Supplementary Information to Asymmetric *anti*-Mannich Reactions in Continuous Flow

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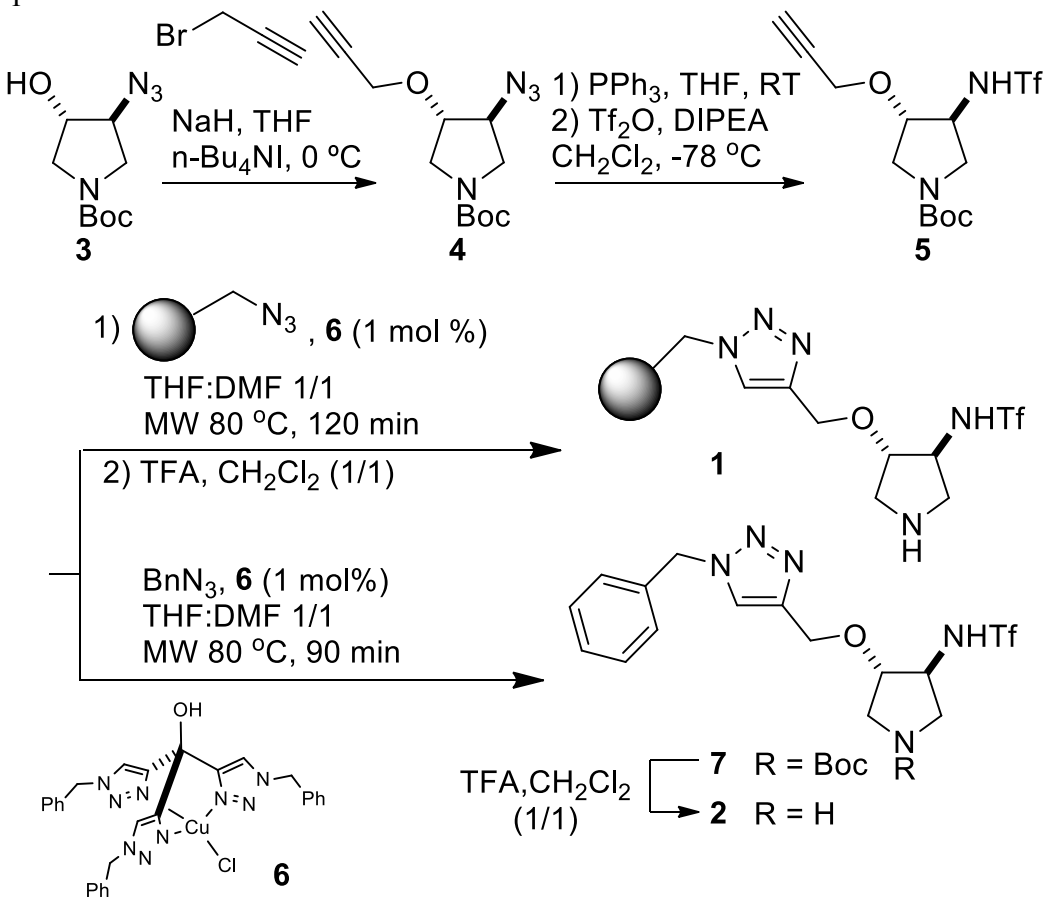
1. General information

All reactions were conducted under air. Synthesis grade solvents were used as received. Unless otherwise stated, all commercial reagents were used as received except the aldehydes that were distilled before using (Aldrich). Merrifield resin (1% DVB, f = 0.53 mmol of Cl g^{-1} resin) was purchased from Novabiochem. PMP-protected α-iminoester **9** was synthesized following reported procedures.[1] All flash chromatography purifications were carried out using 60 mesh silica gel and dry-packed columns. Thin layer chromatography was carried out using Merck TLC Silicagel 60 F254 aluminium sheets. NMR spectra were recorded at 298 K on a Fourier 300 MHz Bruker, a Bruker Avance 400 Ultrashield or a Bruker Avance 500 Ultrashield apparatus. ^{1}H NMR spectroscopy chemical shifts are quoted in ppm relative to tetramethylsilane (TMS). $CDCl_3$ was used as internal standard for ^{13}C NMR spectra. Chemical shifts are given in δ and coupling constants in Hz. IR spectra were recorded on a BrukerTensor 27 /Diamond ATR and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were measured on a Waters LCT Premier instrument operated in ESI mode. Elemental analyses of the PS-resins were performed on a LECO CHNS 932 micro-analyzer at the

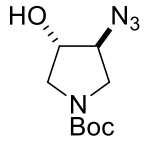
Universidad Complutense de Madrid, Spain. Optical rotations were measured at room temperature on a Jasco P-1030 polarimeter. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatographs (Series 1100 and 1200), using Chiralpak AD-H, Chiralpak AS-H and Chiralpak IC columns and guard columns as noted. Racemic standard products were prepared as described below and using reported procedures[2] in order to establish HPLC conditions.

2. Synthesis of catalysts 1 and 2

Scheme S1. Synthesis of the polymer-supported (PS) organocatalyst **1** and model compound **2**.

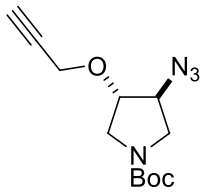


(3S,4S)-tert-Butyl 3-azido-4-hydroxypyrrolidine-1-carboxylate (3)



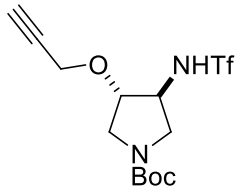
Compound **3** with 96% ee was prepared according to reported methods.[3] Enantiopurity was enhanced 99.5 % ee by recrystallization in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 – 4.17 (m, 1H), 3.98 – 3.87 (m, 1H), 3.74 – 3.63 (m, 1H), 3.63 – 3.51 (m, 1H), 3.50 – 3.26 (m, 2H), 3.24 – 2.88 (m, 1H), 1.45 (s, 9H). ^{13}C {^{1}H} (100 MHz, $CDCl_3$): δ 154.54, 80.24, 80.16, 77.20, 74.13, 73.32, 65.38, 64.84, 51.85, 51.56, 48.63, 48.18, 28.42 (mixture of rotamers). HPLC (Chiralpak® IC, hexane/*i*-PrOH = 90:10, 1.0 mL/min, λ = 210 nm): t_R (major enantiomer) = 9.8 min; t_R (minor enantiomer) = 7.9 min. $[\alpha]_D^{28}$ 36.1 (c 2.0, $CHCl_3$).

(3*S*,4*S*)-*tert*-Butyl 3-azido-4-(prop-2-yn-1-yloxy)pyrrolidine-1-carboxylate (4)



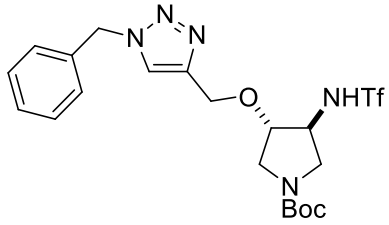
Compound **4** was prepared according to reported methods.[4] A solution of azido alcohol **3** (1.5 g, 6.57 mmol) in anhydrous THF (20 ml) was cooled to 0 ˚C with an ice-water bath and NaH (0.526 g NaH 60% w/w dispersion in mineral oil, 13.14 mmol) was added carefully. The reaction mixture was stirred at 0 ˚C under argon, for 10 minutes and then allowed to warm at room temperature and stirred for 30 minutes. The reaction mixture was cooled again at 0 ˚C with an ice-water bath and tetrabutyl ammonium iodide (121 mg, 0.33 mmol) was added all at once followed by the dropwise addition of propargyl bromide (80 % w/w solution in toluene, 1.46 ml, 13.14 mmol). The reaction was allowed to reach room temperature and stirred for 2 hours. The flask was placed in an ice-water bath and the reaction was first quenched with methanol (2 mL) and then with saturated aqueous solution of NH_4Cl (30 mL). The mixture was extracted twice with ethyl acetate (2 x 20 mL). The organic layers were then combined, washed with brine (20 mL), and dried over Na_2SO_4. After filtration the solvent was removed in the rotatory evaporator. The crude product (yellow-brown oil) was then purified by flash column chromatography with silica gel with hexanes/EtOAc = 100: 0 – 80:20 as eluent. The title product was obtained as a colourless thick oil (1.59 g; 91 % yield).
^{1}H NMR (500 MHz, $CDCl_3$): mixture of rotamers, δ 4.30 – 4.13 (m, 2H), 4.12 – 4.06 (m, 1H), 4.06 – 4.00 (m, 1H), 3.70 – 3.51 (m, 2H), 3.51 – 3.32 (m, 2H), 2.49 (s, 1H), 1.45 (s, 9H). DEPTQ-135 NMR (125 MHz, $CDCl_3$): mixture of rotamers, δ 154.14, 80.54, 79.94, 79.77, 75.43, 63.44, 62.53, 56.97, 49.34, 48.63, 48.59, 48.25, 28.37.

(3*S*,4*S*)-*tert*-butyl 3-(prop-2-yn-1-yloxy)-4-(trifluoromethylsulfonamido) pyrrolidine-1-carboxylate (5)



To an ice-cooled solution of **4** (443 mg, 1.83 mmol) in THF (15 mL) and water (0.2 mL) triphenylphosphine (1.36 mg, 5.19 mmol) was added. After the addition the reaction mixture was allowed to reach room temperature and then heated to 50 ˚C. After stirring for 60 h at 50 ˚C the solvent was removed under vacuum and the residue was redissolved in anhydrous dichloromethane (10 mL) and *N*,*N*-diisopropylethylamine (2,67 mL, 15,28 mmol) was added *via* syringe. The temperature was then set at -78 ˚C and trifluoromethane sulfonic anhydride (0.946 mL, 5.60 mmol) was added dropwise *via* syringe. After the addition the mixture was allowed to reach room temperature and stirred for 16 h. When the reaction was completed, the mixture was diluted with dichloromethane (30 mL) and treated with a saturated aqueous solution of ammonium chloride (10 mL). The organic layer was treated with Na_2SO_4 and filtered. After the removal of the solvent in the rotatory evaporator the residue was purified by flash chromatography (hexanes/EtOAc = 90:10 – 70:30) to afford **5** as a viscous yellow oil after evaporation of the solvent (1.21 g, 64 %).
^{1}H NMR (500 MHz, CD_3OD): mixture of rotamers δ 4.41 – 4.14 (m, 3H), 4.14 – 3.96 (m, 1H), 3.75 – 3.28 (m, 4H), 2.49 (t, *J* = 2.4 Hz, 1H), 1.44 (s, 9H). DEPTQ-135 NMR (125 MHz, CD_3OD): mixture of rotamers, δ 156.12, 121.23 (q, *J* = 320.6 Hz), 82.57, 81.74, 81.56, 76.59, 58.81, 58.05, 57.89, 51.02, 50.47, 50.37, 49.88, 28.66. IR (ATR): ν = 3295, 3104, 2980, 2899, 1665, 1421, 1382, 1370, 1188, 1146 cm^{-1}. HRMS: calcd for $C_{13}H_{19}N_2O_5F_3SNa$ (M-Na) 395.0864, found 395.0883.

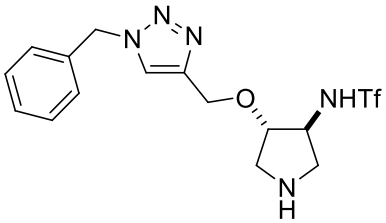
(3*S*,4*S*)-*tert*-butyl 3-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-4-(trifluoromethylsulfonamido)pyrrolidine-1-carboxylate (7)



5 (0.160 g, 0.430 mmol), (azidomethyl)benzene (0.114 g, 0.859 mmol), THF (2 mL) and tris(triazolyl)methyl copper (**6**) complex[5] were place in a tube for a microwave reactor. The reaction mixture was heated at 80 ºC for 1.5 h under microwave irradiation (P_{max} = 100 W). Once **5** was consumed the solvent was removed under reduced pressure and the title product was obtained as a viscous oil after purification by flash column chromatography (hexanes/EtOAc = 2:1 – 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): mixture of rotamers δ 7.46 (bs, 1H), 7.43 – 7.33 (m, 3H), 7.32 – 7.24 (m, 2H), 5.51 (s, 2H), 4.79 – 4.56 (m, 2H), 4.25 – 4.09 (m, 1H), 4.09 – 3.95 (m, 1H), 3.82 – 3.53 (m, 2H), 3.53 – 3.34 (m, 1H), 3.31 (dd, *J* = 12.0, 3.7 Hz, 1H), 1.41 (s, 9H). ^{13}C {^{1}H} (125 MHz, $CDCl_3$): mixture of rotamers δ 154.18, 144.47, 134.14, 129.18, 128.91, 128.20, 122.74, 119.60 (q, *J* = 321.3 Hz), 81.31, 80.56, 80.51, 80.06, 62.99, 57.93, 57.15, 54.33, 49.81, 49.12, 48.77, 48.52, 28.35 IR (ATR): ν = 3070, 2978, 2889, 1679, 1478, 1455, 1408,

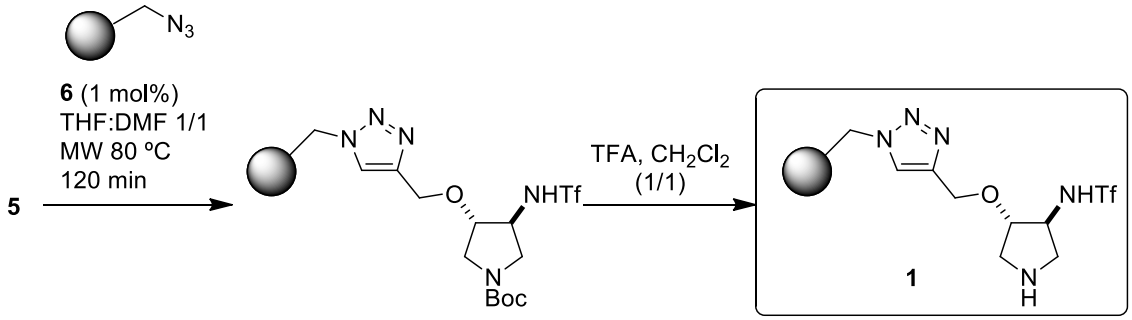
1378, 1188, 1146 cm^{-1}. HRMS: calcd for $C_{20}H_{27}N_5O_5F_3S$ (M-H) 506.1685, found 506.1684. $[\alpha]_D^{25}$ +10,4 (c 1.035, $CHCl_3$).

(3*S*,4*S*)-4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)pyrrolidin-3-yl)-1,1,1-trifluoromethanesulfonamide (2)



To an ice-water-bath cooled solution of **7** (130 mg, 0.26 mmol) in dichloromethane (1 mL), trifluoroacetic acid (1 mL) was added dropwise. After 2 h stirring at room temperature the reaction was completed. The volatiles were removed under reduced pressure. The dry residue was dissolved in water and loaded to Dowex 50WX8-200 ion-exchange resin (H^+ form, activated with 0.1 M HCl). The resin was washed with water and then eluted with 15% ammonium hydroxide. The eluted fractions were concentrated under reduced pressure to afford the title product as a white solid (124 mg, 89%).
^{1}H NMR (500 MHz, MeOD, 333K) δ 7.91 (s, 1H), 7.39 – 7.29 (m, 5H), 5.57 (s, 2H), 4.77 – 4.59 (m, 2H), 4.12-4.08 (m, 1H), 4.08-4.04 (m, 1H), 3.50 (dd, *J* = 12.5, 4.1 Hz, 1H), 3.42 (dd, *J* = 11.6, 5.1 Hz, 1H), 3.26 (d, *J* = 12.5 Hz, 1H), 3.11 (d, *J* = 11.6 Hz, 1H). ^{13}C {^{1}H} (125 MHz, CD_3OD, 333 K) δ 145.73, 136.62, 130.01, 129.58, 129.12, 125.06, 85.22, 63.18, 60.30, 55.03, 53.35, 50.56. IR (ATR): ν = 3259, 3152, 3037, 2977, 2681, 2411, 1621, 1280, 1188, 1150, 1078 cm^{-1}. HRMS: calcd for $C_{15}H_{19}N_5O_3F_3S$ (M-H) 406.1179, found 406.1161.

4-((3*S*,4*S*)-((((4-trifluoromethanesulfonamido)pyrrolidin-3-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl polystyrene (1)



1) Cycloaddition

4-azidomethylpolystyrene[6] (*f* = 0.54 mmol g^{-1}, 0.41 mmol, 0.75 g), **5** (0.49 mmol, 0.18 g) and tris(triazolyl)methyl copper (**6**) complex[5] (0.02 mmol, 13.2 mg) in THF/DMF (3 mL/3 mL) were placed into a tube for microwave reactor. The irradiation was temperature controlled at 80 ˚C with a maximal power of 100 W, and no stirring was used. After 2 h under these conditions the cycloaddition reaction was completed as seen by the disappearance of the ν_{as} ($-N_3$) band at 2097 cm^{-1} in the IR spectrum (Figures S1 and S2 respectively for the starting 4-azidomethylpolystyrene and the product resin). Then the resin was filtered off and subsequently washed with THF(50 mL), water (50 mL), THF (50 mL), THF/MeOH 1/1 (50 mL), MeOH (50 mL) and THF (50 mL), and was air-dried on the fritted glass filter for 0.5 h before submitting it to the next step. IR (ATR) (Figure S2): ν = 3059.6, 3025.7, 2924.0, 1699.0, 1601.1, 1492.5, 1451.9, 1402.6, 1189.7, 1066.2, 906.7, 756.1, 696.6 cm^{-1}.

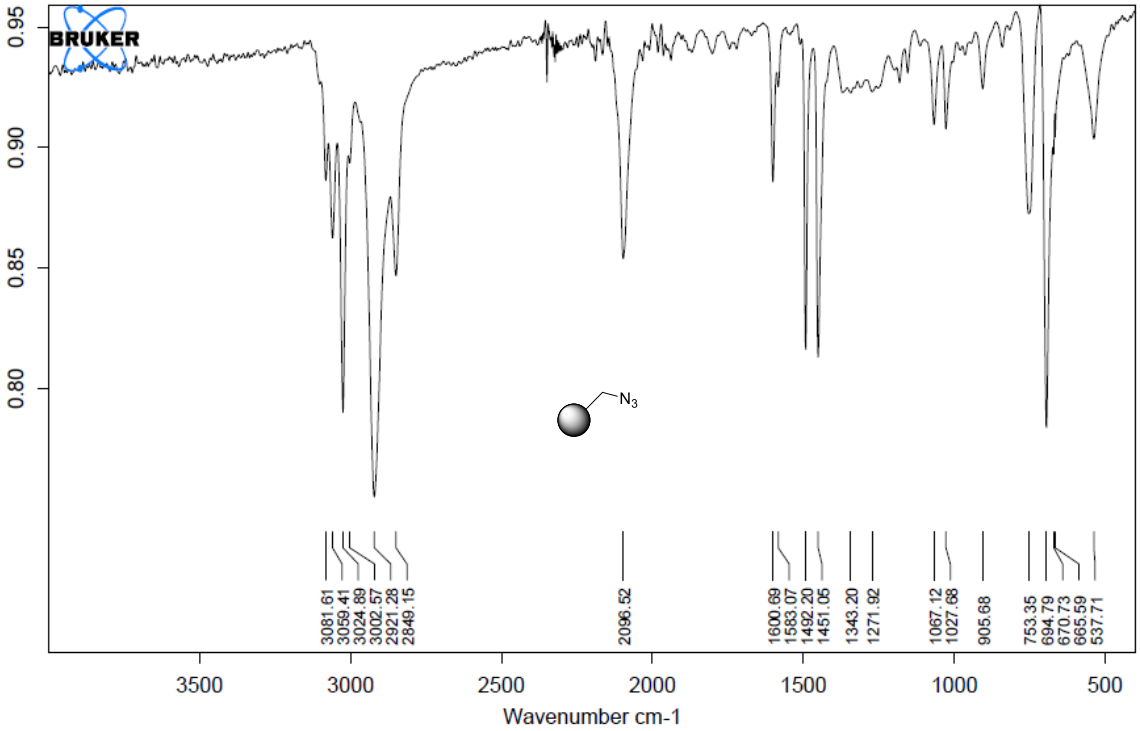


Figure S1. IR spectrum of the initial azidomethylpolystyrene.

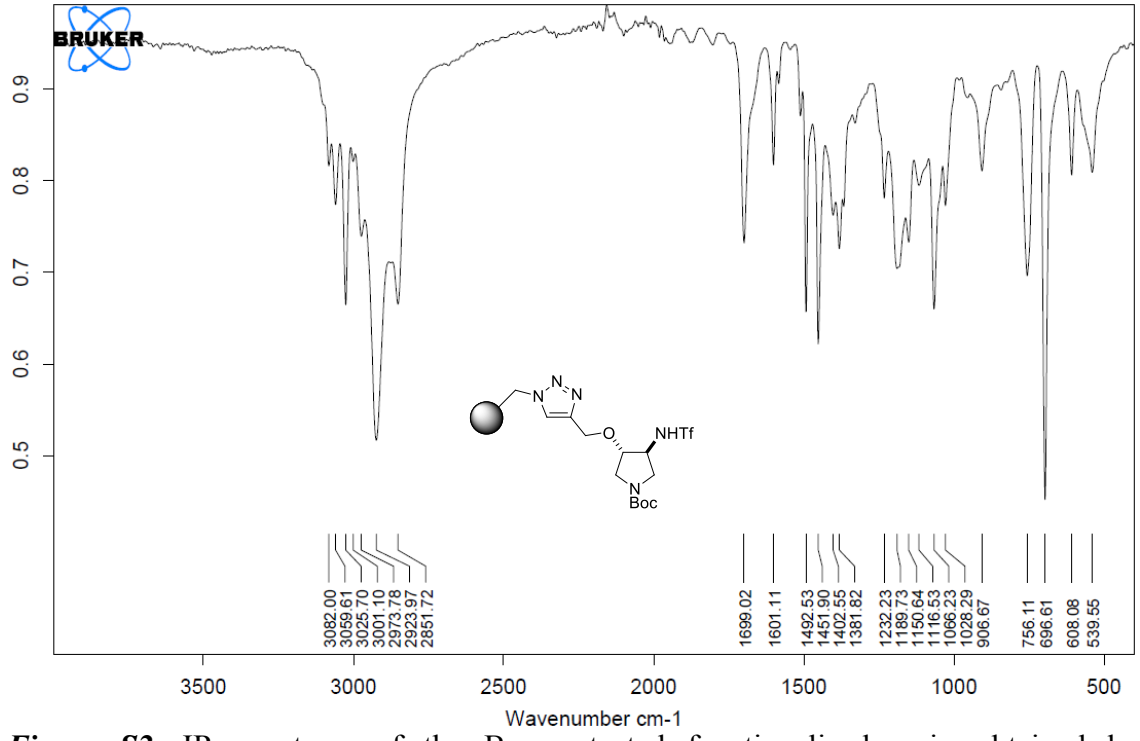


Figure S2. IR spectrum of the Boc-protected functionalized resin obtained by cycloaddition of **5** with azidomethylpolystyrene.

2) Deprotection

Boc-protected functionalized resin obtained in the previous step was placed in a round-bottom flask (100 mL) and suspended in dichloromethane (3 mL). The flask was placed in an ice-water bath and trifluoroacetic acid (3 mL) was added dropwise. The ice-water bath was then removed and the flask was shaken at room temperature while monitoring

the evolution of the deprotection by ATR-FTIR. After the complete disappearance of the IR bands corresponding to the Boc group, the resin was filtered off and dichloromethane (30 mL in total) was used to ensure all the resin was transferred to the fritted glass filter. The resin was then sequentially washed with THF (50 mL), triethylamine 5 % v/v in THF (50 mL), THF (50 mL), water (50 mL), THF/MeOH 1/1 (50 mL), MeOH (50 mL) and THF (50 mL). The resin was then dried under vacuum at 40 ˚C for 3 days.

IR (ATR): ν= 3082.1, 3059.3, 2922.6, 2850.9, 1601.0, 1492.5, 1451.6, 1305.0, 1190.4, 1065.2, 906.2, 755.4, 696.1 cm^{-1}.

The yield of functionalization was calculated on the basis of nitrogen elemental analysis and sulfur elemental analysis as 96 % and 95 % respectively. calcd.: (%): N 3.30, S 1.51; found: N 3.20, S 1.46, C 81.94, H 7.35; f = 0.457 mmol g^{-1} based on % N, 0.456 mmol g^{-1} based on % S.

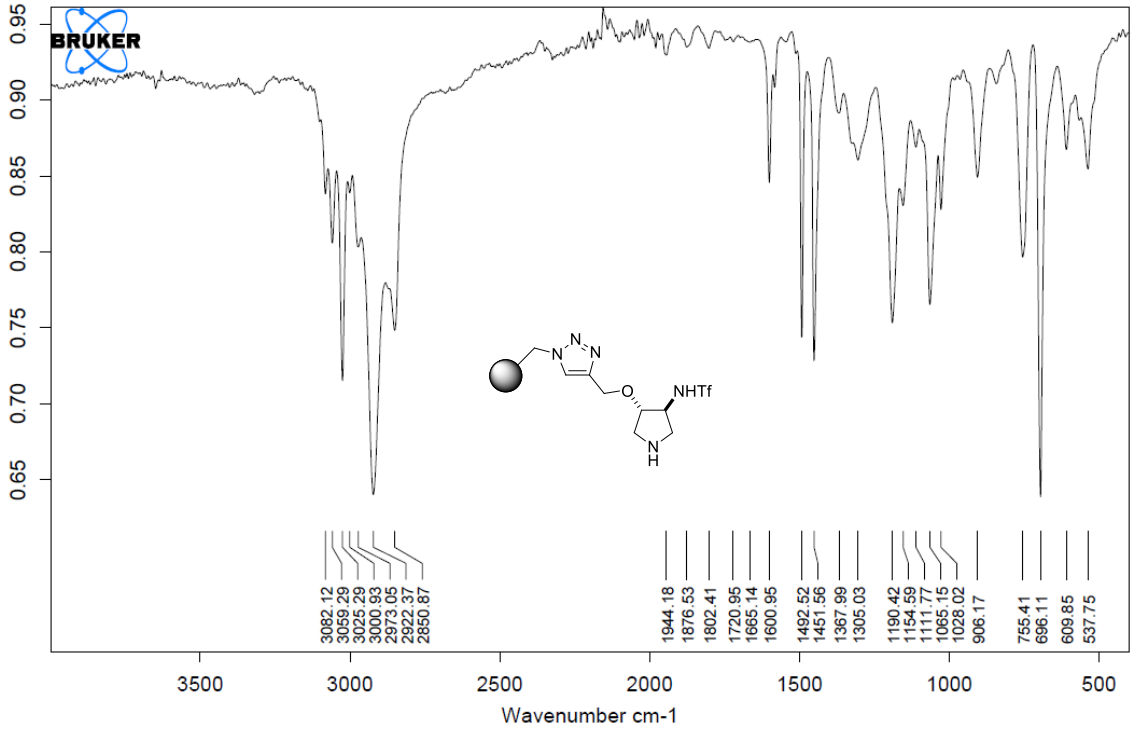


Figure S3. IR spectrum of catalyst **1**.

3. Solvent-uptake tests on resin 1

The solvent uptake of resin **1** was taken as a measurement of its ability to swell in the corresponding solvent.

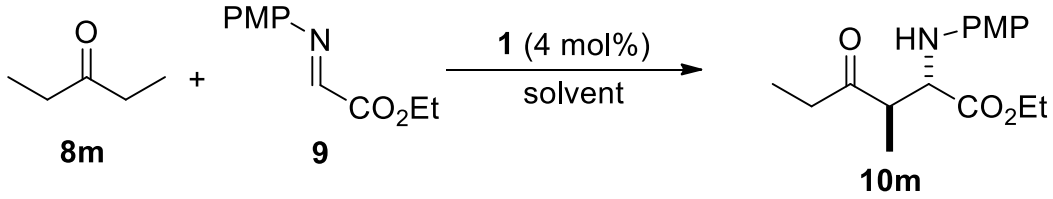
Solvent uptake data for each solvent were determined gravimetrically and expressed as g of solvent per g of dry resin.[7] Resin **1** (19-22 mg) was weighed into a tared 0.5 mL eppendorf tube and solvent (0.3 mL) was added. The eppendorf tubes were then closed and shaken overnight to allow equilibrium to be attained. After centrifugation (30 min at 4000 rpm) a syringe was used to remove excess solventThe eppendorf tube containing the swollen resin was immediately weighed. From this value the weight of solvent absorbed per gram of resin was obtained.[7b]

Table S1: Solvent uptake results.[a]

Ent.	Solvent	Solvent up-take [g g^{-1}][b]	Solvent uptake [mL g^{-1}][c]
1	Dioxane	4.6	4.4
2	DMSO	2.2	2.0
3	EtOAc	2.1	2.3
4	CH_2Cl_2	5.1	3.8
5	CH_3CN	0.7	1.0
6	DMF	4.5	4.8
7	IPA	0.9	1.2
8	THF	4.0	4.5
9	2-MeTHF	3.4	3.9

[a] Precursor Merrifield resin used for the preparation of **1** contains 1 wt% divinyl benzene (DVB) as crosslinker [b] Solvent uptake data for resin **1** as determined by gravimetry and expressed as g of adsorbed solvent per g of dry resin Solvent uptake = (swollen mass - dry mass)/dry mass. [c] Provided in order to facilitate comparison after removing the disturbing effect of the high density of DCM. The number is obtained

4. Solvent screening for *anti*-Selective Mannich reaction between 3-pentanone and α-imino ester 9 catalyzed by 1



8m **9** **10m**

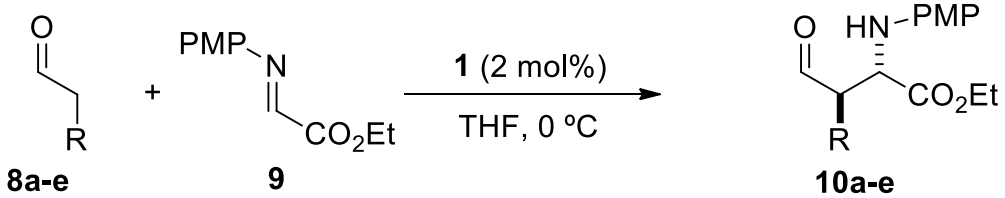
Table S2: Optimization of the anti-selective Mannich reaction between 3-pentanone **8m** and α-Imino Ester **9** catalyzed by **1**.[a]

Entry	Solvent	Conv. [%][b]	*anti/syn*[c]	ee [%][d]
1	Dioxane	53	n.d.	n.d.
2	EtOAc	> 95	75/25	95
3	IPA	> 95	69/31	88
4	DMF	> 95	85/15	95
5	CH_2Cl_2	> 95	72/28	94
6	THF	> 95	71/29	93

[a] Typical reaction conditions: To a solution of **9** (0.125 mmol, 1 equiv) in the appropriate solvent (1 mL), catalyst **1** (4 mol % to the imine) and 3-pentanone (20 equiv) were consecutively added and the mixture was shaken at room temperature for 24 h [b] By ^{1}H NMR. [c] By ^{1}H NMR of reaction crude. [d] By chiral HPLC.

5. Catalytic performance of 1 with aldehydes in THF

Table S3: *anti*-selective Mannich reactions of aldehydes catalyzed by the PS-supported catalyst **1** in THF.[a]



8a-e **9** **10a-e**

Ent.	R (**8**)	Prod.	t [h]	Yield [%][b]	*anti/ syn*[c]	ee [%][d]
1	*i*Pr (**8a**)	**10a**	4	86	91/9	96
2	Me (**8b**)	**10b**	3	80	95/5	96
3	*n*Pent (**8c**)	**10c**	2	93	91/9	97
4	Bn (**8d**))	**10d**	3	70	91/9	96
5	CH_2=CH$(CH_2)_7$ (**8e**)	**10e**	3	85	93/7	97

[a] Typical reaction conditions: The catalyst (2 mol% to **9**) is added to a solution of **9** (0.125 mmol, 1 equiv) in THF (1 mL) at 0 ºC. The aldehyde (**8a-e**, 1.5 equiv) is finally added and the mixture is shaken at 0 ºC. [b] Isolated yield. [c] By ^{1}H NMR of the crude. [d] By chiral HPLC analysis.

6. Procedures for the direct asymmetric *anti*-Mannich-type reactions

General procedure for the catalyzed Mannich-type reactions between aldehydes and α-imino ester 9 catalyzed by 1 in DMF (Table 2).

The reactions were performed in a closed vial under atmospheric conditions. To a solution of protected α-imino ester **9** (0.125 mmol, 1.0 equiv) in DMF (1 mL) catalyst **1** was added. The vial was placed in an ice-water bath and finally aldehyde **8a-e** was added via syringe. The mixture was stirred at 0 ˚C for 4 h and then the catalyst was filtered off and washed with DMF (3 x 1 mL). The solution was treated with water (25 mL) and then extracted with diethyl ether (3 x 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and filtered. After solvent removal under reduced pressure the crude was purified by flash column chromatography. In general the *anti*- and *syn*-isomers of the Mannich products were not separated by column chromatography. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude product. The enantiomeric excess was determined by chiral-phase HPLC analysis of the isolated product.

General procedure for the catalyzed Mannich-type reactions between aldehydes and α-imino ester 9 catalyzed by 2 (Table 2).

The reactions were performed in a closed vial under atmospheric conditions. To a solution of protected α-imino ester **9** (0.250 mmol, 1.0 equiv) in DMF (2 mL) catalyst **2** was added. The vial was placed in an ice-water bath and finally aldehyde **8a-e** was added via syringe. The mixture was shaken at 0 ˚C for 4 h. After reaction the mixture was treated with water (50 mL) and then extracted with diethyl ether (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and filtered. After solvent removal under reduced pressure the crude was purified by flash column chromatography. In general the *anti*- and *syn*-isomers of the Mannich products were not separated by column chromatography. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude product. The enantiomeric excess was determined by chiral-phase HPLC analysis of the isolated product.

General procedure for the catalyzed Mannich-type reactions between aldehydes and α-imino ester 9 catalyzed by 1 in THF (Table S3).

The reactions were performed in a closed vial under atmospheric conditions. To a solution of protected α-imino ester **9** (0.125 mmol, 1.0 equiv) in THF (1 mL) catalyst **1** was added. The vial was placed in an ice-water bath and finally aldehyde **8a-e** was added via syringe. The mixture was stirred at 0 ˚C until **9** was consumed by TLC. The catalyst was then filtered off and washed with THF (3 x 1 mL). After solvent removal under reduced pressure the crude was purified by flash column chromatography. In general the *anti*- and *syn*-isomers of the Mannich products were not separated by column chromatography. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude product. The enantiomeric excess was determined by chiral-phase HPLC analysis of the isolated product.

General procedure for the catalyzed Mannich-type reactions between unmodified ketones and α-imino ester 9 catalyzed by 1 (Table 3).

The reactions were performed in a closed vial under atmospheric conditions. To a solution of protected α-imino ester **9** (0.125 mmol, 1.0 equiv) in DMF (1 mL) catalyst **1**

(4 mol%) was added. Ketone **8f-n** (1.2 equiv unless otherwise stated) was finally added via syringe (except for **8i** and **8j** which are solid). The mixture was shaken until the reaction was finished by TLC. After reaction the catalyst was filtered off and washed with DMF (3 x 1 mL). The solution was treated with water (25 mL) and then extracted with diethyl ether (3 x 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and filtered. After solvent removal under reduced pressure the crude was purified by flash column chromatography. In general the *anti*- and *syn*-isomers of the Mannich products were not separated by column chromatography. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude product. The enantiomeric excess was determined by chiral-phase HPLC analysis of the isolated product.

General procedure for the catalyzed Mannich-type reactions between unmodified ketones and α-imino ester 9 catalyzed by 2 (Table 3).

The reactions were performed in a closed vial under atmospheric conditions. To a solution of protected α-imino ester **9** (0.125 mmol, 1.0 equiv) in DMF (1 mL) catalyst **2** (4 mol%) was added. Ketone **8f** (1.2 equiv) or **8l-m** (20 equiv) was finally added via syringe. The mixture was stirred until the reaction was finished by TLC. After reaction the solution was treated with water (25 mL) and then extracted with diethyl ether (3 x 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and filtered. After solvent removal under reduced pressure the crude was purified by flash column chromatography. In general the *anti*- and *syn*-isomers of the Mannich products were not separated by column chromatography. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude product. The enantiomeric excess was determined by chiral-phase HPLC analysis of the isolated product.

Synthesis of (±)-*anti*- and (±)-*syn*-Mannich product

Racemic mixtures of the diastereomers and enantiomers were synthesized using pyrrolidine-trifluoroacetic acid (0.3 equiv) as catalyst in dichloromethane in the case of ketones, or (±)-pipecolic acid (0.2 equiv) as catalyst in DMF in the case of aldehydes. Alternatively, a racemic standard of the *syn*-Mannich products containing as well the *anti*-Mannich was synthesized using (±)-proline (0.2 equiv) as catalyst in DMF.[2]

7. Description of the experimental setup for the continuous-flow process

The instrumental setup for the continuous flow experiments is shown in Figure S4. The flow reactor consisted on a vertically mounted, fritted and jacketed-low pressure chromatography Omnifit glass column (10 mm bore size and up to a maximal 70 mm of adjustable bed height) filled with 500 mg of swollen resin (19 mm bed height). Cooling water (ca. 8 ˚C) was pumped through the jacket to cool the system below room temperature. The reactor is assembled to an Asia120® flow chemistry system developed by Syrris. A solution with **9** in THF was pumped by an Asia pump and mixed with a solution of carbonyl compound in THF (pumped by another Asia pump) in a mixing chamber (T-type mixer) connected to the reactor inlet. The reactor outlet was connected to a receiving flask in a dry ice bath at -78 ˚C where the product was collected. Conversion and enantioselectivity of the formed product at any moment were determined respectively by ^{1}H NMR and HPLC of periodically collected samples. An additional supply of THF was connected to both pumps for conditioning and cleaning operations. The simplification of the system by using a single pump feeding one solution containing of both reactant species resulted in loss of stereoselectivity with time as a result of non-catalyzed reaction in the feeding solution.

Isolation of the Mannich adduct after the experiment was performed without any aqueous work-up, by simple evaporation of solvent and excess starting carbonyl compound. When lower conversion was achieved the product was further purified by column chromatography. Since no aqueous work-up is required, the high volatility of THF facilitates its evaporative recovery. In this way, the potential disadvantages with respect to its analogue of renewable origin, 2-methyltetrahydrofuran, are partially compensated.

Figure S4. Picture of continuous flow reactor setup for the *anti*-Mannich reaction between *N*-methylpiperidin-4-one **8h** and **9**.

8. Optimization of the conditions for the continuous flow operation

The experiments for the optimization of the continuous flow parameters were performed using propanal (**8b**) as substrate. A representation of the experimental setup used is shown in Figure S5. The figure is analogous to Figure 3 in the main text but includes the broader range of conditions tested for the optimization. All the optimization experiments were performed using the same bed of catalyst.

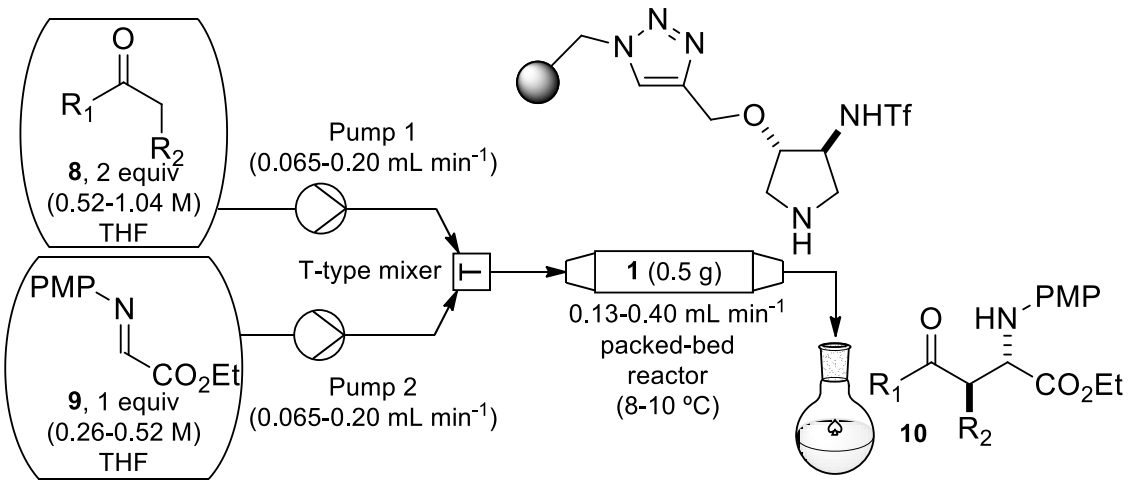
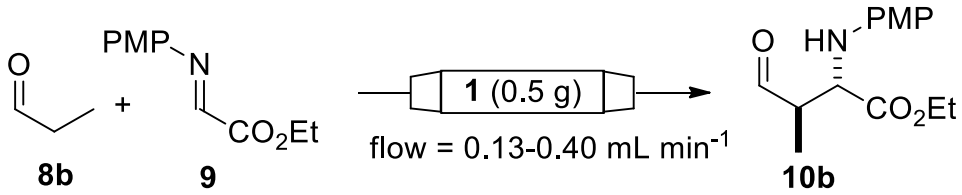


Figure S5. Experimental setup including the optimization parameters for the *anti*-selective Mannich reactions under continuous-flow operation.

Table S4: Optimization experiments for the continuous flow *anti*-selective asymmetric Mannich reaction with immobilized catalyst **1**.[a]



8b **9** **10b**

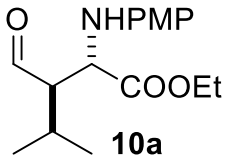
Ent.	Prod. (mmol)[b]	t [h]	Conv. [%][c]	*anti*/ *syn*[c]	ee [%][d]	TON[e]
1[f]	**10b** (3.81)	4	97	>95/5	97	16[j]
2[g]	**10b** (2.84)	1	92	>95/5	97	12[j]
3[g,h]	**10b** (4.99)	1	85	>95/5	96	22[j]
4[h]	**10b** (3.81)	1.3	96	>95/5	96	16[j]
5[h,i]	**10b** (16.66)	6	93	>95/5	96	72[j]

[a] Reactions were performed with 500 mg of resin (0.231 mmol, >99.5% ee) in a reactor jacketed at 8-10 ºC. Unless otherwise stated, the imine **9** (0.26 M) and the carbonyl compound (0.52 M), were fed from separate solutions in THF pumped at the same flow rate into the column. 0.20 mL min^{-1} total flow rate, 0.13 M concentration of **9** in the reactor. The residence time under these conditions was 12 min. [b] Pure product obtained after flash chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] By chiral HPLC analysis. [e] Turnover number (TON) based on the isolated pure product. [f] Both reactants were fed from the same solution, 0.13 mL min^{-1} total flow rate. [g] 0.40 mL min^{-1} total flow rate. [h] 0.26 M concentration of **9** in the reactor. [i] Entry 5 in Table S4 corresponds to the same experiment as entry 2 in Table 4 in the main text. [j] The used resin was the same for entries 1-5, with production only interrupted for cleaning by flushing THF through the packed bed reactor.

9. Characterization of the *anti*-Mannich-type adducts

Products **10a-g**, **10i-j** and **10l-n** are known compounds that exhibited spectroscopic data in agreement with those reported in the literature.[2,8,9] The absolute configuration of the *anti*-Mannich products was assigned by comparing the specific optical rotation of representative products and the chiral HPLC chromatograms with those reported in the literature under the same conditions.[2,8,9]

Ethyl (2*S*,3*R*)-3-formyl-2-(*p*-methoxyphenylamino)-4-methylpentanoate (10a)[2,8]



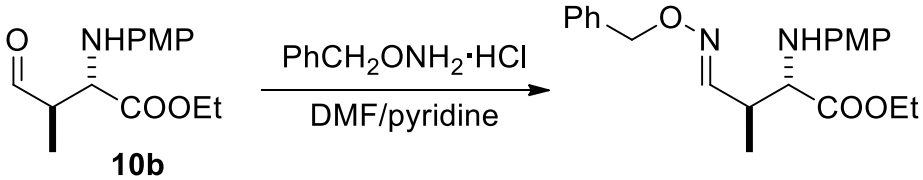
10a

HPLC (Chiralpak® AS-H, hexane/*i*-PrOH = 90:10, 0.5 mL/min, λ = 240 nm): t_R (*anti* major enantiomer) = 18.8 min; t_R (*anti* minor enantiomer) = 35.1 min.

Ethyl (2*S*,3*R*)-3-formyl-2-(*p*-methoxyphenylamino)butanoate (10b)[2,8]

For HPLC analysis the adduct was reacted with *O*-benzylhydroxylamine to obtain the corresponding oxime as reported in the literature (see below).[2,8]

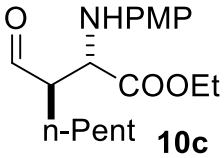
Ethyl (*E*)-(2*S*,3*R*)-3-benzyloxyiminomethyl-2-(*p*-methoxyphenylamino)butanoate[2,8]



10b

HPLC (Chiralpak® AD-H, hexane/*i*-PrOH = 97:3, 0.9 mL/min, λ = 240 nm): t_R (*anti* major enantiomer) = 35.1 min; t_R (*anti* minor enantiomer) = 21.0 min.

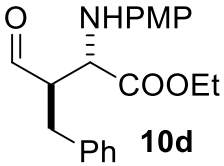
Ethyl (2*S*,3*R*)-3-formyl-2-(*p*-methoxyphenylamino)octanoate (10c)[2,8]



10c

HPLC (Chiralpak® AS-H, hexane/*i*-PrOH = 99:1, 0.90 mL/min, λ = 240 nm): t_R (*anti* major enantiomer) = 28.7 min; t_R (*anti* minor enantiomer) = 31.7 min.

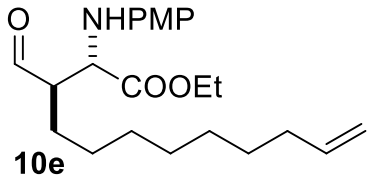
Ethyl (2*S*,3*R*)-3-formyl-2-(*p*-methoxyphenylamino)-4-phenylbutanoate (10d)[2,8]



10d

HPLC (Chiralpak® AS-H, hexane/*i*-PrOH = 98:2, 1.00 mL/min, λ = 240 nm): t_R (*anti* major enantiomer) = 41.2 min; t_R (*anti* minor enantiomer) = 47.7 min.

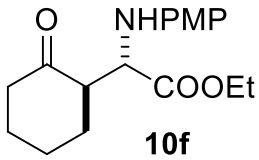
Ethyl (2*S*,3*R*)-3-formyl-2-(*p*-methoxyphenylamino)dodec-11-enoate (10e)[9]



10e

HPLC (Chiralpak® IC, hexane/*i*-PrOH = 95:5, 1.00 mL/min, λ = 240 nm): t_R (*anti* major enantiomer) = 17.1 min; t_R (*anti* minor enantiomer) = 22.2 min.

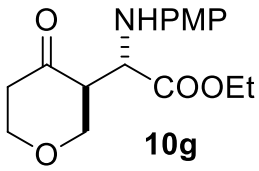
Ethyl (2*S*, 1'*R*)-2-(*p*-methoxyphenylamino)-2-(2'-oxocyclohexyl)acetate (10f)[2,8]



10f

HPLC (Chiralpak® AS-H, hexane/*i*-PrOH = 90:10, 0.50 mL/min, λ = 240 nm): t_R (*anti* major enantiomer) = 26.7 min; t_R (*anti* minor enantiomer) = 35.7 min.

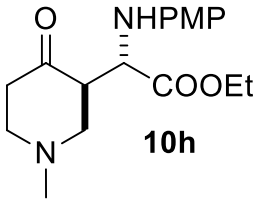
Ethyl (2*S*, 3'*S*)-2-(*p*-methoxyphenylamino)-2-(4'-oxotetrahydropyran-3'-yl)acetate (10g)[2,8]



10g

HPLC (Chiralpak® IC, hexane/*i*-PrOH = 90:10, 1.00 mL/min, λ = 240 nm): t_R (*anti* major enantiomer) = 31.8 min; t_R (*anti* minor enantiomer) = 29.1 min.

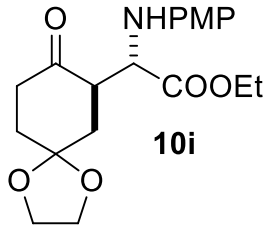
Ethyl (2*S*, 3'*R*)-2-(*p*-methoxyphenylamino)-2-(N-methyl-4'-oxopiperidin-3'-yl) acetate (10h)



10h

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 – 6.69 (m, 2H), 6.67 – 6.56 (m, 2H), 4.21 – 4.08 (m, 3H), 3.72 (s, 3H), 3.29 – 3.18 (m, 1H), 3.01 (ddd, *J* = 11.3, 5.7, 2.1 Hz, 1H), 2.89 (d, *J* = 2.0 Hz, 1H), 2.74 – 2.42 (m, 4H), 2.39 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.00 (*anti*), 207.55 (*syn*), 172.91 (*syn*), 172.39 (*anti*), 153.11 (*syn*), 152.96 (*anti*), 141.43 (*anti*), 141.00 (*syn*), 116.01 (*syn*), 115.65 (*anti*), 114.79 (*anti*), 114.75 (*syn*), 61.33 (*anti*), 61.28 (*syn*), 57.98 (*anti*), 57.57 (*syn*), 57.54 (*anti*), 57.23 (*syn*), 55.67 (*anti*), 55.31 (*syn*), 55.04 (*anti*), 52.62 (*syn*), 52.19 (*anti*), 45.52 (*syn*), 45.44 (*anti*), 40.68 (*syn*), 40.49 (*anti*), 14.08 (*anti*), 14.06 (*syn*). HPLC (Chiralpak® AS-H, hexane/*i*-PrOH = 80:20, 0.75 mL/min, λ = 254 nm): t_R (*anti* major enantiomer) = 15.7 min; t_R (*anti* minor enantiomer) = 22.0 min.

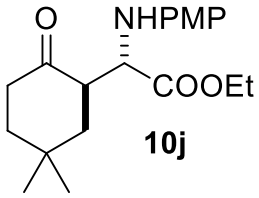
Ethyl (2*S*,1'*R*)-2-(*p*-methoxyphenylamino)-2-(5',5'-ethylenedioxy-2'-oxocyclohexyl) acetate (10i)[2,8]



10i

HPLC (Chiralpak® IC, hexane/*i*-PrOH = 85:15, 1.00 mL/min, λ = 254 nm): t_R (*anti* major enantiomer) = 28.7 min; t_R (*anti* minor enantiomer) = 23.6 min.

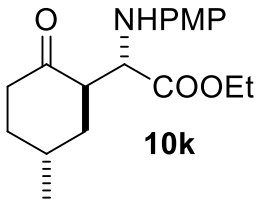
Ethyl (2S, 1'R)-2-(*p*-methoxyphenylamino)-2-(5',5'-dimethyl-2'-oxocyclohexyl) acetate (10j)[2]



10j

HPLC (Chiralpak® AS-H, hexane/*i*-PrOH = 90:10, 0.50 mL/min, λ = 254 nm): t_R (*anti* major enantiomer) = 15.7 min; t_R (*anti* minor enantiomer) = 17.3 min.

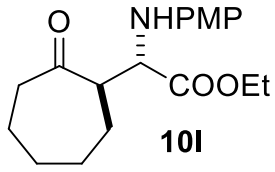
Ethyl (2*S*, 1'*R*, 5'*R*)-2-(*p*-methoxyphenylamino)-2-(5'-methyl-2'-oxocyclohexyl) acetate (10k)



10k

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 – 6.71 (m, 2H), 6.67 – 6.55 (m, 2H), 4.15 (qd, *J* = 7.1, 2.3 Hz, 3H), 4.11 (d, *J* = 6.8 Hz, 1H), 3.73 (s, 3H), 3.07 – 2.97 (m, 1H), 2.48 – 2.33 (m, 2H), 2.28 – 2.15 (m, 1H), 2.13 – 2.02 (m, 1H), 2.00 – 1.91 (m, 1H), 1.77 – 1.69 (m, 1H), 1.69 – 1.59 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.38, 172.83, 152.94, 141.38, 115.55, 114.78, 61.23, 59.03, 55.69, 50.41, 37.79, 36.32, 33.33, 26.87, 19.47, 14.17. HPLC (Chiralpak® AS-H, hexane/*i*-PrOH = 95:5, 1.00 mL/min, λ = 254 nm): t_R (*anti* major enantiomer) = 16.6 min; t_R (*anti* minor enantiomer) = 43.4 min.

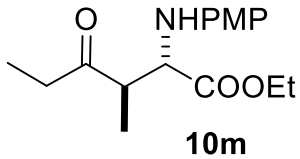
Ethyl (2*S*, 1'*R*)-2-(*p*-methoxyphenylamino)-2-(2'-oxocycloheptyl)acetate (10l)[2,8]



10l

HPLC (Chiralpak® AS-H, hexane/*i*-PrOH = 90:10, 0.50 mL/min, λ = 240 nm): t_R (*anti* major enantiomer) = 23.1 min; t_R (*anti* minor enantiomer) = 46.4 min.

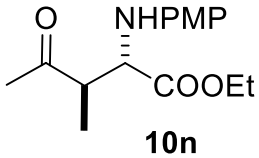
Ethyl (2*S*,3*R*)-2-(*p*-methoxyphenylamino)-3-methyl-4-oxohexanoate (10m)[2,8]



10m

HPLC (Chiralpak® AS-H, hexane/*i*-PrOH = 99:1, 1.00 mL/min, λ = 240 nm): t_R (*anti* major enantiomer) = 27.2 min; t_R (*anti* minor enantiomer) = 44.5 min.

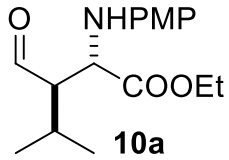
Ethyl (2*S*,3*R*)-2-(*p*-methoxyphenylamino)-3-methyl-4-oxopentanoate (10n)[2,8]



10n

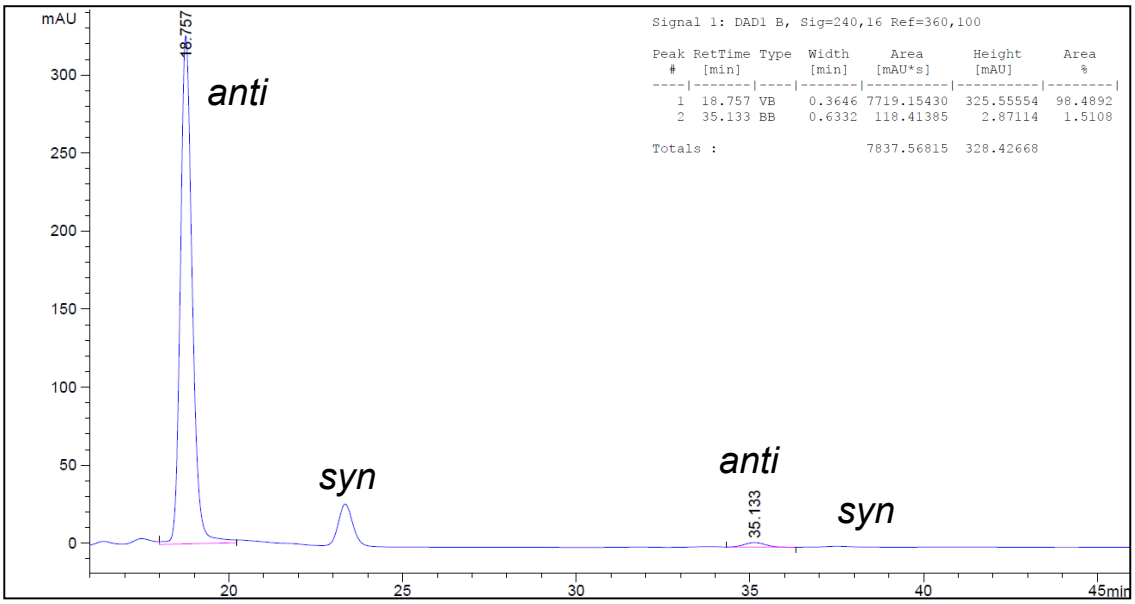
HPLC (Chiralpak® AS-H, hexane/*i*-PrOH = 90:10, 0.50 mL/min, λ = 240 nm): t_R (*anti* major enantiomer) = 21.4 min; t_R (*anti* minor enantiomer) = 32.0 min.

10. HPLC traces of the *anti*-Mannich-type adducts and racemic standards



10a

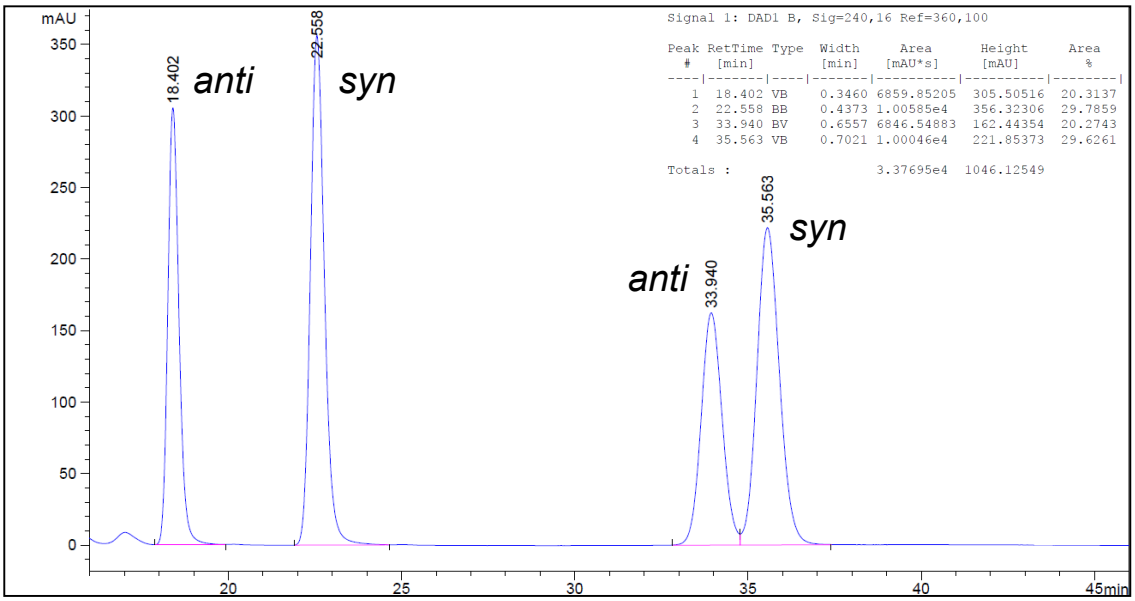
Chiralpak® AS-H column (90/10) hexane/iPrOH – flow rate: 0.50 mL/min



Signal 1: DAD1 B, Sig=240,16 Ref=360,100

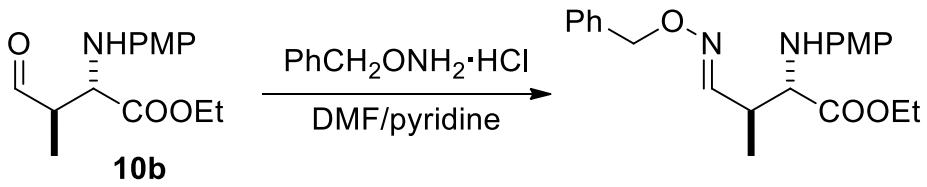
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.757	VB	0.3646	7719.15430	325.55554	98.4892
2	35.133	BB	0.6332	118.41385	2.87114	1.5108
Totals :				7837.56815	328.42668	

Racemic mixture:



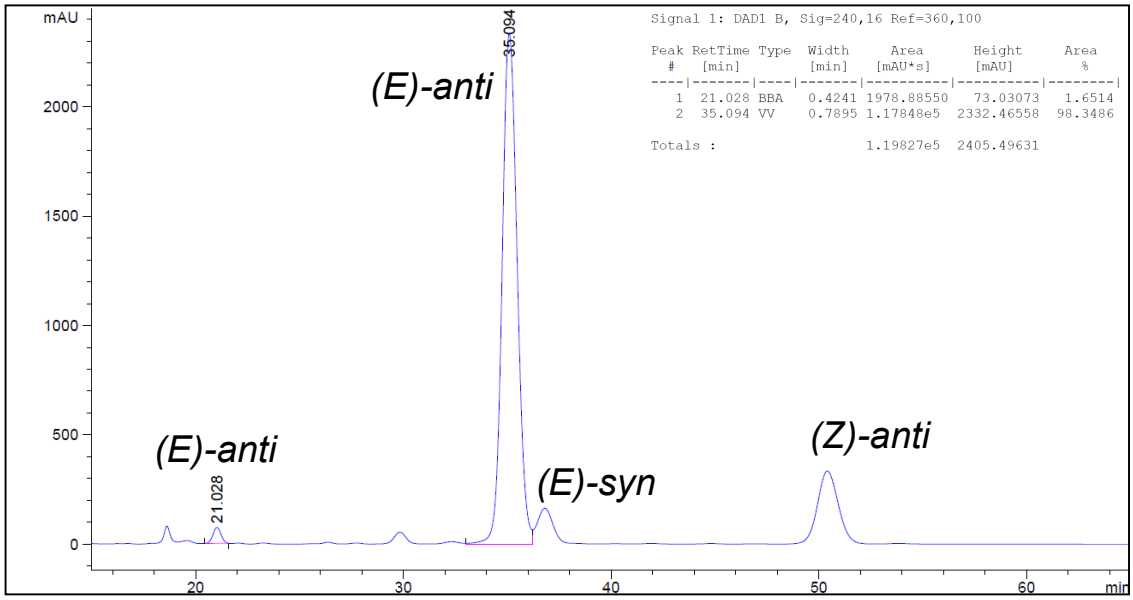
Signal 1: DAD1 B, Sig=240,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.402	VB	0.3460	6859.85205	305.50516	20.3137
2	22.558	BB	0.4373	1.00585e4	356.32306	29.7859
3	33.940	BV	0.6557	6846.54883	162.44354	20.2743
4	35.563	VB	0.7021	1.00046e4	221.85373	29.6261
Totals :				3.37695e4	1046.12549	

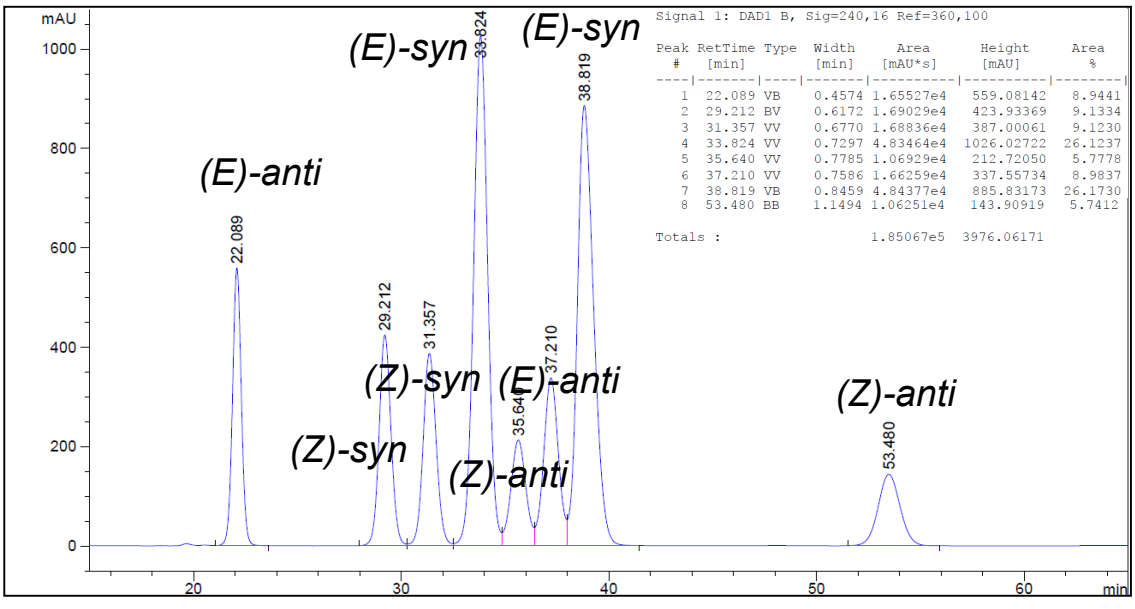


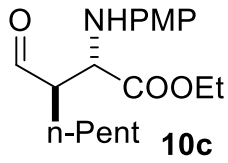
10b

Chiralpak® AD-H column (97/3) hexane/iPrOH – flow rate: 0.90 mL/min



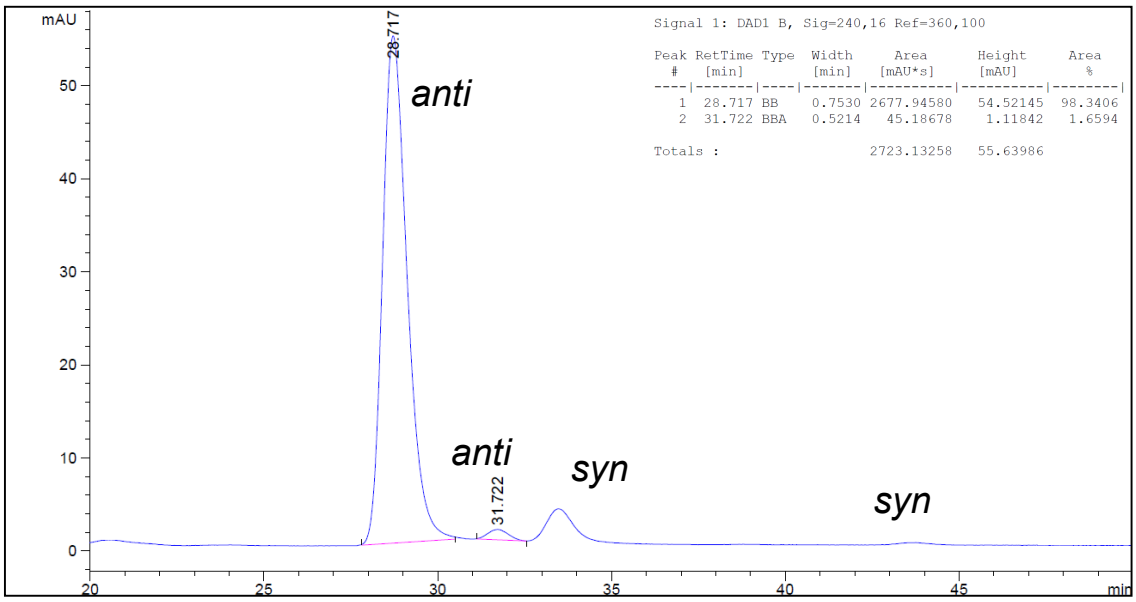
Racemic mixture:



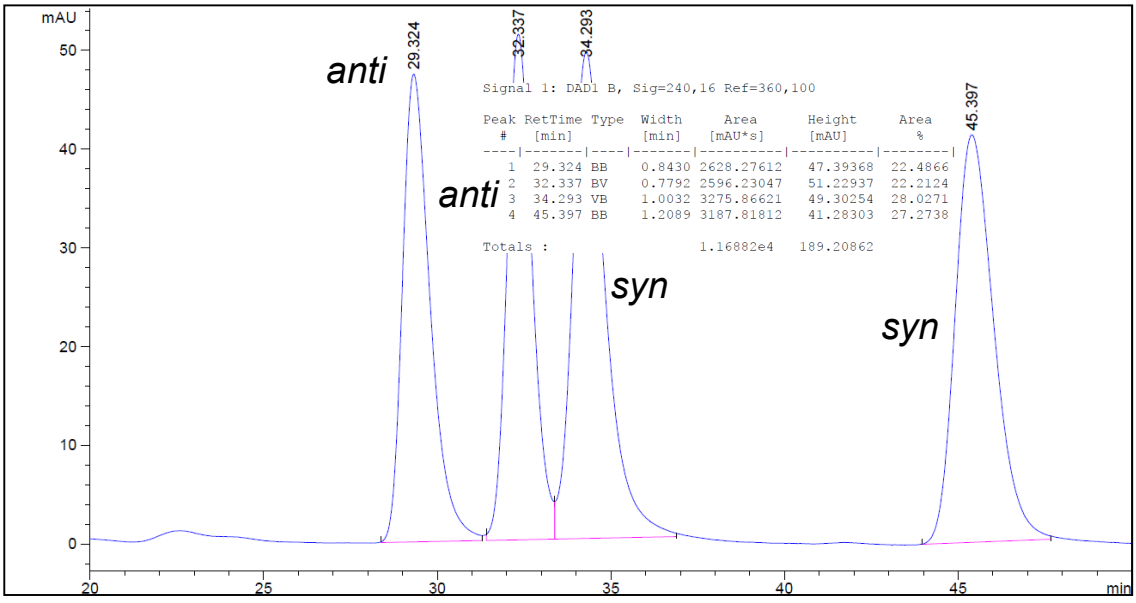


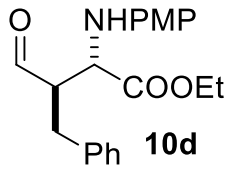
10c

Chiralpak® AS-H column (99/1) hexane/iPrOH – flow rate: 0.90 mL/min



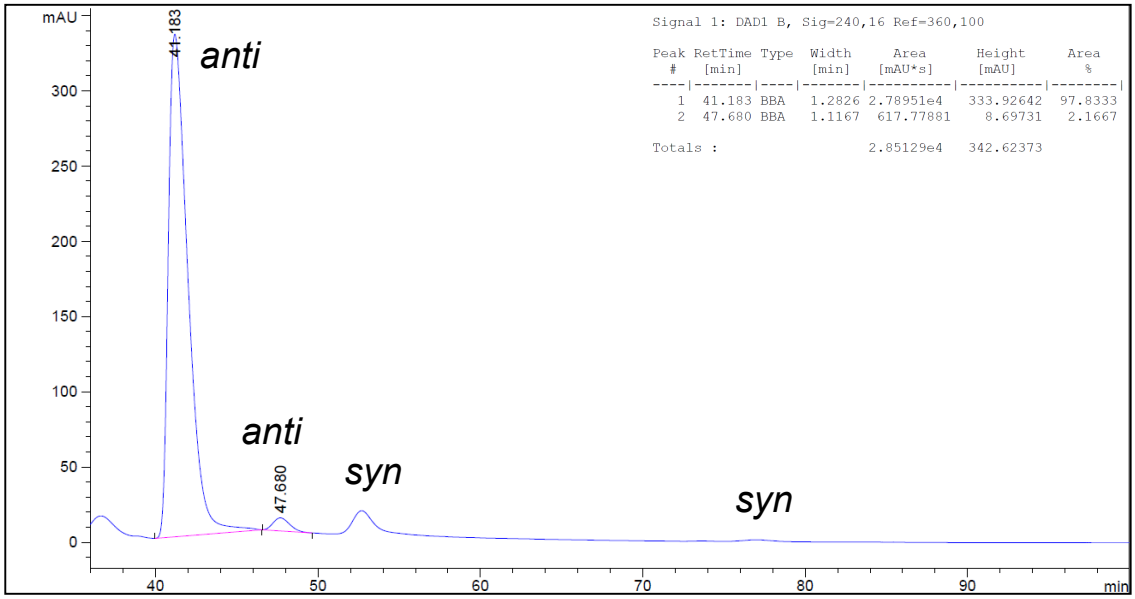
Racemic mixture:



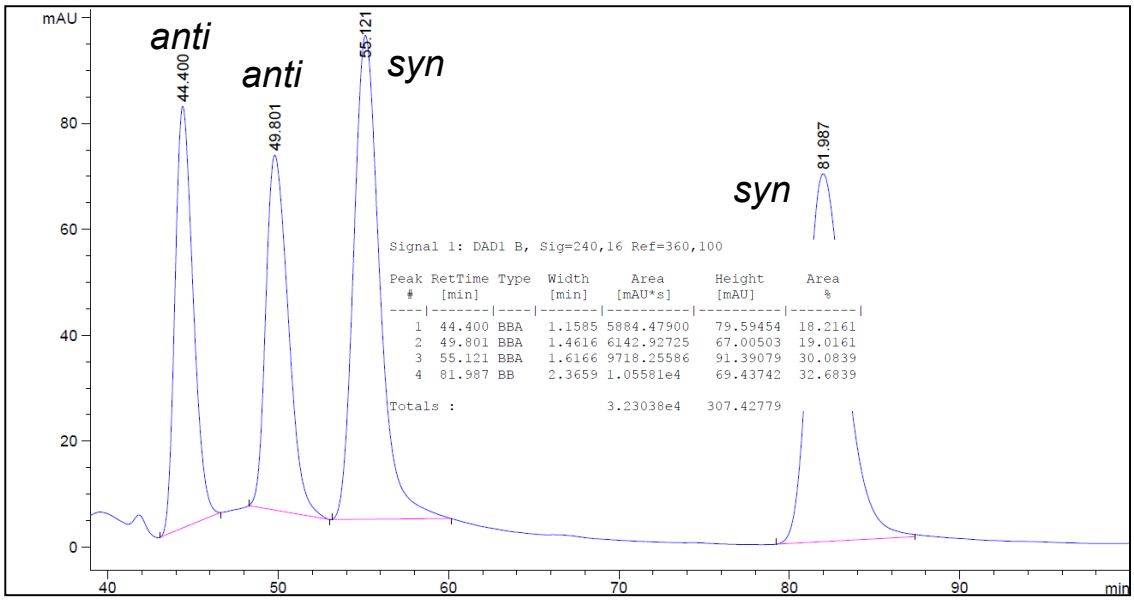


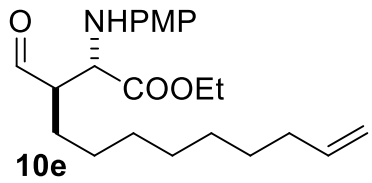
10d

Chiralpak® AS-H column (98/2) hexane/iPrOH – flow rate: 1.00 mL/min



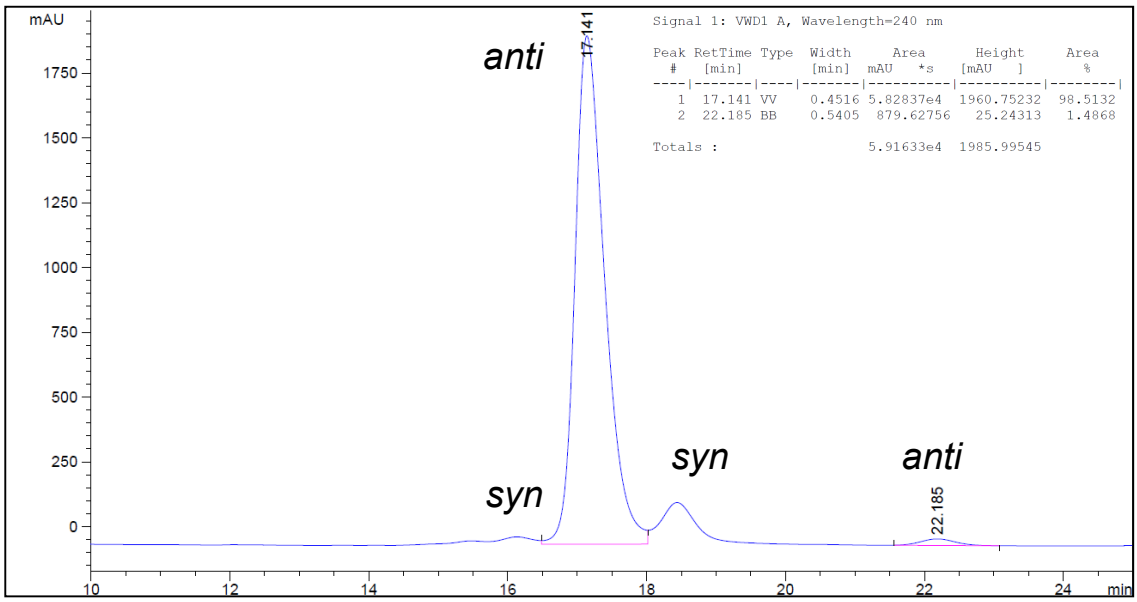
Racemic mixture:





10e

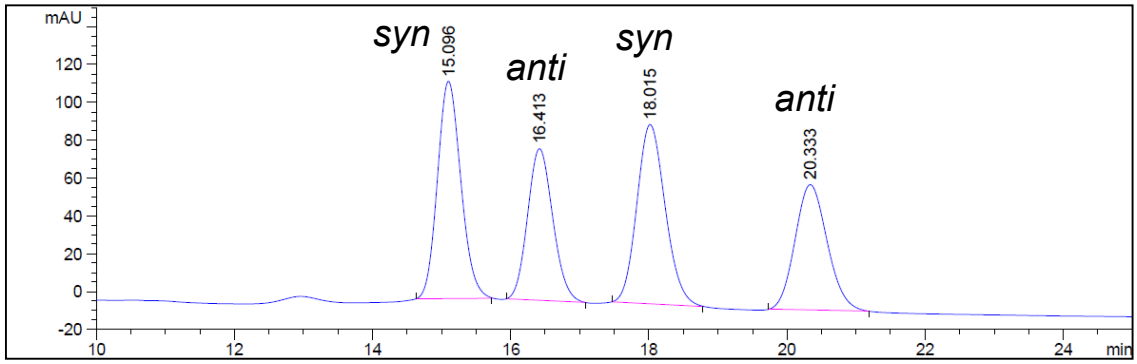
Chiralpak® IC column (95/5) hexane/iPrOH – flow rate: 1.00 mL/min



Signal 1: VWD1 A, Wavelength=240 nm

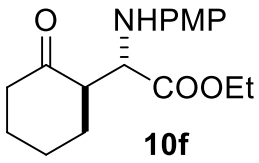
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	17.141	VV	0.4516	5.82837e4	1960.75232	98.5132
2	22.185	BB	0.5405	879.62756	25.24313	1.4868
Totals :				5.91633e4	1985.99545	

Racemic mixture:



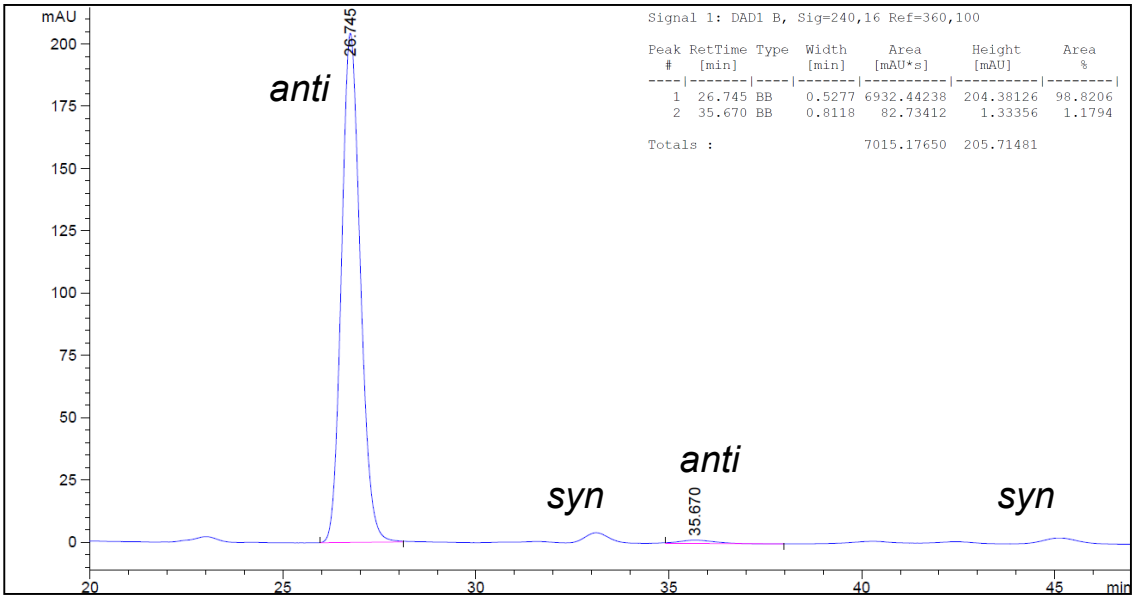
Signal 1: DAD1 B, Sig=240,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.096	BB	0.3676	2718.76001	115.07326	28.2326
2	16.413	BB	0.3952	2047.99280	80.40049	21.2671
3	18.015	BB	0.4431	2707.85522	94.83204	28.1194
4	20.333	BB	0.5047	2155.24951	66.39837	22.3809
Totals :				9629.85754	356.70415	

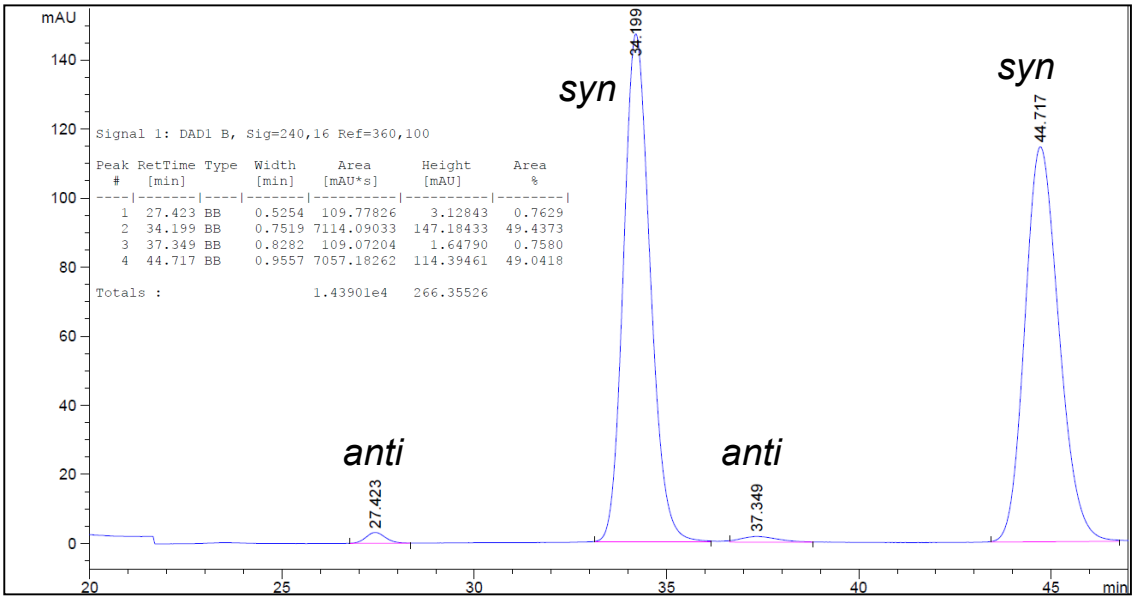


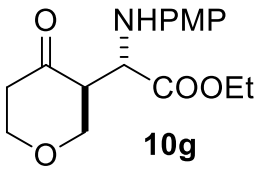
10f

Chiralpak® AS-H column (90/10) hexane/iPrOH – flow rate: 0.50 mL/min



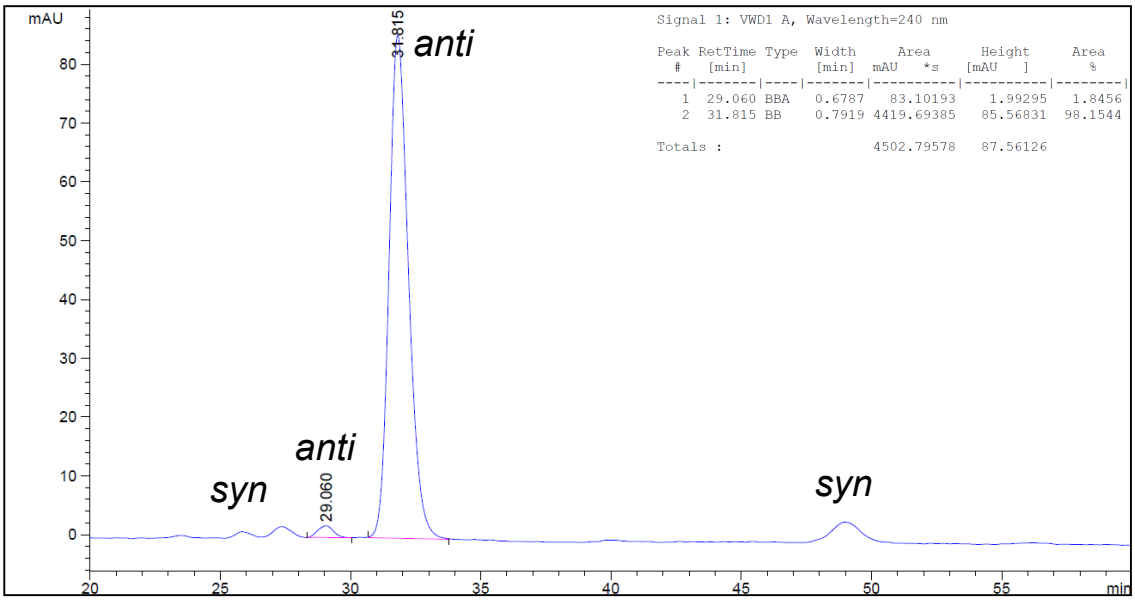
Racemic mixture:





10g

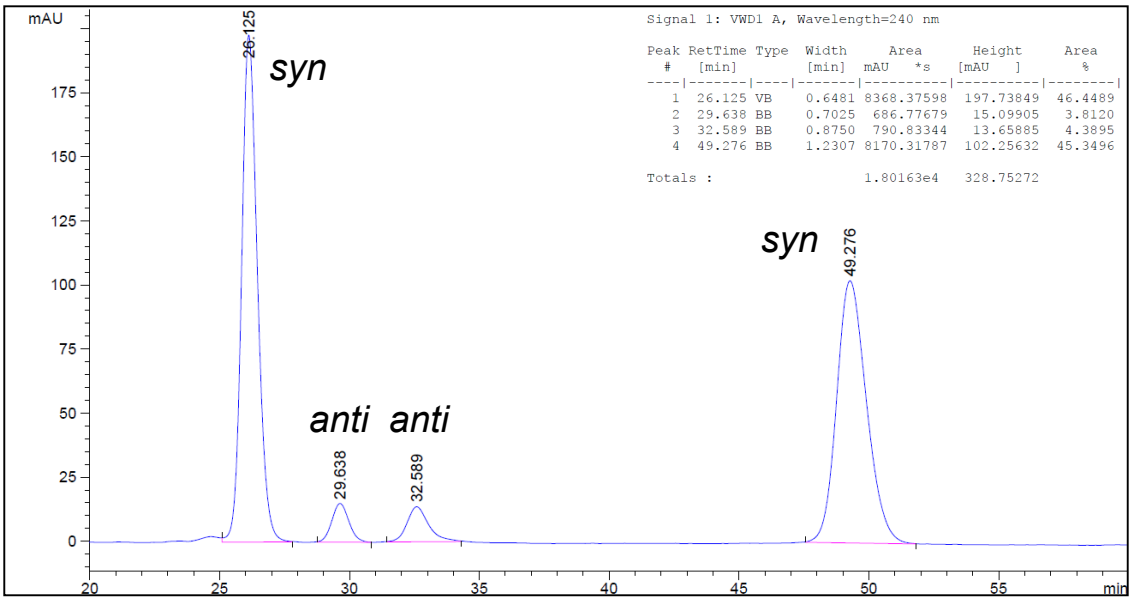
Chiralpak® IC column (90/10) hexane/iPrOH – flow rate: 1.00 mL/min



Signal 1: VWD1 A, Wavelength=240 nm

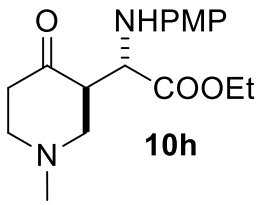
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	29.060	BBA	0.6787	83.10193	1.99295	1.8456
2	31.815	BB	0.7919	4419.69385	85.56831	98.1544
Totals :				4502.79578	87.56126	

Racemic mixture:

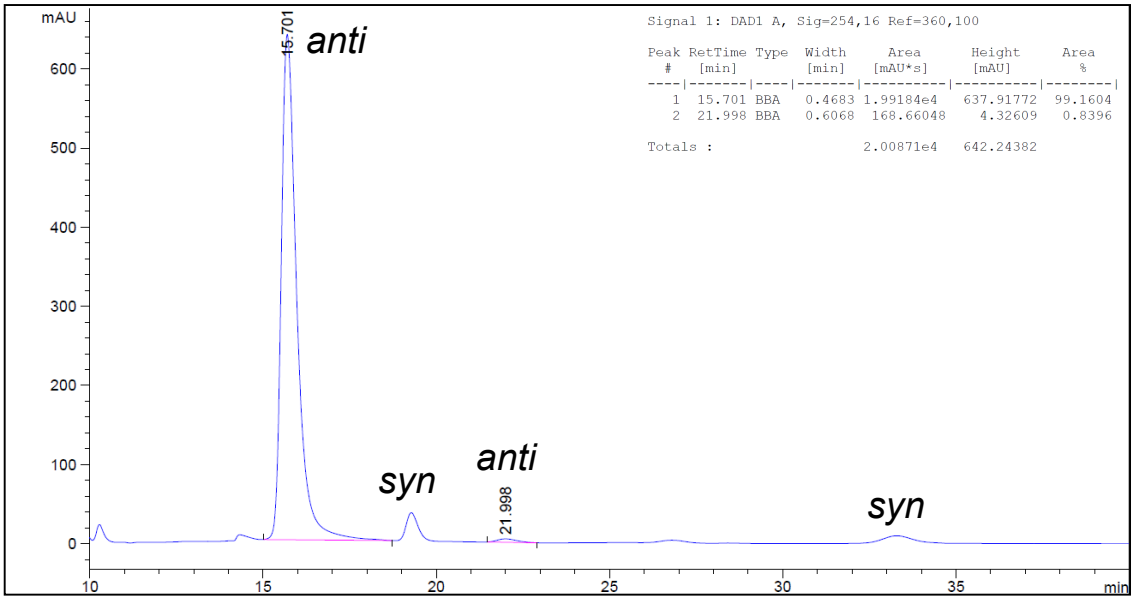


Signal 1: VWD1 A, Wavelength=240 nm

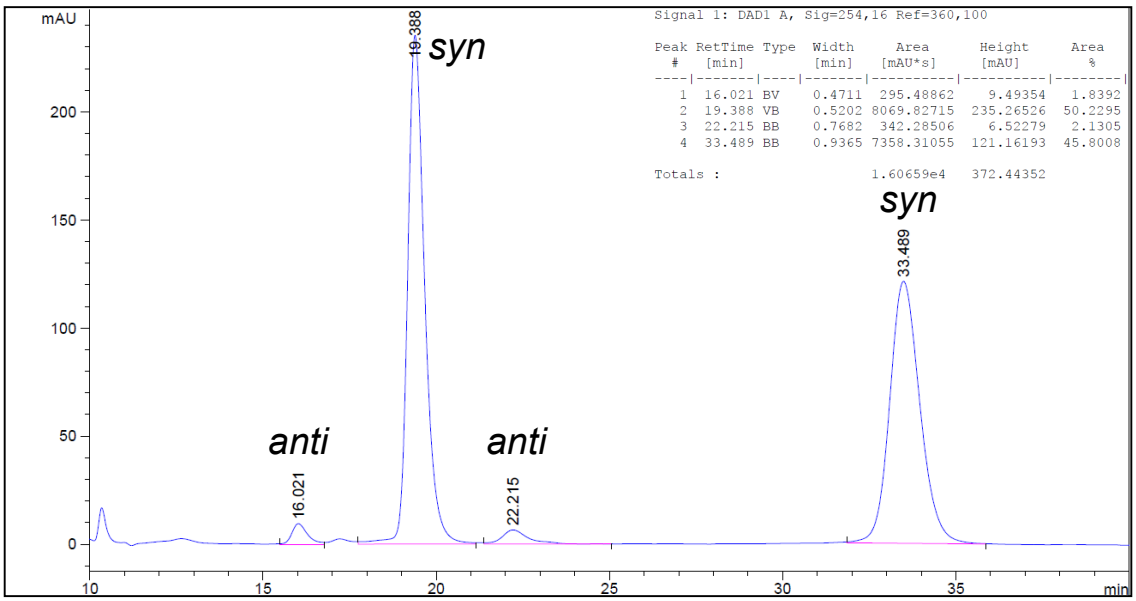
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	26.125	VB	0.6481	8368.37598	197.73849	46.4489
2	29.638	BB	0.7025	686.77679	15.09905	3.8120
3	32.589	BB	0.8750	790.83344	13.65885	4.3895
4	49.276	BB	1.2307	8170.31787	102.25632	45.3496
Totals :				1.80163e4	328.75272	

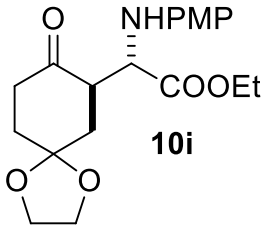


Chiralpak® AS-H column (80/20) hexane/iPrOH – flow rate: 0.75 mL/min



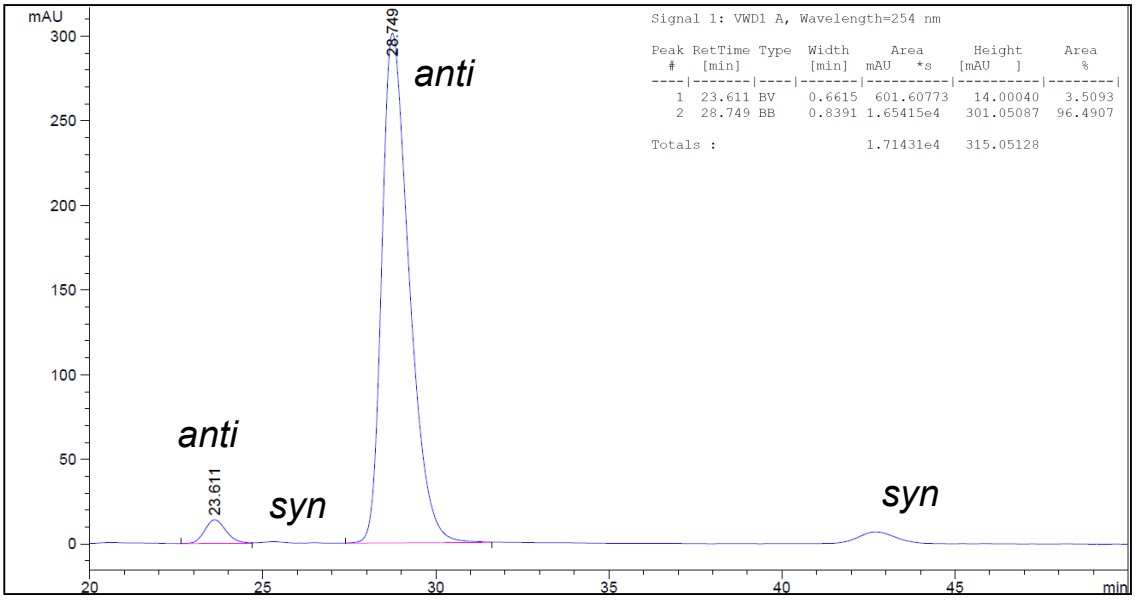
Racemic mixture:



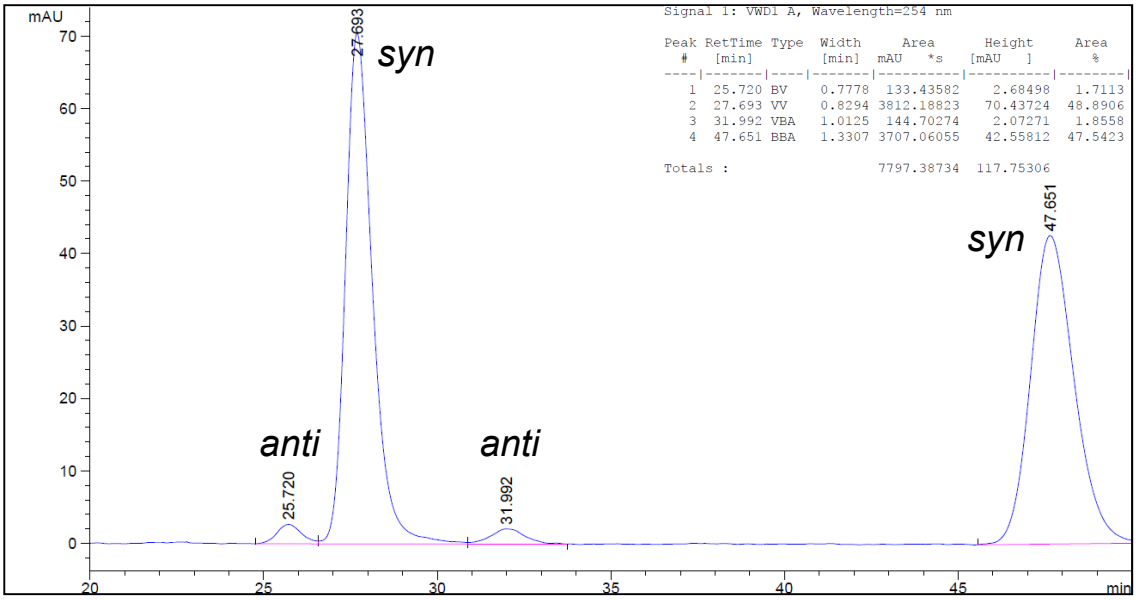


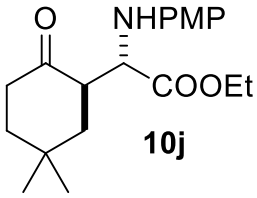
10i

Chiralpak® IC column (85/15) hexane/iPrOH – flow rate: 1.00 mL/min



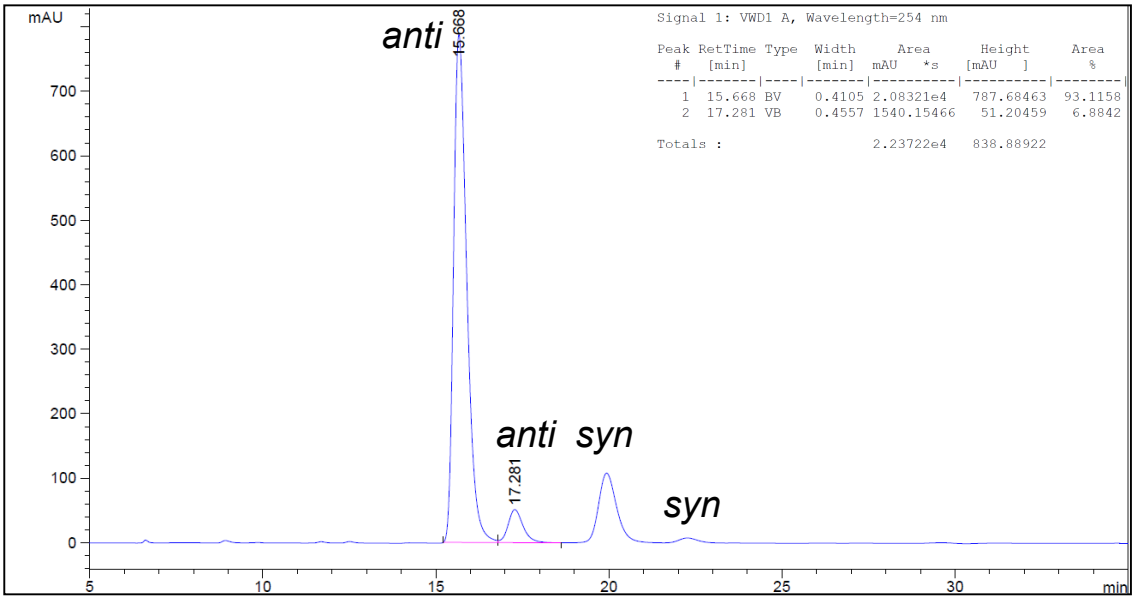
Racemic mixture:



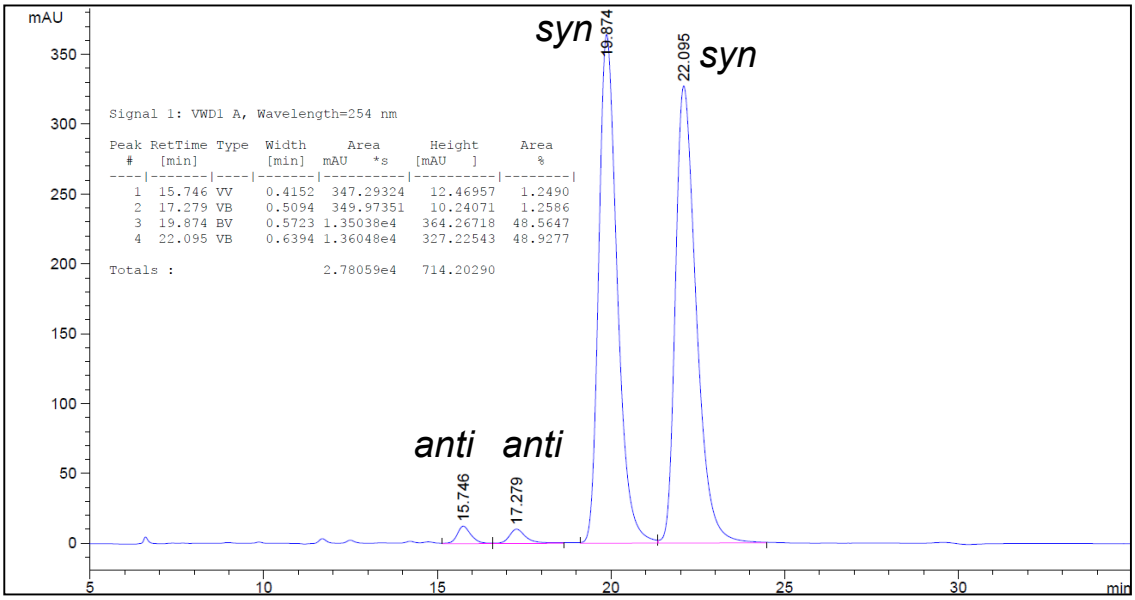


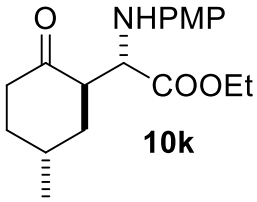
10j

Chiralpak® AS-H column (90/10) hexane/iPrOH – flow rate: 0.50 mL/min

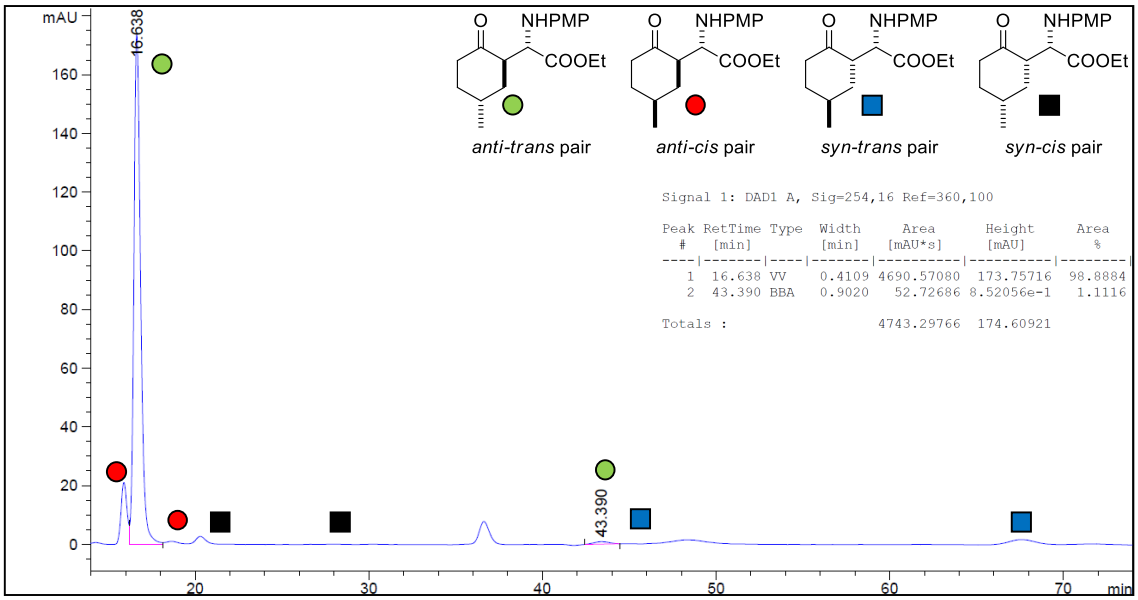


Racemic mixture:

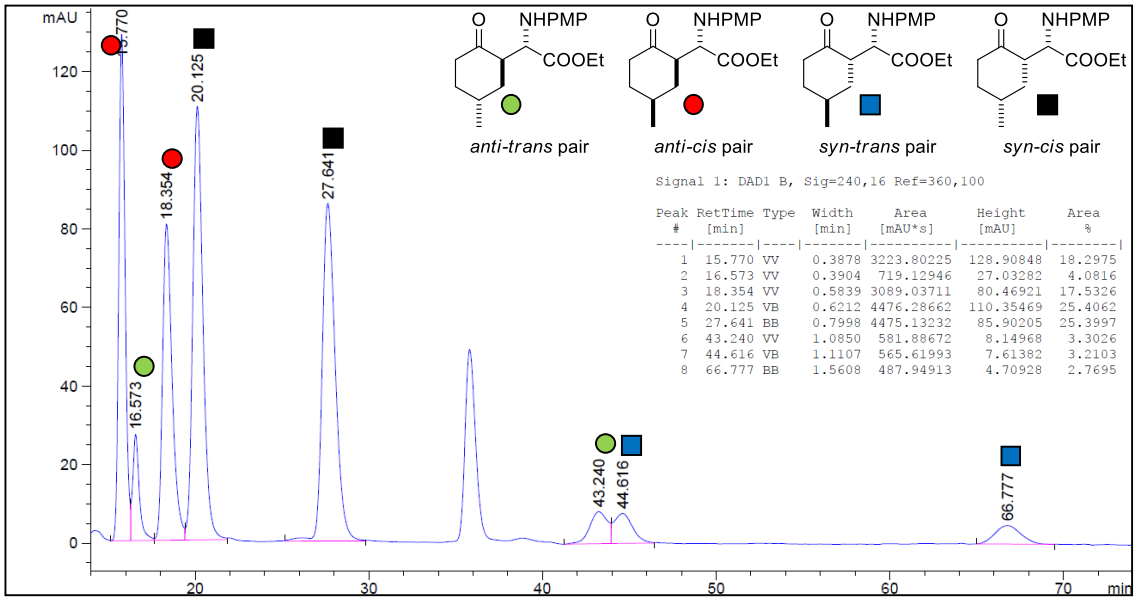




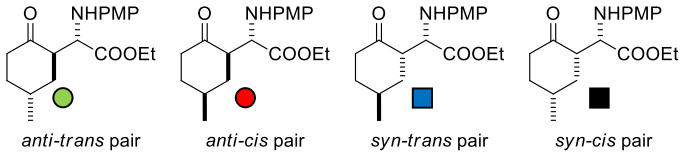
Chiralpak® AS-H column (95/5) hexane/iPrOH – flow rate: 1.00 mL/min

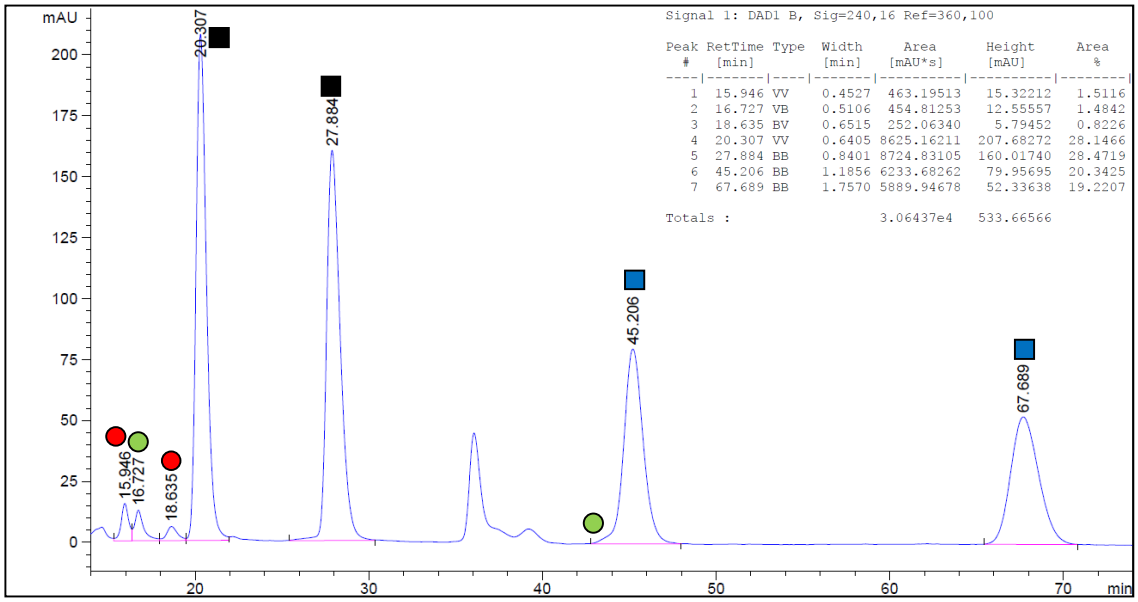


Racemic mixture A



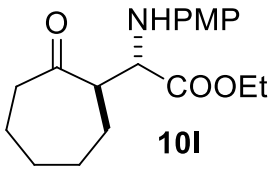
Racemic mixture B





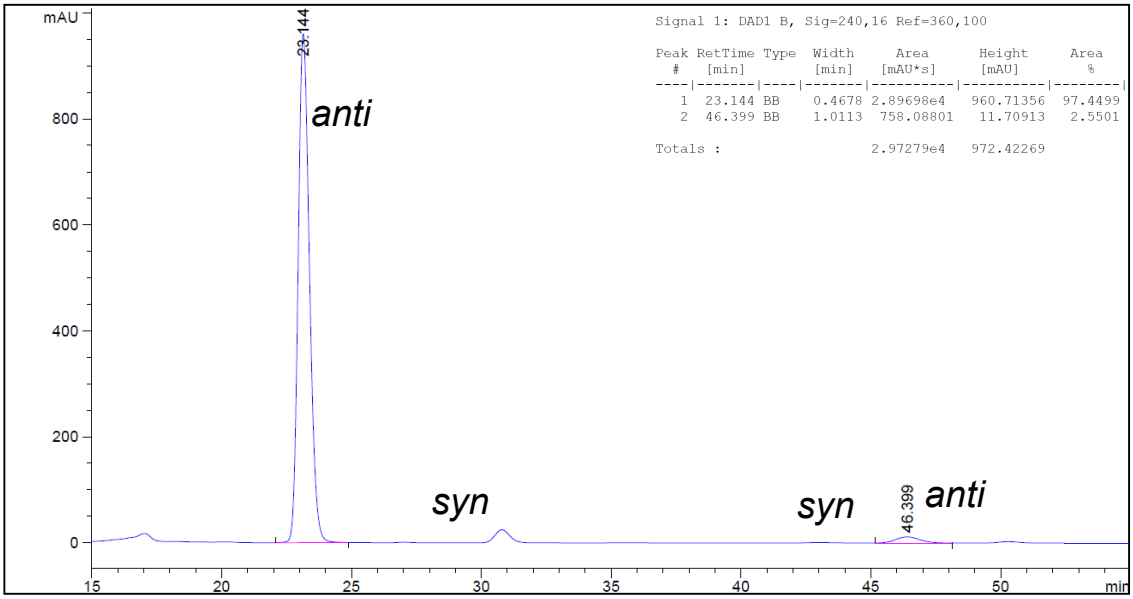
Signal 1: DAD1 B, Sig=240,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.946	VV	0.4527	463.19513	15.32212	1.5116
2	16.727	VB	0.5106	454.81253	12.55557	1.4842
3	18.635	BV	0.6515	252.06340	5.79452	0.8226
4	20.307	VV	0.6405	8625.16211	207.68272	28.1466
5	27.884	BB	0.8401	8724.83105	160.01740	28.4719
6	45.206	BB	1.1856	6233.68262	79.95695	20.3425
7	67.689	BB	1.7570	5889.94678	52.33638	19.2207
Totals :				3.06437e4	533.66566	

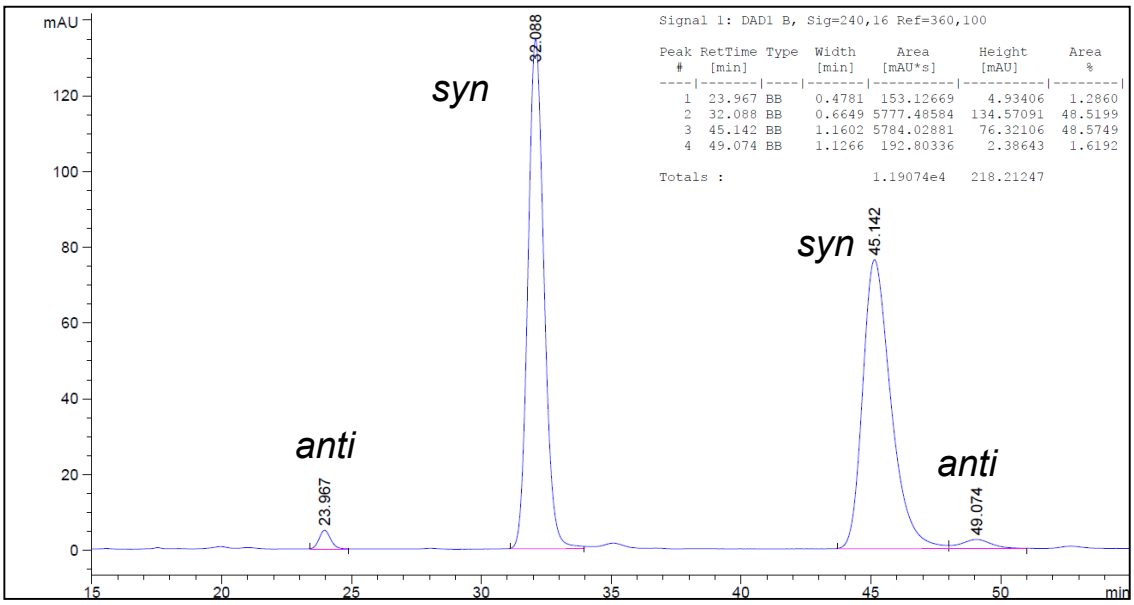


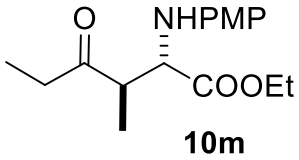
10l

Chiralpak® AS-H column (90/10) hexane/iPrOH – flow rate: 0.50 mL/min



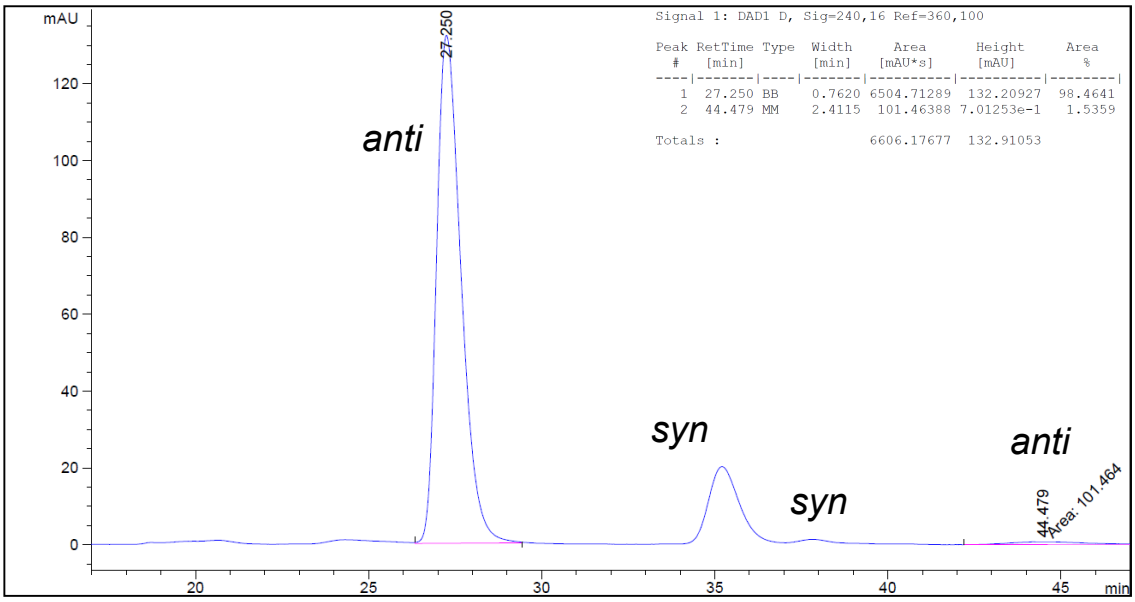
Racemic mixture:



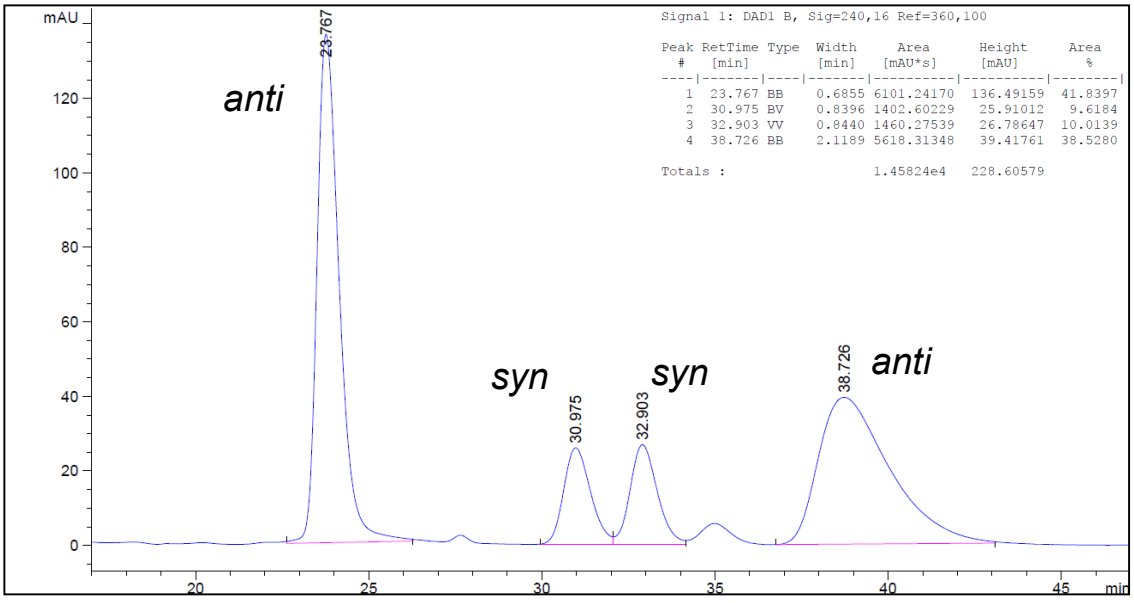


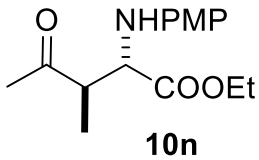
10m

Chiralpak® AS-H column (99/1) hexane/iPrOH – flow rate: 1.00 mL/min



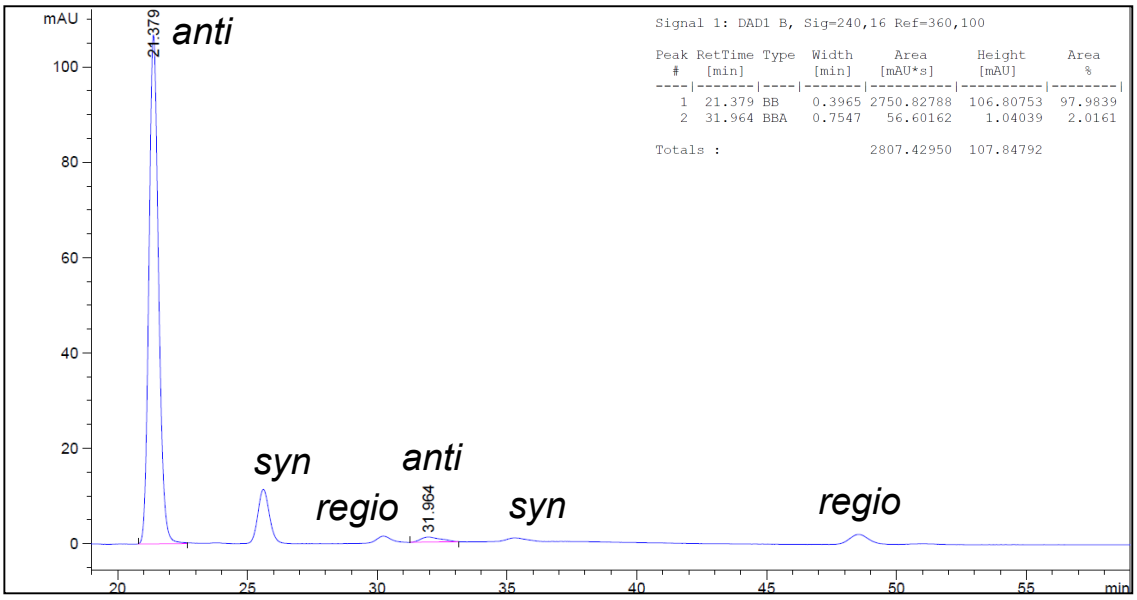
Racemic mixture:



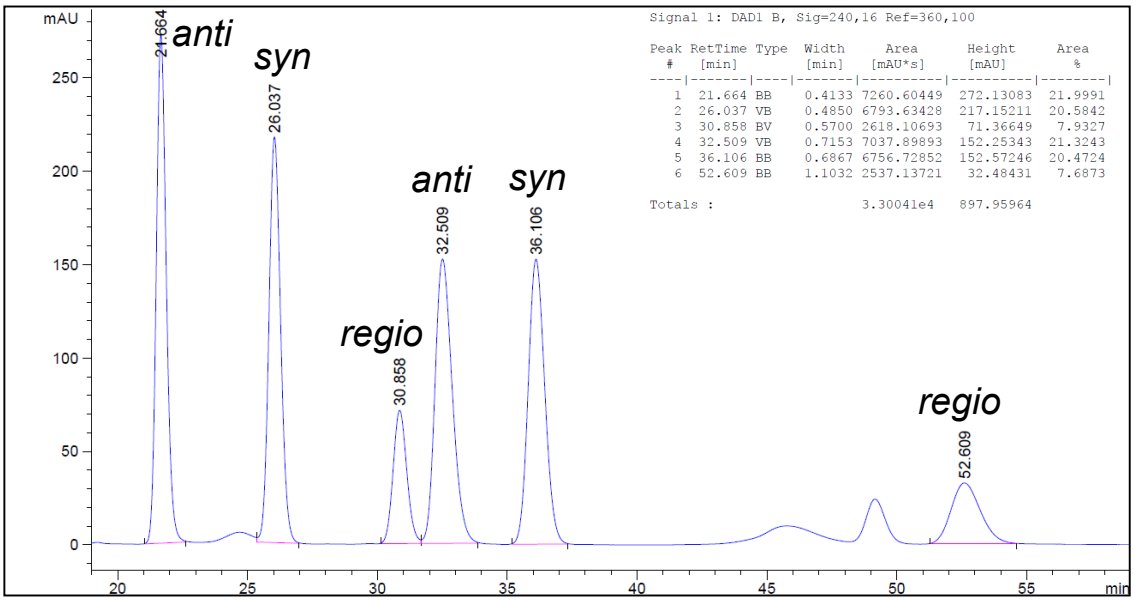


10n

Chiralpak® AS-H column (90/10) hexane/iPrOH – flow rate: 0.50 mL/min

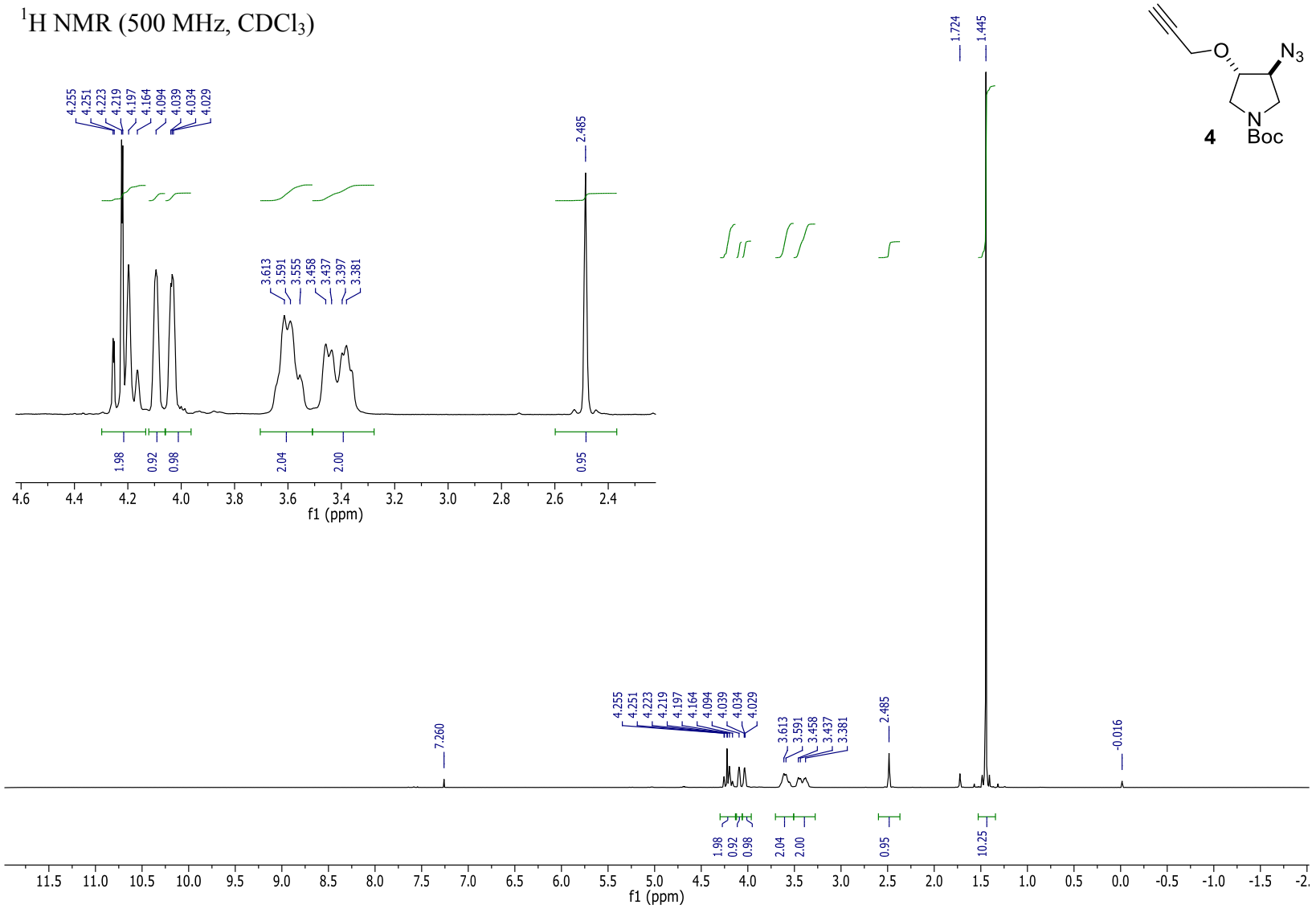


Racemic mixture:

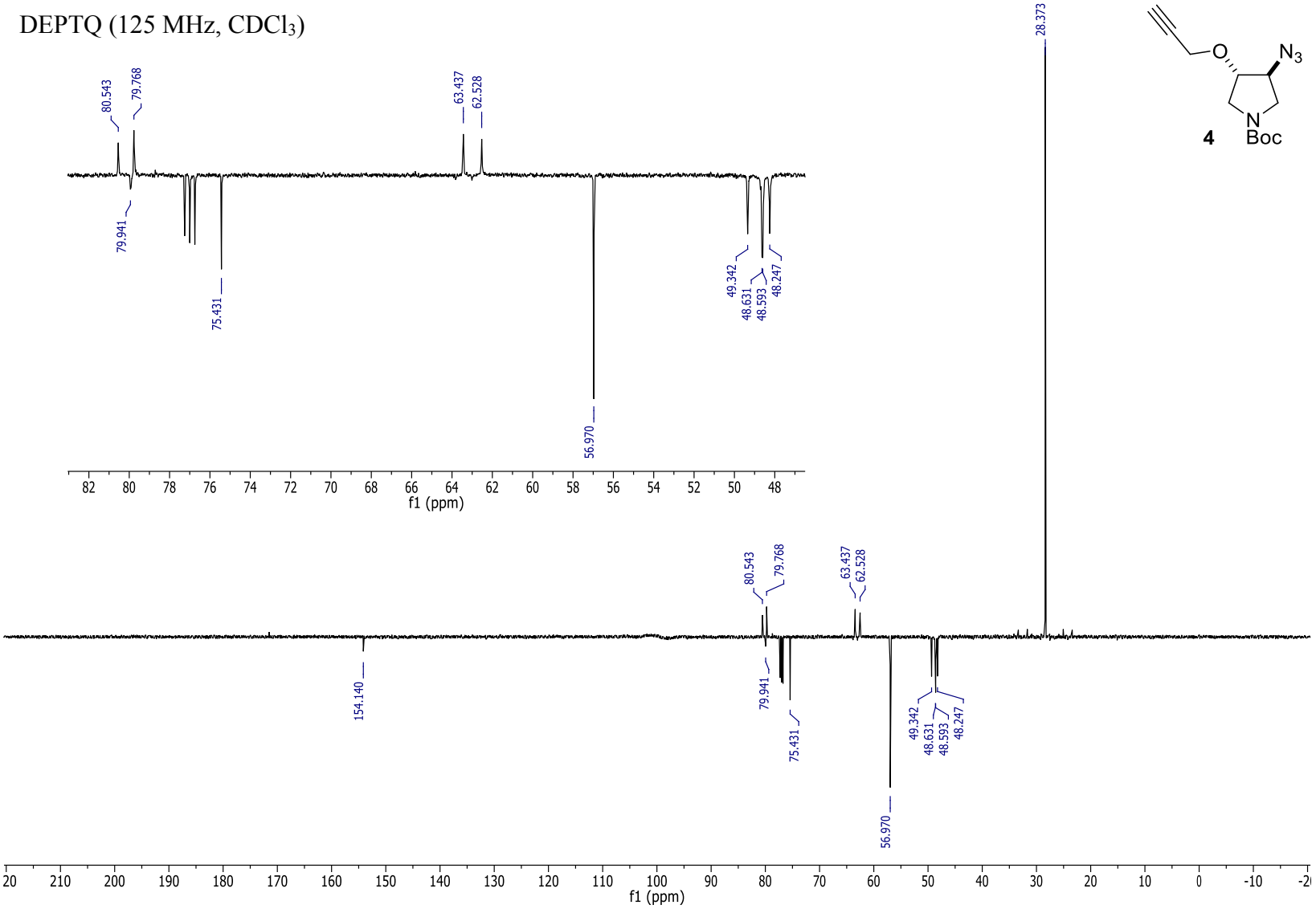


11. NMR spectra of the compounds

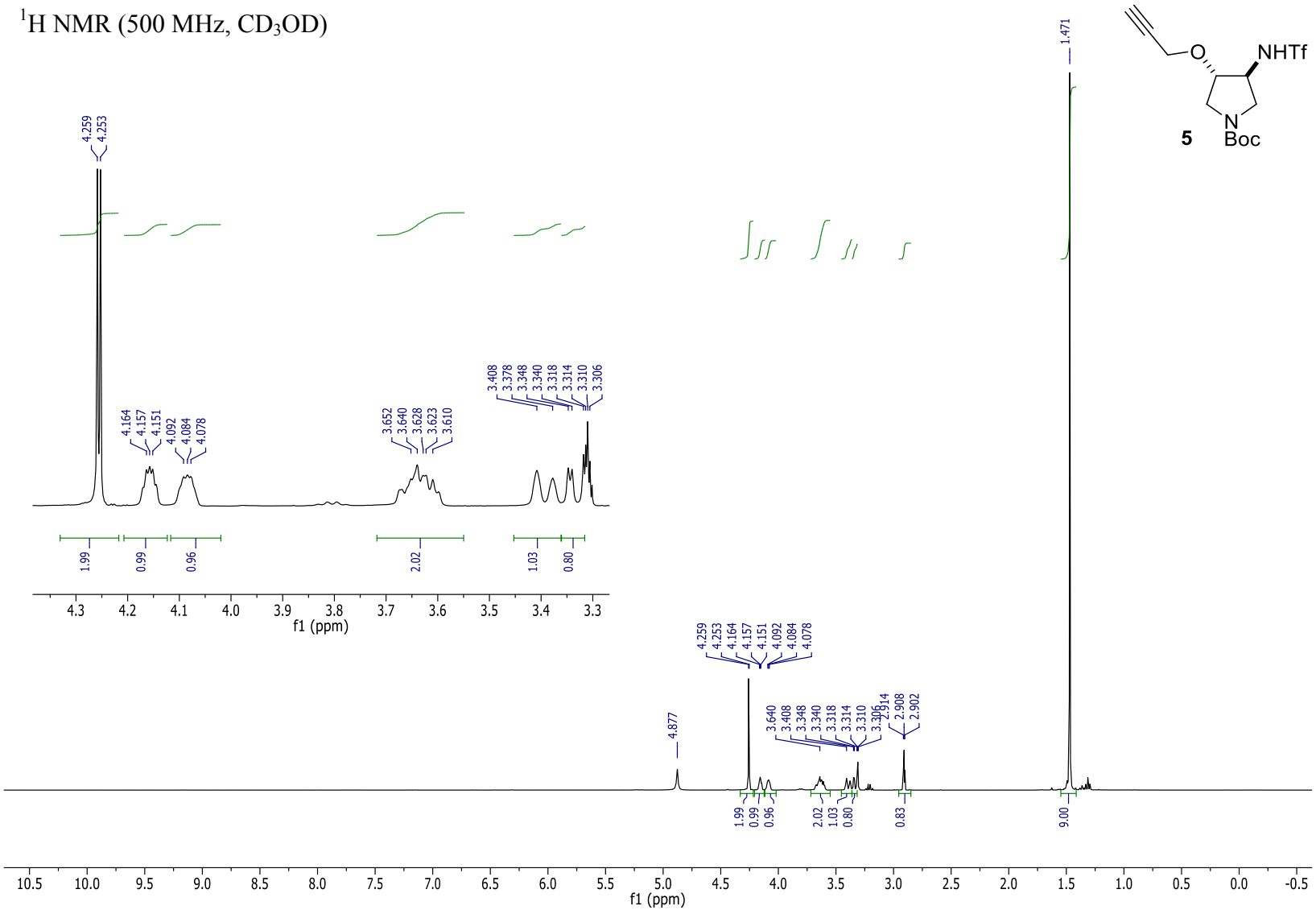
^{1}H NMR (500 MHz, $CDCl_3$)



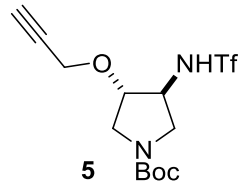
DEPTQ (125 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, CD_3OD)

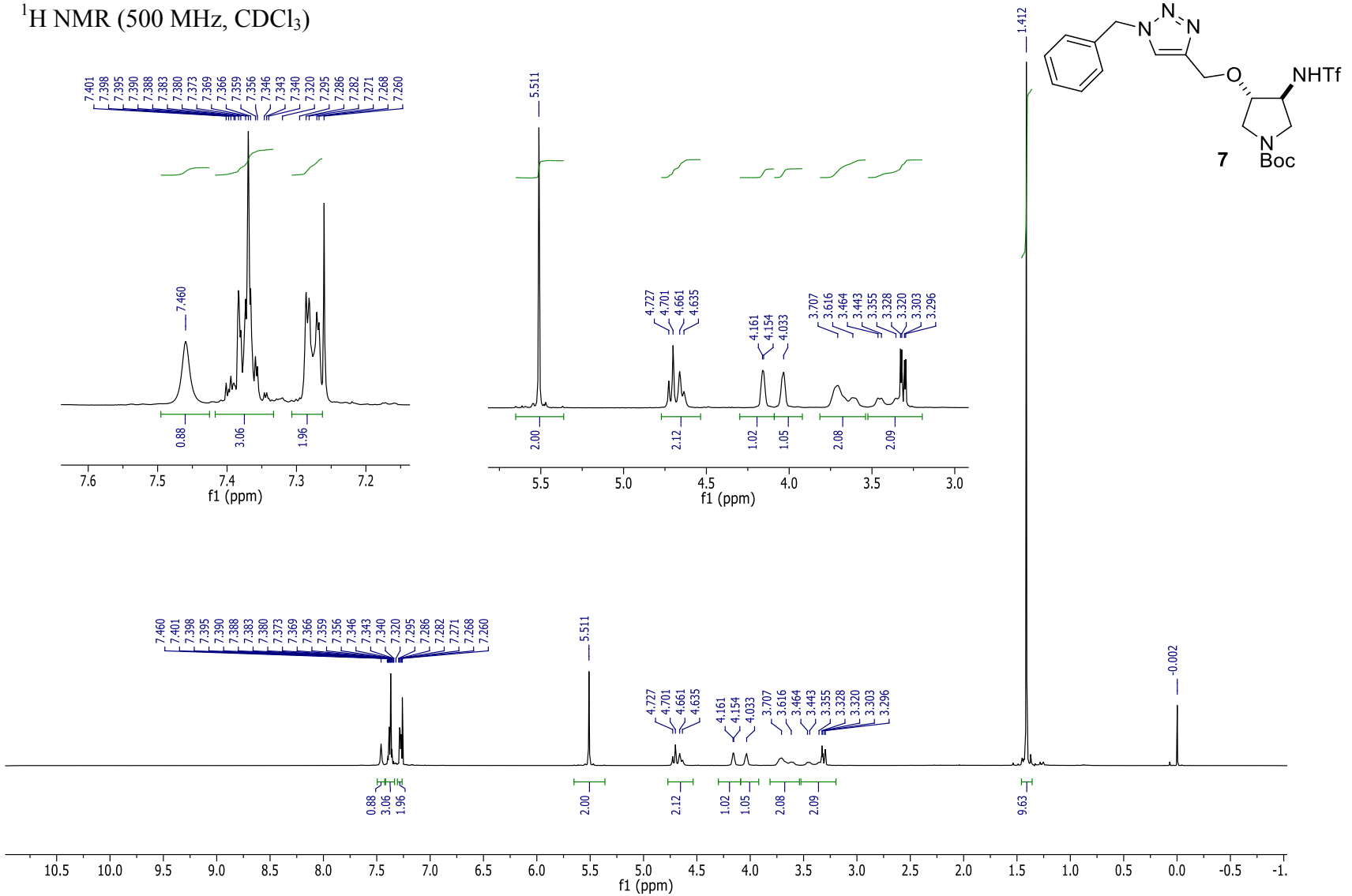


DEPTQ (125 MHz, CD_3OD)

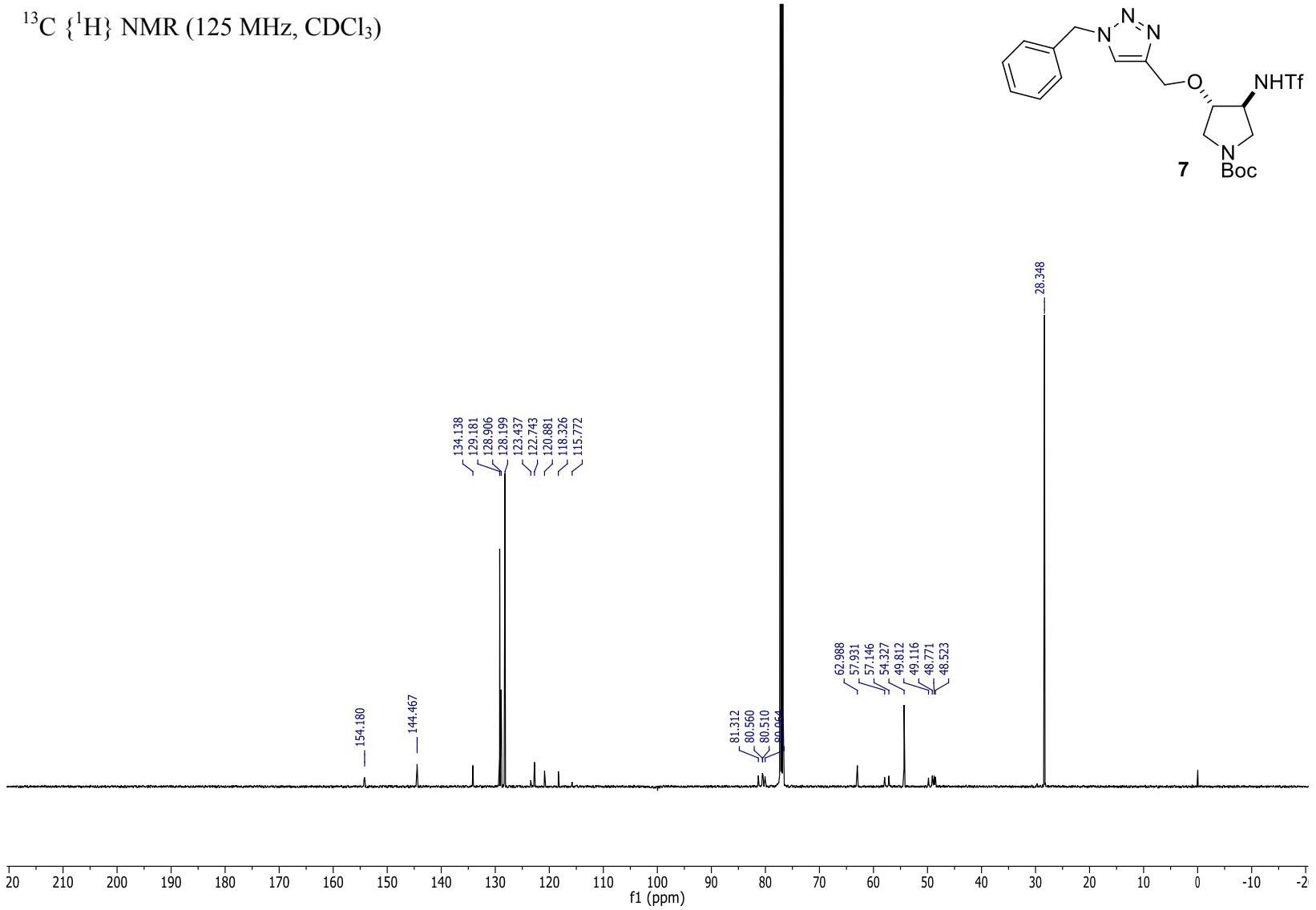


5

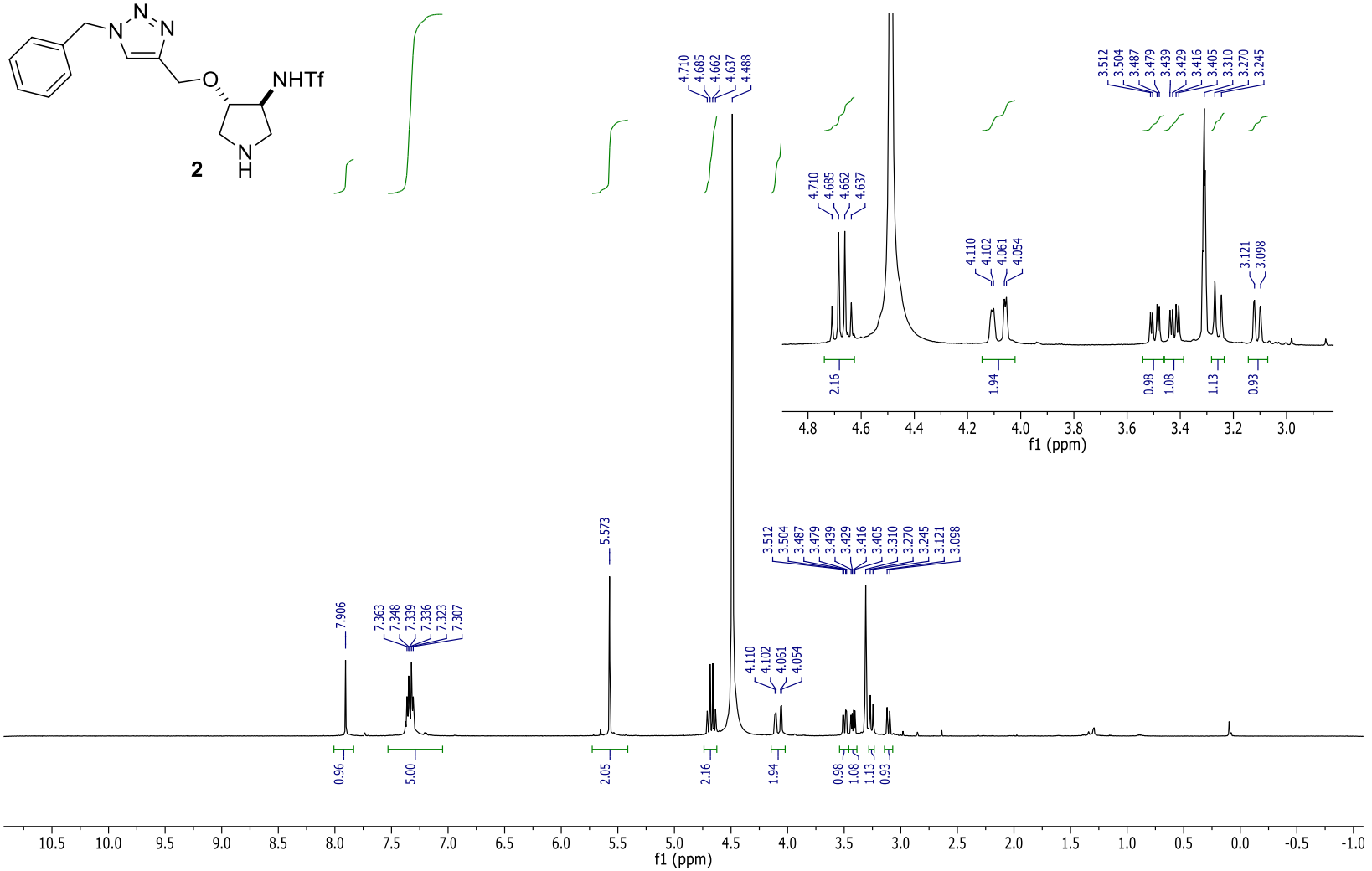
^{1}H NMR (500 MHz, $CDCl_3$)



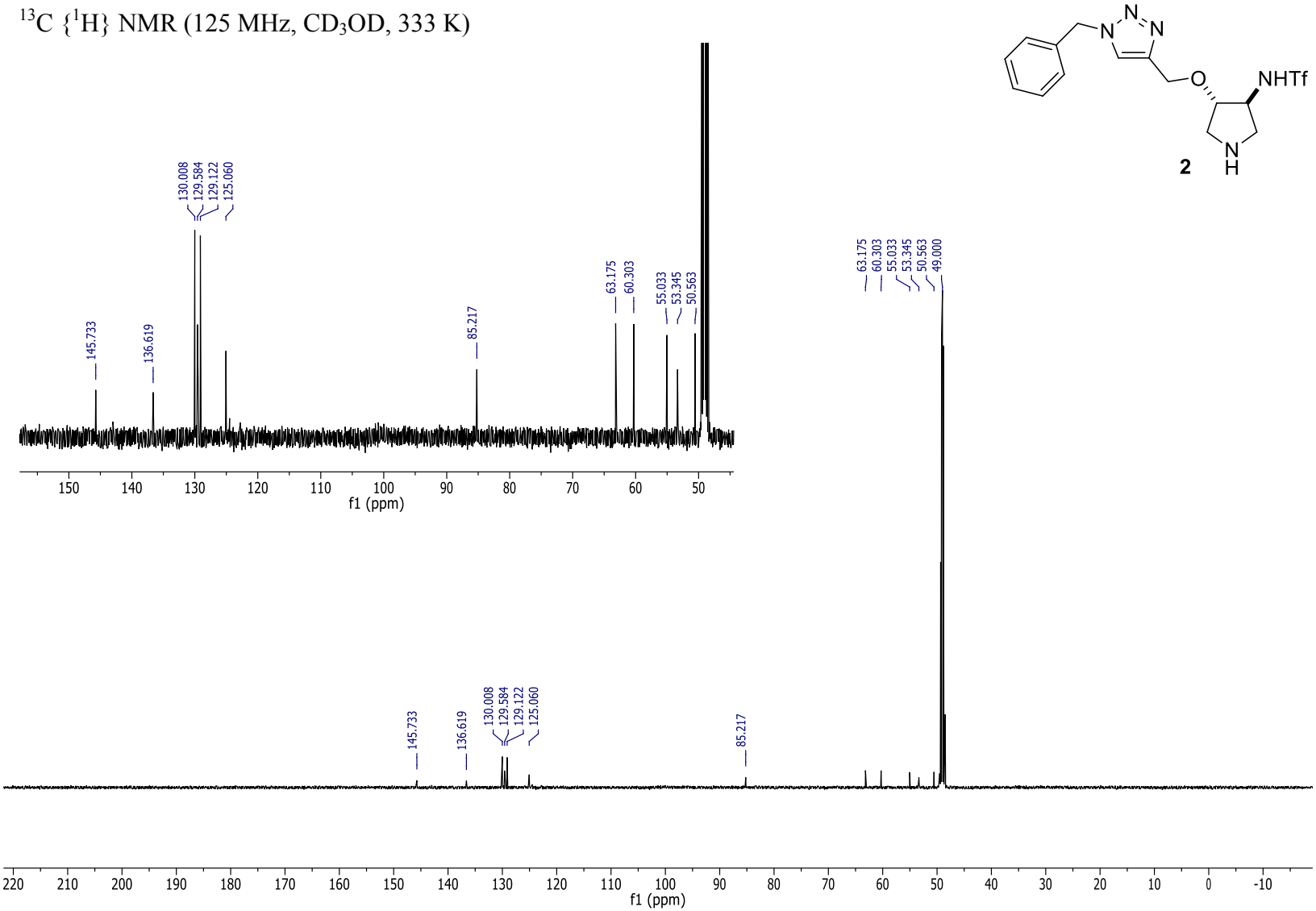
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



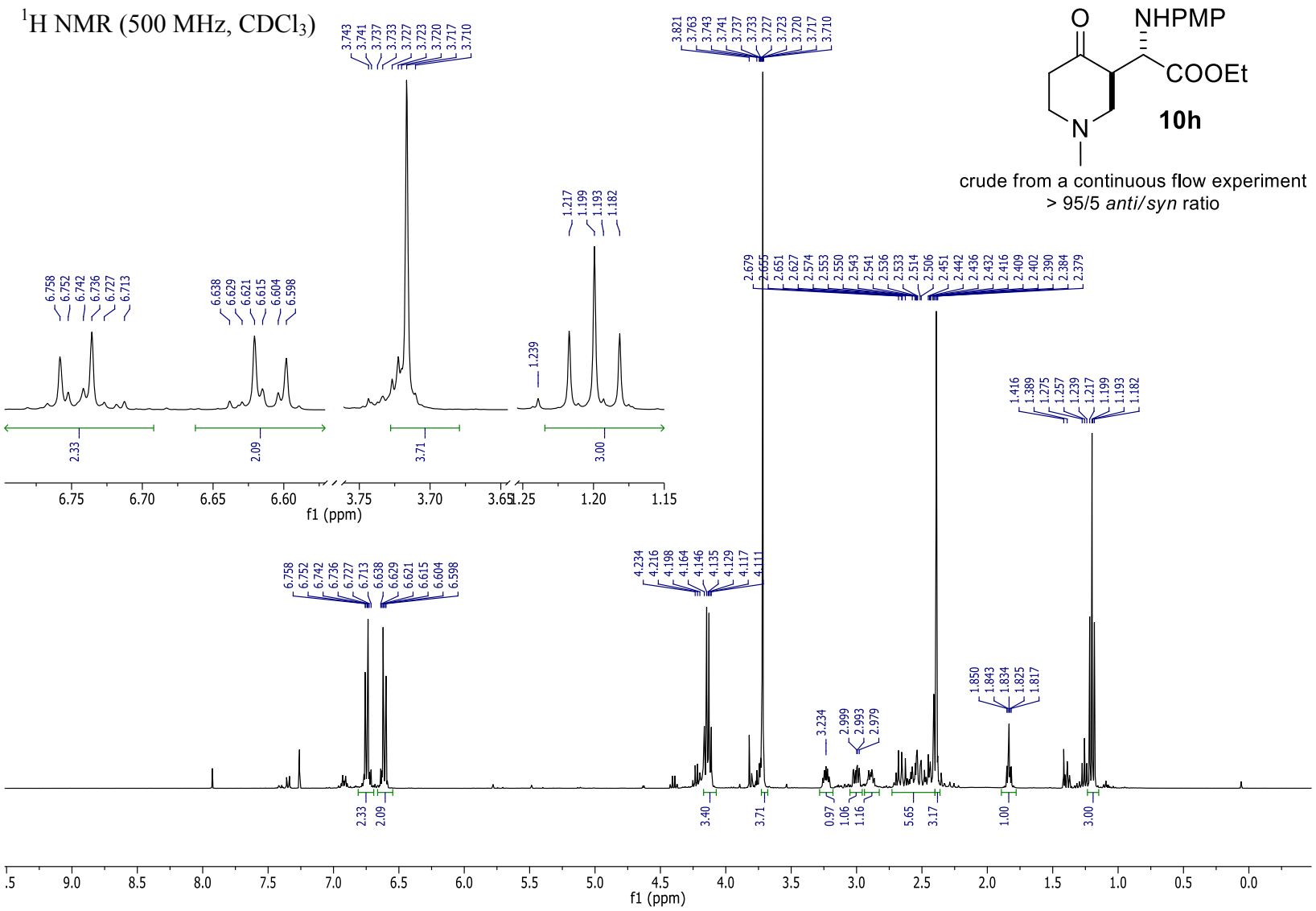
^{1}H NMR (500 MHz, CD_3OD, 333 K)

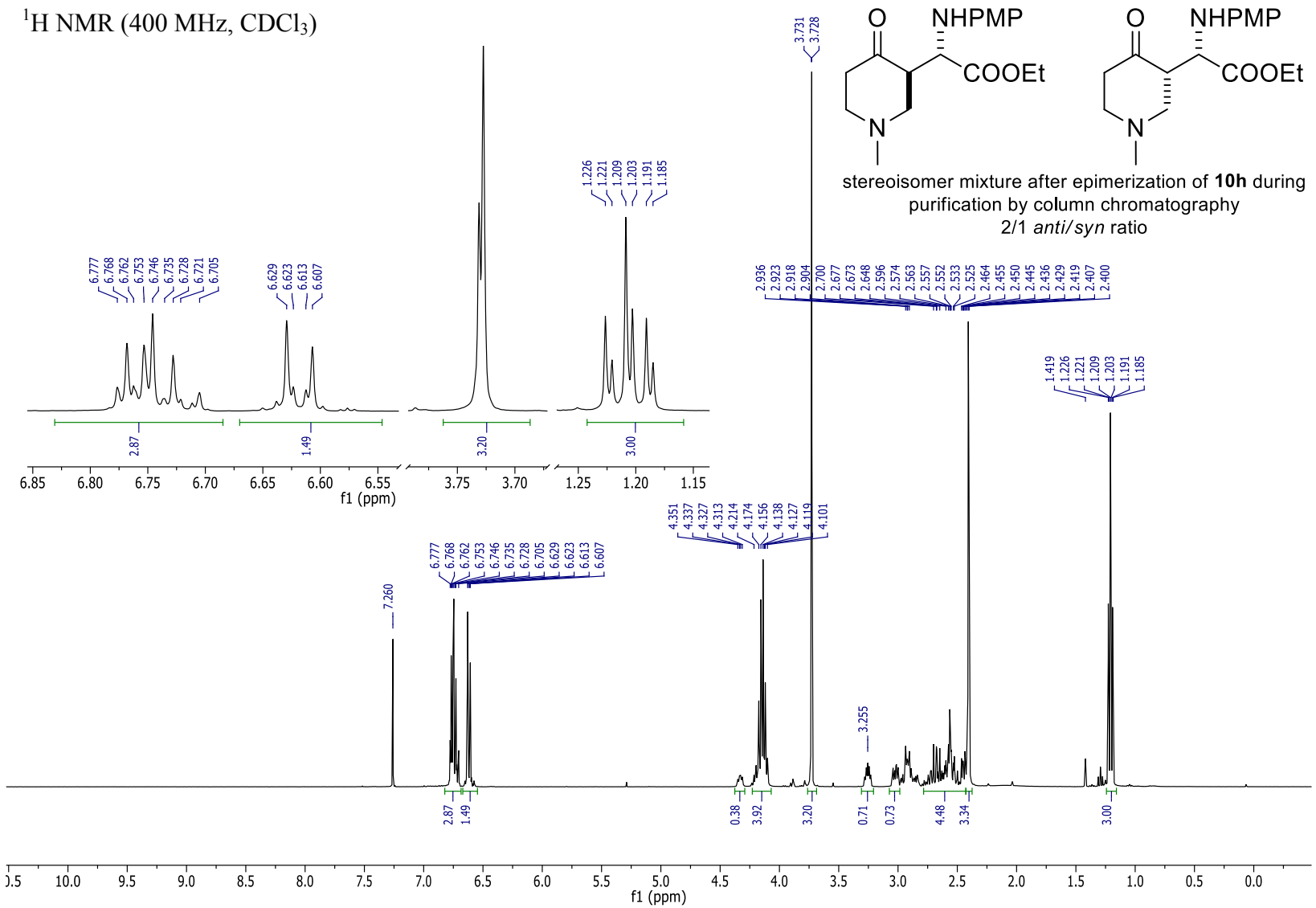


^{13}C {^{1}H} NMR (125 MHz, CD_3OD, 333 K)

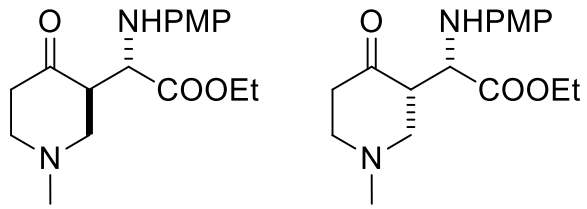


^{1}H NMR (500 MHz, $CDCl_3$)

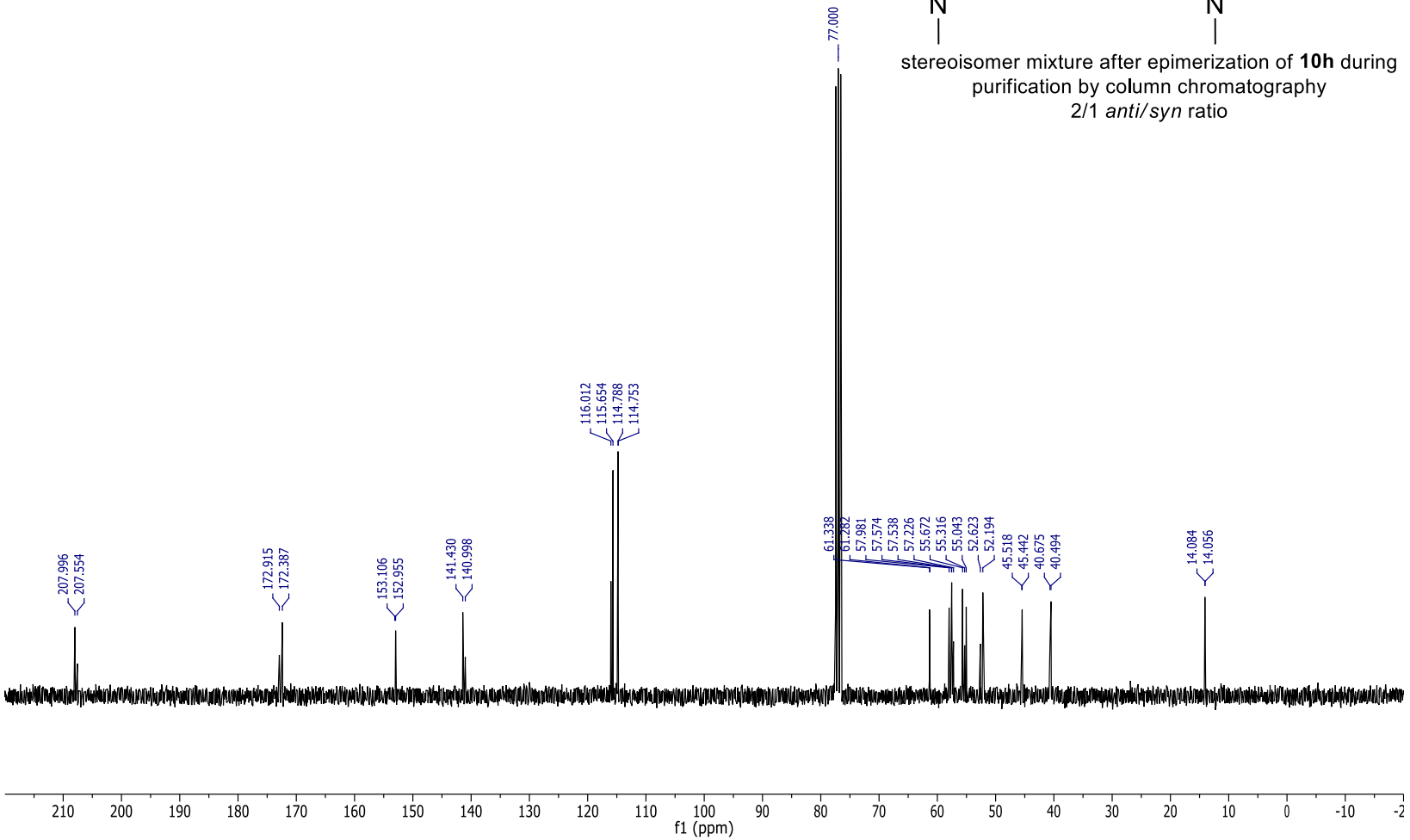




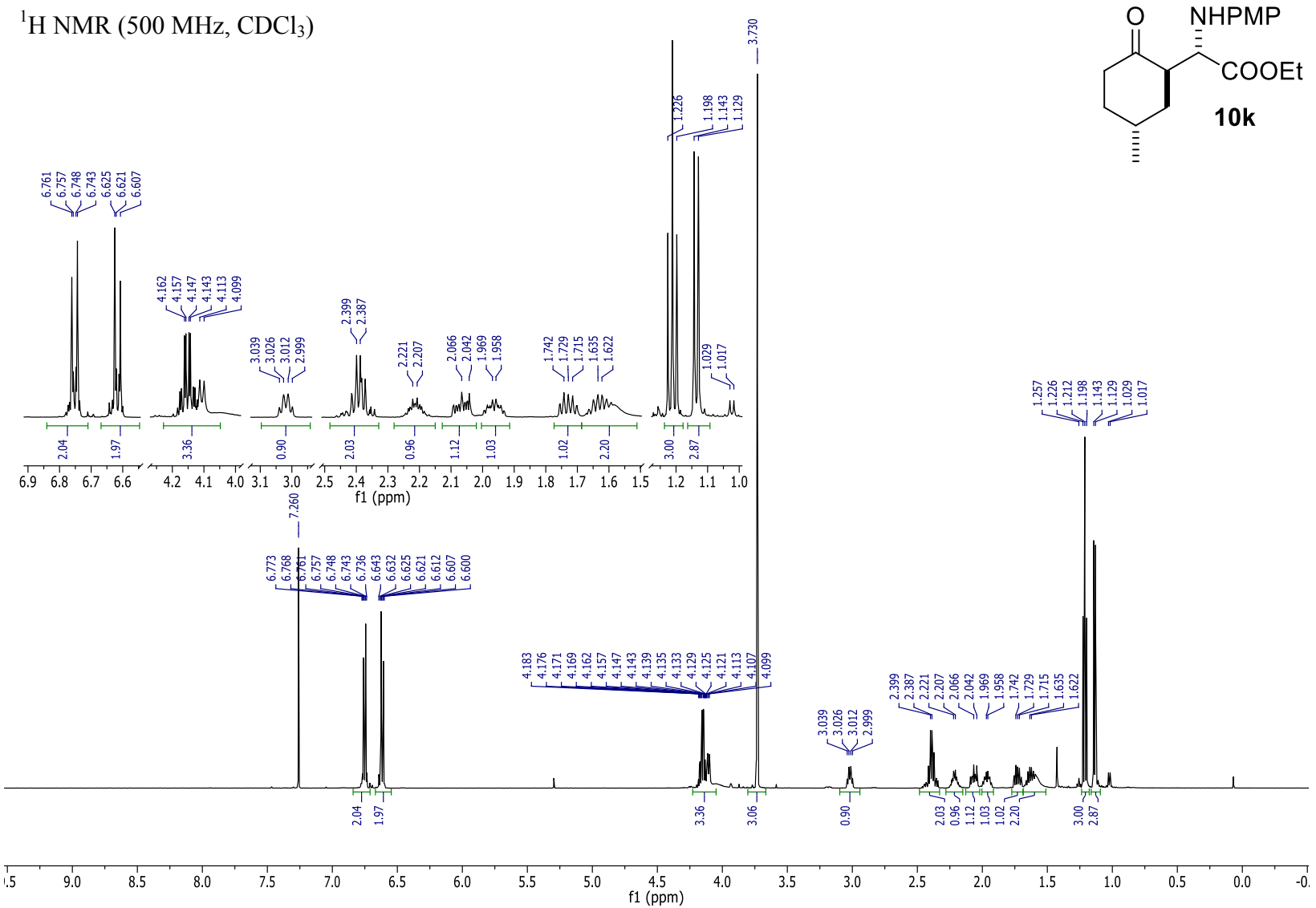
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$)

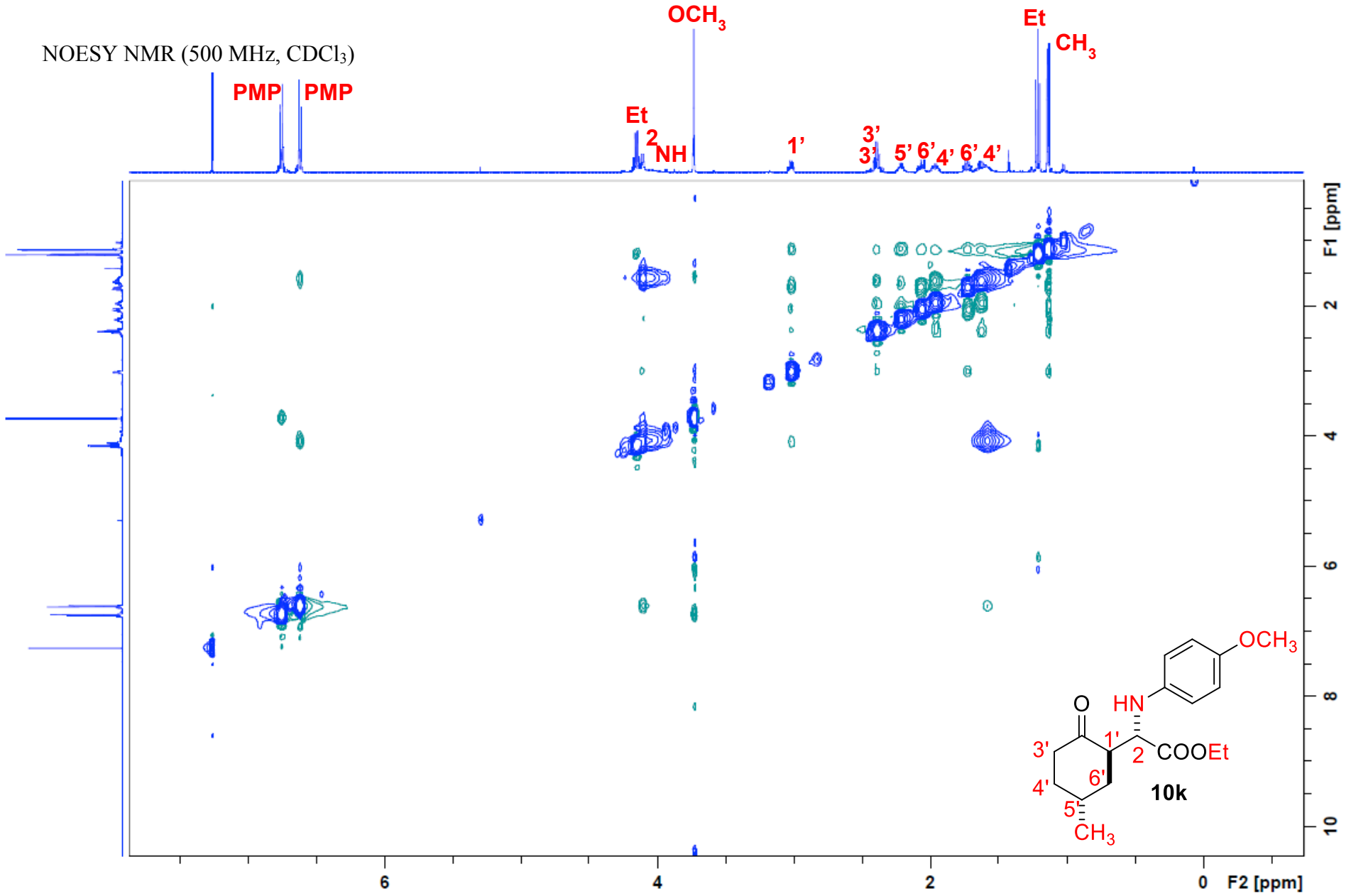


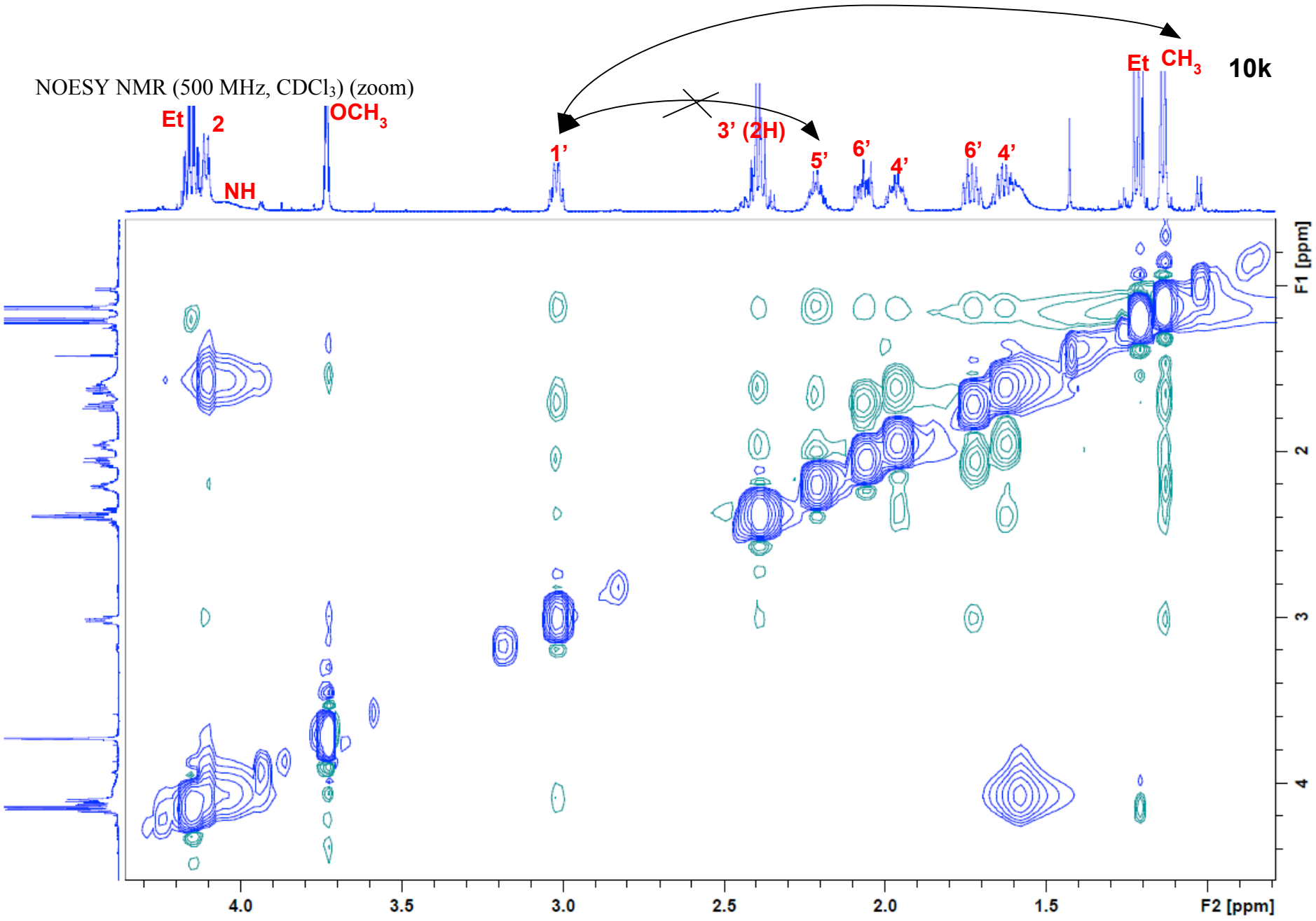
stereoisomer mixture after epimerization of **10h** during purification by column chromatography
2/1 *anti/syn* ratio



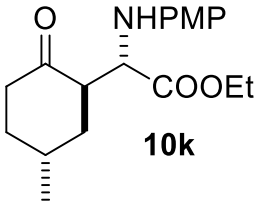
^{1}H NMR (500 MHz, $CDCl_3$)







^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)



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