Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

— Supporting Information —

Optimization and Multigram Scalability of a Catalytic Enantioselective Borylative Migration for the Synthesis of Functionalized Chiral Piperidines

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1. General information and experimental details

1.1. General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. THF and toluene were purified using a MBraun MB SPS* solvent system. Dioxane was distilled over sodium. Diethyl ether (Et_2O) was distilled over sodium/benzophenone ketyl. Anhydrous chlorobenzene, cyclopentyl methyl ether (CPME), methyl *tert*-butyl ether (MTBE), dibutyl ether, 2-methyltetrahydrofuran (2-MeTHF), and diglyme were purchased from Sigma-Aldrich and used as received. *N,N*-Diisopropylethylamine (DIPEA) and *N,N*-dimethylaniline (DMA) were purchased from Sigma-Aldrich and distilled over potassium hydroxide prior to use. Pinacolborane and 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU) were purchased from Oakwood Products and Sigma-Aldrich, respectively, and were used without further purification. 1-*tert*-Butoxycarbonyl-4-piperidone, 1-carbobenzoxy-4-piperidone, 1-benzyl-4-piperidone, and perfluorobutanesulfonyl fluoride (NfF) were purchased from Combi-Blocks Inc. and were used without further purification. All aldehydes were purified by a bulb-to-bulb distillation under reduced pressure. Palladium(II) acetate, allylpalladium(II) chloride dimer, tris(dibenzylideneacetone)dipalladium(0), DPEphos, Taniaphos, and Walphos were purchased from Strem Chemicals. All other palladium catalysts and ligands were purchased from Sigma-Aldrich. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F_{254} plates and visualized with UV light, p-anisaldehyde stain, and $KMnO_4$ stain. Flash column chromatography was performed on ultra-pure silica gel 230-400 mesh. Nuclear magnetic resonance (NMR) spectra were recorded on INOVA-400 or INOVA-500 instruments. The residual solvent protons (^1H) and the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; app s, apparent singlet; t, triplet; app t, apparent triplet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet. Reported *J*-values are deemed accurate within ± 0.3 Hz. NMR data were processed either using VnmrJ from Agilent Technologies or MestReNova from Mestrelab Research. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using electrospray ionization (ESI) method. Infrared spectra were obtained from a Nicolet Magna-IR machine with frequencies expressed in cm^{-1}. Optical rotations were measured using a 1 mL cell with a 1 dm length on a P.E. 241 polarimeter. Regioselectivity of alkenyl to allyl boronate and the diastereomeric ratios for chiral compounds were determined by integration of relevant signals on the crude ^1H NMR spectra. The enantiomeric excess ratios for optically enriched compounds were determined using a HPLC Agilent instrument with a Chiralcel-OD or IB or IC column as specified in the following individual procedures.

1.2. Experimental details

Pinacolborane received in a bottle was transferred to a round bottom flask under a nitrogen atmosphere and

stored in a freezer. DIPEA and DMA were distilled over potassium hydroxide under a nitrogen atmosphere and stored in a refrigerator. Synthesized alkenyl nonaflates were transferred to vials after purification and stored in a refrigerator. Prior to the borylative migration reaction, pinacolborane, the base, and the alkenyl nonaflate were allowed to warm up to room temperature (ca. 20 min). Ultrapure (99.95+%) $Pd(OAc)_2$ was used. All the phosphine ligands were checked for oxidation via ESI-ToF technique prior to use. Palladium and ligand were weighed out carefully and transferred to a reaction flask, which was evacuated and back-filled with nitrogen three times. Due to its instability to a prolonged exposure to air and silica gel, freshly-made crude allylic boronate **5** was filtered through a silica plug (silica gel to crude product, 100/1, w/w) very quickly (ca. 30 seconds) and subjected to the allylboration reaction directly after concentration of solvent. The major side product, alkenyl boronate, was removed during the purification of final products, α-hydroxyalkyl dehydropiperidines.

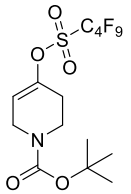
2. Experimental procedure and spectral data for alkenyl nonaflates **8**, **9**, and **13**

*2.1. General procedure for the synthesis of alkenyl nonaflates **8**, **9**, and **13***

N-Protected piperidone (10 mmol, 1.0 equiv) was dissolved in THF (50 mL) under a nitrogen atmosphere. The mixture was cooled in an ice-water bath (0 °C) and stirred for 5 min. DBU (1.8 mL, 12 mmol, 1.2 equiv) and perfluorobutanesulfonyl fluoride (2.2 mL, 12 mmol, 1.2 equiv) were added respectively and the resulting solution was stirred for 10 min. The reaction was then allowed to warm up to rt and stirred for 16 h. The reaction was quenched with a slow addition of water (50 mL) and extracted with Et_2O (3 × 60 mL). The organic layers were combined and washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The brown oil was then purified by flash column chromatography (25% Et_2O/pentane).

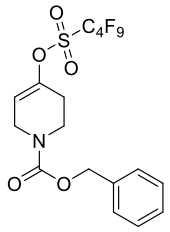
*2.2. Spectral data for alkenyl nonaflates **8**, **9**, and **13***

tert-Butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dhydropyridine-1(*2H*)-carboxylate (8)



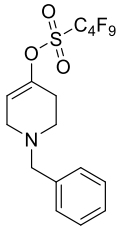
A colorless oil (4.6 g, 95% yield) was obtained according to the general procedure using 1-(*tert*-butoxycarbonyl)-4-piperidone (2.0 g, 10 mmol, 1.0 equiv) as a substrate. Spectral data correspond to that reported.[1] **R_f** = 0.61 (15% EtOAc/hextane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 5.76 (app s, 1 H), 4.04 (app s, 2 H), 3.62 (app s, 2 H), 2.43 (app s, 2 H), 1.46 (s, 9 H).

Benzyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (9)



A light-yellow oil (4.6 g, 89% yield) was obtained according to the general procedure using 1-carbobenzoxy-4-piperidone (2.3 g, 10 mmol, 1.0 equiv) as a substrate. $\mathbf{R_f}$ = 0.41 (15% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.39 – 7.32 (m, 5 H), 5.82 – 5.75 (m, 1 H), 5.16 (s, 2 H), 4.14 (app s, 2 H), 3.72 (app s, 2 H), 2.47 (app s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$, ^{19}F decoupled, 60 °C) δ (ppm) 155.1, 147.0, 136.5, 128.7, 128.3, 128.1, 115.8, 115.4, 114.5, 110.1, 108.7, 67.8, 42.1, 40.8, 28.2; **^{19}F NMR** (376 MHz, $CDCl_3$, ^{1}H decoupled, 60 °C) –80.8, –109.4, –120.6, –125.5; **IR** (Microscope, cm^{-1}) 3035, 2957, 1711, 1423, 1353, 1280; **HRMS** (ESI-ToF) for $C_{17}H_{14}F_9NNaO_5S$ $(M + Na^+)$: calcd. 538.0341; found 538.0337.

1-(Benzyl)-4-[(nonafluorobutanesulfonyl)oxy]-1,2,3,6-tetrahydropyridine (13)

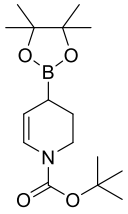


A yellow oil (4.3 g, 91% yield) was obtained according to the general procedure using 1-benzyl-4-piperidone (1.9 mL, 10 mmol, 1.0 equiv) as a substrate. $\mathbf{R_f}$ = 0.56 (15% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.35 – 7.27 (m, 5 H), 5.75 – 5.73 (m, 1 H), 3.64 (s, 2 H), 3.15 – 3.13 (m, 2 H), 2.73 (t, J = 5.7 Hz, 2 H), 2.46 – 2.45 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$, ^{19}F Dec) δ (ppm) 147.5, 137.7, 129.0, 128.5, 127.4, 117.1, 116.3, 114.2, 109.9, 108.5, 61.3, 50.5, 49.1, 28.4; **^{19}F NMR** (376 MHz, $CDCl_3$, ^{1}H decoupled) –80.8, –110.1, –121.1, –126.0; **IR** (Microscope, cm^{-1}) 3031, 2926, 2806, 1699, 1454, 1421; **HRMS** (ESI-ToF) for $C_{16}H_{15}F_9NO_3S$ $(M + H)^+$: calcd. 472.0623; found 472.0618.

3. Experimental procedure and spectral data for allylic boronate **5**

*3.1. Experimental procedure and spectral data for racemic allylic boronate, rac-**5***

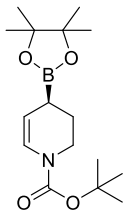
***tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(*2H*)-carboxylate (*rac*-5)**



Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and DPEPhos (18 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with N_2 three times. Et_2O (3 mL) was added and the mixture was stirred for 15 min. DIPEA (192 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated *in vacuo*, followed by a quick filtration through a silica plug (100% Et_2O). The resulting mixture was concentrated *in vacuo* and purified by flash column chromatography (25% Et_2O/pentane) providing a colorless oil (155 mg, 56% yield). Spectral data correspond to that reported.[2] Regioselectivity of alkenyl to allyl boronic ester determined by integration of relevant signals on the crude ^{1}H NMR spectrum was 15:85.

*3.2. Experimental procedure and spectral data for an optically enriched allylic boronate **5***

(4*S*)-*tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(*2H*)-carboxylate (5)



Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and (+)-TANIAPHOS (23 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with nitrogen three times. Et_2O (3 mL) was added and the mixture was stirred for 30 min. DMA (140 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated *in vacuo*, followed by a quick filtration through a silica plug (100% Et_2O). The resulting mixture was concentrated *in vacuo* and purified by flash column chromatography (25% Et_2O/pentane) providing a colorless oil (155 mg, 50% yield). Spectral data correspond to that reported.[2] Regioselectivity of alkenyl to allyl boronic ester determined by integration of relevant signals on the crude ^{1}H NMR spectrum was 1:4. $\mathbf{R_f}$ = 0.35 (25% Et_2O/pentane); **^{1}H NMR** (500 MHz, $CDCl_3$) rotamers are present: δ (ppm) 6.84 – 6.71 (m, 1 H), 4.94 – 4.82 (m, 1 H), 3.58 – 3.53 (m, 2 H), 1.87 – 1.83 (m, 3 H), 1.47 (s, 9 H), 1.23 (s, 12 H).

4. Experimental procedure and spectral data for α-hydroxyalkyl dehydropiperidines

4.1. General procedure for the synthesis of racemic α-hydroxyalkyl dehydropiperidines

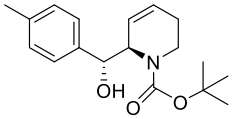
Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and DPEPhos (18 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with nitrogen three times. Et_2O (3 mL) was added and the mixture was stirred for 15 min. DIPEA (192 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and alkenyl nonaflate (1.0 mmol, 1.0 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated *in vacuo*, followed by a quick filtration through a silica plug (100% Et_2O). The resulting mixture was concentrated *in vacuo* and transferred to a pre-dried 5 mL round bottom flask using dry toluene (1 mL). The flask was flushed with nitrogen and aldehyde (1.1 mmol, 1.1 equiv) was added. The solution was stirred at rt under a nitrogen atmosphere for 3 or 16 h as specified in the following individual procedures. The mixture was purified directly by flash column chromatography.

4.2. General procedure for the synthesis of optically enriched α-hydroxyalkyl dehydropiperidines

Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and (+)-TANIAPHOS (23 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with nitrogen three times. Et_2O (3 mL) was added and the mixture was stirred for 30 min. DMA (140 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and alkenyl nonaflate (1.0 mmol, 1.0 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated *in vacuo*, followed by a quick filtration through a silica plug (100% Et_2O). The resulting mixture was concentrated *in vacuo* and transferred to a pre-dried 5 mL round bottom flask using dry toluene (1 mL). The flask was flushed with nitrogen and aldehyde (1.1 mmol, 1.1 equiv) was added. The solution was stirred at rt under nitrogen for 3 or 16 h. The mixture was purified directly by flash column chromatography.

4.3. Spectral data for optically enriched α-hydroxyalkyl dehydropiperidines

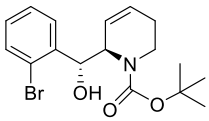
(*R*)-*tert*-Butyl 2-[(*R*)-hydroxy(*p*-tolyl)methyl]-5,6-dihydropyridine-1(*2H*)-carboxylate (7)



The title compound (**7**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and *p*-tolualdehyde (130 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a colorless oil (213 mg, 70% yield) after flash column chromatography (50% Et_2O/pentane). $\mathbf{R_f}$ = 0.50 (20% EtOAc/hexane); $\mathbf{[\alpha]^{20}_D}$ + 135.0 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) rotamers are present: *δ*

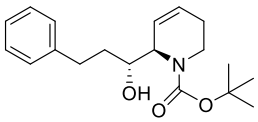
(ppm) 7.25 – 7.23 (m, 2 H), 7.17 – 7.15 (m, 2 H), 5.89 – 5.81 (m, 1 H), 5.34 – 5.17 (m, 1 H), 4.63 – 4.53 (m, 2 H), 4.18 – 3.85 (m, 1 H), 3.04 – 2.78 (m, 1 H), 2.34 (s, 3 H), 2.22 – 2.17 (m, 1 H), 1.95 – 1.90 (m, 1 H), 1.49 (s, 9 H); **^{1}H NMR** (400 MHz, $CDCl_3$, 65 °C) δ (ppm) 7.24 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 5.85 – 5.81 (m, 1 H), 5.30 – 5.28 (m, 1 H), 4.63 – 4.62 (m, 2 H), 4.13 – 4.09 (m, 1 H), 2.92 – 2.86 (m, 1 H), 2.34 (s, 3 H), 2.18 – 2.14 (m, 1 H), 1.95 – 1.89 (m, 1 H), 1.49 (s, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$, 60 °C) δ (ppm) 156.8, 138.6, 137.6, 129.1, 127.1, 125.1, 80.5, 76.4, 58.5, 37.9, 28.5, 24.8, 21.1; **IR** (Microscope, cm^{-1}) 3060, 2975, 2930, 1644, 1611, 1512, 1250; **HRMS** (ESI-ToF) for $C_{18}H_{25}NNaO_3$ $(M + Na)^+$: calcd. 326.1727; found 326.1724; **HPLC** (Chiralcel OD): 3.8% *i*-PrOH/hexane, 6 °C, 0.5 mL/min, λ = 210 nm, T_{major} = 19.6 min, T_{minor} = 17.3 min; 92% *ee*; >96% *de*.

(*R*)-*tert*-Butyl 2-[(*R*)-hydroxy(*o*-bromophenyl)methyl]-5,6-dihydropyridine-1(*2H*)-carboxylate (17)



The title compound (**17**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and 2-bromobenzaldehyde (130 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a colorless oil (258 mg, 70% yield) after flash column chromatography (50% Et_2O/pentane). **R_f** = 0.49 (20% EtOAc/hexane); **$[\alpha]^{20}_D$** + 50.5 (*c* 1.42, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$, 65 °C) δ (ppm) 7.57 (app d, J = 7.7 Hz, 1 H), 7.51 (dd, J = 8.0, 1.2 Hz, 1 H), 7.33 (td, J = 7.7, 1.1 Hz, 1 H), 7.13 (app td, J = 7.7, 1.8 Hz, 1 H), 5.97 – 5.91 (m, 1 H), 5.41 – 5.35 (m, 1 H), 5.25 (d, J = 6.7 Hz, 1 H), 4.73 – 4.72 (m, 1 H), 4.21 – 4.14 (m, 1 H), 3.16 – 3.09 (m, 1 H), 2.21 – 2.19 (m, 1 H), 2.01 – 1.94 (m, 1 H), 1.39 (s, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$, 60 °C) δ (ppm) 156.0, 140.7, 132.7, 129.1, 129.0, 128.0, 127.7, 124.7, 123.3, 80.3, 75.1, 57.5, 38.2, 28.4, 24.8; **IR** (Microscope, cm^{-1}) 3427, 3028, 2976, 2929, 1670, 1592, 1454; **HRMS** (ESI-ToF) for $C_{17}H_{23}BrNO_3$ $(M + H)^+$: calcd. 368.0856; found 368.0850; **HPLC** (Chiralcel OD): 3.8% *i*-PrOH/hexane, 6 °C, 0.5 mL/min, λ = 210 nm, T_{major} = 26.5 min, T_{minor} = 19.3 min; 90% *ee*; >96% *de*.

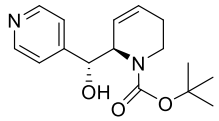
(*R*)-*tert*-Butyl 2-[(*R*)-1-hydroxy-3-phenylpropyl]-5,6-dihydropyridine-1(*2H*)-carboxylate (18)



The title compound (**18**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and hydrocinnamaldehyde (145 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a yellow oil (222 mg, 70% yield) after flash column chromatography (25% Et_2O/pentane). Spectral data correspond to that reported.[2] **R_f** = 0.65 (50% EtOAc/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$, 60 °C) δ (ppm) 7.28 – 7.15 (m, 5 H), 5.96 – 5.93 (m, 1 H), 5.68 – 5.66 (m, 1 H), 4.41 – 4.37 (m, 1 H), 4.16 – 4.06 (m, 1 H), 3.72 – 3.68 (m, 1 H), 3.02 – 2.97 (m, 1 H), 2.93 – 2.88 (m, 1 H), 2.80 – 2.76 (m, 1 H), 2.21 – 2.17 (m, 1 H),

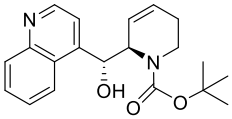
1.98 – 1.85 (m, 2 H), 1.84 – 1.78 (m, 1 H), 1.48 (s, 9 H); **HPLC** (Chiralcel OD): 10% *i*-PrOH/hexane, 25 °C, 0.5 mL/min, λ = 210 nm, T_{major} = 12.2 min, T_{minor} = 9.4 min; 90% *ee*, >96% *de*.

(*R*)-*tert*-Butyl 2-[(*R*)-hydroxy(4-pyridyl)methyl]-5,6-dihydropyridine-1(*2H*)-carboxylate (19)



The title compound (**19**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and 4-pyridinecarboxaldehyde (104 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 3 h. The product was obtained as a colorless oil (206 mg, 71% yield) after flash column chromatography (100% EtOAc). $\mathbf{R_f}$ = 0.27 (100% EtOAc); $\mathbf{[\alpha]^{20}_D}$ + 131.6 (*c* 1.07, $CHCl_3$); **^{1}H NMR** (400 MHz, DMSO-d_6) rotamers are present: *δ* (ppm) 8.48 – 8.47 (m, 2 H), 7.25 – 7.23 (m, 2 H), 5.91 – 5.88 (m, 1 H), 5.71 – 5.66 (m, 2 H), 4.77 (app t, *J* = 4.8 Hz, 1 H), 4.52 – 4.41 (m, 1 H), 3.94 – 3.68 (m, 1 H), 2.71 – 2.62 (m, 1 H), 1.94 – 1.83 (m, 2 H), 1.33 – 1.21 (m, 9 H); **^{1}H NMR** (400 MHz, DMSO-d_6, 80 °C) *δ* (ppm) 8.48 (d, *J* = 5.8 Hz, 2 H), 7.25 (d, *J* = 5.8 Hz, 2 H), 5.89 – 5.88 (m, 1 H), 5.71 – 5.68 (m, 1 H), 5.45 – 5.43 (m, 1 H), 4.78 (app t, *J* = 4.8 Hz, 1 H), 4.51 (app s, 1 H), 3.87 – 3.83 (m, 1 H), 2.64 – 2.57 (m, 1 H), 1.96 – 1.91 (m, 1 H), 1.83 – 1.78 (m, 1 H), 1.32 (s, 9 H); **^{13}C NMR** (100 MHz, DMSO-d_6, 80 °C) *δ* (ppm) 153.6, 151.0, 148.6, 126.7, 124.6, 121.8, 78.3, 72.5, 56.3, 37.2, 27.6, 23.7; **IR** (Microscope, cm^{-1}) 3402, 3189, 2976, 2929, 1691, 1603, 1477, 1455; **HRMS** (ESI-ToF) for $C_{16}H_{23}N_2O_3$ $(M + H)^+$: calcd. 291.1703; found 291.1707; **HPLC** (Chiralcel IC): 50% *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 6.3 min, T_{minor} = 14.2 min; 94% *ee*; >96% *de*.

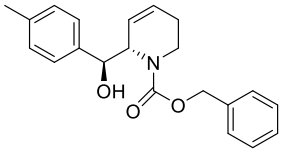
(*R*)-*tert*-Butyl 2-[(*R*)-hydroxy(4-quinolinyl)methyl]-5,6-dihydropyridine-1(*2H*)-carboxylate (20)



The title compound (**20**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and 4-quinolinecarboxaldehyde (173 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 3 h. The product was obtained as a colorless oil (245 mg, 72% yield) after flash column chromatography (100% EtOAc). $\mathbf{R_f}$ = 0.44 (100% EtOAc); $\mathbf{[\alpha]^{20}_D}$ + 51.4 (*c* 1.56, $CHCl_3$); **^{1}H NMR** (500 MHz, DMSO-d_6) rotamers are present: *δ* (ppm) 8.85 – 8.82 (m, 1 H), 8.26 – 8.11 (m, 1 H), 8.04 – 7.98 (m, 1 H), 7.74 – 7.71 (m, 1 H), 7.59 – 7.50 (m, 2 H), 5.98 – 5.80 (m, 2 H), 5.69 – 5.60 (m, 2 H), 4.71 – 4.59 (m, 1 H), 3.99 – 3.95 (m, 1 H), 3.18 – 3.12 (m, 1 H), 1.93 – 1.86 (m, 2 H), 1.30 – 0.67 (m, 9 H); **^{1}H NMR** (500 MHz, DMSO-d_6, 115 °C) *δ* (ppm) 8.83 (d, *J* = 4.4 Hz, 1 H), 8.21 (d, *J* = 8.4 Hz, 1 H), 8.02 (d, *J* = 8.4 Hz, 1 H), 7.70 (dt, *J* = 7.6, 0.91 Hz, 1 H), 7.56 – 7.51 (m, 2 H), 5.92 – 5.89 (m, 1 H), 5.75 – 5.72 (m, 1 H), 5.59 (app t, *J* = 4.5 Hz, 1 H), 5.39 (app s, 1 H), 4.74 (app s, 1 H), 3.85 – 3.84 (m, 1 H), 2.73 (br s, 1 H), 2.01 – 1.93 (m, 1 H), 1.83 – 1.80 (m, 1 H), 1.12 (s, 9 H); **^{13}C NMR** (125 MHz, DMSO-d_6, 115 °C) *δ* (ppm) 153.5, 149.0, 147.5, 147.4, 129.1, 127.9. 126.5, 125.7, 125.2, 125.0, 123.1, 119.0, 77.9, 69.4, 56.0, 36.9, 27.2, 23.5; **IR** (Microscope, cm^{-1}) 3405, 3180, 3041, 2976, 2930, 1687, 1477;

HRMS (ESI-ToF) for $C_{20}H_{25}N_2O_3$ $(M + H)^+$: calcd. 341.1860; found 341.1863; **HPLC** (Chiralcel IC): 50% *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 280 nm, T_{major} = 6.1 min, T_{minor} = 13.2 min; 90% *ee*; >96% *de*.

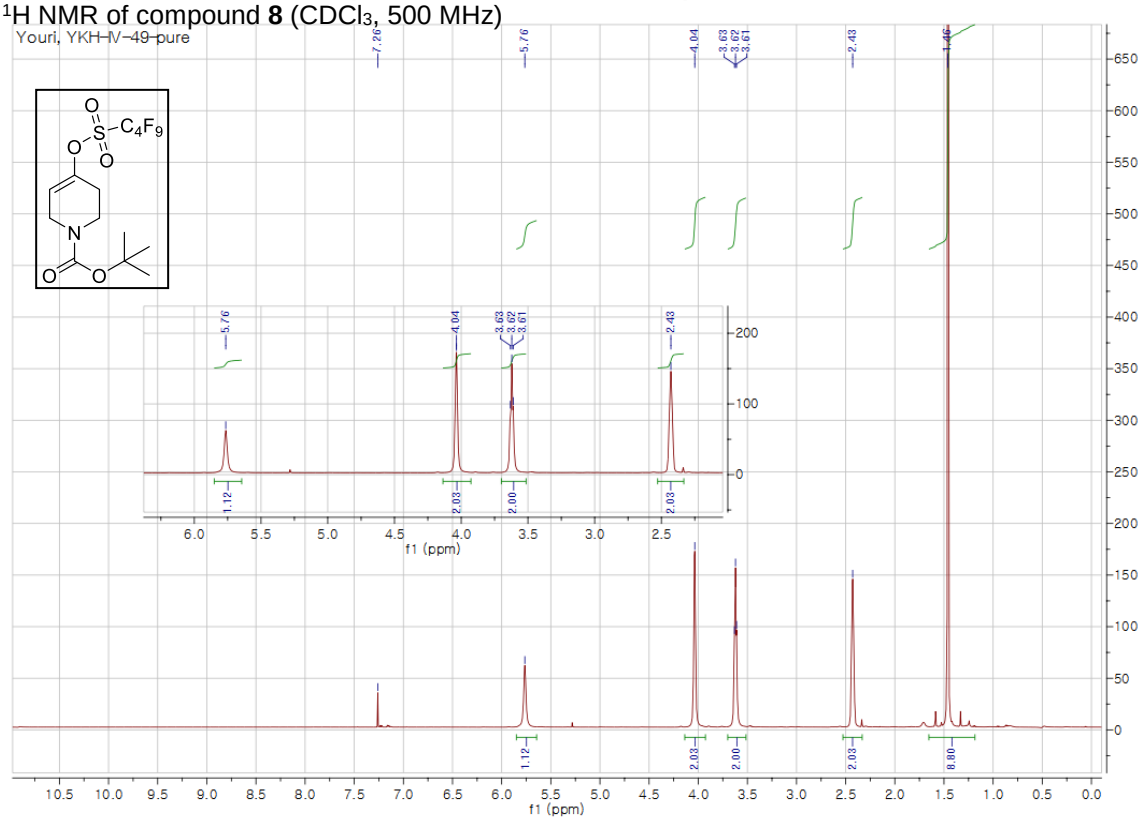
(*S*)-Benzyl 2-[(*S*)-hydroxy(*p*-tolyl)methyl]-5,6-dihydropyridine-1(*2H*)-carboxylate (12)



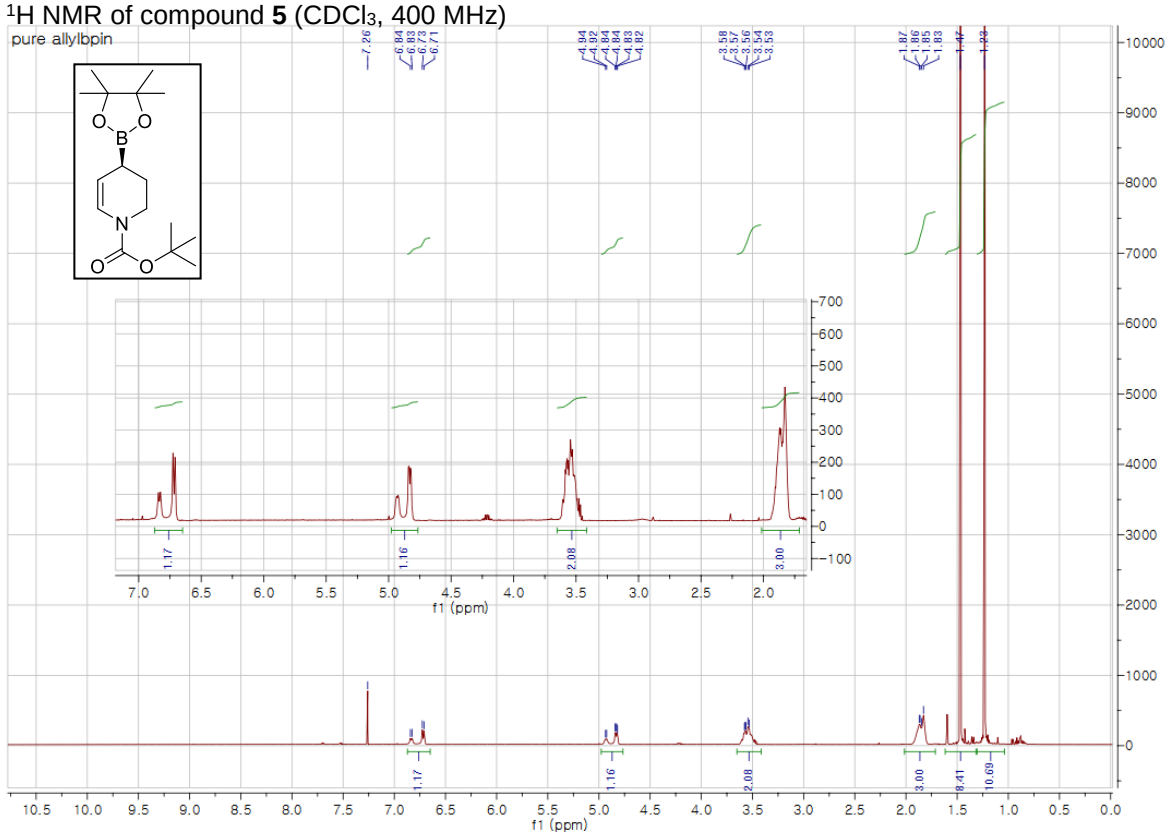
The title compound (**12**) was synthesized by the general procedure (modification: use of (−)-TANIAPHOS instead of (+)-TANIAPHOS) using benzyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**9**) (515 mg, 1.00 mmol, 1.00 equiv) and *p*-tolualdehyde (130 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a colorless oil (202 mg, 60% yield) after flash column chromatography (50% Et_2O/pentane). $\mathbf{R_f}$ = 0.41 (20% EtOAc/hexane); $\mathbf{[\alpha]^{20}_D}$ −109.1 (*c* 0.32, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* (ppm) 7.38 – 7.31 (m, 5 H), 7.31 – 7.12 (m, 4 H), 5.89 – 5.82 (m, 1 H), 5.41 – 5.38 (m, 1 H), 5.23 – 5.11 (m, 2 H), 4.70 – 4.67 (m, 2 H), 4.22 – 3.46 (m, 1 H), 3.03 – 2.83 (m, 1 H), 2.34 (s, 3 H), 2.23 – 2.20 (m, 1 H), 1.97 – 1.93 (m, 1 H); **^{1}H NMR** (400 MHz, $CDCl_3$, 65 °C) *δ* (ppm) 7.39 – 7.29 (m, 5 H), 7.23 (app d, *J* = 7.9 Hz, 2 H), 7.14 (app d, *J* = 7.9 Hz, 2 H), 5.89 – 5.84 (m, 1 H), 5.36 – 5.34 (m, 1 H), 5.18 (s, 2 H), 4.68 – 4.66 (m, 2 H), 4.21 – 4.16 (m, 1 H), 2.98 – 2.90 (m, 1 H), 2.35 (s, 3 H), 2.27 – 2.17 (m, 1 H), 1.97 – 1.90 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$, 65 °C) *δ* (ppm) 156.8, 138.3, 137.8, 136.9, 129.2, 128.6, 128.1, 128.0, 127.1, 124.9, 76.2, 67.6, 58.7, 38.0, 24.8, 21.2; **IR** (Microscope, cm^{-1}) 3438, 3031, 2921, 1697, 1515, 1431, 1391; **HRMS** (ESI-ToF) for $C_{21}H_{23}NNaO_3$ $(M + Na)^+$: calcd. 360.1570; found 360.1567; **HPLC** (Chiralcel IB): 5% *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 210 nm, T_{major} = 15.8 min, T_{minor} = 18.9 min; 90% *ee*; >96% *de*.

5. Copies of ^{1}H NMR spectra for known compounds

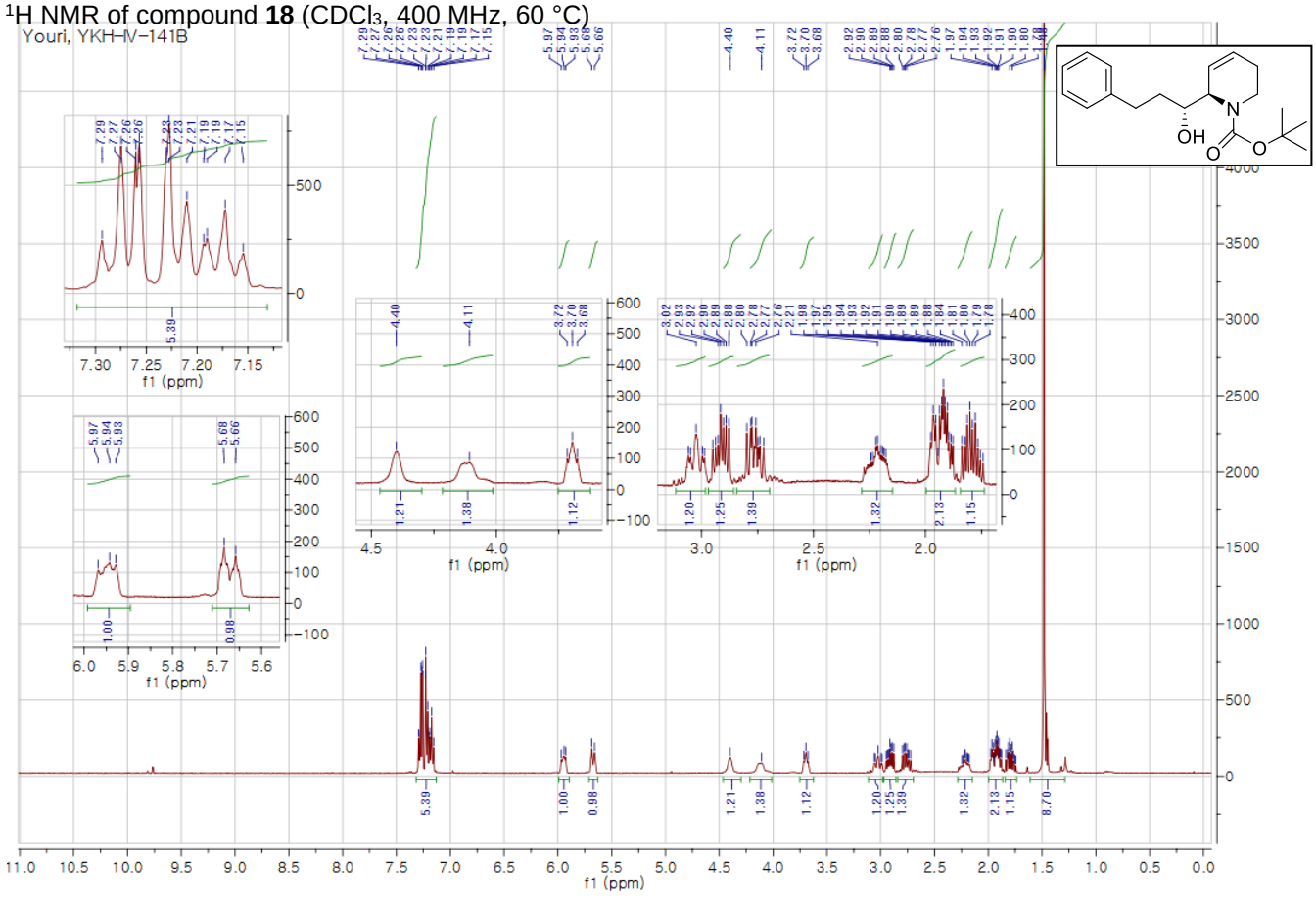
^{1}H NMR of compound **8** ($CDCl_3$, 500 MHz)



^{1}H NMR of compound **5** ($CDCl_3$, 400 MHz)

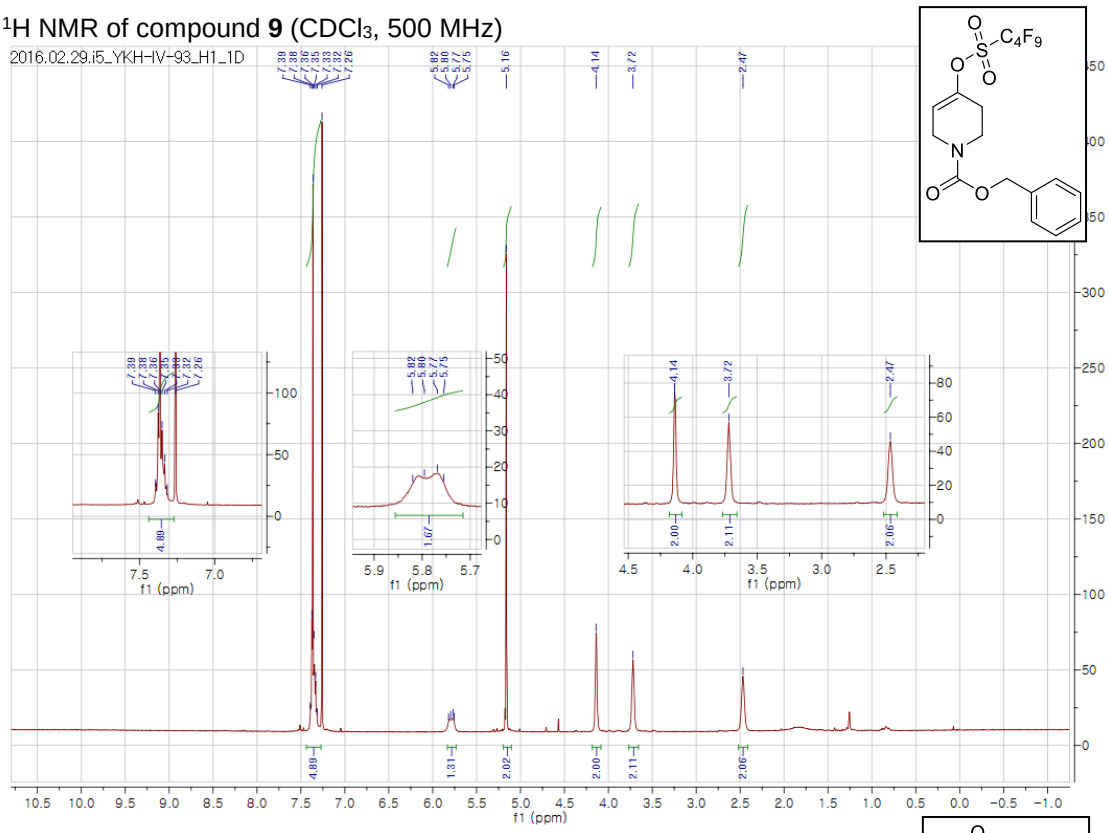


^{1}H NMR of compound **18** ($CDCl_3$, 400 MHz, 60 °C)

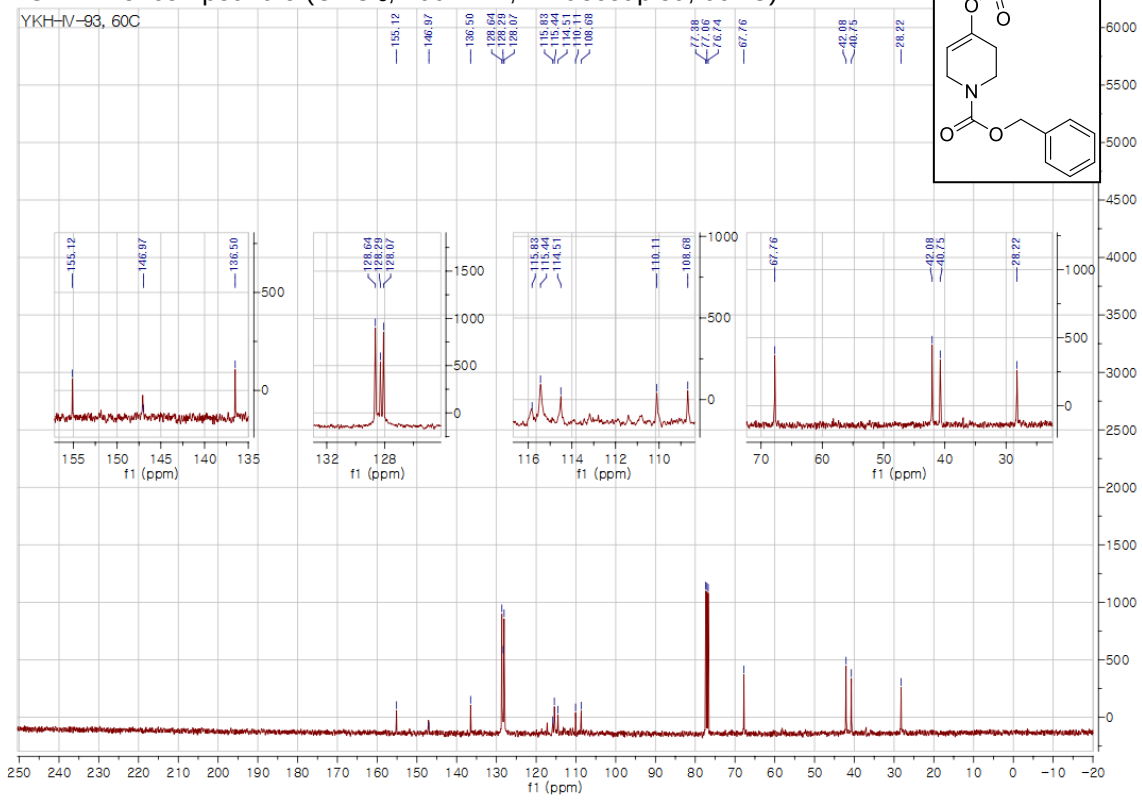


6. Copies of ^{1}H and ^{13}C NMR spectra for new compounds

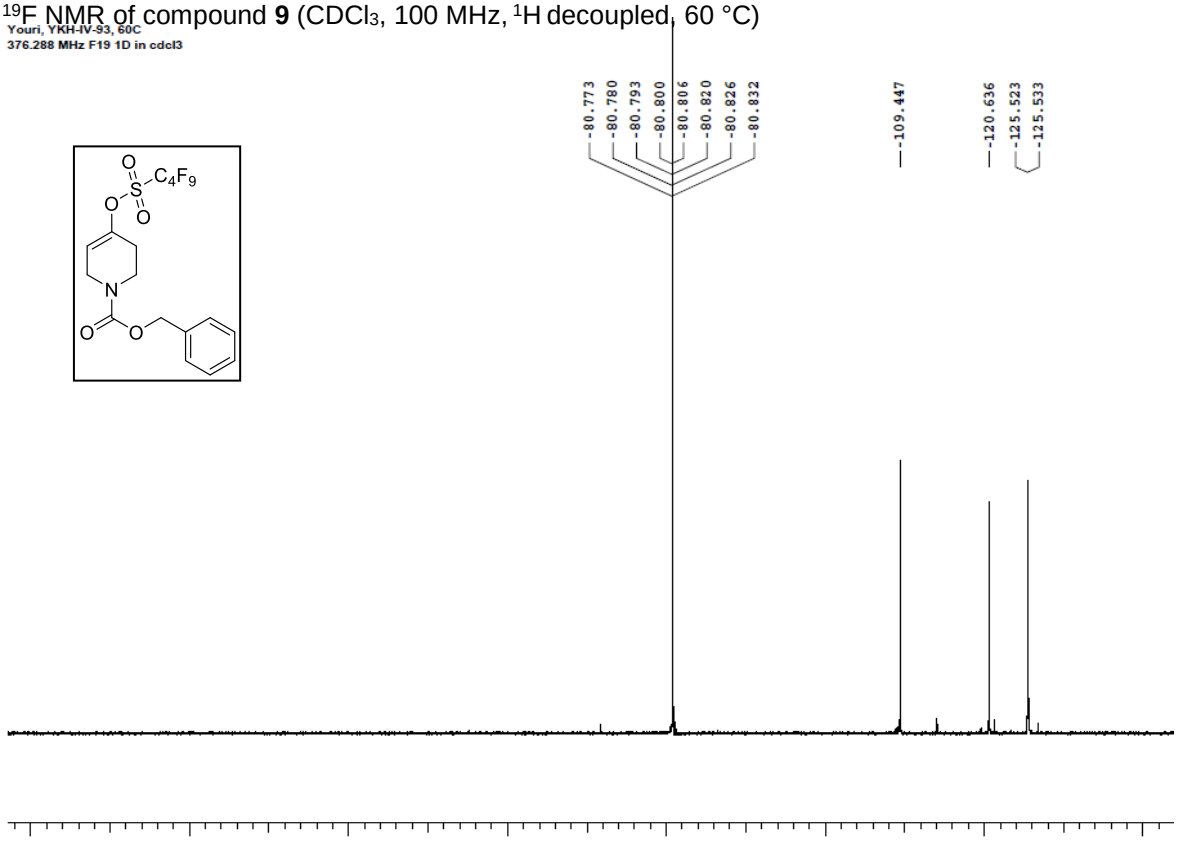
^{1}H NMR of compound **9** ($CDCl_3$, 500 MHz)



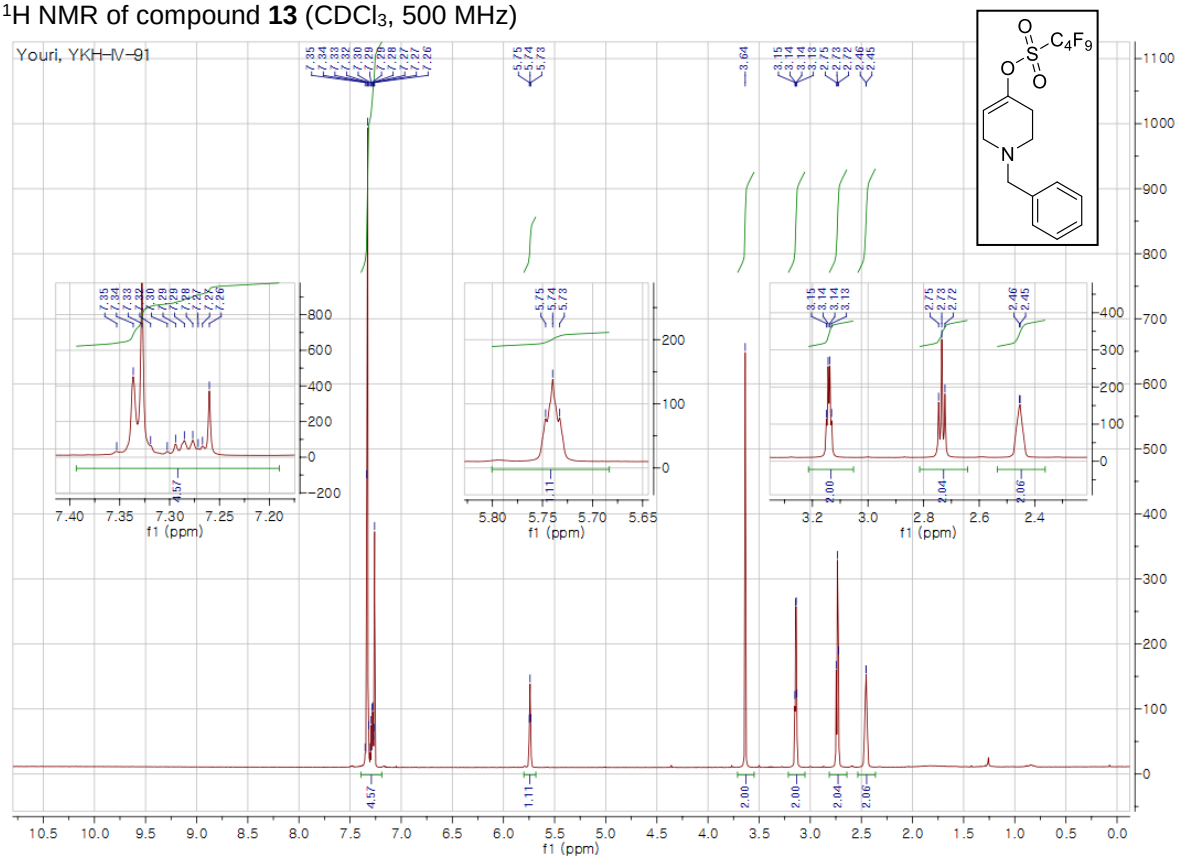
^{13}C NMR of compound **9** ($CDCl_3$, 100 MHz, ^{19}F decoupled, 60 °C)



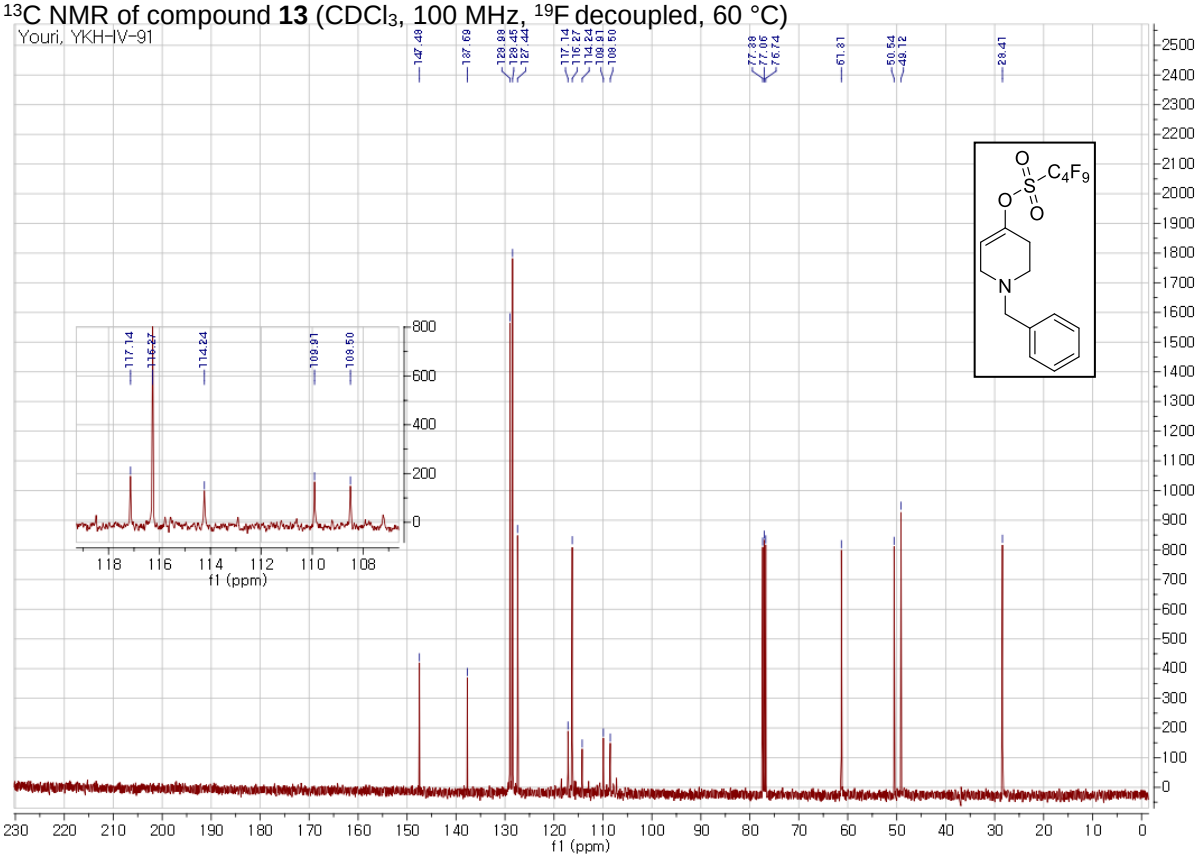
^{19}F NMR of compound **9** ($CDCl_3$, 100 MHz, ^{1}H decoupled, 60 °C)



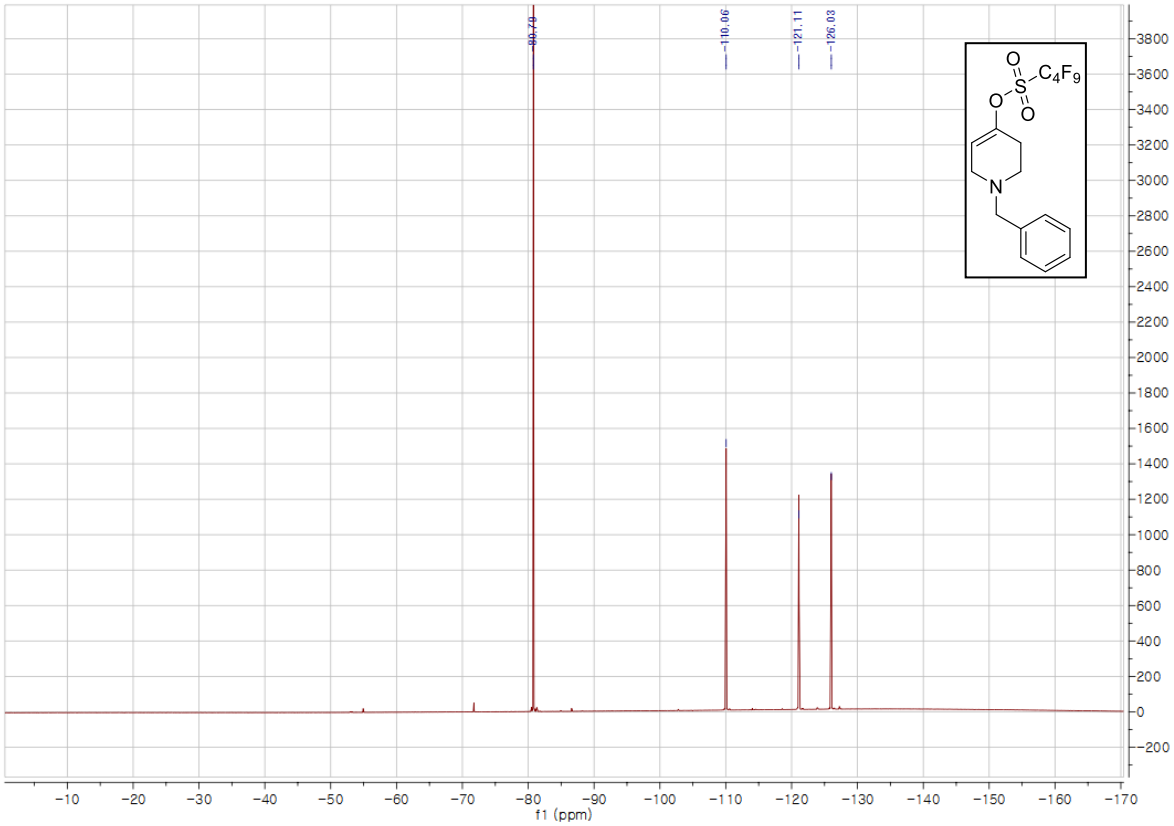
^{1}H NMR of compound **13** ($CDCl_3$, 500 MHz)



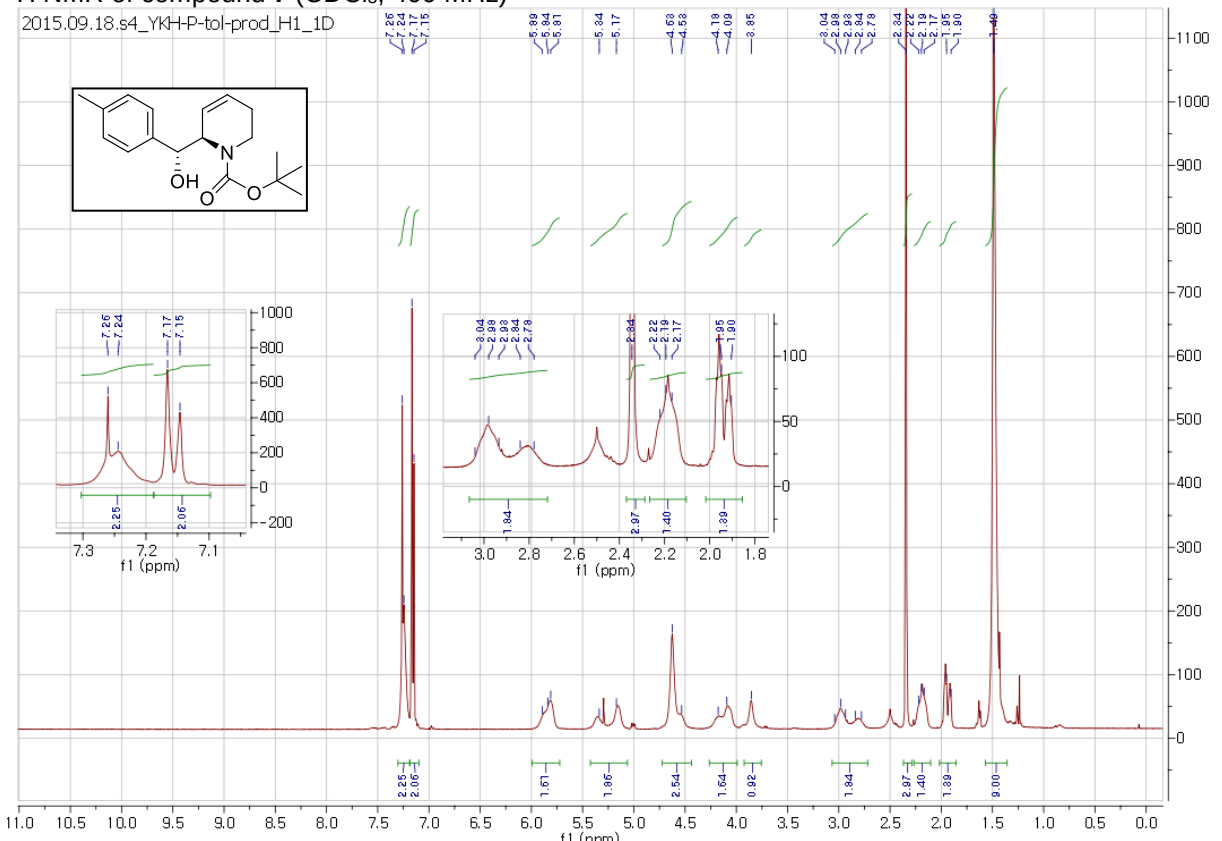
^{13}C NMR of compound **13** ($CDCl_3$, 100 MHz, ^{19}F decoupled, 60 °C)



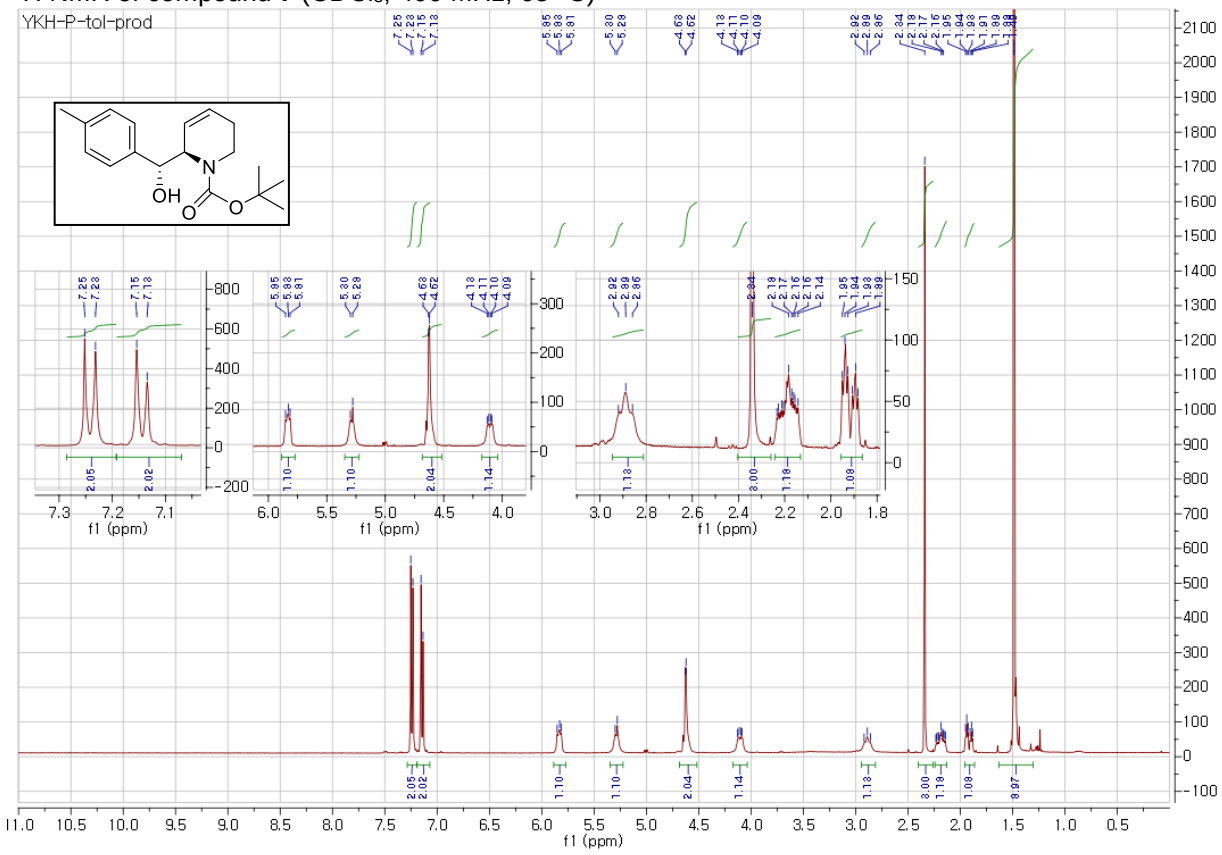
^{19}F NMR of compound **13** ($CDCl_3$, 100 MHz, ^{1}H decoupled)



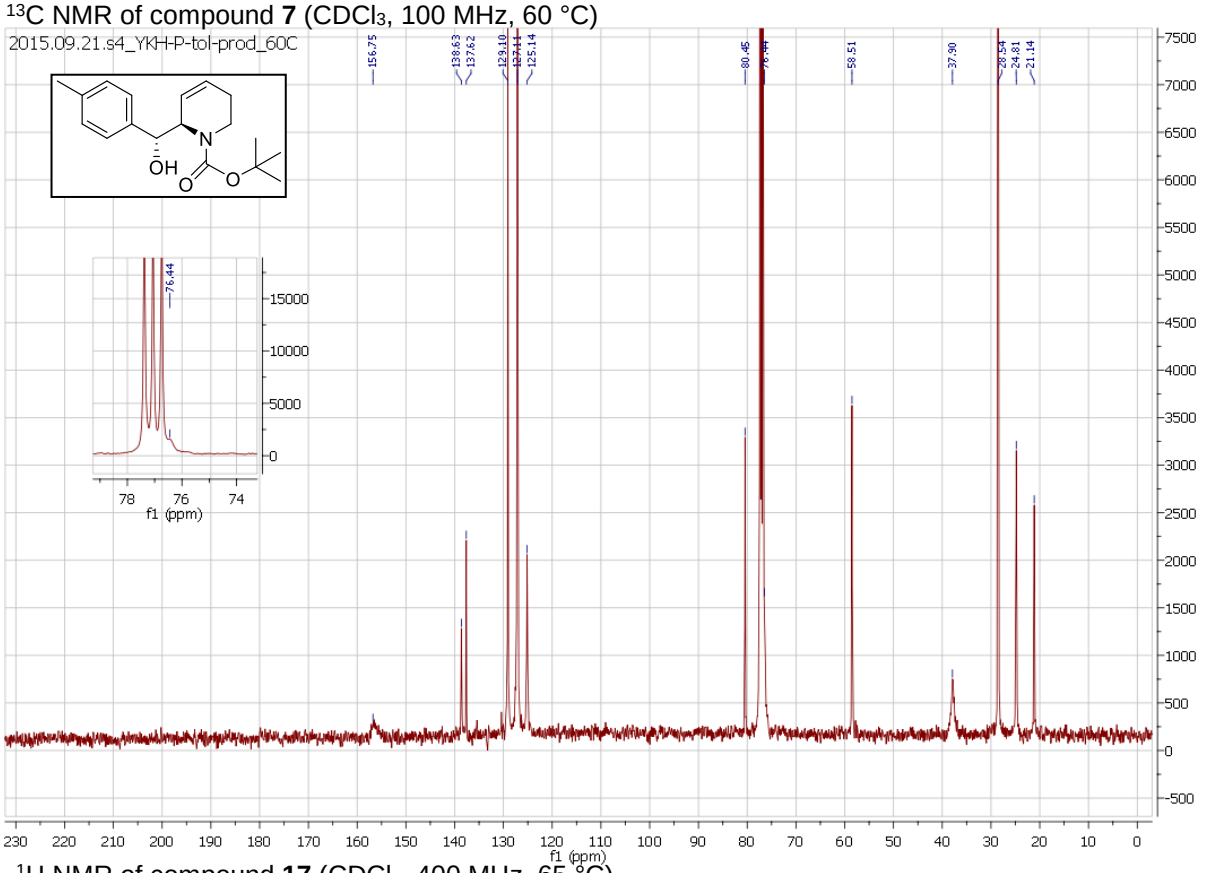
^{1}H NMR of compound **7** ($CDCl_3$, 400 MHz)



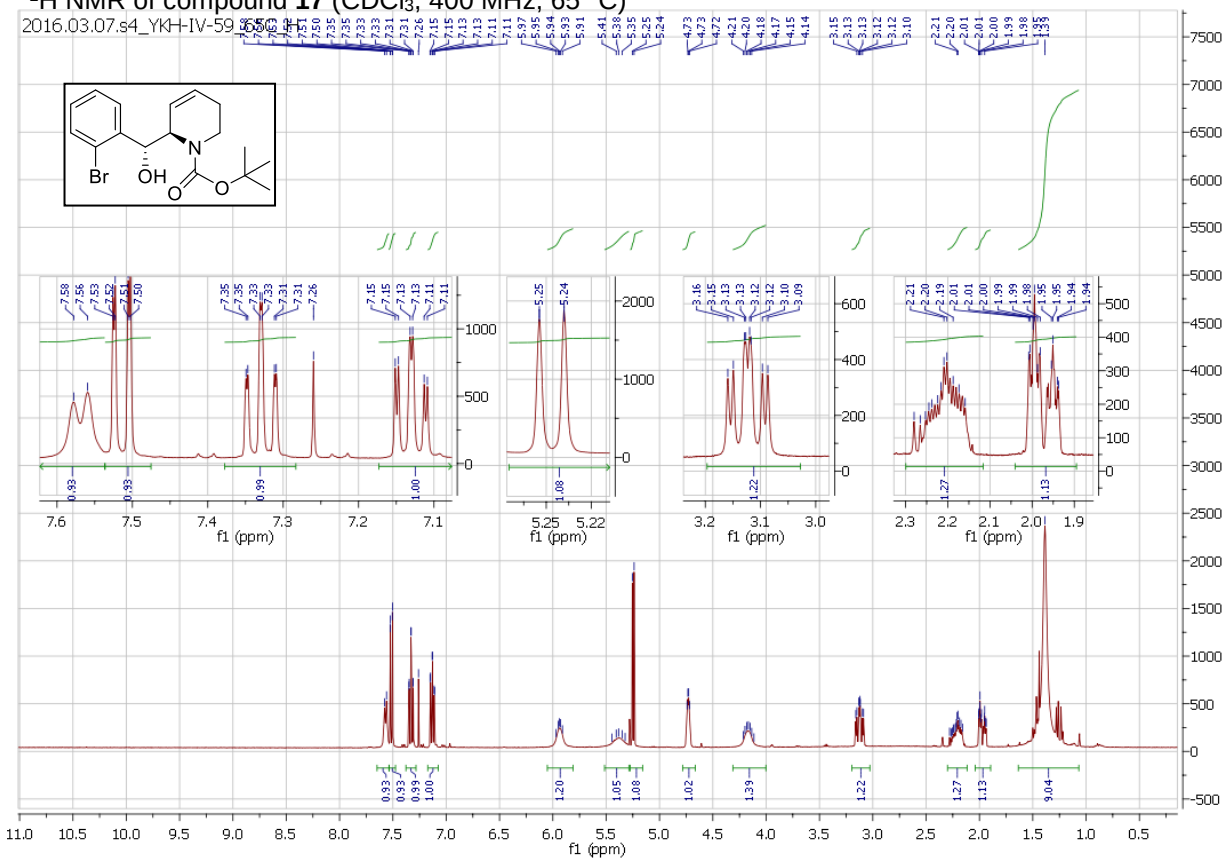
^{1}H NMR of compound **7** ($CDCl_3$, 400 MHz, 65 °C)



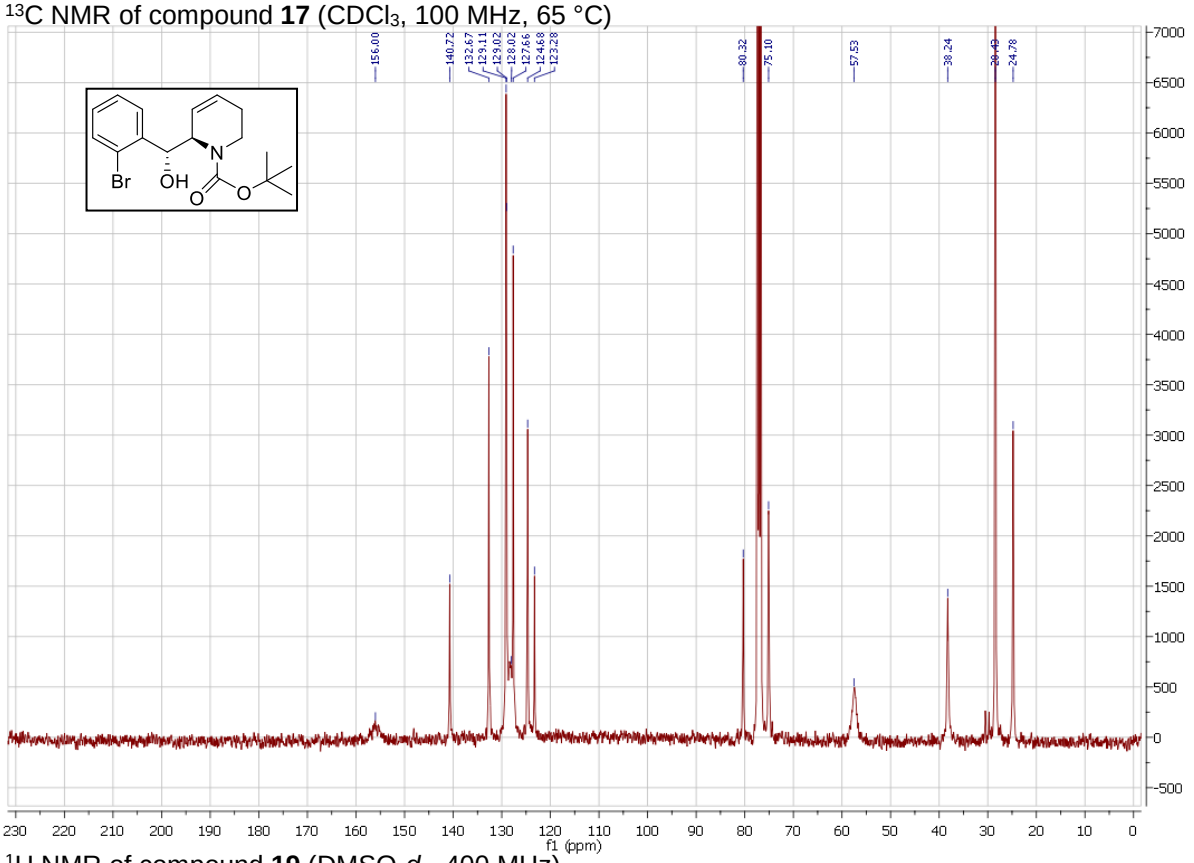
^{13}C NMR of compound **7** ($CDCl_3$, 100 MHz, 60 °C)



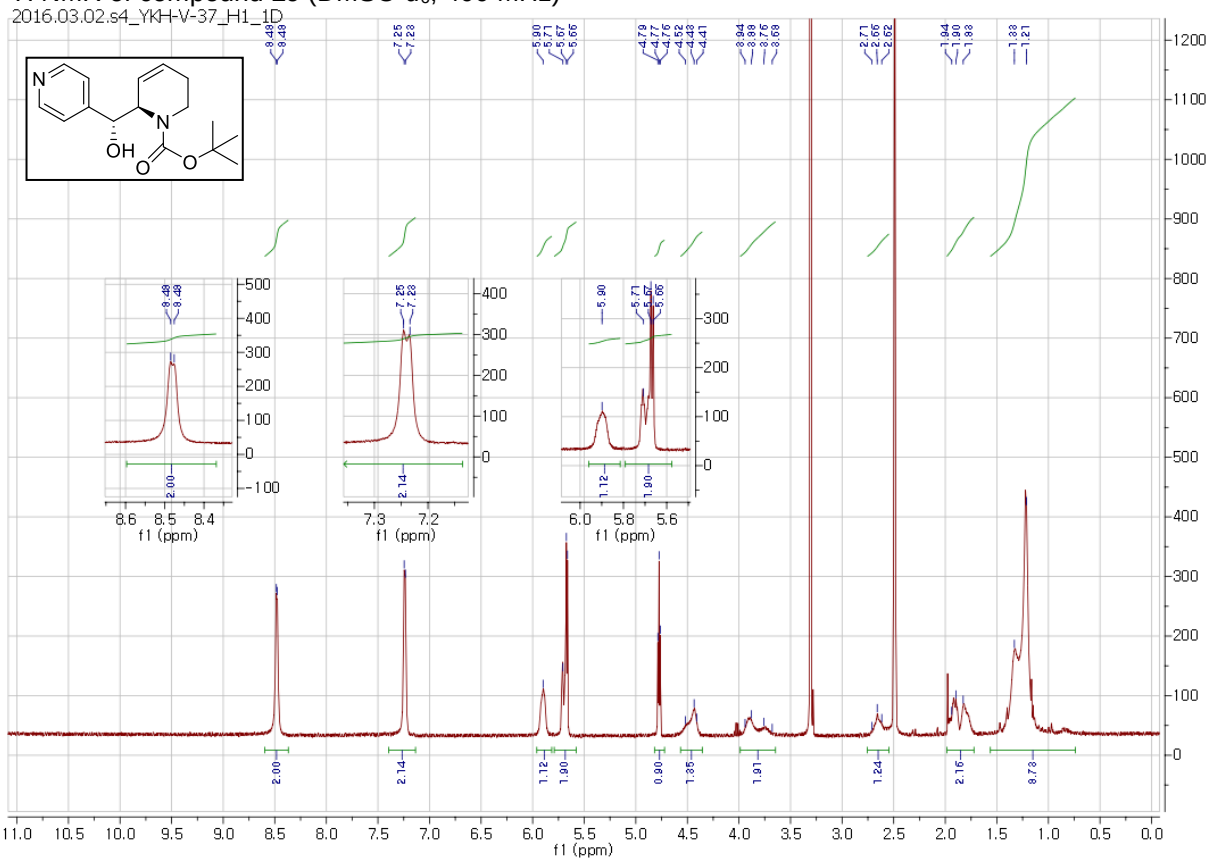
^{1}H NMR of compound **17** ($CDCl_3$, 400 MHz, 65 °C)



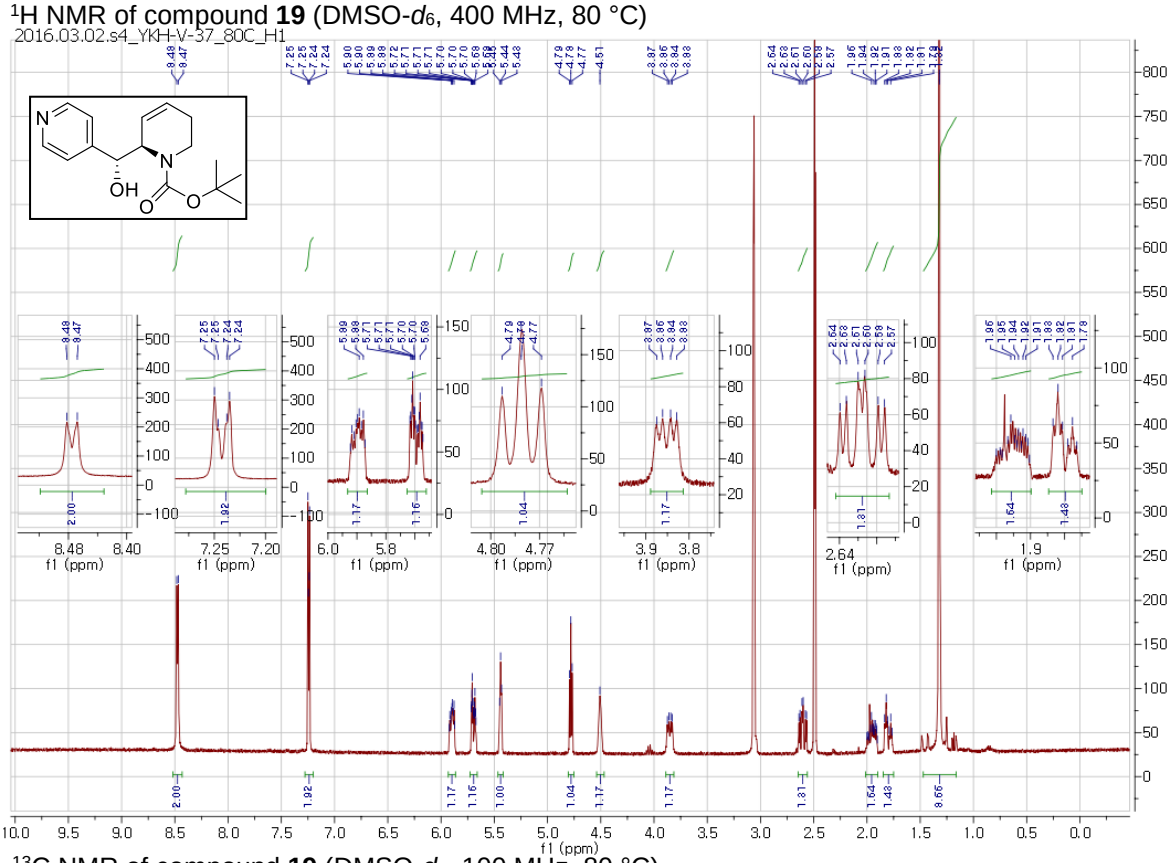
^{13}C NMR of compound **17** ($CDCl_3$, 100 MHz, 65 °C)



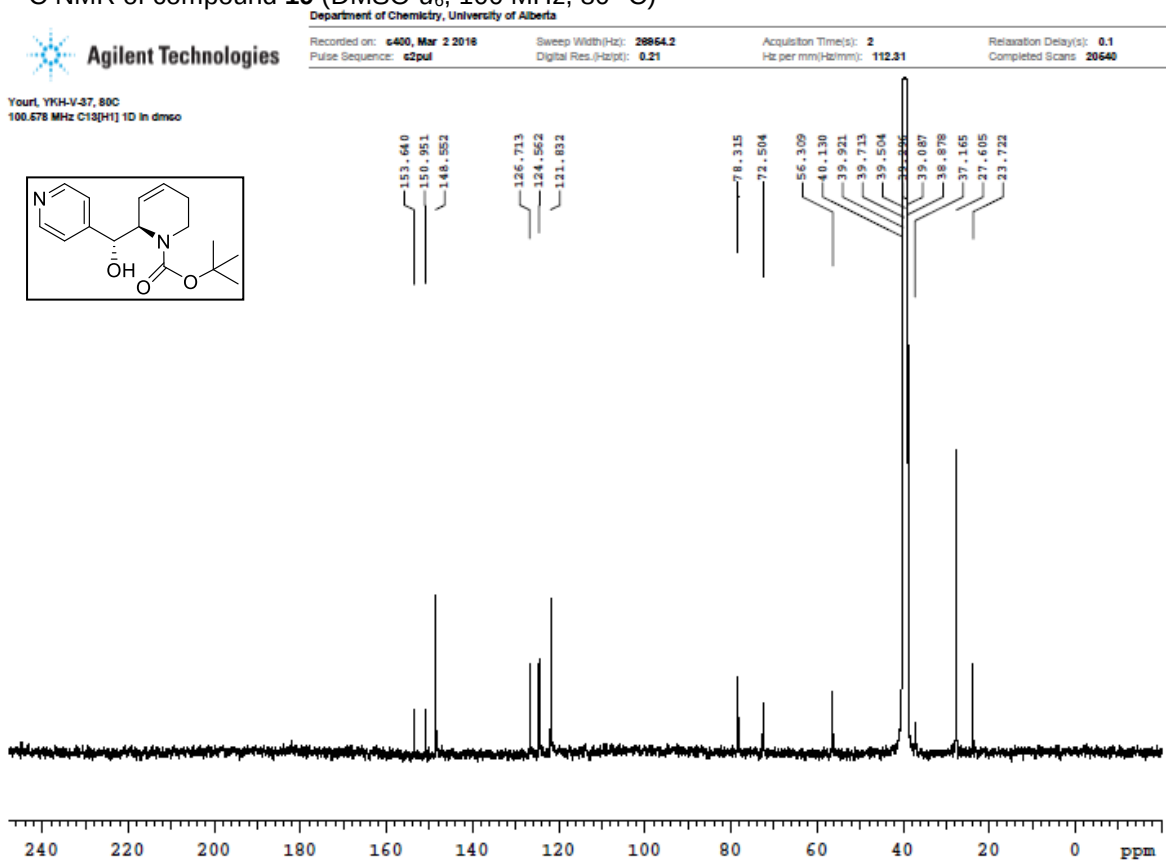
^{1}H NMR of compound **19** (DMSO-d_6, 400 MHz)



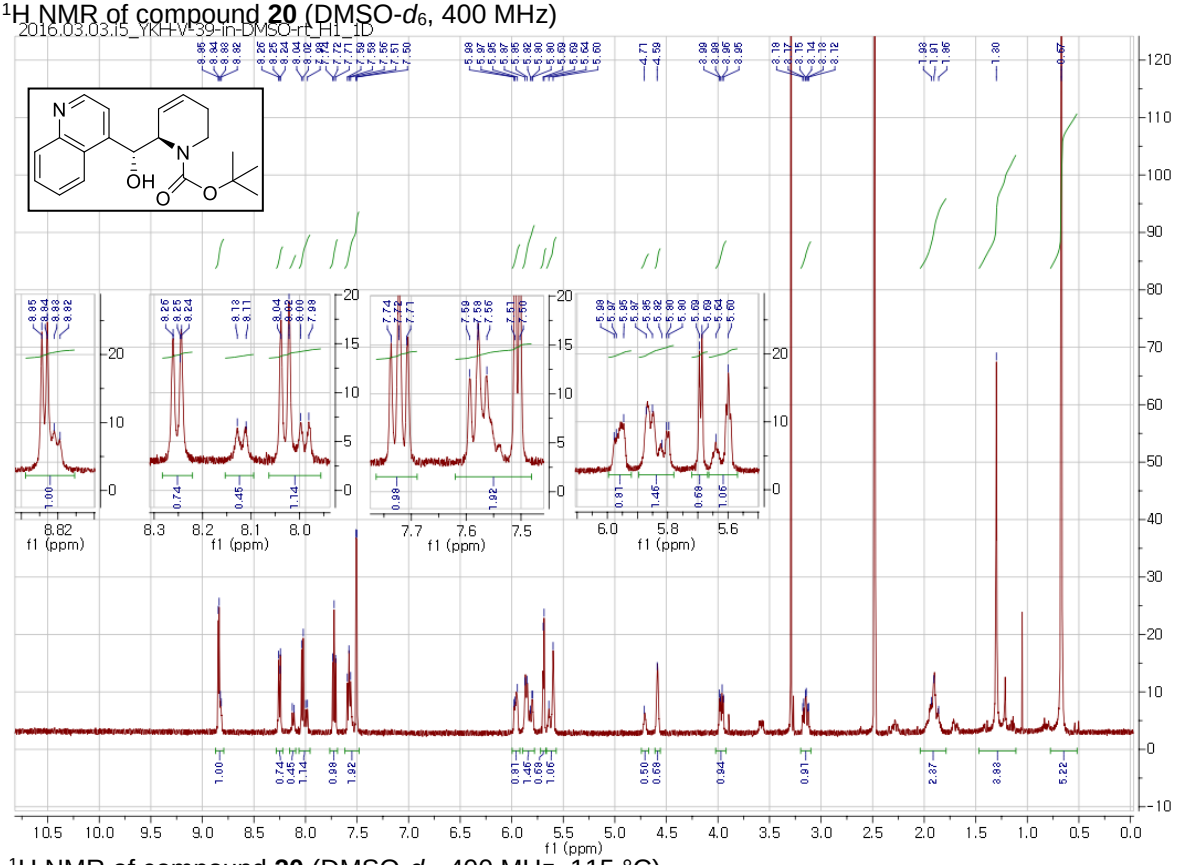
^{1}H NMR of compound **19** (DMSO-d_6, 400 MHz, 80 °C)



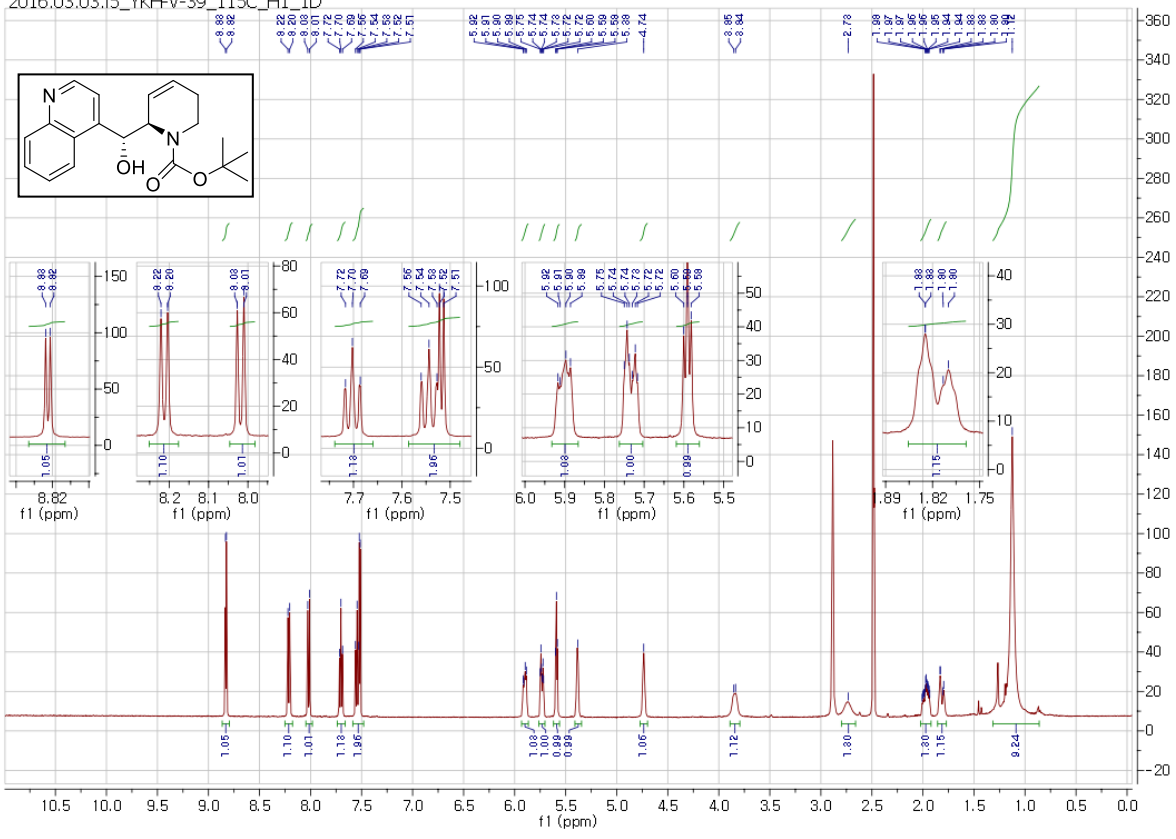
^{13}C NMR of compound **19** (DMSO-d_6, 100 MHz, 80 °C)



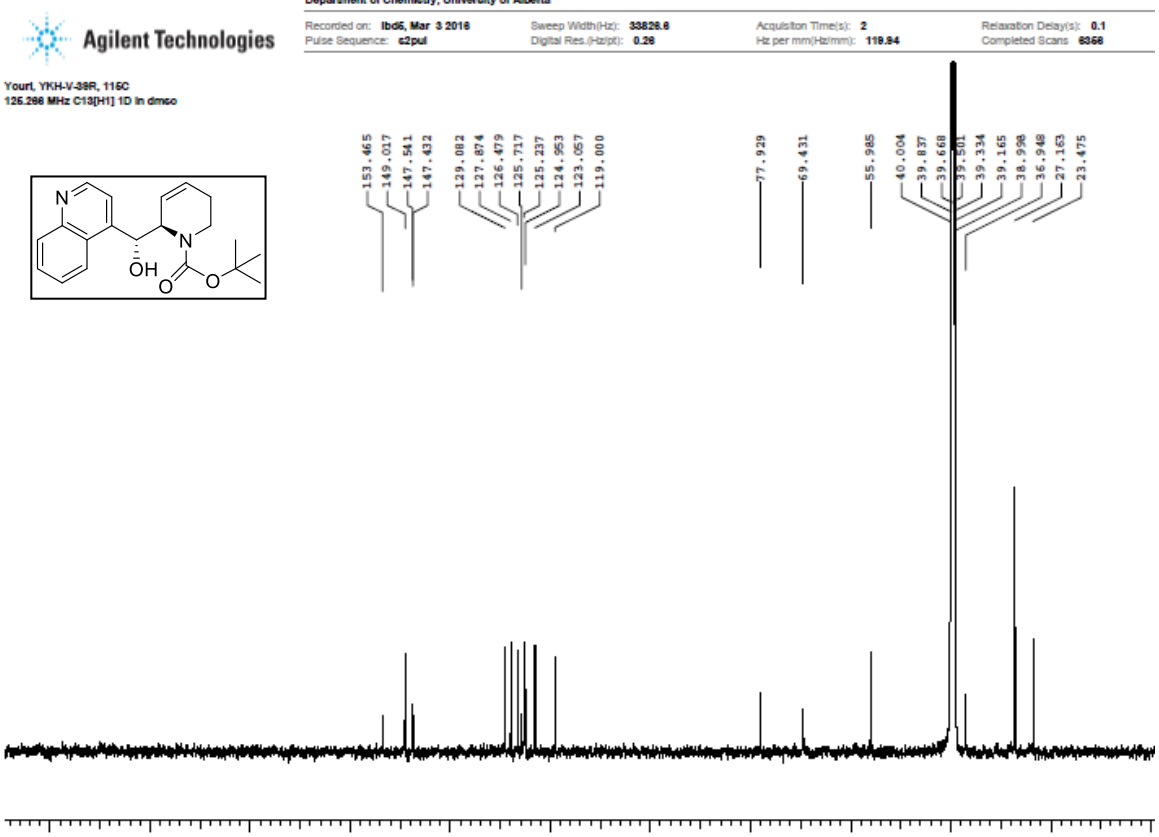
^{1}H NMR of compound **20** (DMSO-d_6, 400 MHz)



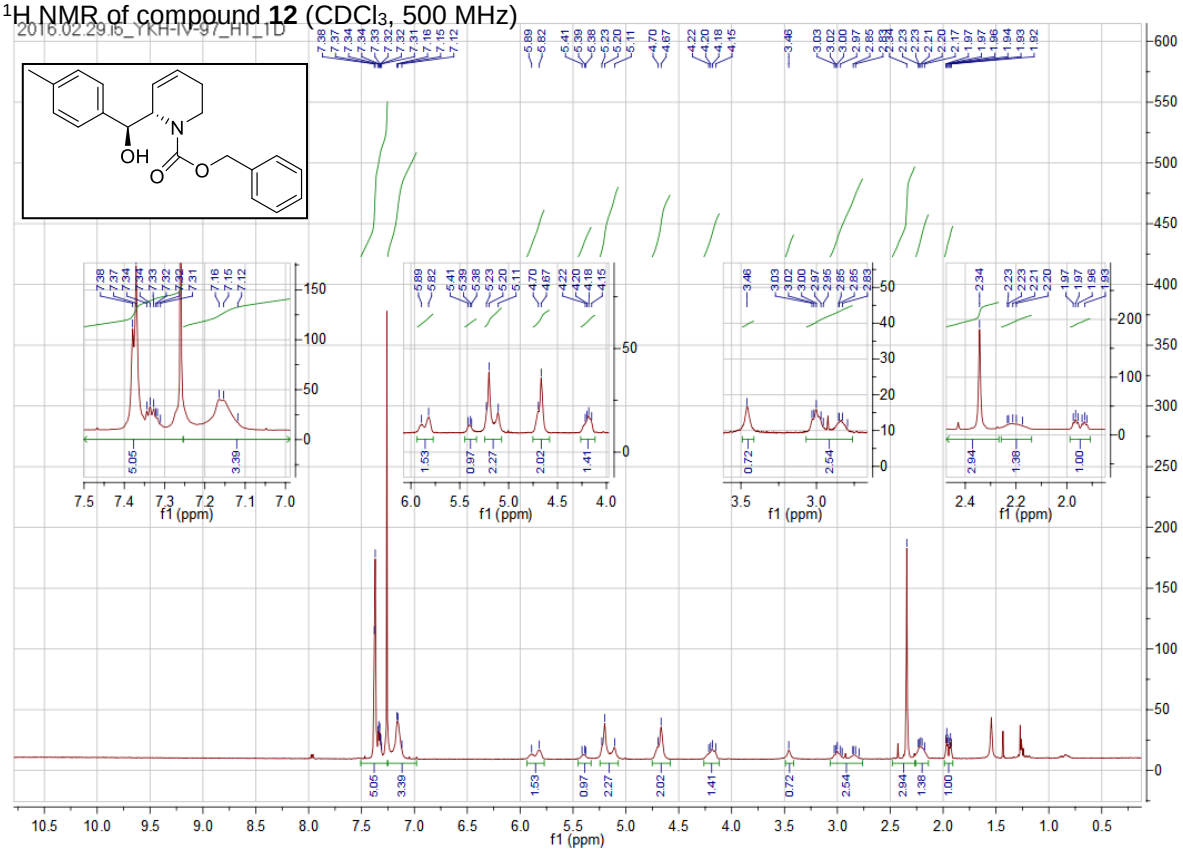
^{1}H NMR of compound **20** (DMSO-d_6, 400 MHz, 115 °C)



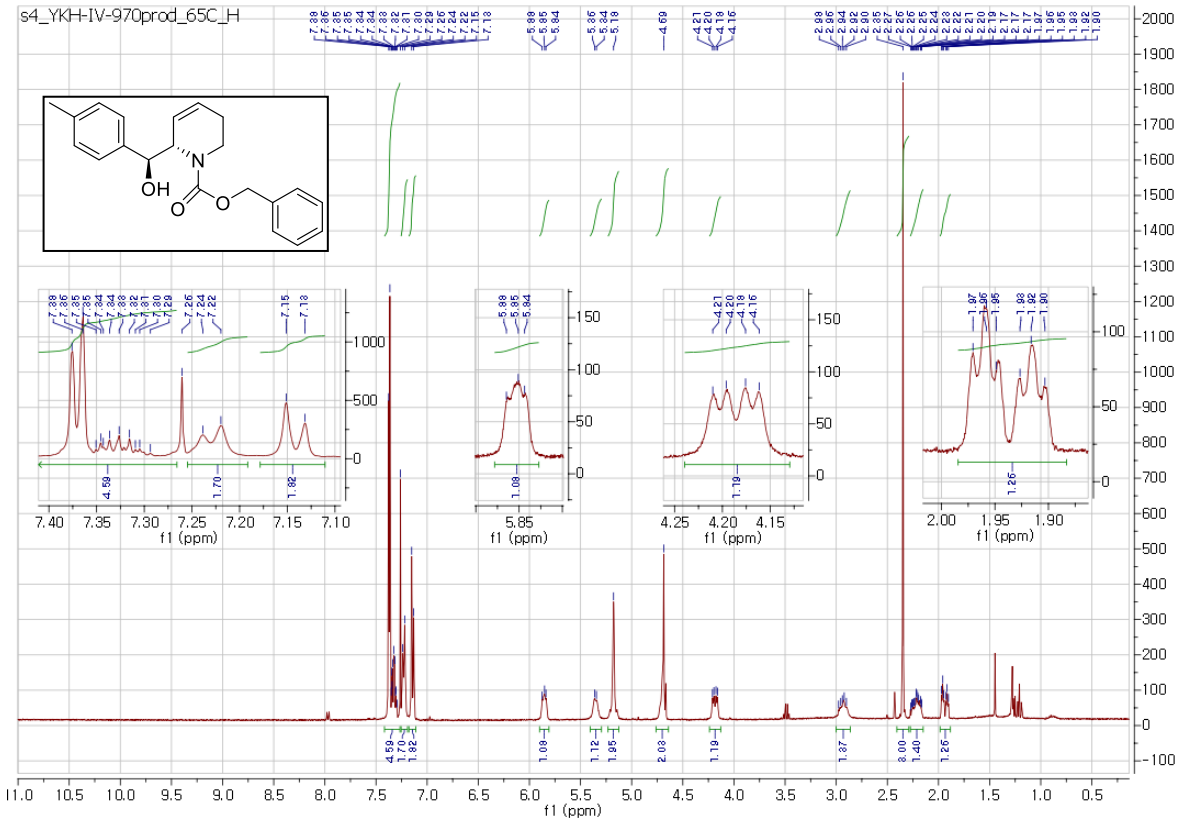
^{13}C NMR of compound **20** (DMSO-d_6, 100 MHz, 115 °C)



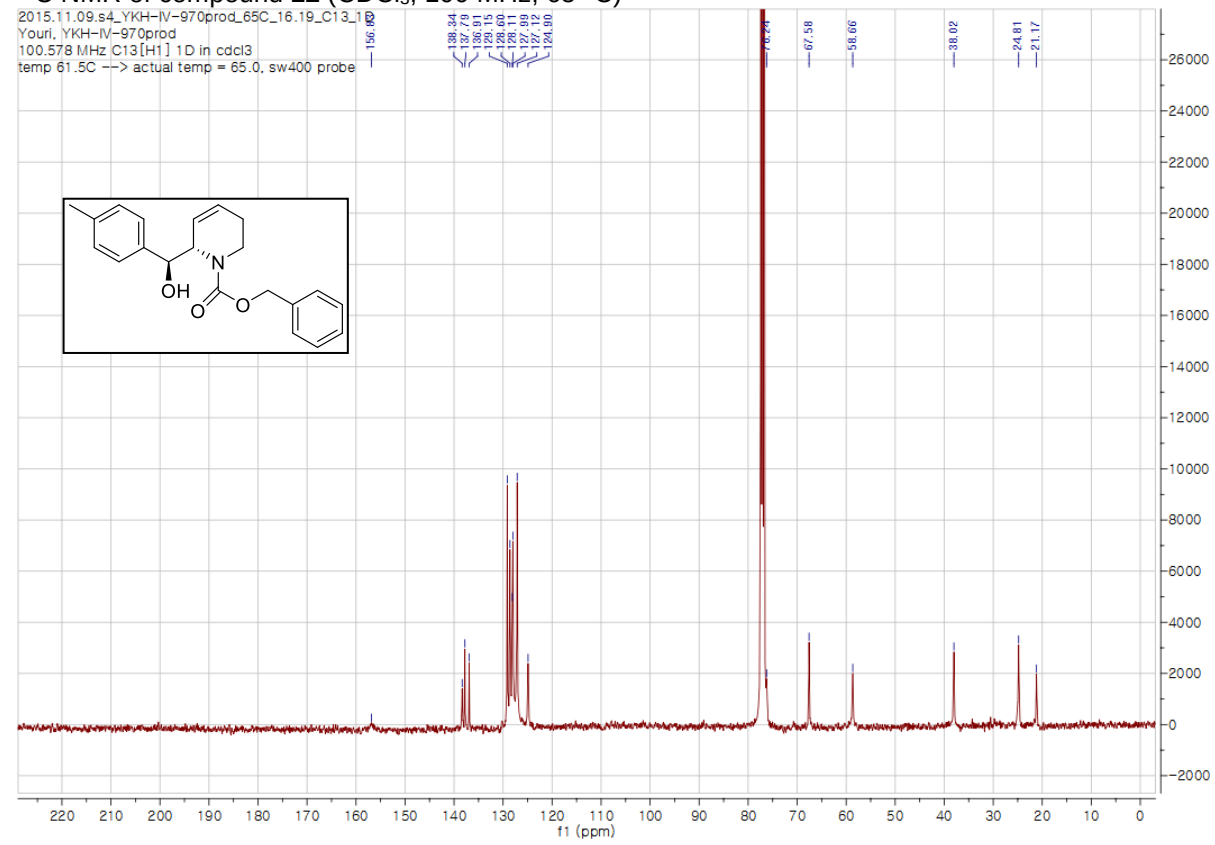
^{1}H NMR of compound **12** (CDCl$_3$, 500 MHz)



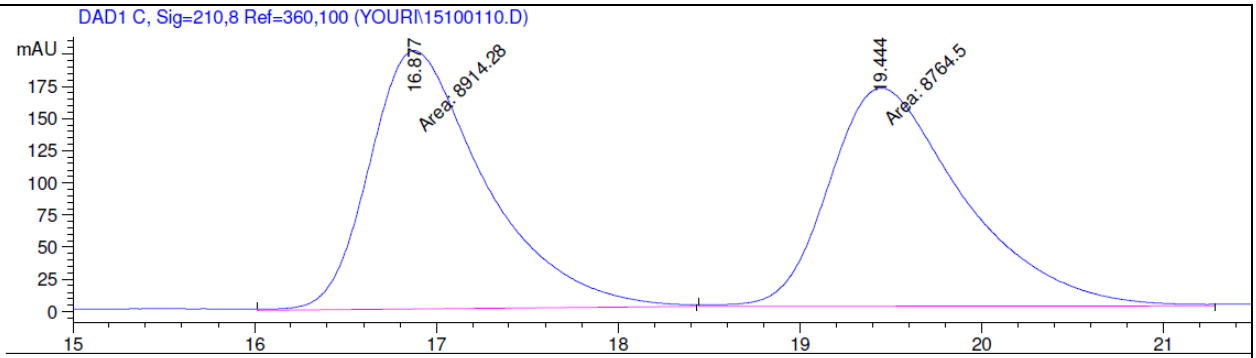
^{1}H NMR of compound **12** ($CDCl_3$, 400 MHz, 65 °C)



^{13}C NMR of compound **12** ($CDCl_3$, 100 MHz, 65 °C)



7. HPLC chromatograms for enantiomeric excess measurements

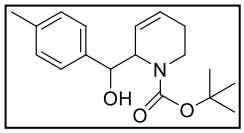


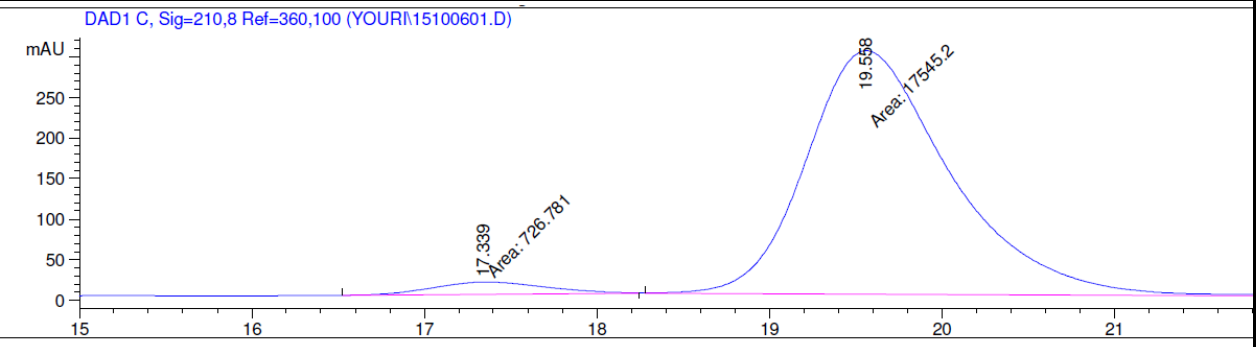
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.877	MM	0.7390	8914.28223	201.04823	50.4236
2	19.444	MM	0.8596	8764.49902	169.93340	49.5764

Totals : 1.76788e4 370.98163

Compound *rac*-**7**



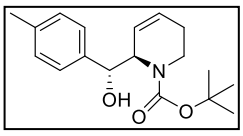


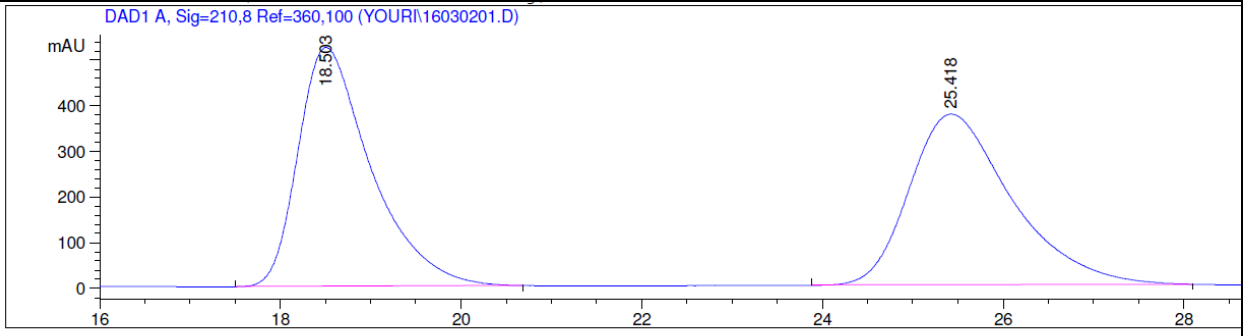
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.339	MM	0.7780	726.78107	15.56991	3.9776
2	19.558	MM	0.9736	1.75452e4	300.34979	96.0224

Totals : 1.82719e4 315.91970

Compound **7**

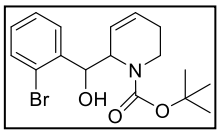


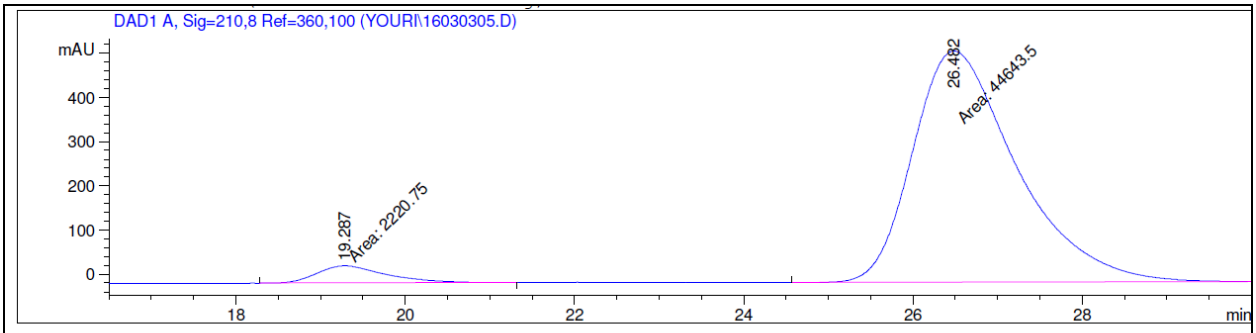


Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.503	BB	0.8022	2.93236e4	522.92322	49.8967
2	25.418	BB	1.1548	2.94451e4	373.89606	50.1033

Compound *rac*-**17**

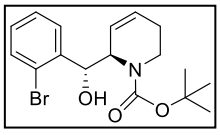


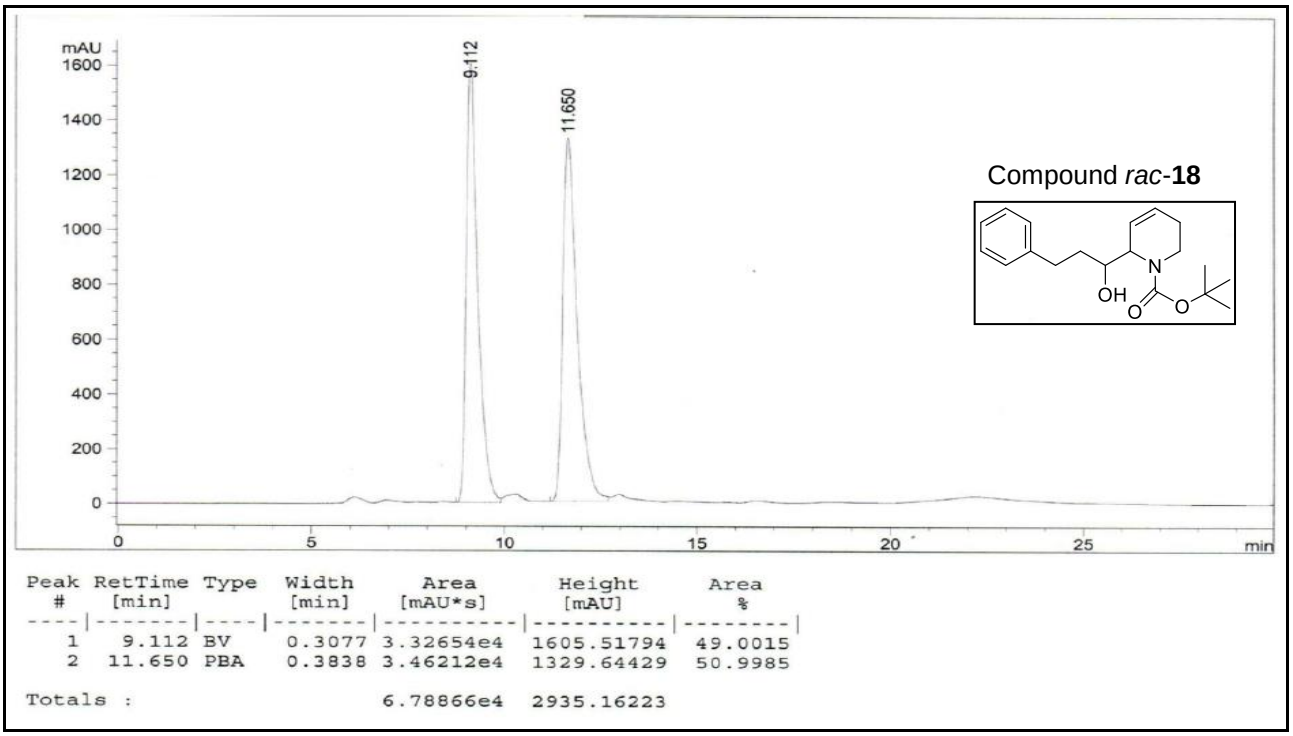


Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.287	MM	0.9569	2220.74780	38.68064	4.7387
2	26.482	MM	1.4230	4.46435e4	522.87378	95.2613
Totals :				4.68643e4	561.55442	

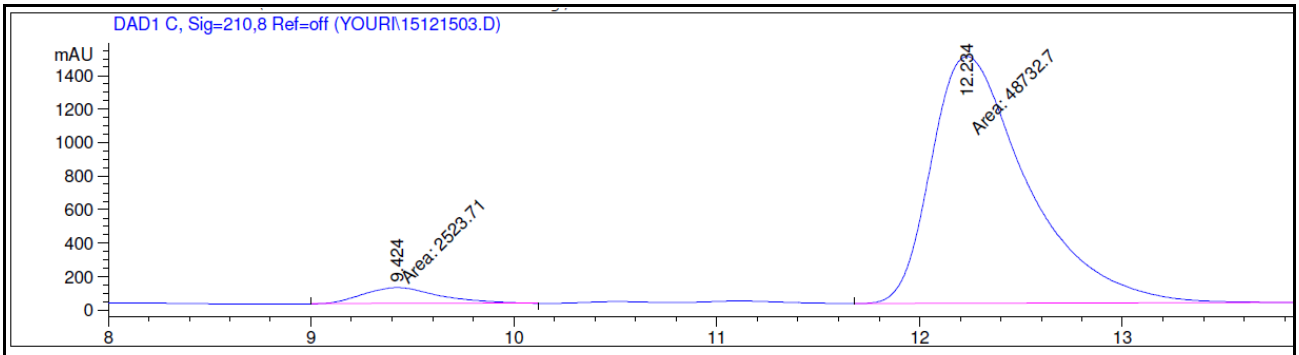
Compound **17**





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.112	BV	0.3077	3.32654e4	1605.51794	49.0015
2	11.650	PBA	0.3838	3.46212e4	1329.64429	50.9985
Totals :				6.78866e4	2935.16223	

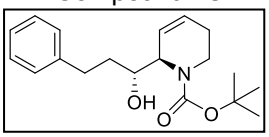
Note: HPLC chromatogram of the above racemate was referenced from our group's former student, Stephanie Lessard[2]

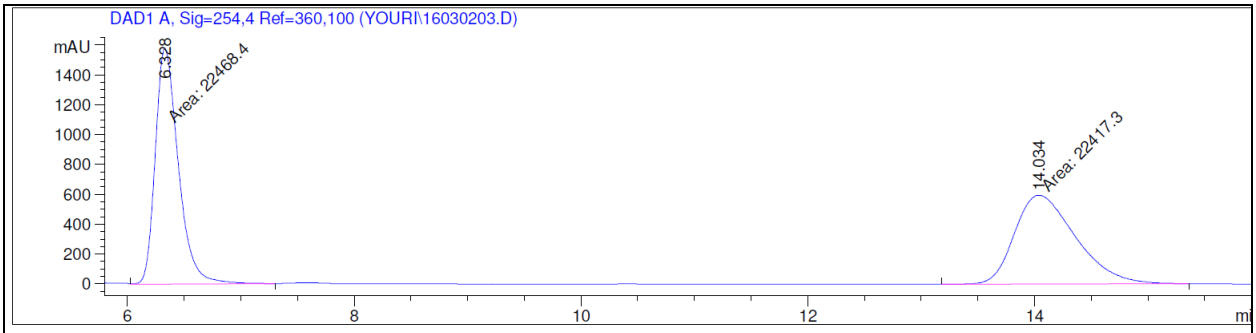


Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.424	MM	0.4364	2523.71484	96.37288	4.9237
2	12.234	MM	0.5508	4.87327e4	1474.67883	95.0763
Totals :				5.12564e4	1571.05171	

Compound **18**

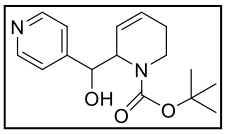


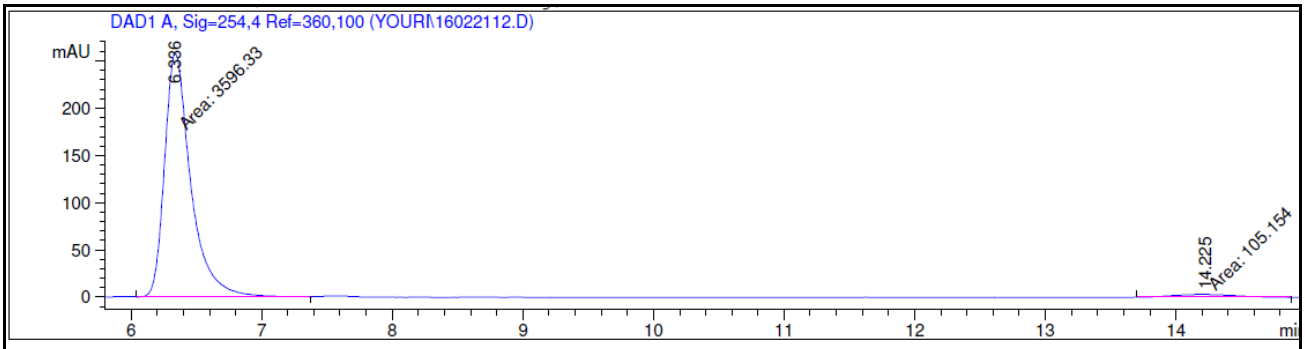


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.328	MM	0.2373	2.24684e4	1578.19604	50.0569
2	14.034	MM	0.6263	2.24173e4	596.55115	49.9431
Totals :				4.48857e4	2174.74719	

Compound *rac*-**19**

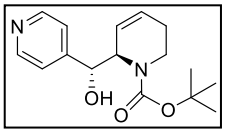


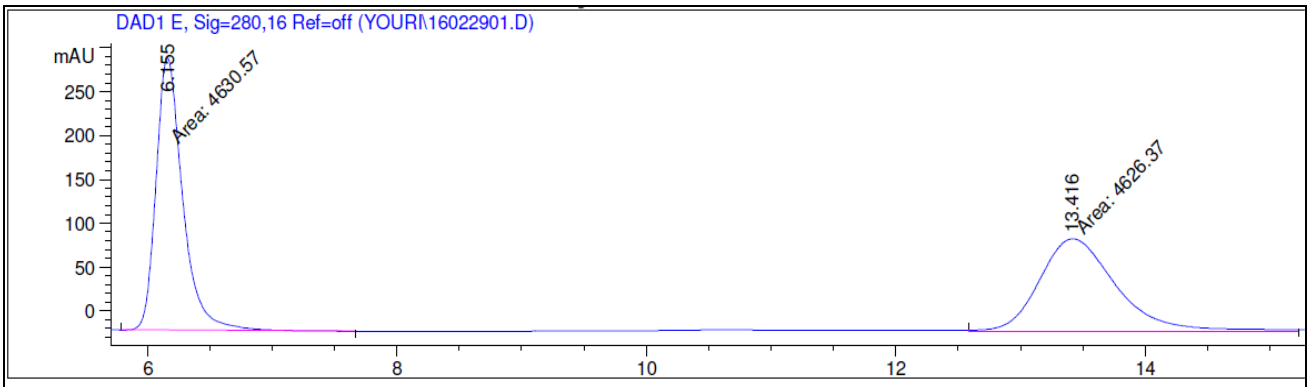


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.336	MM	0.2325	3596.32520	257.84659	97.1591
2	14.225	MM	0.5924	105.15359	2.95818	2.8409
Totals :				3701.47879	260.80477	

Compound **19**

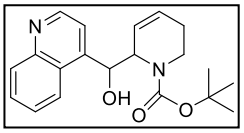


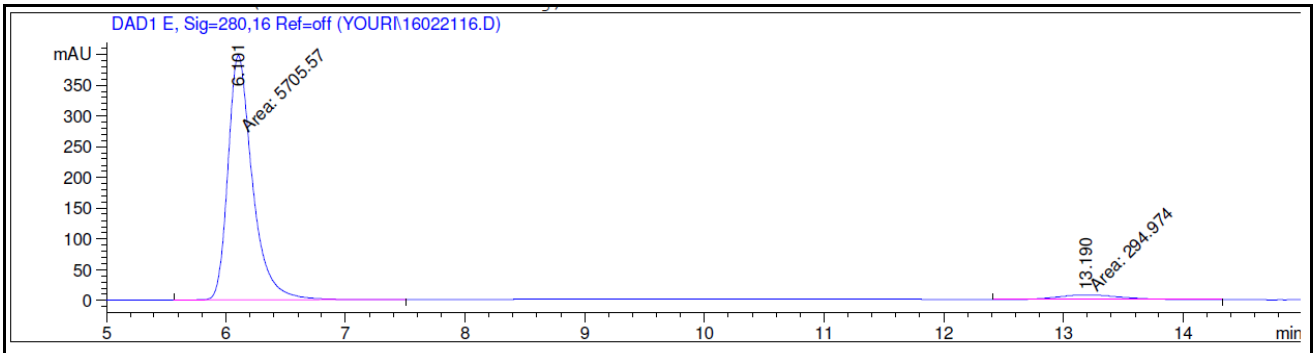


Signal 1: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.155	MM	0.2484	4630.56885	310.67099	50.0227
2	13.416	MM	0.7266	4626.36865	106.12547	49.9773
Totals :				9256.93750	416.79646	

Compound *rac*-**20**

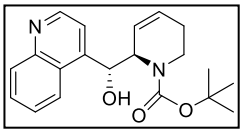


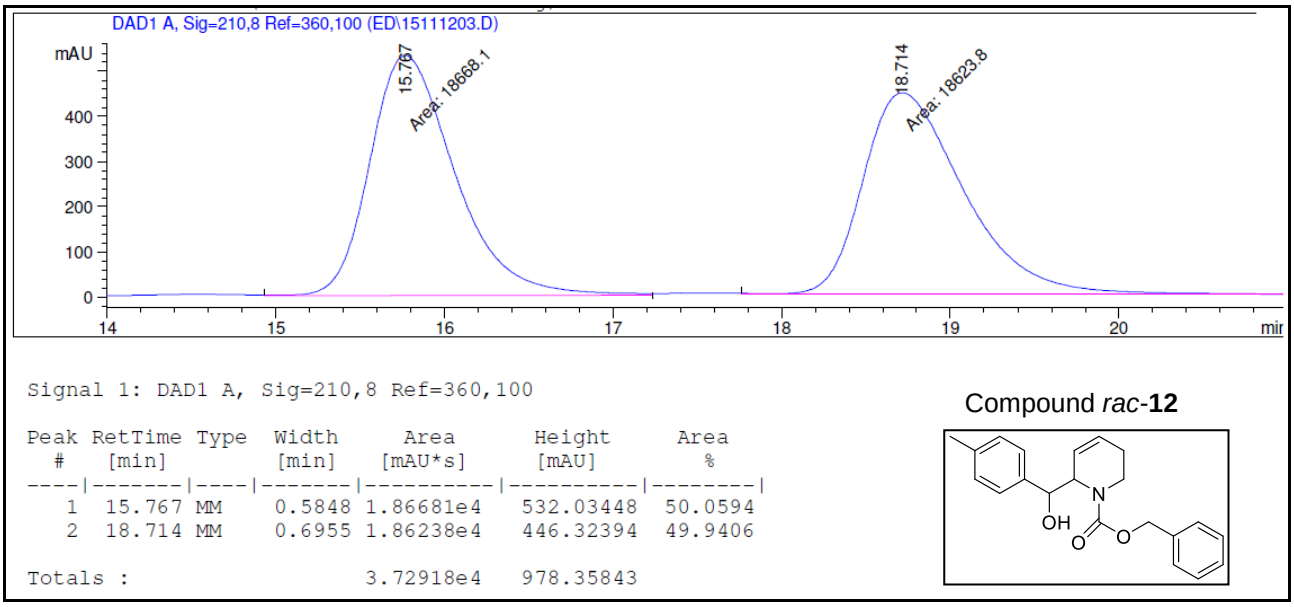


Signal 1: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.101	MM	0.2390	5705.57324	397.95880	95.0842
2	13.190	MM	0.6482	294.97440	7.58408	4.9158
Totals :				6000.54764	405.54288	

Compound **20**

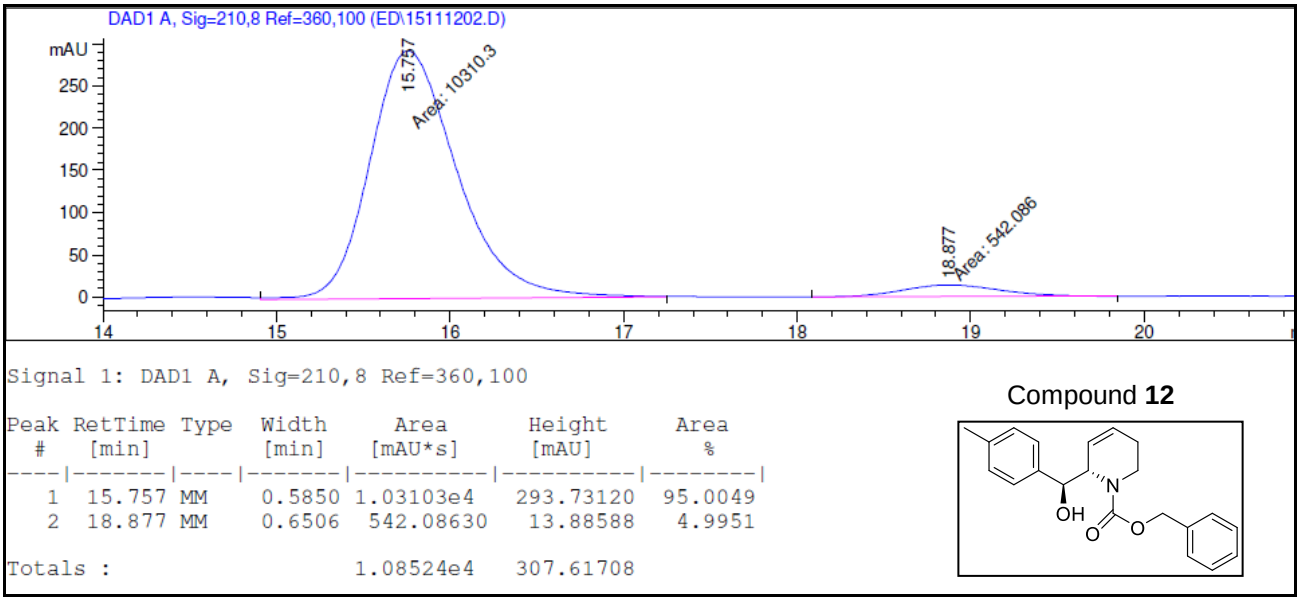




Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.767	MM	0.5848	1.86681e4	532.03448	50.0594
2	18.714	MM	0.6955	1.86238e4	446.32394	49.9406
Totals :				3.72918e4	978.35843	

Compound *rac*-**12**



Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.757	MM	0.5850	1.03103e4	293.73120	95.0049
2	18.877	MM	0.6506	542.08630	13.88588	4.9951
Totals :				1.08524e4	307.61708	

Compound **12**

8. References

1. D. Chang, G. Yang and S. Qilong, *Chem. Eur. J.*, 2015, **21**, 6074

2. S. Lessard, F. Peng and D. G. Hall, *J. Am. Chem. Soc.*, 2009, **131**, 9612