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A first synthesis of sulfonic acid analogues of *N*-acetylneuraminic acid

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Abstract

Sulfonic acid analogues of *N*-acetylneuraminic are synthesized from 1-thio-L-fucoside derivatives with the introduction of an azido group at C-4 of the fucose moiety and carbanionic addition onto fully protected lactones. The analogues in the form of methyl glycosides are subjected to a neuraminidase inhibition assay.

Keywords: *N*-Acetylneuraminic acid analogues; Sulfonic acids; Thioglycosides; Methyl glycosides

N-Acetylneuraminic acid (Neu5Ac **1**, Fig. 1), the most abundant sialic acid, is bound to the exo-terminal β-galactosyl residues of cell-surface glycoproteins or glycolipids, and plays an important role in the carbohydrate–protein recognition events leading to cell adhesion, extravasation of leukocytes and bacterial or viral infections. Mimetics that are able to inhibit sialic acid binding proteins (such as sialoadhesins, selectins, and influenza hemagglutinins), may show potent anti-inflammatory, antiviral or antibacterial effects.[1] While phosphonic acid analogues[2] and sulfate ester homologs[3] of *N*-acetylneuraminic acid, containing an anionic group as a replacement for the carboxylate moiety are known, a sulfonic acid mimic has not been prepared to date. Previously, we reported the synthesis of sulfonatomethyl analogues[4] of aldos-2-ulosonic acids, however, the exact conformation and the *N*-acetyl group were missing from these derivatives. The synthesis of sulfonic acid derivatives **2a**,**b** and **3**, that contain the 5-NHAc function and accurately mimic the ring system of **1** is described in this Letter.

The preparation of **2a** and **2b** started from an L-fucose derivative, since L-fucosides have the same chair conformer as Neu5Ac derivatives. Thus, **4**[5] was mesylated at C-4 and treated with NaN_3 to give **5** (Scheme 1). The thiophenyl aglycon of **5** was firstly hydrolyzed in the presence of *N*-bromosuccinimide and the lactol intermediate was then oxidized with PCC to give lactone **6** in a good overall yield. Next, according to our previously published methodology,[4] lactone **6** was reacted with CH_3SO_3Et in the presence of *n*BuLi, and the formation of **7**, a 1-ethoxysulfonyl-hept-2-

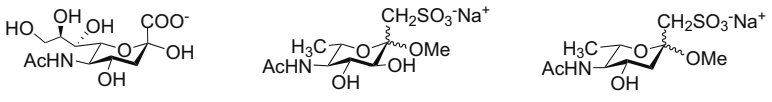

Fig. 1. Structures of Neu5Ac (**1**) and the proposed analogues (**2** and **3**).

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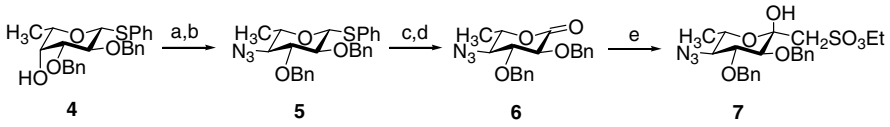
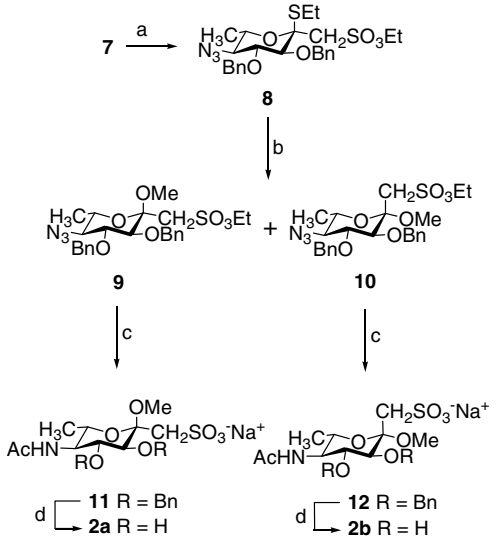


Scheme 1. Reagents and conditions: (a) MsCl (3.5 equiv), Et_3N (1 equiv), CH_2Cl_2, 0 °C, 1 h, 66%; (b) NaN_3 (3.5 equiv), DMF, 115 °C, 1 h, 77%; (c) *N*-bromosuccinimide (1.3 equiv in 3 portions), acetone (aq), 30 min, 89%; (d) PCC (3.5 equiv), 3 Å MS, abs CH_2Cl_2, 3 h, 75%; (e) CH_3SO_3Et (1.1 equiv), *n*BuLi (1.1 equiv), *i*Pr_2NH (1.1 equiv), THF, −78 °C, 1 h, 48%.

ulose sugar occurred in an acceptable (48%) yield. Compound **7** was formed as a single α anomer.

To achieve the synthesis of both **2a** and **2b** the anomeric centre of compounds such as **7** should be fixed in the form of glycosides.[6] Thus, **7** was further derivatized to yield thioglycoside **8**, which occurred also as the α anomer, and was examined by X-ray crystallography.[7] The methanolysis of **8**, under glycosylation conditions, gave a separable mixture of both the α-OMe (**9**) and the β-OMe (**10**) glycosides in a nearly 2: 1 ratio, where the thermodynamically stable α-anomer was the main product. The anomeric configurations of **9** and **10**, were confirmed from the chemical shifts in the ^{13}C NMR spectra, using previously established results.[6] The C-2 atom of **9** (α-OMe derivative) resonated at 98.83 ppm, while that of **10** (β-OMe glycoside) appeared at 100.25 ppm (Scheme 2).

The next step was the transformation of both the sulfonate ethyl ester and the azide moiety of **9** and **10** into a sulfonate salt and an acetamido group, respectively. A one-step procedure for the selective reduction and acetylation of sugar azides has been elaborated by Pavia and co-workers.[8] However, the reaction of **9** and **10** with KSAc/AcSH in DMF resulted not only in the formation



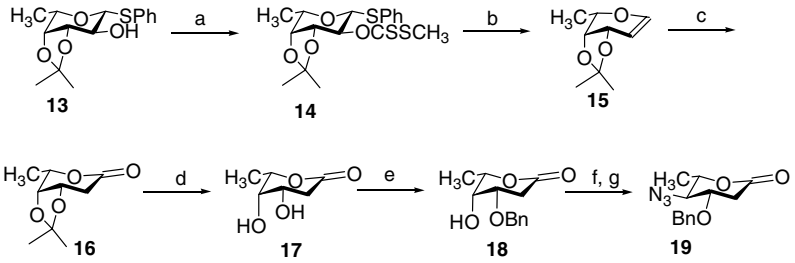
Scheme 2. Reagents and conditions: (a) EtSH (1.8 equiv), $BF_3.Et_2O$ (2.5 equiv), abs CH_2Cl_2, 4 h, 75%; (b) MeOH (15 equiv), NIS (1.5 equiv), TfOH (0.5 equiv), 3 Å MS, abs CH_2Cl_2, −45 °C to −20 °C, 1 h, 55% for **9**, 34% for **10**; (c) KSAc (1.1 equiv), 45 min, then KSAc (2.9 equiv), AcSH (15 equiv), DMF, 24 h; (d) H_2, Pd/C, MeOH, 3 days, 76% for **2a** from **9**, 52% for **2b** from **10**.

of the acetamido group, but also gave rise to cleavage of the sulfonate ethyl ester, due to the strong nucleophilic character of the AcS^- ion. After chromatography on silica **11** and **12** were isolated as sodium salts, according to MALDI-TOF MS analysis. Finally, the 3-*O*- and 4-*O*-benzyl groups were removed from **11** and **12** by catalytic hydrogenation to give **2a** and **2b** in good yields.

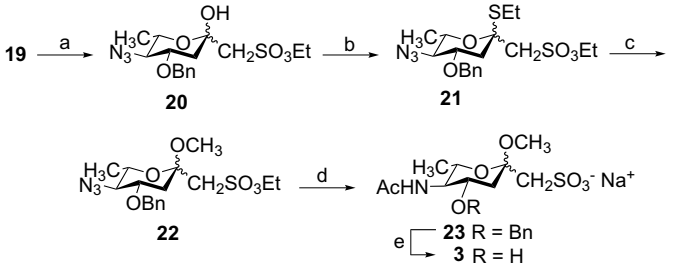
For the preparation of **3** the synthesis of a functionalized 2-deoxy-lactone intermediate was necessary. Starting from **13**,[9] a methyl xanthate ester was introduced to give **14** (Scheme 3). According to a reported procedure,[10] **14** was reacted with Bu_3SnH in the presence of AIBN resulting in a radical reductive elimination yielding 3,4-*O*-isopropylidene-L-fucal, **15**. This volatile, 1,2-unsaturated compound was treated directly with PCC[11] to give lactone **16** in an acceptable yield for the two reaction steps. Deisopropylidenation of **16** and selective benzylation of **17** gave rise to lactone **18**. Finally, the axial 4-OH group of **18** was exchanged to an equatorial azido group to give the desired 4-azido-3-*O*-benzyl-2,4,6-trideoxy-L-*arabino*-hexopyrano-1,5-lactone, **19**.

The carbanionic addition onto lactone **19** to produce **20** was accomplished, unfortunately, in poor yield. NMR spectra revealed that the chromatographically uniform **20** turned out to be a mixture of α and β anomers in a ratio of 7: 3. The loss of stereoselectivity during the addition reaction is probably due to the absence of the 2-*O*-substituent in **19**. Subsequent compounds in the reaction sequence also existed as anomeric mixtures. Azide **20** was reacted with ethanethiol in the presence of $BF_3{\cdot}Et_2O$ at a temperature as low as −20 °C to give **21** ($\alpha/\beta \sim 2{:}1$) in a 60% yield. Methanol was glycosylated with **21** to give **22** ($\alpha/\beta \sim 3{:}2$) in a yield of 81%. Although the anomers of **22** could be separated, their mixture was reacted further due to the small amount of substance available. The azide reduction and salt formation step to produce **23** ($\alpha/\beta \sim 3{:}2$) proceeded in a moderate yield of 38%, while hydrogenolysis of **23** resulted in the formation of sulfonic acid derivative **3** ($\alpha/\beta \sim 3{:}2$), in a 68% yield (Scheme 4).

The inhibitory activity of compounds **2a**,**b** and **3** were measured on *Clostridium perfringens* neuraminidase using fetuin as the substrate with periodate-thiobarbiturate detection.[12] Of the three compounds, only **3** showed moderate inhibition with an IC_{50} value of 4.6 mM. (For the Neu5Ac2en reference compound, an IC_{50} value of 0.56 mM was observed.) The inhibitory activity of **3** is not strong enough for practical applications, nevertheless, the skeleton of **3** can more or less mimic Neu5Ac and



Scheme 3. Reagents and conditions: (a) NaH (1.3 equiv), imidazole (0.2 equiv), CS_2 (7 equiv), 15 min, then MeI (7 equiv), 1 h, quant; (b) Bu_3SnH (4.8 equiv), AIBN, toluene, reflux, 5 min; (c) PCC (5 equiv), abs CH_2Cl_2, reflux, 24 h, 44% for **16** from **14**; (d) HCl (aq), MeOH, 45 °C, 18 h, 91%; (e) Bu_2SnO (1.3 equiv), 3 Å MS, CH_3CN, reflux, 30 h, then CsF (2 equiv), BnBr (2.5 equiv), Bu_4NI, reflux, 72 h, 51%; (f) MsCl (3.5 equiv), Et_3N (1 equiv), CH_2Cl_2, 0 °C, 1 h, 85%; (g) NaN_3 (3.5 equiv), DMF, 115 °C, 1 h, 69%.



Scheme 4. Reagents and conditions: (a) CH_3SO_3Et (1.1 equiv), *n*BuLi (1.1 equiv), *i*Pr_2NH (1.1 equiv), THF, −78 °C, 1 h, 35%, **20α**:**20β** ∼ 7:3; (b) EtSH (1.8 equiv), $BF_3{\cdot}Et_2O$ (2.5 equiv), abs CH_2Cl_2, 4 h, 60%, **21α**:**21β** ∼ 2:1; (c) MeOH (15 equiv), NIS (1.5 equiv), TfOH (0.5 equiv), 3 Å MS, abs CH_2Cl_2, −45 °C, 81%, **22α**:**22β** ∼ 3:2; (d) KSAc (1.1 equiv), 45 min, then KSAc (2.9 equiv), AcSH (15 equiv), DMF, 24 h; 38%, **23α**:**23β** ∼ 3:2; (e) H_2, Pd/C, MeOH, 3 days, 68%, **3α**:**3β** ∼ 3:2.

may become a substituent of the sialyl moiety in a neoglycoconjugate. Comparison of **3** with **2a**,**b** reveals that the 3-deoxy function is essential for these mimetics.

Acknowledgements

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Supplementary data

Experimental procedures for all synthetic steps and characterization (including ^1H and ^{13}C NMR data) for all new compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.043.

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7. Details of the crystal structure analysis are provided as Supplementary data. Crystallographic data (excluding structure factors) for the structure **8** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 661647. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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