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Supplementary Information

Chemoenzymatic preparation of optically active cyclic 4-hydroxy-acylazyridines

Saúl Silva and Christopher D. Maycock*

Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, EAN, 2780-157 Oeiras, Portugal and Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

* Email: maycock@itqb.unl.pt

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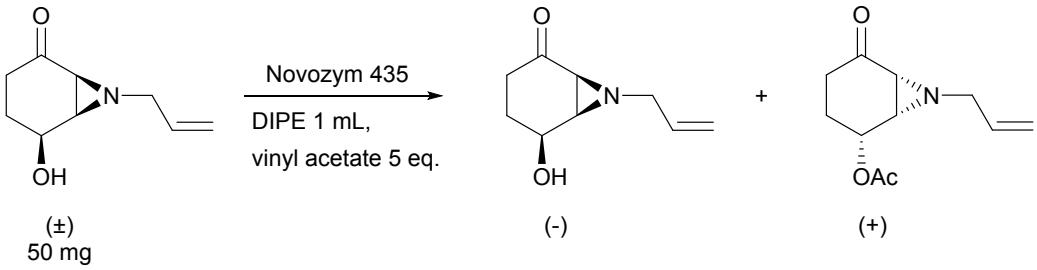
Table 1 – Enzymic resolution using different reaction conditions.



Novozym 435 (mg)	Time (h)	others	Conversion* (%)
25	4		49.5
25	4	Novozym 435 and substrate were aged for 17 h in DIPE before adding vinyl acetate.	49.7
25	4	Novozym 435 was recycled from other batch.	49.4

*Conversions were determined using the substrate/product proportion obtained by NMR analysis of the crude product. The allyl methylene signals were used for this purpose.

General

All chemicals used were of reagent grade. All solvents were dried by established methods.[1] Flash chromatography was performed on Kieselgel 60, particle size 0.032–0.063 mm. Preparative TLC: silica gel Merck 60 GF_{254}. Analytical TLC: Aluminium-backed silica gel Merck 60 F_{254}. Infrared (IR) spectra were obtained using commercial FT-IR spectrophotometer and are in cm^{-1}. Specific rotations were measured using an automatic polarimeter and are reported as follows: $[\propto]_D^T$(c= g/100 mL; solvent). Melting points were determined with a capillary apparatus and are uncorrected. HRMS was recorded on a commercial apparatus (ESI Source). NMR spectra were obtained on a commercial instrument 400 MHz (^{1}H NMR), 101 MHz (^{13}C NMR) using $CDCl_3$ as solvent. Chemical shifts are reported in ppm relative to TMS for ^{1}H NMR and the $CDCl_3$ signal for ^{13}C. The peak assignments of all compounds were made with the help of 2D NMR experiments as COSY, HMQC and HMBC. Chiral HPLC analysis was carried out using a Chiralpak® AD-H or IB (250 x 4.6 mm) column in a commercial system.

4-[(*tert*-butyldimethylsilyl)oxy]-2-iodocyclohex-2-en-1-one 12a

This compound was prepared by a previously described procedure[2].

4-[(*tert*-butyldimethylsilyl)oxy]-2-iodocyclohex-2-en-1-one 12b

This compound was prepared by a previously described procedure[3].

4-[(*tert*-butyldimethylsilyl)oxy]cyclohept-2-en-1-one

To a stirred solution of 4-hydroxycyclohept-2-en-1-one[4] (1.0 g, 7.9 mmol) in dry DCM (16 mL) under argon was added DIPA (2.8 mL, 2.5 eq.), TBSCl (2.4 g, 2 eq.) and DMAP (cat.) at 0^{o}C. After 16 hours of stirring at room temperature the reaction was quenched with H_2O (20 mL) and the mixture was extracted with DCM (3x 10 mL). The combined organic phases were dried with $MgSO_4$ and evaporated to dryness. Purification by flash column chromatography, eluted with Hex:EtOAc (95:5), afforded 1.6 g (84%) of the pure compound as a colourless oil.

^{1}H NMR δ: 6.50 (1H, ddd, $J_{3,2}$=12.5, $J_{3,4}$=3.2, $J_{3,5}$=1.0, H-3); 5.91 (1H, ddd, $J_{2,3}$=12.5, $J_{2,4}$=2.0, $J_{2,7}$=0.8, H-2); 4.56-4.51 (1H, m, H-4); 2.65-2.58 (1H, m, H-7); 2.56-2.49 (1H, m, H-7); 2.12-2.04 (1H, m, H-5); 1.89-1.78 (3H, m, H-5, H-6), 0.91 (9H, s, ^{t}Bu TBS); 0.11 (3H, s, Me TBS); 0.10 (3H, s, Me TBS). ^{13}C NMR δ: 203.5 (C-1); 150.6 (C-3); 129.4 (C-2); 71.0 (C-4); 43.0 (C-7); 35.4 (C-5); 25.8 (3xMe ^{t}Bu); 18.3 (C-6); 18.1 (C_q ^{t}Bu); -4.6 (Me TBS); -4.7 (Me TBS). FTIR(NEAT): 1674 (C=O st.). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{25}O_2Si$ 241.1618; Found 241.1612.

4-[(*tert*-butyldimethylsilyl)oxy]-2-iodocyclohept-2-en-1-one 12c

To a stirred solution of 4-[(*tert*-butyldimethylsilyl)oxy]cyclohept-2-en-1-one (1.0 g, 4.2 mmol) in a 1:1 THF:H_2O mixture (17 mL) was added K_2CO_3 (1.15 g, 2 eq.), I_2 (2.1 g, 2 eq.) and DMAP (100 mg, 20 mol%). After 24 hours of stirring at 60°C the reaction was diluted with Et_2O (20mL) and washed with a $Na_2S_2O_3$ 20%(w/V) (20 mL) and H_2O (20 mL). The combined organic phases were dried with $MgSO_4$ and evaporated to dryness, affording 699 mg (46%) of the pure compound as colourless oil.

^{1}H NMR δ: 7.48 (1H, d, $J_{3,4}$=3.7, H-3); 4.51 (1H, dt, $J_{4,5}$=8.5, $J_{4,3}$=$J_{4,5}$=4.1, H-4); 2.81 (1H, dt, ^2J=15.2, $J_{7,6}$=5.1, H-7); 2.57 (1H, ddd, ^2J=15.0, $J_{7,6}$=10.1, $J_{7,6}$=4.8, H-7); 2.05-1.95 (1H, m, H-5); 1.87-1.76 (3H, m, H-5, H-6), 0.90 (9H, s, ^{t}Bu TBS); 0.10 (3H, s, Me TBS); 0.09 (3H, s, Me TBS). ^{13}C NMR δ: 197.9 (C-1); 159.4 (C-3); 103.3 (C-2); 72.0 (C-4); 39.7 (C-7); 34.0 (C-5); 25.7 (3xMe ^{t}Bu); 18.09 (C-6); 18.06 (C_q ^{t}Bu); -4.79 (Me TBS); -4.83 (Me TBS). FTIR(NEAT): 1682 (C=O st.). HRMS (ESI-TOF) m/z: $[M\text{-TBS+H}]^+$ Calcd for $C_7H_{10}IO_2$ 252.9720; Found 252.9714.

General procedure for the preparation of TBS-protected *cis*-hydroxybenzylaziridines

In a flask under argon a mixture of iodoenone (1.35 mmol), anhydrous Cs_2CO_3 (480 mg, 1.1 eq.), 1,10-phenantroline (240 mg, 1.0 eq.), $BnNH_2$ (220 µL, 1.5 eq.) and dry toluene (10 mL) was stirred at room temperature. After complete reaction (TLC, around 4 hours), the reaction mixture was diluted with DCM (10 mL) and washed with H_2O (10 mL). The organic layer was dried with $MgSO_4$ and evaporated to dryness. Purification by chromatography (flash column eluted with Hex:EtOAc 9:1) afforded the pure aziridine.

(±)-(1*S*,5*S*,6*R*)-7-benzyl-5-[(*tert*-butyldimethylsilyl)oxy]-7-azabicyclo[4.1.0]heptan-2-one 13

Using the general procedure 700 mg (82%) of compound was obtained as colourless oil.

^{1}H NMR δ:7.41 (2H, d, ^3J=7.6, Ar(*o*)), 7.31 (2H, t, ^3J=7.4, Ar(*m*)), 7.25 (2H, t, ^3J =8.0 Hz, Ar(*p*)), 4.12 (1H, ddd, $J_{5,4}$=10.4, $J_{5,4}$=5.2, $J_{5,6}$=1.8, H-5), 3.91 (1H, d, ^2J=14.0, CH_2 Bn), 3.35 (1H, d, ^2J=14.0, CH_2 Bn), 2.45 (1H, ddd, ^2J=18.4, $J_{3,4}$=5.6, $J_{3,4}$=2.0, H-3), 2.32 (1H, br d, $J_{6,1}$=6.4,H-6), 2.29-2.21 (1H, m, H-4), 2.19 (1H, d, $J_{1,6}$=6.0, H-1), 2.08 (1H, ddd, ^2J=18.8, $J_{3,4}$=12.4, $J_{3,4}$=6.4, H-3), 1.67-1.60 (1H, m, H-4), 0.87 (9H, s, ^{t}Bu TBS), 0.08 (3H, s, Me TBS), 0.05 (3H, s, Me TBS). ^{13}C NMR δ: 205.7 (C-2), 138.1 (Ar C_q), 128.3 (Ar(*m*)), 127.5 (Ar(*o*)), 127.1 (Ar(*p*)), 67.9 (C-5), 62.8 (CH_2 Bn), 48.2 (C-6), 46.9 (C-1), 35.3 (C-3), 25.9 (C-4), 25.7 (3xMe ^{t}Bu), 18.1 (C_q ^{t}Bu), -4.66 (Me TBS), -4.72 (Me TBS). FTIR (neat): 1711 (C=O st.). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{30}NO_2Si$ 332.2040; Found 332.2038.

(±)-(1*S*,4*S*,5*R*)-6-benzyl-4-[(tert-butyldimethylsilyl)oxy]-6-azabicyclo[3.1.0]hexan-2-one 14

Using the general procedure 780 mg (83%) of compound was obtained as a colourless oil.

^{1}H NMR δ:7.46 (2H, d, ^3J=7.2, Ar(*o*)), 7.32 (2H, t, ^3J=7.3, Ar(*m*)), 7.26 (2H, t, ^3J =7.3 Hz, Ar(*p*)), 4.39 (1H, td, $J_{4,3}$=8.0, $J_{4,5}$=3.1, H-4), 3.95 (1H, d, ^2J=14.2, CH_2 Bn), 3.26 (1H, d, ^2J=14.2, CH_2 Bn), 2.76 (1H, t, $J_{5,4}$= $J_{5,1}$=3.7, H-5), 2.49 (1H, dd, ^2J=16.8, $J_{3,4}$=8.0, H-3), 2.37 (1H, d, $J_{1,5}$=4.2, H-1), 2.22 (1H, ddd, ^2J=16.8, $J_{3,4}$=8.0, H-3), 0.90 (9H, s, ^{t}Bu TBS), 0.07 (3H, s, Me TBS), 0.06 (3H, s, Me TBS). ^{13}C NMR δ: 205.7 (C-2), 137.9 (Ar C_q), 128.4 (Ar(*m*)), 127.3 (Ar(*o*)), 127.1 (Ar(*p*)), 68.3 (C-4), 60.8 (CH_2 Bn), 50.3 (C-5), 48.6 (C-1), 41.6 (C-3), 25.8 (3xMe ^{t}Bu), 18.1 (C_q ^{t}Bu), -4.7 (Me TBS), -4.8 (Me TBS). FTIR (neat): 1741 (C=O st.). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{28}NO_2Si$ 318.1884; Found 318.1884.

(±)-(1*S*,6*S*,7*R*)-8-benzyl-6-[(*tert*-butyldimethylsilyl)oxy]-8-azabicyclo[5.1.0]octan-2-one 15

Using the general procedure 580 mg (68%) of compound was obtained as colourless oil.

^{1}H NMR δ:7.39 (2H, d, ^3J=7.4, Ar(*o*)), 7.31 (2H, t, ^3J=7.4, Ar(*m*)), 7.25 (2H, d, ^3J =7.2 Hz, Ar(*p*)), 3.85 (1H, dd, $J_{6,5}$=10.8, $J_{6,5}$=3.2, H-6), 3.63 (1H, d, ^2J=13.8, CH_2 Bn), 3.55 (1H, d, ^2J=13.8, CH_2 Bn), 2.83 (1H, ddd, ^2J=13.8, $J_{3,4}$=10.9, $J_{3,4}$=3.1, H-3), 2.23-2.04 (4H, m, H-1, H-3, H-5, H-7), 1.85-1.78 (1H, m, H-4), 1.73-1.68 (1H, m, H-5), 1.17 (1H, q, J=13.7, H-4), 0.86 (9H, s, ^{t}Bu TBS), 0.06 (3H, s, Me TBS), 0.05 (3H, s, Me TBS). ^{13}C NMR δ: 211.7 (C-2), 138.2 (Ar C_q), 128.3 (Ar(*m*)), 127.8 (Ar(*o*)), 127.1 (Ar(*p*)), 72.6 (C-6), 64.0 (CH_2 Bn), 51.2, 48.2 (C-1, C-7), 41.4 (C-3), 34.3 (C-5), 25.7 (3xMe ^{t}Bu), 22.9 (C-4); 18.0 (C_q ^{t}Bu), -4.7 (Me TBS), -4.8 (Me TBS). FTIR (neat): 1696 (C=O st.). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{32}NO_2Si$ 346.2197; Found 346.2202.

(±)-(1*R*,5*S*,6*S*)-5-[(*Tert*-butyldimethylsilyl)oxy]-7-[(4-methylbenzene)sulfonyl]-7-azabicyclo[4.1.0]heptan-2-one 16

This compound was prepared by a previously described procedure[5].

General procedure for the preparation of racemic *cis*-hydroxybenzylaziridines

To a stirred solution of TBS-protected aziridine (1.26 mmol) in dry THF (5 mL) under argon was added TBAF (2.3 mL, 1 M in THF, 1.8 eq.). After 30 minutes the reaction mixture was diluted with DCM (5 mL) and washed with H_2O (5 mL). The organic layer was dried with $MgSO_4$ and evaporated to dryness. Purification by chromatography (flash column eluted with Hex:EtOAc 1:1) afforded the pure aziridine in a yield greater than 95%.

(±)-(1*S*,5*S*,6*R*)-7-benzyl-5-hydroxy-7-azabicyclo[4.1.0]heptan-2-one 17

Using the general procedure 430 mg (quant.) of compound was obtained as colourless oil.

(±)-(1*S*,4*S*,5*R*)-6-benzyl-4-hydroxy-6-azabicyclo[3.1.0]hexan-2-one 18

Using the general procedure 380 mg (98%) of compound was obtained as white solid (m.p. = 90-91°C).

(±)-(1*S*,6*S*,7*R*)-8-benzyl-6-hydroxy-8-azabicyclo[5.1.0]octan-2-one 20

Using the general procedure 360 mg (99%) of compound were obtained as colourless oil.

(±)-(1*R*,5*S*,6*S*)-5-hydroxy-7-(4-methylbenzenesulfonyl)-7-azabicyclo[4.1.0]heptan-2-one 21

A procedure similar to the general was used, but 10 eq. of $Et_3N.3HF$ were used instead of 1.8 eq. of TBAF and the reaction took 16 h to complete. 180 mg of compound (quant.) were obtained as a white solid (m.p. = 121-122°C).

Typical procedure for the enzymic resolution

A mixture of racemic hydroxyaziridine (50 mg), vinyl acetate (5 eq.), novozym 435 (25-75 mg) and diisopropyl ether (1 mL) was agitated (700 r.p.m.) in a closed tube at 24°C. After the resolution was completed the support solid enzyme was removed by decantation and the organic solution was evaporated to dryness. Purification by flash column chromatography, eluted with Hex/EtOAc (1:1), afforded (-)-hydroxyaziridine and (+)-acetoxyaziridine.

Resolution of (±)-(1*S*,5*S*,6*R*)-7-benzyl-5-hydroxy-7-azabicyclo[4.1.0]heptan-2-one 17

The general procedure was used with 25 mg of novozym 435. The resolution was complete after 4 h, affording 24 mg (48%) (-)-(1*S*,5*S*,6*R*)-7-benzyl-5-hydroxy-7-azabicyclo[4.1.0]heptan-2-one **(-)-17** (>99% e.e, HPLC) as a white solid and 28 mg (47%) (+)-(1*S*,2*R*,6*R*)-7-benzyl-5-oxo-7-azabicyclo[4.1.0]heptan-2-yl acetate **(+)-17-acetate** (97% e.e., HPLC) as an oil.

(-)-(1*S*,5*S*,6*R*)-7-benzyl-5-hydroxy-7-azabicyclo[4.1.0]heptan-2-one 17

^{1}H NMR δ: 7.37-7.27 (5H, m, Ar), 4.11-4.05 (1H, m, H-5), 3.77 (1H, d, ^2J=13.2, CH_2 Bn), 3.40 (1H, d, ^2J=13.2, CH_2 Bn), 2.57-2.46 (2H, m, H-3, H-6), 2.31 (1H, br t, *J*=8.6, OH), 2.07-1.94 (2H, m, H-3, H-4), 1.85-1.73 (1H, m, H-4). ^{13}C NMR δ: 206.0 (C-2), 137.8 (Ar C_q), 128.7 (Ar(*m*)), 128.0 (Ar(*o*)), 127.7 (Ar(*p*)), 64.8 (C-5), 63.3 (CH_2 Bn), 48.0, 47.7 (C-1, C-6), 34.9 (C-3), 29.2 (C-4). $[\propto]_D^{20^oC}$ = -81

(c=1.1; CH_2Cl_2). M.p. = 78-79°C. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}NO_2$ 218.1176; Found 218.1171.

(+)-(1*S*,2*R*,6*R*)-7-benzyl-5-oxo-7-azabicyclo[4.1.0]heptan-2-yl acetate 17-acetate

^{1}H NMR δ: 7.34-7.25 (5H, m, Ar), 5.08 (1H, ddd, $J_{2,3}$=10.1, $J_{2,3}$=5.2, $J_{2,1}$=2.3, H-2), 3.96 (1H, d, ^2J=13.2, CH_2 Bn), 3.21 (1H, d, ^2J=13.4, CH_2 Bn), 2.56 (1H, dm, $J_{1,6}$=6.0, H-1), 2.52 (1H, ddd, ^2J=17.3, $J_{4,3}$=4.3, $J_{4,3}$=3.3, H-4), 2.29 (1H, d, $J_{6,1}$=6.1, H-6), 2.26-2.04 (2H, m, H-3, H-4), 1.88 (3H, s, CH_3 Ac), 1.82-1.75 (1H, m, H-3). ^{13}C NMR δ: 206.0 (C-5), 170.7 (C=O Ac), 137.7 (Ar C_q), 128.3 (Ar(*m*)), 128.0 (Ar(*o*)), 127.3 (Ar(*p*)), 69.0 (C-2), 62.9 (CH_2 Bn), 46.9 (C-6), 43.7 (C-1), 34.8 (C-4), 22.8 (C-3), 20.8 (CH_3 Ac). $[\propto]_D^{20^oC}$ = +185 (c=1.0; CH_2Cl_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}NO_3$ 260.1281; Found 260.1279.

Resolution of (±)-(1*S*,4*S*,*5*R)-6-benzyl-4-hydroxy-6-azabicyclo[3.1.0]hexan-2-one 18

The general procedure was used with 25 mg of novozym 435 and the quantity of diisopropyl ether and vinyl acetate used was 2 mL and 10 eq. respectively. The resolution was complete after 16 h, affording 24 mg (48%) (-)-(1*S*,4*S*,*5*R)-6-benzyl-4-hydroxy-6-azabicyclo[3.1.0]hexan-2-one **(-)-18** (99% e.e, HPLC) as a white solid and 30 mg (50%) (+)-(1*S*,2*R*,5*R*)-6-benzyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl acetate **(+)-22** (95% e.e., HPLC) as an oil.

(-)-(1*S*,4*S*,*5*R)-6-benzyl-4-hydroxy-6-azabicyclo[3.1.0]hexan-2-one 18

^{1}H NMR δ: 7.37-7.27 (5H, m, Ar), 4.33 (1H, td, $J_{4,3}$=8.1, $J_{4,5}$=3.3, H-4), 3.65 (1H, d, ^2J=13.4, CH_2 Bn), 3.47 (1H, d, ^2J=13.4, CH_2 Bn), 2.95 (1H, t, $J_{5,1}$=$J_{5,4}$=3.8, H-5), 2.47 (1H, d, $J_{1,5}$=4.2, H-1), 2.45-2.30(1H, br s, OH), 2.38 (1H, dd, ^2J=17.8, $J_{3,4}$=8.4, H-3), 2.22 (1H, dd, ^2J=17.8, $J_{3,4}$=7.0, H-3). ^{13}C NMR δ: 206.8 (C-2), 137.6 (Ar C_q), 128.7 (Ar(*m*)), 127.9 (Ar(*o*)), 127.8 (Ar(*p*)), 67.5 (C-4), 61.3 (CH_2 Bn), 50.1, 49.6 (C-1, C-5), 42.2 (C-3). FTIR (neat): 3260 (OH st), 1731 (C=O st.). $[\propto]_D^{20^oC}$ = -36 (c=1.0; CH_2Cl_2). M.p. = 115.5-117.5°C (decomp.). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{14}NO_2$ 204.1019; Found 204.1020.

(+)-(1*S*,2*R*,5*R*)-6-benzyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl acetate 22

^{1}H NMR δ: 7.37-7.26 (5H, m, Ar), 5.15 (1H, td, $J_{2,3}$=8.1, $J_{2,1}$=3.2, H-2), 3.84 (1H, d, ^2J=13.5, CH_2 Bn), 3.31 (1H, d, ^2J=13.6, CH_2 Bn), 3.08 (1H, t, $J_{1,2}$=$J_{1,5}$=3.7, H-1), 2.49 (1H, dd, ^2J=17.5, $J_{3,2}$=7.8, H-3), 2.48 (1H, d, $J_{5,1}$=4.0, H-5), 2.40 (1H, dd, ^2J=17.6, $J_{3,2}$=6.8, H-3), 1.97 (3H, s, CH_3 Ac). ^{13}C NMR δ: 205.4 (C-2), 170.8 (C=O Ac), 137.6 (Ar C_q), 128.5 (Ar(*m*)), 127.8 (Ar(*o*)), 127.5 (Ar(*p*)), 69.4 (C-2),

60.9 (CH_2 Bn), 48.7 (C-5), 46.5 (C-1), 38.2 (C-3), 20.7 (CH_3 Ac). FTIR (neat): 1732 (C=O st.). $[\propto]_D^{20^oC}$ = +120 (c=0.7; CH_2Cl_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{16}NO_3$ 246.1125; Found 246.1123.

Resolution of (±)-(1*S*,6*S*,7*R*)-8-benzyl-6-hydroxy-8-azabicyclo[5.1.0]octan-2-one 20

The general procedure was used with 75 mg of novozym 435. The resolution was complete after 24 h, affording 24 mg (48%) (-)-(1*S*,6*S*,7*R*)-8-benzyl-6-hydroxy-8-azabicyclo[5.1.0]octan-2-one **(-)-20** (92% e.e, HPLC) as an oil and 30 mg (50%) (+)-(1*S*,2*R*,7*R*)-8-benzyl-6-oxo-8-azabicyclo[5.1.0]octan-2-yl acetate **(+)-20-acetate** (93% e.e., HPLC) as an oil.

(-)-(1*S*,6*S*,7*R*)-8-benzyl-6-hydroxy-8-azabicyclo[5.1.0]octan-2-one 20

^{1}H NMR δ:7.36-7.26 (5H, m, Ar), 3.83 (1H, dd, $J_{6,5}$=10.7, $J_{6,5}$=2.4, H-6), 3.71 (1H, d, ^2J=13.3, CH_2 Bn), 3.43 (1H, d, ^2J=13.3, CH_2 Bn), 2.80 (1H, ddd, ^2J=13.9, $J_{3,4}$=10.9, $J_{3,4}$=3.0, H-3), 2.33 (1H, br d, $J_{1,7}$=7.3, H-1); 2.29 (1H, br d, $J_{7,1}$=7.6, H-7); 2.24-2.19 (1H, m, H-3), 1.98-1.78 (4H, m, H-4, H-5, OH), 1.24-1.13 (1H, m, H-4). ^{13}C NMR δ: 210.8 (C-2), 138.3 (Ar C_q), 128.6 (Ar(*m*)), 128.0 (Ar(*o*)), 127.6 (Ar(*p*)), 71.6 (C-6), 64.1 (CH_2 Bn), 49.6, 49.2 (C-1, C-7), 41.5 (C-3), 34.2 (C-5), 22.3 (C-4). FTIR (neat): 3420 (O-H st.); 1687 (C=O st.). $[\propto]_D^{20^oC}$ = -110 (c=0.8; CH_2Cl_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{18}NO_2$ 232.1332; Found 232.1330.

(+)-(1*S*,2*R*,7*R*)-8-benzyl-6-oxo-8-azabicyclo[5.1.0]octan-2-yl acetate 20-acetate

^{1}H NMR δ:7.34-7.26 (5H, m, Ar), 4.96 (1H, dd, $J_{2,3}$=11.4, $J_{2,3}$=3.2, H-2), 3.71 (1H, d, ^2J=13.4, CH_2 Bn), 3.44 (1H, d, ^2J=13.4, CH_2 Bn), 2.81 (1H, ddd, $J_{5,4}$=13.8, ^2J=11.2, $J_{5,4}$=2.9, H-5), 2.32 (1H, d, $J_{7,1}$=7.4, H-7); 2.27 (1H, d, $J_{1,7}$=7.7, H-1); 2.24 (1H, dd, ^2J=11.1, $J_{5,4}$=5.4, H-5), 2.07 (1H, q, ^2J=$J_{3,2}$=$J_{3,4}$=11.9, H-3), 1.94 (3H, s, CH_3 Ac), 1.89-1.76 (2H, m,H-3, H-4), 1.22 (1H, q, ^2J=$J_{4,3}$=$J_{4,5}$=13.8, H-4). ^{13}C NMR δ: 210.3 (C-6), 170.3 (C=O Ac), 137.8 (Ar C_q), 128.4 (Ar(*m*)), 128.0 (Ar(*o*)), 127.4 (Ar(*p*)), 73.8 (C-2), 63.9 (CH_2 Bn), 48.6 (C-7), 46.7 (C-1), 41.3 (C-5), 30.2 (C-3), 21.9 (C-4), 21.1 (CH_3 Ac). FTIR (neat): 1730, 1693 (C=O st.). $[\propto]_D^{20^oC}$ = +167 (c=0.6; CH_2Cl_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{20}NO_3$ 274.1438; Found 274.1436.

Resolution of (±)-(1*R*,5*S*,6*S*)-5-hydroxy-7-(4-methylbenzenesulfonyl)-7-azabicyclo[4.1.0]heptan-2-one 21

The general procedure was used with 50 mg of novozym 435 and the quantity of diisopropyl ether and vinyl acetate used was 2 mL and 10 eq., respectively. The resolution took 24 h to be complete, affording 23 mg (46%) (+)-(1*R*,5*S*,6*S*)-5-hydroxy-7-(4-methylbenzenesulfonyl)-7-azabicyclo[4.1.0]heptan-2-one **(+)-21** (91% e.e, HPLC) as a white solid and 28 mg (49%) (-)-(1*R*,2*R*,6*S*)-7-(4-methylbenzenesulfonyl)-5-oxo-7-azabicyclo[4.1.0]heptan-2-yl acetate **(-)-21-acetate** (96% e.e., HPLC) as an oil.

(+)-(1*R*,5*S*,6*S*)-5-hydroxy-7-(4-methylbenzenesulfonyl)-7-azabicyclo[4.1.0]heptan-2-one 21

^{1}H NMR δ: 7.81 (2H, d, ^{3}J=8.2, Ar(*o*)), 7.36 (2H, d, ^{3}J=8.0, Ar(*m*)), 4.46 (1H, q, $J_{5,4}$=$J_{5,6}$=2.9, H-5), 3.44 (1H, dm, $J_{6,1}$=6.4, H-6), 3.19 (1H, d, $J_{1,6}$=6.4, H-1), 2.46 (3H, s, CH_3 Ts), 2.41 (1H, ddd, ^{2}J=18.3, $J_{3,4}$=12.1, $J_{3,4}$=6.3, H-3), 2.26 (1H, ddd, ^{2}J=18.3, $J_{3,4}$=5.4, $J_{3,4}$=3.5, H-3), 2.13-2.04 (1H, m, H-4), 1.85 (1H, br s, OH), 1.82-1.75 (1H, m, H-4). ^{13}C NMR δ: 201.0 (C-2), 145.5 (Ar C-SO_2 Ts), 133.6 (Ar(*p*)), 130.1 (Ar(*m*)), 128.1 (Ar(*o*)), 62.8 (C-5), 43.6 (C-1), 43.4 (C-6), 31.8 (C-3), 25.2 (C-4), 21,7 (CH_3 Ts). FTIR (neat): 1701 (C=O st.). $[\propto]_D^{20^oC}$ = +13 (c=1.0; CH_2Cl_2). M.p. = 114-116°C. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}NO_4S$ 282.0795; Found 282.0796.

(-)-(1*R*,2*R*,6*S*)-7-(4-methylbenzenesulfonyl)-5-oxo-7-azabicyclo[4.1.0]heptan-2-yl acetate 21-acetate

^{1}H NMR δ: 7.82 (2H, d, ^{3}J=8.2, Ar(*o*)), 7.37 (2H, d, ^{3}J=8.2, Ar(*m*)), 5.34 (1H, q, $J_{2,3}$=$J_{2,1}$=3.0, H-2), 3.49 (1H, dm, $J_{1,6}$=6.3, H-1), 3.25 (1H, d, $J_{6,1}$=6.3, H-6), 2.46 (3H, s, CH_3 Ts), 2.34-2.30 (2H, m, H-4), 2.17-2.04 (1H, m, H-3), 2.10 (3H, s, CH_3 Ac), 1.89-1.82 (1H, m, H-3). ^{13}C NMR δ: 199.7 (C-5), 170.0 (C=O Ac), 145.6 (Ar C-SO_2 Ts), 133.7 (Ar(*p*)), 130.1 (Ar(*m*)), 128.1 (Ar(*o*)), 65.3 (C-2), 43.0 (C-6), 41.1 (C-1), 32.1 (C-4), 22.4 (C-3), 21,7 (CH_3 Ts), 20,9 (CH_3 Ac). FTIR (neat): 1743, 1722 (C=O st.). $[\propto]_D^{20^oC}$ = -11 (c=0.8; CH_2Cl_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}NO_5S$ 324.0900; Found 324.0897.

General procedure for the hydrolysis of acetoxyaziridines

To a stirred solution of acetoxyaziridine (aprox. 30 mg, 0.12 mmol) in methanol (1 mL) was added K_2CO_3 (1.6 mg, 10 mol%). After 1 hour NH_4Cl (2 mg) was added. The salts were then filtered and the solution evaporated to dryness affording the hydroxyaziridine in quantitative yield.

(+)-(1R,4S,5S)-6-benzyl-4-methoxy-6-azabicyclo[3.1.0]hexan-2-one 19

A procedure similar to the general was used, but 2 eq. of K_2CO_3 were used instead of 10 mol%. 44 mg of compound was obtained as colourless oil in quantitative yield.

^{1}H NMR δ: 7.37-7.26 (5H, m, Ar), 4.07 (1H, $J_{4,5}$=5.6, d, H-4), 3.65 (1H, d, ^2J=13.6, CH_2 Bn), 3.49 (1H, d, ^2J=13.8, CH_2 Bn), 3.35 (3H, s, OMe), 2.89 (1H, d, $J_{5,1}$=3.9, H-5), 2.41 (1H, dd, ^2J=18.2, $J_{3,4}$=5.6, H-3), 2.36 (1H, d, $J_{1,5}$=3.9, H-1), 2.03 (1H, d, ^2J=18.2, H-3). ^{13}C NMR δ: 209.4 (C-2), 137.7 (Ar C_q), 128.6 (Ar(*m*)), 127.7 (Ar(*o*)), 127.5 (Ar(*p*)), 77.4 (C-4), 61.3 (CH_2 Bn), 56.5 (OMe), 48.9 (C-5), 46.0 (C-1), 40.3 (C-3). FTIR (neat): 1744 (C=O st.). $[\propto]_D^{20^oC}$ = +35 (c=0.6; CH_2Cl_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}NO_2$ 218.1176; Found 218.1176.

(±)-1,3-diethyl 2-[(1*R*,2*R*,5*R*)-6-benzyl-4-oxo-6-azabicyclo[3.1.0]hexan-2-yl]propanedioate 24

To a stirred solution of (±)-**22** (40 mg, 0.16 mmol) and diethyl malonate (50 µL, 2eq.) in dry THF (1 mL) was added NaH (8 mg, 2 eq.) at 0°C. After 1 hour of stirring at room the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with DCM (3x5 mL). The combined organic layers were dried with $MgSO_4$ and evaporated to dryness. Purification by chromatography (preparative TLC eluted with Hex:EtOAc 2:1) afforded 40 mg (71%) of pure compound as colourless oil.

^{1}H NMR δ: 7.38-7.25 (5H, m, Ar), 4.26-4.13 (4H, m, 2xCH_2 Et), 3.63 (1H, d, ^2J=13.7, CH_2 Bn), 3.48 (1H, d, ^2J=13.7, CH_2 Bn), 3.44 (1H, d, $J_{2,2'}$=6.9, H-2), 3.11 (1H, ddd, $J_{2',3'}$=8.3, $J_{2',2}$=7.2, J=1.1, H-2'), 2.77 (1H, d, $J_{1',5'}$=3.9, H-1'), 2.62 (1H, dd, ^2J=18.5, $J_{3',2'}$=8.7, H-3'), 2.31 (1H, d, $J_{5',1'}$=3.9, H-5'), 1.96 (1H, d, ^2J=18.5, H-3'), 1.25 (6H, t, ^3J=7.1, 2xCH_3 Et). ^{13}C NMR δ: 209.5 (C-4'), 167.84, 167.81 (C-1, C-3), 137.8 (Ar C_q), 128.5 (Ar(*m*)), 127.7 (Ar(*o*)), 127.4 (Ar(*p*)), 61.9, 61.8 (2xCH_2 Et), 61.4 (CH_2 Bn), 54.2 (C-2), 48.3 (C-1'), 47.0 (C-5'), 38.0 (C-3'), 35.9 (C-2'), 14.0 (2xCH_3 Et). FTIR (neat): 1743, 1728 (C=O st.). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{24}NO_5$ 346.1649; Found 346.1649.

(±)-(1*R*,4*S*,5*R*)-6-benzyl-4-(prop-2-en-1-yl)-6-azabicyclo[3.1.0]hexan-2-one 25

To a stirred solution of (±)-**22** (60 mg, 0.25 mmol) in dry THF (0.5 mL) was added DBU (55 µL, 1.5eq.) at -20°C. After 30 min of stirring at this temperature, this solution was added to a mixture of allyl magnesium bromide (1M in Et_2O, 2.8 eq., 690 µL), CuI (3.2 eq., 150 mg), LiBr (70 mg) and dry THF (1 mL) at -78°C. After 30 minutes of stirring at this temperature, reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (3x5 mL). The combined organic layers were dried with $MgSO_4$ and evaporated to dryness. Purification by chromatography (preparative TLC eluted with Hex:EtOAc 8:2) afforded 30 mg (54%) of pure compound as colourless oil.

^{1}H NMR δ: 7.40 (2H, d, ^3J=7.3, Ar(*o*)), 7.32 (2H, t, ^3J=7.5, Ar(*m*)), 7.25 (1H, d, ^3J=7.2, Ar(*p*)), 5.88 (1H, ddt, $J_{2',3'}$=18.1, $J_{2',3'}$=9.3, $J_{2',1'}$=6.9, H-2'), 5.10-5.04 (2H, m, H-3'); 3.59 (1H, d, ^2J=13.8, CH_2 Bn), 3.47 (1H, d, ^2J=13.8, CH_2 Bn), 2.62 (1H, d, $J_{1,5}$=4.0, H-1), 2.58-2.48 (2H, m, H-3, H-4), 2.24 (1H, d, $J_{5,1}$=4.0, H-5), 2.16 (1H, dt, ^2J=13.7, $J_{1',2'}$=$J_{1',4}$=6.8, H-1'), 2.05 (1H, dt, ^2J=14.4, $J_{1',2'}$=$J_{1',4}$=7.1, H-1'), 1.74 (1H, d, ^2J=16.8, H-5). ^{13}C NMR δ: 211.5 (C-2), 138.3 (Ar C_q), 134.9 (C-2'), 128.5 (Ar(*m*)), 127.6 (Ar(*o*)), 127.3 (Ar(*p*)), 117.6 (C-3'), 61.5 (CH_2 Bn), 50.8 (C-1), 46.6 (C-5), 39.3 (C-3), 37.6 (C-1'), 35.7 (C-4). FTIR (neat): 1741 (C=O st.). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}NO$ 228.1383; Found 228.1383.

(±)-(1*R*,4*S*,5*R*)-6-benzyl-4-(benzylamino)-6-azabicyclo[3.1.0]hexan-2-one 26

To a stirred solution of (±)-**22** (60 mg, 0.25 mmol) and $BnNH_2$ (55 µL, 2 eq.) in dry *tert*-butanol (1 mL) was added K_2CO_3 (70 mg, 2 eq.) at room temeperature. After 1.5 hours of stirring at this temperature, reaction mixture was quenched with H_2O and extracted with EtOAc (3x5 mL). The combined organic layers were dried with Na_2SO_4 and evaporated to dryness. Purification by preparative TLC eluted with EtOAc afforded 47 mg (52%) of pure compound as a fluorescent greenish yellow oil.

^{1}H NMR δ: 7.36-7.24 (10H, m, Ar), 3.83 (1H, d, ^2J=13.1, CH_2 Bn amine), 3.79 (1H, d, ^2J=13.0, CH_2 Bn amine), 3.62 (1H, d, ^2J=13.8, CH_2 Bn aziridine), 3.59 (1H, d, $J_{4,3}$=6.6, H-4), 3.46 (1H, d, ^2J=13.7, CH_2 Bn aziridine), 2.76 (1H, d, $^2J_{5,1}$=4.0, H-5), 2.59 (1H, dd, ^2J=18.0, $J_{3,4}$=6.5, H-3), 2.32 (1H, d, $J_{1,5}$=3.9, H-1), 1.89 (1H, d, ^2J=18.0, H-3), 1.50 (1H, S, NH). ^{13}C NMR δ: 210.5 (C-2), 139.6, 137.9 (2xAr C_q), 128.59, 128.55, 128.2, 127.7, 127.4, 127.3 (6xAr), 61.4 (CH_2 Bn aziridine), 55.1 (C-4), 51.4 (CH_2 Bn amine), 50.6 (C-5), 46.2 (C-1), 41.4 (C-3). FTIR (neat): 1739 (C=O st.). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{21}N_2O$ 293.1648; Found 293.1646.

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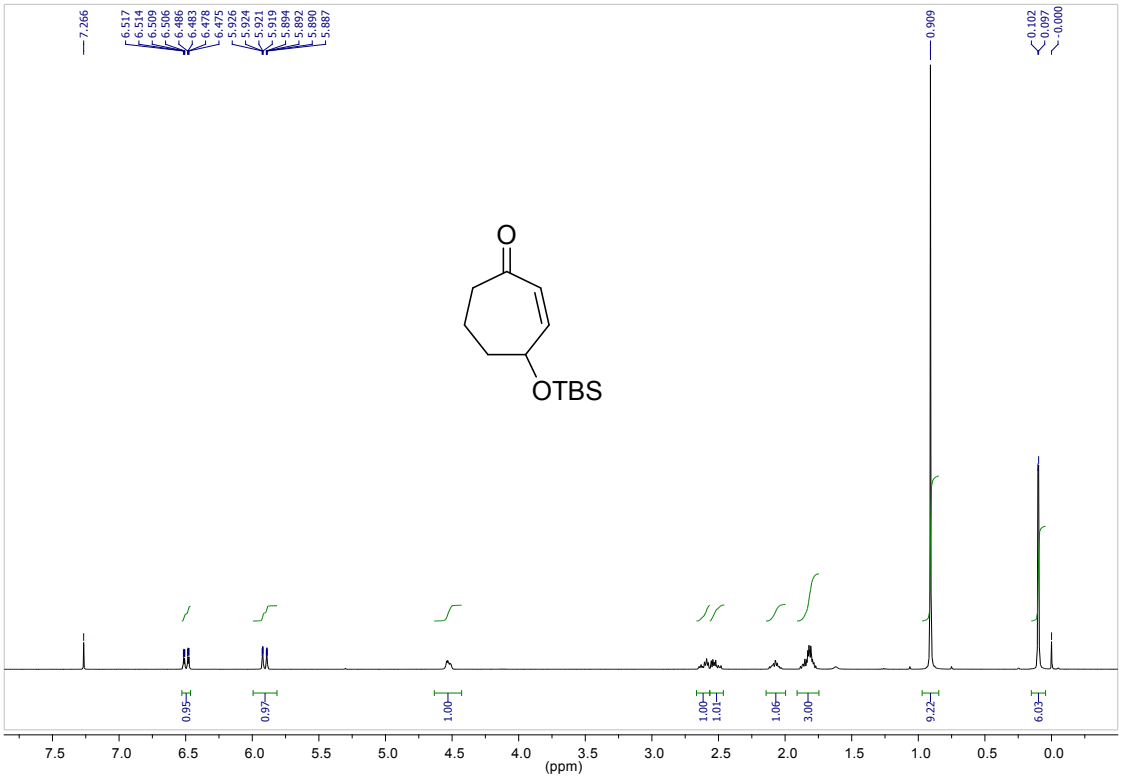
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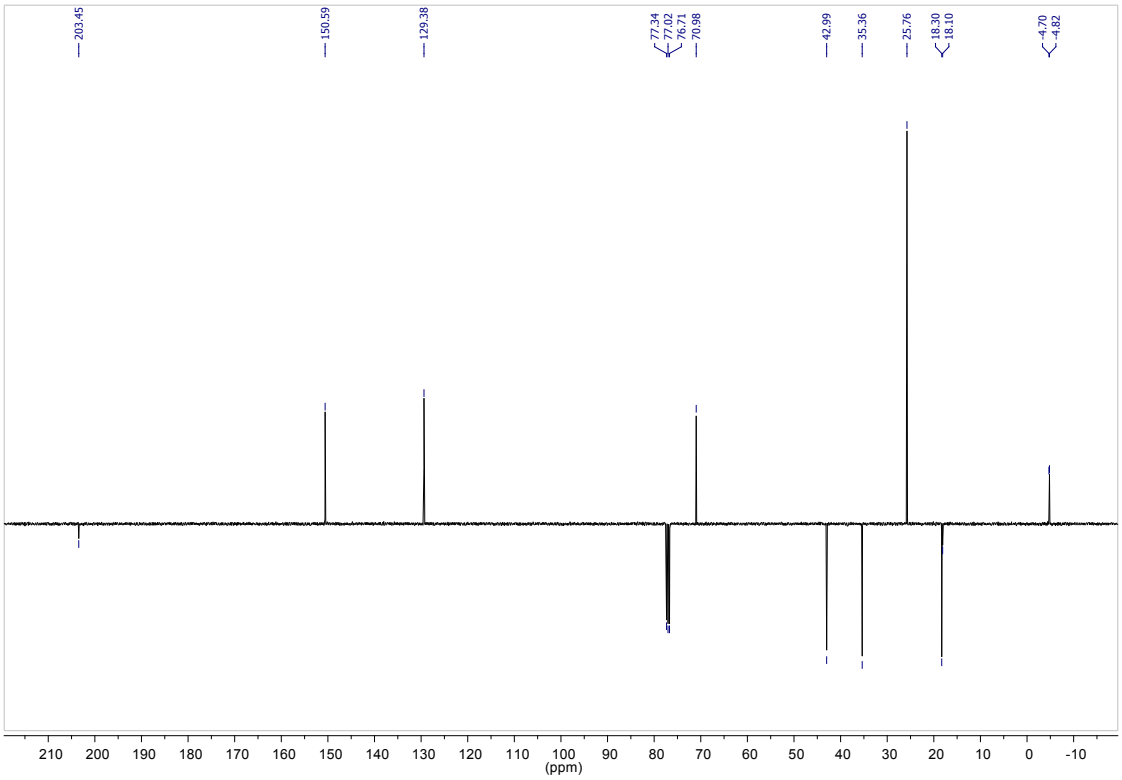
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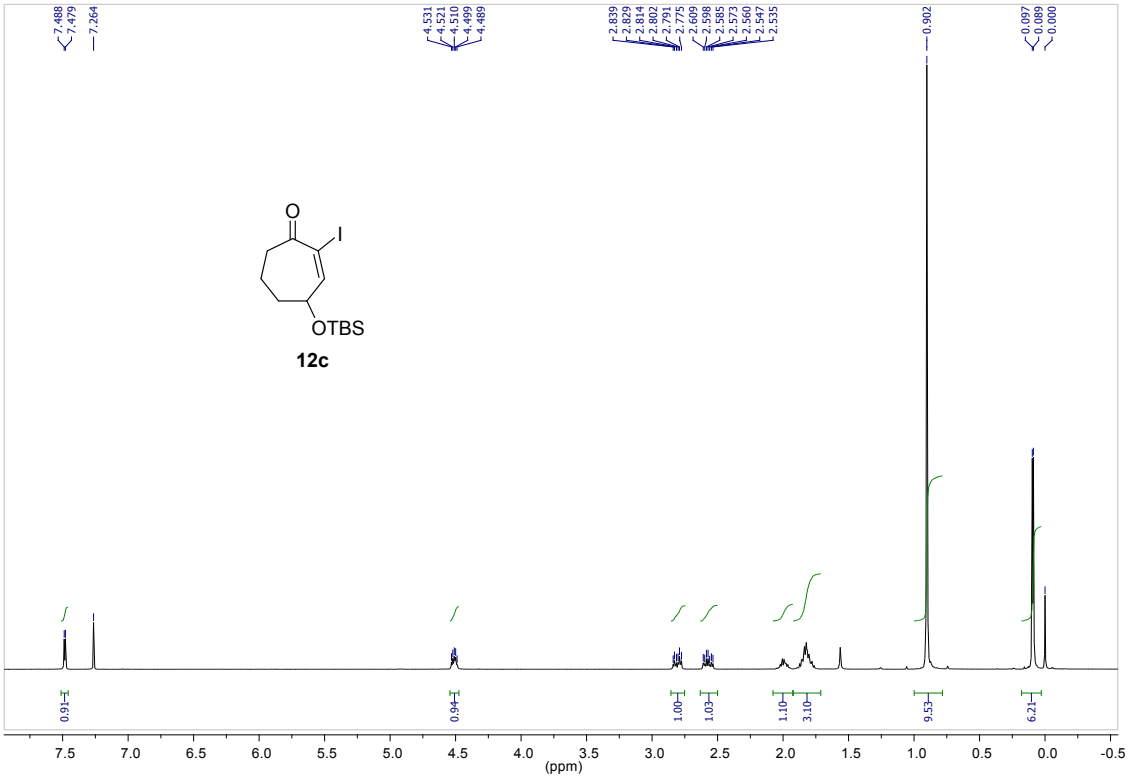
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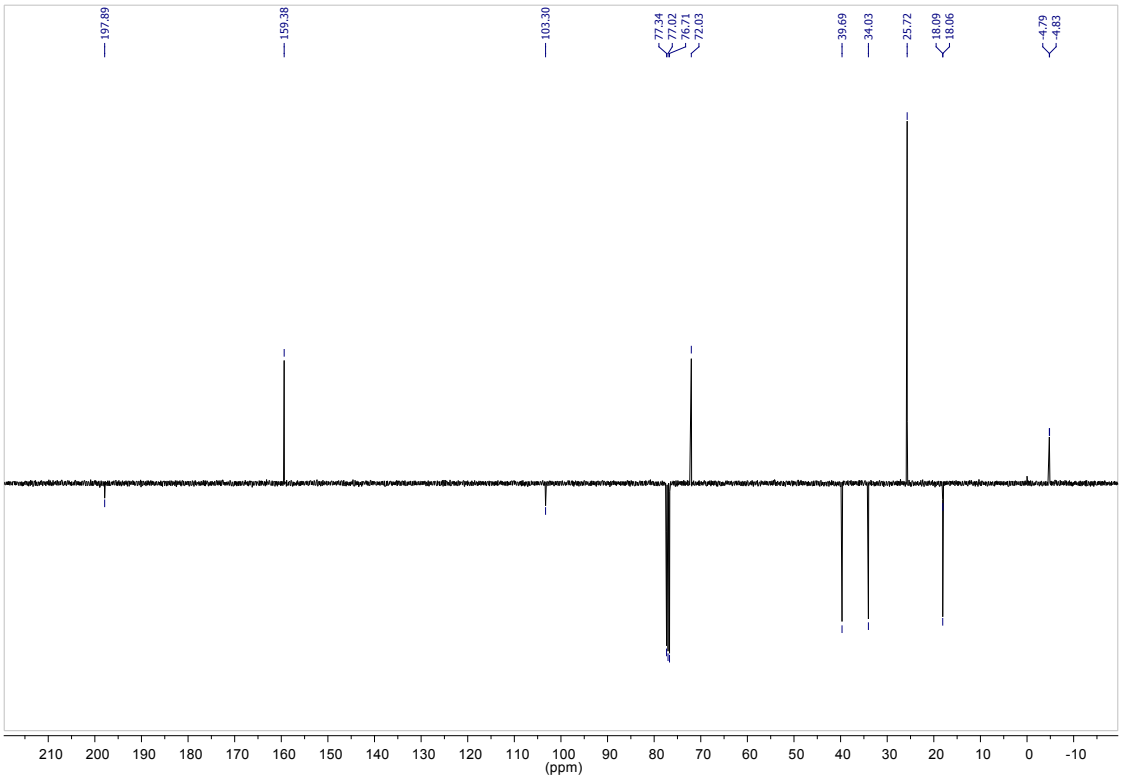
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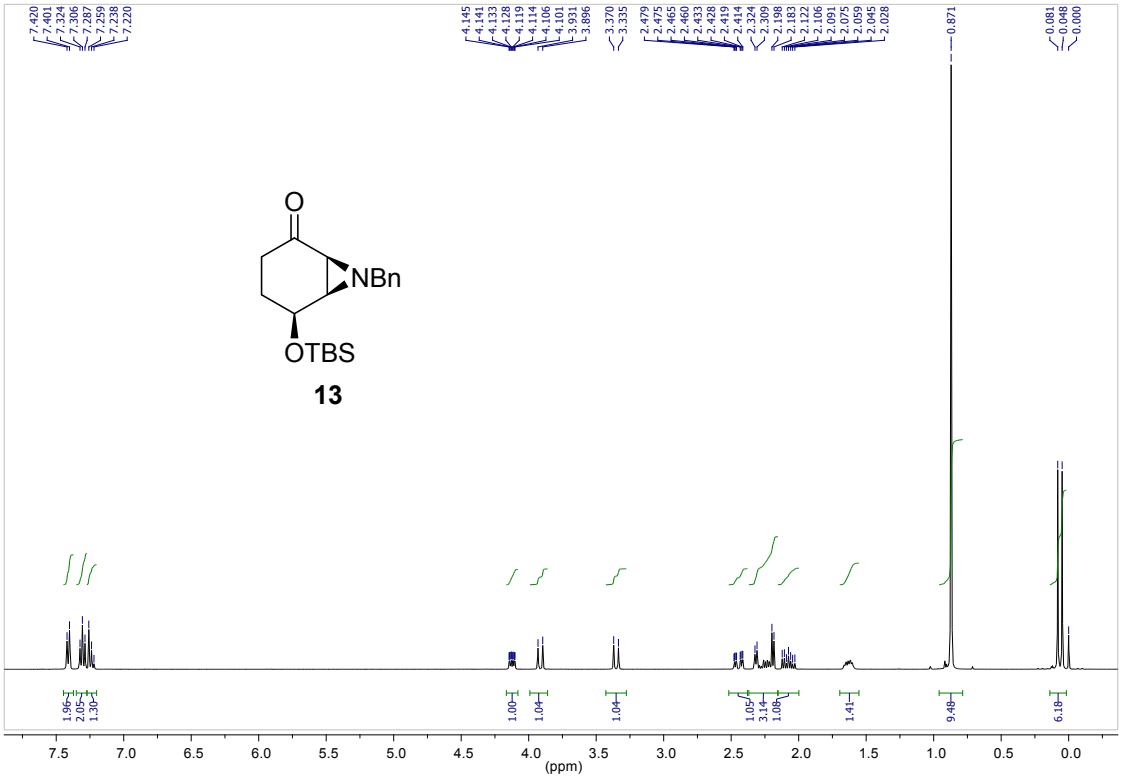
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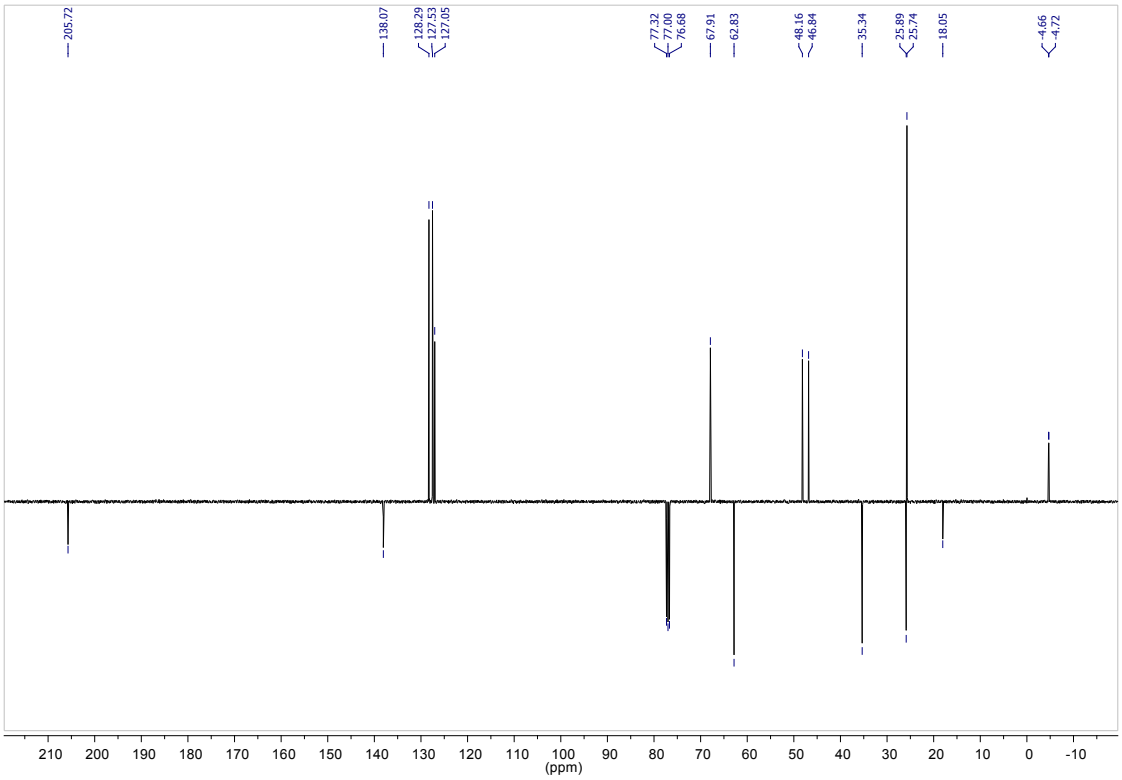
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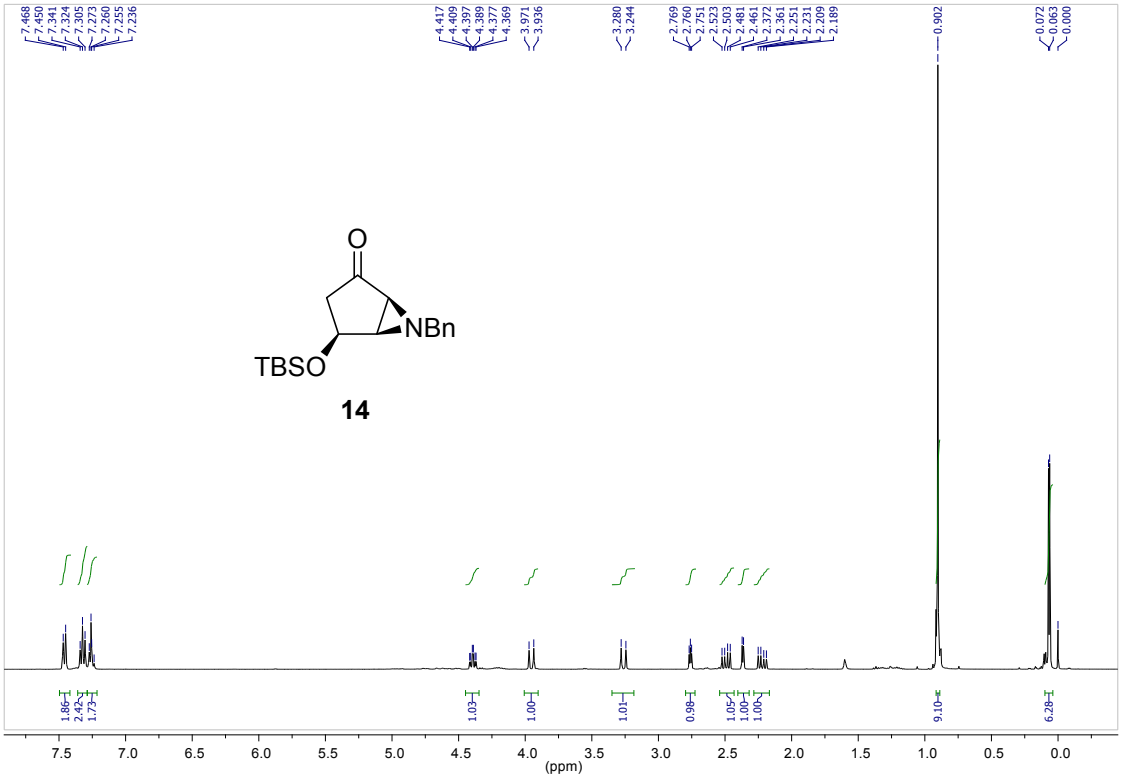
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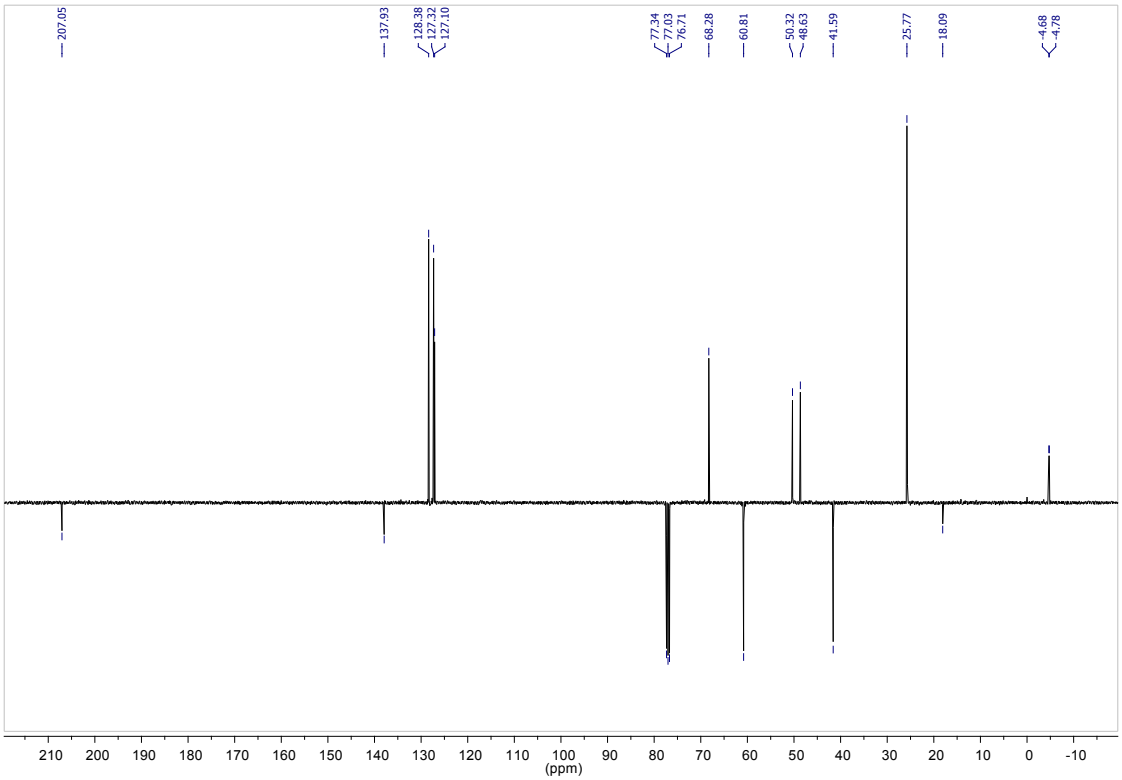
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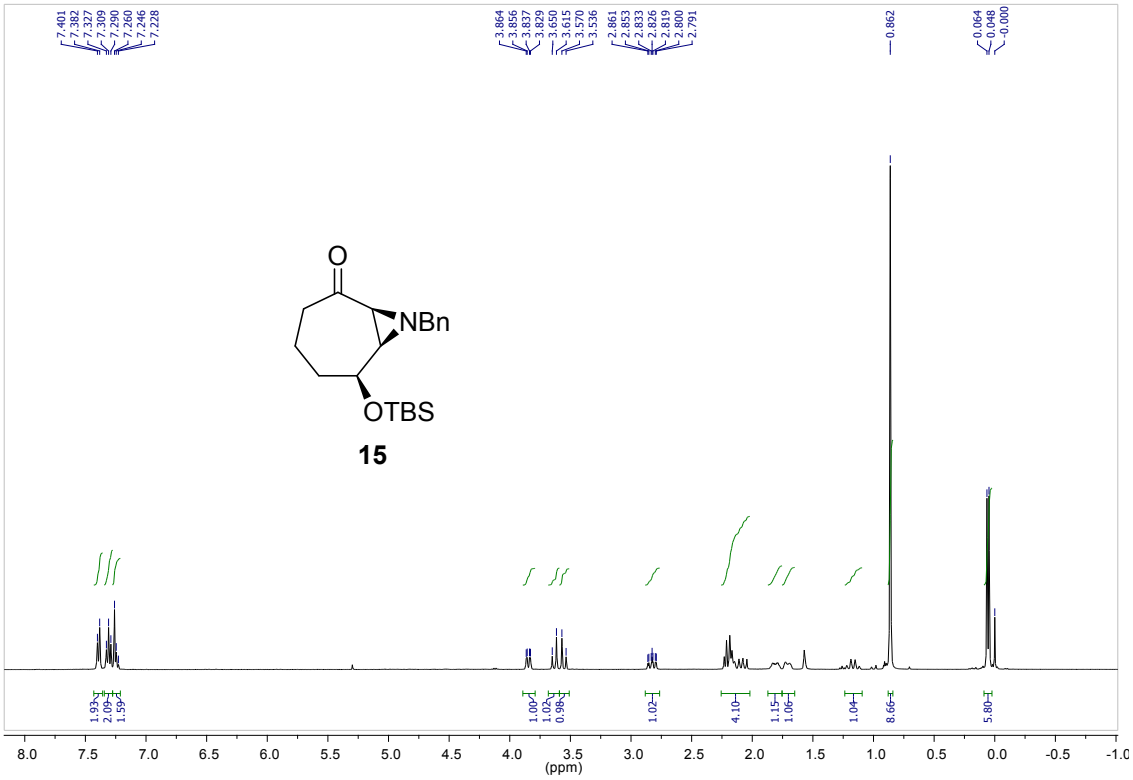
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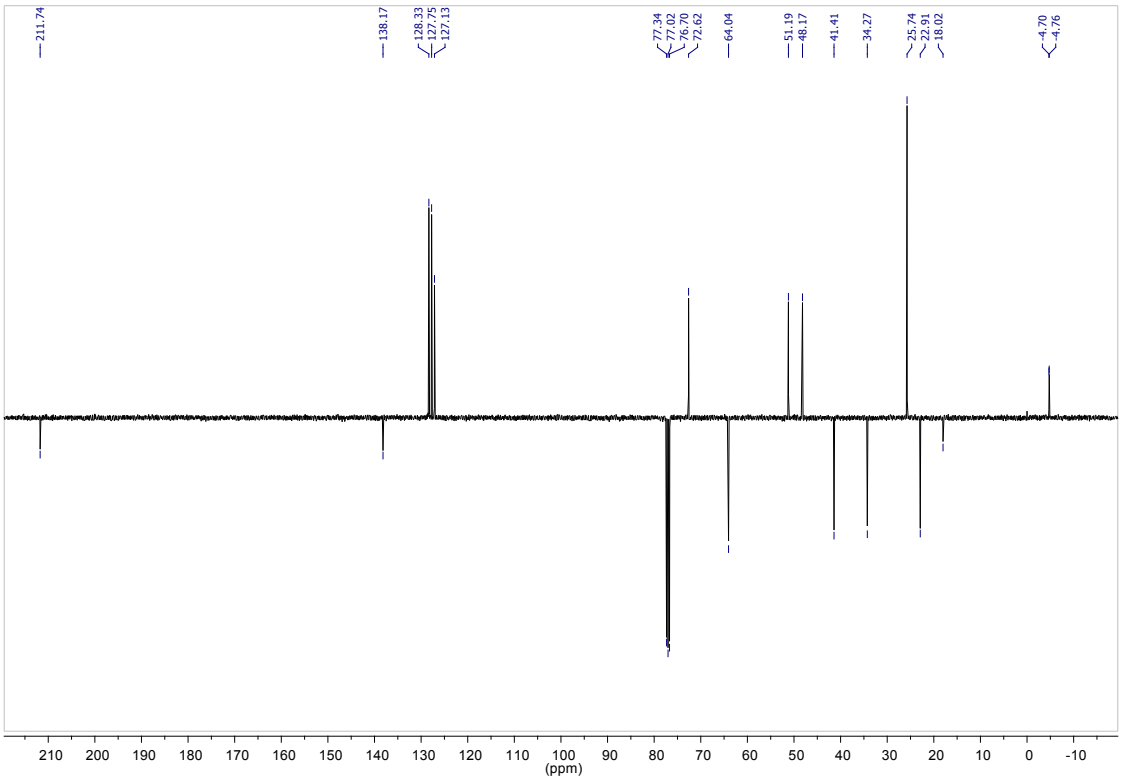
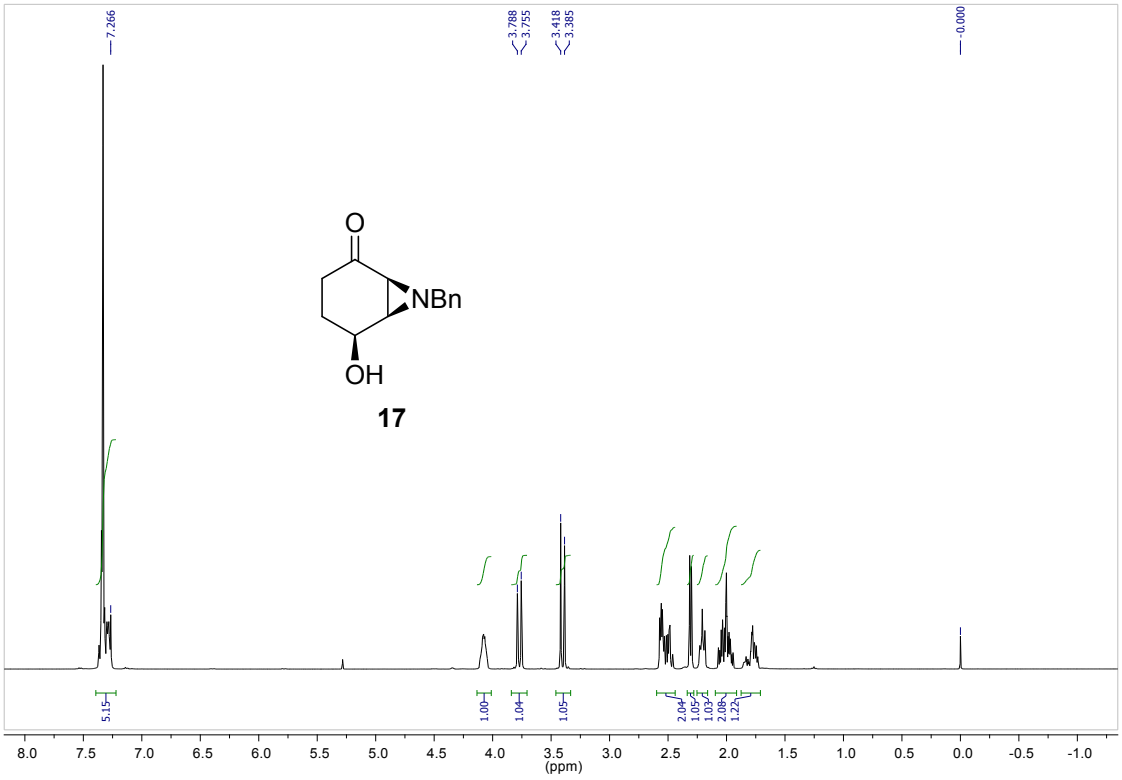
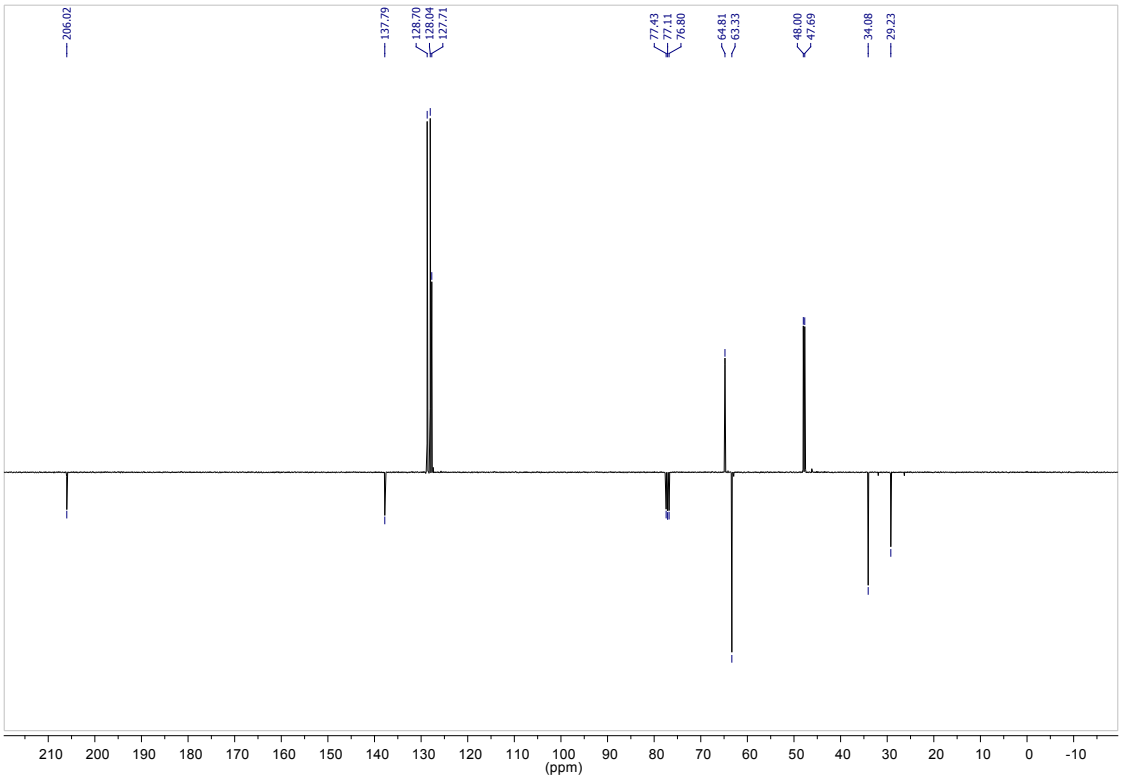
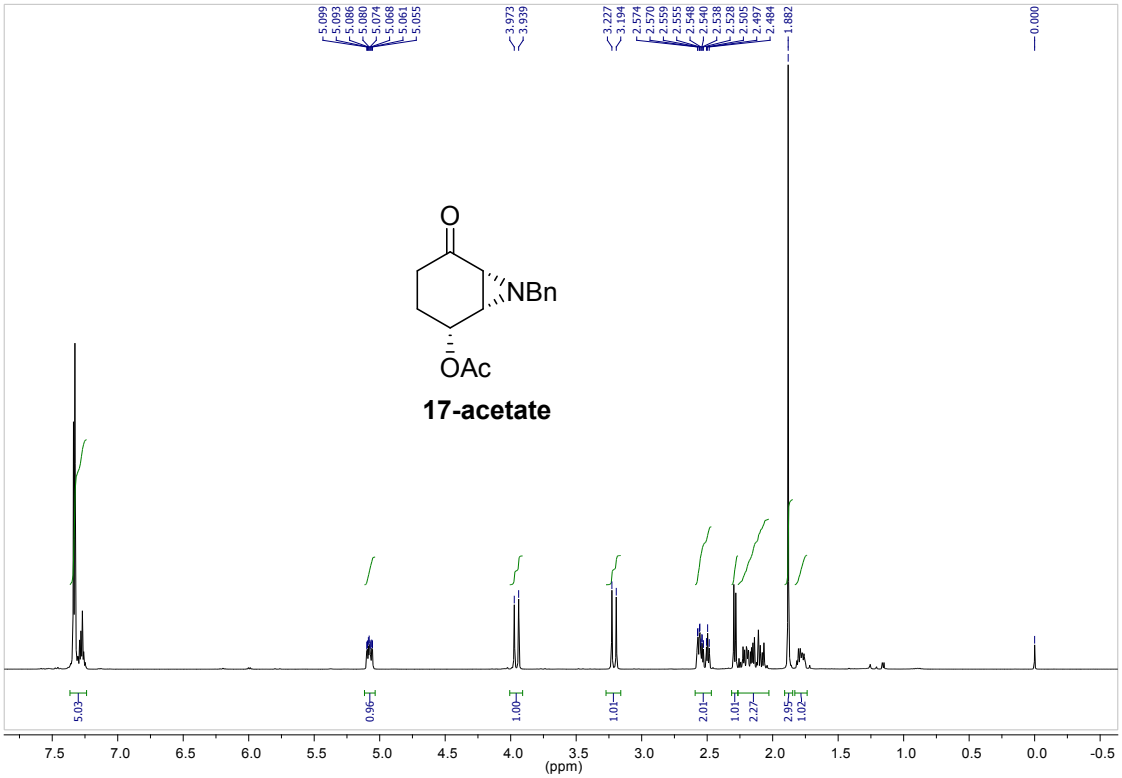
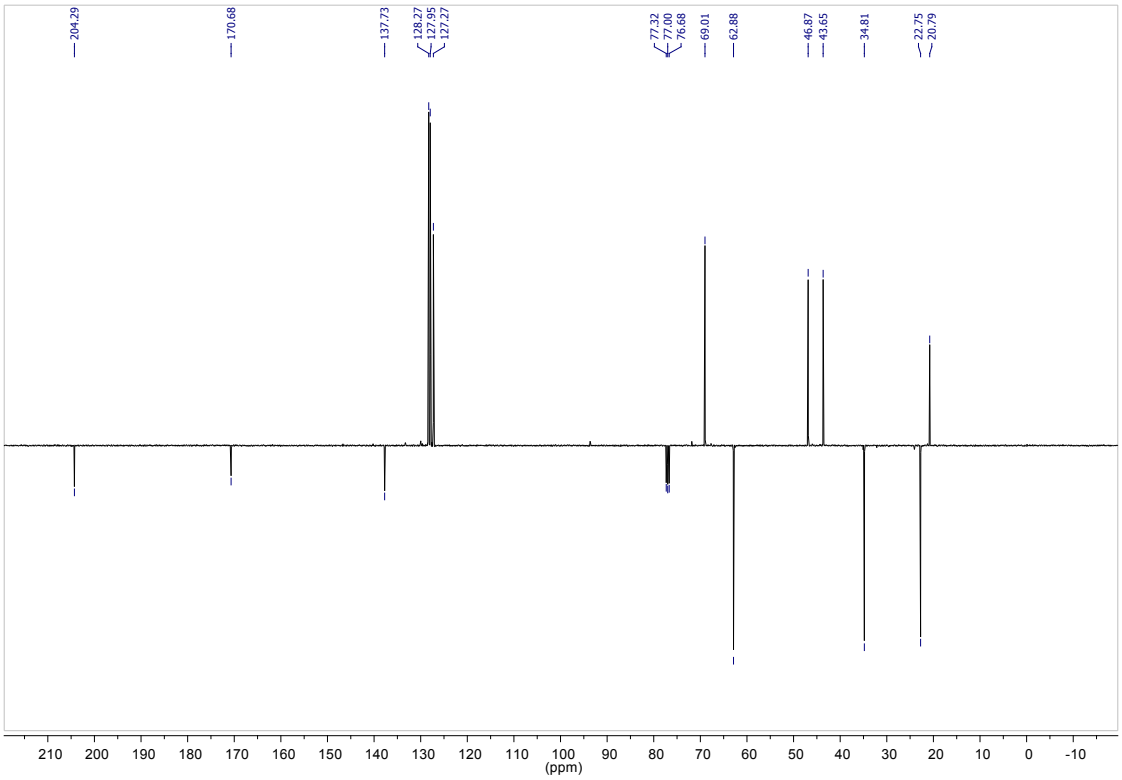

211.74
138.17
128.33
127.75
127.13
77.34
77.02
76.70
72.62
64.04
51.19
48.17
41.41
34.27
25.74
22.91
18.02
-4.70
-4.76
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)

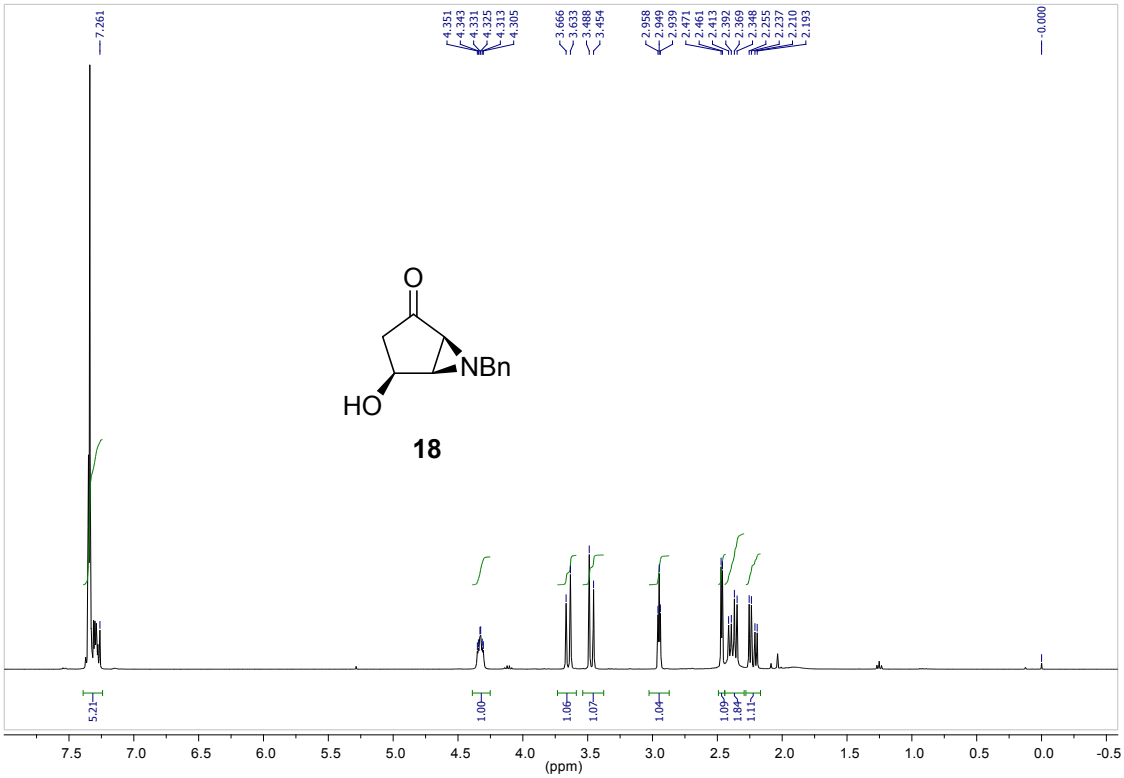

7.266
3.788
3.755
3.418
3.385
0.000
O
NBn
OH
5.15
1.00
1.04
1.05
2.04
1.05
1.03
2.08
1.22
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
(ppm)

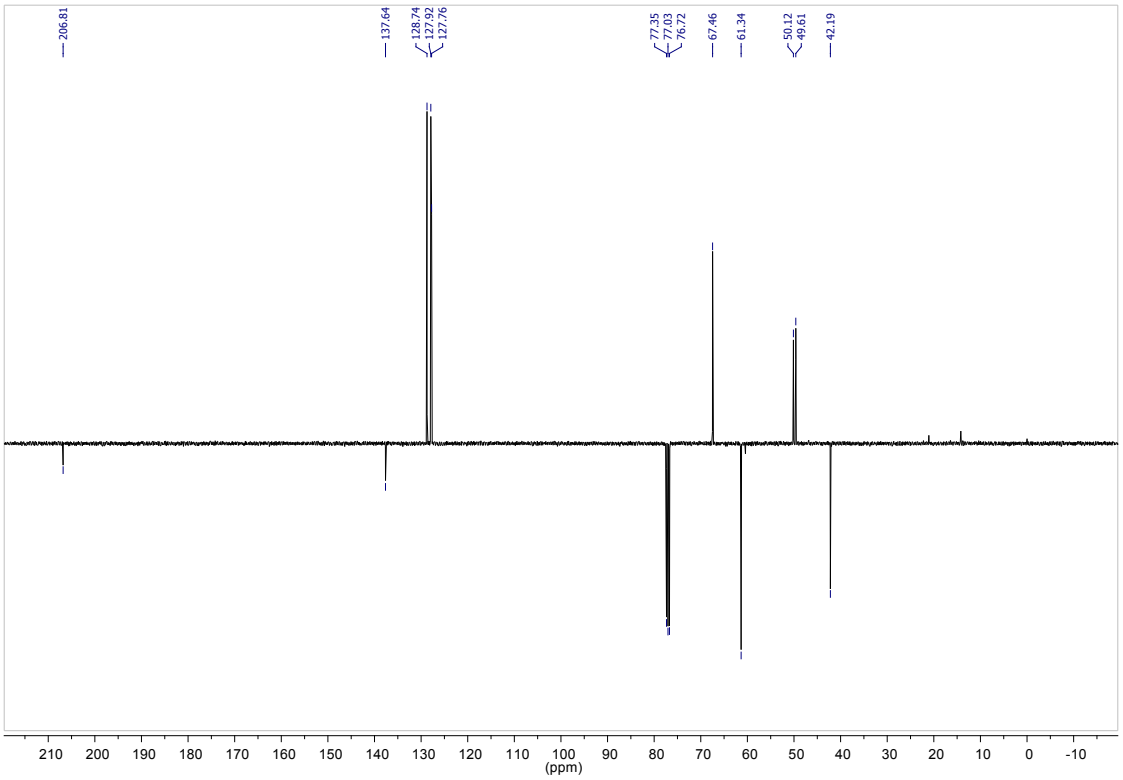
17

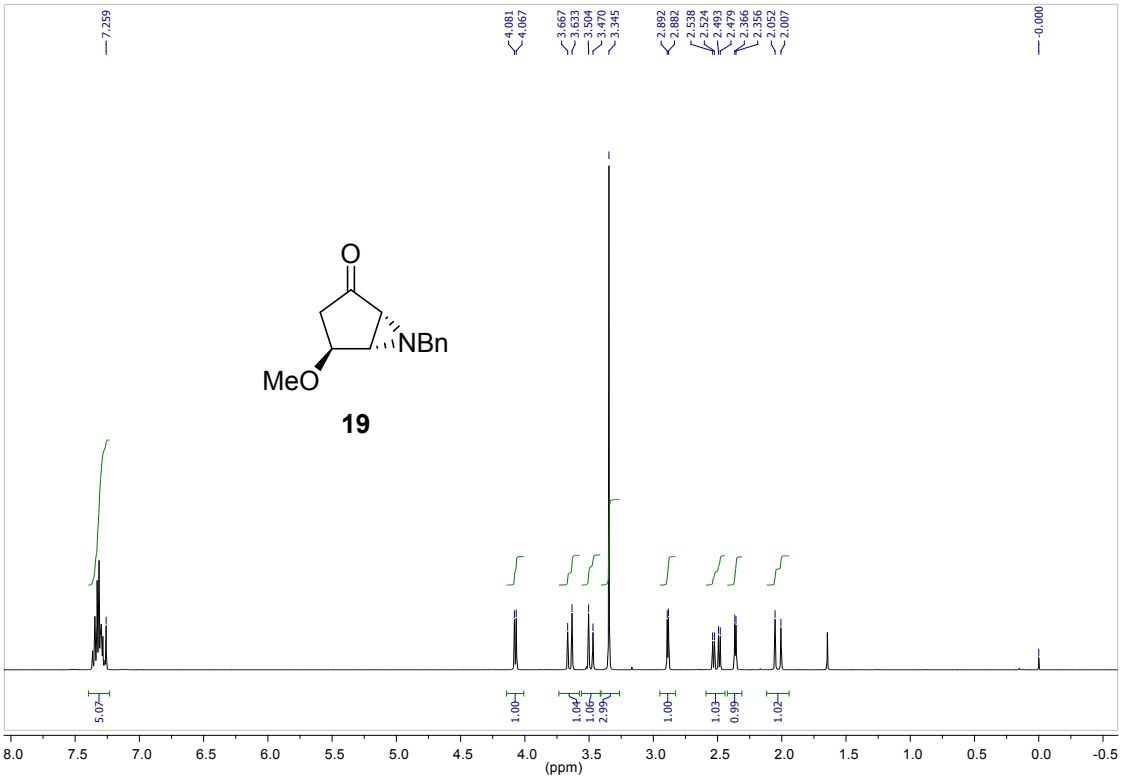

206.02
137.79
128.70
128.04
127.71
77.43
77.11
76.80
64.81
63.33
48.00
47.69
34.08
29.23
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

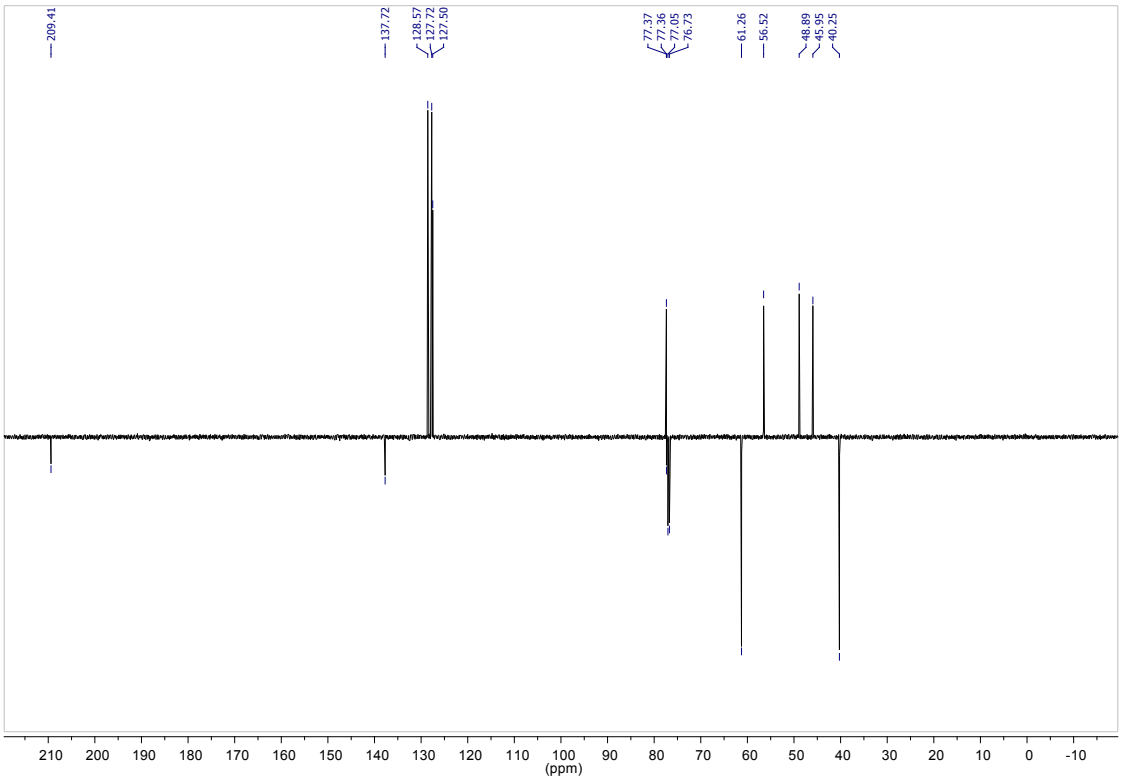

5.099
5.093
5.086
5.080
5.074
5.068
5.061
5.055
3.973
3.939
3.227
3.194
2.574
2.570
2.559
2.555
2.548
2.540
2.538
2.528
2.505
2.497
2.484
1.882
0.000
O
NBn
OAc
17-acetate
5.03
0.96
1.00
1.01
2.01
1.01
2.27
2.95
1.02
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

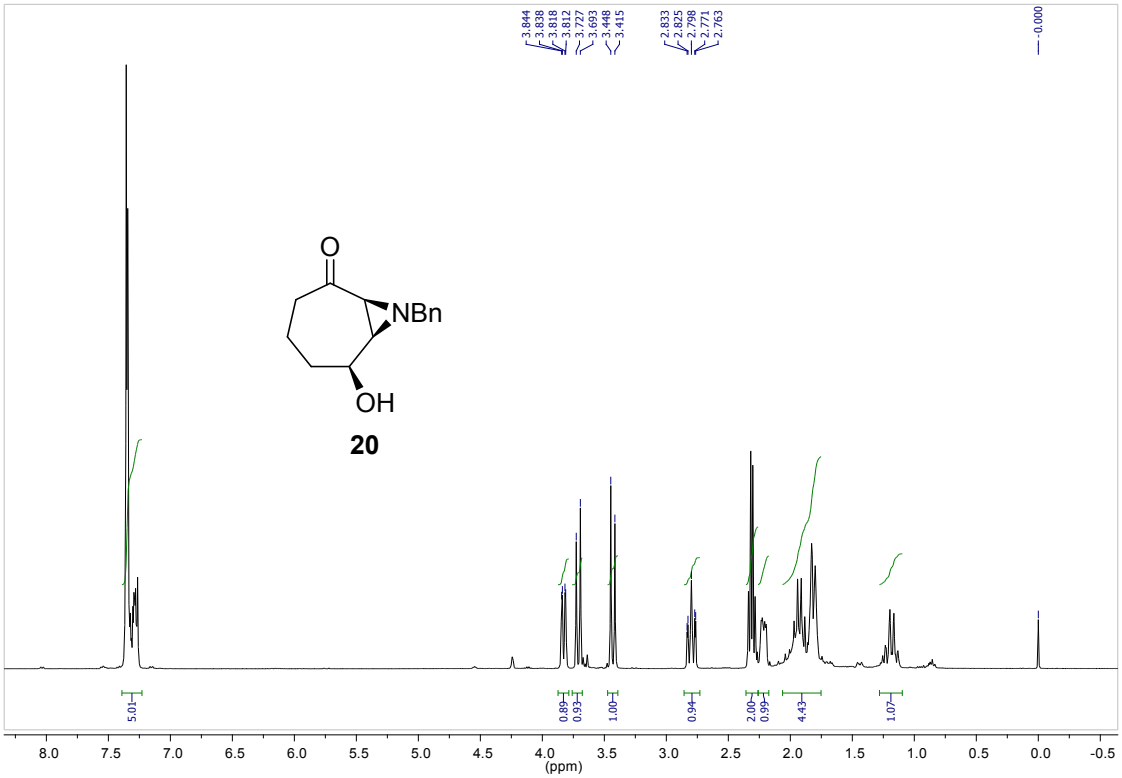

204.29
170.68
137.73
128.27
127.95
127.27
77.32
77.00
76.68
69.01
62.88
46.87
43.65
34.81
22.75
20.79
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

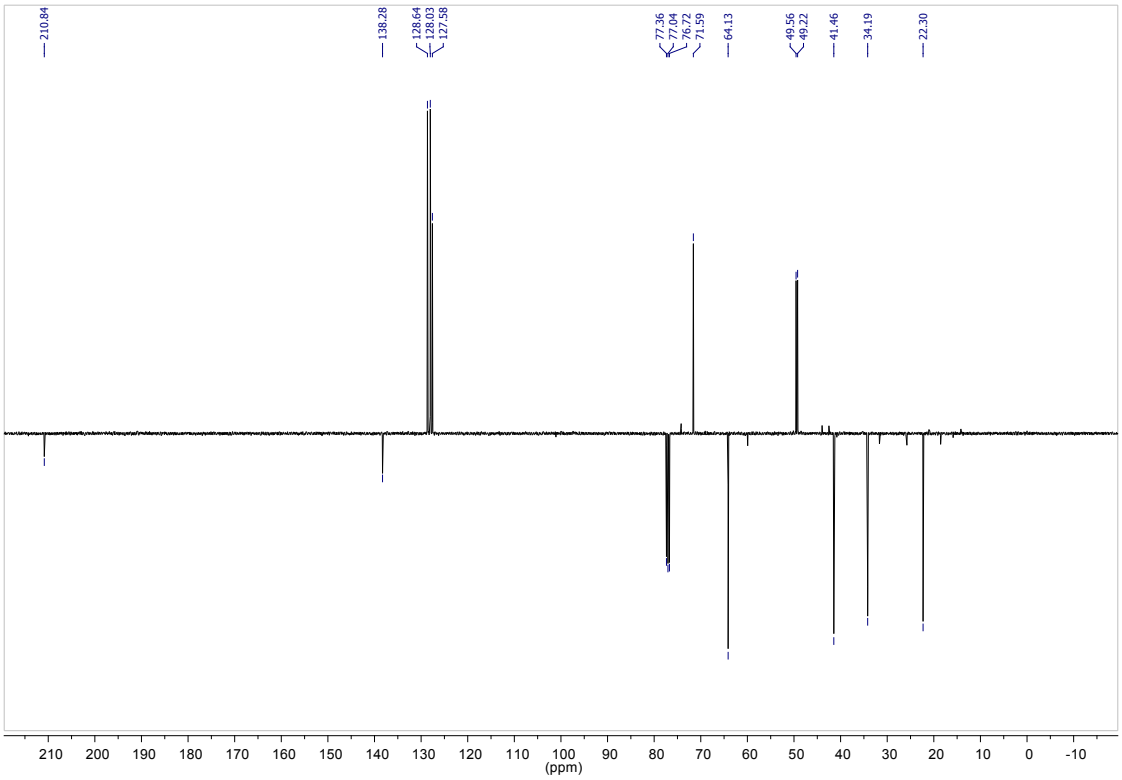

7.261
4.351
4.343
4.331
4.325
4.313
4.305
3.666
3.633
3.488
3.454
2.958
2.949
2.939
2.471
2.461
2.413
2.392
2.369
2.348
2.255
2.237
2.210
2.193
-0.000
O
NBn
HO
18
5.21
1.00
1.06
1.07
1.04
1.09
1.84
1.11
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

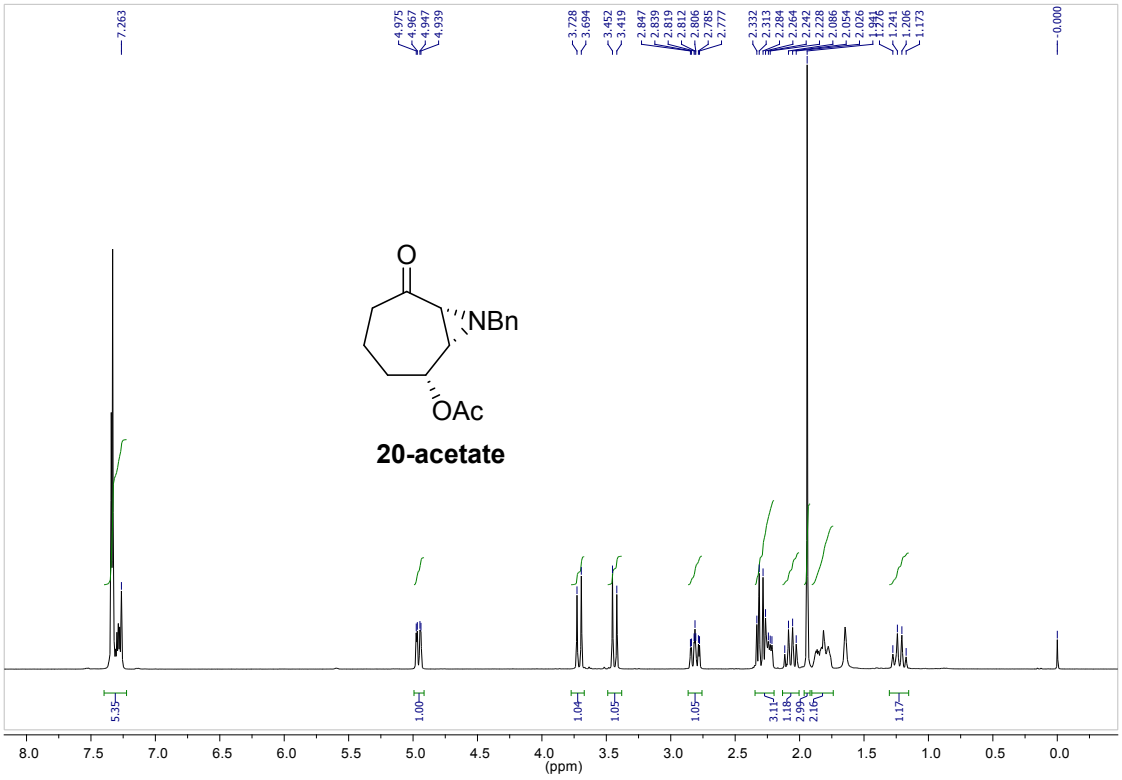

206.81
137.64
128.74
127.92
127.76
77.35
77.03
76.72
67.46
61.34
50.12
49.61
42.19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

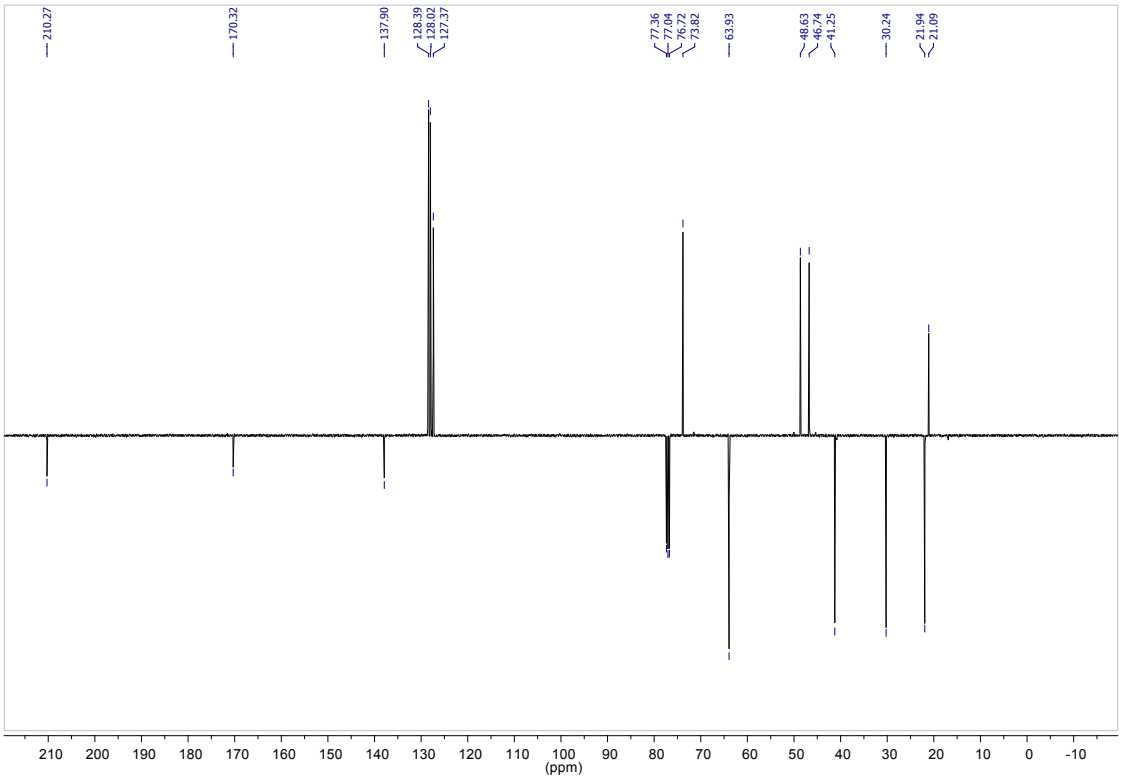

7.259
4.081
4.067
3.667
3.633
3.504
3.470
3.345
2.892
2.882
2.538
2.524
2.493
2.479
2.366
2.356
2.052
2.007
0.000
O
NBn
MeO
19
5.07
1.00
1.04
1.06
2.99
1.00
1.03
0.99
1.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

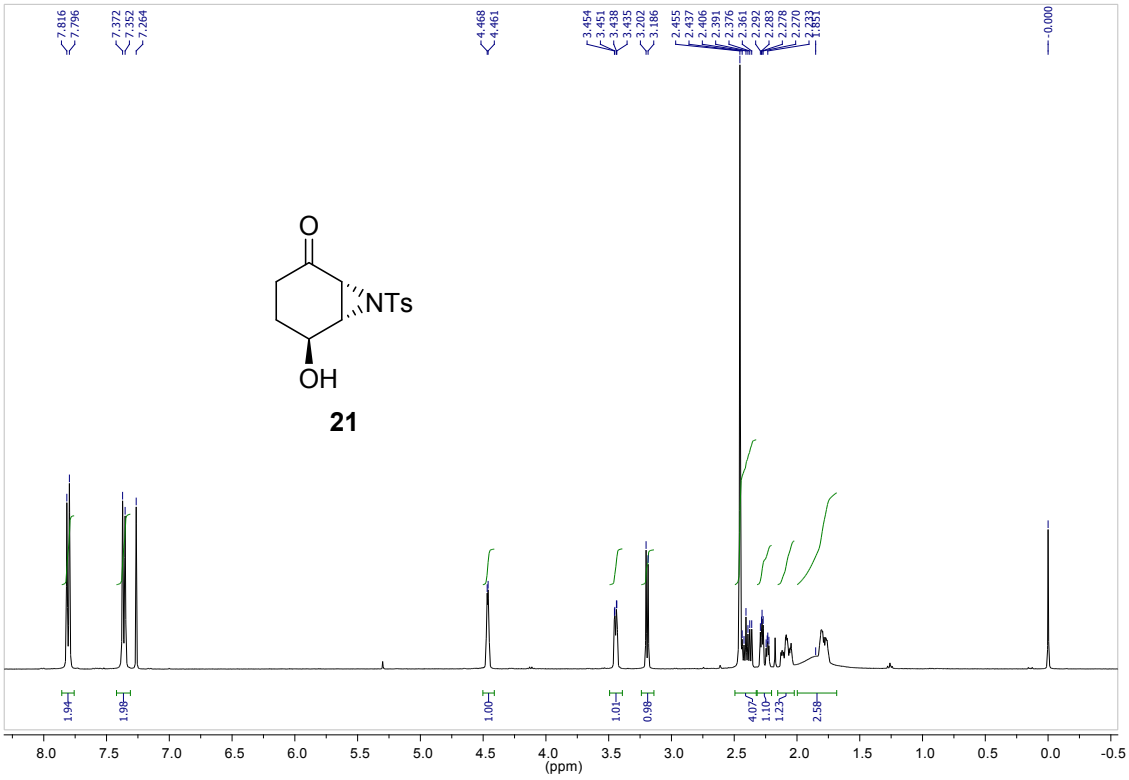

209.41
137.72
128.57
127.72
127.50
77.37
77.36
77.05
76.73
61.26
56.52
48.89
45.95
40.25
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)

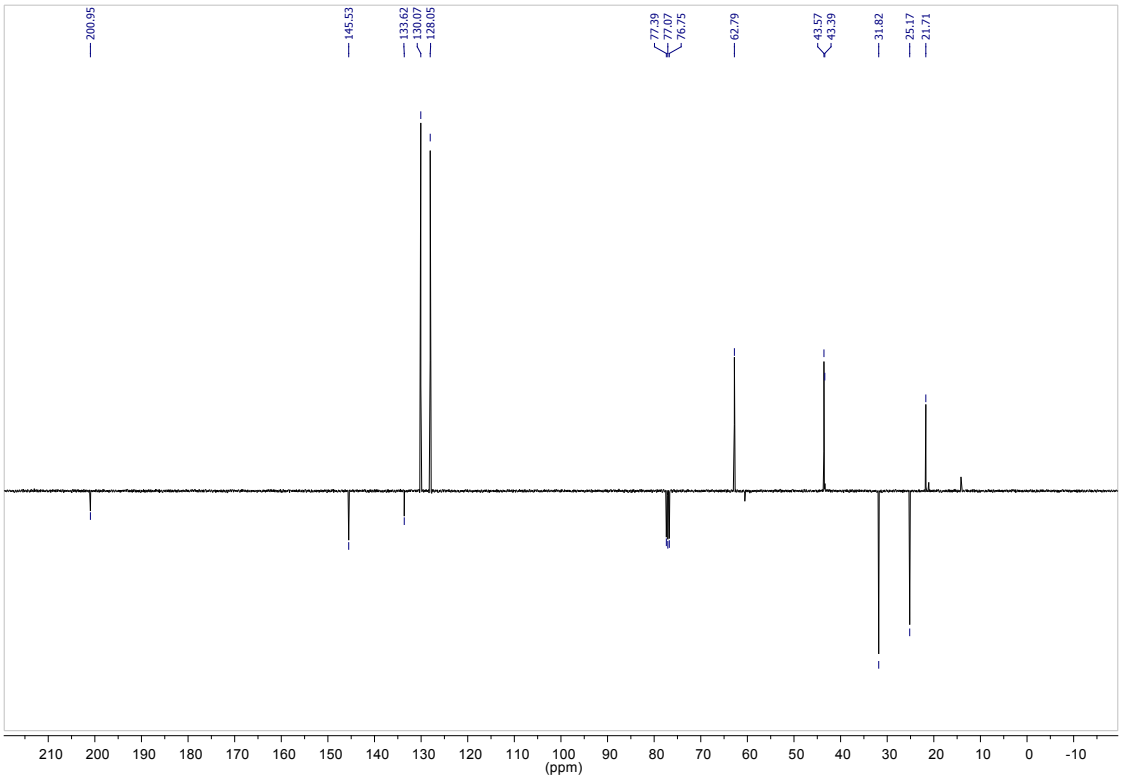

3.844
3.838
3.818
3.812
3.727
3.693
3.448
3.415
2.833
2.825
2.798
2.771
2.763
-0.000
O
NBn
OH
20
5.01
0.89
0.93
1.00
0.94
2.00
0.99
4.43
1.07
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

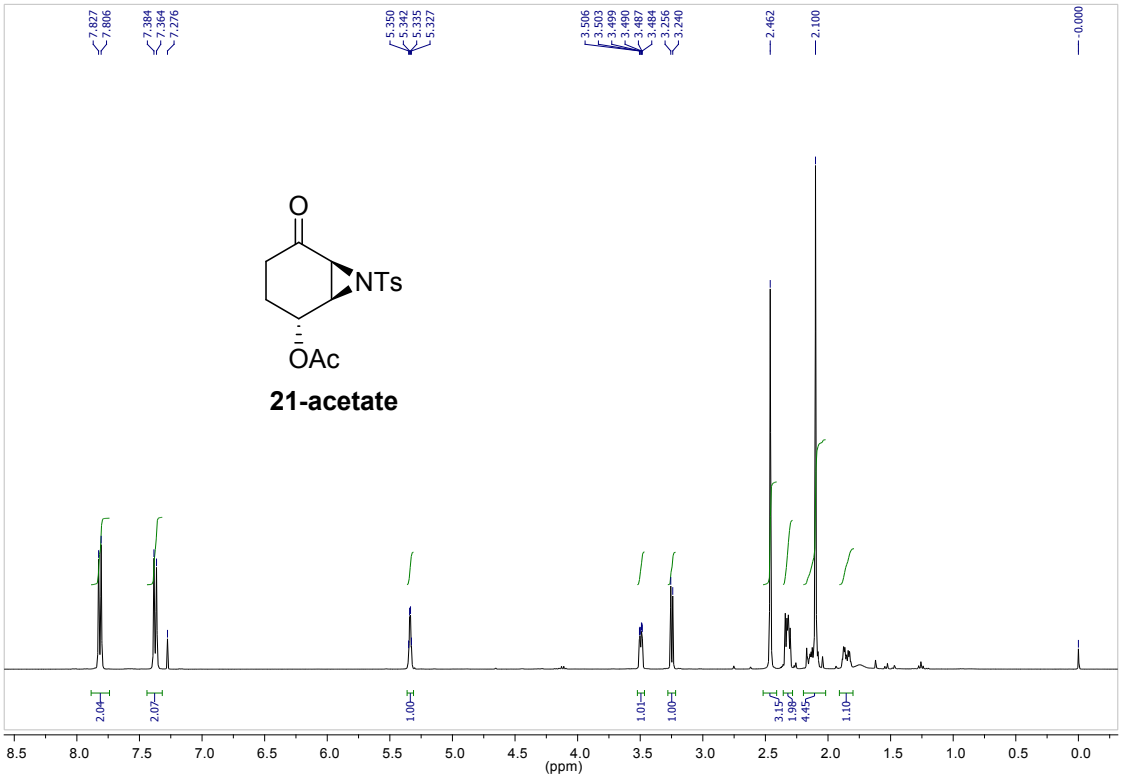

210.84
138.28
128.64
128.03
127.58
77.36
77.04
76.72
71.59
64.13
49.56
49.22
41.46
34.19
22.30
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

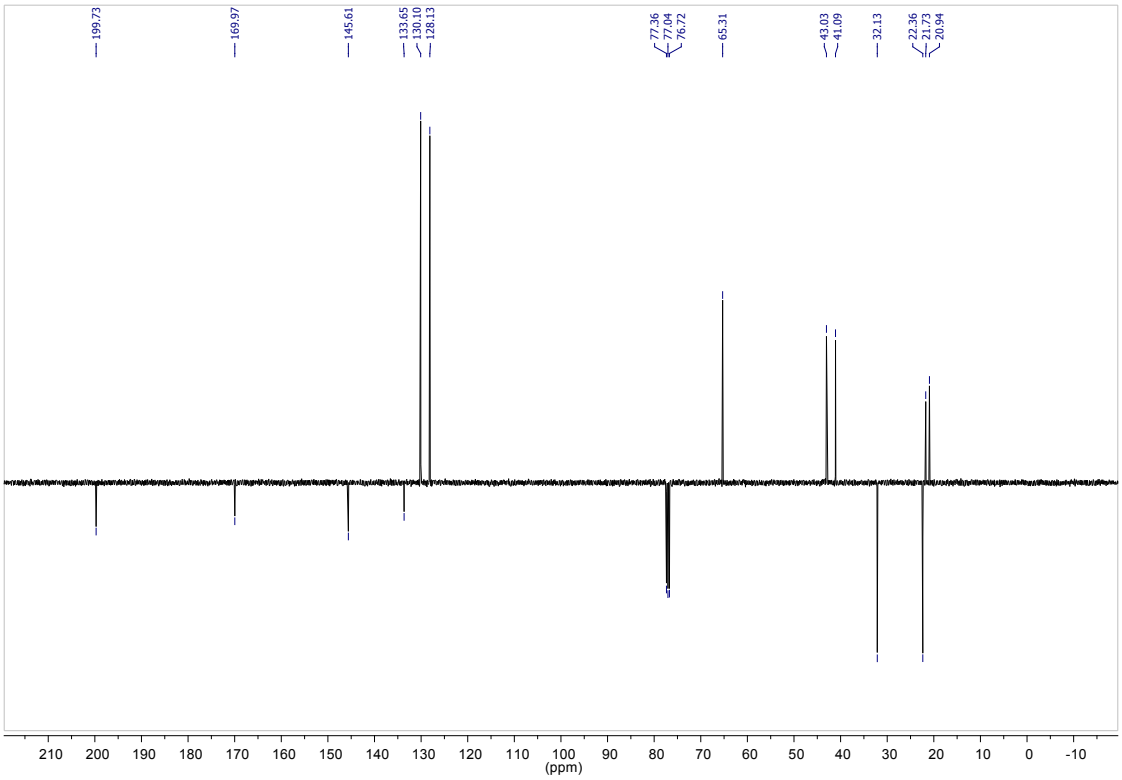

O
NBn
OAc
20-acetate
(ppm)

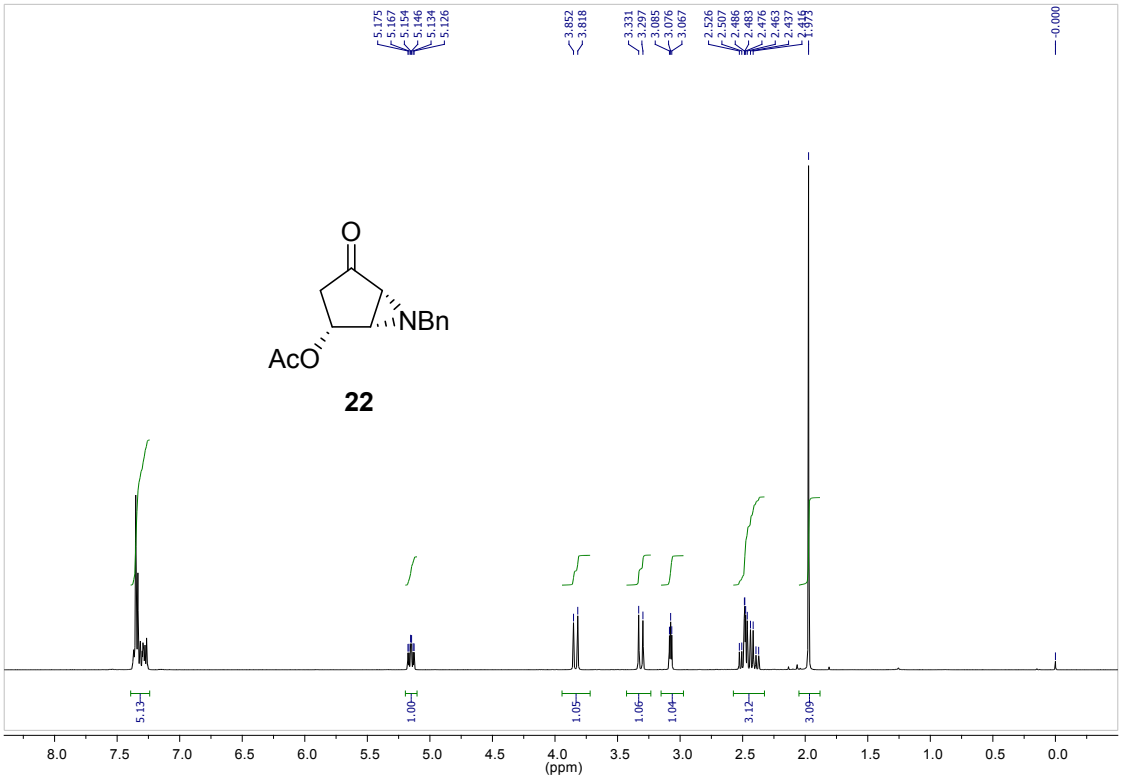

(ppm)


7.816
7.796
7.372
7.352
7.264
4.468
4.461
3.454
3.451
3.438
3.435
3.202
3.186
2.455
2.437
2.406
2.391
2.376
2.361
2.292
2.283
2.278
2.270
1.851
-0.000
O
NTs
OH
21
1.94
1.98
1.00
1.01
0.98
4.07
1.10
1.23
2.58
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

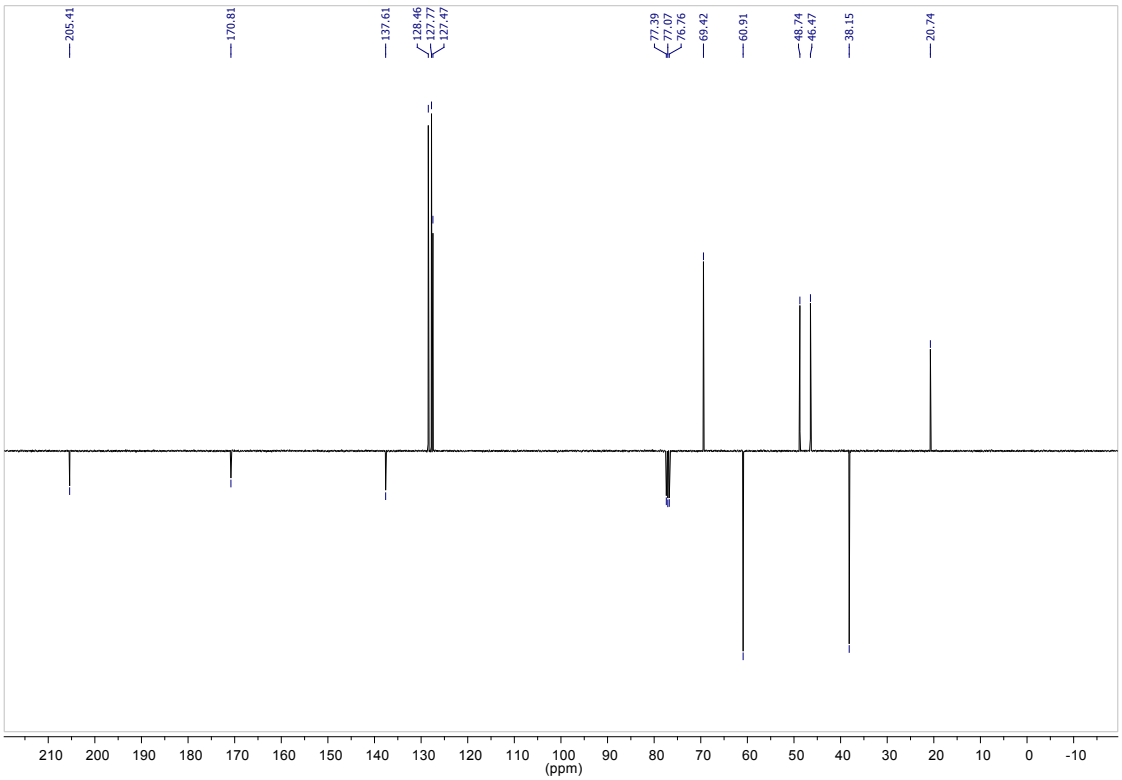

200.95
145.53
133.62
130.07
128.05
77.39
77.07
76.75
62.79
43.57
43.39
31.82
25.17
21.71
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)

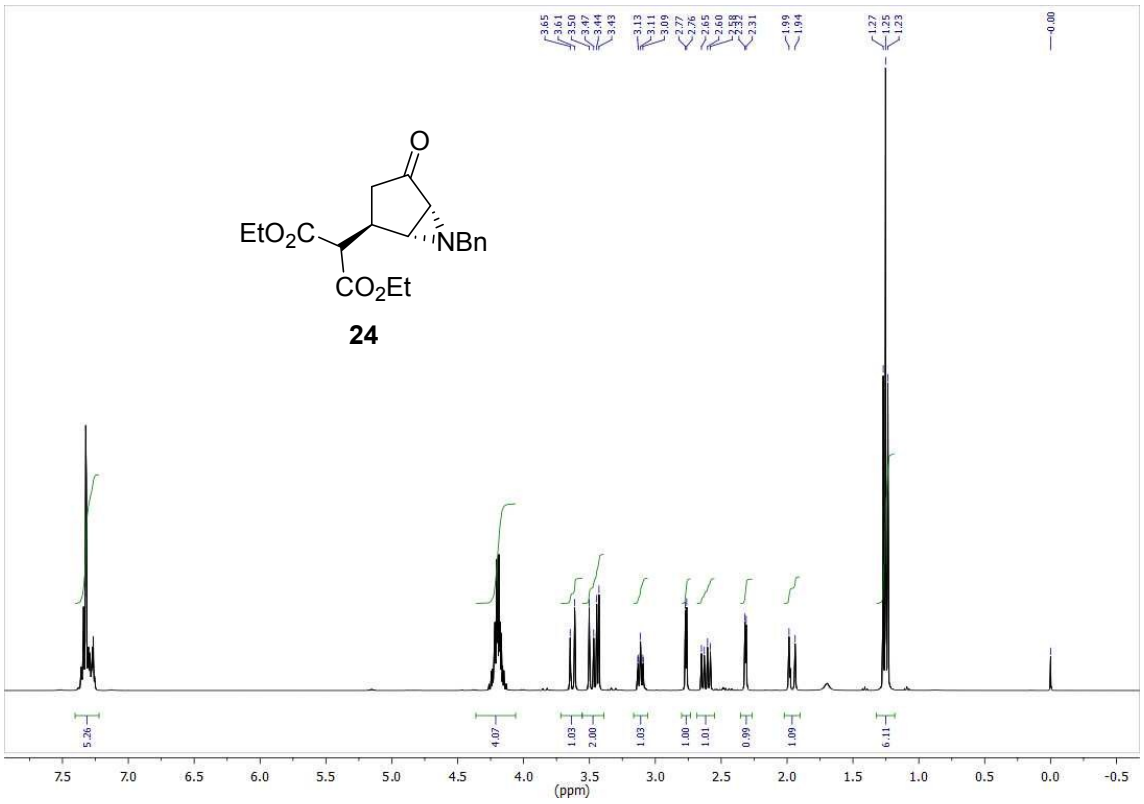

7.827
7.806
7.384
7.364
7.276
5.350
5.342
5.335
5.327
3.506
3.503
3.499
3.490
3.487
3.484
3.256
3.240
2.462
2.100
0.000
O
NTs
OAc
21-acetate
2.04
2.07
1.00
1.01
1.00
3.15
1.98
4.45
1.10
(ppm)


199.73
169.97
145.61
133.65
130.10
128.13
77.36
77.04
76.72
65.31
43.03
41.09
32.13
22.36
21.73
20.94
(ppm)

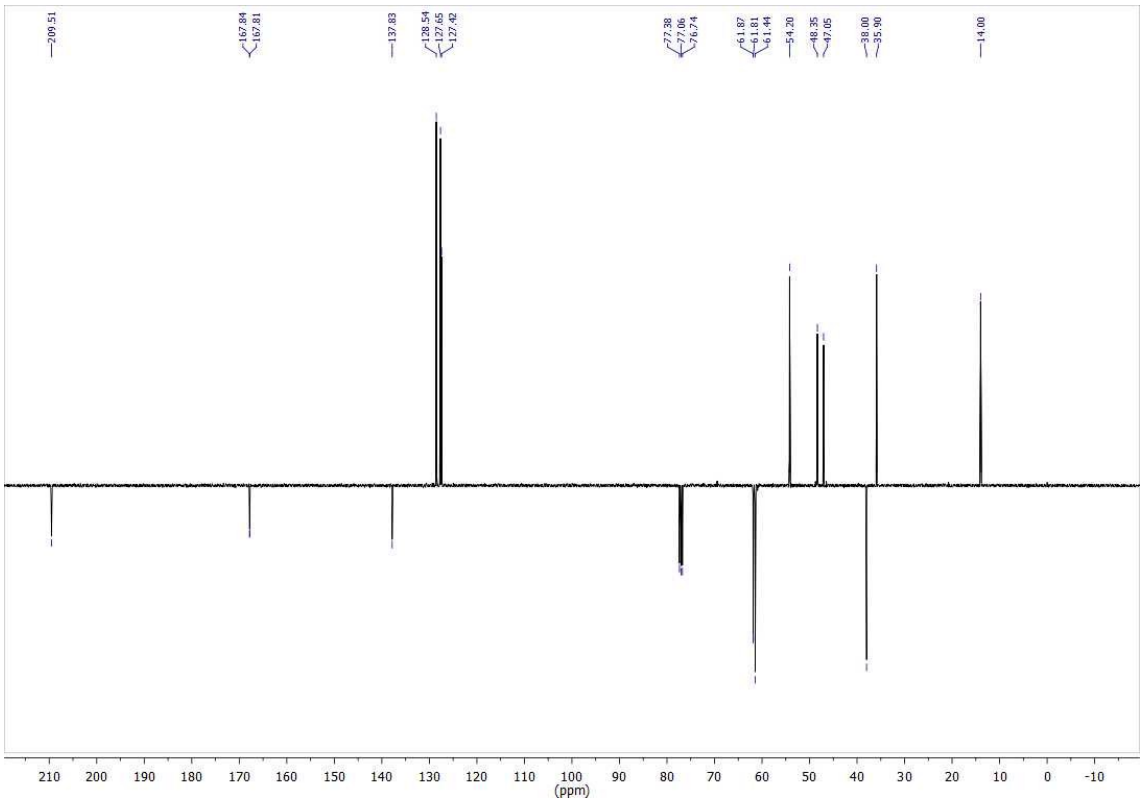

5.175
5.167
5.154
5.146
5.134
5.126
3.852
3.818
3.331
3.297
3.085
3.076
3.067
2.526
2.507
2.486
2.483
2.476
2.463
2.437
2.416
1.973
-0.000
O
NBn
AcO
5.13
1.00
1.05
1.06
1.04
3.12
3.09
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

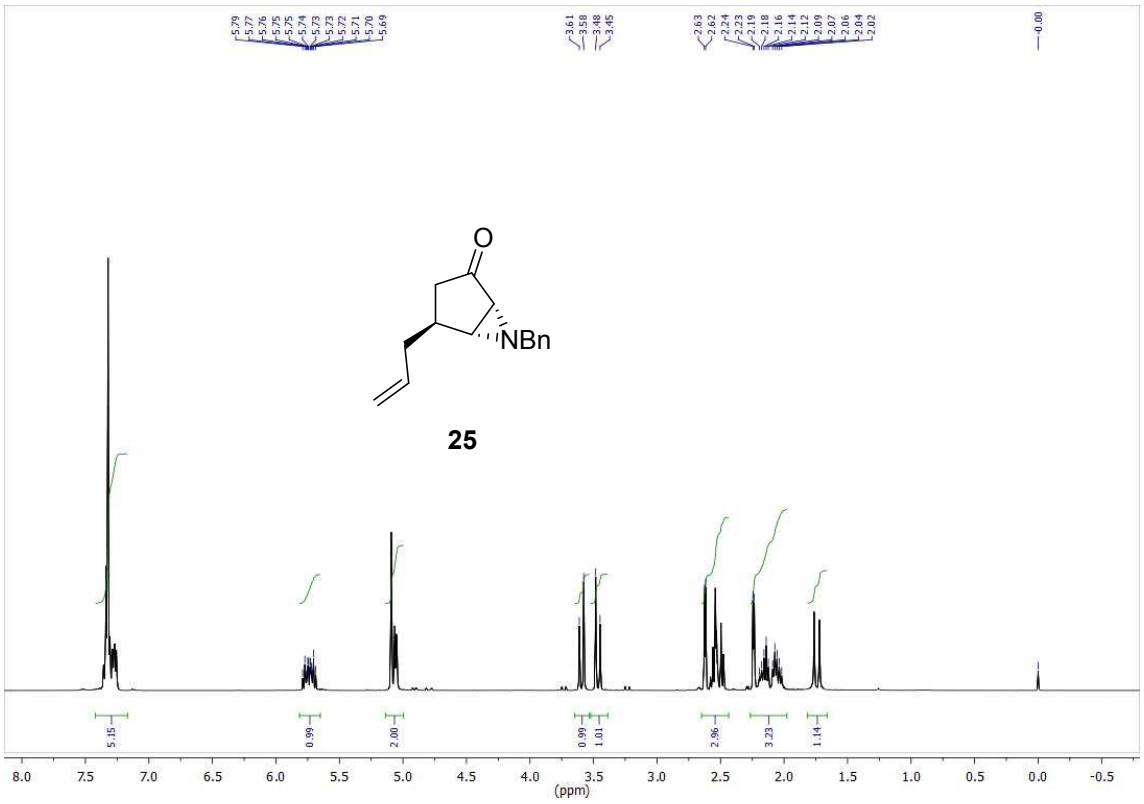
22


205.41
170.81
137.61
128.46
127.77
127.47
77.39
77.07
76.76
69.42
60.91
48.74
46.47
38.15
20.74
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
(ppm)

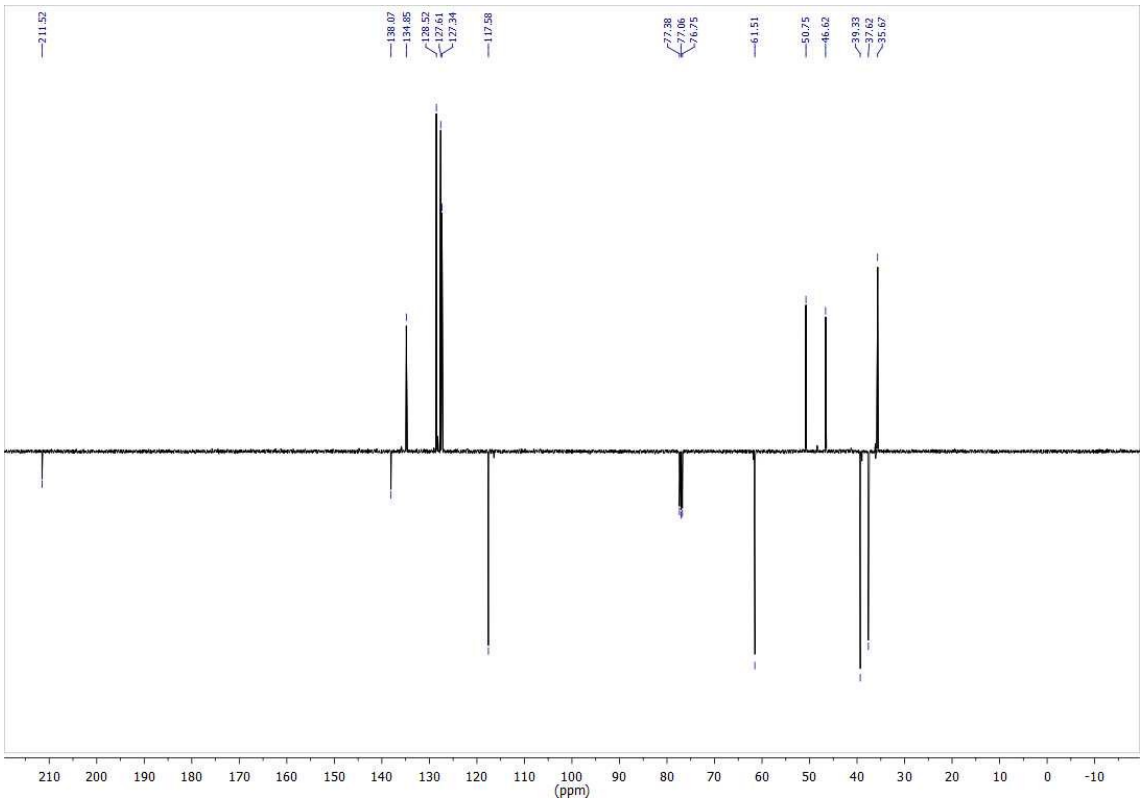


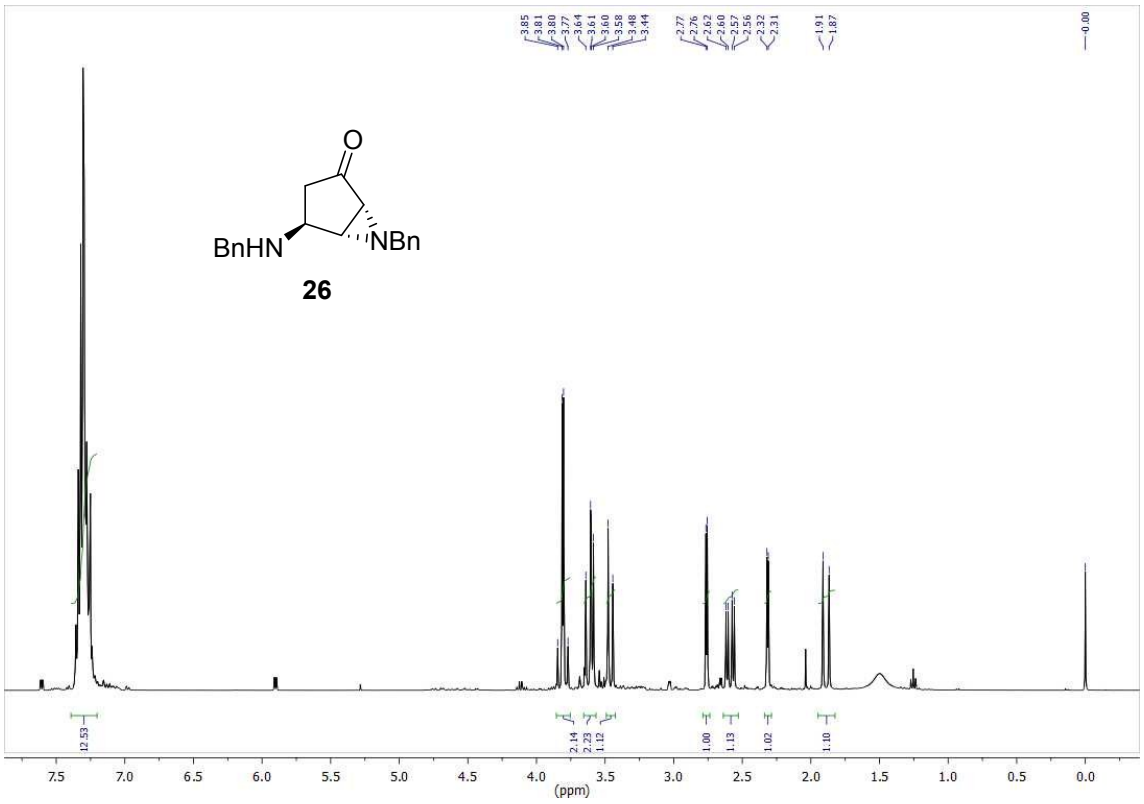
24

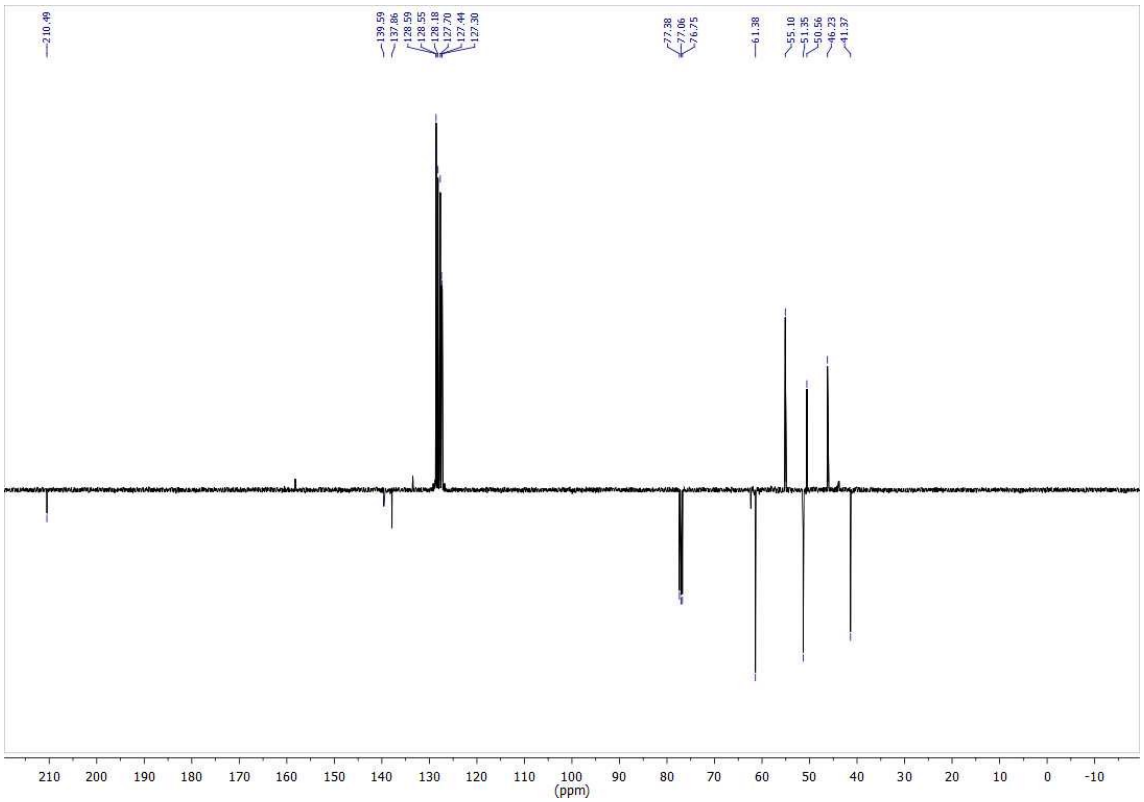


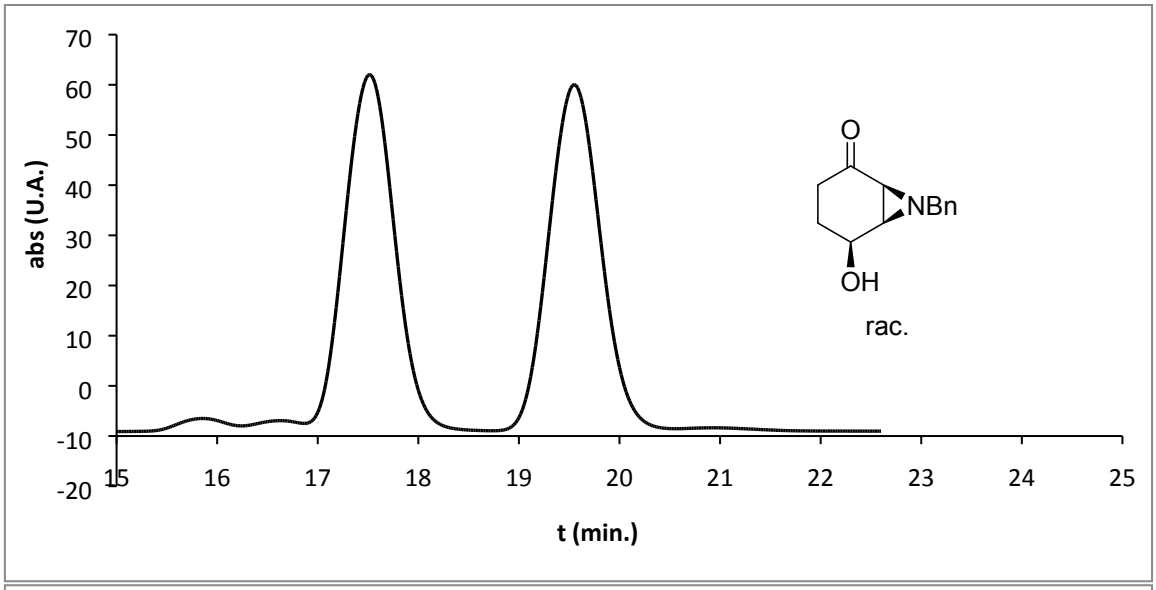


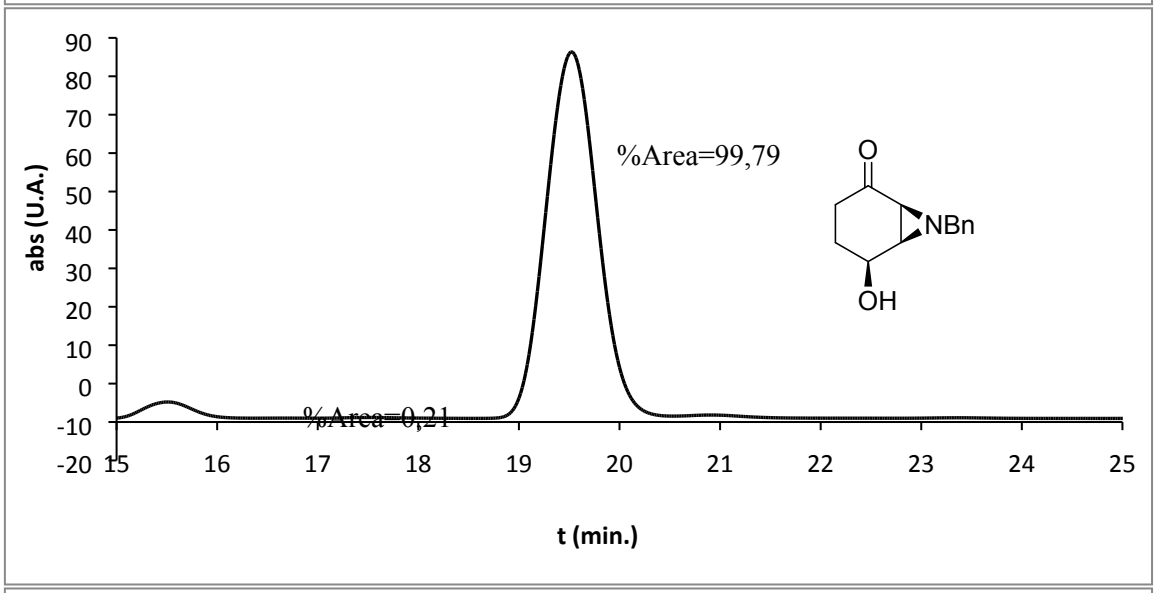
25

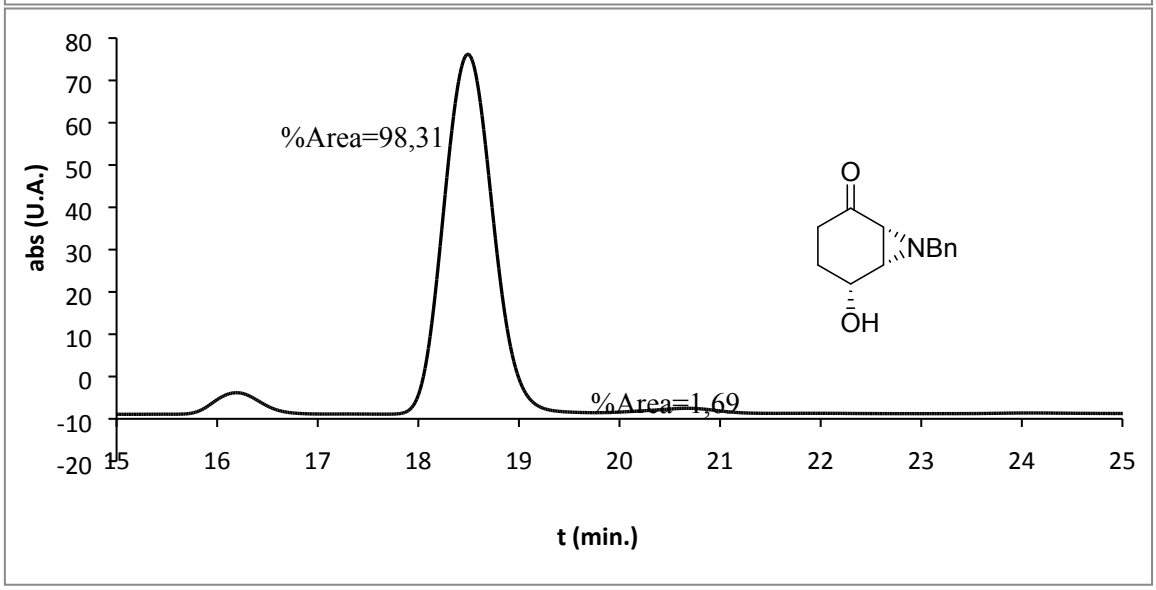



O
BnHN
NBn
26
(ppm)

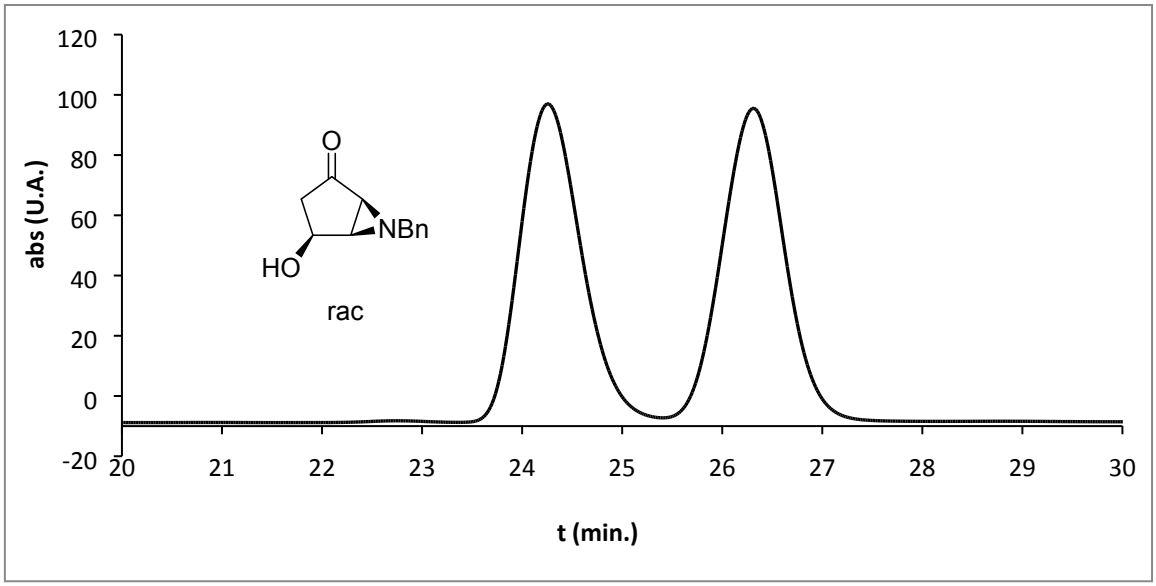

(ppm)

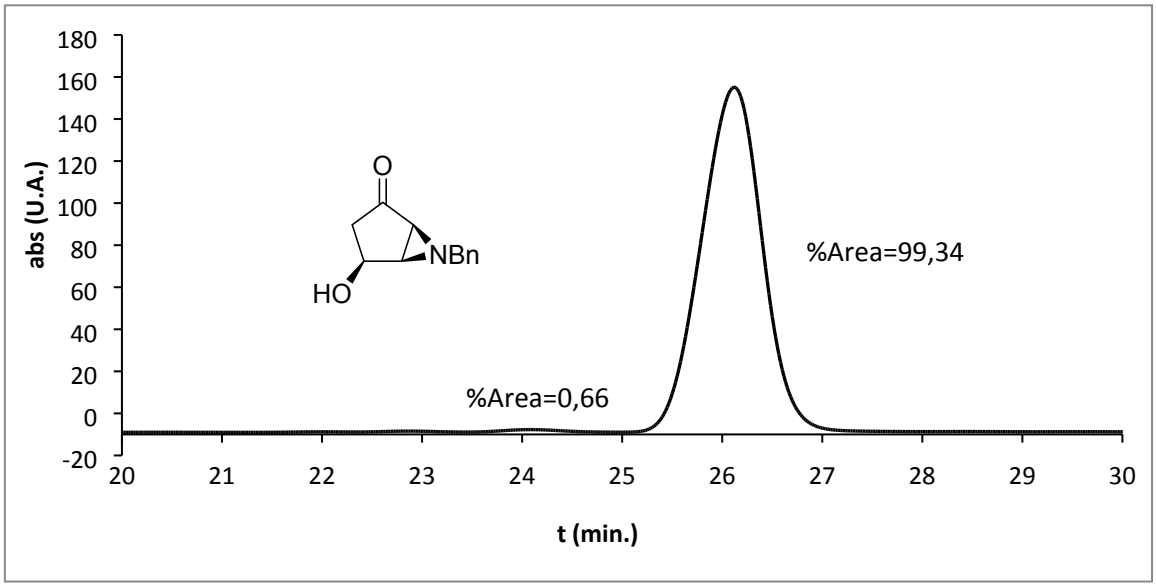




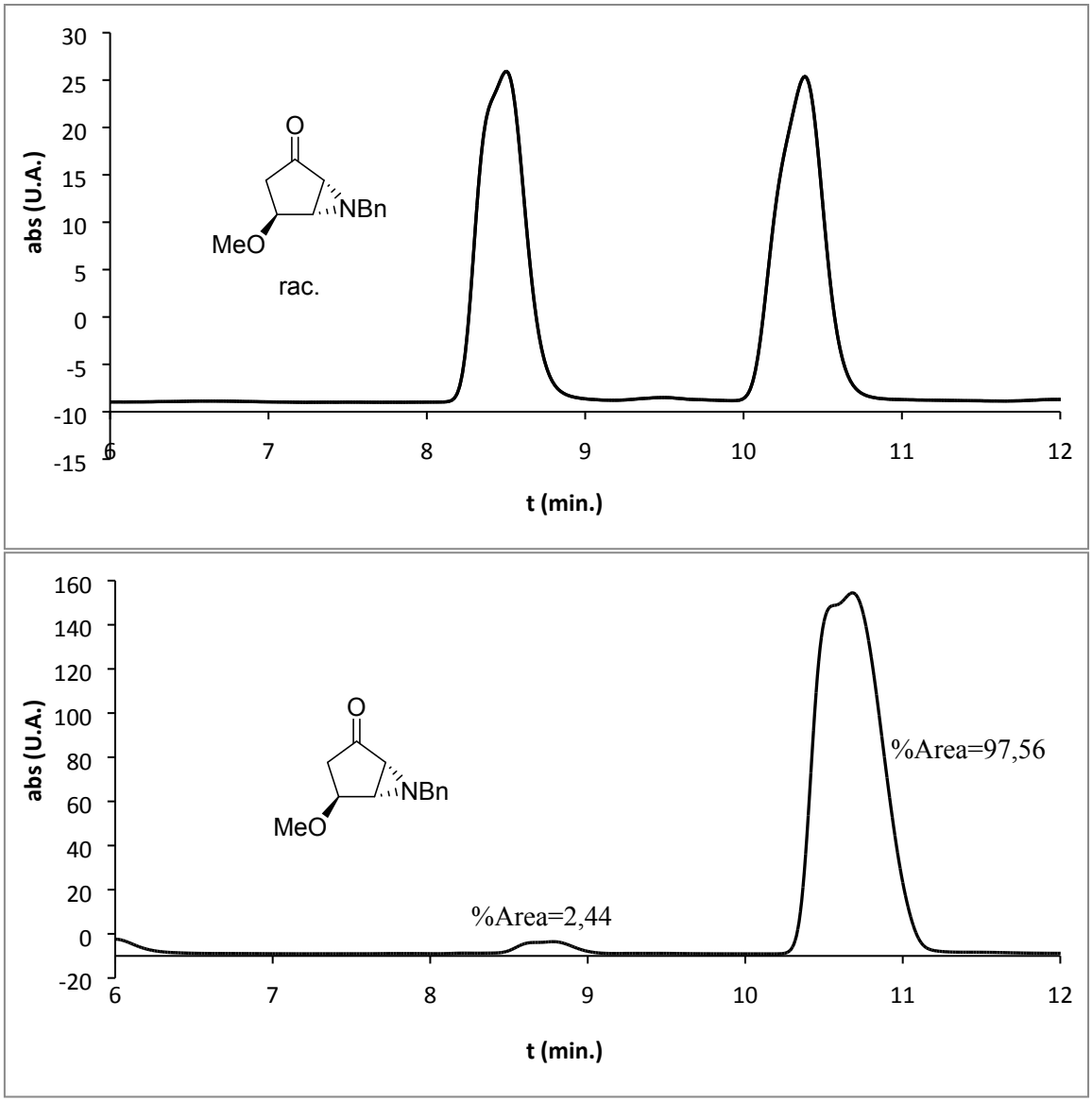


Elution conditions: AD-H; 95:5 hexane:isopropanol; 1.0ml.min^{-1}; 237nm.

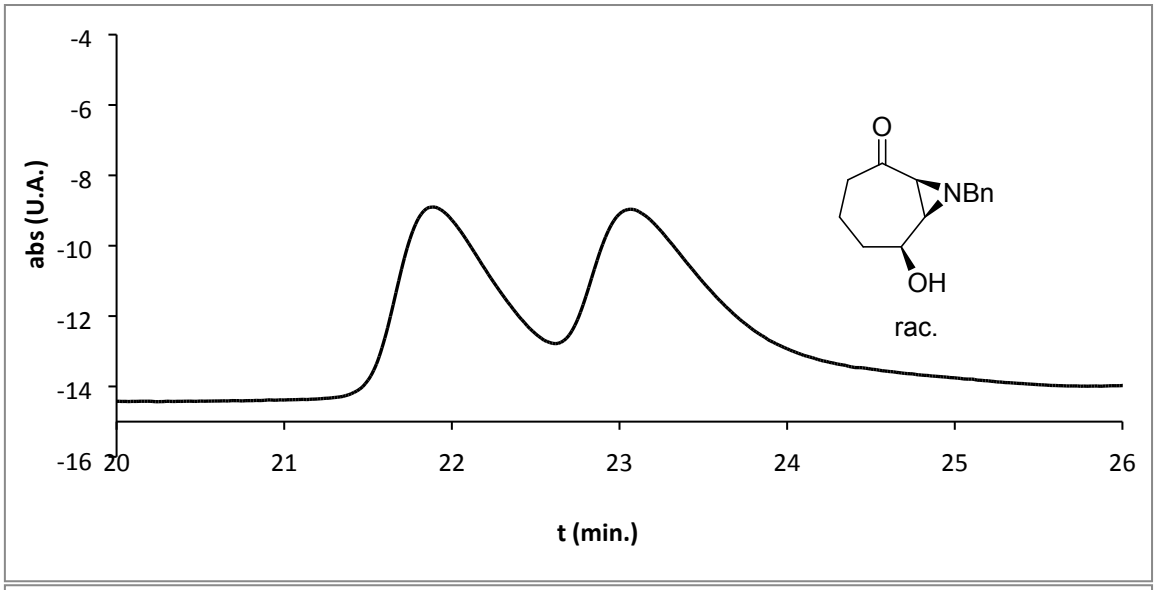


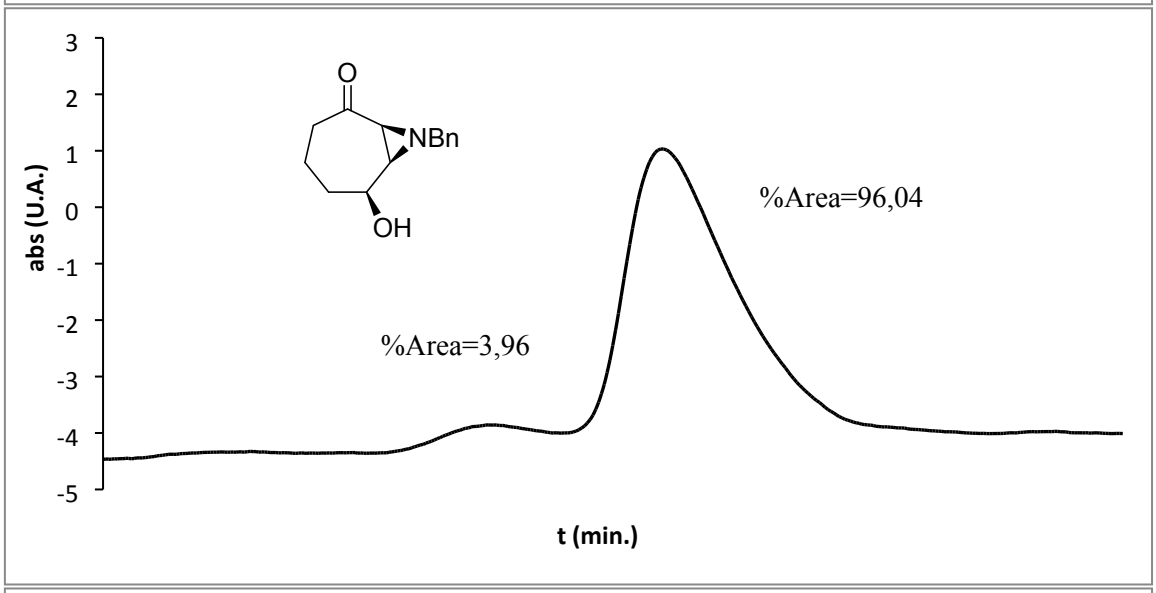


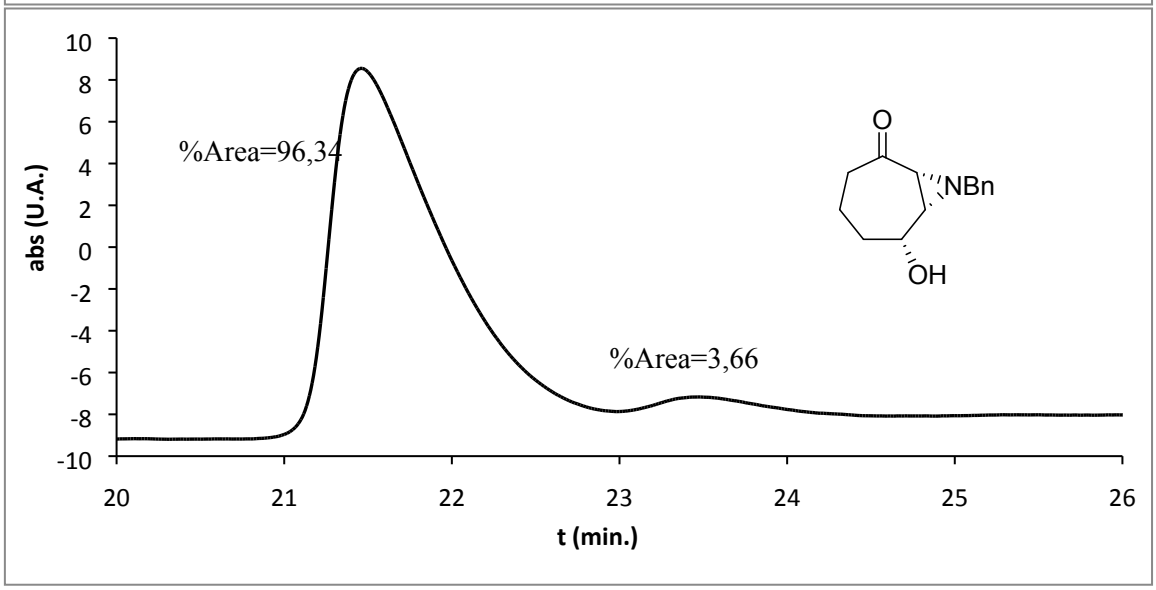
Elution conditions: AD-H; 95:5 hexane:isopropanol; 1.0ml.min^{-1}; 237nm.



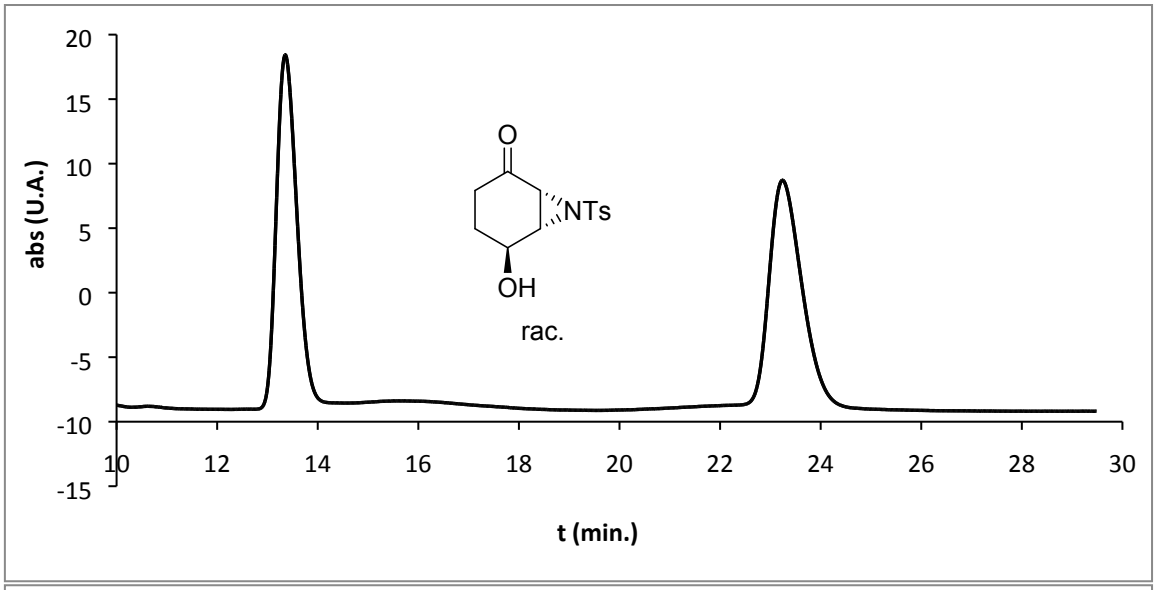
Elution conditions: AD-H; 95:5 hexane:isopropanol; 1.0ml.min^{-1}; 237nm.

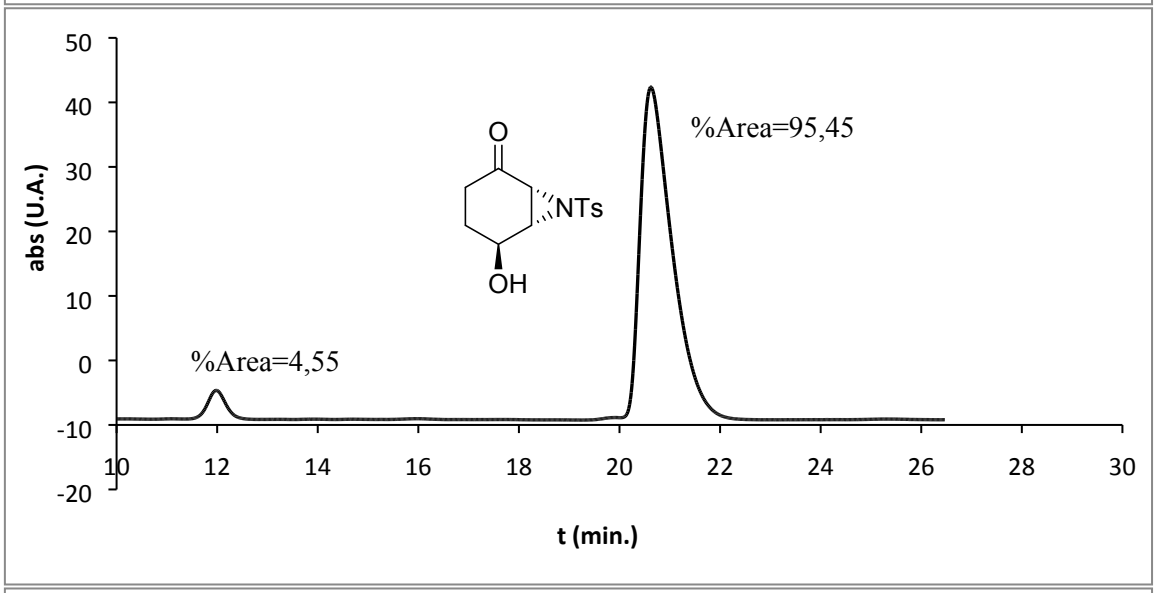


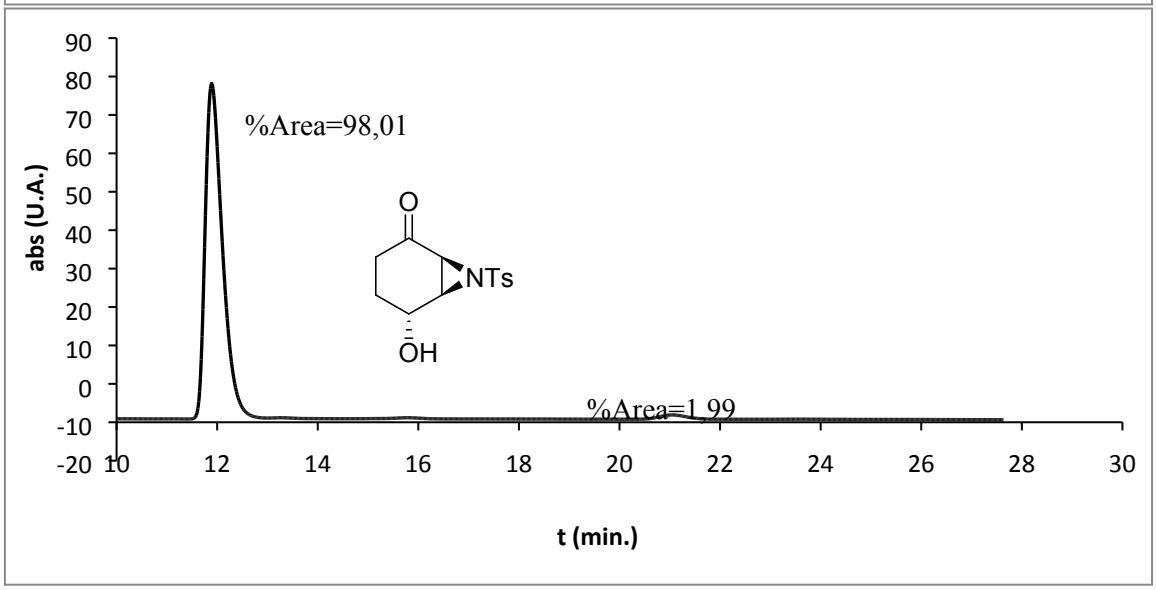




Elution conditions: IB; 98:2 hexane:isopropanol (0.1% Diethylamine); 2.0ml.min^{-1}; 237nm.







Elution conditions: AD-H; 80:20 hexane:isopropanol; 1.0ml.min^{-1}; 254nm.