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Sulfonomethyl analogues of aldos-2-ulosonic acids. Synthesis of a new sialyl Lewis X analogue

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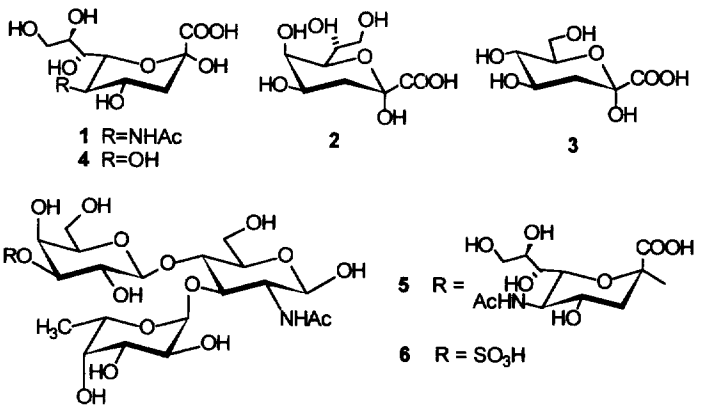
Abstract: Sulfonomethyl derivatives of aldos-2-ulosonic acids have been synthesized by addition of the ethyl methanesulfonate carbanion to aldonolactones. A sulfonylated mimic molecule of the sialyl Lewis X tetrasaccharide has been prepared by using a new sulfonomethyl ulosonic acid analogue.

Keywords: Carbohydrates; Sulfonic acid derivatives; Thioglycosides; Glycosidation

Aldos-2-ulosonic acids such as *N*-acetylneuraminic acid [1] (**1**), 3-deoxy-D-*manno*-2-octulosonic acid [2] (KDO, **2**), 3-deoxy-D-*arabino*-2-heptulosonic acid [3] (**3**) and 3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid [4] (KDN, **4**) play important roles in various biological processes as mediators of cell-viruses or cell-cell recognition [5-7], intermediates of the shikimic acid biosynthesis [3], and constituents of bacterial cell walls [2], etc. The sialyl Lewis X tetrasaccharide (sLe^x) [8] (**5**) - containing *N*-acetylneuraminic acid - is a ligand for E- and P-selectin, therefore is a key interactive molecule of inflammatory reactions and metastasis.



Scheme 1

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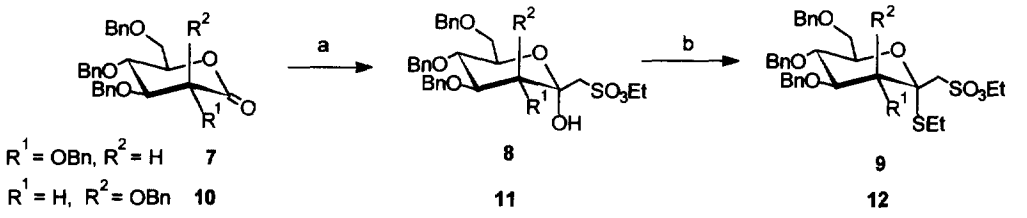
Mimics of **1-5** can be used as inhibitors of enzymes and recognition phenomena [8-10]. The charge of the carboxylic group in 2-ulosonic acids is presumably essential for binding to biomolecules, therefore substitution of carboxyls for another charged moieties could produce bioactive surrogates of **1-5**. While phosphonic acid analogues of **1** are known [11,12], sulfonic acid variants have not been synthesized to date, although several sulfo sugars, having mainly a 6-sulfonic acid moiety, are known [13-20]. Taking into consideration that sulfonic acids are stronger acids then their carboxylic counterparts it can be assumed that sulfonate analogues of 2-ulosonates could bind effectively to the bioreceptors. This idea seems to be confirmed by the fact that the sulfated Lewis X trisaccharide **6** does exist, as a natural analogue of sLe^x, and shows superior binding to E-selectin [21]. This observation has stimulated significant interest in the synthesis of sulfated $Lewis^x$ derivatives [21-25]. In this paper we wish to present preliminary results on the preparation of sulfonomethyl analogues of aldos-2-ulosonic acids and of a sLe^x tetrasaccharide.

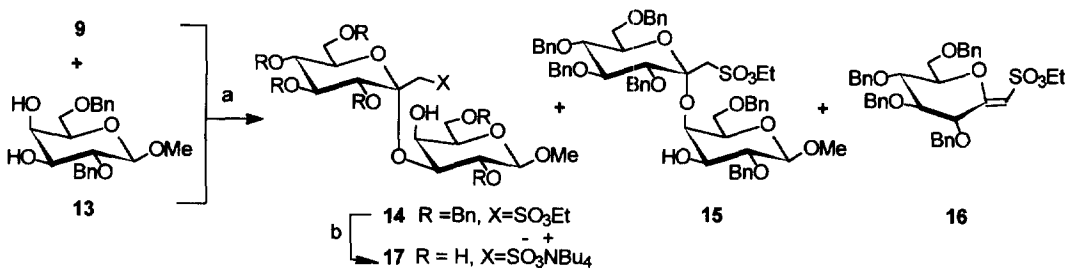
For the synthesis of the model compound **8**, the D-gluconolactone derivative **7** [26] was reacted with the ethyl methanesulfonate anion generated with *n*-butyllithium. Upon nucleophilic addition of the sulfonate ester carbanion to the lactone carbonyl the 1-ethylsulfonyl-D-hept-2-ulose **8** was obtained in α-anomeric form. The anomeric configuration was determined on the basis of the NMR C1-H3 three-bond coupling constant [27], that depends on the dihedral angle in a manner similar to $^3J_{H,H}$.



Scheme 2: a) CH_3SO_3Et, *n*-BuLi, THF, -70 °C, ~90%; b) EtSH, BF_3Et_2O, CH_2Cl_2, ~95%

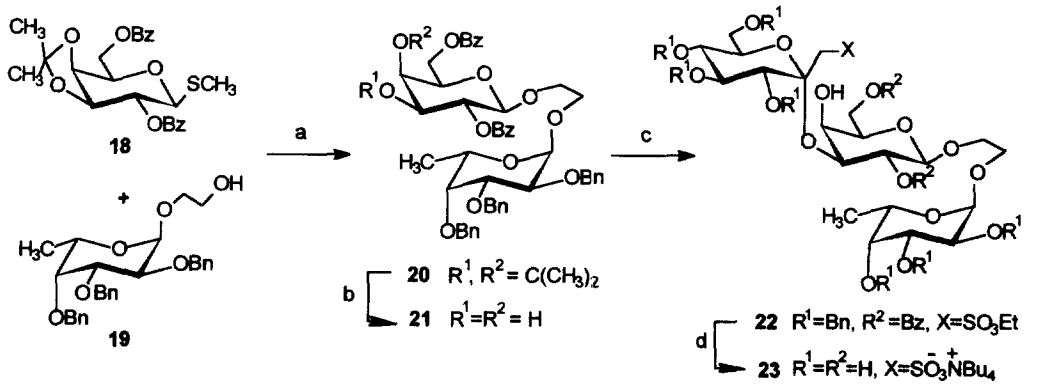
Reaction of **8** with ethanethiol in the presence of Lewis acid resulted in the formation of the α-thioglycoside **9**. The same reaction sequence starting from the D-mannonolactone **10** [28] furnished the thioglycoside **12**.

Since our main goal was the substitution of *N*-acetylneuraminic acid with sulfonomethyl derivatives in sialyl $Lewis^x$ tetrasaccharide analogues we first investigated the regioselective glycosylation of the diol **13** [29] at position 3. Glycosylation of **13** with **9** using *N*-iodosuccinimide – trifluoromethanesulfonic acid (NIS-TfOH) activation afforded a separable 3:1 mixture of the regioisomeric disaccharides **14** and **15**. Formation of the elimination product **16** was also observed with an isolated yield of 13%. The protecting groups were removed from **14** *via* nucleophilic attack by bromide and subsequent catalytic hydrogenation resulted in the tetrabutylammonium salt **17**.



Scheme 3: a) NIS, TfOH, CH_2Cl_2, -50 °C, 55% of **14**, 17% of **15**, 13% of **16**; b) Bu_4NBr, CH_3CN, reflux; EtOH, Pd(C)/H_2, 87% (2 steps)

For the synthesis of the Le^x trisaccharide mimic **19** was glycosylated with the donor **18** [30] using methyl triflate activation to give **20** which, following deisopropylidenation, may serve as the aglycon for further glycosylation. The thioglycoside donor **9** was coupled with the diol **21** using NIS-TfOH activation, and regioselective formation of **22** was observed due to the reduced reactivity of **21**, but the yield was rather low (~35%). The reason for this is the reduced reactivity of the aglycon, and so that an up to 50% increase of the elimination product **16** from the donor **9**. By means of a three-step deprotection procedure **22** was converted into the sulfonic-acid type mimic **23** of the sLe^x tetrasaccharide.



Scheme 4: a) MeOTf, CH_2Cl_2 86%; b) HCl, MeOH, 40 °C, 97%; c) **21**+**9**, NIS, TfOH, CH_2Cl_2, -50 °C, 35% of **22**, 50% of **16**; d) NaOMe, MeOH; Bu_4NBr, CH_3CN, reflux; EtOH, Pd(C)/H_2, 84% (3 steps)

The synthesis of further sulfonomethyl analogues of aldos-2-ulosonic acids and their introduction into oligosaccharides are under way in our laboratory.

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All compounds gave satisfactory spectroscopic data. Selected spectroscopic and physical data are the following: compound **9:** $[\alpha]_D$ +59.94 (c 0.61, $CHCl_3$), ^{13}C *NMR* (125 MHz, benzene): δ 89.7 (C-2), 84.7 (C-4), 80.7 (C-3), 79.8 (C-5), 75.0 (C-6), 69.3(C-7), 66.8 ($SO_3\underline{C}H_2CH_3$), 56.7 (C-1, $J_{H3,C1}$ **2.7 Hz**), 20.1($S\underline{C}H_2CH_3$), 15.1 ($SO_3CH_2\underline{C}H_3$), 13.9 ($SCH_2\underline{C}H_3$). Compound **12:** $[\alpha]_D$ +11.15 (c 0.26, $CHCl_3$), ^{13}C *NMR* (90 MHz, $CDCl_3$): δ 86.6 (C-2), 81.8, 76.8, 74.5, 73.4 (C-3,-4,-5,-6), 69.1(C-7), 66.3 ($SO_3\underline{C}H_2CH_3$), 54.0 (C-1), 20.6($S\underline{C}H_2CH_3$), 14.9 ($SO_3CH_2\underline{C}H_3$), 13.5($SCH_2\underline{C}H_3$). Compound **15:** $[\alpha]_D$ +34.86 (c 0.72, $CHCl_3$), ^{13}C *NMR* (90 MHz, $CDCl_3$): δ 105.2 (C-1), 99.2 (C-2'), 82.6, 80.5, 80.1, 78.4 (C-3', C-5', C-2, C-4), 75.4, 75.3, 75.2, 74.6, 73.4, 72.6 (6 $O\underline{C}H_2Ph$), 73.7, 73.4, 72.8, 72.6 (C-4', C-6', C-3, C-5), 68.8, 68.6, 67.8 (C-6, C-7', $SO_3\underline{C}H_2CH_3$),), 57.2 (OCH_3), 51.8 (C-1, $J_{H3,C1}$ **<1 Hz**), 15.0 ($SO_3CH_2\underline{C}H_3$). Compound **16:** ^{13}C *NMR* (90 MHz, $CDCl_3$) 165.4 (C-2),107.6 (C-1), 85.7, 81.9, 80.3, 80.1 (C-3, -4, -5,-6), 71.3 (C-7), 70.2 ($SO_3\underline{C}H_2CH_3$), 18.3 ($SO_3CH_2\underline{C}H_3$). Compound **17:** $[\alpha]_D$ +44.27 (c 1.10, H_2O), ^{13}C *NMR* (90 MHz, D_2O): δ 106.5 (C-1), 102.7 (C-2'), 77.2 (C-3), 75.8, 75.6, 75.3 (C-3', C-5', C-2, C-4), 72.3, 71.9, 71.5 (C-4', C-6', C-5), 63.7, 63.4 (C-6, C-7'), 60.8 ($N^+\text{-}\underline{C}H_2$-), 59.8 ($OCH_3$), 56.9 (C-1', $J_{H3',C1'}$ **2.0 Hz**), 25.8, 21.8 ($N^+\text{-}CH_2\text{-}\underline{C}H_2\text{-}\underline{C}H_2\text{-}CH_3$), 15.4 ($N^+\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\underline{C}H_3$). Compound **21:** $[\alpha]_D$ –32.94 (0.36, $CHCl_3$), ^{13}C *NMR* (90 MHz, $CDCl_3$) δ 167.1, 166.4 (2 CO), 100.4 (C-1-Fucp), 97.9 (C-1-Galp), 62.9 (C-6-Galp), 67.5, 73.0 ($CH_2\text{-}CH_2$). Compound **22:** $[\alpha]_D$ +22.58 (c 0.17, $CHCl_3$), ^{13}C *NMR* (125 MHz, benzene): δ 166.2, 165.3 (2 CO), 100.6 (C-1), 100.3 (C-2"), 98.1 (C-1'), 64.0 (C-6'), 67.5, 67.7, 68.6 ($CH_2\text{-}CH_2$, C-7", $SO_3\underline{C}H_2CH_3$), 53.9 (C-1", $J_{H3",C1"}$ **<1 Hz**) 16.9 (CH_3-Fucp), 15.1 ($SO_3CH_2\underline{C}H_3$), ESI +QIMS: $M+Na^+$ 1515.7. Compound **23:** ^{13}C *NMR* (125 MHz, D_2O): δ 105.7 (C-1'), 101.7 (C-1), 75.8 (C-6''), 75.3 (C-4''), 74.9 (C-3''), 72.0 (C-5''), 71.7, 69.8 (-$CH_2\text{-}CH_2$-), 63.7 (C-7''), 63.5 (C-6'), 59.1 (C-1''), 18.0 (C-6); ^1H *NMR* (500 MHz, D_2O): δ 4.9 (1 H, d, H-1, $J_{1,2}$ 4.5 Hz), 4.5 (1 H, d, H-1', $J_{1',2'}$ 8.8 Hz), 3.4, 3.5 (2 H, 2 d, H-1_a'', H-1_b'', J_{gem} 14 Hz).

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