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Synthesis of Oligo(ethylene glycol) toward 44-mer

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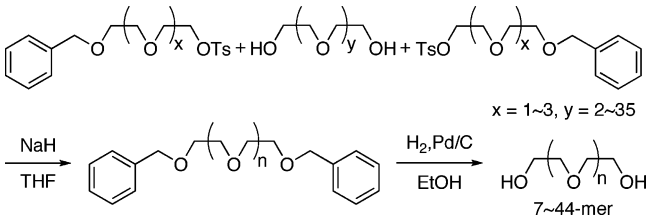

A synthetic method for oligo(ethylene glycol) toward 44-mer (FW = 1956.35) is described. Reiteration of Williamson's ether synthesis and hydrogenation to remove protecting benzyl group affords desired oligo(ethylene glycol) toward 44-mer in moderate yields. The advantages in this method are use of commercially easily available materials as starting materials and procedures avoiding difficulty in purification of the products as much as possible.

Recently, oligo(ethylene glycol) has been a fascinating building compound because of flexibility, chemical stability, water solubility, nontoxicity, property of suppressing nonspecific interaction with protein, and so on.[1] Especially, the property of suppressing nonspecific interaction with protein makes oligo(ethylene glycol) a promising biocompatible material to compose not only various bioactive compounds but also medical analysis devices.[2] Although oligo(ethylene glycol)s below 6-mers and poly(ethylene glycol)s[3] with narrow molecular weight distributions above 2000 molecular weight are commercially available, monodisperse oligo(ethylene glycol)s between 7-mers and 2000 molecular weight are not commercially available; otherwise they are quite expensive and beyond use as starting materials. To the best of our knowledge, a general procedure to synthesize oligo(ethylene glycol) around 2000 molecular weight has not been reported, although there are a few reports including oligo(ethylene glycol) synthesis.[4] On the other hand, monoprotection and monofunctionalization of oligo(ethylene glycol) are quite important procedures for use of oligo(ethylene glycol) as a building compound. Recently, a general synthetic procedure for bifunctional oligo(ethylene glycol) toward 24-mer has been reported,[5] where monoprotection and monofunctionalization of oligo(ethylene glycol) are achieved by using silver(I) oxide[6] without employing an excess amount of oligo(ethylene glycol).[7] This procedure is of great interest; however, there might be room to improve the procedure for longer oligo(ethylene glycol) synthesis, and nonsymmetrical (described in this procedure[5]) and symmetrical oligo(ethylene glycol) syntheses are complementary to each other. This context prompted us to investigate synthesis of oligo(ethylene glycol) by using commercially easily available materials with simple procedures, especially in purification, as much as possible.

As a fundamental synthetic method, we adopted Williamson's ether synthesis where elimination reaction is the most significant side reaction. Two synthetic routes were evaluated as shown in Scheme 1, where PG, OEG, and X represent protecting group, oligo(ethylene glycol), and functional group, respectively. In route 1, excess addition of functionalized monoprotected oligo(ethylene glycol), PG-OEG_1-X, might give better yield against the elimination reaction, and GPC (gel-permeation chromatography) separation of the product and byproducts seems to be easier as the byproducts derived from elimination reaction of PG-OEG_1-X may be much different from the product in molecular weight. To the contrary, the elimination reaction is fatal in route 2, and byproducts derived from elimination reaction of the intermediate, PG-OEG_1-OEG_2-X, could have heavier molecular weights that result in difficulty in GPC separation. In order to reduce influence of the elimination reaction as much as possible, therefore, route 1 was considered to be more suitable than route 2.

First, synthesis of dodeca(ethylene glycol) was examined as a prototype. Monoprotection of tetra(ethylene glycol) was carried out with various common protecting groups as shown in Scheme 2 (step a). With purification at the final step taken into account, benzyl, tetrahydropyranyl, and trityl groups were nominated as protecting groups. After deprotection of those protecting groups, simple procedures such as filtration, solvent evaporation, and solvent extraction are anticipated to give the desired oligo(ethylene glycol) in sufficient purity. All reactions gave sufficient results with small amount of diprotected tetra(ethylene glycol)s by using excess amount of tetra(ethylene glycol), where the excess tetra(ethylene glycol) was easily removed during solvent extraction with chloroform. The obtained crude products were used for subsequent reactions without further purification.

At step b in Scheme 2, tosylation, mesylation, and chlorination were evaluated to functionalize monoprotected tetra-

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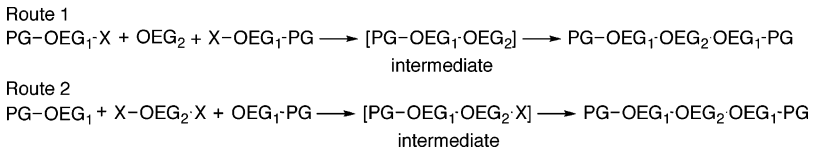
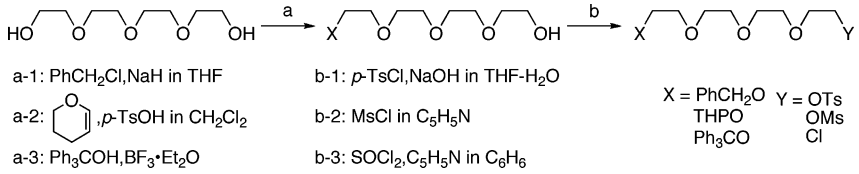
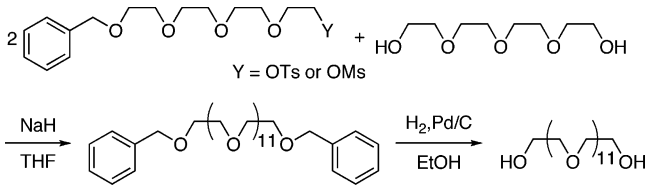
SCHEME 1. Synthesis Route



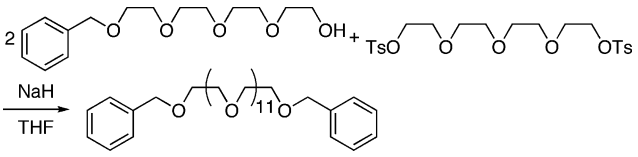
SCHEME 2. Monoprotection and Functionalization of Tetra(ethylene glycol)



SCHEME 3. Synthesis of Dodeca(ethylene glycol)



SCHEME 4. Reaction of Ditosylate with Monoprotected Glycol



(ethylene glycol)s. During tosylation, elimination of the protecting groups was observed in cases of monotetrahydropyranyl- (THP-) and monotrityl-protected tetra(ethylene glycol)s. As a synthetic method for monotetrahydropyranyl-protected oligo(ethylene glycol) tosylate, it has been reported that tetrahydropyranyl protection of oligo(ethylene glycol) monotosylate affords the desired compound in excellent yields.[5] In this procedure, however, strict purification is necessary at the first step, monotosylation of oligo(ethylene glycol), to remove reactive oligo(ethylene glycol) ditosylate which will induce a side reaction. Therefore, benzyl group was employed as a protecting group in this study. Tosylation and mesylation of monobenzyl-protected tetra(ethylene glycol) were successful, but chlorination with thionyl chloride induced bond cleavage of the tetra(ethylene glycol) chain to afford a mixture containing tri(ethylene glycol) derivatives.[5,8] As a consequence, monobenzyl-protected tetra(ethylene glycol) tosylate and mesylate were obtained and used for the subsequent reaction without further purification.[9]

Reaction of monobenzyl-protected tetra(ethylene glycol) tosylate and mesylate (3 equiv) with tetra(ethylene glycol) (1 equiv) was carried out by use of NaH in tetrahydrofuran (THF) to afford dodeca(ethylene glycol) bis(benzyl ether) in 73% and 83% yields, respectively (Scheme 3). Although crude monobenzyl-protected tetra(ethylene glycol) tosylate and mesylate were used, purification by silica gel column chromatography and gel-permeation chromatography afforded pure dodeca(ethylene glycol) bis(benzyl ether).[10] Mesylate showed better results than tosylate, and addition of excess tosylate (4 and 5 equiv) did not improve the yields. However, use of tosylate seemed to be suitable as a general synthetic procedure because the tosylation in THF−H_2O with NaOH is more reasonable than the mesylation in pyridine.[11] Therefore, tosylate was used for further investigation. The final step, benzyl group deprotection, was conducted by hydrogenation in the presence of palladium carbon, and dodeca(ethylene glycol) was obtained in sufficient purity only by filtration off palladium carbon and then evaporation of solvent.[12]

As shown in Scheme 3, the reaction of monobenzyl-protected tetra(ethylene glycol) tosylate with tetra(ethylene glycol) was chosen because this reaction intuitively seemed to better avoid the disadvantageous effect of side reaction induced by tosyl group elimination than did the reaction of tetra(ethylene glycol) ditosylate with monobenzyl-protected tetra(ethylene glycol). In order to evaluate this assumption, reaction of tetra(ethylene glycol) ditosylate with monobenzyl-protected tetra(ethylene glycol) was also conducted under similar conditions (Scheme 4). Similarly, dodeca(ethylene glycol) bis(benzyl ether) was obtained in 62% yield after gel-permeation chromatographic purification, but there was a serious difficulty in purification with silica gel column chromatography, resulting in insufficient purity. This tendency suggests that the reaction of monobenzyl-protected tetra(ethylene glycol) tosylate with tetra(ethylene glycol) (Scheme 3) is superior to the reaction of tetra(ethylene glycol) ditosylate with monobenzyl-protected tetra(ethylene glycol) (Scheme 4) to prevent difficulty in purification.

On the basis of those results in prototype experiments, syntheses of various oligo(ethylene glycol)s were performed, and results are summarized in Table 1. The synthesis of monobenzyl-protected di- and tri(ethylene glycol) tosylate were conducted with similar procedures, and combination of tosylate with oligo(ethylene glycol) depended on desired products. Isolated yields for oligo(ethylene glycol) bis(benzyl ether)s (Bn-OEG) were 66∼80%, and oligo(ethylene glycol)s (OEG) were

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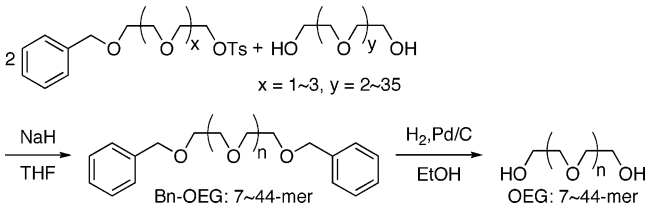
(9) Both crude products contain tetra(ethylene glycol) bis(benzyl ether), which is formed at the monobenzyl protection step in ca. 10% molar ratio.

(10) Eluents for silica gel column and gel-permeation chromatography were 0∼2 vol % $CH_3OH/CHCl_3$ and $CHCl_3$, respectively.

(11) The mesylation of monobenzyl-protected tetra(ethylene glycol) under the same condition as the tosylation gave corresponding mesylate in low yield, and starting material was recovered. Therefore, pyridine was used as solvent and base.

(12) If necessary, oligo(ethylene glycol) was purified by silica gel column chromatography with 5∼10 vol % $CH_3OH/CHCl_3$ as eluent.

TABLE 1. Synthesis of Various Oligo(ethylene glycol)s



-mer	*x*	*y*	Bn-OEG yield[a] (%)	OEG yield (%)
7[b]	1	2	80	98
8[b]	1	3	71	91
9[b]	2	2	79	93
10[b]	2	3	66	98
11[b]	3	2	66	97
12[b]	3	3	73	97
20[c]	3	11	73	93
28[c]	3	19	75	94
36[c]	3	27	77	95
44[c]	3	35	69	98

[a] Bn-OEG yields are calculated based on starting oligoethylene glycols. [b] Reaction conditions: oligo(ethylene glycol) 5 mmol, monobenzyl-protected oligo(ethylene glycol) tosylate 15 mmol, NaH 100 mmol, THF 250 mL, reflux, 24 h; oligo(ethylene glycol) bis(benzyl ether) 5 mmol, 5 wt % Pd/C 200 mg, H_2 8 atm, EtOH 130 mL, 100 °C, 24 h. [c] Reaction conditions: oligo(ethylene glycol) 1 mmol, monobenzyl-protected oligo(ethylene glycol) tosylate 3 mmol, NaH 20 mmol, THF 70 mL, reflux, 24 h; oligo(ethylene glycol) bis(benzyl ether) 1 mmol, 5 wt % Pd/C 200 mg, H_2 8 atm, EtOH 100 mL, 100 °C, 24 h.

obtained in quantitative yields.[13] Until reaching an oligo(ethylene glycol) 44-mer, a series of Williamson's ether synthesis and hydrogenation to remove protecting benzyl group was reiterated five times. Fortunately, oligo(ethylene glycol) bis(benzyl ether), even that of 44-mer, was distributed to the organic layer in solvent extraction, so the same procedure could be applied for all experiments.[14] As shown in Table 1, the yields were almost constant regardless of chain length of oligo(ethylene glycol) where similar reaction conditions were employed. This result shows that any monodisperse oligo(ethylene glycol), at least toward 44-mer, can be synthesized with this method.

In conclusion, a general synthetic method for oligo(ethylene glycol) toward 44-mer (FW = 1956.35), being a reiteration of Williamson's ether synthesis and hydrogenation to remove protecting benzyl group, was established in moderate yields by using commercially easily available materials. The noteworthy feature in this method is that the reaction of monobenzyl-protected tetra(ethylene glycol) tosylate with oligo(ethylene glycol) affords almost constant yields regardless of the chain length of the oligo(ethylene glycol) used.

(13) Purification for oligo(ethylene glycol) bis(benzyl ether) was performed by gel-permeation chromatography. On the other hand, most oligo(ethylene glycol)s were obtained in sufficient purity only by filtration off palladium carbon and evaporation of solvent.

(14) In order to enhance product distribution to organic layer, 4-(dodecyloxy)benzyl group was adopted as a protecting group instead of benzyl group (see Supporting Information). In the synthesis of dodeca(ethylene glycol), yields for each steps with 4-(dodecyloxy)benzyl protecting group were similar to those with benzyl protecting group. However, purification of dodeca(ethylene glycol) bis(4-(dodecyloxy)benzyl ether) by gel-permeation chromatography was much easier, and purification of dodeca(ethylene glycol) was performed by solvent extraction where dodeca(ethylene glycol) and 4-(dodecyloxy)toluene distributed to aqueous and organic layers, respectively. This result implies that improvement in the purification process is possible by modification of the benzyl protecting group.

Experimental Section

General Synthetic Procedures for Bn-OEG (7−∼12-mer). In a three-necked flask were put oligo(ethylene glycol) (5 mmol), NaH (2.40 g, 100 mmol), and dry THF (200 mL), and a dry THF solution (50 mL) of monobenzyl-protected oligo(ethylene glycol) tosylate (15 mmol) was added to the mixture dropwise at room temperature. The reaction mixture was refluxed for 24 h and then allowed to cool at room temperature. Methanol was added to the reaction mixture to quench excess NaH. The solvent was evaporated, and the product was extracted with 5 wt % aqueous HCl and $CHCl_3$. The product obtained by solvent evaporation was purified by gel-permeation chromatography (GPC) as a colorless liquid.

General Synthetic Procedures for OEG (7−∼12-mer). Oligo(ethylene glycol) bis(benzyl ether) (5 mmol), palladium carbon (5 wt %, 200 mg), and EtOH (130 mL) were put in an autoclave, and the autoclave was sealed. H_2 gas (8 atm) was introduced into the autoclave, and the reaction mixture was stirred for 24 h at 100 °C. The autoclave was allowed to cool at room temperature and depressurized to open. The product was obtained by filtration off palladium−carbon and solvent evaporation as a colorless liquid.

General Synthetic Procedures for Bn-OEG (20−∼44-mer). In a three-necked flaskwere put oligo(ethylene glycol) (1 mmol), NaH (480 mg, 20 mmol), and dry THF (50 mL), and dry THF solution (20 mL) of monobenzyl-protected tetra(ethylene glycol) tosylate (90% purity, 1.46 g, 3 mmol) was added to the mixture dropwise at room temperature. The reaction mixture was refluxed for 24 h and then allowed to cool at room temperature. Methanol was added to the reaction mixture to quench excess NaH. The solvent was evaporated, and the product was extracted with 5 wt % aqueous HCl and $CHCl_3$. The product obtained by solvent evaporation was purified by gel-permeation chromatography (GPC) as a colorless solid (only OEG_{20} was a colorless liquid.).

General Synthetic Procedures for OEG (20−∼44-mer). Oligo(ethylene glycol) bis(benzyl ether) (1 mmol), palladium carbon (5 wt %, 200 mg), and EtOH (100 mL) were put in an autoclave, and the autoclave was sealed. H_2 gas (8 atm) was introduced into the autoclave, and the reaction mixture was stirred for 24 h at 100 °C. The autoclave was allowed to cool at room temperature and depressurized to open. The product was obtained by filtration off palladium−carbon and solvent evaporation as a colorless waxy solid.

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Supporting Information Available: Detailed synthetic procedures, compound characterization data, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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