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From Sugars to Carbocycles. 4[1]. Exclusive Seven-membered Ring Formation from D-Glucose

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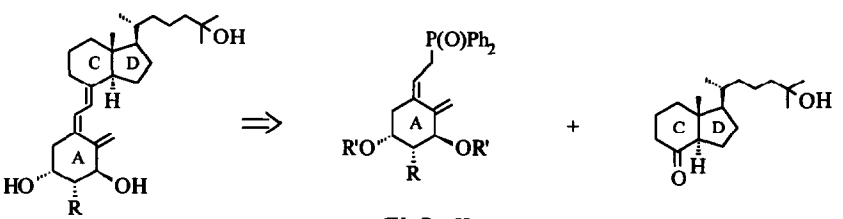
Abstract: An example of the 1,3-dithiane methodology of carbocyclization of sugars leading selectively to a seven-membered ring **16** is presented. The selectivity is discussed in terms of steric hindrance of the respective six-memberd transition states.

In connection with a recently developed new method[1-3] for the conversion of sugars to carbocycles we designed a synthesis of an enantiomerically pure calcitriol building block. Calcitriol (1α,25-dihydroxy vitamin D_3, **I**) is the physiologically active form of vitamin D_3 (calciol) and is formed by hydroxylation in the liver and kidney. In fact, the triol **I** has a key function in the regulation of many physiological functions.[4,5] Some hydroxylated vitamin D_3-derivatives (e.g. the tetraol **II**) are presently in clinical trial for the treatment of cancer, psoriasis, or immunodeficiencies.[6] These interesting biological properties have stimulated a great number of synthesis of calcitriol (**I**) (review[7]). The first total synthesis based on the disconnection method of Lythgoe[8] has been achieved by a Hoffman LaRoche group.[9] In this type of approach hydroxylated ring-A building blocks such as **IV** and **V** are connected with the CD ring part **III** (Scheme 1).

Scheme 1



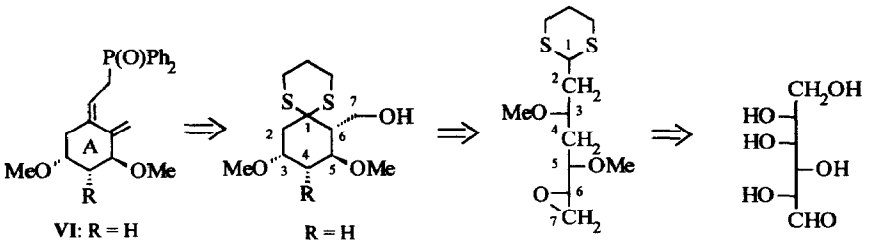
I: R = H 1α,25-$(OH)_2$ Vitamin D_3 (Calcitriol)
II: R = OH 1α,2β,25-$(OH)_3$ Vitamin D_3

IV: R = H
V: R = OH
R' = protecting group

III

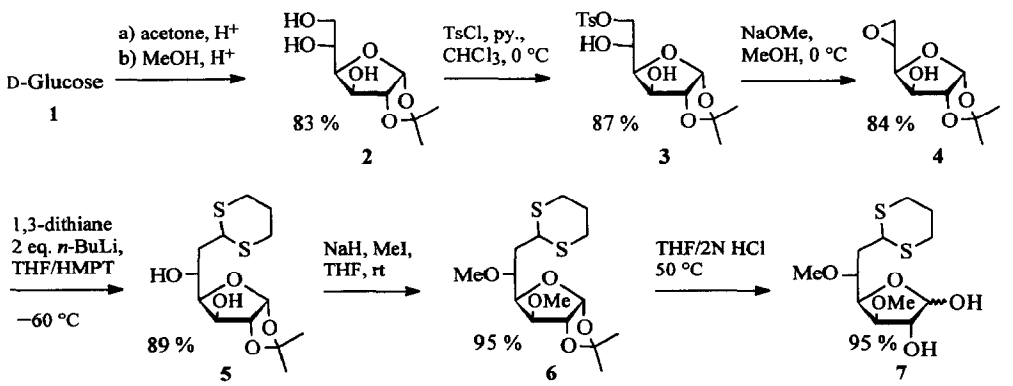
The retrosynthetic analysis (Scheme 2) shows the synthesis of both building blocks **VI** and **VII** from D-glucose (**1**). The chain-elongated 1,3-dithiane derived from D-glucose has the correct configuration at carbon atoms C-3 and C-5. The synthetic scheme involves intermediate epoxides and deoxygenations at C-2 and C-6 along with the dithiane addition and the cyclization step. The correct position and functionality for the conversion to the diene phosphonate are directly generated in the 1,3-dithiane cyclization product. However, it had to be shown whether six- or seven-membered ring systems would result from the cyclization of the epoxy-1,3-dithiane intermediate. In previous work the six-membered ring predominated[2] or was formed exclusively.[1]

Scheme 2



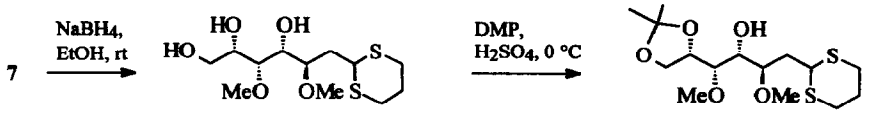
Accordingly, our plan involved the addition of the lithiated 1,3-dithiane to the D-glucose derived epoxide **4**, a step that has been described in the literature.[10] The procedure for the preparation of the required monoacetonide glucose (**2**) was optimized (83 % yield) to an operationally very convenient process without isolation of the diacetonide. Selective tosylation at the primary hydroxy group to **3** (87 %) followed by sodium methoxide induced conversion to the epoxide **4** (84 %) were straightforward. Careful reinvestigation of the dithiane addition reaction showed that only half the amount (1.1 equiv.) of lithiated 1,3-dithiane was required compared to the original procedure[10]; only 2.2 equivalents of *n*-BuLi had to be used to afford the adduct **5** (89 %). Evidently, attack of excess *n*-BuLi on the epoxide was much slower than that of the lithiated 1,3-dithiane leaving sufficient time for prior deprotonation of the 3-OH. Previous work had shown that cyclitol methyl ethers could easily be cleaved by BBr_3 treatment[1] and for that reason the diol **5** was methylated to the dimethyl ether **6** (95 %). However, other acid and base stable protecting groups such as benzyl ethers could certainly also be introduced at this stage if necessary for the synthesis of other derivatives. The remaining reaction sequence required a reduction of the masked aldehyde at C-1 and deoxygenation (or protection) step at C-4. For that purpose the relatively stable acetonide **6** was cleaved by treatment with THF/2 N HCl (1:1.2) at 50 °C (95 %) and the oily furanose **7** (anomeric mixture) was reduced with sodium borohydride in EtOH to afford the triol **8** (80 %, Scheme 3).

Scheme 3



At this stage of the synthesis a manipulation of 4-OH was necessary to afford either the deoxygenated fragment **IV** or the protected triol **V**. Selective protection of the 6- and 7-hydroxyls was easily achieved by acetonide formation to yield **9** that was isolated as the major product (79 %) under both kinetically or thermodynamically controlled conditions (Scheme 4).

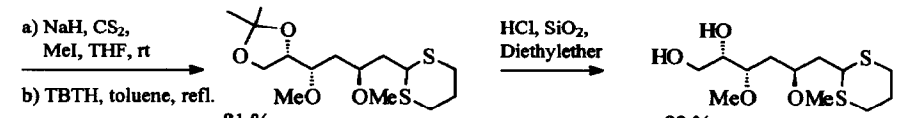
Scheme 4



8 **9**

To get the ring-A building block of calcitriol (I) the hydroxy group at C-4 must be deoxygenated. For this reason the mono alcohol **9** was deoxygenated using the Barton[11] procedure to afford the 2,4-dideoxy heptose derivative **10** (81 %). The acetonide of compound **10** was easily cleaved using a modification of the Huet procedure.[12] In this heterogeneous system a CH_2Cl_2 solution of the acetal is stirred with 6 N HCl on silica gel. We found that the dioxolane ring is more rapidly cleaved in better yield if CH_2Cl_2 is replaced by diethyl ether (Scheme 5).

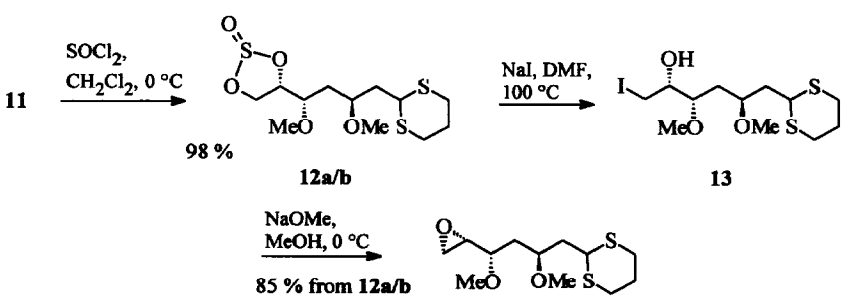
Scheme 5



10 **11**

Next, the terminal hydroxy groups had to be converted into potent electrophiles. A differentation of the secondary and primary hydroxy groups by selective tosylation was not possible yielding only the ditosylate or product mixtures. Also, in agreement with literature,[13,14] a direct conversion of the terminal hydroxy groups into the cyclic sulfate by SO_2Cl_2 treatment was not possible. However, a very convenient and generally applicable stereospecific conversion into the terminal epoxide was finally developed. In this procedure the diol **11** was converted with thionyl chloride into the mixture of the diastereomeric cyclic sulfites **12a/b** (ratio 1:2) in nearly quantitative yield.[15] The epoxide was then obtained by a sequential operation. The sulfites **12a/b** were first treated with sodium iodide in DMF to selectively afford the C-7 iodide **13** by attack on the less hindered primary carbon atom. The epoxide **14** was then generated under mild conditions by NaOMe treatment of the iodide **13** in 85 % overall yield (Scheme 6). We believe that this procedure presents a general solution to the conversion of vicinal diols into epoxides if chemical differention of the hydroxy groups by selective activation (e.g. tosylation) is difficult to achieve.

Scheme 6

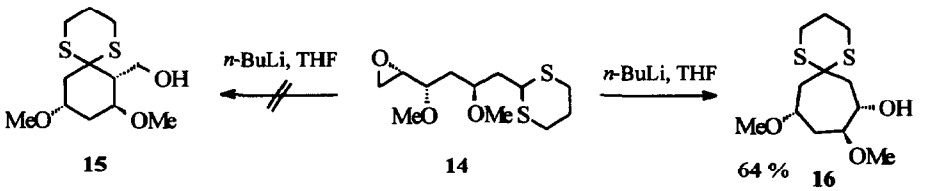


12a/b **13**

14

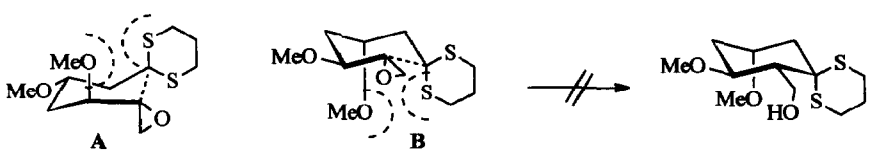
With the epoxide now in hand the cyclization experiment was performed as described previously using BuLi as the base for the dithiane deprotonation.[2,3] Surprisingly, the experiment did not lead to the expected six-membered ring **15**, but in a slow but clean reaction to the cycloheptane derivative **16** (64 %). The structure of **16** was unambiguously established by the occurrence of a signal at 73 ppm in the ^{13}C NMR-spectrum for a tertiary carbon atom (CHOH) and the absence of a signal for a secondary carbon (CH_2OH) expected for six-membered rings at ca. 60 ppm[1,3] (Scheme 7).

Scheme 7



Evidently, formation of the six-membered ring **15** is prevented by severe sterical hinderance of the 1,3-diaxial substituents in both transitions states A and B (see Scheme 8). Inspection of models of the more flexible transition states leading to the seven-membered ring revealed the absence of such sterical hinderance. Enantiomerically pure highly substituted seven-membered rings are much more difficult to synthesize than their six-membered counterparts and the initially dissappointing failure in the vitamin D_3 building block synthesis turned out to be a fortunate event. It is reasonable to assume that deliberate use of 1,3-diaxial strain in six-membered transition states (e.g. A or B) will generally allow the construction of seven-membered carbocycles using the dithiane method.

Scheme 8



1,3-diaxial interaction

Experimental Section

General Methods. M.p. are determined on a Gallenkamp melting point apparatus and are uncorrected. Column chromatography is performed on silica gel Merck 60, 230 – 400 mesh, and TLC on silica gel Merck 60 F_{254}. The detection of the substances is by spraying with $EtOH/H_2SO_4$ (9:1) and heating afterwards. The ^1H NMR and ^{13}C NMR spectra are recorded on Bruker AMX 300 and AMX 200 spectrometers operating at 200, 300, 75, and 50 Mhz, respectively. Chemical shifts (δ) are reported in ppm with TMS as internal standard: J values are quoted in Hz. FT-IR spectra are determined on a Nicolet 510 P FT-IR spectrometer. GCMS were measured on a Fisons Instrument MD 800 Lab Base spectrometer (70 eV), EIMS are measured on a Finnigan MAT 8430. Elemental analyses are carried out on a Perkin-Elmer Elementalanalyzer 240. The OR are measured with a Perkin-Elmer Polarimeter 241 in $CHCl_3$ at 20 °C.

6-Deoxy-6-C-(1,3-dithiane-2-yl)-3,5-di-O-methyl-1,2-O-isopropylidene-α-D-glucofuranoside (6). A suspension of NaH (780 mg of 80 % in oil, 26 mmol) in dry THF (125 mL) is treated dropwise at 20 °C under argon with a solution of **5** (2.80 g, 8.68 mmol) in dry THF (20 mL). The mixture is stirred for 1 h at 20 °C, then MeI (0.82 mL, 26 mmol) is added. After 18 h of stirring (TLC control) the mixture is quenched by addition of a saturated NH_4Cl-solution (35 mL) and the THF is distilled off under reduced pressure. The residue is extracted three times with diethyl ether (each 35 mL), the organic phase is washed with a solution of $KHSO_3$, dried (Na_2SO_4), filtered, and evaporated at reduced pressure to afford the dimethyl ether **6** (2.9 g, 95 % yield). Oily. $[\alpha]_D$ +21.14 (c 1.05, $CHCl_3$). IR (neat): 2985, 2934, 2890, 2829, 1456, 1373, 1244, 1074, 1026, 908 cm^{-1}. ^1H NMR ($CHCl_3$): 1.32, 1.51 (6H, 2s; 2x CH_3-acetonide), 1.82 – 2.36 (4H, m; $SCH_2\underline{CH}_2$, 6a-H, 6b-H), 2.80 – 2.95 (4H, m; SCH_2), 3.45, 3.49 (6H, 2s; 2x OMe), 3.76 – 4.07 (3H, m; 3/4/5-H), 4.27 (1H, dd; 2'-H), 4.60 (1H, d, $J_{1,2}$ = 3.7; 2-H), 5.91 (1H, d, $J_{1,2}$ = 3.7; 1-H). ^{13}C NMR ($CDCl_3$): 26.4 (t, $SCH_2\underline{C}H_2$), 26.7, 27.1 (q, 2x CH_3-acetonide), 29.9, 30.3 (t, SCH_2), 43.7 (d, C-2'), 57.6, 59.0 (q, 2x OMe), 74.6, 82.2, 84.1 (d, C-3/4/5), 81.5 (d, C-2), 105.3 (d, C-1), 112.0 (s, $\underline{C}(CH_3)_2$). GC-MS *m/e* (%): 350(5) [M^+], 318(15), 293(12), 261(7), 221(3), 201(13), 175(21), 145(24), 133(9), 119(100), 101(12).

6-Deoxy-6-C-(1,3-dithiane-2-yl)-3,5-di-O-methyl-α-(and β)-D-glucofuranose (7). A solution of the acetonide **6** (1.80 g, 5.14 mmol) in a mixture of THF/2 N HCl (1:1.2; 100 mL) is stirred for 3 h at 50 °C (TLC control) and solid $NaHCO_3$ is then added for neutralization. The suspension is evaporated at reduce pressure and the residue is extracted three times with ethyl acetate (105 mL). The combined organic phase is dried (Na_2SO_4), filtered, and evaporated at reduced pressure to dryness to afford the furanose **7**. Oily (1.59 g, 95 % yield). $[\alpha]_D$ +20.85 (c 0.95, $CHCl_3$). IR (neat): 3397, 2936, 2890, 2829, 1423, 1277, 1194, 1105, 1061, 908 cm^{-1}. ^1H NMR ($CDCl_3$): 1.75 – 2.31 (4H, m; $SCH_2\underline{CH}_2$, 6a-H, 6b-H), 2.65 – 2.92 (4H, m; SCH_2), 3.35 – 3.52 (6H, 2s; 2x OMe), 3.61 – 4.31 (7H, m; 2'/2/3/4/5-H), 5.11, 5.45 (1H, s, d; α and β Anomer). ^{13}C NMR ($CDCl_3$): 26.3 (t, C-6), 29.9, 30.1, 30.4, 30.7 (t, 2x SCH_2), 38.3, 38.5 (t, $SCH_2\underline{C}H_2$), 43.8, 43.9 (d, C-2'), 57.9, 58.4, 58.7, 58.8 (q, 2x OMe), 74.7, 75.8, 75.9, 77.0, 79.8, 83.2, 84.7, 85.9 (d, C-2/3/4/5), 96.6, 103.6 (d, C-1). EIMS *m/e* (%): 310(8) [M^+], 292(3), 278(6), 233(3), 201(8), 175(27), 132(26), 119(100) Anal. Calcd. for $C_{12}H_{22}O_5S_2$: C 46.43 %, H 7.14 %; Found: C 46.44 %, H 7.32 %.

2-Deoxy-3,5-di-O-methyl-L-manno-heptose Trimethylene Dithioacetal (8). A solution of furanose **7** (1.00 g, 3.2 mmol) in ethanol (35 mL) is treated portionwise with $NaBH_4$ (134 mg, 3.5 mmol). The reaction is stopped after 3 h (TLC control) by dropwise addition of brine (2 mL) and the solution is evaporated under reduced pressure. The residue is extracted five times with ethyl acetate (each 10 mL). The organic phase is dried (Na_2SO_4), filtered, and evaporated at reduced pressure to dryness to afford an oily triol **8** that solidifies on standing (0.80 g, 80 % yield). M.p. 91.5 °C. $[\alpha]_D$ –5.5 (c 1.01, $CHCl_3$). IR (neat): 3412 , 2930, 2890, 2829, 1423, 1277, 1192, 1097, 989, 908 cm^{-1}. ^1H NMR ($CDCl_3$): 1.74 – 2.26 (4H, m; $SCH_2\underline{CH}_2$, 2-H), 2.74 – 3.07 (4H, m; 2 x SCH_2), 3.44, 3.58 (6H, 2s; 2x OMe), 3.51 – 3.92 (6H, m; 3/4/5/6-H and 2x 7-H), 4.26 (1H, dd; 1-H). ^{13}C NMR ($CDCl_3$): 26,3 (t, $SCH_2\underline{C}H_2$), 30.5, 30.7 (t, 2x SCH_2), 36.7 (t, C-2), 43.9 (d, C-1), 57.9, 60.8 (q, 2x OMe), 63.0 (t, C-7), 71.6, 72.0 (d, C-4/6), 78.4, 80.0 (d, C-3/5). EIMS *m/e* (%): 312(6) [M^+], 281(1), 280(7), 263(1), 201(18), 175(27), 132(12), 119(98), 115(100). Anal. Calcd. for $C_{12}H_{24}O_5S_2$: C 46.13 %, H 7.74 %; Found: C 46.27 %, H 7.97 %.

2-Deoxy-6,7-isoporpylidene-3,5-di-O-methyl-L-manno-heptose Trimethylene Dithioacetal (9). A solution of triol **8** (600 mg, 1.92 mmol) in dry dimethoxypropane (DMP) (20 mL) is treated at 0 °C with conc. H_2SO_4 (0.1 mL). The solution is stirred for 4.5 h at 5 °C (TLC control) and solid $NaHCO_3$ (1.2 g) is then added for neutralization. The suspension is filtered, the filtrate evaporated to dryness at reduced pressure and the residue purified by chomatography on silica gel (CH_2Cl_2/MeOH, 95:5) to afford **9** (530 mg, 79 % yield). M.p. 77.4 °C. $[\alpha]_D$ –8.8 (c 0.985, $CHCl_3$). IR (neat): 3427, 2930, 2988, 1456, 1419, 1277, 1197, 1099, 1057, 906 cm^{-1}. ^1H NMR ($CDCl_3$): 1.39, 1.47 (6H, s; 2x OMe), 1.83 – 2.22 (4H, m; SCH_2CH_2, 2x 2-H), 2.54 (1H, d; OH, D_2O exch.), 2.82 – 2.96 (4H, m; 2x SCH_2), 3.36 – 3.59 (3H, m; 4/5/7a-H), 3.47, 3.61 (6H, 2x s; 2x OMe), 3.78 (1H, dd; 1-H), 4.06 (1H, dd; 7b-H), 4.23 – 4.40 (2H, m; 3/6-H). ^{13}C NMR ($CDCl_3$): 25.8, 26.9 (q, 2x CH_3-acetonide), 26.3 (t, SCH_2CH_2), 30.5, 30.7 (t, 2x SCH_2), 37.2 (t, C-2), 44.0 (d, C-1), 58.3, 60.7 (q, 2x OMe), 66.3 (t, C-7), 73.3, 77.7, 78.4, 80.0 (d, C-3/4/5/6), 109.8 (s, quart. C). EIMS *m/e* (%): 352(12) [M^+], 337(5), 320(6), 201(44), 175(34), 145(50), 119(100), 101(30). Anal. Calcd. for $C_{15}H_{28}O_5S_2$: C 51.11%, H 8.01 %; Found: C 51.27 %, H 8.28%.

2,4-Dideoxy-6,7-isopropylidene-3,5-di-O-methyl-L-xylo-heptose Trimethylene Dithioacetal (10). A mixture of NaH (64 mg, 2.66 mmol) and acetonide **9** (500 mg, 1.42 mmol) in dry THF (15 mL) is stirred for 30 min and then treated with CS_2 (0.65 mL, 2.14 mmol). After 1 h stirring at 20 °C, MeI (0.29 mL, 4.46 mmol) is added. The suspension is stirred for 30 min (TLC control), ice-water (1 mL) is added carefully, and the solvent is removed at reduced pressure. The residue is dissolved in water and the solution is extracted three times with diethyl ether (each 20 mL). The combined organic phase is dried (Na_2SO_4), filtered, and evaporated to dryness at reduced pressure. The xanthogenate is dissolved in toluene (5 mL) and this solution is added dropwise under argon to a boiling solution of tributyltin hydride (TBTH) (0.65 mL, 2.41 mmol) in toluene (25 mL). After completion of the addition the mixture is refluxed for 14 h (TLC control) and evaporated to dryness at reduced pressure. The product is chromatographed on silica gel (25 g) [elution with light petroleum (b.p. 30–70 °C) containing an increasing proportion of ether (5 % increments)]. After elution of organic tin compounds, the desired deoxy compound **10** is obtained as an oil (310 mg, 81 % yield). $[\alpha]_D$ –23.7 (c 1.13, $CHCl_3$). IR (neat) 2932, 2826, 1732, 1456, 1423, 1369, 1259, 1213, 1159, 1105, 908 cm^{-1}. ^1H NMR ($CDCl_3$): 1.39, 1.47 (6H, 2s; 2x CH_3-acetonide), 1.54 (2H, ddd; 4-H), 1.77 – 2.22 (4H, m; SCH_2CH_2, 2x 2-H), 2.78 – 3.01 (4H, m; 2x SCH_2), 3.42, 3.58 (6H, 2s; 2x OMe), 3.50 (1H,m_c; 5-H), 3.67 – 3.79 (2H, m; 3/7a-H), 4.00 (1H, dd; 7-H), 4.12 – 4.23 (2H, m; 1/6-H). ^{13}C NMR ($CDCl_3$): 25.7, 26.9 (q, 2x CH_3-acetonide), 26.3 (t, SCH_2CH_2), 30.7, 30.9 (t, 2x SCH_2), 36.5 (t, C-4), 40.8 (t, C-2), 44.0 (d, C-1), 57.3, 59.5 (q, 2x OMe), 66.2 (t, C-7), 74.7 (d, C-3), 78.5 (d, C-6), 78.9 (d, C-5), 109.8 (s, quart. C). EIMS *m/e* (%): 336(8) [M^+], 321(18), 304(38), 289(4), 246(8), 203(10), 175(7), 158(21), 119(100), 101(34).

2,4-Dideoxy-3,5-di-O-methyl-L-xylo-heptose Trimethylene Dithioacetal (11). A suspension of silica gel (1.0 g) in diethyl ether (5 mL) is treated with conc. HCl (0.2 mL). The mixture of the acetonide **10** (310 mg, 0.92 mmol) in diethyl ether (3 mL) is then added and stirring is continued for 4.5 h (TLC control). The mixture is neutralized by addition of solid $NaHCO_3$ (2 g), filtered after 30 min, and the residue is carefully washed with diethyl ether (20 mL). The combined organic phase is evaporated to dryness and purified by column chromatography on silica gel (ethyl acetate/CH_2Cl_2, 9:1) to afford **11** (224 mg, 82 % yield). Oily. ^1H NMR ($CDCl_3$): 1.72 (2H, dd; 4-H), 1.81 – 2.19 (4H, m; SCH_2CH_2, 2-H), 2.48 (1H, OH), 2.71 – 2.97 (5H, m;

SCH_2 and OH), 3.33 – 3.49 (1H, m; 3-H), 3.36 and 3.45 (6H, 2s; 2x OMe), 3.55 – 3.75 (4H, m; 5/6-H and 2x 7-H), 4.12 (1H, dd; 1-H). ^{13}C NMR ($CDCl_3$): 26.3 (t, $SCH_2\underline{C}H_2$), 30.8, 30.9 (t, 2x SCH_2), 36.2 (t, C-2), 40.2 (t, C-4), 44.0 (d, C-1), 56.9, 59.2 (q, 2x OMe), 64.4 (t, C-7), 73.9, 75.2 (d, C-5/6), 79.4 (d, C-3). EIMS *m/e* (%): 296(2) [M^+], 264(18), 249(4), 205(14), 171(14), 119(100). Anal. Calcd. for $C_{12}H_{24}O_4S_2$: C 48.62 %, H 8.16 %, Found: C 48.56 %, H 8.18 %.

6,7-Cylcic Sulfite-2,4-dideoxy-3,5-di-O-methyl-L-xylo-heptose Trimethylene Dithioacetal (12). A solution of the diol **11** (100 mg, 0.297 mmol) in dry dichloromethane (15 mL) is treated dropwise under argon at 0 °C with a solution of thionyl chloride (40 µl, 0.556 mmol) in dichloromethane (5 mL). After completion of the addition the mixture is stirred for 45 min at 20 °C (TLC control). The organic phase is evaporated to dryness to afford the cyclic sulfite **12a** (diastereomer 1) and **12b** (diastereomer 2) (116 mg, 98 % yield, 1:2 ratio). IR (neat): 2932, 2905, 2828, 1462, 1423, 1375, 1277, 1207, 1130, 1086, 1010, 908 cm^{-1}. ^1H NMR ($CDCl_3$) for **12a**: 1.45 – 2.28 (6H, m; 2/4-H and $SCH_2\underline{C}H_2$), 2.73 – 3.04 (4H, m; 2x SCH_2), 3.42, 3.58 (6H, 2s; 2x OMe), 3.62 – 3.83 (2H, m; 5/3-H), 4.11 (1H, dd; 1-H), 4.38 – 4.59 (3H, m; 6-H und 2x 7-H). ^1H NMR ($CDCl_3$) for **12b**: 1.42 – 2.22 (6H, m; 2/4-H and $SCH_2\underline{C}H_2$), 2.72 – 3.04 (4H, m 2x SCH_2), 3.40, 3.51 (6H, 2x s; 2x OMe), 3.54 – 3.78 (2H, m; 5/3-H), 4.11 (1H, dd; 1-H), 4.21 (1H, dd, J = 6.3, J = 8.5; 7a-H), 4.70 (1H, dd, J = 6.7, J = 8.5; 7b-H), 5.04 (1H, dd, J = 6.5; 6-H). ^{13}C NMR ($CDCl_3$) for **12a**: 26.2 (t, $SCH_2\underline{C}H_2$), 30.8, 30.9 (t, 2x SCH_2), 37.5 (t, C-4), 40.4 (t, C-2), 43.9 (d, C-1), 57.4, 60.2 (q, 2x OMe), 67.7 (t, C-7), 74.4 (d, C-3), 78.6 (d, C-6), 86.2 (d, C-5). ^{13}C NMR ($CDCl_3$) for **12b**: 26.2 (t, $SCH_2\underline{C}H_2$), 30.8, 30.9 (t, 2x SCH_2), 36.2 (t, C-4), 40.3 (t, C-2), 43.8 (d, C-1), 57.2, 59.7 (q, 2x OMe), 68.8 (t, C-7), 74.4 (d, C-3), 77.0 (d, C-6), 81.3 (d, C-5). CIMS (isobutane) *m/e* (%): 343(2) [M + 1], 311(56), 279(61), 247(100), 229(7), 215(17), 203(2), 186(3), 133(13), 119(23).

2,4,7-Trideoxy-7-iodo-3,5-di-O-methyl-L-xylo-heptose Trimethylene Dithioacetal (13). A solution of the diastereomeric cyclic sulfites **12a** and **12b** (116 mg, 0.297 mmol) in dry DMF (5 mL) is treated under argon with NaI (444 mg, 2.970 mmol). After heating for 18 h at 100 °C the reaction mixture is evaporated to dryness at reduced pressure. The residue is dissolved in dichloromethane (20 mL), the solution is washed twice with water (each 15 mL), twice with $NaHSO_3$ (each 15 mL), dried (Na_2SO_4), filtered, and evaporated to dryness at reduced pressure to afford the crude iodide **13** as an oil (120 mg). ^1H NMR ($CDCl_3$) 1.44 - 224 (6H, m; 2/4-H and $SCH_2\underline{C}H_2$ 2.61 – 3.04 (4H, m; 2x SCH_2 3.28 (1H, m_c; 3-H), 3.37, 3.48 (s, 2x OMe), 3.34, 3.48 (s, 2x OMe), 3.34 – 3.81 (4H, m; 5-H, 6-H, 2x 7-H), 4.16 (1H, dd; 1-H). ^{13}C NMR ($CDCl_3$): 9.5 (t, C-7), 26.2 (t, $SCH_2\underline{C}H_2$), 30.8, 30.9 (t, 2x SCH_2), 36.2 (t, C-4), 40.2 (t, C-2), 43.9 (d, C-1), 56.8 (q, OMe), 59.7 (q, OMe), 74.0, 75.1, 79.3 (d, C-3/5/6).

6,7-Anhydro-2,4-dideoxy-3,5-di-O-methyl-L-xylo-heptose Trimethylene Dithioacetal (14). The crude iodide **13** (120 mg) is dissolved in dry MeOH (5 mL). At 0 °C the solution is treated with a solution of 1 M sodium methoxide (0.30 mL) and stirred 1 h at 20 °C (TLC monitoring). The mixture is neutralized by addition of solid NH_4Cl, and the MeOH is destilled off at reduced pressure. The residue is purified by column chromatography on silica gel (diethyl ether/*n*-pentane, 3:2) to afford **14** (70 mg, 85 % yield from **12a/b**). Oily. $[\alpha]_D$ –8.63 (c 1.10, $CHCl_3$). IR (neat): 2936, 2903, 2826, 1454, 1423, 1373, 1277, 1259, 1105, 1055, 1016, 908 cm^{-1}. ^1H NMR ($CDCl_3$): 1.52 – 2.25 (6H, m; $SCH_2\underline{C}H_2$, 2x 4-H, 2x 2-H), 2.53 (1H, dd; 7a-H), 2.78 (1H,

dd; 7b-H), 2.82 – 3.12 (6H, m; 2x SCH_2, 3-H, 6-H), 3.42 (3H, s; OMe), 3.58 (3H, s; OMe), 3.72 (1H, m_c; 5-H), 4.17 (1H, dd; 1-H). ^{13}C NMR ($CDCl_3$): 26.3 (t, $SCH_2\underline{C}H_2$), 30.7, 30.9 (t, 2x $S\underline{C}H_2$), 38.1 (t, C-4), 41.0 (t, C-2), 43.2 (d, C-7) 44.0 (d, C-1), 55.3 (d, C-6), 58.0 (q, OMe), 58.4 (q, OMe), 74.6, 79.6 (d, C-3/5). EIMS *m/e* (%): 278(10) [M^+], 246(18), 159(36), 145(48), 119(90), 87(100).

(8S,9S,11S)-9,11-Dimethoxy-1,5-dithia-spiro[5.6]dodecan-8-ol (16). A solution of the epoxide **14** (60 mg, 0.216 mmol) in dry THF (5 mL) was treated at –40 °C with *n*-BuLi (0.15 mL, 0.237 mmol, 1.6 M in *n*-hexane). After 25 min, the cooling bath is removed, and the mixture is stirred for 18 h at 20 °C, neutralized by addition of a saturated aqueous solution of NH_4Cl (5 mL), and extracted three times with diethyl ether (each 5 mL). The combined organic phase is dried (Na_2SO_4), filtered, evaporated to dryness, and purified by thick layer chromatography (ethyl acetate/dichloromethane, 8:2) to afford **16** (39 mg, 64 % yield). Oily. $[\alpha]_D$ +3.4 (c 0.41, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): 1.86 – 2.21 (6H, m; 2x 3-H, 2x 10-H, 2x 12-H), 2.50 – 3.07 (7H m; 2x 2-H, 2x 4-H, 8-H, 11-H, OH), 3.26 – 3.57 (2H, m; 2x 7-H), 3.36 (3H, s; OMe), 3.41 (3H, s; OMe), 3.85 (1H, ddd; J = 2.2 Hz, J = 8.2 Hz, J = 10.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 25.0 (t, C-3), 25.9, 26.9 (t, C-2/4), 34.3 (t, C-10), 42.7 (t, C-12), 45.8 (t, C-7), 47.5 (s, C-6), 56.2, 56.6 (q, 2x OMe), 71.2, 73.5, 81.8 (d, C-8/9/11). EIMS *m/e* (%): 278(9) [M^+], 260(32), 228(34), 214(32), 175(100), 139(39), 101(37).

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