Electronic Supplementary Material (ESI) for Green Chemistry

Continuous Flow Macrocyclization at High Concentrations: Synthesis of Macrocyclic Lipids

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SUPPORTING INFORMATION

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General:

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 ^{o}C or had been flame dried and cooled under a stream of argon or nitrogen.[1] All chemical products were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. 10-Undecyn-1-ol[2] and 1-*O*-benzyl-*rac*-glycerol[3] were prepared according to literature procedures. The macrocyclic precursors non-8-yn-1-yl hex-5-ynoate (**1**), non-8-yn-1-yl undec-10-ynoate (**3**) and methyl 3,5-bis(undec-10-yn-1-yloxy)benzoate as well as macrocycles **4, 5** and **7** have been previously reported in the literature.[4] Technical solvents were obtained from VWR International Co. Anhydrous solvents (CH_2Cl_2, Et_2O, THF, DMF, Toluene, and n-hexane) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still[5] and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F_{254}.). Visualization of TLC plate was performed by UV (254 nm), $KMnO_4$ or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR. NMR spectra were taken in deuterated $CDCl_3$ using Bruker AV-300 and AV-400 instruments unless otherwise noted. Signals due to the solvent served as the internal standard ($CHCl_3$: δ 7.27 for ^{1}H, δ 77.0 for ^{13}C). The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. The ^{1}H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling, 2D COSY experiments. The ^{13}C NMR assignments were made on the basis of chemical shift and multiplicity and were confirmed, where necessary, by two dimensional correlation experiments (HSQC). High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal from an Agilent LC-MSD TOF system using ESI mode of ionization unless otherwise noted.

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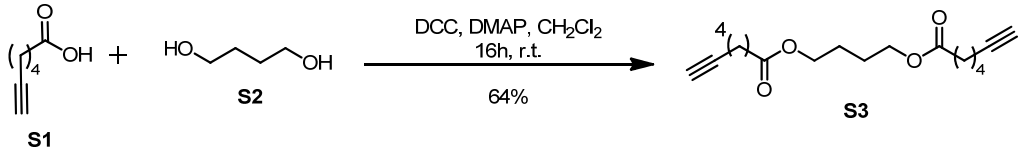
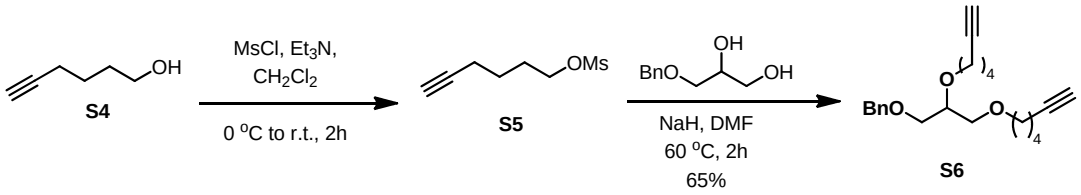
[1] Shriver, D. F.; Drezdon, M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.
[2] Sharma, A.; Chattopadhyay, S. *J. Org. Chem*. **1998**, *63*, 6128.
[3] Karmee, K. S. *Synth. Comm.* **2013**, *43*, 450.
[4] Bédard, A.-C.; Collins, S. K. *J. Am. Chem. Soc*. **2011**, *133*, 19976.
[5] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.

SYNTHESIS OF MACROCYCLIZATION PRECURSORS.

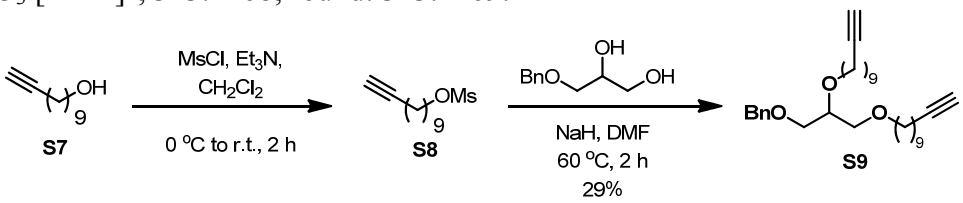


Butane-1,4-diyl dibut-3-ynoate (S3): To a stirred solution of the 1,4-butanediol (0.56 mL, 6.3 mmol, 1 equiv.) and 6-heptynoic acid (1.6 g, 13 mmol, 2.0 equiv.) in anhydrous CH_2Cl_2 (63 mL, 0.1 M) was added *N*,*N*'-dicyclohexylcarbodiimide (5.23 g, 25.4 mmol, 4.0 equiv.) and 4-dimethylaminopyridine (3.88 g, 38 mmol, 6.0 equiv.) at room temperature. The reaction mixture was stirred at room temperature for 15 h. Upon complete conversion of the starting material (TLC), the crude reaction mixture was placed in a freezer for 5 h to induce the precipitation of the urea, which was subsequently removed by filtration. The filtrate was concentrated *in vaccuo* to provide the crude reaction mixture, which was purified by silica gel column chromatography (100% Hexanes to 20% EtOAc/Hexanes) to afford the desired product **S3** as a colorless semi-solid (1.24 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.19 - 4.01 (m, 4H), 2.33 (t, *J* = 7.4 Hz, 4H), 2.21 (dt, *J* = 7.0, 2.6 Hz, 4H), 1.95 (t, *J* = 2.6 Hz, 2H), 1.83 - 1.64 (m, 8H), 1.62 - 1.49 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm = 173.3, 83.9, 68.6, 63.8, 33.7, 27.8, 25.3, 24.0, 18.1; HRMS (ESI) m/z calculated for $C_{18}H_{30}NO_4$ $[M+NH_4]^+$, 324.2169; found: 324.2172.

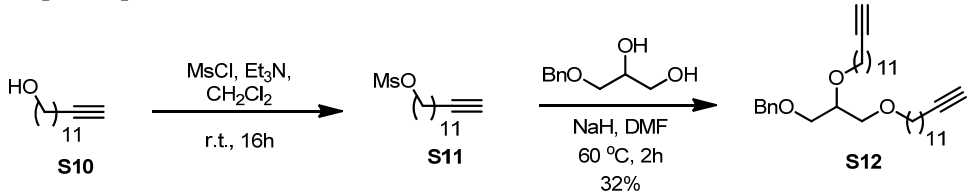


((2,3-bis(prop-2-ynyloxy)propoxy)methyl)benzene (S6): In a flamed-dried flask, 1-hexyn-1-ol (2.0 g, 20.4 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (100 mL) and Et_3N (4.9 mL, 22.4 mmol, 1.1 equiv.) was added. The mixture was cooled to 0 °C and methanesulfonyl chloride (2.8 mL, 24.5 mmol, 1.2 equiv.) was added dropwise. The mixture was slowly warmed to room temperature and stirred for 2h. Water was added to the mixture and the organic and aqueous phases were separated. The aqueous phase was extracted 2x with CH_2Cl_2 and the organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vaccuo*. The product prop-2-ynyl methanesulfonate **S5** was obtained as a crude pale yellow oil was used directly in the next step. To a stirred solution of 1-*O*-benzyl-*rac*-glycerol (570 mg, 3.1 mmol, 1 equiv.) at 0°C in anhydrous DMF (20 mL) was added NaH (60% in oil, 313 mg, 7.8 mmol, 2.5 equiv.) in 5 portions. The mixture was warmed slowly to r.t. and prop-2-ynyl methanesulfonate **S5** (1.38 g, 7.8 mmol, 2.5 equiv.) was added in one portion. The reaction was then warmed to 60 °C for 2h (or until judged complete by TLC) and then cooled back to room temperature. Water and ethyl acetate were added and the organic and aqueous layers were separated. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with brine (3x). The organic layer was dried with Na_2SO_4, filtered and

concentrated *in vaccuo*. The crude oil was purified by silica gel column chromatography (20% EtOAc/Hexanes). The desired product **S6** was obtained as a colorless oil (0.72 g, 65 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 - 7.22 (m, 5H), 4.60 - 4.49 (m, 2H), 3.67 - 3.39 (m, 9H), 2.24 - 2.15 (m, 4H), 2.00 - 1.96 (m, 2H), 1.73 - 1.52 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm =138.3, 128.3, 127.6, 127.5, 84.4, 84.3, 78.0, 73.4, 70.9, 70.8, 70.2, 69.8, 68.4, 68.3, 29.1, 28.6, 25.2, 25.1, 18.18, 18.17; HRMS (ESI) m/z calculated for $C_{22}H_{31}O_3$ $[M+H]^+$, 343.2268; found: 343.2269.

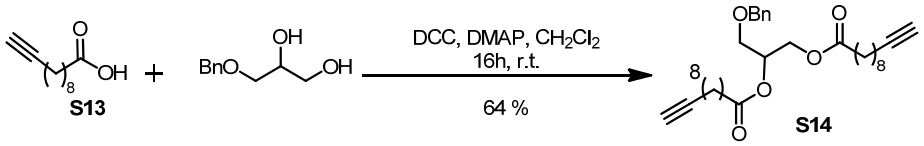


((2,3-bis(non-2-ynyloxy)propoxy)methyl)benzene (S9): In a flamed-dried flask, 1-undecyn-1-ol (1.5g, 8.9 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (45 mL) and Et_3N (2.5 mL, 13.2 mmol, 1.5 equiv.) was added. The mixture was cooled to 0 °C and methanesulfonyl chloride (0.75 mL, 9.7 mmol, 1.1 equiv.) was added dropwise. The mixture was slowly warmed to room temperature and stirred for 2h. Water was added to the mixture and the organic and aqueous phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2x) and the organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vaccuo*. The non-2-ynyl methanesulfonate **S8** was obtained as a yellow oil and was used crude directly in the next step. To a stirred solution of 1-*O*-benzyl-*rac*-glycerol (277 mg, 1.63 mmol, 1 equiv.) at 0 °C in anhydrous DMF (10 mL) was added NaH (60% in oil, 163 mg, 4.1 mmol, 2.5 equiv.) in 5 portions. The mixture was warmed slowly to r.t. and non-2-ynyl methanesulfonate (883 mg, 3.6 mmol, 2.2 equiv.) was added in one portion. The reaction was then warmed to 60 °C for 2 h (or until complete as judged by TLC) and then cooled back to room temperature. Water and ethyl acetate were added and the organic and aqueous layers were separated. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with brine (3x). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vaccuo*. The crude oil was purified by silica gel column chromatography (15% EtOAc/Hexanes) and the desired product **S9** was obtained as a colorless oil (200 mg, 29 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41 - 7.23 (m, 5H), 4.56 (s, 2H), 3.68 - 3.47 (m, 7H), 3.43 (t, *J* = 6.7 Hz, 2H), 2.18 (dt, *J* = 6.9, 2.5 Hz, 4H), 1.94 (t, *J* = 2.5 Hz, 2H), 1.64 - 1.46 (m, 8H), 1.46 - 1.23 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm = 138.4, 128.3, 127.5, 84.7, 77.9, 73.3, 71.6, 70.7, 70.5, 70.3, 68.4 (2C), 30.1, 29.6, 29.41 (2C), 29.39 (2C), 29.0 (2C), 28.7 (2C), 28.4 (2C), 26.1 (2C), 26.0 (2C), 18.4 (2C); HRMS (ESI) m/z calculated for $C_{32}H_{51}O_3$ $[M+H]^+$, 483.3833; found: 483.3844.



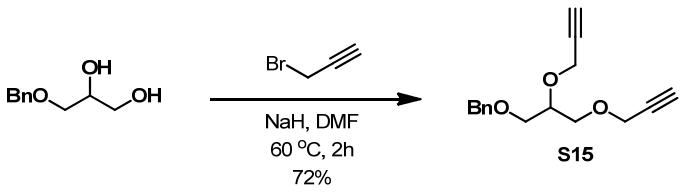
((2,3-bis(undec-2-ynyloxy)propoxy)methyl)benzene (S12): In a flamed-dried flask, 1-tridecyn-1-ol (2.30 g, 11.7 mmol, 1 equiv.) was dissolved in anhydrous DCM (60 mL)

and Et_3N (1.9 mL, 14.0 mmol, 1.2 equiv.) was added. The mixture was cooled to 0 °C and methanesulfonyl chloride (1.0 mL, 12.9 mmol, 1.1 equiv.) was added dropwise. The mixture was slowly warmed to room temperature and stirred for 2 h. Water was added to the mixture and the organic and aqueous phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2x) and the organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vaccuo*. The product undec-2-ynyl methanesulfonate **S11** was obtained as a crude yellow oil which was used directly in the next step. To a stirred solution of 1-*O*-benzyl-*rac*-glycerol (0.85 g, 4.7 mmol, 1 equiv.) at 0 °C in anhydrous DMF (60 mL) was added NaH (60% in oil, 468 mg, 11.7 mmol, 2.5 equiv.) in 5 portions. The mixture was warmed slowly to r.t. and undec-2-ynyl methanesulfonate (3.2 g, 11.7 mmol, 2.5 equiv.) was added in one portion. The reaction was then warmed to 60 °C for 2h (or until judged complete by TLC) and then cooled back to room temperature. Water and ethyl acetate were added and the organic and aqueous layers were separated. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with brine (3x). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vaccuo*. The crude oil was purified by silica gel column chromatography (10% EtOAc/Hexanes). The desired product **S12** was obtained as a pale yellow oil (2.0 g, 32 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.35 (m, 4H), 7.33 - 7.26 (m, 1H), 4.58 (s, 2H), 3.68 - 3.49 (m, 7H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.20 (dt, *J* = 7.1, 2.7 Hz, 4H), 1.96 (t, *J* = 2.7 Hz, 2H), 1.66 - 1.49 (m, 8H), 1.46 - 1.23 (m, 28H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm = 138.4, 128.3, 127.54, 127.47, 84.8, 77.9 (2C), 73.3, 71.6, 70.7, 70.6, 70.3, 68.0 (2C), 30.1 (2C), 29.63 (2C), 29.57 (2C), 29.53 (2C), 29.47 (2C), 29.1 (2C), 28.7 (2C), 28.5 (2C), 26.10 (2C), 26.07 (2C); HRMS (ESI) m/z calculated for $C_{36}H_{59}O_3$ $[M+H]^+$, 539.4459; found: 539.4443.



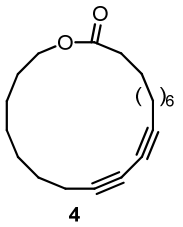
1,2-Bis(10-undecynoyl)-3-*O*-benzylglycerol (S14): To a stirred solution of 1-*O*-benzyl-*rac*-glycerol (0.56 mL, 6.3 mmol, 1 equiv.) and undecynoic acid (1.6 g, 13 mmol, 2 equiv.) in anhydrous dichloromethane (63 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (5.23 g, 25.4 mmol, 4 equiv.) and 4-dimethylaminopyridine (3.88 g, 38 mmol, 6 equiv.) at room temperature. The reaction mixture was stirred at room temperature for 15 h. Upon complete conversion of the starting material (TLC), the crude reaction mixture was placed in a freezer for 5 h to induce the precipitation of the urea, which was subsequently removed by filtration. The filtrate was concentrated *in vaccuo* to provide the crude reaction mixture, which was purified by silica gel column chromatography to afford the desired product **S14** as a colorless semi-solid (1.24 g, 64 %). The NMR data are in agreement with that obtained in the literature.[6]

[6] Bhattacharya, S.; Ghosh, S.; Easwaran, K. R. K. *J. Org. Chem.* **1998**, *63*, 9232.



((2,3-bis(prop-2-ynyloxy)propoxy)methyl)benzene (S15): To a stirred solution of 1-*O*-benzyl-*rac*-glycerol (600 mg, 3.3 mmol) at 0 °C in anhydrous DMF (17 mL) was added NaH (60% in oil, 330 mg, 8.2 mmol) in 5 portions. The mixture was warmed slowly to room temperature and propargyl bromide (0.75 mL, 7.2 mmol) was added in one portion. The reaction was then warmed to 60 °C for 2 h and then cooled back to room temperature. Water and ethyl acetate were added and the organic and aqueous layers were separated. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with brine (3x). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vaccuo*. The crude oil was purified by silica gel column chromatography (10% EtOAc/Hexanes). The desired product **S15** was obtained as a colorless oil in (612 mg, 72 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41 - 7.22 (m, 5H), 4.55 (s, 2H), 4.33 (d, *J* = 2.4 Hz, 2H), 4.16 (d, *J* = 2.4 Hz, 2H), 3.93 (m, 1H), 3.74 - 3.57 (m, 4H), 2.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm = 137.8, 128.0, 127.2 (2C), 79.7, 79.2, 76.0, 74.5, 74.2, 72.9, 69.5, 69.3, 58.1, 57.1; HRMS (ESI) m/z calculated for $C_{16}H_{19}O_3$ $[M+H]^+$, 259.1329; found: 259.1340.

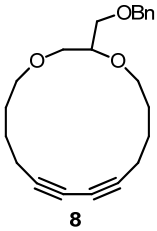
SYNTHESIS OF MACROCYCLES



4

General procedure A for the macrocylization of diynes under Glaser-Hay oxidative coupling conditions using microwave irradiation: Macrocycle (**4**): To a microwave vial equipped with a stirring bar was added $CuCl_2$ (5.5 mg, 0.03 mmol, 25 mol%) and $Ni(NO_3)_2 \cdot 6H_2O$ (9.3 mg, 0.03 mmol, 25 mol%). Polyethylene glycol 400 (3.33 mL), triethylamine (0.05 mL, 0.36 mmol, 3 equiv.) and TMEDA (0.07 mL, 0.6 mmol, 5 equiv.) were added and the mixture was stirred at room temperature for 15 min or until the solution was homogenous. The diyne (0.12 mmol) was added to the mixture as a methanol solution (1.67 mL) in one portion. Oxygen was bubbled in the solution for 5 min and the vial was then closed with a microwave cap. The reaction was warmed to 120°C for 6h using a Biotage Initiator microwave reactor. The crude mixture was loaded directly on a silica column. Purification by chromatography (100% Hexanes→20% EtOAc/Hexanes) afforded the product **4** as a colorless semi-solid (31 mg, 81%).

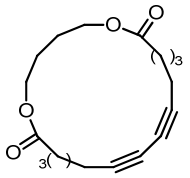
General procedure B for the macrocylization of diynes under Glaser-Hay oxidative coupling conditions using continuous-flow: Macrocycle (**4**): To a pear shaped flask equipped with a stirring bar was added $CuCl_2$ (11 mg, 0.06 mmol, 25 mol%) and $Ni(NO_3)_2 \cdot 6H_2O$ (19 mg, 0.06 mmol, 25 mol%). Polyethylene glycol 400 (5 mL), triethylamine (0.1 mL, 0.72 mmol, 3 equiv.) and TMEDA (0.14 mL, 1.2 mmol, 5 equiv.) were added and the mixture was stirred at room temperature for 15 min or until the solution was homogenous. The diyne (0.24 mmol) was added to the mixture as a methanol solution (5 mL) in one portion. The reaction was then passed through a 5 mL stainless-steel coil at 1 mL/min at 120°C using a VapourTech R4 reactor and a R2+ pumping module. The solution was cycled for a total residence time of 1.5 h (which for a 10mL reaction mixture and a 5 mL coil takes a total reaction time of 3 h). To the crude reaction mixture, silica gel was added and the solvent was removed *in vaccuo*. Purification by silica gel chromatography (100% Hexanes→20% EtOAc/Hexanes) afforded the product as a colorless semi-solid (66 mg, 91%).



8

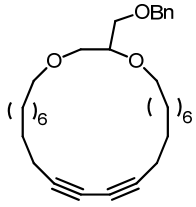
General procedure C for the large scale macrocylization of diynes under Glaser-Hay oxidative coupling conditions using continuous-flow: Macrocycle (**8**): To a pear

shaped flask equipped with a stirring bar was added $CuCl_2$ (160 mg, 0.94 mmol, 25 mol%) and $Ni(NO_3)_2 \cdot 6H_2O$ (273 mg, 0.94 mmol, 25 mol%). Polyethylene glycol 400 (96 mL), triethylamine (1.47 mL, 11.25 mmol, 3 equiv.) and TMEDA (3.0 mL, 18.75 mmol, 5 equiv.) were added and the mixture was stirred at room temperature for 15 min or until the metals were solubilized. The diyne (1.3g, 3.75 mmol) was added to the homogenous mixture as a methanol solution (48 mL) in one portion. The reaction was then passed through two 10 mL stainless-steel coil placed in series (connected with a short isolated stainless steel tube) at 0.22 mL/min at 120°C using a VapourTech R4 reactor and a R2+ pumping module. After collection of the reaction mixture, silica gel was added and the solvent was removed *in vaccuo*. Purification by chromatography (100% Hexanes→20% EtOAc/Hexanes) afforded the product **8** as a colorless semi-solid (860 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ =7.42 - 7.22 (m, 5H), 4.61 (s, 2H), 3.96 - 3.33 (m, 9H), 2.48 - 2.31 (m, 2H), 2.25 - 2.06 (m, 2H), 1.90 - 1.53 (m, 6H), 1.26 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm = 138.7, 128.3, 127.6, 127.4, 79.5, 79.3, 73.3, 71.2, 69.5, 69.2, 69.0, 66.6, 66.3, 29.7, 29.1, 28.4, 23.5, 23.3, 19.3, 19.1; HRMS (ESI) m/z calculated for $C_{22}H_{28}NaO_3$ $[M+Na]^+$, 363.1931; found: 363.1930.



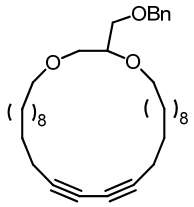
5

Macrocycle (5): Following the general procedure B described above, macrocycle **5** was isolated as a colorless oil. (71 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 4.12 (m, 4H), 2.46 - 2.24 (m, 8H), 1.95 - 1.44 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm = 173.4, 76.7, 66.2, 64.0, 34.6, 27.2, 25.4, 24.4, 18.8; HRMS (ESI) m/z calculated for $C_{18}H_{24}NaO_4$ $[M+Na]^+$, 327.1567; found: 327.1572.



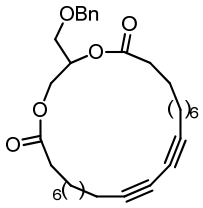
9

Macrocycle (9): Following the general procedure B described above, macrocycle **9** was isolated as a colorless oil (90 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.40 - 7.23 (m, 5H), 4.56 (s, 2H), 3.73 - 3.35 (m, 9H), 2.33 - 2.22 (m, 4H), 1.71 - 1.19 (m, 28H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm = 138.4, 128.3, 127.6, 127.5, 77.9, 77.2, 73.3, 71.53, 71.45, 70.5, 70.3, 70.1, 65.7 (2C), 29.9, 29.7, 29.5 (2C), 29.3 (2C), 29.0, 28.9, 28.8, 28.28, 28.25, 27.82, 27.81, 26.09, 26, 07, 19.1; HRMS (ESI) m/z calculated for $C_{32}H_{49}O_3$ $[M+H]^+$, 481.3676; found: 481.3678.



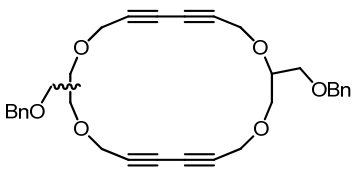
10

Macrocycle (10): Following the general procedure B described above, macrocycle **10** was isolated as a colorless oil (64 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.41 - 7.25 (m, 5H), 4.56 (s, 2H), 3.74 - 3.36 (m, 9H), 2.27 (t, *J* = 6.2 Hz, 4H), 1.68 - 1.20 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm = 138.4, 128.3, 127.6, 127.5, 78.0, 77.49, 77.48, 73.3 (2C), 71.6, 71.3 (2C), 70.6, 70.2 (2C), 65.594, 65.587, 30.0, 29.6, 29.50, 29.48, 29.3, 29.24, 29.214, 29.207, 28.95, 28.94, 28.40, 28.38, 28.0, 26.09, 26.07, 19.14, 19.12; HRMS (ESI) m/z calculated for $C_{36}H_{56}NaO_3$ $[M+Na]^+$, 559.4122; found: 559.4130.



11

Macrocycle (11): Following the general procedure B described above, macrocycle **11** was isolated as a colorless semi-solid (55 mg, 45%). The NMR data are in agreement with that obtained in the literature.[7]

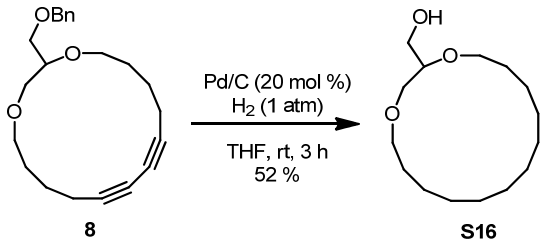


12

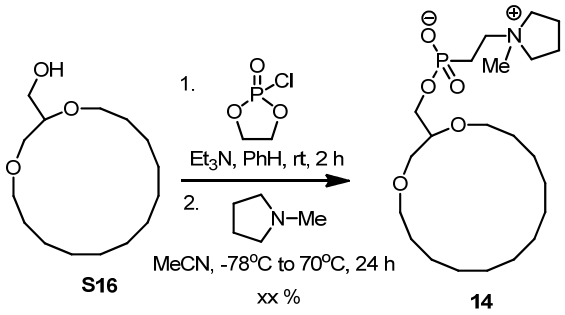
Macrocycle (12): Following the general procedure B described above, macrocycle **13** was isolated as a colorless semi-solid as a mixture of head-to-head and head-to-tail dimers (44 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 - 7.28 (m, 10H), 4.58 - 4.51 (m, 6H), 4.37 - 4.26 (m, 6H), 3.99 - 3.88 (m, 2H), 3.81 - 3.65 (m, 4 H), 3.62 - 3.50 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$, signal for both dimer reported) δ ppm = 138.1, 128.4, 127.7, 127.6 (2C), 78.1, 77.6, 77.20, 77.16, 75.96, 75.91, 75.86, 75.8, 75.4, 75.3, 75.1, 73.5, 70.9, 70.8, 70.74, 70.72, 70.6, 70.4, 70.34, 70.32, 70.25, 70.24, 70.21, 69.73, 69.72, 69.51, 69.45, 59.24, 59.18, 59.15, 59.09, 58.96, 58.85, 58.82. All attempts to characterize macrocycle **12** by ESI-Ms failed. As such macrocycle **12** (44 mg) was completely hydrogenated (THF (5 mL), Pd/C (10 %w/w, 4.4 mg), H_2 (1 atm), 3h, rt) to afford a single compound as a colorless oil. HRMS (ESI) m/z calculated for $C_{18}H_{36}NaO_6$ $[M+Na]^+$ 371.2404; found: 371.2410.

[7] Bhattacharya, S.; Ghosh, S.; Easwaran, K. R. K. *J. Org. Chem.* **1998**, *63*, 9232.

SYNTHESIS OF PHOSPHOLIPID 14



(1,4-dioxacyclohexadecan-2-yl)methanol (S16): A stirring solution of macrocycle **8** (150 mg, 0.44 mmol) in THF (5 mL) at room temperature was degassed with N_2 for 5 minutes. Pd/C (15 mg, 10 %w/w) was added and hydrogen was bubbled through the mixture for 5 minutes. The reaction was then stirred at room temperature for 3-4h under an H_2 atmosphere (or until complete by TLC). Nitrogen was bubbled again through the reaction mixture for 5 minutes and the crude mixture was then filtered on Celite® and washed with THF (3x). The filtrate was concentrated *in vaccuo* and purified by column chromatography (50% EtOAc/Hexanes→100% EtOAc) to afford the hydrogenated product **S16** as a colorless oil (60 mg, 52 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.84 - 3.40 (m, 9H), 2.12 (dd, *J* = 6.6, 5.1 Hz, 1H), 1.72 - 1.21 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 78.7, 71.9, 71.0, 69.8, 62.4, 29.2, 29.0, 26.93, 26.88, 26.75, 26.72, 25.67, 25.66, 24.63, 24.55; HRMS (ESI) m/z calculated for $C_{15}H_{30}NaO_3$ $[M+Na]^+$, 281.2087; found: 281.2095.



(1,4-dioxacyclohexadecan-2-yl)methyl-2-(1-methylpyrrolidinium-1-yl)ethyl phosphate (14): To a solution of (1,4-dioxacyclohexadecan-2-yl)methanol (25 mg, 0.1 mmol) in anhydrous benzene (1 mL) was added triethylamine (0.02 mL, 0.14 mmol). The solution was cooled to 0 °C and 2-chloro-1,3,2-dioxaphospholane-2-oxide (0.011 mL, 0.12 mmol) was added. The resulting mixture was stirred at 0 °C for 5 min, warmed to room temperature and stirred another 2 h. The crystalline Et_3NHCl was removed by filtration and the filtrate was concentrated to afford a crude pale yellow oil. The crude oil was placed in a sealed tube, redissolved in anhydrous acetonitrile (2.4 mL) and cooled to -78°C. *N*-Methylpyrrolidine (0.32 mL) was added in one portion. The tube was then sealed and warmed to 70 °C for 24h. The reaction mixture was then concentrated in *vaccuo* until the excess *N*-Methylpyrrolidine was completely removed. Lipid **14** was obtained as a pale brown semi-solid in 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.53 - 4.06 (m, 9H), 3.83 - 3.49 (m, 12H), 3.17 - 3.13 (m, 2H), 1.55 - 1.26 (m, 22H). ^{13}C NMR

(125 MHz, $CDCl_3$) δ ppm = 78.7, 77.2, 71.8 (2C), 71.03, 70.99 (2C), 70.3, 69.8, 62.3, 30.3, 29.7, 29.2, 29.0, 26.93, 26.89, 26.75, 26.73, 26.69, 25.67, 24.63, 24.55; ^{31}P NMR (162 MHz, $CDCl_3$) δ ppm = 3.31. HRMS (ESI) m/z calculated for $C_{22}H_{45}NNaO_6P$ $[M+Na]^+$, 472.2799; found: 472.2799.

Electronic Supplementary Material (ESI) for Green Chemistry

SPECTRAL DATA