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ELECTRONIC SUPPORTING INFORMATION

Readily Accessible Azido-alkyne-functionalised Monomers for the Synthesis of Cyclodextrin Analogues using Click Chemistry

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1. General considerations

Chemicals and reagents were purchased from Sigma-Aldrich and used as received. Diol **1** was obtained by biotransformation of bromobenzene using a reported procedure.[1] *E. coli* JM109 (pDTG601) was generously donated by Prof.[1] David T. Gibson (1938-2014). All his strains collection is now managed by Prof. Rebecca Parales (University of California, Davis). All solvents were distilled prior to use. NMR spectra were obtained in $CDCl_3$ or CD_3OD on a Bruker Avance Neo-400. Proton chemical shifts (δ) are reported in ppm downfield from TMS as an internal reference, and carbon chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ triplet (77.0ppm). Optical rotation was measured on a Dichrom P-2000 polarimeter using a 3,5mm x 100mm cell $[\alpha]_D$ values are given in units of $deg.cm^2.g^{-1}$ and concentration values are expressed in g/100mL.

Mass spectra (MS) were recorded on a Shimadzu LCMS 8040 using ESI positive mode, and the. LC was performed using a C18 Phenomenex column, length: 15 cm. High resolution mass spectra were obtained on a Thermo Scientific Q Exactive Plus. Infrared spectra (IR) were recorded on neat samples (NaCl disk) on a Shimadzu FT-IR 8101A spectrophotometer. Analytical TLC were performed on silica gel Kieselgel 60 M from Macherey-Nagel and visualized with UV light (254nm) and/or vanillin in acidic ethanolic solution. Flash column chromatography was performed using silica gel (Kieselgel 60 EM reagent, 0,04-0,063mm).

[1] Vila, M. A.; Brovetto, M.; Gamenara, D.; Bracco, P.; Zinola, G.; Seoane, G.; Rodríguez, S.; Carrera, I,. *J. Mol. Catal. B Enzym.* **2013**, *96*, 14–20.

2. Synthetic procedures and spectral data

General procedure for acetylation of alcohols:

The corresponding starting material was dissolved in dry CH_2Cl_2 [0,20M] and stirred at room temperature under nitrogen atmosphere, then it was cooled to 0°C and Et_3N (2eq for each eq of Ac_2O), Ac_2O (2eq for each alcohol) and a catalytic amount of DMAP were added. After the reaction was complete, the solvent was removed under reduced pressure and the crude was dissolved in ethyl acetate. The organic layer was successively washed with satd. aq. $NaHCO_3$, satd. aq. $CuSO_4$, brine and then dried over anh. Na_2SO_4. The solvent was evaporated under reduced pressure and the compound was isolated and purified by flash chromatography using the corresponding mobile phase in each case.

General procedure for epoxidation of olefins:

m-CPBA was added to a stirred solution of the corresponding olefin in dry CH_2Cl_2 [0.20M] under nitrogen atmosphere, at 0°C. The reaction mixture was diluted after complete consumption of the starting material and washed with satd. aq. $NaHSO_3$, satd. aq. $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the compound was isolated and purified by flash chromatography using the corresponding mobile phase in each case.

General procedure for acetate deprotection:

Potassium carbonate (1eq) was added at room temperature to a stirred solution of the corresponding starting material in methanol [0,04M]. After the reaction was complete the mixture was filtered, and the solvent evaporated under reduced pressure. The compound was purified by silica gel chromatography using the corresponding mobile phase in each case.

General procedure for azide formation via mesyl substitution:

1) The corresponding starting material was dissolved in dry CH_2Cl_2 [0.10M] and stirred at room temperature under nitrogen atmosphere, then Et_3N (2eq) and mesyl chloride (1.2eq) were added. After completion, the reaction mixture was diluted with CH_2Cl_2 and the organic layer was washed with satd. aq. $CuSO_4$, brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude mixture was used for the next reaction.

2) The crude obtained above was dissolved in anhydrous DMF (1g/mL) and stirred at room temperature under nitrogen atmosphere, then sodium azide (3eq) and ammonium chloride (2,2eq) were added. After complete consumption of the starting material, the reaction mixture was diluted in Et_2O and the organic layer was washed with water, brine, and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the compound was isolated and purified by silica gel chromatography using the corresponding mobile phase.

General procedure for acetonide hydrolysis:

Copper (II) chloride dihydrate (2eq) was added at room temperature to a solution of the corresponding starting material in acetonitrile [0,1M] and stirred overnight. After the reaction was complete, the solvent was evaporated under reduced pressure. The crude was diluted in AcOEt and the organic layer was washed with satd. aq. $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the compound was isolated and purified by silica gel chromatography using the corresponding mobile phase.

General procedure for CuAAC dimerization using $Cu(PPh_3)_3Br$:

To a stirred mixture of compound **4a** (1eq) and compound **4b** (1eq) in dry tetrahydrofuran [60mM], diisopropylamine (3eq) and $Cu(PPh_3)_3Br$ (0,2eq) were added at room temperature under a nitrogen atmosphere. After the reaction was complete, the solvent was evaporated under reduced pressure. The crude was diluted in AcOEt and the organic layer was washed with satd. aq. $CuSO_4$, brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the compound was isolated and purified by silica gel chromatography using the corresponding mobile phase.

General procedure for CuAAC dimerization using $CuSO_4 \cdot 5H_2O$ / sodium ascorbate:

To a stirred mixture of compound **4a** (1eq) and compound **4b** (1eq) in the corresponding solvent THF:H_2O (9:1) [55mM] or t-BuOH:H_2O (1:1) [12mM], copper(II) sulfate (0,2eq) and ascorbic acid sodium salt (0,4eq) were added at room temperature and under a nitrogen atmosphere. After the reaction was complete, the solvent was evaporated under reduced pressure. The crude was diluted in AcOEt and the organic layer was washed with brine and dried over anhydrous Na_2SO_4.

The solvent was evaporated under reduced pressure and the compound was isolated by silica gel chromatography using the corresponding mobile phase.

General procedure for CuAAC dimerization using CuI:

To a stirred mixture of compound **4a** (1eq) and compound **4b** (1eq) in the corresponding dry solvent (toluene or acetonitrile) [40mM] was added cuprous iodide (0,2eq) at room temperature under a nitrogen atmosphere, then the reaction mixture was heated to reflux. After the reaction was complete, the solvent was evaporated under reduced pressure and the crude was directly purified by silica gel chromatography using the corresponding mobile phase.

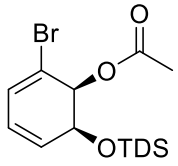
General procedure for CuAAC dimerization and oligomerization using $Cu(OAc)_2 \cdot H_2O$:

For dimerization: To a stirred mixture of compound **4a** (1eq) and compound **4b** (1eq) in dry acetonitrile [65mM] at room temperature under a nitrogen atmosphere was added copper (II) acetate (0,2eq).

For oligomerization: To a stirred solution of compound **4** (1eq) in dry acetonitrile [from 1 to 100 mM] at room temperature under a nitrogen atmosphere was added copper (II) acetate (0,2eq).

After the reaction was complete, the solvent was evaporated under reduced pressure. The crude was diluted in AcOEt and the organic layer was washed with aq. EDTA (aprox. 1eq related to the copper), brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the compound was isolated and purified by silica gel chromatography using the corresponding mobile phase.

(1*S*, 6*S*)-2-bromide-6-[((2,3dimethylbutan-2-yl)dimethylsilyl)oxy]cyclohexa-2,4-diene-1-yl acetate. 5

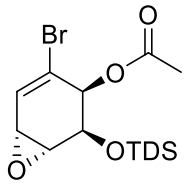


5

Compound **1** (1eq) was dissolved in anh. DMF (1g/mL) under a nitrogen atmosphere. The reaction mixture was stirred and cooled to 0°C, and then imidazole (2.1eq) and dimethylthexylsilyl chloride (TDSCl, 1.1eq) were added. After complete consumption of the starting material, the reaction mixture was diluted in Et_2O and the organic layer was successively washed with water, satd. aq.

$CuSO_4$, brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the silylated compound was isolated by silica gel column chromatograph using Hex(99)/AcOEt(1) as mobile phase yielding compound **5** as a colorless oil (80%): $[\alpha]^{21}_D$ -38.4 (*c* 1.5, CH_2Cl_2); IR (film) ν: 3414 (broad), 2959, 1748, 1254, 1227, 1122, 1101 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.47 (dd, *J* = 4.0, 2.5 Hz, 1H), 5.81 (d, *J* = 3.6 Hz, 2H), 5.54 (d, *J* = 6.6 Hz, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 2.08 (s, 3H), 1.60 (dt, *J* = 13.6, 6.8 Hz, 1H), 0.87 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 170.1, 166.5, 131.9, 129.8, 122.4, 120.3, 72.2, 69.8, 34.2, 25.0, 22.3, 21.0, 20.3, 18.7, -2.9, -3.0. HRMS(ESI+) calculated for $C_{16}H_{27}BrO_3Si$ $[M+H]^+$ 397.08051, experimental value 397.08011.

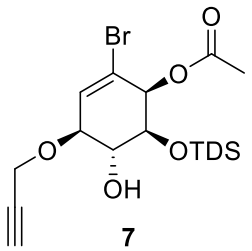
(1*R*, 2*S*, 3*R*, 6*R*)-4-bromo-2-[((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy]-7-oxabicyclo[4.1.0]hept-4-en-3-yl acetate. 6



6

This compound was synthesized following the general procedure for epoxidation. The product was purified by column chromatography using Hex(8)/AcOEt(2) as mobile phase yielding compound **6** (85%) as a colorless oil: $[\alpha]^{21}_D$ +46.5 (*c* 1.5, CH_2Cl_2); IR (film) ν: 3414 (broad), 2959, 2903, 1747, 1628, 1369 1252, 1225, 1125 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.50 (dd, *J* = 4.1, 2.3 Hz, 1H), 5.42 (dd, *J* = 4.3, 2.3 Hz, 1H), 4.60 – 4.40 (m, 1H), 3.52 – 3.26 (m, 2H), 2.16 (s, 3H), 1.65 – 1.55 (m, 1H), 0.88 (d, *J* = 3.0 Hz, 3H), 0.87 (d, *J* = 3.0 Hz, 3H), 0.84 (s, 6H), 0.15 (s, 3H), 0.13 (s, 3H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 169.7, 126.6, 126.5, 69.7, 67.0, 53.4, 48.6, 34.3,24.9, 20.9, 20.4, 20.1, 18.7, 18.5, -2.7, -2.9. HRMS(ESI+) calculated for $C_{16}H_{27}BrO_4Si$ $[M+H]^+$ 391.09347, experimental value 391.09277.

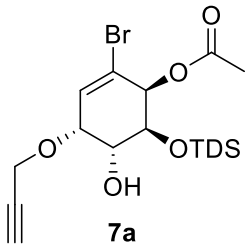
(1*S*, 4*S*, 5*R*, 6*S*)-2-bromo-6[((2,3dimethylbutan-2-yl)dimethylsilyl)oxy]-5-hydroxy-4-(2-propynyloxy)cyclohex-2-en-1-yl acetate. 7



7

Epoxide **6** (74.2mg, 0.18mmol) was dissolved in propargyl alcohol (0,5mL) under nitrogen atmosphere and catalytic amoung of anh. $ZnCl_2$ was added at 0°C. After the reaction was complete the reaction mixture was diluted with AcOEt and washed with water and brine, and then dried over anhydrous Na_2SO_4. The crude was purified by silica gel column chromatography using Hex(95)/AcOEt(5) yielding compound **7** (41%) as a colorless oil: $[\alpha]^{21}_D$ -116.9 (*c* 1.6, CH_2Cl_2); IR (film) ν: 3468 (broad), 3306, 2959,2868, 1748, 1638, 1371, 1327, 1254, 1227, 1082 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.29 (d, *J* = 2.6 Hz, 1H), 5.69 (d, *J* = 4.1 Hz, 1H), 4.43 (d, *J* = 2.4 Hz, 2H), 4.03 (dd, *J* = 7.5, 2.7 Hz, 1H), 3.90 (ddd, *J* = 9.6, 7.5, 1.8 Hz, 1H), 3.72 (dd, *J* = 10.2, 4.2 Hz, 1H), 2.51 (t, *J* = 2.4 Hz, 1H), 2.37 (d, *J* = 2.0 Hz, 1H), 2.10 (s, 3H), 1.62 (p, *J* = 6.8 Hz, 1H), 0.90 (d, *J* = 3.7 Hz, 3H), 0.87 (s, 3H), 0.85 (s, 3H), 0.85 (s, 3H), 0.19 (s, 3H), 0.18 (s, 3H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 169.9, 133.8, 119.5, 79.8, 78.9, 75.1, 73.1, 72.1, 71.1, 58.2, 34.2, 25.1, 20.9, 20.3, 18.7, -2.5, -2.8. HRMS(ESI+) calculated for $C_{19}H_{31}BrO_5Si$ $[M+H]^+$ 447.11969, experimental value 447.11955.

(1S,4R,5R,6S)-2-bromo-6-(((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy)-5-hydroxy-4-(2-propynyloxy)cyclohex-2-en-1-yl acetate. 7a See Table S1

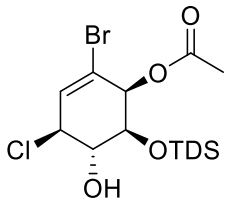


7a

This compound was synthesized following procedure shown for compound **7**. The crude was purified by silica gel column chromatography using Hex(95)/AcOEt(5) yielding compound **7a** (6%) as a colorless oil: ^1H NMR (400 MHz, Chloroform-*d*) δ 6.26 (d, *J* = 3.7 Hz, 1H), 5.75 (d, *J* = 3.7 Hz, 1H), 4.36 (s, 1H), 4.34 – 4.30 (m, 2H), 4.26 (dd, *J* = 7.2, 3.9 Hz, 1H), 4.08 (dd, *J* = 7.1,

3.5 Hz, 1H), 2.49 (t, *J* = 2.2 Hz, 1H), 2.38 (d, *J* = 3.3 Hz, 1H), 2.13 (s, 3H), 1.62 – 1.51 (m, 1H), 0.89 (d, *J* = 2.0 Hz, 3H), 0.87 (d, *J* = 2.0 Hz, 3H), 0.84 (s, 6H), 0.13 (s, 3H), 0.12 (s, 3H). $^{13}C\{^{1}H\}$NMR (100 MHz, Chloroform-*d*) δ 169.9, 129.9, 123.2, 79.1, 75.4, 74.0, 71.7, 70.1, 69.4, 57.3, 34.2, 24.9, 21.0, 20.3, 20.1, 18.6, 18.5, -2.9.

(1S,4S,5S,6S)-2-bromo-4-chloro-6-(((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy)-5-hydroxycyclohex-2-en-1-yl acetate. 7b See Table S1

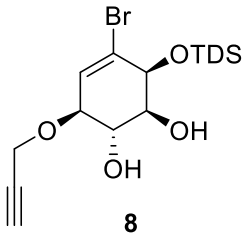


7b

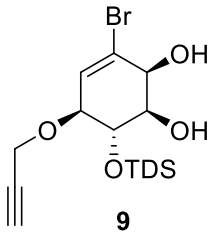
This compound was synthesized following procedure shown for compound **7**. The crude was purified by silica gel column chromatography using Hex(95)/AcOEt(5) yielding compound **7b** (3,5%) as a colorless oil: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.24 (d, *J* = 2.5 Hz, 1H), 5.72 (d, *J* = 4.0 Hz, 1H), 4.34 (dd, *J* = 8.1, 2.5 Hz, 1H), 4.04 – 3.90 (m, 1H), 3.74 (dd, *J* = 10.2, 4.1 Hz, 1H), 2.50 (d, *J* = 2.2 Hz, 1H), 2.12 (s, 3H), 1.57 – 1.49 (m, 1H), 0.87 (s, 6H), 0.84 (d, *J* = 1.6 Hz, 6H), 0.18 (s, 3H), 0.17 (s, 3H). $^{13}C\{^{1}H\}$NMR (100 MHz, Chloroform-*d*) δ 169.7, 133.5, 119.9, 73.1, 72.9, 71.7, 59.7, 34.0, 25.0, 20.2, 20.1, 18.5, -2.7, -2.9.

(1*S*, 2*S*, 3*S*, 6*S*)-4-bromo-3-[((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy]-6-(2-propynyloxy)cyclohex-4-ene-1,2-diol. 8, and

(1*S*, 2*S*, 5*S*, 6*S*)-3-bromo-6-[((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy]-5-(2-propynyloxy)cyclohex-3-ene-1,2-diol. 9.



8

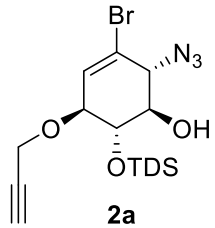


9

These compounds were sinthesized following the general procedure for acetate deprotection. The crude was purified by column chromatography using Hex(8)/AcOEt(2) as mobile phase yielding compounds **8** (29%) and **9** (29%) as colorless oils:

8: $[\alpha]^{21}_D$ -24.9 (*c* 0.3, CH_2Cl_2); IR (film) ν: 3435 (broad), 3312, 2959, 2116, 1643, 1254, 1121, 1078 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.17 (d, *J* = 2.6 Hz, 1H), 4.36 (dt, *J* = 6.1, 3.0 Hz, 3H), 3.99 (dd, *J* = 7.4, 2.6 Hz, 1H), 3.85 (dd, *J* = 10.2, 7.5 Hz, 1H), 3.55 (td, *J* = 10.2, 3.8 Hz, 1H), 2.89 (s, 1H), 2.50 (t, *J* = 2.4 Hz, 1H), 2.39 (d, *J* = 8.2 Hz, 1H), 1.65 (p, *J* = 6.8 Hz, 1H), 0.92 – 0.84 (m, 12H), 0.30 (s, 3H), 0.23 (s, 3H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 131.4, 123.9, 79.8, 79.7, 75.1, 74.6, 71.9, 71.5, 57.6, 34.2, 25.4, 20.7, 20.3, 18.8, 18.6, -1.7, -2.3. HRMS(ESI+) calculated for $C_{17}H_{29}BrO_4Si$ $[M+K]^+$ 443.06500, experimental value 443.06526.
9: $[\alpha]^{21}_D$ -13.3 (*c* 0.3, CH_2Cl_2); IR (film) ν: 3435 (broad), 2959, 1645, 1254, 1076 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.31 (d, *J* = 3.6 Hz, 1H), 4.38 – 4.32 (m, 1H), 4.29 – 4.20 (m, 2H), 4.04 (dd, *J* = 7.3, 5.1 Hz, 1H), 3.96 – 3.89 (m, 1H), 3.84 – 3.76 (m, 1H), 2.98 (d, *J* = 6.3 Hz, 2H), 2.50 (t, *J* = 2.4 Hz, 1H), 1.64 (dq, *J* = 13.7, 6.9 Hz, 1H), 0.89 (d, *J* = 2.7 Hz, 3H), 0.87 (d, *J* = 2.7 Hz, 3H), 0.85 (s, 3H), 0.85 (s, 3H), 0.18 (s, 3H), 0.16 (s, 3H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 128.4, 127.4, 78.8, 78.1, 75.6, 71.4, 71.1, 69.9 57.00, 34.1, 24.9, 20.4, 20.1, 18.7, 18.5, -2.5, -2.9. HRMS(ESI+) calculated for $C_{17}H_{29}BrO_4Si$ $[M+K]^+$ 443.06500, experimental value 443.06529.

(1*R*, 2*R*, 5*S*, 6*S*)-2-azido-3-bromo-6-[((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy]-5-(2-propynyloxy)cyclohex-3-ene-1-ol. 2a.

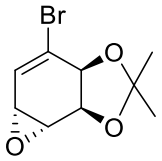


2a

This compound was synthesized following the general procedure for azide formation. The mesylated intermediate was suitable for use in the next step without further purification; however an analytical sample was obtained to calculate the isolated yield, which was purified using silica gel and Hex(9)/AcOEt(1) as mobile phase (93%): ^1H NMR (400 MHz, Chloroform-*d*) δ 6.19 (d, *J* = 2.8 Hz, 1H), 4.81 (dd, *J* = 10.6, 7.7 Hz, 1H), 4.39 (d, *J* = 3.6 Hz, 1H), 4.38 – 4.25 (m, 2H), 4.23 (dd, *J* = 7.7, 2.8 Hz, 1H), 3.72 (td, *J* = 10.5, 3.6 Hz, 1H), 3.16 (s, 3H), 2.59 (d, *J* = 10.5 Hz, 1H), 2.51 (t, *J* = 2.4 Hz, 1H), 1.66 (p, *J* = 6.9 Hz, 1H), 0.94 – 0.88 (m, 12H), 0.30 (s, 3H), 0.23 (s, 3H). After azidation the produc was purified by column chromatography using Hex(9)/AcOEt(1) as mobile phase yielding compound **2a** as a colorless oil (30%): ^1H NMR (400 MHz, Chloroform-*d*)

δ 6.30 (t, *J* = 2.0 Hz, 1H), 4.24 (dd, *J* = 2.4, 1.0 Hz, 2H), 4.06 (dd, *J* = 7.1, 1.9 Hz, 1H), 3.95 (dt, *J* = 7.2, 2.7 Hz, 1H), 3.76 – 3.56 (m, 2H), 2.69 (d, *J* = 2.5 Hz, 1H), 2.48 (t, *J* = 2.4 Hz, 1H), 1.66 (p, *J* = 6.9 Hz, 1H), 0.92 – 0.89 (m, 6H), 0.89 – 0.86 (m, 6H), 0.20 (s, 3H), 0.18 (s, 3H). $^{13}C\{^{1}H\}$NMR (100 MHz, Chloroform-*d*) δ 130.8, 121.4, 79.1, 78.8, 75.6, 74.8, 74.2, 67.9, 57.4, 34.0, 25.1, 20.6, 20.1, 18.78, 18.4, -2.1, -2.8.

(3a*S*, 5a*R*,6a*R*,6b*S*)-4-bromo-2,2-dimethyl-3a,5a,6a,6b-tetrahydrooxireno [2',3':3,4] benzo[1,2-*d*][1,3]dioxole. 10 [2]



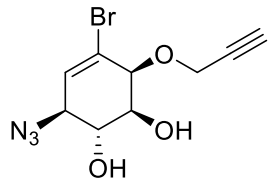
10

Compound **1** (1eq, 3.43g) was protected as its acetonide by dissolution in a minimal amount of dimethoxypropane (20mL) under nitrogen atmosphere and adding a catalytic amount of *p*-tolenesulfonic acid at room temperature. After total consumption of the starting material, a few milligrams of powdered sodium bicarbonate was added and the solvent was evaporated under reduce pressure, then the crude was diluted with AcOEt and washed with satd. aq. $NaHCO_3$, brine and then dried over anhydrous Na_2SO_4. The crude was purified by silica gel column chromatography using Hex(9)/AcOEt(1) yielding the corresponding acetonide, (1*S*, 2*S*)-3-bromo-1,2-(isopropylidenedioxy)-3,5-cyclohexadiene,[2] (80%) as a colorless oil: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.36 (d, *J* = 6.1 Hz, 1H), 6.03 – 5.94 (m, 1H), 5.89 (dd, *J* = 9.6, 6.1 Hz, 1H), 4.74 (d, *J* = 1.9 Hz, 2H)1.45 (s, 3H), 1.44 – 1.43 (s, 3H). $^{13}C\{^{1}H\}$NMR (100 MHz, Chloroform-*d*) δ 125.8, 124.6, 124.4, 124.1, 106.2, 75.9, 72.5, 26.7, 24.9.

The acetonide was epoxidated following the general procedure for epoxidation. The product was purified by column chromatography using Hex(9)/AcOEt(1) as mobile phase yielding compound **10** (85%) as a white solid: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.48 (dd, *J* = 4.4, 1.1 Hz, 1H), 4.87 (dt, *J* = 6.8, 1.3 Hz, 1H), 4.42 (d, *J* = 6.8 Hz, 1H), 3.59 (dd, *J* = 3.6, 1.9 Hz, 1H), 3.39 – 3.22 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H). $^{13}C\{^{1}H\}$NMR (100 MHz, Chloroform-*d*) δ 129.9, 126.5, 111.4, 74.1, 72.6, 49.5, 48.3, 27.5, 25.9.

[2] Hudlicky, T.; Price, J.D.; Rulin, F.; Tsunoda, T., *J. Am. Chem. Soc.* **1990**, 112, 9439–9440.

(1*R*, 2*S*,3*S*,6*S*)-6-azide-4-bromide-3-(2-propynyloxy)cyclohex-4-ene-1,2-diol. 3



3

Compound **10** (1eq, 750mg) was dissolved in tetrahydrofuran (15mL) at room temperature, then ethanol (7,5mL) is added while stirring and sodium azide (3eq, 376mg) and ammonium chloride (2.2eq, 227mg) were dissolved in distilled water and added to the reaction, which was then heated to reflux. After consumption of the starting material, the organic solvents were evaporated under reduced pressure and the aqueous phase was extracted with AcOEt (3x20mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the product was purified by column chromatography using a gradient of Hex(9)/AcOEt(1) to Hex(8)/AcOEt(2) as mobile phase yielding the hydroxy azide (1*R*,2*S*,3*S*,6*S*)-6-azido-4-bromo-2,3-(isopropylidenedioxy)cyclohex-4-ene-1-ol[3] (95%) as a white solid: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.12 (d, *J* = 2.1 Hz, 1H), 4.69 (dd, *J* = 6.3, 1.0 Hz, 1H), 4.17 (dd, *J* = 8.7, 6.4 Hz, 1H), 3.95 – 3.90 (m, 1H), 3.71 (t, *J* = 8.7 Hz, 1H), 3.01 (s, 1H), 1.56 (s, 3H), 1.44 (s, 3H). ^{13}C{^{1}H}NMR (100 MHz, Chloroform-*d*) δ 130.9, 120.4, 111.2, 77.8, 72.8, 62.2, 28.1, 25.9. .

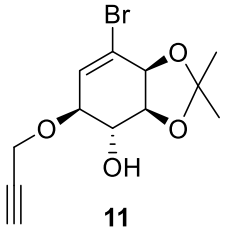
The cleavage of the acetonide group was done according to the general procedure for acetonide hydrolysis. The resulting triol was purified by column chromatography using Hex(4)/AcOEt(6) as mobile phase yielding (1*R*, 2*S*,3*S*,6*S*)-6-azido-4-bromocyclohex-4-ene-1,2,3-triol (80%) as a white solid: ^{1}H NMR (400 MHz, Methanol-*d*4) δ 6.01 (d, *J* = 2.5 Hz, 1H), 4.22 (d, *J* = 4.2 Hz, 1H), 3.83 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 3.73 (dd, *J* = 10.3, 8.0 Hz, 1H), 3.57 (dd, *J* = 10.3, 4.3 Hz, 1H). ^{13}C{^{1}H}NMR (100 MHz, Methanol-*d*4) δ 130.6, 126.6, 74.6, 72.8, 71.5, 66.1

This azido triol (1eq, 749 mg) was dissolved in anhydrous DMF (3mL) and stirred under nitrogen atmosphere, then it was cooled to 0°C and sodium hydride (1,1eq, 131mg) was added over a period of 15 min, and after that time propargyl bromide (1,1eq, 293mg) was added. After consumption of the strating material, the reaction mixture was diluted in diethyl ether and the organic layer was washed with water, brine and dried over Na_2SO_4 anhydrous. The solvent was removed under reduced pressure and the compound was isolated by silica gel chromatography using a gradient of

[3] Pitzer, K.; Hudlicky, T., *Synlett* **1995**; 803-805

Hex(8)/AcOEt(2) to Hex(6)/AcOEt(4) as mobile phase yielding compound **3** (60%) as a white solid: $[\alpha]^{21}_{D}$ -33.3 (*c* 0.79, CH_2Cl_2); IR (film) ν: 3414 (broad), 2108, 1641, 1252, 1107, 1088, 1051 cm^{-1}. ^1H NMR (400 MHz, Methanol-*d*4) δ 6.04 (d, *J* = 2.5 Hz, 1H), 4.53 (d, *J* = 2.4 Hz, 2H), 4.28 (d, *J* = 3.7 Hz, 1H), 3.80 (dd, *J* = 7.6, 2.5 Hz, 1H), 3.74 (dd, *J* = 10.1, 7.6 Hz, 1H), 3.68 (dd, *J* = 10.1, 3.7 Hz, 1H), 2.89 (t, *J* = 2.4 Hz, 1H). $^{13}C\{^1H\}$NMR (100 MHz, Methanol-*d*4) δ 131.7, 123.7, 81.1, 80.6, 76.6, 73.4, 71.8, 66.2, 61.1. m.p.: (78-80)°C. HRMS.(ESI+) calculated for $C_9H_{10}BrN_3O_3$ $[M+H]^+$ 287.99783, experimental value 287.99650.

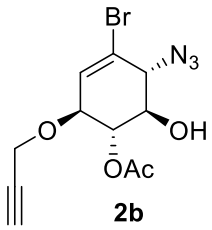
(1*R*,2*S*,3*S*,6*S*)-6-(2-propynyloxy)-4-bromo-2,3-(isopropylidenedioxy)cyclohex-4-ene-1-ol. 11



11

Compound **10** (1eq, 1,16g) was dissolved in dry CH_2Cl_2 [0,2M] and stirred under nitrogen atmosphere at room temperature, then propargylic alcohol (2eq, 526 mg) and a catalytic amount of ytterbium triflate were added and the reaction mixture was heated to reflux. After consumption of the strating material, the solvent was removed under reduced pressure and the compound was isolated and purified by silica gel chromatography using a gradient of Hex(9)/AcOEt(1) to Hex(8)/AcOEt(2) as mobile phase, yielding compound **11** (60%) as a white solid: $[\alpha]^{21}_{D}$ +26.3 (*c* 1.4, CH_2Cl_2); IR (film) ν: 3437 (broad), 3298, 2990, 2936, 2874, 1647, 1381, 1219, 1070 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.30 (d, *J* = 1.7 Hz, 1H), 4.69 (d, *J* = 6.5 Hz, 1H), 4.48 – 4.26 (m, 2H), 4.18 (dd, *J* = 9.0, 6.5 Hz, 1H), 4.01 (dt, *J* = 8.4, 1.5 Hz, 1H), 3.71 (t, *J* = 8.7 Hz, 1H), 2.70 (s, 1H), 2.51 (t, *J* = 2.4 Hz, 1H), 1.55 (s, 3H), 1.43 (s, 3H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 132.7, 118.9, 111.1, 79.3, 78.1, 77.5, 77.1, 75.4, 72.8, 57.8, 28.1, 25.9. m.p.: (81-83)°C. HRMS(ESI+) calculated for $C_{12}H_{15}BrO_4$ $[M+Na]^+$ 325.00459, experimental value 325.00464.

(1*S*,2*R*,3*R*,6*S*)-3-azide-4-bromo-2-hydroxy-6-(2-propynyloxy)cyclohex-4-en-1-yl acetate. 2b



2b

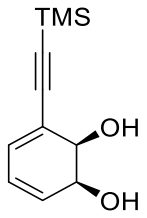
Alcohol **11** was acetylated following the general procedure for acetylation of alcohols. The product was purified by column chromatography using Hex(8)/AcOEt(2) as mobile phase yielding (1*R*,2*S*,3*S*,6*S*)-6-(2-propynyloxy)-4-bromo-2,3-(isopropylidenedioxy)cyclohex-4-ene-1-yl acetate (95%) as a white solid: $[\alpha]^{21}_D$ +57.1 (*c* 1.1, CH_2Cl_2); IR (film) ν: 3431 (broad), 3292, 2986, 2935, 2872, 1746, 1647, 1375, 1229, 1074 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.33 (d, *J* = 2.4 Hz, 1H), 5.20 (t, *J* = 8.0 Hz, 1H), 4.67 (d, *J* = 6.4 Hz, 1H), 4.31 – 4.20 (m, 3H), 4.13 (ddd, *J* = 7.7, 2.4, 1.1 Hz, 1H), 2.46 (t, *J* = 2.4 Hz, 1H), 2.14 (s, 3H), 1.55 (s, 3H), 1.41 (s, 3H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 169.9, 132.2, 120.1, 111.5, 79.1, 77.1, 75.5, 75.4, 75.1, 71.2, 57.2, 27.7, 26.4, 21.1. m.p.: (102-104)°C. HRMS.(ESI+) calculated for $C_{14}H_{17}BrO_5$ $[M+H]^+$ 345.03321, experimental value 345.03255.

Then the acetonide was cleaved following the general procedure for acetonide hydrolysis. The product was purified by column chromatography using Hex(1)/AcOEt(1) as mobile phase yielding (1*S*,2*R*,3*S*,6*S*)-6-(2-propynyloxy)-4-bromo-2,3-dihydroxycyclohex-4-ene-1-yl acetate (80%) as a colorless oil: $[\alpha]^{21}_D$ +26.4 (*c* 1.2, CH_2Cl_2); IR (film) ν: 3387 (broad), 3289, 2916, 1736, 1638, 1371, 1335, 1244, 1078 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.24 (d, *J* = 2.7 Hz, 1H), 5.22 (dd, *J* = 10.1, 7.3 Hz, 1H), 4.35 (d, *J* = 4.1 Hz, 1H), 4.26 (d, *J* = 2.3 Hz, 2H), 4.18 (dd, *J* = 7.2, 2.7 Hz, 1H), 3.77 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.49 (t, *J* = 2.3 Hz, 1H), 2.17 (s, 3H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 171.7, 130.5, 124.6, 79.1, 76.4, 75.3, 72.8, 71.8, 69.9, 57.2, 21.2. HRMS.(ESI+) calculated for $C_{11}H_{13}BrO_5$ $[M+H]^+$ 305.00191, experimental value 305.00152.

Finally, the allylic azide was obtained following the general procedure for azide formation via mesyl substitution. The product was purified by column chromatography using Hex(9)/AcOEt(1) as mobile phase yielding compound **2b** (88% 2 steps) as a colorless oil: $[\alpha]^{21}_D$ -14.7 (*c* 1.2, CH_2Cl_2); IR (film) ν: 3443 (broad), 3296, 2110, 1751, 1730, 1638, 1227, 1051 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.27 (s, 1H), 5.13 (dd, *J* = 10.6, 8.0 Hz, 1H), 4.45 – 4.29 (m, 2H), 4.19 – 4.13 (m, 2H), 3.81 (ddd, *J* = 10.9, 7.4, 3.6 Hz, 1H), 2.63 (d, *J* = 4.6 Hz, 1H), 2.52 (t, *J* = 2.4 Hz,

1H), 2.19 (s, 3H). $^{13}C\{^{1}H\}$NMR (100 MHz, Chloroform-*d*) δ 170.6, 131.8, 120.9, 79.3, 78.9, 75.8, 73.6, 72.8, 66.5, 58.3, 21.0. HRMS (ESI+) calculated for $C_{11}H_{12}BrN_3O_4$ $[M+H]^+$ 330.00839, experimental value 330.00837.

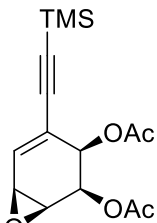
(1*S*,2*R*)-3-((trimethylsilyl)ethynyl)-3-cyclohexa-3,5-diene-1,2-diol. 12



12

Compound **1** (1eq, 2.53g) was dissolved in anhydrous DMF (1g/mL) and stirred under nitrogen atmosphere at room temperature, ethynyltrimethylsilane (2eq, 2.59g) and diethylamine (2.4eq, 2.34g) were added, then copper (I) iodide (0.04eq, 0.10g) and *tetrakis*(triphenylphosphine) palladium (0) were added, and the reaction mixture was warmed to (30-35)°C. After consumption of the strating material, the reaction mixture was diluted with AcOEt and washed with satd. aq.$CuSO_4$, brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the compound was purified by silica gel chromatography using a gradient of Hex(8)/AcOEt(2) to Hex(1)/AcOEt(1) as mobile phase yielding compound **12** (86%) as a white solid: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.33 (ddd, *J* = 4.2, 2.5, 1.2 Hz, 1H), 6.08 – 6.00 (m, 2H), 4.34 (ddd, *J* = 7.4, 6.1, 2.5 Hz, 1H), 4.20 (td, *J* = 6.1, 1.2 Hz, 1H), 2.40 (t, *J* = 6.5 Hz, 2H), 0.22 (s, 9H). $^{13}C\{^{1}H\}$NMR (100 MHz, Chloroform-*d*) δ 130.8, 130.6, 124.9, 123.1, 103.1, 100.9, 69.2, 67.1.

(1*S*,2*R*,3*R*,6*S*)-4-((trimethylsilyl)ethynyl)-7-oxabicyclo[4.1.0]hept-4-ene-2,3-diyl diacetate. 13



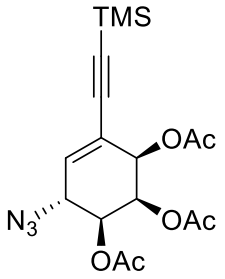
13

This compound was synthesized following the general procedure for epoxidation of olefins (at -5°C) and acetylation. The product was purified by column chromatography using a gradient of

Hex(95)/AcOEt(5) to Hex(9)/AcOEt(1) as mobile phase yielding compound **13** (66% 2 steps) as a colorless oil: $[\alpha]^{21}_D$ -205.4 (*c* 1.2, CH_2Cl_2); IR (film) ν: 3462 (broad), 2961, 1748, 1626, 1369, 1238, 1219, 1036 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.54 (d, *J* = 4.1 Hz, 1H), 5.71 (dd, *J* = 5.3, 2.0 Hz, 1H), 5.29 (dt, *J* = 5.3, 1.1 Hz, 1H), 3.61 – 3.54 (m, 1H), 3.47 (t, *J* = 4.2 Hz, 1H), 2.13 (d, *J* = 0.9 Hz, 3H), 2.08 (d, *J* = 0.9 Hz, 3H), 0.14 (d, *J* = 0.9 Hz, 9H) $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 170.8, 170.2, 134.6, 124.4, 102.2, 98.8, 68.5, 66.7, 54.3, 47.8, 21.1, 20.8, -0.3. HRMS (ESI+) calculated for $C_{15}H_{20}O_5Si$ $[M+H]^+$ 309.11528, experimental value 309.11588.

[Note: The epoxydiol formed in the first step is unstable and decomposes rapidly, therefore it must be quickly protected and used.]

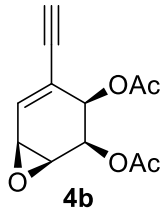
(1*S*,2*R*,3*R*,6*R*)-6-azido-4-((trimethylsilyl)ethynyl)cyclohex-4-ene-1,2,3-triyl triacetate. 4a



4a

Compound **13** (1eq, 547mg) was dissolved in anhydrous DMF (2mL) and stirred under nitrogen atmosphere at room temperature, then sodium azide (3eq, 345mg) and ammonium chloride (2,2eq, 208mg) were added. After consumption of the starting material, the reaction mixture was diluted in Et_2O and the organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture was used for acetylation using the general procedure for acetylation of alcohols. The product was purified by column chromatography using a gradient of Hex(9)/AcOEt(1) to Hex(8)/AcOEt(2) as mobile phase yielding compound **4a** (73%) as a colorless oil: $[\alpha]^{21}_D$ -147.5 (*c* 1.4, CH_2Cl_2); IR (film) ν: 3435 (broad), 2104, 1755, 1638, 1368, 1217, 1038, 847 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.09 (t, *J* = 2.4 Hz, 1H), 5.73 (dd, *J* = 6.0, 3.0 Hz, 1H), 5.61 (dd, *J* = 3.7, 2.0 Hz, 1H), 5.04 (dd, *J* = 9.0, 2.0 Hz, 1H), 4.41 (dt, *J* = 9.0, 2.8 Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 0.18 (s, 9H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 170.2, 169.8, 169.3, 132.2, 122.7, 99.8, 98.7, 71.5, 68.9, 67.3, 58.5, 20.9, 20.8, 20.6, -0.3. HRMS (ESI+) calculated for $C_{17}H_{23}N_3O_6Si$ $[M+H]^+$ 394.14289, experimental value 394.14217.

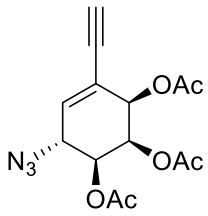
(1*S*,2*R*,3*R*,6*S*)-4-ethynyl-7-oxabicyclo[4.1.0]hept-4-ene-2,3-diyl diacetate. 4b



4b

Compound **13** (1eq, 1,07g) was dissolved in dry THF (17mL) and stirred under nitrogen atmosphere, then the reaction mixture was cooled to 0°C and tetrabutylammonium fluoride in THF (2.1eq, 1,9g) was added. After consumption of the starting material, the solvent was evaporated under reduce pressure. The crude was diluted in CH_2Cl_2, and the organic layer was washed with satd. aq. $NaHCO_3$, brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography using Hex(7)/AcOEt(3) as mobile phase yielding compound **4b** (80%) as a white solid: $[\alpha]^{21}_D$ -301.0 (*c* 1.2, CH_2Cl_2); IR (film) ν: 3414 (broad), 3277, 1744, 1371, 1063, 1030 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.65 – 6.62 (m, 1H), 5.75 (dd, *J* = 5.3, 2.1 Hz, 1H), 5.33 (dd, *J* = 5.3, 1.2 Hz, 1H), 3.62 (ddd, *J* = 4.2, 2.0, 1.3 Hz, 1H), 3.51 (t, *J* = 4.2 Hz, 1H), 3.04 (d, *J* = 0.4 Hz, 1H), 2.16 (s, 3H), 2.11 (s, 3H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 170.8, 170.1, 135.8, 123.4, 81.0, 80.6, 68.3, 66.3, 54.2, 47.5, 20.9, 20.7. m.p.: (106-108)°C. HRMS (ESI+) calculated for $C_{12}H_{12}O_5$ $[M+H]^+$ 237.07575, experimental value 237.07507.

(1*S*,2*R*,3*R*,6*R*)-6-azido-4-ethynylcyclohex-4-ene-1,2,3-triyl triacetate. 4

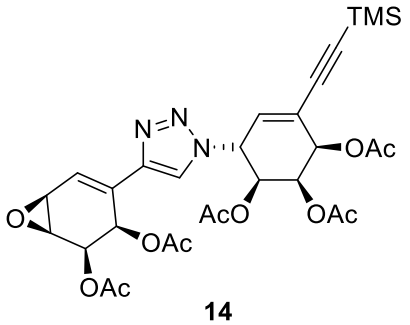


4

Compound **4a** (1eq, 680 mg) was dissolved in acetonitrile (9 mL) and stirred under nitrogen atmosphere at room temperature, then potassium fluoride (1eq, 100 mg) was added. After consumption of the starting material, water was added, and the organic solvent was evaporated under reduced pressure. The crude was diluted in EtOAc and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography using Hex(8)/AcOEt(2) as mobile phase

yielding compound **4** (96%) as a colorless oil: $[\alpha]^{21}_D$ -168.3 (*c* 0.9, CH_2Cl_2); IR (film) ν: 3416, 3292, 2104, 1753, 1630,1369, 1217, 1038 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.16 (t, *J* = 2.5 Hz, 1H), 5.89 – 5.68 (m, 1H), 5.62 (dd, *J* = 3.7, 2.1 Hz, 1H), 5.08 (dd, *J* = 9.0, 2.1 Hz, 1H), 4.60 – 4.38 (m, 1H), 2.99 (s, 1H), 2.14 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H) $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 170.0, 169.6, 169.4, 133.5, 121.6, 80.5, 78.7, 71.2, 68.7, 67.2, 58.3, 20.7, 20.7, 20.5. HRMS (ESI+) calculated for $C_{14}H_{15}N_3O_6$ $[M+H]^+$ 322.10336, experimental value 322.10310.

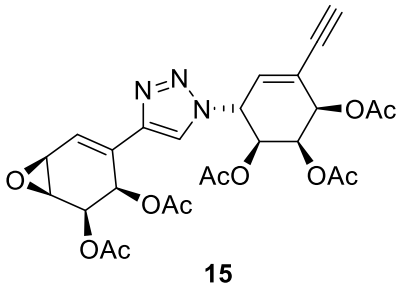
Alkyne-protected dimer, 14



14

The dimer was prepared following the general procedure for CuAAC dimerization using CuI, in acetonitrile at reflux for 6h. The product was purified by column chromatography using a gradient of Hex(9)/AcOEt(1) to Hex(6)/AcOEt(4) as mobile phase yielding the protected dimer as a white solid: ^1H NMR (400 MHz, Chloroform-*d*) δ 7.55 (s, 1H), 7.23 (t, *J* = 3.6 Hz, 1H), 6.10 (dt, *J* = 6.7, 3.7 Hz, 2H), 5.88 (dd, *J* = 5.9, 3.4 Hz, 1H), 5.70 – 5.66 (m, 1H), 5.64 – 5.56 (m, 1H), 5.41 (d, *J* = 5.4 Hz, 1H), 5.36 – 5.29 (m, 1H), 3.71 – 3.65 (m, 2H), 2.21 (s, 3H), 2.15 (d, *J* = 1.3 Hz, 6H), 2.09 (s, 3H), 1.90 (s, 3H), 0.19 (s, 9H). HRMS (ESI+) calculated for $C_{29}H_{35}N_3O_{11}Si$ $[M+H]^+$ 630.21192, experimental value 630.21164.

Alkyne deprotected dimer, 15



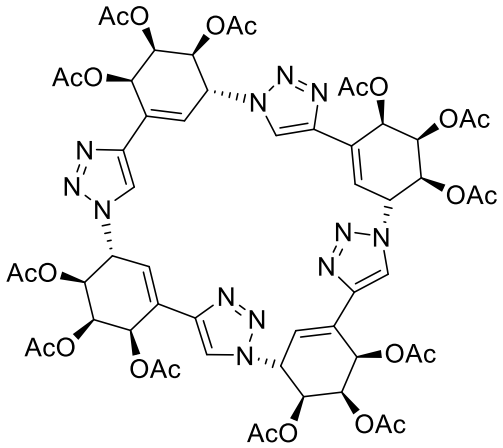
15

The dimer was prepared following the general procedure for CuAAC dimerization using $Cu(OAc)_2 \cdot H_2O$. The product was purified by column chromatography usingz a gradient of Hex(9)/AcOEt(1) to Hex(6)/AcOEt(4) as mobile phase yielding the protected dimer as a white solid: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (s, 1H), 7.25 – 7.19 (m, 1H), 6.20 (t, *J* = 2.5 Hz, 1H), 6.10 (dd, *J* = 5.3, 1.7 Hz, 1H), 5.88 (td, *J* = 3.5, 2.3 Hz, 1H), 5.69 (dd, *J* = 3.6, 2.0 Hz, 1H), 5.60 (dt, *J* = 9.5, 2.7 Hz, 1H), 5.41 (dd, *J* = 5.4, 0.9 Hz, 1H), 5.36 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.68 (d, *J* = 3.4 Hz, 2H), 3.04 (s, 1H), 2.21 (s, 3H), 2.15 (d, *J* = 0.7 Hz, 6H), 2.10 (s, 3H), 1.91 (s, 3H). ^{13}C{^{1}H}NMR (101 MHz, Chloroform-*d*) δ 171.7, 170.2, 170.0, 169.3, 168.9, 145.3, 131.9, 129.5, 125.1 122.83, 119.9, 81.4, 78.3, 70.2, 69.1, 68.8, 67.3, 64.5, 58.6, 53.8, 48.0, 21.0, 20.8, 20.5, 20.3. HRMS (ESI+) calculated for $C_{26}H_{27}N_3O_{11}$ $[M+H]^+$ 558.17239, experimental value 558.17268.

Oligomerization reactions

The reactions were performed according to the general procedure for CuAAC oligomerization using $Cu(OAc)_2 \cdot H_2O$.

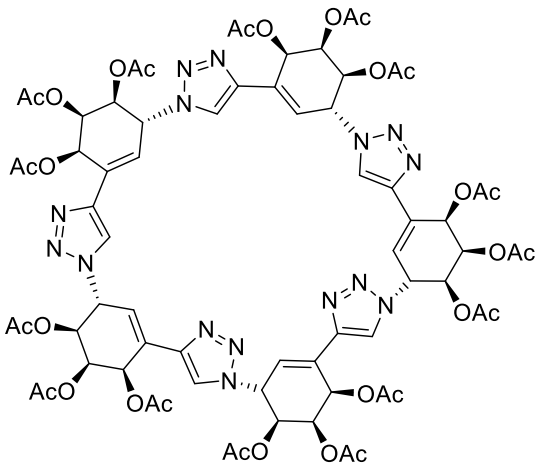
Cyclotetramer, 17



17

This compound was synthesized following the general procedure for CuAAC oligomerization. The product was purified by column chromatography using Toluene (6)/CH_2Cl_2 (4)/AcOEt (6)/CH_3CN (3) as mobile phase yielding compound **17** (19%) as a white solid: $[\alpha]^{21}_D$ -243,7 (*c* 1.1, CH_2Cl_2); IR (film) ν: 3412 (broad), 2075, 1638, 1375, 1221, 1036 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.56 (s, 1H), 6.20 (d, *J* = 2.8 Hz, 2H), 5.86 (dt, *J* = 9.0, 2.7 Hz, 1H), 5.64 (dd, *J* = 4.3, 2.1 Hz, 1H), 5.59 (dd, *J* = 9.2, 2.0 Hz, 1H), 2.21 (s, 3H), 2.00 (s, 3H), 1.93 (s, 3H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 170.4, 170.2, 169.7, 144.7, 130.1, 124.7, 119.7, 69.6, 68.7, 66.5, 58.9, 20.8, 20.6, 20.4. m.p.: 260°C (decomposition). HRMS (ESI+) calculated for $C_{56}H_{60}N_{12}O_{24}$ $[M+H]^+$ 1285.39161, experimental value 1285.39133.

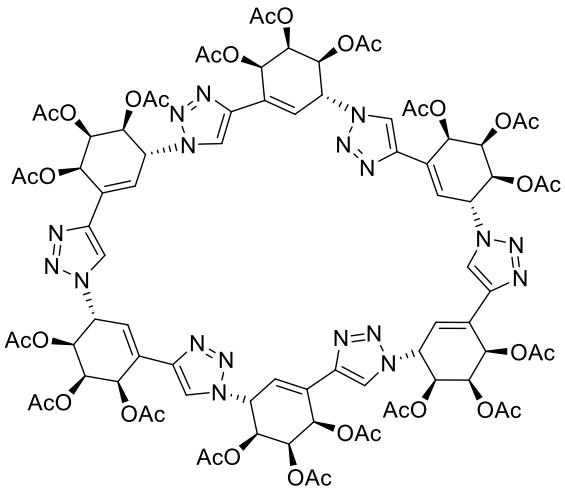
Cyclopentamer, 18



18

This compound was synthesized following the general procedure for CuAAC oligomerization. The product was purified by column chromatography using Toluene (6)/ CH_2Cl_2 (4)/AcOEt (6)/CH_3CN (3) as mobile phase yielding a mixture of compound **18** and **19** (47%). After several runs, an analytical sample of **18** could be obtained, allowing its characterization as a white solid: $[\alpha]^{21}_D$ -240.5 (0.3, CH_2Cl_2); IR (film) ν: 3420 (broad), 2093, 1645, 1373, 1219, 1034 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.58 (s, 1H), 6.48 (t, *J* = 2.2 Hz, 1H), 6.32 – 6.14 (m, 1H), 5.83 (dt, *J* = 9.0, 2.7 Hz, 1H), 5.74 (dd, *J* = 4.0, 2.1 Hz, 1H), 5.37 (dd, *J* = 9.0, 2.0 Hz, 1H), 2.20 (s, 3H), 2.07 (s, 3H), 1.98 (s, 3H). $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 170.2, 170.1, 169.2, 144.2, 130.1, 123.5, 120.1, 70.3, 68.8, 66.7, 58.9, 20.9, 20.7, 20.5. m.p.: 246°C (decomposition). HRMS (ESI+) calculated for $C_{70}H_{75}N_{15}O_{30}$ $[M+H]^+$ 1606.48770, experimental value 1606.48536.

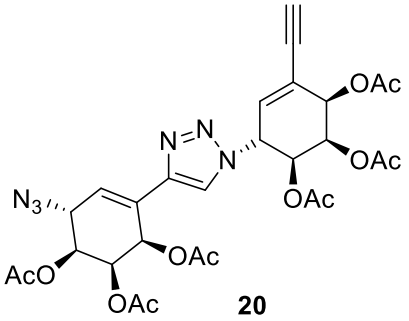
Cyclohexamer, 19



19

This compound was synthesized following the general procedure for CuAAC oligomerization. The product was purified by column chromatography using Toluene (6)/ CH_2Cl_2 (4)/AcOEt (6)/CH_3CN (3) as mobile phase yielding a mixture of **18** and **19** (47%). After several runs, an analytical sample of **19** could be obtained: white solid: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 (s, 1H), 6.26 (d, *J* = 3.2 Hz, 1H), 6.22 (d, *J* = 2.5 Hz, 1H), 5.85 (dt, *J* = 8.8, 2.7 Hz, 1H), 5.65 (dd, *J* = 4.1, 2.1 Hz, 1H), 5.54 (dd, *J* = 8.7, 2.1 Hz, 1H), 2.20 (s, 3H), 2.07 (s, 3H), 1.97 (s, 3H). HRMS (ESI+) calculated for $C_{84}H_{90}N_{18}O_{36}$ $[M+H]^+$ 1927.58379, experimental value 1927.58318.

Azido-alkyne dimer, 20

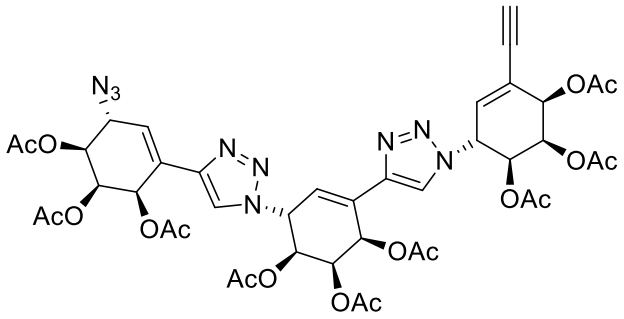


20

This compound was synthesized following the general procedure for CuAAC oligomerization. The product was purified by column chromatography using Toluene (6)/ CH_2Cl_2 (4)/AcOEt (6)/CH_3CN (3) as mobile phase yielding compound **20** (3%) as a white solid: $[\alpha]^{21}_D$ -248.1 (*c* 1.5, CH_2Cl_2); IR (film) ν: 3458, 3285, 2104, 1751, 1638, 1431, 1371, 1240, 1217, 1036, 951, 908, 737 cm^{-1}. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 (s, 1H), 6.66 (dd, *J* = 2.9, 1.8 Hz, 1H), 6.18 (t, *J* = 2.4 Hz,

1H), 6.10 (dt, *J* = 4.3, 2.1 Hz, 1H), 5.88 (td, *J* = 3.5, 2.4 Hz, 1H), 5.69 (dd, *J* = 3.7, 2.0 Hz, 1H), 5.68 – 5.62 (m, 2H), 5.37 (dd, *J* = 9.6, 2.0 Hz, 1H), 5.16 (dd, *J* = 7.6, 2.2 Hz, 1H), 4.56 (dt, *J* = 7.8, 2.7 Hz, 1H), 3.05 (s, 1H), 2.21 (s, 3H), 2.13 (s, 6H), 2.11 (s, 3H), 2.02 (s, 3H), 1.93 (s, 3H). $^{13}C\{^{1}H\}$NMR (100 MHz, Chloroform-*d*) δ 170.5, 170.2, 170.1, 169.9, 169.5, 169.1, 144.3, 132.0, 128.0, 125.1, 123.1, 119.5, 81.7, 78.4, 70.9, 70.1, 68.9, 68.4, 67.4, 66.2, 58.9, 58.5, 20.9, 20.9, 20.9, 20.8, 20.6, 20.5. m.p.: (112-114)°C. HRMS (ESI+) calculated for $C_{28}H_{30}N_6O_{12}$ $[M+H]^+$ 643.19945, experimental value 643.19640.

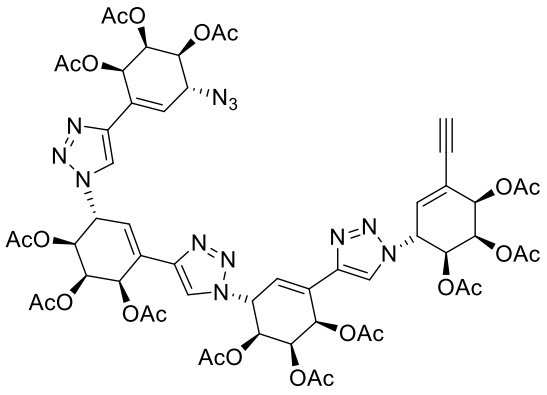
Linear Azido-alkyne trimer 21



21

This compound was synthesized following the general procedure for CuAAC oligomerization. The product was purified by column chromatography using Toluene (6)/ CH_2Cl_2 (4)/AcOEt (6)/CH_3CN (3) as mobile phase yielding compound **21** (3%) as a white solid: $[\alpha]^{21}_D$ -217.0 (*c* 1.0, CH_2Cl_2); IR (film) ν: 2939, 2104, 1753, 1431, 1371, 1240, 1217, 1036 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.45 (s, 1H), 7.44 (s, 1H), 6.68 – 6.56 (m, 2H), 6.22 (td, *J* = 3.5, 2.1 Hz, 1H), 6.18 (t, *J* = 2.5 Hz, 1H), 6.07 (dt, *J* = 4.3, 2.1 Hz, 1H), 5.87 (q, *J* = 3.2 Hz, 1H), 5.80 – 5.73 (m, 2H), 5.71 – 5.65 (m, 2H), 5.61 (dd, *J* = 4.2, 2.2 Hz, 1H), 5.43 (dd, *J* = 9.0, 2.1 Hz, 1H), 5.38 (dd, *J* = 9.6, 2.0 Hz, 1H), 5.13 (dd, *J* = 7.7, 2.2 Hz, 1H), 4.54 (dt, *J* = 7.7, 2.7 Hz, 1H), 3.04 (s, 1H), 2.20 (s, 3H), 2.19 (s, 3H), 2.11 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.94 (s, 3H), 1.93 (s, 3H). $^{13}C\{^{1}H\}$NMR (100 MHz, Chloroform-*d*) δ 170.6, 170.3, 170.2, 170.2, 170.0, 169.9, 169.5, 169.2, 169.1, 144.1, 143.7, 131.9, 129.1, 128.1, 124.9, 124.0, 123.2, 119.8, 81.7, 78.3, 70.9, 70.2, 70.0, 68.9, 68.8, 68.4, 67.37, 66.7, 66.2, 58.9, 58.9, 58.5, 20.9, 20.9, 20.9, 20.8, 20.7, 20.7, 20.6, 20.5, 20.5. m.p.: 200°C (decomposition). HRMS (ESI+) calculated for $C_{42}H_{45}N_9O_{18}$ $[M+H]^+$ 964.29553, experimental value 964.29392.

Linear Azido-alkyne tetramer 22

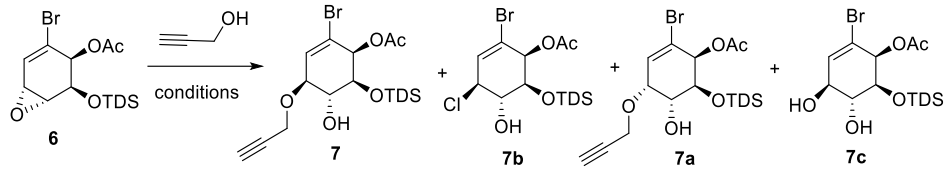


22

This compound was synthesized following the general procedure for CuAAC oligomerization. The product was purified by column chromatography using Toluene (6)/ CH_2Cl_2 (4)/AcOEt (6)/CH_3CN (3) as mobile phase yielding compound **22** (2%) as a white solid: $[\alpha]^{21}_D$ -120,6 (*c* 0.4, CH_2Cl_2); IR (film) ν: 3420 (broad), 1751, 1638, 1373, 1240, 1217, 1036 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.48 (s, 1H), 7.46 (s, 1H), 7.46 (s, 1H), 6.63 (q, *J* = 1.9 Hz, 3H), 6.23 (p, *J* = 3.8 Hz, 2H), 6.19 (t, *J* = 2.5 Hz, 1H), 6.08 (dt, *J* = 4.4, 2.2 Hz, 1H), 5.88 (q, *J* = 3.3 Hz, 1H), 5.82 – 5.74 (m, 4H), 5.71 – 5.66 (m, 2H), 5.63 (dd, *J* = 4.2, 2.2 Hz, 1H), 5.45 (dd, *J* = 4.4, 2.1 Hz, 1H), 5.43 (dd, *J* = 4.4, 2.1 Hz, 1H), 5.37 (dd, *J* = 9.5, 2.0 Hz, 1H), 5.15 (dd, *J* = 7.7, 2.2 Hz, 1H), 4.55 (dt, *J* = 7.8, 2.7 Hz, 1H), 3.05 (s, 1H), 2.21 (s, 3H), 2.21 – 2.18 (6H), 2.12 (6H), 2.11 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.97 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H) $^{13}C\{^1H\}$NMR (100 MHz, Chloroform-*d*) δ 170.4, 170.4, 170.3, 170.1, 170.1, 170.1, 169.9, 169.7, 169.4, 169.2, 169.1, 169.0, 144.1, 143.6, 143.5, 131.8, 129.2, 129.1, 128.0, 124.9, 123.8, 123.2, 119.9, 119.7, 81.6, 78.2, 77.2, 70.9, 70.1, 70.1, 69.9, 68.9, 68.7, 68.3, 67.3, 66.5, 66.1, 58.9, 58.92, 58.8, 58.4, 36.3, 24.7, 23.3, 20.8, 20.8, 20.7, 20.6, 20.5, 20.4, 20.4. m.p.: 220°C (decomposition). ^{1}HRMS (ESI+) calculated for $C_{56}H_{60}N_{12}O_{24}$ $[M+H]^+$ 1285.39161, experimental value 1285.38810.

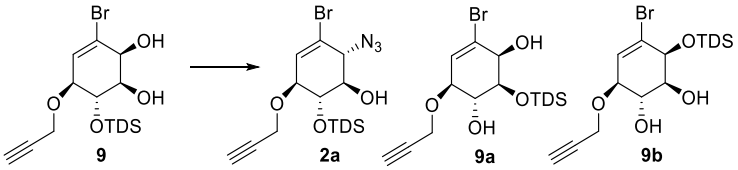
3. Tables of reaction optimization

Table S1. *Study of propargylation of vinyl epoxides.*



Entry	Catalyst	Temperature	Solvent	Time	Product, yield (%)			
					7	**7a**	**7b**	**7c**
1	$ZnCl_2$	RT	CH_2Cl_2	1 day	--	--	--	--
2	$ZnCl_2$	Reflux	CH_2Cl_2	1 day	35	traces	34	20
3	$ZnCl_2$	RT	--	17h	41	6	4	traces
4	Al_2O_3	Reflux	THF	2 days	18	--	6	--
5	$Yb(OTf)_3$	Reflux	CH_2Cl_2	50h	65	--	--	--

Table S2. *Study of azide functionalization.*



Entry	Reagent	Temperature	Solvent	Time	Product, yield (%)
1	DPPA, DIAD, PPh_3	From RT to reflux	THF	1 day	Decomposition, traces of **2a**
2	DPPA, DBU	RT	Toluene	1 day	Decomposition plus Recovery **9** = 12%
3	PPh_3, I_2, Imidazole, NaN_3	From RT to reflux	DMSO	4 h	Decomposition, traces of **2a**
4	1) MsCl, TEA, 2) NaN_3, NH_4Cl	RT RT	CH_2Cl_2 DMF	1 h 1 day	yield= 93% (mesylate) yield= 30% (**2a**)

Table S3. *Study of the desilylation of dimer **14**.*

Entry	Catalytic system	MR	Solvent	Result
1	$Cu(OAc)_2{\cdot}H_2O$	0,2 eq of each	CH_3CN (dry)	Only **15** found after 4h
2	CuI / KOAc			Mixture of **14** and **15** after 24h
3	CuI / KOAc / AcOH			Mixture of **14** and **15** after 24h

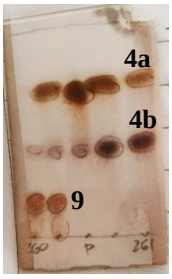
4. Figures

Figure S1. *Influence of light in the kinetics of $Cu(OAc)_2{\cdot}H_2O$ dimerization. A) reaction entry 17 t=40min; B) reaction entry 16 t=40min; C) TLC plate at t=40min. Mobile phase hexanes:ethyl acetate (6:4)*

A

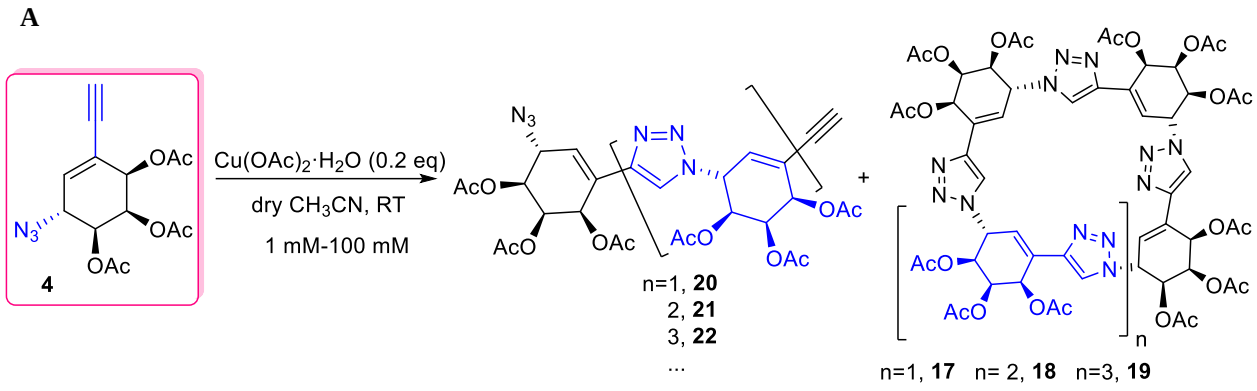
B

C



Entry # in Table 1: 16 17

Figure S2. *Products obtained in the Click oligomerization of monomer **4**.*
A) Scheme of the reaction; B) Stacked ^{1}H NMR traces of the products of Click oligomerization.



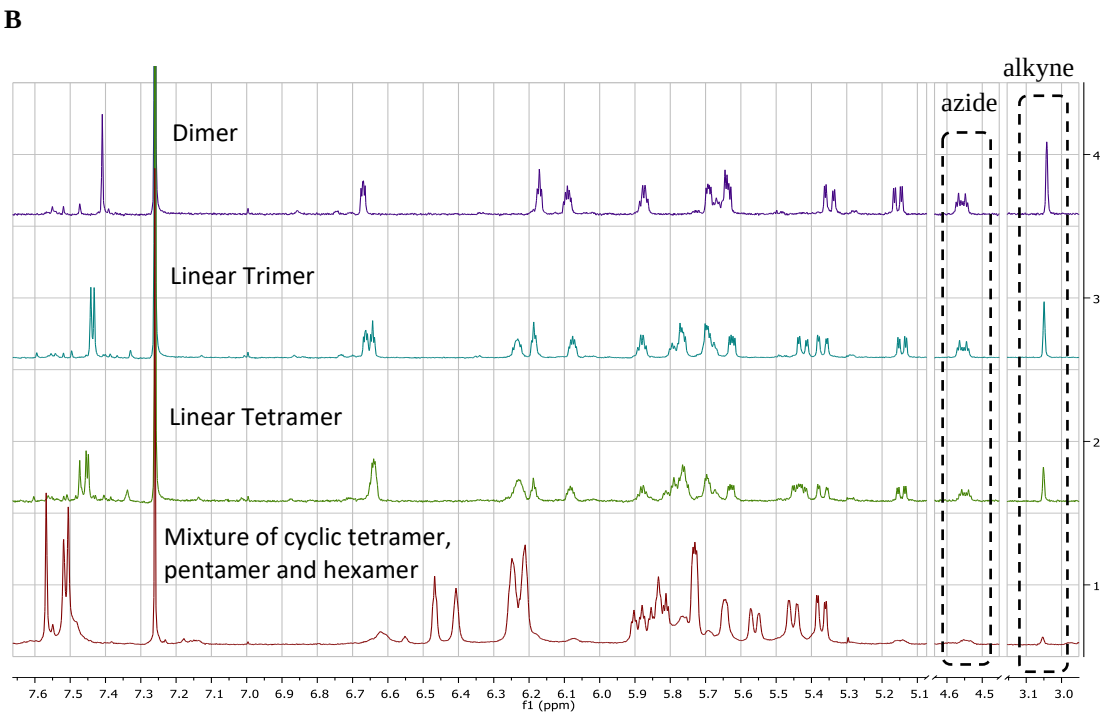
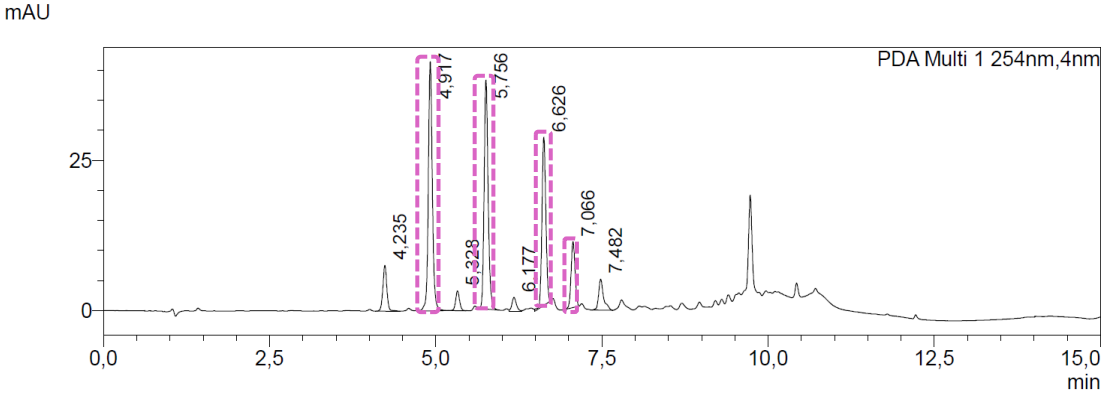
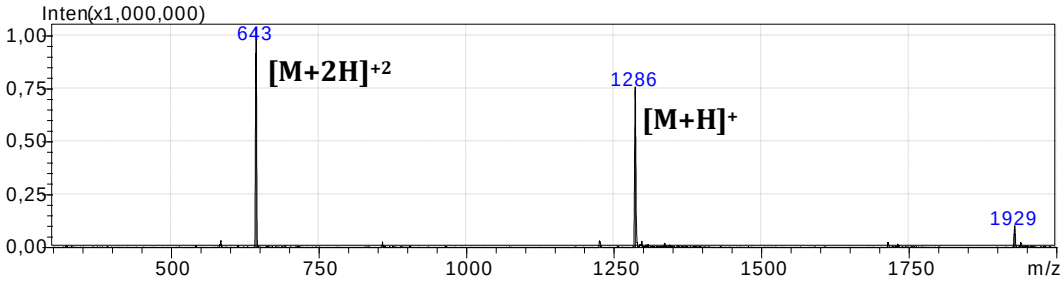


Figure S3. *Chromatograms and mass spectra of oligomers.*

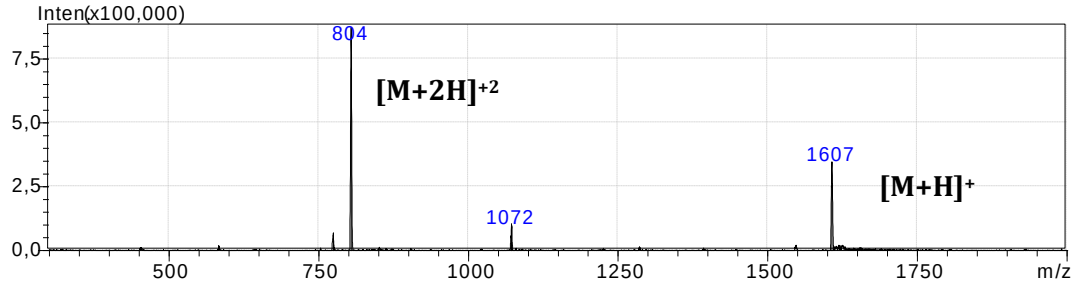
A) Representative chromatogram (and mass spectra) showing mostly cyclic oligomers. Conditions: monomer **4** (10mM in dry MeCN), 0.2 eq $Cu(OAc)_2 \cdot H_2O$, 0.7 eq BHA, RT, 2h.



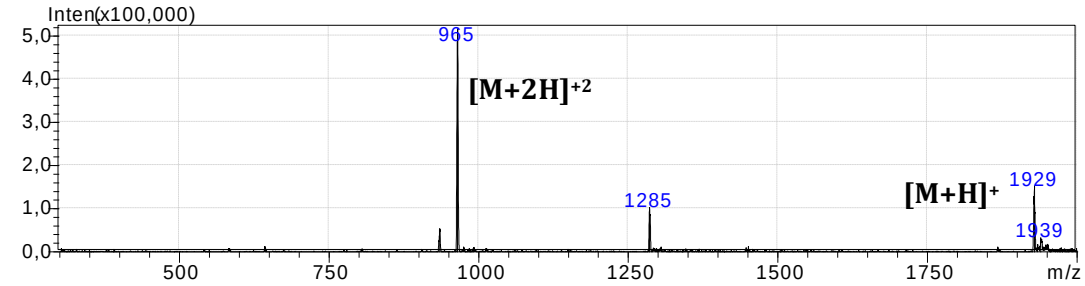
t=4,92min; Cyclotetramer



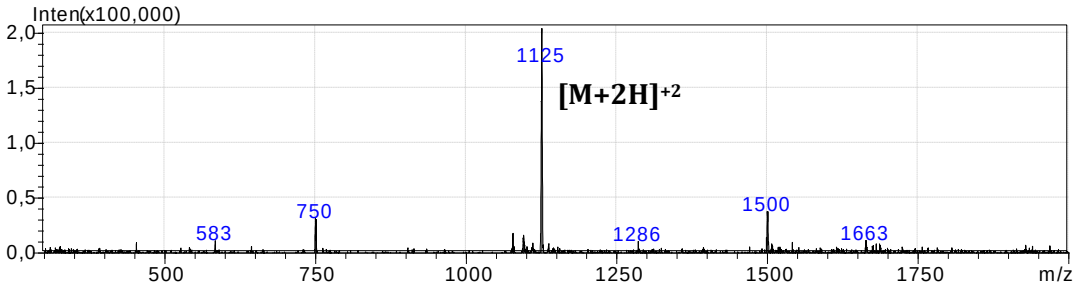
t=5,76min; Cyclopentamer



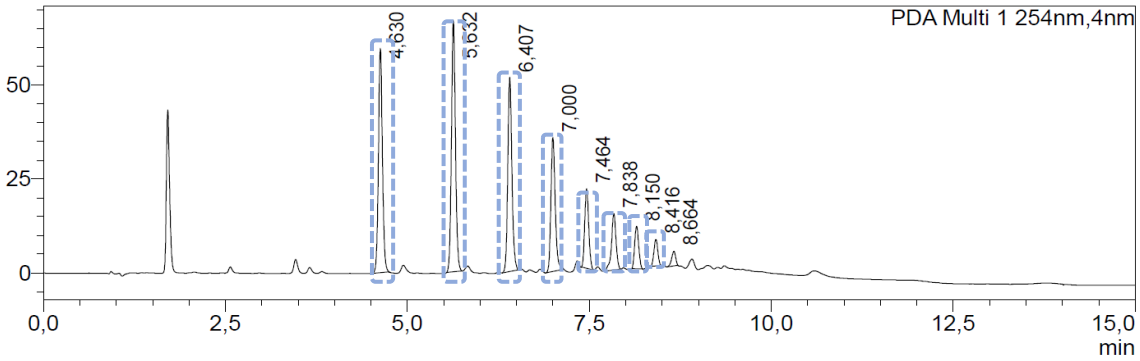
t=6,63min; Cyclohexamer



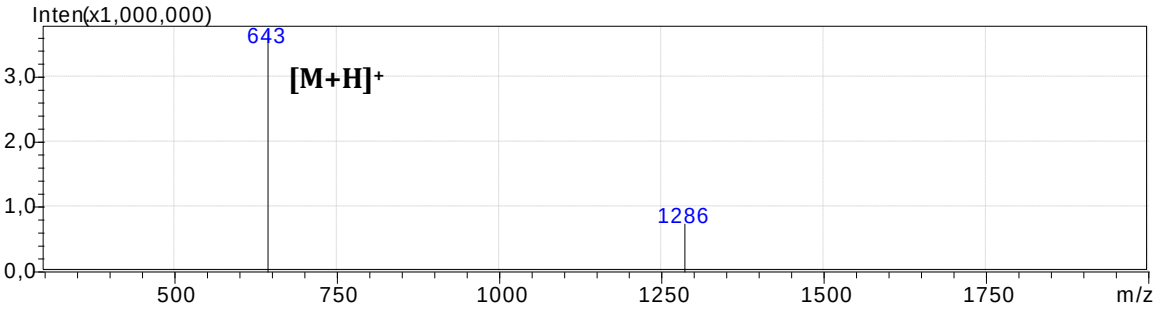
t=7,07min; Cycloheptamer



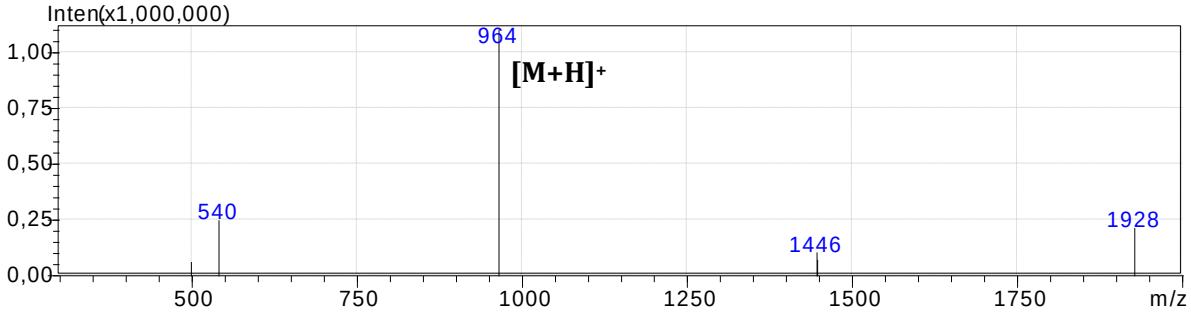
B) Representative chromatogram (and mass spectra) showing mostly linear oligomers. Conditions: monomer **4** (1mM in dry MeCN), 0.2 eq $Cu(OAc)_2 \cdot H_2O$, RT, 8 days.



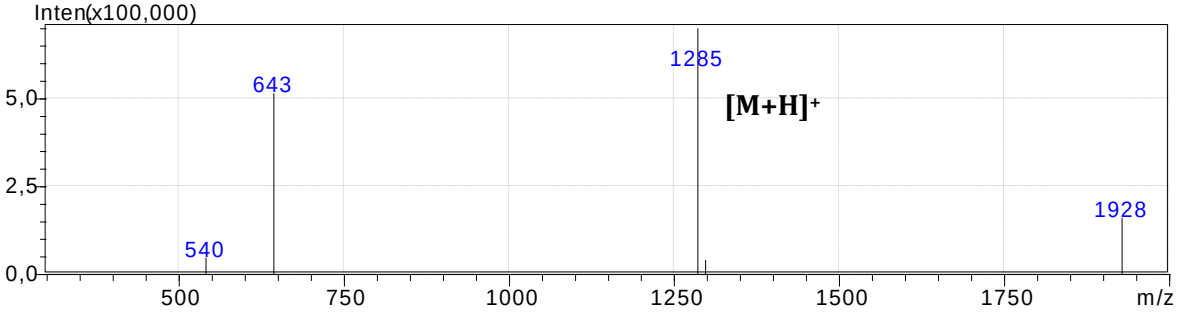
t=4,63min; Dimer



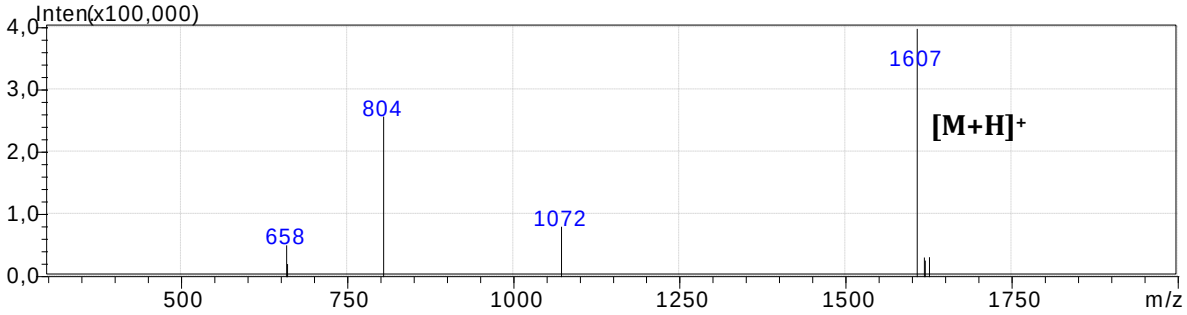
t=5,63min; Linear Trimer



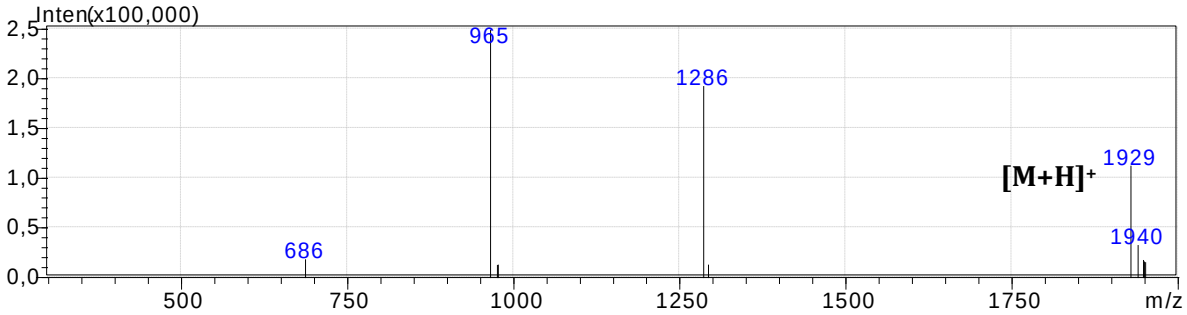
t=6,41min; Linear Tetramer



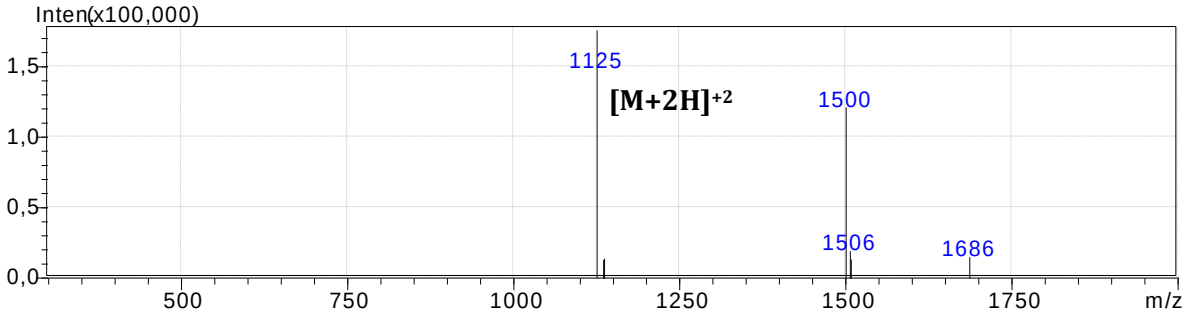
t=7,00min; Linear Pentamer



t=7,46min; Linear Hexamer

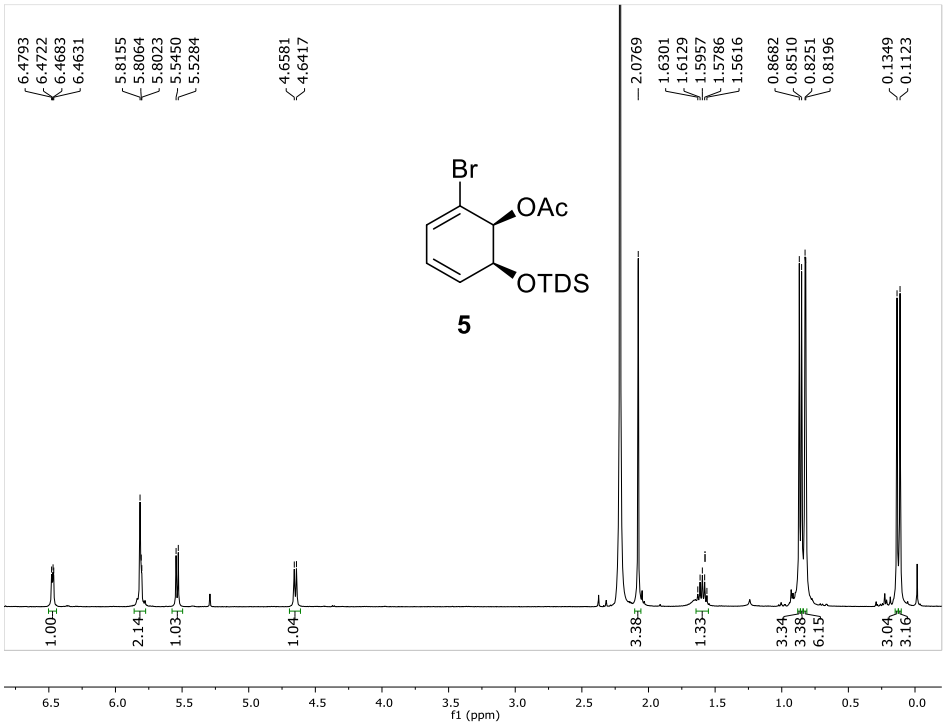


t=7,84min; Linear Heptamer

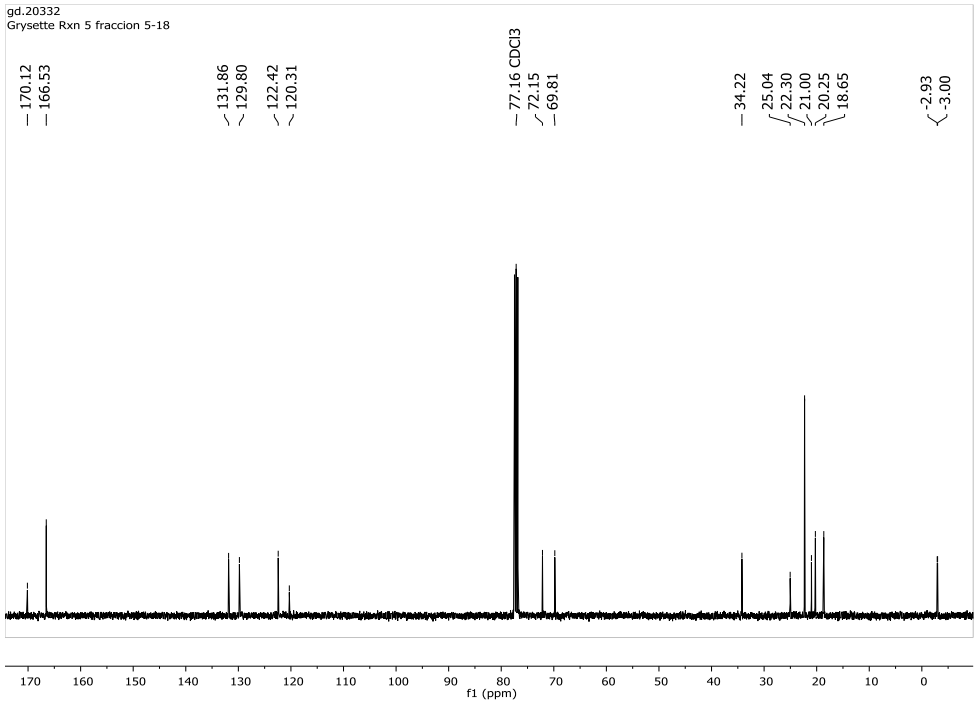


5. ^{1}H and ^{13}C NMR spectra of representative compounds

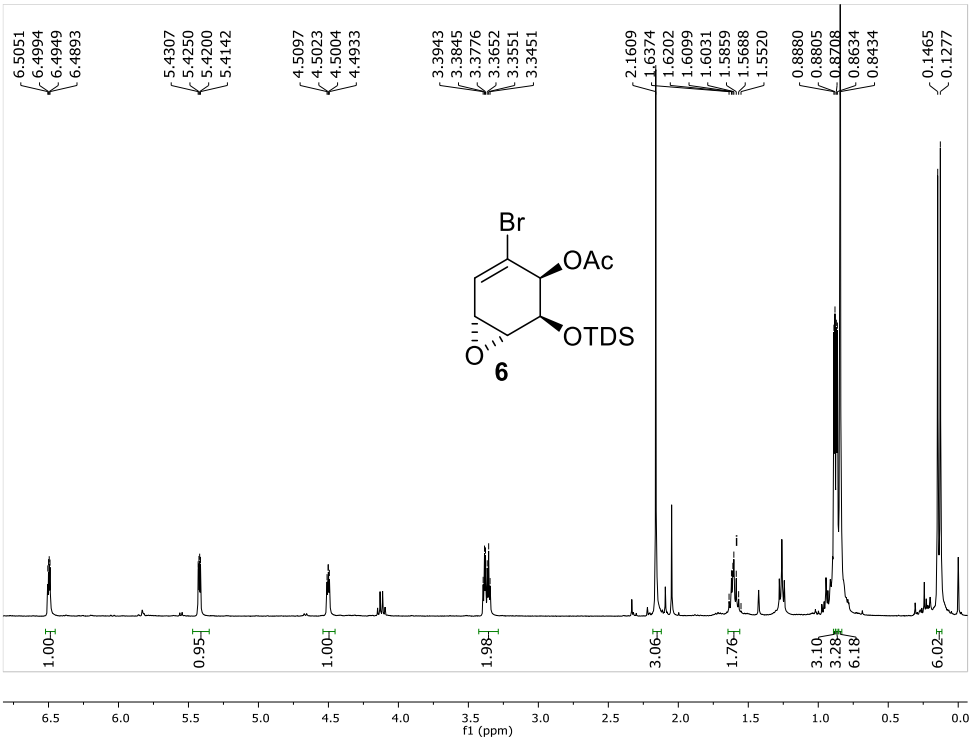
Compound **5, ^{1}H NMR**



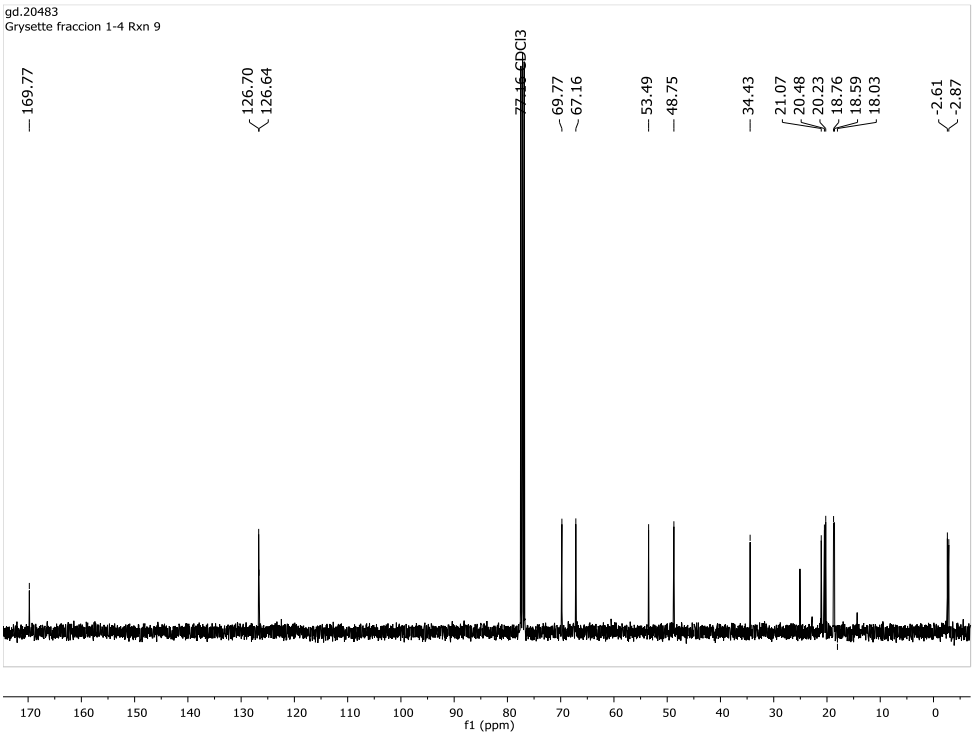
Compound **5, ^{13}C NMR**



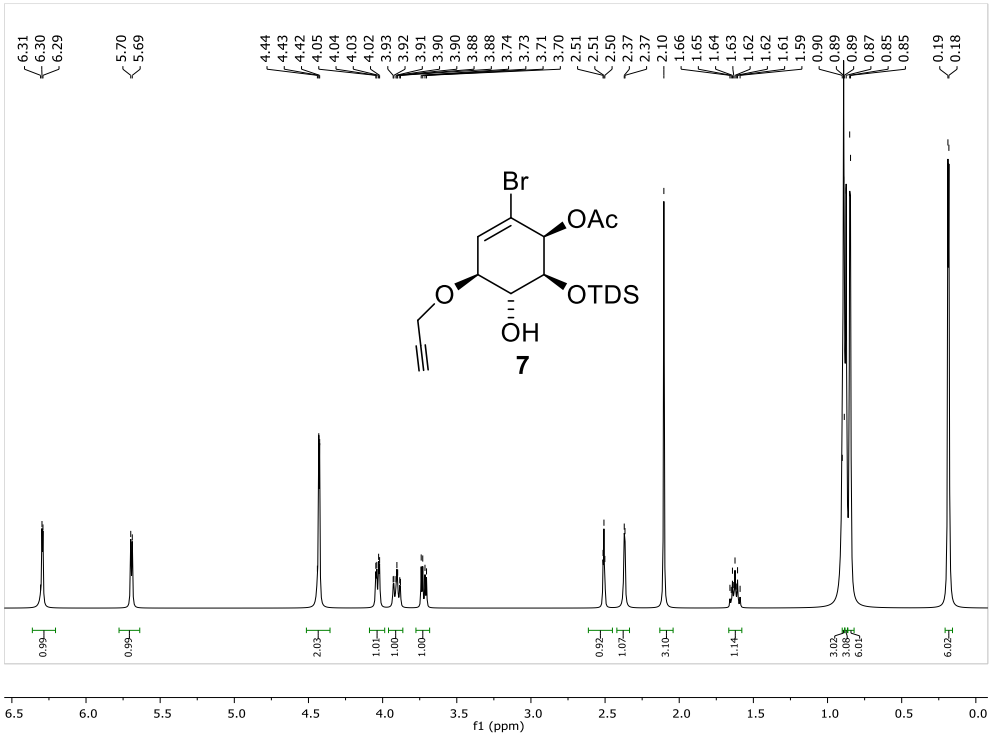
Compound **6, ^{1}H NMR**



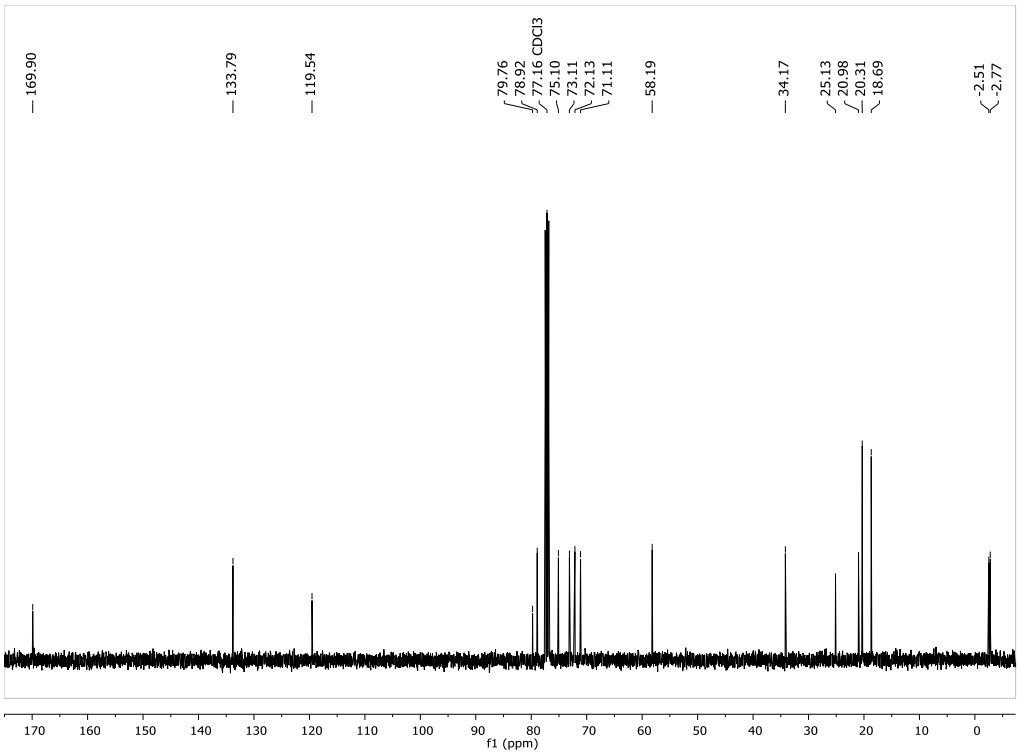
Compound **6, ^{13}C NMR**



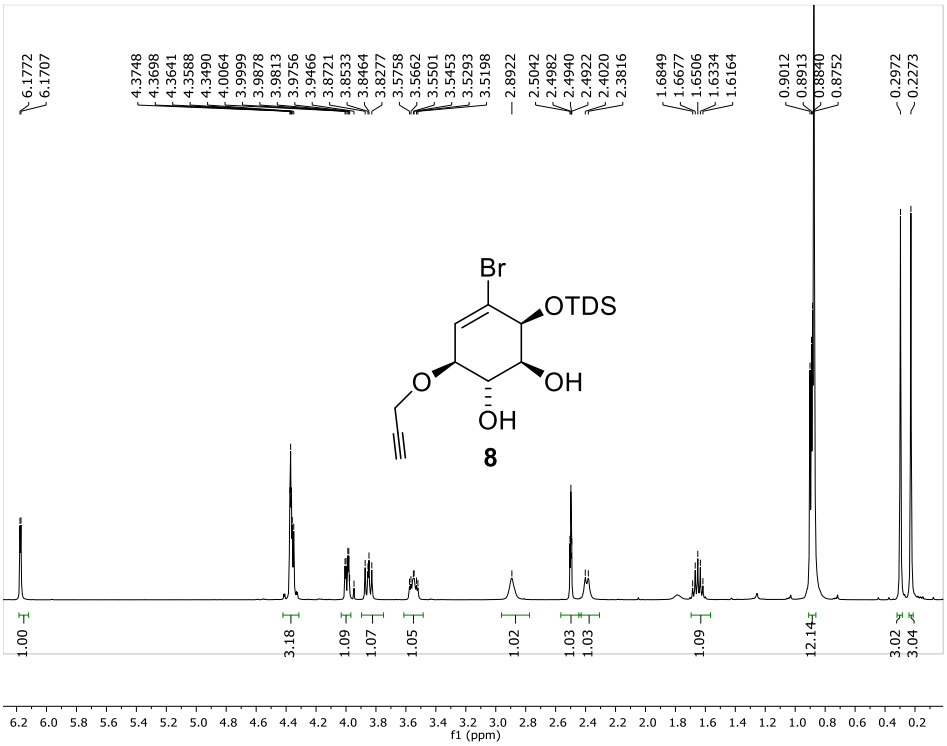
Compound **7, ^{1}H NMR**



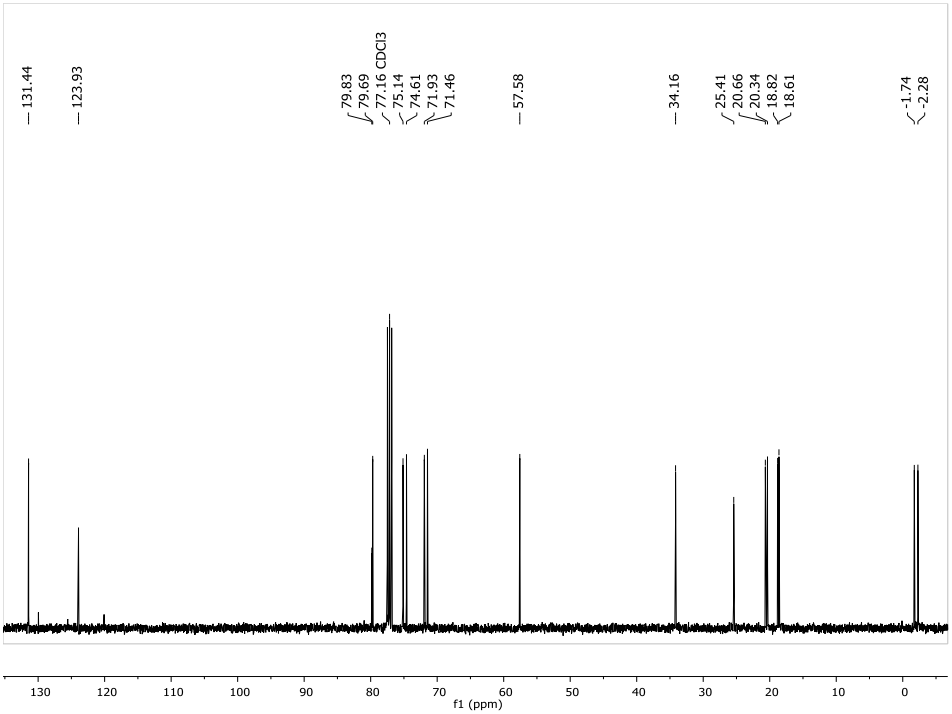
Compound **7, ^{13}C NMR**



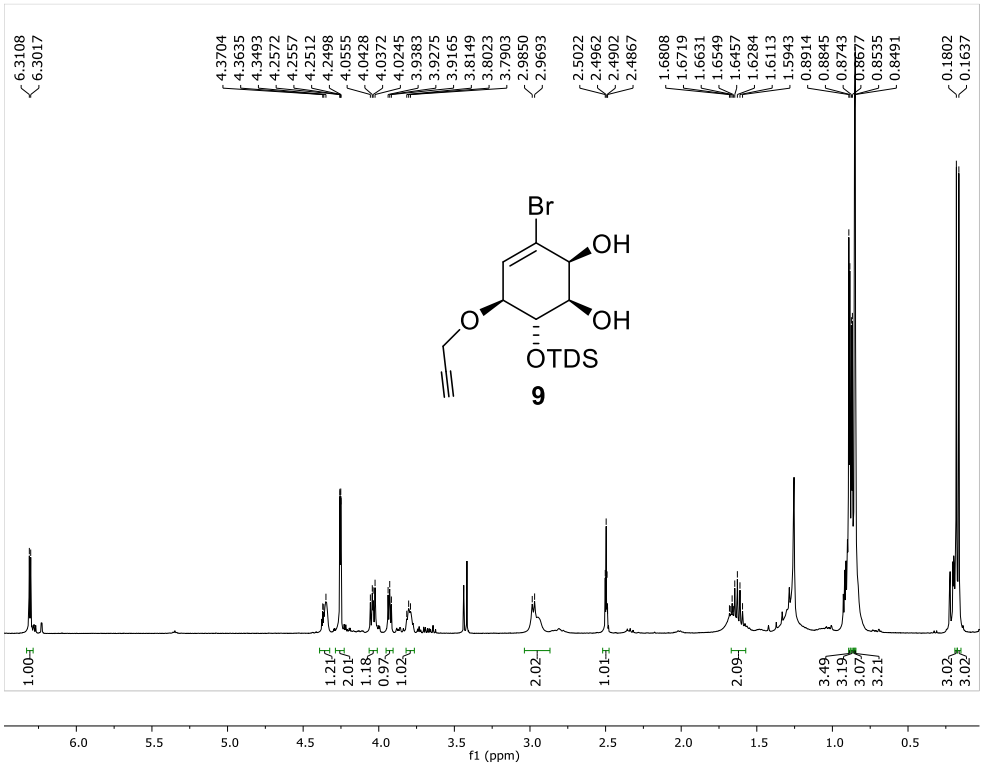
Compound **8, ^{1}H NMR**



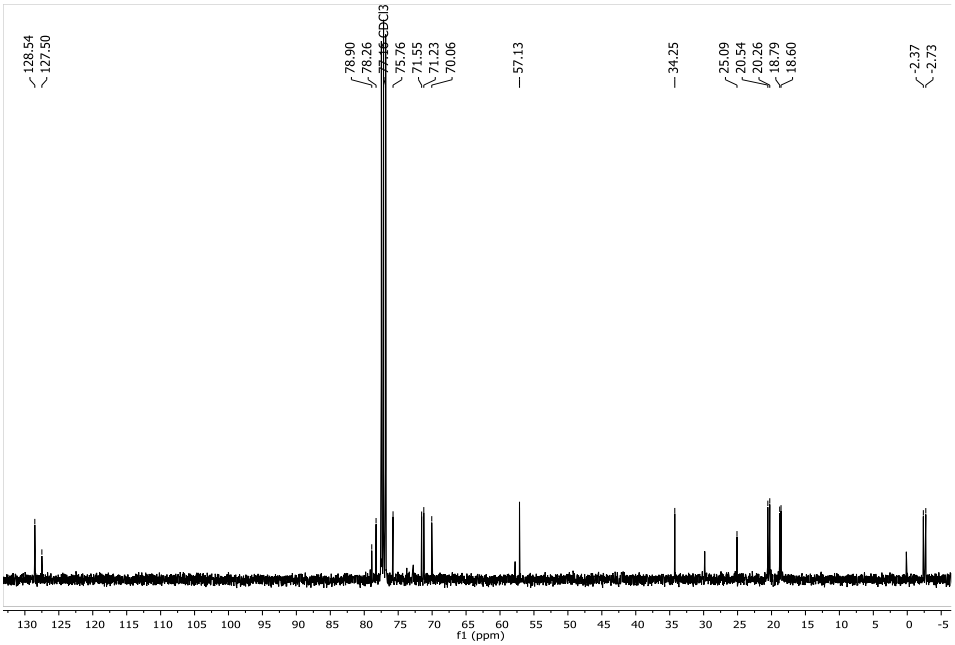
Compound **8, ^{13}C NMR**



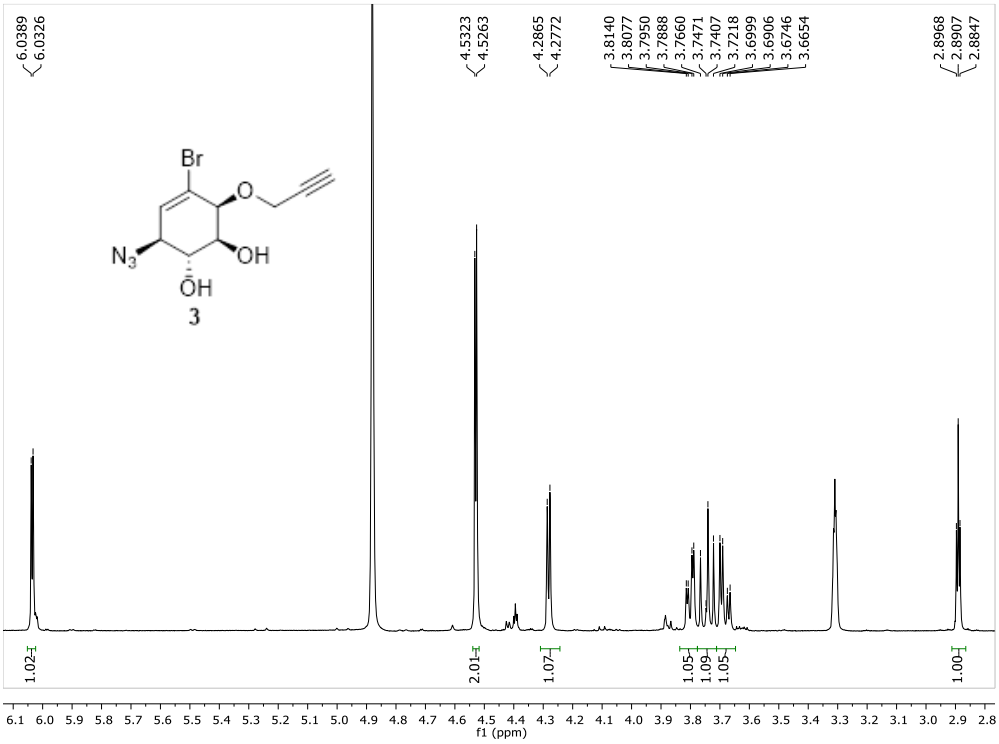
Compound **9, ^{1}H NMR**



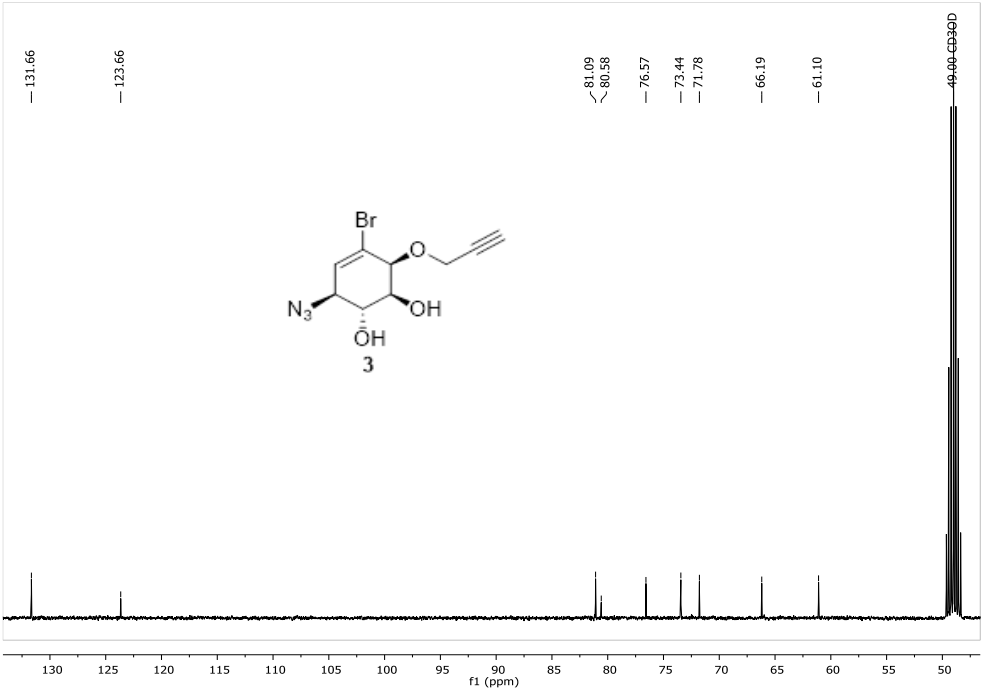
Compound **9, ^{13}C NMR**



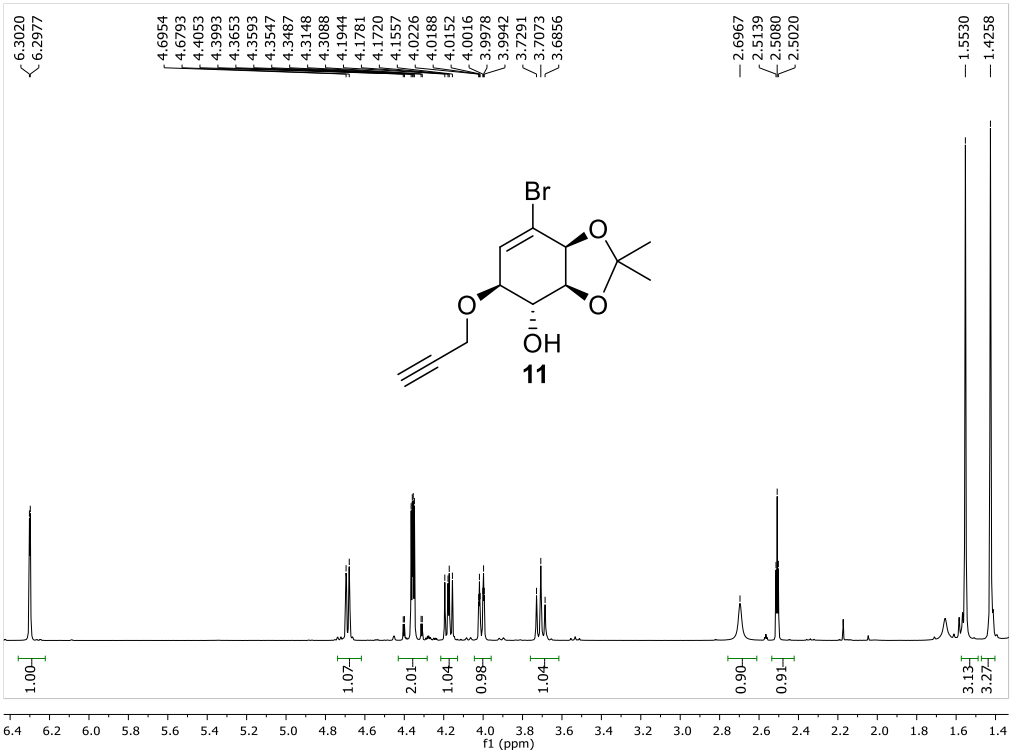
Compound **3, ^{1}H NMR**



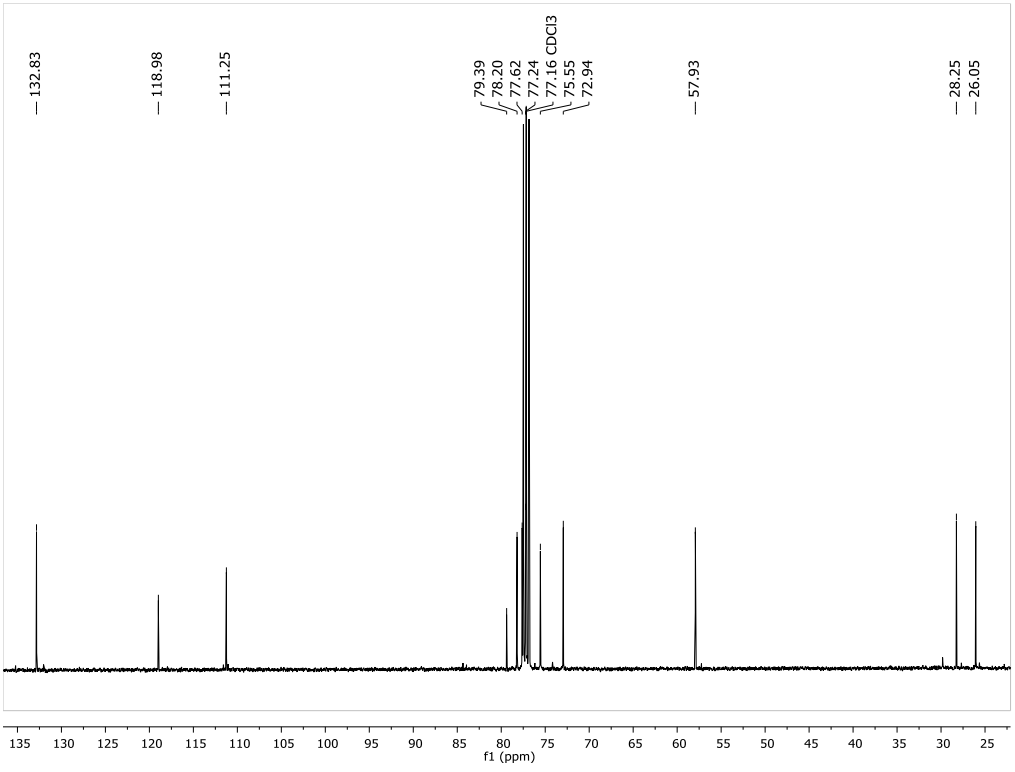
Compound **3, ^{13}C NMR**



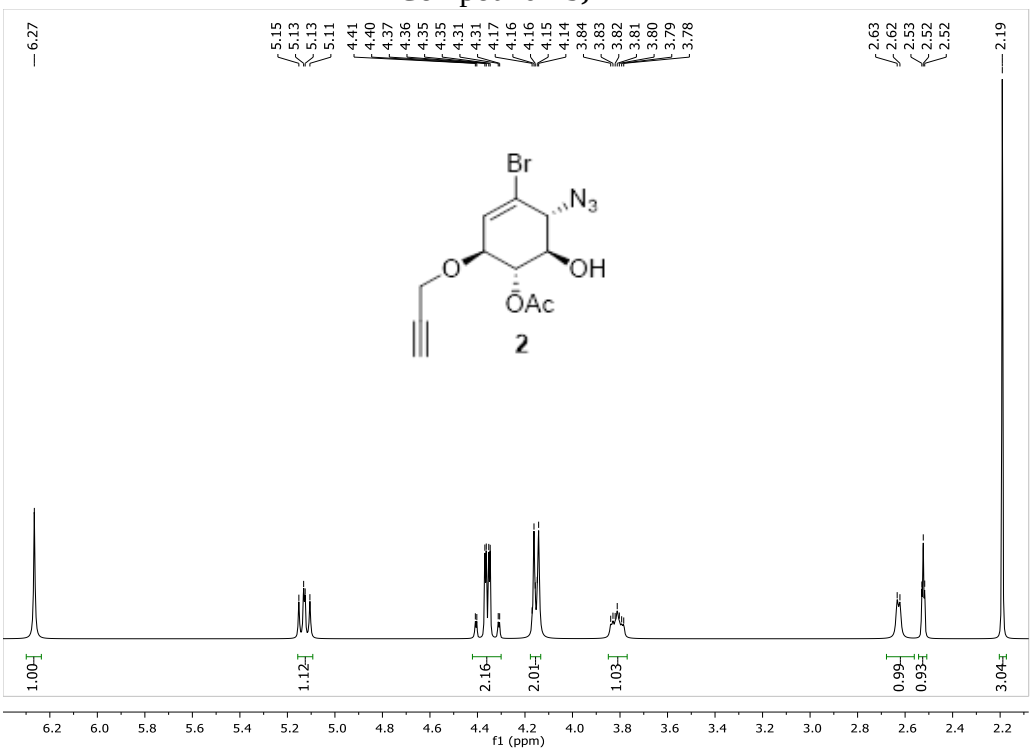
Compound **11, ^{1}H NMR**



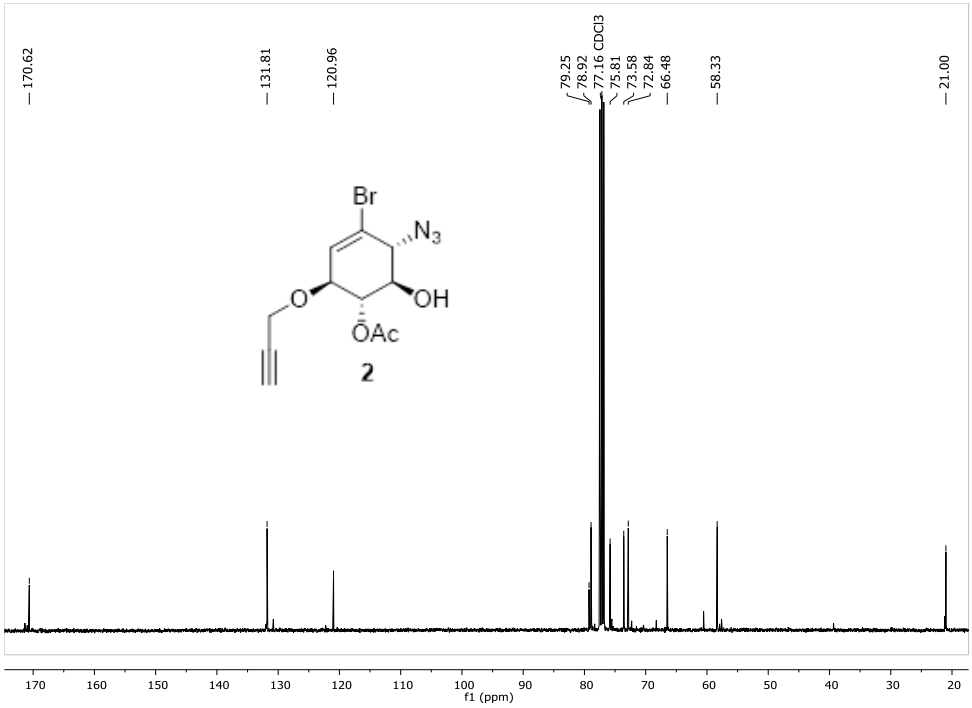
Compound **11, ^{13}C NMR**



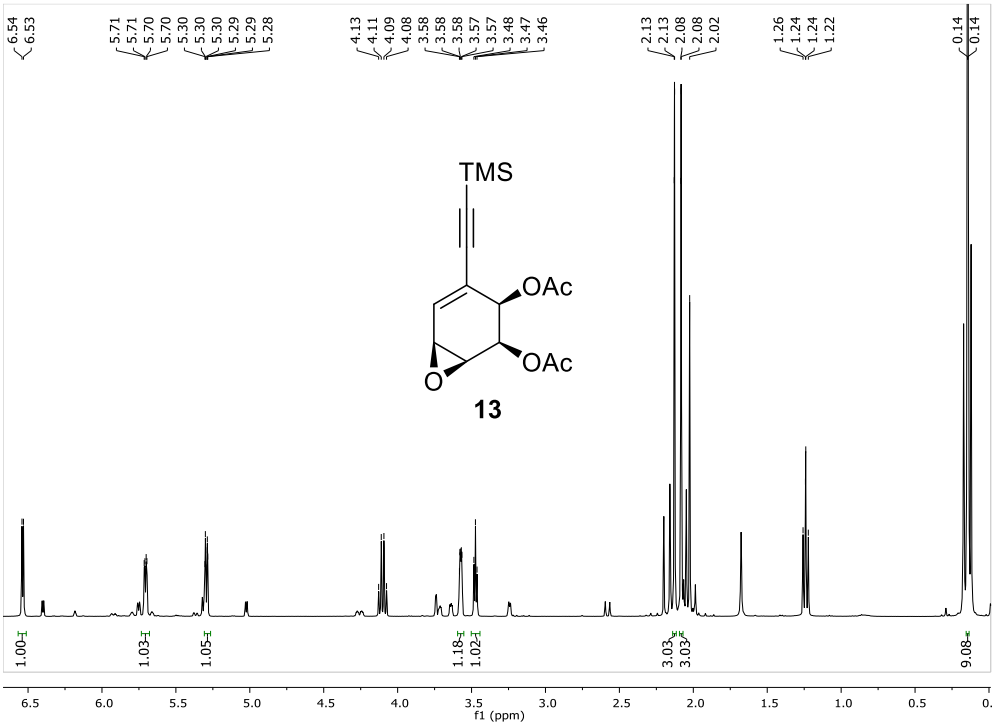
Compound **2b, ^{1}H NMR**



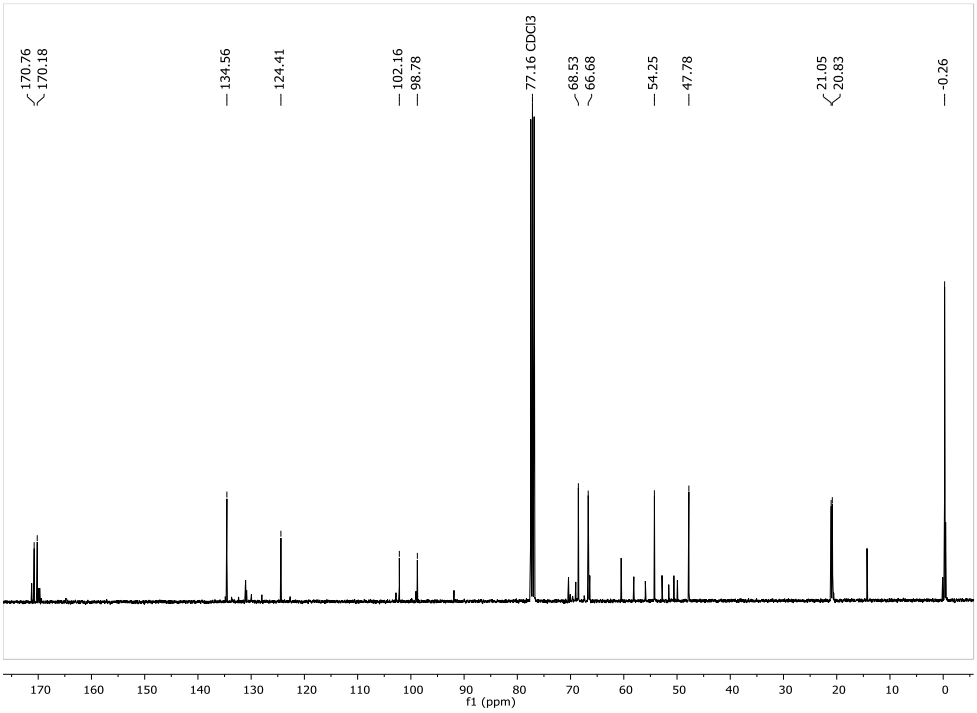
Compound **2b, ^{13}C NMR**



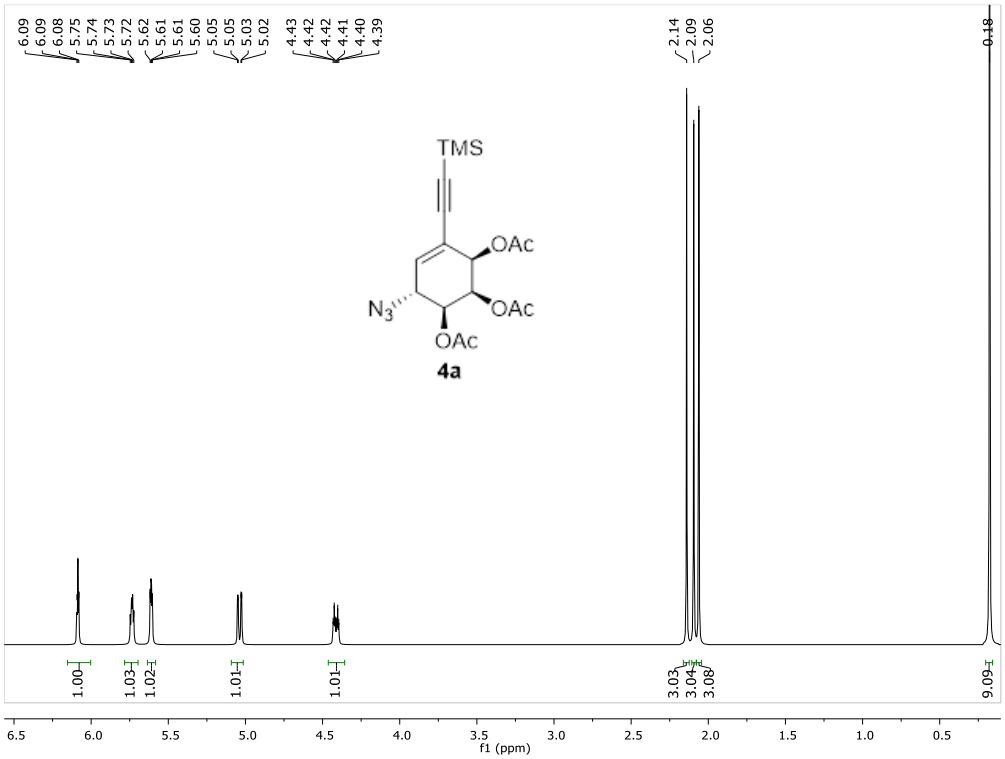
Compound **13, ^{1}H NMR**



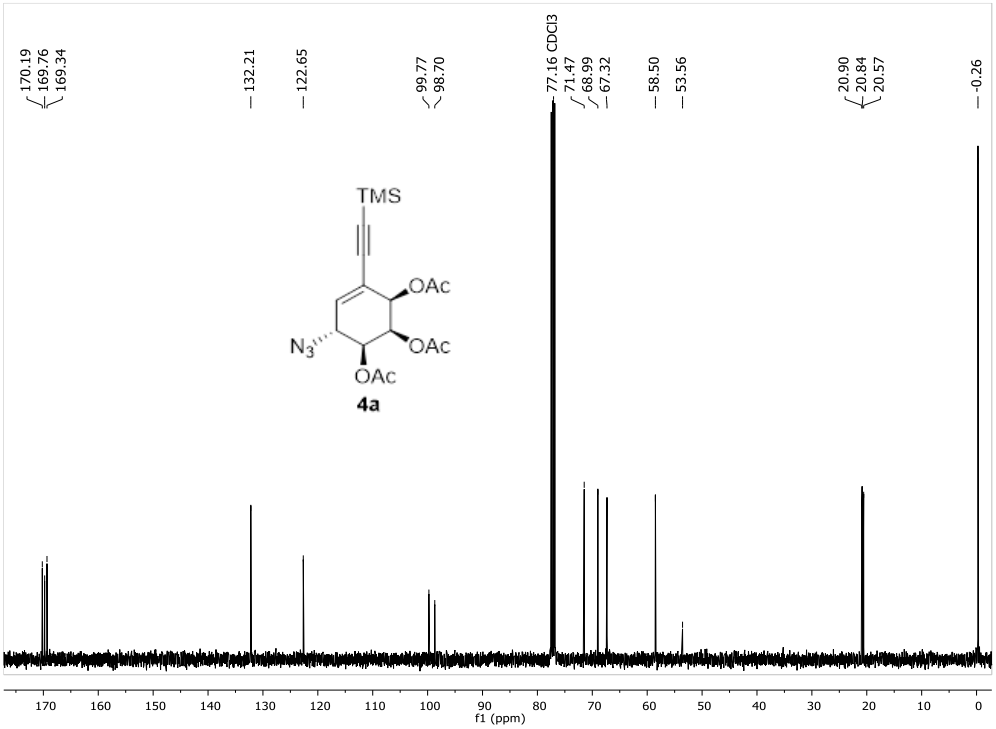
Compound **13, ^{13}C NMR**



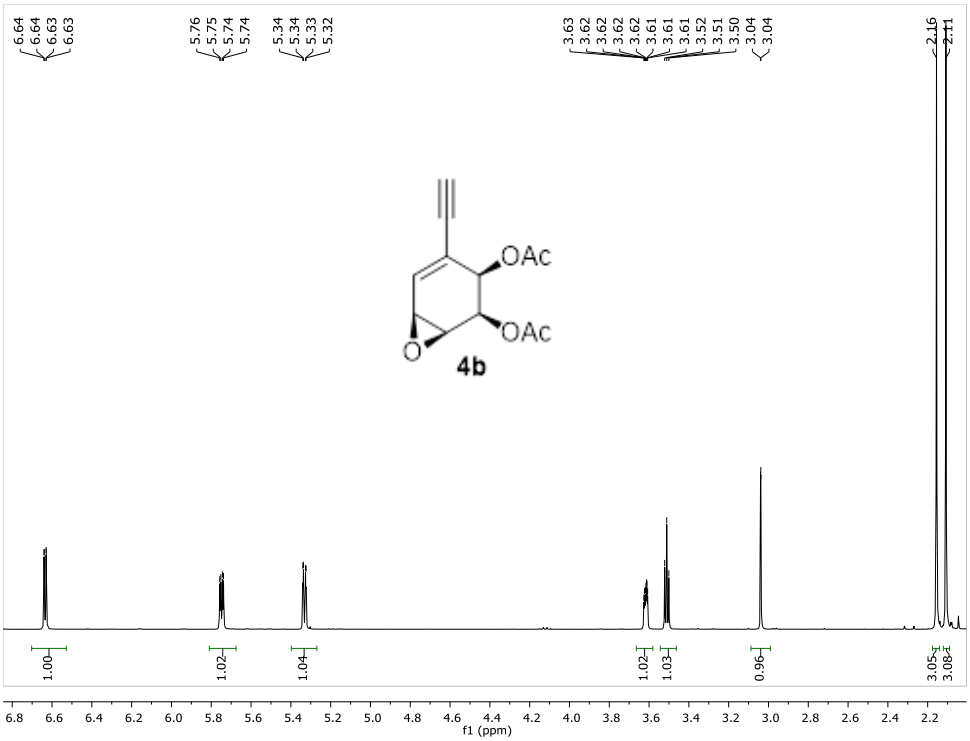
Compound **4a, ^{1}H NMR**



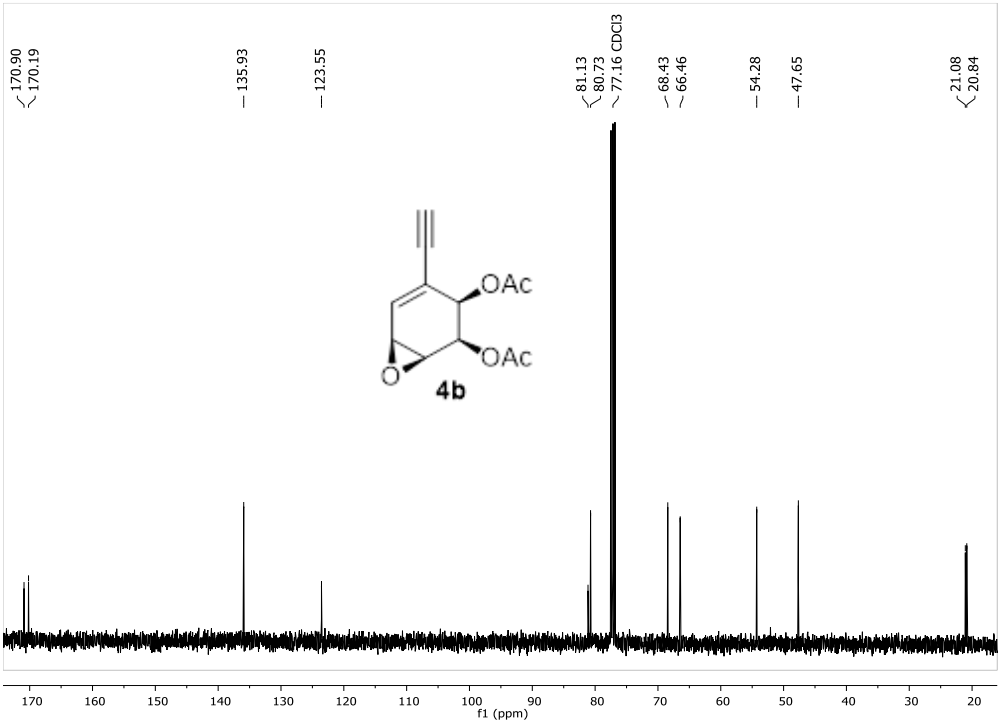
Compound **4a, ^{13}C NMR**



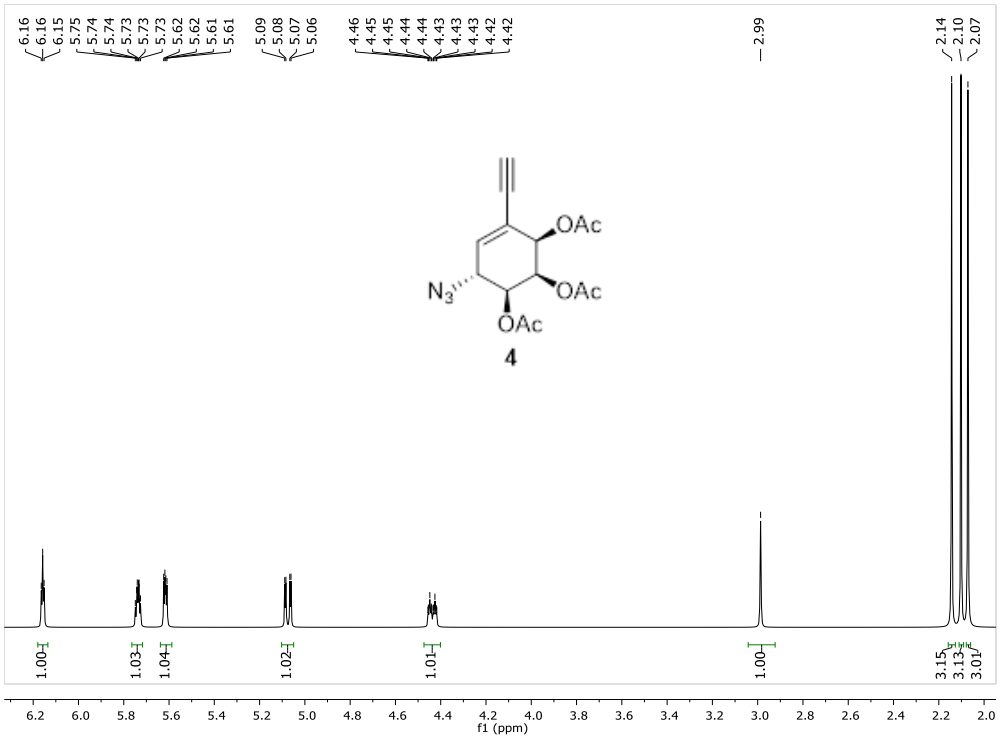
Compound **4b, ^{1}H NMR**



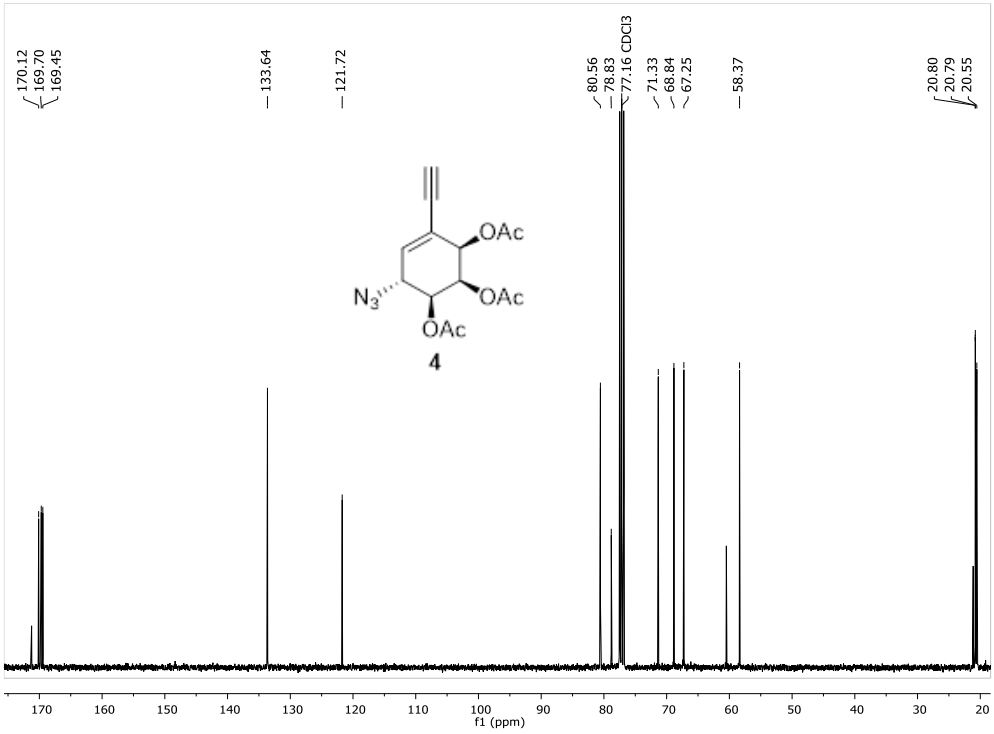
Compound **4b, ^{13}C NMR**



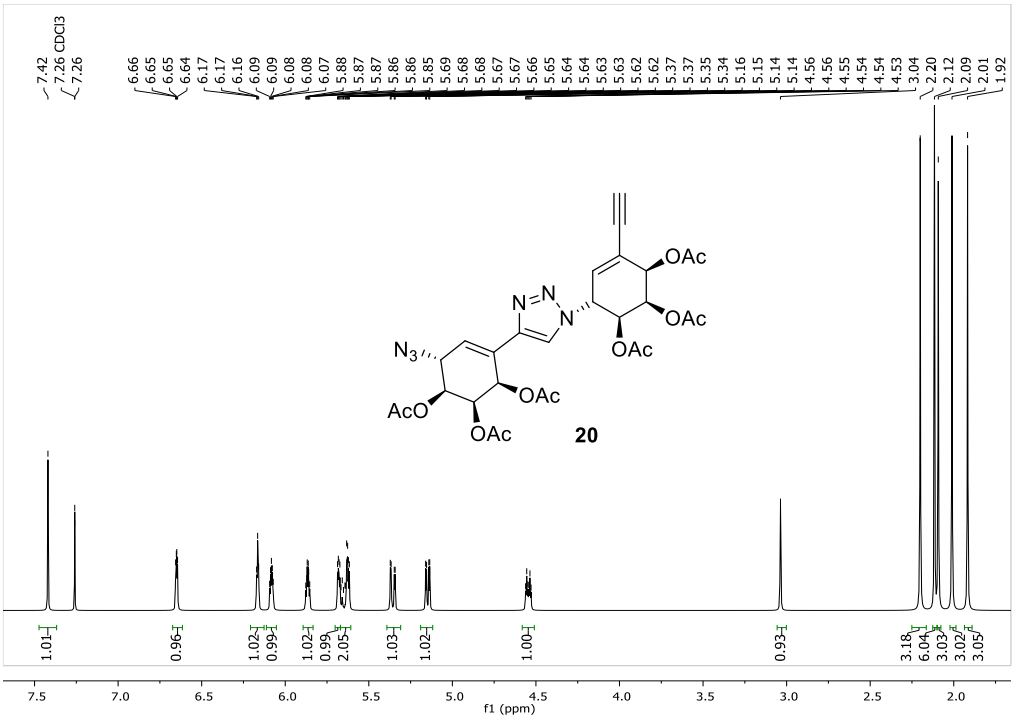
Compound **4, ^{1}H NMR**



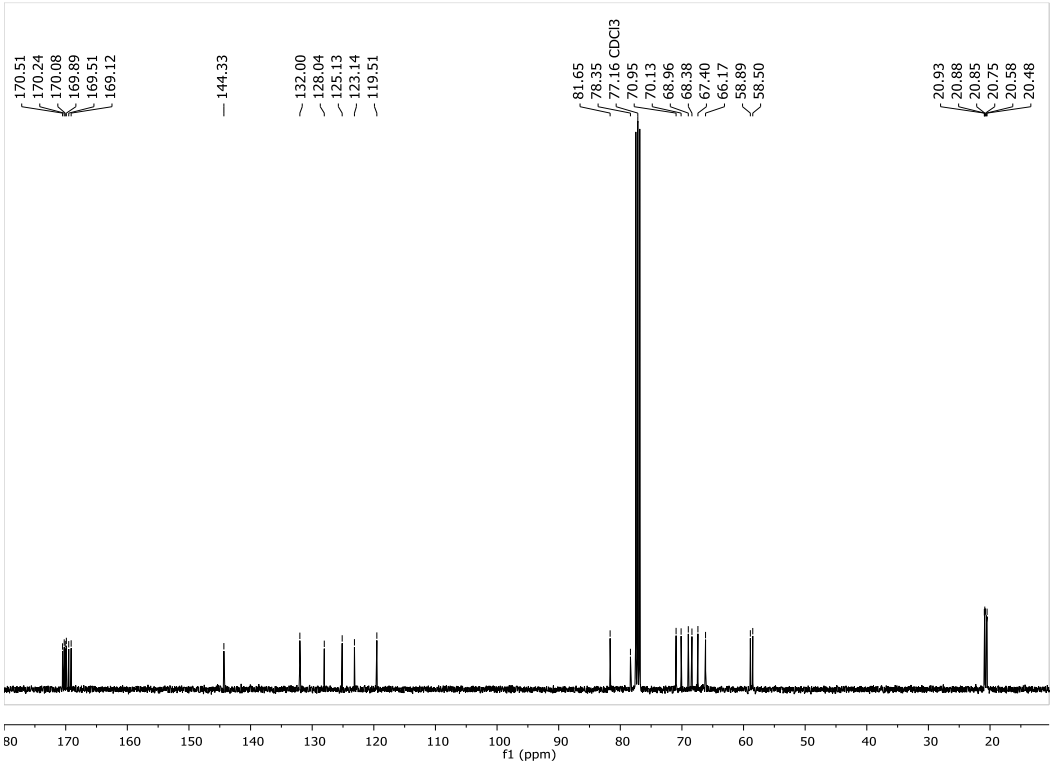
Compound **4, ^{13}C NMR**



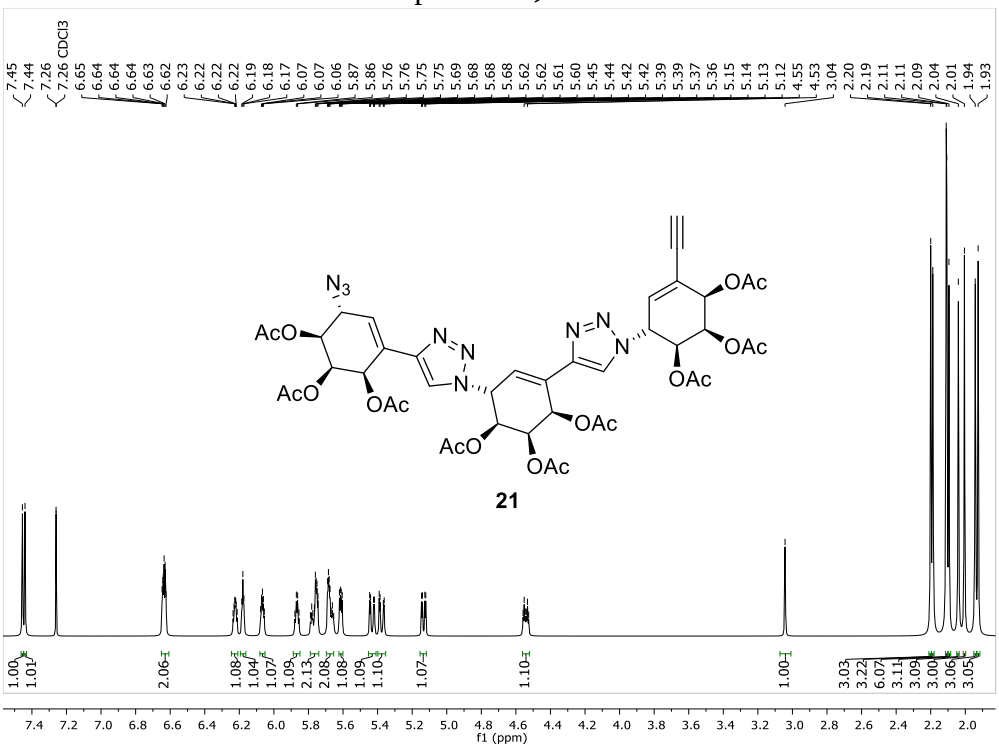
Compound **20, ^{1}H NMR**



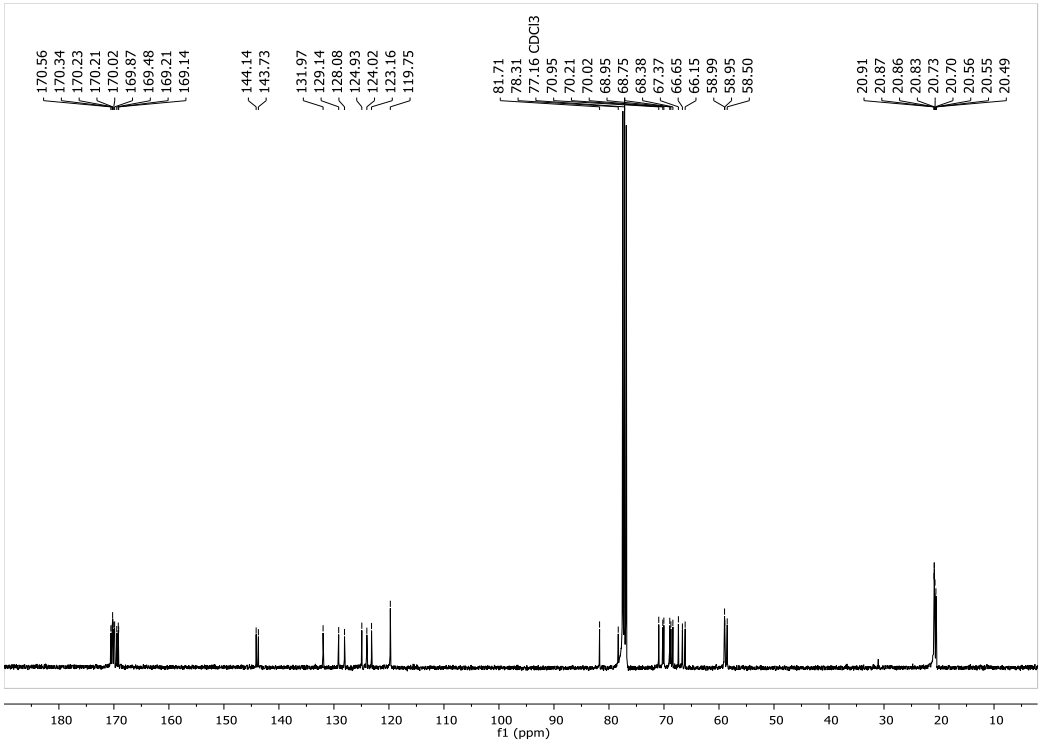
Compound **20, ^{13}C NMR**



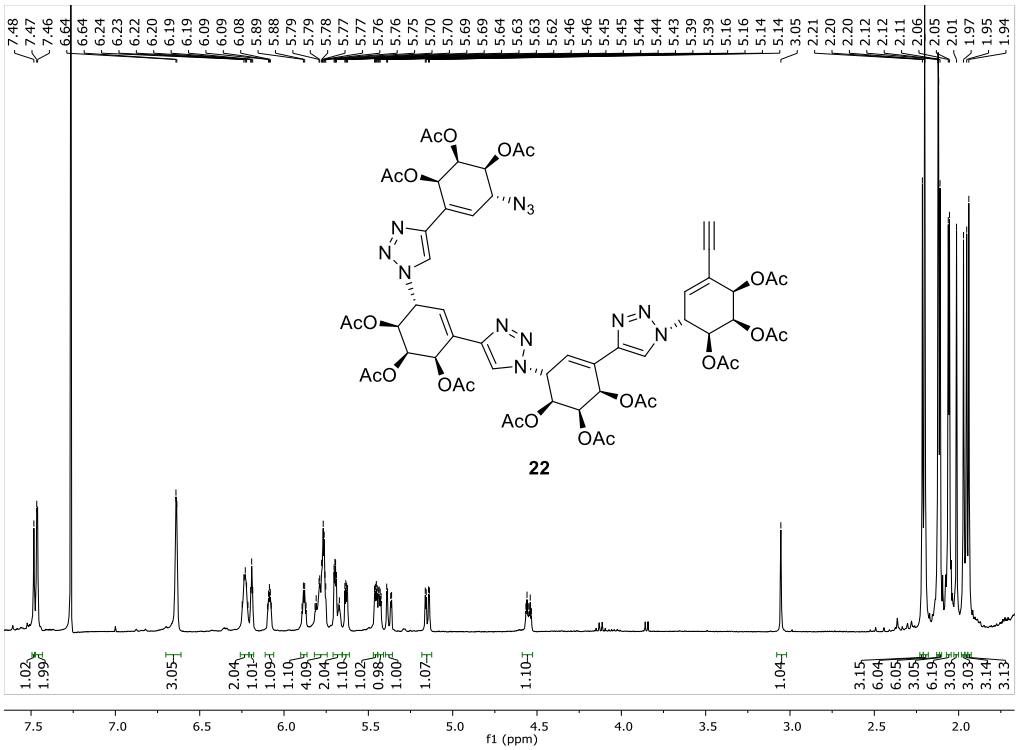
Compound **21, ^{1}H NMR**



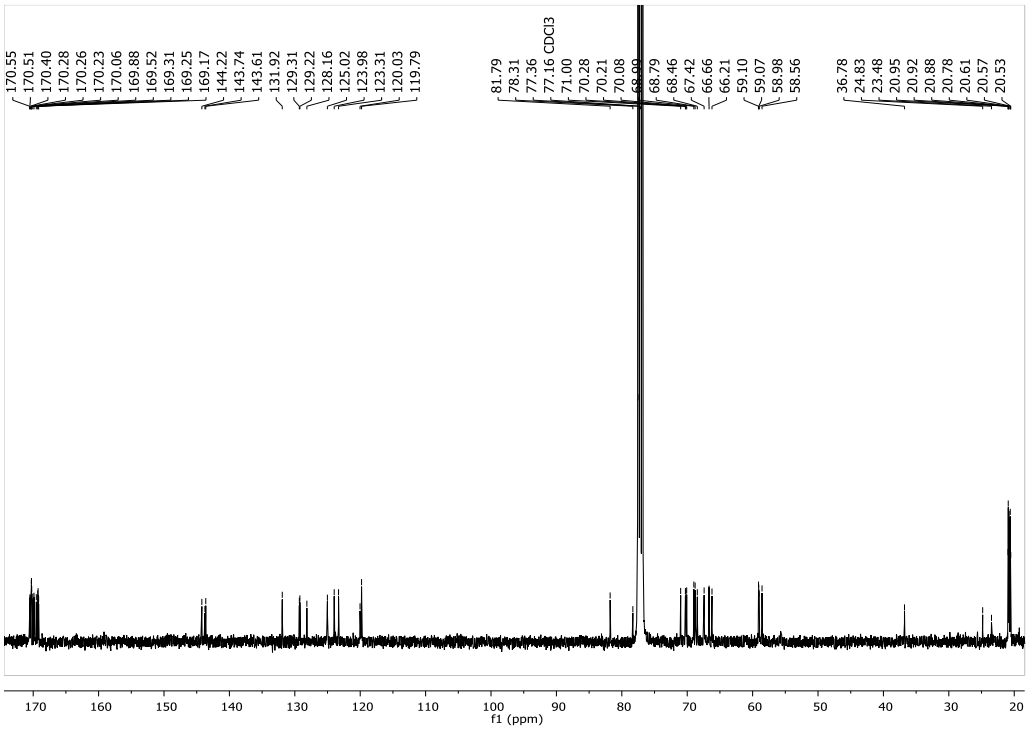
Compound **21, ^{13}C NMR**



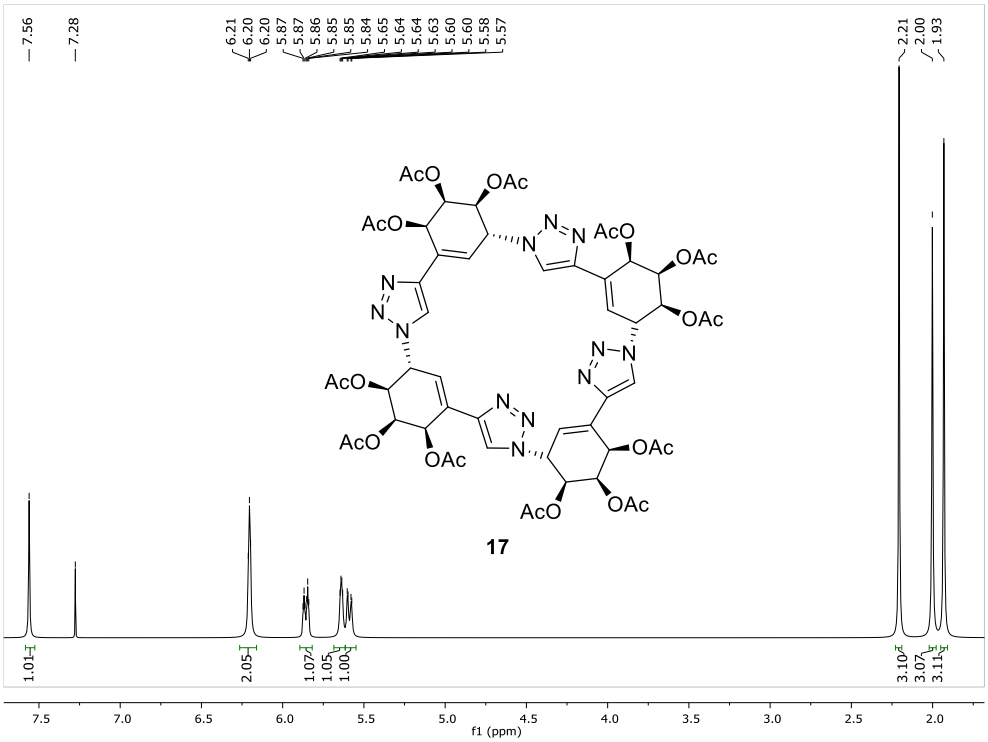
Compound **22, ^{1}H NMR**



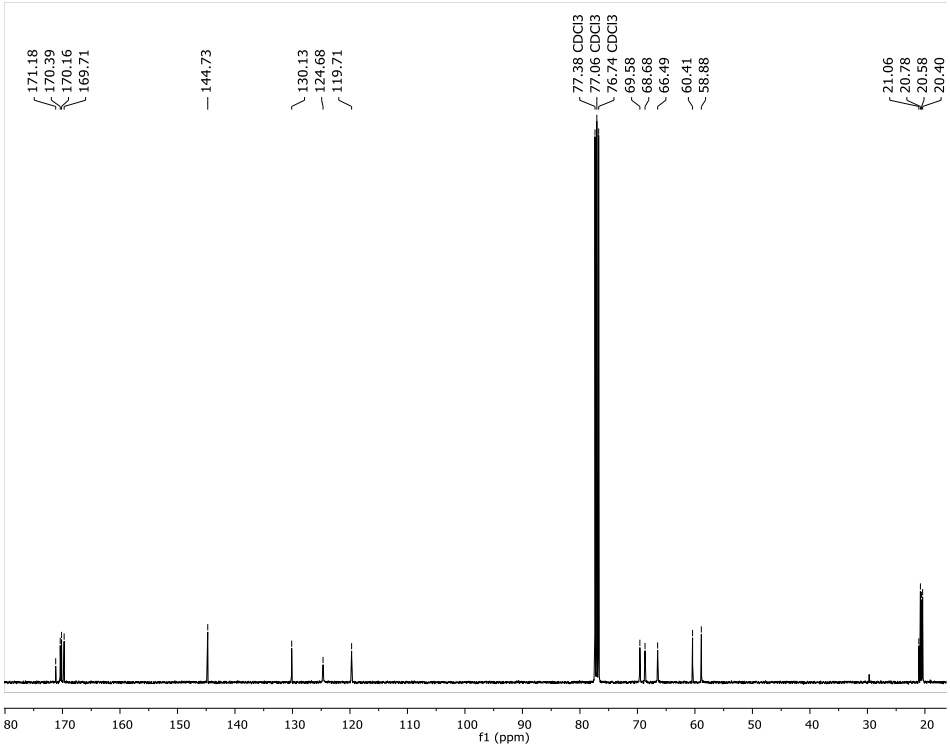
Compound **22, ^{13}C NMR**



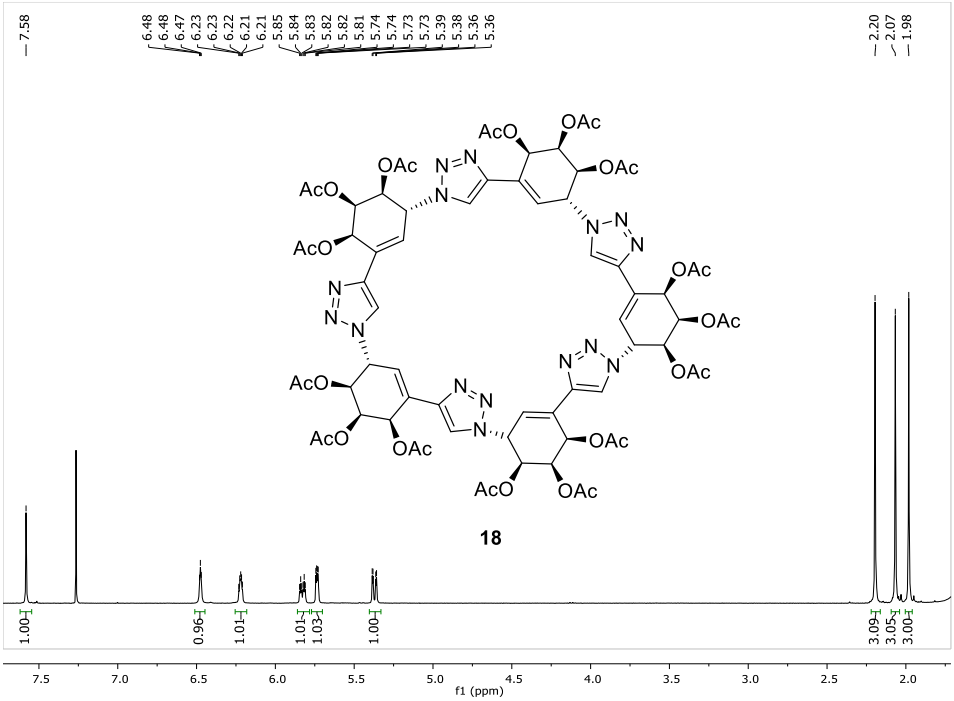
Compound **17, ^{1}H NMR**



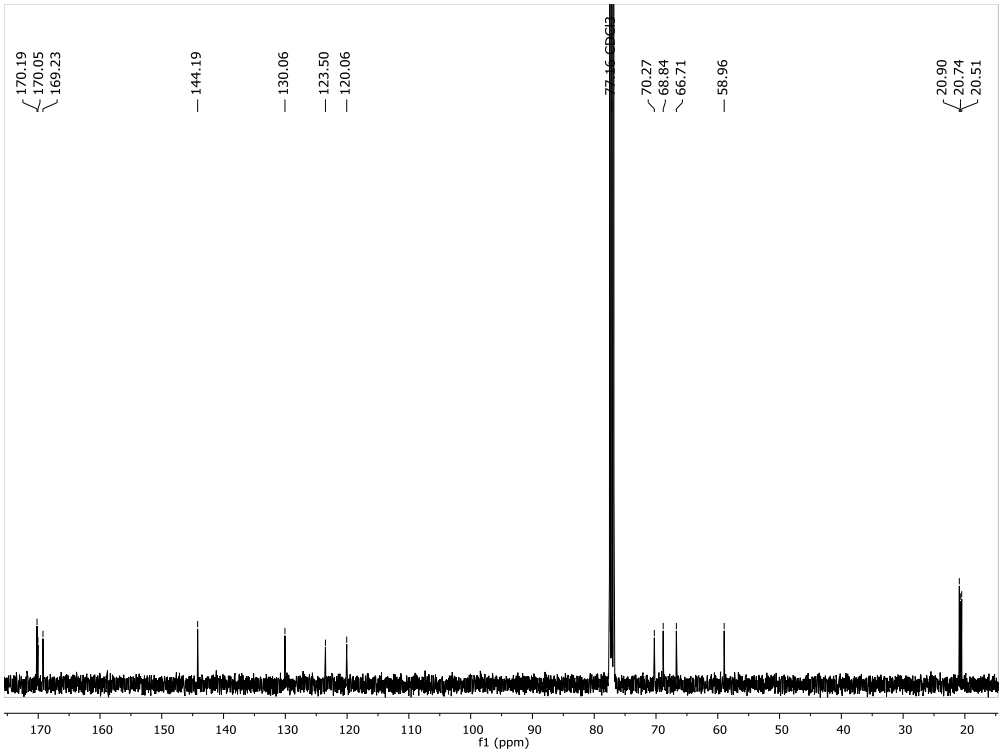
Compound **17, ^{13}C NMR**



Compound **18, ^{1}H NMR**



Compound **18, ^{13}C NMR**



Compound **19, ^{1}H NMR**