Electronic Supplementary Material (ESI) for Chemical Communications

Coupling Biocatalysis and Click Chemistry: One-pot Two-step Convergent Synthesis of Enantioenriched 1,2,3-Triazole-Derived Diols

Aníbal Cuetos, Fabricio R. Bisogno, Iván Lavandera* and Vicente Gotor*

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1. General.

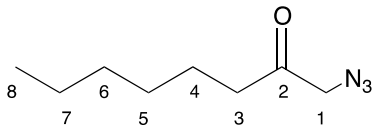
Ketone **1a** and alcohol **2a** and **2b** were purchased from commercial sources. All other reagents and solvents were of the highest quality available. Glucose dehydrogenase (GDH 002, 30 U mg^{-1}), ADH-A from *Rhodococcus ruber* (20 U mg^{-1}), and LBADH from *Lactobacillus brevis* (3.7 U μL^{-1}) were obtained from Jülich-Codexis. LKADH from *Lactobacillus kefir* (0.42 U mg^{-1}) was obtained from Fluka. Overexpressed ADHs from *Rhodococcus ruber* (ADH-A), from *Thermoanaerobium* sp. (ADH-T), and *Thermoanaerobacter ethanolicus* (TesADH) have been obtained from Prof. Wolfgang Kroutil at the University of Graz following the methodology previously described.[1] 1 unit (U) of ADH reduces 1.0 μM of acetophenone to 1-phenylethanol (for ADH-A, LBADH or LKADH) and 2-octanone to 2-octanol (for TesADH and ADH-T) per minute at pH 7.5 and 30ºC in the presence of NAD(P)H. Flash chromatography was performed using silica gel 60 (230-400 mesh). IR spectra were recorded on a Perkin-Elmer 1720-X infrared Fourier transform spectrophotometer on NaCl pellets. ^{1}H-, ^{13}C-NMR, and DEPT were obtained using a Bruker DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) spectrometer for routine experiments. The chemical shifts (δ) are given in ppm and the coupling constants (*J*) in Hertz (Hz). ESI^{+} mode was used to record mass spectra (MS) and ESI-TOF for HRMS. Gas chromatography (GC) analyses were performed on a Hewlett Packard 6890 Series II chromatograph. HPLC analyses were performed with Hewlett Packard 1100 LC liquid chromatograph. The chromatograms shown for each enantioenriched diol derivative correspond to the worked-up reaction crude and were not subjected to any preparative chromatographic separation ensuring that all produced isomers were considered. Optical rotations were measured using a Perkin-Elmer 241 polarimeter and are quoted in units of 10^{-1} deg cm^{2} g^{-1}.

2. Experimental procedures

*2.1. General procedure for the synthesis of ketones **1b** and **1e***

To a solution of the alcohol **2b** or **2e** (3.3 mmol) in acetone (15 mL) at 0ºC, Jones' reagent (CrO_3, 430 mg, 6.3 mmol, 1.5 equiv. in a mixture of 333 μL of H_2SO_4 conc. and 1 mL of H_2O) was added dropwise and shaken at r.t. for 1 hour. After completion, the reaction was filtered over celite and the solvent was evaporated under reduced pressure. The residue was extracted with diethyl ether (2 x 15 mL). The organic layers were pooled together, dried over Na_2SO_4 and evaporated affording the ketone **1b** or **1e** as yellow oil (75-80% yield). Compound **1b**[2] exhibited physical and spectral properties in accordance with those reported.

1-azidooctan-2-one (1e)



Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (*t*, 3H, H_8, $^3J_{HH}$ 6.5 Hz), 1.28 (*m*, 6H, H_5+H_6+H_7), 1.60 (*m*, 2H, H_4), 2.43 (*t*, 2H, H_3, $^3J_{HH}$ 7.4 Hz), 3.93 (*s*, 2H, H_1). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.9 (CH_3, C_8), 22.3 (CH_2, C_7), 23.3 (CH_2, C_6), 28.7 (CH_2, C_5), 31.4 (CH_2, C_4), 39.9 (CH_2, C_3), 57.3 (CH_2, C_1), 204.5 (C, C_2). MS (ESI^+, *m/z*): 192 [$(M+Na)^+$, 100%]. HRMS (ESI^+) calcd for $C_8H_{15}N_3ONa$ $(M+Na)^+$: 192.1113; found: 192.1105.

*2.2. General procedure for the synthesis of ketones **1c**, **1d** and **1f***

To a solution of 2-bromoacetophenone, 2-bromo-2'-acetonaphthone, 2-bromo-4'-nitroacetophenone or 2-bromo-4'-hydroxyacetophenone (10 mmol) in a mixture of H_2O:ethanol (1:2, total volume 12 mL), sodium azide (2 equiv., **CAUTION: sodium**

azide must be carefully handled, risk of explosion) was added. The reaction was stirred at room temperature, and after completion, the solvent was evaporated and the residue was extracted with dichloromethane (2 x 20 mL). The organic layers were pooled together, dried over Na_2SO_4 and evaporated affording ketone **1c** (yellow oil), **1d**, **1f** (brown solids) or **1g** (white solids) (95-99% yield). Compounds **1c**[2], **1d**[3], **1f**[4] and **1g**[1] exhibited physical and spectral properties in accordance with those reported.

*2.3. General procedure for the synthesis of alcohols **2c**, **2d**, **2f** or **2g***

To a solution of ketone **1c**, **1d**, **1f** or **1g** (9.3 mmol) in ethanol (10 mL) at 0ºC, $NaBH_4$ (2 equiv.) was carefully added. After completion, the usual acid work-up (HCl 1N) was carried out. The crude was concentrated under reduced pressure and then the residue was extracted with ethyl acetate (2 x 20 mL). The organic layers were pooled together, dried over Na_2SO_4 and evaporated affording alcohols **2c** (yellow oil), **2d** (brown solid), **2f or 2g** (brown oil) (85-93% yield). Compounds **2c**[2], **2d**[5], **2f**[6] and **2g**[1] exhibited physical and spectral properties in accordance with those reported.

*2.4. General procedure for the synthesis of alcohol **2e***

1-Octene (6.0 mmol, 1 equiv.) reacted with *N*-bromosuccinimide (NBS, 1.3 g, 7.2 mmol, 1.2 equiv.) and ammonium acetate (NH_4Ac, 0.6 mmol, 0.1 equiv.) in a mixture of acetone (6 mL) and water (6 mL).[7] The reaction mixture was stirred at room temperature overnight. Later, 3 mL of water were added followed by extraction with CH_2Cl_2 (3 x 5 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was concentrated under vacuo and the residue subjected to *flash* chromatography (petroleum ether / CH_2Cl_2, 1:1) obtaining *rac*-1-bromooctan-2-ol (73% isolated yield).

Then, to a solution of this bromohydrin (4 mmol) in DMF (6 mL) and water (1 mL), sodium azide (8.2 mmol, 2 equiv., **CAUTION: sodium azide must be carefully handled, risk of explosion**) was added and shaken at 70ºC for 24 hours. After completion, the reaction was extracted with diethyl ether (3 x 10 mL). The organic layers were pooled together, dried over Na_2SO_4 and evaporated affording the alcohol **2e** as yellow oil (65% isolated yield). Compound **2e**[8] exhibited physical and spectral properties in accordance with those reported.

*2.5. ADH-catalysed reduction of ketones **1a-g** by ADH-A, CPADH or LBADH*

In a 1.5 mL Eppendorf vial, ADH-A, CPADH or LBADH (3 U) was added in phosphate buffer (600 µL, 50 mM, pH 7.5, 1 mM NADH for ADH-A and CPADH, or 1 mM NADPH and 1 mM $MgCl_2$ for LBADH), and mixed with 2-propanol (32 µL, 5% v v^{-1}) and the corresponding ketone **1a-g** (20 mM). Reactions were shaken at 30ºC and 250 rpm for 24 h and stopped by extraction with ethyl acetate (2 x 0.5 mL). The organic layer was separated by centrifugation (2 min, 13000 rpm) and dried over Na_2SO_4. Conversions and enantiomeric excess of the corresponding alcohols (see Tables S1 and S2) were determined by GC or HPLC (see Tables S3 and S4). Conversions for substrate **1f** and **1g** were determined by ^{1}H-NMR.

*2.6. ADH-catalysed reduction of ketones **1a-e** by LKADH*

In a 1.5 mL Eppendorf vial, LKADH (3 U) was added in phosphate buffer (600 µL, 50 mM, pH 7.5, 1 mM NADPH) and mixed with 5 U of GDH and glucose (40 mM) with the corresponding ketone **1a-e** (20 mM). Reactions were shaken at 30ºC and 250 rpm for 24 h and stopped by extraction with ethyl acetate (2 x 0.5 mL). The organic layer was separated by centrifugation (2 min, 13000 rpm) and dried over Na_2SO_4.

Conversions and enantiomeric excess of the corresponding alcohols (see Tables S1 and S2) were determined by GC or HPLC (see Tables S3 and S4).

2.7. ADH-catalysed reduction of ketones ***1a-g*** *by* E. coli/*ADH-A*, E. coli/*TesADH or* E. coli/*ADH-T*

In a 1.5 mL Eppendorf vial, 20 mg of *E. coli*/ADH-A, *E. coli*/TesADH or *E. coli*/ADH-T in phosphate buffer (600 µL, 50 mM, pH 7.5, 1 mM NADH for ADH-A, or 1 mM NADPH for TesADH and ADH-T) were mixed with 2-propanol (32 µL, 5% v v^{-1}) and the corresponding ketone **1a-g** (20 mM). Reactions were shaken at 30ºC and 250 rpm for 24 h and stopped by extraction with ethyl acetate (2 x 0.5 mL). The organic layer was separated by centrifugation (2 min, 13000 rpm) and dried over Na_2SO_4. Conversions and enantiomeric excess of the corresponding alcohols (see Tables S1 and S2) were determined by GC or HPLC (see Tables S3 and S4). Conversions for substrate **1f** and **1g** were determined by ^{1}H-NMR.

Table S1 Bioreduction of alkynones **1a** and **1b** employing ADHs (*t*= 24 h)

ADH	**1a**[a]		**1b**[a,b]	
	c	***ee***	***c***	***ee***
E.coli/ADH-A	>99	96 (*S*)	>99	98 (*R*)
E.coli/ADH-T	>99	96 (*S*)	>99	96 (*R*)
E.coli/TesADH	>99	76 (*S*)	99	90 (*R*)
LBADH	>99	64 (*R*)	>99	99 (*S*)
LKADH	82	54 (*R*)	>99	99 (*S*)

[a] Determination of conversion by GC. [b] Change in Cahn-Ingold-Prelog (CIP) priority.

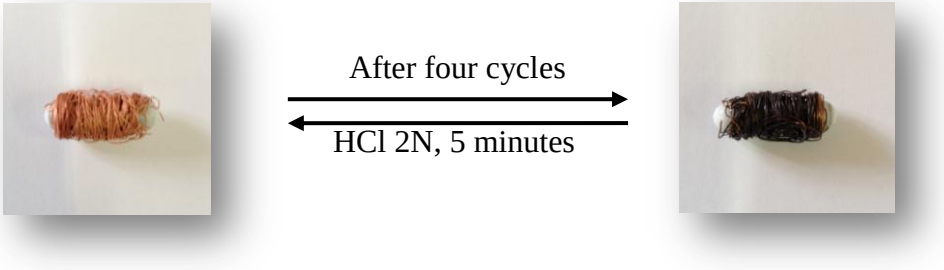
Table S2 Bioreduction of α-azido ketones **1c**, **1d**, **1e**, **1f** and **1g** employing ADHs (*t*= 24 h)

ADH	**1c**[a,b]		**1d**[a,b]		**1e**[a,b]		**1f**[b,c]		**1g**[b,c]	
	c	***ee***	***c***	***ee***	***c***	***ee***	***c***	***ee***	***c***	***ee***
E.coli/ ADH-A	>99	>99 (*R*)	>99	>99 (*R*)	>99	>99 (*R*)	>99	>99 (*R*)	>99	>99 (*R*)
E.coli/ ADH-T	>99	>99 (*R*)	0	n.d.	>99	>99 (*R*)	>99	>99 (*R*)	0	n.d.
E.coli/ TesADH	33	11 (*R*)	0	n.d.	75	92 (*R*)	n.d.	n.d.	0	n.d.
LBADH	>99	>99 (*S*)	6	>99 (*S*)	>99	>99 (*S*)	>99	>99 (*S*)	5	>99 (*S*)
LKADH	>99	98 (*S*)	54	50 (*S*)	>99	>99 (*S*)	n.d.	n.d.	n.d.	n.d.

[a] Determination of conversion by GC. [b] Change in Cahn-Ingold-Prelog (CIP) priority.
[c] Determination of conversion by ^{1}H-NMR. n.d. not determined.

2.8. General procedure for the synthesis of rac-*1,2,3-triazole-derived diols* syn- *and* anti-***3ac-bf***

The cycloaddition of the alkynyl derivatives **2a-b** (1 mmol) and the azido compounds **2c-g** (1 mmol) in a mixture water : ^{t}BuOH (20 mL : 20 mL) was catalysed employing a magnetic stirrer rolled on Cu wire and $CuSO_4$ in a catalytic amount (0.1 mmol). The reaction was shaken at 60-80ºC for 24 h. After completion, the crude was concentrated under reduced pressure and then the residue was extracted with ethyl acetate (2 x 20 mL). The organic layers were pooled together, dried over Na_2SO_4, concentrated under vacuo and the residue was subjected to *flash* chromatography (CH_2Cl_2 / MeOH, 9:1) obtaining the *rac*-1,2,3-triazole-derived diols *syn*- and *anti*-**3ac-bf** as white solids (74-92% isolated yield). The magnetic stirrer with the Cu wire could be reused several times after an acidic wash with HCl 2N during 5 minutes.



2.9. General procedure for the one-pot two-step biosynthesis of chiral 1,2,3-triazole-derived diols ***3ac-bf*** *using 2-propanol as cofactor regeneration system*

In a 5-mL closed-cap test tube, ADH-A, CPADH, or LBADH (5 U) or *E. coli*/ADH-A, *E. coli*/TesADH or *E. coli*/ADH-T (30 mg) were added in phosphate buffer (1.2 mL, 50 mM, pH 7.5, 1 mM NADH for ADH-A and CPADH, or 1 mM NADPH for LBADH, TesADH and ADH-T, and 1 mM $MgCl_2$ for LBADH) mixed with 2-propanol (64 μL, 5% v v^{-1}) and the corresponding alkynyl derivative **1a-b** and the azido derivative **1c-g** (24 μL, 1 M in DMSO, final concentration: 20 mM of each substrate). Reactions were shaken at 30ºC and 250 rpm for 24 h. Then, a magnetic stirrer rolled on Cu wire and $CuSO_4$ (25 μL of a solution in water of 100 mM, 0.1 equiv.) were added and stirred at 60-80ºC for 24 h. The reaction was stopped by extraction with ethyl acetate (2 x 1 mL). The organic layer was separated by centrifugation (2 min, 12000 rpm) and dried over Na_2SO_4. Enantiomeric and diastereomeric excess of the corresponding diols were determined by HPLC (see Tables S5).

2.10. General procedure for the one-pot two-step biosynthesis of chiral 1,2,3-triazole-derived diols ***3ab-cf*** *using GDH/glucose as cofactor regeneration system*

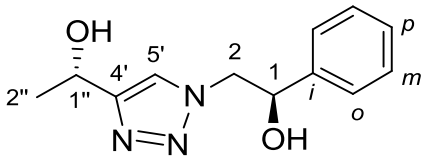
In a 5-mL closed-cap test tube, LKADH (5 U) was added in phosphate buffer (1.2 mL, 50 mM, pH 7.5, 1 mM NADPH) and were mixed with 10 U of GDH and glucose (80 mM) with the corresponding alkynyl derivative **1a-b** and the azido derivative **1c-g** (24

μL, 1 M in DMSO, final concentration: 20 mM of each susbtrate). Reactions were shaken at 30ºC and 250 rpm for 24 h. Then, a magnetic stirrer rolled on Cu wire and $CuSO_4$ (25 μL of a solution in water of 100 mM, 0.1 equiv.) were added and stirred at 60-80ºC for 24 h. The reaction was stopped by extraction with ethyl acetate (2 x 1 mL). The organic layer was separated by centrifugation (2 min, 13000 rpm) and dried over Na_2SO_4. Enantiomeric and diastereomeric excess of the corresponding diols were determined by HPLC (see Tables S5).

2.11. Scale-up of the reactions

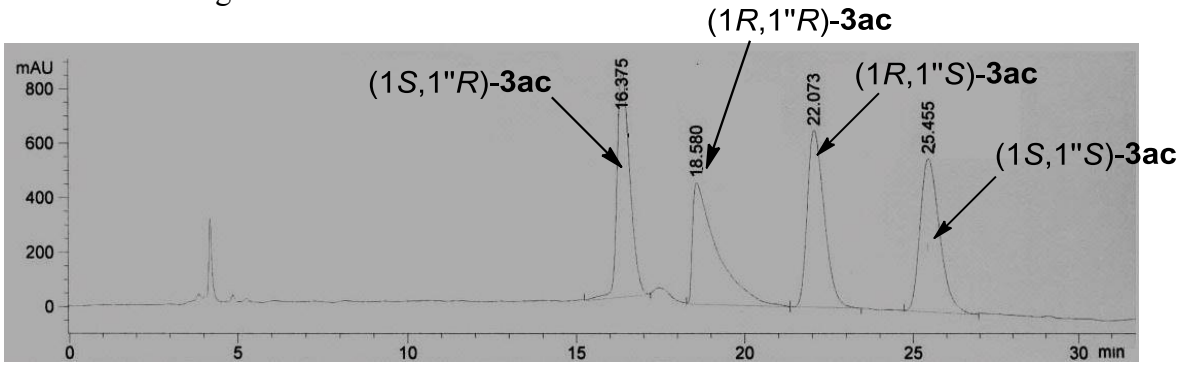
In a Falcon tube (50 mL), *E. coli*/ADH-A (200 mg) or LBADH (50 U) was added in phosphate buffer (12 mL, 50 mM, pH 7.5, 1 mM NADH for *E.coli*/ADH-A, or 1 mM NADPH and 1 mM $MgCl_2$ for LBADH), mixed with 2-propanol (600 μL, 5% v v^{-1}) and the corresponding alkynyl derivative **1a-b** and the azido derivative **1c-g** (240 μL, 1 M in DMSO, final concentration: 20 mM of each substrate). Reactions were shaken at 30ºC and 250 rpm for 24 h. Then, a magnetic stirrer rolled on Cu wire and $CuSO_4$ (250 μL of a solution in water of 100 mM, 0.1 equiv.) were added and the mixture was shaken at 60-80ºC for 24 h. The reaction was centrifuged to remove the pellet and extracted with ethyl acetate (2 x 10 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was concentrated under vacuo and the residue subjected to column chromatography (CH_2Cl_2/ MeOH, 9:1) obtaining the final enantioenriched diols, isolated yield: 69-85%.

(*R*)-2-{4-[(*S*)-1-Hydroxyethyl]-1*H*-1,2,3-triazol-1-yl}-1-phenylethanol [(1*R*,1''*S*)-3ac]

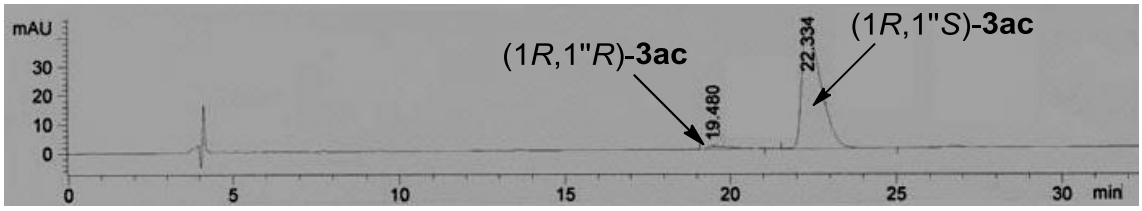


White solid. $[\alpha]_D$ -51.3 (*c* 1.0, 20ºC, MeOH). m.p.: 104-106ºC. IR (KBr): υ 3400, 3140, 2970, 2948, 2913, 1498, 1412, 1303, 1226, 1143, 1085 and 995 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.48 (*d*, 3H, $H_{2''}$, $^3J_{HH}$ 6.5 Hz), 4.15 (*s*, 1H, H_{OH}), 4.27 (*dd*, 1H, H_2, $|^2J_{HH}|$ 14.0 Hz, $^3J_{HH}$ 9.4 Hz), 4.58 (*dd*, 1H, H_2, $|^2J_{HH}|$ 14.0 Hz, $^3J_{HH}$ 2.9 Hz), 4.93 (*q*, 1H, $H_{1''}$, $^3J_{HH}$ 6.6 Hz), 5.06 (*s*, 1H, H_{OH}), 5.22 (*ap d*, 1H, H_1, $^3J_{HH}$ 6.3 Hz), 7.25-7.51 (*m*, 5H, H_{ar}), 7.56 (*s*, 1H, $H_{5'}$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 23.0 (CH_3, $C_{2''}$), 57.8 (CH_2, C_2), 62.7 (CH, $C_{1''}$), 72.4 (CH, C_1), 122.0 (CH, $C_{5'}$), 125.8 (2CH, C_o), 128.2 (CH, C_p), 128.7 (2CH, C_m), 140.2 (C, C_i), 162.2 (C, $C_{4'}$). MS (ESI^+, *m/z*): 256 [$(M+Na)^+$, 100%]. HRMS (ESI^+) calcd for $C_{12}H_{15}N_3O_2Na$ $(M+Na)^+$: 256.1056; found: 256.1053. 69% yield, >99% *ee*, 96% *de*.

HPLC chromatogram of *rac*-**3ac**

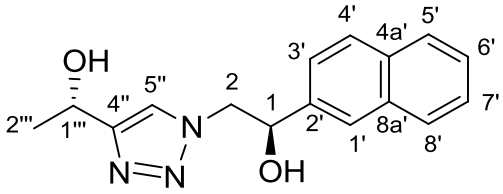


HPLC chromatogram of *anti*-(1*R*,1''*S*)-**3ac**



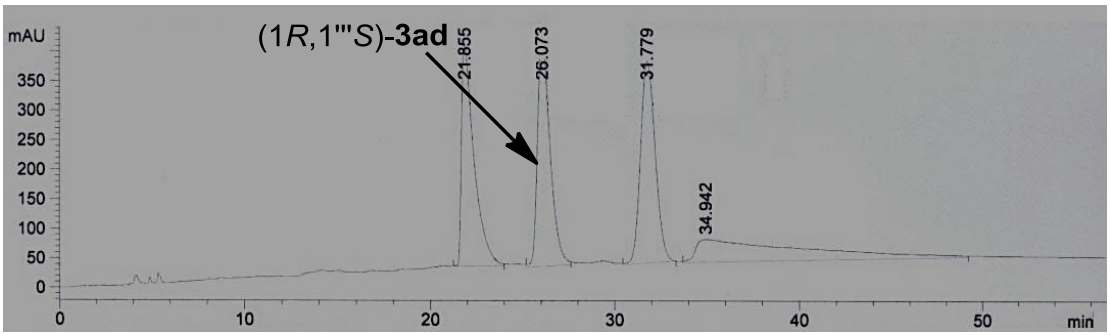
(*R*)-2-{4-[(*S*)-1-Hydroxyethyl]-1*H*-1,2,3-triazol-1-yl}-1-(naphthalen-2-yl)ethanol

[(1*R*,1'''*S*)-3ad]

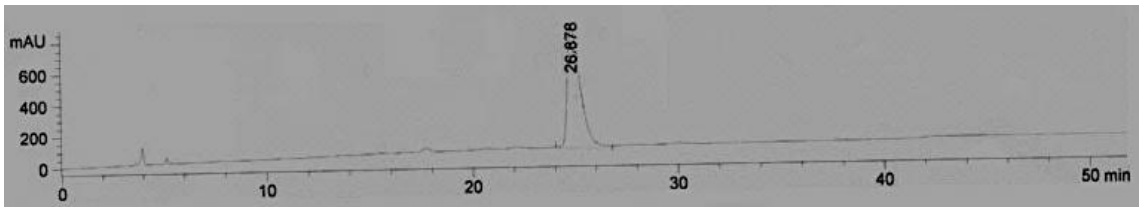


White solid. $[\alpha]_D$ -35.9 (*c* 1.0, 20ºC, MeOH). m.p.: 122-124ºC. IR (KBr): υ 3337, 3149, 2976, 2946, 1603, 1430, 1354, 1297, 1225, 1064, 1003 and 900 cm.$^{-1}$ ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.47 (*d*, 3H, $H_{2'''}$, $^3J_{HH}$ 6.5 Hz), 4.31 (*dd*, 1H, H_2, $|^2J_{HH}|$ 13.5 Hz, $^3J_{HH}$ 9.5 Hz), 4.63 (*dd*, 1H, H_2, $|^2J_{HH}|$ 13.8 Hz, $^3J_{HH}$ 2.8 Hz), 4.94 (*q*, 1H, $H_{1'''}$, $^3J_{HH}$ 6.5 Hz), 5.34 (*dd*, 1H, H_1, $^3J_{HH}$ 9.5, 2.5 Hz), 7.45-7.60 (*m*, 3H, H_{ar}), 7.60 (*s,* 1H, $H_{5''}$), 7.73-7.95 (*m*, 4H, H_{Ar}). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 23.0 (CH_3, $C_{2'''}$), 57.7 (CH_2, C_2), 62.5 (CH, $C_{1'''}$), 72.4 (CH, C_1), 122.1 (CH, $C_{5''}$), 123.5 (CH, C_{Ar}), 124.9 (CH, C_{Ar}), 126.1 (CH, C_{Ar}), 126.2 (CH, C_{Ar}), 127.6 (CH, C_{Ar}), 127.9 (CH, C_{Ar}), 128.5 (CH, C_{Ar}), 133.1 (2C, $C_{4a'}$+$C_{8a'}$), 137.5 (C, $C_{2'}$), 151.8 (C, $C_{4''}$). MS (ESI^+, *m/z*): 306 [$(M+Na)^+$, 100%]. HRMS (ESI^+) calcd for $C_{16}H_{17}N_3O_2Na$ $(M+Na)^+$: 306.1213; found: 306.1203. 82% yield, >99% *ee*, 96% *de.*

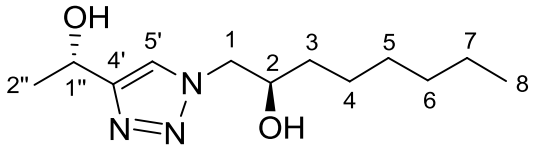
HPLC chromatogram of *rac*-**3ad**



HPLC chromatogram of *anti*-(1*R*,1'''*S*)-**3ad**

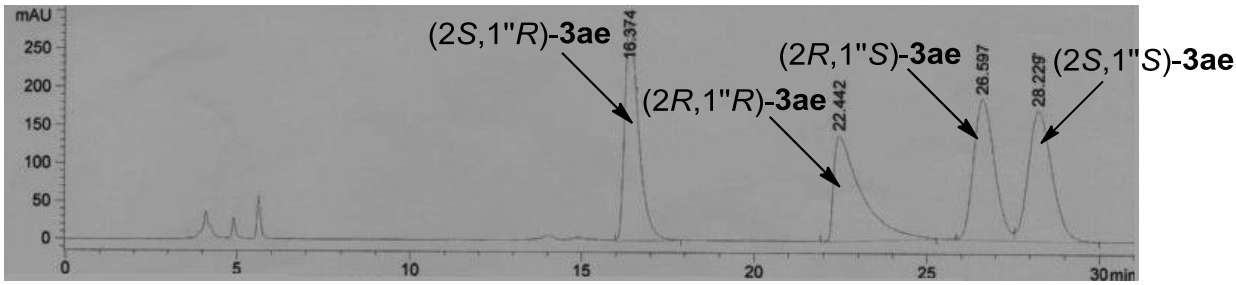


(*R*)-1-{4-[(*S*)-1-Hydroxyethyl]-1*H*-1,2,3-triazol-1-yl}octan-2-ol [(2*R*,1''*S*)-3ae]

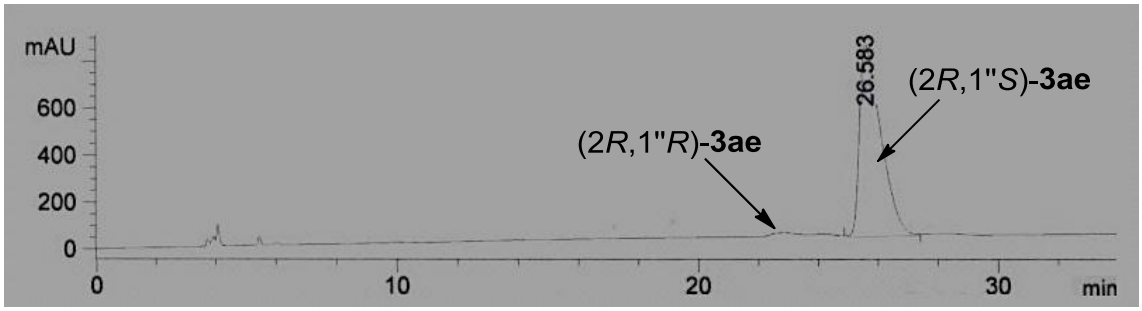


White solid. $[\alpha]_D$ -12.7 (*c* 1.0, 20ºC, MeOH). m.p.: 91-94ºC. IR (KBr): υ 3390, 3148, 2929, 2958, 2856, 1657, 1556, 1525, 1390, 1319, 1130, 1124, 1080 and 928 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (*t*, 3H, H_8, $^3J_{HH}$ 6.7 Hz), 1.28-1.31 (*m*, 6H, H_5+H_6+H_7), 1.48-1.58 (*m*, 7H, $H_{2''}$+H_3+H_4), 4.01-4.10 (*m*, 2H, H_1+H_2), 4.41 (*dd*, 1H, H_1, $|^2J_{HH}|$ 11.8 Hz, $^3J_{HH}$ 6.5 Hz), 4.92 (*q*, 1H, $H_{1''}$, $^3J_{HH}$ 6.6 Hz), 7.55 (*s*, 1H, $H_{5'}$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.0 (CH_3, C_8), 22.5 (CH_2, C_7), 23.0 (CH_3, $C_{2''}$), 25.4 (CH_2, C_6), 29.1 (CH_2, C_5), 31.7 (CH_2, C_4), 34.4 (CH_2, C_3), 56.5 (CH_2, C_1), 62.6 (CH, C_2), 70.2 (CH, $C_{1''}$), 122.0 (CH, $C_{5'}$), 158.6 (C, $C_{4'}$). MS (ESI^+, *m/z*): 264 [$(M+Na)^+$, 100%]. HRMS (ESI^+) calcd for $C_{12}H_{23}N_3O_2Na$ $(M+Na)^+$: 264.1682; found: 264.1703. 71% yield, >99% *ee*, 96% *de*.

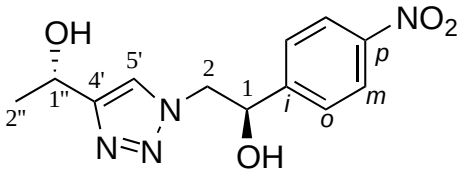
HPLC chromatogram of *rac*-**3ae**



HPLC chromatogram of *anti*-(2*R*,1''*S*)-**3ae**

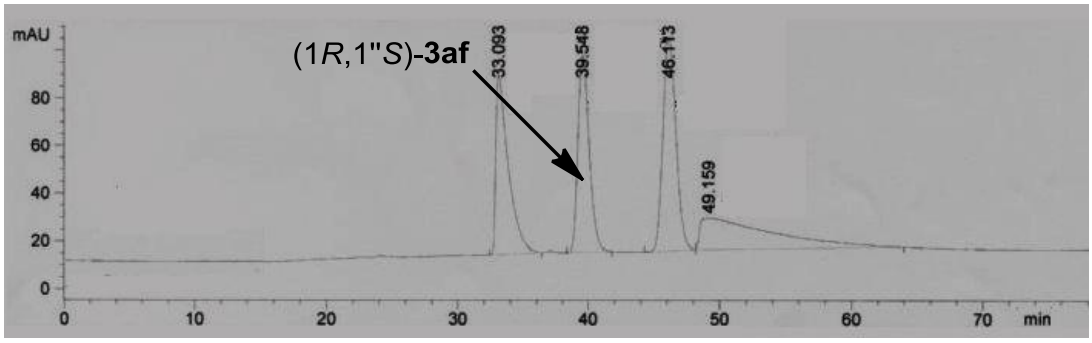


(*R*)-2-{4-[(*S*)-1-Hydroxyethyl]-1*H*-1,2,3-triazol-1-yl}-1-(4-nitrophenyl)ethanol [(1*R*,1''*S*)-3af]

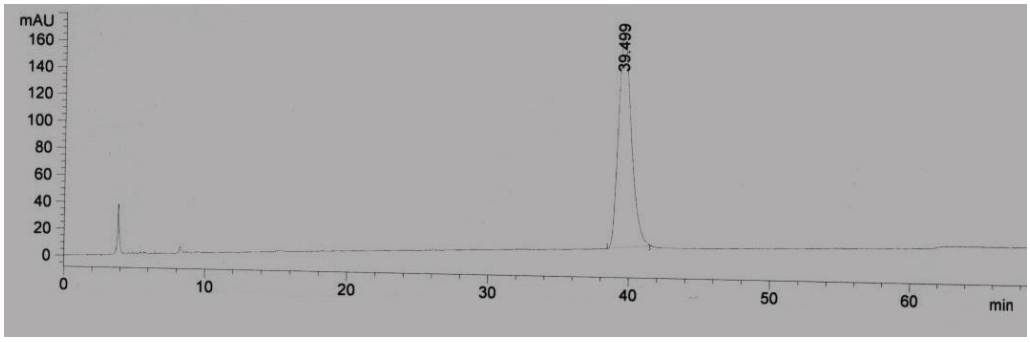


White solid. $[\alpha]_D$ -47.8 (*c* 1.0, 20ºC, MeOH). m.p.: 170-172ºC. IR (KBr): υ 3350, 3294, 2979, 2855, 2450, 1599, 1520, 1461, 1440, 1348, 1312, 1224, 1139, 1107, 1074 and 1003 cm^{-1}. ^{1}H-NMR (300 MHz, MeOH-d_4) δ 1.54 (*d*, 3H, $H_{2''}$, $^3J_{HH}$ 6.6 Hz), 4.58 (*m*, 2H, H_2), 4.99 (*q*, 1H, $H_{1''}$, $^3J_{HH}$ 6.6 Hz), 5.26 (*dd*, 1H, H_1, $^3J_{HH}$ 7.3, 4.4 Hz), 7.64 (*d*, 2H, H_o, $^3J_{HH}$ 8.7 Hz), 7.88 (*s*, 1H, $H_{5'}$), 8.24 (*d*, 2H, H_m, $^3J_{HH}$ 8.7 Hz). ^{13}C-NMR (75 MHz, MeOH-d_4) δ 22.7 (CH_3, $C_{2''}$), 56.8 (CH_2, C_2), 62.6 (CH, $C_{1''}$), 71.6 (CH, C_1), 122.8 (CH, $C_{5'}$), 123.5 (2CH, C_o), 127.7 (2CH, C_m), 149.9 (C, C_p), 150.2 (C, C_i), 153.3 (C, $C_{4'}$). MS (ESI^+, *m/z*): 301 [$(M+Na)^+$, 100%]. HRMS (ESI^+) calcd for $C_{12}H_{14}N_4O_4Na$ $(M+Na)^+$: 301.0907; found: 301.0931. 78% yield, 99% *ee*, 96% *de*.

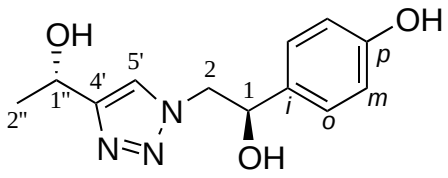
HPLC chromatogram of *rac*-**3af**



HPLC chromatogram of *anti*-(1*R*,1''*S*)-**3af**

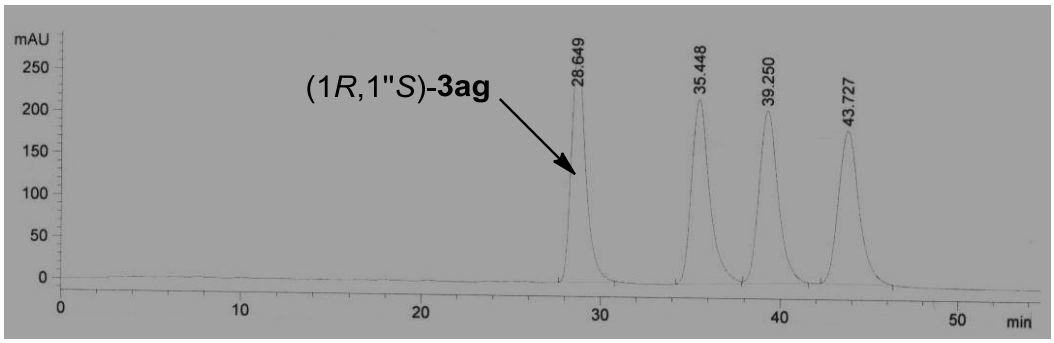


(*R*)-2-{4-[(*S*)-1-Hydroxyethyl]-1*H*-1,2,3-triazol-1-yl}-1-(4-hydroxyphenyl)ethanol [(1*R*,1''*S*)-3ag]

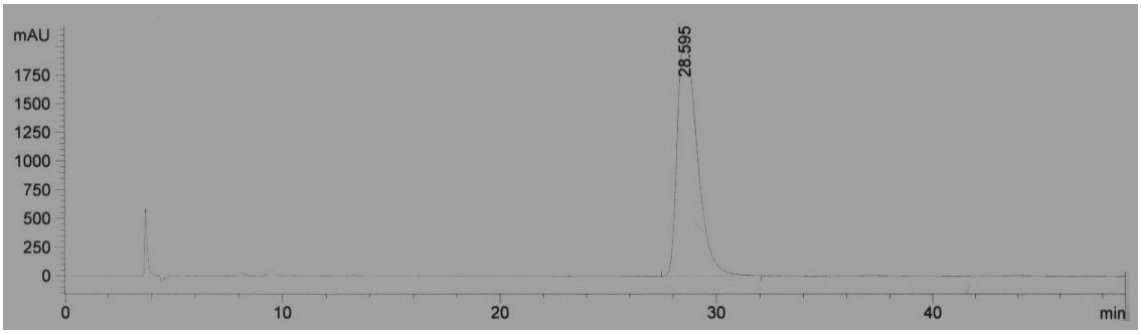


White solid. $[\alpha]_D$ -28.2 (*c* 1.0, 20ºC, MeOH). m.p.: 145-148ºC. IR (KBr): υ 3233, 2983, 2343, 1684, 1617, 1596, 1520, 1455, 1376, 1362, 1304, 1277, 1228, 1164, 1146, 1105, 1074, 1061 and 1004 cm^{-1}. ^{1}H-NMR (300 MHz, MeOH-d_4) δ 1.51 (*d*, 3H, $H_{2''}$, $^3J_{HH}$ 6.5 Hz), 4.53 (*ap d*, 2H, H_2, $^3J_{HH}$ 6.1 Hz), 4.91 (*m*, 2H, $H_{1''}$+H_1), 6.77 (*d*, 2H, H_m, $^3J_{HH}$ 8.5 Hz), 7.20 (*d*, 2H, H_o, $^3J_{HH}$ 8.5 Hz), 7.77 (*s*, 1H, $H_{5'}$). ^{13}C-NMR (75 MHz, MeOH-d_4) δ 23.7 (CH_3, $C_{2''}$), 58.3 (CH_2, C_2), 63.7 (CH, $C_{1''}$), 73.5 (CH, C_1), 116.2 (2CH, C_m), 123.5 (CH, $C_{5'}$), 128.4 (2CH, C_o), 133.2 (CH, C_i), 153.3 (C, C_p), 158.4 (C, $C_{4'}$). MS (ESI^+, *m/z*): 272 [$(M+Na)^+$, 100%]. HRMS (ESI^+) calcd for $C_{12}H_{15}N_3O_3Na$ $(M+Na)^+$: 272.1006; found: 272.1007. 70% yield, 99% *ee*, 96% *de*.

HPLC chromatogram of *rac*-**3ag**

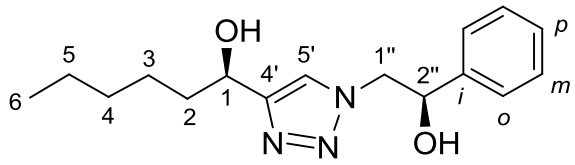


HPLC chromatogram of *anti*-(1*R*,1''*S*)-**3ag**



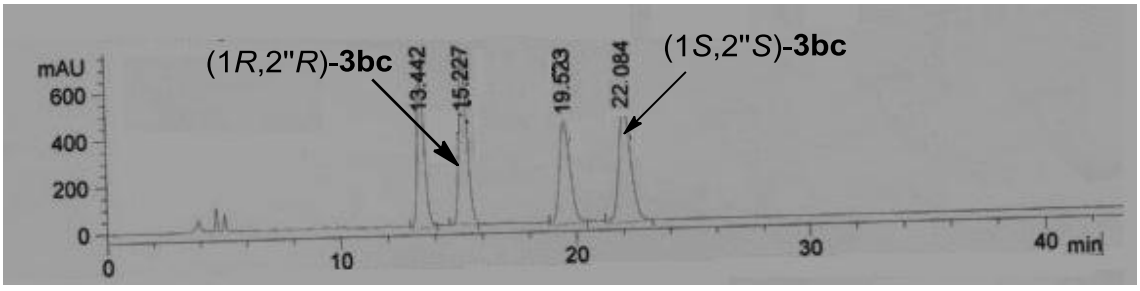
(*R*)-1-{1-[(*R*)-2-Hydroxy-2-phenylethyl]-1*H*-1,2,3-triazol-4-yl}hexan-1-ol

[(1*R*,2''*R*)-3bc]

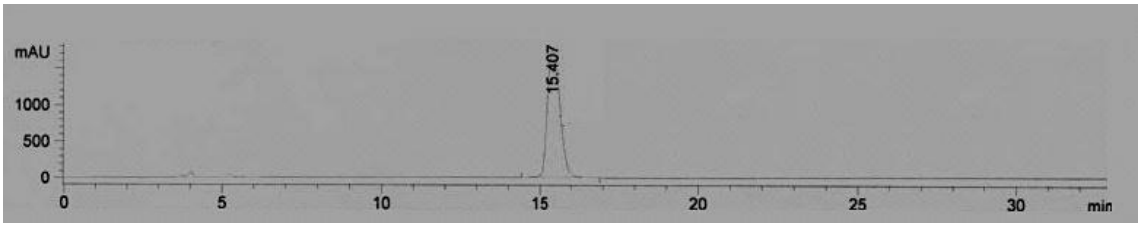


White solid. $[\alpha]_D$ -21.3 (*c* 1.0, 20ºC, MeOH). m.p.: 118-120ºC. IR (KBr): υ 3290, 3148, 2954, 2929, 2848, 1492, 1463, 1428, 1324, 1264, 1216, 1152, 1070, 1033, 980 and 915 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (*t*, 3H, H_6, $^3J_{HH}$ 6.4 Hz), 1.16-1.49 (*m*, 6H, H_3+H_4+H_5), 1.79 (ap *q*, 2H, H_2, $^3J_{HH}$ 6.9 Hz), 4.34 (*dd*, 1H, $H_{1''}$, $|^2J_{HH}|$ 14.0 Hz, $^3J_{HH}$ 9.1 Hz), 4.54 (*dd*, 1H, $H_{1''}$, $|^2J_{HH}|$ 14.0 Hz, $^3J_{HH}$ 3.1 Hz), 4.71 (*t*, 1H, H_1, $^3J_{HH}$ 6.9 Hz), 5.15 (*dd*, 1H, $H_{2''}$, $^3J_{HH}$ 9.2, 3.1 Hz), 7.27-7.46 (*m*, 5H, H_{ar}), 7.53 (*s*, 1H, $H_{5'}$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.9 (CH_3, C_6), 22.5 (CH_2, C_5), 25.2 (CH_2, C_4), 31.5 (CH_2, C_3), 36.8 (CH_2, C_2), 57.5 (CH_2, $C_{1''}$), 66.5 (CH, C_1), 72.4 (CH, $C_{2''}$), 122.4 (CH, $C_{5'}$), 125.8 (2CH, C_o), 128.2 (CH, C_p), 128.6 (2CH, C_m), 140.2 (C, C_i), 150.7 (C, $C_{4'}$). MS (ESI^+, *m/z*): 312 [$(M+Na)^+$, 100%]. HRMS (ESI^+) calcd for $C_{16}H_{23}N_3O_2Na$ $(M+Na)^+$: 312.1682; found: 312.1666. 78% yield, >99% *ee*, 98% *de.*

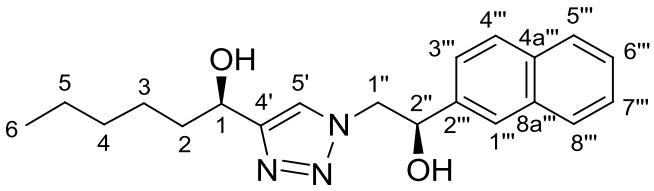
HPLC chromatogram of *rac*-**3bc**



HPLC chromatogram of *syn*-(1*R*,2''*R*)-**3bc**

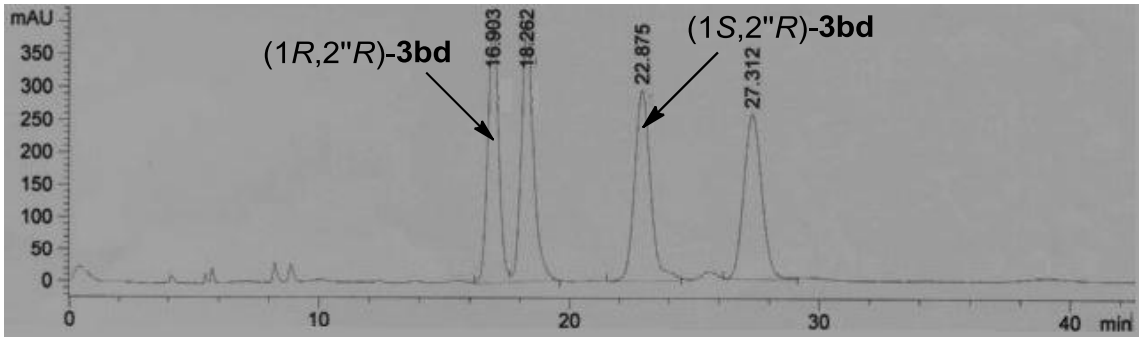


(*R*)-1-{1-[(*R*)-2-Hydroxy-2-(naphthalen-2-yl)ethyl]-1*H*-1,2,3-triazol-4-yl}hexan-1-ol [(1*R*,2''*R*)-3bd]

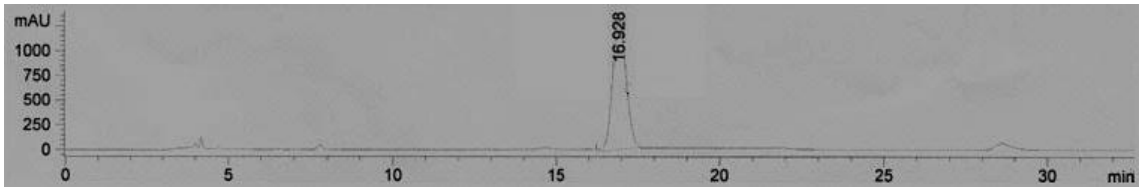


White solid. $[\alpha]_D$ -25.8 (*c* 1.0, 20ºC, MeOH). m.p.: 122-125ºC. IR (KBr): υ 3349, 3139, 2958, 2955, 2858, 1602, 1531, 1467, 1431, 1324, 1216, 1083, 1071, 1040 and 903 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (*t*, 3H, H_6, $^3J_{HH}$ 6.4 Hz), 1.23-1.30 (*m*, 6H, H_3+H_4+H_5), 1.81 (*m*, 2H, H_2), 4.46 (*dd*, 1H, $H_{1''}$, $|^2J_{HH}|$ 14.1 Hz, $^3J_{HH}$ 8.7 Hz), 4.65 (*dd*, 1H, $H_{1''}$, $|^2J_{HH}|$ 13.8 Hz, $^3J_{HH}$ 3.0 Hz), 4.78 (ap *s*, 1H, H_1), 5.33 (*m*, 1H, $H_{2''}$), 7.46-7.52 (*m*, 3H, H_{ar}), 7.56 (*s*, 1H, $H_{5'}$), 7.79-7.86 (*m*, 4H, H_{ar}). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.0 (CH_3, C_6), 22.5 (CH_2, C_5), 25.1 (CH_2, C_4), 31.5 (CH_2, C_3), 36.9 (CH_2, C_2), 50.7 (CH, C_1), 57.4 (CH_2, $C_{1''}$), 72.7 (CH, $C_{2''}$), 123.4 (CH, $C_{5'}$), 125.0 (CH, C_{Ar}), 126.2 (CH, C_{Ar}), 126.4 (CH, C_{Ar}), 127.7 (2CH, C_{Ar}), 128.0 (CH, C_{Ar}), 128.5 (CH, C_{Ar}), 133.1 (2C, $C_{4a'''}$+$C_{8a'''}$), 137.5 (C, C_i), 151.8 (C, $C_{4'}$). MS (ESI^+, *m/z*): 362 [$(M+Na)^+$, 100%]. HRMS (ESI^+) calcd for $C_{20}H_{25}N_3O_2Na$ $(M+Na)^+$: 362.1839; found: 362.1848. 73% yield, >99% *ee*, 98% *de*.

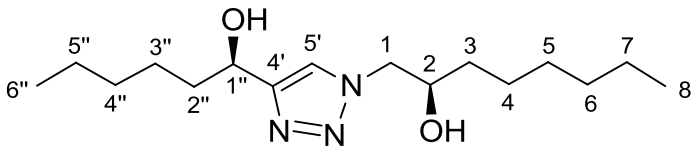
HPLC chromatogram of *rac*-**3bd**



HPLC chromatogram of *syn*-(1*R*,2''*R*)-**3bd**

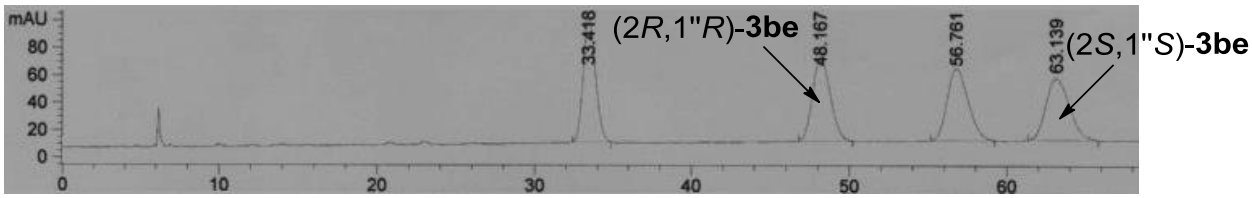


(*R*)-1-{4-[(*R*)-1-Hydroxyhexyl]-1*H*-1,2,3-triazol-1-yl}octan-2-ol [(2*R*,1''*R*)-3be]

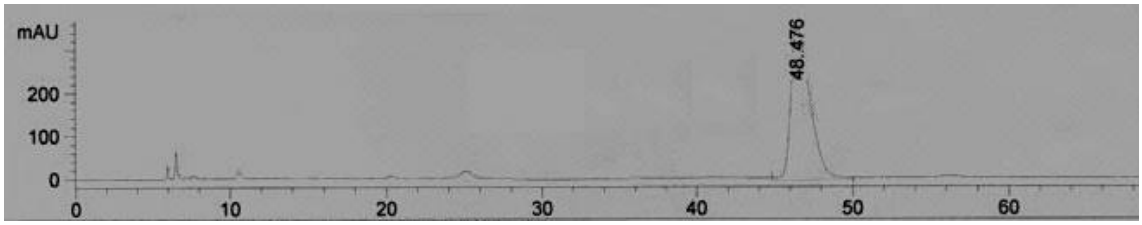


White solid. $[\alpha]_D$ -4.8 (*c* 1.0, 20ºC, MeOH). m.p.: 95-98ºC. IR (KBr): υ 3370, 3150, 2929, 2955, 2856, 1651, 1556, 1567, 1377, 1317, 1217, 1124, 1081 and 927 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (*m*, 6H, $H_{6''}+H_8$), 1.24-1.59 (*m*, 18H, $H_{2''}+H_3+H_{3''}+H_4+H_{4''}+H_5+H_{5''}+H_6+H_7$), 4.01 (*m*, 1H, H_2), 4.16 (*dd*, 1H, H_1, $|^2J_{HH}|$ 13.7 Hz, $^3J_{HH}$ 8.2 Hz), 4.39 (*dd*, 1H, H_1, $|^2J_{HH}|$ 14.0 Hz, $^3J_{HH}$ 2.4 Hz), 4.74 (ap *s*, 1H, $H_{1''}$), 7.56 (*s*, 1H, $H_{5'}$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.9 ($2CH_3$, $C_{6''}+C_8$), 22.5 ($2CH_2$), 25.2 ($2CH_2$), 29.1 (CH_2), 31.6 ($2CH_2$), 34.3 (CH_2), 36.9 (CH_2), 56.2 (CH_2, C_1), 66.5 (CH, C_2), 70.2 (CH, $C_{1''}$), 122.3 (CH, $C_{5'}$), 158.9 (C, $C_{4'}$). MS (ESI^+, *m/z*): 320 $[(M+Na)^+$, 100%]. HRMS (ESI^+) calcd for $C_{16}H_{31}N_3O_2Na$ $(M+Na)^+$: 320.2308; found: 320.2316. 85% yield, 99% *ee*, 98% *de*.

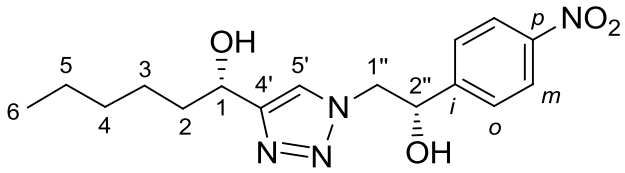
HPLC chromatogram of *rac*-**3be**



HPLC chromatogram of *syn*-(2*R*,1''*R*)-**3be**

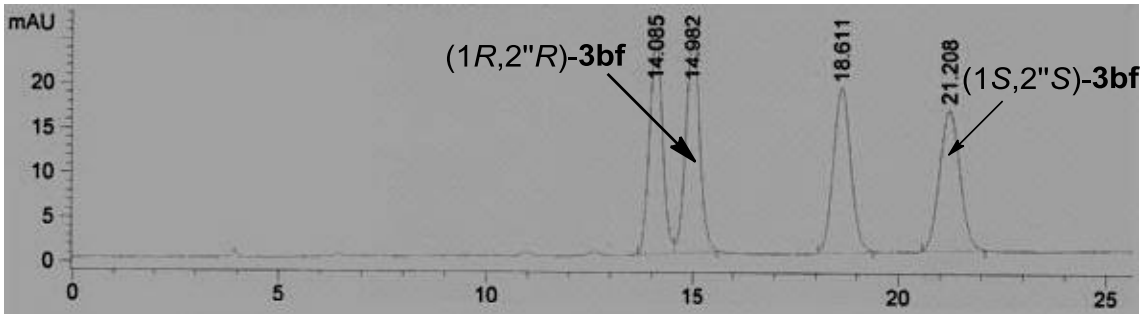


(*S*)-1-{1-[(*S*)-2-Hydroxy-2-(4-nitrophenyl)ethyl]-1*H*-1,2,3-triazol-4-yl]hexan-1-ol [(1*S*,2''*S*)-3bf]

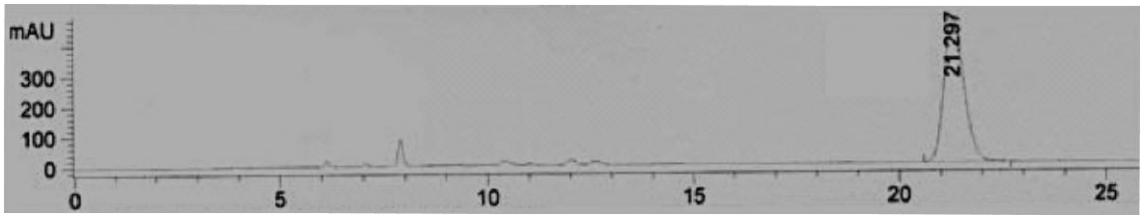


White solid. $[\alpha]_D$ +27.4 (*c* 1.0, 20ºC, MeOH). m.p.: 135-138ºC. IR (KBr): υ 3294, 3146, 2979, 2855, 1599, 1519, 1461, 1440, 1348, 1312, 1254, 1205, 1139, 1106, 1074, 1013, 880 and 856 cm^{-1}. ^{1}H-NMR (300 MHz, MeOH-d_4) δ 0.89 (*t*, 3H, H_6, $^3J_{HH}$ 6 Hz), 1.30-1.33 (*m*, 6H, H_3+H_4+H_5), 1.77-1.80 (*m*, 2H), 4.61-4.65 (*m*, 2H, $H_{1''}$), 4.75 (*t*, 1H, H_1, $^3J_{HH}$ 6.6 Hz), 5.24 (*dd*, 1H, $H_{2''}$, $|^2J_{HH}|$ 6.9 Hz, $^3J_{HH}$ 4.5 Hz), 7.58 (*dd*, 2H, H_o, $^3J_{HH}$ 8.7 Hz, $|^4J_{HH}|$ 3.4 Hz), 7.82 (*s*, 1H, $H_{5'}$), 8.18 (*dd*, 2H, H_m, $^3J_{HH}$ 8.7 Hz, $|^4J_{HH}|$ 2.2 Hz). ^{13}C-NMR (75 MHz, MeOH-d_4) δ 14.3 (CH_3, C_6), 23.5 (CH_2, C_5), 26.0 (CH_2, C_4), 32.6 (CH_2, C_3), 38.2 (CH_2, C_2), 57.5 (CH_2, $C_{1''}$), 67.5 (CH, C_1), 72.5 (CH, $C_{2''}$), 124.2 (CH, $C_{5'}$), 124.5 (2CH, C_o), 128.3 (2CH, C_m), 148.9 (C, C_p), 149.7 (C, C_i), 152.4 (C, $C_{5'}$). MS (ESI^+, *m/z*): 335 [$(M+H)^+$, 100%]. HRMS (ESI^+) calcd for $C_{16}H_{22}N_4O_4Na$ $(M+Na)^+$: 357.1533; found: 357.1533. 71% yield, 99% *ee*, 99% *de*.

HPLC chromatogram of *rac*-**3bf**



HPLC chromatogram of *syn*-(1*S*,2''*S*)-**3bf**



3. Analytics

3.1. GC Analyses for determination of conversions and enantiomeric excess of alcohols ***2***

The following columns were used: **A**: Varian Chirasil Dex CB (25 m x 0.25 mm x 0.25 µm, 12.2 psi N_2); and **B**: Restek RT-BetaDEXse (30 m x 0.25 mm x 0.25 µm, 12.2 psi N_2).

Table S3 Retention times for determination of enzymatic conversions and *ee* by GC

compound	column	program[a]	retention time (min)		
			ketone	alcohol **2**	
			1	(*R*)	(*S*)
a	B	35/10/8/90/0/20/180/2	5.6	13.8	14.5
b	B	70/5/1/95/0/20/180/5	25.3	31.9	32.7
c	B	90/4/5/180/5	22.4	23.6	
c[b]	B	90/5/2.5/105/0/5/135/0/2.5/145/0/20/180/2	-	40.7	39.6
e	B	70/5/1/95/0/20/180/5	37.4	38.8	38.2

[a] Program: initial temp. (°C)/ time (min)/ slope (°C/min)/ temp. (°C)/ time (min)/ slope (°C/min)/ final temp. (°C)/ time (min). [b] Determined as the corresponding *O*-acetyl derivative.

*3.2. HPLC analyses for determination of conversions and enantiomeric excess of alcohol **2d**, **2f** and **2g***

The following HPLC conditions were used: **A**: column Chiralpak OD-H (0.46 cm x 25 cm, Daicel Chemical Ind. Ltd.); isocratic eluent: *n*-hexane / *i*-propanol (80:20), 30°C, flow 0.8 mL min^{-1}. **B**: column Chiralpak IC (4.0 mm x 10 mm, Daicel Chemical Ind. Ltd.); isocratic eluent: *n*-hexane / *i*-propanol (92:8), 40°C, flow 0.8 mL min^{-1}; **C**: column Chiralpak IC (4.0 mm x 10 mm, Daicel Chemical Ind. Ltd.); isocratic eluent: *n*-hexane / *i*-propanol (95:5), 40°C, flow 0.8 mL min^{-1}

Table S4 Retention times for determination of alcohol *ee* values by HPLC

compound	conditions	retention time (min)		
		ketone	alcohol **2**	
		1	(*R*)	(*S*)
d	A	11.4	10.4	8.9
f	B	47.0	37.1	28.8
g	C	19.3	27.4	28.7

3.3. HPLC analyses for determination of ee *and* de *of diols* syn- *and* anti-***3***

The following HPLC conditions were used: **A**: column Chiralpak IC (4.0 mm x 10 mm, Daicel Chemical Ind. Ltd.); isocratic eluent: *n*-hexane / *i*-propanol (80:20), 40°C, flow 0.8 mL min^{-1}; **B**: column Chiralpak IC (4.0 mm x 10 mm, Daicel Chemical Ind. Ltd.); isocratic eluent: *n*-hexane / *i*-propanol (85:15), 40°C, flow 0.8 mL min^{-1}; **C**: column Chiralpak IC (4.0 mm x 10 mm, Daicel Chemical Ind. Ltd.); isocratic eluent: *n*-hexane / *i*-propanol (90:10), 40°C, flow 0.8 mL min^{-1}. **D**: column Chiralpak IC (4.0 mm x 10 mm, Daicel Chemical Ind. Ltd.); isocratic eluent: *n*-hexane / *i*-propanol (84:16), 40°C, flow 0.8 mL min^{-1}. **E**: column Chiralpak OJ-H (4.0 mm x 10 mm, Daicel Chemical Ind. Ltd.); isocratic eluent: *n*-hexane / *i*-propanol (85:15), 40°C, flow 0.8 mL min^{-1}.

Table S5 Retention times for determination of *ee* and *de* values of *syn*- and *anti*-**3** by HPLC

compound	conditions	retention time (min)			
		syn-**3**		*anti*-**3**	
		(*R*,*R*)	(*S*,*S*)	(*S*,*R*)	(*R*,*S*)
ac	A	18.5	25.4	16.3	22.1
ad	A	21.8, 31.7, 34.4[a]			26.6
ae	B	22.4	28.2	16.3	26.5
af	D	33.0, 46.1, 49.2[a]			39.5
ag	E	35.4, 39.2, 43.7[a]			28.6
bc	A	15.2	22.0	13.4, 19.5[a]	
bd	A	16.9	--[b]	22.9	--[b]
be	C	48.1	63.1	33.4, 56.7[a]	
bf	A	15.0	21.2	14.0, 18.6[a]	

[a] At this stage is not possible to assign these retention times to any diastereisomer.
[b] The other two isomers (*S*,*S*) and (*R*,*S*) showed retention times of 18.3 and 27.3 min.

4. Supporting references.

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2. S. Eagon, N. Ball-Jones, D. Haddenham, J. Saavedra, C. Delieto, M. Buckman and B. Singarm, *Tetrahedron Lett.*, 2010, **51**, 6418.

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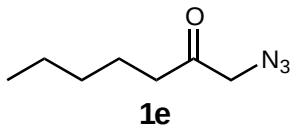
5. Compound NMR spectra



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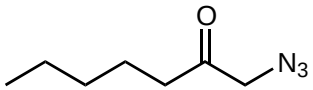

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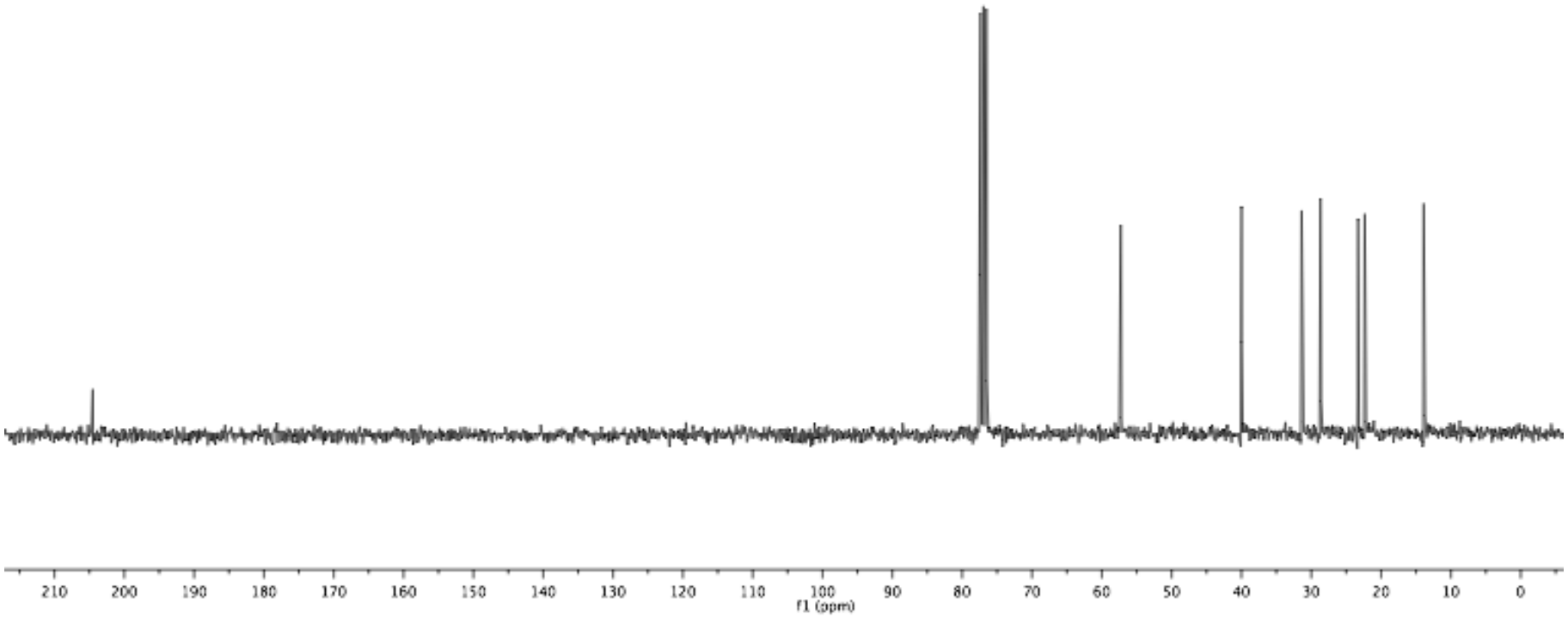

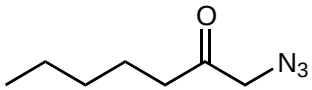

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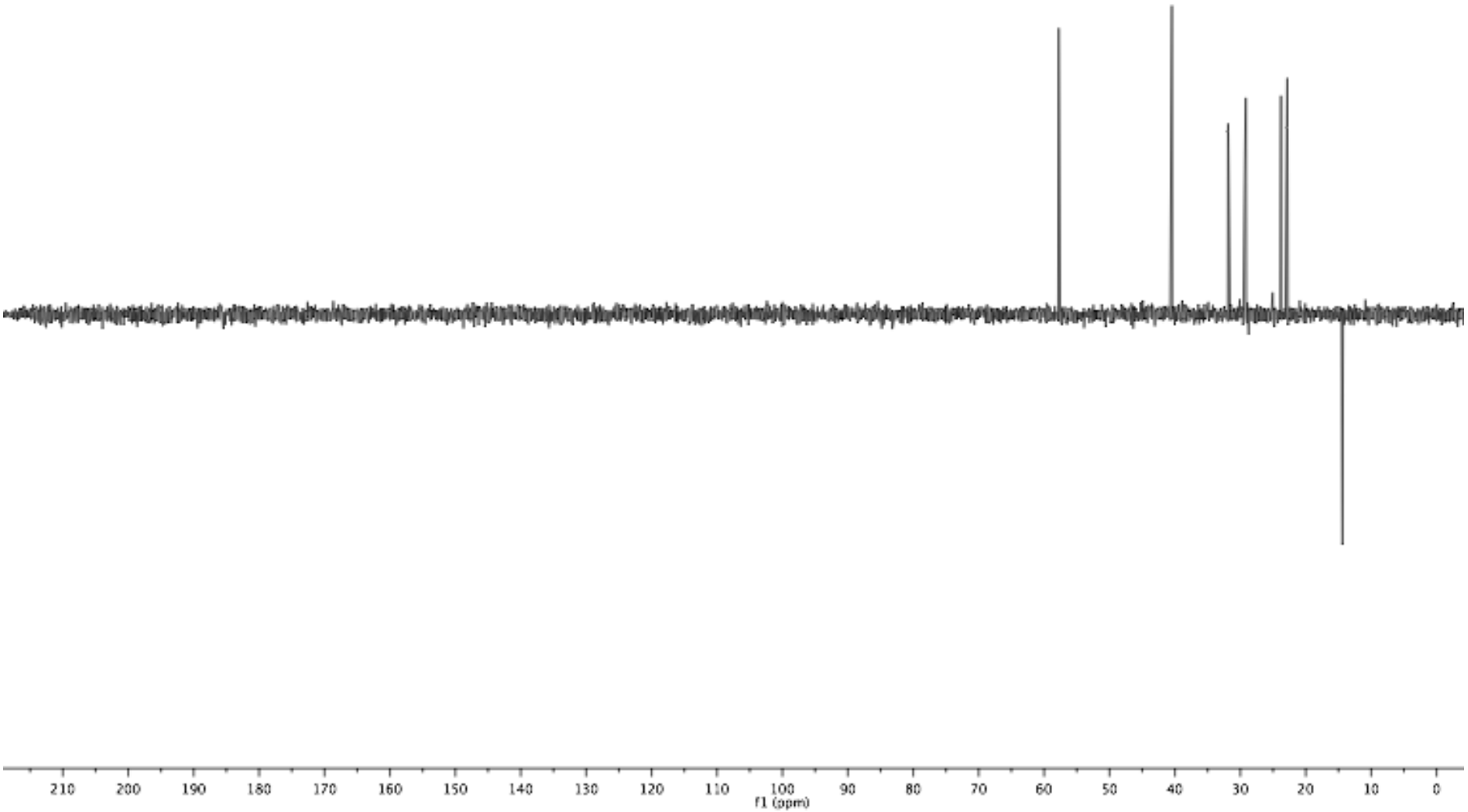

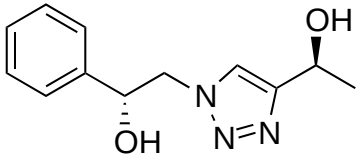

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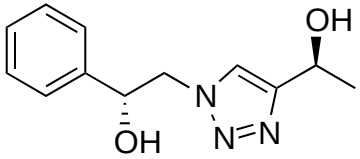

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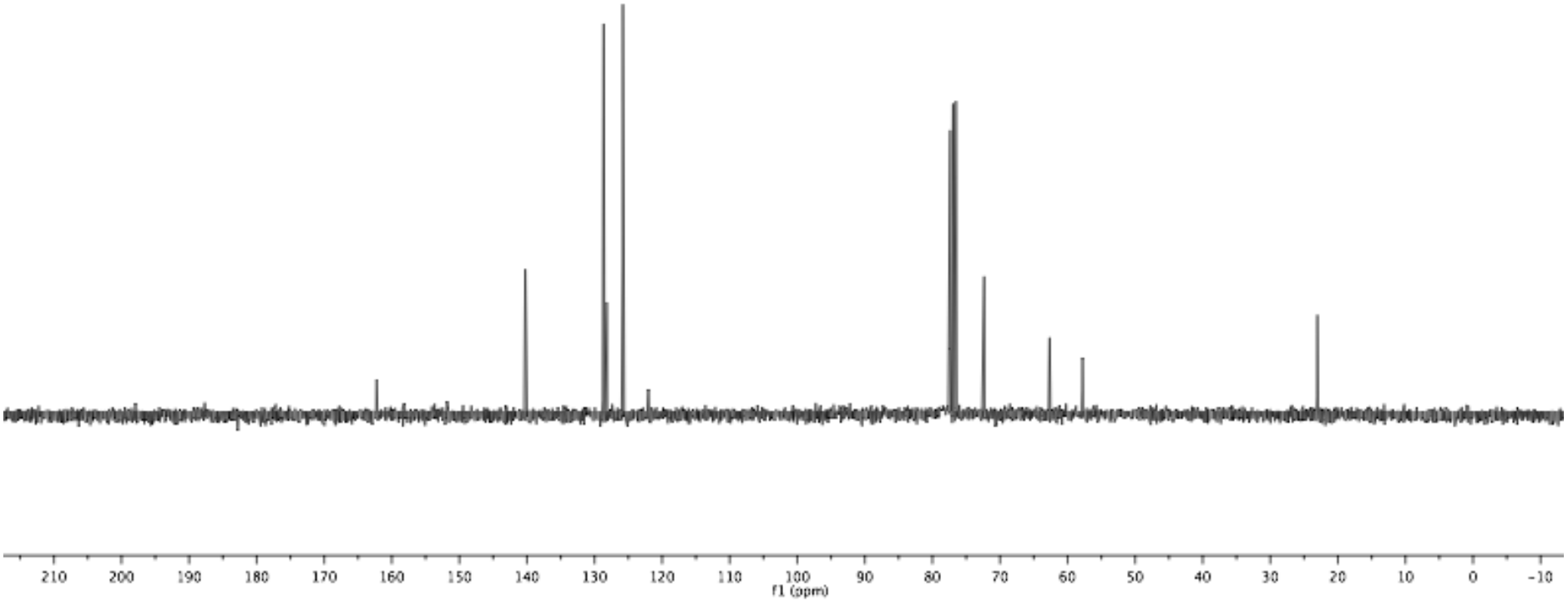

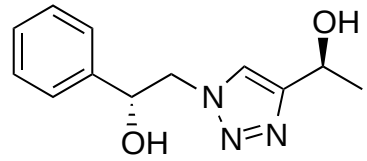

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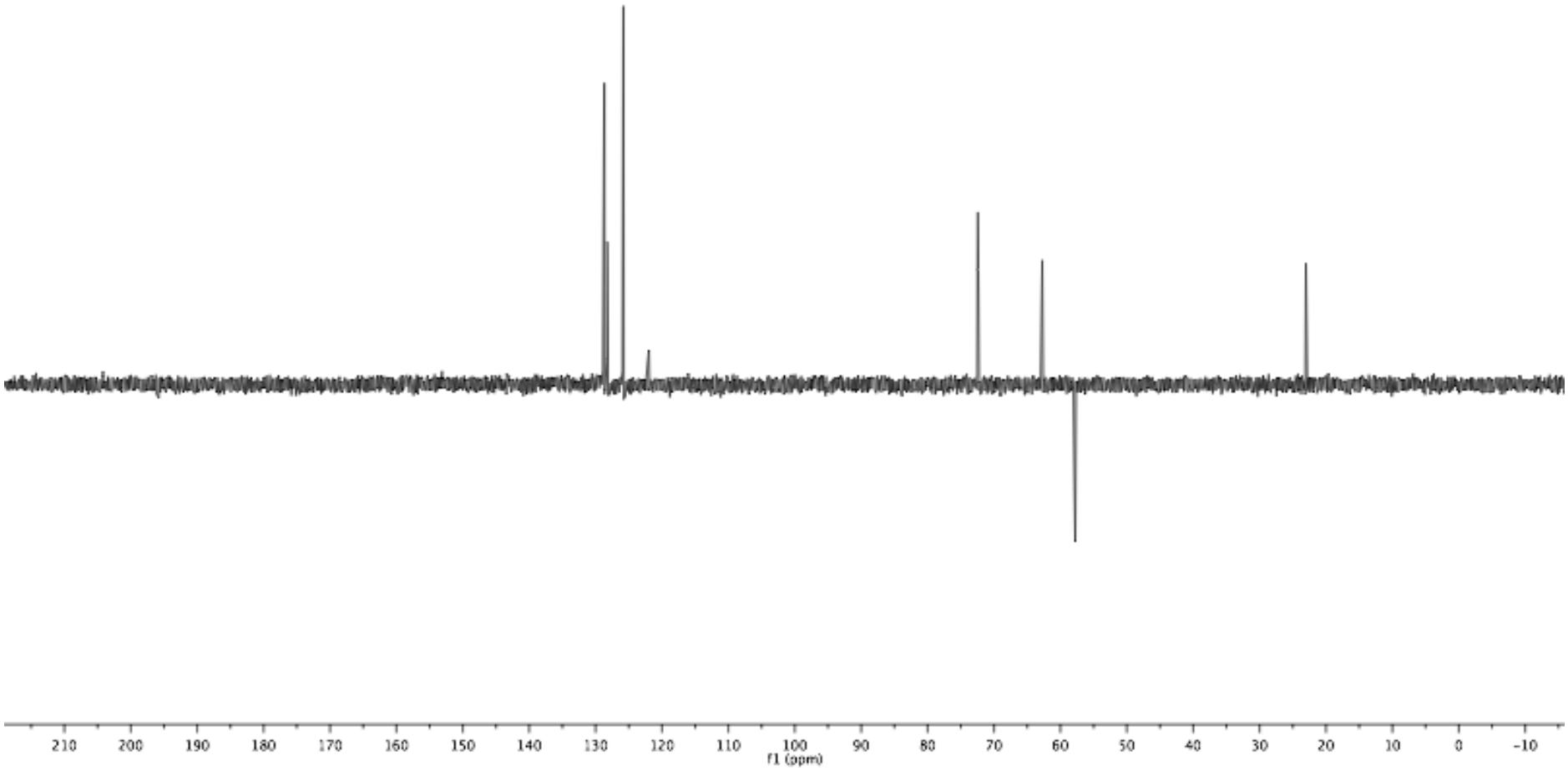

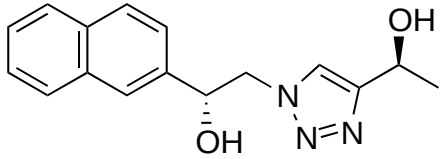

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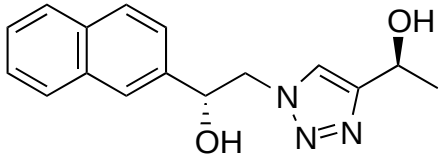

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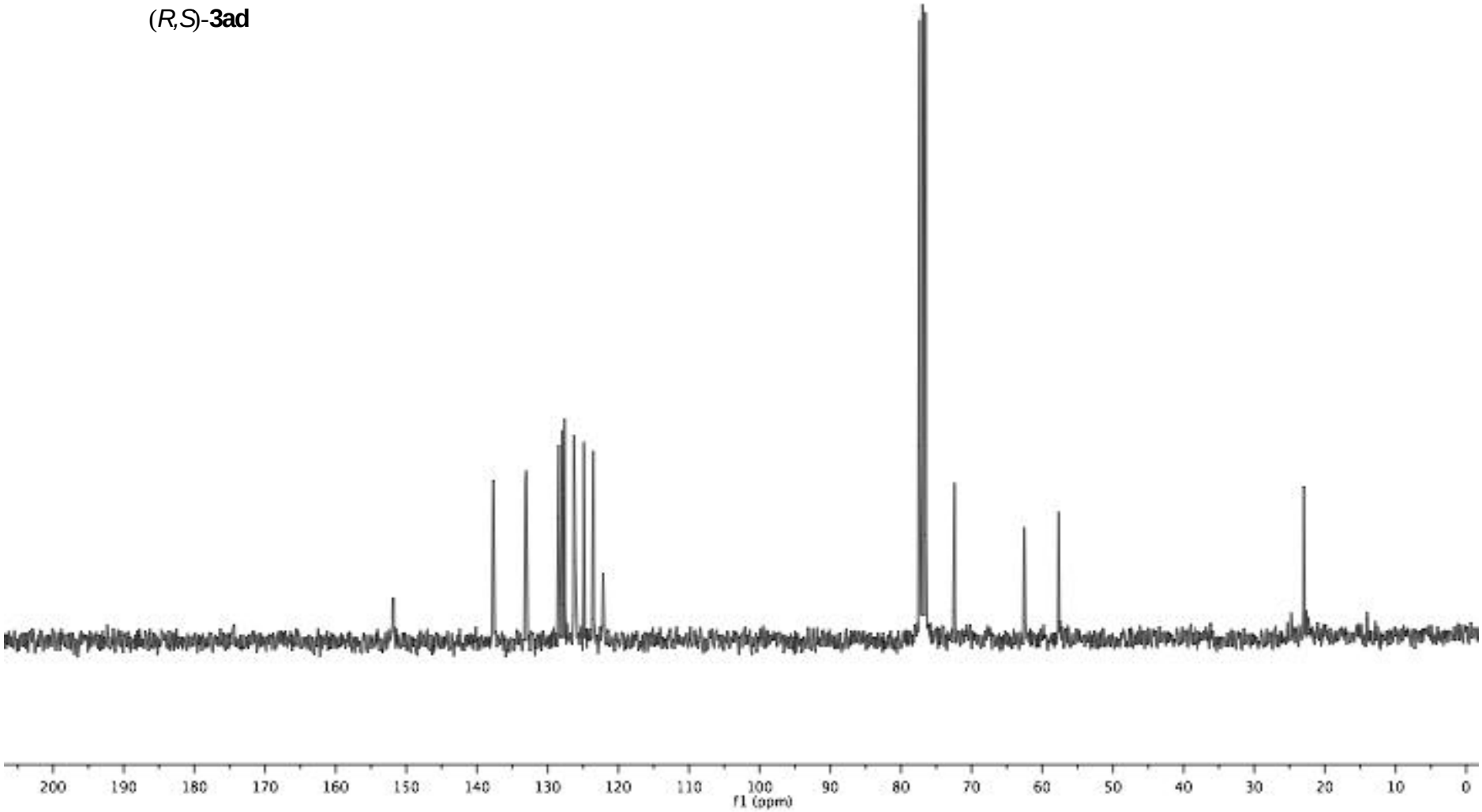

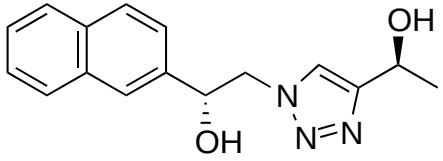
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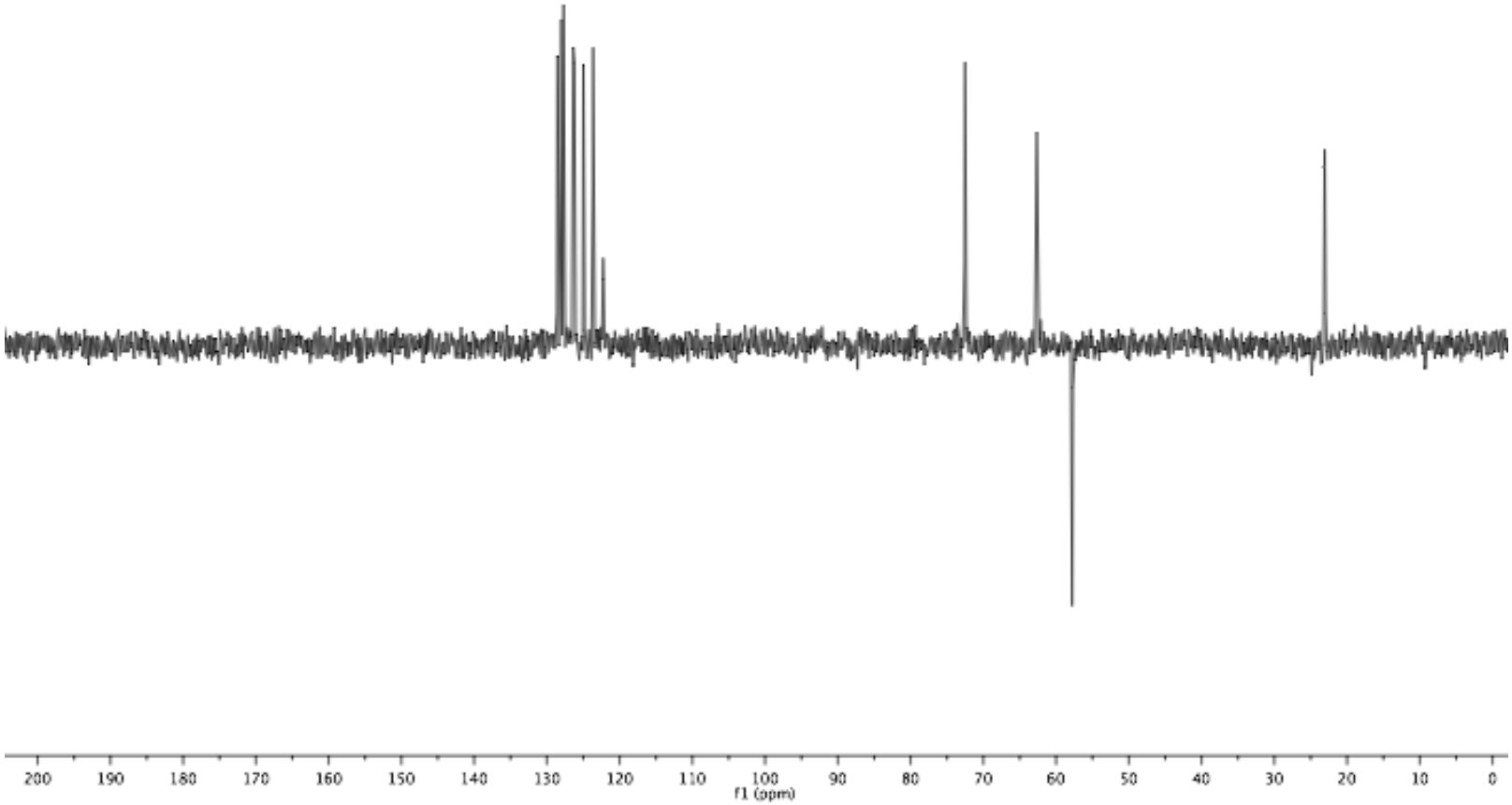
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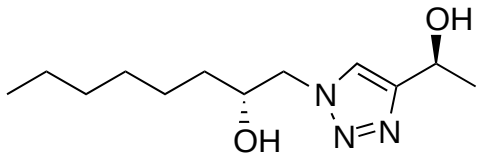

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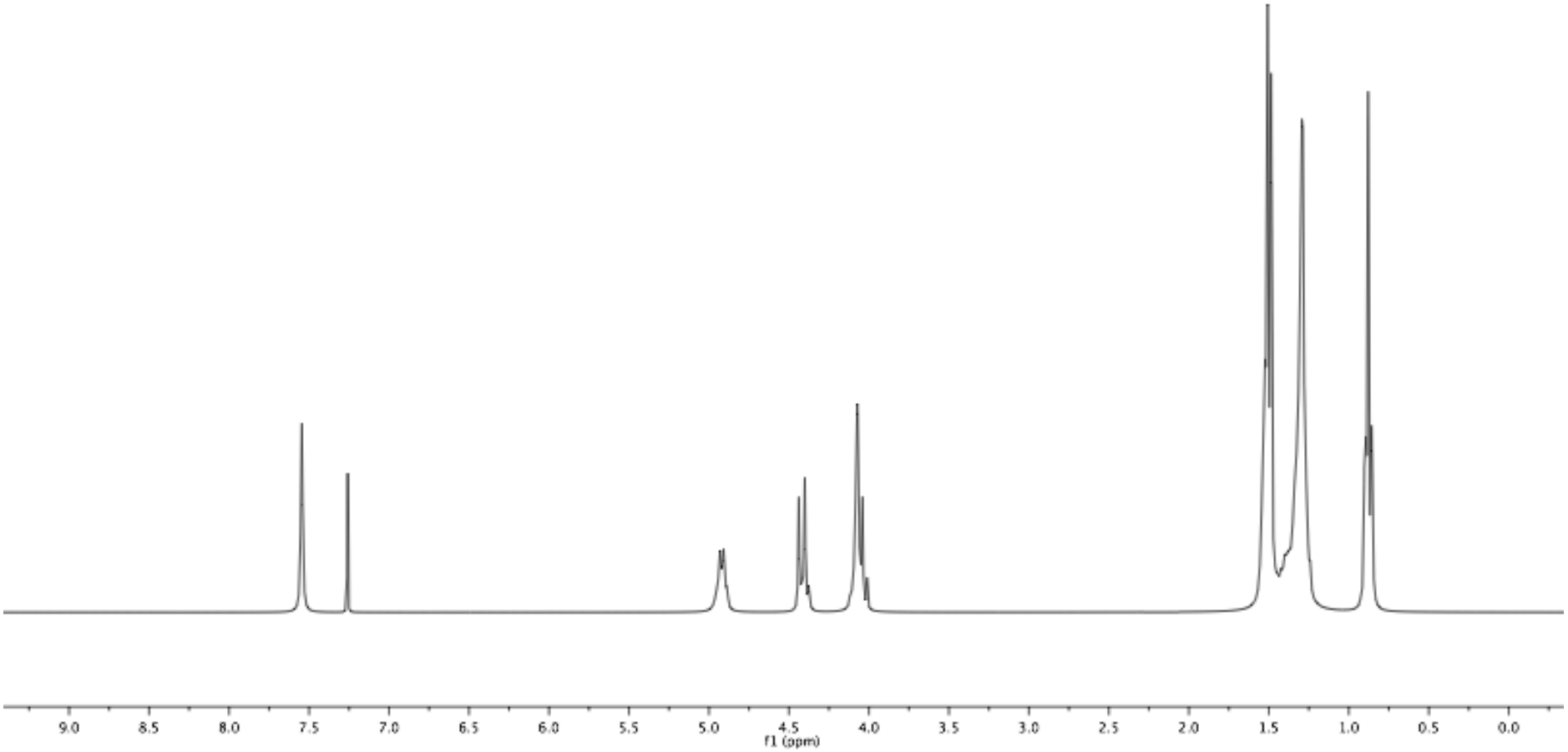

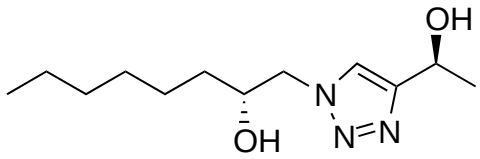

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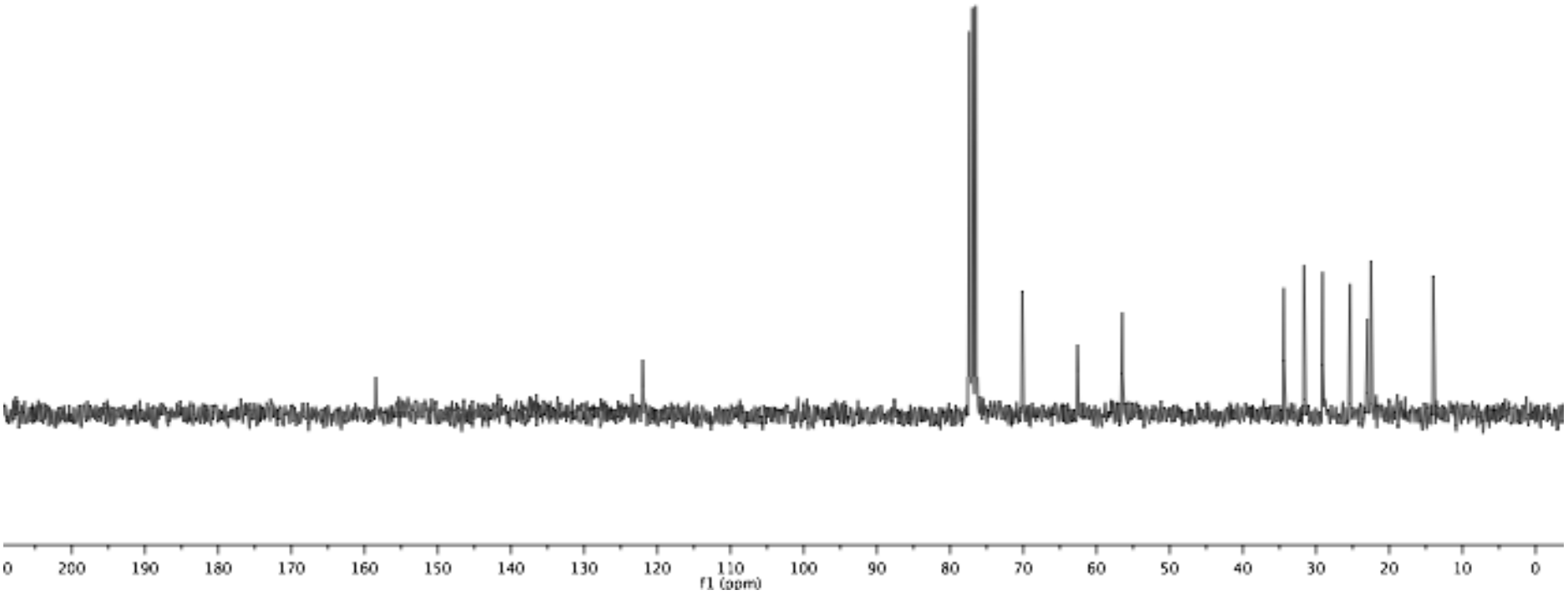

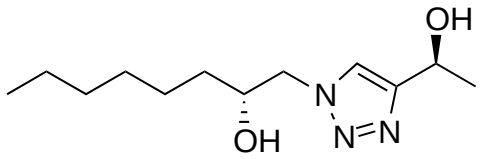

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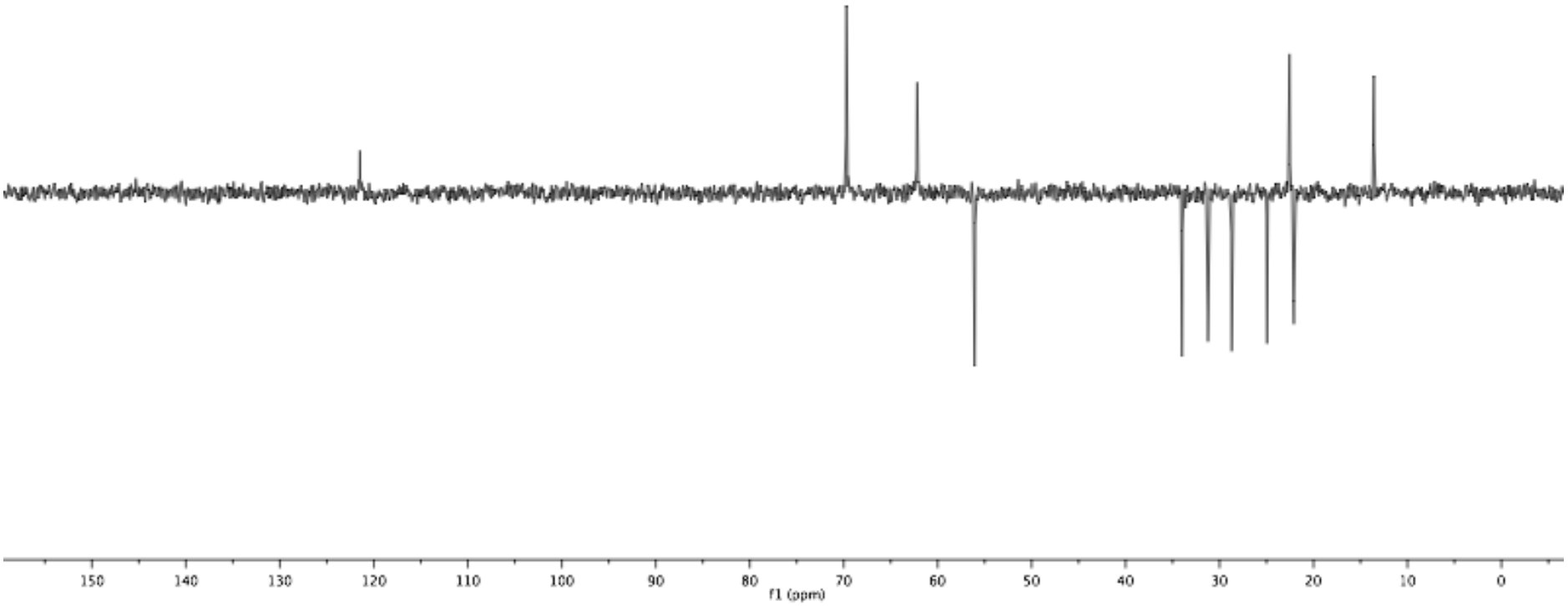

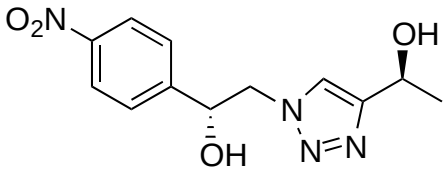

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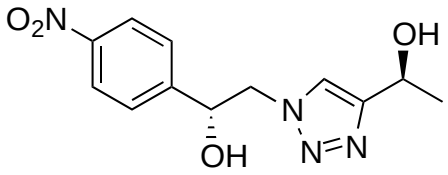

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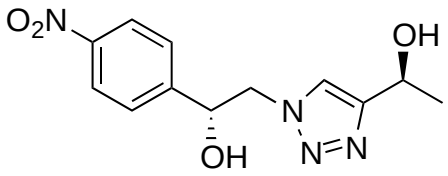

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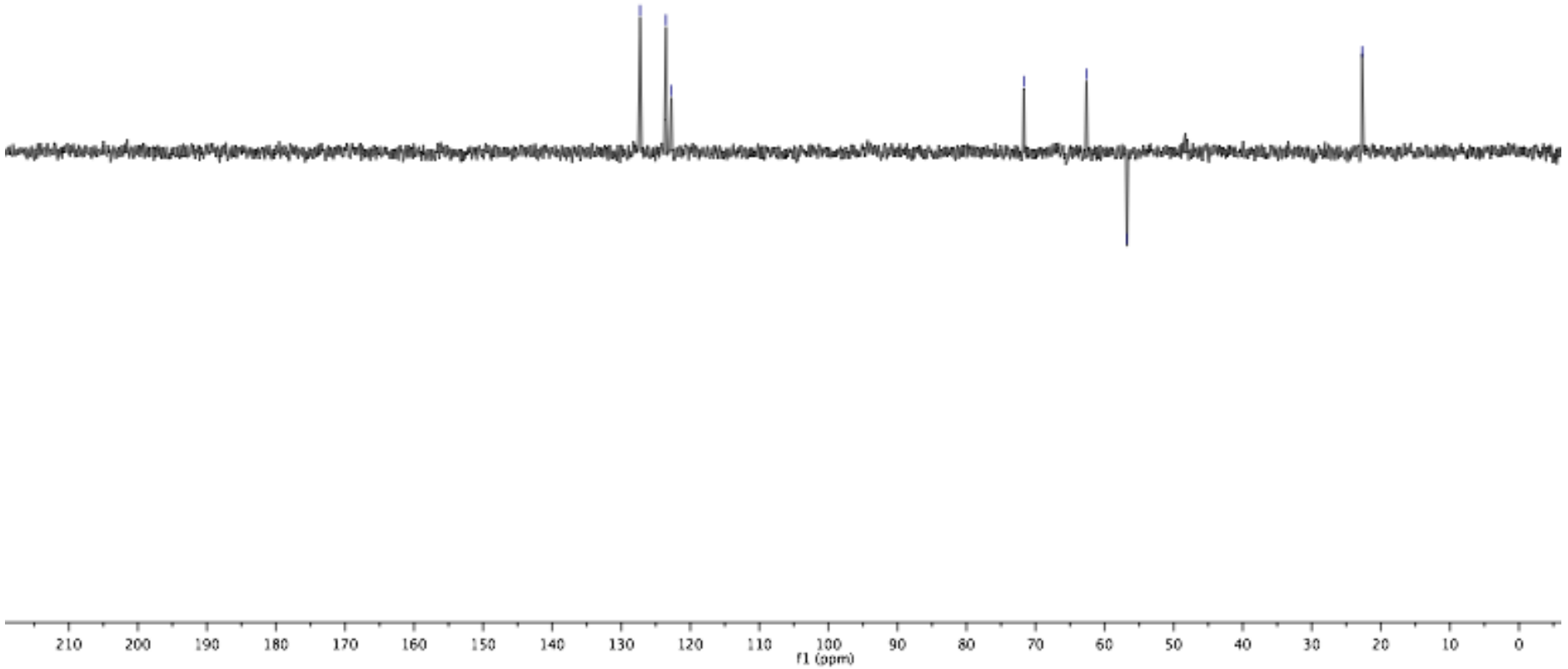

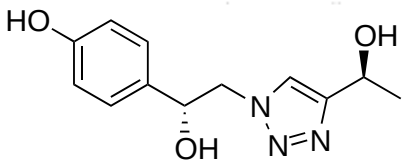

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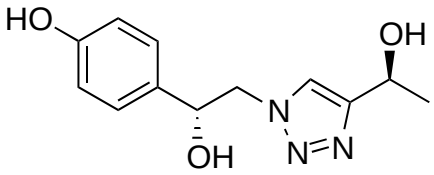

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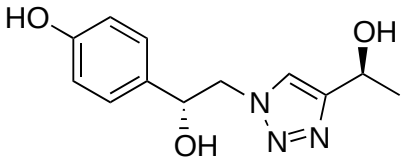

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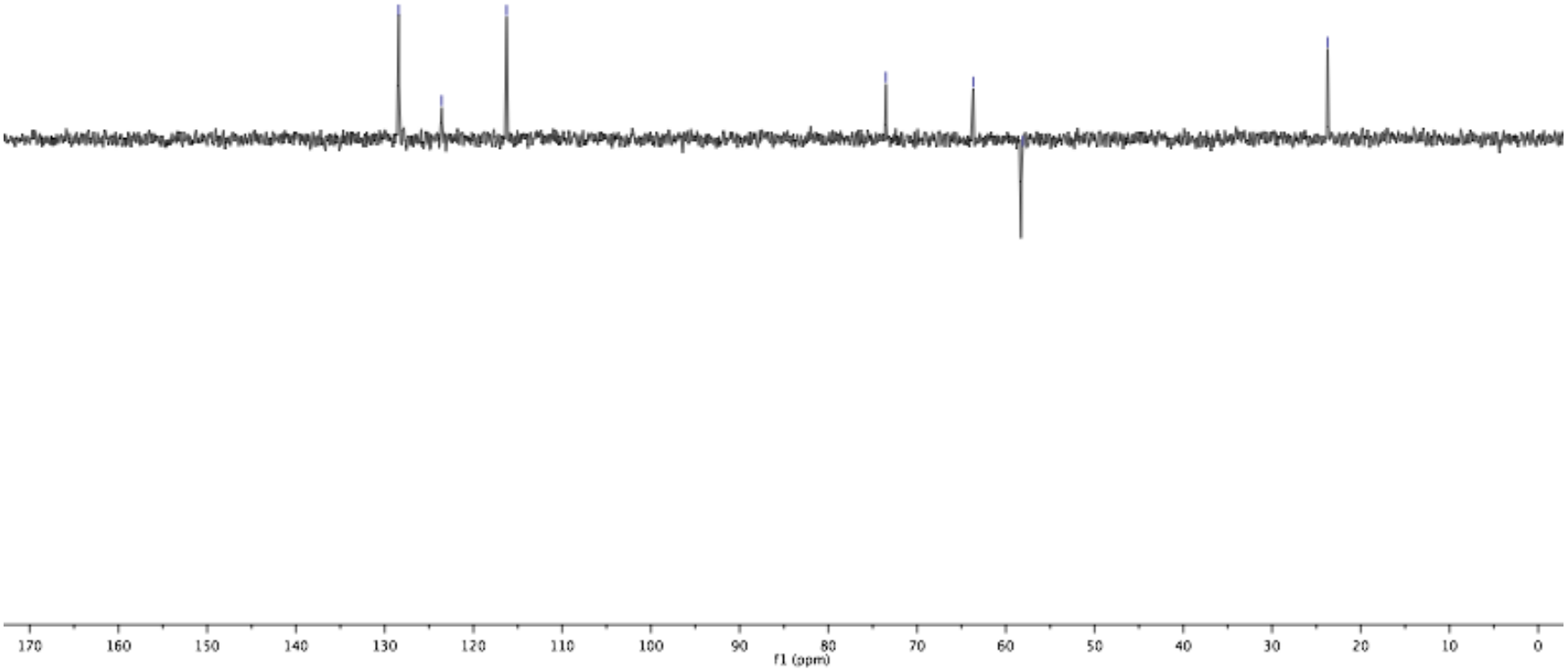

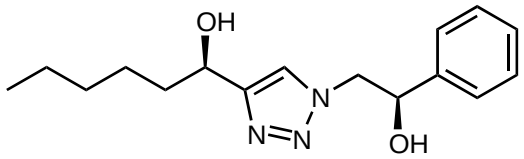

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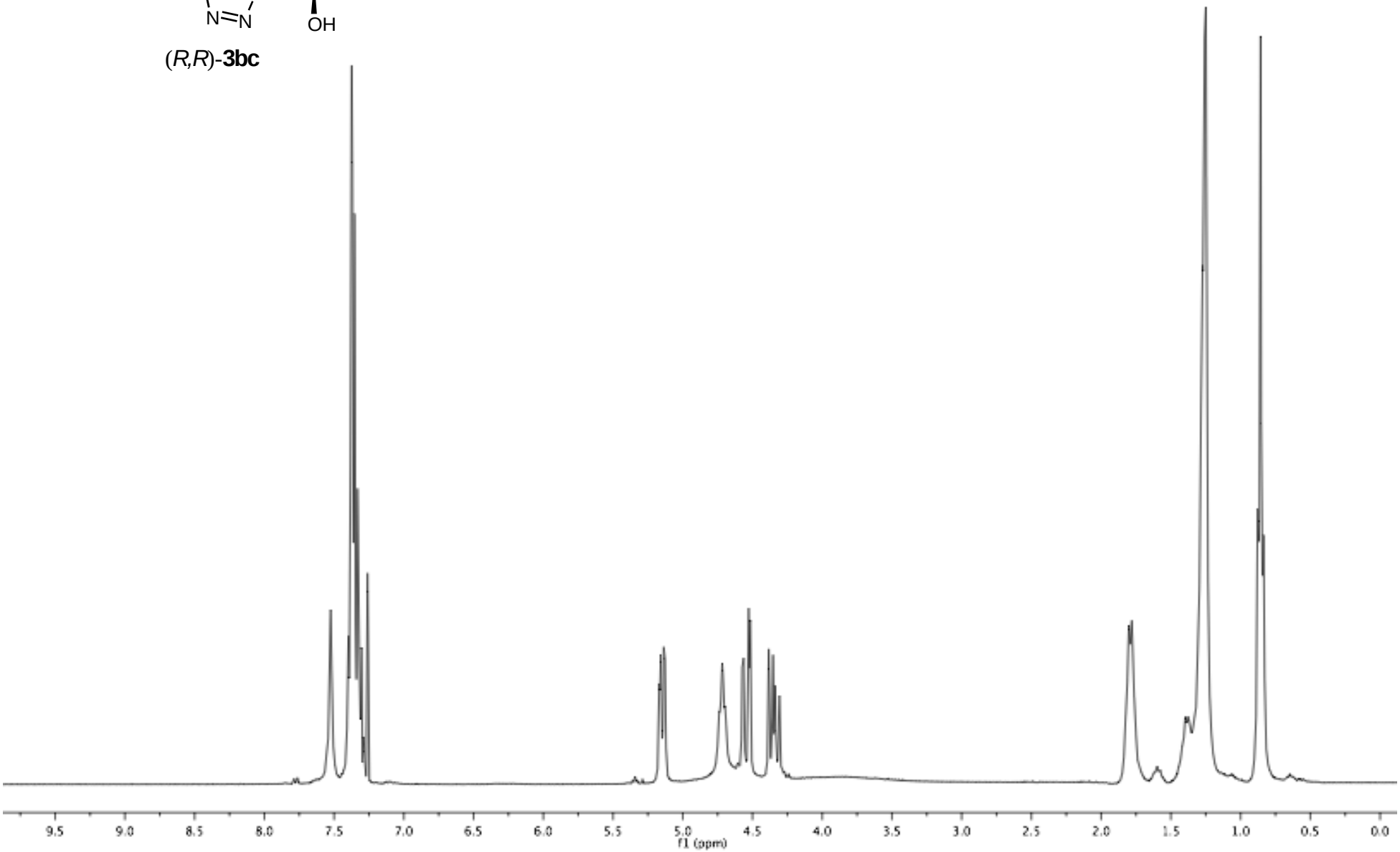

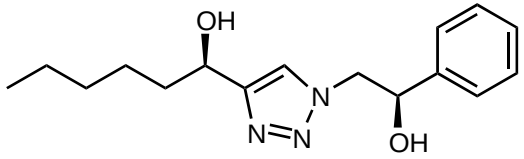

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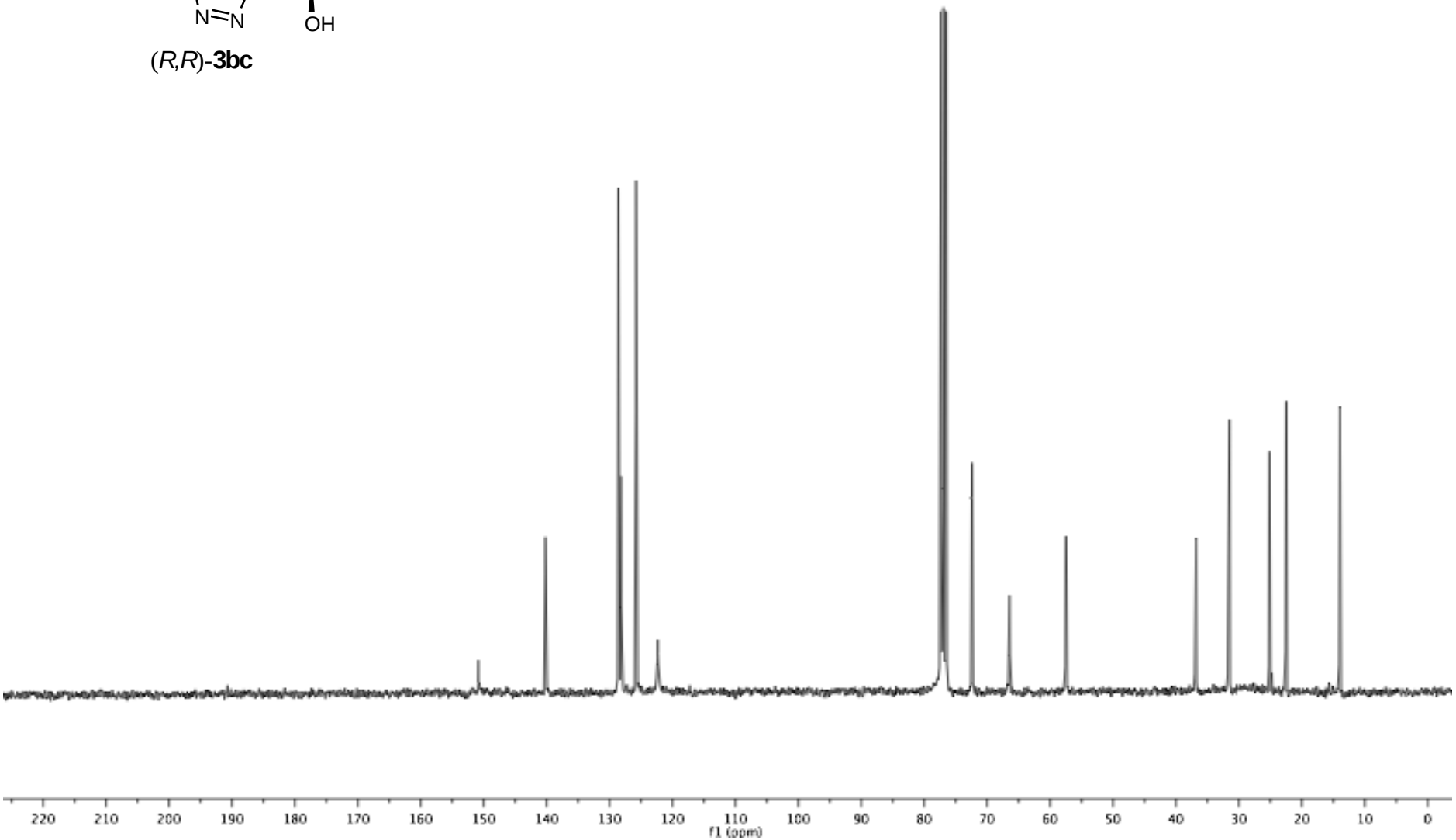

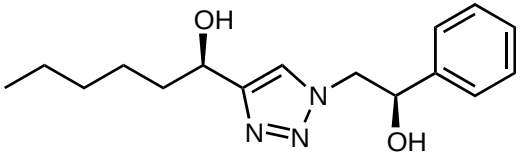

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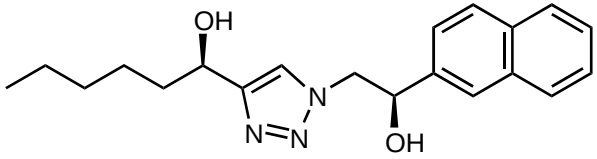

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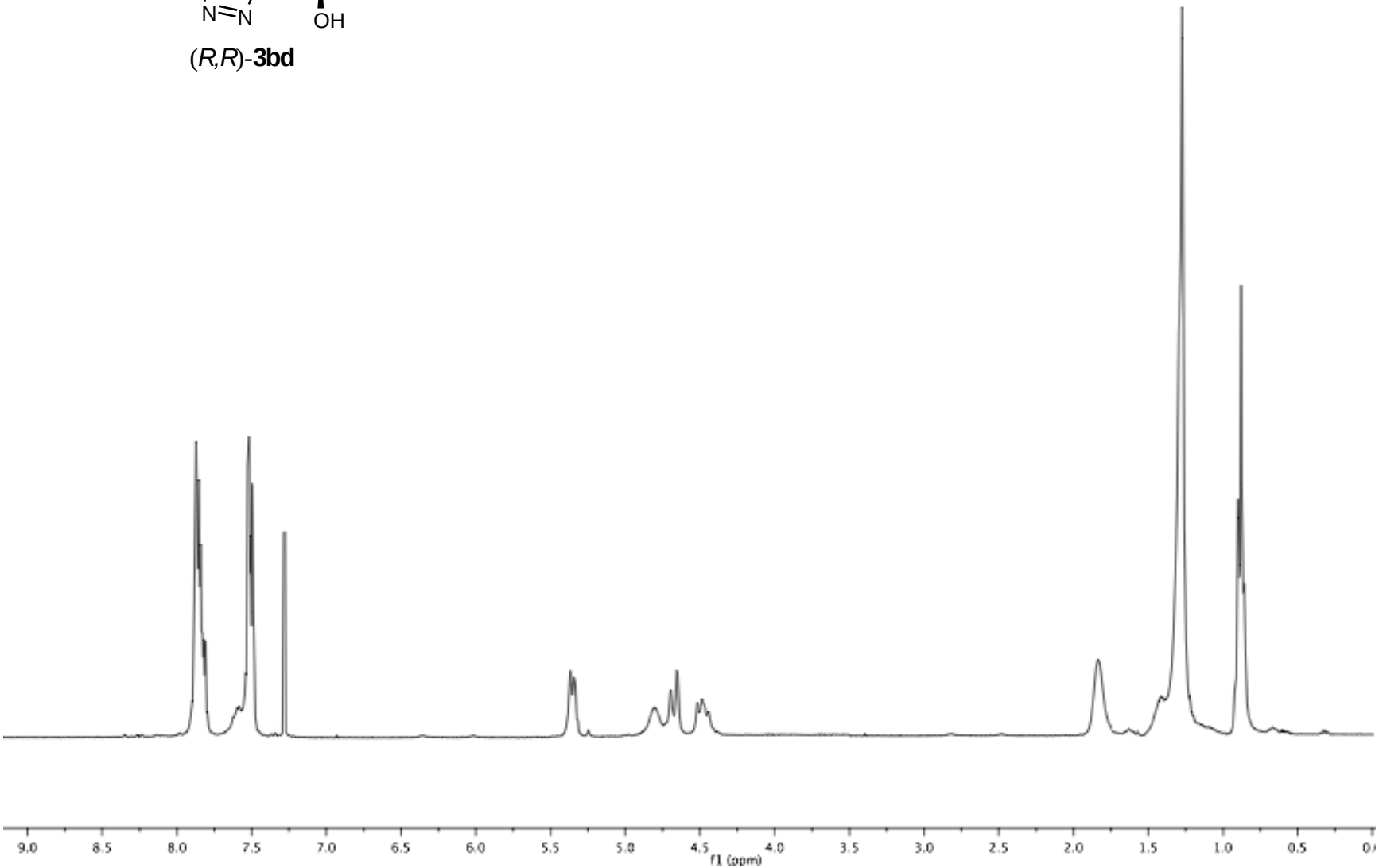

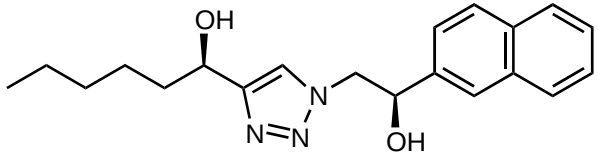
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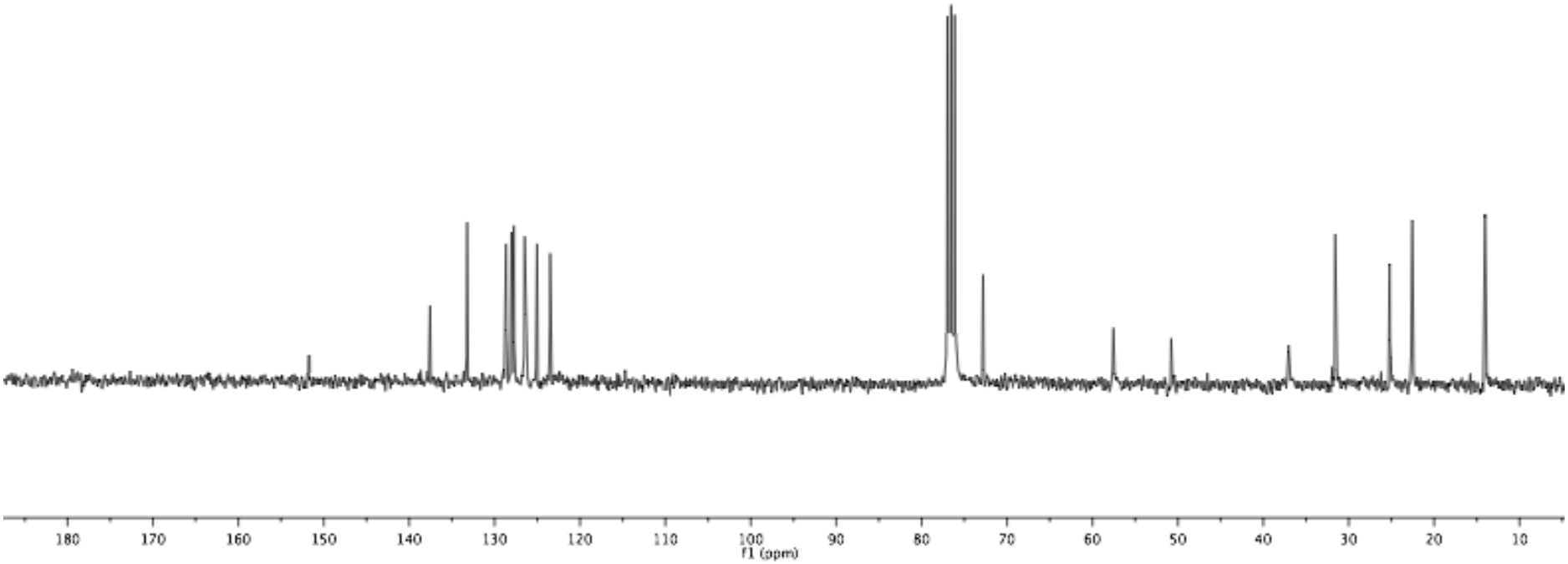
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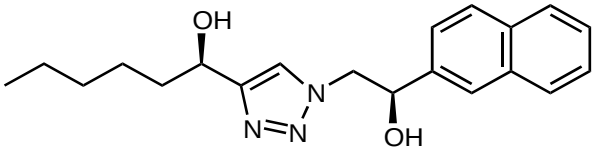

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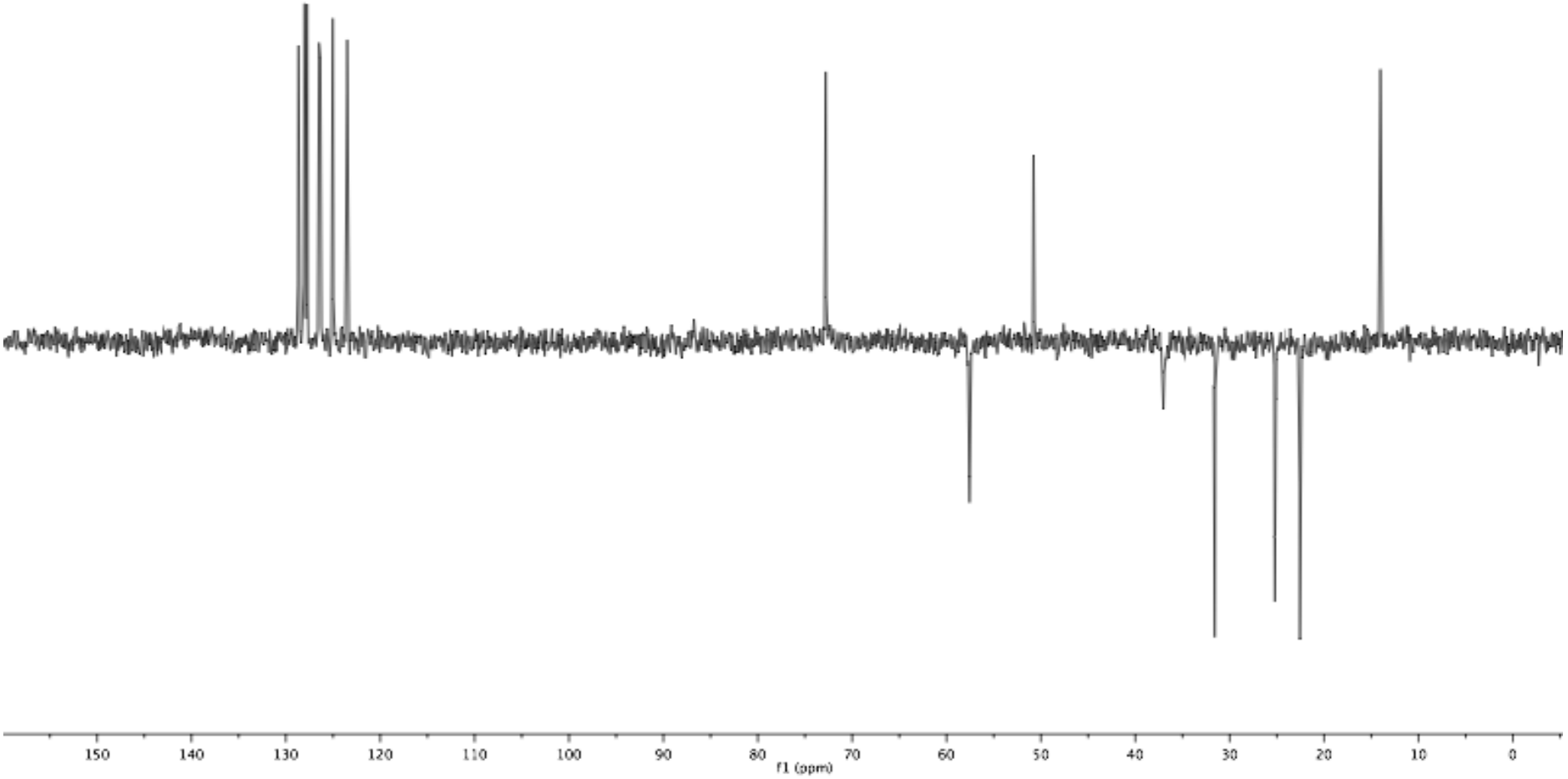

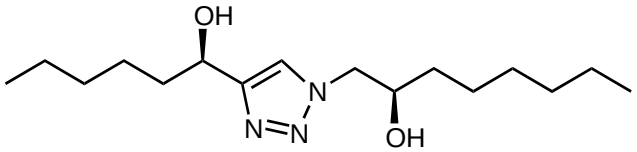

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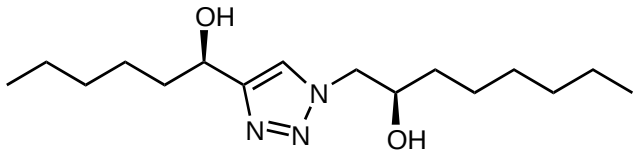

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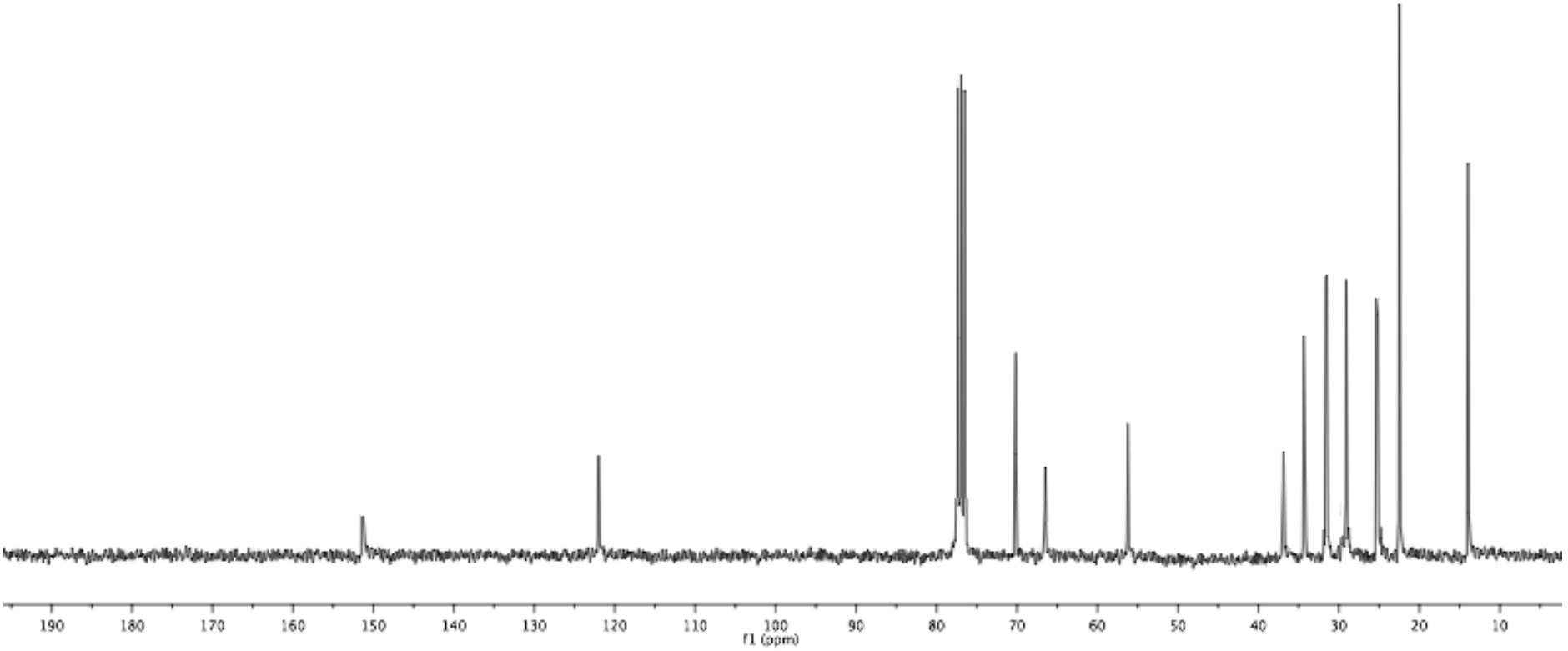

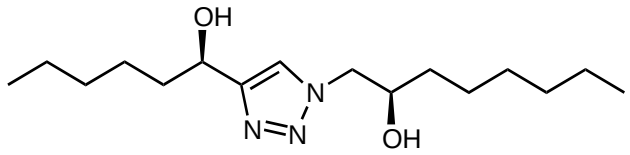

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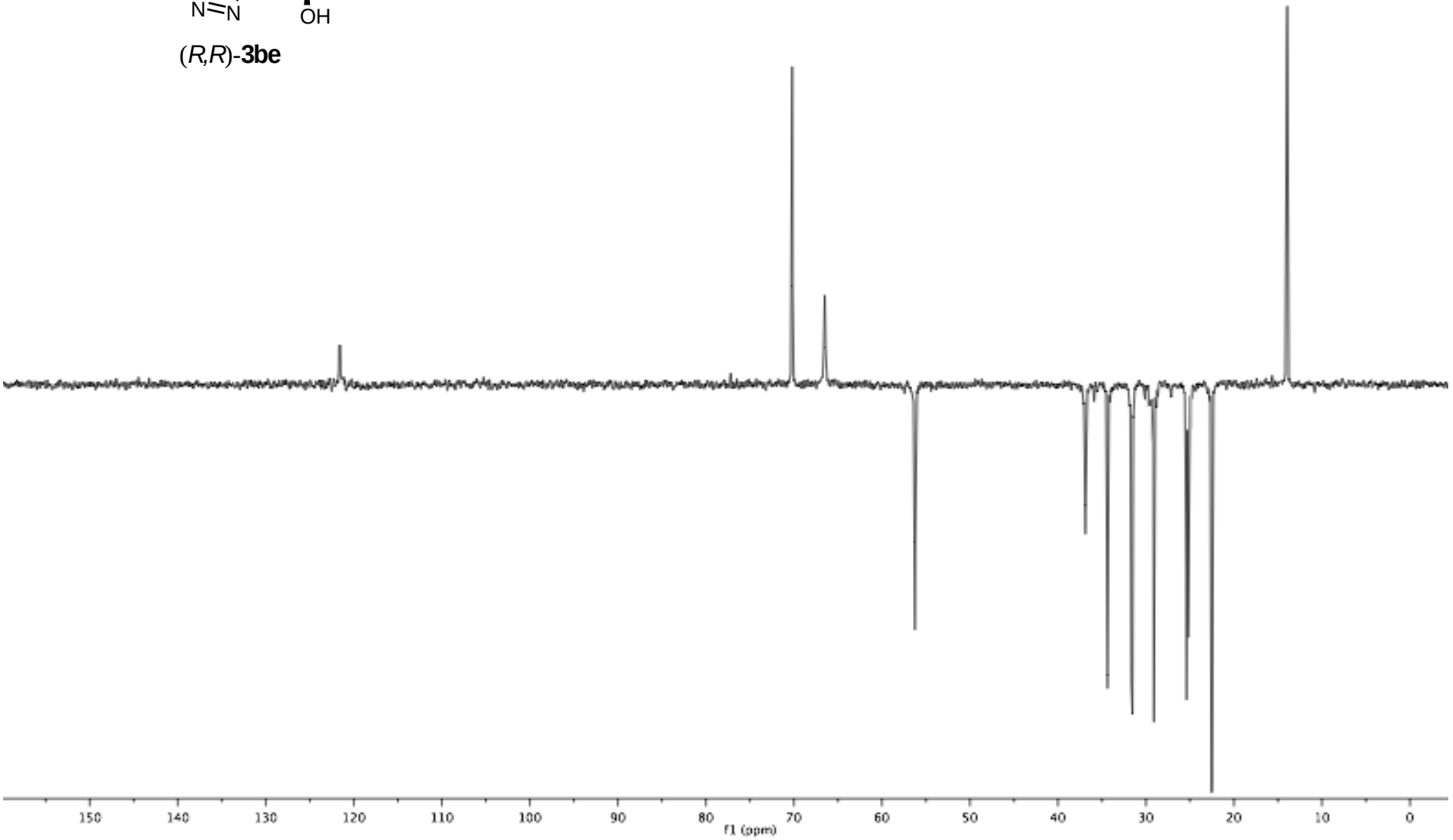

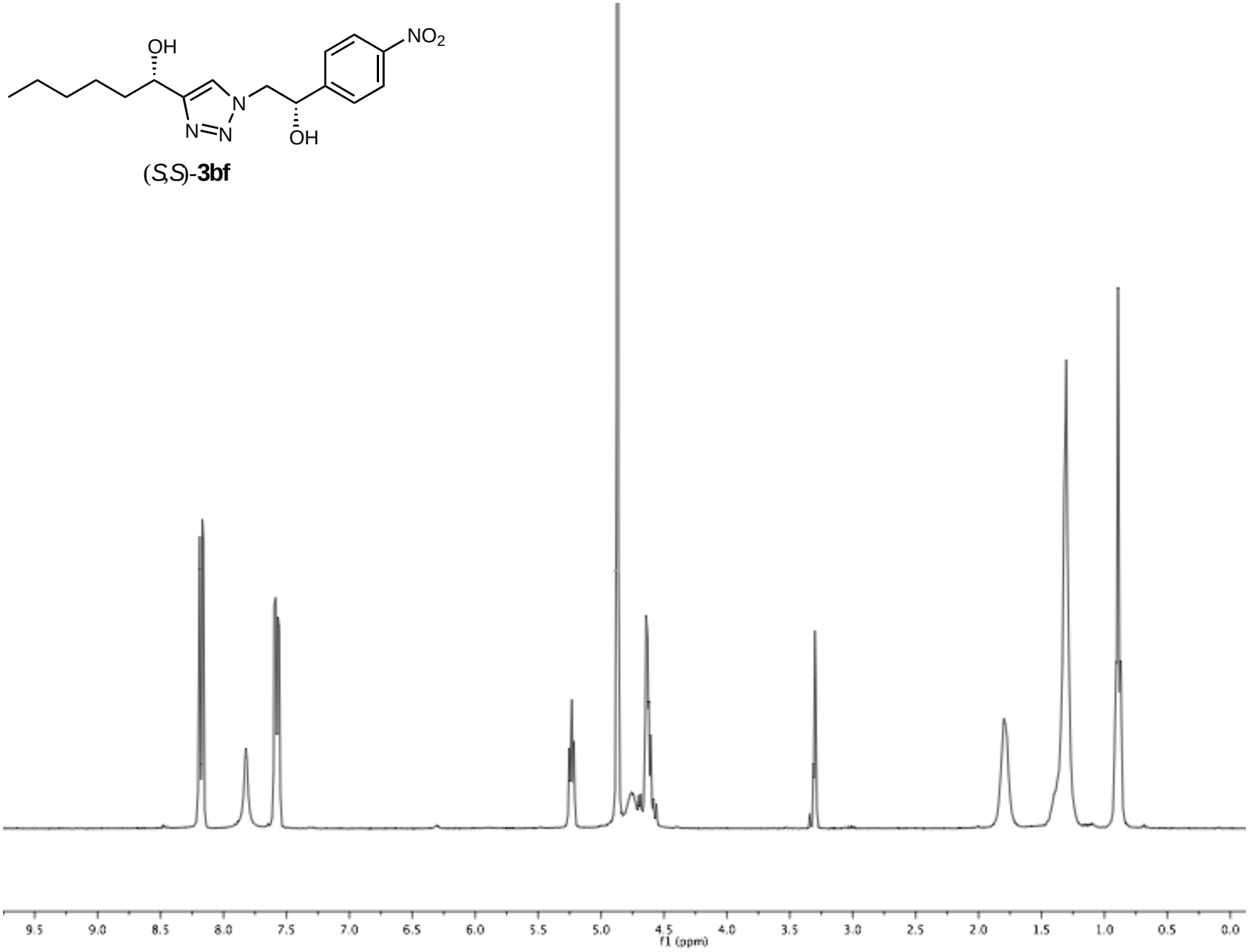

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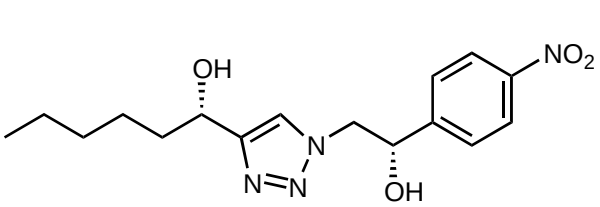

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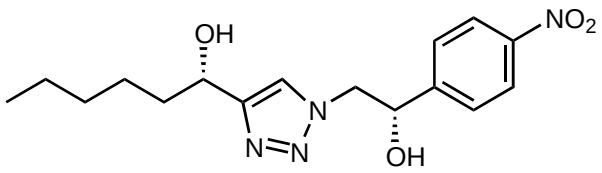

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