From Sugars to Carbocycles. 3.[1] Synthesis of Validatol and 4-*epi*-Validatol from Mannose and Glucose

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Validatol (**4**) and 4-*epi*-validatol (**8**) are synthesized from mannose and glucose, respectively. The key step in the synthesis of **4** is the base-induced intramolecular displacement reaction of the epoxy dithiane **14** to yield the six-membered carbocycle **15** exclusively.

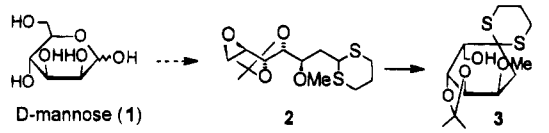
In the preceding paper we have presented a flexible new method of converting sugars into carbocycles of various ring sizes.[1] The methodology comprised addition of 2-lithio-1,3-dithiane to the free anomeric center of a protected sugar, reductive elimination of the newly created hydroxy group, and appropriate activation of one of the hydroxy groups of the chain as an electrophile, followed by base-induced cyclization. Thus, starting from mannose (**1**) the protected epoxy dithiane **2** could be prepared in only eight steps and then cyclized to the six-membered ring **3** (Scheme 1).

Analysis of the stereochemistry of **3** revealed that the synthetic compound was epimeric at C-4 to validatol (**4**), the product of hydrogenolysis[2] of the aminoglycoside anitibiotic validamycin A (**5**).[3] The validamycins A–F are isolated from cultures of *Streptomyces hydroscopicus*[2,3] and are used as fungicides in rice cultures. Validatol (**4**) is also known as the reduction product[4,5] of the important pseudotetra saccharide acarbose (**6**),[6] which is an inhibitor of α-D-glucosidases and saccharases[7] (synthesis[8]) (Scheme 2).

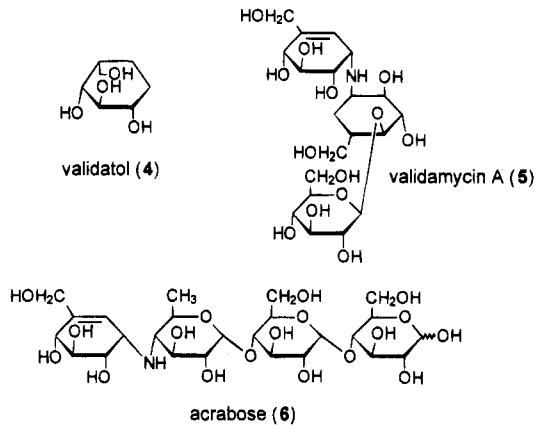
The first synthesis of racemic validatol (**4**) was described in 1980 by Ogawa et al.[9] In 1985 the same group published a synthesis of the enantiomerically pure product starting with the commercially available (±)-7-*endo*-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid, which was cleaved into the enantiomers using (*R*)-(+)-α-methylbenzylamine (0.5% overall yield).[10]

In our synthesis the center at C-3 in **2** had to be inverted at an early stage of the synthesis. Before doing this, we wanted to study the deprotection and desulfurization of the epimer **3**. The desulfurization of **3** was achieved in the usual manner with Raney nickel to afford **7** in 80% yield. The reagent of choice to cleave the acetonide and the methyl ether in **7** simultaneously was BBr_3, yielding 4-*epi*-validatol (**8**) in 76% yield, synthezised

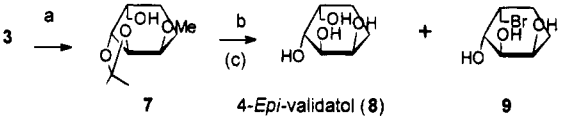
Scheme 1



Scheme 2



Scheme 3



[a] (a) Ra–Ni, EtOH, 76 °C, 2 h (88%); (b) 2.5 equiv of BBr_3, 3 h −35 °C, (76%) (c) 10 equiv of BBr_3, 18 h, 20 °C (37% **8**, 36% **9**).

for the first time. Employing an excess of the reagent and longer reaction times gave also the bromination product **9** (Scheme 3).

Next, the inversion of the hydroxy group at C-3 was investigated starting from the bisacetonide **10** to obtain the desired stereochemistry at C-4 of validatol (**4**). Our initial experiments using the Mitsunobu reaction[11] under a variety of conditions[12,13] failed. Swern oxidation[14] followed by reduction also gave only complex mixtures. The displacement reactions with the mesylate **11b** or the tosylate **11c** using NaOMe resulted in saponification and treatment with NaOAc gave elimination products. How-

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ever, the procedure of Latrell and Lohaus[15] (compare[16,17]) using potassium or sodium nitrite afforded the epimeric alcohol **12a** in 31 and 35% yields starting from **11b** or **11c**, respectively. The yield could be improved to 43% using the corresponding triflate **11a** (unstable, not isolated). The series of transformations of **12a** into validatol (**4**) were performed in a similar manner to that described in the preceding paper for 4-*epi*-validatol precursors. Thus, the alcohol **12a** was methylated to the methyl ether **12b** (95%). Selective cleavage of the terminal acetonide gave the diol **13a** (67%), followed by tosylation to **13b** (78%). The tosylate **13b** was converted into the epoxide **14** almost quantitatively with sodium methoxide (97%) and then cyclized as usual with *n*-BuLi to the cyclohexane derivative **15** (70%). It is also possible to induce epoxide formation and cyclization in one operation using 2 equiv of *n*-BuLi. In contrast to the 3-*epi* compound, investigated in the preceding paper, no formation of a seven-membered ring could be observed. Considering a chair-like six-membered transition state, the methoxy group at C-3, in contrast to that of the epimer, can adopt an equatorial position, decreasing the transition state energy for six-ring formation. The inversion at C-3 is reflected in the ^{1}H NMR spectrum of the cyclization product **15** in comparison to the epimeric analogue [precursor of 4-*epi*-validatol (**8**)][1]: the signal for 3a-H is shifted by 0.41 ppm to high field from δ 4.73 (4-*epi*-validatol precursor) to 4.32 ppm for **15**. This demonstates the influence of the axial methoxy group in 4-*epi*-validatol (**8**) by 1,3-interaction on 3a-H.

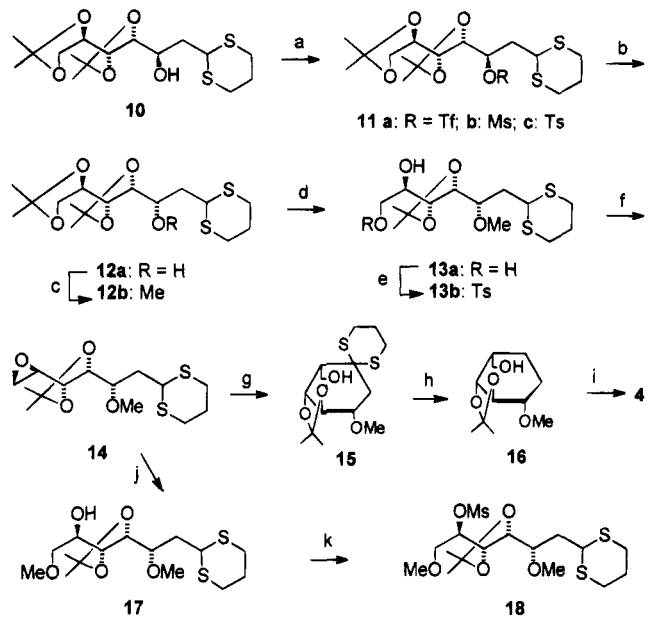
The desulfurization of **15** could be performed by treatment with Raney nickel in boiling ethanol to afford the crystalline protected validatol **16** in 90% yield. Deprotection of both the isopropylidene and methyl ether was achieved in one step with BBr_3 to yield enantiomerically pure crystalline validatol in 82% yield, identical in all data with the natural product[2] (Scheme 4).

At this point it is worth mentioning that the intermediate epoxide **14** could be opened with sodium methoxide under more vigorous conditions to yield the alcohol **17**, which was mesylated to **18**. This mesylate could not be cyclized to six-membered carbocycles, demonstrating that nucleophilic displacement is difficult in sugar derivatives if the leaving group has two neighboring electronegative oxygen groups (see preceding paper[1]).

Synthesis of Validatol from Glucose. Starting from mannose, the synthesis required an inversion of configuration at C-3 (**10** → **12**), which could be performed in only moderate yield. The correct stereochemistry is present in the *gluco* configuration. However, the use of glucose required a minor modification of the protecting procedure as described below.

Since, in contrast to mannose, the unprotected glucose (**19a**) forms the furanoside 1,2:5,6-di-*O*-isopropylidene derivative, we started from the anomeric mixture of the benzyl glycopyranoside **19b**, which formed the diacetonide **20a** (85%) under kinetically controlled conditions using 2-methoxypropene.[18] The benzyl ether was cleaved hydrogenolytically (80% conversion, 90% yield) to form **20b**,[18] which was reacted with 2-lithio-1,3-dithane. In contrast to the reaction with the corresponding mannose

Scheme 4



[a] (a) Py/MsCl/DMAP, 1.5 h, 0 °C (96% **11b**), Py/TsCl/DMAP, 1.5 h, 0 °C (97% **11c**); (b) DMF, $NaNO_2$, (43% from **11a**, 31% from **11b**, 35% from **11c**); (c) THF, NaH, MeI, 18 h, 20 °C (95%); (d) MeOH, 0.5 N HCl, 8 h, 20 °C, (67%); (e) Py/TsCl/36 h, 10 °C (78%); (f) 1.2 equiv of NaOMe/MeOH, 5 h 20 °C (97%); (g) *n*-BuLi, 4 h, −40 to 20 °C (70%); (h) Ra−Ni, EtOH, 76 °C, 2 h (90%); (i) 2.5 equiv of BBr_3, 6 h, −35 °C (82%); (j) 1 N NaOMe/MeOH, 20 °C, 18 h (95%); (k) MsCl, DMAP, 18 h, 20 °C (97%).

derivative, the two diastereomeric alcohols **21a** and **22a** were formed in a 3:2 ratio (71%) in agreement with the model of Redlich.[19] The diastereomers could be separated and converted to the corresponding diacetates **21b** and **22b**. The C-2,3-*erythro* configuration of **21b** was deduced by the coupling of $J_{1,2}$ = 5.3 Hz, the *threo* configuration of **22b** by $J_{1,2}$ = 10.1 Hz in the ^{1}H NMR spectra.[19] The formation of two isomers had no importance for our synthetic scheme, since the hydroxy group was eliminated at a later stage and the synthesis was continued with the mixture of **21a** and **22a**, which yielded the triacetonides **23** and **24** (71%) and the diacetonides **25** and **26** (12%) upon treatment with acetone. The mixture of **23** and **24** was treated with *n*-BuLi and reduced with LAH in one operation to yield **12a** in 89% yield (Scheme 5). With the important intermediate **12a** now available in good yield, the synthesis of validatol (**4**) was carried out as described above (12 steps, 6% overall yield starting from glucose compared to the 0.5% overall yield in the Ogawa synthesis).

The pure isomers **21a** and **22a** offered an opportunity to study the acetonide formation, which has general importance for our carbocyclization strategy. Thus, the diols **21a** and **22a** were treated with acetone/sulfuric acid separately. Compound **22a** exclusively formed the triacetonide **23** (84%), whereas **21a** yielded the triacetonide **24** and the two diacetonides **25** (12%) and **26** (7%). The assignment was primarily based on the ^{13}C NMR spectra with characteristic chemical shifts for the quarternary carbons of the[20] acetonides. The diacetonides **25** and **26**

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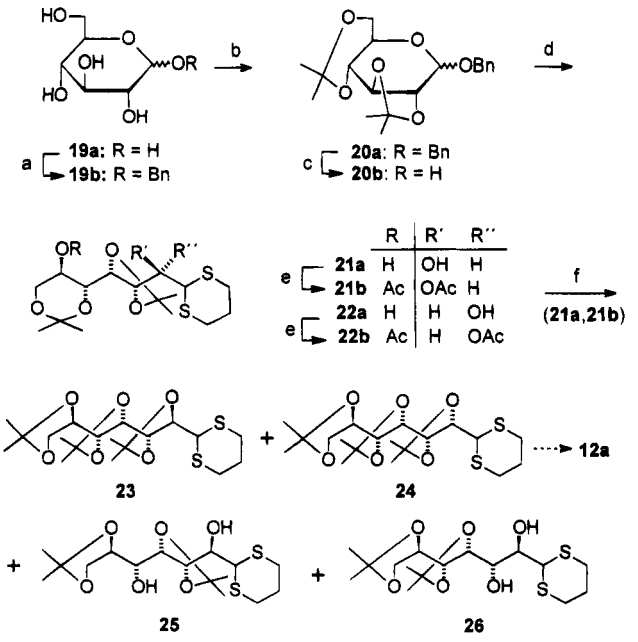
Scheme 5



[a] (a) Reference 21 (70%); (b) ref 18 (85%); (c) ref 18 (90%); (d) 1,3-dithiane, *n*-BuLi, 1.5 h, −50 to 20 °C (71%); (e) Ac_2O/Py/DMAP (quant); (f) acetone, H_2SO_4, 3 h, 20 °C (**23/24** 71%; **25/26** 12%).

can easily be separated from the triacetonide **24** and be recycled because they equilibrate to the mixture of **24/25/26** (64% of triacetonide **24**!) in the presence of acetone/H_2SO_4. Thus, the triacetonide protecting strategy of the open-chain, conformatively flexible 1,3-dithiane sugar derivatives seems to be generally applicable.

Experimental Section

For instrumentation and general and standard procedures, see preceding paper.[1]

2,3-*O*-Isopropylidene-4-*O*-methyl-4-*epi*-validatol (7). A solution of the thicacetal **3** (160 mg, 0.50 mmol) in ethanol (20 mL) was treated with Raney nickel (ca. 1 g, activity W-2), and the mixture was refluxed for ca. 2 h. The suspension was filtered through a batch of Celite, and the filtrate was evaporated to dryness at reduced pressure. The crude product was dissolved in diethyl ether, and the solution was filtered off from solid material and evaporated at reduced pressure to afford **7** (95 mg, 88%) as an oil: $[\alpha]^{20}_D$ −55° (*c* 2.6, CH_2Cl_2); IR (film) 3450 (br, OH), 1459 and 1381 (ketal) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40, 1.43 (s, 6 H, 2 × CH_3-acetonide), 1.10–1.94 (m, 4 H, 5-H, 6-H), 2.49–2.68 (m, 1 H, 1-H), 2.82 (br s, 1 H, OH), 3.43 (s, 3 H, OMe), 3.40–3.58 (m, 1 H), 3.74 (dd, *J* = 2.1 Hz and 10.1 Hz, 1 H, 3-H), 3.85–4.05 (m, 2 H), 4.19 (dd, *J* = 5.2 Hz and 10.1 Hz, 1 H, 2-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.36 (t, C-6), 25.50 (t, C-5), 26.90, 27.18 (q, 2 × CH_3-acetonide), 38.76 (d, C-1), 58.40 (q, OMe), 62.28 (t, CH_2OH), 75.72, 76.05, 76.79 (d, C-2/3/4); MS (70 eV) *m*/*z* (%) 201 (16) [$M^+ - CH_3$], 158 (16) [M^+ − acetone], 140 (48) [$(158)^+ - H_2O$], 127 (100) [M^+ − acetone − OMe], 109 (38). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.16; H, 9.35.

4-*epi*-Validatol (8). A solution of the methyl ether **7** (80 mg, 0.37 mmol) in dry CH_2Cl_2 (15 mL) was treated at −35 °C under argon with BBr_3 (0.09 mL, 2.5 equiv). The mixture was allowed to warm to room temperature within 3 h, and stirring was then continued for 3 h (TLC monitoring). The solution was cooled to −30 °C, and the reaction was quenched by addition of MeOH (5 mL). The solvent was evaporated at reduced pressure, MeOH (10 mL) was added, and the solvent was again evaporated. This procedure was repeated three times. The residue was dissolved in water (10 mL) and washed twice with CH_2Cl_2 (5 mL), and the aqueous phase was evaporated at reduced pressure. The residue was purified by thick layer chromatography (silica gel, EtOAc/*i*-PrOH/H_2O, 7:2:1) to afford **8** (46 mg, 76%) as an oil: $[\alpha]^{20}_D$ 28° (*c* 0.6, H_2O); ^1H NMR (D_2O, 200 MHz) δ 1.08–1.92 (m, 5 H, 1-H, 2 × 5-H, 2 × 6-H), 3.46 (dd, $J_{1,7a}$ = 7.3 Hz, J_{gem} = 10.5 Hz, 1 H, 7a-H), 3.57 (dd, $J_{1,7b}$ = 7.4 Hz, J_{gem} = 10.7 Hz, 1 H, 7b-H), 3.75–3.97 (m, 3 H, 2/3/4-H); ^{13}C NMR (D_2O, 50 MHz) δ 20.94 (t, C-6), 26.74 (t, C-5), 37.65 (d, C-1), 62.90 (t, C-7), 68.47, 70.92, 72.28 (d, C-2/3/4); MS (CI/NH_3, pos) *m*/*z* (rel intensity) 180 (100) [$M^+ + NH_4$], 163 (28) [$M^+ + H$].

(*1R,2R,3R,4R*)-4-(Bromomethyl)cyclohexane-1,2,3-triol (9). A solution of the methyl ether **7** (55 mg, 0.25 mmol) in dry CH_2Cl_2 (10 mL) was treated at 20 °C under argon with BBr_3 (0.24 mL, 10 equiv). After 18 h, workup was performed as described above for **8** to afford a mixture that was separated by silical gel layer chromatography (EtOAc/*i*-PrOH/H_2O, 7:2:1). From the polar fraction, 4-*epi*-validatol (**8**) (15 mg, 37%) and from the less polar fraction the bromo derivative **9** (20 mg, 36%) were obtained: ^1H NMR (200 MHz, $CDCl_3$) δ 1.20–2.50 (m, 8 H, 4-H, 2 × 5-H, 2 × 6-H, 3 × OH), 3.40 (dd, $J_{4,7a}$ = 7.2 Hz, J_{gem} = 9.9 Hz, 1 H, 7a-H), 3.59 (dd, $J_{4,7b}$ = 8.0 Hz, J_{gem} = 9.9 Hz, 1 H, 7b-H), 3.83–3.95, 3.98–4.14 and 4.19–4.30 (3 × m, each 1 H, 1/2/3-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.26 (t, C-5), 26.73 (t, C-6), 35.16 (t, C-7), 38.42 (d, C-4), 68.21, 70.91, 72.23 (d, C-1/2/3); MS (CI/NH_3, pos) *m*/*z* (rel intensity) 244 (96) [$M(^{81}Br)^+ + NH_4$], 242 (100) [$M(^{79}Br)^+ + NH_4$], 144 (8) [M − Br].

2-Deoxy-4,5:6,7-di-*O*-isopropylidene-3-*O*-methanesulfonyl-D-*manno*-heptose Trimethylene Dithioacetal (11b). A solution of the alcohol **10** (350 mg, 0.96 mmol) in dry pyridine (10 mL) was treated under argon at 0 °C with DMAP (50 mg) and methanesulfonyl chloride (0.082 mL, 1.1 equiv). After 1.5 h the mixture was poured into ice-cold 1 N HCl (10 mL), and the solution was extracted with CH_2Cl_2 (30 mL), washed with aqueous saturated $NaHCO_3$ (10 mL) and then water (10 mL), dried ($MgSO_4$), and evaporated at reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/0.5% MeOH) to afford the mesylate **11b** (408 mg, 96%) as an oil: $[\alpha]^{20}_D$ 26° (*c* 0.6, CH_2Cl_2); IR (film) 1358 and 1175 (SO_2), 911 (dithiane) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38, 1.40, 1.45, 1.48 (s, 12 H, 4 × CH_3-acetonide), 1.82–2.28 (m, 3 H, 2a-H and SCH_2CH_2), 2.38 (ddd, $J_{1,2}$ = 5.2 Hz, $J_{2,3}$ = 8.7 Hz, J_{gem} = 15.3 Hz, 1 H, 2b-H), 3.15 (s, 3 H, SCH_3), 3.83 (dd, $J_{4,5}$ = 7.0 Hz, $J_{5,6}$ = 8.3 Hz, 1 H, 5-H), 3.95 (dd, $J_{1,2b}$ = 5.2 Hz, $J_{1,2a}$ = 8.0 Hz, 1 H, 1-H), 4.02–4.24 (m, 3 H, 6-H, 2 × 7-H), 4.31 (dd, $J_{3,4}$ = 2.7 Hz, $J_{4,5}$ = 7.0 Hz, 1 H, 4-H), 5.22 (ddd, $J_{2a,3}$ = 4.0 Hz, $J_{3,4}$ = 2.8 Hz, $J_{2b,3}$ = 8.7 Hz, 1 H, 3-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.67 (q, CH_3-acetonide), 26.16 (t, SCH_2CH_2), 27.07, 27.42, 27.49 (q, 3 × CH_3-acetonide), 29.60, 29.98 (t, SCH_2), 36.25 (t, C-2), 38.95 (q, SCH_3), 42.83 (d, C-1), 68.47 (t, C-7), 77.48, 78.44, 78.53, 81.64 (d, C-3/4/5/6), 110.52, 110.81 (s, CCH_3); MS (CI, isobutane, pos) *m*/*z* (%) 499 (21) [$M^+ + C_4H_9$], 443 (100) [$M^+ + H$]. Anal. Calcd for $C_{17}H_{30}O_7S_3$: C, 46.13; H, 6.83. Found: C, 45.95; H, 6.78.

2-Deoxy-4,5:6,7-di-*O*-isopropylidene-D-*gluco*-heptose Trimethylene Dithioacetal (12a). A solution of the tosylate **11c**[1] (1 mmol) or the mesylate **11b** (1 mmol) in dry DMF (20 mL) was treated with finely powdered $NaNO_2$ (15 mmol) and heated for 24 h at 120 °C under argon. The mixture was evaporated to dryness at reduced pressure and the residue dissolved in a mixture of a saturated aqueous solution of NaCl (20 mL) and CH_2Cl_2 (20 mL). The organic phase was separated, the aqueous phase was extracted twice with CH_2Cl_2 (20 mL), and the combined organic phases were dried ($MgSO_4$), filtered, evaporated to dryness, and purified by flash chromatography on silical gel (CH_2Cl_2/0.5% MeOH) to afford **12a** (35% from tosylate **11c**, 31% from the mesylate **11b**). The triflate **11a** was prepared *in situ* from 100 mg of **10**, (0.274 mmol) and triflic anhydride (0.06 mL, 1.2 equiv) and treated for 2 d with $NaNO_2$ (15 equiv) to yield 43% of **12a** as an oil: $[\alpha]^{20}_D$ −10° (*c* 1.7, CH_2Cl_2); IR (film) 3505 (br, OH), 1420 and 1372 (ketal), 910 (dithiane) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.37, 1.41, 1.44, 1.46 (s, 12 H, 4 × CH_3), 1.75–2.27 (m, 4 H, 2-H, SCH_2CH_2), 2.33 (d, *J* = 9.0 Hz, 1 H, OH), 2.79–3.05 (m, 4 H, SCH_2), 3.88–4.39 (m, 7 H, 1/3/4/5/6/7-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.66 (q, CH_3), 26.40 (t, SCH_2CH_2), 27.11, 27.48, 27.60 (q, 3 × CH_3), 30.29, 30.84 (t, SCH_2), 40.76 (t, C-2), 44.23 (d,

C-1), 67.51 (d, C-3), 77.53, 77.99, 83.17 (d, C-4/5/6), 110.07, 110.28 (s, 2 × CCH_3); MS (70 eV) m/z (%) 364 (100) [M^+], 349 (77) [$M^+ - CH_3$], 249 (45), 161 (35), 132 (39), 119 (40), 101 (25). Anal. Calcd for $C_{15}H_{28}O_5S_2$: C, 52.72; H, 7.74. Found: C, 52.62; H 7.86.

2-Deoxy-4,5:6,7-di-*O*-isopropylidene-3-*O*-methyl-D-*gluco*-heptose Trimethylene Dithioacetal (12b). A suspension of NaH (296 mg (80%), 9.88 mmol, 1.5 equiv, washed with pentane) in dry THF (50 mL) in a three-necked 250 mL flask was treated dropwise at 20 °C under argon with a solution of the sugar **12a** (2.40 g, 6.58 mmol) dry THF (20 mL). After 1 h of stirring, methyl iodide (0.61 mL, 9.88 mmol, 1.5 equiv) was added with a syringe and stirring was continued for 18 h. The reaction was then hydrolyzed with a saturated aqueous solution of NH_4Cl (10 mL). The mixture was filtered, the filtrate was extracted three times with diethyl ether (45 mL), and the combined organic phases were washed with an aqueous solution of $KHSO_3$ (10 mL), dried ($MgSO_4$), and evaporated to dryness to afford the methyl ether **12b** (2.36 g, 95%) as an oil: $[\alpha]^{20}_D$ 4° (*c* 1.2, CH_2Cl_2); IR (film) 2832 (methyl ether), 1450 and 1371 (ketal), 910 (dithiane) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.39, 1.40, 1.45, 1.45 (s, 12 H, 4 × CH_3-acetonide), 1.80–2.25 (m, 4 H, H-2, SCH_2CH_2), 2.78–3.05 (m, 4 H, SCH_2), 3.54 (s, 3 H, OMe), 3.65–3.78 (m, 1 H, 6-H), 3.89–4.30 (m, 6 H, 1/3/4/5/7-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.65 (q, CH_3-acetonide), 26.41 (t, SCH_2CH_2), 26.97, 27.39, 27.62 (q, 3 × CH_3-acetonide), 30.33, 30.73 (t, SCH_2), 37.74 (t, C-2), 44.32 (d, C-1), 59.84 (q, OMe), 68.09 (t, C-6), 77.11, 77.58, 77.99, 82.60 (d, C-3/4/5/6), 109.88, 110.11 (s, CCH_3); MS (70 eV) m/z (%) 378 (35) [M^+], 363 (17) [$M^+ - CH_3$], 346 (10), 320 (8), 305 (12), 288 (10), 219 (19), 187 (12), 175 (65), 143 (80), 132 (45), 119 (100), 101 (32). Anal. Calcd for $C_{17}H_{30}O_5S_2$: C, 53.94; H, 7.99. Found: C, 53.93; H, 7.95.

2-Deoxy-4,5-*O*-isopropylidene-3-*O*-methyl-D-*gluco*-heptose Trimethylene Dithioacetal (13a). A solution of the methyl ether **12b** (900 mg, 2.378 mmol) in MeOH (42 mL) was treated with 0.5 N HCl (14 mL) for 6–8 h at 20 °C (TLC monitoring). The solution was then neutralized with solid $NaHCO_3$, and filtered, and the MeOH was removed at reduced pressure. The aqueous solution was extracted four times with diethyl ether (80 mL), filtered, and dried ($MgSO_4$), and the solvent was removed at reduced pressure. The crude product was purified by flash chromatography (diethyl ether) to afford **13a** (543 mg, 67%) as an oil: $[\alpha]^{20}_D$ −19° (*c* 2.2, CH_2Cl_2); IR (film) 3495 (br, OH), 1441 and 1375 (ketal), 910 (dithiane) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38, 1.40 (s, 6 H, 2 × CH_3-acetonide), 1.76–2.22 (m, 4 H, 2-H, SCH_2CH_2), 2.68 (br t, 1 H, OH), 2.73–2.95 (m, 4 H, SCH_2), 3.54 (s, 3 H, OMe), 3.58–3.94 (m, 6 H), 4.06 (dd, J = 3.8 and 7.8 Hz, 1 H), 4.19 (dd, J = 5.9 and 8.8 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.33 (t, SCH_2CH_2), 27.33, 27.39 (q, 2 × CH_3-acetonide), 30.22, 30.58 (t, SCH_2), 36.43 (t, C-2), 44.35 (d, C-1), 59.70 (q, OMe), 64.43 (t, C-7), 73.11, 77.04, 77.07, 80.29 (d, C-3/4/5/6); MS (CI, isobutane, pos) m/z (%) 339 (100) [M^+ + H], 321 (30) [M^+ − OH], 281 (71) [$(M + H)^+$ − acetone]. Anal. Calcd for $C_{14}H_{26}O_5S_2$: C, 49.68; H, 7.74. Found: C, 49.61; H, 7.89.

2-Deoxy-4,5-*O*-isopropylidene-3-*O*-methyl-7-*O*-tosyl-D-*gluco*-heptose Trimethylene Dithioacetal (13b). A solution of the diol **13a** (525 mg, 1.551 mmol) in dry pyridine (10 mL) was treated at 0 °C with *p*-toluenesulfonyl chloride (325 mg, 1.1 equiv). The mixture was stored at this temperature for 1 h and then at 10 °C for 36 h. The solution was poured into ice-cold 1 N HCl (25 mL), extracted with CH_2Cl_2 (10 mL), washed with a saturated aqueous solution of $NaHCO_3$ (5 mL), then with water (5 mL) and dried ($MgSO_4$), filtered, and the filtrate evaporated at reduced pressure. The crude product was purifed by layer chromatography on silica gel (diethyl ether/pentane, 1:1) to afford **13b** (596 mg, 78%) as an oil that solidified after some days: mp 88 °C; $[\alpha]^{20}_D$ −0.3° (*c* 4.1, CH_2Cl_2); IR (film) 3440 (br, OH), 2848 (methyl ether), 1369 and 1190 (SO_2 valence), 910 (dithiane) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25, 1.29 (s, 6 H, 2 × CH_3-acetonide), 1.71–2.16 (m, 4 H, H-2 and SCH_2CH_2), 2.39 (s, 3 H, CH_3-Ar), 2.71–2.92 (m, 4 H, SCH_2), 3.48 (s, 3 H, OMe), 3.56 (br s, 1 H, OH), 3.63–3.79 (m, 3 H), 3.94–4.03 (m, 2 H), 4.10 (dd, J = 6.0 and 8.7 Hz, 1 H), 4.26 (dd, J = 2.0 and 10.3 Hz, 1 H), 7.38 (d, J = 7.9 Hz, 2 H, H-Ph), 7.85 (d, J = 7.9 Hz, 2 H, H-Ph); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.61 (q, CH_3-Ph), 25.89 (t, SCH_2CH_2), 26.86 (q, 2 × CH_3-acetonide), 29.77, 30.12 (t, SCH_2), 36.02 (t, C-2), 43.86 (d, C-1), 59.25 (q, OMe), 71.17, 75.44, 76.53, 80.31 (d, C-3/4/5/6), 71.75 (t, C-7), 109.51 (s, CCH_3), 127.99, 129.82 (d, each 2 C-Ar), 132.51, 144.83 (s, C-Ar); MS (CI, isobutane, pos) m/z (%) 493 (25) [M^+ + H], 435 (30) [M^+ − acetone], 321 (100) [$(M^+ + H)$ − TsOH], 289 (25) [$(321)^+$ − MeOH]. Anal. Calcd for $C_{21}H_{32}O_7S_3$: C, 51.20; H, 6.55. Found. C, 51.38; H, 6.81.

6,7-Anhydro-2-deoxy-4,5-*O*-isopropylidene-3-*O*-methyl-D-*gluco*-heptose Trimethylene Dithioacetal (14). A solution of the tosylate **13b** (100 mg, 0.203 mmol) in dry MeOH (5 mL) was treated with a solution of 1 N sodium methanolate (0.25 mL) and stirred for 5 h at 20 °C (TLC monitoring). The mixture was neutralized by addition of solid NH_4Cl, and the MeOH was distilled off at reduced pressure to afford **14** (62 mg, 97%) as an oil: $[\alpha]^{20}_D$ −9° (*c* 2.9, CH_2Cl_2); IR (film) 3045 (C-H-valence, epoxide), 910 (dithiane) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (s, 6 H, 2 × CH_3-acetonide), 1.78–2.24 (m, 4 H, 2-H and SCH_2CH_2), 2.73 (dd, J = 2.6 and 5.0 Hz, 1 H, 7a-H), 2.80–2.95 (m, 5 H, 7b-H and SCH_2), 3.07 (m_c, 1 H, 6-H), 3.50 (s, 3 H, OMe), 3.59–3.76 (m, 2 H), 4.06 (dd, J = 4.5 and 7.5 Hz, 1 H), 4.19 (dd, J = 6.5 and 8.2 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.08 (t, SCH_2CH_2), 26.81, 26.92 (q, CH_3-acetonide) 29.77, 30.15 (t, SCH_2), 36.75 (t, C-2), 41.87 (d, C-1), 43.75 (t, C-7), 52.04 (d, C-6), 59.40 (q, OMe), 77.13, 77.36, 80.52 (d, C-3/4/5), 109.83 (s, CCH_3); MS (CI, isobutane, pos) m/z (%) 377 (14) [$M^+ + C_4H_9$], 321 (72) [M^+ + H], 263 (100) [$(321)^+$ − acetone]. Anal. Calcd for $C_{14}H_{24}O_4S_2$: C, 52.47; H, 7.55. Found: C, 52.34; H, 7.56.

((3a*R*)-7*c*-Methoxy-2,2-dimethyl-(3a*r*,7a*t*)-3a,4,7,7a-tetrahydro-6*H*-spiro[benzo[1,3]dioxole-5,2′-[1,3]dithian]-4*t*-yl)methanol (15). A solution of the epoxide **14** (220 mg, 0.686 mmol) in dry THF (10 mL) was treated at −40 °C with *n*-BuLi (0.47 mL, 1.6 M in *n*-hexane, 1.1 equiv). After 10 min, the cooling bath was removed, and the mixture was stirred for 4 h at 20 °C and then neutralized by addition of a saturated aqueous solution of NH_4Cl (3 mL) and extracted three times with diethyl ether (30 mL). The combined organic phases were dried ($MgSO_4$), filtered, evaporated to dryness, and purified by column chromatography (diethyl ether/pentane) to yield **15** (154 mg, 70%) as an oil: $[\alpha]^{20}_D$ 14° (*c* 1.4 in CH_2Cl_2); IR (film) 3505 (br OH), 2849 (methyl ether), 1425 and 1372 (ketal), 910 (dithiane) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.48 (s, 6 H, CH_3-acetonide), 1.69 (dd, J_{gem} = 13.9 Hz, $J_{6ax,7}$ = 10.2 Hz, 1 H, 6ax-H), 1.84–2.01 (m, 1 H, 5′-H), 2.09–2.19 (m, 1 H, 5′-H), 2.46 (dd, $J_{6eq,7}$ = 3.2 Hz, J_{gem} = 14.0 Hz, 1 H, 6eq-H), 2.63–2.82 (m, 2 H, 4-H, 6′-H), 2.95–3.18 (m, 4 H, 4′-H, 6′-H, 4-H, OH), 3.45 (s, 3 H, OMe), 3.63–3.78 (m, 2 H, 7-H, 7a-H), 3.87–4.01 (m, 2 H, CH_2-OH), 4.32 (dd, $J_{3a,7a}$ = 4.6 Hz, $J_{3a,4}$ = 9.6 Hz, 1 H, 3a-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.73 (t, SCH_2CH_2), 26.74, 26.78 (t, SCH_2), 26.87, 26.94 (q, CH_3-acetonide), 40.35 (t, C-6), 43.13 (d, C-4), 51.45 (s, C-5), 57.44 (q, OMe), 60.58 (t, CH_2-OH), 75.74 (d, C-7), 76.97 (d, C-3a), 78.89 (d, C-7a), 110.65 (s, CCH_3); MS (CI, isobutane, pos) m/z (%) 321 (82) [M^+ + H], 263 (100) [M^+ + H], 231 (87) [$(263)^+$ − MeOH]. Anal. Calcd for $C_{14}H_{24}O_4S_2$: C, 52.47; H, 7.55. Found: C, 52.35; H, 7.67.

2,3-*O*-Isopropylidene-4-*O*-methylvalidatol (16). A solution of the thioacetal **15** (120 mg, 0.37 mmol) in ethanol (20 mL) was treated with Raney nickel (ca. 1 g, activity W-2), and the mixture was refluxed for 2 h (TLC monitoring). The suspension was filtered through a batch of Celite, the filtrate was evaporated to dryness at reduced pressure, and the residue was redissolved in diethyl ether, filtered, and evaporated to yield **16** (73 mg, 90%): mp 77 °C; $[\alpha]^{20}_D$ −30° (*c* 0.8, CH_2Cl_2); IR (KBr) 3400 (br, OH), 2810 (methyl ether), 1449 and 1380 (ketal) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12–1.27 (m, 1 H, 5a-H), 1.40 (s, 6 H, 2 × CH_3-acetonide), 1.46 (m_c, 1 H, 6a-H), 1.72 (m_c, 1 H, 6b-H), 1.96 (m_c, 1 H, 1-H), 3.32 (ddd, J = 4.7 Hz and 2 × 9.7 Hz, 1 H, 4-H), 3.41 (s, 3 H, OMe), 3.49–3.59 (m, 2 H, 7-H), 3.68 (t, J = 9.4 Hz, 1 H, 3-H), 3.96 (dd, $J_{2,3}$ = 9.4 Hz, $J_{1,2}$ = 11.0 Hz, 1 H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.57 (t, C-6), 26.39 (t, C-5), 26.72, 26.84 (q, 2 × CH_3-acetonide), 37.62 (d, C-1), 57.09 (q, OMe), 62.29 (t, CH_2OH),

78.15, 79.72, 80.10 (d, C-2/3/4); MS (CI, isobutane, pos) m/z (%) 217 (100) [M^+ + H], 159 (50) [$(217)^+$ − acetone], 141 (5) [$(159)^+ - H_2O$], 127 (2.5). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.13; H, 9.57.

Validatol (4). A solution of the protected validatol **16** (40 mg, 0.19 mmol) in dry CH_2Cl_2 (10 mL) was treated at −35 °C under argon with BBr_3 (0.04 mL, 2.5 equiv). The mixture was allowed to warm to 20 °C within 3 h and was then stirred for a further 6 h (TLC monitoring). The reaction was quenched by addition of MeOH (5 mL) at −30 °C, and the solvent was removed at reduced pressure. The residue was redissolved in MeOH (10 mL) and the solution again evaporated; this procedure was repeated three times. The residue was dissolved in water (10 mL) and washed twice with CH_2Cl_2 (5 mL), and the aqueous phase was evaporated to dryness at reduced pressure. The residue was purified by column chromatography (EtOAc/i-PrOH/H_2O 7:2:1) to afford **4** (25 mg, 82%); mp 118 −120 °C; $[\alpha]^{20}_D$ −39° (*c* 0.6, H_2O) [lit.[2]] mp 119−121 °C, $[\alpha]^{20}_D$ −39° (H_2O)]; ^{1}H NMR (D_2O, 300 MHz) δ 1.32−1.52 and 1.70−1.82 (2 × m, 4 H, 2 × 5-H, 2 × 6-H), 2.08−2.19 (m, 1 H, 1-H), 3.28 (t, J = 9.0 Hz, 1 H), 3.39−3.50 (m, 1 H), 3.52−3.62 (m, 2 H), 3.75 (dd, $J_{1,7}$ = 4.8 Hz, J_{gem} = 11.1 Hz, 1 H, 7b-H); ^{13}C NMR (D_2O, 75 MHz) δ 21.66 (t, C-6), 27.92 (t, C-5), 42.22 (d, C-1), 59.83 (t, C-7), 74.17, 74.69, 76.16 (d, C-2/3/4); MS (CI/NH_3, pos) m/z 180 (65) [M^+ + NH_4], 163 (100) [M^+ + H].

2-Deoxy-4,5-*O*-isopropylidene-3,7-di-*O*-methyl-D-*gluco*-heptose Trimethylene Dithioacetal (17). To a solution of 1 N sodium methoxide (10 mL) was added tosylate **13b** (327 mg, 0.664 mmol), and the mixture was stirred at 20 °C for 18 h. The solution was neutralized by addition of solid NH_4Cl and evaporated to dryness at reduced pressure, and the residue was redissolved in CH_2Cl_2 (20 mL). The solution was filtered and purified by flash chromatography on silica gel (diethyl ether/pentane, 1:1) to yield **17** (222 mg, 95%) as an oil: $[\alpha]^{20}_D$ −3° (*c* 2.3, CH_2Cl_2); IR (film) 3450 (br, OH), 2849 (methyl ether), 910 (dithiane) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 and 1.43 (s, 6 H, 2 × CH_3-acetonide), 1.75−2.27 (m, 4 H, 2-H and SCH_2CH_2), 2.73−2.97 (m, 4 H, SCH_2), 3.48 and 3.55 (s, 6 H, 2 × OMe), 3.25−4.24 (8 H, 1/3/4/5/6/7-H and OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.87 (t, SCH_2CH_2), 26.86, 27.03 (q, 2 × CH_3-acetonide), 29.72 and 30.06 (t, SCH_2), 36.57 (t, C-2), 43.84 (d, C-1), 59.09 (2 q, 2 × OMe), 71.66, 76.26, 76.67, 80.44 (d, C-3/4/5/6), 73.82 (t, C-7), 109.05 (s, CCH_3); MS (CI, isobutane, pos) m/z (%) 409 (8) [M^+ + C_4H_9], 353 (100) [M^+ + H], 321 (10) [M^+ −MeOH], 295 (52) [$(M + H)^+$ − acetone], 263 (10) [$(295)^+$ − MeOH], 245 (46) [$(263)^+ - H_2O$]. Anal. Calcd for $C_{15}H_{28}O_5S_2$: C, 51.12; H, 8.01. Found: C, 50.82; H, 8.32.

2-Deoxy-4,5-*O*-isopropylidene-6-*O*-methanesulfonyl-3,7-di-*O*-methyl-D-*gluco*-heptose Trimethylene Dithioacetal (18). A solution of the dimethyl ether **17** (180 mg, 0.51 mmol) in dry pyridine (10 mL) was treated at 0 °C under argon with DMAP (20 mg) and methansulfonyl chloride (0.044 mL, 1.1 equiv), and the mixture was stirred for 18 h at 20 °C. The solution was poured into ice-cold 1 N HCl (10 mL) and extracted three times with CH_2Cl_2 (30 mL), and the combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and then water (10 mL), dried ($MgSO_4$), filtered, and evaporated to dryness at reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/0.5% MeOH) to afford **18** (212 mg, 97%) as an oil: $[\alpha]^{20}_D$ 22° (*c* 3.29, CH_2Cl_2); IR (film) 2820 (methyl ether), 1360 and 1175 (SO_2), 910 (dithiane) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 6 H, 2 × CH_3-acetonide), 1.69−2.19 (m, 4 H, 2-H and SCH_2CH_2), 2.73−2.95 (m, 4 H, SCH_2), 3.09 (s, 3 H, SCH_3), 3.42, 3.49 (s, 6 H, 2 × OMe), 3.58−3.80 (m, 3 H), 4.08−4.20 (m, 3 H), 4.71 (m_c, 1 H, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.86 (t, SCH_2CH_2), 26.76, 26.96 (q, 2 × CH_3-acetonide), 29.60, 29.83 (t, SCH_2), 36.77 (t, C-2), 3857 (q, SCH_3), 43.42 (d, C-1), 59.00, 59.10 (q, 2 × OMe), 71.56 (t C-7), 74.78, 76.38, 79.59, 80.67 (d, C3/4/5/6), 109.86 (s, CCH_3); MS (CI, isobutane, pos) m/z (%) 487 (22) [M^+ + C_4H_9], 431 (100) [M^+ + H], 373 (49) [$(431)^+$ − acetone]. Anal. Calcd for $C_{16}H_{30}O_7S_3$: C, 44.63; H, 7.02. Found: C, 44.43; H, 6.83.

Benzyl α- and β-D-Glucopyranoside (19b). A solution of dry benzylic alcohol in a three necked vessel containing ca. 2% of HCl was warmed to 100 °C and treated portionwise with dry D-glucose (20.00 g, 0.11 mol), and the mixture was maintained for 3 h at this temperature. The solution was neutralized by addition of solid $PbCO_3$, filtered over a batch of Celite, and evaporated to dryness at 8 mbar and 95 °C. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/10% MeOH) to afford **19b** (21.0 g, 70%): colorless crystals; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05−3.07 (m, 7 H), 4.20−5.45 (m, 6 H), 7.14−7.31 (m, 5 H, H-Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ (selected signals) δ 60.43 (t, C-6, α-anomer), 60.81 (t, C-6, β-anomer), 69.64 (t, CH_2-Ph, α-anomer), 71.44 (t, CH_2-Ph, β-anomer), 97.66 (d, C-1, α-anomer), 101.23 (d, C-1, β-anomer).

Benzyl 2,3:4,6-Di-*O*-isopropylidene-α(and β)-D-glucopyranoside (20a). A solution of benzyl glucose **19b** (18.7 g, 69 mmol) in dry DMF (300 mL) was treated with Sikkon (25 g) and *p*-toluenesulfonic acid (0.2 g). The solution was cooled to 0 °C, a mixture of 2-methoxypropene (26.2 mL, 4 equiv) in dry DMF (20 mL) was added dropwise, and stirring was continued for 20 h at 20 °C. The mixture was neutralized by addition of solid dry Na_2CO_3, filtered, and evaporated to dryness at reduced pressure. The crude product was purified by flash chromatography on silica gel (EtOAc/*n*-hexane/NEt_3 20:80:0.1) to afford **20a** (20.6 g, 85%) as an oil (lit.[18] 89%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46−1.65 (m, 12 H, CH_3-acetonide), 3.14−4.21 (m, 6 H, 2/3/4/5/6-H), 4.69, 4.82 (AB-system, J = 12.0 Hz, CH_2-Ph, α-anomer), 4.79 (d, J = 6.5 Hz, H-1, β-anomer), 4.82, 4.96 (AB-system, J = 11.7 Hz, CH_2-Ph, β-anomer), 5.29 (d, J = 3.1, 1-H, α-anomer), 7.29−7.44 (m, 5 H, H-Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ (selected signals) δ 62.75 (t, C-6, β-anomer), 62.85 (t, C-6, α-anomer), 70.44 (t, CH_2-Ph, α-anomer), 71.24 (t, CH_2-Ph, β-anomer), 97.82 (d, C-1, α-anomer), 101.62 (d, C-1, β-anomer).

2,3:4,6-Di-*O*-isopropylidene-α(and β)-D-glucopyranose (20b). A solution of benzyl 2,3:4,6-di-*O*-isopropylidene-α(and β)-D-glucopyranoside (**20a**) (15.00 g, 42.8 mmol) in ethanol (500 mL) was treated with NEt_3 (5 mL) and hydrogenated with Pd/C (1.50 g, 5%) (TLC monitoring to 80% conversion). The solution was filtered, evaporated to dryness at reduced pressure, and purified by flash chromatography on silica gel (EtOAc/*n*-hexane/NEt_3 80:20:0.1) to afford **20b** (8.35 g, 75%, 90% calculated for 80% conversion) as an oil and 2.55 g (17%) of educt **20a** (lit.[18] 83%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29−1.61 (m, 12 H, CH_3-acetonide), 3.00−5.54 (m, 8 H), 9.74 (d, J = 1.4 Hz, 0.2 H, CHO).

3,4:5,7-Di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptose Trimethylene Dithioacetal (21a) and 3,4:5,7-Di-*O*-isopropylidene-D-*glycero*-D-*ido*-heptose Trimethylene Dithioacetal (22a). A solution of 1,3-dithiane (13.85 g, 115.2 mmol, 3 equiv) in dry THF (250 mL) was treated dropwise at −50 °C under argon with *n*-BuLi (80 mL, 1.6 M in *n*-hexane, 1.1 equiv). The mixture was stirred for 90 min at −40 to −20 °C and cooled to −50 °C, and a solution of 2,3:4,6-di-*O*-isopropylidene-α(and β)-D-glucopyranose (**20b**) (10.00 g, 38.41 mmol) in dry THF (30 mL) was added dropwise. The cooling bath was removed, and the solution was stirred for 18 h at 20 °C, neutralized by addition of a saturated aqueous solution of NH_4Cl (20 mL), and extracted three times with CH_2Cl_2 (25 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to dryness at reduced pressure, and the residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane/NEt_3 70:30:0.1) to afford a mixture of **21a** and **22a** (10.38 g, 71%) as an oil; ratio (NMR) 3:2. Then 200 mg of the mixture was separated for characterization of the isomers by column chromatography on silica gel (diethyl ether).

Data for 21a (less polar fraction): $[\alpha]^{20}_D$ −20° (*c* 0.2, CH_2Cl_2); IR (film) 3450 (br, OH), 1430 and 1389 (ketal), 914 (dithiane) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42, 1.45, 1.48 (s, 12 H, 4 × CH_3-acetonide), 1.82−2.22 (m, 2 H, SCH_2CH_2), 2.77−3.09 (m, 4 H, SCH_2), 3.38−4.02 (m, 7 H), 4.29−4.49 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.87 (q, CH_3), 26.28 (t, SCH_2CH_2), 26.28, 27.16, 27.53 (q, CH_3), 29.49, 30.20 (t, SCH_2), 50.20 (d, C-1), 64.53 (t, C-7), 64.18, 73.29, 75.83, 76.81, 79.39 (d, C-2/3/4/5/6), 99.76 (s, 1,3-dioxane-C), 110.43 (s, 1,3-dioxolane-C); MS (CI/NH_3, pos) m/z (rel intensity) 398 (9) [M^+ + NH_4], 381 (10) [M^+ + H], 340 (50), 323 (100) [$(M + H)^+$ −

acetone], 261 (9), 208 (6), 161 (5), 119 (22). Anal. Calcd for $C_{15}H_{28}O_6S_2$: C, 50.50; H, 7.42. Found: C, 50.59; H, 7.54.

Data for 22a (polar fraction): $[\alpha]^{20}_D$ −26° (*c* 0.1, CH_2Cl_2); IR (film) 3450 (br, OH), 1430 and 1388 (ketal), 910 (dithiane) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40, 1.46, 1.47, 1.48 (s, 12 H, 4 × CH_3-acetonide), 1.87−2.22 (m, 2 H, SCH_2CH_2), 2.68−3.20 (m, 6 H, 2 × OH, 4 × SCH_2), 3.58−4.01 (m, 4 H), 4.12 (d, *J* = 8.2 Hz, 1 H, 1-H), 4.41 (dd, *J* = 3.3 and 8.2 Hz, 1 H), 4.62 (dd, *J* = 1.5 and 8.2 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.75 (q, CH_3), 26.00 (t, SCH_2CH_2), 27.26, 27.41 (q, 2 × CH_3), 28.31, 28.68 (t, SCH_2), 28.57 (q, CH_3), 49.78 (d, C-1), 64.57 (t, C-7), 63.93, 70.81, 72.27, 75.80, 76.78 (d, C-2/3/4/5/6), 99.41 (s, 1,3-dioxolane-C), 110.58 (s, 1,3-dioxolane-C); MS (CI/NH_3, pos) *m*/*z* (rel intensity) 398 (11) [$M^+ + NH_4$], 381 (38) [$M^+ + H$], 363 (11) [$M^+ - H_2O$] 340 (54), 323 (100) [$(M + H)^+$ − acetone], 305 (17), 287 (16), 261 (25), 119 (17). Anal. Calcd for $C_{15}H_{28}O_6S_2$: C, 50.50; H, 7.42. Found: C, 50.60; H, 7.47.

2,6-Di-*O*-acetyl-3,4:5,7-di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptose Trimethylene Dithioacetal (21b). A solution of the *gulo*-diacetonide **21a** (60 mg, 0.158 mmol) in dry pyridine (5 mL) was treated with acetic anhydride (0.05 mL) and DMAP (10 mg). After 2 h the mixture was evaporated to dryness at reduced pressure, codistilled three times with toluene (1 mL), and purified by layer chromatography on silica gel (CH_2Cl_2/EtOAc, 95:5) to afford **21b** (73 mg, quant) as an oil: ^1H NMR (200 MHz, benzene) δ 1.43, 1.50, 1.61(s, 12 H, 4 × CH_3-acetonide), 1.68, 2.00 (s, 6 H, 2 × CH_3-acetate), 2.19−2. 71 (m, 6 H, SCH_2CH_2), 3.72 (dd, $J_{6,7}$ = 5.3 Hz, J_{gem} = 12.2 Hz, 1 H, 7a-H), 4.04 (dd, $J_{4,5}$ = 1.9 Hz, $J_{5,6}$ = 9.0 Hz, 1 H, 5-H), 4.19 (dd, $J_{6,7}$ = 5.0 Hz, J_{gem} = 12.2, 1 H, 7b-H), 4.52 (d, $J_{1,2}$ = 5.2 Hz, 1 H, 1-H), 4.65 (dd, $J_{4,5}$ = 1.9 Hz, $J_{5,6}$ = 7.1 Hz, 1 H, 4-H), 5.16 (dd, $J_{2,3}$ = 6.9 Hz, 1 H, 3-H), 5.00 (m_c, 1 H, 6-H), 6.02 (dd, $J_{1,2}$ = 5.3 Hz, $J_{2,3}$ = 6.6 Hz, 1 H, 2-H).

2,6-Di-*O*-acetyl-3,4:5,7-di-*O*-isopropylidene-D-*glycero*-D-*ido*-heptose Trimethylene Dithioacetal (22b). The *ido*-diacetonide **22a** (60 mg, 0.158 mmol) was acetylated as described for **21b** to afford **22b** (73 mg, quant) as an oil: ^1H NMR (200 MHz, benzene) δ 1.45 (s, 6 H, CH_3-acetonide), 1.61, 1.62 (s, 6 H, 2 × CH_3-acetonide), 1.82, 2.00 (s, 6 H, 2 × CH_3-acetate), 1.48−1.80 (m, 2 H, SCH_2CH_2), 2.08−2.92 (m, 4 H, SCH_2), 3.74 (dd, $J_{6,7}$ = 4.4 Hz, J_{gem} = 12.4 Hz, 1 H, 7a-H), 4.06−4.18 (m, 2 H, H-5, 7b-H), 4.35 (d, $J_{1,2}$ = 10.1 Hz, 1 H, 1-H), 4.38 (dd, $J_{4,5}$ = 2.4 Hz, $J_{3,4}$ = 7.8 Hz, 1 H, 4-H), 5.29 (dd, $J_{2,3}$ = 1.8 Hz, $J_{3,4}$ = 7.9 Hz, 1 H, 3-H), 5.54 (ddd, *J* = 4.4 Hz, 1 H, 6-H), 5.74 (dd, $J_{1,2}$ = 10.2 Hz, $J_{2,3}$ = 1.8 Hz, 1 H, 2-H).

2,3:4,5:6,7-Tri-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptose Trimethylene Dithioacetal (23) and 2,3:4,5:6,7-Tri-*O*-isopropylidene-D-*glycero*-D-*ido*-heptose Trimethylene Dithioacetal (24). A solution of the diastereomeric dithiane derivatives **21a/22a** (5.60 g, 14.7 mmol) in dry acetone (200 mL) was treated at 0 °C with concd sulfuric acid (2 mL). After 3 h at 20 °C, the mixture was neutralized by addition of solid dry Na_2CO_3. The suspension was filtered, the filtrate was evaporated to dryness, and the residue was purified by flash chromatography (silica gel, diethyl ether/pentane, 3:2) to afford the unseparable mixture of triacetonides **23/24** (oil, 4.46 g, 71%) and the mixture of the diacetonides **25/26** (oil, 0.67 g, 12%). For characerization the pure triacetonides **23/24** were prepared separately from **21a** and **22a**. The diacetonides of the *gulo* isomers **25/26** were separated by layer chromatography on silica gel (diethyl ether/pentane, 3:2); yields from **21a**, 64% **23**, 12% **25**, 7% **26**; from **22a**, 84% **24**.

Data for 23: mp 116.6 °C; $[\alpha]^{20}_D$ 25° (*c* 0.8, CH_2Cl_2); IR (film) 1459 and 1385 (ketal), 908 (dithiane) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38, 1.40, 1.45, 1.47, 1.57 (s, 18 H, 6 × CH_3-acetonide), 1.92−2.23 (m, 2 H, SCH_2CH_2), 2.74−3.06 (m, 4 H, SCH_2), 3.92−4.21 and 4.36−4.56 (2 × m, each 4 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.84, (q, 2 × CH_3-acetonide), 26.03 (t, SCH_2CH_2), 27.05, 27.12, 27.35, 27.54 (q, 4 × CH_3-acetonide), 28.25, 28.62 (t, SCH_2), 45.36 (d, C-1), 68.14 (t, C-7), 75.84, 77.21, 77.58, 77.64, 78.21 (d, C-2/3/4/5/6), 109.38, 109.87, 110.14 (s, 3 × 1,3-dioxolane-C); MS (CI/NH_3, pos) *m*/*z* (rel intensity) 421 (12) [$M^+ + H$], 405 (5) [$M^+ - CH_3$], 380 (4) [$(M + H)^+ - C_3H_5$], 363 (100) [$(M + H)^+$ − acetone], 345, 305 (12), 287 (32), 248 (17), 31 (34), 185 (8), 161 (12), 119 (8), 101 (8). Anal. Calcd for $C_{19}H_{32}O_6S_2$: C, 54.26; H, 7.67. Found: C, 54.19; H, 7.59.

Data for 24: $[\alpha]^{20}_D$ 30° (*c* 0.5, CH_2Cl_2); IR (film) 1453 and 1370 (ketal), 910 (dithiane) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.39, 1.43, 1.44, 1.48 (s, 18 H, 6 × CH_3-acetonide), 1.90−2.22 (m, 2 H, SCH_2CH_2), 2.68−3.12 (m, 4 H, SCH_2), 3.94−4.18 (m, 6 H), 4.22 (d, *J* = 7.8 Hz, 1 H, 1-H), 4.51 (dd, *J* = 5.8 and 7.7 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.80 (q, CH_3-acetonide), 26.14 (t, SCH_2CH_2), 27.10, 27.36, 27.61, 27.72 (q, 5 × CH_3-acetonide), 29.01, 29.26 (t, SCH_2), 47.86 (d, C-1), 67.96 (t, C-7), 77.55, 77.69, 78.53, 79.16, 79.42 (d, C-2/3/4/5/6), 109.96, 110.11, 110.16 (s, 3 × 1,3-dioxolane-C); MS (CI/NH_3, pos) *m*/*z* (rel intensity) 421 (38) [$M^+ + H$], 363 (100) [$(M + H)^+$ − acetone], 345 (8), 305 (24), 287 (15), 231 (17), 185 (9), 119 (9), 119 (5), 101 (6). Anal. Calcd for $C_{19}H_{32}O_6S_2$: C, 54.26; H, 7.67. Found: C, 54.29; H, 7.62.

3,4:6,7-Di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptose trimethylene dithioacetal (25): colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 1.39, 1.44, 1.46 (s, 12 H, 4 × CH_3-acetonide), 1.82−2.22 (m, 2 H, SCH_2CH_2), 2.49 (d, *J* = 7 Hz, 1 H, OH), 2.81−3.08 (m, 5 H, OH, 2 × SCH_2), 3.67 (m, 1 H), 4.00−4.16 (m, 3 H), 4.22−4.38 (m, 2 H), 4.43 (d, *J* = 3.0 Hz, 1 H, 1-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.83 (q, CH_3-acetonide), 26.22 (t, SCH_2CH_2), 27.12 (q, CH_3-acetonide), 29.57, 30.34 (t, SCH_2), 51.01 (d, C-1), 67.60 (t, C-7), 72.58, 76.23, 76.83, 77.14, 80.29 (d, C-2/3/4/5/6), 110.07, 110.38 (s, 2 × 1,3-dioxolane-C).

4,5:6,7-Di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptose trimethylene dithioacetal (26): mp 117.5 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.36, 1.41, 1.44, 1.45 (s, 12 H, 4 × CH_3-acetonide), 1.85−2.22 (m, 2 H, SCH_2CH_2), 2.60−2.70 (m, 1 H, OH), 2.79−3.05 (m, 5 H, OH, 2 × SCH_2), 3.86−4.23 (m, 6 H), 4.30 (d, *J* = 7.0 Hz, 1 H), 4.50 (d, *J* = 2.8 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.71, 27.06, 27.30, 27.54, (q, 4 × CH_3-acetonide), 26.25 (t, SCH_2CH_2), 29.40, 30.14 (t, SCH_2), 50.35 (d, C-1), 68.13 (t, C-7), 69.69, 76.02, 77.54 (2 C), 79.85 (d, C-2/3/4/5/6), 110.14, 110.31 (s, 2 × 1,3-dioxolane-C).

2-Deoxy-4,5:6,7-di-*O*-isopropylidene-D-*gluco*-heptose Trimethylene Dithioacetal (12a). A solution of the epimeric triacetonides **23/24** (3.80 g, 9.0 mmol) in dry THF (80 mL) was treated under argon at −40 °C with *n*-BuLi (11.3 mL, 1.6 M in *n*-hexane, 2 equiv). The mixture was stirred for 50 min at −20 °C, and then LAH (0.41 g, 1.2 equiv) was added at 0 °C and stirring was continued for 1.5 h. The suspension was diluted with diethyl ether (100 mL) and hydrolyzed with a satured aqueous solution of $NaHSO_4$ (5 mL). The mixture was filtered over a batch of Celite, the solution was evaporated to dryness at reduced pressure, and the residue was purified by flash chromatography on silica gel (diethyl ether/pentane, 1:1) to afford **12a** (2.92 g, 89%) as an oil.

Supplementary Material Available: Copies of ^1H NMR spectra of **4**, **8**, **9**, **21a/b**, and **22a/b** (7 pages). This material is contained in libaries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.