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Synthesis of Novel C-Pivot Lariat 18-Crown-6 Ethers and Their Efficient Purification

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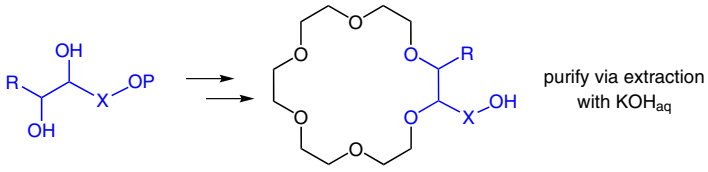

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Abstract The syntheses of various lariat ethers including several not previously reported and their efficient purification are presented. The synthesis route brings together reactions from a variety of previous works leading to a robust and generalized approach to these C-pivot lariats. The main steps are condensation of functionalized diols with pentaethylene glycol ditosylate in the presence of potassium as a templating cation. Purification of the final products was achieved without chromatography by extracting from an aqueous potassium hydroxide solution.

Key words 18-crown-6, C-pivot lariat ethers, crown compounds, potassium hydroxide purification, macrocyles

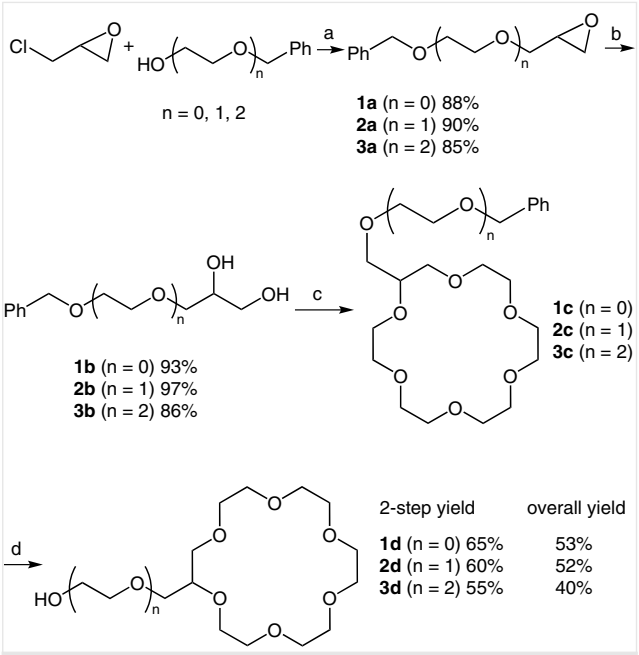
Crown ethers have long been exploited as phase-transfer agents in organic chemistry[1] and thus their efficient preparation has attracted the attention of numerous researchers.[2] An exciting variation of crown ethers involves the inclusion of a side arm on the macrocyclic which often contains metal-coordinating heteroatoms. These lariat ethers, first studied by Gokel and co-workers,[3] were found to confer unique cation-binding properties.[4] Carbon-pivot lariat ethers are a subclass of these compounds in which the side arm (podand) extend from a carbon atom in the macrocycle. These compounds often exhibit increased guest specificity.[5,6]

We have recently used lariat ethers as metal-chelating leaving groups to expedite nucleophilic substitution reactions[7] with emphasis on the expedited radiofluorination of small molecules.[8] Following a similar strategy, we have appended chelating leaving groups to silicon for ultrafast silicon radiofluorination using K^{18}F.[9] In an attempt to further improve the efficiency of silicon fluorination, we have begun to use lariat ethers as nucleophilic catalysts. For this project, we required access to gram quantities of 18-crown-6 (18-C-6) containing side arms possessing a hydroxyl group including some derivatives not previously reported. A careful review of the literature revealed a variety of lariat ether synthesis strategies and purification methods. These reports used either vacuum distillation or column chromatography as the purification method.[10,11] In this letter, we report our development of an optimized route that takes advantage of various elements of previous reports to efficiently prepare a series of C-pivot 18-C-6 compounds.

We began with the synthesis of lariats **1d**–**3d** (Scheme 1). Intermediate epoxides **1a**–**3a** were synthesized from reaction of the appropriate alcohol[12] with epichlorohydrin in aqueous sodium hydroxide in the presence of catalytic TBAB.[13] The resulting epoxides **1a**–**3a** were converted[14] into functionalized diols **1b**–**3b** that then reacted with pentaethylene glycol ditosylate and KO*t*-Bu in THF under reflux conditions to afford benzyl-protected lariats **1c**–**3c**. These intermediates were debenzylated under hydrogenation conditions[2c] (H_2, Pd/C) to afford 18-C-6 lariat ethers **1d**–**3d** in 55–65% two-step yields after purification.

The overall yields for our lariat products were between 40% and 53%, a substantial improvement over previously reported methods. For example, for compound **1d**, synthesized by a number of groups, our overall yield was 53% in four steps. Fukunishi and coworkers reported overall yields of 32% and 24%, respectively, for **1d** using two different pathways with product isolation accomplished by chromatography on alumina.[2c] Others have reported overall yields of 31% and 35% of **1d** using a distillation technique to purify the final compound.[2d–f]

The only synthesis of **5d**, reported in the literature, uses a radical process to functionalize the 18-C-6 with allyl alcohol in 8% yield.[2h] Colera and coworkers reported the synthesis of **7d** in an overall yield of 11% in six steps[2l] compared to



Scheme 1 Synthesis of lariats **1d**–**3d**. *Reagents and conditions*: (a) 40% aq NaOH, TBAB, 0 °C for 1 h and then r.t. for 24 h; (b) 2% H_2SO_4, r.t., 5 h; (c) KO*t*-Bu, pentaethyleneglycol ditosylate, THF, r.t. for 1 h and then reflux for 48 h; (d) Pd/C, H_2, EtOH, r.t., 48 h.

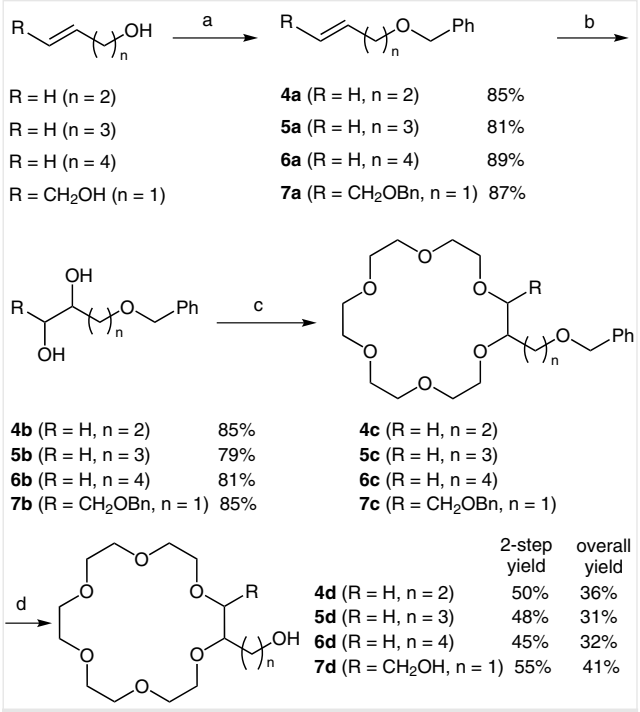
the 41% overall yield in four steps in this work. In this letter, we also report for the first time the synthesis of lariats **2d**, **3d**, **4d**, and **6d**.

The above route to obtain functionalized diols worked well for **1d**–**3d** since the starting materials, benzyl alcohol and its mono- and diethylene glycol derivatives, had reasonable aqueous solubility. This was not the case for the analogous reactions required to give lariats **4d**–**7d**[20] containing alkanol side arms (Scheme 2). The analogous epichlorohydrin addition reactions (not shown) led to low yields (ca. 10%) even after significant attempts at optimization. Therefore, an alternative approach was required. Our synthesis began with a benzylation step using NaH and BnBr to obtain alkene **4a**–**7a**.[15] Diols **4b**–**7b** were then prepared using OsO_4/NMO following a literature procedure.[16] Cyclization reactions between various diols and pentaethyleneglycol ditosylate followed by debenzylation afforded the desired crown ethers in reasonable overall yields (30–40%).

As mentioned, benzyl lariat ethers **1c**–**7c**[19] were formed by condensation with pentaethylene glycol ditosylate in the presence of potassium *tert*-butoxide using the well-known template effect.[17] These reactions usually required more than 48 hours for all starting material to be consumed. Upon completion, the reaction mixture contained byproducts that could not be conveniently separated using flash chromatography. A variety of traditional eluent systems and both silica gel and alumina stationary phases were evaluated to no avail. We carried forward these product mixtures to the hydrogenolysis step. The resulting mixture of debenzylated compounds was then separated on neutral alumina using a gradient elution of 1–10% 2-propanol–dichloromethane or 1–10% MeOH–EtOAc eluent system. However, this gradient method is a lengthy process requiring copious amounts of solvent (> 3 L for 3 g of crude).

In an attempt to isolate the final lariat products more efficiently, we sought to take advantage of their metal-chelating properties to bring about a selective precipitation of the desired compound from the product mixture. A few reports demonstrate that complexation followed by precipitation using KBF_4 is a feasible approach.[18] Along these lines, we also found KNO_3 to be effective in purifying lariat ether products by precipitation. However, these methods were problematic and unreliable on the multigram scale.

As an alternative, we developed a simplified extraction technique using aqueous potassium hydroxide. Thus crude debenzylated reaction mixtures (ca. 5 g) were stirred with 50 mL of aq KOH (1 M) for 5 min. After this time, the impurities were removed by extraction using ethyl acetate until TLC showed the absence of any impurity (usually three extractions). The water layer was then extracted with dichloromethane (3 times, monitored by alumina TLC; 4% 2-PrOH–CH_2Cl_2 eluent). The organic layer was collected, the solvent was removed in vacuo, and the resulting material was passed through a small plug of neutral alumina (10%



Scheme 2 Synthesis of lariats **4d**–**7d**. *Reagents and conditions*: (a) NaH, BnBr, THF, 0 °C to r.t. over 6 h; (b) OsO_4, NMO, acetone–H_2O, r.t., 12 h; (c) KO*t*-Bu, pentaethyleneglycol ditosylate, THF, r.t. for 1 h then reflux for 48 h; (d) Pd/C, H_2, EtOH, r.t., 48 h.

MeOH–EtOAc as eluent) to furnish noncomplexed lariat products. This process was significantly less tedious and offered nearly identical isolated yields as those based on flash chromatography.

In summary, bringing together reactions from a variety of previous works, we have developed a robust approach to a series C-pivot lariat ether compounds. This process involves the condensation of functionalized diols with pentaethylene glycol ditosylate in the presence of templating cations. Purification of the final products was achieved by a simple extraction method that obviated the need for tedious chromatography. We believe that this convenient synthesis of lariat ethers will facilitate their use as novel bifunctional catalysts.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378790.

References and Notes

(1) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495.
(2) (a) Montanari, F.; Tundo, P. *Tetrahedron Lett.* **1979**, 5055. (b) Czech, B. *Tetrahedron Lett.* **1980**, *21*, 4197. (c) Fukunishi, K.; Czech, B.; Regen, S. L. *J. Org. Chem.* **1981**, *46*, 1218. (d) Jungk, S. J.; Moore, J. A.; Gandour, R. D. *J. Org. Chem.* **1983**, *48*, 1116. (e) Ikeda, I.; Emura, H.; Okahara, M. *Synthesis* **1984**, 73. (f) Bělohradský, M.; Stibor, I.; Holý, P.; Závada, J. *Collect. Czech. Chem. Commun.* **1987**, *52*, 2500. (g) Zelechonok, J. B.; Orlovskii, V. V.; Zlotskii, S. S.; Rakhmankulov, D. L. *J. Prakt. Chem.* **1990**, *332*, 719. (h) Hiraoka, M. *Crown Ethers and Analogous Compounds*; Elsevier: Amsterdam, **1992**. (i) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203. (j) List, B.; Castello, C. *Synlett* **2001**, 1687. (k) Hu, H.; Bartsch, R. A. *J. Heterocycl. Chem.* **2004**, *41*, 557. (l) Colera, M.; Costero, A. M.; Gavina, P.; Gil, S. *Tetrahedron: Asymmetry* **2005**, *16*, 2673.
(3) Gokel, G. W. *Crown Ethers and Cryptands*; RSC: Oxford, UK, **1991**.
(4) (a) Gokel, G. W.; Dishong, D. M.; Diamond, C. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1053. (b) Goli, D. M.; Dishong, D. M.; Diamond, C. J.; Gokel, G. W. *Tetrahedron Lett.* **1982**, *23*, 5243. (c) Gustowski, D. A.; Echegoyen, L.; Goli, D. M.; Kaifer, A.; Gokel, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 1633. (d) Echegoyen, L.; Delgado, M.; Gatto, V. J.; Gokel, G. W. *J. Am. Chem. Soc.* **1986**, *108*, 6825.
(5) Rapi, Z.; Bakó, P.; Drahos, L.; Keglevich, G. *Heteroat. Chem.* **2014**, *26*, 63.
(6) (a) Gokel, G. W. *Chem. Soc. Rev.* **1992**, *21*, 39. (b) Gokel, G. W.; Leevy, W. M.; Weber, M. E. *Chem. Rev.* **2004**, *104*, 2723. (c) Gokel, G. W.; Schall, O. F. In *Comprehensive Supramolecular Chemistry*; Pergamon Press: New York, **1996**, 97.
(7) (a) Lepore, S. D.; Mondal, D. *Tetrahedron* **2007**, *63*, 5103. (b) Lepore, S. D.; Bhunia, A. K.; Cohn, P. *J. Org. Chem.* **2005**, *70*, 8117.
(8) Lu, S.; Lepore, S. D.; Li, S. Y.; Mondal, D.; Cohn, P. C.; Bhunia, A. K.; Pike, V. W. *J. Org. Chem.* **2009**, *74*, 5290.
(9) Al-huniti, M. H.; Lu, S.-Y.; Pike, V. W.; Lepore, S. D. *J. Fluorine Chem.* **2014**, *158*, 48.
(10) Späth, A.; König, B. *Beilstein J. Org. Chem.* **2010**, *6*, 32.
(11) (a) Hu, H.; Bartsch, R. A. *J. Heterocycl. Chem.* **2004**, *41*, 557. (b) Czech, B. P.; Desi, D. H.; Koszuk, J.; Czech, A.; Babb, D. A.; Robison, T. W.; Bartsch, R. A. *J. Heterocycl. Chem.* **1992**, *29*, 867. (c) Jungk, S. J.; Moore, J. A.; Gandour, R. D. *J. Org. Chem.* **1983**, *48*, 1116. (d) Fukunishi, K.; Czeck, B.; Regan, S. L. *J. Org. Chem.* **1981**, *46*, 1218. (e) Ikeda, I.; Yamamura, S.; Nakatsuji, Y.; Okahara, M. *J. Org. Chem.* **1980**, *45*, 5355. (f) Czech, B. *Tetrahedron Lett.* **1980**, *21*, 4197.
(12) Xiao, Q.; Liu, Y.; Qiu, Y.; Zhou, G.; Mao, C.; Li, Z.; Yao, Z.-J.; Jiang, S. *J. Med. Chem.* **2011**, *54*, 525.
(13) de Almeida, C. G.; Reis, S. G.; de Almeida, A. M.; Diniz, C. G.; da Silva, V. L.; Hyaric, M. L. *Chem. Biol. Drug Des.* **2011**, *78*, 876.
(14) Tsujigami, T.; Sugai, T.; Ohta, H. *Tetrahedron: Asymmetry* **2001**, *12*, 2543.
(15) (a) Ginotra, S. K.; Friest, J. A.; Berkowitz, D. B. *Org. Lett.* **2012**, *14*, 968. (b) Mantovani, S. M.; Angolini, C. F. F.; Marsaioli, A. J. *Tetrahedron: Asymmetry* **2009**, *20*, 2635.
(16) (a) Borg, T.; Tuzina, P.; Somfai, P. *J. Org. Chem.* **2011**, *76*, 8070. (b) Nishizono, N.; Akama, Y.; Agata, M.; Sugo, M.; Yamaguchi, Y.; Oda, K. *Tetrahedron* **2011**, *67*, 358.
(17) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; John Wiley and Sons: Chichester, **2009**, 2nd ed. 745.
(18) Montanari, F.; Tundo, P. *J. Org. Chem.* **1982**, *47*, 1298.
(19) **General Procedure for the Synthesis of Benzyl-Protected 18-C-6 Lariat Ethers 1c–7c**
To a solution of benzylated diol **1b–7b** (25 mmol) in THF (240 mL) was added KO*t*-Bu (100 mmol) at r.t. After the mixture was allowed to react 1 h under a nitrogen atmosphere, a solution of pentaethylene glycol ditosylate (27.5 mmol) in THF (48 mL) was added over a period of 1 h with stirring. The mixture was stirred for an additional 1 h at r.t., refluxed for 24 h, and cooled to r.t. The volatile solvents were removed by distillation under reduced pressure. The crude solids were dissolved in H_2O, and the resulting solution was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration and evaporation, the crude product (approx. 3.5 g) was directly used for the debenzylation in the next step.
(20) **General Procedure for the Synthesis of 18-C-6 Lariat Ethers 1d–7d**
To a dry round-bottom flask was added 10% (w/w) of 5% Pd/C and anhydrous EtOH (200 mL) was added to the reaction flask. The solution was degassed by bubbling the H_2 gas through it twice. Benzylated lariat ethers **1c**–**7c** (approx. 3.5 g) dissolved in anhydrous EtOH (20 mL) was added into the reaction flask. The solution was degassed twice. The reaction mixture was stirred for 48 h under 1.013 bar of hydrogen. TLC with alumina plates using 4% 2-PrOH–CH_2Cl_2 as the eluent indicated the formation of product (R_f = 0.15). The product mixture was filtered and concentrated. The crude reaction mixture was then stirred into KOH aq (1 M, 50 mL) for 5 min. After this time, the impurities were removed by extraction using EtOAc until TLC showed the absence of any impurity (usually three extractions). The H_2O layer was then extracted with CH_2Cl_2 (3 × 20 mL, monitored by alumina TLC; 4% 2-PrOH–CH_2Cl_2 eluent). The organic layer was collected, the solvent was removed in vacuo, and the resulting

material was passed through a small plug of neutral alumina (10% MeOH–EtOAc as eluent) to furnish noncomplexed lariat products.

2-Hydroxymethyl-18-C-6 (1d)[2a–g]

Obtained in 65% yield (1.74 g) as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.93 (s, 1 H, OH), 3.46–3.82 (m, 25 H, 12 × CH_2 and 1 × CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.0 (CH_2OH), 69.6 (CH_2O), 70.6 (CH_2O), 70.7 (CH_2O), 70.75 (2 × CH_2O), 70.8 (CH_2O), 70.83 (CH_2O), 71.0 (CH_2O), 71.03 (CH_2O), 71.2 (CH_2O), 71.8 (CH_2O), 79.4 (CH). ESI-HRMS: *m/z* [M + H] calcd for $C_{13}H_{26}O_7$: 295.1757; found: 295.1751.

2-[Hydroxy-(ethoxymethyl)]-18-C-6 (2d)

Obtained in 60% yield (1.66 g) as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.84 (s, 1 H, OH), 3.50–3.84 (m, 29 H, 14 × CH_2 and 1 × CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.8 (CH_2OH), 69.8 (CH_2O), 70.7 (CH_2O), 70.73 (CH_2O), 70.77 (CH_2O), 70.8 (CH_2O), 70.83 (CH_2O), 70.9 (CH_2O), 70.95 (CH_2O), 71.0 (CH_2O), 71.1 (CH_2O), 71.13 (CH_2O), 71.4 (CH_2O), 72.7 (CH_2O), 78.3 (CH). ESI-HRMS: *m/z* [M + H] calcd for $C_{15}H_{30}O_8$: 339.2019; found: 339.2017.

2-[Hydroxy-(ethoxy)-(ethoxymethyl)]-18-C-6 (3d)

Obtained in 55% yield (1.56 g) as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.76 (s, 1 H, OH), 3.47–3.81 (m, 33 H, 16 × CH_2 and 1 × CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.8 (CH_2OH), 69.9 (CH_2O), 70.4 (CH_2O), 70.6 (CH_2O), 70.7 (2 x CH_2O), 70.73 (CH_2O), 70.76 (CH_2O), 70.8 (CH_2O), 70.9 (2 × CH_2O), 70.93 (CH_2O), 71.0 (CH_2O), 71.4 (CH_2O), 71.5 (CH_2O), 72.6 (CH_2O), 78.3 (CH). ESI-HRMS: *m/z* [M + H] calcd for $C_{17}H_{34}O_9$: 383.2281; found: 383.2276.

2-Hydroxyethyl-18-C-6 (4d)

Obtained in 50% yield (1.35 g) as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65–1.85 (m, 2 H, CH_2), 3.01 (s, 1 H, OH), 3.58–3.75 (m, 22 H, 11 × CH_2), 3.75–3.90 (m, 3 H, 1 × CH_2 and 1 × CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.8 (CH_2), 60.1 (CH_2OH), 69.4 (CH_2O), 70.6 (CH_2O), 70.7 (CH_2O), 70.77 (CH_2O), 70.8 (CH_2O), 70.86 (CH_2O), 70.9 (CH_2O), 71.0 (CH_2O), 71.05 (CH_2O), 71.7 (CH_2O), 74.5 (CH_2O), 77.7 (CH). ESI-HRMS: *m/z* [M + H] calcd for $C_{14}H_{28}O_7$: 309.1913; found: 309.1908.

2-Hydroxypropyl-18-C-6 (5d)[2h]

Obtained in 48% yield (1.31 g) as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51–1.68 (m, 4 H, 2 × CH_2), 2.30 (s, 1 H, OH), 3.50–3.76 (m, 24 H, 12 × CH_2), 3.83–3.88 (m, 1 H, 1 × CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5 (CH_2), 28.9 (CH_2), 62.8 (CH_2OH), 69.6 (CH_2O), 70.6 (CH_2O), 70.68 (CH_2O), 70.7 (CH_2O), 70.9 (2 x CH_2O), 70.91 (CH_2O), 70.92 (CH_2O), 70.94 (CH_2O), 71.0 (CH_2O), 74.2 (CH_2O), 79.0 (CH). ESI-HRMS: *m/z* [M + H] calcd for $C_{15}H_{30}O_7$: 323.2070; found: 323.2064.

2-Hydroxybutyl-18-C-6 (6d)

Obtained in 45% yield (1.24 g) as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26–1.62 (m, 6 H, 3 × CH_2), 2.48 (s, 1 H, OH), 3.62–3.74 (m, 24 H, 12 × CH_2), 3.80–3.85 (m, 1 H, 1 × CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9 (CH_2), 31.5 (CH_2), 32.9 (CH_2), 62.7 (CH_2OH), 69.5 (CH_2O), 70.67 (4 × CH_2O), 70.7 (CH_2O), 70.8 (CH_2O), 70.9 (CH_2O), 71.0 (CH_2O), 71.1 (CH_2O), 74.3 (CH_2O), 79.3 (CH). ESI-HRMS: *m/z* [M + H] calcd for $C_{16}H_{32}O_7$: 337.2226; found: 337.2221.

1,2-Dihydroxymethyl-18-C-6 (7d)[2l]

Obtained in 55% yield (1.24 g) as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.60 (s, 1 H, OH), 3.44 (s, 1 H, OH), 3.59–3.84 (m, 26 H, 12 × CH_2 and 2 × CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.8 (2 × CH_2OH), 70.2 (2 × CH_2O), 70.3 (2 × CH_2O), 70.5 (2 × CH_2O), 70.9 (2 × CH_2O), 70.91 (2 × CH_2O), 80.7 (2 × CH). ESI-HRMS: [M + H] calcd for $C_{14}H_{28}O_8$: 325.1862; found: 325.1857.