The synthesis of densely functionalised α-acyloxy enaminals and enaminones via a novel homogeneous silver (I) catalysed rearrangement

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Electronic Supplementary Information

General methods

Solvents and reagents: All chemicals and solvents were purchased from Acros, Aldrich, J.T. Baker, Caldeon, Solvay Industries and Fluka and used as received with the following exceptions: deuterated solvents were obtained from ACP Chemicals, Toronto, Canada; tetrahydrofuran (THF), diethyl ether (Et_2O), and toluene were distilled from sodium/benzophenone under an atmosphere of dry nitrogen; dichloromethane (CH_2Cl_2) was distilled from calcium hydride under an atmosphere of dry nitrogen; methanol (MeOH) was distilled from magnesium turnings under an atmosphere of dry nitrogen; triethylamine (NEt_3), *N*,*N*-diisopropylethylamine (Hünig's base) and pyridine were distilled from potassium hydroxide under an atmosphere of dry nitrogen; solid sodium hydride (NaH) was obtained by filtration and washing with *n*-hexanes.

Reaction handling: All non-aqueous reactions were performed in a flame dried round bottom flasks or in non-flame-dried amber 1.5-dram vials. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) unless otherwise noted. TLC was performed on Macherey-Nagel silica gel 60 F_{254} TLC aluminum plates and visualized with UV fluorescence quenching and potassium permanganate ($KMnO_4$) or 2,4-dinitrophenylhydrazine or *p*-anisaldehyde stains.[1] Concentrations under reduced pressure were performed by rotary evaporation at 40°C at the appropriate pressure unless otherwise noted. Column chromatographic purification was performed as flash column chromatography with 0.3–0.5 bar pressure using Silicycle silica gel (40–63, 60 Å) or EcoChrom silica gel (12–26, 60 Å). Distilled technical grade solvents were employed. The yields given refer to chromatographically purified and spectroscopically pure compounds unless stated otherwise.

Melting points: Melting points were measured on a melting point apparatus using open glass capillaries and are uncorrected.

Nuclear Magnetic Resonance (NMR) spectroscopy: ^{1}H, ^{13}C{1H}, DEPTq, COSY, HSQC, and HMBC NMR spectra were obtained on Bruker DRX-500, AV-600 and AV-700 spectrometers. All ^{1}H NMR spectra were referenced relative to $SiMe_4$ through a resonance of the employed deuterated solvent or proteo impurity of the solvent; chloroform (7.26 ppm), acetone (2.05 ppm), DMSO (3.33 ppm) and methanol (3.31 ppm) for ^{1}H NMR; chloroform (77.00 ppm), acetone (29.84 ppm), DMSO (39.52 ppm) and methanol (49.00 ppm) for ^{13}C NMR. All NMR spectra were obtained at RT (*ca*. 22 °C) unless otherwise specified. The data is reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). ^{13}C-NMR spectra were recorded with complete ^{1}H-decoupling. Service measurements were performed by the NMR service team of the Nuclear Magnetic Resonance Facility at McMaster University by Dr. Bob Berno, Dr. Dan Sorensen and Dr. Hilary A. Jenkins.

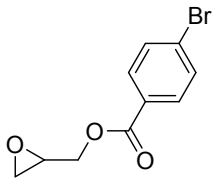
Mass spectrometry: Mass spectrometric analyses were performed as high resolution ESI measurements on a Waters/Micromass QTof Global Ultima (quadrupole time-of-flight mass spectrometer) or high resolution EI in a Waters/Micromass GCT (time-of-flight mass spectrometer) instrument by the mass spectrometry service of the McMaster Regional Centre for Mass Spectrometry (MRCMS) at McMaster University by M.Sc. Sujan Fernando, Tadek Olech and Leah Allan under the supervision of Dr. Kirk Green.

Enantiomeric ratios: Enantiomeric ratios were determined using an Agilent 1220 Infinity HPLC manual injection with a variable wavelength detector, using a Daicel Chiralpak® AD-H column (150 x 4.6 mm, 5μ), *n*-hexane/*i*PrOH (75:25) as a mobile phase; flow rate 0.75 mL/min, column temperature 40°C, λ236 or 287 nm, sample 0.5 mg/mL dissolved in the mobile phase, or a Daicel Chiralpak® AS-RH column (150 x 4.6 mm, 5μ), water/ACN (50:50) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236, sample 0.02 mg/mL dissolved in the mobile phase. The sample was filtered through Parr 0.2 μm GHP Acrodisc (13 mm) syringe filters prior to injections.

Fourier Transform Infrared Spectroscopy (FTIR): FTIR spectra were obtained using a Thermo, Nicolet 6700 FTIR.

Optical rotations: Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter, $[\alpha]$ is given in $deg cm^3 g^{-1} dm^{-1}$ and c is given in $g cm^{-3}$.

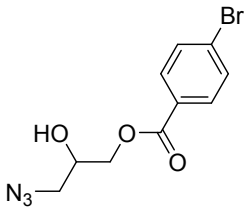
2,3-Epoxypropyl 4-bromobenzoate 8b.



To a solution of (±)-glycidol **7** (1.374 g, 13.93 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added DMAP (0.113 g, 0.93 mmol, 0.05 equiv) and pyridine (1.500 mL, 18.55 mmol, 1.0 equiv). The reaction mixture was stirred for 10 min and 4-bromobenzoyl chloride (4.274 g, 19.48 mmol, 1.1 equiv) was added at 0 °C. The reaction was warmed to room temperature and stirred under nitrogen atmosphere for 8 h, after which TLC (CH_2Cl_2) showed full conversion. The solvent was removed *in vacuo* (35 °C, 0.1 mbar) to produce a yellow oil that was dissolved in EtOAc (30 mL). The organic layer was washed with ammonium chloride (20 mL), sodium bicarbonate (2 x 20 mL), and brine (20 mL). The organic layer was dried with Na_2SO_4 and concentrated to yield 3.345 g of a translucent oil. NMR analysis showed that the product was pure enough for the subsequent reaction, and the crude mixture was used without further purification. To obtain spectroscopic data, a small portion of the crude was purified by flash column chromatography (CH_2Cl_2) to afford a translucent oil.

Yield: 70%; **TLC:** R_f = 0.24 (CH_2Cl_2; UV); **IR** (neat, cm^{-1}) ν 3062, 3002, 2949, 1724, 1591, 1483, 1398, 1271, 1115, 1103, 1012, 756; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.93 – 7.87 (m, 2H, *H*-Ar), 7.59 – 7.54 (m, 2H, *H*-Ar), 4.64 (dd, J = 12.3, 3.0 Hz, 1H, CH_2-OCO), 4.13 (dd, J = 12.3, 6.4 Hz, 1H, CH_2-OCO), 3.31 (dq, J = 4.1, 2.9 Hz, 1H, C*H*), 2.92 – 2.85 (m, 1H, CH_2-O), 2.70 (dd, J = 4.9, 2.6 Hz, 1H, CH_2-O); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.43, 131.70, 131.17, 128.48, 128.31, 65.65, 49.27, 44.58; **HRMS** (ESI): exact mass calculated for $C_{10}H_{10}BrO_3$ [$(M + H)^+$], 256.9813; found 256.9813.

3-Azido-2-hydroxypropyl 4-bromobenzoate 9b.

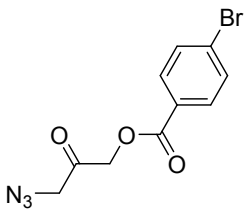


To a mixture of 2,3-epoxypropyl 4-bromobenzoate **8b** (3.299 g, 12.83 mmol) and NH_4Cl (1.373 g, 25.67 mmol, 2.0 equiv) in MeOH and water

(44 mL/6 mL, ~8:1) was added NaN_3 (6.673 g, 102.66 mmol, 8.0 equiv) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated to 1/10 of its volume, diluted with water and extracted with EtOAc (20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated to yield 3.323 g of a translucent oil. NMR analysis showed that the product was pure enough for the subsequent reaction, and the crude mixture was used without further purification. To obtain spectroscopic data, a small portion of the crude was purified by flash column chromatography (CH_2Cl_2).

Yield: 86%; **TLC:** R_f = 0.39 (CH_2Cl_2/ MeOH; 98:2; UV); **IR** (neat, cm^{-1}) ν 3427, 2951, 2103, 1721, 1590, 1398, 1272, 1104, 1012, 756; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 2H, *H*-Ar), 7.54 (d, *J* = 8.6 Hz, 2H, *H*-Ar), 4.36 (dd, *J* = 5.2, 2.8 Hz, 2H, C*H*$_2$-OCO), 4.18 – 4.08 (m, 1H, C*H*-OH), 3.45 (qd, *J* = 12.7, 5.4 Hz, 2H, C*H*$_2$-N_3), 3.08 (br, 1H, O*H*); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.88, 131.73, 131.06, 128.50, 128.17, 68.88, 66.19, 53.42; **HRMS** (ESI): exact mass calculated for $C_{10}H_{11}N_3O_3Br$ [$(M + H)^+$], 299.9984; found 299.9980.

3-Azido-2-oxopropyl 4-bromobenzoate 10b.



3-Azido-2-hydroxypropyl 4-bromobenzoate **9b** (3.301 g, 14.92 mmol), $NaHCO_3$ (3.510 g, 41.78 mmol, 2.8 equiv), NaBr (0.152 g, 1.49 mmol, 0.1 equiv) and TEMPO (0.047 g, 0.30 mmol, 0.02 equiv) were dissolved in CH_2Cl_2 (50 mL). The mixture was cooled to 0 °C, and cold 0.83 M NaOCl (38.148 mL, 74.61 mmol, 5.0 equiv) buffered with $NaHCO_3$ (3.510 g, 41.78 mmol, 2.8 equiv) was added slowly. The reaction turned from red to orange and produced a white-yellow precipitate in the organic layer after 30 min, of which TLC analysis (CH_2Cl_2) showed reaction completion. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The organic extracts were combined, dried with Na_2SO_4 and concentrated to yield 3.247 g of a white solid.

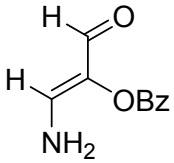
Yield: 73%; **TLC:** R_f = 0.41 (CH_2Cl_2; UV); **M.P.:** 71-72 °C (recrystallized from CH_2Cl_2); **IR** (neat, cm^{-1}) ν 2095, 1736, 1718, 1590, 1412, 1278, 1080, 756; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 1H, *H*-Ar), 7.64 – 7.59 (m, 1H, *H*-Ar), 4.98 (s, 1H, C*H*$_2$-OCO), 4.13 (s, 1H, C*H*$_2$-N_3); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 198.12, 165.03, 131.96, 131.36, 128.99, 127.58, 67.09,

55.39; **HRMS** (ESI): exact mass calculated for $C_{10}H_9N_3O_3Br$ [(M + H)$^+$], 297.9827; found 297.9815.

General procedure for the silver catalyzed rearrangement.

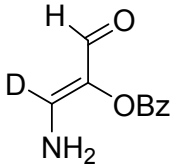
Into a 1 dram vial, the corresponding α azido, α'-*o*-benzoyl ketone (0.054 mmol, 1.0 equiv) and silver catalyst **13** (0.0054 mmol, 0.1 equiv) were dissolved in THF (0.5 mL) and stirred at 60 °C for 1h (acyclic substrates)/3h (cyclic substrates) in nitrogen atmosphere. The reaction mixture was cooled to room temperature and the solvent was evaporated by nitrogen flush. The crude reaction was separated by flash chromatography (eluent CH_2Cl_2/MeOH 100:0 to 95:5) to give the resultant α-*o*-benzoyl, β-amino α, β–unsaturated aldehydes/ketones.

1-amino-3-oxoprop-1-en-2-yl benzoate 11a.

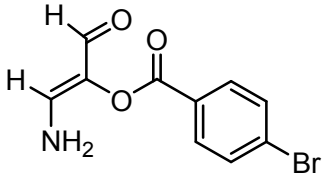


Compound **10a** was prepared from glycidol as previously described.[1] The title compound **11a** was prepared from **10a** following the general procedure and isolated as an oil. **Yield:** 91%; **TLC:** R_f = 0.2 (EtOAc/hexane, 7:3). **^{1}H NMR** (600 MHz, Acetone) δ 8.89 (s, 1 H, *H*-C=O), 8.09 (d, J = 8.10 Hz, 2 H, *H*-Bz), 7.64 (m, 1 H, *H*-Bz), 7.54 (t, J = 7.96 Hz , 2 H, *H*-Bz,), 7.33 (m, 1H, *H*C=C) ppm;**^{13}C NMR** (151 MHz, Acetone) δ 179.68, 163.94, 146.67, 133.97, 131.01, 130.85, 129.30 ppm; **HRMS** (ESI): exact mass calculated for $C_{10}H_9NO_3$ [(M + H)$^+$], 192.0661; found 192.0655.

Compound 11c was prepared from **10c** following the general procedure and was isolated as solid. **Yield**: 91%; **TLC:** R_f = 0.2 (EtOAc/hexane, 7:3); **^{1}H NMR** (600 MHz,$CDCl_3$) δ 8.96 (s, 1 H, *H*-C=O), 8.16 (d, J = 8.06 Hz, 2 H, *H*-Bz), 7.62 (t, J = 7.35, 1 H, *H*-Bz), 7.54 (t, J = 8.13 Hz , 2 H, *H*-Bz,) ppm; **HRMS** (ESI): exact mass calculated for $C_{10}H_8DNO_3$ [(M + H)$^+$], 193.0723; found 193.0715.



1-amino-3-oxoprop-1-en-2-yl 4-bromobenzoate 11b



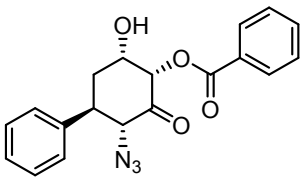
The title compound was prepared from **10b** following the general procedure and was isolated as a white solid. **Yield:** 85%; **TLC:** R_f=

0.3 (EtOAc/hexane, 7:3); **^{1}H NMR** (600 MHz, Acetone) δ 8.90 (s, 1 H, *H*-C=O), 8.04 (d, J = 8.69 Hz, 2 H, *H*-Bz), 7.77 (d, J = 8.69 Hz, 2 H, *H*-Bz), 7.35 (m, 1 H, *H*C=C) ppm; **^{13}C NMR** (151 MHz, Acetone) δ 179.53, 163.34, 146.67, 146.55, 132.67, 132.60, 130.16, 129.63, 128.38 ppm; **HRMS** (ESI): exact mass calculated for $C_{10}H_8BrNO_3$ [(M + H)$^+$], 268.9688; found 268.9687.

General procedure for catalytic asymmetric reactions.[2]

(*E*)-α,β–unsaturated aldehydes were prepared following the procedure of McNulty et al.[3] A solution of the α, β-unsaturated aldehyde (0.11 mmol, 1.05 equiv) and the (*2R*)- or (*2S*)-diphenylprolinol silyl ether (0.01 mmol, 0.10 equiv) in CH_2Cl_2 (0.22 mL, 0.5 M) was stirred for 10 min. α-azido ketone (0.10 mmol) was added dropwise for 10 min. The solution was stirred for 10 min at RT and DABCO (0.01 mmol, 0.10 equiv) was added in one portion. The reaction was stirred at RT for 3-4 h, after which HPLC showed full conversion; the d.r. was determined at this stage. The solvent was evaporated (60 °C, 100 Torr), and the precipitated solid was filtered and washed with cold MeOH to afford the desired product. The enantiomeric purity was determined after the filtration using HPLC.

(1*S*,3*R*,4*R*,6*S*)-3-Azido-6-hydroxy-2-oxo-4-phenylcyclohexyl benzoate 4a.



A solution of cinnamaldehyde (0.024 g, 0.11 mmol, 1.05 equiv) and (*R*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (0.0036 g, 0.011 mmol, 0.10 equiv) in CH_2Cl_2 (0.240 mL) was stirred for 10 min. 3-Azido-2-oxopropyl benzoate (0.024 g, 0.10 mmol) was added drop-wise over 10 min. The solution was stirred for 10 min at RT and DABCO (0.0012 g, 0.010 mmol, 0.10 equiv) was added in one portion. The reaction was stirred at RT for 4 h, after which HPLC showed full conversion; the d.r. was determined at this stage (96:4). The solvent was evaporated obtaining a brown suspension that was filtered and washed with cold MeOH (4 x 0.20 mL) to obtain 0.027 g of a white solid (single diastereomer, after filtration). **Yield:** 71%; **DSC**: Exothermic transition, onset at 200.3 °C; **TLC:** R_f = 0.66 (CH_2Cl_2 / MeOH; 98:2; UV); **M.P.:** 147-148 °C (material solidified from acetone); **IR** (neat, cm^{-1}) ν 3461, 2095, 1707, 1273, 1131, 703; **^{1}H NMR** (600 MHz, Acetone) δ 8.19 (dd, J = 8.2, 1.1 Hz, 2H, *H*-Bz), 7.68 (t, J = 7.4 Hz, 1H, *H*-Bz), 7.55 (t, J = 7.8 Hz, 2H, *H*-Bz), 7.49 (d, J = 7.2 Hz, 2H, *H*-Ph), 7.41 (t, J =

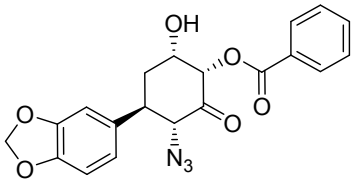
7.7 Hz, 2H, *H*-Ph), 7.31 (t, *J* = 7.4 Hz, 1H, *H*-Ph), 5.84 (d, *J* = 2.8 Hz, 1H, C*H*-OBz), 5.13 (d, *J* = 2.2 Hz, 1H, O*H*), 4.81 (d, *J* = 12.0 Hz, 1H, C*H*-N_3), 4.73 (br, 1H, C*H*-OH), 3.51 (td, *J* = 12.5, 4.0 Hz, 1H, C*H*-Ph), 2.61 (t, *J* = 13.7 Hz, 1H, CH_2), 2.25 (dt, *J* = 14.4, 4.0 Hz, 1H, CH_2); **^{13}C NMR** (151 MHz, Acetone) δ 198.90, 165.79, 142.29, 134.28, 130.74, 130.66, 129.66, 129.39, 128.52, 128.14, 80.07, 70.71, 70.51, 45.37, 37.68, 29.84; **M.P.:** 146-148 °C (material solidified from acetone); **$[\alpha]^{22}_D$** = +62 (*c* = 0.24, Acetone, *l* = 1 dm); **e.e.:** τ_{major} = 12.3 min, τ_{minor} = 8.5 min (99% e.e.). Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5μ), MeCN/Water (50:50) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 24:1 (HPLC).

(1*R*,3*S*,4*S*,6*R*)-3-Azido-6-hydroxy-2-oxo-4-phenylcyclohexyl benzoate *ent*-4a

This compound was prepared in the same way as using (*S*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether and DABCO. The purification was carried out by

Yield: 70% (isolated); **$[\alpha]^{23}_D$** = -60 (*c* = 0.59, Acetone, *l* = 1 dm); **HRMS** (ESI): exact mass calculated for $C_{19}H_{18}N_3O_4$ [$(M + H)^+$], 352.1297; found 352.1308; **e.e.:** τ_{major} = 8.5 min, τ_{minor} = 12.3 min (>98% e.e.). Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5μ), MeCN/Water (50:50) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236. **d.r.:** 24:1 (HPLC).

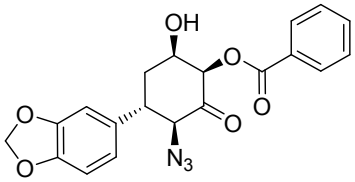
(1*S*,3*R*,4*R*,6*S*)-3-Azido-4-(1,3-benzodioxol-5-yl)-6-hydroxy-2-oxocyclohexyl benzoate 4b.



Yield: 73%; **M.P.:** 179-180 °C (material solidified from acetone); **TLC:** R_f = 0.62 (CH_2Cl_2 / MeOH; 98:2; UV); **$[\alpha]^{23}_D$** = +75.4 (*c* = 0.11, Acetone, *l* = 1 dm); **IR** (neat, cm^{-1}) ν 3475, 2907, 2101, 1709, 1505, 1494, 1444, 1328, 1248, 1128, 1100, 1040, 935, 821; **^{1}H NMR** (600 MHz, Acetone) δ 8.18 (dd, *J* = 8.3, 1.2 Hz, 2H, *H*-Ph), 7.70 – 7.65 (m, 1H, *H*-Ph), 7.54 (t, *J* = 7.8 Hz, 2H, *H*-Ph), 7.08 (d, *J* = 1.7 Hz, 1H, *H*-Ar), 6.92 (dd, *J* = 7.9, 1.7 Hz, 1H, *H*-Ar), 6.85 (d, *J* = 7.9 Hz, 1H, *H*-Ar), 6.02 (s, 2H, OCH_2O), 5.81 (dd, *J* = 3.0, 0.9 Hz, 1H, C*H*-OBz), 4.72 (d, *J* = 12.1 Hz, 1H, C*H*-N_3), 4.70 (br, 1H, C*H*-OH), 3.44 (td, *J* = 12.5, 4.0 Hz, 1H, C*H*-Ar), 2.58 (dd, *J* = 14.5, 1.9 Hz, 1H, CH_2), 2.23 (dt, *J* = 14.4, 4.0 Hz, 1H, CH_2); **^{13}C NMR** (151 MHz, Acetone) δ 198.76, 165.80, 149.06, 147.78, 136.16, 134.28, 130.73, 130.65, 129.38, 122.00, 109.10, 108.39, 102.10, 80.05, 70.76, 70.60, 45.18, 37.73; **HRMS** (ESI): exact mass

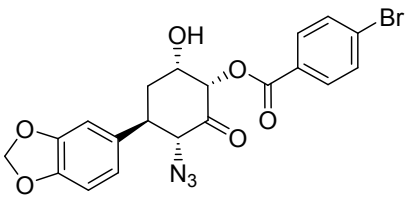
calculated for $C_{20}H_{17}N_3NaO_6$ [(M + Na)$^+$], 418.1015; found 418.1015; **e.e.:** was determined after the filtration. τ_{major} = 12.8 min, τ_{minor} = 8.7 min (>99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5µ), Water/MeCN (60:40) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 96:4 (HPLC).

(1*R*,3*S*,4*S*,6*R*)-3-Azido-4-(1,3-benzodioxol-5-yl)-6-hydroxy-2-oxocyclohexyl benzoate *ent*-4b.



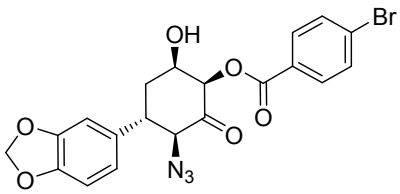
The title compound was isolated by filtration, as a white solid. **Yield:** 70%; **[α]$^{24}_D$** = -67 (*c* = 0.46, Acetone, *l* = 1 dm); **e.e.:** τ_{major} = 8.7 min, τ_{minor} = 12.8 min (>99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5µ), Water/MeCN (60:40) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 96:4 (HPLC).

(1*S*,3*R*,4*R*,6*S*)-3-Azido-4-(1,3-benzodioxol-5-yl)-6-hydroxy-2-oxocyclohexyl 4-bromobenzoate 4c



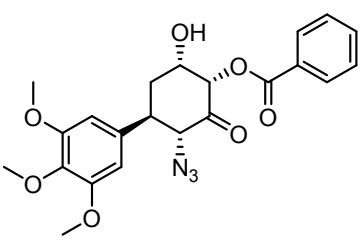
Yield: 62%; **M.P.:** 203-208 °C (material solidified from acetone); **[α]$^{24}_D$** = +88 (*c* = 0.65, Acetone, *l* = 1 dm); **IR** (neat, cm^{-1}) ν 3481, 2925, 2104, 1711, 1590, 1504, 1488, 1273, 1128, 1099, 1037, 1011, 932, 754 ; **^{1}H NMR** (600 MHz, Acetone) δ 8.11 (d, *J* = 8.6 Hz, 2H, *H*-Bz), 7.75 (d, *J* = 8.6 Hz, 2H, *H*-Bz), 7.07 (d, *J* = 1.7 Hz, 1H, *H*-Ar), 6.92 (dd, *J* = 8.0, 1.7 Hz, 1H, *H*-Ar), 6.85 (d, *J* = 7.9 Hz, 1H, *H*-Ar), 6.02 (s, 2H, OC*H*$_2$O), 5.81 (d, *J* = 3.0 Hz, 1H, C*H*-OBz), 4.73 (d, *J* = 12.0 Hz, 1H, C*H*-N$_3$), 4.70 (br, 1H, C*H*-OH), 3.43 (td, *J* = 12.5, 4.0 Hz, 1H, C*H*-Ar), 2.58 (dd, *J* = 13.7, 1.9 Hz, 1H, C*H*$_2$), 2.23 (dt, *J* = 14.4, 4.0 Hz, 1H, C*H*$_2$); **^{13}C NMR** (151 MHz, Acetone) δ 198.65, 165.13, 149.07, 147.80, 136.12, 132.72, 132.58, 129.79, 128.80, 122.01, 109.10, 108.38, 102.11, 80.30, 70.75, 70.41, 45.17, 37.62; **HRMS (ESI):** exact mass calculated for $C_{20}H_{17}BrN_3O_6$ [(M + H)$^+$], 474.0301, found: 474.0301; **e.e.:** τ_{major} = 10.1 min, τ_{minor} = 6.5 min (>99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5µ), Water/MeCN (60:40) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 96:4 (HPLC).

(1*R*,3*S*,4*S*,6*R*)-3-Azido-4-(1,3-benzodioxol-5-yl)-6-hydroxy-2-oxocyclohexyl 4-bromobenzoate *ent*-4c



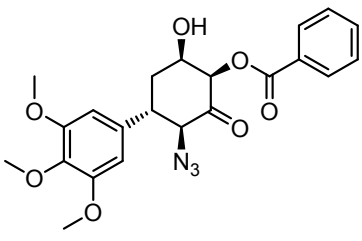
The title compound was isolated by filtration, as a white solid. **Yield:** 65%; **TLC:** R_f = 0.47 (CH_2Cl_2 / MeOH; 98:2; UV); **[α]$^{22}_{D}$** = -81 (*c* = 0.73, Acetone, *l* = 1 dm);; **HRMS (ESI):** exact mass calculated for $C_{20}H_{17}BrN_3O_6$ [(M + H)$^+$], 474.0301, found: 474.0301; **e.e.:** was determined after the filtration. τ_{major} = 6.5 min, τ_{minor} = 10.1 min (>99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5μ), Water/MeCN (60:40) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 96:4 (HPLC); **X-ray:** Cristal structure was previously reported.

(1*S*,3*R*,4*R*,6*S*)-3-Azido-6-hydroxy-2-oxo-4-(3,4,5-trimethoxyphenyl)cyclohexyl benzoate 4d.



The title compound was isolated by filtration, as a white solid. **Yield:** 66%; **M.P.:** 145-148 °C (material solidified from acetone); **[α]$^{24}_{D}$** = +59 (*c* = 2.68, Acetone, *l* = 1 dm); **IR** (neat, cm^{-1}) ν 3473, 2937, 2840, 2102, 1722, 1591, 1509, 1275, 1127, 1003, 711; **^{1}H NMR** (600 MHz, Acetone) δ 8.18 (dd, *J* = 8.2, 1.0 Hz, 2H, *H*-Ph), 7.68 (t, *J* = 7.4 Hz, 1H, *H*-Ph), 7.54 (t, *J* = 7.8 Hz, 2H, *H*-Ph), 6.84 (s, 2H, *H*-Ar), 5.78 (d, *J* = 2.8 Hz, 1H, C*H*-OBz), 5.13 (d, *J* = 2.1 Hz, 1H, O*H*), 4.82 (d, *J* = 12.0 Hz, 1H, C*H*-N_3), 4.71 (br, 1H, C*H*-OH), 3.87 (s, 6H, *m*CH_3O), 3.74 (s, 3H, *p*CH_3O), 3.44 (td, *J* = 12.5, 4.1 Hz, 1H, C*H*-Ar), 2.63 (t, *J* = 13.7 Hz, 1H, CH_2), 2.25 (dt, *J* = 14.4, 4.1 Hz, 1H, CH_2); **^{13}C NMR** (151 MHz, Acetone) δ 198.80, 165.82, 154.64, 138.37, 137.89, 134.29, 130.74, 130.63, 129.39, 105.83, 80.11, 70.71, 70.63, 60.49, 56.49, 45.83, 37.70; **HRMS (ESI):** exact mass calculated for $C_{22}H_{24}N_3O_7$ [(M + H)$^+$], 442.1614; found 442.1599; **e.e.:** τ_{major} = 5.6 min, τ_{minor} = 6.8 min (99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5μ), Water/MeCN (50:50) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 96:4 (HPLC).

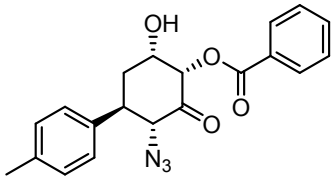
(1*R*,3*S*,4*S*,6*R*)-3-Azido-6-hydroxy-2-oxo-4-(3,4,5-trimethoxyphenyl)cyclohexyl benzoate *ent*-4d.



The title compound was isolated by filtration, as a white solid.

Yield: 63%; **TLC:** R_f = 0.46 (CH_2Cl_2 / MeOH; 98:2; UV); **[α]$^{23}_{D}$** = -66 (*c* = 0.96, Acetone, *l* = 1 dm); **M.P.:** 145-147 °C (material solidified from acetone); **e.e.:** τ_{major} = 5.6 min, τ_{minor} = 6.8 min (>99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5μ), Water/MeCN (50:50) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 96:4 (HPLC).

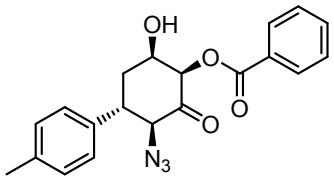
(1*S*,3*R*,4*R*,6*S*)-3-Azido-6-hydroxy-2-oxo-4-*p*-tolylcyclohexyl benzoate 4e.



The title compound was isolated by filtration, as a white solid.

Yield: 66%; **M.P.:** 158-160 °C (material solidified from acetone**;** **[α]$^{24}_{D}$** = +69 (*c* = 0.66, Acetone, *l* = 1 dm);); **IR** (neat, cm^{-1}) ν 3470, 2906, 2094, 1752, 1704, 1265, 1215, 1132, 1104, 906, 809, 712; **^{1}H NMR** (600 MHz, Acetone) δ 8.19 (dd, *J* = 8.3, 1.2 Hz, 2H, *H*-Ph), 7.68 (t, *J* = 7.4 Hz, 1H, *H*-Ph), 7.54 (t, *J* = 7.8 Hz, 2H, *H*-Ph), 7.36 (d, *J* = 8.0 Hz, 2H, *H*-Ar), 7.21 (d, *J* = 7.9 Hz, 2H, *H*-Ar), 5.83 (d, *J* = 3.0 Hz, 1H, C*H*-OBz), 5.13 – 5.09 (m, 1H, O*H*), 4.76 (d, *J* = 12.0 Hz, 1H, C*H*-N_3), 4.72 (br, 1H, C*H*-OH), 3.47 (td, *J* = 12.5, 4.0 Hz, 1H, C*H*-Ar), 2.59 (t, *J* = 13.7 Hz, 1H, CH_2), 2.33 (s, 3H, CH_3), 2.23 (dt, *J* = 14.4, 4.0 Hz, 1H, CH_2); **^{13}C NMR** (151 MHz, Acetone) δ 198.92, 165.79, 139.27, 137.59, 134.27, 130.73, 130.66, 130.26, 129.38, 128.38, 80.07, 70.70, 70.64, 44.98, 37.73, 21.06; **e.e.:** τ_{major} = 16.3 min, τ_{minor} = 10.2 min (>99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5μ), MeCN/Water (50:50) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 24:1 (HPLC).

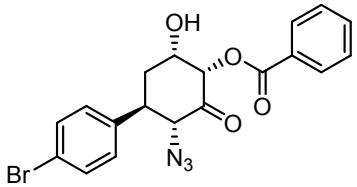
(1*R*,3*S*,4*S*,6*R*)-3-Azido-6-hydroxy-2-oxo-4-*p*-tolylcyclohexyl benzoate *ent*-4e.



The title compound was isolated by filtration, as a white solid.

Yield: 67%; **TLC:** R_f = 0.67 (CH_2Cl_2 / MeOH; 98:2; UV); **[α]$^{23}_{D}$** = -65 (*c* = 0.69, Acetone, *l* = 1 dm); **HRMS** (ESI): exact mass calculated for $C_{20}H_{20}N_3O_4$ [$(M + H)^+$], 366.1454; found 366.1453; **e.e.:** τ_{major} = 10.2 min, τ_{minor} = 16.3 min (>99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5μ), MeCN/Water (50:50) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 24:1 (HPLC).

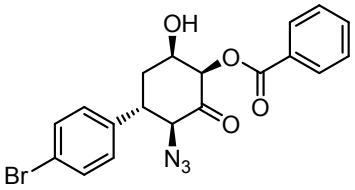
(1*S*,3*R*,4*R*,6*S*)-3-Azido-4-(4-bromophenyl)-6-hydroxy-2-oxocyclohexyl benzoate 4f.



The title compound was isolated by filtration, as a white solid.

Yield: 53%; **M.P.:** 201-204 °C (material solidified from acetone); **[α]$^{24}_{D}$** = +68 (*c* = 0.88, Acetone, *l* = 1 dm); **IR** (neat, cm^{-1}) ν 3466, 2921, 2097, 1749, 1705, 1324, 1265, 1208, 1132, 1058, 1009, 904, 813, 708; **^{1}H NMR** (600 MHz, Acetone) δ 8.18 (d, *J* = 7.3 Hz, 2H, *H*-Ph), 7.68 (t, *J* = 7.4 Hz, 1H, *H*-Ph), 7.59 (d, *J* = 8.3 Hz, 2H, *H*-Ar), 7.54 (t, *J* = 7.8 Hz, 2H, *H*-Ph), 7.47 (d, *J* = 8.4 Hz, 2H, *H*-Ar), 5.84 (d, *J* = 2.9 Hz, 1H, C*H*-OBz), 5.16 (d, *J* = 2.8 Hz, 1H, O*H*), 4.82 (d, *J* = 12.0 Hz, 1H, C*H*-N_3), 4.73 (br, 1H, C*H*-OH), 3.50 (td, *J* = 12.5, 4.0 Hz, 1H, C*H*-Ar), 2.61 (t, *J* = 13.6 Hz, 1H, CH_2), 2.25 (dt, *J* = 14.4, 4.0 Hz, 1H, CH_2); **^{13}C NMR** (151 MHz, Acetone) δ 198.73, 165.78, 141.73, 134.30, 132.66, 130.73, 130.61, 129.39, 121.45, 80.01, 70.61, 70.24, 44.84, 37.37; **HRMS** (ESI): exact mass calculated for $C_{19}H_{17}N_3O_4Br$ [(M + H)$^{+}$], 430.0402; found 430.0411; **e.e.:** τ_{major} = 21.3 min, τ_{minor} = 14.3 min (99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5μ), MeCN/Water (50:50) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 94:6 (HPLC).

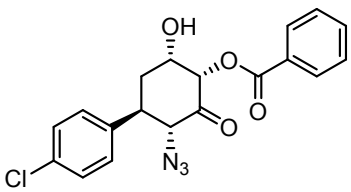
(1*R*,3*S*,4*S*,6*R*)-3-Azido-4-(4-bromophenyl)-6-hydroxy-2-oxocyclohexyl benzoate *ent*-4f.



The title compound was isolated by filtration, as a white solid.

Yield: 55%; **TLC:** R_f = 0.67 (CH_2Cl_2 / MeOH; 98:2; UV); **[α]$^{22}_{D}$** = -61 (*c* = 1.08 , Acetone, *l* = 1 dm); **e.e.:** τ_{major} = 14.3 min, τ_{minor} = 21.3 min (>99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5μ), MeCN/Water (50:50) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 93:7 (HPLC).

(1*S*,3*R*,4*R*,6*S*)-3-Azido-4-(4-chlorophenyl)-6-hydroxy-2-oxocyclohexyl benzoate 4g.

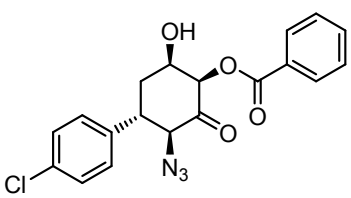


The title compound was isolated by filtration, as a white solid.

Yield: 48%; **[α]$^{24}_{D}$** = +77 (*c* = 0.59, Acetone, *l* = 1 dm); **M.P.:** 161-163 °C (material solidified from acetone); **IR** (neat, cm^{-1}) ν 3469, 2907, 2098, 1752, 1705, 1490, 1326, 1265, 1097, 906, 818, 709; **^{1}H NMR** (600 MHz, Acetone) δ 8.18 (dd, *J* = 8.2, 1.2 Hz, 2H, *H*-Ph), 7.68 (t, *J* = 7.4 Hz, 1H, *H*-Ph), 7.55 (t, *J* = 7.7 Hz, 2H, *H*-Ph), 7.53 (d, *J* = 8.4 Hz, 2H, *H*-Ar), 7.44 (d, *J* = 8.4 Hz, 2H, *H*-Ar), 5.84 (d, *J* = 2.9 Hz, 1H, C*H*-OBz), 5.16 (d, *J* = 2.2 Hz, 1H, O*H*), 4.82 (d, *J* = 12.0 Hz, 1H,

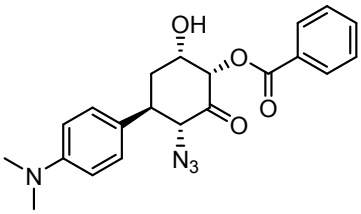
C*H*-N_3), 4.73 (br, 1H, C*H*-OH), 3.51 (td, *J* = 12.5, 4.0 Hz, 1H, C*H*-Ar), 2.61 (t, *J* = 13.7 Hz, 1H, CH_2), 2.25 (dt, *J* = 14.4, 4.1 Hz, 1H, CH_2); **^{13}C NMR** (151 MHz, Acetone) δ 198.73, 165.78, 141.25, 134.30, 133.37, 130.73, 130.62, 130.36, 129.66, 129.39, 80.02, 70.61, 70.31, 44.78, 37.43; **HRMS** (ESI): exact mass calculated for $C_{19}H_{17}N_3O_4Cl$ [(M + H)$^+$], 386.0908; found 386.0912; **e.e.:** τ_{major} = 11.3 min, τ_{minor} = 8.0 min (>99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5μ), Water/MeCN (55:45) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 95:5 (HPLC).

(1*R*,3*S*,4*S*,6*R*)-3-Azido-4-(4-chlorophenyl)-6-hydroxy-2-oxocyclohexyl benzoate *ent*-4g.



The title compound was isolated by filtration, as a white solid. **Yield:** 47%; **TLC:** R_f = 0.63 (CH_2Cl_2 / MeOH; 98:2; UV); **[α]$^{23}_D$** = -80 (*c* = 0.64, Acetone, *l* = 1 dm); **e.e.:** τ_{major} = 8.0 min, τ_{minor} = 11.2 min (>99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5μ), Water/MeCN (55:45) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 95:5 (HPLC).

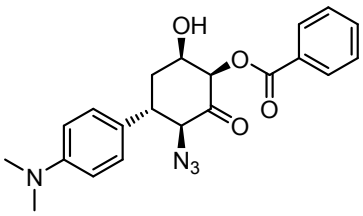
(1*S*,3*R*,4*R*,6*S*)-3-Azido-4-(4-(dimethylamino)phenyl)-6-hydroxy-2-oxocyclohexyl benzoate



4h. The title compound was isolated by filtration, as a white solid. **Yield:** 61%; **TLC:** R_f = 0.60 (CH_2Cl_2 / MeOH; 98:2; UV); **M.P.:** 164-167 °C (material solidified from acetone); **[α]$^{24}_D$** = +91 (*c* = 0.27, Acetone, *l* = 1 dm); **IR** (neat, cm^{-1}) ν 3469, 2906, 2091, 1752, 1707, 1524, 1324, 1272, 1028, 806, 709, 519; **^{1}H NMR** (600 MHz, Acetone) δ 8.18 (dd, *J* = 8.3, 1.2 Hz, 2H, *H*-Ph), 7.68 (t, *J* = 7.4 Hz, 1H, *H*-Ph), 7.54 (t, *J* = 7.8 Hz, 2H, *H*-Ph), 7.29 (d, *J* = 8.7 Hz, 2H, *H*-Ar), 6.77 (d, *J* = 8.7 Hz, 2H, *H*-Ar), 5.80 (d, *J* = 2.6 Hz, 1H, C*H*-OBz), 5.09 – 5.03 (m, 1H, O*H*),), 4.70 (br, 1H, C*H*-OH), 4.66 (d, *J* = 12.0 Hz, 1H, C*H*-N_3), 3.40 (td, *J* = 12.5, 4.0 Hz, 1H, C*H*-Ar), 2.94 (s, 6H, CH_3), 2.56 (t, *J* = 13.6 Hz, 1H, CH_2), 2.20 (dt, *J* = 14.4, 4.0 Hz, 1H, CH_2); **^{13}C NMR** (151 MHz, Acetone) δ 198.97, 165.80, 151.04, 134.25, 130.73, 129.63, 129.37, 128.95, 113.67, 80.12, 71.09, 70.67, 44.54, 40.68, 37.83; **HRMS** (ESI): exact mass calculated for $C_{21}H_{23}N_4O_4$ [(M + H)$^+$], 395.1719; found 395.1718; **e.e.:** τ_{major} = 14.4 min, τ_{minor} =

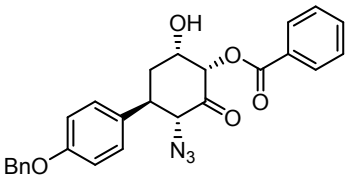
9.8 min (94% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5µ), Water/MeCN (50:50) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 96:4 (HPLC).

(1*R*,3*S*,4*S*,6*R*)-3-Azido-4-(4-(dimethylamino)phenyl)-6-hydroxy-2-oxocyclohexyl benzoate *ent*-4h.



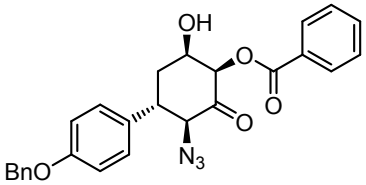
Yield: 56%; $[\alpha]^{23}_{D}$ = -70 (*c* = 0.35, Acetone, *l* = 1 dm); **e.e.:** τ_{major} = 9.8 min, τ_{minor} = 14.4 min (99% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5µ), Water/MeCN (50:50) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 96:4 (HPLC).

(1*S*,3*R*,4*R*,6*S*)-3-Azido-4-(4-(benzyloxy)phenyl)-6-hydroxy-2-oxocyclohexyl benzoate 4i.



The title compound was isolated by filtration, as a white solid. **Yield:** 65%; **TLC:** R_f = 0.39 (CH_2Cl_2 / MeOH; 98:2; UV); **M.P.:** 159-161 °C (material solidified from acetone); $[\alpha]^{24}_{D}$ = +43 (*c* = 0.31, Acetone, *l* = 1 dm); **IR** (neat, cm^{-1}) ν 3453, 2924, 2094, 1706, 1514, 1453, 1253 1131, 1059, 815, 733, 710, 697; **^{1}H NMR** (600 MHz, Acetone) δ 8.18 (dd, *J* = 8.2, 1.2 Hz, 2H, *H*-Bz), 7.68 (t, *J* = 7.4 Hz, 1H, *H*-Bz), 7.54 (t, *J* = 7.8 Hz, 2H, *H*-Bz), 7.50 (d, *J* = 7.2 Hz, 2H, *H*-Bn), 7.41 (d, *J* = 8.7 Hz, 2H, *H*-Ar), 7.40 (t, *J* = 7.6 Hz, 2H, *H*-Bz), 7.34 (t, *J* = 7.4 Hz, 1H, *H*-Bz), 7.05 (d, *J* = 8.6 Hz, 2H), 5.82 (d, *J* = 2.9 Hz, 1H, C*H*-OBz), 5.14 (s, 2H, CH_2-Ph), 5.10 (m, 1H, O*H*), 4.73 (d, *J* = 12.2 Hz, 1H, C*H*-N_3), 4.71 (br, 1H, C*H*-OH), 3.46 (td, *J* = 12.5, 4.0 Hz, 1H, C*H*-Ar), 2.58 (t, *J* = 13.6 Hz, 1H, CH_2), 2.23 (dt, *J* = 14.4, 4.0 Hz, 1H, CH_2); **^{13}C NMR** (151 MHz, Acetone) δ 198.87, 165.79, 159.10, 138.50, 134.46, 134.27, 130.74, 130.67, 129.55, 129.38, 129.32, 128.65, 128.47, 115.91, 80.08, 70.83, 70.65, 70.50, 44.62, 37.75; **e.e.:** τ_{major} = 11.1 min, τ_{minor} = 7.8 min (95% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5µ), Water/MeCN (60:40) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 96:4 (HPLC).

(1*R*,3*S*,4*S*,6*R*)-3-Azido-4-(4-(benzyloxy)phenyl)-6-hydroxy-2-oxocyclohexyl benzoate *ent*-4i.



The title compound was isolated by filtration, as a white solid.

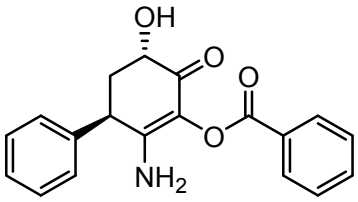
Yield: 61%; **[α]$^{23}_{D}$** = -48 (*c* = 0.37, Acetone, *l* = 1 dm); **HRMS** (ESI): exact mass calculated for $C_{26}H_{24}N_3O_5$ [(M + H)$^+$], 458.1716; found 458.1731; **e.e.:** τ_{major} = 7.8 min, τ_{minor} = 11.1 min (97% e.e.), Daicel Chiralpak AS-RH column (150 x 4.6 mm, 5μ), Water/MeCN (60:40) as a mobile phase; flow rate 0.75 mL/min, column temperature 20 °C, λ236; **d.r.:** 96:4 (HPLC).

General Procedure for the synthesis of cyclic enaminones.

In a 1 dram vial, the corresponding α azido, α'-*o*-benzoyl ketone (0.054 mmol, 1.0 equiv) and silver catalyst **13** (0.0054 mmol, 0.1 equiv) were dissolved in THF (0.5 mL) and stirred at 60 °C for 1h (acyclic substrates)/3h (cyclic substrates) under a nitrogen atmosphere.* The reaction mixture was cooled to room temperature and the solvent was evaporated by nitrogen flush. The crude reaction product was partitioned between CH_2Cl_2 and water and the organic phase concentrated and purified by flash chromatography (eluent CH_2Cl_2/MeOH 100:0 to 95:5) to give the resultant α-*o*-benzoyl, β-amino α, β–unsaturated aldehydes/ketones.

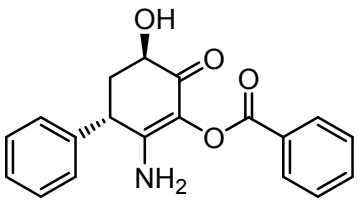
***Caution:** due to nitrogen gas release, a balloon is mandatory for larger scale reactions.

(3*R*, 5*S*)-2-amino-5-hydroxy-6-oxo-3-phenylcyclohex-1-enyl benzoate 6a. The title compound was prepared from **4a** and was isolated as an amorphous white solid. **Yield:** 70%; **[α]$^{22}_{D}$** = -74 (*c* = 0.35, Acetone, *l* = 1 dm). **^{1}H NMR** (600 MHz, Acetone) *δ* 8.17 (dd, *J* = 8.29, 1.4 Hz, 2H, *H*-Bz), 7.70 (m, 1H, *H*-Bz), 7.58 (t, *J* = 8.0 Hz, 2H, *H*-Bz), 7.54 (d, *J* = 7.3 Hz, 2H, *H*-Ph), 7.42 (t, *J* = 7.2 Hz, 2H, *H*-Ph), 7.32 (t, *J* = 7.2 Hz, 1H, *H*-Ph), 4.15 (t, *J* = 3.9 Hz, 1H, C*H*-Ph), 3.91 (dd, *J* = 6.7, 10.9 Hz, 1H, C*H*-OH), 2.33 (m, 2H, CH_2) ppm; **^{13}C NMR** (151 MHz, Acetone) *δ* 188.12, 164.93, 156.33, 141.10, 134.04, 131.08, 130.93, 129.50, 129.33, 128.92, 127.93, 123.27, 67.74, 43.37, 38.85 ppm; **HRMS** (ESI): exact mass calculated for $C_{19}H_{18}NO_4$ [(M + H)$^+$], 324.1236; found 324.1238.

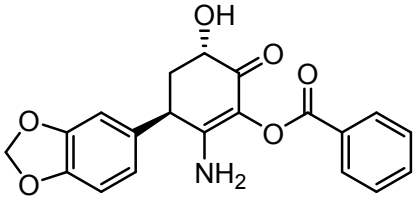


(3*S*, 5*R*)-2-amino-5-hydroxy-6-oxo-3-phenylcyclohex-1-enyl benzoate *ent*-6a.

The title compound was prepared from ***ent*-4a** and was isolated as a white solid. **Yield:** 68%; R_f = 0.45 (EtOAc/hexane, 1:1); **[α]$^{22}_{D}$** = +68 (*c* = 0.32, Acetone, *l* = 1 dm).

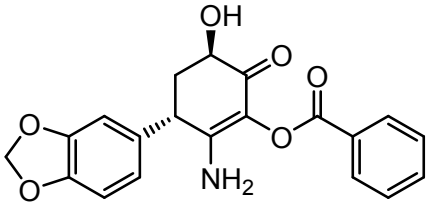


(3*R*,5*S*)-2-amino-3-(benzo[d][1,3]dioxol-5-yl)-5-hydroxy-6-oxocyclohex-1-enyl benzoate *ent*-6b.



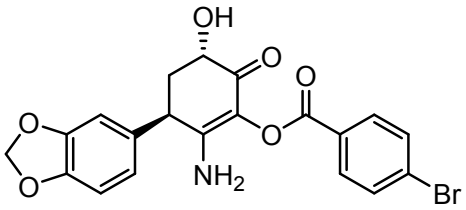
The title compound was prepared from **4b** and was isolated as a white solid. **Yield:** 70%; R_f= 0.3 (EtOAc/hexane, 1:1); **[α]$^{22}_{D}$** = -86 (*c* = 0.33, Acetone, *l* = 1 dm). **^{1}H NMR** (600 MHz, Acetone) *δ* 8.15 (dd, *J* = 8.1, 1.1 Hz, 2H, *H*-Bz), 7.68 (m, 1H, *H*-Bz), 7.56 (t, *J* = 7.43 Hz , 2H, *H*-Bz,), 7.08 (d, *J* = 1.77 Hz, 1H, *H*-Ph), 7.01 (dd, *J* = 8.61, 2.46 Hz, 1H, *H*-Ph), 6.87 (d, *J* = 7.78 Hz, 1H, *H*-Ph), 6.01 (dd, *J* = 2.04, 1.13 Hz, 2H, PhO-C*H*$_2$-OPh), 4.07 (dd, *J* = 5.15, 2.97 Hz, 1H, C*H*-Ph), 3.95 (dt, *J* = 11.26 ,4.25 Hz, 1H, C*H*-OH), 2.28 (m, 2H, C*H*$_2$) ppm; **^{13}C NMR** (151 MHz, Acetone) *δ* 188.13, 164.99, 156.44, 148.94, 147.62, 134.81, 134.05, 131.05, 130.93, 129.33, 123.20, 122.10, 109.41, 109.04, 102.10, 67.86, 43.07, 38.95 ppm; **HRMS** (ESI): exact mass calculated for $C_{20}H_{17}NO_4$ [(M + H)$^+$], 368.1134; found 368.1126.

(3*S*, 5*R*)-2-amino-3-(benzo[d][1,3]dioxol-5-yl)-5-hydroxy-6-oxocyclohex-1-enyl benzoate *ent*-6b.



The title compound was prepared from ***ent*-4b** and was isolated as a white solid. **Yield:71%** **[α]$^{22}_{D}$** = +81 (*c* = 0.29, Acetone, *l* = 1 dm).

(3*R*,5*S*)-2-amino-3-(benzo[d][1,3]dioxol-5-yl)-5-hydroxy-6-oxocyclohex-1-enyl-4-bromobenzoate 6c

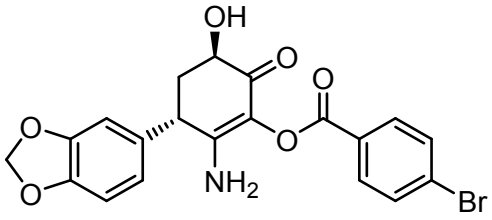


The title compound was prepared from **4c** and was isolated as a white solid. **Yield:** 68%. R_f = 0.4 (EtOAc/hexane, 1:1); **[α]$^{22}_{D}$** = -64 (*c* = 0.25, Acetone, *l* = 1 dm); **^{1}H NMR** (600 MHz, Acetone) *δ* 8.07 (dt, *J* = 9.19, 2.19 Hz, 2H, *H*-Bz), 7.78 (dt, *J* = 9.09, 2.19 Hz, 2H, *H*-Bz), 7.06 (d, *J* = 1.64 Hz, 1H, *H*-Ph), 6.99 (dd, *J* = 8.34, 2.08 Hz, 1H, *H*-Ph), 6.87 (d, *J* = 8.34 Hz, 1H, *H*-Ph), 6.01 (dd, *J* = 1.86, 1.22

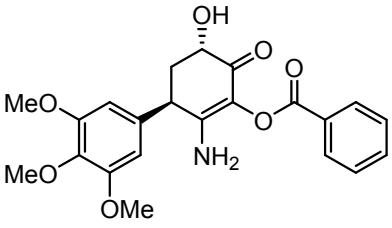
Hz, 2H, PhO-CH_2-OPh), 4.07 (dd, J = 5.15, 2.62 Hz, 1H, CH-Ph), 3.95 (dt, J = 11.37 ,3.97 Hz, 1H, CH-OH), 2.28 (m, 2H, CH_2) ppm; **^{13}C NMR** (151 MHz, Acetone) δ 188.00, 164.38, 156.42, 148.95, 147.64, 134.73, 132.76, 132.63, 130.40, 130.22, 128.47, 122.07, 109.37, 109.05, 102.11, 67.85, 42.99, 38.91 ppm; **HRMS** (ESI): exact mass calculated for $C_{20}H_{16}BrNO_6$ [(M + H)$^+$], 446.0239; found 446.0240.

(3*S*,5*R*)-2-amino-3-(benzo[d][1,3]dioxol-5-yl)-5-hydroxy-6-oxocyclohex-1-enyl-4-bromobenzoate *ent*-6c.

The title compound was prepared from ***ent*-4c** and was isolated as a white solid. **Yield:** 71%. **[α]$^{22}_{D}$** = +62 (c = 0.38, Acetone, l = 1 dm). **X-ray** quality crystals were grown in a 5 mm NMR tube by layering CH_2Cl_2 (1.0 mL) onto a dissolved solution (0.005g) of ***ent*-6c** in Acetone (0.5 mL). The layers slowly mixed, forming micro crystals over 6 days.

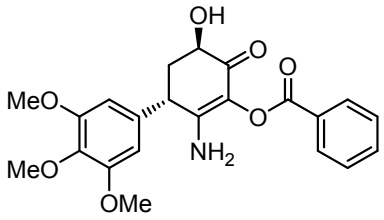


(3*R*, 5*S*)-2-amino-5-hydroxy-6-oxo-3-(3,4,5-trimethoxyphenyl)cyclohex-1-enyl benzoate 6d:



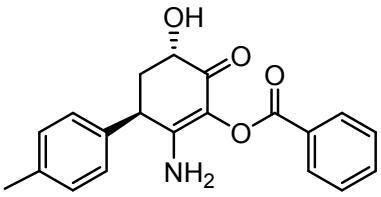
The title compound was prepared from **4d** and was isolated as a white solid. **Yield:** 68%. R_f= 0.15 (EtOAc/hexane, 1:1); **[α]$^{22}_{D}$** = -80 (c = 0.15, Acetone, l = 1 dm); **^{1}H NMR** (600 MHz, Acetone) δ 8.15 (dd, J = 8.4, 1.1 Hz, 2H, H-Bz), 7.69 (m, 1H, H-Bz), 7.56 (t, J = 8.25 Hz , 2H, H-Bz,), 6.92 (s, 2H, H-Ph), 4.07 (dd, J = 4.84, 2.82 Hz, 1H, CH-Ph), 3.97 (dt, J = 11.82 ,4.43 Hz, 1H, CH-OH), 3.86 (s, 6H, O-CH_3), 3.73 (s, 3H, O-CH_3), 2.37 (ddd, J = 2.69, 5.12, 12.68 Hz, 1H, CH), 2.37 (td, J = 4.70, 12.09 Hz, 1H, CH) ppm; **^{13}C NMR** (151 MHz, Acetone) δ 188.20, 165.27, 156.47, 154.53, 136.47, 134.09, 129.33, 106.43, 68.03, 60.49, 56.54, 43.56, 38.68 ppm; **HRMS** (ESI): exact mass calculated for $C_{22}H_{23}NO_7$ [(M + H)$^+$], 414.1553; found 414.1535. R_f = 0.15 (EtOAc/hexane, 1:1).

(3*S*, 5*R*)-2-amino-5-hydroxy-6-oxo-3-(3,4,5-trimethoxyphenyl)cyclohex-1-enyl benzoate *ent*-6d



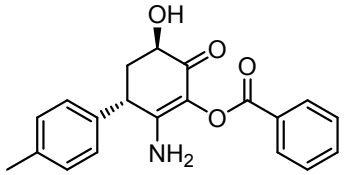
The title compound was prepared from ***ent*-4d** and was isolated as a white solid. **Yield:**67%. $[\alpha]^{22}_{D}$ = +76 (*c* = 0.15, Acetone, *l* = 1 dm).

(3*R*, 5*S*)-2-amino-5-hydroxy-6-oxo-3-p-tolylcyclohex-1-enyl benzoate 6e.



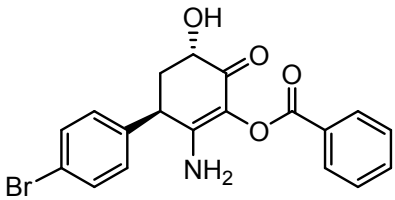
The title compound was prepared from **4e** and was isolated as a white solid. **Yield**: 60%. R_f= 0.45 (EtOAc/hexane, 1:1); $[\alpha]^{22}_{D}$ = -69 (*c* = 0.27, Acetone, *l* = 1 dm); **^{1}H NMR** (600 MHz, Acetone) *δ* 8.15 (dd, *J* = 8.9, 1.9 Hz, 2H, *H*-Bz), 7.68 (m, 1H, *H*-Bz), 7.56 (t, *J* = 8.15 Hz, 2H, *H*-Bz), 7.40 (d, *J* = 8.15 Hz, 2H, *H*-Ph), 7.23 (d, *J* = 7.90 Hz, 2H, *H*-Ph), 4.09 (t, *J* = 3.7 Hz, 1H, C*H*-Ph), 3.92 (m, 1H, C*H*-OH), 2.33 (s, 3H, CH_3-Ph), 2.29 (m, 2H, CH_2) ppm; **^{13}C NMR** (151 MHz, Acetone) *δ* 188.09, 164.90, 156.39, 137.99, 137.41, 134.02, 131.11, 130.92. 130.09, 129.32, 128.81, 67.67, 42.90, 38.89, 21.03 ppm; **HRMS** (ESI): exact mass calculated for $C_{20}H_{19}NO_4$ [(M + Na)$^+$], 360.1212; found 360.1205.

(3*S*, 5*R*)-2-amino-5-hydroxy-6-oxo-3-p-tolylcyclohex-1-enyl benzoate *ent*-6e.



The title compound was prepared from ***ent*-4e** and was isolated as a white solid. **Yield**: 62% $[\alpha]^{22}_{D}$ = +63 (*c* = 0.32, Acetone, *l* = 1 dm).

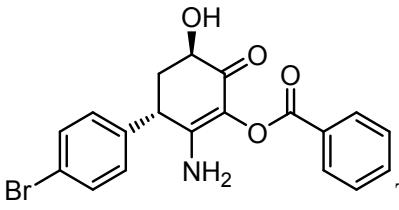
(3*R*, 5*S*)-2-amino-3-(4-bromophenyl)-5-hydroxy-6-oxocyclohex-1-enyl benzoate 6f.



The title compound was prepared from **4f** and white solid. **Yield:** 65%. R_f = 0.3 (EtOAc/hexane, 1:1). $[\alpha]^{22}_{D}$ = -77 (*c* = 0.09, Acetone, *l* = 1 dm); **^{1}H NMR** (600 MHz, Acetone) *δ* 8.15

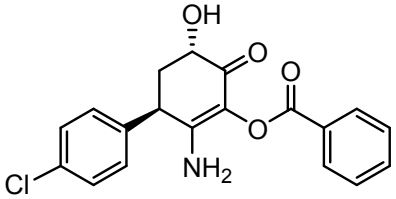
(dd, *J* = 8.27, 1.1 Hz, 2H, *H*-Bz), 7.69 (m, 1H, *H*-Bz), 7.58 (m, 4H, *H*-Bz, *H*-Ph), 7.43 (d, *J* = 7.96 Hz, 2H, *H*-Ph), 4.16 (t, *J* = 4.18 Hz, 1H, C*H*-Ph), 3.88 (t, *J* = 4.18 Hz, 1H, C*H*-OH), 2.23 (m, 2H, CH_2) ppm; **^{13}C NMR** (151 MHz, Acetone) *δ* 188.00, 164.96, 155.61, 140.62, 134.08, 132.52, 131.08, 131.00, 130.93, 129.34, 123.18, 121.32, 67.55, 42.71, 38.49 ppm; **HRMS** (ESI): exact mass calculated for $C_{19}H_{16}BrNO_4$ [$(M + H)^+$], 402.0341; found 402.0334.

(3*S*, 5*R*)-2-amino-3-(4-bromophenyl)-5-hydroxy-6-oxocyclohex-1-enyl benzoate *ent*-6f.



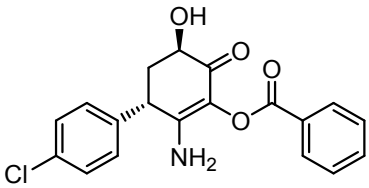
The title compound was prepared from ***ent*-4f** and its white solid. **Yield:** 67%. R_f= 0.3 (EtOAc/hexane, 1:1). **[α]$^{22}_{D}$** = +75 (*c* = 0.12, Acetone, *l* = 1 dm);

(3*R*, 5*S*)-2-amino-3-(4-chlorophenyl)-5-hydroxy-6-oxocyclohex-1-enyl benzoate 6g.



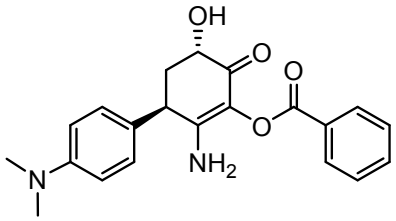
The title compound was prepared from **4g** and obtained as a white solid. **Yield:** 67%. R_f= 0.3 (EtOAc/hexane, 1:1); **[α]$^{22}_{D}$** = -45 (*c* = 0.09, Acetone, *l* = 1 dm); **^{1}H NMR** (600 MHz, Acetone) *δ* 8.14 (dd, *J* = 8.3, 1.1 Hz, 2H, *H*-Bz), 7.67 (m, 1H, *H*-Bz), 7.55 (m, 4H, *H*-Bz, *H*-Ph), 7.43 (dt, *J* = 9.0, 2.3 Hz, 2H, *H*-Ph), 4.16 (t, *J* = 3.7 Hz, 1H, C*H*-Ph), 3.89 (m, 1H, C*H*-OH), 2.34(m, 2H, CH_2) ppm; **^{13}C NMR** (151 MHz, Acetone) *δ* 187.90, 164.84, 153.63, 140.00, 133.96, 133.14, 130.88, 130.81, 130.59, 129.39, 129.22, 123.10, 67.52, 42.58, 38.45 ppm; **HRMS** (ESI): exact mass calculated for $C_{19}H_{16}ClNO_4$ [$(M + H)^+$], 358.0838; found 358.0831.

(3*R*, 5*S*)-2-amino-3-(4-chlorophenyl)-5-hydroxy-6-oxocyclohex-1-enyl benzoate *ent*-6g.



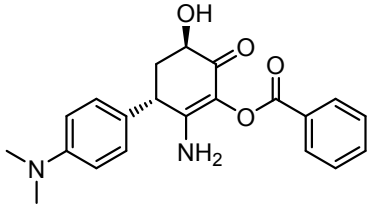
The title compound was prepared from ***ent*-4g** as a white solid. **Yield:**69%. R_f = 0.3 (EtOAc/hexane, 1:1); **[α]$^{22}_{D}$** = +44 (*c* = 0.35, Acetone, *l* = 1 dm);

(3R,5S)-2-amino-3-(4-(dimethylamino)phenyl)-5-hydroxy-6-oxocyclohex-1-enyl benzoate 6h.



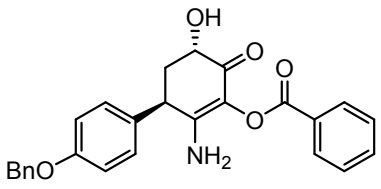
The title compound was prepared from **4h** and was isolated as a white solid. **Yield:** 60%. R_f = 0.25 (EtOAc/hexane, 1:1). **[α]$^{22}_{D}$** = -80 (*c* = 0.22, Acetone, *l* = 1 dm); **^{1}H NMR** (600 MHz, Acetone) *δ* 8.15 (dd, *J* = 8.2, 1.1 Hz, 2H, *H*-Bz), 7.68 (m, 1H, *H*-Bz), 7.56 (t, *J* = 7.56 Hz, 2H, *H*-Bz), 7.33 (dt, *J* = 8.82, 2.3 Hz, 2H, *H*-Ph), 6.78 (dt, *J* = 9.9, 2.7 Hz, 2H, *H*-Ph), 4.00 (dd, *J* = 5.16, 2.58 Hz, 1H, C*H*-ph), 3.96 (dd, *J* = 12.57, 5.48 Hz, 1H, C*H*-OH), 2.94 (s, 6H (CH_3)-N), 2.25 (m, 2H, CH_2) ppm; **^{13}C NMR** (151 MHz, Acetone) *δ* 188.14, 164.89, 157.09, 150.90, 133.98, 131.17, 130.97, 129.42, 129.31, 128.20, 113.54, 67.92, 42.50, 40.70, 39.15 ppm; **HRMS** (ESI): exact mass calculated for $C_{21}H_{22}N_2O_4$ [(M + H)$^+$], 367.1658; found 367.1643.

(3*S*,5*R*)-2-amino-3-(4-(dimethylamino)phenyl)-5-hydroxy-6-oxocyclohex-1-enyl benzoate *ent*-6h. The title compound was prepared from ***ent*-4h** and was isolated as a white solid. **Yield:** 62%. R_f = 0.25 (EtOAc/hexane, 1:1). **[α]$^{22}_{D}$** = +76 (*c* = 0.3, Acetone, *l* = 1 dm).



(3*R*, 5*S*)-2-amino-3-(4-(benzyloxy)phenyl)-5-hydroxy-6-oxocyclohex-1-enyl benzoate 6i.

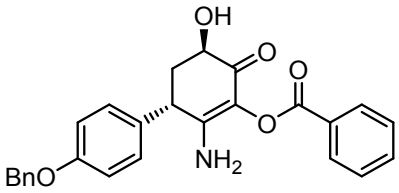
The title compound was prepared from **4i**. and was isolated as a white solid. **Yield:** 58%; R_f = 0.35 (EtOAc/hexane, 1:1). **[α]$^{22}_{D}$** = -88 (*c* = 0.05, Acetone, *l* = 1 dm); **^{1}H NMR** (600 MHz, Acetone) *δ* 8.15 (dd, *J* = 8.27, 1.1 Hz, 2H, *H*-Bz), 7.68 (m, 1H, *H*-Bz), 7.56 (t, *J* = 7.89 Hz ,2H, *H*-Bz,), 7.50 (d, *J* = 7.22 Hz, 2H, *H*-Ph), 7.44 (d, *J* = 6.57 Hz, 2H, *H*-Ph), 7.40 (d, *J* = 7.71 Hz, 2H, *H*-Ph), 7.33 (d, *J* = 3.39 Hz, 1H, *H*-Ph), 7.05 (dt, *J* = 9.54, 2.62 Hz, 2H,



H-Ph), 5.16 (s, 2H, OCH_2Ph) 4.08 (m, 1H, C*H*-Ph), 3.92 (m, 1H, C*H*-OH), 2.29 (m, 2H, CH_2) ppm; **^{13}C NMR** (151 MHz, Acetone) δ 188.10, 164.94, 158.88, 156.61, 138.49, 134.03, 133.09, 131.10, 130.92, 129.98, 129.32, 128.63, 128.42, 123.08, 115.83. 70.44, 67.78, 42.58, 38.96 ppm; **HRMS** (ESI): exact mass calculated for $C_{26}H_{23}NO_5$ [(M + H)$^+$], 430.1654; found 430.1642.

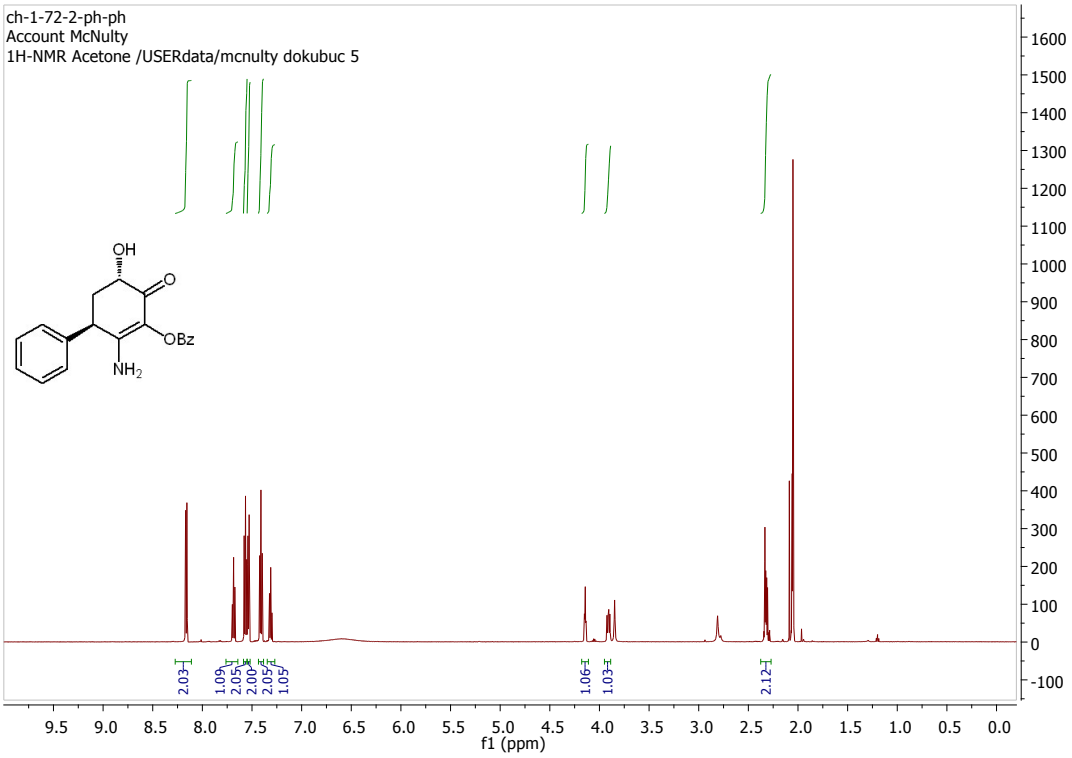
(3*S*, 5*R*)-2-amino-3-(4-(benzyloxy)phenyl)-5-hydroxy-6-oxocyclohex-1-enyl benzoate *ent*-6i.

The title compound was prepared from ***ent*-4i**. and was isolated as a white solid. **Yield:** 60%; R_f = 0.35 (EtOAc/hexane, 1:1). **[α]$^{22}_D$** = +86 (*c* = 0.4, Acetone, *l* = 1 dm).



References

1. McNulty, J., et al. iPSC neuronal assay identifies Amaryllidaceae pharmacophore with multiple effects against herpesvirus infections. *ACS Med. Chem. Lett.*, 7 (1), 46–50 (2016).
2. McNulty, J. & Zepeda-Velázquez, C. Enantioselective organocatalytic Michael/Aldol sequence: Anticancer natural product (+)-*trans*-Dihydrolycoricidine. *Angew. Chem. Int. Ed.* **53,** 8450–8454 (2014).
3. McNulty, J., Zepeda-Velázquez, C. & McLeod, D. Development of a robust reagent for the two-carbon homologation of aldehydes to (E)-α,β-unsaturated aldehydes in water. *Green Chem*. **15**, 3146-3149 (2013).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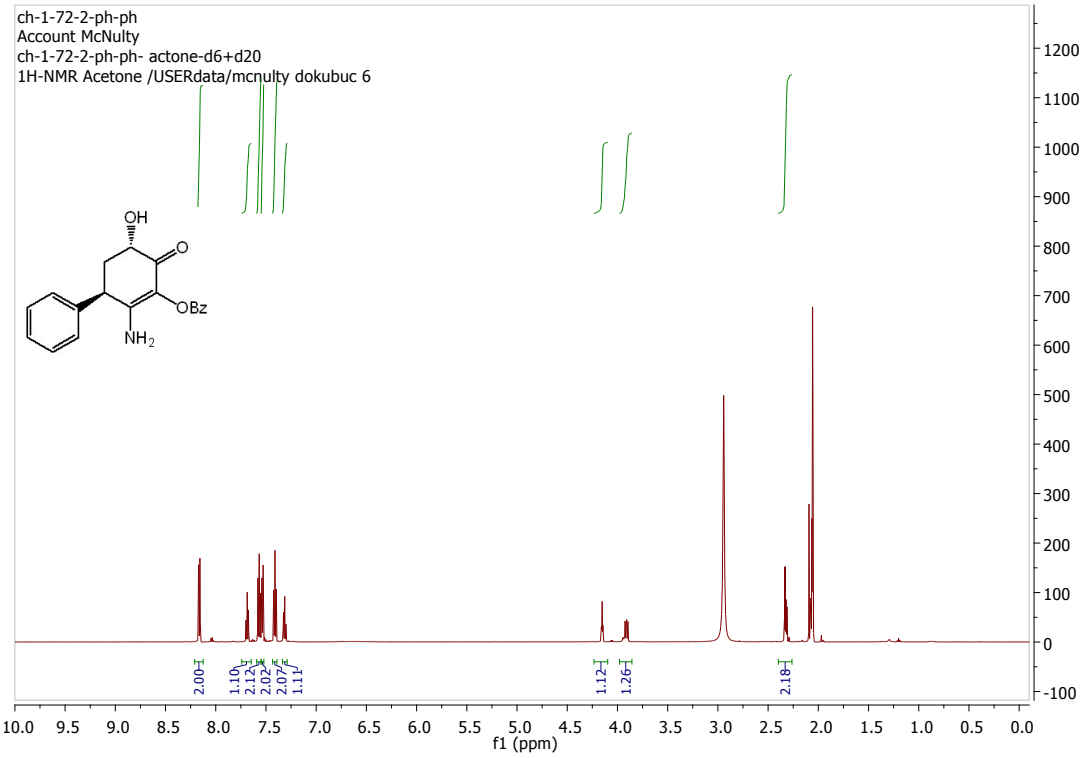
2.12
f1 (ppm)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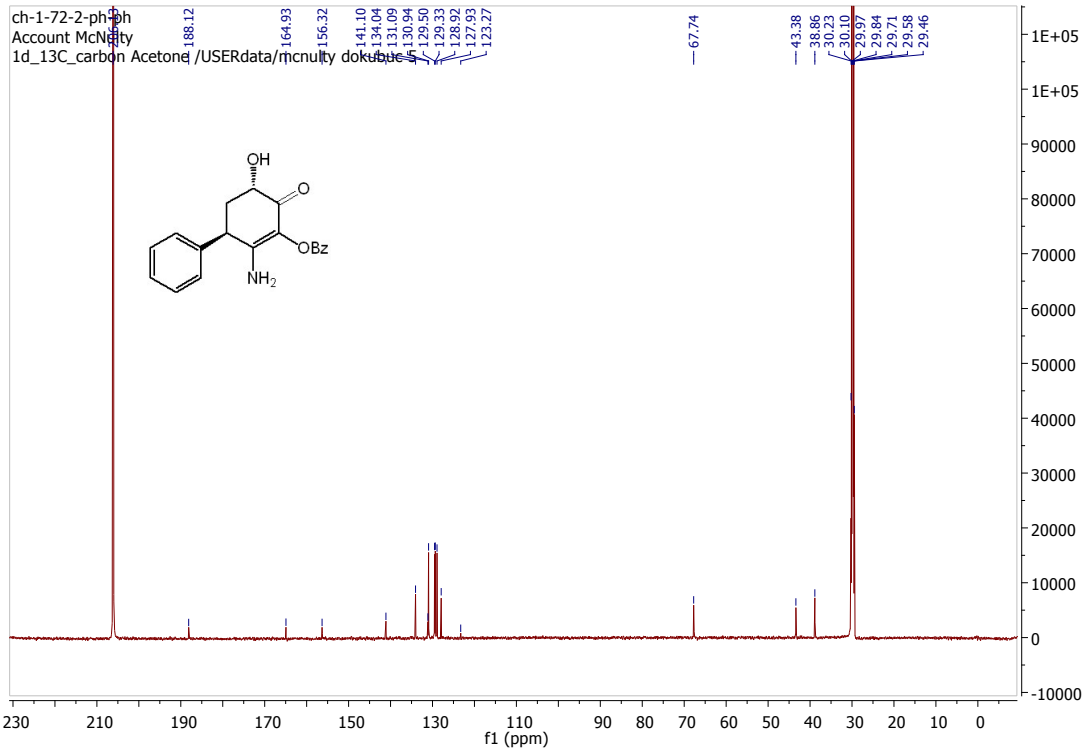
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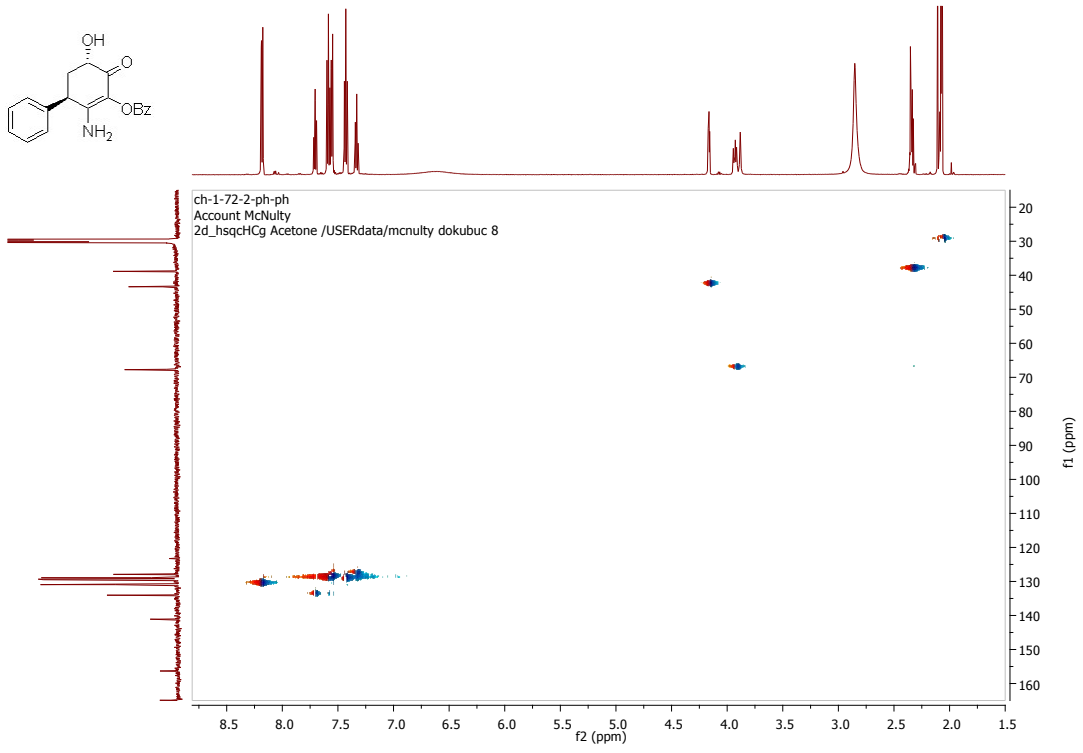
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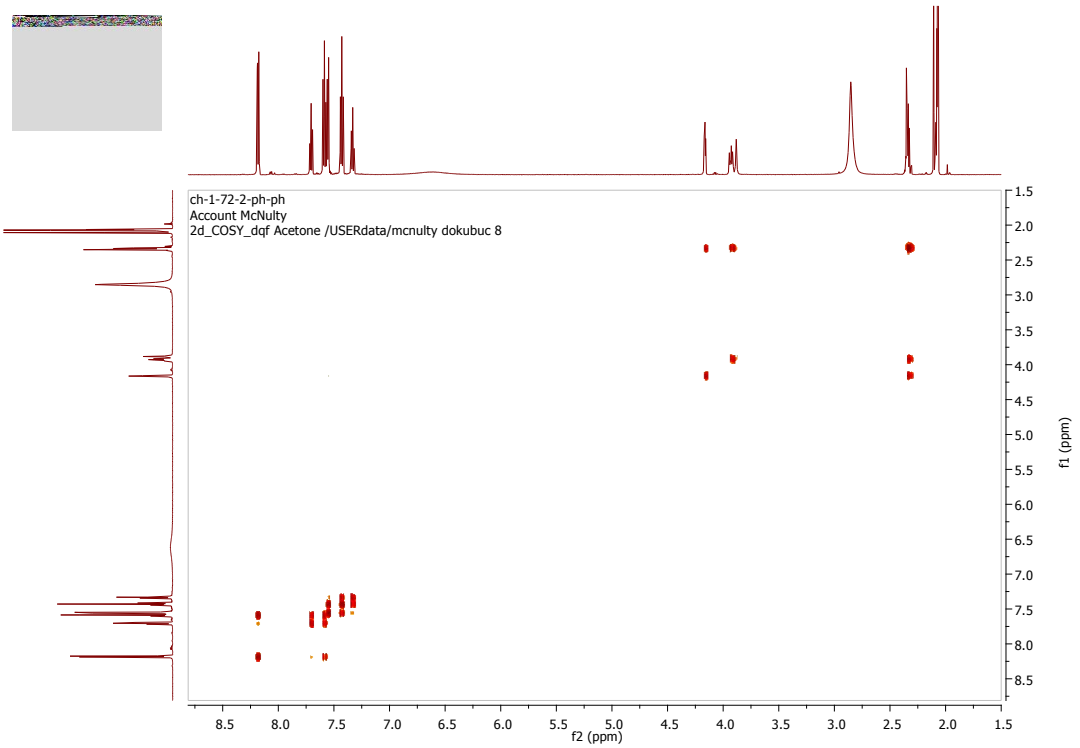
f1 (ppm)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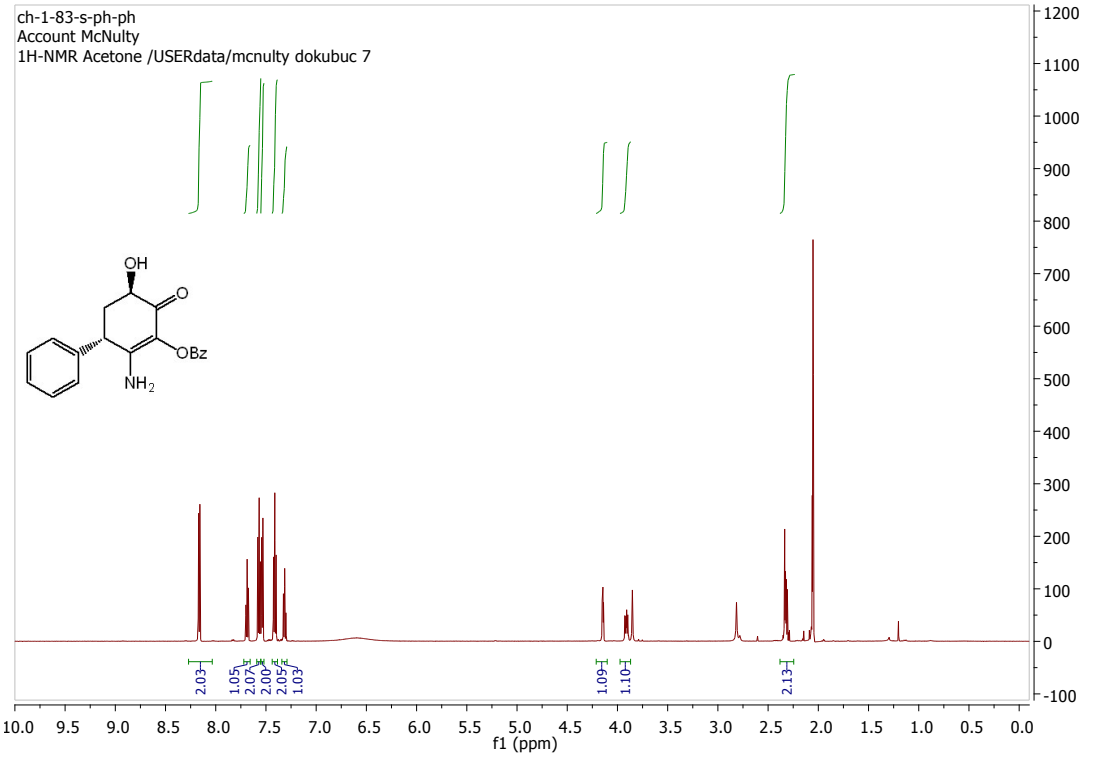
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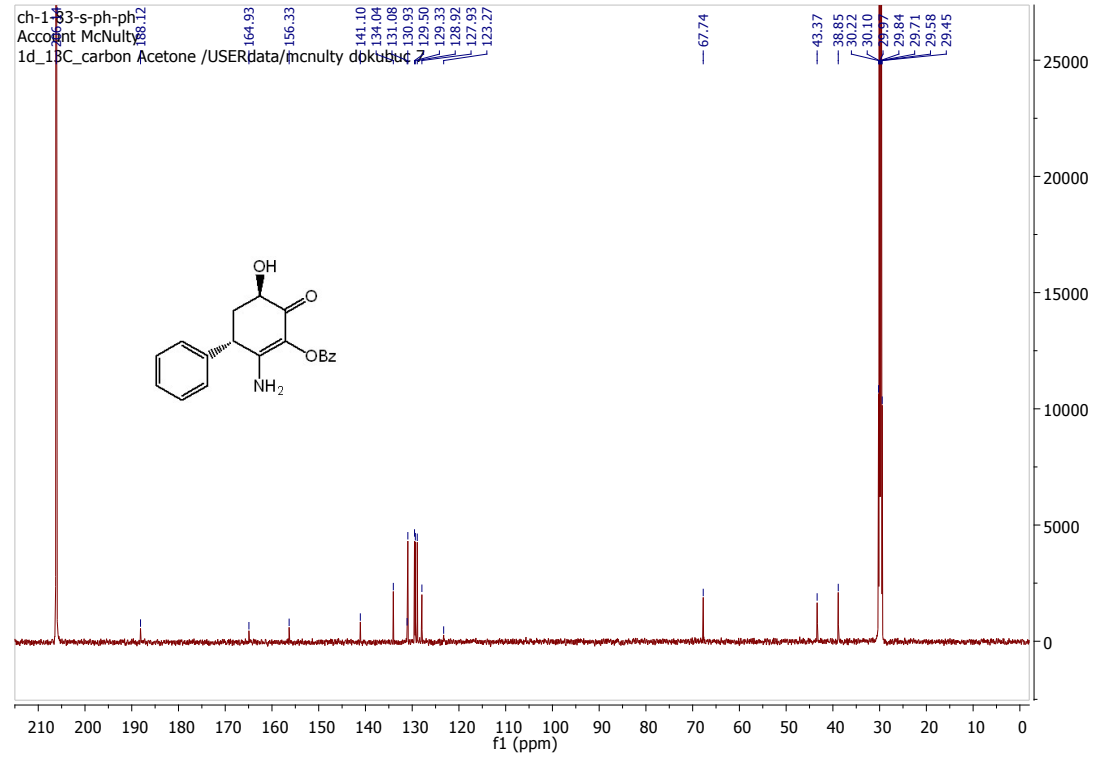
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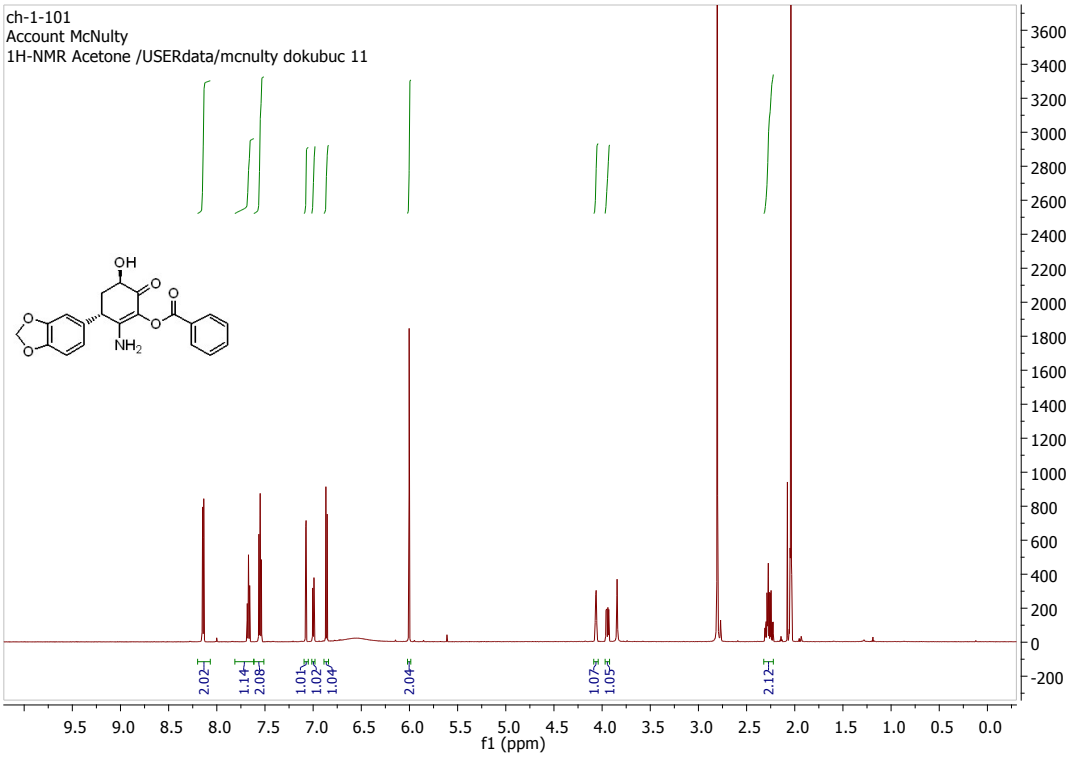
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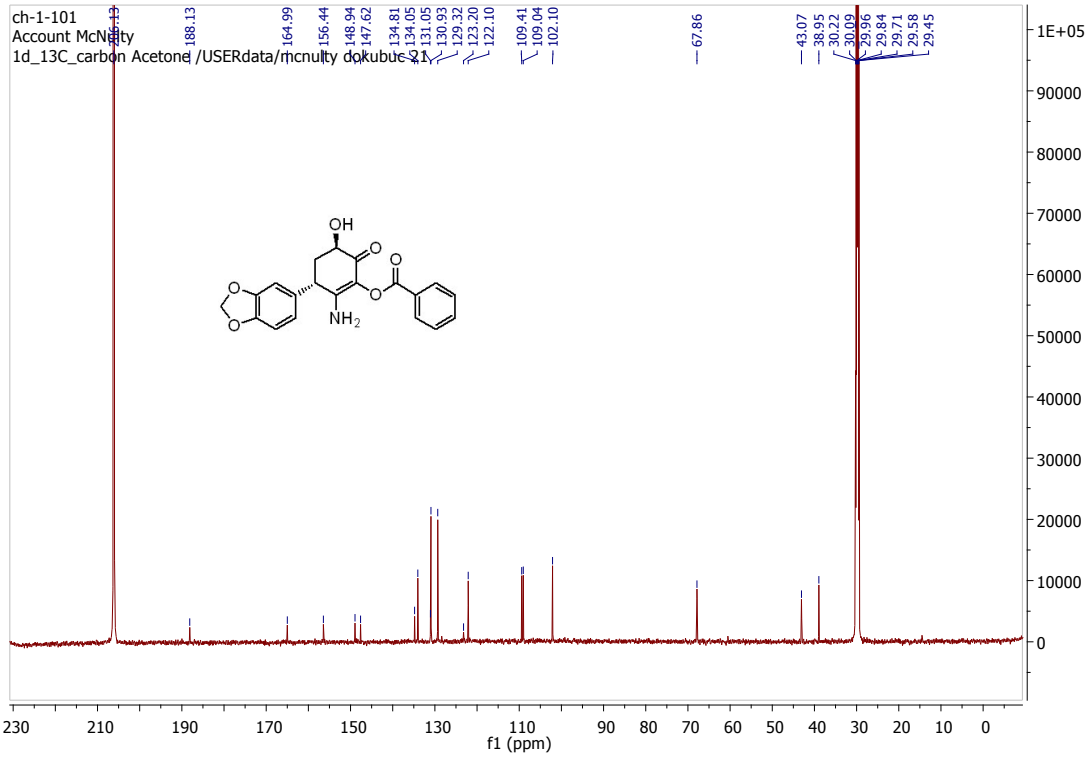
f1 (ppm)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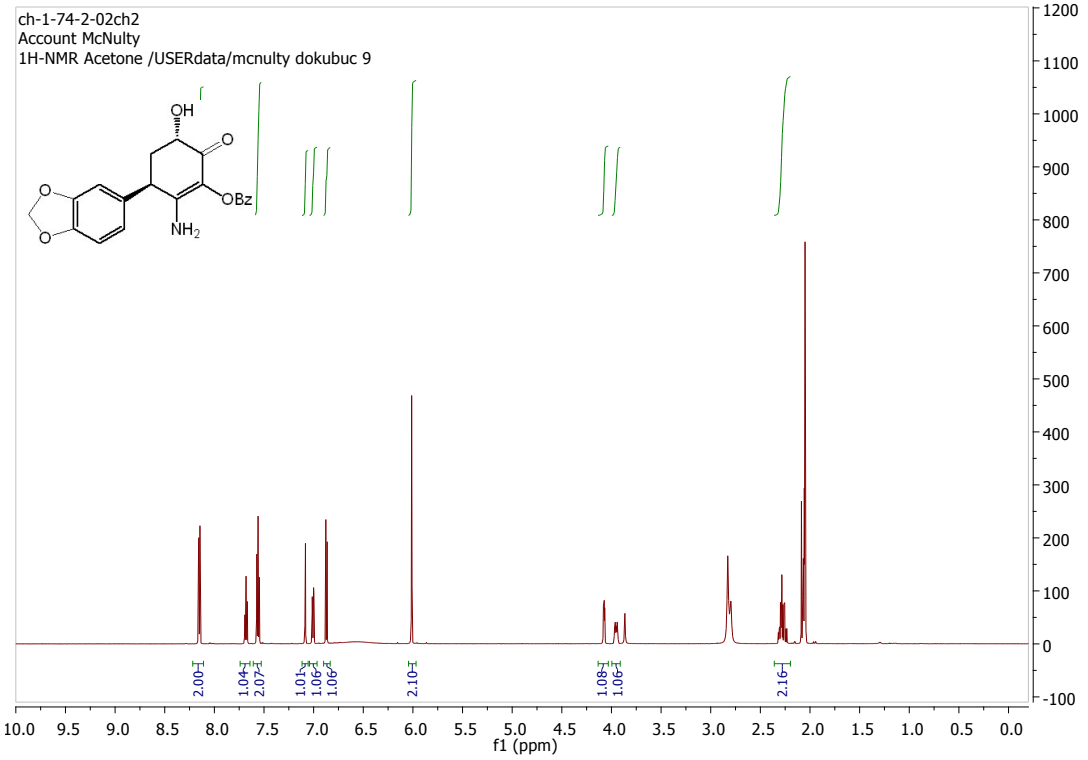
f1 (ppm)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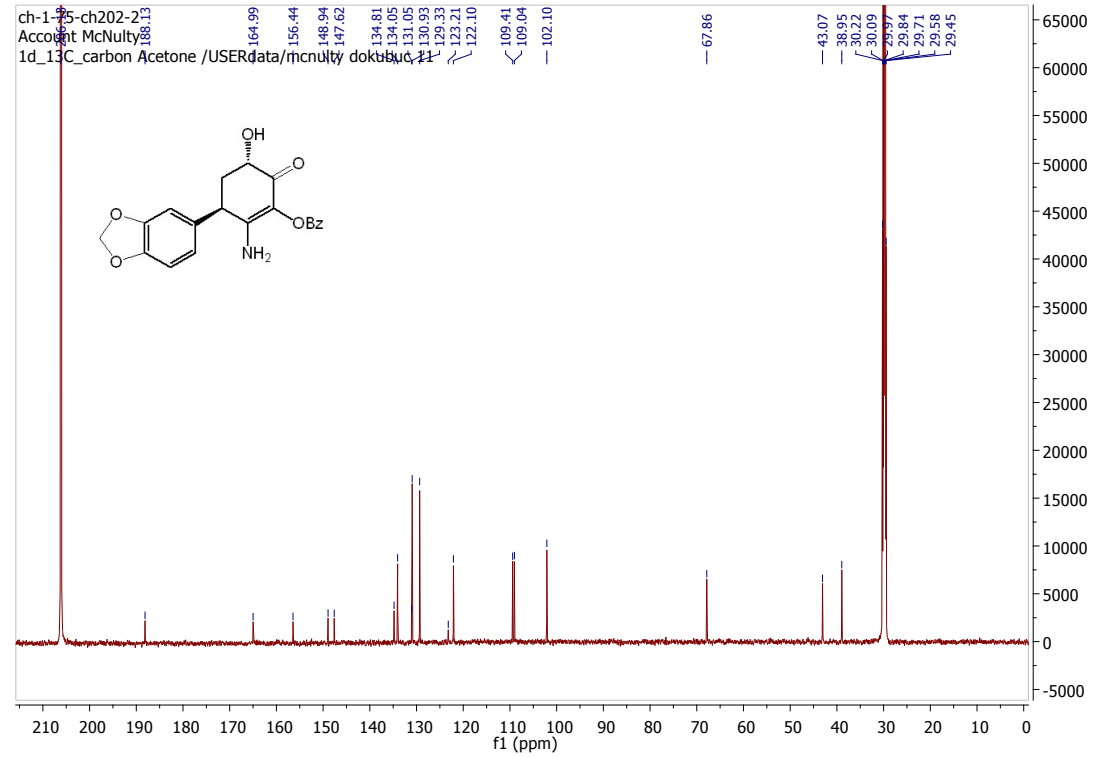
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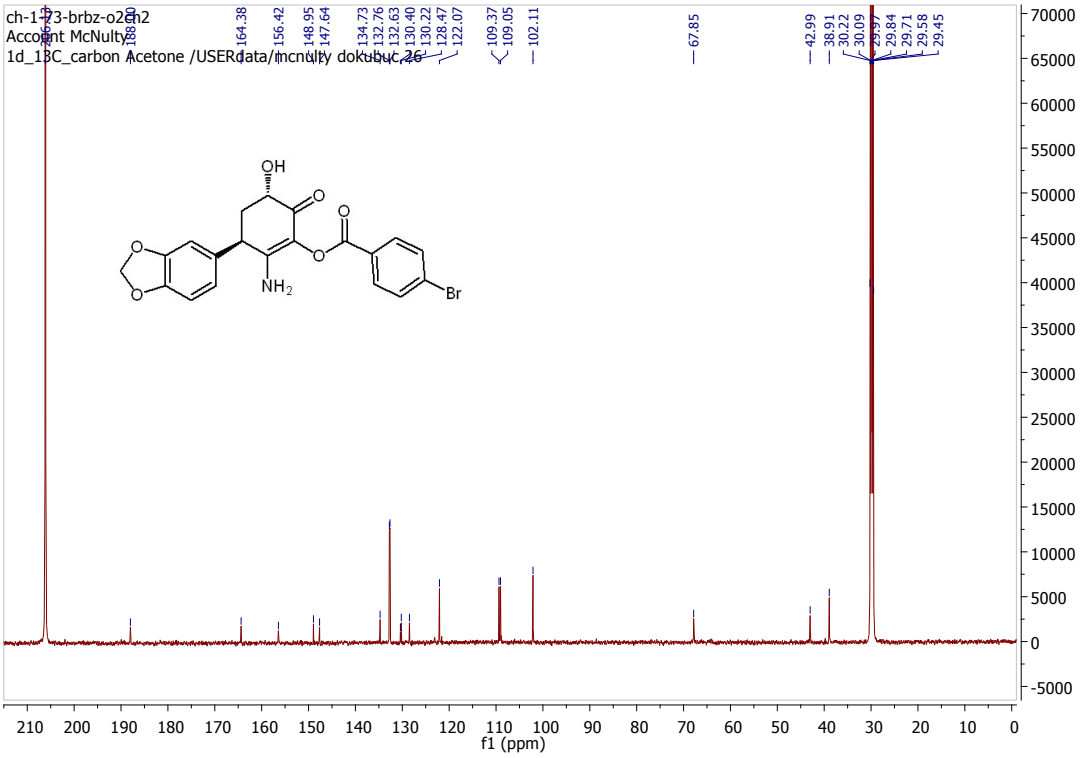
NH2
O
O
f1 (ppm)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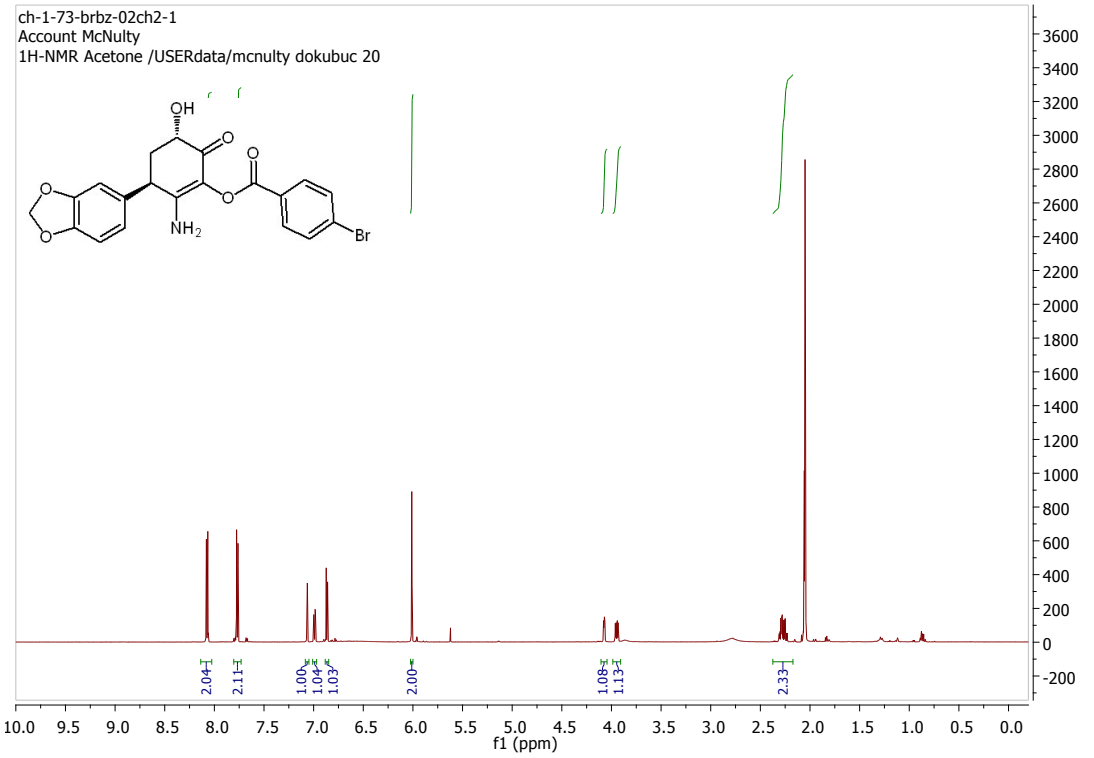
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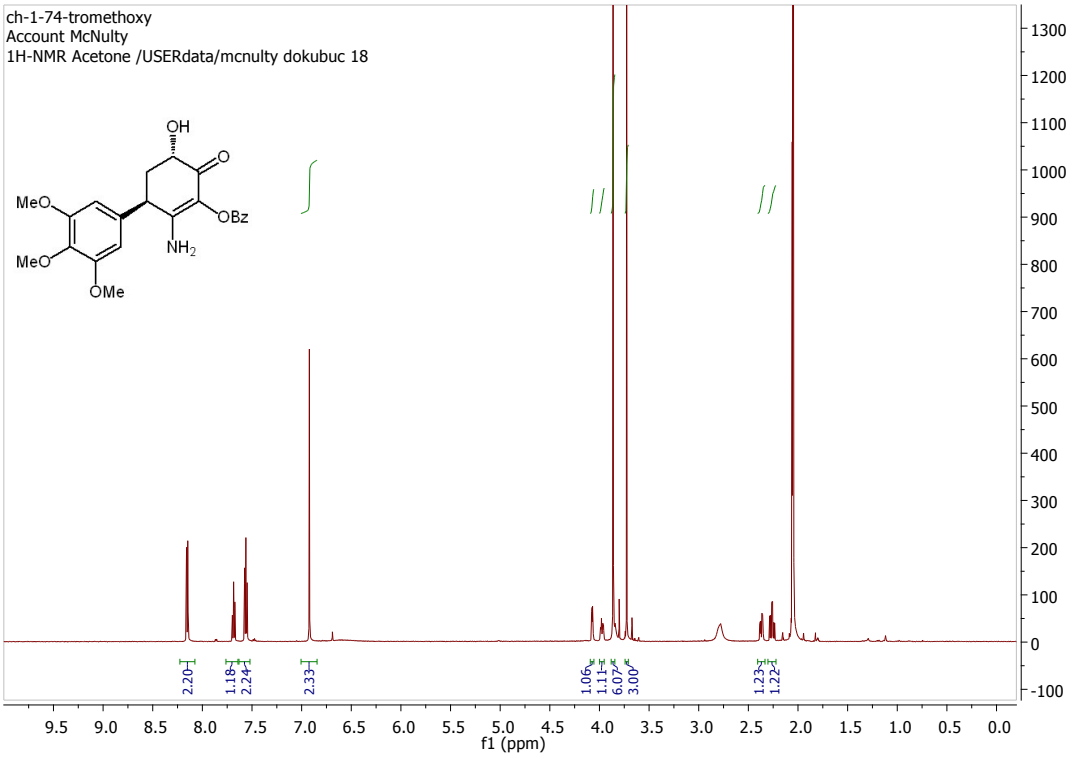
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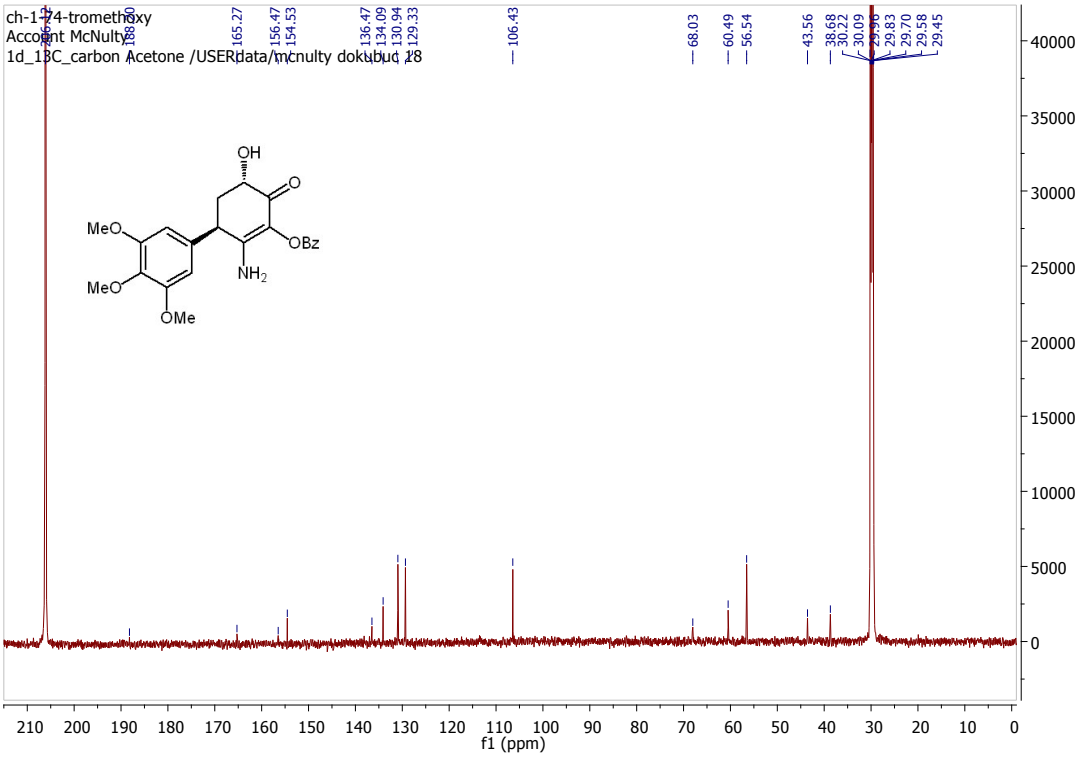
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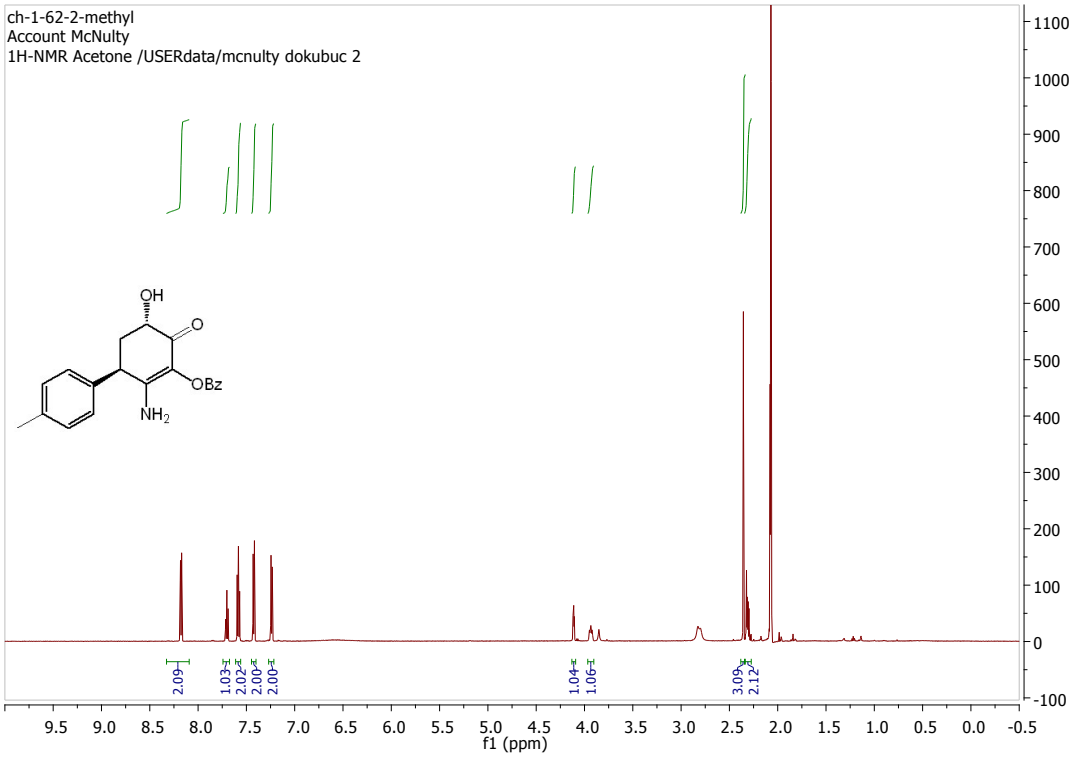
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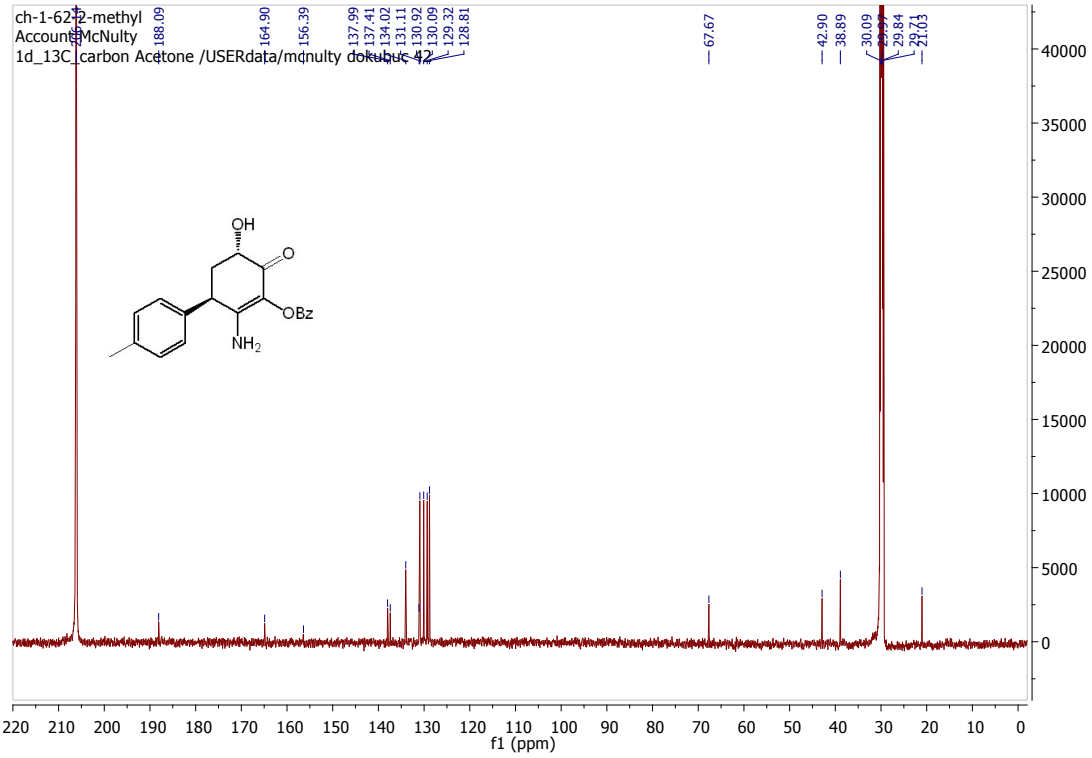
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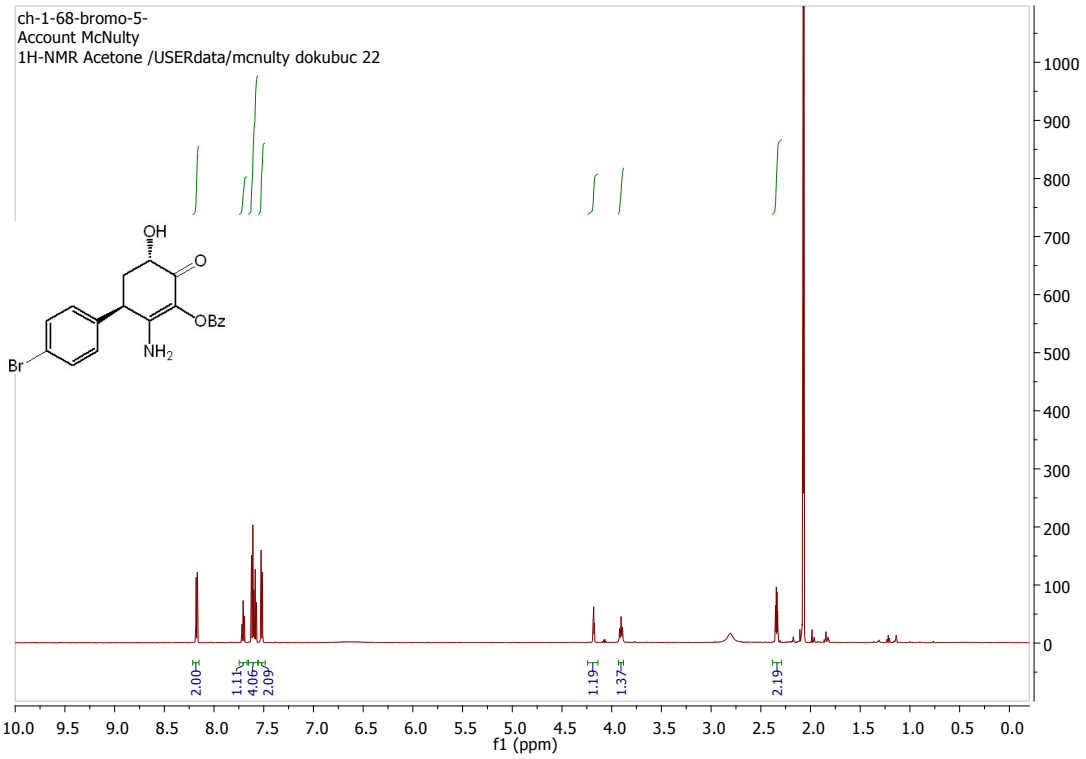
f1 (ppm)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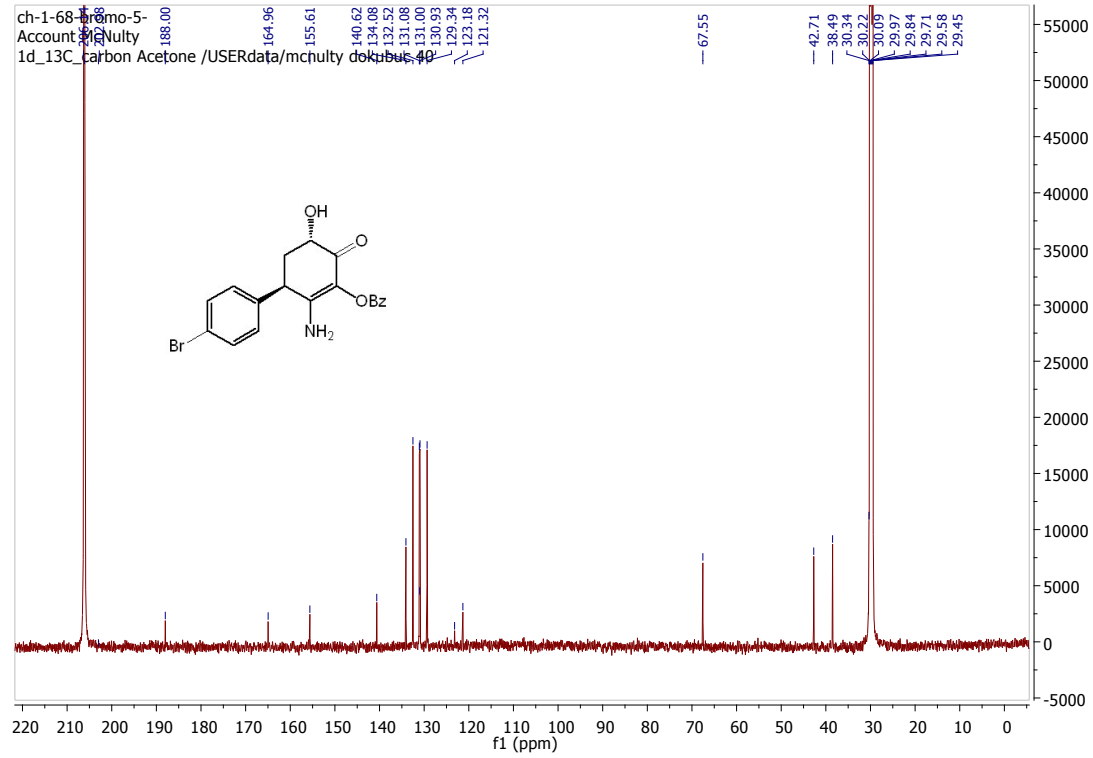
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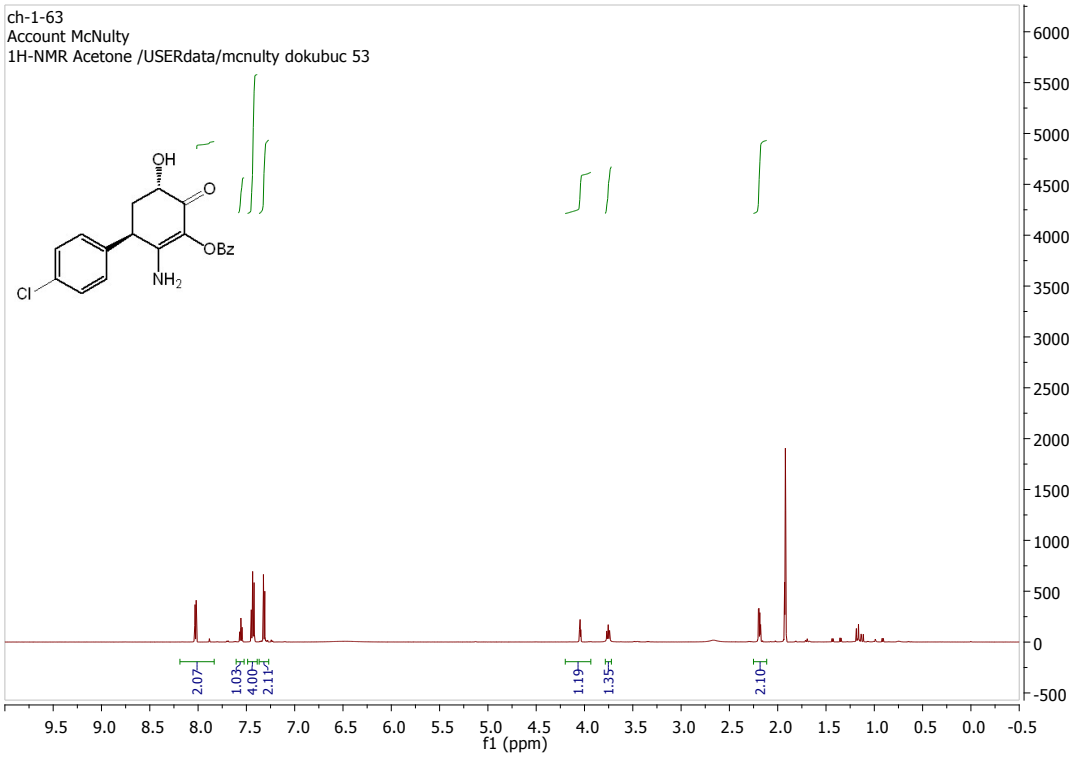
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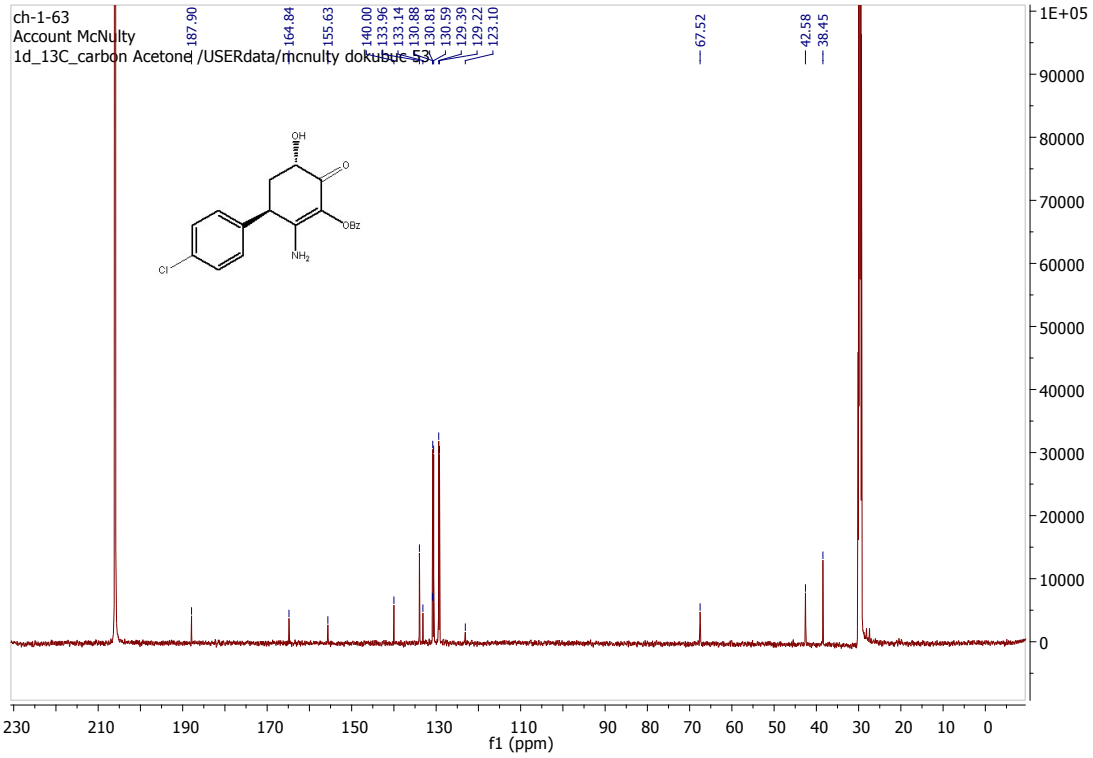
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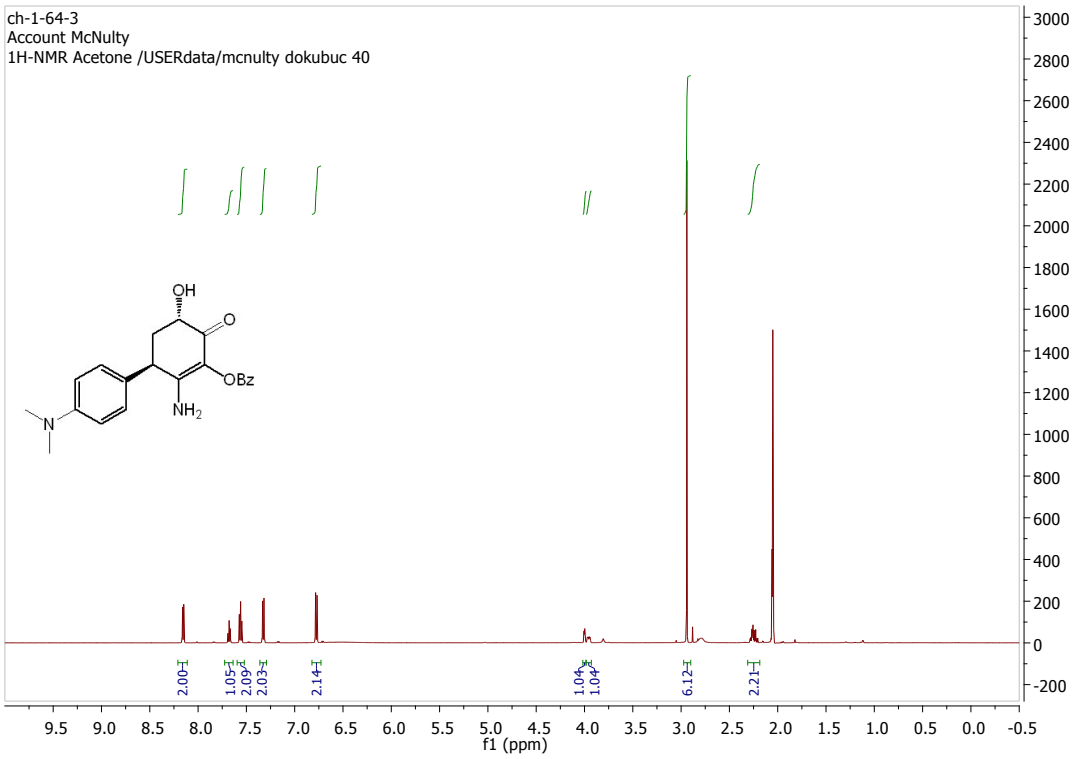
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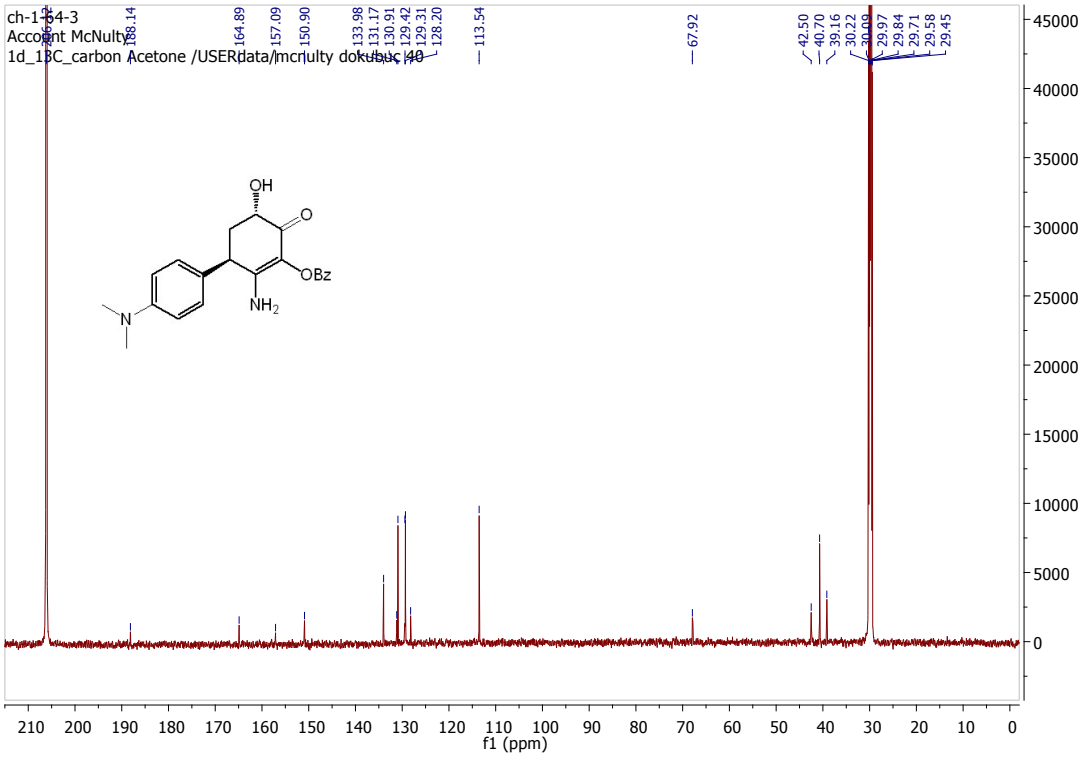
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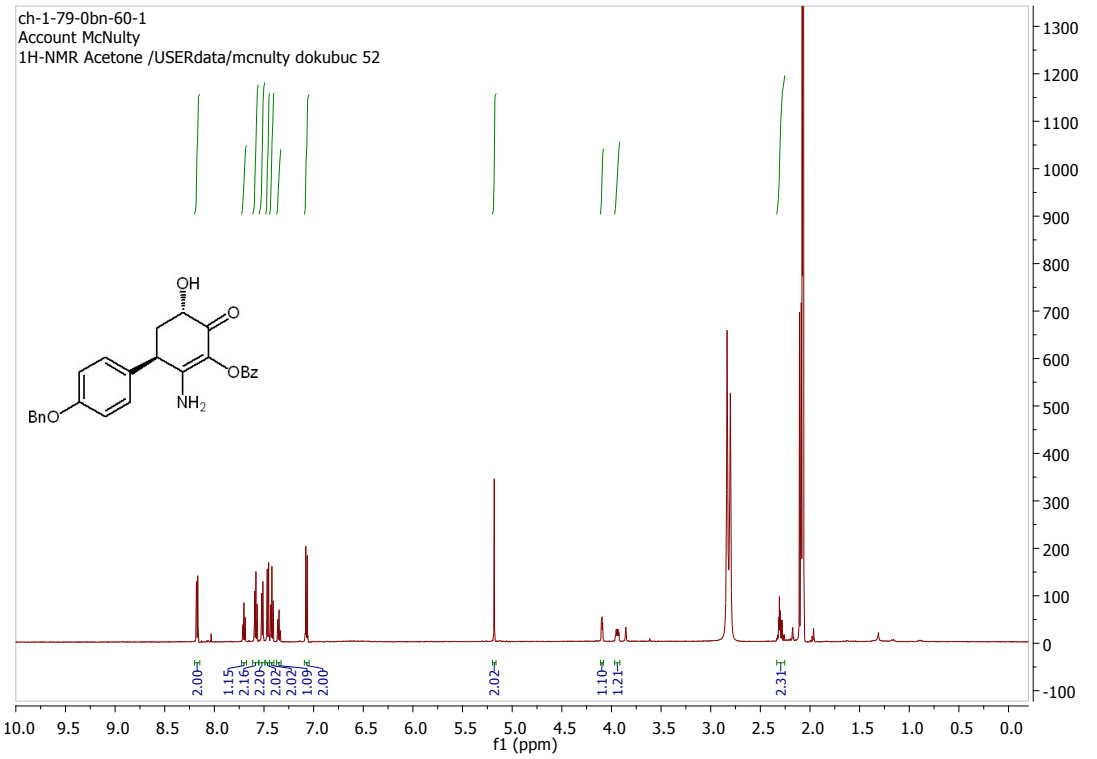
f1 (ppm)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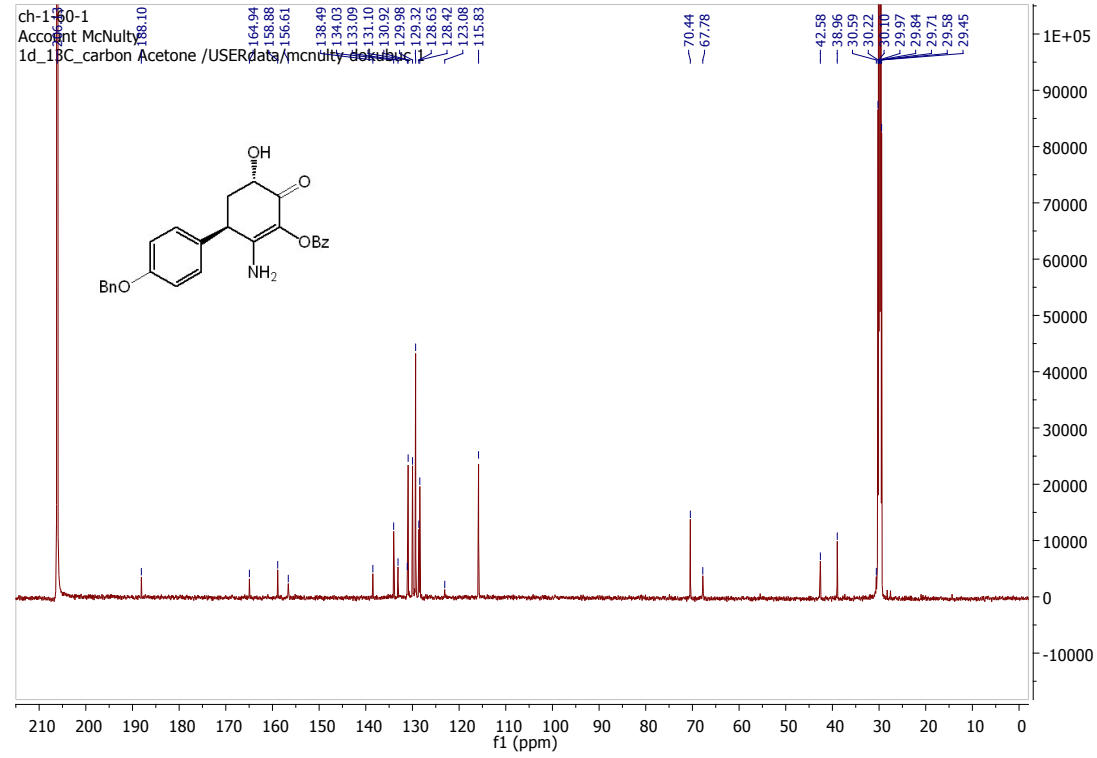
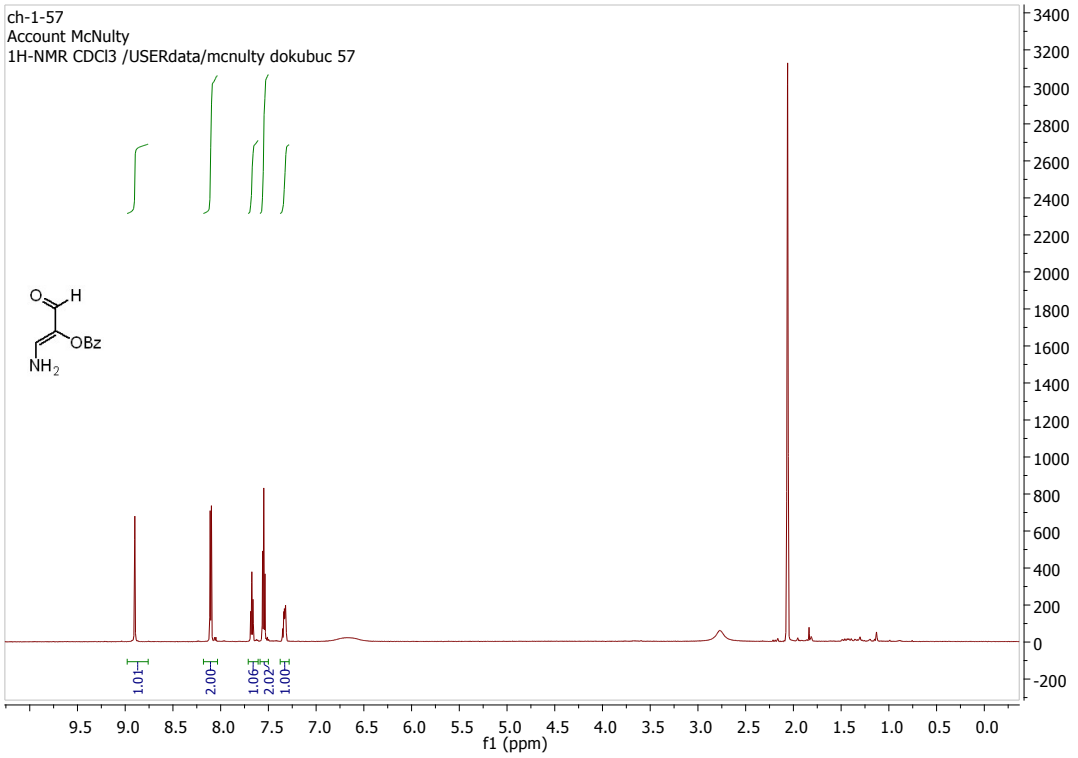
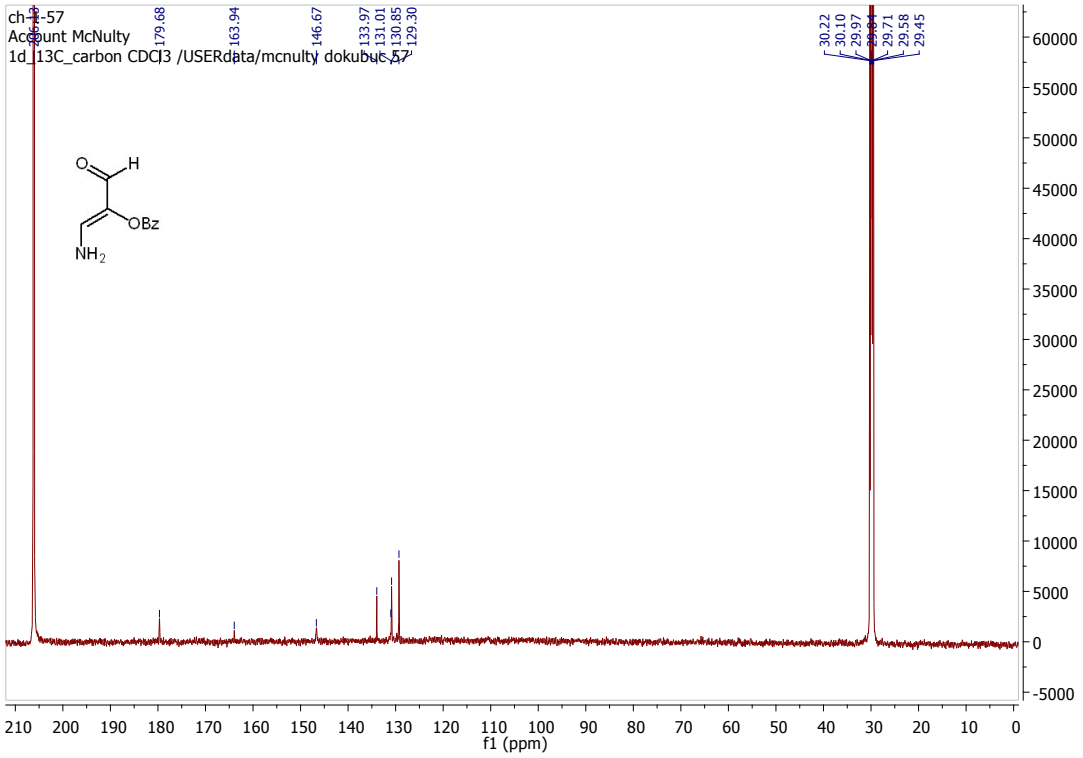
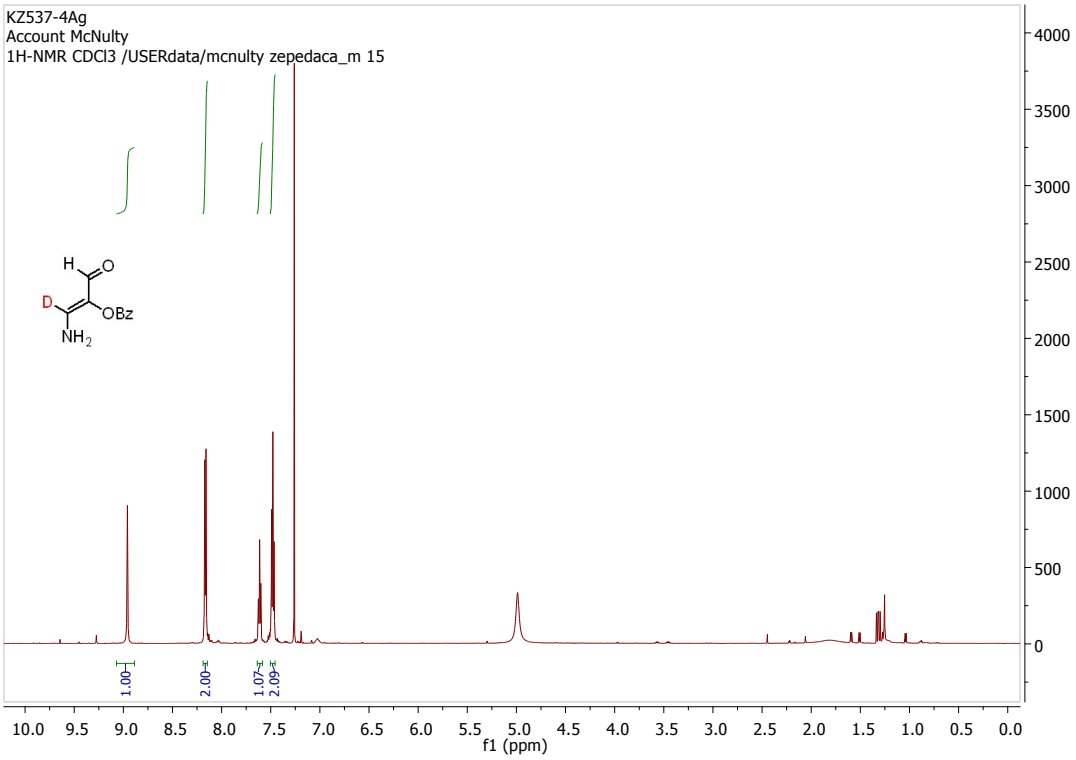
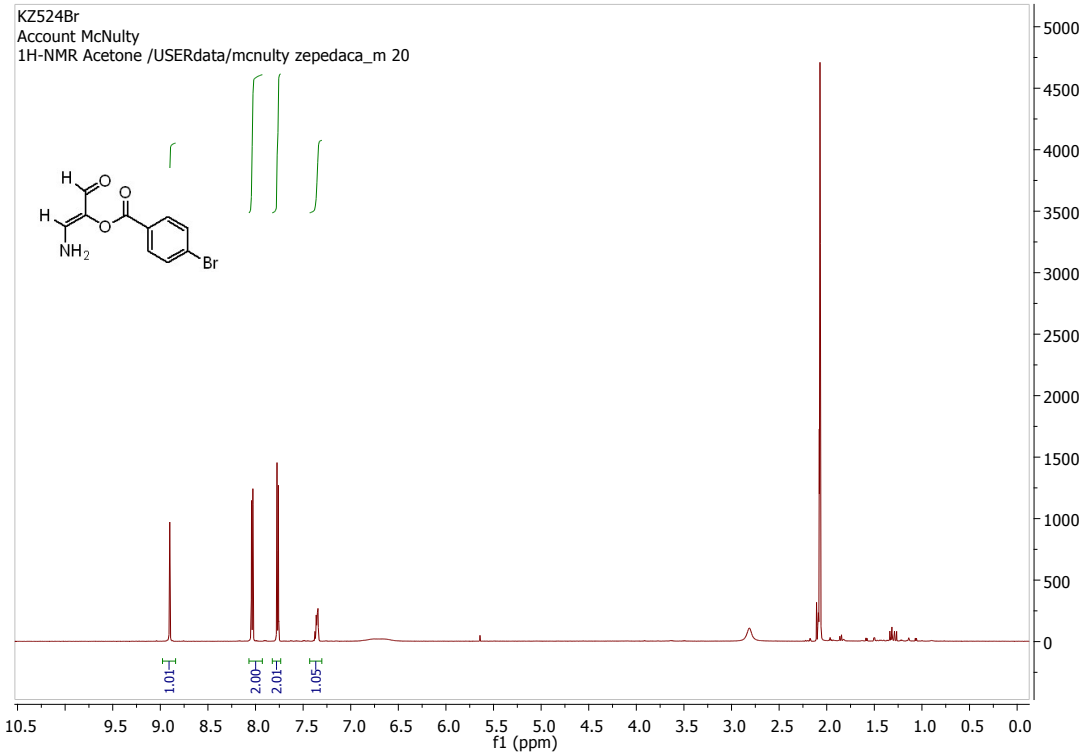
1.21
2.31
f1 (ppm)

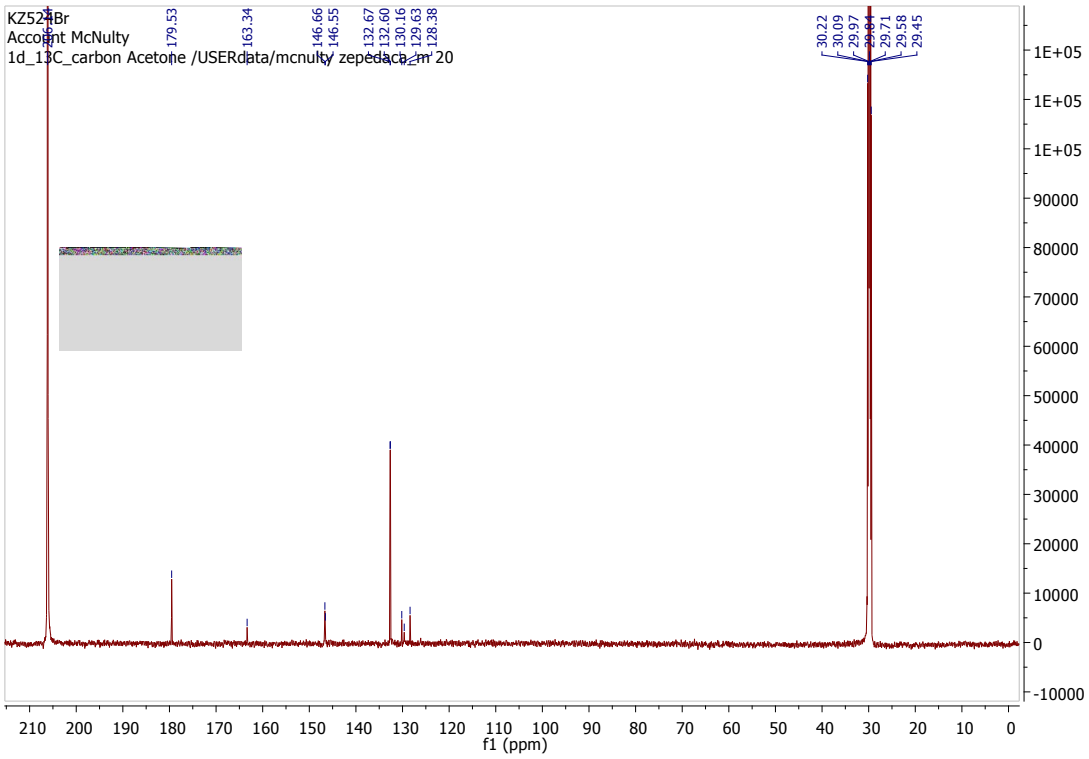

ch-1-60-1
Account McNulty
1d_13C_carbon Acetone /USERdata/mcnulty dokubuc 1
188.10
164.94
158.88
156.61
138.49
134.03
133.09
131.10
130.92
129.98
129.32
128.63
128.42
123.08
115.83
70.44
67.78
42.58
38.96
30.59
30.22
30.10
29.97
29.84
29.71
29.58
29.45
OH
O
OBz
NH2
BnO
f1 (ppm)

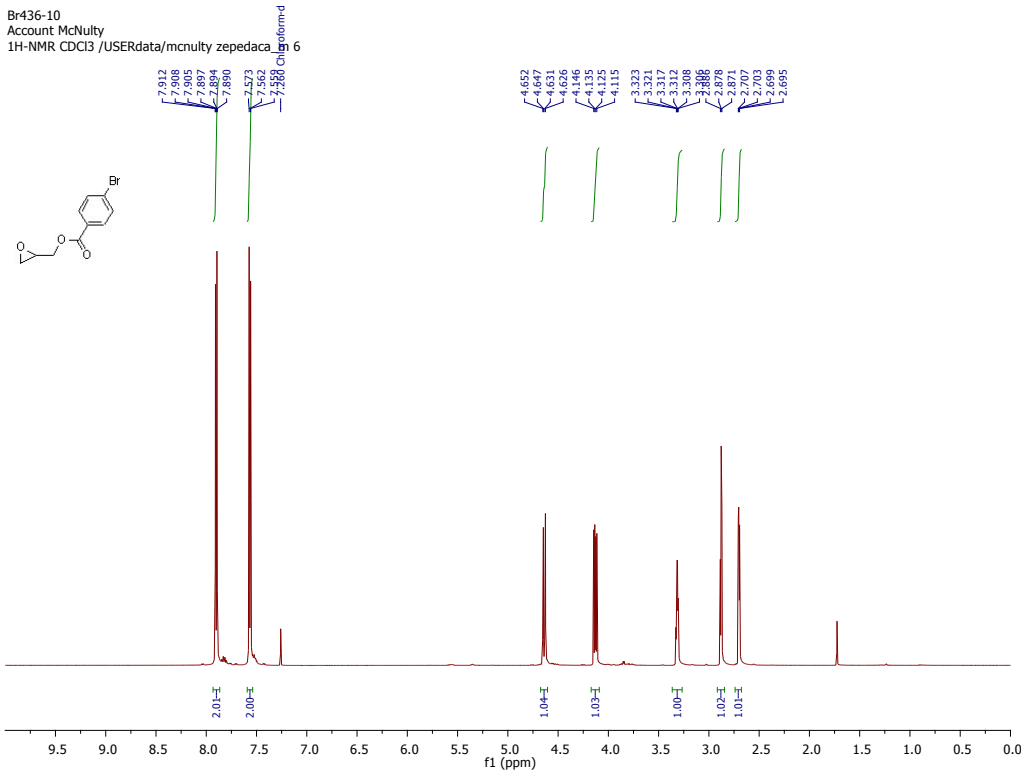

ch-1-57
Account McNulty
1H-NMR CDCl3 /USERdata/mcnulty dokubuc 57
O
H
OBz
NH2
1.01
2.00
1.06
2.02
1.00
f1 (ppm)

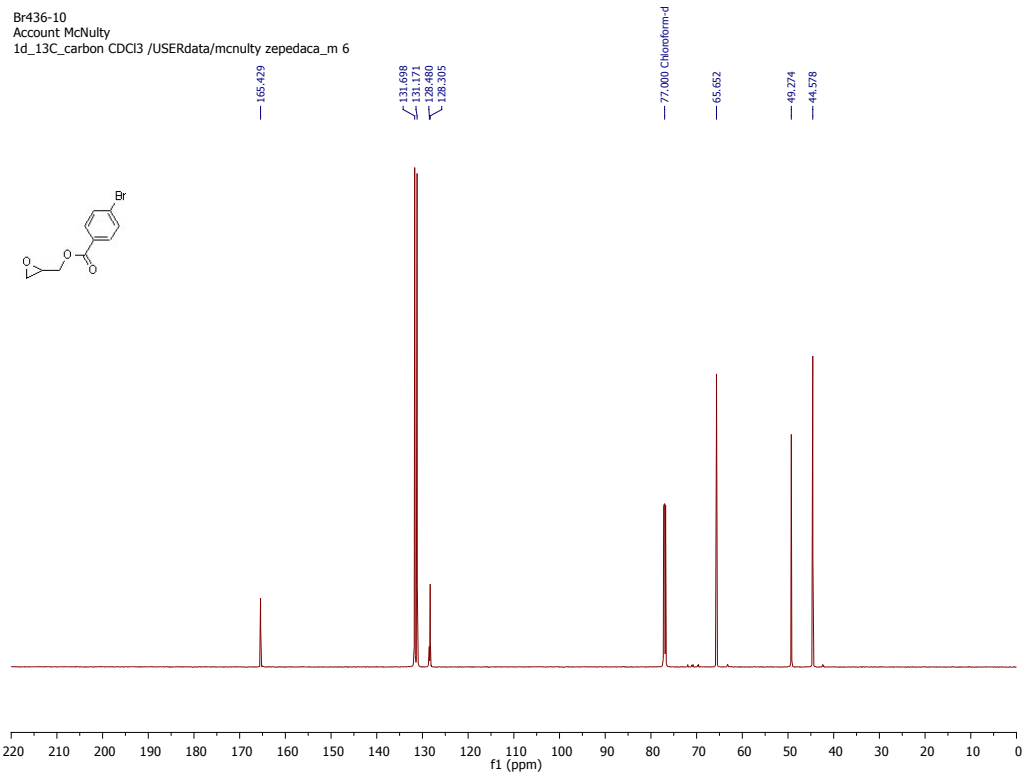

ch-1-57
Account McNulty
1d_13C_carbon CDCl3 /USERdata/mcnulty dokubuc 57
179.68
163.94
146.67
133.97
131.01
130.85
129.30
30.22
30.10
29.97
29.84
29.71
29.58
29.45
O
H
OBz
NH2
f1 (ppm)

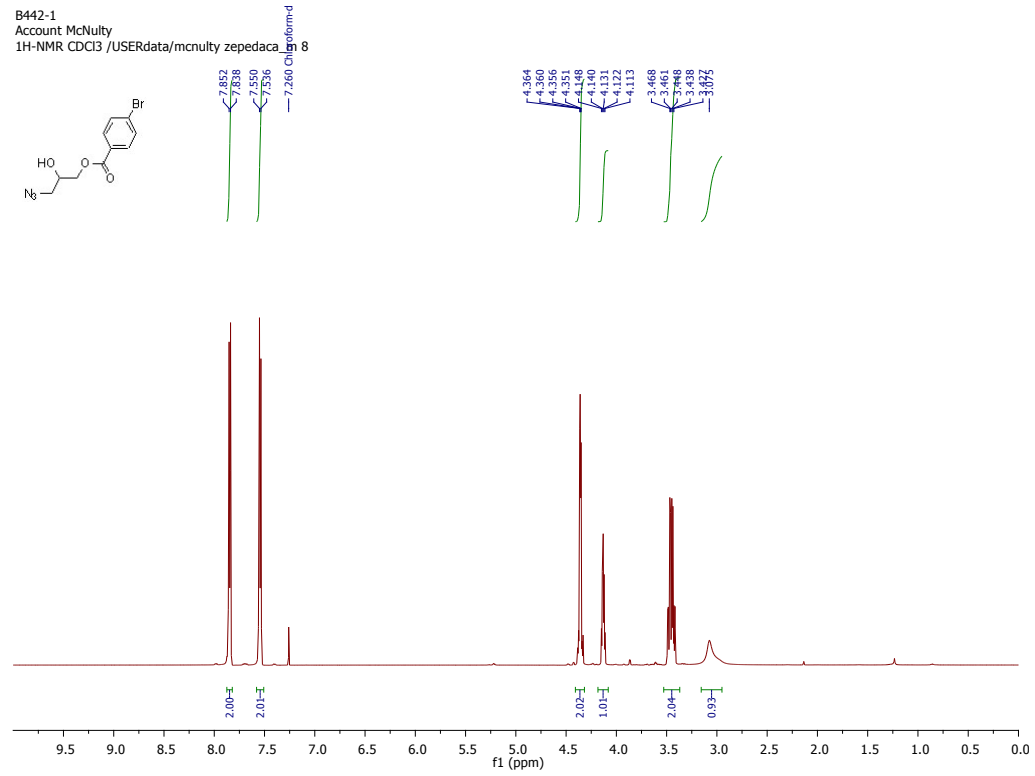

KZ537-4Ag
Account McNulty
1H-NMR CDCl3 /USERdata/mcnulty zepedaca_m 15
H
O
D
OBz
NH2
1.00
2.00
1.07
2.09
4000
3500
3000
2500
2000
1500
1000
500
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

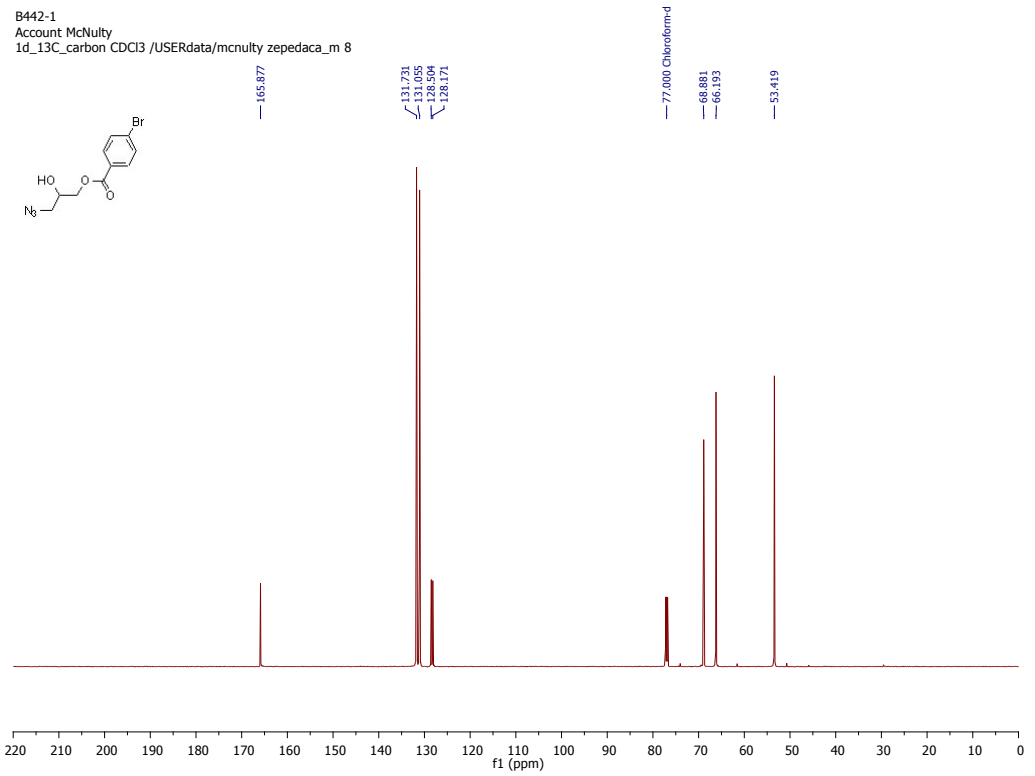

KZ524Br
Account McNulty
1H-NMR Acetone /USERdata/mcnulty zepedaca_m 20
H
O
H
O
O
NH2
Br
1.01
2.00
2.01
1.05
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

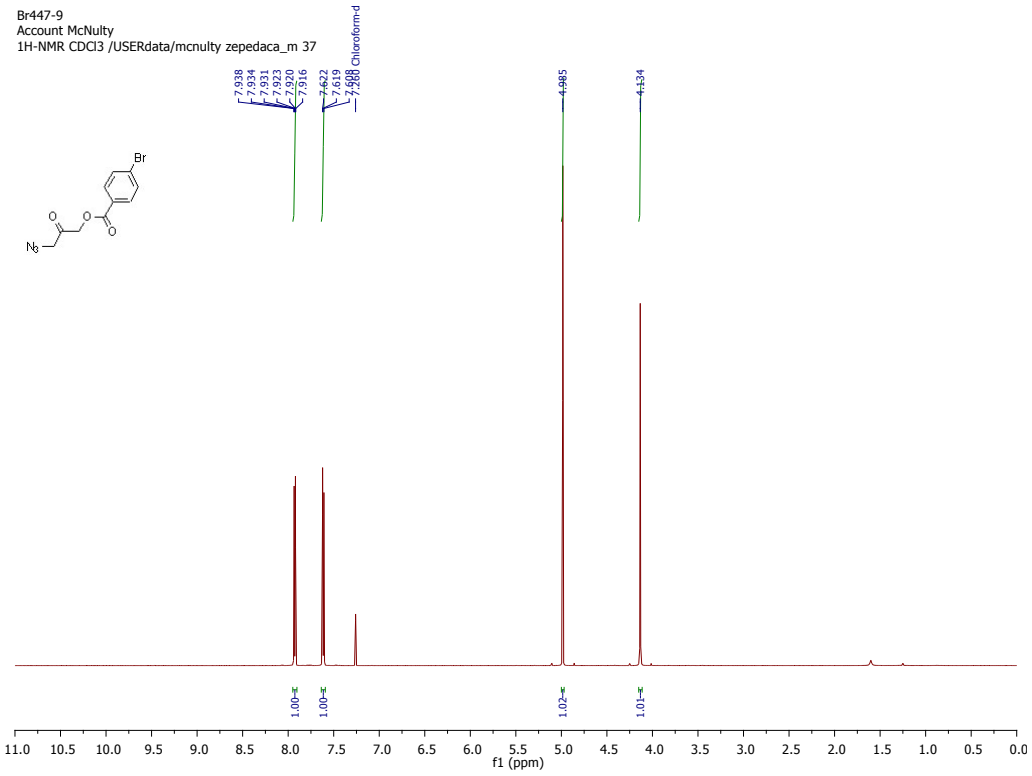

KZ524Br
Account McNulty
1d_13C_carbon Acetone /USERdata/mcnulty zepeda/ca_m 20
179.53
163.34
146.66
146.55
132.67
132.60
130.16
129.63
128.38
30.22
30.09
29.97
29.84
29.71
29.58
29.45
1E+05
1E+05
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

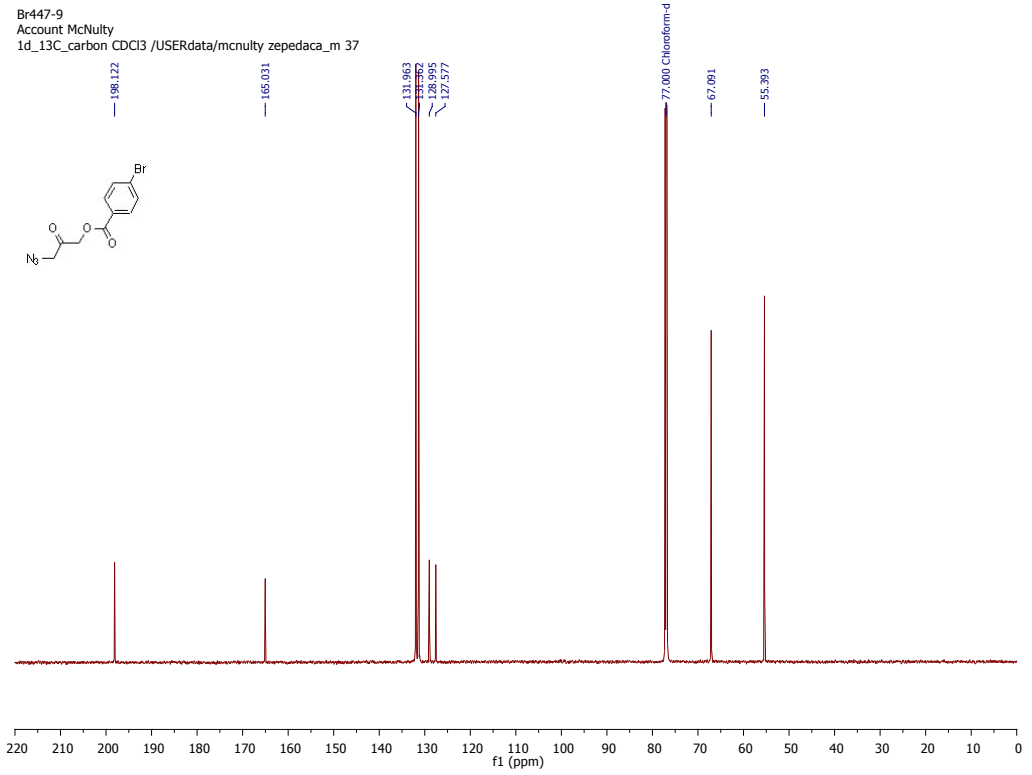

Br436-10
Account McNulty
1H-NMR CDCl3 /USERdata/mcnulty zepedaca_m 6
7.912
7.908
7.905
7.897
7.894
7.890
7.573
7.562
7.558
7.260 Chloroform-d
4.652
4.647
4.631
4.626
4.146
4.135
4.125
4.115
3.323
3.321
3.317
3.312
3.308
2.878
2.871
2.707
2.703
2.699
2.695
Br
O
O
O
2.01
2.00
1.04
1.03
1.00
1.02
1.01
9.5 9.0 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
f1 (ppm)

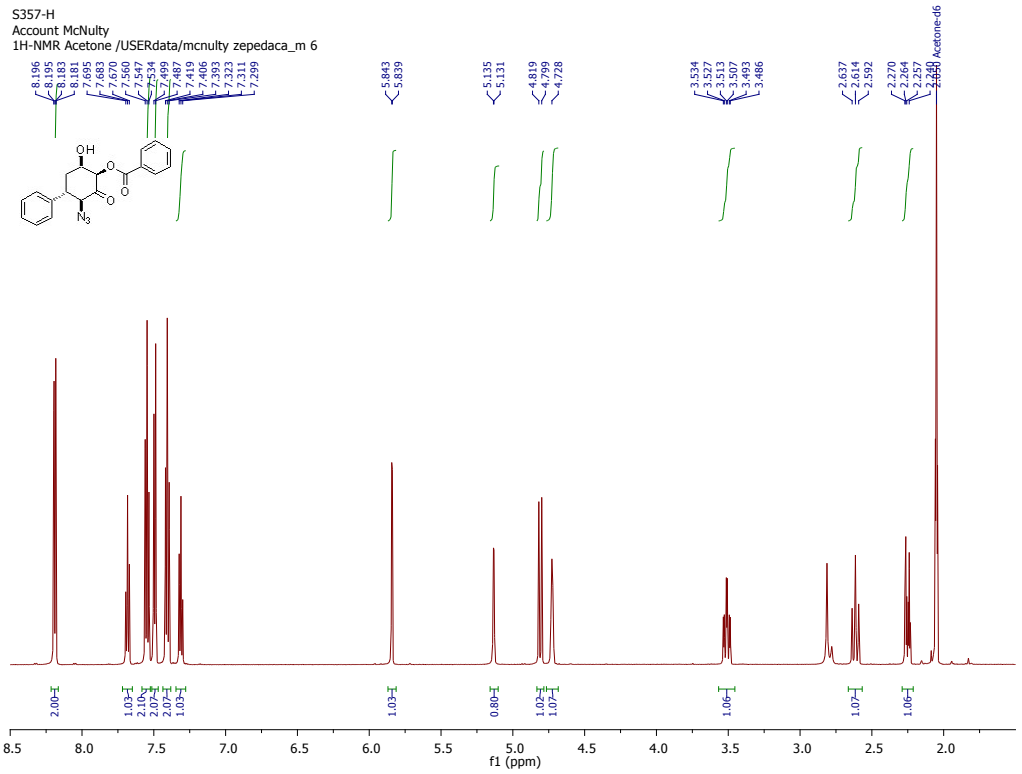

Br436-10
Account McNulty
1d_13C_carbon CDCl3 /USERdata/mcnulty zepedaca_m 6
165.429
131.698
131.171
128.480
128.305
77.000 Chloroform-d
65.652
49.274
44.578
Br
O
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

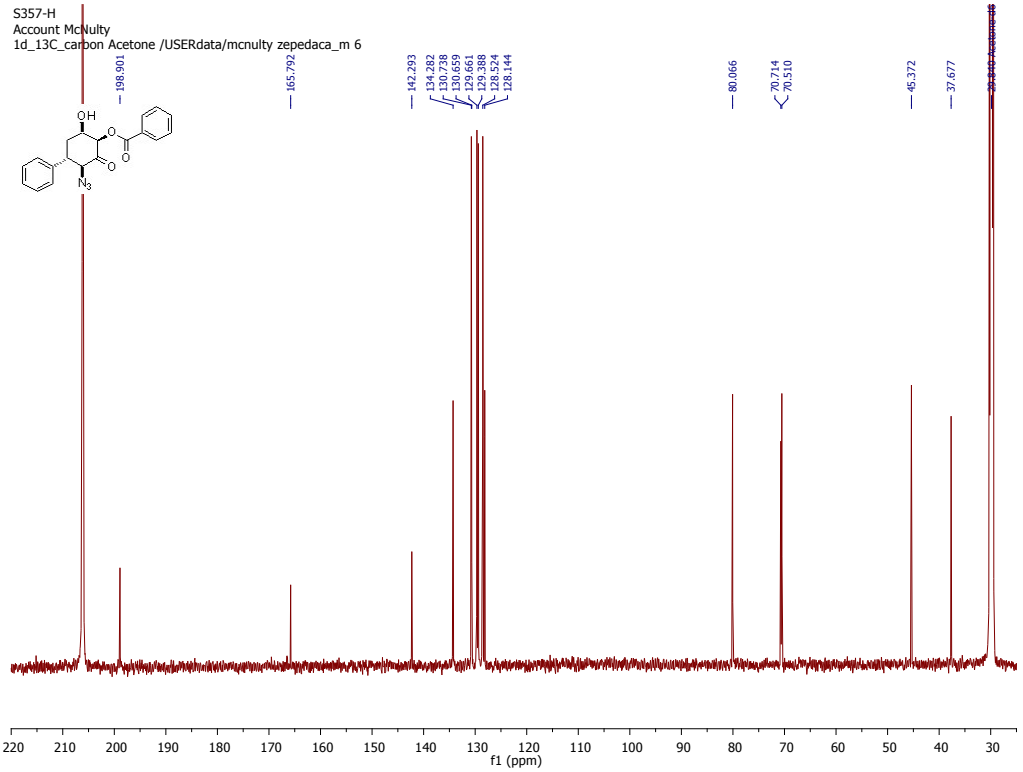

B442-1
Account McNulty
1H-NMR CDCl3 /USERdata/mcnulty zepedaca_m 8
7.852
7.838
7.550
7.536
7.260 Chloroform-d
4.364
4.360
4.356
4.351
4.148
4.140
4.131
4.122
4.113
3.468
3.461
3.448
3.438
3.432
3.075
Br
HO
O
O
N3
2.00
2.01
2.02
1.01
2.04
0.93
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

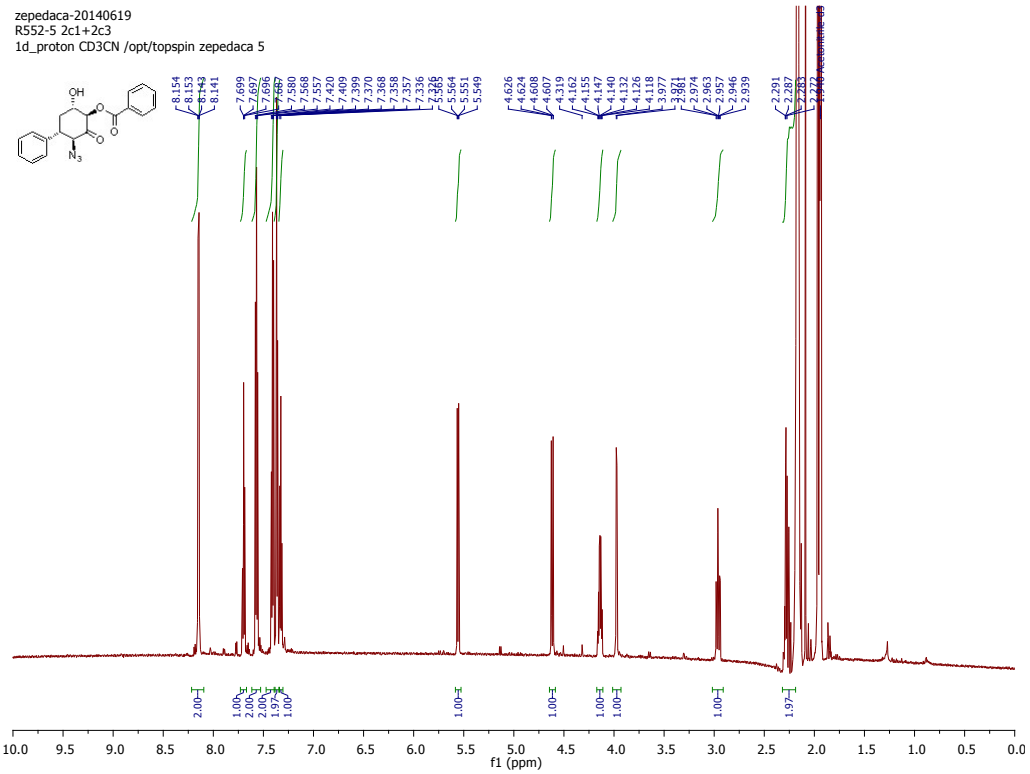

B442-1
Account McNulty
1d_13C_carbon CDCl3 /USERdata/mcnulty zepedaca_m 8
165.877
131.731
131.055
128.504
128.171
77.000 Chloroform-d
68.881
66.193
53.419
Br
HO
O
O
N3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

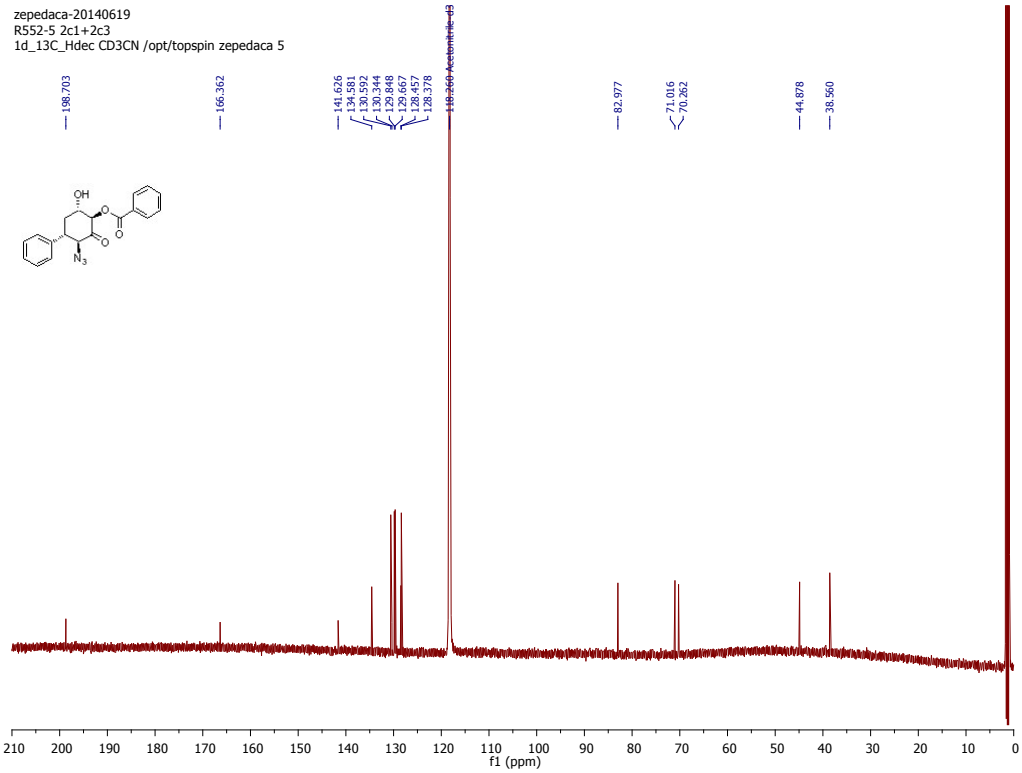

Br447-9
Account McNulty
1H-NMR CDCl3 /USERdata/mcnulty zepedaca_m 37
7.938
7.934
7.931
7.923
7.920
7.916
7.622
7.619
7.608
7.600 Chloroform-d
4.985
4.434
Br
O
O
O
N3
1.00
1.00
1.02
1.01
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

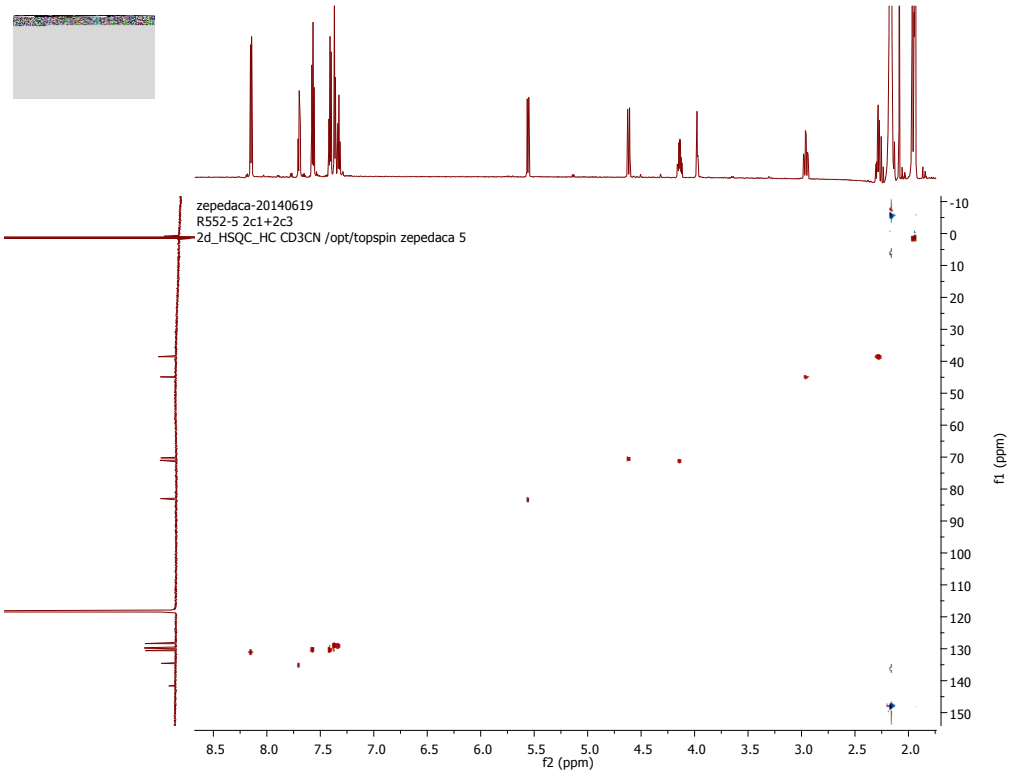

Br447-9
Account McNulty
1d_13C_carbon CDCl3 /USERdata/mcnulty zepedaca_m 37
198.122
165.031
131.963
131.362
128.995
127.577
77.000 Chloroform-d
67.091
55.393
Br
O
O
O
N3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

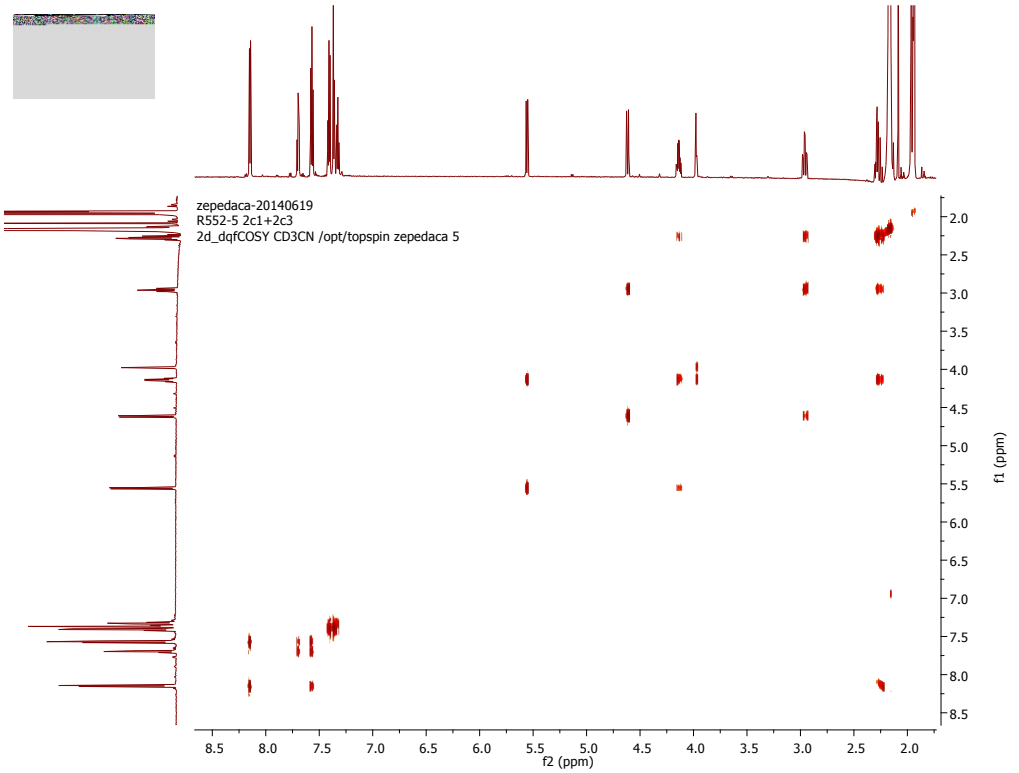

S357-H
Account McNulty
1H-NMR Acetone /USERdata/mcnulty zepedaca_m 6
8.196
8.195
8.183
8.181
7.691
7.683
7.670
7.560
7.547
7.534
7.499
7.487
7.419
7.406
7.393
7.331
7.311
7.299
5.843
5.839
5.135
5.131
4.819
4.799
4.728
3.534
3.527
3.513
3.507
3.493
3.486
2.637
2.614
2.592
2.270
2.264
2.257
2.053 Acetone-d6
OH
O
O
O
N3
2.00
1.03
2.10
2.07
2.07
1.03
1.03
0.80
1.02
1.07
1.06
1.07
1.06
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
f1 (ppm)

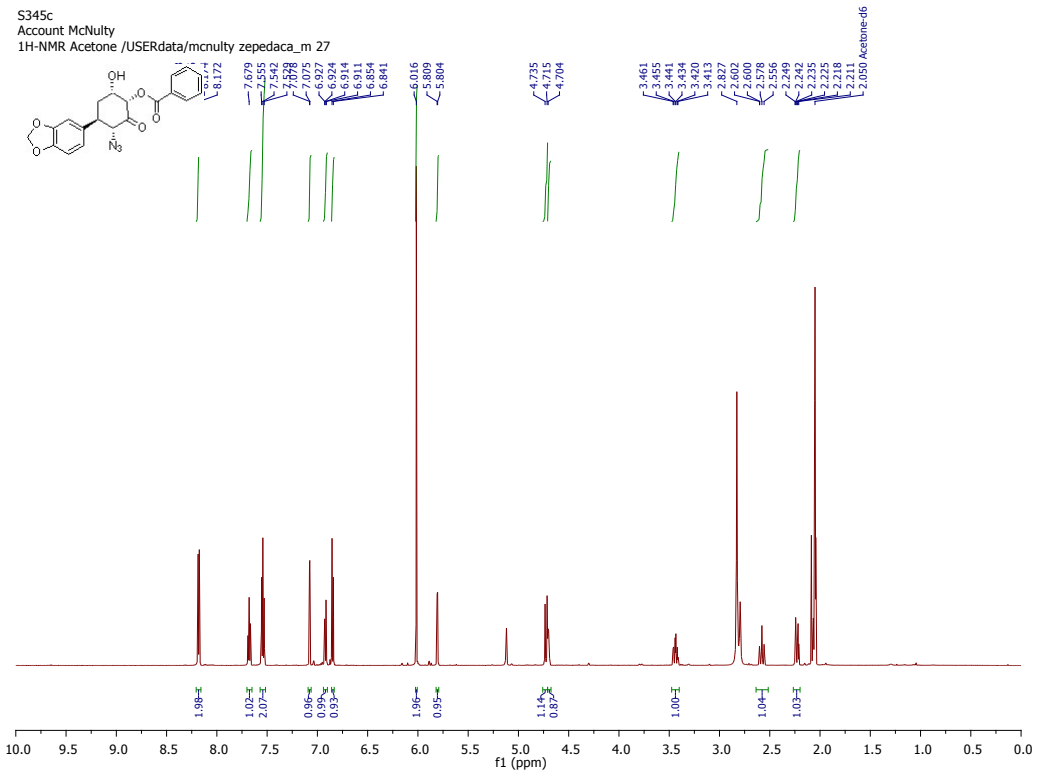

S357-H
Account McNulty
1d_13C_carbon Acetone /USERdata/mcnulty zepedaca_m 6
198.901
165.792
142.293
134.282
130.738
130.659
129.661
129.388
128.524
128.144
80.066
70.714
70.510
45.372
37.677
29.840 Acetone-d6
OH
O
O
O
N3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

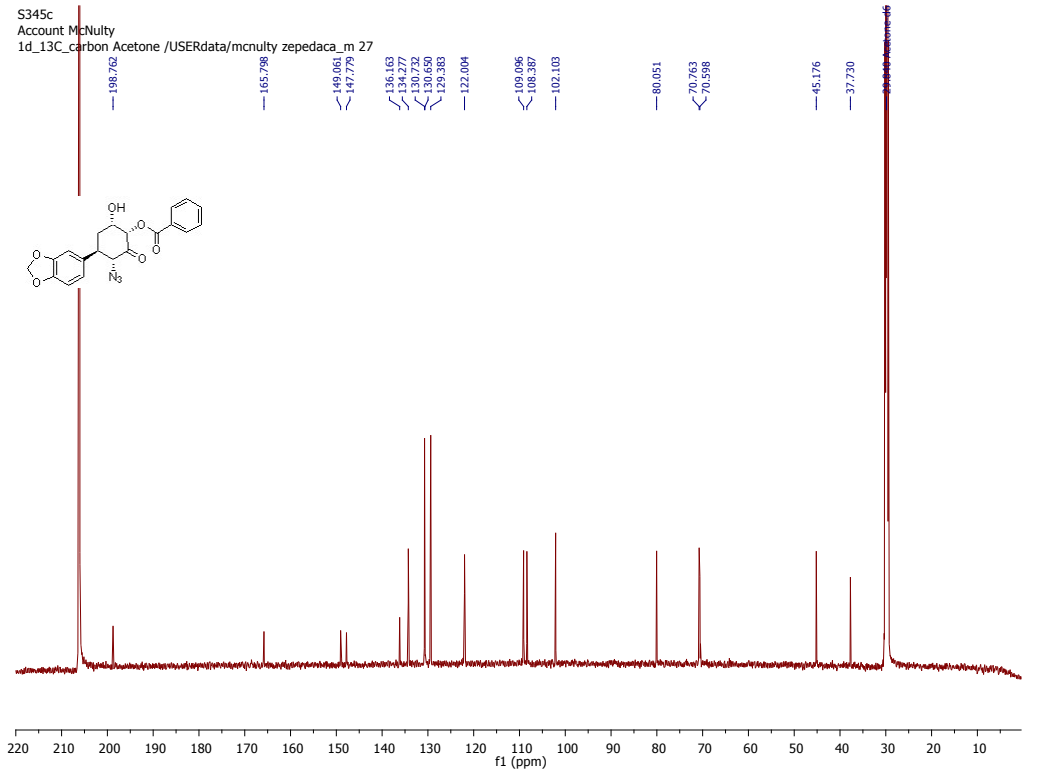

zepedaca-20140619
R552-5 2c1+2c3
1d_proton CD3CN /opt/topspin zepedaca 5
f1 (ppm)

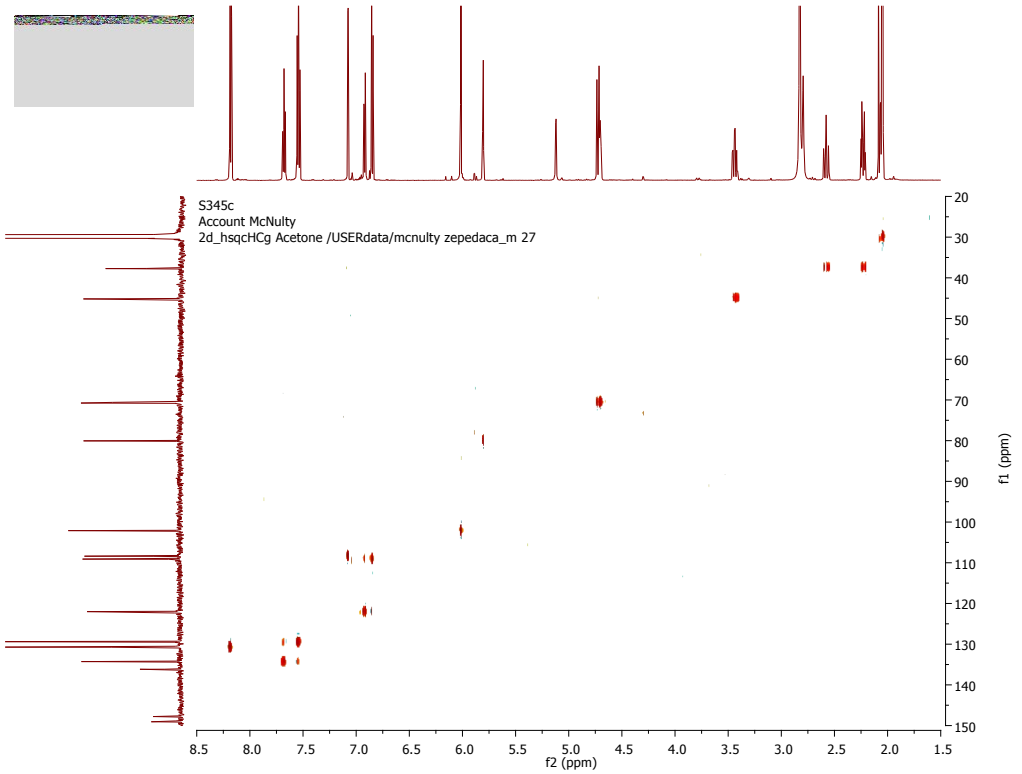

zepedaca-20140619
R552-5 2c1+2c3
1d_13C_Hdec CD3CN /opt/topspin zepedaca 5
198.703
166.362
141.626
134.581
130.592
130.344
129.848
129.667
128.457
128.378
82.977
71.016
70.262
44.878
38.560
f1 (ppm)

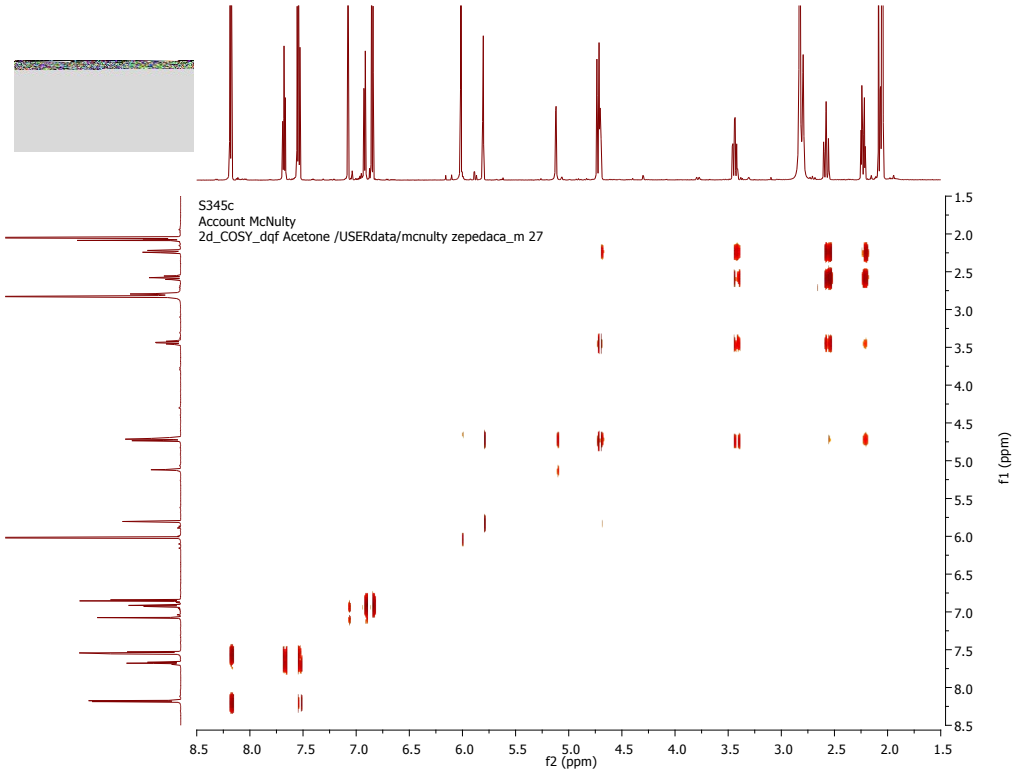

zepedaca-20140619
R552-5 2c1+2c3
2d_HSQC_HC CD3CN /opt/topspin zepedaca 5
f2 (ppm)
f1 (ppm)

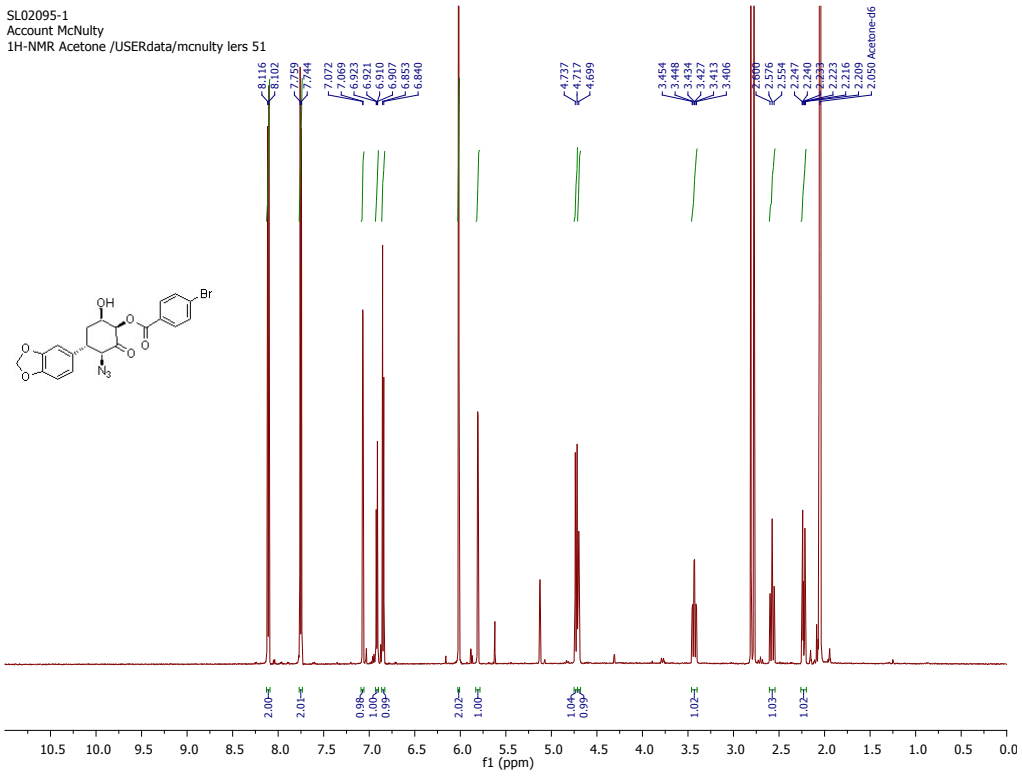

zepedaca-20140619
R552-5 2c1+2c3
2d_dqfCOSY CD3CN /opt/topspin zepedaca 5
f2 (ppm)
f1 (ppm)

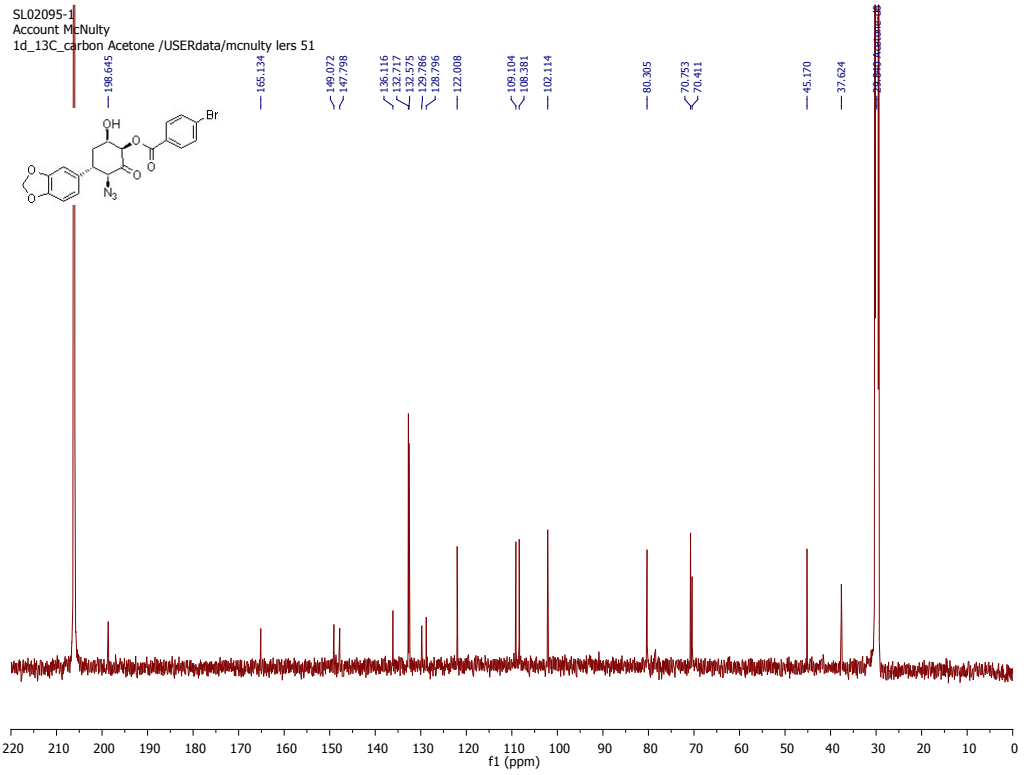

S345c
Account McNulty
1H-NMR Acetone /USERdata/mcnulty zepedaca_m 27
f1 (ppm)

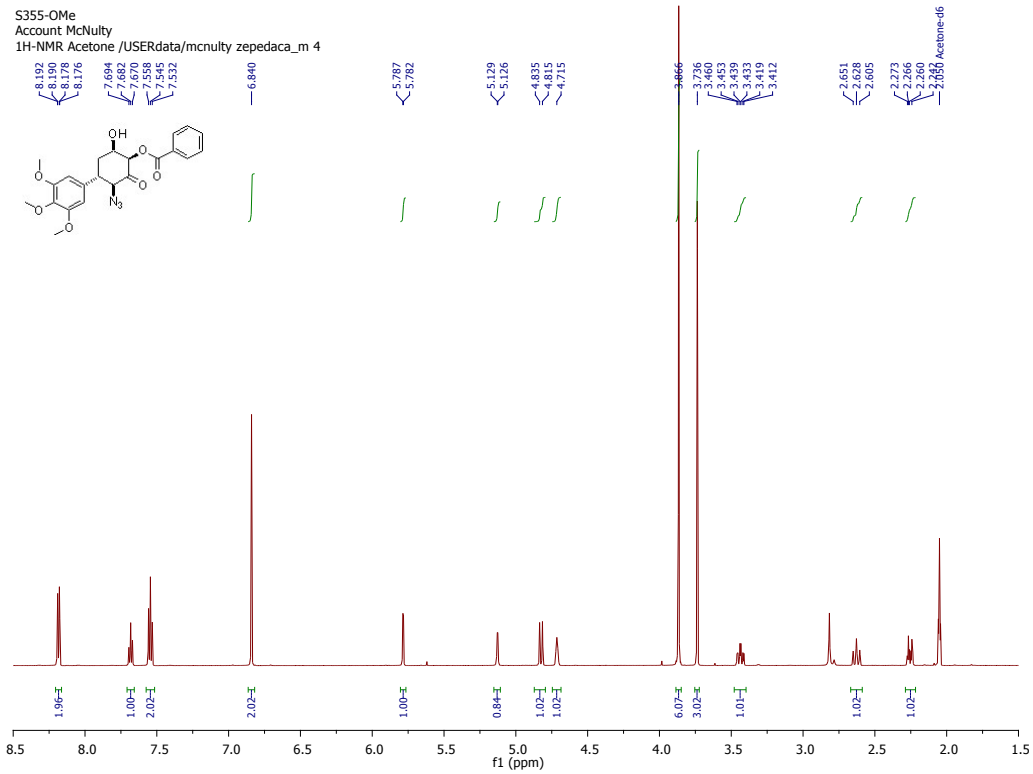

S345c
Account McNulty
1d_13C_carbon Acetone /USERdata/mcnulty zepedaca_m 27
f1 (ppm)

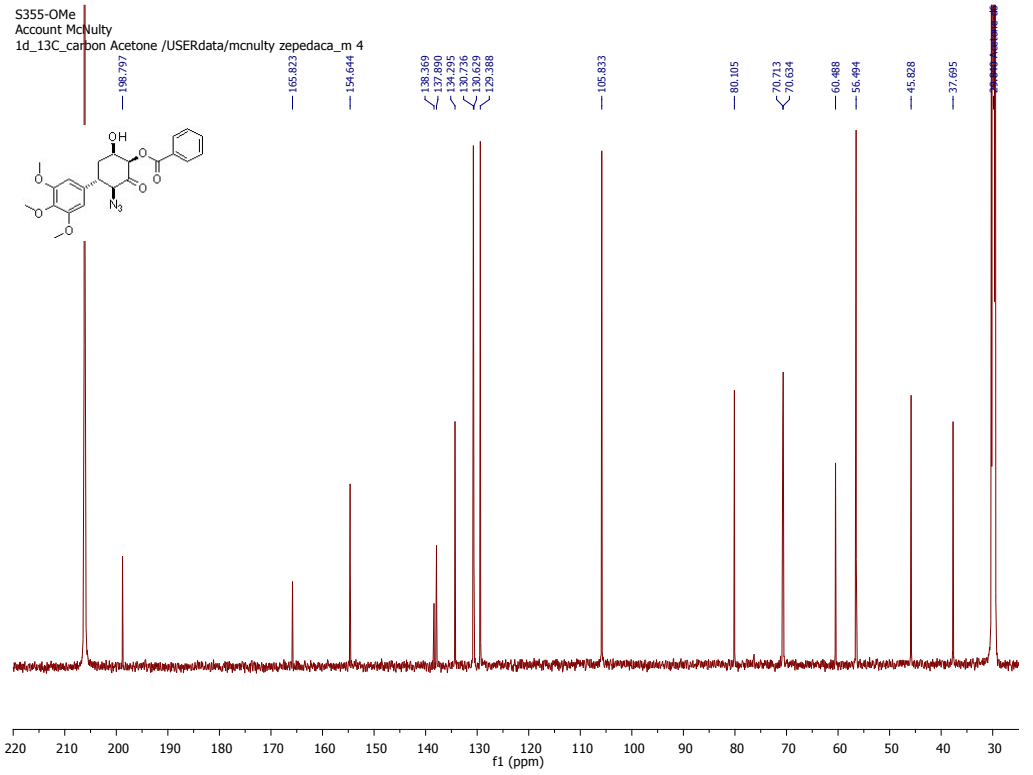

S345c
Account McNulty
2d_hsqcHCg Acetone /USERdata/mcnulty zepedaca_m 27
f2 (ppm)
f1 (ppm)

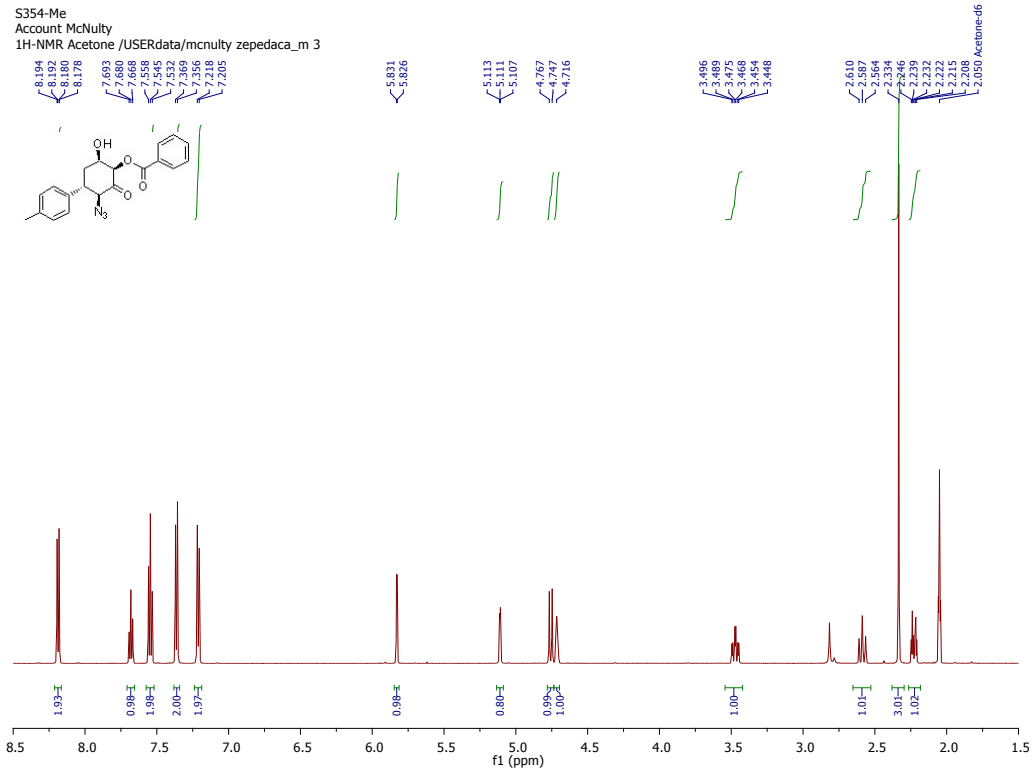

S345c
Account McNulty
2d_COSY_dqf Acetone /USERdata/mcnulty zepedaca_m 27
f2 (ppm)
f1 (ppm)


SL02095-1
Account McNulty
1H-NMR Acetone /USERdata/mcnulty lers 51
8.116
8.102
7.759
7.744
7.072
7.069
6.923
6.921
6.910
6.907
6.853
6.840
4.737
4.717
4.699
3.454
3.448
3.434
3.427
3.413
3.406
2.880
2.576
2.554
2.247
2.240
2.233
2.223
2.216
2.209
2.050 Acetone-d6
OH
Br
O
O
O
O
O
N3
2.00
2.01
0.98
1.00
0.99
2.02
1.00
1.04
0.99
1.02
1.03
1.02
f1 (ppm)


SL02095-1
Account McNulty
1d_13C_carbon Acetone /USERdata/mcnulty lers 51
198.645
165.134
149.072
147.798
136.116
132.717
132.555
129.786
128.796
122.008
109.104
108.381
102.114
80.305
70.753
70.411
45.170
37.624
OH
Br
O
O
O
O
O
N3
f1 (ppm)


S355-OMe
Account McNulty
1H-NMR Acetone /USERdata/mcnulty zepedaca_m 4
f1 (ppm)


S355-OMe
Account McNulty
1d_13C_carbon Acetone /USERdata/mcnulty zepedaca_m 4
f1 (ppm)


S354-Me
Account McNulty
1H-NMR Acetone /USERdata/mcnulty zepedaca_m 3
8.194
8.192
8.180
8.178
7.693
7.680
7.668
7.558
7.545
7.532
7.369
7.356
7.218
7.205
5.831
5.826
5.113
5.111
5.107
4.767
4.747
4.716
3.496
3.489
3.475
3.468
3.454
3.448
2.610
2.597
2.564
2.334
2.246
2.239
2.232
2.222
2.215
2.208
2.050 Acetone-d6
OH
O
O
O
N3
1.93
0.98
1.98
2.00
1.97
0.98
0.80
0.99
1.00
1.00
1.01
3.01
1.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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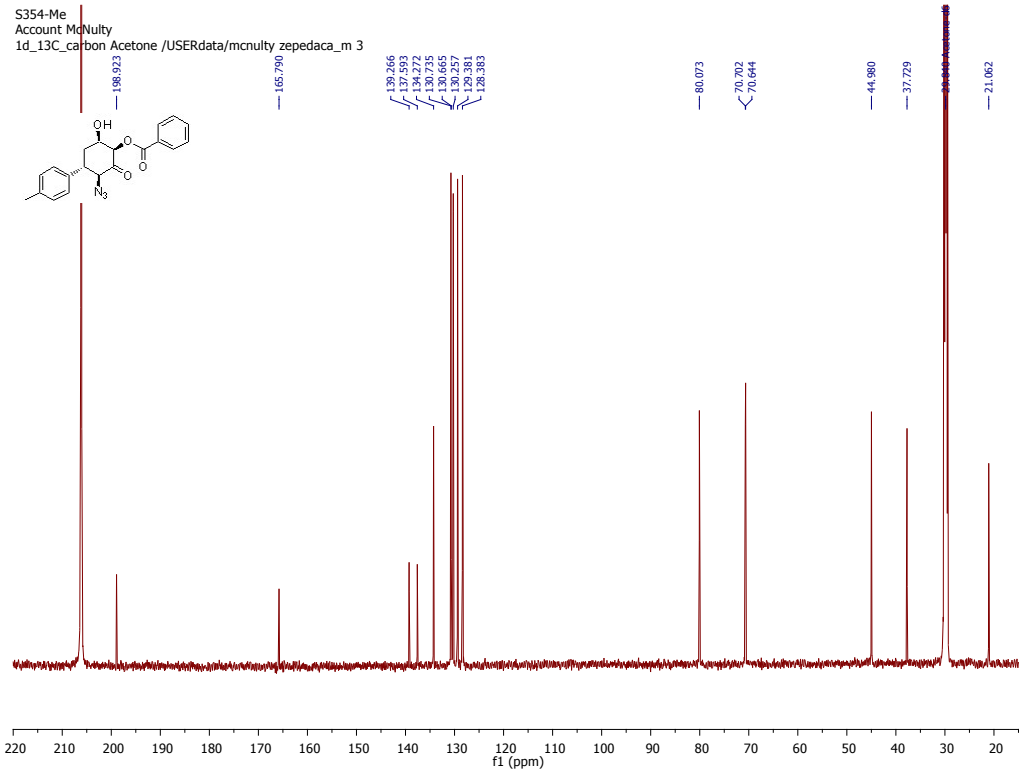
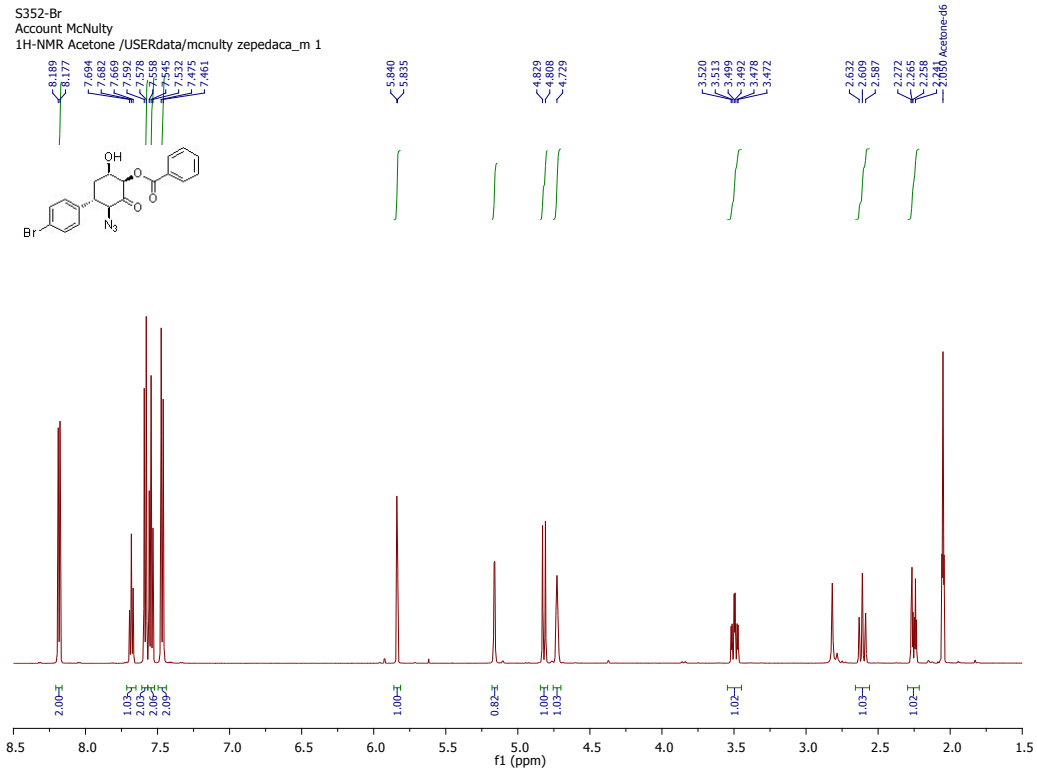
3.0
2.5
2.0
1.5
f1 (ppm)


S354-Me
Account McNulty
1d_13C_carbon Acetone /USERdata/mcnulty zepedaca_m 3
198.923
165.790
139.266
137.593
134.272
130.735
130.665
130.257
129.381
128.383
80.073
70.702
70.644
44.980
37.729
21.062
OH
O
O
O
N3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


S352-Br
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8.189
8.177
7.694
7.682
7.669
7.592
7.578
7.558
7.545
7.532
7.475
7.461
5.840
5.835
4.829
4.808
4.729
3.520
3.513
3.499
3.492
3.478
3.472
2.632
2.609
2.587
2.272
2.265
2.258
2.050 Acetone-d6
OH
O
O
O
N3
Br
2.00
1.03
2.03
2.06
2.09
1.00
0.82
1.00
1.03
1.02
1.03
1.02
8.5
8.0
7.5
7.0
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6.0
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4.0
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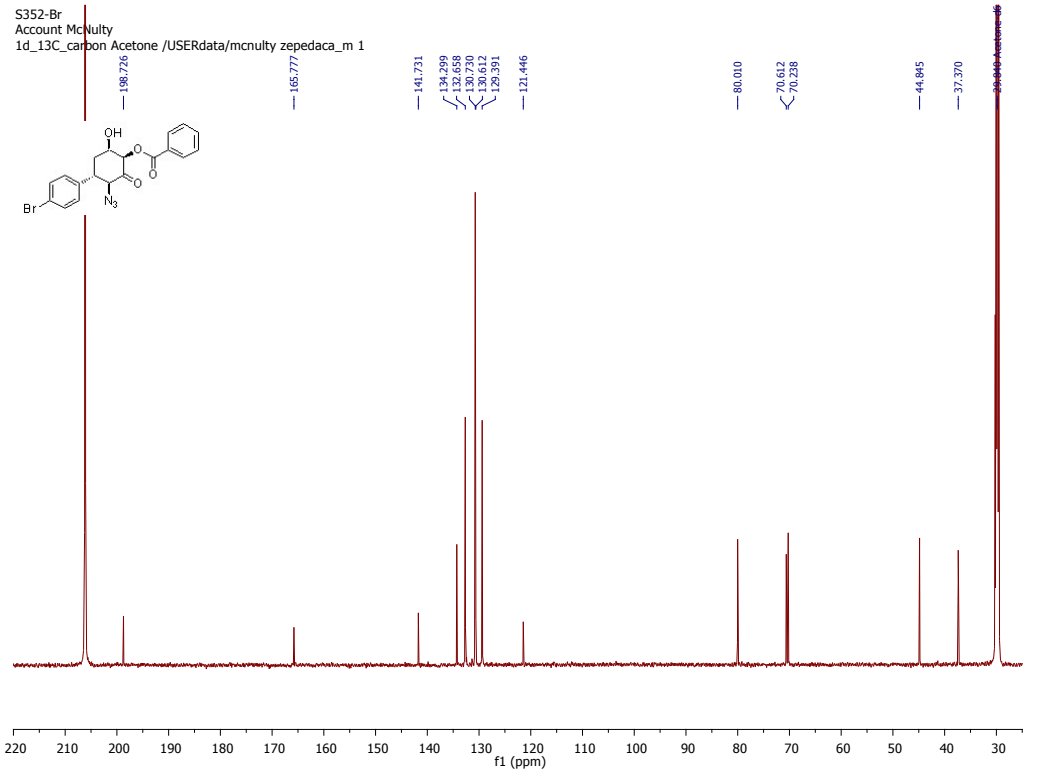
3.0
2.5
2.0
1.5
f1 (ppm)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134.299
132.658
130.730
130.612
129.391
121.446
80.010
70.612
70.238
44.945
37.370
29.840 Acetone-d6
OH
O
O
O
N3
Br
220
210
200
190
180
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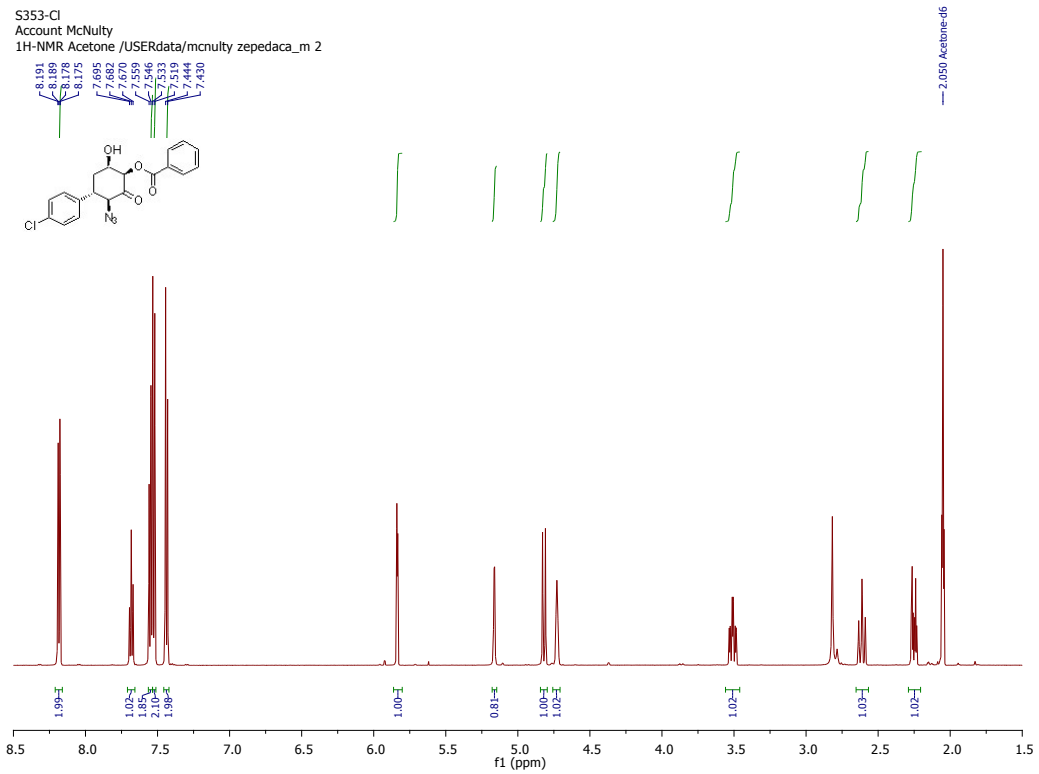
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)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8.175
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7.682
7.670
7.658
7.546
7.533
7.519
7.444
7.430
2.050 Acetone-d6
OH
O
O
O
N3
Cl
1.99
1.02
1.85
2.10
1.98
1.00
0.81
1.00
1.02
1.02
1.03
1.02
8.5
8.0
7.5
7.0
6.5
6.0
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5.0
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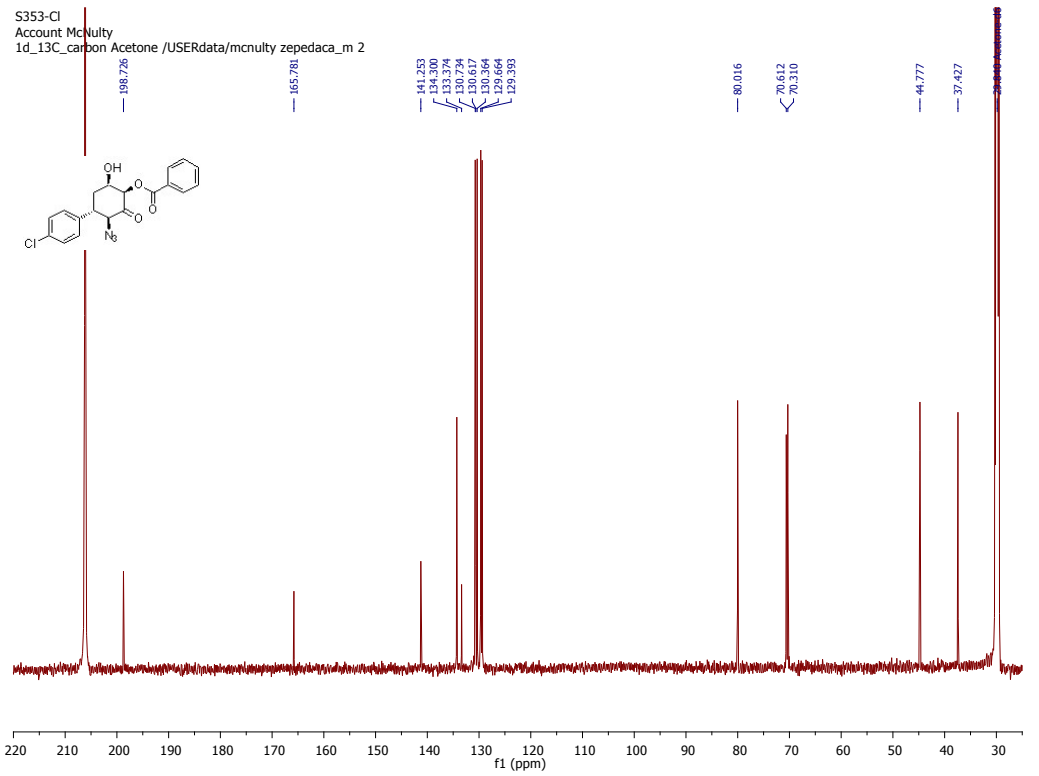
3.0
2.5
2.0
1.5
f1 (ppm)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141.253
134.300
133.374
130.734
130.537
130.064
129.664
129.393
80.016
70.612
70.310
44.777
37.427
OH
O
O
O
N3
Cl
220
210
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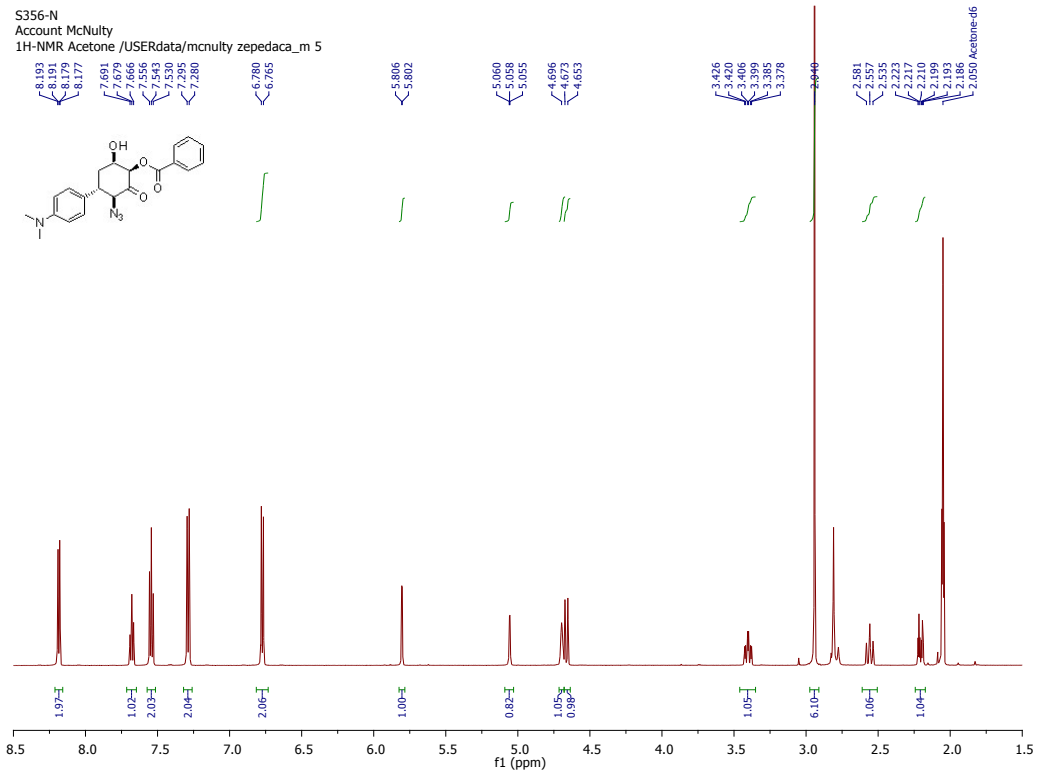
90
80
70
60
50
40
30
f1 (ppm)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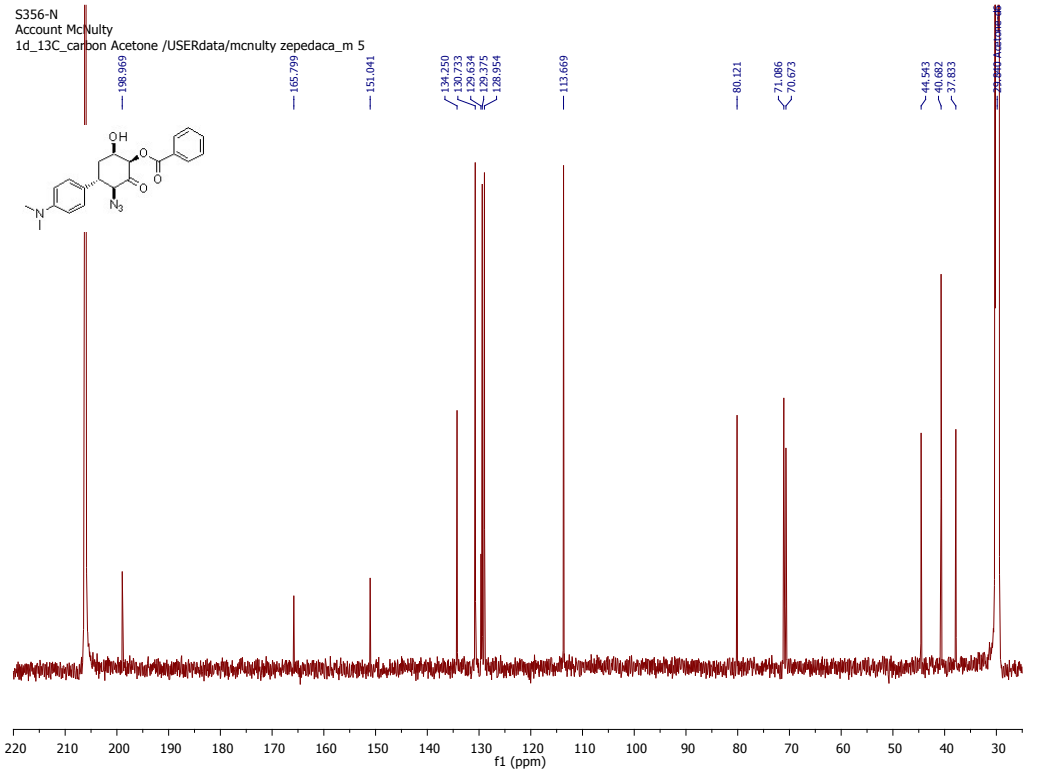
f1 (ppm)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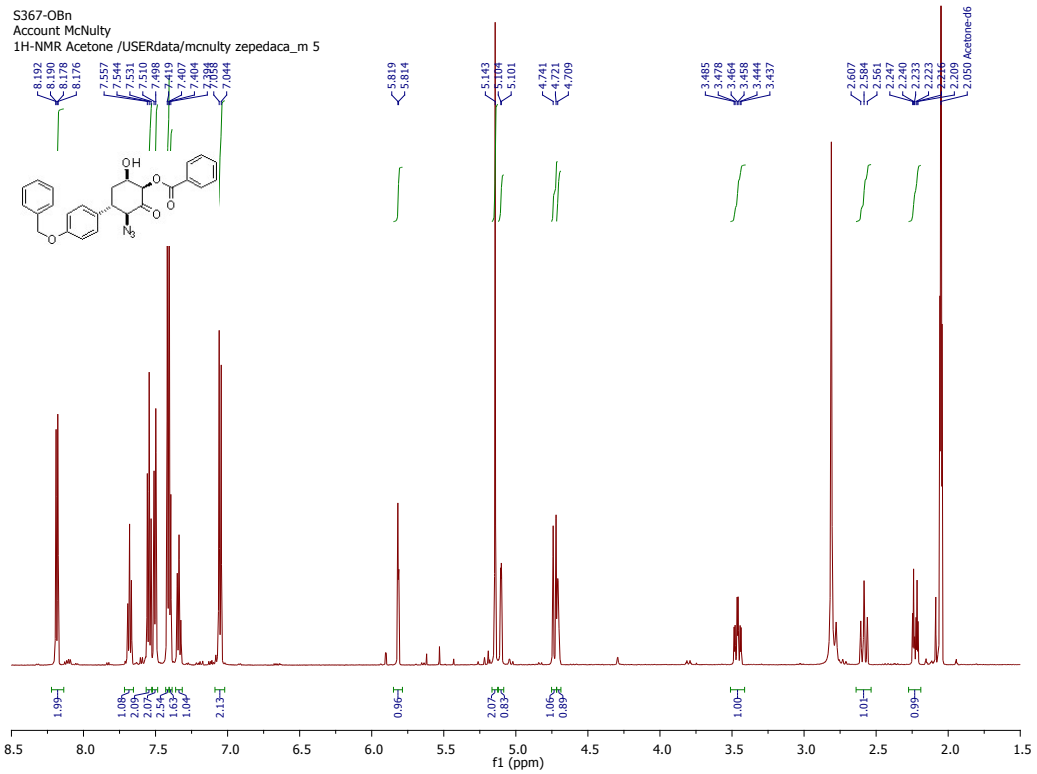
f1 (ppm)



HPLC chromatograms of racemic/chiral products (enantiomeric excess)

Enantiomeric Purity ent-**4a** (as example).

Method:	in house method.
Reagents:	Deionized Water from Milli-Q equipment or Water HPLC grade.
	Acetonitrile, HPLC grade.
Standards:	(1*R*,3*S*,4*S*,6*R*)-3-azido-6-hydroxy-2-oxo-4-phenylcyclohexyl benzoate ent-**4a**.
	(1*S*,3*R*,4*R*,6*S*)-3-azido-6-hydroxy-2-oxo-4-phenylcyclohexyl benzoate (**4a**).

Chromatographic Conditions:

Instrument and Materials:	Agilent 1220 Infinity.
	Analytical Balance.
	Solvent filtration Millipore-Kit.

	Ultrasonic bath Branson 5510.
	Durapore HV, 0.45 μm, Millipore filtration membranes Cat No. HVLP04700.
	Acrodisc 13mm Syringe Filter, 0.2 μm GHP membrane, minispike outlet, PALL. PN: S4554.
Column:	Type: Chiralpak® AS-RH.
	Length: 150 mm.
	Internal Diameter: 4.6 mm.
	Particle Size: 5 μm.
	Part No.: 20724.
	Manufacturer: Daicel.
Column Temperature:	20-23 °C.
Mobile Phase:	Solution A: Water. Filter through a Durapore HV, 0.45 μm, Millipore membrane. Degas in the ultrasonic bath.
	Solution B: Acetronitrile. Filter through a 0.45 μm Millipore membrane. Degas in the ultrasonic bath.
Isocratic Program:	Water/Acetonitrile (Solution A: 50% / Solution B: 50%).
Flow Rate:	0.75 mL/minute.
Injector:	Manual Injector.
Needle Wash:	Water/Acetonitrile (50:50).
Injection Volume:	20 μL.
Detection:	UV.
Wavelength:	236 nm.
Run Time:	25 minutes.
Data Acquisition Time:	20 minutes.
Diluent:	Water/Acetonitrile (50:50).
Data Collection:	Computer equipped with OpenLab software.
Standard preparation:	
	Note: The preparation of the Stock Solution of **4a** and its addition to the *ent*-**4a** solution is only conducted when the *ent*-**4a** standard does not contain **4a.**

4a Stock solution:

1) Accurately weigh about 6 mg of **4a** and transfer into a 100 mL volumetric flask.
2) Add 20 mL of diluent and if necessary sonicate for a couple of minutes to dissolve.
3) Allow the solution to reach room temperature. Dilute to volume with diluent. Mix well. [0.06 mg/mL **4a**].

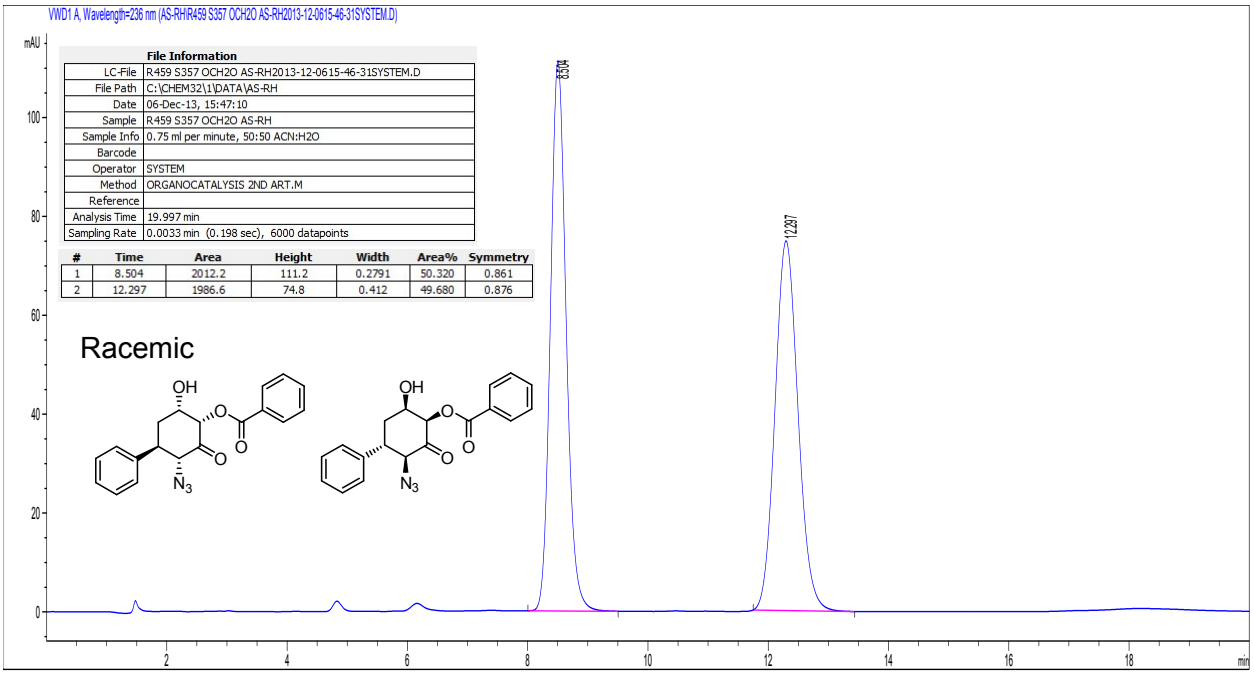
System Suitability Solution Preparation: (SS)

1) Accurately weigh about 20 mg of *ent*-**4a** and transfer into a 100 mL volumetric flask.
2) Add about 20 mL of diluent and dissolve, sonicating, if necessary, for about 15 minutes.
3) Allow the solution to reach room temperature.
4) Add 1.0 mL of the **4a** Stock solution.
5) Dilute to volume with diluent. Mix well [0.2mg/mL *ent*-**4a** and 0.6µg/mL **4a**)].
6) Fill a vial with the solution from step 5).
7) Label as SS filter using an acrodisc and inject.

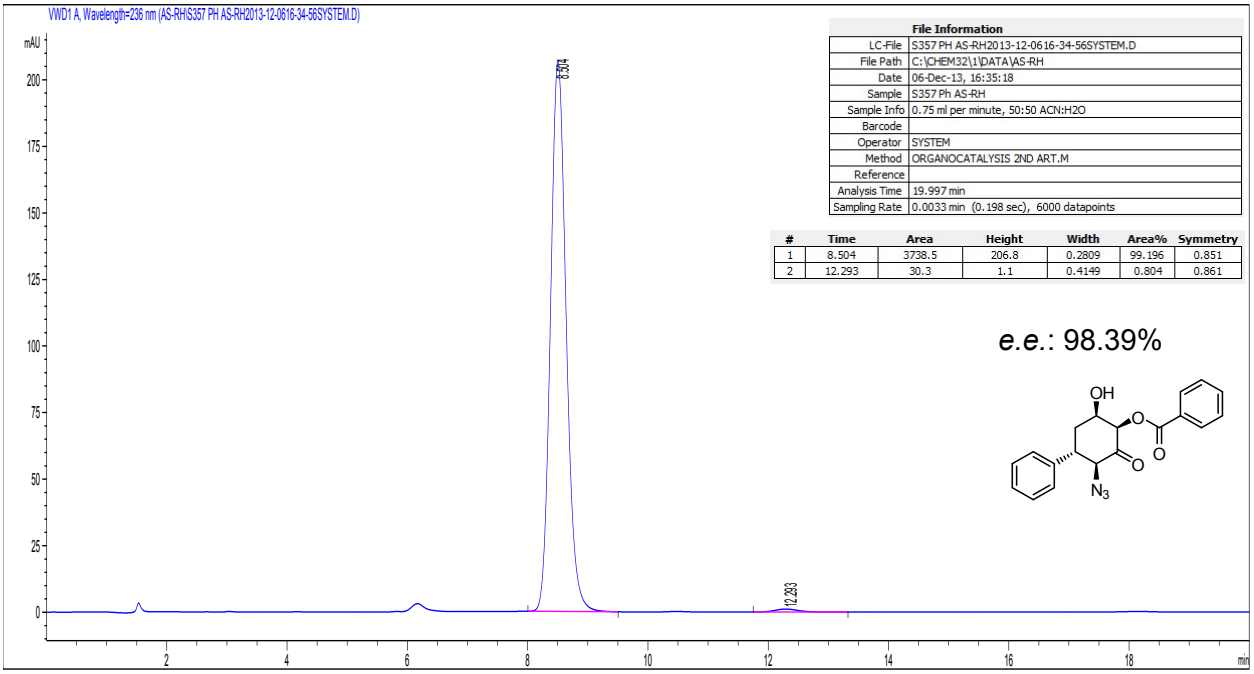
Sample Preparation:

The sample solution is stable for 1.0 hour at 20 °C after the preparation. *Note: Inject immediately after preparation.*

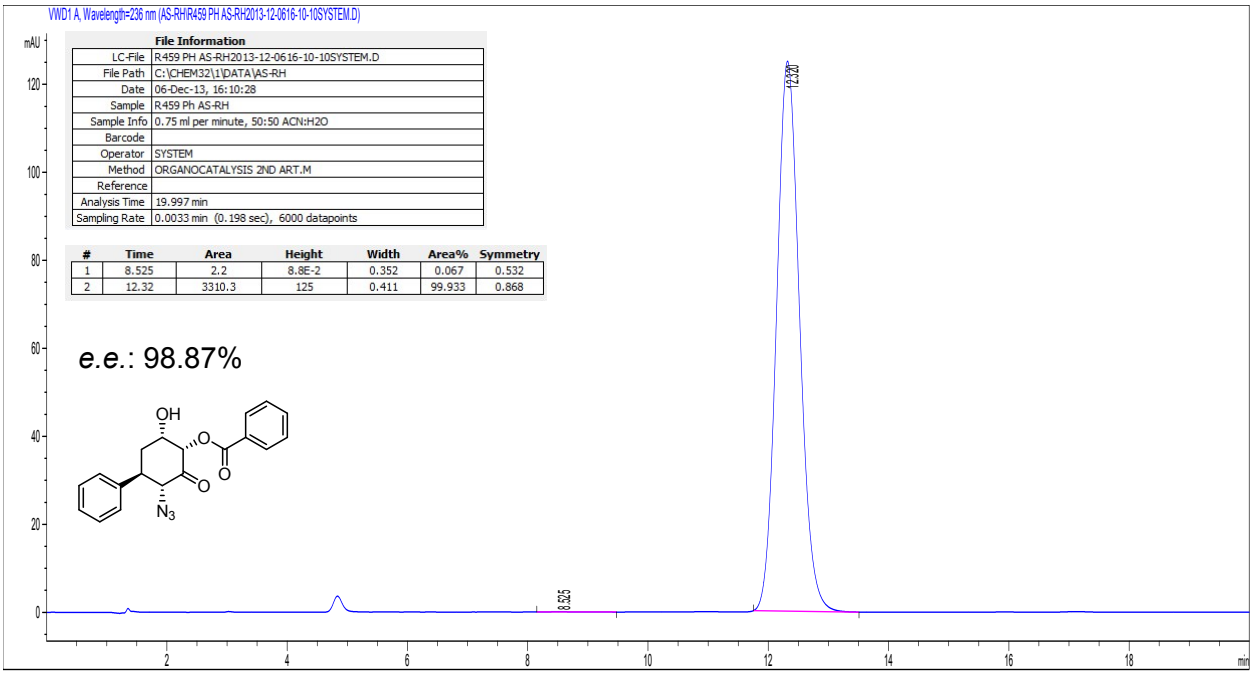
1) Accurately weigh about 20 mg of *ent*-**4a** sample and transfer into a 100 mL volumetric flask.
2) Add 80 mL of diluent, if necessary sonicate for about 10 minutes to dissolve.
3) Allow the solution to reach room temperature. Dilute to volume with diluent. Mix well [0.2 mg/mL]
4) Fill a vial with the solution from step 3).
5) Label as sample, filter using an acrodisc and inject.



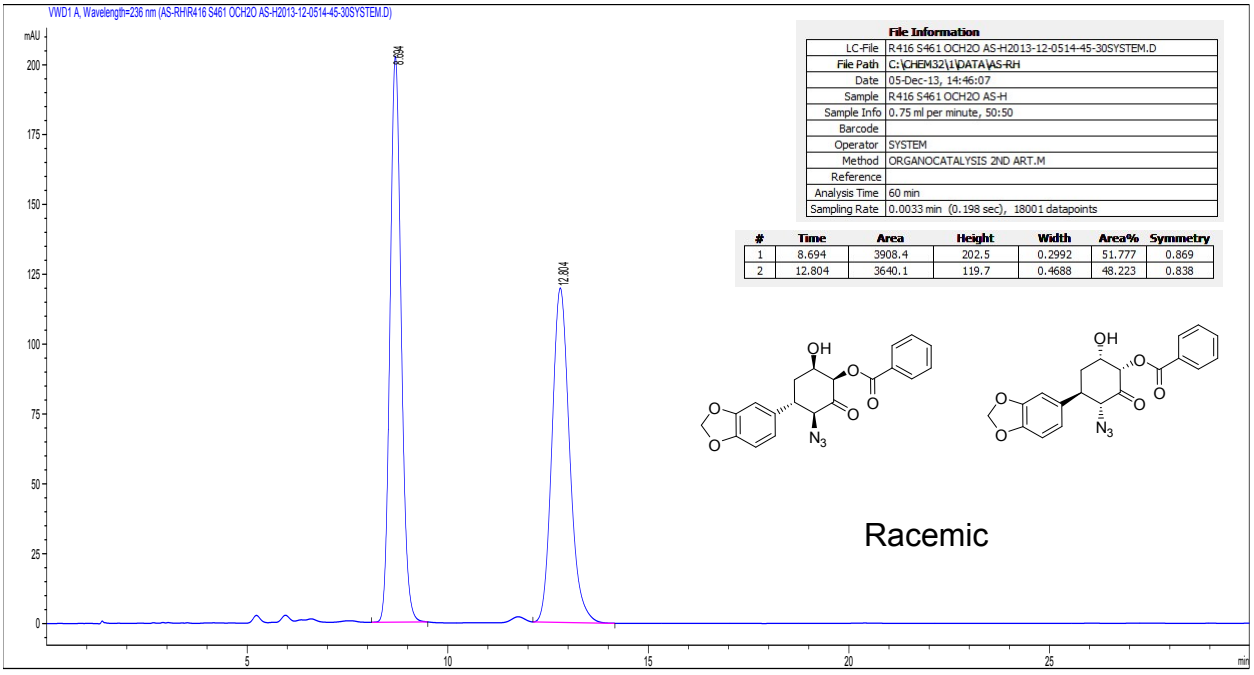
racemic 3-azido-6-hydroxy-2-oxo-4-phenylcyclohexyl benzoate. H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



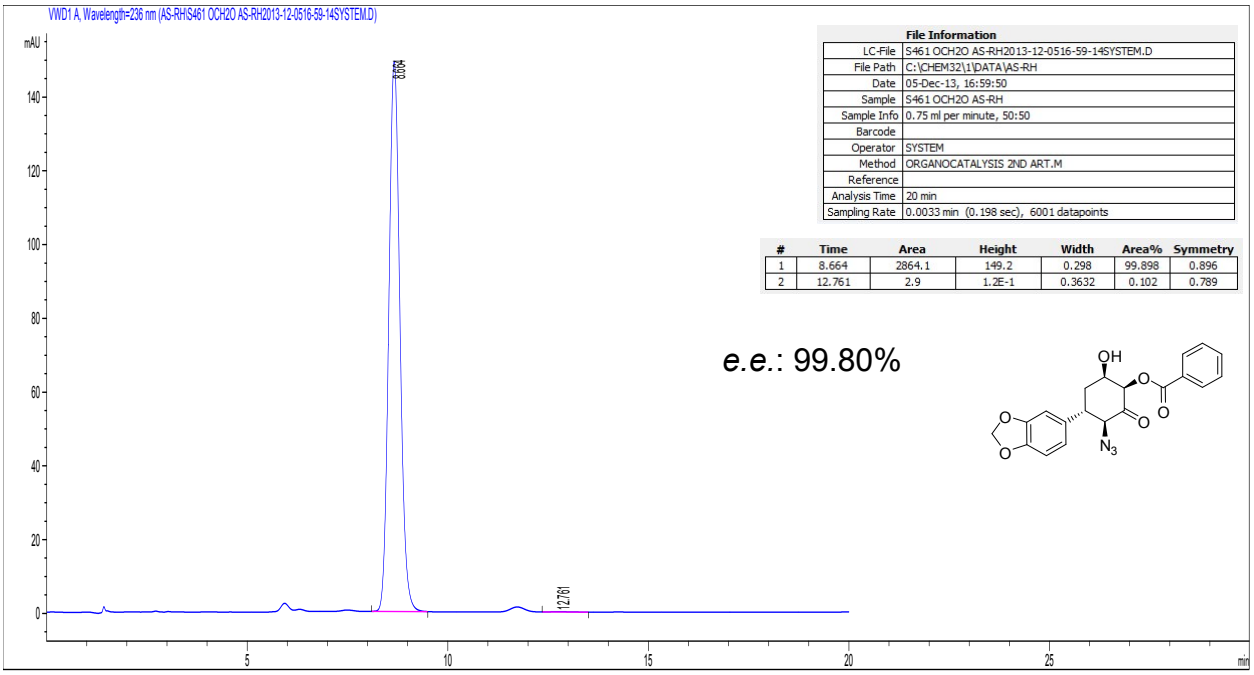
(1*R*,3*S*,4*S*,6*R*)-3-azido-6-hydroxy-2-oxo-4-phenylcyclohexyl benzoate. H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



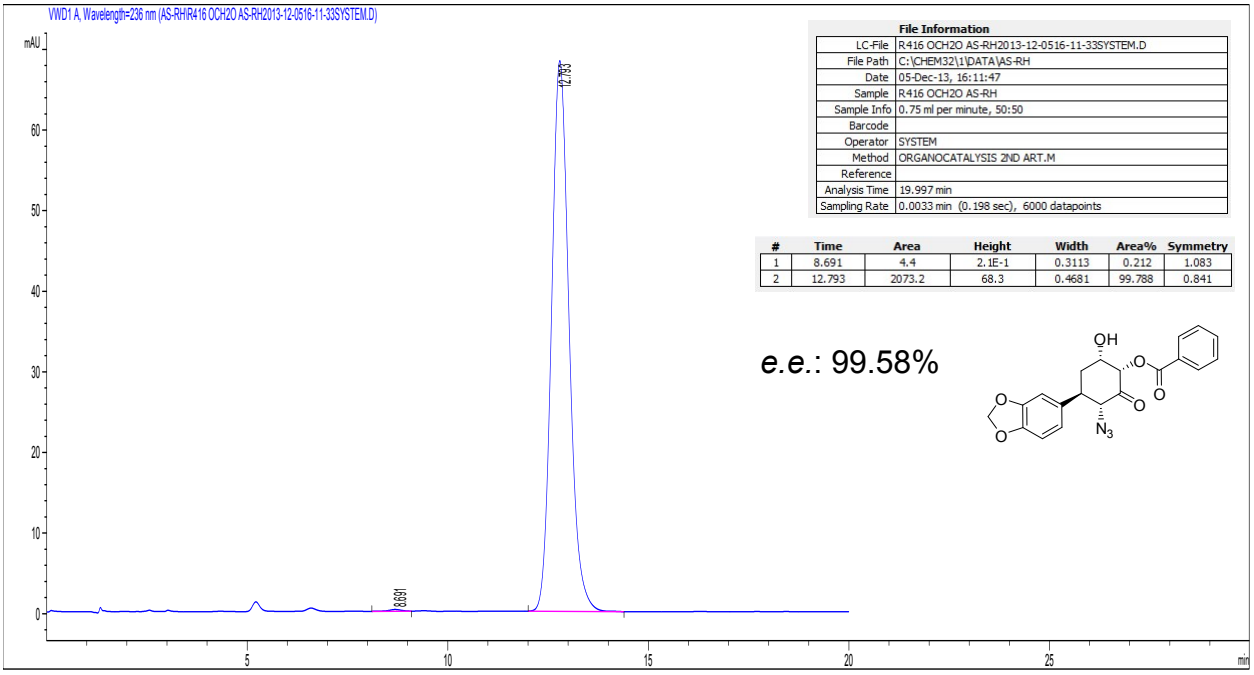
(1*S*,3*R*,4*R*,6*S*)-3-azido-6-hydroxy-2-oxo-4-phenylcyclohexyl benzoate. H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



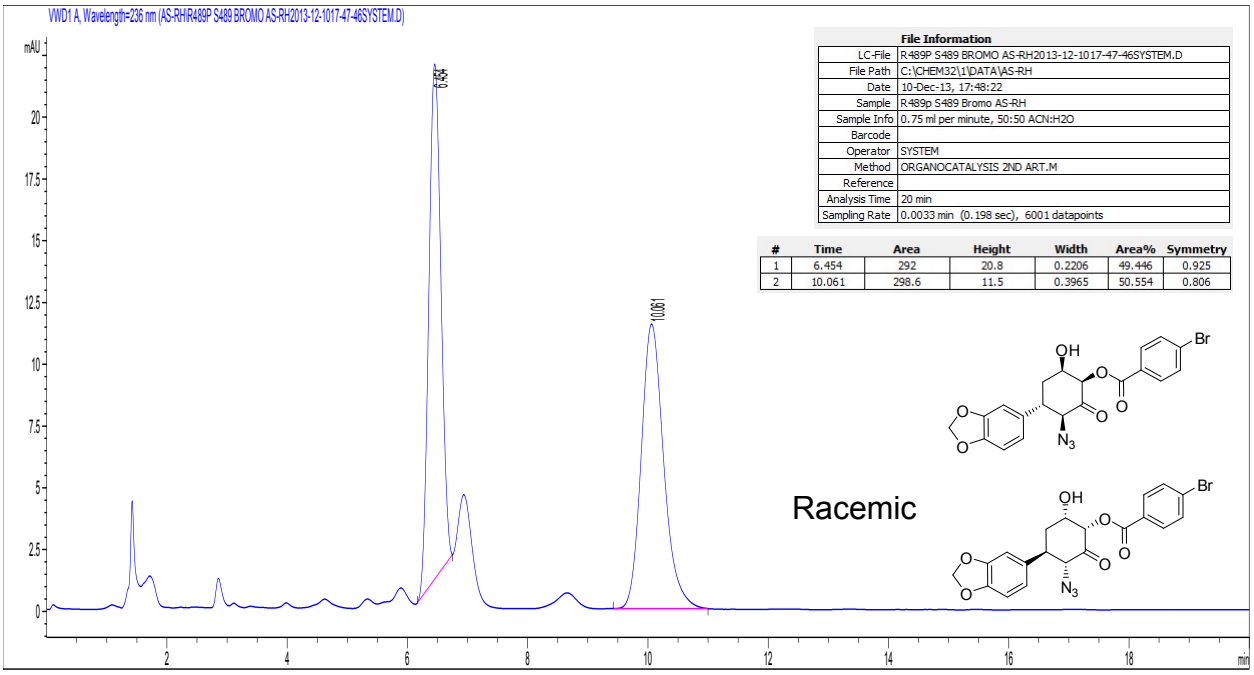
racemic 3-azido-4-(1,3-benzodioxol-5-yl)-6-hydroxy-2-oxocyclohexyl benzoate H_2O/ACN (60:40) as a mobile phase; flow rate 0.75 ml/min.



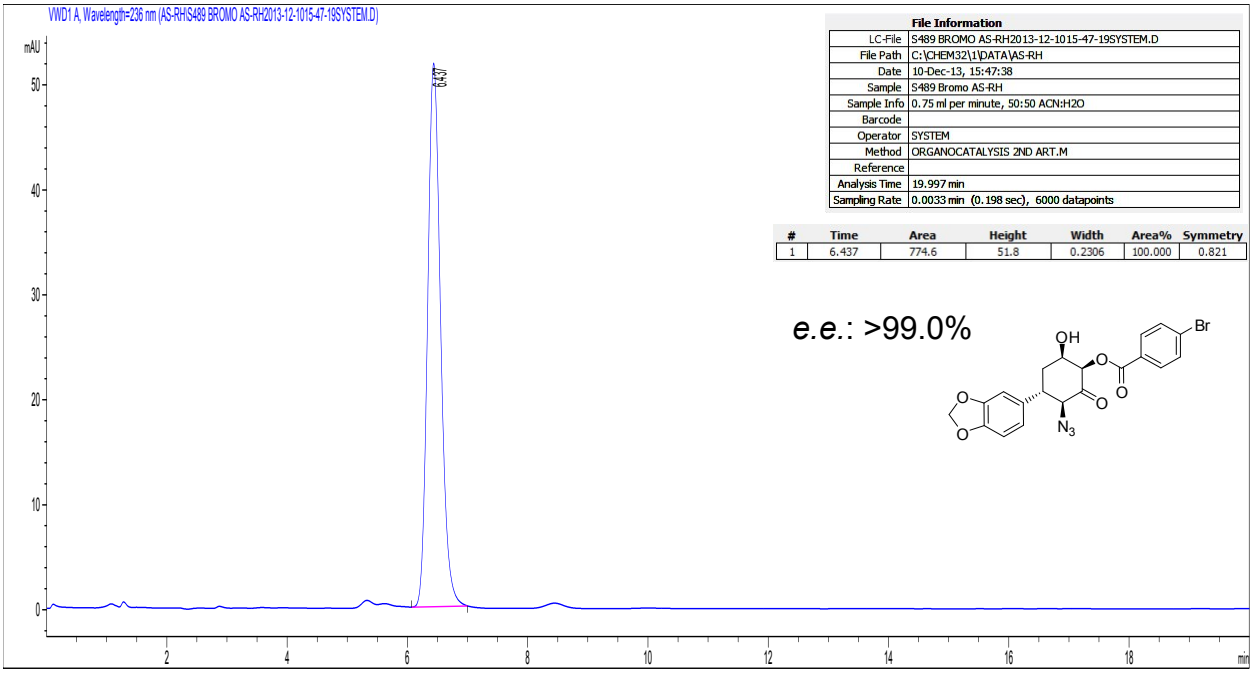
(1*R*,3*S*,4*S*,6*R*)-3-azido-4-(1,3-benzodioxol-5-yl)-6-hydroxy-2-oxocyclohexyl benzoate H_2O/ACN (60:40) as a mobile phase; flow rate 0.75 ml/min.



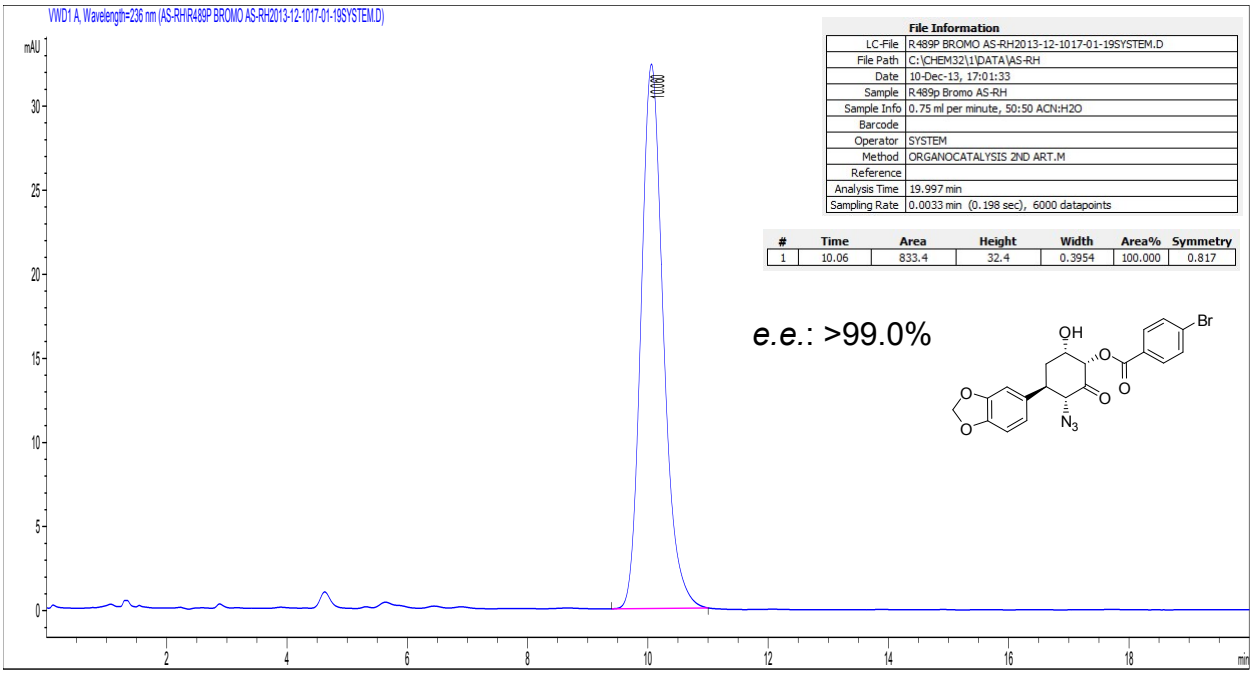
(1*S*,3*R*,4*R*,6*S*)-3-azido-4-(1,3-benzodioxol-5-yl)-6-hydroxy-2-oxocyclohexyl benzoate H_2O/ACN (60:40) as a mobile phase; flow rate 0.75 ml/min.



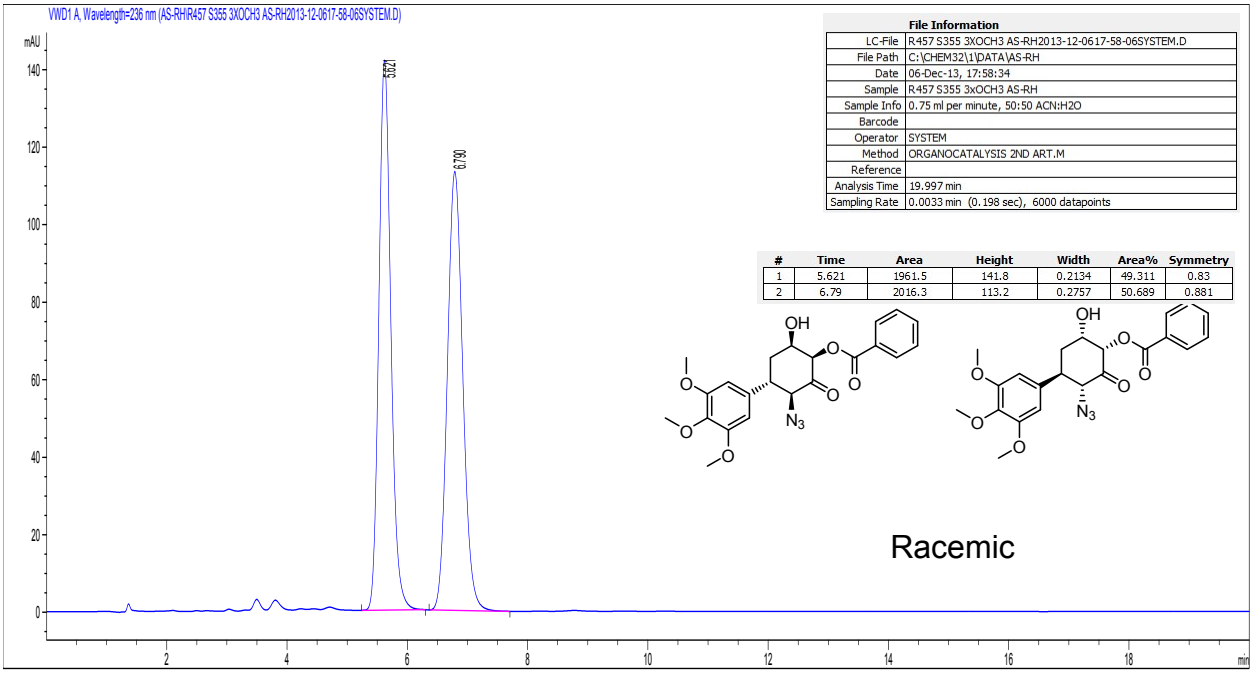
racemic 3-azido-4-(1,3-benzodioxol-5-yl)-6-hydroxy-2-oxocyclohexyl 4-bromobenzoate H_2O/ACN (60:40) as a mobile phase; flow rate 0.75 ml/min.



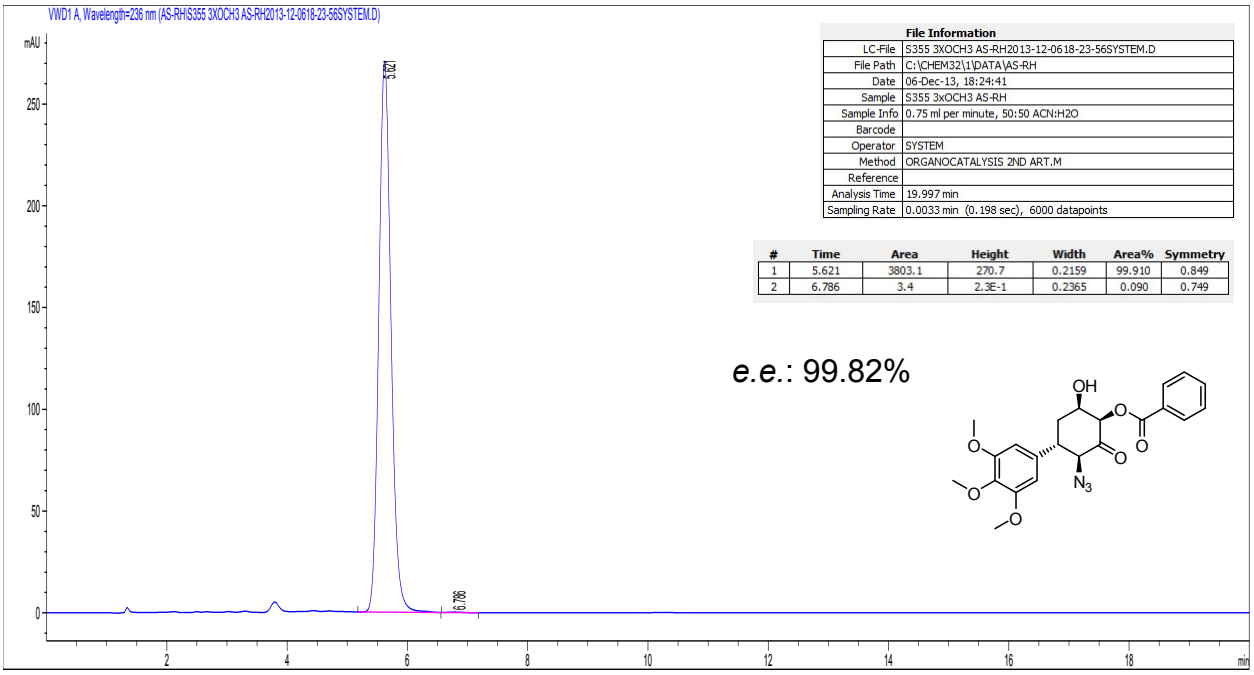
(1*R*,3*S*,4*S*,6*R*)-3-azido-4-(1,3-benzodioxol-5-yl)-6-hydroxy-2-oxocyclohexyl 4-bromobenzoate H_2O/ACN (60:40) as a mobile phase; flow rate 0.75 ml/min.



(1*S*,3*R*,4*R*,6*S*)-3-azido-4-(1,3-benzodioxol-5-yl)-6-hydroxy-2-oxocyclohexyl 4-bromobenzoate H_2O/ACN (60:40) as a mobile phase; flow rate 0.75 ml/min.



racemic 3-azido-6-hydroxy-2-oxo-4-(3,4,5-trimethoxyphenyl)cyclohexyl benzoate H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



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Sample Info	0.75 ml per minute, 50:50 ACN:H2O
Barcode	
Operator	SYSTEM
Method	ORGANOCATALYSIS 2ND ART.M
Reference	
Analysis Time	19.997 min
Sampling Rate	0.0033 min (0.198 sec), 6000 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
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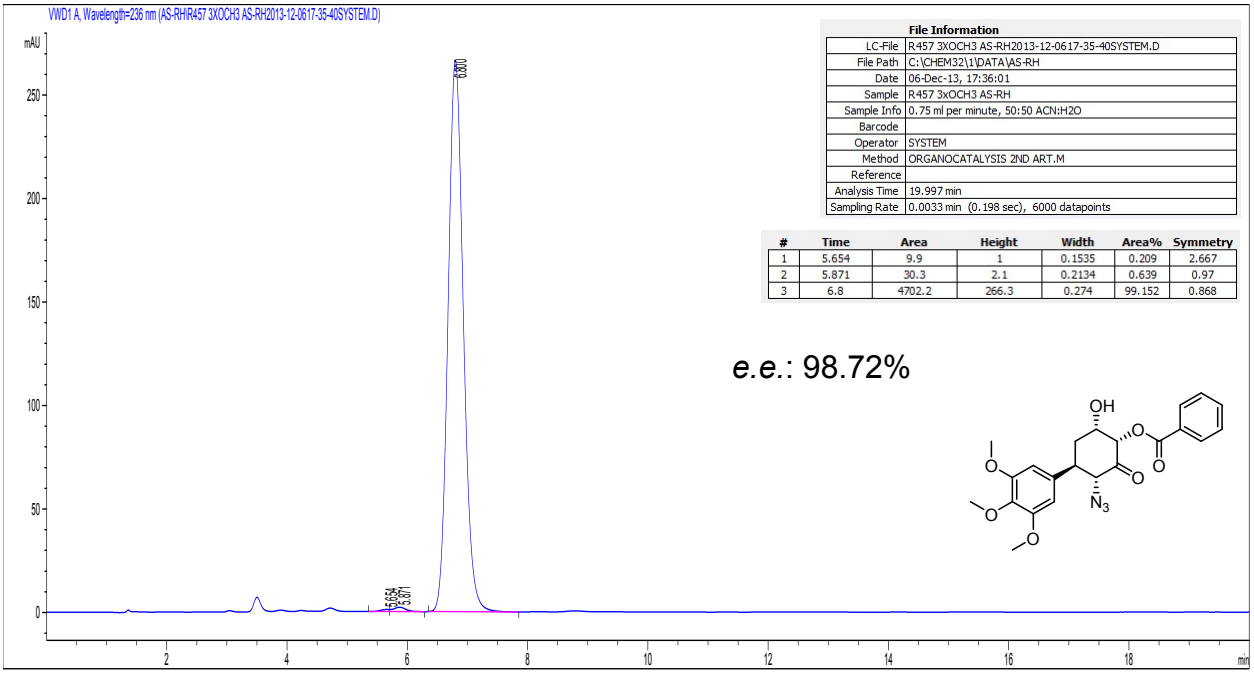
2	6.786	3.4	2.3E-1	0.2365	0.090	0.749

e.e.: 99.82%

(1*R*,3*S*,4*S*,6*R*)-3-azido-6-hydroxy-2-oxo-4-(3,4,5-trimethoxyphenyl)cyclohexyl benzoate H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



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Sample Info	0.75 ml per minute, 50:50 ACN:H2O
Barcode	
Operator	SYSTEM
Method	ORGANOCATALYSIS 2ND ART.M
Reference	
Analysis Time	19.997 min
Sampling Rate	0.0033 min (0.198 sec), 6000 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
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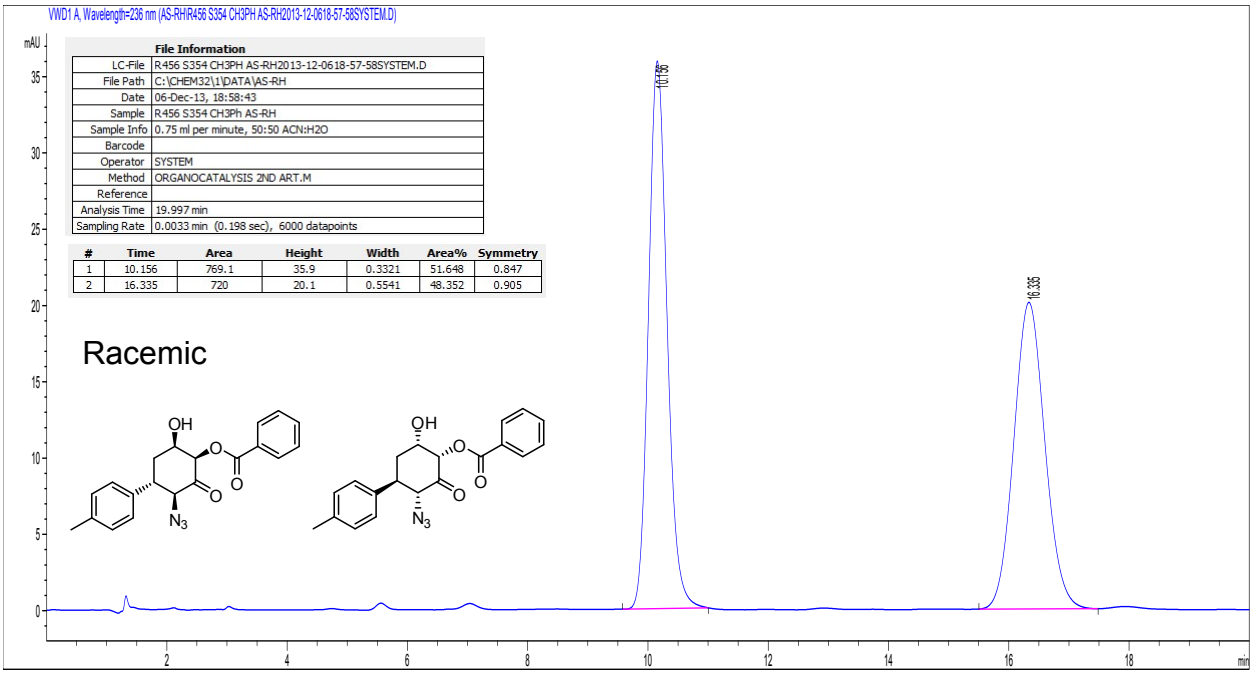
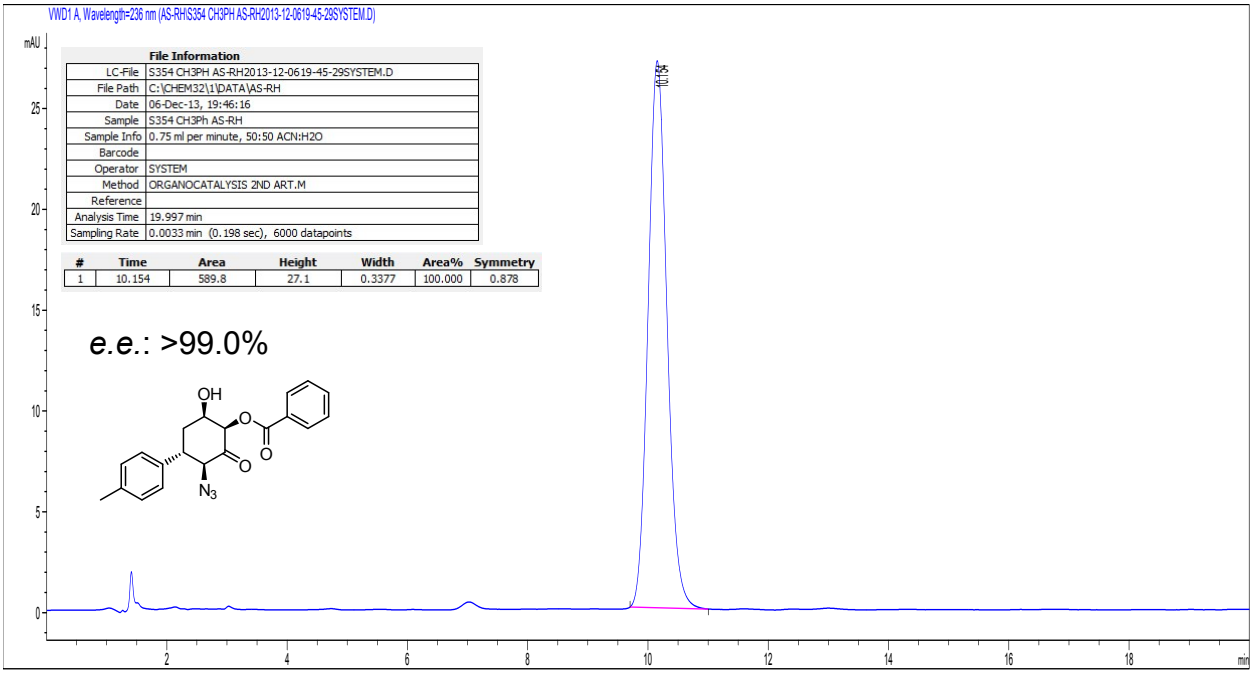
2	5.871	30.3	2.1	0.2134	0.639	0.97
3	6.8	4702.2	266.3	0.274	99.152	0.868

e.e.: 98.72%

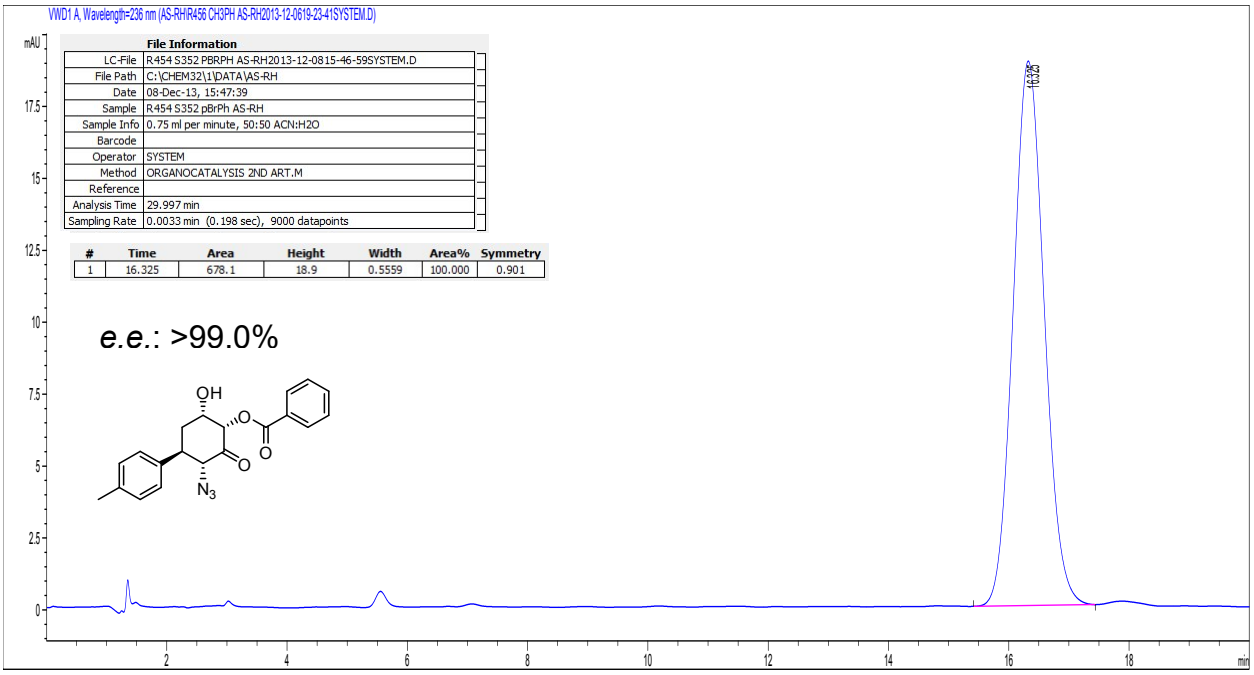
(1*S*,3*R*,4*R*,6*S*)-3-azido-6-hydroxy-2-oxo-4-(3,4,5-trimethoxyphenyl)cyclohexyl benzoate H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



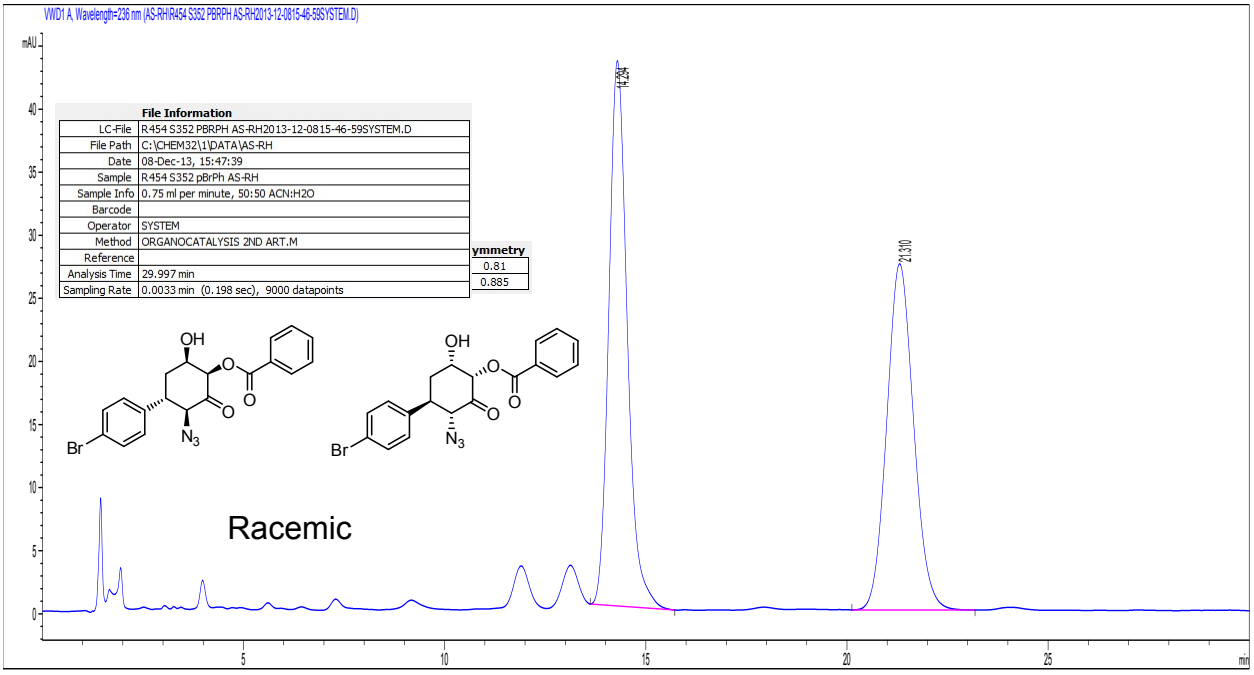
racemic 3-azido-6-hydroxy-2-oxo-4-*p*-tolylcyclohexyl benzoate. H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



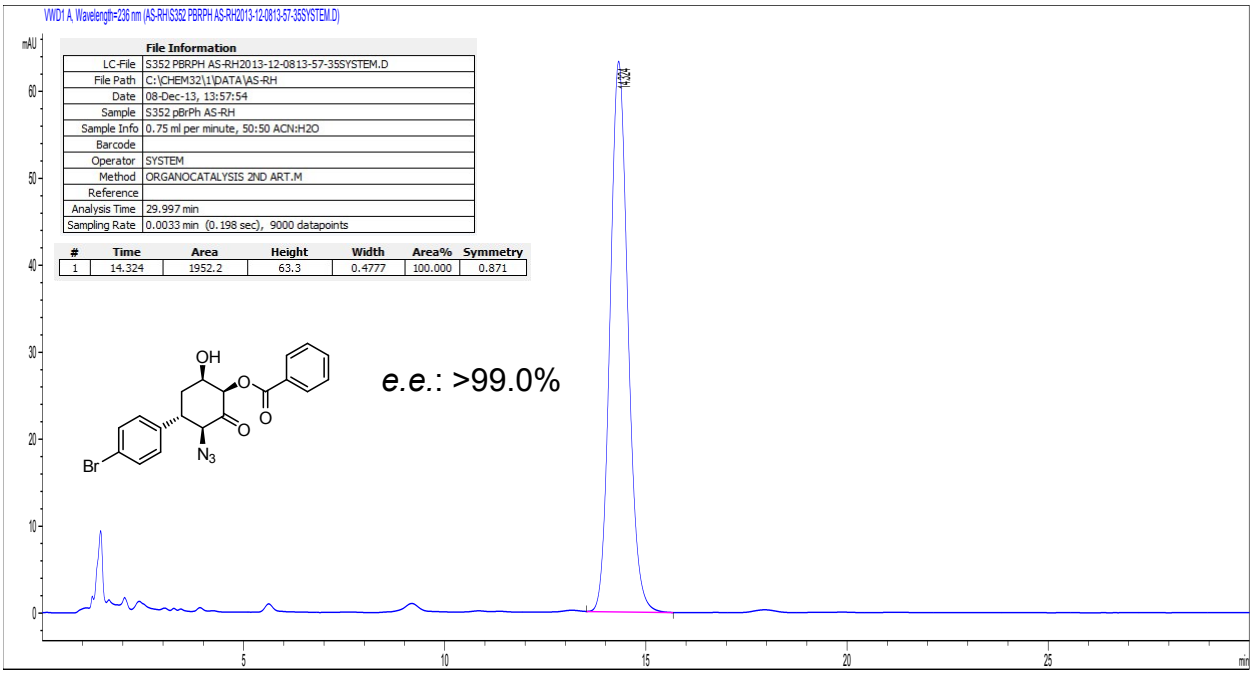
(1*R*,3*S*,4*S*,6*R*)-3-azido-6-hydroxy-2-oxo-4-*p*-tolylcyclohexyl benzoate. H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



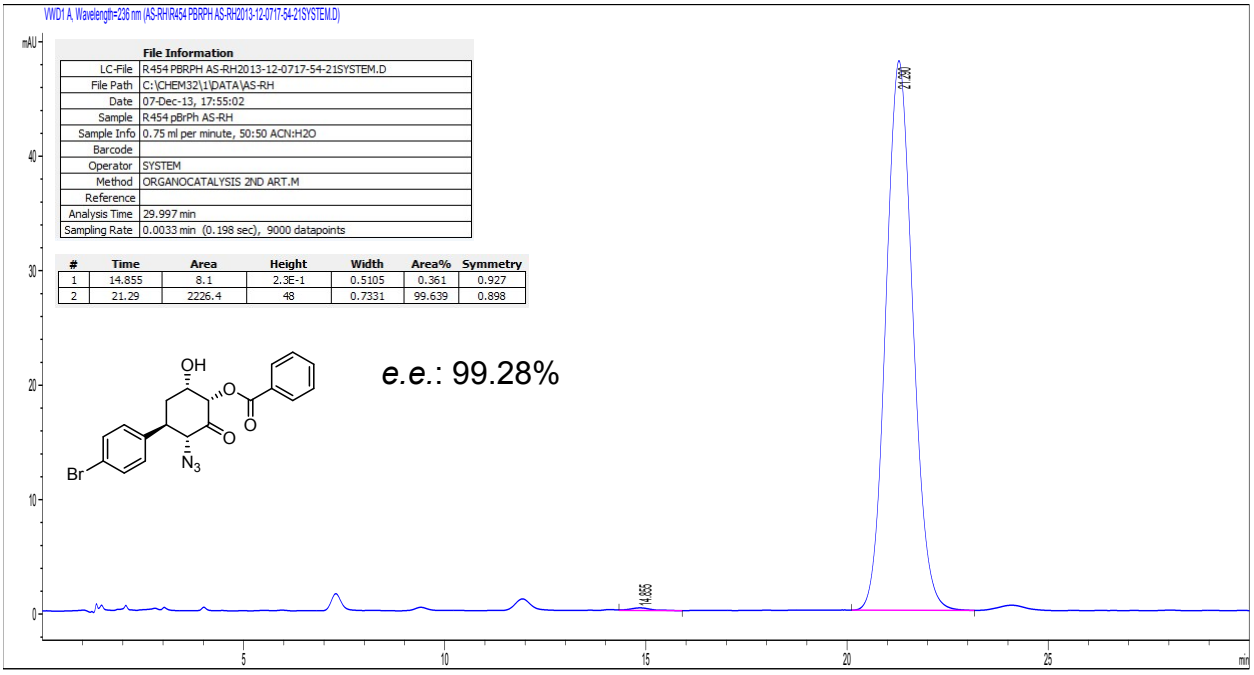
(1*S*,3*R*,4*R*,6*S*)-3-azido-6-hydroxy-2-oxo-4-*p*-tolylcyclohexyl benzoate. H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



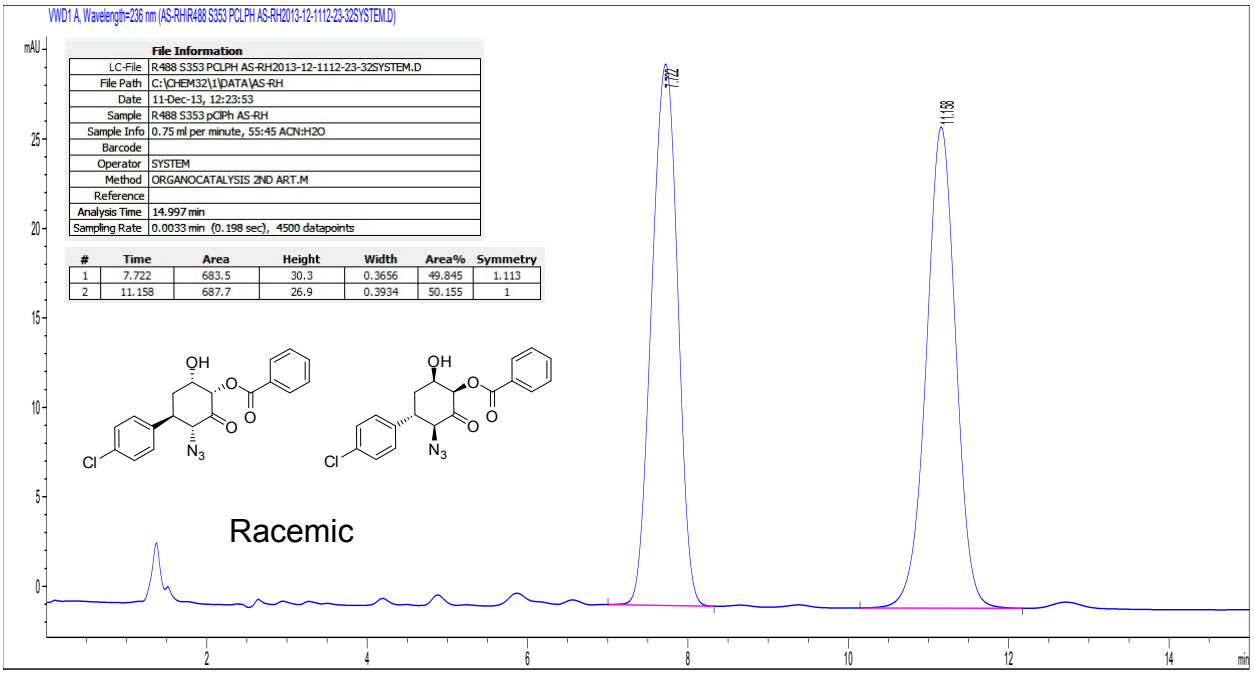
racemic 3-azido-4-(4-bromophenyl)-6-hydroxy-2-oxocyclohexyl benzoate. H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



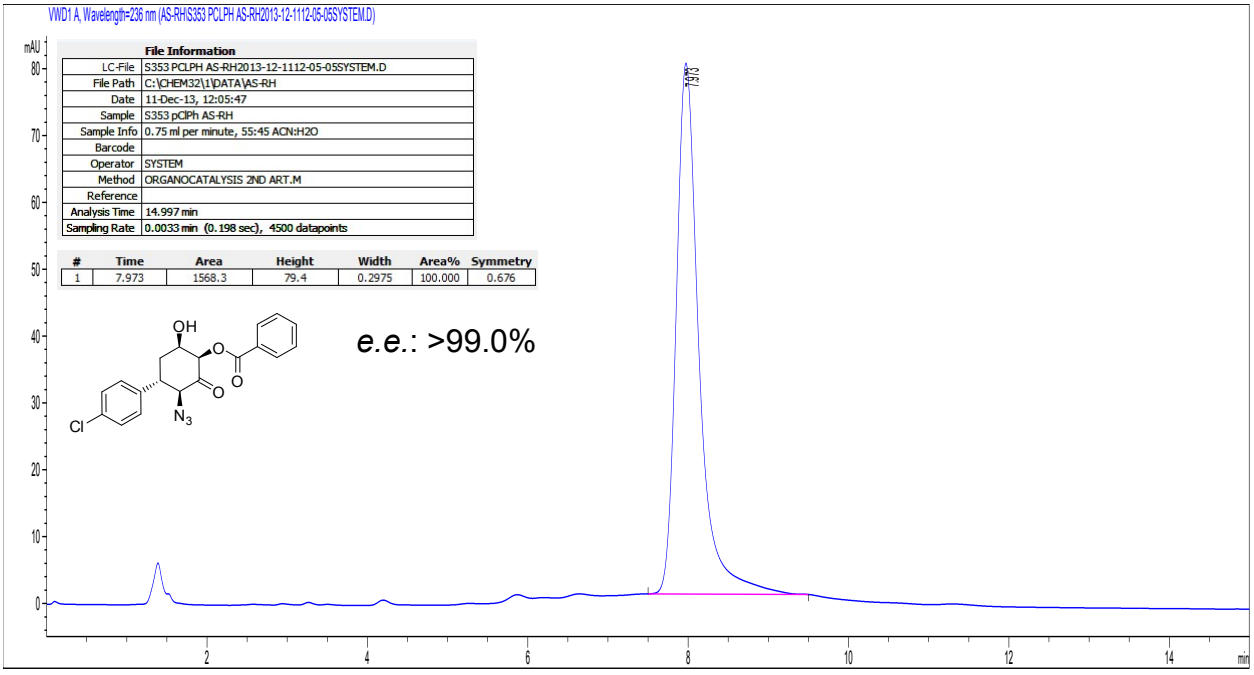
(1*R*,3*S*,4*S*,6*R*)-3-azido-4-(4-bromophenyl)-6-hydroxy-2-oxocyclohexyl benzoate. H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



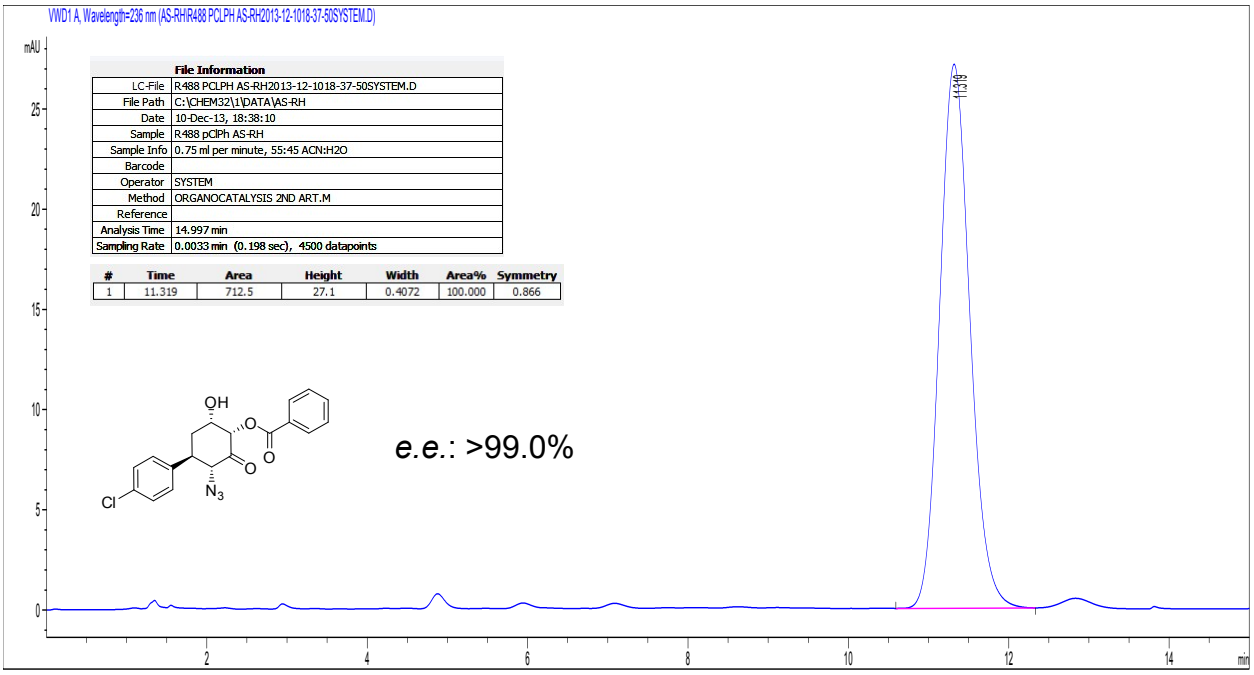
(1*S*,3*R*,4*R*,6*S*)-3-azido-4-(4-bromophenyl)-6-hydroxy-2-oxocyclohexyl benzoate. H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



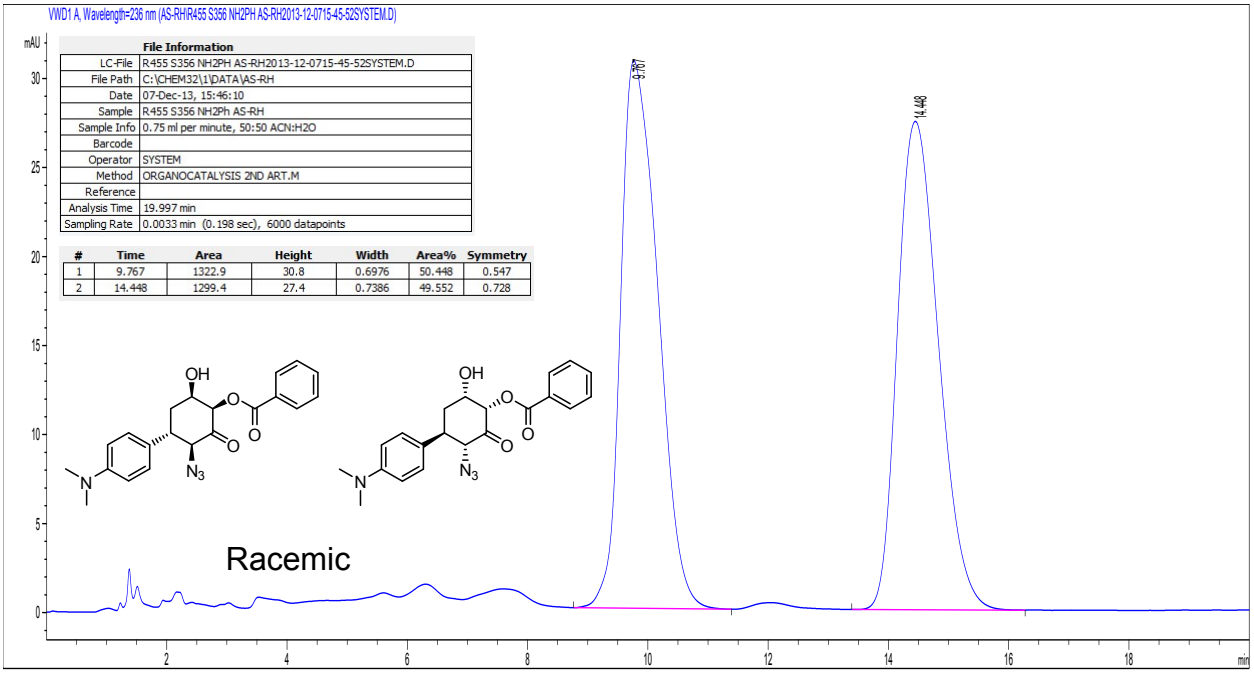
racemic 3-azido-4-(4-chlorophenyl)-6-hydroxy-2-oxocyclohexyl benzoate. H_2O/ACN (55:45) as a mobile phase; flow rate 0.75 ml/min.



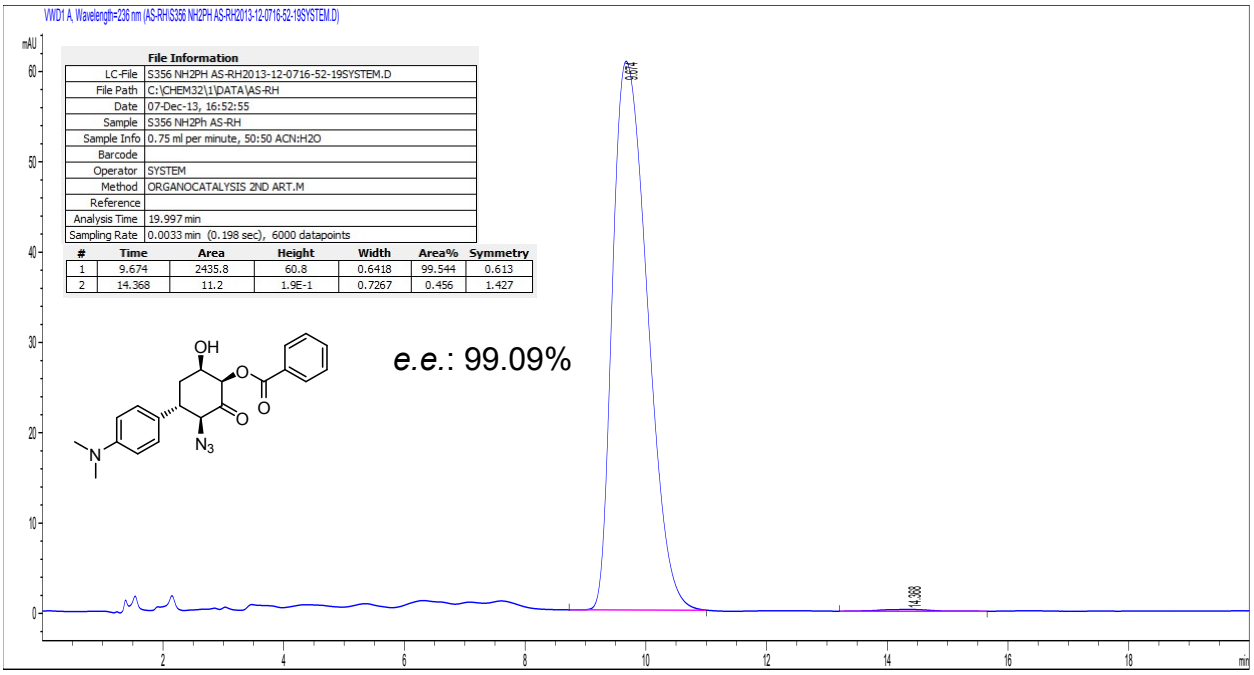
(1*R*,3*S*,4*S*,6*R*)-3-azido-4-(4-chlorophenyl)-6-hydroxy-2-oxocyclohexyl benzoate. H_2O/ACN (55:45) as a mobile phase; flow rate 0.75 ml/min.



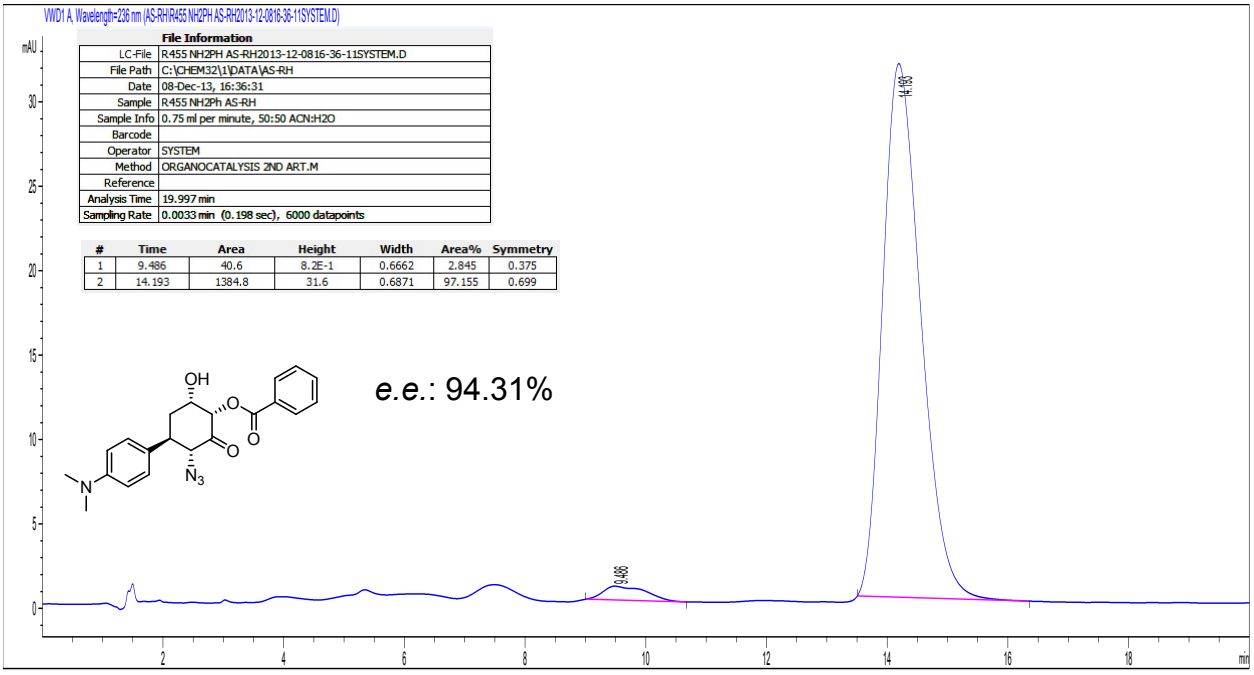
(1*S*,3*R*,4*R*,6*S*)-3-azido-4-(4-chlorophenyl)-6-hydroxy-2-oxocyclohexyl benzoate. H_2O/ACN (55:45) as a mobile phase; flow rate 0.75 ml/min.



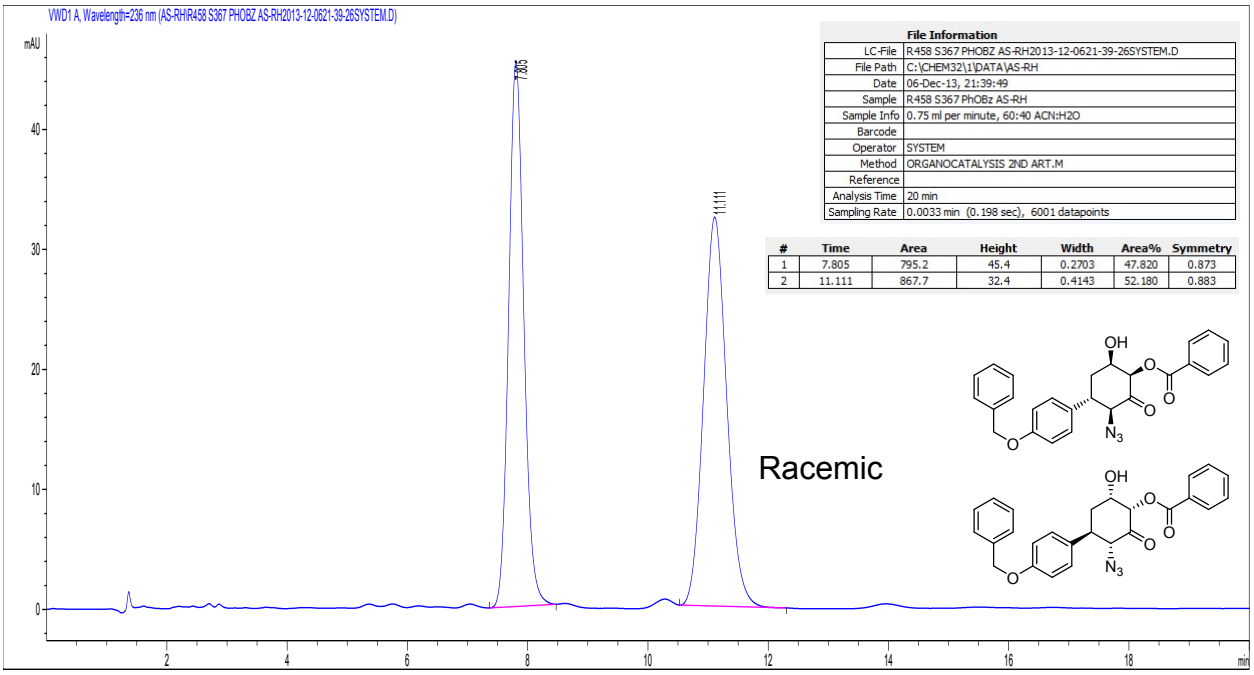
racemic 3-azido-4-(4-(dimethylamino)phenyl)-6-hydroxy-2-oxocyclohexyl benzoate H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



(1*R*,3*S*,4*S*,6*R*)-3-azido-4-(4-(dimethylamino)phenyl)-6-hydroxy-2-oxocyclohexyl benzoate H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



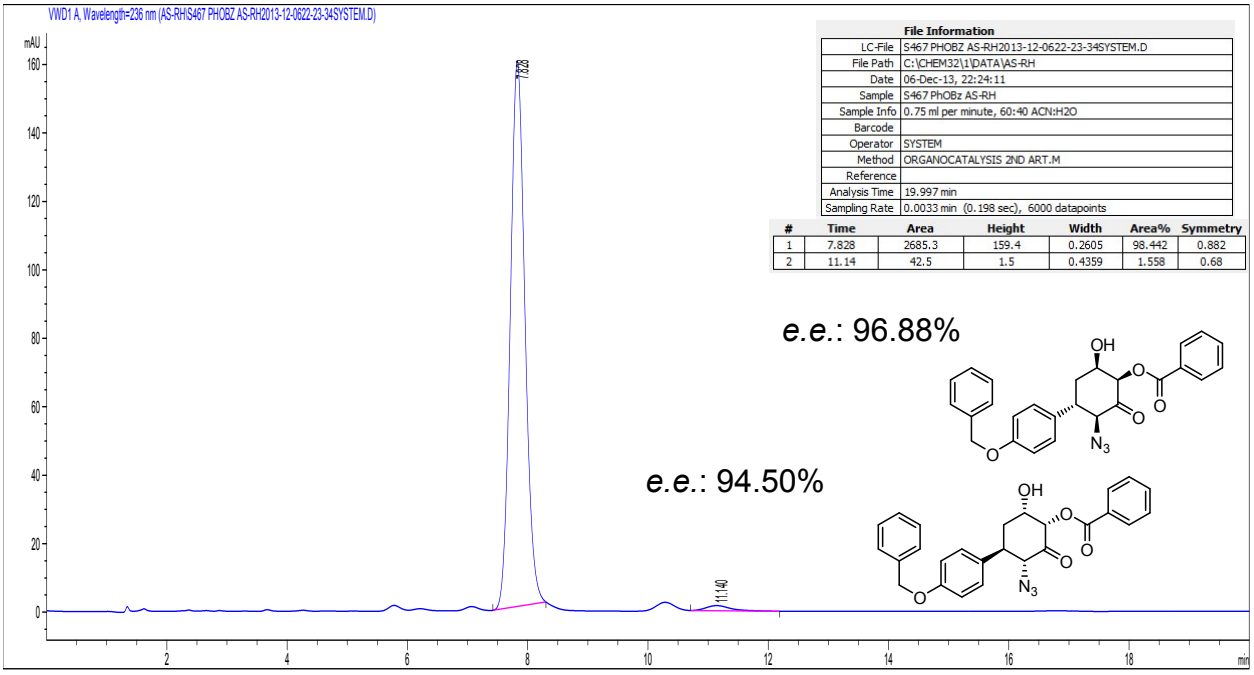
(1*S*,3*R*,4*R*,6*S*)-3-azido-4-(4-(dimethylamino)phenyl)-6-hydroxy-2-oxocyclohexyl benzoate H_2O/ACN (50:50) as a mobile phase; flow rate 0.75 ml/min.



File Information	
LC-File	R458 S367 PHOBZ AS-RH2013-12-0621-39-26SYSTEM.D
File Path	C:\CHEM32\1\DATA\AS-RH
Date	06-Dec-13, 21:39:49
Sample	R458 S367 PhOBz AS-RH
Sample Info	0.75 ml per minute, 60:40 ACN:H2O
Barcode	
Operator	SYSTEM
Method	ORGANOCATALYSIS 2ND ART.M
Reference	
Analysis Time	20 min
Sampling Rate	0.0033 min (0.198 sec), 6001 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	7.805	795.2	45.4	0.2703	47.820	0.873
2	11.111	867.7	32.4	0.4143	52.180	0.883

racemic 3-azido-4-(4-(benzyloxy)phenyl)-6-hydroxy-2-oxocyclohexyl benzoate. H_2O/ACN (60:40) as a mobile phase; flow rate 0.75 ml/min.



File Information	
LC-File	S467 PHOBZ AS-RH2013-12-0622-23-34SYSTEM.D
File Path	C:\CHEM32\1\DATA\AS-RH
Date	06-Dec-13, 22:24:11
Sample	S467 PhOBz AS-RH
Sample Info	0.75 ml per minute, 60:40 ACN:H2O
Barcode	
Operator	SYSTEM
Method	ORGANOCATALYSIS 2ND ART.M
Reference	
Analysis Time	19.997 min
Sampling Rate	0.0033 min (0.198 sec), 6000 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	7.828	2685.3	159.4	0.2605	98.442	0.882
2	11.14	42.5	1.5	0.4359	1.558	0.68

(1*R*,3*S*,4*S*,6*R*)-3-azido-4-(4-(benzyloxy)phenyl)-6-hydroxy-2-oxocyclohexyl benzoate. H_2O/ACN (60:40) as a mobile phase; flow rate 0.75 ml/min.

Crystal data and structure refinement for Ent-6c.

Identification code	Ent-**6c**	
Empirical formula	C20.84 H16.84 Br Cl2.53 N O6.31	
Formula weight	551.99	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 28.1961(9) Å	α= 90°.
	b = 13.3772(4) Å	β= 93.0930(18)°.
	c = 11.8239(4) Å	γ = 90°.
Volume	4453.3(2) $Å^3$	
Z	8	
Density (calculated)	1.647 Mg/m^3	
Absorption coefficient	5.673 mm^{-1}	
F(000)	2220	
Crystal size	0.400 x 0.080 x 0.020 mm^3	
Theta range for data collection	3.139 to 68.416°.	
Index ranges	-32<=h<=33, -16<=k<=15, -14<=l<=13	
Reflections collected	19243	
Independent reflections	4026 [R(int) = 0.0966]	
Completeness to theta = 67.679°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7531 and 0.4700	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4026 / 22 / 329	

Goodness-of-fit on F^2	1.113
Final R indices [I>2sigma(I)]	R1 = 0.0726, wR2 = 0.2010
R indices (all data)	R1 = 0.0816, wR2 = 0.2088
Extinction coefficient	n/a
Largest diff. peak and hole	0.868 and -0.417 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Ent-**6c** . U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(21)	3258(2)	-437(4)	8341(5)	30(1)
C(22)	3217(2)	301(5)	7505(7)	36(2)
C(23)	3591(3)	501(6)	6830(7)	42(1)
C(24)	4007(2)	-44(6)	6988(6)	38(1)
C(25)	4057(3)	-764(6)	7813(7)	48(2)
C(26)	3684(2)	-965(5)	8478(6)	42(2)
Br(1)	4516(1)	210(1)	6042(2)	53(1)
C(21A)	3250(20)	-700(60)	8290(70)	30(1)
C(22A)	3163(19)	110(70)	7560(80)	36(2)
C(23A)	3520(20)	480(60)	6920(80)	42(1)
C(24A)	3940(20)	-50(60)	6890(60)	38(1)
C(25A)	4040(20)	-840(70)	7600(80)	48(2)
C(26A)	3690(20)	-1190(60)	8260(70)	42(2)
Br(1A)	4377(11)	283(13)	5780(20)	53(1)
O(7)	986(1)	-2032(3)	8653(3)	48(1)
O(14)	1256(1)	-2038(3)	14653(3)	46(1)
O(16)	1951(1)	-2955(3)	14659(3)	43(1)
N(17)	2227(2)	627(3)	10837(3)	33(1)
O(18)	2459(1)	-201(2)	8773(3)	32(1)
O(20)	2882(1)	-1356(3)	9776(3)	41(1)
O(28)	1807(1)	-1545(3)	7788(3)	36(1)

C(1)	1749(2)	-1221(3)	8753(4)	29(1)
C(2)	1342(2)	-1623(4)	9411(4)	34(1)
C(3)	1136(2)	-822(4)	10141(4)	31(1)
C(4)	1519(2)	-380(3)	10957(4)	29(1)
C(5)	1949(2)	-77(3)	10333(4)	28(1)
C(6)	2051(2)	-508(3)	9322(4)	28(1)
C(8)	1657(2)	-1110(3)	11918(4)	29(1)
C(9)	1349(2)	-1207(4)	12808(4)	33(1)
C(10)	1484(2)	-1852(4)	13671(4)	34(1)
C(11)	1898(2)	-2389(4)	13685(4)	32(1)
C(12)	2207(2)	-2308(4)	12826(4)	34(1)
C(13)	2074(2)	-1658(3)	11932(4)	30(1)
C(15)	1509(2)	-2853(4)	15184(4)	39(1)
C(19)	2862(2)	-733(3)	9048(4)	31(1)
C(1S)	-71(3)	-2156(6)	9301(6)	47(2)
Cl(3S)	-466(1)	-3031(1)	8631(1)	51(1)
Cl(1S)	-267(1)	-935(2)	8967(2)	77(1)
Cl(2S)	-33(1)	-2345(2)	10759(2)	81(1)
O(1S)	245(12)	-2600(20)	10710(20)	46(6)
O(2S)	-329(13)	-2050(20)	9070(30)	60(8)

Table 3. Bond lengths [Å] and angles [°] for Ent-**6c**.

C(21)-C(26)	1.396(8)
C(21)-C(22)	1.397(8)
C(21)-C(19)	1.484(7)
C(22)-C(23)	1.383(8)
C(22)-H(22A)	0.9500
C(23)-C(24)	1.384(9)
C(23)-H(23A)	0.9500
C(24)-C(25)	1.373(8)
C(24)-Br(1)	1.898(6)
C(25)-C(26)	1.373(8)
C(25)-H(25A)	0.9500
C(26)-H(26A)	0.9500
C(21A)-C(26A)	1.396(10)
C(21A)-C(22A)	1.398(9)
C(21A)-C(19)	1.45(3)
C(22A)-C(23A)	1.384(10)
C(22A)-H(22B)	0.9500
C(23A)-C(24A)	1.384(10)
C(23A)-H(23B)	0.9500
C(24A)-C(25A)	1.373(10)
C(24A)-Br(1A)	1.898(7)
C(25A)-C(26A)	1.373(9)
C(25A)-H(25B)	0.9500
C(26A)-H(26B)	0.9500

O(7)-C(2)	1.420(6)
O(7)-H(7A)	0.87(8)
O(14)-C(10)	1.379(6)
O(14)-C(15)	1.428(6)
O(16)-C(11)	1.379(6)
O(16)-C(15)	1.429(7)
N(17)-C(5)	1.345(6)
N(17)-H(17A)	0.850(10)
N(17)-H(17B)	0.852(10)
O(18)-C(19)	1.367(6)
O(18)-C(6)	1.411(6)
O(20)-C(19)	1.198(6)
O(28)-C(1)	1.240(6)
C(1)-C(6)	1.424(7)
C(1)-C(2)	1.518(7)
C(2)-C(3)	1.512(7)
C(2)-H(2A)	1.0000
C(3)-C(4)	1.529(6)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.507(7)
C(4)-C(8)	1.532(6)
C(4)-H(4A)	1.0000
C(5)-C(6)	1.372(6)
C(8)-C(13)	1.385(7)
C(8)-C(9)	1.406(7)

C(9)-C(10)	1.374(7)
C(9)-H(9)	0.9500
C(10)-C(11)	1.370(7)
C(11)-C(12)	1.378(7)
C(12)-C(13)	1.404(7)
C(12)-H(12A)	0.9500
C(13)-H(13A)	0.9500
C(15)-H(15B)	0.9900
C(15)-H(15A)	0.9900
C(1S)-Cl(2S)	1.740(7)
C(1S)-Cl(1S)	1.762(8)
C(1S)-Cl(3S)	1.773(8)
C(1S)-H(1SA)	1.0000

C(26)-C(21)-C(22)	118.6(5)
C(26)-C(21)-C(19)	117.9(5)
C(22)-C(21)-C(19)	123.4(5)
C(23)-C(22)-C(21)	120.5(5)
C(23)-C(22)-H(22A)	119.7
C(21)-C(22)-H(22A)	119.7
C(22)-C(23)-C(24)	119.1(5)
C(22)-C(23)-H(23A)	120.4
C(24)-C(23)-H(23A)	120.4
C(25)-C(24)-C(23)	121.4(5)
C(25)-C(24)-Br(1)	119.4(4)
C(23)-C(24)-Br(1)	119.2(4)

C(26)-C(25)-C(24)	119.4(5)
C(26)-C(25)-H(25A)	120.3
C(24)-C(25)-H(25A)	120.3
C(25)-C(26)-C(21)	121.0(5)
C(25)-C(26)-H(26A)	119.5
C(21)-C(26)-H(26A)	119.5
C(26A)-C(21A)-C(22A)	118.4(9)
C(26A)-C(21A)-C(19)	134(4)
C(22A)-C(21A)-C(19)	107(4)
C(23A)-C(22A)-C(21A)	120.3(10)
C(23A)-C(22A)-H(22B)	119.8
C(21A)-C(22A)-H(22B)	119.8
C(22A)-C(23A)-C(24A)	118.8(10)
C(22A)-C(23A)-H(23B)	120.6
C(24A)-C(23A)-H(23B)	120.6
C(25A)-C(24A)-C(23A)	121.1(8)
C(25A)-C(24A)-Br(1A)	119.5(8)
C(23A)-C(24A)-Br(1A)	119.3(8)
C(26A)-C(25A)-C(24A)	119.3(9)
C(26A)-C(25A)-H(25B)	120.4
C(24A)-C(25A)-H(25B)	120.4
C(25A)-C(26A)-C(21A)	121.0(9)
C(25A)-C(26A)-H(26B)	119.5
C(21A)-C(26A)-H(26B)	119.5
C(2)-O(7)-H(7A)	105(5)
C(10)-O(14)-C(15)	105.3(4)

C(11)-O(16)-C(15)	104.7(4)
C(5)-N(17)-H(17A)	122(4)
C(5)-N(17)-H(17B)	112(4)
H(17A)-N(17)-H(17B)	126(4)
C(19)-O(18)-C(6)	115.3(4)
O(28)-C(1)-C(6)	124.4(4)
O(28)-C(1)-C(2)	119.2(4)
C(6)-C(1)-C(2)	116.4(4)
O(7)-C(2)-C(3)	110.6(4)
O(7)-C(2)-C(1)	110.0(4)
C(3)-C(2)-C(1)	111.5(4)
O(7)-C(2)-H(2A)	108.2
C(3)-C(2)-H(2A)	108.2
C(1)-C(2)-H(2A)	108.2
C(2)-C(3)-C(4)	110.7(4)
C(2)-C(3)-H(3A)	109.5
C(4)-C(3)-H(3A)	109.5
C(2)-C(3)-H(3B)	109.5
C(4)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	108.1
C(5)-C(4)-C(3)	110.8(4)
C(5)-C(4)-C(8)	110.9(4)
C(3)-C(4)-C(8)	111.3(4)
C(5)-C(4)-H(4A)	107.9
C(3)-C(4)-H(4A)	107.9
C(8)-C(4)-H(4A)	107.9

N(17)-C(5)-C(6)	122.3(5)
N(17)-C(5)-C(4)	115.9(4)
C(6)-C(5)-C(4)	121.8(4)
C(5)-C(6)-O(18)	119.6(4)
C(5)-C(6)-C(1)	122.9(4)
O(18)-C(6)-C(1)	117.3(4)
C(13)-C(8)-C(9)	120.0(4)
C(13)-C(8)-C(4)	121.8(4)
C(9)-C(8)-C(4)	118.2(4)
C(10)-C(9)-C(8)	117.2(5)
C(10)-C(9)-H(9)	121.4
C(8)-C(9)-H(9)	121.4
C(11)-C(10)-C(9)	122.7(4)
C(11)-C(10)-O(14)	109.3(4)
C(9)-C(10)-O(14)	128.0(5)
C(10)-C(11)-C(12)	121.5(4)
C(10)-C(11)-O(16)	110.5(4)
C(12)-C(11)-O(16)	127.9(5)
C(11)-C(12)-C(13)	116.7(5)
C(11)-C(12)-H(12A)	121.6
C(13)-C(12)-H(12A)	121.6
C(8)-C(13)-C(12)	122.0(4)
C(8)-C(13)-H(13A)	119.0
C(12)-C(13)-H(13A)	119.0
O(14)-C(15)-O(16)	107.9(4)
O(14)-C(15)-H(15B)	110.1

O(16)-C(15)-H(15B)	110.1
O(14)-C(15)-H(15A)	110.1
O(16)-C(15)-H(15A)	110.1
H(15B)-C(15)-H(15A)	108.4
O(20)-C(19)-O(18)	122.6(4)
O(20)-C(19)-C(21A)	117(3)
O(18)-C(19)-C(21A)	119(3)
O(20)-C(19)-C(21)	125.7(5)
O(18)-C(19)-C(21)	111.7(4)
Cl(2S)-C(1S)-Cl(1S)	111.0(4)
Cl(2S)-C(1S)-Cl(3S)	110.5(4)
Cl(1S)-C(1S)-Cl(3S)	109.3(4)
Cl(2S)-C(1S)-H(1SA)	108.7
Cl(1S)-C(1S)-H(1SA)	108.7
Cl(3S)-C(1S)-H(1SA)	108.7

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Ent-**6c** . The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(21)	39(3)	26(3)	26(2)	-2(3)	6(2)	-4(2)
C(22)	41(3)	34(4)	34(3)	6(2)	5(2)	-1(3)
C(23)	41(4)	49(3)	38(3)	7(2)	10(2)	-4(3)
C(24)	36(3)	41(3)	37(3)	-5(2)	5(3)	-7(2)
C(25)	39(3)	47(3)	59(5)	5(3)	15(3)	7(3)
C(26)	48(3)	37(3)	43(4)	9(3)	13(3)	8(3)
Br(1)	47(1)	67(1)	47(1)	3(1)	21(1)	-6(1)
C(21A)	39(3)	26(3)	26(2)	-2(3)	6(2)	-4(2)
C(22A)	41(3)	34(4)	34(3)	6(2)	5(2)	-1(3)
C(23A)	41(4)	49(3)	38(3)	7(2)	10(2)	-4(3)
C(24A)	36(3)	41(3)	37(3)	-5(2)	5(3)	-7(2)
C(25A)	39(3)	47(3)	59(5)	5(3)	15(3)	7(3)
C(26A)	48(3)	37(3)	43(4)	9(3)	13(3)	8(3)
Br(1A)	47(1)	67(1)	47(1)	3(1)	21(1)	-6(1)
O(7)	42(2)	66(3)	36(2)	-21(2)	6(2)	-15(2)
O(14)	52(2)	59(2)	28(2)	11(2)	18(2)	12(2)
O(16)	52(2)	49(2)	28(2)	13(2)	9(2)	9(2)
N(17)	41(2)	35(2)	24(2)	-2(2)	9(2)	-7(2)
O(18)	38(2)	34(2)	25(2)	4(1)	7(1)	-2(1)
O(20)	46(2)	42(2)	34(2)	13(2)	8(2)	2(2)
O(28)	46(2)	42(2)	22(2)	-4(1)	7(1)	0(2)

C(1)	35(3)	29(2)	22(2)	0(2)	4(2)	5(2)
C(2)	37(3)	40(3)	26(2)	-2(2)	2(2)	-7(2)
C(3)	34(3)	36(2)	22(2)	-2(2)	6(2)	-2(2)
C(4)	40(3)	28(2)	20(2)	-1(2)	5(2)	2(2)
C(5)	40(3)	28(2)	17(2)	4(2)	2(2)	2(2)
C(6)	31(3)	29(2)	26(2)	0(2)	7(2)	-2(2)
C(8)	39(3)	28(2)	20(2)	-3(2)	5(2)	-1(2)
C(9)	41(3)	34(2)	24(2)	-1(2)	4(2)	4(2)
C(10)	39(3)	37(2)	26(2)	-1(2)	9(2)	-3(2)
C(11)	40(3)	35(2)	22(2)	2(2)	4(2)	-1(2)
C(12)	37(3)	38(2)	28(2)	5(2)	7(2)	6(2)
C(13)	38(3)	31(2)	21(2)	0(2)	7(2)	-2(2)
C(15)	45(3)	43(3)	30(2)	6(2)	8(2)	1(2)
C(19)	35(3)	29(2)	27(2)	-2(2)	2(2)	-4(2)
C(1S)	36(4)	60(4)	44(4)	2(3)	9(3)	4(3)
Cl(3S)	49(1)	56(1)	49(1)	-7(1)	4(1)	5(1)
Cl(1S)	83(2)	53(1)	97(2)	3(1)	14(1)	4(1)
Cl(2S)	70(2)	122(2)	49(1)	8(1)	-11(1)	-16(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Ent-**6c** .

	x	y	z	U(eq)
H(22A)	2930	669	7400	44
H(23A)	3563	1005	6264	51
H(25A)	4348	-1120	7923	58
H(26A)	3717	-1472	9039	51
H(22B)	2856	405	7495	44
H(23B)	3479	1095	6520	51
H(25B)	4340	-1149	7631	58
H(26B)	3741	-1775	8703	51
H(7A)	1120(30)	-2140(50)	8030(70)	58
H(17A)	2469(13)	860(40)	10530(40)	39
H(17B)	2139(18)	780(40)	11490(20)	39
H(2A)	1468	-2171	9917	41
H(3A)	880	-1113	10578	37
H(3B)	996	-286	9652	37
H(4A)	1386	235	11302	35
H(9)	1060	-842	12813	39
H(12A)	2496	-2674	12837	41
H(13A)	2276	-1592	11319	36
H(15B)	1321	-3476	15091	47
H(15A)	1565	-2721	16004	47

H(1SA)	252	-2252	9005	56

Table 6. Torsion angles [°] for Ent-**6c** .

C(26)-C(21)-C(22)-C(23)	0.0(8)
C(19)-C(21)-C(22)-C(23)	-176.2(6)
C(21)-C(22)-C(23)-C(24)	0.3(9)
C(22)-C(23)-C(24)-C(25)	-1.1(10)
C(22)-C(23)-C(24)-Br(1)	178.8(6)
C(23)-C(24)-C(25)-C(26)	1.6(11)
Br(1)-C(24)-C(25)-C(26)	-178.3(7)
C(24)-C(25)-C(26)-C(21)	-1.2(11)
C(22)-C(21)-C(26)-C(25)	0.4(10)
C(19)-C(21)-C(26)-C(25)	176.8(7)
C(26A)-C(21A)-C(22A)-C(23A)	-8(13)
C(19)-C(21A)-C(22A)-C(23A)	164(9)
C(21A)-C(22A)-C(23A)-C(24A)	10(11)
C(22A)-C(23A)-C(24A)-C(25A)	-10(9)
C(22A)-C(23A)-C(24A)-Br(1A)	166(9)
C(23A)-C(24A)-C(25A)-C(26A)	8(12)
Br(1A)-C(24A)-C(25A)-C(26A)	-168(10)
C(24A)-C(25A)-C(26A)-C(21A)	-5(15)
C(22A)-C(21A)-C(26A)-C(25A)	5(15)
C(19)-C(21A)-C(26A)-C(25A)	-164(10)
O(28)-C(1)-C(2)-O(7)	-22.3(6)
C(6)-C(1)-C(2)-O(7)	159.8(4)
O(28)-C(1)-C(2)-C(3)	-145.4(4)
C(6)-C(1)-C(2)-C(3)	36.7(6)

O(7)-C(2)-C(3)-C(4)	-179.9(4)
C(1)-C(2)-C(3)-C(4)	-57.2(5)
C(2)-C(3)-C(4)-C(5)	50.2(5)
C(2)-C(3)-C(4)-C(8)	-73.6(5)
C(3)-C(4)-C(5)-N(17)	156.6(4)
C(8)-C(4)-C(5)-N(17)	-79.4(5)
C(3)-C(4)-C(5)-C(6)	-24.3(6)
C(8)-C(4)-C(5)-C(6)	99.7(5)
N(17)-C(5)-C(6)-O(18)	-0.8(7)
C(4)-C(5)-C(6)-O(18)	-179.8(4)
N(17)-C(5)-C(6)-C(1)	-177.0(4)
C(4)-C(5)-C(6)-C(1)	3.9(7)
C(19)-O(18)-C(6)-C(5)	90.9(5)
C(19)-O(18)-C(6)-C(1)	-92.6(5)
O(28)-C(1)-C(6)-C(5)	172.3(4)
C(2)-C(1)-C(6)-C(5)	-9.9(7)
O(28)-C(1)-C(6)-O(18)	-4.1(7)
C(2)-C(1)-C(6)-O(18)	173.7(4)
C(5)-C(4)-C(8)-C(13)	-20.4(6)
C(3)-C(4)-C(8)-C(13)	103.3(5)
C(5)-C(4)-C(8)-C(9)	158.8(4)
C(3)-C(4)-C(8)-C(9)	-77.5(5)
C(13)-C(8)-C(9)-C(10)	0.4(7)
C(4)-C(8)-C(9)-C(10)	-178.8(4)
C(8)-C(9)-C(10)-C(11)	-0.1(7)
C(8)-C(9)-C(10)-O(14)	176.7(5)

C(15)-O(14)-C(10)-C(11)	-10.0(5)
C(15)-O(14)-C(10)-C(9)	172.9(5)
C(9)-C(10)-C(11)-C(12)	0.3(8)
O(14)-C(10)-C(11)-C(12)	-177.1(4)
C(9)-C(10)-C(11)-O(16)	178.4(5)
O(14)-C(10)-C(11)-O(16)	1.1(6)
C(15)-O(16)-C(11)-C(10)	8.3(5)
C(15)-O(16)-C(11)-C(12)	-173.7(5)
C(10)-C(11)-C(12)-C(13)	-0.7(7)
O(16)-C(11)-C(12)-C(13)	-178.5(5)
C(9)-C(8)-C(13)-C(12)	-0.9(7)
C(4)-C(8)-C(13)-C(12)	178.3(4)
C(11)-C(12)-C(13)-C(8)	1.0(7)
C(10)-O(14)-C(15)-O(16)	15.1(5)
C(11)-O(16)-C(15)-O(14)	-14.3(5)
C(6)-O(18)-C(19)-O(20)	-6.4(6)
C(6)-O(18)-C(19)-C(21A)	160(4)
C(6)-O(18)-C(19)-C(21)	173.6(4)
C(26A)-C(21A)-C(19)-O(20)	-7(13)
C(22A)-C(21A)-C(19)-O(20)	-177(6)
C(26A)-C(21A)-C(19)-O(18)	-174(9)
C(22A)-C(21A)-C(19)-O(18)	15(8)
C(26)-C(21)-C(19)-O(20)	4.2(8)
C(22)-C(21)-C(19)-O(20)	-179.6(6)
C(26)-C(21)-C(19)-O(18)	-175.9(5)
C(22)-C(21)-C(19)-O(18)	0.4(7)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for Ent-**6c** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(23)-H(23A)...O(20)#1	0.95	2.58	3.269(9)	129.8
C(23A)-H(23B)...O(20)#1	0.95	2.62	3.25(8)	124.6
O(7)-H(7A)...O(28)	0.87(8)	2.11(7)	2.661(5)	120(6)
N(17)-H(17A)...O(16)#2	0.850(10)	2.30(3)	3.076(6)	152(5)
N(17)-H(17B)...O(28)#3	0.852(10)	2.10(2)	2.921(5)	160(6)
C(12)-H(12A)...O(28)#4	0.95	2.38	3.292(6)	160.8

Symmetry transformations used to generate equivalent atoms:

#1 x,-y,z-1/2 #2 -x+1/2,y+1/2,-z+5/2 #3 x,-y,z+1/2

#4 -x+1/2,-y-1/2,-z+2