# Biocatalysis as a Versatile Tool for Macrolactonization: Comparative Evaluation of Catalytic and Stoichiometric Approaches.

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**SUPPORTING INFORMATION**

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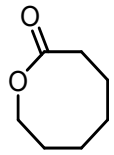
## GENERAL

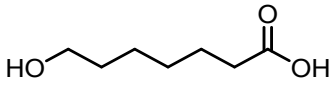
All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 °C or had been flame dried and cooled under a stream of argon or nitrogen.[1] All chemical products were obtained from Millipore-Sigma, Thermo Fisher Scientific, AA Block or Oakwood Chemicals and were reagent quality. Anhydrous solvents ($CH_2Cl_2$, $Et_2O$, THF, DMF, toluene, and n-hexanes) 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, F254.). Visualization of TLC plate was performed by UV (254 nm), $KMnO_4$, p-anisaldehyde, or bromo cresol 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 1H NMR. NMR spectra were taken in deuterated $CDCl_3$ using Bruker AV-400 and AV-500 instruments unless otherwise noted. Signals due to the solvent served as the internal standard ($CHCl_3$: δ 7.26 for $^1H$, δ 77.16 for $^{13}C$). The $^1H$ 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. 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. SFC analyses were done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal from an Agilent 1260 Infinity Analytical SFC System coupled with an Agilent Single Quadrupole MS 6120.

## SUBTRATE SYNTHESIS

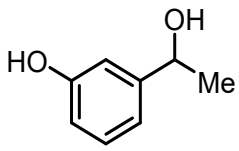
[1] Shriver, D. F.; Drezdzon, M. A., *The manipulation of air-sensitive compounds*. John Wiley & Sons: 1986.
[2] Still, W. C.; Kahn, M.; Mitra, A., *J. Org. Chem.* **1978,** *43*, 2923.



**Oxocan-2-one** (**S1**): To a solution of 3-chloroperbenzoic acid (5.52 g, 24.0 mmol) in DCM (40.0 mL), was added cycloheptanone (2.36 mL, 20.0 mmol) at 0°C. After stirring for 5 days at room temperature, the reaction mixture was filtered, washed with a saturated solution of $NaHCO_3$ (30 mL) and water (30 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuum. The crude reaction mixture was purified by column chromatography on silica-gel (5 % EtOAc in hexanes) to afford the desired product as a colorless oil (1.89 g, 74% yield). NMR data was in accordance with what was previously reported.[3] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.38 – 4.30 (m, 2H), 2.58 – 2.51 (m, 2H), 1.93 – 1.76 (m, 4H), 1.64 – 1.53 (m, 4H).

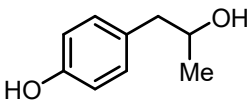


**7-Hydroxyheptanoic acid** (**S2**): In a round bottom flask equipped with a stir bar was added the oxocan-2-one (555 mg, 4.33 mmol, 1.0 equiv.) in a 1:1 mixture of water (8.66 mL) and ethanol (8.66 mL, 250 mM). Potassium hydroxide (1.21 g, 21.7 mmol, 5.0 equiv.) was slowly added and the reaction mixture was stirred at room temperature for 18 h. After completion, the reaction mixture was transferred into a separatory funnel with ethyl acetate (20 mL) and HCl 1M solution (20 mL) solution. The phases were mixed and separated. The aqueous phase was extracted with more ethyl acetate (2 x 20 mL) and the combined organic phases were dried over $Na_2SO_4$ and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica-gel (40 % EtOAc in hexanes) to afford the desired product as a white solid (184 mg, 29%). NMR data was in accordance with what was previously reported.[4-5] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 6.07 (Brs, 1H), 3.65 (t, $J$ = 6.5 Hz, 2H), 2.36 (t, $J$ = 7.4 Hz, 2H), 1.66 – 1.61 (m, 2H), 1.61 – 1.52 (m, 2H), 1.42 – 1.36 (m, 4H).

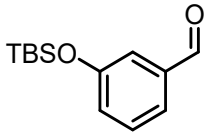


[3] Kai, K.; Takeuchi, J.; Kataoka, T.; Yokoyama, M.; Watanabe, N., *Tetrahedron* **2008,** *64*, 6760.
[4] Berdeaux, O.; Fontagné, S.; Sémon, E.; Velasco, J.; Sébédio, J. L.; Dobarganes, C., *Chem. Phys. Lipids* **2012,** *165*, 338.
[5] Liu, Y.; Cornella, J.; Martin, R., *J. Am. Chem. Soc.* **2014,** *136*, 11212.

**3-(1-Hydroxyethyl)phenol (S3)**: In a round bottom flask equipped with a stir bar under nitrogen, 3-hydroxyacetophenone (22.0 mmol, 1.0 equiv.) was dissolved in methanol (110 mL, 200 mM). The solution was cooled to 0 °C in an ice/water bath, and $NaBH_4$ (3.33 g, 88.0 mmol, 4.0 equiv.) was slowly added over a period of 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. A saturated aqueous solution of $NH_4Cl$ (100 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The organic layers were combined and washed with brine, dried with $Na_2SO_4$ and concentrated. The crude reaction mixture was purified by column chromatography on silica-gel (35 % EtOAc in hexanes) to afford the desired product as a white solid (2.45 g, 80 % yield). NMR data was in accordance with what was previously reported.[6] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.26 – 7.18 (m, 1H), 7.05 – 6.89 (m, 1H), 6.91 – 6.86 (m, 1H), 6.78 – 6.71 (m, 1H), 4.87 (q, *J* = 6.5 Hz, 1H), 4.80 (s, 1H), 1.79 (s, 1H), 1.49 (d, *J* = 6.5 Hz, 3H).

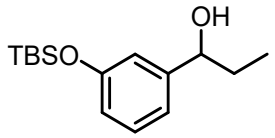



**4-(2-Hydroxypropyl)phenol (S4):** In a round bottom flask equipped with a stir bar under nitrogen, 1-(4-hydroxyphenyl)propan-2-one (801 mg, 5.36 mmol, 1.0 equiv.) was dissolved in methanol (21.4 mL, 250 mM). The solution was cooled to 0 °C in an ice/water bath, and $NaBH_4$ (406 mg, 10.7 mmol, 2.0 equiv.) was slowly added over a period of 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. A saturated aqueous solution of $NH_4Cl$ (40 mL) was added and the mixture was extracted with EtOAc (3 x 25 mL). The organic layers were combined and washed with brine, dried with $Na_2SO_4$ and concentrated. The crude reaction mixture was purified by column chromatography on silica-gel (30 % EtOAc in hexanes) to afford the desired product as a white solid (808 mg, 99 % yield). NMR data was in accordance with what was previously reported.[7] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.13 – 7.00 (m, 2H), 6.85 – 6.71 (m, 2H), 5.90 (s, 1H), 4.03 – 3.91 (m, 1H), 2.80 – 2.68 (m, 1H), 2.66 – 2.55 (m, 1H), 1.84 (s, 1H), 1.24 (d, *J* = 6.2 Hz, 3H).

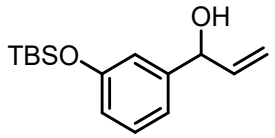



[6] Liu, J.-t.; Yang, S.; Tang, W.; Yang, Z.; Xu, J., *Green Chem.* **2018,** *20*, 2118.
[7] Zhao, Y.; Weix, D. J., *J. Am. Chem. Soc.* **2014,** *136*, 48.

**3-((tert-Butyldimethylsilyl)oxy)benzaldehyde (S5):** To a solution of 3-hydroxybenzaldehyde (3.42 g, 28 mmol), triethylamine (4.25 g, 1.5 equiv.) and 4-dimethylaminopyridine (86 mg, 0.7 mmol, 0.025 equiv.) in DCM (175 mL, 160 mM) was added *tert*-butyldimethylsilyl chloride (6.20 g, 41.2 mmol, 1.5 equiv.) portion wise. After stirring for 2 h at room temperature, water was added. The aqueous phase was extracted with DCM, the combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo to afford the desired product as a colorless oil (6.6 g, 99 % yield). NMR data was in accordance with what was previously reported.[8] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.95 (s, 1H), 7.50 – 7.43 (m, 1H), 7.42 – 7.37 (m, 1H), 7.35 – 7.29 (m, 1H), 7.13 – 7.08 (m, 1H), 1.00 (s, 9H), 0.22 (s, 6H).



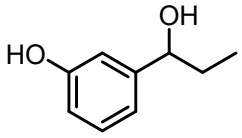

**1-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)propan-1-ol (S6):** In a flame dried round bottom flask equipped with a stir bar under a nitrogen atmosphere was added aldehyde **S5** (1.18 g, 5 mmol, 1 equiv.) with anhydrous THF (10 mL, 500 mM). The solution was cooled at -78°C in a dry ice/acetone bath and an ethylmagnesium chloride solution 2M in THF (12.5 mL, 5 equiv.) was slowly added dropwise to the aldehyde solution under inert atmosphere. Following the addition, the reaction was stirred for 5 min at -78 °C which was then warmed to room temperature and left to stir for an additional 2 h. Afterwards, the crude mixture was treated with a saturated aqueous solution of $NH_4Cl$ (30 mL). The aqueous phase was extracted three times with ethyl acetate (3x30 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica-gel (10 % EtOAc in hexanes) to afford the desired product as a colorless oil (1.17 g, 88 % yield). NMR data was in accordance with what was previously reported.[9] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.19 (dd, $J$ = 7.8, 7.8 Hz, 1H), 6.92 (d, $J$ = 7.8 Hz, 1H), 6.83 (dd, $J$ = 2.1, 2.1 Hz, 1H), 6.77 – 6.72 (m, 1H), 4.58 – 4.50 (m, 1H), 1.86 – 1.81 (m, 1H), 1.80 – 1.66 (m, 2H), 0.99 (s, 9H), 0.91 (t, $J$ = 7.4 Hz, 3H), 0.20 (s, 6H).



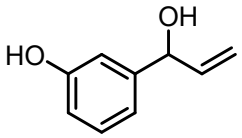

**1-(3-((tert-Butyldimethylsilyl)oxy)phenyl)prop-2-en-1-ol (S7)**: In a flame dried round bottom flask equipped with a stir bar under a nitrogen atmosphere was added aldehyde **S5**

[8] Gerken, P. A.; Wolstenhulme, J. R.; Tumber, A.; Hatch, S. B.; Zhang, Y.; Müller, S.; Chandler, S. A.; Mair, B.; Li, F.; Nijman, S. M., *Angew. Chem. Int. Ed.* **2017,** *56*, 15555.
[9] Guerrero-Morales, J.; Scaglia, M.; Faurand, E.; Lepage, G.; Collins, S.K.; *Nat. Synth* **2024**, https://doi.org/10.1038/s44160-024-00591-9

(1.18 g, 10 mmol, 1 equiv.) with anhydrous THF (10 mL, 500 mM). The solution was cooled at -78 °C in a dry ice/acetone bath and a vinyl magnesium bromide solution 1 M in THF (12,5 mL, 2.5 equiv.) was slowly added dropwise to the aldehyde solution under inert atmosphere. Following the addition, the reaction was stirred for 5 min at -78 °C which was then warmed to room temperature and left to stir for an additional 2 h. Afterwards, the crude mixture was treated with HCl solution (1M). The aqueous phase was extracted three times with ethyl acetate (3x30 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuum. The crude reaction mixture was purified by column chromatography on silica-gel (10 % EtOAc in hexanes) to afford the desired product as a colorless oil (0.998 g, 75% yield). **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.21 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.99 – 6.92 (m, 1H), 6.86 (dd, *J* = 2.1, 2.1 Hz, 1H), 6.79 – 6.73 (m, 1H), 6.08 – 5.97 (m, 1H), 5.38 – 5.29 (m, 1H), 5.23 – 5.17 (m, 1H), 5.17 – 5.12 (m, 1H), 1.97 – 1.88 (m, 1H), 0.99 (s, 9H), 0.20 (s, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 156.0, 144.4, 140.3, 129.6, 119.5, 119.3, 118.2, 115.3, 75.3, 25.8, 18.3, -4.3; **HRMS (ESI)** m/z calculated for $[C_{15}H_{24}O_2Si]$, $[M+H]^+$ 263.1465; found 263.1473.

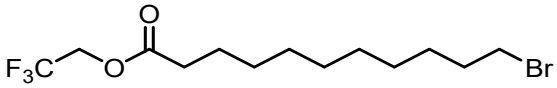



**3-(1-Hydroxypropyl)phenol (S8):** In a round bottom flask equipped with a stir bar was added the *tert*-butyldimethylsilyl ether **S6** (1.07 g, 4.00 mmol, 1.0 equiv.) in methanol (16.0 mL, 250 mM) and potassium carbonate (1.66 g, 12.0 mmol, 3.0 equiv.) under nitrogen atmosphere. After stirring overnight at room temperature, water was added (30 mL). The aqueous phase was extracted with EtOAc (3x 30 mL), the combined organic phases dried over $Na_2SO_4$ and concentrated in vacuo. The crude reaction mixture was purified by column chromatography on silica-gel (35 % EtOAc in hexanes) to afford the desired product as a white solid (446 mg, 73% yield). NMR data was in accordance with what was previously reported.[9] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.24 – 7,18 (m, 1H), 6.92 – 6.87 (m, 1H), 6.87 – 6.83 (m, 1H), 6.77 – 6.71 (m, 1H), 4.88 (s, 1H), 4.60 – 4.54 (m, 1H), 1.85 (d, *J* = 3.4 Hz, 1H), 1.82 – 1.69 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

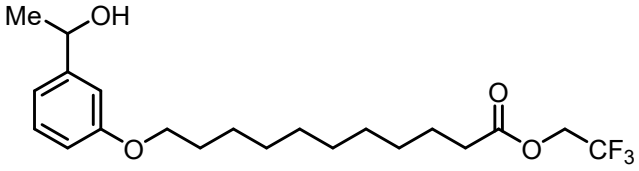



**3-(1-Hydroxyallyl)phenol (S9):** In a round bottom flask equipped with a stir bar was added the *tert*-butyldimethylsilyl ether **S7** (900 mg, 3.40 mmol, 1.0 equiv.) in methanol (11.3 mL, 300 mM) and potassium carbonate (1.18 g, 14.1 mmol, 2.5 equiv.) under nitrogen atmosphere. After stirring overnight at room temperature, water was added (30 mL). The aqueous phase was extracted with EtOAc (3x 30 mL), the combined organic

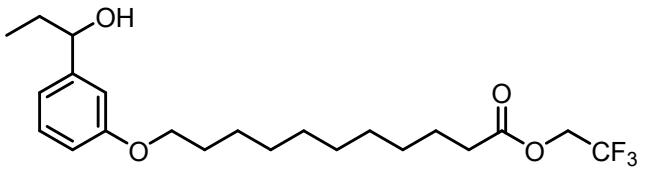
phases dried over $Na_2SO_4$ and concentrated in vacuo. The crude reaction mixture was purified by column chromatography on silica-gel (40 % EtOAc in hexanes) to afford the desired product as a white solid (347 mg, 68% yield). **$^1$H NMR (400 MHz, Acetone)** δ 8.27 (s, 1H), 7.17 – 7.09 (m, 1H), 6.89 (dd, *J* = 2.1, 2.1 Hz, 1H), 6.86 – 6.80 (m, 1H), 6.70 (dd, *J* = 8.1, 2.7 Hz, 1H), 6.04 – 5.91 (m, 1H), 5.34 – 5.24 (m, 1H), 5.09 (t, *J* = 5.2 Hz, 1H), 5.05 – 5.01 (m, 1H), 4.45 – 4.36 (m, 1H); **$^{13}$C NMR (101 MHz, Acetone)** δ 158.2, 146.7, 142.7, 130.0, 118.2, 114.7, 114.0, 113.7, 75.2; **HRMS (ESI)** m/z calculated for $[C_9H_{10}O_2]$, $[M-H]^-$ 149.0608; found 149.0613.



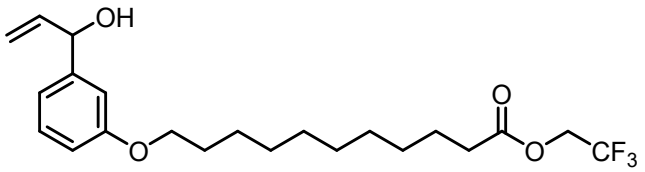

**2,2,2-Trifluoroethyl 11-bromoundecanoate (S10)**: To an open cylindrical pressure vessel equipped with a stir bar was added 11-bromoundecanoic acid (5.0 g, 18.7 mmol, 1.0 equiv.), 2,2,2-trifluoroethanol (37.3 mL, 500 mM) and a few drops of sulfuric acid (cat.). The vessel was sealed with a screw cap and the reaction mixture was stirred at 70 °C for 18 h. The reaction was then cooled to room temperature and the crude reaction mixture was purified by column chromatography on silica-gel (5 % EtOAc in hexanes) to afford the desired product as a colorless oil (5.99 g, 92 % yield). NMR data was in accordance with what was previously reported.[9] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.46 (q, *J* = 8.0 Hz, 2H), 3.40 (t, *J* = 8.0 Hz, 2H), 2.41 (t, *J* = 8.0 Hz, 2H), 1.89 – 1.80 (m, 2H), 1.71 – 1.60 (m, 2H), 1.45 – 1.38 (m, 2H), 1.34 – 1.28 (m, 10H).



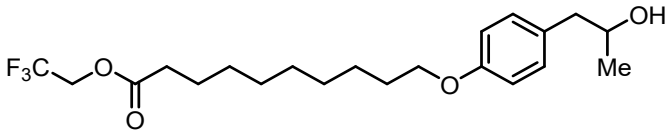

**2,2,2-Trifluoroethyl 11-(3-(1-hydroxyethyl)phenoxy)undecanoate (S11)**: To a cylindrical pressure vessel equipped with a stir bar was added the bromotrifluoroethylester **S10** (2.92 g, 8.40 mmol, 1.20 equiv.), the phenol **S3** (967 mg, 7.00 mmol, 1.0 equiv.), potassium carbonate (1.93 g, 14.00 mmol, 2 equiv.), potassium iodide (1.16 g, 7.00 mmol, 1 equiv.) and acetone (28.0 mL, 0.25 M). The reaction mixture was stirred at 90 °C for 48 h. The reaction was then cooled to room temperature, filtered on Celite® and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica-gel (20 % EtOAc in hexanes) to afford the desired product as a colorless oil (2.27 g, 80 % yield). NMR data was in accordance with what was previously reported.[9] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.24 (dd, *J* = 8.7, 7.2 Hz, 1H), 6.93 (dd, *J* = 7.4, 1.5 Hz, 2H), 6.83 – 6.77 (m, 1H), 4.86 (q, *J* = 6.5 Hz, 1H), 4.46 (q, *J* = 8.5 Hz, 2H), 3.96 (t, *J* = 6.5 Hz, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 1.86 (s, 1H), 1.81 – 1.72 (m, 2H), 1.71 – 1.59 (m, 2H), 1.49 (d, *J* = 6.4 Hz, 3H), 1.46 – 1.39 (m, 2H), 1.38 – 1.27 (m, 10H).



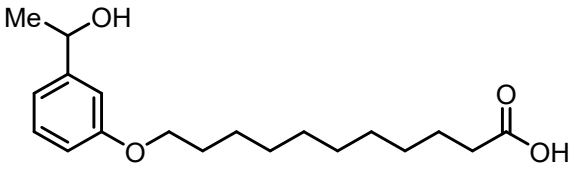

**2,2,2-Trifluoroethyl 11-(3-(1-hydroxypropyl)phenoxy)undecanoate (S12):** To a cylindrical pressure vessel equipped with a stir bar was added the bromotrifluoroethylester **S10** (1.37 g, 3.94 mmol, 1.20 equiv.), the phenol **S8** (500 mg, 3.29 mmol, 1.0 equiv.), potassium carbonate (908 mg, 6.58 mmol, 2 equiv.), potassium iodide (545 mg, 3.29 mmol, 1 equiv.) and acetone (13.1 mL, 0.50 M). The vial was sealed and the reaction mixture was stirred at 90 °C for 48 h. The reaction was then cooled to room temperature, filtered on Celite® and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica-gel (20 % EtOAc in hexanes) to afford the desired product as a colorless oil (1.09 g, 79% yield). NMR data was in accordance with what was previously reported.[9] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.28 – 7.19 (m, 1H), 6.89 (dd, *J* = 7.5, 1.6 Hz, 2H), 6.83 – 6.76 (m, 1H), 4.55 (t, J = 6.7 Hz, 1H), 4.46 (q, *J* = 8.5 Hz, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 1.96 (s, 1H), 1.86 – 1.71 (m, 4H), 1.70 – 1.57 (m, 2H), 1.51 – 1.39 (m, 2H), 1.39 – 1.28 (m, 10H), 0.92 (t, *J* = 7.4 Hz, 3H).



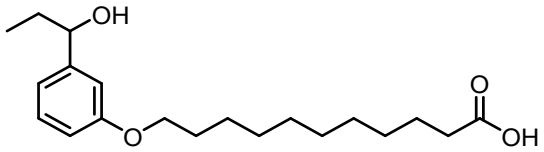

**2,2,2-Trifluoroethyl 11-(3-(1-hydroxyallyl)phenoxy)undecanoate (S13):** To a cylindrical pressure vessel equipped with a stir bar was added the bromotrifluoroethylester **S10** (1.39 g, 4.00 mmol, 1.20 equiv.), the phenol **S9** (500 mg, 3.33 mmol, 1.0 equiv.), potassium carbonate (920 mg, 6.66 mmol, 2 equiv.), potassium iodide (553 mg, 3.33 mmol, 1 equiv.) and acetone (14.0 mL, 0.25 M). The vial was sealed and the reaction mixture was stirred at 90 °C for 48 h. The reaction was then cooled to room temperature, filtered on Celite® and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica-gel (20 % EtOAc in hexanes) to afford the desired product as a colorless oil (778 mg, 56% yield). **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.25 (d, *J* = 8.1 Hz, 1H), 6.95 – 6.91 (m, 2H), 6.84 – 6.79 (m, 1H), 6.04 (ddd, *J* = 17.2, 10.3, 6.0 Hz, 1H), 5.40 – 5.32 (m, 1H), 5.24 – 5.14 (m, 2H), 4.46 (q, *J* = 8.5 Hz, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 1.96 – 1.87 (m, 1H), 1.83 – 1.71 (m, 2H), 1.71 – 1.57 (m, 2H), 1.44 (m, 2H), 1.39 – 1.23 (m, 11H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.3, 159.5, 144.4, 140.2, 129.7, 121.9 (q, *J* = 277.8 Hz), 118.5, 115.3, 113.9, 112.5, 75.4, 68.1, 60.2 (q, *J* = 36.5 Hz), 33.8, 29.6, 29.5, 29.4, 29.4, 29.3, 29.1, 26.2, 24.8; **HRMS (ESI)** m/z calculated for $[C_{22}H_{31}F_3O_4]$, $[M+Na]^+$ 439.2067; found 439.2056.



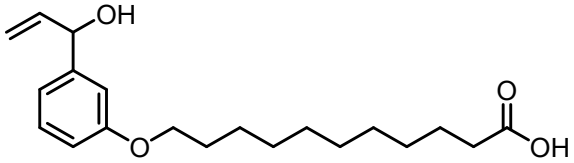

**2,2,2-Trifluoroethyl 10-(4-(2-hydroxypropyl)phenoxy)decanoate (S14):** To a cylindrical pressure vessel equipped with a stir bar was added the bromotrifluoroethylester **S11** (1.40 g, 4.20 mmol, 1.20 equiv.), the phenol **S4** (533 mg, 3.50 mmol, 1.0 equiv.), potassium carbonate (967 mg, 7.00 mmol, 2 equiv.), potassium iodide (581 mg, 3.50 mmol, 1 equiv.) and acetone (14.0 mL, 0.25 M). The reaction mixture was stirred at 90 °C for 48 h. The reaction was then cooled to room temperature, filtered on Celite® and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica-gel (20 % EtOAc in hexanes) to afford the desired product as a white solid (1.08 g, 76% yield). NMR data was in accordance with what was previously reported.[9] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.12 – 7.10 (m, 2H), 6.85 – 6.83 (m, 2H), 4.46 (q, *J* = 8.5 Hz, 2H), 3.93 (t, *J* = 6.5 Hz, 3H), 2.73 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.67 – 2.54 (m, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 1.80 – 1.73 (m, 2H), 1.67 – 1.62 (m, 2H), 1.54 (s, 1H), 1.48 – 1.41 (m , 2H), 1.40 – 1.28 (m, 9H), 1.28 – 1.19 (m, 6H).



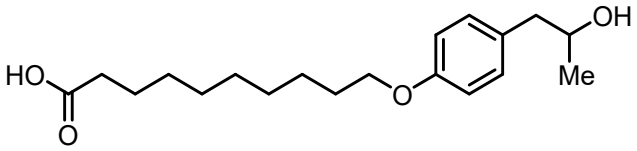

**11-(3-(1-Hydroxyethyl)phenoxy)undecanoic acid (S15):** In a 4 mL vial equipped with a stir bar was added the TFE ester **S11** (112 mg, 0.895 mmol, 1.0 equiv.) in a 1:1 mixture of water (0.535 mL) and ethanol (0.535 mL, 250 mM). Potassium hydroxide (90.1 mg, 1.61 mmol, 5.0 equiv.) was slowly added and the reaction mixture was stirred at room temperature for 18 h. After completion, the reaction mixture was transferred into a separatory funnel with ethyl acetate (10 mL) and HCl 1M solution (15 mL) solution. The phases were mixed and separated. The aqueous phase was extracted with more ethyl acetate (2 x 10 mL) and the combined organic phases were dried over $Na_2SO_4$ and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica-gel (40 % EtOAc in hexanes) to afford the desired product as a white solid (263 mg, 91%). NMR data was in accordance with what was previously reported.[9] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.23 – 7.20 (m, 1H), 6.95 – 6.87 (m, 2H), 6.82 – 6.76 (m, 1H), 4.85 (q, *J* = 6.5 Hz, 1H), 3.95 (t, *J* = 6.6 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.83 – 1.71 (m, 2H), 1.62 – 1.56 (m, 2H), 1.47 (d, *J* = 6.5 Hz, 3H), 1.46 – 1.41 (m, 2H), 1.39 – 1.28 (m, 11H).



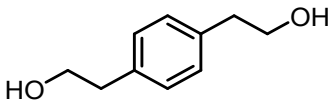

**11-(3-(1-Hydroxypropyl)phenoxy)undecanoic acid (S16):** In a 4 mL vial equipped with a stir bar was added the TFE ester **S12** (112 mg, 0.268 mmol, 1.0 equiv.) in a 1:1 mixture of water (0.535 mL) and ethanol (0.535 mL, 250 mM). Potassium hydroxide (90.1 mg, 1.61 mmol, 5.0 equiv.) was slowly added and the reaction mixture was stirred at room temperature for 18 h. After completion, the reaction mixture was transferred into a separatory funnel with ethyl acetate (10 mL) and HCl 1M solution (15 mL) solution. The phases were mixed and separated. The aqueous phase was extracted with more ethyl acetate (2 x 10 mL) and the combined organic phases were dried over $Na_2SO_4$ and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica-gel (40 % EtOAc in hexanes) to afford the desired product as a white solid (62 mg, 69%). NMR data was in accordance with what was previously reported.[9] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.23 (d, *J* = 7.9 Hz, 1H), 6.93 – 6.85 (m, 2H), 6.84 – 6.76 (m, 1H), 4.57 (t, *J* = 6.6 Hz, 1H), 3.95 (t, *J* = 6.5 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.89 – 1.69 (m, 4H), 1.69 – 1.57 (m, 2H), 1.45 (m, 2H), 1.38 – 1.27 (d, *J* = 9.9 Hz, 11H), 0.92 (t, *J* = 7.4 Hz, 3H).




**11-(3-(1-Hydroxyallyl)phenoxy)undecanoic acid (S17):** In a 4 mL vial equipped with a stir bar was added the TFE ester **S13** (260 mg, 0.624 mmol, 1.0 equiv.) in a 2:1 mixture of water (2.08 mL) and ethanol (1.04 mL, 200 mM). Potassium hydroxide (105 mg, 1.87 mmol, 5.0 equiv.) was slowly added and the reaction mixture was stirred at 50°C for 18 h. After completion, the reaction mixture was transferred into a separatory funnel with ethyl acetate (10 mL) and HCl 1M solution (15 mL) solution. The phases were mixed and separated. The aqueous phase was extracted with more ethyl acetate (2 x 10 mL) and the combined organic phases were dried over $Na_2SO_4$ and concentrated under vacuum to afford the desired product without further purification as a white solid (192 mg, 92%). **$^1$H NMR (500 MHz, Acetone)** δ 10.40 (s, 1H), 7.24 – 7.18 (m, 1H), 6.99 – 6.94 (m, 1H), 6.92 – 6.89 (m, 1H), 6.82 – 6.76 (m, 1H), 5.99 (ddd, *J* = 17.2, 10.3, 5.9 Hz, 1H), 5.34 – 5.26 (m, 1H), 5.13 (d, *J* = 5.9 Hz, 1H), 5.05 (dt, *J* = 10.3, 1.6 Hz, 1H), 3.97 (t, *J* = 6.5 Hz, 2H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.81 – 1.72 (m, 2H), 1.64 – 1.54 (m, 2H), 1.52 – 1.43 (m, 2H), 1.37 – 1.31 (m, 11H); **$^{13}$C NMR (126 MHz, Acetone)** δ 174.6, 160.2, 146.7, 142.7, 129.9, 119.2, 113.8, 113.7, 113.2, 75.2, 68.4, 34.2, 30.26, 30.24, 30.1, 30.05, 30.04, 29.9, 26.8, 25.7. **HRMS (ESI)** m/z calculated for $[C_{20}H_{30}O_4]$ $[M+Na]^+$ 357.2036; found 357.2040.

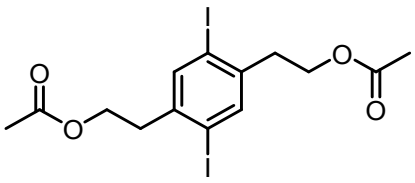



**10-(4-(2-Hydroxypropyl)phenoxy)decanoic acid (S18):** In a round bottom flask equipped with a stir bar was added the TFE ester **S14** (492 mg, 1.22 mmol, 1.0 equiv.) in a 1:1 mixture of water (2.43 mL) and ethanol (2.43 mL, 250 mM). Potassium hydroxide (341 mg, 6.08 mmol, 5.0 equiv.) was slowly added and the reaction mixture was stirred at room temperature for 18 h. After completion, the reaction mixture was transferred into a separatory funnel with ethyl acetate (15 mL) and HCl 1M solution (15 mL) solution. The phases were mixed and separated. The aqueous phase was extracted with more ethyl acetate (2 x 15 mL) and the combined organic phases were dried over $Na_2SO_4$ and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica-gel (40 % EtOAc in hexanes) to afford the desired product as a white solid (390 mg, 99% yield). NMR data was in accordance with what was previously reported.[9] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.11 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.02 – 3.90 (m, 3H), 2.74 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.61 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.82 – 1.72 (m, 2H), 1.69 – 1.58 (m, 2H), 1.52 – 1.40 (m, 2H), 1.40 – 1.27 (m, 8H), 1.23 (d, *J* = 6.2 Hz, 3H).

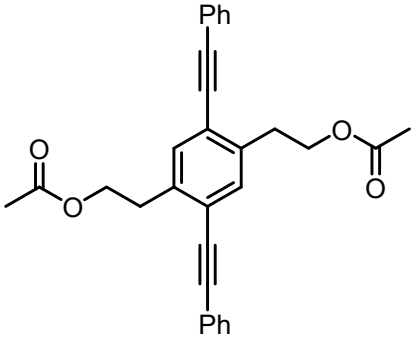



**2,2'-(1,4-Phenylene)bis(ethan-1-ol) (S19)**: In a flame dried round bottom flask equipped with a stir bar under a nitrogen atmosphere was added 1,4-phenylenediacetic acid (5.83 g, 30 mmol,) with anhydrous THF (200 mL, 150 mM). The solution was cooled at 0°C and borane dimethyl sulfide complex (8.54 mL, 90 mmol, 3 equiv.) was added dropwise to the reaction vessel. The reaction was warmed to room temperature and stirred for 18 h. After completion, the reaction mixture was quenched with saturated $NH_4Cl$ (100 ml) solution. The aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, dried over $Na_2SO_4$ and concentrated under reduced pressure. Following purification by column chromatography (50 % EtOAc in hexanes), the desired product was obtained as a white solid (3.29 g, 66 % yield). NMR data was in accordance with what was previously reported.[10] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.18 (s, 4H), 3.89 – 3.80 (m, 4H), 2.85 (t, *J* = 6.6 Hz, 4H), 1.43 (t, *J* = 5.7 Hz, 2H).

[10] Feng, F.; Yang, J.; Xie, D.; McCarley, T. D.; Schanze, K. S., *J. Phys. Chem. Lett.* **2013,** *4*, 1410.



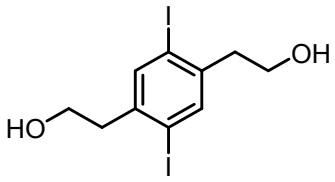
**(2,5-Diiodo-1,4-phenylene)bis(ethane-2,1-diyl) diacetate (S20)**: In a flame dried round bottom flask equipped with a stir bar under a nitrogen atmosphere was added diol (1.00 g, 6.02 mmol, 1.0 equiv), iodine (6.11 g, 24.1 mmol, 4.0 equiv), iodic acid (794 mg, 4.51 mmol, 0.75 equiv), acetic acid (4.95 mL, 86.6 mmol) and sulfuric acid (991 µL, 18.6 mmol) were dissolved in chloroform (12.0 mL, 0.50 M) in a round bottom flask equipped with a stir bar. The reaction mixture was then stirred at 80 °C for 18 h. The reaction was cooled to room temperature and quenched with a saturated aqueous solution of sodium bisulfite. The aqueous layer was extracted with DCM (3 x 30 mL). The organic layers were combined, dried over $Na_2SO_4$ and concentrated under reduced pressure. Following purification by column chromatography (10 % EtOAc in hexanes), the desired product was obtained as a white solid (1.22 g, 40 % yield). NMR data was in accordance with what was previously reported.[11] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.67 (s, 2H), 4.24 (t, *J* = 6.9 Hz, 4H), 2.99 (t, *J* = 6.9 Hz, 4H), 2.06 (s, 6H).



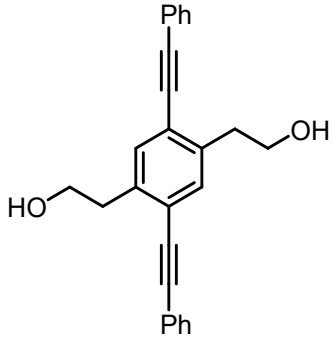
**(2,5-Bis(phenylethynyl)-1,4-phenylene)bis(ethane-2,1-diyl) diacetate (S21)**: In a flame dried round bottom flask equipped with a stir bar under a nitrogen atmosphere was added diacetate **S20** (879 mg, 1.75 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (125 mg, 0.175 mmol, 10 mol%), copper iodide (33.3 mg, 0.175 mmol, 10 mol%), triethylamine (1.46 mL, 10.5 mmol, 6 equiv.) and dry THF (7.0 mL, 250 mL). The solution was bubbled with nitrogen and phenylacetylene (536 µL, 5.25 mmol, 3.0 equiv) was finally added. The vessel was

[11] Gagnon, C.; Godin, É.; Minozzi, C.; Sosoe, J.; Pochet, C.; Collins, S. K., *Science* **2020,** *367*, 917.

sealed with a screw cap and the solution was heated at 50 °C for 18 h. The reaction was cooled to room temperature and filtered on a pad of Celite, rinsing with ethyl acetate. Following purification by column chromatography (10 % EtOAc in hexanes), the desired product was obtained as an orange solid (485 mg, 62 % yield). NMR data was in accordance with what was previously reported.[11] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.59 – 7.52 (m, 4H), 7.44 (s, 2H), 7.40 – 7.35 (m, 6H), 4.40 (t, *J* = 6.9 Hz, 4H), 3.17 (t, *J* = 6.9 Hz, 4H), 2.05 (s, 6H).

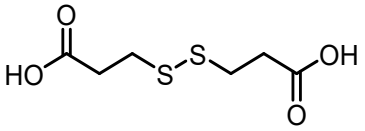



**2,2'-(2,5-Diiodo-1,4-phenylene)bis(ethan-1-ol) (S22)**: In a round bottom flask equipped with a stir bar was added diacetate **S20** (753 mg, 1.50 mmol, 1.0 equiv) and potassium carbonate (2.07 g, 15.0 mmol, 10 equiv.) were dissolved in in a 4:1 mixture of MeOH (17.1 mL) and DCM (4.29 mL, 70 mM). The reaction was then stirred at 25 °C for 2 h. After completion, the solvents were removed under reduced pressure. The crude mixture was dissolved in water and the aqueous layer was extracted with EtOAc (3 x 25 mL). The organic layers were combined, dried over $Na_2SO_4$ and concentrated under reduced pressure. Following purification by column chromatography (50 % EtOAc in hexanes), the desired product was obtained as a white solid (504 mg, 80 % yield). NMR data was in accordance with what was previously reported.[11] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.71 (s, 2H), 3.85 (t, *J* = 6.6 Hz, 4H), 2.93 (t, *J* = 6.6 Hz, 4H), 1.38 (Brs, 2H).

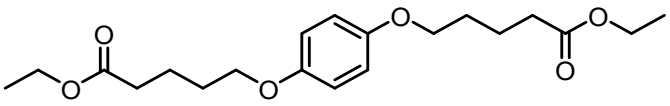



**2,2'-(2,5-Bis(phenylethynyl)-1,4-phenylene)bis(ethan-1-ol) (S23)**: In a round bottom flask equipped with a stir bar was added diacetate **S21** (485 mg, 1.08 mmol, 1.0 equiv) and potassium carbonate (1.49 g, 10.8 mmol, 10 equiv.) were dissolved in in a 1:1 mixture of MeOH (2.15 mL) and DCM (2.15 mL, 70 mM). The reaction was then stirred at 25 °C for 2 h. After completion, the solvents were removed under reduced pressure. The crude mixture was dissolved in water and the aqueous layer was extracted with EtOAc (3 x 15 mL). The organic layers were combined, dried over $Na_2SO_4$ and concentrated under reduced pressure. Following purification by column chromatography (50 % EtOAc in

hexanes), the desired product was obtained as a white solid (326 mg, 83 % yield). NMR data was in accordance with what was previously reported.[11] **$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.56 – 7.51 (m, 4H), 7.48 (s, 2H), 7.40 – 7.34 (m, 6H), 4.02 – 3.96 (m, 4H), 3.12 (t, *J* = 6.6 Hz, 4H), 1.43 (t, *J* = 5.7 Hz, 2H).

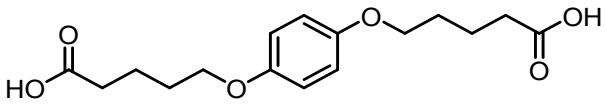



**3,3'-Disulfanediyldipropionic acid (S24)**: 3-Mercaptopropionic acid (1.06 g, 10 mmol, 2.0 equiv.), copper(II) chloride dihydrate (170 mg, 1 mmol, 10 mol%) and TMEDA (4.65 g, 40 mmol, 4 equiv.) were dissolved in methanol (16.7 mL) in a open to air round bottom flask equipped with a stir bar and stirred at 25 °C for 5 h. NaOH 1 M was added to the crude reaction mixture and extracted 3 times with ethyl acetate. The basic aqueous layer was acidified with HCl 6 M and extracted three times with ethyl acetate. The organic layers were combined, dried over $Na_2SO_4$ and concentrated under reduced pressure. The desired product was obtained without further purification as a white solid (990 mg, 94 % yield). NMR data was in accordance with what was previously reported.[12] **$^1$H NMR (400 MHz, DMSO)** δ 12.32 (s, 2H), 2.88 (t, *J* = 6.9 Hz, 2H), 2.61 (t, *J* = 6.9 Hz, 3H).

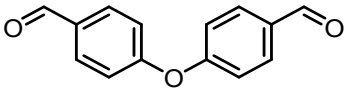



**Diethyl 5,5'-(1,4-phenylenebis(oxy))dipentanoate (S25):** To a cylindrical pressure vessel equipped with a stir bar was added ethyl 5-bromovalerate (6.90 g, 33 mmol, 2.20 equiv), hydroquinone (1.65 g, 15 mmol, 1.0 equiv), potassium carbonate (8.29 g, 40 mmol, 4.0 equiv), potassium iodide (2.49 g, 15 mmol, 1 equiv) and acetone (0.25 M). The vessel was sealed and the reaction mixture was stirred at 90 °C for 72 h. The reaction was then cooled to room temperature, filtered on Celite® and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica-gel (15 % EtOAc in hexanes) to afford the desired product as a white powder (3.90 g, 71% yield). **$^1$H NMR (700 MHz, $CDCl_3$)** δ 6.80 (s, 4H), 4.13 (q, *J* = 7.1 Hz, 4H), 3.94 – 3.88 (m, 4H), 2.37 (t, *J* = 6.9 Hz, 4H), 1.84 – 1.76 (m, 8H), 1.25 (t, *J* = 7.1 Hz, 6H); **$^{13}$C NMR (176 MHz, $CDCl_3$)** δ 173.6, 153.2, 115.5, 68.1, 60.5, 60.4, 34.1, 28.9, 21.8, 14.4; **HRMS (ESI)** m/z calculated for $[C_{20}H_{30}O_6]$, $[M+NH_4]^+$ 384.2381; found 384.2375.

[12] Zolfigol, M. A.; Niknam, K.; Bagherzadeh, M.; Ghorbani-Choghamarani, A.; Koukabi, N.; Hajjami, M.; Kolvari, E., *J. Chin. Chem. Soc.* **2007,** *54*, 1115.

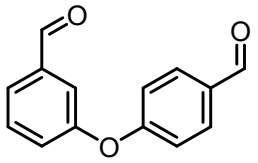


**5,5'-(1,4-Phenylenebis(oxy))dipentanoic acid (S26):** In a 50 mL round bottom flask equipped with a stir bar was added the diethylester **S25** (2.0 g, 5.46 mmol, 1.0 equiv.) in a 1:1 mixture of water (10.9 mL) and ethanol (10.9 mL, 250 mM). Potassium hydroxide (1.53 g, 27.3 mmol, 5.0 equiv.) was slowly added and the reaction mixture was stirred at room temperature for 18 h. After completion, the reaction mixture was transferred into a separatory funnel with ethyl acetate (30 mL) and HCl 1M solution (50 mL) solution. The phases were mixed and separated. The aqueous phase was extracted with more ethyl acetate (2 x 30 mL) and the combined organic phases were dried over $Na_2SO_4$ and concentrated under vacuum to afford the desired product without further purification as a white solid (1.19 g, 70%). **$^1$H NMR (700 MHz, MeOD)** δ 6.82 (s, 4H), 3.98 – 3.89 (m, 4H), 2.44 – 2.33 (m, 4H), 1.85 – 1.74 (m, *J* = 3.4 Hz, 8H); **$^{13}$C NMR (176 MHz, MeOD)** δ 177.4, 154.6, 116.4, 69.2, 34.6, 29.9, 22.8; **HRMS (ESI)** m/z calculated for $[C_{16}H_{22}O_6]$, $[M+NH_4]^+$ 328.1755; found 328.1748.

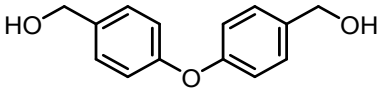


**4,4'-Oxydibenzaldehyde** (**S26**): To a oven dried cylindrical pressure vessel equipped with a stir bar was added 4-hydroxybenzaldehyde (611 mg, 5.00 mmol, 1.0 equiv), 4-fluorobenzaldehyde (621 mg, 5.00 mmol, 1.0 equiv), potassium carbonate (691 mg, 5.00 mmol, 1 equiv) and anhydrous DMF (10.0 mL, 500 mM). The vessel was sealed and the reaction mixture was then stirred at 120 °C for 18 h. After completion, the reaction mixture was then cooled to room temperature. The crude mixture was dissolved in EtOAc (50 mL) and the organic layer washed with water (30 mL) and brine (2 x 30 mL). The organic layers were combined, dried over $Na_2SO_4$ and concentrated under reduced pressure. Following purification by column chromatography (25 % EtOAc in hexanes), the desired product was obtained as a white solid (968 mg, 86 % yield). NMR data was in accordance with what was previously reported.[13] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.98 (s, 2H), 7.96 – 7.89 (m, 4H), 7.21 – 7.13 (m, 4H).

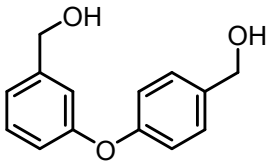
[13] Begum, T.; Mondal, M.; Borpuzari, M. P.; Kar, R.; Gogoi, P. K.; Bora, U., *Eur. J. Org. Chem.* **2017,** *2017*, 3244.



**3-(4-Formylphenoxy)benzaldehyde (S27)** : To a oven dried cylindrical pressure vessel equipped with a stir bar was added 3-hydroxybenzaldehyde (611 mg, 5.00 mmol, 1.0 equiv), 4-fluorobenzaldehyde (621 mg, 5.00 mmol, 1.0 equiv), potassium carbonate (691 mg, 5.00 mmol, 1 equiv) and anhydrous DMF (10.0 mL, 500 mM). The vessel was sealed and the reaction mixture was then stirred at 120 °C for 18 h. After completion, the reaction mixture was then cooled to room temperature. The crude mixture was dissolved in EtOAc (50 mL) and the organic layer washed with water (30 mL) and brine (2 x 30 mL). The organic layers were combined, dried over $Na_2SO_4$ and concentrated under reduced pressure. Following purification by column chromatography (25 % EtOAc in hexanes), the desired product was obtained as a colorless oil (1.06 g, 94 % yield). **$^1$H NMR (400 MHz, $CDCl_3$)** δ 10.00 (s, 1H), 9.95 (s, 1H), 7.92 – 7.86 (m, 2H), 7.76 – 7.70 (m, 1H), 7.62 – 7.55 (m, 2H), 7.40 – 7.34 (m, 1H), 7.13 – 7.07 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 191.3, 190.8, 162.3, 156.4, 138.5, 132.2, 132.1, 131.0, 126.6, 126.2, 119.9, 118.4; **HRMS (ESI)** m/z calculated for $[C_{14}H_{10}O_3]$, $[M+H]^+$ 227.0712; found 227.0703.

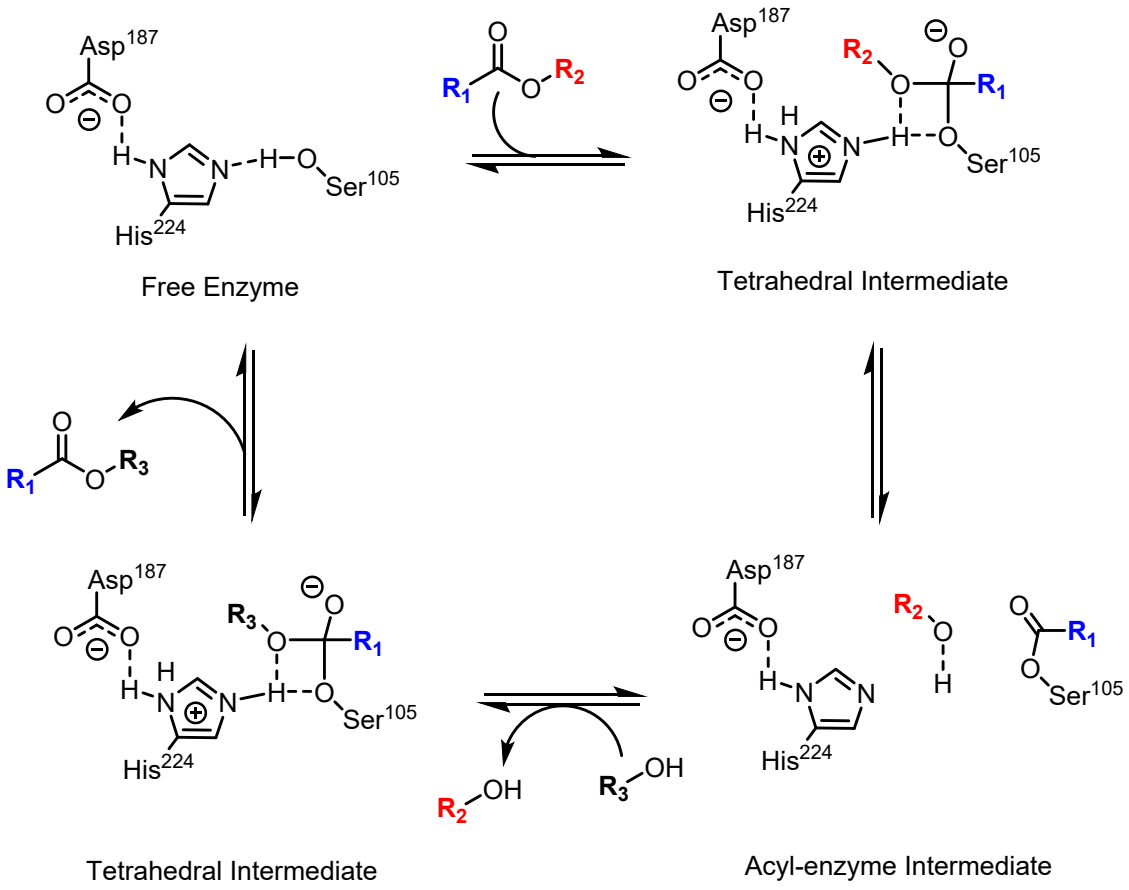


**(Oxybis(4,1-phenylene))dimethanol** (**S28**): In a round bottom flask equipped with a stir bar under nitrogen, aldehyde **S26** (679 mg, 3.00 mmol, 1.0 equiv.) was dissolved in methanol (12.0 mL, 250 mM). The solution was cooled to 0 °C in an ice/water bath, and $NaBH_4$ (454 mg, 12.0 mmol, 4.0 equiv.) was slowly added over a period of 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. A saturated aqueous solution of $NH_4Cl$ (30 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined and washed with brine, dried with $Na_2SO_4$ and concentrated. The crude reaction mixture was purified by column chromatography on silica-gel (50 % EtOAc in hexanes) to afford the desired product as a white solid (558 mg, 81 % yield). **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.37 – 7.32 (m, 4H), 7.03 – 6.97 (m, 4H), 4.68 (d, $J$ = 5.2 Hz, 4H), 1.61 (t, $J$ = 5.7 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 156.9, 136.0, 128.9, 119.1, 65.1; **HRMS (ESI)** m/z calculated for $[C_{14}H_{14}O_3]$, $[M+Na]^+$ 253.0835; found 253.0847.



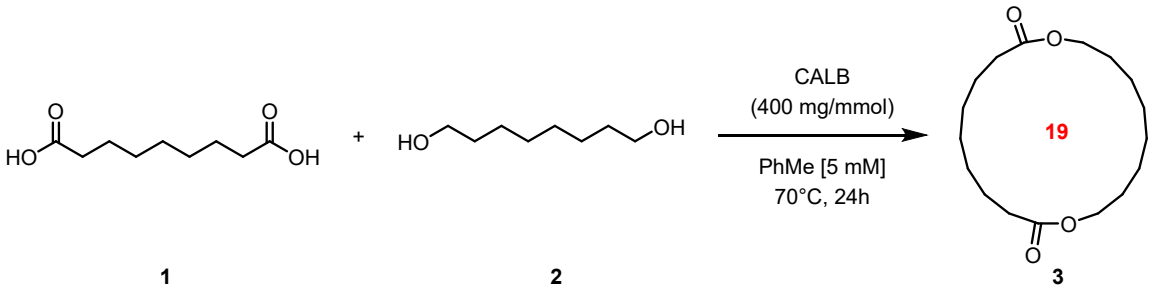
**(3-(4-(Hydroxymethyl)phenoxy)phenyl)methanol** (**S29**): In a round bottom flask equipped with a stir bar under nitrogen, aldehyde **S27** (1.00 g, 4.42 mmol, 1.0 equiv.) was dissolved in methanol (12.0 mL, 250 mM). The solution was cooled to 0 °C in an ice/water bath, and $NaBH_4$ (669 mg, 17.7 mmol, 4.0 equiv.) was slowly added over a period of 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. A saturated aqueous solution of $NH_4Cl$ (30 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined and washed with brine, dried with $Na_2SO_4$ and concentrated. The crude reaction mixture was purified by column chromatography on silica-gel (50 % EtOAc in hexanes) to afford the desired product as a colorless oil (953 mg, 94 % yield). **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.36 – 7.27 (m, 3H), 7.12 – 7.06 (m, 1H), 7.04 – 6.96 (m, 3H), 6.96 – 6.89 (m, 1H), 4.65 (s, 4H), 1.93 (s, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 157.7, 156.7, 143.1, 136.0, 130.0, 128.9, 121.7, 119.3, 118.0, 117.1, 65.0, 65.0; **HRMS (ESI)** m/z calculated for $[C_{14}H_{14}O_3]$, $[M+Na]^+$ 253.0840; found 253.0835.

## ENZYME MECHANISM




For additional images of the enzyme active site see: (a) Dhawan, M. S.; Barton, S. C.; Yadav, G. D. Interesterification of triglycerides with methyl acetate for the co-production biodiesel and triacetin using hydrotalcite as a heterogenous base catalyst. *Catalysis Today* **2021**, *375*, 101-111. (b) Uppenberg, J.; Hansen, M. T.; Patkar, S.; Jones, T. A., The sequence, crystal structure determination and refinement of two crystal forms of lipase B from Candida antarctica. *Structure* **1994**, *2*, 293-308.

## ENZYME RECYCLING EXPERIMENTS




To an oven dried 100 mL vessel was added azelaic acid **1** (47.1 mg, 0.25 mmol, 1.0 equiv) and 1,8-octanediol **2** (36.6 mg, 0.25 mmol, 1.0 equiv), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (100 mg, 400 mg/mmol). The reaction mixture was heated at 70 °C for 24 h. The reaction mixture was then cooled to room temperature. The solution was slowly poured into another vessel making sure to leave the supported enzyme beads behind. Another portion of toluene, diol and diacid was added to the 100 mL vessel with the recycled beads and the recycle was repeated for a total number of eight times.

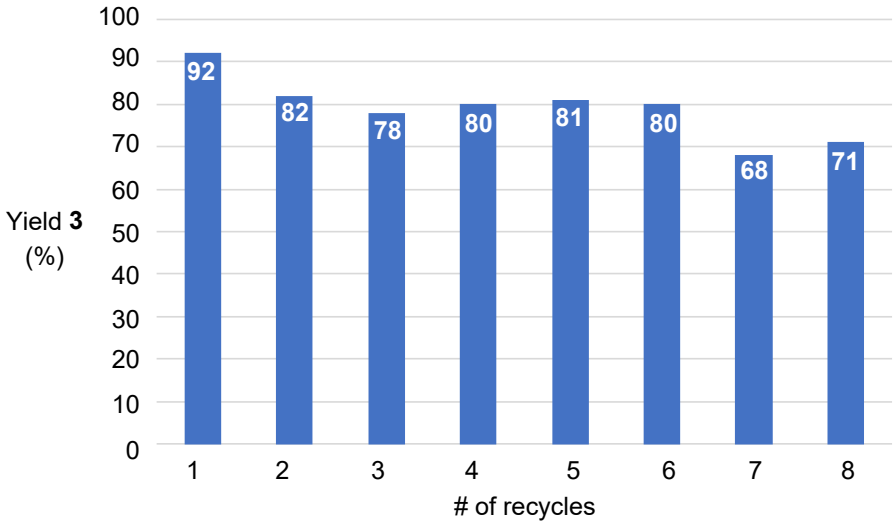
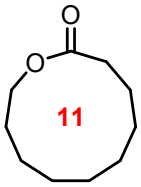


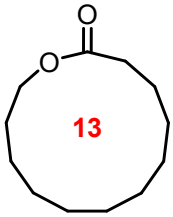

**Figure S1:** Recycling of the supported enzyme beads.

**Note**: Every cycle was purified by column chromatography on silica-gel (10 % EtOAc in hexanes) to afford the desired macrocycle **3** as a colorless oil.

## ENZYMATIC MACROCYCLE SYNTHESIS

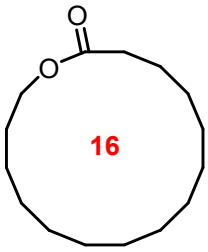



**Oxacycloundecan-2-one** (**4**): To an oven dried 100 mL vessel equipped with a stir bar was added 10-hydroxydecanoic acid (47.1 mg, 0.25 mmol, 1.0 equiv.), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (33 mg, 78% yield). NMR data was in accordance with what was previously reported.[14] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.11 (t, *J* = 5.8 Hz, 2H), 2.31 (t, *J* = 7.0 Hz, 2H), 1.69 – 1.56 (m, 4H), 1.42 – 1.26 (m, 10H).

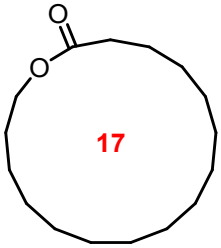



**Oxacyclotridecan-2-one (5):** To an oven dried 100 mL vessel equipped with a stir bar was added 12-hydroxypentadecanoic acid (54.1 mg, 0.25 mmol, 1.0 equiv.), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (39 mg, 79% yield). NMR data was in accordance with what was previously reported.[14] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.10 (t, *J* = 5.9 Hz, 2H), 2.31 (t, *J* = 7.1 Hz, 2H), 1.71 – 1.56 (m, 4H), 1.41 – 1.23 (m, 14H).

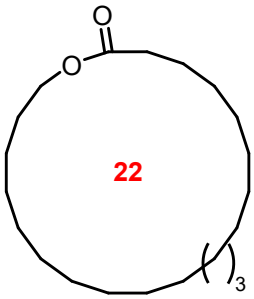
[14] Force, G.; Perfetto, A.; Mayer, R. J.; Ciofini, I.; Lebœuf, D., *Angew. Chem. Int. Ed.* **2021,** *60*, 19843.



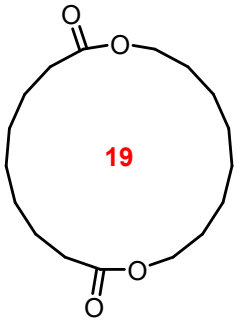

**Oxacyclohexadecan-2-one (6):** To an oven dried 100 mL vessel equipped with a stir bar was added 15-hydroxylpentadecanoic acid (64.6 mg, 0.25 mmol, 1.0 equiv.), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (45 mg, 75% yield). NMR data was in accordance with what was previously reported.[14] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.13 (t, *J* = 5.5 Hz, 2H), 2.32 (t, *J* = 6.7 Hz, 2H), 1.72 – 1.57 (m, 4H), 1.46 – 1.28 (m, 20H).




**Oxacycloheptadecan-2-one (7):** To an oven dried 100 mL vessel equipped with a stir bar was added 16-hydroxyhexadecanoic acid (68.1 mg, 0.25 mmol, 1.0 equiv.), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (43 mg, 68% yield). NMR data was in accordance with what was previously reported.[14] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.12 (t, *J* = 5.4 Hz 2H), 2.32 (m, *J* = 6.5 Hz, 2H), 1.70 – 1.58 (m, 4H), 1.44 – 1.24 (m, 22H).

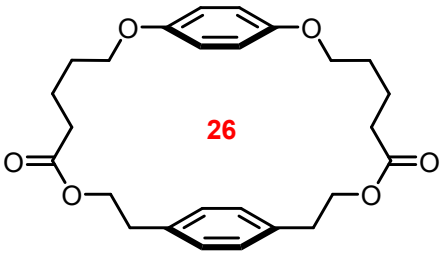



**Oxacyclodocosan-2-one (8)**: To an oven dried 100 mL vessel equipped with a stir bar was added 21-hydroxyhenicosanoic acid (85.6 mg, 0.25 mmol, 1.0 equiv.), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (71.4 mg, 88% yield). **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 4.10 (t, *J* = 6.1 Hz, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.70 – 1.57 (m, 4H), 1.41 – 1.26 (m, 32H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 174.2, 64.4, 34.8, 29.0, 28.96, 28.88, 28.85, 28.8, 28.71, 28.65, 28.5, 28.2, 28.04, 27.98, 27.97, 27.9, 27.7, 27.4, 26.0, 25.3; **HRMS (ESI)** m/z calculated for $[C_{21}H_{40}O_2]$, $[M+H]^+$ 325.3103; found 325.3101.

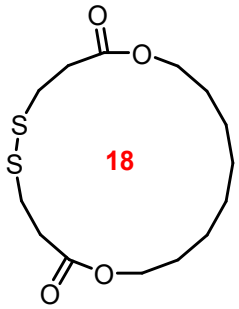



**1,10-Dioxacyclononadecane-11,19-dione (3):** To an oven dried 100 mL vessel equipped with a stir bar was added azelaic acid (47.1 mg, 0.25 mmol, 1.0 equiv) and 1,8-octanediol (36.6 mg, 0.25 mmol, 1.0 equiv), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (10% EtOAc in hexanes) to afford the desired product as a white solid (68.6 mg, 92% yield). NMR data was in accordance with what was previously reported.[15] **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 4.11 (t, *J* = 5.4 Hz, 4H), 2.32 (t, *J* = 6.6 Hz, 4H), 1.71 – 1.56 (m, 8H), 1.44 – 1.28 (m, 14H).

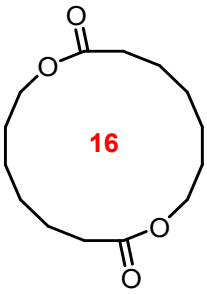
[15] de Léséleuc, M.; Collins, S. K., *Chem. Commun.* **2015,** *51*, 10471.



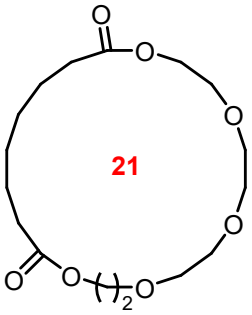

**2,8,14,20-Tetraoxa-1,11(1,4)-dibenzenacycloicosaphane-7,15-dione (16)**: To an oven dried 100 mL vessel equipped with a stir bar was added diacid **S26** (77.6 mg, 0.25 mmol, 1.0 equiv) and diol **S19** (41.6 mg, 0.25 mmol, 1.0 equiv), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (34 mg, 31% yield). **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.01 (s, 4H), 6.79 (s, 4H), 4.08 (t, *J* = 7.1 Hz, 4H), 3.87 (t, *J* = 5.7 Hz, 4H), 2.67 (t, *J* = 7.1 Hz, 4H), 2.35 (t, *J* = 6.4 Hz, 4H), 1.79 – 1.63 (m, 8H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.4, 152.7, 135.9, 129.1, 115.7, 67.7, 64.7, 34.5, 34.4, 28.2, 21.9; **HRMS (ESI)** m/z calculated for $[C_{26}H_{32}O_6]$, $[M+ NH_4]^+$ 458.2537; found 458.2540.



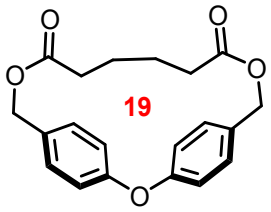

**1,10-Dioxa-5,6-dithiacyclooctadecane-2,9-dione** (**14**): To an oven dried 100 mL vessel equipped with a stir bar was added diacid **S24** (52.6 mg, 0.25 mmol, 1.0 equiv) and 1,8-octanediol (36.6 mg, 0.25 mmol, 1.0 equiv), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (43 mg, 52% yield). **$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.16 (t, *J* = 8.0 Hz, 4H), 2.98 (t, *J* = 7.0 Hz, 4H), 2.73 (t, *J* = 7.0 Hz, 4H), 1.69 – 1.57 (m, 4H), 1.49 – 1.32 (m, 8H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.8, 64.9, 34.7, 34.4, 28.3, 28.0, 25.2; **HRMS (ESI)** m/z calculated for $[C_{14}H_{24}O_4S_2]$, $[M+NH_4]^+$ 338.1454; found 338.1461.



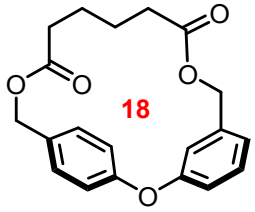

**1,9-Dioxacyclohexadecane-2,10-dione (13):** To an oven dried 100 mL vessel equipped with a stir bar was added hydroxyacid **S2** (36.5 mg, 0.25 mmol, 1.0 equiv.), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (21 mg, 66% yield). **$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.13 – 4.05 (m, 4H), 2.40 – 2.30 (m, 4H), 1.75 – 1.60 (m, 8H), 1.47 – 1.27 (m, 8H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.9, 63.8, 34.1, 28.6, 28.0, 25.6, 25.3; **HRMS (ESI)** m/z calculated for $[C_{14}H_{24}O_2]$, $[M+NH_4]^+$ 274.2013; found 274.2025.



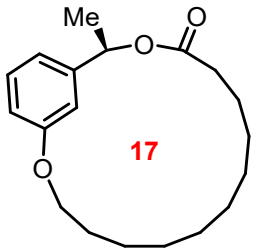

**1,4,7,10,13-Pentaoxacyclohenicosane-14,21-dione** (**15):** To an oven dried 100 mL vessel equipped with a stir bar was added suberic acid (43.5 mg, 0.25 mmol, 1.0 equiv) and tetraethylene glycol (48.6 mg, 0.25 mmol, 1.0 equiv), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (28 mg, 34% yield). **$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.28 – 4.20 (m, 4H), 3.73 – 3.60 (m, 12H), 2.33 (t, $J$ = 7.3 Hz, 4H), 1.70 – 1.59 (m, 4H), 1.41 – 1.31 (m, 4H). **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.8, 71.2, 70.8, 69.3, 63.7, 34.6, 28.4, 25.0; **HRMS (ESI)** m/z calculated for $[C_{16}H_{28}O_7]$, $[M+H]^+$ 333.1908; found 333.1907.



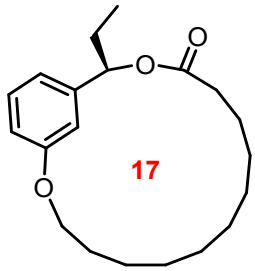

**2,5,12-Trioxa-1,3(1,4)-dibenzenacyclotridecaphane-6,11-dione** (**21**): To an oven dried 100 mL vessel equipped with a stir bar was added adipic acid (36.5 mg, 0.25 mmol, 1.0 equiv) and diol **S28** (57.6 mg, 0.25 mmol, 1.0 equiv), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 48 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (70 mg, 82% yield). **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.33 – 7.25 (m, 4H), 6.99 – 6.92 (m, 4H), 5.07 (s, 4H), 2.44 – 2.27 (m, 4H), 1.70 – 1.64 (m, 4H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.2, 157.2, 131.2, 130.1, 119.1, 65.8, 34.0, 24.5; **HRMS (ESI)** m/z calculated for $[C_{20}H_{20}O_5]$, $[M+H]^+$ 341.1384; found 341.1393.



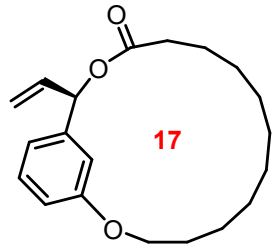

**2,5,12-Trioxa-1(1,3),3(1,4)-dibenzenacyclotridecaphane-6,11-dione** (**22**): To an oven dried 100 mL vessel equipped with a stir bar was added adipic acid (36.5 mg, 0.25 mmol, 1.0 equiv) and diol **S29** (57.6 mg, 0.25 mmol, 1.0 equiv), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 48 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (70 mg, 82% yield). **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.52 – 7.46 (m, 2H), 7.32 – 7.27 (m, 1H), 7.12 – 7.07 (m, 1H), 7.07 – 7.03 (m, 2H), 6.84 – 6.79 (m, 1H), 6.28 (dd, *J* = 2.6, 1.5 Hz, 1H), 5.14 (s, 2H), 5.08 (s, 2H), 2.36 – 2.30 (m, 2H), 2.23 – 2.16 (m, 2H), 1.65 – 1.53 (m, 2H), 1.31 – 1.20 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.0, 172.7, 160.2, 156.0, 138.2, 133.4, 131.8, 129.8, 122.1, 119.4, 117.2, 112.0, 65.9, 64.7, 35.0, 34.2, 25.7, 24.2; **HRMS (ESI)** m/z calculated for $[C_{20}H_{20}O_5]$, $[M+H]^+$ 341.1384; found 341.1388.




**(*R*)-15-Methyl-2,14-dioxa-1(1,3)-benzenacyclopentadecaphan-13-one (9):** To an oven dried 100 mL vessel equipped with a stir bar was added hydroxyacid **S15** (80.6 mg, 0.25 mmol, 1.0 equiv.), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (3% EtOAc in hexanes) to afford the desired product as a colorless oil (25 mg, 33% yield, 99% *ee*). NMR data was in accordance with what was previously reported.[9] **$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.25 – 7.20 (m, 1H), 6.97 – 6.92 (m, 1H), 6.89 – 6.84 (m, 1H), 6.83 – 6.78 (m, 1H), 5.88 (q, *J* = 6.6 Hz, 1H), 4.14 – 4.07 (m, 1H), 4.06 – 3.98 (m, 1H), 2.45 – 2.36 (m, 1H), 2.34 – 2.25 (m, 1H), 1.82 – 1.71(m, 2H), 1.71 – 1.59 (m, 2H), 1.53 (d, *J* = 6.6 Hz, 3H), 1.52 – 1.44 (m, 2H), 1.43 – 1.31 (m, 2H), 1.30 – 1.21 (m, 8H).

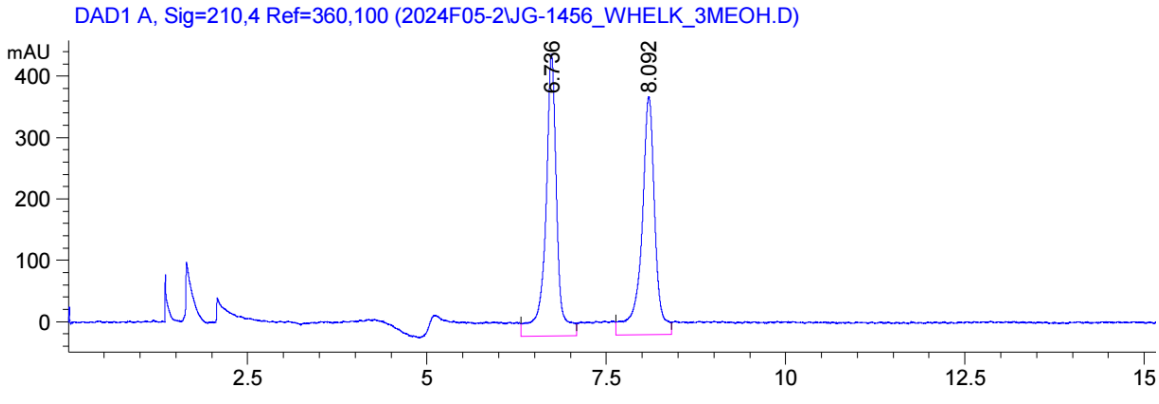


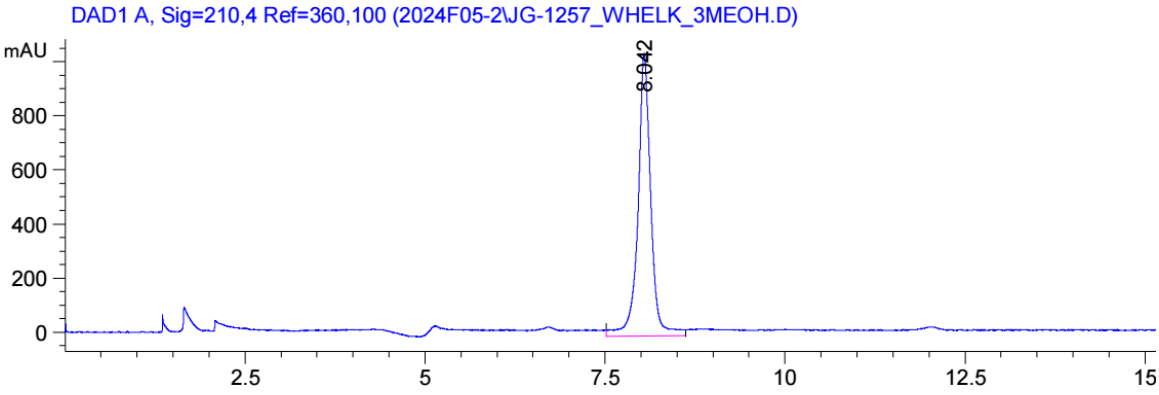

**(*R*)-15-Ethyl-2,14-dioxa-1(1,3)-benzenacyclopentadecaphan-13-one (11)**: To an oven dried 100 mL vessel equipped with a stir bar was added hydroxyacid **S16** (84.1 mg, 0.25 mmol, 1.0 equiv.), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (3% EtOAc in hexanes) to afford the desired product as a colorless oil (32 mg, 40% yield, 99% *ee*). NMR data was in accordance with what was previously reported.[9] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.22 – 7.18 (m, 1H), 6.92 (dd, *J* = 2.1, 2.1 Hz, 1H), 6.88 – 6.76 (m, 2H), 5.65 (dd, *J* = 7.5, 6.1 Hz, 1H), 4.16 – 4.07 (m, 1H), 4.04 – 3.96 m, 1H), 2.48 – 2.37 (m, 1H), 2.35 – 2.23 (m, 1H), 1.96 – 1.78 (m, 2H), 1.78 – 1.68 (m, 2H), 1.68 – 1.53 (m, 2H), 1.53 – 1.43 (m, 2H), 1.42 – 1.30 (m, 2H), 1.29 – 1.16 (m, 9H), 0.90 (t, *J* = 7.4 Hz, 3H).

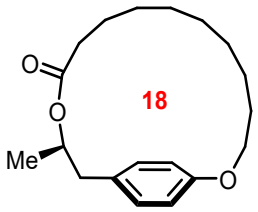



**(*R*)-15-Vinyl-2,14-dioxa-1(1,3)-benzenacyclopentadecaphan-13-one (10):** To an oven dried 100 mL vessel equipped with a stir bar was added hydroxyacid **S17** (83.6 mg, 0.25 mmol, 1.0 equiv.), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (3% EtOAc in hexanes) to afford the desired product as a colorless oil (35 mg, 44% yield, 99% *ee*). **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.23 (d, $J$ = 7.8 Hz, 1H), 6.94 (dd, $J$ = 2.1, 2.1 Hz, 1H), 6.88 (d, $J$ = 7.6 Hz, 1H), 6.83 (dd, $J$ = 8.2, 2.5 Hz, 1H), 6.31 – 6.22 (m, 1H), 6.09 – 5.96 (m, 1H), 5.37 – 5.28 (m, 1H), 5.28 – 5.22 (m, 1H), 4.15 – 4.07 (m, 1H), 4.07 – 3.99 (m, 1H), 2.50 – 2.41 (m, 1H), 2.39 – 2.29 (m, 1H), 1.85–1.55 (m, 4H), 1.54 – 1.44 (m, 2H), 1.44 – 1.31 (m, 2H), 1.31 – 1.22 (m, 8H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.8, 159.4, 140.9, 136.2, 129.5, 119.9, 117.2, 114.6, 113.3, 75.8, 68.0, 34.8, 28.5, 28.2, 27.8, 27.8, 27.5, 27.4, 25.3, 24.3; **HRMS (ESI)** m/z calculated for $[C_{20}H_{28}O_3]$, $[M+H]^+$ 317.2121; found 317.2111. The enantiomeric purity was determined by **SFC-MS** analysis in comparison with authentic racemic material (Whelk-01, BPR pressure: 150 bar, column temperature: 30 °C, injection volume: 10 µL into 20 µL loop, solvent: 3 % MeOH, signal = 210.4 nm): $t_R$ of **10**: 6.7 min (minor) and 8.0 min (major). The macrocycle was formed in its racemic form using general procedure **B.** Purification occurred via chromatography using the identical conditions shown above.

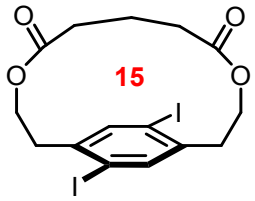
| **Racemic Procedure** | | | **DKR using CALB** | | |
|---|---|---|---|---|---|
| **Peak #** | **Ret. Time** | **Area %** | **Peak #** | **Ret. Time** | **Area %** |
| 1 | 6.736 | 49.8961 | 1 | - | - |
| 2 | 8.092 | 50.1039 | 2 | 8.042 | 100 |



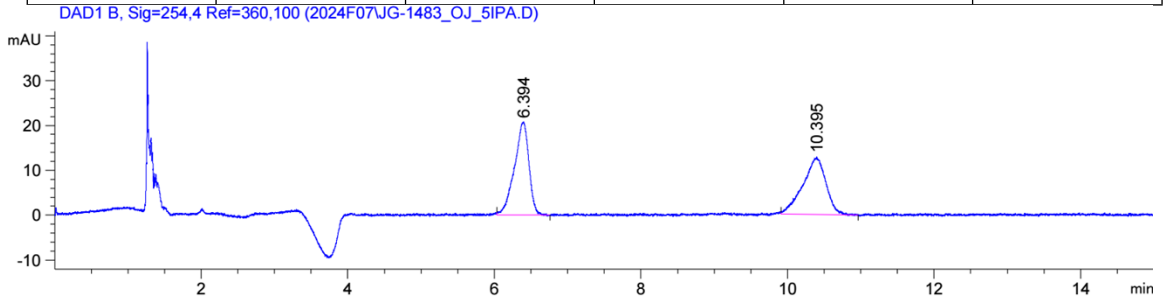



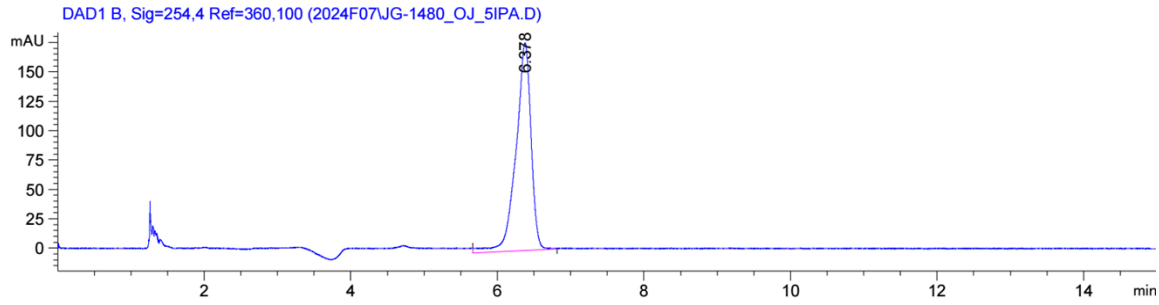

**(*R*)-14-Methyl-2,13-dioxa-1(1,4)-benzenacyclopentadecaphan-12-one (12):** To an oven dried 100 mL vessel equipped with a stir bar was added hydroxyacid **S18** (80.6 mg, 0.25 mmol, 1.0 equiv.), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a colorless oil (30.4 mg, 40% yield, 99% *ee*). NMR data was in accordance with what was previously reported.[9] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.09 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.16 – 5.03 (m, 1H), 4.26 – 4.03 (m, 2H), 2.86 (dd, *J* = 14.1, 2.9 Hz, 1H), 2.63 (dd, *J* = 14.1, 11.3 Hz, 1H), 2.15 – 2.04 (m, 2H), 1.80 – 1.65 (m, 1H), 1.64 – 1.44 (m, 2H), 1.46 – 1.34 (m, 2H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.33 – 1.12 (m, 5H), 1.13 – 0.95 (m, 4H), 0.98 – 0.75 (m, 3H).

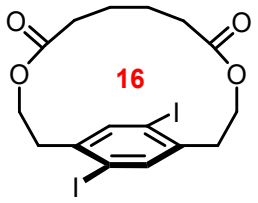



**12,15-Diiodo-4,10-dioxa-1(1,4)-benzenacyclododecaphane-5,9-dione** (**17**): To an oven dried 100 mL vessel equipped with a stir bar was added adipic acid (33.0 mg, 0.25 mmol, 1.0 equiv) and diol **S22** (105 mg, 0.25 mmol, 1.0 equiv), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (30 mg, 23% yield, 99% *ee*). **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.58 (s, 2H), 4.94 (ddd, *J* = 11.2, 9.0, 5.2 Hz, 2H), 4.15 (ddd, *J* = 11.0, 6.0, 4.9 Hz, 2H), 3.10 (dt, *J* = 13.9, 5.0 Hz, 2H), 2.96 (ddd, *J* = 14.4, 9.0, 6.0 Hz, 2H), 2.19 – 2.09 (m, 2H), 2.08 – 1.97 (m, 2H), 1.67 – 1.56 (m, 2H). **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.5, 141.5, 140.7, 99.7, 60.4, 38.7, 30.9, 18.8. **HRMS (ESI)** m/z calculated for $[C_{20}H_{28}O_3]$, $[M+H]^+$ 514.9211; found 514.9217. The enantiomeric purity was determined by **SFC-MS** analysis in comparison with authentic racemic material (Whelk-01, BPR pressure: 150 bar, column temperature: 30 °C, injection volume: 10 µL into 20 µL loop, solvent: 5 % IPA, signal = 254.4 nm): $t_R$ of **17**: 6.4 min (minor) and 10.4 min (major). The macrocycle was formed in its racemic form using general procedure **D**. Purification occurred via chromatography using the identical conditions shown above.

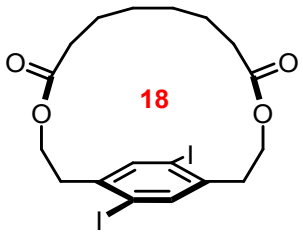
| **Racemic Procedure** | | | **DKR using CALB** | | |
|---|---|---|---|---|---|
| **Peak #** | **Ret. Time** | **Area %** | **Peak #** | **Ret. Time** | **Area %** |
| 1 | 6.394 | 50.6800 | 1 | 6.378 | 100 |
| 2 | 10.395 | 49.3200 | 2 | - | - |





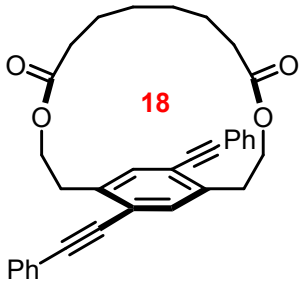




**12,15-Diiodo-4,11-dioxa-1(1,4)-benzenacyclotridecaphane-5,10-dione** (**18**): To an oven dried 100 mL vessel equipped with a stir bar was added adipic acid (36.5 mg, 0.25 mmol, 1.0 equiv) and diol **S22** (105 mg, 0.25 mmol, 1.0 equiv), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (94 mg, 71% yield, 99% *ee*). NMR data was in accordance with what was previously reported.[11] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.63 (s, 2H), 4.44 (ddd, *J* = 11.5, 7.0, 4.7 Hz, 2H), 4.27 (ddd, *J* = 11.1, 7.4, 4.8 Hz, 2H), 3.18 (ddd, *J* = 14.2, 7.4, 4.7 Hz, 2H), 2.96 (ddd, *J* = 14.2, 7.0, 4.8 Hz, 2H), 2.30 – 2.06 (m, 4H), 1.22 – 1.16 (m, 4H).




**12,15-Diiodo-4,13-dioxa-1(1,4)-benzenacyclopentadecaphane-5,12-dione** (**19**): To an oven dried 100 mL vessel equipped with a stir bar was added suberic acid (43.5 mg, 0.25 mmol, 1.0 equiv) and diol **S22** (105 mg, 0.25 mmol, 1.0 equiv), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude

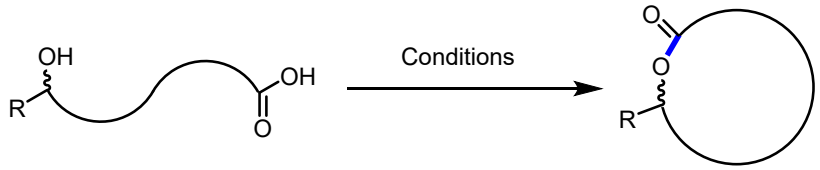
reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (113 mg, 81% yield, 99% *ee*). NMR data was in accordance with what was previously reported.[11] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.69 (s, 2H), 4.50 – 4.39 (m, 2H), 4.30 – 4.22 (m, 2H), 3.21 – 3.11 (m, 2H), 2.98 – 2.86 (m, 2H), 2.35 – 2.15 (m, 4H), 1.50 – 1.29 (m, 4H), 1.15 – 1.01 (m, 2H), 1.01 – 0.89 (m, 2H).




**12,15-Bis(phenylethynyl)-4,13-dioxa-1(1,4)-benzenacyclopentadecaphane-5,12-dione** (**20**): To an oven dried 100 mL vessel equipped with a stir bar was added suberic acid (34.8 mg, 0.20 mmol, 1.0 equiv) and diol **S23** (73.3 mg, 0.20 mmol, 1.0 equiv), toluene (50 mL, 5.00 mM) and immobilized CALB enzyme (65 mg, 260 mg/mmol). The reaction mixture was stirred at 70 °C for 24 h. The reaction was then cooled to room temperature, the supported enzyme beads were filtered off, and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography on silica-gel (5% EtOAc in hexanes) to afford the desired product as a white solid (74 mg, 73% yield, 99% *ee*). NMR data was in accordance with what was previously reported.[11] **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.58 – 7.50 (m, 4H), 7.46 (s, 2H), 7.42 – 7.33 (m, 6H), 4.62 (ddd, $J$ = 11.0, 7.2, 3.6 Hz, 2H), 4.35 (ddd, $J$ = 11.3, 8.0, 3.6 Hz, 2H), 3.53 (ddd, $J$ = 14.6, 8.0, 3.7 Hz, 2H), 2.90 (ddd, $J$ = 14.6, 7.3, 3.6 Hz, 2H), 2.34 – 2.11 (m, 4H), 1.49 – 1.34 (m, 4H), 1.14 – 0.97 (m, 4H).

## GENERAL PROCEDURES FOR MACROCYCLE SYNTHESIS

### 1. Macrolactones

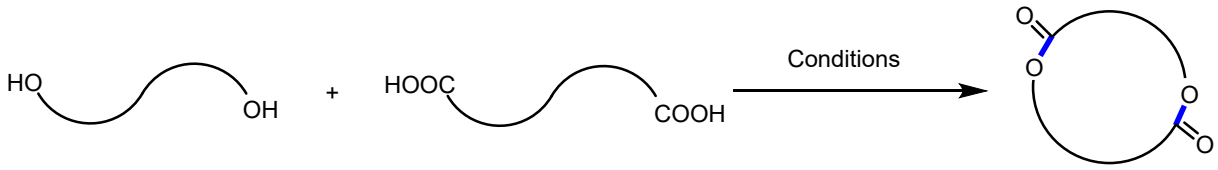



**General procedure (A) for the macrocyclization by Steglish/Boden/Keck reaction**: To an open, oven dried 100 mL cylindrical pressure vessel equipped with a stir bar was added the hydroxyacid (0.25 mmol, 1.0 equiv.), DMAP (0.275 mmol, 1.1 equiv), DMAP·HCl (0.275 mmol, 1.1 equiv), N,N'-dicyclohexylcarbodiimide (0.275 mmol, 1.1 equiv) and DCM (62,5 mL, 4 mM). The vessel was sealed and the reaction mixture was stirred for a total of 24 h at 40 °C. Upon completion, the solvent was removed under reduced pressure, the crude mixture was resolubilized in a few drops of DCM and filtered to get rid of solids. The filtrate was then concentrated in vacuo and the crude reaction mixture was purified by silica gel column chromatography.

**General procedure (B) for the macrocyclization by Yamaguchi reaction**: To an open, oven dried 100 mL vessel equipped with a stir bar was added the hydroxyacid (0.25 mmol, 1.0 equiv.), and toluene (50 mL, 5 mM). The solution was cooled to 0 °C in an ice/water bath, and triethylamine (0.5 mmol, 2.0 equiv.) and 2,4,6-trichlorobenzoyl chloride (0.275 mmol, 1.1 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was heated to 75 °C, DMAP (0.275 mmol, 1.1 equiv) was added and the reaction was stirred for a total of 24 h. After cooling to room temperature, silica gel was added and the slurry was concentrated under reduced pressure and purified by silica gel column chromatography.

**General procedure (C) for the macrocyclization via Hafnium catalysis**: To an open, oven dried 100 mL cylindrical pressure vessel equipped with a stir bar was added the hydroxyacid (0.25 mmol, 1.0 equiv.) and toluene (50 mL, 5 mM). The reaction mixture was preheated to 110°C and then $Hf(OTf)_4$ (0.0125 mmol, 5 mol%) was added to the solution. The reaction mixture was stirred for a total of 24 h at reflux. After cooling to room temperature, silica gel was added and the slurry was concentrated under reduced pressure and purified by silica gel column chromatography.

## 2. Macrodiolides




**General procedure (D) for the macrocyclization by Steglish/Boden/Keck reaction**: To an open, oven dried 100 mL cylindrical pressure vessel equipped with a stir bar was added the diol (0.25 mmol, 1.0 equiv.), diacid (0.25 mmol, 1.0 equiv.), DMAP (0.55 mmol, 2.2 equiv), DMAP·HCl (0.55 mmol, 2.2 equiv), N,N'-dicyclohexylcarbodiimide (0.55 mmol, 2.2 equiv) and DCM (62,5 mL, 4 mM). The vessel was sealed and the reaction mixture was stirred for a total of 24 h at 40 °C. Upon completion, the solvent was removed under reduced pressure, the crude mixture was resolubilized in a few drops of DCM and filtered to get rid of solids. The filtrate was then concentrated in vacuo and the crude reaction mixture was purified by silica gel column chromatography.

**General procedure (E) for the macrocyclization by Yamaguchi reaction**: To an open, oven dried 100 mL vessel equipped with a stir bar was added the diol (0.25 mmol, 1.0 equiv.), diacid (0.25 mmol, 1.0 equiv.), and toluene (50 mL, 5 mM). The solution was cooled to 0 °C in an ice/water bath, and triethylamine (1.0 mmol, 4.0 equiv.) and 2,4,6-trichlorobenzoyl chloride (0.55 mmol, 2.2 equiv.) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was heated to 75 °C, DMAP (0.55 mmol, 2.2 equiv) was added and the reaction was stirred for a total of 24 h. After cooling to room temperature, silica gel was added and the slurry was concentrated under reduced pressure and purified by silica gel column chromatography.

**General procedure (F) for the macrocyclization via Hafnium catalysis**: To an open, oven dried 100 mL cylindrical pressure vessel equipped with a stir bar was added the diol (0.25 mmol, 1.0 equiv.), diacid (0.25 mmol, 1.0 equiv.) and toluene (50 mL, 5 mM). The reaction mixture was preheated to 110°C and then $Hf(OTf)_4$ (0.025 mmol, 10 mol%) was added to the solution. The reaction mixture was stirred for a total of 24 h at reflux. After cooling to room temperature, silica gel was added and the slurry was concentrated under reduced pressure and purified by silica gel column chromatography.

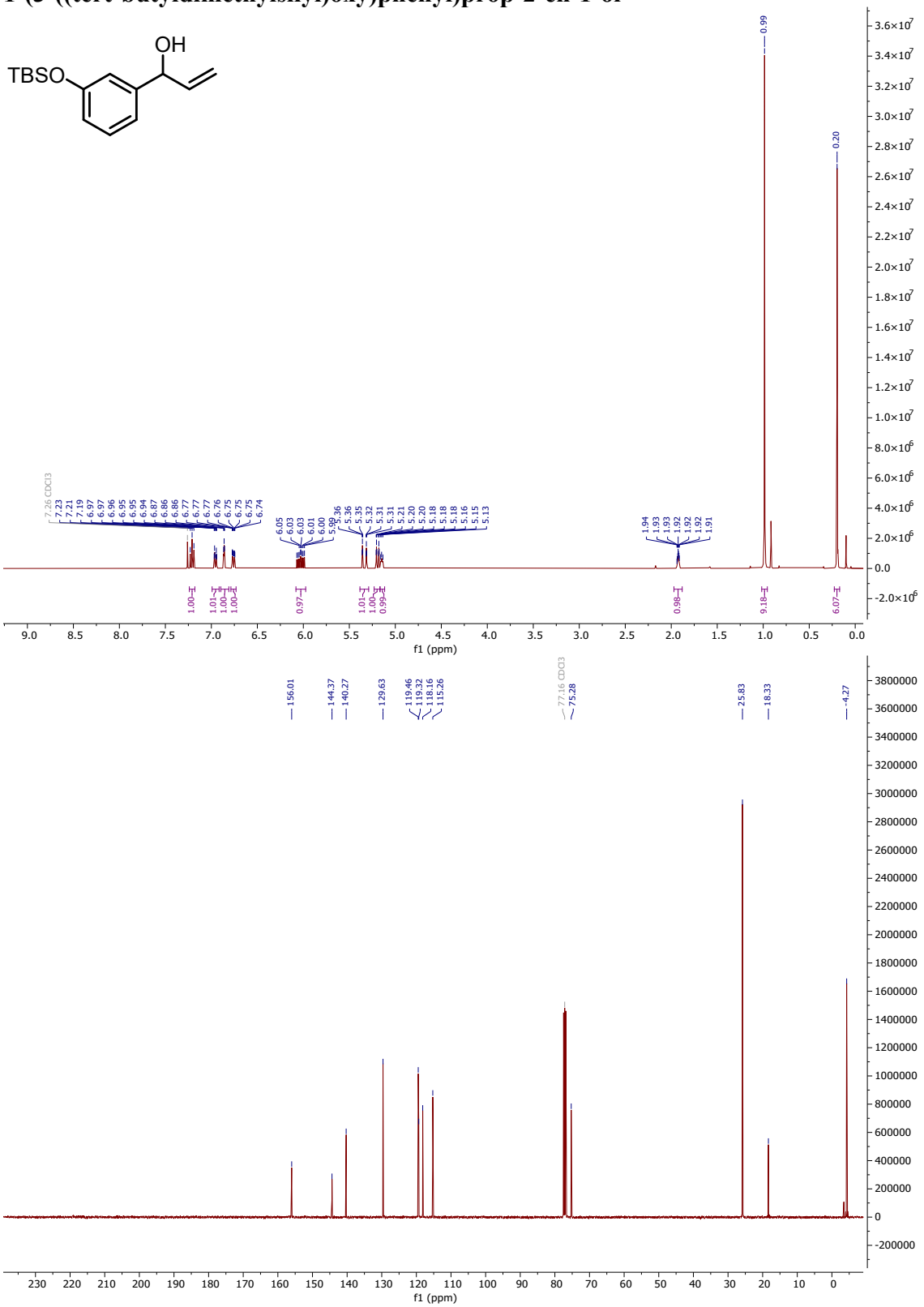
**General procedure (G) for the macrocyclization via Mitsonobu reaction**: To an open, oven dried 100 mL cylindrical pressure vessel equipped with a stir bar was added the diol (0.25 mmol, 1.0 equiv.), diacid (0.25 mmol, 1.0 equiv.) and toluene (50 mL, 5 mM). Triphenylphosphine (0.55 mmol, 2.2 equiv) and diisopropyl-azodicarboxylate (0.55 mmol, 2.2 equiv) were added to the solution. The reaction mixture was stirred for a total of 24 h at 40°C. After cooling to room temperature, silica gel was added and the slurry was concentrated under reduced pressure and purified by silica gel column chromatography.

**General procedure (H) for the macrocyclization via Corey/Nicoloau reaction**: To an open, oven dried 100 mL cylindrical pressure vessel equipped with a stir bar was added the diol (0.25 mmol, 1.0 equiv.), diacid (0.25 mmol, 1.0 equiv.) and toluene (50 mL, 5 mM). Triphenylphosphine (0.750 mmol, 3.0 equiv) and 2,2′-dithiodipyridine (0.750 mmol, 3.0 equiv) were added to the solution. The reaction mixture was stirred for 2h at room temperature. The reaction mixture was heated to 75 °C, DMAP (0.55 mmol, 2.2 equiv) was added and the reaction was stirred for a total of 22 h. After cooling to room temperature, silica gel was added and the slurry was concentrated under reduced pressure and purified by silica gel column chromatography.

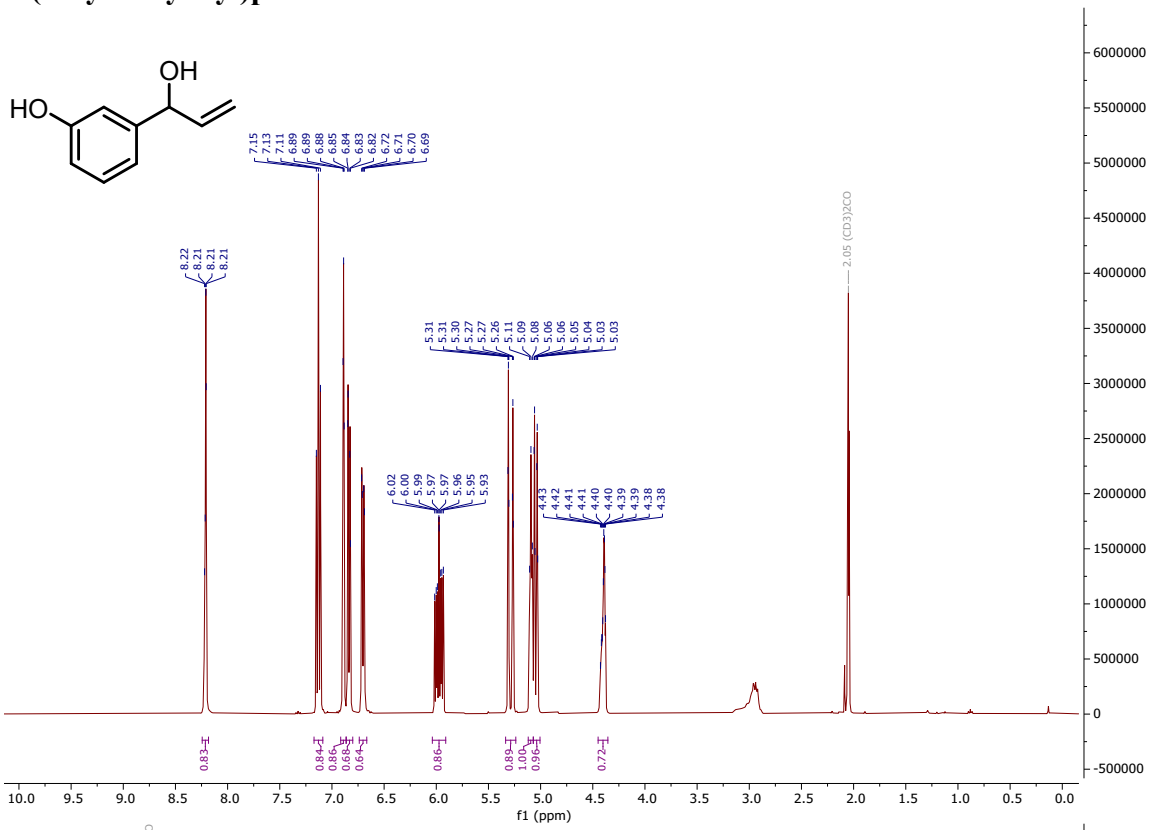
**General procedure (I) for the macrocyclization via Boronic acid Catalysis**: To an open, oven dried 100 mL cylindrical pressure vessel equipped with a stir bar was added the diol (0.25 mmol, 1.0 equiv.), diacid (0.25 mmol, 1.0 equiv.) triethylamine (0.55 mmol, 2.2 equiv.) and toluene (50 mL, 5 mM). The reaction mixture was preheated to 110°C and then pentafluorophenylboronic acid (0.0625 mmol, 25 mol%) was added to the solution. The reaction mixture was stirred for a total of 24 h at reflux. After cooling to room temperature, silica gel was added and the slurry was concentrated under reduced pressure and purified by silica gel column chromatography.

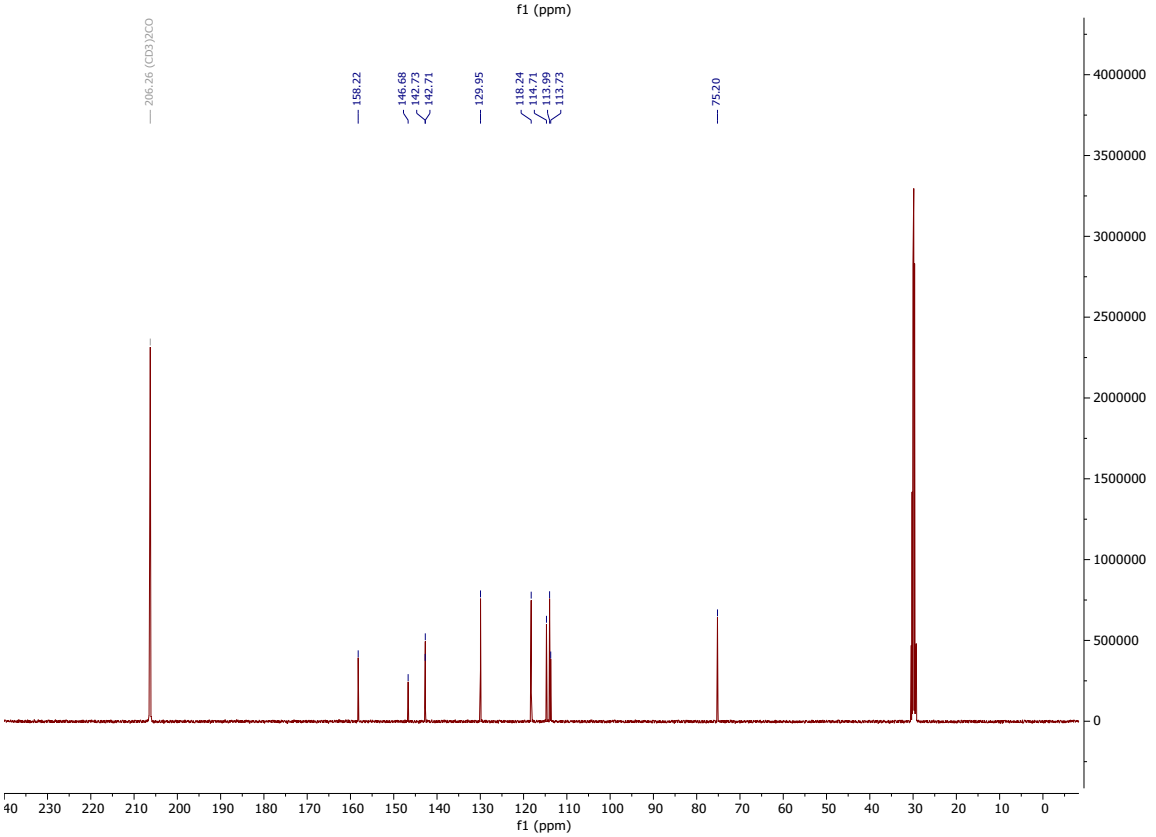
**NMR DATA**

**1-(3-((tert-butyldimethylsilyl)oxy)phenyl)prop-2-en-1-ol**

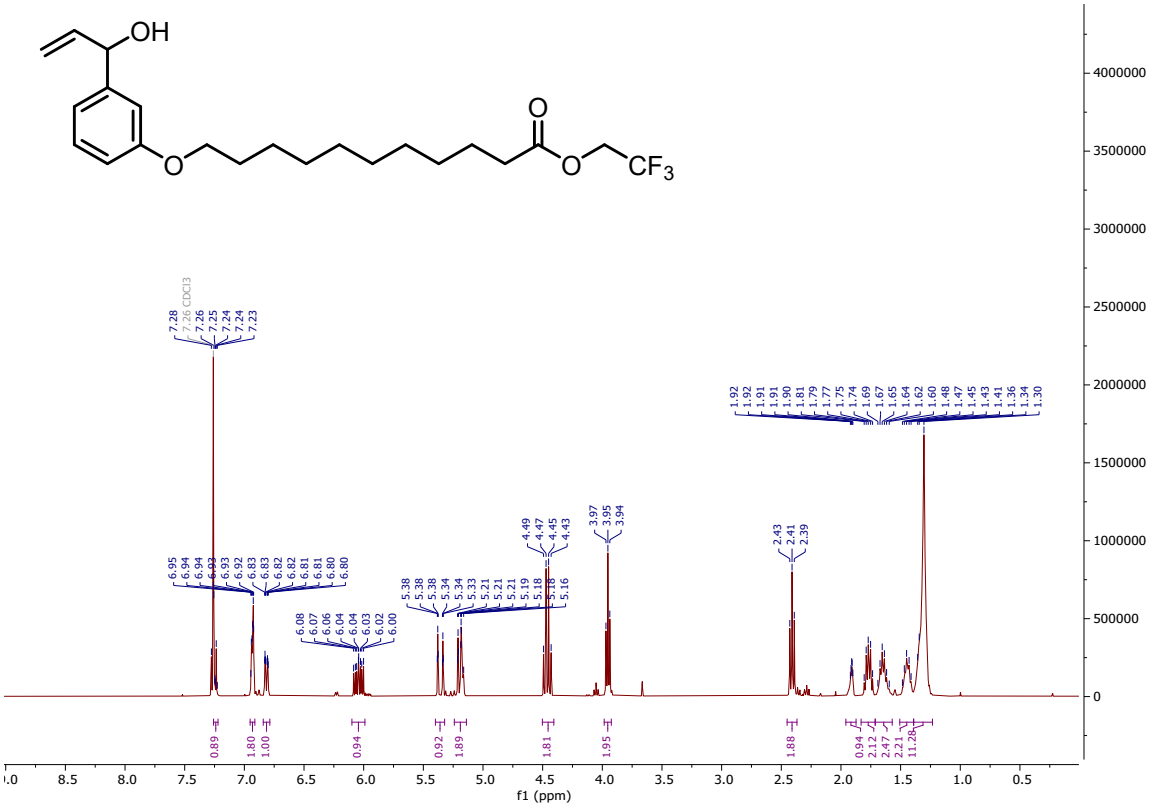


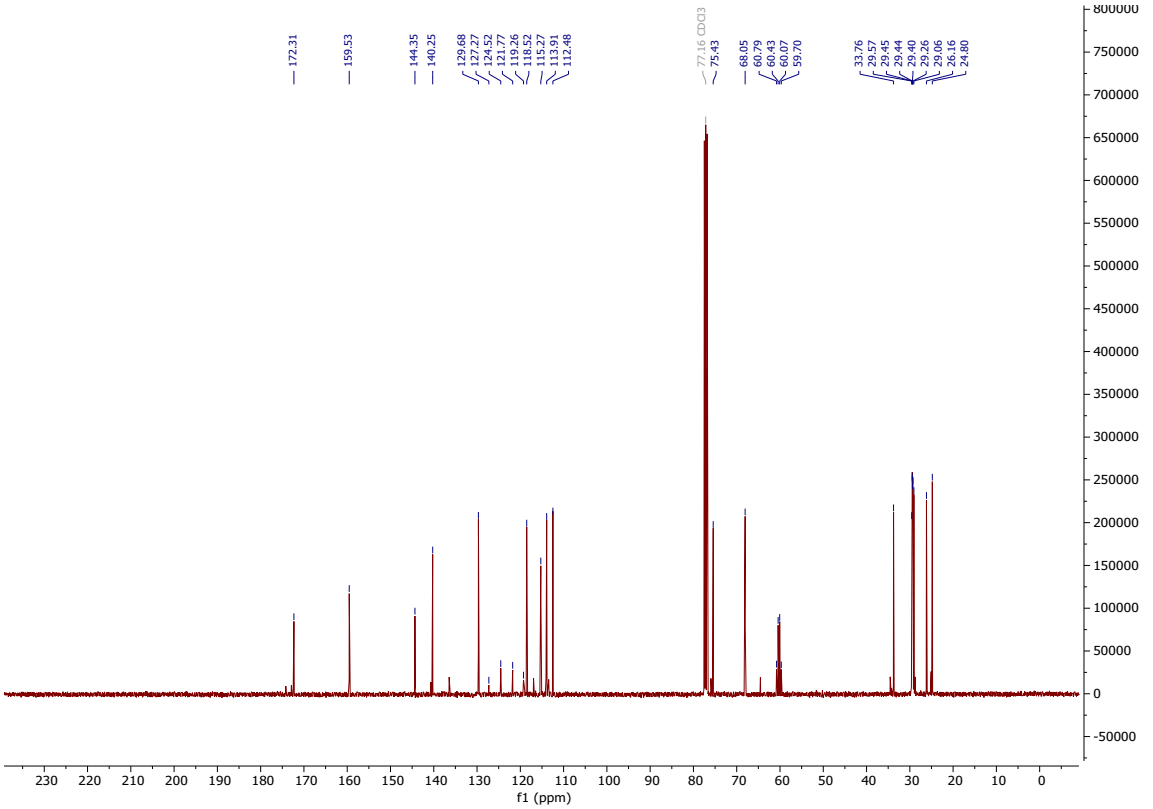
## 3-(1-hydroxyallyl)phenol



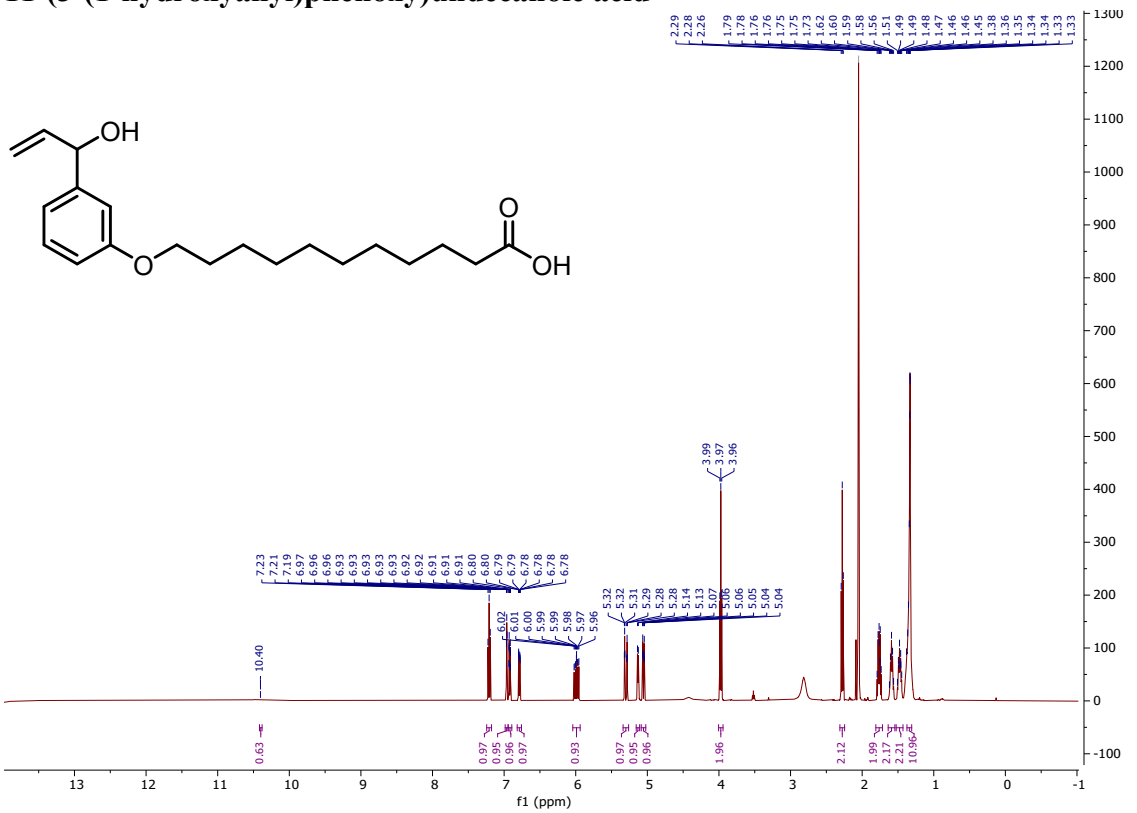



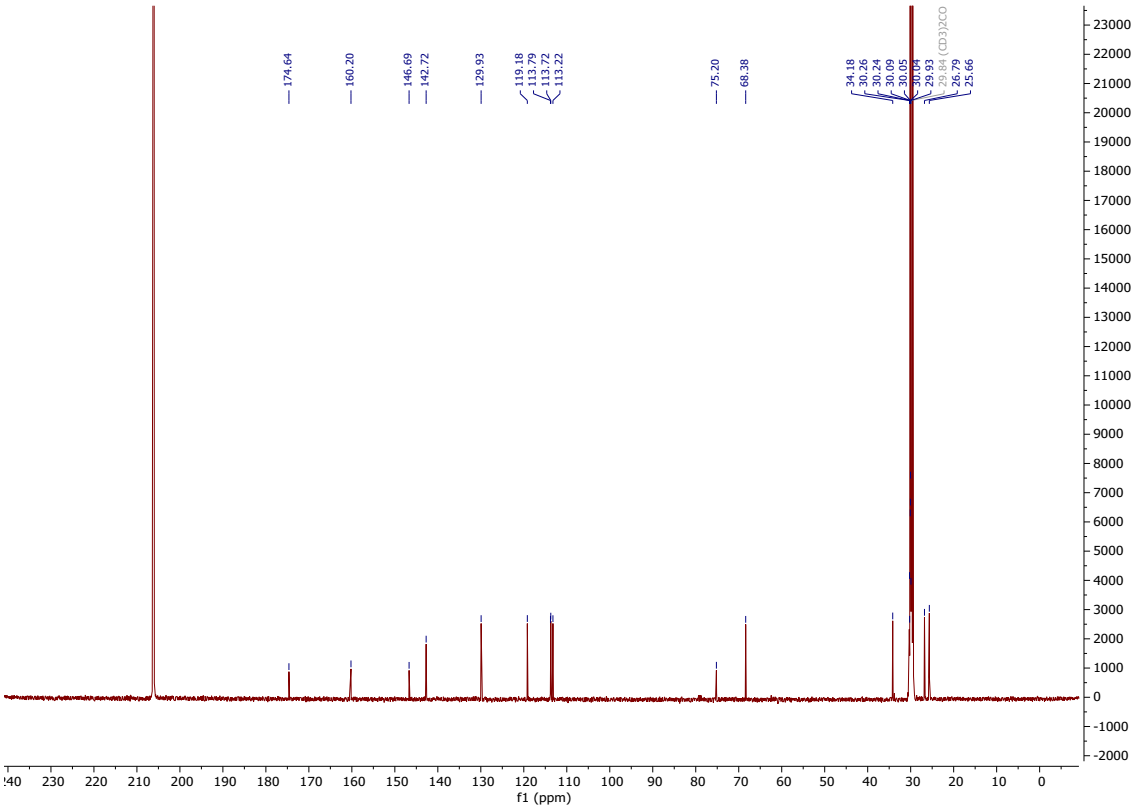
## 2,2,2-Trifluoroethyl 11-(3-(1-hydroxyallyl)phenoxy)undecanoate



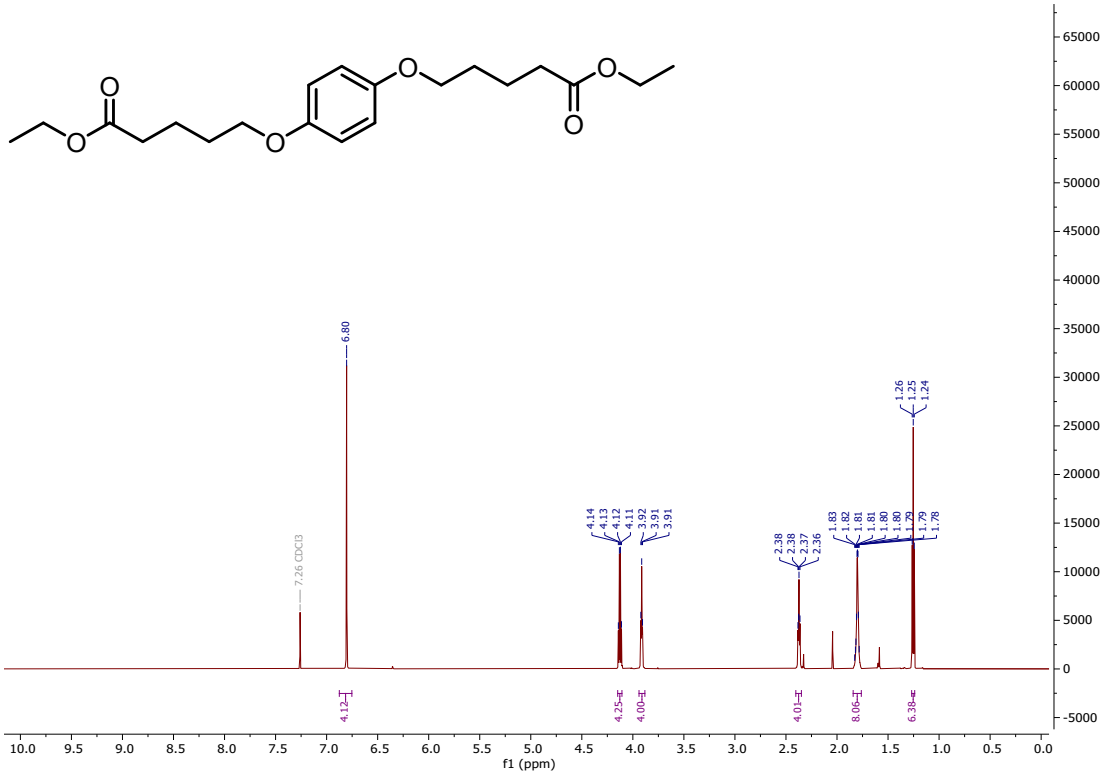



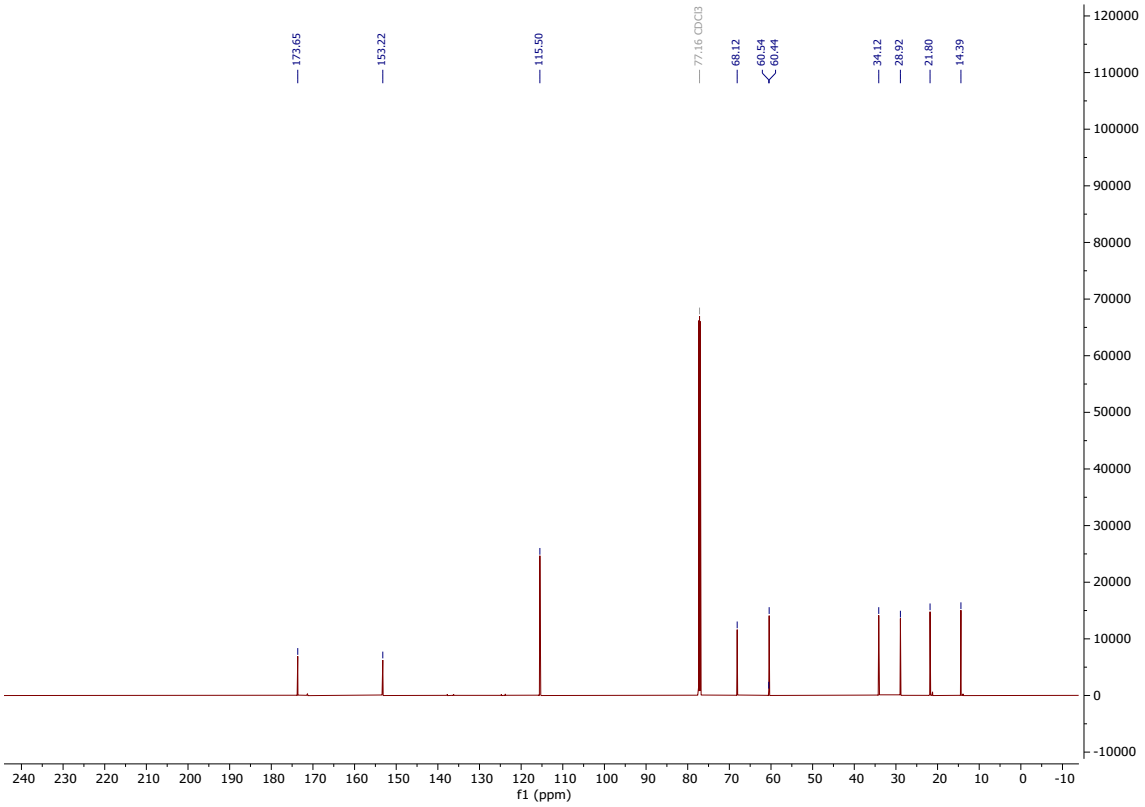
**11-(3-(1-hydroxyallyl)phenoxy)undecanoic acid**



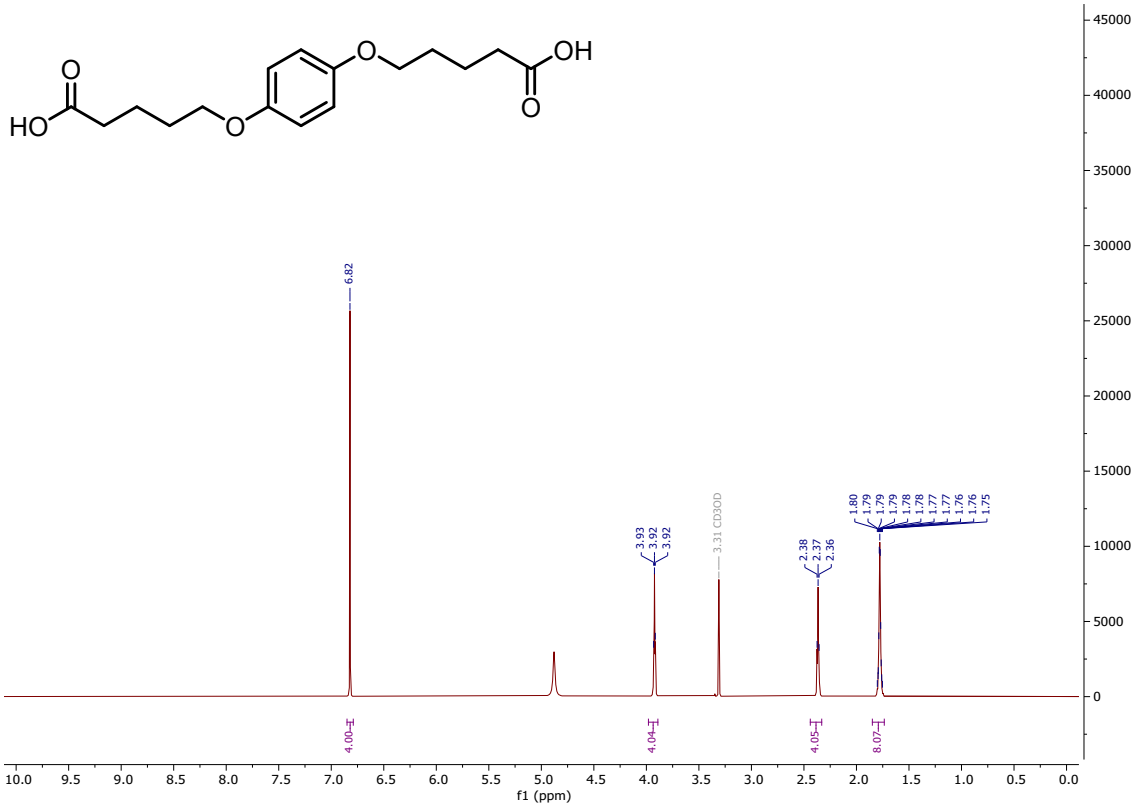



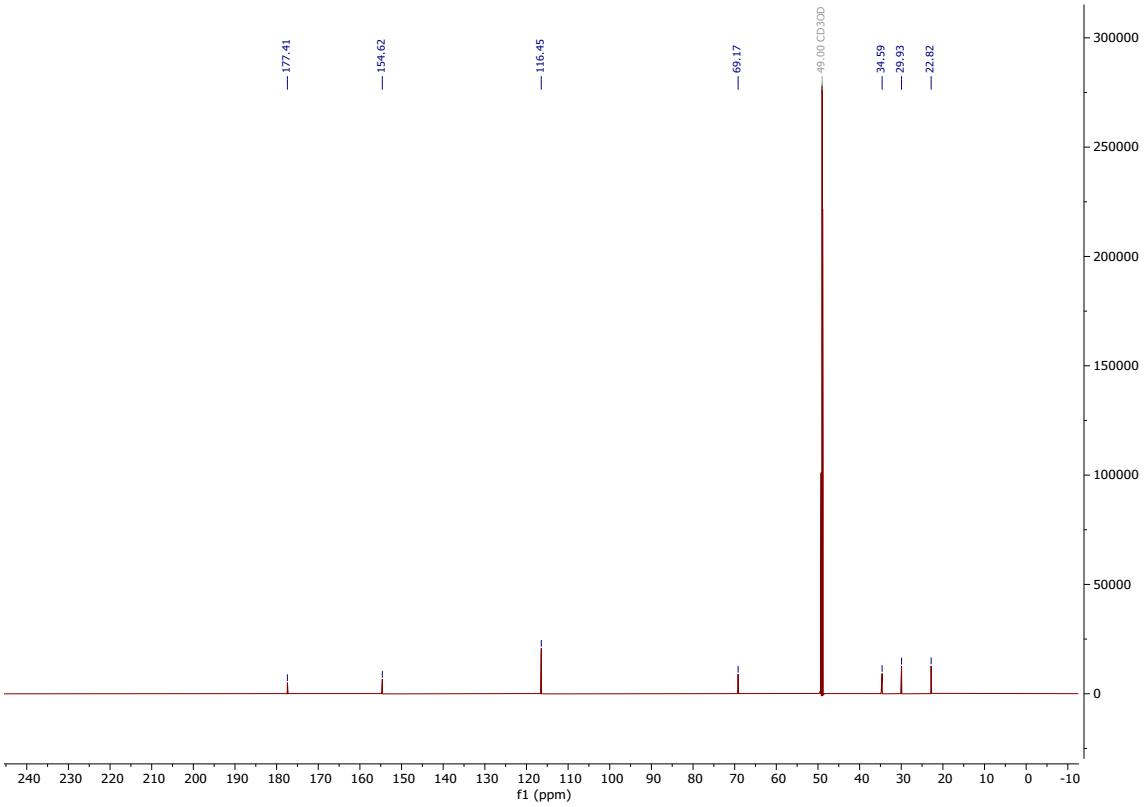
**diethyl 5,5'-(1,4-phenylenebis(oxy))dipentanoate**



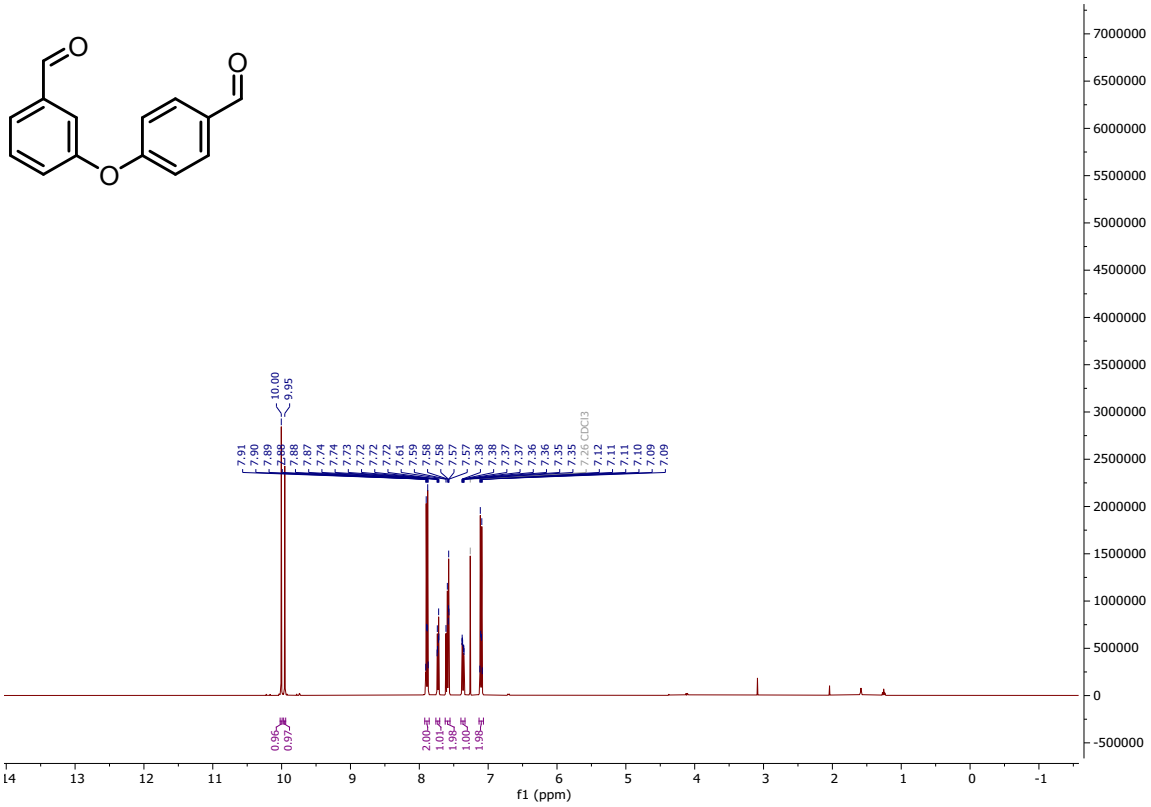



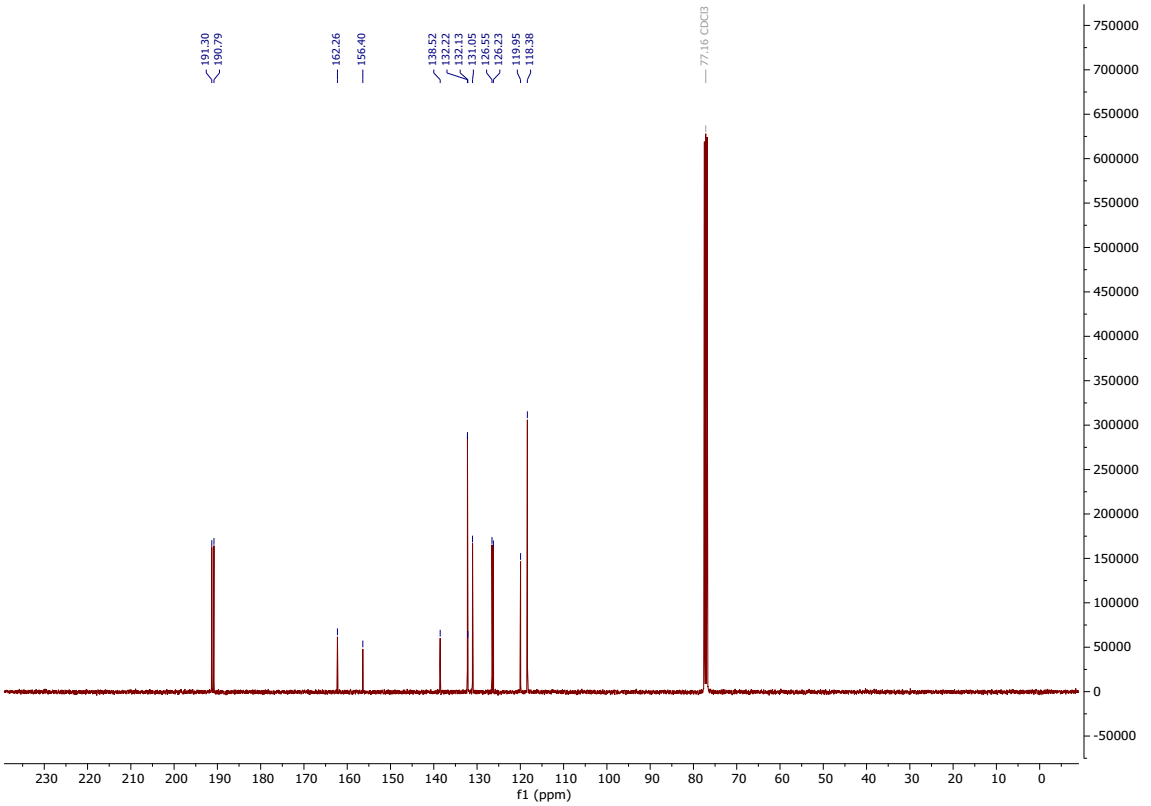
## 5,5'-(1,4-phenylenebis(oxy))dipentanoic acid



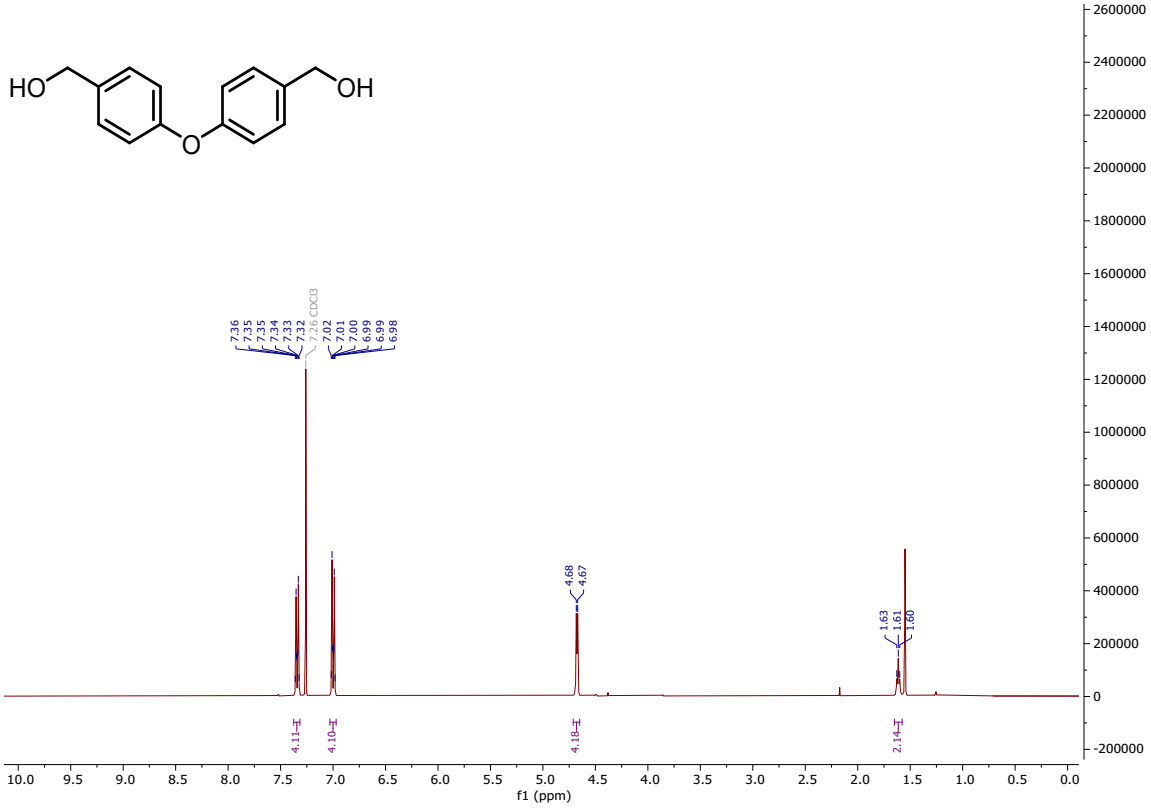



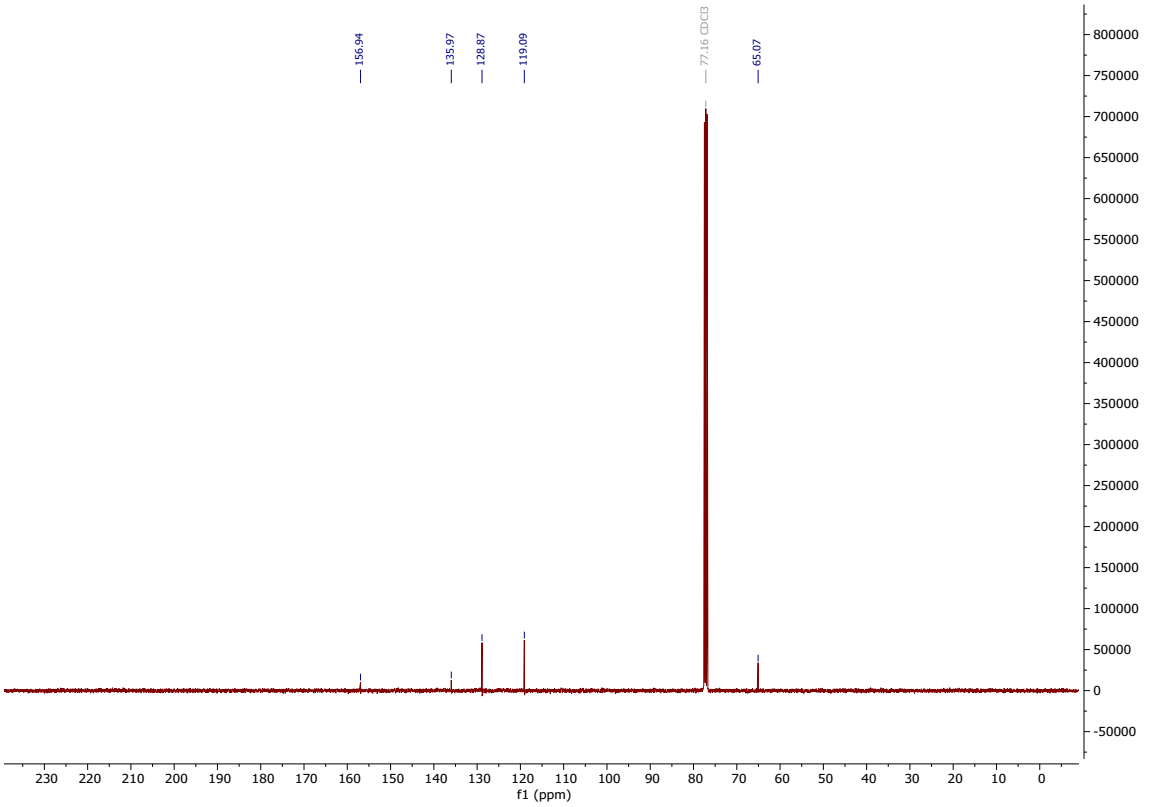
## 3-(4-formylphenoxy)benzaldehyde



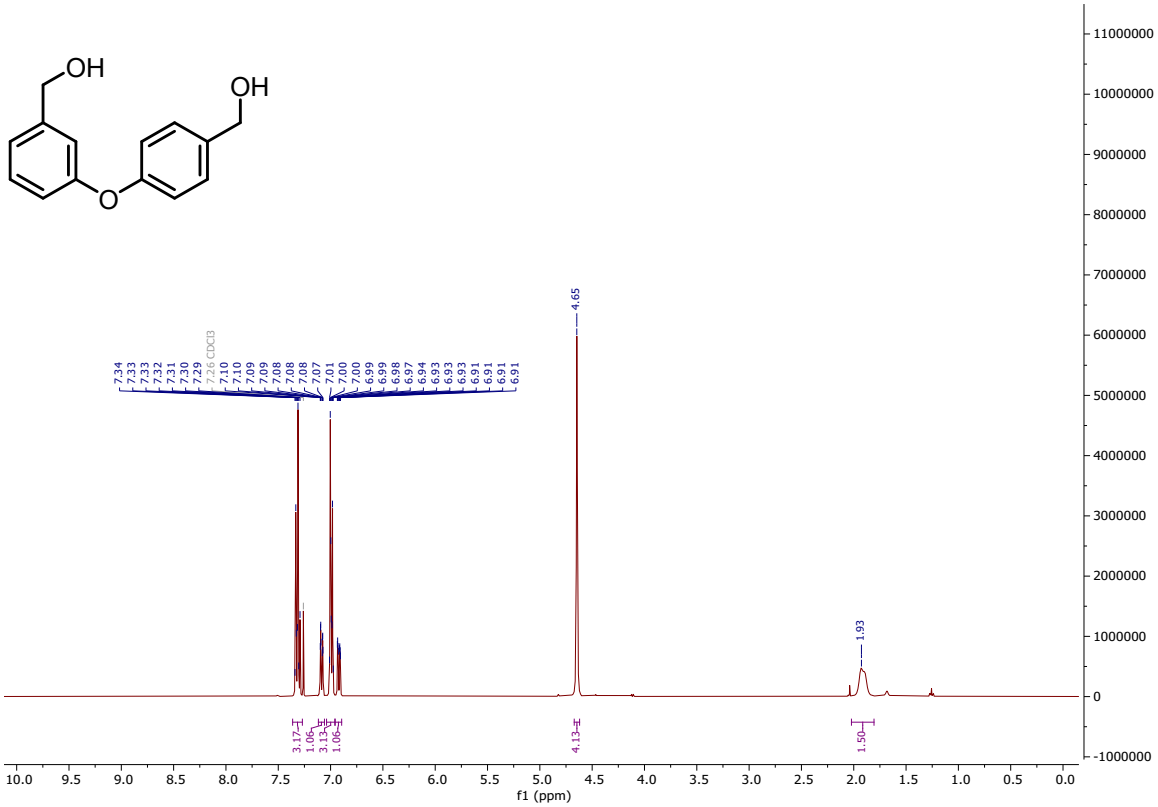



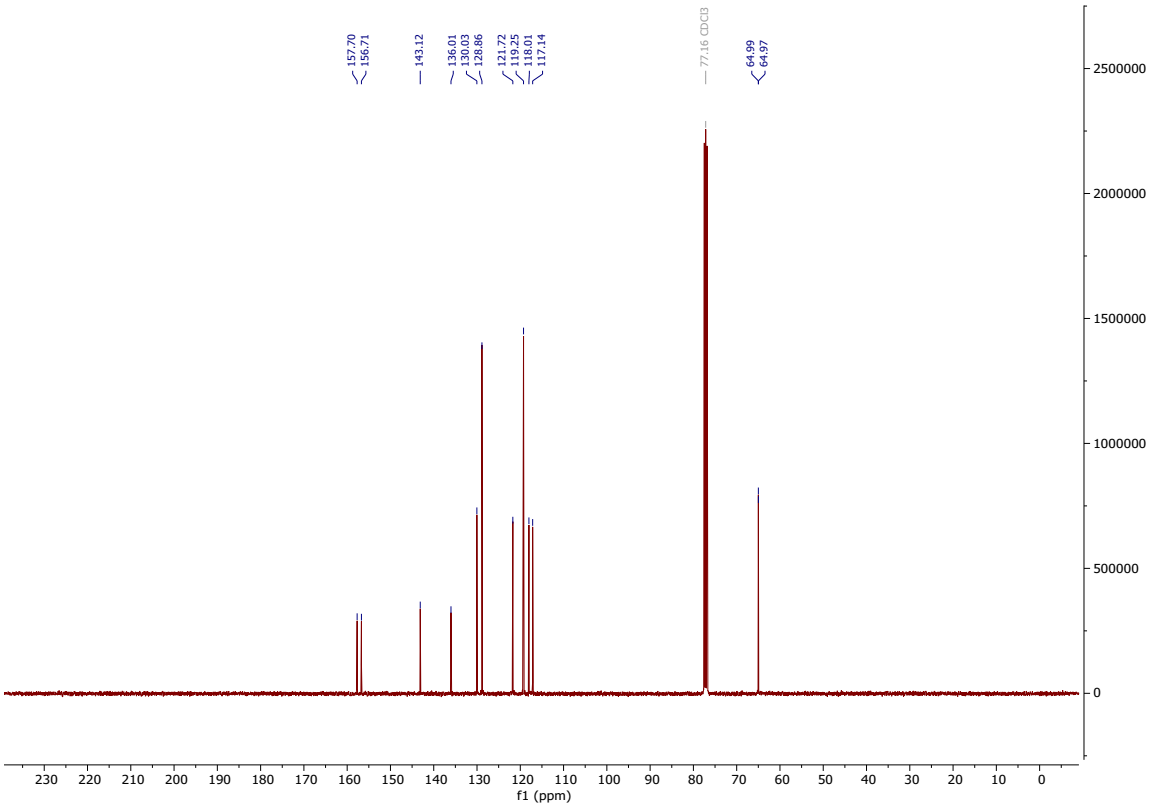
**(Oxybis(4,1-phenylene))dimethanol**



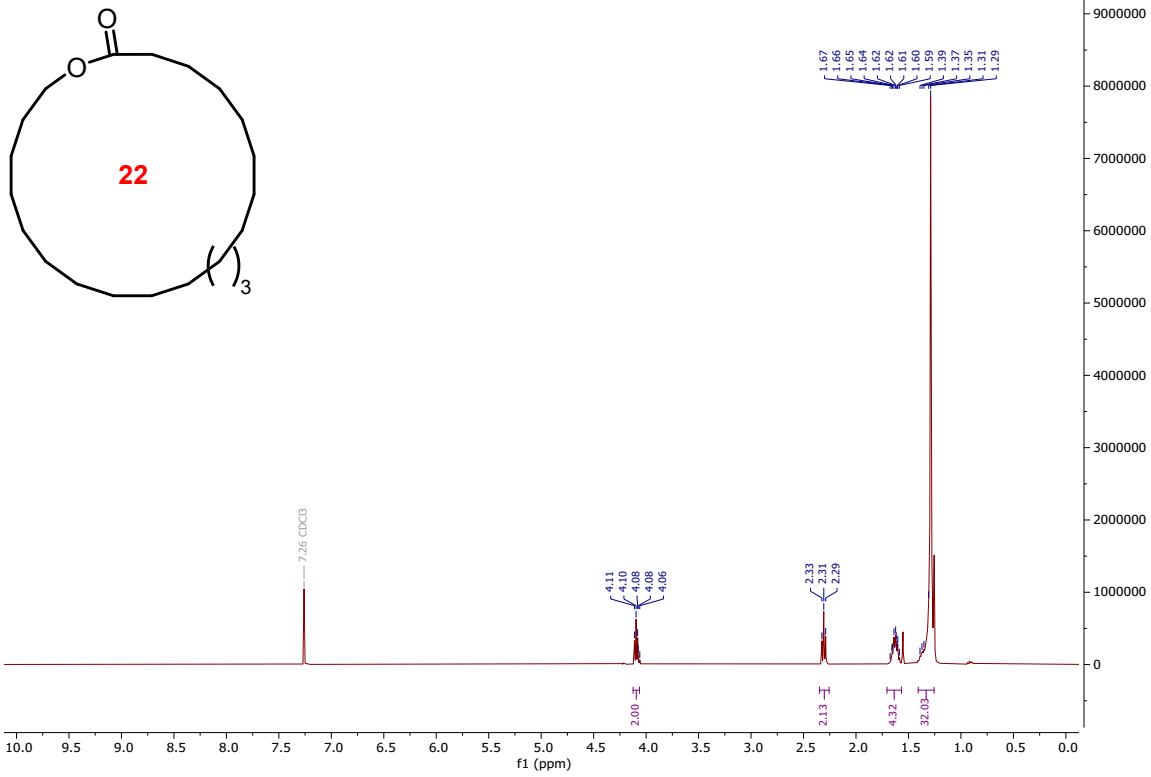



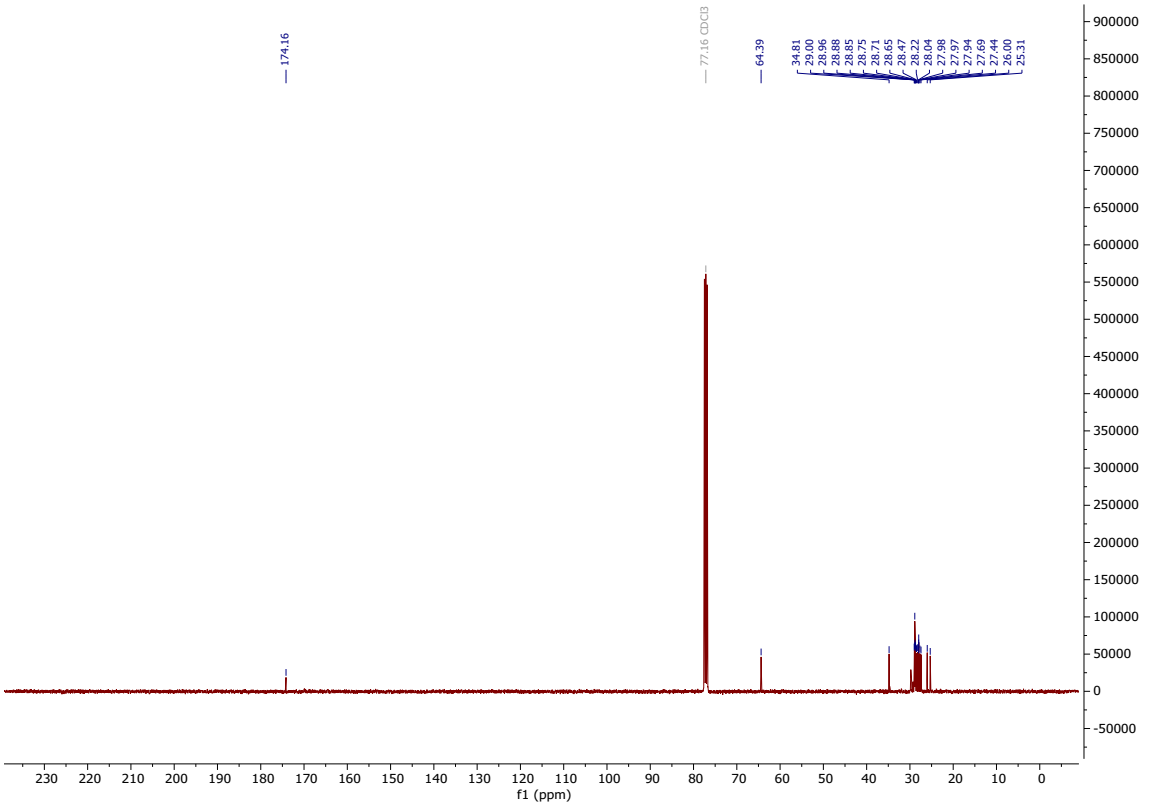
## (3-(4-(hydroxymethyl)phenoxy)phenyl)methanol



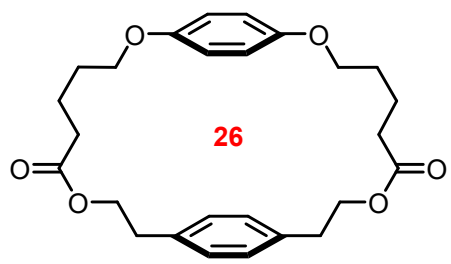



## Oxacyclodocosan-2-one



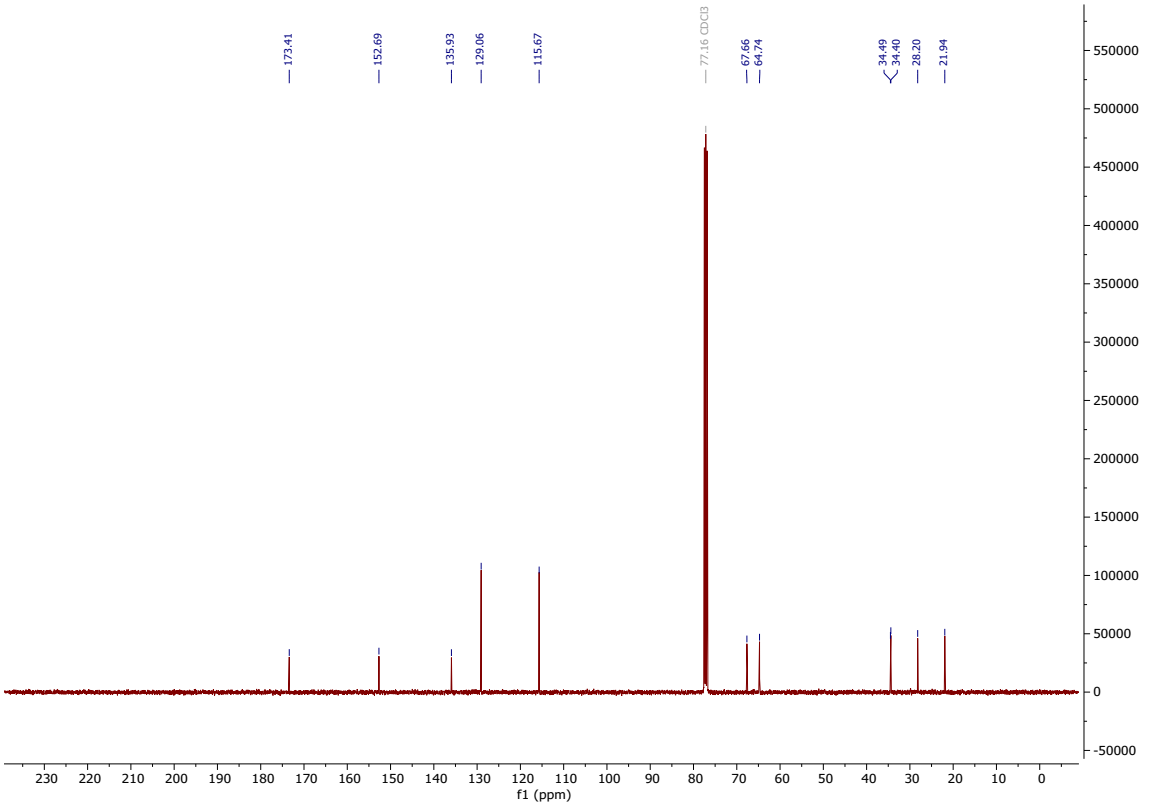



## 2,8,14,20-Tetraoxa-1,11(1,4)-dibenzenacycloicosaphane-7,15-dione

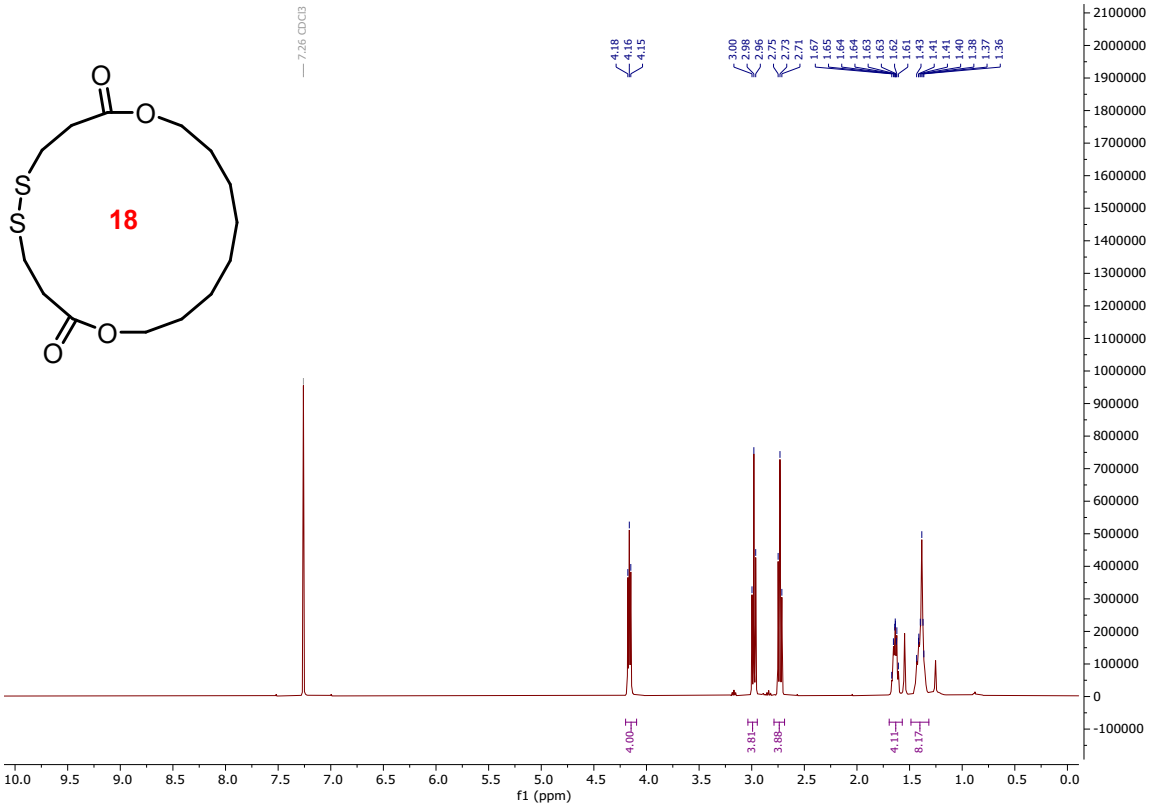


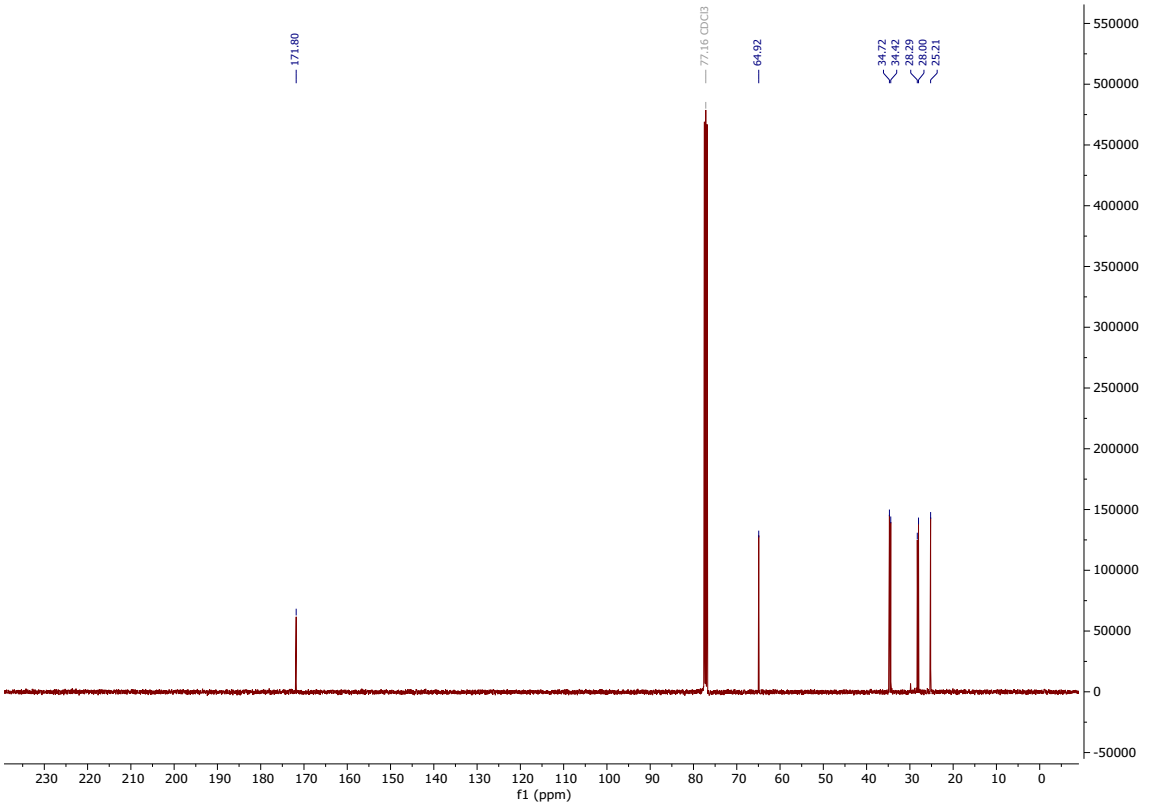




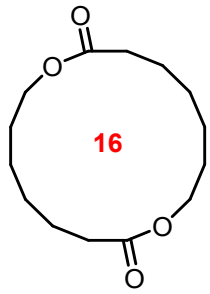


## 1,10-Dioxa-5,6-dithiacyclooctadecane-2,9-dione



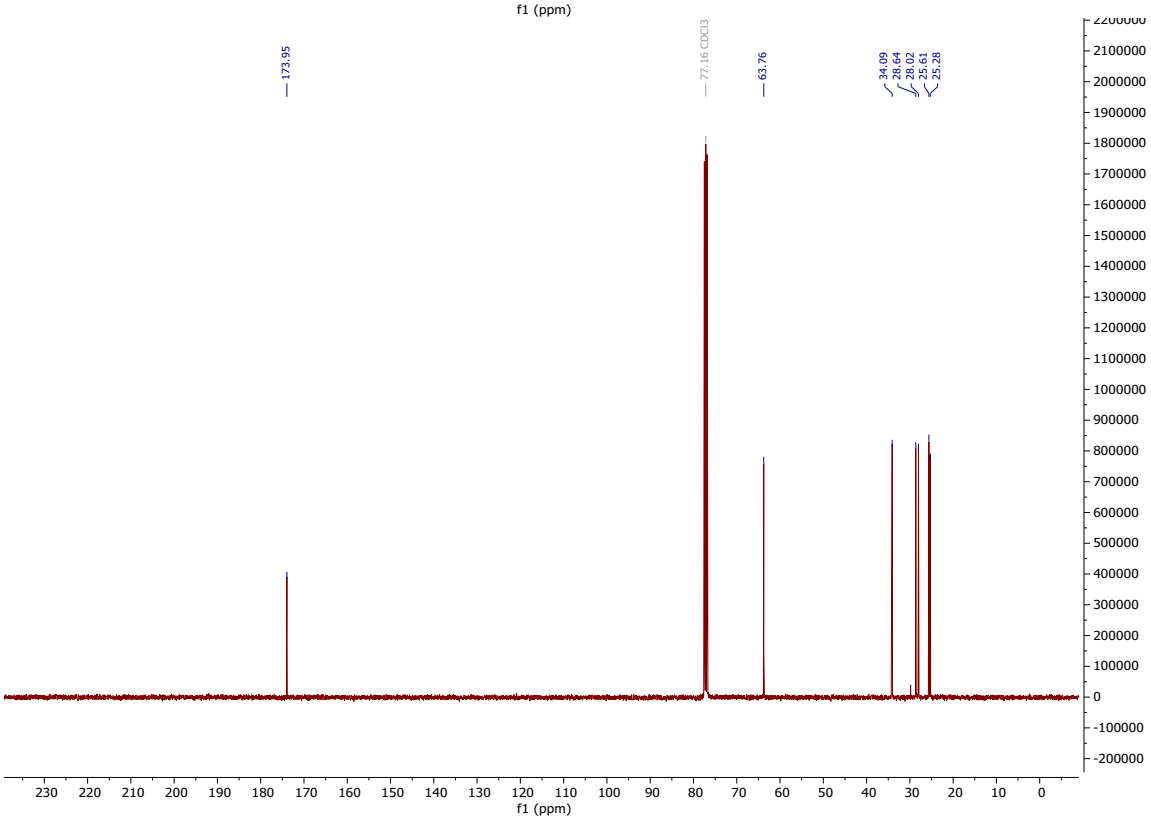



## 1,9-Dioxacyclohexadecane-2,10-dione

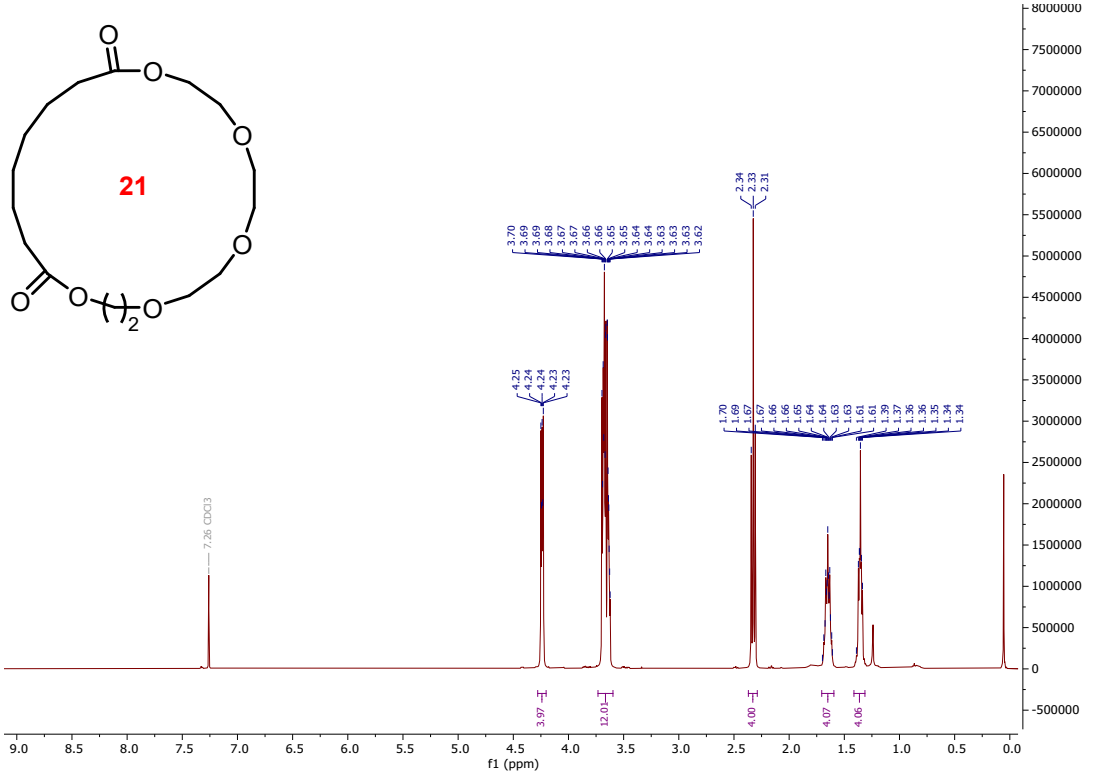


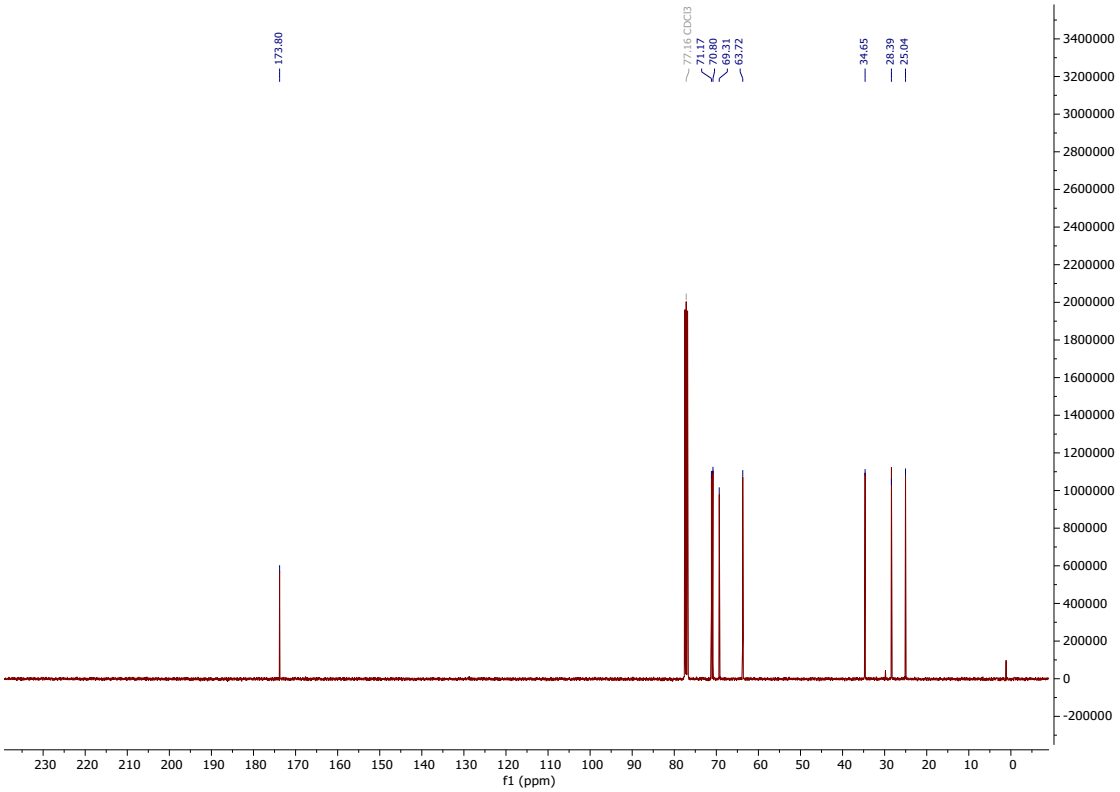




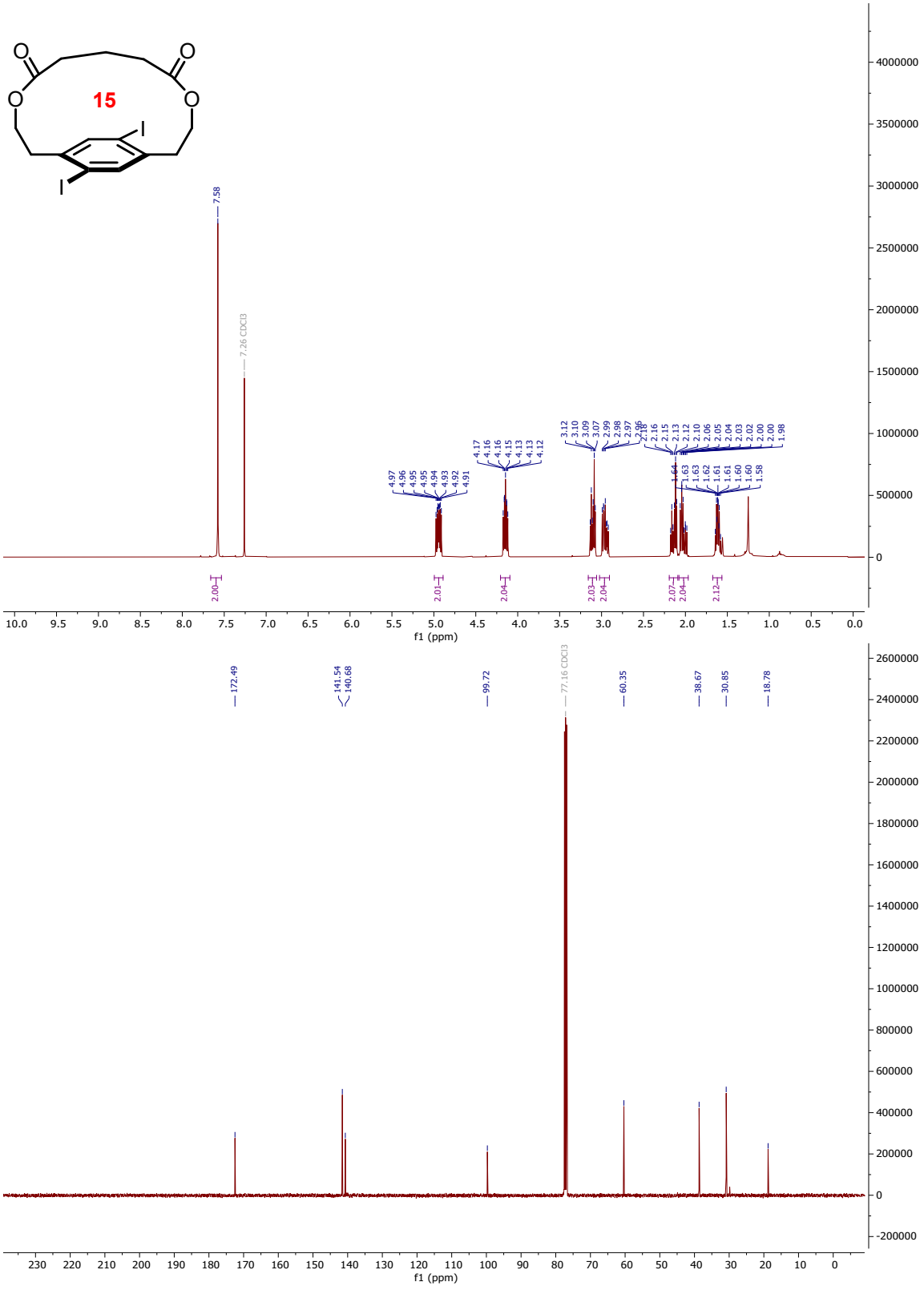


## 1,4,7,10,13-Pentaoxacyclohenicosane-14,21-dione

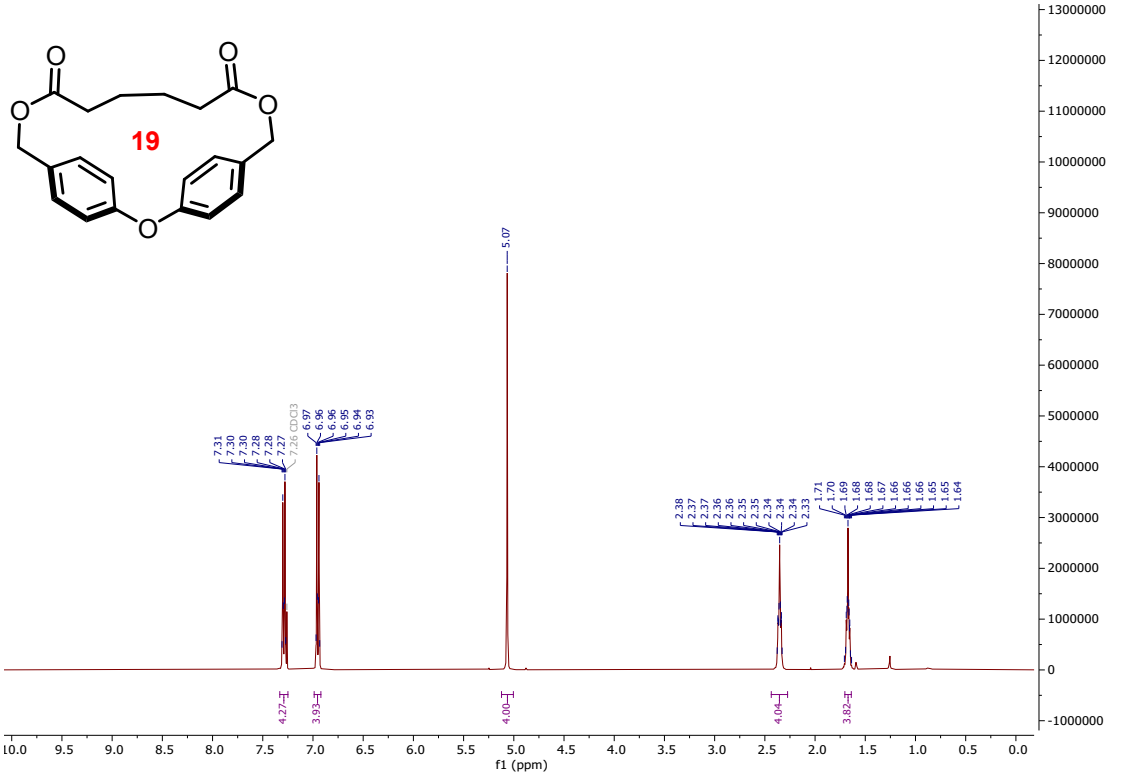


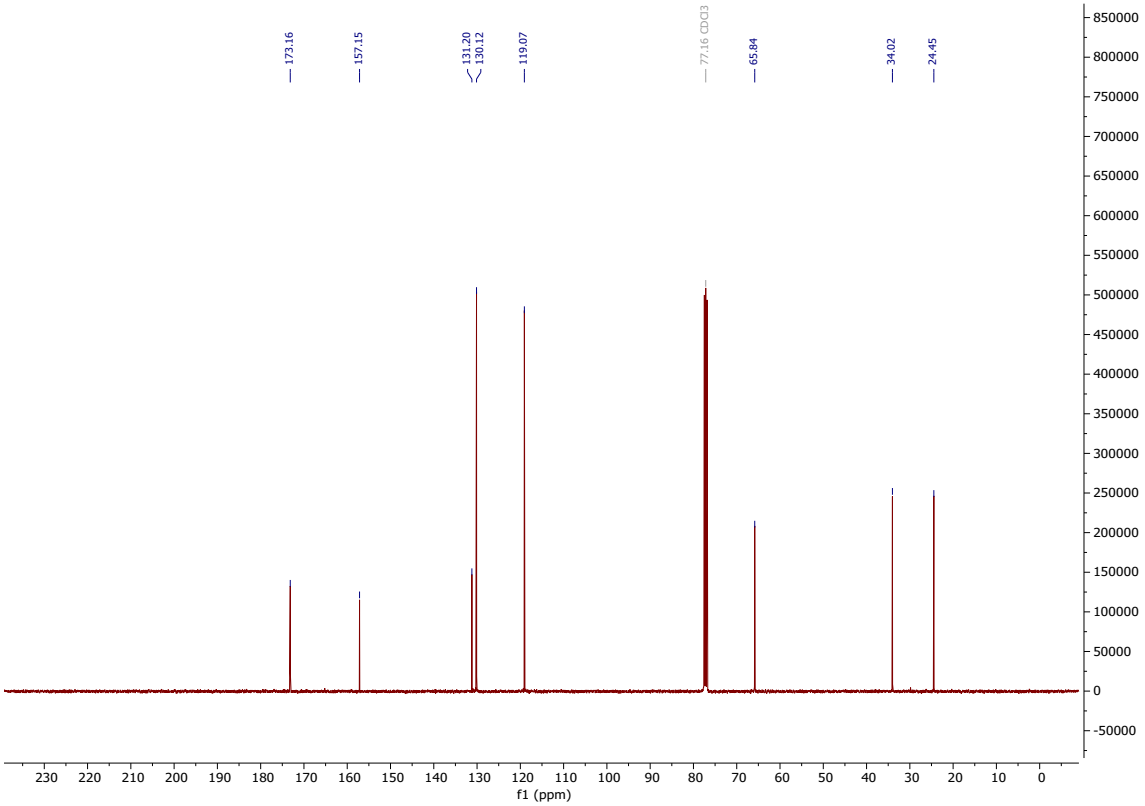



**12,15-diiodo-4,10-dioxa-1(1,4)-benzenacyclododecaphane-5,9-dione**

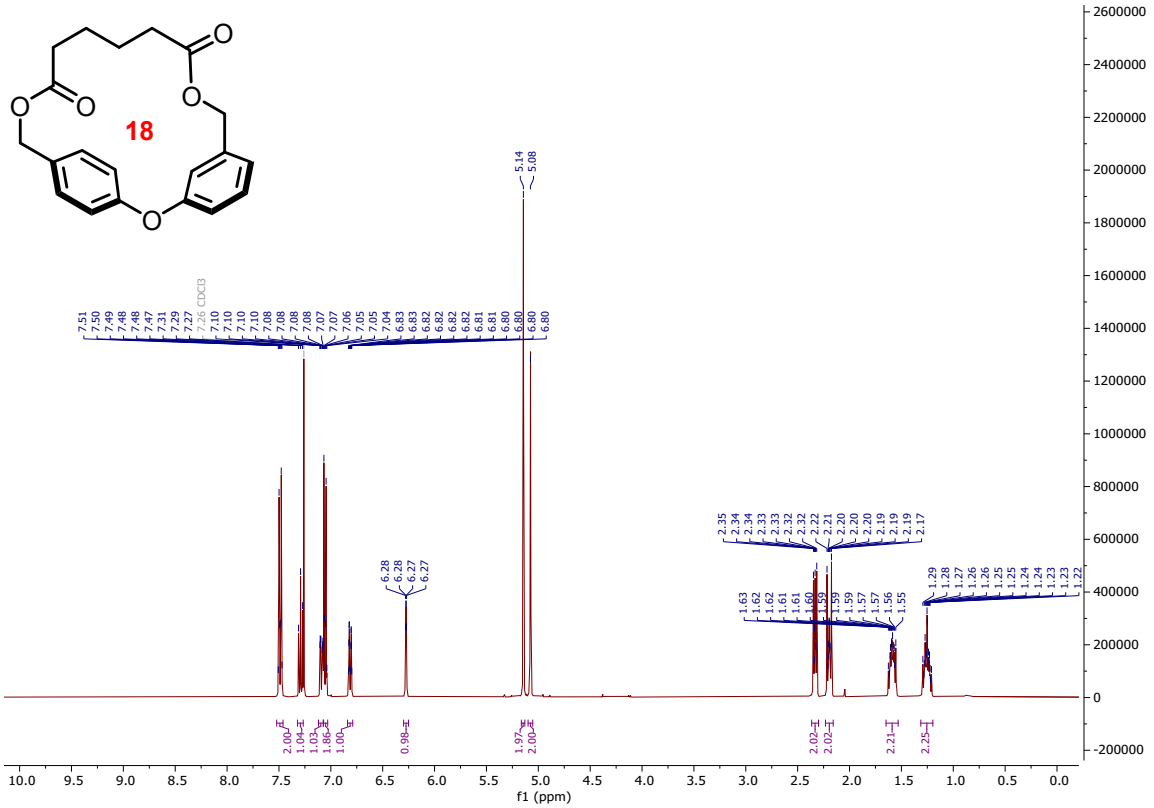


**2,5,12-trioxa-1,3(1,4)-dibenzenacyclotridecaphane-6,11-dione**




**2,5,12-trioxa-1(1,3),3(1,4)-dibenzenacyclotridecaphane-6,11-dione**


18
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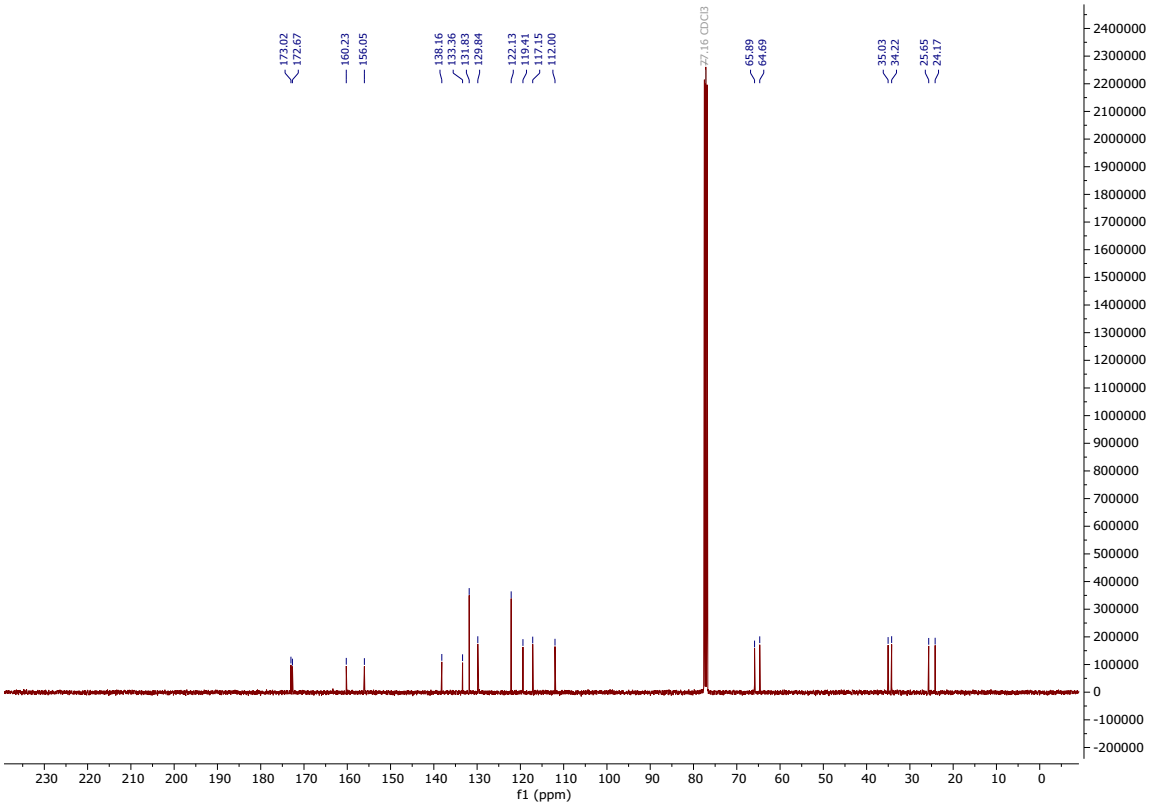
f1 (ppm)

**(*R*)-15-vinyl-2,14-dioxa-1(1,3)-benzenacyclopentadecaphan-13-one**