Enantioselective synthesis of bio-relevant 3,5-diarylpyrazolines

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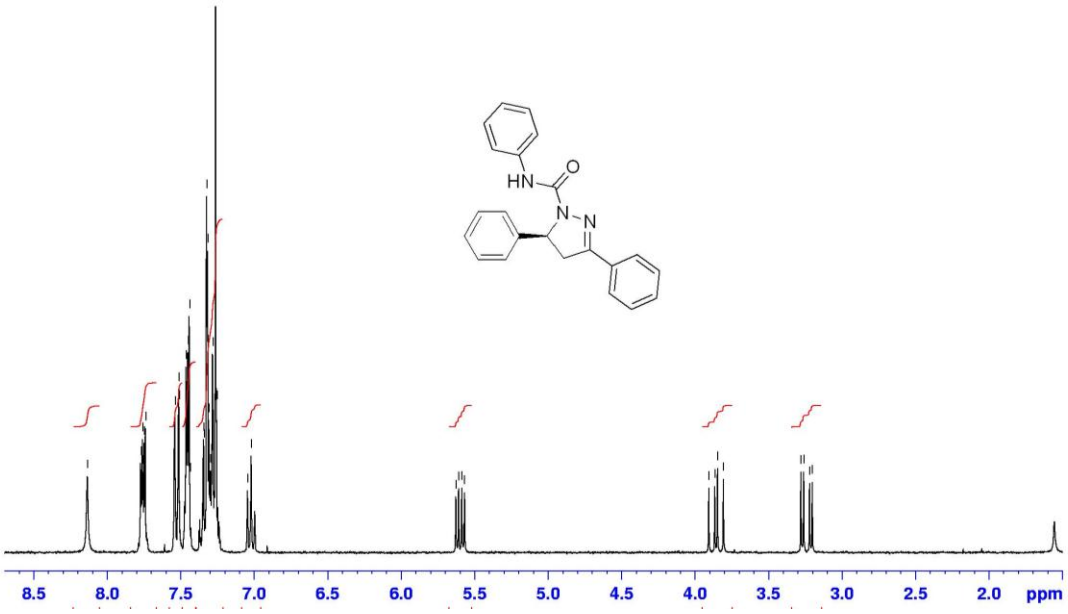
I General information

Chromatographic purification of compounds was achieved with 60 silica gel (40-63 μm).[1] Thin layer chromatography was carried out on silica gel 60 F_{254} (1.1 mm) with spot detection under UV light or phosphomolybdic acid or $KMnO_4$ oxidation. ^{1}H NMR spectra were recorded at 300 MHz. Data appear in the following order: chemical shifts in ppm, number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant *J* in Hz. ^{13}C NMR spectra were acquired at 75.4 MHz operating with broad band ^{1}H decoupling. The hydrogen multiplicity was obtained by DEPT135 or Attached Proton Test (APT) using JMOD pulse program. IR spectra were recorded on a IRTF spectrometer with solid dispersed on KBr pastille. Mp's stand uncorrected. HPLC analyses were performed with with Daicel Chiralpack® columns (4.6 mm × 25 cm) and a mixture of heptane/*iso*propanol solvents. A spectrosystem UV detector and a chiral detector (polarimeter) were used. Optical rotations were measured at 20 °C in $CHCl_3$ with a micropolarimeter.

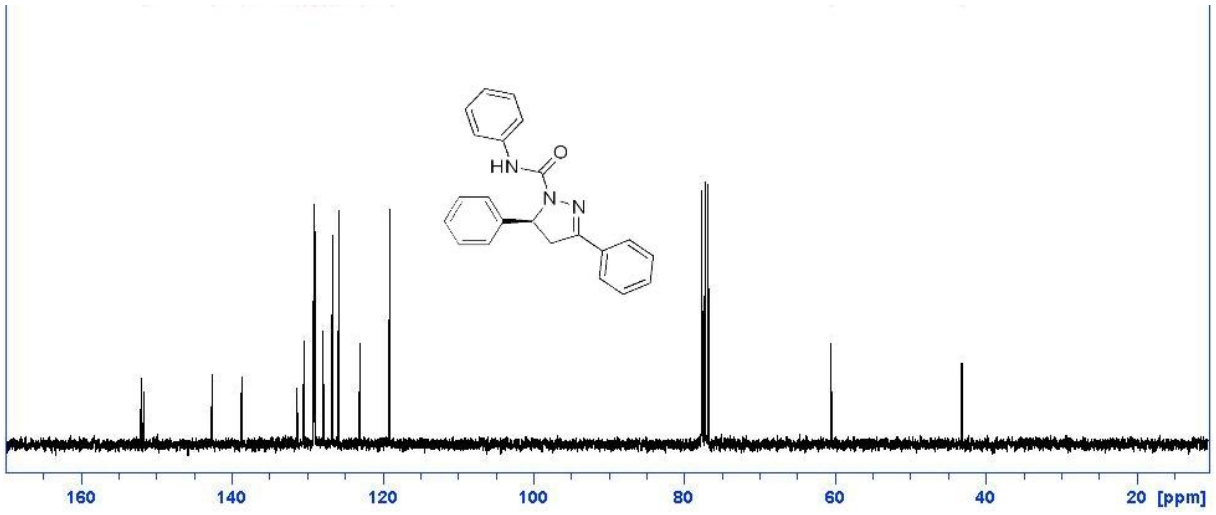
[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.*, 1978, **43**, 2923.

II NMR spectra and HPLC chromatograms

II.1 N-3,5-triphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 11a

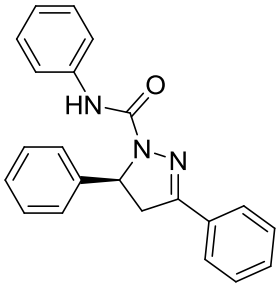


II.1 N-3,5-triphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (13C) 11a

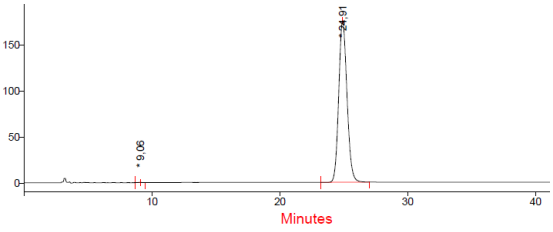


II.1 N-3,5-triphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (HPLC) 11a

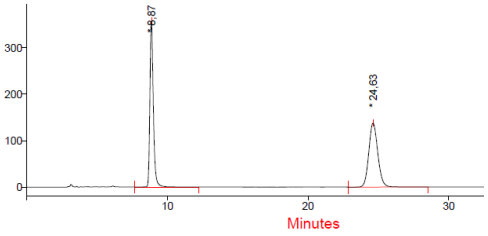
HPLC using a *Chiralpack IA Daicel* chiral column, *i*PrOH/heptane (50/50) eluent at a flow rate of 1 mL/min at 20°C, λ = 230 nm. The major enantiomer at 24.9 min. (the *levo* (-) isomer) and the minor enantiomer 9.1 min (the *dextro* (+) isomer) giving > 99% *ee*.



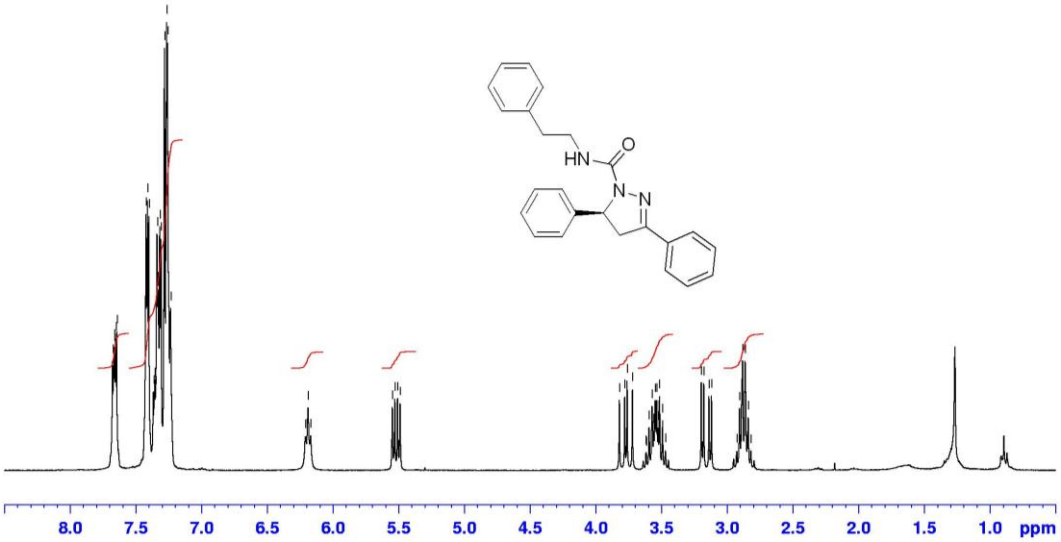
> 99% ee



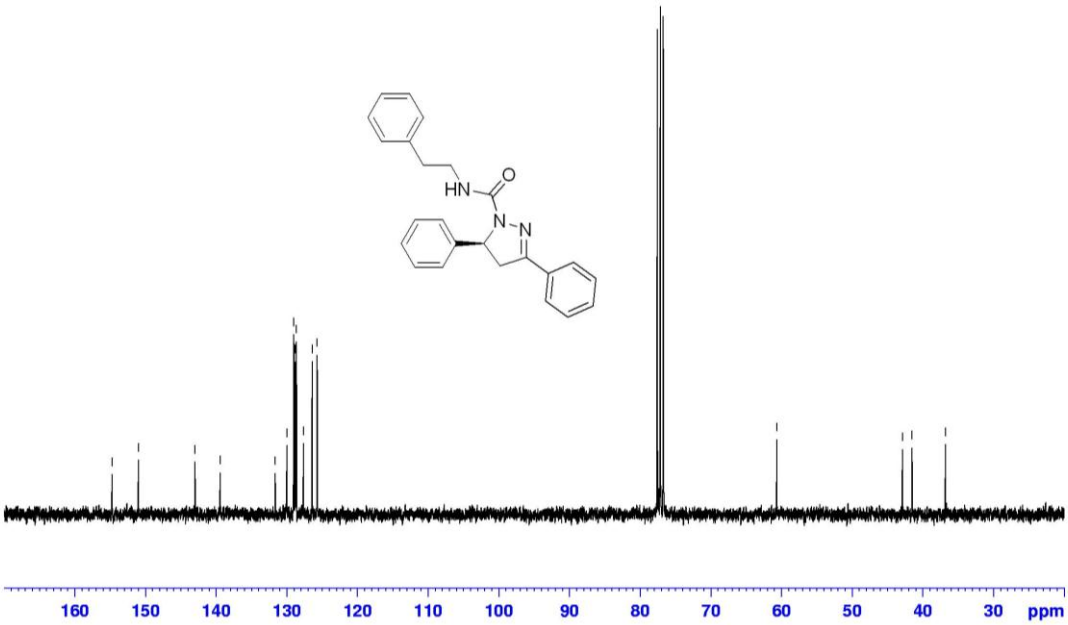
Racemic



II.2 N-phenethyl-3,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 11c



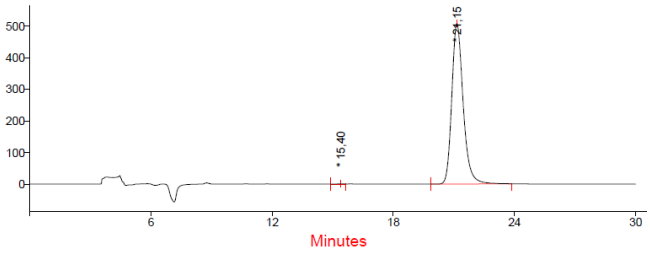
II.2 N-phenethyl-3,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (13C) 11c



II.2 N-phenethyl-3,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (HPLC) 11c

HPLC using a *Chiralpack IA Daicel* chiral column, *i*PrOH/heptane (20/80) eluent at a flow rate of 0.8 mL/min at 20°C, λ = 230 nm. The major enantiomer at 21.1 min. (the *levo* (-) isomer) and the minor enantiomer 15.4 min (the *dextro* (+) isomer) giving >99% *ee*.

> 99% ee



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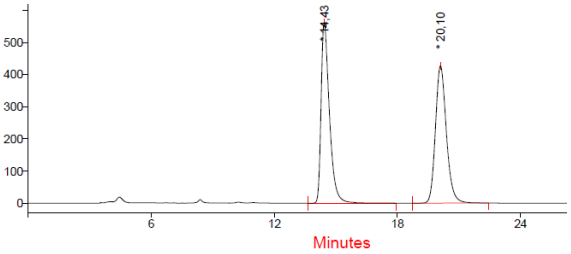
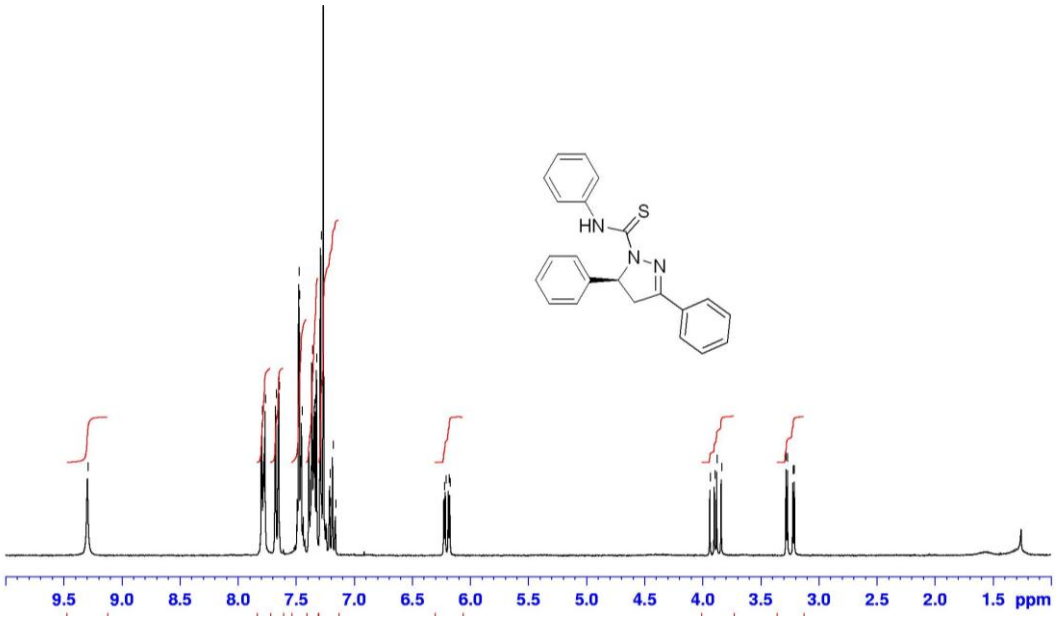
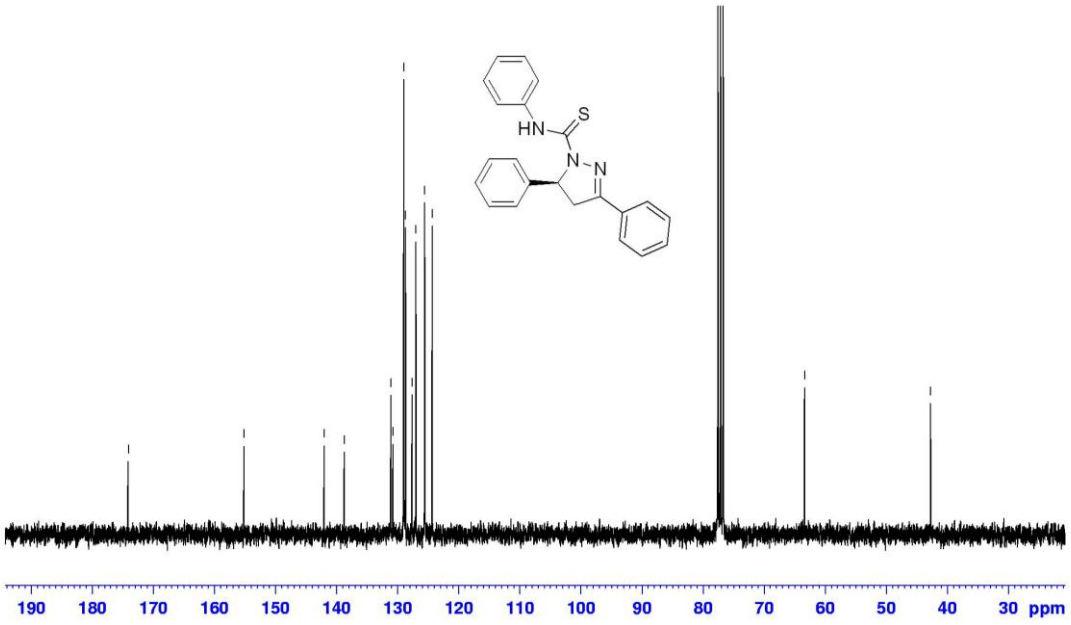


II.3 N,3,5-triphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (1H) 11d



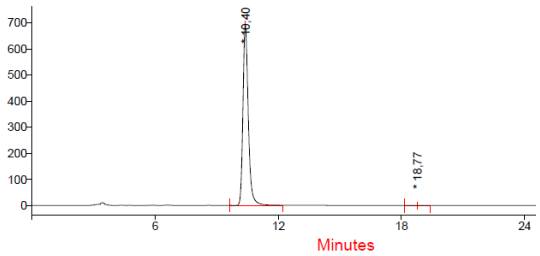
II.3 N,3,5-triphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (13C) 11d



II.3 N,3,5-triphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (HPLC) 11d

HPLC using a *Chiralpack IA Daicel* chiral column, *i*PrOH/heptane (40/60) eluent at a flow rate of 1 mL/min at 20°C, λ = 230 nm. The major enantiomer at 10.4 min. (the *levo* (-) isomer) and the minor enantiomer 18.8 min (the *dextro* (+) isomer) giving >99% *ee*.

> 99% ee



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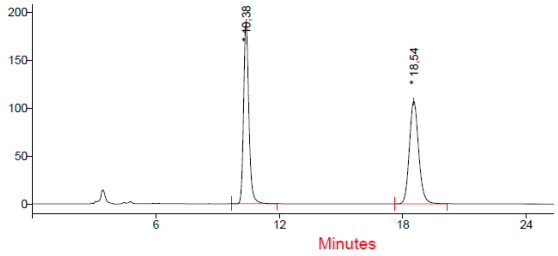
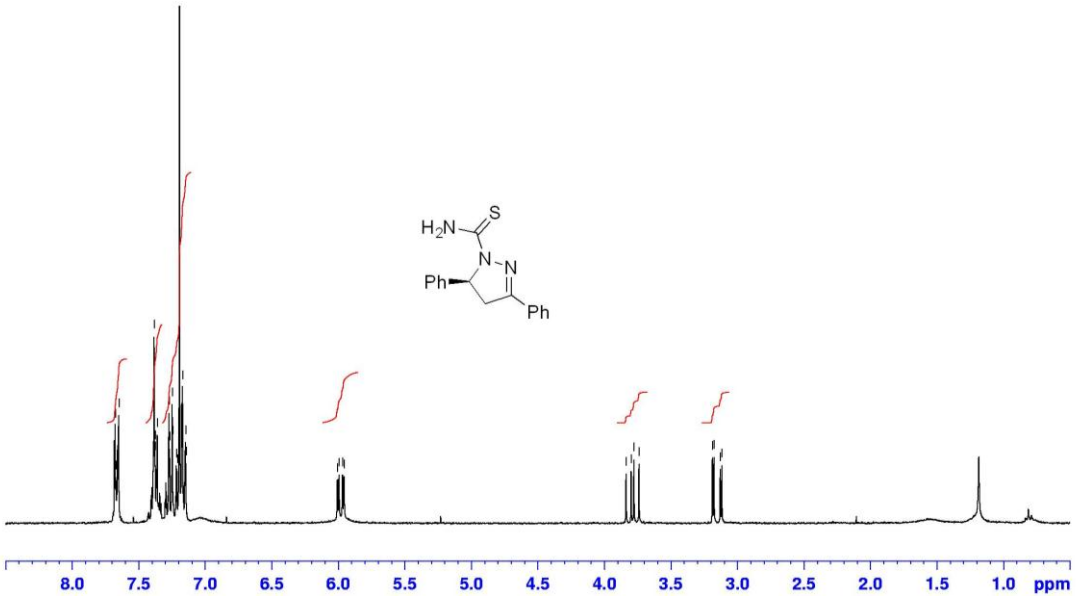
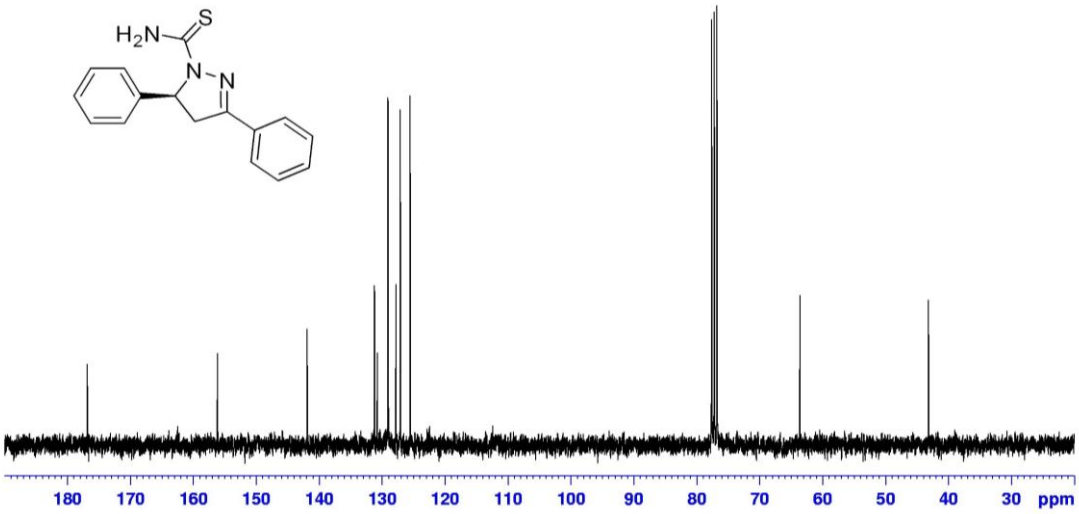


II.4 3,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (1H) 11b

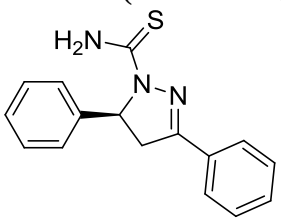


II.4 3,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (13C) 11b

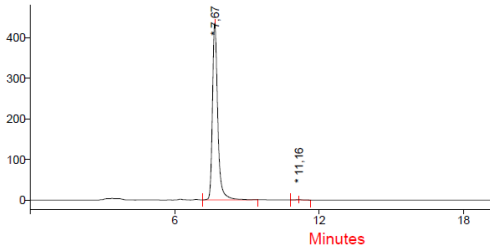


II.4 3,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (HPLC) 11b

HPLC using a *Chiralpack IA Daicel* chiral column, *i*PrOH/heptane (50/50) eluent at a flow rate of 1 mL/min at 20°C, λ = 230 nm. The major enantiomer at 7.7 min. (the *levo* (-) isomer) and the minor enantiomer 11.2 min (the *dextro* (+) isomer) giving >99% *ee*.



> 99% ee



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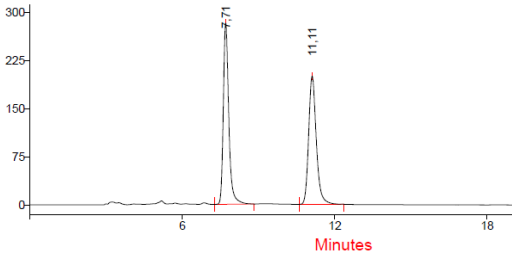
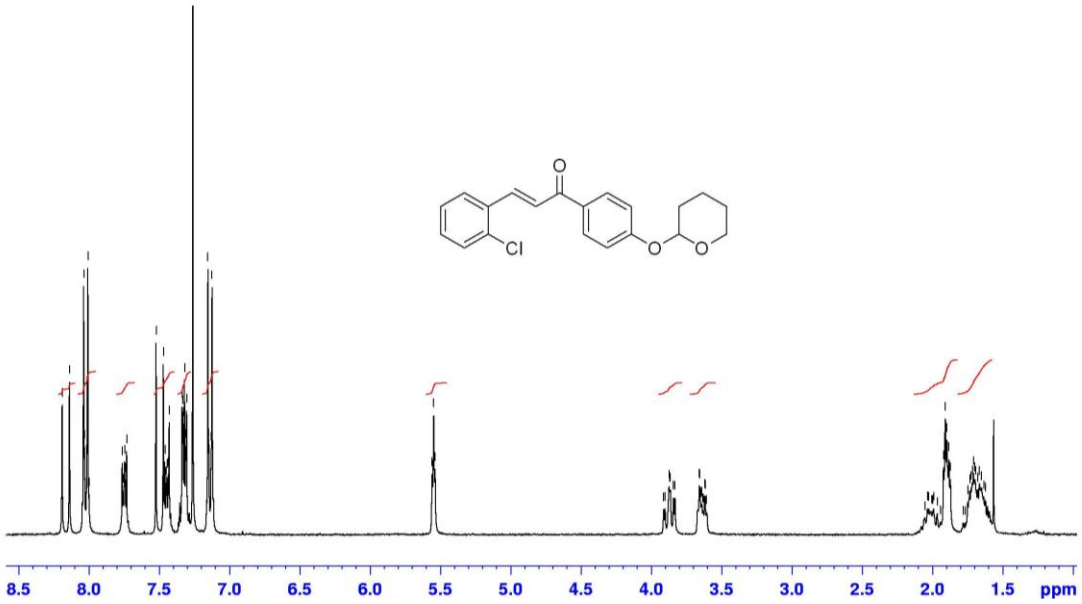
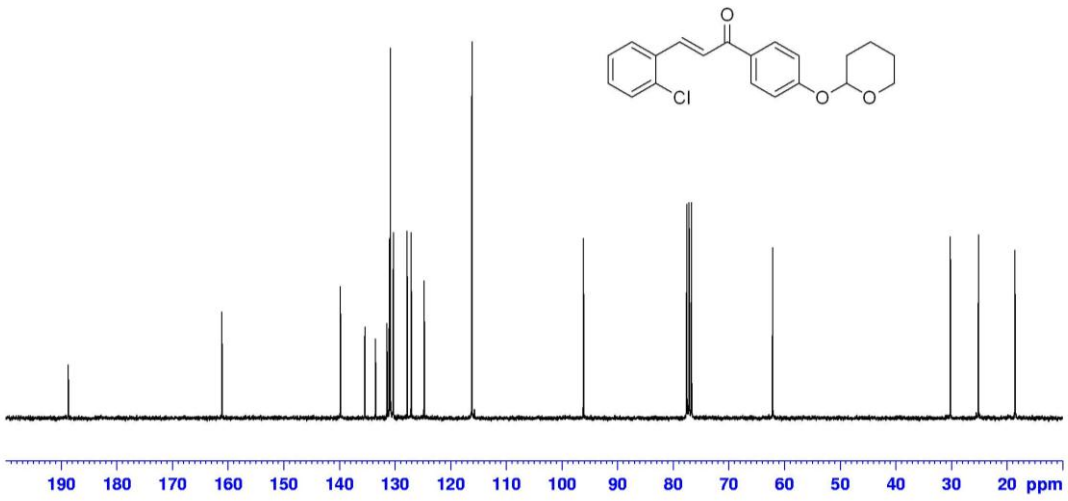


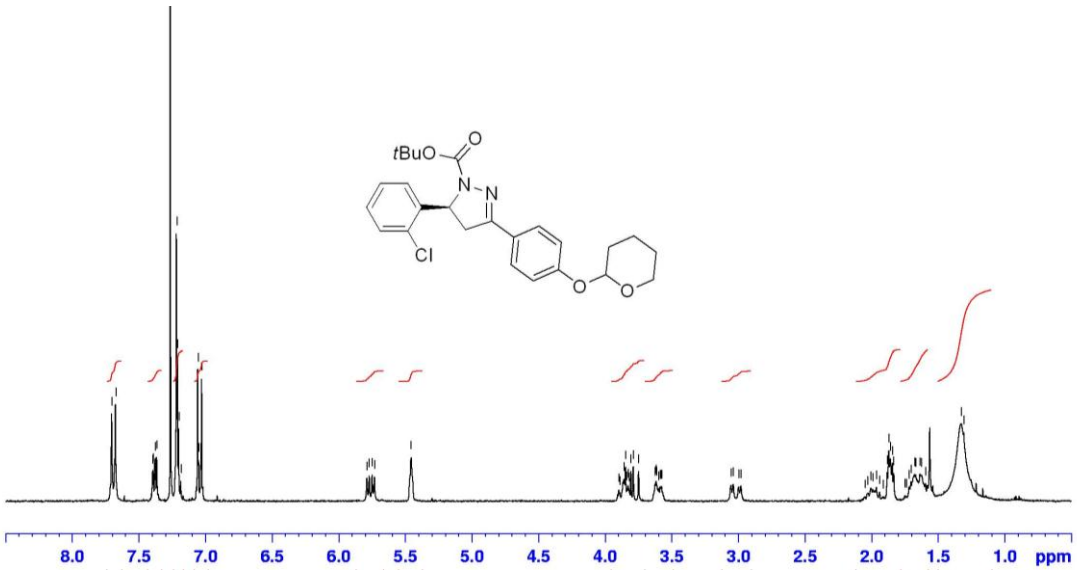
II.5 (E)-3-(2-chlorophenyl)-1-(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)prop-2-enone (1H) 18



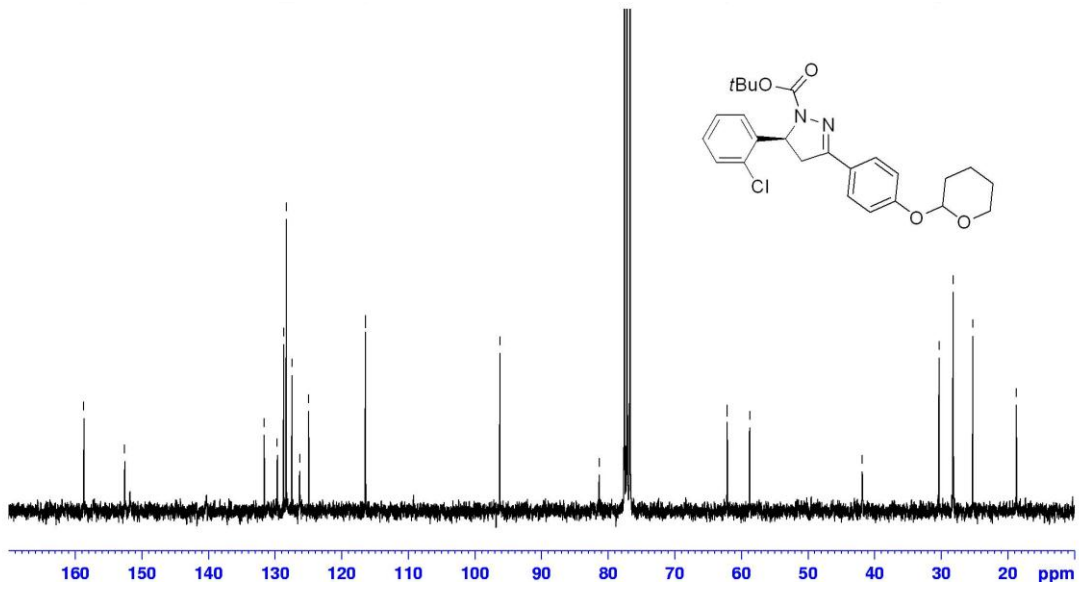
II.5 (E)-3-(2-chlorophenyl)-1-(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)prop-2-enone (13C) 18



II.6 tert-butyl-3-(4-(tetrahydropyran-2-yloxy)phenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (1H) 19



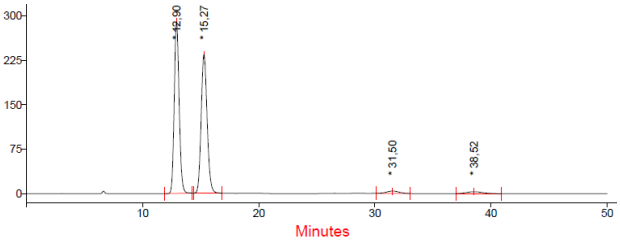
II.6 tert-butyl-3-(4-(tetrahydropyran-2-yloxy)phenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (13C) 19



II.6 tert-butyl-3-(4-(tetrahydropyran-2-yloxy)phenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (HPLC) 19

HPLC using a *Chiralpack AD-H Daicel* chiral column, *i*PrOH/heptane (20/80) eluent at a flow rate of 1 mL/min at 20°C, λ = 298 nm. The major enantiomer (considering the absolute configuration of carbon C5) at 12.9 min. and 15.3 min. (two pics because of the presence of two diastereosisomers due to the chirality of the protecting group THP) (the *levo* (-) isomer) and the minor enantiomer 31.5 min. and 38.5 min. (the *dextro* (+) isomer) giving 93% *ee*.

93% ee



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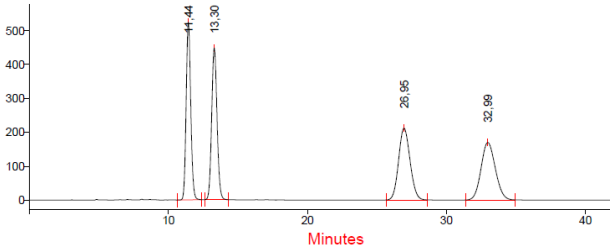
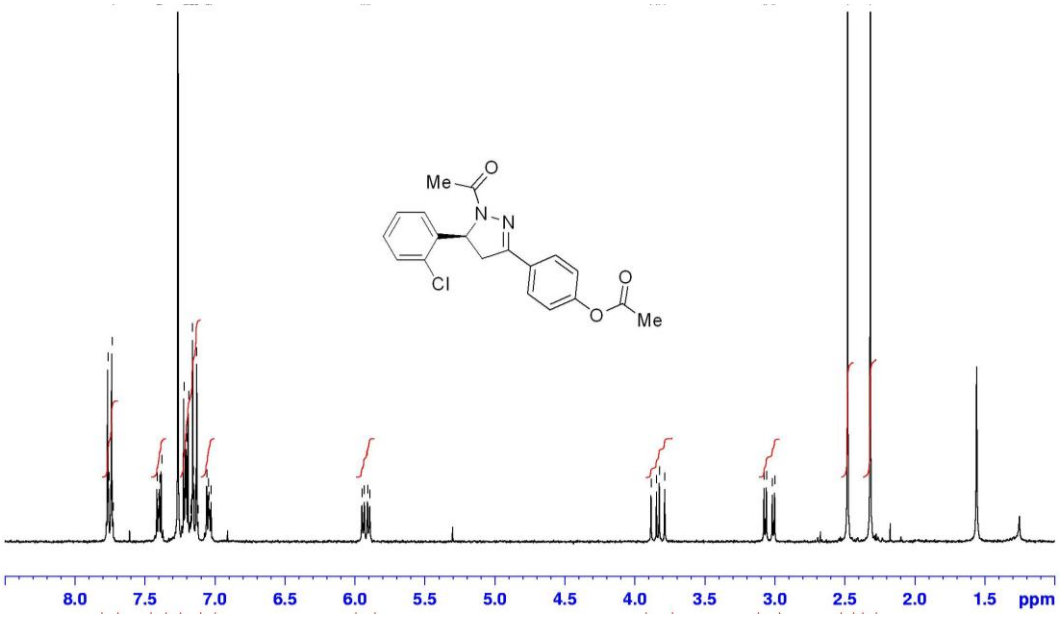
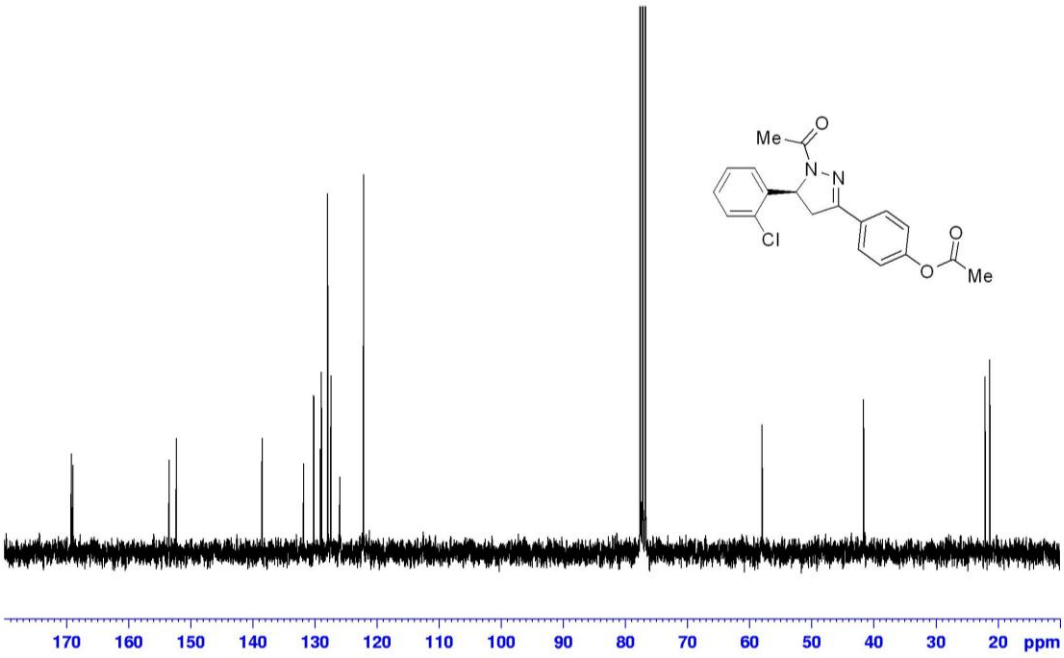


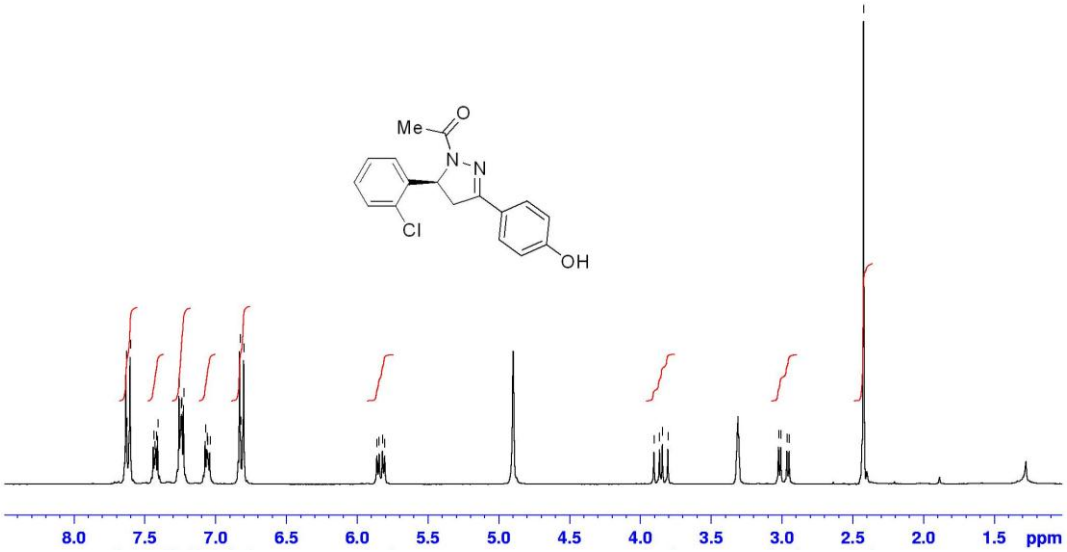
II.7 1-acetyl-3-(4-acetoxyphenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazole (1H) 20



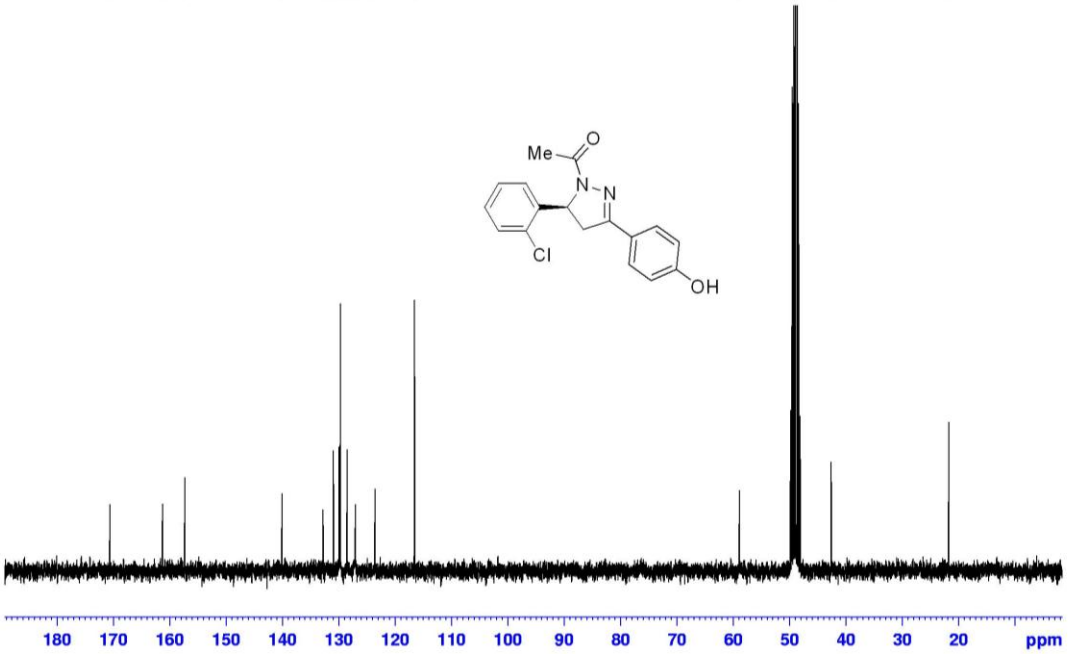
II.7 1-acetyl-3-(4-acetoxyphenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazole (13C) 20



II.8 1-acetyl-3-(4-hydroxyphenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazole (1H) 4



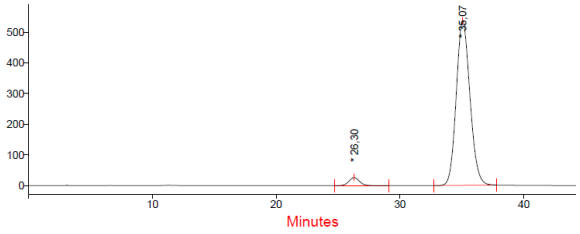
II.8 1-acetyl-3-(4-hydroxyphenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazole (13C) 4



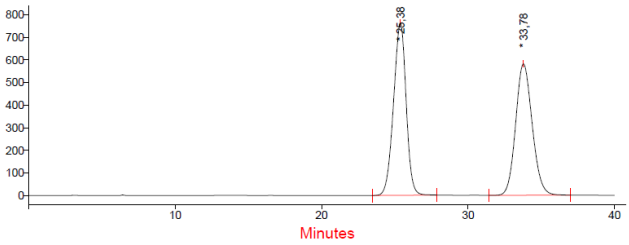
II.8 1-acetyl-3-(4-hydroxyphenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazole (HPLC) 4

HPLC using a *Chiralpack AD-H Daicel* chiral column, *i*PrOH/heptane (20/80) eluent at a flow rate of 1 mL/min at 20°C, λ = 298 nm. The minor enantiomer at 26.3 min. (the *dextro* (+)-*R* isomer) and the major enantiomer at 35.0 min (the *levo* (-)-*S* isomer) giving 93% *ee*.

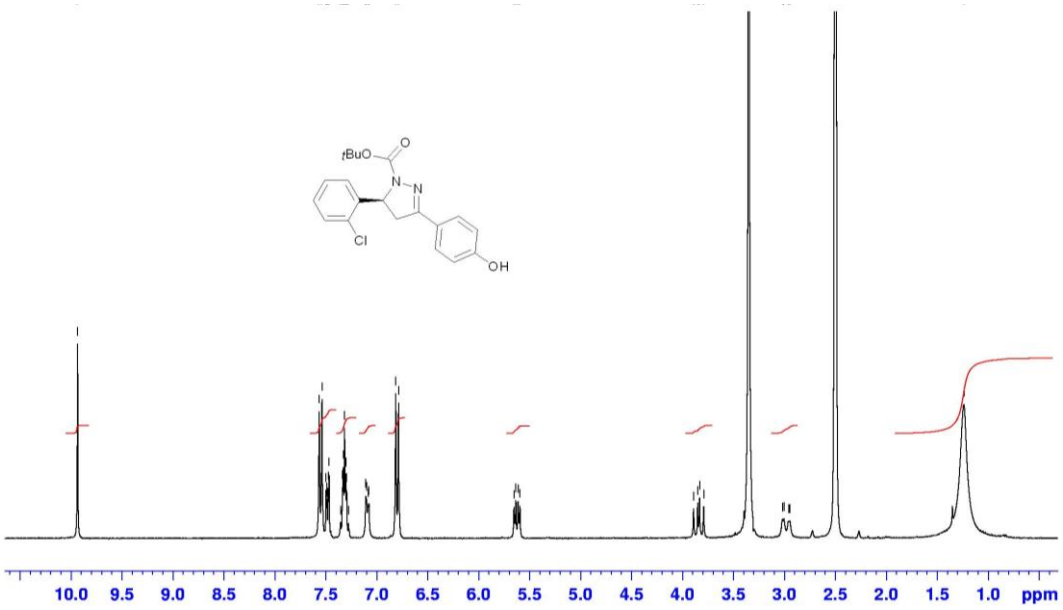
93% ee



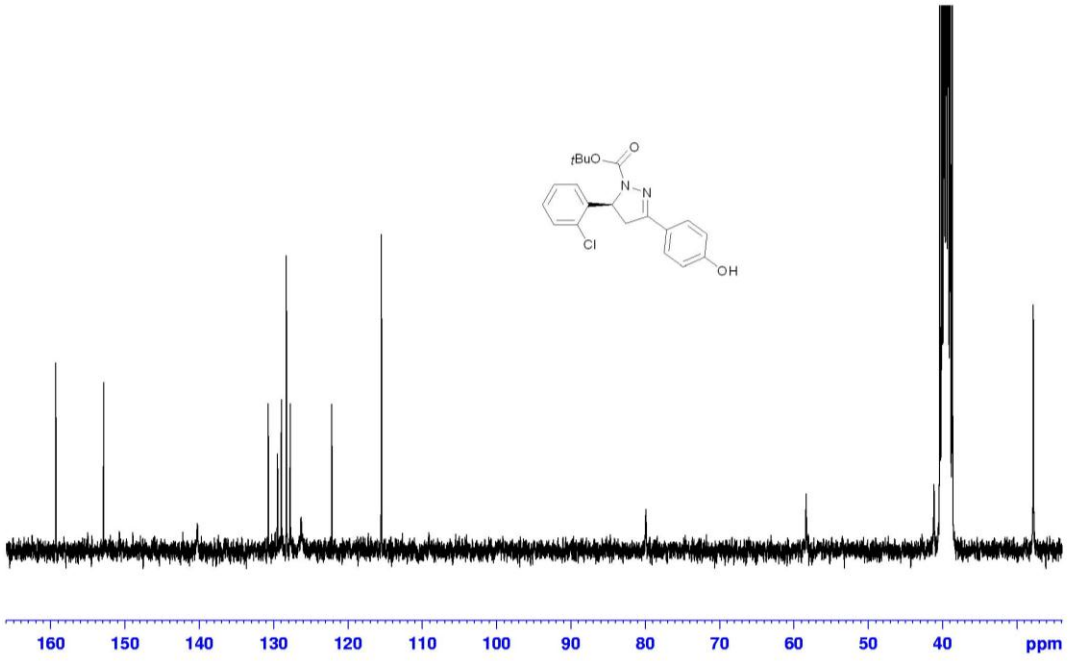
Racemic



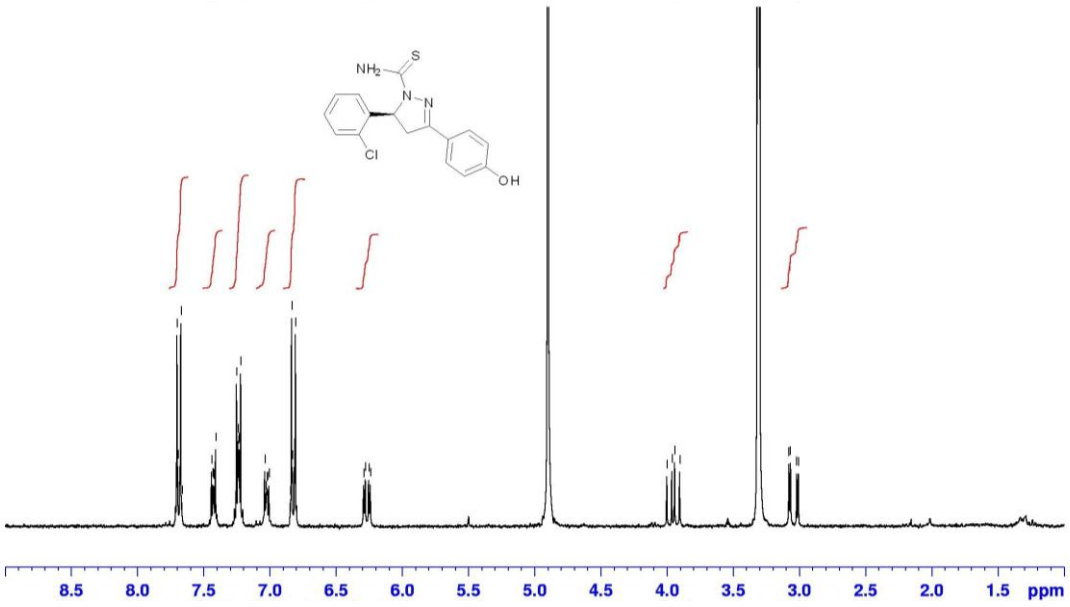
II.9 tert-butyl 5-(2-chlorophenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (1H – DMSO, crude product) 21



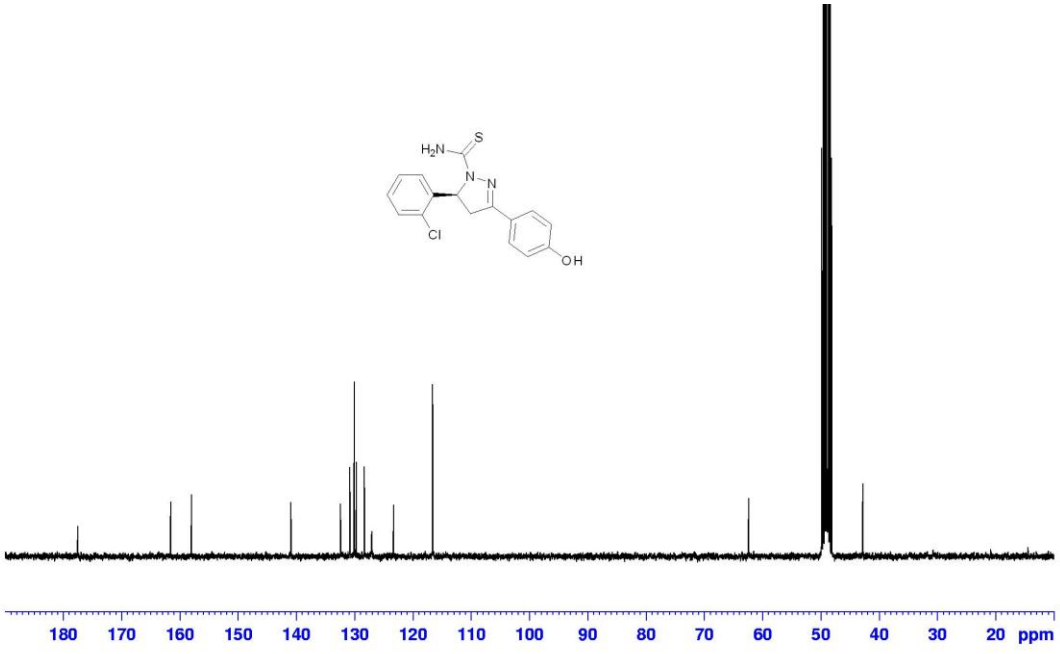
II.9 tert-butyl 5-(2-chlorophenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carboxylate (1H – DMSO, crude product) 21



II.10 5-(2-chlorophenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (1H – CD_3OD) 22



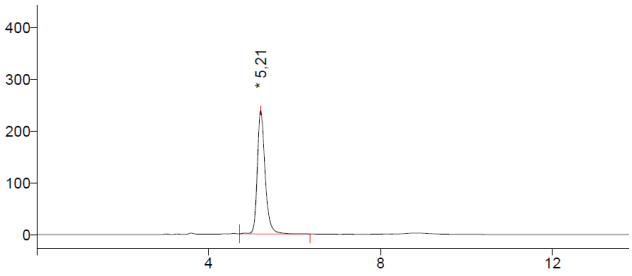
II.10 5-(2-chlorophenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (13C – CD_3OD) 22



II.10 5-(2-chlorophenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (13C – CD_3OD) 22

HPLC using a Chiralpack IA Daicel chiral column, iPrOH/heptane (50/50) eluent at a flow rate of 1 mL/min at 20°C, λ = 254 nm. The major enantiomer at 5.4 min. (the levo (-) isomer) and the minor enantiomer 7.1 min (the dextro (+) isomer) giving > 93 % ee.

> 93% ee



Racemic