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

by **Marco Born** and **Christoph Tamm***

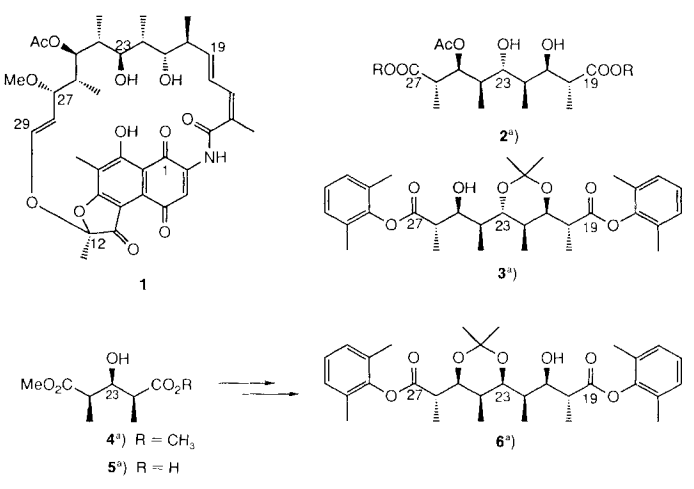
Institut für Organische Chemie der Universität, St. Johanns-Ring 19, CH–4056 Basel

(22.X.90)

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*

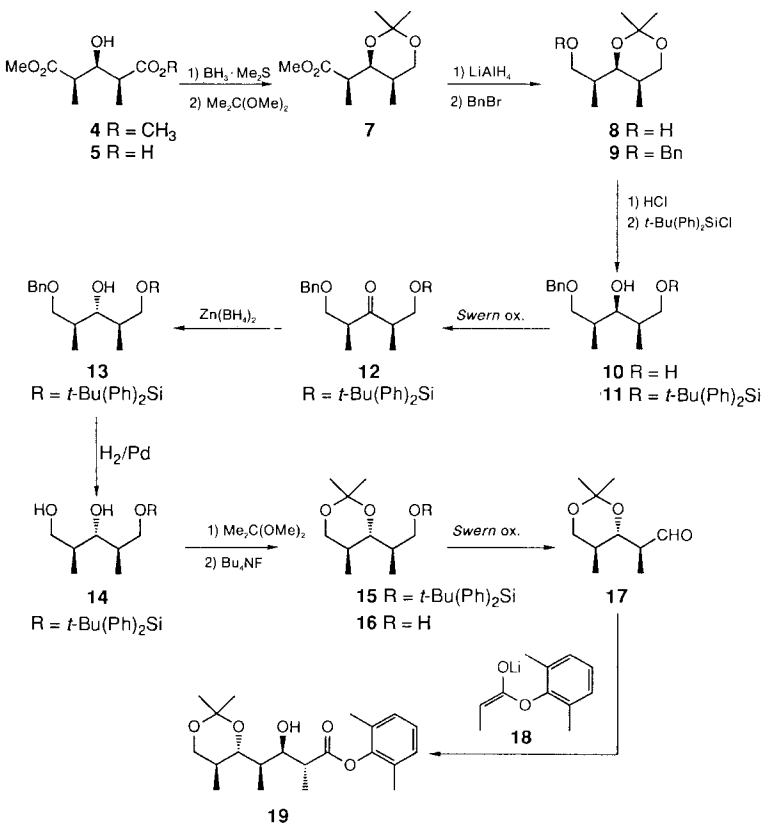



a) Rifamycin-S(**1**) numbering.

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 $BH_3 \cdot Me_2S$ 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 $LiAlH_4$ (→**8**) and benzylation in the presence of $Et_4NI$ [8] (→**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 $Zn(BH_4)_2$ 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 cyclc with a variety of aluminium hydrides and borohydrides. Among all tested variants, $Zn(BH_4)_2$ 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 analysis[1]) 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**.

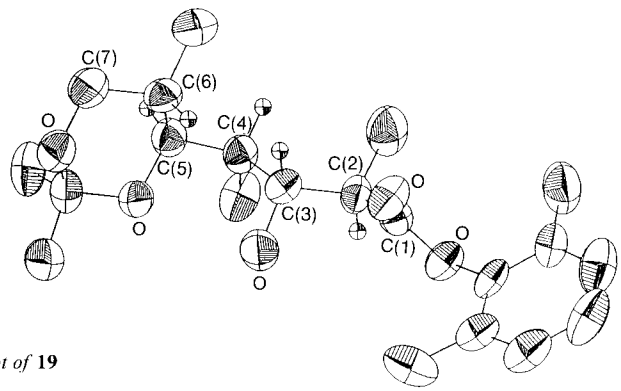
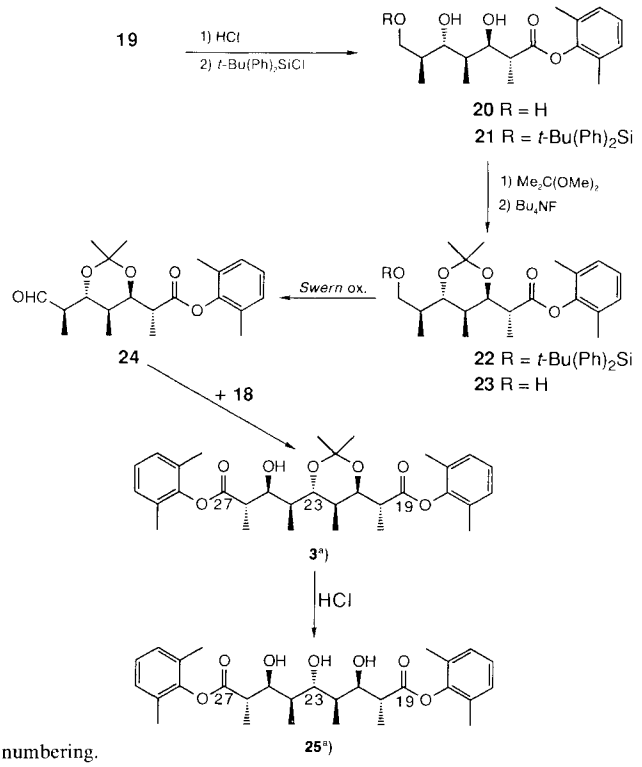



Figure. *ORTEP plot of* **19**

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)$_2$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. $[\alpha]_D$: *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 (corrclation 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, $BH_3 \cdot Me_2S$ (10 ml) was added within 20 min. After stirring for 1.5 h, additional $BH_3 \cdot Me_2S$ (6 ml) was added. After stirrring 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. $[\alpha]_D^{21} = -0.8$ ($c = 2$, $CCl_4$). $^1$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, $CH_2$(5)); 3.7 (*s*, $COOCH_3$); 3.95 (*dd*, $J = 10$, 2, H–C(3)); 4.1 (*dd*, $J = 12$, 3, 1 H, $CH_2$(5)).

*(2S,3R,4R)-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. $[\alpha]_D^{21} = +6.93$ ($c = 1.5$, $CHCl_3$). IR (NaCl): 3440 (OH), 2990, 2960, 2940, 2880. $^1$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), $CH_2$(1)); 3.75 (*dd*, $J = 10$, 2, H–C(3)); 4.1 (*dd*, $J = 12$, 3, 1 H, $CH_2$(5)). CI-MS ($NH_3$): 206 (9, $[M + NH_4]^+$); 189 (100, $[M + 1]^+$), 171 (38), 148 (28), 131 (26), 113 (59).

*(2S,3R,4R)-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. $[\alpha]_D^{23} = +9.52$ ($c = 5.65$, $CHCl_3$). IR (NaCl): 3060, 3030, 2990, 2960, 2940, 2860. $^1$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*, $J = 5$, $CH_2$(5)); 3.65 (*dd*, $J = 12$, 2, 1 H, $CH_2$(1)); 3.75 (*dd*, $J = 10$, 2, H–C(3)); 4.1 (*dd*, $J = 12$, 3, 1 H, $CH_2$(1)); 4.5 (s, $PhCH_2O$); 7.3 (*s*, 5 arom. H). CI-MS ($NH_3$): 279 (34, $[M + 1]^+$), 263 (23), 238 (11), 221 (52), 203 (35), 171 (22), 129 (16), 113 (100), 99 (23), 91 (85).

*(2R,3S,4S)-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. $[\alpha]_D^{21} = -4.1$ ($c = 2.72$, $CHCl_3$). M.p. 39–41°. IR (NaCl): 3380 (OH), 3060, 3030, 2960, 2920, 2870. $^1$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, $CH_2$(1)); 3.62 (*d*, $J = 6.4$, $CH_2$(5)); 3.75 (*t*(*dd*), $J = 5.1$, H–C(3)); 4.49 (*s*, $PhCH_2O$); 7.26–7.37 (*s*, 5 arom. H). $^{13}$C-NMR (101 MHz, APT): 11.51 ($CH_3$–C(2)); 12.49 ($CH_3$–C(4)); 36.33 (C(4)); 37.65 (C(2)); 66.94 (C(1)); 73.37 (C(5)); 74.5 ($PhCH_2O$); 76.03 (C(3)); 126.95 ($C_o$); 127.7 ($C_p$); 128.27 ($C_m$); 138.18 ($C_{ipso}$).

*(2S,3R,4R)-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. $[\alpha]_D^{21} = -5.13$ ($c = 2.34$, $CHCl_3$). IR (NaCl): 3510 (OH), 3070, 3030, 2960, 2930, 2860. $^1$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*, $CH_2$(5), $CH_2$(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).

*(2S,4R)-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. $[\alpha]_D^{22} = -15.6$ ($c = 1.11$, $CHCl_3$). IR (NaCl): 3070, 3050, 3030, 2960, 2930, 2860, 1715. $^1$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, $CH_2$(5) or $CH_2$(1)); 3.57, 3.88 (2*dd*, $J = 6.9$, 10 and 7.3, 10, resp., $CH_2$(1) or $CH_2$(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). $^{13}$C-NMR (101 MHz, APT): 13.67, 13.99 ($CH_3$–C(2), $CH_3$–(C(4)); 20.04 ($(CH_3)_3CSi$); 27.38 ($(CH_3)_3CSi$); 47.22, 48.91 (C(2), C(4)); 67.08 (C(5)); 73.06 (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 (C(3)).

*(2S,3S,4R)-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. $Et_2O$ (200 ml) at −78°, 0.15M $Zn(BH_4)_2/Et_2O$ [12] (250 ml) was added slowly during 3 h. After stirring for 7 h at −78°, the mixture was brought to r.t., $H_2O$ (18 ml) added slowly, and stirring continued for 3 h. The suspension was dried ($Na_2SO_4$), 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. $[\alpha]_D^{22} = -6.18$ ($c = 0.76$, $CHCl_3$). IR (NaCl): 3500 (OH), 3070, 3050, 3030, 2960, 2930, 2860, 1600. $^1$H-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*, $J = 9.2, 5.6$, $CH_2$(1) or $CH_2$(5)); 3.61 (*d*, $J = 4.6$, OH); 3.73 (*d*, $J = 5.5$, $CH_2$(5) or $CH_2$(1)); 4.50 (*s*, $PhCH_2O$); 7.26–7.44, 7.66–7.69 (2*m*, 15 arom. H). CI-MS ($NH_3$): 477 (57, $[M + 1]^+$), 399 (8), 341 (3), 291 (12), 251 (13), 231 (25), 108 (46), 91 (100), 78 (5).

*(2S,3S,4R)-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. $[\alpha]_D^{22} = -7.5$ ($c = 1.54$, $CHCl_3$). IR ($CHCl_3$, 0.2 mm): 3440 (OH), 3070, 3050, 3000, 2960, 2930, 2860. $^1$H-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*, $J = 10.3, 6.2$, $CH_2$(5)); 3.87 (*dd*, $J = 10.3, 3.7$, $CH_2$(1)); 7.32–7.46, 7.66–7.70 (2*m*, 10 arom. H).

*(2R,3S,4S)-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 $Et_3N$ (314 µl), and the mixture was evaporated. The residue was purified by CC (AcOEt/pentane 1:9): 4.166 g (92%) of **15**. Colourless oil. $[\alpha]_D^{24} = +4.5$ ($c = 1.57$, $CHCl_3$). IR ($CCl_4$, 0.2 mm): 3070, 3050, 3000, 2960, 2920, 2860. $^1$H-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*, $Me_2CO_2$); 1.95 (*m*, H–C(4), H–C(2)); 3.41 (*dd*, $J = 11, 3$, 1 H, $CH_2$(1)); 3.43 (*dd*, $J = 2.3, 10.2$, H–C(3)); 3.52 (*dd*, $J = 7, 10.2$, 1 H, $CH_2$(5)); 3.62 (*dd*, $J = 5, 11.4$, 1 H, $CH_2$(1)); 3.84 (*dd*, $J = 6.2, 10.2$, 1 H, $CH_2$(5)); 7.35–7.44, 7.67–7.70 (2*m*, 10 arom. H).

*(2R,3R,4S)-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 $Bu_4NF$ (7.543 g, 24.43 mmol). After stirring for 16 h at r.t., $Et_2O$ (45 ml) and brine (45 ml) were added, and the $H_2O$ layer was extracted with $Et_2O$. The combined $Et_2O$ 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. $[\alpha]_D^{22} = +18.9$ ($c = 3.14$, $CHCl_3$). IR ($CCl_4$, 0.2 mm): 3530 (OH), 2980, 2960, 2920, 2850. $^1$H-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*, $Me_2CO_2$); 1.86, 1.99 (2*m*, H–C(4), H–C(2)); 2.78 (br. *s*, OH); 3.50 (*dd*, $J = 11, 2$, $CH_2$(1)); 3.55 (*dd*, $J = 2.3, 10.4$, H–C(3)); 3.73 (*dd*, $J = 5.1, 11.4$, 1 H, $CH_2$(5)); 3.95 (*dd*, $J = 2.9, 11.4$, 1 H, $CH_2$(5)). CI-MS ($NH_3$): 189 (69, $[M + 1]^+$), 173 (10), 148 (14), 131 (100), 113 (88), 95 (16), 58 (8).

*(2S,3S,4S)-3,5-(Isopropylidenedioxy)-2,4-dimethylpentanal* (**17**). To oxalyl chloride (1.02 ml, 11.92 mmol) in $CH_2Cl_2$ (18 ml) at −78° was added DMSO (1.12 ml) in $CH_2Cl_2$ (4 ml). After stirring for 5 min, a soln. of **16** (1.494 g, 7.947 mmol) in $CH_2Cl_2$ (8 ml) was added dropwise within 15 min. The mixture was stirred for 25 min and then treated with $Et_3N$ (5.1 ml). After additional 15 min at −78°, the mixture was brought to r.t. and quenched with $H_2O$ (40 ml). The $H_2O$ phase was extracted with $CH_2Cl_2$, 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. $^1$H-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*, $Me_2CO_2$); 2.1 (*m*, H–C(4)); 2.6 (*m*, H–C(2)); 3.4–3.9 (*m*, H–C(3), $CH_2$(5)); 9.75 (*d*, $J = 3$, CHO).

*2,6-Dimethylphenyl (2R,3R,4R,5S,6S)-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 $(i\text{-}Pr)_2NH$ (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. $NH_4Cl$ soln. (23 ml) and brought to r.t. The mixture was extracted with $Et_2O$, 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°. $[\alpha]_D^{22} = +7.69$ ($c = 1.04$, $CCl_4$). IR ($CCl_4$, 0.2 mm): *ca.* 3520 (OH), 3050, 2990, 2960, 2930, 2880, 2860, 1760. $^1$H-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 (2*s*, $Me_2CO_2$); 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, $CH_2$(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, $CH_2$(7)); 4.33 (*d*, *J* = 10.1, OH); 7.03–7.06 (*m*, 3 arom. H). $^{13}$C-NMR (101 MHz, APT): 10.40 ($CH_3$–C(2)); 12.42 ($CH_3$–C(4)); 14.13 ($CH_3$–C(6)); 16.42 (2 arom. $CH_3$); 18.69 (C(6)); 29.75, 30.99 (($CH_3$)$_2CO_2$); 32.64 (C(4)); 44.01 (C(2)); 66.1 (C(7)); 72.16 (C(3)); 81.56 (C(5)); 98.99 (($CH_3$)$_2CO_2$); 125.65 ($C_p$); 128.48 ($C_m$); 130.54 ($C_o$); 148.12 ($C_{ipso}$); 173.41 (C(1)). CI-MS ($NH_3$): 365 (13, $[M + 1]^+$), 307 (29), 289 (19), 243 (18), 187 (41), 129 (83), 122 (18), 111 (100), 58 (7). Anal. calc. for $C_{21}H_{32}O_5$ (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 | orthorombic, $P2_12_12_1$ | $\Theta_{max}$ [°] | 28 |
| *a* [Å] | 14.444 (9) | Radiation | Mo$K_\alpha$ ($\lambda$ = 0.71069 Å) |
| *b* [Å] | 14.952 (5) | Scan type | $\omega/2\Theta$ |
| *c* [Å] | 9.792 (1) | Collected intensities | $\pm h$, $\pm k$, $\pm l$ |
| $\alpha$ [°] | 90 | No. of ind. reflections | 1780 |
| $\beta$ [°] | 90 | No. of refl. used in ref. | 1179 |
| $\gamma$ [°] | 90 | No. of variables | 256 |
| *V* [Å$^3$] | 2114.95 | Final *R* value | 0.0709 |
| *Z* | 4 | | |

*2,6-Dimethylphenyl (2*R*,3*R*,4*S*,5*S*,6*S*)-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 $NaHCO_3$ and stirred together with solid $Na_2SO_4$ 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. $[\alpha]_D^{22}$ = +11.46 (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$, 0.2 mm): 3680, 3620 and 3430 (OH), 3030, 3000, 2970, 2930, 2880, 1740. $^1$H-NMR (300 MHz): 0.84 (*d*, *J* = 7, Mc–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, $CH_2$(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 $D_2O$. $^{13}$C-NMR (75 MHz, APT): 10.42 ($CH_3$–C(2)); 13.56 ($CH_3$–C(4)); 14.00 ($CH_3$–C(6)); 16.45 (2 arom. $CH_3$); 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 ($NH_3$): 325 (14, $[M + 1]^+$), 220 (100), 203 (29), 185 (21), 167 (15), 122 (13), 111 (8).

*2,6-Dimethylphenyl (2*R*,3*R*,4*S*,5*S*,6*S*)-7-[(*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)$_2$SiCl (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. $NH_4Cl$ soln. (10 ml). The $H_2O$ layer was extracted with $Et_2O$, the combined org. extract washed with brine, dried, and evapoated, and the resulting yellow oil purified by CC (AcOEt/pentane 1:9 to 1:4): 2.497 g (96%) of **21**. Viscous oil. $[\alpha]_D^{22}$ = +19.21 (*c* = 4.55, $CHCl_3$). IR (NaCl): 3440 (OH), 3070, 3040, 2960, 2930, 2880, 2860, 1740. $^1$H-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, $CH_2$(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*, $Me_2C_6H_3$); 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 $CD_3OD$. $^{13}$C-NMR (75 MHz, APT): 10.22 ($CH_3$–C(2)); 12.86 ($CH_3$–C(4)); 13.77 ($CH_3$–C(6)); 16.15 (2 arom. $CH_3$); 18.75 (($CH_3$)$_3C$Si); 26.54 (($CH_3$)$_3$CSi); 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 (2*R*,3*R*,4*S*,5*S*,6*S*)-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. $[\alpha]_D^{22} = +24.29$ ($c = 1.4$, $CHCl_3$). IR ($CCl_4$, 0.2 mm): 3070, 3050, 2960, 2930, 2880, 2860, 1760. $^1$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*-BuSi); 1.19 (*d*, $J = 7$, Me–C(2)); 1.22, 1.27 (2*s*, $Me_2CO_2$); 1.82, 1.95 (2*m*, 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*, $CH_2$(7)); 3.99 (*dd*, $J = 4.2$, 11, H–C(3)); 7.03 (*s*, $Me_2C_6H_3$); 7.35–7.41 (*m*, 6 H, $H_m$, $H_p$ of PhSi); 7.66–7.69 (*m*, 4 H, $H_o$ of PhSi). $^{13}$C-NMR (75 MHz, APT): 12.09 ($CH_3$–C(2)); 13.56 ($CH_3$–C(4)); 16.12 (2 arom. $CH_3$); 19.67 (($CH_3$)$_3$CSi); 23.26 ($CH_3$–C(6)); 24.95 (($CH_3$)$_2CO_2$); 26.7 (($CH_3$)$_3$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 (($CH_3$)$_2CO_2$); 125.88 ($C_p$ 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 (2*R*,3*R*,4*S*,5*S*,6*S*)-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. $^1$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 (2*s*, $Me_2CO_2$); 1.82, 1.94 (2*m*, 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, $CH_2$(7)); 3.75 (*dd*, $J = 3.2$, 11.2, 1 H, $CH_2$(7)); 4.12 (*dd*, $J = 4.1$, 11, H–C(3)); 7.05 (*s*, 3 arom. H). $^{13}$C-NMR (75 MHz, APT): 12.38 ($CH_3$–C(2)); 13.85, 14.05 ($CH_3$–C(4), $CH_3$–C(6)); 16.37 (2 arom. $CH_3$); 23.17, 24.88 (($CH_3$)$_2CO_2$); 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 (($CH_3$)$_2CO_2$); 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 (2*R*,3*R*,4*S*,5*R*,6*R*)-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. $^1$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 (2*s*, $Me_2CO_2$); 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). $^{13}$C-NMR (75 MHz, APT): 10.78, 11.69, 13.46 ($CH_3$–C(2), $CH_3$–C(4), $CH_3$–C(6)); 15.98 (2 arom. $CH_3$); 23.01, 24.37 (($CH_3$)$_2CO_2$); 34.71 (C(4)); 40.4 (C(2)); 49.65 (C(6)); 70.49 (C(3)); 76.27 (C(5)); 101.36 (($CH_3$)$_2CO_2$); 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) (2*S*,3*S*,4*S*,5*S*,6*S*,7*R*,8*R*)-3-Hydroxy-5,7-(isopropylidenedioxy)-2,4,6,8-tetramethylnonane-1,9-dioate* (**3**). The starting materials were dried and used as described for **19**. A soln. of (i-Pr)$_2$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. $^1$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 (2*d*, $J = 6.4$, Me–C(2), Me–C(8)); 1.31, 1.33 (2*s*, $Me_2CO_2$); 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 $CD_3OD$, H–C(3)); 7.05 (*s*, 6 arom. H); the 2 OH exchanched with $CD_3OD$. $^{13}$C-NMR (75 MHz, APT): 10.82 ($CH_3$–C(2)); 12.0 ($CH_3$–C(8)); 14.03, 14.40 ($CH_3$–C(4), $CH_3$–C(6)); 16.37, 16.47 (4 arom. $CH_3$); 23.37, 24.72 (($CH_3$)$_2CO_2$); 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 (($CH_3$)$_2CO_2$); 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, $[M+1]^+$), 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 $C_{32}H_{44}O_7$ (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 $NaHCO_3$ and $Na_2SO_4$ 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, $CHCl_3$). $^1$H-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 $CD_3OD$, $J$ = 6.5, H–C(5)); 4.37 (br. *d*, sharp *dd* with $CD_3OD$, $J$ = 1.7, 10.2, H–C(3), H–C(7)); 7.06 (*s*, 6 arom. H). $^{13}$C-NMR (101 MHz, APT): 10.17 ($CH_3$–C(2), $CH_3$–C(8)); 14.1 ($CH_3$–C(4), $CH_3$–C(6)); 16.4 (4 arom. $CH_3$); 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)).

## REFERENCES


[1] P. Sensi, P. Margalith, M.T. Timbal, *Farmaco, Ed. Sci.* **1954,** *14,* 146; W. Oppolzer, V. Prelog, P. Sensi, *Experientia* **1964,** *20,* 336; W. Oppolzer, V. Prelog, *Helv. Chim. Acta* **1973,** *56,* 2287; M. Brufani, W. Fedeli, G. Giacomelli, A. Vaciago, *Experientia* **1964,** *20,* 339; K.L. Rinehart, L.S. Shield, in 'Progress in the Chemistry of Organic Natural Products', Eds. W. Hertz, H. Grisebach, and G.M. Kirby, Springer Verlag, New York, 1976, Vol. 33, p. 231; M. Brufani, 'Topics in Antibiotic Chemistry', Ed. P.G. Sammes, Wiley, New York, 1977, Vol. 1, p. 91.

[2] W. Wehrli, *Topics Curr. Chem.* **1977,** *72,* 21.

[3] E.J. Corey, T. Hase, *Tetrahedron Lett.* **1979,** 335; M. Nakata, H. Takao, Y. Ikeyama, T. Sakai, K. Tatsuta, M. Kinoshita, *Bull. Chem. Soc. Jpn.* **1981,** *54,* 1749; H. Nagaoka, Y. Kishi, *Tetrahedron* **1981,** *37,* 3873; S. Masamune, B. Imperiali, D.S. Garvey, *J. Am. Chem. Soc.* **1982,** *104,* 5528; M. Nakata, H. Enari, M. Kinoshita, *Bull. Chem. Soc. Jpn.* **1982,** *55,* 3282; W.C. Still, J.C.J. Barrish, *J. Am. Chem. Soc.* **1983,** *105,* 2487; B. Fraser-Reid, L. Magdzinski, B. Molino, *ibid.* **1984,** *106,* 731; S. Hanessian, J.-R. Pougny, I.K. Boessenkool, *Tetrahedron* **1984,** *40,* 1289; A.V. Rama Rao, J.S. Yadav, V. Vidyasagar, *J. Chem. Soc., Chem. Commun.* **1985,** 55; I. Paterson, M. Mansuri, *Tetrahedron* **1985,** *41,* 3569; S.J. Danishefsky, D.C. Myles, D.F. Harvey, *J. Am. Chem. Soc.* **1987,** *109,* 862; W.R. Roush, A.D. Palkowitz, M.A.J. Palmer, *J. Org. Chem.* **1987,** *52,* 316; W.R. Roush, A.D. Palkowitz, *J. Am. Chem. Soc.* **1987,** *109,* 953; F.E. Ziegler, W.T. Cain, A. Kneisley, E.P. Stirchak, R.T. Wester, *ibid.* **1988,** *110,* 5442; T. Katsuki, T. Hanamoto, M. Yamaguchi, *Chem. Lett.* **1989,** 117; I. Paterson, C.K. McClure, R.C. Schumann, *Tetrahedron Lett.* **1989,** *30,* 1293; W.R. Roush, A.D. Palkowitz, K. Ando, *J. Am. Chem. Soc.* **1990,** *112,* 6348.

[4] H. Nagaoka, W. Rutsch, G. Schmid, H. Iio, M.R. Johnson, Y. Kishi, *J. Am. Chem. Soc.* **1980,** *102,* 7965.

[5] T. Tschamber, N. Waespe-Šarčević, Ch. Tamm, *Helv. Chim. Acta* **1986,** *69,* 621.

[6] P. Mohr, N. Waespe-Šarčević, Ch. Tamm, K. Gawronska, J.K. Gawronski, *Helv. Chim. Acta* **1983,** *66,* 2501.

[7] M. Larcheveque, J. Lalonde, *Tetrahedron* **1984,** *40,* 1061.

[8] S. Czernecki, C. Georgoulis, C. Provenlenghiou, *Tetrahedron Lett.* **1976,** *18,* 3535.

[9] A.J. Mancuso, S.L. Huang, D. Swern, *J. Org. Chem.* **1978,** *43,* 2480.

[10] O. Mitsunobu, *Synthesis* **1981,** 1.

[11] C.H. Heathcock, M.C. Pirrung, S.H. Montgomery, J. Lampe, *Tetrahedron* **1981,** *37,* 4087.

[12] W.J. Genseler, F. Johnson, A. Sloan, *J. Am. Chem. Soc.* **1960,** *82,* 6074.

[13] G.M. Sheldrick, 'SHELXS-76', University of Cambridge, 1976.

[14] G.M. Sheldrick, 'SHELXS-86', Universität Göttingen, 1986.

[15] D.T. Cromer, J.B. Mann, *Acta Crystallogr., Sect. A* **1968,** *24,* 321; D.T. Cromer, D. Libermann, *J. Chem. Phys.* **1970,** *53,* 1891.

[16] R.F. Stewart, E.R. Davidson, W.T. Simpson, *J. Chem. Phys.* **1965,** *42,* 3175.