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A CONVENIENT SYNTHETIC ROUTE TO DIFFERENTIALLY FUNCTIONALIZED LONG CHAIN POLYETHYLENE GLYCOLS

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Abstract: A convenient and efficient synthetic route to differentially functionalized polyethylene glycols (PEGs) starting from cheap commercially available materials is reported. Selectively protected triethylene glycol or tetraethylene glycol have been reacted with a second PEG bearing both a protecting group and a leaving group.

Polyethylene glycols (PEGs) are important components of crown ethers, cryptands and various other types of ion receptors.[1] PEGs are capable of binding metal ions in both their cyclic and non-cyclic form,[2] however their importance stretches beyond their metal ion binding properties. For example, PEGs provide a good anchor for biological receptors,[3] and they are known to reduce the nonspecific binding of proteins and other biological molecules to membrane

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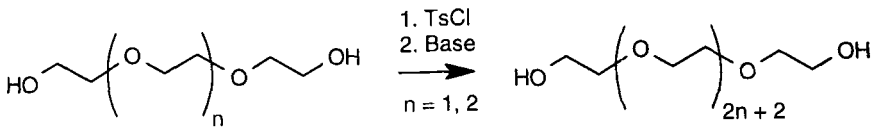
surfaces.[4,5] Furthermore, polyethylene glycol segments (specifically tetraethylene glycols) have been employed as the hydrophilic linkers in a tethered bilayer membrane system recently reported as the integral component of an ion channel switch biosensor.[6] The necessity to integrate polyethylene glycol units of defined length into synthetic molecular devices has made it necessary to develop approaches to the general synthesis of PEGs with (and without) the terminal hydroxyl groups differentiated.

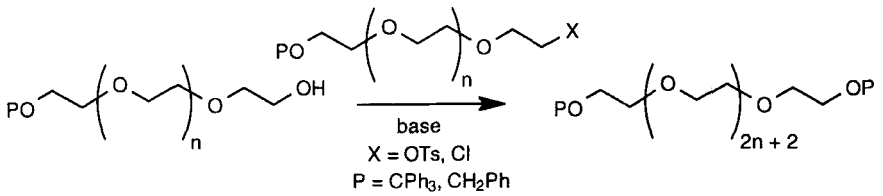
Most reported polyethylene glycol syntheses have employed a classical Williamson-type ether synthesis. For example, in a reported one-pot synthesis of hexa- and octa-ethylene glycols, the precursor glycol was treated with a small mole fraction of *p*-toluenesulfonyl chloride and subsequent base treatment generated the glycol dimer (Scheme 1).[7] In an alternative approach, reaction of the chloro or tosyl derivative of a monobenzylated (or tritylated) polyethylene glycol with one equivalent of a monobenzyl (or -trityl) protected polyethylene glycol afforded a bis-protected polyethylene glycol in good yield (Scheme 2).[8,9]

Mono-deprotection of the products from reactions like Scheme 2 is technically difficult, while monoprotection of the polyethylene glycol *e.g.* from Scheme 1, proceeds in poor yield and generally generates a mixture of products once the system becomes longer than ~12 atoms.[10] In this paper we describe a synthetic route to differentially protected polyethylene glycols. The method involves protection of a precursor ethylene glycol and coupling with a THP-

Scheme 1[7]



Scheme 2[8,9]



protected polyethylene glycol functionalised as the bromide or chloride. The product polyethylene glycol is differentially protected at the two ends and can be fully deprotected to give the desired PEG or selectively deprotected to permit further elaboration.

Tetraethylene glycol was monobenzylated in aqueous media (33% NaOH) with benzyl chloride following the procedure of Coudert.[8] Chain extension was carried out with a range of tetrahydropyranyl (THP) protected polyethylene glycols bearing a suitable leaving group (Cl or Br), under phase transfer conditions,[11] or using sodium hydride as the base (see Table 1). The THP-protected chloro and bromo-substituted ethylene glycols **1-4** were easily prepared from the corresponding halo alcohols in high yield.[12]

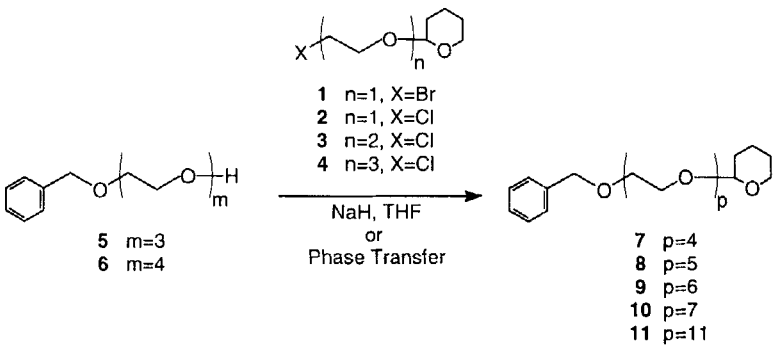


Table 1 Synthesis of doubly protected polyethylene glycols $PhCH_2OCH_2CH_2(OCH_2CH_2)_pOTHP$

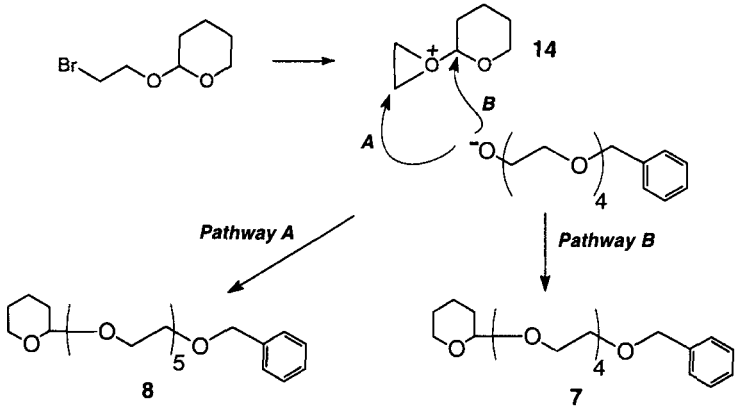
Alcohol	Halide	Method[a]	Product (yield)
6	**1**	**A**	**8** (16%)[b]
6	**2**	**A**	**8** (47%)
5	**3**	**A**	**8** (65%)
6	**3**	**A**	**9** (80%)
6	**4**	**B**	**10** (68%)
13[c]	**12**[c]	**B**	**11** (77%)

a. Method A is the reaction between the alkoxide and halide under phase transfer conditions.[11,12] Method B is the reaction of alkoxide and halide using NaH as base in THF solution.[13]
b. See text and Scheme 3.
c. See text and Scheme 4.

The use of the protected ethylene glycol derivatives **1** and **2** as reagents to extend the polyethylene glycol chain by 1 ethylene glycol unit was complicated by an unexpected THP transfer process. Reaction of the bromide **1**, with the benzyl-protected tetraethylene glycol **6**, afforded the desired pentaethylene glycol product **8** in only 16% yield, however the tetraethylene glycol derivative **7** was also

formed in the reaction (in 22% yield). When the chloro derivative **2** was employed in the same reaction, the yield of **8** was improved to 47%, however 22% of **7** was still obtained. These results can be rationalised by formation of an intermediate oxiranium cation **14** which can suffer attack at either the epoxide carbon (pathway A) or the acetal carbon (pathway B) as depicted in Scheme 3. Pathway B effectively leads to simple THP transfer from **1** to the free hydroxyl group of **6**.

Scheme 3



Pentaethylene glycol **8** can be synthesised readily by an alternative pathway. Reaction of monobenzylated triethylene glycol **5** with the diethylene glycol derivative **3** affords **8** in good yield with no competition from the THP-transfer pathway. The doubly protected polyether chain can be readily deprotected in a stepwise fashion to give the monoprotected PEG or the non-

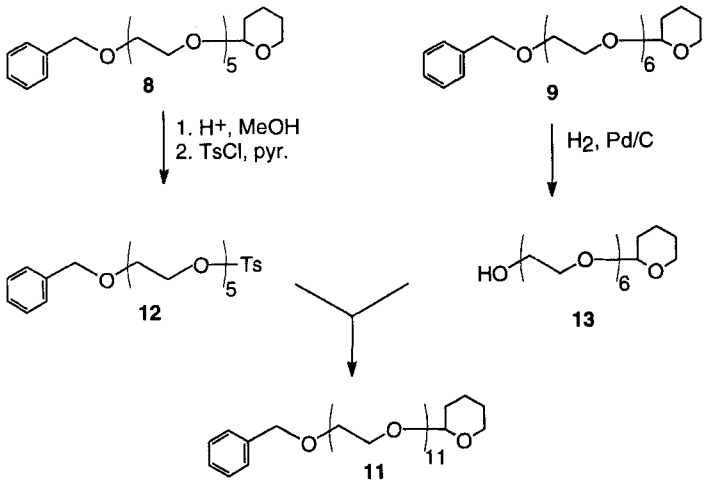
protected diol. THP protection was most easily removed by stirring with HCl/methanol.[13] Benzyl protection was readily removed by catalytic hydrogenation.[14] The polyether chain derived from a coupling sequence can be further extended by selective deprotection of one protecting group and coupling with another protected polyether bearing an appropriate leaving group. For example, the synthesis of a doubly protected 11-mer, **11**, depicted in Scheme 4, was achieved by coupling **12** (formed by deprotection of **8** and derivatisation of the free –OH as a -OTs group) with **13** (formed by deprotection of **9**) with sodium hydride.

Experimental

^{1}H-n.m.r spectra were recorded on Bruker AC-200 (200 MHz) and AMX-400 (400 MHz) spectrometers with samples dissolved in $CDCl_3$ containing tetramethylsilane as internal reference. Electron ionisation (EI) mass spectra were recorded on a modified Kratos Mass Spectrometer calibrated to perfluorokerosene. Chemical ionisation (CI) mass spectra were recorded on a AEI Ms30 spectrometer with methane as the ionising gas. Microanalyses were performed by the Campbell Microanalytical Laboratory, Department of Chemistry, University of Otago, Dunedin, New Zealand.

Preparation of differentially protected polyethylene glycols under phase transfer conditions (Method A). In a typical reaction, an aqueous sodium hydroxide

Scheme 4



solution (33% w/w, 20 eq., 65 ml) was added dropwise to a mixture of the THP protected chlorodiethylene glycol, **3**, (8.4g, 40.2 mmol), tetrabutylammonium hydrogen sulfate (2.0g, 0.1 eq.) and mono-benzyl protected tetraethylene glycol, **6**, (12.7g, 44.7 mmol). The two-phase mixture was stirred vigorously and heated at 85°C for two days under nitrogen. More chlorodiethylene glycol **3** (3.7g, 17.7 mmol) was added and the reaction mixture was stirred at 85°C for further two days. The reaction mixture was cooled, diluted with water (120 ml) and extracted with CH_2Cl_2 (1x100 ml and 3x50 ml). The combined extracts were washed with brine (50 ml) and dried (Na_2SO_4). Removal of the solvent gave the crude product as an orange/yellow liquid, which was purified by flash chromatography using ethyl acetate as the eluent, to yield **9** as a clear oil (16.3g, 80%). ^{1}H NMR, (200

MHz, δ, ppm) 1.4 - 1.9 (m, 6H, THP), 3.59 - 3.69 (m, 24H, O-C$\underline{H}_2$C$\underline{H}_2$-O), 3.85 (m, 2H, O$\underline{THP}$), 4.56 (s, 2H, Ph-C$\underline{H}_2$), 4.63 (t, 1H, $\underline{THP}$), 7.34 (m, 5H, ArH); *m/z* (EI), 456(M^+, 0%), 371(48), 133(10), 105(10), (Found 371.2010, M-THP requires $C_{19}H_{31}O_7$, 371.2070).

Preparation of differentially protected polyethylene glycols using sodium hydride as base (Method B). In a typical reaction, the monobenzyl protected tetraethylene glycol, **6**, (0.5g, 1.76 mmol) in THF (4 ml) was added dropwise to a solution of sodium hydride (1.2 eq., 2.1 mmol) in THF (4 ml) at 0°C and stirred at room temperature for 30 minutes. A solution of 2-THP-chloroethane, **2**, (1.3 eq., 0.38g, 2.29 mmol) in THF (4 ml) was added and stirred under nitrogen at room temperature for 48 hours. Ethanol (10 ml) was added and the mixture was filtered through a Celite plug and the solvent removed. The crude product was purified by flash chromatography with ethyl acetate as the eluent, to give **8** as a colorless liquid (0.27g, 37%). ^{1}H NMR, (200 MHz, δ, ppm) 1.3 - 1.9 (m, 6H, THP), 3.6 - 3.7 (m, 20H, O-C$\underline{H}_2$C$\underline{H}_2$-O), 3.8 (m, 2H, -O$\underline{THP}$), 4.56 (s, 2H, Ph-C$\underline{H}_2$), 4.62 (t, 1H, $\underline{THP}$), 7.26 - 7.33 (m, 5H, Ar$\underline{H}$); *m/z* (EI) 412(M^+, 0%), 327(M-THP, 3), 207(3), 179(17), (Found 327.1790, M-THP requires $C_{17}H_{27}O_6$, 327.1808). Analytical data for **10**; ^{1}H NMR, (200 MHz, δ, ppm) 1.21-1.63 (m, 6H, THP), 3.52-3.69 (m, 28H, O-C$\underline{H}_2$C$\underline{H}_2$-O), 3.81-3.90 (m, 2H, O$\underline{THP}$), 4.56 (s, 2H, Ph-

CH_2-), 4.62 (t, 1H, THP), 7.28-7.35 (m, 5H, ArH); elemental analysis C, 61.6; H, 9.4; calc'd (for $C_{26}H_{44}O_9.0.5\ H_2O$) C; 61.28, H; 8.90.

Analytical data for **11**; ^{1}H NMR, (200 MHz, δ, ppm) 1.21-1.63 (m, 6H, THP), 3.52-3.69 (m, 44H, O-CH_2CH_2-O), 3.81-3.90 (m, 2H, -OTHP), 4.56 (s, 2H, Ph-CH_2), 4.62 (t, 1H, THP), 7.28-7.35 (m, 5H, ArH); *m/z* (CI), 676 (M , 0%), 593(M - THP), 503; elemental analysis C; 60.1, H; 9.0, calc'd (for $C_{34}H_{60}O_{13}$) C; 60.33, H; 8.94.

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12 3,4-Dihydro-2H-pyran (7.1g, 84.7 mmol) was added dropwise to a solution of 2-(2-chloroethoxy)ethanol (8.8g, 70.6 mmol) and the mixture was stirred for 4 hours at room temperature. Solid sodium hydrogencarbonate (2g) was added, the reaction mixture was filtered through Celite and washed with ether. The product **3** was purified by

vacuum distillation (b.p. 50-60°C, Kügelrohr, 0.2 mmHg) and obtained as a clear liquid (12.3g, 80%).

13 In a typical reaction, benzyl-pentaethylene glycol-THP, **8**, (2.95g, 7.19 mmol) was stirred in a mixture of methanol and dichloromethane (1:1 ratio, 50 ml) with a catalytic amount of concentrated hydrochloric acid for 8 hours. Sodium hydrogencarbonate (1g) was added and the mixture then filtered. The solvent was removed under reduced pressure and the resultant clear oil purified by flash chromatography (ethyl acetate as the eluent) to give monobenzyl-pentaethyleneglycol as a colorless clear oil (2.00g, 6.07 mmol, 85%).

14 In a typical reaction, benzyl-hexaethyleneglycol-THP, **9**, (1.27g, 2.78 mmol), 10% Pd/C (0.1 eq.) in absolute ethanol (40 ml) was stirred under hydrogen for 3 hours at room temperature. The reaction mixture was filtered thought a plug of Celite, and the solvent removed by reduced pressure. The crude product was purified by flash chromatography (eluted with 5% MeOH in CH_2Cl_2) to afford pure **13** as a clear oil (0.75g, 74%). Analytical data for **13**; ^{1}H NMR, (200 MHz, δ, ppm) 1.5-1.7 (m, 6H, THP), 3.57-3.74 (m, 22H, O-C$\underline{H_2}$C$\underline{H_2}$-O), 3.81-3.90 (m, 2H, O$\underline{THP}$), 4.62 (t, 1H, $\underline{THP}$); elemental analysis C, 55.3; H, 9.6; calc'd (for $C_{17}H_{34}O_8$) C, 55.72; H, 9.37.

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