Supplementary data for the article:

Bihelovic, F.; Ferjancic, Z. Total Synthesis of (±)-Alstoscholarisine A. *Angewandte Chemie - International Edition* **2016**, *55* (7), 2569–2572. https://doi.org/10.1002/anie.201510777

Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

Total Synthesis of (±)-Alstoscholarisine A

Filip Bihelovic and Zorana Ferjancic**

anie_201510777_sm_miscellaneous_information.pdf

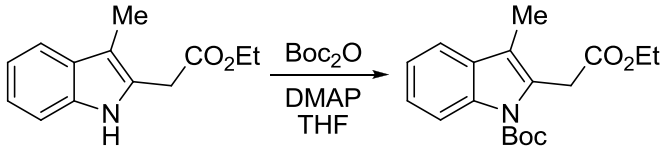
Contents

General experimental

All chromatographic separations[1] were performed on Silica gel 60 (0.063-0.2 mm), Merck. Standard techniques were used for the purification of reagents and solvents.[2] NMR spectra were recorded on Bruker Avance III 500 (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz), in deuterated chloroform, if not otherwise stated. Chemical shifts are expressed in ppm (δ) using tetramethylsilane as internal standard, coupling constants (*J*) are in Hz. IR spectra were recorded on a Nicolet 6700 FT instrument, and are expressed in cm^{-1}. Mass spectra were obtained on Agilent technologies 6210 TOF LC/MS instrument (LC: series 1200). Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

1 Experimental procedures

1.1 *tert*-Butyl 2-(2-ethoxy-2-oxoethyl)-3-methyl-1*H*-indole-1-carboxylate (12)



22 **12**

DMAP (48 mg; 0.39 mmol; 10 mol%) and Boc_2O (1.03 g; 4.75 mmol; 1.2 eq) were added to a solution of ethyl 2-(3-methyl-1*H*-indol-2-yl)acetate[3] (860 mg; 3.90 mmol) in THF (9.4 mL) and the mixture was stirred at room temperature for 20 min. The mixture was diluted with dichloromethane, washed with 1M $KHSO_4$, saturated $NaHCO_3$ and brine and dried over anhydrous $MgSO_4$. The solvent was removed on rotovap, and the residue was purified by dry-flash chromatography (petroleum ether/EtOAc=95:5), to afford product **12**, which was further purified by recrystallization from EtOAc/petroleum ether. A total of 740 mg (60%) of pure product **12** was obtained, as a white microcrystalline solid.

mp 114–115 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J=8.2, 1H), 7.46 (d, J=7.6, 1H), 7.27 (dt, J_1=1.3, J_2=7.2, 1H), 7.23 (dt, J_1=1.2, J_2=7.6, 1H), 4.16 (q, J=7.1, 2H), 4.02 (s, 2H), 2.21 (s, 3H), 1.65 (s, 9H), 1.25 (t, J=7.1, 3H).

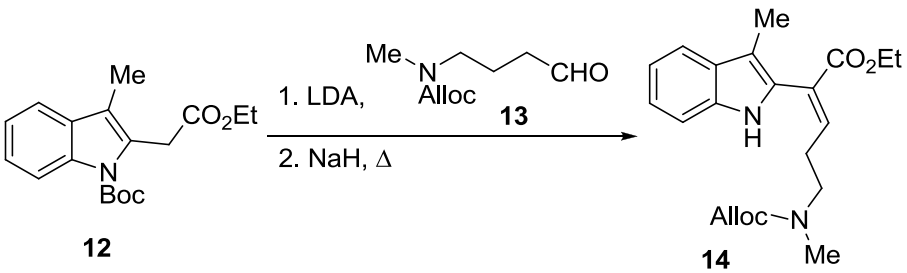
^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 150.6, 135.7, 130.3, 128.8, 124.0, 122.3, 118.4, 116.4, 115.6, 83.7, 60.8, 33.2, 28.2, 14.2, 8.7.

IR (film): $\tilde{\nu}$=2980, 1728, 1458, 1358, 1332, 1175 cm^{-1}.

HRMS (m/z) $[M+Na]^+$ calcd. for $C_{18}H_{23}NO_4Na$: 340.1519, found: 340.1521.

R_f=0.43 (petroleum ether/EtOAc=9:1).

1.2 (*E*)-Ethyl 5-((allyloxycarbonyl)(methyl)amino)-2-(3-methyl-1*H*-indol-2-yl)pent-2-enoate (14)

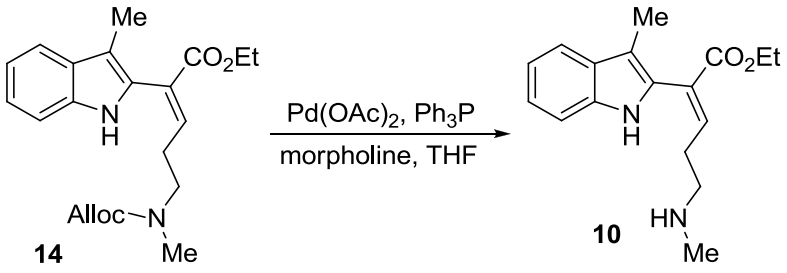


12 **14**

n-Butyl lithium (c=1.3 M, 0.65 mL; 0.847 mmol; 1.1 eq) was added to a solution of diisopropylamine (120 μL; 0.847 mmol; 1.1 eq) in dry THF (2 mL) at –20 °C, under argon. After 20 minutes of stirring, the solution of LDA was cooled down to –78 °C, and a solution of ester **12** (245 mg; 0.77 mmol) in THF (2 mL) was added. The pale yellow solution was stirred for 20 minutes, and a solution of aldehyde **13**[4] (145 mg; 0.847 mmol; 1.1 eq) in THF (2 mL) was introduced. The reaction mixture was allowed to reach –40 °C, over 30 minutes, and the reaction was quenched with saturated NH_4Cl. The mixture was partitioned between water and ether, the organic extract was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in dry THF (5 mL) and sodium hydride (24 mg; 1.0 mmol; 1.3 eq) was added in two portions, under an argon atmosphere. The reaction mixture was brought to reflux and, after 5 minutes, cooled down to the room temperature. Saturated NH_4Cl solution was added, the product was extracted with ether, the organic extract was washed with brine, dried over anhydrous $MgSO_4$ and concentrated on rotovap. The residue was purified by column chromatography (PhH/EtOAc=8:2), to afford 213 mg (75%) of acrylate **14**, as a colorless oil. The yield of product **14**, based on the recovered starting material **12** (49 mg), was 93%.

^{1}H NMR (500 MHz, DMSO, 343 K) δ 10.56 (bs, 1H), 7.47 (d, *J*=8.1, 1H), 7.31 (d, *J*=7.6, 1H), 7.13 (t, *J*=6.9, 1H), 7.08 (dt, J_1=1.0, J_2=7.1, 1H), 6.99 (dt, J_1=1.0, J_2=7.5, 1H), 5.83 (bs, 1H), 5.19 (d, *J*=16.6, 1H), 5.09 (d, *J*=9.1, 1H), 4.43 (d, *J*=4.3, 2H), 4.17 (q, *J*=7.0, 2H), 3.36 (t, *J*=6.7, 2H), 2.74 (s, 3H), 2.34 (q, *J*=6.7, 2H), 2.08 (s, 3H), 1.21 (t, *J*=7.1, 3H).
^{13}C NMR (125 MHz, DMSO, 343 K) δ 165.2, 154.8, 144.4, 135.6, 133.1, 127.9, 127.8, 126.9, 120.7, 117.8, 117.7, 116.3, 110.5, 108.4, 64.7, 60.0, 46.7, 33.5, 28.0, 13.7, 8.5.
IR (film): $\tilde{\nu}$=3328, 2936, 1705, 1261, 1208 cm^{-1}.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{21}H_{26}N_2O_4Na$: 393.1785, found: 393.1784.
***R*$_f$**=0.47 (PhH/EtOAc=8:2).

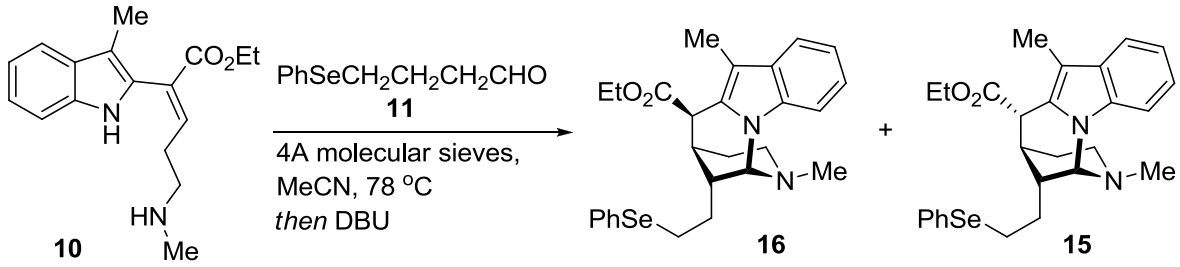
1.3 (*E*)-Ethyl 2-(3-methyl-1*H*-indol-2-yl)-5-(methylamino)pent-2-enoate (10)



A solution of palladium acetate (19.6 mg; 10 mol%) and triphenylphosphine (114 mg; 50 mol%) in THF (16 mL) was stirred for 10 minutes under argon, at room temperature. A solution of carbamate **14** (324 mg; 0.875 mmol) and morpholine (1.5 mL; 17.2 mmol; 20 eq) in THF (16 mL) was added, and the reaction mixture was stirred for 60 minutes. The mixture was evaporated to dryness and the residue was purified by column chromatography (CH_2Cl_2/MeOH=6:4), to yield 180 mg (72%) of amine **10**, as a pale yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.10 (bs, 1H), 7.56 (d, *J*=7.5, 1H), 7.31 (d, *J*=8.0, 1H), 7.17 (dt, J_1=1.1, J_2=7.1, 1H), 7.12–7.07 (m, 2H), 4.25 (q, *J*=7.1, 2H), 2.78 (t, *J*=6.2, 2H), 2.45 (s, 3H), 2.35 (dt, J_1=6.5, J_2=7.8, 2H), 2.18 (s, 3H), 1.42 (bs, 1H), 1.28 (t, *J*=7.1, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 144.4, 135.7, 128.9, 128.1, 127.7, 121.8, 118.7 (two signals), 110.9, 110.8, 61.1, 49.8, 36.4, 30.3, 14.2, 9.7.
IR (film): $\tilde{\nu}$=3369, 3180, 2955, 1712, 1463, 1247 cm^{-1}.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{17}H_{23}N_2O_2$: 287.1754, found: 287.1761.
R_f=0.30 (CH_2Cl_2/MeOH=6:4).

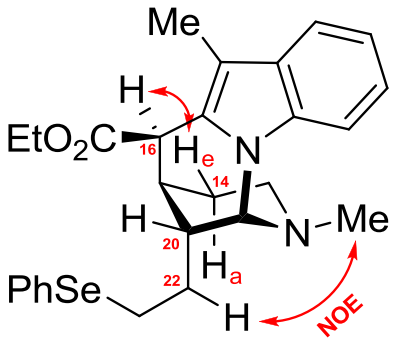
1.4 Tetracyclic aminoacetals 15 and 16



A solution of amine **10** (180 mg; 0.629 mmol) and aldehyde **11**[5] (285 mg; 1.257 mmol; 2 eq) in dry acetonitrile (15 mL) was heated to 78 °C for 9 h, in the presence of 4Å molecular sieves (200 mg). The reaction mixture was filtered through a plug of celite, the celite was washed with MeCN, and the filtrate was evaporated to dryness. The residue was dissolved in ethanol (10 mL) and sodium borohydride (31 mg; 0.817 mmol; 1.3 eq) was added at rt, to reduce the excess of selenoaldehyde **11**. After 15 minutes of stirring, saturated ammonium chloride was added and the organics were extracted with ether, washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed on rotovap to afford a 1:1 mixture of diastereomeric esters **15** and **16**, separable on TLC. In order to perform the isomerization of **15** to **16**, the crude mixture was dissolved in ethanol (10 mL), DBU (470 μL; 3.143 mmol; 5 eq) was added and the mixture was stirred at 70 °C for 45 minutes. The mixture was diluted with ether, washed with saturated NH_4Cl and brine, dried over anhydrous $MgSO_4$ and concentrated on rotovap. The residue was purified by column chromatography (PhH/EtOAc=95:5), to yield 220 mg (71%) of ester **16**, as a pale yellow oil. A smaller amount of a more polar diastereomer **15** was isolated (59 mg; 19%), which could be isomerized with DBU in another isomerization cycle.

*Major diastereomer **16***
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.48 (m, 3H), 7.37 (d, *J*=8.0, 1H), 7.28–7.22 (m, 3H), 7.12 (dt, J_1=1.2, J_2=7.0, 1H), 7.06 (dt, J_1=1.2, J_2=7.6, 1H), 5.11 (d, *J*=2.7, 1H), 4.20–4.10 (m, 2H), 3.97 (s, 1H), 3.06–2.97 (m, 2H), 2.62 (t, *J*=6.1, 1H), 2.40-2.28 (m, 3H), 2.23 (s, 3H), 2.25-2.18 (m, 1H), 2.19 (s, 3H), 2.10–1.99 (m, 2H), 1.56 (bd, *J*=13.1, 1H), 1.23 (t, *J*=7.2, 3H).

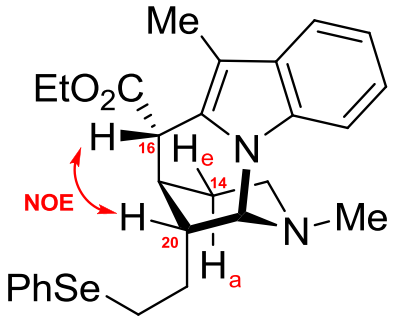
^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 136.6, 132.4, 130.3, 129.4, 129.1, 128.3, 126.8, 120.7, 118.8, 118.0, 110.2, 106.8, 69.4, 61.1, 45.9, 45.6, 45.1, 38.2, 32.1, 30.8, 27.3, 25.4, 14.3, 8.5.
IR (film): $\tilde{\nu}$=2933, 1729, 1456, 1176, 1157 cm^{-1}.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{27}H_{33}N_2O_2Se$: 497.1702, found: 497.1691.
***R*$_f$**=0.48 (PhH/EtOAc=95:5).



The NOESY spectrum didn't show NOE correlation between H-20 and H_a-14, which would be present if the selenium containing side chain adopted equatorial position. On the other hand, NOESY spectrum showed correlation between H-22 and N-Me, additionally proving the relative configuration of C-20. The stereochemistry of C-16 was determined by the presence of NOESY correlation between H-16 and H_e-14, while the correlation between H-16 and H-20 is missing.

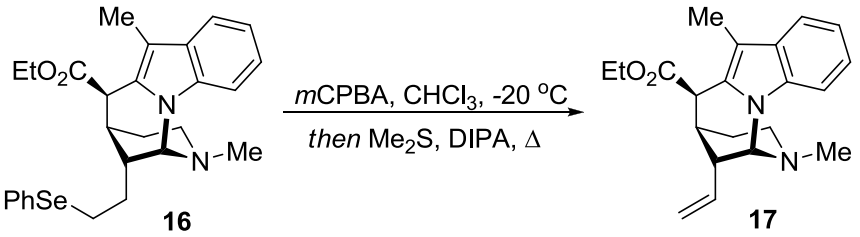
Minor diastereomer ***15***

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.47 (m, 3H), 7.35 (d, *J*=7.9, 1H), 7.28–7.22 (m, 3H), 7.14 (dt, J_1=1.3, J_2=7.1, 1H), 7.08 (dt, J_1=1.0, J_2=7.1, 1H), 5.05 (d, *J*=2.5, 1H), 4.33–4.21 (m, 2H), 4.17 (d, *J*=6.8, 1H), 3.05–2.95 (m, 2H), 2.51–2.46 (m, 1H), 2.40–2.29 (m, 3H), 2.35 (s, 3H), 2.17–2.08 (m, 1H), 2.12 (s, 3H), 2.08–1.98 (m, 2H), 1.40 (bd, *J*=15.1, 1H), 1.31 (t, *J*=7.3, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 136.4, 132.4, 130.1, 129.6, 129.1, 128.4, 126.8, 120.8, 118.9, 117.9, 109.6, 107.2, 69.5, 60.9, 45.8, 45.4, 44.7, 41.4, 31.0, 30.9, 25.4, 23.2, 14.3, 9.0.
IR (film): $\tilde{\nu}$=2935, 1738, 1457, 1169 cm^{-1}.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{27}H_{33}N_2O_2Se$: 497.1702, found: 497.1694.
***R*$_f$**=0.30 (PhH/EtOAc=95:5).



The NOESY spectrum showed NOE correlation between H-20 and H-16, proving the relative configuration of both C-16 and C-20.

1.5 Alkene 17



*m*CPBA (77%; 132 mg; 0.441 mmol; 1.1 eq) was added to a cold (–20 °C) solution of ester **16** (200 mg; 0.404 mmol) in chloroform (13 mL) and the mixture was stirred for 20 minutes. Me_2S (60 μL; 0.818 mmol; 2 eq) was added, followed by DIPA (340 μL; 2.426 mmol; 6 eq) and the mixture was stirred at 65 °C for 45 minutes. The volatiles were removed under reduced pressure, and the residue was purified by column chromatography (PhH/EtOAc=9:1), to yield 113 mg (83%) of alkene **17**, as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J*=7.7, 1H), 7.40 (d, *J*=8.1, 1H), 7.13 (dt, J_1=1.2, J_2=7.1, 1H), 7.07 (dt, J_1=1.0, J_2=7.4, 1H), 6.36 (ddd, J_1=7.4, J_2=10.7, J_3=17.2, 1H), 5.27 (dt, J_1=1.5, J_2=8.5, 1H), 5.24 (d, *J*=1.2, 1H), 5.18 (d, *J*=2.9, 1H), 4.22–4.09 (m, 2H), 4.00 (s, 1H), 3.22 (d, *J*=6.9, 1H), 2.47–2.41 (m, 2H), 2.40–2.30 (m, 1H), 2.26 (s, 3H), 2.21 (s, 3H), 2.10 (dt, J_1=4.1, J_2=12.7, 1H), 1.60 (bd, *J*=14.1, 1H), 1.24 (t, *J*=7.0, 3H).

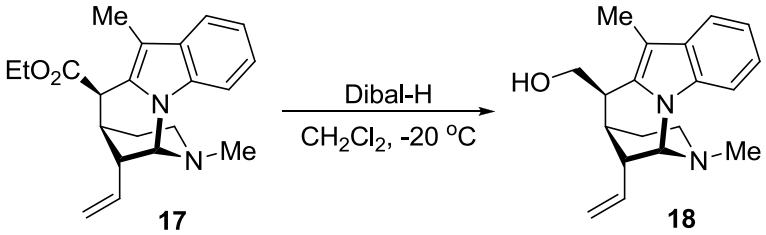
^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 138.4, 136.7, 129.0, 128.3, 120.8, 118.9, 118.1, 116.6, 110.2, 106.9, 70.2, 61.1, 45.8, 45.7, 45.1, 42.0, 33.6, 27.5, 14.3, 8.6.

IR (film): $\tilde{\nu}$=2934, 1730, 1454, 1176, 1157 cm^{-1}.

HRMS (m/z) $[M+H]^+$ calcd. for $C_{21}H_{27}N_2O_2$: 339.2067, found: 339.2067.

R_f=0.60 (PhH/EtOAc=9:1).

1.6 Alcohol 18



A solution of Dibal-H in hexane (1M; 7 mL; 6.97 mmol; 20 eq) was added to a cold (–20 °C) solution of alkene **17** (118 mg; 0.349 mmol) in dichloromethane (30 mL), under argon. The mixture was stirred for 30 minutes, and then quenched by a careful addition of a saturated aqueous solution of Rochelle's salt. After additional 1 h of stirring at room temperature, the mixture was extracted with ether. The organic extract was washed with brine, dried over anhydrous $MgSO_4$, concentrated under reduced pressure and the residue was purified by column chromatography (PhH/EtOAc=1:1), to afford 83 mg (81%) of the alcohol **18**, as a white solid.

mp 88–90 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J=7.9, 1H), 7.39 (d, J=8.2, 1H), 7.11 (dt, J_1=1.6, J_2=7.5, 1H), 7.07 (dt, J_1=1.2, J_2=7.4, 1H), 6.40 (ddd, J_1=7.3, J_2=10.7, J_3=17.8, 1H), 5.29 (dt, J_1=1.5, J_2=9.9, 1H), 5.26 (t, J=1.6, 1H), 5.16 (d, J=2.6, 1H), 3.88 (dd, J_1=3.5, J_2=10.2, 1H), 3.67 (t, J=9.2, 1H), 3.27 (dd, J_1=4.4, J_2=9.4, 1H), 2.94 (d, J=6.9, 1H), 2.47–2.40 (m, 2H), 2.40–2.33 (m, 1H), 2.32 (s, 3H), 2.21 (s, 3H), 2.08 (dt, J_1=3.8, J_2=12.3, 1H), 1.56 (bs, 1H, OH), 1.51 (bd, J=13.3, 1H).

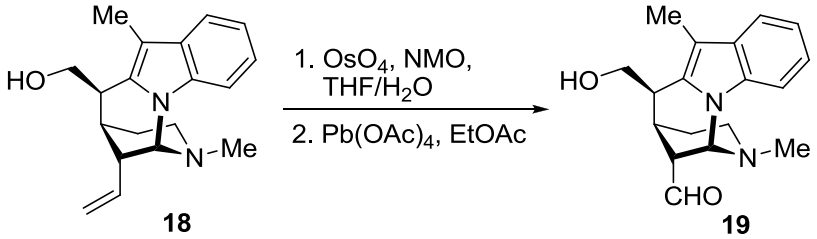
^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 136.6, 132.5, 128.4, 120.5, 118.8, 117.7, 116.2, 110.1, 105.3, 70.5, 64.3, 46.3, 45.1, 42.2, 41.3, 30.9, 27.5, 9.1.

IR (film): $\tilde{\nu}$=3361, 2932, 1457, 1323, 1038 cm^{-1}.

HRMS (m/z) $[M+H]^+$ calcd. for $C_{19}H_{25}N_2O$: 297.1961, found: 297.1956.

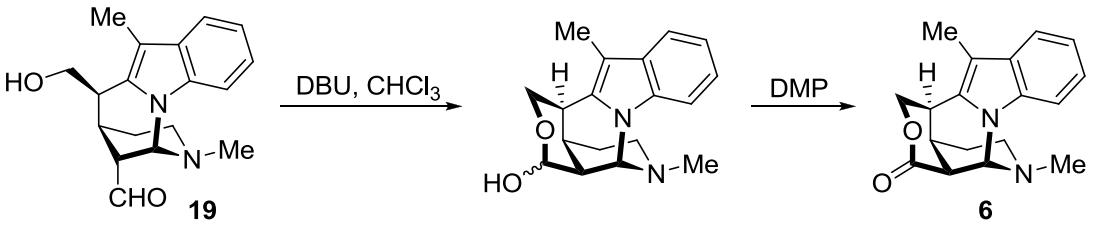
R_f=0.58 (PhH/EtOAc=1:1).

1.7 Aldehyde 19



A solution of alcohol **18** (81 mg; 0.273 mmol), OsO_4 (2.5% in *t*-BuOH; 73 μL; 2 mol%) and NMO (50% solution in water; 280 μL; 1.37 mmol; 5 eq) in THF/H_2O=2:1 (6 mL) was stirred 13 h at room temperature. Excess of solid sodium-sulfite was added and the suspension was stirred for additional 30 minutes. The reaction mixture was diluted with ether, the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, to afford 88 mg (98%) of the dihydroxylated product, as a mixture of inseparable diastereoisomers, in form of a colorless solid. Lead tetraacetate (180 mg; 0.41 mmol; 1.5 eq) was added to a solution of crude triol (88 mg; 0.266 mmol) in ethyl acetate (75 mL) and the mixture was stirred at room temperature for 30 minutes. The resulting orange suspension was filtered through a pad of celite and silica (eluted with CH_2Cl_2/MeOH=9:1) and the clear filtrate was evaporated on rotovap, to yield crude aldehyde **19**. This aldehyde (77 mg) was used immediately for the preparation of lactone **6**, due to its high instability.

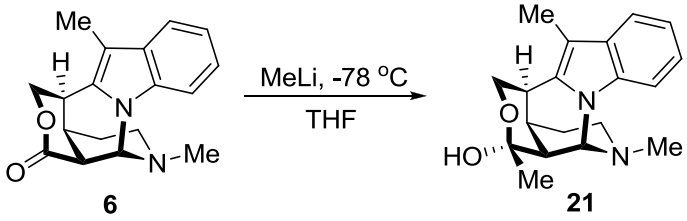
1.8 Lactone 6



DBU (34 μL; 0.23 mmol; 1 eq) was added to a solution of a freshly prepared aldehyde **19** in chloroform (2 mL), and the mixture was stirred at room temperature for 45 minutes. Dess-Martin periodinane (390 mg; 0.92 mmol; 4 eq) was added to the reaction mixture and stirring was continued for 60 minutes. The mixture was diluted with ether, washed with 10% sodium thiosulfate solution, saturated sodium bicarbonate and brine, and the organic extract was dried over anhydrous $MgSO_4$. After concentration on rotovap, the residue was purified by column chromatography (PhH/EtOH=9:1), to afford 23 mg (34% over 4 steps, from alkene **18**) of pure lactone **6**, as a white solid.

mp 180–182 °C
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J*=7.9, 1H), 7.39 (d, *J*=8.3, 1H), 7.14 (dt, J_1=1.2, J_2=7.1, 1H), 7.09 (dt, J_1=1.1, J_2=7.9, 1H), 5.54 (d, *J*=3.1, 1H), 4.56 (dd, J_1=2.5, J_2=10.0, 1H), 4.23 (dd, J_1=1.3, J_2=10.3, 1H), 3.47–3.41 (m, 2H), 2.65 (bs, 1H), 2.44–2.36 (m, 1H), 2.38 (s, 3H), 2.27 (s, 3H), 2.17–2.08 (m, 1H), 1.98 (dt, J_1=3.8, J_2=12.5, 1H), 1.88 (bd, *J*=13.8, 1H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 136.9, 132.0, 128.8, 121.3, 119.5, 118.1, 110.8, 105.9, 76.3, 69.7, 45.5, 45.1, 44.8, 32.8, 29.4, 28.0, 8.2.
IR (film): $\tilde{\nu}$=2921, 2853, 1730, 1457, 1242 cm^{-1}.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{18}H_{21}N_2O_2$: 297.1598, found: 297.1597.
R_f=0.22 (PhH/EtOAc=1:4).

1.9 Hemiketal 21

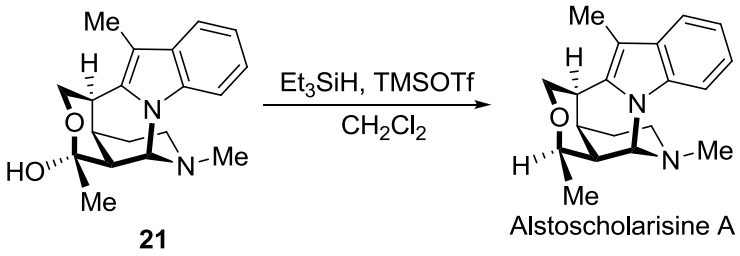


MeLi (3M in diethoxymethane; 30 μL; 0.10 mmol; 2 eq) was added to a cold (–78 °C) solution of lactone **6** (15 mg; 0.05 mmol) in dry tetrahydrofuran (2 mL), under argon. After 15 minutes of stirring, the reaction mixture was diluted with ether, washed with brine and dried over anhydrous $MgSO_4$. The

solvent was removed on rotovap and the residue was purified by column chromatography (PhH/EtOH=9:1), to afford 10.3 mg (66%) of the hemiketal **21**, as a colorless film.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J*=7.6, 1H), 7.38 (d, *J*=7.9, 1H), 7.09 (dt, J_1=1.4, J_2=7.0, 1H), 7.05 (dt, J_1=1.3, J_2=7.3, 1H), 5.30 (d, *J*=2.5, 1H), 4.12 (dd, J_1=1.3, J_2=10.0, 1H), 3.44 (dd, J_1=2.3, J_2=9.9, 1H), 3.05 (bs, 1H), 2.78–2.74 (m, 1H), 2.45–2.42 (m, 1H), 2.37–2.32 (m, 1H), 2.32 (s, 3H), 2.24 (s, 3H), 2.11–2.04 (m, 1H), 1.91 (dt, J_1=3.8, J_2=12.0, 1H), 1.80 (bd, *J*=13.6, 1H), 1.44 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 135.1, 128.9, 120.3, 118.8, 118.0, 109.9, 104.0, 96.1, 68.4, 68.0, 45.8, 45.6, 44.8, 34.3, 30.1, 28.2, 27.4, 8.0.
IR (film): $\tilde{\nu}$=3380, 2927, 2861, 1457, 1323, 1130, 1072 cm^{-1}.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{19}H_{25}N_2O_2$: 313.1910, found: 313.1900.
R_f=0.26 (PhH/EtOH=9:1).

1.10 (±)-Alstoscholarisine A (1)



Triethylsilane (16 μL; 0.1 mmol; 3.5 eq) and trimethylsilyl trifluoromethanesulfonate (13 μL; 0.072 mmol; 2.5 eq) were added to a cold (–78 °C) solution of hemiketal **21** (9 mg; 0.029 mmol) in dry dichloromethane (0.9 mL), under argon. The mixture was stirred at –78 °C for 45 minutes, before the reaction was quenched by the addition of 3 drops of triethylamine. The reaction mixture was diluted with ether, washed with saturated sodium bicarbonate and brine, dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography (PhH/EtOH=9:1), to afford 6.5 mg (77 %) of pure (±)-alstoscholarisine A (**1**), as a colorless film.

^{1}H NMR (500 MHz, CD_3OD) δ 7.52 (d, *J*=8.4, 1H), 7.42 (d, *J*=7.8, 1H), 7.05 (t, *J*=7.5, 1H), 6.99 (t, *J*=7.5, 1H), 5.50 (s, 1H), 3.82–3.75 (m, 1H), 3.70 (d, *J*=10.5, 1H), 3.63 (d, *J*=10.5, 1H), 3.14 (bs, 1H), 2.36 (dd, J_1=6.1, J_2=12.2, 1H), 2.31 (bs, 1H), 2.29 (s, 3H), 2.23 (s, 3H), 2.19 (bs, 1H), 2.15–2.06 (m, 1H), 1.90 (dt, J_1=3.3, J_2=12.7, 1H), 1.83 (bd, *J*=14.1, 1H), 1.25 (d, *J*=6.6, 3H).
^{13}C NMR (125 MHz, CD_3OD) δ 138.7, 137.0, 130.4, 121.5, 120.0, 118.8, 111.5, 105.3, 75.6, 74.5, 67.9, 47.5, 45.7, 43.3, 36.2, 34.8, 31.4, 18.8, 8.2.
IR (film): $\tilde{\nu}$=2917, 2852, 1459, 1334, 1319, 1121, 1091 cm^{-1}.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{19}H_{25}N_2O$: 297.1961, found: 297.1954.
R_f=0.36 (PhH/EtOH=9:1).

2 References

[1] For description of the technique of dry-flash chromatography, see: a) L. M. Harwood, *Aldrichimica Acta,* **1985**, *18*, 25; b) *Vogel's Textbook of Practical Organic Chemistry*, Longman Scientific & Technical, 5th edition, London, 1989, p. 220; c) A recent account which includes some improvements of the separation technique: D. S. Pedersen, C. Rosenbohm, *Synthesis,* **2001**, 2431-2434.

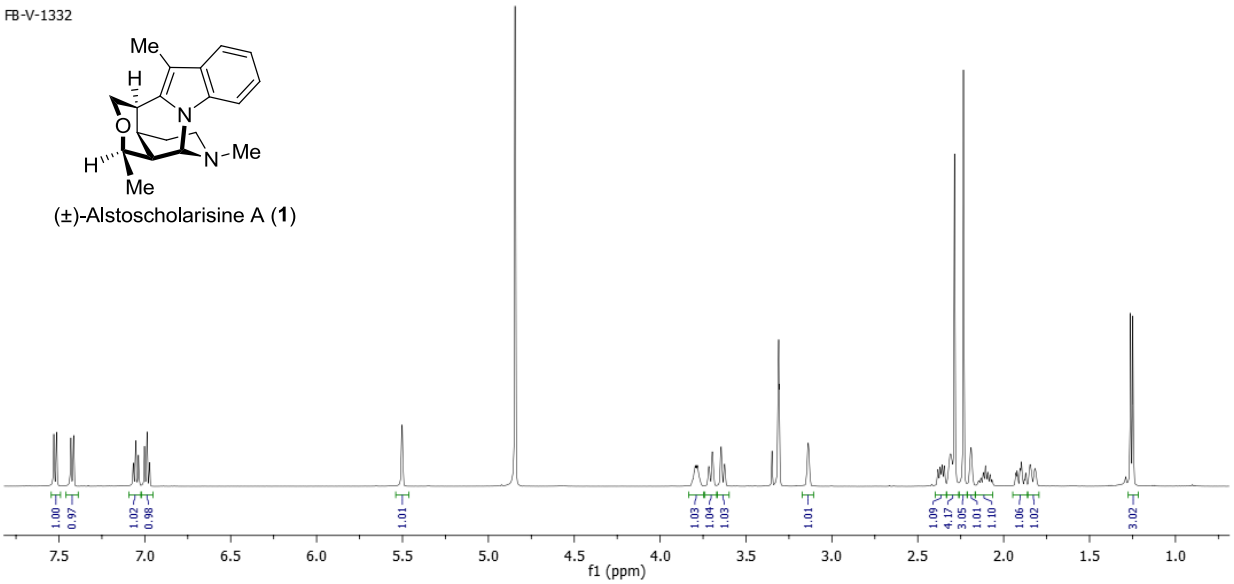
[2] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd edition, Pergamon Press, **1988**.

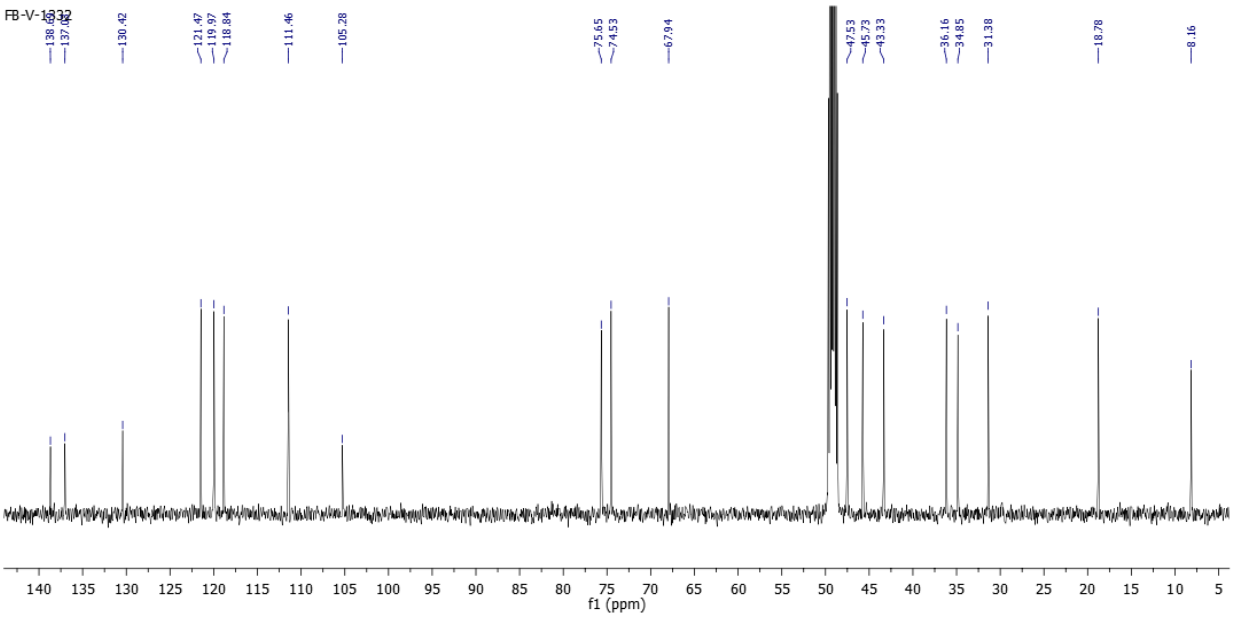
[3] J. Huang, L. Zhao, Y. Liu, W. Cao, X. Wu, *Org. Lett*. **2013**, *15*, 4338-4341.

[4] a) S. Blechert, R. Knier, H. Schroers, T. Wirth, *Synthesis*, **1995**, 592-604; b) A. Wohl, M. S. Losanitsch, *Chem. Ber*. **1907**, *96*, 4685.

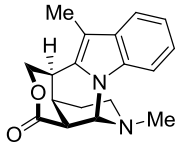
[5] J. Becker, L. Butt, V. von Kiedrowski, E. Mischler, F. Quentin, M. Hiersemann, *J. Org. Chem*. **2014**, *79*, 3040-3051.

3 Scanned spectra in numerical order



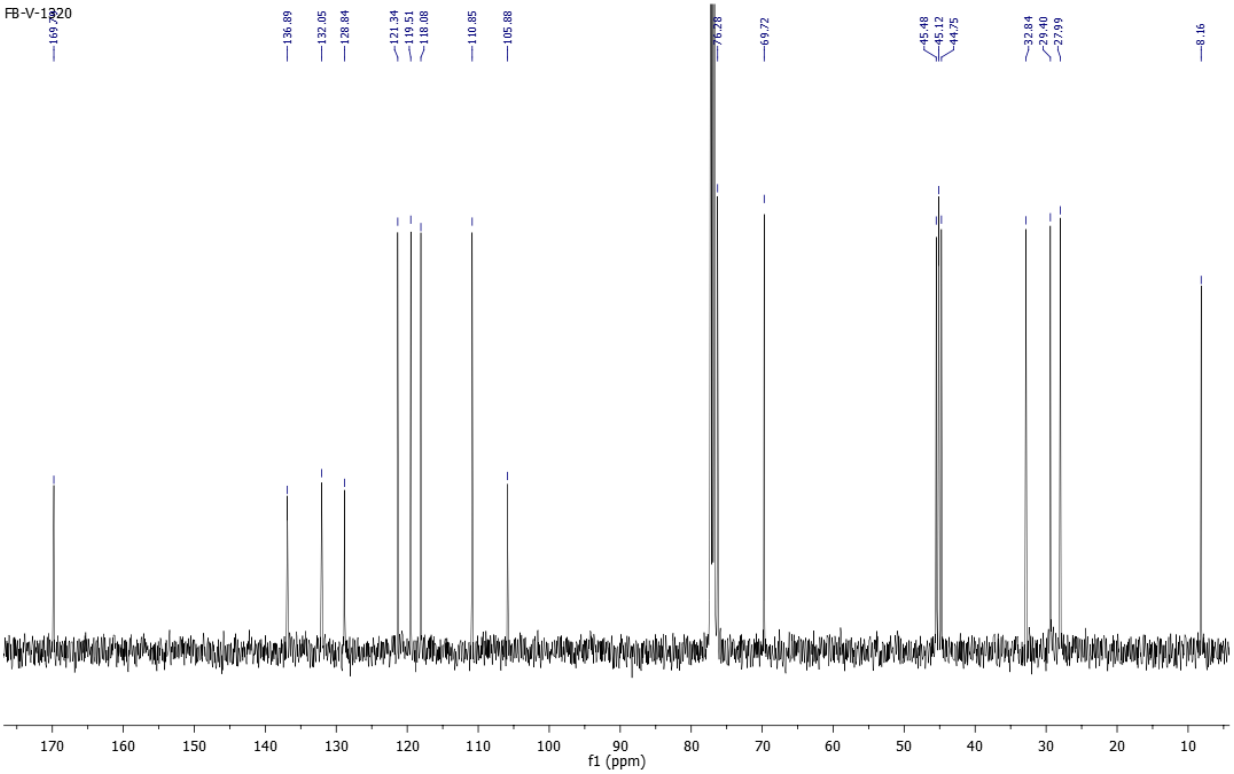


FB-V-1320-k2

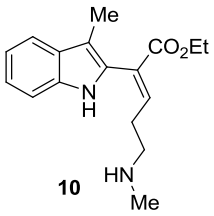

Me
H
O
N
O
N
Me

6

1.01
1.00
2.09
1.01
1.01
1.01
2.01
1.03
4.13
3.02
1.15
1.09
1.01
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)

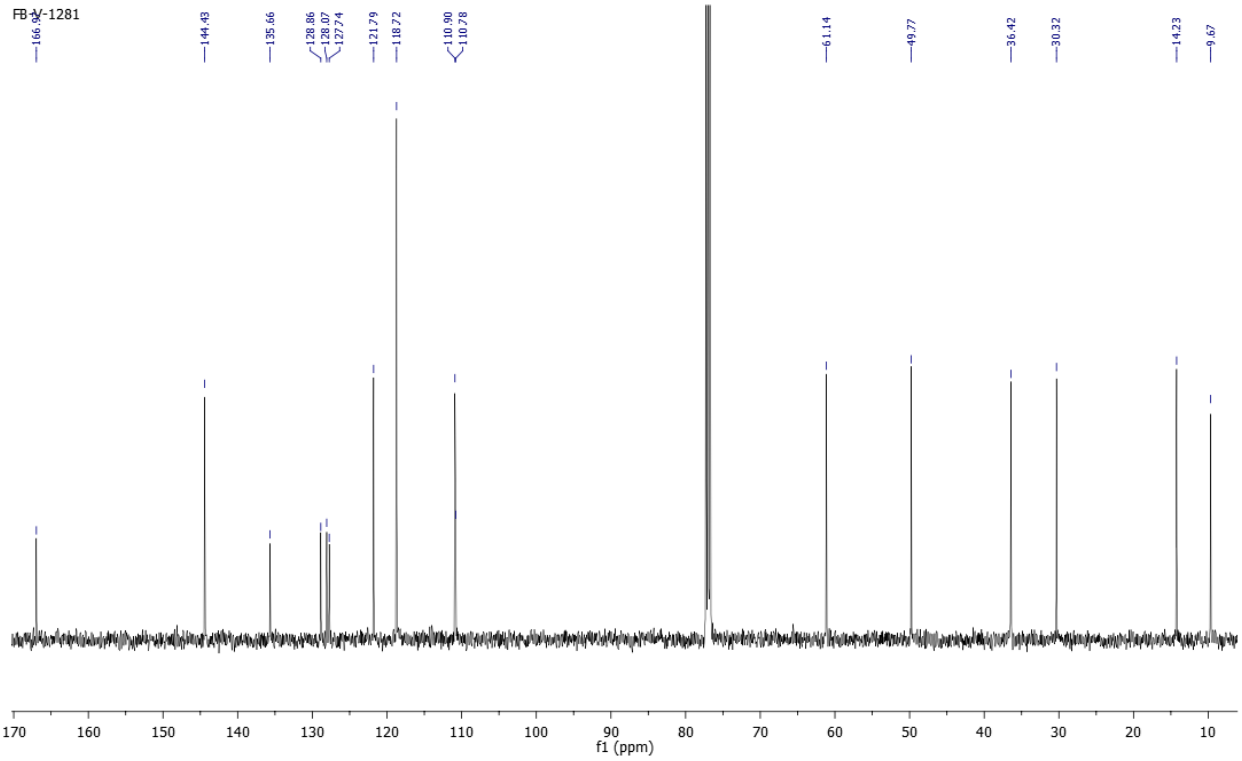

FB-V-1320
169.74
136.89
132.05
128.84
121.34
119.51
118.08
110.85
105.88
76.28
69.72
45.48
45.12
44.75
32.84
29.40
27.99
8.16
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

FB-V-1281

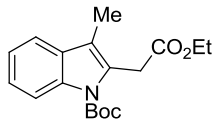

Me
CO2Et
N
H
HN
Me

10

0.96
1.00
1.00
1.04
2.04
2.08
2.04
3.06
2.15
3.15
1.04
3.27
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)

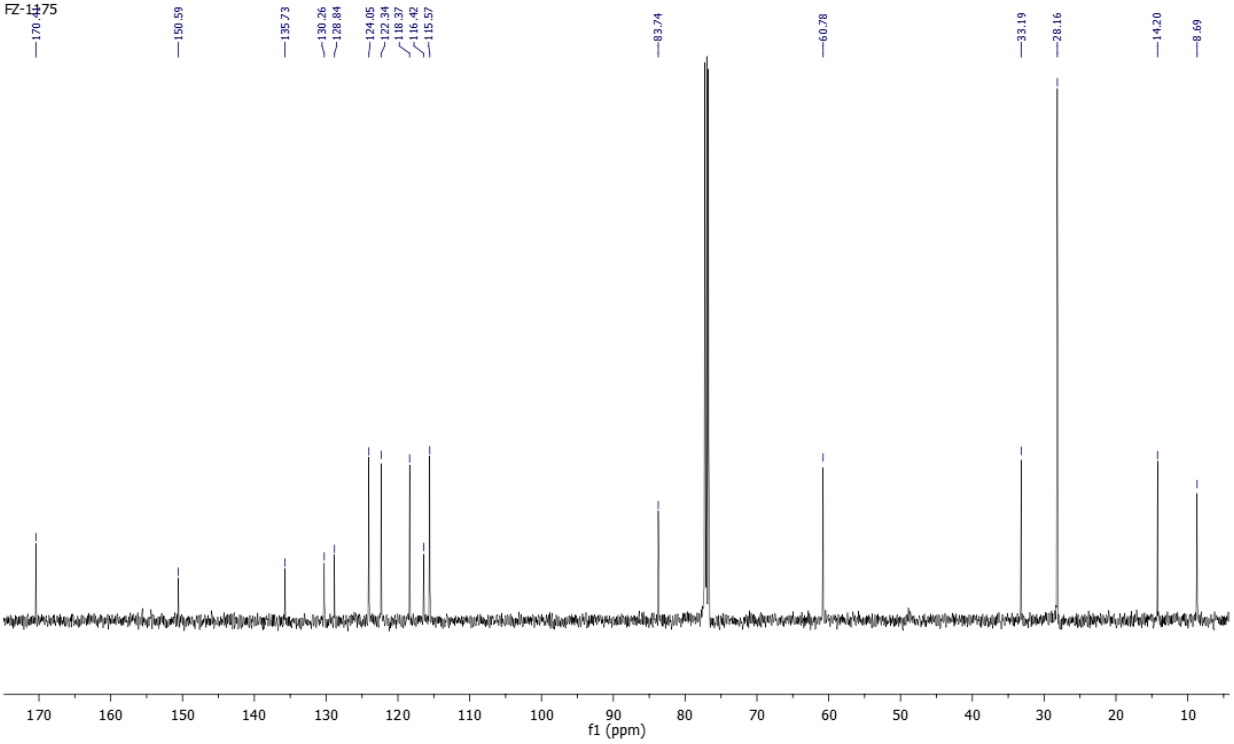

FB-V-1281
166.90
144.43
135.66
128.86
128.07
127.74
121.79
118.72
110.90
110.78
61.14
49.77
36.42
30.32
14.23
9.67
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

FZ-1175

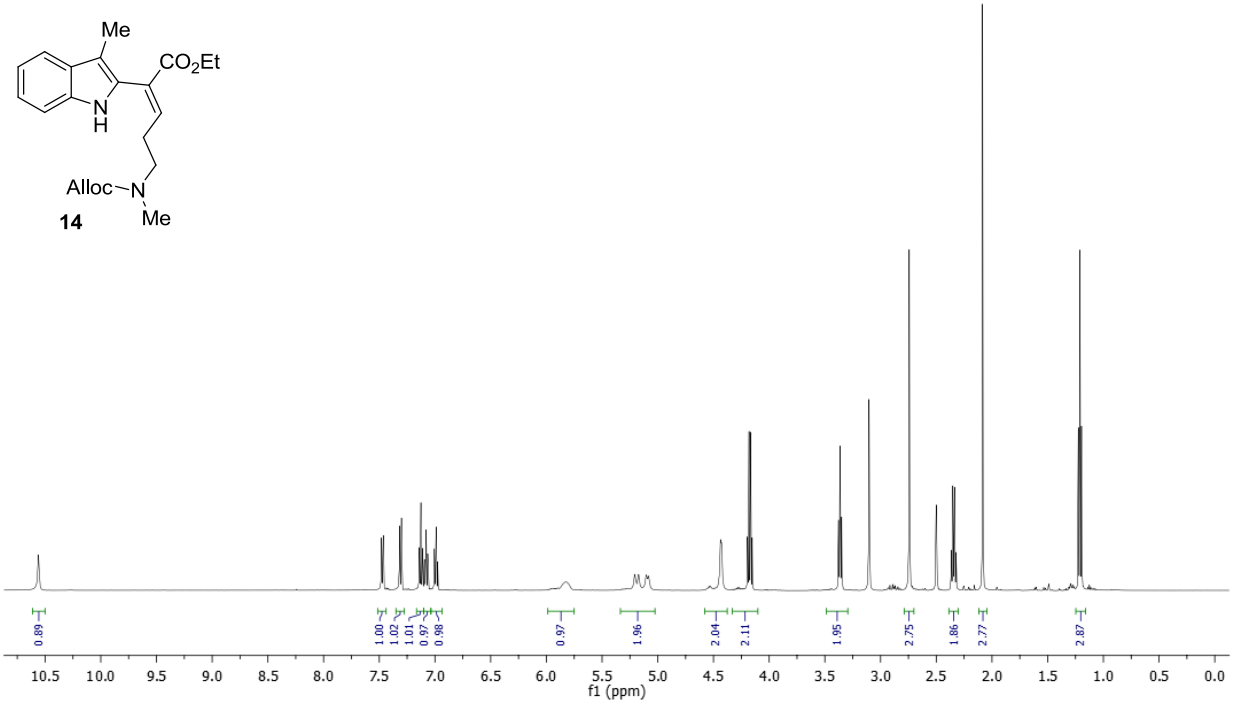


12

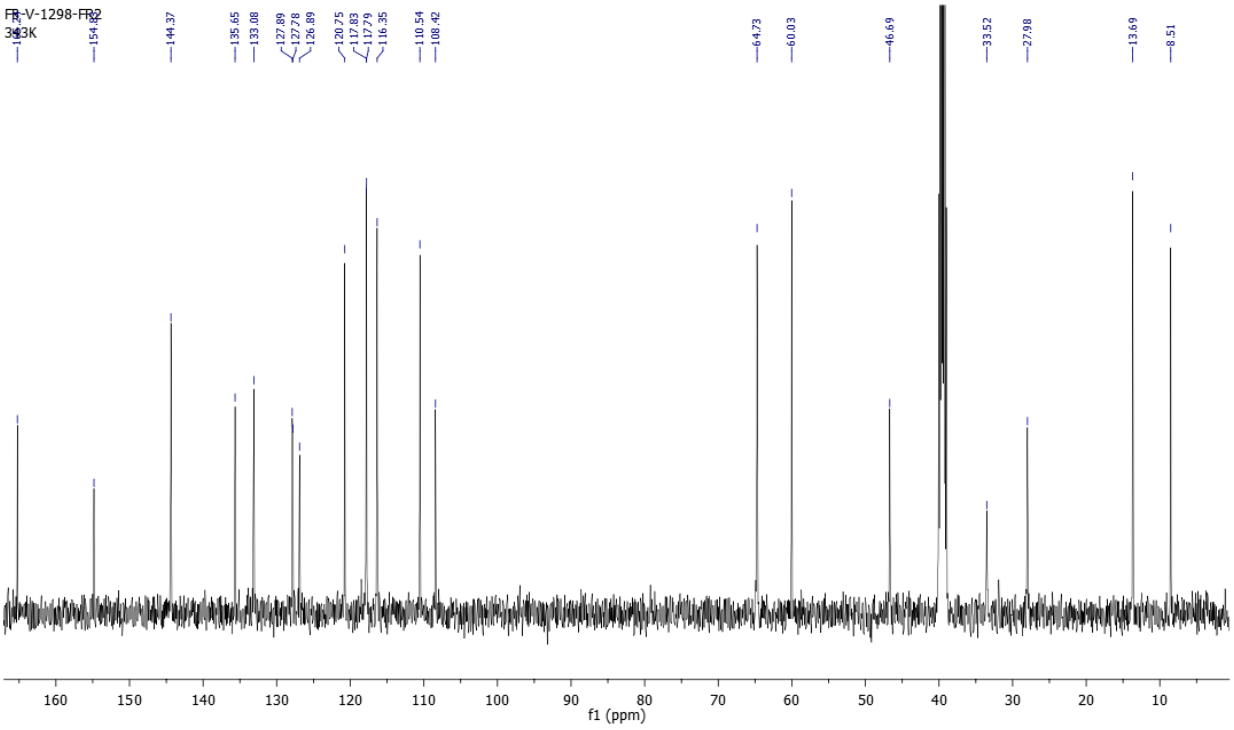
FZ-1175



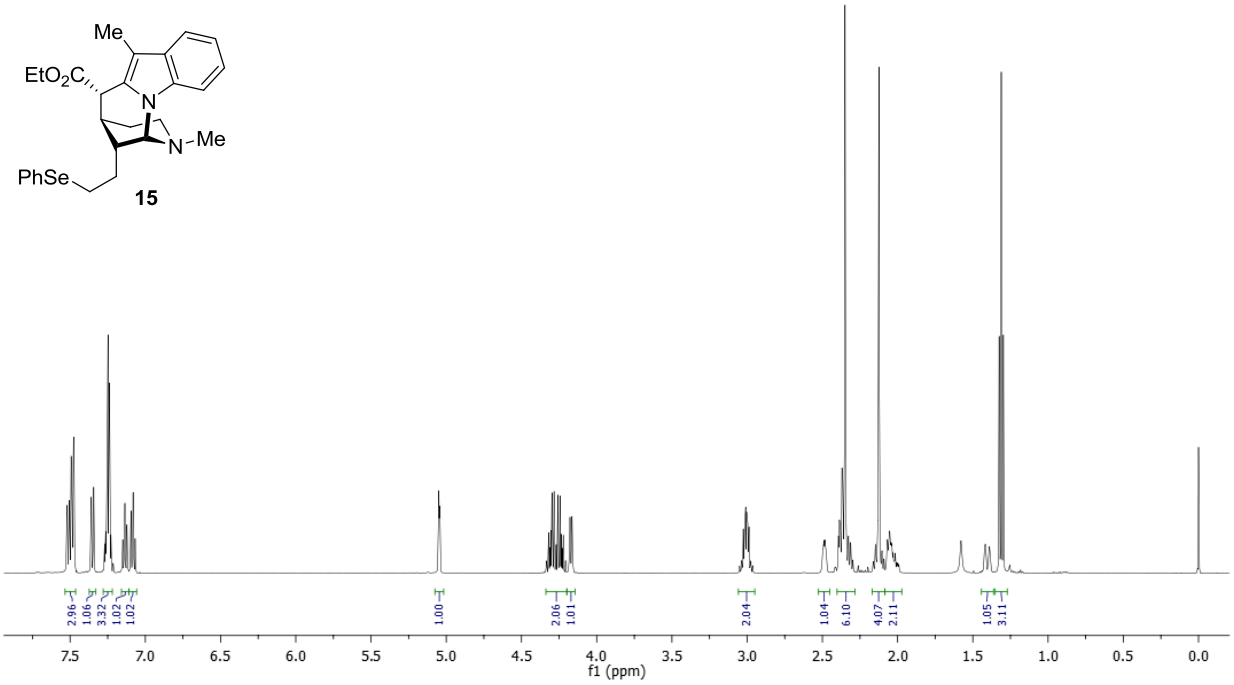
FB-V-1298-FR2
343K



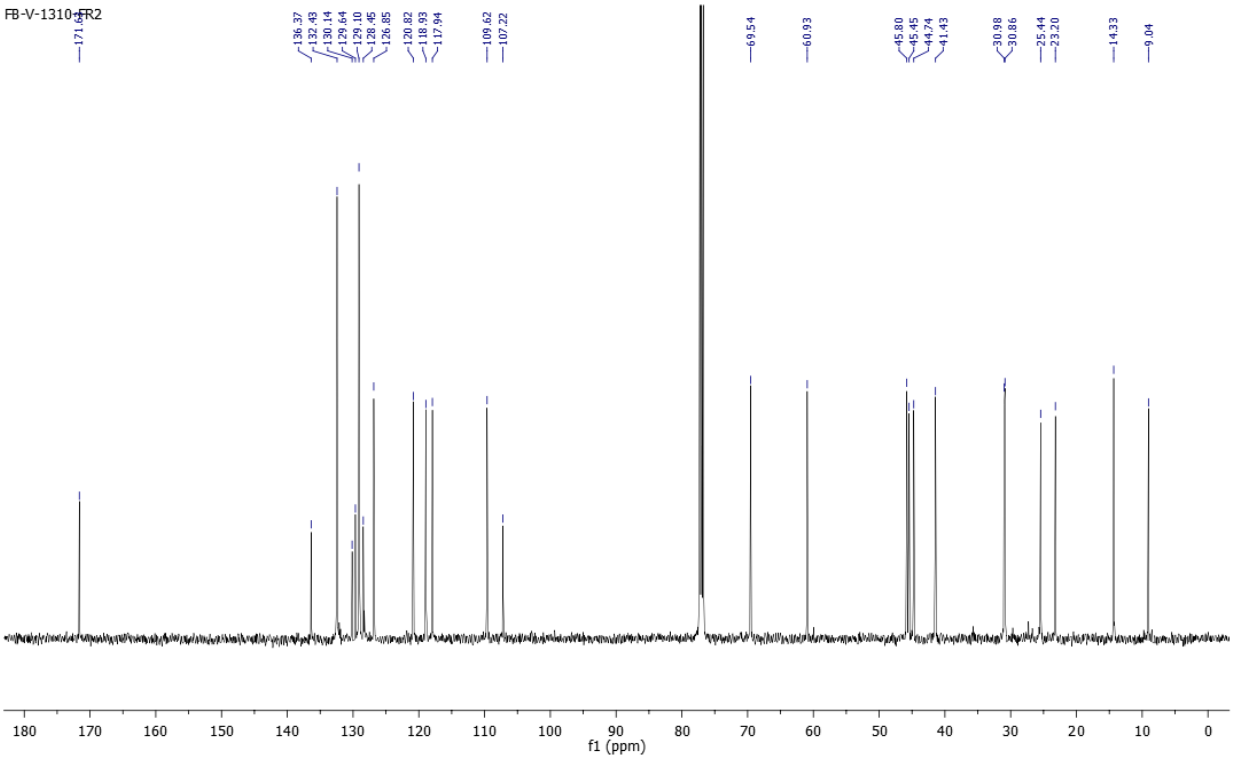
FB-V-1298-FR2
343K

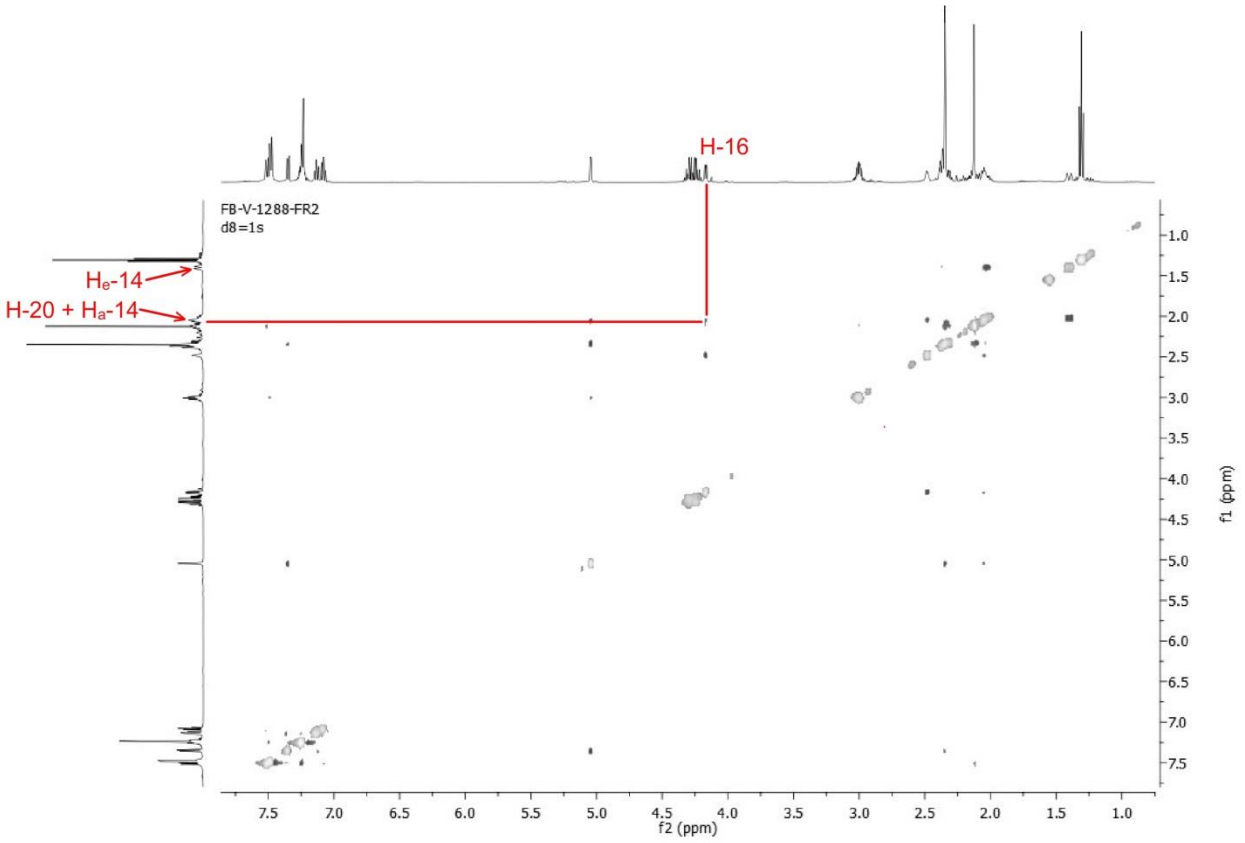


FB-V-1294-FR2

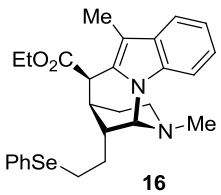


FB-V-1310-FR2



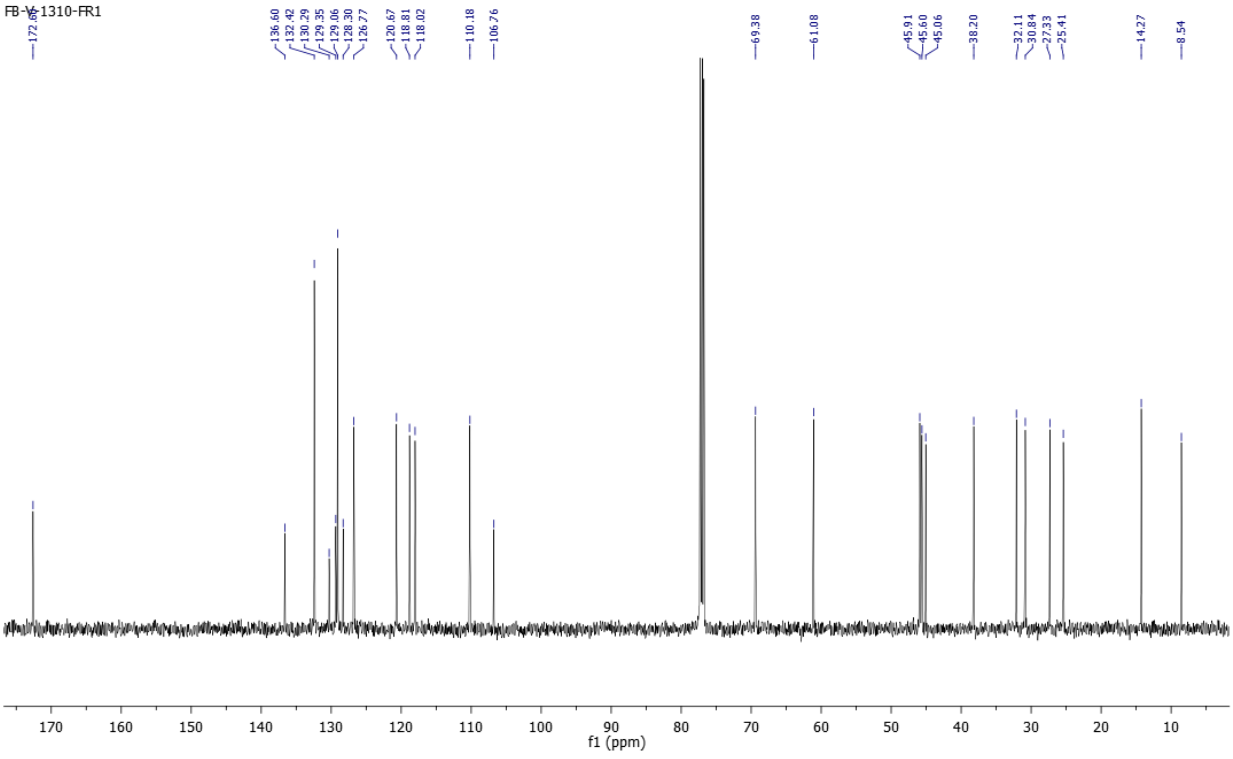

H-16
FB-V-1288-FR2
d8=1s
He-14
H-20 + Ha-14
f2 (ppm)
f1 (ppm)

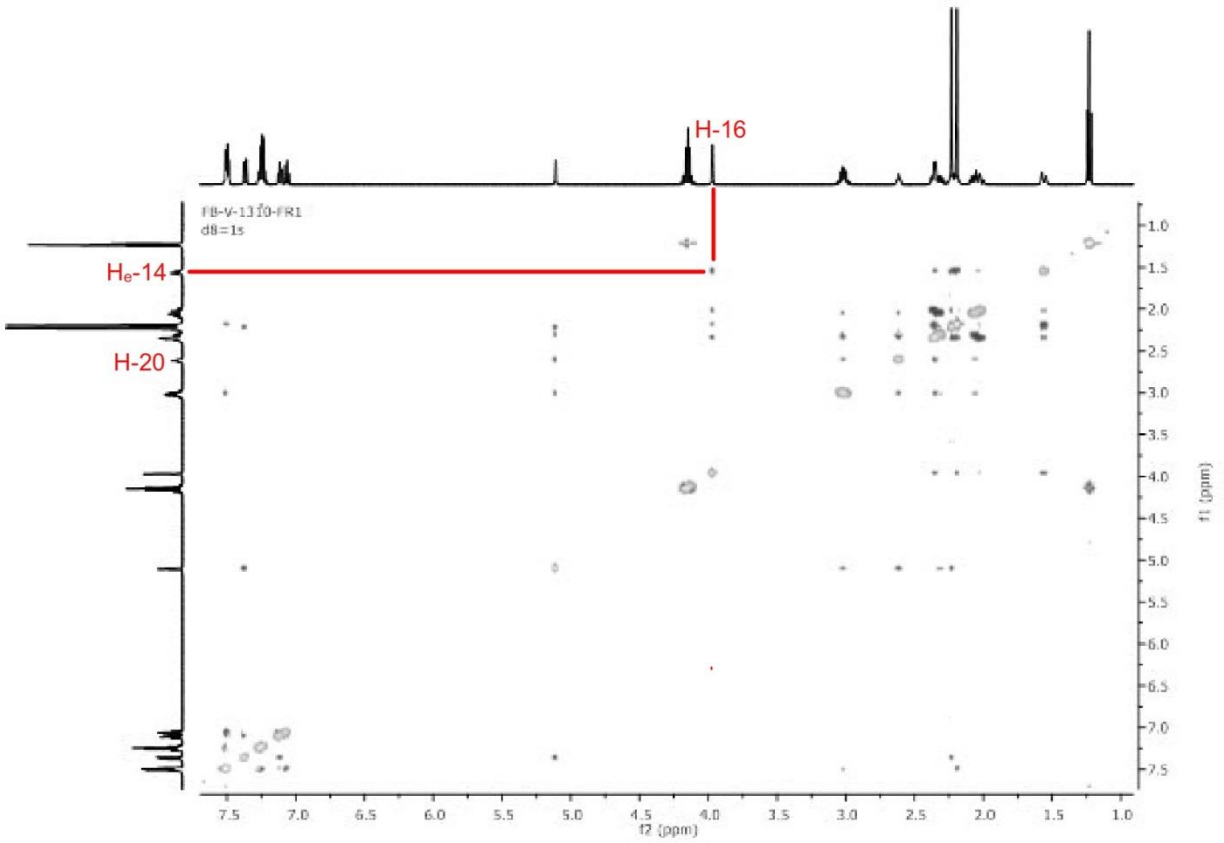
FB-V-1310-FR1

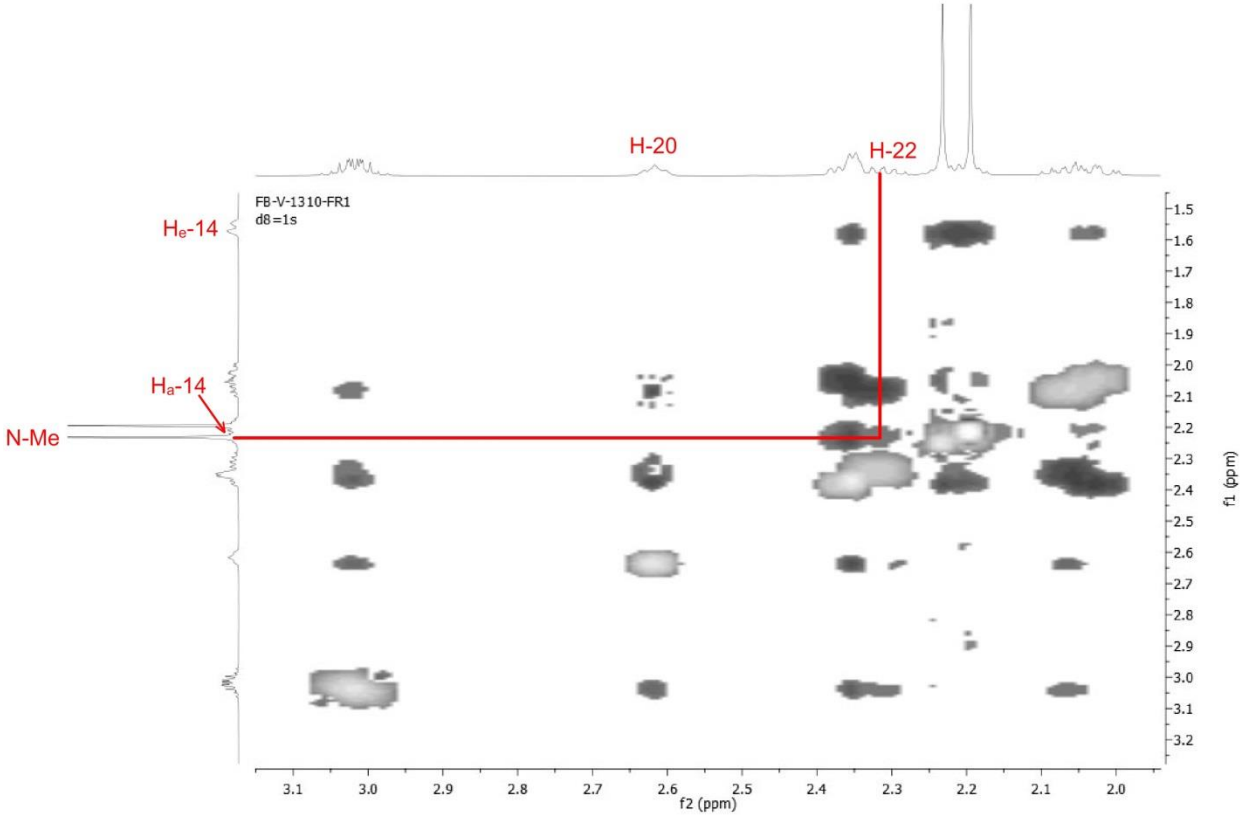


16

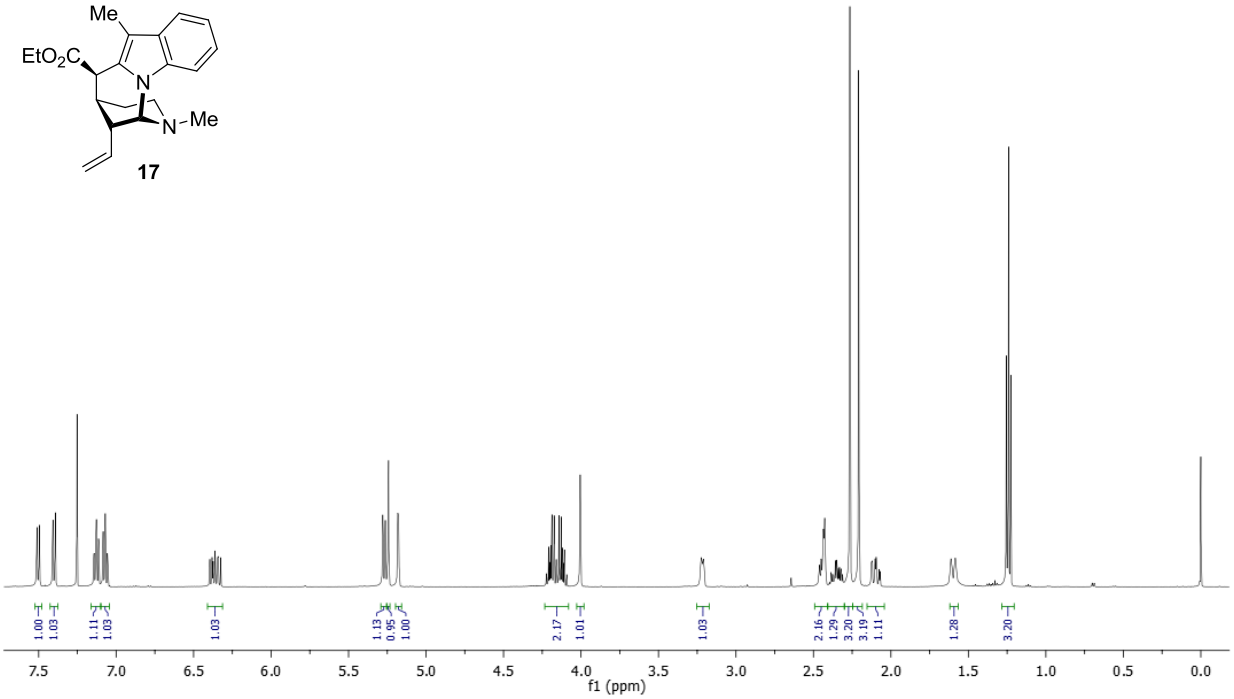
FB-V-1310-FR1




H-16
FB-V-1310-FR1
d8=1s
He-14
H-20
f2 (ppm)
f1 (ppm)

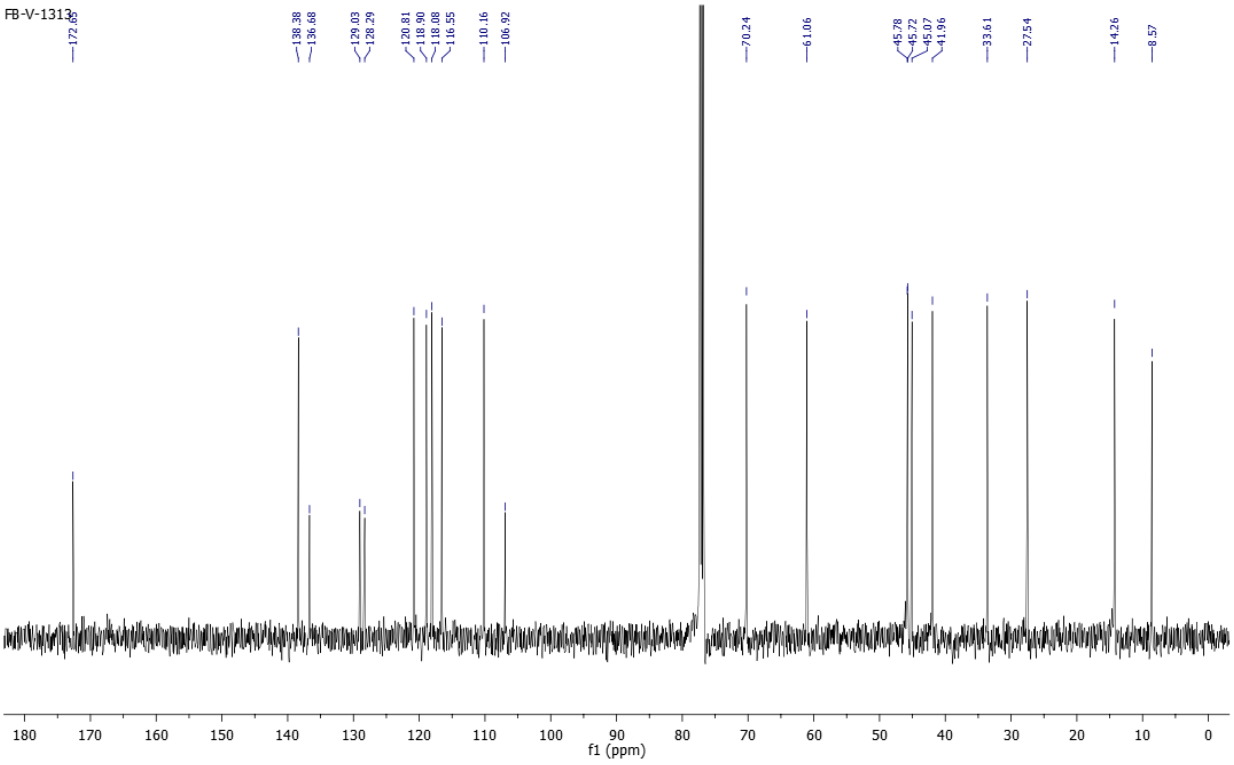

H-20
H-22
FB-V-1310-FR1
d8=1s
He-14
Ha-14
N-Me
f2 (ppm)
f1 (ppm)

FB-V-1328

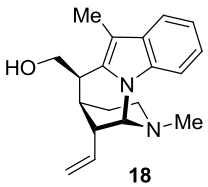


17

FB-V-1313

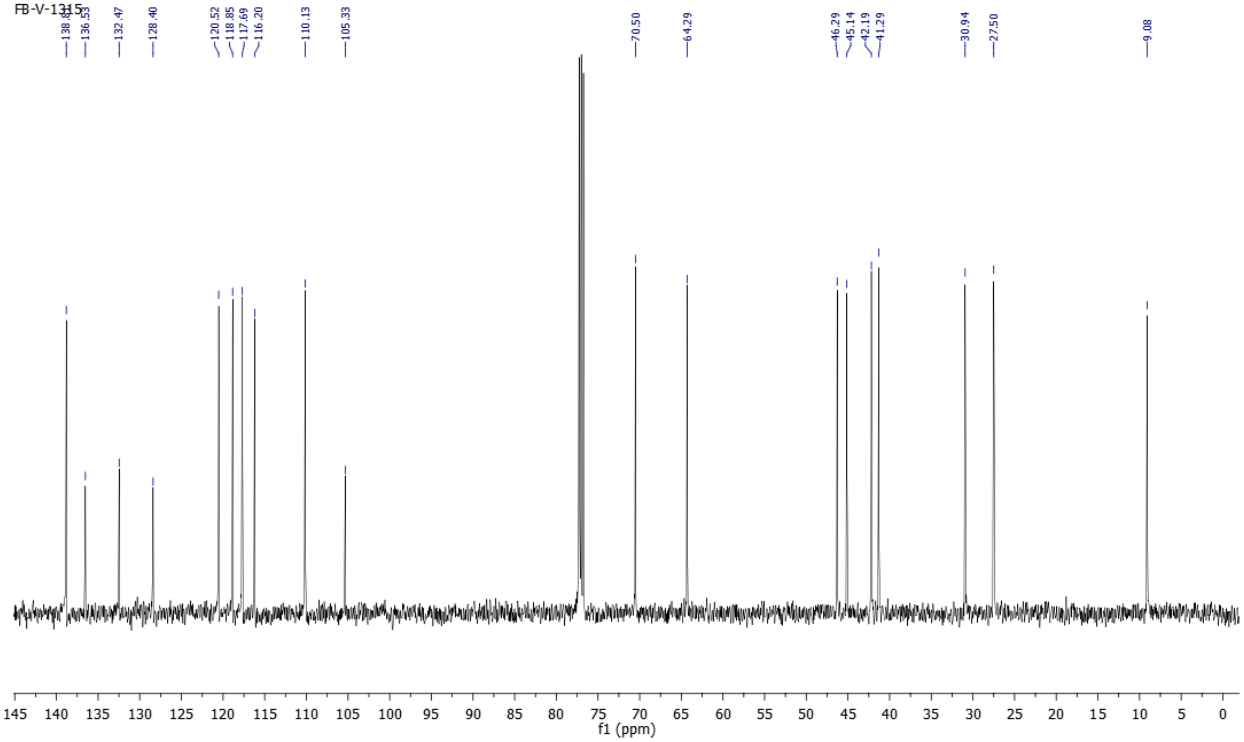


FB-V-1329-K

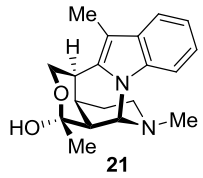


18

FB-V-1315



FB-V-1331



21

FB-V-1334