Electronic Supplementary Material (ESI) for Chemical Communications

Microwave Accelerated Glaser-Hay Macrocyclizations at High Concentrations.

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SUPPORTING INFORMATION

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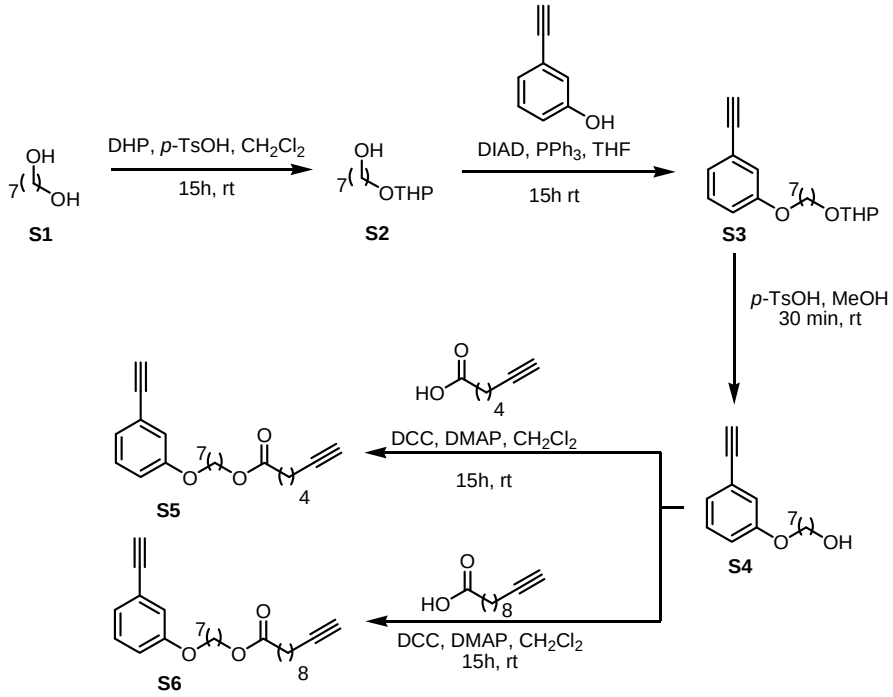
General:

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. 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[2] 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 (CHCl3: δ 7.27 for ^{1}H, δ 77.0 for ^{13}C). The acquisition parameters are shown on all spectra. 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. The ^{13}C NMR assignments were made on the basis of chemical shift and multiplicity. 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. The microwave used is a Biotage Initiator Sixty®.

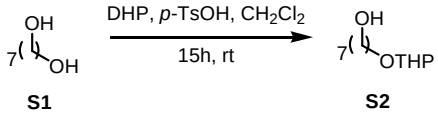
[1] Shriver, D. F.; Drezdon, M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.
[2] Still, W. C.; Kahn, M.; Mitra, A.*J. Org. Chem*. **1978**, *43*, 2923.

SYNTHESIS OF MACROCYCLIZATION PRECURSORS.

Note that macrocyclic diyne precursors for macrocycles **3-7** have been previous prepared.[3]

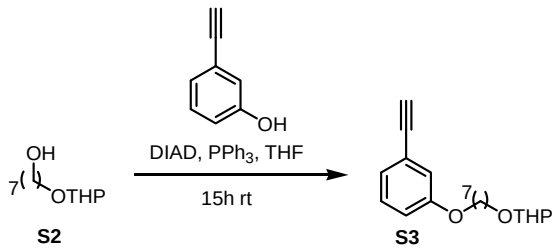


The synthesis of the acyclic precursors to macrocycles **S5** and **S6** are described below.

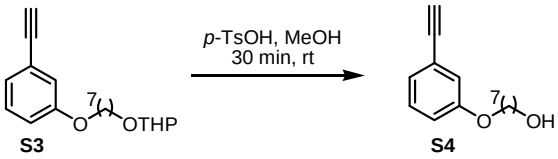


7-((tetrahydro-2H-pyran-2-yl)oxy)heptan-1-ol (S2): To a stirred solution of 1,7-heptane diol (2.0 g, 15.1 mmol, 1 equiv.) in dry dichloromethane (30 mL) at room temperature was added dihydropyran (1.3 g, 15.1 mmol, 1 equiv.) in one portion, followed by *p*-toluenesulfonic acid (154 mg, 0.8 mmol, 0.05 equiv.). The mixture was stirred for 20 h at room temperature. A saturated solution of $NaHCO_3$ was then added and the mixture was extracted with ether (3X), then the organic layers were combined and dried with Na_2SO_4. Following purification by column chromatography on silica gel (10% ethyl acetates in hexanes), the product was obtained as a colorless oil (60 %, 1.9 g). The NMR data are in agreement with that obtained in the literature.[4]

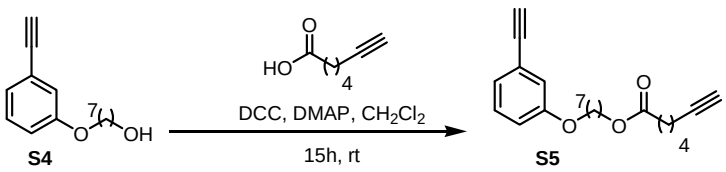
[3] Bédard, A.-C.; Collins, S. K. *J. Am. Chem. Soc.* **2011**, *133*, 19976-19981.
[4] Poppe, L.; Hull, W. E.; Rétey, J. *Helv. Chim. Acta* **1993**, *76*, 2367-2383.



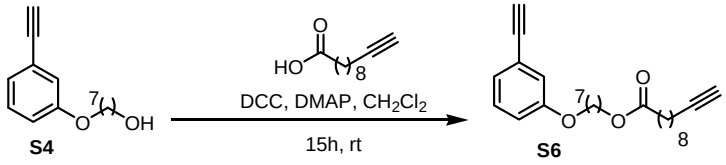
2-((7-(3-ethynylphenoxy)heptyl)oxy)tetrahydro-2H-pyran (S3): To a stirred solution of 3-hydroxyphenylacetylene (0.9 g, 7.5 mmol, 1 equiv.) in anhydrous THF (40 mL) was added triphenylphosphine (3.0 g, 11.3 mmol, 1.5 equiv.), 7-((tetrahydro-2H-pyran-2-yl)oxy)heptan-1-ol (**S2**) (1.9 g, 8.9 mmol, 1 equiv.) and diisopropyl azodicarboxylate (2.2 mL, 11.3 mmol, 1.5 equiv.) in that order under a N_2 atmosphere. The reaction mixture was heated at reflux for 15 hours. The reaction was concentrated under vacuum to provide a crude reaction mixture which was purified by silica gel column chromatography (100% hexanes → 10% ethyl acetates in hexanes) to afford the desired product as a colorless oil (26 %, 0.6 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 - 7.18 (m, 1H), 7.07 (td, *J* = 7.6, 1.1 Hz, 1H), 7.01 (dd, *J* = 2.4, 1.5 Hz, 1H), 6.90 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 4.58 (dd, *J* = 4.2, 2.7 Hz, 1H), 3.97 - 3.84 (m, 3H), 3.75 (td, *J* = 9.6, 6.8 Hz, 1H), 3.56 - 3.46 (m, 1H), 3.40 (td, *J* = 9.6, 6.7 Hz, 1H), 3.06 (s, 1H), 1.91 - 1.67 (m, 4H), 1.67 - 1.35 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.8, 129.3, 124.4, 123.0, 117.6, 116.0, 98.8, 83.6, 76.8, 68.0, 67.6, 62.3, 30.8, 29.7, 29.2, 29.1, 26.2, 26.0, 25.5, 19.7 ppm; HRMS (ESI) m/z calculated for $C_{20}H_{29}O_3$ $[M+H]^+$, 317.2111; found: 317.2117.



7-(3-ethynylphenoxy)heptan-1-ol (S4): To a stirred solution of (**S3**) (0.5 g, 1.6 mmol, 1 equiv.) in methanol (10 mL) at room temperature was added *p*-toluenesulfonic acid (30 mg, 0.16 mmol, 0.1 equiv.). The mixture was stirred for 30 min at room temperature, then water and ethyl acetate were added to the mixture and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3X). The organic phases were combined and washed with brine then dried with Na_2SO_4. The reaction was concentrated under vacuum to provide a crude reaction mixture which was purified by silica gel column chromatography (20% ethyl acetate in hexanes → 50% ethyl acetate in hexanes) to afford the desired product as a colorless oil (99 %, 0.46 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 - 7.18 (m, 1H), 7.08 (td, *J* = 7.6, 1.1 Hz, 1H), 7.02 (dd, *J* = 2.5, 1.4 Hz, 1H), 6.90 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 3.95 (t, *J* = 6.5 Hz, 2H), 3.66 (t, *J* = 6.6 Hz, 2H), 3.06 (s, 1H), 1.87 - 1.72 (m, 2H), 1.66 - 1.53 (m, 2H), 1.52 - 1.31 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.8, 129.3, 124.5, 123.0, 117.6, 115.9, 83.6, 76.8, 68.0, 63.0, 32.7, 29.11, 29.08, 26.0, 25.6 ppm; HRMS (ESI) m/z calculated for $C_{15}H_{21}O_2$ $[M+H]^+$, 233.1536; found: 233.1529.



7-(3-ethynylphenoxy)heptyl hept-6-ynoate (S5): To a stirred solution of 7-(3-ethynylphenoxy)heptan-1-ol (**S4**) (210 mg, 0.92 mmol, 1 equiv.) and the 6-heptynoic acid (232 mg, 1.84 mmol, 2.0 equiv.) in dry dichloromethane (5 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (590 mg, 2.76 mmol, 3 equiv.) and 4-dimethylaminopyridine (337 mg, 2.76 mmol, 3 equiv.) at room temperature. The reaction mixture was stirred at room temperature for 15h. The crude reaction mixture was placed in a freezer for 5h to induce the precipitation of the urea, which was subsequently removed by filtration. The filtrate was concentrated under vacuum to provide the crude reaction mixture which was purified by silica gel column chromatography (100 % hexanes → 10% ethyl acetates in hexanes) to afford the desired product as a colorless oil (15 %, 53 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25 - 7.19 (m, 1H), 7.08 (td, *J* = 7.6, 1.1 Hz, 1H), 7.01 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.90 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 4.08 (t, *J* = 6.7 Hz, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 3.06 (s, 1H), 2.34 (t, *J* = 7.4 Hz, 2H), 2.27 - 2.19 (m, 2H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.84 - 1.71 (m, 4H), 1.70 - 1.53 (m, 4H), 1.53 - 1.36 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.5, 158.8, 129.4, 124.5, 123.0, 117.6, 115.9, 84.0, 83.6, 76.8, 68.6, 67.4, 64.4, 33.8, 29.1, 29.0, 28.6, 27.9, 25.9 (2C), 24.0, 18.1 ppm; HRMS (ESI) m/z calculated for $C_{22}H_{29}O_3$ $[M+H]^+$, 341.2111; found: 341.2126.

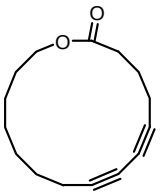


7-(3-ethynylphenoxy)heptyl undec-10-ynoate (S6) : To a stirred solution of 7-(3-ethynylphenoxy)heptan-1-ol (**S4**) (210 mg, 0.92 mmol, 1 equiv.) and the 10-undecynoic acid (335 mg, 1.84 mmol, 2.0 equiv.) in dry dichloromethane (5 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (590 mg, 2.76 mmol, 3 equiv.) and 4-dimethylaminopyridine (337 mg, 2.76 mmol, 3 equiv.) at room temperature. The reaction mixture was stirred at room temperature for 15h. The crude reaction mixture was placed in a freezer for 5h to induce the precipitation of the urea, which was subsequently removed by filtration. The filtrate was concentrated under vacuum to provide the crude reaction mixture which was purified by silica gel column chromatography (100 % hexanes → 10% ethyl acetates in hexanes) to afford the desired product as a colorless oil (50 %, 97 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 - 7.19 (m, 1H), 7.08 (td, *J* = 7.6, 1.1 Hz, 1H), 7.01 (dd, *J* = 2.4, 1.5 Hz, 1H), 6.90 (ddd, *J* = 8.3, 2.7, 0.9 Hz, 1H), 4.07 (t, *J* = 6.8 Hz, 2H), 3.94 (t, *J* = 6.5 Hz, 2H), 3.06 (s, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.22 - 2.13 (m, 3H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.83 - 1.73 (m, 3H), 1.68 - 1.57 (m, 4H), 1.57 - 1.44 (m, 4H), 1.44 - 1.22 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.9, 158.8, 129.3, 124.5, 123.0, 117.6, 115.9, 84.7, 83.6, 76.8, 68.1, 67.9, 64.3, 34.3, 29.08 (2C), 29.06, 29.0, 28.9, 28.64, 28.57, 28.4, 25.9,

25.0, 18.4 (2C) ppm; HRMS (ESI) m/z calculated for $C_{26}H_{37}O_3$ $[M+H]^+$, 397.2737; found: 397.2746.

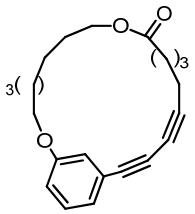
SYNTHESIS OF MACROCYCLES

Note that macrocycles **3**, **4**, **5**, **6** and **7** have been previous prepared.[3]

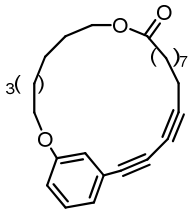


General procedure for the macrocyclization of diynes under Glaser-Hay oxidative coupling conditions using thermal heating: Macrocycle (**2**): To a vial equipped with a stirring bar was added $CuCl_2$ (5.5 mg, 0.48 mmol, 25 mol%) and $Ni(NO_3)_2 \cdot 6H_2O$ (9.3 mg, 0.48 mmol, 25 mol%). Polyethylene glycol 400 (3.33 mL), triethylamine (0.05 mL, 0.36 mmol, 3 equiv.) and pyridine (0.05 mL, 0.6 mmol, 5 equiv.) were added and the mixture was stirred at room temperature for 15 min or until the metals were solubilized. The diyne (28 mg, 0.12 mmol) was added to the homogenous 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 screw cap. The reaction was warmed to 60°C and monitored by TLC for consumption of the starting material (oxygen was bubbled again through the solution every 12h). When the starting material was completely consumed (TLC), the reaction was cooled to room temperature and the crude mixture was loaded directly on a silica column. Purification by silica gel chromatography (100 % hexanes →10% ethyl acetate in hexanes) afforded the product as a colorless semi-solid (31 mg, 73%).

General procedure for the macrocylization of diynes under Glaser-Hay oxidative coupling conditions using microwave irradition: Macrocycle (**2**): To a microwave vial equipped with a stirring bar was added $CuCl_2$ (5.5 mg, 0.48 mmol, 25 mol%) and $Ni(NO_3)_2 \cdot 6H_2O$ (9.3 mg, 0.48 mmol, 25 mol%). Polyethylene glycol 400 (3.33 mL), triethylamine (0.05 mL, 0.36 mmol, 3 equiv.) and tetramethylethylene diamine (0.09 mL, 0.6 mmol, 5 equiv.) were added and the mixture was stirred at room temperature for 15 min or until the metals were solubilized. The diyne (28 mg, 0.12 mmol) was added to the homogenous 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 sealed with a microwave cap. The reaction was warmed to 120°C for 3 to 6h. The crude mixture was loaded directly onto silica gel for purification by chromatography (100 % hexanes → 10% ethyl acetate in hexanes) and afforded the product as a colorless semi-solid (16 mg, 57%).



Macrocycle (8): Following the general procedure described above, macrocycle **8** was isolated. (25 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 - 7.17 (m, 1H), 7.08 - 7.02 (m, 2H), 6.89 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 4.08 (t, *J* = 6.4 Hz, 2H), 4.03 (t, *J* = 6.9 Hz, 2H), 2.42 - 2.38 (m, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.78 (quin, *J* = 6.9 Hz, 2H), 1.72 - 1.60 (m, 4H), 1.60 - 1.44 (m, 4H), 1.44 - 1.33 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm = 173.9, 158.6, 129.5, 124.2, 123.0, 118.3, 117.3, 85.1, 75.0, 74.3, 68.2, 64.1, 34.1, 28.5, 28.4, 28.1, 28.0, 27.6, 25.9, 25.6, 24.8, 19.5; HRMS (ESI) m/z calculated for $C_{22}H_{27}O_3$ $[M+H]^+$, 339.1955; found: 339.1964.



Macrocycle (9): Following the general procedure described above, macrocycle **9** was isolated. (32 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 - 7.16 (m, 1H), 7.09 - 7.01 (m, 2H), 6.89 (dd, *J* = 8.3, 1.7 Hz, 1H), 4.08 (t, *J* = 6.4 Hz, 2H), 4.03 (t, *J* = 6.9 Hz, 2H), 2.42 - 2.37 (m, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.78 (quin, *J* = 6.8 Hz, 2H), 1.71 - 1.60 (m, 4H), 1.60 - 1.45 (m, 4H), 1.45 - 1.34 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm = 173.9, 158.6, 129.5, 124.2, 123.0, 118.3, 117.3, 85.1, 74.9, 74.3, 68.2, 65.6, 64.1, 34.1, 29.0, 28.5 (2C), 28.42, 28.40, 28.1, 27.6, 25.9, 25.5, 19.5; HRMS (ESI) m/z calculated for $C_{24}H_{34}NaO_3$ $[M+Na]^+$, 417.2400; found: 417.2408.

Complete References From Text:

(3) Lamarre, D.; Anderson, P. C.; Bailey, M.; Beaulieu, P.; Bolger, G.; Bonneau, P.; Bös, M.; Cameron, D. R.; Cartier, M.; Cordingley, M. G.; Faucher, A.-M.; Goudreau, N.; Kawai, S. H.; Kukolj, G.; Lagacé, L.; Laplante, S. R.; Narjes, H.; Poupart, M.-A.; Rancourt, J.; Sentjens, R. E.; St-George, R.; Simoneau, B.; Steinmann, G.; Thibeault, D.; Tsantrizos, Y. S.; Weldon, S. M.; Yong, C.-L.; Llinàs-Brunet, M. *Nature* **2003**, *426*, 186-189.

NMR DATA