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Multigram Synthesis of Well-Defined Extended Bifunctional Polyethylene Glycol (PEG) Chains

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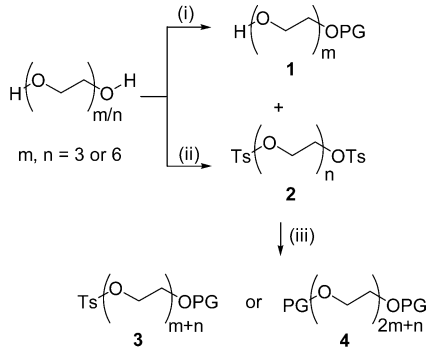
A series of novel, well-defined, unsymmetrical poly(ethylene glycol) chains of the type $X(OCH_2CH_2)_nY$ (where X = protecting group; Y = nucleofuge or a different protecting group; n = 3, 6, 9, 12, 15, 18, and 24) were prepared in high yields by applying orthogonal protecting groups. The purity of the compounds was fully verified by elemental and high-resolution mass spectrometry analyses.

Introduction

The incorporation of hydrophilic poly(ethylene glycol) (PEG) units into peptides, proteins, and biopolymers often transforms their physical properties and biological activities.[1] Exploited extensively in the design and synthesis of biomolecules, the efficacy of these modified compounds are often dependent on the length of the PEG chains attached. Nevertheless, the synthesis of long monodisperse PEG_n chains $H(OCH_2CH_2)_nOH$ (where $n \geq 12$) is rare and remains a synthetic challenge. Extended homologues are most commonly prepared from shorter, commercially available PEG chains from mono- or difunctionalized derivatives **1** and **2** (Scheme 1). This strategy is limited by the availability of monoprotected and bifunctional PEGs (**1** and **3**).[2,3] As an excess of one of the reactants is needed to maximize the yield of these unsymmetrical PEGs,[4] further extension of the chain length becomes an impractical and expensive exercise. To date, examples of long PEGs are limited to no more than a handful of symmetrical diols $H(OCH_2CH_2)_nOH$, where n = 12,[5,6] 13,[7] 14,[8] 18,[9] 28,[6] and 42.[9] Purification procedures for these compounds were rarely reported, and characterization data were often poor or nonexistent.

SCHEME 1. Reported Synthesis of Extended Symmetrical PEG Chains[a]



[a] Key: (i) Monoprotection; (ii) ditosylation; (iii) coupling.

Unsymmetrical PEG_n chains were prepared by Williamson reaction between a monoprotected diol with a monoprotected halide (Scheme 2). PEGs with up to 12 ethylenoxy units were obtained by this method with yields between 16 and 80%.[10] However, due to the forcing conditions required for the ether synthesis (>100 °C for 3 days), the formation of side products becomes a significant issue for certain chain lengths.[11] In a different approach, 2-(benzyloxy)ethanol and potassium hydride were used, as initiator and base, respectively, in a controlled anionic polymerization of ethylene oxide, to

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† Exeter University.

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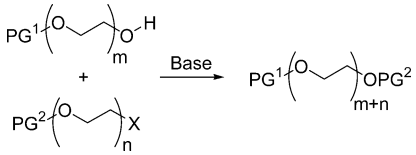
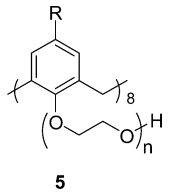
SCHEME 2. Reported Synthesis of Extended Unsymmetrical PEG Chains (X = Nucleofuge)[a]



[a] PG = CPh_3, CH_2Ph, THP.



5

FIGURE 1.

give PEG monobenzyl ethers with molecular weights of 1000, 2000, and 4500 amu with polydispersities (M_w/M_n) of 1.04 or less. However, the procedures are technically demanding, as the purity of the reagents and solvents were found to be critical for reproducible results.[12]

As part of our ongoing study of hydrophilic and functionalized calix-[8]-arenes **5** (Figure 1),[2] we required access to extended unsymmetrical bifunctional PEG_ns (particularly those with $n \geq 12$). In this paper, we report the development of a general procedure for the preparation of unsymmetrical PEG_n chains of the type $X(OCH_2CH_2)_nY$ (where X = protecting group; Y = nucleofuge or a different protecting group; n = 3, 6, 9, 12, 15, 18, and 24), by the introduction of orthogonal protecting groups in a specific sequence. Successive chain extensions may then be achieved using these unsymmetrical PEGs (Scheme 3).

Results and Discussion

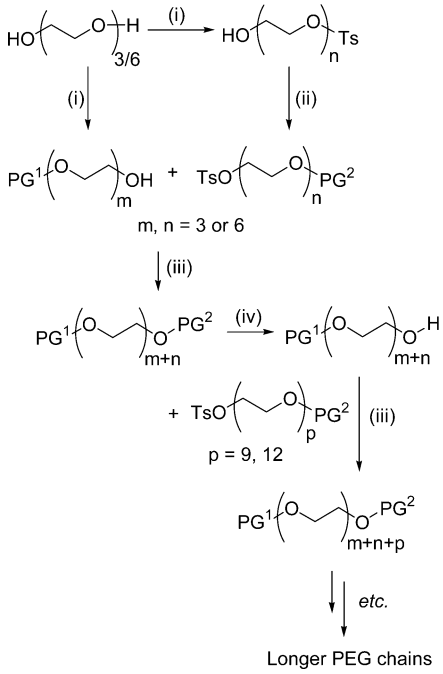
Monofunctionalization of Poly(ethylene glycol) Diols (Scheme 4). Using substoichiometric amounts of dihydropyran (Method A), the introduction of a THP protecting group furnished products **6** and **7** only in low to moderate yields (≤55%). Coupled this with known problems of THP transfer during subsequent ether synthesis,[10] the use of this fragile protecting group was generally not used in this initial step.

In contrast, monotosylation (Method B) and benzylation (Method C) of symmetrical diols may be achieved in the presence of freshly prepared silver(I) oxide, using stoichiometric amounts of the reagents.[13] The presence of potassium iodide is not always necessary, e.g., for the preparation of **8**, a very high yield (92%) can be achieved without the presence of the additive. Commercially available PEG_3 and PEG_6 diols can thus be desymmetrized, furnishing monofunctionalized tosylate and benzyl-protected PEGs **8**−**11** in good to excellent yields and high purity.

With slight modifications, the procedure is applicable for the introduction of a *p*-methoxybenzyl (PMB) group, furnishing **12** and **13** in reasonably good yields. Rather surprisingly (Table 1), the introduction of the PMB group onto the PEG_6 diol was considerably slower than the corresponding benzylation reaction, requiring elevated temperatures for a respectable yield of the monoprotected diol **13** (Method D, 67%).

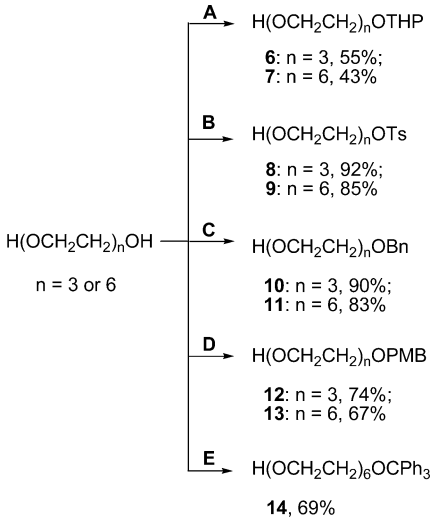
Using similar reaction conditions, the bulky trityl protecting group may also be introduced onto PEG_6 diol to furnish **14** in a fairly good yield (Method E).

SCHEME 3. Proposed Route for the Preparation of Long PEG Chains[a]



[a] Key: (i) Desymmetrization; (ii) tosylation; (iii) extension; (iv) deprotection.

SCHEME 4. Desymmetrization of PEG-diols[a]



[a] Method A: dihydropyran, *p*-TsOH, 2 h, room temperature. Method B: TsCl, Ag_2O, KI (needed only for PEG_6), CH_2Cl_2, 15−20 min, 0 °C. Method C: BnBr, Ag_2O, KI, CH_2Cl_2, 2 h, room temperature. Method D: PMBCl, Ag_2O, KI, toluene, reflux (2 h, room temperature for PEG_3). Method E: TrCl, Ag_2O, KI, CH_2Cl_2, reflux.

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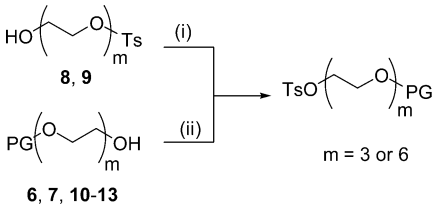
TABLE 1. Reaction Optimization for the Synthesis of 13 by Method D (Scheme 4)[a]

reaction time/h	KI/equiv	solvent	temperature	% yield[b]
2	0.2	CH_2Cl_2	ambient	36
15	0.2	CH_2Cl_2	reflux	51
15	0.2	toluene	reflux	58
16	0.5	toluene	reflux	66
17	0.6	toluene	reflux	67
17	0.8	toluene	reflux	64

[a] Typical reaction conditions: PEG_6 diol (1 equiv), PMBCl (1.1 equiv), Ag_2O (1.5 equiv). [b] Isolated yields after purification.

SCHEME 5. Bifunctional PEG_3 and PEG_6 Units[a]



[a] Key: (i) protection; (ii) tosylation.

TABLE 2. Preparation of $TsO(CH_2CH_2O)_mPG$ (Scheme 5)[a]

entry	*m*	product	method	% yield[b]
1	3	$TsO(CH_2CH_2O)_3Bn$ (**15**)	A	66 (61)
2			B	90 (81)
3	6	$TsO(CH_2CH_2O)_6Bn$ (**16**)	A	83 (71)
4			B	91 (76)
5	3	$TsO(CH_2CH_2O)_3PMB$ (**17**)	A	74 (68)
6			B	81 (60)
7	6	$TsO(CH_2CH_2O)_6PMB$ (**18**)	A	67 (57)
8			B	74 (50)
9	3	$TsO(CH_2CH_2O)_3THP$ (**19**)	A	98 (90)
10			B	79 (43)
11	6	$TsO(CH_2CH_2O)_6THP$ (**20**)	A	96 (82)
12			B	85 (37)

[a] Method A: protection of monotosylate. Method B: tosylation of monoprotected diol. [b] Isolated yields after purification. Value in parentheses is the overall yield over two steps from the commercially available diol.

These desymmetrization reactions were not applicable to the longer PEG diols. Attempted monotosylation of PEG_{12} and PEG_{18} diols (prepared earlier through the nondirectional route, described in Scheme 1) led to a mixture of the starting material, as well as mono- and ditosylated products in roughly statistical ratios.

Monoprotected PEG_3 and PEG_6 Tosylates (Scheme 5, Table 2). The desymmetrized diols may either be subjected to protection (**8** and **9**, Method A, with THP, Bn, or PMB) or tosylation (**6**, **7**, **10**−**13**, Method B) to furnish bifunctional PEGs in high yields. The synthesis of tosylates **15**−**20** can be accomplished in moderate to good yields (57−90%) from the corresponding diols over two steps. To the best of our knowledge, this represents the shortest, highest yielding synthesis of these bifunctional molecules.

In contrast, we failed repeatedly in our attempts to chlorinate the monobenzyl-protected **11** using thionyl chloride (with or without pyridine), even though it has been previously reported to proceed in high yields.[14] GC-MS analysis of the crude reaction mixture revealed the presence of the desired product $Bn(OCH_2CH_2)_6Cl$ (36%), accompanied by a significant amount of the truncated $Bn(OCH_2CH_2)_4Cl$ (34%), which corresponded to a loss of two ethylenoxy units. Attempted chlorination of $Bn(OCH_2CH_2)_9OH$ led similarly to a mixture of $Bn(OCH_2CH_2)_9Cl$ (43%) and, interestingly, $Bn(OCH_2CH_2)_8Cl$ (24%), with a loss of only one ethylenoxy unit in this instance. Indeed, the reaction between polyethylenoxy alcohols and thionyl chloride is known to be prone to competitive "depolymerization" reactions, as was reported previously by Bushby et al.[11] As a result, only the tosylates **15**−**20** were utilized as electrophilic precursors in our subsequent work on PEG chain extensions.

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SCHEME 6. First Extension for the Synthesis of Unsymmetrical PEG_9 and PEG_{12} Chains

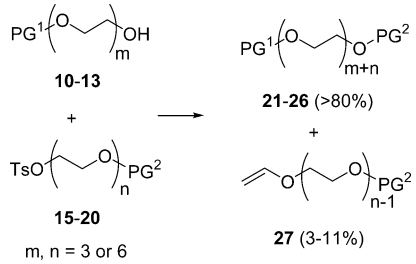


TABLE 3. Synthesis of Unsymmetrically Protected PEG_9 to PEG_{12} Chains[a]

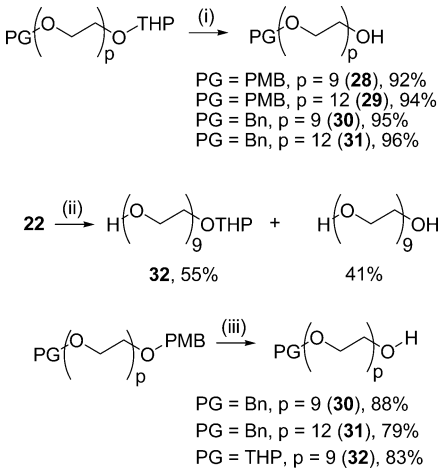
entry	PG_1 (*m*)	PG_2 (*n*)	product	% yield[b]
1	PMB (6)	THP (3)	$PMB(OCH_2CH_2)_9OTHP$ (**21**)	80 (11)
2	Bn (3)	THP (6)	$Bn(OCH_2CH_2)_9OTHP$ (**22**)	84 (6)
3	Bn (6)	THP (3)		81 (7)
4	Bn (3)	PMB (6)	$Bn(OCH_2CH_2)_9OPMB$ (**23**)	83 (8)
5	PMB (6)	Bn (3)		87 (3)
6	PMB (6)	THP (6)	$PMB(OCH_2CH_2)_{12}OTHP$(**24**)	86 (4)
7	PMB (6)	Bn (6)	$Bn(OCH_2CH_2)_{12}OPMB$ (**25**)	84 (9)
8	Bn (6)	PMB (6)		83 (5)
9	Bn (6)	THP (6)	$Bn(OCH_2CH_2)_{12}OTHP$ (**26**)	85 (6)

[a] Reaction conditions: the alcohol was stirred with 1.8 equiv of NaH in THF for 20 to 24 h, prior to the addition of the tosylate, and reacted further for 3 days. [b] Isolated yields after purification. Value in parentheses correspond to % yield of the vinyl ether side product **27**.

First Extension−**Synthesis of Unsymmetrical PEG_9 and PEG_{12} Chains** (Scheme 6, Table 3). Reaction of the bifunctional PEG chains **15**−**20** with the monoprotected alcohols **10**−**13** led to orthogonally protected PEGs containing up to 12 ethylenoxy units. Provided that the alcohol component was allowed to react with the base up to 24 h prior to the addition of the electrophilic component, very little vinyl ether side product **27** (resulting from elimination of the tosylate[11]) was formed, which can be easily removed by column chromatography, furnishing the requisite extended chains in good yields (>80%).

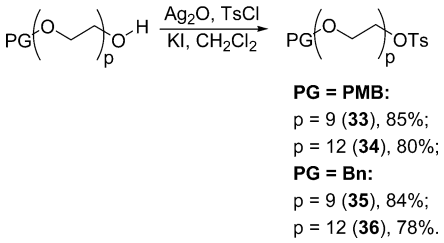
Selective (Mono-) Deprotection and Tosylation (Scheme 7). The protecting groups were selectively removed, furnishing a hydroxyl site for further chain extension. Compatibility issues between the three different protecting groups needed to be taken into account at this stage. For example, the benzylic protecting groups were stable under the acidic conditions required for the deprotection of the THP group, but not vice versa. Likewise, PMB may be oxidatively cleaved in the pres-

SCHEME 7. Selective Monodeprotection of Bifunctional PEGs[a]

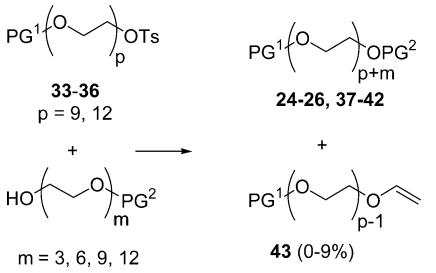


[a] Key: (i) H^+, $MeOH/CH_2Cl_2$, rt; (ii) 10% $Pd(OH)_2/C$, EtOH, cyclohexene, reflux; (iii) CAN, CH_3CN/H_2O, rt.

SCHEME 8. Tosylation of Compounds 28−31



SCHEME 9. Second Extension for the Synthesis of Unsymmetrical PEG_{p+m}, Where $p + m = 12-24$



ence of Bn in high yields.[15] These trends dictate that selective monodeprotection of these bifunctional molecules has to be performed in the following order: THP > PMB > Bn.

Tosylation of the monoprotected **28**−**31** diols using TsCl/pyridine led to persistent, inseparable mixtures of the tosylate $PG(OCH_2CH_2)_nOTs$ and chloride $PG(OCH_2CH_2)_nCl$ derivatives. This problem was overcome by adopting the silver(I) oxide-mediated tosylation described previously, which furnished the desired bifunctional PEG_9 and PEG_{12} chains **33**−**36** in high yields (Scheme 8).

Second Chain Extension−Synthesis of Higher Homologues (Scheme 9, Table 4). These unsymmetrical bifunctional PEGs **33**−**36** were subjected to further chain extensions to access higher homologues. Adopting the previously described reaction procedure, unsymmetrical elongated PEG chains up to 24 ethylenoxy units (PEG_{24}) may be prepared in high yields. Concomitant formation of a small amount of the vinyl ether product **43** was once again observed, which may be removed by column chromatography.

TABLE 4. Synthesis of Unsymmetrically Protected PEG_{12} to PEG_{24} Chains[a]

entry	PG_1 (*p*)	PG_2 (*m*)	product	% yield[b]
1	PMB (9)	THP (3)	$PMB(OCH_2CH_2)_{12}OTHP$ (**24**)	81 (9)
2	Bn (9)	PMB (3)	$Bn(OCH_2CH_2)_{12}OPMB$ (**25**)	88 (0)
3	PMB (9)	Bn (3)		84 (5)
4	Bn (9)	THP (3)	$Bn(OCH_2CH_2)_{12}OTHP$ (**26**)	83 (7)
5	Bn (9)	PMB (6)	$Bn(OCH_2CH_2)_{15}OPMB$ (**37**)	87 (4)
6	PMB (12)	Bn (3)		81 (0)
7	Bn (9)	THP (6)	$Bn(OCH_2CH_2)_{15}OTHP$ (**38**)	88 (0)
8	Bn (9)	THP (9)	$Bn(OCH_2CH_2)_{18}OTHP$ (**39**)	81 (7)
9	Bn (12)	THP (6)		80 (7)
10	Bn (9)	PMB (9)	$Bn(OCH_2CH_2)_{18}OPMB$ (**40**)	85 (8)
11	Bn (12)	PMB (6)		91 (3)
12	PMB (9)	THP (9)	$PMB(OCH_2CH_2)_{18}OTHP$ (**41**)	90 (4)
13	Bn (12)	PMB (12)	$Bn(OCH_2CH_2)_{24}OPMB$ (**42**)	83 (0)

[a] Reaction conditions: same as before (Table 3). [b] Isolated yields after purification. Value in parentheses corresponds to isolated yield of the vinyl ether side product **43**.

Due to the relatively high molecular weight and fragility of these molecules, the veracity of all the compounds prepared above was validated by high-resolution ES or FAB mass spectrometry, in addition to microanalysis data (Table 5).[11] In all cases, the HRMS revealed the presence of a monodispersed species with the predicted molecular weight (Figure 2). In all but one of the samples analyzed, the $[M + Na^+]$ ion was observed as the predominant ion.

Conclusion

In summary, we have developed a viable and high-yielding strategy for the preparation of elongated, monodispersed PEGs. A series of novel unsymmetrical PEG_3, PEG_6, PEG_9, PEG_{12}, PEG_{15}, PEG_{18}, and PEG_{24} of distinct chain lengths were synthesized from commercially available PEG_3 and PEG_6 diols. The methodology is used routinely in our laboratory for the synthesis of these elongated PEGs on a multigram scale (>10 g demonstrated in a few cases). Proof of purity is provided by comprehensive microanalytical data, as well as high-resolution MS data.

Experimental Section

Special Note on Nomenclature. To avoid excessive use of a long series of numbers, the mathematical shorthand for expressing arithmetic progressions is used to denote the positions of oxygen atoms in the elongated PEG chains, e.g., 35-benzyloxy-3n_{33}^3-undecaoxapentatriacontan-1-ol (compound **31**) refers to 35-benzyloxy-3,6,9,12,15,18,21,24,27,30,33-undecaoxapentatriacontan-1-ol.

General Procedures for the Monoprotection of Poly(ethylene glycol)s (Scheme 4): **Method A.** To an ice-cold (0 °C) solution of the diol (1 equiv) and 2,3-dihydro-2*H*-pyran (1.1 equiv) in DCM was added *p*-toluenesulfonic acid monohydrate (0.2 equiv). The mixture was stirred for 10 min and then warmed gradually to room temperature and stirred for an additional 2 h. H_2O was then added to the mixture and the solution extracted with DCM. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered,

(15) Wright, J. A.; Yu, J.; Spencer, J. B. *Tetrahedron Lett.* **2001**, *42*, 4033−4036.

TABLE 5. Elemental and HRMS Data for All Prepared PEG Chains

compd (molecular formula)	microanalysis/%[a] C	H	HRMS[b]
6 ($C_{11}H_{22}O_5$)	56.57 (56.39)	9.39 (9.46)	257.1346 (257.1365, M + Na^+)
7 ($C_{17}H_{34}O_8$)	55.70 (55.72)	9.38 (9.35)	389.2187 (389.2151, M + Na^+)
8 ($C_{13}H_{20}O_6S$)	51.18 (51.30)	6.52 (6.62)	305.1054[c] (305.1059, MH^+)
9 ($C_{19}H_{32}O_9S$)	52.19 (52.28)	7.47 (7.39)	459.1624 (459.1665, M + Na^+)
10 ($C_{13}H_{20}O_4$)	65.03 (64.98)	8.46 (8.39)	263.1246[c] (263.1259, M + Na^+)
11 ($C_{19}H_{32}O_7$)	61.47 (61.27)	8.68 (8.66)	395.2051[c] (395.2046, M + Na^+)
12 ($C_{14}H_{22}O_5$)	62.17 (62.20)	8.18 (8.20)	293.1376[c] (293.1365, M + Na^+)
13 ($C_{20}H_{34}O_8$)	59.59 (59.68)	8.71 (8.51)	425.2164[c] (425.2151, M + Na^+)
14 ($C_{31}H_{40}O_7$)	70.85 (70.97)	7.59 (7.68)	547.2620 (547.2672, M + Na^+)
15 ($C_{20}H_{26}O_6S$)	60.90 (60.89)	6.71 (6.64)	417.1343[c] (417.1348, M + Na^+)
16 ($C_{26}H_{38}O_9S$)	59.25 (59.30)	7.21 (7.27)	549.2105 (549.2134, M + Na^+)
17 ($C_{21}H_{28}O_7S$)	59.49 (59.42)	6.73 (6.65)	447.1489 (447.1453, M + Na^+)
18 ($C_{27}H_{40}O_{10}S$)	58.29 (58.26)	7.40 (7.24)	579.2194 (579.2240, M + Na^+)
19 ($C_{18}H_{28}O_7S$)	55.77 (55.65)	7.41 (7.27)	411.1450 (411.1453, M + Na^+)
20 ($C_{24}H_{40}O_{10}S$)	55.49 (55.37)	7.67 (7.74)	543.2289 (543.2240, M + Na^+)
21 ($C_{31}H_{54}O_{12}$)	60.30 (60.17)	8.72 (8.80)	641.3443 (641.3513, M + Na^+)
22 ($C_{30}H_{52}O_{11}$)	61.26 (61.20)	8.82 (8.90)	611.3343 (611.3407, M + Na^+)
23 ($C_{33}H_{52}O_{11}$)	63.41 (63.44)	8.34 (8.39)	647.3430[c] (647.3407, M + Na^+)
24 ($C_{37}H_{66}O_{15}$)	59.09 (59.18)	8.84 (8.86)	773.4300 (773.4299, M + Na^+)
25 ($C_{39}H_{64}O_{14}$)	61.74 (61.89)	8.63 (8.52)	779.4124 (779.4194, M + Na^+)
26 ($C_{36}H_{64}O_{14}$)	59.82 (59.98)	8.85 (8.95)	743.4120 (743.4194, M + Na^+)
28 ($C_{26}H_{46}O_{11}$)	58.39 (58.41)	8.79 (8.67)	557.2866 (557.2938, M + Na^+)
29 ($C_{32}H_{58}O_{14}$)	57.76 (57.64)	8.91 (8.77)	689.3663 (689.3724, M + Na^+)
30 ($C_{25}H_{44}O_{10}$)	59.65 (59.51)	8.61 (8.79)	527.2774 (527.2832, M + Na^+)
31 ($C_{31}H_{56}O_{13}$)	58.37 (58.47)	8.89 (8.86)	659.3622 (659.3619, M + Na^+)
32 ($C_{23}H_{46}O_{11}$)	55.32 (55.40)	9.34 (9.30)	521.2856 (521.2938, M + Na^+)
33 ($C_{33}H_{52}O_{13}S$)	57.36 (57.54)	7.57 (7.61)	711.2915 (711.3026, M + Na^+)
34 ($C_{39}H_{64}O_{16}S$)	56.97 (57.06)	7.79 (7.86)	843.3845 (843.3813, M + Na^+)
35 ($C_{32}H_{50}O_{12}S$)	58.21 (58.34)	7.76 (7.65)	681.2870 (681.2921, M + Na^+)
36 ($C_{38}H_{62}O_{15}S$)	57.84 (57.70)	8.07 (7.90)	813.3478 (813.3707, M + Na^+)
37 ($C_{45}H_{76}O_{17}$)	60.62 (60.79)	8.78 (8.62)	911.4876 (911.4980, M + Na^+)
38 ($C_{42}H_{76}O_{17}$)	59.06 (59.14)	9.02 (8.98)	875.4961 (875.4980, M + Na^+)
39 ($C_{48}H_{88}O_{20}$)	58.39 (58.52)	8.96 (9.00)	1007.5746 (1007.5767, M + Na^+)
40 ($C_{51}H_{88}O_{20}$)	60.18 (59.98)	8.55 (8.69)	1043.5641 (1043.5767, M + Na^+)
41 ($C_{49}H_{90}O_{21}$)	57.81 (57.97)	9.04 (8.94)	1037.5761 (1037.5872, M + Na^+)
42 ($C_{63}H_{112}O_{26}$)	58.74 (58.86)	8.96 (8.78)	1307.7168 (1307.7340, M + Na^+)

[a] Calculated values are in parentheses (%). [b] Observed values (expected values and assignments are in parentheses), ES ionization unless otherwise specified. [c] FAB ionization.

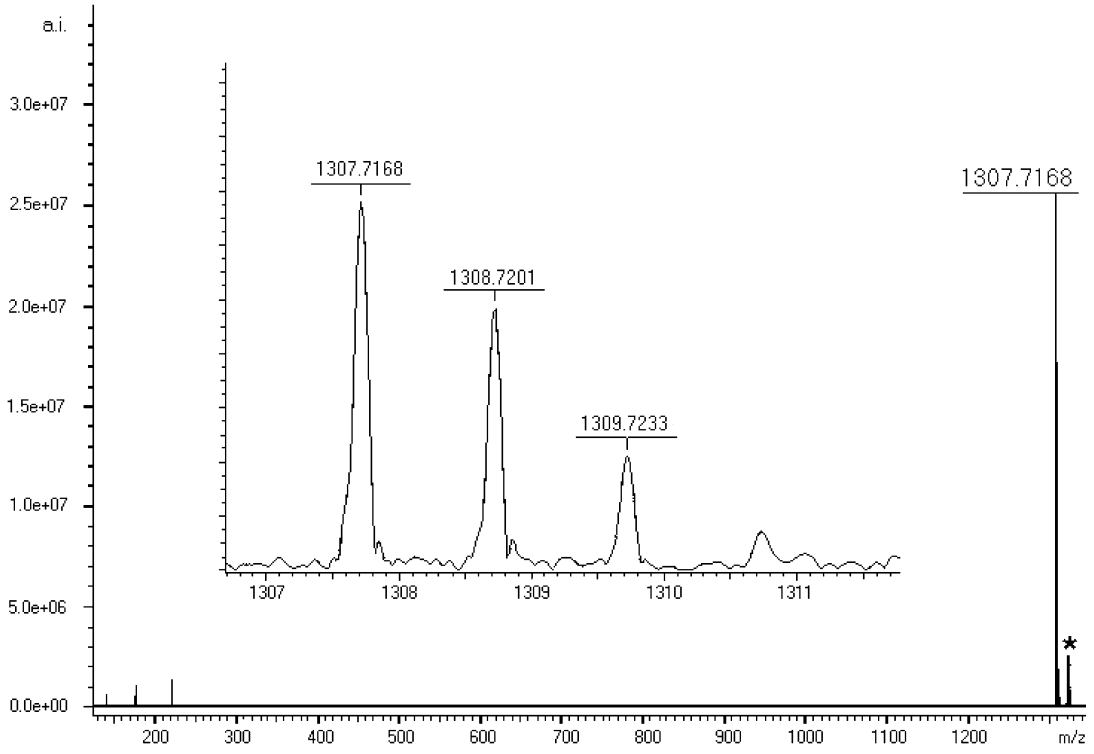


FIGURE 2. High-resolution ESMS of $Bn(OCH_2CH_2)_{24}OPMB$, **42** ($C_{63}H_{112}O_{26}$). Inset: Isotopic distribution of the [M + Na^+] ion peak. The asterisk indicates the [M + H_2O + Na^+] peak.

and concentrated under vacuum. The remaining oil was purified by column chromatography.

Method B. To a chilled (0 °C) and stirred solution of tri- or hexa-ethylene glycol (1 equiv) in DCM were added Ag_2O (1.5 equiv), TsCl (1.1 equiv), and KI (0.2 equiv, for PEG_6 only). After stirring for 15 to 20 min., the precipitated silver salts were removed by filtration through a pad of Celite, which was washed thoroughly with EtOAc. The combined filtrate was concentrated under vacuum, and the residue was purified by column chromatography.

Method C. At ambient temperature, the corresponding diol (1 equiv) was added dropwise to a solution of Ag_2O (1.5 equiv) and KI (0.4 equiv, for PEG_6 only) in DCM. BnBr (1.1 equiv) was then added over 5 min, and the mixture was stirred for 2 h. After this time, the suspension was filtered through a pad of Celite, which was thoroughly washed with DCM. The combined filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography.

Method D. To a solution of diol (1 equiv), Ag_2O (1.5 equiv), and KI (0.2 equiv for PEG_3, 0.6 equiv for PEG_6) in toluene was added PMBCl (1.1 equiv) in a dropwise manner at room temperature. The mixture was subsequently stirred at room temperature for 2 h (PEG_3) or heated at reflux for 17 h (PEG_6). After cooling to room temperature, the salts were removed by filtration through a pad of Celite, which was rinsed thoroughly with EtOAc. The combined filtrate was evaporated and the residue purified by column chromatography.

Method E. To a solution of diol (1.81 g, 6.41 mmol) in DCM (40 mL) were added Ag_2O (2.23 g, 9.62 mmol), KI (0.43 g, 2.59 mmol), and TrCl (1.97 g, 7.06 mmol). The resulting mixture was heated at reflux for 14 h. After this time, the silver salts were removed by filtration through a pad of Celite, which was thoroughly washed with EtOAc. The combined filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography.

8-(2*H*-Tetrahydropyran-2-yloxy)-3n_6^{3}-dioxaoctan-1-ol (6): colorless oil (3.49 g, 55%, **Method A**) from tri-ethylene glycol HO−PEG_3−OH (4.07 g, 27.1 mmol), EtOAc/hexane 1:1, R_f 0.23; ^{1}H NMR ($CDCl_3$) δ 1.48−1.81 (m, 6H), 2.75 (t, J = 6.1 Hz, 1H, OH), 3.50−3.87 (m, 14H), 4.61−4.63 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.8 (CH_2), 25.8 (CH_2), 30.9 (CH_2), 62.1 (CH_2), 62.6 (CH_2), 66.9 (CH_2), 70.7 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 72.9 (CH_2), 99.3 (CH); LR-MS (EI) 235 (MH^+, 9), 151 (100), 121 (21), 98 (58); IR (υ, cm^{-1}) 3459.0, 1125.3, 1076.0.

8-(*p*-Methoxybenzyloxy)-3n_6^{3}-dioxaoctan-1-ol (12): yellow oil (9.43 g, 74%, **Method D**) from tri-ethylene glycol HO−PEG_3−OH (7.08 g, 47.1 mmol), EtOAc, R_f 0.38; ^{1}H NMR ($CDCl_3$) δ 2.81 (s, 1H, OH), 3.47−3.68 (m, 12H), 3.71 (s, 3H), 4.41 (s, 2H), 6.79 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.1 (CH_3), 61.6 (CH_2), 68.9 (CH_2), 70.7 (CH_2), 71.5 (CH_2), 72.5 (CH_2), 72.8 (CH_2), 113.6 (CH), 129.3 (CH), 130.1 (C), 159.1 (C); LR-MS (EI) 293 ($M + Na^+$, 13), 208 (7), 132 (9), 121 (100); IR (υ, cm^{-1}) 3464.3, 1107.1, 821.7.

17-(*p*-Methoxybenzyloxy)-3n_{15}^{3}-pentaoxaheptadecan-1-ol (13): yellow oil (11.8 g, 67%, **Method D**) from hexa-ethylene glycol HO−PEG_6−OH (12.3 g, 43.6 mmol), EtOAc/acetone 3:2, R_f 0.31; ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 1H, OH), 3.59−3.87 (m, 24H), 3.81 (s, 3H), 4.50 (s, 2H), 6.87 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.6 (CH_3), 62.1 (CH_2), 69.4 (CH_2), 70.7 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 72.9 (CH_2), 73.2 (CH_2), 114.1 (CH), 129.8 (CH), 130.7 (C), 159.5 (C); LR-MS (FAB) 425 ($M + Na^+$, 21), 164 (9), 121 (100); IR (υ, cm^{-1}) 3468.7, 1102.7, 823.1.

General Procedures for the Synthesis of TsO(CH_2-CH_2O)$_m$PG (Scheme 5, Table 2). Method A: Protection of Monotosylate with THP. To a solution of monotosylated glycol (**8**, **9**) (1 equiv) in DCM were added pyridinium toluenesulfonate (0.2 equiv) and 2,3-dihydro-2*H*-pyran (1.5 equiv). The resulting mixture was refluxed for 3 h. The solution was then concentrated under vacuum, poured into ice−water, and extracted with DCM. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. The crude product was purified by column chromatography.

Protection of Monotosylate with Bn or PMB. The monotosylated glycol (**8**, **9**) (1 equiv) was dissolved in THF. Pyridine (1.5 equiv) and benzyl bromide or *p*-methoxybenzyl chloride (1.3 equiv) were added, and the solution was refluxed for 16 h. After this time, the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography.

Method B. Tosylation of Monoprotected Glycol. The monoprotected glycol (**6**, **7**, **10**−**13**, 1 equiv) was dissolved in pyridine at 0 °C and stirred for 30 min. A solution of TsCl (1.5 equiv) in pyridine was then added dropwise via cannula. The reaction mixture was then stirred for 5−17 h at room temperature before it was poured into ice−water and extracted with diethyl ether. The pH of the aqueous layer was neutralized with 2 M HCl (pH paper) and re-extracted with ether. The combined ether extracts were then washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under vacuum. The desired product was purified by chromatography.

1-(*p*-Methoxybenzyloxy)-8-tosyloxy-3n_6^{3}-dioxaoctane (17). Method A (Table 2, entry 5) yielded a colorless oil (4.50 g, 74%) from **8** (4.36 g, 14.3 mmol), while **Method B** (Table 2, entry 6) yielded a colorless oil (2.89 g, 81%) from PMBO−PEG_3−OH **12** (2.27 g, 8.40 mmol), EtOAc, R_f 0.58: ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 3.51−3.64 (m, 10H), 3.71 (s, 3H), 4.08−4.09 (m, 2H), 4.47 (s, 2H), 6.75 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.0 (CH_3), 55.7 (CH_3), 69.0 (CH_2), 69.5 (CH_2), 70.8 (CH_2), 70.9 (CH_2), 71.1 (CH_2), 73.2 (CH_2), 114.1 (CH), 128.4 (CH), 129.7 (CH), 130.2 (CH), 130.7 (C), 133.4 (C), 145.2 (C), 159.5 (C); LR-MS (FAB) 447 ($M + Na^+$, 35), 424 (M^+, 2), 243 (16), 121 (100); IR (υ, cm^{-1}) 1354.9, 1188.3, 1098.7.

1-(*p*-Methoxybenzyloxy)-17-tosyloxy-3n_{15}^{3}-pentaoxaheptadecane (18). Method A (Table 2, entry 7) yielded a yellow oil (2.38 g, 67%) from **9** (2.78 g, 6.37 mmol), while **Method B** (Table 2, entry 8) yielded a yellow oil (8.54 g, 74%) from **13** (8.35 g, 20.7 mmol), EtOAc/acetone 4:1, R_f 0.44: ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.50−3.61 (m, 22H), 3.72 (s, 3H), 4.07−4.09 (m, 2H), 4.41 (s, 2H), 6.78 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.0 (CH_3), 55.6 (CH_3), 69.0 (CH_2), 69.5 (CH_2), 69.6 (CH_2), 70.8 (CH_2), 70.9 (CH_2), 70.95 (CH_2), 71.0 (CH_2), 71.1 (CH_2), 73.2 (CH_2), 114.1 (CH), 128.4 (CH), 129.7 (CH), 130.2 (CH), 130.7 (C), 133.4 (C), 145.2 (C), 159.5 (C); LR-MS (EI, 70 eV) 556 (M^+, 9), 287 (5), 243 (10), 199 (62), 155 (21), 121 (100); IR (υ, cm^{-1}) 1355.5, 1097.9.

1-(2*H*-Tetrahydropyran-2-yloxy)-8-tosyloxy-3n_6^{3}-dioxaoctane (19). Method A (Table 2, entry 9) yielded a yellow oil (22.0 g, 98%) from **8** (17.6 g, 57.8 mmol), while **Method B** (Table 2, entry 10) yielded a yellow oil (7.32 g, 79%) from **6** (5.59 g, 23.9 mmol), EtOAc/hexane 4:1, R_f 0.58: ^{1}H NMR ($CDCl_3$) δ 1.49−1.81 (m, 6H), 2.45 (s, 3H), 3.50−3.71 (m, 10H), 3.82−3.87 (m, 2H), 4.13−4.17 (m, 2H), 4.61−4.63 (m, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.9 (CH_2), 22.0 (CH_3), 23.8 (CH_2), 31.0 (CH_2), 62.7 (CH_2), 67.0 (CH_2), 69.1 (CH_2), 69.6 (CH_2), 70.9 (CH_2), 70.95 (CH_2), 71.2 (CH_2), 99.4 (CH), 128.4 (CH), 130.2 (CH), 133.4 (C), 145.2 (C); LR-MS (EI) 387 ($M - H^+$, 1), 229 (20), 199 (100), 172 (45), 155 (85), 85 (37); IR (υ, cm^{-1}) 1358.9, 1176.7, 1034.4, 776.3, 664.4.

1-(2*H*-Tetrahydropyran-2-yloxy)-17-tosyloxy-3n_{15}^{3}-pentaoxaheptadecane (20). Method A (Table 2, entry 11) yielded a colorless oil (4.00 g, 96%) from **9** (3.49 g, 8.00 mmol), while **Method B** (Table 2, entry 12) yielded a colorless oil (3.59 g, 85%) from **7** (2.97 g, 8.10 mmol), EtOAc/hexane 4:1, R_f 0.51: ^{1}H NMR ($CDCl_3$) δ 1.41−1.65 (m, 6H), 2.38 (s, 3H), 3.44−3.63 (m, 22H), 3.76−3.80 (m, 2H), 4.07−4.09 (m, 2H), 4.54−4.57 (m, 1H), 7.26 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.9 (CH_2), 22.0 (CH_3), 25.8 (CH_2),

30.9 (CH_2), 62.6 (CH_2), 67.0 (CH_2), 69.0 (CH_2), 69.6 (CH_2), 70.8 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 71.1 (CH_2), 99.3 (CH), 128.4 (CH), 130.2 (CH), 133.3 (C), 145.2 (C); LR-MS (CI) 538 ($M + NH_4^+$, 34), 520 (M^+, 2), 454 (100), 410 (7), 366 (62), 322 (7), 282 (34), 278 (10), 234 (4), 85 (57); IR (υ, cm^{-1}) 1356.3, 1177.5, 1034.6, 776.7, 664.3.

General Procedure for the Synthesis of Unsymmetrical Elongated Poly(ethylene glycol)s (Scheme 6, Table 3). NaH (60% in mineral oil, 1.8 equiv) was placed in a three-neck round-bottom flask and washed with *n*-pentane. The residue was dried under vacuum, and THF was added to form a suspension. A solution of the monoprotected glycol (1 equiv) in THF was added dropwise, and the reaction mixture was stirred at room temperature for between 20 and 24 h. A solution of the monoprotected tosylate (1 equiv) in THF was then added to the solution via cannula. The resulting mixture was stirred at room temperature for 70 h to 76 h. The excess of NaH was carefully destroyed by the addition of MeOH at 0 °C. The solution was then concentrated under vacuum, and the resulting precipitate was partitioned between EtOAc/H_2O (1:1 v/v). The aqueous layer was then extracted with EtOAc. The combined organic layers were washed with water and brine, dried on $MgSO_4$, filtered, and concentrated under reduced pressure. The remaining oil was purified by column chromatography.

1-(*p*-Methoxybenzyloxy)-26-(2*H*-tetrahydropyran-2-yloxy)-3n_{24}^3-octaoxahexacosane (21) (Table 3, Entry 1)**:** yellow oil (8.46 g, 80%) from **13** (6.88 g, 17.1 mmol) and **19** (6.64 g, 17.1 mmol), EtOAc/acetone 3:2, R_f 0.47; ^{1}H NMR ($CDCl_3$) δ 1.49−1.88 (m, 6H), 3.48−3.69 (m, 36H), 3.80 (s, 3H), 3.83−3.88 (m, 2H), 4.49 (s, 2H), 4.62 (t, J = 3.2 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.9 (CH_2), 25.8 (CH_2), 30.9 (CH_2), 55.7 (CH_3), 62.6 (CH_2), 67.0 (CH_2), 69.4 (CH_2), 70.9 (CH_2), 70.95 (CH_2), 71.0 (CH_2), 73.3 (CH_2), 99.3 (CH), 114.1 (CH), 129.8 (CH), 130.7 (C), 159.5 (C); LR-MS (EI) 618 (M^+, 1), 533 (100), 489 (10), 340 (7), 283 (7), 221 (10), 177 (21), 133 (53), 121 (37), 89 (69); IR (υ, cm^{-1}) 1121.8.

1-Benzyloxy-26-(2*H*-tetrahydropyran-2-yloxy)-3n_{24}^3-octaoxahexacosane (22) (Table 3, entry 3)**:** yellow oil (10.0 g, 81%) from **11** (7.83 g, 21.0 mmol) and **19** (8.17 g, 21.0 mmol), EtOAc/acetone 3:2, R_f 0.45; ^{1}H NMR ($CDCl_3$) δ 1.42−1.76 (m, 6H), 3.42−3.63 (m, 36H), 3.76−3.82 (m, 2H), 4.49 (s, 2H), 4.56 (t, J = 3.3 Hz, 1H), 7.19−7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.9 (CH_2), 25.8 (CH_2), 30.9 (CH_2), 62.6 (CH_2), 67.0 (CH_2), 69.8 (CH_2), 70.9 (CH_2), 70.95 (CH_2), 70.97 (CH_2), 71.0 (CH_2), 73.6 (CH_2), 99.3 (CH), 128.0 (CH), 128.1 (CH), 128.7 (CH), 138.6 (C); LR-MS (EI) 588 (M^+, 2), 503 (54), 398 (8), 354 (11), 310 (12), 265 (12), 221 (25), 177 (58), 133 (100); IR (υ, cm^{-1}) 1119.6, 740.6, 699.6.

1-Benzyloxy-26-(*p*-methoxybenzyloxy)-3n_{24}^3-octaoxahexacosane (23) (Table 3, Entry 5)**:** yellow oil (10.3 g, 87%) from **13** (7.64 g, 19.0 mmol) and **15** (7.47 g, 18.9 mmol), DCM/EtOAc 4:1, R_f 0.20; ^{1}H NMR ($CDCl_3$) δ 3.58−3.75 (m, 36H), 3.80 (s, 3H), 4.49 (s, 2H), 4.57 (s, 2H), 6.87 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 7.29−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 55.6 (CH_3), 69.5 (CH_2), 69.8 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 73.3 (CH_2), 73.6 (CH_2), 114.1 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 129.8 (CH), 130.7 (C), 138.7 (C), 159.5 (C); LR-MS (FAB) 647 ($M + Na^+$, 100), 623 (22), 533 (32), 239 (47); IR (υ, cm^{-1}) 1122.7.

1-(*p*-Methoxybenzyloxy)-35-(2*H*-tetrahydropyran-2-yloxy)-3n_{33}^3-undecaoxapentatriacontane (24) (Table 3, Entry 6)**:** yellow oil (1.46 g, 86%) from **13** (0.91 g, 2.27 mmol) and **20** (1.18 g, 2.27 mmol), EtOAc/acetone 4:1, R_f 0.24; ^{1}H NMR ($CDCl_3$) δ 1.42−1.81 (m, 6H), 3.43−3.63 (m, 48H), 3.73 (s, 3H), 3.77−3.81 (m, 2H), 4.42 (s, 2H), 4.56−4.57 (m, 1H), 6.80 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.9 (CH_2), 25.8 (CH_2), 30.9 (CH_2), 55.6 (CH_3), 62.6 (CH_2), 67.0 (CH_2), 69.5 (CH_2), 70.8 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 73.3 (CH_2), 99.3 (CH), 114.1 (CH), 129.8 (CH), 130.7 (C), 159.5 (C); IR (υ, cm^{-1}) 1120.9.

1-Benzyloxy-35-(*p*-methoxybenzyloxy)-3n_{33}^3-undecaoxapentatriacontane (25) (Table 3, Entry 7)**:** yellow oil (3.17 g, 84%) from **13** (2.01 g, 4.99 mmol) and **16** (2.63 g, 4.99 mmol), EtOAc/Acetone 4:1, R_f 0.58; ^{1}H NMR ($CDCl_3$) δ 3.58−3.71 (m, 48H), 3.79 (s, 3H), 4.49 (s, 2H), 4.56 (s, 2H), 6.86 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 7.29−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 55.6 (CH_3), 69.5 (CH_2), 69.8 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 73.3 (CH_2), 73.6 (CH_2), 114.1 (CH), 128.0 (CH), 128.1 (CH), 128.7 (CH), 129.7 (CH), 130.7 (C), 138.7 (C), 159.6 (C); LR-MS (EI) 756 (M^+, 2), 665 (100), 635 (13), 621 (13), 177 (32), 133 (65), 121 (33), 89 (33); IR (υ, cm^{-1}) 1103.1, 743.0, 700.2.

1-Benzyloxy-35-(2*H*-tetrahydropyran-2-yloxy)-3n_{33}^3-undecaoxapentatriacontane (26) (Table 3, Entry 9)**:** yellow oil (11.4 g, 85%) from **20** (9.68 g, 18.6 mmol) and **11** (6.91 g, 18.6 mmol), EtOAc/Acetone 3:2, R_f 0.23; ^{1}H NMR ($CDCl_3$) δ 1.42−1.65 (m, 6H), 3.44−3.82 (m, 50H), 4.49 (s, 2H), 4.55−4.57 (m, 1H), 7.19−7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.9 (CH_2), 25.8 (CH_2), 30.9 (CH_2), 62.6 (CH_2), 67.0 (CH_2), 69.8 (CH_2), 70.9 (CH_2), 70.95 (CH_2), 71.0 (CH_2), 71.05 (CH_2), 73.6 (CH_2), 99.3 (CH), 128.0 (CH), 128.1 (CH), 128.8 (CH), 138.6 (C); IR (υ, cm^{-1}) 1122.8, 1035.4, 740.4, 669.5.

General Procedures for Selective Deprotection of Bifunctional PEGs (Scheme 7)**: Removal of THP Group.** The glycol (**21**, **22**, **24**, **26**) was deprotected according to a previously reported procedure.[4]

Removal of Bn Group. Pearlman's catalyst (10% Pd, 0.27 g) was added to a solution of glycol **22** (1.12 g, 1.90 mmol) in a mixture of EtOH/cyclohexene (40 mL, 5:3, v/v), and the solution was heated at reflux for 17 h. After this time, the reaction mixture was filtered through a pad of Celite, which was washed with EtOAc (100 mL). The combined filtrate was concentrated under vacuum, and the remaining oil was purified by column chromatography.

Removal of PMB Group. The glycol (**21**, **23**, **25**) was dissolved in a mixture of MeCN/H_2O (9:1, v/v) and cooled to 0 °C. CAN (3 equiv) was added in three portions over 1.5 h, and the solution was stirred at room temperature for 2.5 h. The resulting mixture was extracted with DCM, and the combined extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography.

26-(*p*-Methoxybenzyloxy)-3n_{24}^3-octaoxahexacosan-1-ol (28): yellow oil (2.94 g, 92%) from **21** (3.68 g, 5.95 mmol), EtOAc/Acetone 1:1, R_f 0.27; ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 1H, OH), 3.58−3.72 (m, 36H), 3.80 (s, 3H), 4.50 (s, 2H), 6.87 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.7 (CH_3), 62.1 (CH_2), 69.4 (CH_2), 70.7 (CH_2), 70.95 (CH_2), 71.05 (CH_2), 72.9 (CH_2), 73.3 (CH_2), 114.1 (CH), 129.8 (CH), 130.7 (C), 159.5 (C); LR-MS (EI) 534 (M^+, 36), 489 (5), 283 (12), 221 (19), 177 (47), 133 (94), 121 (68), 89 (100); IR (υ, cm^{-1}) 3479.9, 1103.2.

35-(*p*-Methoxybenzyloxy)-3n_{33}^3-undecaoxapentatriacontan-1-ol (29): yellow oil (1.14 g, 94%) from **24** (1.37 g, 1.82 mmol), EtOAc/acetone 4:1, R_f 0.32. ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 1H, OH), 3.51−3.70 (m, 48H), 3.73 (s, 3H), 4.42 (s, 2H), 6.80 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.7 (CH_3), 62.1 (CH_2), 69.5 (CH_2), 70.7 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 71.05 (CH_2), 73.0 (CH_2), 73.3 (CH_2), 114.1 (CH), 129.8 (CH), 130.7 (C), 159.6 (C); IR (υ, cm^{-1}) 3465.0, 1106.9, 820.3.

26-Benzyloxy-3n_{24}^3-octaoxahexacosan-1-ol (30): colorless oil from **22** (3.98 g, 6.76 mmol) in 95% yield (3.24 g) or **23** (9.57 g, 16.3 mmol) in 88% yield (7.22 g), EtOAc/acetone 1:1, R_f 0.28; ^{1}H NMR ($CDCl_3$) δ 2.64 (t, J = 6.2 Hz, 1H, OH), 3.52−3.67 (m, 36H), 4.49 (s, 2H), 7.19−7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 62.1 (CH_2), 69.8 (CH_2), 70.7 (CH_2), 70.9 (CH_2), 70.95 (CH_2), 71.0 (CH_2), 72.9 (CH_2), 73.6 (CH_2), 128.0 (CH), 128.1 (CH), 128.7 (CH), 138.6 (C); LR-MS (EI) 504 (M^+, 7), 372 (2), 208 (8), 147 (10), 133 (23), 91 (100); IR (υ, cm^{-1}) 3479.6, 1104.2.

35-Benzyloxy-3n_{33}^3-undecaoxapentatriacontan-1-ol (31): yellow oil from **26** (7.41 g, 10.2 mmol) in 96% yield (6.29 g) or **25** (2.97 g, 3.92 mmol) in 79% yield (1.97 g), EtOAc/acetone

3:2, R_f (acetone) 0.21; ^{1}H NMR ($CDCl_3$) δ 2.63 (t, J = 6.2 Hz, 1H, OH), 3.60−3.73 (m, 48H), 4.57 (s, 2H), 7.26−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 62.0 (CH_2), 69.8 (CH_2), 70.7 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 72.9 (CH_2), 73.6 (CH_2), 127.9 (CH), 128.1 (CH), 128.7 (CH), 138.7 (C); LR-MS (CI) 655 ($M + NH_4^+$, 100), 636 (M^+, 36), 514 (14), 339 (13); IR (υ, cm^{-1}) 3502.0, 1107.1.

26-(2*H*-Tetrahydropyran-2-yloxy)-3n_{24}^3-octaoxahexacosan-1-ol (32): colorless oil from **22** (1.12 g, 1.90 mmol) in 55% yield (0.52 g) or **21** (1.36 g, 2.20 mmol) in 83% yield (0.91 g), EtOAc/acetone 3:2, R_f 0.45; ^{1}H NMR ($CDCl_3$) δ 1.49−1.72 (m, 6H), 2.64 (t, J = 6.2 Hz, 1H, OH), 3.59−3.73 (m, 36H), 3.85−3.87 (m, 2H), 4.62−4.64 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.9 (CH_2), 25.8 (CH_2), 30.9 (CH_2), 62.1 (CH_2), 62.6 (CH_2), 67.0 (CH_2), 70.7 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 72.9 (CH_2), 99.3 (CH); IR (υ, cm^{-1}) 3478.9, 1122.5, 1035.0.

General Procedure for Tosylation of Monoprotected Oligomeric Glycols (Scheme 8)**.** To a solution of monoprotected glycol (**28**−**31**, 1 equiv) in DCM at room temperature were added successively TsCl (1.5 equiv), KI (0.4 equiv), and Ag_2O (1.5 equiv), and the mixture was heated at reflux for 14−18 h. After this time, the silver salts were removed by filtration through a pad of Celite, which was thoroughly washed with EtOAc. The filtrate was concentrated under vacuum, and the resulting oil was purified by column chromatography.

1-(*p*-Methoxybenzyloxy)-26-tosyloxy-3n_{24}^3-octaoxahexacosane (33): colorless oil (2.25 g, 85%) from **28** (2.06 g, 3.85 mmol), EtOAc/acetone 3:2, R_f 0.60; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.57−3.69 (m, 34H), 3.78 (s, 3H), 4.12−4.14 (m, 2H), 4.48 (s, 2H), 6.85 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.0 (CH_3), 55.6 (CH_3), 69.0 (CH_2), 69.5 (CH_2), 69.6 (CH_2), 70.8 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 71.1 (CH_2), 73.2 (CH_2), 114.1 (CH), 128.3 (CH), 129.7 (CH), 130.2 (CH), 130.7 (C), 133.4 (C), 145.2 (C), 159.5 (C); LR-MS (EI) 711 ($M + Na^+$, 100), 237 (7), 121 (4); IR (υ, cm^{-1}) 1356.4, 1189.0, 1099.3.

1-(*p*-Methoxybenzyloxy)-35-tosyloxy-3n_{33}^3-undecaoxapentatriacontane (34): colorless oil (2.63 g, 80%) from **29** (2.67 g, 4.00 mmol), EtOAc/acetone 1:1, R_f 0.39; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.58−3.70 (m, 46H), 3.76 (s, 3H), 4.12−4.14 (m, 2H), 4.49 (s, 2H), 6.86 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.0 (CH_3), 55.7 (CH_3), 69.0 (CH_2), 69.5 (CH_2), 69.6 (CH_2), 70.9 (CH_2), 70.95 (CH_2), 71.0 (CH_2), 71.1 (CH_2), 73.3 (CH_2), 114.1 (CH), 128.3 (CH), 129.8 (CH), 130.2 (CH), 130.7 (C), 133.4 (C), 145.2 (C), 159.6 (C); IR (υ, cm^{-1}) 1355.7, 1100.3.

1-Benzyloxy-26-tosyloxy-3n_{24}^3-octaoxahexacosane (35): colorless oil (6.18 g, 84%) from **30** (5.62 g, 11.1 mmol), EtOAc/acetone 4:1, R_f 0.63; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.51−3.64 (m, 34H), 4.07−4.10 (m, 2H), 4.49 (s, 2H), 7.19−7.28 (m, 7H), 7.72 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.0 (CH_3), 69.0 (CH_2), 69.6 (CH_2), 69.8 (CH_2), 70.9 (CH_2), 70.95 (CH_2), 71.0 (CH_2), 71.05 (CH_2), 71.1 (CH_2), 73.6 (CH_2), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.7 (CH), 130.2 (CH), 133.4 (C), 138.7 (C), 145.2 (C); IR (υ, cm^{-1}) 1356.1, 1103.3.

1-Benzyloxy-35-tosyloxy-3n_{33}^3-undecaoxapentatriacontane (36): colorless oil (4.39 g, 78%) from **31** (4.52 g, 7.10 mmol), EtOAc/acetone 1:1, R_f 0.23; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.51−3.63 (m, 46H), 4.07−4.10 (m, 2H), 4.49 (s, 2H), 7.20−7.28 (m, 7H), 7.72 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.0 (CH_3), 69.0 (CH_2), 69.6 (CH_2), 69.8 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 73.6 (CH_2), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.7 (CH), 130.2 (CH), 133.4 (C), 138.7 (C), 145.2 (C); IR (υ, cm^{-1}) 1354.4, 1100.0.

General Procedure for the Synthesis of Elongated PEGs. Second Extension (Scheme 9, Table 4). The same synthetic procedure described previously for Scheme 6 was applied to the synthesis of the higher homologues.

1-(*p*-Methoxybenzyloxy)-35-(2*H*-tetrahydropyran-2-yloxy)-3n_{33}^3-undecaoxapentatriacontane (24) (Table 4, Entry 1): yellow oil (5.22 g, 81%) from **6** (2.01 g, 8.58 mmol) and **33** (5.91 g, 8.58 mmol).

1-Benzyloxy-35-(*p*-methoxybenzyloxy)-3n_{33}^3-undecaoxapentatriacontane (25) (Table 4, Entry 3): yellow oil (3.94 g, 84%) from **10** (1.49 g, 6.20 mmol) and **33** (4.27 g, 6.20 mmol).

1-Benzyloxy-35-(2*H*-tetrahydropyran-2-yloxy)-3n_{33}^3-undecaoxapentatriacontane (26) (Table 4, Entry 4): yellow oil (2.91 g, 83%) from **35** (3.20 g, 4.86 mmol) and **6** (1.14 g, 4.87 mmol).

1-Benzyloxy-44-(*p*-methoxybenzyloxy)-3n_{42}^3-tetradecaoxatetratetracontane (37) (Table 4, Entry 5): colorless oil (7.18 g, 87%) from **35** (6.11 g, 9.27 mmol) and **13** (3.72 g, 9.27 mmol), EtOAc/acetone 7:3, R_f 0.30; ^{1}H NMR ($CDCl_3$) δ 3.53−3.71 (m, 60H), 3.79 (s, 3H), 4.49 (s, 2H), 4.56 (s, 2H), 6.86 (d, J = 8.6 Hz, 2H), 7.25−7.34 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 55.6 (CH_3), 69.5 (CH_2), 69.8 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 73.3 (CH_2), 73.6 (CH_2), 114.1 (CH), 128.0 (CH), 128.1 (CH), 128.7 (CH), 129.7 (CH), 130.7 (C), 138.7 (C), 159.5 (C); IR (υ, cm^{-1}) 1106.7, 742.4, 700.0.

1-Benzyloxy-44-(2*H*-tetrahydropyran-2-yloxy)-3n_{42}^3-tetradecaoxatetratetracontane (38) (Table 4, Entry 7): colorless oil (2.75 g, 88%) from **35** (2.41 g, 3.66 mmol) and **7** (1.34 g, 3.66 mmol), EtOAc/acetone 1:1, R_f 0.28; ^{1}H NMR ($CDCl_3$) δ 1.49−1.69 (m, 6H), 3.51−3.67 (m, 60H), 3.79−3.82 (m, 2H), 4.53 (s, 2H), 4.60−4.62 (m, 1H), 7.24−7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.9 (CH_2), 25.8 (CH_2), 30.9 (CH_2), 62.6 (CH_2), 66.9 (CH_2), 69.4 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 73.6 (CH_2), 99.3 (CH), 128.0 (CH), 128.1 (CH), 128.8 (CH), 130.7 (C); IR (υ, cm^{-1}) 1107.1.

1-Benzyloxy-53-(2*H*-tetrahydropyran-2-yloxy)-3n_{51}^3-heptadecaoxatripentacontane (39) (Table 4, Entry 8): colorless oil (2.80 g, 81%) from **35** (2.31 g, 3.51 mmol) and **32** (1.75 g, 3.51 mmol), EtOAc/MeOH 9:1, R_f 0.30; ^{1}H NMR ($CDCl_3$) δ 1.39−1.61 (m, 6H), 3.39−3.77 (m, 74H), 4.48 (s, 2H), 4.53−4.56 (m, 1H), 7.17−7.25 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.9 (CH_2), 25.8 (CH_2), 30.8 (CH_2), 62.5 (CH_2), 67.0 (CH_2), 69.8 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 71.05 (CH_2), 73.6 (CH_2), 99.4 (CH), 128.0 (CH), 128.1 (CH), 128.8 (CH), 138.6 (C); IR (υ, cm^{-1}) 1122.7, 1034.8, 741.0, 669.6.

1-Benzyloxy-53-(*p*-methoxybenzyloxy)-3n_{51}^3-heptadecaoxatripentacontane (40) (Table 4, Entry 11): yellow oil (4.19 g, 91%) from **36** (3.60 g, 4.54 mmol) and **13** (1.83 g, 4.53 mmol), EtOAc/MeOH 9:1, R_f 0.59: ^{1}H NMR ($CDCl_3$) δ 3.54−3.70 (m, 72H), 3.80 (s, 3H), 4.50 (s, 2H), 4.57 (s, 2H), 6.87 (d, J = 8.6 Hz, 2H), 7.26−7.35 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 55.7 (CH_3), 69.5 (CH_2), 69.8 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 73.3 (CH_2), 73.6 (CH_2), 114.1 (CH), 128.0 (CH), 128.2 (CH), 128.8 (CH), 129.8 (CH), 130.7 (C), 138.7 (C), 159.6 (C); IR (υ, cm^{-1}) 1104.3, 742.8, 700.4.

1-(*p*-Methoxybenzyloxy)-53-(2*H*-tetrahydropyran-2-yloxy)-3n_{51}^3-heptadecaoxatripentacontane (41) (Table 4, Entry 12): colorless oil (2.99 g, 90%) from **33** (2.03 g, 2.95 mmol) and **32** (1.47 g, 2.95 mmol), EtOAc/MeOH 9:1, R_f 0.18; ^{1}H NMR ($CDCl_3$) δ 1.52−1.82 (m, 6H), 3.59−3.70 (m, 72H), 3.80 (s, 3H), 3.84−3.88 (m, 2H), 4.50 (s, 2H), 4.62−4.64 (m, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.9 (CH_2), 25.8 (CH_2), 30.9 (CH_2), 55.7 (CH_3), 62.6 (CH_2), 67.0 (CH_2), 69.5 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 73.3 (CH_2), 99.3 (CH), 114.1 (CH), 129.8 (CH), 130.7 (C), 159.6 (C); IR (υ, cm^{-1}) 1107.1, 740.3, 699.8.

1-Benzyloxy-71-(*p*-methoxybenzyloxy)-3n_{69}^3-tricosaoxahenheptacontane (42) (Table 4, Entry 13): waxy white solid (1.65 g, 83%) from **36** (1.23 g, 1.55 mmol) and **29** (1.04 g, 1.56 mmol), EtOAc/MeOH 7:1, R_f 0.21; mp 26−27 °C; ^{1}H NMR ($CDCl_3$) δ 3.55−3.75 (m, 96H), 3.81 (s, 3H), 4.50 (s, 2H), 4.57 (s, 2H), 6.87−6.89 (m, 2H), 7.26−7.35 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 55.7 (CH_3), 69.5 (CH_2), 69.8 (CH_2), 70.9 (CH_2), 71.0 (CH_2), 73.3 (CH_2), 73.6 (CH_2), 114.1 (CH), 128.0 (CH), 128.1 (CH), 128.7 (CH), 129.8 (CH), 130.7 (C), 138.7 (C), 159.6 (C); IR (υ, cm^{-1}) 1104.6, 741.9, 702.1.

Isolation of Vinyl Poly(ethylene glycol) Ether. The vinyl ether side products (**27**, **43**) were isolated by column chromatography following the extension reactions (Schemes

6 and 9). Characterization data for these compounds are provided as Supporting Information.

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Supporting Information Available: Full characterization data for compounds **7**−**11** and **14**−**16** (data were previously reported, but preparation/characterization data are inadequate); also included are characterization data for vinyl side products **27** and **43**, as well as selected ^{1}H, ^{13}C, and HR-ESMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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