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# An easy access to asymmetrically substituted oligoethylene glycols from 18-crown-6

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ABSTRACT

A new route for the preparation of multi-gram quantities of the heterobifunctional oligoethylene glycol (OEG) derivatives ($n = 6, 7$) is reported based on decyclization of 18-crown-6.



Asymmetrically functionalized poly- and oligoethylene glycols [PEG and OEG, respectively, $R^1(OCH_2CH_2)_nOR^2$] have found widespread use in a variety of applied areas due to their hydrophilic,[1,2] nonimmunogenic,[3] and nontoxic[4] properties. They are used as spacers for (bio)molecules, as good anchors for ligands of receptors, and they are known to reduce the nonspecific binding of proteins and other bioactive molecules.[5]

Heterobifunctional OEG derivatives can generally be prepared from commercially available $H(OCH_2CH_2)_nOH$ diols.[6] The key step involves the differentiation of two chemically equivalent terminal hydroxyl groups. This desymmetrization can usually be achieved by preparation of monosubstituted derivatives from symmetrical diols, which was until recently considered a rather ineffective process. This situation changed when an efficient method for selective mono-tosylation of diols in the presence of silver(I) oxide was introduced[7] (note that mesylation proceeds somewhat less selectively[5,8]). This approach is also applicable to benzylation and tritylation and has been used for multigram syntheses of heterobifunctional OEG chains.[9,10]

However, penta- and hexaethylene glycols ($n = 5, 6$) are much more expensive in contrast to shorter analogs.[11] For this reason, we propose an alternative route for the preparation of multigram quantities of the heterobifunctional OEG derivatives ($n = 6, 7$) based on decyclization of crown-ethers, which are several times cheaper than the corresponding OEGs of similar chain length.

The ring-opening reaction of 18-crown-6 (**1**) with $ZrCl_4$ in a toluene–THF mixture at 100 °C is known to lead (in 25% yield) to the formation of a complex with a formula $[ZrCl_2{\cdot}(OCH_2CH_2)_5OCH_2CH_2Cl^+][ZrCl_5(THF)^-]$.[12–15]

After considerable experimentation we developed a preparative version of this process which provided reliable access to gram quantities of $H(OCH_2CH_2)_6Cl$ (**2**)[16] (Scheme 1). The key to the success was the use of nitrobenzene as the solvent, which enabled the reaction temperature to be increased to 135 °C. Product **2** was isolated in 88% yield and further transformed by reaction with $NaN_3$, (DMF, 75 °C) into the corresponding azide $H(OCH_2CH_2)_6N_3$ (**3**)[5] in 81% yield, which was purified by silica gel chromatography. The purity of the isolated azide **3** was sufficient for further chemical transformations including syntheses of valuable and difficult to access targets, such as hexa(hepta)ethylene glycols **8** and **10** (Scheme 2) and *N*-acetylglucosamine derivative **16** with a hexaethylene glycol-based spacer (Scheme 3).

In order to introduce a carboxyl group into hexaethylene glycol azide **3** we examined two different approaches. The first was based on oxidation of the primary hydroxy group in **3** by treatment with $(PyH)_2Cr_2O_7$ in *tert*-butyl alcohol,[17] which resulted in the formation of hexaethylene glycol-derived *tert*-butyl ester **4**, which was purified by silica gel chromatography (27%). Ester **4** was treated with KOH in aq. EtOH to give after acidification the corresponding ω-azidocarboxylic acid **6**.[18–21] Staudinger reduction of the azido group ($Ph_3P/H_2O$) in **6** followed by ion-exchange chromatography gave hexaethylene glycol-derived acid **8** in 77% yield (from **4**).

A more efficient alternative route for the introduction of a carboxy group was based on alkylation of the hydroxy group in

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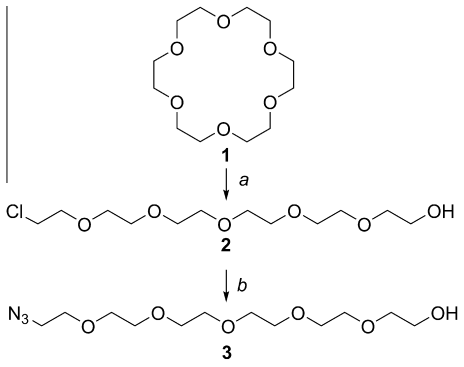


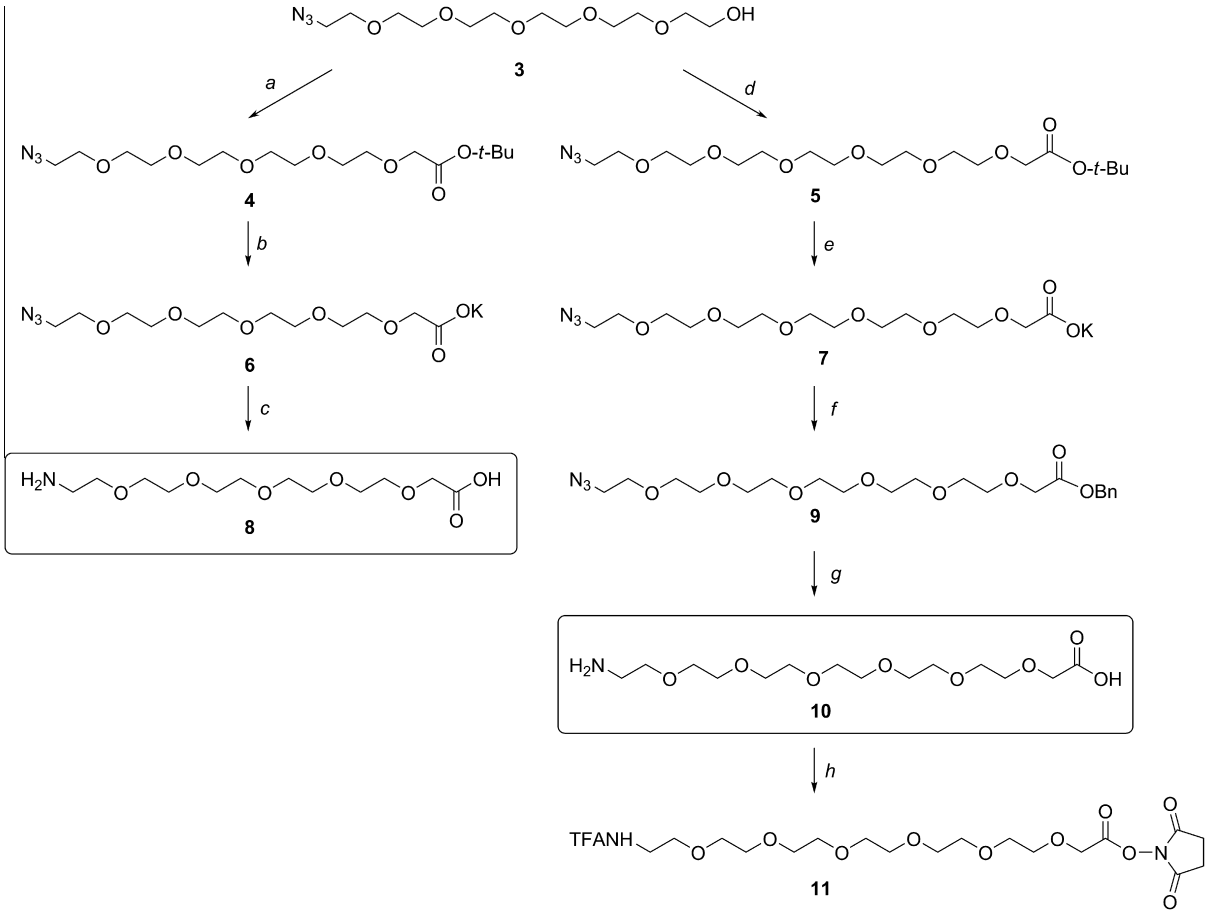
**Scheme 1.** Reagents and conditions: (a) $ZrCl_4$, $PhNO_2$, 135 °C, 36 h, 88%; (b) $NaN_3$, DMF, 75 °C, 15 h, 81%.

hexaethylene glycol azide **3** with *tert*-butyl bromoacetate in DMF in the presence of NaH,[22] which led to the heptaethylene glycol-derived *tert*-butyl ester **5** with a longer chain.[5,8,10] Unlike in reference 5, in our case, product **5** was contaminated with the corresponding carboxylic acid salt, apparently formed by cleavage of the *tert*-butyl ester **5**.[23] For this reason, the crude mixture containing partially hydrolyzed **5** was treated with KOH in aq EtOH to ensure complete hydrolysis into salt **7**[18] followed by benzylation with $PhCH_2Br$ in DMF in the presence of $K_2CO_3$ with subsequent $SiO_2$ chromatography to give benzyl ester **9** in 38% yield (from **3**). Alkaline hydrolysis of benzyl ester in **9** followed by Staudinger reduction of the azido group ($Ph_3P/H_2O$) and subsequent ion-exchange chromatography gave heptaethylene glycol-derived amino acid **10** in 97% yield (from **9**).

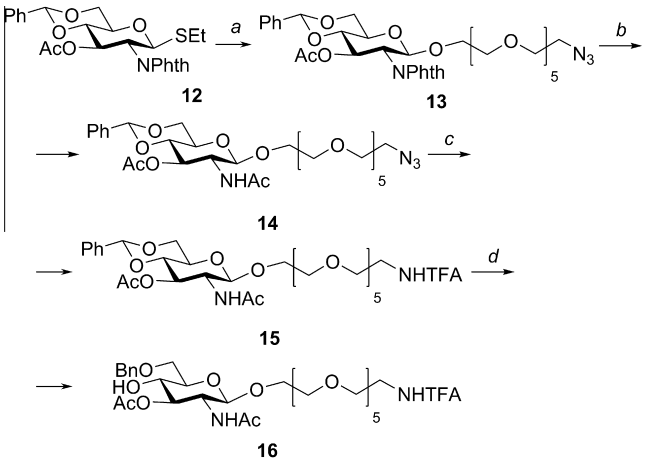
The overall yields of hexa(hepta)ethylene glycol-derived acids **8**[24] and **10** were 17% and 26%, respectively, from inexpensive and commercially available 18-crown-6 (**1**),[25] which makes our approach economically useful and competitive.

Straightforward protection of the amino group in **10** as the *N*-trifluoroacetyl derivative and transformation of the carboxy function into an activated *N*-oxysuccinimidyl ester gave the protected derivative of heptaethylene glycol-derived acid **11** in 91% yield, which was recently applied in the synthesis of spacer-armed glycosides of a hexaarabinofuranoside fragment of *Mycobacterium tuberculosis* lipoarabinomannan, which after conjugation with the recombinant mycobacterial proteins MPB-64 and Rv0934 were transformed into artificial antigens useful for tuberculosis diagnosis.[26]

To demonstrate the synthetic potential of our approach toward hexaethylene glycol-based azide **3**, we also present here the preparation of *N*-acetylglucosamine derivative **16** with a hexaethylene glycol-based aglycon-spacer (Scheme 3). Crude ω-azidoalcohol **3** was glycosylated using known selectively protected 2-deoxy-2-phthalimido-β-D-glucopyranoside (**12**)[27] to give *N*-acetylglucosaminide **13** with a hexaethylene glycol azide spacer in 56% yield after column chromatography. After replacement of the *N*-phthaloyl with an *N*-acetyl group (**13**→**14**) and modification of the



**Scheme 2.** Reagents and conditions: (a) $(PyH)_2Cr_2O_7$, *t*-BuOH, $Ac_2O$, $CH_2Cl_2$, 1 h, 27%; (b) KOH (aq), EtOH; (c) (1). $Ph_3P$, EtOH–25% aq $NH_3$–THF, (2) ion-exchange chromatography (Dowex 50 W × 4 ($H^+$), 1 M py (aq)), 86% from **4**, 23% from **3**, 17% from **1**; (d) NaH, DMF, $BrCH_2CO_2$-*t*-Bu; (e) KOH (aq), EtOH; (f) BnBr, $K_2CO_3$,DMF, 38%; (g) (1) KOH, MeOH; (2). $Ph_3P$, 25% aq $NH_3$, THF, (3) ion-exchange chromatography (Dowex 50 W × 4($H^+$), 1 M py (aq)), 97% from **9**, 37% from **3**, 26% from **1**; (h) (1) $CF_3CO_2Et$, $Et_3N$, MeOH, 5 h, (2) *N*-hydroxysuccinimide, DMAP, DCC, DMF, 0 °C → rt, 91%.




**Scheme 3.** Reagents and conditions: (a) **3**, NIS, $Et_3SiOTf$, $CH_2Cl_2$, −20 °C, 4 Å MS, 1 h, $SiO_2$, 56%; (b) (1) $NH_2(CH_2)_2NH_2$, *i*-$C_5H_{11}OH$, reflux (bath temperature 140 °C), 4 h, (2) $Ac_2O$, py, 1.5 h, $SiO_2$, (20→60 vol % $Me_2CO$ in benzene), 82%; (c) (1) MeONa, MeOH, 16 h, (2) $Ph_3P$, 25% aq $NH_3$–THF–MeOH, 40 °C, 5 h, (3) $CF_3CO_2Et$, $Et_3N$, MeOH, 3 h, (4) $Ac_2O$, py, 16 h, 78%; (d) $NaBH_3CN$, MsOH, THF, 4 Å MS, 4 h, $SiO_2$, 90%.

aglycon (**14**→**15**), compound **15** was obtained in 78% yield. The benzylidene group in *N*-acetylglucosamine **15** was opened selectively by $NaBH_3CN$–MsOH[28] in anhydrous THF to afford new glycosyl acceptor **16** in 90% yield containing an *N*-trifluoroacetamido hexaethylene glycol spacer.

In summary, new routes to asymmetrically substituted OEGs starting from cheap and commercially available 18-crown-6 have been developed.

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## Supplementary data

Supplementary data (experimental procedures and characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.065.

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