-to-C(27) Segment of Rifamycin S

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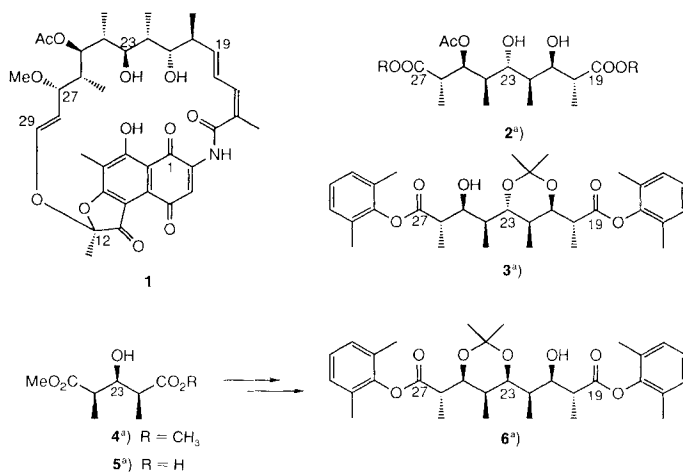
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The synthesis of diester **3**, a synthon for the C(19)-to-C(27) segment of rifamycin S (**1**), is described, starting from the *meso*-diester **4** (Schemes 2 and 3). Inversion of the configuration at the later C(23) and two aldol condensations with the lithium enolate **18** of 2,6-dimethylphenyl propionate each producing two new chiral centres of *threo*-configuration, led to the desired diester **3**. The absolute configuration of the new chiral centres was proven by a single X-ray analysis of intermediate **19** (Fig.) and by converting diester **3** into *meso*-diester **25**.

Introduction. – The antibiotic rifamycin S (**1**; Scheme 1) [1] is a prominent member of the ansamycin family [2]. The complex structure of this microbial secondary metabolite consists of a naphthoquinone system and an aliphatic bridge, which is attached to the aromatic nucleus at the positions 2 and 12. The construction of this ansa-chain, characterized by the sequence of eight contiguous chiral centres, is a challenging problem and has, therefore, been the subject of many synthetic efforts [3]. A total synthesis of rifamycin S (**1**) has been reported by Kishi and coworkers in 1980 [4]. We have recently reported a stereocontrolled synthesis of compound **6** which corresponds to the C(19)-to-C(27) segment of rifamycin S (**1**) except for the configuration at C(23) [5]. Use was made of the chiral monoester **5** as starting material which could be obtained in high enantiome-

Scheme 1

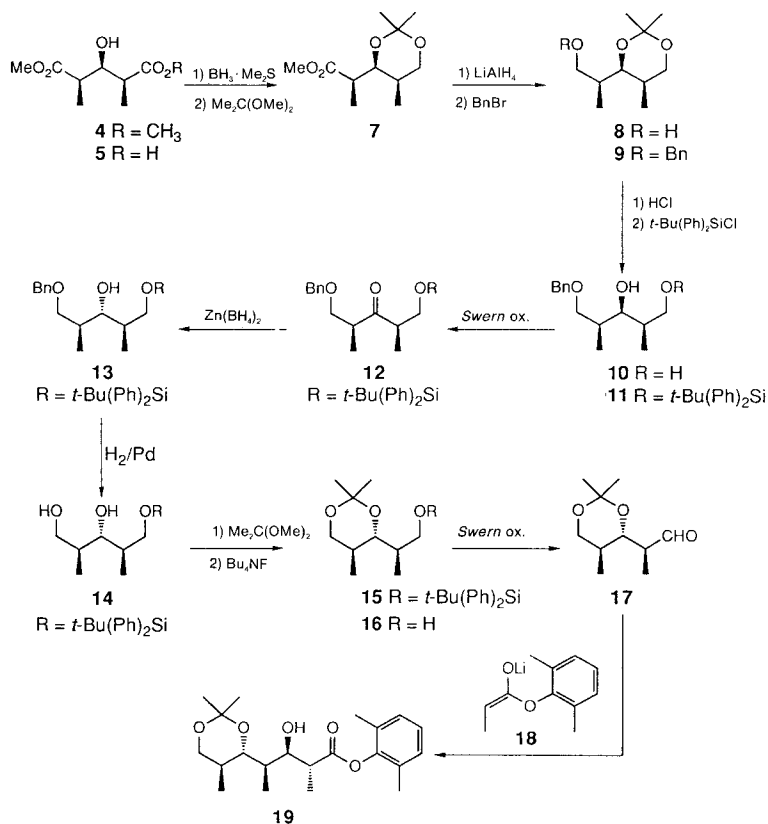


^{a)} Rifamycin-S(1) numbering.

ric purity by hydrolysis of the *meso*-diester **4** with pig-liver esterase (PLE) [6]. For the preparation of segment **2** with all configurations corresponding to **1**, the configuration at C(23) had to be inverted. We have tried this inversion on different stages of the pathway outlined earlier and wish now to report the synthesis of the C(19)-to-C(23) segment **3** having the correct configuration at all 7 chiral centres. Diester **3** was obtained in 20 steps and in an overall yield of 10.6% starting from **4**.

Results. – Reduction of the half-ester **5** by $\text{BH}_3 \cdot \text{Me}_2\text{S}$ and treatment with 2,2-dimethoxypropane in the presence of *Amberlyst 15* in MeOH [7] to prevent undesired lactonization gave acetonide **7** (*Scheme 2*). After reduction with LiAlH_4 ($\rightarrow$ **8**) and benzylation in the presence of Et_4NI [8] ($\rightarrow$ **9**), the isopropylidene group was removed with HCl, and selective silylation of the primary OH group with *t*-Bu(Ph) $_2$ SiCl led to alcohol **11**. The latter was oxidized to ketone **12** according to the method of Swern [9]. Reduction with $\text{Zn}(\text{BH}_4)_2$ gave the desired alcohol **13** with inverted configuration at the central C-atom in 69% yield.

Scheme 2



The epimerization at C(3) of **5** (=C(23) of **1**) was tried on different stages of the synthesis as well as by applying different methods as, *e.g.*, the *Mitsunobu* reaction [10], nucleophilic substitution reactions with various leaving groups, and an oxidation/reduc-

tion cycle with a variety of aluminium hydrides and borohydrides. Among all tested variants, $\text{Zn}(\text{BH}_4)_2$ reduction of **12** proved to be best since the epimeric mixture **11/13** was obtained quantitatively in the ratio 34:66 and the undesired epimer **11** could be recycled after chromatographic separation (see *Exper. Part*).

Subsequent conversion of the protecting groups was achieved by benzyl-ether cleavage with H_2/Pd (**13**→**14**), reprotection with 2,2-dimethoxypropane in the presence of camphorsulfonic acid as catalyst (→**15**), and cleavage of the silyl ether with Bu_4NF which produced the alcohol **16** in excellent yield. After *Swern* oxidation [9] to aldehyde **17**, two additional chiral centres were introduced by applying the aryl-ester aldol condensation as described by *Heathcock et al.* [11]. Thus, **17** was added to a solution of enolate **18** of 2,6-dimethylphenyl propionate in THF at -78° . After 1 h, ester **19** was obtained as the only product possessing the desired *threo*-configuration at the two additional chiral centres. The yield of 50% could be optimized up to 88% by treating the THF solutions of **17** and 2,6-dimethylphenyl propionate separately with molecular sieves (4 Å) prior to enolate formation. The absolute configuration of **19** was proved by an X-ray analysis¹⁾ which established the relationship of the new chiral centres with the three known chiral centres of aldehyde **17**. The *Figure* shows the ORTEP plot of the X-ray analysis of **19**.

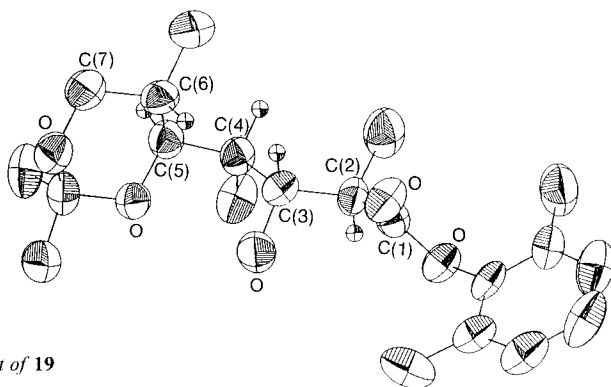
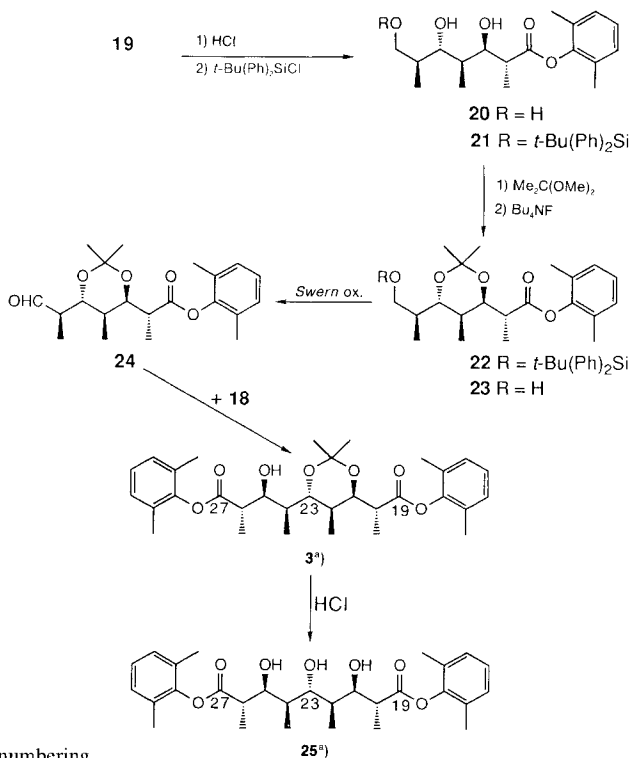


Figure. ORTEP plot of **19**

The further chain elongation was achieved by similar protecting-group transformations and *Swern* oxidation (*Scheme 3*): removal of the isopropylidene group with conc. HCl (**19**→**20**), selective protection by treatment with *t*-Bu(Ph) $_2\text{SiCl}$ and imidazole (→**21**), protection of the remaining two free OH groups with 2,2-dimethoxypropane (→**22**), and cleavage of the silyl-ether group with Bu_4NF led to alcohol **23** in excellent yield. After *Swern* oxidation [9], aldehyde **24** was submitted to the aldol condensation with enolate **18** of 2,6-dimethylphenyl propionate under the same conditions as described above, except for the use of more concentrated solutions because of the lower reactivity of **24**. The desired diester **3** was isolated in 81% yield as the only product and its absolute configuration established by transformation to *meso*-diester **25** by treatment with conc. HCl . *Meso*-Diester **25** was optically inactive, and its NMR spectra exhibited a characteristic simplification.

¹⁾ We thank PD Dr. M. Zehnder and Dr. D. Bur, Institut für Anorganische Chemie der Universität Basel, for this measurement.

Scheme 3



^{a)} Rifamycin-S(1) numbering.

Diester **3** was obtained in 20 steps and in an overall yield of 10.6%. All 7 chiral centres of **3** possess the desired configuration, and thus, **3** represents a useful synthon for an economic total synthesis of antibiotic **1**.

Financial support of these investigations by the *Swiss National Science Foundation* is gratefully acknowledged.

Experimental Part

General. Water- and air-sensitive reactions were carried out under Ar. THF was freshly distilled over Na-K alloy; CH_2Cl_2 was dried over molecular sieves (4 Å); Et_2O was freshly distilled over LiAlH_4 . All org. extracts were dried (Na_2SO_4) and evaporated under reduced pressure below 50°. Pig-liver esterase (EC 3.1.1.1) was purchased from *Boehringer*. TLC: silica gel 60 F_{254} (*Merck*). Column chromatography (CC): silica gel (60–200 μm ; *Chemische Fabrik Uetikon*). M.p.: *Kofler* block; corrected. $[\alpha]_D^{25}$: *Perkin-Elmer-141* polarimeter. IR spectra (cm^{-1}): *Perkin-Elmer-781* IR spectrometer. NMR: *Varian-EM-390* (^1H , 90 MHz), *Varian-Gemini-300* (^1H , 300 MHz; ^{13}C , 75 MHz), and *Varian-VXR-400* spectrometer (^1H , 400 MHz; ^{13}C , 101 MHz (correlation of the signals was accomplished by BB and APT experiments)); CDCl_3 solns.; chemical shifts in ppm rel. to internal TMS (= 0 ppm). MS: *VG-70-250* spectrometer. X-Ray diffraction: *Enraf Nonius CAD 4*.

Methyl (2R,3S,4R)-3,5-(Isopropylidenedioxy)-2,4-dimethylpentanoate (7). To a soln. of **5** (8 g, 42 mmol) in THF (20 ml) at -10° under Ar, $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (10 ml) was added within 20 min. After stirring for 1.5 h, additional $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (6 ml) was added. After stirring for 3 h at r.t., the mixture was cooled to 0° and treated with H_2O (10 ml). Solid K_2CO_3 and H_2O (6 ml) were added. The mixture was extracted with AcOEt, the soln. dried and evaporated, and the residue filtered over silica gel (10 g; AcOEt/pentane 7:3). The resulting colourless solid (6.89 g)

was dissolved in MeOH (7 ml) containing 2,2-dimethoxypropane (26 ml) and Amberlyst 15 (448 mg). The mixture was stirred under Ar for 68 h, filtered, and evaporated. The residue was purified by CC (AcOEt/pentane 1:9): 5.55 g (61 %) of **7**. Slightly yellow oil. $[\alpha]_D^{25} = -0.8$ ($c = 2$, CCl_4). $^1\text{H-NMR}$ (90 MHz): 1.1 (*d*, $J = 7.5$, Me–C(4)); 1.2 (*d*, $J = 7.5$, Me–C(2)); 1.4, 1.45 (2*s*, Me_2CO_2); 1.5 (*m*, H–C(4)); 2.6 (*dq*, $J = 10$, 7.5, H–C(2)); 3.55 (*dd*, $J = 12.2$, 1 H, $\text{CH}_2(5)$); 3.7 (*s*, COOCH_3); 3.95 (*dd*, $J = 10$, 2, H–C(3)); 4.1 (*dd*, $J = 12$, 3, 1 H, $\text{CH}_2(5)$).

(2*S*,3*R*,4*R*)-3,5-(Isopropylidenedioxy)-2,4-dimethylpentan-1-ol (**8**). To a soln. of LiAlH_4 (172 mg, 4.52 mmol) in Et_2O (9 ml) was added at -20° dropwise a soln. of **7** (1.11 g, 5.16 mmol) in Et_2O (4 ml) under Ar. After stirring at -20° for 3 h and 1.5 h at r.t., the mixture was hydrolyzed with H_2O (0.5 ml), 15% Na_2CO_3 soln. (0.5 ml), and H_2O (1.3 ml). The colourless precipitate was filtered and washed with Et_2O . The combined Et_2O layers were dried and evaporated, and the resulting product was purified by CC (AcOEt/pentane 1:4): 0.932 g (96 %) of **8**. Colourless oil. $[\alpha]_D^{25} = +6.93$ ($c = 1.5$, CHCl_3). IR (NaCl): 3440 (OH), 2990, 2960, 2940, 2880. $^1\text{H-NMR}$ (90 MHz): 0.9 (*d*, $J = 7$, Me–C(4)); 1.0 (*d*, $J = 7$, Me–C(2)); 1.4, 1.45 (2*s*, Me_2CO_2); 1.4–2.1 (*m*, H–C(4), H–C(2), OH); 3.3–3.6 (*m*, 1 H–C(5), $\text{CH}_2(1)$); 3.75 (*dd*, $J = 10$, 2, H–C(3)); 4.1 (*dd*, $J = 12$, 3, 1 H, $\text{CH}_2(5)$). CI-MS (NH_3): 206 (9, $[\text{M} + \text{NH}_4]^+$); 189 (100, $[\text{M} + 1]^+$), 171 (38), 148 (28), 131 (26), 113 (59).

(2*S*,3*R*,4*R*)-1-(Benzyloxy)-3,5-(isopropylidenedioxy)-2,4-dimethylpentane (**9**). NaH (55 % in oil; 2.09 g, 47.89 mmol) was washed 3 times under Ar with hexane (10 ml). Then, DMF (40 ml) was added and the suspension cooled to 0° . A soln. of **8** (4.561 g, 23.96 mmol) in DMF (10 ml) was added dropwise to this suspension. After stirring 1 h at r.t., the mixture was recooled to 0° , and Et_4NI (616 mg, 2.4 mmol) and benzyl bromide (8.54 ml, 71.83 mmol) were added. The soln. was stirred for 16 h at r.t., then quenched with H_2O (150 ml) and extracted with Et_2O . After drying and evaporation, the crude product was purified by CC (AcOEt/pentane 5:95 to 1:9): 6.132 g (92 %) of **9**. Colourless oil. $[\alpha]_D^{25} = +9.52$ ($c = 5.65$, CHCl_3). IR (NaCl): 3060, 3030, 2990, 2960, 2940, 2860. $^1\text{H-NMR}$ (90 MHz): 1.05, 1.1 (2*d*, $J = 7$, Me–C(4), Me–C(2)); 1.4 (*s*, Me_2CO_2); 1.6–2.1 (*m*, H–C(4), H–C(2)); 3.35 (*d*, $J = 5$, $\text{CH}_2(5)$); 3.65 (*dd*, $J = 12$, 2, 1 H, $\text{CH}_2(1)$); 3.75 (*dd*, $J = 10$, 2, H–C(3)); 4.1 (*dd*, $J = 12$, 3, 1 H, $\text{CH}_2(1)$); 4.5 (*s*, PhCH_2O); 7.3 (*s*, 5 arom. H). CI-MS (NH_3): 279 (34, $[\text{M} + 1]^+$), 263 (23), 238 (11), 221 (52), 203 (35), 171 (22), 129 (16), 113 (100), 99 (23), 91 (85).

(2*R*,3*S*,4*S*)-5-(Benzyloxy)-2,4-dimethylpentane-1,3-diol (**10**). A soln. of **9** (6.132 g, 22.06 mmol) in THF (125 ml) was treated with 10 drops of conc. HCl soln. and stirred for 6 h at r.t. The mixture was neutralized with solid NaHCO_3 and stirred together with solid Na_2SO_4 for 1 additional h. The mixture was filtered and the solvent removed under reduced pressure. Purification of the crude product by CC (AcOEt/pentane 1:1) yielded 4.8171 g (92 %) of **10**. Colourless solid. $[\alpha]_D^{25} = -4.1$ ($c = 2.72$, CHCl_3). M.p. $39\text{--}41^\circ$. IR (NaCl): 3380 (OH), 3060, 3030, 2960, 2920, 2870. $^1\text{H-NMR}$ (400 MHz): 1.0, 1.05 (2*d*, $J = 6.9$, Me–C(4), Me–C(2)); 1.25 (*t*, $J = 7$, OH–C(1)); 1.36 (*d*, $J = 5.5$, OH–C(3)); 1.81, 1.95 (2*m*, H–C(4), H–C(2)); 3.46 (*ddd*, $J = 5$, 7.1, 13.3, $\text{CH}_2(1)$); 3.62 (*d*, $J = 6.4$, $\text{CH}_2(5)$); 3.75 (*t* (*dd*), $J = 5.1$, H–C(3)); 4.49 (*s*, PhCH_2O); 7.26–7.37 (*s*, 5 arom. H). $^{13}\text{C-NMR}$ (101 MHz, APT): 11.51 ($\text{CH}_3\text{--C}(2)$); 12.49 ($\text{CH}_3\text{--C}(4)$); 36.33 ($\text{C}(4)$); 37.65 ($\text{C}(2)$); 66.94 ($\text{C}(1)$); 73.37 ($\text{C}(5)$); 74.5 (PhCH_2O); 76.03 ($\text{C}(3)$); 126.95 (C_o); 127.7 (C_p); 128.27 (C_m); 138.18 (C_{ipso}).

(2*S*,3*R*,4*R*)-1-(Benzyloxy)-5-[(*tert*-butyl)diphenylsilyloxy]-2,4-dimethylpentan-3-ol (**11**). A soln. of **10** (4.817 g, 20.24 mmol) in DMF (50 ml) was treated with imidazole (2.067 g, 30.36 mmol), *t*-Bu(Ph) $_2$ SiCl (5.54 ml, 21.65 mmol), and 4 Å molecular sieves. After stirring at r.t. for 23 h, the mixture was filtered and quenched with H_2O (100 ml). The aq. layer was extracted with Et_2O , the combined Et_2O extract washed with brine, dried, and evaporated, and the product purified by CC (AcOEt/pentane 1:99 to 1:9): 7.982 g (94 %) of **11**. Colourless oil. $[\alpha]_D^{25} = -5.13$ ($c = 2.34$, CHCl_3). IR (NaCl): 3510 (OH), 3070, 3030, 2960, 2930, 2860. $^1\text{H-NMR}$ (400 MHz): 1.0, 1.02 (2*d*, $J = 6.9$, Me–C(4), Me–C(2)); 1.05 (*s*, *t*-BuSi); 1.80, 1.91 (2*m*, H–C(4), H–C(2)); 2.82 (*d*, $J = 3$, OH); 3.42, 3.63 (2*m*, $\text{CH}_2(5)$, $\text{CH}_2(1)$); 3.71 (*m*, H–C(3)); 4.48 (*s*, PhCH_2O); 7.25–7.45, 7.64–7.67 (2*m*, 15 arom. H).

(2*S*,4*R*)-1-(Benzyloxy)-5-[(*tert*-butyl)diphenylsilyloxy]-2,4-dimethylpentan-3-one (**12**). To oxalyl chloride (2.2 ml, 24.55 mmol) in abs. CH_2Cl_2 (70 ml) at -78° was added DMSO (2.42 ml, 34.06 mmol) in CH_2Cl_2 (6 ml). After stirring for 5 min, **11** (8.112 g, 17.0 mmol) in CH_2Cl_2 (25 ml) was added dropwise. After 25 min, Et_3N (11.2 ml) was added and the mixture stirred for additional 15 min. Then, the mixture was cooled to r.t., H_2O (120 ml) added, the org. layer separated, the aq. phase extracted twice with CH_2Cl_2 (100 ml), the combined org. extract washed with brine, dried, and evaporated, and the residue filtered over silica gel (20 g; AcOEt/pentane 1:9): 8.027 g (99 %) of **12**. Slightly yellow oil. $[\alpha]_D^{25} = -15.6$ ($c = 1.11$, CHCl_3). IR (NaCl): 3070, 3050, 3030, 2960, 2930, 2860, 1715. $^1\text{H-NMR}$ (400 MHz): 1.02 (*s*, *t*-BuSi); 1.03, 1.15 (2*d*, $J = 7$, Me–C(4), Me–C(2)); 3.04 (*m*, H–C(4), H–C(2)); 3.39, 3.68 (2*dd*, $J = 6.6$, 9.2, $\text{CH}_2(5)$ or $\text{CH}_2(1)$); 3.57, 3.88 (2*dd*, $J = 6.9$, 10 and 7.3, 10, resp., $\text{CH}_2(1)$ or $\text{CH}_2(5)$); 4.44 (*q*, $J = 6.4$, PhCH_2O); 7.23–7.32, 7.35–7.44, 7.62–7.66 (3*m*, 15 arom. H). $^{13}\text{C-NMR}$ (101 MHz, APT): 13.67, 13.99 ($\text{CH}_3\text{--C}(2)$, $\text{CH}_3\text{--C}(4)$); 20.04 ($(\text{CH}_3)_3\text{CSi}$); 27.38 ($(\text{CH}_3)_3\text{CSi}$); 47.22, 48.91 ($\text{C}(2)$, $\text{C}(4)$); 67.08 ($\text{C}(5)$); 73.06 ($\text{C}(1)$); 74.16 (PhCH_2O); 128.61, 128.71, 128.85, 128.87, 129.35, 130.97, 136.72, 136.73, 136.76 (C_o , C_m , C_p); 134.57, 139.59 (C_{ipso}); 217.46 ($\text{C}(3)$).

(2*S*,3*S*,4*R*)-1-(*Benzyloxy*)-5-[*(tert-butyl)diphenylsilyloxy*]-2,4-dimethylpentan-3-ol (**13**). To a soln. of **12** (8.028 g, 16.92 mmol) in abs. Et₂O (200 ml) at –78°, 0.15M Zn(BH₄)₂/Et₂O [**12**] (250 ml) was added slowly during 3 h. After stirring for 7 h at –78°, the mixture was brought to r.t., H₂O (18 ml) added slowly, and stirring continued for 3 h. The suspension was dried (Na₂SO₄), filtered, and evaporated: 8.05 g (99.9%) of **11**/**13**. CC (AcOEt/pentane 1:5) yielded 4.244 g (53%) of **13** and 2.666 g (33%) of **11**. An additional amount of 1.32 g of **13** was obtained from **11** by a second reaction cycle. Total yield: 5.56 g (69%) of **13**. Colourless oil. $[\alpha]_D^{25} = -6.18$ ($c = 0.76$, CHCl₃). IR (NaCl): 3500 (OH), 3070, 3050, 3030, 2960, 2930, 2860, 1600. ¹H-NMR (400 MHz): 0.96, 0.98 (2*d*, $J = 7$, Me–C(4), Me–C(2)); 1.05 (*s*, *t*-BuSi); 1.91, 2.01 (2*m*, H–C(4), H–C(2)); 3.41 (*m*, H–C(3)); 3.53, 3.61 (2*dd*, $J = 9.2$, 5.6, CH₂(1) or CH₂(5)); 3.61 (*d*, $J = 4.6$, OH); 3.73 (*d*, $J = 5.5$, CH₂(5) or CH₂(1)); 4.50 (*s*, PhCH₂O); 7.26–7.44, 7.66–7.69 (2*m*, 15 arom. H). CI-MS (NH₃): 477 (57, $[M + 1]^+$), 399 (8), 341 (3), 291 (12), 251 (13), 231 (25), 108 (46), 91 (100), 78 (5).

(2*S*,3*S*,4*R*)-5-[*(tert-Butyl)diphenylsilyloxy*]-2,4-dimethylpentane-1,3-diol (**14**). To a soln. of **13** (5.306 g, 11.14 mmol) in AcOEt (340 ml), 10% Pd/C (2.123 g) was added and the mixture hydrogenated for 7 h at r.t. and normal pressure under constant shaking. The mixture was filtered over *Celite* and evaporated. The product was purified by CC (AcOEt/pentane 1:2): 4.01 g (93%) of **14**. Colourless oil. $[\alpha]_D^{25} = -7.5$ ($c = 1.54$, CHCl₃). IR (CHCl₃, 0.2 mm): 3440 (OH), 3070, 3050, 3000, 2960, 2930, 2860. ¹H-NMR (400 MHz): 0.94, 0.97 (2*d*, $J = 7$, Me–C(4), Me–C(2)); 1.06 (*s*, *t*-BuSi); 1.62 (*m*, 2 OH); 1.87, 1.94 (2*m*, H–C(4), H–C(2)); 3.57 (*t*(*dd*), $J = 6$, H–C(3)); 3.64 (*dd*, $J = 10.3$, 6.2, CH₂(5)); 3.87 (*dd*, $J = 10.3$, 3.7, CH₂(1)); 7.32–7.46, 7.66–7.70 (2*m*, 10 arom. H).

(2*R*,3*S*,4*S*)-1-[*(tert-Butyl)diphenylsilyloxy*]-3,5-(*isopropylidenedioxy*)-2,4-dimethylpentane (**15**). To a soln. of **4** (4.125 g, 10.67 mmol) in 2,2-dimethoxypropane (260 ml), camphorsulfonic acid (206.3 mg) was added and stirred for 6 h at r.t. Then, the acid was neutralized by adding Et₃N (314 μ l), and the mixture was evaporated. The residue was purified by CC (AcOEt/pentane 1:9): 4.166 g (92%) of **15**. Colourless oil. $[\alpha]_D^{25} = +4.5$ ($c = 1.57$, CHCl₃). IR (CCl₄, 0.2 mm): 3070, 3050, 3000, 2960, 2920, 2860. ¹H-NMR (400 MHz): 0.67 (*d*, $J = 6.6$, Me–C(4)); 0.97 (*d*, $J = 7$, Me–C(2)); 1.05 (*s*, *t*-BuSi); 1.33, 1.37 (2*s*, Me₂CO₂); 1.95 (*m*, H–C(4), H–C(2)); 3.41 (*dd*, $J = 11$, 3, 1 H, CH₂(1)); 3.43 (*dd*, $J = 2.3$, 10.2, H–C(3)); 3.52 (*dd*, $J = 7$, 10.2, 1 H, CH₂(5)); 3.62 (*dd*, $J = 5$, 11.4, 1 H, CH₂(1)); 3.84 (*dd*, $J = 6.2$, 10.2, 1 H, CH₂(5)); 7.35–7.44, 7.67–7.70 (2*m*, 10 arom. H).

(2*R*,3*R*,4*S*)-3,5-(*Isopropylidenedioxy*)-2,4-dimethylpentan-1-ol (**16**). A soln. of **15** (4.166 g, 9.77 mmol) in THF (90 ml) was treated with Bu₄NF (7.543 g, 24.43 mmol). After stirring for 16 h at r.t., Et₂O (45 ml) and brine (45 ml) were added, and the H₂O layer was extracted with Et₂O. The combined Et₂O extract was dried and evaporated, the residue filtered over silica gel (15 g; AcOEt/pentane 2:1), and the product purified by CC (AcOEt/pentane 1:4 to 1:2): 1.82 g (99%) of **16**. Colourless oil. $[\alpha]_D^{25} = +18.9$ ($c = 3.14$, CHCl₃). IR (CCl₄, 0.2 mm): 3530 (OH), 2980, 2960, 2920, 2850. ¹H-NMR (400 MHz): 0.76 (*d*, $J = 6.6$, Me–C(4) or Me–C(2)); 1.12 (*d*, $J = 7.1$, Me–C(2) or Me–C(4)); 1.39, 1.41 (2*s*, Me₂CO₂); 1.86, 1.99 (2*m*, H–C(4), H–C(2)); 2.78 (*br. s*, OH); 3.50 (*dd*, $J = 11$, 2, CH₂(1)); 3.55 (*dd*, $J = 2.3$, 10.4, H–C(3)); 3.73 (*dd*, $J = 5.1$, 11.4, 1 H, CH₂(5)); 3.95 (*dd*, $J = 2.9$, 11.4, 1 H, CH₂(5)). CI-MS (NH₃): 189 (69, $[M + 1]^+$), 173 (10), 148 (14), 131 (100), 113 (88), 95 (16), 58 (8).

(2*S*,3*S*,4*S*)-3,5-(*Isopropylidenedioxy*)-2,4-dimethylpentanal (**17**). To oxalyl chloride (1.02 ml, 11.92 mmol) in CH₂Cl₂ (18 ml) at –78° was added DMSO (1.12 ml) in CH₂Cl₂ (4 ml). After stirring for 5 min, a soln. of **16** (1.494 g, 7.947 mmol) in CH₂Cl₂ (8 ml) was added dropwise within 15 min. The mixture was stirred for 25 min and then treated with Et₃N (5.1 ml). After additional 15 min at –78°, the mixture was brought to r.t. and quenched with H₂O (40 ml). The H₂O phase was extracted with CH₂Cl₂, the combined org. extract washed with brine, dried, and evaporated, and the crude product filtered over silica gel (20 g; AcOEt/pentane 1:4): 1.403 g (95%) of **17** as a slightly yellow oil. The product was directly dissolved in abs. THF (17.4 ml) with a small amount of 4 Å molecular sieves and stored overnight under Ar in the refrigerator. This soln. was used for the next reaction step. IR (NaCl): 2990, 2980, 2940, 2880, 2850, 2730, 1730. ¹H-NMR (90 MHz): 0.85 (*d*, $J = 6$, Me–C(4)); 1.2 (*d*, $J = 6$, Me–C(2)); 1.4, 1.45 (2*s*, Me₂CO₂); 2.1 (*m*, H–C(4)); 2.6 (*m*, H–C(2)); 3.4–3.9 (*m*, H–C(3), CH₂(5)); 9.75 (*d*, $J = 3$, CHO).

2,6-Dimethylphenyl (2*R*,3*R*,4*R*,5*S*,6*S*)-3-Hydroxy-5,7-(*isopropylidenedioxy*)-2,4,6-trimethylheptanoate (**19**). Aldehyde **17** was used directly in dried THF soln. as prepared above. Similarly, a THF soln. of 2,6-dimethylphenyl propionate (preparation according to [11]) was dried with 4 Å molecular sieves (0.1 g ester/1 ml THF). To (i-Pr)₂NH (2.35 ml, 16.595 mmol) in THF (11.5 ml) at 0° under Ar was added 1.59M BuLi in hexane (10.44 ml). After stirring for 10 min, the soln. was cooled to –78°. Then, 2,6-dimethylphenyl propionate (2.98 g, 16.78 mmol) in THF (29.8 ml) was added slowly and the mixture stirred for 1 h. Then, **17** (1.403 g, 7.543 mmol) in THF (17.4 ml) was added and stirring continued for 1 h at –78°. The mixture was treated with sat. NH₄Cl soln. (23 ml) and brought to r.t. The mixture was extracted with Et₂O, the combined org. extract washed with brine, dried, and evaporated, and the resulting yellow oil purified by CC (AcOEt/pentane 1:9 to 1:4): 2.418 g (88%) of **19**. After recrystallization from hexane, the m.p. was 124–126°. $[\alpha]_D^{25} = +7.69$ ($c = 1.04$, CCl₄). IR (CCl₄, 0.2 mm): *ca.* 3520 (OH), 3050, 2990, 2960, 2930, 2880, 2860, 1760. ¹H-NMR (400 MHz): 0.77 (*d*, $J = 6.7$, Me–C(6)); 1.08 (*d*, $J = 7.2$,

Me-C(4)); 1.24 (*d*, *J* = 7, Me-C(2)); 1.4, 1.43 (2s, Me₂CO₂); 1.94 (br. *q*, *J* = 7.2, H-C(4)); 2.15 (*m*, H-C(6)); 2.2 (*s*, 2 arom. Me); 2.87 (*dq*, *J* = 10.1, 7, H-C(2)); 3.53 (*t*(*dd*), *J* = 11.5, 1 H, CH₂(7)); 3.64 (*m*, H-C(5)); 3.66 (*dd*, *J* = 2.1, 10.6, H-C(3)); 3.75 (*dd*, *J* = 5.1, 11.6, 1 H, CH₂(7)); 4.33 (*d*, *J* = 10.1, OH); 7.03–7.06 (*m*, 3 arom. H). ¹³C-NMR (101 MHz, APT): 10.40 (CH₃-C(2)); 12.42 (CH₃-C(4)); 14.13 (CH₃-C(6)); 16.42 (2 arom. CH₃); 18.69 (C(6)); 29.75, 30.99 ((CH₃)₂CO₂); 32.64 (C(4)); 44.01 (C(2)); 66.1 (C(7)); 72.16 (C(3)); 81.56 (C(5)); 98.99 ((CH₃)₂CO₂); 125.65 (C_p); 128.48 (C_m); 130.54 (C_o); 148.12 (C_{ipso}); 173.41 (C(1)). CI-MS (NH₃): 365 (13, [*M* + 1]⁺), 307 (29), 289 (19), 243 (18), 187 (41), 129 (83), 122 (18), 111 (100), 58 (7). Anal. calc. for C₂₁H₃₂O₅ (364.49): C 69.20, H 8.85; found: C 69.12, H 8.94.

X-Ray Diffraction of 19. Suitable crystals of **19** were obtained by recrystallization from hexane. Details of crystal data and parameters of data of collections are given in the *Table*. Unit cell parameters were determined from accurate centering of 25 strong reflections by the least-squares method. Four standard reflections monitored every 3600 s showed no significant variation of the intensity. The raw data set was corrected for polarization, but no correction for absorbance was applied. The structure was determined by the direct method using the programs SHELXS-76 [13] and SHELXS-86 [14]. Anisotropic least-squares refinements were carried out on all non-H-atoms. Scattering factors are from *Cromer et al.* [15], except those for H-atoms which are from *Stewart et al.* [16]. The *Figure* shows an ORTEP plot for **19**. Fractional coordinates and supplementary material are deposited in the *Cambridge Crystallographic Data Base*.

Table. Crystal Data and Parameters of the Data Collection for **19**

Formula	C ₂₁ H ₃₂ O ₅	Temperature [K]	293
Space group	orthorhombic, <i>P</i> 2 ₁ 2 ₁ 2 ₁	Θ _{max} [°]	28
<i>a</i> [Å]	14.444 (9)	Radiation	MoK _α (λ = 0.71069 Å)
<i>b</i> [Å]	14.952 (5)	Scan type	ω/2θ
<i>c</i> [Å]	9.792 (1)	Collected intensities	± <i>h</i> , ± <i>k</i> , ± <i>l</i>
α [°]	90	No. of ind. reflections	1780
β [°]	90	No. of refl. used in ref.	1179
γ [°]	90	No. of variables	256
<i>V</i> [Å ³]	2114.95	Final <i>R</i> value	0.0709
<i>Z</i>	4		

2,6-Dimethylphenyl (2R,3R,4S,5S,6S)-3,5,7-Trihydroxy-2,4,6-trimethylheptanoate (20). A soln. of **19** (2.418 g, 6.643 mmol) in THF (45 ml) was treated with 30 drops of conc. HCl soln. and stirred for 2.5 h at r.t. The mixture was neutralized with solid NaHCO₃ and stirred together with solid Na₂SO₄ for 1 additional h. The mixture was filtered and evaporated and the resulting product purified by CC (AcOEt/pentane 1:1): 1.434 g (67%) of **20**. Glassy viscous wax. [α]_D²⁵ = +11.46 (*c* = 1.3, CHCl₃). IR (CHCl₃, 0.2 mm): 3680, 3620 and 3430 (OH), 3030, 3000, 2970, 2930, 2880, 1740. ¹H-NMR (300 MHz): 0.84 (*d*, *J* = 7, Me-C(6)); 1.12 (*d*, *J* = 7.1, Me-C(4)); 1.27 (*d*, *J* = 7.1, Me-C(2)); 1.87, 2.05 (2*m*, H-C(4), H-C(6)); 2.18 (*s*, 2 arom. Me); 2.94 (*dq*, *J* = 10.1, 7.1, H-C(2)); 3.59–3.65 (*m*, OH, CH₂(7)); 3.79 (*dd*, *J* = 3.5, 10.7, H-C(5)); 4.06 (br. *s*, OH); 4.33 (*d*, *J* = 10.1, H-C(3)); 4.65 (br. *s*, OH); 7.06 (*s*, 3 arom. H); the 3 OH exchanged with D₂O. ¹³C-NMR (75 MHz, APT): 10.42 (CH₃-C(2)); 13.56 (CH₃-C(4)); 14.00 (CH₃-C(6)); 16.45 (2 arom. CH₃); 33.93 (C(6)); 37.47 (C(4)); 44.08 (C(2)); 69.06 (C(7)); 72.79 (C(3)); 83.39 (C(5)); 126.37 (C_p); 129.09 (C_m); 130.72 (C_o); 148.56 (C_{ipso}); 174.67 (C(1)). CI-MS (NH₃): 325 (14, [*M* + 1]⁺), 220 (100), 203 (29), 185 (21), 167 (15), 122 (13), 111 (8).

*2,6-Dimethylphenyl (2R,3R,4S,5S,6S)-7-[*t*-tert-Butyl)diphenylsilyloxy]-3,5-dihydroxy-2,4,6-trimethylheptanoate (21).* To **20** (1.445 g, 4.456 mmol) in abs. DMF (6 ml) was added *t*-Bu(Ph)₂SiCl (1.25 ml, 4.901 mmol), imidazole (0.4854 g, 7.13 mmol), and a small amount of 4 Å molecular sieves. This mixture was stirred for 7 h at r.t., filtered, and then quenched with ice-cooled sat. NH₄Cl soln. (10 ml). The H₂O layer was extracted with Et₂O, the combined org. extract washed with brine, dried, and evaporated, and the resulting yellow oil purified by CC (AcOEt/pentane 1:9 to 1:4): 2.497 g (96%) of **21**. Viscous oil. [α]_D²⁵ = +19.21 (*c* = 4.55, CHCl₃). IR (NaCl): 3440 (OH), 3070, 3040, 2960, 2930, 2880, 2860, 1740. ¹H-NMR (300 MHz): 0.75 (*d*, *J* = 6.9, Me-C(6)); 1.05 (*s*, *t*-BuSi); 1.15 (*d*, *J* = 7.1, Me-C(4)); 1.26 (*d*, *J* = 7.1, Me-C(2)); 1.86, 2.17 (2*m*, H-C(4), H-C(6)); 2.22 (*s*, 2 arom. Me); 2.93 (*dq*, *J* = 10.1, 7.1, H-C(2)); 3.64–3.79 (*m*, OH, CH₂(7)); 3.81 (*dd*, *J* = 4.1, 10.3, H-C(5)); 4.36 (*d*, *J* = 10, H-C(3)); 4.83 (br. *s*, OH); 7.05 (*s*, Me₂C₆H₃); 7.26–7.49 (*m*, 6 H, H_m, H_p of PhSi); 7.67–7.7 (*m*, 4 H, H_o of PhSi); the 2 OH exchanged with CD₃OD. ¹³C-NMR (75 MHz, APT): 10.22 (CH₃-C(2)); 12.86 (CH₃-C(4)); 13.77 (CH₃-C(6)); 16.15 (2 arom. CH₃); 18.75 ((CH₃)₃CSi); 26.54 ((CH₃)₃CSi); 33.85 (C(6)); 36.85 (C(4)); 43.9 (C(2)); 70.21 (C(7)); 72.5 (C(3)); 82.83 (C(5)); 125.83 (C_p of ArO); 128.06, 128.11 (C_m, C_p of PhSi); 128.66 (C_m of ArO); 130.2, 130.26 (C_m, C_p of PhSi); 130.66 (C_o of ArO); 132.41, 132.61 (C_{ipso} of PhSi); 135.74 (C_o of PhSi); 148.5 (C_{ipso}

of ArO); 174.15 (C(1)). FAB-MS (3-nitrobenzyl alcohol): 563 (19, $[M + 1]^+$), 363 (3), 333 (6), 269 (7), 239 (16), 199 (69), 183 (16), 135 (100), 121 (29), 105 (30).

2,6-Dimethylphenyl (2R,3R,4S,5S,6S)-7-[(tert-Butyl)diphenylsilyloxy]-3,5-(isopropylidenedioxy)-2,4,6-trimethylheptanoate (22). A soln. of **21** (2.113 g, 3.754 mmol) in 2,2-dimethoxypropane (100 ml) was treated with camphorsulfonic acid (105.6 mg). After stirring for 5 h, the acid was neutralized with Et_3N (161 μl) and the solvent evaporated. The product was purified by CC (AcOEt/pentane 5:95): 2.192 g (97%) of **22**. Glassy viscous oil. $[\alpha]_D^{25} = +24.29$ ($c = 1.4$, CHCl_3). IR (CCl_4 , 0.2 mm): 3070, 3050, 2960, 2930, 2880, 2860, 1760. $^1\text{H-NMR}$ (300 MHz): 0.93 (d , $J = 6.7$, Me–C(6)); 1.0 (d , $J = 7$, Me–C(4)); 1.04 (s , $t\text{-BuSi}$); 1.19 (d , $J = 7$, Me–C(2)); 1.22, 1.27 (2s, Me_2CO_2); 1.82, 1.95 (2m, H–C(4), H–C(6)); 2.15 (s , 2 arom. Me); 2.87 (dq , $J = 11$, 7, H–C(2)); 3.37 (t (dd), $J = 6.5$, H–C(5)); 3.64–3.68 (m , $\text{CH}_2(7)$); 3.99 (dd , $J = 4.2$, 11, H–C(3)); 7.03 (s , $\text{Me}_2\text{C}_6\text{H}_3$); 7.35–7.41 (m , 6 H, H_m , H_p of PhSi); 7.66–7.69 (m , 4 H, H_o of PhSi). $^{13}\text{C-NMR}$ (75 MHz, APT): 12.09 ($\text{CH}_3\text{--C}(2)$); 13.56 ($\text{CH}_3\text{--C}(4)$); 16.12 (2 arom. CH_3); 19.67 ($(\text{CH}_3)_3\text{CSi}$); 23.26 ($\text{CH}_3\text{--C}(6)$); 24.95 ($(\text{CH}_3)_2\text{CO}_2$); 26.7 ($(\text{CH}_3)_2\text{CSi}$); 33.77 (C(6)); 39.86 (C(4)); 40.64 (C(2)); 65.05 (C(7)); 70.83 (C(3)); 75.81 (C(5)); 100.86 ($(\text{CH}_3)_2\text{CO}_2$); 125.88 (C_o of ArO); 127.79 (C_m , C_p of PhSi); 128.66 (C_m of ArO); 129.74 (C_m , C_p of PhSi); 130.49 (C_o of ArO); 133.83 (C_o of PhSi); 134.1 (C_{ipso} of PhSi); 148.5 (C_{ipso} of ArO); 173.58 (C(1)). FAB-MS (3-nitrobenzyl alcohol): 603 (2, $[M + 1]^+$), 545 (5), 487 (6), 345 (4), 309 (6), 289 (16), 269 (18), 239 (18), 199 (39), 183 (18), 135 (100), 121 (32), 105 (27).

2,6-Dimethylphenyl (2R,3R,4S,5S,6S)-7-Hydroxy-3,5-(isopropylidenedioxy)-2,4,6-trimethylheptanoate (23). To a soln. of **22** (2.192 g, 3.636 mmol) in THF (30 ml), Bu_4NF (2.868 g, *ca.* 9 mmol) was added and stirred for 7 h at r.t. The soln. was diluted with Et_2O (30 ml) and washed with brine (40 ml). The H_2O layer was extracted with Et_2O , the combined Et_2O layer dried and evaporated, and the product purified by CC (AcOEt/pentane 1:3): 1.315 g (99%) **23**. After recrystallization from hexane, the m.p. was 77–79°. $[\alpha]_D^{21} = +44.06$ ($c = 1.28$, CHCl_3). IR (CCl_4 , 0.2 mm): 3640 and 3550 (OH), 3070, 3050, 3030, 2980, 2940, 2920, 2880, 1760. $^1\text{H-NMR}$ (300 MHz): 0.98 (d , $J = 7.1$, Me–C(6)); 1.02 (d , $J = 7.1$, Me–C(4)); 1.27 (d , $J = 7.1$, Me–C(2)); 1.29, 1.34 (2s, Me_2CO_2); 1.82, 1.94 (2m, H–C(4), H–C(6)); 2.17 (s , 2 arom. Me); 2.35 (br. s , exchanged with CD_3OD , OH); 2.91 (dq , $J = 11$, 7.1, H–C(2)); 3.33 (t (dd), $J = 6.5$, H–C(5)); 3.6 (dd , $J = 6.1$, 11.2, 1 H, $\text{CH}_2(7)$); 3.75 (dd , $J = 3.2$, 11.2, 1 H, $\text{CH}_2(7)$); 4.12 (dd , $J = 4.1$, 11, H–C(3)); 7.05 (s , 3 arom. H). $^{13}\text{C-NMR}$ (75 MHz, APT): 12.38 ($\text{CH}_3\text{--C}(2)$); 13.85, 14.05 ($\text{CH}_3\text{--C}(4)$, $\text{CH}_3\text{--C}(6)$); 16.37 (2 arom. CH_3); 23.17, 24.88 ($(\text{CH}_3)_2\text{CO}_2$); 35.28 (C(6)); 39.09 (C(4)); 40.46 (C(2)); 66.54 (C(7)); 70.72 (C(3)); 80.32 (C(5)); 101.2 ($(\text{CH}_3)_2\text{CO}_2$); 125.9 (C_p); 128.65 (C_m); 130.34 (C_o); 148.31 (C_{ipso}); 173.67 (C(1)). FAB-MS (3-nitrobenzyl alcohol): 365 (32, $[M + 1]^+$), 349 (6), 307 (24), 289 (20), 259 (19), 243 (14), 185 (100), 167 (53), 139 (54), 129 (65), 111 (63), 105 (30), 59 (78), 43 (83).

2,6-Dimethylphenyl (2R,3R,4S,5R,6R)-3,5-(Isopropylidenedioxy)-2,4,6-trimethyl-7-oxoheptanoate (24). To oxalyl chloride (219 μl , 2.44 mmol) in abs. CH_2Cl_2 (8 ml) at -78° was added DMSO (232 μl , 3.26 mmol) in abs. CH_2Cl_2 (2 ml) and the mixture was stirred for 5 min. Then, a soln. of **23** (0.593 g, 1.628 mmol) in abs. CH_2Cl_2 (4 ml) was added slowly, and stirring was continued for another 20 min. Et_3N (1.04 ml, 7.4 mmol) was added, and after 15 min at -78° , the mixture was brought to r.t. and quenched with H_2O (30 ml). The H_2O layer was extracted with CH_2Cl_2 , the extract washed with brine, dried, and evaporated, and the product filtered over silica gel (15 g; AcOEt/pentane 1:2): 0.652 g (100%) of **24**. Slightly yellow oil. Aldehyde **24** was treated as described for **17** and its dried THF soln. used directly for the next step. $[\alpha]_D^{20} = +26.69$ ($c = 2.6$, CCl_4). IR (CCl_4 , 0.2 mm): 3070, 3050, 3030, 2980, 2940, 2880, 2820, 2720, 1760. $^1\text{H-NMR}$ (300 MHz): 0.99 (d , $J = 6.9$, Me–C(4)); 1.17 (d , $J = 7.1$, Me–C(6)); 1.26 (d , $J = 7$, Me–C(2)); 1.27, 1.32 (2s, Me_2CO_2); 2.04 (m , H–C(4)); 2.16 (s , 2 arom. Me); 2.49 (m , H–C(6)); 2.81 (dq , $J = 11$, 7, H–C(2)); 3.51 (dd , $J = 5.7$, 7.2, H–C(5)); 4.10 (dd , $J = 4.2$, 11, H–C(3)); 7.04 (s , 3 arom. H); 9.76 (d , $J = 2.6$, CHO). $^{13}\text{C-NMR}$ (75 MHz, APT): 10.78, 11.69, 13.46 ($\text{CH}_3\text{--C}(2)$, $\text{CH}_3\text{--C}(4)$, $\text{CH}_3\text{--C}(6)$); 15.98 (2 arom. CH_3); 23.01, 24.37 ($(\text{CH}_3)_2\text{CO}_2$); 34.71 (C(4)); 40.4 (C(2)); 49.65 (C(6)); 70.49 (C(3)); 76.27 (C(5)); 101.36 ($(\text{CH}_3)_2\text{CO}_2$); 125.86 (C_p); 128.6 (C_m); 130.28 (C_o); 148.25 (C_{ipso}); 173.55 (C(1)); 204.85 (C(7)).

Bis(2,6-dimethylphenyl) (2S,3S,4S,5S,6S,7R,8R)-3-Hydroxy-5,7-(isopropylidenedioxy)-2,4,6,8-tetramethyl-nonane-1,9-dioate (3). The starting materials were dried and used as described for **19**. A soln. of (i-Pr) $_2\text{NH}$ (0.554 ml, 3.91 mmol) in THF (3 ml) was treated with 1.59M BuLi /hexane (2.46 ml, 3.91 mmol) and stirred for 10 min at 0° . Then, the mixture was cooled to -78° , 2,6-dimethylphenyl propionate (0.75 g, 4.2 mmol) in THF (7.5 ml) added, and stirring continued for 1 h. Then, **24** (0.643 g, 1.629 mmol) in THF (3 ml) was added. After stirring for 1 h at -78° , sat. NH_4Cl soln. (15 ml) was added and the mixture brought to r.t. The mixture was diluted with Et_2O , the H_2O layer extracted with Et_2O , the combined Et_2O extract washed with brine, dried, and evaporated, and the crude product purified by CC (AcOEt/pentane 5:95 to 1:9): 0.713 g (81%) of **3**. Colourless solid. After recrystallization from pentane, the m.p. was 135–137°. $[\alpha]_D^{21} = +34.31$ ($c = 1.09$, CHCl_3). IR (CCl_4 , 0.2 mm): 3530 (OH), 3070, 3050, 3030, 2980, 2940, 2880, 1760. $^1\text{H-NMR}$ (300 MHz): 0.99 (d , $J = 6.6$, Me–C(6)); 1.1 (d , $J = 7.3$, Me–C(4)); 1.28, 1.30 (2d, $J = 6.4$, Me–C(2), Me–C(8)); 1.31, 1.33 (2s, Me_2CO_2); 1.78 (m , H–C(6)); 2.09 (m , H–C(4)); 2.16, 2.2 (2

s, 4 arom. Me); 2.9–2.97 (*m*, H–C(2), H–C(8)); 3.29 (*d*, $J = 1.6$, OH); 3.45 (*dd*, $J = 3.6, 7.7$, H–C(5)); 4.13 (*dd*, $J = 4.6, 11$, H–C(7)); 4.13 (*br. d*, $J = 10.1$, sharper in CD₃OD, H–C(3)); 7.05 (*s*, 6 arom. H); the 2 OH exchanced with CD₃OD. ¹³C-NMR (75 MHz, APT): 10.82 (CH₃–C(2)); 12.0 (CH₃–C(8)); 14.03, 14.40 (CH₃–C(4), CH₃–C(6)); 16.37, 16.47 (4 arom. CH₃); 23.37, 24.72 ((CH₃)₂CO₂); 34.76 (C(6)); 35.99 (C(4)); 40.95 (C(8)); 44.07 (C(2)); 71.3 (C(7)); 72.79 (C(3)); 80.15 (C(5)); 101.96 ((CH₃)₂CO₂); 126.19, 126.24 (C_p); 128.98 (C_m); 130.68, 130.87 (C_o); 148.64, 148.66 (C_{ipso}); 173.87 (C(8)); 174.45 (C(1)). FAB-MS (3-nitrobenzyl alcohol): 541 (32, [M+]⁺), 483 (16), 465 (13), 419 (16), 361 (39), 343 (21), 259 (42), 239 (61), 221 (33), 183 (47), 149 (41), 122 (77), 109 (87), 105 (45), 85 (49), 77 (32), 69 (100), 57 (39), 43 (68). Anal. calc. for C₃₂H₄₄O₇ (540.69): C 71.08, H 8.20; found: C 70.93, H 8.24.

Bis(2,6-dimethylphenyl) (2S,3S,4R,5R,6S,7R,8R)-3,5,7-Trihydroxy-2,4,6,8-tetramethylnonane-1,9-dioate (25). A soln. of 3 (72.8 mg, 0.135 mmol) in THF (2 ml) was treated with 6 drops of conc. HCl soln. and stirred for 3 h at r.t. Before the reaction was completed, solid NaHCO₃ and Na₂SO₄ were added and stirring continued for additional 15 min. The mixture was filtered and the solvent evaporated. The crude product was purified by CC (AcOEt/pentane 1:2): 21.5 mg (32%) of 25. Colourless oil. $[\alpha]_D^{21} = \pm 0$ ($c = 2.15$, CHCl₃). ¹H-NMR (400 MHz): 1.04 (*d*, $J = 7.1$, Me–C(6), Me–C(4)); 1.34 (*d*, $J = 7.1$, Me–C(2), Me–C(8)); 1.97 (*m*, H–C(6), H–C(4)); 2.17 (*s*, 4 arom. Me); 2.97 (*dq*, $J = 9.9, 7.1$, H–C(2), H–C(8)); 3.28 (*d*, $J = 3.6$, OH–C(3), OH–C(7)); 3.45 (*d*, $J = 7.3$, OH–C(5)); 3.71 (*m*, *t* with CD₃OD, $J = 6.5$, H–C(5)); 4.37 (*br. d*, sharp *dd* with CD₃OD, $J = 1.7, 10.2$, H–C(3), H–C(7)); 7.06 (*s*, 6 arom. H). ¹³C-NMR (101 MHz, APT): 10.17 (CH₃–C(2), CH₃–C(8)); 14.1 (CH₃–C(4), CH₃–C(6)); 16.4 (4 arom. CH₃); 35.26 (C(4), C(6)); 43.9 (C(2), C(8)); 72.31 (C(3), C(7)); 77.99 (C(5)); 125.94 (C_p); 128.63 (C_m); 130.15 (C_o); 147.97 (C_{ipso}); 174.19 (C(1), C(9)).

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