Nucleophilic displacements on a cyclic sulfamidate derived from allosamine: application to the synthesis of thiooligosaccharides

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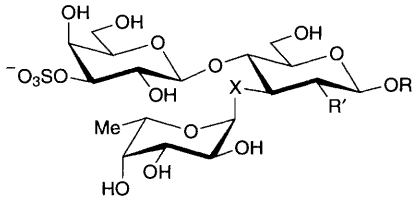
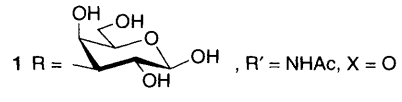
The cyclic sulfamidate of the allosamine derivative 11 is efficiently prepared by reaction with 1,1′-sulfuryl diimidazole; the regioselective opening of this compound by sulfur nucleophiles furnishes 3-thioglucosamine derivatives, useful intermediates in synthesis of thiooligosaccharides.

Sulfated tetrasaccharide **1** has been shown to be recognized by E-selectin,[1] a protein involved in the acute inflammatory process.[2] We have reported the synthesis of some oligosaccharides structurally related to E-selectin ligands that are inhibitors of neural cell division.[3,4] Among the substrates tested, the sulfated trisaccharide **2**, analogue of **1**, showed the highest antimitotic activity on tumor C-6 glioma cells.[4] A recent report showed that sulfated oligosaccharides of similar structure activate lymphocytes (natural killer cells) to destroy certain tumours and virally infected cells.[5] Owing to the important biological interest of these compounds, we planned to prepare novel oligosaccharides stable at acidic pH and toward glycosidases. Since thioglycosides fulfill these requirements[6] we designed the synthesis of sulfated thiotrisaccharide **3**, containing a sulfur atom linking the fucosyl and glucosaminyl moieties. In our synthetic scheme toward **3** the key step is the formation of the thioglycosidic bond. This reaction can be achieved by nucleophilic displacement at C-3 of an allosamine derivative with a fucose thiolate. In this work we have found that a cyclic sulfamidate derived from D-allosamine is regioselectively opened by nucleophiles in a reaction where conventional leaving groups, such as the triflate or tosylate, gave no reaction.

The allosamine **5**† (Scheme 1) was prepared in a simple and direct way from benzyl 2-acetamido-2-deoxy-β-D-glucopyranoside **4**.[7] A selective inversion took place at C-3 of the glucose derivative. Debenzoylation of **5** followed by benzylidenation furnished **6**. Treatment of **6** with Tf_2O–pyridine did not afford the corresponding triflate at C-3, but instead a complex mixture of products was obtained. The reaction under the same conditions on the 2-phthalimide derivative **7** gave cleanly triflate **8**, however, when **8** was subjected to nucleophilic displacement with KSAc the elimination product **9** was the main product. With the 3-tosylate **10** no reaction occurred with KSAc at 80 °C for 24 h.





1 R = , R′ = NHAc, X = O

2 R = Me, R′ = OH, X = O

3 R = H, R′ = NHAc, X = S

The recent application of cyclic sulfamidates derived from serine to activate the β-position to nucleophilic attack,[8,9] suggested to us that such a methodology could be applicable to our problem. Direct formation of the cyclic sulfamidate **11** from **6** by reaction with sulfuryl chloride[8] failed and the starting material remained unalterated. The two step procedure,[9] *i.e.* reaction with thionyl chloride followed by oxidation, gave under the best conditions only a 45% yield of **11**. We found that **11** could be obtained‡ in higher yield if **6** is treated with 1,1′-sulfuryl diimidazole followed by acetyl chloride to reinstall the acetyl group on the nitrogen atom that was cleaved under the basic conditions used. Without further optimization a 74% yield of **11** was obtained. The regioselective opening of **11** with KSAc afforded the 3-thio derivative **12** (82%) which is already an appropriate intermediate for the synthesis of thioglycosides. Nevertheless, by the reaction of the fucose 1-thiolate **13** with **11** the thiodisaccharide **14** is directly obtained in satisfactory yield (50%). To illustrate the potential of cyclic sulfamidates in substitution reactions, **11** was treated with a different nucleophile, sodium azide. The azide displacement took place at room temperature in only 2 h to give **15** in 92% yield. An azide displacement on a similar mesylated substrate has been reported[10] to proceed in 85% yield after 4 d at 90 °C.

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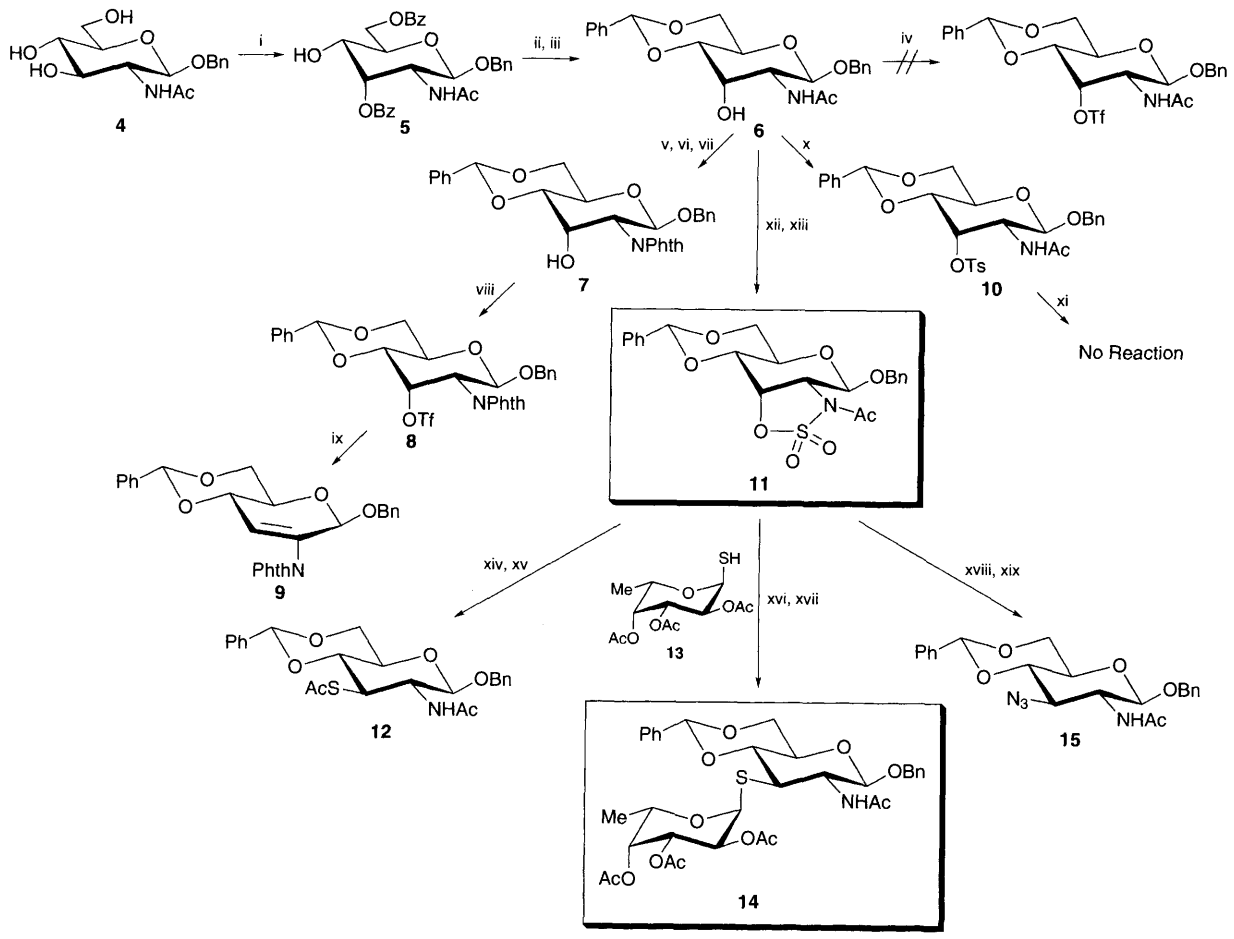
Footnotes

† All new compounds gave satisfactory elemental analyses and the expected ^{13}C NMR spectra. *Selected data* (*J*/Hz) for **5**: mp 137 °C; $[\alpha]_D$ −52.0 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.9 (3 H, s, NHAc), 2.88 (1 H, d, *J* 3.4, OH), 4.1 (2 H, m, H-4, H-5), 4.4 (1 H, dt, $J_{1,2}$ 7.9, $J_{NH,2}$ 8.0, $J_{2,3}$ 2.7, H-2), 4.87 (1 H, d, $J_{1,2}$ 7.9, H-1), 5.85 (1 H, t, *J* 2.7, H-3). For **6**: mp 265 °C, $[\alpha]_D$ −128.1 (*c* 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$), δ 1.99 (3 H, s, NHAc), 2.5 (1 H, d, *J* 1.5, OH), 3.7 (1 H, dd, $J_{3,4}$ 2.3, $J_{4,5}$ 9.2, H-4), 4.25 (2 H, m, H-2, H-3), 4.7 (1 H, d, $J_{1,2}$ 7.96, H-1), 5.6 (1 H, s, CHPh), 5.87 (1 H, d, *J* 8.8, NH). For **11**: mp 165 °C, $[\alpha]_D$ −55.2; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (3 H, s, NAc), 3.83 (1 H, t, *J* 10.3, H-6_a), 4.0 (2 H, m, H-5, H-4), 4.49 (1 H, dd, $J_{6a,6e}$ 10.3, $J_{5,6e}$ 4.5, H-6_e), 4.64 (1 H, d, *J* 11.8, CH_2Ph), 4.71 (1 H, m, H-2), 4.93 (1 H, d, *J* 11.8, CH_2Ph), 4.97 (1 H, d, $J_{1,2}$ 7.3, H-1), 5.22 (1 H, dd, *J* 2.5, *J* 4.3, H-3), 5.6 (1 H, s, CHPh). For **12** ^1H NMR (500 MHz, CD_3COCD_3) δ 1.8 (3 H, s, NHAc), 2.24 (3 H, s, SAc), 3.68 (1 H, dd, $J_{4,5}$ 8.97, $J_{3,4}$ 10.8, H-4), 3.87 (1 H, t, *J* 10.8, H-3), 4.09 (1 H, m, H-2), 4.85 (1 H, d, $J_{1,2}$ 8.2, H-1), 5.6 (1 H, d, $J_{NH,2}$ 7.1, NH). For **14**: mp 132 °C, $[\alpha]_D$ −122.3 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.63 (3 H, d, *J* 6.6, CH_3, Fuc), 3.38 (2 H, m, H-3, H-4), 3.58 (2 H, m, H-2, H-5), 3.74 (1 H, t, *J* 10.4, H-6_a), 4.34 (1 H, dd, $J_{5,6e}$ 4.7, $J_{6a,6e}$ 10.4, H-6_e), 4.41 (1 H, q, H-5′), 4.56 (1 H, d, *J* 11.9, CH_2Ph), 4.83 (1 H, d, $J_{1,2}$ 7.87, H-1), 4.88 (1 H, d, *J* 11.9, CH_2Ph), 5.03 (1 H, dd, $J_{2',3'}$ 10.9, $J_{1',2'}$ 5.7, H-2′), 5.08 (1 H, d, *J* 3.0, H-4′), 5.14 (1 H, dd, $J_{2',3'}$ 10.9, $J_{3',4'}$ 3.0, H-3′), 5.52 (2 H, d, $J_{NH,2}$ 6.96, NH, CHPh). For **15**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.97 (3 H, s, NHAc), 3.20 (1 H, m, H-2), 3.81 (1 H, t, *J* 10.4, H-4), 4.44 (1 H, dd, $J_{2,3}$ 10.8, $J_{3,4}$ 9.18, H-4), 5.1 (1 H, d, $J_{1,2}$ 8.3, H-1), 5.62 (1 H, d, $J_{NH,2}$ 7.5, NH).



Scheme 1 *Reagents and conditions*: i, BzOH, Ph_3P, DEAD, THF, 65 °C, 1.5 h, 85%; ii, NaOMe (0.1 mol dm^{-3}), MeOH, room temp., 1 h; iii, $PhCH(OMe)_2$, *p*-TsOH, MeCN, room temp., 2 h, 94% (2 steps); iv, Tf_2O, Py, CH_2Cl_2, −30 °C, 30 min; v, KOH, MeOH (32% *m/m*), 125 °, 20 h vi, phthalic anhydride, $CHCl_3$, room temp., 1 h; vii, Ac_2O, Pyridine, reflux, 5 h, 70% (3 steps); viii, Tf_2O, Py, CH_2Cl_2, −30 °C, 30 min; ix, KSAc, DMF, 0 °C, 1 h, 75%; x, TsCl, Py, CH_2Cl_2, room temp., 4 h, 65%; xi, KSAc, DMF, 80 °C, 24 h; xii, 1,1′-sulfuryl-diimidazole, NaH, DMF, −40 °C → room temp.; xiii, AcCl, Py, CH_2Cl_2, room temp., 2 h, 74% (2 steps); xiv, KSAc, DMF, room temp., 30 min; xv, H_2SO_4, H_2O, THF, room temp., 30 min, 82%; xvi, **13**, NaH, DMF, 0 °C, 15 min; xvii, H_2SO_4, H_2O, THF, room temp., 30 min, 50% (2 steps); xviii, NaN_3, DMF, room temp., 2 h; xix, H_2SO_4, H_2O, THF, room temp., 30 min, 92% (2 steps). Py = pyridine.

‡ *Preparation* of **11**: To a stirred solution of **6** (300 mg, 0.75 mmol) in dry DMF (2 cm^3) was added sodium hydride (54 mg, 2.25 mmol) at 0 °C under argon. When the hydrogen bubbling ceased, the reaction mixture was cooled at −40 °C, and 1,1′-sulfuryl diimidazole (222 mg, 1.12 mmol) in dry DMF (1 cm^3) was added dropwise. After being warmed to room temperature over a period of 1 h, the solvent was removed. The residue was dissolved in CH_2Cl_2 (9 cm^3), then acetyl chloride (64 mm^3 0.9 mmol) and pyridine (146 mm^3 1.8 mmol) were added, and the solution stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2, washed successively with saturated aq. $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (CH_2Cl_2–AcOEt 110 : 1) gave the sulfamidate **11** (256 mg, 74%).

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