Supplementary Material

Polyether Macrocycles from Intramolecular Cyclopropanation and Ylide Formation. Effect of Catalyst and Coordination.

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General. All reagents were obtained commercially and used as received unless otherwise noted. Reactions were carried out under an atmosphere of nitrogen. Anhydrous tetrahydrofuran (THF) and dichloromethane (DCM) were obtained from nitrogen forced flow of HPLC grade solvents over activated alumina prior to use.[1] Thin layer chromatography was performed on EM Scientific Silica Gel 60 F_{254} glass-backed plates. Flash chromatographic purification was performed using Silicycle 40-63 μm, 60 Å silica gel. Reverse phase (HPLC) chromatographic analyses were performed on a Varian Prostar instrument with dual wavelength detection at 220 and 254 nm employing a Varian Dynamax 250x10mm microsorb C18 column. Reverse phase solvents were 18MΩ water and HPLC grade acetonitrile obtained from Pharmco and used as received. Sodium hydride was used as a 60% suspension in mineral oil. ^{1}H and ^{13}C spectra were obtained as solutions in $CDCl_3$; ^{1}H chemical shifts are reported as parts per million (ppm, δ) downfield from Me_4Si (TMS); ^{13}C chemical shifts are reported as parts per million (ppm, δ) relative to $CDCl_3$ (77.0 ppm). Infrared spectra were obtained from thin film depositions on KBr plates with absorptions recorded in wave numbers (cm^{-1}). Glyoxylic acid chloride *p*-

toluenesulphonylhydrazone was prepared as previously reported.[2] Preparation of copper(I) hexfluorophosphate,[3] 2,2-bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane [(*S*,*S*)^{t}Bu-BOX],[4] Rh_2(4*S*-MEOX)$_4$,[5] and Rh_2(4*S*-MEAZ)$_4$[6] have been previously reported.

2-(2-(2-(2-(2-Allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)ethan-1-ol. To a 100 mL round bottom flask charged with allyloxyethanol (5.00 g, 49.0 mmol) dissolved in THF (50 ml) was added methanesulfonyl chloride (4.2 ml, 54 mmol) all at once, followed by triethylamine (7.6 ml, 54 mmol) at ambient temperature. The resulting suspension was stirred for 1.5 h then filtered, followed by washing the filter cake with diethyl ether (3 x 25 mL). The combined filtrates were concentrated under reduced pressure yielding 2-allyloxyethyl-1-methanesulfonate as a colorless oil (6.48 g, 36.0 mmol, 74 %): ^{1}H NMR (300 MHz) δ 5.90 (ddt, *J* = 17.3, 10.3, 5.7 Hz, 1 H), 5.32 (ddd, *J* = 17.3, 3.3, 1.7 Hz, 1 H), 5.20 (ddt, *J* = 10.3, 1.7, 1.3 Hz, 1 H), 4.38 (dt, *J* = 2.7, 4.5 Hz, 2H), 4.04 (dt, *J* = 5.7, 1.3 Hz, 2 H), 3.73 (dt, *J* = 2.7, 4.5 Hz, 2H), 3.07 (s, 3H); ^{13}C NMR (75 MHz) δ 133.90, 117.62, 72.10, 69.14, 67.66, 37.58; HRMS (FAB+): calculated for $C_6H_{12}SO_4$: 181.0535; found 181.0536.

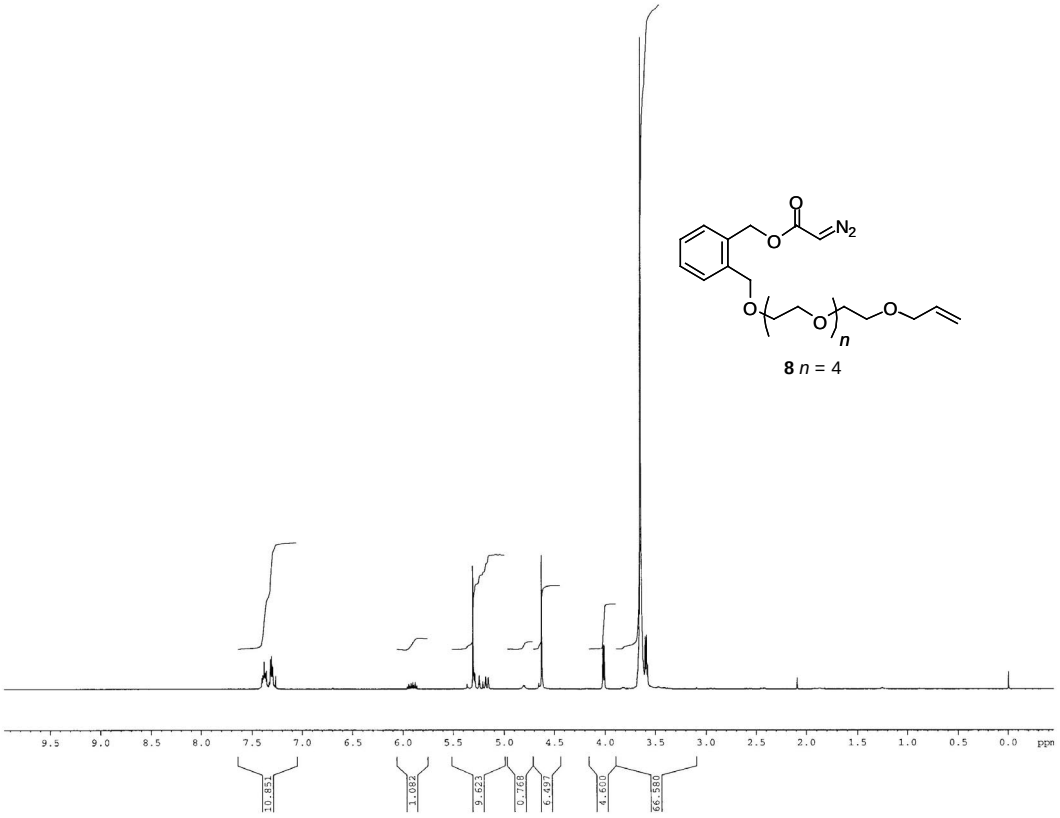
To a flame-dried round bottom flask charged with tetra(ethylene glycol) (9.9 mL, 57 mmol, 1.0 eq) and THF (500 mL) was added NaH (2.40 g, 60 mmol, 1.1 eq.) in one portion. After gas evolution subsided, the solution was brought to reflux and 2-allyloxy-1-ethyl methanesulfonate (13 g, 74 mmol, 1.3 eq) in THF (10 mL) was added in one aliquot, after which the reaction mixture was heated with stirring at reflux for 12 h. The resulting cloudy solution was filtered through a pad of Celite, and the solid residue was rinsed with ethyl ether (3 x 150 mL). The filtrate was concentrated under reduced pressure, and the resultant yellow oil was purified by flash chromatography on silica gel

(EtOAc:hexanes:Et_2O, 55:35:10), yielding (2-(2-(2-(2-(2-allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)ethan-1-ol as a clear oil (9.71 g, 34.8 mmol, 61 %): TLC R_f = 0.11 (88:10:2 EtOAc:Et_2O:MeOH) visualized using cerium molybdate (Hanessian's Stain);[7] ^{1}H NMR (400 MHz) δ 5.93 (ddt, *J* = 17.3, 10.3, 5.7 Hz, 1 H), 5.29 (ddd, *J* = 17.3, 3.3, 1.7 Hz, 1 H), 5.19 (ddt, *J* = 10.3, 1.7, 1.3 Hz, 1 H), 4.04 (dt, *J* = 5.7, 1.3 Hz, 2 H), 3.76-3.60 (comp, 20 H), 2.59 (s, broad, 1 H); ^{13}C NMR (100 MHz) δ 134.7, 117.1, 72.5, 72.2, 70.6, 70.56, 70.54, 70.3, 69.4, 61.7; HRMS (FAB+) calculated for $C_{13}H_{26}O_7$: 279.1808; found: 279.1821.

2-(2-(2-(2-(2-(2-Allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxymethyl)phenyl-methanol. To a 250 mL round bottom flask charged with (2-(2-(2-(2-(2-allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)ethan-1-ol (3.90 g, 14.0 mmol, 1.00 eq) in THF (100 mL) was added methanesulfonyl chloride (1.14 mL, 14.7 mmol, 1.05 eq) followed by triethylamine (2.05 mL, 14.7 mmol, 1.05 eq). The reaction solution was stirred for 1 h at ambient temperature. The resultant cloudy white solution was filtered, and the collected solid was washed with diethyl ether (3 x 25 mL). The combined filtrates were concentrated under reduced pressure, resulting in a clear oil. To a second flame-dried 1000 mL flask charged with 1,2-benzenedimethanol[8] (2.89 g, 21.0 mmol, 1.50 eq) in THF (500 mL) was added NaH (0.870 g, 21.7 mmol, 1.55 eq) in one portion. After gas evolution subsided the suspension was brought to reflux, and the resultant oil from the initial flask was added in one aliquot. After refluxing for 12 h, the solution was cooled to room temperature then filtered through a pad of Celite, and the pad was washed with diethyl ether (3 x 150 mL). The combined filtrates were concentrated under reduced pressure to provide a pale yellow

oil, from which residual 1,2-benzenedimethanol (bp = 140 ºC @ 0.8 torr)[9] was removed by kugelrohr distillation (160 ˚C @ 0.7 torr). The remaining viscous oil was purified by flash chromatography on silica gel (EtOAc:hexanes:Et_2O 55:35:10) to yield the title compound as a clear, viscous oil (4.47 g, 11.2 mmol, 80 %): TLC R_f = 0.16 (88:10:2 EtOAc:Et_2O:MeOH) visualized using a solution of $KMnO_4$; ^{1}H NMR (400 MHz) δ 7.41 (d, *J* = 7.6 Hz, 1 H), 7.34 (dt, *J* = 2.8, 6.8 Hz, 1 H), 7.30-7.25 (comp, 2 H), 5.91 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1 H), 5.26 (ddd, *J* = 17.2, 3.1, 1.5 Hz, 1 H), 5.17 (ddd, *J* = 10.4, 1.5, 1.2 Hz, 1 H), 4.66 (s, 2 H) 4.65 (d, *J* = 6.4 Hz, 2 H), 4.01 (dt, *J* = 5.7, 1.2 Hz, 2 H), 3.65-3.57 (comp, 20 H), 3.48 (t, *J* = 6.4 Hz, 1 H); ^{13}C NMR (100 MHz) δ 140.7, 135.8, 134.6, 129.9, 129.7, 128.7, 127.6, 116.9, 72.3, 72.1, 70.46, 70.43, 70.40, 70.3, 70.2, 69.3, 69.0, 63.2; HRMS (FAB+) calculated for $C_{21}H_{34}O_7$: 399.2383; found: 399.2377.

8-Allyl-5,10,11,13,14,16,17,19,20,22,23,25-dodecahydro-6,9,12,15,18,21,24-heptaoxa-benzocylotricosen-7-one (12). ^{1}H NMR (400MHz) δ 7.49-7.27 (comp, 4 H), 5.81 (m, 1 H), 5.35 (s, 2 H), 5.02-5.12 (m, 2 H), 4.70 (s, 2 H), 4.10-4.17 (m, 1 H), 3.65-3.57 (comp, 20 H), 2.5 (m, 2 H); ^{13}C NMR (100 MHz) δ 174.0, 137.2, 135.1, 129.9, 129.8, 128.7, 128.5, 118.3, 79.6, 72.9, 71.2, 71.1, 70.9, 70.5, 70.3, 70.2, 70.1, 68.6, 64.6, 37.7; HRMS (ESI) calculated for $C_{23}H_{35}O_8$: 439.23319; found: 439.23586.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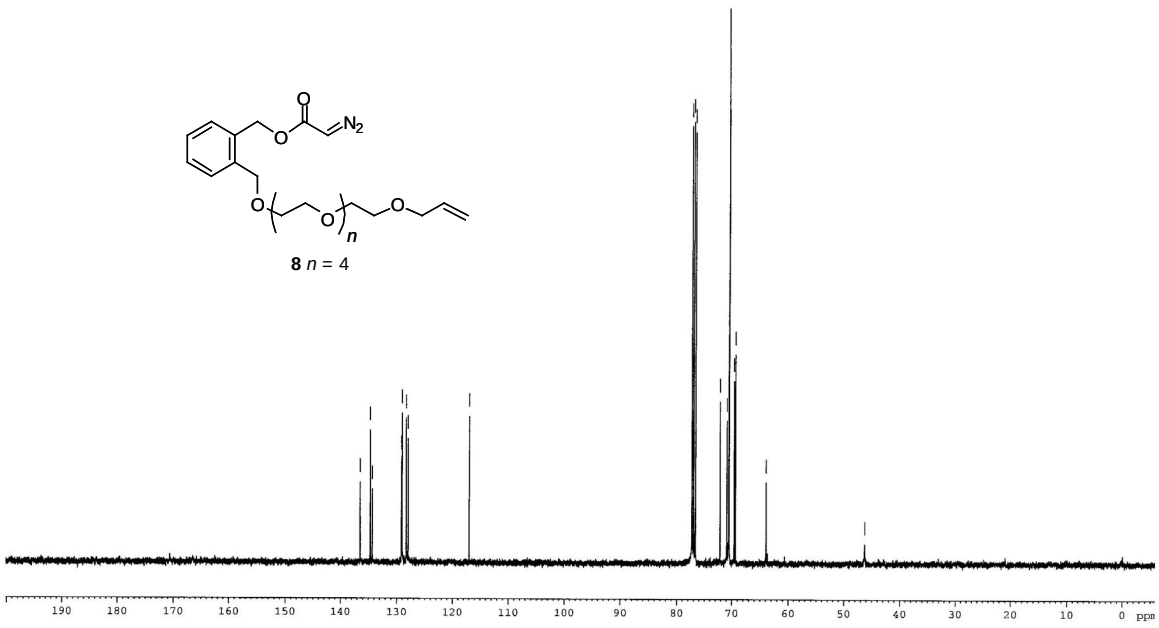
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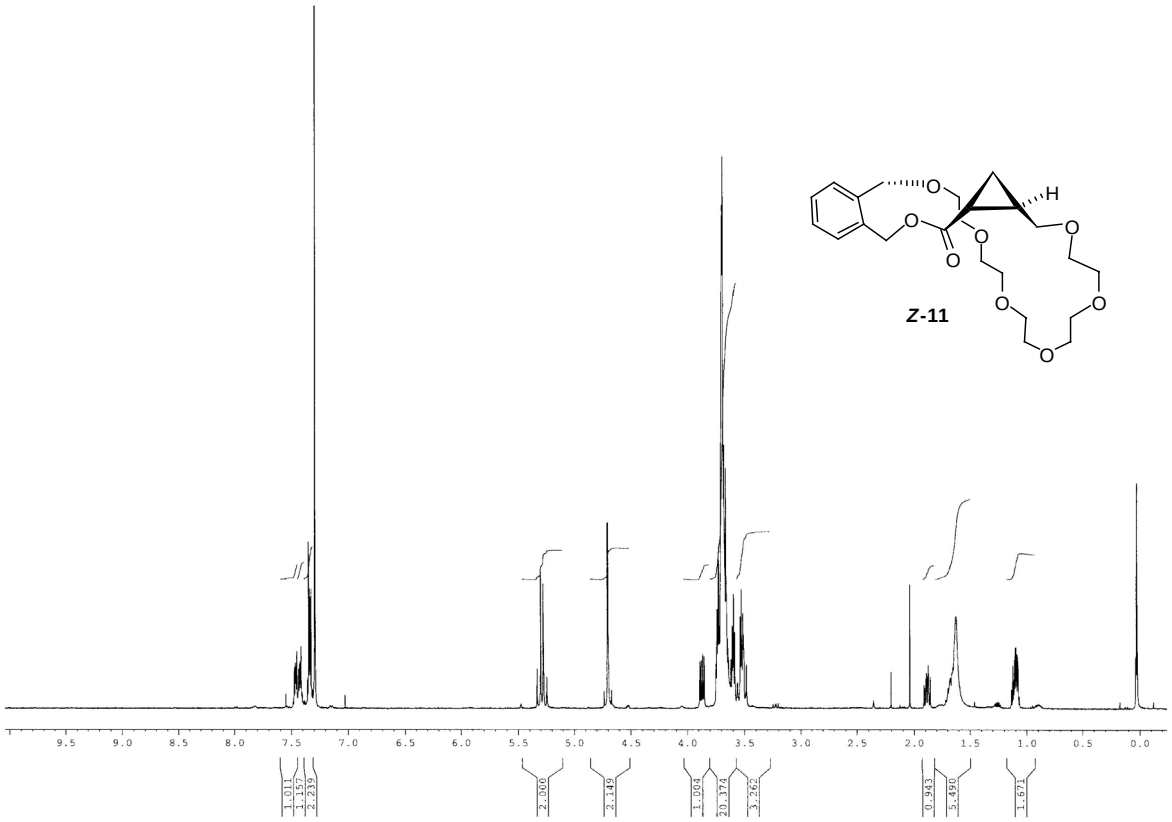
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7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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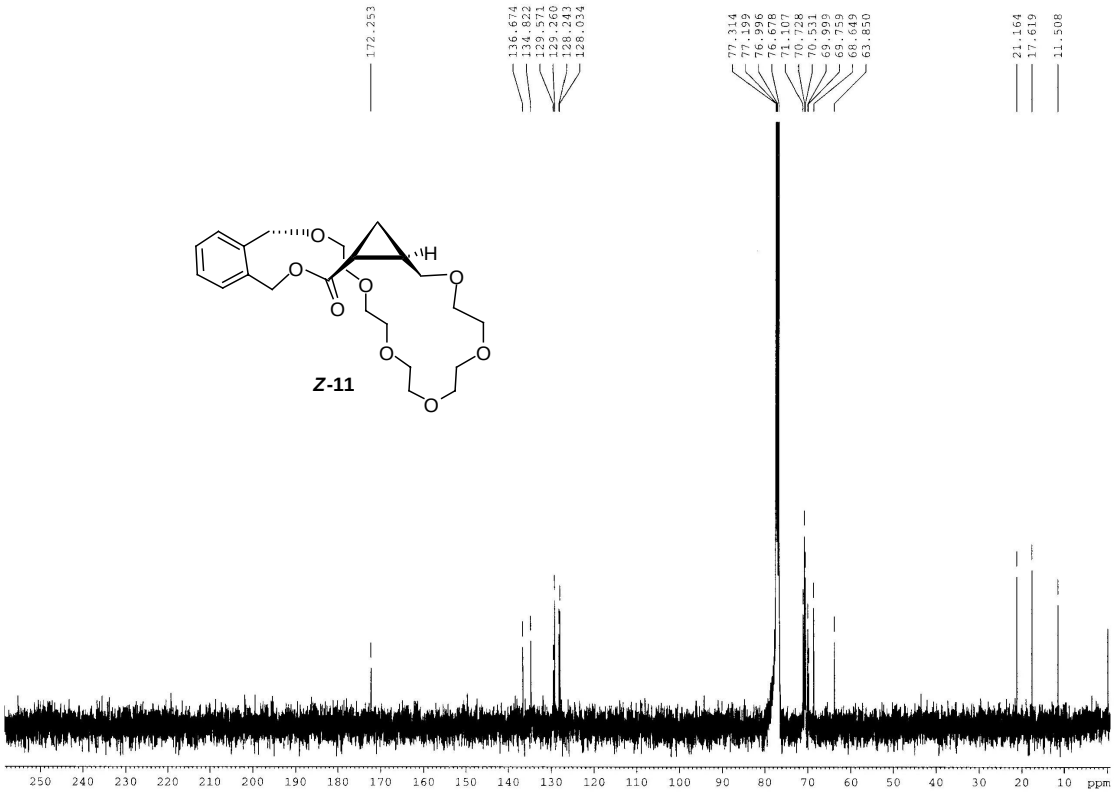
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70.531
69.999
69.759
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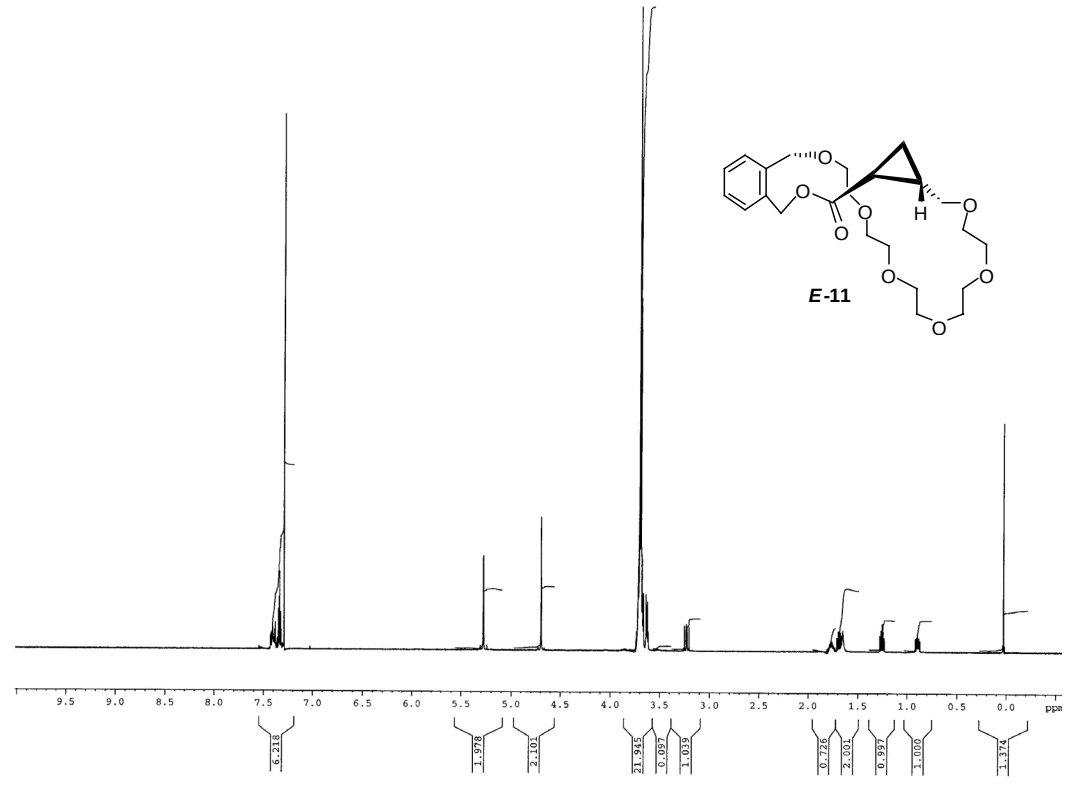
***Z*-11**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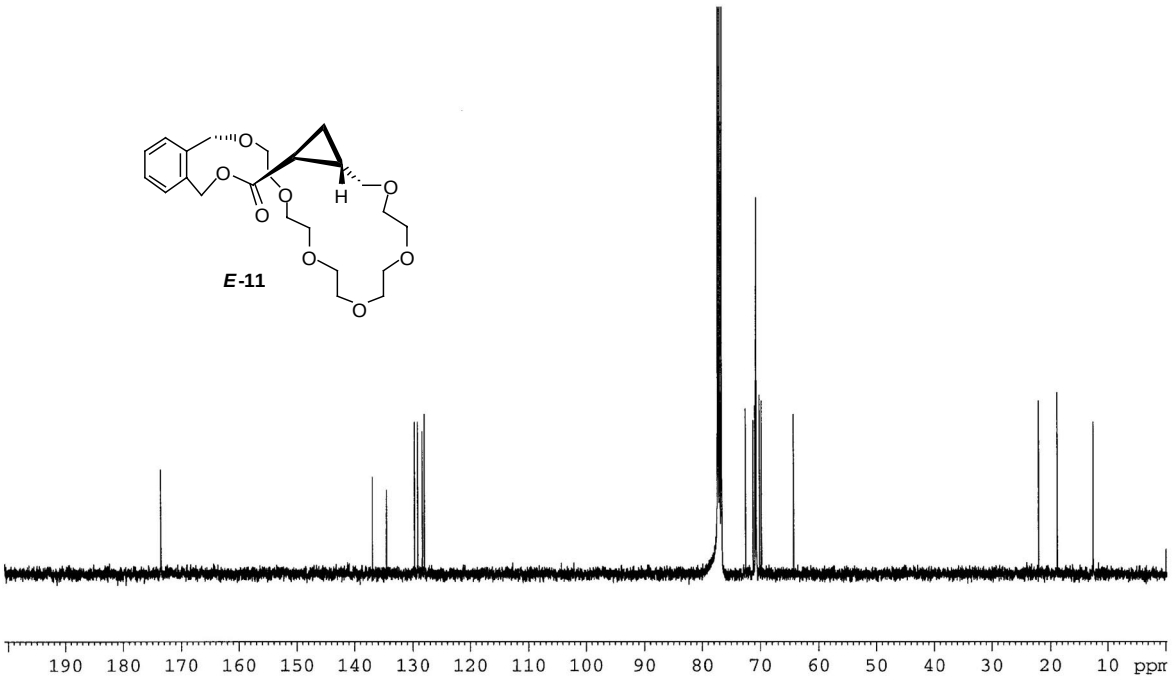
1.039
0.726
2.001
0.997
1.000
1.374

***E*-11**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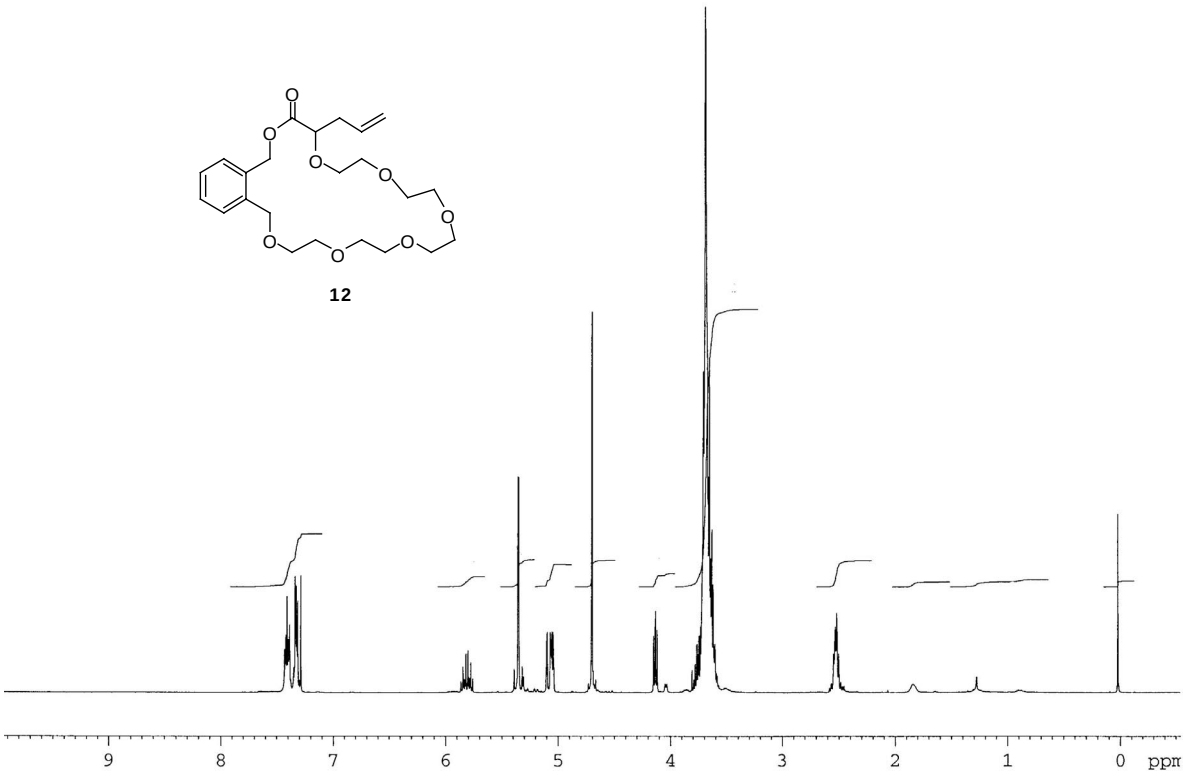
***E*-11**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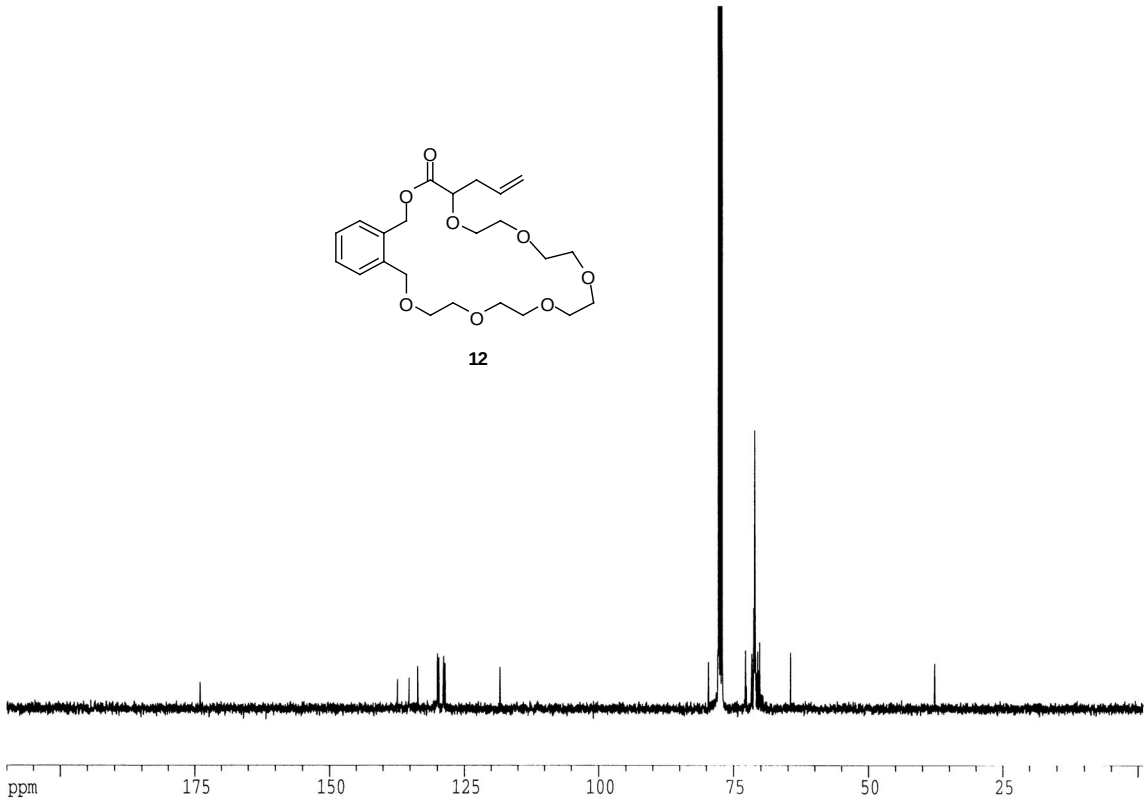
12



Example Procedure for Diazo Decomposition of 8, 9, and 10 with Copper(I) Hexafluorophosphate/(*S*,*S*)-^{t}Bu-BOX. An oven dried flask was charged with copper(I) hexafluorophosphate (8.3 mg, 23.7 μmol, 0.10 eq), (*S*,*S*)-^{t}Bu-BOX (9.3 mg, 28.4 μmol, 0.12 eq) and DCM (5 mL) and brought to reflux. After the catalyst solution was at reflux for 30 min., a solution of **9** (111 mg, 0.24 mmol, 1.0 eq) dissolved in anhydrous DCM (5 mL) was added over 2 h using a Kazel syringe pump. The resultant yellow solution was allowed to reflux for an additional 2 h after addition, cooled to room temperature, and concentrated under reduced pressure. The crude reaction mixture was filtered through a glass pipet loaded with 2 inches of silica gel using a solution of EtOAc:Et_2O (3:1, 15 mL) to remove the catalyst. The filtrate was concentrated under reduced pressure, to yield a clear oil (90 mg, 96 % theoretical mass), and a ^{1}H NMR spectrum was obtained

immediately. The absence of starting material was evident, but neither products from intramolecular cyclopropanation, nor that from oxonium ylide formation were observed. Instead the ^{1}H NMR spectrum of the reaction materials isolated by reverse phase HPLC show absorbances at chemical shifts consistent with the 1,2-disubstituted phenyl ring, the allyl group, benzylic protons, and the protons associated with the polyether at 3.6-3.5 ppm. Though multiple compounds were isolated the only observable difference in the proton spectrum is the peak shape and chemical shift range of the signal at 3.6-3.5 ppm.

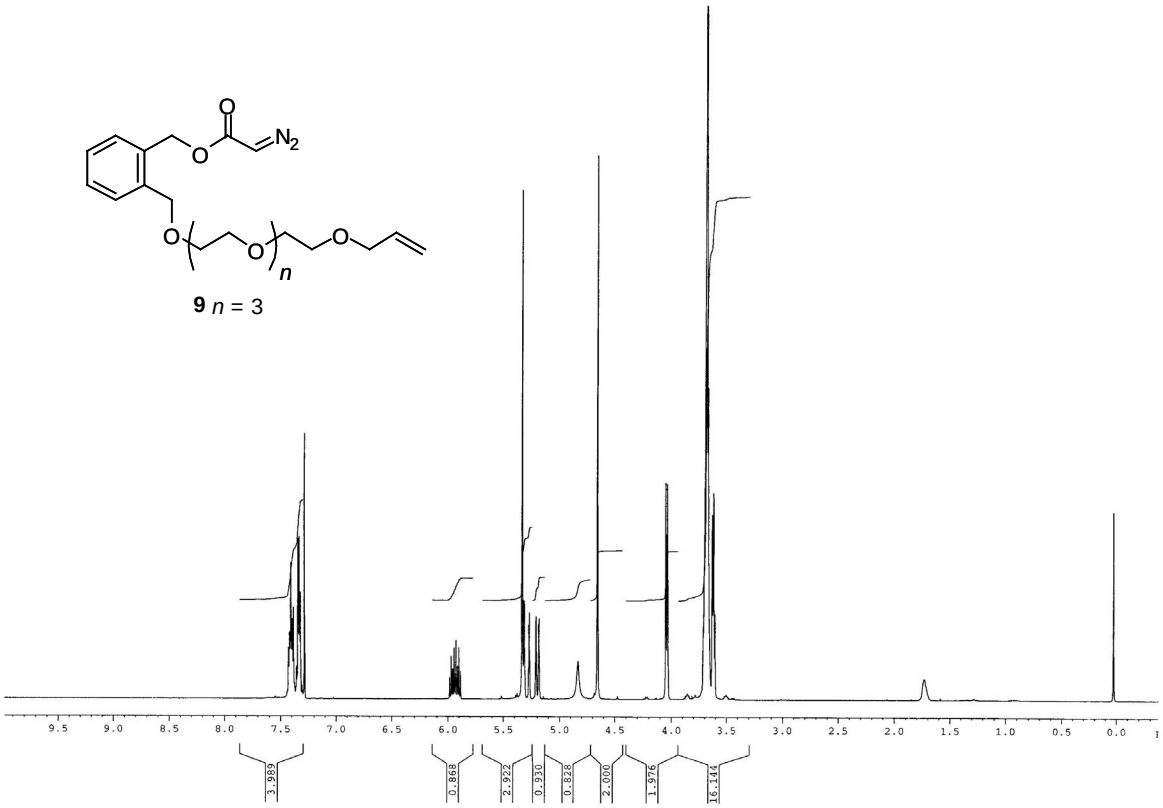
2-(2-(2-(2-(2-Allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxymethyl)phenylmethyl Diazoacetate (9). To a flame-dried 500 mL round bottom flask charged with tetra(ethylene glycol) (5.01 g, 25.7 mmol, 1.00 eq) in THF (300 mL) was added NaH (1.08 g, 27.0 mmol, 1.05 eq) in one portion, and the resulting mixture was stirred vigorously until gas evolution subsided and a clear solution was obtained. Allyl bromide (3.20 mL, 36.0 mmol, 1.40 eq) was then added in one aliquot, and the resultant yellow solution was stirred for 12 h at ambient temperature, filtered through a pad of Celite that was subsequently washed with ethyl ether (3 x 75 mL), and the combined filtrates were concentrated under reduced pressure to yield a clear oil. The oil was purified by flash chromatography on silica gel (EtOAc:hexanes:Et_2O, 55:35:10) and 2-(2-(2-(2-allyloxyethoxy)-ethoxy)-ethoxy)ethan-1-ol was isolated as a clear, viscous oil (3.98 g, 17.0 mmol, 66 %): TLC R_f = 0.15 (88:10:2 EtOAc:Et_2O:MeOH) visualized using cerium molybdate. ^{1}H NMR (400 MHz) δ 5.92 (ddt, J = 17.2, 10.4, 5.7 Hz, 1 H), 5.29 (ddd, J = 17.2, 3.2, 1.3 Hz, 1 H), 5.19 (ddd, J = 10.4, 3.2, 1.3 Hz, 1 H), 4.04 (dt, J = 5.7, 1.3 Hz, 2 H), 3.77-3.61 (comp, 16 H), 2.56 (t, J = 6.0 Hz, 1

H); ^{13}C NMR (100 MHz) δ 135.1, 117.6, 72.9, 72.8, 72.7, 71.1, 71.02, 71.00, 70.8, 69.8, 62.2; HRMS (FAB+) calculated for $C_{11}H_{22}O_5$: 235.1545; found: 235.1563.

To a 250 mL round bottom flask charged with 2-(2-(2-(2-allyloxyethoxy)-ethoxy)-ethoxy)ethan-1-ol (1.59 g, 6.77 mmol, 1.00 eq) in THF (100 mL) was added methanesulfonyl chloride (0.550 mL, 7.11 mmol, 1.05 eq) followed by triethylamine (0.991 mL, 7.11 mmol, 1.05 eq). The reaction solution was stirred for 1 h at ambient temperature. The resultant cloudy white solution was filtered, and the collected solid was rinsed with diethyl ether (3 x 25 mL). The combined filtrates were concentrated under reduced pressure to produce a clear oil. To a second flame-dried flask charged with 1,2-benzenedimethanol (1.41 g, 10.2 mmol, 1.50 eq) in THF (300 mL) was added NaH (0.408 g, 10.2 mmol, 1.50 eq) in one portion. After gas evolution had subsided, the suspension was brought to reflux, and the resultant oil from the initial flask was added as one aliquot. After refluxing for 12 h, the solution was cooled to room temperature, then filtered through a pad of Celite, which was rinsed with diethyl ether (3 x 100 mL). The combined filtrates were concentrated under reduced pressure to afford a pale yellow oil, from which residual 1,2-benzenedimethanol was removed by kugelrohr distillation (160 ˚C @ 0.7 torr).[4] The remaining viscous oil was purified by flash chromatography on silica gel (EtOAc:hexanes:Et_2O 55:35:10) to yield 2-(2-(2-(2-(2-allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxymethyl)phenylmethanol as a clear, viscous oil (1.77 g, 4.99 mmol, 74 %): TLC R_f = 0.16 (88:10:2 EtOAc:Et_2O:MeOH) visualized using a solution of $KMnO_4$; ^{1}H NMR (400 MHz) δ 7.42 (d, *J* = 7.3 Hz, 1 H), 7.34 (td, *J* = 6.7, 2.8 Hz, 1 H), 7.30-7.25 (comp, 2 H), 5.91 (ddt, *J* = 17.3, 10.4, 5.6 Hz, 1 H), 5.27 (ddd, *J* = 17.3, 3.2, 1.3 Hz, 1 H), 5.17 (ddd, *J* = 10.4, 3.2 , 1.3 Hz, 1 H), 4.67 (s, 2 H), 4.66 (d, *J* = 6.7 Hz, 2 H), 4.02 (dt, *J* = 5.6, 1.3 Hz, 2

H), 3.66-3.57 (comp, 16 H), 3.46 (t, *J* = 6.7 Hz, 1 H); ^{13}C NMR (100 MHz) δ 141.3, 136.3, 135.2, 130.7, 130.4, 129.4, 128.2, 117.5, 73.0, 72.7, 71.1, 71.0, 70.9, 70.8, 69.8, 69.6, 63.9; HRMS (FAB+) calculated for $C_{19}H_{30}O_6$: 355.2121; found: 355.2115.

To a flame-dried 100 mL round bottom flask was added 2-(2-(2-(2-(2-allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxymethyl)phenylmethanol (1.60 g, 4.51 mmol, 1.00 eq) and DCM (10.0 mL). The stirred solution was cooled to 0 ºC and glyoxylic acid chloride *p*-tolusulphonylhydrazone (1.77 g, 6.77 mmol, 1.50 eq) was added in one portion followed by addition of *N*,*N*-dimethylaniline (0.858 mL, 6.77 mmol, 1.50 eq) as one aliquot, producing a clear yellow solution. After stirring for 1 h, during which time the solution changed to a deep green color, triethylamine (3.14 mL, 22.6 mmol, 5.00 eq) was added as one aliquot, instantly changing the solution color to deep red, and the reaction mixture was stirred for an additional hour, then concentrated under reduced pressure. Concentration produced a heterogeneous mixture that was dissolved in a minimal amount of methanol and subjected to flash chromatography on silica gel (Et_2O:petroleum ether:MeOH 50:50:0 to 48:48:4), yielding diazoacetate **9** as a viscous yellow oil (1.39 g, 3.29 mmol, 73 %): ^{1}H NMR (400 MHz) δ 7.40-7.27 (comp, 4 H), 5.91 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1 H), 5.31 (s, 2 H), 5.26 (ddd, *J* =17.3, 3.1, 1.3 Hz, 1 H), 5.17 (ddd, *J* = 10.4, 3.1, 1.3 Hz, 1 H), 4.81 (s, broad, 1 H), 4.62 (s, 2 H), 4.02 (td, *J* = 5.7, 1.3 Hz, 2 H), 3.67-3.58 (comp, 16 H); ^{13}C NMR (100 MHz) δ 136.5, 134.7, 134.3, 129.2, 129.1, 128.3, 128.0, 117.0, 72.2, 70.9, 70.6, 69.6, 69.4, 64.0, 46.2; IR (neat oil): (C=N_2) 2112 cm^{-1}, (C=O) 1694 cm^{-1}; HRMS (FAB+) calculated for $C_{21}H_{31}O_7N_2$: 423.2131; found: 423.2116.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4.5
4.0
3.5
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2.0
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1.0
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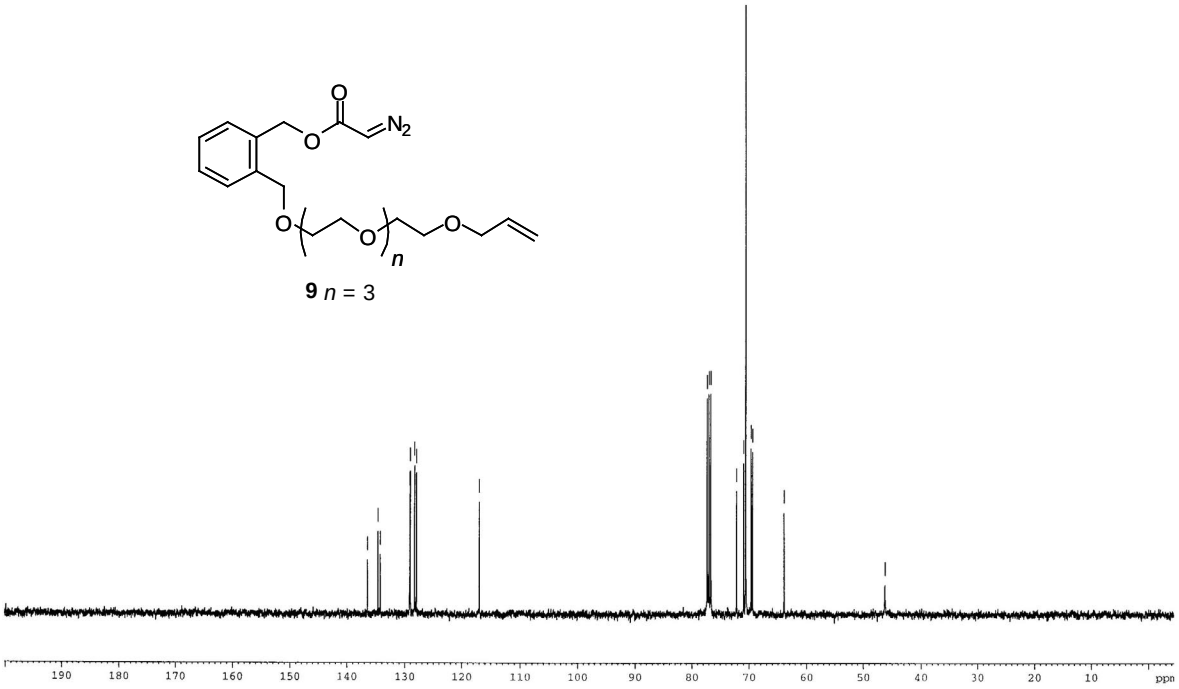
9 $n = 3$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110
100
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50
40
30
20
10
ppm

9 $n = 3$

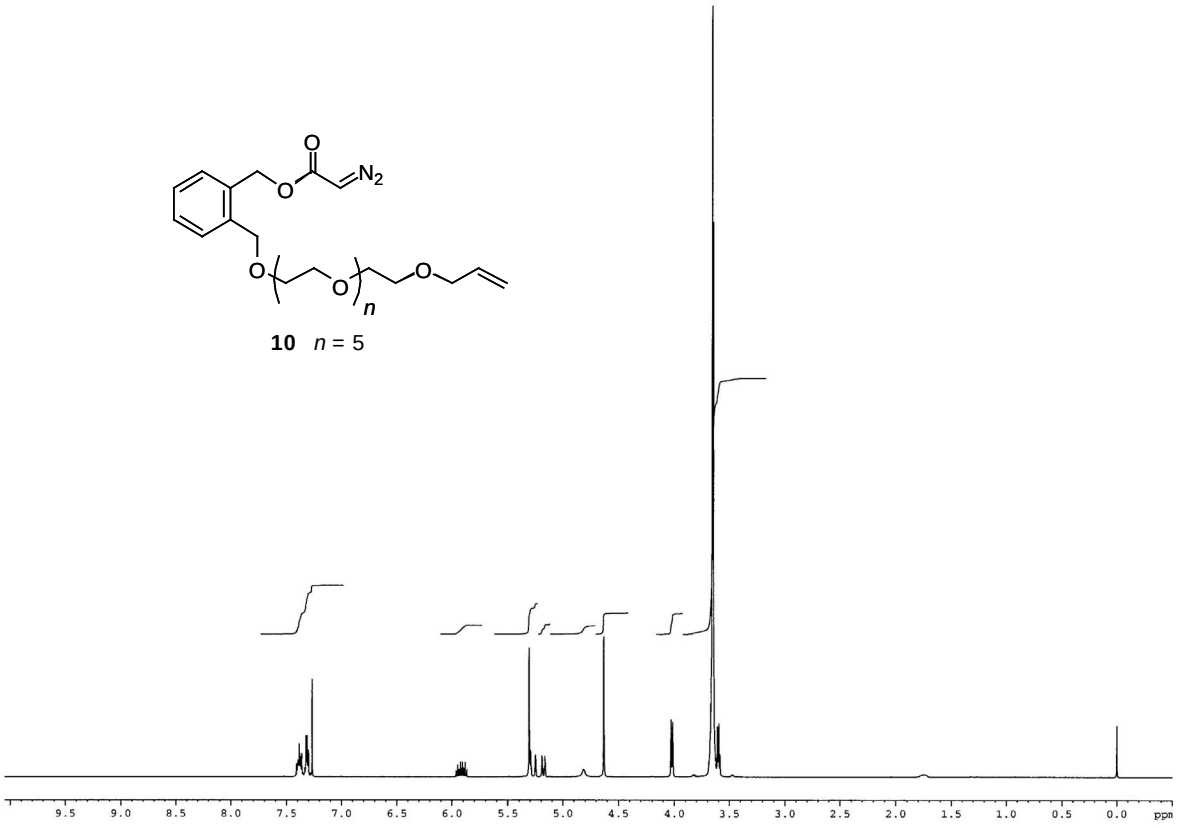
2-(2-(2-(2-(2-(2-(2-Allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxymethyl)-phenylmethyl Diazoacetate (10). To a 250 mL round bottom flask charged with penta(ethylene glycol) (1.00 mL, 4.73 mmol, 1.00 eq) and THF (75 mL) was added NaH (0.199 g, 4.97 mmol, 1.05 eq) in one portion. After gas evolution subsided, the solution was brought to reflux, and 2-allyloxy-1-ethyl methanesulfonate (1.11 g, 6.14 mmol, 1.30 eq) was added in one aliquot, after which the reaction mixture was heated at reflux for 12 h. The resulting cloudy solution was processed as described in the procedure for the synthesis of **9**, and the resultant yellow oil was purified by flash chromatography on silica gel (EtOAc:hexanes:Et_2O, 55:35:10) yielding 2-(2-(2-(2-(2-(2-allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxy)ethan-1-ol as a clear oil (1.18 g, 3.66 mmol, 60 %): ^{1}H NMR (400 MHz) δ 5.91 (ddt, *J* = 17.3, 10.4, 5.6 Hz, 1 H), 5.28 (ddd, *J* = 17.3, 3.1, 1.4 Hz, 1 H), 5.18 (ddd, *J* = 10.4, 3.1, 1.4 Hz, 1 H), 4.02 (dt, *J* = 5.6, 1.4 Hz, 2 H), 3.75-3.59 (comp, 24 H), 2.53 (t, *J* = 4.9 Hz, 1 H); ^{13}C NMR (100 MHz) δ 134.7, 116.9, 72.4, 72.1, 70.51, 70.48, 70.3, 69.3, 63.3; HRMS (FAB+) calculated for $C_{15}H_{31}O_7$: 323.2070; found: 323.2089.

To a round bottom flask charged with 2-(2-(2-(2-(2-(2-allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxy)ethan-1-ol (2.75 g, 8.53 mmol, 1.00 eq) in THF (250 mL) was added methanesulfonyl chloride (0.693 mL, 8.96 mmol, 1.05 eq) followed by triethylamine (1.25 mL, 8.96 mmol, 1.05 eq). The reaction solution was stirred for 1 h at ambient temperature. The resultant cloudy white solution was processed as previously described to produce a clear oil. To a second flame-dried flask charged with 1,2-benzenedimethanol (1.77 g, 12.8 mmol, 1.50 eq) in THF (300 mL) was added NaH (0.544 g, 13.6 mmol, 1.60 eq) in one portion, as previously described. The residual viscous oil obtained in this procedure was purified by flash chromatography on silica gel (EtOAc:hexanes:Et_2O

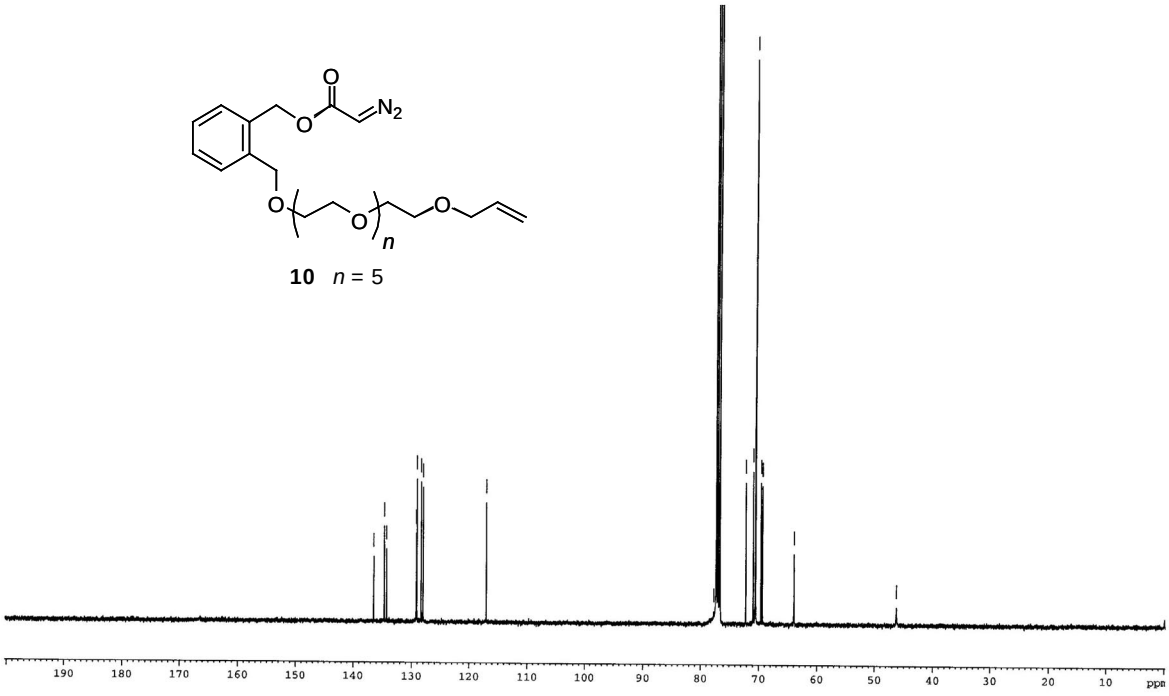
55:35:10) to yield 2-(2-(2-(2-(2-(2-allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxymethyl)phenylmethanol as a clear, viscous oil (2.79 g, 6.30 mmol, 74 %): ^{1}H NMR (400MHz) δ 7.41 (d, *J* = 7.3 Hz, 1H), 7.32 (dt, *J* = 2.8, 6.7 Hz, 1H), 7.30-7.25 (comp, 2H), 5.90 (ddt, *J* = 17.3, 10.4, 5.6 Hz, 1H), 5.26 (ddd, *J* = 17.3, 3.2, 1.3 Hz, 1H), 5.17 (ddd, *J* = 10.4, 3.2, 1.3 Hz, 1H), 4.66 (s, 2H), 4.65 (d, *J* = 6.7 Hz, 2H), 4.02 (dt, *J* = 5.6, 1.3 Hz, 2H), 3.68-3.59 (comp, 24H), 3.46 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (100 MHz) δ 140.8, 135.8, 134.7, 129.9, 129.8, 128.7, 127.6, 116.9, 72.4, 72.1, 70.5, 70.47, 70.44, 70.38, 70.3, 69.3, 69.0, 63.3; HRMS (FAB+) calculated for $C_{23}H_{39}O_8$: 443.2645; found: 443.2631.

To a flame-dried 100 mL round bottom flask was added 2-(2-(2-(2-(2-(2-(2-allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxymethyl)phenylmethanol (1.48 g, 3.34 mmol, 1.00 eq) and DCM (16.0 mL). The stirring solution was cooled to 0 ºC, and glyoxylic acid chloride *p*-tolusulphonylhydrazone (1.30 g, 5.00 mmol, 1.50 eq) was added in one portion followed by dropwise addition of *N*,*N*-dimethylaniline (0.634 mL, 5.00 mmol, 1.50 eq) over 5 min., producing a clear, yellow solution. The reaction and workup followed the previously described procedure to yield heterogeneous mixture that was dissolved in a minimal amount of methanol and subjected to flash chromatography on silica gel (Et_2O:petroleum ether:MeOH 50:50:0 to 47:47:6) to afford the title compound as a viscous yellow oil (1.34 g , 2.62 mmol, 79 %): ^{1}H NMR (400 MHz) δ 7.40-7.29 (comp, 4 H), 5.91 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1 H), 5.31 (s, 2 H), 5.26 (ddd, *J* =17.2, 3.3, 1.5 Hz, 1 H), 5.17 (ddd, *J* = 10.4, 3.0 1.5 Hz, 1 H), 4.81 (s, broad, 1 H), 4.62 (s, 2 H), 4.02 (dt, *J* = 5.7, 1.5 Hz, 2 H), 3.67-3.58 (comp, 24 H) ^{13}C NMR (100 MHz) δ 136.5, 134.8, 134.4, 129.2, 129.1, 128.4, 128.1, 117.1, 72.2, 71.0, 70.63, 70.61, 70.58, 70.56, 69.7, 69.4, 64.0,

46.3; IR (neat oil): ($C{=}N_2$) 2110cm^{-1}, (C=O) 1692cm^{-1}; HRMS (FAB+) calculated for $C_{25}H_{38}O_9N_2Li$: 517.2737; found: 517.2725.

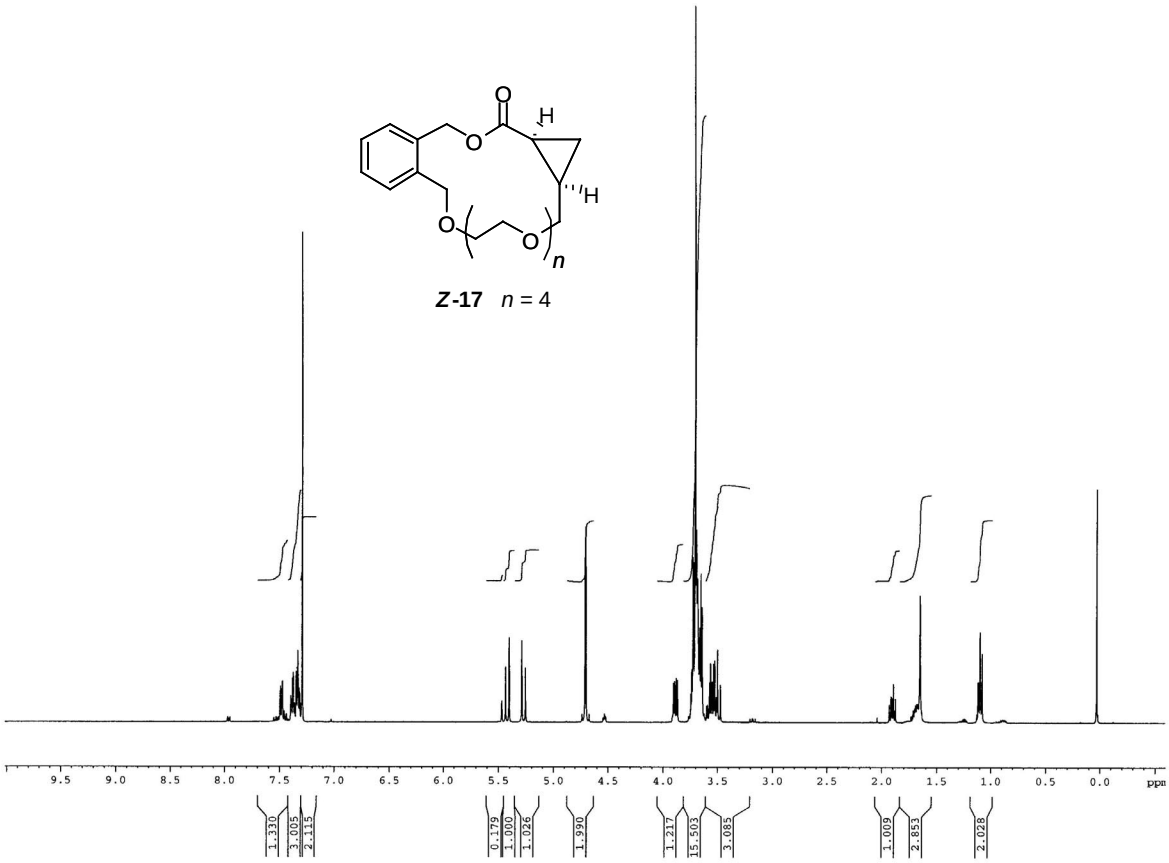


10 *n* = 5



10 $n = 5$

***Z*-3,9,12,15,18,21-Hexaoxa-tricyclo[21.4.0.0^{5,7}]heptacosa-1(23),24,26-trien-4-one (*Z*-17).** ^{1}H NMR (400MHz) δ 7.49-7.31 (comp, 4 H), 5.42 (d, J = 13.0 Hz, 1 H), 5.27 (d, J = 13.0 Hz, 1 H), 4.70 (s, 2 H), 3.88 (dd, J = 10.4, 4.8 Hz, 1 H), 3.74-3.64 (comp, 17 H), 1.90 (ddd, J = 8.5, 7.3, 6.1 Hz, 1 H), 1.69 (dddt, J = 12.7, 8.4, 7.6, 4.8 Hz, 1 H), 1.13-1.07 (comp, 2 H); ^{13}C NMR (100 MHz) δ 172.2, 136.4, 135.4, 129.3, 129.2, 128.1, 128.0, 71.5, 71.1, 71.0, 70.72, 70.67, 70.5, 70.3, 69.9, 69.8, 68.6, 63.6, 21.2, 17.7, 11.4; HRMS (FAB+) calculated for $C_{21}H_{30}O_7$: 395.2070; found: 395.2077.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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
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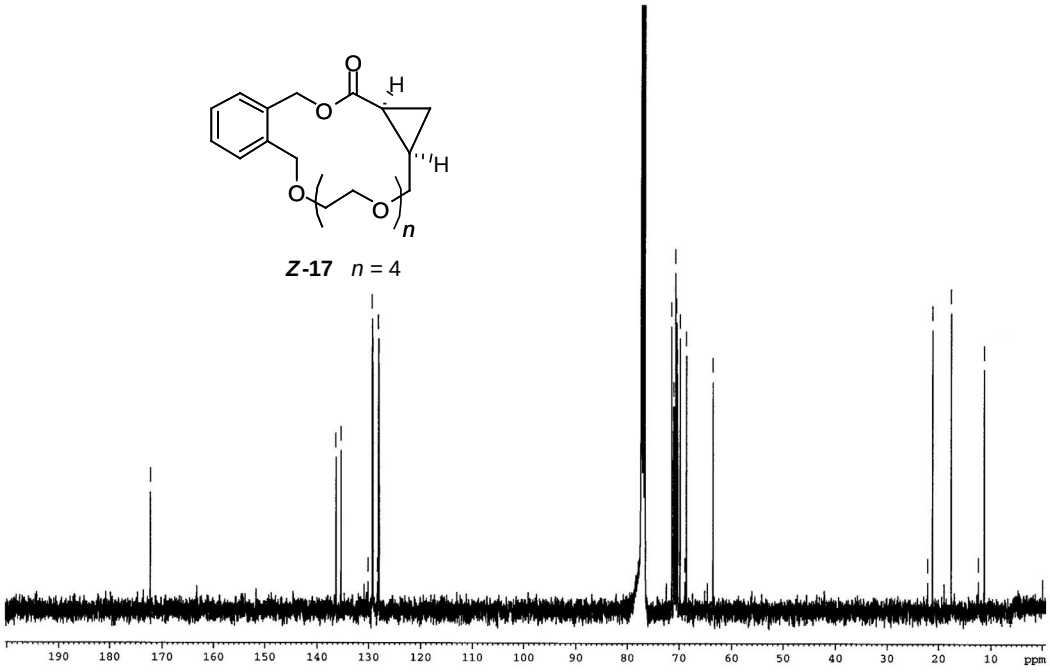
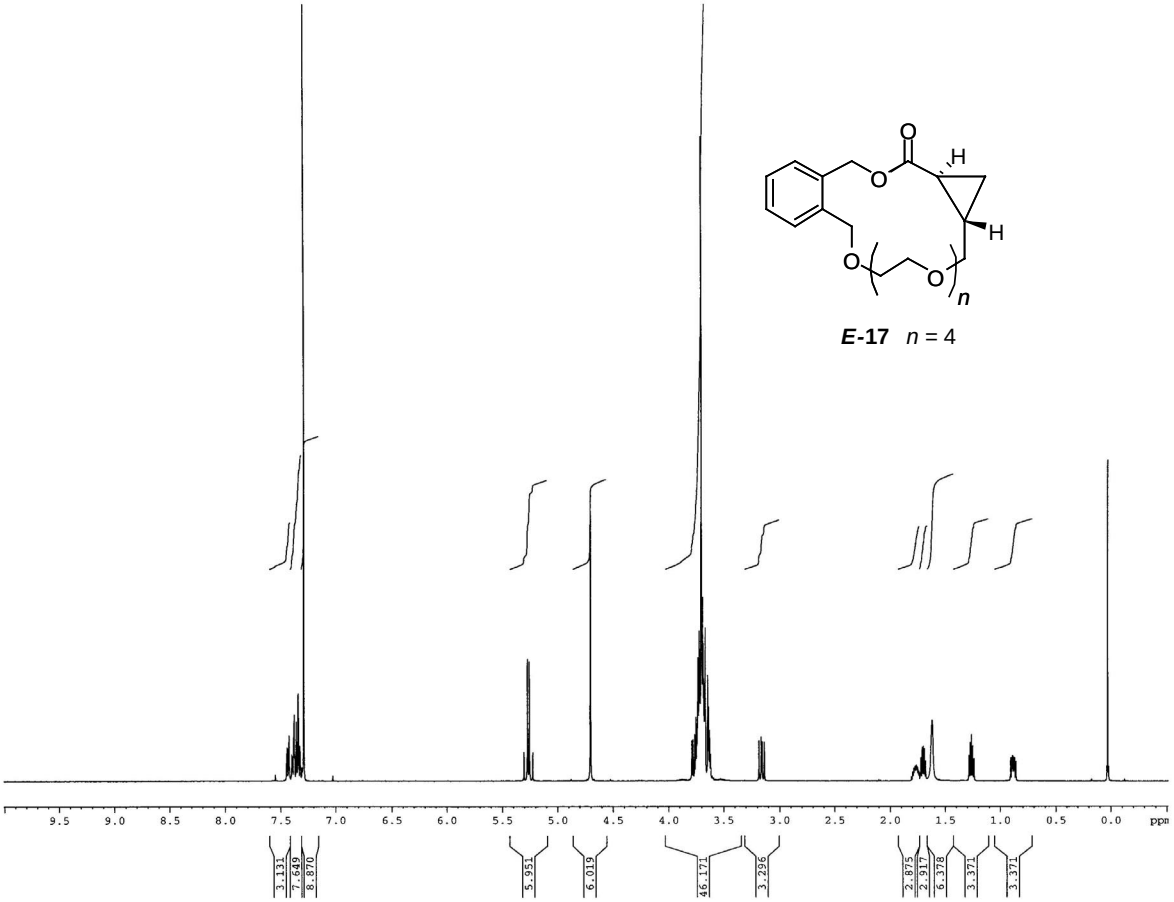
***Z*-17** $n = 4$



***Z*-17** $n = 4$

***E*-3,9,12,15,18,21-Hexaoxa-tricyclo[21.4.0.0^{5,7}]heptacosa-1(23),24,26-trien-4-one (*E*-17).** ^{1}H NMR (400 MHz) δ 7.45-7.30 (comp, 4 H), 5.28 (d, J = 12.4 Hz, 1 H), 5.24 (d, J = 12.4 Hz, 1 H), 4.70 (s, 2 H), 3.77 (dd, J = 10.8, 4.8 Hz, 1 H), 3.74-3.62 (comp, 16 H), 3.16 (dd, J = 10.8, 7.9 Hz, 1 H), 1.77 (ddddd, J = 10.8, 7.0, 6.4, 4.6, 4.4 Hz, 1 H),1.70 (dt, J = 8.3, 4.6 Hz, 1 H), 1.26 (dt, J = 10.8, 4.6 Hz, 1 H), 0.88 (ddd, J = 8.3, 6.3, 4.4 Hz, 1 H); **^{13}C** NMR (100 MHz) δ 173.7, 137.2, 134.4, 130.1, 129.3, 128.6, 128.0, 72.5, 71.2, 70.89, 70.84, 70.80, 70.78, 70.0, 69.9, 64.5, 22.2, 19.0, 12.4; HRMS (FAB+) calculated for $C_{21}H_{30}O_7$: 395.2070; found: 395.2077.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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
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5.951
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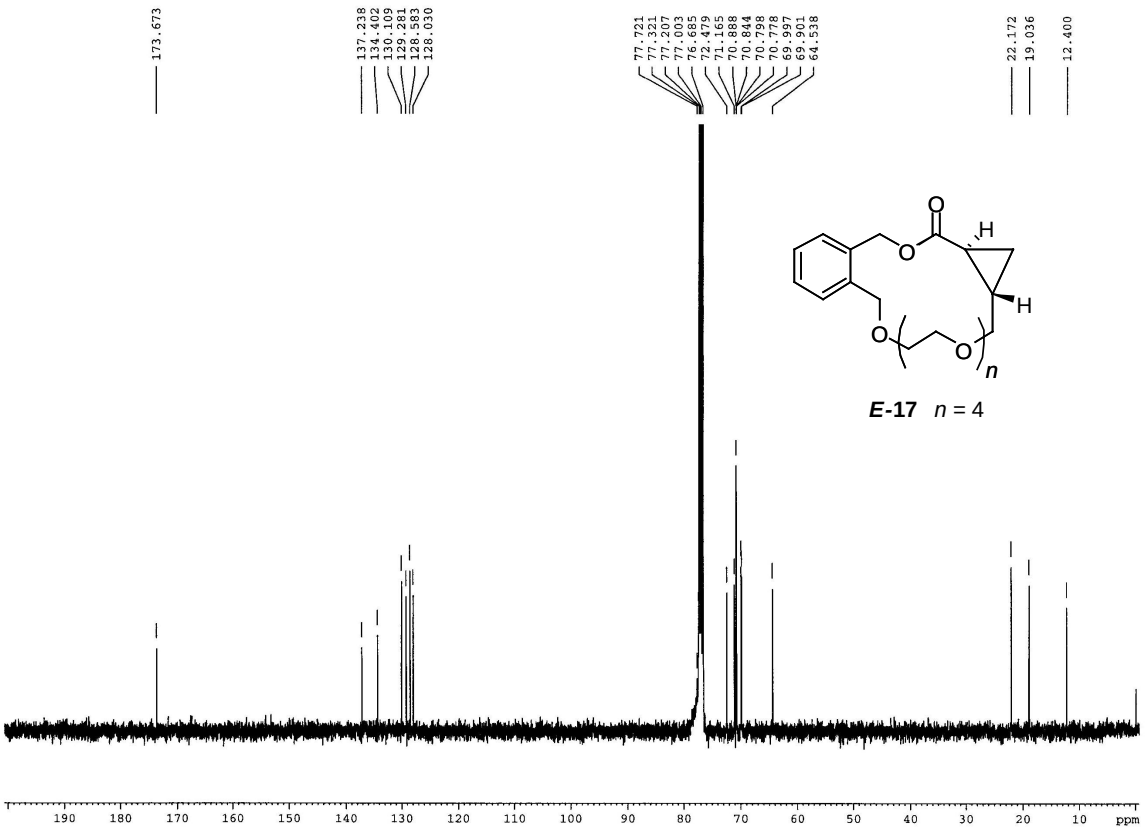
46.171
3.296
2.875
2.917
6.378
3.371
3.371

***E*-17** *n* = 4

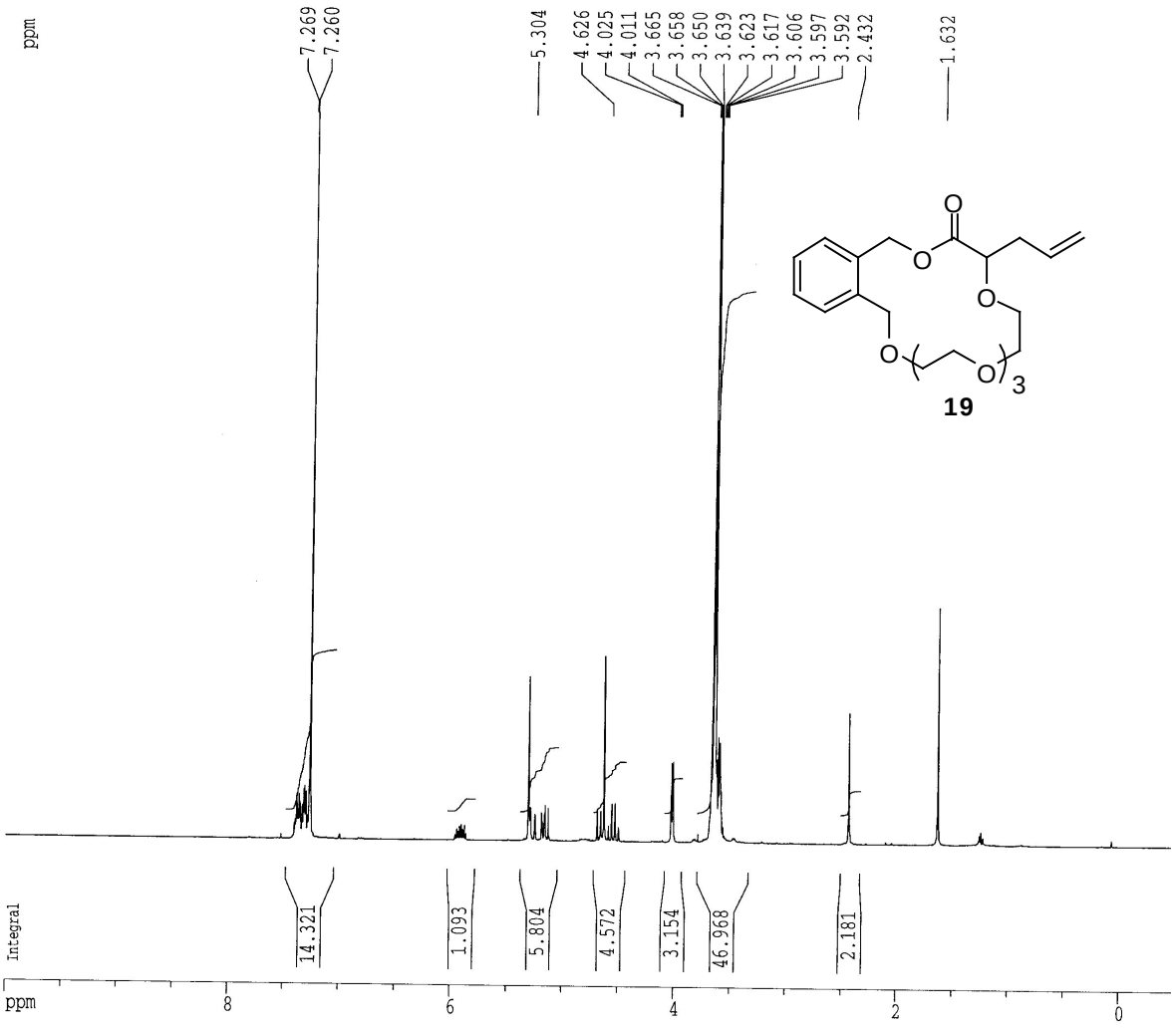


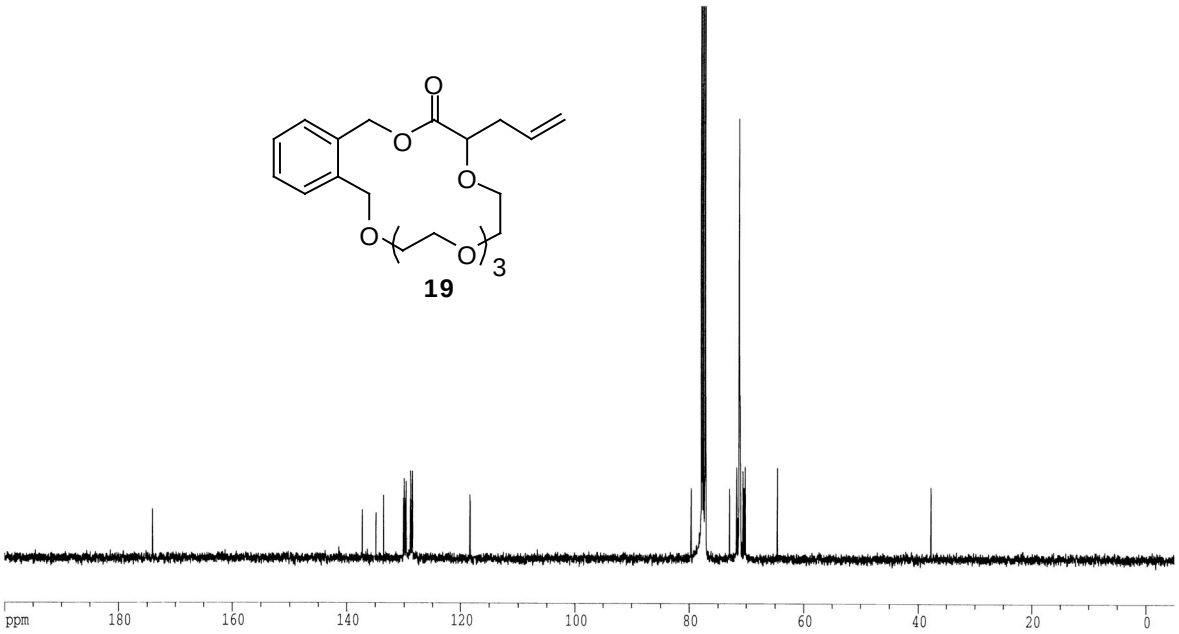
***E*-17** $n = 4$

Purification of the crude reaction mixture containing *Z*-**17** and *E*-**17** was achieved using semi-preparative reverse phase chromatography at a flow rate of 2.7 mL/min with water:acetonitrile (62:48) for 36 min, ramped at 8.9 %/min to water:acetonitrile (0:100) and maintained 15 min, *Z*-**17** was eluted at 20.8 min and *E*-**17** eluted at 22.3 min. The collected fractions were concentrated under reduced pressure to remove acetonitrile, frozen, and residual water was sublimed under reduced pressure.

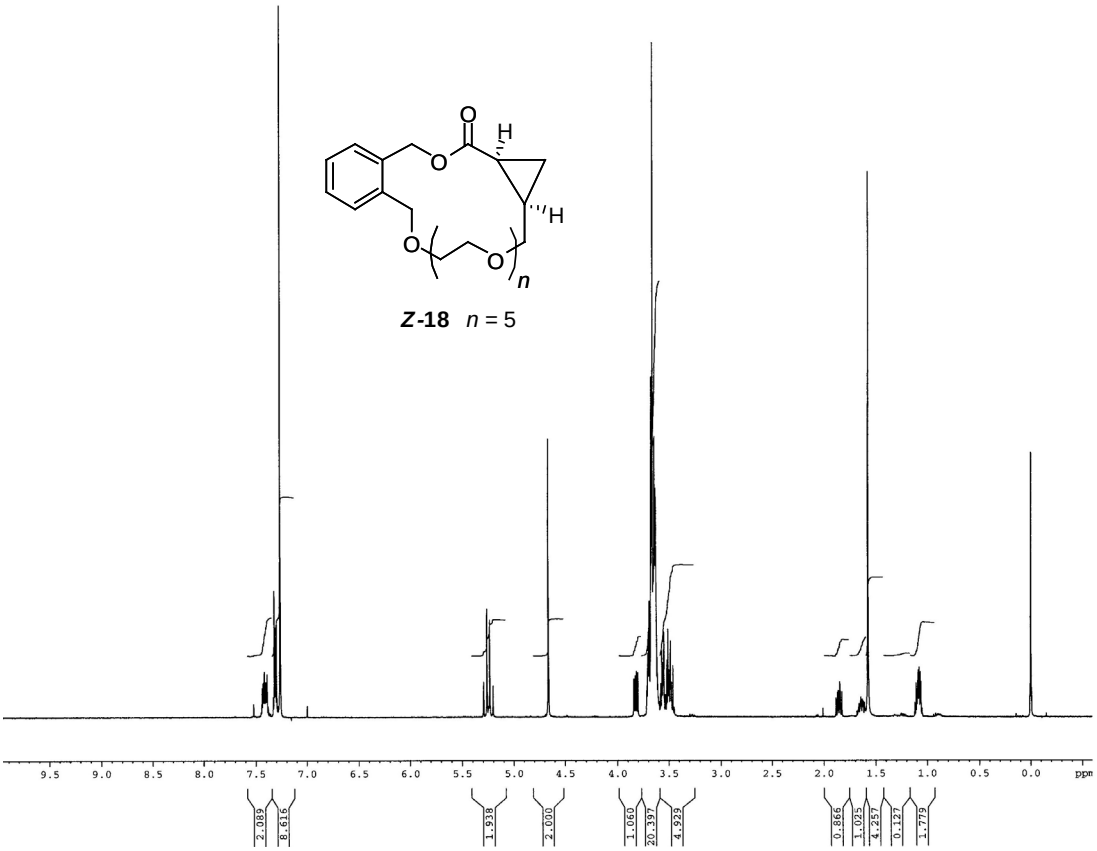
8-Allyl-5,10,11,13,14,16,17,19,20,22-decahydro-6,9,12,15,18,21-hexaoxabenzo-cyloicosen-7-one (19). ^{1}H NMR (400MHz) δ 7.42-7.26 (comp, 4 H), 5.79 (m, 1 H), 5.30 (s, 2 H), 5.02-5.08 (m, 2 H), 4.66 (s, 2 H), 4.08-4.11 (m, 1 H), 3.65-3.57 (comp, 16 H), 2.50 (m, 2 H); ^{13}C NMR (100 MHz) δ 172.4, 137.2, 135.1, 129.9, 129.6, 128.7, 128.5, 118.3,

79.6, 72.9, 71.6, 71.1, 70.9, 70.5, 70.3, 70.2, 70.1, 69.1, 64.6, 37.7; HRMS (ESI) calculated for $C_{21}H_{31}O_7$: 395.20698; found: 395.17062.





***Z*-3,9,12,15,18,21,24,27-Octaoxa-tricyclo[27.4.0.0^{5,7}]tritriaconta-1(29),30,32-trien-4-one (*Z*-18).** ^{1}H NMR (400 MHz) δ 7.44 (dd, *J* = 8.9, 4.7 Hz, 2 H), 7.31 (comp, 2 H), 5.27 (d, *J* = 12.8 Hz, 1 H), 5.22 (d, *J* = 12.8 Hz, 1 H), 4.66 (s, 2 H), 3.82 (dd, *J* = 10.5, 5.4 Hz, 1 H), 3.71-3.45 (comp, 24 H), 1.86 (ddd, *J* = 8.6, 7.6, 5.8 Hz, 1 H), 1.64 (dddt, *J* = 8.6, 7.6, 5.4, 8.8 Hz, 1 H), 1.12-1.05 (comp, 2 H); **^{13}C** NMR (100 MHz) δ 172.2, 136.6, 134.7, 129.4, 129.2, 128.2, 128.0, 71.0, 70.8, 70.5, 69.9, 69.8, 68.7, 63.8, 21.1, 17.6, 11.7; HRMS (FAB +) calculated for $C_{25}H_{38}O_9Li$: 489.2676; found: 489.2681.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H
O
O
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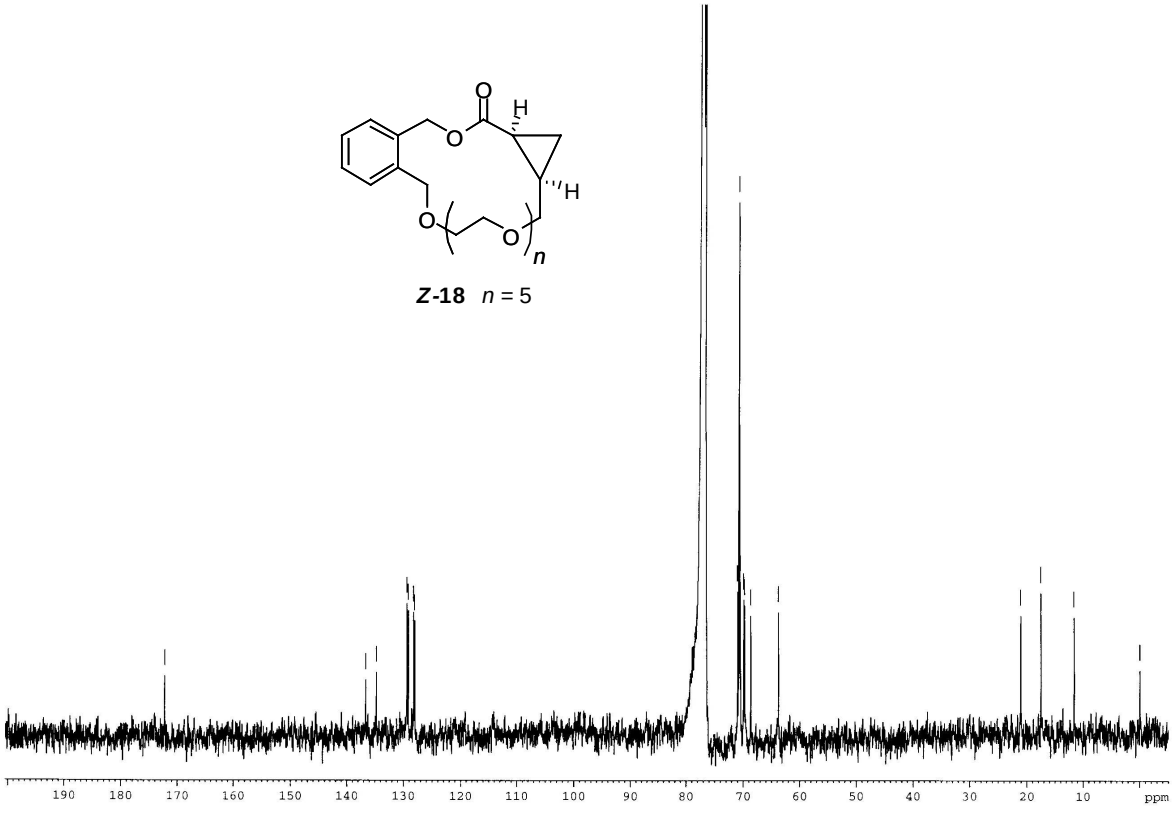
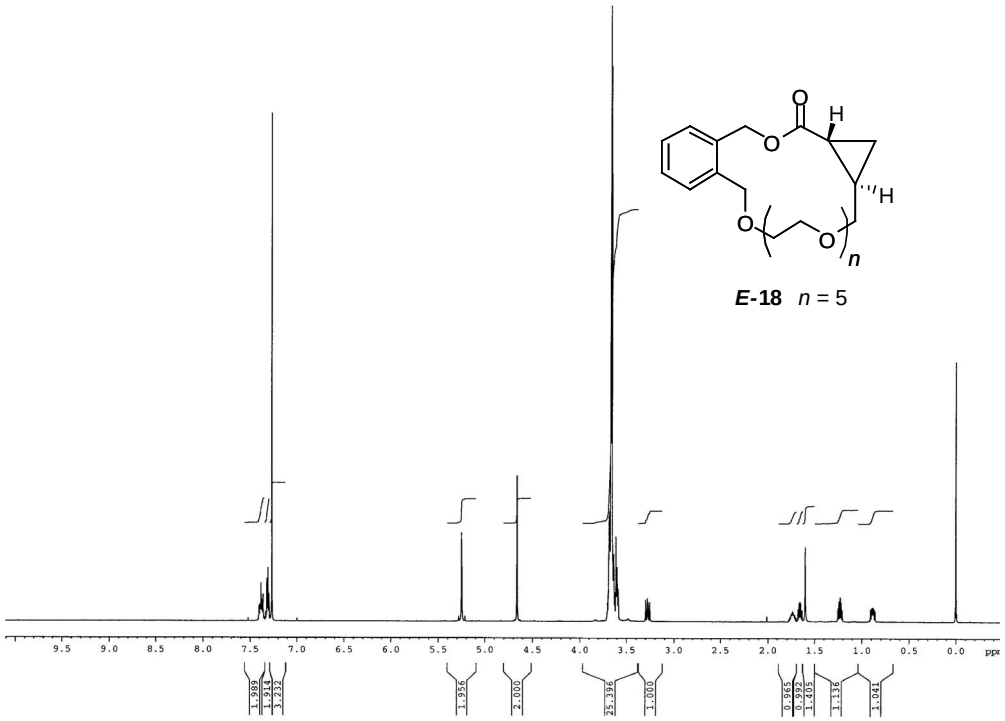
2.089
8.616
1.938
2.000
1.066
20.397
4.923
0.866
1.025
4.257
0.187
1.779

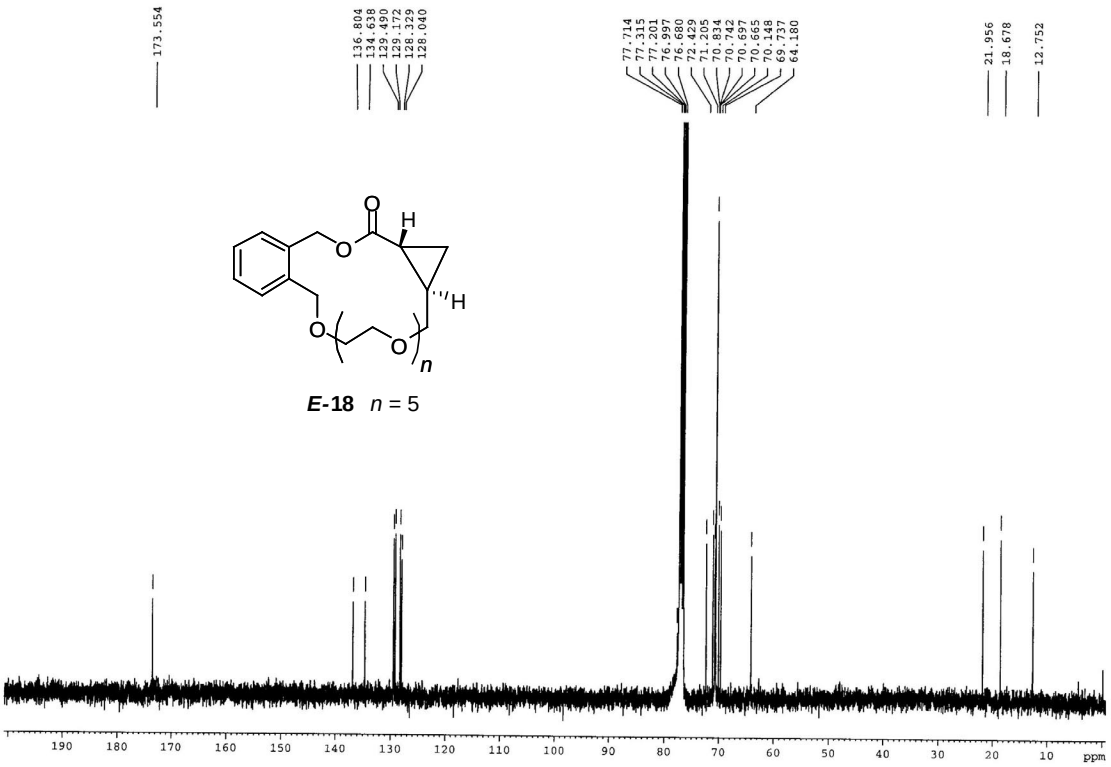
***Z*-18** $n = 5$


O
H
O
H
O
O
n
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

***Z*-18** $n = 5$

***E*-3,9,12,15,18,21,24,27-Octaoxa-tricyclo[27.4.0.0^{5,7}]tritriaconta-1(29),30,32-trien-4-one (*E*-18).** ^{1}H NMR (400 MHz) δ 7.40-7.26 (comp, 4 H), 5.27 (d, *J* = 12.7 Hz, 1 H), 5.23 (d, *J* = 12.7 Hz, 1 H), 4.68 (d, *J* = 12.0 Hz, 1 H), 4.64 (d, *J* = 12.0 Hz, 1 H), 3.71-3.59 (comp, 24 H), 3.27 (dd, *J* = 10.6, 7.1 Hz, 1 H), 1.74 (ddddd, *J* = 9.1, 7.1, 6.3, 4.5, 4.3 Hz, 1 H), 1.66 (ddd, *J* = 8.4, 4.5, 4.3 Hz, 1 H), 1.23 (ddd, *J* = 9.1, 4.5, 4.5 Hz, 1 H), 0.88 (ddd, *J* = 8.4, 6.3, 4.3 Hz, 1 H); **^{13}C** NMR (100 MHz) δ 173.6, 136.8, 134.6, 129.5, 129.2, 128.3, 128.0, 72.4, 71.2, 70.83, 70.74, 70.70, 70.67, 70.1, 69.7, 64.2, 22.0, 18.7, 12.8; HRMS (FAB+) calculated for $C_{25}H_{38}O_9Li$: 489.2676; found: 489.2681.



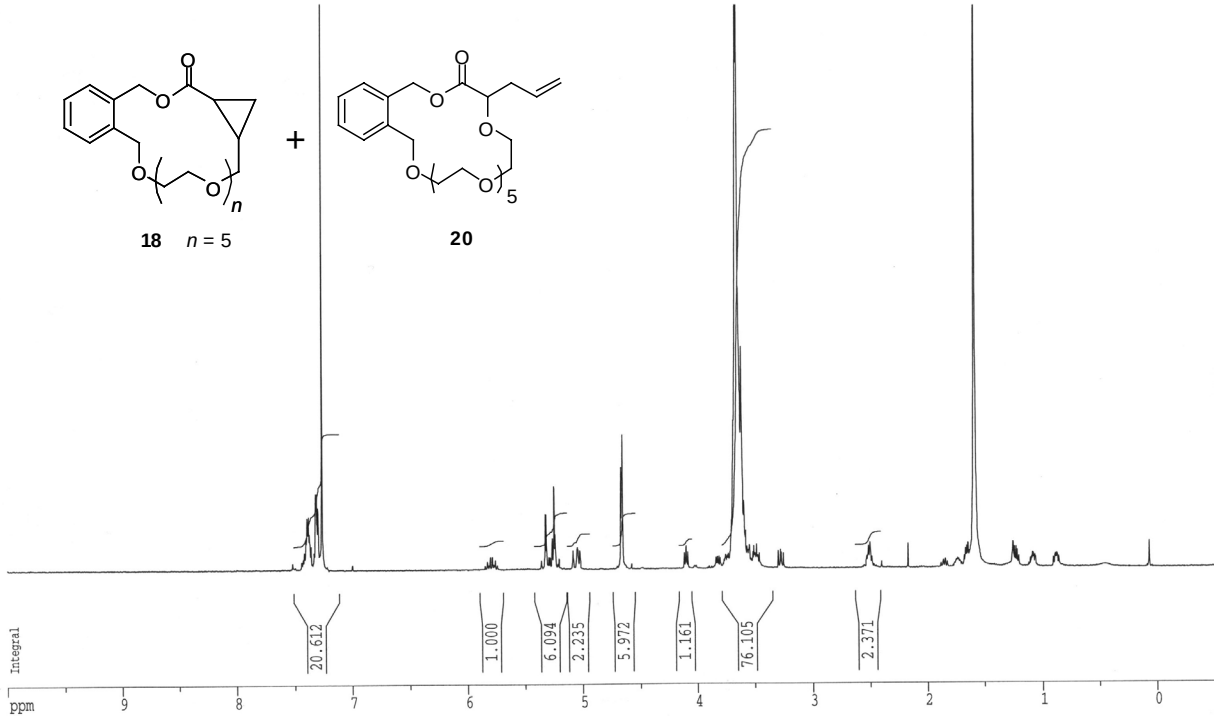


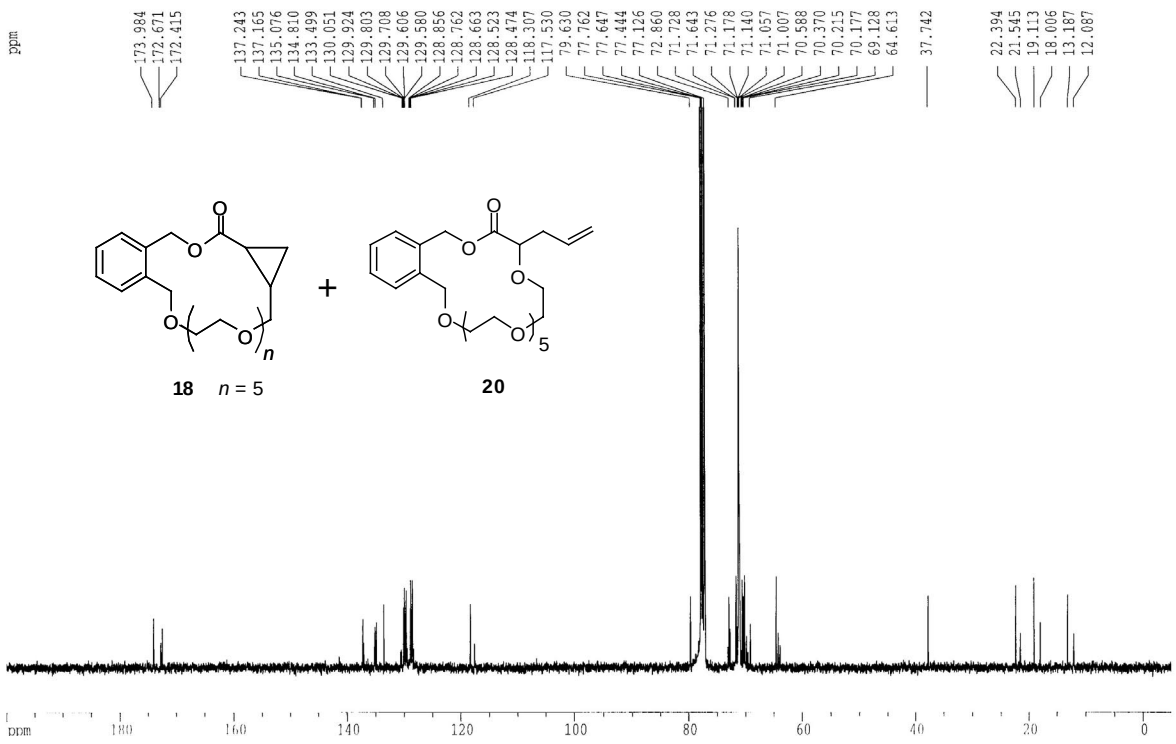
***E*-18** $n = 5$

Purification of the crude reaction mixture containing *Z*-**18** and *E*-**18** was achieved using semi-preparative reverse phase chromatography at a flow rate of 2.8 mL/min with water:acetonitrile (60:40) for 33 min, ramped at 0.36 %/min to water:acetonitrile (55:45) then ramped at 4.5 %/min to water:acetonitrile (55:45) and maintained 15 min. *Z*-**18** was eluted at 30.2 min and *E*-**18** eluted at 31.6 min. The collected fractions were concentrated under reduced pressure to remove acetonitrile, frozen, and residual water was sublimed under reduced pressure.

8-Allyl-5,10,11,13,14,16,17,19,20,22,23,25,26,28-tetradecahydro-6,9,12,15,18,21,24-octaoxabenzocylohexacosen-7-one (20). Repeated attempts to fully extract the cyclopropane products from the ylide product failed to purify compound **20** beyond 35%. Eight runs by column chromatography on silica gel using mainly 50:1

chloroform:methanol, with careful fractionation, reached a steady state where no further improvement in product composition could be achieved. A selection of the absorptions for **20** from the mixture of ylide product and cyclopropane product are reported**:** ^{1}H NMR (400 MHz) δ 5.79 (m, 1 H), 5.24 (s, 2 H), 5.02-5.08 (m, 2 H), 4.66 (s, 2 H), 4.08-4.11 (m, 1 H), 2.50 (m, 2 H); ^{13}C NMR (100 MHz) δ 172.4, 137.2, 134.8, 130.0, 129.8, 118.3, 79.6, several from 72 to 69, 64.6, 37.7; HRMS (ESI) calculated for $C_{25}H_{39}O_9$: 483.25941; found: 483.20277.





2-(2-(2-(2-(2-(2-Allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxymethyl)phenylmethyl Acetate.

To a flame dried 100-mL round bottom flask containing 2-(2-(2-(2-(2-(2-allyloxy-ethoxy)-ethoxy)-ethoxy)-ethoxy)ethoxymethyl)phenylmethanol (0.313 g, 0.75 mmol, 1.0 eq.) dissolved in DCM (3.0 mL) was added Et_3N (0.34 mL, 2.4 mmol, 3.2 eq) in one aliquot, and the solution was cooled to 0 ºC. Acetyl chloride (0.17 mL, 2.3 mmol, 3.0 eq) was added dropwise and the solution was allowed to stand overnight. The cloudy solution was filtered through a short plug of silica gel , followed by washing with diethyl ether (3 x 15 mL), and concentrated under reduced pressure. The resultant clear oil was purified by flash chromatography on silica gel (45:45:10 hexanes:EtOAc:Et_2O) to yield the title compound as a clear oil (0.239 g, 72% yield). **^{1}H NMR** (400 MHz) δ 7.38 (mult., 2 H), 7.31 (mult., 2 H), 5.90 (ddt, *J* = 17.3, 10.4, 5.6 Hz, 1 H), 5.26 (ddd, *J* = 17.3, 3.2, 1.7 Hz, 1 H), 5.21 (s, 2

H), 5.17 (ddd, *J* = 10.4, 3.2, 1.7 Hz, 1 H), 4.63 (s, 2 H),4.02 (dt, *J* = 5.6, 1.7 Hz, 2 H), 3.75-3.58 (mult., 20 H), 2.15 (s, 3 H); **^{13}C NMR** (100 MHz) δ 171.2, 136.9, 135.2, 134.8, 129.7, 129.6, 128.8, 117.6, 72.7, 71.4, 71.05, 71.02, 71.00, 70.7, 70.1, 69.8, 64.2, 53.9, 21.4.

References and Notes

1. Panghonr, A.B.; Giardello, M.A.; Grubbs, R.H.; Rosen, R.K.; Timmers, F.J. Organometallics, 1996, 15, 1518.

2. (a) House, H.O.; Blankley, C. J. J. Org. Chem. 1968, 33, 53; (b) Blankely, C.J.; Sauter, F.J.; House, H.O. Org. Synth. 1969, 49, 22.

3. Kubas, G. J. Inorg. Synth. 1979, 19, 90.

4. Evans, D. A.; Woerpel, K. A.; Hinman, , M. M.; Faul, M. M. J. Am. Chem. Soc. 1991, 113, 726.

5. Doyle, M.P.; Dyatkin, A.B.; Protopopova, M.N.; Yang, C.I.; Miertschin, C.S.; Winchester, W.R.; Simonsen, S.I.; Lynch, V.; Ghosh, R. Recueil Trav. Chim. Pays-Bas 1995, 114, 163.

6. Doyle, M. P.; Davies, S. B.; Hu, W. Organic Lett. 2000, 2, 1145.

7. [1] *Handbook of Thin-Layer Chromatography* J. Sherman and B. Fried, Eds.; Marcel Dekker: New York, NY, 1991.

8. 1,2-Benzendimethanol prepared by the following method: Doyle, M.P.; Peterson, C.S.; Protopopova, M.N.; Marnett, A.B.; Parker, D.L., Jr.; Ene, D.G.; Lynch, V. *J. Am. Chem. Soc.* **1997**, *119*, 8826.

9. Entel, J; Ruof, C.F; Howar, H.C, *J. Am. Chem. Soc.* **1952**, *74*, 441.