Use of low molecular weight polyethylene glycol linker for polymer-supported solution synthesis of oligosaccharides

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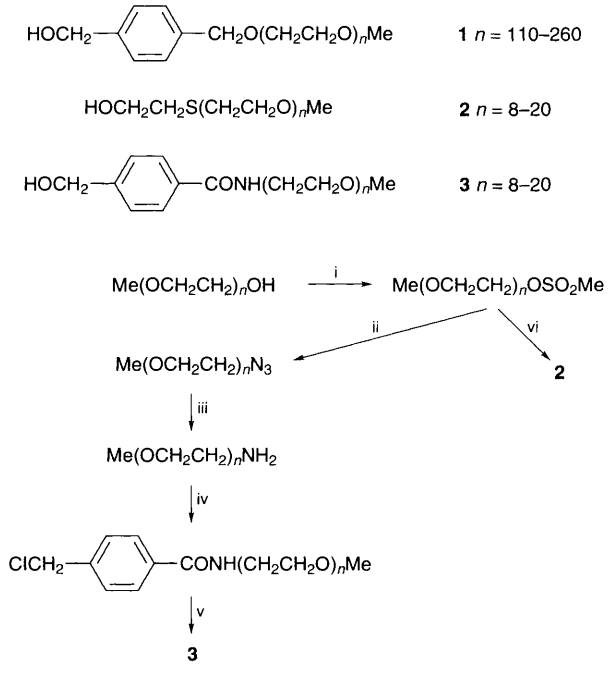
Two novel low molecular weight polyethylene glycol linkers are developed for the solution synthesis of oligosaccharides.

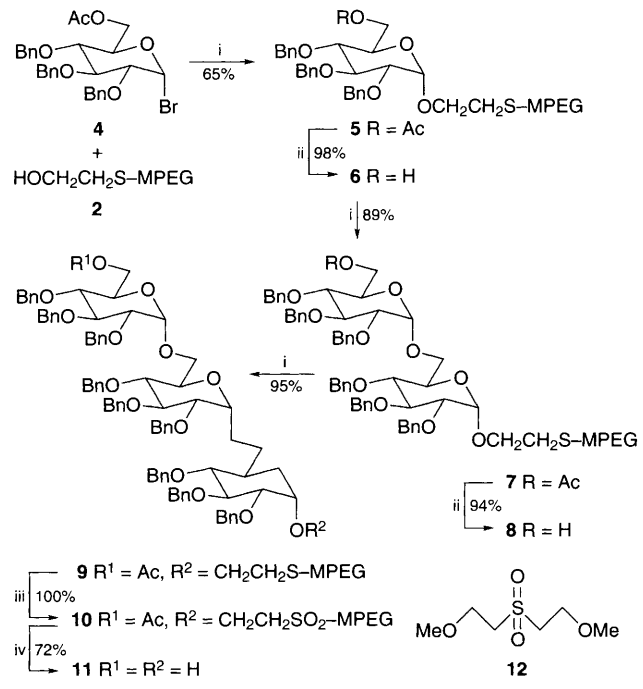
Because of the emerging recognition of the important role of oligosaccharides in many biological processes, the efficient synthesis of oligosaccharides has become a subject of much current interest. In analogy to the oligopeptide and oligonucleotide fields, solid-phase synthesis of oligosaccharides on polystyrene polymers[1] or on silica[2] have been explored. Alternatively, polymer-supported solution synthesis of oligosaccharides using the polyethylene glycol linker **1** has been used.[3] Solution-phase synthesis is believed to offer advantages over solid-phase synthesis because of the greater efficiency of the glycosylation step in solution. The number of repeating ethylene glycol units in **1** is about 110 or about 260. The selection of the molecular weight of the polymer is based on the consideration that the polymer-bound oligosaccharide must remain soluble in the glycosylation step but can be precipitated readily from the solution without contamination of the reagents.[4]

We report here the use of low molecular weight poly(ethyleneglycol)-ω-monomethyl ether (MPEG, average M_w 550, n = *ca.* 8–20) as the supporting polymer. Two novel linkers, **2** and **3**, have been developed. Their syntheses are outlined in Scheme 1.

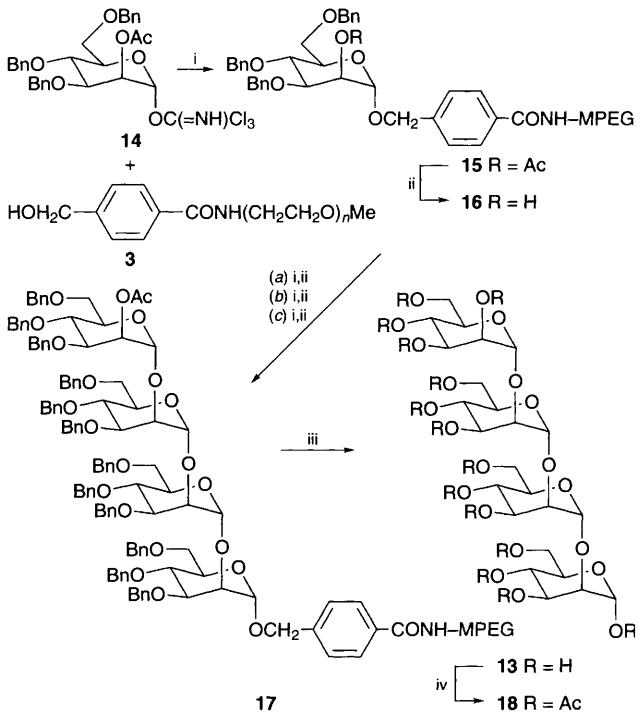


Scheme 1 *Reagents and conditions*: i, Et_3N, 2.0 equiv. $MeSO_2Cl$, CH_2Cl_2, 98.5%; ii, 3.0 equiv. NaN_3, DMF, 80 °C, 5 h, 95%; iii, 40 psi H_2, 10% Pd–C, 3 h, quantitative; iv, 1.5 equiv. 4-chloromethylbenzoic acid, 1.5 equiv. DCC, cat. DMAP, CH_2Cl_2, 24 h, 96%; v, 1.0 equiv. Ag_2CO_3, 0.1 equiv. $AgClO_4$, 24 h, 95%; vi, 2.0 equiv. $HOCH_2CH_2SH$, Et_3N, 24 h, 93%

The use of **2** as a linker is demonstrated by the synthesis of the trisaccharide **11** using a sequence of reactions (Scheme 2) patterned after the chemistry previously developed by us.[5] The MPEG-thioethanol **2** was glycosylated with **4** to give the MPEG-monoasaccharide **5** in 65% yield. Deacetylation of **5** gave the alcohol **6** in 98% yield. A second glycosylation gave the disaccharide **7** in 89% yield. Deacetylation of **7** went in 94% yield to give alcohol **8** which was in turn glycosylated to give the trisaccharide **9** in 95% yield. The trisaccharide can be detached from the polymer linker by first quantitative oxidation of **9** with dioxirane at −78 °C to the corresponding sulfone **10**. Treatment of the sulfone **10** with 3 equiv. of 1 M sodium methoxide in methanol to a cooled (< 0 °C) dilute (0.006 M) solution of the sulfone in THF released the trisaccharide **11** in 72% yield. The use of low molecular weight MPEG as the polymer support retains the normal advantages of polymer-supported solution synthesis of oligosaccharides, *viz*: (1) **2** and its supported synthons were completely soluble in the normal reaction solvents and the efficiency of the various steps followed that expected of solution chemistry; and (2) purification of **2** and its supported synthons by fast column chromatography on silica gel 60 (230–400 mesh, E. Merck) is simplified by the fact that even in neat EtOAc, the MPEG derivatives remain on the baseline while the sugar reagents move rapidly through the column. Changing the solvent to dichloromethane–methanol (4 : 1) or to ethyl acetate–methanol (4 : 1) allows quick elution of the MPEG derivatives. Another advantage of using



Scheme 2 *Reagents and conditions*: i, 2.0 equiv. **4**, 2.0 equiv. Hunig base, CH_2Cl_2, 35 °C, 24 h; ii, K_2CO_3, wet MeOH, 4 h; iii, 2.5 equiv. dioxirane, −78 °C; iv, 3 equiv. NaOMe, MeOH–THF, 0 °C



Scheme 3 *Reagents and conditions*: i, 2.0 equiv. imidate **14**, 0.8 equiv. $Me_3SiOSO_2CF_3$-4, 4 Å molecular sieves, CH_2Cl_2, 0 °C, 2 h; ii, K_2CO_3, wet MeOH, 4 h; iii, 40 psi H_2, 10% Pd–C, MeOH, AcOH, 48 h; iv, Ac_2O, Py, DMAP, 24 h

low molecular weight MPEG is that the reaction can be monitored readily by the usual arsenal of spectroscopic techniques. Thus, in Scheme 2, in each of the coupling steps, the MPEG derivatives **5**, **7** and **9** can be analysed by electrospray mass spectrometry to show clearly the incorporation of the additional saccharide unit. The use of ^1H NMR to monitor the progress of the reactions is also facilitated by the use of the methyl group of MPEG as an internal reference. The one problem in the use of **2** is that in the final cleavage step of the trisaccharide **11** from the MPEG support, compound **12** was obtained as the other product and was only separated from **11** with difficulty.

The problem can be avoided with the use of **3** as the linker. Its application was demonstrated by the synthesis of the tetramannan **13** according to Scheme 3. In this case, the polymer **3** was glycosylated with 2-*O*-acetyl-3,4,6-tribenzyl-α-D-mannopyranosyl trichloroacetimidate **14** using Schmidt's protocol.[6] The acetyl group of the MPEG-monosaccharide **15** was readily removed by base treatment to yield the alcohol **16**. Repetition of the glycosylation and hydrolysis steps three times gave the protected MPEG-tetrasaccharide **17**. Hydrogenolysis of **17** over Pd–C in methanol released the tetrasaccharide **13** from the polymer. Purification and characterisation of **13** were achieved by conversion to the peracetyl derivative **18**. Compound **18** was characterised by electrospray mass spectrometry, ^1H NMR (anomeric hydrogens at δ 6.23, 5.11, 5.08 and 4.95) and ^{13}C NMR (anomeric carbons at δ 91.61, 99.16, 99.57 and 99.96). The overall yield of the peracetyltetramannopyranoside **18** was found to be 10% based on the starting polymer **3**. Again, the use of low molecular weight MPEG aided considerably in the analyses of the progress of the reaction by using conventional spectroscopic techniques. For example, complete NMR ($CDCl_3$, 500 MHz) analyses of the MPEG-supported intermediate **17** revealed fully the extent of coupling, as well as the stereochemistries at the anomeric centres of the tetrasaccharide.

References

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