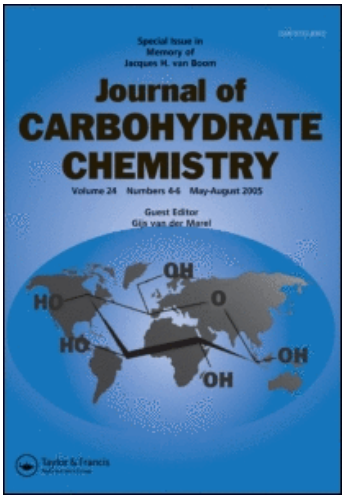

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Krohn, Karsten , Ahmed, Ishtiaq , Gehle, Dietmar and Sahli, Mohammed Al(2009) 'Open Chain Chiral Macrolide Building Blocks by Opening of Deoxygenated 1,6-Anhydrosugars with 1,3-Propanedithiol', Journal of Carbohydrate Chemistry, 28: 2, 64 — 77
To link to this Article: DOI: 10.1080/07328300802691851
URL: http://dx.doi.org/10.1080/07328300802691851

Journal of Carbohydrate Chemistry, 28:64–77, 2009

ISSN: 0732-8303 print / 1532-2327 online
DOI: 10.1080/07328300802691851

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Open Chain Chiral Macrolide Building Blocks by Opening of Deoxygenated 1,6-Anhydrosugars with 1,3-Propanedithiol

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Chiral building blocks for macrolides and related natural products are obtained from 1,6-anhydrosugars by conversion of the bicyclic acetals **2** or **12** into the open chain chiral 1,3-dithianes **6** and **13**. Branched precursors can be obtained by opening of the Černý epoxide **1** with the 1,3-dithiane anion to yield **7**, followed by ring opening with 1,3-propanedithiol to the bis-1,3-dithiane **8**.

Keywords 1,6-Anhydrosugars, Chiral building blocks, Ring opening with 1,3-propandithiol, 1,3-Dithianes, Černý epoxides

INTRODUCTION

In connection with investigations to use 1,6-anhydrosugars and their derivatives as chiral starting materials for more complex targets such as macrolides,[1–3] we probed the opening of a number of 1,6-anhydrosugar derivatives with different degrees of substitution and deoxygenation with 1,3-propanedithiol. In this proton- or Lewis acid-catalyzed reaction (Sch. 1), the cyclic acetals of the anhydrosugars **A** are converted with good yields into open chain 1,3-dithianes **B** in a smooth and reliable reaction.

This conversion has several advantages. No new chiral centers are formed during the dithiane formation, the stereogenic centers present in the sugar

Received August 26, 2008; accepted December 16, 2008.
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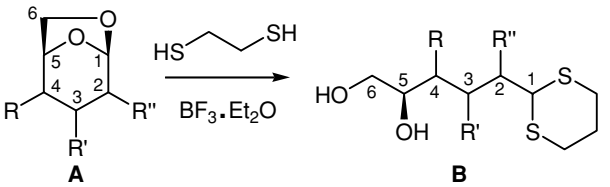


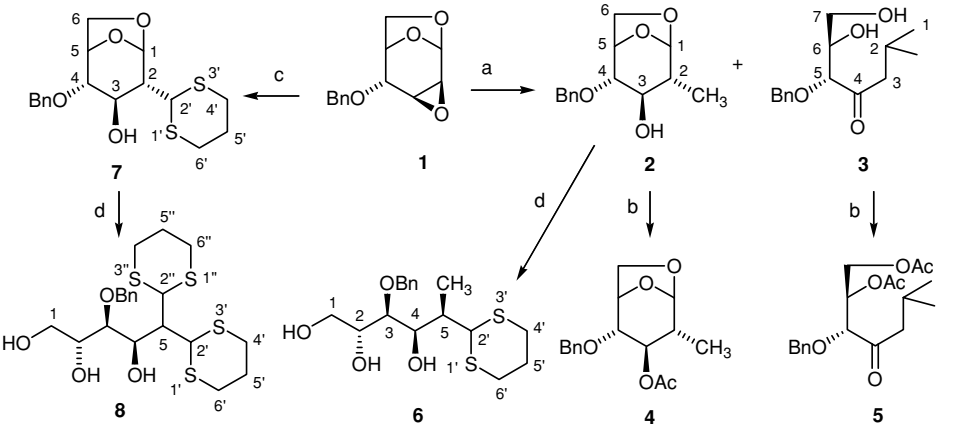
Scheme 1: Lewis acid-catalyzed opening of 1,6-anhydrosugars **A** with 1,3-propanedithiol to afford open chain 1,3-dithianes **B**.

molecule generally do not epimerize under these conditions, and double bonds are also not affected. Moreover, the chemically reactive groups on both ends of the linear fragment **B** allow incorporation into larger units. Both the left and right ends of the molecule can be converted into either nucleophiles or electrophiles. Thus, the inherent C-H acidity of 1,3-dithiane allows conversion into a nucleophile after deprotonation and formation of new C—C bonds in the reaction with various electrophiles. This dithiane reactivity was pioneered by the work of Corey and Seebach[4] and has been compiled in a recent review by Yus et al.[5] Particularly interesting is the formation of the 1,3-dioxygen pattern by reaction with terminal epoxides as shown by Smith et al.[6,7] Applications of this approach in natural products synthesis have been demonstrated, inter alia, by Redlich et al.,[8] Smith et al.,[9,10] Guo et al.,[11] Hodges and Procter,[12] and Kochetkov et al.[13–15] Boron trifluoride etherate in dilute solution at rt has been effectively used by Procter et al.[11,16] and Kochetkov et al.[13,14] including incorporation of the resulting 1,3-dithianes into target molecules. Alternatively, the 1,3-dithiane can also be converted into an electrophilic aldehyde group.

On the left side of the molecule, the hydroxyl groups at C-5 and C-6, hidden in the cyclic acetal of the anhydrosugar **A**, are liberated in **B** and open the door to a number of subsequent transformations. For instance, cleavage of the diol generates reactive aldehydes and terminal epoxides are easily obtained via the primary tosylate.[17] Protection of the diols as cyclic acetals or esters is also possible.

RESULTS AND DISCUSSION

The aim of the present study was to provide these functionalized stereotriads of type **B** with different degrees of substitution, branching, and deoxygenation for potential use as building blocks for macrolides and other target molecules. The first series started from the benzyloxy-alcohol **2**,[18–20] readily available by reaction of epoxide **1**[21] with dimethyl cuprate (Sch. 2). The anhydrosugar **2** has been used in a number of further transformations and applications in natural product chemistry,[22–26] but in a different way than



Scheme 2: a) CuI (4 eq.), MeLi (8 eq.), Et_2O/THF, −10°C to 20°C, 12 h, 67%; b) Ac_2O, pyridine, DMAP, 85%; c) 1,3-dithiane (1 eq.), *n*-BuLi, (1 eq.), THF, −78°C to 20°C, 71%; d) $HS(CH_2)_3SH$ (1.5 eq.), $BF_3.Et_2O$ (2.1 eq.), 4 h, rt, 77%.

described here. Interestingly, in the opening of the epoxide with the dimethyl cuprate reagent,[22] the formation of the open chain keto diol **3** was observed as a side reaction. This unusual reaction was previously observed in a similar transformation[27] and seems to be of general importance.

In the ^{13}C NMR spectrum of the diol **3**, the signals at $\delta = 85.0$ ppm for the methylene carbon at C-3 and at $\delta = 212.7$ for the carbonyl carbon at C-4 were particularly characteristic. The structures of the alcohols **2** and **3** were further confirmed by conversion to the respective monoacetate **4** and the diacetate **5**.

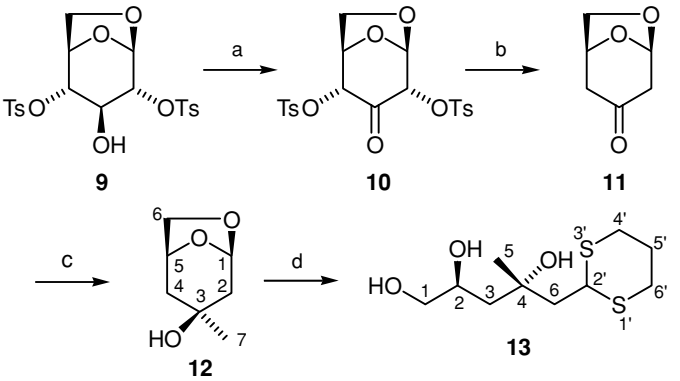
The crucial opening of both the five- and six-membered rings in the anhydrosugar **2** was effected by treatment of the cyclic acetal **2** with a slight excess of 1,3-propanedithiol in the presence of boron trifluoride dietherate at rt to afford the desired 1,3-dithiane derivative **6** in 77% yield (Sch. 2). In addition to occurrence of the new signals for the 1,3-dithiane ring ($\delta = 1.69$–174, 1.93–1.96 [2 × m, 2 × 2 H, 4′,6′-H]), the coupling pattern of the protons at C-1 and C-2 were typical for an open chain arrangement of **6** in contrast to the rigid structure in **2**. The constitution of **6** was further fully confirmed by the mass spectrum and the HRMS spectrum with $m/z = 358.12751$ (calc. 358.12726). This 1,2-dioxo-3-methyl stereotriad has the great advantage that the two oxygens are chemically differentiated and allow regioselective derivatizations, for instance, selective glycosylation. The stereotriad with the correct absolute configuration present in **6** and differentiated vicinal hydroxyl groups (e.g., selectively monoglycosylated diols) is present in a number of macrolide antibiotics such as cytovaricin H,[28,29] yokonolide A,[30] and antibiotic A 82548A.[31]

Next we tried the nucleophilic opening of the epoxide **1** with the 1,3-dithiane anion. Epoxides react smoothly with 1,3-dithiane anions[5] and sugar epoxides have often been subjected to this transformation either

extramolecularly[32] or intramolecularly.[33] However, to the best of our knowledge, they have not yet been added to Černý epoxides such as **1**. As expected, the reaction of epoxide **1** with the lithium salt of 1,3-dithiane went smoothly and the adduct **7** was isolated in 71% yield after chromatographic purification. In building block **7**, the dithiane moiety introduces a branching of the linear chain (after ring opening) and the dithiane group can serve to modify the nature of the side chain in great variety. The amphidinolides[34–36] and the pinolidoxins[37] are just two examples of macrocyclic bioactive natural products containing such a branching in combination with the absolute configuration of the other stereocenters in building block **7**. Finally, we demonstrated that ring opening of the sugar is no problem with the highly functionalized molecule **7** by reaction with 1,3-propandithiol in the presence of boron trifluoride dietherate to afford the bis-dithiane **8** in 77% yield.

Next, we wanted to probe the ring opening via conversion to the 1,3-dithianes on a more highly deoxygenated molecule. As a model, we selected the tertiary alcohol **12**. The synthesis started from the readily available ditosylate **9**,[24,38] which was oxidized in high yield to the ketone **10**, using the perruthenate (TPAP) reagent[39] (Sch. 3). Several procedures for the reductive removal of the two tosyl groups using Raney nickel[40,41] or superhydride[42] have been described. However, in our hands, the reduction of **10** was best performed using activated zinc dust and ammonium acetate as proposed by Belyk et al.[43] to afford the ketone **11** in 85% yield. The subsequent Grignard reaction with methylmagnesium chloride gave the tertiary alcohol **12** stereoselectively in 90% yield with exclusive attack of the nucleophile from the less hindered bottom side of the molecule.

Finally, the ring opening by reaction of **12** with 1,3-propanedithiol was performed as described above to afford the chiral 1,3-dithiane derivative **13** in



Scheme 3: a) $RuCl_3 \cdot 3\ H_2O$ (1 mol%), $NaBrO_3$ (65 mol%), MeCN:AcOH (10:1), 0°C, 4 h, 93%; b) Zn, NH_4OAc (25 eq.), THF, 0°C to rt, 22 h then K_2CO_3, 24 h, 85%; c) MeMgCl (1.1Äq.), Et_2O, −20°C to rt, 30 min, 90%, 100% de; d) $HS(CH_2)_3SH$ (1.5 eq.), $BF_3 \cdot Et_2O$ (2.1 eq.), 3 h, RT, 68%.

68% yield after chromatographic purification. The structure elucidation was performed by comparison with related compounds.[13] In particular, the new signals for the dithiane protons at $\delta = 2.7–2.8$, 2.9–3.0, and 4.3 ppm were characteristic. The 2-D NMR spectra fully confirmed the structure. The tertiary alcohol with vicinal methylene groups present in building block **13** is a frequently occurring motive in natural products. For example, within a pyranose ring it can be found in the songistatins (altohyrtins),[44–46] in trisphaerolide A,[47] or within macrocyclic compounds such as in the dermocanarins.[48,49]

In conclusion, we have shown that anhydrosugars with different groups such as free secondary or tertiary hydroxyl groups, benzyloxy, 1,3-dithianyl, or methyl groups can be converted effectively to the open chain 1,3-dithiane derivatives. Branched side chains can be introduced easily by reaction of Černý epoxides with 1,3-dithiane anions.

EXPERIMENTAL

For general methods and instrumentations see reference 3.

4-*O*-Benzyl-2-methyl-1,6-anhydro-β-D-glucopyranose (2)

A solution of CuI (7.1 g, 37.6 mmol, 4 eq.) in dried THF (25 mL) was treated under argon at −10°C with a solution of methyllithium (1.6 M in diethyl ether, 54 mL, 73.7 mmol, 8 eq.). The mixture was stirred at 0°C for10 min and the epoxide (**1**)[21] (2.2 g, 9.4 mmol) in dried THF (30 mL) was added drop-wise. After 40 min of stirring at 0°C, the reaction mixture was warmed to rt and stirred for another 12 h. The mixture was then diluted with diethyl ether (50 mL) and saturated NH_4Cl solution (50 mL) was added. The mixture was vigorously stirred for another 1 h. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (PE/EtOAc 7:3) to obtain benzyl ether **2** as a colorless oil (1.57 g, 6.35 mmol, 67% yield) along with a very polar ring opened ketone **3** as colorless oil in 23% yield (574 mg, 2.16 mmol). $[\alpha]_D = -33.2°$ (c 0.78, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.19$ (d, $J_{7,2} = 7.5$ Hz, 3 H, CH_3), 1.87 (q, $J_{7,2} = 7.4$ Hz, 1 H, 2-H), 3.34 (s, 1 H, 3-H), 3.67–3.74 (m, 2 H, 6-H), 4.07 (d, $J_{4,3} = 7.3$ Hz, 1 H, 4-H), 4.58 (d, $J_{5,6a} = 5.1$ Hz, 1 H, 5-H), 4.67 (s, 2 H, Ar-CH_2), 5.38 (s, 1 H, 1-H), 7.36–7.38 (m, 5 H, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.4$ (q, C-7), 41. 6 (d, C-2), 65.7 (t, C-Ar), 71.7 (t, C-6), 71.8 (d, C-3), 75.0 (d, C-4), 79.7 (d, C-5), 104.9 (d, C-1), 128.0 (d, C-Ar), 128.8 (d, C-Ar), 138.5 (s, C-Ar). IR (Film): $\tilde{\nu} = 3458$ (O−H), 2956 (C−H), 1547 (C-H), 1472 (C−H), 1371 (C−H), 1222 (C−O). MS (EI, 70 eV): m/z (%) = 250 (9) [M^+], 208 (22), 168 (18), 151 (7), 126 (4), 91 (100), 57 (12). HREIMS: Calc. for $C_{14}H_{18}O_4$ 250.29034. Found 250.29018.

(2S,3R)-1,2-Dihydroxy-3-benzyloxy-6-methylheptan-4-one (3)

$[\alpha]_D = +53.9$ (*c* 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): 0.92 (d, $J_{8,2} = 6.4$ Hz, 3 H, 8-H), 0.94 (d, $J_{1,2} = 6.4$ Hz, 3 H, 1-H), 2.19 (m, 1 H, 2-H), 2.47 (m, 2 H, 3-H), 2.91 (m, 1 H, 5-H), 3.46 (m, 1 H, 7a-H), 3.56 (m, 1 H, 6-H), 3.70 (br, 1 H, 7b-H), 4.56 (d, $J_{gem} = 8.4$ Hz, 2 H, CH_2-Ar), 7.29–7.37 (m, 5 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): 23.0 (q, C-8), 23.1 (q, C-1), 23.9 (d, C-2), 48.7 (t, C-3), 63.3 (t, C-7), 69.3 (d, C-6), 73.8 (t, CH_2-Bn), 85.0 (d, C-5), 128.4 (d, C-Ar), 128.5 (d, C-Ar), 128.6 (d, C-Ar), 129.0 (d, C-Ar), 137.4 (d, C-Ar), 144.5 (s, C-Ar), 212.7 (s, C-4). IR (Film): $\tilde{\nu} = 3413$ (brs, O−H), 2956 (m, C−H), 2910 (m, C−H), 2897 (m, C−H), 1712 (C=O), 1458 (m, C−H), 1254 (s, C-H), 1177 (s, C-O). MS (EI, 70 eV): *m/z* (%) = 266 (30) [M^+], 248 (48), 181 (4), 159 (24), 91 (32), 57 (100), 43 (66). HREIMS: Calc. for $C_{15}H_{22}O_4$ 266.15194. Found 266.15183.

4-*O*-Benzyl-2-methyl-3-acetoxy-1,6-anhydro-β-D-glucopyranose (4)

A solution of compound **2** (100 mg, 0.40 mmol) in pyridine (0.5 mL) was treated with acetic anhydride (0.1 mL) and DMAP (10 mg). The solution was kept at 20°C for 2 h, quenched by addition of 2 N HCl (2 mL), and extracted with diethyl ether (3 × 20 mL). The combined organic phase was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (elution petroleum ether/EtOAc 7:3) to afford the monoacetate **4** as an oil (98 mg, 0.33 mmol, 85%).

$[\alpha]_D = -38.6$ (c 1.1, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.23$ (d, $J_{7,2} = 7.6$ Hz, 3 H, CH_3), 1.88 (m, 1 H, 2-H), 2.09 (s, 3H, OAc), 3.27 (s, 1 H, 3-H), 3.71–4.01 (m, 2 H, 6-H), 4.23 (m, 1H, 5-H), 4.58 (d, $J_{gem} = 6.6$ Hz, 2 H, CH_2-Ar), 4.80 (m, 1H, 4-H), 5.34 (s, 1 H, 1-H), 7.30–7.42 (m, 5 H, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.4$ (q, C-7), 21.7 (q, C-8, OAc), 38.6 (d, C-2), 65.1 (t, C-6), 71.5 (d, C-3), 71.9 (t, C-9, CH_2-Bn), 74.8 (d, C-5), 78.1 (d, C-4), 104.0 (d, C-1), 128.1 (d, C-Ar), 128.8 (d, C-Ar), 138.2 (s, C-Ar), 170.5 (C=O, ester). IR (Film): $\tilde{\nu}$ =2967 (C−H), 1731 (C=O, ester), 1517 (C-H), 1376 (C−H), 1243 (C−O). MS (EI, 70 eV): *m/z* (%) = 292 (2) [M^+], 208 (38), 168 (16), 151 (20), 126 (16), 91 (100), 67(14). HREIMS: Calc. for $C_{16}H_{20}O_5$ 292.13107. Found 292. 13128.

(2S,3R)-1,2-Diacetoxy-3-benzyloxy-6-methylheptan-4-one (5)

A solution of diol **3** (100 mg, 0.37 mmol) in pyridine (0.5 mL) was treated with acetic anhydride (0.1 mL) and DMAP (10 mg). The solution was kept at 20°C for 2 h, quenched by addition of 2 N HCl (2 mL), and extracted with diethyl ether (3 × 20 mL). The combined organic phase was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The residue

was purified by column chromatography on silica gel (elution petroleum ether/EtOAc 7:3) to afford the diacetate **5** as an oil (108 mg, 0.308 mmol, 83%).

$[\alpha]_D = +22.8$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.89$ (d, $J_{8,6} = 3.5$ Hz, 3 H, 8-H), 0.92 (d, $J_{1,2} = 3.5$ Hz, 3 H, 1-H), 2.00 (s, 3 H, 9-H), 2.03 (s, 3 H, 10-H), 2.18 (m, 1 H, 2-H), 2.35 (d, $J_{5,6} = 5.4$ Hz, 2 H, 3-H), 2.27 (br, 1 H, 5-H), 4.22–4.32 (m, 2 H, 7-H), 4.54 (d, $J_{gem} = 6.8$ Hz, 2H, CH_2-Bn), 5.36 (m, 1 H, 6-H), 7.34–736 (m, 5 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.0$ (q, C-8), 21.1 (q, C-1), 22.9 (q, C-9), 23.0 (q, C-10), 23.9 (d, C-2), 48.0 (t, C-3), 62.3 (t, C-7) 71.2 (d, C-6), 73.4 (t, CH_2-Bn), 82.6 (d, C-5), 128.5, (d, C-Ar) 128.6 (d, C-Ar), 128.9 (d, C-Ar), 137.0 (s, C-Ar), 170.3 (s, C-9), 170.9 (s, C-10), 209.1 (s, C-4). IR (Film): $\tilde{\nu} = 2958$ (C−H), 1747 (C=O, ester), 1558 (C-H), 1461 (C−H), 1371 (C−H), 1222 (C−O). MS (EI, 70 eV): *m/z* (%) = 350 (1) [M^+], 279 (2), 265 (8), 247 (2), 184 (4), 168 (74), 153 (44), 125 (20), 91 (100), 85 (46), 57 (16). HREIMS: Calc. for $C_{19}H_{26}O_6$ 350.17294. Found 350.17303.

(2R,3S,4R,5R)-3-(Benzyloxy)-5-(1,3-dithian-2-yl)hexane-1,2,4-triol (6)

To a solution of D-*glucopyranose* **2** (200 mg, 0.80 mmol) in absolute CH_2Cl_2 (10 mL) at 0°C was added 1,3-propanedithiol (0.12 mL 1.20 mmol, 1.5 eq.) and $BF_3{\cdot}Et_2O$ (0.20 mL, 1.68 mmol, 2.1 eq.). The mixture was stirred at rt for 3 h. After complete conversion of the starting material (TLC monitoring), saturated $NaHCO_3$ solution (15 mL) was added and the mixture was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (5 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc 3:1) to obtain triol **6** (2.65 g, 11.3 mmol) as a colorless oil (215 mg, 0.60 mmol, 77% yield).

$[\alpha]_D = -18.5$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.16$ (d, $J_{6,5} = 6.8$ Hz, 3 H, 6-H), 1.69–174, 1.93–1.96 (2 × m, 2 H, 5′-H), 2.10–2.14 (m, 1 H, 5-H), 2.58–2.72 (m, 4 H, 4′,6′-H), 3.57 (dd, $J_{3,2} = 1.8$ Hz, $J_{3,4} = 3.1$ Hz 1 H, 3-H), 3.63–3.66 (m, 1 H, 1a-H), 3.72–3.79 (m, 1 H, 1b-H), 3.88–3.98 (m, 6 H, 2-H, 4-H, 2′-H,OH), 4.57 (d, $J_{gem} = 11.3$ Hz, 1 H, 11-H, CH_2-Bn), 4.69 (d, $J_{gem} = 11.3$ Hz, 1 H, 11-H, CH_2-Bn), 7.23–7.33 (m, 5H, Ar-H). ^{13}C-NMR (125 MHz, $CDCl_3$): $\delta = 12.8$ (q, C-6, CH_3), 26.0 (t, C-5′), 30.4 (t, C-4′), 31.0 (t, C-6′), 40.4 (d, C-5), 52.5 (d, C-2′), 63.6 (t, C-1), 71.9 (d, C-4), 72.0 (d, C-2), 72.9 (t, C-11, CH_2-Bn), 77.9 (d, C-3), 128.0 (d, C-Ar), 128.4 (d, C-Ar), 128.5 (d, C-Ar), 137.6 (s, C-Ar). IR (Film): $\tilde{\nu} = 3405$ (brs, O−H), 2898 (C−H), 1633 (C−H), 1454 (C-H), 1276 (C−O). MS (EI, 70 eV): *m/z* (%) = 358 (10) [M^+], 327 (2), 297 (3), 267 (6), 249 (12), 219 (4), 176 (8), 159 (48), 119 (88), 91 (100), 75 (8), 41 (6), 27 (2). HREIMS: Calc. for $C_{17}H_{26}O_4S_2$ 358.12726. Found 358.12751.

4-*O*-Benzyl-2-(1,3-dithian-2-yl)-1,6-anhydro-β-D-glucopyranose (7)

To a solution of 1,3-dithiane (102 mg, 0.85 mmol) in dried THF at −20°C (ice/NaCl) was added *n*-BuLi (23% in hexane, 0.40 mL, 0.85 mmol). After stirring for 1 h at −20°C, the solution was cooled to −78°C and the epoxide **1** (200 mg, 0.85 mmol) was added. The reaction mixture was warmed to rt and stirred overnight. To quench the reaction, saturated NH_4Cl (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (PE/EtOAc 7:3) to obtain compound **7** as colorless oil in 71% yield (213 mg, 0.60 mmol).

$[\alpha]_D = -23.3$ (*c* 0.8, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.93$ (m, 1H, 2-H), 2.00–2.10 (m, 2 H, 5′-H), 2.72–2.79 (m, 2 H, 4′-H), 2.83–2.91 (m, 2 H, 6′-H), 2.97 (d, $J_{2',2} = 6.4$ Hz, 1 H, 2′-H), 3.40 (brs, 1 H, 3-H), 3.68 (dd, $J_{6a,6b} = 7.5$ Hz, $J_{6a,5} = 5.3$ Hz, 1 H, 6a-H), 4.01 (d, $J_{6b,6a} = 7.5$ Hz, 1 H, 6b-H), 4.27 (d, $J_{4,3} = 9.9$ Hz ,1 H, 4-H), 4.31 (brs, 1H, OH), 4.56 (d, $J_{5,6a} = 5.3$ Hz, 1 H, 5-H), 4.61 (d, $J_{11a,11b} = 11.8$ Hz, 1 H, 11a, CH_2-Bn), 4.68 (d, $J_{11b,11a} = 11.8$ Hz, 1 H, 11b, CH_2-Bn), 5.91 (s, 1H, 1-H), 7.26–7.37 (m, 5H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 25.7$ (t, C-5′), 28.5 (t, C-4′), 28.9 (t, C-6′), 45.4 (d, C-2′), 48.7 (d, C-2), 66.4 (t, C-6), 67.1 (d, C-3), 71.7 (t, C-11, CH_2-OBn), 75.5 (d, C-5), 79.6 (d, C-4), 101.4 (d, C-1), 127.8 (d, C-Ar), 127.9 (d, C-Ar), 128.0 (d, C-Ar), 128.3 (d, C-Ar), 128.4 (d, C-Ar), 137.8 (s, C-Ar). IR (Film): $\tilde{\nu}$ =3444 (brs, O−H), 2896 (C−H), 1619 (C−H), 1454 (C-H), 1461 (C−H), 1371 (C−H), 1276 (C−O), 1039 (C−O). MS (EI, 70 eV): *m/z* (%) = 354 (14) [M^+], 308 (2), 263 (10), 234 (26), 217 (4), 161 (10), 119 (96), 91 (100), 47 (14), 35 (6). HREIMS: Calc. for $C_{17}H_{22}O_4S_2$ 354.09595. Found 354.09605.

(2R,3S,4R)-3-(Benzyloxy)-5,5-di(1,3-dithian-2-yl)pentane-1,2,4-triol (8)

The reaction was carried out according to the procedure as described for compound **6**. Dithiane **7** (100 mg, 0.28 mmol) in CH_2Cl_2 (10 mL) was reacted with 1,3-propanedithiol (0.042 mL, 0.42 mmol, 1.5 eq.) and BF_3-Et_2O (0.075 mL, 0.60 mmol, 2.1 eq.) to afford triol **8** (91 mg, 0.20 mmol, 68% yield).

m.p = 64–65°C. $[\alpha]_D = -10.7$ (*c* 0.9, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.84$ (m, 2 H, 5′-H), 2.05 (m, 2 H, 5′-H), 2.38 (m, 1 H, 5-H), 2.71–3.05 (m, 8 H, 4′-H, 4″-H, 6′-H, 6″-H), 3.41 (brs, 1 H, OH), 3.72 (m, 1 H, 1a-H), 3.82 (m, 1 H, 1b-H), 4.13 (m, 2 H, 2-H,3-H), 4.58 (d, $J_{2',5} = 1.8$ Hz, 1 H, 2′-H), 4.75 (d, $J_{2'',5} = 1.8$ Hz, 1 H, 2″-H), 4.78 (s, 2H, CH_2-Bn), 7.26–7.39 (m, 5H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 25.8$ (t, C-5′), 25.9 (t, C-5″), 31.3 (t, C-4′), 31.4 (t, C-4″, 31.7 (t, C-6′), 32.2 (t, C-6″), 48.6 (d, C-2′) , 49.9 (d, C-2″), 51.8 (d, C-5),

63.7 (t, C-1), 68.8 (d, C-4), 72.2 (t, C-10, CH_2-OBn), 72.3 (d, C-2), 78.0 (d, C-3), 127.8 (d, C-Ar), 128.1 (d, C-Ar), 128.3 (d, C-Ar), 128.4 (d, C-Ar), 128.5 (d, C-Ar), 137.9 (s, C-Ar). IR (Film): $\tilde{\nu} = 3421$ (brs, O−H), 2896 (C−H), 1654 (C−H), 1424 (C-H), 1287 (C−H), 1047 (C−O). MS (EI, 70 eV): m/z (%) = 462 (10) [M^+], 444 (2) 383 (2), 356 (4), 355 (26), 343 (12), 265 (6), 251 (82), 197 (4), 177 (12), 145 (22), 119 (100), 91 (72), 75 (52). HREIMS: Calc. for $C_{20}H_{30}O_4S_4$ 462.10269. Found 462.10225.

1,6-Anhydro-2,4-di-O-tosyl-β-D-ribohexapyrano-3-ulose (10)

A solution of ditosylate **9**[24,38] (30.2 g, 64.2 mmol) in acetonitrile (90 mL) was treated under argon at 0°C with acetic acid (18.6 mL) and $RuCl_3 \cdot 3\ H_2O$ (150 mg, 0.64 mmol, 1 mol%) and a solution of $NaBrO_3$ (6.3 g, 41.7 mmol) in water (30 mL) was then added drop-wise with vigorous stirring over 2.5 h. The temperature should not exceed 10°C. After stirring for 2 h at 0°C, 2-propanol (1 mL) was added and stirring was continued for 1 h. The mixture was diluted with EtOAc (350 mL) and the organic phase was washed with a 10% aqueous solution of $Na_2S_2O_3$ (2 × 50 mL). The organic phase was washed successively with water (50 mL), saturated $NaHCO_3$ solution (3 × 50 mL), and brine (50 mL). The solution was dried ($MgSO_4$) and filtered, and the solvent was removed at reduced pressure to afford the ketone **10** as an oil (28.3 g, 60.3 mmol, 94%). $[\alpha]_D = -21.6°$ (c 1.5, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.48$ (s, 6 H, 2 × Ar–CH_3), 3.80 (dd, $J_{6a,6b} = 8.5$ Hz, $J_{6a,5} = 5.0$ Hz, 1 H, 6a-H), 3.92 (dd, $J_{6b,6a} = 8.5$ Hz, $J_{6b,5} = 1.0$ Hz, 1 H, 6b-H), 4.52 (d, $J_{2,1} = 1.2$ Hz, 1 H, 2-H), 4.69 (d, $J_{4,5} = 1.0$ Hz, 1 H, 4-H), 4.90 (ddd, $J_{5,6a} = 5.0$ Hz, $J_{5,6b} = 1.0$ Hz, $J_{5,4} = 1.0$ Hz, 1 H, 5-H), 5.62 (d, $J_{1,2} = 1.2$ Hz, 1 H, 1-H), 7.33–7.38 (m, 4 H, Ar-H), 7.75–7.78 (m, 4 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.0$ (q, CH_3–Ar), 21.7 (q, CH_3–Ar), 66.7 (t, C-6), 76.9 (d, C-5), 77.6 (d, C-2), 79.3 (d, C-4), 101.3 (d, C-1), 127.9, 128.0, 128.1, 128.3, 129.9, 130.0 (d, C-Ar), 132.5, 132.4 (s, C-Ar), 145.7, 145.8 (s, C-Ar), 190.7 (s, C-3). IR (Film): $\tilde{\nu} = 2965$ (m, C–H), 2924 (m, C–H), 2913 (m, C–H), 1750 (s, C=O), 1594 (s, C=C), 1372 (s, S–O_2) 1196 (s, C–H), 1175 (s, C–H), 1129 (m, C–O), 1089 (m, C–O), 1015 (s, C–O), 989 (s, C–H). MS (EI, 70 eV): m/z (%) = 468 (5) [M^+], 313 (47), 172 (12), 155 (99), 142 (29), 113 (23), 91 (100), 85 (7), 65 (19), 57 (9), 29 (5). HREIMS: Calc. for $C_{20}H_{20}O_9S_2$468.0548. Found 468.0549. Anal $C_{20}H_{20}O_9S_2$ (468.5) Calc. C, 51.27; H, 4.30. Found: C, 51.37; H, 4.22.

1,6-Anhydro-2,4-dideoxy-β-D-glycerohexopyrano-3-ulose (11)

Zinc dust (250 g) was activated by stirring with diluted HCl (600 mL, 1.5%) at rt for 45 min. The aqueous phase was decanted, and the residue was washed with THF or diethyl ether (600 mL) and subsequently dried under high vacuum. For detosylation, part of the activated zinc dust (90 g) was suspended

in dry THF (450 mL) in a three-necked flask. Dry NH_4OAc (103 g, 1.34 mol, 25 eq.) was added and the mixture was stirred for 45 min at rt. A solution of ditosylate **10** (26.0 g, 55.5 mmol) in THF (200 mL) was then added drop-wise at 0–5°C over 2.5 h. The mixture was then stirred for 20 h at rt (TLC monitoring) and filtered, and the zinc washed with THF (500 mL). The filtrate was treated with K_2CO_3 (100 g) and stirred for a further 24 h. The salt was filtered off and washed with THF (200 mL) and the solvent was removed at reduced pressure. The residue was purified by column chromatography on silica gel to afford the ketone **11** (5.9 g, 46.7 mmol, 85%) as an oil.

$[\alpha]_D = -103^\circ$ (c = 0.81, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.40$ (d, $J_{4a,4b} = 16.8$ Hz, 1 H, 4a-H), 2.50 (m, 2 H, 2-H), 2.71 (ddd, $J_{4b,4a} = 16.8$ Hz, $J_{4b,5} = 5.0$ Hz, $J_{4b,2b} = 2.0$ Hz, 1 H, 4b-H), 3.76 (m, 1 H, 6a-H), 3.80 (m, 1 H, 6b-H), 4.79 (t, $J_{5,4} = 5.0$ Hz, 1 H, 5-H), 5.73 (t, $J_{1,2} = 1.6$ H, 1-H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 46.9$ (t, C-4), 48.6 (t, C-2), 69.6 (t, C-6), 72.2 (d, C-5), 100.5 (d, C-1), 204.5 (s, C-3). IR (Film): $\tilde{\nu} = 2965$ (m, C–H), 2893 (m, C–H), 2889 (m, C–H), 1713 (s, C=O), 1594 (s, CH), 1408 (s, C–H), 1367 (s, C–O), 1284 (s, C–H), 1139 (s, CO), 1036 (s, C–O), 989 (s, C–H), 860 (s, C–H). MS (EI, 70 eV): *m/z* (%) = 128 (8) [M^+], 111 (9), 100 (6), 97 (5), 86 (8), 83 (7), 82 (100), 71 (10), 70 (9), 69 (6), 58 (12), 57 (59), 55 (14), 54 (11), 44 (6), 43 (42), 42 (62), 41 (19), 31 (17), 29 (22), 27 (18). HREIMS: Calc. for $C_6H_8O_3$: 128.0473. Found: 128.0439.

1,6-Anhydro-2,4-dideoxy-3-methyl-β-D-threo-hexopyranose (12)

A solution of ketone **12** (1.1 g, 8.6 mmol) in dry diethyl ether (180 mL) was treated drop-wise at −20°C with a solution of MeMgCl (9.5 mmol, 1.1 eq.) in THF (3.2 mL). After stirring for 20 min at rt (TLC monitoring), $Na_2SO_4 \cdot 10\ H_2O$ (5 g) was added portion-wise. The mixture was filtered, the solvent removed at reduced pressure, and the residue purified by flash chromatography on silica gel (CH_2Cl_2/acetone 95:5) to afford the alcohol **12** (1.15 g, 7.98 mmol, 90%) as an oil.

$[\alpha]_D = -53^\circ$ (c = 0.77, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.20$ (s, 3 H, 7-H), 1.83–1.96 (m, 3 H, 2a,b-H, 4a-H), 2.03 (ddd, $J_{4b,4a} = 14.5$ Hz, $J_{4b,5} = 4.3$ Hz, $J_{4b,6a} = 1.7$ Hz, 1 H, 4b-H), 3.40 (s, 1 H, OH), 3.73 (ddd, $J_{6a,6b} = 7.0$ Hz, $J_{6a,5} = 4.9$ Hz, $J_{6a,4b} = 1.7$ Hz, 1 H, 6a-H), 4.34 (d, $J_{6b,6a} = 7.0$ Hz, 1 H, 6b-H), 4.58 (m, 1 H, 5-H), 5.68 (brs, 1 H, 1-H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 31.5$ (q, C-7), 41.9 (t, C-4), 44.3 (t, C-2), 68.0 (t, C-6), 68.3 (s, C-3), 72.8 (d, C-5), 101.2 (d, C-1). IR (Film): $\tilde{\nu} = 3467$ (s, OH), 2970 (m, C–H), 2918 (m, C–H), 2898 (m, C–H), 1503 (w, C–H), 1377 (m, C–H), 1351 (m, C–H), 1268 (s, C–H), 1170 (s, C–O), 1118 (s, C–O), 1093 (s, C–O), 1062 (s, C–O). MS (EI, 70 eV): *m/z* (%) = 144 (9) [M^+], 126 (69), 97 (59), 89 (37), 87 (70), 71 (42), 69 (56), 59 (48), 57 (96), 55 (70), 43 (100), 41 (71), 39 (33), 29 (41). HREIMS: Calc. for $C_7H_{12}O_3$144.0786. Found 144.0778. Anal. $C_7H_{12}O_3$ (144.17): Calc. C, 58.32; H, 8.39. Found C, 58.49; H, 8.85.

(2S,4S)-4-((1,3-Dithian-2-yl)methyl)pentane-1,2,4-triol (13)

As solution of hexopyranose **12** (220 mg, 1.72 mmol) in dry CH_2Cl_2 (15 mL) was treated at 0°C with 1,3-propanedithiol (0.26 mL, 2.58 mmol, 1.5 eq.) and $BF_3{\cdot}Et_2O$ (0.46 mL, 3.61 mmol, 2.1 eq.). Workup was done as described for **6** to afford the triol **13** as an oil (295 mg, 1.17 mmol, 68%). $[\alpha]_D = +21.5^\circ$ (c = 0.27, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.28$ (s, 3 H, 5-H), 2.02 (dd, $J_{6a,6b} = 6.5$ Hz, $J_{6a,2'} = 6.4$ Hz, 1 H, 6a-H), 2.08–2.15 (m, 5 H, 6b-H, 3-H, 5′-H), 2.77–2.85, 2.91–3.02 (2 × m, 2 × 2 H, 4′-H, 6′-H), 3.85 (ddd, $J_{1a,1b} = 10.0$ Hz, $J_{1a,2} = 2.0$ Hz, $J_{1a,3a} = 1.4$ Hz, 1 H, 1a-H), 3.89 (dd, $J_{1b,1a} = 10.0$ Hz, $J_{1b,2} = 4.0$ Hz, 1 H, 1b-H), 4.31 (t, $J_{2',5} = 6.4$ Hz, 1 H, 2′-H), 4.47 (ddd, $J_{2,1a} = 2.0$ Hz, $J_{2,1b} = 4.0$ Hz, $J_{2,3a} = 8.4$ Hz, 1 H, 2-H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 25.4$ (t, C-5′), 27.3 (q, C-5), 30.8, 31.0 (2 × t, C-4′, C-6′), 43.3 (d, C-2′), 46.2 (t, C-3), 46.3 (t, C-6), 73.4 (d, C-2), 74.2 (t, C-1), 82.1 (s, C-4). IR (Film): $\tilde{\nu} = 3469$ (brs, OH), 2974 (m, C–H), 2910 (m, C–H), 2897 (m, C–H), 1371 (m, C–H), 1349 (m, C–H), 1272 (s, C–H), 1170 (s, C–O), 1112 (s, C–O), 1089 (s, C–O). MS (EI, 70 eV): *m/z* (%) = 234 (74) [$M^+ - H_2O$], 216 (18), 188 (19), 173 (40), 159 (70), 133 (53), 127 (32), 119 (81), 106 (35), 101 (90), 98 (50), 83 (69), 73 (33), 55 (29), 45 (33), 43 (100), 41 (61).

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