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Strained Alkynes Derived from 2,2'-Dihydroxy-1,1'-Biaryls; Synthesis and Copper-Free Cycloaddition with Azides.

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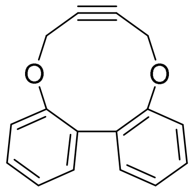
Supporting information:

Synthetic procedures and NMR spectra.

General experimental.

Solvents and reagents for the synthesis of complexes and catalytic reactions were degassed prior to use and all reactions were carried out under either a nitrogen or argon atmosphere. Reactions were monitored by TLC using aluminum backed silica gel 60 (F254) plates, visualized using UV 254 nm and phosphomolybdic acid, potassium permanganate or vanillin dips as appropriate. Flash column chromatography was carried out routinely on silica gel. Reagents were used as received from commercial sources unless otherwise stated. Dry solvents were purchased and used as received. ^{1}H NMR spectra were recorded on a Bruker DPX (400 or 500 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million relative to the singlet at 7.26 ppm for chloroform and 0.00 ppm for TMS. Mass spectra for analysis of synthetic products were recorded on a Bruker Esquire2000 or a Bruker MicroTOF mass spectrometer. FTICR Mass Spectrometry to measure the binding to peptides and proteins was carried using a Bruker SolariX 12T, Bruker Daltonics (Bremen, Germany) instrument. Coupling constants (J) are measured in Hertz. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR Golden Gate. Melting points were recorded on a Stuart Scientific SMP 1 instrument and are uncorrected.

Synthesis of compound 1; 8,13-dioxatricyclo[12.4.0.0^{2,7}]octadeca-1(14),2,4,6,15,17-hexaen-10-yne **1**.



This is a known compound (U. Koch-Pomeranz, H.-J. Hansen, H. Schmid, *Helv. Chim. Acta.* **1971**, *56*, 2981-3004). In a round bottom flask under nitrogen atmosphere 2,2’-biphenol (94.4 mg, 0.51 mmol) and but-2-yne-1,4-diyl bis(4-methylbenzenesulfonate) (200 mg, 0.51 mmol) were dissolved in anhydrous acetonitrile (25 mL). K_2CO_3 (350 mg, 2.53 mmol) was added and the mixture was stirred at room temperature for 12 days. The volatiles were removed and H_2O (50 mL) was added. The product was extracted with DCM (3x50 mL). The reunited organic layers were washed with brine (30 mL) and dried over Na_2SO_4. The product was purified by flash chromatography on silica gel (eluent: Pentane/DCM = 4:1 to DCM) to give the product **1** (42 mg, 0.18 mmol, 29%) as colourless solid.

m.p. 129.7-132.5 ºC.

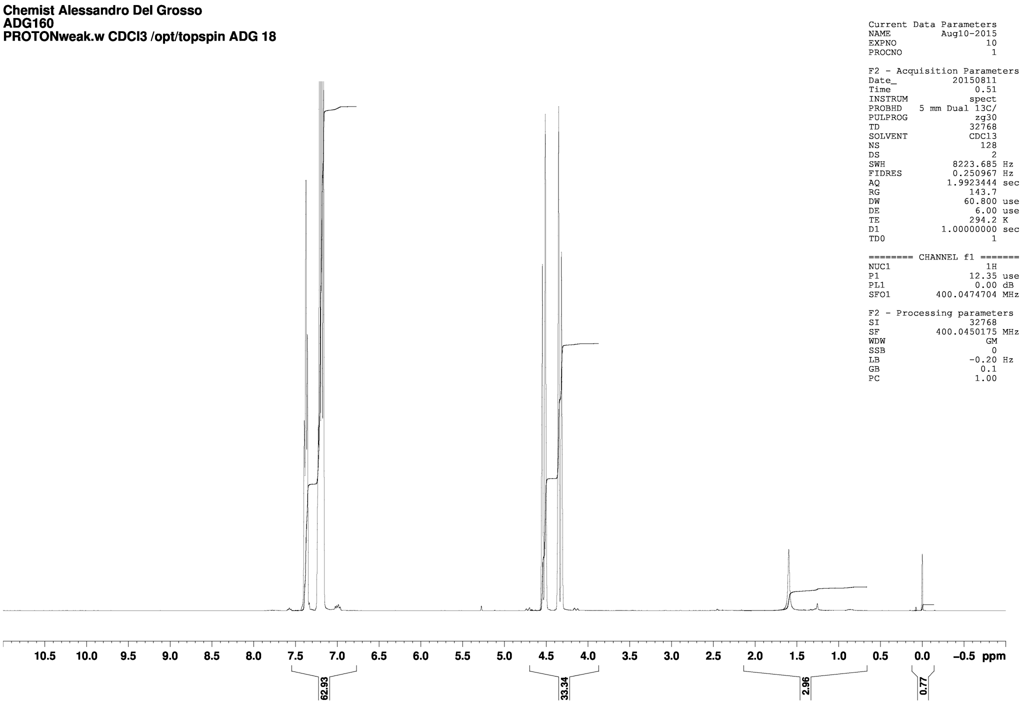
$IR_{(neat)}$ 3053, 3023, 2989, 1952, 2919, 2863, 1595, 1574, 1499, 1470, 1451, 1434, 1348, 1258, 1248 cm^{-1}.

δ_H (500 MHz, $CDCl_3$) 7.37 (2H, ddd, *J* = 8.0, 7.0, 2.1 Hz, Ar*H*), 7.11 - 7.27 (6H, m, Ar*H*), 4.47 - 4.58 (2H, m, CH*H*), 4.27 - 4.39 (2H, m, C*H*H).

δ_C (125 MHz, $CDCl_3$) 154.4(C), 135.9 (C), 132.0 (CH), 129.0 (CH), 124.2 (CH), 122.5 (CH), 86.6 (C), 63.5 (CH_2).

HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{12}O_2Na$ 259.0730; Found 259.0725.

^1H NMR (500 MHz, $CDCl_3$)



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PROCNO                 1

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PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                   128
DS                     2
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RG                 143.7
DW                60.800 use
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TE                 294.2 K
D1            1.00000000 sec
TD0                    1

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PL1                 0.00 dB
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F2 - Processing parameters
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SF           400.0450175 MHz
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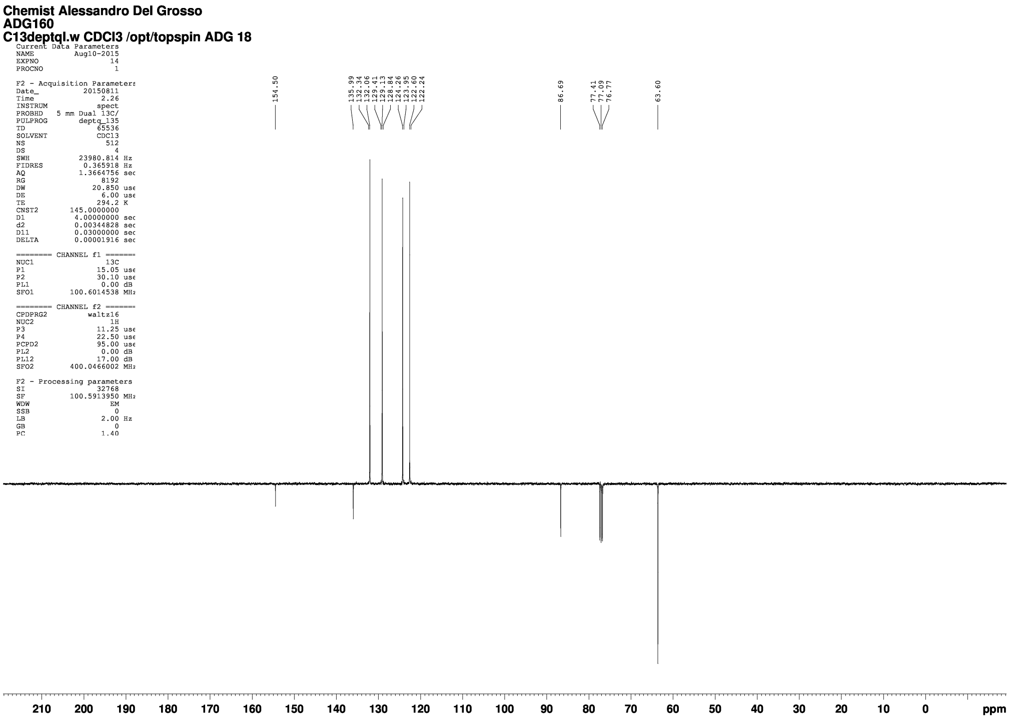
^{13}C NMR (125 MHz, $CDCl_3$)



Chemist Alessandro Del Grosso
ADG160
C13deptql.w CDCl3 /opt/topspin ADG 18

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PROCNO                 1

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PULPROG        deptq_135
TD                 65536
SOLVENT            CDCl3
NS                   512
DS                     4
SWH            23980.814 Hz
FIDRES          0.365918 Hz
AQ             1.3664756 sec
RG                  8192
DW                20.850 usec
DE                  6.00 usec
TE                 294.2 K
CNST2        145.0000000
D1            4.00000000 sec
d2            0.00344828 sec
D11           0.03000000 sec
DELTA         0.00001916 sec

======== CHANNEL f1 =======
NUC1                 13C
P1                 15.05 usec
P2                 30.10 usec
PL1                 0.00 dB
SFO1         100.6014538 MHz

======== CHANNEL f2 =======
CPDPRG2          waltz16
NUC2                  1H
P3                 11.25 usec
P4                 22.50 usec
PCPD2              95.00 usec
PL2                 0.00 dB
PL12               17.00 dB
SFO2         400.0466002 MHz

F2 - Processing parameters
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PC                  1.40
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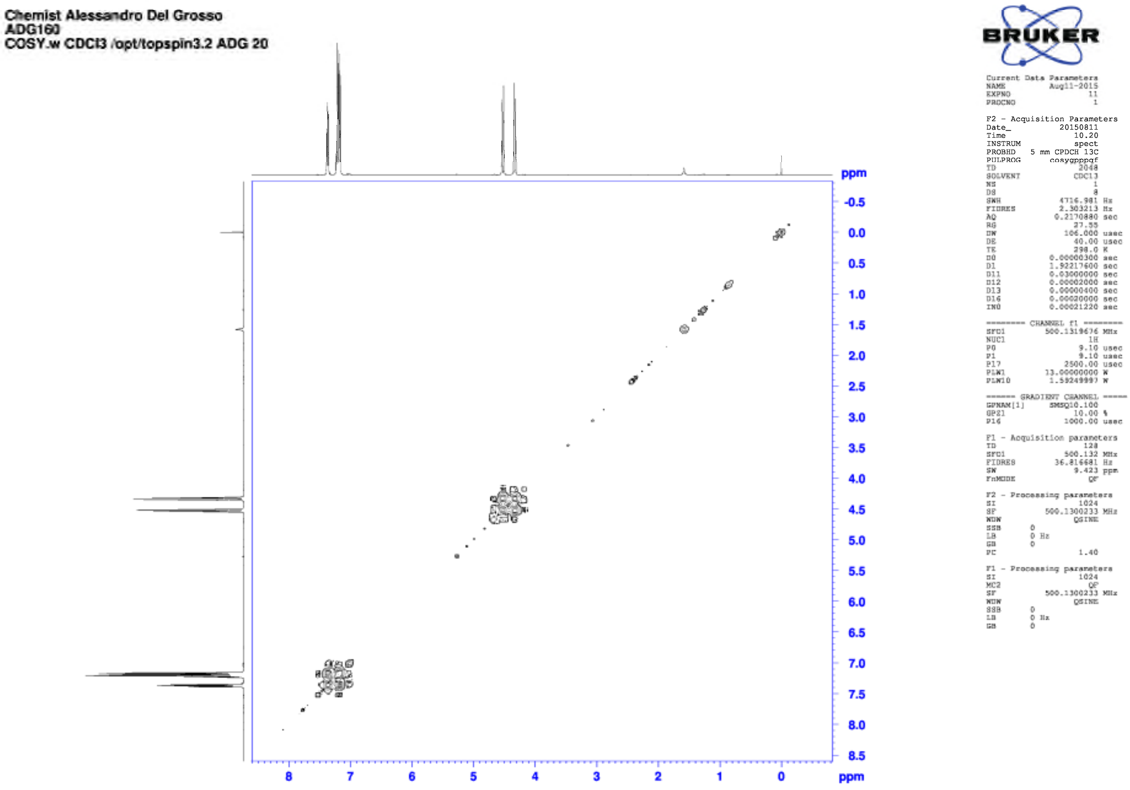

Chemist Alessandro Del Grosso
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PROCNO                 1

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PULPROG      cosygpppqf
TD                  2048
SOLVENT            CDCl3
NS                     1
DS                     8
SWH             4716.981 Hz
FIDRES          2.303213 Hz
AQ             0.2170880 sec
RG                 27.55
DW               106.000 usec
DE                 40.00 usec
TE                 298.0 K
D0            0.00000300 sec
D1            1.92217600 sec
D11           0.03000000 sec
D12           0.00002000 sec
D13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00021220 sec

======== CHANNEL f1 ========
SFO1         500.1319676 MHz
NUC1                  1H
P0                  9.10 usec
P1                  9.10 usec
P17              2500.00 usec
PLW1         13.00000000 W
PLW10         1.59249997 W

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GPZ1               10.00 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1             500.132 MHz
FIDRES         36.816681 Hz
SW                 9.423 ppm
FnMODE                QF

F2 - Processing parameters
SI                  1024
SF           500.1300233 MHz
WDW                QSINE
SSB      0
LB       0 Hz
GB       0
PC                  1.40

F1 - Processing parameters
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MC2                   QF
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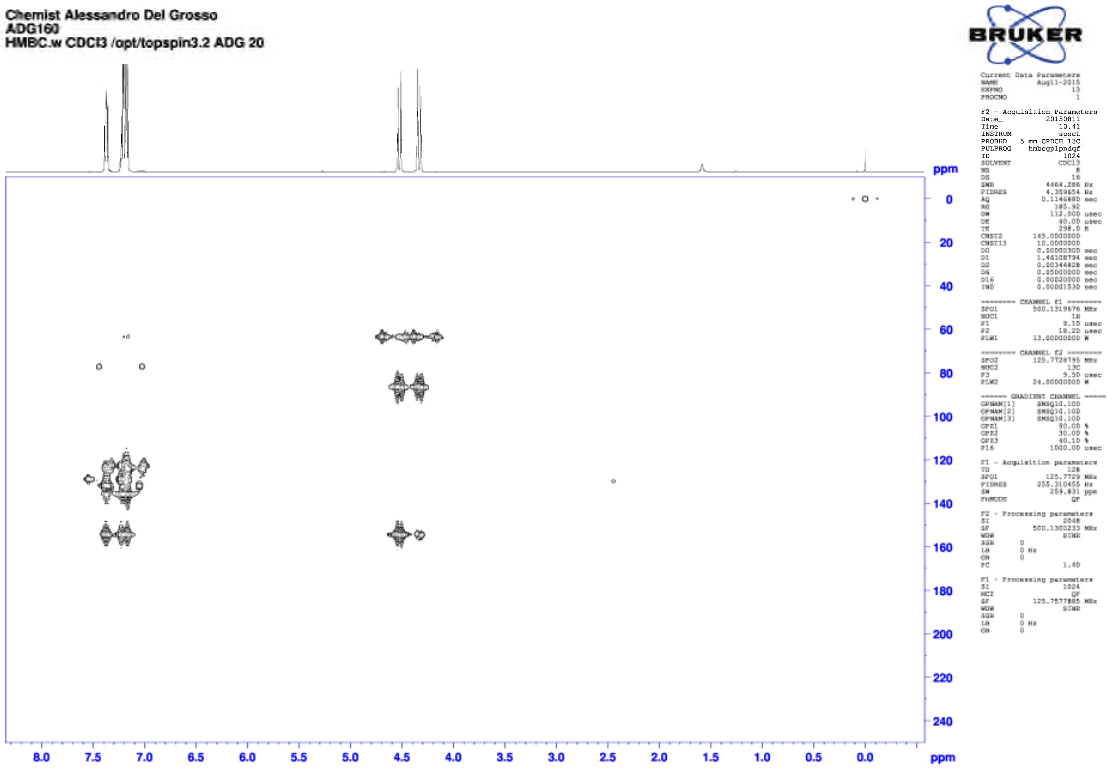
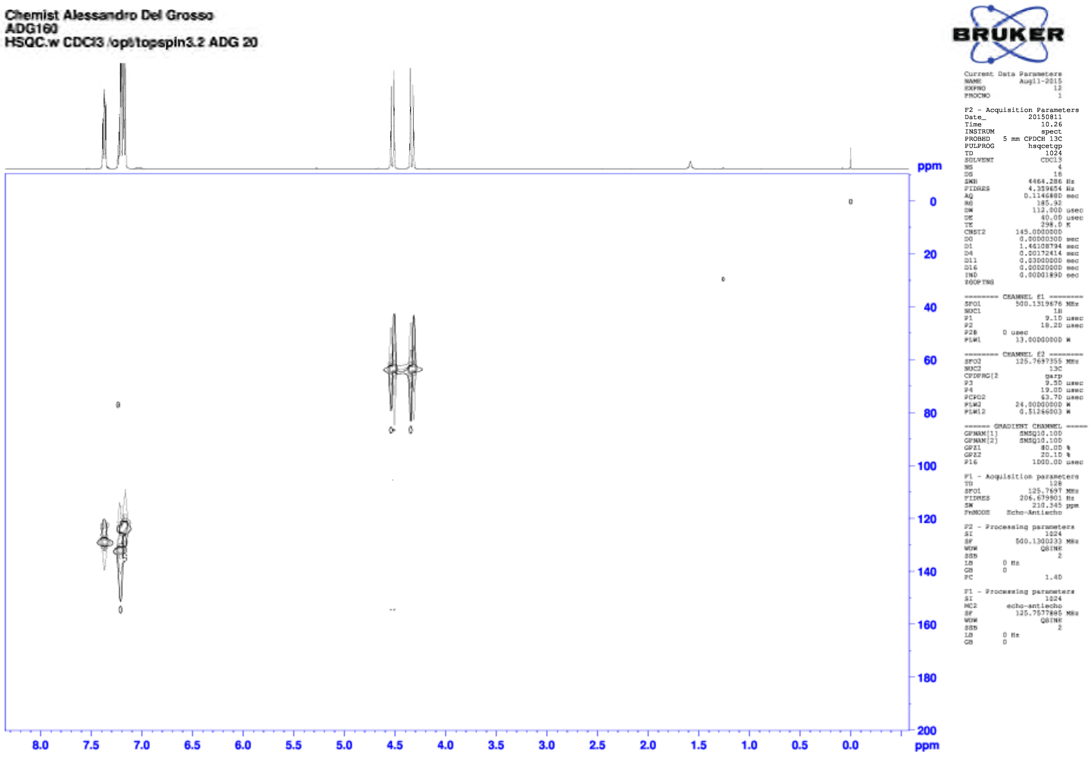
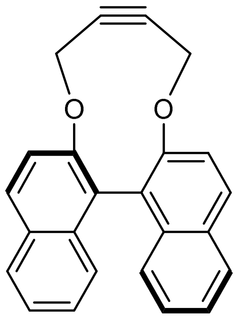




Synthesis of Compound 2 *R*-12,17-dioxapentacyclo[16.8.0.0^{2,11}.0^{3,8}.0^{21,26}]hexacosa-1(26),2,4,6,8,10,18,20,22,24-decaen-14-yne **2**.



In a round bottom flask under nitrogen atmosphere (*R*)-BINOL (726 mg, 2.54 mmol) and but-2-yne-1,4-diyl bis(4-methylbenzenesulfonate) (2.0 g, 5.07 mmol) were dissolved in anhydrous acetonitrile (250 mL). K_2CO_3 (3.5 g, 25.32 mmol) was added and the mixture was stirred at room temperature for 68 hours. The mixture was filtered through a plug of celite. The volatiles were removed and the product was purified by flash chromatography on silica gel (eluent: Petroleum Ether/EtOAc = 9:1 to EtOAc) to give compound **2** (121 mg, 0.36 mmol, 14%) as colourless solid. Crystals suitable for X-ray spectroscopy were grown by slow evaporation of DCM.

$[\alpha]_D^{25}$ +263.6 (*c* 0.505, $CHCl_3$).

m.p. 177.2-178.4 ºC

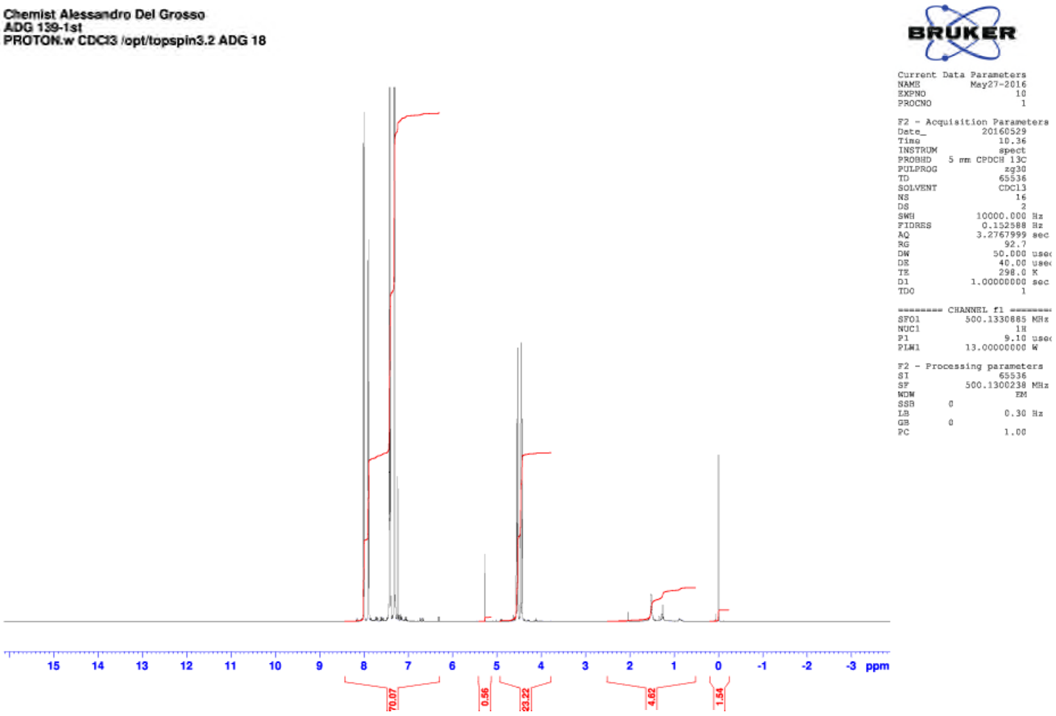
$IR_{(neat)}$ 3060, 2954, 2913, 2861, 1662, 1619, 1586, 1503, 1472, 1457, 1426, 1405, 1349, 1333, 1268, 1251, 1207, 1194 cm^{-1}.

δ_H (500 MHz, $CDCl_3$) 8.01 (2H, d, *J* = 8.9 Hz, Ar*H*), 7.90 (2H, d, *J* = 8.2 Hz, , Ar*H*), 7.38 - 7.45 (4H, m, Ar*H*), 7.31 (4H, d, *J* = 3.7 Hz, Ar*H*), 4.51 - 4.58 (2H, m, CH*H*), 4.41 - 4.48 (2H, m, C*H*H).

δ_C (125 MHz, $CDCl_3$) 152.5 (C), 133.7 (C), 131.1 (C), 130.3 (CH), 128.0 (CH), 127.8 (C), 126.6 (CH), 126.1 (CH), 125.2 (CH), 121.1 (CH), 88.0 (C), 62.3 (CH_2).

HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{17}O_2$ 337.1223; Found 337.1224.

^1H NMR (500 MHz, $CDCl_3$)



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PROCNO                 1

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Time               10.36
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PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                  92.7
DW                50.000 usec
DE                 40.00 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                  1H
P1                  9.10 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
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WDW                   EM
SSB      0
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GB       0
PC                  1.00
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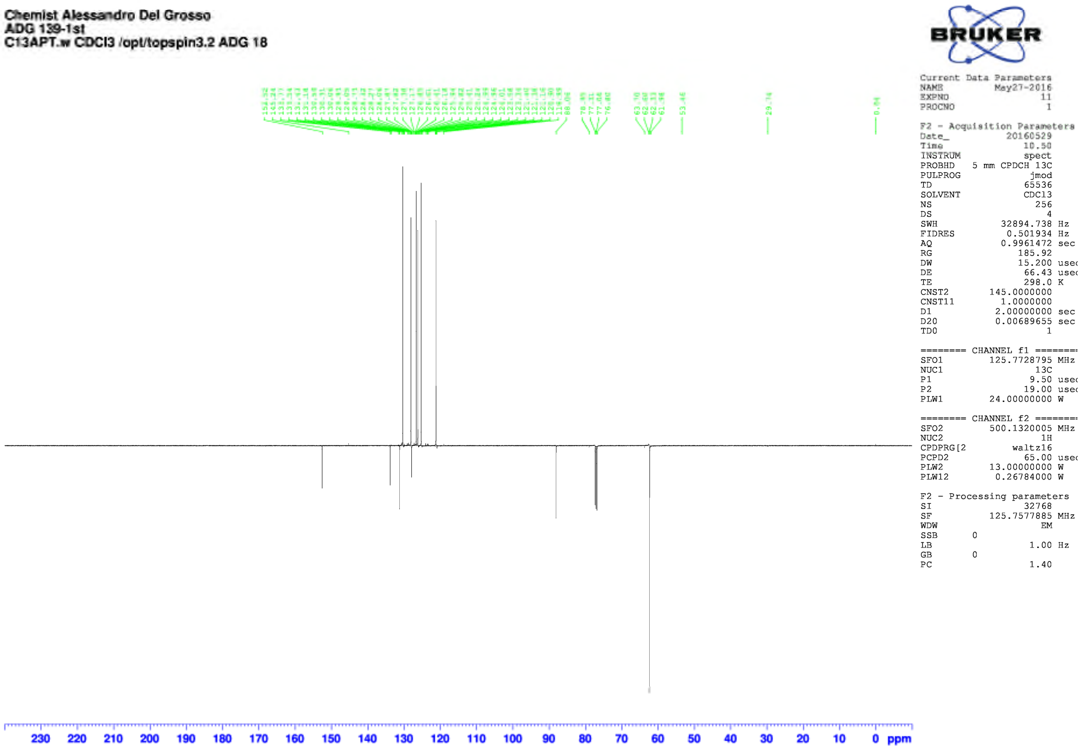
^{13}C NMR (125 MHz, CDCl$_3$)



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EXPNO                 11
PROCNO                 1

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Time               10.50
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             jmod
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            32894.738 Hz
FIDRES          0.501934 Hz
AQ             0.9961472 sec
RG                185.92
DW                15.200 usec
DE                 66.43 usec
TE                 298.0 K
CNST2        145.0000000
CNST11         1.0000000
D1            2.00000000 sec
D20           0.00689655 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7728795 MHz
NUC1                 13C
P1                  9.50 usec
P2                 19.00 usec
PLW1         24.00000000 W

======== CHANNEL f2 ========
SFO2         500.1320005 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              65.00 usec
PLW2         13.00000000 W
PLW12         0.26784000 W

F2 - Processing parameters
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WDW                   EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  1.40
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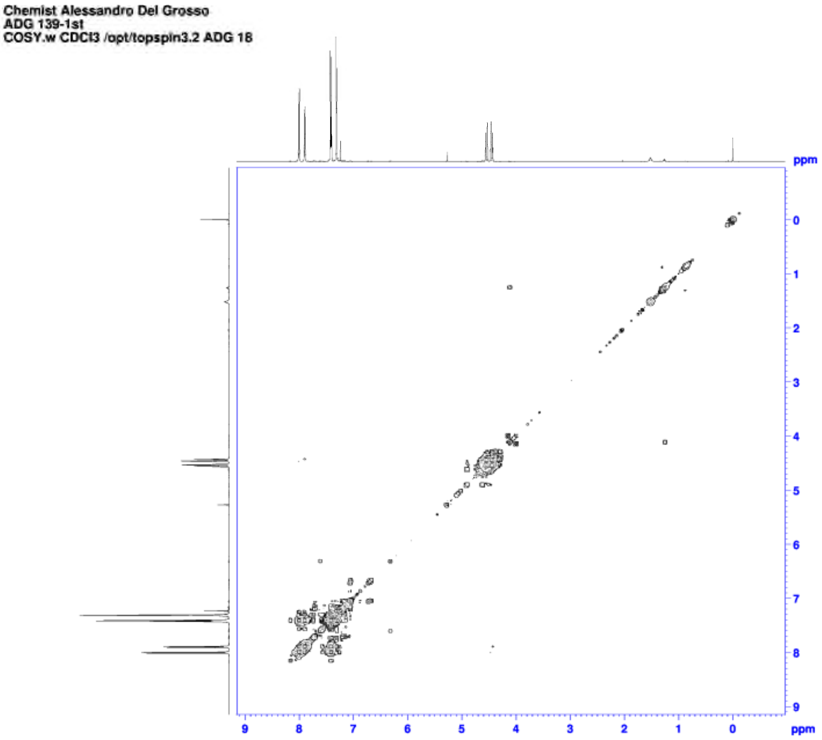

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PROBHD    5 mm CPDCH 13C
PULPROG            cosygpppqf
TD                      2048
SOLVENT                CDCl3
NS                         1
DS                         8
SWH                 5060.729 Hz
FIDRES              2.471059 Hz
AQ                 0.2023424 sec
RG                     60.07
DW                    98.800 usec
DE                     40.00 usec
TE                     298.0 K
D0                0.00000300 sec
D1                1.93856001 sec
D11               0.03000000 sec
D12               0.00002000 sec
D13               0.00000400 sec
D16               0.00020000 sec
IN0               0.00019780 sec

======== CHANNEL f1 ========
SFO1             500.1320712 MHz
NUC1                      1H
P0                      9.10 usec
P1                      9.10 usec
P17                  2500.00 usec
PLW1             13.00000000 W
PLW10             1.59249997 W

====== GRADIENT CHANNEL =====
GPNAM[1]          SMSQ10.100
GPZ1                   10.00 %
P16                  1000.00 usec

F1 - Acquisition parameters
TD                       128
SFO1                500.1321 MHz
FIDRES             39.496967 Hz
SW                    10.109 ppm
FnMODE                    QF

F2 - Processing parameters
SI                      1024
SF               500.1300238 MHz
WDW                    QSINE
SSB         0
LB          0 Hz
GB          0
PC                      1.40

F1 - Processing parameters
SI                      1024
MC2                       QF
SF               500.1300238 MHz
WDW                    QSINE
SSB         0
LB          0 Hz
GB          0
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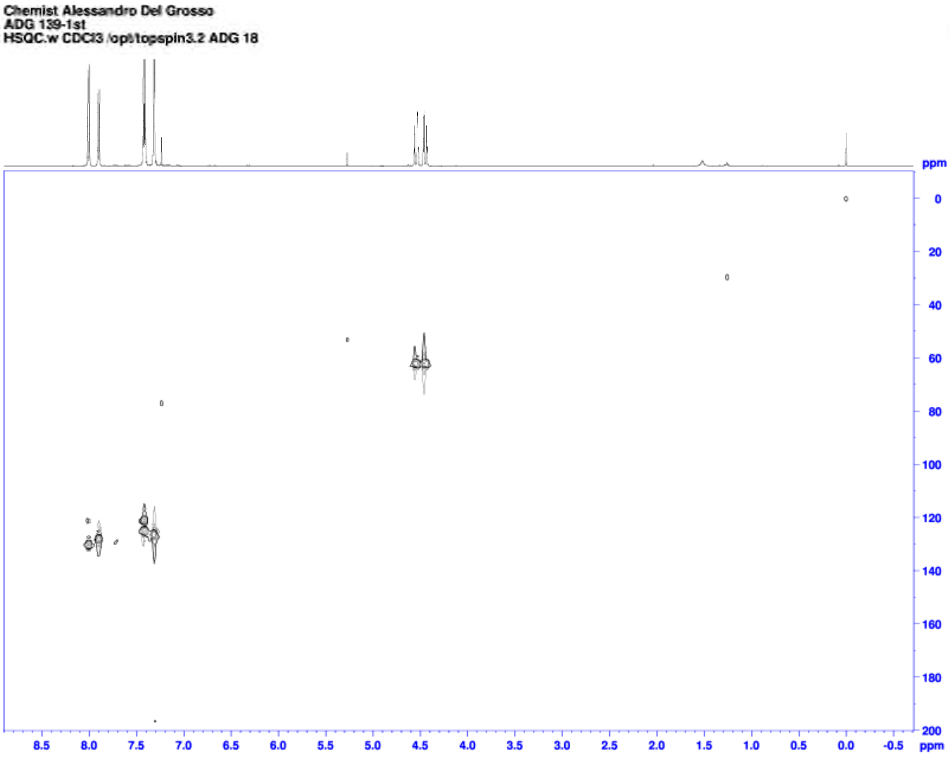

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PROCNO                     1

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INSTRUM                spect
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PULPROG             hsqcetgp
TD                      1024
SOLVENT                CDCl3
NS                         4
DS                        16
SWH                 4807.692 Hz
FIDRES              4.695012 Hz
AQ                 0.1064960 sec
RG                    185.92
DW                   104.000 usec
DE                     40.00 usec
TE                     298.0 K
CNST2            145.0000000
D0                0.00000300 sec
D1                1.46928000 sec
D4                0.00172414 sec
D11               0.03000000 sec
D16               0.00020000 sec
IN0               0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1             500.1320712 MHz
NUC1                      1H
P1                      9.10 usec
P2                     18.20 usec
P28         0 usec
PLW1             13.00000000 W

======== CHANNEL f2 ========
SFO2             125.7697355 MHz
NUC2                     13C
CPDPRG[2                garp
P3                      9.50 usec
P4                     19.00 usec
PCPD2                  63.70 usec
PLW2             24.00000000 W
PLW12             0.51266003 W

====== GRADIENT CHANNEL =====
GPNAM[1]          SMSQ10.100
GPNAM[2]          SMSQ10.100
GPZ1                   80.00 %
GPZ2                   20.10 %
P16                  1000.00 usec

F1 - Acquisition parameters
TD                       128
SFO1                125.7697 MHz
FIDRES            206.679901 Hz
SW                   210.345 ppm
FnMODE          Echo-Antiecho

F2 - Processing parameters
SI                      1024
SF               500.1300238 MHz
WDW                    QSINE
SSB                        2
LB          0 Hz
GB          0
PC                      1.40

F1 - Processing parameters
SI                      1024
MC2             echo-antiecho
SF               125.7577885 MHz
WDW                    QSINE
SSB                        2
LB          0 Hz
GB          0
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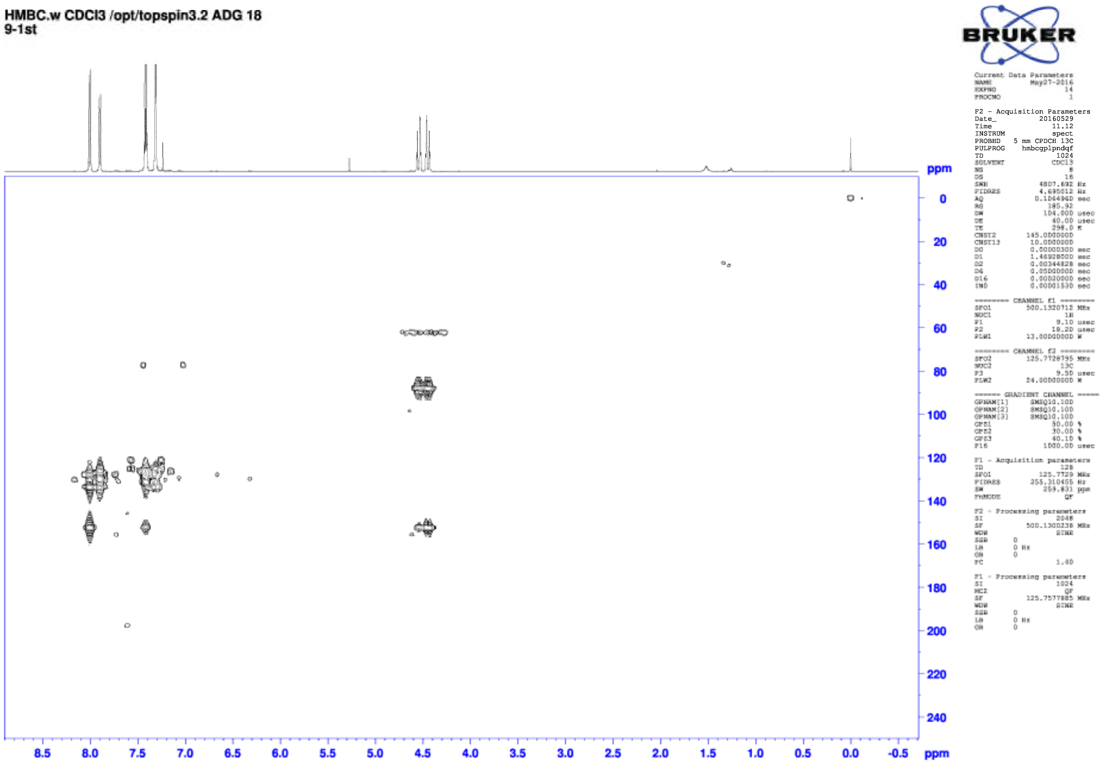
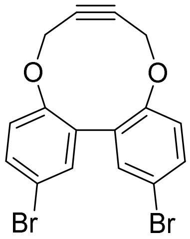


Synthesis of Compound 3; 4-17-dibromo-8,13-dioxatricyclo[12.4.0.02,7]octadeca-1(14),2,4,6,15,17-hexaen-10-yne **3**.



In a round bottom flask under nitrogen atmosphere 5,5'-dibromo-[1,1'-biphenyl]-2,2'-diol (436 mg, 1.27 mmol) and but-2-yne-1,4-diyl bis(4-methylbenzenesulfonate) (500 mg, 1.27 mmol) were dissolved in anhydrous acetonitrile (63 mL). K_2CO_3 (876 mg, 6.34 mmol) was added and the mixture was stirred at room temperature for 5 days. The volatiles were removed and H_2O (100 mL) was added. The product was extracted with DCM (3 x 100 mL). The reunited organic layers were washed with brine (100 mL) and dried over Na_2SO_4. The product was purified by flash chromatography on silica gel (eluent: Pentane/DCM = 1:1) to give the product **3** (122 mg, 0.31 mmol, 24%) as colourless solid.

m.p. 169.4 °C dec.

$IR_{(neat)}$ 2963, 2908, 2858, 1734, 1585, 1566, 1556, 1490, 1461, 1440, 1406, 1371, 1343, 1248, 1192cm^{-1}.

δ_H (500 MHz, $CDCl_3$) 7.49 (2H, dd, *J* = 8.6, 2.4 Hz, Ar*H*), 7.32 (2H, d, *J* = 2.4 Hz, Ar*H*), 7.04 (2H, d, *J* = 8.6 Hz, Ar*H*), 4.50 - 4.62 (2H, m, CH*H*), 4.25 - 4.35 (2H, m, C*H*H).

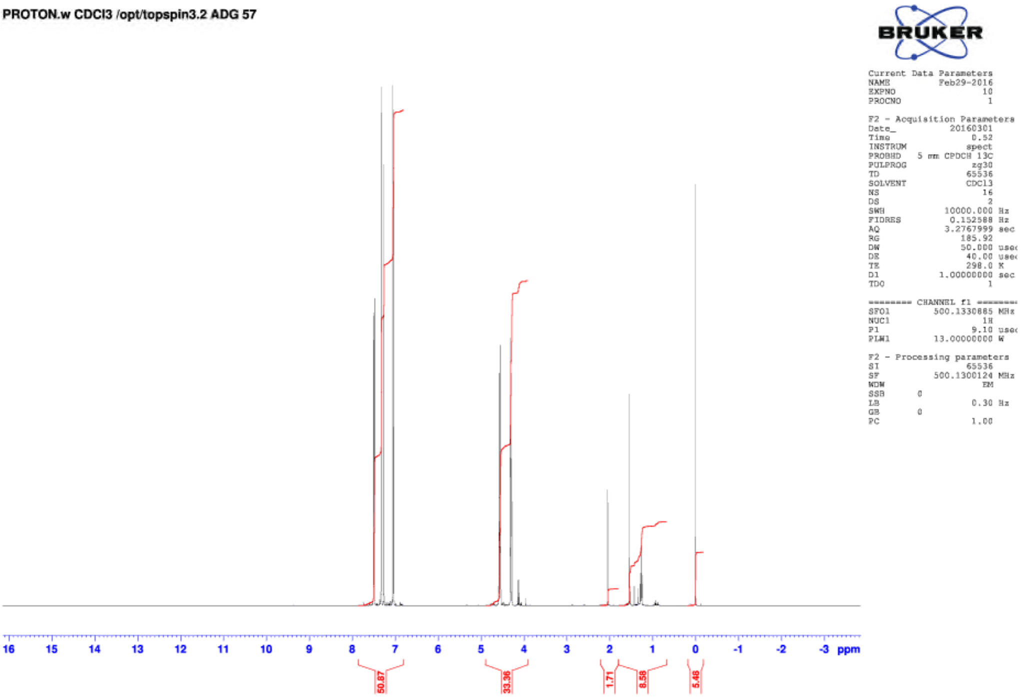
δ_C (125 MHz, $CDCl_3$) 153.5 (C), 136.6 (C), 134.6 (CH), 132.5 (CH), 124.4 (CH), 117.3 (C), 86.6 (C), 63.6 (CH_2).

HRMS (ESI-Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{11}{}^{79}Br_2O_2$ 392.9120; Found 392.9126.

Alternative procedure using butanone as solvent.

In a round bottom flask under a nitrogen atmosphere, 5,5'-dibromo-2'-methyl-3',4'-dihydro-[1,1'-biphenyl]-2-ol (689 mg, 2.00 mmol), potassium carbonate (1.38 g, 10.0 mmol) and but-2-yne-1,4-diyl bis(4-methylbenzenesulfonate) (789 mg, 2.00 mmol) were dissolved in butan-2-one (100 mL). The mixture was degassed, stirred at 80 °C for 5 days. The butan-2-one was evaporated under reduced pressure. The organic fractions were redissolved with water (100 mL) and extracted with DCM (3 x 50 mL). The organic extracts were dried over magnesium sulphate, filtered and the DCM was evaporated under reduced pressure. The product was purified by column chromatography (eluent: hexane to hexane/ethyl acetate 88:12) to obtain the product **3** as a white solid (363 mg, 0.92 mmol, 46%). The data for the product matched that reported above.

^1H NMR (500 MHz, $CDCl_3$)



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PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH              10000.000 Hz
FIDRES            0.152588 Hz
AQ               3.2767999 sec
RG                  185.92
DW                  50.000 usec
DE                   40.00 usec
TE                   298.0 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           500.1330885 MHz
NUC1                    1H
P1                    9.10 usec
PLW1           13.00000000 W

F2 - Processing parameters
SI                   65536
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SSB       0
LB                    0.30 Hz
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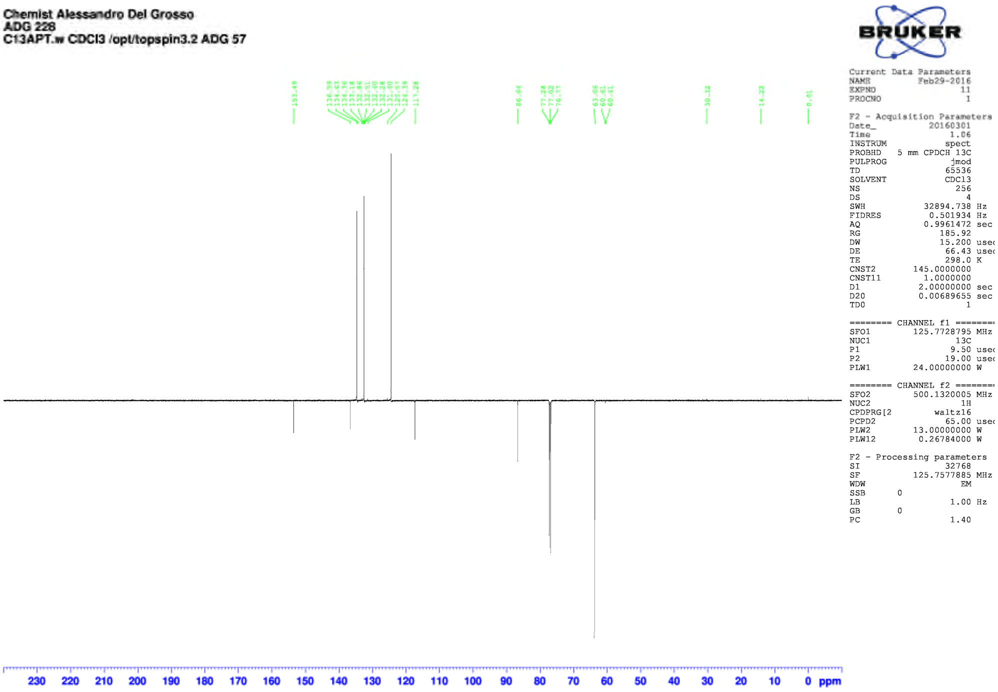
^{13}C NMR (125 MHz, $CDCl_3$)



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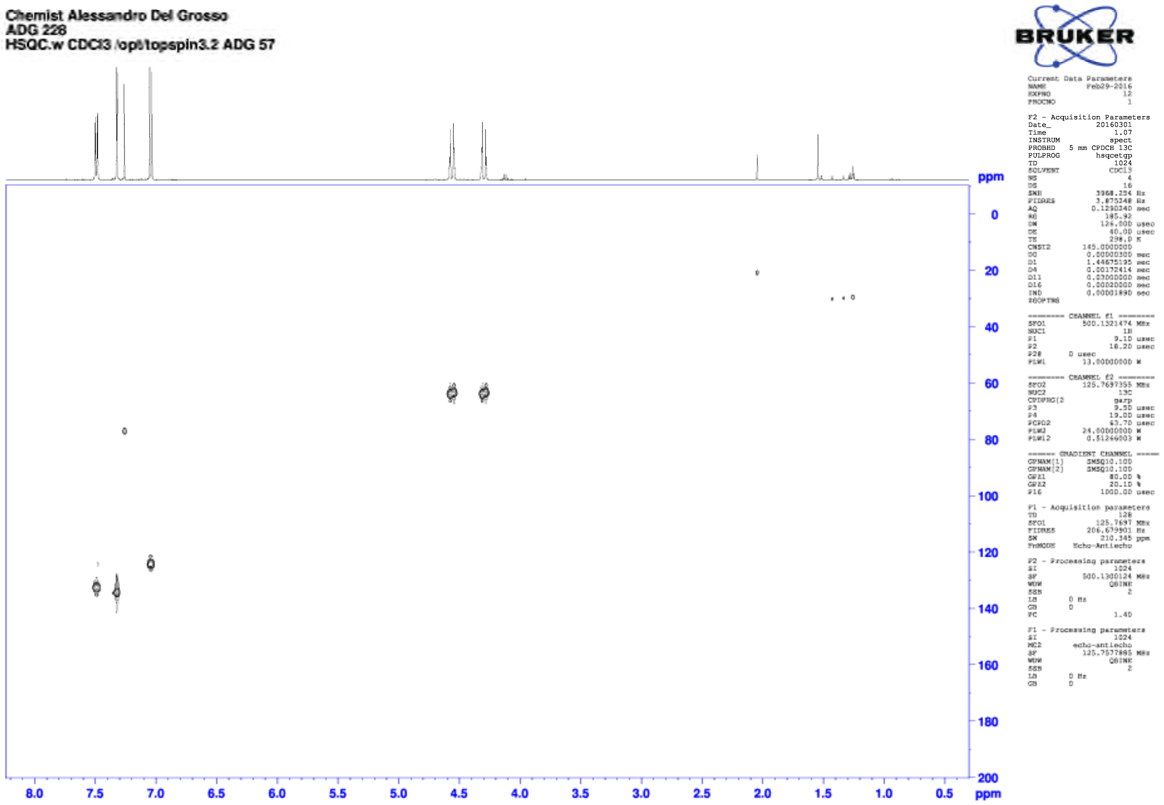
PULPROG               jmod
TD                   65536
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              32894.738 Hz
FIDRES            0.501934 Hz
AQ               0.9961472 sec
RG                  185.92
DW                  15.200 usec
DE                   66.43 usec
TE                   298.0 K
CNST2          145.0000000
CNST11           1.0000000
D1              2.00000000 sec
D20             0.00689655 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           125.7728795 MHz
NUC1                   13C
P1                    9.50 usec
P2                   19.00 usec
PLW1           24.00000000 W

======== CHANNEL f2 ========
SFO2           500.1320005 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                65.00 usec
PLW2           13.00000000 W
PLW12           0.26784000 W

F2 - Processing parameters
SI                   32768
SF             125.7577885 MHz
WDW                     EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.40
```

Chemist Alessandro Del Grosso
ADG 228
HSQC.w CDCl3 /opt/topspin3.2 ADG 57



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Current Data Parameters
NAME          Feb29-2016
EXPNO                 12
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160301
Time                1.07
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG         hsqcetgp
TD                  1024
SOLVENT            CDCl3
NS                     4
DS                    16
SWH             3968.254 Hz
FIDRES          3.875248 Hz
AQ             0.1290240 sec
RG                185.92
DW               126.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
D0            0.00000300 sec
D1            1.44675195 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
IN0           0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         500.1321474 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
P28        0 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7697355 MHz
NUC2                 13C
CPDPRG[2            garp
P3                  9.50 usec
P4                 19.00 usec
PCPD2              63.70 usec
PLW2         24.00000000 W
PLW12         0.51266003 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7697 MHz
FIDRES        206.679901 Hz
SW               210.345 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI                  1024
SF           500.1300124 MHz
WDW                QSINE
SSB                    2
LB         0 Hz
GB         0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2         echo-antiecho
SF           125.7577885 MHz
WDW                QSINE
SSB                    2
LB         0 Hz
GB         0
```
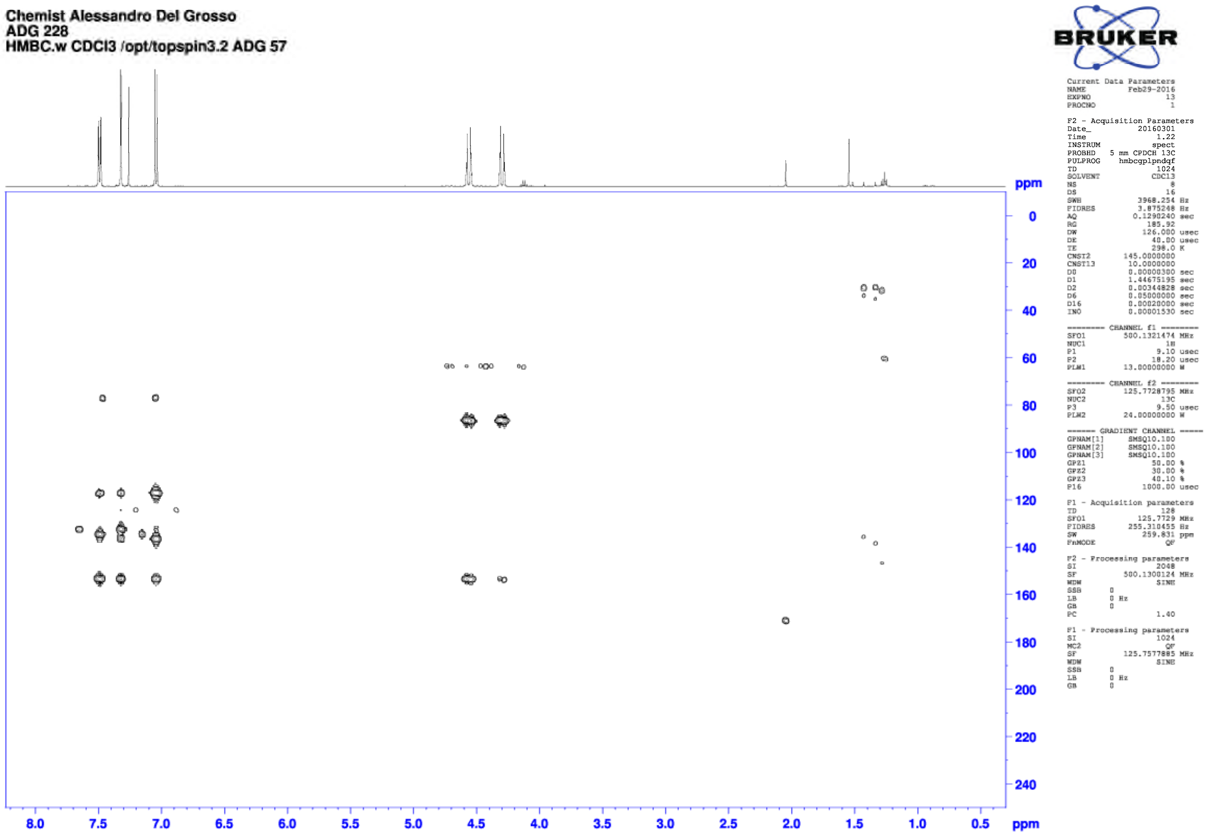

Chemist Alessandro Del Grosso
ADG 228
HMBC.w CDCl3 /opt/topspin3.2 ADG 57



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Current Data Parameters
NAME          Feb29-2016
EXPNO                 13
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160301
Time                1.22
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG      hmbcgplpndqf
TD                  1024
SOLVENT            CDCl3
NS                     8
DS                    16
SWH             3968.254 Hz
FIDRES          3.875248 Hz
AQ             0.1290240 sec
RG                185.92
DW               126.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
CNST13        10.0000000
D0            0.00000300 sec
D1            1.44675195 sec
D2            0.00344828 sec
D6            0.05000000 sec
D16           0.00020000 sec
IN0           0.00001530 sec

======== CHANNEL f1 ========
SFO1         500.1321474 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7728795 MHz
NUC2                 13C
P3                  9.50 usec
PLW2         24.00000000 W

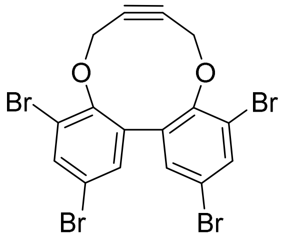
====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPNAM[3]      SMSQ10.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7729 MHz
FIDRES        255.310455 Hz
SW               259.831 ppm
FnMODE                QF

F2 - Processing parameters
SI                  2048
SF           500.1300124 MHz
WDW                 SINE
SSB        0
LB         0 Hz
GB         0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           125.7577885 MHz
WDW                 SINE
SSB        0
LB         0 Hz
GB         0
```

Synthesis of Compound 4; 4-6-15-17-tetrabromo-8,13-dioxatricyclo[12.4.0.0^{2},^{7}]octadeca-1(14),2,4,6,15,17-hexaen-10-yne **4**.



In a round bottom flask under nitrogen atmosphere 3,3',5,5'-dibromo-[1,1'-biphenyl]-2,2'-diol (636 mg, 1.27 mmol) and but-2-yne-1,4-diyl bis(4-methylbenzenesulfonate) (500 mg, 1.27 mmol) were dissolved in anhydrous acetonitrile (63 mL). K_2CO_3 (876 mg, 6.34 mmol) was added and the mixture was stirred at room temperature for 10 days. The volatiles were removed and H_2O (100 mL) was added. The product was extracted with DCM (3x150 mL). The reunited organic layers were washed with brine (100 mL) and dried over Na_2SO_4. The product was purified by flash chromatography on silica gel (eluent: Petroleum ether/EtOAc = 4:1 to 3:1) to give the product **4** (411 mg, 0.74 mmol, 59%) as colourless solid.

m.p. 170.7 ºC dec.

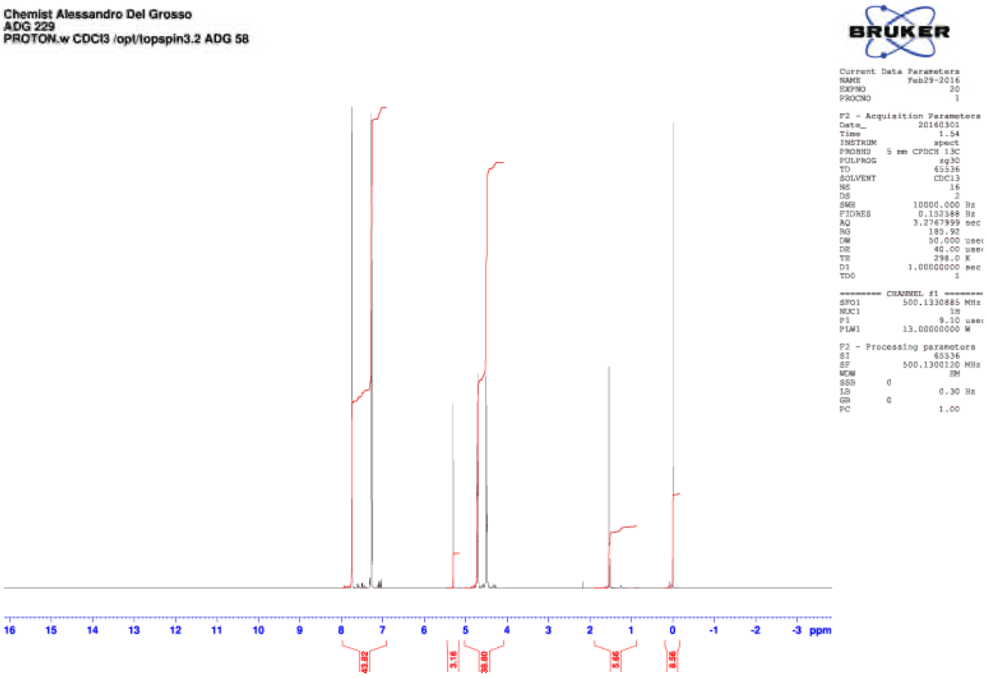
$IR_{(neat)}$ 3094, 3065, 2976, 2961, 2930, 2907, 2854, 1569, 1537, 1461, 1443, 1420, 1369, 1336, 1238, 1207 cm^{-1}.

δ_H (500 MHz, $CDCl_3$) 7.75 (2H, d, *J* = 2.4 Hz, Ar*H*), 7.28 (2H, d, *J* = 2.4 Hz, Ar*H*), 4.68 - 4.75 (2H, m, CH*H*), 4.47 - 4.54 (2H, m, C*H*H).

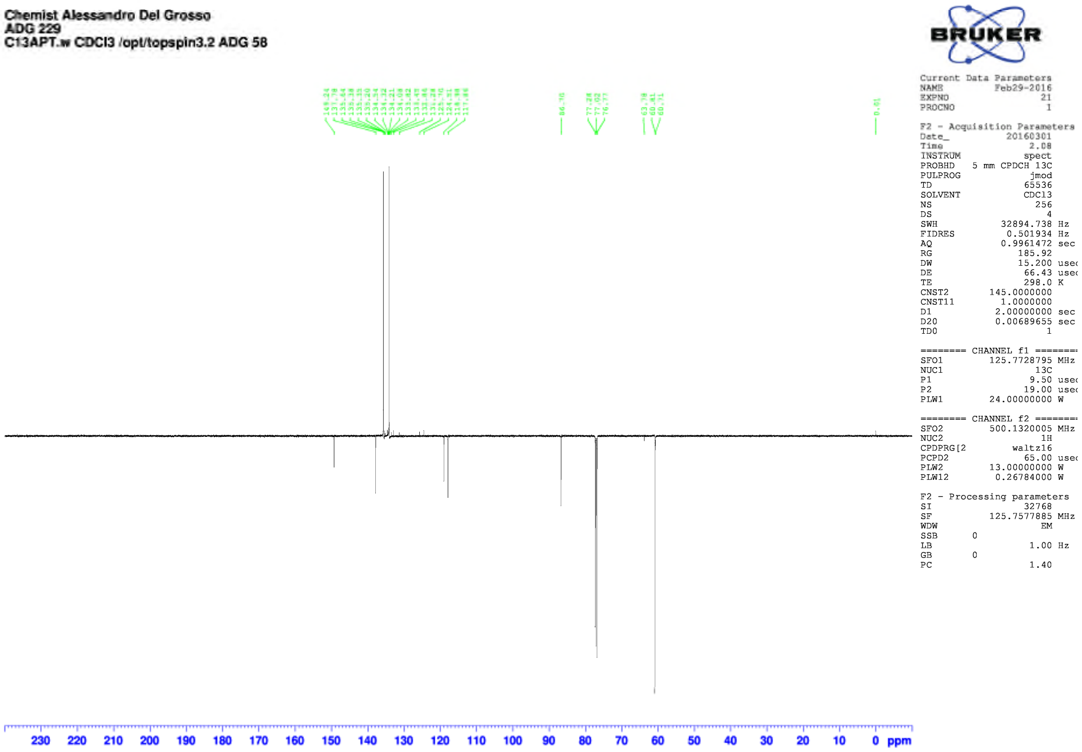
δ_C (125 MHz, $CDCl_3$) 149.2 (C), 137.8 (C), 135.6 (CH), 134.1 (CH), 119.0 (C), 117.8 (C), 86.7 (C), 60.8 (CH_2).

HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_8{}^{79}Br_4O_2Na$ 570.7150; Found 570.7135.

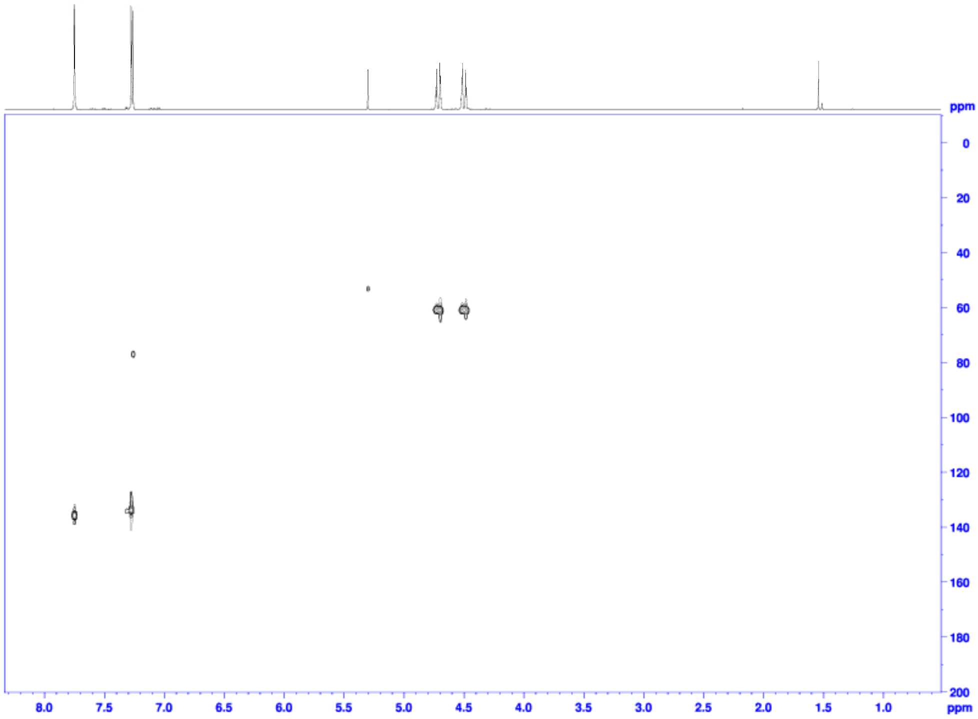
^{1}H NMR (500 MHz, $CDCl_3$).



^{13}C NMR (125 MHz, CDCl$_3$)



Chemist Alessandro Del Grosso
ADG 229
HSQC.w CDCl3 /opt/topspin3.2 ADG 58



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Current Data Parameters
NAME          Feb29-2016
EXPNO                 22
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160301
Time                2.10
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG         hsqcetgp
TD                  1024
SOLVENT            CDCl3
NS                     4
DS                    16
SWH             3906.250 Hz
FIDRES          3.814697 Hz
AQ             0.1310720 sec
RG                185.92
DW               128.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
D0            0.00000300 sec
D1            1.44470406 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
IN0           0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         500.1322256 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
P28        0 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7697355 MHz
NUC2                 13C
CPDPRG[2            garp
P3                  9.50 usec
P4                 19.00 usec
PCPD2              63.70 usec
PLW2         24.00000000 W
PLW12         0.51266003 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7697 MHz
FIDRES        206.679901 Hz
SW               210.345 ppm
FnMODE      Echo-Antiecho

F2 - Processing parameters
SI                  1024
SF           500.1300120 MHz
WDW                QSINE
SSB                    2
LB         0 Hz
GB         0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2        echo-antiecho
SF           125.7577885 MHz
WDW                QSINE
SSB                    2
LB         0 Hz
GB         0
```
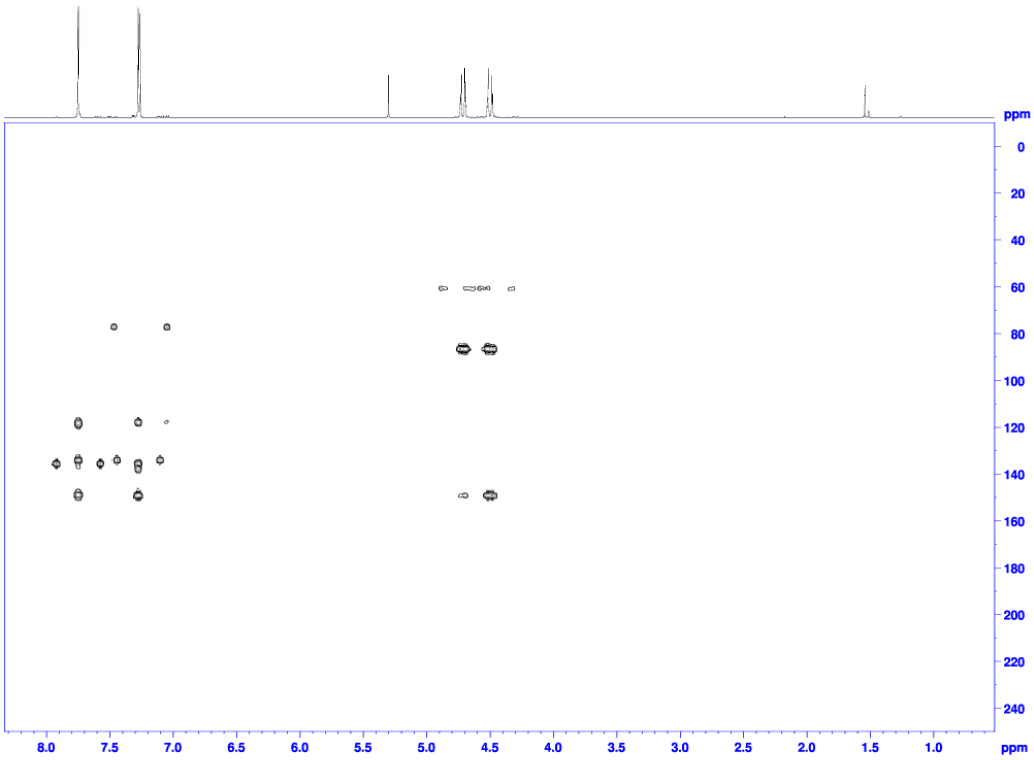
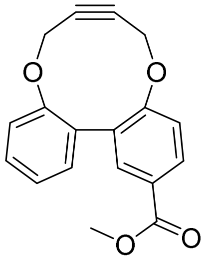

Chemist Alessandro Del Grosso
ADG 229
HMBC.w CDCl3 /opt/topspin3.2 ADG 58



```
Current Data Parameters
NAME          Feb29-2016
EXPNO                 23
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160301
Time                2.24
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG      hmbcgplpndqf
TD                  1024
SOLVENT            CDCl3
NS                     8
DS                    16
SWH             3906.250 Hz
FIDRES          3.814697 Hz
AQ             0.1310720 sec
RG                185.92
DW               128.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
CNST13        10.0000000
D0            0.00000300 sec
D1            1.44470406 sec
D2            0.00344828 sec
D6            0.05000000 sec
D16           0.00020000 sec
IN0           0.00001530 sec

======== CHANNEL f1 ========
SFO1         500.1322256 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7728795 MHz
NUC2                 13C
P3                  9.50 usec
PLW2         24.00000000 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPNAM[3]      SMSQ10.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7729 MHz
FIDRES        255.310455 Hz
SW               259.831 ppm
FnMODE                QF

F2 - Processing parameters
SI                  2048
SF           500.1300120 MHz
WDW                 SINE
SSB        0
LB         0 Hz
GB         0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           125.7577885 MHz
WDW                 SINE
SSB        0
LB         0 Hz
GB         0
```

Synthesis of Compound 11; Methyl 8,13-dioxatricyclo[12.4.0.0^{2},^{7}]octadeca-1(18),2(7),3,5,14,16-hexaen-10-yne-4-carboxylate **11**.



In a round bottom flask under nitrogen atmosphere methyl 2',6-dihydroxy-[1,1'-biphenyl]-3-carboxylate (313 mg, 1.28 mmol) **12** and but-2-yne-1,4-diyl bis(4-methylbenzenesulfonate) (500 mg, 1.27 mmol) were dissolved in anhydrous acetonitrile (63 mL). K_2CO_3 (876 mg, 6.34 mmol) was added and the mixture was stirred at room temperature for 13 days. The volatiles were removed and H_2O (100 mL) was added. The product was extracted with DCM (3x150 mL). The reunited organic layers were washed with brine (100 mL) and dried over Na_2SO_4. The product was purified by flash chromatography on silica gel (eluent: Petroleum ether/EtOAc = 4:1 to 3:1) to give compound **11** (188 mg, 0.64 mmol, 50%) as colourless solid.

m.p. 121.1-122.4 ºC.

IR$_{(neat)}$ 2952, 2921, 2854, 1713, 1608, 1598, 1577, 1499, 1475, 1434, 1405, 1346, 1307, 1288, 1266, 1232, 1190 cm^{-1}.

δ_H (500 MHz, $CDCl_3$) 8.07 (1H, dd, *J* = 8.5, 2.2 Hz, Ar*H*), 7.93 (1H, d, *J* = 2.2 Hz, Ar*H*), 7.37 - 7.44 (1H, m, Ar*H*), 7.16 - 7.25 (4H, m, Ar*H*), 4.49 - 4.62 (2H, m, CH*H*), 4.30 - 4.41 (2H, m, C*H*H), 3.88 (3H, s, CH_3).

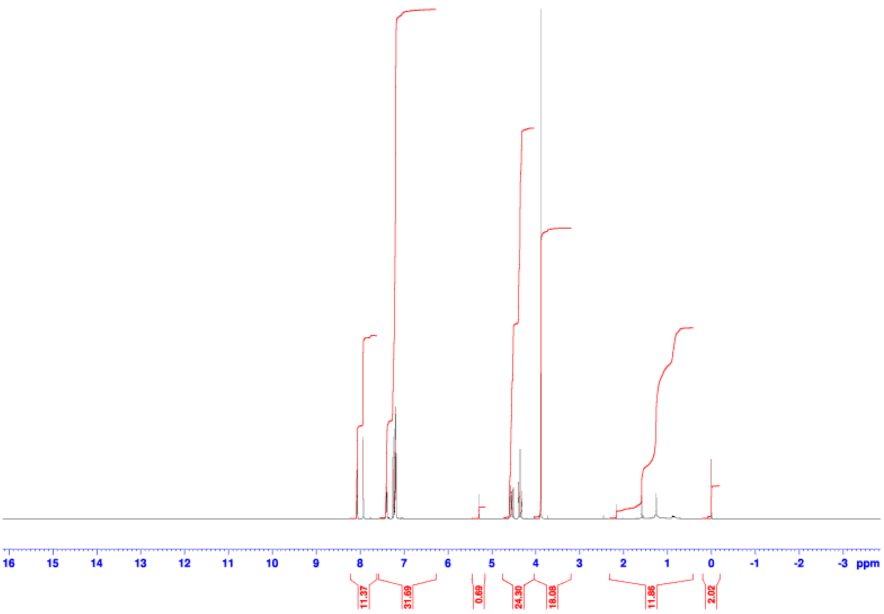
δ_C (125 MHz, $CDCl_3$) 166.6 (C), 158.5 (C), 154.4 (C), 136.0 (C), 135.0 (C), 133.7 (CH), 131.8 (CH), 130.7 (CH), 129.5 (CH), 126.2 (C), 124.3 (CH), 122.8 (CH), 122.6 (CH), 87.2 (C), 86.1 (C), 63.7 (CH_2), 63.5 (CH_2), 52.1 (CH_3).

m/z (ESI) [M + Na]$^+$, 317.1

HRMS (ESI-Q-TOF) m/z: [M + Na]$^+$ Calcd for $C_{18}H_{14}O_4Na$ 317.0784; Found 317.0789.

^{1}H NMR (500 MHz, $CDCl_3$)

Chemist Alessandro Del Grosso
ADG298
PROTON.w CDCl3 /opt/topspin3.2 ADG 56



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Current Data Parameters
NAME          Feb18-2016
EXPNO                 10
PROCNO                 1

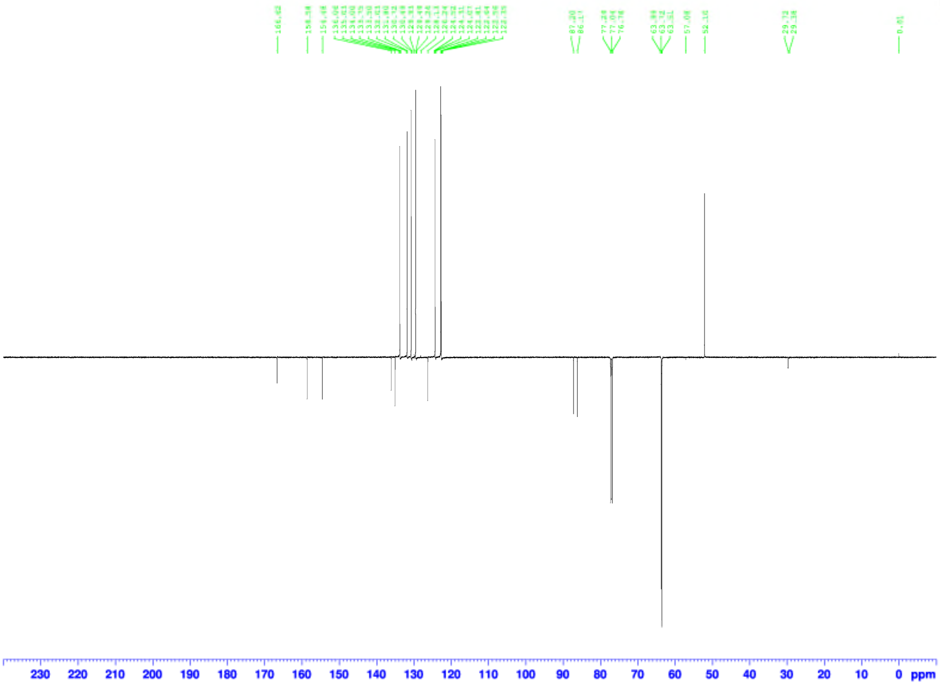
F2 - Acquisition Parameters
Date_           20160218
Time                8.46
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                118.71
DW                50.000 usec
DE                 40.00 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                  1H
P1                  9.10 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1300127 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```

^{13}C NMR (125 MHz, CDCl$_3$)

C13APT.w CDCl3 /opt/topspin3.2 ADG 56



```
Current Data Parameters
NAME          Feb18-2016
EXPNO                 14
PROCNO                 1

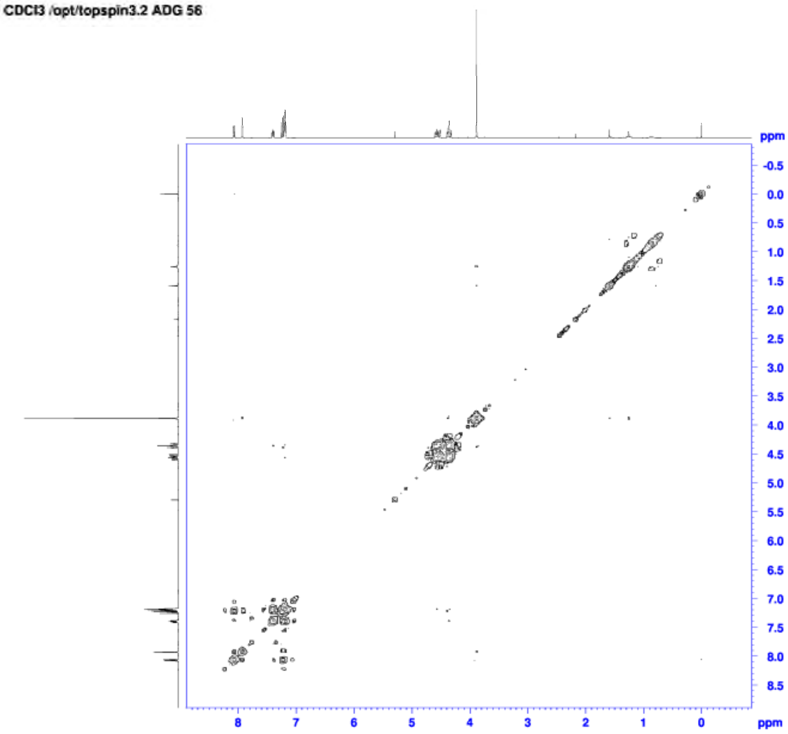
F2 - Acquisition Parameters
Date_           20160218
Time                9.50
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             jmod
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            32894.738 Hz
FIDRES          0.501934 Hz
AQ             0.9961472 sec
RG                185.92
DW                15.200 usec
DE                 66.43 usec
TE                 298.0 K
CNST2        145.0000000
CNST11         1.0000000
D1            2.00000000 sec
D20           0.00689655 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7728795 MHz
NUC1                 13C
P1                  9.50 usec
P2                 19.00 usec
PLW1         24.00000000 W

======== CHANNEL f2 ========
SFO2         500.1320005 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              65.00 usec
PLW2         13.00000000 W
PLW12         0.26784000 W

F2 - Processing parameters
SI                 32768
SF           125.7577885 MHz
WDW                   EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  1.40
```

Chemist Alessandro Del Grosso
ADG298
COSY.w CDCl3 /opt/topspin3.2 ADG 56



```
Current Data Parameters
NAME          Feb18-2016
EXPNO                 11
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160218
Time                8.48
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG        cosygpppqf
TD                  2048
SOLVENT            CDCl3
NS                     1
DS                     8
SWH             4882.812 Hz
FIDRES          2.384186 Hz
AQ             0.2097152 sec
RG                 60.07
DW               102.400 usec
DE                 40.00 usec
TE                 298.0 K
D0            0.00000300 sec
D1            1.93036795 sec
D11           0.03000000 sec
D12           0.00002000 sec
D13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00020500 sec

======== CHANNEL f1 ========
SFO1         500.1320217 MHz
NUC1                  1H
P0                  9.10 usec
P1                  9.10 usec
P17              2500.00 usec
PLW1         13.00000000 W
PLW10         1.59249997 W

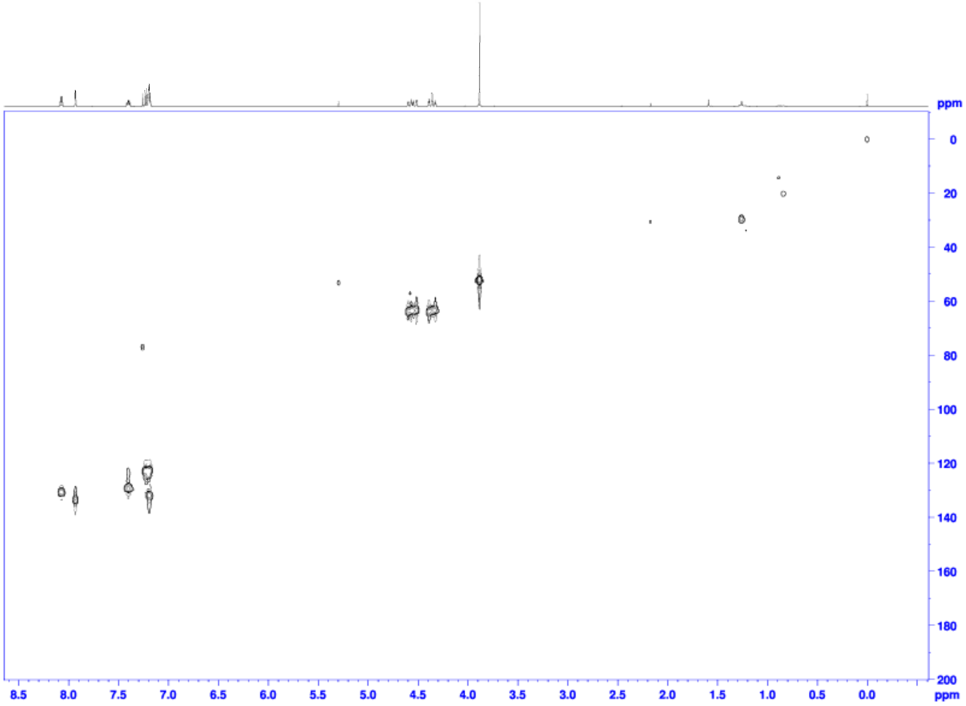
====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPZ1               10.00 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1             500.132 MHz
FIDRES         38.109756 Hz
SW                 9.754 ppm
FnMODE                QF

F2 - Processing parameters
SI                  1024
SF           500.1300127 MHz
WDW                QSINE
SSB      0
LB       0 Hz
GB       0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           500.1300127 MHz
WDW                QSINE
SSB      0
LB       0 Hz
GB       0
```

Chemist Alessandro Del Grosso
ADG298
HSQC.w CDCl3 /opt/topspin3.2 ADG 56



```
Current Data Parameters
NAME          Feb18-2016
EXPNO                 12
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160218
Time                8.54
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG         hsqcetgp
TD                  1024
SOLVENT            CDCl3
NS                     4
DS                    16
SWH             4629.629 Hz
FIDRES          4.521122 Hz
AQ             0.1105920 sec
RG                185.92
DW               108.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
D0            0.00000300 sec
D1            1.46518397 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
IN0           0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         500.1320217 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
P28      0 usec
PLW1         13.00000000 W

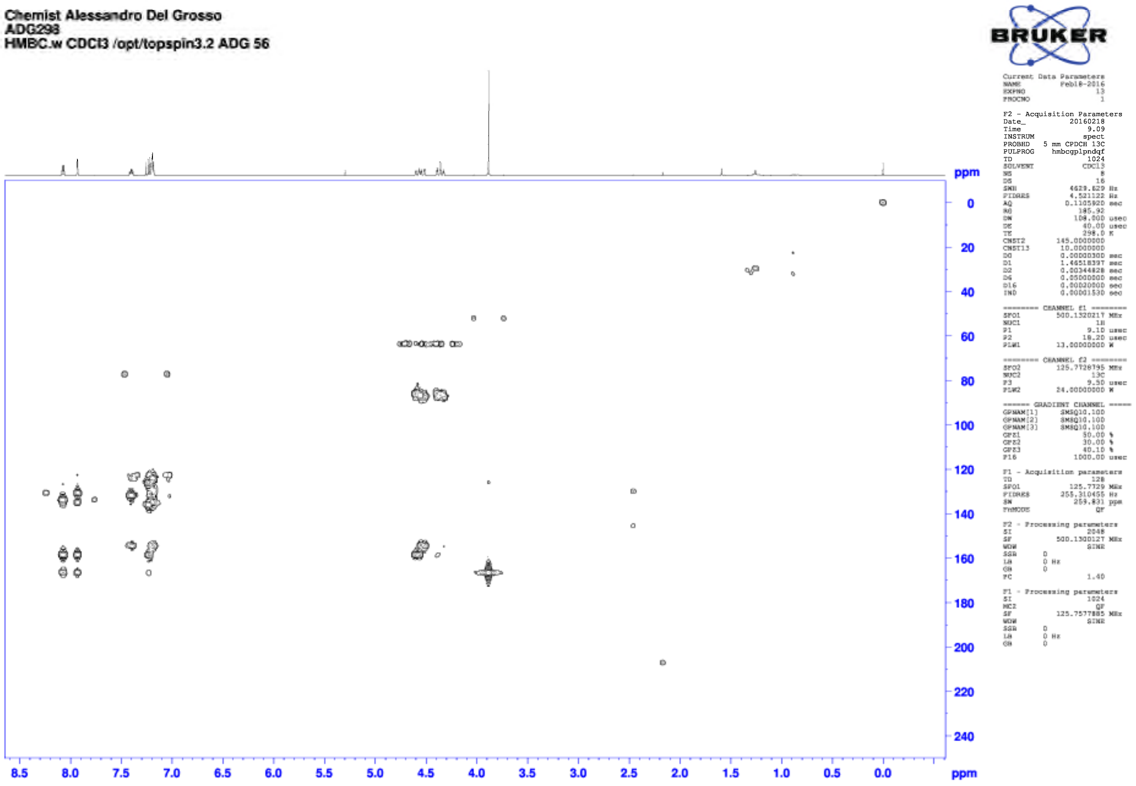
======== CHANNEL f2 ========
SFO2         125.7697355 MHz
NUC2                 13C
CPDPRG[2            garp
P3                  9.50 usec
P4                 19.00 usec
PCPD2              63.70 usec
PLW2         24.00000000 W
PLW12         0.51266003 W

====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPNAM[2]       SMSQ10.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

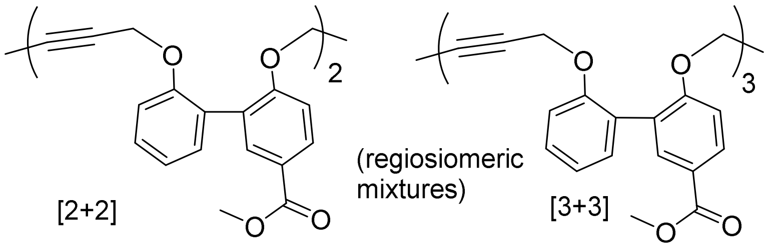
F1 - Acquisition parameters
TD                   128
SFO1            125.7697 MHz
FIDRES        206.679901 Hz
SW               210.345 ppm
FnMODE      Echo-Antiecho

F2 - Processing parameters
SI                  1024
SF           500.1300127 MHz
WDW                QSINE
SSB                    2
LB       0 Hz
GB       0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2        echo-antiecho
SF           125.7577885 MHz
WDW                QSINE
SSB                    2
LB       0 Hz
GB       0
```

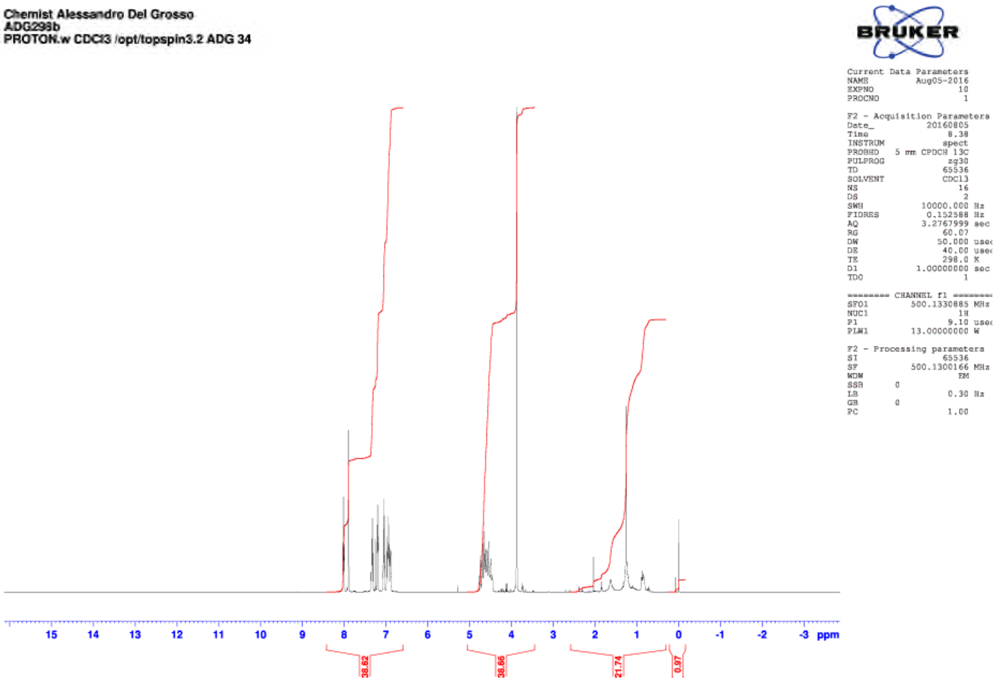


From this procedure, some 2+2 (54 mg, 15 %) and some 3+3 (36 mg, 10 %) product were also isolated.



The 2+2 product NMRs are below (298b). The HRMS is also shown, to confirm the structure of the macrocycle:

^{1}H NMR (500 MHz, CDCl$_3$).



```
Chemist Alessandro Del Grosso
ADG298b
PROTON.w CDCl3 /opt/topspin3.2 ADG 34
```

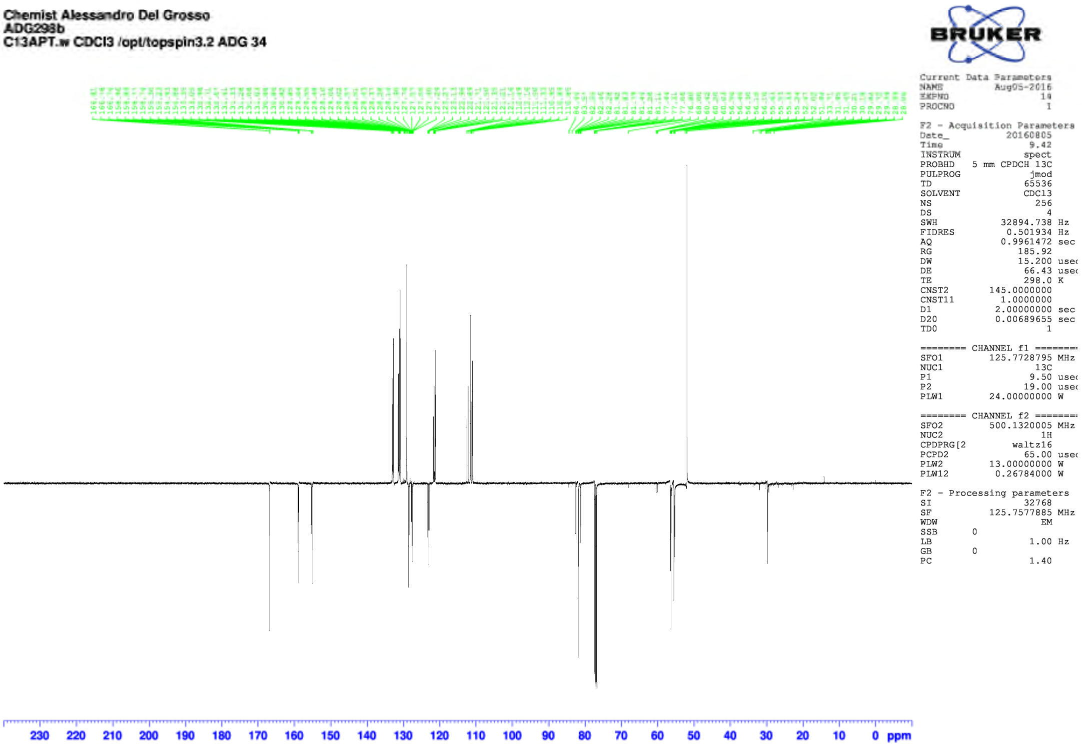
```
Current Data Parameters
NAME          Aug05-2016
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160805
Time                8.38
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                 60.07
DW                50.000 usec
DE                 40.00 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                  1H
P1                  9.10 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1300166 MHz
WDW                   EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

^{13}C NMR (125 MHz, $CDCl_3$).



```
Chemist Alessandro Del Grosso
ADG298b
C13APT.w CDCl3 /opt/topspin3.2 ADG 34
```

```
Current Data Parameters
NAME          Aug05-2016
EXPNO                 14
PROCNO                 1

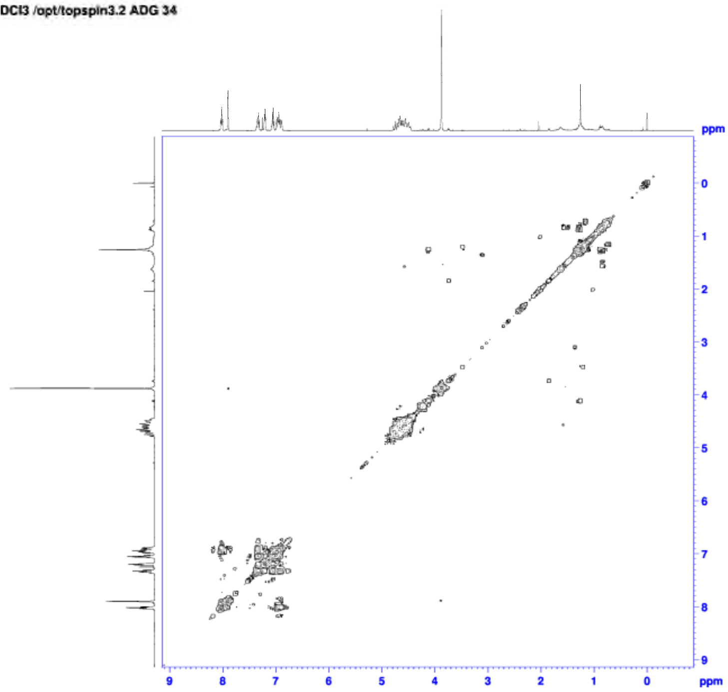
F2 - Acquisition Parameters
Date_           20160805
Time                9.42
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             jmod
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            32894.738 Hz
FIDRES          0.501934 Hz
AQ             0.9961472 sec
RG                185.92
DW                15.200 usec
DE                 66.43 usec
TE                 298.0 K
CNST2        145.0000000
CNST11         1.0000000
D1            2.00000000 sec
D20           0.00689655 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7728795 MHz
NUC1                 13C
P1                  9.50 usec
P2                 19.00 usec
PLW1         24.00000000 W

======== CHANNEL f2 ========
SFO2         500.1320005 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              65.00 usec
PLW2         13.00000000 W
PLW12         0.26784000 W

F2 - Processing parameters
SI                 32768
SF           125.7577885 MHz
WDW                   EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```

Chemist Alessandro Del Grosso
ADG298b
COSY.w CDCl3 /opt/topspin3.2 ADG 34



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Current Data Parameters
NAME           Aug05-2016
EXPNO                  11
PROCNO                  1

F2 - Acquisition Parameters
Date_            20160805
Time                 8.40
INSTRUM             spect
PROBHD   5 mm CPDCH 13C
PULPROG        cosygpppqf
TD                   2048
SOLVENT             CDCl3
NS                      1
DS                      8
SWH              5013.369 Hz
FIDRES           2.447934 Hz
AQ              0.2042539 sec
RG                  24.09
DW                 99.733 usec
DE                  40.00 usec
TE                  298.0 K
D0             0.00000300 sec
D1             1.93651199 sec
D11            0.03000000 sec
D12            0.00002000 sec
D13            0.00000400 sec
D16            0.00020000 sec
IN0            0.00019960 sec

======== CHANNEL f1 ========
SFO1          500.1320841 MHz
NUC1                   1H
P0                   9.10 usec
P1                   9.10 usec
P17               2500.00 usec
PLW1          13.00000000 W
PLW10          1.59249997 W

====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPZ1                10.00 %
P16               1000.00 usec

F1 - Acquisition parameters
TD                    128
SFO1             500.1321 MHz
FIDRES          39.140781 Hz
SW                 10.017 ppm
FnMODE                 QF

F2 - Processing parameters
SI                   1024
SF            500.1300166 MHz
WDW                 QSINE
SSB      0
LB       0 Hz
GB       0
PC                   1.40

F1 - Processing parameters
SI                   1024
MC2                    QF
SF            500.1300166 MHz
WDW                 QSINE
SSB      0
LB       0 Hz
GB       0
```
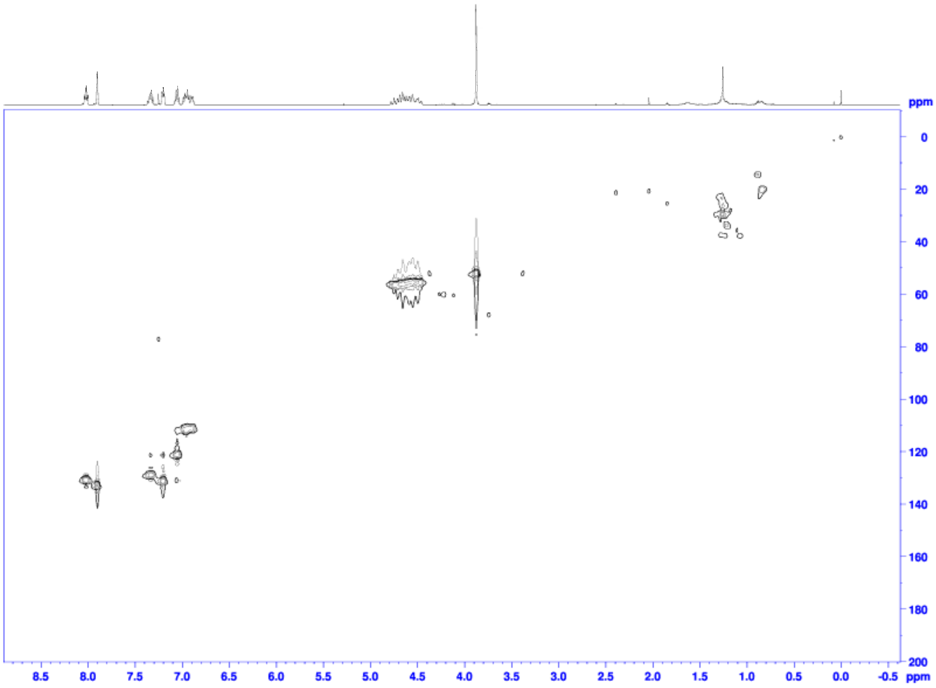
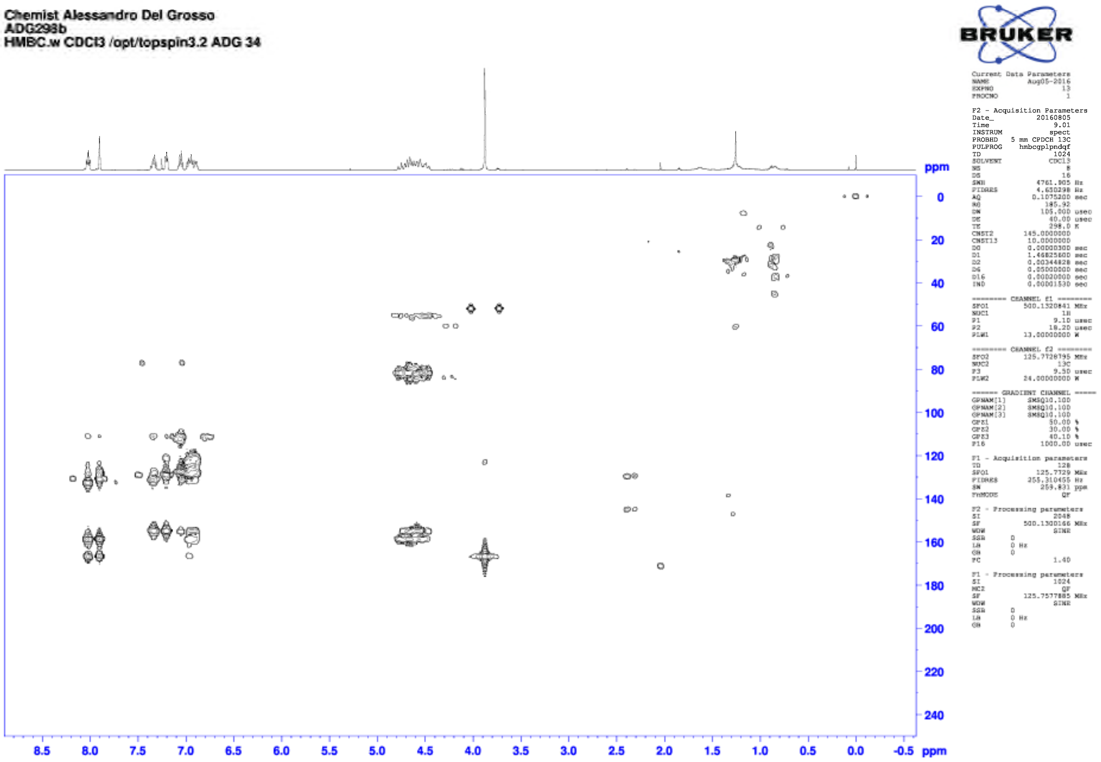
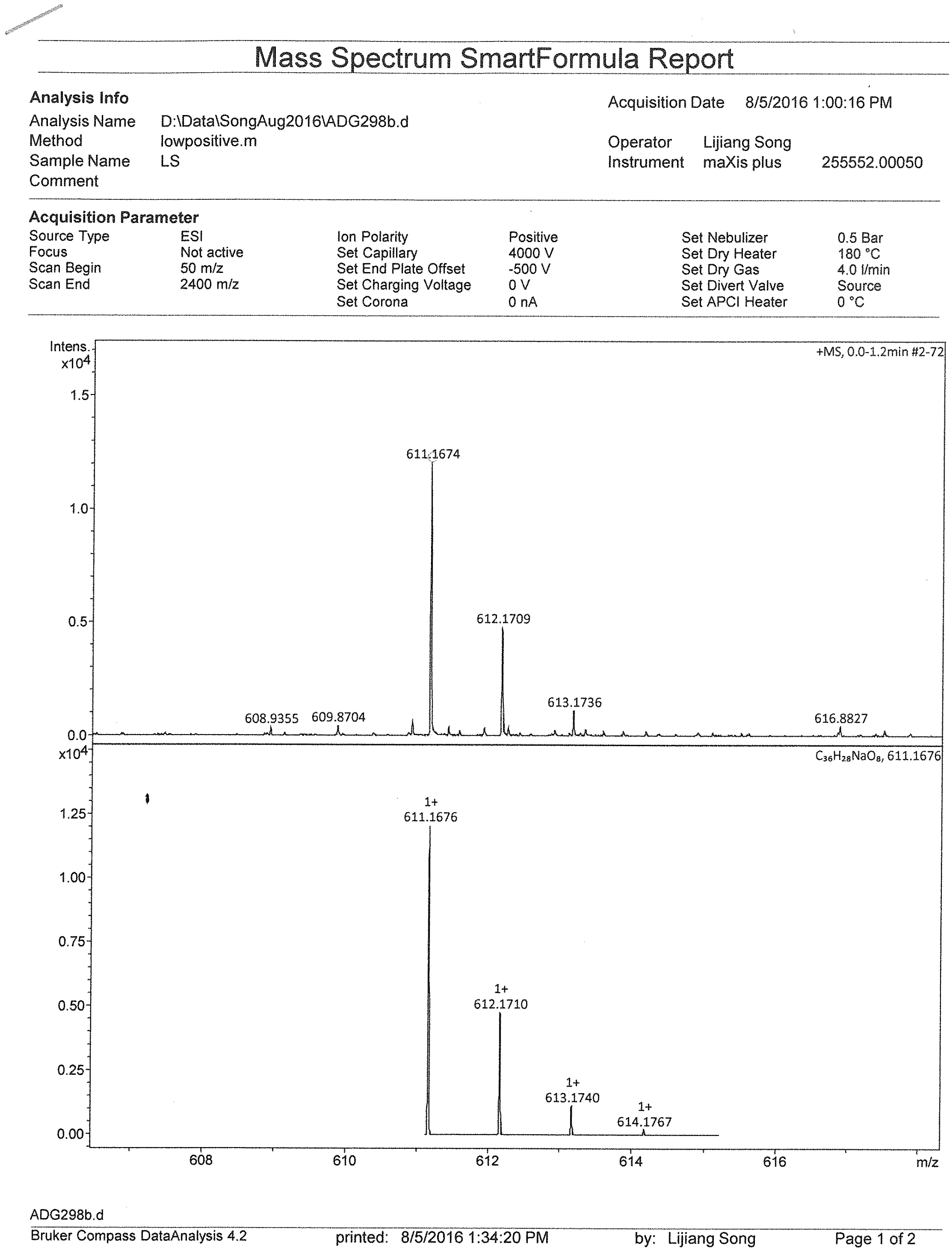

Chemist Alessandro Del Grosso
ADG298b
HSQC.w CDCl3 /opt/topspin3.2 ADG 34



```
Current Data Parameters
NAME           Aug05-2016
EXPNO                  12
PROCNO                  1

F2 - Acquisition Parameters
Date_            20160805
Time                 8.46
INSTRUM             spect
PROBHD   5 mm CPDCH 13C
PULPROG          hsqcetgp
TD                   1024
SOLVENT             CDCl3
NS                      4
DS                     16
SWH              4761.905 Hz
FIDRES           4.650298 Hz
AQ              0.1075200 sec
RG                 185.92
DW                105.000 usec
DE                  40.00 usec
TE                  298.0 K
CNST2         145.0000000
D0             0.00000300 sec
D1             1.46825600 sec
D4             0.00172414 sec
D11            0.03000000 sec
D16            0.00020000 sec
IN0            0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1          500.1320841 MHz
NUC1                   1H
P1                   9.10 usec
P2                  18.20 usec
P28      0 usec
PLW1          13.00000000 W

======== CHANNEL f2 ========
SFO2          125.7697355 MHz
NUC2                  13C
CPDPRG[2             garp
P3                   9.50 usec
P4                  19.00 usec
PCPD2               63.70 usec
PLW2          24.00000000 W
PLW12          0.51266003 W

====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPNAM[2]       SMSQ10.100
GPZ1                80.00 %
GPZ2                20.10 %
P16               1000.00 usec

F1 - Acquisition parameters
TD                    128
SFO1             125.7697 MHz
FIDRES         206.679901 Hz
SW                210.345 ppm
FnMODE       Echo-Antiecho

F2 - Processing parameters
SI                   1024
SF            500.1300166 MHz
WDW                 QSINE
SSB                     2
LB       0 Hz
GB       0
PC                   1.40

F1 - Processing parameters
SI                   1024
MC2         echo-antiecho
SF            125.7577895 MHz
WDW                 QSINE
SSB                     2
LB       0 Hz
GB       0
```


Chemist Alessandro Del Grosso
ADG298b
HMBC.w CDCl3 /opt/topspin3.2 ADG 34
BRUKER
Current Data Parameters
NAME Aug05-2016
EXPNO 13
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160805
Time 9.01
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG hmbcgplpndqf
TD 1024
SOLVENT CDCl3
NS 8
DS 16
SWH 4761.905 Hz
FIDRES 4.650298 Hz
AQ 0.1075200 sec
RG 185.92
DW 105.000 usec
DE 40.00 usec
TE 298.0 K
CNST2 145.0000000
CNST13 10.0000000
D0 0.00000300 sec
D1 1.46825600 sec
D2 0.00344828 sec
D6 0.05000000 sec
D16 0.00020000 sec
IN0 0.00001530 sec
======== CHANNEL f1 ========
SFO1 500.1320841 MHz
NUC1 1H
P1 9.10 usec
P2 18.20 usec
PLW1 13.00000000 W
======== CHANNEL f2 ========
SFO2 125.7728795 MHz
NUC2 13C
P3 9.50 usec
PLW2 24.00000000 W
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 128
SFO1 125.7729 MHz
FIDRES 255.310455 Hz
SW 259.831 ppm
FnMODE QF
F2 - Processing parameters
SI 2048
SF 500.1300166 MHz
WDW SINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 1024
MC2 QF
SF 125.7577885 MHz
WDW SINE
SSB 0
LB 0 Hz
GB 0
ppm
0
20
40
60
80
100
120
140
160
180
200
220
240
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

HRMS:



Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name D:\Data\SongAug2016\ADG298b.d
Method lowpositive.m
Sample Name LS
Comment

Acquisition Date 8/5/2016 1:00:16 PM

Operator Lijiang Song
Instrument maXis plus 255552.00050

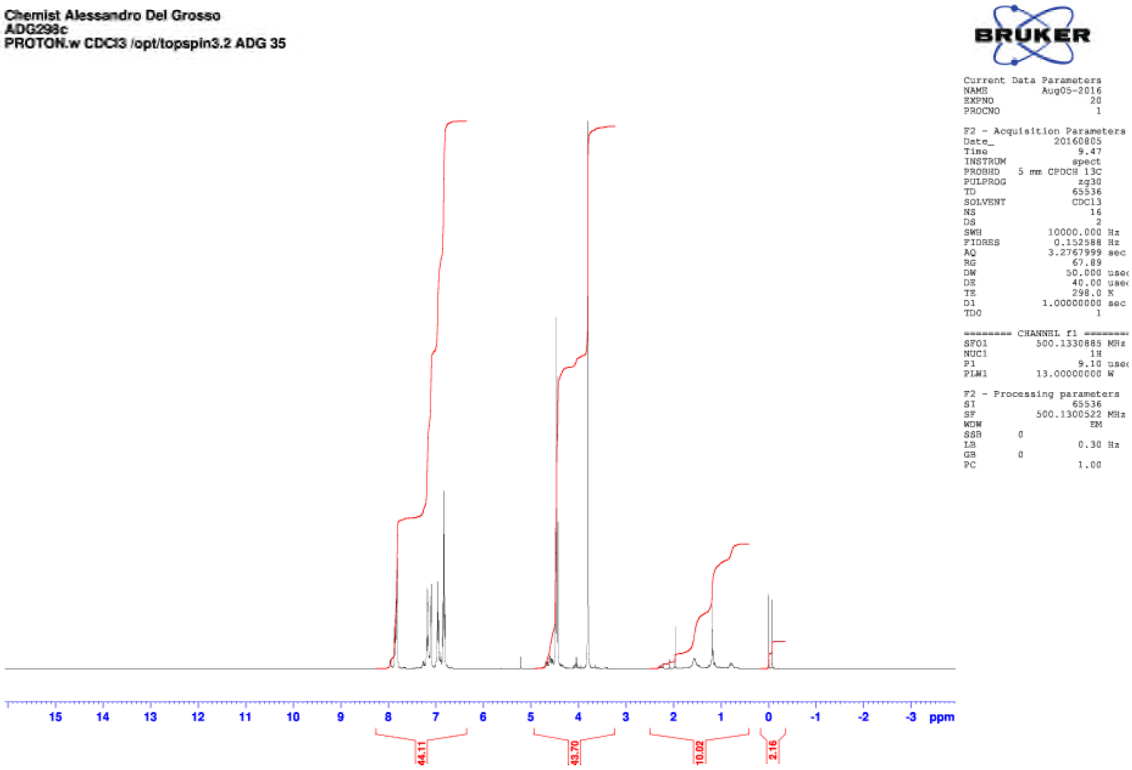
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	2400 m/z	Set Charging Voltage	0 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C

ADG298b.d
Bruker Compass DataAnalysis 4.2 printed: 8/5/2016 1:34:20 PM by: Lijiang Song Page 1 of 2

The 3+3 product NMRs are below (298c). The HRMS is also shown, to confirm the structure of the macrocycle:

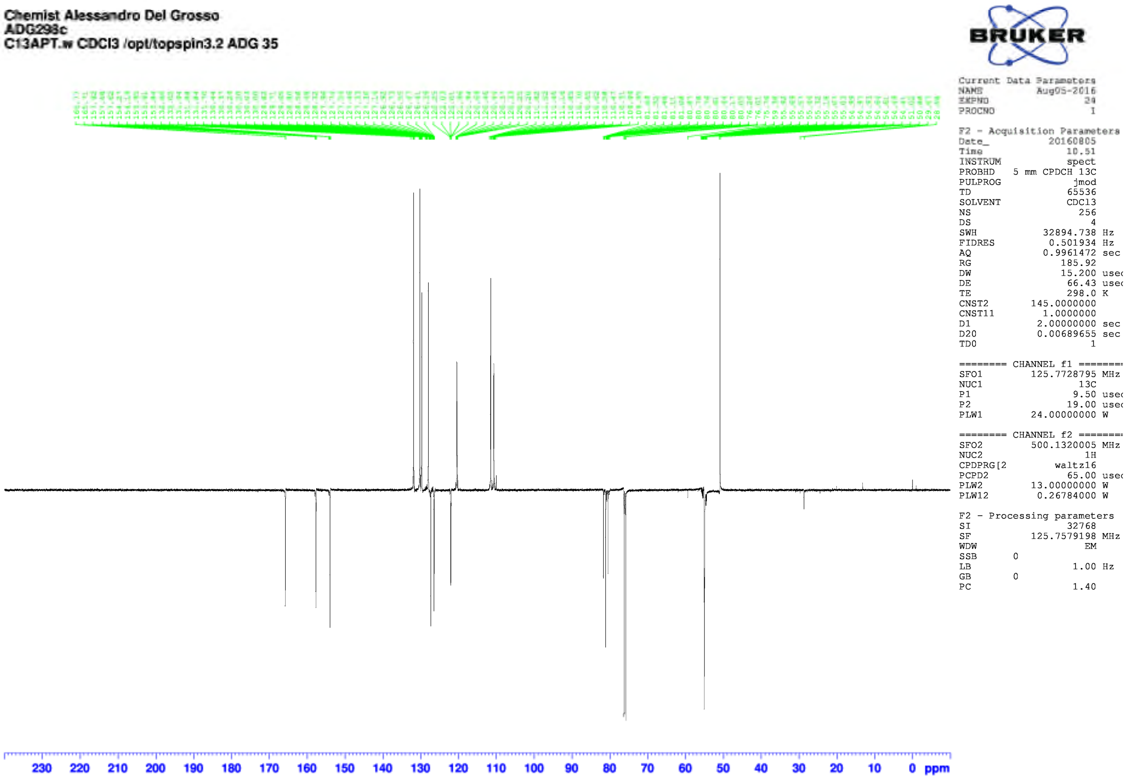
^{1}H NMR (500 MHz, $CDCl_3$).



```
Chemist Alessandro Del Grosso
ADG298c
PROTON.w CDCl3 /opt/topspin3.2 ADG 35
```

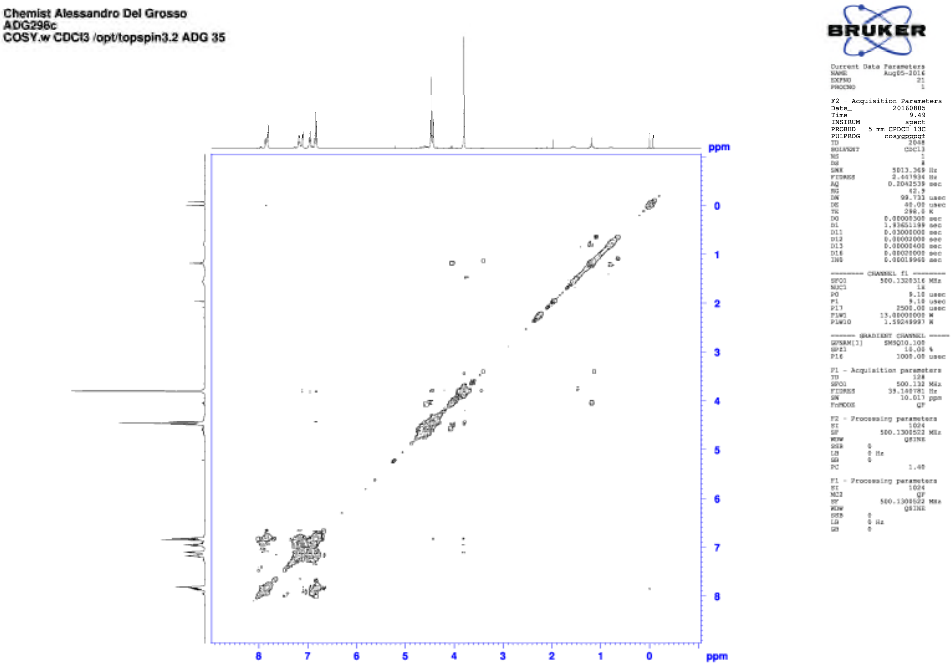
```
Current Data Parameters
NAME          Aug05-2016
EXPNO                 20
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160805
Time                9.47
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                 67.89
DW                50.000 usec
DE                 40.00 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                  1H
P1                  9.10 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1300522 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```

^{13}C NMR (125 MHz, $CDCl_3$).



Chemist Alessandro Del Grosso
ADG298c
C13APT.w CDCl3 /opt/topspin3.2 ADG 35

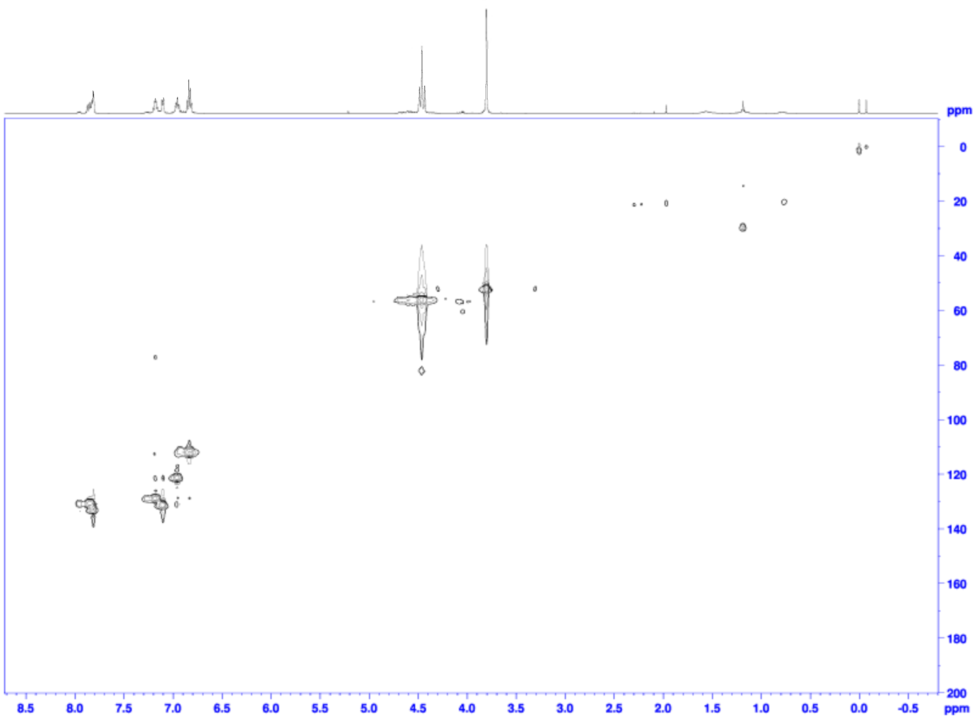
```
Current Data Parameters
NAME         Aug05-2016
EXPNO                24
PROCNO                1

F2 - Acquisition Parameters
Date_          20160805
Time              10.51
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG            jmod
TD                65536
SOLVENT           CDCl3
NS                  256
DS                    4
SWH           32894.738 Hz
FIDRES         0.501934 Hz
AQ            0.9961472 sec
RG               185.92
DW               15.200 use
DE                66.43 use
TE                298.0 K
CNST2       145.0000000
CNST11        1.0000000
D1           2.00000000 sec
D20          0.00689655 sec
TD0                   1

======== CHANNEL f1 =======
SFO1        125.7728795 MHz
NUC1                13C
P1                 9.50 use
P2                19.00 use
PLW1        24.00000000 W

======== CHANNEL f2 =======
SFO2        500.1320005 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             65.00 use
PLW2        13.00000000 W
PLW12        0.26784000 W

F2 - Processing parameters
SI                32768
SF          125.7579198 MHz
WDW                  EM
SSB      0
LB                 1.00 Hz
GB       0
PC                 1.40
```



Chemist Alessandro Del Grosso
ADG298c
COSY.w CDCl3 /opt/topspin3.2 ADG 35

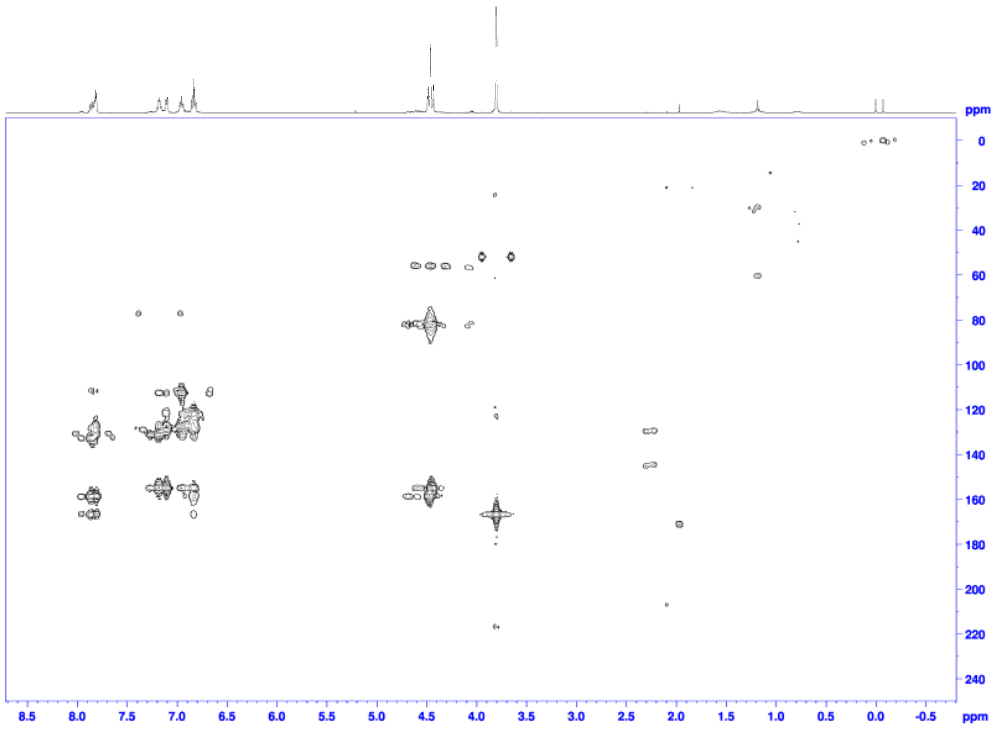
```
Current Data Parameters
NAME         Aug05-2016
EXPNO                21
PROCNO                1

F2 - Acquisition Parameters
Date_          20160805
Time               9.49
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG       cosygpppqf
TD                 2048
SOLVENT           CDCl3
NS                    1
DS                    8
SWH            5013.369 Hz
FIDRES         2.447934 Hz
AQ            0.2042539 sec
RG                 42.9
DW               99.733 usec
DE                40.00 usec
TE                298.0 K
D0           0.00000300 sec
D1           1.93651199 sec
D11          0.03000000 sec
D12          0.00002000 sec
D13          0.00000400 sec
D16          0.00020000 sec
IN0          0.00019960 sec

======== CHANNEL f1 ========
SFO1        500.1328316 MHz
NUC1                 1H
P0                 9.10 usec
P1                 9.10 usec
P17             2500.00 usec
PLW1        13.00000000 W
PLW10        1.59249997 W

====== GRADIENT CHANNEL =====
GPNAM[1]     SMSQ10.100
GPZ1              10.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                  128
SFO1            500.132 MHz
FIDRES        39.168781 Hz
SW               10.017 ppm
FnMODE               QF

F2 - Processing parameters
SI                 1024
SF          500.1300522 MHz
WDW               QSINE
SSB      0
LB       0 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                 1024
MC2                  QF
SF          500.1300522 MHz
WDW               QSINE
SSB      0
LB       0 Hz
GB       0
```

Chemist Alessandro Del Grosso
ADG298c
HSQC.w CDCl3 /opt/topspin3.2 ADG 35



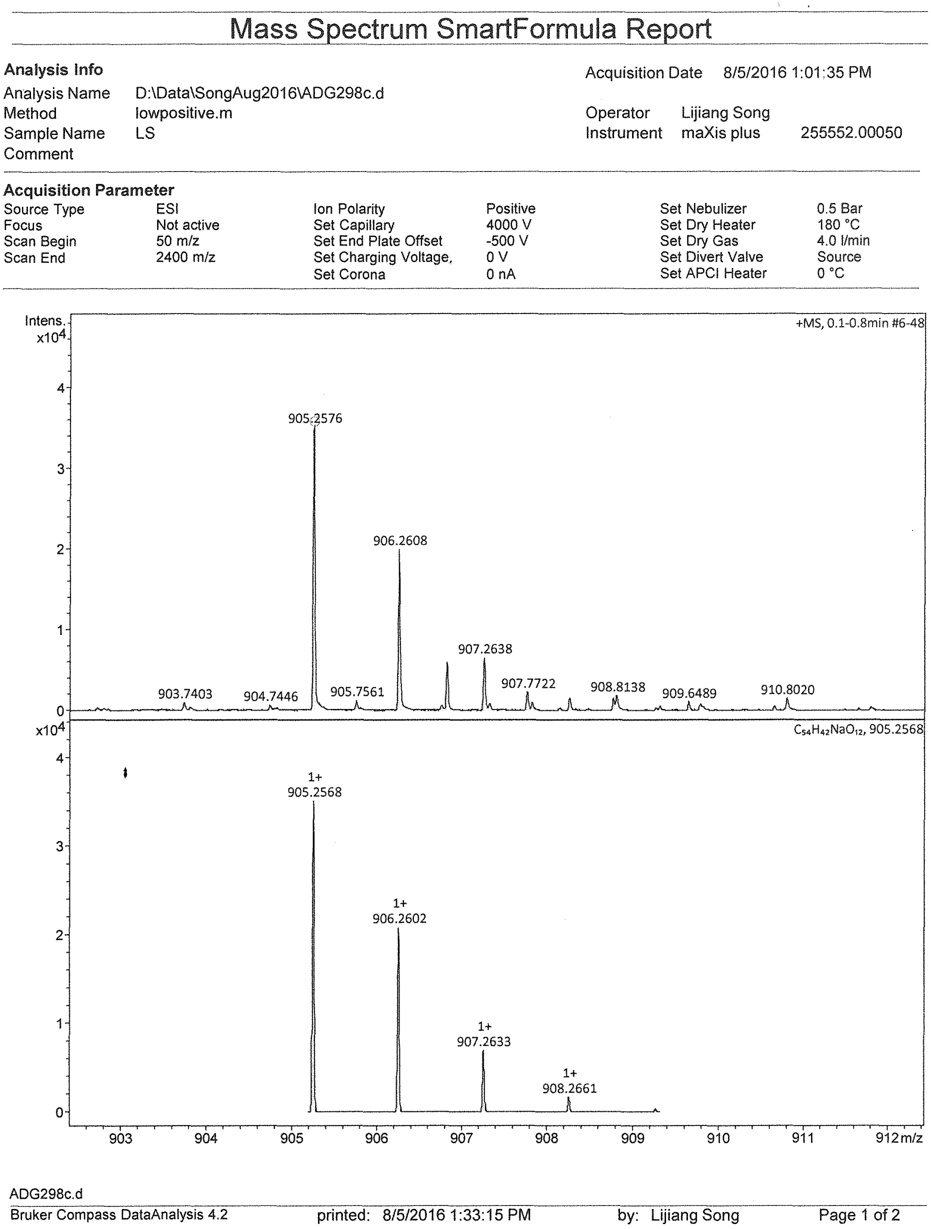
```
Current Data Parameters
NAME          Aug05-2016
EXPNO                 22
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160805
Time                9.55
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG         hsqcetgp
TD                  1024
SOLVENT            CDCl3
NS                     4
DS                    16
SWH             4761.905 Hz
FIDRES          4.650298 Hz
AQ             0.1075200 sec
RG                185.92
DW               105.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
D0            0.00000300 sec
D1            1.46825600 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
IND           0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         500.1320316 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
P28      0 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7697355 MHz
NUC2                 13C
CPDPRG[2            garp
P3                  9.50 usec
P4                 19.00 usec
PCPD2              63.70 usec
PLW2         24.00000000 W
PLW12         0.51266003 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7697 MHz
FIDRES        206.679901 Hz
SW               210.345 ppm
FnMODE      Echo-Antiecho

F2 - Processing parameters
SI                  1024
SF           500.1300522 MHz
WDW                QSINE
SSB                    2
LB       0 Hz
GB       0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2         echo-antiecho
SF           125.7577885 MHz
WDW                QSINE
SSB                    2
LB       0 Hz
GB       0
```

HMBC.w CDCl3 /opt/topspin3.2 ADG 35
c



```
Current Data Parameters
NAME          Aug05-2016
EXPNO                 23
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160805
Time               10.10
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG      hmbcgplpndqf
TD                  1024
SOLVENT            CDCl3
NS                     8
DS                    16
SWH             4761.905 Hz
FIDRES          4.650298 Hz
AQ             0.1075200 sec
RG                185.92
DW               105.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
CNST13        10.0000000
D0            0.00000300 sec
D1            1.46825600 sec
D2            0.00344828 sec
D6            0.05000000 sec
D16           0.00020000 sec
IND           0.00001530 sec

======== CHANNEL f1 ========
SFO1         500.1320316 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7728795 MHz
NUC2                 13C
P3                  9.50 usec
PLW2         24.00000000 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPNAM[3]      SMSQ10.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7729 MHz
FIDRES        255.310455 Hz
SW               259.831 ppm
FnMODE                QF

F2 - Processing parameters
SI                  2048
SF           500.1300522 MHz
WDW                 SINE
SSB      0
LB       0 Hz
GB       0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           125.7577885 MHz
WDW                 SINE
SSB      0
LB       0 Hz
GB       0
```

HRMS:



Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name D:\Data\SongAug2016\ADG298c.d
Method lowpositive.m
Sample Name LS
Comment

Acquisition Date 8/5/2016 1:01:35 PM
Operator Lijiang Song
Instrument maXis plus 255552.00050

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.5 Bar
Focus	Not active	Set Capillary	4000 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	2400 m/z	Set Charging Voltage,	0 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C

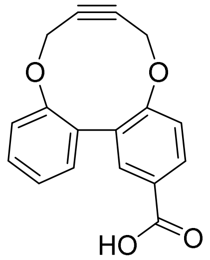
ADG298c.d
Bruker Compass DataAnalysis 4.2 printed: 8/5/2016 1:33:15 PM by: Lijiang Song Page 1 of 2

Alternative procedure using butanone as solvent;

In a round bottom flask under nitrogen atmosphere, methyl 2',6-dihydroxy-[1,1'-biphenyl]-3-carboxylate (500 mg, 2.05 mmol) and but-2-yne-1,4-diyl bis(4-methylbenzenesulfonate) (808 mg, 2.05 mmol) were dissolved in butan-2-one (102 mL). The mixture was degassed and heated to 80 °C for 5 days. After this time the solvent was removed under reduced pressure. The resulting oil was dissolved in DCM

(50 mL) and washed with water (100 mL). The aqueous phase was extracted with DCM (2 x 50 mL). The combined organic extracts were dried over magnesium sulphate, filtered and the DCM was evaporated under reduced pressure. The product was purified by column chromatography, (eluent hexane to hexane/ethyl acetate 88:12) to obtain the product as a white solid (193 mg, 0.656 mmol, 32 %). The data for the product matched that reported above.

Synthesis of Compound 13; 8,13-dioxatricyclo[12.4.0.0^2,^{7}]octadeca-1(18),2(7),3,5,14,16-hexaen-10-yne-4-carboxylic acid **13**.



In a round bottom flask, methyl 8,13-dioxatricyclo[12.4.0.0^2,^{7}]octadeca-1(18),2(7),3,5,14,16-hexaen-10-yne-4-carboxylate **11** (100 mg, 0.325 mmol) was dissolved in 1:1 MeOH/H_2O (3 mL). NaOH (26 mg, 0.65 mmol) was added. The mixture was refluxed at 100 ˚C overnight. The mixture was acidified at pH ≈5 by adding 0.5 M HCl dropwise. The organic fractions were extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with saturated sodium chloride solution and then were dried over sodium sulphate. The solution was filtered and the solvent removed under reduced pressure to yield the product **13** as a white solid (88 mg, 0.315 mmol, 97 %).

m.p. 176.0 ºC dec.

$IR_{(neat)}$ 2955, 2921, 2852, 1681, 1607,1597, 1579, 1499, 1476, 1446, 1423, 1399, 1348, 1310, 1272, 1249, 1191 cm^{-1}.

m/z (ESI) $[M + H]^+$, 428.1; $[M + Na]^+$, 303.0

δ_H (500 MHz, *d*$_6$-Acetone) δ = 8.07 (1H, dd, *J* = 8.5, 2.0 Hz, Ar*H*), 7.86 (1H, d, *J* = 2.1 Hz, Ar*H*), 7.39 - 7.46 (1H, m, Ar*H*), 7.37 (1H, d, *J* = 8.4 Hz, Ar*H*), 7.28 (1H, d, *J*

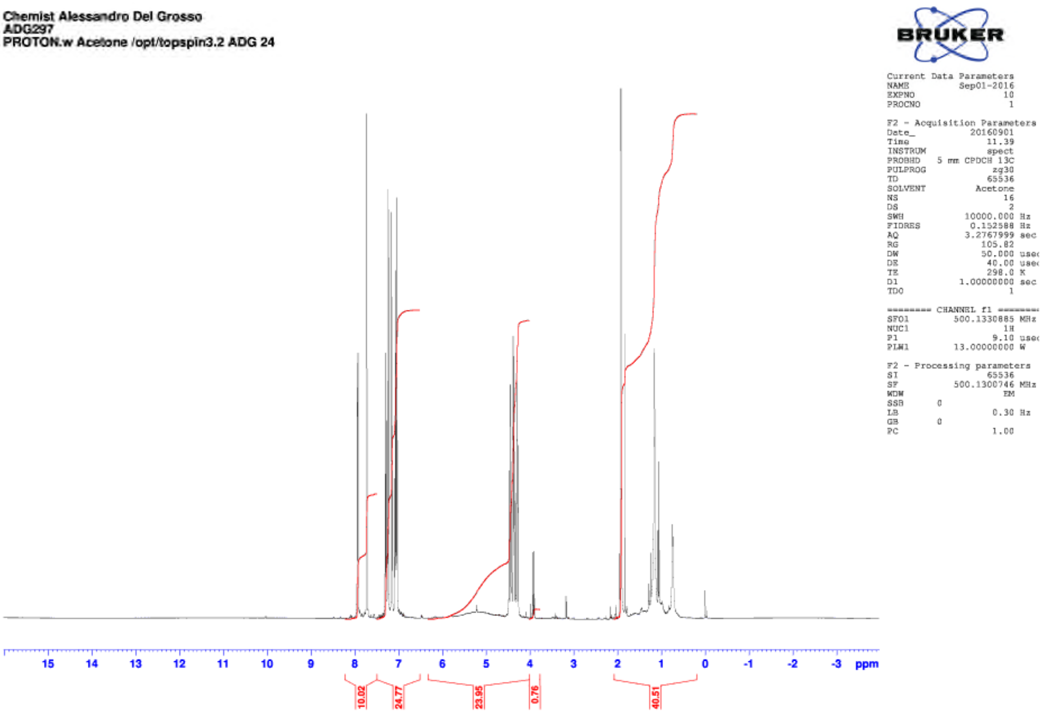
= 8.1, 0, Ar*H*), 7.13 - 7.25 (2H, m, Ar*H*), 5.30 (1H, br. s., O*H*), 4.36 - 4.64 (4H, m, C*H*$_2$).

δ_C (125 MHz, *d*$_6$-Acetone) δ = 168.1 (C), 159.7 (C), 155.9 (C), 137.0 (C), 136.2 (C), 134.5 (CH), 132.7 (CH), 131.6 (CH), 130.4 (CH), 128.1 (C), 124.9 (CH), 123.9 (CH), 123.8 (CH), 88.1(C), 87.3(C), 64.2(CH$_2$), 64.0 (CH$_2$).

m/*z* (ESI) 303.0 ([M + Na]$^+$, 100%).

HRMS (ESI-Q-TOF) m/z: [M + Na]$^+$ Calcd for $C_{17}H_{12}NaO_4$ 303.0628; Found 303.0627.

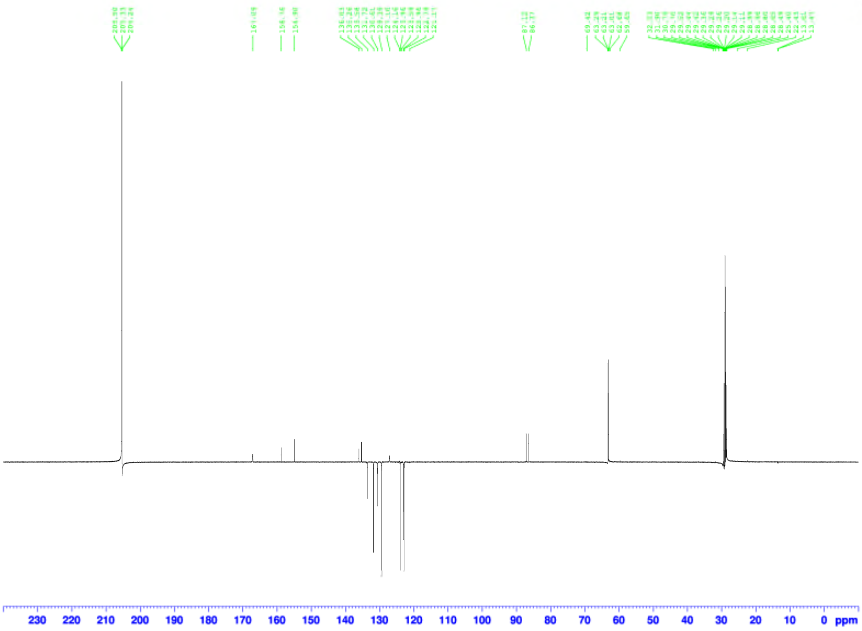
^{1}H NMR (500 MHz, *d*$_6$-Acetone)



```
Current Data Parameters
NAME          Sep01-2016
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160901
Time               11.39
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 65536
SOLVENT          Acetone
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                105.82
DW                50.000 usec
DE                 40.00 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                  1H
P1                  9.10 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1300746 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```

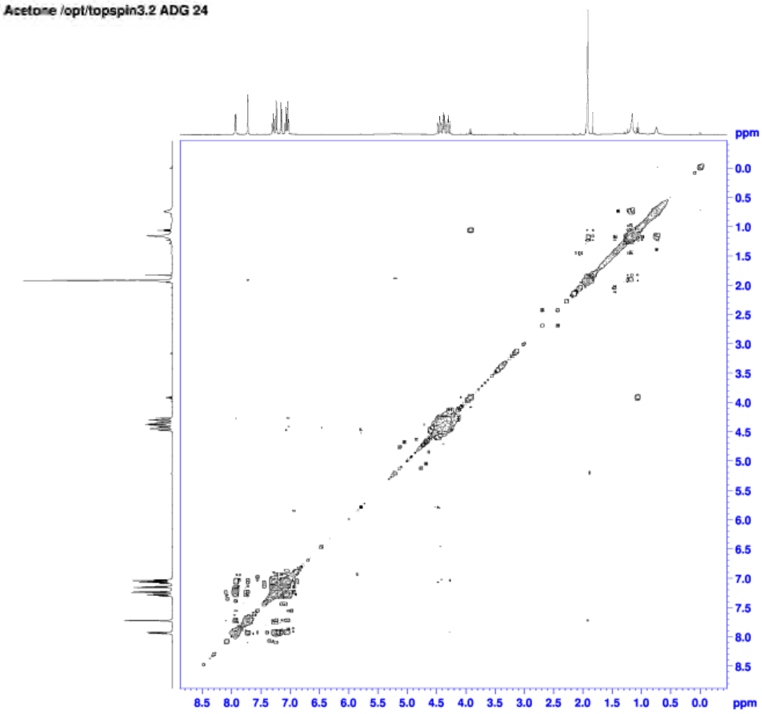
^{13}C NMR (125 MHz, *d*$_6$-Acetone)

Chemist Alessandro Del Grosso
ADG297



```
Current Data Parameters
NAME             Sep01-2016
EXPNO                    14
PROCNO                    1

F2 - Acquisition Parameters
Date_              20160901
Time                  12.44
INSTRUM               spect
PROBHD     5 mm CPDCH 13C
PULPROG                jmod
TD                    65536
SOLVENT             Acetone
NS                      256
DS                        4
SWH              32894.738 Hz
FIDRES            0.501934 Hz
AQ               0.9961472 sec
RG                  185.92
DW                  15.200 usec
DE                   66.43 usec
TE                   298.0 K
CNST2          145.0000000
CNST11           1.0000000
D1              2.00000000 sec
D20             0.00689655 sec
TD0                       1

======== CHANNEL f1 ========
SFO1           125.7728795 MHz
NUC1                    13C
P1                     9.50 usec
P2                    19.00 usec
PLW1           24.00000000 W

======== CHANNEL f2 ========
SFO2           500.1320005 MHz
NUC2                     1H
CPDPRG[2            waltz16
PCPD2                 65.00 usec
PLW2           13.00000000 W
PLW12           0.26784000 W

F2 - Processing parameters
SI                    32768
SF             125.7577885 MHz
WDW                      EM
SSB      0
LB                     1.00 Hz
GB       0
PC                     1.40
```

Chemist Alessandro Del Grosso
ADG297
COSY.w Acetone /opt/topspin3.2 ADG 24



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Current Data Parameters
NAME             Sep01-2016
EXPNO                    11
PROCNO                    1

F2 - Acquisition Parameters
Date_              20160901
Time                  11.41
INSTRUM               spect
PROBHD     5 mm CPDCH 13C
PULPROG          cosygpppqf
TD                     2048
SOLVENT             Acetone
NS                        1
DS                        8
SWH               4672.897 Hz
FIDRES            2.281688 Hz
AQ               0.2191360 sec
RG                    67.89
DW                  107.000 usec
DE                    40.00 usec
TE                    298.0 K
D0              0.00000300 sec
D1              1.92012799 sec
D11             0.03000000 sec
D12             0.00002000 sec
D13             0.00000400 sec
D16             0.00020000 sec
IN0             0.00021400 sec

======== CHANNEL f1 ========
SFO1           500.1321797 MHz
NUC1                     1H
P0                     9.10 usec
P1                     9.10 usec
P17                 2500.00 usec
PLW1           13.00000000 W
PLW10           1.59249997 W

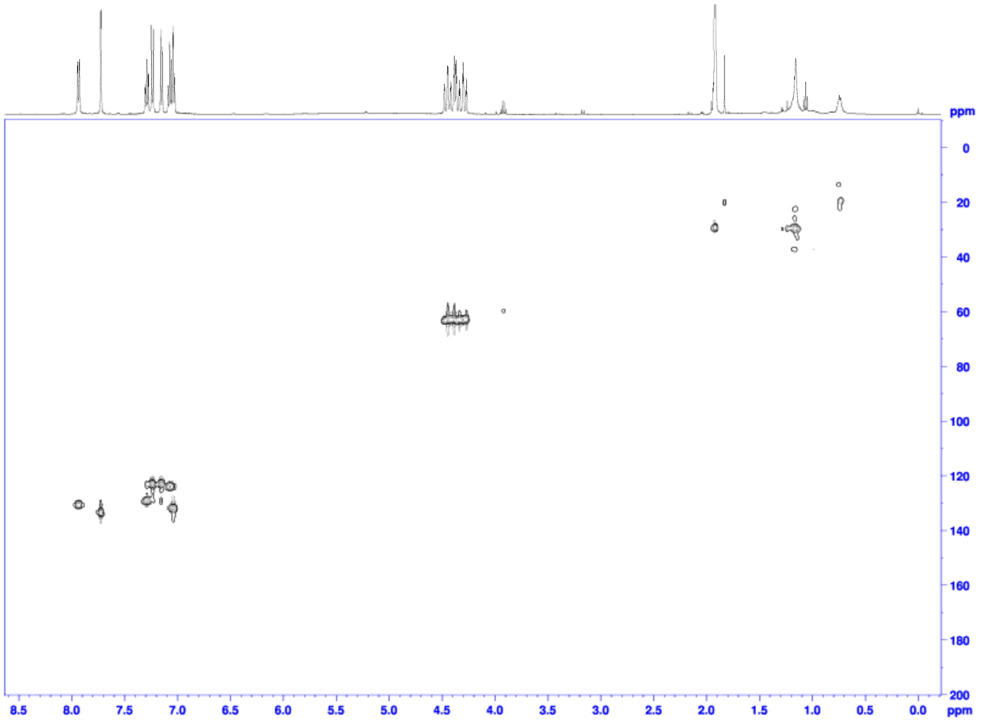
====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPZ1                  10.00 %
P16                 1000.00 usec

F1 - Acquisition parameters
TD                      128
SFO1               500.1322 MHz
FIDRES            36.507008 Hz
SW                    9.343 ppm
FnMODE                   QF

F2 - Processing parameters
SI                     1024
SF             500.1300746 MHz
WDW                   QSINE
SSB      0
LB       0 Hz
GB       0
PC                     1.40

F1 - Processing parameters
SI                     1024
MC2                      QF
SF             500.1300746 MHz
WDW                   QSINE
SSB      0
LB       0 Hz
GB       0
```

Chemist Alessandro Del Grosso
ADG297
HSQC.w Acetone /opt/topspin3.2 ADG 24



```
Current Data Parameters
NAME          Sep01-2016
EXPNO                 12
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160901
Time               11.47
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG         hsqcetgp
TD                  1024
SOLVENT           Acetone
NS                     4
DS                    16
SWH             4424.779 Hz
FIDRES          4.321073 Hz
AQ             0.1157120 sec
RG                185.92
DW               113.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
D0            0.00000300 sec
D1            1.46006405 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
IN0           0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         500.1321797 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
P28       0 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7697355 MHz
NUC2                 13C
CPDPRG[2            garp
P3                  9.50 usec
P4                 19.00 usec
PCPD2              63.70 usec
PLW2         24.00000000 W
PLW12         0.51266003 W

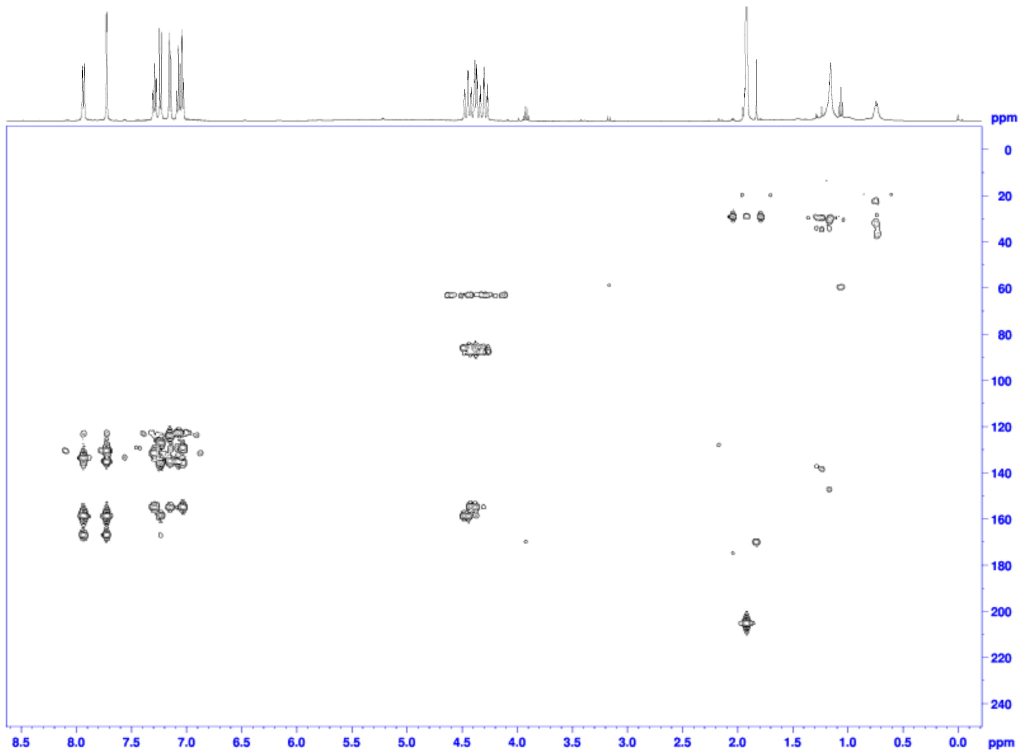
====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7697 MHz
FIDRES        206.679901 Hz
SW               210.345 ppm
FnMODE      Echo-Antiecho

F2 - Processing parameters
SI                  1024
SF           500.1300746 MHz
WDW                QSINE
SSB                    2
LB        0 Hz
GB        0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2         echo-antiecho
SF           125.7577885 MHz
WDW                QSINE
SSB                    2
LB        0 Hz
GB        0
```

HMBC.w Acetone /opt/topspin3.2 ADG 24



```
Current Data Parameters
NAME          Sep01-2016
EXPNO                 13
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160901
Time               12.02
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG      hmbcgplpndqf
TD                  1024
SOLVENT           Acetone
NS                     8
DS                    16
SWH             4424.779 Hz
FIDRES          4.321073 Hz
AQ             0.1157120 sec
RG                185.92
DW               113.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
CNST13        10.0000000
D0            0.00000300 sec
D1            1.46006405 sec
D2            0.00344828 sec
D6            0.05000000 sec
D16           0.00020000 sec
IN0           0.00001530 sec

======== CHANNEL f1 ========
SFO1         500.1321797 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7728795 MHz
NUC2                 13C
P3                  9.50 usec
PLW2         24.00000000 W

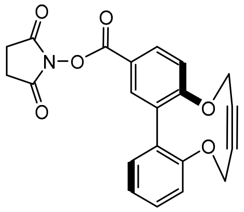
====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPNAM[3]      SMSQ10.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7729 MHz
FIDRES        255.310455 Hz
SW               259.831 ppm
FnMODE                QF

F2 - Processing parameters
SI                  2048
SF           500.1300746 MHz
WDW                 SINE
SSB       0
LB        0 Hz
GB        0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           125.7577885 MHz
WDW                 SINE
SSB       0
LB        0 Hz
GB        0
```

Synthesis of Activated ester 14; 5-dioxopyrrolidin-1-yl 8,13-dioxatricyclo[12.4.0.0^{2,7}]octadeca-1(14),2(7),3,5,15,17-hexaen-10-yne-4-carboxylate **14**.



In a round bottom flask, a solution of compound **13** (82 mg, 0.29 mmol) in dry DCM (1.2 mL) N-hydroxysuccinimide (54 mg, 0.464 mmol) and EDC.HCl (67 mg, 0.348 mmol) were added and the mixture was stirred overnight at room temperature. The reaction mixture was extracted with diethyl ether (2 x 20 mL), washed twice with water (2 x 20 mL) and saturated sodium chloride solution (20 mL). After drying of the organic phase over sodium sulphate and filtration, the solvents were evaporated under reduced pressure. The product was purified by column chromatography (eluent: Hexane to Hexane/Ethyl acetate 80:20) to obtain the product **14** as a white solid (63.1 mg, 0.167 mmol, 55 %).

Mp: 220-223 °C.

(found (ESI): M^+ + Na,. $C_{21}H_{15}NO_6Na$ requires M, 400.0752 (0.5 ppm errror)).

$IR_{(neat)}$ 1734, 1189, 1066, 963, 729 cm^{-1}.

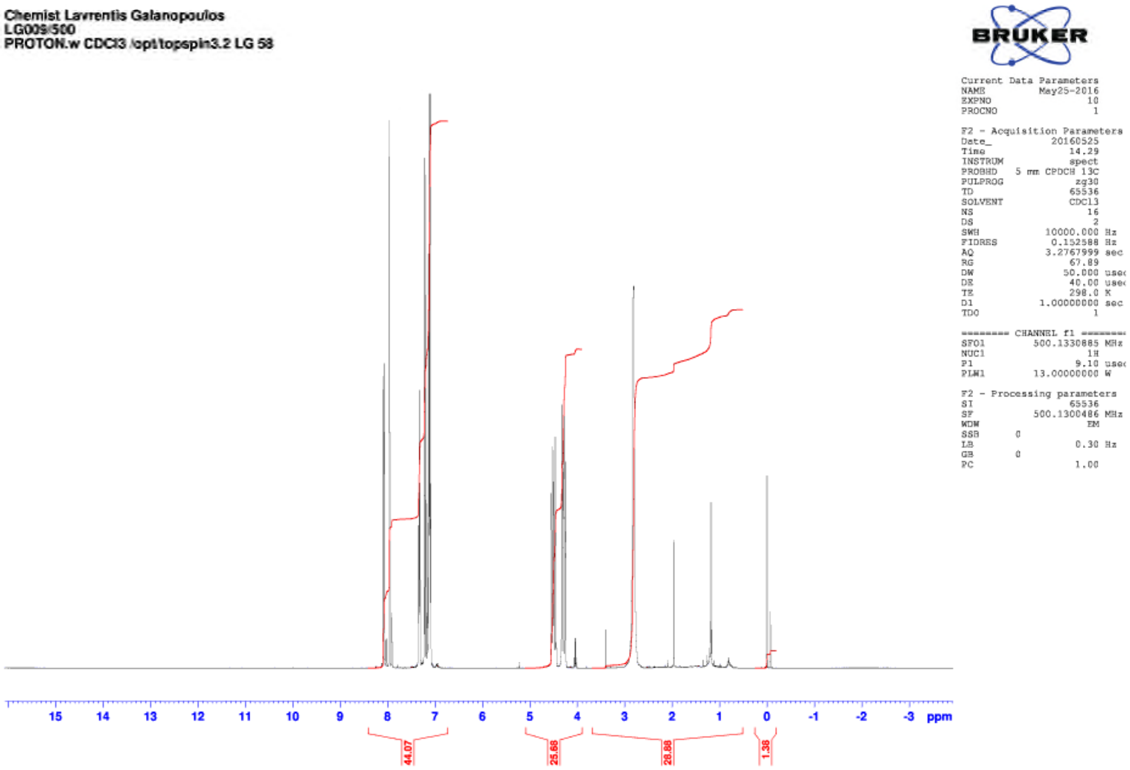
δ_H ($CDCl_3$, 500 MHz) 8.08 (1H, dd, *J* 9.0, 2.0, Ar*H*), 7.96 (1H, d, *J* 2.0, Ar*H*), 7.33 (1H, dt, *J* 8.0, 2.0, Ar*H*), 7.22 (1H, d, *J* 8.5, Ar*H*), 7.15-7.08 (3H, m, Ar*H*), 4.57-5.46 (2H, m, OCH_2), 4.34-4.24 (1H, m, OCH_2), 2.82 (4H, brs, CH_2CH_2).

δ_C ($CDCl_3$, 125 MHz) 168.3 (C), 160.3 (C), 159.4 (C), 153.4 (C), 135.9 (C), 133.9 (CH), 133.3 (C), 130.7 (CH), 130.6 (CH), 128.7 (CH), 123.3 (CH), 122.5 (CH), 121.7 (CH), 120.0 (C), 86.5 (C triple), 84.8 (C triple), 62.9 (OCH_2), 62.4 (OCH_2), 24.6 (CH_2CH_2).

m/*z* (ESI) 400.1 (M^+ + Na, 100%).

HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{15}NO_6Na$ 400.0752; Found 400.0790.

^{1}H NMR (CDCl$_3$, 500MHz)


Chemist Lavrentis Galanopoulos
LG009/500
PROTON.w CDCl3 /opt/topspin3.2 LG 58

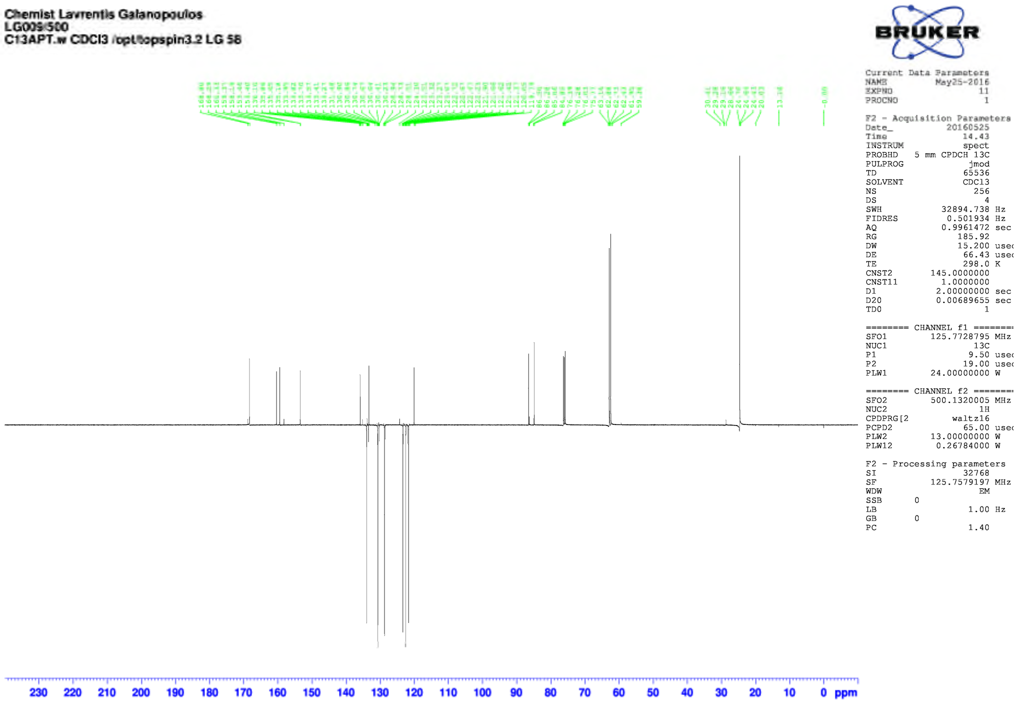
```
Current Data Parameters
NAME          May25-2016
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160525
Time               14.29
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                 67.89
DW                50.000 usec
DE                 40.00 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                  1H
P1                  9.10 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1300486 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```

^{13}C NMR (CDCl$_3$, 125 MHz).


Chemist Lavrentis Galanopoulos
LG009/500
C13APT.w CDCl3 /opt/topspin3.2 LG 58

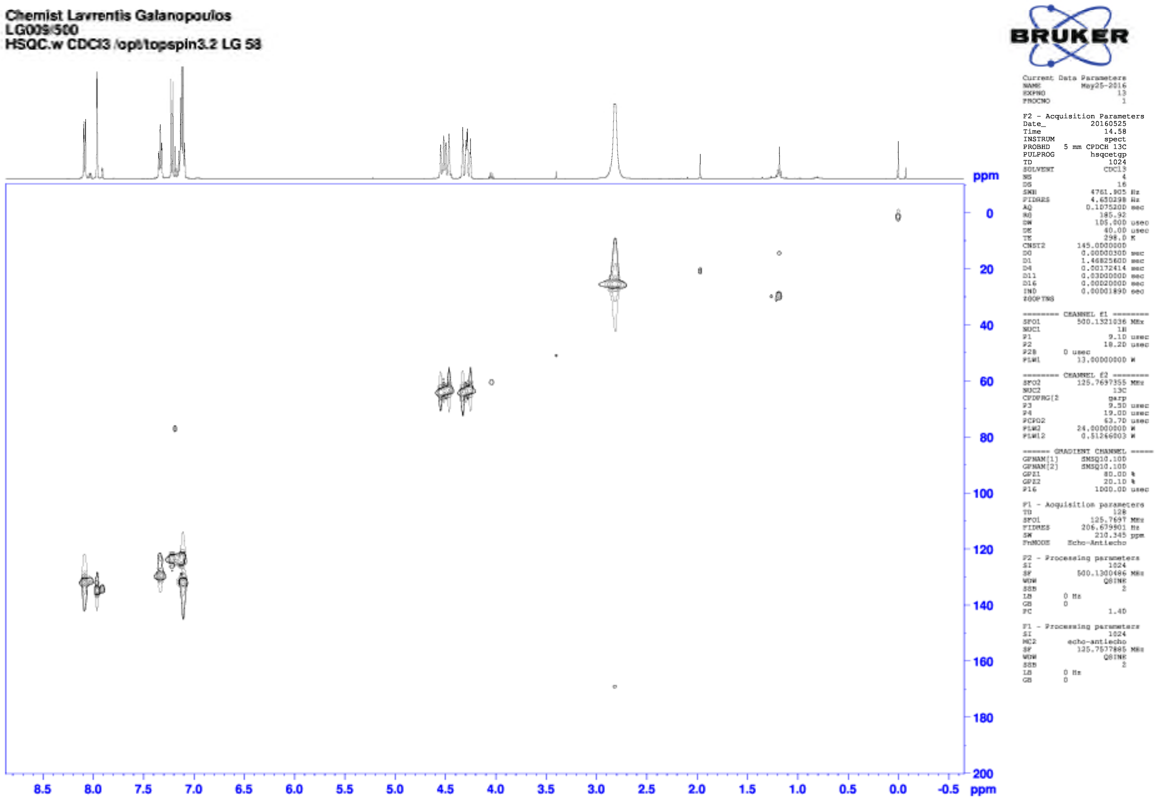
```
Current Data Parameters
NAME          May25-2016
EXPNO                 11
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160525
Time               14.43
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             jmod
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            32894.738 Hz
FIDRES          0.501934 Hz
AQ             0.9961472 sec
RG                185.92
DW                15.200 usec
DE                 66.43 usec
TE                 298.0 K
CNST2        145.0000000
CNST11         1.0000000
D1            2.00000000 sec
D20           0.00689655 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7728795 MHz
NUC1                 13C
P1                  9.50 usec
P2                 19.00 usec
PLW1         24.00000000 W

======== CHANNEL f2 ========
SFO2         500.1320005 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              65.00 usec
PLW2         13.00000000 W
PLW12         0.26784000 W

F2 - Processing parameters
SI                 32768
SF           125.7579197 MHz
WDW                   EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  1.40
```



Chemist Lavrentis Galanopoulos
LG009/500
HSQC.w CDCl3 /opt/topspin3.2 LG 58

```
Current Data Parameters
NAME          May25-2016
EXPNO                 13
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160525
Time               14.58
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG         hsqcetgp
TD                  1024
SOLVENT            CDCl3
NS                     4
DS                    16
SWH             4761.905 Hz
FIDRES          4.650298 Hz
AQ             0.1075200 sec
RG                185.92
DW               105.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
D0            0.00000300 sec
D1            1.46825600 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
IN0           0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         500.1321036 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
P28      0 usec
PLW1         13.00000000 W

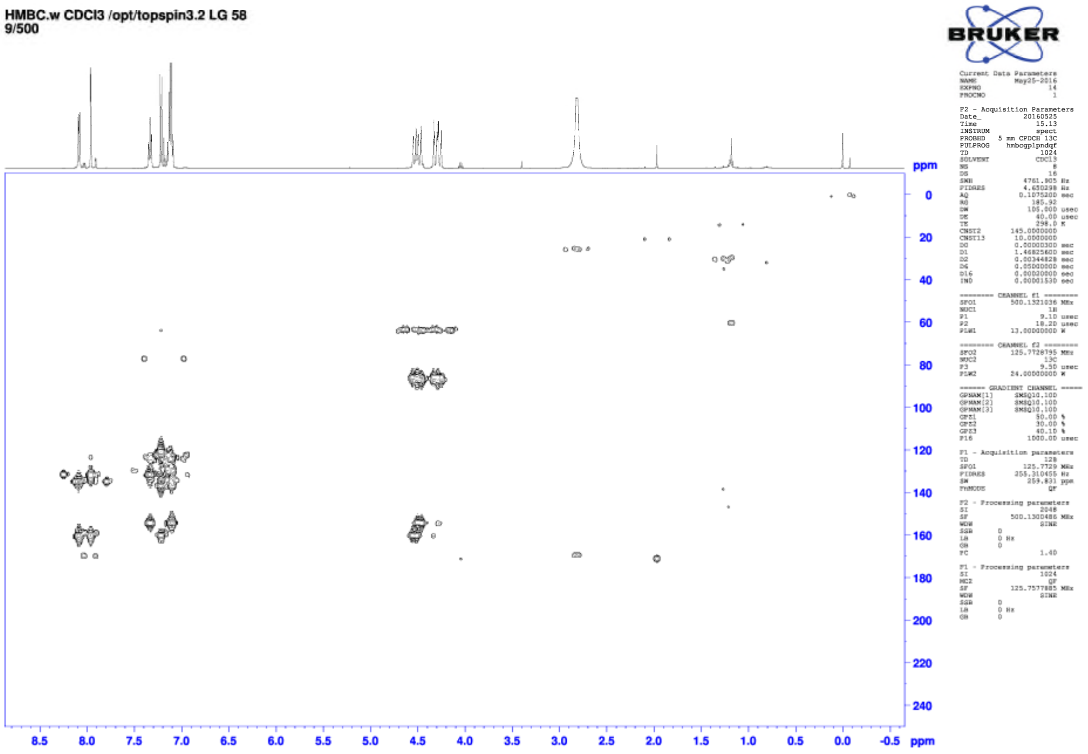
======== CHANNEL f2 ========
SFO2         125.7697355 MHz
NUC2                 13C
CPDPRG[2            garp
P3                  9.50 usec
P4                 19.00 usec
PCPD2              63.70 usec
PLW2         24.00000000 W
PLW12         0.51266003 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7697 MHz
FIDRES        206.679901 Hz
SW               210.345 ppm
FnMODE      Echo-Antiecho

F2 - Processing parameters
SI                  1024
SF           500.1300486 MHz
WDW                QSINE
SSB                    2
LB       0 Hz
GB       0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2         echo-antiecho
SF           125.7577885 MHz
WDW                QSINE
SSB                    2
LB       0 Hz
GB       0
```



HMBC.w CDCl3 /opt/topspin3.2 LG 58
9/500

```
Current Data Parameters
NAME          May25-2016
EXPNO                 14
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160525
Time               15.13
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG      hmbcgplpndqf
TD                  1024
SOLVENT            CDCl3
NS                     8
DS                    16
SWH             4761.905 Hz
FIDRES          4.650298 Hz
AQ             0.1075200 sec
RG                185.92
DW               105.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
CNST13        10.0000000
D0            0.00000300 sec
D1            1.46825600 sec
D2            0.00344828 sec
D6            0.05000000 sec
D16           0.00020000 sec
IN0           0.00001530 sec

======== CHANNEL f1 ========
SFO1         500.1321036 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
PLW1         13.00000000 W

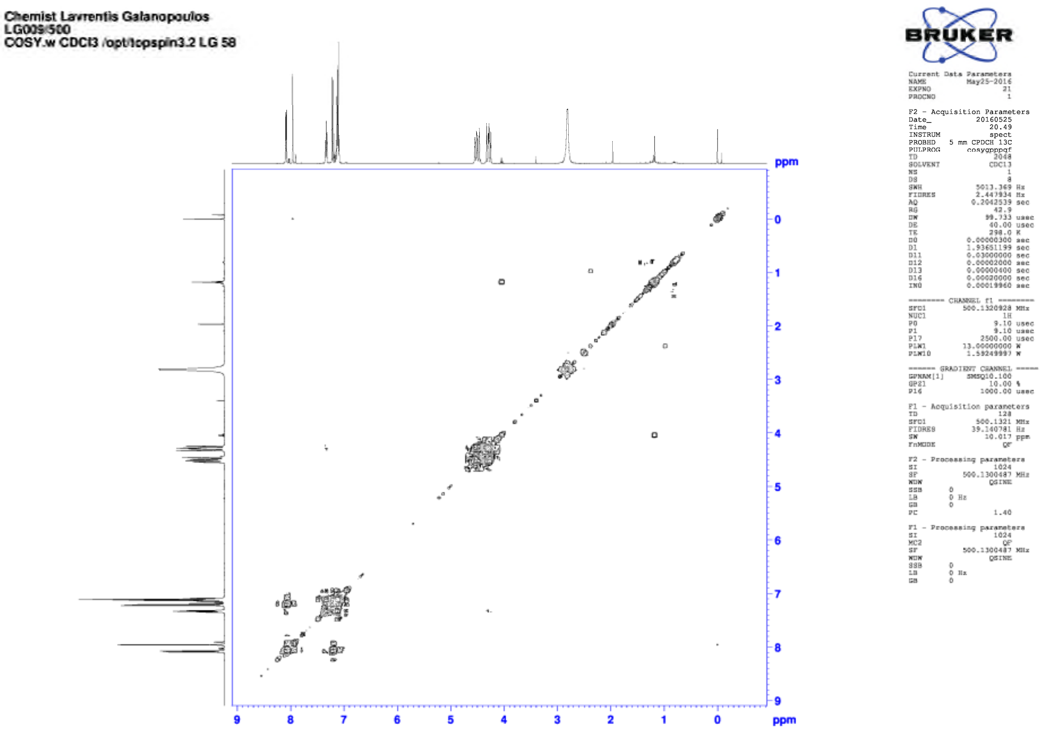
======== CHANNEL f2 ========
SFO2         125.7728795 MHz
NUC2                 13C
P3                  9.50 usec
PLW2         24.00000000 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPNAM[3]      SMSQ10.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7729 MHz
FIDRES        255.310455 Hz
SW               259.831 ppm
FnMODE                QF

F2 - Processing parameters
SI                  2048
SF           500.1300486 MHz
WDW                 SINE
SSB      0
LB       0 Hz
GB       0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           125.7577885 MHz
WDW                 SINE
SSB      0
LB       0 Hz
GB       0
```



```
Current Data Parameters
NAME          May25-2016
EXPNO                 21
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160525
Time               20.49
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG        cosygpppqf
TD                  2048
SOLVENT            CDCl3
NS                     1
DS                     8
SWH             5013.369 Hz
FIDRES          2.447934 Hz
AQ             0.2042539 sec
RG                  42.9
DW                99.733 usec
DE                 40.00 usec
TE                 298.0 K
D0            0.00000300 sec
D1            1.93651199 sec
D11           0.03000000 sec
D12           0.00002000 sec
D13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00019960 sec

======== CHANNEL f1 ========
SFO1         500.1320928 MHz
NUC1                  1H
P0                  9.10 usec
P1                  9.10 usec
P17              2500.00 usec
PLW1         13.00000000 W
PLW10         1.59249997 W

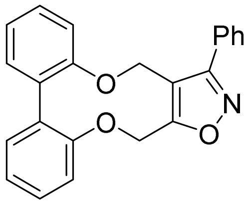
====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPZ1               10.00 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            500.1321 MHz
FIDRES         39.140781 Hz
SW                10.017 ppm
FnMODE                QF

F2 - Processing parameters
SI                  1024
SF           500.1300487 MHz
WDW                QSINE
SSB       0
LB        0 Hz
GB        0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           500.1300487 MHz
WDW                QSINE
SSB       0
LB        0 Hz
GB        0
```

Synthesis of compound 9; 13-phenyl-8,11,16-trioxa-12-azatetracyclo[15.4.0.0^{2,7}.0^{10,14}]henicosa-1(17),2,4,6,10(14),12,18,20-octaene **9**.



A mixture of strained alkyne **1** (50 mg, 0.21 mmol) and PhC(Cl)NOH (39 mg, 0.25 mmol) was stirred in DMF (0.5 mL) in the presence of 4Å MS (350 mg) for 3 days at rt. At the end of this time water (10 mL) and EtOAc (10 ml) were added and the organic layer was separated. The water layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with water (3 x 20 mL). The solvent was removed to leave a crude product which was purified by chromatography on silica gel (hexane/EtOAC gradient) to give the product **9** as a clear oil (33 mg, 0.842 mmol, 40%).

The Product was below the strained alkyne by TLC; 4/1 hexane/EtOAc, silica gel, product Rf 0.30, alkyne Rf 0.60, visualised by uv and $KMnO_4$.

IR$_{(neat)}$ 1460, 1440, 1257, 1188, 1104, 837, 751, 725, 696 cm^{-1};

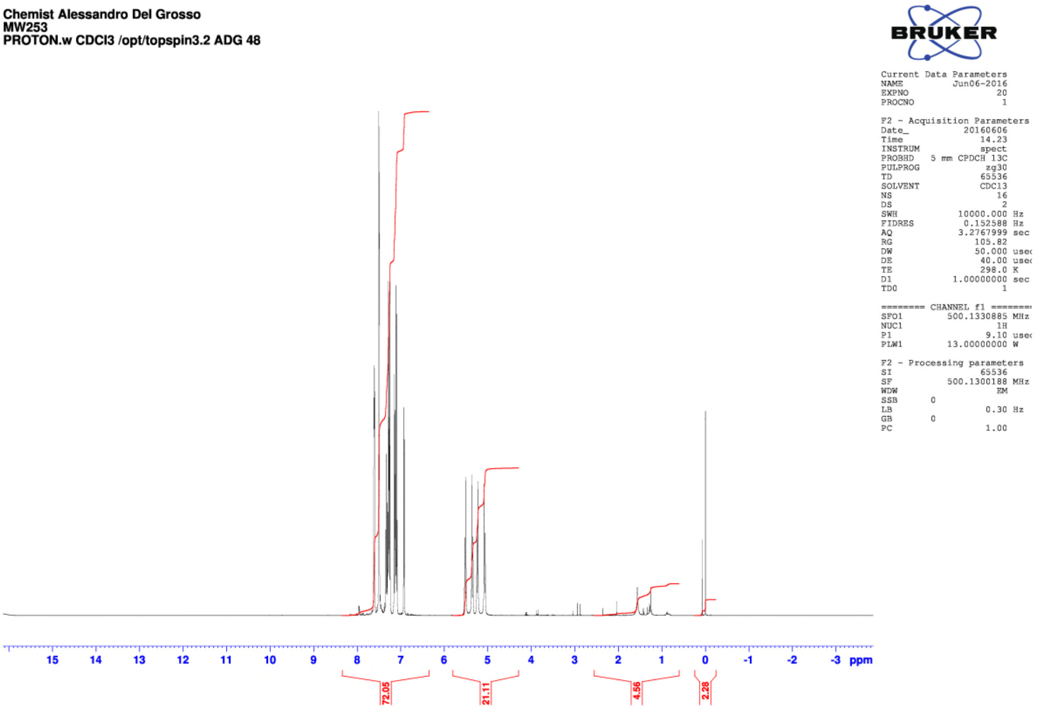
δ_H (500 MHz, $CDCl_3$) 7.65-7.58 (2H, m, ArH), 7.54-6.45 (3H, m, ArH), 7.35-7.24 (4H, m, ArH), 7.18-7.07 (3H, m, ArH), 6.93 (1H, d, *J* =8.5, ArH), 5.52 (1H, d, *J* = 13.5, C*H*H), 5.35 (1H, d, *J* = 13.5, CH*H*), 5.23 (1H, d, *J* = 13.5, C*H*H), 5.07 (1H, d, *J* = 13.5, CH*H*). COSY, HSQC,

δ_C (120 MHz, $CDCl_3$) 168.9 (C), 162.7 (C), 157.0 (C), 155.5 (C), 131.0 (CH), 130.66 (CH), 130.5 (C), 130.1 (C), 130.0 (CH), 129.0 (CH), 128.9 (CH), 128.9 (CH), 128.55 (CH), 128.2 (C), 123.0 (CH), 122.9 (CH), 116.0 (CH), 113.7 (CH), 113.6 (C), 62.0 (CH_2), 61.8 (CH_2)..

m/*z* (ESI+) 356.1 (M^+ + H, 45%), 378.1 (M^+ + Na, 100%).

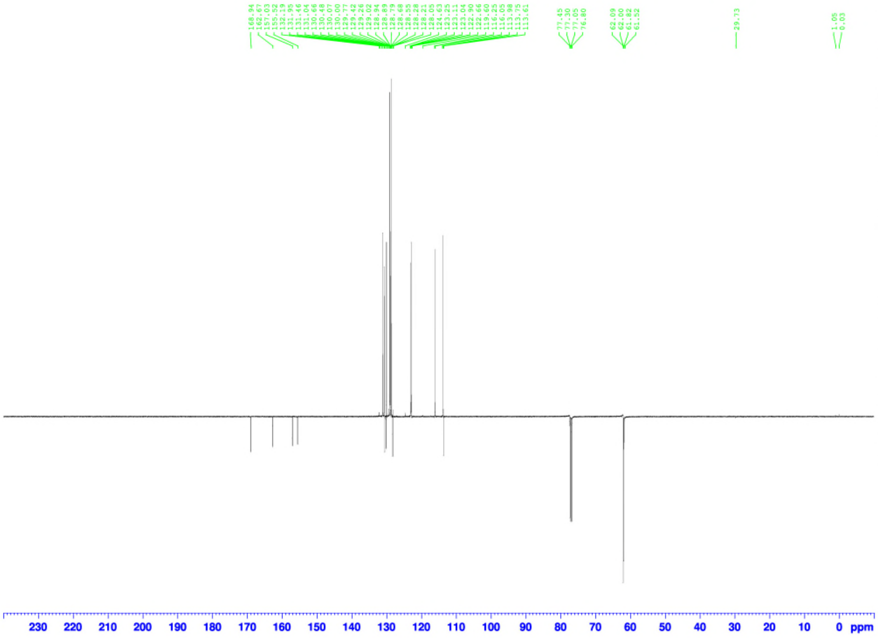
HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{17}NO_3Na$ 378.1101; Found 378.1105.

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

C13APT.w CDCl3 /opt/topspin3.2 ADG 48



```
Current Data Parameters
NAME            Jun06-2016
EXPNO                   24
PROCNO                   1

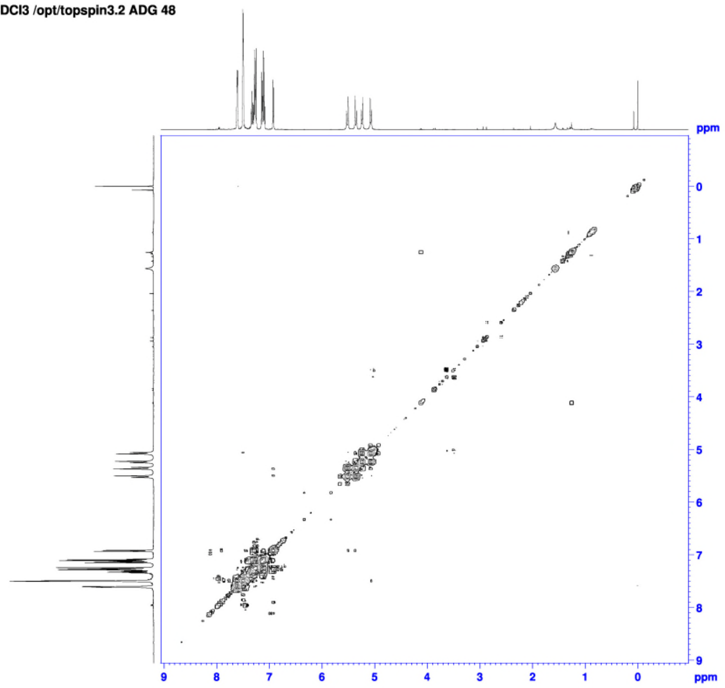
F2 - Acquisition Parameters
Date_             20160606
Time                 15.28
INSTRUM              spect
PROBHD   5 mm CPDCH 13C
PULPROG               jmod
TD                   65536
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              32894.738 Hz
FIDRES            0.501934 Hz
AQ               0.9961472 sec
RG                  185.92
DW                  15.200 use
DE                   66.43 use
TE                   298.0 K
CNST2          145.0000000
CNST11           1.0000000
D1              2.00000000 sec
D20             0.00689655 sec
TD0                      1

======== CHANNEL f1 =======
SFO1           125.7728795 MHz
NUC1                   13C
P1                    9.50 use
P2                   19.00 use
PLW1           24.00000000 W

======== CHANNEL f2 =======
SFO2           500.1320005 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                65.00 use
PLW2           13.00000000 W
PLW12           0.26784000 W

F2 - Processing parameters
SI                   32768
SF             125.7577885 MHz
WDW                     EM
SSB        0
LB                    1.00 Hz
GB         0
PC                    1.40
```

Chemist Alessandro Del Grosso
MW253
COSY.w CDCl3 /opt/topspin3.2 ADG 48



```
Current Data Parameters
NAME            Jun06-2016
EXPNO                   21
PROCNO                   1

F2 - Acquisition Parameters
Date_             20160606
Time                 14.25
INSTRUM              spect
PROBHD   5 mm CPDCH 13C
PULPROG          cosygpppqf
TD                    2048
SOLVENT              CDCl3
NS                       1
DS                       8
SWH               5013.369 Hz
FIDRES            2.447934 Hz
AQ               0.2042539 sec
RG                   60.07
DW                  99.733 usec
DE                   40.00 usec
TE                   298.0 K
D0              0.00000300 sec
D1              1.93651199 sec
D11             0.03000000 sec
D12             0.00002000 sec
D13             0.00000400 sec
D16             0.00020000 sec
IN0             0.00019960 sec

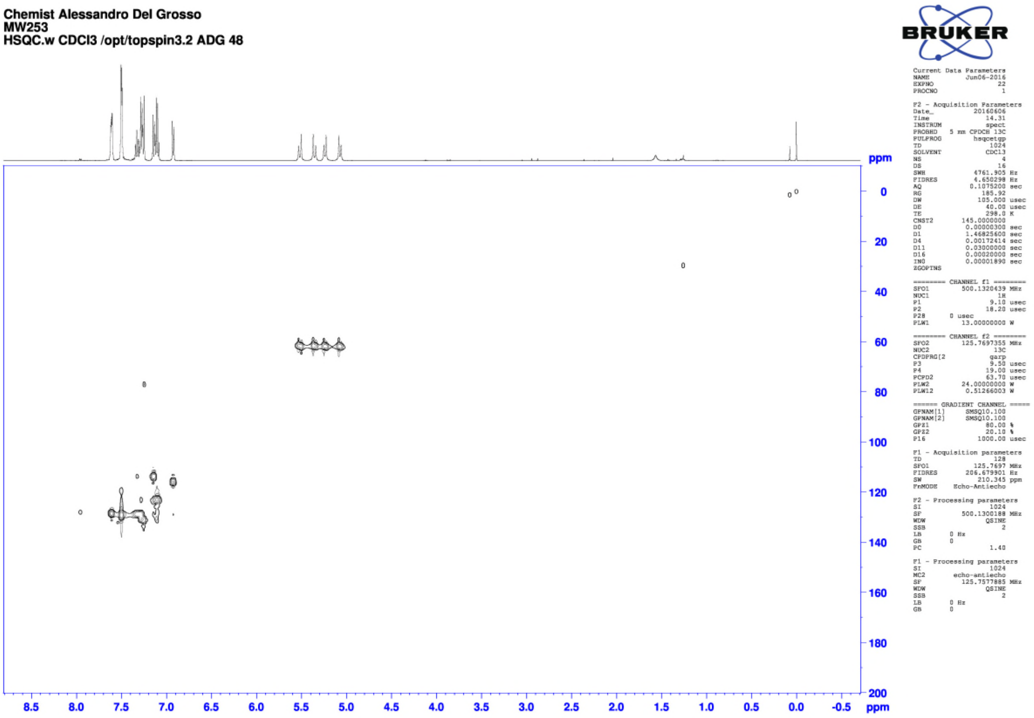
======== CHANNEL f1 ========
SFO1           500.1320439 MHz
NUC1                    1H
P0                    9.10 usec
P1                    9.10 usec
P17                2500.00 usec
PLW1           13.00000000 W
PLW10           1.59249997 W

====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPZ1                 10.00 %
P16                1000.00 usec

F1 - Acquisition parameters
TD                     128
SFO1               500.132 MHz
FIDRES           39.140781 Hz
SW                  10.017 ppm
FnMODE                  QF

F2 - Processing parameters
SI                    1024
SF             500.1300188 MHz
WDW                  QSINE
SSB        0
LB         0 Hz
GB         0
PC                    1.40

F1 - Processing parameters
SI                    1024
MC2                     QF
SF             500.1300188 MHz
WDW                  QSINE
SSB        0
LB         0 Hz
GB         0
```



```
Current Data Parameters
NAME          Jun06-2016
EXPNO                 22
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160606
Time               14.31
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG         hsqcetgp
TD                  1024
SOLVENT            CDCl3
NS                     4
DS                    16
SWH             4761.905 Hz
FIDRES          4.650298 Hz
AQ             0.1075200 sec
RG                185.92
DW               105.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
D0            0.00000300 sec
D1            1.46825600 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
IN0           0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         500.1320439 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
P28      0 usec
PLW1         13.00000000 W

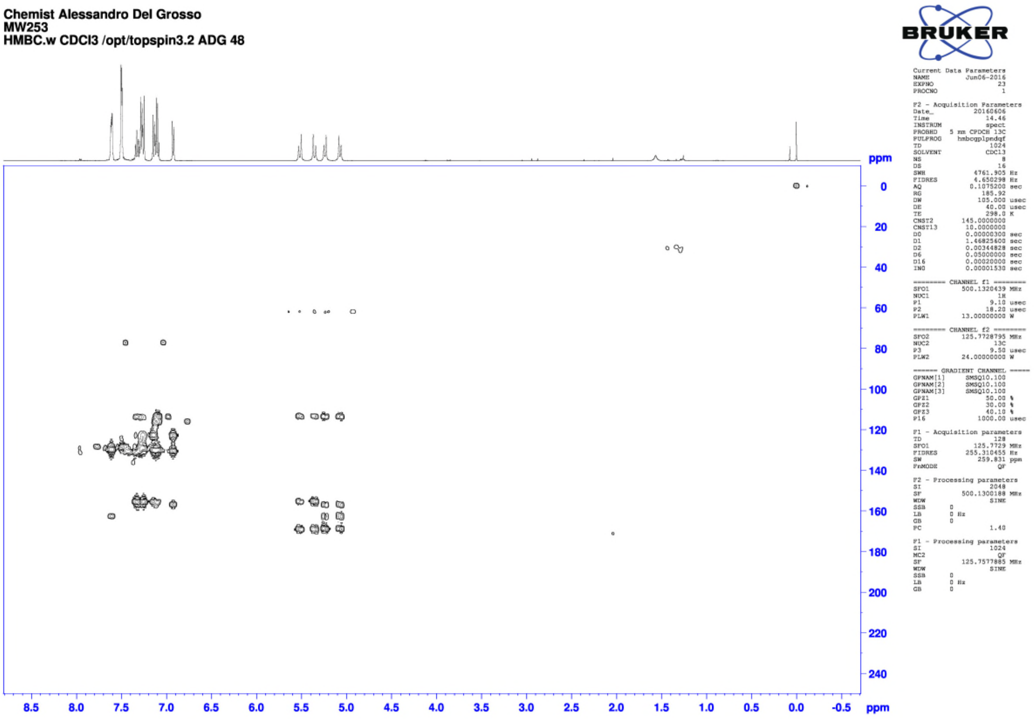
======== CHANNEL f2 ========
SFO2         125.7697355 MHz
NUC2                 13C
CPDPRG[2            garp
P3                  9.50 usec
P4                 19.00 usec
PCPD2              63.70 usec
PLW2         24.00000000 W
PLW12         0.51266003 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7697 MHz
FIDRES        206.679901 Hz
SW               210.345 ppm
FnMODE      Echo-Antiecho

F2 - Processing parameters
SI                  1024
SF           500.1300188 MHz
WDW                QSINE
SSB                    2
LB       0 Hz
GB       0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2         echo-antiecho
SF           125.7577885 MHz
WDW                QSINE
SSB                    2
LB       0 Hz
GB       0
```



```
Current Data Parameters
NAME          Jun06-2016
EXPNO                 23
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160606
Time               14.46
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG      hmbcgplpndqf
TD                  1024
SOLVENT            CDCl3
NS                     8
DS                    16
SWH             4761.905 Hz
FIDRES          4.650298 Hz
AQ             0.1075200 sec
RG                185.92
DW               105.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
CNST13        10.0000000
D0            0.00000300 sec
D1            1.46825600 sec
D2            0.00344828 sec
D6            0.05000000 sec
D16           0.00020000 sec
IN0           0.00001530 sec

======== CHANNEL f1 ========
SFO1         500.1320439 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7728795 MHz
NUC2                 13C
P3                  9.50 usec
PLW2         24.00000000 W

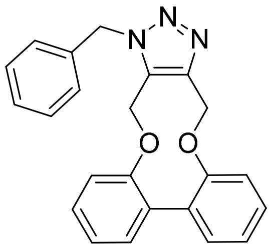
====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPNAM[3]      SMSQ10.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7729 MHz
FIDRES        255.310455 Hz
SW               259.831 ppm
FnMODE                QF

F2 - Processing parameters
SI                  2048
SF           500.1300188 MHz
WDW                 SINE
SSB      0
LB       0 Hz
GB       0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           125.7577885 MHz
WDW                 SINE
SSB      0
LB       0 Hz
GB       0
```

Compound 5a; 1-Benzyl-4,15-dihydro-1*H*-dibenzo[7,8:9,10][1,6]dioxecino[3,4-*d*][1,2,3]triazole **5a**.



In a round bottom flask, compound **1** (35.4 mg, 0.15 mmol) was dissolved in acetonitrile (0.6 mL). Benzyl azide (19.9 mg, 0.15 mmol) was added and the mixture was heated at 60 ºC. After 20 hours the mixture was cooled to room temperature and the volatiles were removed. The product was purified by flash chromatography on silica gel (eluent: Petroleum ether/EtOAc = 3:2 to 2:3) to give compound **5a** (52 mg, 0.14 mmol, 93%) as colourless solid.

m.p. 207.6-208.8 ºC.

IR$_{\text{(neat)}}$ 3059, 3016, 2969, 2945, 1603, 1593, 1571, 1497, 1478, 1453, 1440, 1391, 1368, 1353, 1339, 1303, 1285, 1259, 1244, 1214, 1204 cm^{-1}.

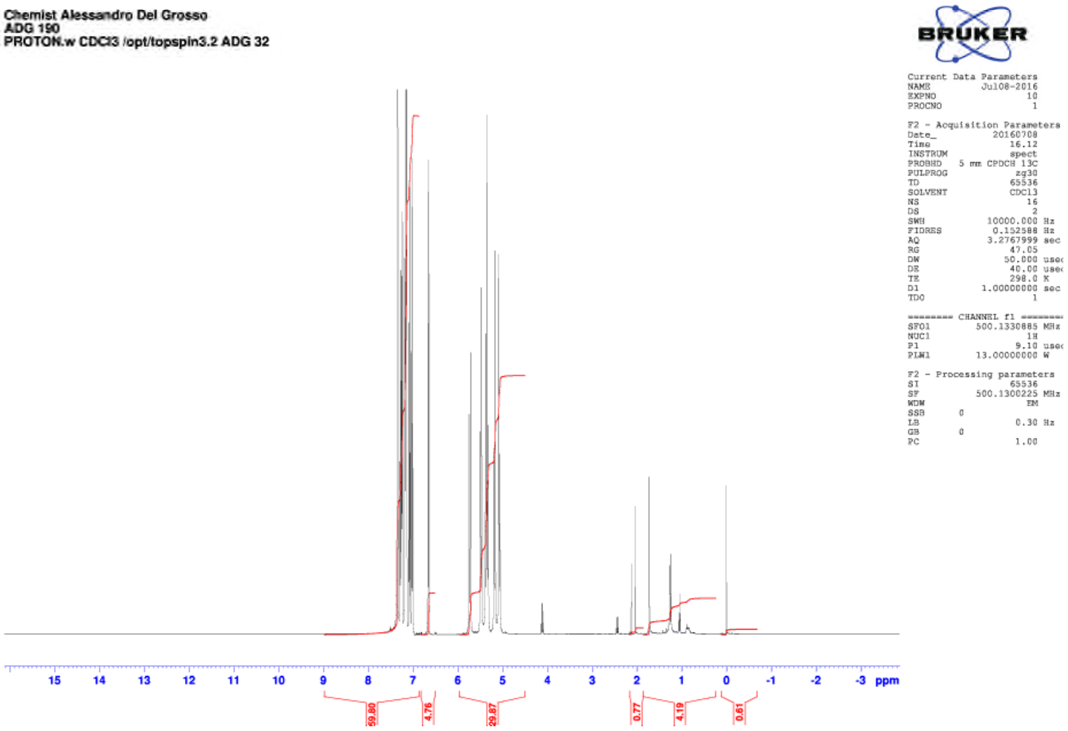
δ_H (500 MHz, $CDCl_3$) 7.32 - 7.39 (3H, m, Ar*H*), 7.22 - 7.31 (2H, m, Ar*H*), 7.12 - 7.21 (5H, m, Ar*H*), 7.07 (1H, t, *J* = 7.3 Hz, Ar*H*), 6.99 - 7.05 (1H, m, Ar*H*), 6.65 (1H, d, *J* = 7.9 Hz, Ar*H*), 5.73 (1H, d, *J* = 15.7 Hz, C*H*H), 5.48 (1H, d, *J* = 13.4 Hz, C*H*H), 5.28 - 5.42 (2H, m, 2xCH*H*), 5.18 (1H, d, *J* = 13.2 Hz, C*H*H), 5.07 (1H, d, *J* = 13.2 Hz, CH*H*).

δ_C (125 MHz, $CDCl_3$) 156.5 (C), 155.5 (C), 144.8 (C), 134.6 (C), 132.3 (C), 130.7 (CH), 130.6 (C), 130.4 (CH), 129.4 (C), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.1 (CH), 123.2 (CH), 122.1 (CH), 115.3 (CH), 114.2 (CH), 62.9 (CH_2), 60.5 (CH_2), 52.3 (CH_2).

m/z (ESI) $[M + H]^+$, 370.2; $[M + Na]^+$, 392.1.

HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{19}N_3O_2Na$ 392.1369; Found 392.1369.

^{1}H NMR (500 MHz, $CDCl_3$)



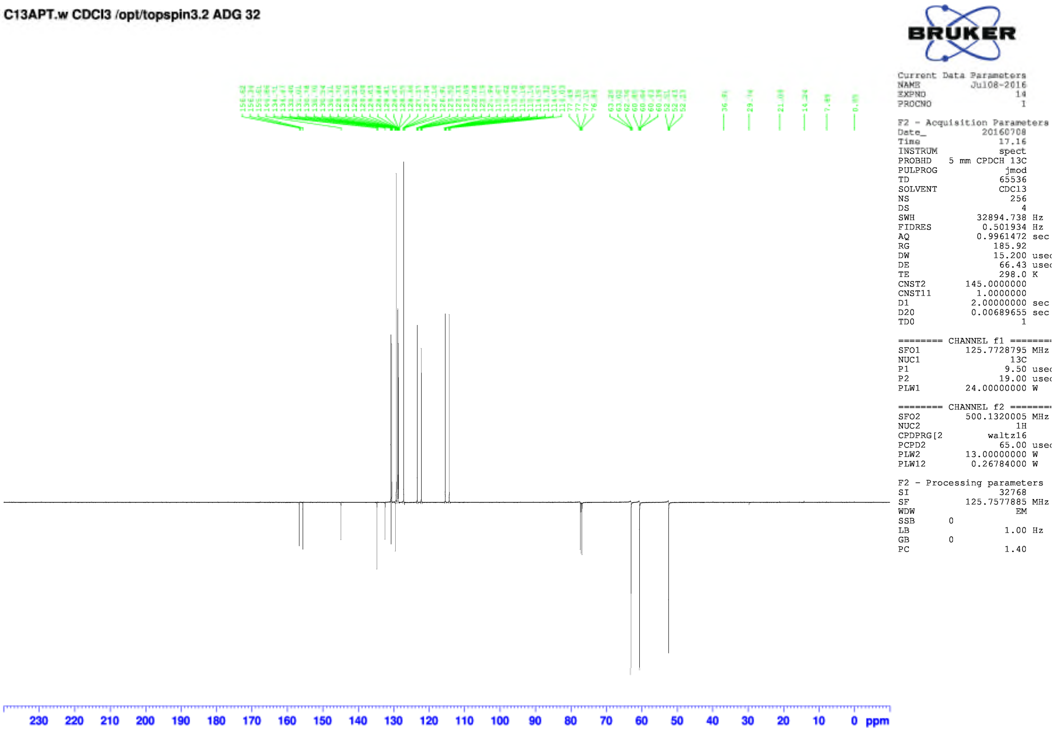
```
Current Data Parameters
NAME          Jul08-2016
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160708
Time               16.12
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                 47.05
DW                50.000 usec
DE                 40.00 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                  1H
P1                  9.10 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1300225 MHz
WDW                   EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

^{13}C NMR (125 MHz, $CDCl_3$)



```
Current Data Parameters
NAME          Jul08-2016
EXPNO                 14
PROCNO                 1

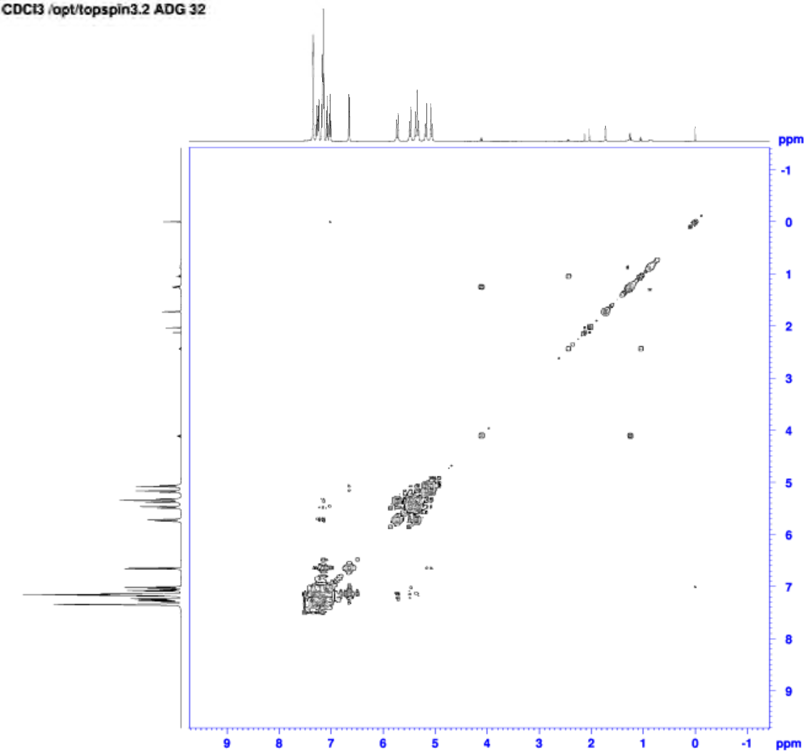
F2 - Acquisition Parameters
Date_           20160708
Time               17.16
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             jmod
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            32894.738 Hz
FIDRES          0.501934 Hz
AQ             0.9961472 sec
RG                185.92
DW                15.200 usec
DE                 66.43 usec
TE                 298.0 K
CNST2        145.0000000
CNST11         1.0000000
D1            2.00000000 sec
D20           0.00689655 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7728795 MHz
NUC1                 13C
P1                  9.50 usec
P2                 19.00 usec
PLW1         24.00000000 W

======== CHANNEL f2 ========
SFO2         500.1320005 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              65.00 usec
PLW2         13.00000000 W
PLW12         0.26784000 W

F2 - Processing parameters
SI                 32768
SF           125.7577885 MHz
WDW                   EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```

Chemist Alessandro Del Grosso
ADG 190
COSY.w CDCl3 /opt/topspin3.2 ADG 32



```
Current Data Parameters
NAME          Jul08-2016
EXPNO                 11
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160708
Time               16.14
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG        cosygpppqf
TD                  2048
SOLVENT            CDCl3
NS                     1
DS                     8
SWH             5580.357 Hz
FIDRES          2.724784 Hz
AQ             0.1835008 sec
RG                 21.55
DW                89.600 usec
DE                 40.00 usec
TE                 298.0 K
D0            0.00000300 sec
D1            1.95904005 sec
D11           0.03000000 sec
D12           0.00002000 sec
D13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00017960 sec

======== CHANNEL f1 ========
SFO1         500.1320979 MHz
NUC1                  1H
P0                  9.10 usec
P1                  9.10 usec
P17              2500.00 usec
PLW1         13.00000000 W
PLW10         1.59249997 W

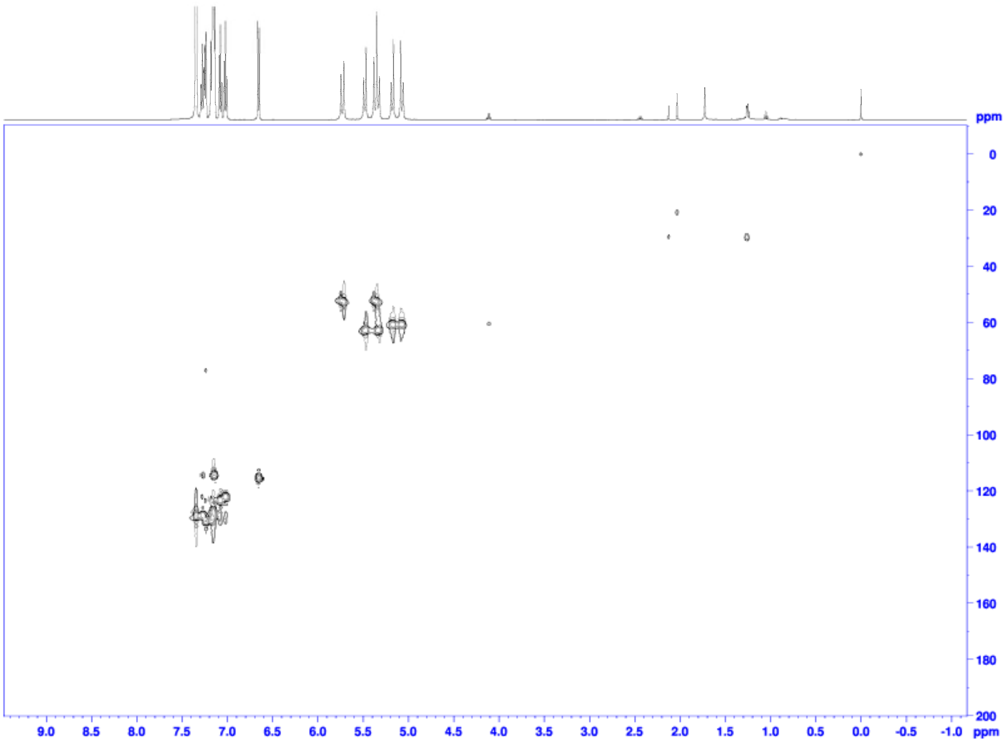
====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPZ1               10.00 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            500.1321 MHz
FIDRES         43.499443 Hz
SW                11.133 ppm
FnMODE                QF

F2 - Processing parameters
SI                  1024
SF           500.1300225 MHz
WDW                QSINE
SSB       0
LB        0 Hz
GB        0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           500.1300225 MHz
WDW                QSINE
SSB       0
LB        0 Hz
GB        0
```

HSQC.w CDCl3 /opt/topspin3.2 ADG 32
0



```
Current Data Parameters
NAME          Jul08-2016
EXPNO                 12
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160708
Time               16.20
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG         hsqcetgp
TD                  1024
SOLVENT            CDCl3
NS                     4
DS                    16
SWH             5319.149 Hz
FIDRES          5.194481 Hz
AQ             0.0962560 sec
RG                185.92
DW                94.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
D0            0.00000300 sec
D1            1.47951996 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
IN0           0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         500.1320979 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
P28       0 usec
PLW1         13.00000000 W

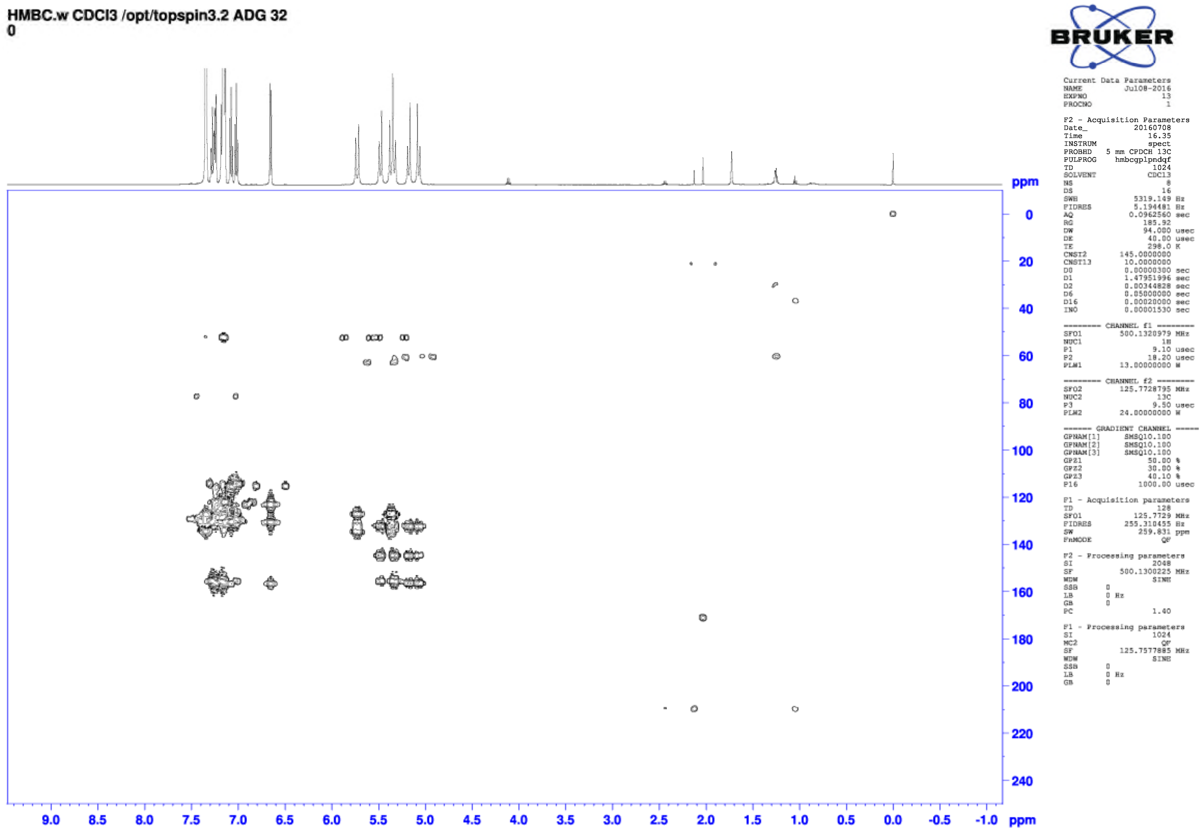
======== CHANNEL f2 ========
SFO2         125.7697355 MHz
NUC2                 13C
CPDPRG[2            garp
P3                  9.50 usec
P4                 19.00 usec
PCPD2              63.70 usec
PLW2         24.00000000 W
PLW12         0.51266003 W

====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPNAM[2]       SMSQ10.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

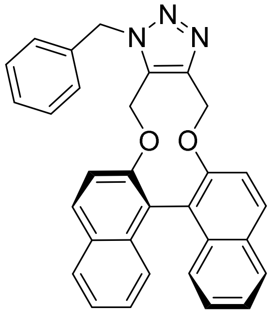
F1 - Acquisition parameters
TD                   128
SFO1            125.7697 MHz
FIDRES        206.679901 Hz
SW               210.345 ppm
FnMODE      Echo-Antiecho

F2 - Processing parameters
SI                  1024
SF           500.1300225 MHz
WDW                QSINE
SSB                    2
LB        0 Hz
GB        0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2         echo-antiecho
SF           125.7577805 MHz
WDW                QSINE
SSB                    2
LB        0 Hz
GB        0
```



Compound 6; 1-Benzyl-4,19-dihydro-1*H*-dinaphtho[2',1':7,8;1'',2'':9,10][1,6]dioxecino[3,4-*d*][1,2,3]triazole **6**.



In a round bottom flask, compound **2** (50 mg, 0.15 mmol) was dissolved in DCM(1 mL). Benzyl azide (19.9 mg, 0.15 mmol) was added. After 4 days the volatiles were removed and the product was purified by flash chromatography on silica gel (eluent: Pentane/EtOAc = 4:1 to 1:3) to give compound **6** (64 mg, 0.14 mmol, 92%) as colourless solid.

$[\alpha]_D^{25}$ -152.7 (*c* 0.53, $CHCl_3$).

m.p. 114 ºC dec.

IR$_{(neat)}$ 3055, 3034, 3009, 2944, 2892, 1619, 1590,1471, 1455, 1431, 1355, 1326, 1267, 1218 cm^{-1}.

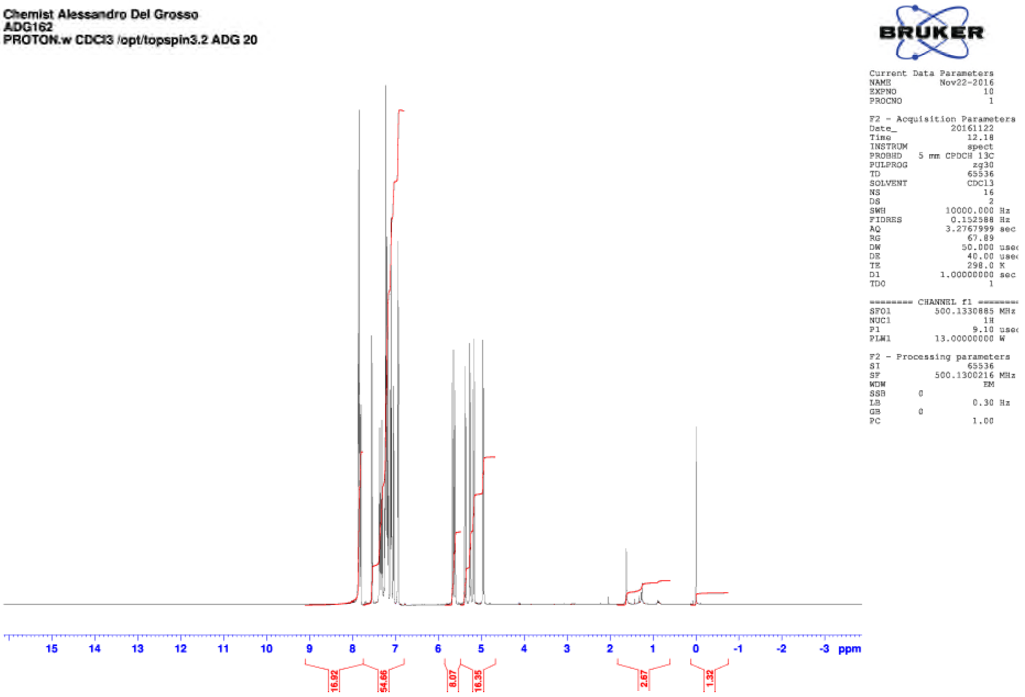
δ_H (500 MHz, $CDCl_3$) 7.77 - 7.94 (4H, m, Ar*H*), 7.55 (1H, d, *J* = 9.0 Hz, Ar*H*), 7.28 – 7.43 (2H, m, Ar*H*), 7.15 - 7.28 (5H, m, Ar*H*), 7.11 (2H, t, *J* = 7.7 Hz, Ar*H*), 7.05 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.94 (2H, d, *J* = 7.5 Hz, Ar*H*), 5.57 – 5.73 (2H, m, C*H*H), 5.38 (1H, d, *J* = 15.7 Hz, C*H*H), 5.26 (1H, d, *J* = 14.0 Hz, CH*H*), 5.18 (1H, d, *J* = 13.1 Hz, CH*H*), 4.96 (1H, d, *J* = 13.1 Hz, C*H*H).

δ_C (125MHz, $CDCl_3$) 155.1 (C), 152.8 (C), 144.5 (C), 134.7 (C), 133.6 (C), 132.1 (C), 130.6 (C), 130.0 (CH), 129.6 (C), 129.5 (CH), 128.9 (CH), 128.3 (CH), 128.06 (CH), 128.05 (CH), 126.8 (CH), 126.7 (CH), 126.4 (CH), 126.1 (CH), 125.5 (CH), 124.8 (CH), 124.0 (CH), 123.4 (C), 121.4 (C), 118.8 (CH), 116.6 (CH), 63.3 (CH_2), 61.9 (CH_2), 52.1 (CH_2).

m/*z* (ESI) 470.2 ([M + H]$^+$, 100%).

HRMS (ESI-Q-TOF) m/z: [M + Na]$^+$ Calcd for $C_{31}H_{23}N_3O_2Na$ 492.1682; Found 492.1686.

^1H NMR (500 MHz, $CDCl_3$).



```
Current Data Parameters
NAME          Nov22-2016
EXPNO                 10
PROCNO                 1

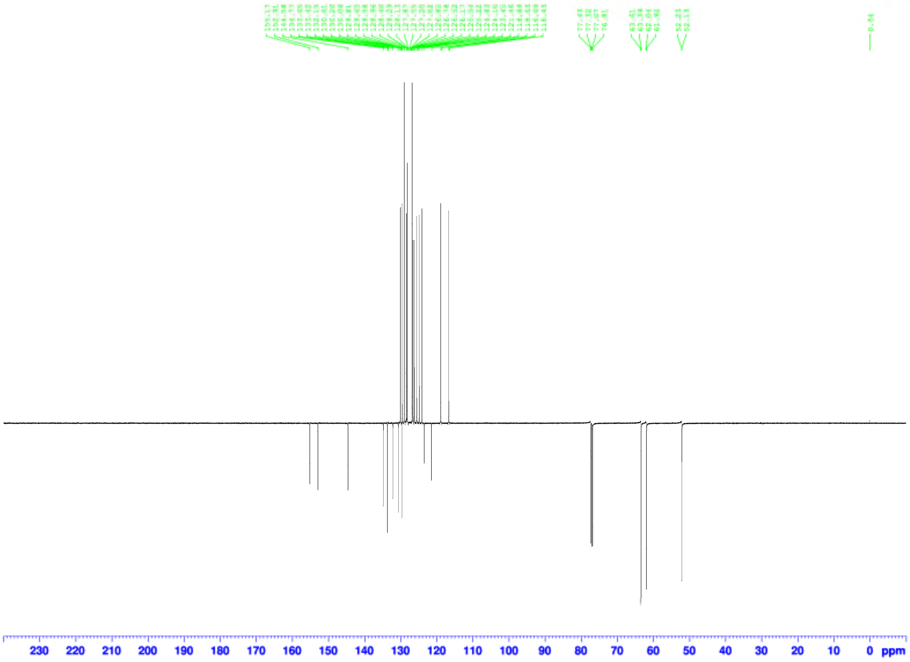
F2 - Acquisition Parameters
Date_           20161122
Time               12.18
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                 67.89
DW                50.000 usec
DE                 40.00 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                  1H
P1                  9.10 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1300216 MHz
WDW                   EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

^{13}C NMR (125 MHz, $CDCl_3$).

C13APT.w CDCl3 /opt/topspin3.2 ADG 20



```
Current Data Parameters
NAME            Nov22-2016
EXPNO                   14
PROCNO                   1

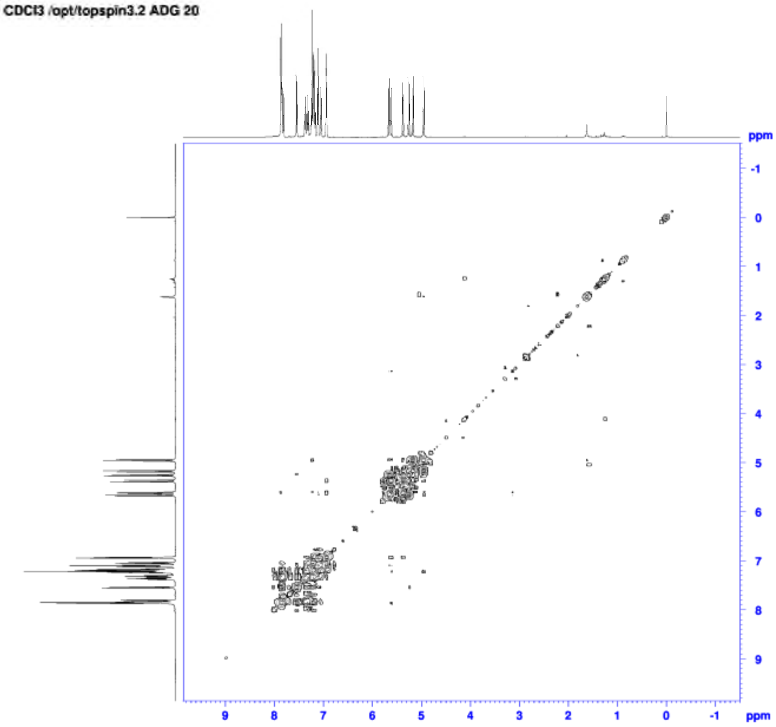
F2 - Acquisition Parameters
Date_             20161122
Time                 13.23
INSTRUM              spect
PROBHD   5 mm CPDCH 13C
PULPROG               jmod
TD                   65536
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              32894.738 Hz
FIDRES            0.501934 Hz
AQ               0.9961472 sec
RG                  185.92
DW                  15.200 usec
DE                   66.43 usec
TE                   298.0 K
CNST2          145.0000000
CNST11           1.0000000
D1              2.00000000 sec
D20             0.00689655 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           125.7728795 MHz
NUC1                   13C
P1                    9.50 usec
P2                   19.00 usec
PLW1           24.00000000 W

======== CHANNEL f2 ========
SFO2           500.1320005 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                65.00 usec
PLW2           13.00000000 W
PLW12           0.26784000 W

F2 - Processing parameters
SI                   32768
SF             125.7577885 MHz
WDW                     EM
SSB      0
LB                    1.00 Hz
GB       0
PC                    1.40
```

Chemist Alessandro Del Grosso
ADG162
COSY.w CDCl3 /opt/topspin3.2 ADG 20



```
Current Data Parameters
NAME            Nov22-2016
EXPNO                   11
PROCNO                   1

F2 - Acquisition Parameters
Date_             20161122
Time                 12.20
INSTRUM              spect
PROBHD   5 mm CPDCH 13C
PULPROG         cosygpppqf
TD                    2048
SOLVENT              CDCl3
NS                       1
DS                       8
SWH               5681.818 Hz
FIDRES            2.774325 Hz
AQ               0.1802240 sec
RG                    42.9
DW                  88.000 usec
DE                   40.00 usec
TE                   298.0 K
D0              0.00000300 sec
D1              1.96313596 sec
D11             0.03000000 sec
D12             0.00002000 sec
D13             0.00000400 sec
D16             0.00020000 sec
IN0             0.00017600 sec

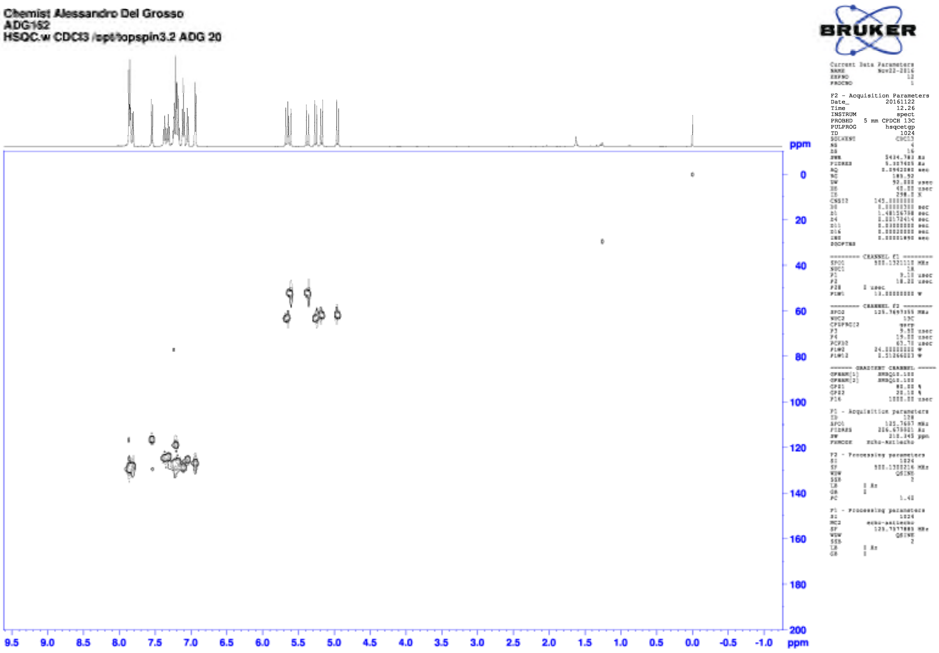
======== CHANNEL f1 ========
SFO1           500.1321110 MHz
NUC1                    1H
P0                    9.10 usec
P1                    9.10 usec
P17                2500.00 usec
PLW1           13.00000000 W
PLW10           1.59249997 W

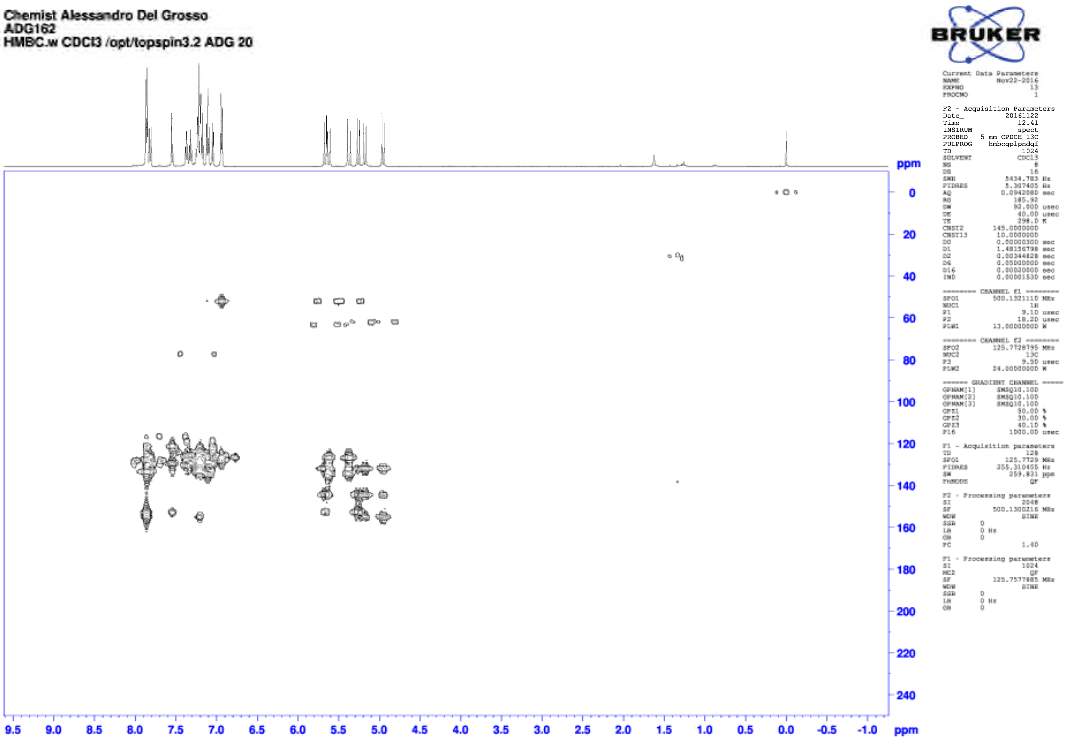
====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPZ1                 10.00 %
P16                1000.00 usec

F1 - Acquisition parameters
TD                     128
SFO1              500.1321 MHz
FIDRES           44.389206 Hz
SW                  11.361 ppm
FnMODE                  QF

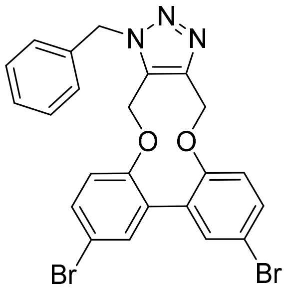
F2 - Processing parameters
SI                    1024
SF             500.1300216 MHz
WDW                  QSINE
SSB      0
LB       0 Hz
GB       0
PC                    1.40

F1 - Processing parameters
SI                    1024
MC2                     QF
SF             500.1300216 MHz
WDW                  QSINE
SSB      0
LB       0 Hz
GB       0
```





Compound 5b; 1-Benzyl-8,11-dibromo-4,15-dihydro-1*H*-dibenzo[7,8:9,10][1,6]dioxecino[3,4-*d*][1,2,3]triazole **5b**.



In a round bottom flask, compound **3** (59 mg, 0.15 mmol) was dissolved in acetonitrile (1.5 mL). Benzyl azide (19.9 mg, 0.15 mmol) was added and the mixture was stirred at room temperature for 5 days. The volatiles were removed and the product was purified by flash chromatography on silica gel (eluent: Petroleum ether/EtOAc = 3:2 to 2:3) to give compound **5b** (73 mg, 0.14 mmol, 93%) as a colourless solid.

m.p. 101.2-102.6 ºC.

$\mathrm{IR}_{\mathrm{(neat)}}$ 3062, 3032, 1721, 1486, 1455, 1397, 1332, 1270, 1252, 1232, 1207 cm^{-1}.

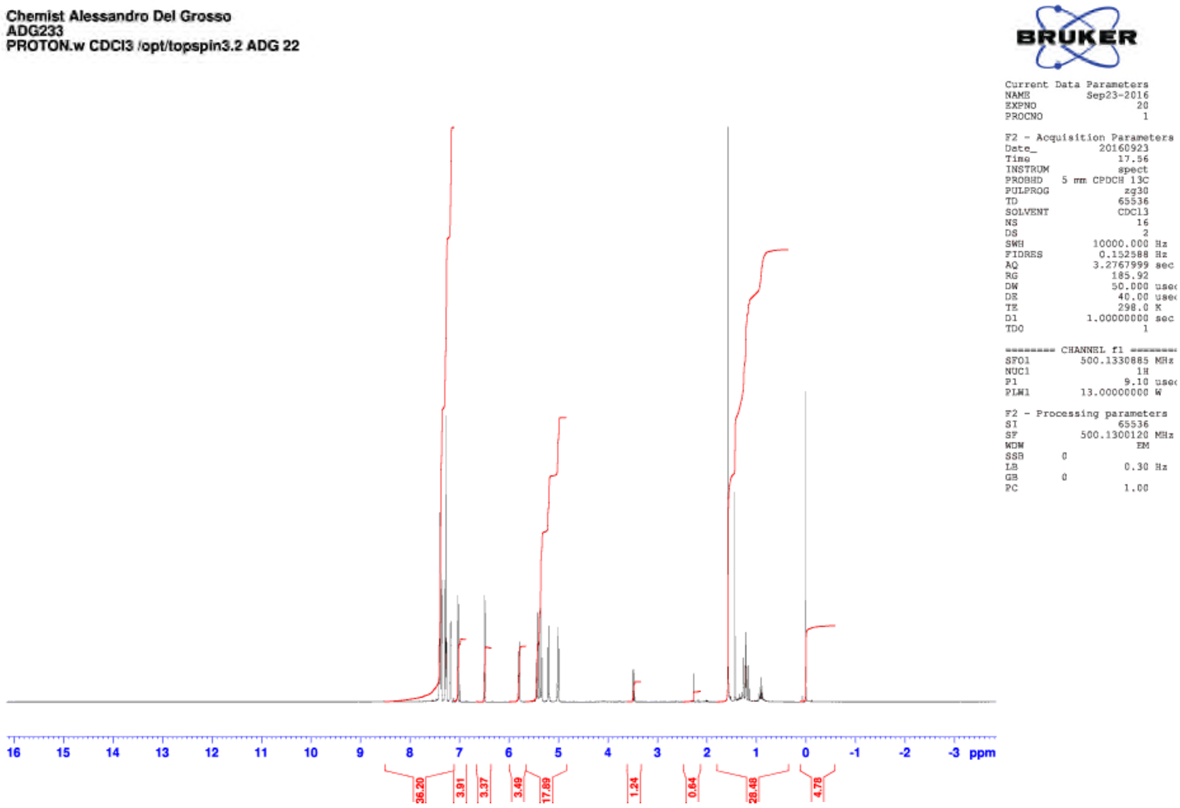
δ_H (500MHz, $CDCl_3$) 7.33 - 7.43 (5H, m, Ar*H*), 7.29 (1H, d, *J* = 2.4 Hz, Ar*H*), 7.24 - 7.28 (1H, m, Ar*H*), 7.14 - 7.21 (2H, m, Ar*H*), 7.03 (1H, d, *J* = 8.7 Hz, Ar*H*), 6.49 (1H, d, *J* = 8.7 Hz, Ar*H*), 5.80 (1H, d, *J* = 15.7 Hz, C*H*H), 5.30 - 5.48 (3H, m, C*H*H), 5.20 (1H, d, *J* = 13.3 Hz, CH*H*), 5.00 (1H, d, *J* = 13.3 Hz, CH*H*).

δ_C (125 MHz, $CDCl_3$) 155.6 (C), 154.6 (C), 144.4 (C), 134.4 (C), 133.2 (CH), 133.0 (CH), 131.96 (CH), 131.94 (C), 131.92(CH), 131.4 (C), 130.2 (C), 129.3 (CH), 128.8 (CH), 127.1 (CH), 117.2 (CH), 116.1 (CH), 115.7 (C), 114.4 (C), 63.2 (CH_2), 60.9 (CH_2), 52.6 (CH_2).

m/z (ESI) $[M + H]^+$, 525.9; $[M + Na]^+$, 547.9.

HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{17}{}^{79}Br_2N_3O_2Na$ 547.9580; Found 547.9577.

^{1}H NMR (500 MHz, $CDCl_3$).



Chemist Alessandro Del Grosso
ADG233
PROTON.w CDCl3 /opt/topspin3.2 ADG 22

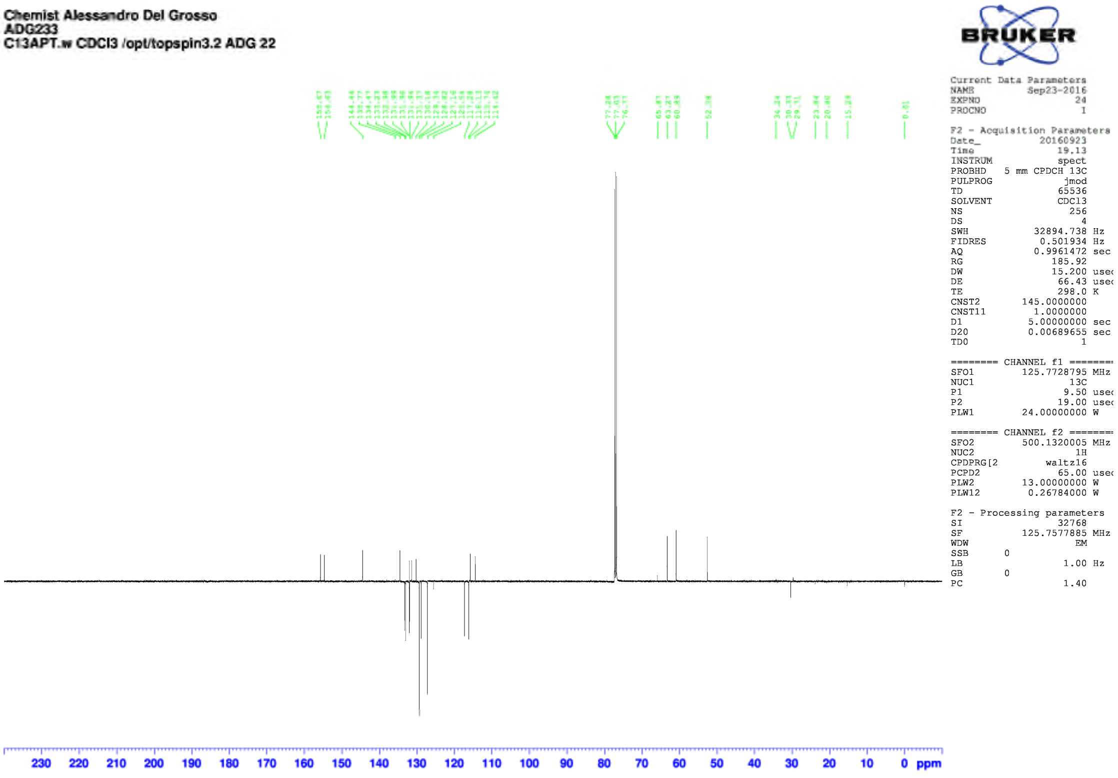
```
Current Data Parameters
NAME          Sep23-2016
EXPNO                 20
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160923
Time               17.56
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                185.92
DW                50.000 usec
DE                 40.00 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                  1H
P1                  9.10 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1300120 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```

^{13}C NMR (125 MHz, CDCl$_3$).



Chemist Alessandro Del Grosso
ADG233
C13APT.w CDCl3 /opt/topspin3.2 ADG 22

```
Current Data Parameters
NAME          Sep23-2016
EXPNO                 24
PROCNO                 1

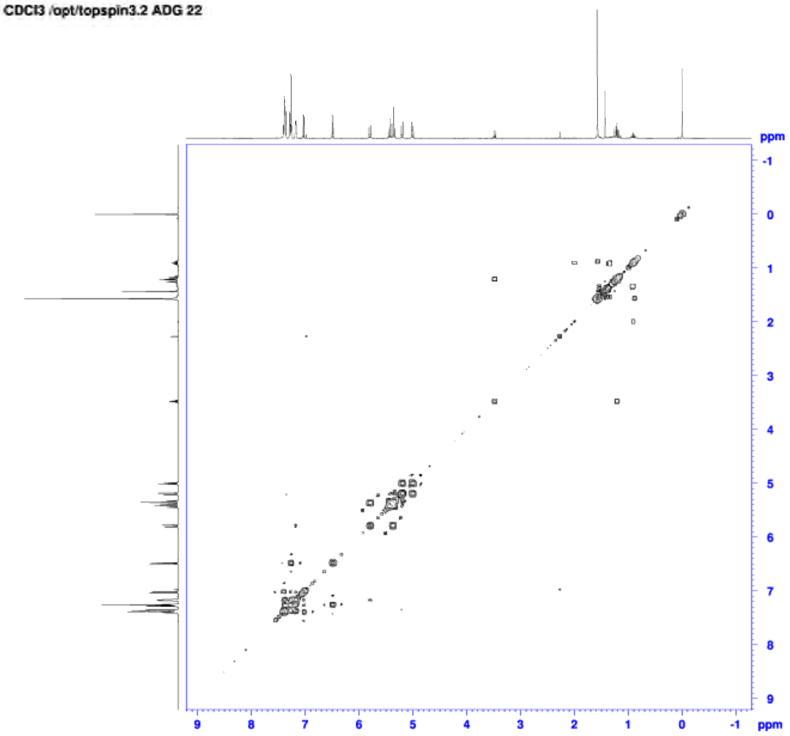
F2 - Acquisition Parameters
Date_           20160923
Time               19.13
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             jmod
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            32894.738 Hz
FIDRES          0.501934 Hz
AQ             0.9961472 sec
RG                185.92
DW                15.200 usec
DE                 66.43 usec
TE                 298.0 K
CNST2        145.0000000
CNST11         1.0000000
D1            5.00000000 sec
D20           0.00689655 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7728795 MHz
NUC1                 13C
P1                  9.50 usec
P2                 19.00 usec
PLW1         24.00000000 W

======== CHANNEL f2 ========
SFO2         500.1320005 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              65.00 usec
PLW2         13.00000000 W
PLW12         0.26784000 W

F2 - Processing parameters
SI                 32768
SF           125.7577885 MHz
WDW                   EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  1.40
```

Chemist Alessandro Del Grosso
ADG233
COSY.w CDCl3 /opt/topspin3.2 ADG 22



```
Current Data Parameters
NAME            Sep23-2016
EXPNO                   21
PROCNO                   1

F2 - Acquisition Parameters
Date_             20160923
Time                 17.58
INSTRUM              spect
PROBHD    5 mm CPDCH 13C
PULPROG         cosygpppqf
TD                    2048
SOLVENT              CDCl3
NS                       1
DS                       8
SWH               5252.101 Hz
FIDRES            2.564502 Hz
AQ               0.1949696 sec
RG                  154.41
DW                  95.200 usec
DE                   40.00 usec
TE                   298.0 K
D0              0.00000300 sec
D1              1.94675195 sec
D11             0.03000000 sec
D12             0.00002000 sec
D13             0.00000400 sec
D16             0.00020000 sec
IN0             0.00019040 sec

======== CHANNEL f1 ========
SFO1           500.1319920 MHz
NUC1                    1H
P0                    9.10 usec
P1                    9.10 usec
P17                2500.00 usec
PLW1           13.00000000 W
PLW10           1.59249997 W

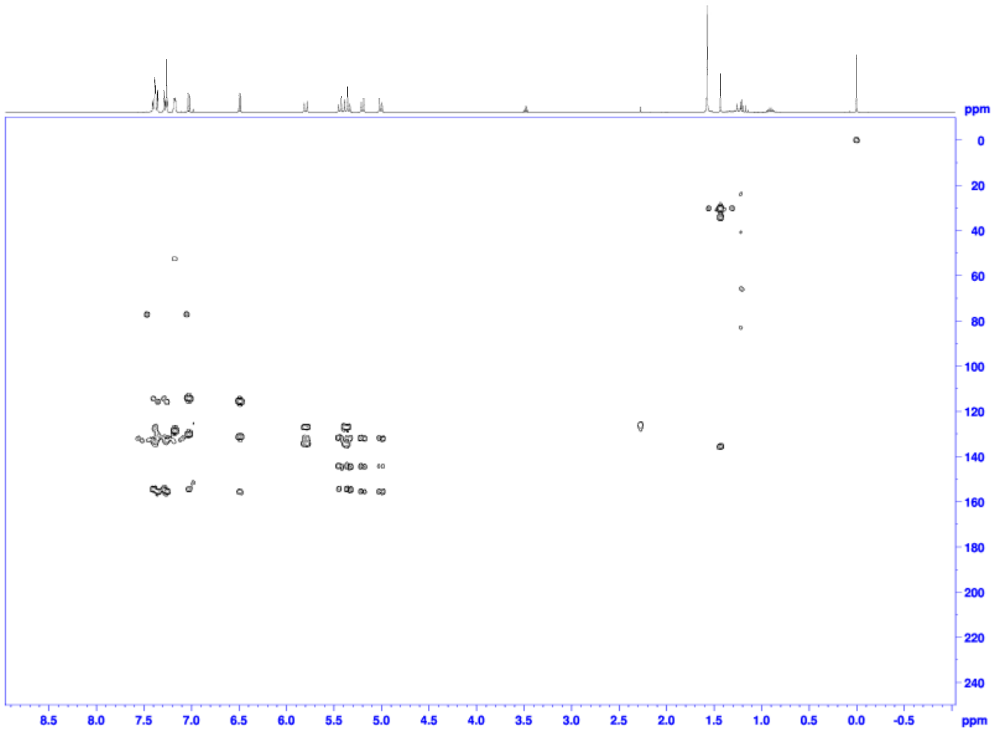
====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPZ1                 10.00 %
P16                1000.00 usec

F1 - Acquisition parameters
TD                     128
SFO1               500.132 MHz
FIDRES           41.032040 Hz
SW                  10.501 ppm
FnMODE                  QF

F2 - Processing parameters
SI                    1024
SF             500.1300120 MHz
WDW                  QSINE
SSB        0
LB         0 Hz
GB         0
PC                    1.40

F1 - Processing parameters
SI                    1024
MC2                     QF
SF             500.1300120 MHz
WDW                  QSINE
SSB        0
LB         0 Hz
GB         0
```

HMBC.w CDCl3 /opt/topspin3.2 ADG 22



```
Current Data Parameters
NAME            Sep23-2016
EXPNO                   23
PROCNO                   1

F2 - Acquisition Parameters
Date_             20160923
Time                 18.18
INSTRUM              spect
PROBHD    5 mm CPDCH 13C
PULPROG        hmbcgplpndqf
TD                    1024
SOLVENT              CDCl3
NS                       8
DS                      16
SWH               5000.000 Hz
FIDRES            4.882812 Hz
AQ               0.1024000 sec
RG                  185.92
DW                 100.000 usec
DE                   40.00 usec
TE                   298.0 K
CNST2          145.0000000
CNST13          10.0000000
D0              0.00000300 sec
D1              1.47337604 sec
D2              0.00344828 sec
D6              0.05000000 sec
D16             0.00020000 sec
IN0             0.00001530 sec

======== CHANNEL f1 ========
SFO1           500.1319920 MHz
NUC1                    1H
P1                    9.10 usec
P2                   18.20 usec
PLW1           13.00000000 W

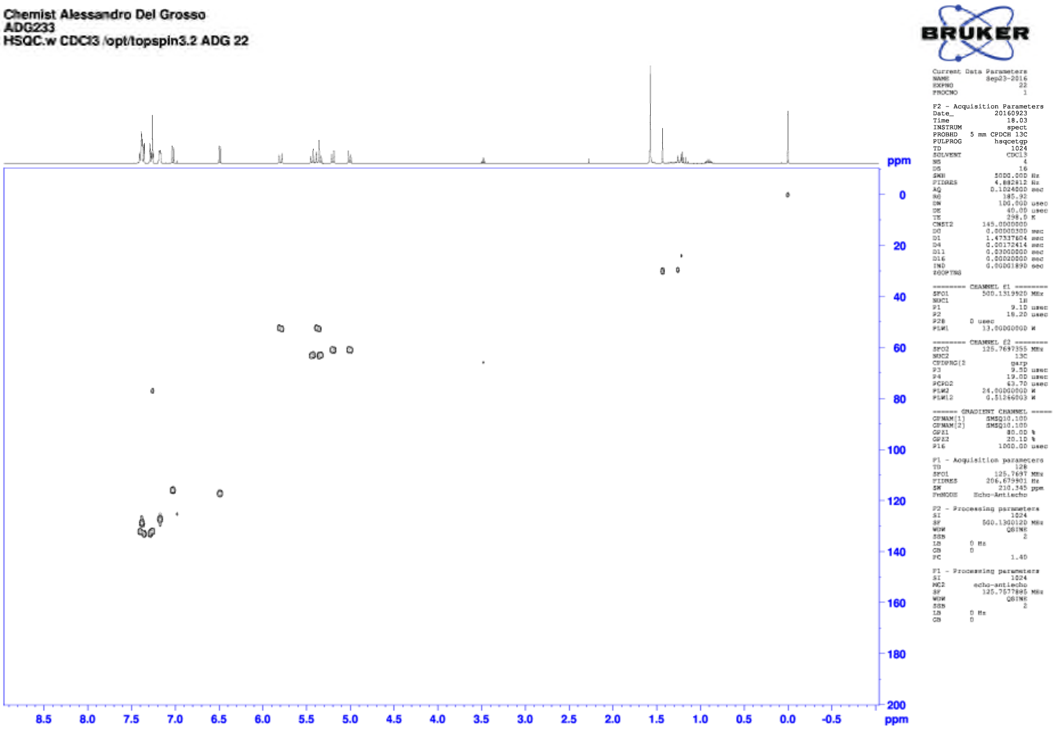
======== CHANNEL f2 ========
SFO2           125.7728795 MHz
NUC2                   13C
P3                    9.50 usec
PLW2           24.00000000 W

====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPNAM[2]        SMSQ10.100
GPNAM[3]        SMSQ10.100
GPZ1                 50.00 %
GPZ2                 30.00 %
GPZ3                 40.10 %
P16                1000.00 usec

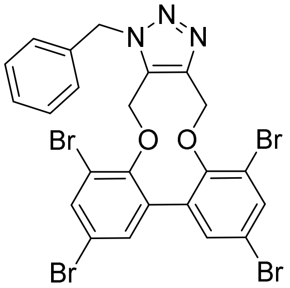
F1 - Acquisition parameters
TD                     128
SFO1              125.7729 MHz
FIDRES          255.310455 Hz
SW                 259.831 ppm
FnMODE                  QF

F2 - Processing parameters
SI                    2048
SF             500.1300120 MHz
WDW                   SINE
SSB        0
LB         0 Hz
GB         0
PC                    1.40

F1 - Processing parameters
SI                    1024
MC2                     QF
SF             125.7577885 MHz
WDW                   SINE
SSB        0
LB         0 Hz
GB         0
```



Compound 5c; 1-Benzyl-6,8,11,13-tetrabromo-4,15-dihydro-1*H*-dibenzo[7,8:9,10][1,6]dioxecino[3,4-*d*][1,2,3]triazole **5c**.



In a J. Young NMR tube compound **4** (50 mg, 0.09 mmol) was dissolved in $CDCl_3$ (0.9 mL). Benzyl azide (11.9 mg, 0.15 mmol) was added. After 14 days the volatiles were removed and the products was purified by flash chromatography on silica gel (eluent: Hexane/EtOAc = 4:1 to 7:3) to give compound **5c** (57 mg, 0.08 mmol, 92%) as colourless solid.

m.p. 203.1-204.5 °C.

IR$_{\text{(neat)}}$ 3068, 3060, 3032, 2920, 2850, 1742, 1729, 1550, 1463, 1437, 1399, 1372, 1330, 1282, 1256, 1222 cm^{-1}.

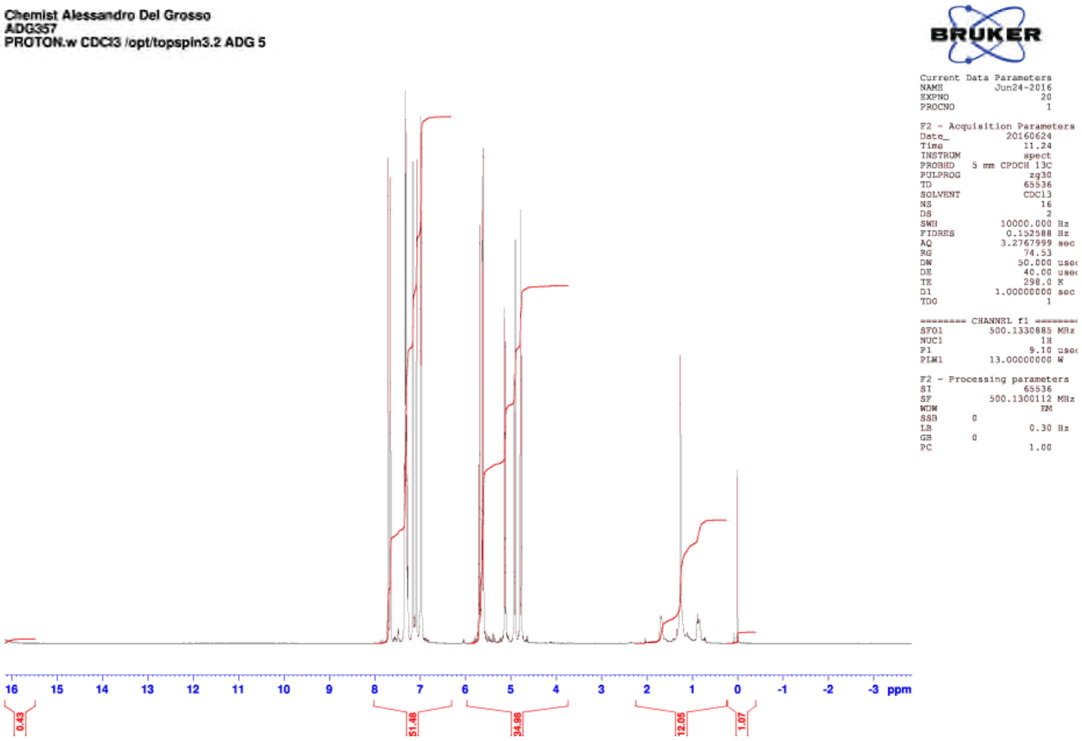
δ_H (500 MHz, $CDCl_3$) 7.70 (1H, d, *J* = 2.1 Hz, Ar*H*), 7.65 (1H, d, *J* = 2.1 Hz, Ar*H*), 7.26 - 7.38 (3H, m, Ar*H*), 7.15 (1H, d, *J* = 2.1 Hz, Ar*H*), 7.07 (1H, d, *J* = 2.1 Hz, Ar*H*), 6.97 (2H, d, *J* = 7.0 Hz, Ar*H*), 5.69 (1H, d, *J* = 15.7 Hz, C*H*H), 5.55 - 5.65 (2H, m, C*H*H), 5.12 (1H, d, *J* = 13.3 Hz, CH*H*), 4.91 (1H, d, *J* = 14.2 Hz, CH*H*), 4.78 (1H, d, *J* = 14.2 Hz, CH*H*).

δ_C (125 MHz, $CDCl_3$) 152.0 (C), 151.7 (C), 143.3 (C), 136.3 (CH), 135.8 (CH), 134.3 (C), 134.2 (C), 133.8 (CH), 133.2 (C), 132.4 (CH), 131.6 (C), 129.1 (CH), 128.6 (CH), 126.9 (CH), 118.5 (C), 117.5 (C), 117.2 (C), 116.6 (C), 65.8 (CH_2), 62.6 (CH_2), 52.6 (CH_2).

m/*z* (ESI) 707.8 ($[M + Na]^+$, 100%).

HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{15}{}^{79}Br_4N_3O_2Na$ 703.7790; Found 703.7787.

^1H NMR (500 MHz, $CDCl_3$)



```
Chemist Alessandro Del Grosso
ADG357
PROTON.w CDCl3 /opt/topspin3.2 ADG 5
```

```
Current Data Parameters
NAME            Jun24-2016
EXPNO                   20
PROCNO                   1

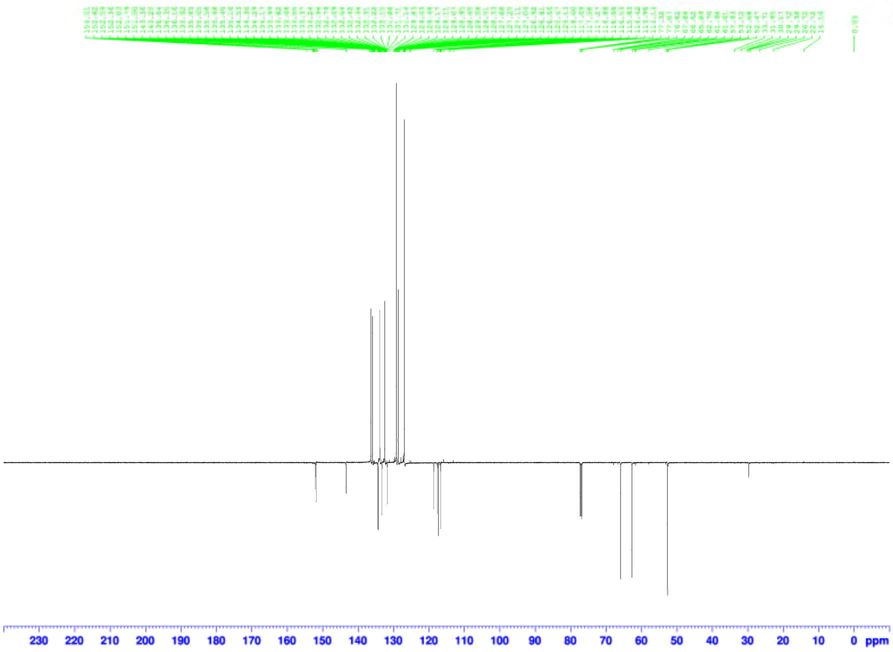
F2 - Acquisition Parameters
Date_             20160624
Time                 11.24
INSTRUM              spect
PROBHD   5 mm CPDCH 13C
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH              10000.000 Hz
FIDRES            0.152588 Hz
AQ               3.2767999 sec
RG                   74.53
DW                  50.000 use
DE                   40.00 use
TE                   298.0 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 =======
SFO1           500.1330885 MHz
NUC1                    1H
P1                    9.10 use
PLW1           13.00000000 W

F2 - Processing parameters
SI                   65536
SF             500.1300112 MHz
WDW                     EM
SSB      0
LB                    0.30 Hz
GB       0
PC                    1.00
```

^{13}C NMR (125 MHz, $CDCl_3$)

Chemist Alessandro Del Grosso
ADG357
C13APT.w CDCl3 /opt/topspin3.2 ADG 5



```
Current Data Parameters
NAME          Jun24-2016
EXPNO                 24
PROCNO                 1

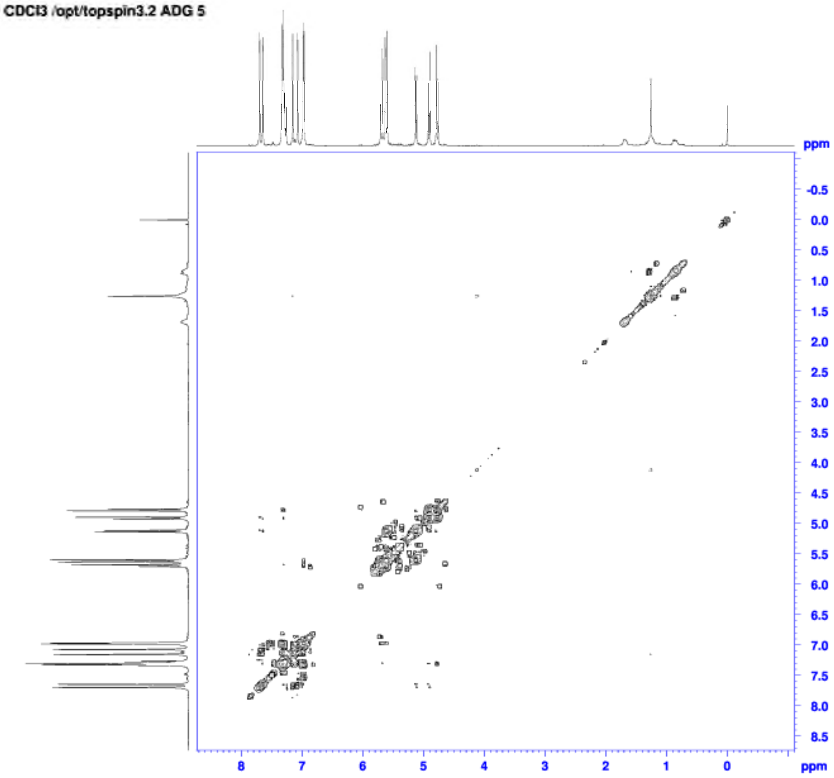
F2 - Acquisition Parameters
Date_           20160624
Time               12.29
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             jmod
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            32894.738 Hz
FIDRES          0.501934 Hz
AQ             0.9961472 sec
RG                185.92
DW                15.200 usec
DE                 66.43 usec
TE                 298.0 K
CNST2        145.0000000
CNST11         1.0000000
D1            2.00000000 sec
D20           0.00689655 sec
TD0                    1

======= CHANNEL f1 =======
SFO1         125.7728795 MHz
NUC1                 13C
P1                  9.50 usec
P2                 19.00 usec
PLW1         24.00000000 W

======= CHANNEL f2 =======
SFO2         500.1320005 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              65.00 usec
PLW2         13.00000000 W
PLW12         0.26784000 W

F2 - Processing parameters
SI                 32768
SF           125.7577885 MHz
WDW                   EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  1.40
```

Chemist Alessandro Del Grosso
ADG357
COSY.w CDCl3 /opt/topspin3.2 ADG 5



```
Current Data Parameters
NAME          Jun24-2016
EXPNO                 21
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160624
Time               11.26
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG        cosygpppqf
TD                  2048
SOLVENT            CDCl3
NS                     1
DS                     8
SWH             4921.260 Hz
FIDRES          2.402959 Hz
AQ             0.2080768 sec
RG                 27.55
DW               101.600 usec
DE                 40.00 usec
TE                 298.0 K
D0            0.00000300 sec
D1            1.93241596 sec
D11           0.03000000 sec
D12           0.00002000 sec
D13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00020320 sec

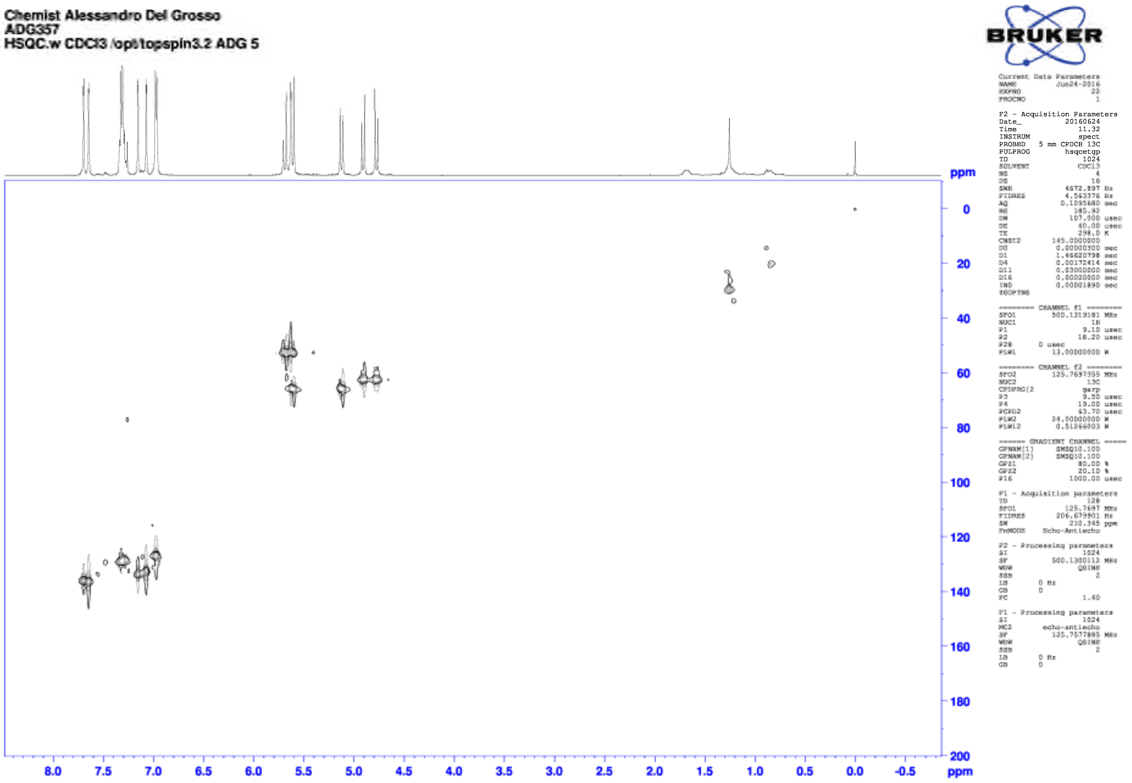
======== CHANNEL f1 ========
SFO1         500.1319181 MHz
NUC1                  1H
P0                  9.10 usec
P1                  9.10 usec
P17              2500.00 usec
PLW1         13.00000000 W
PLW10         1.59249997 W

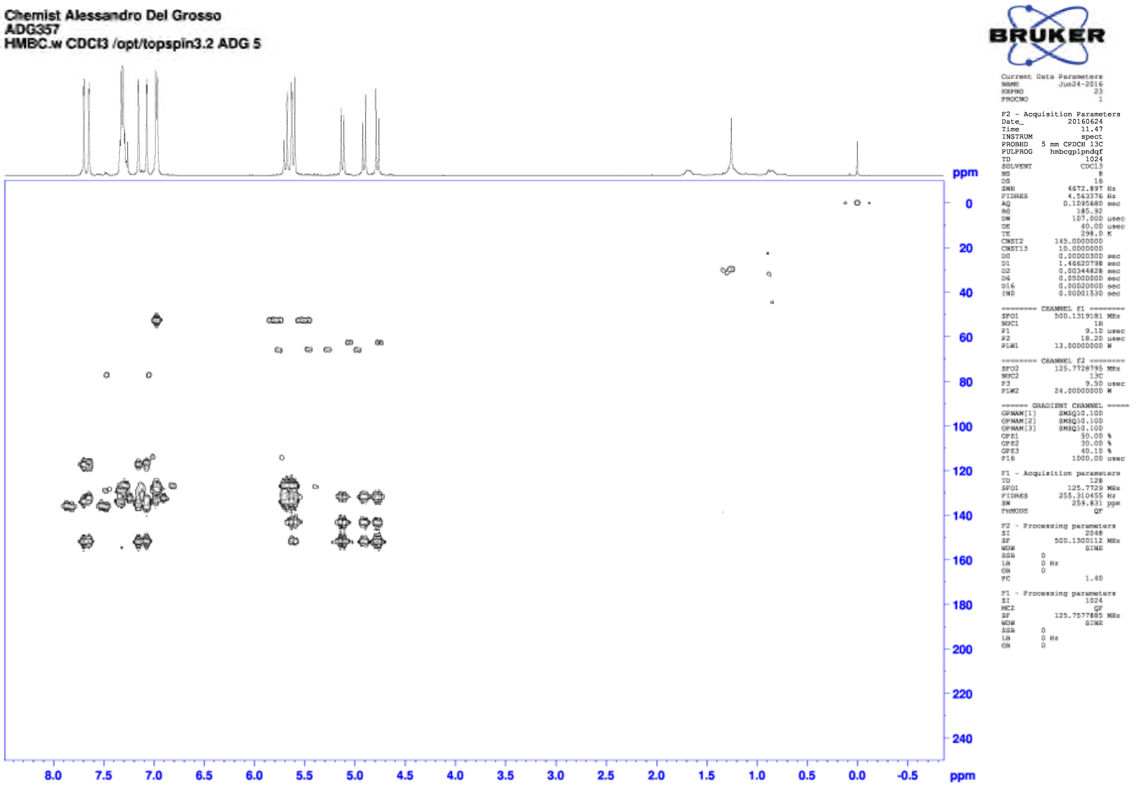
====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPZ1               10.00 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            500.1319 MHz
FIDRES         38.447342 Hz
SW                 9.840 ppm
FnMODE                QF

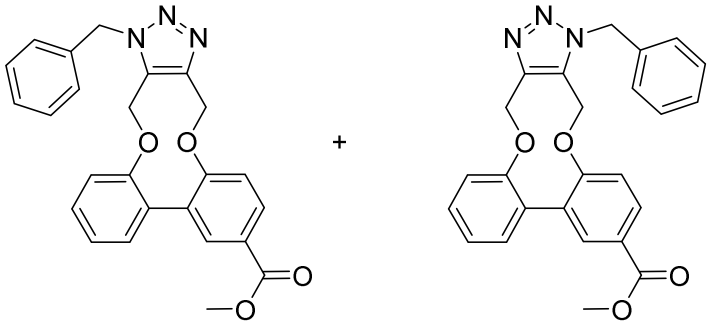
F2 - Processing parameters
SI                  1024
SF           500.1300112 MHz
WDW                QSINE
SSB      0
LB       0 Hz
GB       0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           500.1300112 MHz
WDW                QSINE
SSB      0
LB       0 Hz
GB       0
```


Chemist Alessandro Del Grosso
ADG357
HSQC.w CDCl3 /opt/topspin3.2 ADG 5
BRUKER
ppm
0
20
40
60
80
100
120
140
160
180
200
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm


Chemist Alessandro Del Grosso
ADG357
HMBC.w CDCl3 /opt/topspin3.2 ADG 5
BRUKER
ppm
0
20
40
60
80
100
120
140
160
180
200
220
240
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

Compound 15; Methyl 1-benzyl-4,15-dihydro-1*H*-dibenzo[7,8:9,10][1,6]dioxecino[3,4-*d*][1,2,3]triazole-8-carboxylate and methyl 1-benzyl-4,15-dihydro-1*H*-dibenzo[7,8:9,10][1,6]dioxecino[3,4-*d*][1,2,3]triazole-11-carboxylate **15**.



In a round bottom flask compound **11** (44.1 mg, 0.15 mmol) was dissolved in d_3-acetonitrile (0.6 mL). Benzyl azide (19.9 mg, 0.15 mmol) was added. After 4 days the volatiles were removed and the products was purified by flash chromatography on silica gel (eluent: Hexane/EtOAc = 1:1) to give a ~ 1:1 ratio of isomers of compound **15** (59 mg, 0.14 mmol, 92%) as colourless solid.

m.p. 138.5 ºC dec.

IR$_{\text{(neat)}}$ 3062, 3031, 2950, 1709, 1597, 1575, 1496, 1434, 1412, 1372, 1311, 1239, 1210, 1140 cm^{-1}.

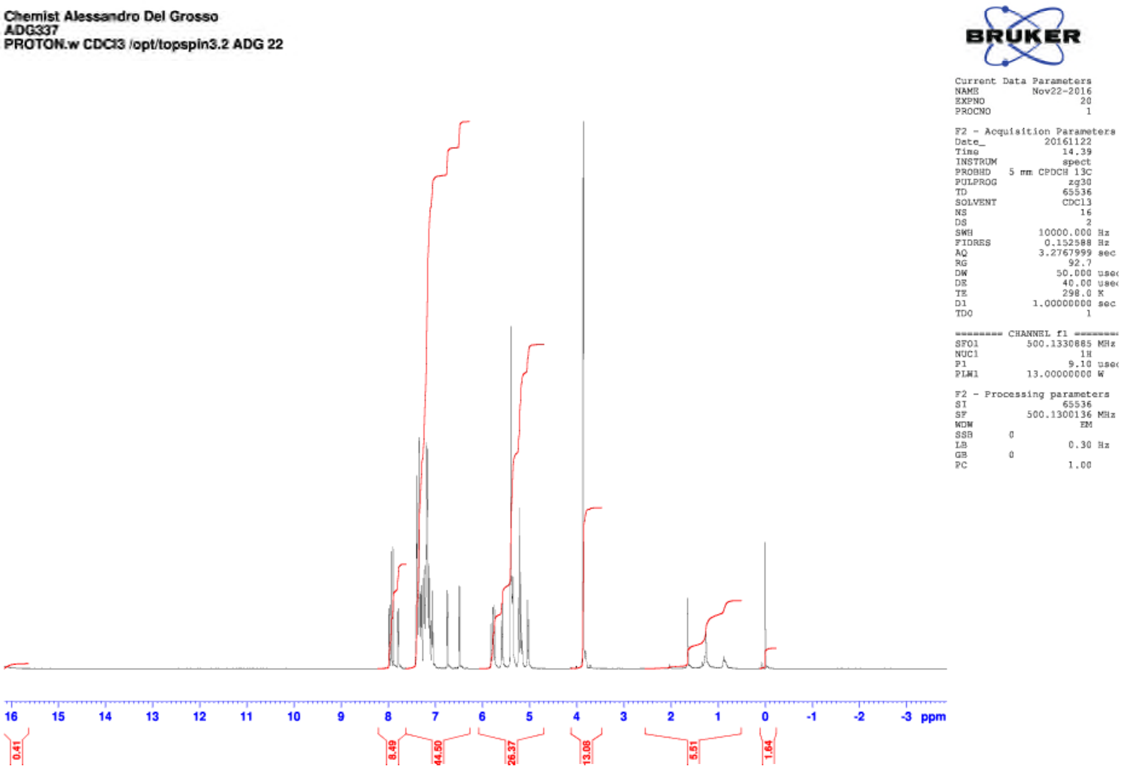
δ_H (500 MHz, $CDCl_3$) 7.97 (1H, dd, *J* = 8.5, 2.1 Hz, Ar*H*), 7.89 (1H, d, *J* = 2.1 Hz, Ar*H*), 7.93 (1H, d, *J* = 2.1 Hz, Ar*H*), 7.77 (1H, dd, *J* = 8.5, 2.0 Hz, Ar*H*), 7.25 - 7.42 (8H, m, Ar*H*), 7.09 - 7.24 (9H, m, Ar*H*), 7.06 (1H, t, *J* = 7.5 Hz, Ar*H*), 6.73 (1H, d, *J* = 8.1 Hz, Ar*H*), 6.47 (1H, dd, *J* = 8.5, 1.7 Hz, Ar*H*), 5.68 - 5.83 (2H, m, CH_2), 5.56 (1H, d, J = 13.7 Hz, CH_2), 5.30 - 5.44 (5H, m, CH_2), 5.12 - 5.26 (3H, m, CH_2), 5.03 (1H, d, *J* = 13.1 Hz, CH_2), 3.85 (3H, s, CH_3), 3.86 (3H, s, CH_3).

δ_C ($CDCl_3$, 125 MHz) 166.6 (C), 166.4 (C), 159.8 (C), 159.2 (C), 156.8 (C), 156.0 (C), 144.7 (C), 144.4 (C), 134.6 (C), 134.4 (C), 132.4 (CH), 132.3 (C), 132.2 (CH), 132.0 (C), 130.8 (CH), 130.7 (CH), 130.6 (CH), 130.5 (C), 130.3 (CH), 129.8 (C), 129.5 (C), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.6 (C), 127.2 (CH), 127.1 (CH), 124.9 (C), 123.9 (C), 123.5 (CH), 122.4 (CH), 115.9 (CH), 114.8 (CH), 114.1 (CH), 113.5 (CH), 63.7 (CH_2), 62.9 (CH_2), 60.9 (CH_2), 60.2 (CH_2), 52.6 (CH_2), 52.4 (CH_2), 52.0 (CH_3), 51.9 (CH_3).

m/z (ESI) [M + H]$^+$, 428.1; [M + Na]$^+$, 450.1.

HRMS (ESI-Q-TOF) m/z: [M + Na]$^+$ Calcd for $C_{25}H_{21}N_3O_4Na$ 450.1424; Found 450.1427.

^{1}H NMR (500 MHz, $CDCl_3$)



```
Current Data Parameters
NAME             Nov22-2016
EXPNO                    20
PROCNO                    1

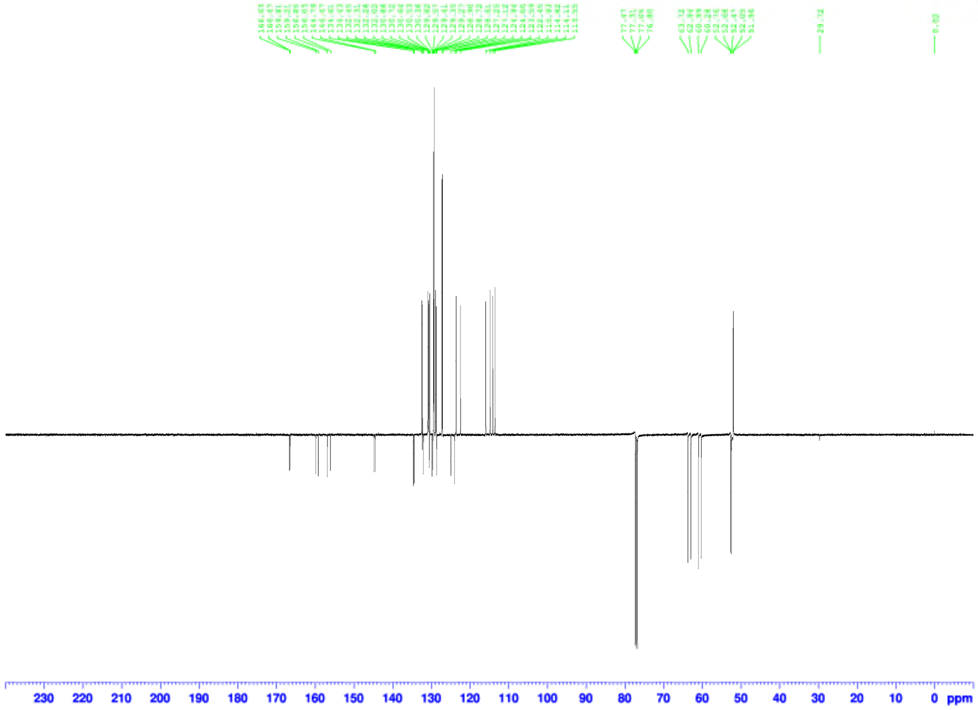
F2 - Acquisition Parameters
Date_              20161122
Time                  14.39
INSTRUM               spect
PROBHD   5 mm CPDCH 13C
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH           10000.000 Hz
FIDRES         0.152588 Hz
AQ            3.2767999 sec
RG                     92.7
DW               50.000 usec
DE                40.00 usec
TE                298.0 K
D1           1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1        500.1330885 MHz
NUC1                     1H
P1                 9.10 usec
PLW1        13.00000000 W

F2 - Processing parameters
SI                    65536
SF          500.1300136 MHz
WDW                      EM
SSB       0
LB                  0.30 Hz
GB        0
PC                     1.00
```

^{13}C NMR (125 MHz, $CDCl_3$)..

Chemist Alessandro Del Grosso
ADG337
C13APT.w CDCl3 /opt/topspin3.2 ADG 22



```
Current Data Parameters
NAME             Nov22-2016
EXPNO                    24
PROCNO                    1

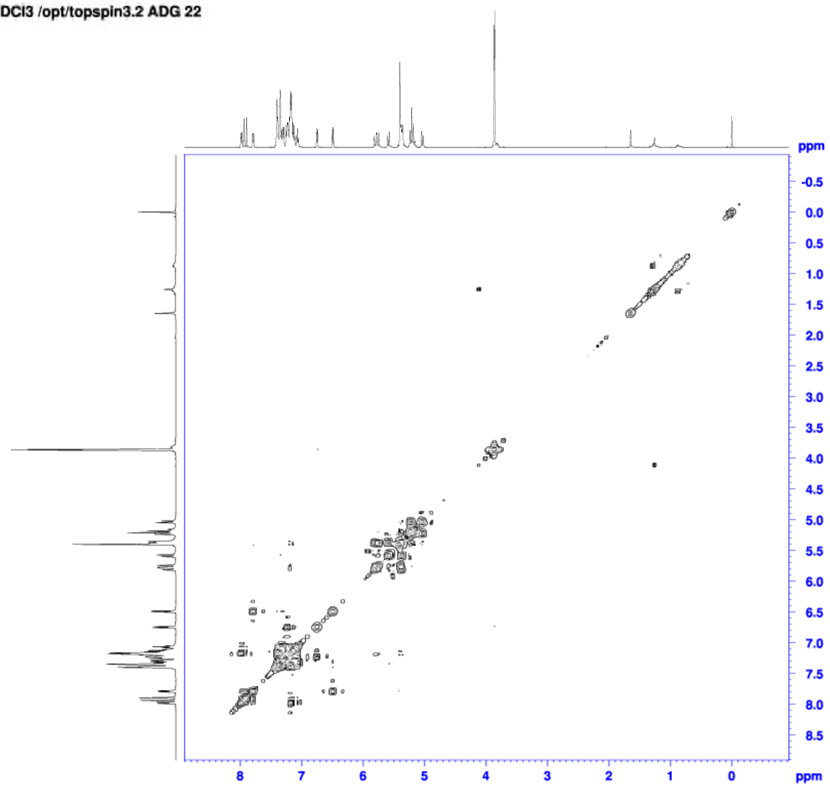
F2 - Acquisition Parameters
Date_              20161122
Time                  15.43
INSTRUM               spect
PROBHD    5 mm CPDCH 13C
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                      256
DS                        4
SWH               32894.738 Hz
FIDRES             0.501934 Hz
AQ                0.9961472 sec
RG                   185.92
DW                   15.200 usec
DE                    66.43 usec
TE                    298.0 K
CNST2           145.0000000
CNST11            1.0000000
D1               2.00000000 sec
D20              0.00689655 sec
TD0                       1

======== CHANNEL f1 ========
SFO1            125.7728795 MHz
NUC1                    13C
P1                     9.50 usec
P2                    19.00 usec
PLW1            24.00000000 W

======== CHANNEL f2 ========
SFO2            500.1320005 MHz
NUC2                     1H
CPDPRG[2            waltz16
PCPD2                 65.00 usec
PLW2            13.00000000 W
PLW12            0.26784000 W

F2 - Processing parameters
SI                    32768
SF              125.7577885 MHz
WDW                      EM
SSB      0
LB                     1.00 Hz
GB       0
PC                     1.40
```

Chemist Alessandro Del Grosso
ADG337
COSY.w CDCl3 /opt/topspin3.2 ADG 22



```
Current Data Parameters
NAME             Nov22-2016
EXPNO                    21
PROCNO                    1

F2 - Acquisition Parameters
Date_              20161122
Time                  14.41
INSTRUM               spect
PROBHD    5 mm CPDCH 13C
PULPROG           cosygpppqf
TD                     2048
SOLVENT               CDCl3
NS                        1
DS                        8
SWH                4921.260 Hz
FIDRES             2.402959 Hz
AQ                0.2080768 sec
RG                    60.07
DW                  101.600 usec
DE                    40.00 usec
TE                    298.0 K
D0               0.00000300 sec
D1               1.93241596 sec
D11              0.03000000 sec
D12              0.00002000 sec
D13              0.00000400 sec
D16              0.00020000 sec
IN0              0.00020320 sec

======== CHANNEL f1 ========
SFO1            500.1320088 MHz
NUC1                     1H
P0                     9.10 usec
P1                     9.10 usec
P17                 2500.00 usec
PLW1            13.00000000 W
PLW10            1.59249997 W

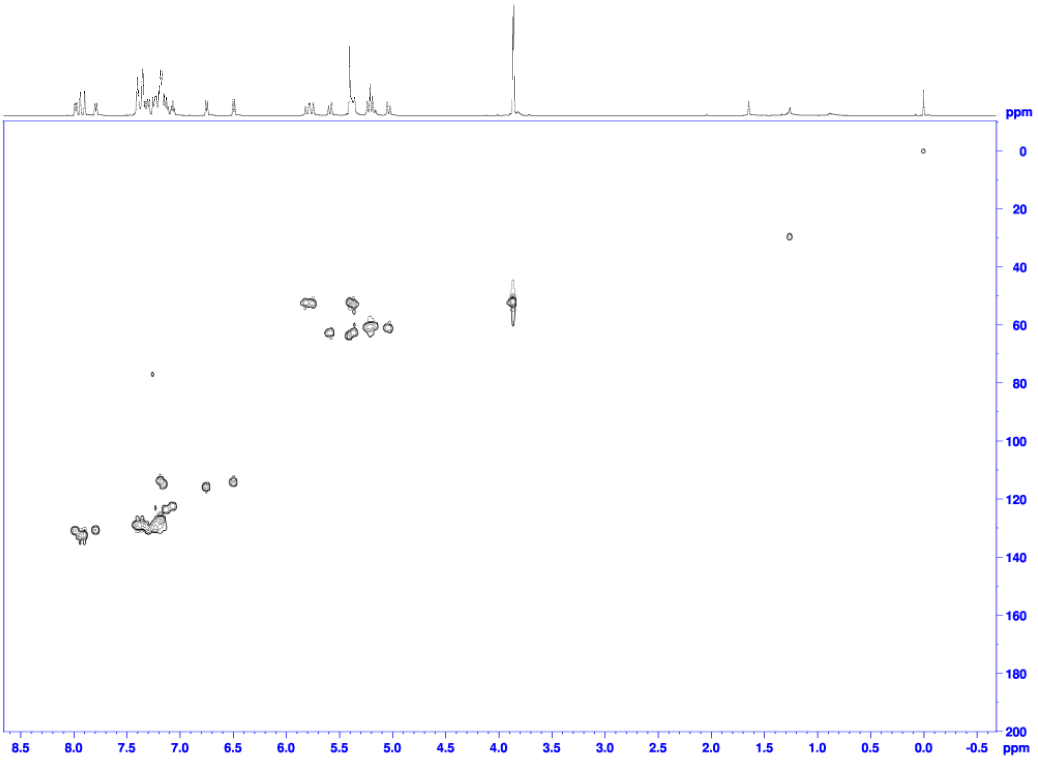
====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPZ1                  10.00 %
P16                 1000.00 usec

F1 - Acquisition parameters
TD                      128
SFO1                500.132 MHz
FIDRES            38.447342 Hz
SW                    9.840 ppm
FnMODE                   QF

F2 - Processing parameters
SI                     1024
SF              500.1300136 MHz
WDW                   QSINE
SSB      0
LB       0 Hz
GB       0
PC                     1.40

F1 - Processing parameters
SI                     1024
MC2                      QF
SF              500.1300136 MHz
WDW                   QSINE
SSB      0
LB       0 Hz
GB       0
```

Chemist Alessandro Del Grosso
ADG337
HSQC.w CDCl3 /opt/topspin3.2 ADG 22



```
Current Data Parameters
NAME          Nov22-2016
EXPNO                 22
PROCNO                 1

F2 - Acquisition Parameters
Date_           20161122
Time               14.47
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG         hsqcetgp
TD                  1024
SOLVENT            CDCl3
NS                     4
DS                    16
SWH             4672.897 Hz
FIDRES          4.563376 Hz
AQ             0.1095680 sec
RG                185.92
DW               107.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
D0            0.00000300 sec
D1            1.46620798 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
IN0           0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         500.1320088 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
P28       0 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7697355 MHz
NUC2                 13C
CPDPRG[2            garp
P3                  9.50 usec
P4                 19.00 usec
PCPD2              63.70 usec
PLW2         24.00000000 W
PLW12         0.51266003 W

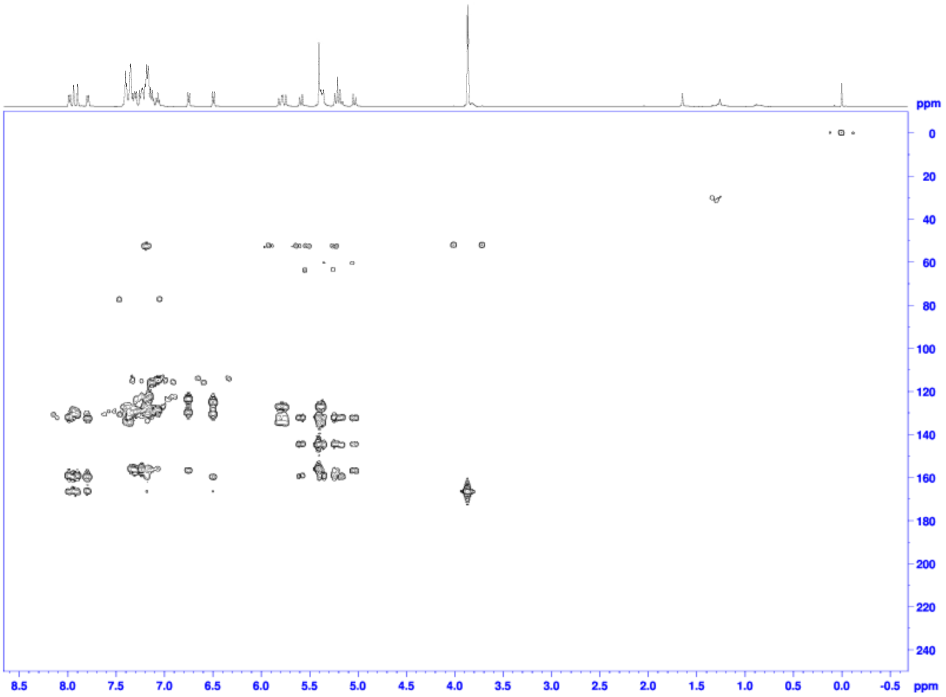
====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7697 MHz
FIDRES        206.679901 Hz
SW               210.345 ppm
FnMODE      Echo-Antiecho

F2 - Processing parameters
SI                  1024
SF           500.1300136 MHz
WDW                QSINE
SSB                    2
LB        0 Hz
GB        0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2         echo-antiecho
SF           125.7577885 MHz
WDW                QSINE
SSB                    2
LB        0 Hz
GB        0
```

Chemist Alessandro Del Grosso
ADG337
HMBC.w CDCl3 /opt/topspin3.2 ADG 22



```
Current Data Parameters
NAME          Nov22-2016
EXPNO                 23
PROCNO                 1

F2 - Acquisition Parameters
Date_           20161122
Time               15.01
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG      hmbcgplpndqf
TD                  1024
SOLVENT            CDCl3
NS                     8
DS                    16
SWH             4672.897 Hz
FIDRES          4.563376 Hz
AQ             0.1095680 sec
RG                185.92
DW               107.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
CNST13        10.0000000
D0            0.00000300 sec
D1            1.46620798 sec
D2            0.00344828 sec
D6            0.05000000 sec
D16           0.00020000 sec
IN0           0.00001530 sec

======== CHANNEL f1 ========
SFO1         500.1320088 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7728795 MHz
NUC2                 13C
P3                  9.50 usec
PLW2         24.00000000 W

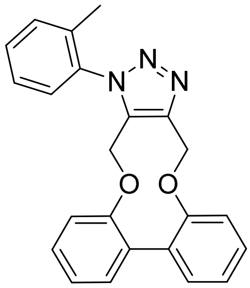
====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPNAM[3]      SMSQ10.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7729 MHz
FIDRES        255.310455 Hz
SW               259.831 ppm
FnMODE                QF

F2 - Processing parameters
SI                  2048
SF           500.1300136 MHz
WDW                 SINE
SSB       0
LB        0 Hz
GB        0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           125.7577885 MHz
WDW                 SINE
SSB       0
LB        0 Hz
GB        0
```

1-Benzyl-6,8,11,13-tetrabromo-4,15-dihydro-1*H*-dibenzo[7,8:9,10][1,6]dioxecino[3,4-*d*][1,2,3]triazole **7.**



In a round bottom flask 8,13-dioxatricyclo[12.4.0.0^{2},^{7}]octadeca-1(14),2,4,6,15,17-hexaen-10-yne (30 mg, 0.127 mmol) **1** was dissolved in DCM (0.3 mL). *o*-Tolyl azide (~0.5 M in *tert*-butyl methyl ether, 0.5 mL, 0.25 mmol) was added. After 10 days the volatiles were removed and the products was purified by flash chromatography on silica gel (eluent: Hexane/EtOAc = 4:1 to 3:2) to give 1-(o-tolyl)-4,15-dihydro-1H-dibenzo[7,8:9,10][1,6]dioxecino[3,4-d][1,2,3]triazole **7** (45 mg, 0.122 mmol, 96%) as a colourless solid.

m.p. 76.2 °C dec.

IR$_{(neat)}$ 3059, 3026, 2928, 2891, 1594, 1573, 1499, 1479, 1440, 1382, 1372, 1336, 1260, 1242, 1212 cm^{-1}.

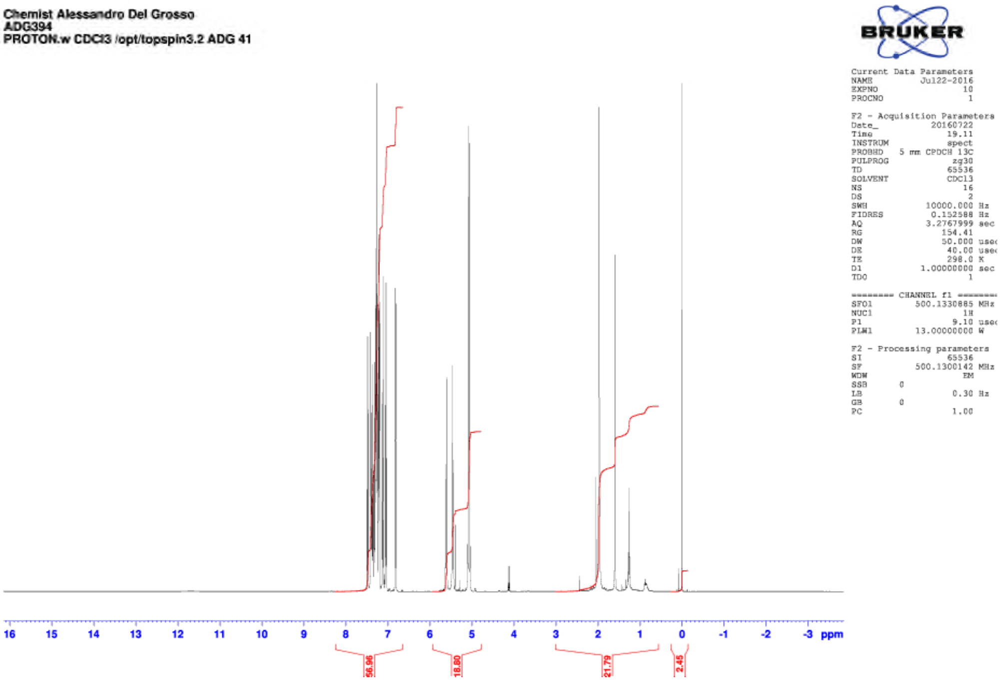
δ_H (500 MHz, $CDCl_3$) 7.45 - 7.51 (1H, m, Ar*H*), 7.23 - 7.44 (6H, m, Ar*H*), 7.18 - 7.23 (2H, m, Ar*H*), 7.12 (1H, td, *J* = 7.4, 0.9 Hz, Ar*H*), 7.04 (1H, td, *J* = 7.4, 0.8 Hz, Ar*H*), 6.81 (1H, d, *J* = 7.8 Hz, Ar*H*), 5.61 (1H, d, *J* = 13.4 Hz, C*H*H), 5.45 (1H, d, *J* = 13.4 Hz, CH*H*), 5.07 (2H, d, *J* = 6.7 Hz, C*H*$_2$), 1.97 (3H, br. s., C*H*$_3$).

δ_C (125 MHz, $CDCl_3$) 156.7 (C), 155.6 (C), 143.8 (C), 135.8 (C), 134.4 (C), 133.6 (C), 131.5 (CH), 130.9 (C), 130.8 (CH), 130.7 (CH), 130.6 (CH), 129.6 (C), 128.8 (CH), 128.7 (CH), 127.2 (CH), 126.8 (CH), 123.3 (CH), 122.1 (CH), 115.5 (CH), 114.2 (CH), 62.9 (CH_2), 61.0 (CH_2), 17.1 (CH_3).

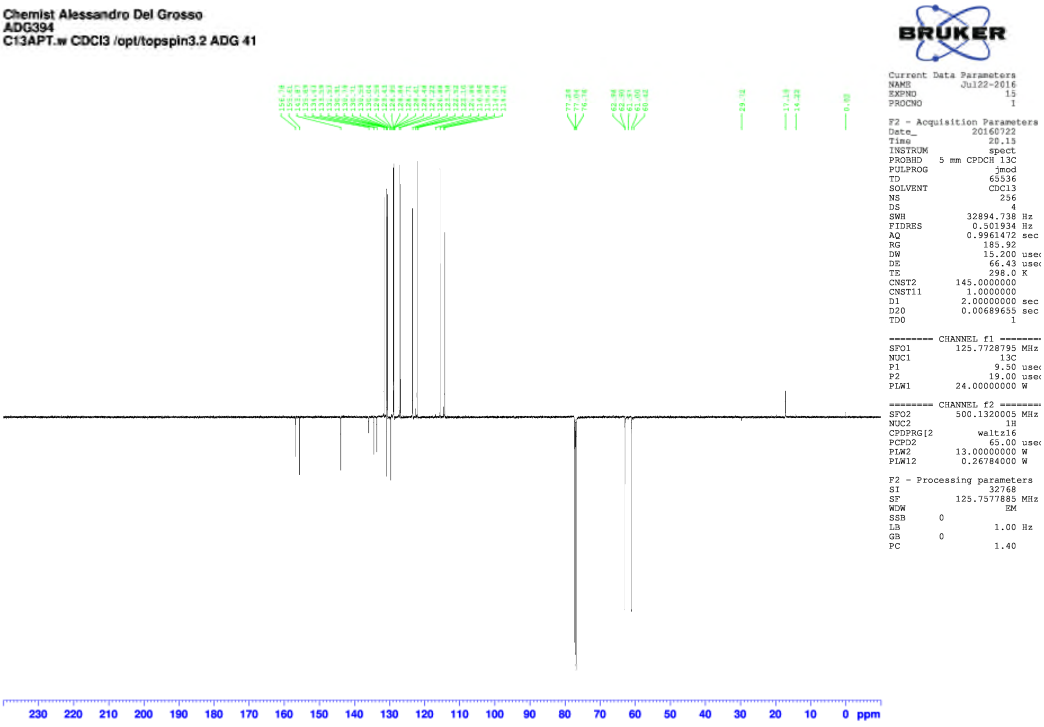
m/z (ESI) [M + Na]$^+$, 392.1.

HRMS (ESI-Q-TOF) m/z: [M + Na]$^+$ Calcd for $C_{23}H_{19}N_3O_2Na$ 392.1369; Found 392.1368.

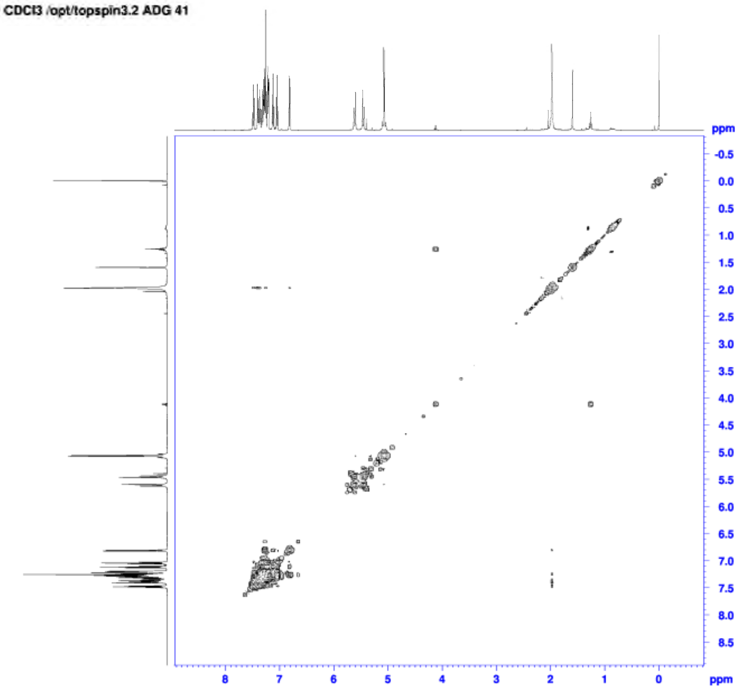
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, CDCl$_3$)



Chemist Alessandro Del Grosso
ADG394
COSY.w CDCl3 /opt/topspin3.2 ADG 41



```
Current Data Parameters
NAME            Jul22-2016
EXPNO                   11
PROCNO                   1

F2 - Acquisition Parameters
Date_             20160722
Time                 19.13
INSTRUM              spect
PROBHD   5 mm CPDCH 13C
PULPROG         cosygpppqf
TD                    2048
SOLVENT              CDCl3
NS                       1
DS                       8
SWH               4882.812 Hz
FIDRES            2.384186 Hz
AQ               0.2097152 sec
RG                   60.07
DW                 102.400 usec
DE                   40.00 usec
TE                   298.0 K
D0              0.00000300 sec
D1              1.93036795 sec
D11             0.03000000 sec
D12             0.00002000 sec
D13             0.00000400 sec
D16             0.00020000 sec
IN0             0.00020500 sec

======== CHANNEL f1 ========
SFO1           500.1320413 MHz
NUC1                    1H
P0                    9.10 usec
P1                    9.10 usec
P17                2500.00 usec
PLW1           13.00000000 W
PLW10           1.55249997 W

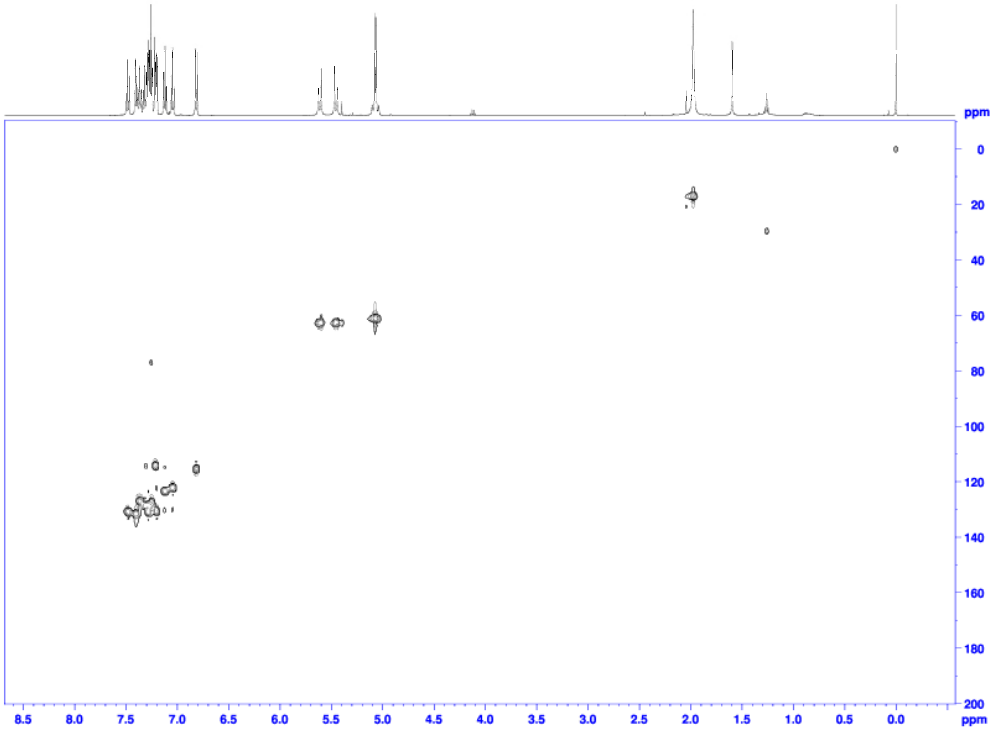
====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPZ1                 10.00 %
P16                1000.00 usec

F1 - Acquisition parameters
TD                     128
SFO1               500.132 MHz
FIDRES           38.109756 Hz
SW                   9.754 ppm
FnMODE                  QF

F2 - Processing parameters
SI                    1024
SF             500.1300142 MHz
WDW                  QSINE
SSB      0
LB       0 Hz
GB       0
PC                    1.40

F1 - Processing parameters
SI                    1024
MC2                     QF
SF             500.1300142 MHz
WDW                  QSINE
SSB      0
LB       0 Hz
GB       0
```

Chemist Alessandro Del Grosso
ADG394
HSQC.w CDCl3 /opt/topspin3.2 ADG 41



```
Current Data Parameters
NAME            Jul22-2016
EXPNO                   12
PROCNO                   1

F2 - Acquisition Parameters
Date_             20160722
Time                 19.19
INSTRUM              spect
PROBHD   5 mm CPDCH 13C
PULPROG           hsqcetgp
TD                    1024
SOLVENT              CDCl3
NS                       4
DS                      16
SWH               4629.629 Hz
FIDRES            4.521122 Hz
AQ               0.1105920 sec
RG                  185.92
DW                 108.000 usec
DE                   40.00 usec
TE                   298.0 K
CNST2          145.0000000
D0              0.00000300 sec
D1              1.46518397 sec
D4              0.00172414 sec
D11             0.03000000 sec
D16             0.00020000 sec
IN0             0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1           500.1320413 MHz
NUC1                    1H
P1                    9.10 usec
P2                   18.20 usec
P28      0 usec
PLW1           13.00000000 W

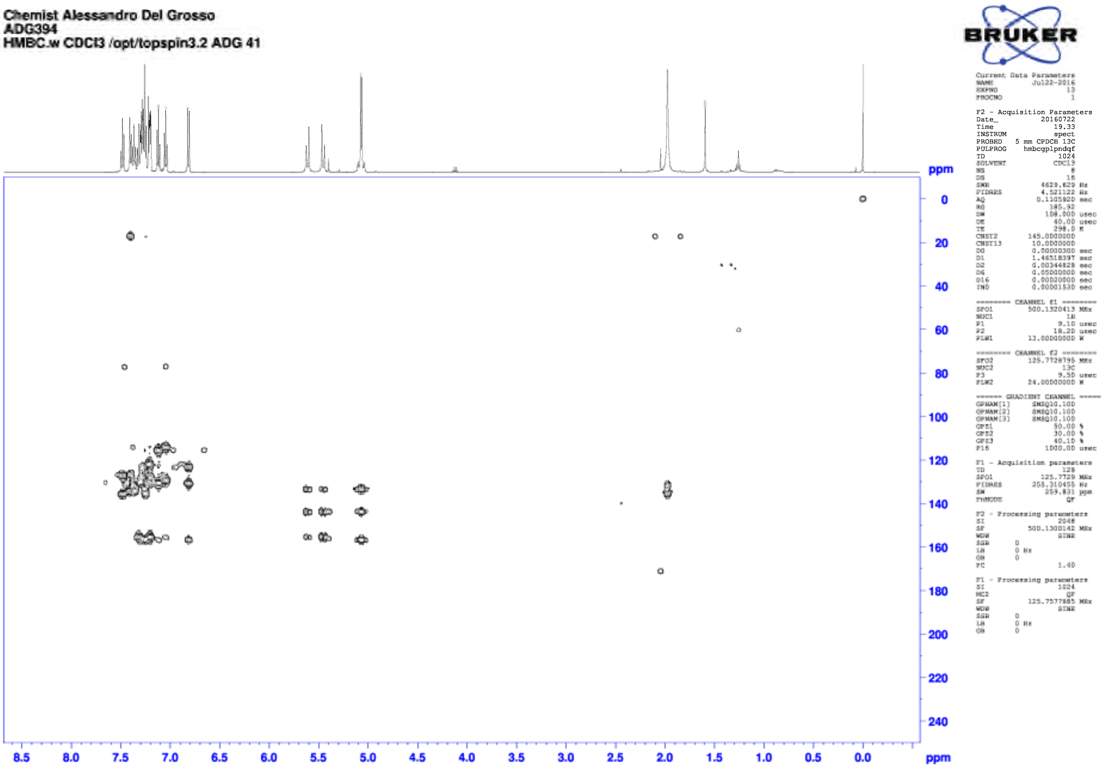
======== CHANNEL f2 ========
SFO2           125.7697355 MHz
NUC2                   13C
CPDPRG[2              garp
P3                    9.50 usec
P4                   19.00 usec
PCPD2                63.70 usec
PLW2           24.00000000 W
PLW12           0.51266003 W

====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPNAM[2]        SMSQ10.100
GPZ1                 80.00 %
GPZ2                 20.10 %
P16                1000.00 usec

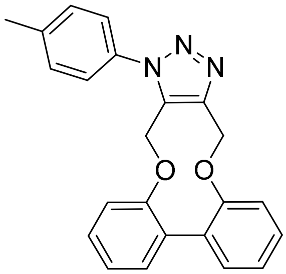
F1 - Acquisition parameters
TD                     128
SFO1              125.7697 MHz
FIDRES          206.679901 Hz
SW                 210.345 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI                    1024
SF             500.1300142 MHz
WDW                  QSINE
SSB                      2
LB       0 Hz
GB       0
PC                    1.40

F1 - Processing parameters
SI                    1024
MC2           echo-antiecho
SF             125.7577895 MHz
WDW                  QSINE
SSB                      2
LB       0 Hz
GB       0
```



1-(p-Tolyl)-4,15-dihydro-1*H*-dibenzo[7,8:9,10][1,6]dioxecino[3,4-*d*][1,2,3]triazole **8.**



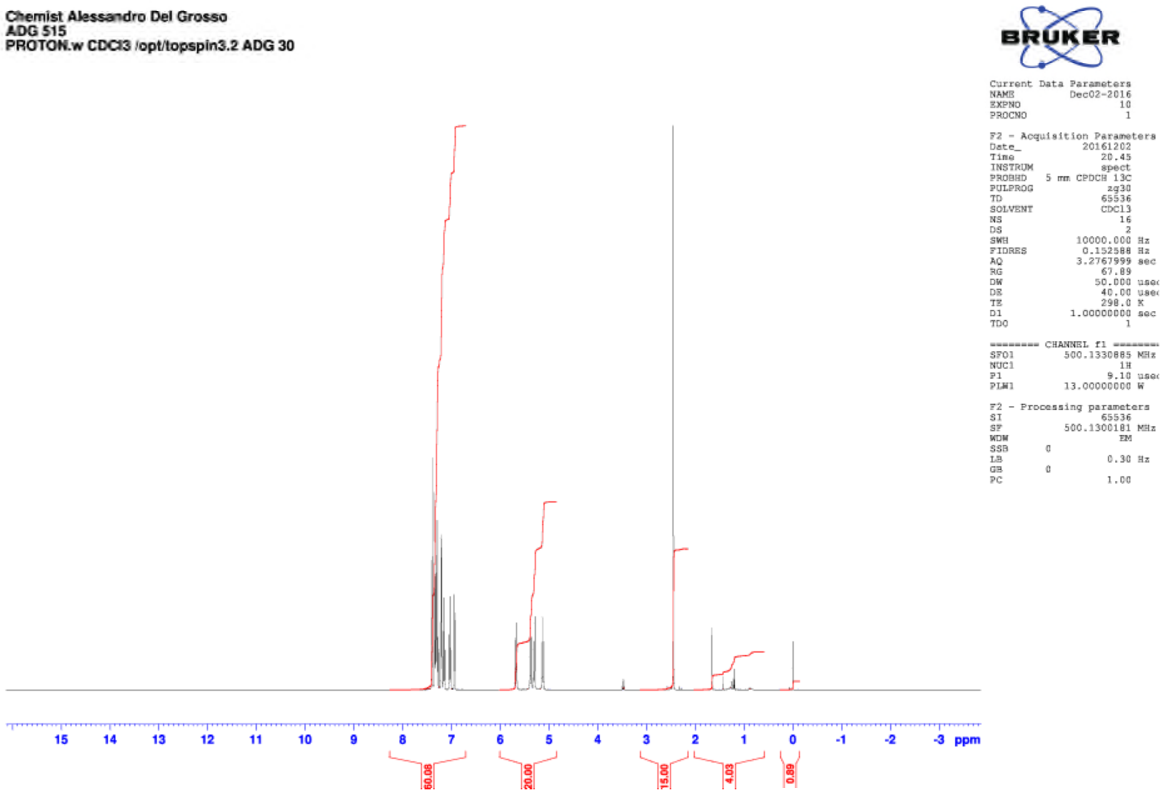
In a J. Young NMR tube 8,13-dioxatricyclo[12.4.0.0^{2,7}]octadeca-1(14),2,4,6,15,17-hexaen-10-yne **1** (23.6 mg, 0.10 mmol) was dissolved in $CDCl_3$ (1 mL). Benzyl azide (13.3 mg, 0.10 mmol) was added and the mixture was heated to 60 ºC. After 24 hours the volatiles were removed and the products was purified by flash chromatography on silica gel (eluent: Hexane/Et_2O = 4:1 to 8:2) to give 1-(p-tolyl)-4,15-dihydro-1*H*-dibenzo[7,8:9,10][1,6]dioxecino[3,4-*d*][1,2,3]triazole **8** (34 mg, 0.92 mmol, 92%) as a colourless solid.

m.p. 194.5-195.6 ºC.

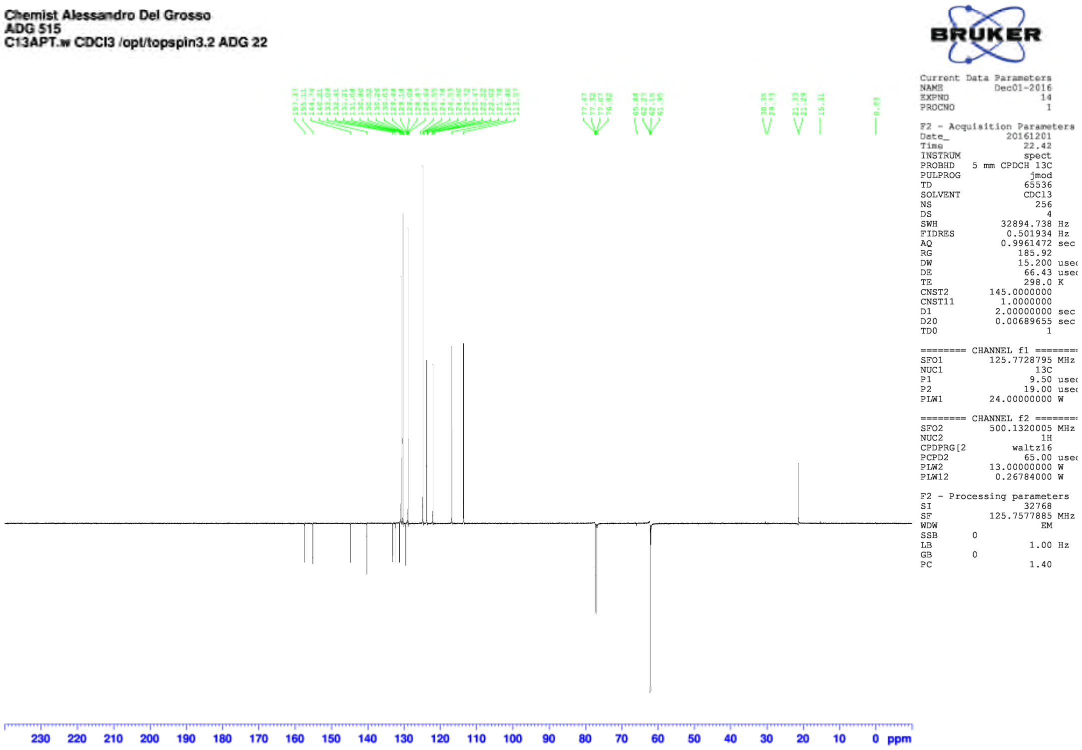
IR$_{(neat)}$ 3054, 3034, 2954, 2880, 1606, 1593, 1572, 1517, 1499, 1480, 1455, 1442, 1390, 1365, 1340, 1304, 1285, 1264, 1240, 1212 cm^{-1}.

δ_H (500 MHz, $CDCl_3$) 7.36 - 7.44 (2H, m, Ar*H*), 7.26 - 7.36 (5H, m, Ar*H*), 7.18 - 7.23 (2H, m, Ar*H*), 7.15 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.03 (1H, d, *J* = 7.3 Hz, Ar*H*), 6.90 - 6.96 (1H, m, Ar*H*), 5.67 (1H, d, *J* = 13.9 Hz, C*H*H), 5.37 (1H, d, *J* = 13.9 Hz, CH*H*), 5.30 (1H, d, *J* = 12.4 Hz, C*H*H), 5.12 (1H, d, *J* = 12.5 Hz, CH*H*), 2.45 (3H, s, CH_3).
δ_C (125 MHz, $CDCl_3$) 157.3 (C), 155.0 (C), 144.7 (C), 140.1 (C), 133.0 (C), 132.3 (C), 131.1 (C), 130.7 (CH), 130.2 (CH), 129.4 (C), 128.8 (CH), 124.7 (CH), 123.6 (CH), 122.0 (CH), 116.7 (CH), 113.5 (CH), 62.1 (CH_2), 61.9 (CH_2), 21.2 (CH_3).
m/z (ESI) $[M + H]^+$, 369.9; $[M + Na]^+$, 392.0.
HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{19}N_3O_2Na$ 392.1369; Found 392.1364.

^1H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)



Chemist Alessandro Del Grosso
ADG 515
C13APT.w CDCl3 /opt/topspin3.2 ADG 22

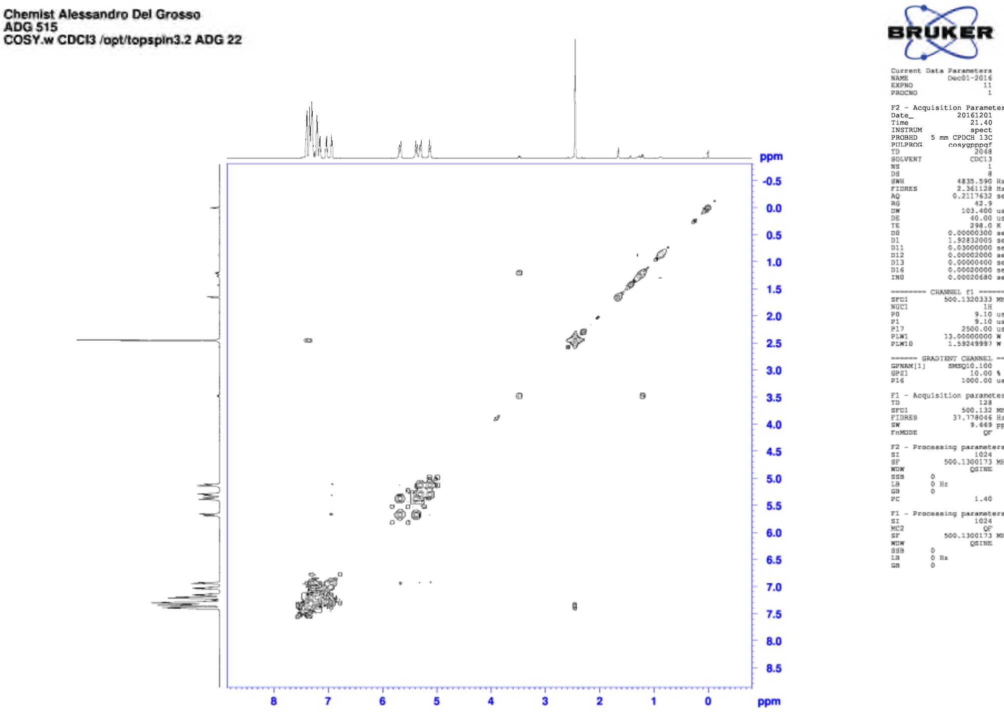
```
Current Data Parameters
NAME            Dec01-2016
EXPNO                   14
PROCNO                   1

F2 - Acquisition Parameters
Date_             20161201
Time                 22.42
INSTRUM              spect
PROBHD   5 mm CPDCH 13C
PULPROG               jmod
TD                   65536
SOLVENT              CDCl3
NS                     256
DS                       4
SWH              32894.738 Hz
FIDRES            0.501934 Hz
AQ               0.9961472 sec
RG                  185.92
DW                  15.200 usec
DE                   66.43 usec
TE                   298.0 K
CNST2          145.0000000
CNST11           1.0000000
D1              2.00000000 sec
D20             0.00689655 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           125.7728795 MHz
NUC1                   13C
P1                    9.50 usec
P2                   19.00 usec
PLW1           24.00000000 W

======== CHANNEL f2 ========
SFO2           500.1320005 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                65.00 usec
PLW2           13.00000000 W
PLW12           0.26784000 W

F2 - Processing parameters
SI                   32768
SF             125.7577885 MHz
WDW                     EM
SSB      0
LB                    1.00 Hz
GB       0
PC                    1.40
```



Chemist Alessandro Del Grosso
ADG 515
COSY.w CDCl3 /opt/topspin3.2 ADG 22

```
Current Data Parameters
NAME            Dec01-2016
EXPNO                   11
PROCNO                   1

F2 - Acquisition Parameters
Date_             20161201
Time                 21.40
INSTRUM              spect
PROBHD   5 mm CPDCH 13C
PULPROG         cosygpppqf
TD                    2048
SOLVENT              CDCl3
NS                       1
DS                       8
SWH               4835.590 Hz
FIDRES            2.361128 Hz
AQ               0.2117632 sec
RG                    42.9
DW                 103.400 usec
DE                   40.00 usec
TE                   298.0 K
D0              0.00000300 sec
D1              1.92832005 sec
D11             0.03000000 sec
D12             0.00002000 sec
D13             0.00000400 sec
D16             0.00020000 sec
IN0             0.00020680 sec

======== CHANNEL f1 ========
SFO1           500.1320333 MHz
NUC1                    1H
P0                    9.10 usec
P1                    9.10 usec
P17                2500.00 usec
PLW1           13.00000000 W
PLW10           1.59249997 W

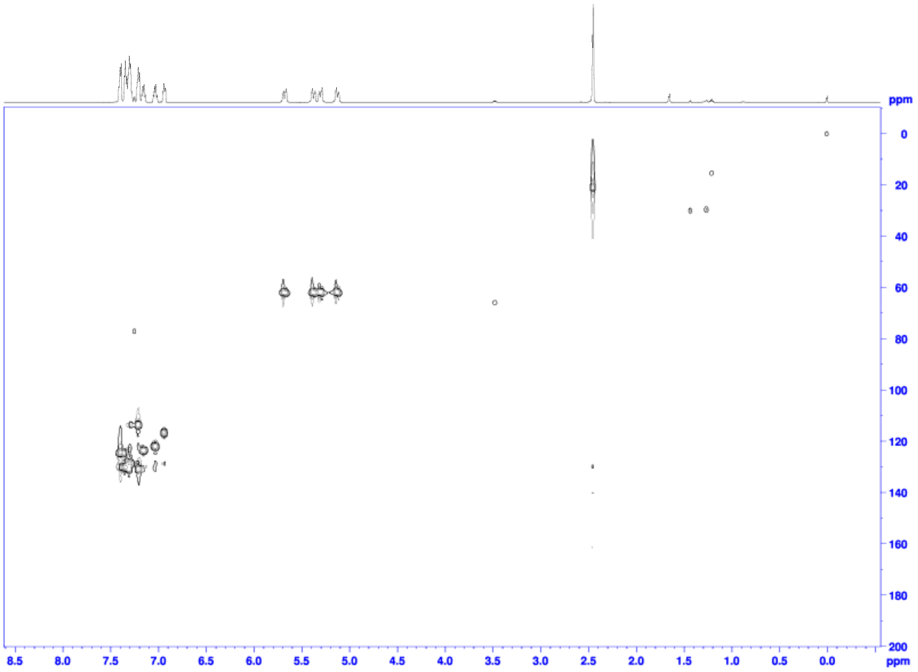
====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPZ1                 10.00 %
P16                1000.00 usec

F1 - Acquisition parameters
TD                     128
SFO1               500.132 MHz
FIDRES           37.778046 Hz
SW                   9.669 ppm
FnMODE                  QF

F2 - Processing parameters
SI                    1024
SF             500.1300173 MHz
WDW                  QSINE
SSB      0
LB       0 Hz
GB       0
PC                    1.40

F1 - Processing parameters
SI                    1024
MC2                     QF
SF             500.1300173 MHz
WDW                  QSINE
SSB      0
LB       0 Hz
GB       0
```

Chemist Alessandro Del Grosso
ADG 515
HSQC.w CDCl3 /opt/topspin3.2 ADG 22



```
Current Data Parameters
NAME          Dec01-2016
EXPNO                 12
PROCNO                 1

F2 - Acquisition Parameters
Date_           20161201
Time               21.46
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG         hsqcetgp
TD                  1024
SOLVENT            CDCl3
NS                     4
DS                    16
SWH             4587.156 Hz
FIDRES          4.479644 Hz
AQ             0.1116160 sec
RG                185.92
DW               109.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
D0            0.00000300 sec
D1            1.46415997 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
IN0           0.00001890 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         500.1320333 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
P28        0 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7697355 MHz
NUC2                 13C
CPDPRG[2            garp
P3                  9.50 usec
P4                 19.00 usec
PCPD2              63.70 usec
PLW2         24.00000000 W
PLW12         0.51266003 W

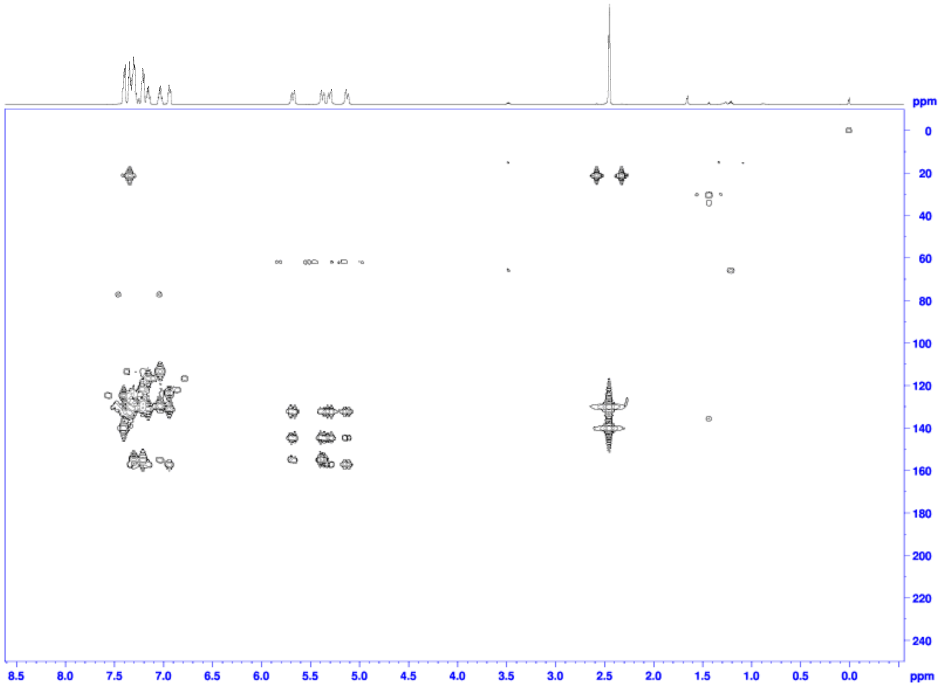
====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7697 MHz
FIDRES        206.679901 Hz
SW               210.345 ppm
FnMODE      Echo-Antiecho

F2 - Processing parameters
SI                  1024
SF           500.1300173 MHz
WDW                QSINE
SSB                    2
LB         0 Hz
GB         0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2        echo-antiecho
SF           125.7577885 MHz
WDW                QSINE
SSB                    2
LB         0 Hz
GB         0
```

Chemist Alessandro Del Grosso
ADG 515
HMBC.w CDCl3 /opt/topspin3.2 ADG 22



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SOLVENT            CDCl3
NS                     8
DS                    16
SWH             4587.156 Hz
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RG                185.92
DW               109.000 usec
DE                 40.00 usec
TE                 298.0 K
CNST2        145.0000000
CNST13        10.0000000
D0            0.00000300 sec
D1            1.46415997 sec
D2            0.00344828 sec
D6            0.05000000 sec
D16           0.00020000 sec
IN0           0.00001530 sec

======== CHANNEL f1 ========
SFO1         500.1320333 MHz
NUC1                  1H
P1                  9.10 usec
P2                 18.20 usec
PLW1         13.00000000 W

======== CHANNEL f2 ========
SFO2         125.7728795 MHz
NUC2                 13C
P3                  9.50 usec
PLW2         24.00000000 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPNAM[3]      SMSQ10.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            125.7729 MHz
FIDRES        255.310455 Hz
SW               259.831 ppm
FnMODE                QF

F2 - Processing parameters
SI                  2048
SF           500.1300173 MHz
WDW                 SINE
SSB        0
LB         0 Hz
GB         0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           125.7577885 MHz
WDW                 SINE
SSB        0
LB         0 Hz
GB         0
```
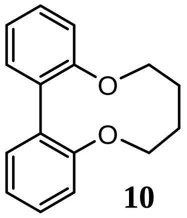

Synthesis of compound 10.



10

This is a known compound (a) Allen, D. W.; Braunton, P. N.; Millar, I. T.; Tebby, J. C. *J. Chem. Soc. C* **1971**, 3454-3468. B) Braunton, P. N.; Millar, I. T.; Tebby, J. C.; J. *Chem. Soc. Perkin II* **1972**, 138-412. c) Simpson, J. E.; Daub, G. H.; Hayes, F. N. *J. Org. Chem.* **1973**, *38*, 1771. d) Surry, D. S.; Fox, D. J.; Macdonald, S. J. F.; Spring, D. R. *Chem. Commun.* **2005**, 2589-2590). The procedure used below was adapted from: Benniston , A. C.; Harriman, A.; Li , P.; Patel , P. V.; Sams, C. A. *J. Org. Chem.* **2006**, *71*, 3481-3493. 1,4-Dibromobutane (484 mg, 2.20 mmol) was added dropwise to a stirred solution of 2,2'-biphenol (376 mg, 2.0 mmol) and K_2CO_3 (560 mg, 4.00 mmol) in DMF (10 mL) at room temperature. The mixture was stirred overnight. At the end of this time, water (50 mL) was added followed by EtOAc (50 mL). The water phase was extracted with EtOAc (2 x 40 mL) and the combined organic extracts were then washed with water (3 x 40 mL). The solvent was removed using a rotary evaporator to yield a crude product which was purified by chromatography on silica gel (hexane/EtOAC, gradient from 100:1-75:25-50:50 in increments). This yielded product **10** as a white crystalline solid (398 mg, 1.64 mmol, 82%).

TLC: Silica gel, 4:1 hexane:EtOAc, Rf 0.85, uv nd $KMnO_4$ to visualise.

Mp 109-110 °C.

$IR_{(neat)}$ 1434 1261, 1228, 939, 756 cm^{-1}.

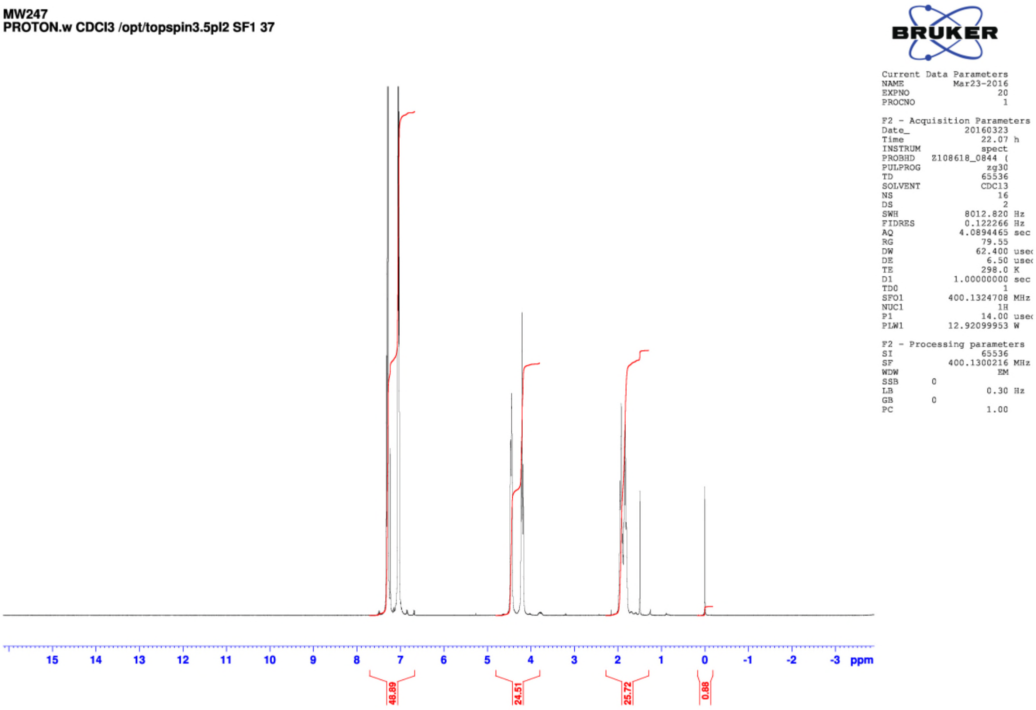
δ_H (400 MHz, $CDCl_3$) 7.45-7.40 (4H, m, ArH), 7.10-7.00 (4H, m, ArH), 4.55-4.50 (4H, m,OCH_2), 4.25-4.20 (4H, m, OCH_2), 2.00-1.85 (4H, m, CH2CH2).

δ_C (100 MHz, $CDCl_3$) 157.06 (C), 131.30 (CH), 129.61 (C), 128.53 (CH), 121.83 (CH), 115.79 (CH), 70.96 (CH_2), 27.15 (CH_2).

m/z (CI) 241.1 (M+ + H, 65%), 263 (M+ + Na, 95%).

HRMS (found (EI+): M+ + Na, 263.1038. $C_{16}H_{16}O_2Na$ requires M+Na, 263.1043, 1.5 ppm error).

^1H NMR (400 MHz, $CDCl_3$).



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PROCNO                 1

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PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ             4.0894465 sec
RG                 79.55
DW                62.400 usec
DE                  6.50 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1
SFO1         400.1324708 MHz
NUC1                  1H
P1                 14.00 usec
PLW1         12.92099953 W

F2 - Processing parameters
SI                 65536
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WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
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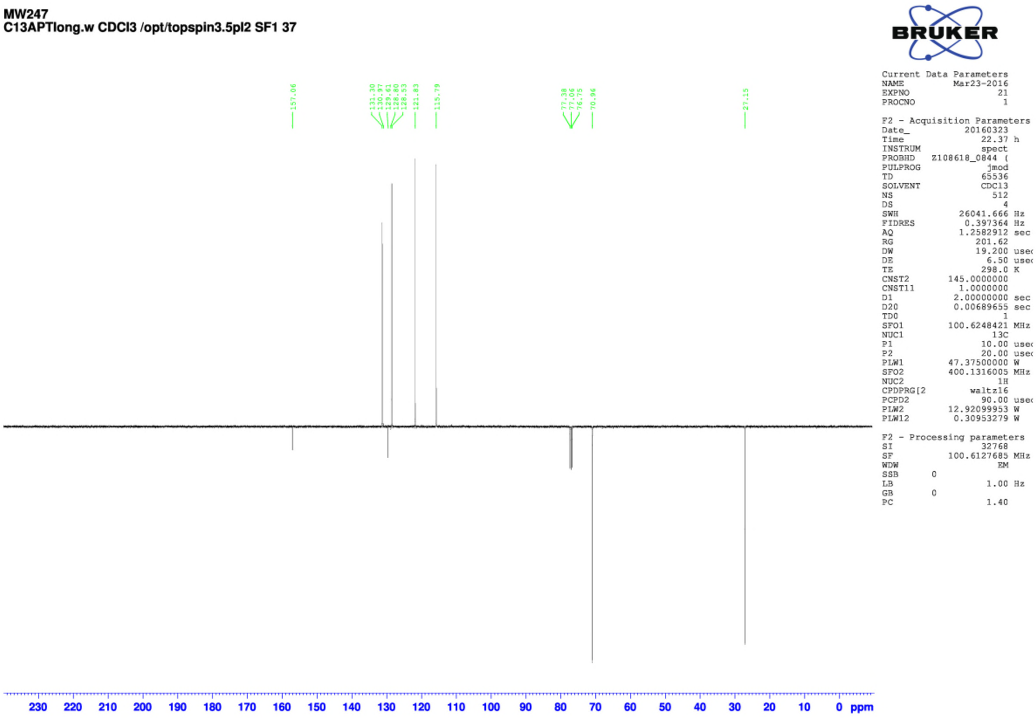
^{13}C NMR (100 MHz, CDCl$_3$)



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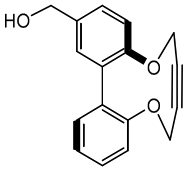
PULPROG             jmod
TD                 65536
SOLVENT            CDCl3
NS                   512
DS                     4
SWH            26041.666 Hz
FIDRES          0.397364 Hz
AQ             1.2582912 sec
RG                201.62
DW                19.200 usec
DE                  6.50 usec
TE                 298.0 K
CNST2        145.0000000
CNST11         1.0000000
D1            2.00000000 sec
D20           0.00689655 sec
TD0                    1
SFO1         100.6248421 MHz
NUC1                 13C
P1                 10.00 usec
P2                 20.00 usec
PLW1         47.37500000 W
SFO2         400.1316005 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              90.00 usec
PLW2         12.92099953 W
PLW12         0.30953279 W

F2 - Processing parameters
SI                 32768
SF           100.6127685 MHz
WDW                   EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  1.40
```

Synthesis of compound 16; 8,13-dioxatricyclo[12.4.0.0^{2,7}]octadeca-1(18),2(7),3,5,14,16-hexaen-10-yn-4-ylmethanol **16**.



In a Schlenk tube under a nitrogen atmosphere, compound **11** (50 mg, 0.17 mmol) was dissolved in THF (1 mL). The solution was cooled to -78 °C and DiBAL-H (0.17 mmol, 2 M solution in hexane) was added dropwise. The mixture was degassed, stirred at -78 °C for 1 hour. The mixture was warmed to room temperature. After 2 hours, water (5 mL) and HCl (2-3 mL) were added and the product was extracted with ethyl acetate (3 x 15 mL). The organic extracts were dried over magnesium sulphate. The solvent was removed under reduced pressure to give the product **16** (31 mg, 0.117 mmol, 69%) as a brown solid.

TLC: Silica gel, 1:4 Hexane: EtOAc, Rf 0.18.

IR$_{(neat)}$ 3391, 2913, 2863, 1449, 1189, 1105, 966 cm^{-1}.

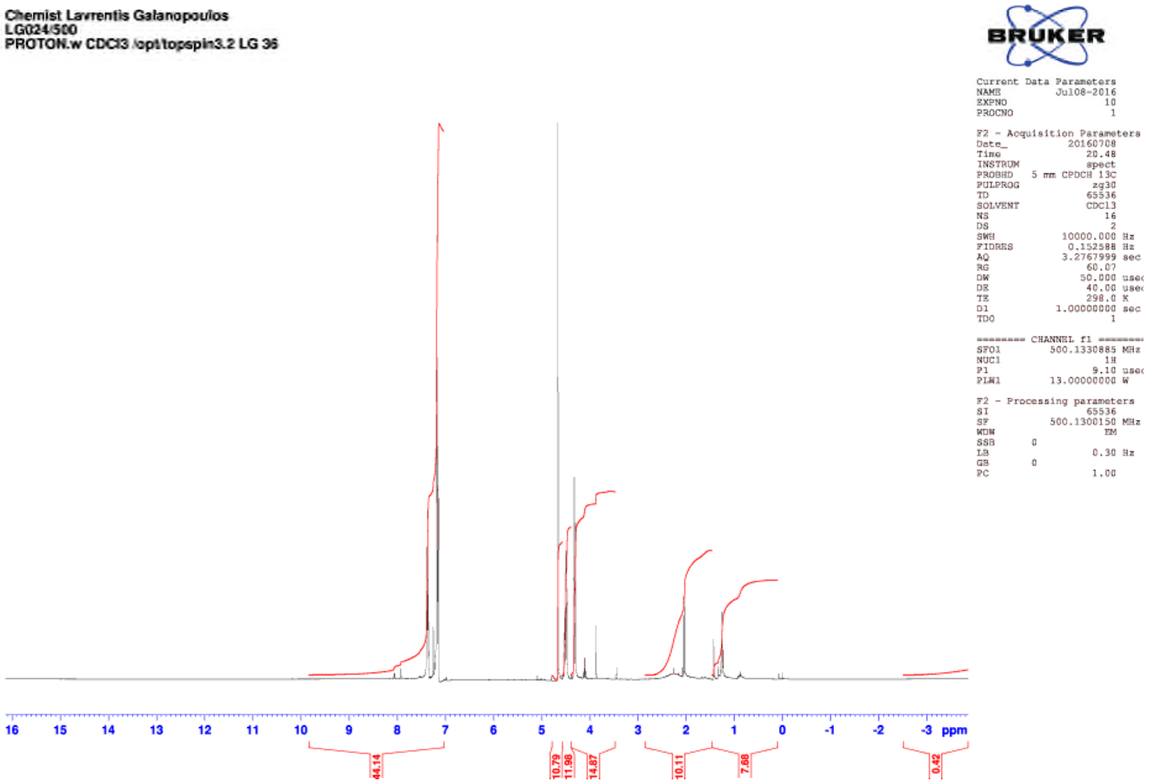
δ_H ($CDCl_3$, 500 MHz) 7.40-7.35 (2H, m, ArH), 7.20-7.10 (5H, m, ArH), 4.66 (2H, s, $HOCH_2$), 4.54-4.47 (2H, m, OCH_2), 4.31 (2H, brd, *J* = 14.0, OCH_2), 2.05 (1H, d, *J* = 12.1, OH)

δ_C ($CDCl_3$, 125 MHz) 154.4 (C), 153.9 (C), 136.8 (C), 135.9 (C), 135.8 (C), 132.0 (CH), 130.7 (CH), 129.2 (CH), 127.9 (CH), 124.3 (CH), 122.7 (CH), 122.7 (CH), 86.7 (C triple), 86.7 (C triple), 64.8 (OCH_2), 63.6 ($HOCH_2$). Note; two CH_2 groups are overlapped.

m/*z* (ESI) 289 (M^+ + Na, 100).

HRMS (ESI-Q-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{14}O_3Na$ 289.0835; Found 289.0837.

^{1}H NMR ($CDCl_3$, 500 MHz)



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PROCNO                 1

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PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                 60.07
DW                50.000 usec
DE                 40.00 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                  1H
P1                  9.10 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1300150 MHz
WDW                   EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
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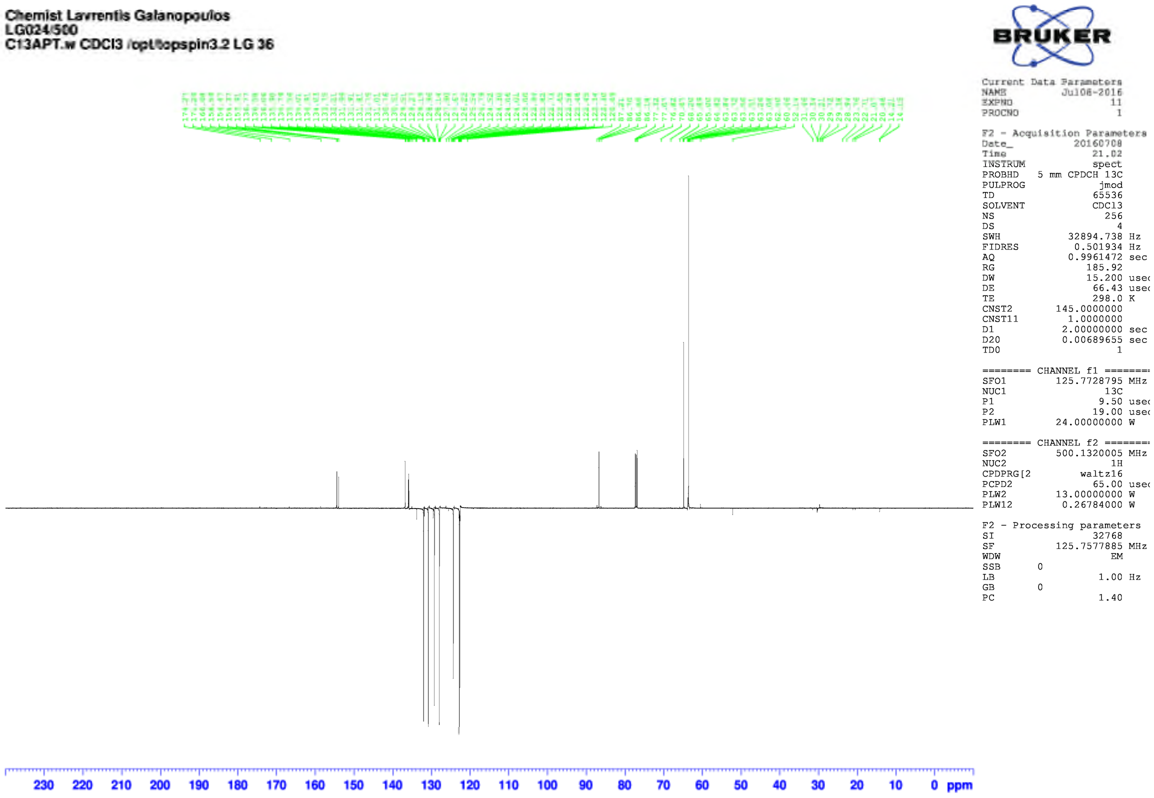
^{13}C NMR ($CDCl_3$, 125 MHz).



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PROCNO                 1

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PULPROG             jmod
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     4
SWH            32894.738 Hz
FIDRES          0.501934 Hz
AQ             0.9961472 sec
RG                185.92
DW                15.200 usec
DE                 66.43 usec
TE                 298.0 K
CNST2        145.0000000
CNST11         1.0000000
D1            2.00000000 sec
D20           0.00689655 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7728795 MHz
NUC1                 13C
P1                  9.50 usec
P2                 19.00 usec
PLW1         24.00000000 W

======== CHANNEL f2 ========
SFO2         500.1320005 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              65.00 usec
PLW2         13.00000000 W
PLW12         0.26784000 W

F2 - Processing parameters
SI                 32768
SF           125.7577885 MHz
WDW                   EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```

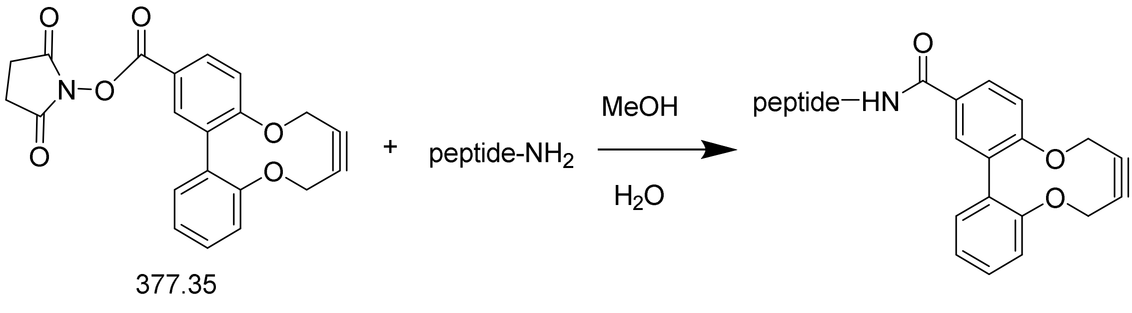
Reactions of activated ester 14 with peptide and proteins, followed by addition of benzyl azide.

FT-ICR MS experiments were run to test if compound **14** could react with and conjugate to the peptides; substance P, Lys 8 vasopressin and Lys 3 bombesin. This was achieved by combining a 1 mM solution of each peptide with 1, 2 and 3 equivalents respectively of **14**. The final concentrations of the peptide and the binding agent are summarised in Table 1. However due to competing hydrolysis of the activated ester, full functionalisation was not anticipated.

Table 1.

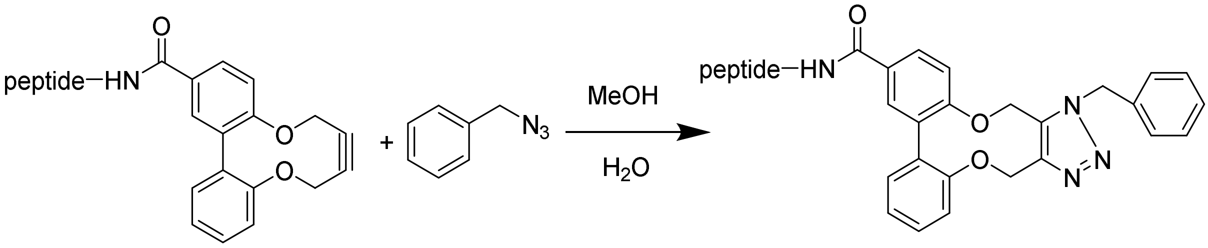
Entry	Peptide	Concentration of peptide	Concentration of 14	Ratio of peptide to 14
1	Substance P	0.67 mM	0.67 mM	1:1
2	Substance P	0.50 mM	1.00 mM	1:2
3	Substance P	0.40 mM	1.20 mM	1:3
4	vasopressin	0.67 mM	0.67 mM	1:1
5	vasopressin	0.50 mM	1.00 mM	1:2
6	vasopressin	0.40 mM	1.20 mM	1:3
7	bombesin	0.67 mM	0.67 mM	1:1
8	bombesin	0.50 mM	1.00 mM	1:2
9	bombesin	0.40 mM	1.20 mM	1:3

Reaction of activated ester 14 with peptides:



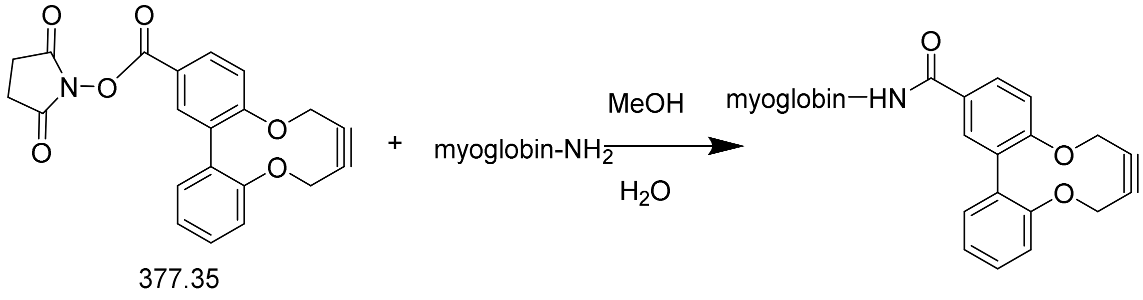
In a round bottom flask, compound **14** (7.5 mg, 0.019 mmol) was dissolved in MeOH/H_2O (50%-50%, 10 mL) to create a 2 mM stock solution. Solutions of three peptides (1 mM solutions of Substance P, Lys 8 Vasopressin, Lys 3 Bombesin) were prepared. To portions of 100 μL of each peptide solution was added respectively 50 μL, 100 μL and 150 μL of the solution of compound **7** to create the following solutions respectively; i) 0.67 mM peptide + 0.67 mM ester (1:1), ii) 0.50 mM peptide + 1 mM ester (1:2) and iii) 0.40 mM peptide + 1.2 mM ester (1:3) respectively. The solutions were allowed to stand at room temperature for 1 day and were then analysed by FT-ICR MS.

Reaction of peptide from reaction above with benzyl azide.



In a round bottom flask, $PhCH_2N_3$ (250 μL, 2 mmol) was dissolved in MeOH/H_2O (50%-50%, 10 mL) to create a 0.2 M stock solution. Volumes of 0.25 mL, 0.50 mL and 0.75 mL of this solution were added to the previously prepared 1:1, 1:2 and 1:3 solutions of each peptide respectively. The solutions were allowed to stand at room temperature for 7 days and were then analysed by FT-ICR MS.

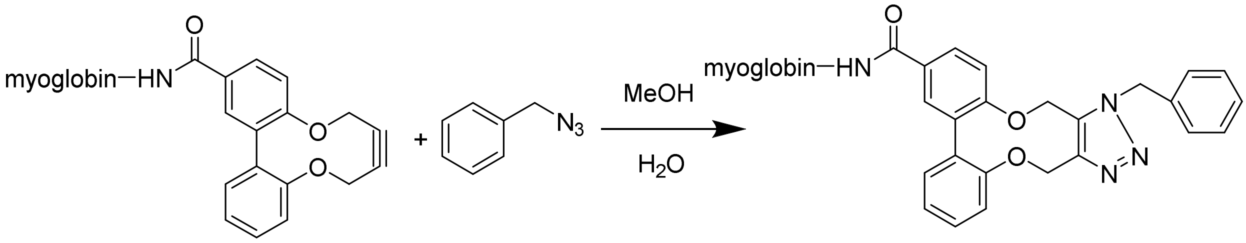
Reaction between compound 14 and myoglobin.



In a round bottom flask, compound **14** (7.5 mg, 0.019 mmol) was dissolved in MeOH/H_2O (50%-50%, 10 mL) to create a 2 mM stock solution. Myoglobin (8.45 mg) was dissolved in 0.5 mL ultra-pure water. The stock myoglobin solution was left in the vortexer for 5 min and afterwards put in the centrifuge for stirring at 14.000 rpm for 5 min. To portions of 100 μL of myoglobin solution was added respectively

50 μL, 100 μL and 150 μL of the solution of compound **14** to create the following solutions respectively; i) 0.67 mM protein + 0.67 mM ester (1:1), ii) 0.50 mM protein + 1 mM ester (1:2) and iii) 0.40 mM protein + 1.2 mM ester (1:3) respectively. The solutions were allowed to stand at room temperature for 1 day and were then analysed by FT-ICR MS.

Reaction of functionalised myoglobin with benzyl azide.



In a round bottom flask, $PhCH_2N_3$ (250 μL, 2 mmol) was dissolved in MeOH/H_2O (50%-50%, 10 mL) to create a 0.2 M stock solution. Volumes of 0.25 mL, 0.50 mL and 0.75 mL of this solution were added to the 1:1, 1:2 and 1:3 solutions of each peptide respectively. The solutions were allowed to stand at room temperature for 7 day and were then analysed by FT-ICR MS.

Mass spectra of products from peptide and protein conjugation studies.

Substance P.

The mass spectra (MS) of substance P with and without the addition of compound **14** are presented in Figures 1 and 2 respectively. The data was obtained with the 1:2 ratio mixture (Table 1 entry 2) is illustrated. The comparison of the shapes illustrates the form of a new peak at the latter MS spectrum. This peak at 805.40393 is corresponds to the peptide bound with the conjugation agent **14** [Substance P + allyne + 2H]$^{2+}$. Furthermore, this was verified by creating a mathematical simulation and comparing it with the experimental isotope pattern.

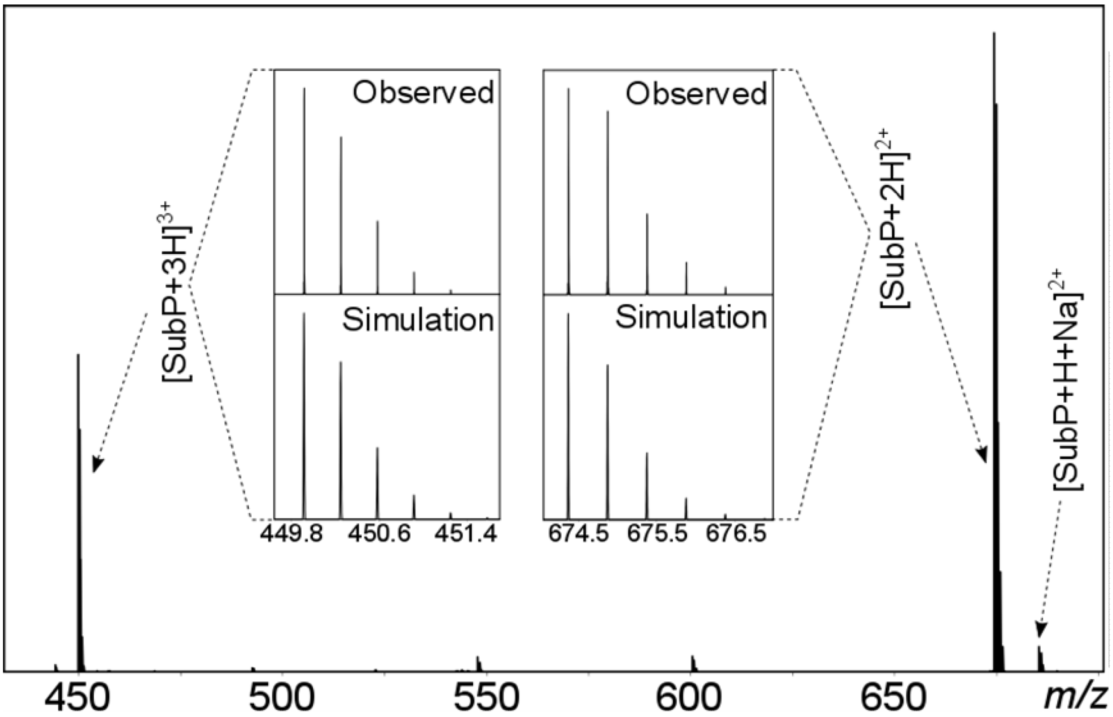


*Figure 1. The mass spectrum of Substance P (Sub P) without adding compound **14**.*

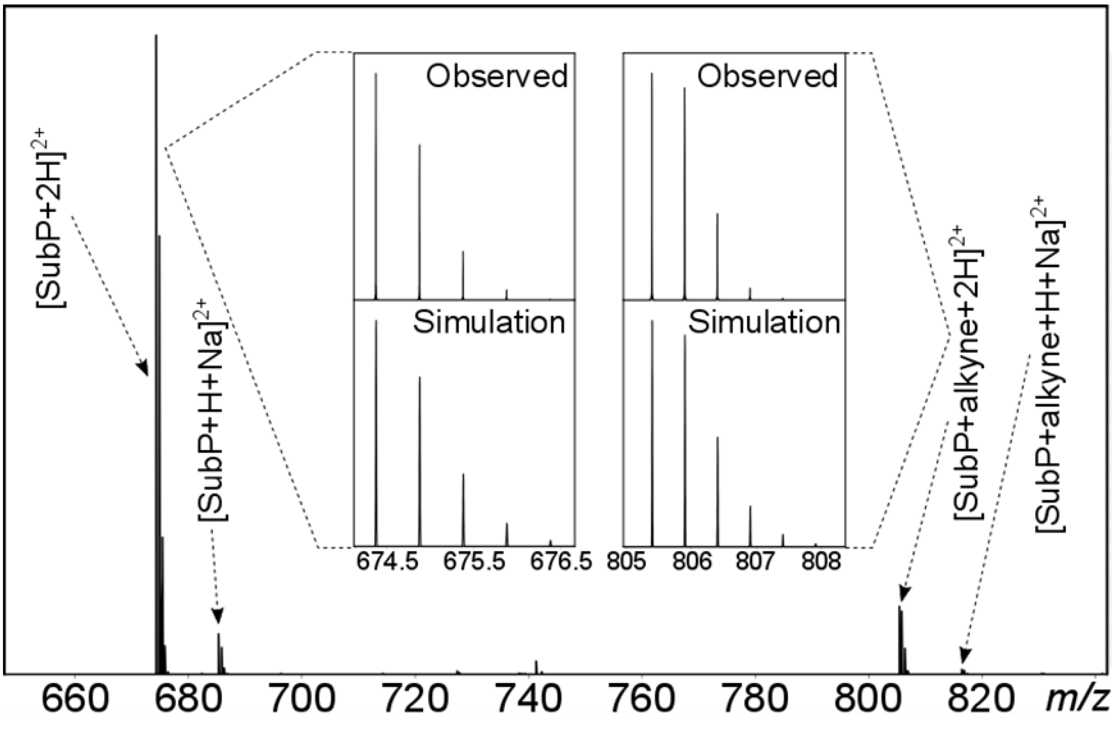
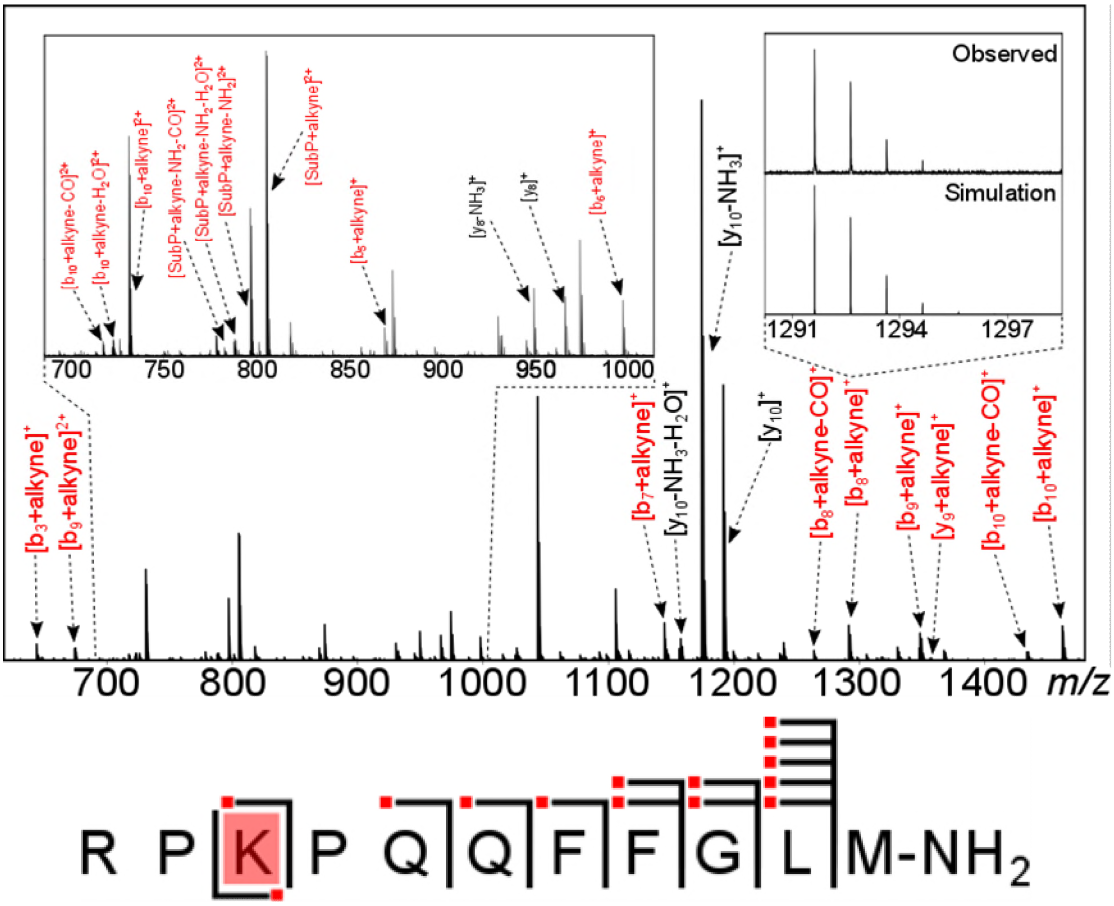


*Figure 2: The mass spectrum of Substance P (Sub P) with compound **14** ('alkyne'). On the top right, the comparison of the experimental result with the simulation is shown.*

After verifying that the conjugation agent **14** was attached to the peptide, the position which is bonded the molecule was examined, to determine, the amino acid which is attached to the agent. Therefore, a MS/MS experiment was run. The MS/MS spectrum revealed a b_3, b_6, b_7, b_8, b_{10} and an y_{10} ion of substance P attached to **14**. Based on this outcome, a fragmentation map was created (Figure 3). As indicated in Figure 3, lysine and proline are the potential bindings sites of the peptide. This goes to pinpoint that the primary assumption was valid and the molecule actually binds to the lysine.



Assignment	*Theoretical m/z*	*Observed m/z*	*Error/ ppm*
$[b3+alkyne]^{+}$	*644.319109*	*644.31911*	*0.00*
$[b9+alkyne]^{2+}$	*674.827298*	*674.82713*	*-0.25*
$[b10+alkyne-CO]^{2+}$	*717.371872*	*717.37164*	*-0.32*
$[b10+alkyne-H_2O]^{2+}$	*722.364047*	*722.36406*	*0.02*
$[b10+alkyne]^{2+}$	*731.36933*	*731.37*	*0.92*
$[SubP+alkyne-NH_2-CO]^{2+}$	*782.892115*	*782.89187*	*-0.31*

[SubP+alkyne-NH$_2$-H$_2$O]$^{2+}$	*787.88429*	*787.88402*	*-0.34*
[SubP+alkyne-NH$_2$]$^{2+}$	*796.889572*	*796.89001*	*0.55*
[b5+alkyne]$^{+}$	*869.43045*	*869.43027*	*-0.21*
[y8-NH$_3$]$^{+}$	*949.460035*	*949.46024*	*0.22*
y8^{+}	*966.486585*	*966.48658*	*-0.01*
[b6+alkyne]$^{+}$	*997.489207*	*997.48923*	*0.02*
[b7+alkyne]$^{+}$	*1144.557441*	*1144.55782*	*0.33*
[y10-NH$_3$-H$_2$O]$^{+}$	*1156.597198*	*1156.59741*	*0.18*
[y10-NH$_3$]$^{+}$	*1174.607762*	*1174.60767*	*-0.08*
y10^{+}	*1191.634312*	*1191.63482*	*0.43*
[b8+alkyne-CO]$^{+}$	*1263.630941*	*1263.63106*	*0.09*
[b8+alkyne]$^{+}$	*1291.625855*	*1291.62651*	*0.51*
[b9+alkyne]$^{+}$	*1348.647319*	*1348.64822*	*0.67*
[y9+alkyne]$^{+}$	*1356.644542*	*1356.64546*	*0.68*
[b10+alkyne-CO]$^{+}$	*1433.736468*	*1433.73578*	*-0.48*
[b10+alkyne]$^{+}$	*1461.731383*	*1461.73207*	*0.47*
		Absolute average	*0.32*
		Standard deviation	*0.38*

Figure 3: The fragmentation map of Substance P with compound ***14*** *based on the MS/MS spectrum (above), and the MS/MS mass error listing.*

Excess azide was added to the sample (ca. 0.1 M solution), and it was left for one week at room temperature. The mass spectrum (Figure 4) with the addition of the azide showed the absence of the peak at 805.40393 and the formation of a peak at 871.93351. This peak indicates to [Substance P + **14** + $C_7H_7N_3$ + 2H]$^{2+}$ and it is confirmed by the comparison of the mathematical simulation with the experimental isotope pattern. By the absence of the peak 805.39641 that all of the substance P-**14** adduct had reacted with the azide.

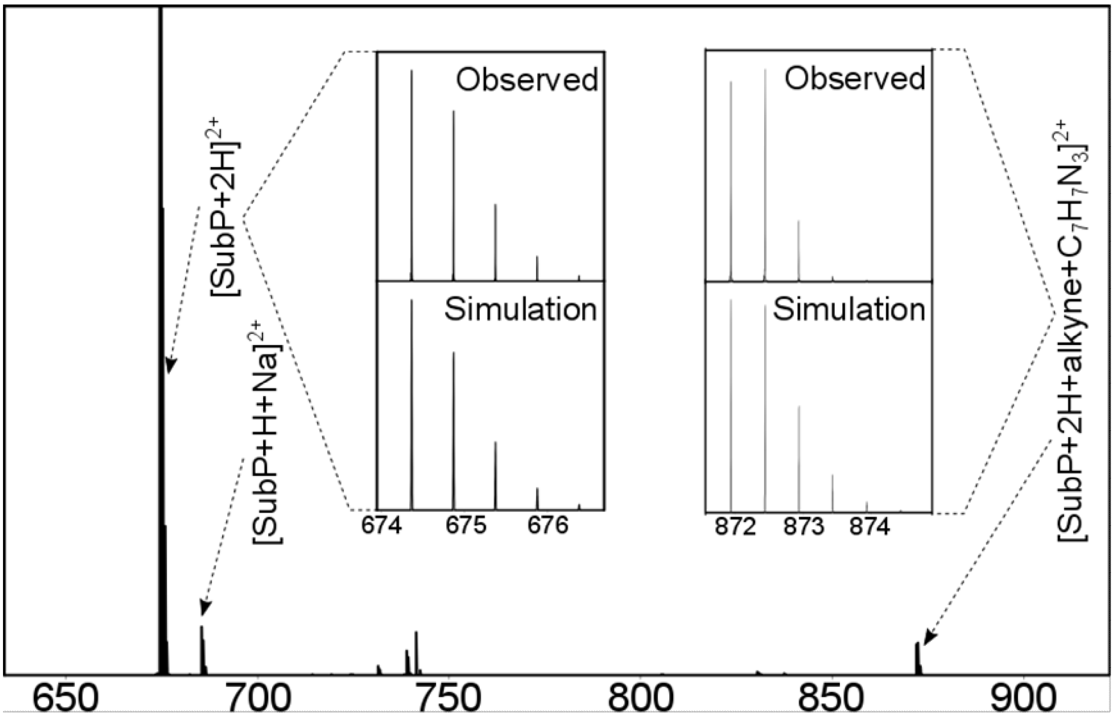


Figure 4: The mass spectrum of Substance P (Sub P) with compound ***14*** *('alkyne') and azide* ($C_7H_7N_3$)*. The comparison of the experimental result with the simulation is shown.*

An illustration with the three spectra is shown in Figure 5. A peak at 805.39641 appeared after the addition of compound **14**. In addition, a new peak at 871.93351 was formed as a result of the addition of the azide.

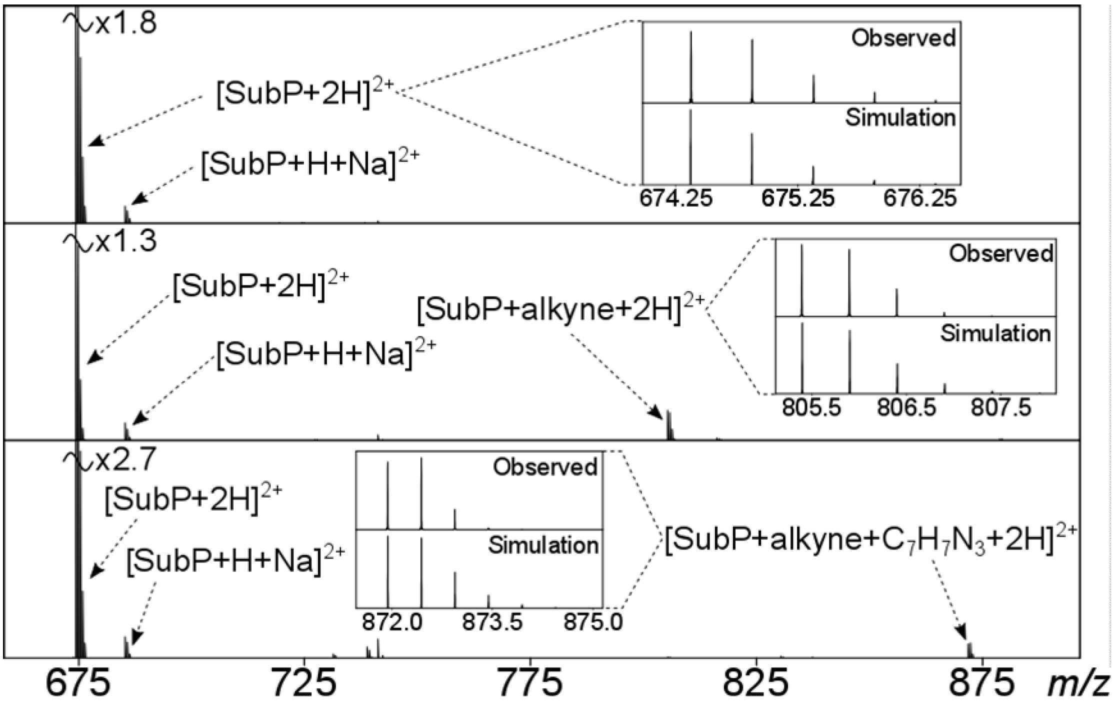


*Figure 5: The three mass spectra of Substance P (Sub P). The first one is without compound **14**, the second with the addition of compound **14** ('alkyne') and the last with the addition of both compound **14** and the azide ($C_7H_7N_3$).*

Lys 8 Vasopressin.

The mass spectra of Lys 8 Vasopressin were obtained with and without the addition of compound **14** (Figures 6 and 7 respectively). The result obtained with the 1:1 ratio mixture (Table 1, entry 4) is illustrated. In Figure 7, a peak at 670.73929 has appeared which indicates the binding of **14** with the peptide [K8Vaso + 'alkyne' + H + Na]$^{2+}$. The experimental isotope pattern matched the mathematical simulation.

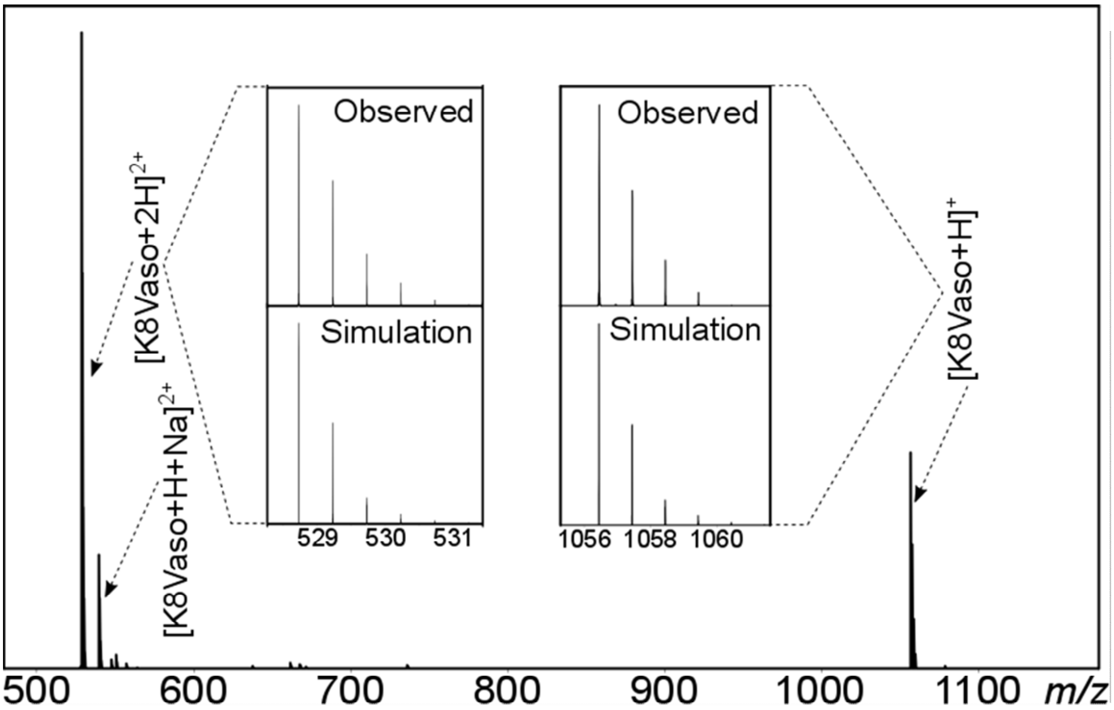


Figure 6: The mass spectrum of Lys 8 Vasopressin (K8Vaso) without adding compound ***14***.

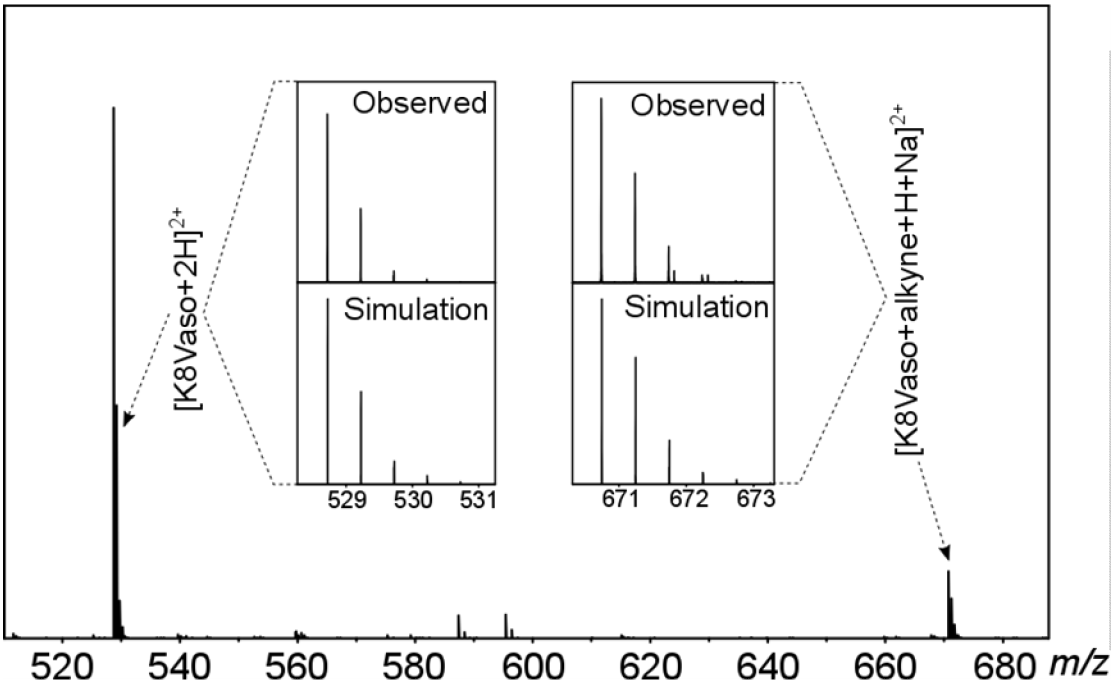
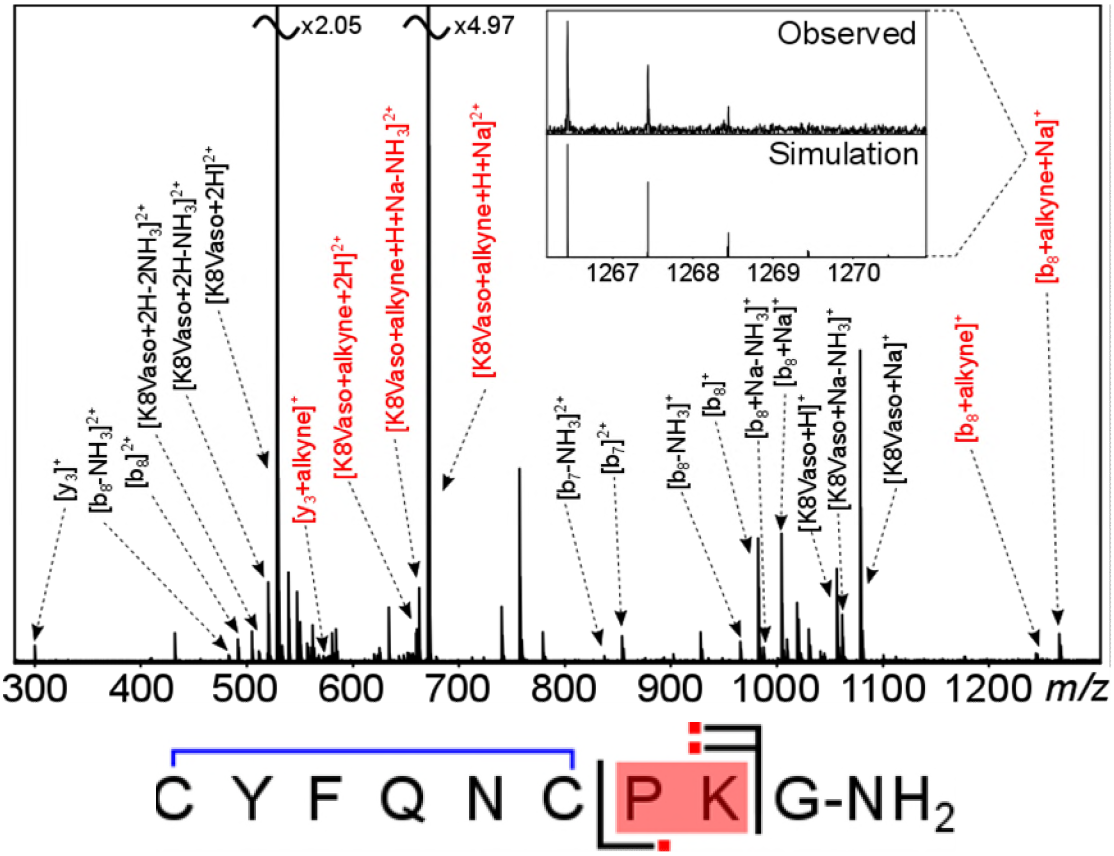


Figure 7: The mass spectrum of Lys 8 Vasopressin (K8Vaso) with compound ***14*** *('alkyne'). On the top right, the comparison of the experimental result with the simulation is shown.*

As before, it was assumed that **14** is bound to the lysine. An MS/MS experiment was run to investigate this assumption. The MS/MS revealed a y_3 ion of the protein attached to **14**. A fragmentation map was created (Figure 8) based on this outcome. As is illustrated, there are only one fragment with the conjugation agent attached. This is due to the cysteine bond; it is difficult to break a cysteine bond by collisionally activated dissociation (CAD). The possible binding sites are the lysine, proline and glutamine. It can be assumed based on proline's and glutamine's structure that the binding couldn't occur to these residues. Therefore, based on the above there are one possible binding site, i.e. the lysine residue.



Assignment	Theoretical m/z	Observed m/z	Error/ ppm
$y3^{+}$	300.203016	300.20302	0.01
$[b8\text{-}NH_3]^{2+}$	483.185848	483.18581	-0.08
$b8^{2+}$	491.699	491.699123	0.25
$[K8Vaso+2H\text{-}2NH_3]^{2+}$	511.69658	511.69661	0.06
$[K8Vaso+2H\text{-}NH_3]^{2+}$	520.209855	520.20988	0.05
$[K8Vaso+2H]^{2+}$	528.723129	528.72316	0.06

[y3+alkyne]$^{+}$	562.26601	562.26599	-0.04
[K8Vaso+alkyne]$^{2+}$	659.754627	659.75473	0.16
[K8Vaso+alkyne+Na-NH$_3$]$^{2+}$	662.232324	662.23231	-0.02
[K8Vaso+alkyne+Na]$^{2+}$	670.745599	670.74556	-0.06
[b7-NH$_3$]$^{+}$	837.269458	837.26959	0.16
b7^{+}	854.296007	854.29603	0.03
[b8-NH$_3$]$^{+}$	965.364421	965.36446	0.04
b8^{+}	982.39097	982.3911	0.13
[b8+Na-NH$_3$]$^{+}$	987.346365	987.34643	0.07
[b8+Na]$^{+}$	1004.372914	1004.37315	0.23
[K8Vaso+H]$^{+}$	1056.438982	1056.43942	0.41
[K8Vaso+Na-NH$_3$]$^{+}$	1061.394378	1061.39459	0.20
[K8Vaso+Na]$^{+}$	1078.420927	1078.42129	0.34
[b8+alkyne]$^{+}$	1244.453964	1244.45515	0.95
[b8+alkyne+Na]$^{+}$	1266.435908	1266.43596	0.04
		Absolute average	0.13
		Standard deviation	0.22

Figure 8: The fragmentation map of the Lys 8 Vasopressin (K8Vaso) with compound ***14*** *based on the MS/MS spectra.*

Benzyl azide was added in excess (0.2 M) to the sample and the solution was left for one week at room temperature. The MS spectrum (Figure 9) displayed the absence of the peak at 670.73929 and the formation of a peak at 737.27534. This peak confirms the attachment of the peptide to the azide [K8Vaso + **14** + $C_7H_7N_3$ + H + Na]$^{2+}$. This is verified by the comparison of the mathematical simulation with the experimental isotope pattern. The absence of the 670.73929 peak indicates that all of the functionalised peptide reacted with the azide.

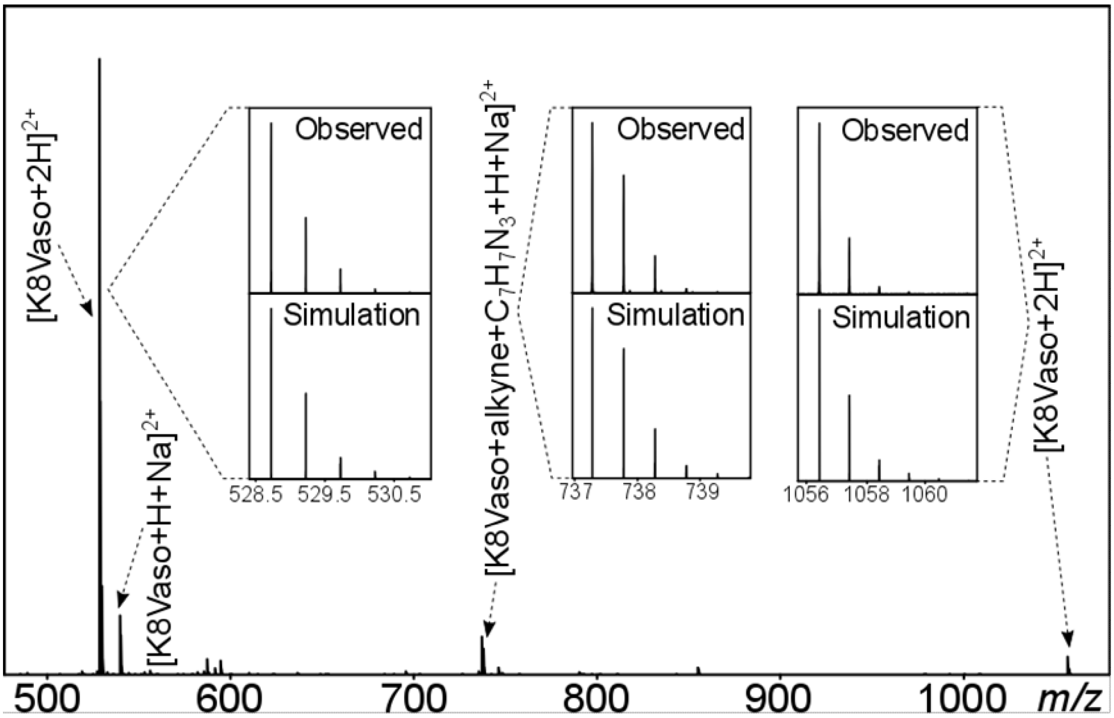


Figure 9: The mass spectrum of the Lys 8 Vasopressin (K8Vaso) with compound ***14*** *('alkyne') and the benzyl azide ($C_7H_7N_3$). The comparison of the experimental result with the simulation is shown.*

The three spectra illustrated in Figure 10. These three spectra are without any addition, with addiiton of compound **14** and the last with adding both compound **14** and the azide.

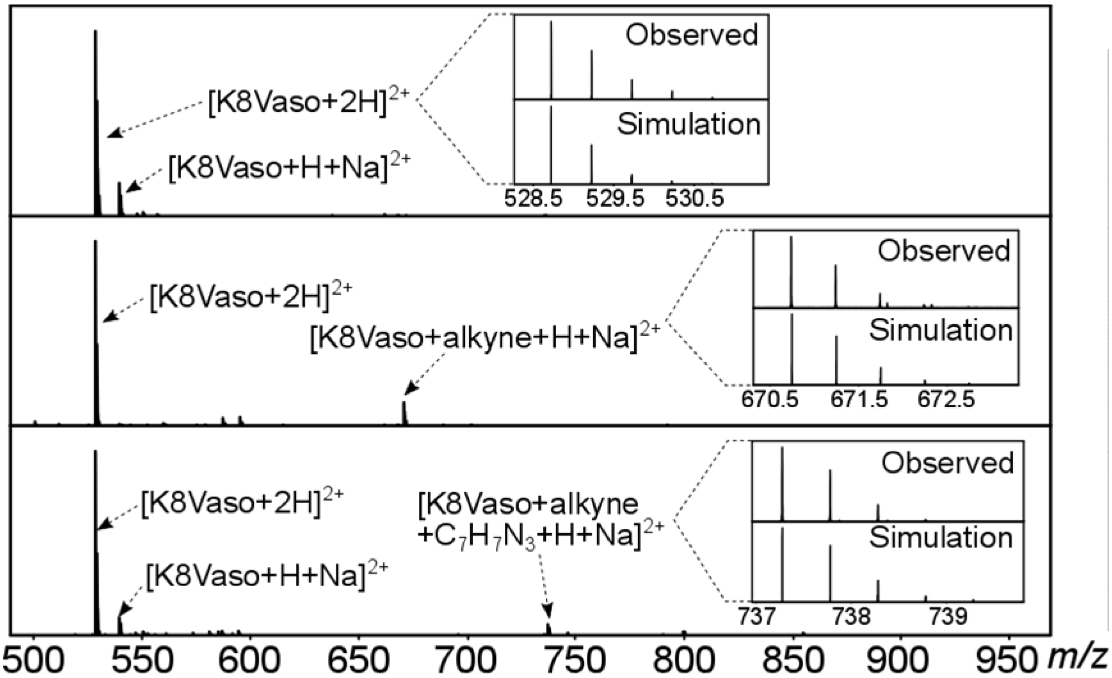


*Figure 10: The three mass spectra of Lys 8 Vasopressin (K8Vaso); without compound **14**, with the addition of compound **14** ('alkyne') and with the addition of both compound **14** and the azide ($C_7H_7N_3$).*

Lys 3 Bombesin.

The mass spectra of Lys 3 Bombesin with and without the addition of compound **14** are shown in Figures 11 and 12 respectively. The result was obtained with the 1:3 ratio mixture (Table 1, entry 9) is shown. The comparison showed the appearance of a new peak at the latter MS spectrum. This peak at 938.41993 indicates the peptide bound with the conjugation agent [K3BBs + **14** + H + Na]$^{2+}$. Furthermore, this was verified by creating a mathematical simulation and comparing it with the experimental isotope pattern.

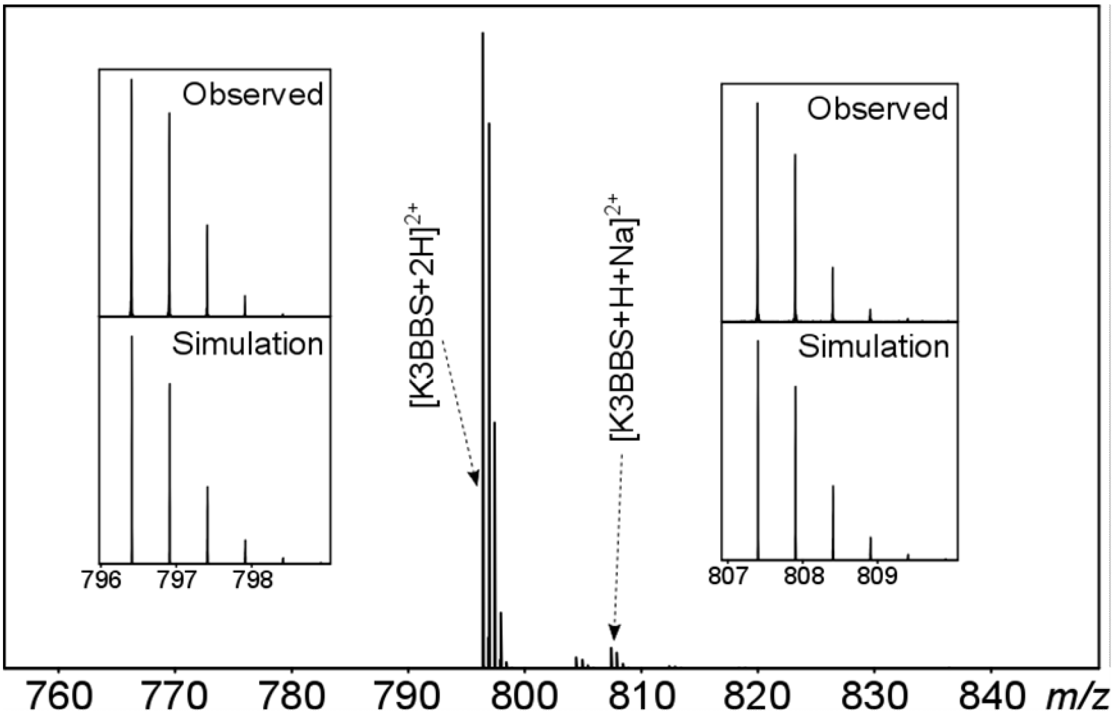


*Figure 11: The MS spectra of Lys 3 Bombesin (K3BBS) without adding compound **14**.*

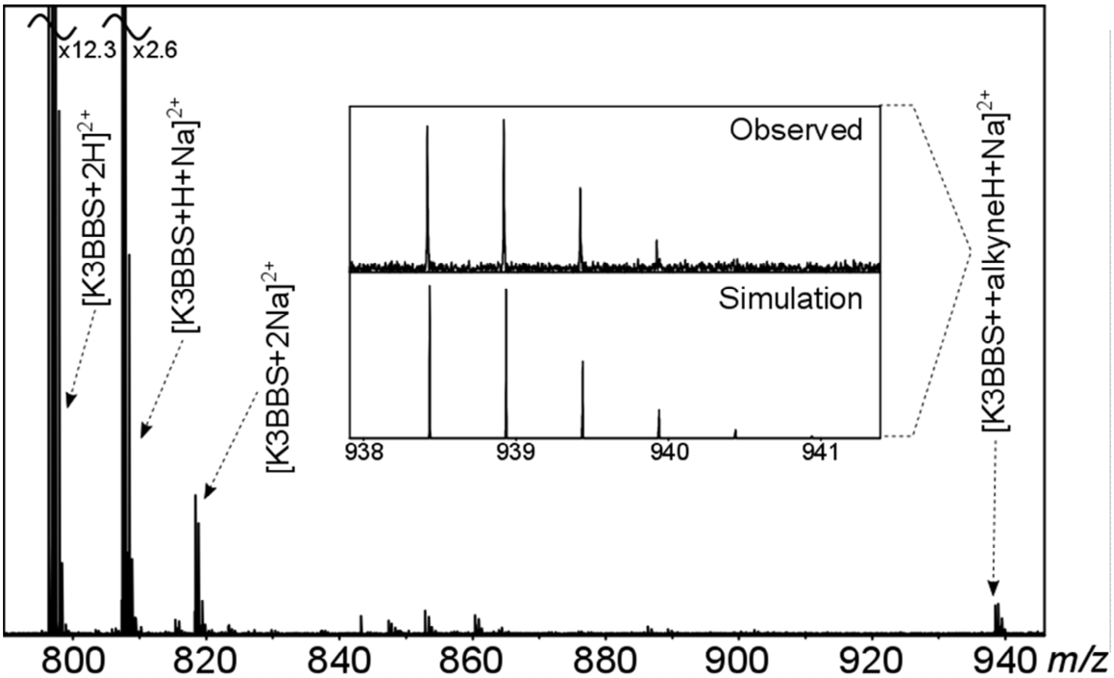
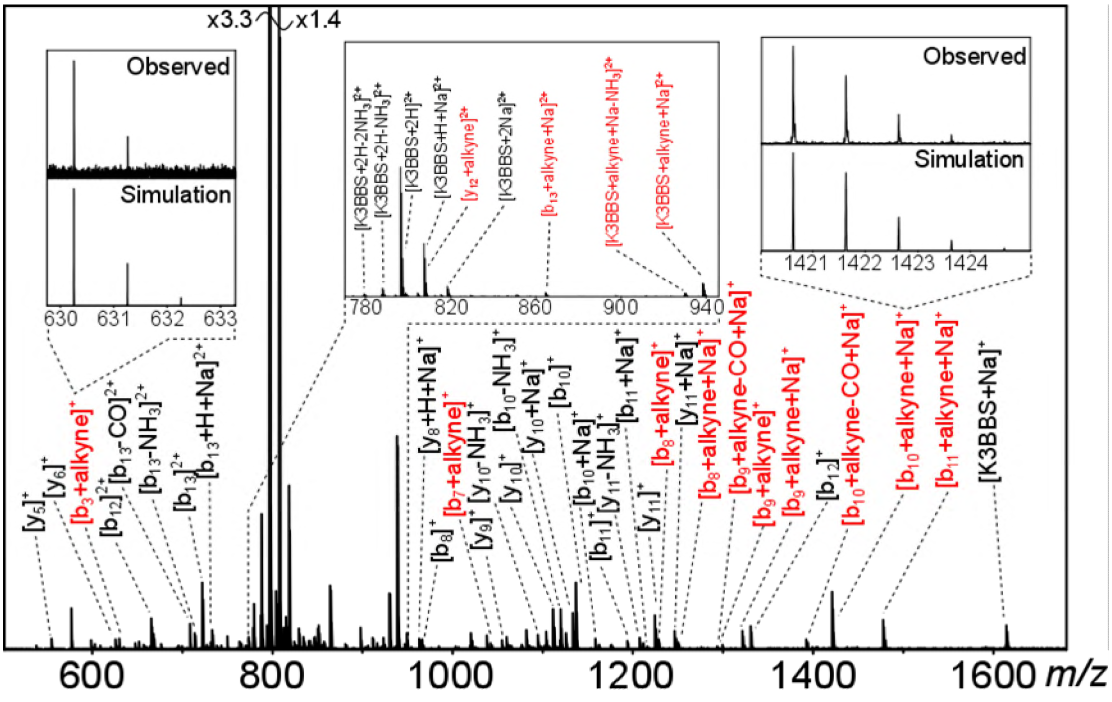


*Figure 12: The MS spectra of Lys 3 Bombesin (K3BBS) with compound **14** (‘alkyne’). The comparison of the experimental result with the simulation is shown.*

After verifying that the conjugation agent was conjugaed to the peptide, it was necessary to determine which amino acid is bound the molecule. The MS/MS spectrum revealed a b_5, b_6, b_7, b_8, b_{10} and a y_{10} ion of the protein attached to the molecule. Based on this outcome, a fragmentation map was created (Figure 13). It can be concluded that the **14** binds to the lysine residue.



Assignment	Theoretical m/z	Observed m/z	Error/ ppm
y5^{+}	555.307164	555.30719	0.05
y6^{+}	626.344278	626.34414	-0.22
[b3+alkyne]$^{+}$	630.25584	630.25577	-0.11
b12^{2+}	665.836185	665.83621	0.04
[b13-CO]$^{2+}$	708.38076	708.38106	0.42
[b13-NH$_3$]$^{2+}$	713.864943	713.86487	-0.10
b13^{2+}	722.378217	722.37809	-0.18
[b13+H+Na]$^{2+}$	733.36919	733.36936	0.23
[K3BBS+2H-2NH$_3$]$^{2+}$	779.385185	779.38506	-0.16
[K3BBS+2H-NH$_3$]$^{2+}$	787.89846	787.89816	-0.38
[K3BBS+2H]$^{2+}$	796.411734	796.41182	0.11
[K3BBS+H+Na]$^{2+}$	807.402707	807.4026	-0.13
y12^{2+}	807.897928	807.89787	-0.07
[K3BBS+2Na]$^{2+}$	818.393679	818.3936	-0.10
[b13+alkyne+Na]$^{+}$	864.400687	864.40072	0.04
[K3BBS+alkyne+H+Na-NH$_3$]$^{2+}$	929.920929	929.92086	-0.07
[K3BBS+alkyne+H+Na]$^{2+}$	938.434204	938.43421	0.01
[y8+Na]$^{1+}$	962.464113	962.46392	-0.20
[b8]$^{1+}$	966.479191	966.47905	-0.15
[b7+alkyne]$^{1+}$	1042.462872	1042.46275	-0.12
y9^{+}	1054.525096	1054.52488	-0.20
[y10-NH$_3$]$^{+}$	1094.52001	1094.5203	0.26
[y10]$^{+}$	1111.546559	1111.54666	0.09
[b10-NH$_3$]$^{+}$	1119.55817	1119.55817	0.00
[y10+Na]$^{+}$	1133.528504	1133.52876	0.23
b10^{+}	1136.584719	1136.58472	0.00
[b10+Na]$^{+}$	1158.566663	1158.56637	-0.25

$b11^{+}$	*1193.606182*	*1193.60621*	*0.02*
$[y11\text{-}NH_3]^{+}$	*1207.604074*	*1207.60431*	*0.20*
$[b11+Na]^{+}$	*1215.588127*	*1215.58733*	*-0.66*
$y11^{+}$	*1224.630623*	*1224.63057*	*-0.04*
$[b8+alkyne]^{1+}$	*1228.542185*	*1228.5423*	*0.09*
$[y11+Na]^{+}$	*1246.612568*	*1246.61224*	*-0.26*
$[b8+alkyne+Na]^{1+}$	*1250.52413*	*1250.52428*	*0.12*
$[b9+alkyne\text{-}CO+Na]^{1+}$	*1293.566329*	*1293.56605*	*-0.22*
$[b9+alkyne]^{1+}$	*1299.579299*	*1299.57935*	*0.04*
$[b9+alkyne+Na]^{1+}$	*1321.561244*	*1321.5612*	*-0.03*
$b12^{+}$	*1330.665094*	*1330.66519*	*0.07*
$[b10+alkyne\text{-}CO+Na]^{1+}$	*1392.634743*	*1392.63529*	*0.39*
$[b10+alkyne+Na]^{1+}$	*1420.629658*	*1420.62944*	*-0.15*
$[b11+alkyne+Na]^{1+}$	*1477.651121*	*1477.65109*	*-0.02*
$[K3BBS+Na]^{1+}$	*1613.798137*	*1613.79805*	*-0.05*
	Absolute average		*0.15*
	Standard deviation		*0.20*

Figure 13: The fragmentation map of the Lys 3 Bombesin (K3BBS) with compound ***14*** *('alkyne') based on the MS/MS spectra.*

The addition of excess azide was undertaken, following the procedure previously described. The reaction mixture was left for one week at room temperature. MS spectrum (Figure 14) with the addition of the azide was obtained. The absence of the peak at 938.41993 and the formation of a novel peak at 1004.96868 was observed. This peak indicates the attachment of the peptide to compound **14** and to the azide [K3BBs + **14** + $C_7H_7N_3$ + H + Na]$^{2+}$. This is supported by the comparison of the mathematical simulation with the experimental isotope pattern.

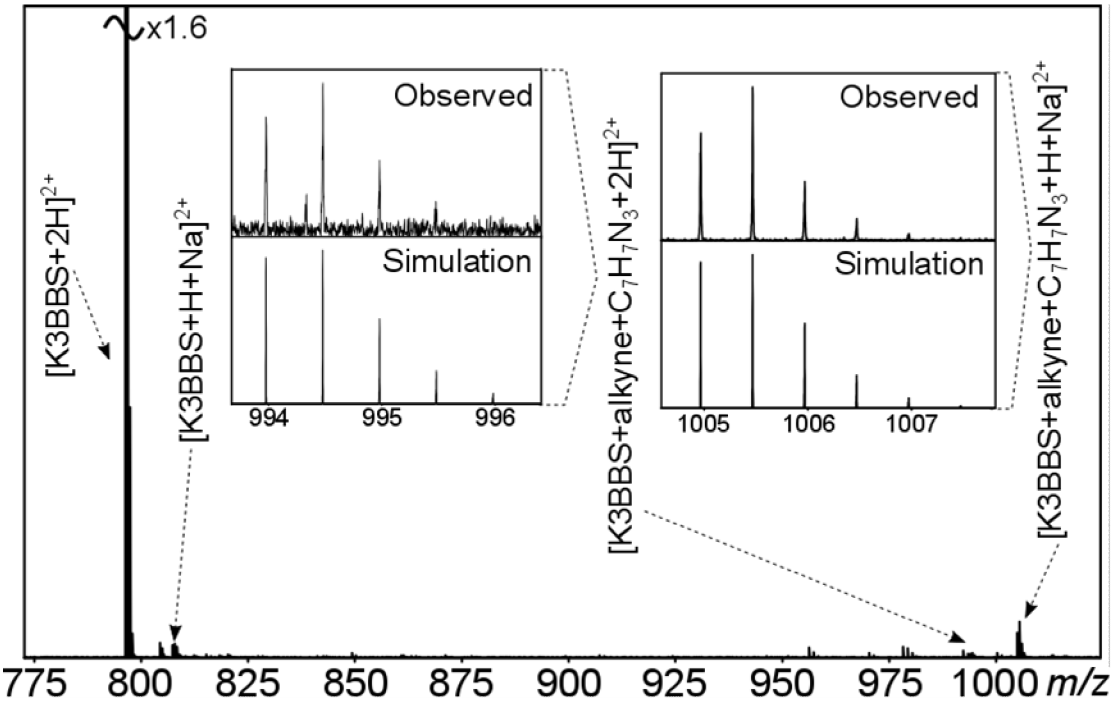


Figure 14: The mass spectrum of the Lys 3 Bombesin (K3BBS) with compound ***14*** *('alkyne') and the azide ($C_7H_7N_3$). The comparison of the experimental result with the simulation is shown.*

All these changes are summarised in Figure 15.

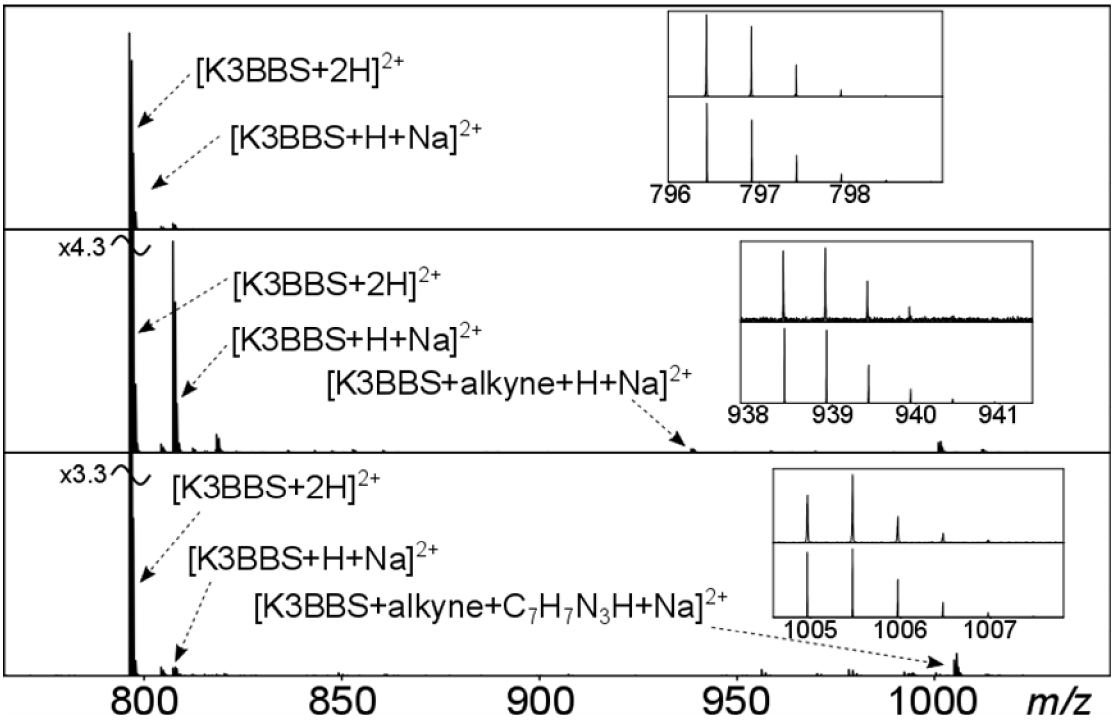


Figure 15: The mass spectra of the Lys 3 Bombesin (K3BBS) with compound ***14*** *('alkyne') and the azide ($C_7H_7N_3$).*

Myoglobin.

After veryfing that compound **14** attached to several peptides, a protein (myoglobin) was tested. The mass spectra of myoglobin with and without the addition of compound **14** are shown in Figures 16 and 17 respectively. The appearance of new peaks at the latter mass spectrum were observed. These peaks correspond to the peptide bound with the conjugation agent in various charge states. This was confirmed using a mathematical simulation and comparing it with the experimental isotope pattern (Figure 18).

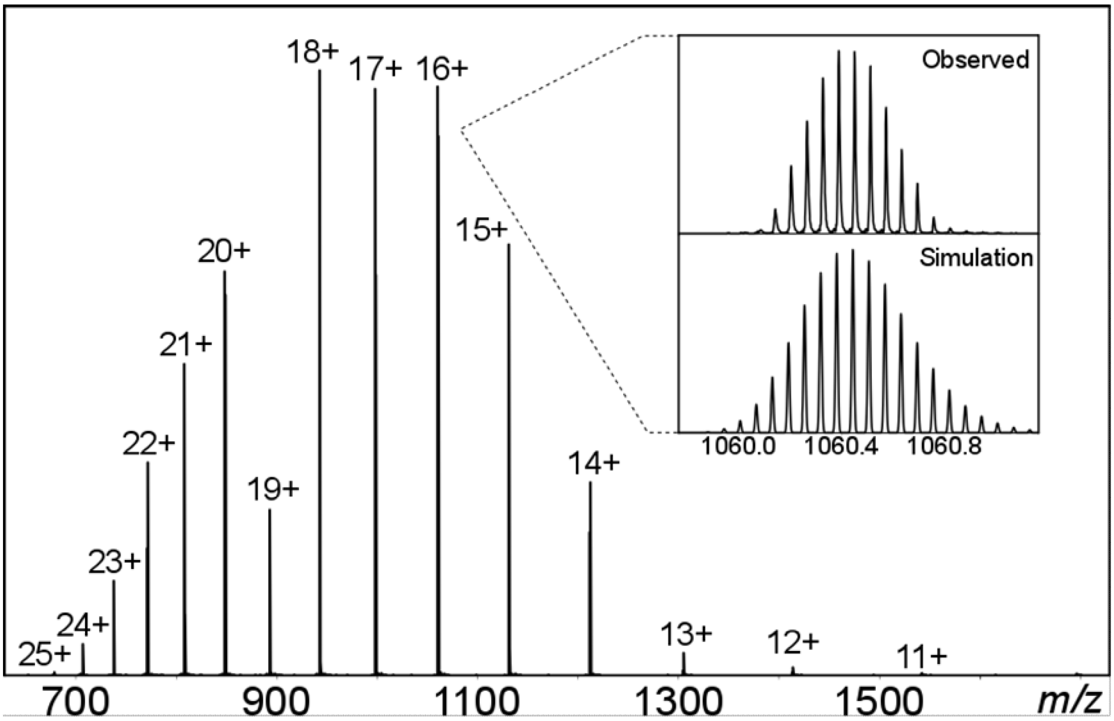


Figure 16: The mass spectrum of Myoglobin without adding compound ***14****.*

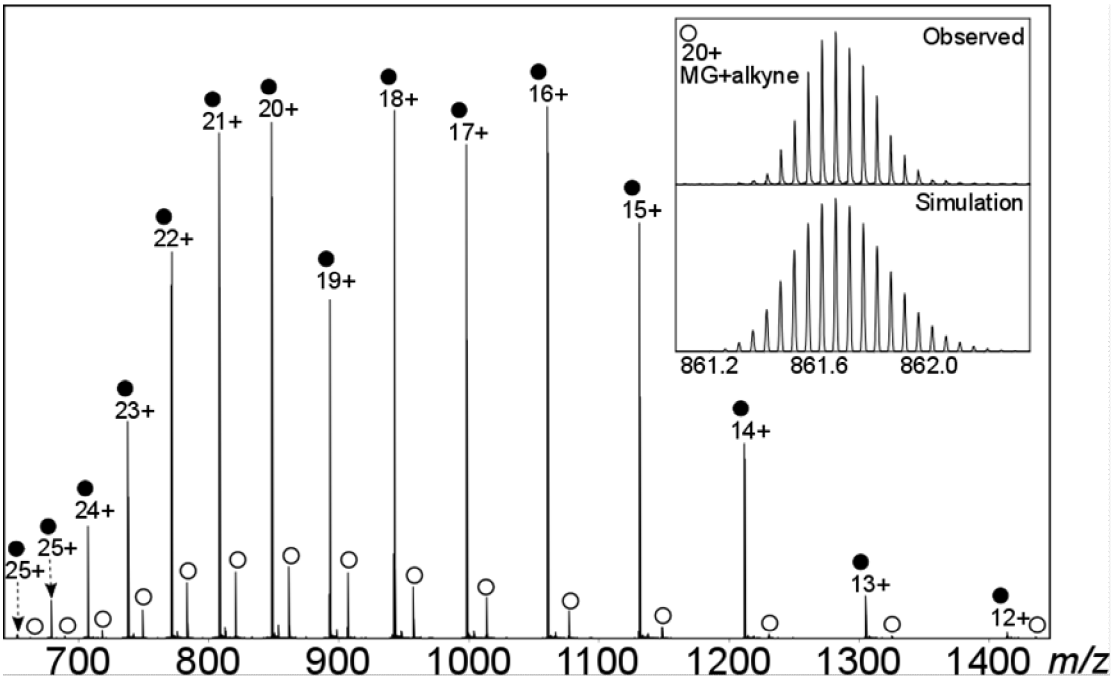


Figure 17: The mass spectrum of Myoglobin following reaction with compound ***14*** *('alkyne').*

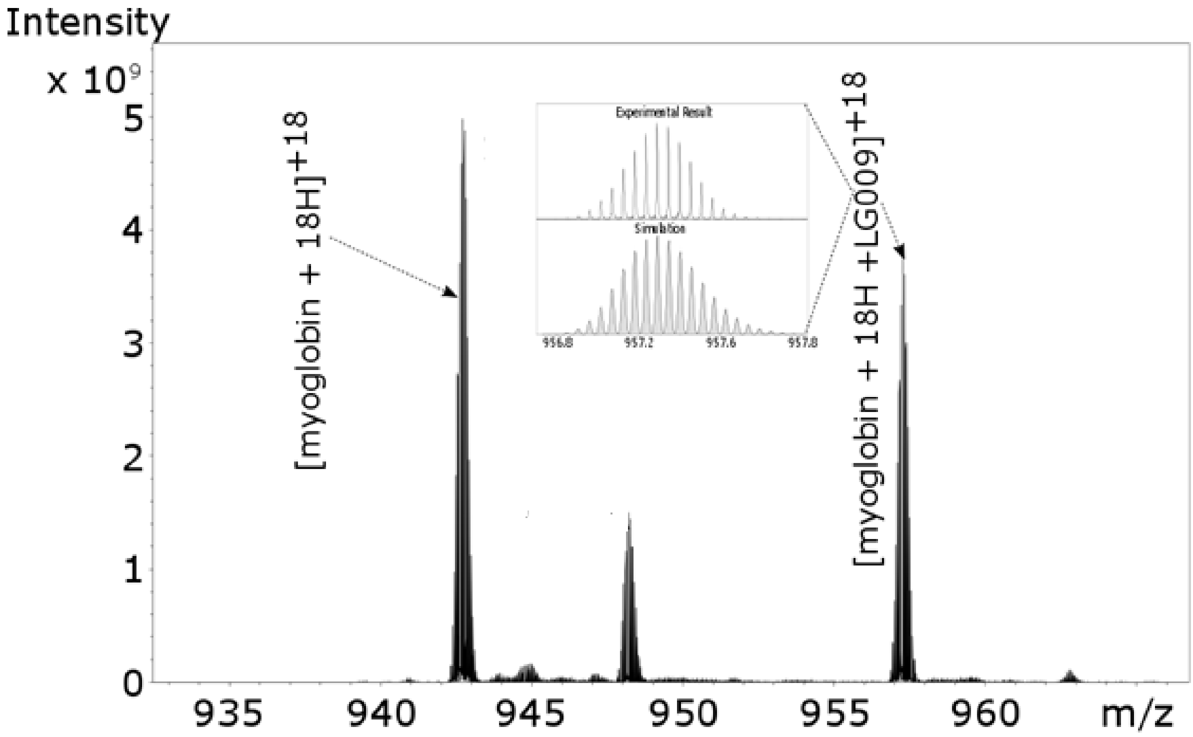


Figure 18: The specified region MS spectra of Myoglobin with compound ***14*** *(identified here as 'LG009'). On the centre, the comparison of the experimental result with the simulation is shown.*

Benzyl azide was added in excess and the sample was left for one week at room temperature. The mass spectrum (Figure 19) with the addition of the azide was obtained. The peaks which indicate the binding of **14** with the myoglobin were replaced by novel peaks which indicate the attachment of the myoglobin to compound **14** and to the azide which is confirmed by the comparison of the mathematical simulation with the experimental isotope pattern (Figure 20).

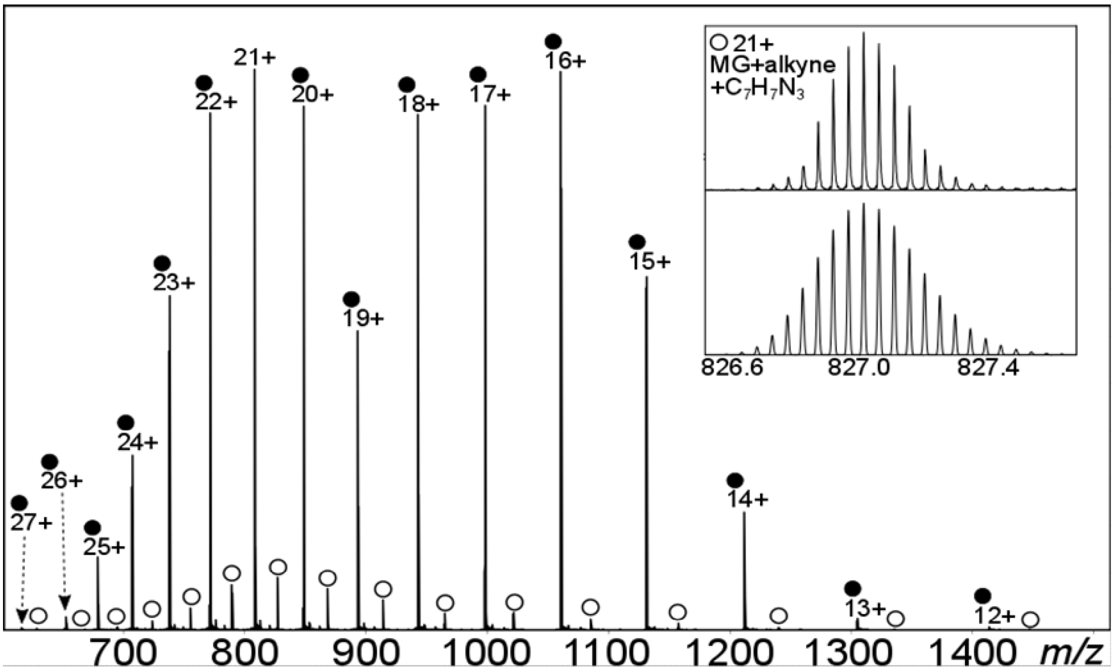


*Figure 19: The mass spectrum of Myoglobin with compound **14** and the azide ($C_7H_7N_3$).*

All the modifications are summarised in Figure 20, for one charge state of the myoglobin derivatives.

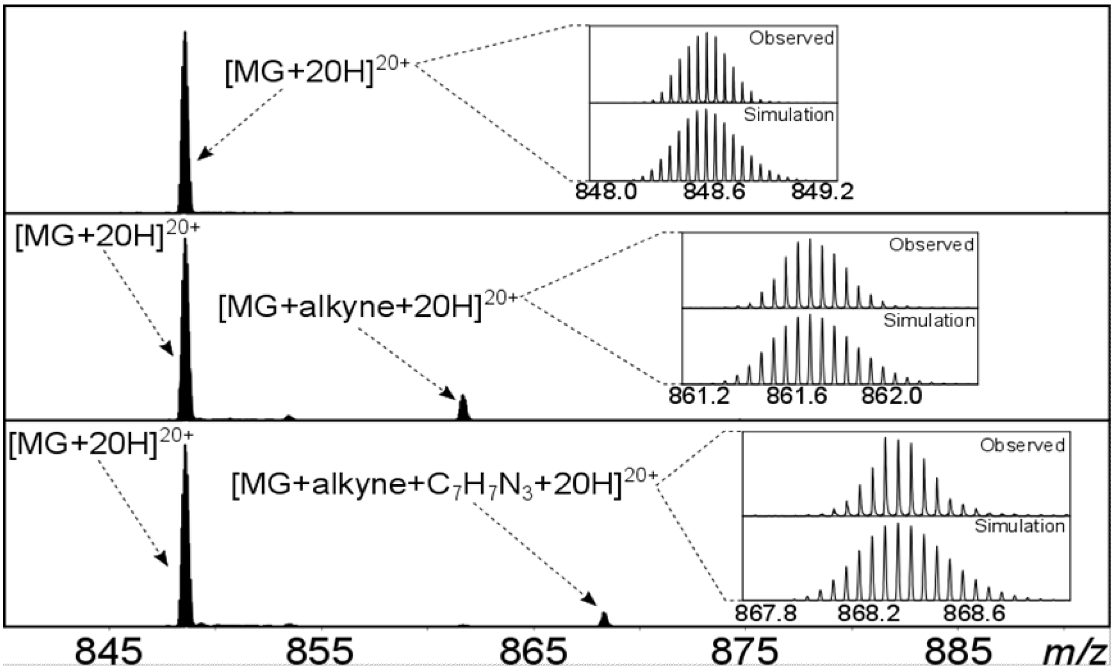


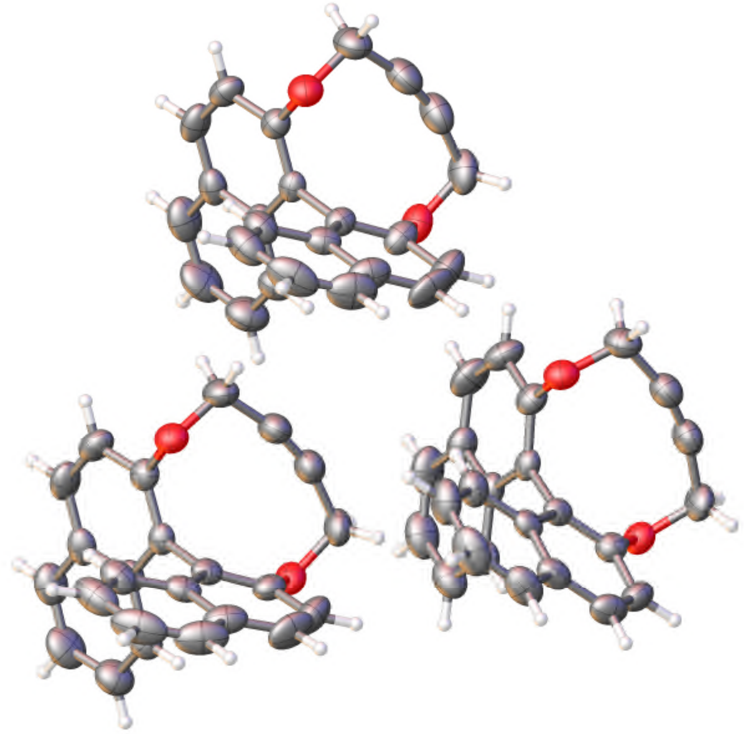
*Figure 20: The specified region MS spectra of Myoglobin (MG). The first one is without compound **14**, the second with the addition of compound **14** ('alkyne') and the last with the addition of both compound **14** and the azide ($C_7H_7N_3$).*

X-Ray Crystallographic data:

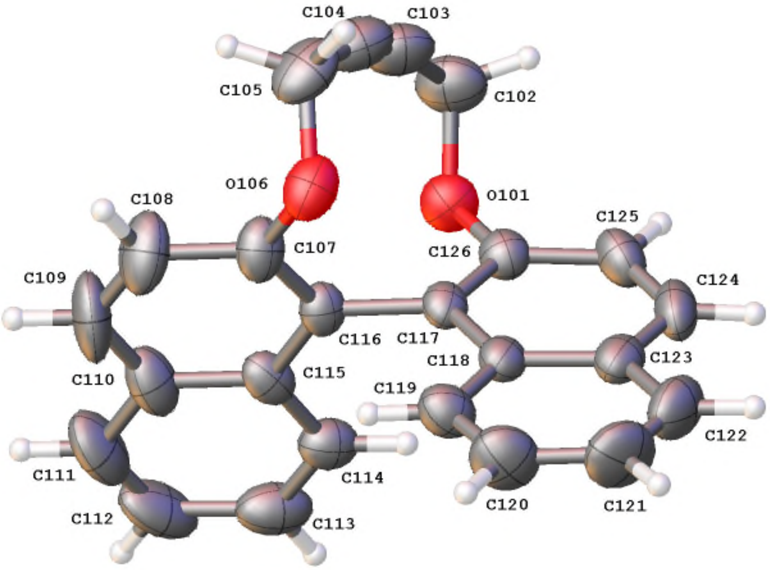
Table 2. Summary of X-ray crystallographic data.

Complex	BINOL **2**	diBr **3**	tetraBr **4**	Acid **13**	Ester **11**	**5a**	$(CH_2)_4$ **10**
Formula	$C_{24}H_{16}O_2$	$C_{16}H_{10}Br_2O_2$	$C_{16}H_8Br_4O_2$	$C_{17}H_{12}O_4$	$C_{18}H_{14}O_4$	$C_{23}H_{19}N_3O_2$	$C_{16}H_{16}O_2$
Crystal system	Hexagonal	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P6_1$	I2/a	$2_1/n$	C2/c	$P2_1/c$	$P2_12_12_1$	Pbcn
a/Å	13.54378(8)	14.16761(6)	7.84858(5)	23.6448(5)	19.9896(4)	9.54430(10)	15.81826(15)
b/Å	13.54378(8)	7.46338(4)	15.11182(7)	7.08950(10)	7.31234(10)	19.2006(2)	9.23296(10)
c/Å	48.3660(3)	28.10737(12)	13.51546(9)	18.3229(4)	20.2663(4)	20.0739(2)	8.32936(9)
α/°	90	90	90	90	90	90	90
β/°	90	103.6158(4)	101.0480(6)	119.266(2)	106.1392(19)	90	90
γ/°	120	90	90	90	90	90	90
Volume/Å^3	7683.33(10)	2888.50(2)	1573.310(16)	2679.42(10)	2845.58(9)	3678.66(7)	1216.50(2)
Z	18	8	4	8	8	8	4
F(000)	3168.0	1536.0	1040.0	1168.0	1232.0	1552.0	512.0
Goodness-of-fit on F^2	1.041	1.083	1.173	1.054	1.131	1.012	1.109
Final R indexes [I>=2σ (I)]	R_1 = 0.0315, wR_2 = 0.0829	R_1 = 0.0304, wR_2 = 0.0799	R_1 = 0.0251, wR_2 = 0.0636	R_1 = 0.0378, wR_2 = 0.1028	R_1 = 0.0672, wR_2 = 0.1835	R_1 = 0.0369, wR_2 = 0.0911	R_1 = 0.0370, wR_2 = 0.1057
Final R indexes [all data]	R_1 = 0.0318, wR_2 = 0.0830	R_1 = 0.0306, wR_2 = 0.0801	R_1 = 0.0257, wR_2 = 0.0640	R_1 = 0.0419, wR_2 = 0.1072	R_1 = 0.0699, wR_2 = 0.1850	R_1 = 0.0407, wR_2 = 0.0939	R_1 = 0.0380, wR_2 = 0.1068
Flack parameter	0.07(5)	-	-	-	-	-	-

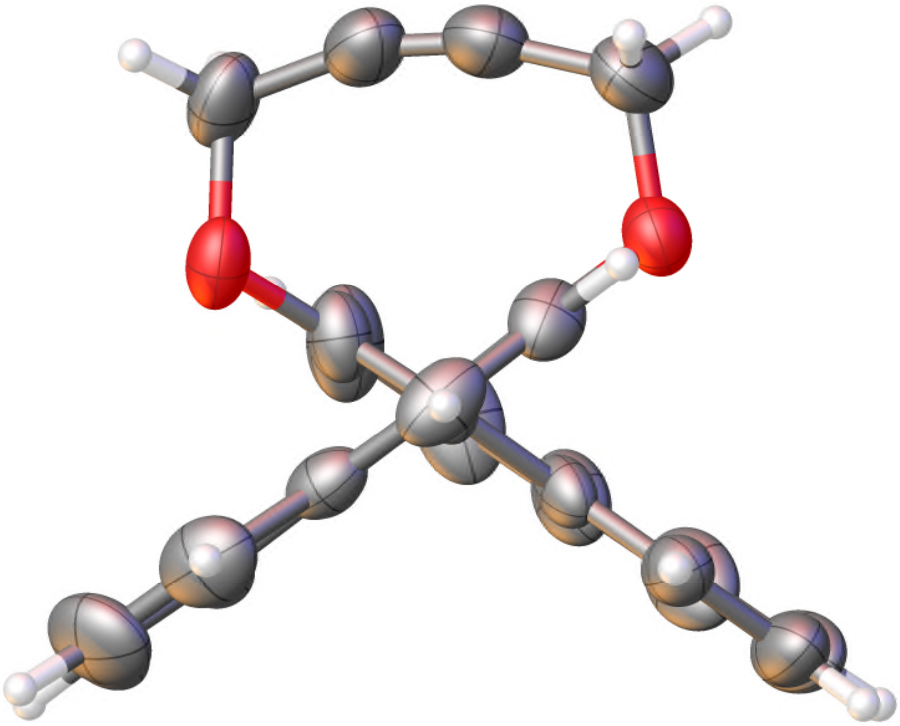
Compound 2 (BINOL-derived, local code adg1) CCDC1515151:



The three crystallographically independent but chemically equivalent macrocycles in the asymmetric unit of adg1.



One of the crystallographically independent macrocycles in the asymmetric unit of adg1 with atom labeling and thermal ellipsoids drawn at 50% probability level.



looking down the naphthyl-naphthyl bond of the macrocycle above showing the bend in the alkyne bridge.

Crystal structure determination of [adg1]

The asymmetric unit contains three crystallographically independent but chemically identical molecules. There are 18 in the unit cell.

<u>Angle between mean planes through the naphthalene groups on each macrocycle</u>

Naphthalene ring C107 C108 C109 C110 C111 C112 C113 C114 C115 C116 to naphthalene ring C117 C118 C119 C120 C121 C122 C123 C124 C125 C126 is 70.633 (0.043) degrees

Naphthalene ring C207 C208 C209 C210 C211 C212 C213 C214 C215 C216 to naphthalene ring C217 C218 C219 C220 C221 C222 C223 C224 C225 C226 is 78.518 (0.041) degrees

Naphthalene ring C307 C308 C309 C310 C311 C312 C313 C314 C315 C316 to naphthalene ring C317 C318 C319 C320 C321 C322 C323 C324 C325 C326 is 74.258 (0.043) degrees

The bridging butyne chain is characterized by a torsion angle between the CH_2s of each butyne chain and the angle between each CH_2 and the alkyne bond

<u>Torsion angles</u>

Torsion angle C102 C103 C104 C105 -10.85 (2.44) degrees (the minus charge is just by definition, torsion angle C105 C104 C103 C102 is +10.85)

Torsion angle C202 C203 C204 C205 -21.37 (2.14) degrees

Torsion angle C302 C303 C304 C305 -20.50 (2.12) degrees

Each CH2 alkyne angle

Angle C102 C103 C104 166.32 (0.29) degrees

Angle C103 C104 C105 163.82 (0.30) degrees

Angle C202 C203 C204 166.88 (0.29) degrees

Angle C203 C204 C205 162.98 (0.29) degrees

Angle C302 C303 C304 163.98 (0.28) degrees

Angle C303 C304 C305 165.91 (0.28) degrees

Hooft y: 0.11(6) Olex2

Flack x: 0.07(5) Shelxl 2014

The Flack parameter is a little high 0.07(5) (should preferably be close to zero with a low esd) but there are no heavy atoms and it is from a known chiral starting material.

All crystals examined were twinned to some extent. The best crystal was measured and the data is presented here.

The crystal is a merohedral twin and the twin component ratio refined to BASF 0.6670(14).

Experimental

Single crystals of $C_{24}H_{16}O_2$ **[adg1]** were grown from slow evaporation of DCM. A suitable crystal was selected and mounted on a glass fibre with Fromblin oil and placed on an Oxford Diffraction diffractometer with a Ruby CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2 [1], the structure was solved with the XS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1 Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.

2 Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

3 Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

Crystal Data for $C_{24}H_{16}O_2$ (M =336.37 g/mol): hexagonal, space group $P6_1$ (no. 169), a = 13.54378(8) Å, c = 48.3660(3) Å, V = 7683.33(10) Å^3, Z = 18, T = 150(2) K,

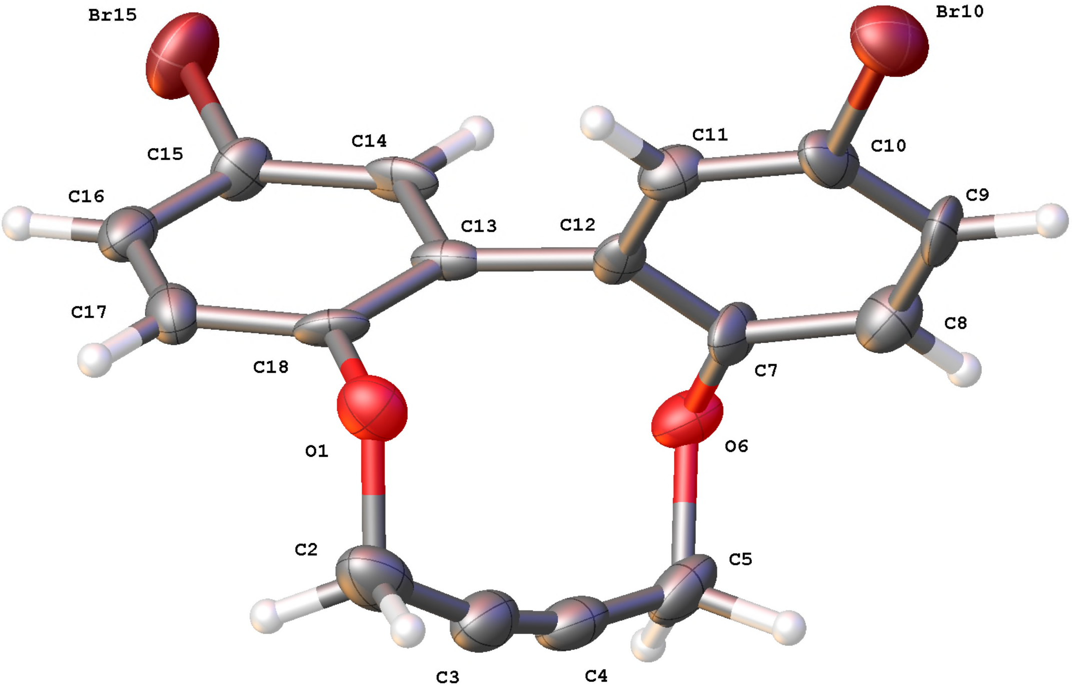
μ(CuKα) = 0.650 mm^{-1}, *Dcalc* = 1.309 g/cm^3, 42875 reflections measured (7.31° ≤ 2Θ ≤ 155.924°), 10592 unique (R_{int} = 0.0357, R_{sigma} = 0.0233) which were used in all calculations. The final R_1 was 0.0315 (I > 2σ(I)) and wR_2 was 0.0830 (all data).

Crystal data and structure refinement for adg1.

Identification code	adg1
Empirical formula	$C_{24}H_{16}O_2$
Formula weight	336.37
Temperature/K	150(2)
Crystal system	Hexagonal
Space group	$P6_1$
a/Å	13.54378(8)
b/Å	13.54378(8)
c/Å	48.3660(3)
α/°	90
β/°	90
γ/°	120
Volume/Å^3	7683.33(10)
Z	18
ρ_{calc}g/cm^3	1.309
μ/mm^{-1}	0.650
F(000)	3168.0
Crystal size/mm^3	0.5 × 0.2 × 0.14 colourless block
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.31 to 155.924
Index ranges	$-17 \leq h \leq 14$, $-17 \leq k \leq 15$, $-59 \leq l \leq 60$
Reflections collected	42875
Independent reflections	10592 [R_{int} = 0.0357, R_{sigma} = 0.0233]
Data/restraints/parameters	10592/1/704
Goodness-of-fit on F^2	1.041
Final R indexes [I>=2σ (I)]	R_1 = 0.0315, wR_2 = 0.0829
Final R indexes [all data]	R_1 = 0.0318, wR_2 = 0.0830
Largest diff. peak/hole / e Å^{-3}	0.19/-0.21

Flack parameter	0.07(5)

Compound 3 (DiBr, local code adg4) CCDC 1515152:



The solid state structure of the macrocycle in adg4 with atom labeling and thermal ellipsoids drawn at 50% probability level.

Crystal structure determination of [adg4]

The asymmetric unit contains the macrocycle, there are eight in the unit cell.

The angle between mean planes through the two aromatic rings of the biphenyl are C7 C8 C9 C10 C11 C12 to C13 C14 C15 C16 C17 C18 is 67.140 (0.065) degrees

There is a close contact (halogen bonding anyone) that shows up as a B alert in the cif checker; O1 - Br10_$1 3.0467 (0.0015) Angstroms.

Symmetry operator used to generate symmetry equivalent atoms in above contact were $1 1.5-X,1.5-Y,1.5-Z

Experimental

Single crystals of $C_{16}H_{10}Br_2O_2$ **[adg4]** were grown from slow evaporation of DCM.. A suitable crystal was selected and mounted on a glass fibre with Fromblin oil and placed on an Xcalibur Gemini diffractometer with a Ruby CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the XL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
3. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

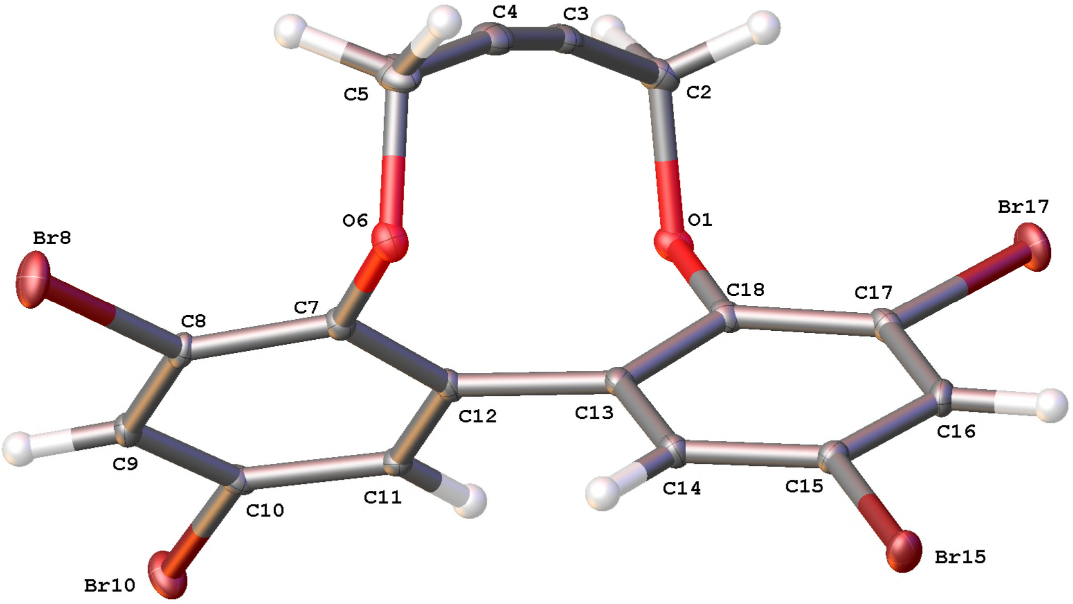
Crystal Data for $C_{16}H_{10}Br_2O_2$ (M =394.06 g/mol): monoclinic, space group I2/a (no. 15), a = 14.16761(6) Å, b = 7.46338(4) Å, c = 28.10737(12) Å, β = 103.6158(4)°, V = 2888.50(2) Å^3, Z = 8, T = 150(2) K, μ(CuKα) = 7.105 mm^{-1}, $Dcalc$ = 1.812 g/cm^3, 27581 reflections measured (6.472° ≤ 2Θ ≤ 156.314°), 3075 unique (R_{int} = 0.0448, R_{sigma} = 0.0177) which were used in all calculations. The final R_1 was 0.0304 (I > 2σ(I)) and wR_2 was 0.0801 (all data).

Crystal data and structure refinement for adg4.

Identification code	adg4
Empirical formula	$C_{16}H_{10}Br_2O_2$
Formula weight	394.06
Temperature/K	150(2)
Crystal system	monoclinic
Space group	I2/a
a/Å	14.16761(6)
b/Å	7.46338(4)
c/Å	28.10737(12)
α/°	90
β/°	103.6158(4)
γ/°	90
Volume/Å^3	2888.50(2)

Z	8
ρ_{calc}g/cm^3	1.812
μ/mm^{-1}	7.105
F(000)	1536.0
Crystal size/mm^3	0.3 × 0.2 × 0.1 colourless block
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.472 to 156.314
Index ranges	$-17 \leq h \leq 17$, $-9 \leq k \leq 7$, $-35 \leq l \leq 35$
Reflections collected	27581
Independent reflections	3075 [R_{int} = 0.0448, R_{sigma} = 0.0177]
Data/restraints/parameters	3075/0/181
Goodness-of-fit on F^2	1.083
Final R indexes [I>=2σ (I)]	R_1 = 0.0304, wR_2 = 0.0799
Final R indexes [all data]	R_1 = 0.0306, wR_2 = 0.0801
Largest diff. peak/hole / e Å^{-3}	0.68/-0.68

Compound 4 (tetraBr, local code adg5) CCDC1515153:



molecular structure of the tetrabromomacrocycle in adg5 with atom labels and thermal ellipsoids at 50% probability level

Crystal structure determination of [adg5]

The asymmetric unit contains the tetrabromomacrocycle, there are 4 in the unit cell. No problems to report in the refinement.

The angle between mean planes through the two aromatic rings define by the following atoms C7 C8 C9 C10 C11 C12 to was C13 C14 C15 C16 C17 C18 was 57.881 (0.066) degrees. Closest atomic contact C9 - C11_$1 3.4789 (0.0030) Angstroms

Symmetry operator used to generate symmetry related atoms discussed in above contacts was $1 -X,1-Y,1-Z

Experimental

Single crystals of $C_{16}H_8Br_4O_2$ **[adg5]** were grown from slow evaporation of DCM. A suitable crystal was selected and mounted on a glass fibre with Fromblin oil and placed on an Xcalibur Gemini diffractometer with a Ruby CCD area detector. The crystal was kept at 175(2) K during data collection. Using Olex2 [1], the structure was solved with the ShelXT [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

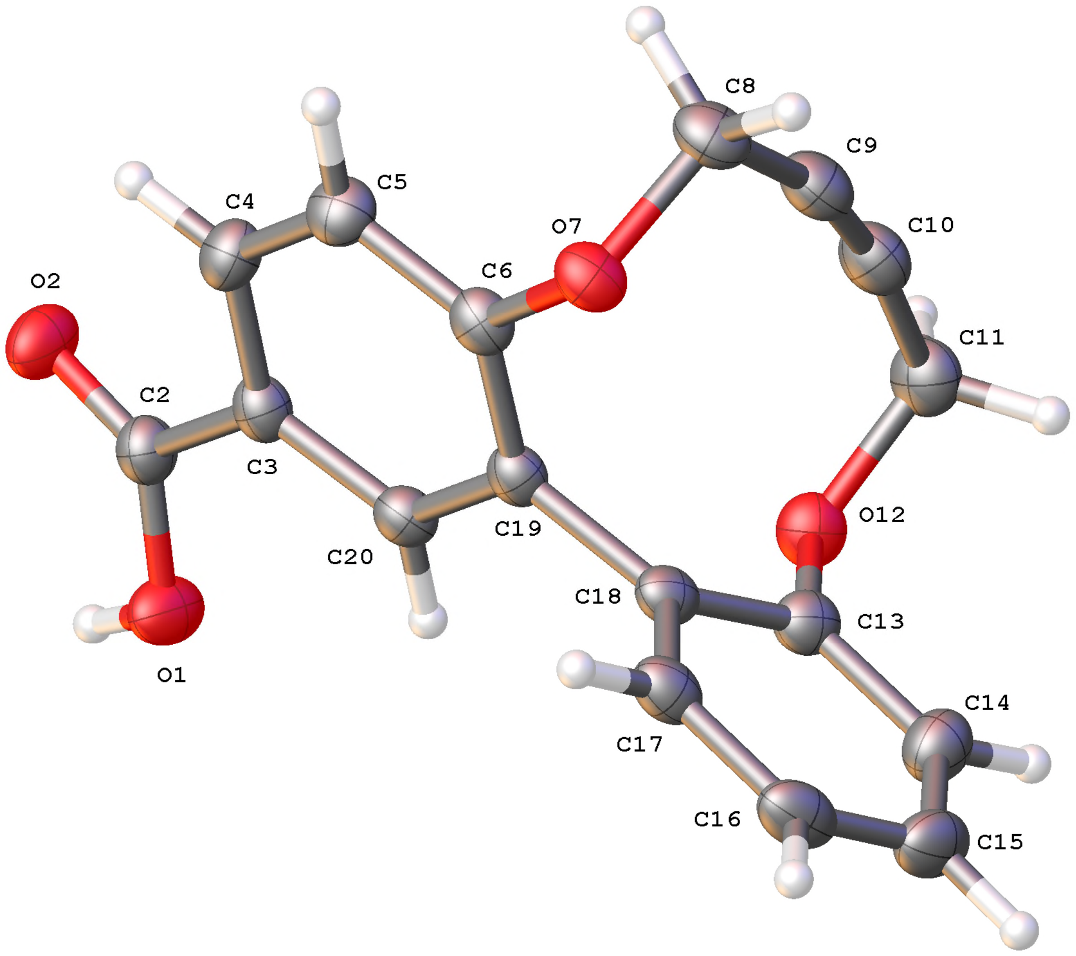
1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data for $C_{16}H_8Br_4O_2$ (M =551.86 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 7.84858(5) Å, b = 15.11182(7) Å, c = 13.51546(9) Å, β = 101.0480(6)°, V = 1573.310(16) Å^3, Z = 4, T = 175(2) K, μ(CuKα) = 12.522 mm^{-1}, $Dcalc$ = 2.330 g/cm^3, 21338 reflections measured (8.87° ≤ 2Θ ≤ 155.778°), 3343 unique (R_{int} = 0.0383, R_{sigma} = 0.0218) which were used in all calculations. The final R_1 was 0.0251 (I > 2σ(I)) and wR_2 was 0.0640 (all data).

Crystal data and structure refinement for adg5.

Identification code	adg5
Empirical formula	$C_{16}H_8Br_4O_2$
Formula weight	551.86
Temperature/K	175(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	7.84858(5)
b/Å	15.11182(7)
c/Å	13.51546(9)
α/°	90
β/°	101.0480(6)
γ/°	90
Volume/Å^3	1573.310(16)
Z	4
ρ_{calc}g/cm^3	2.330
μ/mm^{-1}	12.522
F(000)	1040.0
Crystal size/mm^3	0.2 × 0.2 × 0.2 colourless block
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.87 to 155.778
Index ranges	$-9 \leq h \leq 9$, $-19 \leq k \leq 19$, $-17 \leq l \leq 17$
Reflections collected	21338
Independent reflections	3343 [R_{int} = 0.0383, R_{sigma} = 0.0218]
Data/restraints/parameters	3343/0/199
Goodness-of-fit on F^2	1.173
Final R indexes [I>=2σ (I)]	R_1 = 0.0251, wR_2 = 0.0636
Final R indexes [all data]	R_1 = 0.0257, wR_2 = 0.0640
Largest diff. peak/hole / e Å^{-3}	0.45/-0.90

Compound 13 (acid, local code adg9) CCDC 1515154:



solid sate structure of adg9 with atom labeling and thermal ellipsoids drawn at 50% probability level

Crystal structure determination of [local code adg9]

The asymmetric unit contains the alkyne carboxylic acid. There are eight times of these in the unit cell.

The OH of the carboxylic acid was located in a difference map. It was allowed to refine freely but given thermal parameters Uiso 1.5 times the Uequiv of the parent oxygen. It forms the classic carboxylic acid H-bonded dimer with a symmetry related carboxylic acid.

Specified hydrogen bonds (with esds except fixed and riding H)

D-H	H...A	D...A	<(DHA)	
0.89(2)	1.74(2)	2.6307(12)	178(2)	O1-H1...O2_$1

The atoms used to define mean planes between the two aromatic rings and the angle between these mean planes is

C3 C4 C5 C6 C19 C20 to C13 C14 C15 C16 C17 C18 is 65.968 (0.037) degrees

Experimental

Single crystals of $C_{17}H_{12}O_4$ **[adg9]** were grown from acetone. A suitable crystal was selected and mounted on a Mitegen head with Fromblin oil and placed on an Xcalibur Gemini diffractometer with a Ruby CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2 [1], the structure was solved with the ShelXT [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

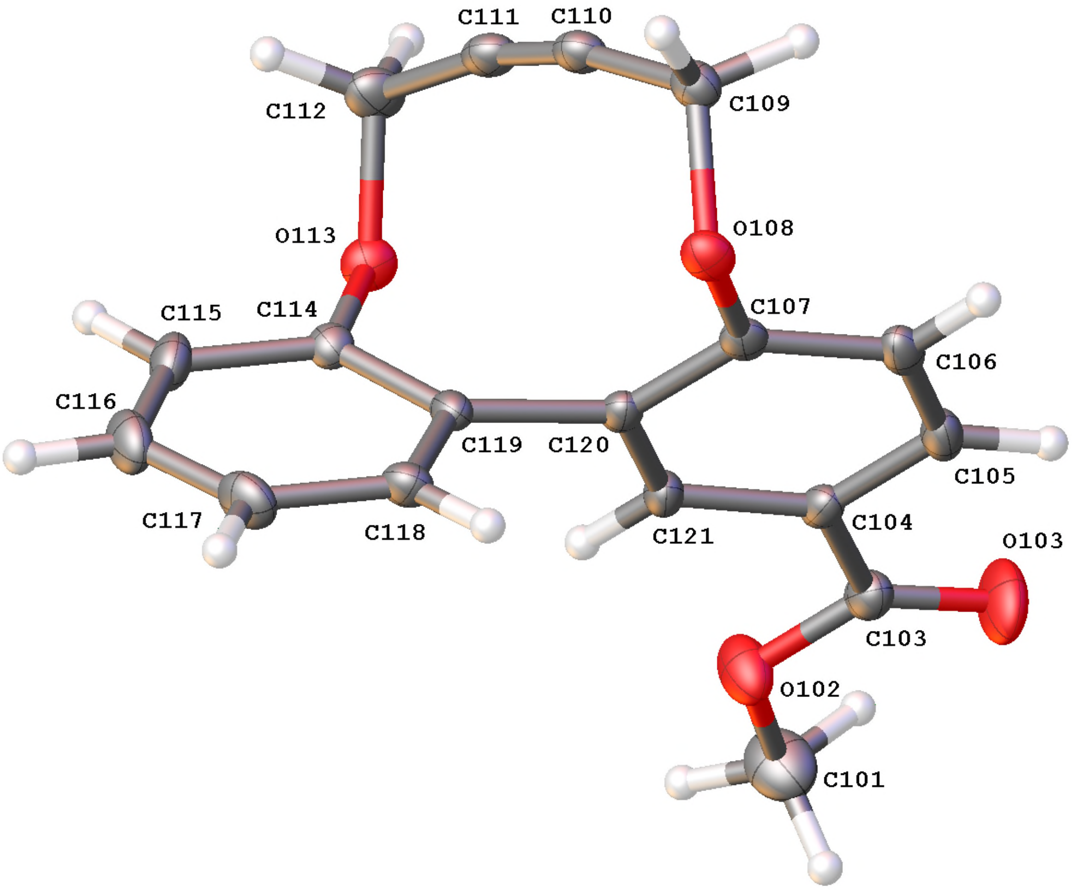
Crystal Data for $C_{17}H_{12}O_4$ (M =280.27 g/mol): monoclinic, space group C2/c (no. 15), a = 23.6448(5) Å, b = 7.08950(10) Å, c = 18.3229(4) Å, β = 119.266(2)°, V = 2679.42(10) Å^3, Z = 8, T = 150(2) K, μ(CuKα) = 0.822 mm^{-1}, $Dcalc$ = 1.390 g/cm^3, 7620 reflections measured ($8.574° \leq 2\Theta \leq 155.73°$), 2804 unique ($R_{int}$ = 0.0245, R_{sigma} = 0.0274) which were used in all calculations. The final R_1 was 0.0378 ($I > 2\sigma(I)$) and wR_2 was 0.1072 (all data).

Crystal data and structure refinement for adg9.

Identification code	adg9
Empirical formula	$C_{17}H_{12}O_4$
Formula weight	280.27
Temperature/K	150(2)
Crystal system	monoclinic
Space group	C2/c
a/Å	23.6448(5)
b/Å	7.08950(10)
c/Å	18.3229(4)

α/°	90
β/°	119.266(2)
γ/°	90
Volume/Å^3	2679.42(10)
Z	8
ρ_{calc}g/cm^3	1.390
μ/mm^{-1}	0.822
F(000)	1168.0
Crystal size/mm^3	0.2 × 0.16 × 0.08 colourless
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	8.574 to 155.73
Index ranges	$-29 \le h \le 29$, $-8 \le k \le 8$, $-23 \le l \le 19$
Reflections collected	7620
Independent reflections	2804 [R_{int} = 0.0245, R_{sigma} = 0.0274]
Data/restraints/parameters	2804/0/193
Goodness-of-fit on F^2	1.054
Final R indexes [I>=2σ (I)]	R_1 = 0.0378, wR_2 = 0.1028
Final R indexes [all data]	R_1 = 0.0419, wR_2 = 0.1072
Largest diff. peak/hole / e Å^{-3}	0.31/-0.19

Compound 11 (Ester, local code mw10) CCDC 1515156:



Solid state structure of one of the crystallographically independent molecules in mw10 with atom labelling and thermal ellipsoids drawn at 50% probability level.

Crystal structure determination of [local code mw10]

The asymmetric unit contains two crystallographically independent but chemically identical molecules, eight molecules in the unit cell.

The angle between the phenyl groups is defined by mean planes through the aromatic systems of each ester

Plane C204 C221 C220 C207 C206 C205 to C219 C218 C217 C216 C215 C214 is 63.401 (0.089) degrees

Plane C104 C121 C120 C107 C106 C105 to plane C119 C118 C117 C116 C115 C114 is 62.773 (0.085) degrees

The angle between a mean plane through the biphenyl unit and the alkyne handle for each compound is;

Mean plane C104 C106 C120 C114 C116 C118 to a mean plane through the alkyne handle O108 C109 C110 C111 C112 O113 is 88.597 (0.125) degrees.

Mean plane C204 C206 C220 C214 C216 C218 to a mean plane through the alkyne handle O208 C209 C210 C211 C212 O213 is 88.717 (0.115) degrees.

Experimental

Single crystals of $C_{18}H_{14}O_4$ **[mw10]** were grown from slow evaporation of EtOAc. A suitable crystal was selected and mounted on a glass fibre with Fromblin oil and placed on a Rigaku Oxford Diffraction diffractometer with a Dual source (Cu at zero) with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2 [1], the structure was solved with the ShelXT [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

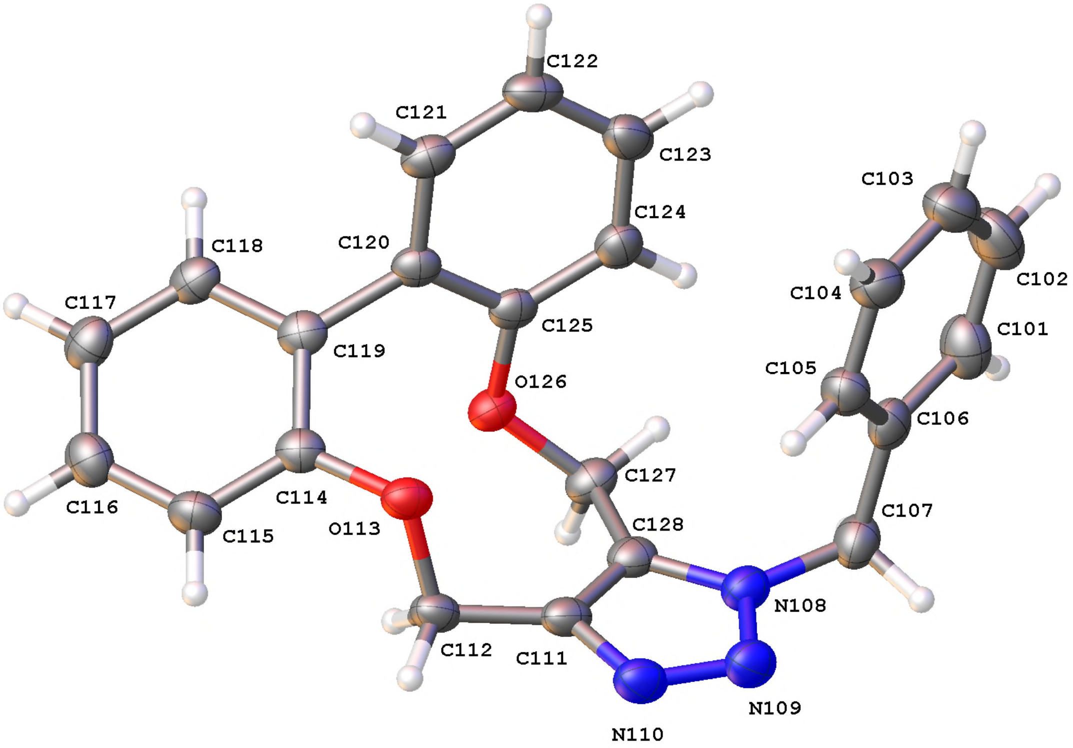
Crystal Data for $C_{18}H_{14}O_4$ (M =294.29 g/mol): monoclinic, space group P2$_1$/c (no. 14), a = 19.9896(4) Å, b = 7.31234(10) Å, c = 20.2663(4) Å, β = 106.1392(19)°, V = 2845.58(9) Å^3, Z = 8, T = 150(2) K, μ(CuKα) = 0.799 mm^{-1}, $Dcalc$ = 1.374 g/cm^3, 51652 reflections measured (8.972° ≤ 2Θ ≤ 147.348°), 5692 unique (R_{int} = 0.1165, R_{sigma} = 0.0414) which were used in all calculations. The final R_1 was 0.0672 (I > 2σ(I)) and wR_2 was 0.1850 (all data).

Crystal data and structure refinement for mw10.

Identification code	mw10
Empirical formula	$C_{18}H_{14}O_4$
Formula weight	294.29
Temperature/K	150(2)
Crystal system	monoclinic
Space group	P2$_1$/c

a/Å	19.9896(4)
b/Å	7.31234(10)
c/Å	20.2663(4)
α/°	90
β/°	106.1392(19)
γ/°	90
Volume/Å^3	2845.58(9)
Z	8
ρ_{calc}g/cm^3	1.374
μ/mm^{-1}	0.799
F(000)	1232.0
Crystal size/mm^3	0.2 × 0.14 × 0.1 colourless block
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.972 to 147.348
Index ranges	$-24 \leq h \leq 24$, $-9 \leq k \leq 9$, $-24 \leq l \leq 24$
Reflections collected	51652
Independent reflections	5692 [R_{int} = 0.1165, R_{sigma} = 0.0414]
Data/restraints/parameters	5692/0/399
Goodness-of-fit on F^2	1.131
Final R indexes [I>=2σ (I)]	R_1 = 0.0672, wR_2 = 0.1835
Final R indexes [all data]	R_1 = 0.0699, wR_2 = 0.1850
Largest diff. peak/hole / e Å^{-3}	0.35/-0.37

Compound 5a (Cycloadduct, local code adg) CCDC 1515150:



Solid state structure of one of the crystallographically independent but chemically identical triazines in adg with atom labeling and thermal ellipsoids drawn at 50% probability level

Crystal structure determination of [local code adg]

The asymmetric unit contains two crystallographically independent but chemically identical triazines in the asymmetric unit. Four times this in the unit cell. This was not a chiral synthesis, however the molecules have crystallised in an achiral space group. The correct assignment of the handedness of the crystal chosen is measured by the Flack parameter

Flack x: -0.05(8) Shelx 2014

Hooft y: -0.03(8) Olex2

As this number is relatively small (-0.05(8)) with a error that takes it to zero you can have confidence in the assignment of the handedness of the crystal chosen.

SIMU restraints were used to give the nitrogens and benzylic carbons of one of the triazines (C107 N108 N109 N110 C111 C128) similar thermal parameters to chemically equivalent atoms.

Experimental

Single crystals of $C_{23}H_{19}N_3O_2$ **[adg]** were grown from slow evaporation of DCM. A suitable crystal was selected and mounted on a glass fibre with Fromblin oil and placed on an Xcalibur Gemini diffractometer with a Ruby CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2 [1], the structure was solved with the ShelXT [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

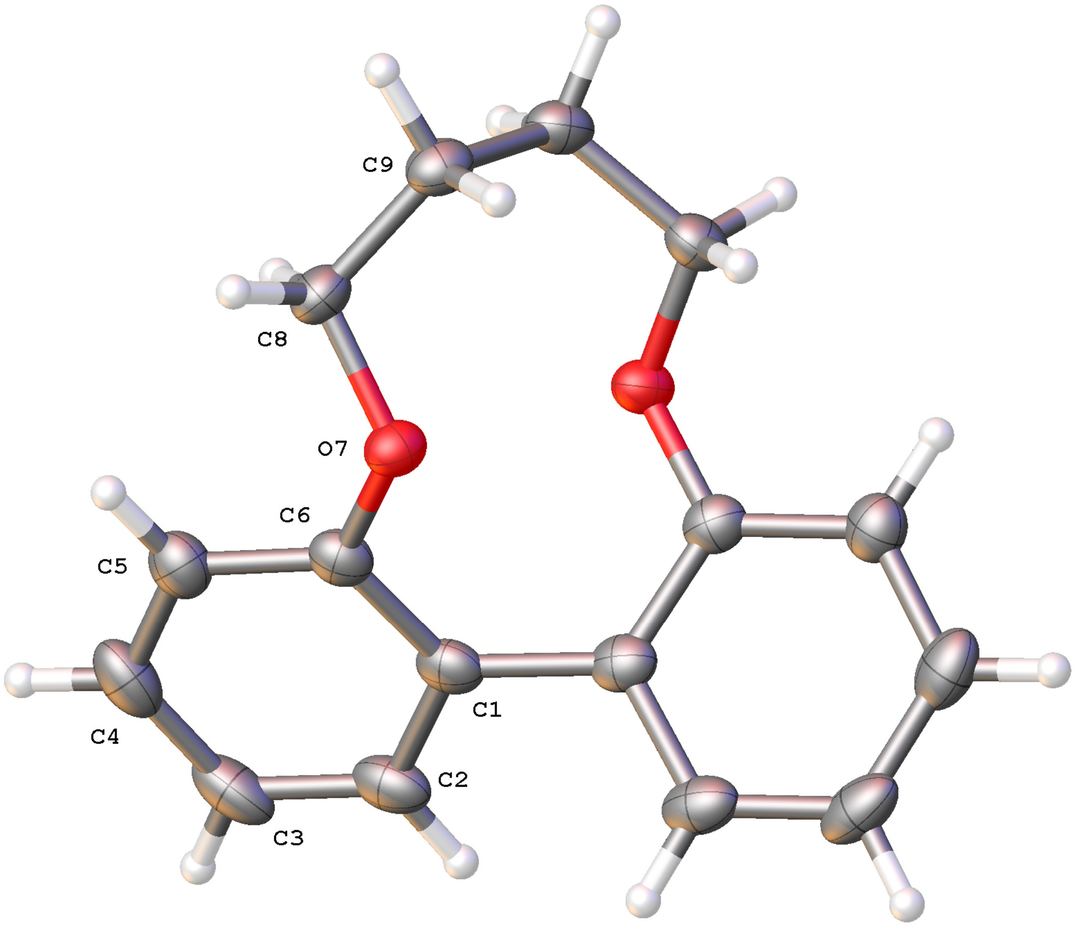
Crystal Data for $C_{23}H_{19}N_3O_2$ (M =369.41 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 9.54430(10) Å, b = 19.2006(2) Å, c = 20.0739(2) Å, V = 3678.66(7) Å^3, Z = 8, T = 150(2) K, μ(CuKα) = 0.697 mm^{-1}, $Dcalc$ = 1.334 g/cm^3, 22984 reflections measured ($8.81° \leq 2\Theta \leq 156.046°$), 7685 unique ($R_{int}$ = 0.0306, R_{sigma} = 0.0298) which were used in all calculations. The final R_1 was 0.0369 (I > 2σ(I)) and wR_2 was 0.0939 (all data).

Crystal data and structure refinement for adg.

Identification code	adg
Empirical formula	$C_{23}H_{19}N_3O_2$
Formula weight	369.41
Temperature/K	150(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.54430(10)
b/Å	19.2006(2)
c/Å	20.0739(2)
α/°	90
β/°	90
γ/°	90

Volume/Å^3	3678.66(7)
Z	8
ρ_{calc}g/cm^3	1.334
μ/mm^{-1}	0.697
F(000)	1552.0
Crystal size/mm^3	0.3 × 0.1 × 0.1 colorless
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.81 to 156.046
Index ranges	$-8 \leq h \leq 11, -21 \leq k \leq 24, -25 \leq l \leq 25$
Reflections collected	22984
Independent reflections	7685 [R_{int} = 0.0306, R_{sigma} = 0.0298]
Data/restraints/parameters	7685/54/505
Goodness-of-fit on F^2	1.012
Final R indexes [I>=2σ (I)]	R_1 = 0.0369, wR_2 = 0.0911
Final R indexes [all data]	R_1 = 0.0407, wR_2 = 0.0939
Largest diff. peak/hole / e Å^{-3}	0.27/-0.29
Flack parameter	-0.05(8)

Compound 10 ((CH_2)$_4$, (local code MW9) CCDC 1515155.



solid state structure of mw9 with only the asymmetric unit labelled and thermal ellipsoids drawn at 50% probability level

Crystal structure determination of [local code mw9]

The asymmetric unit contains half the macrocycle which lies on a two fold axis. Four macrocycles in the unit cell (two R and two S, related by inversion centres).

The angle between mean planes through ring C1 C2 C3 C4 C5 C6 and symmetry related ring C1_$1 C2_$1 C3_$1 C4_$1 C5_$1 C6_$1 is 47.844 (0.033) degrees. Distance between oxygens O7 - O7_$1 in the macrocycle is 2.6562 (0.0015) Angstroms. There is a stack of macrocycles that alter S to R traveling along the ‘c’ axis of the cell and are connected by short C-H… O contacts and C-H- pi contacts.

Short contact tabulated below

Specified hydrogen bonds (with esds except fixed and riding H)

D-H	H...A	D...A	<(DHA)

0.99	2.59	3.5572(14)	166.0	C9-H9A...O7_$2

CH-pi contact between both C-Hs of C9 and the benzene ring

C-H pi bond C9-H9B to centroid of C1 C2 C3 C4 C5 C6

H9B to Centroid distance: 3.17375(4) A (Olex2

C-H pi bond C9-H9A to centroid of C1 C2 C3 C4 C5 C6

H9A to Centroid distance: 3.23698(4) A (Olex2)

(Olex2 generates an esd on this measurement by just using the cell e.s.d as a matrix for the calculation and not by refinement)

Symmetry operators used to define symmetry related atoms in above discussions were

$1 1-X,+Y,0.5-Z

$2 1-X,1-Y,-Z

Experimental

Single crystals of $C_{16}H_{16}O_2$ **[mw9]** were grown from DCM/hexane. A suitable crystal was selected and mounted on a Mitegen head and placed on an Xcalibur Gemini diffractometer with aRuby CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2 [1], the structure was solved with the ShelXT [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

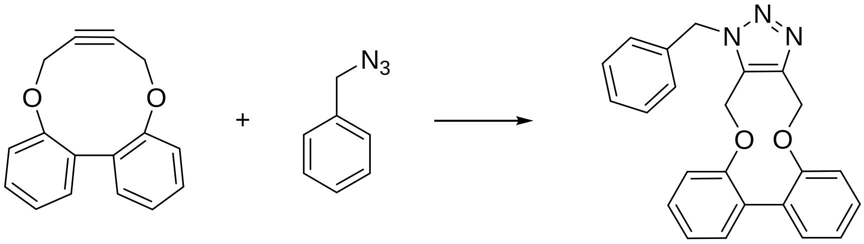
1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

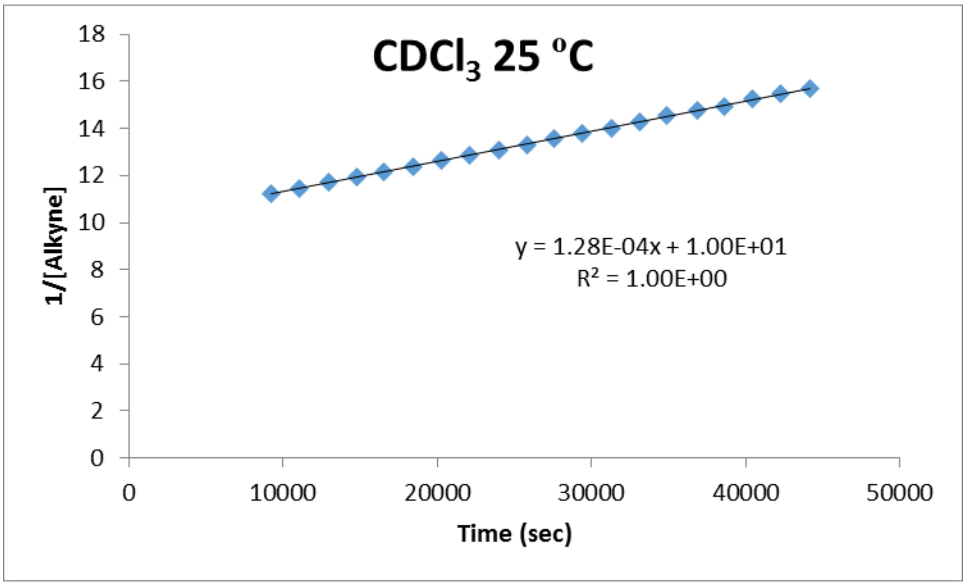
Crystal Data for $C_{16}H_{16}O_2$ (M =240.29 g/mol): orthorhombic, space group Pbcn (no. 60), a = 15.81826(15) Å, b = 9.23296(10) Å, c = 8.32936(9) Å, V = 1216.50(2) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 0.676 mm^{-1}, $Dcalc$ = 1.312 g/cm^3, 9414 reflections measured (11.096° ≤ 2Θ ≤ 156.52°), 1299 unique (R_{int} = 0.0305, R_{sigma} = 0.0147) which were used in all calculations. The final R_1 was 0.0370 (I > 2σ(I)) and wR_2 was 0.1068 (all data).

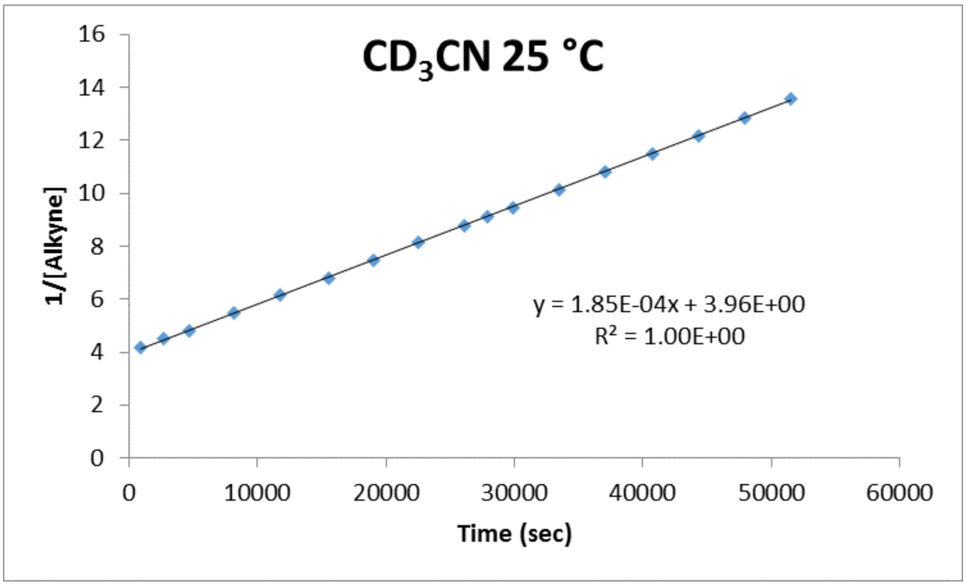
Crystal data and structure refinement for mw9.

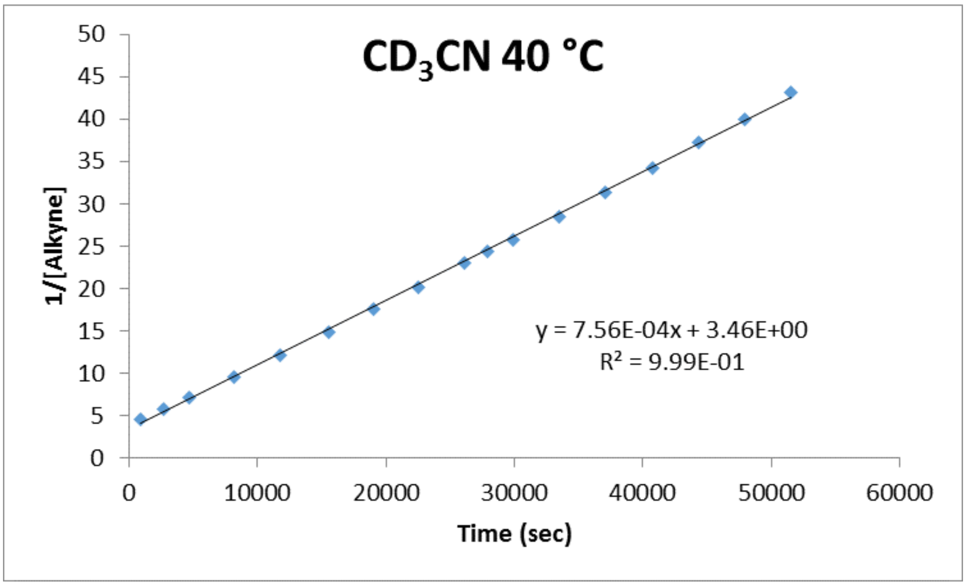
Identification code	mw9
Empirical formula	$C_{16}H_{16}O_2$
Formula weight	240.29
Temperature/K	150(2)
Crystal system	orthorhombic
Space group	Pbcn
a/Å	15.81826(15)
b/Å	9.23296(10)
c/Å	8.32936(9)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1216.50(2)
Z	4
ρ_{calc}g/cm^3	1.312
μ/mm^{-1}	0.676
F(000)	512.0
Crystal size/mm^3	0.6 × 0.4 × 0.2 colourless block
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	11.096 to 156.52
Index ranges	$-19 \leq h \leq 19$, $-10 \leq k \leq 11$, $-9 \leq l \leq 10$
Reflections collected	9414
Independent reflections	1299 [R_{int} = 0.0305, R_{sigma} = 0.0147]
Data/restraints/parameters	1299/0/83
Goodness-of-fit on F^2	1.109
Final R indexes [I>=2σ (I)]	R_1 = 0.0370, wR_2 = 0.1057
Final R indexes [all data]	R_1 = 0.0380, wR_2 = 0.1068
Largest diff. peak/hole / e Å^{-3}	0.24/-0.20

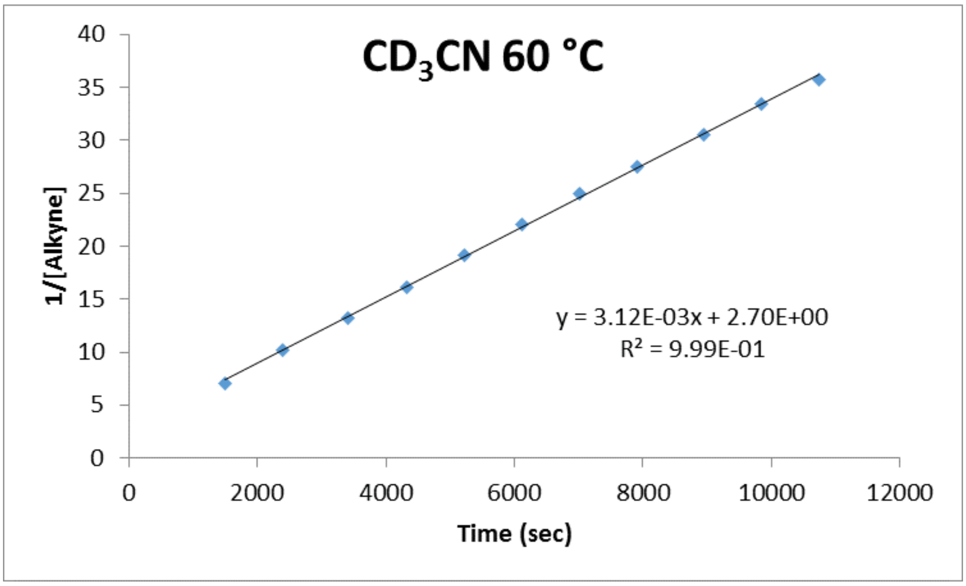
Graphs of Kinetic Data: *General procedure:* A solution of strained alkyne, azide (1:1) ratio and anisole as internal standard, in the solvent indicated, were held at the indicated temperature in a J. Young's NMR tube. The initial concentrations in each case are given in Table 1 of the main paper. At the time intervals indicated on the graph, NMR spectra were recorded. The second order rate constants were calculated by plotting 1/[alkyne] against time.

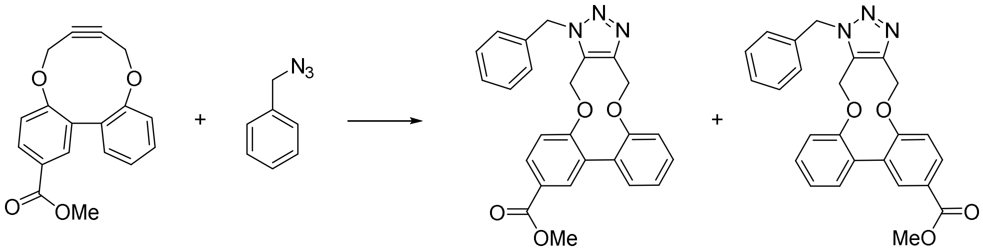


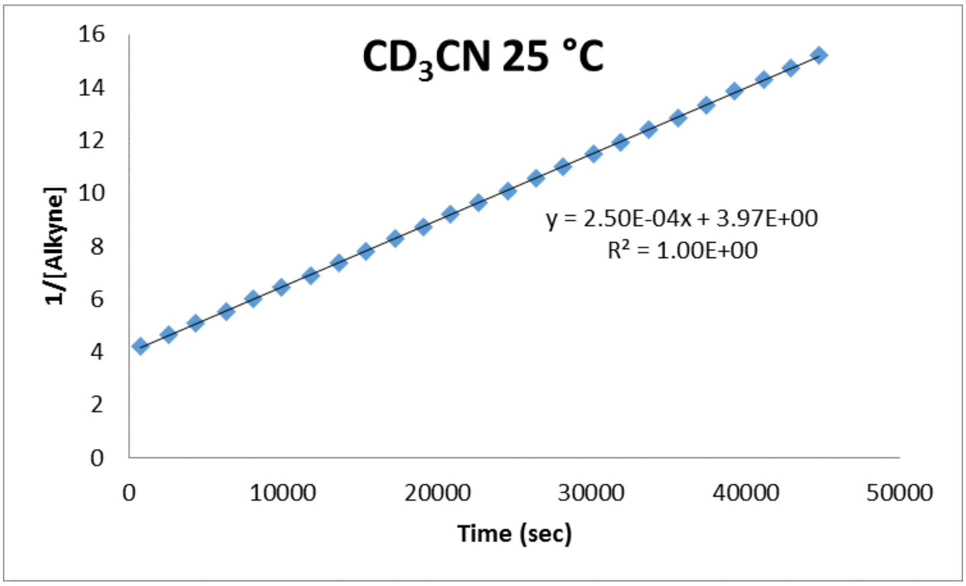


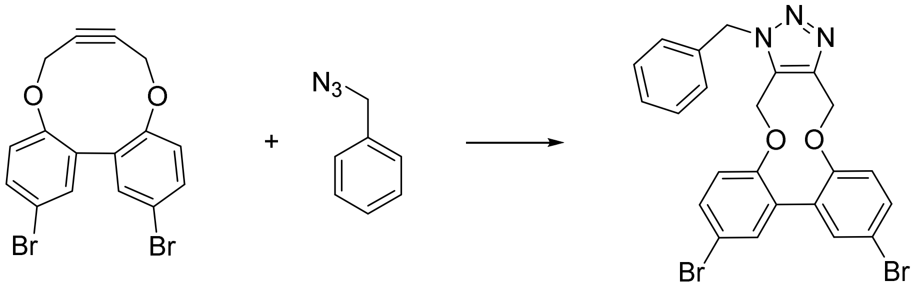

CD$_3$CN 25 °C
1/[Alkyne]
0
2
4
6
8
10
12
14
16
Time (sec)
0
10000
20000
30000
40000
50000
60000
y = 1.85E-04x + 3.96E+00
R² = 1.00E+00

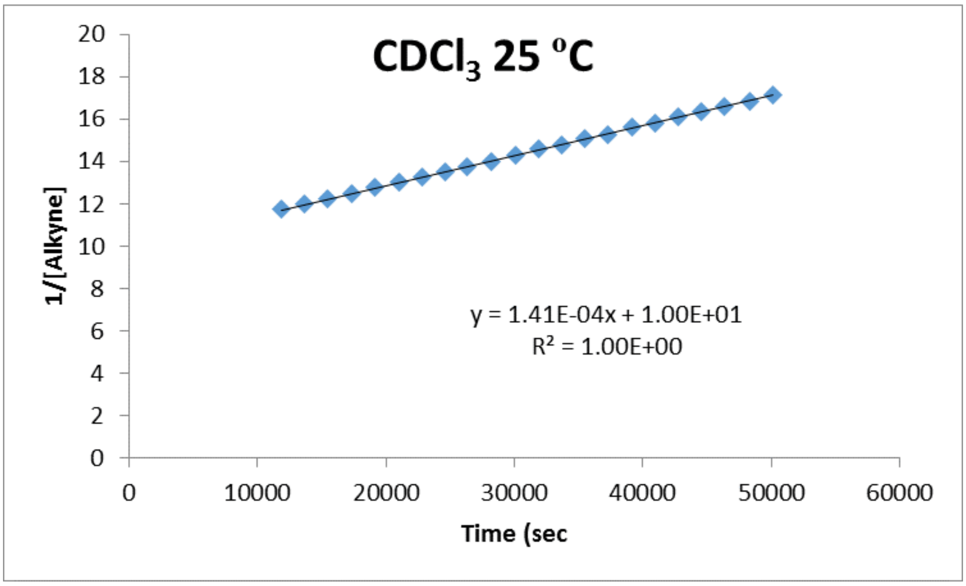

CD$_3$CN 40 °C
1/[Alkyne]
0
5
10
15
20
25
30
35
40
45
50
Time (sec)
0
10000
20000
30000
40000
50000
60000
y = 7.56E-04x + 3.46E+00
R² = 9.99E-01

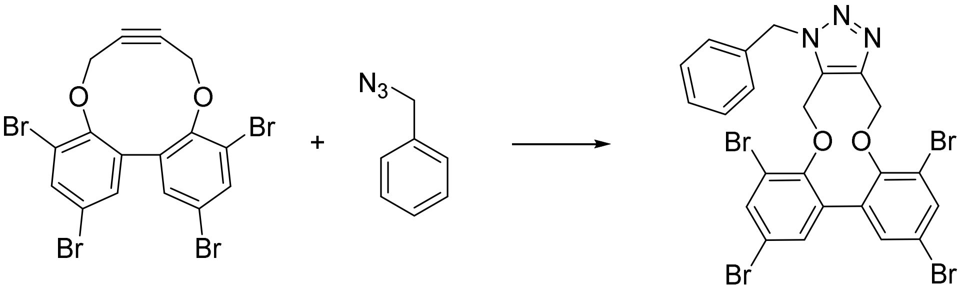

CD$_3$CN 60 °C
1/[Alkyne]
0
5
10
15
20
25
30
35
40
Time (sec)
0
2000
4000
6000
8000
10000
12000
y = 3.12E-03x + 2.70E+00
R² = 9.99E-01

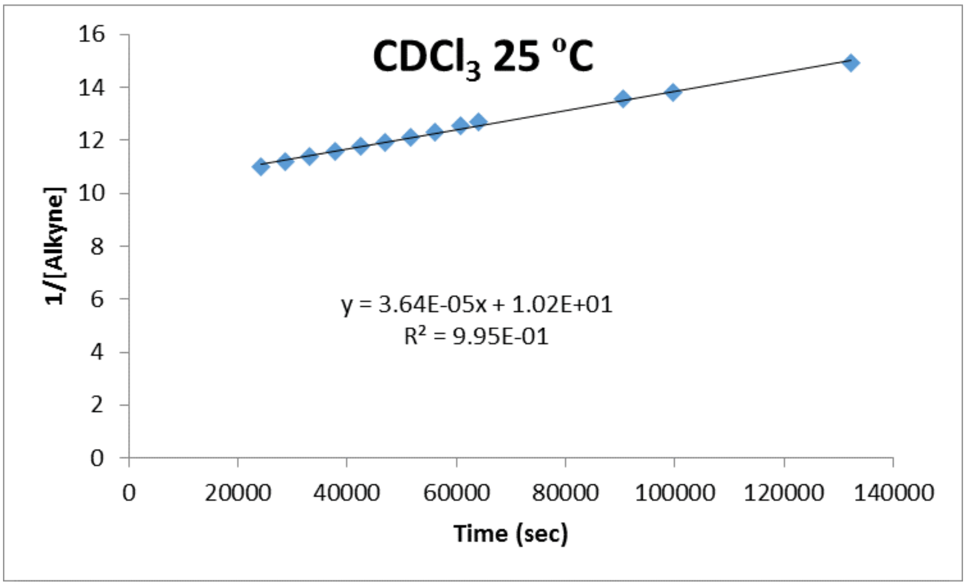

OMe
N3
OMe
MeO

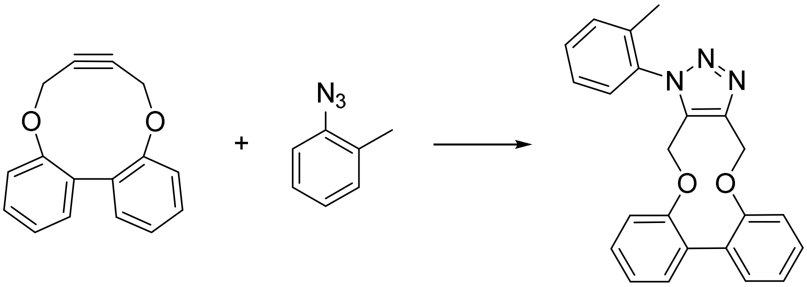

CD$_3$CN 25 °C
1/[Alkyne]
Time (sec)
y = 2.50E-04x + 3.97E+00
R² = 1.00E+00
0
2
4
6
8
10
12
14
16
0
10000
20000
30000
40000
50000

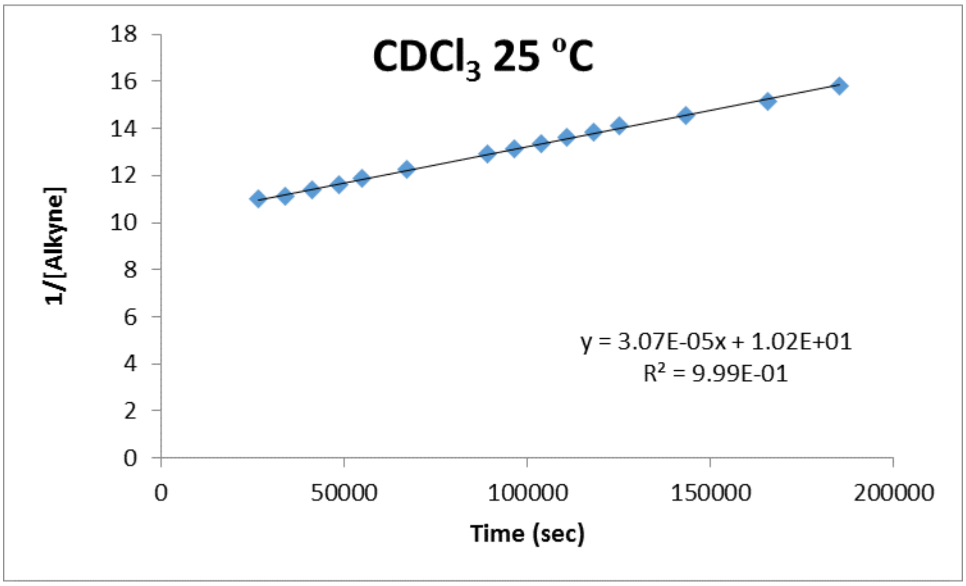


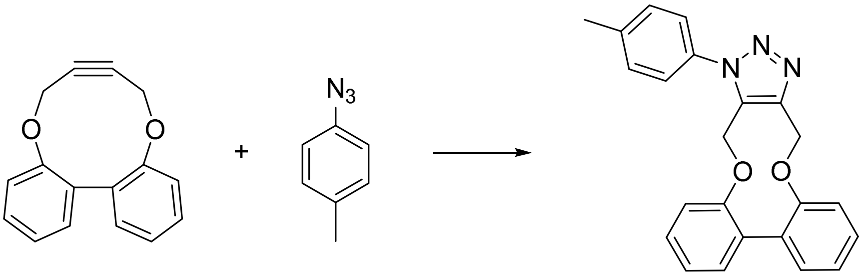

CDCl$_3$ 25 °C
1/[Alkyne]
Time (sec
y = 1.41E-04x + 1.00E+01
R² = 1.00E+00
0
2
4
6
8
10
12
14
16
18
20
0
10000
20000
30000
40000
50000
60000


Br
Br
Br
Br
O
O
+
N3
N
N
N
O
O
Br
Br
Br
Br

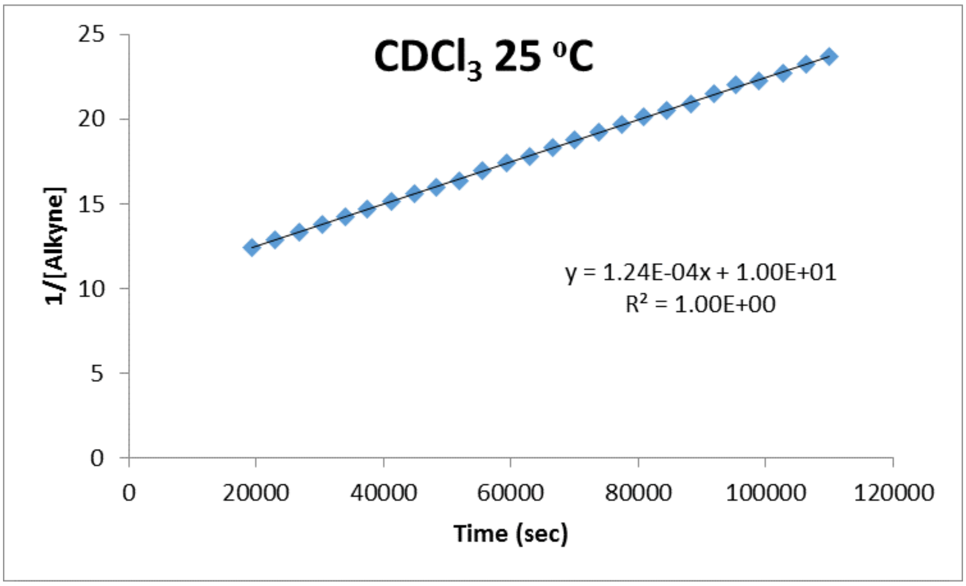

CDCl3 25 °C
y = 3.64E-05x + 1.02E+01
R² = 9.95E-01
1/[Alkyne]
Time (sec)
0
2
4
6
8
10
12
14
16
0
20000
40000
60000
80000
100000
120000
140000

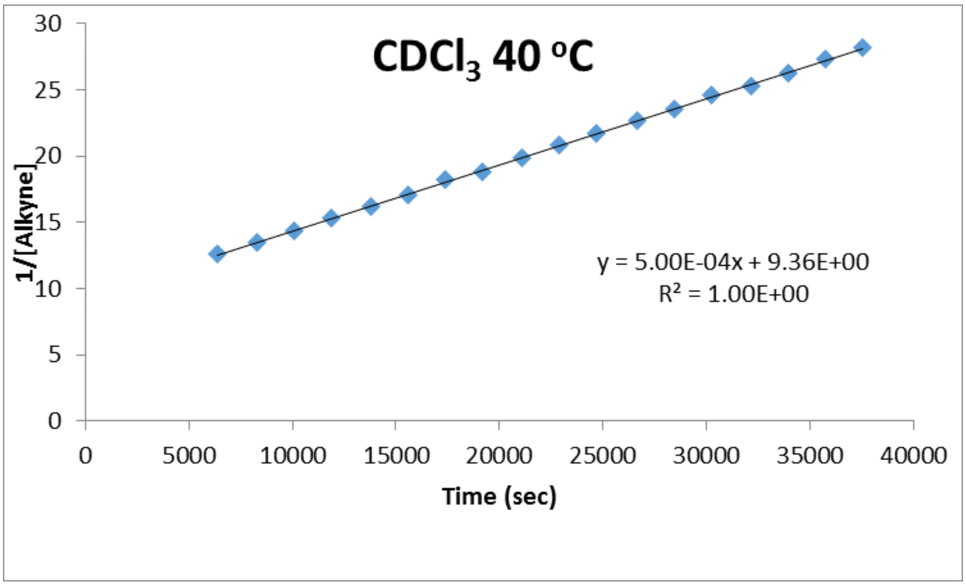

O
O
+
N3
N
N
N
O
O

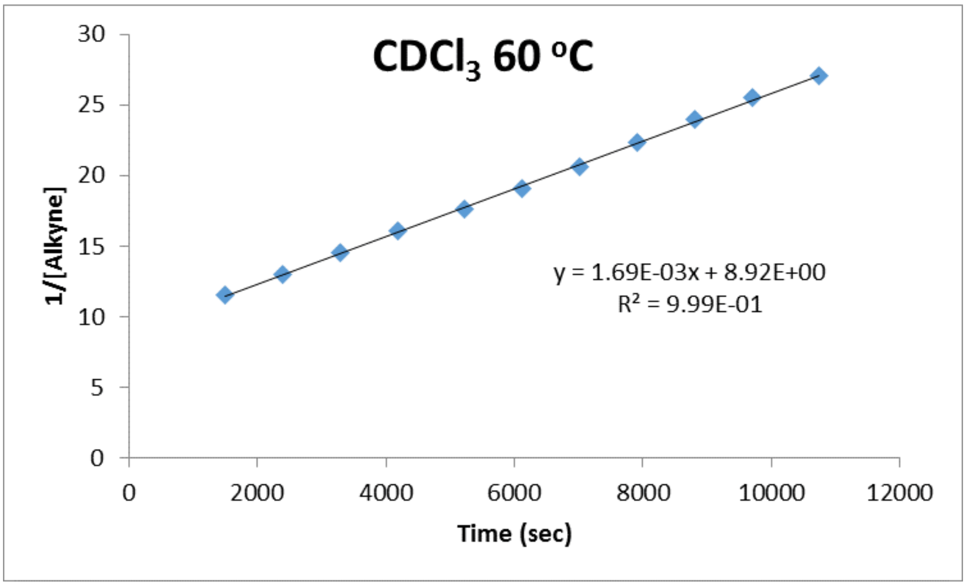




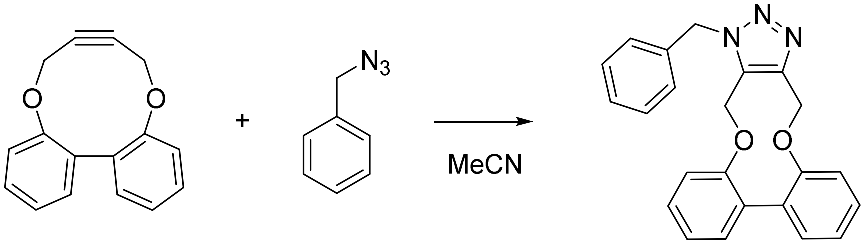
$\Delta E^{\ddagger}$ = 14.6 kcal/mol
$\Delta H^{\ddagger}$ = 14.0 kcal/mol
$\Delta S^{\ddagger}$ = -29.2 cal/mol*K




CDCl3 40 oC
1/[Alkyne]
Time (sec)
y = 5.00E-04x + 9.36E+00
R² = 1.00E+00
0
5
10
15
20
25
30
0
5000
10000
15000
20000
25000
30000
35000
40000

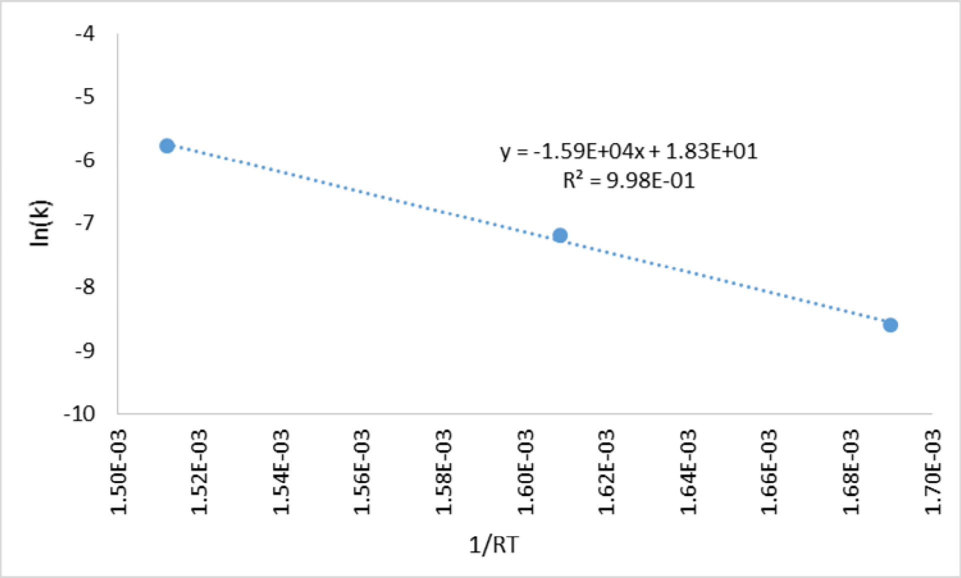

CDCl3 60 oC
1/[Alkyne]
Time (sec)
y = 1.69E-03x + 8.92E+00
R² = 9.99E-01
0
5
10
15
20
25
30
0
2000
4000
6000
8000
10000
12000

Arrhenius and Eyring plots for reactions with benzyl azide and with p-tolylazide.

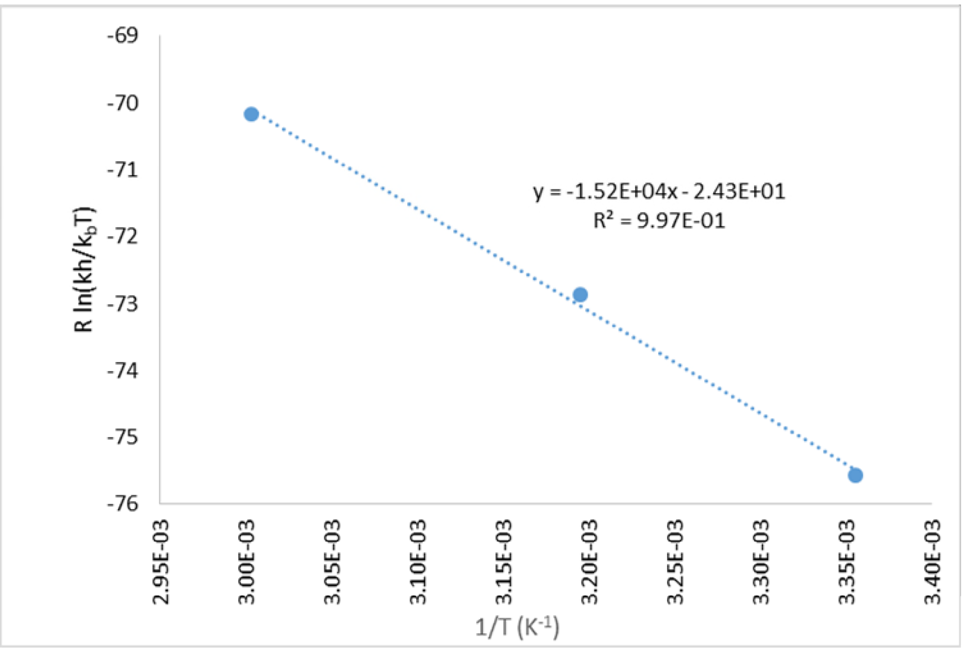


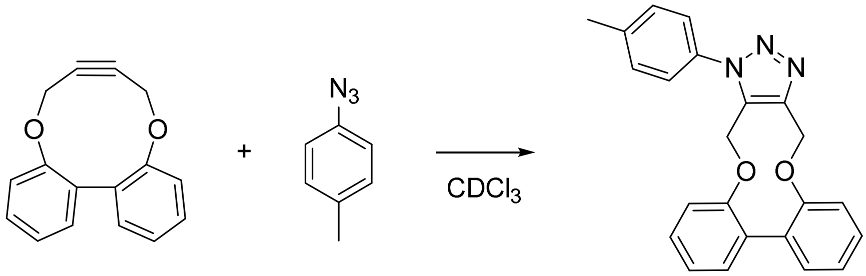
$\Delta E^{\ddagger}$ = 15.9 kcal/mol
$\Delta H^{\ddagger}$ = 15.2 kcal/mol
$\Delta S^{\ddagger}$ = -24.3 cal/mol*K

Arrhenius plot



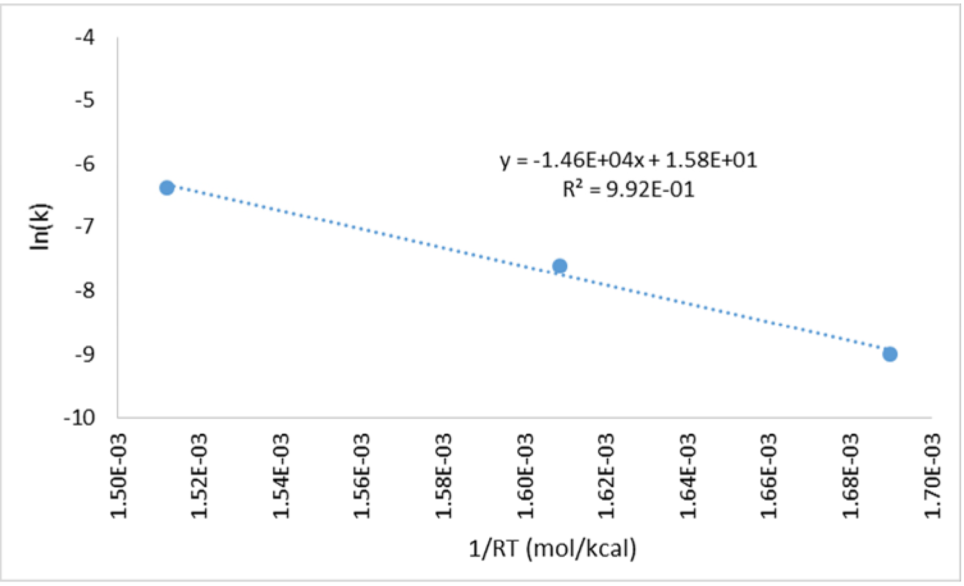
Eyring plot



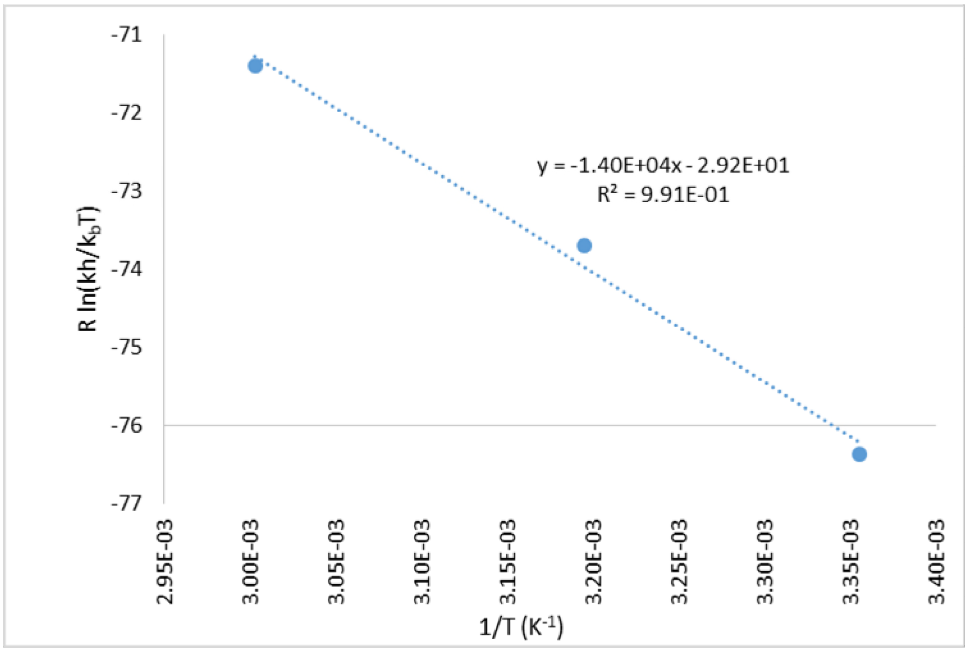


$\Delta E^{\ddagger}$ = 14.6 kcal/mol
$\Delta H^{\ddagger}$ = 14.0 kcal/mol
$\Delta S^{\ddagger}$ = -29.2 cal/mol*K

Arrhenius plot



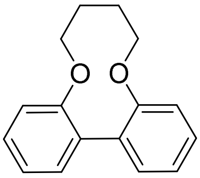
Eyring plot



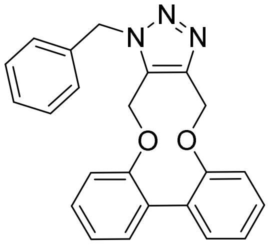
Variable Temperature NMR studies:

The Gibbs free energy $\Delta G^{\#}$ required for atropisomer interconversion has been calculated by variable temperature NMR experiments to be 16.7 kcal mol^{-1} (coalescence temperature for the OCH_2 peaks is 74 °C) for **10** and 16.3 kcal mol^{-1} (coalescence temperature for the OCH_2 peaks is 56 °C) for **5a**.[1] In contrast, the Gibbs free energy $\Delta G^{\#}$ of atropisomer interconversion for **1** cannot be calculated by variable temperature NMR experiments since no broadening has been observed even at 100 °C, which was the highest temperature permitted by the instrument.

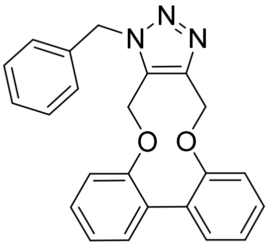
10 =



5a =



Variable Temperature NMR spectra for 5a:



in d_6-DMSO

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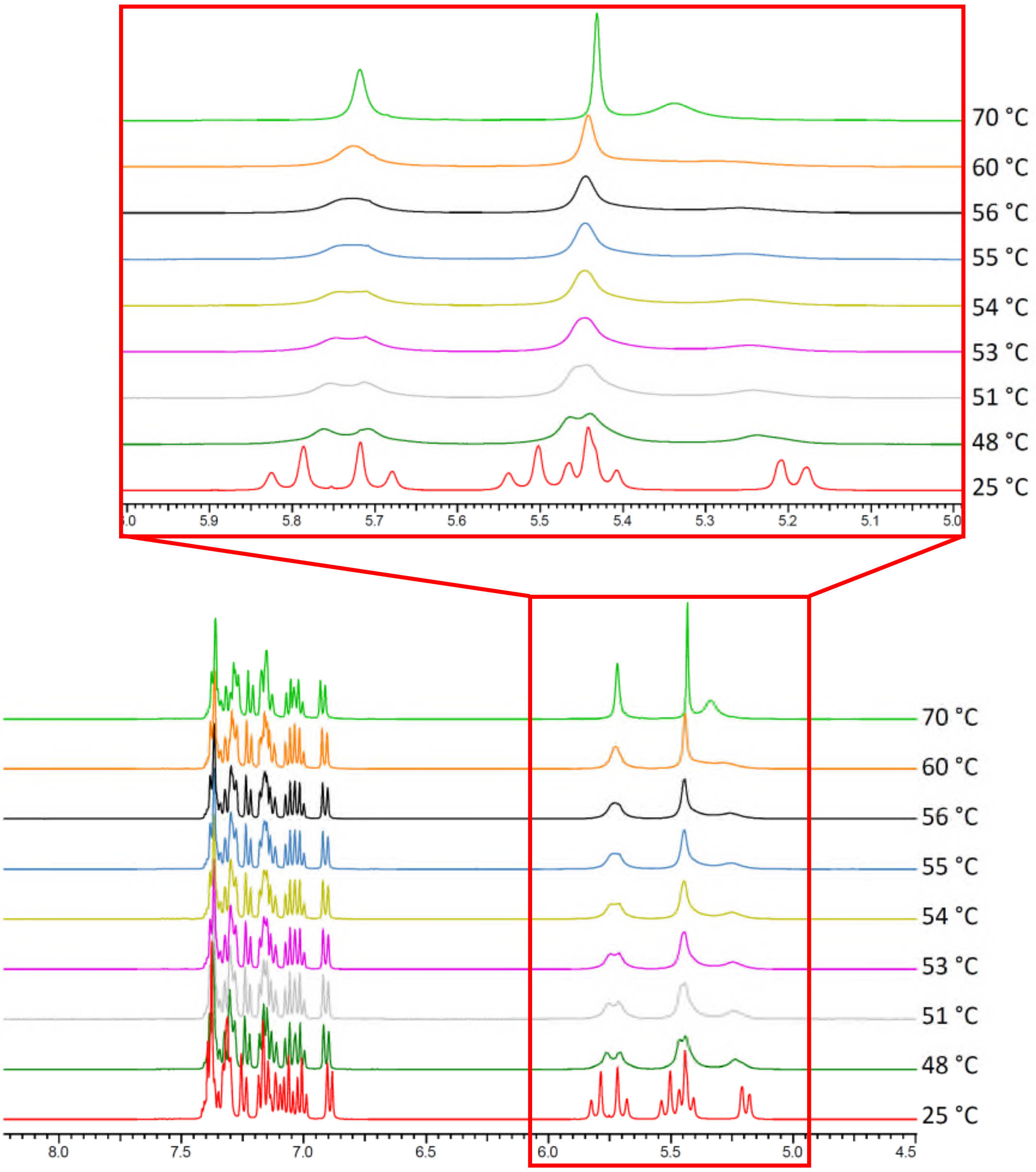
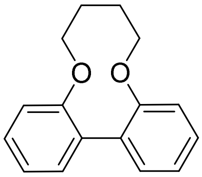
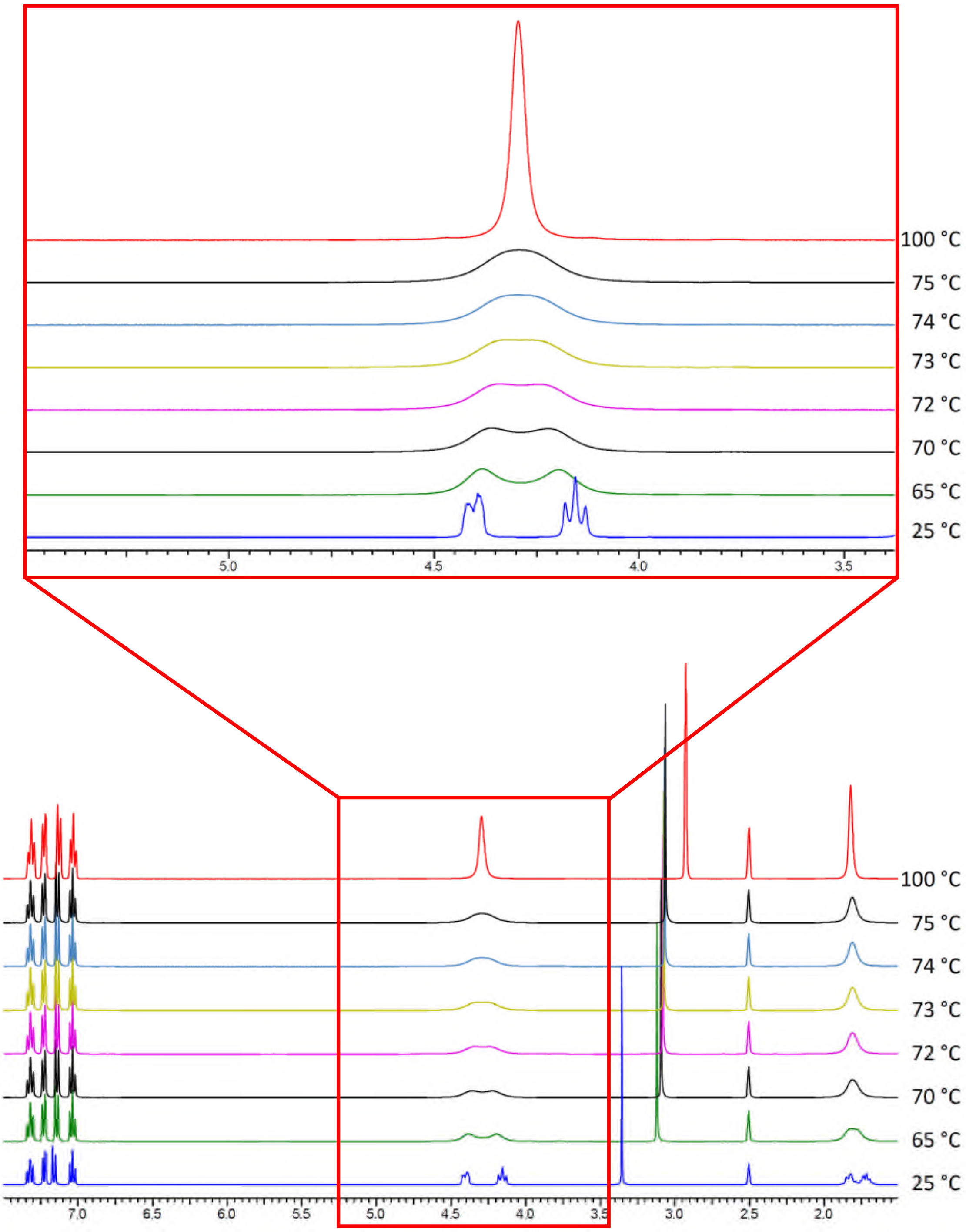
[1] $\Delta G^{\#} = 4.58T_c[9.97+\log(T_c/\delta\nu)]$ where T_c = Temperature of coalescence and $\delta\nu$ = the chemical shift difference in Hz between the two resonance at low temperature; J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance*, McGraw-Hill Book Company, New York, 1959.



Variable Temperature NMR spectra for 10:

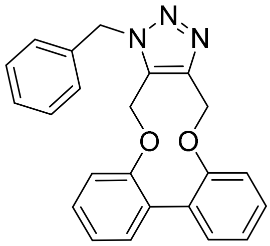


in d_6-DMSO

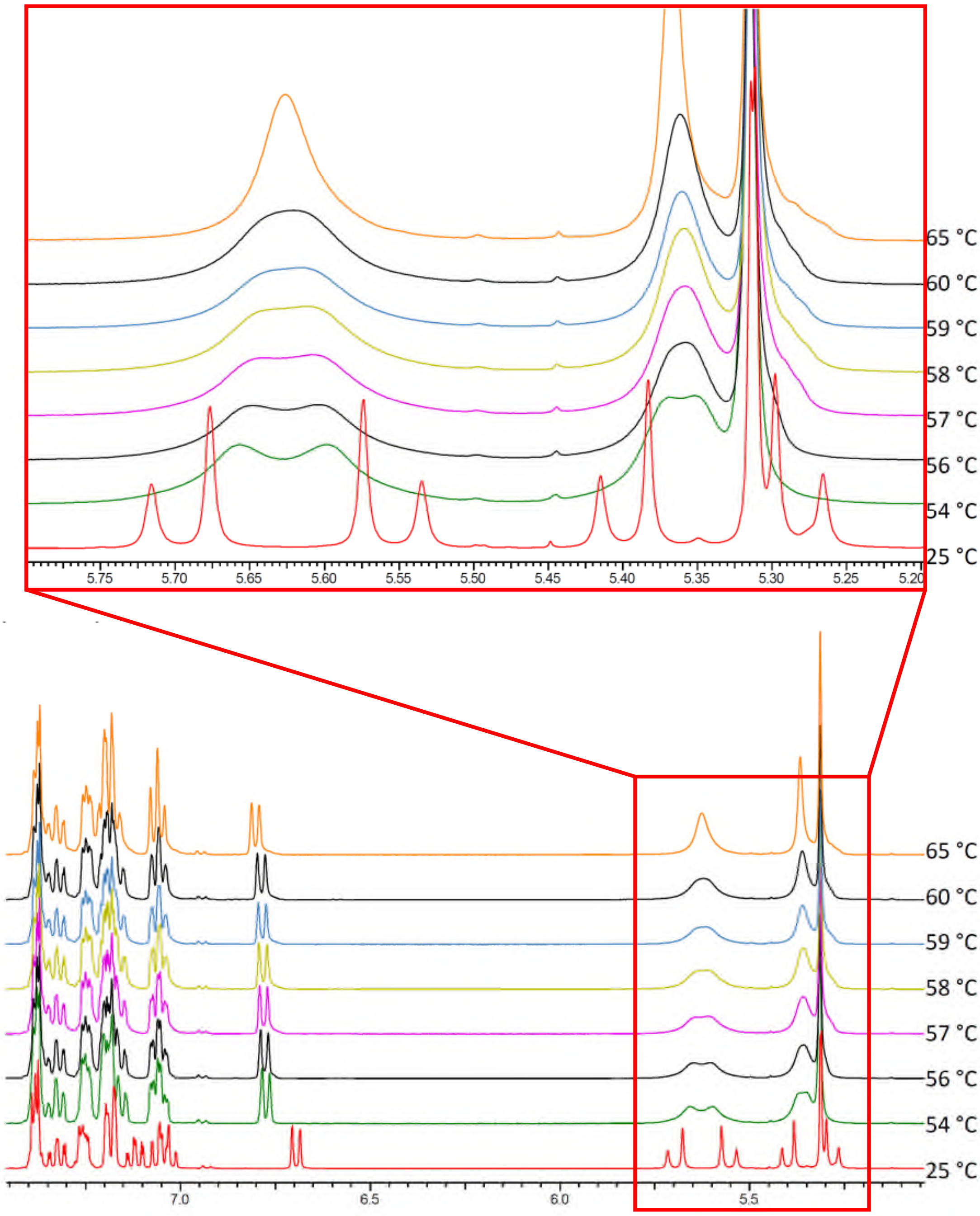


Note a VT-NMR study has been reported on an analogous bipyridyl compound; Durand, J.; Zangrando, E.’ Carfagna, C.; Milani, B. *Dalton Trans.* **2008**, 2171-2182.

Variable Temperature NMR spectra for 5a:



in CD$_3$CN


65 °C
60 °C
59 °C
58 °C
57 °C
56 °C
54 °C
25 °C
5.75
5.70
5.65
5.60
5.55
5.50
5.45
5.40
5.35
5.30
5.25
5.20
7.0
6.5
6.0
5.5