Total Synthesis of Protected D-*altro*- and D-*galacto*-3,6-Dideoxy-3-*C*-methylhexoses; Key Intermediates of a Rifamycin S Synthesis[1]

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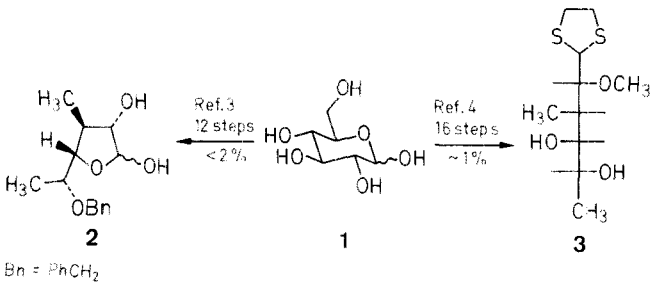
Two particular derivatives of the title compound, used in the Kinoshita synthesis of the Rifamycin S ansa chain, were prepared by total synthesis from isobutyl (*R*)-lactate. The best conditions were worked out for the inversion of the 2-hydroxy group in the appropriate α-D-allo- and β-D-talofuranosides, readily available with few steps from (*R*)-2-benzyloxypropanal by the homoaldol reaction, with an α-metalated (*E*)-2-butenyl carbamate.

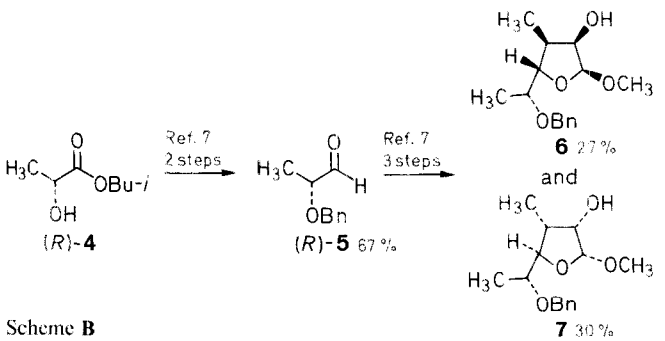
For the synthesis of branched carbohydrate analogues, the "chiron approach",[2] which consists in the partial synthetic modification of common sugars like D-glucose (**1**), is the most frequently applied strategy. Although inexpensive chiral starting materials are used, the necessary differentiation between several similar hydroxy groups leads rapidly to an increasing number of synthetic steps as the chemical and configurational distance from the target molecule increases.

Recently, Kinoshita et al. accomplished the syntheses of the key intermediates **2**[3] and **3**[4] from D-glucose (**1**), which were utilized in their total synthesis of the Rifamycin S ansa chain.[5,6] 5-*O*-Benzyl-3,6-dideoxy-3-*C*-methyl-D-altrofuranose (**2**) and 3,6-dideoxy-2-*O*,3-*C*-dimethyl-D-galactose ethylene dithioacetal (**3**) were prepared with 12 steps (yield < 2%) and 16 steps (yield ≈ 1%), respectively.



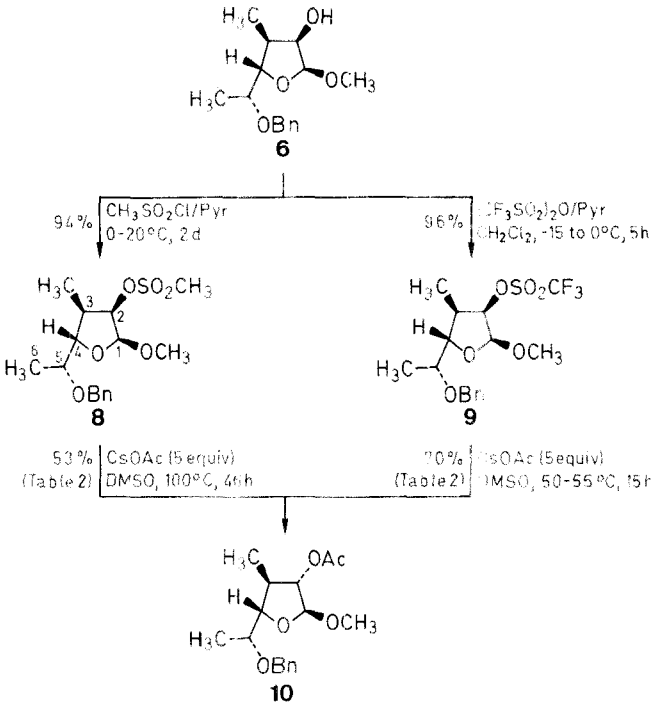
Scheme A

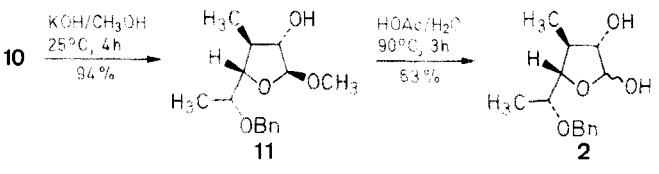
In the preceding paper,[7] we reported on a new total synthetic approach, which is based on the homoaldol reaction of metalated 2-alkenyl carbamates with enantiomerically pure 2-hydroxyalkanals. By this method, (*R*)-2-benzyloxypropanal [(*R*)-**5**], prepared from commercially available isobutyl D-lactate (*R*)-**4**, affords the methyl α-D-allo- and the β-D-talofuranosides **6**[7] and **7**[7] with 18 and 20% yields, respectively, in only five synthetic steps from **4**, including one facile diastereoisomer separation (Scheme **B**).

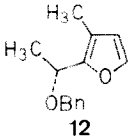


Scheme B

For the transformations **6** → **2** and **7** → **3**, the key step is the inversion of the configuration at C-2. Several attempts to apply Misunobu inversions,[8] even the powerful formate method,[9] failed, presumable due to the electron deficiency at the 2-position caused by the inductive effect of the adjacent acetal group. We therefore took a different approach. The mesylates **8** and **13** were prepared by the usual method in 94% and 98% yield, respectively, after chromatography (Table 1). The triflates **9** and **14** (96% and 84% yield), obtained with triflic anhydride,[10,11] turned out to be surprisingly stable: after chromatography on silica gel, they were isolated analytically pure.

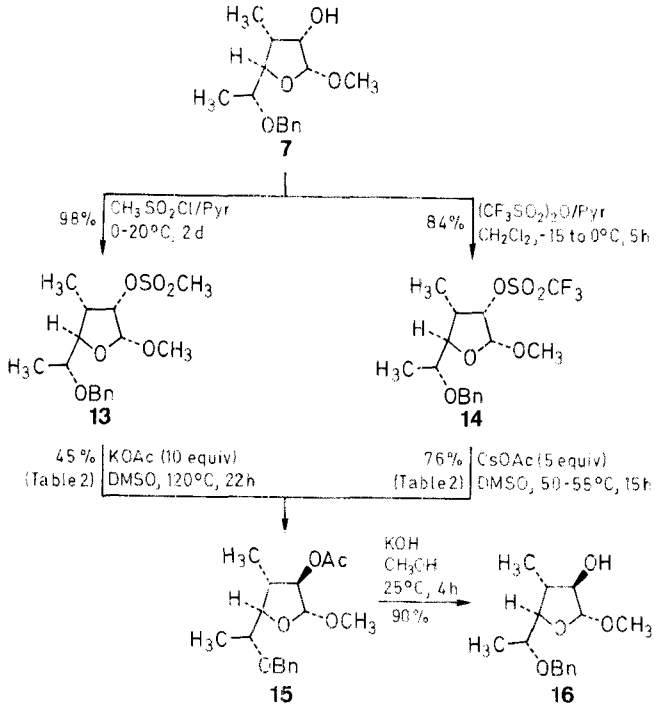




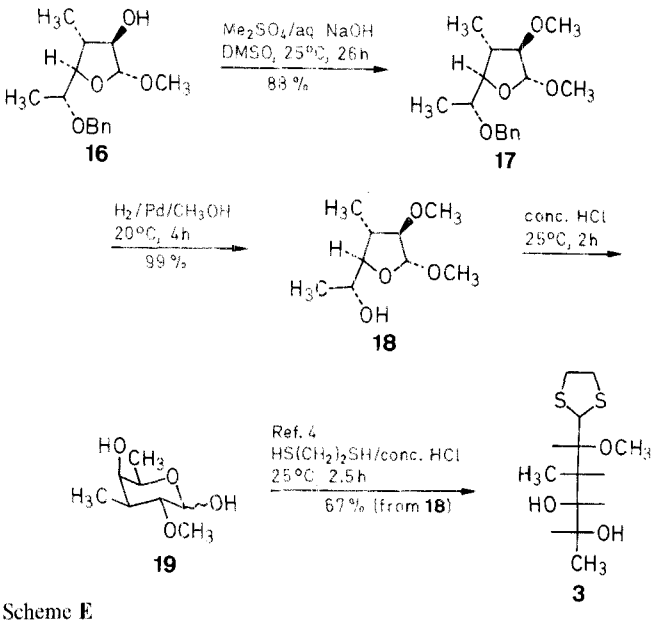


Scheme C

The acetolysis of the mesylates **8** and **13** proves to be difficult, because at elevated temperatures the acetates **10** and **15** undergo a double elimination with formation of the furan **12**. Some studies are summarized in Table 2. The triflates, using cesium acetate[12–14] (5 equivalents) in dimethyl sulfoxide,



Scheme D



Scheme E

15–28 h at 50°C, gave the best results: **9** afforded 70% of the acetate **10** together with a small amount of furan **12** (10%); **14** yielded 76% of **15** together with 16% of **12**.

The 2-hydroxy group was liberated by alkaline hydrolysis to give **11** and **16**, respectively. The NMR data, in particular the vicinal proton coupling constants, are in agreement with the expectations (Tables 3 and 4).

The hydrolysis of the altrofuranoside **11** with aqueous acetic acid yielded the furanose **2** (63%), whose physical data are in agreement with the reported ones.[3]

For the transformation of **16** into the dithiolane **3**, **16** was *O*-methylated (**17**, 88%), the 5-*O*-benzyl group hydrogenolytically removed (**18**, 99%), the furanoside hydrolyzed by the action of aqueous hydrochloric acid, and the intermediate pyranose **19**[4] treated with 1,2-ethanedithiol/concentrated hydrochloric acid to yield **3** in 67% based on **18**. The physical data of **3** are in excellent agreement with the literature values.[4]

Thus starting from (*R*)-lactate **4**, the furanose **2** was prepared in 8.5% yield with 9 steps, and the ethylene dithioacetal **3** in 5.7% with 11 steps; only a single diastereoisomer separation was required.

By the same reaction sequences, starting from (*S*)-**5**,[7] the L-enantiomers *ent*-**2** and *ent*-**3** were synthesized. The optical rotation of (*S*)-**5** and those of the subsequent intermediates were identical in value (± 2%) with those of the D-series but opposite in sign.

This underlines another advantage of the so-called de novo synthesis:[15] Unlike partial synthetic approaches, based on naturally occurring hexoses, here both enantiomers are usually available with equal ease.

Table 1. D-*altro*- and D-*galacto*-3,6-Dideoxy-3-*C*-methylhexoses **2** and **3** and the Intermediates Leading to Them[a]

Product	Configuration	Educt	Yield (%)	Appearance	$[\alpha]_D^{20}$ (solvent, *c*)	R_f (eluent)[b]	Molecular Formula[c]	IR (neat) ν (cm^{-1})
8	α-D-*allo*	**6**	94	oil	+65.2° (CH_2Cl_2, 4)	0.50 (E)	$C_{16}H_{24}O_6S$ (344.4)	1355, 1180
9	α-D-*allo*	**6**	96	oil	+65.3° (CH_2Cl_2, 4)	0.54 (E/P, 1:1)	$C_{16}H_{21}F_3O_6S$ (398.4)	1415, 1145
10	α-D-*altro*	**9**	70[d]	oil	+44.1° (CH_2Cl_2, 4)	0.64 (E/P, 1:1)	$C_{17}H_{24}O_5$ (308.4)	1735
11	α-D-*altro*	**10**	94	oil	+60.0° (CH_3OH, 4)	0.46 (E)	$C_{15}H_{22}O_4$ (266.3)	3440
12	(1*R*)	–[e]	–[e]	oil	−86.2° (CH_2Cl_2, 4)	0.59 (E/P, 1:1)	$C_{14}H_{16}O_2$ (216.3)	1510, 1495
13	β-D-*talo*	**7**	98	oil	−85.2° (CH_2Cl_2, 4)	0.15 (E/P, 1:1)	$C_{16}H_{24}O_6S$ (344.4)	1360, 1180
14	β-D-*talo*	**7**	84	oil	−87.7° (CH_2Cl_2, 4)	0.53 (E/P, 1:1)	$C_{16}H_{21}F_3O_6S$ (398.4)	1415, 1145
15	β-D-*galacto*	**14**	76[d]	oil	−65.3° (CH_2Cl_2, 4)	0.63 (E/P, 1:1)	$C_{17}H_{24}O_5$ (308.4)	1740
16	β-D-*galacto*	**15**	90	oil	−88.9° (CH_3OH, 4)	0.47 (E)	$C_{15}H_{22}O_4$ (266.3)	3430
17	β-D-*galacto*	**16**	88	oil	−68.5° (CH_2Cl_2, 4)	0.65 (E)	$C_{16}H_{24}O_4$ (280.4)	2830, 1110, 1070
18	β-D-*galacto*	**17**	99	oil	−89.9° (CH_3OH, 4)	0.19 (E/P, 1:1)	$C_9H_{18}O_4$ (190.2)	3470
2	D-*altro*	**11**	63	oil	–[f]		$C_{14}H_{20}O_{43}$ (252.3)	
3	β-D-*galacto*	**18**	67	oil	–[f]		$C_{10}H_{20}O_3S_{24}$ (252.4)	

[a] The appropriate L enantiomers were also prepared. The physical data are identical, except for the sign of optical rotation.
[b] E: ether; P: pentane.
[c] Satisfactory microanalyses obtained: C ± 0.21, H ± 0.11; except for **12**.
[d] For further experiments see Table 2 and text.
[e] See Table 2 and text.
[f] See Experimental Part.

Table 2. Acetolysis of Mesylates and Triflates in DMSO[a]

Educt	Acetate (equiv)	Temp.(°C)/ Time (h)	Acetate (Yield, %)	Furan **12** (%)	Recovered Educt (%)
8	CsOAc (5.0)	100/46	**10** (53)	40	0
9	CsOAc (5.0)	50/28	**10** (70)	16	0
13	NaOAc (10.0)	120/52	**15** (27)	[b]	14
13	KOAc (10.0)	120/22	**15** (45)	22	[b]
13	CsOAc (5.0)	100/24	**15** (58)	16	18
14	CsOAc (5.0)	50/15	**15** (76)	10	0

[a] Approx. 0.4 M solution of the educt.
[b] Not determined.

Furanoses of type **6** and **7** proved their value also for the synthesis of 2-aminodeoxy furanosides and of enantiomerically pure 4-hydroxy-2-amino carboxylic acid lactones.[16,17]

^{1}H- and ^{13}C-NMR spectra were recorded on Varian XL-200, FT 80A, and Bruker AM 300 spectrometer. IR spectra were recorded on Perkin-Elmer 298 or 283b spectrophotometer. Optical rotations were recorded on Perkin-Elmer polarimeter 241. Dimethyl sulfoxide (DMSO) and pyridine were dried by distillation over CaH_2 in Argon atmosphere. Microanalyses were performed by the Microanalytical Laboratory Beller, Göttingen.

Methyl 2-*O*-Alkylsulfonyl-5-*O*-benzyl-3,6-dideoxy-3-*C*-methyl-D-aldohexofuranosides 8, 9, 13, and 14; General Procedures:

Mesylates: To a solution of the furanoside[7] **6** or **7** (2.66 g, 10 mmol) in dry pyridine (30 mL) at 0°C, methanesulfonyl chloride (2.29 g, 20 mmol) is added, and the reaction mixture kept at room temperature for 48 h. For the work-up, the reaction mixture is poured into an ice-cold mixture of ether (100 mL)/2N HCl (50 mL), and the aqueous phase is extracted with ether (3 × 20 mL). The organic layer is washed with 2N aq. HCl (20 mL), sat. aq. $NaHCO_3$ (2 × 30 mL), and brine (30 mL). The combined ethereal solution is dried (Na_2SO_4) and evaporated in vacuum with a bath temperature of < 40°C.

Table 3. ^{1}H-NMR Data of Compounds **8**–**18**[a]

Compound	1-H ($J_{1,2}$)	2-H ($J_{2,3}$)	3-H (ddq) ($J_{3,4}$)	4-H (dd) ($J_{4,5}$)	5-H (dq) ($J_{5,6}$)	6-H_3 (d)	3-CH_3 (d) ($J_{3,3'}$)	1-OR (s)	2-OR ($J_{2,OH}$)	5-OCH_2(AB) (J_{gem})
8	5.04 (d) (4.0)	4.92 (dd) (8.3)	2.52 (5.8)	3.81 (3.9)	3.65 (6.4)	1.19	1.17 (7.2)	3.45	3.06 (s)	4.52, 4.64 (12.2)
9	5.07 (d) (4.0)	5.05 (dd) (8.3)	2.57 (6.0)	3.82 (3.8)	3.66 (6.5)	1.20	1.19 (7.2)	3.46	–	4.51, 4.65 (11.7)
10	4.88 (s) (0)	4.70 (d) (1.9)	2.15 (6.8)	3.67 (6.1)	3.67 (6.2)	1.25	1.24 (7.3)	3.34	1.97 (s)	4.58, 4.65 (11.9)
11	4.83 (s)[b] (0)	3.70 (d) (0)	2.19[b] (3.5)	3.75 (2.3)	3.82 (6.5)	1.16	1.21 (7.5)	3.34	3.65 (d) (11.0)	4.55, 4.67 (11.5)
13	5.09 (d) (3.9)	4.98 (dd) (7.4)	2.45 (7.4)	3.80 (3.0)	3.55 (6.4)	1.28	1.02 (7.0)	3.47	3.07 (s)	4.46, 4.68 (12.0)
14	5.04 (d) (4.1)	5.05 (dd) (8.2)	2.50 (5.9)	3.82 (3.7)	3.55 (6.4)	1.29	0.99 (7.0)	3.48	–	4.51, 4.65 (12.0)
15	4.92 (s) (0)	4.71 (d) (2.7)	2.13 (7.1)	3.72 (4.4)	3.63 (6.4)	1.26	1.15 (7.2)	3.35	2.04 (s)	4.56, 4.70 (12.3)
16	4.82 (s) (0.5)	3.58 (ddd) (1.3)	2.03 (3.9)	3.72 (2.0)	3.52 (6.4)	1.36	1.16 (7.4)	3.33	3.70 (d) (10)	4.42, 4.71 (11.4)
17	4.89 (d) (1.3)	3.38 (dd) (4.7)	2.10 (8.2)	3.67 (4.5)	3.63 (6.3)	1.24	1.06 (7.0)	3.36	3.36 (s)	4.58, 4.67 (12.0)
18	4.89 (d)[b] (0.8)	3.42 (dd) (3.2)	1.99[b] (7.0)	3.52 (5.0)	3.74 (6.4)	1.23	1.16 (7.1)	3.36	3.36 (s)	2.43 (d) (5.2)
12[d]	~7.2[c] (2.5)	6.15 (d) –			4.55 (q) (7.0)	1.5	1.95 (s)	–	–	4.25, 4.45 (12)

[a] 300 MHz, $CDCl_3$; δ.
[b] Additional splitting of the signal by $^4J_{1,3}$ = 0.8 Hz.
[c] Covered by the phenyl absorption.
[d] Numbering of the starting furanoside is retained.

Table 4. ^{13}C-NMR Data of Compounds **8**–**18**[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	3-CH_3	1-OCH_3	5-OCH_2	2-OR
8	102.00	79.49	34.65	86.88	75.89	15.85	14.08	55.28	71.26	38.20
9	101.62	85.86	34.92	86.95	75.91	16.11	13.93	55.73	71.59	118.6[b]
10	107.20	84.79	41.12	88.36	76.06	17.92	16.55	54.32	71.18	20.87, 170.10
11	110.51	80.88	41.00	89.27	75.94	18.62	15.96	54.48	71.66	–
13	101.84	79.87	34.77	85.53	73.31	14.75	12.02	54.92	70.32	37.50
14	101.90	85.74	35.81	86.83	72.77	15.34	11.64	56.03	71.04	118.6[b]
15	106.88	84.60	40.15	87.26	74.10	16.60	15.51	54.19	71.04	20.72, 170.00
16	110.47	81.12	43.08	88.74	74.55	17.43	15.58	54.54	71.11	–
17	107.02	86.58	39.93	92.96	74.15	16.32	15.63	54.48	71.13	57.31
18	107.01	88.71	40.48	92.55	68.33	19.35	16.74	54.39	–	57.14
12[c]	141.11	112.73	117.15	149.50	67.89	19.73	9.68	–	69.75	–

[a] $CDCl_3$; δ.
[b] q, J_{CF} = 319 Hz.
[c] Numbering of the starting furanoside is retained.

Triflates: To a solution of the furanoside[7] **6** or **7** (2.66 g, 10 mmol) in CH_2Cl_2 (40 mL) and dry pyridine (2.37 g, 30 mmol) is added at −15 °C trifluoromethanesulfonic anhydride (4.23 g, 15 mmol). During 5 h the solution is allowed to warm up to 0 °C and is then worked up as described above.

For the subsequent reactions the crude products were used. For analyses and yield determination, aliquots were purified by chromatography on silica gel (10 g/mmol) with ether/pentane (1:2) as eluent.

Methyl 2-*O*-Acetyl-5-*O*-benzyl-3,6-dideoxy-3-*C*-methyl-D-aldohexofuranosides 10 and 15; Typical Procedure:
A solution of crude triflate **14** (3.00 g, 7.6 mmol) and cesium acetate (7.26 g, 37.8 mmol) in dry DMSO (20 mL) is stirred at 50–55 °C for 15 h in a dry nitrogen atmosphere. The cold reaction mixture is diluted with water (30 mL) and ether (100 mL); the ether solution is washed with water (20 mL) and brine (20 mL), and is dried (Na_2SO_4). After evaporation of the solvent, the residue is purified by chromatography on silica gel (80 g) with ether/pentane (1:8) as eluent yielding **15** (1.77 g, 76%) and **12** (0.17 g, 10%).

Methyl 5-*O*-Benzyl-3,6-dideoxy-3-*C*-methyl-D-aldohexofuranosides 11 and 16; Typical Procedure:
To a solution of acetate **15** (1.62 g, 5.27 mmol) and pulverized KOH (0.59 g, 10.5 mmol) in CH_3OH (15 mL) is stirred at 25 °C for 4 h. The CH_3OH is evaporated in vacuum, the residue is dissolved in water (10 mL) and ether (30 mL), and the aqueous layer is extracted with ether (4 × 20 mL). The combined ethereal solution is washed with brine (20 mL) and dried (Na_2SO_4); the ether is evaporated in vacuum, and the residue is purified by chromatography on silica gel (40 g) with ether/pentane (1:2) as eluent; yield: 1.27 g (90%) of **16**.

Usually, the crude acetates were used, because the separation from furan **12** is simpler at the stages of **11** or **16**.

5-*O*-Benzyl-3,6-dideoxy-3-*C*-methyl-D-altrofuranose[3] (2):
The methyl furanoside **11** (0.80 g, 3 mmol) in 50% aq. HOAc (8.0 mL) is stirred at 90 °C for 3 h. The solvents are removed in vacuum, and the residue is purified by chromatography on silica gel (12 g) with ether/pentane (1:2) as eluent; yield: 0.48 g (63%) of **2**. $[\alpha]_D^{20}$ −64.3° (after 30 min), −22.8° (after 2 d, CH_3OH, c = 1.5) (Lit.[3] $[\alpha]_D$ −25°).

Methyl 5-*O*-Benzyl-3,6-dideoxy-2-*O*,3-*C*-dimethyl-β-D-galactofuranoside (17):
To furanoside **16** (0.60 g, 2.26 mmol) in DMSO (2 mL) is added 20% aqueous NaOH solution (0.57 mL, 2.9 mmol) and then dimethyl sulfate (0.22 mL, 2.3 mmol). After 2.5 h stirring at 25 °C, the addition of the above reagents in the amounts given is repeated and stirring continued for 24 h. The reaction mixture is diluted with water (20 mL) and ether (30 mL), the aqueous phase is extracted with ether (2 × 10 mL), and the combined ethereal solution is washed with brine, dried (Na_2SO_4), and evaporated in vacuum. The residue is purified by chromatography on silica gel (12 g) with ether/pentane (1:8) as eluent; yield: 0.56 g (88%) of **17**.

Methyl 3,6-Dideoxy-2-*O*,3-*C*-dimethyl-β-D-galactofuranoside (18):
$PdCl_2$ (0.110 g, 19 mol-%) in CH_3OH (15 mL) is reduced by a gentle stream of H_2, then the CH_3OH is decanted. The palladium black is thoroughly washed with CH_3OH (2 × 20 mL) for removal of disturbing HCl. Benzyl ether **17** (0.927 g, 3.31 mmol) in CH_3OH (15 mL) is added and the reaction mixture is subjected to a hydrogen stream (4 h, TLC control). After flushing with N_2 and separation of the solution from the catalyst by filtration, evaporation in vacuum affords homogeneous (TLC) **18**; yield: 0.621 g (99%).

An analytical sample was obtained by chromatography on silica gel with ether/pentane (1:1) as eluent.

3,6-Dideoxy-2-*O*,3-*C*-dimethyl-D-galactose Ethylene Dithioacetal[4] (3):
Furanoside **18** (300 mg, 1.58 mmol) and conc. (37%) aq. HCl (0.3 mL) are stirred at 25 °C for 2 h. To the resultant solution of pyranose[4] **19**, is added conc. aq. HCl (0.3 mL) and 1,2-ethanedithiol (0.6 mL, 7.2 mmol), and stirring is continued for 2.5 h before the reaction mixture is diluted with CH_2Cl_2 (20 mL) and water (5 mL). The aqueous layer is extracted with CH_2Cl_2 (3 × 10 mL); the combined CH_2Cl_2 solution is washed with sat. aq. $NaHCO_3$ and with brine (each 10 mL), is dried (Na_2SO_4) and evaporated in vacuum. Chromatography on silica gel with ether/pentane (1:1) as eluent affords **3** as a colorless oil; yield: 266 mg (67%); $[\alpha]_D^{21}$ +4.95° ($CHCl_3$, c = 2) (Lit.[4] $[\alpha]_D$ +5°).

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(1) Preliminary Report: Hoppe, D., Tarara, G., Wilckens, M., Jones, P.G., Schmidt, D., Stezowski, J.J. *Angew. Chem.* **1987**, *99*, 1079; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1034.
(2) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon Press, Oxford, 1983.
(3) Nakata, M., Takao, M., Ikeyama, Y., Sakai, T., Tatsuta, K., Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1749.
(4) Nakata, M., Ikeyama, Y., Takao, M., Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3252.
(5) Nakata, M., Toshima, K., Kai, T., Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3457.
(6) For further syntheses of the Rifamycin ansa chain see:
Nagaoka, H., Kishi, Y. *Tetrahedron* **1981** *37*, 3873.
Masamune, S., Imperiali, B., Garvey, O.S. *J. Am. Chem. Soc.* **1982**, *104*, 5528.
Still, W.C., Barrish, J.C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.
Hanessian, S., Pougnyt, J.-R., Boessenkoo, I.K. *Tetrahedron* **1984**, *40*, 1289.
Tschamber, T., Waespe-Sarcevic, N., Tamm, C. *Helv. Chim. Acta* **1986**, *64*, 621.
Roush, W.R., Palkowitz, A.D. *J. Am. Chem. Soc.* **1987**, *109*, 953.
Ziegler, F.E., Kneisley, A. *Tetrahedron Lett.* **1987**, *28*, 1725.
Danishefsky, S.J., Myles, D.C., Harvey, D.F. *J. Am. Chem. Soc.* **1987**, *109*, 862.
(7) Hoppe, D., Tarara, G., Wilckens, M. *Synthesis* **1989**, 83; preceding paper.
(8) Review: Mitsunobu, O. *Synthesis* **1981**, 1.
(9) Georg, G.I., Kant, J., Gill, H.S. *J. Am. Chem. Soc.* **1987**, *109*, 1129.
(10) Binkley, R.M., Ambrose, M.G. *J. Carbohydr. Res.* **1984**, *3* (1), 1.
(11) Review: Stang, P.J., Hanack, M., Subramanian, L.R. *Synthesis* **1982**, 85.
(12) Review: Klieser, B., Rossa, L., Vögtle, F. *Kontakte (Darmstadt)* **1984**, No. 1, 3.
(13) Koepp, E., Vögtle, F. *Synthesis* **1987**, 177.
(14) Dijkstra, G., Kruizinga, W.H., Kellogg, R.M. *J. Org. Chem.* **1987**, *52*, 4230.
(15) Reviews:
Schmidt, R.R. *Pure Appl. Chem.* **1987** *59*, 415.
Zamojski, A., Banaszek, A., Grynkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 1.
(16) Tarara, G. *Dissertation*, Universität Göttingen, 1988.
(17) Tarara, G., Hoppe, D., manuscript in preparation.