Supporting Information

Highly Enantioselective Catalytic 1, 3-Dipolar Cycloaddition of α-Alkyl Diazoacetates: Efficient Synthesis of Functionalized 2-Pyrazolines

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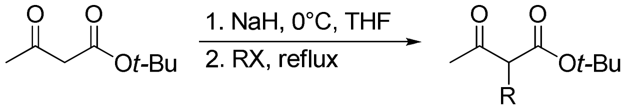
General Methods

Unless stated otherwise, reactions were carried out under a dry argon atmosphere in vacuum-flame dried glassware. Dichloromethane, toluene and THF were purified by ULVAC solvent purification system. Thin layer chromatography was carried out on Merck silica gel 60 F254. Column chromatography was carried out on Merck silica gel 60 (230-400 mesh).

^{1}H NMR spectra were recorded on a Varian at 300 or 600 MHz and Bruker 500 MHz. ^{13}C NMR spectra were recorded on a Varian at 75 or 150 MHz and Bruker 125 MHz. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (C**H**Cl$_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, spd = septet of doublet, dd=doublet of doublet, dt=doublet of triplet, qd=quartet of doublet, br=broad, m=multiplet), coupling constants (Hz), integration. Infrared spectra were recorded on a Bruker Vertex 70. LRMS data were obtained by Varian LC/MS 500 system.

Synthesis of α-Substituted *tert*-Butyl diazoacetates

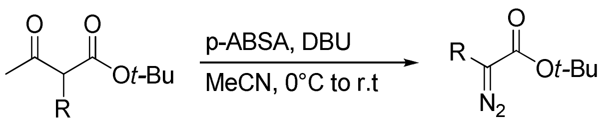
2-Substituted *tert*-Butyl Acetoacetate



2-Substituted *tert*-Butyl Acetoacetates were prepared according to the literature.[1]

A 100 ml round bottom flask fitted with a rubber septum was charged with NaH (60%, dispersion in mineral oil, 1.56 g, 39 mmol) in 30 ml of freshly distilled THF. At 0 ºC *tert*-butyl acetoacetate (30 mmol) was added dropwise and the solution was stirred for 10min. The reaction mixture was moved to ambient temperature then R-X (33 mmol) was added to the mixture in one portion. The resulting solution was refluxed and monitored by TLC. After completion of the reaction, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$(20 ml) and H_2O (2 ml). The product was extracted with CH_2Cl_2 (3 × 15 ml) and dried with Na_2SO_4. The volatiles were evaporated and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1) to give 2-substituted *tert*-butyl acetoacetates as clear colorless liquid.

2-Substituted *tert*-Butyldiazoacetate



2-Substituted *tert*-Butyl diazoacetates were prepared according to the literature.[1]

To a stirred solution of 2-substituted *tert*-butyl acetoacetate (10 mmol) in MeCN(30 ml) were added a 4-acetamidobenzenesulfonyl azide (2.88 g, 12 mmol) and DBU (2.24 ml, 15 mmol) at 0 ºC.The reaction mixture was stirred under ambient temperature and monitored by TLC. After completion of the reaction, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$(10 ml). The product was extracted with hexanes (2 × 10 ml) and dried with Na_2SO_4. The volatiles were evaporated and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 20:1) to give corresponding 2-substituted *tert*-butyl diazoacetate as clear yellow liquid.

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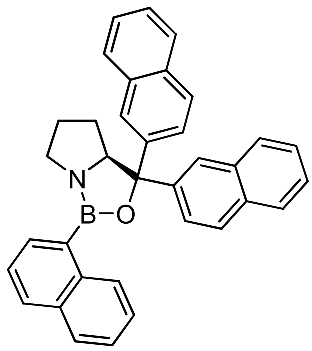
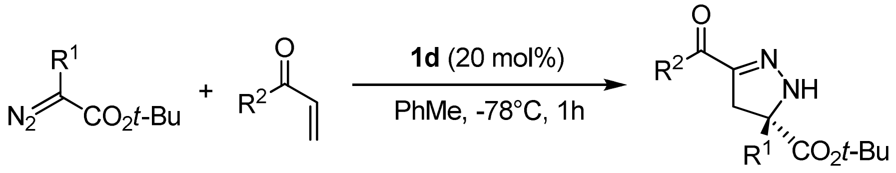
[1] T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc*. **2011**, *133*, 8834.

(*S*)-Oxazaborolidine (0.05M PhMe solution)



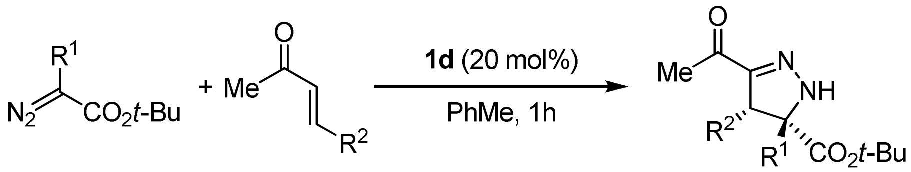
A 50 ml, one-necked, round-bottomed flask and a Dean-Stark apparatus (containing ca. 10 g of 4 Å molecular sieves) fitted on top with a reflux condenser and a nitrogen inlet adaptor were charged with (*S*)-(-)-*α*,*α*-di-2-naphthyl-2-pyrrolidinemethanol (0.707 g, 2.0 mmol), tri-1-naphthylboroxine (0.308 g, 0.67 mmol), and 35 ml of toluene. The resulting mixture was heated to reflux (bath temperature 145 ºC). After 3 h, the reaction mixture was cooled to ca. 60 ºC, and the Dean-Stark apparatus and condenser were quickly replaced with a short-path distillation head. The mixture was concentrated to a volume of ca. 5 ml by distillation (air-cooling). This distillation protocol was repeated three times by re-charging with 20 ml of toluene. The solution was then allowed to cool to room temperature, and the distillation head was quickly replaced with a vacuum adaptor. Concentration in *vacuo* (ca. 0.1 mmHg, 1 h) afforded the corresponding oxazaborolidine as clear oil. Oxazaborolidine was dissolved in 40 ml of PhMe and stored at -40 ºC.

General procedure for oxazaborolidinium catalyzed asymmetric 1,3-dipolar cycloaddition reaction



3

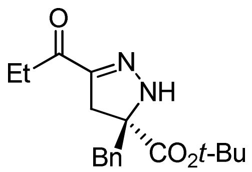
A freshly prepared solution of trifluoromethanesulfonic acid in PhMe (0.20 M solution, 0.25 mL, 0.05 mmol) was added dropwise to an oxazaborolidine solution (0.05M for oxazaborolidine in PhMe, 1.2 ml, 0.06 mmol for oxazaborolidine) at -40 ºC under nitrogen. After stirring for 20 min at -40 ºC, a pale yellow homogeneous solution of oxazaborolidinium catalyst was obtained. Enone (0.30 mmol) was then added in one portion to the solution of oxazaborolidinium catalyst at -78 ºC. After 20 min of stirring, diazoester (0.25 mmol) was added in one portion. TLC was used to monitor the reaction. After completion, the reaction was quenched at -78 ºC by adding Et_3N (14 μl, 0.1 mmol). The reaction mixture was directly purified by flash chromatography on silica gel by eluting with ethyl acetate/hexanes (v/v, 1/9) to give a 2-pyrazoline product.



3

A freshly prepared solution of trifluoromethanesulfonic acid in PhMe (0.20M solution, 0.25 mL, 0.05 mmol) was added dropwise to an oxazaborolidine solution (0.05M for oxazaborolidine in PhMe, 1.2 ml, 0.06 mmol for oxazaborolidine) at -40 ºC or -20 ºC under nitrogen. After stirring for 20 min (10 min at -20 ºC), a pale yellow homogeneous solution of oxazaborolidinium catalyst was obtained. Enone (0.30 mmol) was then added in one portion to the solution of oxazaborolidinium catalyst. After 10 min of stirring, diazoester (0.25 mmol) was added in one portion. TLC was used to monitor the reaction. After completion, the reaction was quenched by adding Et_3N (14 μl, 0.1 mmol). The reaction mixture was directly purified by flash chromatography on silica gel by eluting with ethyl acetate/hexanes (v/v, 1/9) to give a 2-pyrazoline product.

(*S*)-*tert*-butyl 5-benzyl-3-propionyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3a**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24-7.31 (m, 3H), 7.20-7.21 (m, 2H), 6.66 (s, 1H), 3.34 (d, *J*=18.0 Hz, 1H), 3.23 (d, *J*=13.2 Hz, 1H), 3.03 (d, *J*=13.8 Hz, 1H), 2.87 (d, *J*=18.0 Hz, 1H), 2.80 (ddd, J_{AB}=22.2 Hz, J_{AC}=7.2 Hz, J_{AD}=3.0 Hz, 2H), 1.40 (s, 9H), 1.09 (t, *J*=7.2 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 197.56, 172.22, 149.84, 135.35, 130.10, 128.61, 127.48, 83.17, 74.06, 43.68, 39.28, 30.97, 28.02, 8.39.

IR υ_{max} 3729, 3334, 2979, 1729, 1665, 1370, 1151, 843, 702 cm^{-1}.

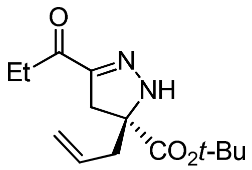
LRMS (APCI): m/z (%) = 317 (M+1, 16), 276 (20), 261 (100), 205 (42), 159 (22).

HRMS (FAB): m/z calcd for $C_{18}H_{25}N_2O_3^+$: 317.1865, found: 317.1865.

HPLC AS-H, (2-propanol: Hexane=1:9):Hexane=1:9, flow: 1.0ml/min, T_R = 14.6 min (minor) and T_R = 15.7 min (major).

$[\alpha]^{25}_D$ = +165.2 (*c* 0.89 $CHCl_3$)

(*S*)-*tert*-butyl 5-allyl-3-propionyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3b**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 6.69 (s, 1H), 5.64-5.71 (m, 1H), 5.14-5.18 (m, 2H), 3.30 (d, *J*=18.0 Hz, 1H), 2.82 (q, *J*=7.2 Hz, 2H), 2.80 (d, *J*=16.2 Hz, 1H), 2.62 (ddt, J_{AB}=13.8 Hz, J_{AC}=6.6 Hz, J_{AD}=1.2 Hz, 1H), 2.48 (ddt, J_{AB}=13.8 Hz, J_{AC}=7.8 Hz, J_{AD}=1.2 Hz, 1H), 1.46 (s, 9H) 1.11 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 197.58, 172.26, 149.84, 131.53, 120.10, 83.04, 72.76, 42.41, 38.32, 31.00, 28.08, 8.39.

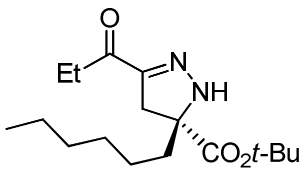
IR υ_{max} 3728, 3703, 3627, 3599, 3340, 2980, 1732, 1666, 1556, 1370, 1153, 845 cm^{-1}.

LRMS (APCI): m/z (%) = 267 (M+1, 22), 228 (56), 211 (100), 196 (53), 155 (51), 113 (29).

HPLC AS-H, (2-propanol: Hexane=1:9):Hexane=1:9, flow: 1.0ml/min, T_R = 10.5 min (minor) and T_R = 12.2 min (major).

$[\alpha]^{25}_D$ = +203.3 (*c* 0.63 $CHCl_3$)

(*S*)-*tert*-butyl 5-hexyl-3-propionyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3c**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 6.72 (s, 1H), 3.34 (d, *J*=18.0 Hz, 1H), 2.82 (q, *J*=7.2 Hz, 2H), 2.73 (d, *J*=18.0 Hz, 1H), 1.82-1.86 (m, 1H), 1.72-1.77 (m, 1H), 1.46 (s, 9H), 1.27-1.29 (m, 8H), 1.11 (t, *J*=7.2 Hz, 3H), 0.88 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 197.66, 173.06, 149.87, 82.79, 73.49, 38.65, 38.30, 31.65, 30.99, 29.35, 28.06, 24.53, 22.61, 14.15, 8.42.

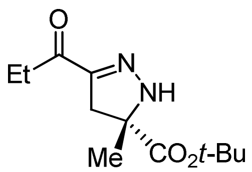
IR υ_{max} 3344, 2932, 2859, 1729, 1665, 1459, 1370, 1253, 1151, 844 cm^{-1}.

LRMS (APCI): m/z (%) = 311 (M+1, 3), 274 (17), 255 (100), 215 (42), 199 (32), 153 (26).

HPLC AS-H, (2-propanol: Hexane=1:9):Hexane=1:9, flow: 1.0ml/min, T_R = 6.9 min (minor) and T_R = 8.1 min (major).

$[\alpha]^{25}_{D}$ = +125.0 (*c* 1.17 $CHCl_3$)

(*S*)-*tert*-butyl 5-methyl-3-propionyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3d**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 6.74 (s, 1H), 3.40 (d, *J*=17.4 Hz, 1H), 2.82 (q, *J*=7.2 Hz, 2H), 2.70 (d, *J*=18.0 Hz, 1H), 1.50 (s, 3H), 1.46 (s, 9H), 1.11 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 197.58, 173.30, 149.92, 82.76, 69.99, 39.93, 30.95, 27.96, 24.52, 8.38.

IR υ_{max} 3338, 2979, 1732, 1664, 1551, 1371, 1153, 842 cm^{-1}.

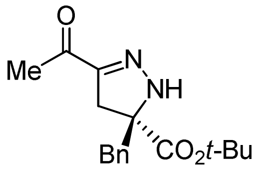
LRMS (APCI): m/z (%) = 241 (M+1, 25), 228 (100), 196 (86), 185 (93), 129 (42).

HRMS (FAB): m/z calcd for $C_{12}H_{20}N_2O_3^+$: 241.1552, found: 241.1552.

HPLC OD-H, (2-propanol: Hexane=1:9):Hexane=1:9, flow: 1.0ml/min, T_R = 7.9 min (major) and T_R = 8.8 min (minor).

$[\alpha]^{25}_{D}$ = +311.8 (*c* 0.52 $CHCl_3$)

(*S*)-*tert*-butyl 3-acetyl-5-benzyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3e**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24-7.31 (m, 3H), 7.18-7.21 (m, 2H), 6.71 (s, 1H), 3.34 (d, *J*=17.4 Hz, 1H), 3.23 (d, *J*=13.2 Hz, 1H), 3.03 (d, *J*=13.2 Hz, 1H), 2.87 (dd, J_{AB}=17.4 Hz, J_{AC}=1.2 Hz, 1H), 2.37 (s, 3H), 1.40 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 194.50, 172.12, 150.27, 135.26, 130.09, 128.62, 127.49, 83.22, 74.33, 43.67, 38.97, 28.03, 25.41.

IR υ_{max} 3333, 2979, 1728, 1665, 1252, 1151, 1080, 832, 702 cm^{-1}.

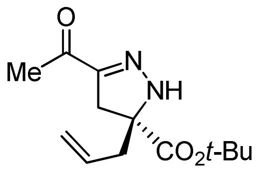
LRMS (APCI): m/z (%) = 301 (M-1, 28), 288 (53), 215 (100), 187 (35), 139 (32).

HRMS (FAB): m/z calcd for $C_{17}H_{23}N_2O_3^+$: 303.1709, found: 303.1710.

HPLC AS-H, (2-propanol: Hexane=1:9):Hexane=2:8, flow: 1.0ml/min, T_R = 12.4 min (major) and T_R = 14.2 min (minor).

$[\alpha]^{25}_D$ = +204.7 (*c* 0.68 $CHCl_3$)

(*S*)-*tert*-butyl 3-acetyl-5-allyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3f**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 6.76 (s, 1H), 5.64-5.70 (m, 1H), 5.14-5.18 (m, 2H), 3.30 (d, *J*=17.4 Hz, 1H), 2.80 (dd, J_{AB}=17.4 Hz, J_{AC}=0.6 Hz, 1H), 2.62 (ddt, J_{AB}=13.8 Hz, J_{AC}=7.2 Hz, J_{AD}=1.2 Hz, 1H), 2.48 (ddt, J_{AB}=13.8 Hz, J_{AC}=7.8 Hz, J_{AD}=1.2 Hz, 1H), 2.39 (s, 3H), 1.46 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 194.50,172.14, 150.22, 131.43, 120.15, 83.07, 73.05, 42.39, 37.99, 28.07, 25.42.

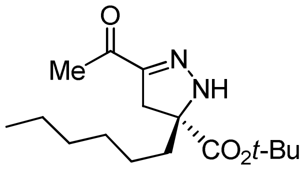
IR υ_{max} 3335, 2980, 1731, 1665, 1551, 1416, 1251, 1152, 843 cm^{-1}.

LRMS (APCI): m/z (%) = 251 (M-1, 45), 233 (46), 213 (100), 209 (69), 165 (38), 109 (36).

HPLC AS-H, (2-propanol: Hexane=1:9):Hexane=1:9, flow: 1.0ml/min, T_R = 11.6 min (minor) and T_R = 12.6 min (major).

$[\alpha]^{25}_D$ = +165.3 (*c* 0.94 $CHCl_3$)

(*S*)-*tert*-butyl 3-acetyl-5-hexyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3g**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 6.78 (s, 1H), 3.34 (d, *J*=17.4 Hz, 1H), 2.72 (dd, J_{AB}=18.0 Hz, J_{AC}=0.6 Hz, 1H), 2.39 (s, 3H), 1.82-1.85 (m, 1H), 1.72-1.77 (m, 1H), 1.46 (s, 9H), 1.23-1.32 (m, 8H), 0.88 (t, *J*=6.6 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 194.59, 172.93, 150.26, 82.82, 73.79, 38.28, 31.63, 29.32, 28.04, 25.43, 25.41, 24.47, 22.59, 14.13.

IR υ_{max} 3337, 2930, 2859, 1730, 1665, 1551, 1252, 1152, 762 cm^{-1}.

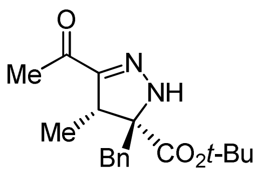
LRMS (APCI): m/z (%) = 297 (M+1, 24), 273 (16), 241 (100), 199 (29), 153 (38).

HRMS (FAB): m/z calcd for $C_{16}H_{29}N_2O_3^+$: 297.2178, found: 297.2179.

HPLC AS-H, (2-propanol: Hexane=1:9):Hexane=1:9, flow: 1.0ml/min, T_R = 7.5 min (minor) and T_R = 8.2 min (major).

$[\alpha]^{25}_D$ = +196.5 (*c* 0.31 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-benzyl-4-methyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3h**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.30 (m, 3H), 7.16-7.19 (m, 2H), 6.45 (s, 1H), 3.24 (q, *J*=7.2 Hz, 1H), 3.18 (d, *J*=13.2 Hz, 1H), 2.82 (d, *J*=13.2 Hz, 1H), 2.39 (s, 3H), 1.45 (s, 9H), 1.18 (d, *J*=7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.30, 169.40, 152.20, 135.05, 130.11, 128.64, 127.54, 83.20, 77.77, 46.91, 42.52, 28.20, 25.79, 12.80.

IR υ_{max} 3381, 2981, 2859, 1710, 1661, 1153, 736, 706 cm^{-1}.

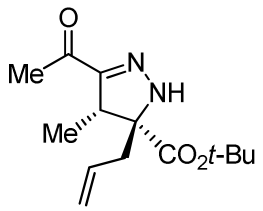
LRMS (APCI): m/z (%) = 315 (M-1, 30), 279 (100), 233 (39), 199 (45), 162 (60).

HRMS (FAB): m/z calcd for $C_{18}H_{25}N_2O_3^+$: 317.1865, found: 317.1865.

HPLC AS-H, (2-propanol: Hexane=1:9):Hexane=2:8, flow: 1.0ml/min, T_R = 9.3 min (major) and T_R = 14.7 min (minor).

$[\alpha]^{25}_D$ = -36.36 (*c* 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-allyl-4-methyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3i**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (s, 1H), 5.60-5.73 (m, 1H), 5.13-5.21 (m, 2H), 3.13 (q, J=7.2 Hz, 1H), 2.57 (dd, J_{AB}=13.5 Hz, J_{AC}=6.0 Hz, 1H), 2.38 (s, 3H), 2.30 (dd, J_{AB}=13.5 Hz, J_{AC}=8.4 Hz, 1H), 1.50 (s, 9H), 1.16 (d, J=7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.34, 169.62, 152.38, 131.29, 120.72, 82.97, 46.02, 42.10, 28.21, 25.83, 12.91.

IR υ_{max} 3346, 2979, 1727, 1658, 1370, 1235, 1145, 996, 921, 844, 620 cm^{-1}.

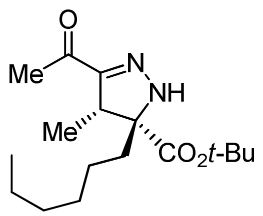
LRMS (APCI): m/z (%) = 267 (M+1, 20), 246 (84), 229 (86), 211 (100), 169 (49).

HRMS (FAB): m/z calcd for $C_{14}H_{23}N_2O_3^+$: 267.1709, found: 267.1709.

HPLC AY-H, 2-propanol: Hexane=1:9, flow: 1.0ml/min, T_R = 8.0 min (major) and T_R = 19.5 min (minor).

$[\alpha]^{25}_D$ = -59.88 (c 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-hexyl-4-methyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3j**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (s, 1H), 3.10 (q, J=7.2 Hz, 1H), 2.38 (s, 3H), 1.55-1.85 (m, 2H), 1.49 (s, 9H), 1.26-1.37 (m, 8H), 1.17 (d, J=7.2 Hz, 3H), 0.88 (t, J=6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.25, 170.27, 152.08, 82.57, 77.42, 46.55, 38.15, 31.46, 29.23, 28.02, 25.69, 23.80, 22.42, 13.94, 13.02.

IR υ_{max} 3348, 2933, 1728, 1644, 1455, 1394, 1135, 1029, 843 cm^{-1}.

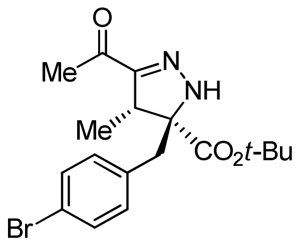
LRMS (APCI): m/z (%) = 311 (M+1, 9), 271 (39), 267 (30), 255 (100), 183 (23), 167 (27).

HRMS (FAB): m/z calcd for $C_{17}H_{31}N_2O_3^+$: 311.2335, found: 311.2335.

HPLC AY-H, 2-propanol: Hexane=1:9, flow: 1.0ml/min, T_R = 8.0 min (major) and T_R = 13.6 min (minor).

$[\alpha]^{25}_D$ = 36.80 (c 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-(4-bromobenzyl)-4-methyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3k**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J*=8.1 Hz, 2H), 7.06 (d, *J*=8.4 Hz, 2H), 6.41 (s, 1H), 3.22 (q, *J*=7.2 Hz, 1H), 3.14 (d, *J*=13.2 Hz, 1H), 2.78 (d, *J*=13.5 Hz, 1H), 2.38 (s, 3H), 1.45 (s, 9H), 1.19 (d, *J*=7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.26, 169.27, 152.17, 134.07, 131.83, 131.70, 121.64, 83.49, 77.42, 47.13, 42.02, 28.21, 25.83, 12.90.

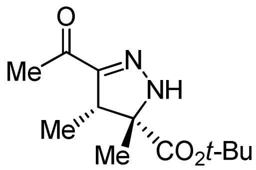
IR υ_{max} 3373, 2978, 2932, 1712, 1561, 1416, 1241, 1156, 1013, 618 cm^{-1}.

LRMS (APCI): m/z (%) = 393 (M-1, 19), 395 (19), 352 (68), 255 (45), 233 (100).

HPLC AS-H, (2-propanol: Hexane=1:9):Hexane=2:8, flow: 1.0ml/min, T_R = 16.1 min (major) and T_R = 20.4 min (minor).

$[\alpha]^{25}_{D}$ = -34.1 (*c* 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-4,5-dimethyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3l**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (s, 1H), 3.08 (q, *J*=7.2 Hz, 1H), 2.38 (s, 3H), 1.49 (s, 9H), 1.40 (s, 3H), 1.16 (d, *J*=7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.52, 170.85, 151.99, 82.68, 74.20, 46.96, 28.14, 25.82, 24.62, 12.86.

IR υ_{max} 3292, 2978, 2935, 1733, 1636, 1394, 1370, 1124, 924, 816, 627 cm^{-1}.

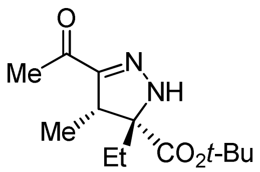
LRMS (APCI): m/z (%) = 239 (M-1, 34), 187 (36), 185 (100), 172 (36), 141 (57), 127 (50).

HRMS (FAB): m/z calcd for $C_{12}H_{21}N_2O_3^+$: 241.1552, found: 241.1552.

HPLC AY-H, 2-propanol: Hexane=1:9, flow: 1.0ml/min, T_R = 8.3 min (major) and T_R = 13.2 min (minor).

$[\alpha]^{25}_{D}$ = +47.8 (*c* 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-ethyl-4-methyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3m**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (s, 1H), 3.11 (q, *J*=7.2 Hz, 1H), 2.38 (s, 3H), 1.79-1.91 (m, 1H), 1.62-1.74 (m, 1H), 1.50 (s, 9H), 1.18 (d, *J*=7.2 Hz, 3H), 0.89 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.39, 170.30, 152.31, 82.76, 77.92, 46.32, 31.16, 28.18, 25.83, 13.24, 8.31.

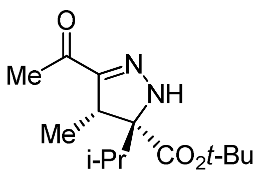
IR υ_{max} 3252, 2970, 2924, 1732, 1624, 1437, 1253, 1160, 1129, 936, 836 cm^{-1}.

LRMS (APCI): m/z (%) = 255 (M+1, 46), 211 (57), 199 (100), 181 (30), 157 (24), 127 (27).

HPLC OZ-H, (2-propanol: Hexane=1:9):Hexane=1:9, flow: 1.0ml/min, T_R = 14.0 min (major) and T_R = 15.0 min (minor).

$[\alpha]^{25}_{D}$ = +112.7 (*c* 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-isopropyl-4-methyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3n**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (s, 1H), 3.28 (q, *J*=7.2 Hz, 1H), 2.36 (s, 3H), 2.05-2.18 (m, 1H), 1.50 (s, 9H), 1.20 (d, *J*=7.2 Hz, 3H), 0.91 (d, *J*=6.6 Hz, 3H), 0.83 (d, *J*=6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.19, 170.54, 151.96, 82.94, 80.16, 44.16, 35.82, 28.21, 25.91, 17.51, 16.44, 14.48.

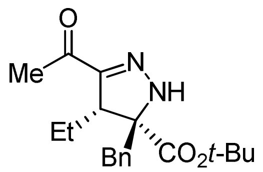
IR υ_{max} 3318, 2973, 2933, 1730, 1634, 1430, 1371, 1277, 1168, 1128, 939 cm^{-1}.

LRMS (APCI): m/z (%) = 269 (M+1, 39), 213 (100), 167 (9), 125 (14).

HPLC AY-H, (2-propanol: Hexane=1:9):Hexane=5:5, flow: 1.0ml/min, T_R = 16.8 min (major) and T_R = 31.1 min (minor).

$[\alpha]^{25}_{D}$ = +154.8 (*c* 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-benzyl-4-ethyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3o**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.34 (m, 3H), 7.13-7.16 (m, 2H), 6.41 (s, 1H), 3.23 (t, *J*=5.4 Hz, 1H), 3.13 (d, *J*=13.2 Hz, 1H), 2.83 (d, *J*=13.2 Hz, 1H), 2.41 (s, 3H), 1.69-1.85 (m, 2H), 1.44 (s, 9H), 0.83 (t, *J*=7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.55, 169.51, 151.18, 134.80, 130.18, 128.64, 127.58, 83.14, 77.35, 52.68, 43.50, 28.13, 25.73, 20.86, 10.74.

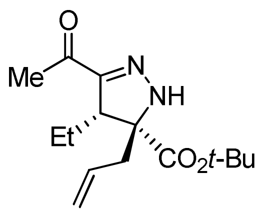
IR υ_{max} 3402, 3382, 2979, 2932, 1712, 1651, 1153, 846, 738, 704 cm^{-1}.

LRMS (APCI): m/z (%) = 331 (M+1, 40), 330 (90), 276 (57), 275 (100), 233 (16), 187 (18).

HPLC AS-H, (2-propanol: Hexane=1:9):Hexane=2:8, flow: 1.0ml/min, T_R = 7.6 min (major) and T_R = 11.7 min (minor).

$[\alpha]^{25}_D$ = -87.24 (*c* 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-benzyl-4-ethyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3p**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (s, 1H), 5.58-5.72 (m, 1H), 5.11-5.22 (m, 2H), 3.12 (t, *J*=5.1 Hz, 1H), 2.53 (ddt, J_{AB}=13.5 Hz, J_{AC}=7.5 Hz, J_{AD}=0.9 Hz, 1H), 2.40 (s, 3H), 2.30 (dd, J_{AB}=13.2 Hz, J_{AC}=8.4 Hz, 1H), 1.67-1.84 (m, 2H), 1.51 (s, 9H), 0.83 (t, *J*=7.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.57, 169.76, 151.29, 131.07, 120.86, 82.93, 76.12, 51.77, 43.23, 28.14, 25.76, 20.90, 10.57.

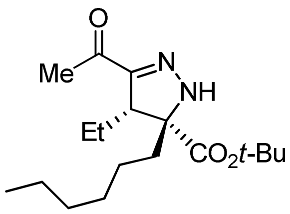
IR υ_{max} 3343, 2978, 1727, 1661, 1543, 1165, 1144, 1131, 843, 758, 623 cm^{-1}.

LRMS (APCI): m/z (%) = 281 (M+1, 14), 269 (92), 255 (100), 246 (44), 225 (41), 167 (36).

HPLC OZ-H, (2-propanol: Hexane=1:9):Hexane=2:8, flow: 1.0ml/min, T_R = 7.1 min (major) and T_R = 15.5 min (minor).

$[\alpha]^{25}_D$ = -161.7 (*c* 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-4-ethyl-5-hexyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3q**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (s, 1H), 3.09 (t, *J*=4.8 Hz, 1H), 2.39 (s, 3H), 1.63-1.81 (m, 4H), 1.51 (s, 9H), 1.26 (br s, 8H), 0.87 (t, *J*=6.6 Hz, 3H), 0.80 (t, *J*=7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.56, 170.54, 150.97, 82.68, 76.99, 52.45, 39.57, 31.63, 29.37, 28.12, 25.75, 23.69, 22.58, 20.90, 14.10, 10.64.

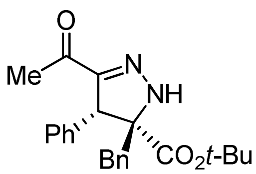
IR υ_{max} 3336, 2934, 2860, 1727, 1648, 1370, 1134, 1032, 843 cm^{-1}.

LRMS (APCI): m/z (%) = 325 (M+1, 33), 323 (74), 269 (100), 228 (29), 182 (34).

HPLC OZ-H, (2-propanol: Hexane=1:9):Hexane=1:9, flow: 1.0ml/min, T_R = 7.6 min (major) and T_R = 11.6 min (minor).

$[\alpha]^{25}_D$ = -48.9 (*c* 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-benzyl-4-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3r**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.34 (m, 10H), 6.61 (s, 1H), 4.22 (s, 1H), 3.28 (d, *J*=13.5 Hz, 1H), 2.99 (d, *J*=13.5 Hz, 1H), 2.36 (s, 3H), 0.99 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 193.32, 168.29, 151.74, 136.45, 134.67, 130.12, 128.66, 128.60, 127.78, 127.66, 82.65, 78.69, 77.36, 58.15, 43.98, 27.40, 25.75.

IR υ_{max} 3350, 2941, 2831, 1727, 1650, 1454, 1156, 1027, 756, 701 cm^{-1}.

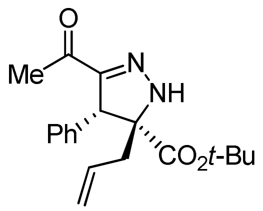
LRMS (APCI): m/z (%) = 379 (M+1, 89), 378 (92), 323 (100), 281 (54), 235 (37).

HRMS (FAB): m/z calcd for $C_{23}H_{27}N_2O_3^+$: 379.2022, found: 379.2021.

HPLC OD-H, (2-propanol: Hexane=1:9):Hexane=5:5, flow: 1.0ml/min, T_R = 7.8 min (major) and T_R = 8.9 min (minor).

$[\alpha]^{25}_D$ = -235.6 (*c* 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-allyl-4-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3s**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.26 (m, 3H), 7.09-7.12 (m, 2H), 6.72 (s, 1H), 5.62-5.76 (m, 1H), 5.19-5.25 (m, 2H), 4.10 (s, 1H), 2.68 (dd, J_{AB}=13.2 Hz, J_{AC}=6.3 Hz, 1H), 2.47 (dd, J_{AB}=13.5 Hz, J_{AC}=8.4 Hz, 1H), 2.37 (s, 3H), 1.01 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 193.40, 168.68, 151.97, 136.79, 130.96, 128.63, 128.48, 127.72, 120.99, 82.40, 77.69, 57.41, 43.72, 27.40, 25.84.

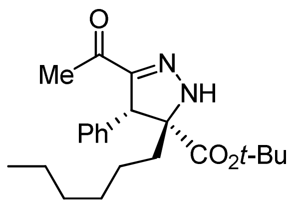
IR υ_{max} 3316, 2925, 2854, 1729, 1669, 1458, 1370, 1166, 1139, 699 cm^{-1}.

LRMS (APCI): m/z (%) = 329 (M+1, 20), 328 (100), 311 (62), 274 (11), 273 (55).

HPLC OD-H, (2-propanol: Hexane=1:9):Hexane=2:8, flow: 1.0ml/min, T_R = 8.9 min (major) and T_R = 10.6 min (minor).

$[\alpha]^{25}_D$ = -195.8 (*c* 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-hexyl-4-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3t**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.26 (m, 3H), 7.06-7.09 (m, 2H), 6.72 (s, 1H), 4.08 (s, 1H), 2.36 (s, 3H), 1.74-1.95 (m, 2H), 1.26-1.31 (m, 8H), 1.00 (s, 9H), 0.88 (t, *J*=6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 193.23, 169.31, 151.58, 137.13, 128.41, 128.21, 127.42, 82.00, 78.55, 57.98, 39.90, 31.46, 29.19, 27.19, 25.66, 23.68, 22.42, 13.94.

IR υ_{max} 3323, 2923, 2861, 1728, 1662, 1140, 1055, 1033, 1018, 698 cm^{-1}.

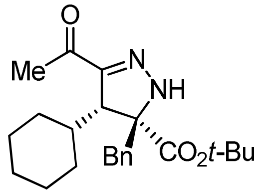
LRMS (APCI): m/z (%) = 373 (M+1, 16), 372 (97), 318 (9), 317 (34), 118 (100).

HRMS (FAB): m/z calcd for $C_{22}H_{33}N_2O_3^+$: 373.2491, found: 373.2490.

HPLC OZ-H, (2-propanol: Hexane=1:9):Hexane=2:8, flow: 1.0ml/min, T_R = 9.3 min (major) and T_R = 35.8 min (minor).

$[\alpha]^{25}_D$ = -157.4 (*c* 1.00 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-benzyl-4-cyclohexyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3u**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.34 (m, 3H), 7.09-7.12 (m, 2H), 6.35 (s, 1H), 3.08 (d, *J*=13.2 Hz, 1H), 3.06 (s, 1H), 2.76 (d, *J*=13.2 Hz, 1H), 2.44 (s, 3H), 1.70-1.76 (m, 3H), 1.56-1.64 (m, 2H), 1.45 (s, 9H), 1.08-1.31 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.91, 169.48, 151.62, 134.60, 130.14, 128.69, 127.62, 83.02, 78.63, 56.78, 42.94, 39.03, 33.50, 28.33, 28.21, 27.33, 26.40, 26.14, 25.92.

IR υ_{max} 3362, 2925, 2854, 1725, 1660, 1154, 1030 cm^{-1}.

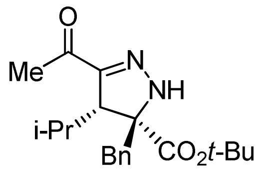
LRMS (APCI): m/z (%) = 385 (M+1, 24), 384 (94), 373 (79), 330 (19), 329 (100), 317 (39), 273 (29).

HRMS (FAB): m/z calcd for $C_{23}H_{32}N_2O_3^+$: 385.2491, found: 385.2491.

HPLC OZ-H, (2-propanol: Hexane=1:9):Hexane=2:8, flow: 1.0ml/min, T_R = 9.3 min (major) and T_R = 18.8 min (minor).

$[\alpha]^{25}_D$ = -115.7 (*c* 0.50 $CHCl_3$)

(4*S*,5*S*)-*tert*-butyl 3-acetyl-5-benzyl-4-isopropyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3u**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.34 (m, 3H), 7.09-7.12 (m, 2H), 6.37 (s, 1H), 3.14 (d, *J*=2.4 Hz, 1H), 3.09 (d, *J*=13.2 Hz, 1H), 2.76 (d, *J*=13.2 Hz, 1H), 2.44 (s, 3H), 2.11-2.22 (m, 1H), 1.43 (s, 9H), 1.01 (d, *J*=7.2 Hz, 3H), 0.80 (d, *J*=6.6 Hz, 3H).

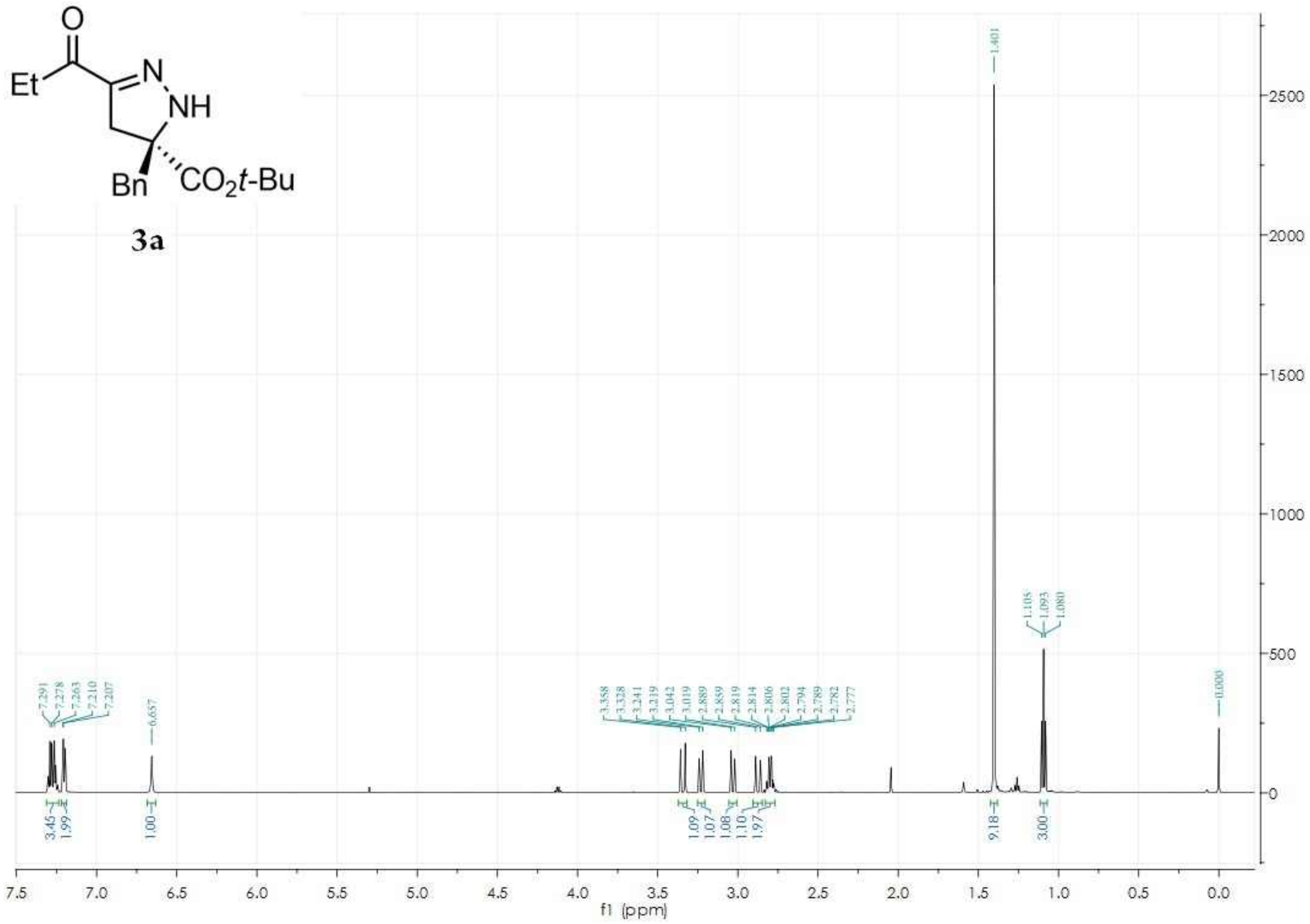
^{13}C NMR (75 MHz, $CDCl_3$) δ 194.85, 169.47, 150.89, 134.58, 130.15, 128.67, 127.60, 83.02, 78.48, 57.13, 43.03, 28.53, 28.09, 25.85, 23.24, 17.82.

IR υ_{max} 3353, 2941, 2832, 1724, 1651, 1155, 1027, 703 cm^{-1}.

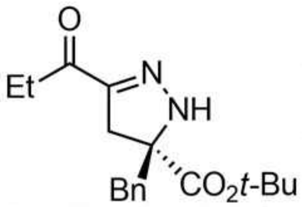
LRMS (APCI): m/z (%) = 345 (M+1, 17), 326 (16), 318 (19), 242 (22), 146 (13), 118 (100).

HPLC AS-H, (2-propanol: Hexane=1:9):Hexane=2:8, flow: 1.0ml/min, T_R = 5.8 min (major) and T_R = 8.2 min (minor).

$[\alpha]^{25}_D$ = -57.84 (*c* 1.00 $CHCl_3$)

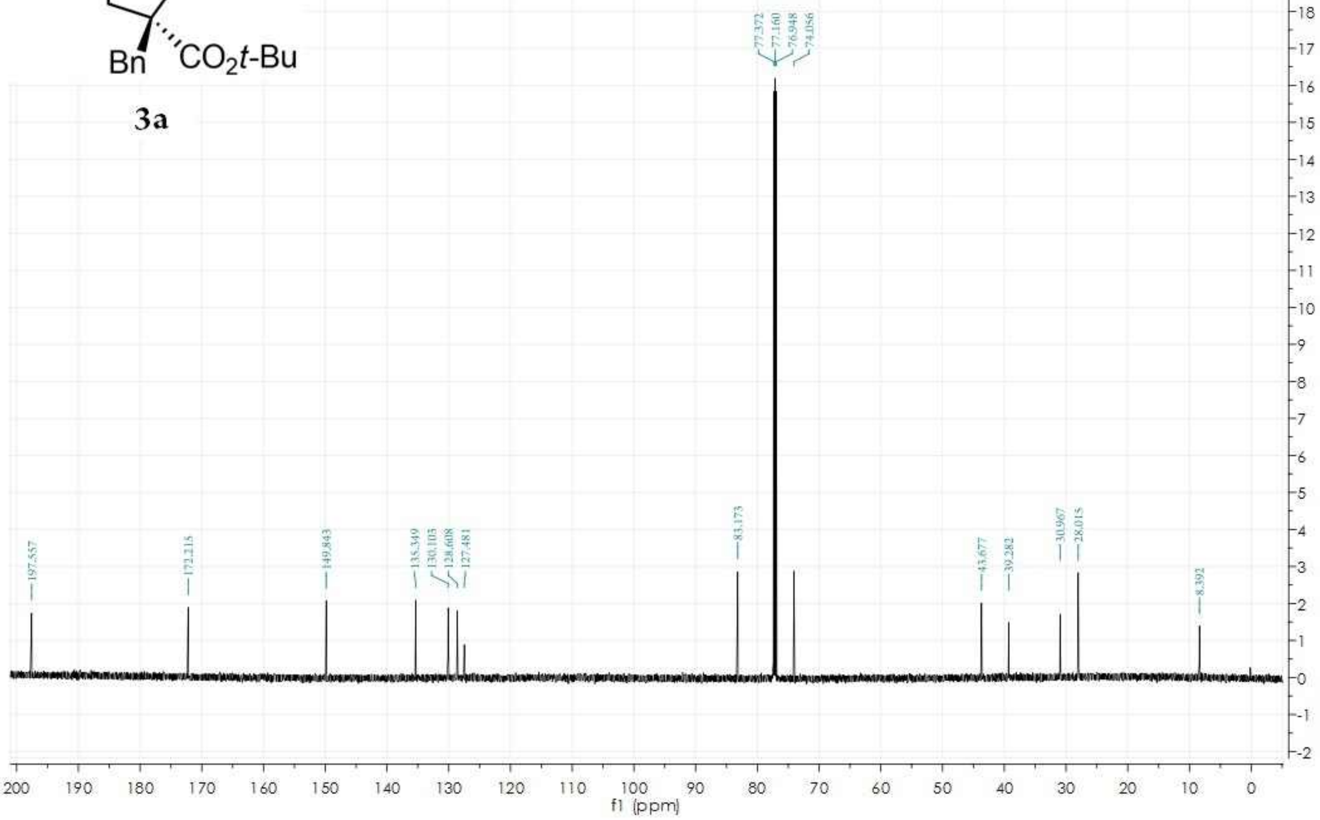


3a



O
Et
N
NH
Bn
CO2t-Bu

3a



197.557
172.215
149.843
135.349
130.103
128.608
127.481
83.173
77.372
77.160
76.948
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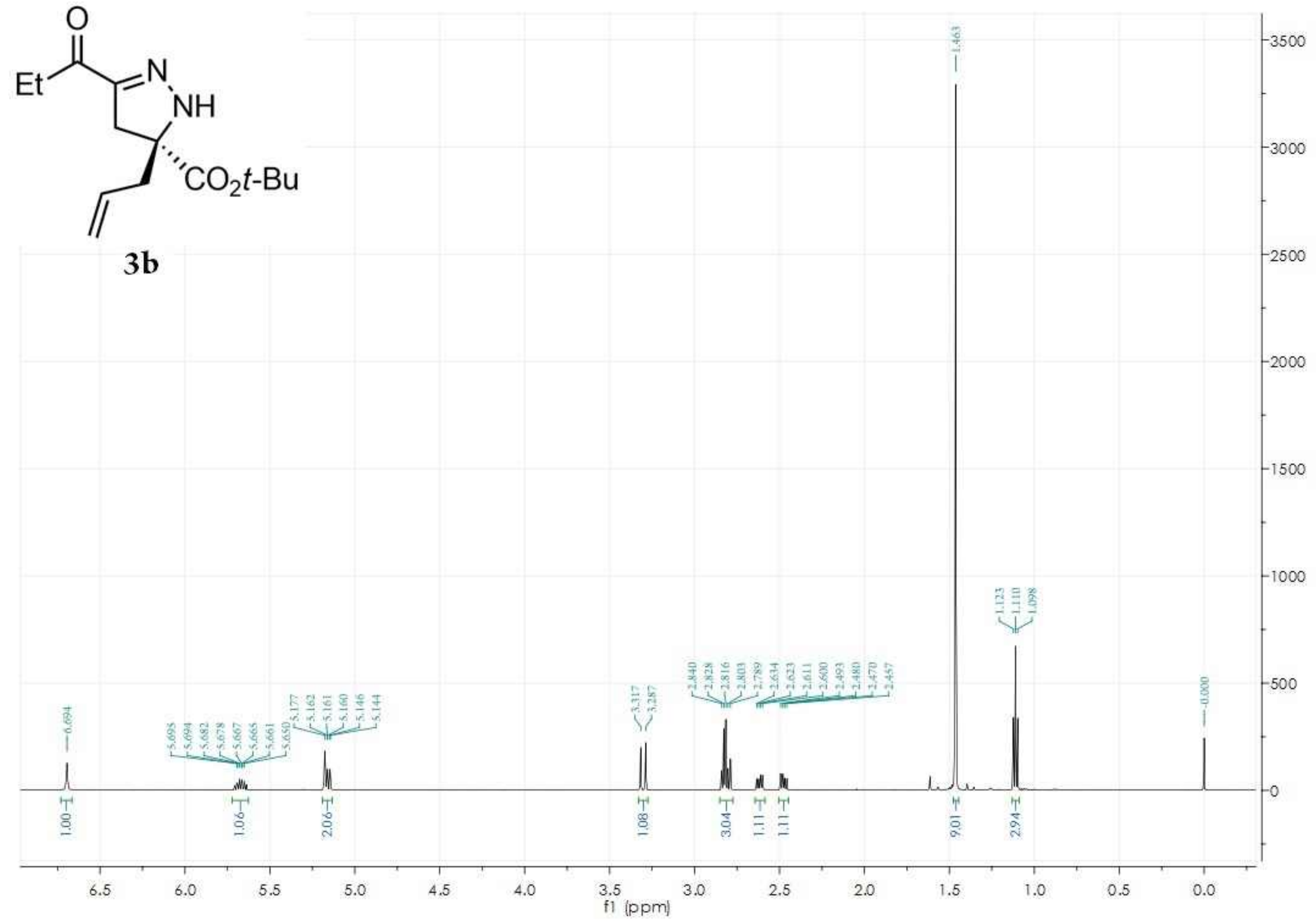
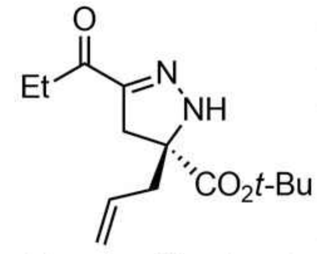
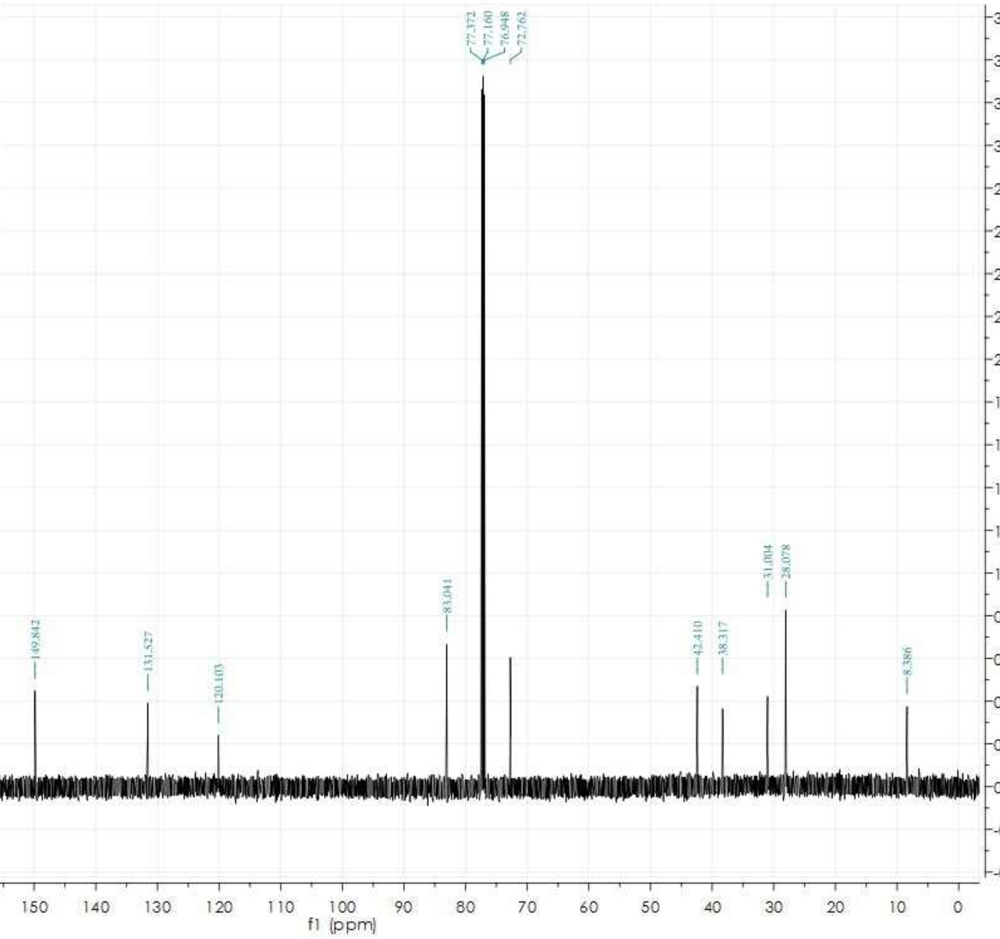
30.967
28.015
8.392
f1 (ppm)


O
Et
N
NH
CO2t-Bu
3b
3500
3000
2500
2000
1500
1000
500
0
1.00
1.06
2.06
1.08
3.04
1.11
1.11
9.01
2.94
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)



3b



197.575
172.265
149.842
131.527
120.103
83.041
77.372
77.160
76.948
72.762
42.410
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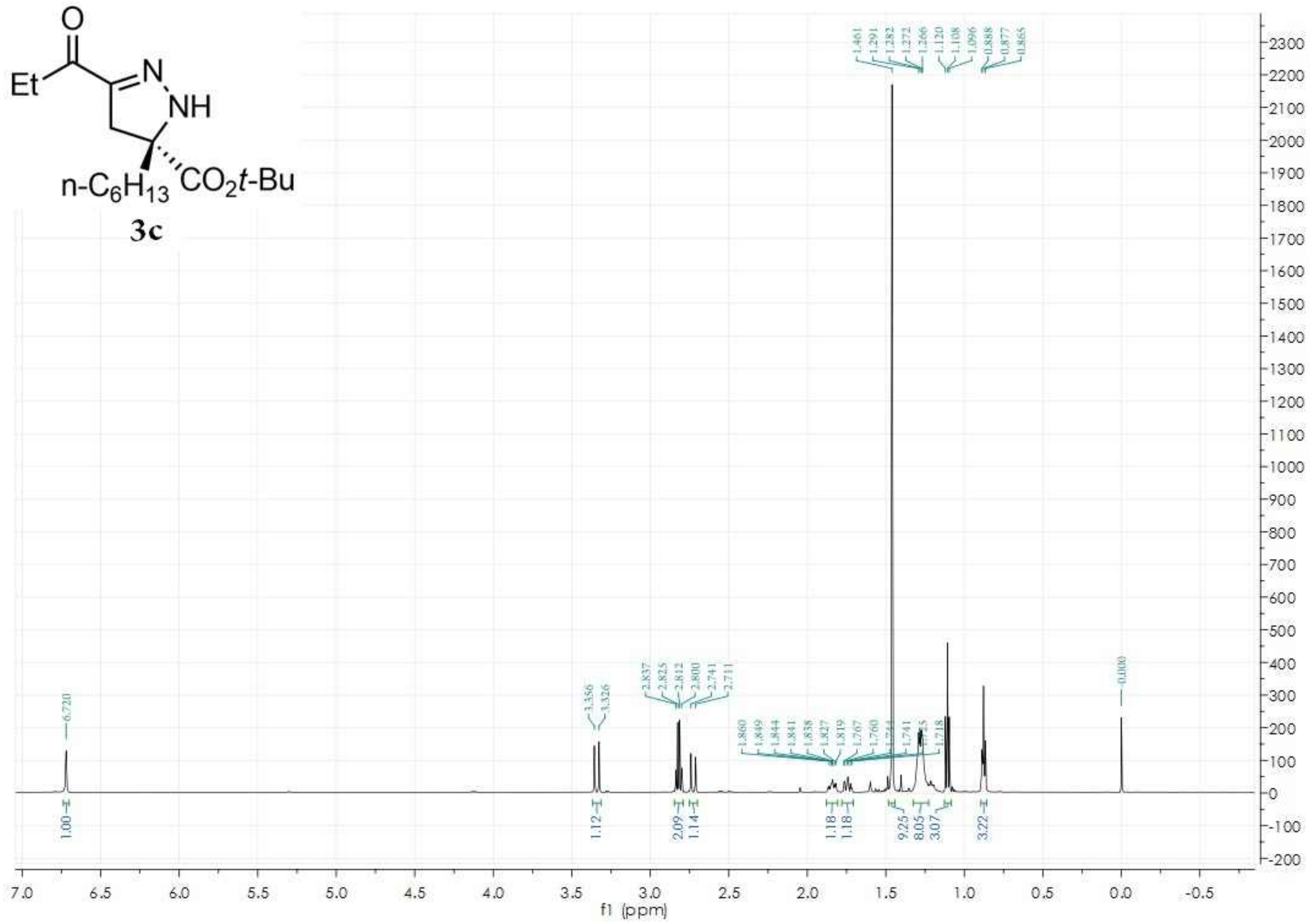
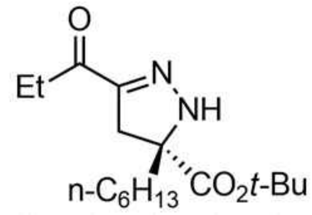
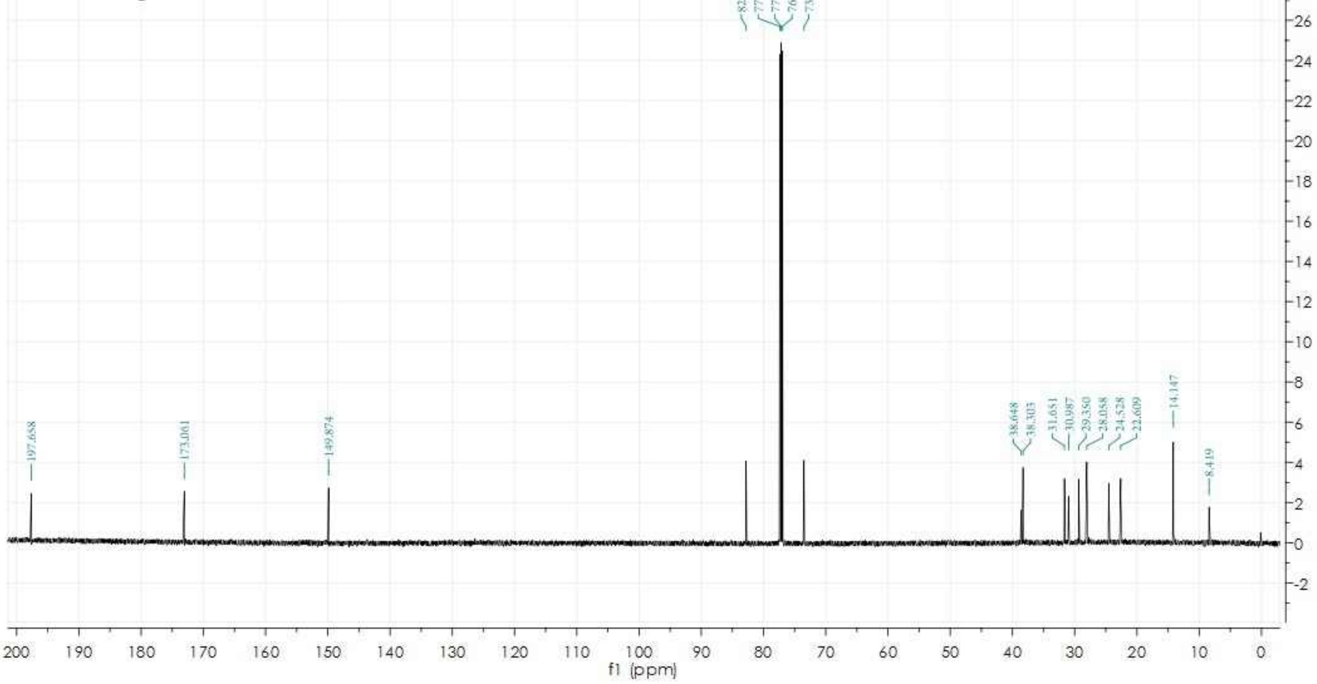
31.004
28.078
8.386
f1 (ppm)



3c


O
Et
N
NH
n-C6H13
CO2t-Bu

3c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77.160
76.949
73.490
38.648
38.303
31.651
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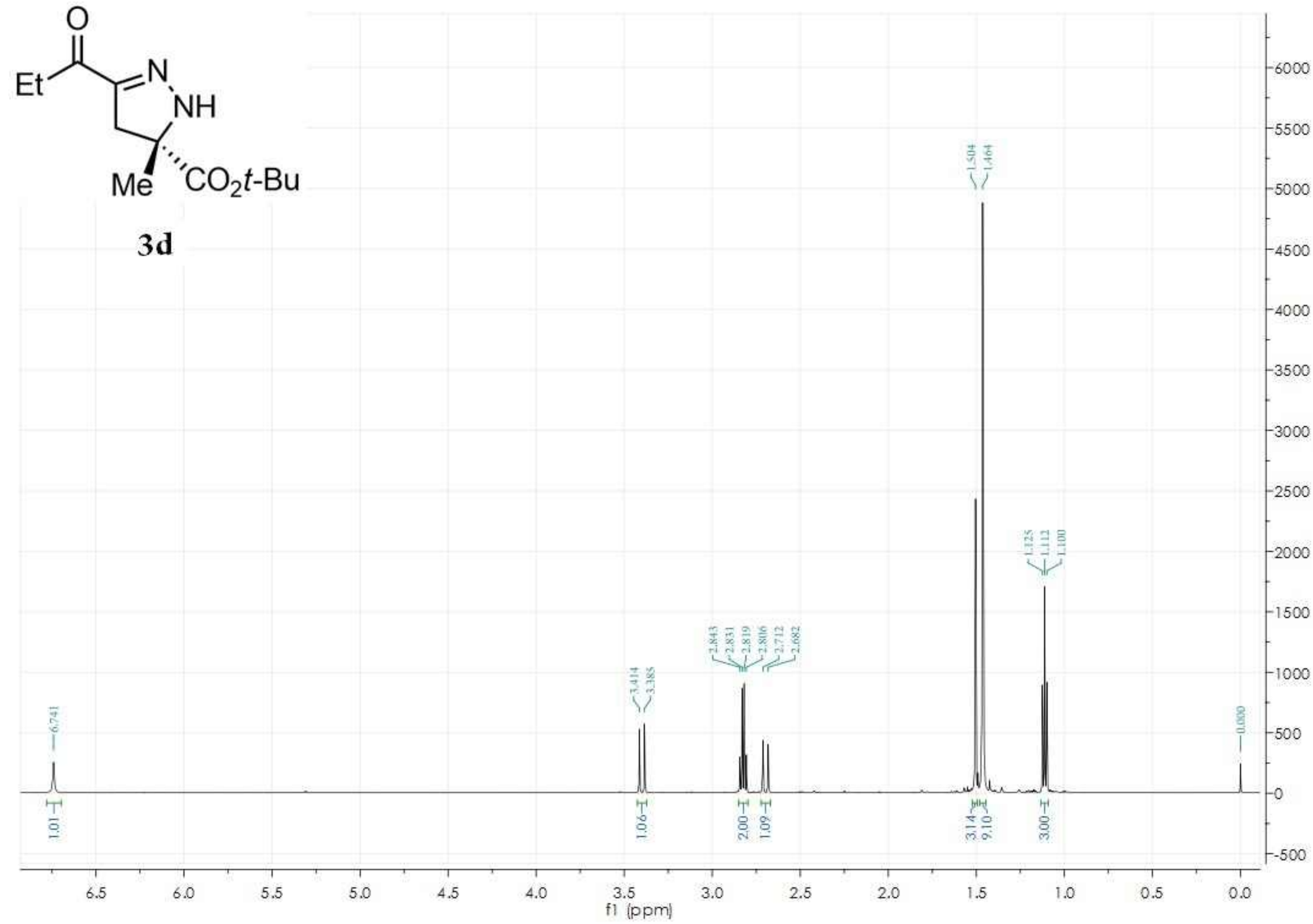
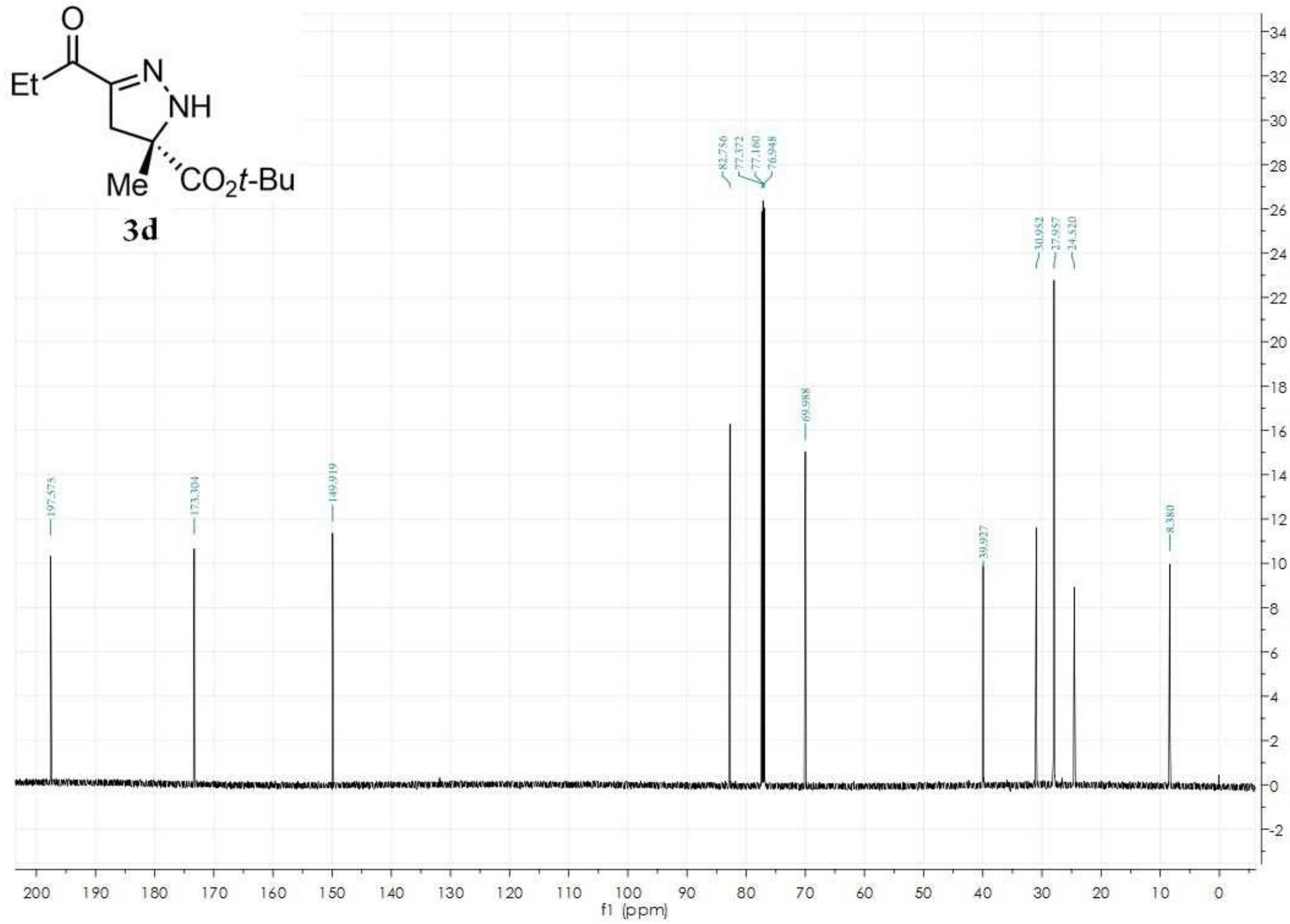
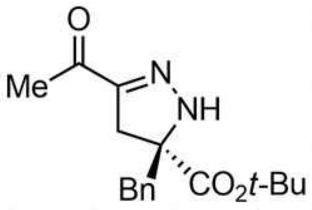
14.147
8.419
f1 (ppm)

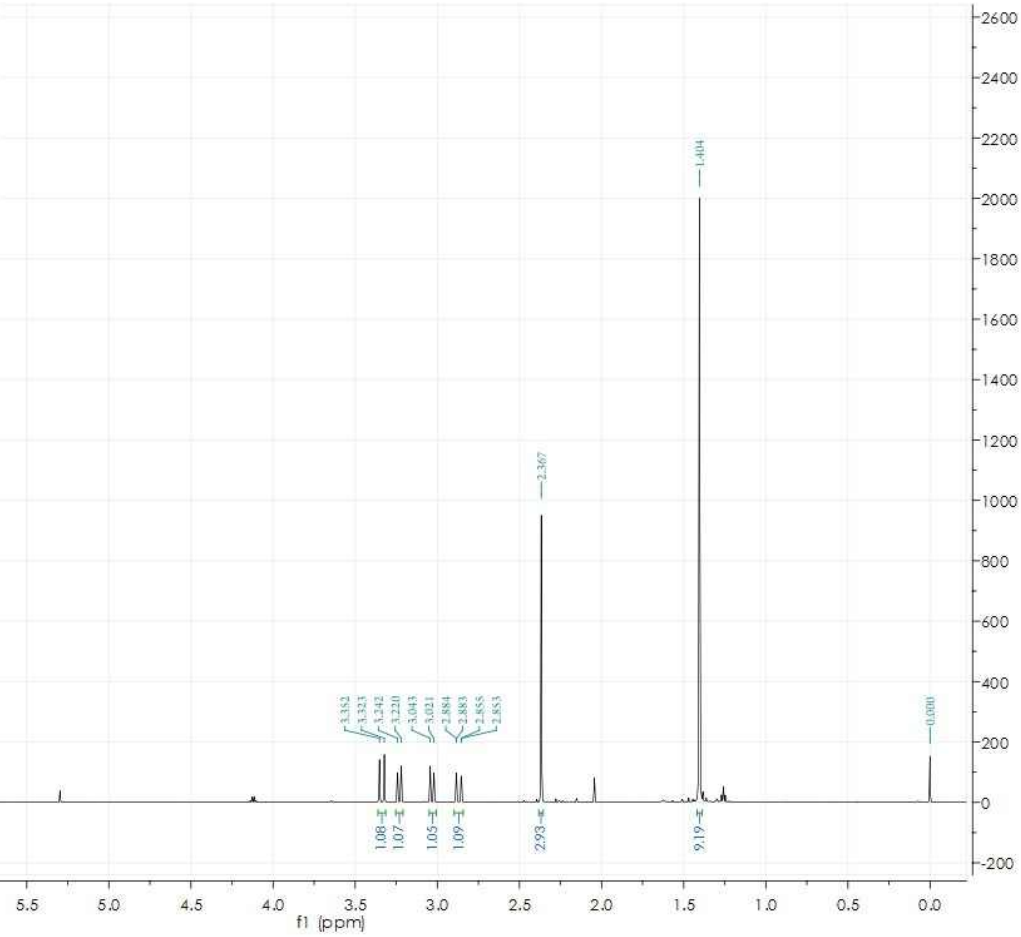

O
Et
N
NH
Me
CO2t-Bu
3d
6.741
3.414
3.385
2.843
2.831
2.819
2.806
2.712
2.682
1.504
1.464
1.125
1.112
1.100
0.000
1.01
1.06
2.00
1.09
3.14
9.10
3.00
f1 (ppm)

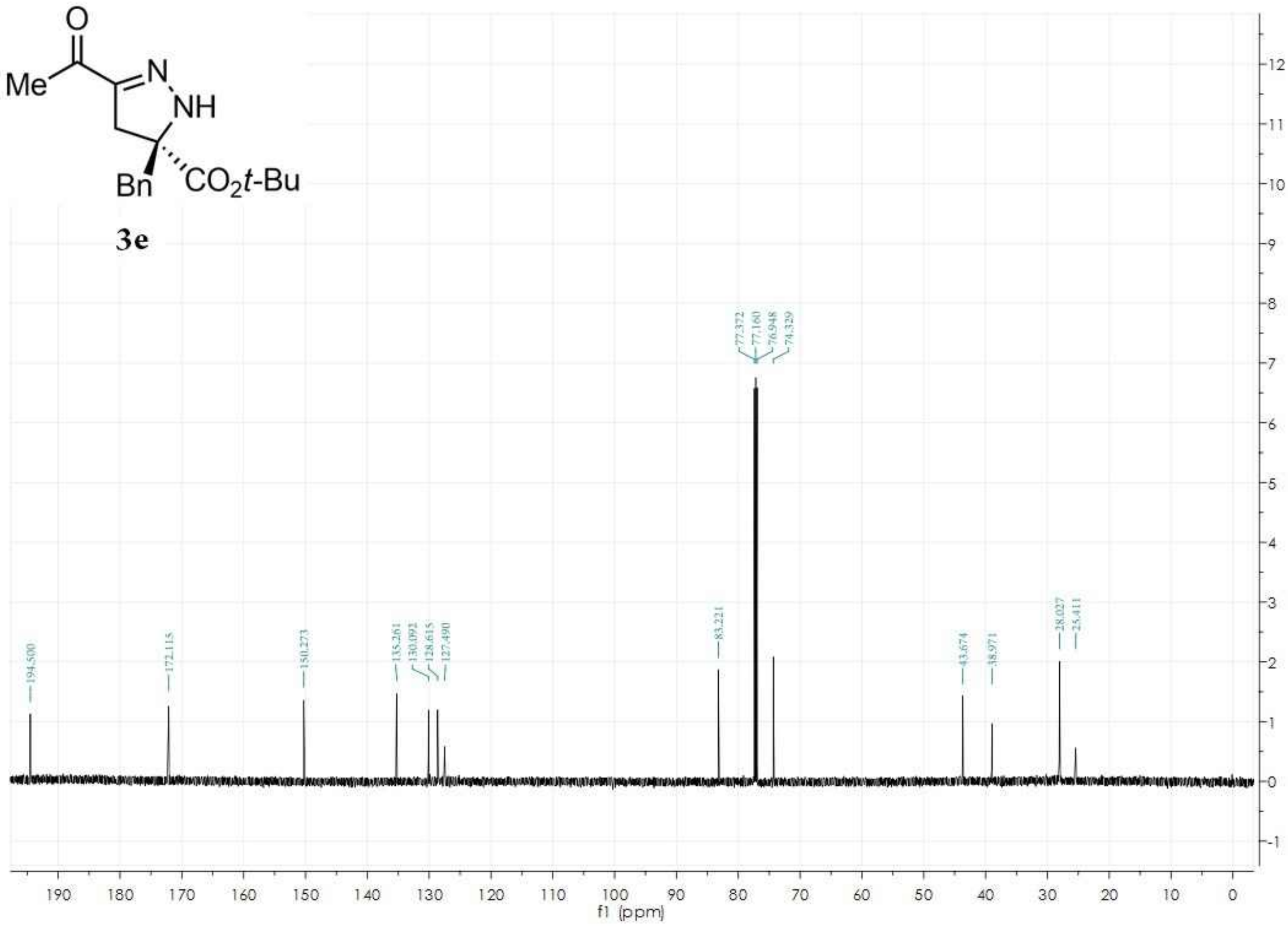


O
N
Et
NH
Me
CO2t-Bu
3d
197.575
173.304
149.919
82.756
77.372
77.160
76.948
69.988
39.927
30.952
27.957
24.520
8.380
f1 (ppm)

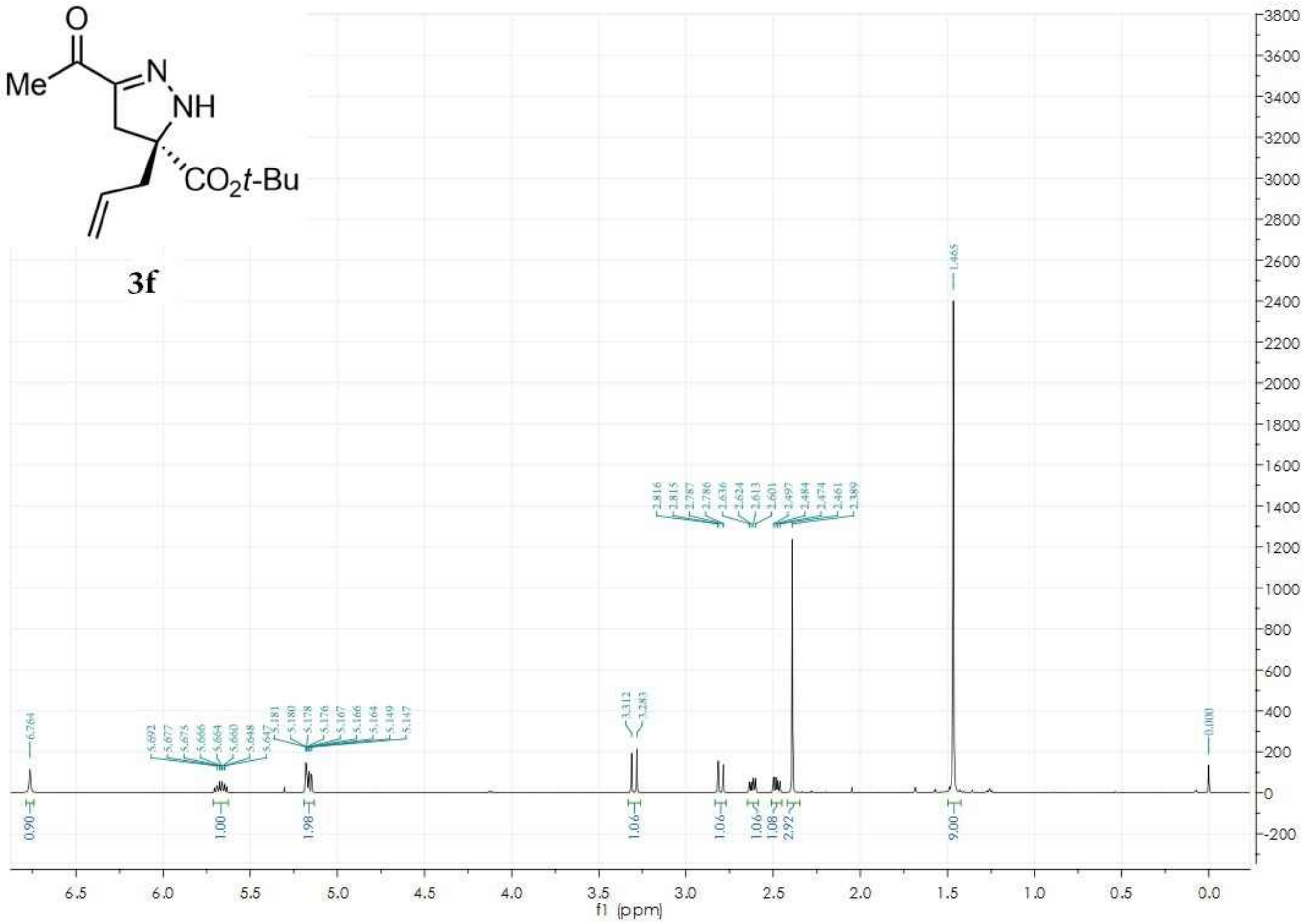


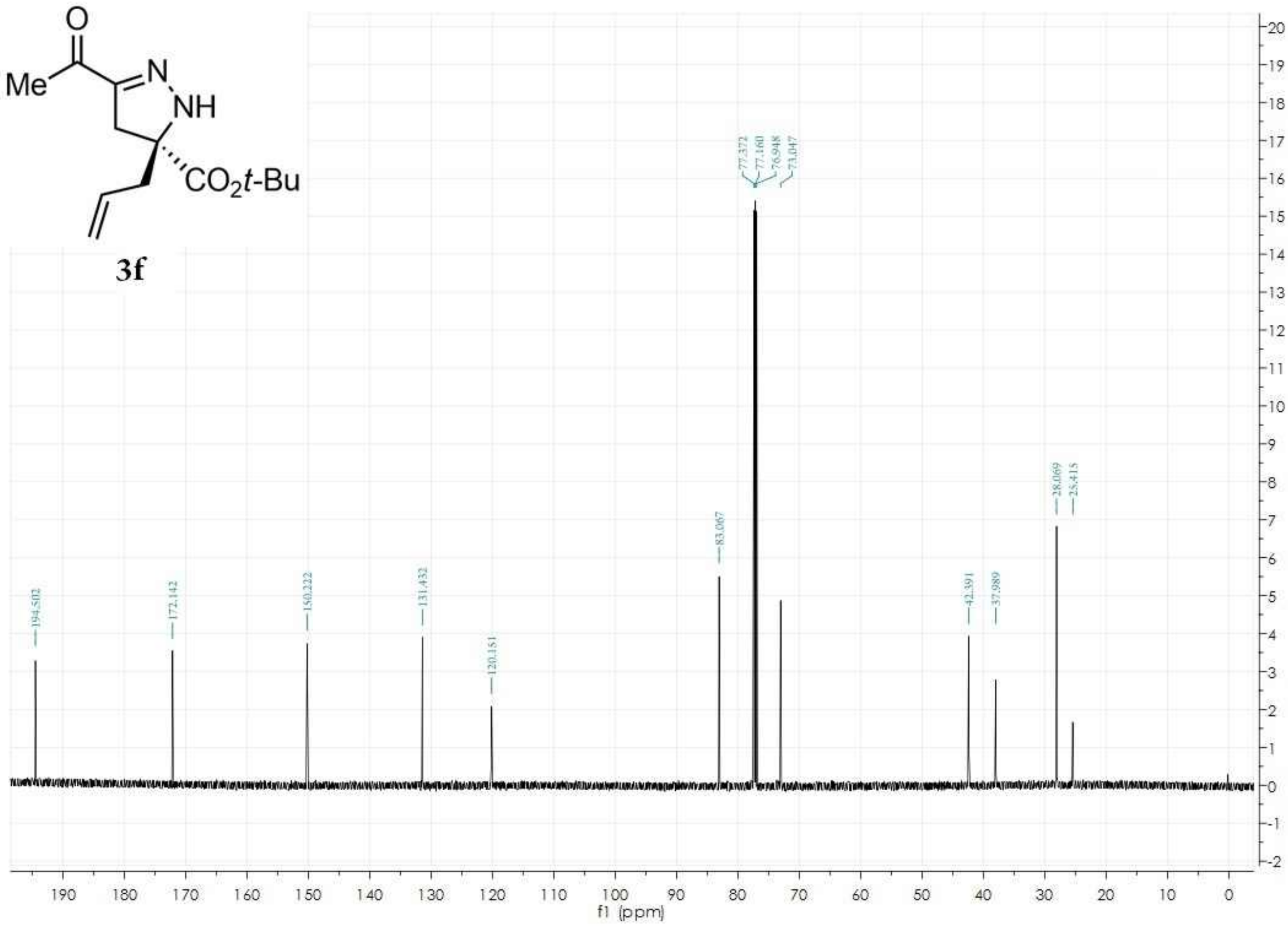
3e



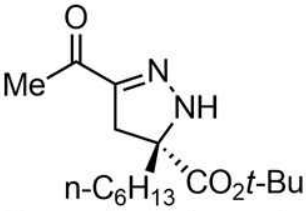


O
Me
N
NH
Bn
CO2t-Bu
3e
194.500
172.115
150.273
135.261
130.092
128.615
127.490
83.221
77.372
77.160
76.948
74.329
43.674
38.971
28.027
25.411
f1 (ppm)

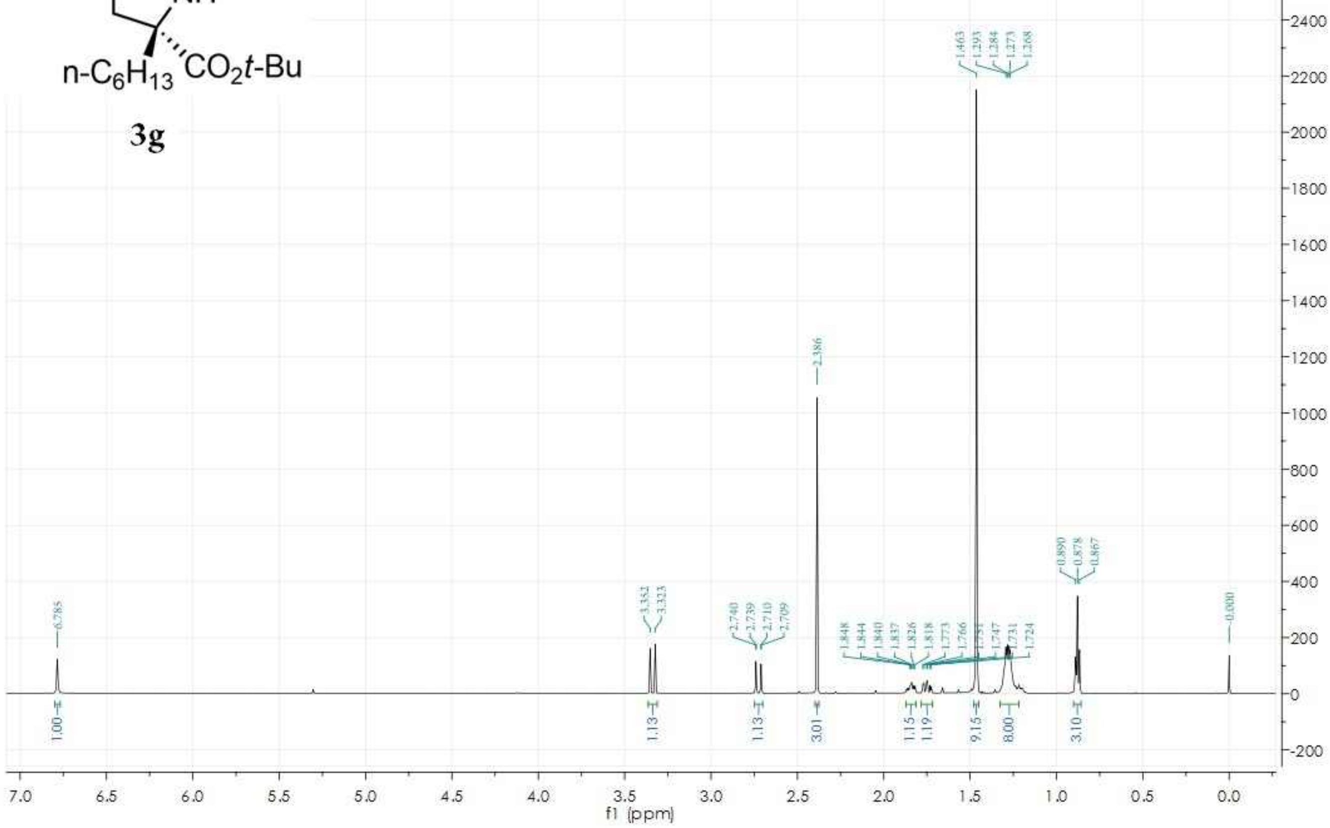

O
Me
N
NH
CO2t-Bu
3f
6.764
5.692
5.677
5.675
5.666
5.664
5.660
5.648
5.647
5.181
5.180
5.178
5.176
5.167
5.166
5.164
5.149
5.147
3.312
3.283
2.816
2.815
2.787
2.786
2.636
2.624
2.613
2.601
2.497
2.484
2.474
2.461
2.389
1.465
0.000
0.90
1.00
1.98
1.06
1.06
1.06
1.08
2.92
9.00
f1 (ppm)

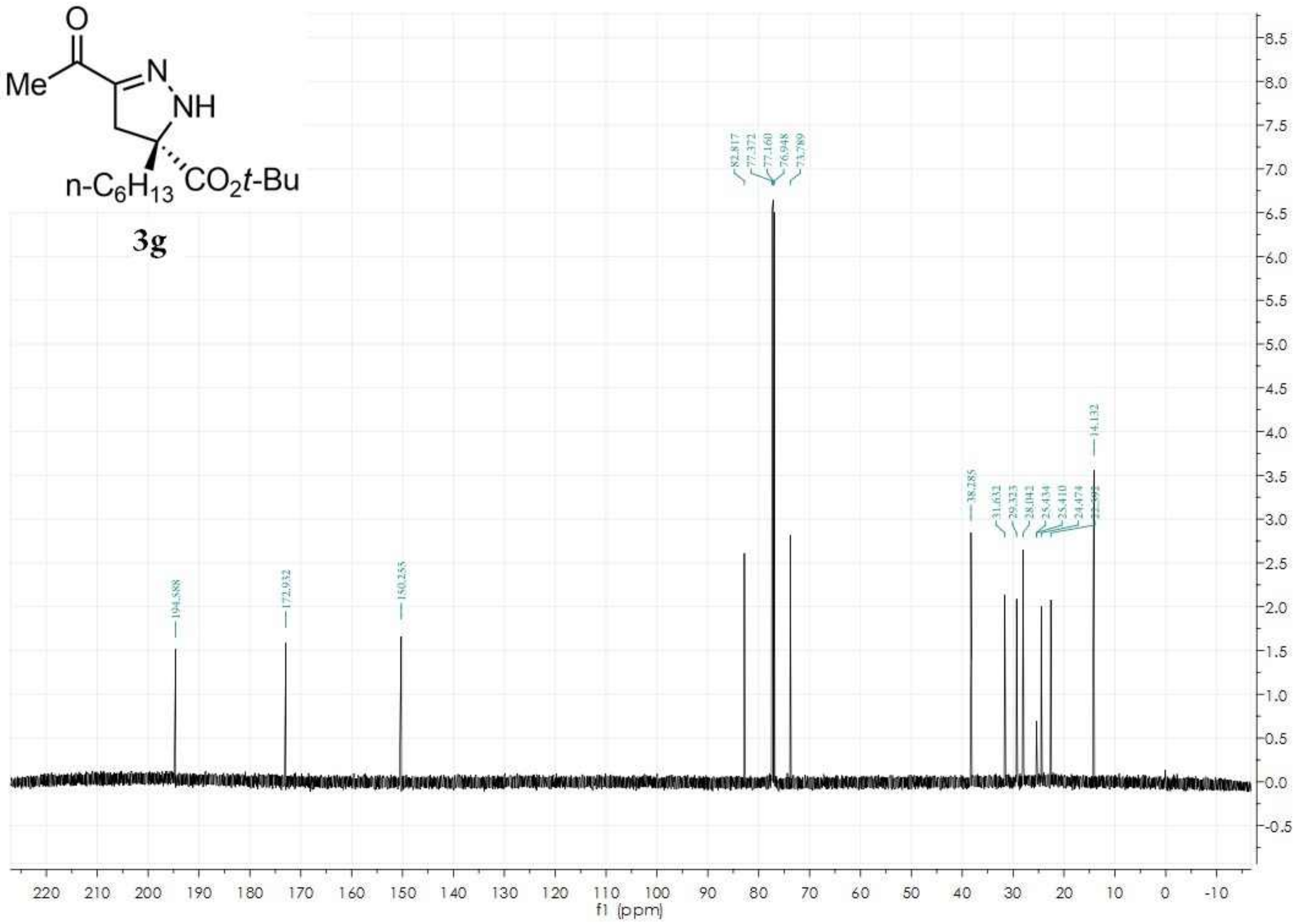


Me
O
N
NH
CO2t-Bu
3f
194.502
172.142
150.222
131.432
120.151
83.067
77.372
77.160
76.948
73.047
42.391
37.989
28.069
25.415
f1 (ppm)


O
Me
N
NH
n-C6H13
CO2t-Bu

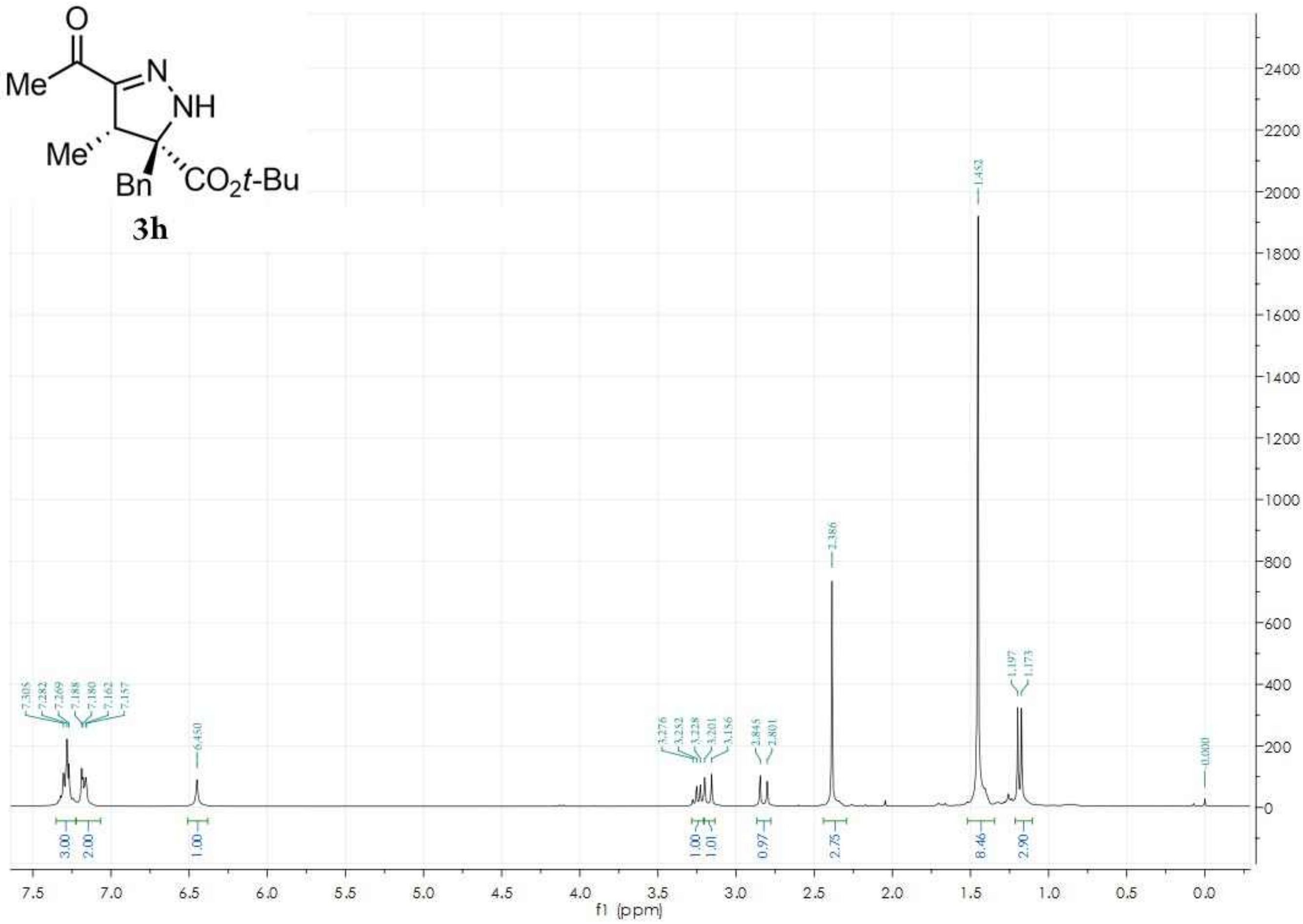
3g

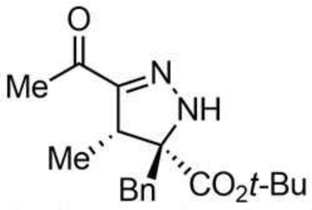

6.785
3.352
3.323
2.740
2.739
2.710
2.709
2.386
1.848
1.844
1.840
1.837
1.826
1.818
1.773
1.766
1.751
1.747
1.731
1.724
1.463
1.293
1.284
1.273
1.268
0.890
0.878
0.867
0.000
1.00
1.13
1.13
3.01
1.15
1.19
9.15
8.00
3.10
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200



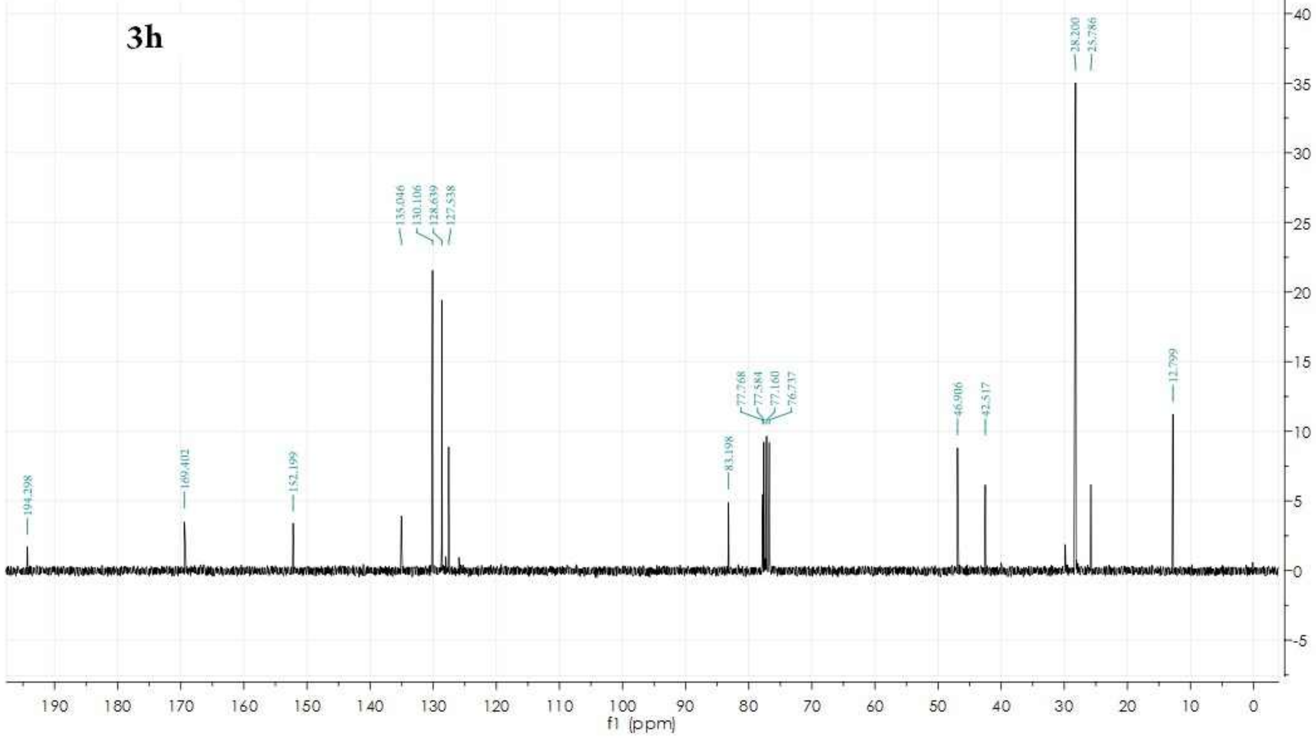
O
Me
N
NH
n-C6H13
CO2t-Bu
194.588
172.932
150.255
82.817
77.372
77.160
76.948
73.789
38.285
31.632
29.323
28.042
25.434
25.410
24.474
14.132
f1 (ppm)

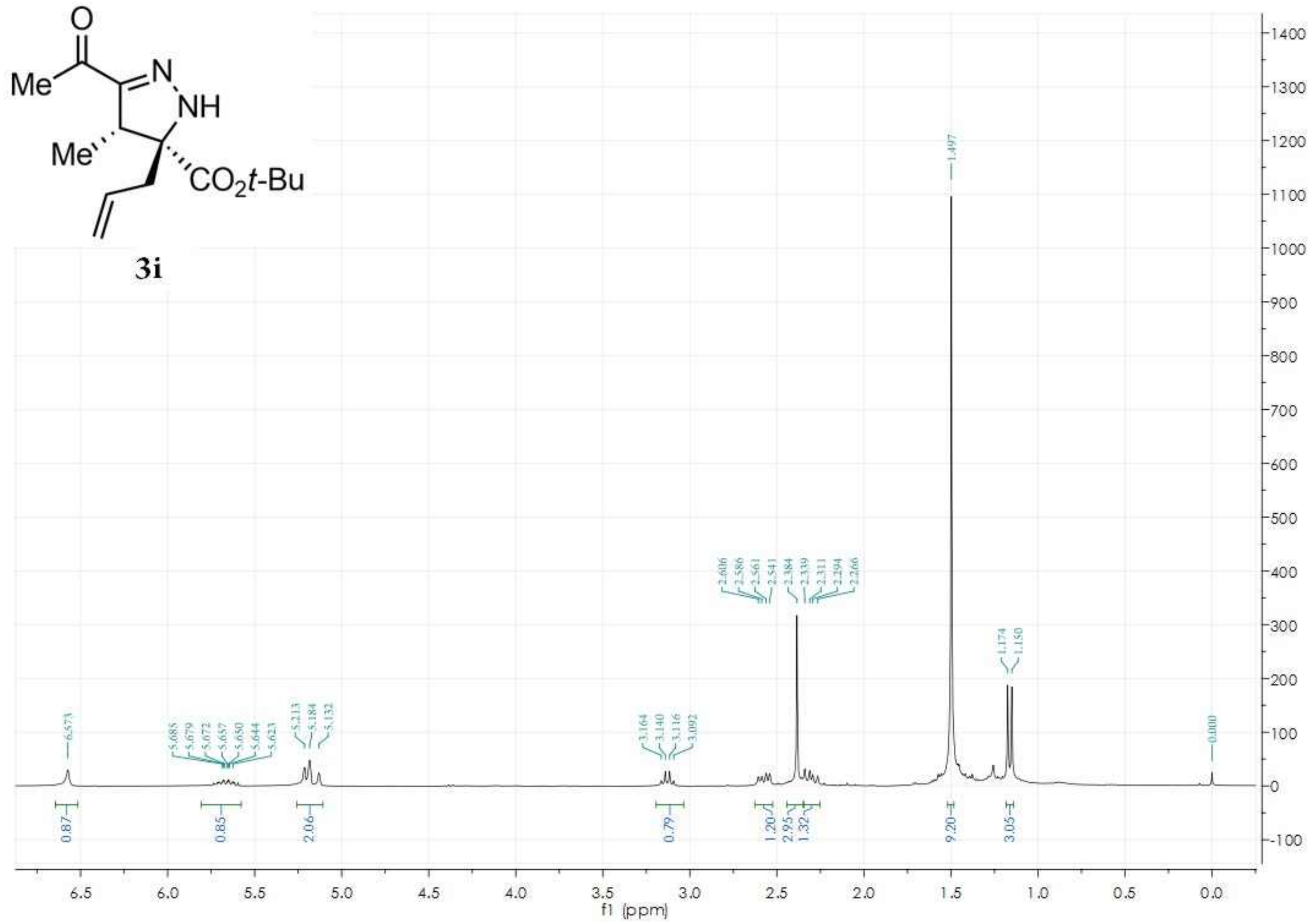
3g

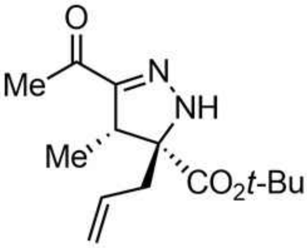

Me
N
NH
Me
Bn
CO2t-Bu
3h
f1 (ppm)


O
Me
N
NH
Me
Bn
CO_2t-Bu

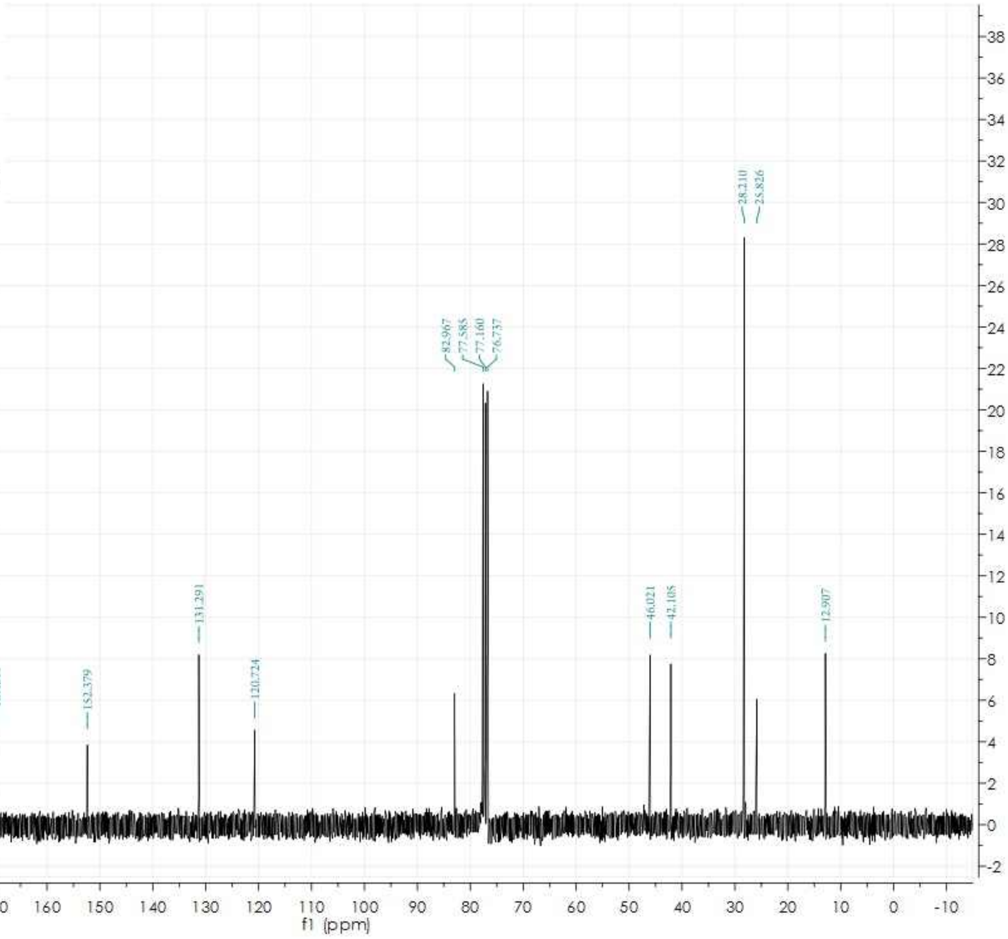
3h

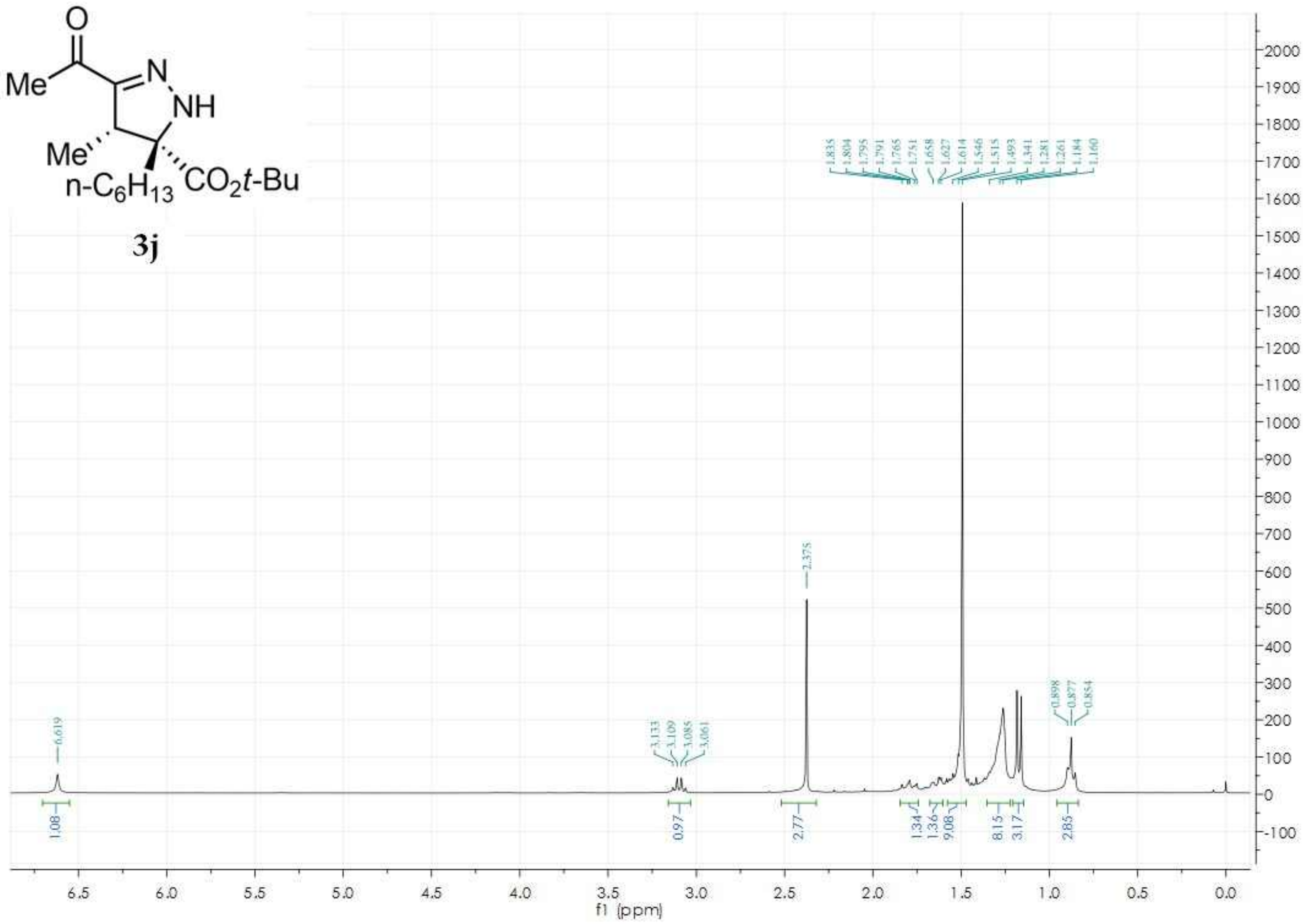

194.298
169.402
152.199
135.046
130.106
128.639
127.538
83.198
77.768
77.584
77.160
76.737
46.906
42.517
28.200
25.786
12.799
f1 (ppm)

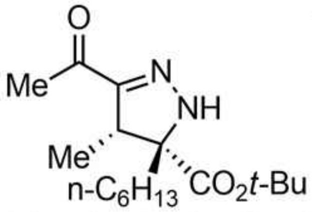

Me
N
NH
Me
CO2t-Bu
3i
f1 (ppm)
1.497
0.87
0.85
2.06
0.79
1.20
2.95
1.32
9.20
3.05


O
Me
N
NH
Me
CO2t-Bu

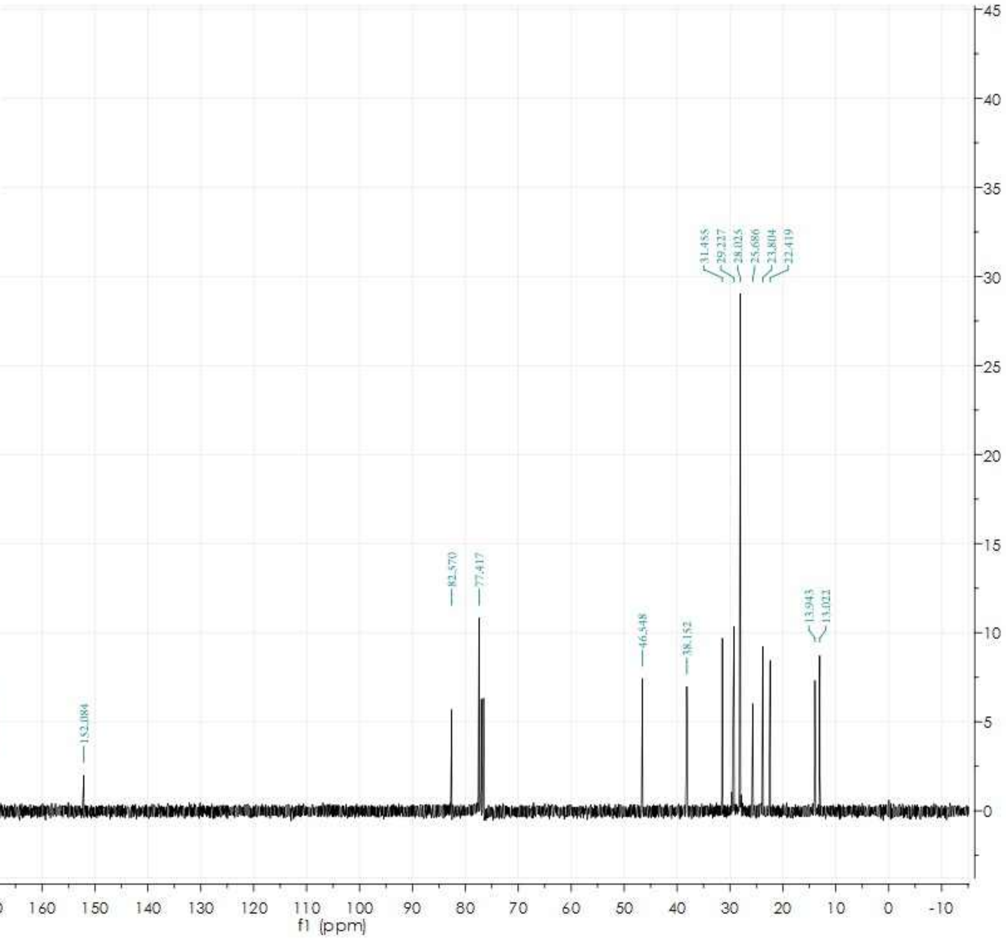
3i


194.338
169.619
152.379
131.291
120.724
82.967
77.585
77.160
76.737
46.021
42.105
28.210
25.826
12.907
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2

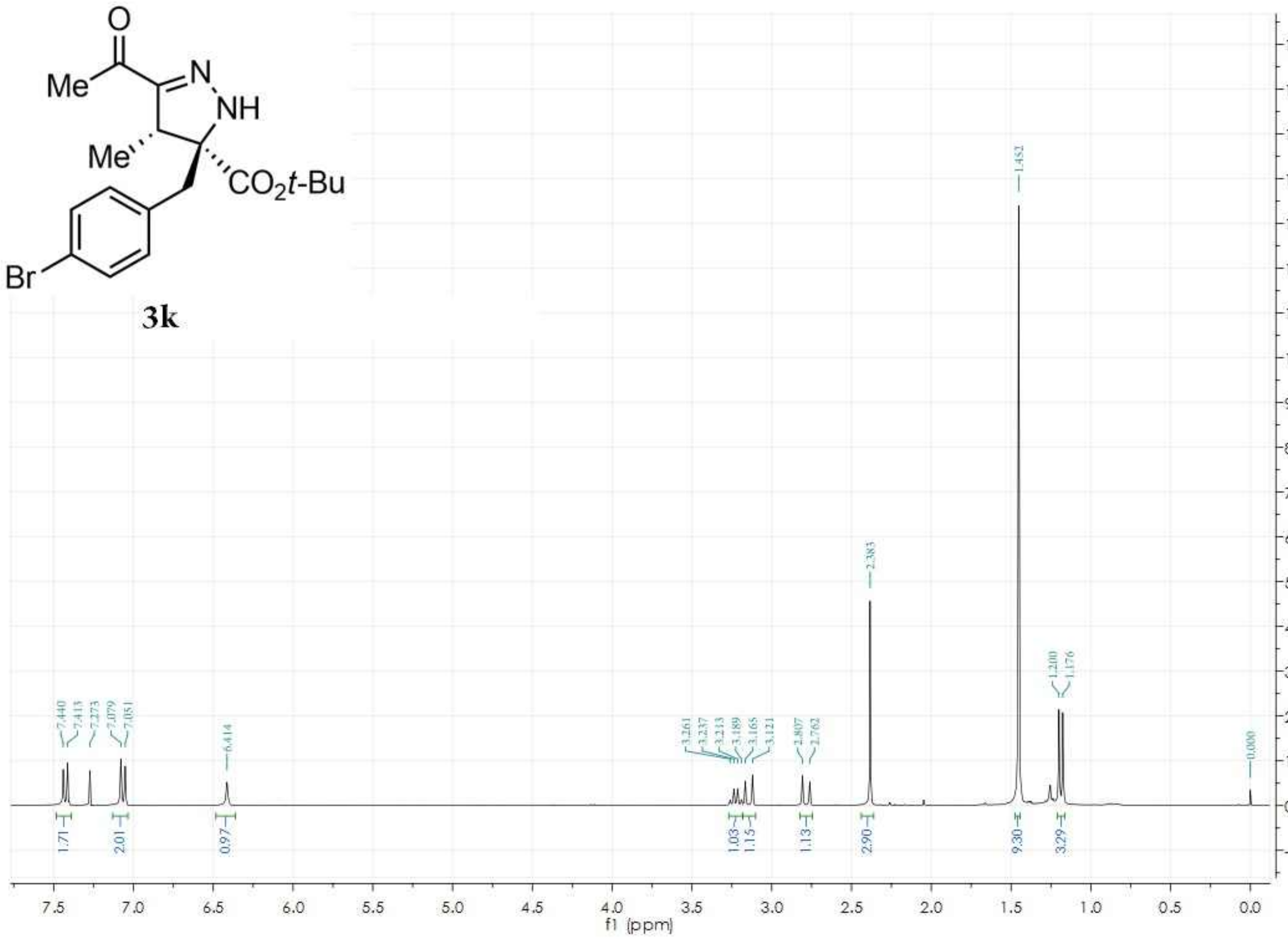

O
Me
N
NH
Me
n-C_6H_{13}
CO_2t-Bu
3j
6.619
3.133
3.109
3.085
3.061
2.375
1.835
1.804
1.795
1.791
1.765
1.751
1.658
1.627
1.614
1.546
1.515
1.493
1.341
1.281
1.261
1.184
1.160
0.898
0.877
0.854
1.08
0.97
2.77
1.34
1.36
9.08
8.15
3.17
2.85
f1 (ppm)



3j

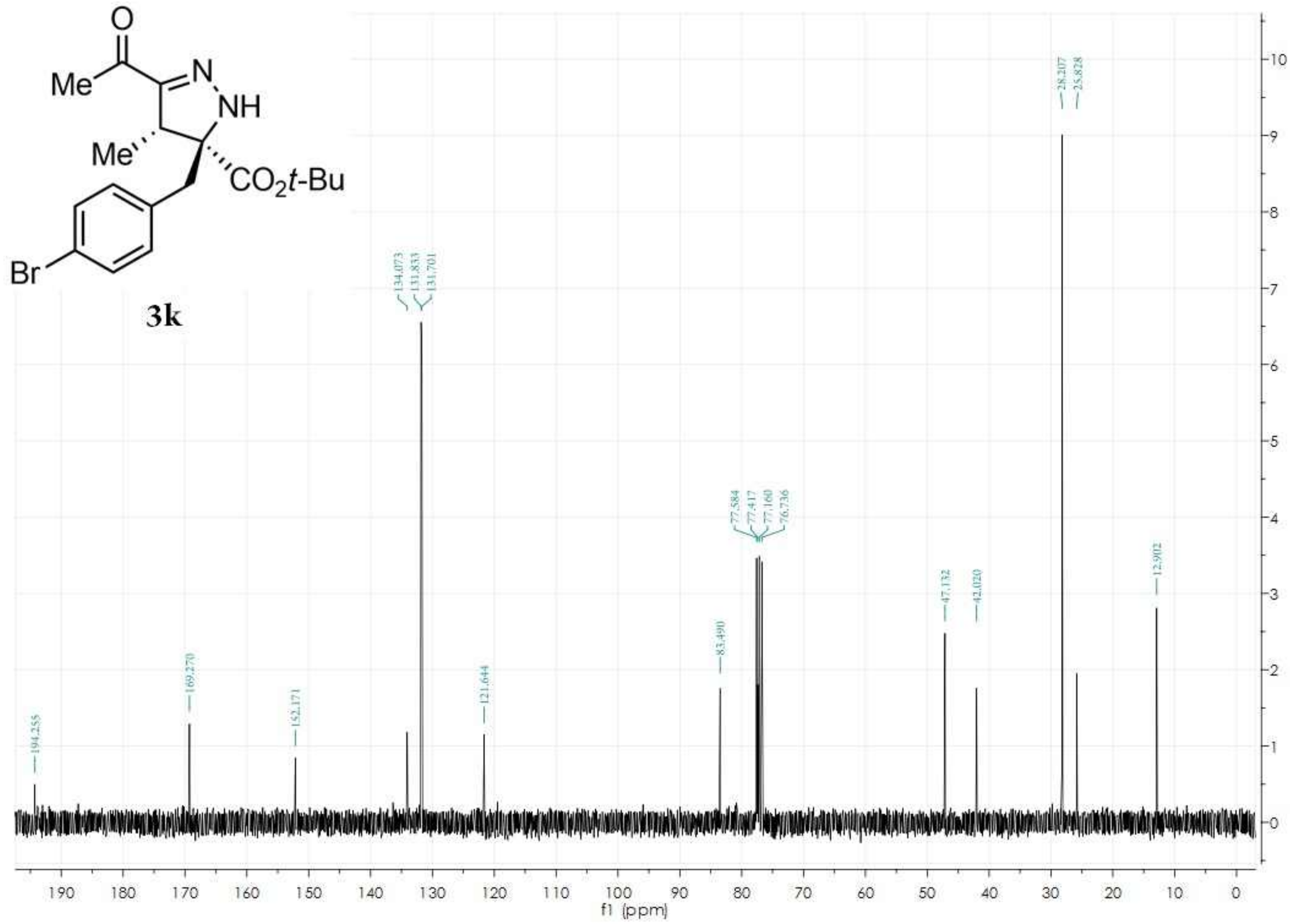


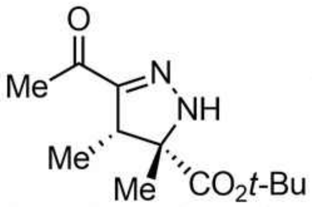
194.252
170.271
152.084
82.570
77.417
46.548
38.152
31.455
29.237
28.025
25.686
23.804
22.419
13.943
13.022
f1 (ppm)



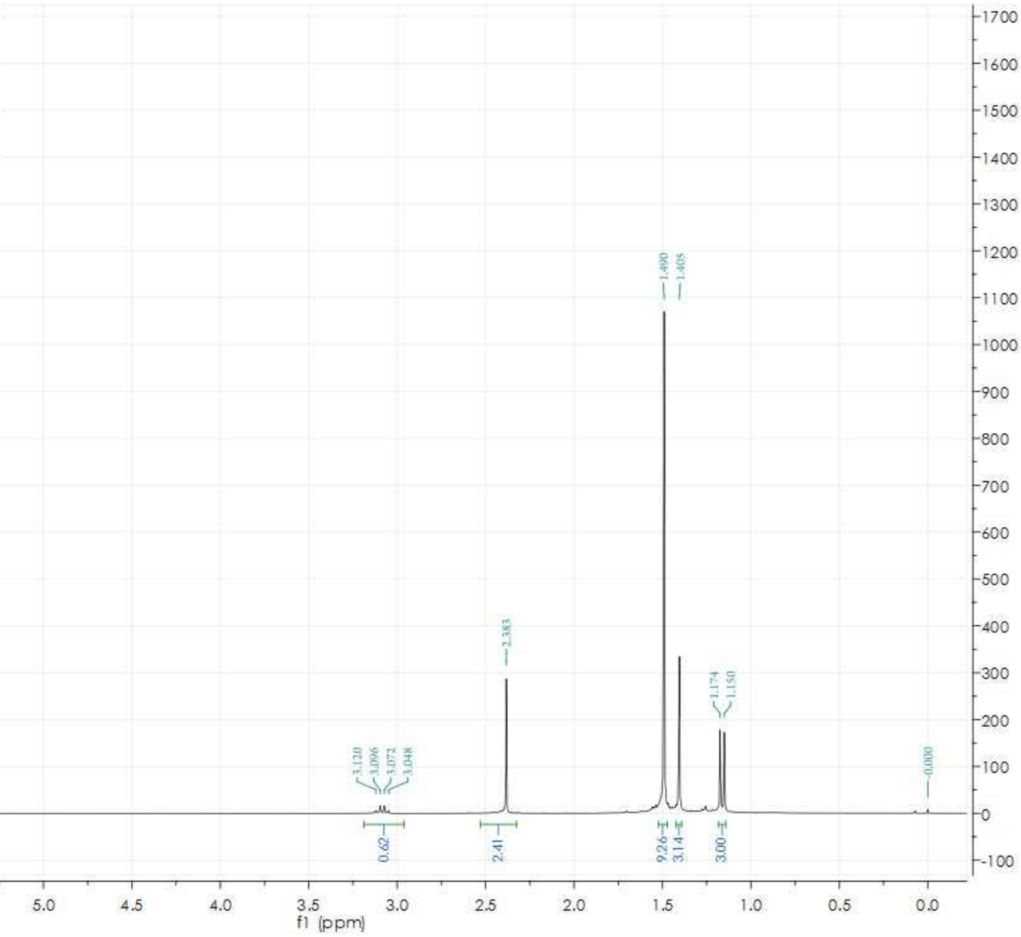
O
Me
N
NH
Me
CO2t-Bu
Br
7.440
7.413
7.273
7.079
7.051
6.414
3.261
3.237
3.213
3.189
3.165
3.121
2.807
2.762
2.383
1.452
1.200
1.176
0.000
1.71
2.01
0.97
1.03
1.15
1.13
2.90
9.30
3.29
f1 (ppm)

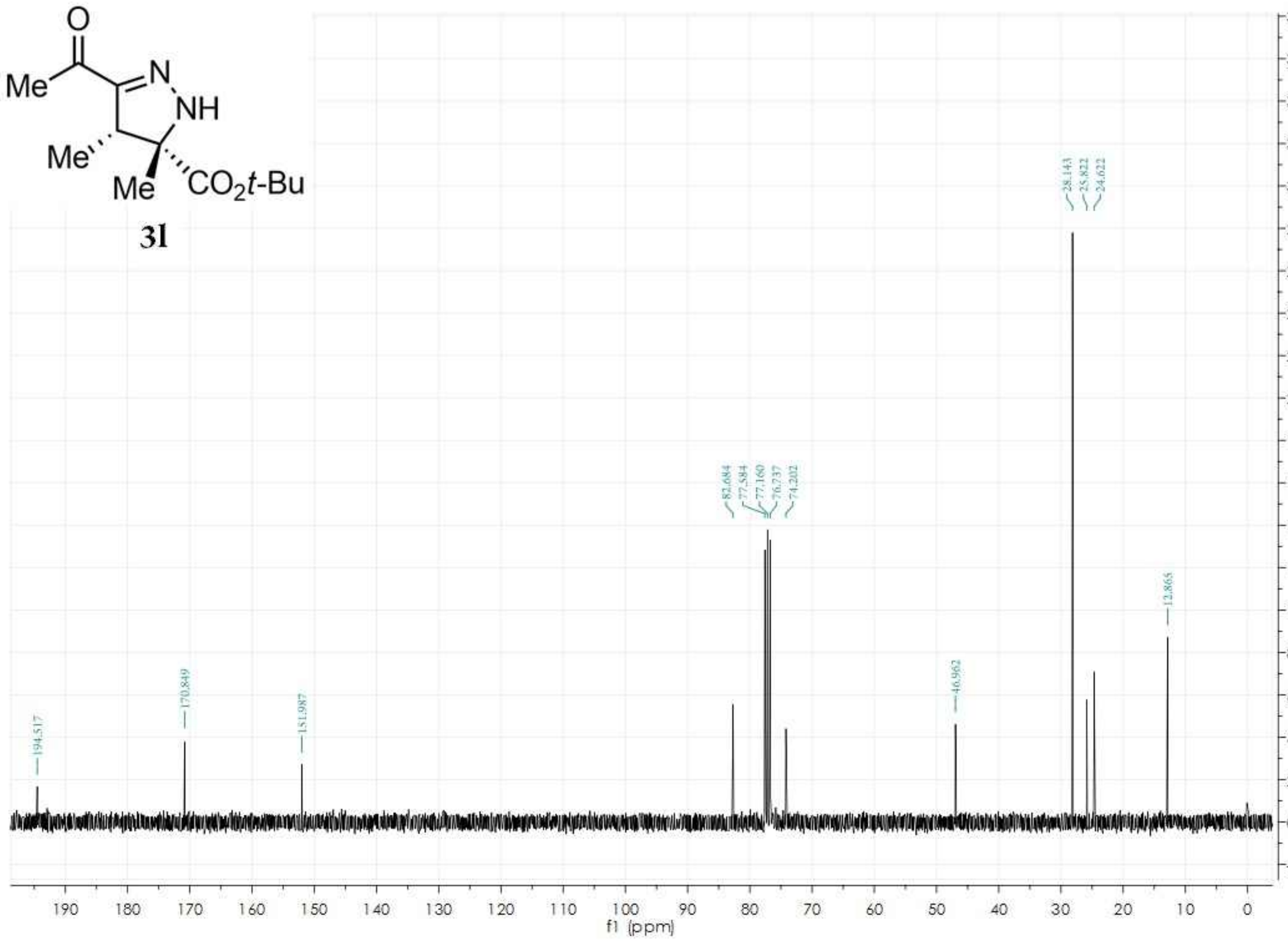
3k


O
Me
N
NH
Me
CO2t-Bu
Br
3k
194.255
169.270
152.171
134.073
131.833
131.701
121.644
83.490
77.584
77.417
77.160
76.736
47.132
42.020
28.207
25.828
12.902
f1 (ppm)

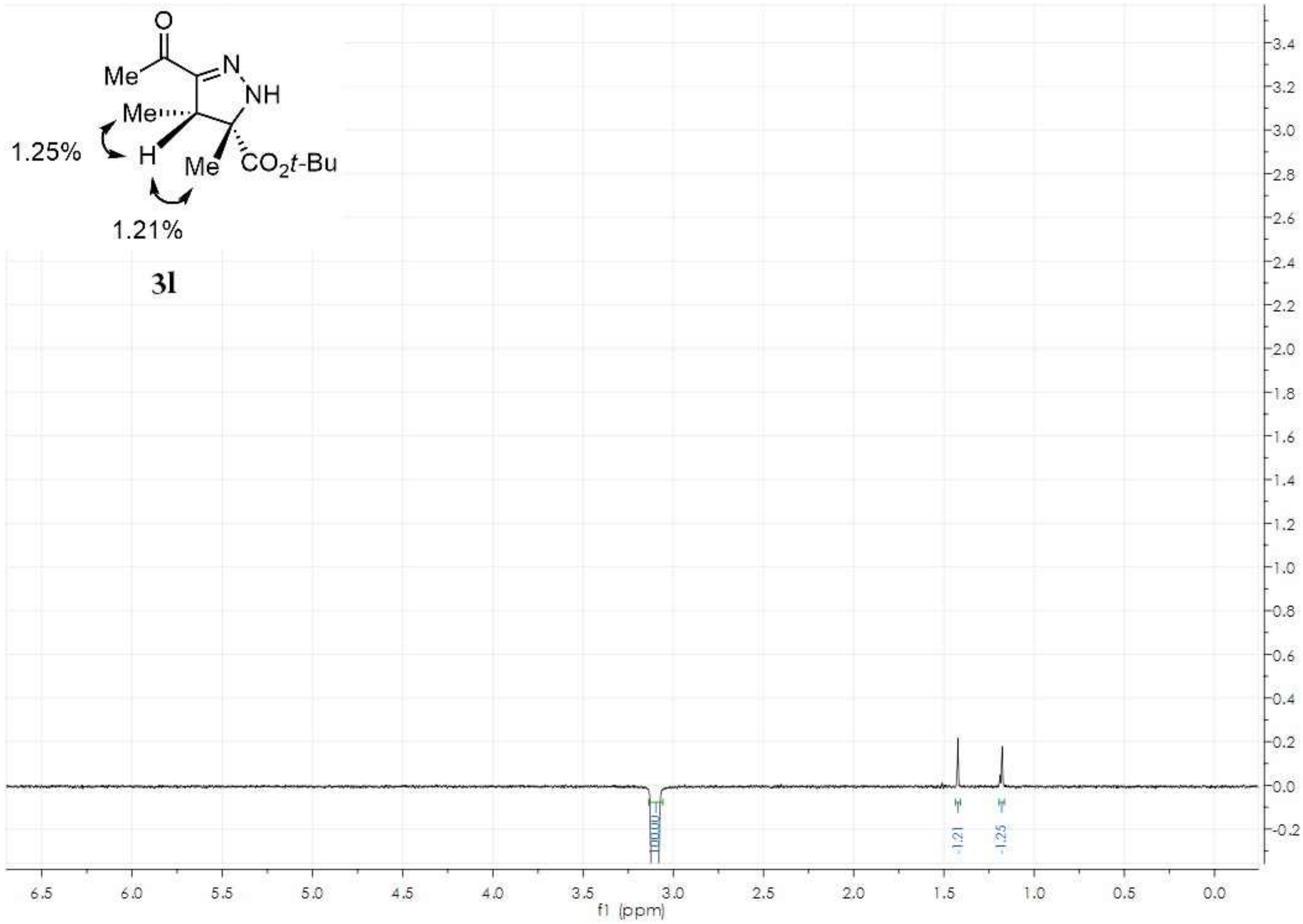

O
Me
N
NH
Me
Me
CO2t-Bu

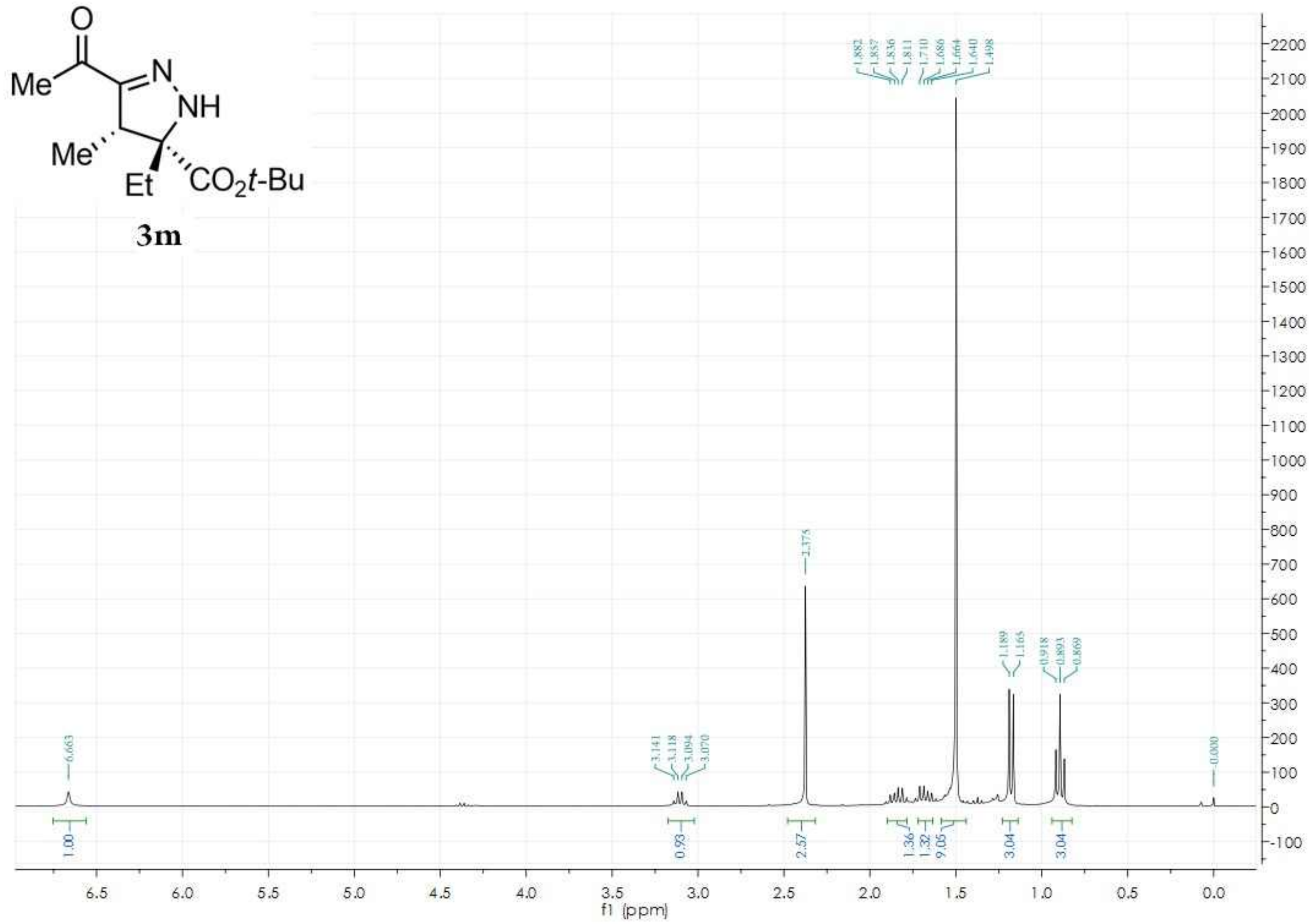
3l


6.464
3.120
3.096
3.072
3.048
2.383
1.490
1.405
1.174
1.150
0.000
0.93
0.62
2.41
9.26
3.14
3.00
f1 (ppm)

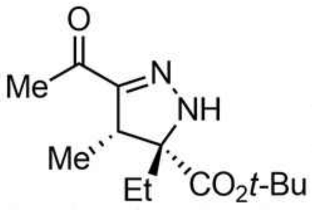


O
Me
N
NH
Me
Me
CO2t-Bu
3l
194.517
170.849
151.987
82.684
77.584
77.160
76.737
74.202
46.962
28.143
25.822
24.622
12.865
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2


O
Me
N
NH
Me
H
Me
CO2t-Bu
1.25%
1.21%
3l
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-1.21
-1.25
-100.00
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)

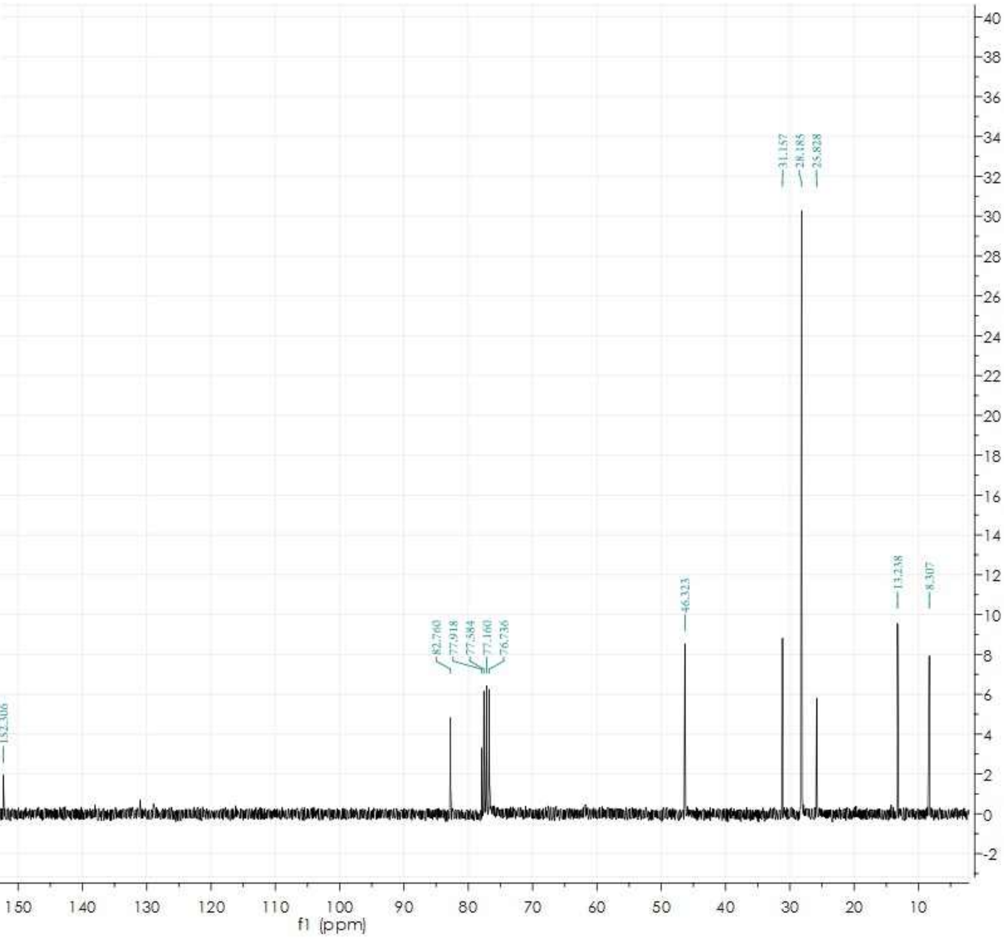

Me
O
N
NH
Me
Et
CO2t-Bu
1.882
1.857
1.836
1.811
1.710
1.686
1.664
1.640
1.498
2.375
1.189
1.165
0.918
0.893
0.869
6.663
3.141
3.118
3.094
3.070
0.000
1.00
0.93
2.57
1.36
1.32
9.05
3.04
3.04
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

3m

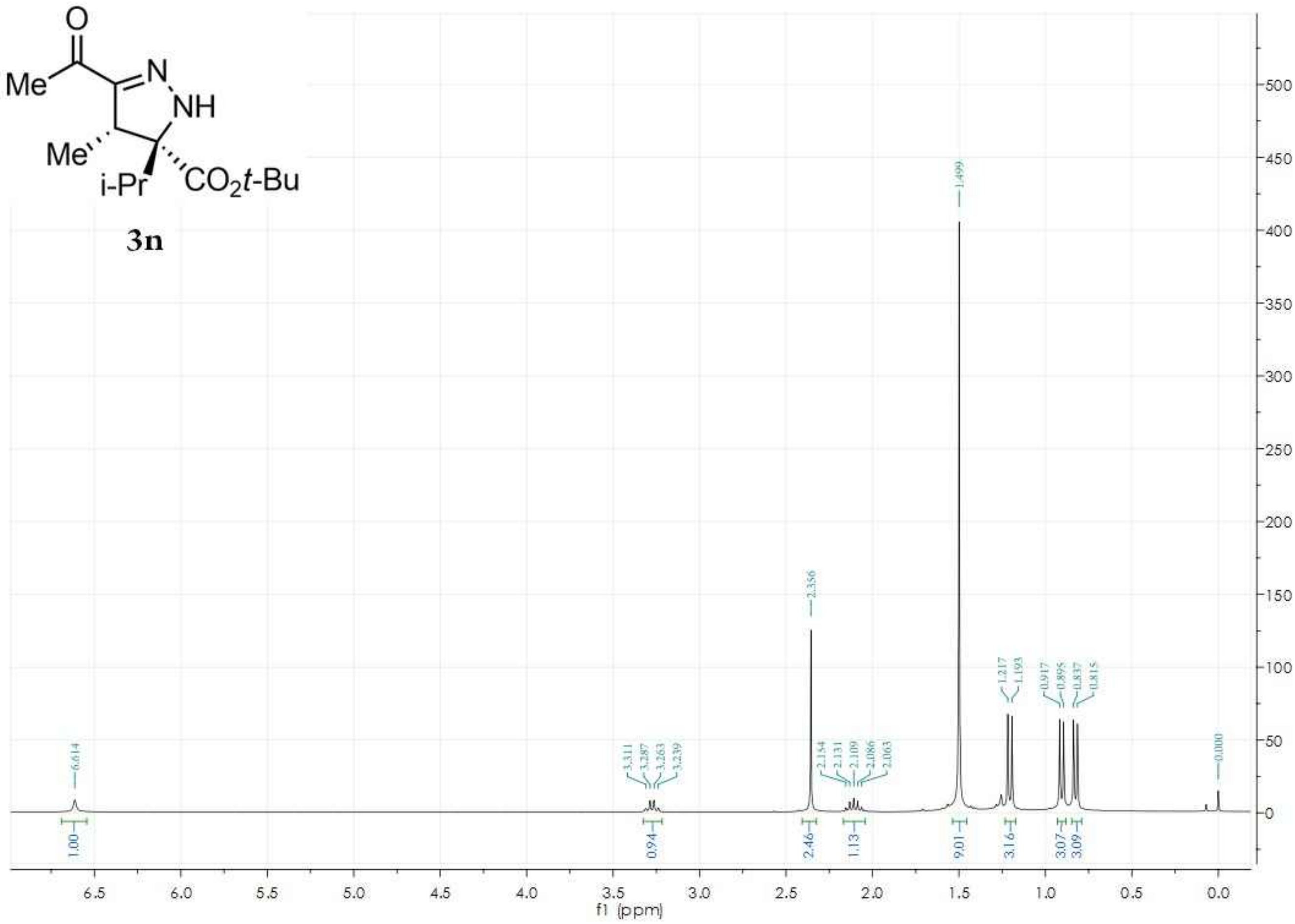


O
Me
N
NH
Me
Et
CO2t-Bu

3m

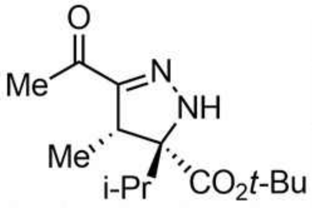


194.394
170.297
152.306
82.760
77.918
77.584
77.160
76.736
46.323
31.157
28.185
25.828
13.238
8.307
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)
40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2

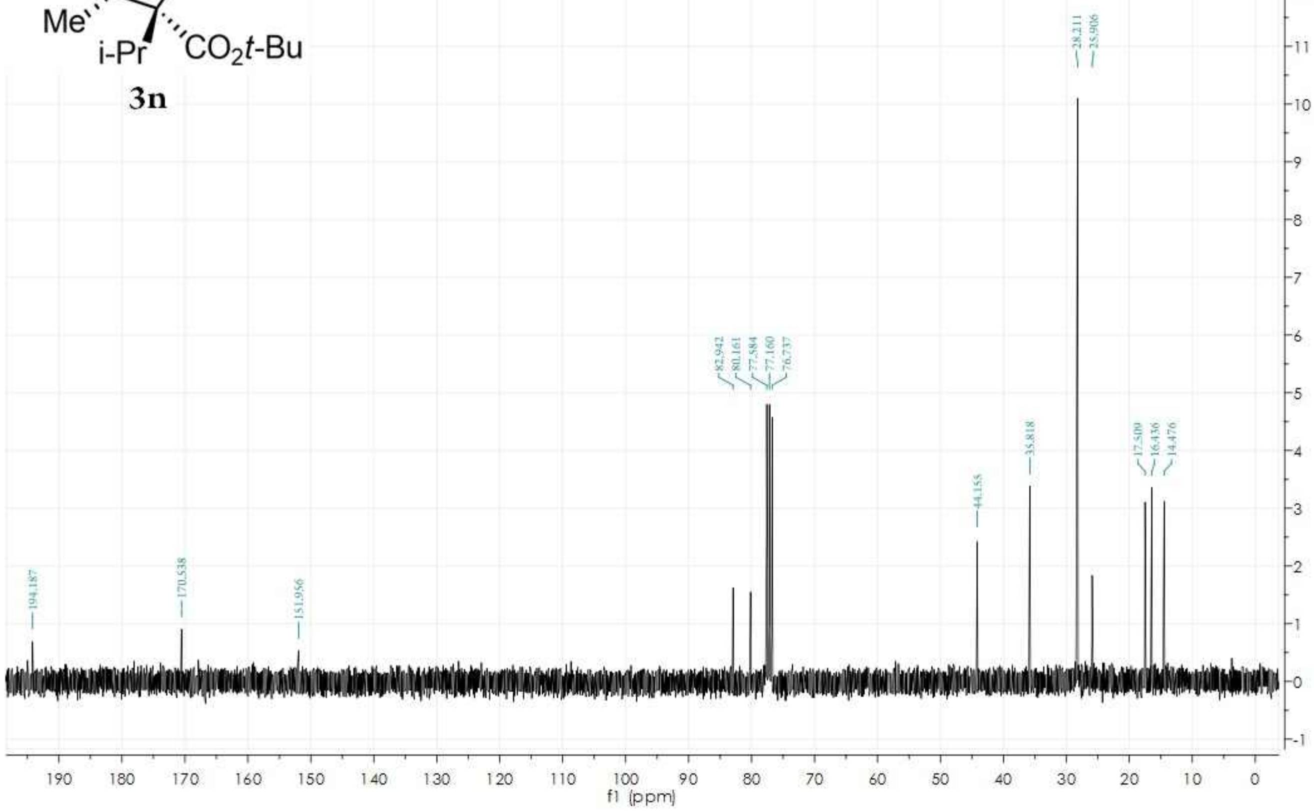


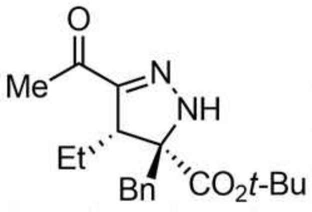
O
Me
N
NH
Me
i-Pr
CO2t-Bu
6.614
3.311
3.287
3.263
3.239
2.356
2.154
2.131
2.109
2.086
2.063
1.499
1.217
1.193
0.917
0.895
0.837
0.815
0.000
1.00
0.94
2.46
1.13
9.01
3.16
3.07
3.09
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
500
450
400
350
300
250
200
150
100
50
0

3n

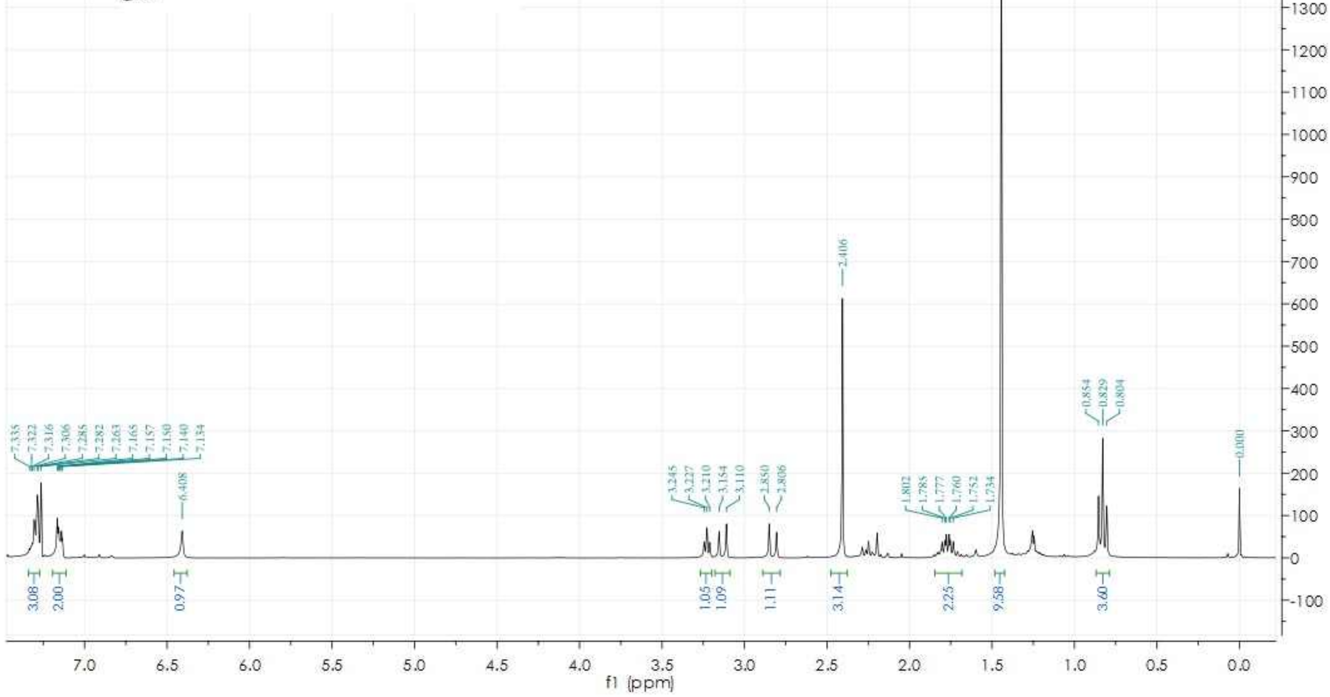


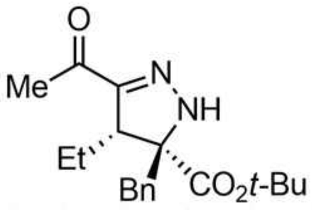
3n


194.187
170.538
151.956
82.942
80.161
77.584
77.160
76.737
44.155
35.818
28.211
25.906
17.509
16.436
14.476
f1 (ppm)

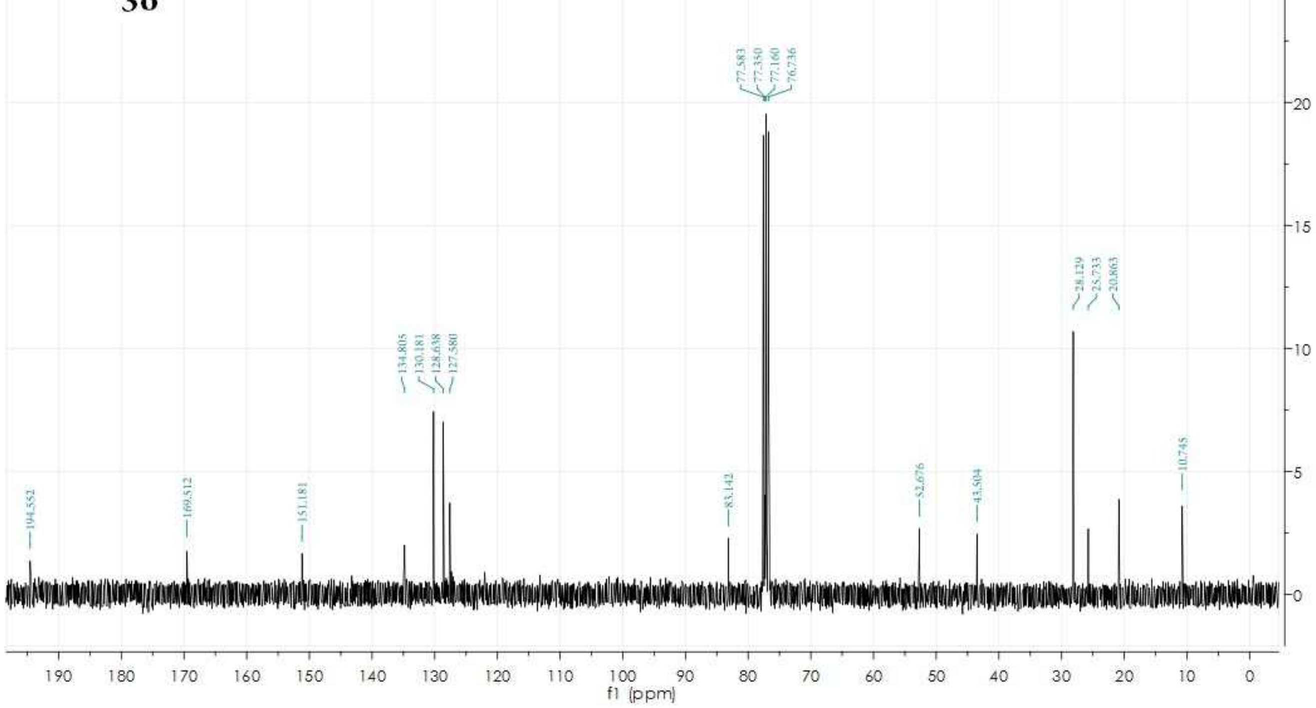


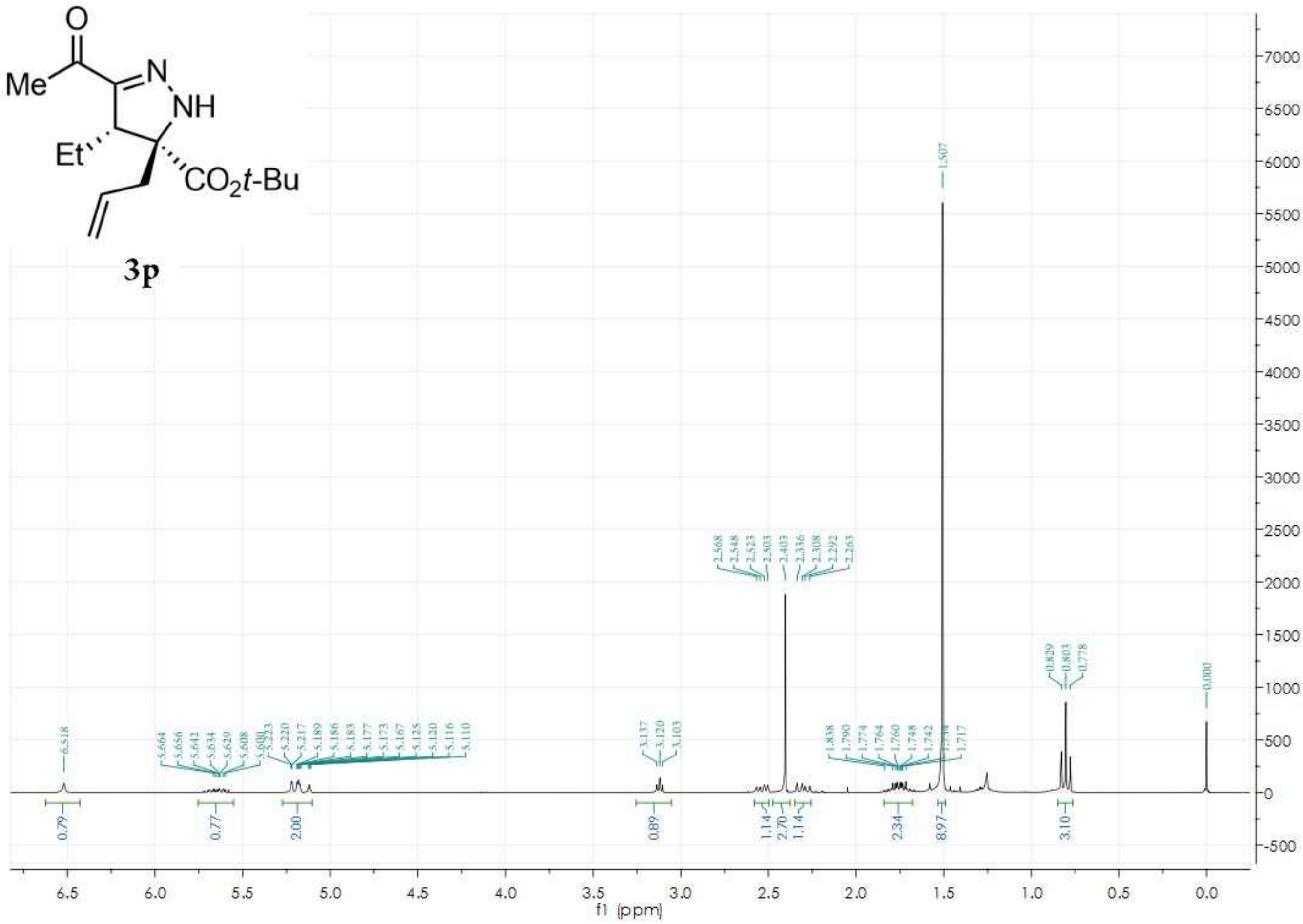
3o



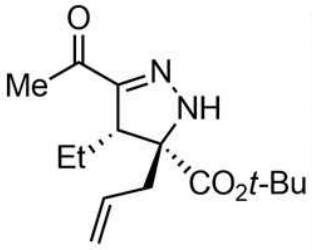

O
Me
N
NH
Et
Bn
CO2t-Bu

3o

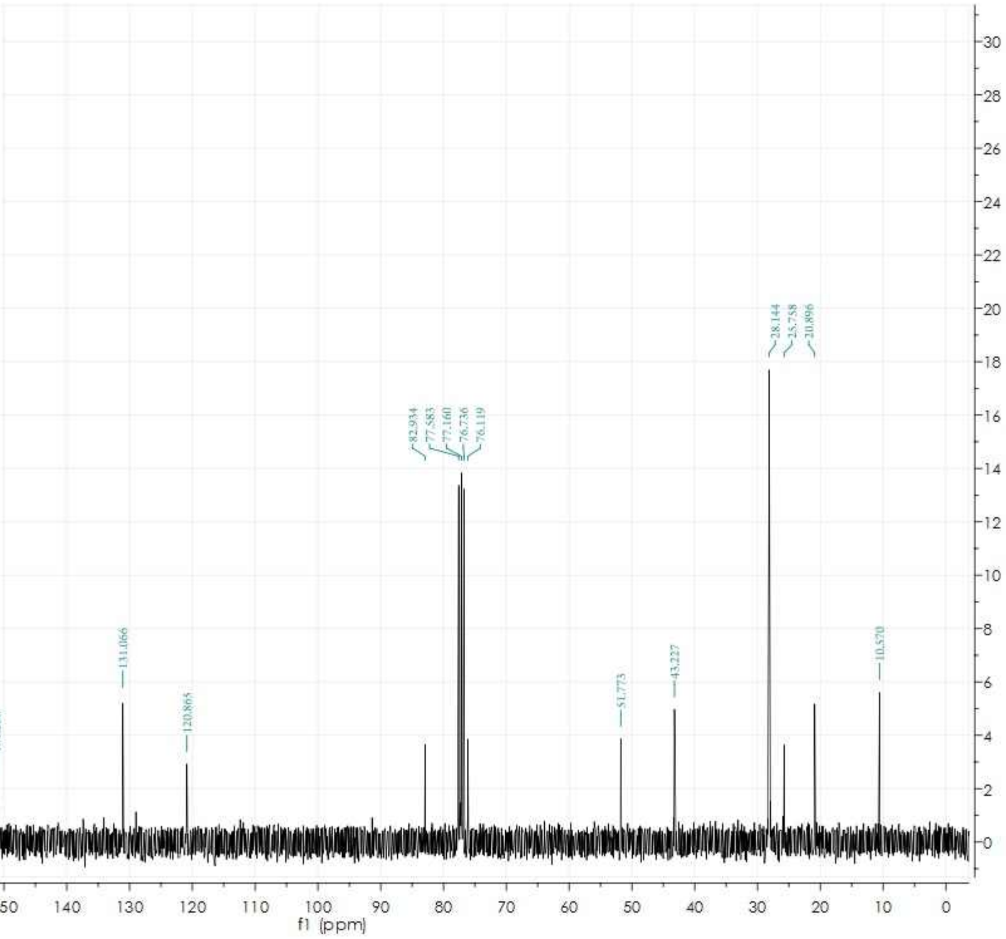

194.552
169.512
151.181
134.805
130.181
128.638
127.580
83.142
77.583
77.350
77.160
76.736
52.676
43.504
28.129
25.733
20.863
10.745
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
0 5 10 15 20 25 30

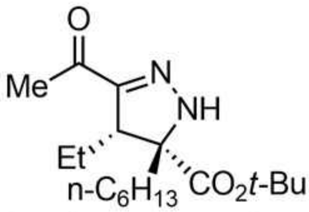


3p

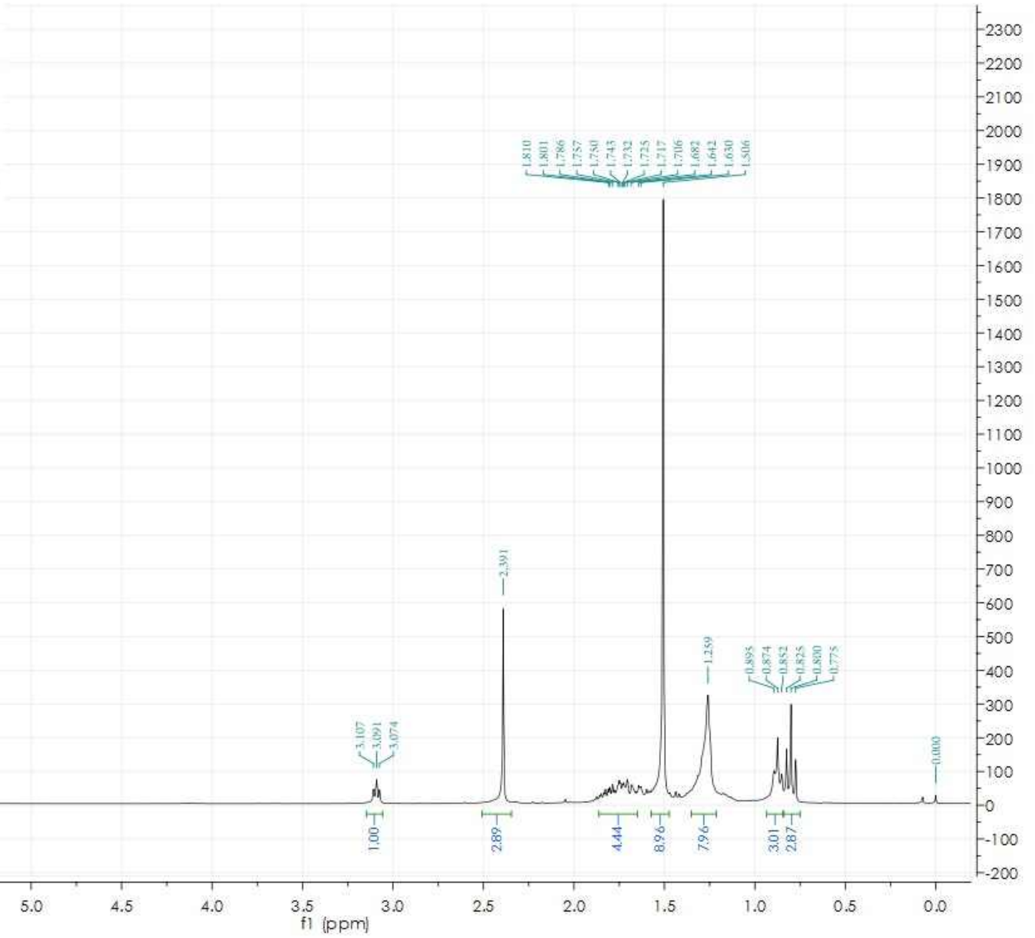


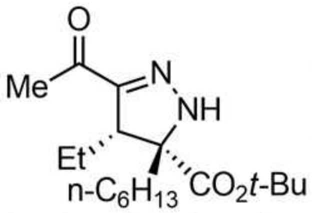
3p


194.573
169.763
151.286
131.066
120.865
82.934
77.583
77.160
76.736
76.119
51.773
43.227
28.144
25.758
20.896
10.570
f1 (ppm)

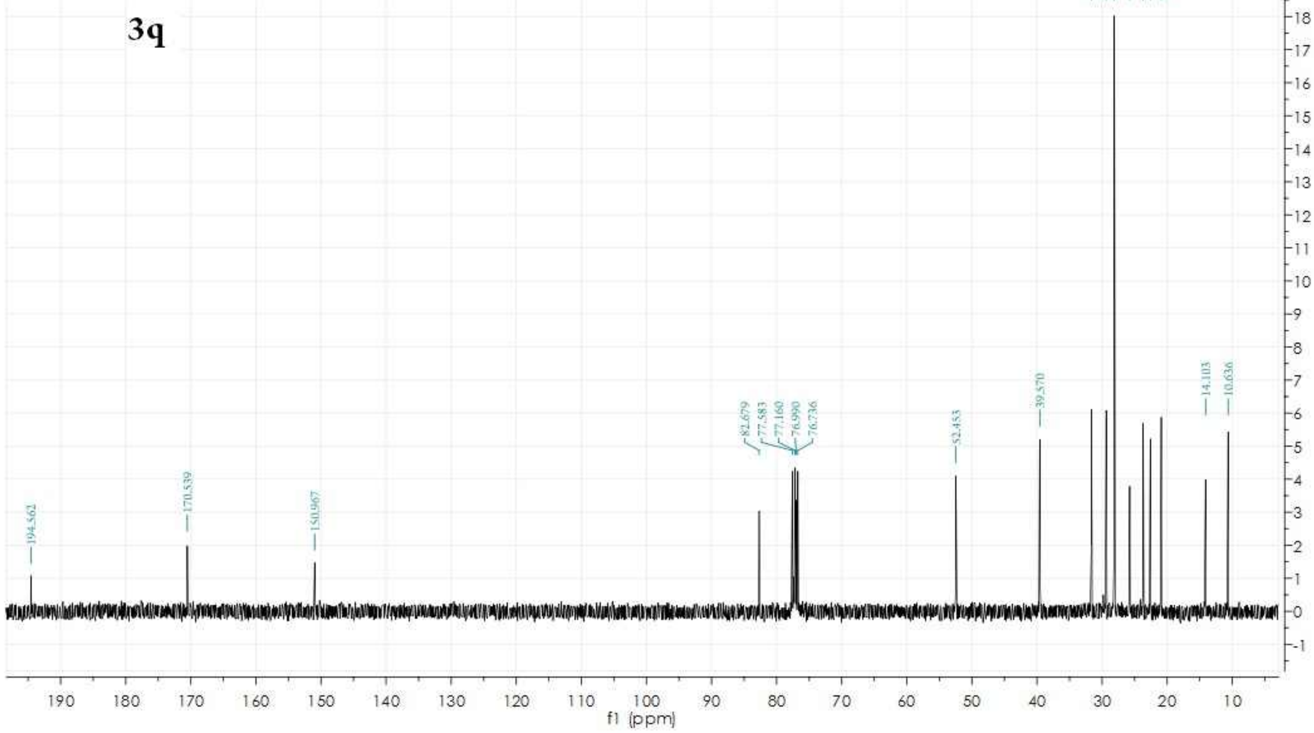


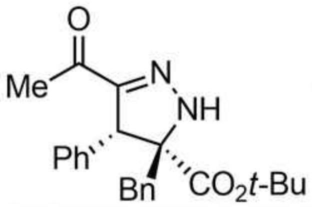
3q



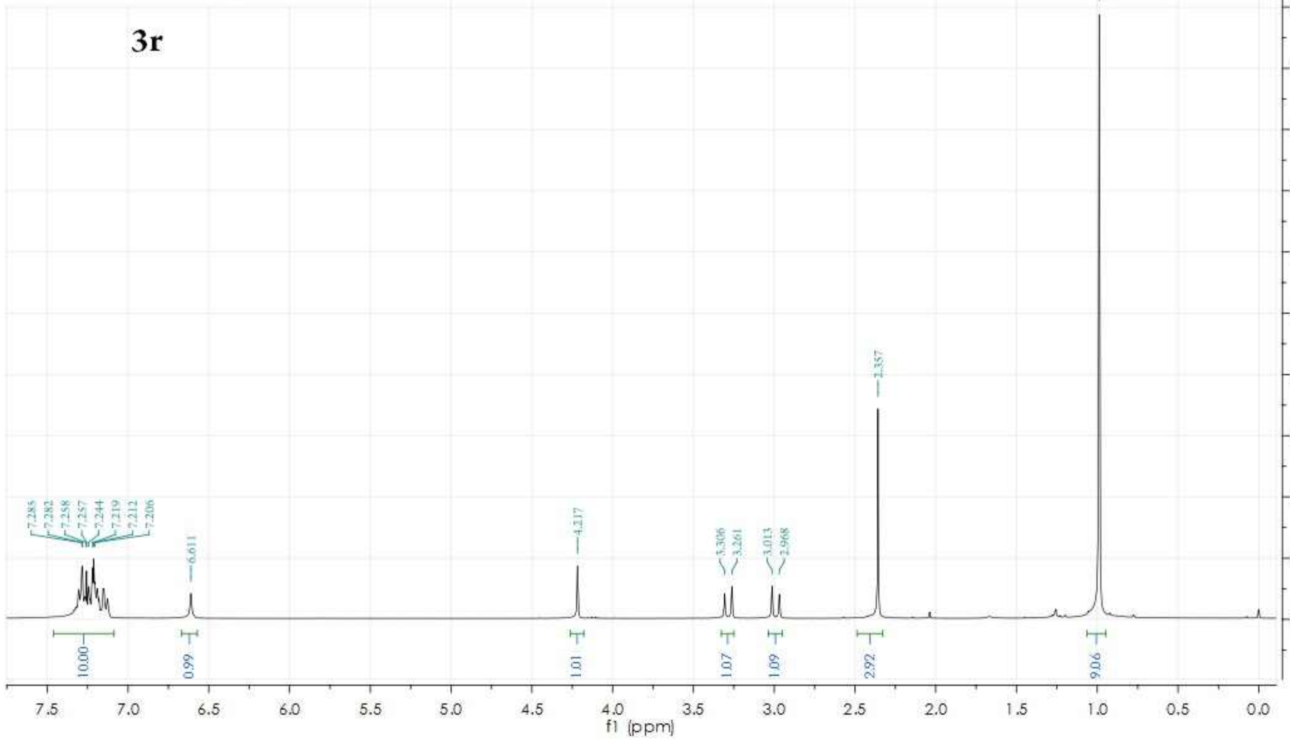

O
Me
N
NH
Et
n-C_6H_{13}
CO_2t-Bu

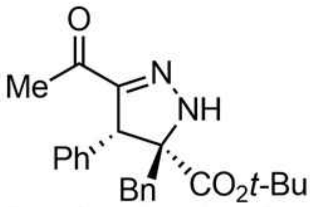
3q


194.562
170.539
150.967
82.679
77.583
77.160
76.990
76.736
52.453
39.570
31.629
29.366
28.116
25.749
23.686
22.585
20.904
14.103
10.636
f1 (ppm)

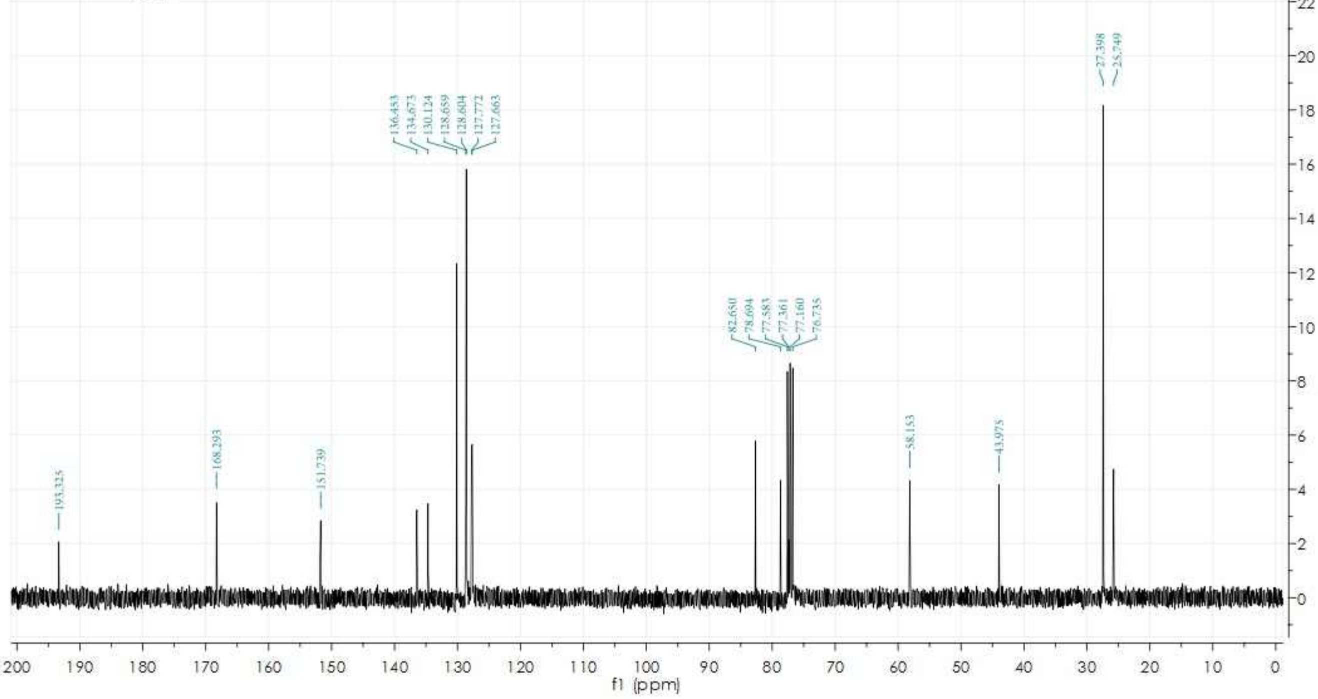

O
Me
N
NH
Ph
Bn
CO2t-Bu

3r

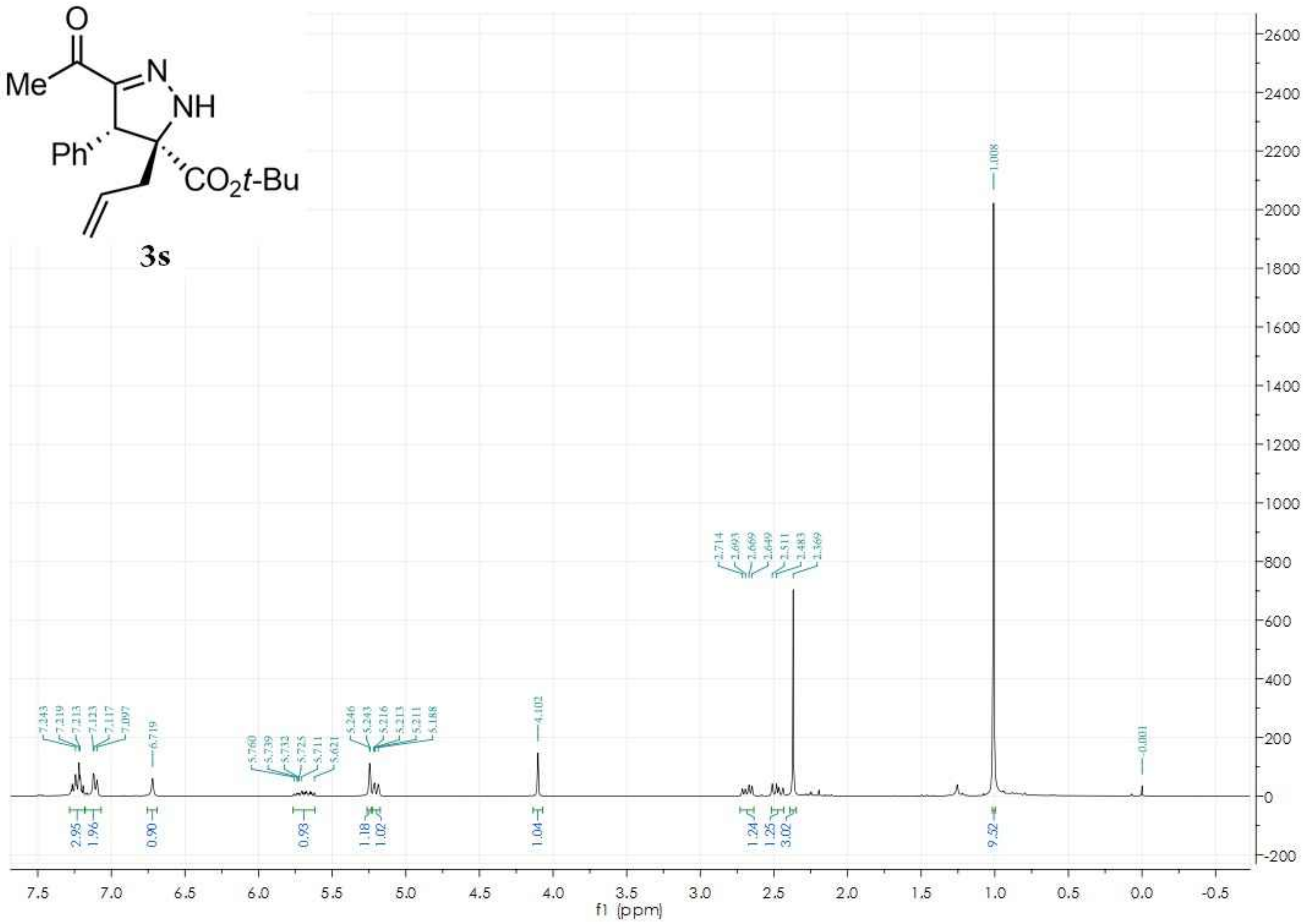

7.285
7.282
7.258
7.257
7.244
7.219
7.212
7.206
6.611
4.217
3.306
3.261
3.013
2.968
2.357
0.988
10.00
0.99
1.01
1.07
1.09
2.92
9.06
f1 (ppm)



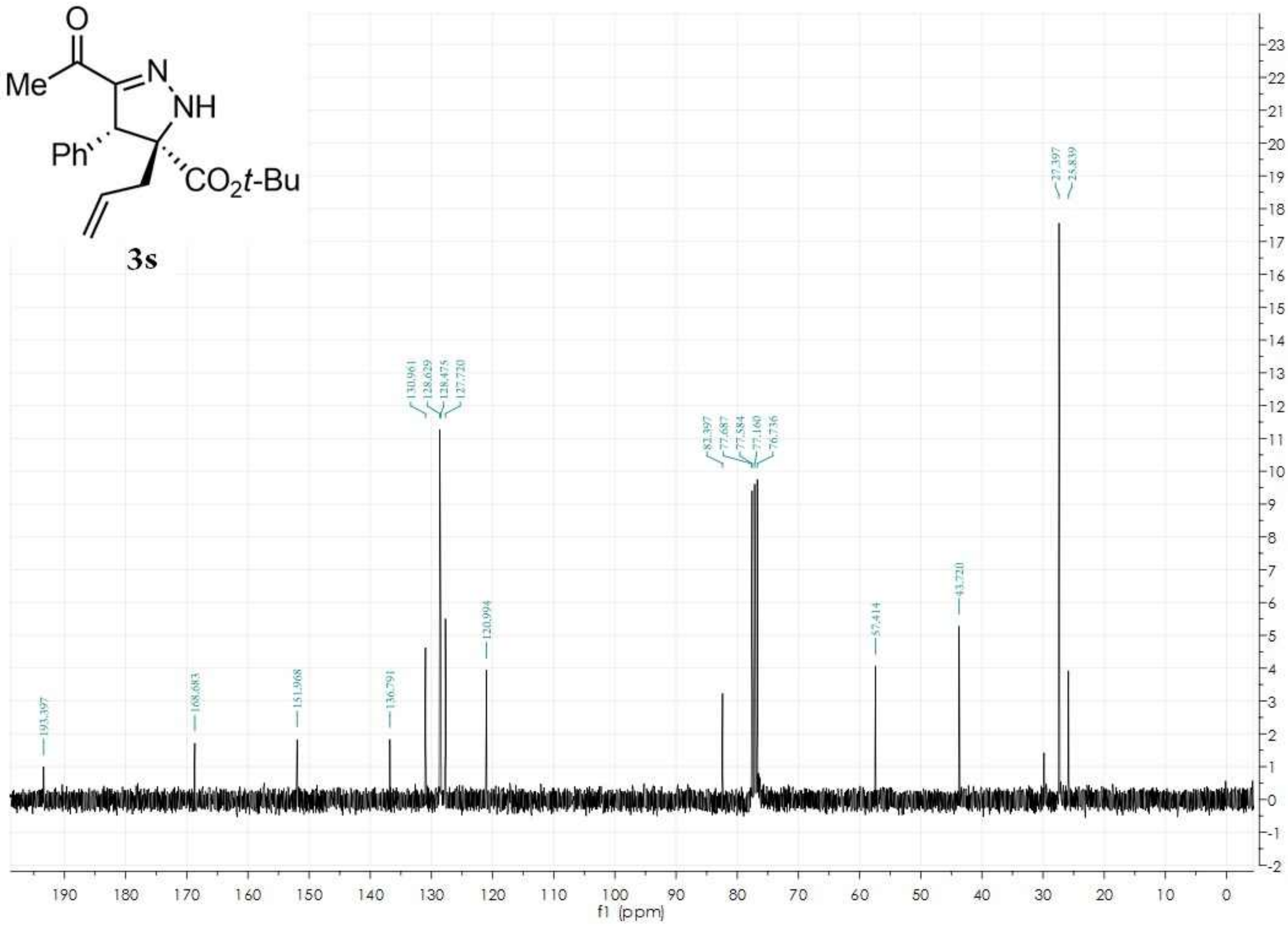
3r



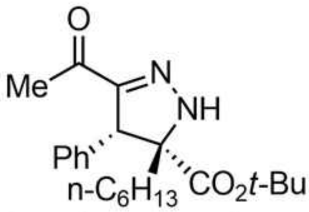
193.325
168.293
151.739
136.453
134.673
130.124
128.659
128.604
127.772
127.663
82.650
78.694
77.583
77.361
77.160
76.735
58.153
43.975
27.398
25.749
f1 (ppm)



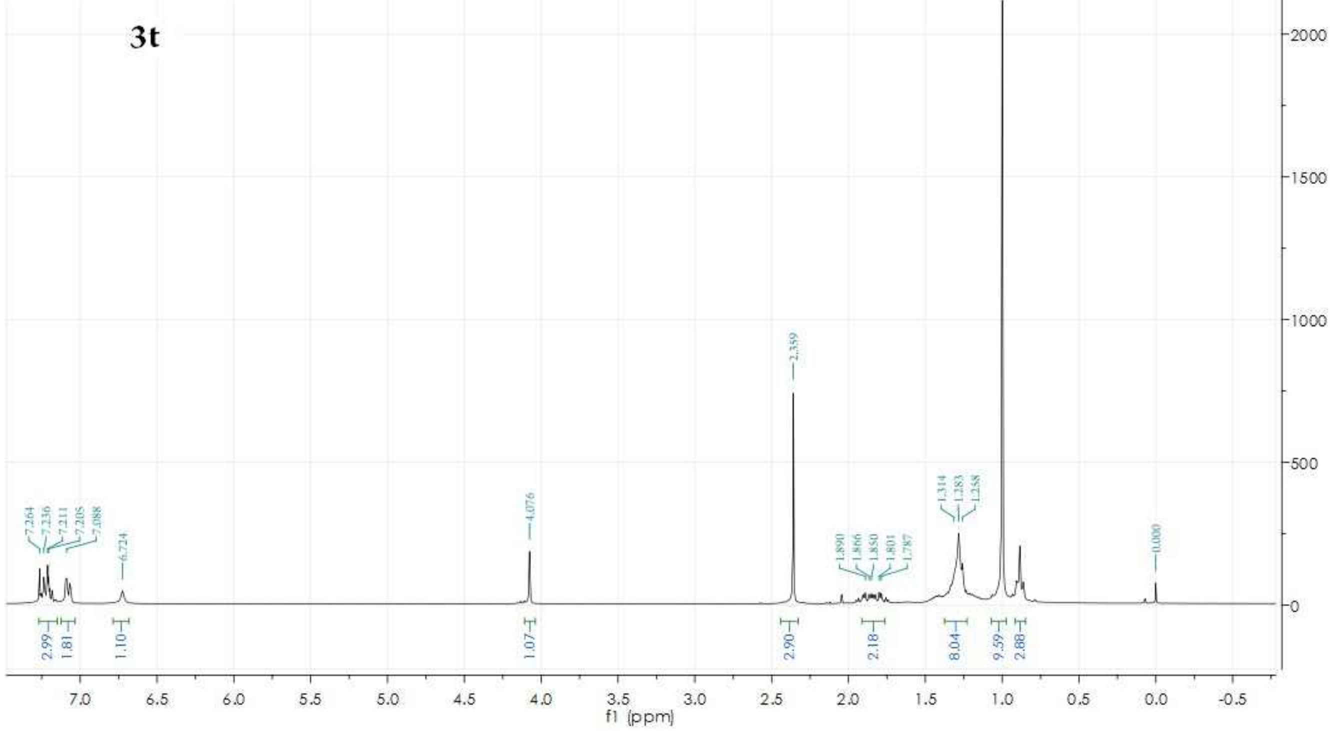
3s

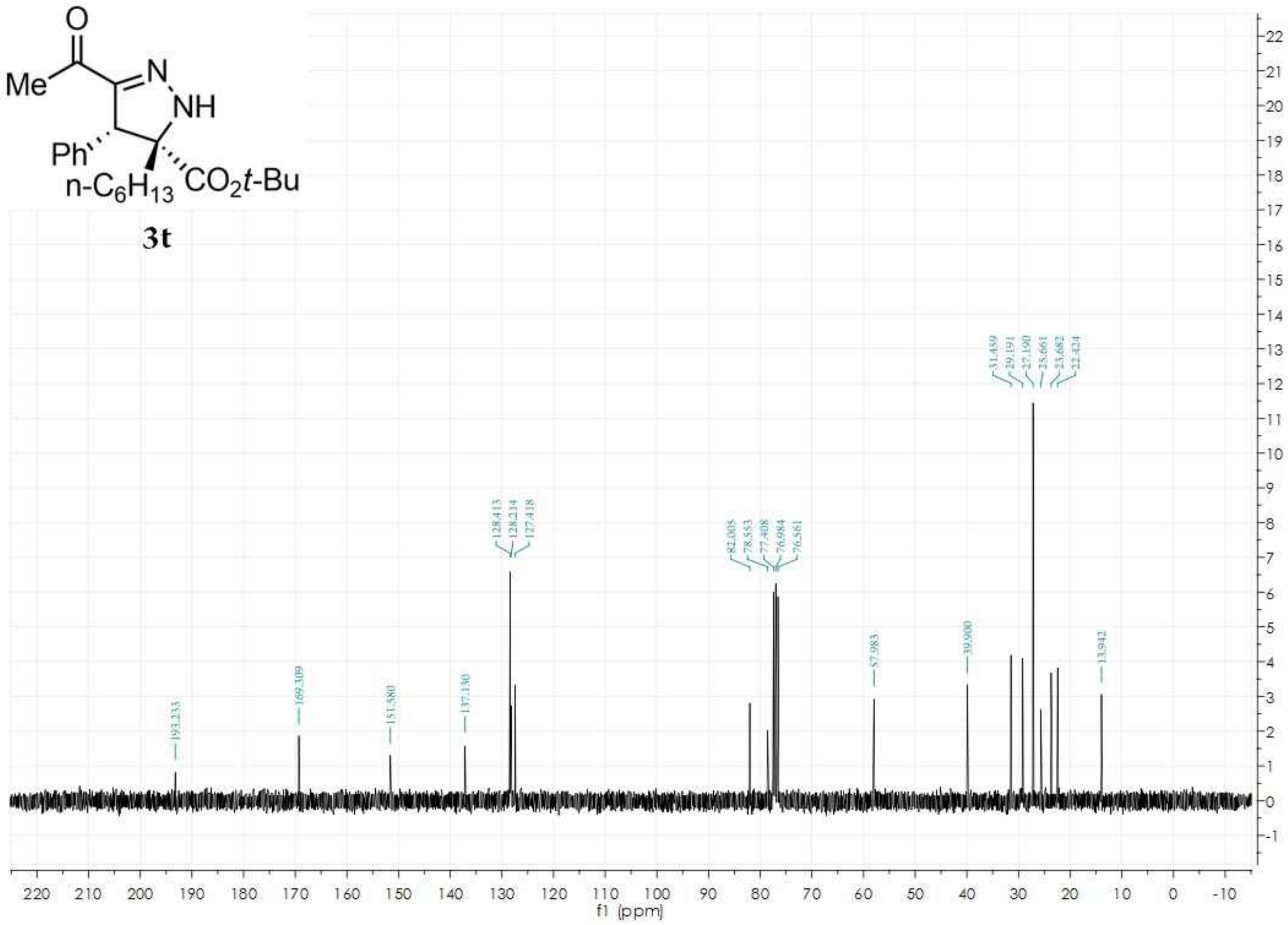

O
Me
N
NH
Ph
CO_2t-Bu
193.397
168.683
151.968
136.791
130.961
128.629
128.475
127.720
120.994
82.397
77.687
77.584
77.160
76.736
57.414
43.720
27.397
25.839
f1 (ppm)

3s


O
Me
N
NH
Ph
n-C6H13
CO2t-Bu

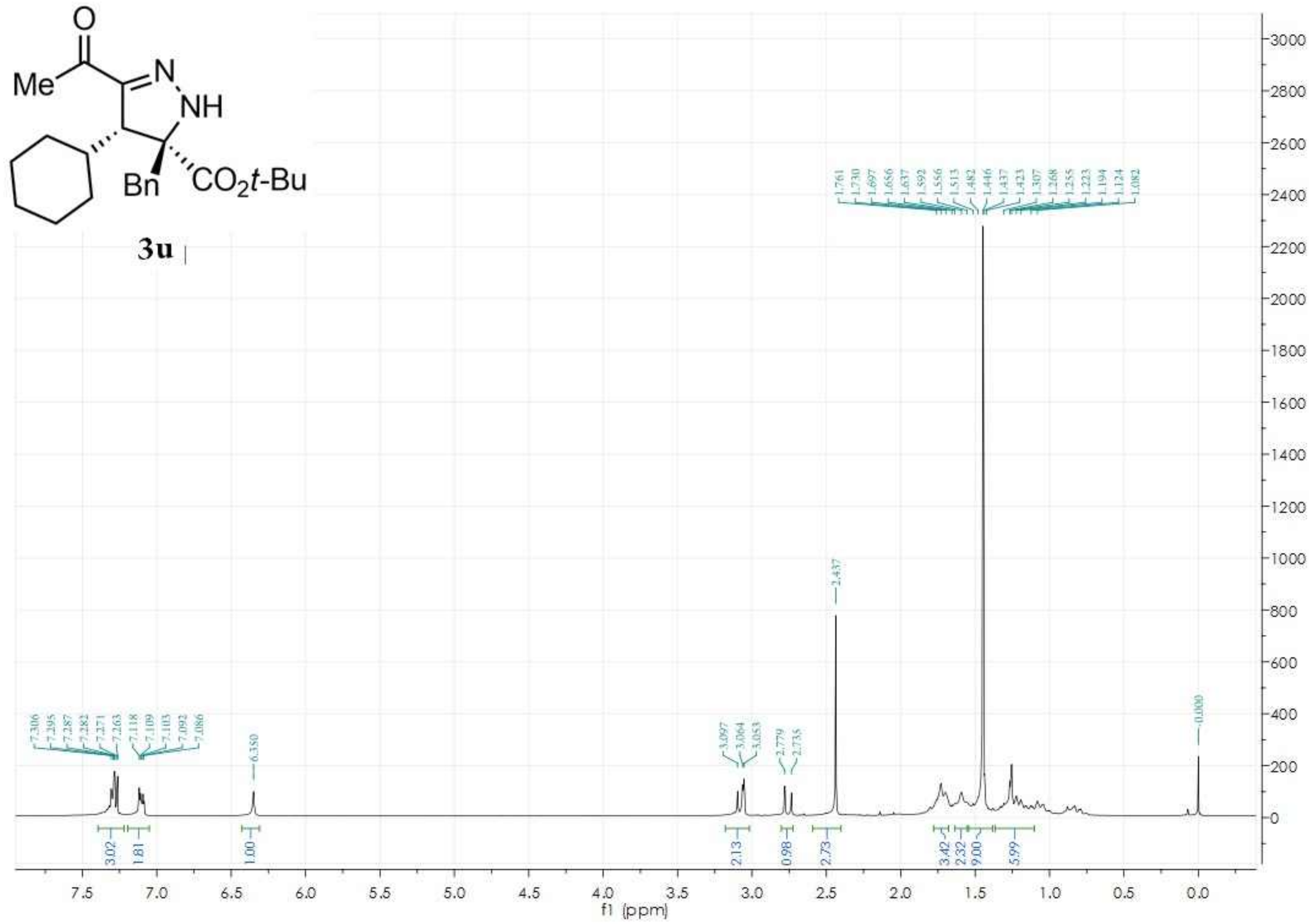
3t


7.264
7.236
7.211
7.205
7.088
6.724
4.076
2.359
1.890
1.866
1.850
1.801
1.787
1.314
1.283
1.258
1.000
0.907
0.901
0.885
0.862
0.000
2.99
1.81
1.10
1.07
2.90
2.18
8.04
9.59
2.88
2500
2000
1500
1000
500
0
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
f1 (ppm)

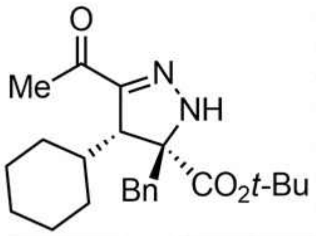


O
Me
N
NH
Ph
n-C6H13
CO2t-Bu
193.233
169.309
151.580
137.130
128.413
128.214
127.418
82.005
78.553
77.408
76.984
76.561
57.983
39.900
31.459
29.191
27.190
25.661
23.682
22.424
13.942
f1 (ppm)

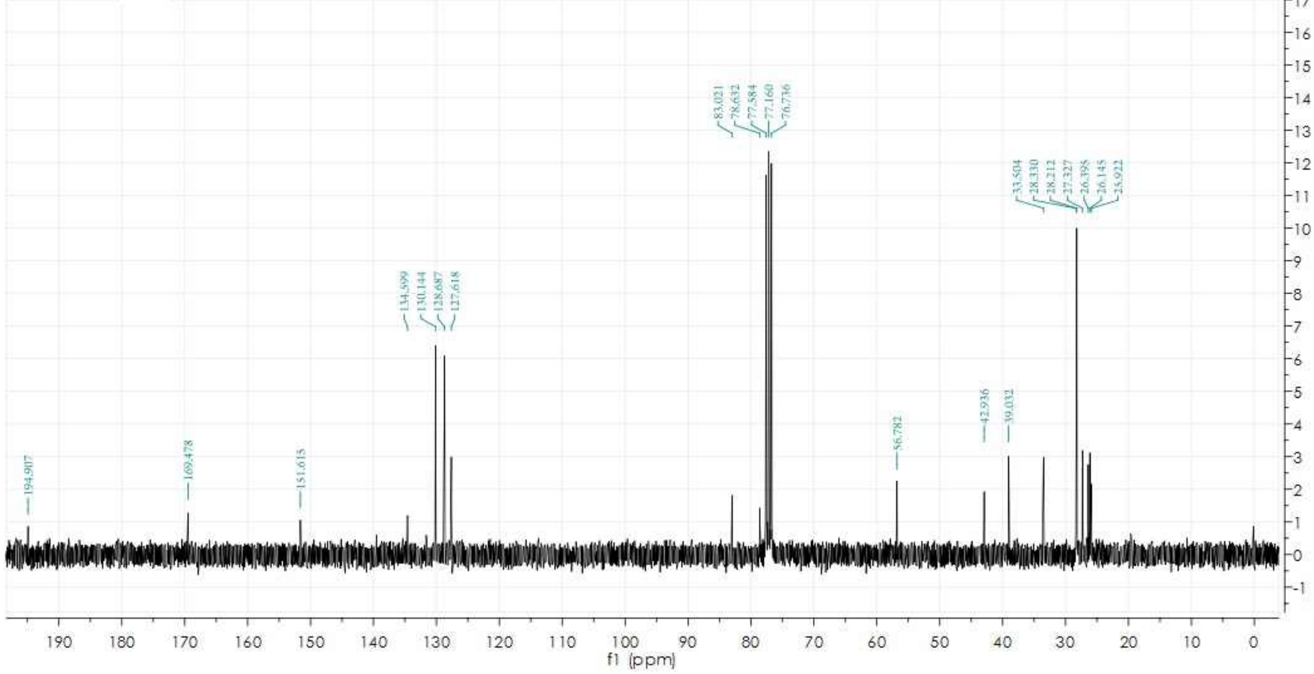
3t

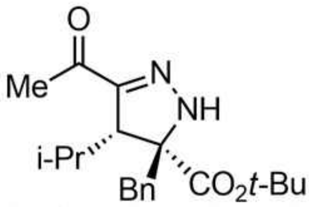


3u

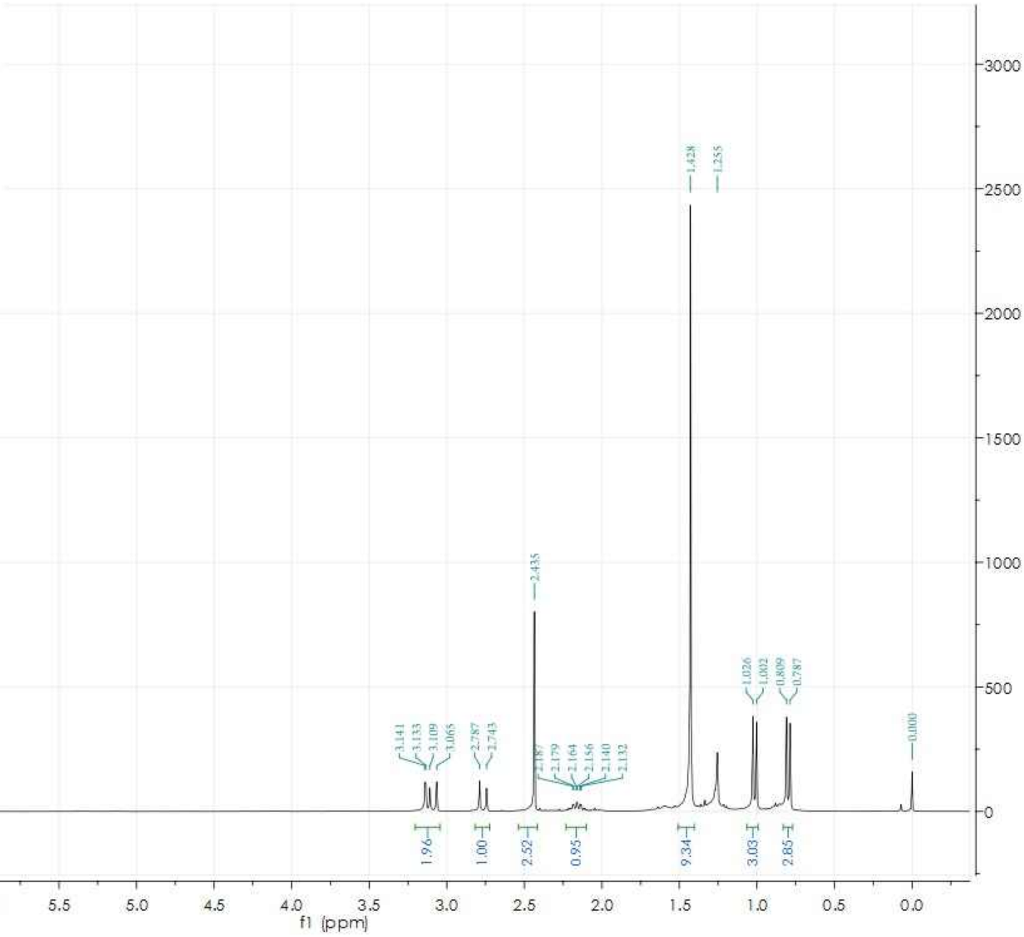


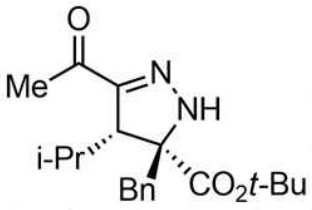
3u


194.907
169.478
151.615
134.599
130.144
128.687
127.618
83.021
78.632
77.584
77.160
76.736
56.782
42.936
39.032
33.504
28.330
28.212
27.327
26.395
26.145
25.922
f1 (ppm)

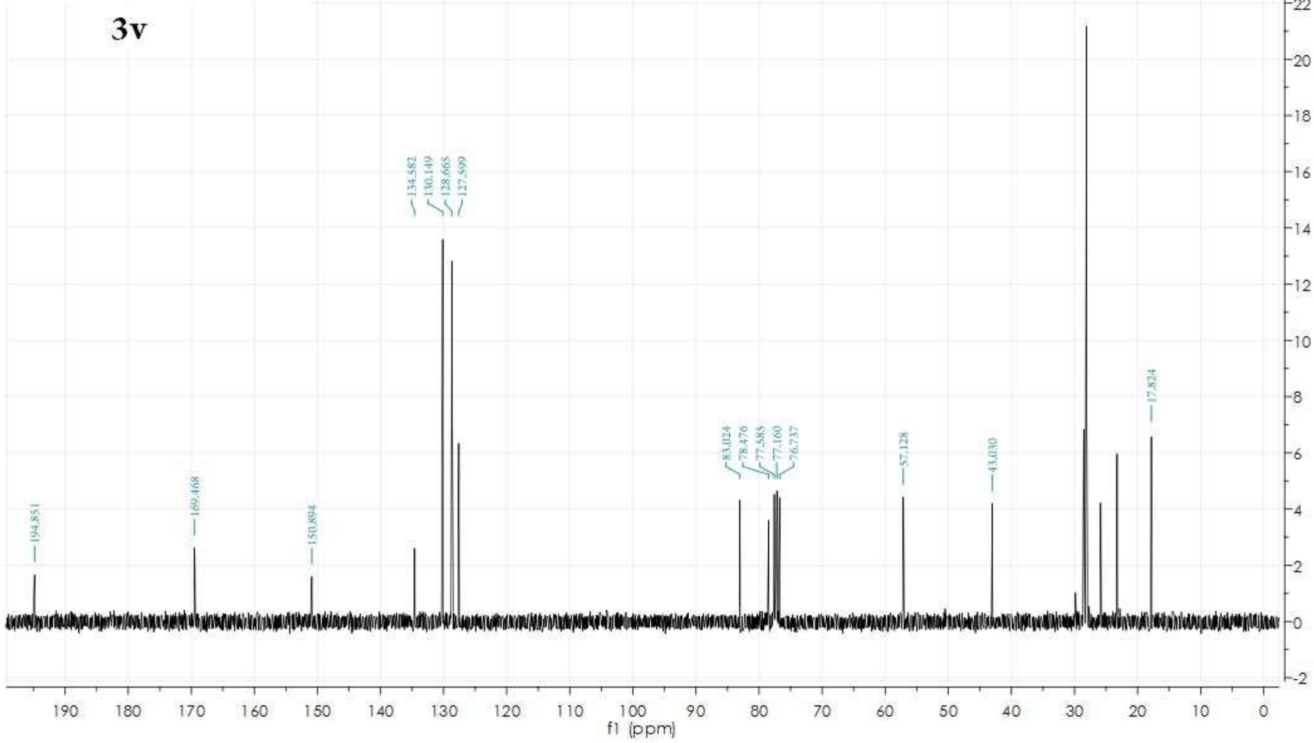

O
Me
N
NH
i-Pr
Bn
CO2t-Bu

3v


7.306
7.295
7.286
7.282
7.263
7.124
7.115
7.098
6.370
3.141
3.133
3.109
3.065
2.787
2.743
2.435
2.187
2.179
2.164
2.156
2.140
2.132
1.428
1.255
1.026
1.002
0.809
0.787
0.000
2.98
1.71
0.85
1.96
1.00
2.52
0.95
9.34
3.03
2.85
f1 (ppm)

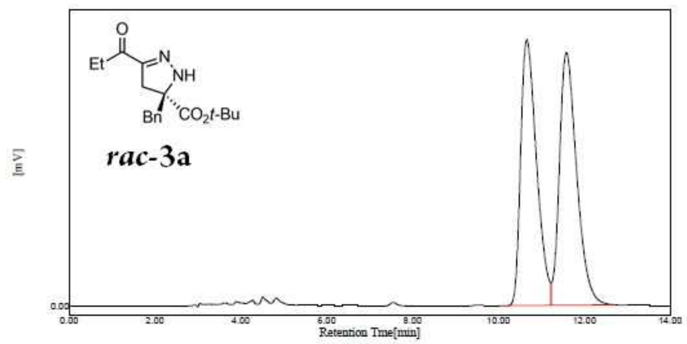


3v


194.851
169.468
150.894
134.582
130.149
128.665
127.599
83.024
78.476
77.585
77.160
76.737
57.128
43.030
28.536
28.091
25.852
23.241
17.824
f1 (ppm)

Chiral HPLC Analysis

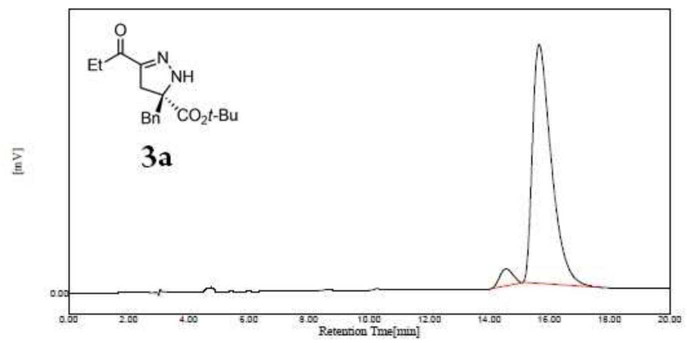
LSI-23-96	



	RT	[mV*s]	[%]
1	10.6650	3921.3906	49.16
2	11.5867	4055.1348	50.84
		7976.5250	

Chiral HPLC Analysis

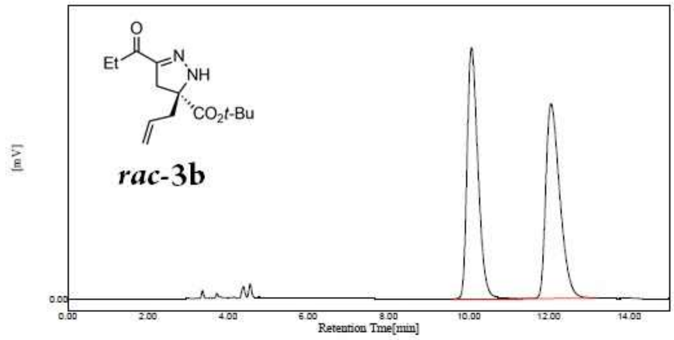
LSI-23-122	



	RT	[mV*s]	[%]
1	14.5600	126.8881	4.72
2	15.6600	2560.7672	95.28
		2687.6553	

Chiral HPLC Analysis

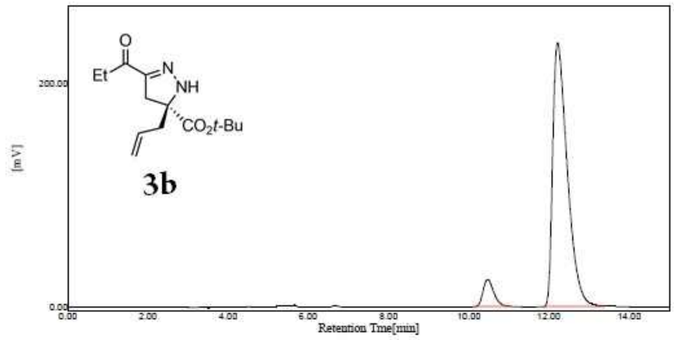
LSI-27-111	



	RT	[mV*s]	[%]
1	10.0700	1925.6408	49.95
2	12.0550	1929.4213	50.05
		3855.0621	

Chiral HPLC Analysis

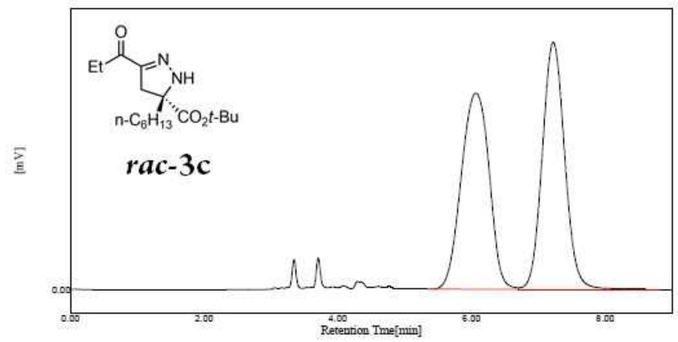
LSI-24-31	



	RT	[mV*s]	[%]
1	10.4717	450.6677	7.06
2	12.2183	5936.1879	92.94
		6386.8555	

Chiral HPLC Analysis

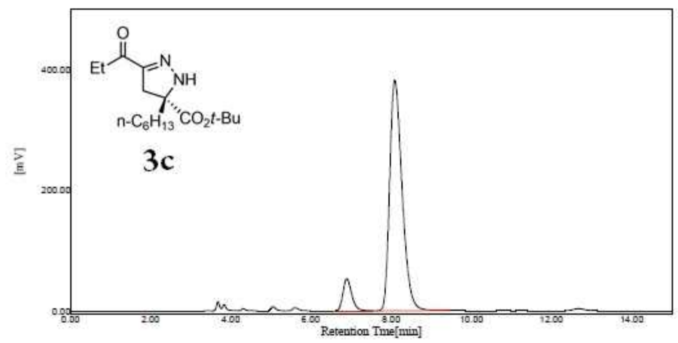
LSI-27-112	



	RT	[mV*s]	[%]
1	6.0683	1214.8153	49.70
2	7.2267	1229.7101	50.30
		2444.5254	

Chiral HPLC Analysis

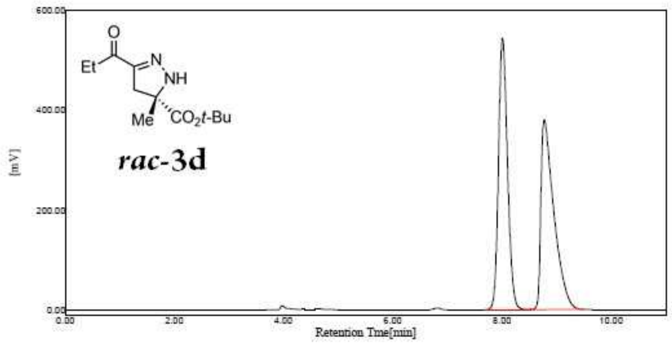
LSI-24-32	



	RT	[mV*s]	[%]
1	6.8950	814.1473	9.03
2	8.0933	8202.2336	90.97
		9016.3813	

Chiral HPLC Analysis

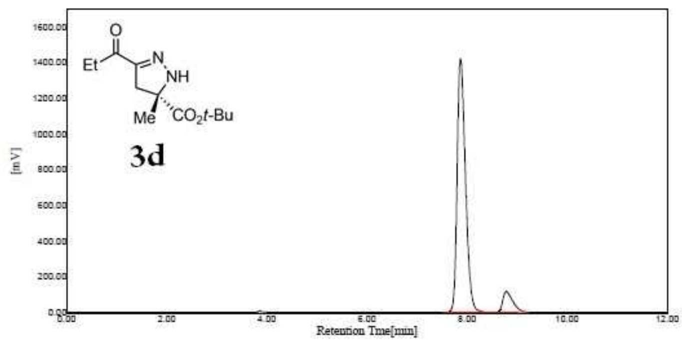
LSI-27-107	



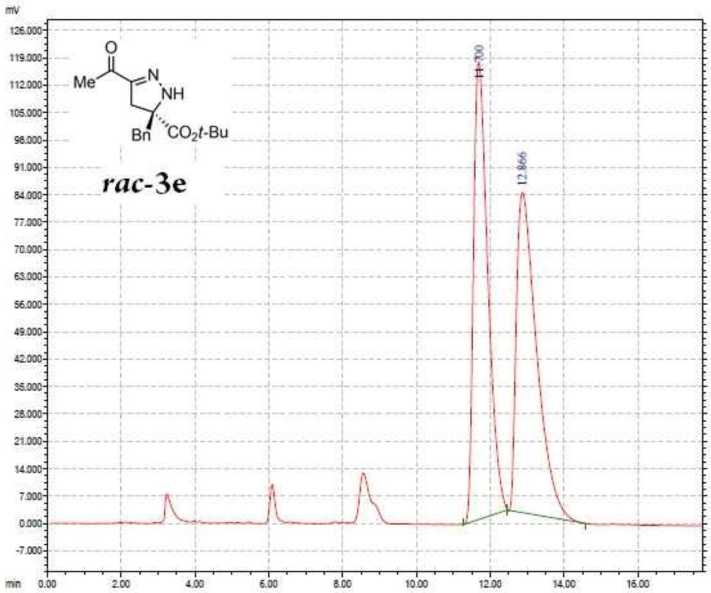
	RT	[mV*s]	[%]
1	8.0083	6228.1406	49.83
2	8.7767	6270.5059	50.17
		12498.6469	

Chiral HPLC Analysis

LSI-27-106	



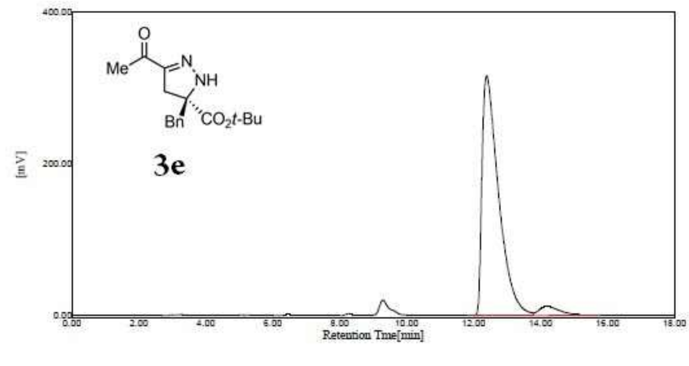
	RT	[mV*s]	[%]
1	7.8733	16324.5281	91.07
2	8.7850	1599.7766	8.93
		17924.3047	



	[min]	[uV*sec]	[%]	
	11.700	3153437.12	50.250	BMB
	12.866	3122100.51	49.750	BMB
Σ		6275537.63	100.000	

Chiral HPLC Analysis

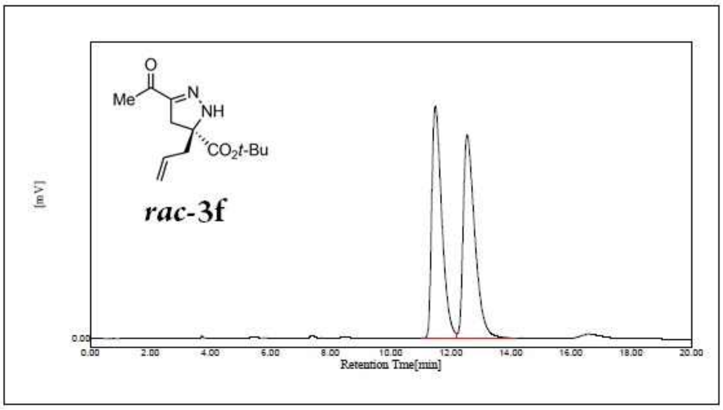
LSI-24-3	



	RT	[mV*s]	[%]
1	12.3950	10849.4680	95.38
2	14.1817	525.4703	4.62
		11374.9383	

Chiral HPLC Analysis

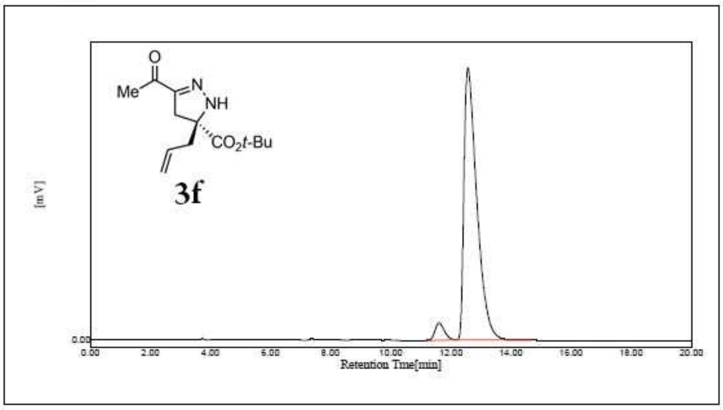
LSI-24-15	



	RT	[mV*s]	[%]
1	11.4867	1811.6660	49.68
2	12.5467	1834.6717	50.32
		3646.3375	

Chiral HPLC Analysis

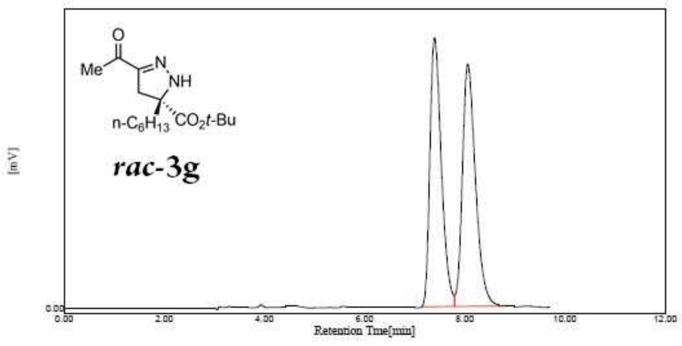
LSI-24-14'	



	RT	[mV*s]	[%]
1	11.6083	152.3510	4.46
2	12.5683	3261.1062	95.54
		3413.4570	

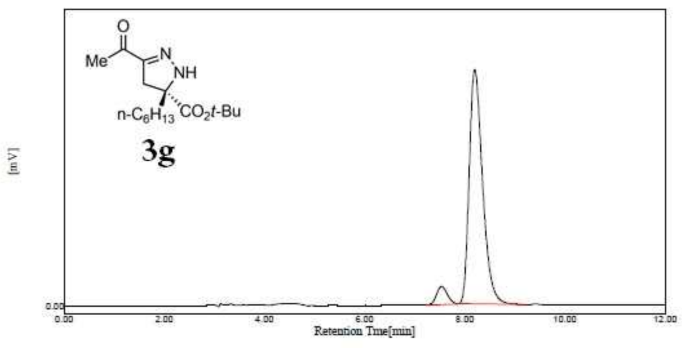
Chiral HPLC Analysis

LSI-24-26	



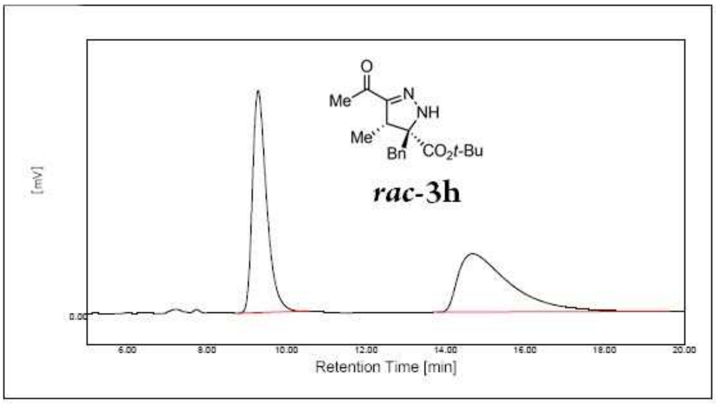
	RT	[mV*s]	[%]
1	7.4000	2553.9418	49.09
2	8.0633	2649.1520	50.91
		5203.0938	

LSI-24-25	



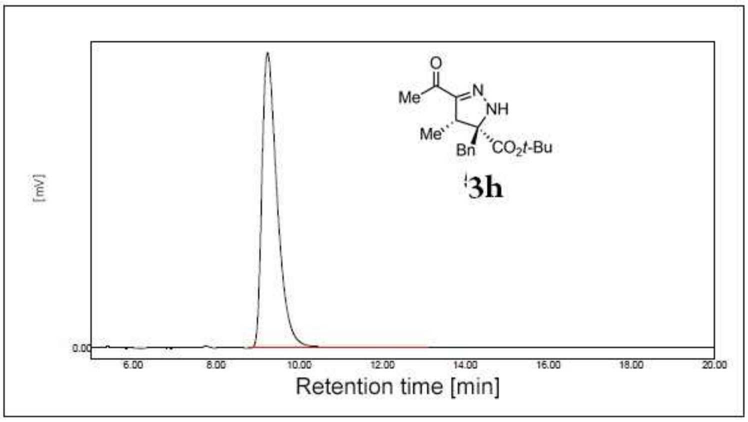
	RT	[mV*s]	[%]
1	7.5383	100.8119	5.88
2	8.2017	1614.8868	94.12
		1715.6986	

KAR-2-48-p-rac	



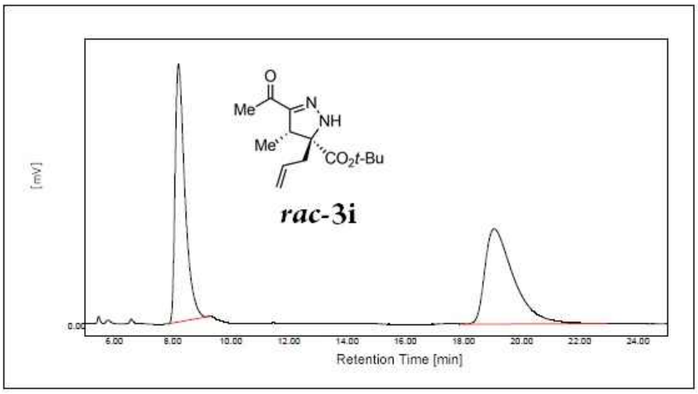
	RT	[mV*s]	[%]
1	9.2883	990.7404	50.59
2	14.6783	967.5701	49.41
		1958.3105	

KAR-2-49-p	



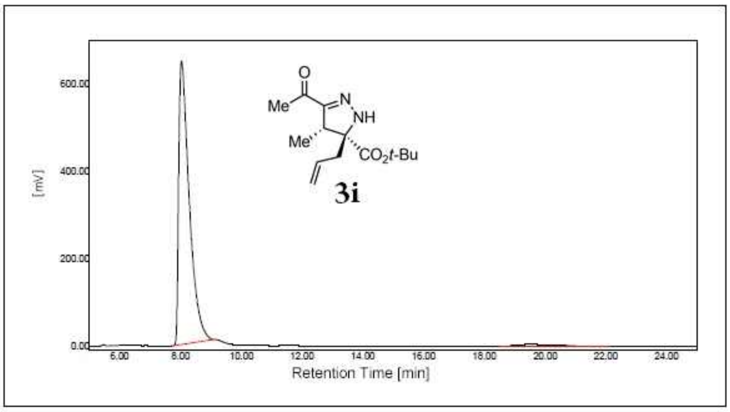
	RT	[mV*s]	[%]
1	9.2433	3471.6176	100.00
		3471.6176	

KAR-2-54-RACEMIC



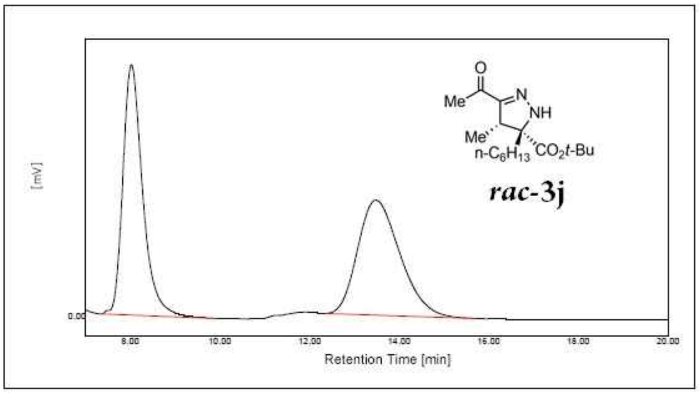
	RT	[mV*s]	[%]
1	8.2033	2946.9354	48.10
2	19.0567	3179.5820	51.90
		6126.5172	

KAR-2-53-CHIRAL



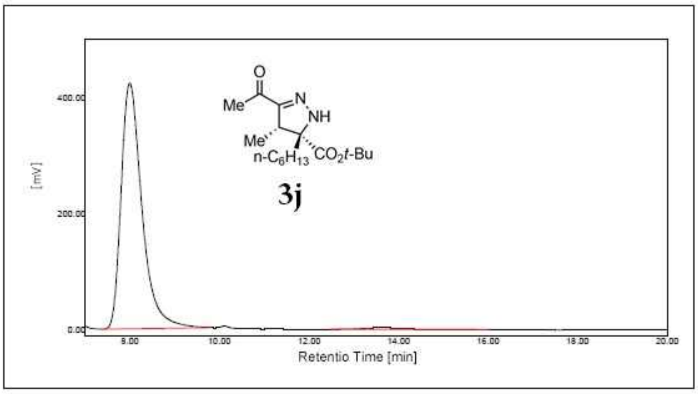
	RT	[mV*s]	[%]
1	8.0383	15668.2750	98.46
2	19.5417	245.5514	1.54
		15913.8266	

KAR-2-57-ra-AYH	



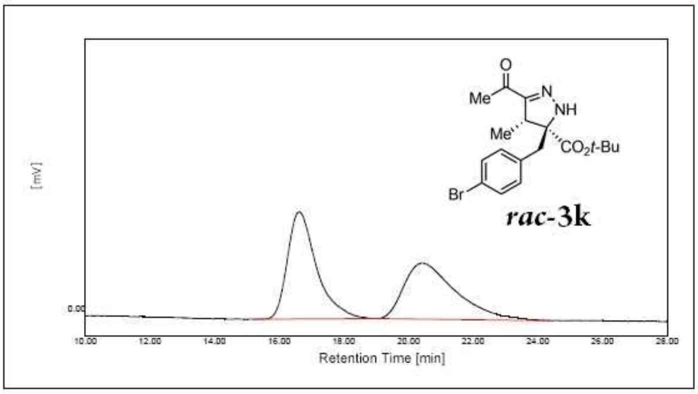
	RT	[mV*s]	[%]
1	8.0217	1945.4344	50.51
2	13.4817	1906.4836	49.49
		3851.9180	

KAR-2-56	



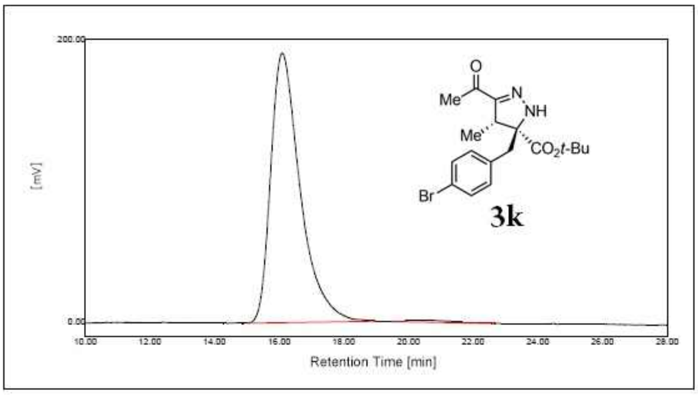
	RT	[mV*s]	[%]
1	7.9917	13684.1563	98.54
2	13.6267	202.4490	1.46
		13886.6047	

KAR-2-88-1	



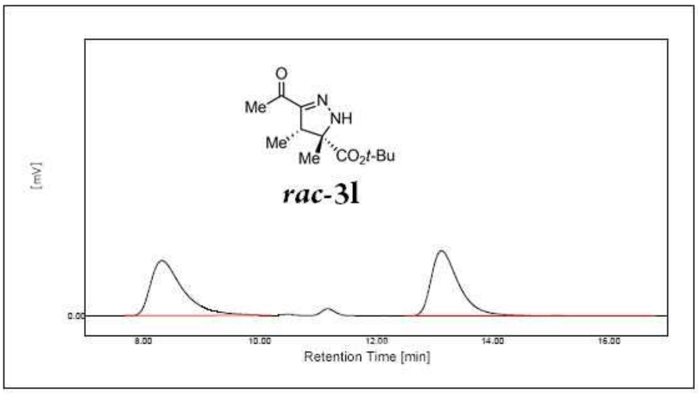
	RT	[mV*s]	[%]
1	16.6150	250.5343	51.82
2	20.4567	232.8952	48.18
		483.4294	

KAR-2-87	



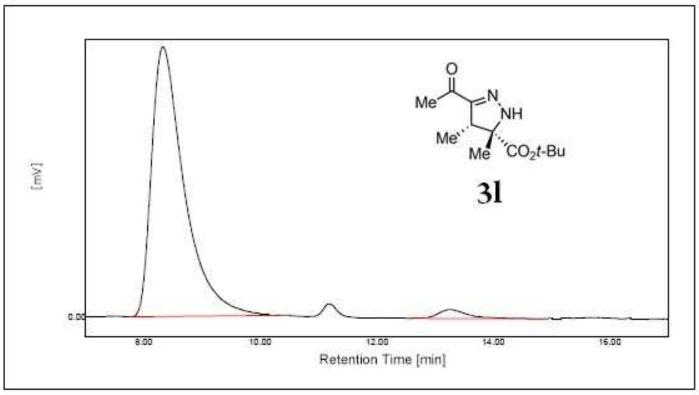
	RT	[mV*s]	[%]
1	16.0883	12111.1875	98.80
2	20.4383	146.6214	1.20
		12257.8086	

KKE-3-57-AYH-2	



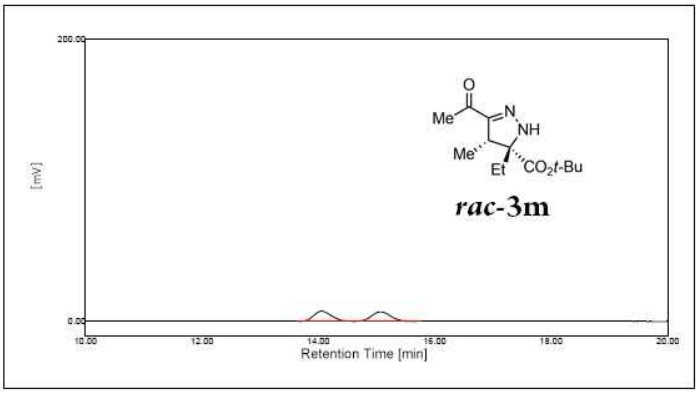
	RT	[mV*s]	[%]
1	8.3167	540.3916	49.41
2	13.1217	553.3960	50.59
		1093.7877	

KKE-3-56	



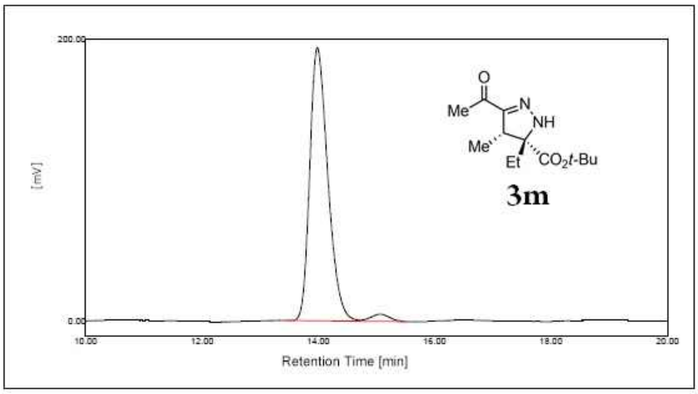
	RT	[mV*s]	[%]
1	8.3283	2661.2391	97.03
2	13.2567	81.5013	2.97
		2742.7404	

KKE-3-54-OZH	



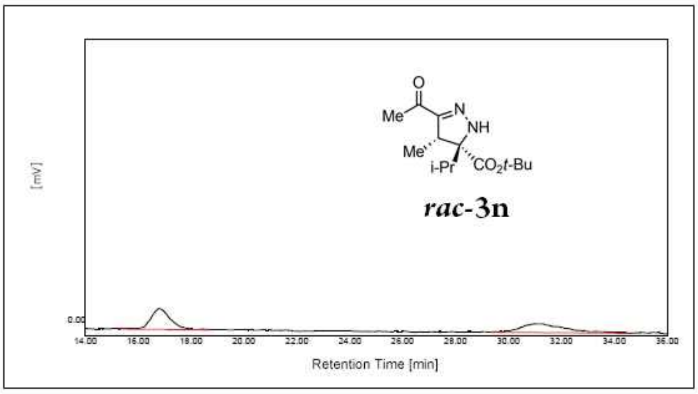
	RT	[mV*s]	[%]
1	14.0583	154.9771	50.05
2	15.0700	154.6506	49.95
		309.6278	

KKE-3-53	



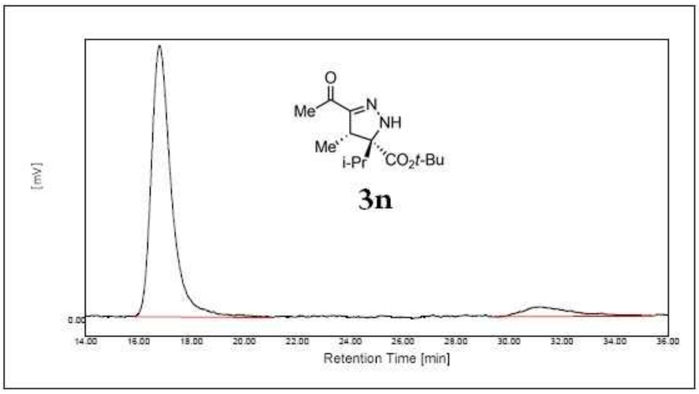
	RT	[mV*s]	[%]
1	13.9850	4180.7391	97.28
2	15.0567	116.9641	2.72
		4297.7031	

KKE-3-59-AYH-2	



	RT	[mV*s]	[%]
1	16.8117	137.1303	50.61
2	31.0200	133.8309	49.39
		270.9612	

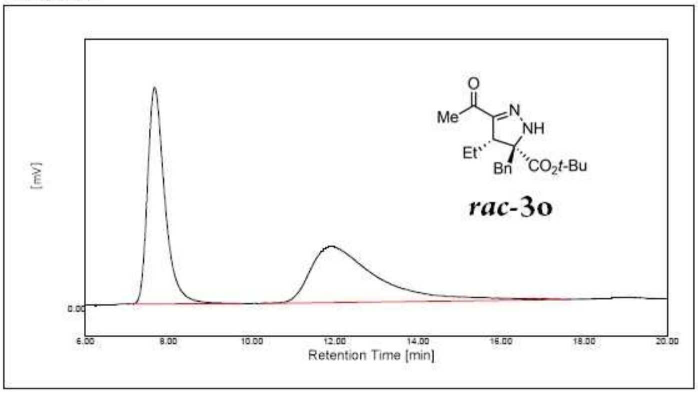
KKE-3-58	



	RT	[mV*s]	[%]
1	16.7883	1792.0451	91.35
2	31.0867	169.7857	8.65
		1961.8309	

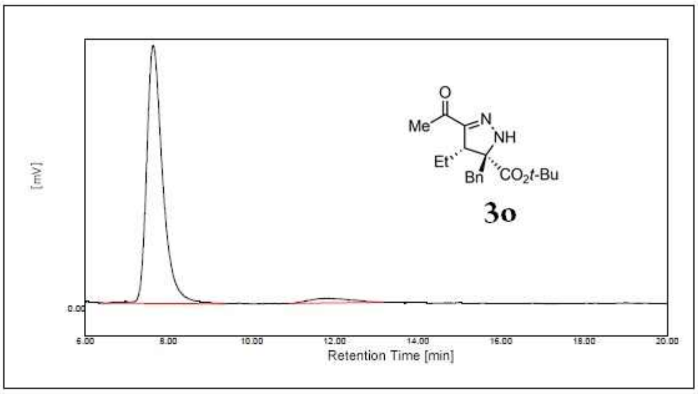
KAR-2-90	

크로마토그램



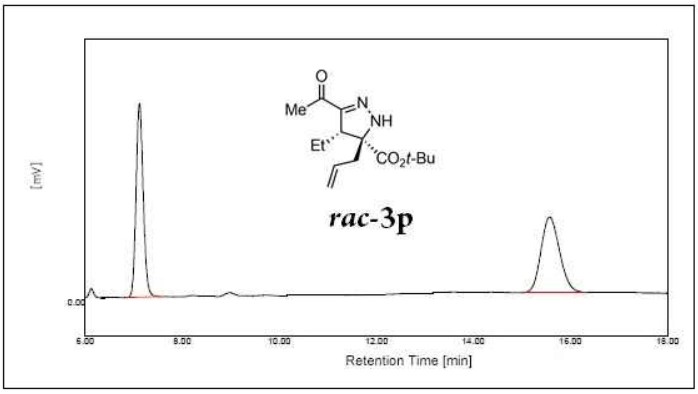
	RT	[mV*s]	[%]
1	7.6667	231.3148	49.88
2	11.9283	232.4312	50.12
		463.7460	

KAR-2-89	



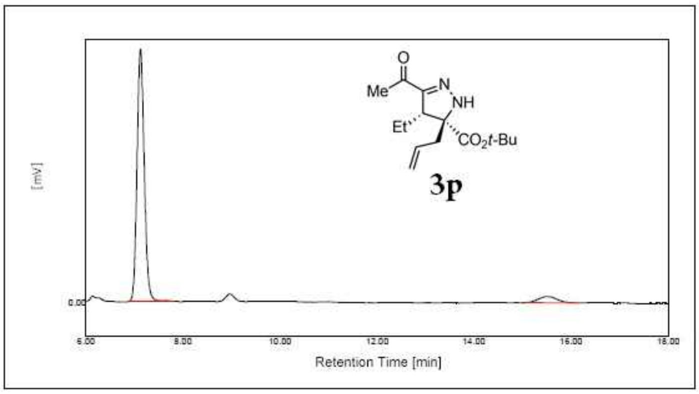
	RT	[mV*s]	[%]
1	7.6333	255.4964	95.28
2	11.7433	12.6467	4.72
		268.1432	

KAR-3-6-OZH	



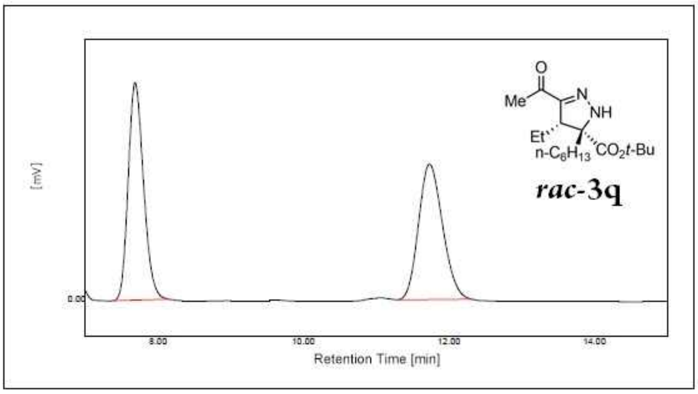
	RT	[mV*s]	[%]
1	7.1200	120.6331	49.63
2	15.5733	122.4245	50.37
		243.0576	

KAR-3-5-OZH	



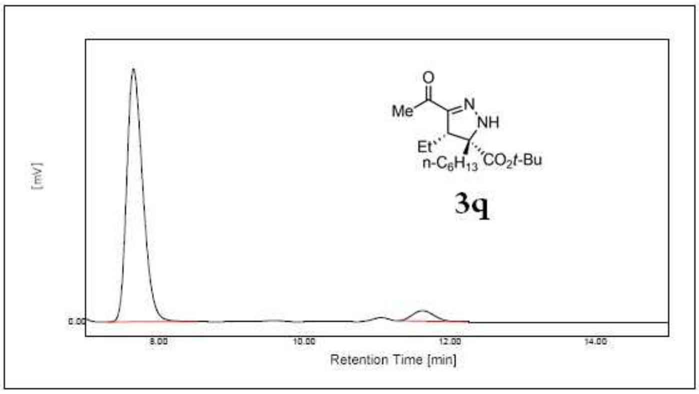
	RT	[mV*s]	[%]
1	7.1250	159.1054	93.75
2	15.5117	10.6055	6.25
		169.7109	

KAR-3-4-OZH-2	



	RT	[mV*s]	[%]
1	7.6850	344.2479	50.65
2	11.7317	335.4061	49.35
		679.6540	

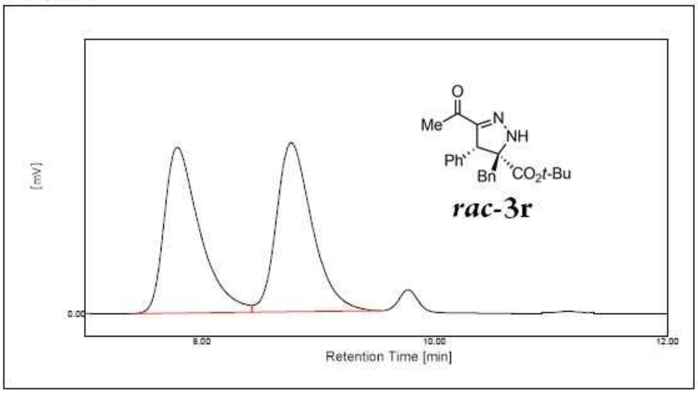
KAR-3-3-OZH	



	RT	[mV*s]	[%]
1	7.6550	1098.4383	94.58
2	11.6233	62.9270	5.42
		1161.3652	

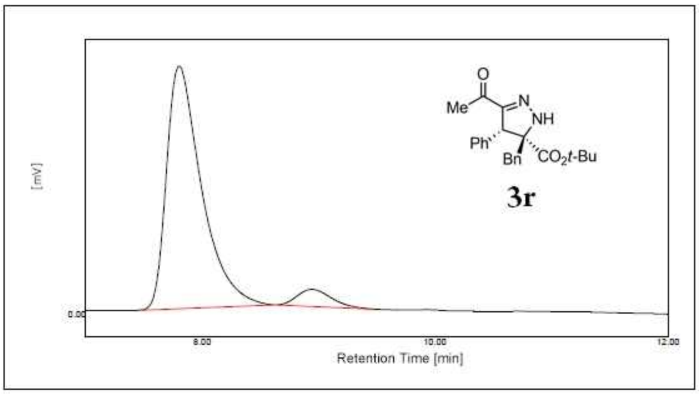
KAR-2-62-ra-ODH-2	

크로마토그램



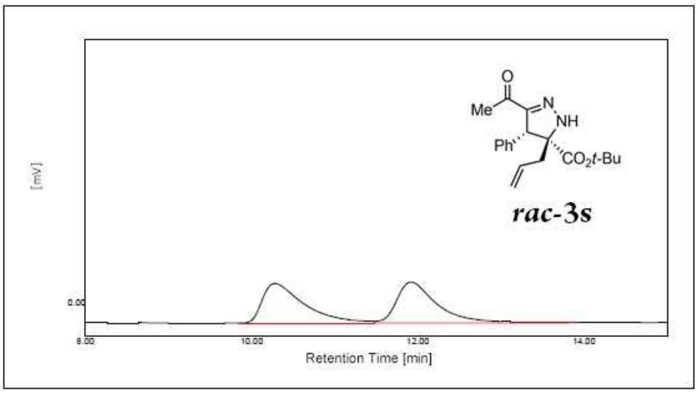
	RT	[mV*s]	[%]
1	7.7900	644.9000	49.44
2	8.7683	659.4290	50.56
		1304.3290	

KAR-2-64	



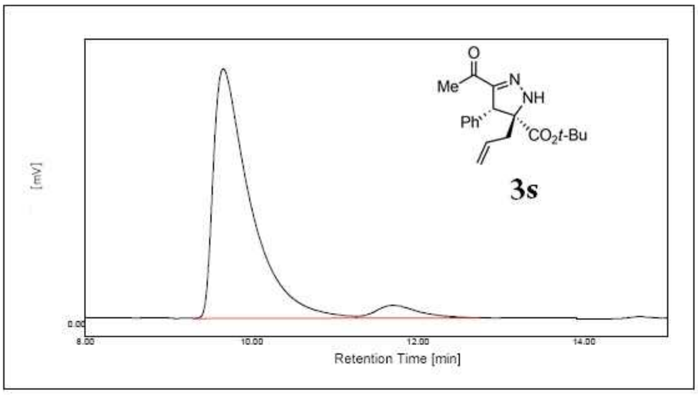
	RT	[mV*s]	[%]
1	7.8033	923.0334	93.58
2	8.9433	63.3450	6.42
		986.3784	

KAR-3-14-ODH	



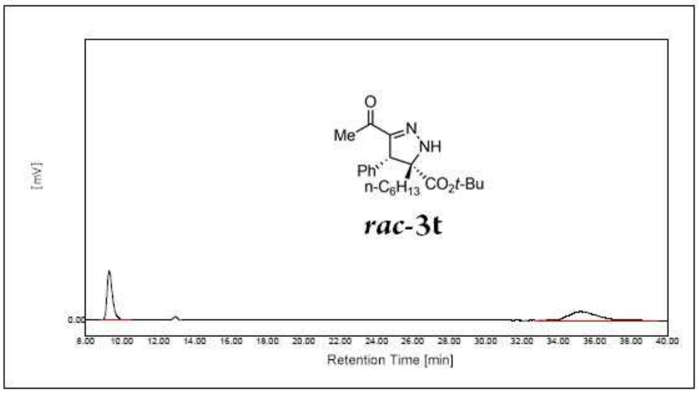
	RT	[mV*s]	[%]
1	10.2817	211.9730	50.33
2	11.9183	209.1969	49.67
		421.1699	

KAR-3-13	



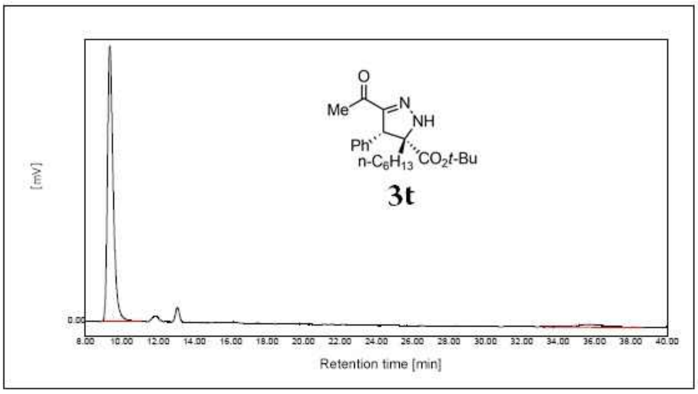
	RT	[mV*s]	[%]
1	9.6583	3247.8363	94.29
2	11.7000	196.6766	5.71
		3444.5129	

KAR-3-16-OZH	



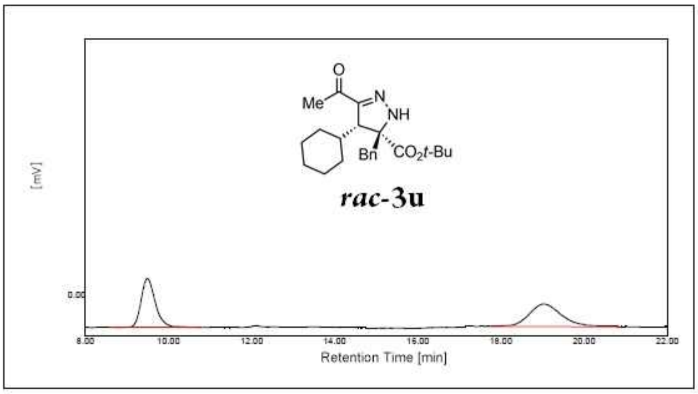
	RT	[mV*s]	[%]
1	9.3000	655.3310	50.15
2	35.2433	651.4099	49.85
		1306.7408	

KAR-3-15-OZH	



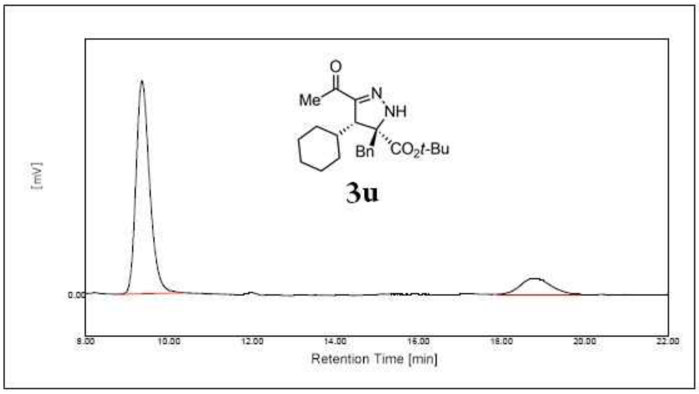
	RT	[mV*s]	[%]
1	9.3450	3914.2773	94.58
2	35.7733	224.4389	5.42
		4138.7164	

KAR-3-18-OZH-2	



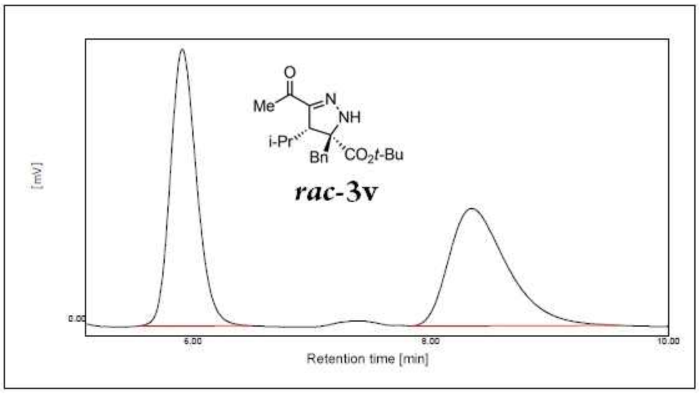
	RT	[mV*s]	[%]
1	9.4933	234.3335	49.48
2	19.0383	239.2315	50.52
		473.5650	

KAR-3-17-OZH	



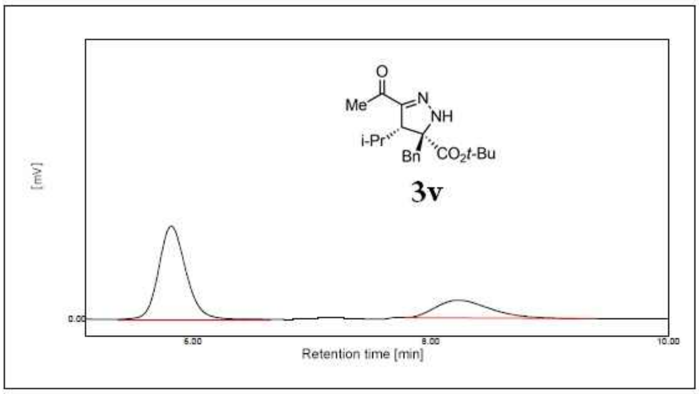
	RT	[mV*s]	[%]
1	9.3567	949.2372	85.71
2	18.7800	158.2483	14.29
		1107.4855	

KAR-2-68-ASH-2	



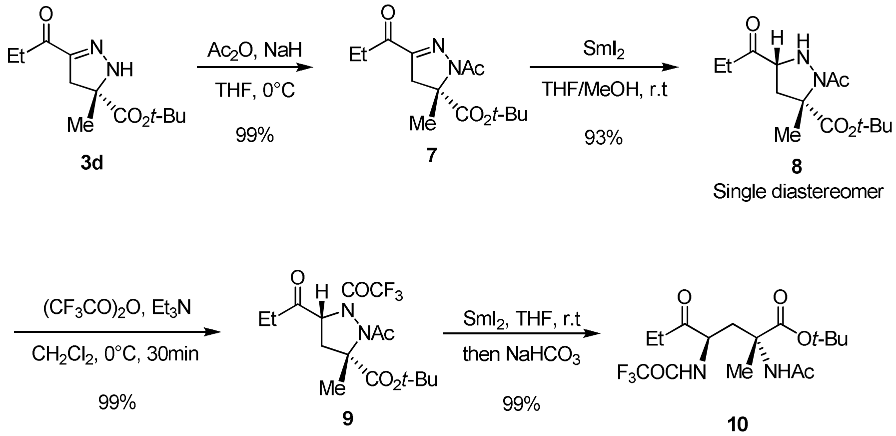
	RT	[mV*s]	[%]
1	5.9117	761.3275	51.54
2	8.3467	715.8251	48.46
		1477.1526	

KAR-2-67-ASH	

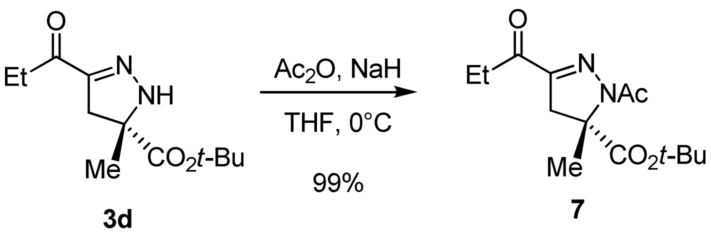


	RT	[mV*s]	[%]
1	5.8183	264.4437	72.38
2	8.2350	100.9219	27.62
		365.3656	

Synthesis of 2,4-diamino carbonyl compound



(*S*)-*tert*-butyl 1-acetyl-5-methyl-3-propionyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**7**)



A 100 ml round bottom flask was charged with enone **3d** (1.9 g, 8.1 mmol), a magnetic stir bar and freshly distilled THF (50 ml). The mixture was cooled to 0 ºC. To this solution was added a NaH (0.39 g 60% dispersion in mineral oil, 9.7 mmol) and Ac_2O (1.1 ml, 11.3 mmol). After completion of reaction, the reaction was quenched with saturated $NH_4Cl_{(aq)}$. The aqueous layer was extracted with dichloromethane (3 × 20 ml) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (ethyl acetate:hexane=1:10) provided **7** (2.28 g, 8.1 mmol, 99% yield) as a colorless oil.

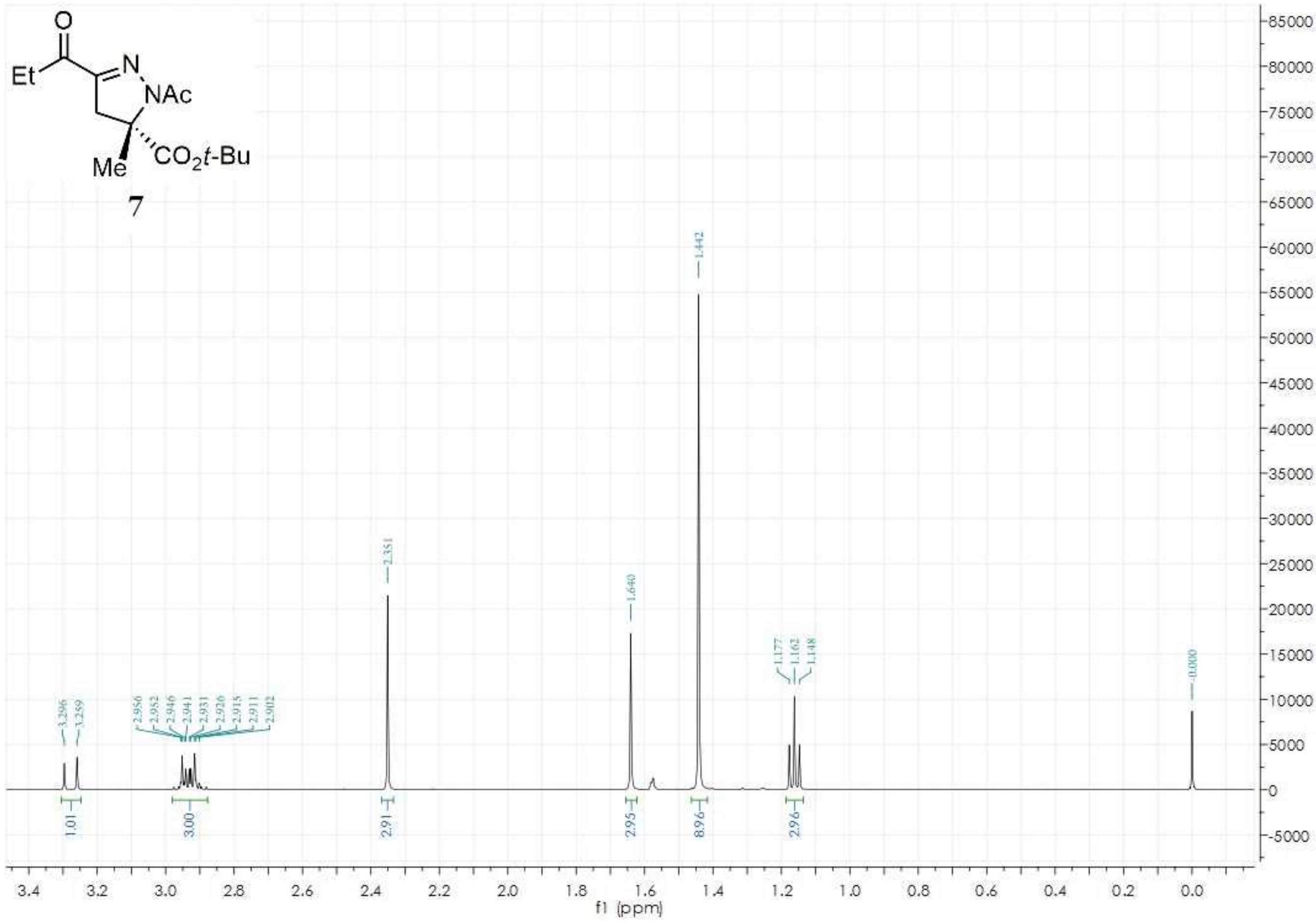
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.28 (d, *J*=18.5 Hz, 1H), 2.87-2.99 (m, 3H), 2.35 (s, 3H), 1.64 (s, 3H), 1.44 (s, 9H), 1.16 (t, *J*=7.0 Hz, 3H).

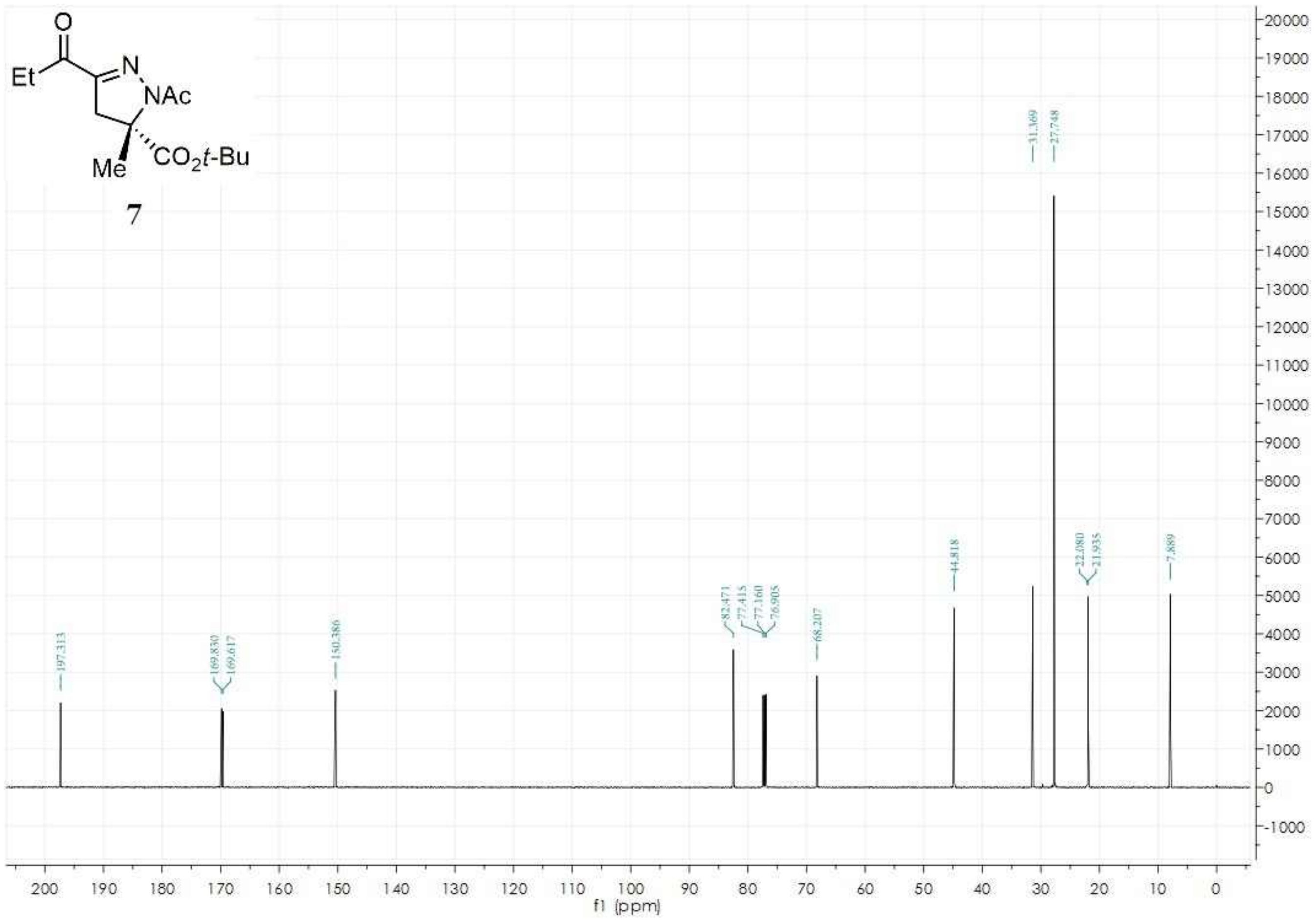
^{13}C NMR (125 MHz, $CDCl_3$) δ 197.31, 169.83, 169.62, 150.39, 82.47, 68.21, 44.82, 31.37, 27.75, 22.08, 21.94, 7.89.

IR υ_{max} 2981, 2939, 1741, 1681, 1579, 1369, 1227, 1136, 865, 734 cm^{-1}.

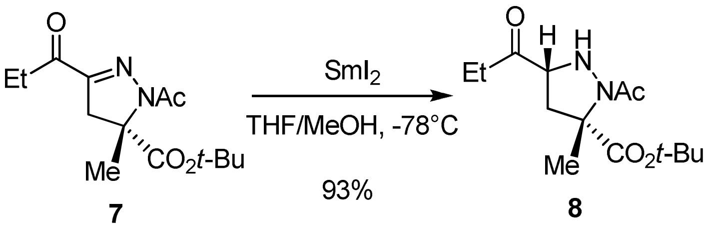
LRMS (APCI): m/z (%) = 283 (M+1, 16), 282 (21), 248 (100), 227 (70), 195 (90), 162 (41), 105 (52).

$[\alpha]^{25}_D$ = +167.7 (*c* 1.61 $CHCl_3$).


Et
N
NAc
Me
CO2t-Bu
7
3.296
3.259
2.956
2.952
2.946
2.941
2.931
2.926
2.915
2.911
2.902
2.351
1.640
1.442
1.177
1.162
1.148
0.000
1.01
3.00
2.91
2.95
8.96
2.96
f1 (ppm)


Et
N
NAc
Me
CO_2t-Bu
7
197.313
169.830
169.617
150.386
82.471
77.415
77.160
76.905
68.207
44.818
31.369
27.748
22.080
21.935
7.889
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(3*S*,5*R*)-*tert*-butyl 2-acetyl-3-methyl-5-propionylpyrazolidine-3-carboxylate (**7**)



A 100 ml round bottom flask was charged with **7** (515 mg, 1.82 mmol), a magnetic stir bar and anhydrous MeOH (23 ml). The mixture was cooled to -78 ºC. To this solution was added a samarium(II) iodide solution (46 ml, 0.1M in THF, 4.56 mmol). The reaction was stirred -78 ºC for 10min. The reaction was quenched with 20 ml saturated $NaHCO_{3(aq)}$. The aqueous layer was extracted with ethyl acetate (3 × 30 ml) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (ethyl acetate:hexane=1:1) provided **8** (481 mg, 1.69 mmol, 93% yield) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.96 (d, *J*=10.2 Hz, 1H), 3.93-3.97 (m, 1H), 2.66-2.73 (m, 1H), 2.56-2.62 (m, 1H), 2.46 (br s, 1H), 2.30 (dd, J_{AB}=12.6 Hz, J_{AC}=7.2 Hz, 1H), 2.18 (s, 3H), 1.62 (s, 3H), 1.42 (s, 9H), 1.11 (t, *J*=7.2 Hz, 3H).

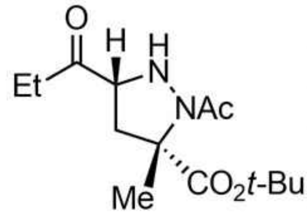
^{1}H NMR (600 MHz, CD_3OD) δ 3.86 (dd, J_{AB}=8.4 Hz, J_{AC}=1.8 Hz, 1H), 2.90 (dq, J_{AB}=18.6 Hz, J_{AC}=7.2 Hz, 1H), 2.83 (d, *J*=13.2 Hz, 1H), 2.61 (dq, J_{AB}=18.6 Hz, J_{AC}=7.2 Hz, 1H), 2.26 (dd, J_{AB}=13.2 Hz, J_{AC}=8.4 Hz, 1H), 2.20 (s, 3H), 1.51 (s, 3H), 1.36 (s, 9H), 1.03 (t, *J*=7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 208.42, 171.32, 168.33, 82.05, 66.66, 64.94, 45.95, 34.03, 27.85, 22.36, 21.77, 7.37.

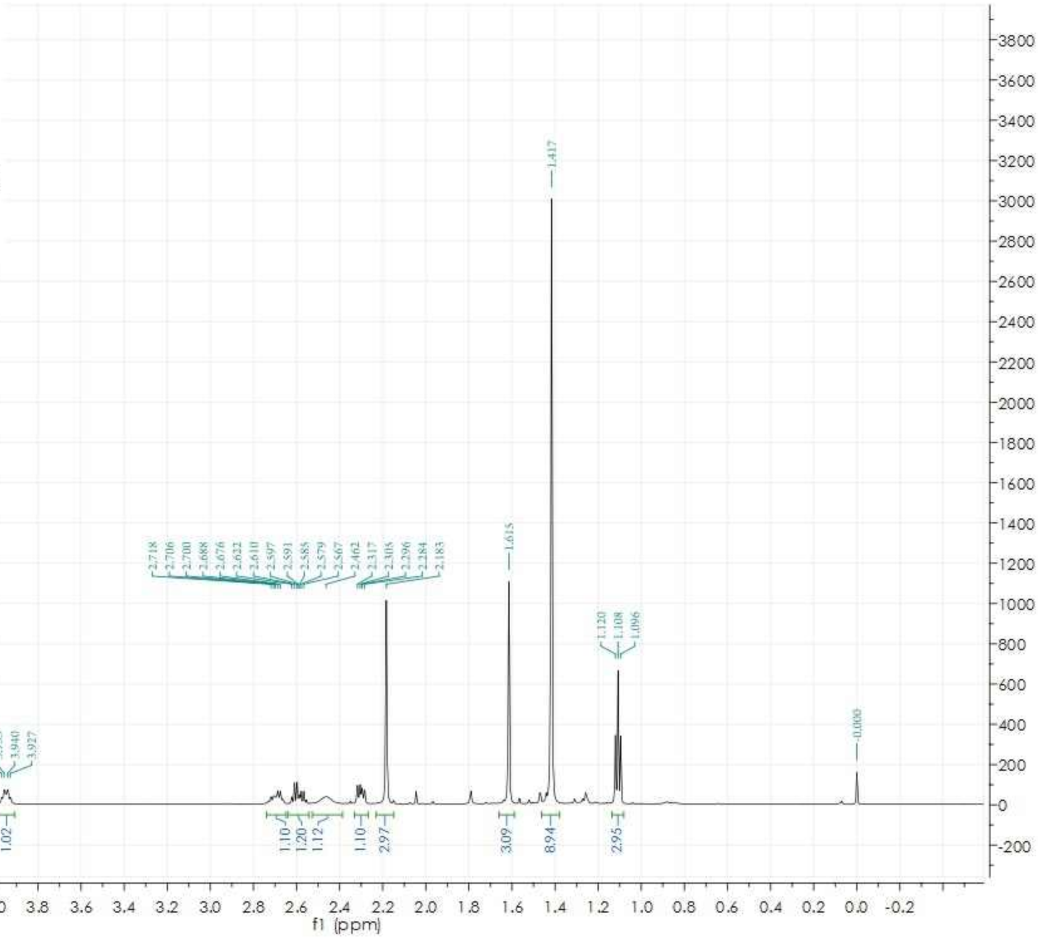
IR υ_{max} cm^{-1} 3212, 2982, 1736, 1720, 1618, 1455, 1291, 1150, 1131, 931, 853, 747.

LRMS (APCI): m/z (%) = 285 (M+1, 4), 284 (2), 277 (8), 248 (20), 119 (100), 211 (17), 187 (30), 170 (21), 141 (51).

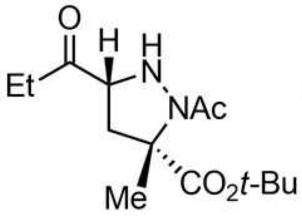
$[\alpha]^{25}_D$ = -19.11 (*c* 0.27 $CHCl_3$).



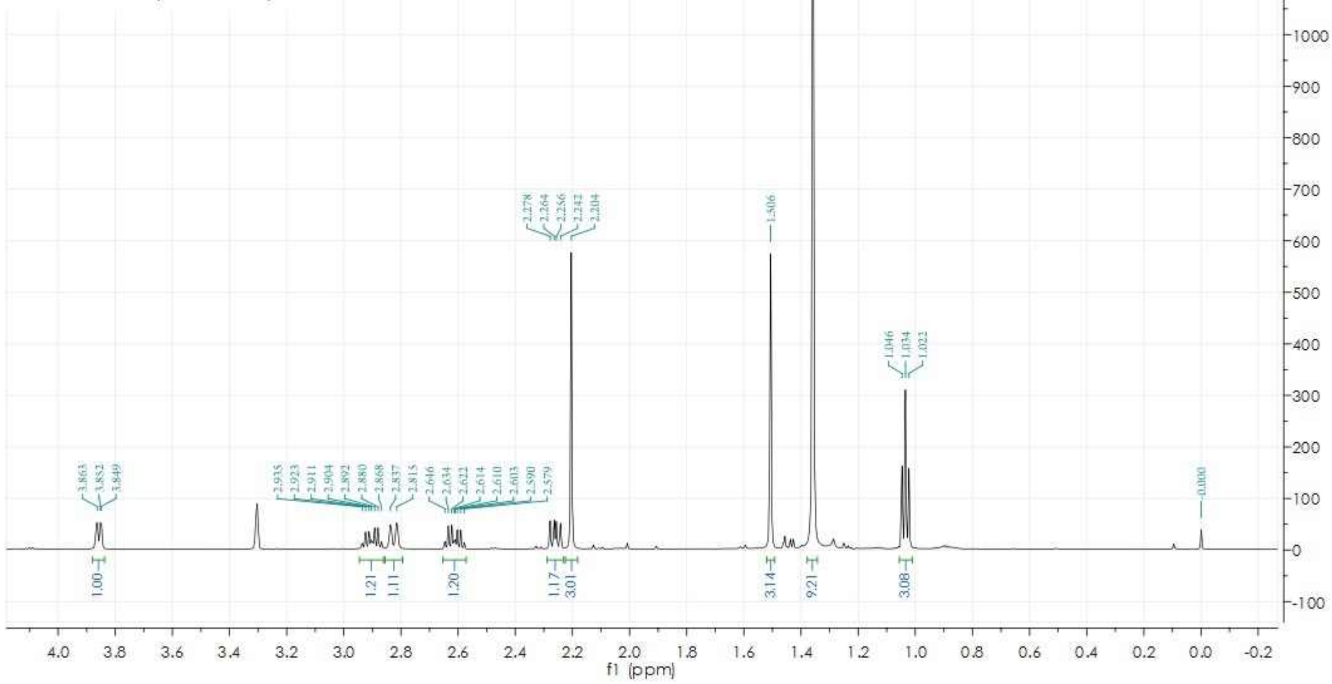
8 (CDCl3)

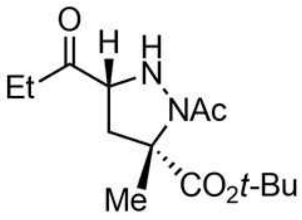


4.971
4.954
3.968
3.955
3.940
3.927
2.718
2.706
2.700
2.688
2.676
2.622
2.610
2.597
2.591
2.585
2.579
2.567
2.462
2.317
2.305
2.296
2.284
2.183
1.615
1.417
1.120
1.108
1.096
0.000
1.00
1.02
1.10
1.20
1.12
1.10
2.97
3.09
8.94
2.95
f1 (ppm)



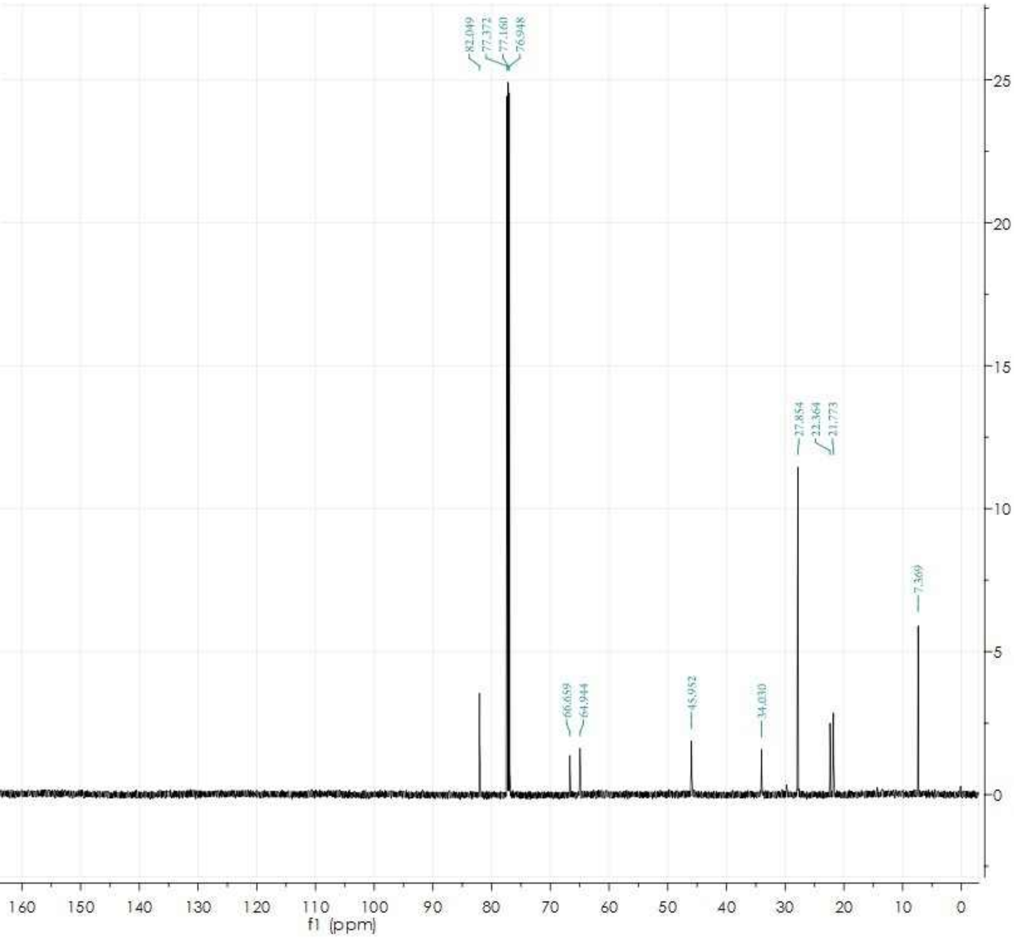
8 (CD3OD)



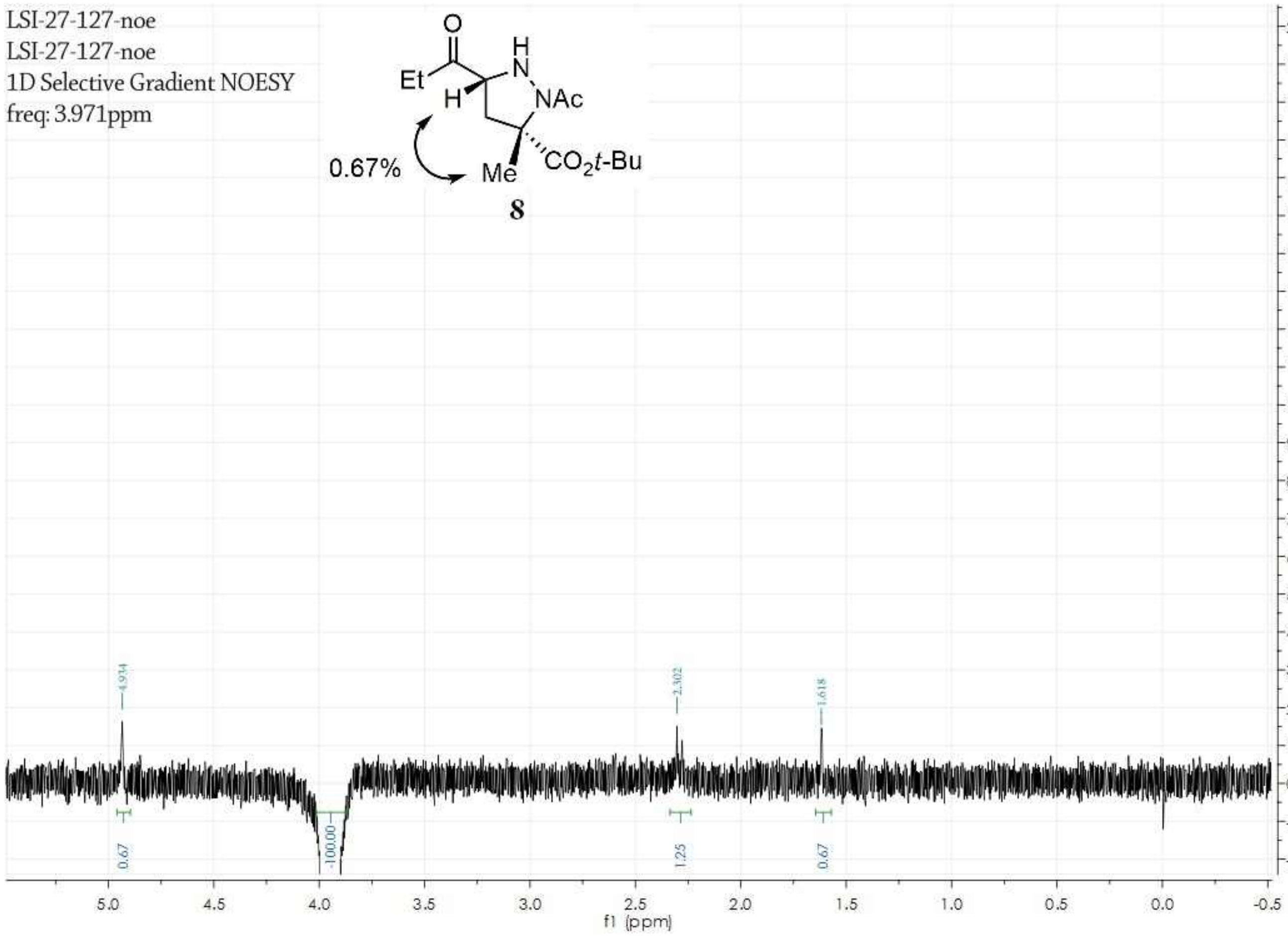


O
H
H
N
Et
NAc
Me
CO2t-Bu

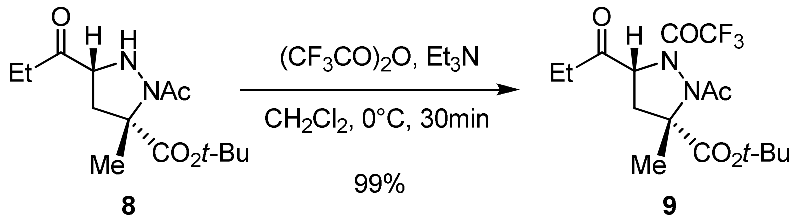
8



82.049
77.372
77.160
76.948
171.325
168.334
208.421
66.659
64.944
45.952
34.030
27.854
22.364
21.773
7.369
f1 (ppm)


LSI-27-127-noe
LSI-27-127-noe
1D Selective Gradient NOESY
freq: 3.971ppm
O
Et
H
N
NAc
H
0.67%
Me
CO_2t-Bu
8
4.934
2.302
1.618
0.67
-100.00
1.25
0.67
f1 (ppm)

(3*S*,5*R*)-*tert*-butyl 2-acetyl-3-methyl-5-propionyl-1-(2,2,2-trifluoroacetyl)pyrazolidine-3-carboxylate (**9**)



Amine (**8**) (450 mg, 1.58 mmol) was dissolved in 20 ml of dichloromethane. The mixture was cooled to 0 ºC. To this solution was added a triethylamine (0.44 ml, 3.16 mmol), trifluoroacetic anhydride (0.33ml, 2.37 mmol) and reaction mixture was kept at 0 ºC for 30 min. The mixture was quenched with 10 mL saturated $NaHCO_{3(aq)}$ and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried on Na_2SO_4. The solvent was removed and the obtained oil was purified by flash chromatography (ethyl acetate:hexane=1:5) which yielded **9** (600 mg, 1.58 mmol, 99% yield) as colorless oil.

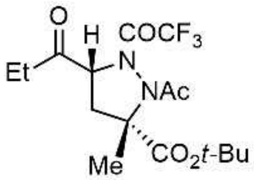
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (s, 1H), 3.00 (d, *J*=13.5 Hz, 1H), 2.64-2.72 (m, 1H), 2.62 (br s, 1H), 2.31 (dd, J_{AB}=13.5 Hz, J_{AC}=9.5 Hz, 1H), 2.17 (s, 3H), 1.58 (s, 3H), 1.40 (s, 9H), 1.13 (t, *J*=7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 203.59, 169.35, 168.19, 157.70, 115.93 (q, *J*=286.2 Hz), 83.14, 66.80, 65.57, 42.57, 31.92, 27.58, 23.00, 21.13, 7.21.

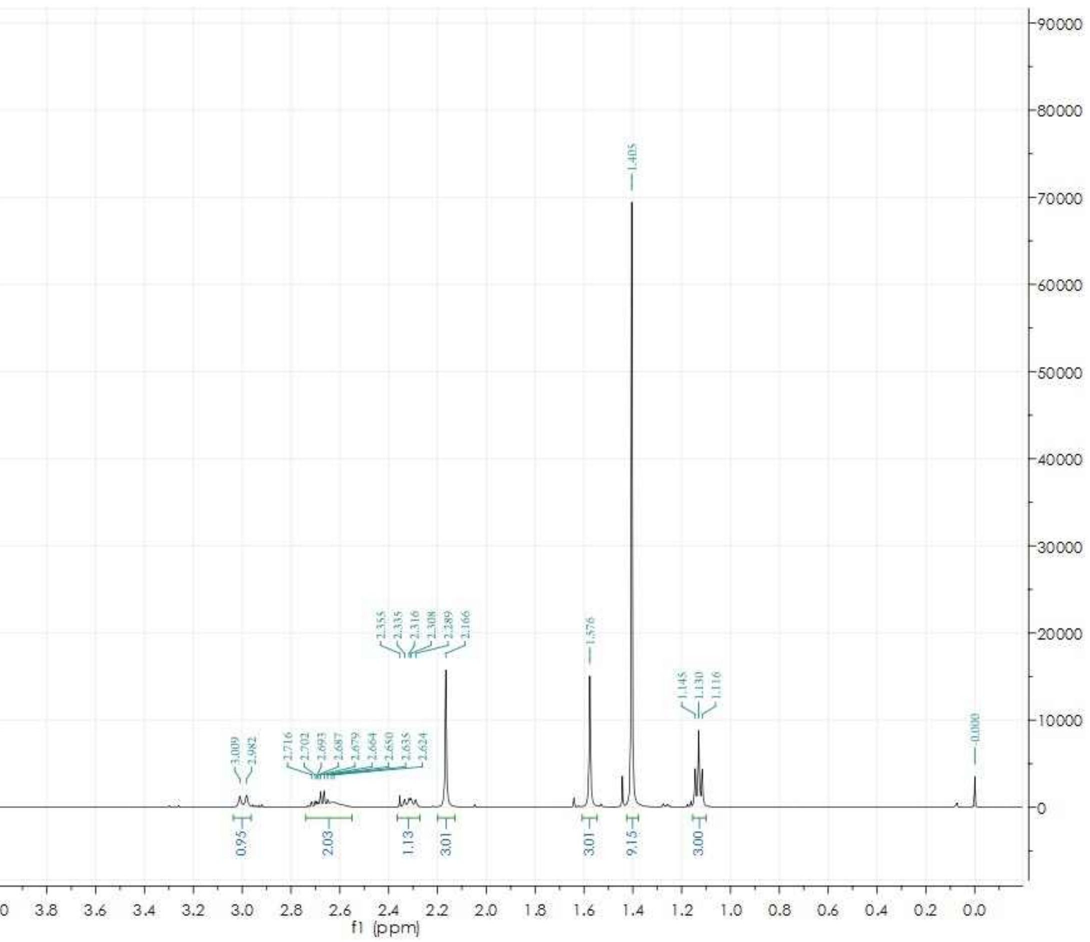
IR υ_{max} 2985, 1729, 1679, 1372, 1212, 1150, 844, 725 cm^{-1}.

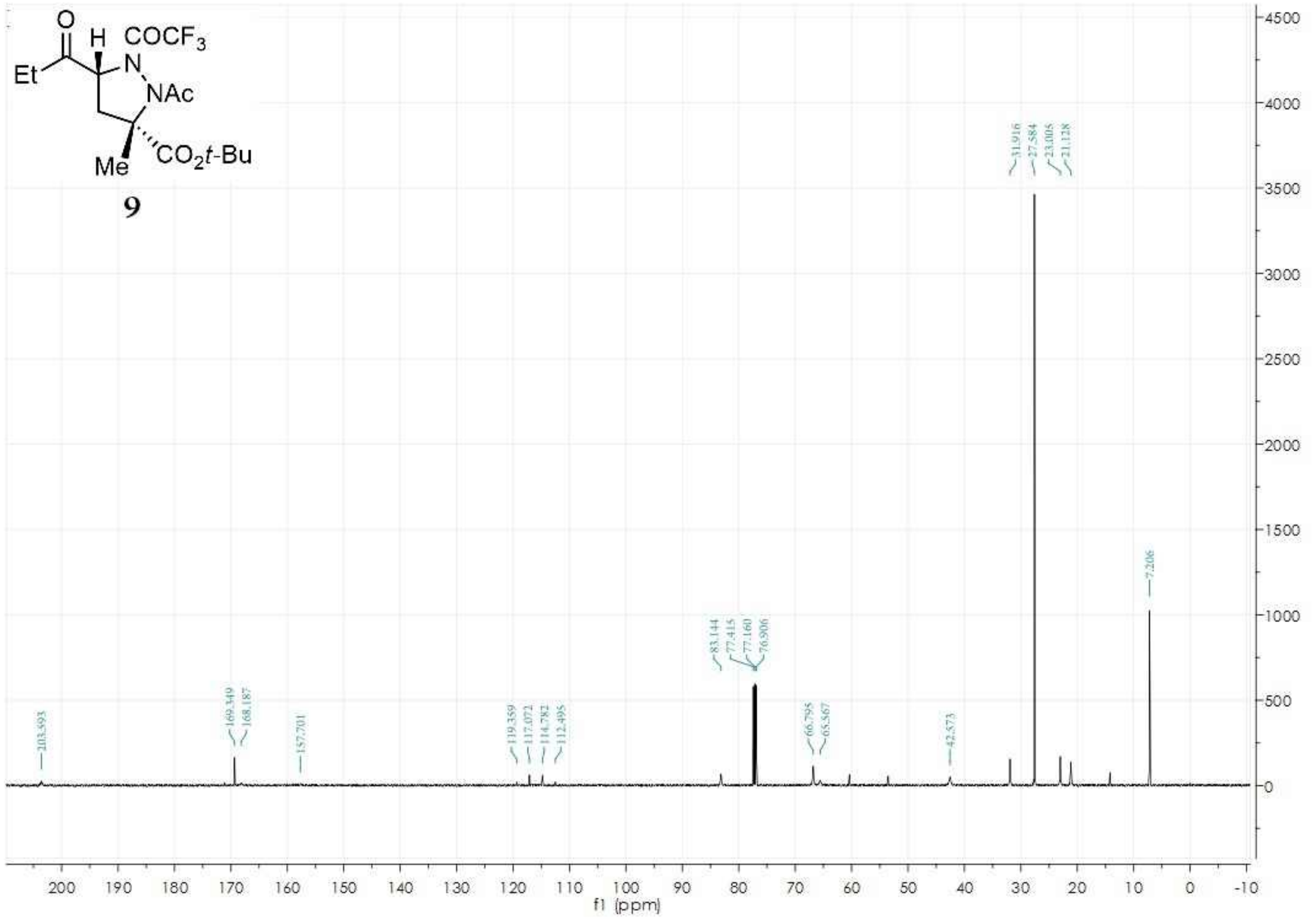
LRMS (APCI): m/z (%) = 379 (M-1, 28), 323 (84), 194 (100), 124 (27), 69 (8)

$[\alpha]^{25}_D$ = +84.74 (*c* 2.5 $CHCl_3$).



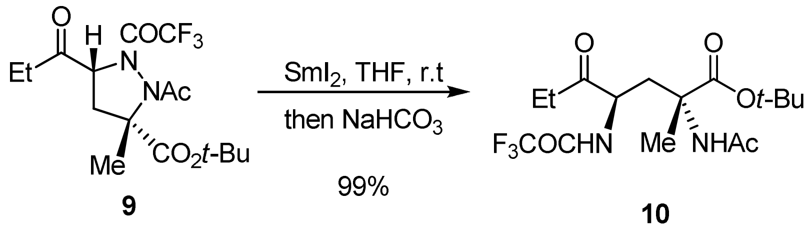
9


4.748
3.009
2.982
2.716
2.702
2.693
2.687
2.679
2.664
2.650
2.635
2.624
2.355
2.335
2.316
2.308
2.289
2.166
1.576
1.405
1.145
1.130
1.116
0.000
0.88
0.95
2.03
1.13
3.01
3.01
9.15
3.00
f1 (ppm)



COCF3
NAc
CO2t-Bu
Me
Et
H
9
203.593
169.349
168.187
157.701
119.359
117.072
114.782
112.495
83.144
77.415
77.160
76.906
66.795
65.567
42.573
31.916
27.584
23.005
21.128
7.206
f1 (ppm)

(2*R*,4*R*)-*tert*-butyl 2-acetamido-2-methyl-5-oxo-4-(2,2,2-trifluoroacetamido)heptanoate (**10**)



A 100 ml frame-dried round bottom flask was charged with **9** (600 mg, 1.58 mmol). The flask was purged with nitrogen, and samarium(II) iodide solution (32 ml, 0.1M in THF, 3.16 mmol) was added. The reaction was stirred r.t for 10min. The reaction was quenched with 20 ml saturated $NaHCO_{3(aq)}$ and vigorously stirred for 10 min at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 10 ml) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (ethyl acetate:hexane=1:1) provided **10** (603 mg, 1.58 mmol, 99% yield) as a white solid.

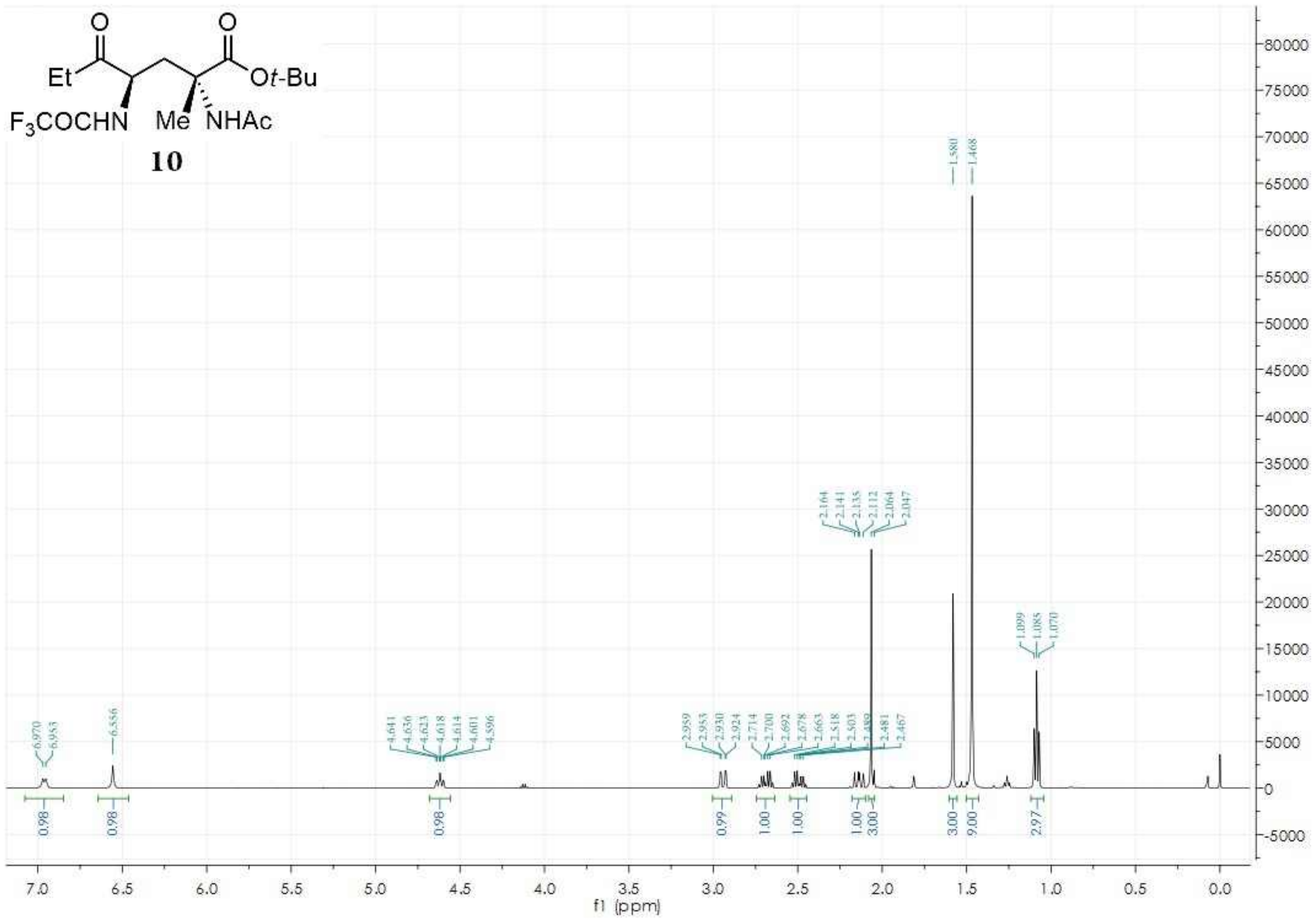
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, *J*=8.5 Hz, 1H), 6.56 (s, 1H), 4.60-4.64 (m, 1H), 2.94 (dd, J_{AB}=14.5 Hz, J_{AC}=3.0 Hz, 1H), 2.69 (dq, J_{AB}=18.0 Hz, J_{AC}=7.0 Hz, 1H), 2.49 (dq, J_{AB}=18.0 Hz, J_{AC}=7.0 Hz, 1H), 2.14 (dd, J_{AB}=14.5 Hz, J_{AC}=11.5 Hz, 1H), 2.06 (s, 3H), 1.58 (s, 3H), 1.47 (s, 9H), 1.08 (t, *J*=7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.97, 172.86, 170.50, 157.4 (q, *J*=37.1 Hz), 115.66 (q, *J*=286.0 Hz), 83.72, 58.75, 55.43, 36.25, 33.07, 27.83, 24.70, 24.09, 7.65.

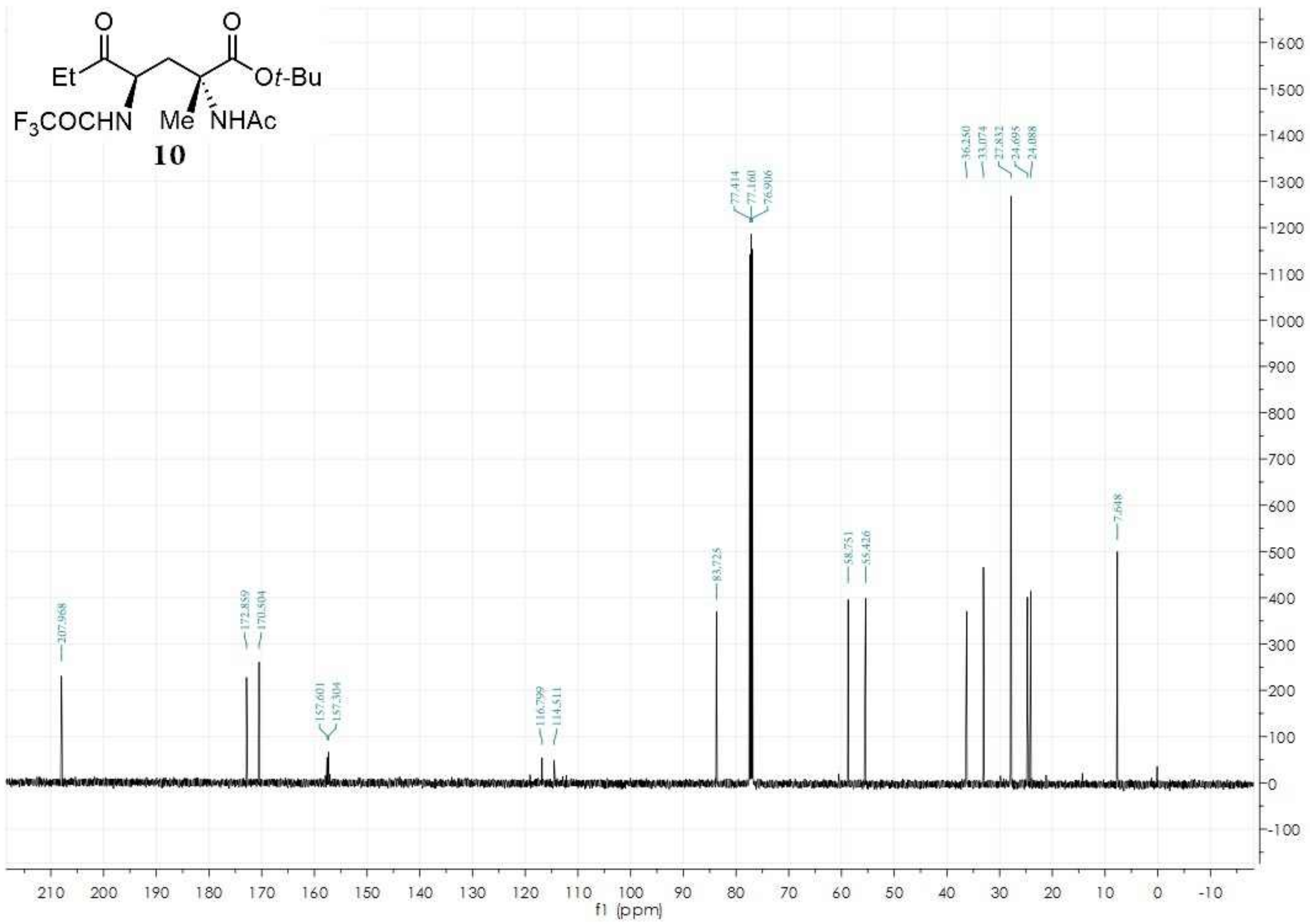
IR υ_{max} 2983, 1720, 1658, 1543, 1306, 1167, 1045, 847 cm^{-1}.

LRMS (APCI): m/z (%) = 381 (M-1, 100), 325 (17), 306 (6), 265 (1), 194 (4), 112 (1).

$[\alpha]^{25}_D$ = -29.62 (*c* 1.19 $CHCl_3$).

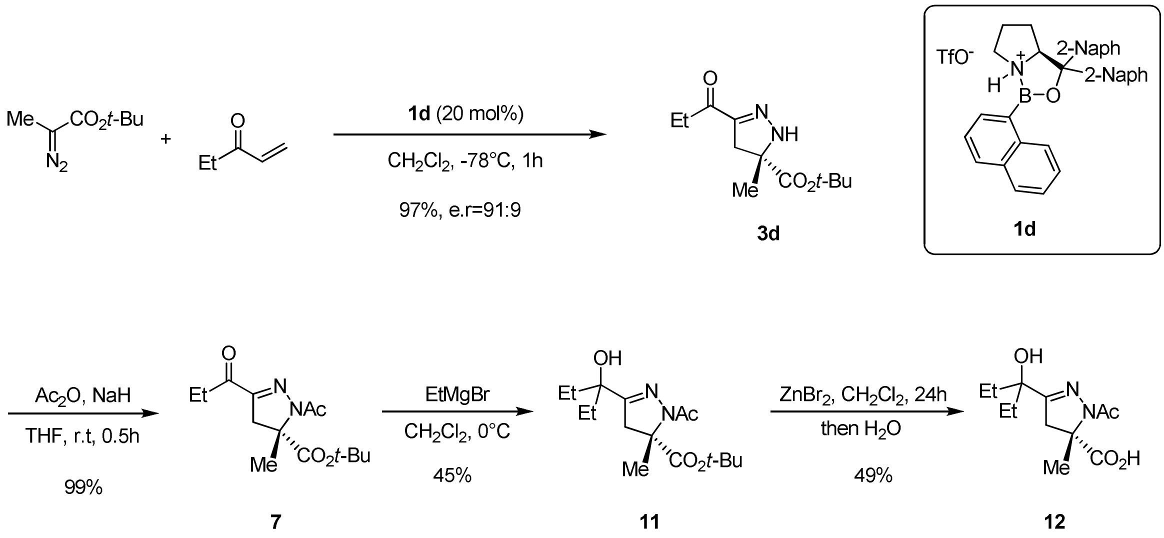


10



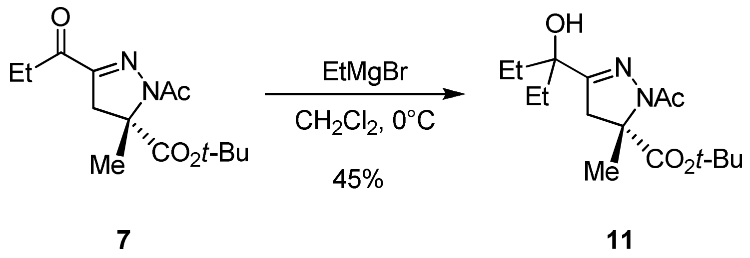
10
207.968
172.859
170.504
157.601
157.304
116.799
114.511
83.725
77.414
77.160
76.906
58.751
55.426
36.250
33.074
27.832
24.695
24.088
7.648
f1 (ppm)

Absolute structure determination of 2-pyrazoline



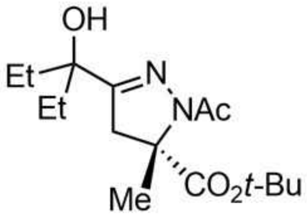
$[\alpha]^{25}_{D}$ = +95.17 (c 0.60, MeOH)

(*S*)-*tert*-butyl 1-acetyl-3-(3-hydroxypentan-3-yl)-5-methyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**11**)

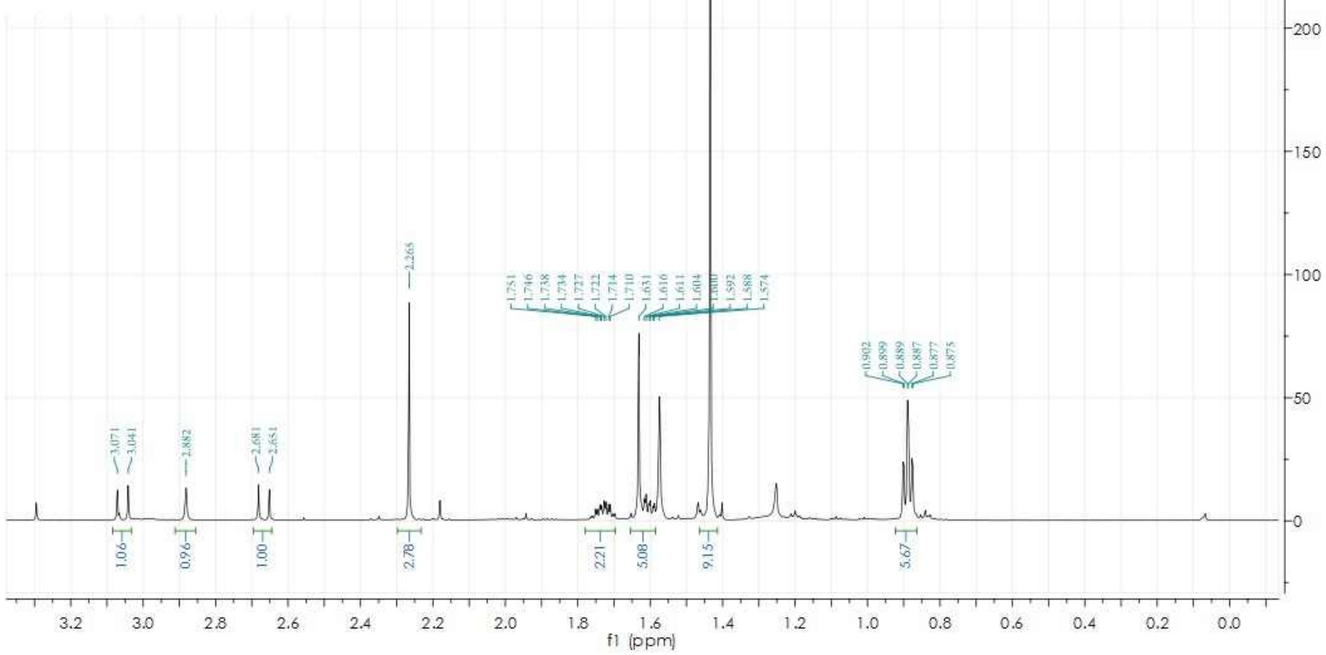


To a -78 ^{o}C solution of **7** (1 g, 3.54 mmol) in 40ml of CH_2Cl_2 was added ethylmagnesium bromide (2.3 ml, 4.6 mmol) as a 2 M solution in THF via sylinge. The reaction was maintained for 30 min, quenched by adding 20 ml of saturated $NH_4Cl_{(aq)}$ and extracted with dichloromethane (3 × 10 ml) and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (ethyl acetate:hexane=1:5) provided tertiary alcohol **11** (0.497 g, 1.59 mmol, 45% yield) as a colorless oil.

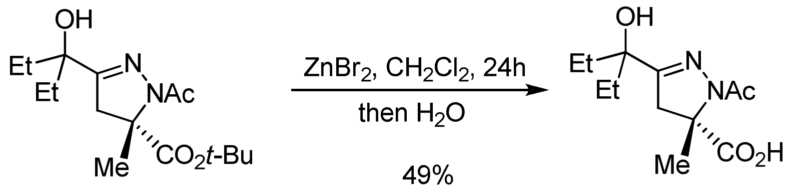
^{1}H NMR (600 MHz, $CDCl_3$) δ 3.06 (d, *J*=18.0 Hz, 1H), 2.88 (s, 1H), 2.67 (d, *J*=18.0 Hz, 1H), 2.26 (s, 3H), 1.70-1.76 (m, 2H), 1.63 (s, 3H), 1.59-1.63 (m, 2H), 1.43 (s, 9H), 0.89 (t, *J*=7.2 Hz, 3H), 0.89 (t, *J*=7.2 Hz, 3H).


OH
Et
Et
N
NAc
Me
CO2t-Bu

11


3.071
3.041
2.882
2.681
2.651
2.265
1.434
0.902
0.899
0.889
0.887
0.877
0.875
1.06
0.96
1.00
2.78
2.21
5.08
9.15
5.67
f1 (ppm)

(*S*)-1-acetyl-3-(3-hydroxypentan-3-yl)-5-methyl-4,5-dihydro-1H-pyrazole-5-carboxylic acid (**12**)



11 **12**

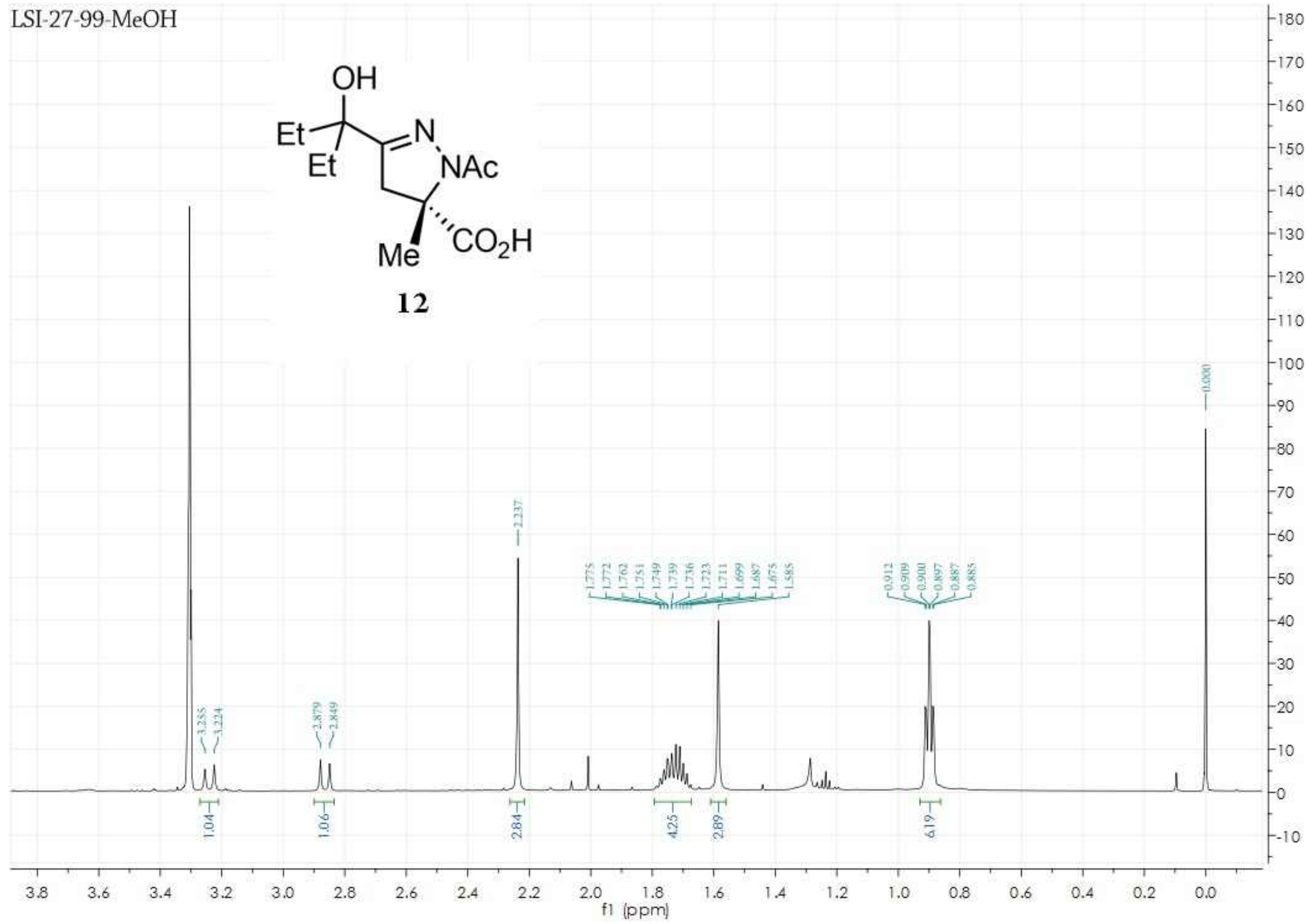
$[\alpha]^{25}_{D}$ = +95.17 (c 0.60, MeOH)

To a solution of **11** (144 mg, 0.48 mmol) in 5 ml CH_2Cl_2 was added $ZnBr_2$ (935 mg, 4.15 mmol) and the solution stirred for 24 h at room temperature[2]. At this time, 5 ml of water was added and the mixture was stirred for 3 h. The aqueous layer was extracted with ethyl acetate (10 × 5 ml) and the combined organics were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (ethyl acetate:MeOH:AcOH=95:5:0.5) provided carboxylic acid **12** (60 mg, 0.24 mmol, 49% yield) as a colorless oil.

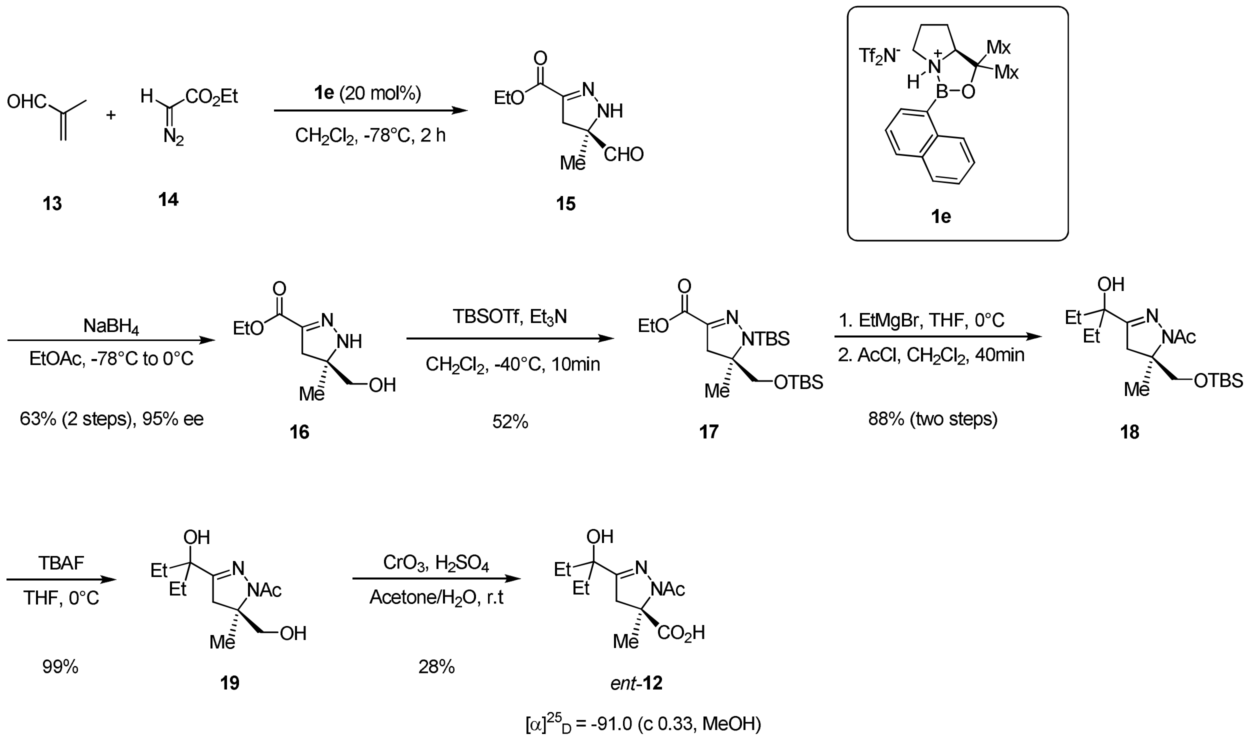
^{1}H NMR (600 MHz, CD_3OD) δ 3.24 (d, *J*=18.6 Hz, 1H), 2.86 (d, *J*=18.0 Hz, 1H), 2.24 (s, 3H), 1.67-1.79 (m, 4H), 1.58 (s, 3H), 0.90 (td, J_{AB}=7.2 Hz, J_{AC}=1.8 Hz, 6H).

---

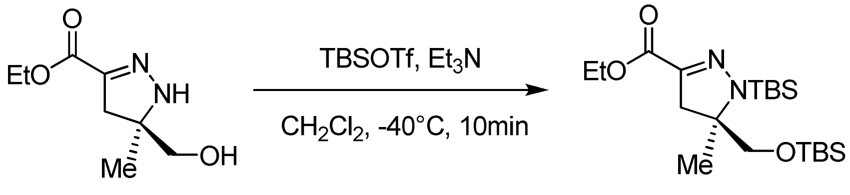
[2] (1) Y.-q. Wu, D. C. Limburg, D. E. Wilkinson, M. J. Vaal, G. S. Hamilton, *Tetrahedron Lett*. **2000**, *41*, 2847. (2) R. Kaul, Y. Brouillette, Z. Sajjadi, K. A. Hansford, W. D. Lubell, *J. Org. Chem*. **2004**, *69*, 6131.



LSI-27-99-MeOH
OH
Et
Et
N
NAc
Me
CO2H
12
2.237
3.255
3.224
2.879
2.849
1.775
1.772
1.762
1.751
1.749
1.739
1.736
1.723
1.711
1.699
1.687
1.675
1.585
0.912
0.909
0.900
0.897
0.887
0.885
0.000
1.04
1.06
2.84
4.25
2.89
6.19
f1 (ppm)


OHC
+
H
CO_2Et
N_2
13
14
1e (20 mol%)
CH_2Cl_2, -78°C, 2 h
EtO
N
NH
Me
CHO
15
Tf_2N^-
Mx
H
B–O
1e
$NaBH_4$
EtOAc, -78°C to 0°C
63% (2 steps), 95% ee
OH
16
TBSOTf, Et_3N
CH_2Cl_2, -40°C, 10min
52%
NTBS
OTBS
17
1. EtMgBr, THF, 0°C
2. AcCl, CH_2Cl_2, 40min
88% (two steps)
Et
NAc
18
TBAF
THF, 0°C
99%
19
CrO_3, H_2SO_4
Acetone/H_2O, r.t
28%
CO_2H
ent-12
$[\alpha]^{25}_D$ = -91.0 (c 0.33, MeOH)

(*R*)-ethyl 1-(*tert*-butyldimethylsilyl)-5-((*tert*-butyldimethylsilyloxy)methyl)-5-methyl-4,5-dihydro-1H-pyrazole-3-carboxylate (**17**)

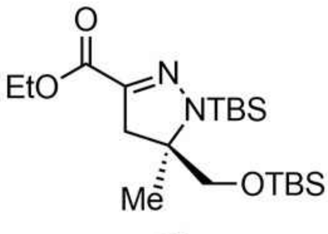


16 **17**

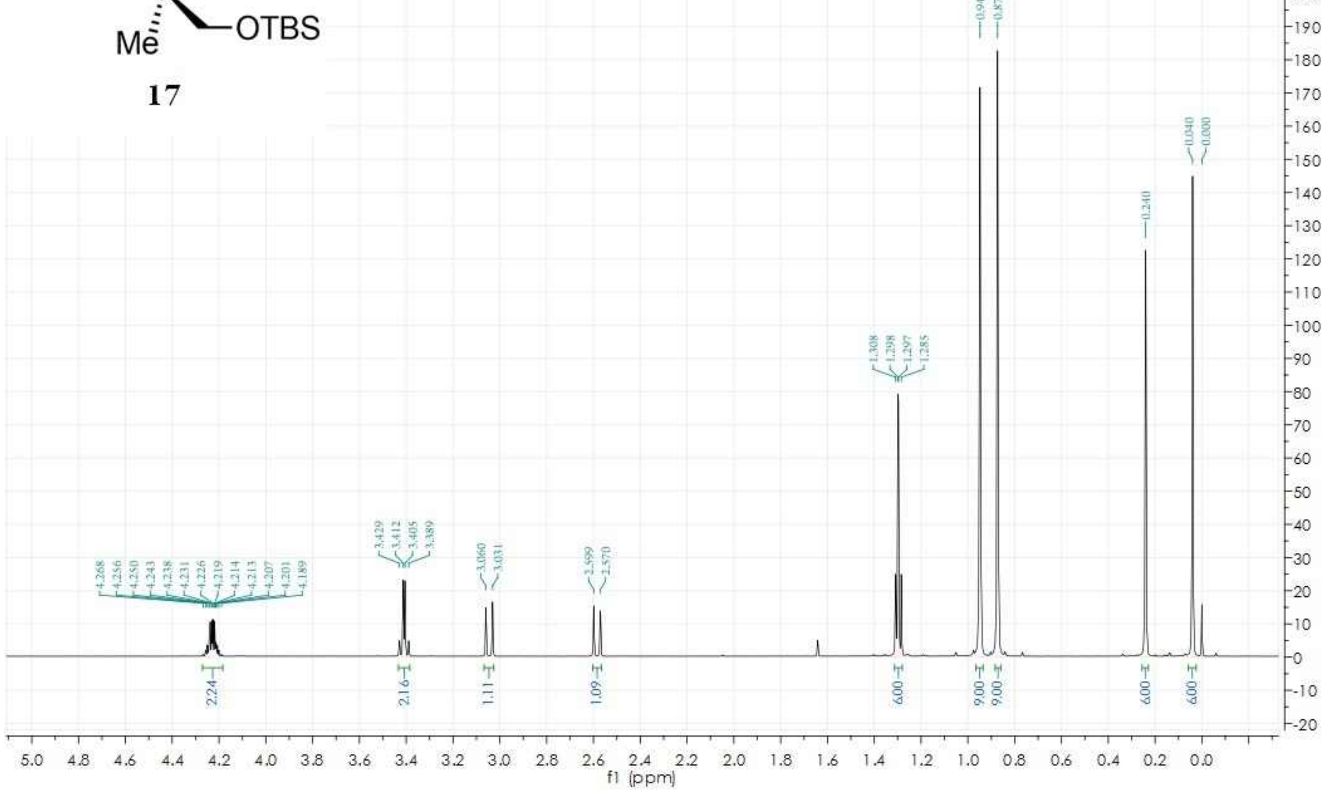
To a -40 °C solution of **16**[3] (154 mg, 0.83 mmol) and triethylamine (577 µl, 4.14 mmol) in 5.0 ml of CH_2Cl_2 was added TBSOTf (0.76 ml, 3.32 mmol). The reaction was stirred for 15 min. The reaction was quenched by adding 3 ml of saturated $NH_4Cl_{(aq)}$ and the layer were stirred and separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 ml) and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (ethyl acetate:hexane=1:30) to afford the desired product **17** (172 mg, 0.43 mmol, 52 % yield) as colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.19-4.27 (m, 2H), 3.42 (d, *J*=10.2 Hz, 1H), 3.40 (d, *J*=9.6 Hz, 1H), 3.04 (d, *J*=17.4 Hz, 1H), 2.58 (d, *J*=17.4 Hz, 1H), 1.30 (s, 3H), 1.30 (t, *J*=6.9 Hz, 3H), 0.95 (s, 9H), 0.87 (s, 9H), 0.24 (s, 6H), 0.04 (s, 6H).

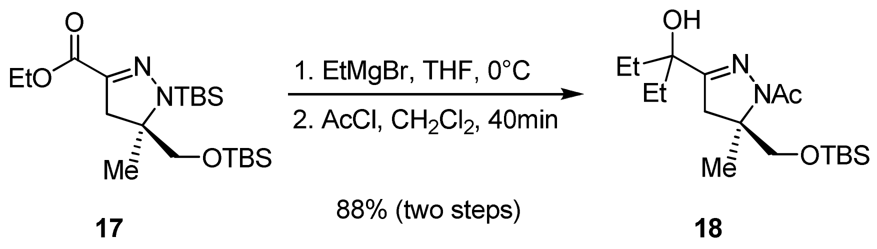
[3] Gao, L.; Hwang, G.-S.; Lee, M. Y.; Ryu, D. H. *Chem. Commun*. **2009**, 5460.



17

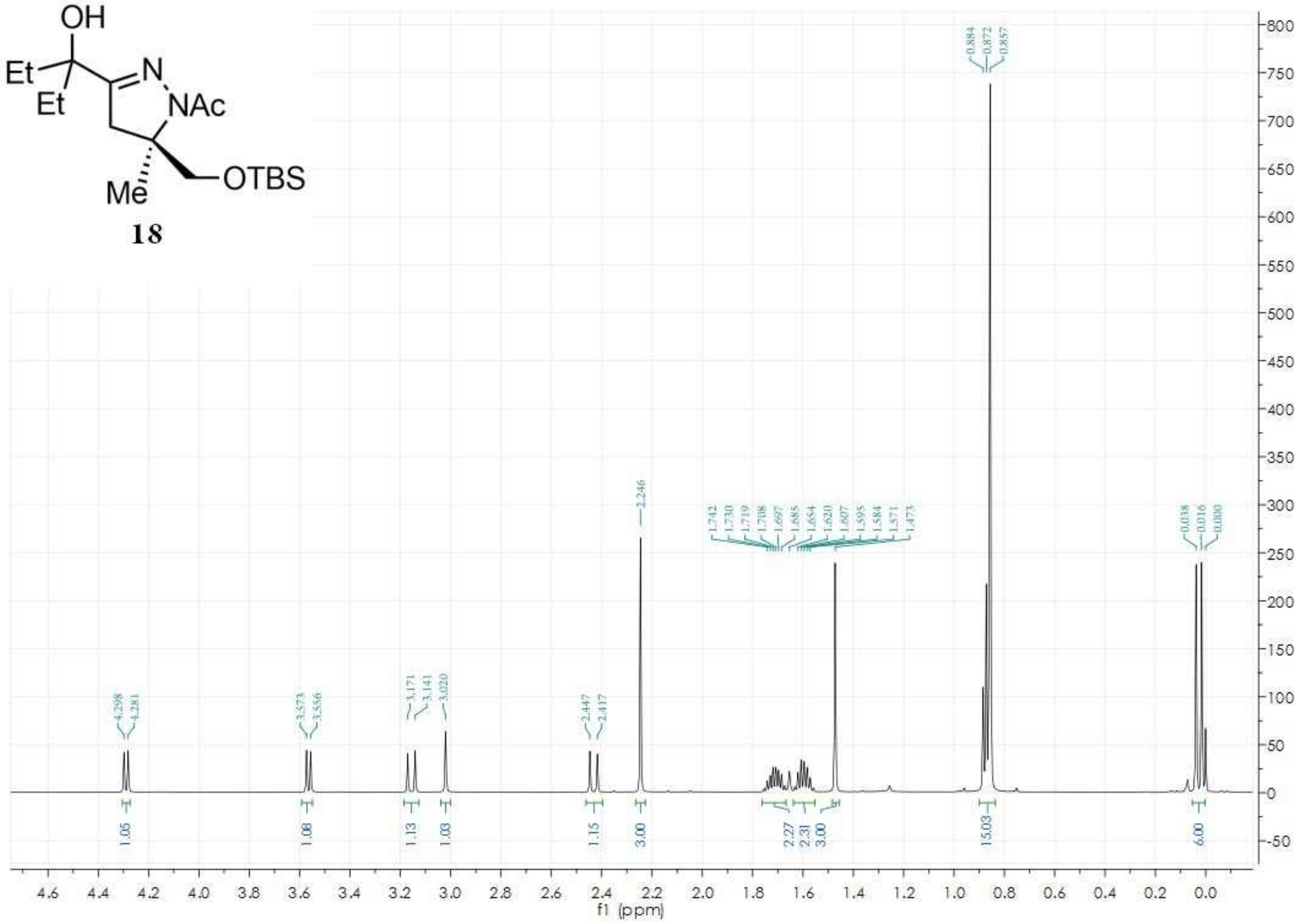


(*R*)-1-(5-((*tert*-butyldimethylsilyloxy)methyl)-3-(3-hydroxypentan-3-yl)-5-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**18**)

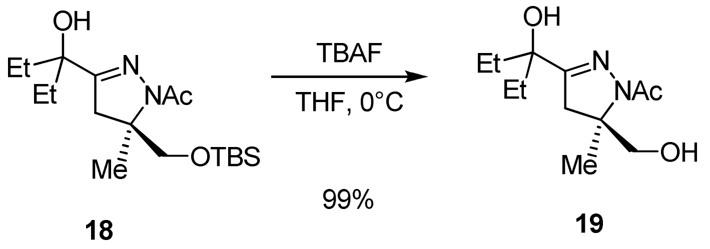


The ethylmagnesium bromide in 1 M THF solution (1 ml, 1 mmol) was added dropwise to a 0 ^{o}C solution of **17** (41 mg, 0.1 mmol) in 1 ml THF for 30 min. After completion of dropwise addition, the resulting mixture was quenched by adding 2 ml of saturated $NaHCO_{3(aq)}$ and extracted with dichloromethane (3 × 2 ml) and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product was dissolved in 1 ml of dichloromethane. To this solution was added a Ac_2O (7.8 µl, 0.11 mmol) and reaction mixture was kept at room temperature for 40 min. The mixture was quenched with 1 mL saturated $NaHCO_{3(aq)}$ and extracted with CH_2Cl_2 (3 × 2 mL). The organic layer was dried on Na_2SO_4. The solvent was removed and the obtained oil was purified by flash chromatography (ethyl acetate:hexane=1:5) which yielded **18** (32 mg, 0.09 mmol, 88% yield) as colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.29 (d, *J*=10.2 Hz, 1H), 3.56 (d, *J*=10.2 Hz, 1H), 3.16 (d, *J*=18.0 Hz, 1H), 3.02 (s, 1H), 2.43 (d, *J*=18.0 Hz, 1H), 2.25 (s, *3*H), 1.67-1.76 (m, 2H), 1.56-1.63 (m, 2H), 1.47 (s, 3H), 0.87 (t, *J*=7.2 Hz, 6H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

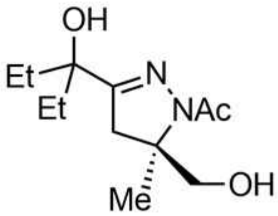

OH
Et
Et
N
NAc
Me
OTBS
18
f1 (ppm)

(*R*)-1-(5-(hydroxymethyl)-3-(3-hydroxypentan-3-yl)-5-methyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (**19**)

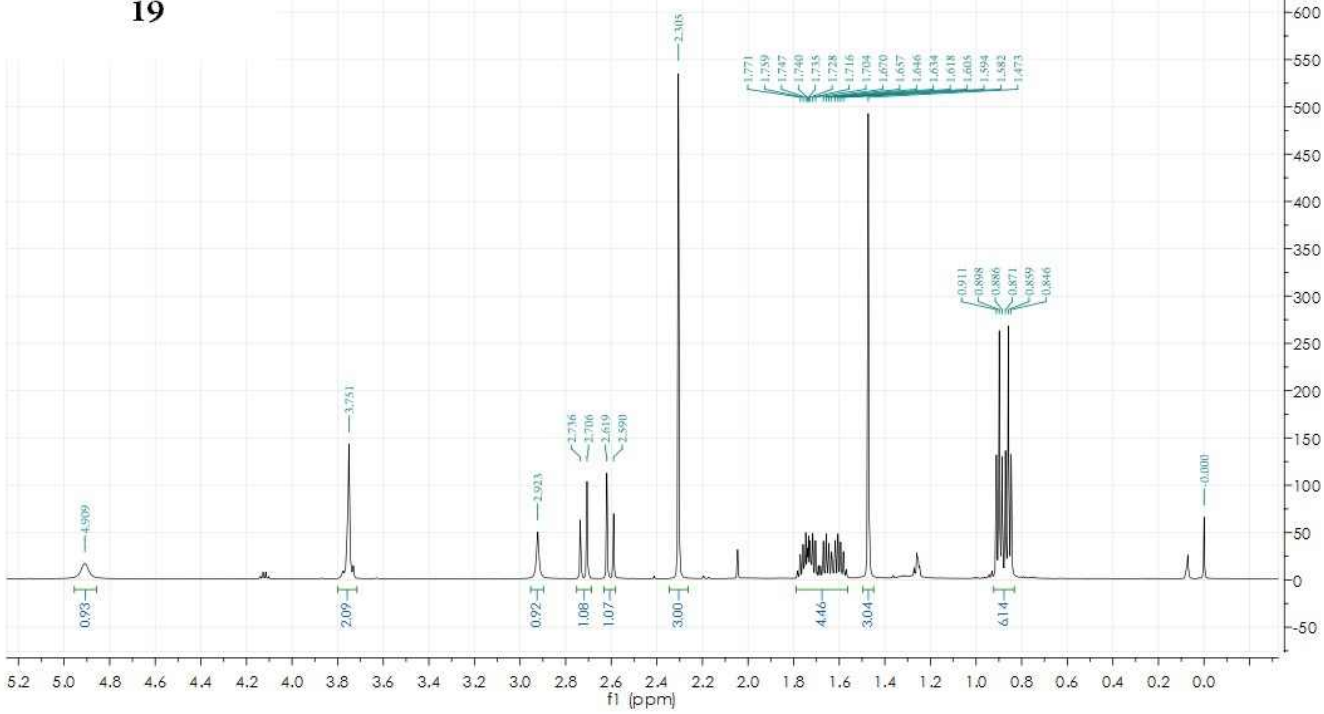


To a 0 °C solution of **18** (28 mg, 0.077 mmol) in 1.0 ml of THF was added tetrabutylammonium fluoride (230 µl, 0.23 mmol) as a 1 M solution in THF via microsylinge. The reaction was maintained for 2 h, quenched by adding 1 ml of saturated $NH_4Cl_{(aq)}$ and extracted with CH_2Cl_2 (3 × 2 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (ethyl acetate:hexane=1:1) to afford the desired product **19** (19 mg, 0.077 mmol, 99%) as colorless oil.

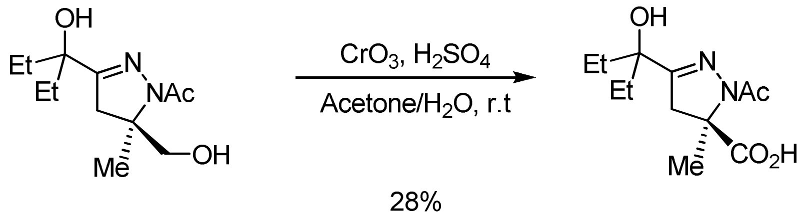
^{1}**H NMR** (600 MHz, $CDCl_3$) δ 4.91 (br s, 1H), 3.75 (s, 2H), 2.92 (br s, 1H), 2.72 (d, *J*=16.0 Hz, 1H), 2.60 (d, *J*=17.4 Hz, 1H), 2.30 (s, 3H), 1.57-1.78 (m, 4H), 1.47 (s, 3H), 0.90 (t, *J*=7.2 Hz, 3H), 0.86 (t, *J*=7.2 Hz, 3H).


OH
Et
Et
N
NAc
Me
OH

19


4.909
3.751
2.923
2.716
2.706
2.619
2.590
2.305
1.771
1.759
1.747
1.740
1.735
1.728
1.716
1.704
1.670
1.657
1.646
1.634
1.618
1.605
1.594
1.582
1.473
0.911
0.898
0.886
0.871
0.859
0.846
0.000
0.93
2.09
0.92
1.08
1.07
3.00
4.46
3.04
6.14
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2 0.0
f1 (ppm)

(*R*)-1-acetyl-3-(3-hydroxypentan-3-yl)-5-methyl-4,5-dihydro-1H-pyrazole-5-carboxylic acid (*ent*-**12**)



19 *ent*-**12**

$[\alpha]^{25}_D$ = -91.0 (c 0.33, MeOH)

The Johns reagent is prepared by dissolving CrO_3 (24 mg, 0.24 mmol) in 0.5 ml of distilled water. To this solution is added H_2SO_4 (21 µl, 0.4 mmol). The Johns reagent is added to a 1 ml Acetone solution of **19** (14.5 mg, 0.06 mmol) and the solution stirred for 18 h at room temperature. The reaction was quenched by adding small porting of 2-isoprropanol and 1 ml of saturated $NH_4Cl_{(aq)}$ and the layer were stirred and separated. The aqueous layer was extracted with ethyl acetate (10 × 3 ml) and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (ethyl acetate:MeOH:AcOH=95:5:0.5) to afford the desired product *ent*-**12** (4.3 mg, 0.016 mmol, 28 % yield) as colorless oil.