64. Stereocontrolled Synthesis of an Epimer of the C(19)-to-C(27) Segment of Rifamycin S

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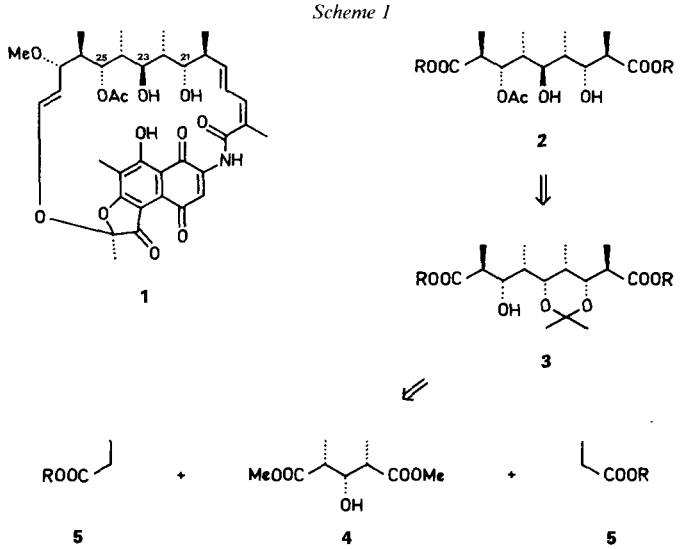
The synthesis of the ansa chain of rifamycin S (**1**), corresponding to the C(19) to C(27) moiety, epimeric at C(23), is described starting from dimethyl *xylo*-3-hydroxy-2,4-dimethylglutarate (**4**). The diester **4** was transformed to the C_{10}-diester **16** by two *threo*-aldol condensations with 2,6-dimethylphenyl propionate (**5**).

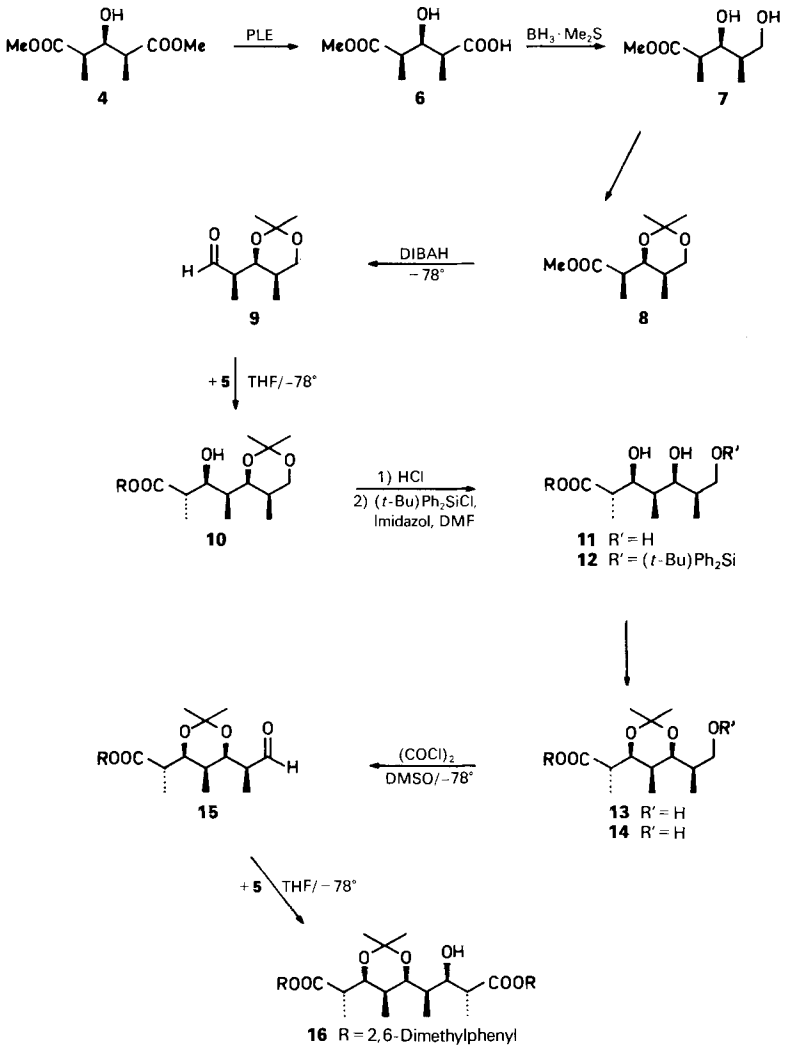
The construction of the sequence of the eight chiral centres in the ansa moiety of the antibiotic rifamycin S (**1**) is a challenge for synthetic chemistry [1]. An interesting feature of this segment is the presence of a symmetry element at C(23). This fact has already been recognized and explored [2]. It also plays an important role in the retrosynthetic analysis of the ester **2** of the dicarboxylic acid, which corresponds to the C(19)-to-C(27) fragment of **1** *(Scheme 1)*. The diester **2** was transformed to dimethyl *xylo*-3-hydroxy-2,4-dimethylglutarate (**4**) and 2 equiv. of the propionate **5** *via* the intermediate **3**.

In [3], we have reported on the high enantioselectivity of the hydrolysis of the achiral dimethylester **4** by pig liver esterase (PLE). We have now made use of the chiral monoester **6**, which was obtained as starting material, for the synthesis of the diester **16** [4]

Scheme 1



Scheme 2



(Scheme 2). The latter is a 23-epimer of the diester **2**. The centres of chirality of **6** correspond to the C(22)-to-C(24) sequence of the ansa fragment of rifamycin S (**1**) with opposite configuration of the OH–C(23) group. It is known that Li-enolates of hindered aryl esters, condens with α-branched aliphatic aldehydes leading to the *threo*-configuration [5]. We, therefore, chose this method for the introduction of the remaining four chiral centres. For this purpose, it was necessary to prepare the corresponding aldehyde and to perform a *threo*-aldolization on both ends of the C_5-unit. Reduction of **6** with $BH_3 \cdot Me_2S$ afforded the diol **7**. The OH-groups were protected as acetonide by treatment of **7** with 2,2-dimethoxypropane in the presence of *Amberlyst 15* in MeOH [6]. Subsequent reduction of the ester **8** using DIBAH in toluene at −78° gave the aldehyde **9** in excellent yield.

To carry out the aldol condensation as the next step, the enolate of 2,6-dimethylphenyl propionate (**5**) was prepared by treatment of the latter with lithium diisopropylamide (LDA) in THF at −78° for 1 h. After addition of the aldehyde **9** to this solution and standing for 1 h at −78°, the ester **10** was obtained (yield 52%). This was followed by removing the protecting isopropylidene group with HCl. Selective silylation of the primary OH-group of the trihydroxy acid **11** was achieved with (*t*-Bu)Ph_2SiCl in DMF using imidazole as the condensing agent. The two remaining secondary OH-groups were blocked again by formation of the acetonide with 2,2-dimethoxypropane in MeOH in the presence of *Amberlyst 15*. Compound **13** was formed in excellent yield. Removal of the (*t*-Bu)Ph_2Si group with Bu_4NF led to the alcohol **14**, which was oxidized to the aldehyde **15** with $(COCl)_2$ in DMSO at −78° according to [6] (yield 96%). The subsequent second aldol condensation of **15** with enolate of 2,4-dimethylphenyl propionate (**5**) was performed under the same conditions as described before. The desired diester **16** was isolated in 70% yield. This epimer of the natural C(19)-to-C(27) segment of rifamycin S (**1**) might be useful for the synthesis of the corresponding epimeric antibiotic.

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Experimental Part

General. H_2O and air-sensitive reactions were carried out under Ar. CH_2Cl_2 and Et_2O were dried by passing through an Al_2O_3 column, THF by distilling over $LiAlH_4$. All org. extracts were dried over Na_2SO_4 and evaporated under reduced pressure below 50°. Pig liver esterase (*EC 3.1.1.1*) was purchased from *Boehringer*. TLC were performed on silica gel *60* F_{254} (*Merck*), and the spots were observed by spraying with a soln. of $KMnO_4$ (2 g) and $NaHCO_3$ (4 g) in H_2O (100 ml), followed by heating. For the flash chromatography, silica gel *60* (230–400 mesh, *Merck*) was used. The m.p. were determined on a *Kofler* block and are uncorrected. Optical rotations and IR (cm^{-1}) were measured with a *Perkin-Elmer* model *141* polarimeter and a *Perkin-Elmer* model *177* grating spectrometer, respectively. The 60-MHz ^{1}H-NMR spectra were recorded with a *Varian EM 360* spectrometer, the 90-MHz ^{1}H-NMR and 22.63-MHz ^{13}C-NMR spectra on a *Bruker WH-90* spectrometer with *Fourier* transform. The 400-MHz ^{1}H-NMR, the 100.58-MHz ^{13}C-NMR, and the 2D spectra were recorded on a *Bruker WM-400* spectrometer. Chemical shifts are reported in ppm downfield from an internal standard of Me_4Si.

Methyl (2R,3S,4R)-3,5-Isopropylidenedioxy-2,4-dimethylpentanoate (**8**). To a soln. of *3-hydroxy-4-(methoxycarbonyl)-2,4-dimethylbutyric acid* **6** (3.06 g, 16.1 mmol) in 6 ml of THF at 0° under Ar was added dropwise, over a period of 20 min, 5 ml (50 mmol) of $BH_3 \cdot Me_2S$. After stirring at r.t. for 2 h, the mixture was cooled again to 0° and treated with brine. The white precipitate was extracted with Et_2O. The org. extracts were washed with brine and dried. After removing the solvent under reduced pressure, the residue was purified by flash column chromatography (AcOEt/petroleum ether 1:1). The isolated *methyl 3,5-dihydroxy-2,4-dimethylpentanoate* (**7**) was dissolved in 4.5 ml of MeOH containing 15 ml of 2,2-dimethoxypropane and stirred overnight, at r.t. under Ar, with 140 mg of *Amberlyst 15*. The mixture was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (AcOEt/petroleum ether 0.5:9.5) to yield 1.75 g (50%) of **8**. $[\alpha]_D^{20} = -0.8°$ (c = 2.0, CCl_4). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.08 (*d*, J = 7, CH_3–C(4)); 1.20 (*d*, J = 7, CH_3–C(2)); 1.38 (*s*, CH_3–C–O); 1.43 (*s*, CH_3–C–O); 1.45 (*m*, H–C(4)); 2.57 (*dq*, J = 10, 7, H–C(2)); 3.52 (*dd*, J = 12, 2, H–C(5)); 3.68 (*s*, $COOCH_3$); 3.93 (*dd*, J = 10, 2, H–C(3)); 4.12 (*dd*, J = 12, 3, H–C(5)).

(2R,3S,4R)-3,5-Isopropylidenedioxy-2,4-dimethylpentanal (**9**). To a soln. of 3.5 g (16.2 mmol) **8** in 20 ml of toluene was added dropwise over 2 h, at −78°, 18 ml (18 mmol) of DIBAH (1M in hexane). After stirring for 50 min at −78°, the mixture was quenched with MeOH and a sat. soln. of *Seignette* salt. The mixture was allowed to warm up to r.t., and it was extracted with Et_2O. The combined org. layers were washed with brine, dried, and evaporated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/petroleum ether 1:4) to yield 2.6 g (86%) of pure **9**. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.10 (*d*, J = 7, CH_3–C(4)); 1.15 (*d*, J = 7, CH_3–C(2)); 1.42 (*s*,

CH_3–C–O); 1.47 (*s*, CH_3–C–O); 1.67 (*m*, H–C(4)); 2.61 (*dqd*, *J* = 9, 7, 2, H–C(2)); 3.56 (*dd*, *J* = 12, 1.5, H–C(5)); 4.08 (*dd*,*J* = 9, 2, H–C(3)); 4.12 (*dd*, *J* = 12, 2, H–C(5)); 9.73 (*d*, *J* = 2, H–C(1)).

2′,6′-Dimethylphenyl (2S,3S,4S,5S,6R)-3-Hydroxy-5,7-isopropylidenedioxy-2,4,6-trimethylheptanoate (**10**). To 4.25 ml (30 mmol) of $(i\text{-Pr})_2NH$ in 10 ml of THF at 0° was added 18.8 ml (30 mmol) of BuLi (1.6M in hexane). After stirring for 5 min at 0°, the soln. was cooled to −78°, and 5.4 g (30.2 mmol) of *2,6-dimethylphenyl propionate* (**5**) in 4 ml of THF was added during 10 min. The mixture was stirred for 1 h at −78°. Then 2.6 g (13.9 mmol) of **9** in 5 ml of THF was added, and the stirring was continued for 1 h at −78°. The mixture was quenched with NH_4Cl soln. (6 ml) and extracted with Et_2O. The combined org. layers were washed with brine, dried, and evaporated *in vacuo*. The residue, after purification by flash column chromatography (AcOEt/petroleum ether 1:4), afforded 2.67 g (52%) of **10**. After crystallization from hexane the product had a m.p. of 96.5–98.5°. $[\alpha]_D^{20} = -1.7°$ (*c* = 1, CCl_4). IR (KBr): 3545–3510, 2985–2890, 1760, 1480, 1460, 1380. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.01 (*d*, *J* = 7.5, CH_3–C(6)); 1.13 (*d*, *J* = 7.5, CH_3–C(4)); 1.36 (*d*, *J* = 6, CH_3–C(2)); 1.43 (*s*, CH_3–C–O); 1.46 (*s*, CH_3–C–O); 1.74 (*m*, H–C(6)); 1.78 (*dqd*, *J* = 9.5, 7, 2, H–C(4)); 2.17 (*s*, 2 PhCH_3); 2.53 (*d*, *J* = 5, OH); 2.96 (*dq*, *J* = 9.7, 7.3, H–C(2)); 3.62 (*dd*, *J* = 11.5, 1.5, H–C(7)); 3.97 (*ddd*, *J* = 9.7, 5, 2, H–C(3)); 4.13 (*dd*, *J* = 11.5, 2.5, H–C(7)); 7.07 (*s*, 3 arom. H). ^{13}C-NMR (22.63, MHz, $CDCl_3$): 174.0 (COO); 148.2 (C(1′)), 130.2 (C(2′), C(6′)); 128.7 (C(3′), C(5′)); 125.9 (C(4′)); 98.9 ($(CH_3)_2C$); 73.7 (C(3)); 71.2 (C(5)); 67.1 (C(7)); 44.5 (C(2)); 35.6 (C(4)); 29.9 (CH_3–C–O), 29.7 (CH_3–C–O); 19.2 (C(6)); 16.3 (CH_3–C(2′), CH_3–C(6′)); 14.0 (CH_3–C(6)); 10.9 (CH_3–C(4)); 7.9 (CH_3–C(2)). Anal. calc. for $C_{21}H_{32}O_5$ (364.47): C 69.20, H 8.85; found: C 68.96, H 8.83.

2′,6′-Dimethylphenyl (2S,3S,4R,5S,6R)-7-Hydroxy-3,5-isopropylidenedioxy-2,4,6-trimethylheptanoate (**14**). To 2.0 g (5.6 mmol) of **10** in 32 ml of THF was added at r.t. 20 drops of conc. HCl. The reaction was monitored by TLC. After 15 min, powdered $NaHCO_3$ and Na_2SO_4 were added. The solid was filtered off and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/petroleum ether 4:1) to yield 1.4 g (78%) of *2′,6′-Dimethylphenyl 3,5,7-Trihydroxy-2,4,6-trimethylheptanoate* (**11**). Compound **11** (1.4 g, 4.35 mmol) was stirred at r.t. with 4 ml of DMF, 1.6 ml (6.15 mmol) of (*t*-Bu)Ph_2SiCl, and imidazole (747 mg, 11.0 mmol). After 2 h, ice and 5 ml of NH_4Cl soln. were added. The mixture was extracted with Et_2O, and the combined org. layers dried and evaporated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/petroleum ether 1:4) to yield 2.45 g (99%) of *2′,6′-Dimethylphenyl 7-[(*tert*-Butyl)diphenylsilyloxy]-3,5-dihydroxy-2,4,6-trimethylheptanoate* (**12**).

Compound **12** was taken up in 3 ml of MeOH and 18 ml of 2,2-dimethoxypropane, and stirred overnight with 210 mg of *Amberlyst 15*. The mixture was filtered, and the solvents were removed *in vacuo*. The residue was purified by flash column chromatography to yield 2.4 g (91%) of *2′,6′-Dimethylphenyl 7-[(*tert*-Butyl)diphenylsilyloxy]-3,5-isopropylidenedioxy-2,4,6-trimethylheptanoate* (**13**). To the solution of **13** in 8 ml of THF was added in small portions in 10-min intervals Bu_4NF. The completion of the reaction was followed by TLC. Then, Et_2O (10 ml), H_2O (1 ml), and silica gel were added to the mixture. The solvents were evaporated *in vacuo*, and the powdery residue was transfered to the flash column and chromatographed with AcOEt/petroleum ether 1:4 to yield 1.4 g (96%) of **14**. After crystallization from hexane, the product had a m.p. of 126.5–127.5°. $[\alpha]_D^{20} = +1.1$ (*c* = 2, CCl_4). IR (KBr): 3545, 2980–2870, 1754, 1739. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.97 (*d*, *J* = 7, CH_3–C(4)); 1.05 (*d*, *J* = 7, CH_3–C(6)); 1.26 (*d*, *J* = 7, CH_3–C(2)); 1.41 (*s*, $(CH_3)_2C$); 1.7 (*m*, H–C(4), H–C(6), OH); 2.18 (*s*, 2 PhCH_3); 2.92 (*dq*, *J* = 10, 7, H–C(2)); 3.57 (*m*, H–C(5), H–C(3)); 3.73 (*dd*, *J* = 9.5, 2, H–C(7)); 4.19 (*dd*, *J* = 9.5, 2, H–C(7)); 7.03 (*s*, 3 arom. H). Anal. calc. for $C_{21}H_{32}O_5$ (364.47): C 69.20, H 8.85; found: C 69.15, H 8.77.

2′,6′-Dimethylphenyl (2S,3S,4R,5R,6S)-3,5-Isopropylidenedioxy-2,4,6-trimethyl-7-oxo-1-heptanoate (**15**). To 0.28 ml (3.15 mmol) of $(COCl)_2$ in 8 ml of CH_2Cl_2 at −78° was added 0.3 ml (4.2 mmol) of DMSO in 0.6 ml of CH_2Cl_2. After stirring for 5 min, a soln. of **14** (765 mg, 2.10 mmol) in 3 ml of CH_2Cl_2 was added dropwise. The mixture was stirred for 20 min. Then, 1.5 ml of Et_3N was added dropwise, and the stirring was continued for an additional 15 min at −78°. Then, the mixture was brought to r.t. H_2O was added, and the mixture was extracted with benzene/Et_2O. The combined org. layers were washed with brine, dried, and evaporated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/petroleum ether 15:85) to yield 733 mg (96%) of **15**. The compound was stored under Ar at −20°. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.90 (*d*, *J* = 7, CH_3–C(4)); 1.12 (*d*, *J* = 7, CH_3–C(6)); 1.20 (*d*, *J* = 7, CH_3–C(2)); 1.37 (*s*, CH_3–C–O); 1.40 (*s*, CH_3–C–O); 1.68 (*m*, H–C(4)); 2.13 (*s*, 2 PhCH_3); 2.75 (*m*, H–C(2), H–C(6)); 4.02 (*dd*, *J* = 9, 2, H–C(5)); 4.18 (*dd*, *J* = 10, 2, H–C(3)); 6.95 (*s*, 3 arom. H); 9.62 (*d*, *J* = 2, H–C(7)).

Di(2′,6′-Dimethylphenyl) (2R,3R,4R,5S,6R,7S,8S)-3-Hydroxy-5,7-isopropylidenedioxy-2,4,6,8-tetramethyl-1,9-nonandioat (**16**). To a soln. of $(i\text{-Pr})_2NH$ (0.71 ml, 5.0 mmol) in 6 ml of THF at 0° was added 3.1 ml (5.0 mmol) of BuLi (1.6M in hexane). After stirring for 5 min at 0°, the soln. was cooled to −78°, and **5** (895 mg, 5.0 mmol) in 3.5 ml of THF was added. After stirring for 50 min, 733 mg (2.02 mmol) of **15** in 3.5 ml of THF was added, and the stirring was continued for 1 h at −78°. The mixture was quenched with NH_4Cl soln. and extracted

at r.t. with Et_2O. The org. phase was washed with brine, dried, and evaporated *in vacuo*. The residue was purified by flash column chromatography (AcOEt/petroleum ether 0.5:9.5) to yield 796 mg (70%) of **16**. The product was crystallized from pentane and had a m.p., of 85–87°. $[\alpha]_D^{20} = +1.8°$ (c = 5, CCl_4). IR (KBr): 3550–3440, 2980, 2940, 1758, 1480–1455, 1380, 1265, 1203, 1165–1140, 1047, 1012, 994, 973, 770. ^{1}H-NMR (400 MHz, $CDCl_3$)[1]): 0.95 (*d*, J = 7, CH_3–C(6)); 1.03 (*d*, J = 7, CH_3–C(4)); 1.27 (*d*, J = 7, CH_3–C(8)); 1.35 (*d*, J = 7, CH_3–C(2)); 1.40 (*s*, CH_3–C–O); 1.42 (*s*, CH_3–C–O); 1.83 (*qt*, J = 7, 2, H–C(6)); 1.87 (*dqd*, J = 9, 7, 2, H–C(4)); 2.17 (*s*, 2 PhCH_3); 2.18 (*s*, 2 PhCH_3); 2.56 (*d*, J = 5, OH); 2.92 (*dq*, J = 10.3, 7, H–C(8)); 2.99 (*dq*, J = 10, 7, H–C(2)); 3.92 (*dd*, J = 9, 2, H–C(5)); 3.99 (*ddd*, J = 10, 5, 2, H–C(3)); 4.23 (*dd*, J = 10.3, 2.0, H–C(7)); 7.05 (*s*, 3 arom. H); 7.09 (*s*, 3 arom. H). ^{13}C-NMR (100.58 MHz, $CDCl_3$)[1]): 5.01 (C(6)); 8.30 (C(4)); 12.91 (C(8)); 13.84 (C(2)); 16.29, 16.34 (2 PhCH_3); 19.47 (CH_3–C–O); 29.25 (C(6)); 29.79 (CH_3–C–O); 35.08 (C(4)); 42.35 (C(8)); 44.09 (C(2)); 70.08 (C(3)); 75.14, 75.16 (C(5), C(7)); 99.29 ((CH_3)$_2$C); 125.66, 126.0 (2 C(4')); 128.44, 128.65 (2 C(3')); 129.97, 130.24 (2 C(2')); 147.87, 148.16 (2 C(1')); 173.50, 174.28 (2 COO). Anal. calc. for $C_{32}H_{44}O_7$ (540.67): C 71.08, H 8.20; found: C 70.81, H 8.46.

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