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The first synthesis of secondary sugar sulfonic acids by nucleophilic displacement reactions

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Dedicated to Professor Pál Nánási on the occasion of his 80th birthday

Abstract—The 4-deoxy-4-*C*-sulfonic acid and 6-deoxy-6-*C*-sulfonic acid derivatives of methyl α-D-gluco- and α-D-galactopyranosides were prepared by triflate-mediated nucleophilic displacement reactions, either with $NaHSO_3$ or with AcSK. The triflate esters of methyl 2,3,4-tri-*O*-benzyl- **1**, methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **9** and methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside **5** provided methyl 6-deoxy-6-*C*-sulfo-α-D-glucopyranoside **4**, methyl 4-deoxy-4-*C*-sulfo-α-D-galactopyranoside **12** and α-D-glucopyranoside **8**, respectively. The triflate derivative of methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside **13** gave methyl 3,6-anhydro-2,4-di-*O*-benzyl-α-D-galactopyranoside **14**. Formation of the 3,6-anhydro derivative was prevented by using 3,4-*O*-isopropylidene acetal protection to obtain methyl 6-deoxy-6-*C*-sulfo-α-D-galactopyranoside **19**. The aim of the research is to replace the sulfate esters by sulfonic acids in the repeating oligosaccharide units of glycosaminoglycans or in different oligosaccharide ligands.

In 1959 Benson et al.[1] isolated a sulfur-containing glycolipid from the photosynthetic tissues of plants and microorganisms. The sugar component of this glycolipid proved to be 6-deoxy-6-*C*-sulfo-D-glucopyranose, which was synthesized by the same authors[2] from 1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranose. The primary sulfonate group underwent a replacement reaction with sodium sulfite to afford 6-deoxy-1,2-*O*-isopropylidene-6-*C*-sulfo-α-D-glucofuranose. Acid hydrolysis resulted in 6-sulfo-D-quinovose.

Structural studies identified the glycolipid as 1,2-di-*O*-acyl-3-*O*-(6-deoxy-6-*C*-sulfo-α-D-glucopyranosyl)-L-glycerol. Fatty acid compositions in natural lipids from various sources have been determined and a rather rich spectrum of fatty acids has been found in most phospholipids and glycolipids. Gigg et al.[3] were the first to successfully synthesize 3-*O*-(6-deoxy-6-*C*-sulfo-α-D-glucopyranosyl)-1,2-di-*O*-hexadecanoyl-L-glycerol. Similar sulfolipids with very high anti-HIV-1 activity (EC_{50} 0.1–1 μg/mL) were isolated from various cyanobacterial (blue-green algae) media,[4] and four compounds were also synthesized.[5] The sulfonic acid moiety was introduced at position 6 by the oxidation of a thioacetate group with oxone. Later, 2-amino-2,3-dideoxyhexose-3-*C*-sulfonic acid was identified[6] in the hydrolysates of sulfite-treated glycoproteins, and 2-amino-2,6-dideoxy-6-*C*-sulfonic acid was found in the cell-wall hydrolysates of *Halococcus* sp., strain 24.

Recently, it has turned out that sulfoquinovosyldiacyl glycerol (SQDG) and sulfoquinovosylmonoacyl glycerol (SQMG) are DNA polymerase inhibitors.[7] These types of compound were isolated from fern, alga and marine invertebrates and they are potent inhibitors of DNA polymerase α and β, in vitro and of human lung cancer in vivo. SQDGs possess various biological activities such as anti-tumour effects,[8] P-selectin receptor inhibition,[9] HIV-RT inhibition,[10] AIDS-anti-viral[4] and many others. As a consequence, significant interest has been aroused for the synthesis of related compounds. Concerning the synthesis of secondary sugar sulfonic acids, Musicki and Widlanski[11] reported that sulfonate-stabilized Horner–Emmons reagents readily react with

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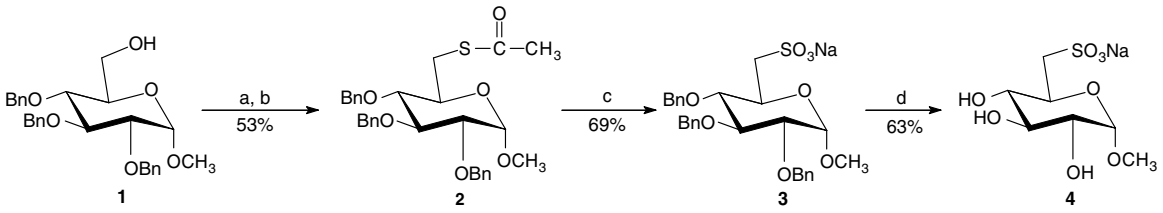


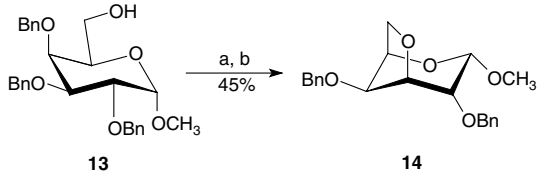
Scheme 1. Reagents and conditions: (a) Tf_2O/Py, CH_2Cl_2, −10 °C, 1 h; (b) CH_3COSK, DMF, 90 °C, 3 h; (c) oxone, KOAc, AcOH, rt, 5 h; (d) H_2/Pd–C, AcOH, EtOH, rt, 24 h.

1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-3-ulofuranose to give a mixture of *cis* - and *trans*-unsaturated sulfonates, which were reduced with $NaBH_4$ to afford the saturated 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose. This compound is a 3-deoxy-3-methylene-sulfo derivative rather than a 3-sulfo-sugar.

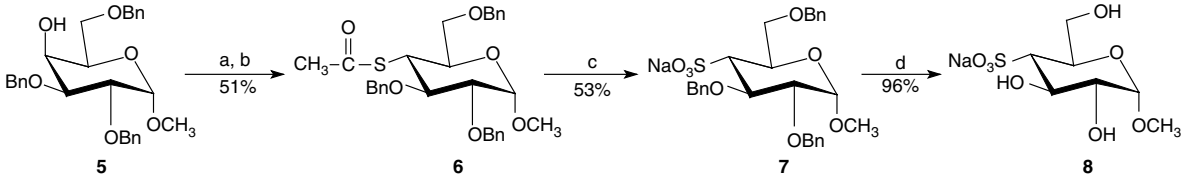
Recently, we have reported the synthesis[12] of methyl 2-deoxy-2-*C*-sulfo-α-D-manno- and -β-D-glucopyranosides using a $1 \rightarrow 2$ arylthio group migration in acid sensitive thioglycosides, and to the best of our knowledge, this is the first report on the preparation of a secondary sugar sulfonic acid.

Our aim is to replace the sulfate esters by sulfonic acids in the repeating oligosaccharide units of glycosaminoglycans or in different oligosaccharide ligands. We have decided to apply nucleophilic displacement reactions for the preparation of the appropriate sugar sulfonic acids. Reactions with tosyl or mesyl esters were sluggish, so we decided to apply triflate esters. Now, we report the synthesis of 4-*C*- and 6-*C*-sulfonic acid derivatives of methyl α-D-gluco- (**8** and **4**) and α-D-galactopyranosides (**12** and **19**). The starting compounds (**1**,[13] **5**,[14] **9**[15] and **13**) were trifluoromethylsulfonylated and treated with CH_3COSK to give crude products, which were used for the next step without further purification. Methyl 2,3,4-tri-*O*-benzyl-6-*S*-acetyl-6-thio-α-D-glucopyranoside **2** was obtained from compound **1** (and characterized by its ^1H and ^{13}C NMR spectra). The 6-*S*-acetyl functionality can be directly oxidized with H_2O_2[16] or with organic peracids[17] to give 6-sulfonates. To avoid the formation of disulfide derivatives we applied oxone–acetic acid[18] solution and compound **3** was obtained in excellent yield. The presence of three *O*-benzyl groups was advantageous for the chromatographic purification of the sodium salt of the protected 6-sulfonate **3**. Compound **3** was hydrogenolyzed in ethanol in the presence of 10% Pd–C catalyst to give the end product **4** (Scheme 1).

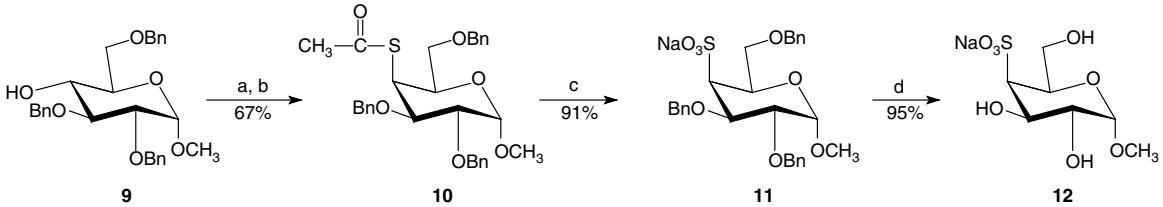
For the preparation of methyl 4-deoxy-4-*C*-sulfo-α-D-glucopyranoside **8** we used methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside[14] **5**, followed by the same sequence of reactions as was used for the preparation of **4**. The S_N2-displacement reaction at C-4 resulted in the D-galacto $\rightarrow$ D-gluco-configurational change and proceeded with excellent yield and with complete stereoselectivity. The 4-*S*-acetyl intermediate **6** was oxidized to **7** by oxone, and the benzyl groups were removed by catalytic hydrogenolysis to give the target compound **8** (Scheme 2).



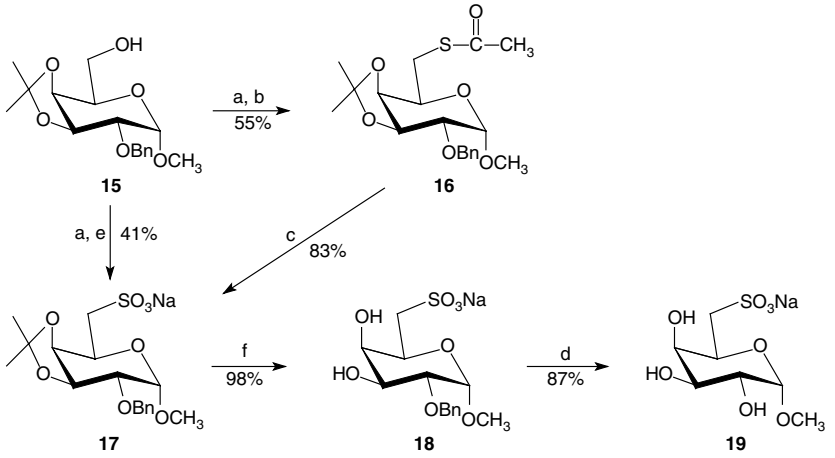
Scheme 4. Reagents and conditions: (a)–(d) as for Scheme 1.



Scheme 2. Reagents and conditions: (a)–(d) as for Scheme 1.



Scheme 3. Reagents and conditions: (a)–(d) as for Scheme 1.



Scheme 5. Reagents and conditions: (a)–(d) as for Scheme 1; (e) Na_2SO_3, $EtOH/H_2O = 1:1$, reflux, 45 min; (f) 3% AcOH, $CH_2Cl_2/H_2O = 99.5:0.5$, reflux, 5 h.

Table 1. Comparison of the ^{13}C NMR data of the target compounds (**4**, **8**, **19** and **12**)[22]

	C-1	C-2	C-3	C-4	C-5	C-6	OCH_3	Solvent
4	100.83	73.41	74.97	74.91	69.41	**54.98**	55.95	CD_3OD
8	100.77	73.75	70.00	**63.49**	70.00	63.98	55.80	CD_3OD
19	101.50	69.98	71.42	72.43	68.55	**53.47**	56.06	CD_3OD
	99.24	67.76	69.30	70.92	66.62	**51.91**	55.19	D_2O
12	100.82	70.18	71.96	**61.87**	70.37	63.50	55.77	CD_3OD

Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside[15] **9** was transformed into compound **10** as described by Elhalabi and Rice.[15] The oxidation was achieved with oxone and after catalytic hydrogenolysis compound **12** was isolated and characterized (Scheme 3).

The approach used for the synthesis of compound **4** was unsuccessful for the preparation of methyl 6-deoxy-6-*C*-sulfo-α-D-galactopyranoside **19**. Triflation of **13** resulted in the 6-*O*-triflate derivative, but an intramolecular displacement reaction occurred during treatment with potassium thioacetate and methyl 3,6-anhydro-2,4-di-*O*-benzyl-α-D-galactopyranoside[19] **14** was formed (Scheme 4).

A similar reaction was observed[20] earlier in the case of benzylated or methylated galactopyranoside derivatives bearing good leaving groups at position 6. It was also found[19] that the presence of a 3,4-*O*-isopropylidene ring can prevent the $^4C_1 \rightarrow {}_4C^1$ conformational flip. Based on this observation a new route was worked out for the synthesis of compound **19**.

Methyl 2-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranoside[21] **15** was first treated with trifluoromethanesulfonic anhydride. The triflyloxy group was then converted into a thioacetyl moiety with potassium thioacetate in DMF to yield **16**. Treatment with $NaHSO_3$ in ethanol–water resulted in the sodium sulfonate **17**. Compound **17** could equally well be obtained by the oxidation of **16** with oxone (Scheme 5).

Compound **17** was transformed into the methyl 6-deoxy-6-*C*-sulfo-α-D-galactopyranoside sodium salt **19** after removal of the isopropylidene (→**18**) and benzyl protecting groups. The structures of both intermediates (**17** and **18**), as well as that of the product **19** were confirmed by 2D NMR (Table 1).

Acknowledgements

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22. Selected physical and spectral data for the new compounds: **2**: $[\alpha]_D^{22}$ +24.8° (*c* 0.24, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3COS–); ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.90 (C-6), 30.47 (CH_3COS–); **3**: $[\alpha]_D^{22}$ +41.0° (*c* 0.09, MeOH); ^{13}C NMR (50 MHz, CD_3OD): δ 53.75 (C-6). **4**: $[\alpha]_D^{22}$ +82.1° (*c* 0.29, MeOH); ^1H NMR (400 MHz, CD_3OD): δ 4.68 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 4.07 (dd, 1H, $J_{5,6a} = 1.9$ Hz, $J_{5,6b} = 9.2$ Hz, H-5), 3.65 (t, 1H, $J_{3,4} = 9.3$ Hz, H-3), 3.45 (dd, 1H, $J_{2,3} = 9.7$ Hz, H-2), 3.29 (dd, 1H, $J_{6a,6b} = 14.5$ Hz, H-6a), 3.12 (t, 1H, $J_{4,5} = 9.5$ Hz, H-4), 2.95 (dd, 1H, H-6b). **6**: $[\alpha]_D^{22}$ +30.2° (*c* 0.53, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 2.23 (s, 3H, CH_3COS–); ^{13}C NMR (50 MHz, $CDCl_3$): δ 45.67 (C-4), 30.49 (CH_3COS–). **7**: $[\alpha]_D^{22}$ +41.1° (*c* 2.3, MeOH); ^1H NMR (200 MHz, CD_3OD): δ 3.27 (t, 1H, $J_{4,5} = 10.5$ Hz, H-4); ^{13}C NMR (50 MHz, CD_3OD): 63.07 (C-4). **8**: $[\alpha]_D^{22}$ +87.2° (*c* 0.92, MeOH); ^1H NMR (400 MHz, CD_3OD): δ 4.72 (d, 1H, $J_{1,2} = 3.7$ Hz, H-1), 4.15 (t, 1H, $J_{3,4} = 9.7$ Hz, H-3), 4.03–3.85 (m, 3H, H-5, H-6a, H-6b), 3.53 (dd, 1H, $J_{2,3} = 9.3$ Hz, H-2), 3.42 (s, 3H, OCH_3), 2.96 (t, 1H, $J_{4,5} = 9.8$ Hz, H-4). **10**: $[\alpha]_D^{22}$ +41.8° (*c* 0.60, $CHCl_3$); ^1H NMR δ 4.51 (t, 1H, $J_{4,5} = 1.7$ Hz, H-4), 2.39 (CH_3COS–); ^{13}C NMR (125 MHz, $CDCl_3$): δ 47.10 (C-4), 30.63 (CH_3COS–). **11**: $[\alpha]_D^{22}$ +97.1° (*c* 0.46, MeOH); ^1H NMR (200 MHz, CD_3OD) δ 4.54 (H-4); ^{13}C NMR (50 MHz, CD_3OD): δ 60.59 (C-4). **12**: $[\alpha]_D^{22}$ +111.5° (*c* 0.52, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 4.83 (d, 1H, $J_{1,2} = 3.6$ Hz, H-1), 4.23 (dd, 1H, $J_{2,3} = 10.3$ Hz, H-2), 4.13 (m, 1H, H-3), 4.11 (dd, 1H, $J_{5,6a} = 7.8$ Hz, $J_{5,6b} = 4.2$ Hz, H-5), 4.04 (dd, 1H, $J_{6a,6b} = 12.1$ Hz, H-6a), 3.92 (dd, 1H, H-6b), 3.52 (dd, 1H, H-4). **16**: ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.70 (C-6). **17**: $[\alpha]_D^{22}$ +80.2° (*c* 0.49, MeOH); ^{13}C NMR (50 MHz, CD_3OD): δ 52.92 (C-6). **18**: $[\alpha]_D^{22}$ +74.7° (*c* 0.95, H_2O); ^{13}C NMR (50 MHz, D_2O): δ 52.70 (C-6). **19**: $[\alpha]_D^{22}$ +83.6° (*c* 1.4, H_2O); ^1H NMR (400 MHz, CD_3OD) δ 4.84 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 4.31 (t, 1H, $J_{5,6a} = 6.0$ Hz, H-5), 4.00 (d, 1H, $J_{3,4} = 3.1$ Hz, H-4), 3.88 (dd, 1H, $J_{2,3} = 10.3$, H-3), 3.83 (dd, 1H, overlap, H-2), 3.22 (m, 2H, H-6a, 6b).