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Preparation of Discrete Oligoethers: Synthesis of Pentabutylene Glycol and Hexapropylene Glycol by Two Complementary Methods

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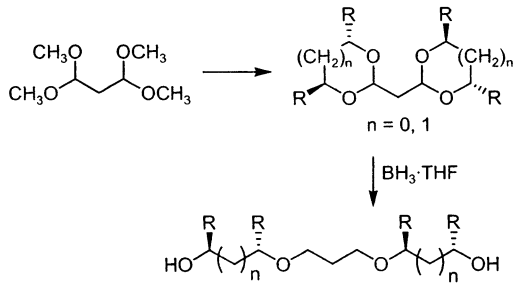
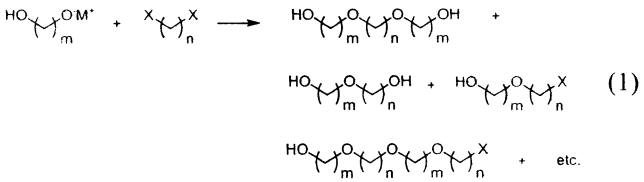
Abstract: Two experimentally facile methods for the preparation of discrete oligoethers are reported. The first involves an iterative sequence of oxidation, acetal formation, and reductive ring opening for the synthesis of penta-1,4-butylene glycol. The second method is also iterative, comprising phase-transfer etherification and end-group deprotection to form hexa-1,3-propylene glycol. These methods offer significantly improved yields and purification protocols over previously reported syntheses.

Polyethers such as polyethylene glycol, polypropylene glycol, and polybutylene glycol are gaining prominence as components of macromolecular systems because of the robust nature of the ether backbones and because the polarity of the chain can be adjusted by the relative proportion of methylene units and oxygens. Polyethylene glycol has proven useful in biomedical applications such as drug delivery[1] and surface coatings to prevent adsorption of proteins.[2] Additionally, oligomers of ethylene glycol, propylene glycol, and butylene glycol are attractive chains for linking multiple chemical or biochemical components to generate complex systems.[3] We are interested in taking advantage of the versatility of these oligoethers as membrane-spanning chains of synthetic transmembrane ion channels.

To acquire channel dimensions that match the thickness of a phospholipid bilayer, we require the preparation of discrete, monodisperse oligomers. While ethylene glycol oligomers are readily available, the same cannot be said of oligopropylene glycols or of oligobutylene glycols. The most commonly cited preparation of such oligomers involves the reaction of a central fragment functionalized with leaving groups on both ends with an excess of terminal ω-hydroxy alkoxide units (eq 1).[4] While this protocol does afford the desired ethers, additional products of various lengths also form, presumably due to partial hydrolysis of the leaving groups prior to ether formation in conjunction with proton exchange between the numerous hydroxyl groups. The desired oligoethers are isolated in low yields following laborious purification.

SCHEME 1





(1)

We have circumvented these problems using two alternative, complementary strategies for the preparation of discrete oligo-1,4-butylene glycol and 1,3-propylene glycol chains. For the former, we employ a strategy of oxidation, acetal formation, and reductive ring opening to obtain oligobutylene glycols having an odd number of units. To access oligopropylene glycols with an even number of units, we perform etherification under phase-transfer conditions with monoprotected terminal units. Both methods employ high-yielding reactions to form products that are readily purified. The details of the two approaches are reported herein.

Our first oligoether target capable of serving as a component of a membrane-spanning macromolecule was penta-1,4-butylene glycol. In an effort to circumvent the problems highlighted in eq 1 above, we were inspired by a report by Gutiérrez and co-workers in which diether diols were prepared in high yield following a two-step protocol involving formation of the biscyclic acetal and reductive opening of the acetals (Scheme 1).[5] The authors reported the preparation of a number of diether diols from five- and six-membered ring bisacetals with the intent of forming substituted crown ethers.

Although there are limited examples of the preparation of the seven-membered ring cyclic acetals required for our oligobutylene glycol target,[6] and even fewer examples of reductive cleavage of such medium-ring acetals,[7] we were pleased to discover that the reactions work well to give clean ether diol products (Scheme 2). Thus, treatment of the masked dialdehyde 2,5-dimethoxy tetrahy-

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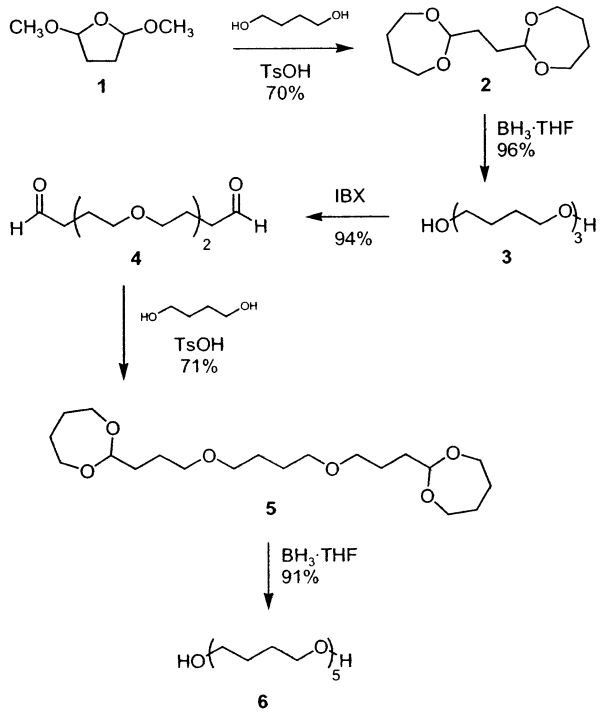
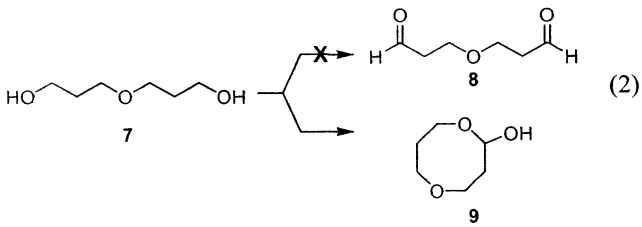
SCHEME 2



drofuran (**1**) with 1,4-butanediol and catalytic *p*-toluenesulfonic acid (TsOH) resulted in the formation of bisacetal **2** in 70% yield. Subsequent exposure to borane−THF in refluxing THF for 2 days afforded tributylene glycol (**3**) in 96% yield as the sole product. Oxidation of the diol to the dialdehyde with *o*-iodoxybenzoic acid (IBX) in ethyl acetate[8] yielded dialdehyde **4**, and subsequent reaction with 1,4-butanediol and TsOH afforded bisacetal **5** in 67% yield for the two-step sequence. Further reaction of pure diacetal **5** with borane−THF afforded pentabutylene glycol (**6**) in 91% yield. Using this protocol, we can readily access multigram quantities of **6**.

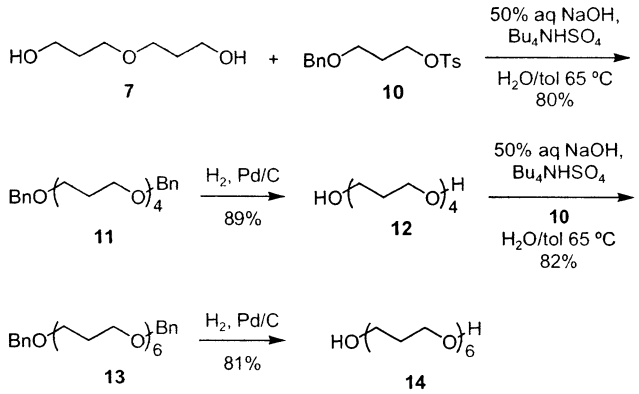
To obtain an oligopropylene glycol chain of similar length to pentabutylene glycol **6**, we sought to prepare hexa-1,3-propylene glycol. We first attempted a strategy similar to that discussed above but encountered difficulty converting ether diol **7**[9] to dialdehyde **8** (eq 2). Rather, oxidation occurred at one end of the molecule followed by intramolecular hemiacetal formation to yield **9**[10] along with other unidentified products.



(2)

In light of this undesired cyclization, we revisited the ether synthesis outlined above (eq 1). The problems

SCHEME 3



encountered were due primarily to two side reactions: reaction of both alcohols of the terminal diol instead of only one and hydrolysis of the leaving group to generate a new reactive alcohol. To overcome these side reactions, we used monoprotected 3-benzyloxypropyl sulfonate (**10**) as the terminal unit and diol **7** as the central fragment and performed the etherification reaction under mild phase-transfer conditions (50% aqueous NaOH and Bu_4NHSO_4 in water and toluene at 65 °C) to afford dibenzyl tetrapropylene glycol (**11**) cleanly in 80% yield (Scheme 3). Because of the hydrophobic benzyl protecting group, the starting diol, the monoreacted intermediate alcohol, and the doubly reacted product have polarity differences that allow facile purification of the desired product. Reductive debenzylation using palladium on carbon under an atmosphere of hydrogen gave the triether diol **12** in 89% yield. The two-step sequence of ether formation and debenzylation was repeated with similar results to afford hexapropylene glycol (**14**) in 66% yield for the two steps.[11]

The preferred strategy for discrete oligoether synthesis depends primarily on the number of ether units desired. The sequence of oxidation, acetal formation, and reductive ring opening used to prepare pentabutylene glycol **6** utilizes inexpensive starting materials and is readily performed on multigram quantities to afford oligoethers with odd numbers of ether units. The second protocol requires the preparation of starting materials **7** and **10** but then allows rapid access to oligoethers with even numbers of units. In practice, both methods enable straightforward preparation of discrete oligoether diols as pure compounds.

In conclusion, two experimentally facile methods for the preparation of discrete oligoethers are reported. The first involves an iterative sequence of oxidation, acetal formation, and reductive ring opening for the synthesis of penta-1,4-butylene glycol. The second method is also iterative, comprising phase-transfer etherification and debenzylation to form hexa-1,3-propylene glycol. These methods offer significantly improved yields and purification protocols over previously reported syntheses.

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Experimental Section

Unless otherwise specified, all starting materials were obtained from commercially available sources and used without further purification. All air- or moisture-sensitive reactions were performed under an atmosphere of dry argon, utilizing standard Schlenk line techniques. Benzene was distilled from sodium metal, pyridine and CH_2Cl_2 were distilled from calcium hydride, THF was distilled from sodium benzophenone ketyl, and MeOH was distilled from magnesium dust. Analytical TLC visualization was accomplished with UV light, ceric ammonium molybdate, *p*-anisaldehyde, I_2, or $KMnO_4$.

Bisacetal 2. To a solution of **1** (0.50 mL, 3.9 mmol, 1.0 equiv) and 1,4-butane diol (3.0 mL, 34 mmol, 8.7 equiv) in 50 mL of CH_2Cl_2 was added TsOH (40 mg 0.2 mmol, 0.05 equiv). The reaction mixture was heated to 40 °C for 20 h, then the reaction quenched with 50 mL of saturated aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous NaCl and concentrated in vacuo. Purification of the oily solid by filtration through silica gel (8:1 hexane/acetone) afforded 625 mg (70%) of **2** as a white crystalline solid: TLC $R_f = 0.47$ (3:1 hexane/acetone); mp 49−50 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.68 (m, 2H), 3.87 (m, 4H), 3.62 (m, 4H), 1.71−1.64 (m, 12H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 102.4, 65.7, 29.7, 29.3; IR (thin film) ν 2939 (m), 2872 (m), 1461, 1368, 1291, 1135 (s), 1062, 986 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{23}O_4^+$ (MH^+) 231.1596, found 231.1596.

Tributylene Glycol 3. To a solution of **2** (2.0 g, 8.7 mmol, 1 equiv) in 90 mL of THF at 0 °C was added BH_3−THF (1.0 M in THF, 22 mL, 22 mmol, 2.5 equiv) dropwise. The solution was stirred at 0 °C for 20 min and then warmed to 23 °C. The flask was equipped with a reflux condenser, and the solution was heated to 90 °C. After 48 h at reflux, the solution was cooled to 0 °C and quenched by the dropwise addition of 10 mL of MeOH. The solution was then concentrated in vacuo to give 1.95 g (96%) of **3** as a colorless oil: TLC $R_f = 0.18$ (80% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (t, 4H, $J = 6$ Hz), 3.47 (t, 8H, $J = 6$ Hz), 2.72 (br s, 2H), 1.68 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.9, 70.7, 2.7, 30.4, 27.0, 26.3; IR (thin film) ν 3364 (s), 2941, 2865, 1372, 1112, 738 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{27}O_4^+$ (MH^+) 235.1909, found 235.1909.

Dialdehyde 4. A solution of **3** (530 mg, 2.62 mmol, 1 equiv) and IBX (4.4 g, 16 mmol, 7.0 equiv) in 10 mL of EtOAc was heated to 80 °C open to the atmosphere. After the solution was stirred vigorously for 2 h, it was cooled to 23 °C and filtered through a medium fritted funnel.[12] The filtrate was concentrated in vacuo to yield 492 mg (94%) of **4**[13] as an oil: TLC $R_f = 0.44$ (2:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.76 (t, 2H, $J = 1.6$ Hz), 3.44−3.38 (m, 8H), 2.51 (td, 4H, $J = 7.2$, 1.6 Hz), 1.90 (m, 4H), 1.59 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.4, 70.6, 69.6, 41.0, 26.4, 22.6; IR (thin film) ν 2861, 1724 (s), 1114 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{23}O_4^+$ (MH^+) 231.1596, found 231.1605.

Bisacetal 5. To a solution of freshly prepared **4** (264 mg, 1.15 mmol, 1 equiv) and 1,4-butane diol (1.25 mL, 14.1 mmol, 12 equiv) in 100 mL of CH_2Cl_2 was added TsOH (11 mg, 0.057 mmol, 0.05 equiv). After 4 h, the reaction mixture was neutralized with 100 mL of saturated aqueous $NaHCO_3$. The organic layer was removed and washed with saturated aqueous NaCl and then concentrated in vacuo, and the resultant oil was purified by column chromatography (6:1 hexane/acetone) to afford 305 mg (71%) of **5** as an oil: TLC $R_f = 0.32$ (6:1 hexane/acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.68 (m, 2H), 3.87 (m, 4H), 3.62 (m, 4H), 3.41 (m, 8H), 1.64 (m 20 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 102.6, 70.6, 70.5, 65.7, 31.0, 29.3, 26.5, 25.1; IR (thin film) ν 2940, 2868, 1139, 1116, 1062, 981 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{39}O_6^+$ (MH^+) 375.2747, found 375.2747.

Pentabutylene Glycol 6. The procedure for the formation of **3** was followed using 1.1 g (2.9 mmol, 1 equiv) of **5**. Column chromatography (70% hexane/acetone) afforded 1.0 g (91%) of **6** as an oil that solidified upon standing: TLC $R_f = 0.18$ (80% EtOAc/hexane); mp 33−34 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 (dt, 4H, $J = 8.4$, 5.2 Hz), 3.44 (m, 16H) 2.53 (t, 2H, $J = 5.4$ Hz), 1.65 (m, 20 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 70.87, 70.85, 70.65, 70.55, 62.8, 30.4, 26.91, 26.54, 26.48 26.47; IR (thin film) ν 3400 (br), 2939, 2858, 1447, 1368, 1126, 750 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{42}O_6^+$ (MH^+) 379.3060, found 379.3060.

Benzyloxypropyl Tosylate 10.[14] To a solution of 3-benzyloxypropanol[15] (664 mg, 4.00 mmol, 1 equiv) in pyridine (3.3 mL) at −10 °C was added a solution of TsCl (920 mg, 4.80 mmol, 1.2 equiv) in 1.7 mL of pyridine dropwise over 5 min. The mixture was allowed to warm to 23 °C and continued to react for 3 h. The reaction was quenched upon addition of 30 mL of ice water. The aqueous solution was extracted with Et_2O, and the combined organic layers were washed with 5% aqueous HCl. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography on silica gel (1:1 Et_2O/hexane) afforded 1.18 g (93%) of **10** as a colorless oil: TLC $R_f =$ 0.70 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 2H, $J = 8.4$ Hz), 7.32 (d, 2H, $J = 8.4$ Hz), 7.22−7.37 (m, 5H), 4.40 (s, 2H), 4.17 (t, 2H, $J = 6.0$ Hz), 3.50 (t, 2H, $J = 6.0$ Hz), 2.42 (s, 3H), 1.94 (app qn, 2H, $J = 6.0$ Hz).

1-Benzyloxy-3-(3-benzyloxy-propoxy) Propane. To a mixture of 3-benzyloxy propanol (332 mg, 2.00 mmol, 1 equiv), **10** (768 mg, 2.00 mmol, 1.2 equiv), and Bu_4NHSO_4 (339 mg, 1.00 mmol, 0.5 equiv) was added 50% (wt/wt) aqueous NaOH (3.9 mL) and benzene (4.7 mL). The mixture was stirred at 65 °C for 12 h. After the mixture had cooled to 23 °C, 10 mL of H_2O was added and the organic material was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography on silica gel (1:10 EtOAc/hexane) afforded 480 mg (76%) of the triether product as a colorless oil: TLC $R_f = 0.65$ (1:4 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24−7.36 (m, 10 H), 4.50 (s, 4H), 3.55 (t, 4H, $J = 6.4$ Hz), 3.52 (t, 4H, $J = 6.4$ Hz), 1.87 (app qn, 4H, $J = 6.4$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 128.3, 127.6, 127.5, 73.0, 67.8, 67.4, 30.1; IR (neat) ν 3063, 3030, 2924, 2863, 1275, 1110 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{27}O_3$ (MH^+) 315.1960, found 315.1959.

Ether Diol 7.[9] To a solution of 1-benzyloxy-3-(3-benzyloxy-propoxy) propane (456 mg, 1.45 mmol, 1 equiv) in MeOH (20 mL) was added Pd/C (200 mg, 10 wt % Pd). The atmosphere was replaced with H_2, and the mixture was stirred under 1 atm H_2 for 5 h. The Pd/C was filtered off, and the filtrate was concentrated in vacuo. Flash chromatography (1:10 MeOH/EtOAc) afforded 194 mg (100%) of **7** as a colorless oil: TLC $R_f =$ 0.57 (1:5 MeOH/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76 (t, 4H, $J = 6.0$ Hz), 3.62 (t, 4H, $J = 6.0$ Hz), 2.45 (s, 2H), 1.83 (app qn, 4H, $J = 6.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 69.8, 61.4, 32.0; MS (EI) 135 (MH^+), 117 (7), 89 (38), 75(66), 59 (100).

Dibenzyl Tetrapropylene Glycol 11. To a mixture of **7** (194 mg, 1.45 mmol, 1 equiv), **10** (1.12 g, 3.48 mmol, 2.4 equiv), and Bu_4NHSO_4 (492 mg, 1.45 mmol, 1 equiv) was added 50% (wt/wt) aqueous NaOH (3.9 mL) and benzene (4.7 mL). The mixture was heated to 65 °C for 36 h. After the mixture had cooled to 23 °C, 10 mL of H_2O was added and the organic material was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography (1:10 EtOAc/hexane) afforded 500 mg (80%) of **11** as a colorless oil: TLC $R_f = 0.55$ (1:4 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24−7.38 (m, 10H), 4.50 (s, 4H), 3.43−3.58 (m, 16H), 1.78−1.90 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 128.3, 127.6, 127.5, 72.9, 67.9, 67.84, 67.79, 67.4, 30.12, 30.07; IR (neat) ν 3064, 3031, 2923, 2860, 1275, 1110 cm^{-1}; HRMS (CI) calcd for $C_{26}H_{39}O_5$ (MH^+) 431.2799, found 431.2798.

Tetrapropylene Glycol 12. The procedure for the preparation of **7** was followed using 490 mg (1.14 mmol, 1 equiv) of **11**.

(12) It is important to quench the reaction upon complete conversion to the dialdehyde as extended reaction times lead to decomposition of the product.

(13) Although ^{1}H NMR indicates that the product is >95% pure, further purification can be performed without significant decomposition of the product by column chromatography using 2% Et_3N in 2:1 EtOAc/hexane.

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Flash chromatography (1:10 MeOH/EtOAc) afforded 254 mg (89%) of **12** as a colorless oil: TLC $R_f = 0.60$ (1:10 MeOH/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76 (t, 4H, $J = 5.6$ Hz), 3.61 (t, 4H, $J = 5.6$ Hz), 3.52 (t, 4H, $J = 6.4$ Hz), 3.49 (t, 4H, $J = 6.4$ Hz), 2.45−2.57 (br s, 2H), 1.78−1.88 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 70.2, 68.2, 67.8, 62.1, 31.9, 29.9; IR (neat) ν 3369, 2944, 2868, 1371, 1113 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{27}O_5$ (MH^+) 251.1858, found 251.1868.

Dibenzyl Hexapropylene Glycol 13. The procedure for the preparation of **11** was followed using 142 mg (0.568 mmol, 1 equiv) of **12**. Flash chromatography (1:2 EtOAc/hexane) afforded 254 mg (82%) of **13** as a colorless oil: TLC $R_f = 0.45$ (1:1 EtOAc/*n*-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17−7.30 (m, 10H), 4.42 (s, 4H), 3.36−3.50 (m, 24H), 1.70−1.85 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 128.3, 127.6, 127.5, 73.0, 67.9, 67.8, 67.4, 30.12, 30.08; IR (neat) ν 3030, 2923, 2860, 1366, 1275, 1110 cm^{-1}; HRMS (CI) calcd for $C_{32}H_{51}O_7$ (MH^+) 547.3630, found 547.3635.

Hexapropylene Glycol 14. The procedure for the preparation of **7** was followed using 111 mg (0.203 mmol, 1 equiv) of **13**. Flash chromatography (1:10 MeOH/EtOAc) afforded 60 mg (81%) of **14** as a colorless oil: TLC $R_f = 0.58$ (1:5 MeOH/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.57 (t, 4H, $J = 6.0$ Hz), 3.61 (t, 4H, $J = 6.0$ Hz), 3.52 (t, 4H, $J = 6.0$ Hz), 3.48 (t, 12 H, $J = 6.0$ Hz), 2.37−2.44 (br s, 2H), 1.75−1.86 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 70.1, 68.3, 67.9, 67.82, 67.76, 62.0, 32.1, 30.1; IR (neat) ν 3435, 2945, 2859, 1371, 1115 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{39}O_7$ (MH^+) 367.2696, found 367.2693.

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Supporting Information Available: Proton and ^{13}C NMR spectra of compounds **2**−**6** and **11**−**14** in PDF. This material is available free of charge via the Internet at http://pubs.acs.org.

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