Supporting information

Generation of 1-azabicyclo[3.2.1]octane and 5-azatricyclo[3.2.1.$0^{2,7}$]octane systems by carbenium ion rearrangements during production of the antihistamine drug Quifenadine

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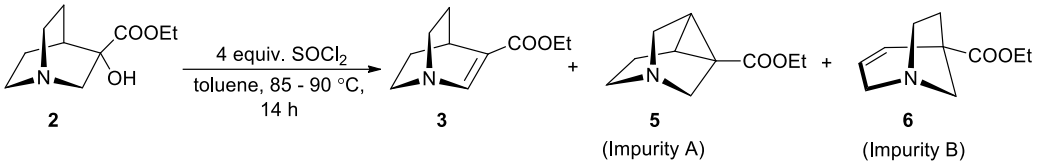
1. General information

The solvents used in the reactions were dried with standard drying agents and freshly distilled prior to use. Commercially available reagents were used as received. 3-Hydroxy-3-ethoxycarbonylquinuclidine (**2**) can be prepared either from 3-quinuclidinone[1] or its cyanohydrin.[2] pH was determined using *Macherey-Nagel* pH-fix 0-14 pH strips. Melting points were recorded with a *Stuart* SMP 10 apparatus. ^{1}H and ^{13}C NMR spectra were recorded with a Varian 400 MHz or Bruker 300 MHz spectrometer in $CDCl_3$ or CD_3OD. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Residual solvent (^{1}H) or solvent (^{13}C) peaks were used as internal reference ($CDCl_3$: δ = 7.26 ppm for ^{1}H NMR; $CDCl_3$ δ = 77.16 ppm for $\{^{1}H\}^{13}C$ NMR; CD_3OD δ = 3.31 ppm for ^{1}H NMR; CD_3OD δ = 49.0 ppm for $\{^{1}H\}^{13}C$ NMR). Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Crystallographic diffraction data were collected with a NoniusKappa CCD diffractometer (Mo-Kα, λ = 0.71073 Å) equipped with a low-temperature Oxford Cryosystems Cryostream Plus device. GC analyses were performed using *Hewlett-Packard Agilent Technologies 6890* gas chromatograph with mass selective detector, equipped with capillary column *Agilent technologies* DB-1MS (30 m × 0.32 mm × 0.25 μm). Injection temperature: 250 °C; splitless and injection volume 1 μL or split 1:300 and injection volume 0.2 μL; Gas type: Helium; flow rate: 2.0 ml/min; detector temperature: 230 °C; MS-detector (EI, 70 eV). High resolution mass spectra were recorded with an Agilent 1290 Infinity series UPLC connected to an Agilent 6230 TOF mass spectrometer (calibration at m/z = 121.050873 and m/z = 922.009798).

2. Preparation and isolation of impurities A and B



2 **3** **5** (Impurity A) **6** (Impurity B)

A 50 ml pressure flask equipped with Teflon-coated magnetic stirrer was charged with 3-hydroxy-3-ethoxycarbonylquinuclidine (9.0 g, 0.045 mol, 1.0 equiv.), $SOCl_2$ (13 ml, 21.3 g, 0.178 mol, 4.0 equiv.) and toluene (16 ml, technical grade). Then the flask was heated in oil bath at 85 – 90 °C for 14 hours. The reaction mixture was cooled to room temperature and evaporated *in vacuo* to a thick crude oil. Toluene (100 ml) was added and then the mixture was carefully neutralized with aqueous ammonia (~25% NH_3) to pH 5.5. The aqueous phase was extracted with toluene (2×50 ml) and then basified to pH 6.5 with aqueous ammonia. The mixture was further extracted with toluene (3×50 ml) and then basified to pH 7.5 with aqueous ammonia. The mixture was again extracted with toluene (3 × 50ml) and then basified to pH 8.0 with aqueous ammonia. The resulting mixture was extracted with $CHCl_3$ (2×100 ml) to obtain chloroform extract No 1 and chloroform extract No 2 respectively.

Chloroform extract No 1 contains:

Impurity B **6**: 50%-80%

Main product **3**: 5%-20%

Impurity A **5**: 10%-20%

Chloroform extract No 2 contains:

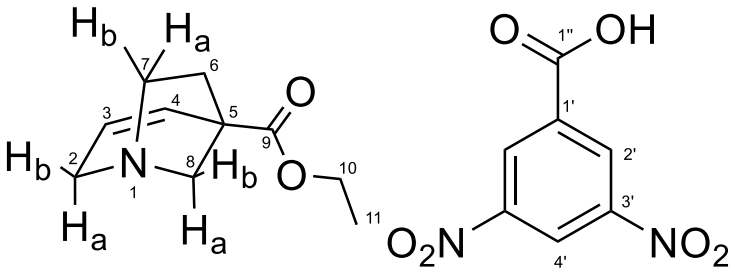
Impurity B **6**: 40% - 60%

Main product **3**: 0.5% - 5%

Impurity A **5**: 35% - 45%

Impurity B

Ethyl 1-azabicyclo[3.2.1]oct-3-ene-5-carboxylate 3,5-dinitrobenzoic acid salt (6·3,5-$(NO_2)_2C_6H_3COOH$)



Chloroform extract No 1 was dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo to give a brown oil (0.8 – 1.0 g). Methanol (12 ml), water (0.6 ml) and picric acid (0.3 equiv. to impurity B) was added to the crude oil and the resulting mixture was agitated until the dissolution of the picric acid. After approx. 5 min bright yellow precipitate was observed. After 1 h at room temperature the mixture was filtered and washed with cold methanol (- 20 °C; 2 × 1 ml). The filter cake was dried under reduced pressure (4 torr) for 12 h to give impurity B (0.3 – 0.4 g) as a picrate salt with B:A ratio approx. 85/15 – 95/5 determined by GC-MS.* This procedure can be repeated with additional picric acid (0.3 equiv. to impurities A and B) to give another portion of impurity B picrate salt (0.3 g) with B/A ratio 85/15.

Picric acid salts are better for quantitative recovery of impurity B; however, recrystallization is with poor reproducibility and is not recommended for isolation of pure impurity B.
Therefore, to impurity B picric acid salt (0.57 g with B/A ratio 80/20 by ^{1}H-NMR, 1.4 mmol, 1.0 equiv.) $CHCl_3$ (14 ml) was added and the resulting mixture washed with aqueous 2M NH_4OAc (pH 10.0, 5 × 14 ml). The organic layer still contained some residual picric acid; therefore, it was filtered through a pad of Al_2O_3 (1 g) and washed with additional $CHCl_3$ (10 ml). Combined colorless organic phase was concentrated *in vacuo* to give a colorless oil (0.2 g). Then EtOAc (2.5 ml) and 3,5-dinitrobenzoic acid (0.17 g, 0.9 equiv. to impurity B) was added and immediate formation of a precipitate was observed. The mixture was heated in hot water bath until complete dissolution and then cooled to room temperature and after 2 h was cooled to 4 - 6 °C. After 4 h the precipitate was filtered and washed with cold EtOAc

* Relative ratio of *in situ* generated freebase forms in GC-MS chromatogram. ^{1}H-NMR is more suitable to determine the ratio than uncalibrated GC-MS.

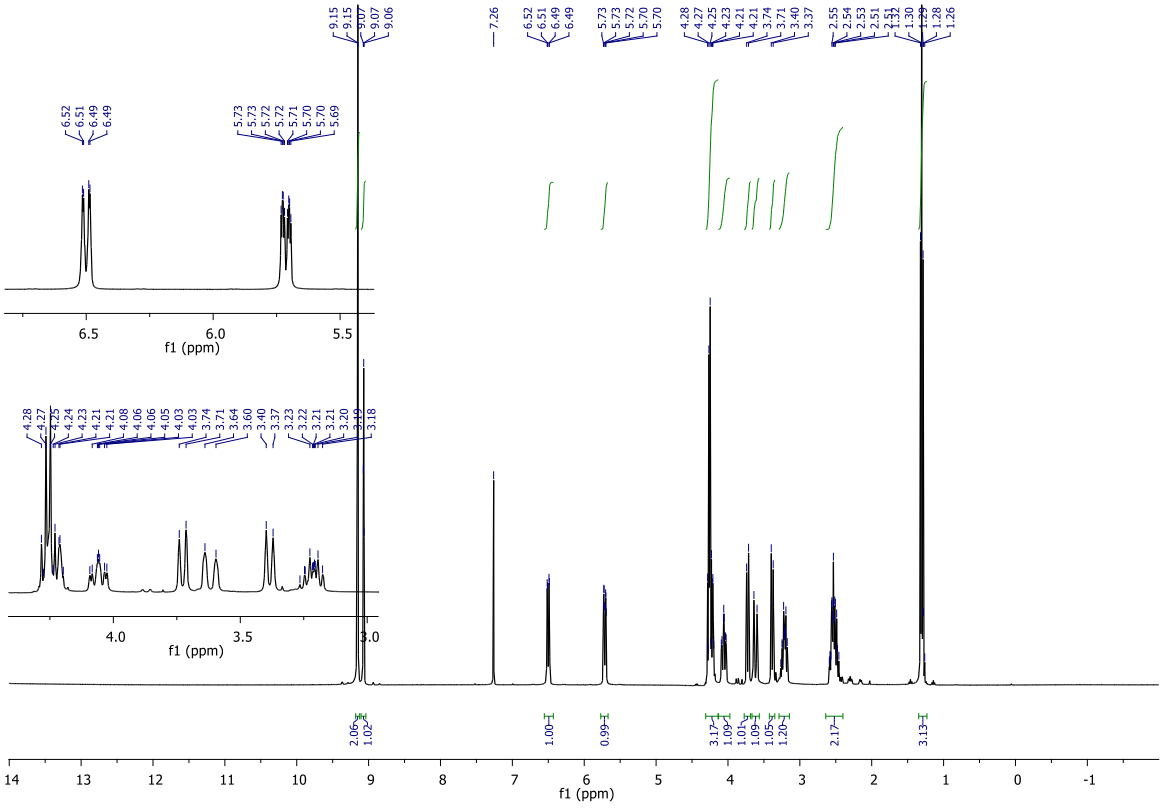
(- 20 °C; 2 × 1 ml). The filter cake was dried under reduced pressure (4 torr) for 12 h to give impurity B 3,5-dinitrobenzoic acid salt (0.23 g) with B:A ratio 93/7 by ^{1}H-NMR.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (d, ^{4}J = 2.1 Hz, 2H, HC(2´)), 9.07 (t, ^{4}J = 2.1 Hz, 1H, HC(4´)), 6.50 (ddd, ^{3}J = 10.2 Hz, ^{4}J = 3.8, 1.9 Hz, 1H, HC(4)), 5.71 (ddd, ^{3}J = 10.2 Hz, ^{4}J = 3.3, 2.0 Hz, 1H, HC(3)), 4.26 (q, ^{3}J = 7.1 Hz, 2H, H_2C(10)), 4.26 – 4.18 (m, 1H, H_aC(2)), 4.06 (ddd, ^{2}J = 13.2 Hz, ^{3}J = 11.6, 3.7 Hz, 1H, H_aC(7)), 3.73 (d, ^{3}J = 10.7 Hz, 1H, H_aC(8)), 3.62 (br. d, ^{2}J = 17.4 Hz, 1H, H_bC(2)), 3.38 (d, ^{2}J = 10.7 Hz, 1H, H_bC(8)), 3.29 – 3.14 (td, ^{2}J = 13.2 Hz, ^{3}J = 8.5 Hz, 1H, H_bC(7)), 2.64 – 2.40 (m, 2H, H_2C(6)), 1.30 (t, ^{3}J = 7.1 Hz, 3H, H_3C(11)).

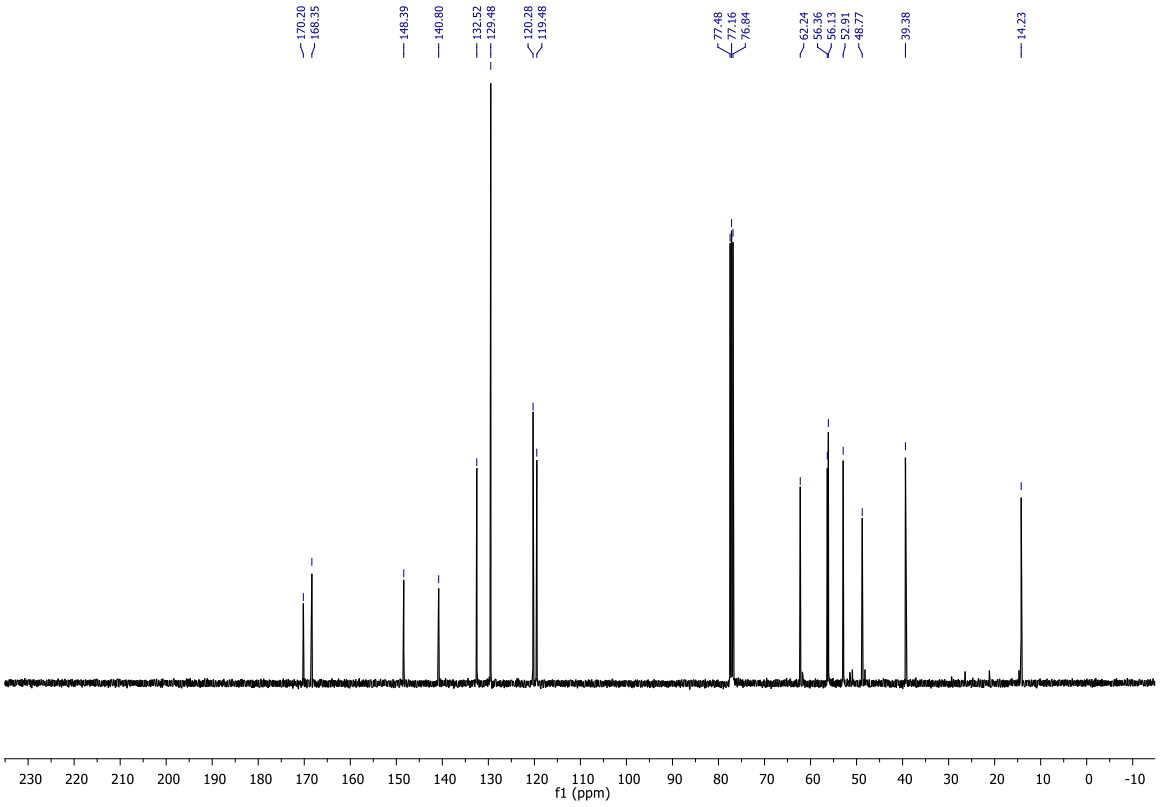
{^{1}H}^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2 (C(9)), 168.4 (C(1´´)), 148.4 (C(3´)), 140.8 (C(1´)), 132.5 (C(4)), 129.5 (C(2´)), 120.3 (C(4´)), 119.5 (C(3)), 62.2 (C(10)), 56.4 (C(8)), 56.1 (C(2)), 52.9 (C(7)), 48.8 (C(5)), 39.4 (C(6)), 14.2 (C(11)).

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_{16}NO_2^+$ 182.1181; Found 182.1186.

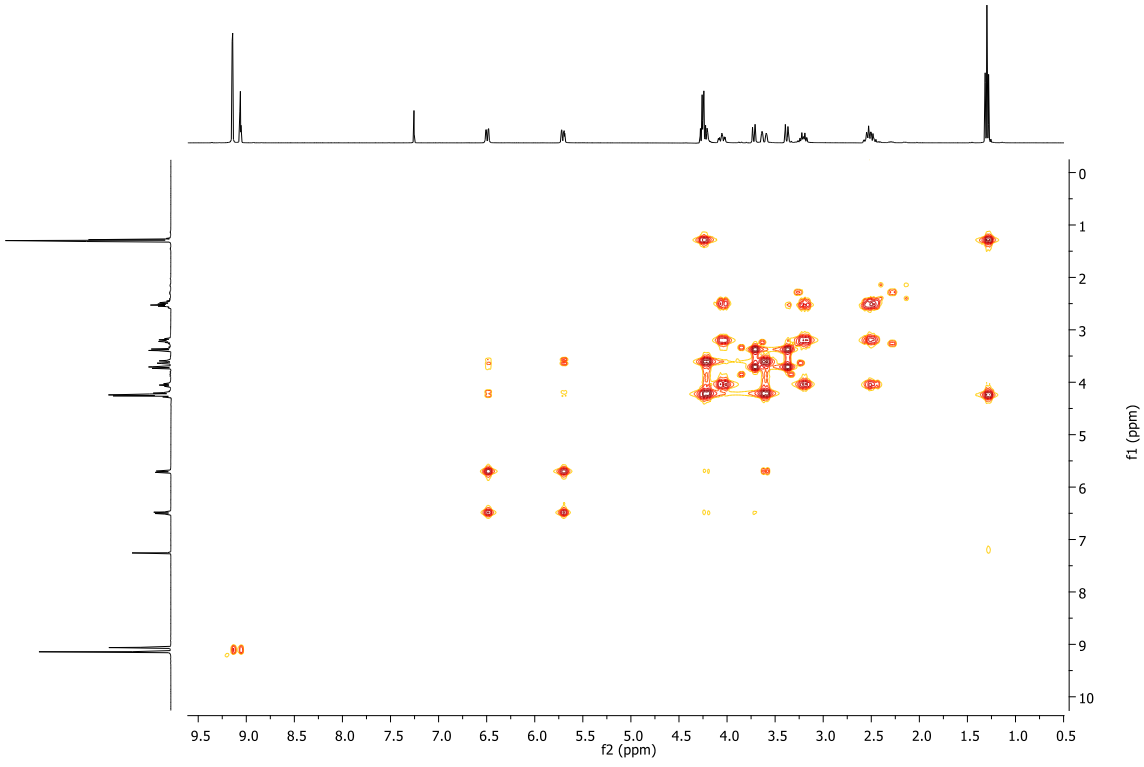
^{1}H NMR (400 MHz, $CDCl_3$):



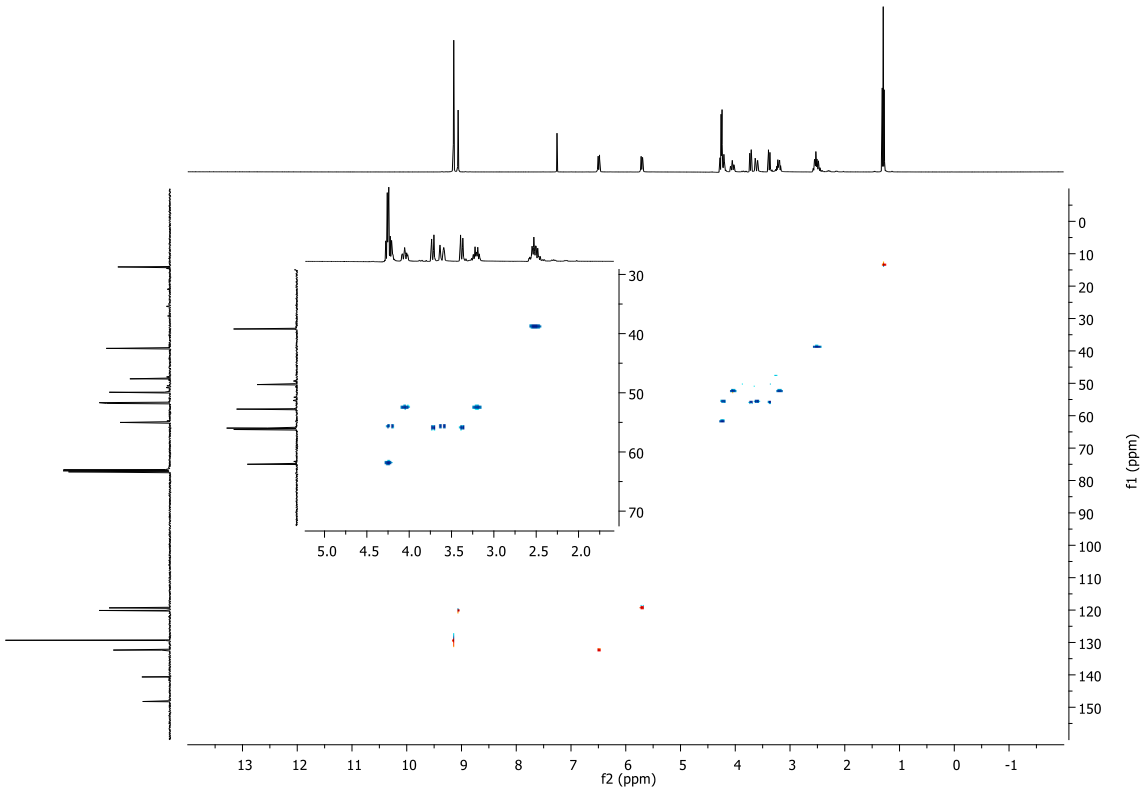
{^{1}H}^{13}C NMR (101 MHz, $CDCl_3$



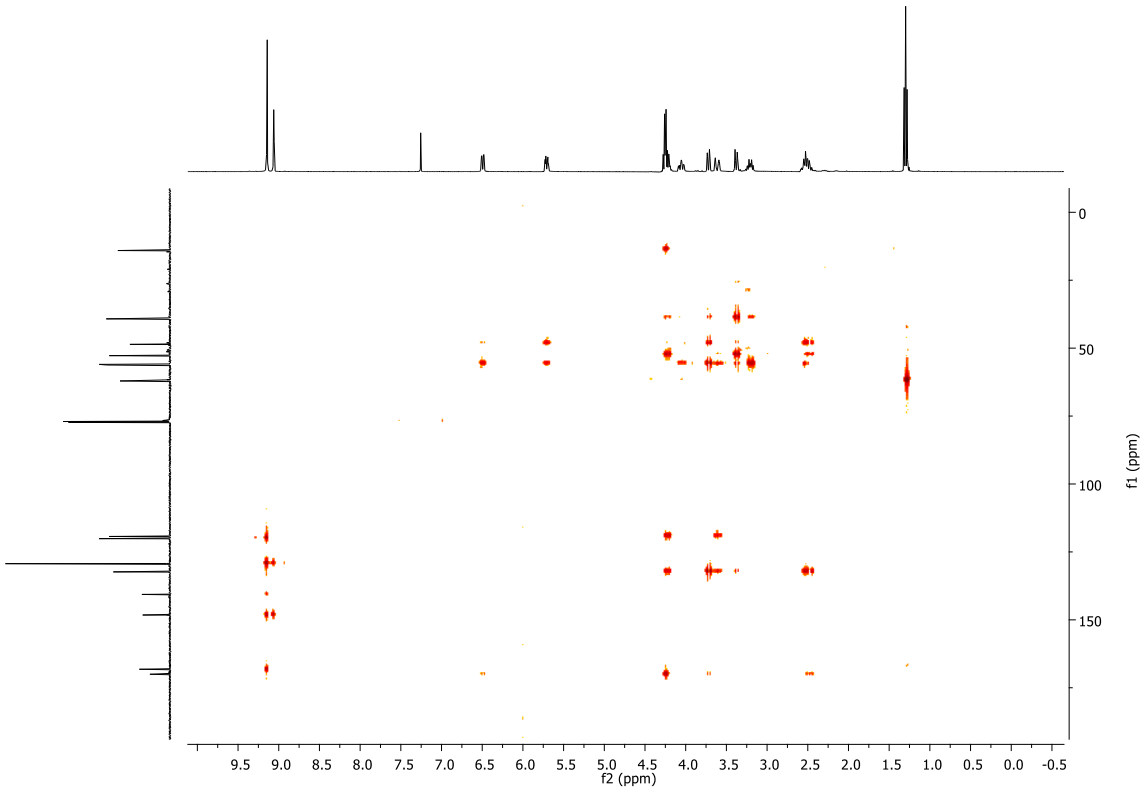
^{1}H-^{1}H COSY NMR (400 MHz, $CDCl_3$)



^{1}H-^{13}C HSQC NMR (400 MHz for ^{1}H, $CDCl_3$)

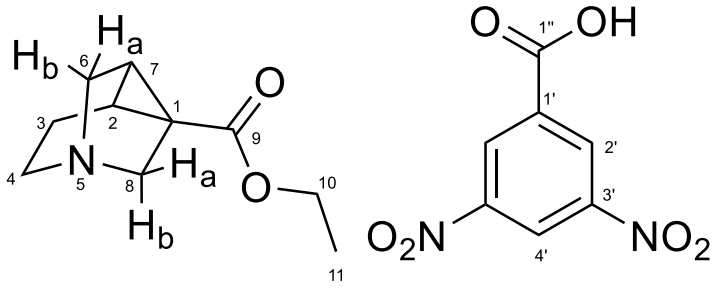


^{1}H-^{13}C HMBC NMR (400 MHz for ^{1}H, $CDCl_3$)



Impurity A

Ethyl 5-azatricyclo[3.2.1.02,7]octane-1-carboxylate 3,5-dinitrobenzoic acid salt (5·3,5-$(NO_2)_2C_6H_3COOH$)



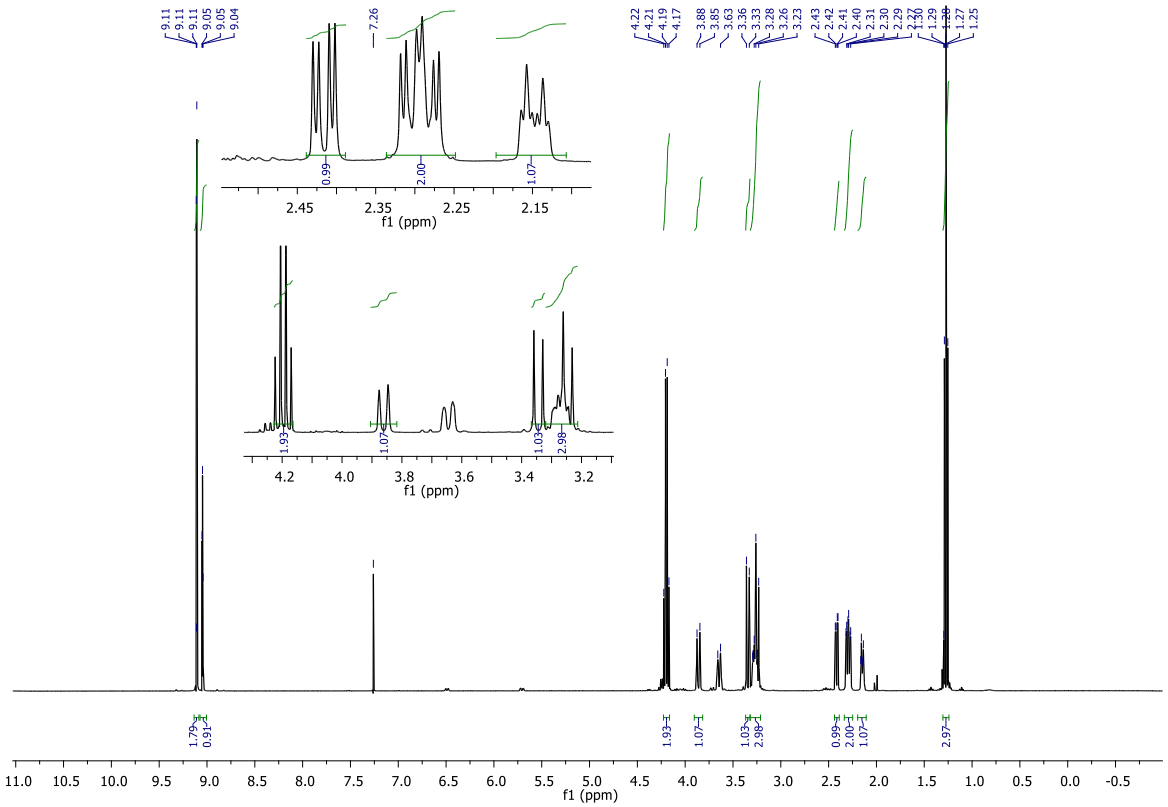
Chloroform extract No 2 was dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to give brown oil (0.3 – 0.45 g). Then, MeCN (5 ml) and 3,5-dinitrobenzoic acid was added (0.9 equiv. to impurity A). The mixture was agitated and then cooled to 4-6 °C. After 14 h the white precipitate was filtered and washed with MeCN cooled to -20 °C (2 × 1 ml). The filter cake was dried under reduced pressure (4 torr) for 12 h to give impurity A 3,5-dinitrobenzoic acid salt (0.3 g) with A:B ratio 75/25 – 85/15 by ^{1}H-NMR. The salt was re-precipitated from MeCN to give impurity A 3,5-dinitrobenzoic acid salt (0.2 g) with A:B ratio 95/5 by ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (d, ^4J = 2.2 Hz, 2H, HC(2´)), 9.05 (d, ^4J = 2.2 Hz, 1H, HC(4´)), 4.20 (q, ^3J = 7.1 Hz, 2H, H_2C(10)), 3.86 (d, ^2J = 12.0 Hz, 1H, H_aC(8)), 3.64 (br. d, ^{2}J = 11.5 Hz, 1H, H_aC(6)), 3.34 (d, ^2J = 12.0 Hz, 1H, H_bC(8)), 3.30 – 3.24 (m, 2H, H_2C(4)), 3.23 (br. d, ^{2}J = 11.5 Hz, 1H, H_bC(6)), 2.42 (dd, ^3J = 8.3 Hz, 2.9 Hz, 1H, H-C(7)), 2.30 (dt, ^3J = 8.4 Hz, 2.9 Hz, 2H, H_2C(3)), 2.15 (td, ^3J = 8.3, 2.8, 1H, HC(2)), 1.27 (t, ^3J = 7.1 Hz, 3H, H_3C(11)).

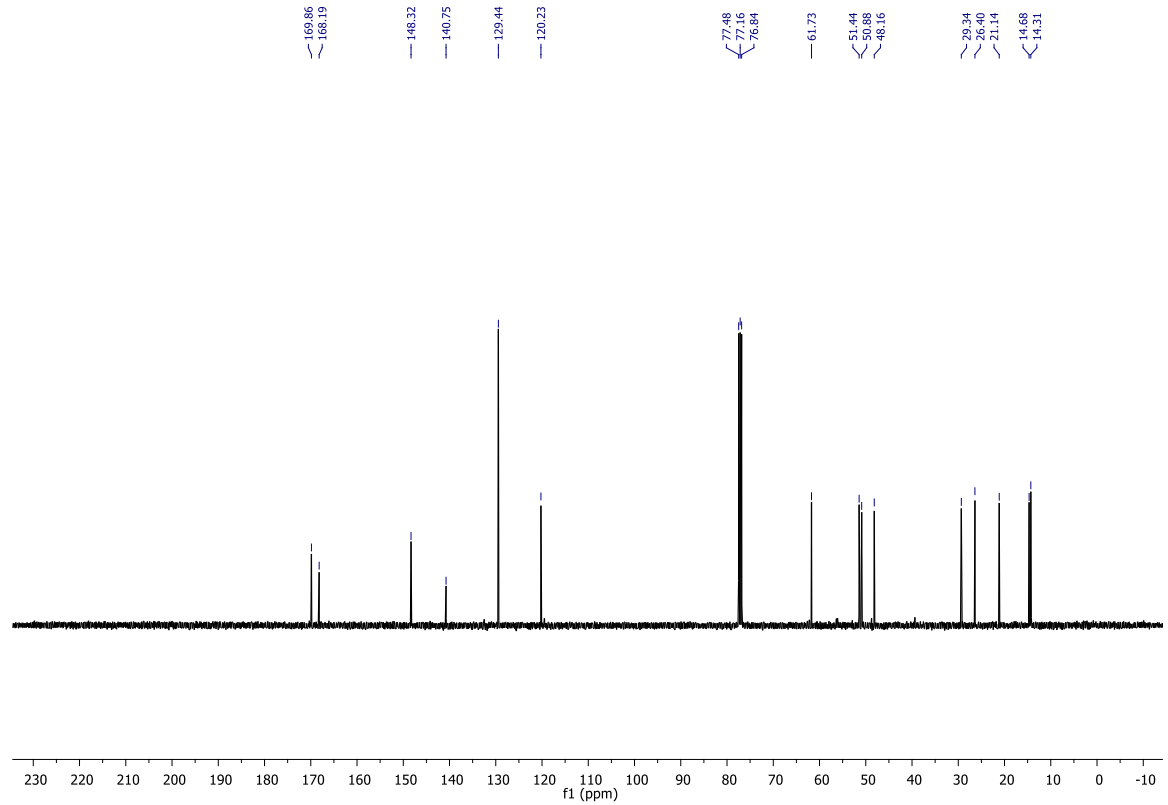
{^{1}H}^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9 (C(9)), 168.2 (C(1´´)), 148.3 (C(3´)), 140.8 (C(1´)), 129.4 (C(2´)), 120.2 (C(4´)), 61.7 (C(10)), 51.4 (C(6)), 50.9 (C(8)), 48.2 (C(4)), 29.3 (C(1)), 26.4 (C(7)), 21.1 (C(2)), 14.7 (C(3)), 14.3 (C(11)).

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_{16}NO_2^+$ 182.1181; Found 182.1195.

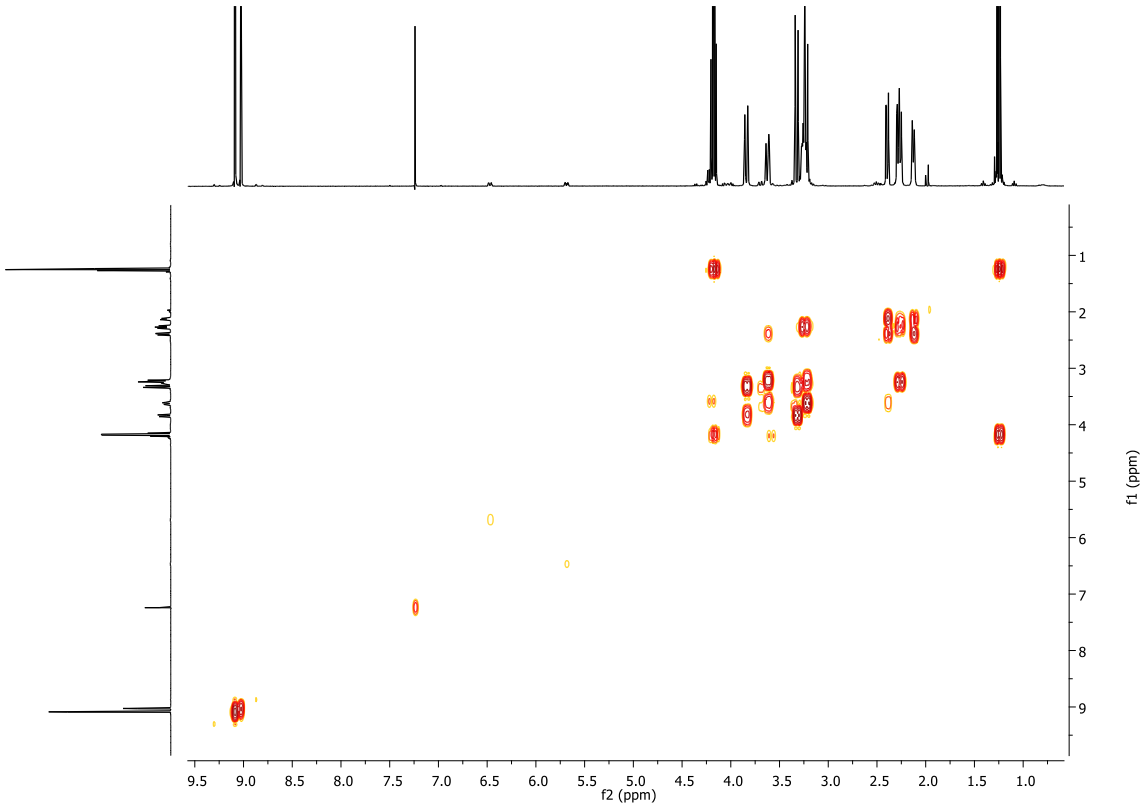
^{1}H NMR (400 MHz, $CDCl_3$)



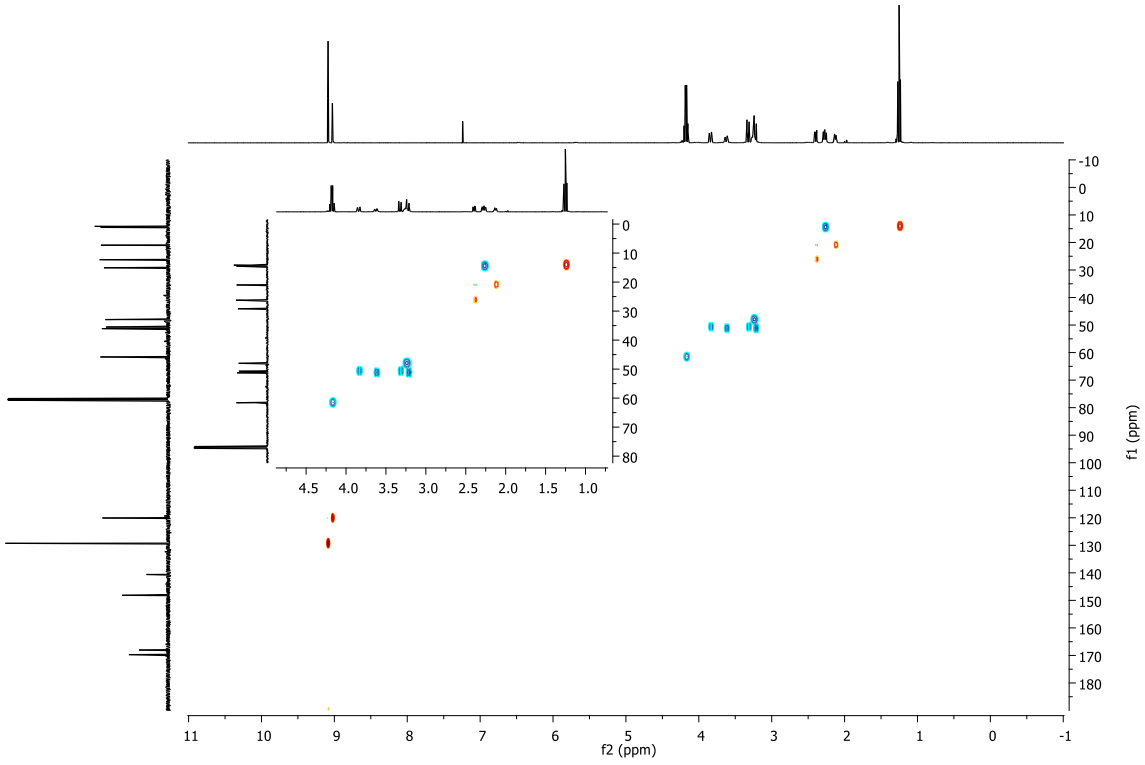
{^{1}H}^{13}C NMR (101 MHz, $CDCl_3$)



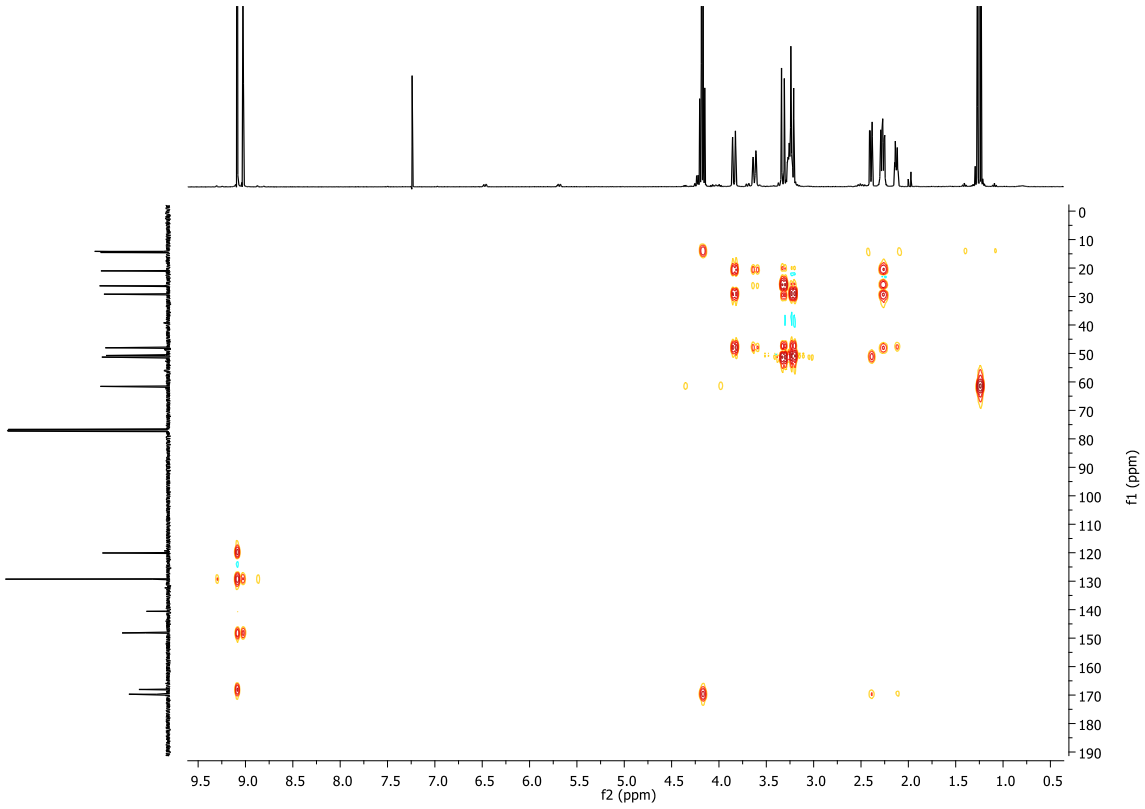
^{1}H-^{1}H COSY NMR (400 MHz, $CDCl_3$)



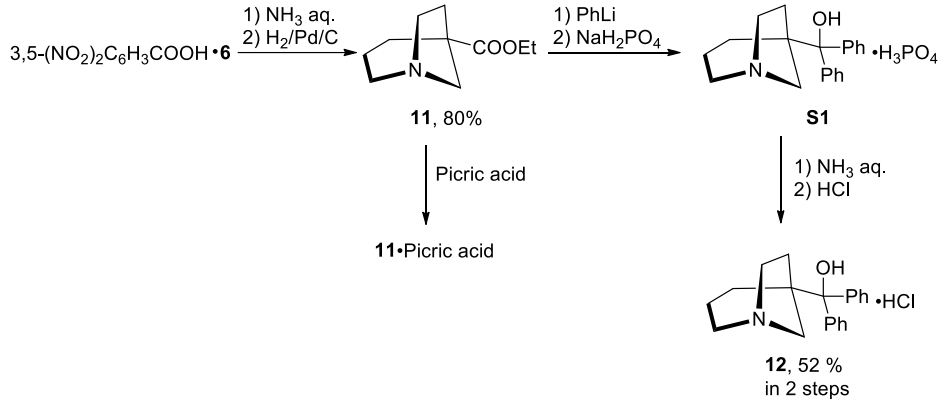
^{1}H-^{13}C HSQC NMR (400 MHz for ^{1}H, $CDCl_3$)



^{1}H-^{13}C HMBC NMR (400 MHz for ^{1}H, $CDCl_3$)



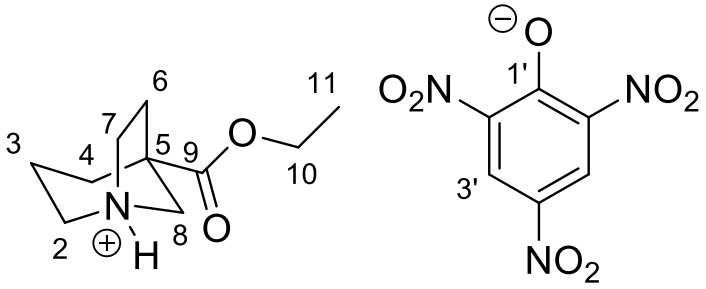
3. Preparation of Quifenadine impurity standarts



To impurity B 3,5-dinitrobenzoic acid salt (0.8 g, 2.03 mmol, B:A ration 93/7 by ^{1}H-NMR) $CHCl_3$ (14 ml) was added and the resulting mixture with aqueous ammonia solution (~ 25% NH_3, 2 × 4 ml). The organic layer was filtered through short neutral Al_2O_3 (1 g) pad, which was washed with additional $CHCl_3$ (10 ml). The combined organic phase was evaporated *in vacuo* to give colorless oil (0.3 g). Then, MeOH (10 ml) was added and the mixture was transferred to a 20 ml pressure flask equipped with a Teflon-coated magnetic stirrer and charged with 5% Pd/C (0.06 g) and barbotated with H_2 for 3 min. Then the pressure flask was charged with H_2 (2 – 4 bar) and the mixture was stirred for 12 h at room temperature. The mixture was filtered through a pad of Celite, which was washed with additional MeOH (5 ml). The combined organic layers were evaporated in vacuo to give a pale-yellow oil (**11**, 0.3 g, η = 80 %). The crude product was used in further stages without additional purification.

Compound 11·picric acid

Ethyl 1-azabicyclo[3.2.1]octane-5-carboxylate picric acid salt (11·picric acid)



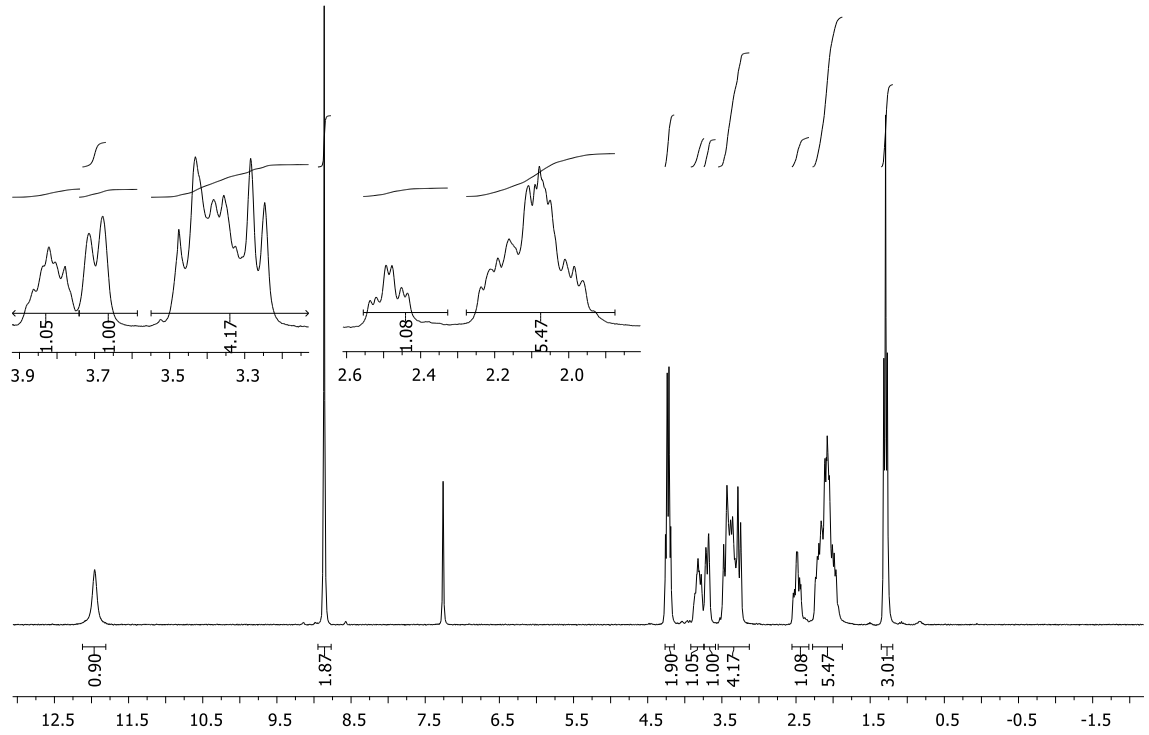
To the crude oil (**11**, 0.15 g, 0.82 mmol, 1.0 equiv.) MeOH (2 ml) and picric acid (0.17 g, 0.74 mmol, 0.9 equiv.) were added. The mixture was agitated until complete dissolution. The resulting mixture was cooled to 4 – 6 °C. After 3 h the precipitate was filtered and washed with cold MeOH (– 20 °C;2 × 1ml). The filter cake was dried under reduced pressure (2 torr) for 12 h to give compound **11** picrate salt (0.21 g, η = 62 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 11.91 (s, 1H, H-N), 8.86 (s, 2H, 2×HC(3′)), 4.22 (q, ^{3}J = 6.8 Hz, 2H, H_2C-O), 3.91 – 3.75 (m, 1H, $H_aC(7)$), 3.70 (d, ^{2}J = 11.3 Hz, 1H, $H_aC(8)$), 3.56 – 3.19 (m, 4H, $H_2C(2)$, $H_bC(7)$ and $H_bC(8)$), 2.48 (td, J = 12.5, 4.6 Hz, 1H, $H_aC(6)$), 2.28 – 1.78 (m, 5H, $H_bC(6)$, $H_2C(3)$, $H_2C(4)$), 1.29 (t, ^{3}J = 6.8 Hz, 3H, H_3C-H_2C-O).

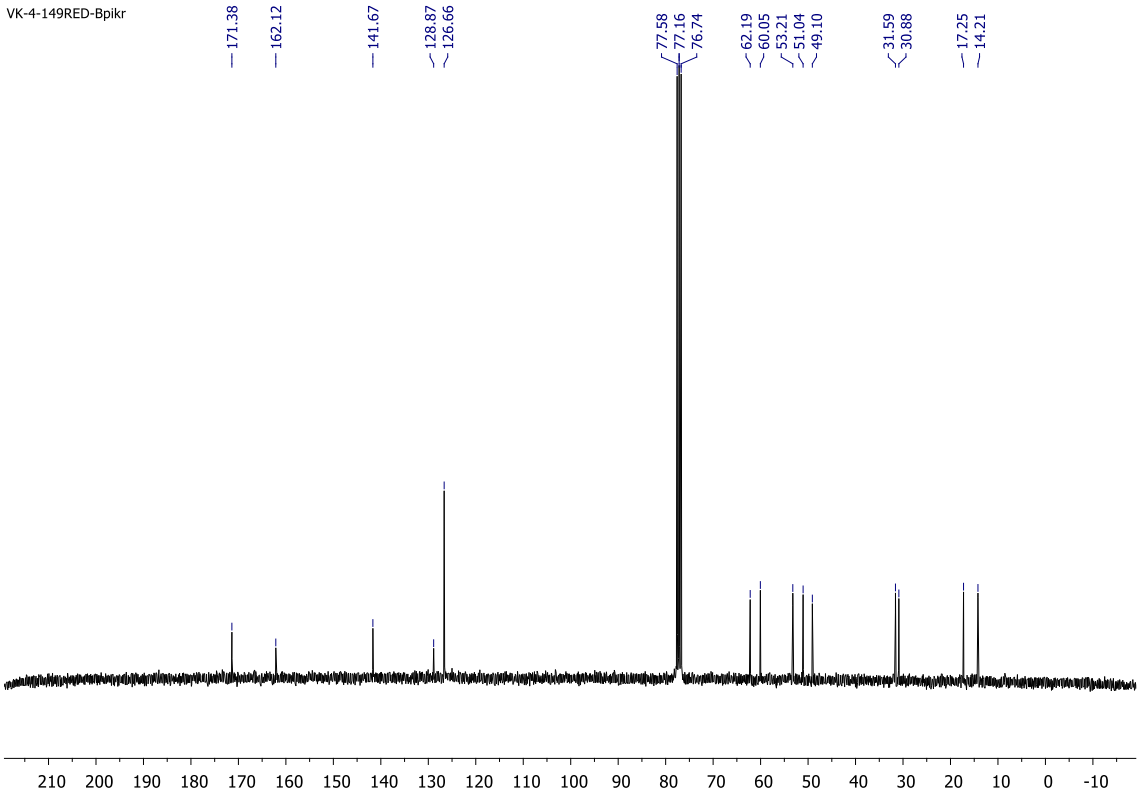
{^{1}H}^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.4 (C(9)), 162.1 (C(1′)), 141.7 (C(2′)), 128.9 (C(4′)), 126.7 C(3′)), 62.2 (C(10)), 60.1 C(8)), 53.2 (C(2)), 51.0 (C(7)), 49.1 (C(5)), 31.6 (C(3)), 30.9 (C(6)), 17.3 (C(4)), 14.2 (C(11)).

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_{18}NO_2^+$ 184.1338; Found 184.1362.

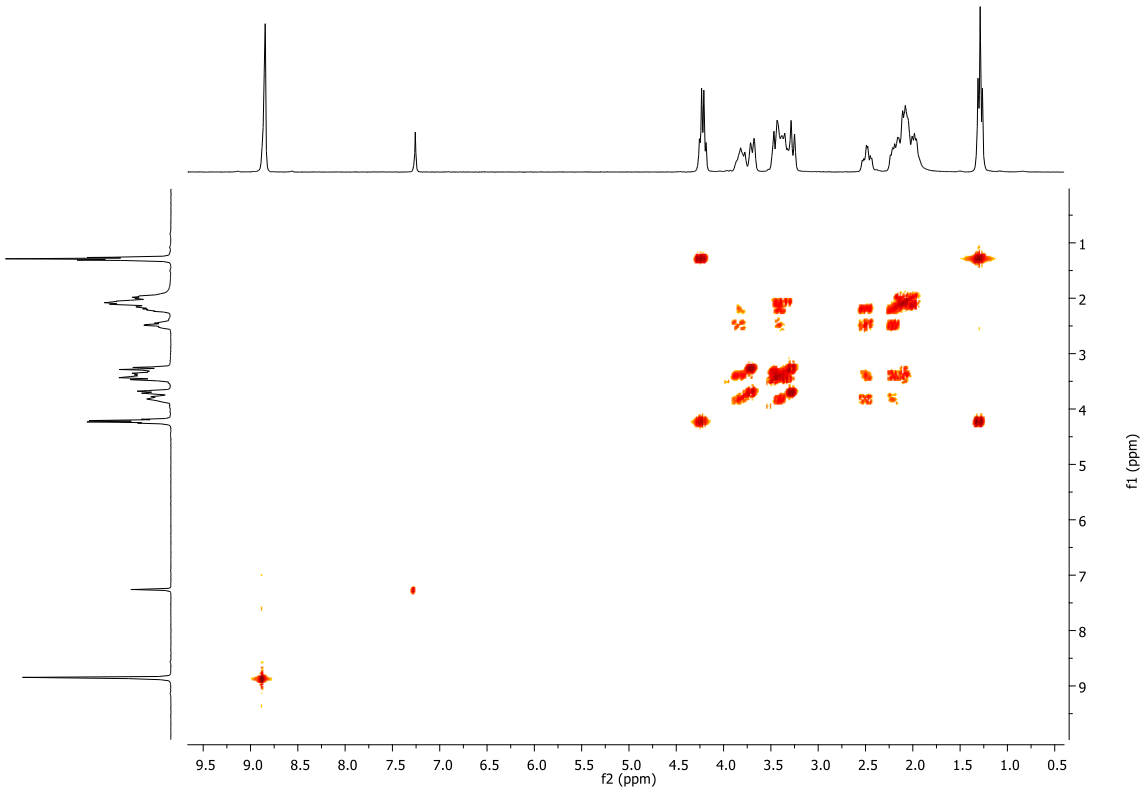
^{1}H NMR (300 MHz, $CDCl_3$)



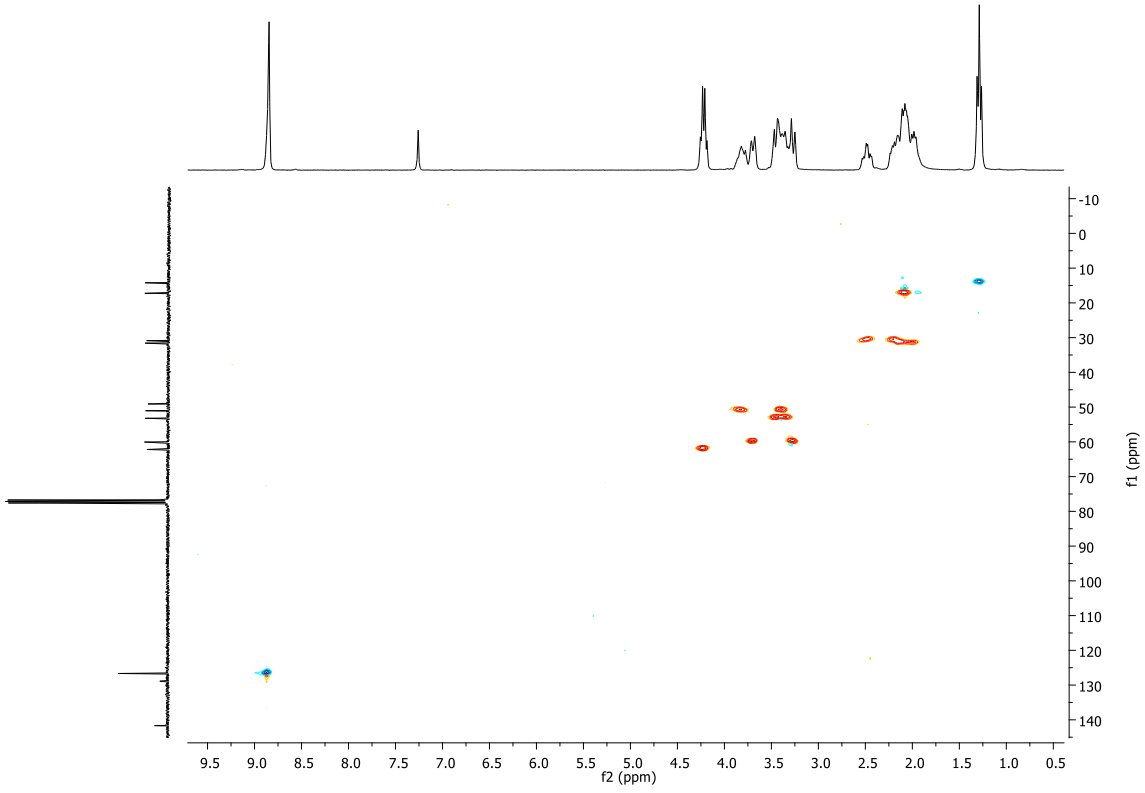
{^{1}H}^{13}C NMR (75.5 MHz, $CDCl_3$)



^{1}H-^{1}H COSY NMR (300 MHz, $CDCl_3$)

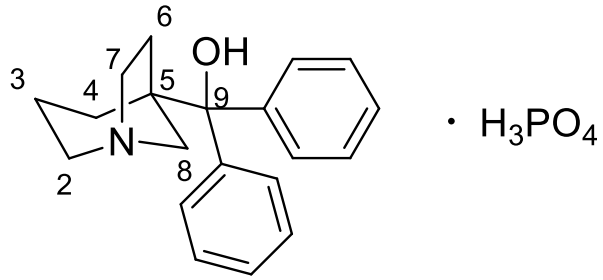


^{1}H-^{13}C HSQC NMR (300 MHz for ^{1}H, $CDCl_3$)



Compound S1

1-Azabicyclo[3.2.1]octan-5-yl)diphenylmethanol ortophosphoric acid salt (S1)



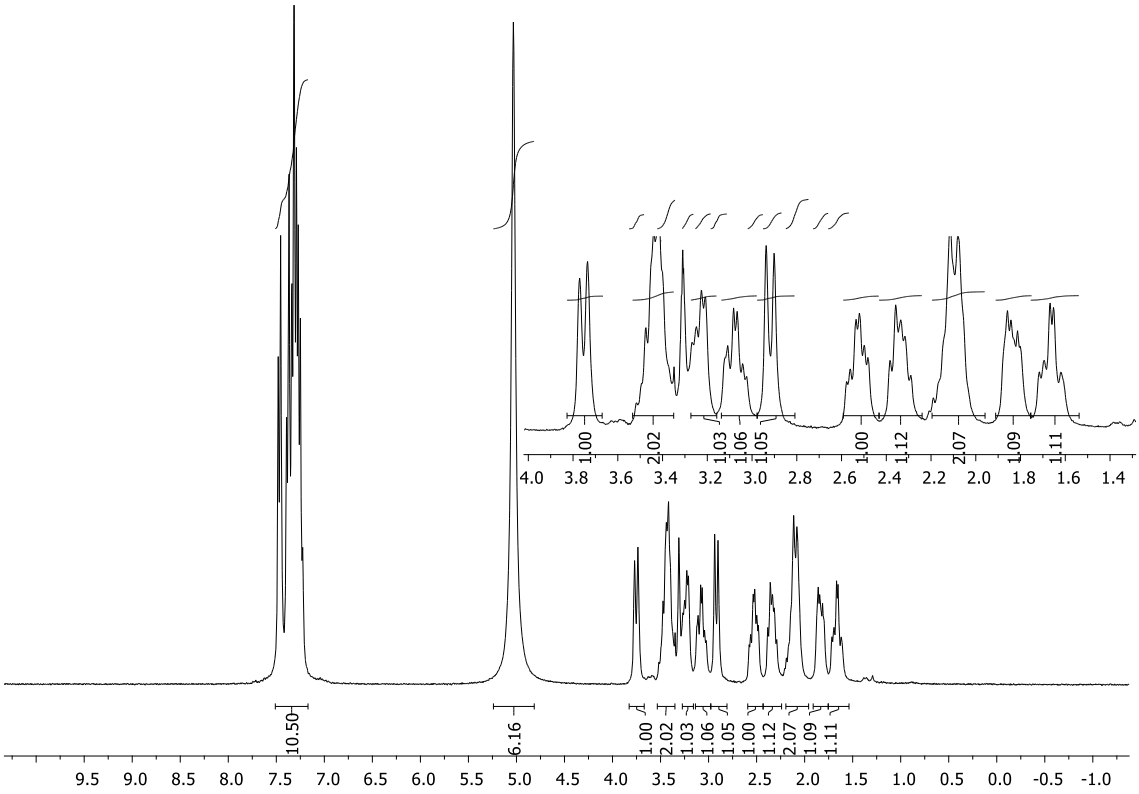
· H_3PO_4

To remove traces of water the crude oil (**11**, 0.15 g, 0.82 mmol, 1.0 equiv.) was re-evaporated with anhydrous THF (2×8 ml). Then anhydrous THF (8 ml) was added under Ar and the mixture was cooled to -60 °C. PhLi (1.9 M in Bu_2O, 0.91 ml, 1.73 mmol, 2.1 equiv.) was added portion-wise over 5 minutes and the mixture was stirred for 5 min at -60 °C, warmed to room temperature and stirred for 1h. The mixture was poured into aqueous 1.5 M KH_2PO_4 (30 ml) and agitated. The resulting mixture was stirred for 1 h at room temperature and the resulting precipitate was filtered and washed with distilled water cooled to 0 °C (2 × 2ml). The filter cake was dried under reduced pressure (2 mbar) for 12 h to give compound **S1**.

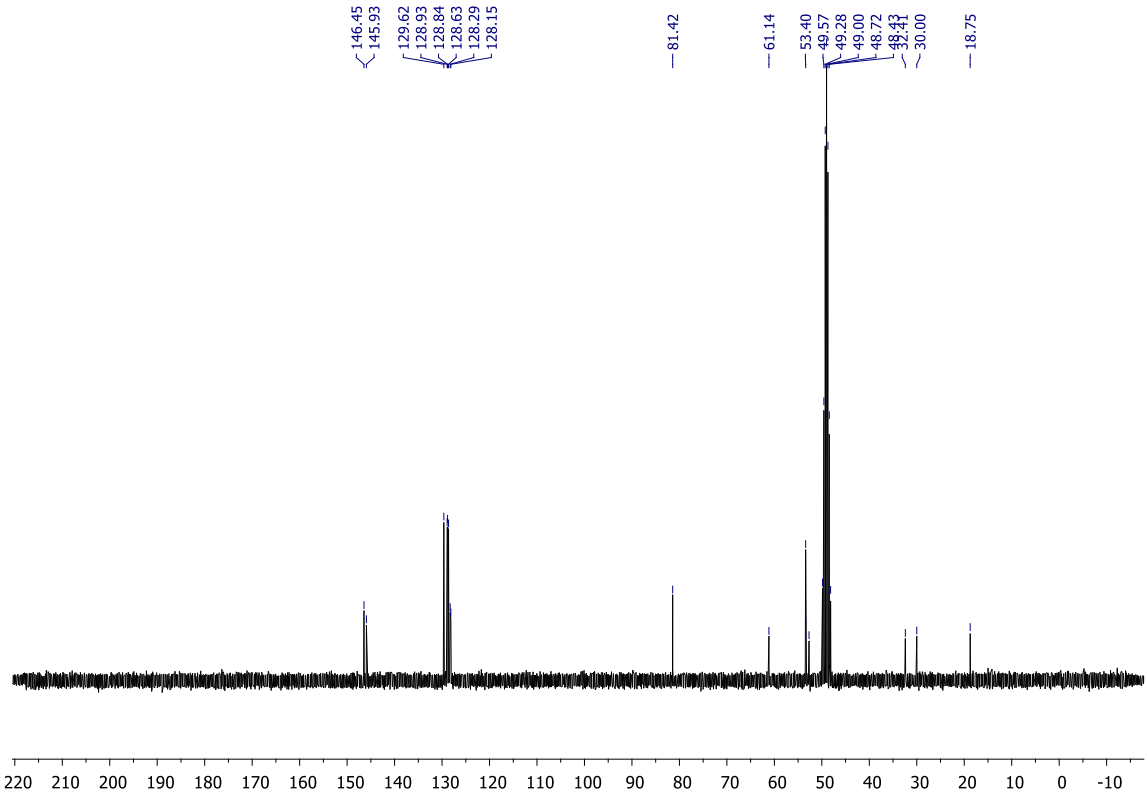
^{1}H NMR (300 MHz, CD_3OD): δ 7.51 – 7.17 (m, 10H, ArH), 3.75 (d, ^2J = 10.6 Hz, 1H, $H_aC(8)$), 3.53 – 3.35 (m, 2H, $H_2C(7)$), 3.27 – 3.16 (m, 1H, $H_aC(2)$), 3.14 – 2.98 (m, 1H, $H_bC(2)$), 2.92 (d, ^2J = 10.6 Hz, 1H, $H_bC(8)$), 2.59 – 2.43 (m, 1H, $H_a(C(6))$, 2.43 – 2.24 (m, 1H, $H_bC(6)$), 2.20 – 1.96 (m, 2H, $H_aC(3)$ and $H_a(C(4))$, 1.91 – 1.75 (m, 1H, $H_bC(3)$), 1.75 – 1.54 (m, 1H, $H_bC(4)$).

{^{1}H}^{13}C NMR (75.5 MHz, CD_3OD): δ 146.5 (C(Ar)), 145.9 (C(Ar)), 129.6 (C(Ar)), 128.9 (C(Ar)), 128.8 (C(Ar)), 128.6 (C(Ar)), 128.3 (C(Ar)), 128.2 (C(Ar)), 81.4 (C(9)), 61.1 (C(8), 53.40 (C(2)), 53.39 (C(5)), 52.7 (C(7)), 32.4 (C(4)), 30.0 (C(6)), 18.8 (C(3)).

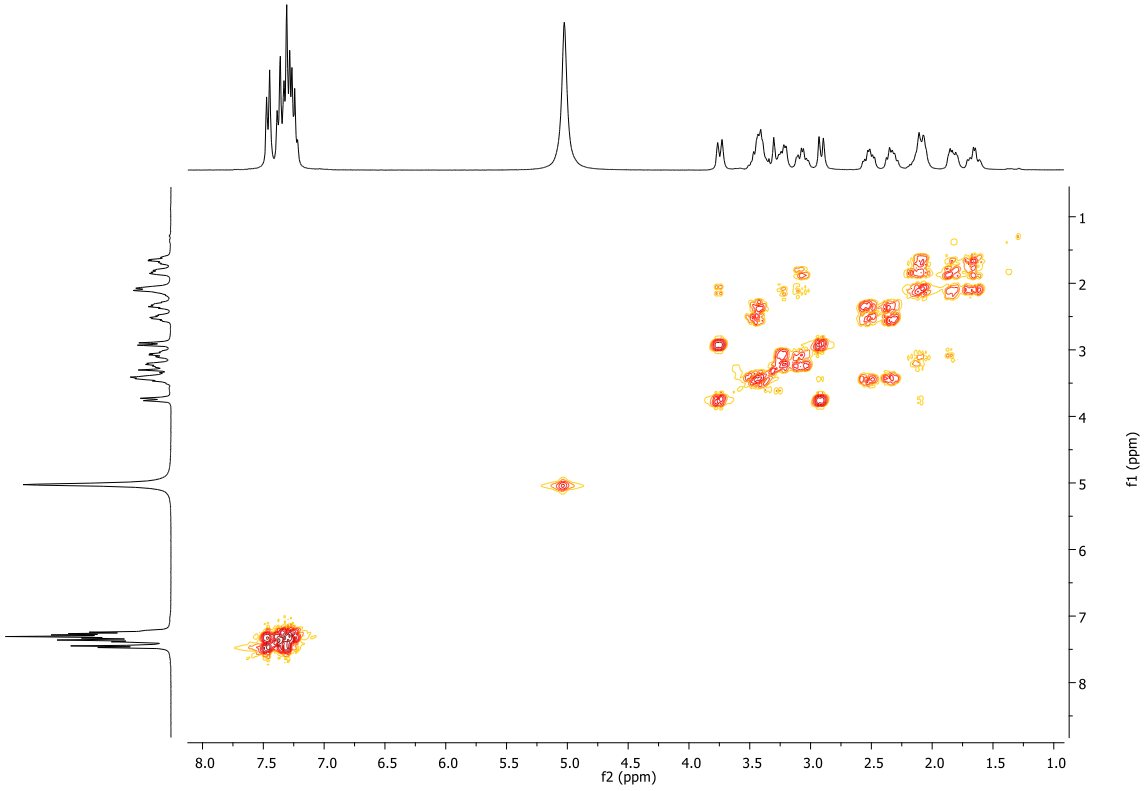
^{1}H NMR (300 MHz, CD_3OD)



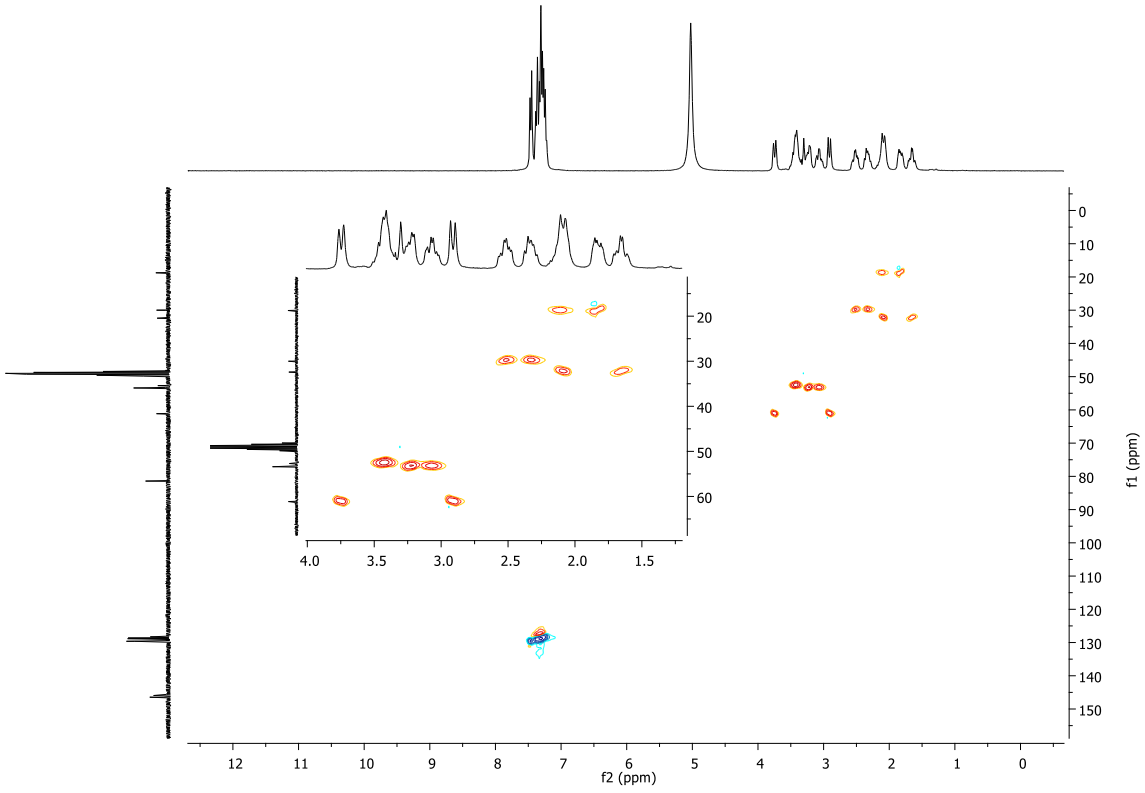
{^{1}H}^{13}C NMR (75.5 MHz, CD_3OD)



^{1}H-^{1}H COSY NMR (300 MHz, $CDCl_3$)

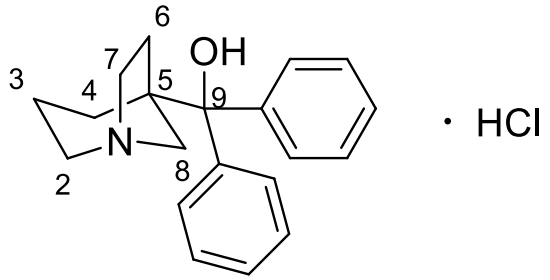


^{1}H-^{13}C HSQC NMR (300 MHz for ^{1}H, $CDCl_3$)



Compound 12

1-Azabicyclo[3.2.1]octan-5-yl)diphenylmethanol hydrochloride



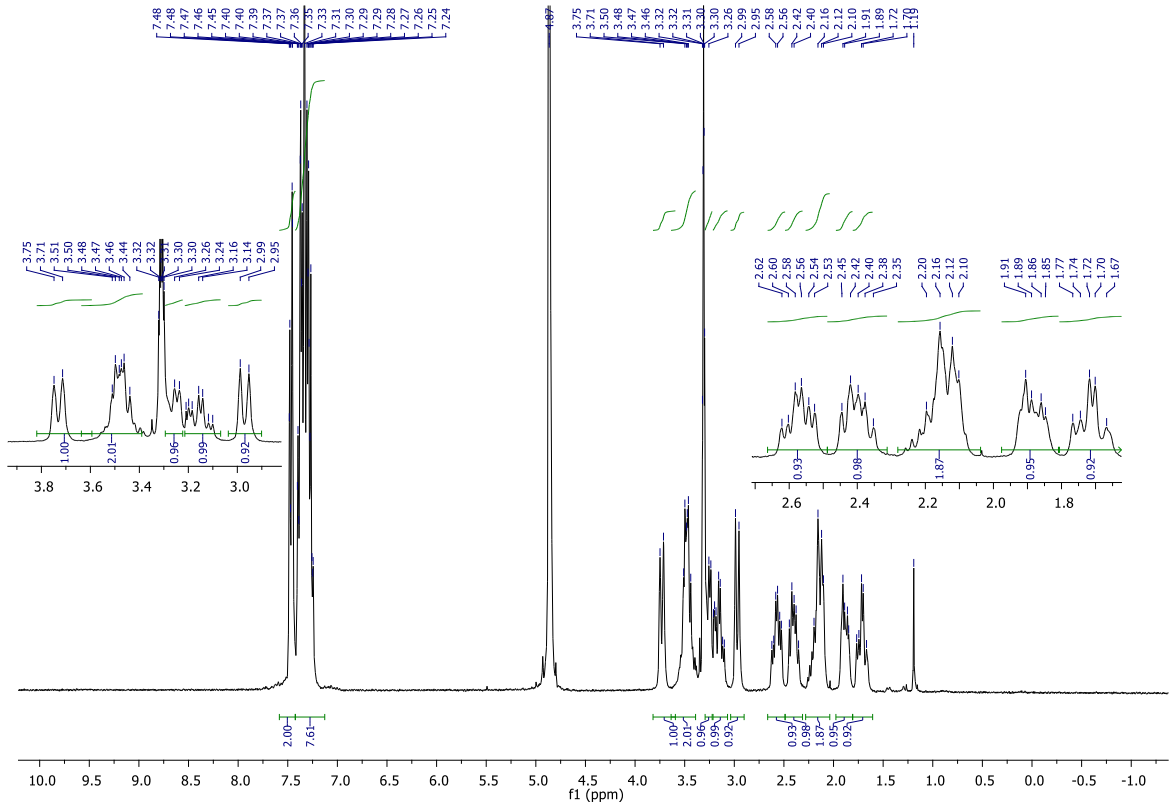
To the crude phosphoric acid salt **S1** $CHCl_3$ (12 ml) was added and the resulting mixture was washed with aqueous NH_3 (3×5 ml). The chloroform layer was filtered through a pad of neutral Al_2O_3 (1 g), which was washed with additional $CHCl_3$ (10 ml). The combined organic layer was concentrated *in vacuo* to give a colorless oil. Then MeCN (10 ml) was added and hydrochloric acid H_2O/MeCN solution (pre-mixed, 1:3 concentrated HCl (aq)/MeCN) was added dropwise until pH 3. The resulting mixture was concentrated *in vacuo* to give solid foam. Then MeCN (10 ml) was added and MTBE was added until formation of a cloudy precipitate was observed. Resulting mixture was evaporated to approx. half of the total volume. Then MTBE (20 ml) was added and again evaporated to approx. half of the total volume. The resulting precitipate was filtered to give reduced impurity compound **12** salt as a white solid (0.14 g, η = 52 % from **11**).

^{1}H NMR (300 MHz, CD_3OD): δ 7.55 – 7.42 (m, 2H, ArH), 7.42 – 7.13 (m, 8H, ArH), 3.73 (d, ^2J = 10.5 Hz, 1H, $H_aC(8)$), 3.63 – 3.37 (m, 2H, $H_2C(7)$), 3.30 – 3.21 (m, 1H, $H_aC(2)$), 3.15 (td, J = 12.3, 4.8 Hz, 1H, $H_bC(2)$), 2.97 (d, ^2J = 10.5 Hz, 1H, $H_bC(8)$), 2.72 – 2.47 (m, 1H, $H_aC(6)$), 2.47 – 2.30 (m, 1H, $H_bC(6)$), 2.27 – 2.05 (m, 2H, $H_aC(3)$ and $H_bC(4)$), 1.94 – 1.80 (m, 1H, $H_bC(3)$), 1.79 – 1.61 (m, 1H, $H_bC(4)$).

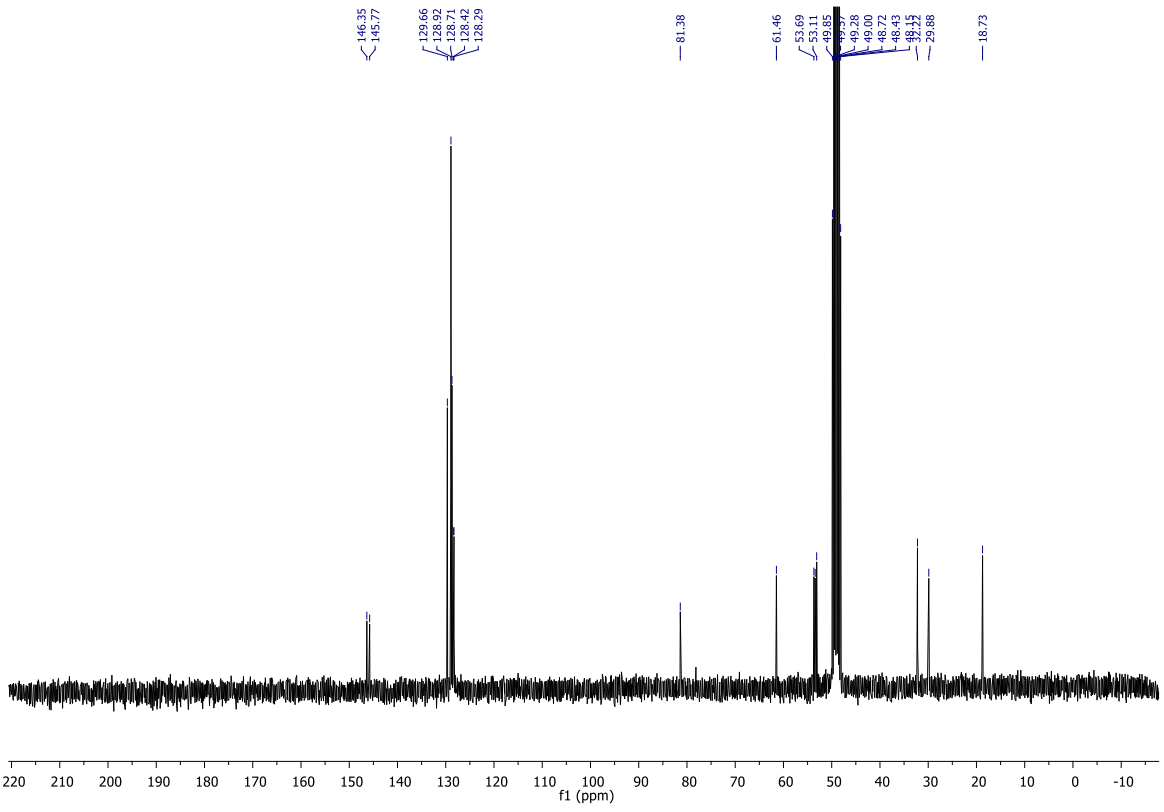
{^{1}H}^{13}C NMR (75.5 MHz, CD_3OD): δ 146.4, 145.8, 129.7, 128.9, 128.7, 128.4, 128.3, 81.4, 61.5, 53.7, 53.4, 53.1, 32.2, 29.9, 18.7.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{24}NO^+$ 294.1858; Found 294.1853.

^{1}H NMR (300 MHz, CD_3OD)

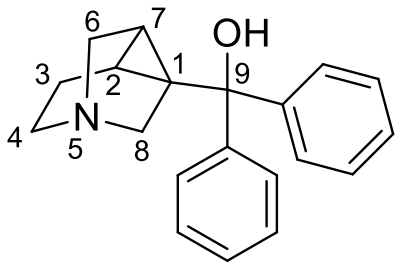


{^{1}H}^{13}C NMR (75.5 MHz, CD_3OD)



Compound 10

Diphenyl(5-azatricyclo[3.2.1.02,7]octan-1-yl)methanol



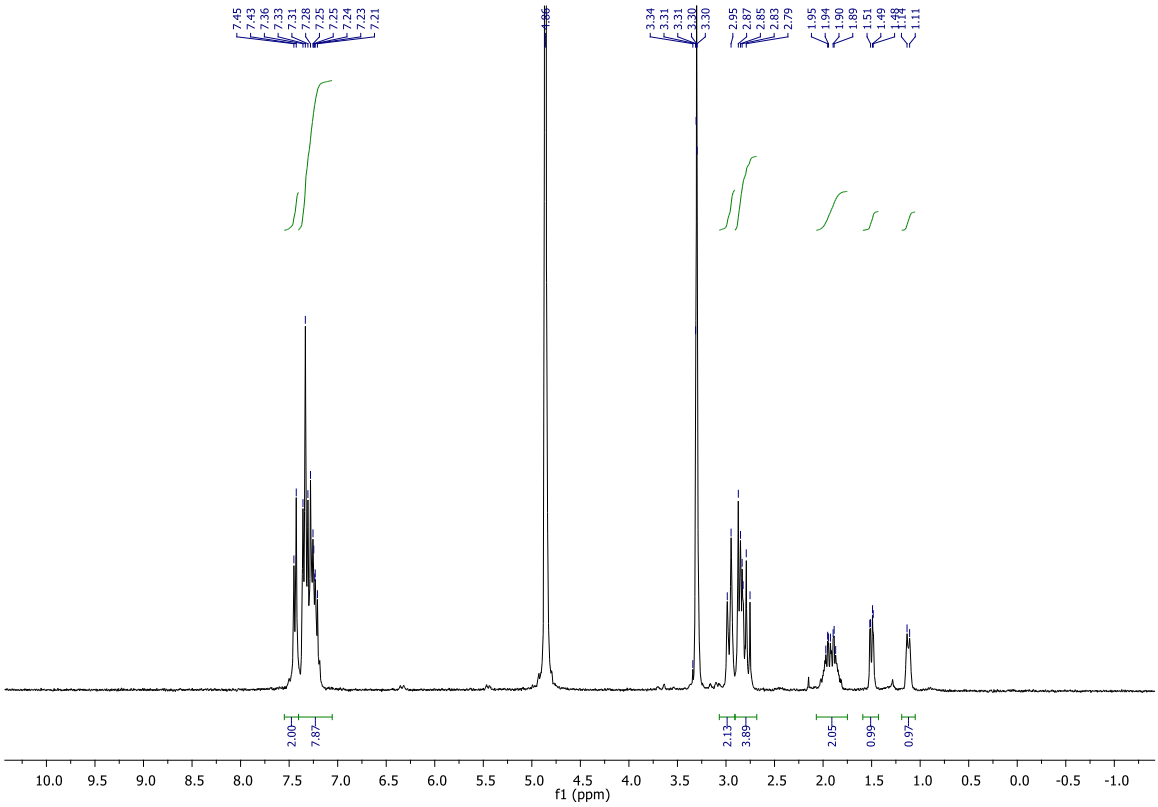
To impurity A 3,5-dinitrobenzoic acid salt (347 mg, 0.88 mmol, B/A ratio 7:93 by ^{1}H-NMR) DCM (10 ml) was added and washed with aqueous NH_4OAc pH 10 buffer (5×10 ml). The organic layer was washed with saturated aqueous NaCl solution (10 ml), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to give colorless oil (122 mg, 0.67 mmol, 1 equiv.). To remove traces of water the crude oil was re-evaporated with anhydrous THF (10 ml). Then anhydrous THF (10 ml) was added under N_2 and the mixture was cooled to -78 ^{o}C. PhLi (1.9 M in Bu_2O, 0.71 ml, 1.35 mmol, 2.0 equiv.) was added portion-wise over 5 minutes and the mixture was stirred for 5 min at -78 ^{o}C, warmed to room temperature and stirred for 1h. The mixture was cooled to 0 °C and quenched with $(NH_4)_2SO_4$ aqueous solution (107 mg, 0.81 mmol, 1.2 equiv, 1 ml water). The resulting mixture was warmed to room temperature and distilled water (15 ml) was added. Formation of a white precipitate was observed. Then DCM (30 ml) was added and the organic suspension was washed with distilled water (4×20 ml). The organic suspension was evaporated *in vacuo*, re-evaporated with toluene and dried under reduced pressure (2 torr) to give technical compound **10** as a white solid (160 mg, η = 62 %). To the technical product MeOH (15 ml) was added and the mixture was heated on a hot plate until complete dissolution. After cooling to room temperature, diisopropyl ether (6 ml) was added and the mixture was evaporated *in vacuo* to total volume of approx. 5 ml. Then the mixture was ultrasonified and a white precipitate was formed. The precipitate was filtered and washed with cold diisopropyl ether (–20 °C; 1 ml) and dried under reduced pressure (2 torr) to give compound **10** (82 mg, η = 32 %) as a white solid. Crystalline material could be obtained by slow evaporation from MeOH/CH_3COCH_3, melting point 241 – 242 °C.

^{1}H NMR (300 MHz, CD_3OD): δ 7.50 – 7.41 (m, 2H, HC(Ar)), 7.38 – 7.18 (m, 8H, HC(Ar)), 3.03 – 2.91 (m, 2H, $H_aC(6)$, $H_aC(8)$), 2.91 – 2.70 (m, 4H, $H_bC(6)$, $H_2C(4)$, $H_bC(8)$), 2.06 – 1.78 (m, 2H, $H_2C(3)$), 1.55 – 1.44 (m, 1H, HC(2)), 1.18 – 1.05 (m, 1H, HC(7)).

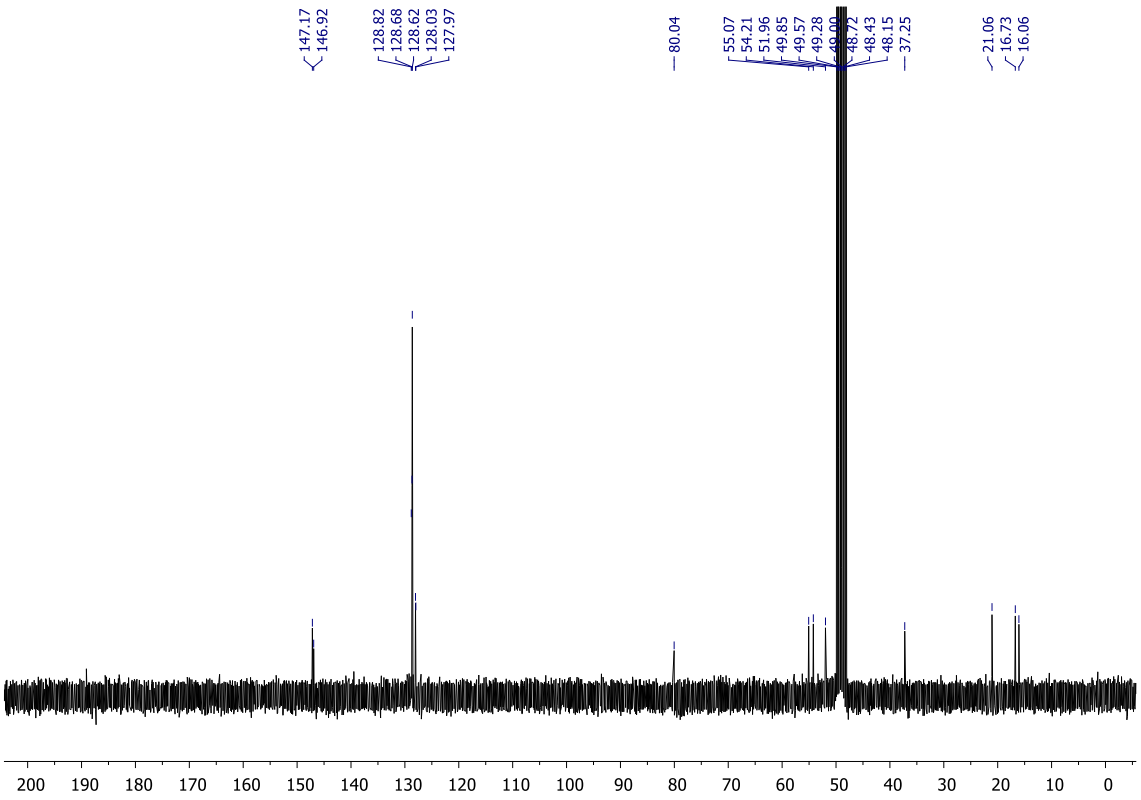
{^{1}H}^{13}C NMR (75.5 MHz, CD_3OD): δ 147.2 (C(Ar)), 146.9 (C(Ar)), 128.8 (C(Ar)), 128.7 (C(Ar)), 128.6 (2×C(Ar)), 128.03 (C(Ar)), 127.97 (C(Ar)), 80.0 C(9), 55.1 (C(8)), 54.2 (C(6)), 52.0 (C(4)), 37.3 (C(1)), 21.1 (C(2)), 16.7 (C(7)), 16.1 (C(3)).

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{22}NO^+$ 292.1696; Found 292.1703.

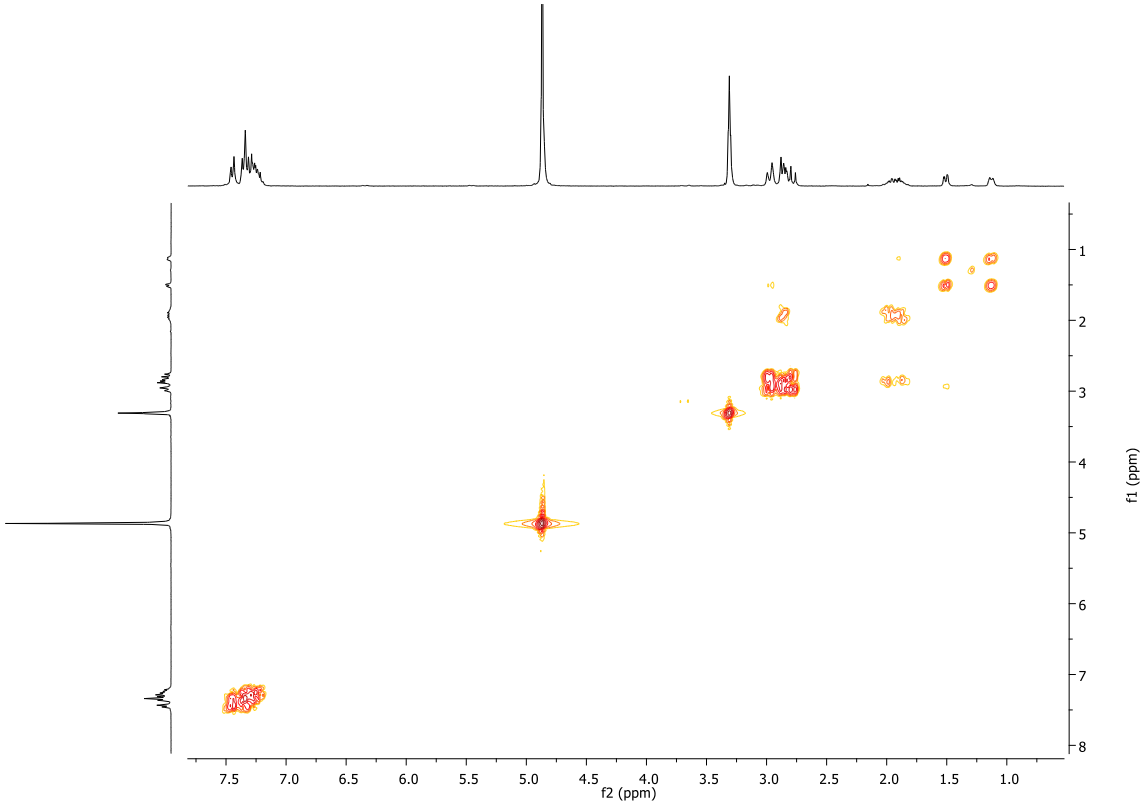
^{1}H NMR (300 MHz, CD_3OD)



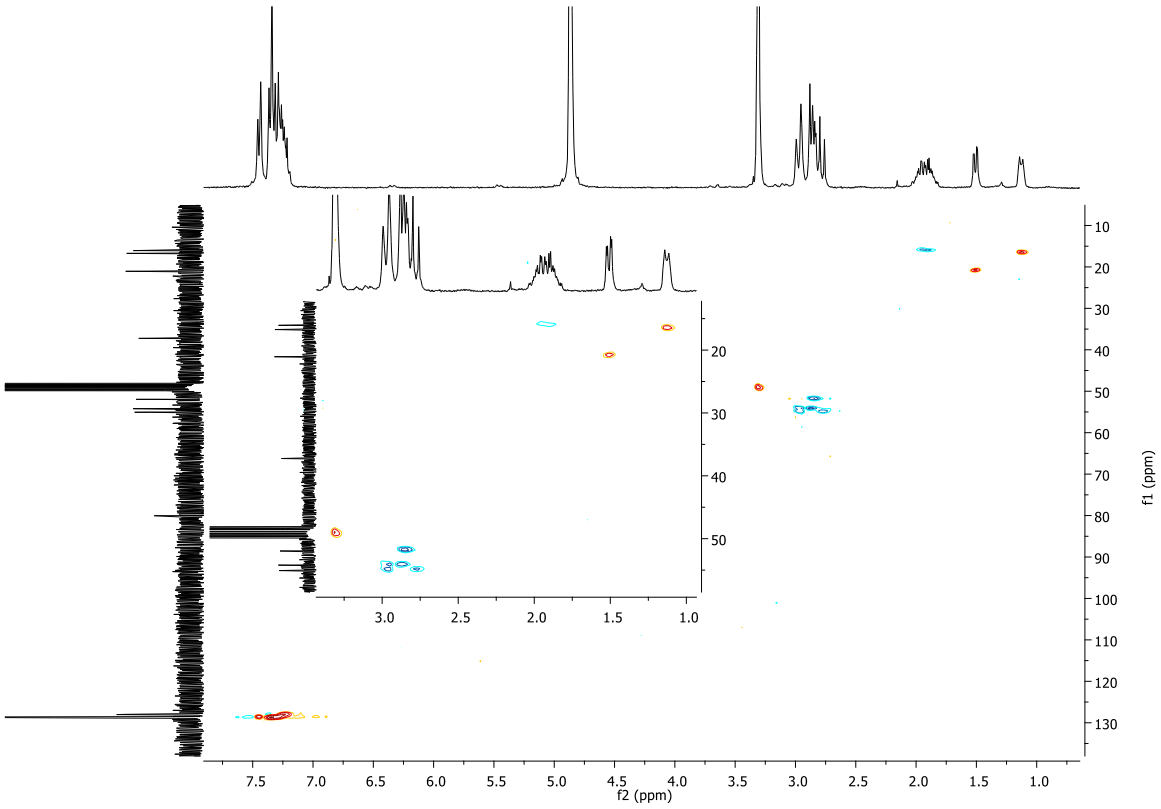
{^{1}H}^{13}C NMR (75.5 MHz, CD_3OD)



^{1}H-^{1}H COSY NMR (300 MHz, $CDCl_3$)



^{1}H-^{13}C HSQC NMR (300 MHz for ^{1}H, $CDCl_3$)



4. References

(1) Trigo, G. G.; Martinez, M.; Galvez, E.; Cabezas, R. *J. Heterocycl. Chem.* **1981**, *18* (8), 1507–1511.

(2) Arias-Pérez, M.; Cosme, A.; Gálvez, E.; Sanz-Aparicio, J.; Fonseca, I.; Bellanato, J. *J. Mol. Struct.* **2003**, *644* (1–3), 171–179.