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A Highly Efficient and Stereocontrolled Synthesis of 2-Deoxy-1,5-thioanhydro-L-hexitols from D-Glycals in a Tandem Nucleophilic Displacement Reaction

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2-Deoxy-1,5-thioanhydro-L-hexitols have been synthesized in a concise sequence that includes: i) ring opening of glycals with aqueous mercury(II) acetate/sodium borohydride; ii) mesylation of the free hydroxy groups of the multifunctionalized open intermediates; and iii) S-heterocyclization by treatment with sodium sulfide. The thiosugar derivatives are obtained with a 60–80% yield. Thus, D-glucal and D-galactal can be converted into the corresponding 2-deoxy-1,5-thioanhydro-L-hexitols, while L-rhamnal gives 3,4-di-*O*-benzyl-2,6-dideoxy-1,5-thioanhydro-D-*xylo*-hexitol. This straightforward chemistry is shown to be useful for the synthesis of glycosyl derivatives of 2-deoxy-1,5-thioanhydro-L-hexitol, starting from glycosyl glycals such as D-lactal, D-cellobial, D-maltal, D-melibial and D-gentiobial, thus avoiding the usually lengthy glycosylation procedures.

Introduction

Thiosugars are carbohydrate analogues in which one or more oxygen atoms are substituted by a sulfur atom both in the pyranoside and furanoside structures.[1,2] In recent years, these compounds have attracted considerable interest from chemists and biochemists because of their biological activity.[3] For example, both mono- and oligosaccharide thiosugars have become increasingly important targets due to their potential value as enzyme inhibitors[3f,4] and therapeutic agents, such as for diabetes,[3c] and for antiviral[5,6] and antineoplastic[6,7] treatments. Of the several different thiosugars described to date, only 5-thio-D-mannose has been isolated some years ago from a marine sponge;[8] the majority of the thiosugars are obtained by transformation of natural sugars.[9] It is worth noting that a potent α-glucosidase inhibitor with a unique thiosugar sulfonium sulfate structure (a derivative of 1-deoxy-4-thioarabinofuranose) has recently been isolated from the Ayurvedic traditional medicine *Salacia reticulata* in Sri Lanka and India.[10] A good inhibitory activity was found for a six-membered ring analogue that is not naturally available.[11]

Furthermore, much attention has been focused on the synthesis of 5-thiosugar-containing di- and oligosaccharides, since the glycosidic bond of 5-thiosugars is known to be resistant to enzymatic degradation by glycosidases.[12–14]

All the strategies described in the literature to obtain, for instance, 5-thiohexopyranoses are based on a multi-step reaction sequence, generally through a novel ring opening/recyclization protocol of suitably modified D-sugar derivatives.[9a–9c,12,15] The net retention of the (*R*)-stereogenic center located at the 5-position during the introduction of the sulfur functionality is usually achieved by double inversion of the original (*R*)-hydroxycarbon center.[9c,12,15] The other stereogenic centers present in the original sugars are left unchanged. For example, 5-thio-D-glucopyranose is synthesized from D-glucopyranose.[16]

As part of our continuing exploitation of the reactivity and usefulness of carbohydrate derivatives in organic synthesis,[17] we describe here a new and expeditious strategy for the synthesis of 2-deoxy-1,5-thioanhydro-L-hexitols that allows access to these compounds in three steps, starting from easily available D-glycal derivatives. The versatility of this methodology is demonstrated by its application in disaccharide chemistry.

To the best of our knowledge, there is no general and flexible approach to prepare six-membered L-configured thiosugar derivatives in a small number of steps.

Results and Discussion

All the starting materials were prepared in one step from *O*-benzyl derivatives of glycals and glycosyl glycals according to our previously reported procedure[18] by treatment with aqueous mercury(II) acetate/sodium borohydride in one reaction flask and on a large scale (Scheme 1).

To test the efficiency of our strategy, we prepared enantiomerically pure (2*R*,3*R*)-2,3-dibenzyloxypentane-1,5-diol (**2a**) and the corresponding (2*R*,3*S*)-diastereoisomer **2b** from the per-*O*-benzylated D-xylal **1a** and the D-arabinal **1b**,

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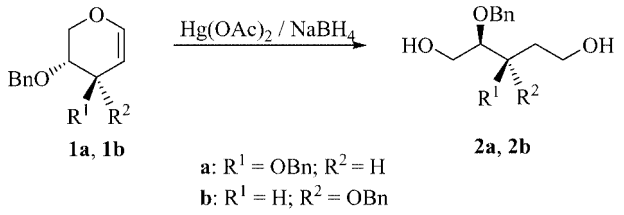
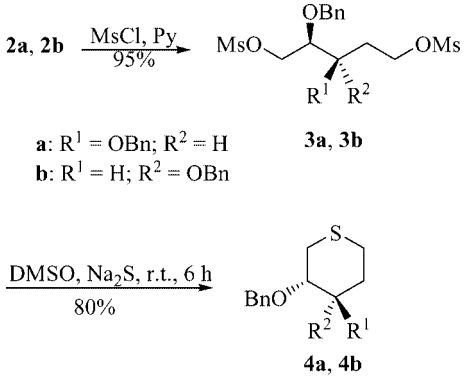


Scheme 1.

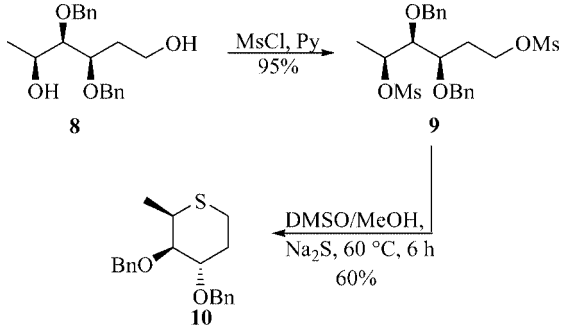
respectively (Scheme 1). The intermediates **2a** and **2b** have a carbon skeleton with the protected required functionality and free hydroxy groups for the introduction of the sulfur atom in the right position to prepare 5-thiosugar derivatives. Activation of the two primary alcohol groups as their mesylates **3a**,**b**, and subsequent cyclization by treatment with sodium sulfide in DMSO at room temp. for six hours, gave the corresponding 3,4-(dibenzyloxy)tetrahydrothiopyrans **4a** and **4b** in 80% yield (Scheme 2). Their structure was completely in agreement with spectroscopic and analytical data (see Exp. Sect.).



Scheme 2.

Stimulated by these results, we turned our attention to exploring the reactivity of more densely functionalized (3*R*,4*R*,5*R*)-3,4,6-tribenzyloxyhexane-1,5-diol (**5a**) and the corresponding (3*R*,4*S*,5*R*)-diastereoisomer **5b**, which are available from the corresponding D-glucal and D-galactal, respectively, and are characterized by the presence of a secondary and a primary alcohol. The free hydroxy groups were easily mesylated at room temperature in pyridine to obtain the corresponding dimesyl derivatives **6a** and **6b**, which contain good leaving groups for the following domino process (nucleophilic displacement followed by S-heterocyclization). In fact, the subsequent reaction with sodium sulfide in DMSO/methanol at 60 °C for six hours gave the corresponding 3,4,6-tri-*O*-benzyl-2-deoxy-1,5-thioanhydro-L-hexitols **7a** and **7b** directly in 60–65% yield (Scheme 3). Their structure was completely in agreement with the spectroscopic and analytical data (see Exp. Sect.).

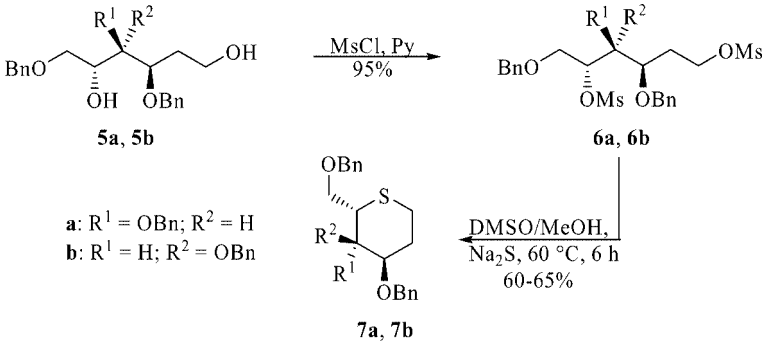
Interestingly, (3*R*,4*R*,5*S*)-3,4-dibenzyloxyhexane-1,5-diol (**8**), which was obtained from per-*O*-benzylated L-rhamnal, could be easily converted into 3,4-di-*O*-benzyl-2,6-dideoxy-1,5-thioanhydro-D-*xylo*-hexitol (**10**) in 60% yield via the intermediate **9** (Scheme 4). The structure of **10** was determined from its spectroscopic data (see Exp. Sect.).



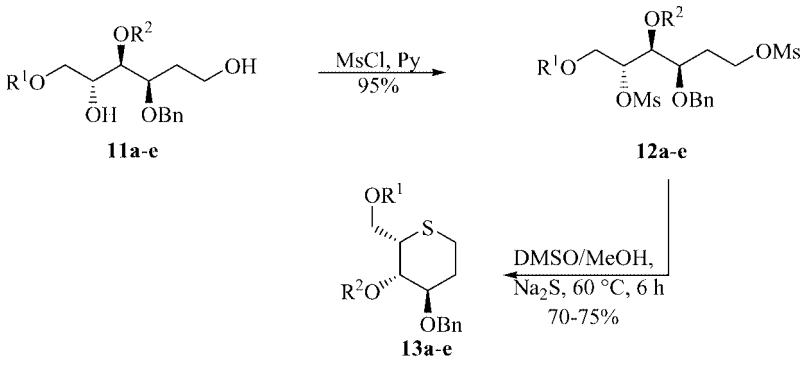
Scheme 4.

Prompted by these findings, we decided it would be interesting to exploit the reactivity of glycosyl glycals in order to develop a short and efficient protocol for preparing glycosyl derivatives of 2-deoxy-1,5-thioanhydro-L-hexitol. The success of this strategy should render these compounds readily accessible, thereby avoiding the usually lengthy glycosylation procedures. It is well known that in the synthesis of 5-thiosugar-containing oligosaccharide the regio- and stereospecific glycoside formation is the most important step.[12,14] This step has been investigated by using different protocols, mainly a coupling reaction between thiosugars and glycosyl acceptors and the use of a reaction promoter for the coupling, generally a Lewis acid or an enzyme.[12,14] The yields vary from poor to good.[4a,19]

The enantiomerically pure 4-benzyloxyhexane-1,2,3,6-tetraol derivatives **11a**–**e**, with a sugar moiety located either at C1 or at C3, were easily prepared by the usual reaction



Scheme 3.



a: R^1 = Bn; R^2 = 2',3',4',6'-tetra-*O*-benzyl-β-D-galactopyranosyl
b: R^1 = Bn; R^2 = 2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl
c: R^1 = Bn; R^2 = 2',3',4',6'-tetra-*O*-benzyl-α-D-glucopyranosyl
d: R^1 = 2',3',4',6'-tetra-*O*-benzyl-α-D-galactopyranosyl; R^2 = Bn
e: R^1 = 2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl; R^2 = Bn

Scheme 5.

with aqueous mercury(II) acetate/sodium borohydride in very high yields (ca. 90%) from per-*O*-benzylated D-lactal, D-cellobial, D-maltal, D-melibial, and D-gentiobial, respectively (see Exp. Sect.).[17b]

The generation of the S-heterocyclized compounds **13a**–**e** in 70–75% yield proceeded smoothly following the above protocol in a two-step sequence starting from **11a**–**e**, namely formation of 2,6-di-*O*-mesylates **12a**–**e** by reaction with methanesulfonyl chloride in pyridine and their subsequent treatment with sodium sulfide in DMSO/CH_3OH at 60 °C for six hours (Scheme 5).

The outcome of the reaction clearly indicates that the presence of a sugar derivative adjacent to the secondary hydroxy group in **11a**–**e** does not influence the intramolecular ring closure between the sulfide anion, first introduced at C6 by a nucleophilic substitution by treatment with sodium sulfide, and the mesylate at C2 as leaving group. In particular, the steric hindrance due to the presence of a perbenzylated sugar unit close to the reaction center does not affect the reactivity.

Conclusion

In conclusion, we have demonstrated that glycals and glycosyl glycals are attractive starting materials for the construction of previously unknown L-thiosugar analogues that should be biologically important. It is worth noting that our initial aim was to find simplified synthetic strategies and to be guided by readily available starting materials in conjunction with straightforward chemistry. This new strategy shows high flexibility, particularly in disaccharide chemistry, and avoids the extensive manipulations reported for classical glycosylation sequences.

Further extension of this strategy to the synthesis of more complex thiosugars from trisaccharides is currently in progress.

Experimental Section

General: ^1H (200 MHz) and ^{13}C NMR (50.3 MHz) spectra were recorded with a Varian Gemini 200 spectrometer with $CDCl_3$ as the solvent and as the internal standard. IR spectra were recorded on an IR Equinox 55 Bruker. HR mass spectra were recorded with a Micromass Q-TOF micro Mass Spectrometer (Waters). Optical rotations were measured using the sodium D-line on a DIP 370 Jasco digital polarimeter. Yields are given for products isolated after column chromatography that show a single spot by TLC and no detectable impurities in the ^1H NMR spectrum. All reactions were performed under an inert atmosphere of N_2 in flame-dried glassware. All solvents and commercially available reagents were used without purification, unless otherwise noted. All reactions were monitored by TLC on Merck F-254 silica glass plates visualized with UV/light and heat-gun treatment with 2 N H_2SO_4 solution. Column chromatography was performed with Merck silica gel 60 (230–400 mesh).

Preparation of Diols 2a,b, 5a,b, 8, and 11a–e. General Procedure:[18] The appropriate per-*O*-benzyl derivative (1 equiv.) was dissolved in THF (20 mL per mmol) and treated with a solution of $Hg(OAc)_2$ (3 equiv.) in H_2O (8 mL per mmol). The reaction mixture was then stirred at room temp. until TLC (*n*-hexane/diethyl ether, 7:3) showed the disappearance of the starting material (ca. 30 min.). The reaction flask was then cooled with an ice bath and $NaBH_4$ (60 equiv.) and MeOH (4 mL per mmol) were added. After stirring for 1 h at 0 °C, the solvent was evaporated under reduced pressure and the residue was dissolved in Et_2O, washed in a separating funnel with H_2O (till neutral), then with brine, dried with anhydrous Na_2SO_4, and the solvent removed. The crude product was then purified by column chromatography.

(2*R*,3*R*)-2,3-Bis(benzyloxy)pentane-1,5-diol (2a): This compound was prepared from **1a** (200 mg, 0.67 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 2:8) and obtained as a viscous oil (196 mg, 92%). $[a]_D$ = +23.7 (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3100, 2950, 2900, 1600, 1500, 1372, 1278, 1120, 1076 cm^{-1}. ^1H NMR: δ = 7.31–7.25 (m, 10 H, Ph), 4.65 (d, *J* = 11 Hz, 1 H, H_A of CH_2Ph), 4.61 (s, 2 H, CH_2Ph), 4.51 (d, *J* = 11 Hz, 1 H, H_B of CH_2Ph), 3.85–3.55 (m, 6 H, 1-H_A, 1-H_B, 2-H, 3-H, 5-H_A, 5-H_B),

2.42 (s, 2 H, 2 OH), 2.22–1.80 (m, 2 H, 4-H_A, 4-H_B) ppm. ^{13}C NMR: δ = 138.0, 137.9 (C_q, Ph), 128.3, 127.9, 127.8 (Ph), 80.1, 77.6 (C-2, C-3), 72.8 (CH_2Ph), 61.4, 59.8 (C-1, C-5), 32.6 (C-4) ppm. HRMS calcd. for $C_{19}H_{24}O_4$ 334.2018 $[M + NH_4]^+$; found 334.2010.

(2*R*,3*S*)-2,3-Bis(benzyloxy)pentane-1,5-diol (2b): This compound was prepared from **1b** (200 mg, 0.67 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 2:8) and obtained as a viscous oil (196 mg, 92%). $[\alpha]_D$ = +12.3 (*c* = 1.4, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3120, 2950, 2900, 1620, 1500, 1460, 1378, 1275, 1072 cm^{-1}. ^{1}H NMR: δ = 7.31–7.25 (m, 10 H, Ph), 4.64 (d, *J* = 12 Hz, 1 H, H_A of CH_2Ph), 4.59 (s, 2 H, CH_2Ph), 4.53 (d, *J* = 12 Hz, 1 H, H_B of CH_2Ph), 3.75–3.50 (m, 6 H, 1-H_A, 1-H_B, 2-H, 3-H, 5-H_A, 5-H_B), 2.31 (s, 2 H, 2 OH), 2.22–1.84 (m, 2 H, 4-H_A, 4-H_B) ppm. ^{13}C NMR: δ = 138.1, 137.9 (C_q, Ph), 128.3, 127.8, 127.7 (Ph), 78.2, 77.6 (C-2, C-3), 72.8 (CH_2Ph), 61.2, 59.9 (C-1, C-5), 32.4 (C-4) ppm. HRMS calcd. for $C_{19}H_{24}O_4$ 334.2018 $[M + NH_4]^+$; found 334.2022.

(3*R*,4*R*,5*R*)-3,4,6-Tris(benzyloxy)hexane-1,5-diol (5a): This compound was prepared from perbenzylated D-glucal (200 mg, 0.48 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 1:1) and obtained as a viscous oil (192 mg, 92%). $[\alpha]_D$ = +22.8 (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3250, 2940, 2900, 1600, 1510, 1460, 1368, 1270, 1077 cm^{-1}. ^{1}H NMR: δ = 7.45–7.30 (m, 15 H, Ph), 4.70–4.50 (m, 6 H, 3 CH_2Ph), 4.10–3.85 (m, 2 H, 4-H, 5-H), 3.75–3.62 (m, 5 H, 1-H_A, 1-H_B, 3-H, 6-H_A, 6-H_B), 2.60 (br. s, 2 H, 2 OH), 1.90–1.85 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.0, 137.9, 137.6 (C_q Ph), 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6 (Ph), 77.9, 77.2 (C-3, C-4), 73.5, 73.4, 72.6, 70.7 (C-6, CH_2Ph), 70.3 (C-5), 59.3 (C-1), 32.5 (C-2) ppm. HRMS calcd. for $C_{27}H_{32}O_5$ 454.2593 $[M + NH_4]^+$; found 454.2588.

(3*R*,4*S*,5*R*)-3,4,6-Tris(benzyloxy)hexane-1,5-diol (5b): This compound was prepared from perbenzylated D-galactal (200 mg, 0.48 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 1:1) and obtained as a viscous oil (192 mg, 92%). $[\alpha]_D$ = –5.0 (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3120, 2950, 2900, 1600, 1520, 1460, 1378, 1278 cm^{-1}. ^{1}H NMR: δ = 7.42–7.20 (m, 15 H, Ph), 5.40–4.20 (m, 7 H, 3 CH_2Ph, 4-H), 4.18–3.70 (m, 6 H, 1-H_A, 1-H_B, 5-H, 3-H, 6-H_A, 6-H_B), 2.73 (br. s, 2 H, 2 OH), 2.54–2.13 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 137.9, 137.8 (C_q, Ph), 128.4, 128.3, 128.0, 127.9, 127.7, 127.6 (Ph), 79.2, 78.1 (C-3, C-4), 73.9, 73.3, 72.4, 70.9 (C-6, CH_2Ph), 69.9 (C-5), 59.7 (C-1), 33.2 (C-2) ppm. HRMS calcd. for $C_{27}H_{32}O_5$ 454.2593 $[M + NH_4]^+$; found 454.2583.

(3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)hexane-1,5-diol (8): This compound was prepared from perbenzylated L-rhamnal (200 mg, 0.64 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 1:1) and obtained as a viscous oil (197 mg, 92%). $[\alpha]_D$ = –26.5 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3100, 2950, 2840, 1600, 1500, 1460, 1378, 1260, 1070 cm^{-1}. ^{1}H NMR: δ = 7.42–7.20 (m, 10 H, Ph), 4.88 (d, *J* = 11 Hz, 1 H, H_A of CH_2Ph), 4.82 (s, 2 H, CH_2Ph), 4.76 (d, *J* = 11 Hz, 1 H, H_B of CH_2Ph), 4.28–3.62 (m, 5 H, 1-H_A, 1-H_B, 3-H, 4-H, 5-H), 3.02 (br. s, 2 H, 2 OH), 2.22–1.98 (m, 2 H, 2-H_A, 2-H_B), 1.68 (d, *J* = 5 Hz, 3 H, CH_3) ppm. ^{13}C NMR: δ = 137.8, 137.4 (C_q, Ph), 128.4, 128.3, 128.1, 128.0, 127.9, 127.8 (Ph), 81.4, 77.6 (C-3, C-4), 73.6, 72.6 (CH_2Ph), 67.4 (C-5), 59.7 (C-1), 32.6 (C-2), 19.6 (C-6) ppm. HRMS calcd. for $C_{20}H_{26}O_4$ 348.2175 $[M + NH_4]^+$; found 348.2170.

(3*R*,4*R*,5*R*)-3,6-Bis(benzyloxy)-4-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-galactopyranosyl)hexane-1,5-diol (11a): This compound was prepared from perbenzylated D-lactal (200 mg, 0.23 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 1:1) and obtained as a viscous oil (187 mg, 92%). $[\alpha]_D$ = –15.5 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3120, 2950, 2930, 1650, 1500, 1470, 1378, 1275, 1070 cm^{-1}. ^{1}H NMR: δ = 7.42–7.22 (m, 30 H, Ph), 5.20–4.58 (m, 13 H, 6 CH_2Ph, 1′-H), 4.32–3.65 (m, 13 H, 1-H_A, 1-H_B, 3-H, 4-H, 5-H, 6-H_A, 6-H_B, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 3.04 (br. s, 2 H, 2 OH), 2.38–2.14 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.5, 138.2, 137.8, 137.6 (C_q, Ph), 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4 (Ph), 104.0 (C-1′), 82.3, 79.2, 78.2, 77.6, 77.1, 75.1, 73.6 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 74.4, 73.3, 73.2, 72.8, 72.3, 71.8, 70.8, 68.8 (C-6, C-6′, CH_2Ph), 60.3 (C-1), 32.2 (C-2) ppm. HRMS calcd. for $C_{54}H_{60}O_{10}$ 886.4530 $[M + NH_4]^+$; found 886.4538.

(3*R*,4*R*,5*R*)-3,6-Bis(benzyloxy)-4-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)hexane-1,5-diol (11b): This compound was prepared from perbenzylated D-cellobial (200 mg, 0.23 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 6:4) and obtained as a viscous oil (187 mg, 92%). $[\alpha]_D$ = +21.6 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3150, 3000, 2900, 1650, 1500, 1450, 1378, 1268, 1072 cm^{-1}. ^{1}H NMR: δ = 7.40–7.20 (m, 30 H, Ph), 5.00–4.40 (m, 13 H, 6 CH_2Ph, 1′-H), 4.18–3.35 (m, 13 H, 1-H_A, 1-H_B, 3-H, 4-H, 5-H, 6-H_A, 6-H_B, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 2.58 (br. s, 2 H, 2 OH), 2.25–1.85 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 139.1, 138.9, 138.7, 138.6, 138.5, 138.3 (C_q, Ph), 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1 (Ph), 104.1 (C-1′), 85.3, 82.7, 78.4, 74.9, 71.3 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 75.4, 73.9, 73.8, 72.8, 71.4, 69.5 (C-6, C-6′, CH_2Ph), 60.8 (C-1), 32.9 (C-2) ppm. HRMS calcd. for $C_{54}H_{60}O_{10}$ 886.4530 $[M + NH_4]^+$; found 886.4540.

(3*R*,4*R*,5*R*)-3,6-Bis(benzyloxy)-4-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-glucopyranosyl)hexane-1,5-diol (11c): This compound was prepared from perbenzylated D-maltal (200 mg, 0.23 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 6:4) and obtained as a viscous oil (187 mg, 92%). $[\alpha]_D$ = +42.6 (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3100, 2950, 2900, 1600, 1500, 1460, 1378, 1278, 1072 cm^{-1}. ^{1}H NMR: δ = 7.50–7.15 (m, 30 H, Ph), 5.25–4.62 (m, 13 H, 6 CH_2Ph, 1′-H), 4.45–3.50 (m, 13 H, 1-H_A, 1-H_B, 3-H, 4-H, 5-H, 6-H_A, 6-H_B, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 3.05 (br. s, 2 H, 2 OH), 2.40–2.25 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.5, 138.2, 138.1, 137.7, 137.6, 137.4 (C_q, Ph), 128.4, 128.2, 128.0, 127.9, 127.7, 127.5, 127.4 (Ph), 97.9 (C-1′), 81.5, 79.1, 77.3, 76.9, 72.8, 70.7 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 77.2, 75.9, 75.1, 74.5, 73.2, 73.0, 71.8, 67.8 (C-6, C-6′, CH_2Ph), 59.3 (C-1), 32.4 (C-2) ppm. HRMS calcd. for $C_{54}H_{60}O_{10}$ 886.4530 $[M + NH_4]^+$; found 886.4535.

(3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-6-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-galactopyranosyl)hexane-1,5-diol (11d): This compound was prepared from perbenzylated D-melibial (200 mg, 0.23 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 6:4) and obtained as a viscous oil (187 mg, 92%). $[\alpha]_D$ = +48.0 (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3200, 2950, 2850, 1650, 1500, 1480, 1370, 1278, 1082 cm^{-1}. ^{1}H NMR: δ = 7.45–7.20 (m, 30 H, Ph), 5.20–4.38 (m, 13 H, 6 CH_2Ph, 1′-H), 4.18–3.51 (m, 13 H, 1-H_A, 1-H_B, 3-H, 4-H, 5-H, 6-H_A, 6-H_B, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 2.82 (br. s, 2 H, 2 OH), 1.88–1.80 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ

= 138.5, 138.2, 138.1, 138.0, 137.8 (C_q, Ph), 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 127.3 (Ph), 98.8 (C-1′), 79.7, 78.8, 77.3, 76.4, 74.8, 70.3, 69.6 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 74.6, 73.8, 73.6, 73.3, 72.8, 72.7, 70.2, 68.8 (C-6, C-6′, CH_2Ph), 59.7 (C-1), 33.4 (C-2) ppm. HRMS calcd. for $C_{54}H_{60}O_{10}$ 886.4530 [M + NH_4]$^+$; found 886.4539.

(3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-6-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)hexane-1,5-diol (11e): This compound was prepared from perbenzylated D-gentiobial[17b] (200 mg, 0.23 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 6:4) and obtained as a viscous oil (187 mg, 92%). $[\alpha]_D$ = +24.0 (*c* = 1.8, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3500, 3140, 2950, 2850, 1640, 1500, 1460, 1360, 1275, 1077 cm^{-1}. ^{1}H NMR: δ = 7.45–7.20 (m, 30 H, Ph), 5.10–4.38 (m, 13 H, 6 CH_2Ph, 1′-H), 4.18–3.51 (m, 13 H, 1-H_A, 1-H_B, 3-H, 4-H, 5-H, 6-H_A, 6-H_B, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 2.70 (br. s, 2 H, 2 OH), 1.90–1.80 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.5, 138.2, 138.1, 138.0, 137.9 (C_q, Ph), 128.3, 128.2, 128.0, 127.8, 127.7, 127.5, 126.6 (Ph), 102.3 (C-1′), 82.7, 79.7, 78.8, 77.3, 74.8, 70.3, 69.6 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 74.6, 73.8, 73.6, 73.4, 72.9, 72.5, 70.1, 69.0 (C-6, C-6′, CH_2Ph), 59.7 (C-1), 33.2 (C-2) ppm. HRMS calcd. for $C_{54}H_{60}O_{10}$ 886.4530 [M + NH_4]$^+$; found 886.4537.

General Procedure for the Preparation of Compounds 4a,b, 7a,b, 10, and 13a–e: CH_3SO_2Cl (2.4 equiv.) was added at 0 °C to a stirred solution of the appropriate linear diol (1 equiv.) in dry pyridine (4.5 mL per mmol). The reaction mixture was stirred at room temp. until the TLC (*n*-hexane/EtOAc, 1:1) showed the disappearance of the starting material (about 1 h) and then diluted with EtOAc (200 mL per mmol), washed in a separating funnel with 6 N HCl (12 mL per mmol), saturated aqueous $NaHCO_3$ (until basic), H_2O (until neutral), brine (20 mL per mmol), dried with anhydrous Na_2SO_4, and the solvent removed under reduced pressure. The residue was then purified by column chromatography to give the dimesylate as a viscous oil (95% yield). The latter compound was dissolved in dry DMSO (4.8 mL per mmol) (a 2:1 DMSO/MeOH mixture was used for compounds **7a**,**b**, **10**, and **13a**–**e**) and treated at room temp. with $Na_2S{\cdot}9H_2O$ (3 equiv.). The reaction mixture was stirred at room temp. (compounds **7a**,**b**, **10** and **13a**–**e** require a temperature of 60 °C) until the TLC (*n*-hexane/EtOAc, 8:2) showed the disappearance of the starting material (about 6 h) and then diluted with Et_2O (200 mL per mmol), washed in a separating funnel with H_2O (until neutral), brine (20 mL per mmol), dried with anhydrous Na_2SO_4, and the solvent removed under reduced pressure. The residue was then purified by column chromatography.

(3*S*,4*R*)-3,4-Bis(benzyloxy)tetrahydrothiopyran (4a): This compound was prepared from **2a** (196 mg, 0.62 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 9:1) and obtained as a viscous oil (148 mg, 0.47 mmol, 80%). The intermediate dimesylate compound **3a** was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 1:1) and obtained as a viscous oil (278 mg, 0.59 mmol, 95%).

3a: $[\alpha]_D$ = +12.3 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3250, 2940, 2900, 1600, 1510, 1460, 1368, 1270, 1100 cm^{-1}. ^{1}H NMR: δ = 7.41–7.15 (m, 10 H, Ph), 4.85–4.45 (m, 6 H, 2-H, 3-H, 2 CH_2Ph), 4.35–4.25 (m, 2 H, 1-H_A, 1-H_B); 4.00–3.80 (m, 2 H, 5-H_A, 5-H_B); 3.21 (s, 3 H, CH_3SO_2), 3.18 (s, 3 H, CH_3SO_2), 2.21–1.83 (m, 2 H, 4-H_A, 4-H_B) ppm. ^{13}C NMR: δ = 137.4, 137.3 (C_q, Ph), 128.4, 128.0 (Ph), 76.8, 73.9 (C-2, C-3), 73.0, 72.9 (CH_2Ph), 68.7, 66.5 (C-1, C-5), 37.2, 37.1 (CH_3SO_2), 29.6 (C-4) ppm. HRMS calcd. for $C_{21}H_{28}O_8S_2$ 490.1569 [M + NH_4]$^+$; found 490.1560.

4a: $[\alpha]_D$ = –9.5 (*c* = 1.4, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 3010, 2950, 2900, 1650, 1500, 1450, 1350, 1050, 1010 cm^{-1}. ^{1}H NMR: δ = 7.31–7.15 (m, 10 H, Ph), 4.82–4.66 (m, 4 H, 2 CH_2Ph), 3.72–3.68 (m, 1 H, 4-H); 3.60–3.48 (m, 1 H, 3-H); 3.30–3.15 (m, 2 H, 2-H), 2.85–2.45 (m, 4 H, 5-H_A, 5-H_B, 6-H_A, 6-H_B) ppm. ^{13}C NMR: δ = 138.6, 138.4 (C_q, Ph), 128.3, 127.6, 127.5, 127.4 (Ph), 79.5, 79.3 (C-3, C-4), 72.3, 72.1 (CH_2Ph), 32.8, 30.7, 26.1 (C-2, C-5, C-6) ppm. HRMS calcd. for $C_{19}H_{22}O_2S$ 332.1684 [M + NH_4]$^+$; found 332.1680.

(3*S*,4*S*)-3,4-Bis(benzyloxy)tetrahydrothiopyran (4b): This compound was prepared from **2b** (196 mg, 0.62 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 9:1) and obtained as a viscous oil (148 mg, 0.47 mmol, 80%). The intermediate dimesylate compound **3b** was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 1:1) and obtained as a viscous oil (278 mg, 0.59 mmol, 95%).

3b: $[\alpha]_D$ = +7.4 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3250, 3000, 2930, 1600, 1510, 1460, 1368, 1270, 1077 cm^{-1}. ^{1}H NMR: δ = 7.40–7.20 (m, 10 H, Ph), 4.85–4.45 (m, 6 H, 2-H, 3-H, 2 CH_2Ph), 4.30–4.25 (m, 2 H, 1-H_A, 1-H_B), 4.10–3.70 (m, 2 H, 5-H_A, 5-H_B), 3.18 (s, 3 H, CH_3SO_2), 3.16 (s, 3 H, CH_3SO_2), 2.10–1.83 (m, 2 H, 4-H_A, 4-H_B) ppm. ^{13}C NMR: δ = 137.4, 137.3 (C_q, Ph), 128.4, 128.0, 127.9 (Ph), 77.1, 74.2 (C-2, C-3) 73.2, 72.9 (CH_2Ph), 68.8, 67.0 (C-1, C-5), 37.4, 37.2 (CH_3SO_2), 29.4 (C-4) ppm. HRMS calcd. for $C_{21}H_{28}O_8S_2$ 490.1569 [M + NH_4]$^+$; found 490.1576.

4b: $[\alpha]_D$ = –8.5 (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 3000, 2950, 2850, 1640, 1500, 1480, 1350, 1050, 1010 cm^{-1}. ^{1}H NMR: δ = 7.33–7.20 (m, 10 H, Ph), 4.80–4.70 (m, 4 H, 2 CH_2Ph), 3.70–3.65 (m, 1 H, 4-H), 3.60–3.45 (m, 1 H, 3-H), 3.28–3.15 (m, 2 H, 2-H), 2.85–2.45 (m, 4 H, 5-H_A, 5-H_B, 6-H_A, 6-H_B) ppm. ^{13}C NMR: δ = 138.6, 138.4 (C_q, Ph), 128.3, 128.2, 127.8, 127.5, (Ph), 79.5, 77.2 (C-3, C-4), 72.3, 72.1 (CH_2Ph), 32.6, 30.5, 23.1 (C-2, C-5, C-6) ppm. HRMS calcd. for $C_{19}H_{22}O_2S$ 332.1684 [M + NH_4]$^+$; found 332.1679.

3,4,6-Tri-*O*-benzyl-2-deoxy-1,5-thioanhydro-L-*xylo*-hexitol (7a): This compound was prepared from **5a** (192 mg, 0.44 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 9:1) and obtained as a viscous oil (107 mg, 0.25 mmol, 60%). The intermediate dimesylate compound **6a** was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 7:3) and obtained as a viscous oil (247 mg, 0.42 mmol, 95%).

6a: $[\alpha]_D$ = +12.7 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3250, 2970, 2900, 1650, 1510, 1460, 1368, 1270, 1077 cm^{-1}. ^{1}H NMR: δ = 7.34–7.21 (m, 15 H, Ph), 5.28–5.20 (m, 1 H, 5-H), 5.07–4.71 (m, 6 H, 3 CH_2Ph), 4.52–4.31 (m, 2 H, 3-H, 4-H), 4.21–3.94 (m, 4 H, 1-H_A, 1-H_B, 6-H_A, 6-H_B), 3.24 (s, 3 H, CH_3SO_2), 3.13 (s, 3 H, CH_3SO_2), 2.45–2.13 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 137.5, 137.3 137.2 (C_q, Ph), 128.4, 128.2, 128.0 127.8, 127.7 (Ph), 82.4, 79.5, 75.0 (C-3, C-4, C-5), 74.1 73.3, 72.9, 68.8, 66.4 (C-1, C-6, CH_2Ph), 38.3, 37.0 (CH_3SO_2), 30.4 (C-2) ppm. HRMS calcd. for $C_{29}H_{36}O_9S_2$ 610.2144 [M + NH_4]$^+$; found 610.2148.

7a: $[\alpha]_D$ = –58.8 (*c* = 1.4, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 3010, 2960, 2910, 1620, 1510, 1460, 1350, 1060, 1020 cm^{-1}. ^{1}H NMR: δ = 7.38–7.20 (m, 15 H, Ph), 4.83 (s, 2 H, CH_2Ph), 4.75 (s, 4 H, 2 CH_2Ph), 4.04–3.76 (m, 5 H, 1-H_A, 1-H_B, 3-H, 4-H, 5-H), 3.25–3.12 (m, 1 H, 6-H_A), 2.73–2.62 (m, 1 H, 6-H_B), 2.52–2.16 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.5, 138.3, 138.2 (C_q, Ph), 128.3, 128.0, 127.6, 127.5, 127.4 (Ph), 74.6, 73.5 (C-3, C-4), 73.0, 72.7, 71.3, 69.4 (CH_2Ph, C-6), 40.9 (C-5), 28.1, 22.6 (C-2, C-1) ppm.

HRMS calcd. for $C_{27}H_{30}O_3S$ 452.2259 [M + NH_4]$^+$; found 452.2265.

3,4,6-Tri-*O*-benzyl-2-deoxy-1,5-thioanhydro-L-*ribo*-hexitol (7b): This compound was prepared from **5b** (192 mg, 0.44 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 9:1) and obtained as a viscous oil (107 mg, 0.25 mmol, 60%). The intermediate dimesylate compound **6b** was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 7:3) and obtained as a viscous oil (247 mg, 0.42 mmol, 95%).

6b: $[\alpha]_D$ = +24.7 (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3250, 2940, 2900, 1660, 1510, 1460, 1370, 1270, 1077 cm^{-1}. ^{1}H NMR: δ = 7.42–7.25 (m, 15 H, Ph), 5.12–4.55 (m, 10 H, 1-H_A, 1-H_B, 4-H, 5-H, 3 CH_2Ph), 4.28–3.96 (m, 3 H, 3-H, 6-H_A, 6-H_B), 3.18 (s, 3 H, CH_3SO_2), 3.12 (s, 3 H, CH_3SO_2); 2.42–2.20 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 137.6, 137.4 137.1 (C_q, Ph), 128.3, 128.0, 127.9 127.8 (Ph), 80.9, 77.8, 74.9 (C-3, C-4, C-5), 74.0 73.1, 71.7, 68.8, 66.4 (C-1, C-6, CH_2Ph), 38.0, 36.7 (CH_3SO_2), 29.8 (C-2) ppm. HRMS calcd. for $C_{29}H_{36}O_9S_2$ 610.2144 [M + NH_4]$^+$; found 610.2138.

7b: $[\alpha]_D$ = –79.5 (*c* = 1.4, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 3000, 2950, 2900, 1610, 1500, 1450, 1350, 1050, 1010 cm^{-1}. ^{1}H NMR: δ = 7.40–7.21 (m, 15 H, Ph), 4.91–4.68 (m, 7 H, 4-H, 3 CH_2Ph), 4.12–3.85 (m, 4 H, 3-H, 5-H, 6-H_A, 6-H_B), 3.38–3.20 (m, 1 H, 1-H_A), 2.70–2.45 (m, 2 H, 2-H_A, 2-H_B), 2.10–1.92 (m, 1 H, 1-H_B) ppm. ^{13}C NMR: δ = 138.8, 138.3, 138.1 (C_q, Ph), 128.2, 127.8, 127.7, 127.5, 127.4 (Ph), 79.8, 73.0 (C-3, C-4), 73.2, 71.8, 71.3, 69.3 (CH_2Ph, C-6), 41.1 (C-5), 31.9, 22.7 (C-1, C-2) ppm. HRMS calcd. for $C_{27}H_{30}O_3S$ 452.2259 [M + NH_4]$^+$; found 452.2265.

3,4-Di-*O*-benzyl-2,6-dideoxy-1,5-thioanhydro-D-*xylo*-hexitol (10): This compound was prepared from **8** (197 mg, 0.60 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 9:1) and obtained as a viscous oil (121 mg, 0.37 mmol, 60%). The intermediate dimesylate compound **9** was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 6:4) and obtained as a viscous oil (275 mg, 0.57 mmol, 95%).

9: $[\alpha]_D$ = –22.1 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3250, 2940, 2900, 1600, 1510, 1460, 1368, 1270, 1077 cm^{-1}. ^{1}H NMR: δ = 7.45–7.32 (m, 10 H, Ph), 5.28–5.18 (m, 1 H, 5-H), 5.02 (d, *J* = 11 Hz, 1 H, H_A of CH_2Ph), 4.88 (d, *J* = 12 Hz, 1 H, $H_{A'}$ of CH_2Ph), 4.86 (d, *J* = 11 Hz, 1 H, H_B of CH_2Ph), 4.76 (d, *J* = 12 Hz, 1 H, $H_{B'}$ of CH_2Ph), 4.45–4.40 (m, 2 H, 3-H, 4-H), 4.12–3.84 (m, 2 H, 1-H_A, 1-H_B), 3.18 (s, 3 H, CH_3SO_2), 3.16 (s, 3 H, CH_3SO_2), 2.40–2.08 (m, 2 H, 2-H_A, 2-H_B), 1.78 (d, *J* = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR: δ = 137.6 (C_q, Ph), 128.4, 128.1, 128.0 127.9 (Ph), 81.0, 79.1, 75.0 (C-3, C-4, C-5), 74.1 73.1 (CH_2Ph), 66.5 (C-1), 38.5, 37.1 (CH_3SO_2), 30.6 (C-2), 16.7 (CH_3) ppm. HRMS calcd. for $C_{22}H_{30}O_8S_2$ 504.1726 [M + NH_4]$^+$; found 504.1720.

10: $[\alpha]_D$ = +37.8 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 3000, 2940, 2890, 1600, 1500, 1450, 1360, 1050, 1015 cm^{-1}. ^{1}H NMR: δ = 7.45–7.25 (m, 10 H, Ph), 4.92 (d, *J* = 11 Hz, 1 H, H_A of CH_2Ph), 4.90 (d, *J* = 11 Hz, 1 H, $H_{A'}$ of CH_2Ph), 4.79 (d, *J* = 11 Hz, 1 H, H_B of CH_2Ph), 4.76 (d, *J* = 11 Hz, 1 H, $H_{B'}$ of CH_2Ph), 3.91–3.49 (m, 3 H, 3-H, 4-H, 5-H), 3.20–2.60 (m, 2 H, 1-H_A, 1-H_B), 2.45–2.12 (m, 2 H, 2-H_A, 2-H_B), 1.49 (d, *J* = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR: δ = 138.6, 138.4 (C_q, Ph), 128.3, 128.0, 127.6, 127.5, 127.4 (Ph), 78.6, 74.0 (C-2, C-3), 72.6, 71.5 (CH_2Ph), 35.8 (C-5), 28.6, 22.5 (C-1, C-2), 16.5 (CH_3) ppm. HRMS calcd. for $C_{20}H_{24}O_2S$ 346.1841 [M + NH_4]$^+$; found 346.1849.

3,6-Di-*O*-benzyl-4-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-galactopyranosyl)-2-deoxy-1,5-thioanhydro-L-*xylo*-hexitol (13a): This compound was prepared from **11a** (187 mg, 0.22 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 9:1) and obtained as a viscous oil (133 mg, 0.15 mmol, 75%). The intermediate dimesylate compound **12a** was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 7:3) and obtained as a viscous oil (210 mg, 0.21 mmol, 95%).

12a: $[\alpha]_D$ = +7.0 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3250, 2940, 2900, 1600, 1510, 1460, 1368, 1290, 1077 cm^{-1}. ^{1}H NMR: δ = 7.44–7.18 (m, 30 H, Ph), 5.03–4.15 (m, 16 H, 1-H_A, 1-H_B, 5-H, 1′-H, 6 CH_2Ph), 3.98–3.52 (m, 10 H, 3-H, 4-H, 6-H_A, 6-H_B, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 2.92 (s, 3 H, CH_3SO_2), 2.72 (s, 3 H, CH_3SO_2), 2.32–2.05 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.5, 138.4, 138.1, 137.7, 137.6, 137.5 (C_q, Ph), 128.4, 128.3, 128.1 127.8, 127.7, 127.6, 127.5, 127.4 (Ph), 102.9 (C-1′), 82.4, 82.2, 79.0, 77.7, 74.9, 73.8, 73.3 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 74.9, 74.8, 73.2, 72.8, 72.0, 68.9, 68.4, 66.9 (C-1, C-6, C-6′, CH_2Ph), 38.4, 36.9 (CH_3SO_2), 29.4 (C-2) ppm. HRMS calcd. for $C_{56}H_{64}O_{14}S_2$ 1042.4081 [M + NH_4]$^+$; found 1042.4075.

13a: $[\alpha]_D$ = –26.4 (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 3000, 2940, 2900, 1600, 1520, 1450, 1350, 1050, 1010 cm^{-1}. ^{1}H NMR: δ = 7.42–7.18 (m, 30 H, Ph), 5.10–4.32 (m, 13 H, 1′-H, 6 CH_2Ph), 4.02–3.38 (m, 11 H, 3-H, 4-H, 5-H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B, 6-H_A, 6-H_B), 3.09–1.98 (m, 4 H, 1-H_A, 1-H_B, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.7, 138.5, 138.4, 138.0, 137.7 (C_q, Ph), 128.3, 128.2, 128.1, 127.7, 127.6, 127.3, 127.2 (Ph), 104.8 (C-1′), 82.1, 79.1, 74.5, 73.6, 73.3, 72.8 (C-3, C-4, C-2′, C-3′, C-4′, C-5′), 74.9, 74.5, 73.4, 73.2, 72.6, 70.7, 68.9, 68.7 (C-6, C-6′, CH_2Ph), 40.3 (C-5), 26.6, 22.5 (C-1, C-2) ppm. HRMS calcd. for $C_{54}H_{58}O_8S$ 884.4196 [M + NH_4]$^+$; found 884.4190.

3,6-Di-*O*-benzyl-4-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)-2-deoxy-1,5-thioanhydro-L-*xylo*-hexitol (13b): This compound was prepared from **11b** (187 mg, 0.22 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 9:1) and obtained as a viscous oil (124 mg, 0.14 mmol, 70%). The intermediate dimesylate compound **12b** was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 7:3) and obtained as a viscous oil (210 mg, 0.21 mmol, 95%).

12b: $[\alpha]_D$ = +9.3 (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3250, 2940, 2900, 1600, 1510, 1460, 1368, 1270, 1077 cm^{-1}. ^{1}H NMR: δ = 7.43–7.20 (m, 30 H, Ph), 5.04–4.20 (m, 16 H, 1-H_A, 1-H_B, 5-H, 1′-H, 6 CH_2Ph), 3.98–3.88 (m, 10 H, 3-H, 4-H, 6-H_A, 6-H_B, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 2.92 (s, 3 H, CH_3SO_2), 2.86 (s, 3 H, CH_3SO_2), 2.32–2.05 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.4, 138.2, 138.0, 137.9, 137.7, 137.4 (C_q, Ph), 128.3, 128.1, 127.8, 127.7, 127.6, 127.5 (Ph), 102.4 (C-1′), 84.6, 82.2, 82.0, 77.1, 77.0, 74.6 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 75.6, 74.84, 74.80, 73.2, 72.9, 72.0, 68.7, 66.8 (C-1, C-6, C-6′, CH_2Ph), 38.5, 37.0 (CH_3SO_2), 29.3 (C-2) ppm. HRMS calcd. for $C_{56}H_{64}O_{14}S_2$ 1042.4081 [M + NH_4]$^+$; found 1042.4088.

13b: $[\alpha]_D$ = –16.2 (*c* = 1.4, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3040, 3010, 2950, 2900, 1600, 1500, 1450, 1350, 1100, 1010 cm^{-1}. ^{1}H NMR: δ = 7.44–7.20 (m, 30 H, Ph), 5.28–4.36 (m, 13 H, 1′-H, 6 CH_2Ph), 4.10–3.30 (m, 11 H, 3-H, 4-H, 5-H, 6-H_A, 6-H_B, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 3.21–3.16 (m, 1 H, 1-H_A), 2.42–2.00 (m, 3 H, 1-H_B, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.7, 138.6, 138.1, 138.0 (C_q, Ph), 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3 (Ph), 104.4 (C-1′), 84.6, 82.0, 77.7, 74.8, 74.7 (C-3, C-4, C-2′, C-3′, C-4′, C-5′), 75.6, 74.8, 74.6, 73.4, 72.7, 70.9, 69.9, 68.8 (C-6, C-6′, CH_2Ph), 40.1 (C-5), 26.5, 22.4 (C-1, C-2) ppm. HRMS calcd. for $C_{54}H_{58}O_8S$ 884.4196 [M + NH_4]$^+$; found 884.4189.

3,6-Di-*O*-benzyl-4-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-glucopyranosyl)-2-deoxy-1,5-thioanhydro-L-*xylo*-hexitol (13c): This compound was prepared from **11c** (187 mg, 0.22 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 9:1) and obtained as a viscous oil (124 mg, 0.14 mmol, 70%). The intermediate dimesylate compound **12c** was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 7:3) and obtained as a viscous oil (210 mg, 0.21 mmol, 95%).

12c: $[\alpha]_D$ = +45.0 (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2940, 2900, 1600, 1510, 1460, 1368, 1270, 1077 cm^{-1}. ^1H NMR: δ = 7.42–7.22 (m, 30 H, Ph), 5.13–4.18 (m, 16 H, 1-H_A, 1-H_B, 5-H, 1′-H, 6 CH_2Ph), 4.04–3.58 (m, 10 H, 3-H, 4-H, 6-H_A, 6-H_B, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 2.98 (s, 3 H, CH_3SO_2), 2.82 (s, 3 H, CH_3SO_2), 2.36–1.76 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.5, 138.0, 137.8, 137.3 (C_q, Ph), 128.4, 128.2, 128.1, 127.9, 127.7 (Ph), 96.7 (C-1′), 82.1, 81.6, 79.3, 77.4, 77.2, 76.5, 73.7 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 75.4, 75.0, 73.2, 72.4, 71.0, 68.9, 67.9, 66.5 (C-1, C-6, C-6′, CH_2Ph), 38.2, 36.8 (CH_3SO_2), 30.0 (C-2) ppm. HRMS calcd. for $C_{56}H_{64}O_{14}S_2$ 1042.4081 $[M + NH_4]^+$; found 1042.4090.

13c: $[\alpha]_D$ = +16.0 (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 3000, 2950, 2900, 1610, 1500, 1450, 1350, 1050, 1010 cm^{-1}. ^1H NMR: δ = 7.42–7.18 (m, 30 H, Ph), 4.98–4.38 (m, 13 H, 1′-H, 6 CH_2Ph), 4.03–3.45 (m, 11 H, 4-H, 5-H, 6-H_A, 6-H_B, 3-H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 2.45–2.18 (m, 2 H, 1-H_A, 1-H_B) 1.96–1.70 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.6, 138.3, 138.1, 138.0, 137.7 (C_q, Ph), 128.2, 127.8, 127.6, 127.5, 127.4, 127.1 (Ph), 97.8 (C-1′), 81.7, 79.9, 77.6, 71.1 (C-3, C-4, C-2′, C-3′, C-4′, C-5′), 75.5, 75.0, 73.4, 73.2, 72.9, 70.8, 69.8, 68.2 (C-6, C-6′, CH_2Ph), 41.1 (C-5), 27.5, 22.6 (C-1, C-2) ppm. HRMS calcd. for $C_{54}H_{58}O_8S$ 884.4196 $[M + NH_4]^+$; found 884.4192.

3,4-Di-*O*-benzyl-6-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-deoxy-1,5-thioanhydro-L-*xylo*-hexitol (13d): This compound was prepared from **11d** (187 mg, 0.22 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 9:1) and obtained as a viscous oil (124 mg, 0.14 mmol, 70%). The intermediate dimesylate compound **12d** was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 7:3) and obtained as a viscous oil (210 mg, 0.21 mmol, 95%).

12d: $[\alpha]_D$ = +27.4 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3250, 2940, 2900, 1600, 1510, 1460, 1368, 1270, 1100 cm^{-1}. ^1H NMR: δ = 7.42–7.23 (m, 30 H, Ph), 5.02–4.38 (m, 14 H, 5-H, 1′-H, 6 CH_2Ph), 4.22–3.68 (m, 12 H, 1-H_A, 1-H_B, 3-H, 4-H, 6-H_A, 6-H_B, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 2.86 (s, 3 H, CH_3SO_2), 2.82 (s, 3 H, CH_3SO_2), 2.12–1.82 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.4, 138.3, 137.5, 137.4, 137.3 (C_q, Ph), 128.4, 128.3, 128.1, 127.9, 127.7, 127.5, 127.4 (Ph), 97.5 (C-1′), 81.7, 79.9, 78.2, 77.1, 75.1, 73.3, 69.7 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 74.7, 74.5, 73.3, 72.8, 72.2, 69.8, 68.9, 66.4, 65.7 (C-1, C-6, C-6′, CH_2Ph), 38.2, 37.0 (CH_3SO_2), 30.4 (C-2) ppm. HRMS calcd. for $C_{56}H_{64}O_{14}S_2$ 1042.4081 $[M + NH_4]^+$; found 1042.4090.

13d: $[\alpha]_D$ = +7.4 (*c* = 1.4, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 3000, 2950, 2900, 1610, 1500, 1450, 1350, 1050, 1010 cm^{-1}. ^1H NMR: δ = 7.45–7.25 (m, 30 H, Ph), 5.22–4.61 (m, 13 H, 1′-H, 6 CH_2Ph), 4.28–3.72 (m, 11 H, 3-H, 4-H, 5-H, 6-H_A, 6-H_B, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 3.08–2.72 (m, 2 H, 1-H_A, 1-H_B), 2.54–2.06 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.8, 138.7, 138.5, 138.0 (C_q, Ph), 128.2, 128.1, 127.9, 127.8, 127.7, 127.5, 127.4 (Ph), 98.2 (C-1′), 78.7, 77.1, 76.4, 74.9, 74.5, 69.5 (C-3, C-4, C-2′, C-3′, C-4′, C-5′), 74.7, 73.3, 72.8, 72.6, 71.6, 68.9, 68.0 (C-6, C-6′, CH_2Ph), 41.0 (C-5), 29.9, 23.1 (C-1, C-2) ppm. HRMS calcd. for $C_{54}H_{58}O_8S$ 884.4196 $[M + NH_4]^+$; found 884.4199.

3,4-Di-*O*-benzyl-6-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)-2-deoxy-1,5-thioanhydro-L-*xylo*-hexitol (13e): This compound was prepared from **11e** (187 mg, 0.22 mmol) following the general procedure described above. It was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 9:1) and obtained as a viscous oil (124 mg, 0.14 mmol, 70%). The intermediate dimesylate compound **12e** was purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 7:3) and obtained as a viscous oil (210 mg, 0.21 mmol, 95%).

12e: $[\alpha]_D$ = +13.4 (*c* = 1.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3250, 2950, 2930, 1600, 1510, 1460, 1368, 1270, 1077 cm^{-1}. ^1H NMR: δ = 7.42–7.23 (m, 30 H, Ph), 5.00–4.38 (m, 14 H, 5-H, 1′-H, 6 CH_2Ph), 4.22–3.68 (m, 12 H, 1-H_A, 1-H_B, 3-H, 4-H, 6-H_A, 6-H_B, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B), 2.86 (s, 3 H, CH_3SO_2), 2.80 (s, 3 H, CH_3SO_2), 2.12–1.80 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.4, 138.3, 137.5, 137.4, 137.1 (C_q, Ph), 128.5, 128.3, 128.0, 127.9, 127.7, 127.4 (Ph), 102.5 (C-1′), 81.7, 79.9, 78.4, 77.4, 75.1, 73.3, 69.6 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 74.8, 74.6, 73.3, 72.8, 72.2, 69.8, 68.9, 66.5, 65.9 (C-1, C-6, C-6′, CH_2Ph), 38.2, 37.4 (CH_3SO_2), 29.2 (C-2) ppm. HRMS calcd. for $C_{56}H_{64}O_{14}S_2$ 1042.4081 $[M + NH_4]^+$; found 1042.4089.

13e: $[\alpha]_D$ = +5.3 (*c* = 1.4, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 3000, 2970, 2930, 1650, 1500, 1450, 1350, 1050, 1010 cm^{-1}. ^1H NMR: δ = 7.45–7.25 (m, 30 H, Ph), 5.20–4.60 (m, 13 H, 1′-H, 6 CH_2Ph), 4.25–3.70 (m, 11 H, 3-H, 4-H, 5-H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_A, 6′-H_B, 6-H_A, 6-H_B), 3.10–2.74 (m, 2 H, 1-H_A, 1-H_B), 2.54–2.06 (m, 2 H, 2-H_A, 2-H_B) ppm. ^{13}C NMR: δ = 138.7, 138.6, 138.5, 138.0 (C_q, Ph), 128.2, 128.1, 127.9, 127.8, 127.5, 127.4 (Ph), 102.2 (C-1′), 81.7, 78.7, 76.4, 74.9, 74.5, 69.5 (C-3, C-4, C-2′, C-3′, C-4′, C-5′), 74.7, 74.2, 72.8, 76.6, 71.6, 70.1, 68.9, 68.1 (C-6, C-6′, CH_2Ph), 41.2 (C-5), 29.9, 23.1 (C-1, C-2) ppm. HRMS calcd. for $C_{54}H_{58}O_8S$ 884.4196 $[M + NH_4]^+$; found 884.4213.

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[1] H. Driguez, in *Glycoscience: Synthesis of Substrate Analogs and Mimetics* (Eds.: H. Driguez, J. Thiem), Springer, Berlin, **1997**, pp. 86–116.

[2] S. Mehta, B. M. Pinto, in *Modern Methods in Carbohydrate Synthesis* (Eds.: S. H. Khan, R. A. O'Neill), Harwood Academic, Amsterdam, **1996**, pp. 107–129.

[3] For the biological activity, see, for instance: a) D. J. Hoffman, R. L. Whistler, *Biochemistry* **1968**, *7*, 4479–4483; b) R. L. Whistler, W. C. Lake, *Biochem. J.* **1972**, *130*, 919–925; c) B. Hellman, A. Lernmark, J. B. Sehlin, J. B. Taljedal, R. L. Whistler, *Biochem. Pharmacol.* **1973**, *22*, 29–35; d) J. Zysk, A. A. Bushway, R. L. Whistler, W. W. Carlton, *J. Reprod. Fertil.* **1975**, *45*, 69–72; e) J. H. Kim, S. H. Kim, E. W. Hahn, C. W. Song, *Science* **1978**, *200*, 206–207; f) H. Hashimoto, T. Fujimori, H. Yuasa, *J. Carbohydr. Chem.* **1990**, *9*, 683–694; g) C.-H. Wong, Y. Ichikawa, T. Krach, C. G.-L. Narvor, D. P. Dumas, G. C. Look, *J. Am. Chem. Soc.* **1991**, *113*, 8137–8145; h) B. D. Johnston, B. P. Pinto, *J. Org. Chem.* **1998**, *63*, 5797–5800; i) H. Yuasa, M. Izumi, H. Hashimoto, *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 774–782.

[4] For example: a) S. Mehta, J. S. Johnston, B. D. Andrews, B. M. Pinto, *J. Am. Chem. Soc.* **1994**, *116*, 1569–1570; b) S. Mehta, J. S. Johnston, B. D. Andrews, B. Svensson, B. M. Pinto, *J. Am. Chem. Soc.* **1995**, *117*, 9783–9790.

[5] D. L. Selwood, K. Carter, R. J. Young, K. S. Jandu, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 991, and references cited therein.
[6] Y. Yoshimura, K. Kitano, H. Satoh, M. Watanabe, S. Miura, S. Sakata, T. Sasaki, A. Matsuda, *J. Org. Chem.* **1996**, *61*, 822–823, and references cited therein.
[7] Y. Yoshimura, M. Endo, S. Sakata, *Tetrahedron Lett.* **1999**, *40*, 1937–1940 and references cited therein.
[8] R. J. Capon, J. K. MacLeod, *J. Chem. Soc., Chem. Commun.* **1987**, 1200–1201.
[9] See, for instance: a) M. Fuzier, Y. Le Merrer, J.-C. Depezay, *Tetrahedron Lett.* **1995**, *36*, 6443–6446; b) V. Cerè, F. Peri, S. Pollicino, *J. Org. Chem.* **1997**, *62*, 8572–8574; c) J. Uenishi, H. Ohmiya, *Tetrahedron* **2003**, *59*, 7011–7022; d) Y. Yoshimura, T. Kuze, M. Ueno, F. Komiya, K. Haraguchi, H. Tanaka, F. Kano, K. Yamada, K. Asami, N. Kaneko, H. Takahata, *Tetrahedron Lett.* **2006**, *47*, 591–594, and references cited therein.
[10] M. Yoshikawa, T. Murakami, H. Shimada, H. Matsuda, J. Yamahara, G. Tanabe, O. Muraoka, *Tetrahedron Lett.* **1997**, *38*, 8367–8370.
[11] E. Gallienne, M. Benazza, G. Demailly, J. Bolte, M. Lemaire, *Tetrahedron* **2005**, *61*, 4557–4568.
[12] J. Isac-García, F. G. Calvo-Flores, F. Hernández-Mateo, F. Santoyo-González, *Chem. Eur. J.* **1999**, *5*, 1512–1525 and references cited therein, especially references [16–36].
[13] O. Tsuruta, H. Yuasa, H. Hashimoto, K. Sujino, A. Otter, H. Li, M. M. Palcic, *J. Org. Chem.* **2003**, *68*, 6400–6406.
[14] M. Izumi, O. Kajihara, Y. Tsurata, S. Yazawa, H. Yuasa, H. Hashimoto, *Chem. Eur. J.* **2005**, *11*, 3032–3038, and references cited therein.
[15] a) A. Fleetwood, N. A. Hughes, *Carbohydr. Res.* **1999**, *317*, 204–209; b) E. Bozò, T. Gàti, A. Demeter, J. Kuszmann, *Carbohydr. Res.* **2002**, *337*, 1351–1365, and references cited therein.
[16] For the synthesis of 5-thio-D-glucopyranose, see, for instance: a) M. S. Feather, R. L. Whistler, *Tetrahedron Lett.* **1962**, *3*, 667–668; b) C.-W. Chiu, R. L. Whistler, *J. Org. Chem.* **1973**, *38*, 832–834; c) H. Driguez, B. Henrissat, *Tetrahedron Lett.* **1981**, *22*, 5061–5062; d) H. Yuasa, J. Tamura, H. Hashimoto, *J. Chem. Soc., Perkin Trans. 1* **1990**, 2763–2769.
[17] See, for example: a) F. Leonelli, M. Capuzzi, V. Calcagno, P. Passacantilli, G. Piancatelli, *Eur. J. Org. Chem.* **2005**, 2671–2676; b) P. Passacantilli, C. Centore, E. Ciliberti, G. Piancatelli, F. Leonelli, *Eur. J. Org. Chem.* **2004**, 5083–5091 and references cited therein.
[18] E. Bettelli, P. D'Andrea, P. Cherubini, P. Passacantilli, G. Piancatelli, *Tetrahedron* **1998**, *54*, 6011–6018.
[19] See ref.[14] and references cited therein, especially references [5–15].

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