Supplementary Material (ESI) for Chemical Communications

Supplementary Information

Organocatalytic Asymmetric Aza-Michael Reaction of Nitrogen Heterocycles and α,β-Unsaturated Aldehydes

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1. General methods:

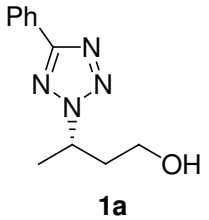
Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or $CHCl_3$ solution (oils), were recorded on a Perkin-Elmer FT-IR 600 and only characteristic signals are reported. NMR spectra were recorded in a Bruker AC-300 at 20ºC, running at 300 MHz for ^1H and 75 MHz or for ^{13}C in $CDCl_3$ solution unless otherwise stated. Resonances are reported in ppm relative to tetramethylsilane and the coupling constants *J* are given in Hz. Mass spectra were recorded under electron impact at 70 eV in a Waters Micromass GCT or in a Hewlett Packard 5989B mass spectrometer. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter (λ = 589 nm, 1 dm cell). Microanalyses were obtained with a LECO CHNS-932 element analyser. TLC was carried out with 0.2 mm. thick silica gel plates (Merck Kiesegel GF_{254}) and visualization was accomplished by UV light or by spraying with phosphomolybdic acid. Flash column chromatography on silica gel was performed with Merck Kiesegel 60 (230-400 mesh). All solvents used in reactions were purified according to standard procedures.[1] (2*S*,5*S*)-2-*tert*-butyl-3-methyl-5-benzyl-4-imidazolidinone, 5-phenyltetrazole, benzotriazole, 4,5-dicyanoimidazole and the α,β-unsaturated aldehydes employed as starting materials were used as purchased. Enantiomeric excesses were determined by HPLC in a Waters600 chromatograph equipped with a photodiode array UV detector Waters996 and using a Chiracel OD or Chiracel OJ chiral column under conditions specified in each case. The racemic standards needed for the optimization of the conditions for the separation of both enantiomers were prepared using DL-proline as catalyst for each case.

[1] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 1997.

2.- General procedure for the organocatalytic aza-Michael reaction.

The starting α,β-Unsaturated aldehyde (1.00 mmol) was added over a cooled (0 ºC) solution of the TFA salt of (2*S*,5*S*)-2-*tert*-butyl-3-methyl-5-benzyl-4-imidazolidinone (0.10 mmol) in propionitrile (4 mL). After stirring for 10 min at this temperature, the mixture was cooled down to –88ºC and 5-phenyltetrazole (5.00 mmol) was added at once. The reaction was stirred at –88 ºC for 10 days, after which $LiBH_4$ (5.00 mmol) was added. After stirring for 10 min, a saturated NH_4Cl aqueous solution (4 mL) was slowly added and the mixture was allowed to reach to 0 ºC. Brine (4 mL) was added and the mixture was extracted with CH_2Cl_2 (8 x 15 mL). The collected organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The corresponding γ-(5-phenyltetrazolyl)alcohol was isolated after flash column chromatography purification (hexanes/AcOEt 7:3). Determination of enantiomeric excess was carried out on its corresponding acetate, which was prepared by the addition of Ac_2O (1.20 mmol) over a solution of the adduct **1** (0.40 mmol) in CH_2Cl_2 (2 mL) and DMAP (4 mg), followed by stirring for 3-4h at rt. Next, water (4 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 5 mL) the collected organic fractions were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The acetate derivative was isolated after flash column chromatography purification (hexanes/AcOEt 6:4).

(3*S*)-3-(5-Phenyltetrazol-2-yl)-butan-1-ol (1a).



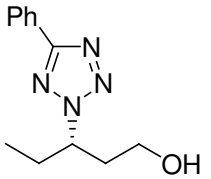
1a

Adduct **1a** (170 mg, 0.78 mmol) was prepared according to the general procedure using crotonaldehyde (83 μL, 1.00 mmol), catalyst **2** (25 mg, 0.10 mmol), TFA (8 μL, 0.10 mmol), 5-phenyltetrazole (730 mg, 5.00 mmol) and $LiBH_4$ (109 mg, 5.00 mmol). Yield: 78%. $[\alpha]_D^{20}$ = +30.3 (*c*=1.0, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 300MHz): 1.57 (d, 3H, *J*=7.1 Hz); 2.11 (m, 1H); 2.41 (m, 1H); 3.78 (m, 2H); 3.84 (m, 1H); 5.35 (m, 1H); 7.26 (m, 3H); 8.09 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75MHz): 20.6; 38.7; 57.7; 58.3; 126.8; 127.3; 128.9; 130.3; 164.8. IR ($CHCl_3$): ν, cm^{-1} 3386 (OH). MS (EI) *m/z* (rel. Int.): 190 (M^+-28, 14), 175 (11), 145 (56), 104 (100), 89 (12), 77 (14), 63 (11). HRMS: Calcd for $C_{11}H_{14}N_4O$: 218.1168. Found: 218.1175.

Determination of enantiomeric excess was carried out on its corresponding acetate prepared from **1a** (100 mg, 0.46 mmol) and Ac_2O (0.11 mL, 1.20 mmol).

Yield: 89%. ^{1}H-NMR ($CDCl_3$, 300MHz): 1.58 (d, 3H, *J*=7.0 Hz); 1.88 (s, 3H); 2.10 (m, 1H); 2.43 (m, 1H); 3.84 (m, 1H); 4.09 (m, 1H); 5.16 (m, 1H); 7.24 (m, 3H); 8.12 (d, 2H, *J*=7.8 Hz). ^{13}C-NMR ($CDCl_3$, 75MHz): 20.5; 20.6; 34.9; 57.9; 60.6; 126.7; 128.8; 130.2; 164.9; 170.6. IR ($CHCl_3$): ν, cm^{-1} 1739 (C=O). MS (EI) *m*/*z* (rel. Int.): 232 (M^+-28, 6), 217 (9), 202 (18), 160 (11), 145 (46), 112 (9), 104 (100), 89 (11), 77 (12), 63 (7). e.e.: 84 %. (Chiralcel OJ column, UV detector): Flow rate 0.85 mL·min^{-1}, hexanes/*i*-PrOH 95:5). Retention time for the (3*S*) isomer: t_R = 27.66 min Retention time for the (3*R*) isomer: t_R = 31.52 min.

(3*S*)-3-(5-Phenyltetrazol-2-yl)-pentan-1-ol (1b).



1b

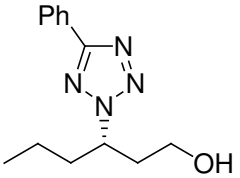
Adduct **1b** (155 mg, 0.67 mmol) was prepared according to the general procedure using (*E*)-2-pentenal (98 μL, 1.00 mmol), catalyst **2** (25 mg, 0.10 mmol), TFA (8 μL, 0.10 mmol), 5-phenyltetrazole (730 mg, 5 mmol) and $LiBH_4$ (109 mg, 5.00 mmol). Yield: 67%. $[\alpha]_D^{20}$ = +15.5 (*c*=1.0, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 300MHz): 0.80 (t, 3H, *J*=7.3 Hz); 2.03 (m, 1H); 2.23 (m, 2H); 3.41 (m, 1H); 3.05 (bs, 1H); 3.37 (m, 1H); 3.63 (m, 1H); 5.03 (m, 1H); 7.45 (m, 3H); 8.10 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75MHz): 10.4; 28.1; 37.1; 58.3; 63.7; 126.8; 127.4; 128.9; 130.3; 164.9. IR ($CHCl_3$): ν, cm^{-1} 3410 (OH). MS (EI) *m*/*z* (rel. Int.): 204 (M^+-28, 11), 175 (48), 159 (26), 104 (100), 89 (10), 77 (12), 72 (10), 56 (9). HRMS: Calcd for $C_{12}H_{16}N_4O$: 232.1324. Found: 232.1317.

Determination of enantiomeric excess was carried out on its corresponding acetate prepared from **1b** (100 mg, 0.43 mmol) and Ac_2O (0.11 mL, 2.37 mmol).

Yield: 87%. ^{1}H-NMR ($CDCl_3$, 300MHz): 0.79 (t, 3H, *J*=7.1 Hz); 1.95 (s, 3H); 2.01 (m, 1H); 2.11 (m, 1H); 2.27 (m, 1H); 2.48 (m, 1H); 3.84 (m, 1H); 4.08 (m, 1H); 4.92 (m, 1H); 7.49 (m, 3H); 8.12 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75MHz): 10.3; 20.8; 28.2; 33.4; 60.7; 63.9; 126.8; 127.5; 128.9; 130.3; 165.1; 170.7. IR ($CHCl_3$): ν, cm^{-1} 1739 (C=O). MS (EI) *m*/*z* (rel. Int.): 246 (M^+-28, 5), 207 (11), 157 (23), 147 (10), 126 (11), 104 (100), 89 (11), 77 (11), 54 (16).

e.e.: 98 %. (Chiralcel OJ column, UV detector): Flow rate 1.00 mL·min^{-1}, hexanes/*i*-PrOH 97:3). Retention time for the (3*S*) isomer: t_R = 25.93 min Retention time for the (3*R*) isomer: t_R = 28.32 min.

(3*S*)-3-(5-Phenyltetrazol-2-yl)-hexan-1-ol (1c).



1c

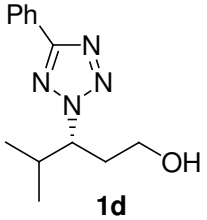
Adduct **1c** (244 mg, 0.99 mmol) was prepared according to the general procedure using (*E*)-2-hexenal (0.12 mL, 1.00 mmol), catalyst **2** (25 mg, 0.10 mmol), TFA (8 μL, 0.10 mmol), 5-phenyltetrazole (730 mg, 5 mmol) and $LiBH_4$ (109 mg, 5.00 mmol). Yield: 99%. $[\alpha]_D^{20}$ = +10.8 (*c*=1.0, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 300MHz): 0.89 (t, 3H, *J*=7.6 Hz); 1.09 (m, 1H); 1.23 (m, 1H); 1.87 (m, 1H); 2.14 (m, 2H); 2.34 (m, 1H); 3.02 (bs, 1H); 3.36 (m, 1H); 3.59 (m, 1H); 5.13 (m, 1H); 7.44 (m, 3H); 8.11 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75MHz): 13.4; 19.1; 36.8; 37.4; 58.3; 61.9; 126.8; 127.3; 128.9; 130.3; 165.1. IR ($CHCl_3$): ν, cm^{-1} 3409 (OH). MS (EI) *m*/*z* (rel. Int.): 218 (M^+-28, 11), 175 (33), 173 (33), 104 (100), 89 (14), 77 (13), 72 (13), 63 (10). HRMS: Calcd for $C_{13}H_{18}N_4O$: 246.1481. Found: 246.1488.

Determination of enantiomeric excess was carried out on its corresponding acetate prepared from **1c** (100 mg, 0.41 mmol) and Ac_2O (0.11mL, 1.20 mmol).

Yield: 87%. ^{1}H-NMR ($CDCl_3$, 300MHz): 0.90 (t, 3H, *J*=7.4 Hz); 1.12 (m, 1H); 1.25 (m, 1H); 1.88 (m, 1H); 1.95 (s, 3H); 2.11 (m, 1H); 2.26 (m, 1H); 2.47 (m, 1H); 3.89 (m, 1H); 4.09 (m, 1H); 5.02 (m, 1H); 7.46 (m, 3H); 8.13 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75MHz): 13.4; 19.0; 20.8; 33.7; 36.8; 60.7; 62.2; 126.8; 127.5; 128.9; 130.3; 165.0; 170.7. IR ($CHCl_3$): ν, cm^{-1} 1740 (C=O). MS (EI) *m*/*z* (rel. Int.): 260 (M^+-28, 3), 217 (9), 173 (32), 157 (21), 140 (9), 104 (100), 97 (10), 89 (13), 77 (11), 54 (19).

e.e.: 91 %. (Chiralcel OJ column, UV detector): Flow rate 0.85 mL·min^{-1}, hexanes/*i*-PrOH 95:5). Retention time for the (3*R*) isomer: t_R = 18.33 min. Retention time for the (3*S*) isomer: t_R = 19.95 min.

(3*R*)-3-(5-Phenyltetrazol-2-yl)-4-methylpentan-1-ol (1d).



1d

Adduct **1d** (224 mg, 0.91 mmol) was prepared according to the general procedure using (*E*)-4-methyl-2-pentenal (0.12 mL, 1.00 mmol), catalyst **2** (25 mg, 0.10 mmol), TFA (8 μL, 0.10 mmol), 5-phenyltetrazole (730 mg, 5 mmol) and $LiBH_4$ (109 mg, 5.00 mmol). Yield: 91%. $[\alpha]_D^{20}$ = +11.6 (*c*=1.0, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 300MHz): 0.80 (d, 3H, *J*=6.6 Hz); 1.03 (d, 3H, *J*=6.6 Hz); 1.92 (bs, 1H); 2.26 (m, 3H); 3.32 (m, 1H); 3.61 (m, 1H); 4.82 (m, 1H); 7.51 (m, 3H); 8.16 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75MHz): 18.9; 19.3; 33.0; 34.1; 58.7; 67.5; 126.8; 127.2; 128.9; 130.3;

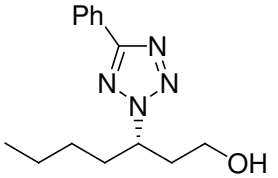
165.3. IR ($CHCl_3$): ν, cm^{-1} 3411 (OH). MS (EI) *m*/*z* (rel. Int.): 218 (M^+-28, 7), 175 (67), 147 (6), 104 (100), 89 (8), 77 (11), 72 (16), 55 (7). HRMS: Calcd for $C_{13}H_{18}N_4O$: 246.1481. Found: 246.1485.

Determination of enantiomeric excess was carried out on its corresponding acetate prepared from **1d** (100 mg, 0.41 mmol) and Ac_2O (0.11 mL, 1.20 mmol).

Yield: 90%. ^{1}H-NMR ($CDCl_3$, 300MHz): 0.79 (d, 3H, *J*=6.7 Hz); 0.99 (d, 3H, *J*=6.7 Hz); 1.89 (s, 3H); 2.28 (m, 2H); 2.48 (m, 1H); 3.77 (m, 1H); 4.03 (m, 1H); 4.73 (m, 1H); 7.42 (m, 3H); 8.12 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75MHz): 18.6; 19.2; 20.7; 30.6; 33.0; 60.9; 67.8; 126.8; 127.5; 128.8; 130.2; 164.8; 170.6. IR ($CHCl_3$): ν, cm^{-1} 1739 (C=O). MS (EI) *m*/*z* (rel. Int.): 260 (M^+-28, 2), 217 (36), 179 (9), 157 (32), 104 (100), 87 (12), 77 (10), 54 (22).

e.e.: 99 %. (Chiralcel OJ column, UV detector): Flow rate 0.85 mL·min^{-1}, hexanes/*i*-PrOH 95:5). Retention time for the (3*S*) isomer: t_R = 17.92 min. Retention time for the (3*R*) isomer: t_R = 20.48 min.

(3*S*)-3-(5-Phenyltetrazol-2-yl)-heptan-1-ol (1e).



1e

Adduct **1e** (205 mg, 0.79 mmol) was prepared according to the general procedure using (*E*)-2-heptenal (0.14 mL, 1.00 mmol), catalyst **2** (25 mg, 0.10 mmol), TFA (8 μL, 0.10 mmol), 5-phenyltetrazole (730 mg, 5 mmol) and $LiBH_4$ (109 mg, 5.00 mmol). Yield: 79%. $[\alpha]_D^{20}$ = +4.0 (*c*=1.0, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 300MHz): 0.83 (t, 3H, *J*=7.3 Hz); 1.06 (m, 1H); 1.27 (m, 3H); 1.92 (m, 1H); 2.14 (m, 2H); 2.29 (m, 1H); 2.66 (bs, 1H); 3.37 (m, 1H); 3.61 (m, 1H); 5.11 (m, 1H); 7.45 (m, 3H); 8.13 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75MHz): 13.8; 22.1; 27.9; 34.5; 37.4; 58.4; 62.1; 126.8; 127.2; 128.9; 130.3; 165.7. IR ($CHCl_3$): ν, cm^{-1} 3403 (OH). MS (EI) *m*/*z* (rel. Int.): 232 (M^+-28, 6), 187 (46), 175 (23), 159 (10), 144 (15), 104 (100), 89 (12), 77 (14), 72 (11), 57 (12). HRMS: Calcd for $C_{14}H_{20}N_4O$: 260.1637. Found: 260.1633.

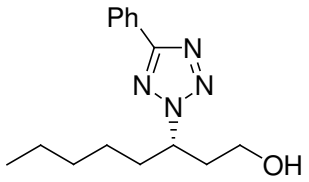
Determination of enantiomeric excess was carried out on its corresponding acetate prepared from **1e** (100 mg, 0.39 mmol) and Ac_2O (0.11 mL, 1.20 mmol).

Yield: 92%. ^{1}H-NMR ($CDCl_3$, 300MHz): 0.84 (t, 3H, *J*=7.2 Hz); 1.05 (m, 1H); 1.27 (m, 3H); 1.95 (s, 3H); 2.11 (m, 1H); 2.27 (m, 1H); 2.45 (m, 1H); 3.90 (m, 1H); 4.10 (m, 1H); 5.00 (m, 1H); 7.46 (m, 3H); 8.16 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75MHz): 13.8; 20.8;

22.1; 27.8; 33.7; 34.6; 60.7; 62.5; 126.8; 127.5; 128.9; 130.3; 165.0; 170.7. IR ($CHCl_3$): ν, cm^{-1} 1738 (C=O). MS (EI) *m/z* (rel. Int.): 274 (M^+-28, 9), 259 (6), 217 (7), 187 (69), 170 (9), 157 (22), 144 (14), 104 (100), 89 (12), 77 (11), 57 (18), 54 (18).

e.e.: 87 %. (Chiralcel OJ column, UV detector): Flow rate 0.85 mL·min^{-1}, hexanes/*i*-PrOH 95:5). Retention time for the (3*R*) isomer: t_R = 14.37 min. Retention time for the (3*S*) isomer: t_R = 16.60 min.

(3*S*)-3-(5-Phenyltetrazol-2-yl)-octan-1-ol (1f).



1f

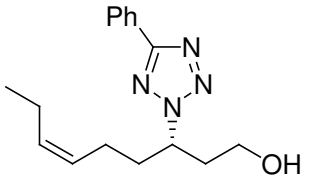
Adduct **1f** (241 mg, 0.88 mmol) was prepared according to the general procedure using (*E*)-2-octenal (0.15 mL, 1.00 mmol), catalyst **2** (25 mg, 0.10 mmol), TFA (8 μL, 0.10 mmol), 5-phenyltetrazole (730 mg, 5 mmol) and $LiBH_4$ (109 mg, 5.00 mmol). Yield: 88%. $[\alpha]_D^{20}$ = -2.4 (*c*=1.0, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 300MHz): 0.87 (t, 3H, *J*=7.1 Hz); 0.95 (m, 1H); 1.09 (m, 5H); 1.95 (m, 1H); 2.11 (m, 2H); 2.35 (m, 1H); 2.50 (bs, 1H); 3.32 (m, 1H); 3.55 (m, 1H); 5.02 (m, 1H); 7.49 (m, 3H); 8.09 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75MHz): 13.9; 22.3; 25.5; 31.1; 34.8; 37.4; 58.4; 62.2; 126.8; 127.4; 128.9; 130.3; 165.8. IR ($CHCl_3$): ν, cm^{-1} 3407 (OH). MS (EI) *m/z* (rel. Int.): 246 (M^+-28, 3), 201 (55), 257 (23), 104 (100), 89 (12), 87 (12), 77 (10), 72 (14), 54 (20). HRMS: Calcd for $C_{15}H_{22}N_4O$: 274.1794. Found: 274.1788.

Determination of enantiomeric excess was carried out on its corresponding acetate prepared from **1f** (100 mg, 0.36 mmol) and Ac_2O (0.11 mL, 1.20 mmol).

Yield: 94%. ^{1}H-NMR ($CDCl_3$, 300MHz): 0.83 (t, 3H, *J*=7.1 Hz); 1.08 (m, 1H); 1.25 (m, 5H); 1.90 (m, 1H); 1.96 (s, 3H); 2.09 (m, 1H); 2.25 (m, 1H); 2.47 (m, 1H); 3.88 (m, 1H); 4.08 (m, 1H); 5.02 (m, 1H); 7.47 (m, 3H); 8.16 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75MHz): 13.9; 20.8; 22.3; 25.3; 31.1; 33.7; 34.8; 60.8; 62.5; 126.8; 127.5; 128.9; 130.3; 165.0; 170.8. IR ($CHCl_3$) ν, cm^{-1}: 1741 (C=O). MS (EI) *m/z* (rel. Int.): 288 (M^+-28, 11), 273 (9), 259 (6), 217 (6), 201 (75), 184 (11), 157 (25), 147 (11), 104 (100), 87 (12), 77 (11), 69 (12), 54 (19).

e.e.: 85 %. (Chiralcel OJ column, UV detector): Flow rate 0.85 mL·min^{-1}, hexanes/*i*-PrOH 95:5). Retention time for the (3*R*) isomer: t_R = 11.15 min. Retention time for the (3*S*) isomer: t_R = 13.18 min.

(3*S*,6*Z*)-3-(5-Phenyltetrazol-2-yl)-6-nonen-1-ol (1g).

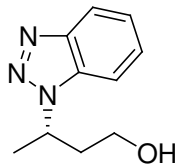


1g

Adduct **1g** (200 mg, 0.70 mmol) was prepared according to the general procedure using (6*Z*,2*E*)-2-octenal (0.16 mL, 1.00 mmol), catalyst **2** (25 mg, 0.10 mmol), TFA (8 μL, 0.10 mmol), 5-phenyltetrazole (730 mg, 5 mmol) and $LiBH_4$ (109 mg, 5.00 mmol). Yield: 70%. $[\alpha]_D^{20}$ = -19.6 (*c*=1.0, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 300MHz): 0.87 (t, 3H, *J*=7.5 Hz); 1.85 (m, 4H); 2.17 (m, 4H); 2.41 (bs, 1H); 3.36 (m, 1H); 3.58 (m, 1H); 5.09 (m, 1H); 5.17 (m, 1H); 5.24 (m, 1H); 7.43 (m, 3H); 8.12 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75MHz): 14.2; 20.5; 23.5; 34.7; 37.5; 58.4; 61.6; 126.5; 126.8; 127.6; 128.9; 130.3; 133.4; 165.7. IR ($CHCl_3$): ν, cm^{-1} 3405 (OH). MS (EI) *m*/*z* (rel. Int.): 258 (M^+-28, 2), 241 (12), 213 (15), 149 (38), 127 (23), 104 (100), 88 (25), 73 (32), 55 (21). HRMS: Calcd for $C_{16}H_{22}N_4O$: 286.1794. Found: 286.1805.

e.e.: 76 %. (Chiralcel OD column, UV detector): Flow rate 0.85 mL·min^{-1}, hexanes/*i*-PrOH 99:1). Retention time for the (3*S*) isomer: t_R = 41.95 min. Retention time for the (3*R*) isomer: t_R = 49.34 min.

(3*S*)-3-(benzotriazol-1-yl)-butan-1-ol (6).



6

Adduct **8** (101 mg, 0.53 mmol) was prepared according to the general procedure using crotonaldehyde (83 μL, 1.00 mmol), catalyst **2** (25 mg, 0.10 mmol), TFA (8 μL, 0.10 mmol), benzotriazole (595 mg, 5.00 mmol) and $LiBH_4$ (109 mg, 5.00 mmol). Yield: 53%. ^{1}H-NMR ($CDCl_3$, 300MHz): 1.73 (d, 3H, *J*=7.2 Hz); 2.25 (m, 2H); 2.41 (m, 1H); 2.85 (bs, 1H); 3.31 (m, 1H); 3.64 (m, 1H); 5.21 (m, 1H); 7.31 (t, 1H, *J*=7.7 Hz); 7.39 (t, 1H, *J*=7.7 Hz); 7.45 (d, 1H, *J*=8.3 Hz); 7.99 (d, 1H, *J*=8.3 Hz). ^{13}C-NMR ($CDCl_3$, 75MHz): 20.8; 38.7; 52.2; 58.5; 109.9; 119.8; 124.0; 127.1; 132.7; 145.7. IR ($CHCl_3$): ν, cm^{-1} 3389 (OH). HRMS: Calcd for $C_{10}H_{13}N_3O$: 191.1059. Found: 191.1065.

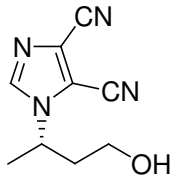
Determination of enantiomeric excess was carried out on its corresponding acetate prepared from **6** (80 mg, 0.42 mmol) and Ac_2O (0.11 μl, 1.20 mmol).

Yield: 93%. ^{1}H-NMR ($CDCl_3$, 300MHz): 1.68 (t, 3H, *J*=7.3 Hz); 1.91 (S, 3H); 2.35 (m, 1H); 2.53 (m, 1H); 3.85 (m, 1H); 4.17 (m, 1H); 5.07 (m, 1H); 7.39 (t, 1H, *J*=7.7 Hz); 7.71 (t, 1H, *J*=7.7 Hz); 7.68 (d, 1H, *J*=8.2 Hz); 8.09 (d, 1H, *J*=8.2 Hz). ^{13}C-NMR

($CDCl_3$, 75MHz): 20.7; 20.9; 35.0; 52.7; 61.0; 109.4; 120.0; 123.8; 127.0; 132.4; 145.9; 170.5. IR ($CHCl_3$) ν, cm^{-1}: 1746 (C=O). MS (EI) *m/z* (rel. Int.): 288 (M^+-28, 11), 273 (9), 259 (6), 217 (6), 201 (75), 184 (11), 157 (25), 147 (11), 104 (100), 87 (12), 77 (11), 69 (12), 54 (19).

e.e.: 66 %. (Chiralcel OD column, UV detector): Flow rate 1.00 mL·min^{-1}, hexanes/*i*-PrOH 99:1). Retention time for the (3*S*) isomer: t_R = 46.63 min. Retention time for the (3*R*) isomer: t_R = 50.45 min.

(3*S*)-1-(3-Hydroxy-1-methylpropyl)-1*H*-imidazole-4,5-dicarbonitrile (8).



8

Adduct **8** (120 mg, 0.63 mmol) was prepared according to the general procedure using crotonaldehyde (83 μL, 1.00 mmol), catalyst **2** (25 mg, 0.10 mmol), TFA (8 μL, 0.10 mmol), 4,5-dicyanoimidazole (118 mg, 1.00 mmol) and $LiBH_4$ (175 mg, 5.00 mmol). Yield: 93%. ^{1}H-NMR ($CDCl_3$, 300MHz): 1.71 (d, 3H, *J*=7.1 Hz); 2.11 (m, 2H); 2.68 (bs, 1H); 3.42 (m, 1H); 3.67 (m, 1H); 4.75 (m, 1H); 7.81 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75MHz): 21.1; 38.5; 53.6; 57.9; 108.3; 111.3; 111.8.; 123.0; 140.5. IR ($CHCl_3$): ν, cm^{-1} 3396 (OH); 2238 (CN). HRMS: Calcd for $C_9H_{10}N_4O$: 190.0855. Found: 190.0848.

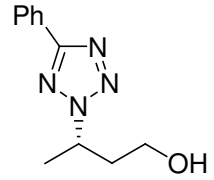
Determination of enantiomeric excess was carried out on its corresponding acetate prepared from **8** (100 mg, 0.53 mmol) and Ac_2O (0.11 mL, 1.20 mmol).

Yield: 94%. ^{1}H-NMR ($CDCl_3$, 300MHz): 1.68 (d, 3H, *J*=7.0 Hz); 2.03 (S, 3H); 2.25 (m, 2H); 3.91 (m, 1H); 4.11 (m, 1H); 4.59 (m, 1H); 7.74 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75MHz): 20.7; 21.3; 35.7; 53.5; 59.9; 108.0; 111.5; 123.4; 139.5; 170.6. IR ($CHCl_3$): ν, cm^{-1} 2237 (CN); 1738 (C=O);

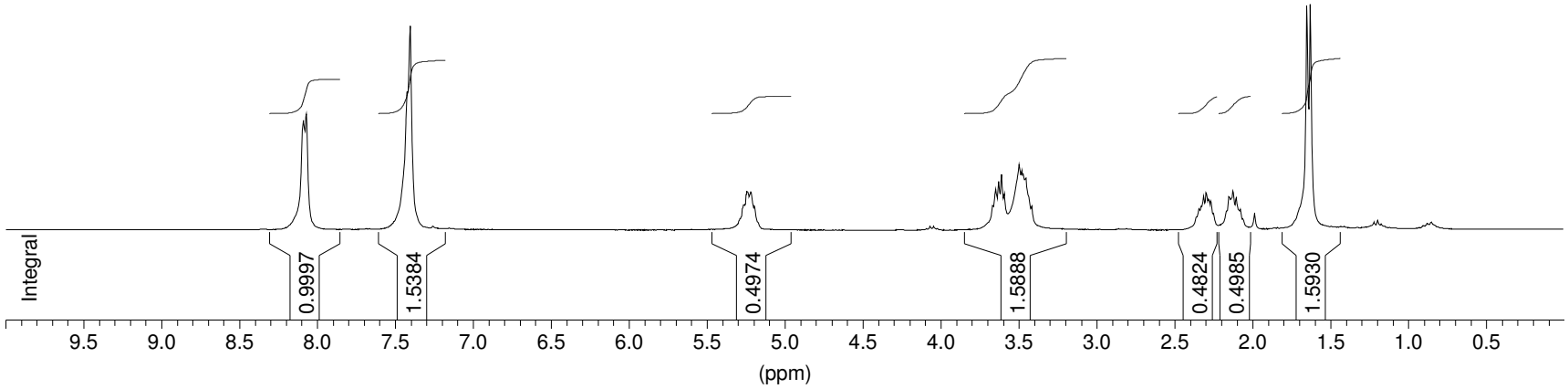
e.e.: 31 %. (Chiralcel OD column, UV detector): Flow rate 1.00 mL·min^{-1}, hexanes/*i*-PrOH 80:20). Retention time for the (3*R*) isomer: t_R = 24.18 min. Retention time for the (3*S*) isomer: t_R = 27.78 min.

4.- ^{1}H- and ^{13}C-NMR spectra of compounds 1a-g.

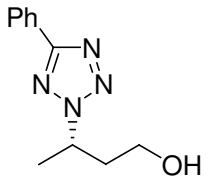
4.1.- ^{1}H-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1a**.



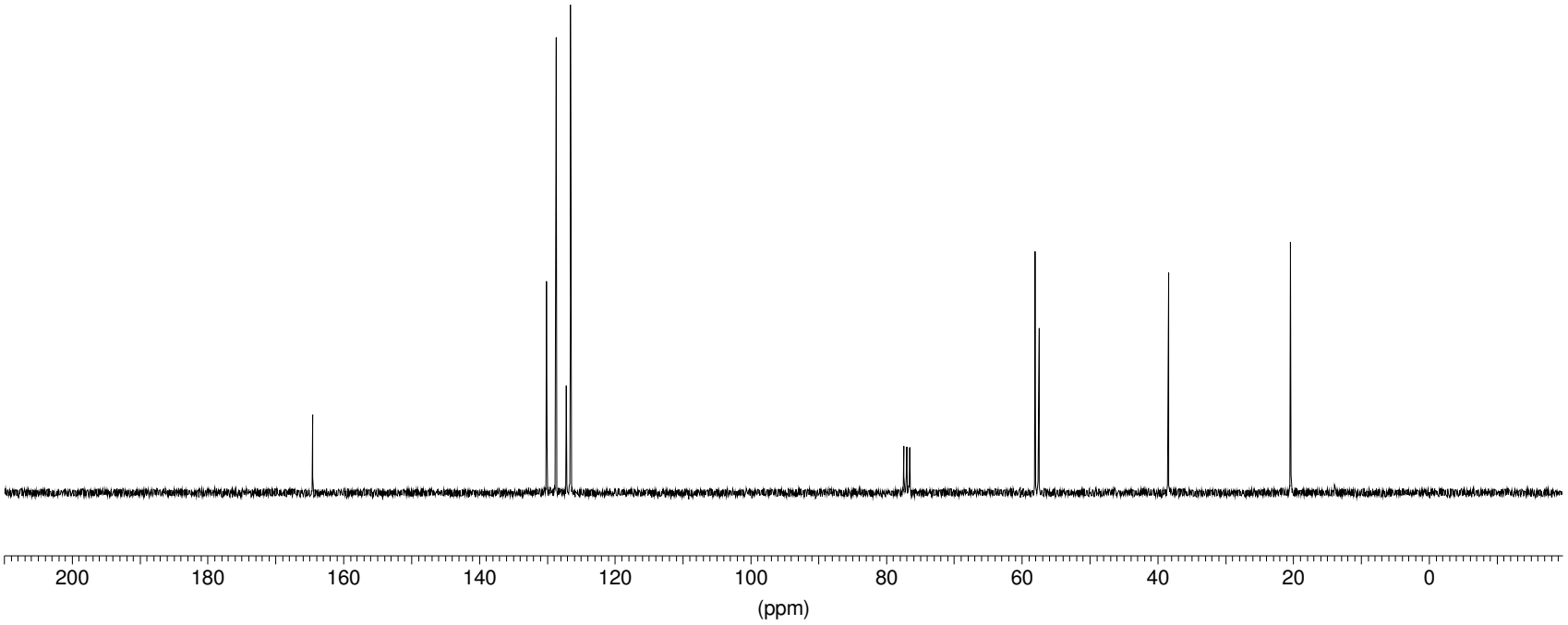
1a



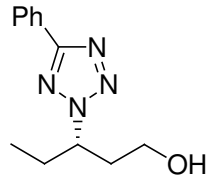
4.2.- ^{13}C-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1a**.



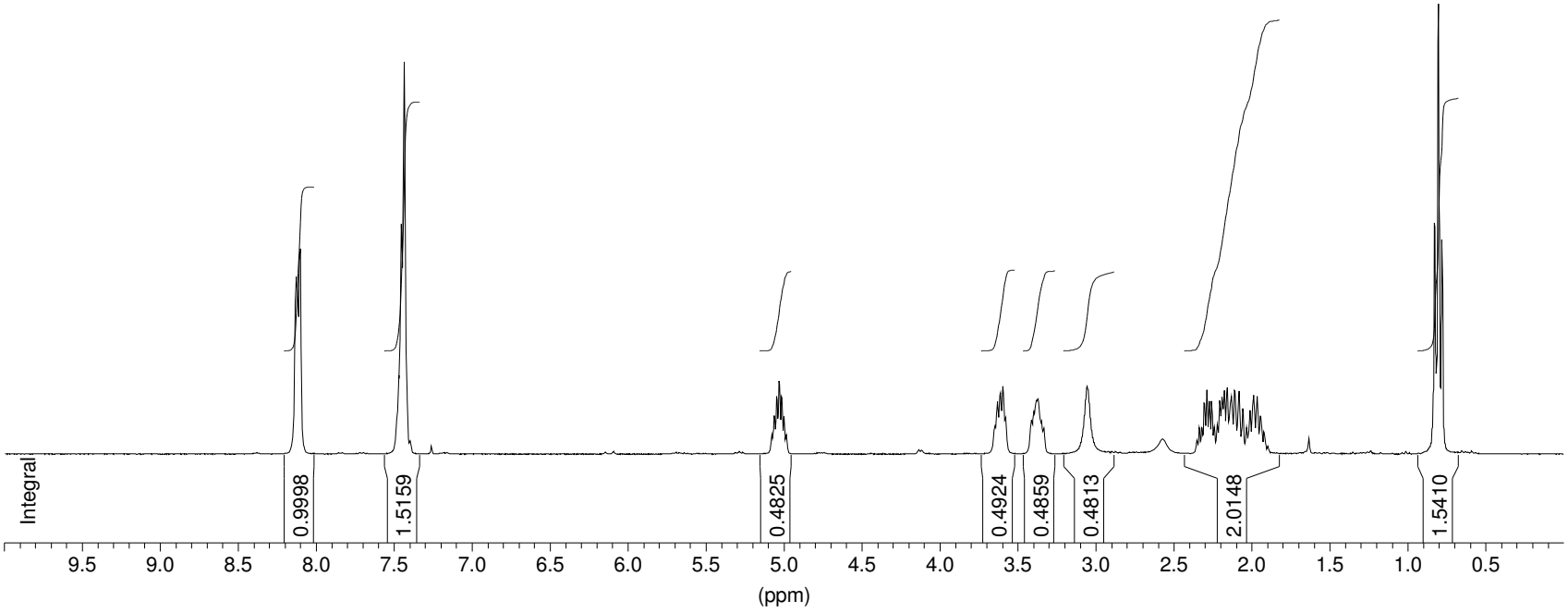
1a



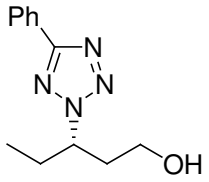
4.3.- ^{1}H-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1b**.



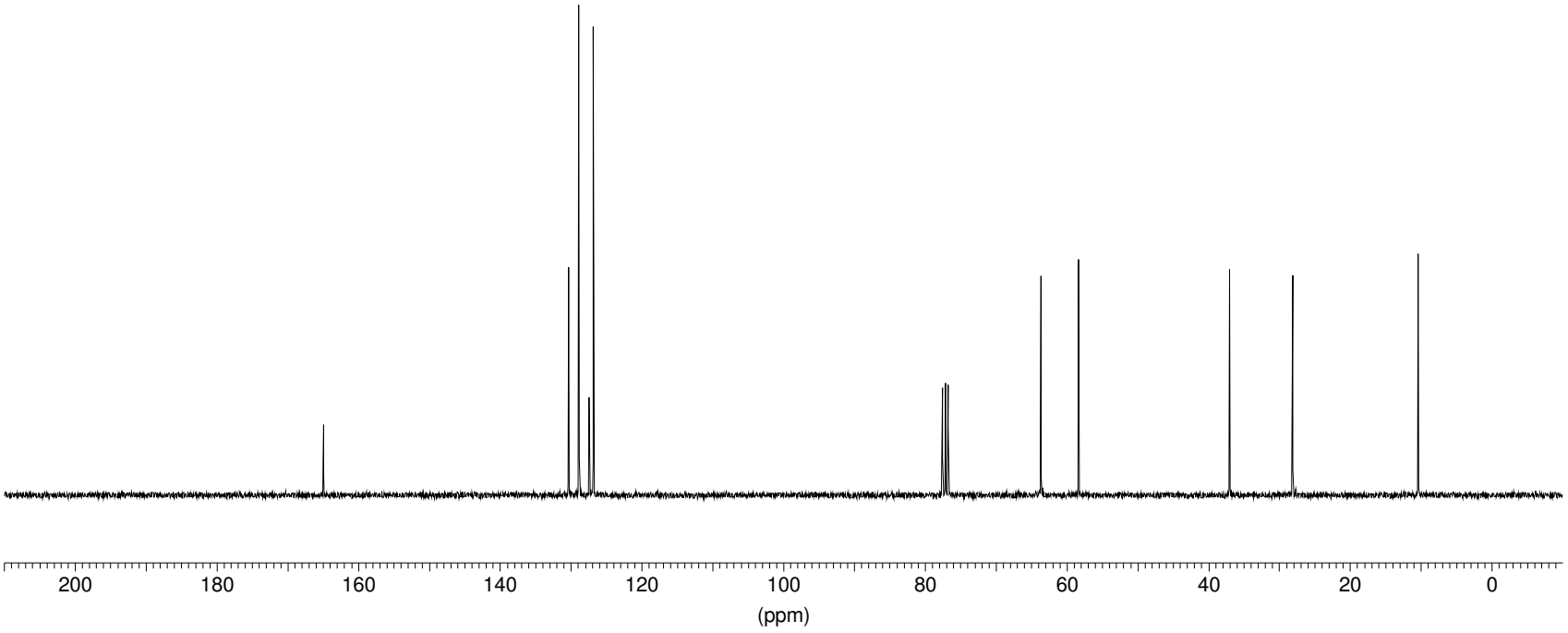
1b



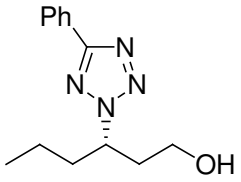
4.4.- ^{13}C-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1b**.



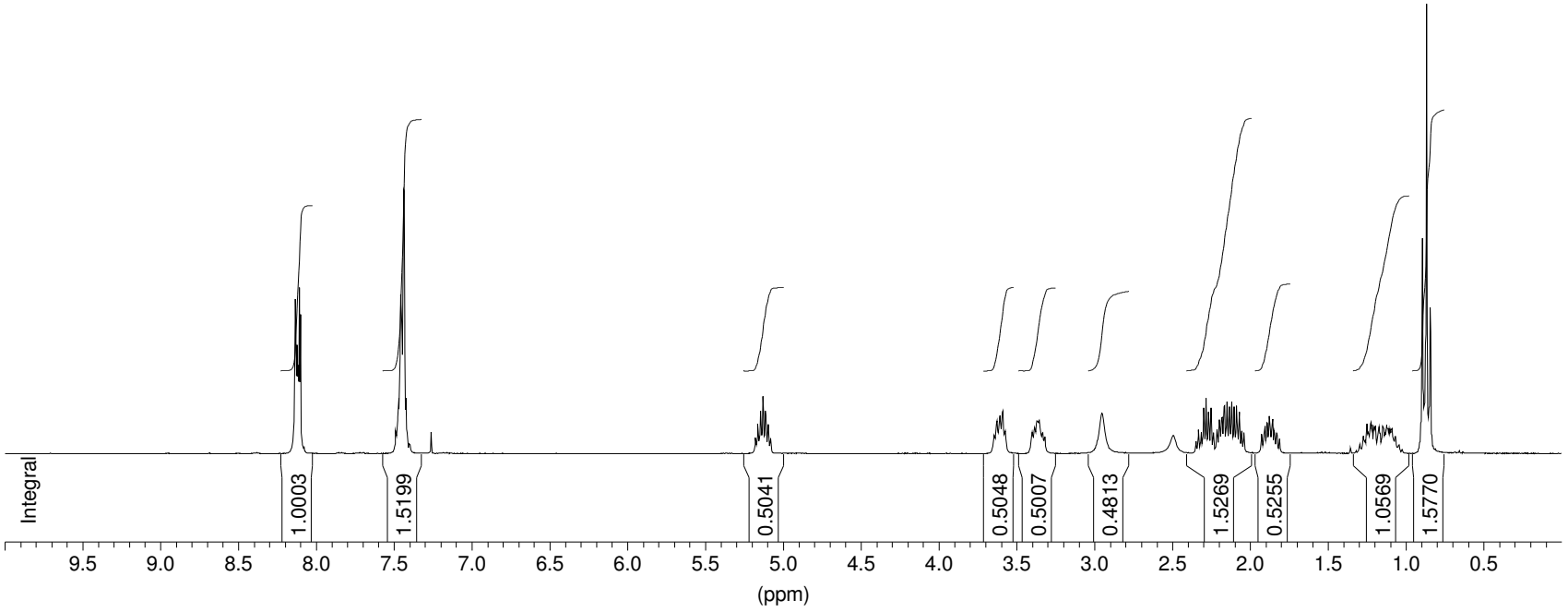
1b



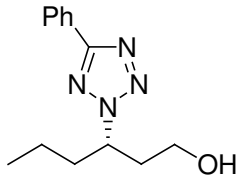
4.5.- ^{1}H-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1c**.



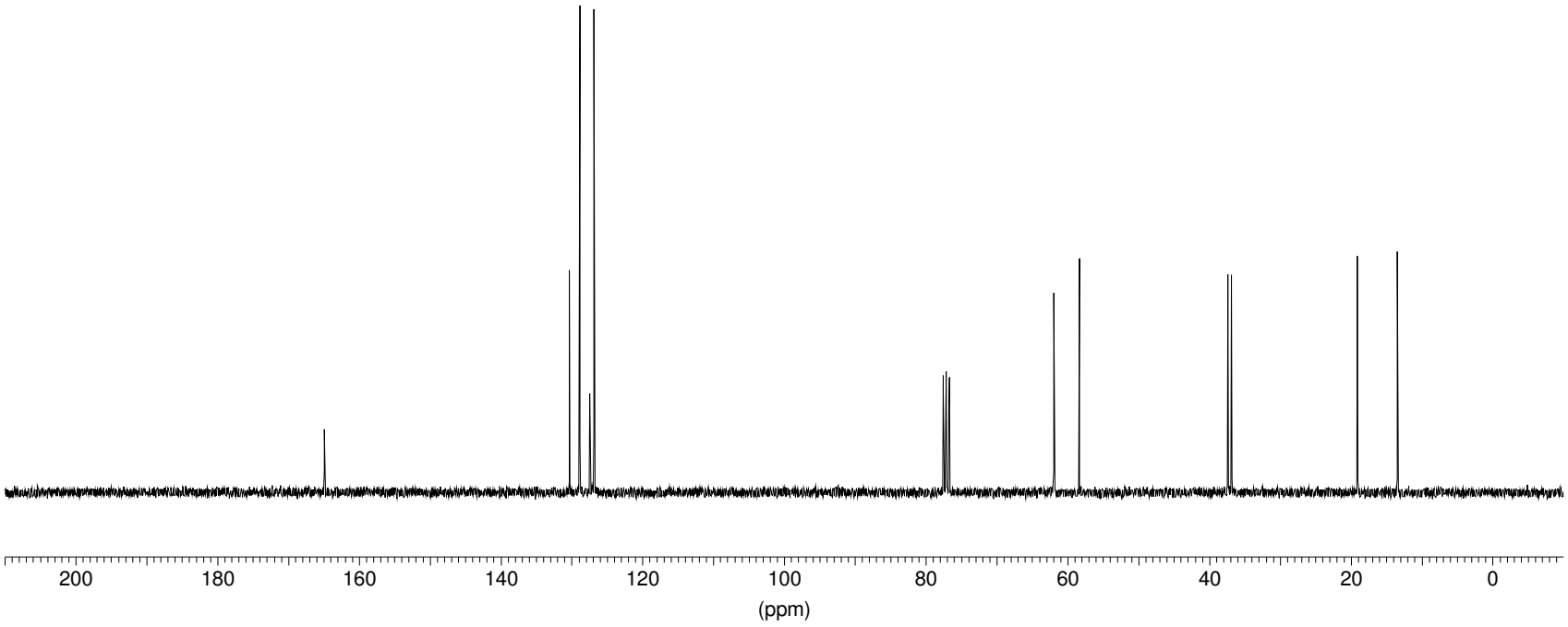
1c



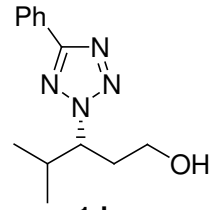
4.6.- ^{13}C-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1c**.



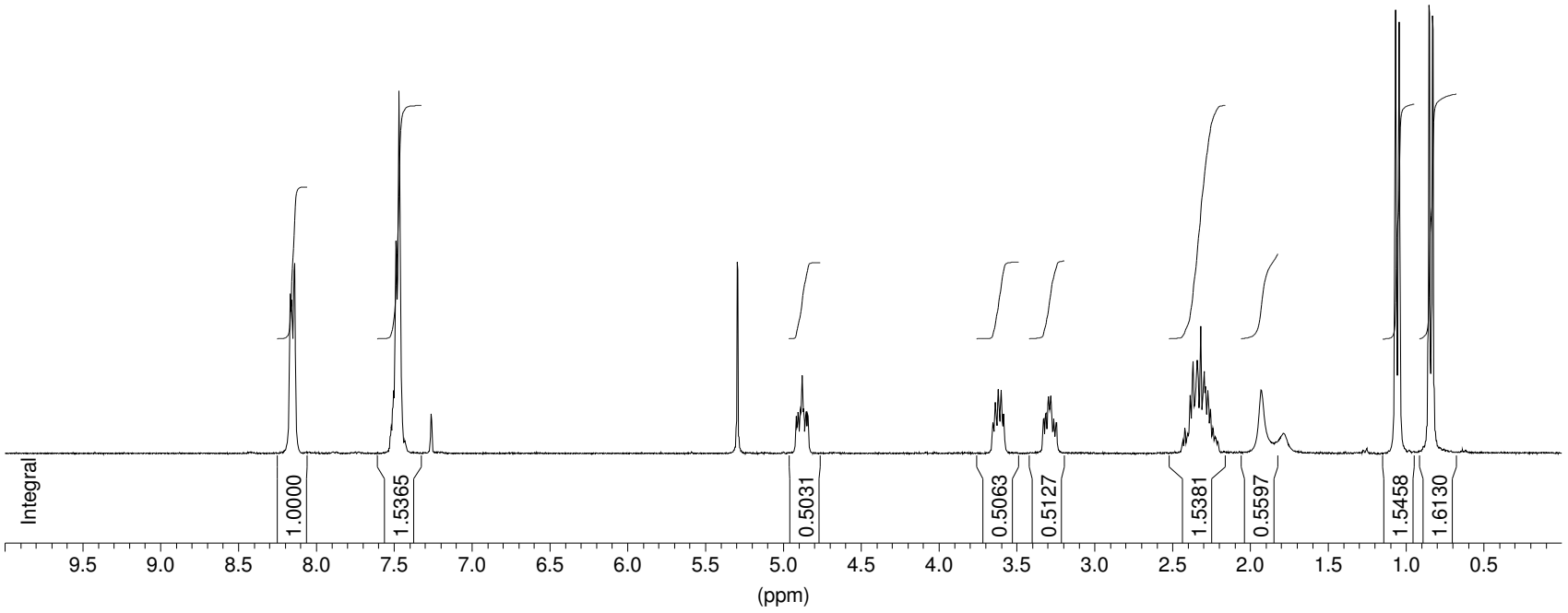
1c



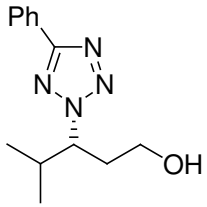
4.7.- ^{1}H-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1d**.



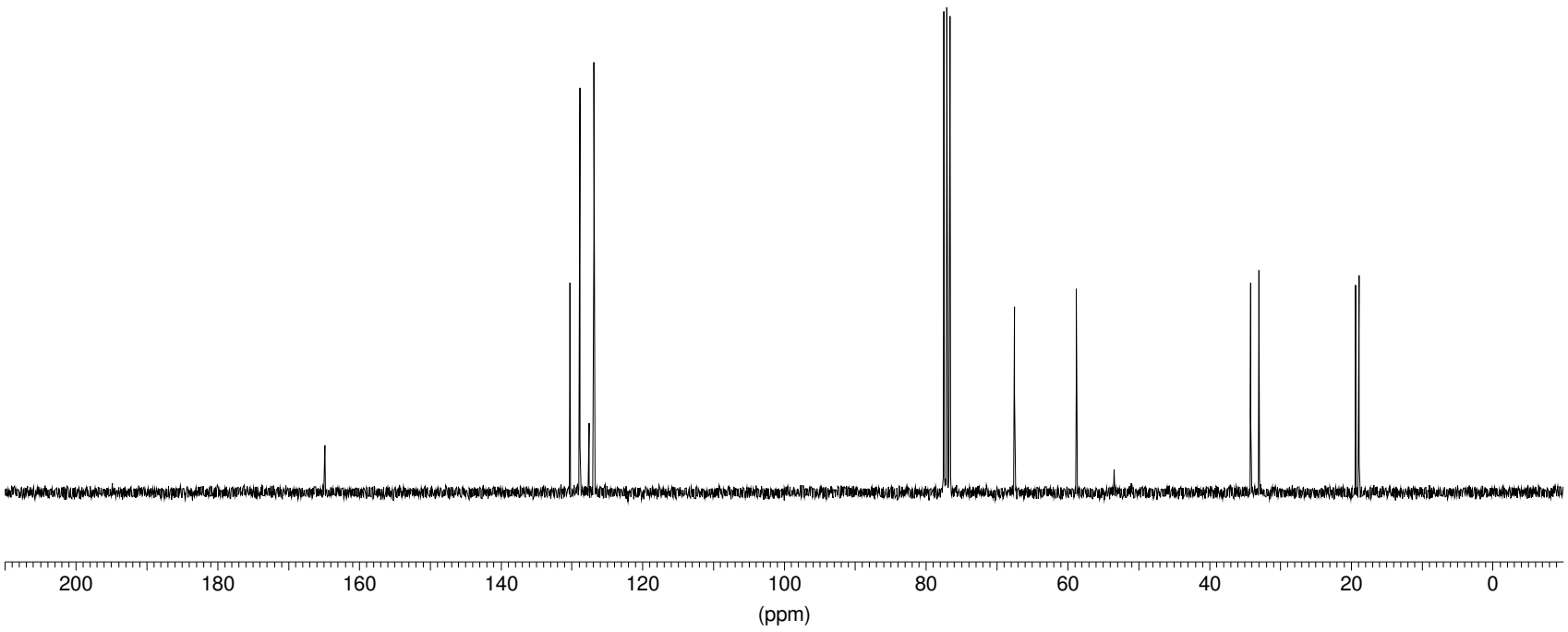
1d



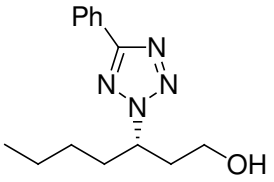
4.8.- ^{13}C-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1d**.



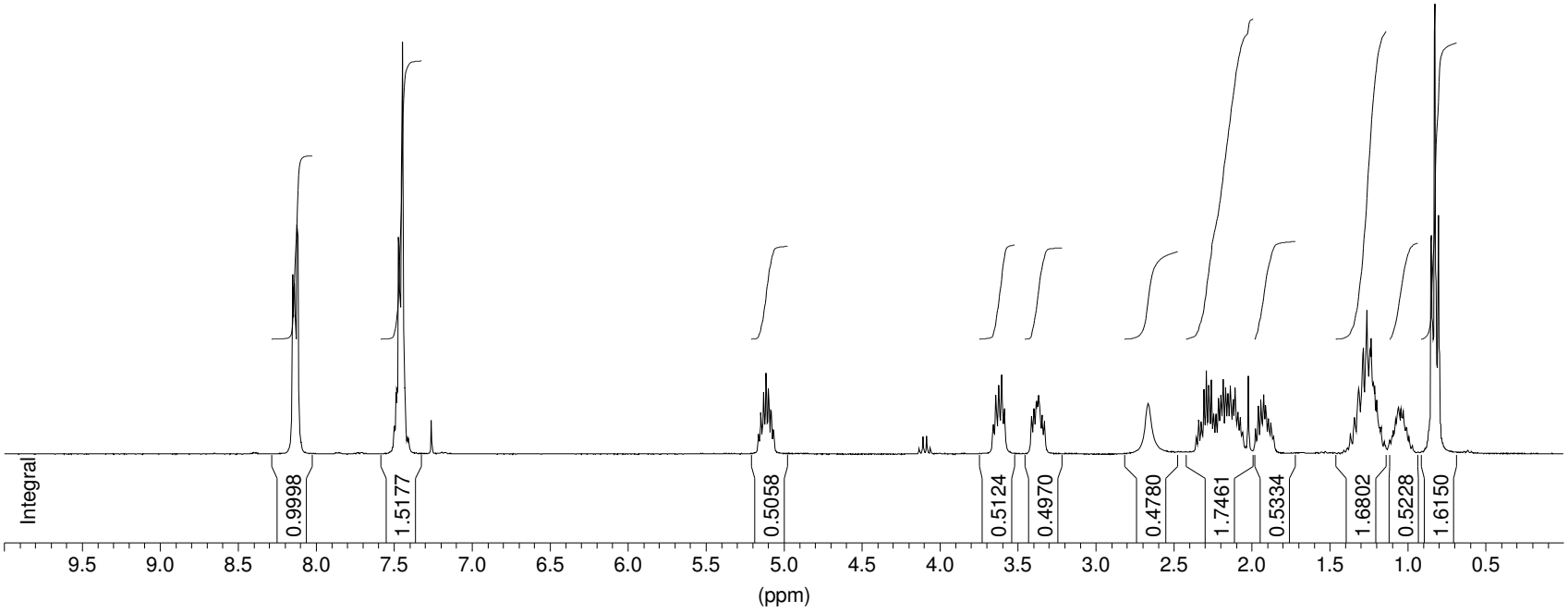
1d



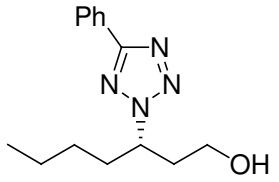
4.9.- ^{1}H-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1e**.



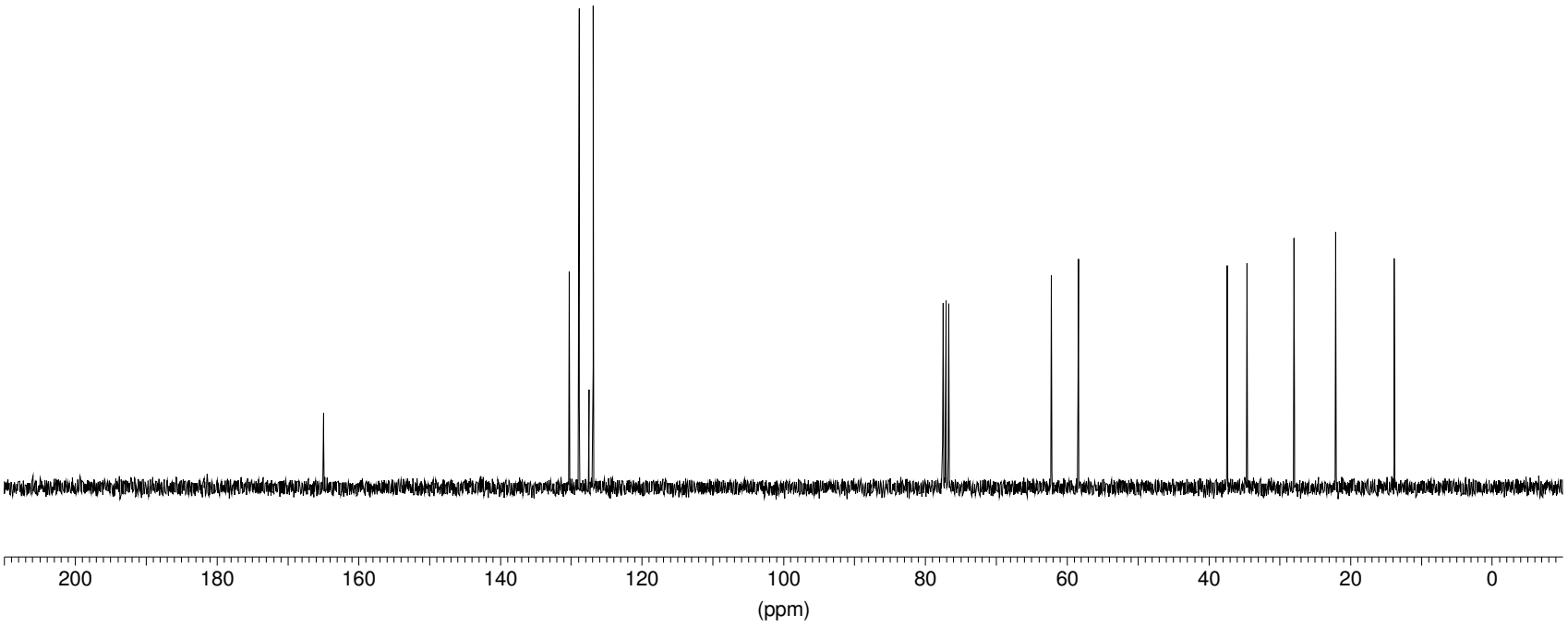
1e



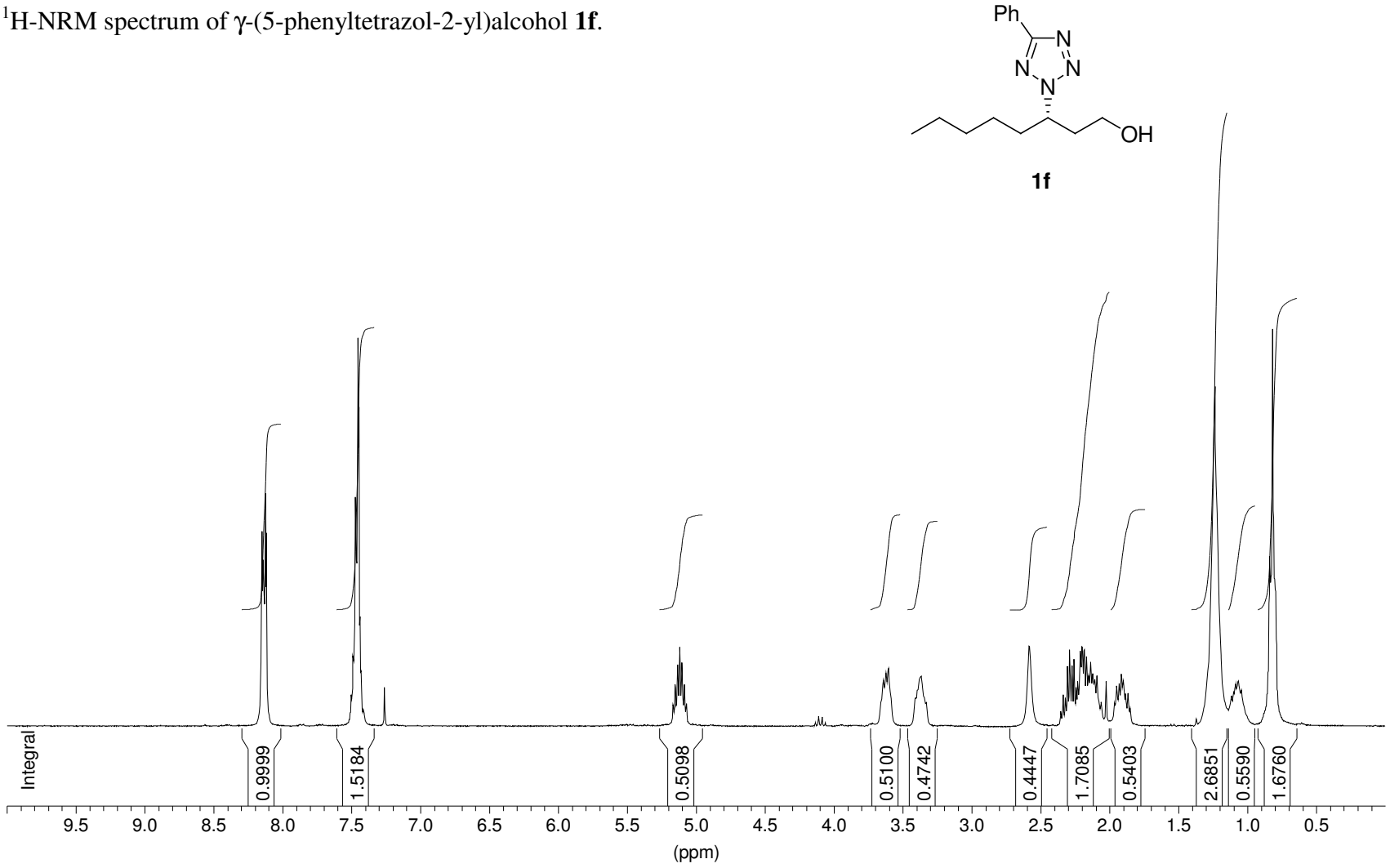
4.10.- ^{13}C-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1e**.



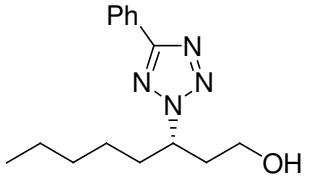
1e



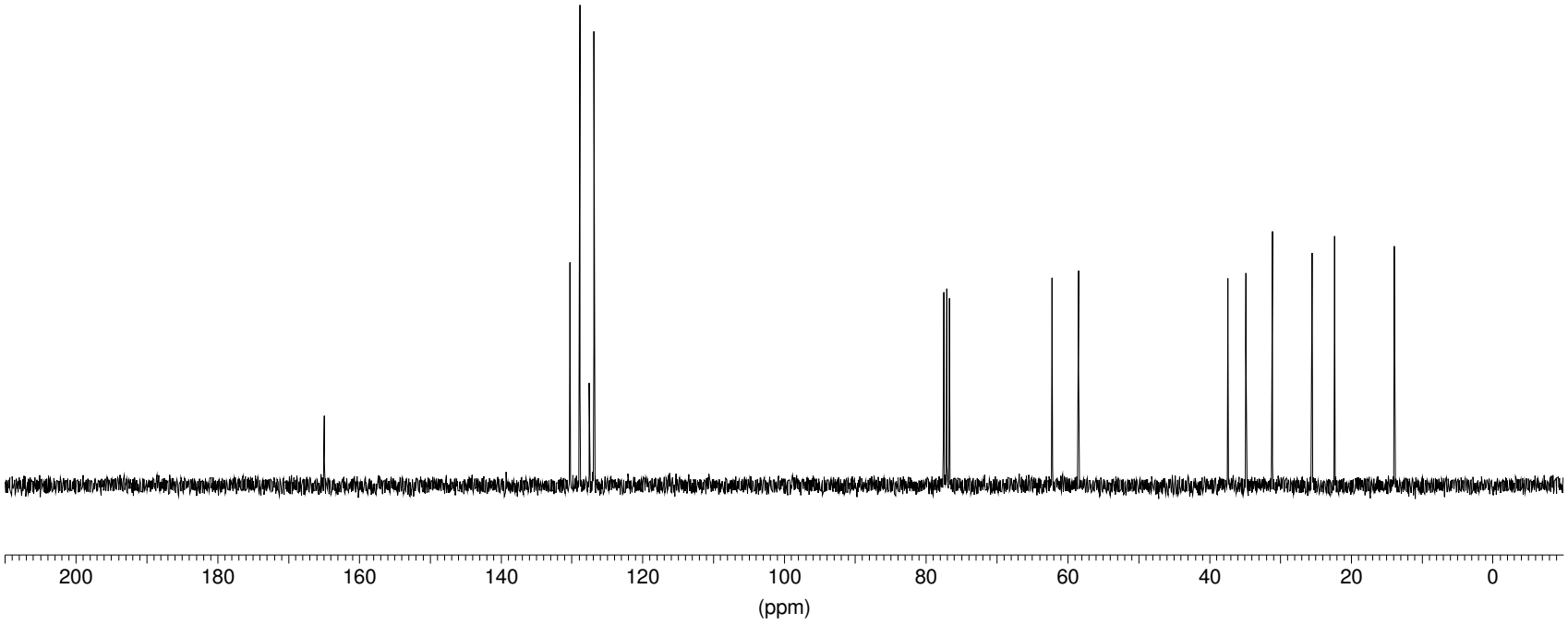
4.11.- ^{1}H-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1f**.



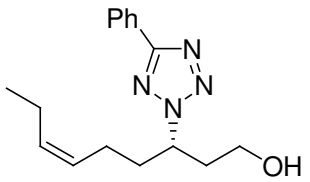
4.12.- ^{13}C-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1f**.



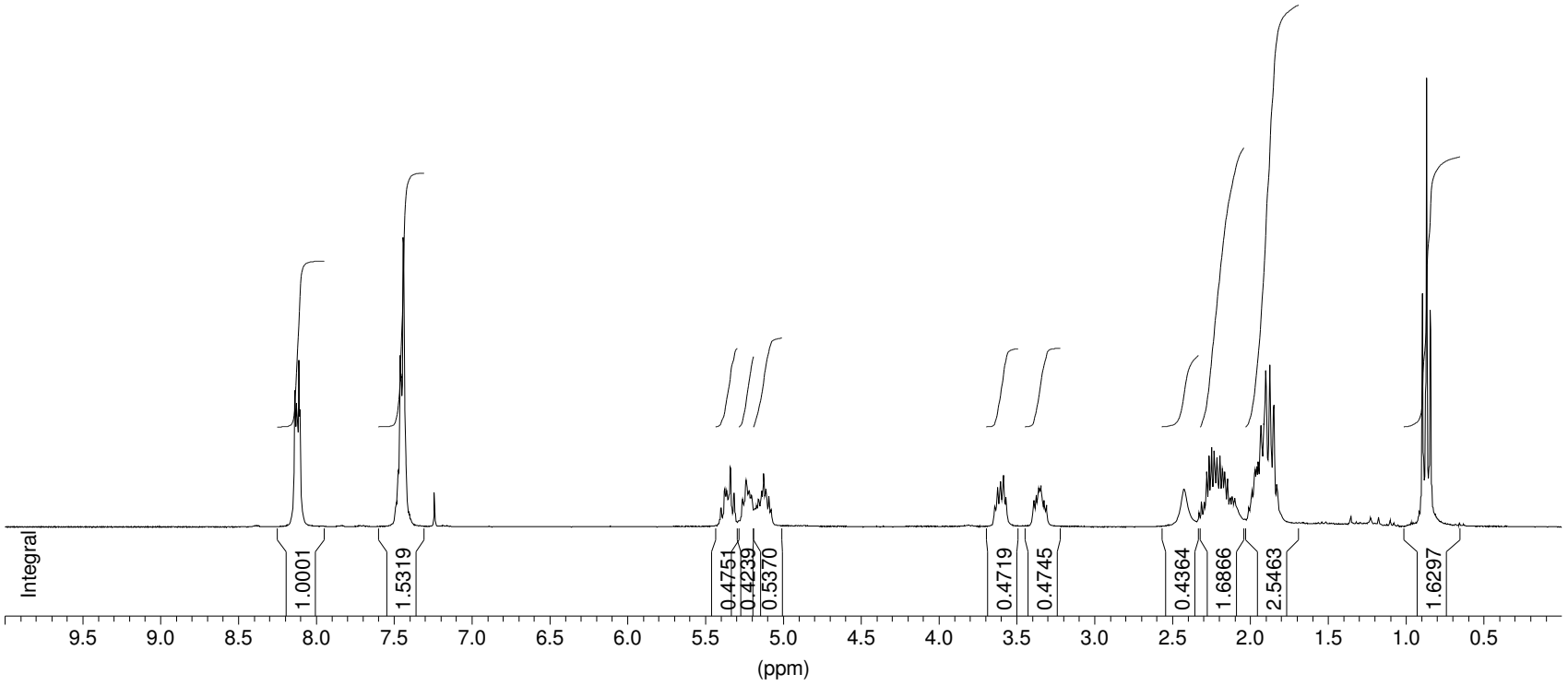
1f



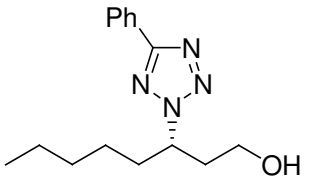
4.13.- ^{1}H-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1g**.



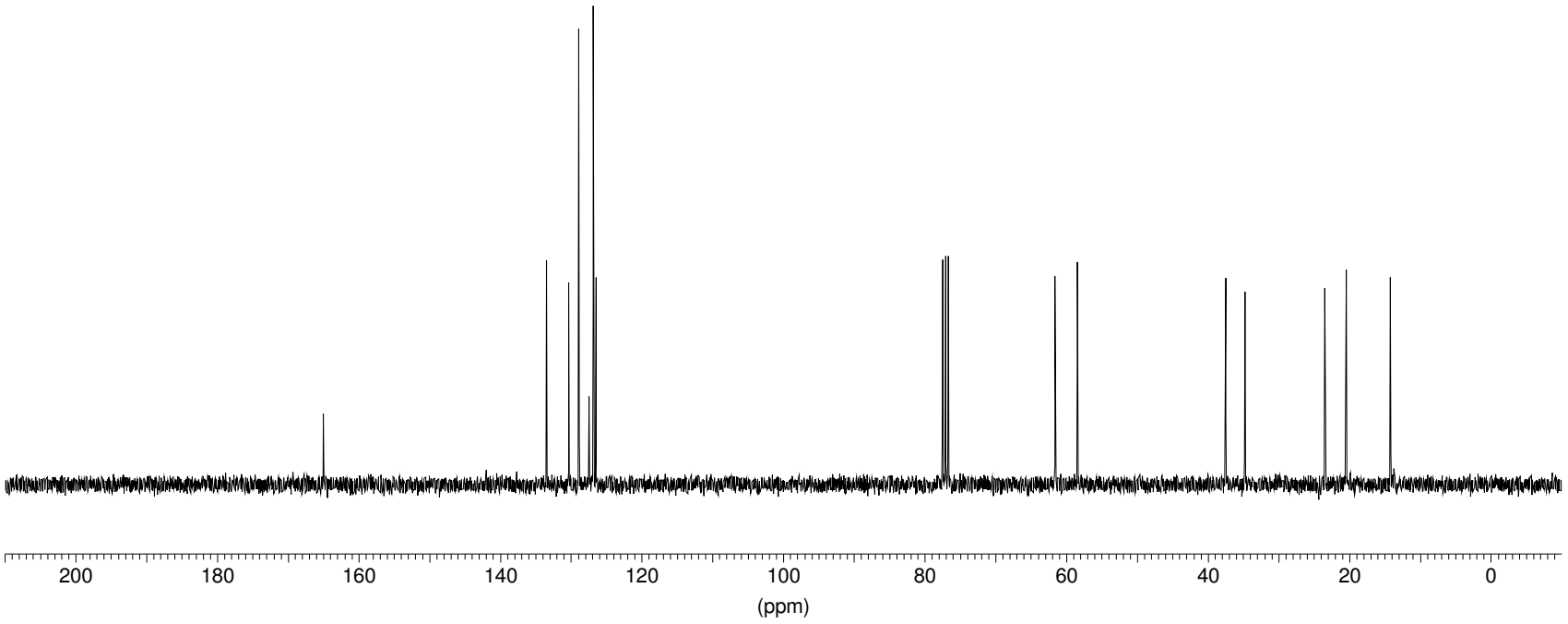
1g



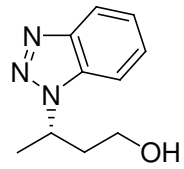
4.14.- ^{13}C-NRM spectrum of γ-(5-phenyltetrazol-2-yl)alcohol **1g**.



1f



4.15.- ^{1}H-NRM spectrum of 3-(benzotriazol-1-yl)-butan-1-ol **6**.



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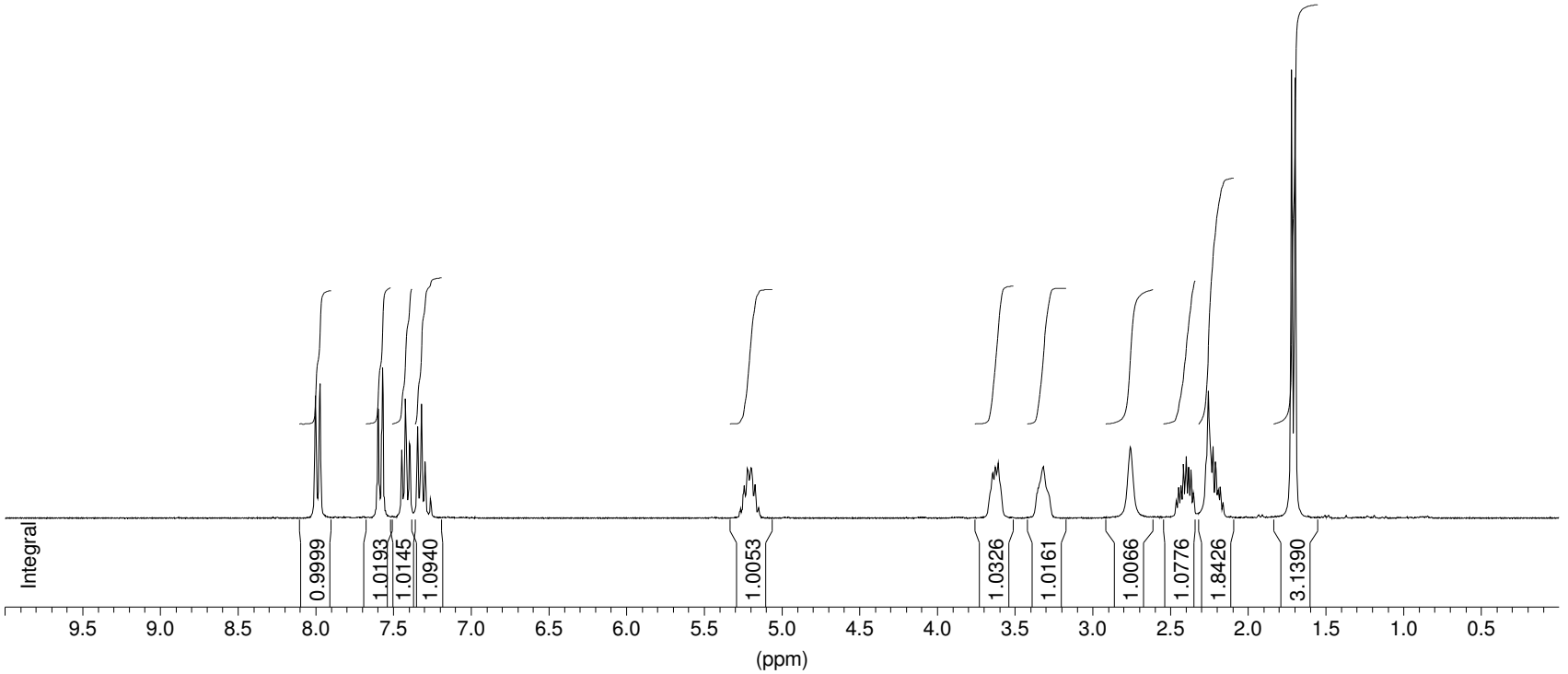
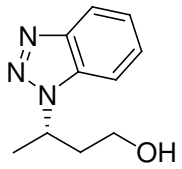
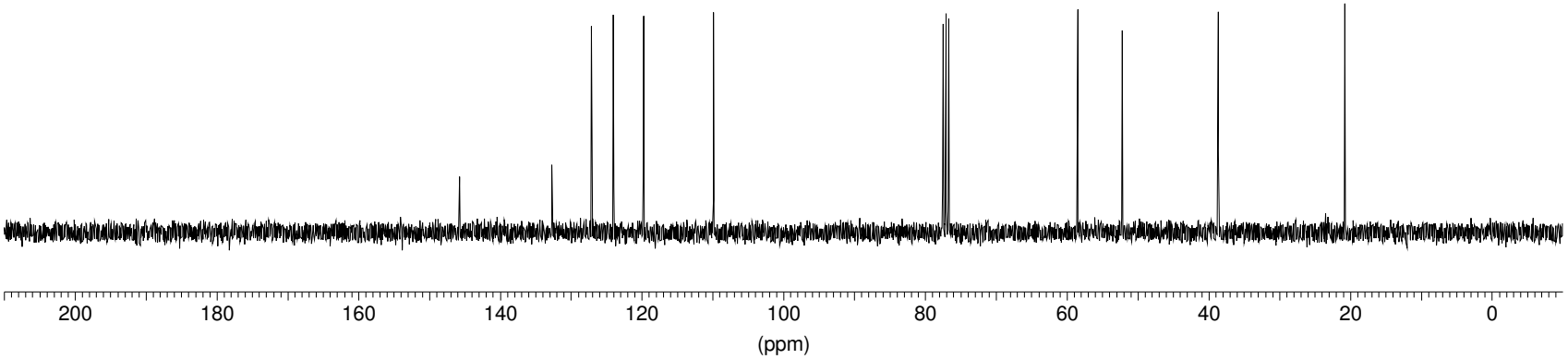


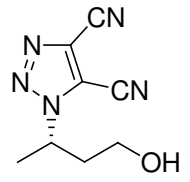
4.16.- ^{13}C-NRM spectrum of 3-(benzotriazol-1-yl)-butan-1-ol **6**.



6



4.17.- ^{1}H-NRM spectrum of 1-(3-Hydroxy-1-methylpropyl)-1H-imidazole-4,5-dicarbonitrile **8**.



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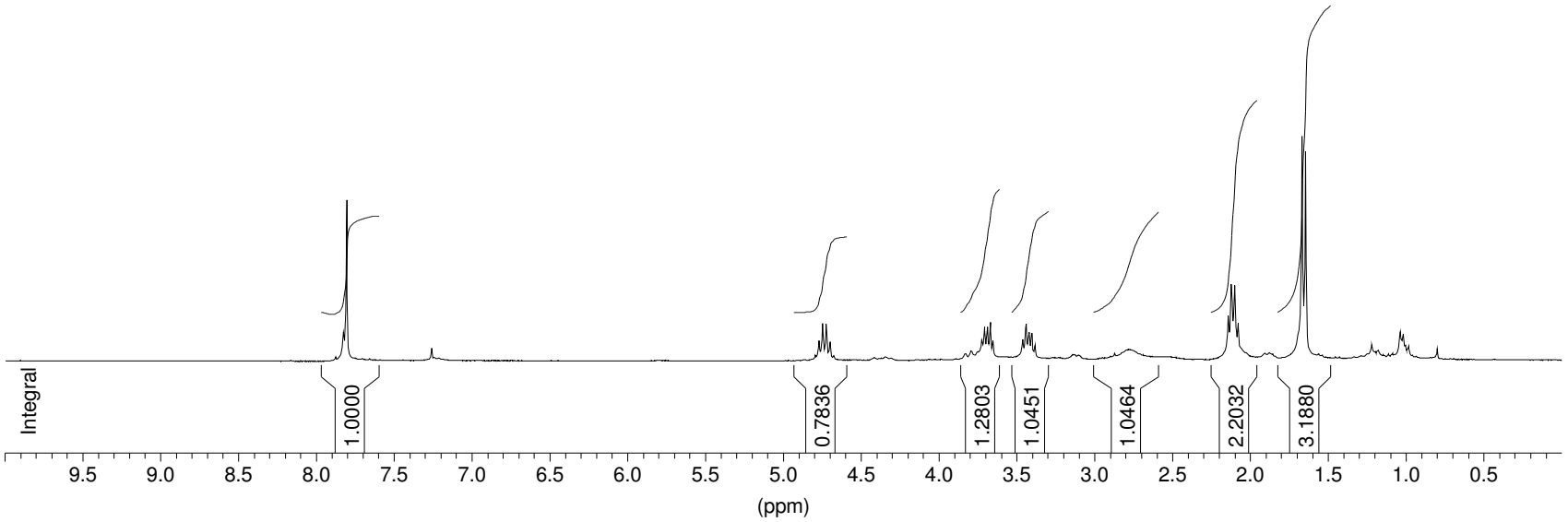
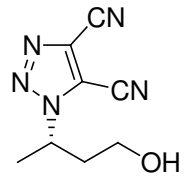


4.18.- ^{13}C-NRM spectrum of 1-(3-Hydroxy-1-methylpropyl)-1H-imidazole-4,5-dicarbonitrile **8**.



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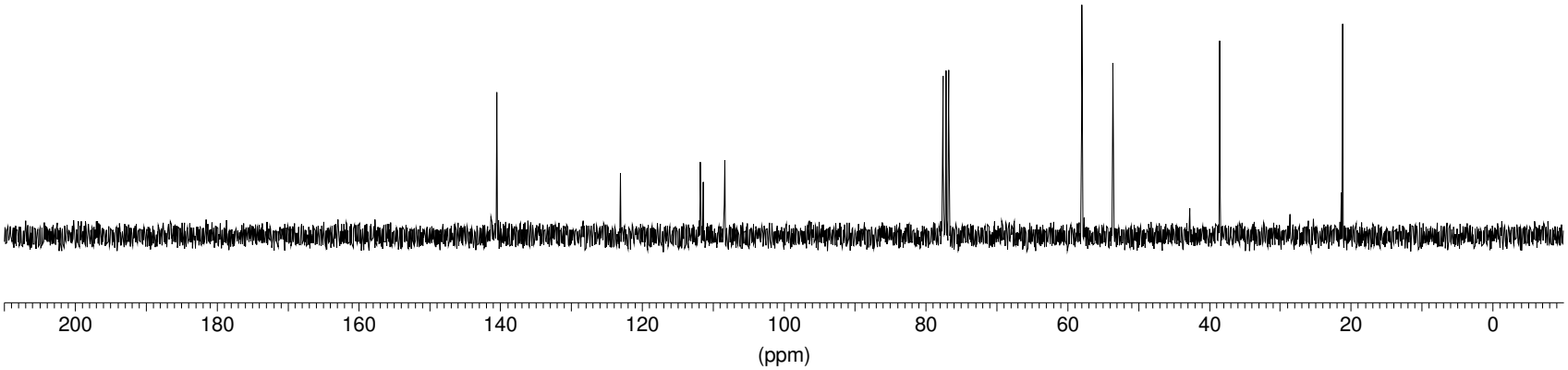
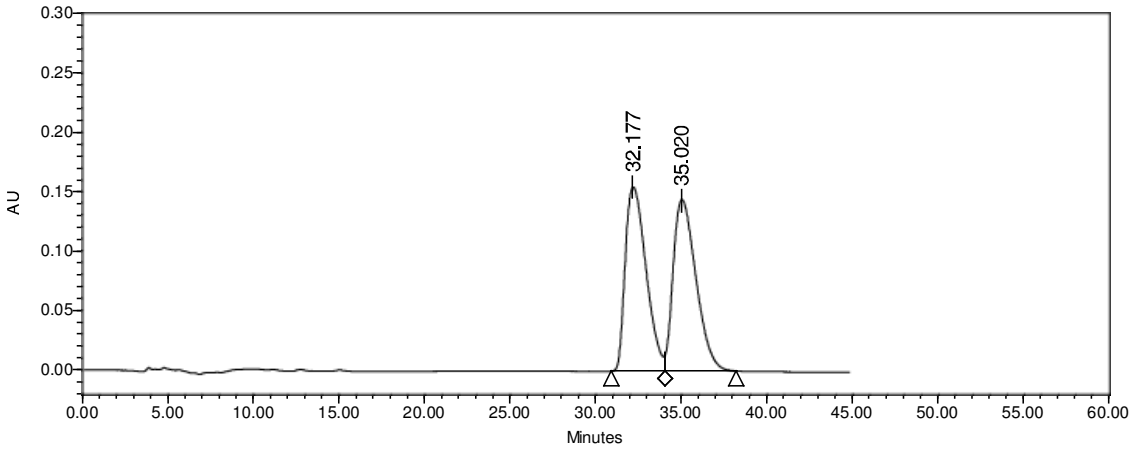


5.- Chiral HPLC chromatograms

5.1.- - Chiral HPLC chromatograms of racemic and enantioenriched **1a**.

SampleName	e584i(OJ 085 95 5)	Sample Type	Unknown
Vial	1	Date Acquired	18/01/06 4:59:25 PM
Injection	9	Acq Method Set	OJ 085 95 5
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	15/01/07 5:16:20 PM
Run Time	50.0 Minutes		

Auto-Scaled Chromatogram

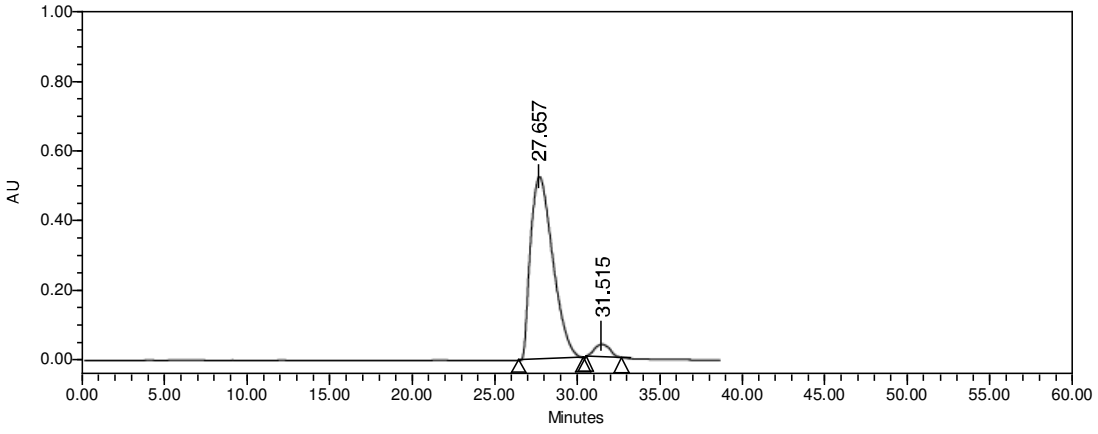


Peak Results

	RT	Area	Height	% Area
1	32.177	13118063	154882	49.72
2	35.020	13263655	143324	50.28

SampleName	UX103A(OJ 085 95 05)	Sample Type	Unknown
Vial	1	Date Acquired	20/10/06 3:47:27 PM
Injection	1	Acq Method Set	OJ 085 95 05
Injection Volume	5.00 ul	Processing Method	fenetilamida2
Channel	996	Date Processed	15/01/07 9:54:20 AM
Run Time	70.0 Minutes		

Auto-Scaled Chromatogram



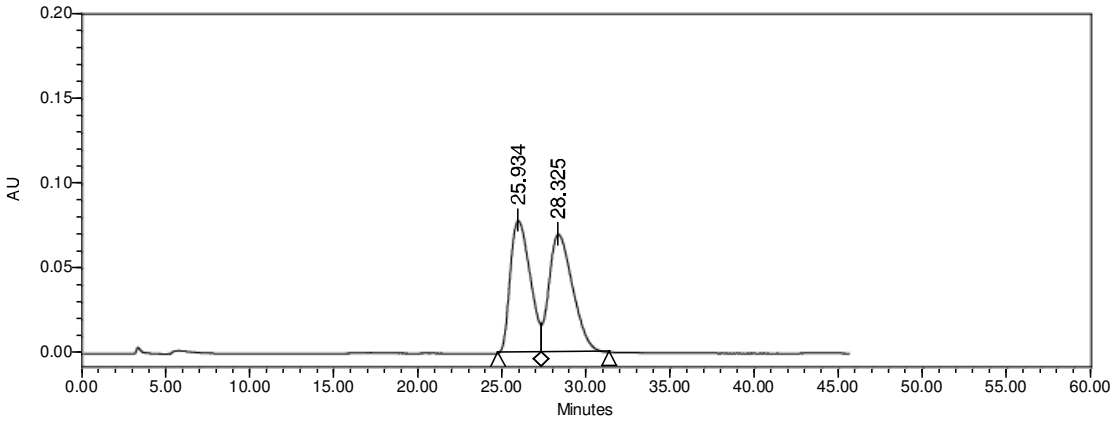
Peak Results

	RT	Area	Height	% Area
1	27.657	49302093	525956	92.24
2	31.515	4147704	21388	7.76

5.2.- - Chiral HPLC chromatograms of racemic and enantioenriched **1b**.

SampleName	UX80A(OJ 100 97 03)	Sample Type	Unknown
Vial	1	Date Acquired	5/05/06 10:29:17 AM
Injection	1	Acq Method Set	OJ 100 97 03
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	15/01/07 1:21:51 PM
Run Time	50.0 Minutes		

Auto-Scaled Chromatogram

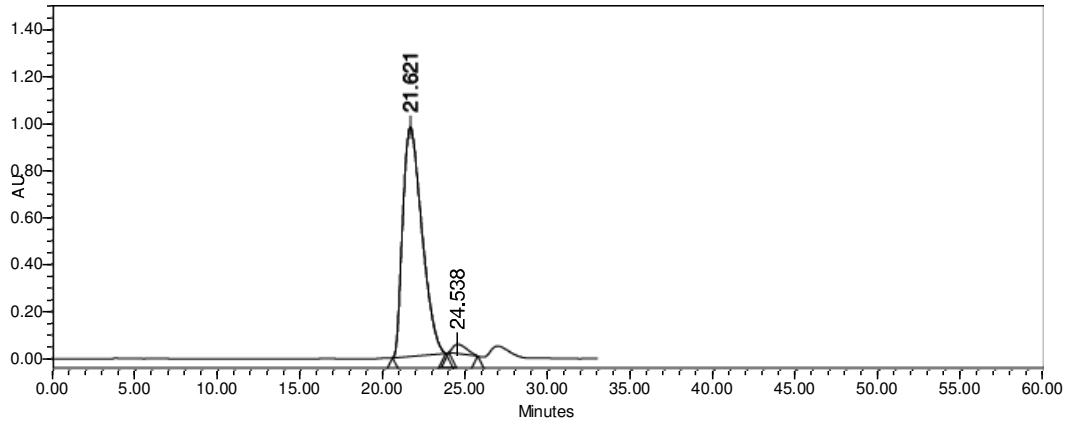


Peak Results

	RT	Area	Height	% Area
1	25.934	6409920	77621	48.46
2	28.325	6817452	69378	51.54

SampleName	UX103B(OJ 085 95 05)	Sample Type	Unknown
Vial	1	Date Acquired	20/10/06 1:35:20 PM
Injection	1	Acq Method Set	OJ 085 95 05
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	15/01/07 10:21:00 AM
Run Time	70.0 Minutes		

Auto-Scaled Chromatogram



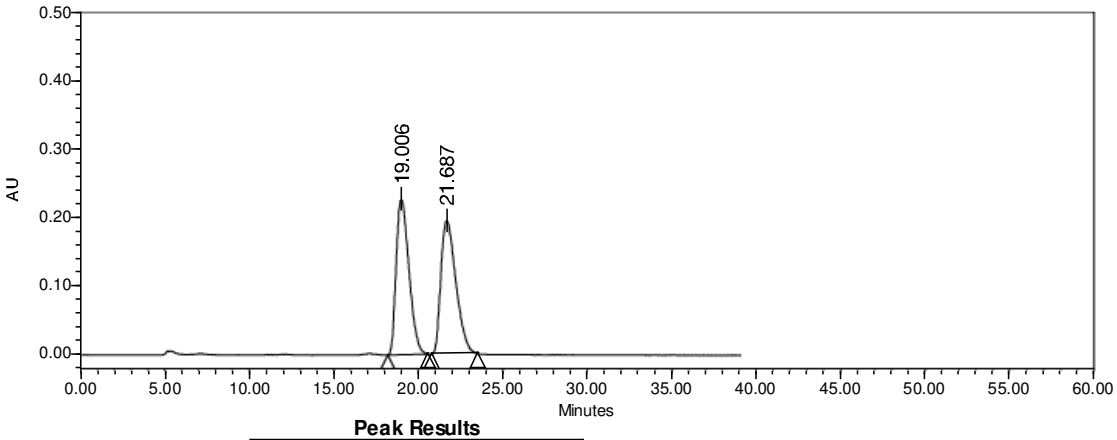
Peak Results

	RT	Area	Height	% Area
1	21.621	78486591	975289	97.18
2	24.538	2277614	39287	2.82

5.3.- - Chiral HPLC chromatograms of racemic and enantioenriched **1c**.

SampleName	UX94A(OJ 085 95 05)	Sample Type	Unknown
Vial	1	Date Acquired	6/09/06 11:07:20 AM
Injection	1	Acq Method Set	OJ 085 95 05
Injection Volume	5.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	15/01/07 1:28:03 PM
Run Time	70.0 Minutes		

Auto-Scaled Chromatogram

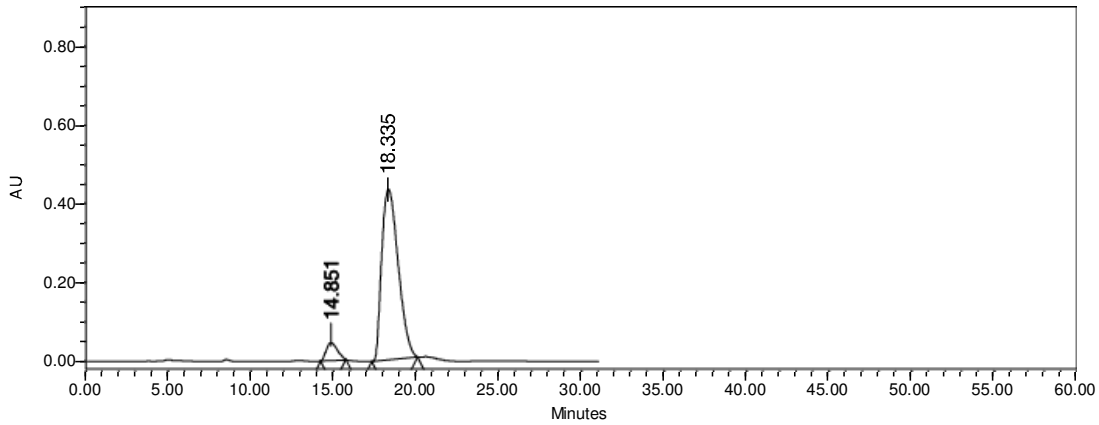


Peak Results

	RT	Area	Height	% Area
1	19.006	11874294	226525	49.70
2	21.687	12018673	193866	50.30

SampleName	UX103D(OJ 085 95 05)	Sample Type	Unknown
Vial	1	Date Acquired	20/10/06 4:28:45 PM
Injection	1	Acq Method Set	OJ 085 95 05
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	15/01/07 11:14:35 AM
Run Time	70.0 Minutes		

Auto-Scaled Chromatogram



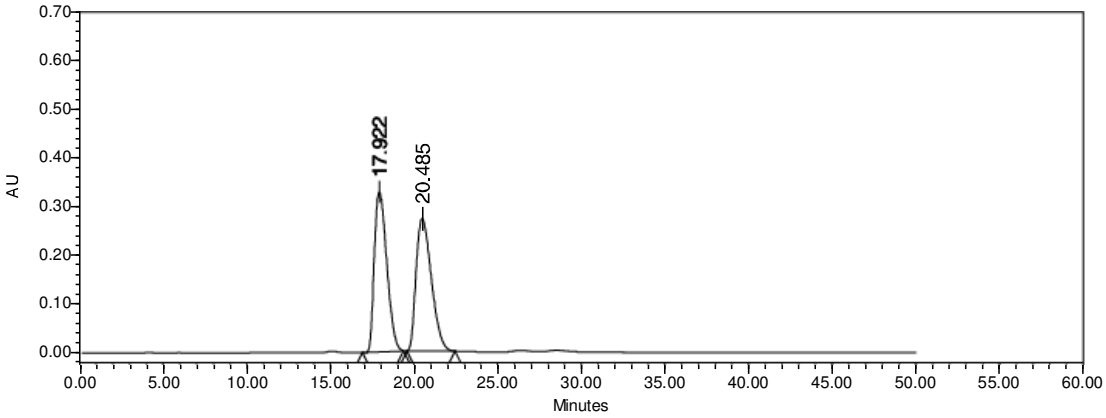
Peak Results

	RT	Area	Height	% Area
1	14.851	1445716	45562	4.61
2	18.335	29914737	433283	95.39

5.4.- - Chiral HPLC chromatograms of racemic and enantioenriched **1d**.

SampleName	UX80B(OJ 085 95 05)	Sample Type	Unknown
Vial	1	Date Acquired	5/05/06 11:18:43 AM
Injection	1	Acq Method Set	OJ 085 95 05
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	15/01/07 1:37:06 PM
Run Time	50.0 Minutes		

Auto-Scaled Chromatogram

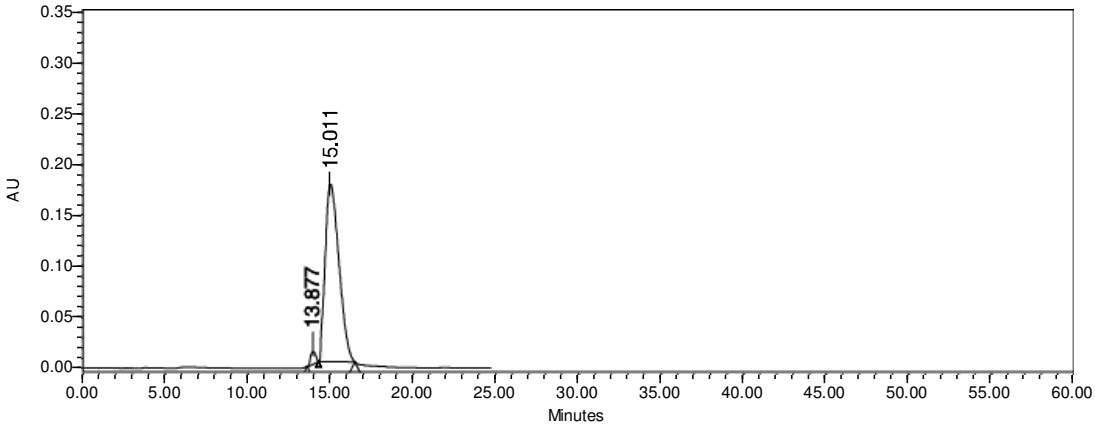


Peak Results

	Name	RT	Area	Height	% Area
1		17.922	17029243	329027	49.65
2		20.485	17266794	270929	50.35

SampleName	UX103C(OJ 085 95 05)	Sample Type	Unknown
Vial	1	Date Acquired	24/10/06 11:22:56 AM
Injection	1	Acq Method Set	OJ 085 95 05
Injection Volume	5.00 ul	Processing Method	OJ 085 95 05
Channel	996	Date Processed	24/10/06 11:52:12 AM
Run Time	40.0 Minutes		

Auto-Scaled Chromatogram



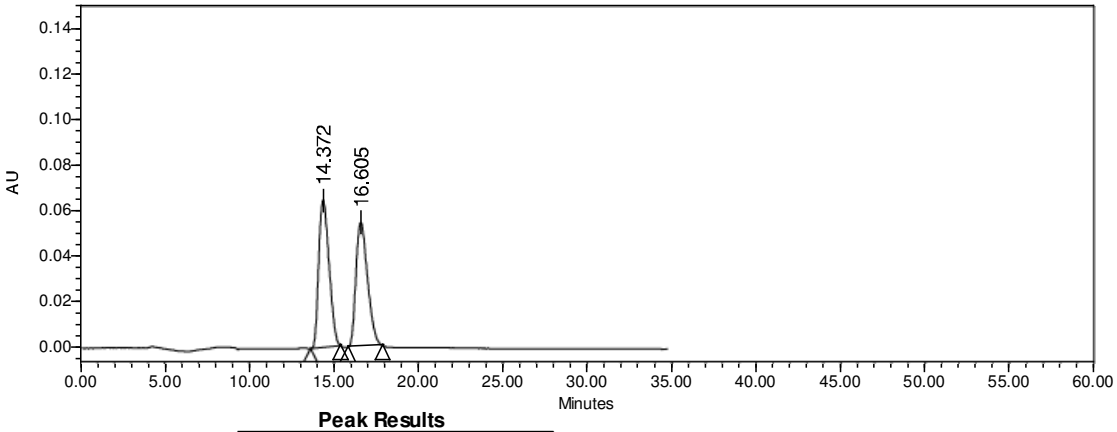
Peak Results

	RT	Area	Height	% Area
1	13.877	47371	6149	0.56
2	15.011	8411750	154957	99.44

5.5.- - Chiral HPLC chromatograms of racemic and enantioenriched **1e**.

SampleName	UX94B(OJ 085 95 05)	Sample Type	Unknown
Vial	1	Date Acquired	6/09/06 11:49:16 AM
Injection	1	Acq Method Set	OJ 085 95 05
Injection Volume	5.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	15/01/07 1:40:02 PM
Run Time	70.0 Minutes		

Auto-Scaled Chromatogram

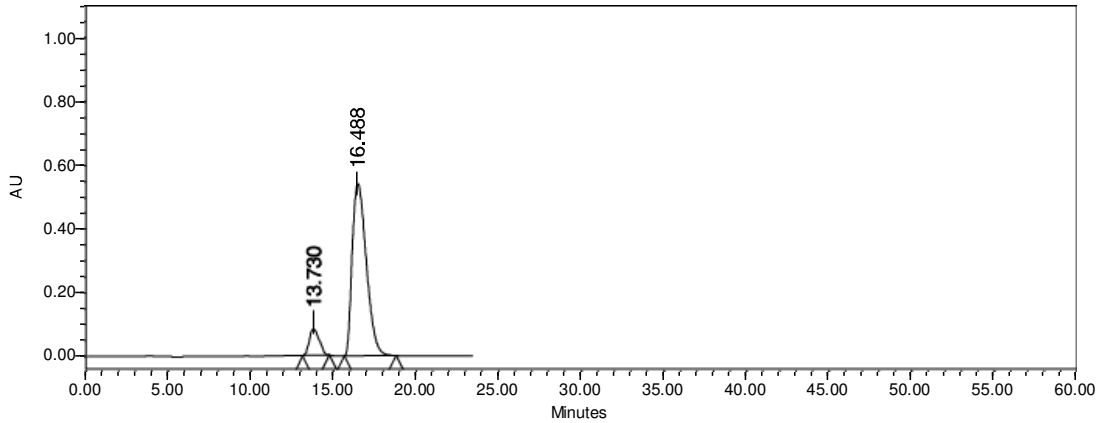


Peak Results

	RT	Area	Height	% Area
1	14.372	2719965	64126	51.08
2	16.605	2604965	54243	48.92

SampleName	UX103E(OJ 085 95 05)	Sample Type	Unknown
Vial	1	Date Acquired	20/10/06 3:20:28 PM
Injection	1	Acq Method Set	OJ 085 95 05
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	15/01/07 11:32:56 AM
Run Time	70.0 Minutes		

Auto-Scaled Chromatogram



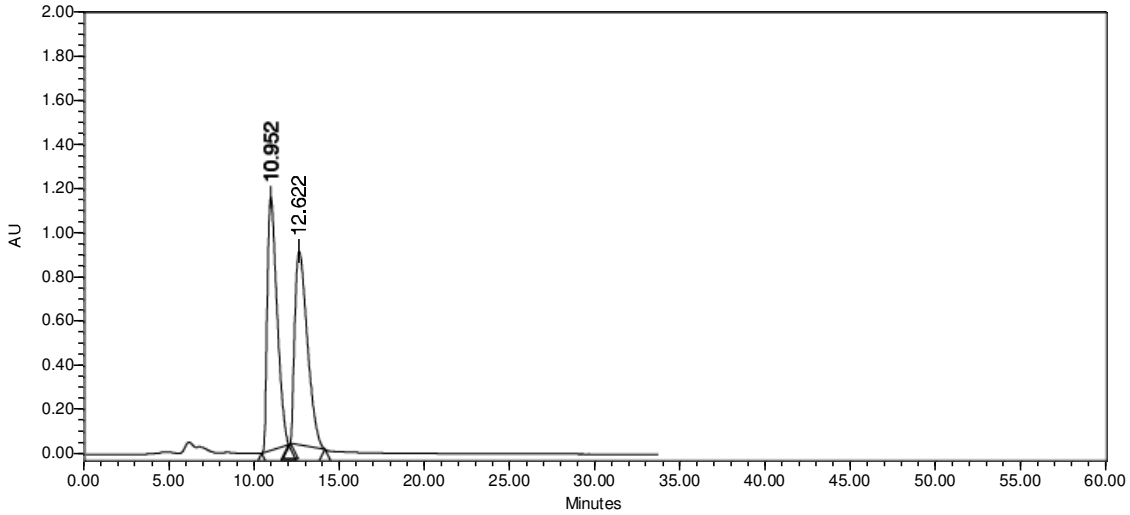
Peak Results

	RT	Area	Height	% Area
1	13.730	2267828	80999	6.59
2	16.488	32145344	542176	93.41

5.6.- - Chiral HPLC chromatograms of racemic and enantioenriched **1f**.

SampleName	UX94C(OJ 085 95 05)	Sample Type	Unknown
Vial	1	Date Acquired	15/01/07 4:41:10 PM
Injection	2	Acq Method Set	OJ 085 95 05
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	15/01/07 5:23:29 PM
Run Time	70.0 Minutes		

Auto-Scaled Chromatogram

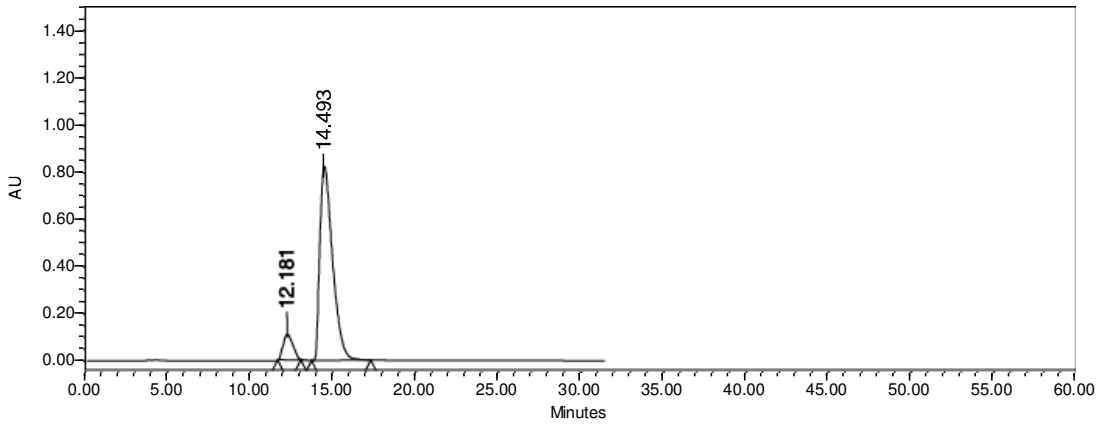


Peak Results

	RT	Area	Height	% Area
1	10.952	45465339	1148159	50.30
2	12.622	44919688	874443	49.70

SampleName	UX103F(OJ 085 95 05)	Sample Type	Unknown
Vial	1	Date Acquired	20/10/06 2:46:49 PM
Injection	1	Acq Method Set	OJ 085 95 05
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	15/01/07 11:35:50 AM
Run Time	70.0 Minutes		

Auto-Scaled Chromatogram



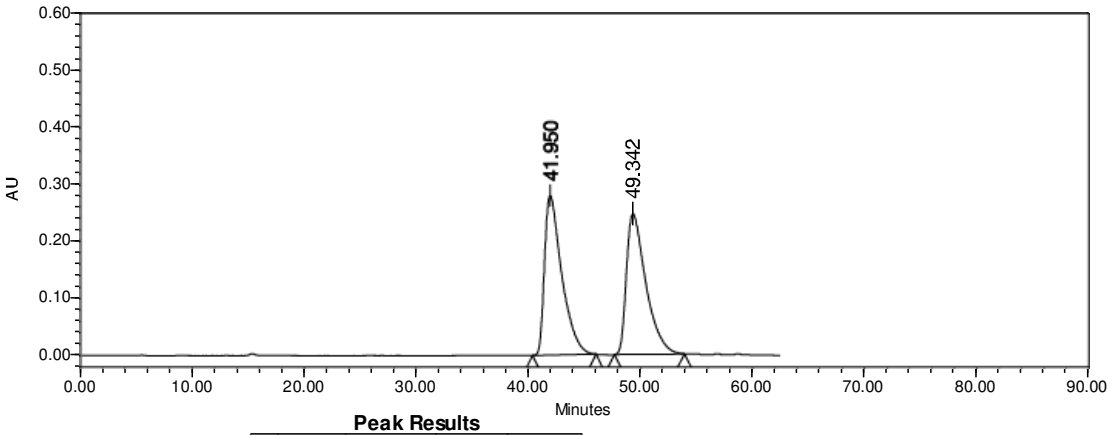
Peak Results

	RT	Area	Height	% Area
1	12.181	11175959	82417	7.75
2	14.493	44004494	825036	92.25

5.7.- - Chiral HPLC chromatograms of racemic and enantioenriched **1g**.

SampleName	UX94DOL(OD 085 99 01)	Sample Type	Unknown
Vial	1	Date Acquired	8/09/06 12:46:38 PM
Injection	1	Acq Method Set	OD 085 99 01
Injection Volume	5.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	15/01/07 1:44:12 PM
Run Time	70.0 Minutes		

Auto-Scaled Chromatogram

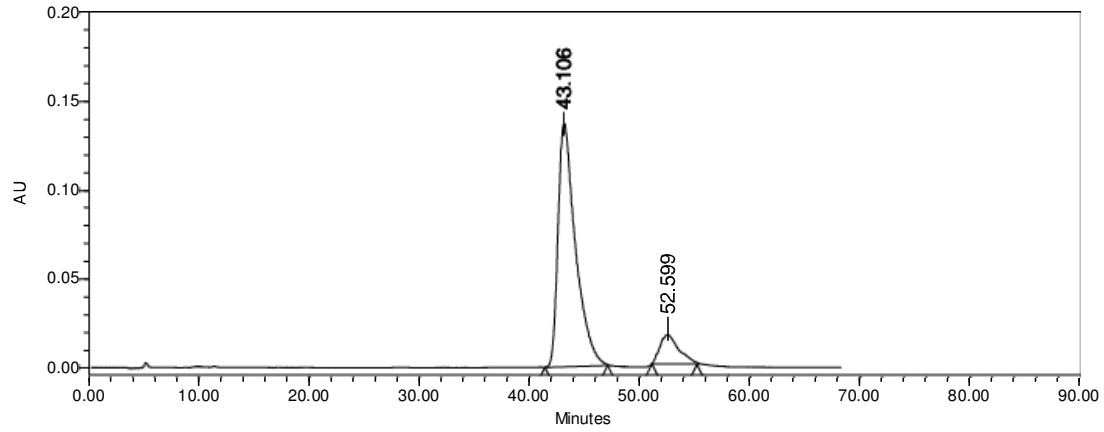


Peak Results

	RT	Area	Height	% Area
1	41.950	29812296	279994	50.20
2	49.342	29573915	245779	49.80

SampleName	UX103GOL(OD 085 99 01)	Sample Type	Unknown
Vial	1	Date Acquired	23/10/06 5:02:32 PM
Injection	1	Acq Method Set	OD 085 99 01
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	15/01/07 11:44:13 AM
Run Time	70.0 Minutes		

Auto-Scaled Chromatogram



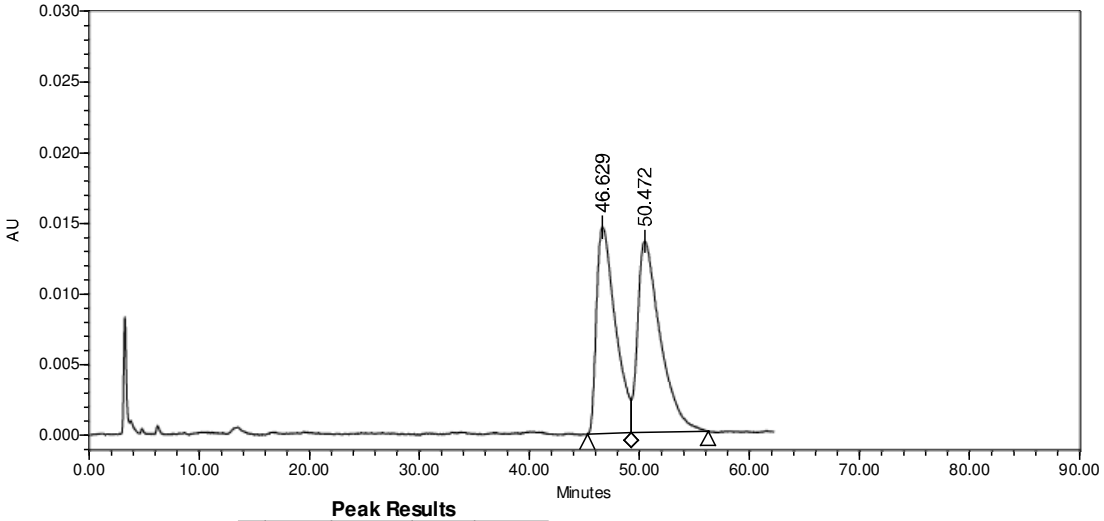
Peak Results

	RT	Area	Height	% Area
1	43.106	14986572	136671	88.12
2	52.599	2020432	16090	11.88

5.8.- - Chiral HPLC chromatograms of racemic and enantioenriched **8**.

SampleName	UX98A22 (OD 100 99 01)	Sample Type	Unknown
Vial	1	Date Acquired	10/11/06 3:35:12 PM
Injection	1	Acq Method Set	OD 100 99 01
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	15/01/07 3:22:03 PM
Run Time	70.0 Minutes		

Auto-Scaled Chromatogram

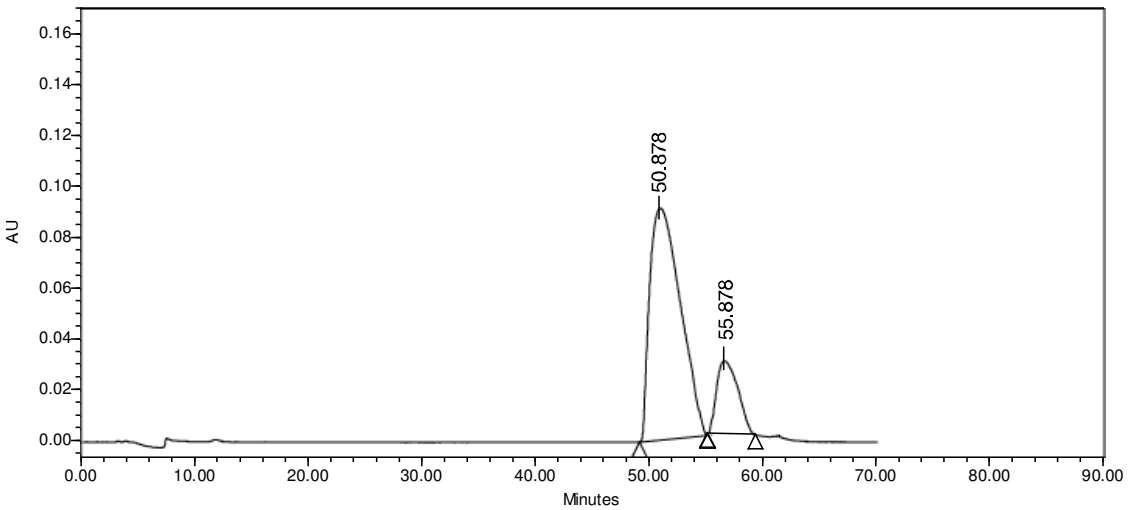


Peak Results

	RT	Area	Height	% Area
1	46.629	1747232	14611	47.45
2	50.472	1934887	13526	52.55

SampleName	UX102AB (OD 100 99 01)	Sample Type	Unknown
Vial	1	Date Acquired	13/11/06 1:00:10 PM
Injection	1	Acq Method Set	OD 100 99 01
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	15/01/07 3:22:40 PM
Run Time	70.0 Minutes		

Auto-Scaled Chromatogram



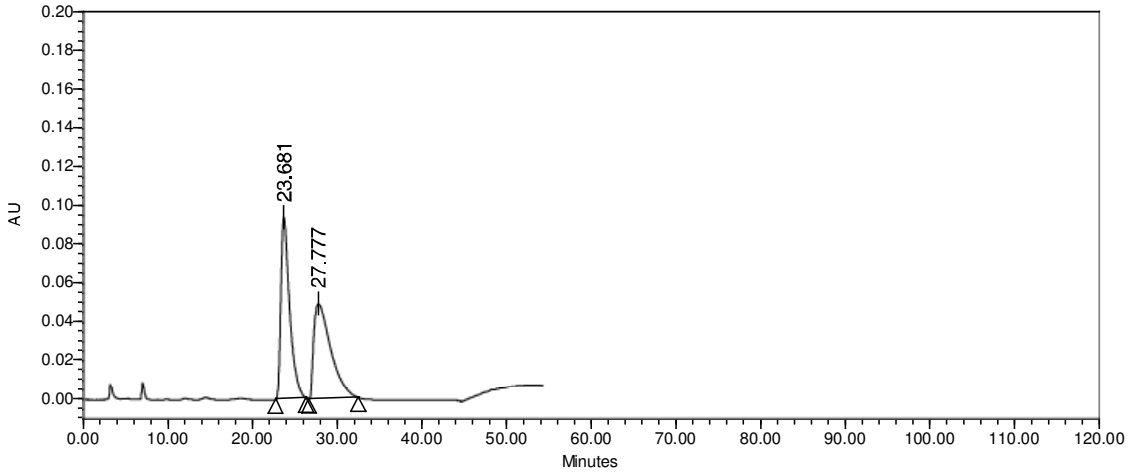
Peak Results

	RT	Area	Height	% Area
1	50.878	14470166	85421	83.39
2	55.878	2882233	16856	16.61

5.9.- - Chiral HPLC chromatograms of racemic and enantioenriched **10**.

SampleName	UX133ACE2(OD 100 80 20)	Sample Type	Unknown
Vial	1	Date Acquired	16/01/07 5:17:00 PM
Injection	1	Acq Method Set	OD 100 80 20
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	17/01/07 5:14:39 PM
Run Time	120.0 Minutes		

Auto-Scaled Chromatogram

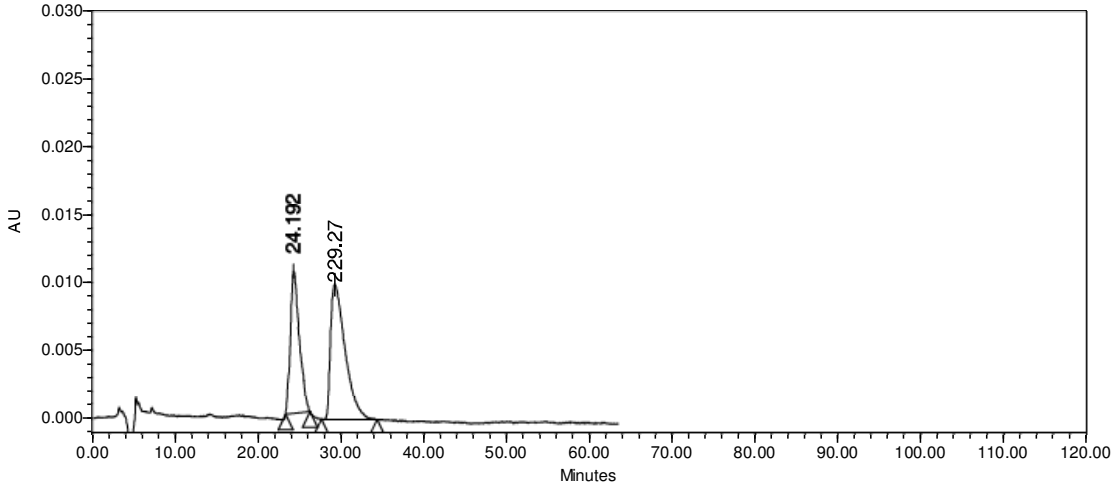


Peak Results

	RT	Area	Height	% Area
1	23.681	6871626	93747	49.92
2	27.777	6894843	49029	50.08

SampleName	UX149BACE(OD 100 80 20)	Sample Type	Unknown
Vial	1	Date Acquired	17/01/07 12:35:48 PM
Injection	1	Acq Method Set	OD 100 80 20
Injection Volume	5.00 ul	Processing Method	fenetilamida
Channel	996	Date Processed	17/01/07 5:26:11 PM
Run Time	120.0 Minutes		

Auto-Scaled Chromatogram



Peak Results

	RT	Area	Height	% Area
1	24.192	640193	10091	34.65
2	29.272	1207405	9911	65.35