

## A New Base-Labile Anchoring Group for Polymer-Supported Oligosaccharide Synthesis

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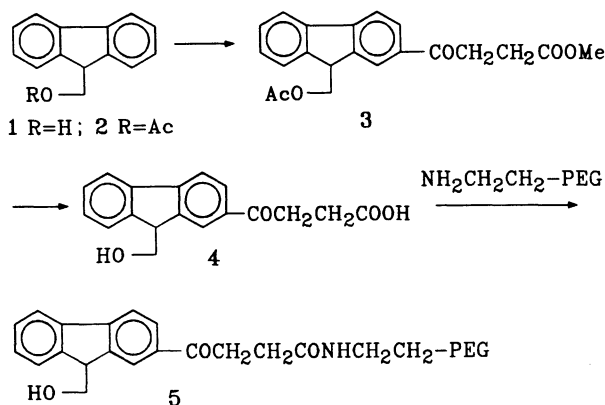
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A new base-labile 9-hydroxymethylfluorene-2-succinic acid-based anchoring group, coupled to amino-ethylated polyethylene glycol, opens a new approach for polymer-supported syntheses of oligosaccharides using phenyl 1-thioglycopyranoside sulfoxides as highly efficient glycosyl donors.

Insoluble functionalized polymer supports have been extensively applied for the syntheses of polypeptides<sup>1</sup> and polynucleotides.<sup>2</sup> The advantages of solid phase methods are that purification of the polymer-bound growing molecule can be achieved at each intermediate step by simple filtration and washing, the reaction rates can be increased by using a large excess of reagents and repetitive steps are amenable to automation. Compared to numerous successful solid phase syntheses of peptides and polynucleotides,<sup>1,2</sup> relatively few reports appeared in the literature in the carbohydrate field.<sup>3</sup> Insufficient reactivity, incomplete stereoselectivity and instability of the glycosyl donors and the lack of suitable anchoring groups are responsible for the low yields received for the target molecules, which often contaminated with a whole series of side products after removal from the resin.<sup>4</sup> Due to the general attractive features of solid phase synthesis of biopolymers a new approach for the polymer-based polysaccharide synthesis has been tried.

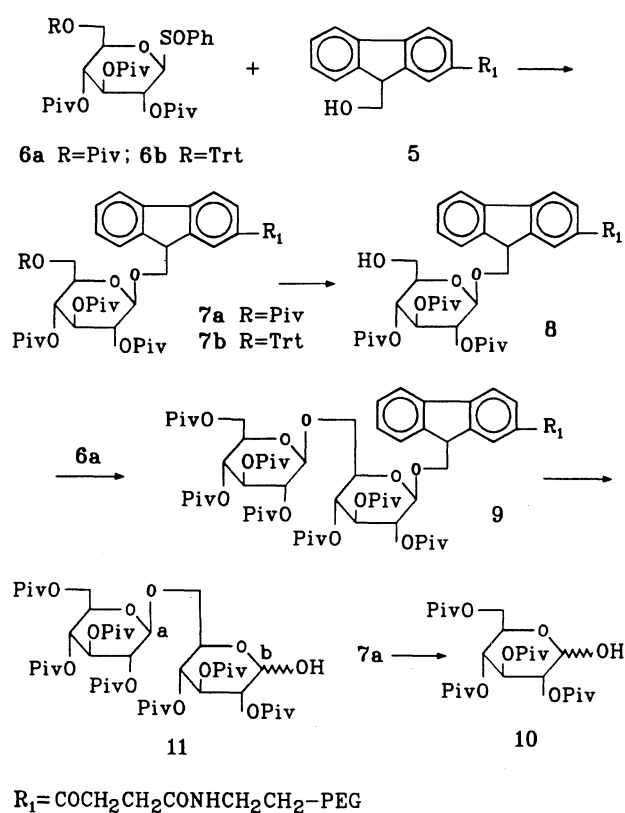
In this communication we would like to introduce a new handle (4) which allows the cleavage of fully protected oligosaccharides from the polymer support under mild conditions. Besides, phenyl 1-thioglycopyranoside sulfoxides<sup>5</sup> are used as highly efficient glycosyl donors in our polymer-supported oligosaccharide synthesis.



Scheme 1.

The approach leading to the base-labile anchoring group 4 is summarized in Scheme 1. 9-Hydroxymethylfluorene (1) was acetylated with pyridine and acetic anhydride in dichloromethane to give 9-acetoxymethylfluorene (2)<sup>6</sup> in 98 % yield. In the presence of aluminum chloride, 2 was acylated in

dichloromethane with succinyl chloride methyl ester to produce 9-acetoxymethylfluorene-2-succinic acid methyl ester (3)<sup>6</sup> in 89 % yield. After removal of the protecting groups with 18 % hydrochloric acid / acetone (1:2), the carboxylic acid 4<sup>6</sup> was isolated (68 % yield) and coupled to amino-ethylated polyethylene glycol (PEG, MW 6000) with *N,N'*-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) in DMF/dichloromethane (1:1) to yield the polymer 5 (>90 % yield).



Scheme 2.

As shown in Scheme 2, phenyl 2,3,4,6-tetra-O-pivaloyl-1-thio-β-D-glucopyranoside sulfoxide 6a and phenyl 2,3,4-tri-O-pivaloyl-6-O-trityl-1-thio-β-D-glucopyranoside sulfoxide 6b were coupled in twofold excess to the polymer 5 in the presence of 2,6-di-*tert*-butyl-pyridine (DtBP) and triflic anhydride (Tf<sub>2</sub>O) in dichloromethane within 16 h.<sup>5</sup> The reaction mixtures were washed with water, dried over sodium sulfate, precipitated with ether to yield the carbohydrate-polymers 7a and 7b respectively. After precipitation from dichloromethane-ether (1:2), the trityl group of 7b was removed with 4 % trifluoroacetic acid (TFA) in dichloromethane within 40 min to form the polymer 8 and trityl trifluoroacetate. The latter was collected, and based on its weight

the coupling yield was determined to be 86 %. After precipitation of **8** from dichloromethane-ether (1:2), a further glycosylation with **6a** produced the polymer **9** (in 80 % yield). 2,3,4,6-Tetra-O-pivaloyl-D-glucopyranose (**10**)<sup>6</sup> and 2,3,4-tri-O-pivaloyl-6-O-(2,3,4,6-tetra-O-pivaloyl-β-D-glucopyranosyl)-D-glucopyranose (**11**)<sup>6</sup> were removed with 20 % triethylamine (TEA) in dichloromethane from the polymers **7a** and **9** in 90 % and 70 % purity respectively, and their structures were confirmed by the spectroscopic data given below.

In summary, these investigations demonstrate that the 9-hydroxymethylfluorene-2-succinic acid-based anchoring group proves to be very useful for stepwise synthesis of polysaccharides on polymer supports and the protected polysaccharide chain can be removed under extremely mild conditions with 20 % triethylamine from the anchoring group. The phenyl 1-thioglycopyranoside sulfoxide was found to be an excellent glycosyl donor for the polymer-supported oligosaccharide synthesis. Some further studies are in progress in our laboratory.

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#### References and Notes

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- Selected physical data for compounds **2**, **3**, **4**, **10** and **11**: **2**: mp 82-83 °C. **3**: mp 94-95 °C; MS (EI) m/z 352 (M<sup>+</sup>), 292 (M-HOAc<sup>+</sup>); <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 8.11 (m, J=0.8, 0.7 Hz, 1H, Ar-H-1), 7.93 (dd, J=8.0, 1.1 Hz, 1H, Ar-H), 7.69 (m, 2H, Ar-H), 7.51 (dd, J=8.1, 0.6 Hz, 1H, Ar-H), 7.27 (m, 2H, Ar-H), 4.28 (m, 2H, CH<sub>2</sub>-OAc), 4.15 (t, J=7.1 Hz, 1H, CH), 3.62 (s, 3H, COOMe), 3.26 (t, J=6.6 Hz, 2H, CH<sub>2</sub>), 2.69 (t, J=6.6 Hz, 2H, CH<sub>2</sub>), 2.04 (s, 3H, COMe); <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>) δ 197.5 (CO), 173.4, 170.8 (COO), 146.1, 145.0, 144.1, 140.0, 135.3, 128.4, 128.4, 128.1, 125.2, 124.7, 121.1, 119.9 (Ar-C), 65.9, 51.8, 46.7, 33.5, 28.1, 20.9. **4**: mp 182-183 °C; MS (FAB) m/z 297 (M-H<sup>+</sup>); <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>) δ 12.20 (s, 1H, COOH), 8.30 (s, 1H, Ar-H-1), 8.05 (dd, J=8.1, 1.3 Hz, 1H, Ar-H), 7.95 (m, 2H, Ar-H), 7.70 (dd, J=8.0, 1.8 Hz, 1H, Ar-H), 7.41 (m, 2H, Ar-H), 5.13 (s, 1H, CH<sub>2</sub>OH), 4.11 (t, J=6.6 Hz, 1H, CH), 3.90 (dd, J=10.1, 6.3 Hz, 1H, CH<sub>2</sub>OH), 3.75 (dd, J=9.9, 7.4 Hz, 1H, CH<sub>2</sub>OH), 3.3 (t, J=6.3 Hz, 2H, CH<sub>2</sub>), 2.63 (t, J=6.3 Hz, 2H, CH<sub>2</sub>); <sup>13</sup>C NMR (62.9 MHz, DMSO-d<sub>6</sub>) δ 198.1 (CO), 173.9 (COO), 146.4, 145.7, 145.4, 139.6, 134.9, 128.1, 127.6, 127.4, 125.3, 124.7, 121.0, 119.9 (Ar-C), 63.5, 50.2, 33.3, 28.0. **10**: MS (FD) m/z 515 (M-H<sup>+</sup>), 415 (M-OCOCMe<sub>3</sub><sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) α-form: δ 5.64 (t, J=9.7 Hz, 1H), 5.48 (d, J=3.7 Hz, 1H, H-1), 5.14 (t, J=10.1 Hz, 1H), 4.84 (dd, J=10.1, 3.7 Hz, 1H, H-2), 4.32-4.08 (m, 3H), 3.20 (b, 1H, OH), 1.22 (s, CMe<sub>3</sub>), 1.20 (s, CMe<sub>3</sub>), 1.18 (s, CMe<sub>3</sub>), 1.15 (s, CMe<sub>3</sub>); β-form: δ 5.38 (t, J=9.5 Hz, 1H), 4.92 (dd, J=9.1, 8.1 Hz, 1H, H-2), 4.74 (d, J=8.1 Hz, 1H, H-1), 4.32-4.08 (m, 3H), 3.77 (ddd, J=10.0, 4.6, 1.8 Hz, 1H, H-5), 3.2 (b, 1H, OH), 1.22 (s, CMe<sub>3</sub>), 1.20 (s, CMe<sub>3</sub>), 1.17 (s, CMe<sub>3</sub>), 1.14 (s, CMe<sub>3</sub>); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) α-form: δ 179.9, 179.3, 178.7, 178.1 (COO), 90.6 (C-1), 72.4, 70.4, 68.7, 68.6, 62.6, 39.7-39.5 [C(CH<sub>3</sub>)<sub>3</sub>], 27.9-27.8 [C(CH<sub>3</sub>)<sub>3</sub>]; β-form: δ 180.2, 179.9, 178.8, 178.1 (COO), 96.6 (C-1), 74.5, 73.6, 72.6, 68.8, 62.7, 39.7-39.5 [C(CH<sub>3</sub>)<sub>3</sub>], 27.9-27.8 [C(CH<sub>3</sub>)<sub>3</sub>]. **11**: MS (FD) m/z 1844 (2M-H<sub>2</sub>O<sup>+</sup>), 1761 (2M-OCOCMe<sub>3</sub><sup>+</sup>), 931 (M<sup>+</sup>), 846 (M-COCMe<sub>3</sub><sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) α-form: δ 5.32 (d, J=3.8 Hz, 1H, Hb-1), 4.73 (dd, J=10.1, 3.6 Hz, 1H, Hb-2), 4.51 (d, J=7.9 Hz, 1H, Ha-1), 1.14 (s, 9H, CMe<sub>3</sub>), 1.12 (s, 9H, CMe<sub>3</sub>), 1.11 (s, 9H, CMe<sub>3</sub>), 1.09 (s, 9H, CMe<sub>3</sub>), 1.08 (s, 9H, CMe<sub>3</sub>), 1.05 (s, 9H, CMe<sub>3</sub>), 1.04 (s, 9H, CMe<sub>3</sub>); β-form: δ 4.54 (d, J=7.9 Hz, 1H, Hb-1), 4.51 (d, J=7.9 Hz, 1H, Ha-1), 1.14 (s, 9H, CMe<sub>3</sub>), 1.12 (s, 9H, CMe<sub>3</sub>), 1.11 (s, 9H, CMe<sub>3</sub>), 1.09 (s, 9H, CMe<sub>3</sub>), 1.08 (s, 9H, CMe<sub>3</sub>), 1.05 (s, 9H, CMe<sub>3</sub>), 1.04 (s, 9H, CMe<sub>3</sub>).