Synthesis of Branched Heptaglycerol Bearing Eight Hydroxyl Groups with Four Cyclic Protecting Groups

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Abstract: A large series of branched oligoglycerols, **BGL07** (heptamer) with cyclic protecting groups, was synthesized.

Key words: glycerol, water solubility, branched-type, cyclic protecting groups, oligomer, hydroxyl group

Linear macromolecules consist of a number of bifunctionalized units such as ethylene glycol[1a] or 1,3-linked glycerol;[1b] in contrast, branched macromolecules[2] consist of trifunctionalized (or further functionalized) units. Such oligomers or macromolecules have been synthesized using 3,3′-dichloroisobutene,[2a] lactic acid,[2b] and iminodiacetic acid with serinol.[2c] These have attracted much attention due to the unique molecular skeleton which may show novel properties and evaluations.[2]

The glyceryl unit is one of the simplest trifunctionalized molecules. The preparation of compounds bearing a single glyceryl unit at each dendrimeric terminus such as **1** has been reported[2] (Figure 1). In contrast, compounds such as **2**, which bear repetitive branched glyceryl (BGL) units, have not been reported except in our previous papers dealing with BGL.[3] It is often difficult to create ether linkage in high yield (especially at sterically hindered positions) since the alkoxy anion often behaves as a base rather than a nucleophile, and its nucleophilicity is generally weaker than that of carbanions or electron-negative heteroatom species.

Despite this, we succeeded in preparing **4**,[3a,b] a precursor of triglyceryl derivatives **BGL03** (Scheme 1). In **BGL03**, the secondary alcohol at the apex position is used to a create covalent bond with a lipophilic compound, and four primary hydroxyl groups at the branched termini confer water solubility.

However, the preparation of large analogues bearing further repetitive linkages, such as **5**, a precursor of heptaglyceryl derivatives **BGL07** has yet to be reported.[4,5]

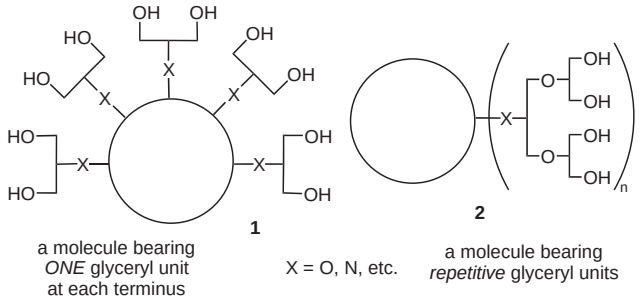
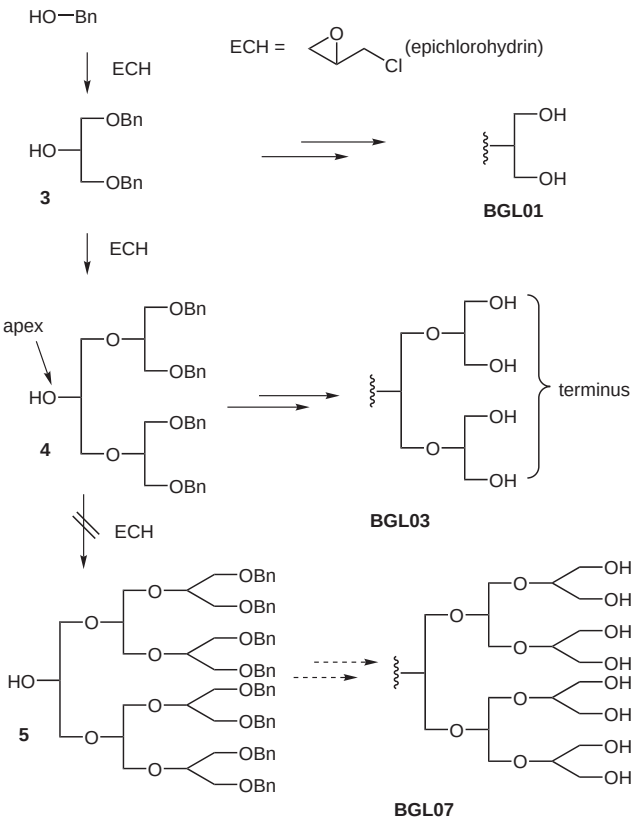


Figure 1 Two types of branched oligo- or polyglycerols



Scheme 1

Alkoxy anions **7** and **8** were sufficiently reactive towards glycidyl ether **6** to afford **3** and **4**, respectively (Scheme 2). However, it was likely that the nucleophilicity of alkoxy anion **9** would be remarkably reduced by the presence of four benzyl groups, in which the anion is swathed.

In order to increase the nucleophilicity of the triglyceryl unit, preparation of an alternative molecule with reduced steric hindrance around the secondary alkoxy anion is a potential solution.

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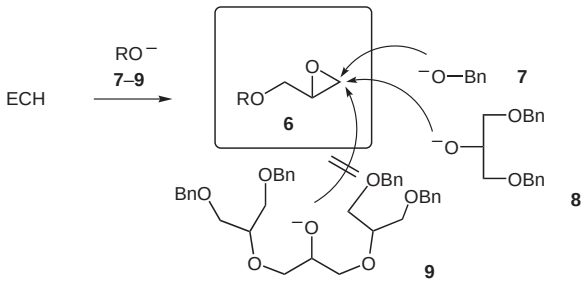
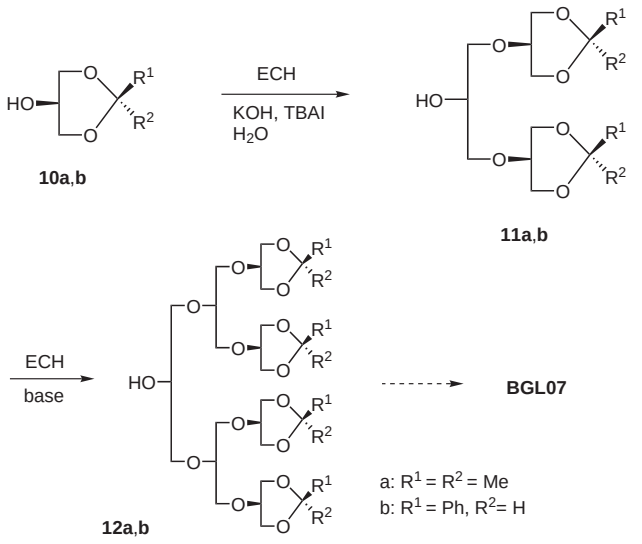


Scheme 2

In this paper, we report the first synthesis of protected heptaglyceryl derivatives. The 1,3-protected cyclic glycerols **10a**[6] and **10b**[7] were chosen as starting materials instead of 1,3-dibenzyl glycerol (**3**) (Scheme 3). It is expected that the presence of six-membered rings would reduce the conformational flexibility of the whole molecule. Furthermore, the total molecular weights of **11a** (320.38) and **11b** (416.46) are each less than that of **4** (600.74).



Scheme 3

Triglycerol **11a**[8] was easily obtained from **10a** in 56% yield under the conditions previously reported for a similar reaction [epichlorohydrin (ECH), tetrabutylammonium iodide (TBAI), H_2O, and KOH].[3a,b] Another triglycerol **11b**[9] was also obtained in 73% yield from **10b** in the same manner.

Compound **12a** was obtained from **11a** in 10% yield on our first attempt, using the same conditions. The yield was low but of appreciable value, since our previous attempts to prepare compounds of this type, and even a detection of octabenzyl ether **5** from **4** had failed entirely. The identification of **12a** encouraged us to continue with further optimization of the reaction.

After attempting the reaction under various conditions (changing the base, solvent, temperature, counter alkali-metal cation, phase-transfer catalyst, or ratio of ECH and **11**), the yield of **12a** from **11a** was improved at 80 °C (Table 1,[10] entry 1). In the case of reaction from **11b** to **12b**, we noticed that anhydrous conditions generally gave better results than our previous use of aqueous conditions. Typical results obtained using sodium hydride as a base are summarized (entries 2–4, 6–9). For the reaction of **11a**, performing the reaction with no solvent gave the best result (entry 1). When solvents were used, better results were obtained at higher temperature (entries 2–4). Since **11b** is not a liquid, the same reaction condition as entry 1 could not be examined (entry 5). By using THF (bp 65°C) as a solvent, desired **12b** was not obtained but the corresponding glycidyl ether was detected (entry 6). In refluxing 1,2-dimethoxyethane (DME, bp 85 °C), **12b** was obtained with good reproducibility (entry 7). The reaction in refluxing cyclopentyl methyl ether (CPME, bp 106 °C) gave lower yield of **12b** than in DME in spite of its higher boiling point (entry 8). Finally, in refluxing 1,4-dioxane (bp 101 °C), best result for **12b** was obtained (entry 9) among we have examined (entries 6–9). The synthesis of **12b** may require both high temperature and polarity of solvent as well as **12a**.

The details of the syntheses of **12a** (entry 1) and **12b** (entry 9) are as follows.

To a vigorously stirred mixture of **11a** (6.00 g, 18.7 mmol), TBAI (0.30 g, 0.90 mmol), finely ground KOH in a mortar (0.93 g, 14.0 mmol), and water (1.0 mL) was added ECH (0.43 g, 4.70 mmol) slowly and dropwise. The resulting mixture was stirred for 48 hours at 80 °C, then poured into water (100 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over anhydrous potassium carbonate, and concentrated in vacuo. The residue was purified by silica gel column chromatography with diethyl ether–methanol (15:1) as an eluent to afford **12a**[11] as a pale yellow oil (2.71 g, 3.89 mmol, 57% yield[10]) and the starting material **11a** (1.62 g, 5.05 mmol, 27% recovered yield[10]).

To a solution of **11b** (2.807 g, 6.74 mmol) in anhydrous 1,4-dioxane (5 mL) was added sodium hydride (0.441 g, 10.1 mmol). After the mixture has been stirred for 30 minutes at room temperature, ECH (0.26 mL, 3.37 mmol) was added slowly. The resulting solution was refluxed for 48 hours, poured into water (100 mL), and extracted with ethyl acetate (5 × 80 mL). The combined organic layers were washed with brine, dried over anhydrous potassium carbonate, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using diethyl ether–methanol (100:5 to 100:10) as an eluent to afford **12b**[12] (1.219 g, 1.37 mmol, 54% yield[10]) and **11b** (0.713 g, 1.71 mmol, 25% recovered[10]).

Next, we demonstrated the synthesis of **14**[16] which bears an activated ester at the apex position for covalent bond formation with various lipophilic materials, as shown in Scheme 4.[17,18] A similar procedure to that used for benzyl ethers **3** and **4** (tosylation, azidation, and reduction)[3f] afforded amines **13a** in 63% yield from **12a**. The same procedure was applied to **12b** to afford **13b** in 85% yield. The amine **13a** was then transformed to **14a** in 74% yield

Table 1 Preparation of **12** from **11** and ECH with Sodium Hydride in Various Solvents at Reflux[a]

Entry	**11**	Solvent	Recovered yield of **11** (%)	Yield of **12** (%)
1[b]	**11a**	Neat	27	57
2	**11a**	THF	37	5
3	**11a**	DME	38	26
4	**11a**	MeCN	55	33
5	**11b**[c]	Neat	n.e.	n.e.
6	**11b**	THF	–	0[d]
7	**11b**[e]	DME	27	40
8	**11b**[e]	CPME	20	36
9	**11b**[e]	1,4-Dioxane	25	55

[a] Compound **11** (4.0 equiv),[14,15] ECH (1.0 equiv), NaH (1.2 equiv), reflux, 48 h.
[b] Reaction carried out with TBAI, KOH, and H_2O at 80 °C.
[c] Since **11b** was not a liquid but gummy solid, reaction could not be carried out without solvent (n.e. = not examined).
[d] Formation of **12b** was not observed but the corresponding glycidyl ether was detected.[13]
[e] 2.0 Equiv of **11b** were used.[15]

in one step using the asymmetric glutaric acid based dual-activated ester **15**[19] with diisopropylethylamine (DIPEA) in CH_2Cl_2. Meanwhile, a stepwise procedure, involving treatment of glutaric anhydride with triethylamine (Et_3N) followed by condensation reaction with *N*-hydroxysuccinimide (HOSu) using ethyl 2-(*N*,*N*-dimethylamino)propyl carbodiimide (EDC) afforded **14b** in 57% yield from **13b**.

In conclusion, a branched heptaglycerol skeleton was first synthesized by choosing an appropriate protecting group. The successful synthesis of the triply repetitive glycerol oligomer is probably due to the reduction of both conformational flexibility and molecular weight compared to species used in previous preparation. We now have a larger series of branched oligoglycerols allowing more flexible and practical research into BGL modification of lipophilic compounds.

Acknowledgment

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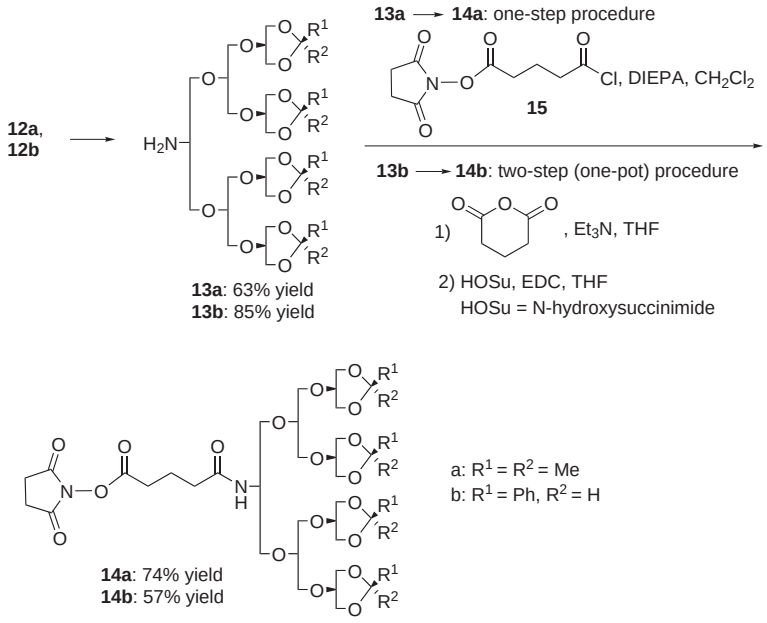
(3) Our previous papers on BGL: (a) Nemoto, H.; Wilson, J. G.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 435. (b) Nemoto, H.; Wilson, J. G.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 1478. (c) Nemoto, H.; Iwamoto, S.; Nakamura, H.; Yamamoto, Y. *Chem. Lett.* **1993**, 465. (d) Yamamoto, Y.; Asao, N.; Meguro, M.; Tsukada, N.; Nemoto, H.; Sadayori, N.; Wilson, J. G. *J. Chem. Soc., Chem. Commun.* **1993**, 1201. (e) Nemoto, H.; Cai, J.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 577. (f) Nemoto, H.; Cai, J.; Iwamoto, S.; Yamamoto, Y. *J. Med. Chem.* **1995**, *38*, 1673. (g) Yamamoto, Y.; Cai, J.;

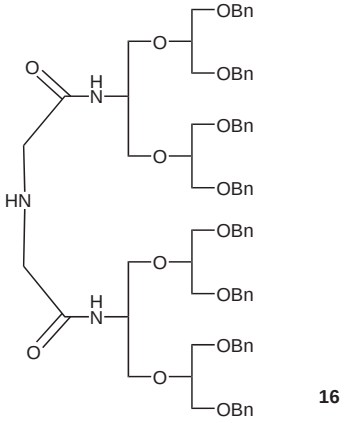


Scheme 4

Nakamura, H.; Sadayori, N.; Asao, N.; Nemoto, H. *J. Org. Chem.* **1995**, *60*, 3352. (h) Takagaki, M.; Ono, K.; Oda, Y.; Kikuchi, H.; Nemoto, H.; Iwamoto, S.; Cai, J.; Yamamoto, Y. *Cancer Res.* **1996**, *56*, 2017. (i) Nemoto, H.; Kikuishi, J.; Yanagida, S.; Kawano, T.; Yamada, M.; Harashima, H.; Kiwada, H.; Shibuya, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 205. (j) Nemoto, H.; Araki, T.; Kamiya, M.; Kawamura, T.; Hino, T. *Eur. J. Org. Chem.* **2007**, 3003.

(4) (a) In Scheme 15 of ref. 4b, the reaction of **4** and **3** with ECH to afford a mixture of **5** (**4** + **4** + ECH) and asymmetrical pentaglycerol (**4** + **3** + ECH), is drawn with a plain arrow but not with a dotted arrow. However, the authors mention in the main text that 'One can imagine repeating this step to give higher degree oligomers (pentamer, heptamer,…) with dendrimer-like structures' (around Scheme 15, our paper[3a,b] was the only one referenced). Furthermore, no experimental details are provided for Scheme 15. It is possible that they misread our paper,[3a,b] or mistakenly used a plain arrow rather than a dotted one. Accordingly, the preparation (either isolation or identification) of octabenzyl ether **5** has not been demonstrated. (b) Cassel, S.; Debaig, C.; Benvegnu, T.; Chaimbault, P.; Lafosse, M.; Plusquellec, D.; Rollin, P. *Eur. J. Org. Chem.* **2001**, 875.

(5) **BGL07** is a heptamer containing triply repetitive glyceryl units. In contrast, compound **16**, recently reported by us,[3j] contains a doubly repetitive glyceryl unit attached to a disparate trifunctionalized molecule (iminodiacetic acid). This octabenzyl ether **16** should be called **BGL06** (Figure 2).



16

Figure 2

(6) Preparation of **10a**. See: Forbes, D. C.; Ene, D. G.; Doyle, M. P. *Synthesis* **1998**, 879.

(7) Preparation of **10b**. See: (a) Crich, D.; Beckwith, A. L. J.; Chen, C.; Yao, Q.; Davison, I. G. E.; Longmore, R. W.; Anaya, d. e. P. C.; Quintero-Cortes, L.; Sandoval-Ramirez, J. *J. Am. Chem. Soc.* **1995**, *117*, 8757. (b) Carlsen Per, H. J.; Soerbye, K.; Ulven, T.; Aasboe, K. *Acta Chem. Scand.* **1996**, *50*, 185. (c) Based on ^{1}H NMR analysis, it is considered that **10b** has a chair form bearing phenyl group at equatorial position, and hydroxyl group at axial position. The hydroxyl group may have electronic affinity among oxygen atoms of the 1,3-dioxirane ring as shown in the following Figure 3.

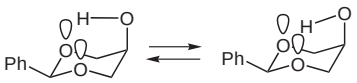


Figure 3

(8) **Preparation of 11a**
To a vigorously stirred mixture of **10a** (500 mg, 3.78 mmol), TBAI (61.0 mg, 0.19 mmol), finely ground KOH in a mortar (187.3 mg, 2.84 mmol), and H_2O (0.04 mL) was added ECH (87.5 mg, 0.95 mmol) slowly and dropwise. After stirring for 40 h at 60 °C, the resulting mixture was diluted with EtOAc, and the resulting suspension was filtered. The filtrate was dried over anhyd K_2CO_3, and concentrated in vacuo. The residue was purified by silica gel column chromatography using hexane–EtOAc (1:3) as an eluent to afford **11a** as a colorless oil (169.7 mg, 0.53 mmol, 56% yield) and **10a** (250 mg, 1.89 mmol, 50% recovered). FT-IR (KBr): 518, 561, 731, 829, 949, 1016, 1086, 1124, 1120, 1254, 1333, 1377, 1452, 1473, 2879, 2973, 3442 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.04–3.89 (m, 5 H), 3.83–3.73 (m, 4 H), 3.63–3.51 (m, 4 H), 3.49–3.41 (m, 2 H), 2.81 (br s, 1 H), 1.43 (s, 6 H), 1.41 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.0 (2 × C), 70.8 (2 × CH), 69.6 (2 × CH_2), 69.5 (CH), 62.3 (4 × CH_2), 23.5 (2 × CH_3), 23.4 (2 × CH_3). Anal. Calcd for $C_{15}H_{28}O_7$: C, 56.23; H, 8.81. Found: C, 55.88; H, 8.73.

(9) **Preparation of 11b**
To a mixture of **10b** (5.613 g, 31.2 mmol), TBAB (0.518 g, 1.56 mmol), finely ground KOH in a mortar (1.543 g, 31.2 mmol), and H_2O (0.04 mL) was added Et_2O (adequate amount for stirring). To the resulting suspension was added ECH (0.61 mL, 7.79 mmol) slowly and dropwise while stirring vigorously at r.t. The mixture was then stirred for 5 h at 40 °C, for 5 h at 60 °C, and then for 17 h at 80 °C. The mixture was poured into H_2O (50 mL), and extracted with EtOAc (5 × 50 mL). The combined organic layers were washed with brine, dried over anhyd K_2CO_3, and concentrated in vacuo. The residue was purified by silica gel column chromatography using hexane–EtOAc (1:4) as an eluent to afford **11b** (2.212 g, 5.32 mmol, 73% yield based on conversion of **10b**) and **10b** (2.955 g, 16.4 mmol, 53% recovered). FT-IR (neat): 700, 750, 800, 839, 916, 980, 1011, 1092, 1153, 1217, 1238, 1277, 1340, 1392, 1454, 2860, 2974, 3477 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.43 (m, 4 H), 7.40–7.32 (m, 6 H), 5.54 (s, 2 H), 4.41–4.31 (m, 4 H), 4.10–3.98 (m, 5 H), 3.79–3.65 (m, 4 H), 3.77–3.67 (m, 2 H), 2.85 (d, *J* = 5.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9 (2 × C), 128.6 (2 × CH), 127.9 (4 × CH), 125.8 (4 × CH), 100.9 (2 × CH), 70.9 (2 × CH), 69.5 (CH), 69.1 (2 × CH_2), 68.7 (4 × CH_2). HRMS (EI): *m/z* calcd for $C_{23}H_{28}O_7$ [M$^+$]: 416.1809; found: 416.1835.

(10) The recovered yield of **11** was calculated using the following equation (Equation 1). Accordingly, 50% is the ideal value for entries 1–6, and 0% is the ideal value for entries 7–9 (Table 1). Equation 2 was also used to calculate the yield of **12** since **12** consists of two moieties of **11** and an excess of **11** was used.

$$\text{recovered yield of } \mathbf{11} = \frac{(\text{recovered weight of 11})}{(\text{molecular weight of 11})}$$

Equation 1

$$\text{Yield of } \mathbf{12} = \frac{(\text{weight of } \mathbf{12} \text{ obtained}) \div (\text{molecular weight of } \mathbf{12} \text{ obtained})}{\left[\dfrac{(\text{weight of starting } \mathbf{11}) - (\text{recovered weight of } \mathbf{11})}{(\text{molecular weight of } \mathbf{11})} \div 2\right]}$$

Equation 2

(11) Compound **12a**: FT-IR (neat): 521, 733, 827, 941, 1084, 1120, 1252, 1286, 1375, 1454, 1651, 1716, 2877, 2991, 3417 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.00–3.86 (m, 9 H), 3.80–3.50 (m, 22 H), 3.48–3.40 (m, 4 H), 1.43 (s, 12 H), 1.40 (s, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.1 (4 × C), 78.7 (2 × CH), 71.9 (2 × CH_2), 70.9 (4 × CH), 69.6 (CH), 68.7, 68.6 (4 × CH_2), 62.4, 62.4, 62.3, 62.3 (8 × CH_2), 30.9, 29.6, 24.0, 24.0, 23.1, 23.0 (8 × CH_3). ESI-HRMS: *m/z* calcd for $C_{33}H_{60}O_{15}Na$ $[M + Na]^+$: 719.3830; found: 719.3832.

(12) Compound **12b**: FT-IR (neat): 699, 749, 799, 841, 916, 982, 1011, 1092, 1216, 1238, 1278, 1278, 1344, 1392, 1454, 1496, 1604, 2864, 3034, 3477 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.44 (m, 8 H), 7.43–7.29 (m, 12 H), 5.60–5.41 (s, 4 H), 4.43–4.22 (m, 8 H), 4.02–3.87 (m, 9 H), 3.85–3.56 (m, 14 H), 3.40–3.25 (s, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7 (4 × C), 128.0 (4 × CH), 127.3 (8 × CH), 125.4 (8 × CH), 100.2 (4 × CH), 78.1 (2 × CH), 71.0 (2 × CH_2), 70.4 (4 × CH), 69.1 (CH), 68.2, 67.9 (8 × CH_2), 67.7, 67.5 (4 × CH_2). HRMS–FAB: *m/z* calcd for $C_{49}H_{61}O_{15}$ $[M + H]^+$: 889.4018; found: 889.4010.

(13) Structure of the glycidyl ether (Figure 4):

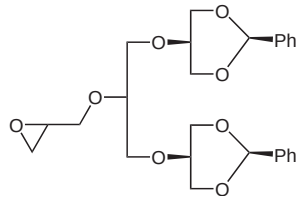


Figure 4

(14) A molar ratio **11a**/ECH = 4:1 was finally applied, otherwise nucleophilic attack by **11a** to the glycidyl ether (**11a** + ECH) slowed down, affording an unidentified mixture and some identified oligomers such as an asymmetrical tetramer (**11a** + ECH + H_2O) and an asymmetrical undecamer (**12a** + ECH + **11a** = three of **11a** + two of ECH).

(15) In contrast to the reaction with **11a**,[14] compounds with high molecular weight such as undecamers, were not detected when **11b** was used. Therefore, a molar ration of **11b**/ECH = 2:1 was applied.

(16) Compound **14a**: pale yellow oil. FT-IR (neat): 520, 665, 754, 827, 941, 995, 1087, 1373, 1454, 1553, 1666, 1739, 1783, 1815, 2875, 2941, 2993, 3334, 3508 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.63 (d, *J* = 8.8 Hz, 1 H), 4.18–4.08 (m, 1 H), 3.98–3.87 (m, 8 H), 3.77–3.64 (m, 10 H), 3.61–3.44 (m, 12 H), 3.42–3.33 (m, 4 H), 2.80 (s, 4 H), 2.65 (t, *J* = 7.2 Hz, 2 H), 2.30 (t, *J* = 7.2 Hz, 2 H), 2.03 (quin, *J* = 7.2 Hz, 2 H), 1.42–1.34 (m, 24 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3 (C), 168.9 (2 × C), 168.1 (C), 98.1 (2 × C), 98.0 (2 × C), 78.7 (2 × CH), 71.0 (2 × CH), 70.9 (2 × CH), 68.8 (2 × CH_2), 68.7 (2 × CH_2), 68.6 (2 × CH_2), 62.5 (4 × CH_2), 62.3 (2 × CH_2), 62.2 (2 × CH_2), 49.3 (CH), 34.3 (CH_2), 30.0 (CH_2), 25.5 (2 × CH_2), 23.9 (2 × CH_3), 23.6 (2 × CH_3), 23.6 (2 × CH_3), 23.3 (2 × CH_3), 20.5 (CH_2). ESI-HRMS: *m/z* calcd for $C_{42}H_{70}N_2O_{19}Na$ $[M + Na]^+$: 929.4470; found: 929.4470.

Compound **14b**: pale yellow oil. FT-IR (neat): 699, 749, 799, 1012, 1092, 1208, 1389, 1454, 1495, 1529, 1667, 1739, 1783, 1813, 2862, 3346 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.42 (m, 8 H), 7.41–7.29 (m, 12 H), 6.83–6.73 (m, 1 H), 5.48 (s, 4 H), 4.40–4.22 (m, 8 H), 4.19–4.08 (m, 1 H), 4.04–3.85 (m, 8 H), 3.82–3.46 (m, 14 H), 3.35–3.21 (m, 4 H), 2.71 (s, 4 H), 2.45 (t, 2 H, *J* = 8.0 Hz), 2.06 (t, 2 H, *J* = 8 Hz), 1.83 (quin, 2 H, *J* = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4 (C), 169.5 (C), 168.1 (C), 138.1 (4 × C), 128.6 (4 × CH), 127.9 (8 × CH), 125.9 (8 × CH), 100.9, 100.8 (4 × CH), 78.6 (2 × CH), 71.1, 71.0 (4 × CH), 69.0, 68.9, 68.6, 68.5 (8 × CH_2), 67.9 (2 × CH_2), 49.4 (CH), 34.1 (CH_2), 29.8 (CH_2), 25.4 (2 × CH_2), 20.3 (CH_2). HRMS–FAB: *m/z* calcd for $C_{58}H_{71}N_2O_{19}$ $[M + H]^+$: 1099.4633; found: 199.4651.

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