Supporting Information for:

Asymmetric Supramolecular Primary Amine Catalysis in Aqueous Buffer: Connections of Selective Recognition and Asymmetric Catalysis

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General Information: Commercial reagents were used as received, unless otherwise stated. ^{1}H and ^{13}C NMR were recorded on Bruker-DPX 300 spectrometer. TOCSY, COSY, ROCSY and HSQC were recorded on Bruker-DPX 600 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift mutiplicities: s= singlet, d= doublet, t= triplet, q= quartet, h= heptet, m= multiplet, br= broad. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Mass spectra were obtained using electron ionization (EI) mass spectrometer and matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry. Mono(O-6-tosyl)-β-cyclodextrin[1], catalysts **7**[2], **8**[3] and **9**[2] were prepared following the literature procedure. Catalyst **10** is the byproduct of when preparing the catalyst **9**.

Representative procedure for the synthesis of catalysts:

Synthesis of CD-1

Under argon atmosphere, mono(O-6-tosyl)-β-cyclodextrin (2.0 g, 1.55 mmol) was suspended in dry DMF (2.0 mL); after warming to 80°C, the mixture became homogeneous. (1S,2S)-cyclohexane-1,2-diamine(1.0g, 8.77 mmol) was added and the reaction mixture was stirred at 80°C for 24 h. The reaction was cooled to room temperature and 1M NaOH aqueous solution (2 mL) was then added. The resulting yellow solution was added drop-wise to acetone (300 mL), the precipitate was filtered and washed successively with ethanol (50 mL) and acetone (20 mL×2) to give the crude product. The obtained crude product was then dissolved in water (2 mL) and precipitated with acetone (200 mL). The precipitation was collected and the procedure was repeated. The purified product was dried under vacuum overnight to yield a light yellow powder (1.6 g, 84%). $[\alpha]_D^{25}$= +107.6 ^{o} (c = 1.0, H_2O); ^{1}H NMR (600 MHz, D_2O): δ 5.15-5.05 (7H, m), 4.01-3.75 (28H, m), 3.64-3.43 (14H, m), 3.16-3.14 (1H, m), 2.91-2.81 (1H, m), 2.43-2.50 (1H, m), 2.20-2.18 (1H, m), 2.06-1.91 (2H, m),

1.75-1.60 (2H, m), 1.26-1.12 (4H, m) ppm; ^{13}C NMR (125 MHz, D_2O), δ 102.1, 101.9, 101.4, 83.7, 81.3, 81.2, 73.3, 73.2, 72.7, 72.1, 72.0, 69.2, 61.3, 60.5, 60.2 (C8), 54.6 (C7), 46.2, 34.2 (C12), 30.0 (C9), 25.0 (C11), 24.8 (C10) ppm; MALDI-TOF *m/z* calcd for [$C_{48}H_{82}N_2O_{34}$] 1230.4, found 1231.3 $[M+H]^+$, 1253.3 $[M+Na]^+$. MS (EI^+) calcd. for [$C_{48}H_{82}N_2O_{34}$] 1230.47.; found $[M+H]^+$, 1231.64. ***Anal.*** Calcd. for $C_{48}H_{82}N_2O_{34}$: C, 46.83; H, 6.71; N, 2.28. Found: C, 46.77; H, 6.89; N, 2.19.

Synthesis of CD-2

The catalyst was prepared according to similar procedure as a light yellow powder in 86% yield. $[\alpha]_D^{25}$= +114.0 ^{o} (c = 1.0, H_2O); ^{1}H NMR (600 MHz, D_2O): δ 5.14-5.06 (7H, m), 3.93-3.73 (28H, m), 3.73-3.52 (14H, m), 3.30-3.22 (1H, m), 2.72-2.78 (1H, m), 2.48-2.54 (1H, m), 2.23-2.20 (1H, m), 2.02-1.88 (2H, m), 1.72-1.65 (2H, m), 1.27-1.12 (4H, m) ppm; ^{13}C NMR (125 MHz, D_2O): δ 102.1, 101.9, 83.4, 81.3, 73.3, 73.2, 72.1, 72.0, 71.7, 62.8, 60.3 (C8), 54.2 (C7), 46,9, 34.0 (C12), 30.5 (C9), 24.8 (C11), 24.6 (C10) ppm; MALDI-TOF *m/z* calcd for [$C_{48}H_{82}N_2O_{34}$] 1230.4, found 1231.3 $[M+H]^+$, 1253.4 $[M+Na]^+$.; MS (EI^+) *m/z* calcd. for [$C_{48}H_{82}N_2O_{34}$] 1230.47.; found $[M+H]^+$, 1231.62. ***Anal.*** Calcd. for $C_{48}H_{82}N_2O_{34}\cdot 3H_2O$: C, 44.86; H, 6.90; N, 2.18. Found: C, 44.84; H, 7.01; N, 2.12.

Synthesis of CD-3

The catalyst was prepared from *cis*-1,2-diamniocycohexane according to the synthesis of **CD-1** as a light yellow powder in 85% yield. The obtained product was a mixture of two inseparable diastereo isomers. ^{1}H NMR (300 MHz, D_2O): δ 5.42-5.04 (7H, m), 4.40-3.70 (24H, m), 3.70-2.95 (13H, m), 2.95-2.45 (2H, m), 2.43-2.09 (1H, m), 2.07-0.69 (7H, m) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): δ 101.9, 81.5, 73.1, 72.5, 72.0, 60.2, 59.9, 46.4, 30.6 ppm, MALDI-TOF *m/z* calcd for [$C_{48}H_{82}N_2O_{34}$] , found 1231.5 $[M+H]^+$, 1253.5 $[M+Na]^+$. MS (EI^+) *m/z* calcd. for [$C_{48}H_{82}N_2O_{34}$] 1230.47.; found $[M+H]^+$, 1231.77.

Synthesis of CD-4

Under argon atmosphere, a neat solution of mono(O-6-tosyl)-β-cyclodextrin (1.0 g, 0.77 mmol) and ethane-1,2-diamine (5 mL) was stirred at 60° C for 12 h. The reaction was cooled to room temperature and treated similarly according to the synthesis of **CD-1** to give the desired product as a light yellow powder in 90% yield. $[\alpha]_D^{25}$= +102.4 ^{o} (c = 1.0, H_2O); ^{1}H NMR (300 MHz, D_2O): 4.98 (7H, s), 3.90-3.78 (27H, m), 3.54-3.41 (14H, m), 3.38-3.35 (1H, m), 3.07-2.94 (2H, m), 2.78-2.64 (4H, m) ppm; ^{13}C NMR (75 MHz, D_2O): δ 101.8, 101.6, 83.4, 81.2, 80.9, 73.1, 73.0, 72.1, 71.8, 70.5, 60.3 (C8), 49.1, 49.0, 39.3 (C7) ppm. MALDI-TOF *m/z* calcd for $[C_{44}H_{76}N_2O_{34}]$ 1176.4, found 1177.3 $[M+H]^+$, 1199.4 $[M+Na]^+$. MS (EI^+) *m/z* calcd. for $[C_{44}H_{76}N_2O_{34}]$ 1176.43.; found $[M+H]^+$, 1177.57. *Anal.* Calcd. for $C_{44}H_{76}N_2O_{34}$: C, 44.90; H, 6.51; N, 2.38. Found: C, 45.10; H, 6.52; N, 2.55

Synthesis of CD-5

The catalyst was prepared according to the synthesis of **CD-1** as a yellow powder in 83% yield. $[\alpha]_D^{25}$= +111.8 ^{o} (c = 1.0, DMSO); ^{1}H NMR (300MHz, DMSO): δ 6.02-5.18 (14H, br), 4.88-4.61 (7H, m), 4.61-4.27 (10H, br), 4.04-3.45 (46H, m, overlap with HOD), 3.48-3.07 (23H, m), 2.89-2.86 (2H, m), 2.43-2.40 (2H, br), 2.2 (3H, s), 2.05 (3H, s), 1.92 (2H, m), 1.68 (2H, m), 1.58 (1H, m), 1.12 (3H, m), 0.86 (1H, m) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): δ 103.1, 102.2, 101.9, 101.562, 84.7, 81.5, 80.8, 73.3, 73.0, 72.4, 72.0, 70.0, 66.8, 60.1, 59.9, 46.4, 35.0, 33.5 (C12), 30.541, 25.1, 24.2, 21.7 ppm; MALDI-TOF *m/z* calcd for $[C_{50}H_{86}N_2O_{34}]$ 1258.5, found $[M+H]^+$, 1260.1. MS (EI^+) *m/z* calcd. for $[C_{50}H_{86}N_2O_{34}]$ 1258.51.; found $[M+H]^+$, 1259.62.

Synthesis of CD-6

The catalyst was prepared according to the synthesis of **CD-1** as a yellow powder in 98% yield. $[\alpha]_D^{25}$=+99.4 ^{o} (c = 1.0, DMSO); ^{1}H NMR (300MHz, d_6-DMSO): δ 6.02-4.99 (12H, br), 4.82-4.81 (7H, m), 4.54-4.03 (6H, br), 3.75-3.47 (26H, m), 3.47-2.94 (60H, m, overlap with HOD), 2.77-2.71 (2H, m), 2.40-2.27 (2H, m), 2.13 (6H, s), 1.95-1.92 (2H, m), 1.69 (2H, m), 1.63-1.58 (1H, m), 1.10 (3H, m), 0.86-0.83

(1H, m) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): δ 102.3, 101.9, 101.7, 101.4, 84.6, 81.6, 81.4, 80.7, 73.4, 73.1, 72. 8, 72.5, 71.9, 71.2, 66.4, 59.9, 59.4, 58.0, 48.0, 31.3, 25.0, 24.1, 20.2 ppm; MALDI-TOF *m/z* calcd for $[C_{50}H_{86}N_2O_{34}]$ 1258.5, found $[M+H]^+$, 1259.9. MS (EI^+) *m/z* calcd. for $[C_{50}H_{86}N_2O_{34}]$ 1258.51.; found $[M+H]^+$, 1259.65.

Synthesis of 10

The catalyst 10 was the byproduct when preparing catalyst 9.[2] $[\alpha]_D^{20}$=+41.0 ^{o} (c = 1.0, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$): δ 2.76-2.67 (1H, m), 2.48-2.41 (1H, m), 2.39-2.30 (1H, m), 2.06-1.95 (2H, m), 1.88-1.83 (1H, m), 1.71-1.64 (2H, m), 1.48-1.43 (3H, m). 1.25 (20H, s), 0.89-0.94 (3H, t) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ77.3, 64.1, 55.3, 47.3, 36.3, 32.0, 31.5, 30.7, 29.7, 29.7, 29.4, 27.6, 25.4, 25.4, 22.8, 14.2. MS (EI^+) *m/z* calcd. for $[C_{16}H_{34}N_2]$ 254.27; found $[M+H]^+$, 255.45.

ESI-MS study

To a stirred solution of **CD-1** (12.3mg, 0.01 mmol) in 1M acetate buffer (pH=4.88, 400 μL) was added acetone (100 μL). The mixture was stirred for 10 min and 4-nitrobenzaldehyde was then added. The reaction mixture was stirred for 1 hr before the addition of $NaBH_4$ and the mixture was stirred for another 1 h. An aliquot was taken and subjected to ESI-MS after dilution to homogeneity.

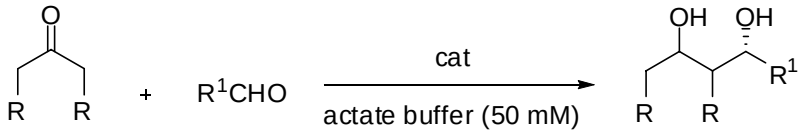
Kinetic study by RP-HPLC:

Kinetic studies of the reaction were conducted in acetate buffer (50 mM) with 5-10% v/v donor and 0.05-0.4 mM aldehyde. Aldehydes were soluble within the condition used. The reaction was conveniently monitored by the analytical RP-HPLC in situ **(Table 1)**

Aldehydes were used as 40 mM stock solutions in acetone/water (1:1, v/v). Catalysts were used as 20 mM stock solutions in water. To a small vial containing acetate buffer (890 μL) was added 10 μL of stock solution of catalyst and 100 μL of

stock solution of aldehyde. The sample was stirred to ensure homogeneity. The final solution was obtained containing 4 mM aldehyde, 0.2 mM catalyst, 5% v/v acetone in acetate buffer (1 mL). The reaction was allowed to run under 25 ^{o}C. During intervals, the samples (50 μL) were taken and mixed with a standard solution containing the internal standard compound (50 μL). The obtained solution was then analyzed by RP-HPLC. The standard curves of product and internal standard was first determined. The concentration of product can be calculated by the ration of the aldol product and internal standard (see **scheme S1**). And the reaction initial rate can be determined by the slope of the linear correlation of [product] and reaction time (For an example, see **Figure S1)**

Table S1 RP-HPLC conditions for aldol reaction of aldehyde [a]

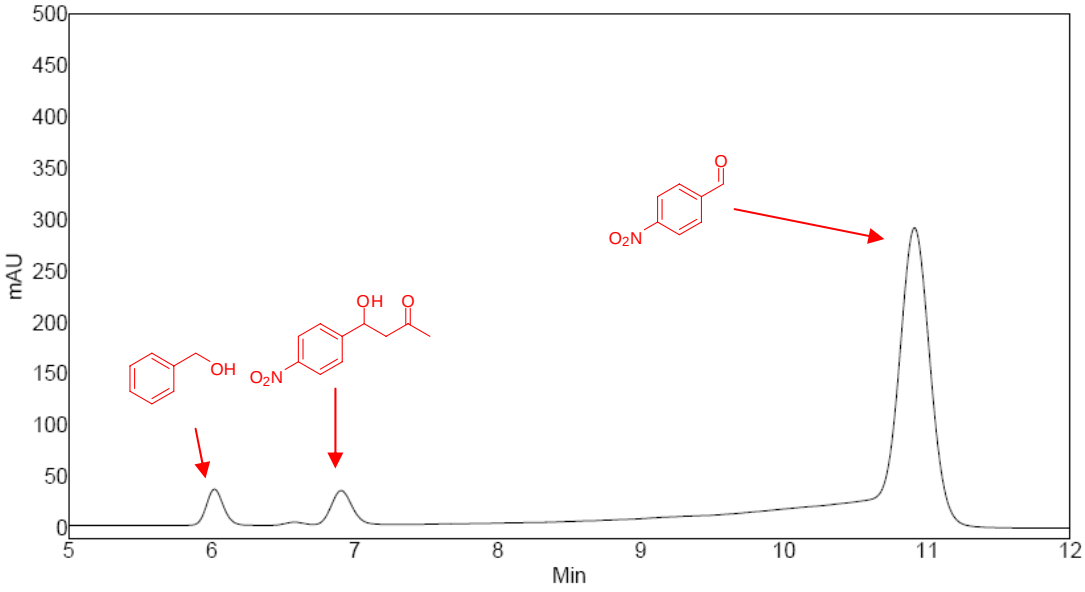


1. R=H, R^1=4-NO_2Ph
2. R=H, R^1=Ph
3. R=H, R^1=4-MePh
4. R=H, R^1=4-OMePh
5. R=H, R^1=1-Naphth
6. R=H, R^1=2-Naphth
7. R=H, R^1=4-PhPh
8. R=H, R^1=Piperon
9. R=-$(CH_2)_2$-, R^1=4-NO_2Ph
10. R=-$(CH_2)_2$-, R^1=4-NO_2Ph
11. R=H, Me, R^1=4-NO_2Ph

Entry	Internal standard	Flow (mL/min)	t_R (aldehyde) (min)	t_R (aldol) (min)	t_R (internal standard) (min)
1	BnOH	0.8	11.36	6.70	6.18
2	phenol	0.8	10.07	6.17	7.07
3	BnOH	0.8	13.31	7.57	6.18
4	phenol	0.8	9.94	5.97	7.07
5	BnOH	1.2	15.62	7.90	4.38
6	BnOH	0.8	19.90	9.60	6.18
7	2-naphthol	1.5	23.23	10.44	8.68
8	phenol	0.8	9.00	5.87	7.07
9	BnOH	0.8	11.08	10.14	6.18
10	BnOH	0.8	11.08	12.48/13.57	6.18
11	BnOH	0.8	11.08	8.72	6.18

[a]. detection by 210 nm, elution solvent H_2O/CH_3CN=50/50, column: Diamonsil 5u C18 250×4.6 mm

Scheme S1. HPLC spectra for kinetic study



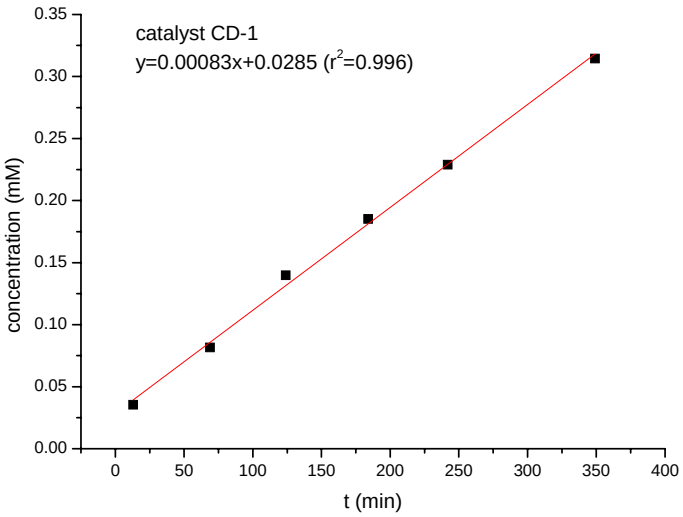


Figure S1. Correlation of time with concentration of product catalyzed by **CD-1**

Enzyme kinetic study of CD-1

The enzyme kinetic study **CD-1** was operated just according to the general experimental procedure of kinetic study expect that different concentration of aldol acceptor. 4-nitrobenzaldehyde was used as 4, 5, 8, 10, 15, 20 mM stock solutions of water/actone (1/1).

The measurement of binding constants

Determination of k_s was conducted in 50 mM acetate buffer (pH=4.80) with 2% glycol, 0.02 mM substrate as guest and 0.5-4 mM catalyst as host. The substrates were used as 1 mM stock solution of glycol. Catalysts were used as 250 mM stock solution of 50 mM acetate buffer. To each 2.45 mL acetate buffer (50 mM, pH=4.80) was added 50 μL stock solution of substrate. The solution obtained contained 0.02 mM substrate and 2% glycol. 5 μL stock solution of catalyst was added to this solution each time and the fluorescence intensity was recorded after 5 min. Job's method was used to determine the the stoichiometry of host-guest complexion. In the spectra titration experiment, the excellent linear correlation of $1/\Delta F$ and 1/[host] can proved as well (Figure S3a). Finally, the method of least squares was used following the equation 4 in scheme S1 to calculate the binding constants between different naphthalene derivatives and cyclodextrin host. (Figure S3b)

$$H + G \rightleftharpoons H \bullet G$$

$$\Delta F = F(\text{Guest system added with host}) - F(\text{Guest system without host}) = a[H \bullet G] \quad (1)$$

$$K_s = \frac{[H \bullet G]}{[H][G]} = \frac{\Delta F / a}{([H]_0 - \Delta F / a)([G]_0 - \Delta F/a)} \quad (2)$$

$$\frac{[G][H]_i}{\Delta F_i} = \frac{1}{K_s \bullet \alpha} + \frac{[G]}{\alpha} \quad (3)$$

$$\Delta F = \frac{a([H]_0 + [G]_0 + 1/K_s) \pm \sqrt{a^2([H]_0 + [G]_0 + 1/K_s)^2 - 4a^2[H]_0[G]_0}}{2} \quad (4)$$

Scheme S2 The different expression of Benesi-Hildebrand relation

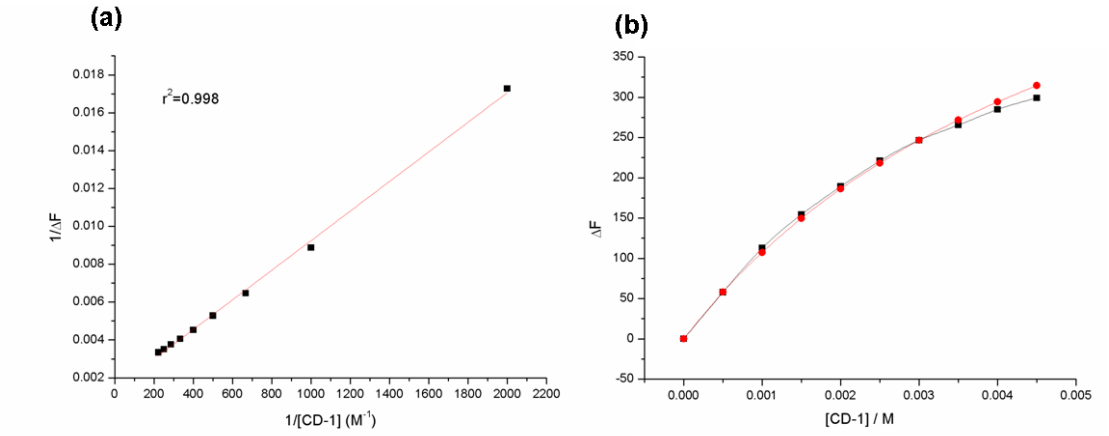


Figure S2. The calculation of binding constants between 2-naphthaldehyde and CD-1 using (a) the method of linear regression; (b) the method of least squares.

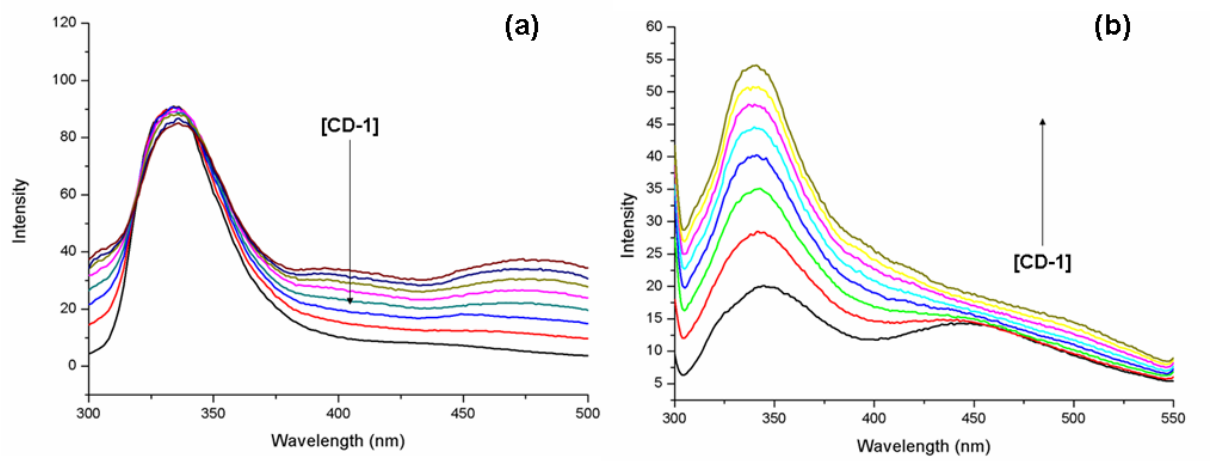


Figure S3. The series of fluorescence spectra of (a) 0.02 mM of 1-naphthaldehyde aqueous solution at various concentrations of CD-1 (0 to 3.5 mM). (b) 0.02 mM of G6 aqueous solution at various concentration s of CD-1 (0 to 3.5 mM)

General procedure for the deuteration of the aldol donor

All deuteration reactions were conducted by using 0.02M catalyst and 0.05M sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standard in acetate buffer (pH=4.80) prepared from D_2O, CD_3COOD and CD_3COONa. The control reaction was measured in acetate buffer without catalyst. The concentration of acetone was varied as demanded.

The initial rate of hydrogen exchange was monitered during the first 24h at time intervals of 4h. Each sample was analyzed by 16 scans. The enzyme kinetic study was conducted following the measuring procedure of aldol reaction.

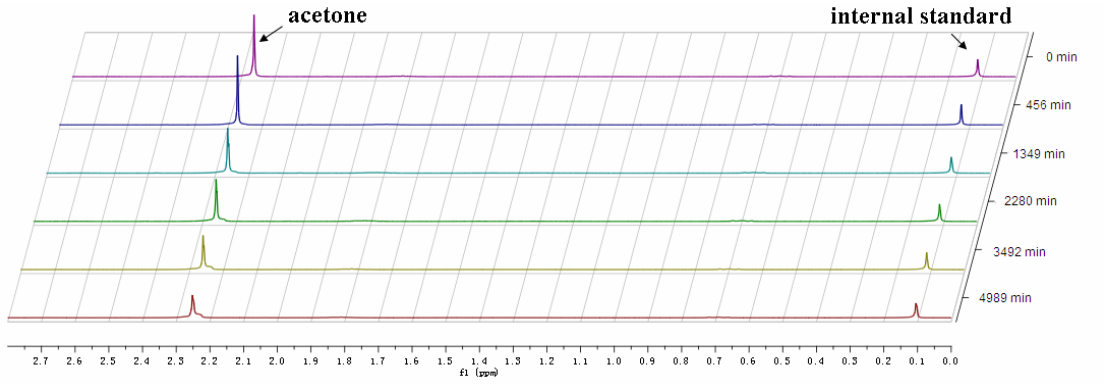
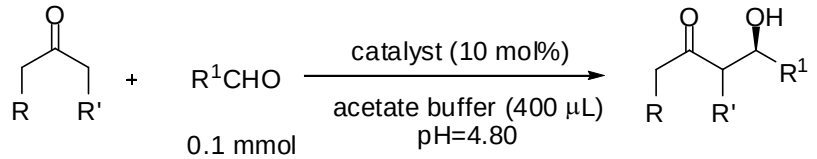


Figure S4 Time-resolved ^1H NMR monitoring of **CD-1**-catalyzed deuteration of actone. The signal of a-position hydrogen (δ=2.26) decreased with time

General experimental procedure for aldol reaction under high concentration

To a stirred solution of **CD-1** (12.3 mg, 0.01 mmol) in 1 M acetate buffer (pH=4.80, 400 μL) was added acetone (100 μL) and 4-nitrobenzaldehyde (15.2 mg, 0.1 mmol). The resulting heterogeneous reaction was stirred at ambient temperature and monitored by TLC. After 24 h, the solution was extracted with ethyl acetate. The ethyl acetate was rotary evaporated and the crude product was purified by flash chromatography on silica gel to afford the desired product. All the aldol products are known compounds[4-8].

Table S2 Aldol reaction under high concentration[a]



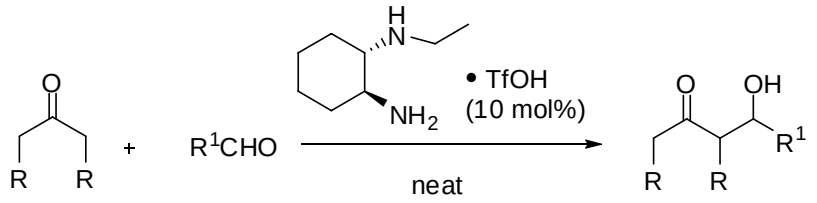
Entry	R	R'	Cat	R^1	t (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	H	H	**CD-1**	3-NO_2Ph	24	91	---	88
2	H	H	**CD-1**	2-NO_2Ph	24	82	---	80
3	H	H	**CD-1**	4-CNPh	36	90	---	85
4	H	H	**CD-1**	4-CF_3Ph	36	56	---	89
5	H	H	**CD-1**	4-ClPh	48	56	---	91
6	H	H	**CD-1**	4-MeOPh	72	36	---	91
7	H	H	**CD-1**	2- Naphth	72	61	---	93
8	H	H	**CD-1**	1-Naphth	72	N. R.	---	---
9	H	OH	**CD-1**	4-NO_2Ph	24	N. R.	---	---
10	OH	OH	**CD-1**	4-NO_2Ph	24	N. R.	---	---
11	H	$(OMe)_2$	**CD-1**	4-NO_2Ph	24	N.R.	---	---
12	-$(CH_2)_2$-		**CD-2**	3-NO_2Ph	12	56	32/68	19/80
13	-$(CH_2)_2$-		**CD-1**	3-NO_2Ph	12	77	38/62	82/57
14	-$(CH_2)_2$-		**CD-1**	2-NO_2Ph	12	68	16/84	16/94
15	-$(CH_2)_2$-		**CD-1**	4-CF_3Ph	12	78	42/58	78/81
16	-$(CH_2)_2$-		**CD-2**	4-CF_3Ph	12	72	63/37	71/19
17	-$(CH_2)_2$-		**CD-1**	Ph	12	79	35/65	40/70
18	-$(CH_2)_2$-		**CD-1**	4-PhPh	24	50	30/70	15/82
19	-$(CH_2)_2$-		**CD-2**	4-PhPh	36	34	74/26	82/5
20	-$(CH_2)_3$-		**CD-1**	4-NO_2Ph	12	44	14/86	23/96
21	-$(CH_2)_3$-		**CD-2**	4-NO_2Ph	12	trace	---	---
22	-$(CH_2)_4$-		**CD-1**	4-NO_2Ph	12	N. R.	---	---

[a.] Conditions: 25°C, entry 1-14, donor 100 μL; entry 15-29, donor 20 μL. [b.]Isolated yield. [c.] *syn/anti* determined by NMR. [d.] ee determined by HPLC. N. R. no reaction observed.

Control Reaction catalyzed by organocatalyst

Control reactions catalyzed by organocatalyst **ent-8** were carried out under neat condition. In the control reaction, the phenomenon of substrate recognition was not observed **(Table S3)**.

Table S3 Control reaction catalyzed by organocatalyst



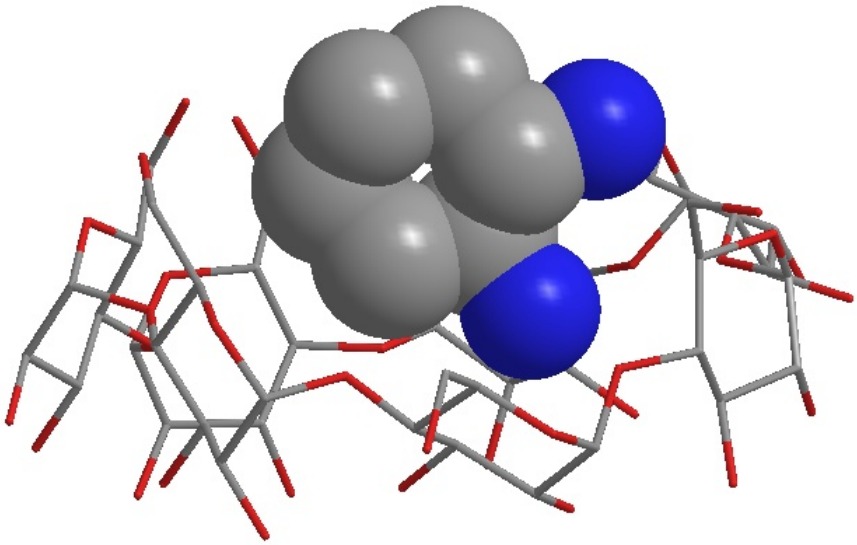
200 μL 0.2 mmol

Entry	R	R^1	t (h)	yield (%)[a]	ee (%)[b]	dr [c]
1	$-(CH_2)_2-$	4-NO_2Ph	24	34	26/87	26/74
2	$-(CH_2)_3-$	4-NO_2Ph	24	84	72/70	48/52
3	H	2- Naphth	24	74	36	---
4	H	1-Naphth	24	84	36	---

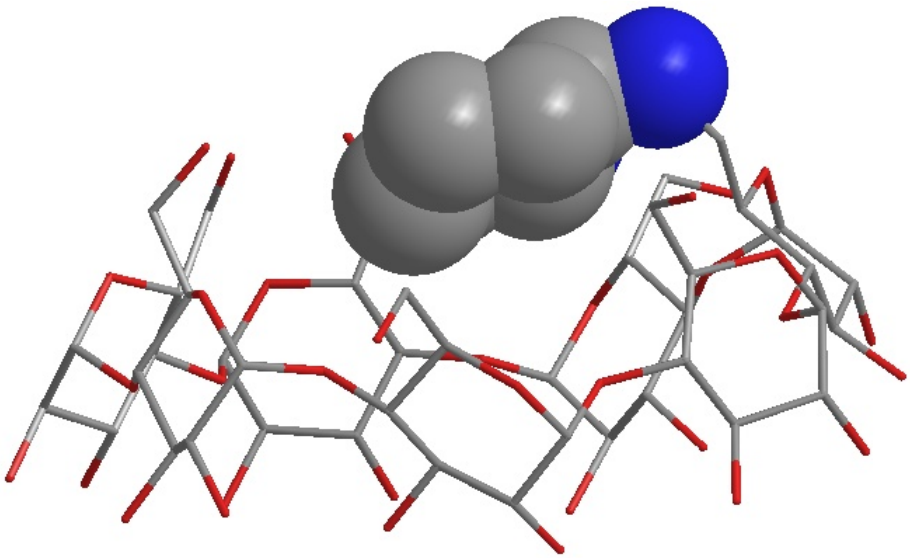
a. Isolated yield. [b.] *syn/anti* determined by NMR. [c.] ee determined by HPLC

Molecular Modeling

The molecular modeling calculation was performed just following the literature.[9] The CVFF force field in insightII 2005/discover package (Accelrys Inc.) was used. A water sphere of diamether was set to 5 Å and relatively permittivity of 78 was used. The cut-off distances for van der Waals and electrostatic interactions were set to 100 Å. The diamine groups were protonated and the pH value was set to 5.0.



(a)



(b)

Figure S5 Energy minimum conformations of (a) **CD-1** and (b) **CD-2** in acidic buffer solution.

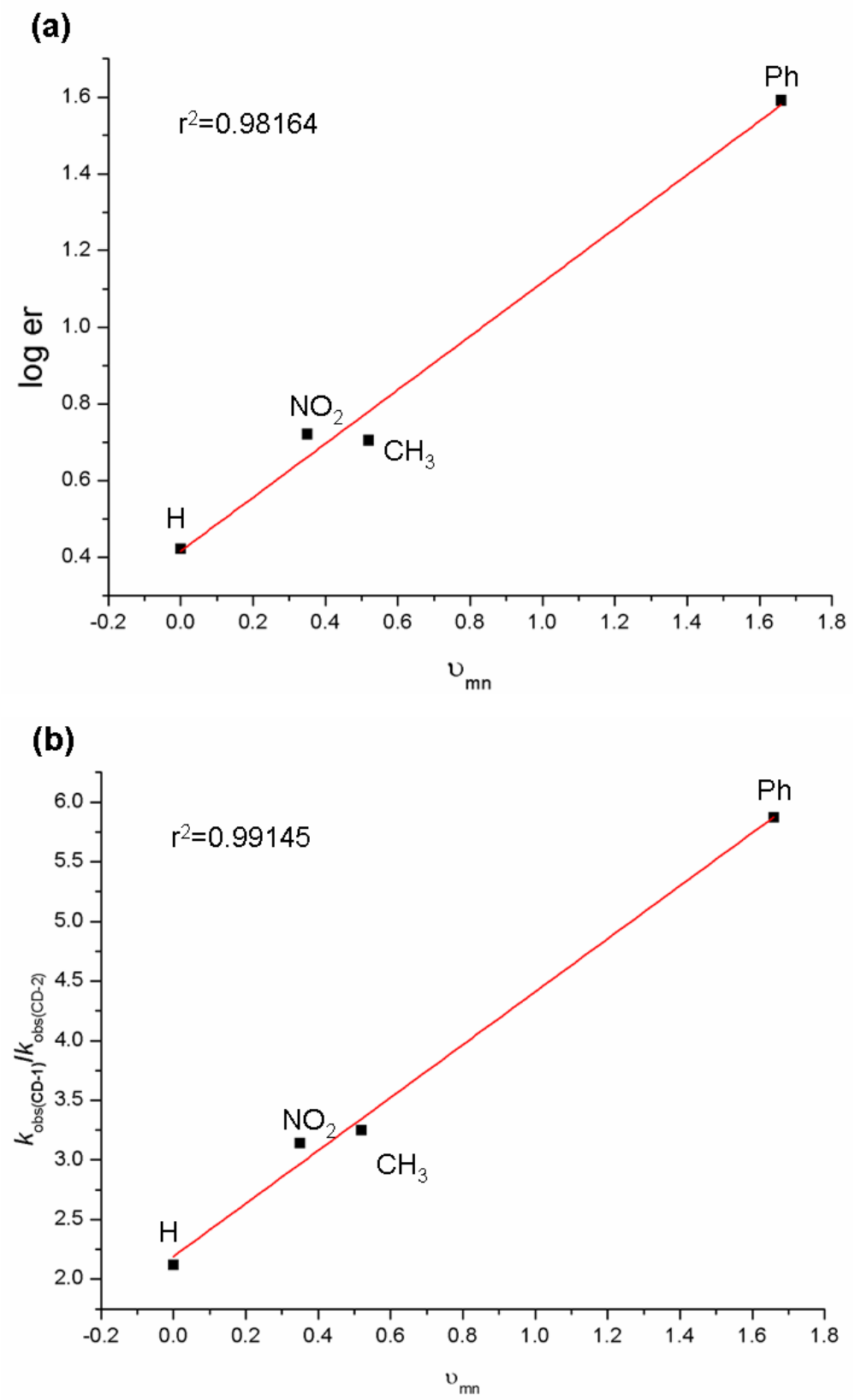


Figure S6 (a) The correlation between size effect[10] of substrate and stereoselectivity in **CD-2** catalyzed system. (b) The correlation between size effect[10] of substrate and catalytic rate differences between **CD-1** and **CD-2**

Reference

1. Petter, R. C.; Salek, J. S., Sikorski C. T. Kumaravel, G. Lin F. T. *J. Am. Chem. Soc.* **1990**, *112,* 3860-3868

2. Mithcell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431

3. Shi, M., Zhang, W. *Tetrahedron: Asymmetry*. **2003**, *14,* 3407.

4. Samanta, S.; Liu, J.; Dodda, R.; Zhao, C. G. *Org. Lett.* **2005**, *7,* 5321.

5. Gu, L. Q.; Yu, M. L.; Wu, X. Y.; Zhang, Y. Z.; Zhao, G. *Adv. Synth. Catal.* **2006**, *348*, 2223.

6. Chen, J. R,; Lu, H. H.; Li, X. Y.; Chen, L.; Wan, J.; Xiao, W. J. *Org. Lett.* **2005***, 7*, 4543.

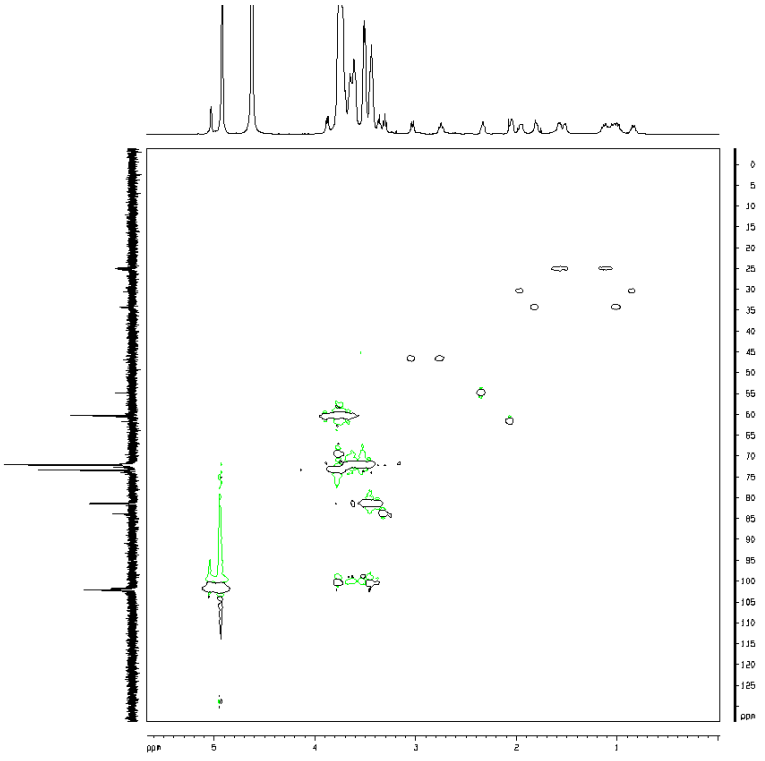
7. Wu, Y. Y.; Zhang, Y. Z.; Yu, M. L.; Zhao, G. S.; Wang, W. *Org. Lett.* **2006**, *8*, 4417

8. Mase, N.; Tanaka, F.; Barbas, C. F. III. *Angew. Chem. Int. Ed.* **2004**, *43*, 2420.

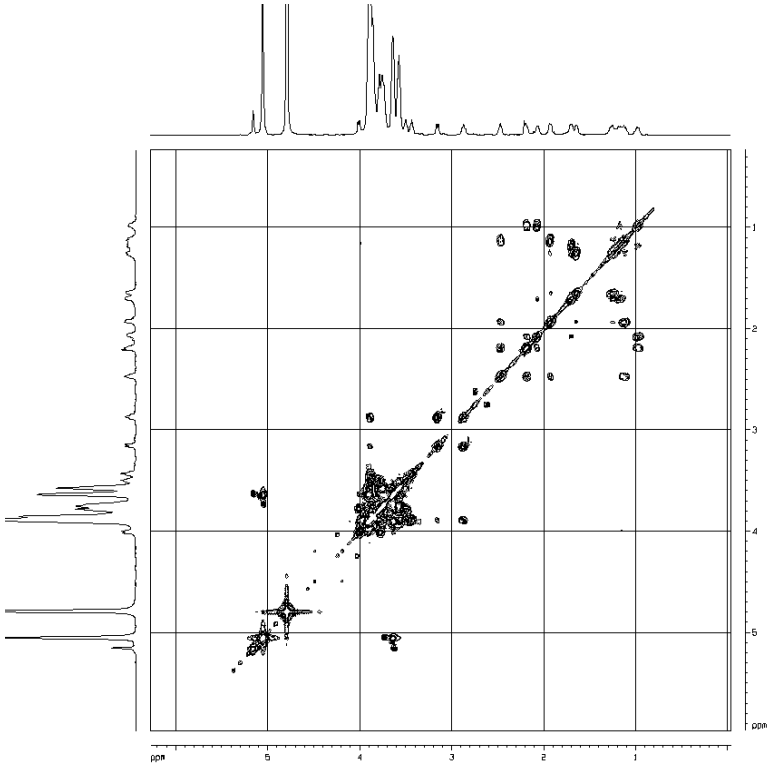
9. Park, K. K.; Kim, Y. S.; Lee. S. Y.; Song. H. E.; Park. J. W. *J. Chem. Soc., Perkin Trans. 2,* **2001**, 2114.

10. The size effect of substrate is measured by upsilon steric parameter according to Charton, M.; Motoc, I., Ed.; *Steric Effects in Drug Design*; Springer; Berlin / Heidelberg, **1983**. p68-75

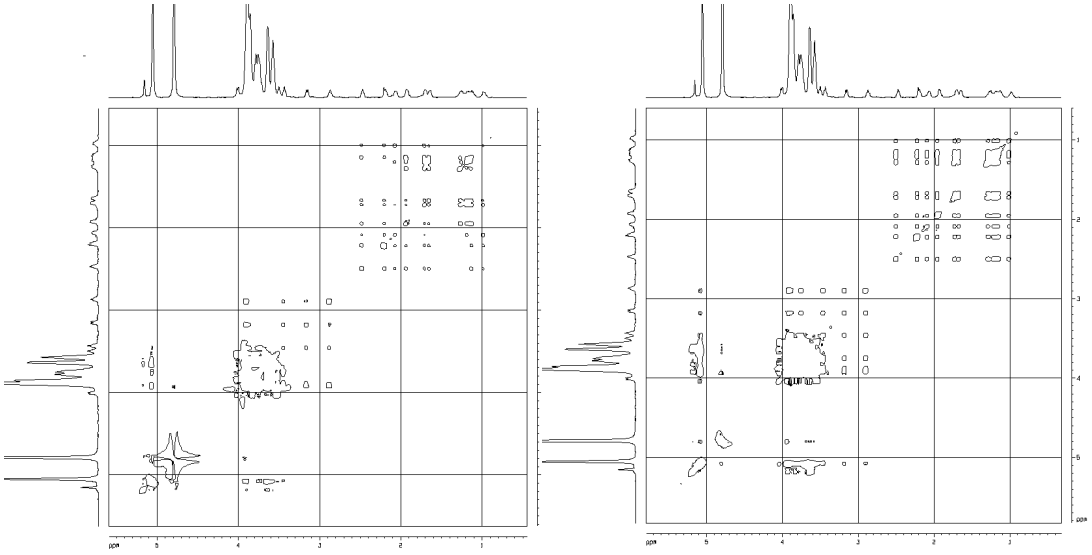
2D NMR spectrum of CD-1 in pure water



(a)



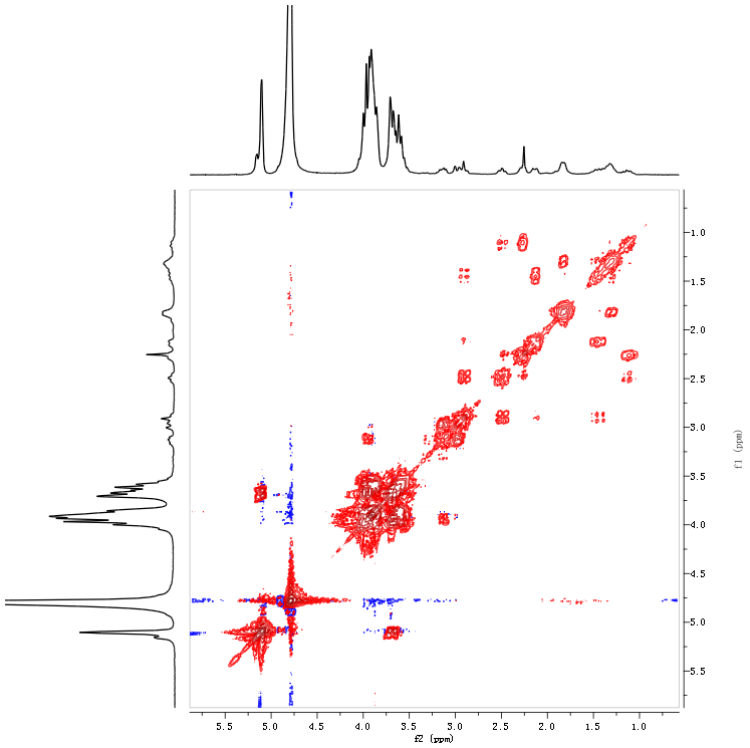
(b)



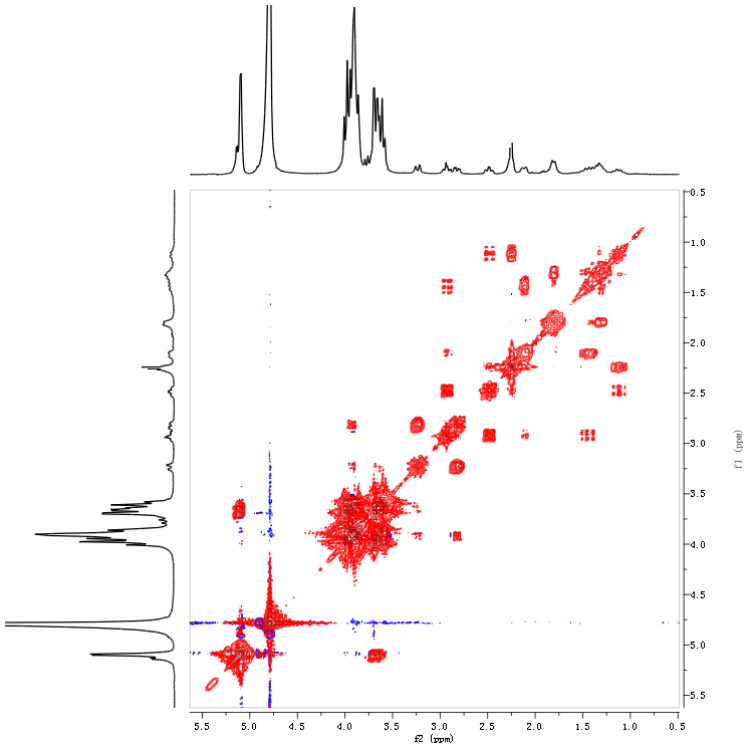
(c) **(d)**

Figure S7. (a) HMQC of **CD-1**; (b) COSY of **CD-1**; (c) ROCSY of **CD-1**; (c) TOCSY of **CD-1**, mixing time=70 ms; (d) TOCSY of **CD-1**, mixing time=170 ms

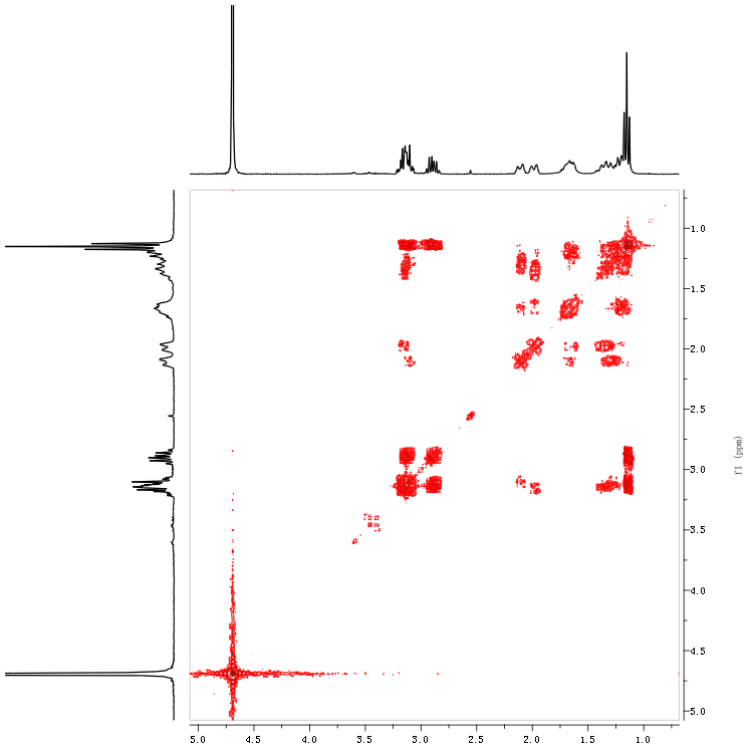
H-H COSY spectra of CD-1, CD-2, 8 in acetate buffer (pH=4.80)



(a)



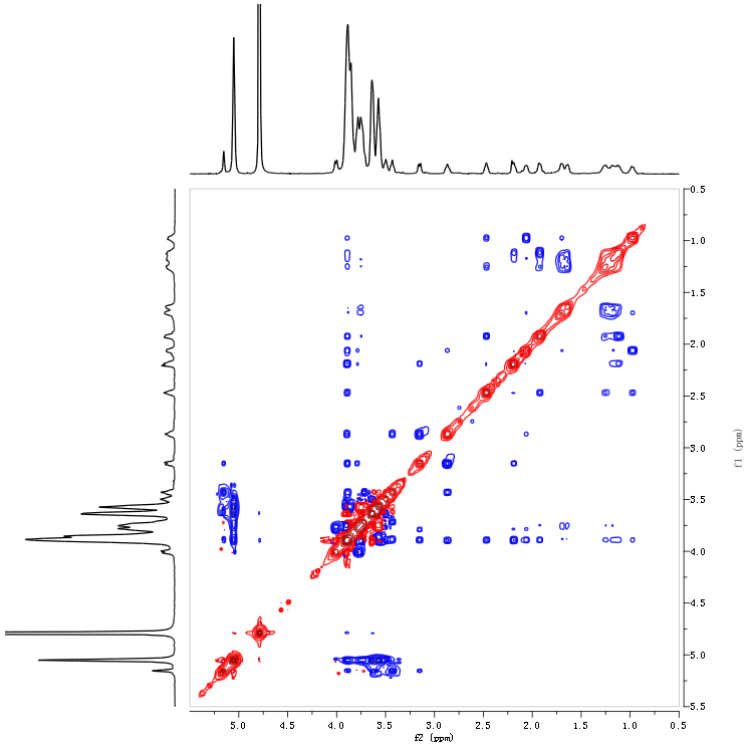
(b)



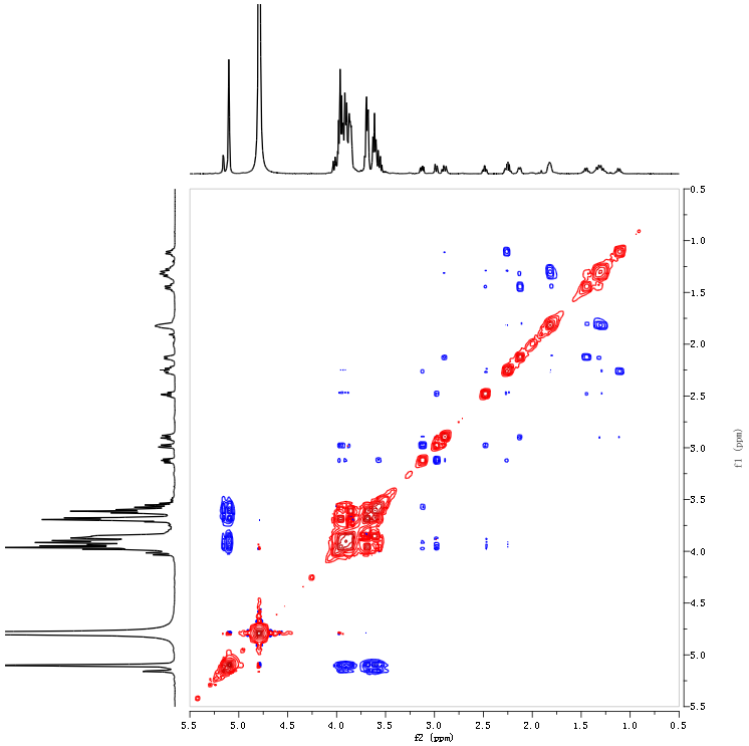
(c)

Figure S8 H-H COSY spectra of (a) CD-1 (0.02 M) in acetate buffer (pH=4.80); (b) CD-2 (0.02 M) in acetate buffer (pH=4.80); (c) 8 (0.02 M) in acetate buffer (pH=4.80)

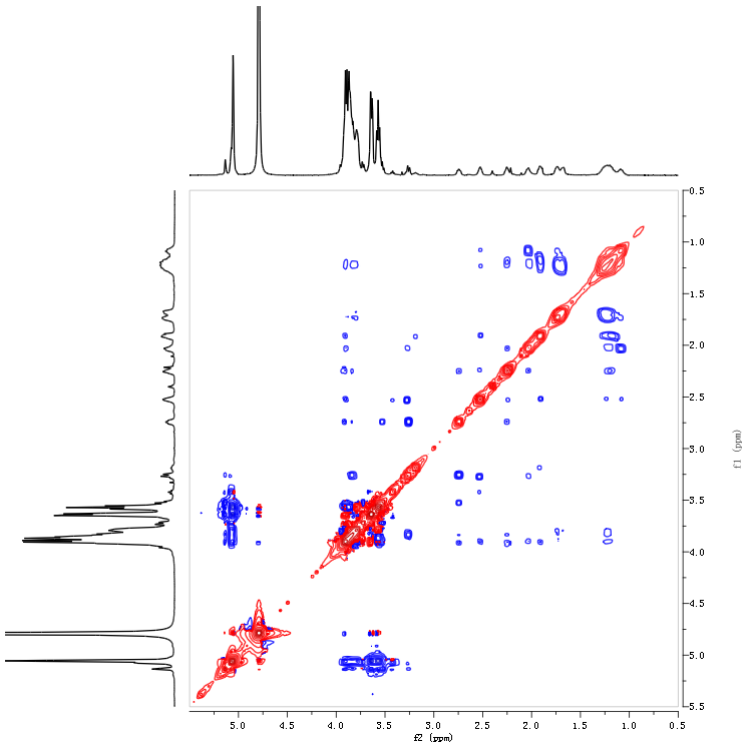
Full ROESY spectrum of CD-1 and CD-2 under different conditions



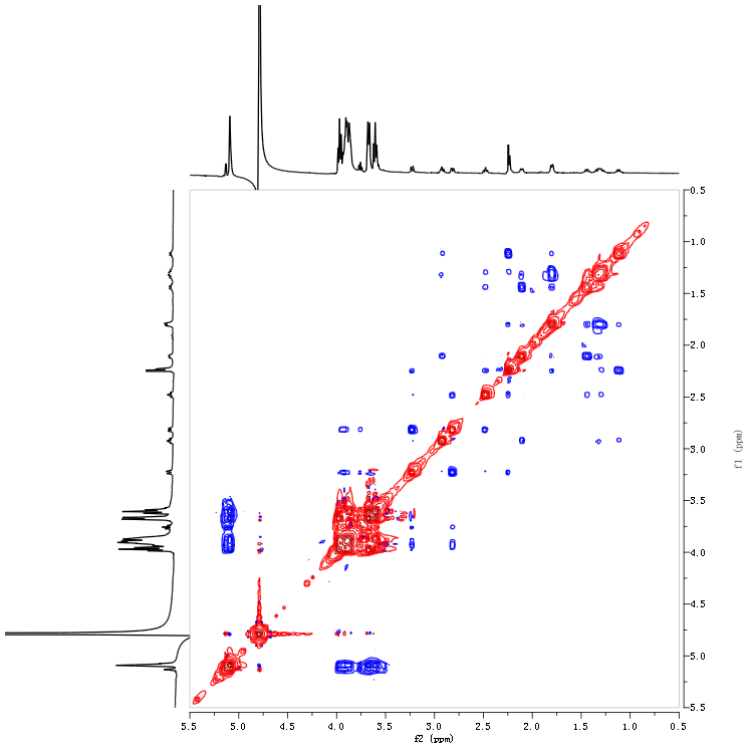
(a)



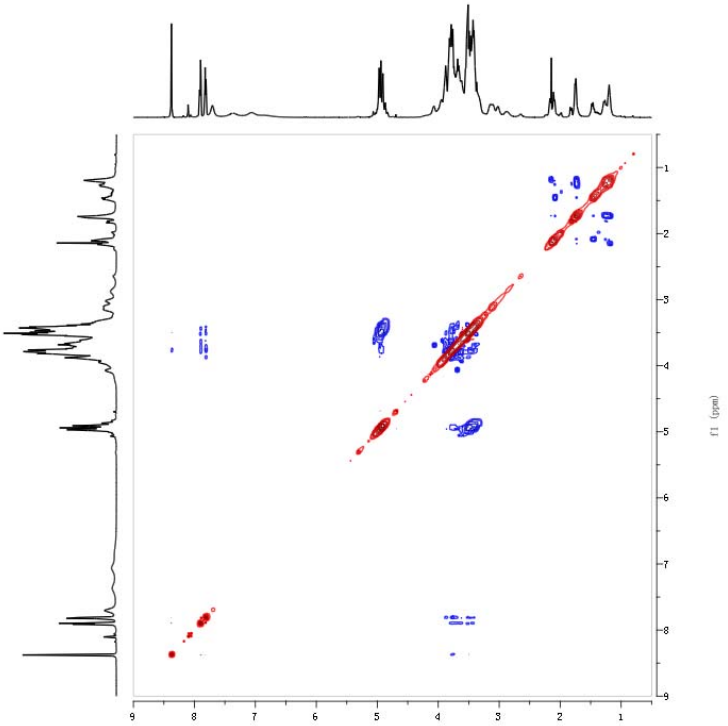
(b)


5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
f1 (ppm)

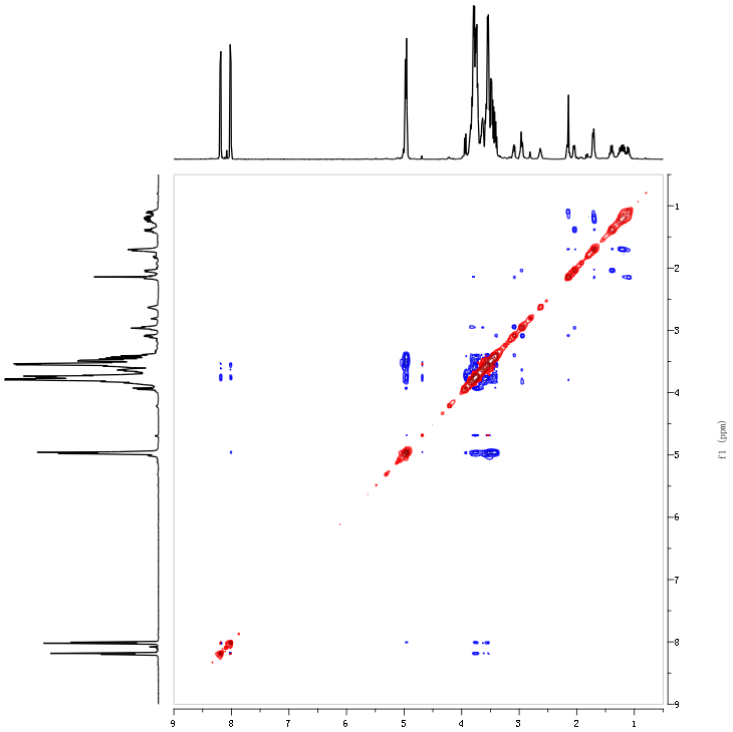
(c)


5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
f1 (ppm)

(d)



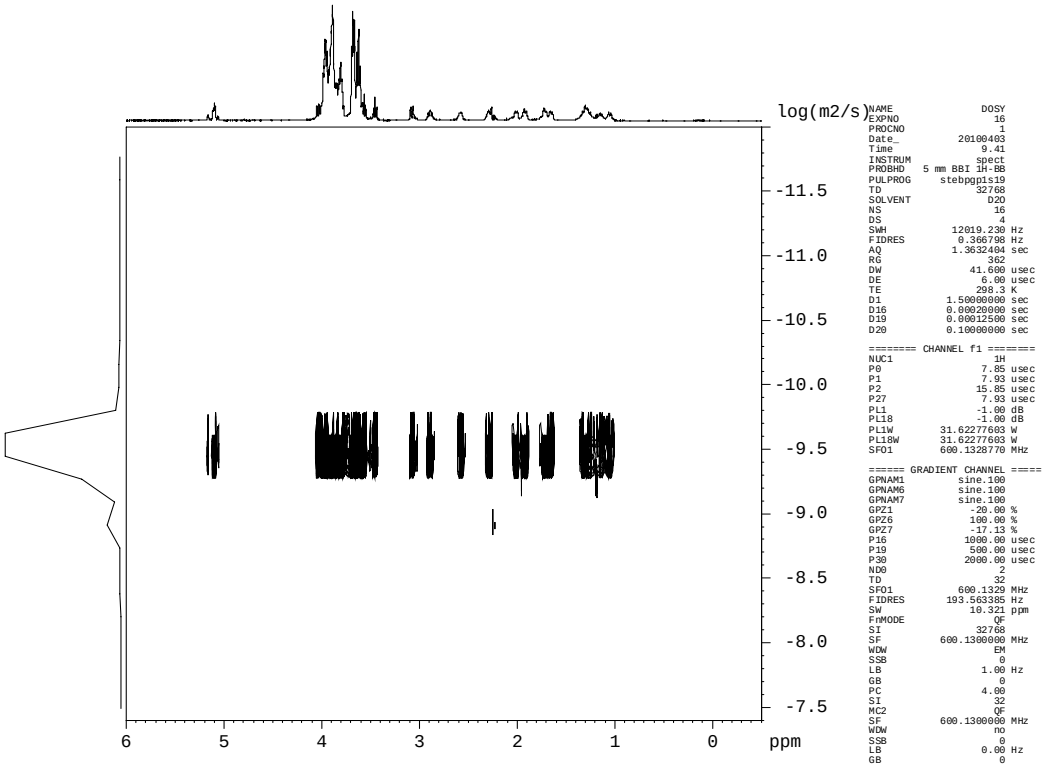
(e)



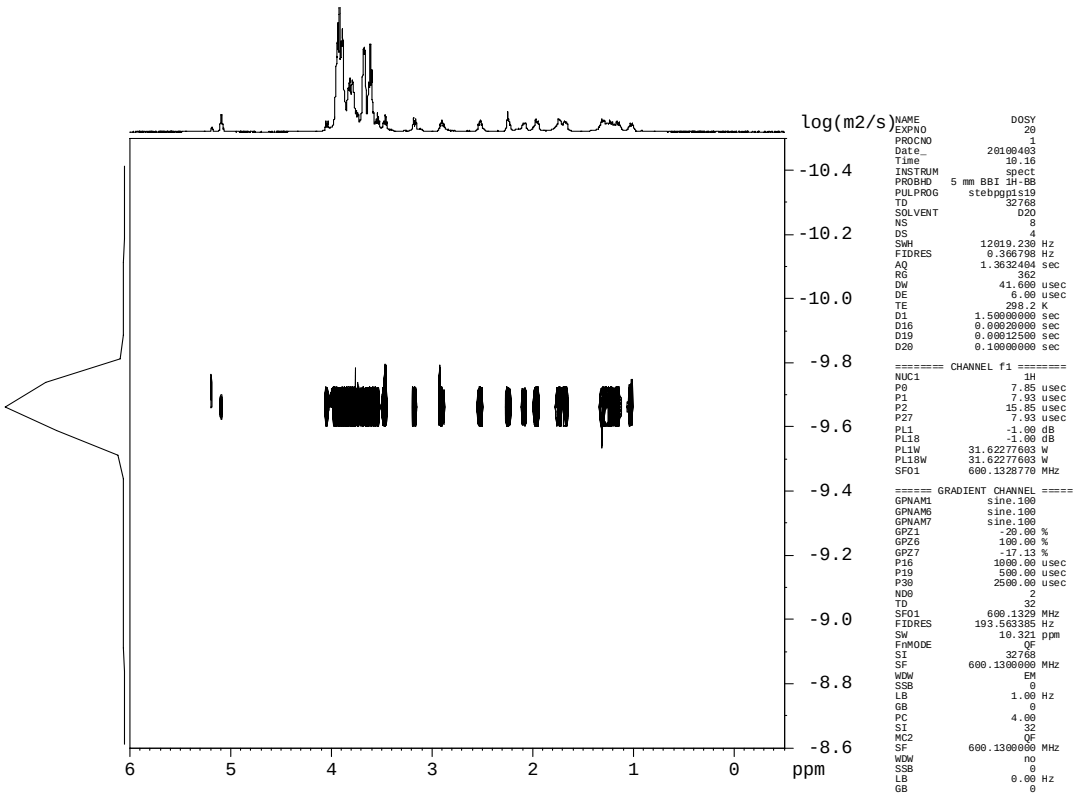
(f)

Figure S9 The full ROESY spectrum of (a) **CD-1** (0.02 M) in D_2O; (b) **CD-1** (0.02 M) in acetate buffer (pH = 4.80); (c) **CD-2** (0.02 M) in D_2O; (d) **CD-2** (0.02 M) in acetate

buffer (pH = 4.80); (e) **CD-1** (0.02 M) and 2-naphthoic acid (0.02M) in acetate buffer (pH = 4.80, containing 2% d6-acetone); (f) **CD-1** (0.02 M) and *p*-nitrobenzoic acid (0.02 M) in acetate buffer (pH = 4.80, containing 2% d6-acetone).



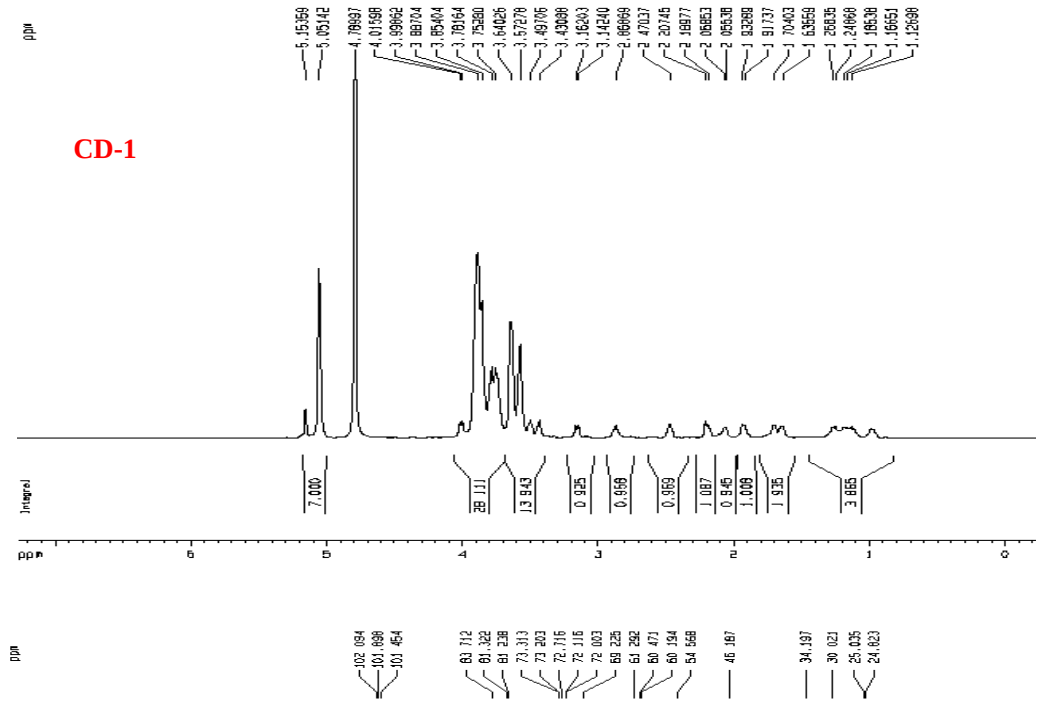
(**a**)

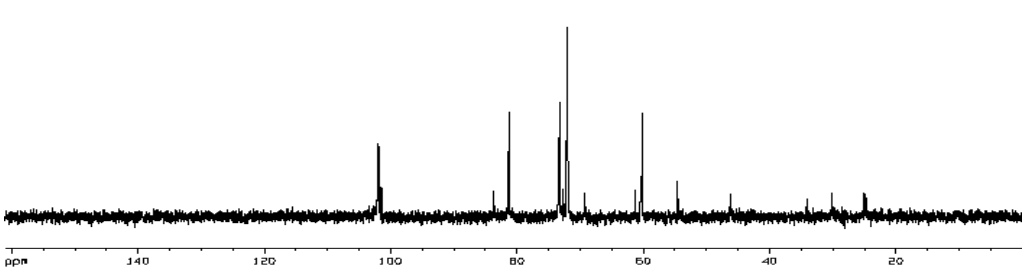


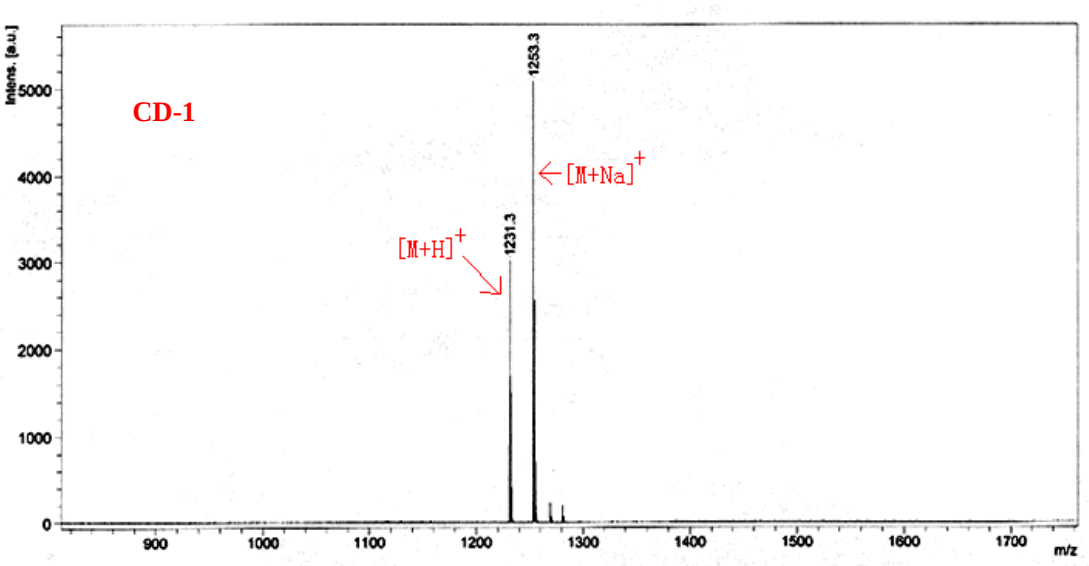
(b)

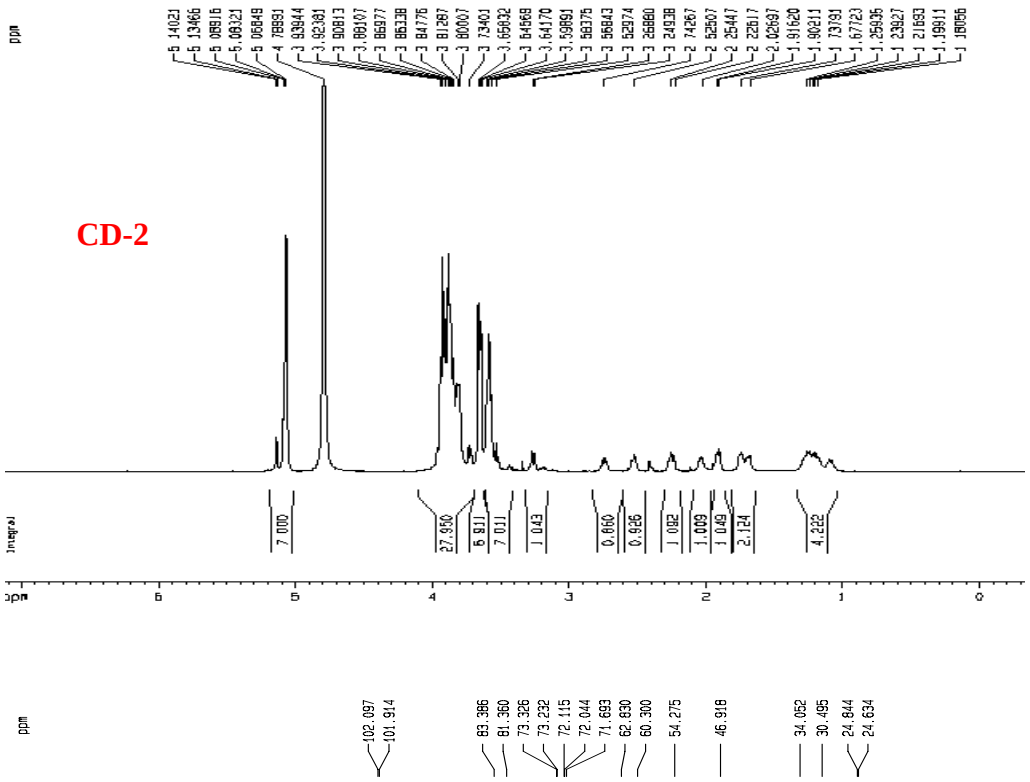
Figure S10 The DOSY spectrum of **CD-1** (D_2O, T = 298 K, 600 Hz) under 2 mM (**a**) and 20 mM (**b**), showing the same diffusion coefficient.

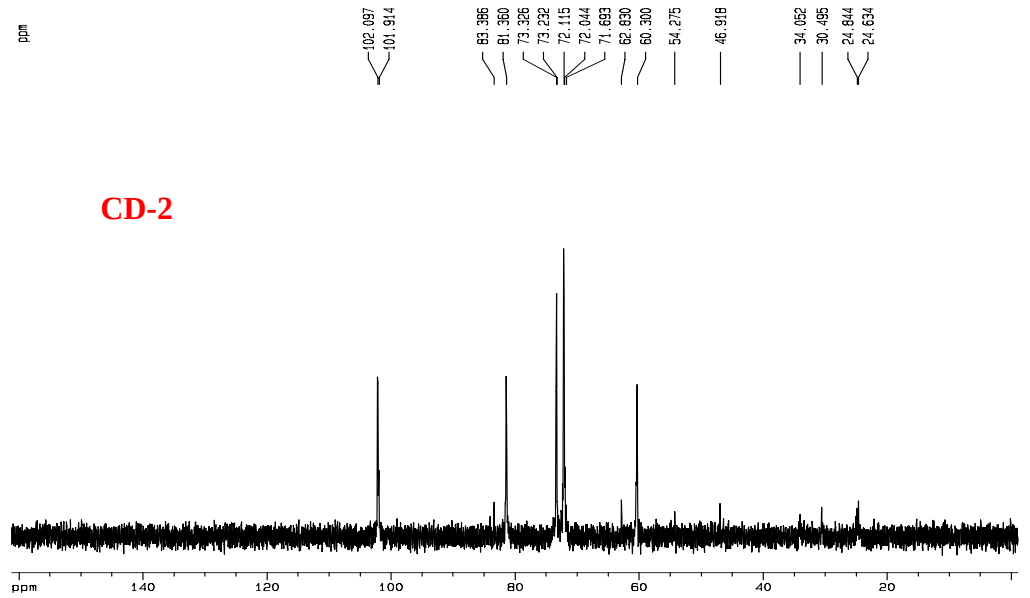
NMR spectrum and MALDI-TOF for all the new catalysts



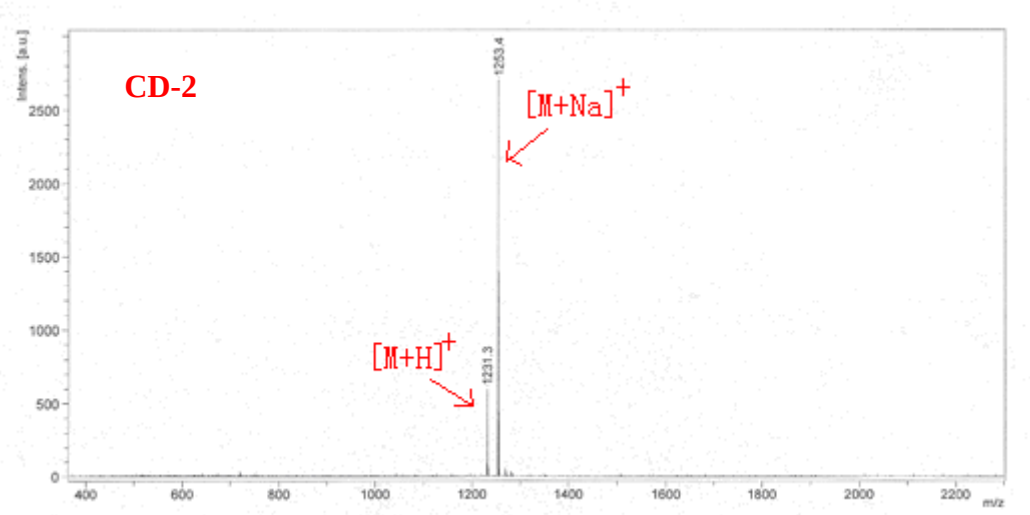




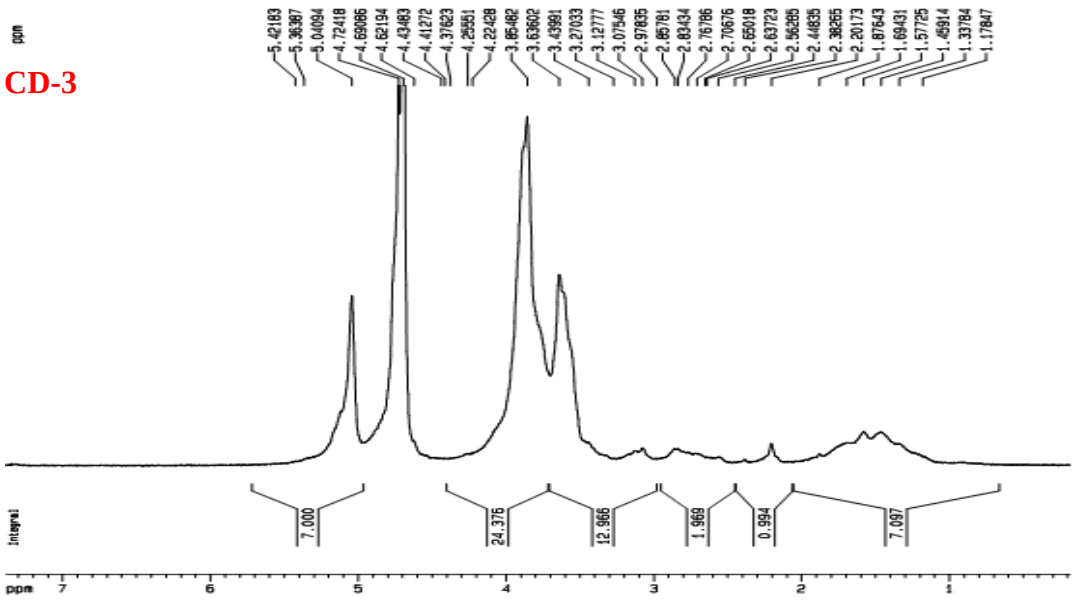

CD-2
ppm
Integral
7.000
27.950
6.811
7.011
1.043
0.860
0.986
1.082
1.000
1.049
2.124
4.222


CD-2
ppm
102.097
101.914
83.386
81.360
73.326
73.232
72.115
72.044
71.693
62.830
60.300
54.275
46.918
34.052
30.495
24.844
24.634

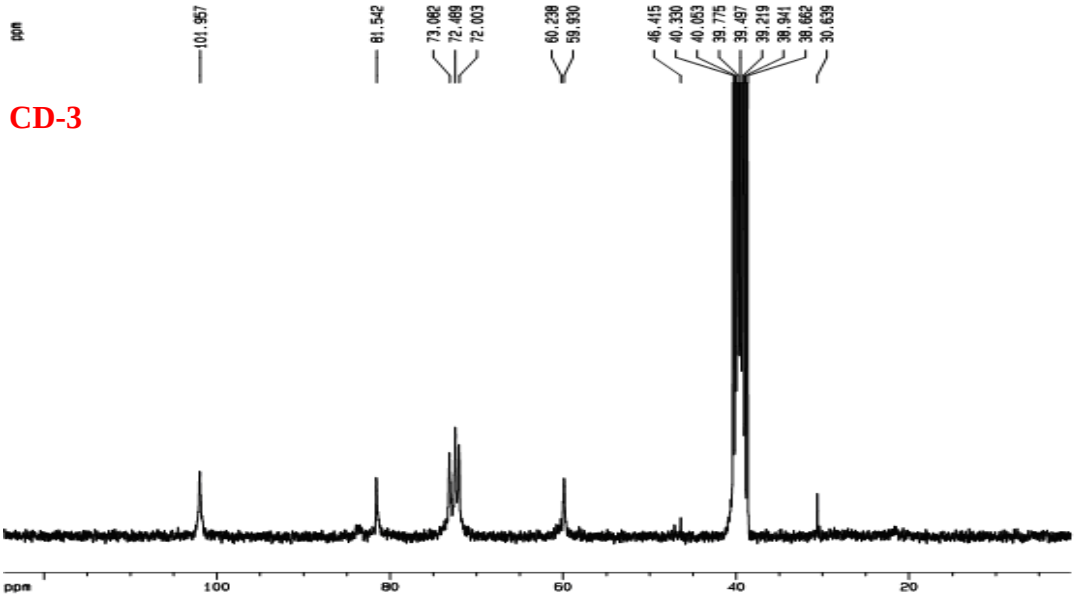
CD-2
ppm
140
120
100
80
60
40
20


CD-2
Intens. [a.u.]
1253.4
[M+Na]+
[M+H]+
1231.3
m/z

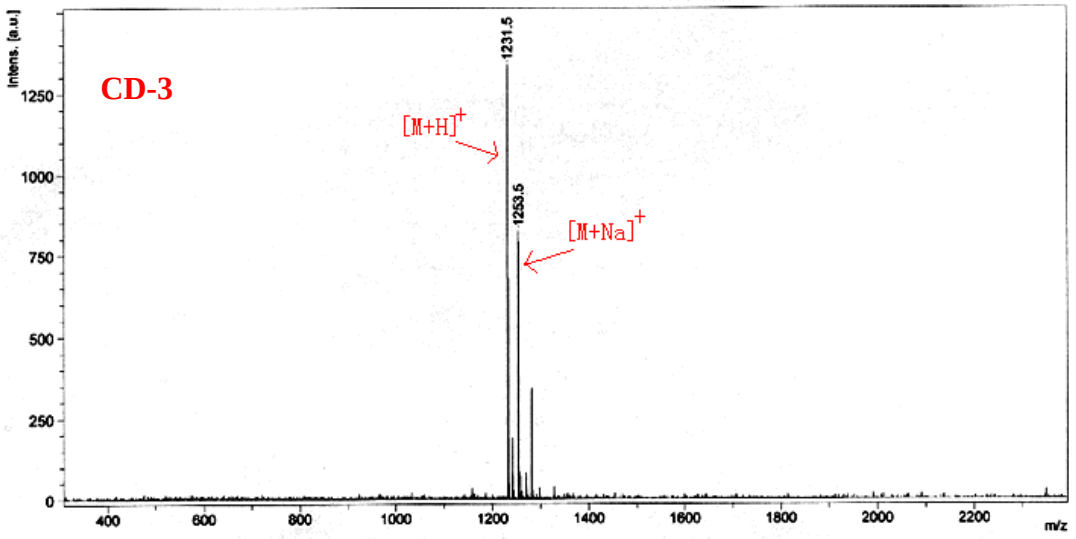
CD-3

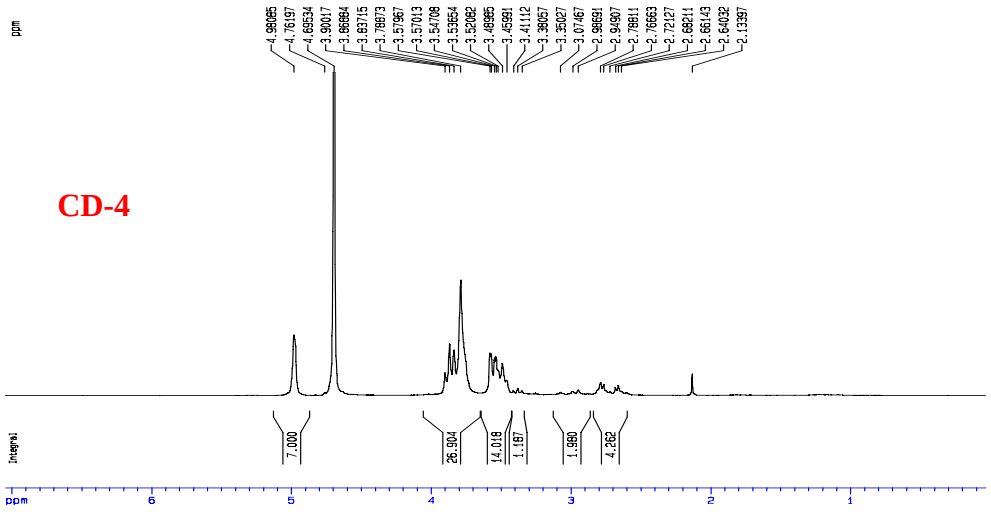

ppm
5.42183
5.36387
5.04094
4.72418
4.69086
4.62194
4.43483
4.41272
4.37623
4.29551
4.22428
3.85482
3.63602
3.43991
3.27033
3.12777
3.07546
2.97835
2.85781
2.83434
2.76786
2.70676
2.65018
2.63723
2.56285
2.44835
2.38265
2.20173
1.87643
1.69431
1.57725
1.49914
1.33784
1.17847
Integral
7.000
24.375
12.966
1.969
0.994
7.097
ppm
7
6
5
4
3
2
1

CD-3


ppm
101.957
81.542
73.082
72.489
72.003
60.238
59.930
46.415
40.330
40.053
39.775
39.497
39.219
38.941
38.662
30.639
ppm
100
80
60
40
20

CD-3


Intens. [a.u.]
1250
1000
750
500
250
0
1231.5
[M+H]+
1253.5
[M+Na]+
400
600
800
1000
1200
1400
1600
1800
2000
2200
m/z


CD-4
ppm
Integral
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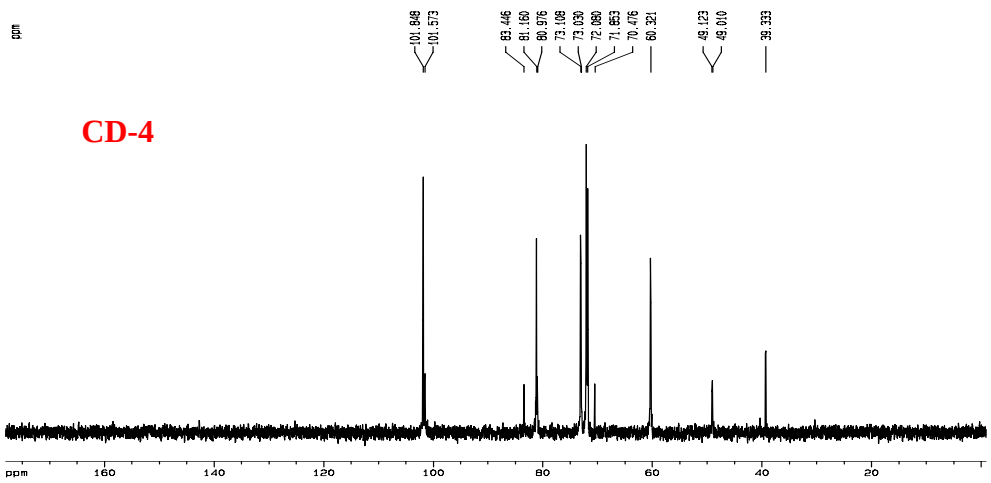
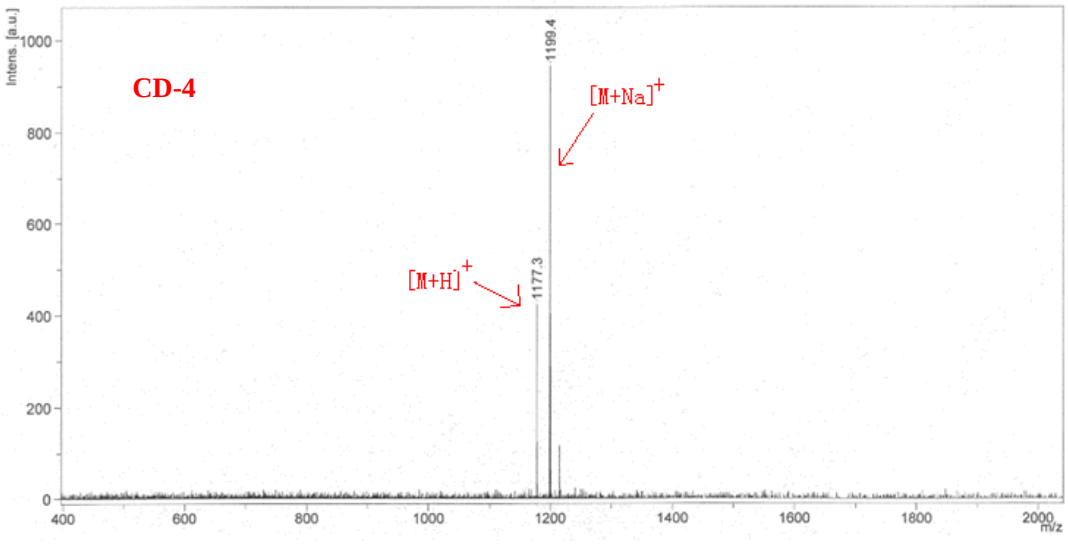
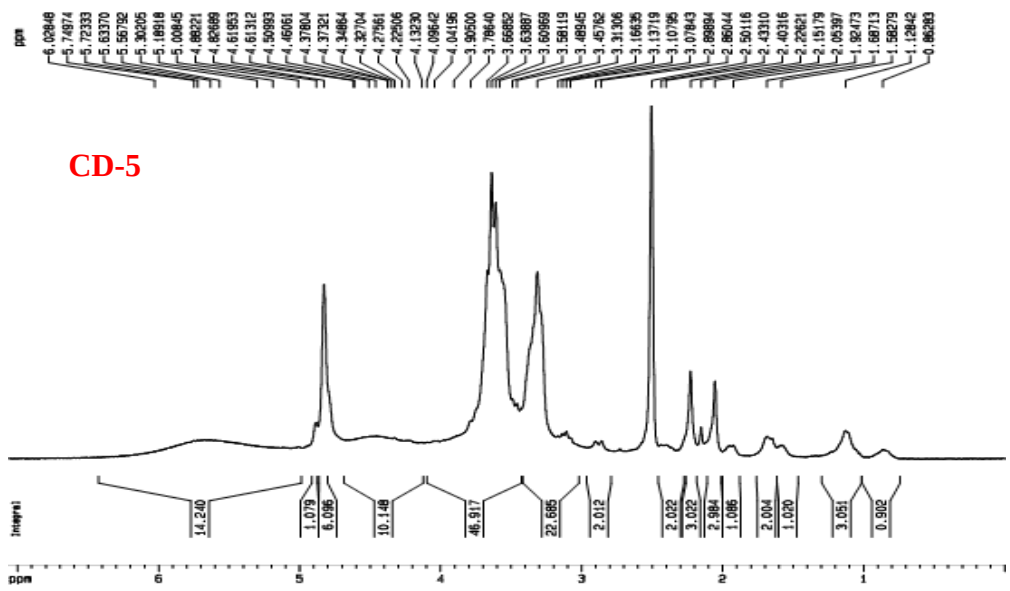
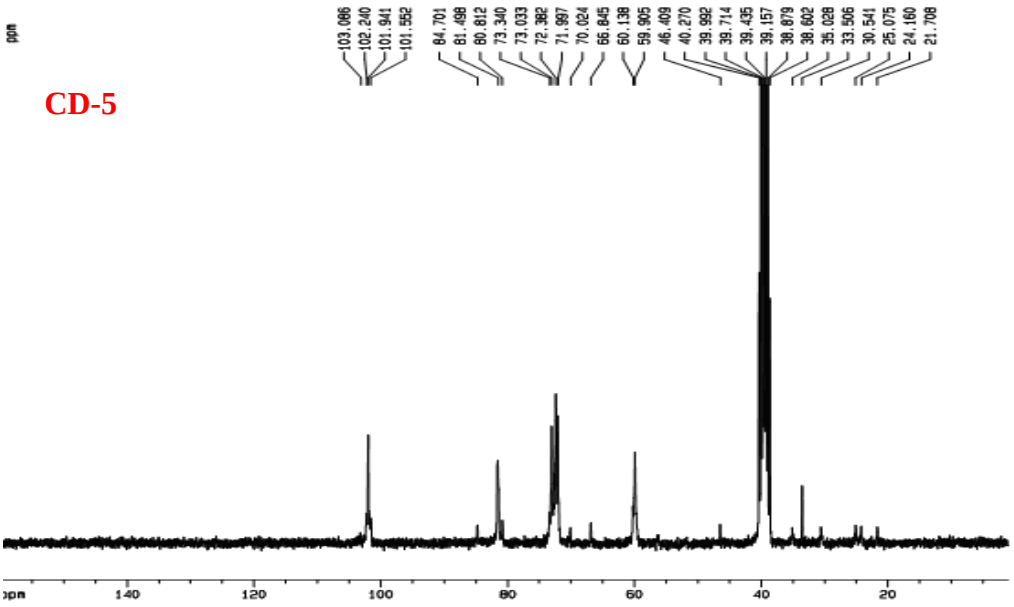
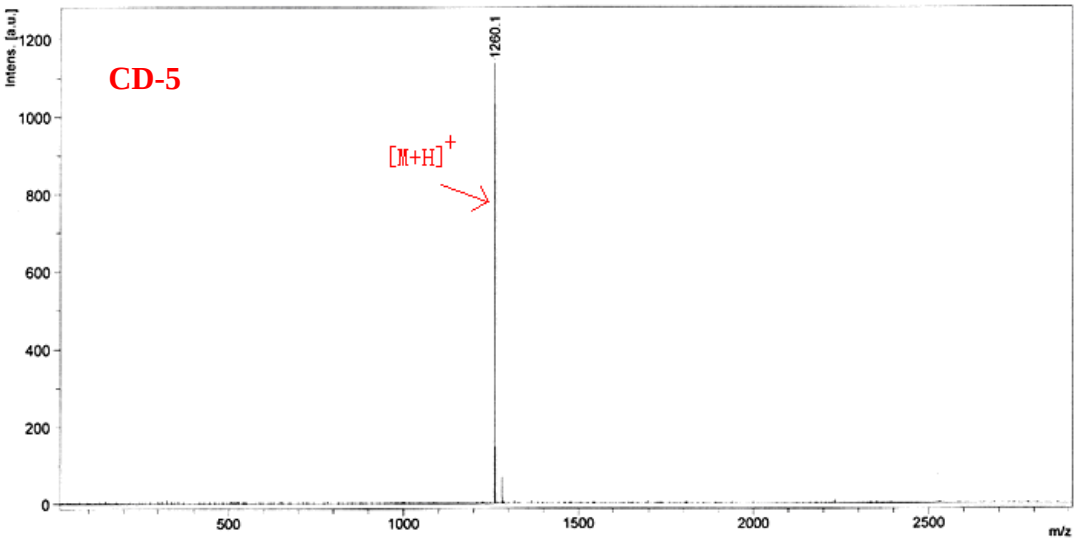
26.904
14.018
1.167
1.950
4.262

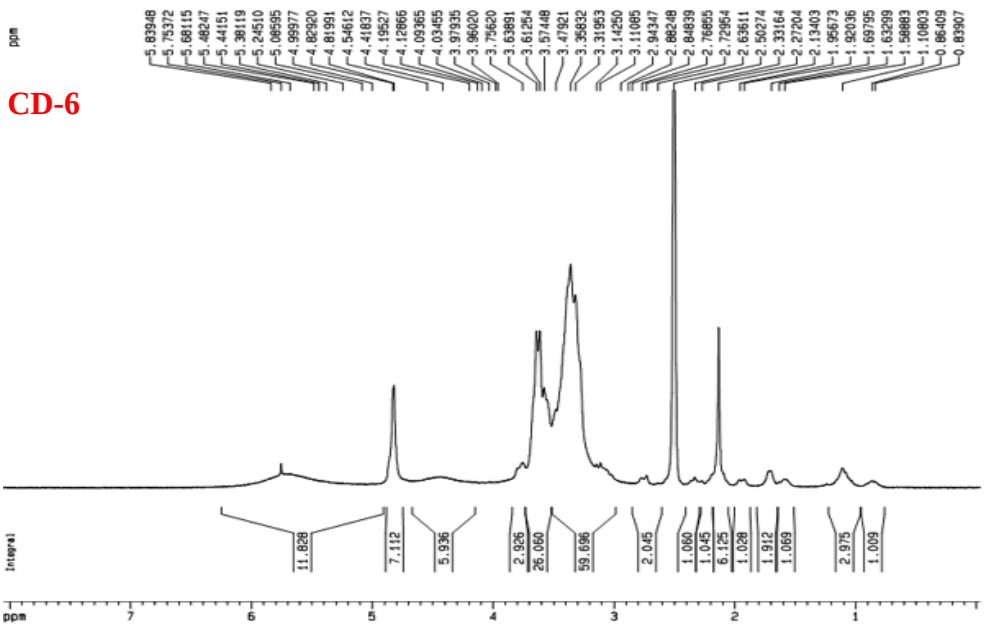

CD-4
ppm

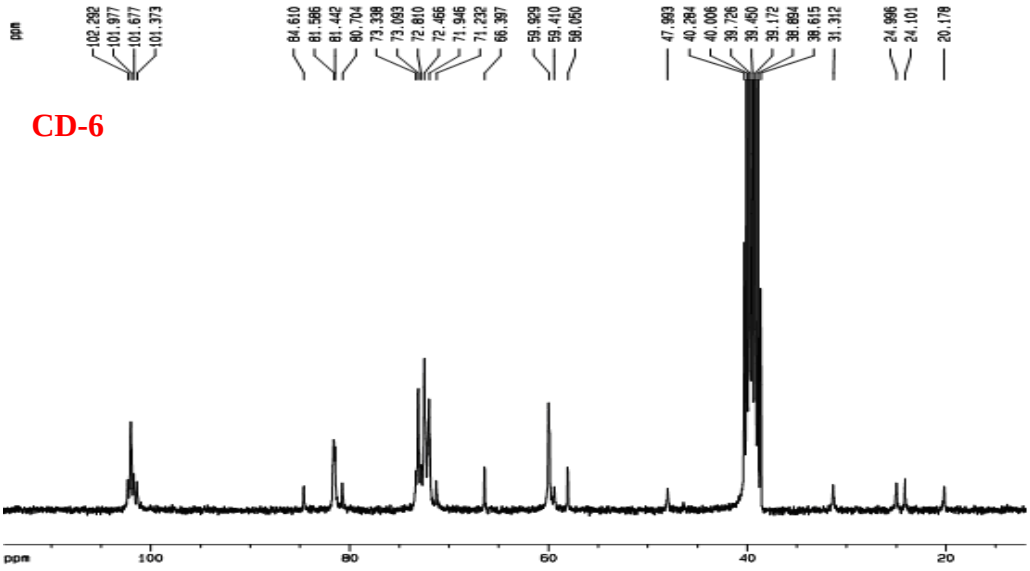

CD-4
Intens. [a.u.]
1199.4
[M+Na]+
1177.3
[M+H]+
m/z

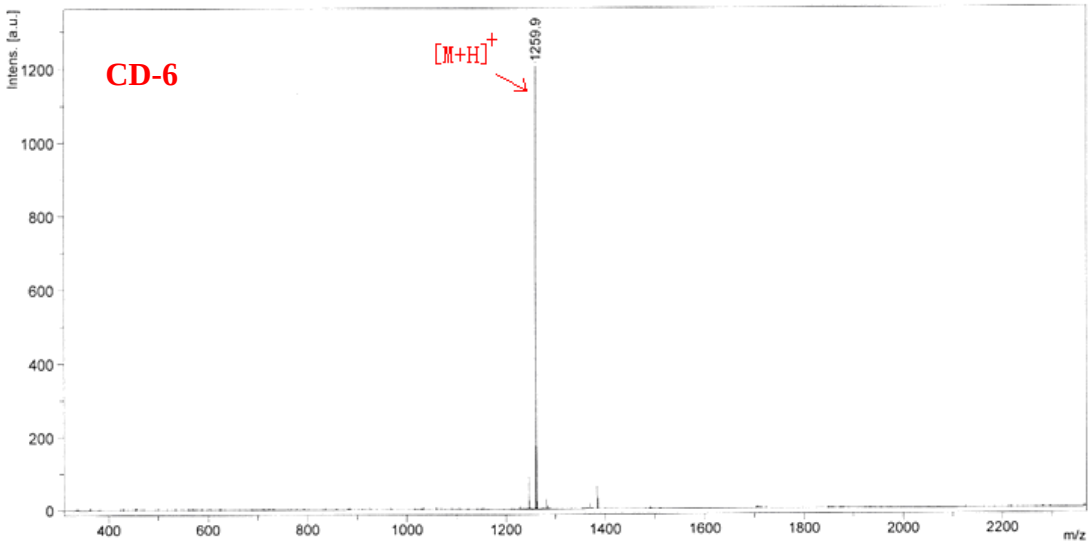

CD-5
ppm
Integral
14.240
1.079
6.096
10.148
46.917
22.685
2.012
2.022
3.022
2.984
1.086
2.004
1.020
3.051
0.902

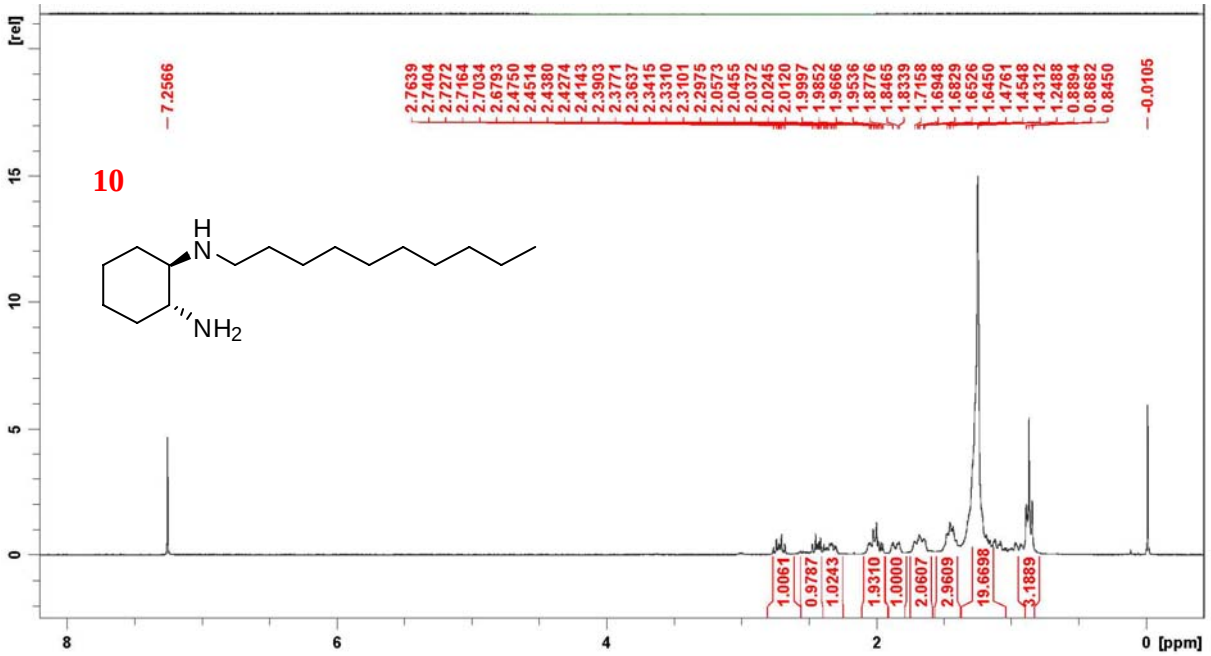

CD-5
ppm

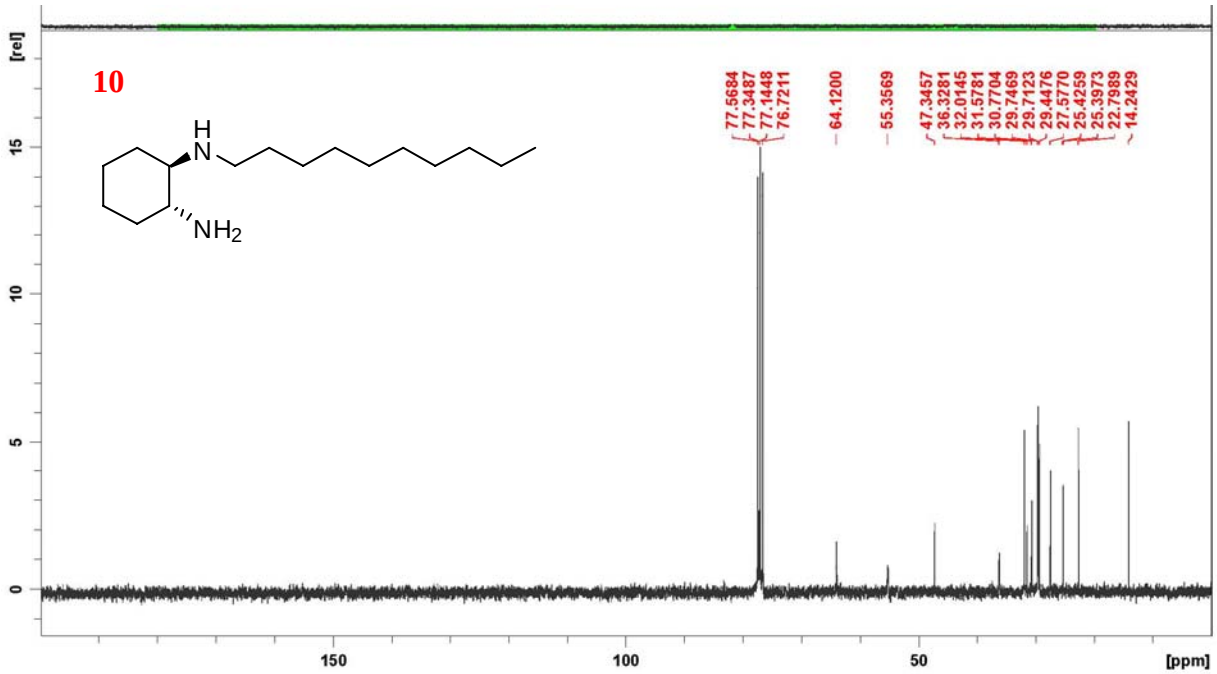

CD-5
Intens. [a.u.]
1260.1
[M+H]+
m/z


CD-6
ppm
Integral
11.828
7.112
5.936
2.926
26.060
59.696
2.045
1.060
1.045
6.125
1.028
1.912
1.069
2.975
1.009

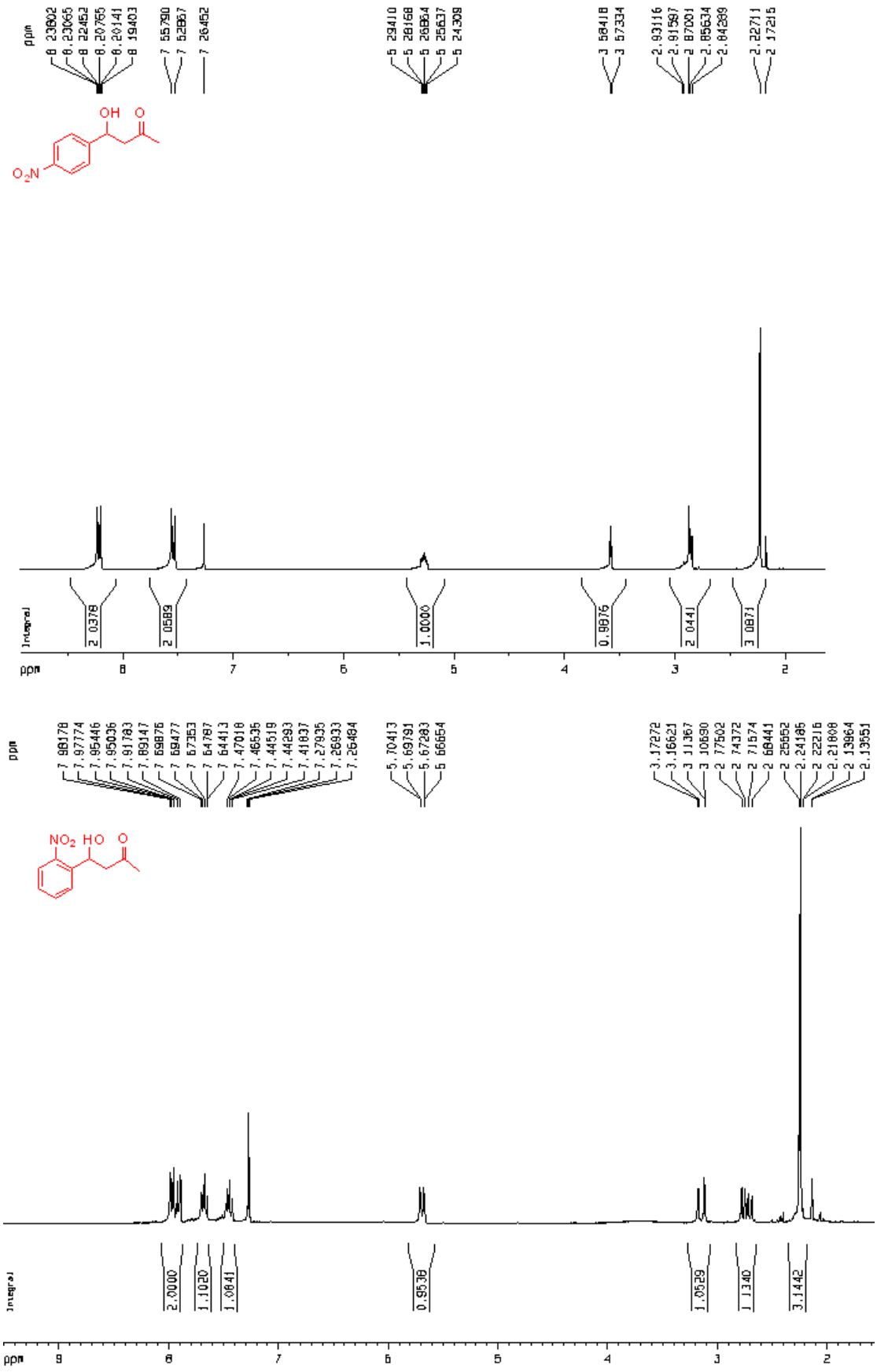

CD-6
ppm

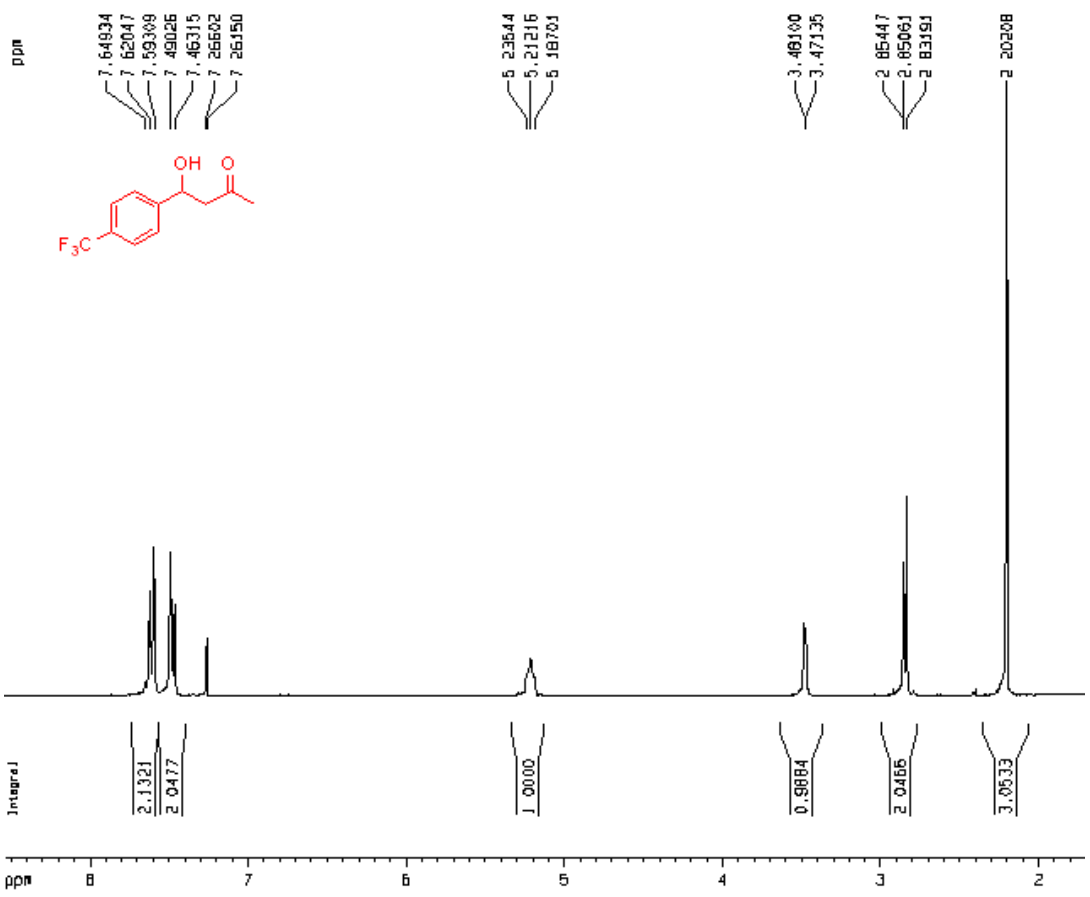

CD-6
Intens. [a.u.]
[M+H]+
1259.9
m/z

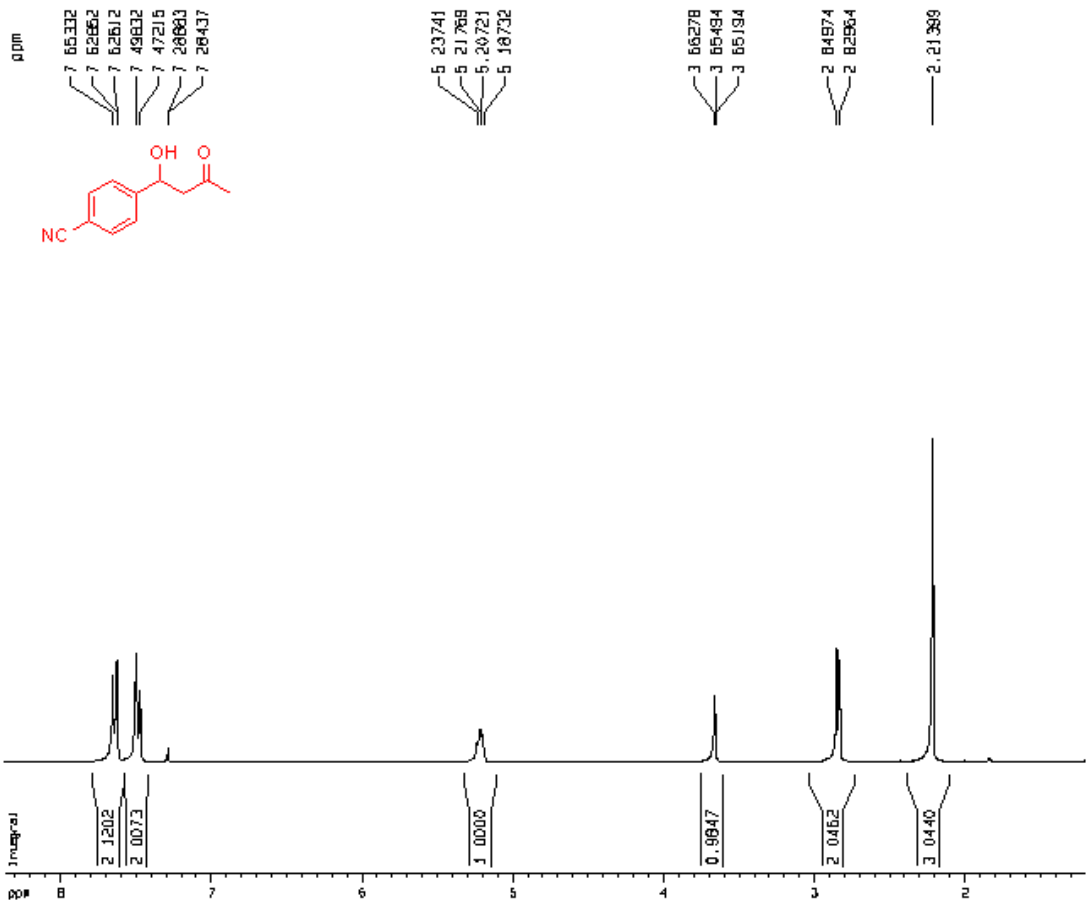

10
[rel]
7.2566
2.7639
2.7404
2.7272
2.7164
2.7034
2.6793
2.4750
2.4514
2.4380
2.4274
2.4143
2.3903
2.3771
2.3637
2.3415
2.3310
2.3101
2.2975
2.0573
2.0455
2.0372
2.0245
2.0120
1.9997
1.9852
1.9666
1.9536
1.8776
1.8465
1.8339
1.7158
1.6948
1.6829
1.6526
1.6450
1.4761
1.4548
1.4312
1.2488
0.8894
0.8682
0.8450
-0.0105
1.0061
0.9787
1.0243
1.9310
1.0000
2.0607
2.9609
19.6698
3.1889
8
6
4
2
0 [ppm]


10
[rel]
77.5684
77.3487
77.1448
76.7211
64.1200
55.3569
47.3457
36.3281
32.0145
31.5781
30.7704
29.7469
29.7123
29.4476
27.5770
25.4259
25.3973
22.7989
14.2429
150
100
50
[ppm]

NMR spectrum for the aldol products




ppm
7.64934
7.62047
7.59309
7.49026
7.46315
7.26602
7.26150
5.23644
5.21216
5.18701
3.46100
3.47135
2.85447
2.85061
2.83191
2.20208
OH
O
F3C
Integral
2.1321
2.0477
1.0000
0.9884
2.0466
3.0533
ppm
8
7
6
5
4
3
2


ppm
7.65332
7.62662
7.62612
7.49832
7.47216
7.26803
7.26437
5.23741
5.21768
5.20721
5.18732
3.66278
3.65494
3.65194
2.84574
2.82964
2.21399
OH
O
NC
Integral
2.1202
2.0073
1.0000
0.9847
2.0462
3.0440
ppm
8
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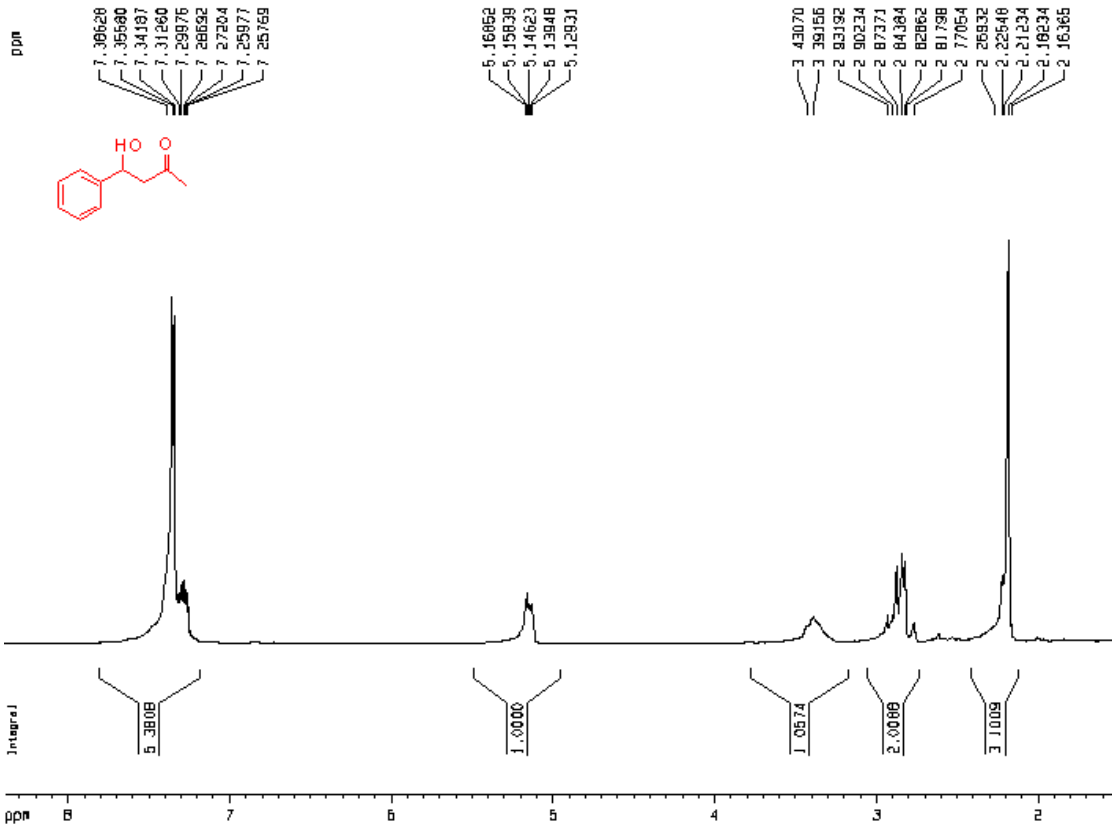
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4
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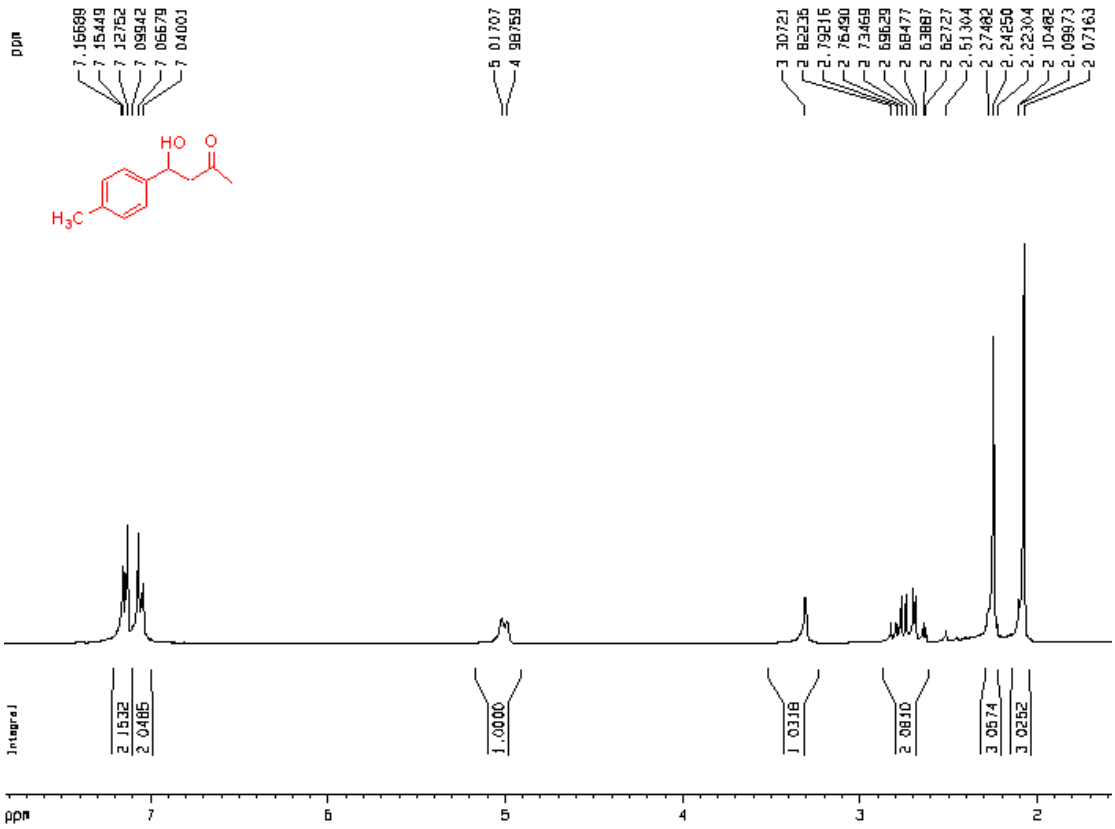
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Integral
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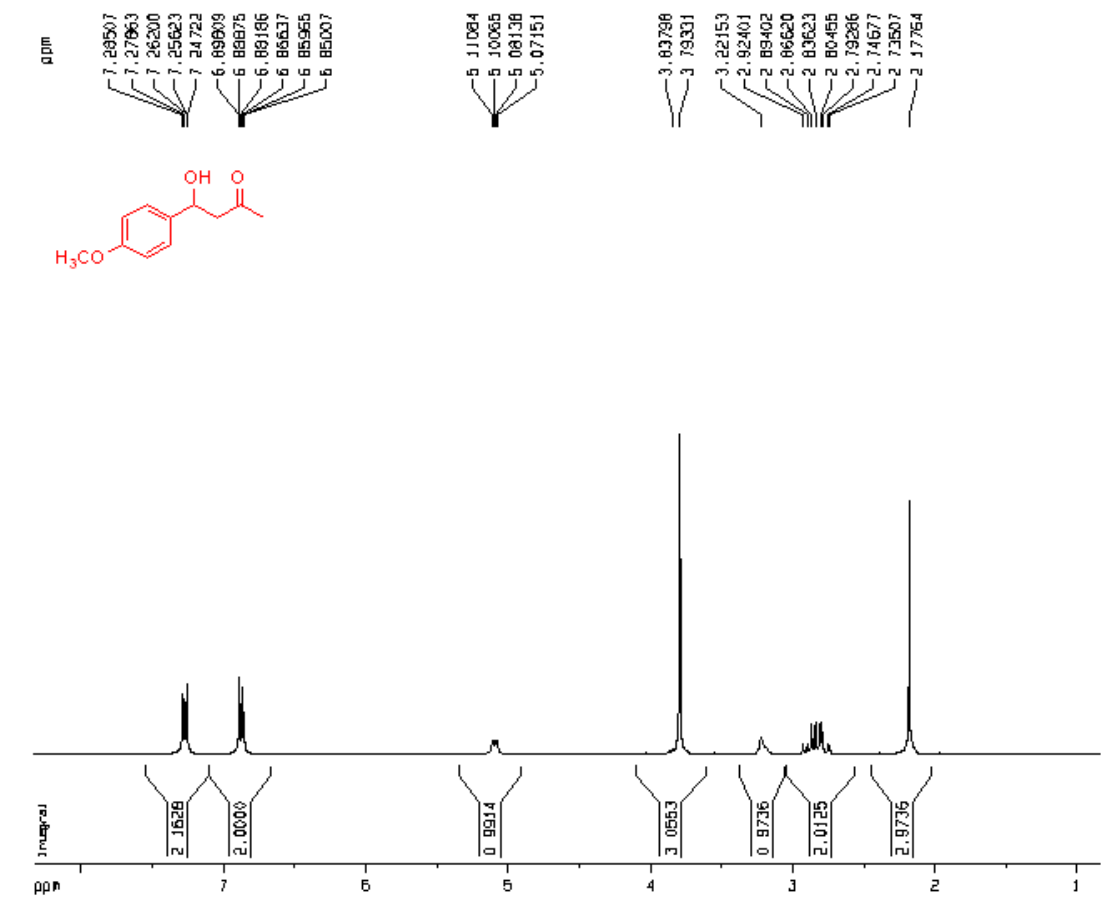
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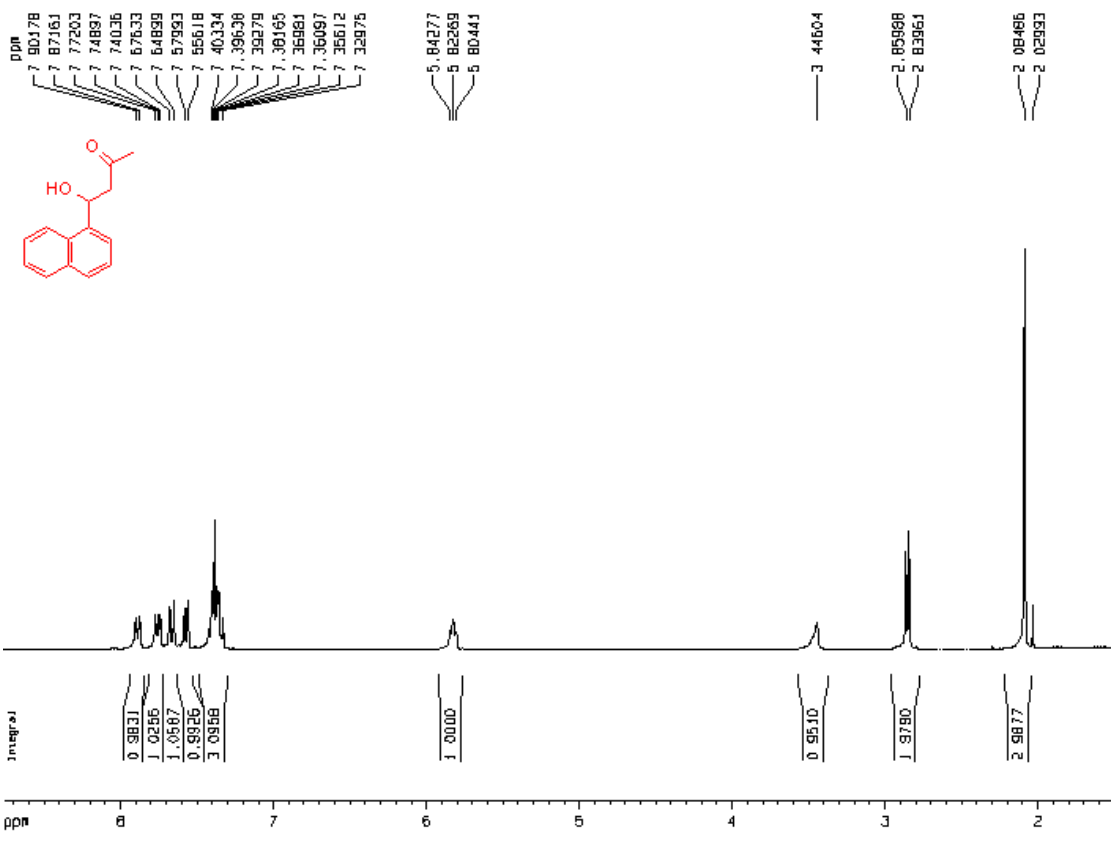
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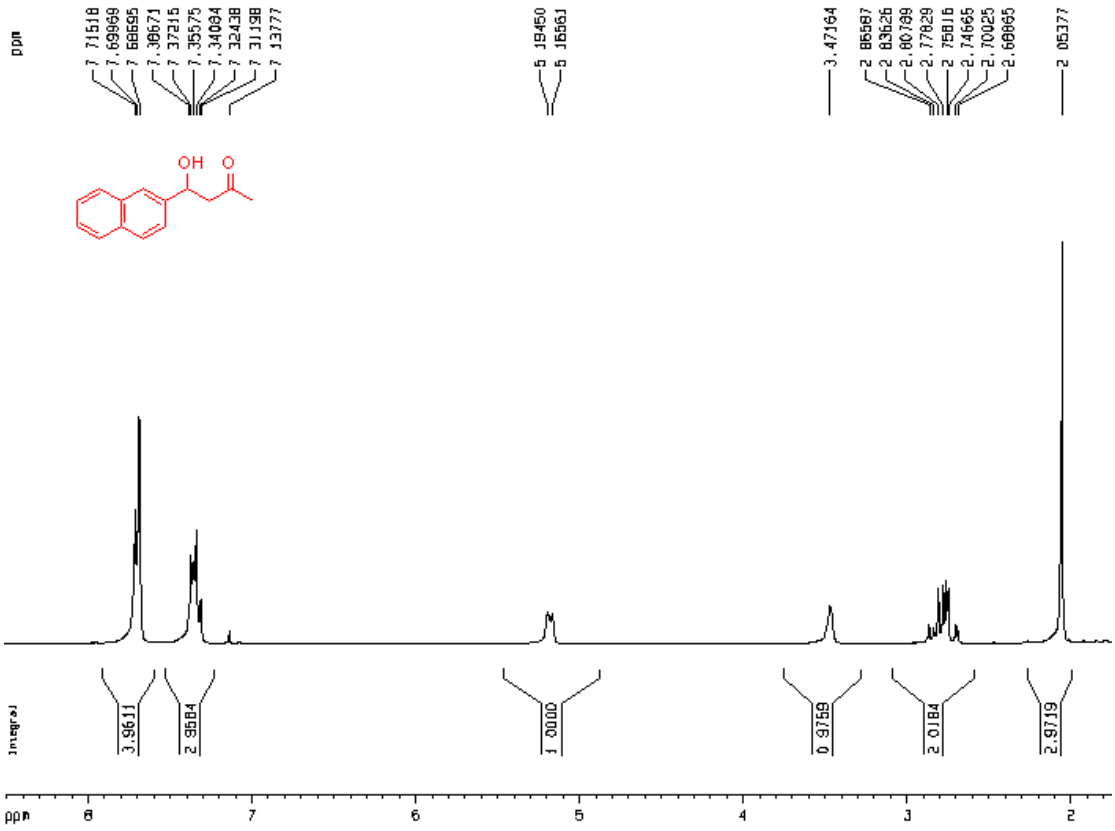
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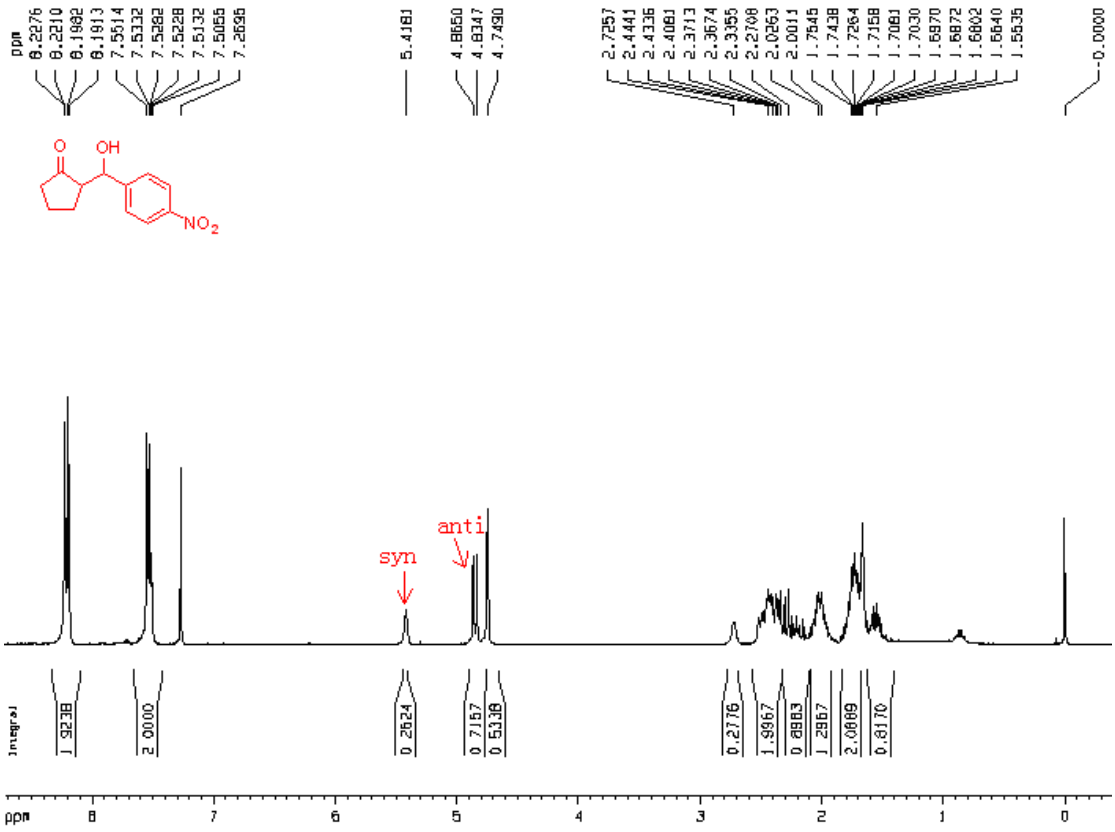
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2.4441
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1.7030
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Integral
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5
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3
2
1
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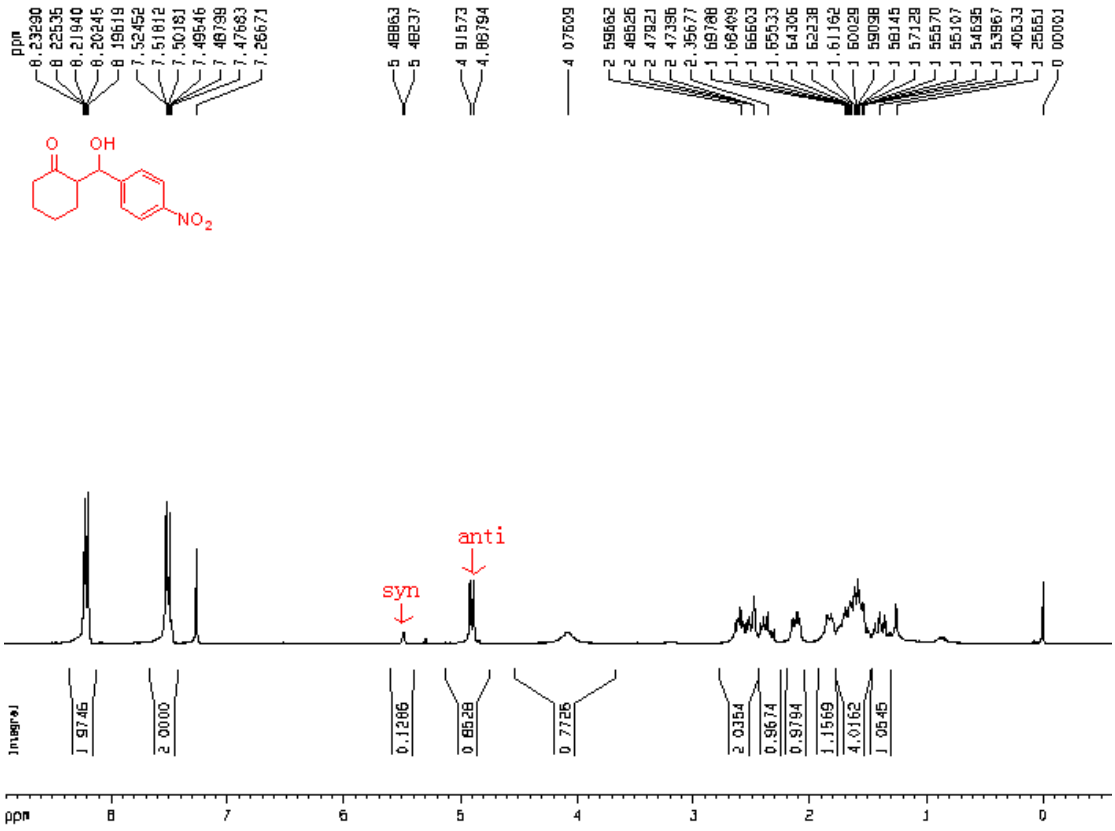
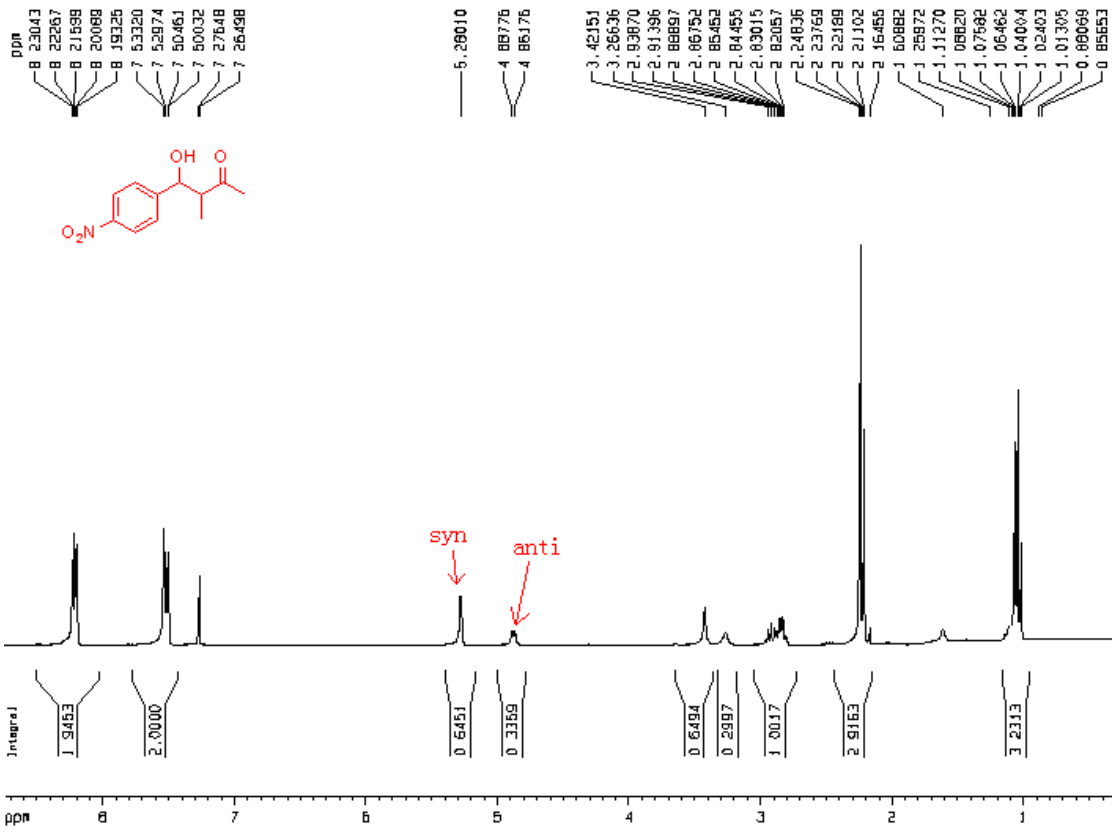
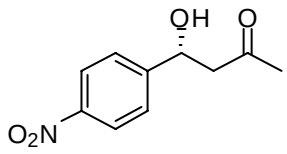
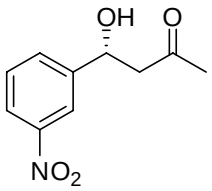

syn
anti


syn
anti

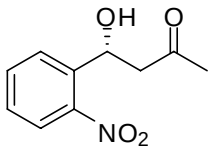
HPLC condition for all aldol product:



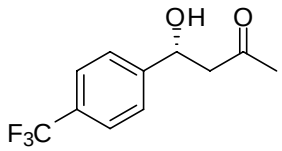
The enantiometric excess was determined by HPLC with an AS-H column at 240 nm (2-propanol: Hexane=30/70), 25ºC, 0.5 mL/min. t_R=23.50 (major); t_R=27.73 (minor)



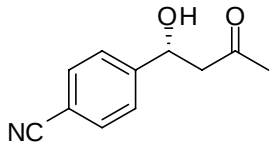
The enantiometric excess was determined by HPLC with an OJ-H column at 240 nm (2-propanol: Hexane=20/40), 25ºC, 0.8 mL/min. t_R=18.37 (major); t_R=20.42 (minor)



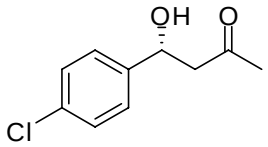
The enantiometric excess was determined by HPLC with an OJ-H column at 254 nm (2-propanol: Hexane=30/70), 25ºC, 0.8 mL/min. t_R=10.00 (major); t_R=12.67 (minor)



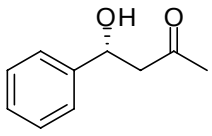
The enantiometric excess was determined by HPLC with an AS-H column at 240 nm (2-propanol: Hexane=20/80), 25ºC, 0.5 mL/min. t_R=12.18 (major); t_R=14.54 (minor)



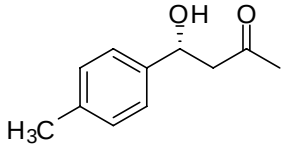
The enantiometric excess was determined by HPLC with an AS-H column at 240 nm (2-propanol: Hexane=20/80), 25ºC, 0.5 mL/min. t_R=22.60 (major); t_R=41.57 (minor)



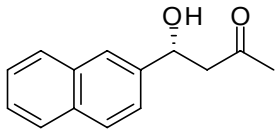
The enantiometric excess was determined by HPLC with an AS-H column at 254 nm (2-propanol: Hexane=10/90), 25ºC, 0.8 mL/min. t_R=22.36 (major); t_R=28.51 (minor)



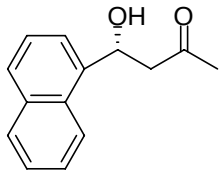
The enantiometric excess was determined by HPLC with an AS-H column at 254 nm (2-propanol: Hexane=10/90), 25ºC, 0.8 mL/min. t_R=16.41 (major); t_R=19.42 (minor)



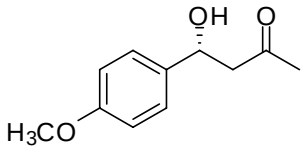
The enantiometric excess was determined by HPLC with an AS-H column at 254 nm (2-propanol: Hexane=10/90), 25ºC, 0.8 mL/min. t_R=15.19 (major); t_R=19.30 (minor)



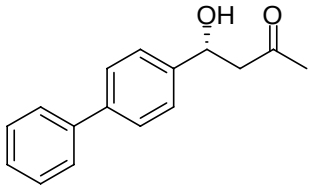
The enantiometric excess was determined by HPLC with an AS-H column at 254 nm (2-propanol: Hexane=10/90), 25ºC, 0.8 mL/min. t_R=25.85 (major); t_R=28.42 (minor)



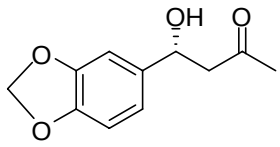
The enantiometric excess was determined by HPLC with an AS-H column at 254 nm (2-propanol: Hexane=15/85), 25ºC, 0.8 mL/min. t_R=13.31 (minor); t_R=14.13 (major)



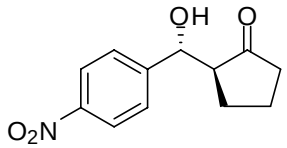
The enantiometric excess was determined by HPLC with an AS-H column at 254 nm (2-propanol: Hexane=15/85), 25ºC, 0.8 mL/min. t_R=36.30 (major); t_R=38.41 (minor)



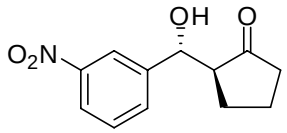
The enantiometric excess was determined by HPLC with an AS-H column at 254 nm (2-propanol: Hexane=10/90), 25ºC, 0.8 mL/min. t_R=18.58 (major); t_R=22.33 (minor)



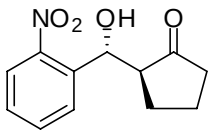
The enantiometric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol: Hexane=20/80), 25ºC, 0.8 mL/min. t_R=17.89 (major); t_R=21.78 (minor)



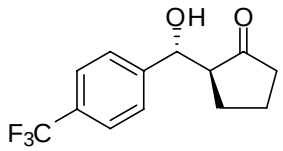
The enantiometric excess was determined by HPLC with an OJ-H column at 254 nm (2-propanol: Hexane=10/90), 25ºC, 0.8 mL/min. t_R=35.57 (major); t_R=51.57 (minor)



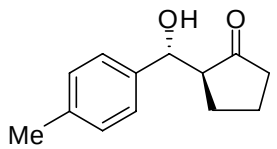
The enantiometric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol: Hexane=5/95), 25ºC, 0.8 mL/min. t_R=41.23 (major); t_R=62.37 (minor)



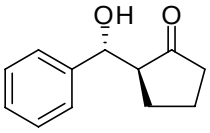
The enantiometric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol: Hexane=5/95), 25ºC, 0.8 mL/min. t_R=35.38 (minor); t_R=38.31 (major)



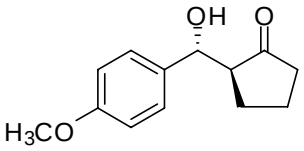
The enantiometric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol: Hexane=5/95), 25ºC, 0.8 mL/min. t_R=17.44 (major); t_R=19.35 (minor)



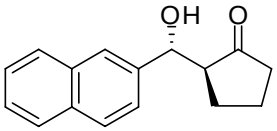
The enantiometric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol: Hexane=5/95), 25ºC, 0.8 mL/min. t_R=14.47 (major); t_R=16.52 (minor)



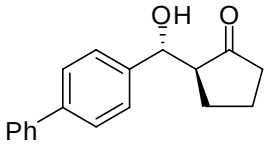
The enantiometric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol: Hexane=5/95), 25ºC, 0.8 mL/min. t_R=21.22 (major); t_R=24.25 (minor)



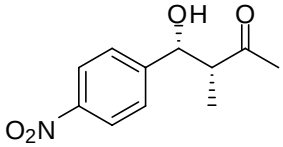
The enantiometric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol: Hexane=5/95), 25ºC, 0.8 mL/min. t_R=33.33 (major); t_R=38.16 (minor)



The enantiometric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol: Hexane=5/95), 25ºC, 0.8 mL/min. t_R=35.48 (major); t_R=39.40 (minor)



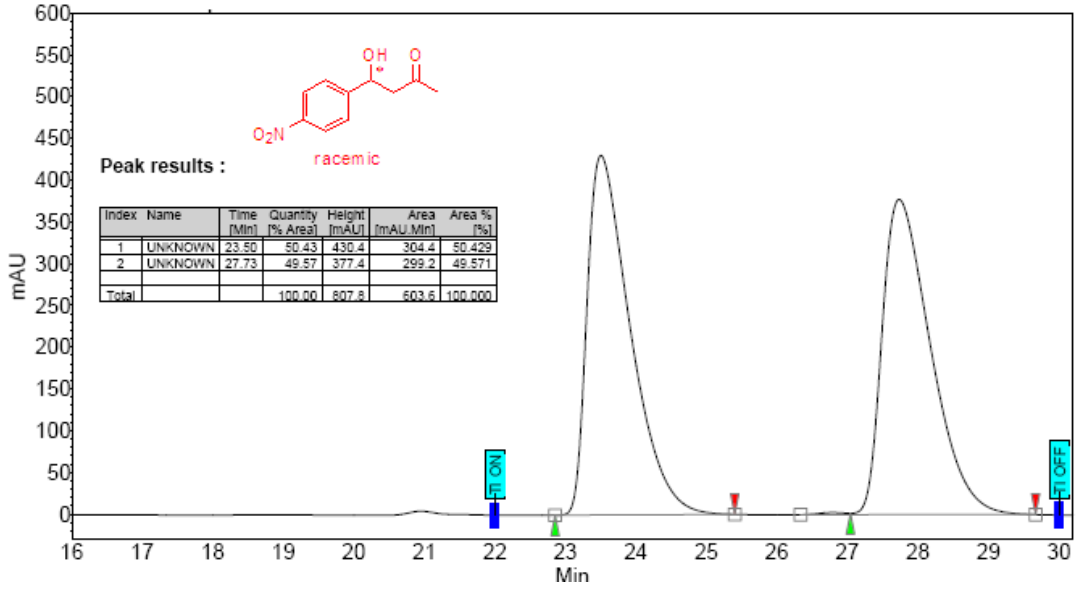
The enantiometric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol: Hexane=5/95), 25ºC, 0.8 mL/min. t_R=33.29 (minor); t_R=35.00 (major)

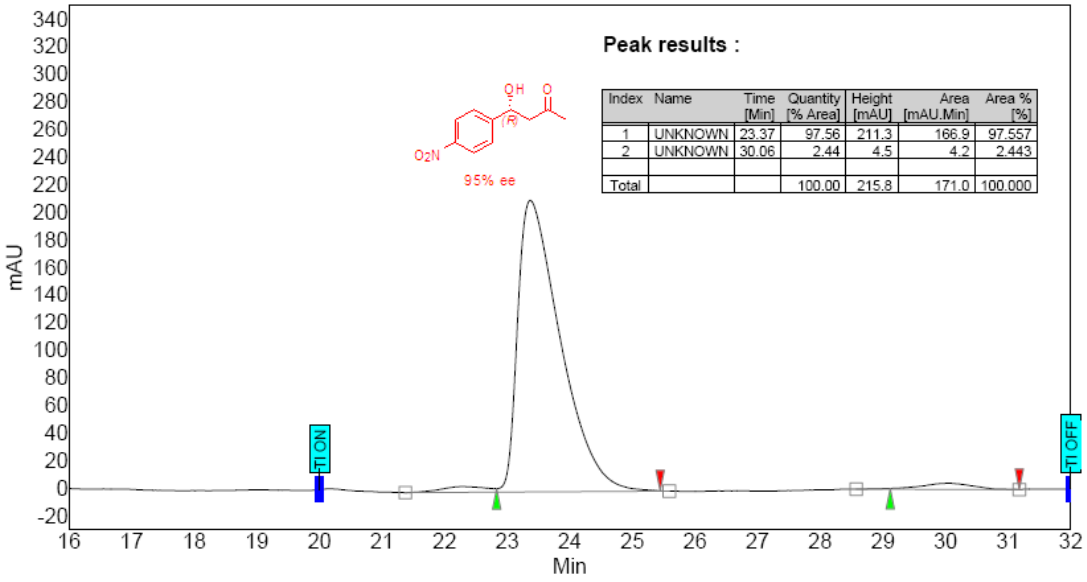


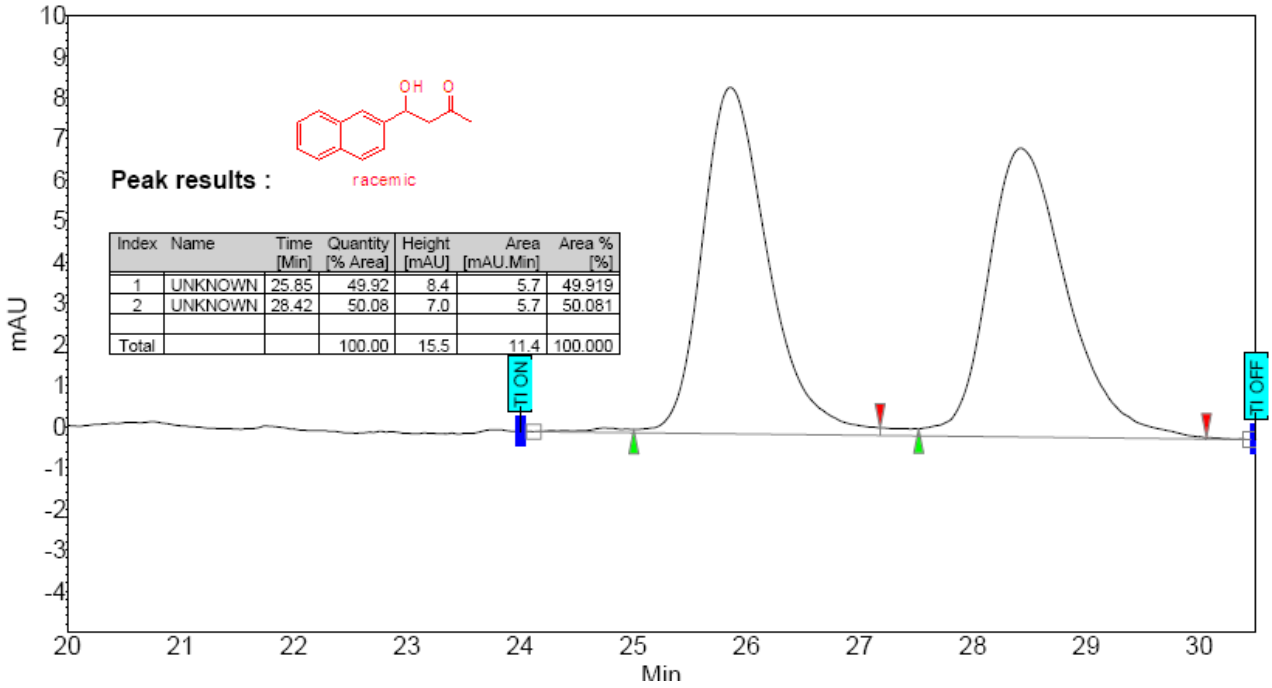
The enantiometric excess was determined by HPLC with an AS-H column at 254 nm (2-propanol: Hexane=3/7), 25ºC, 0.8 mL/min. t_R=18.95 (major); t_R=22.61 (minor)

Representative HPLC traces for aldol products

Determination of absolutely configuration






OH O
racemic
Peak results :
Index Name Time [Min] Quantity [% Area] Height [mAU] Area [mAU.Min] Area % [%]
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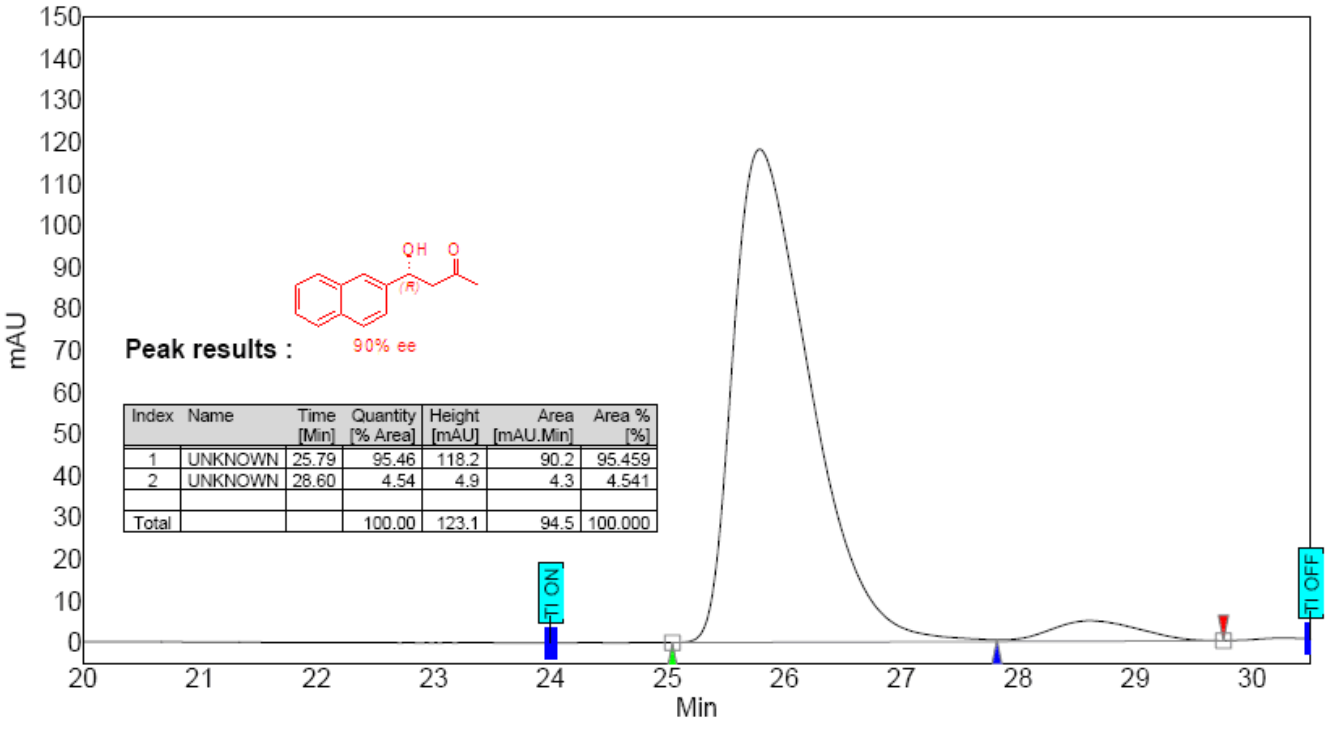
2 UNKNOWN 28.42 50.08 7.0 5.7 50.081
Total 100.00 15.5 11.4 100.000
TI ON
TI OFF
mAU
Min


OH O
(R)
90% ee
Peak results :
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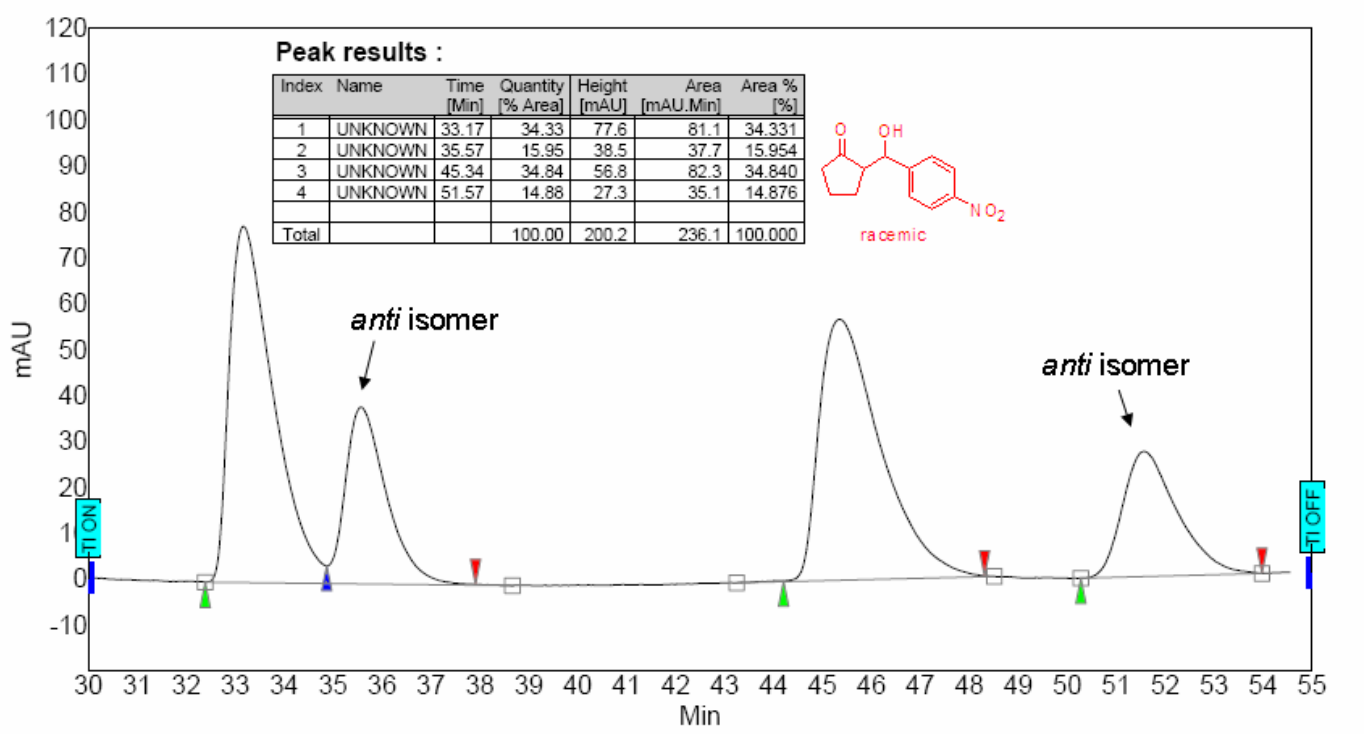
TI ON
TI OFF
mAU
Min


Peak results :
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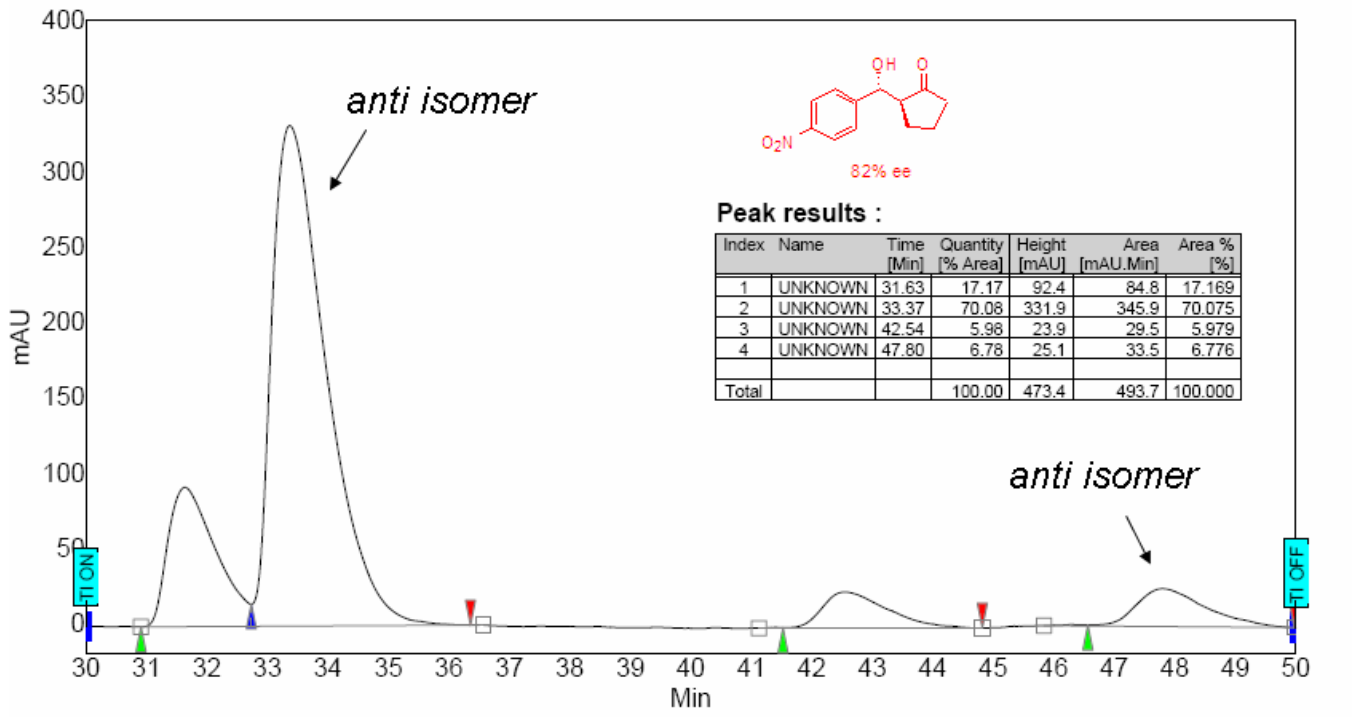
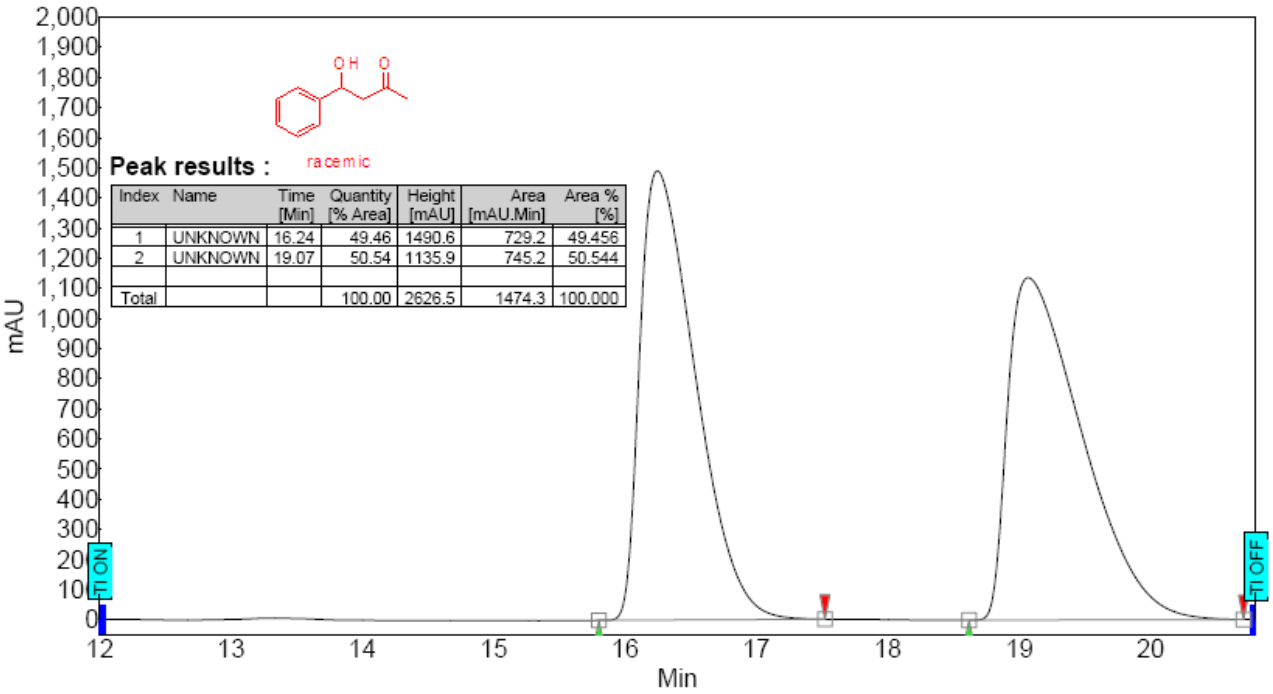
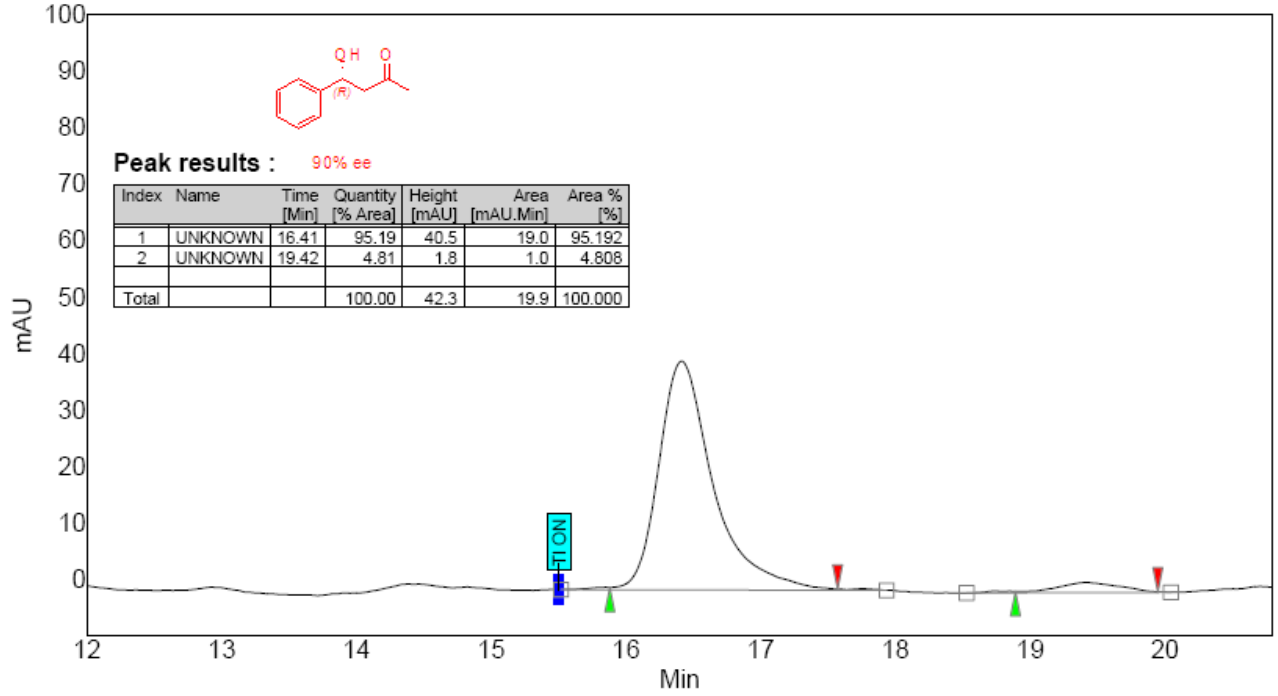
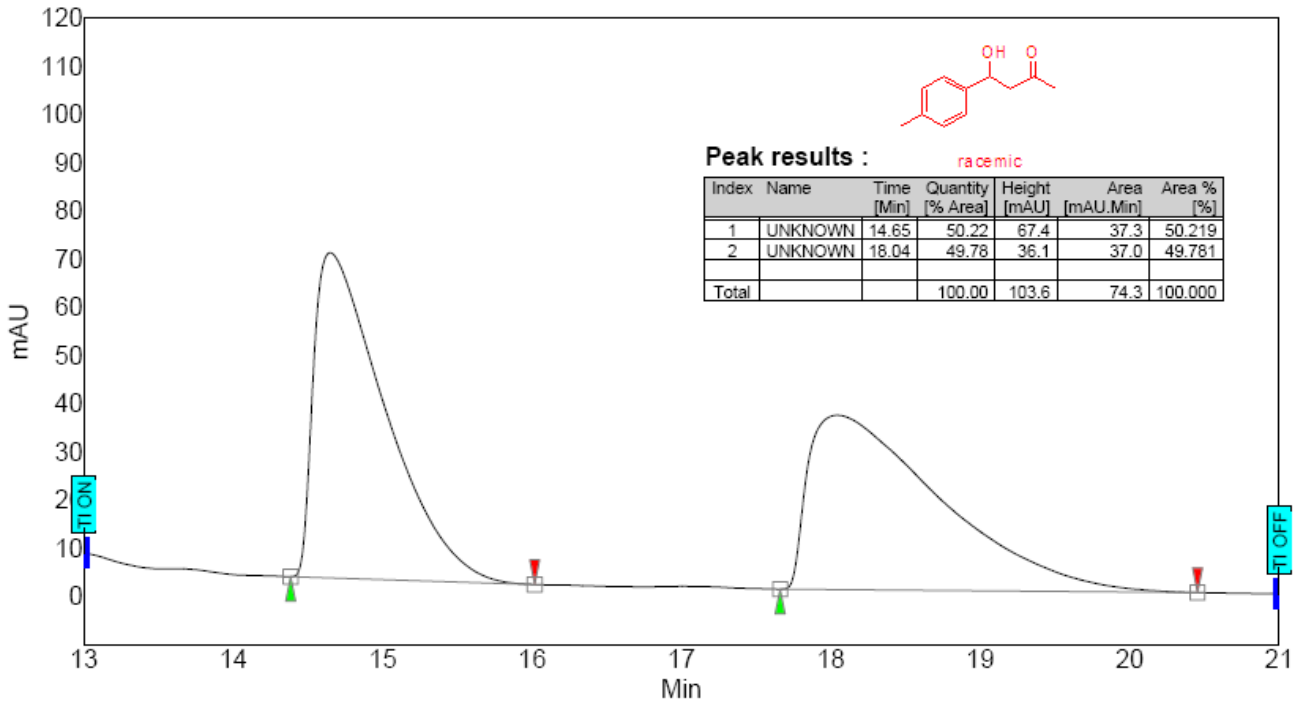
2 UNKNOWN 35.57 15.95 38.5 37.7 15.954
3 UNKNOWN 45.34 34.84 56.8 82.3 34.840
4 UNKNOWN 51.57 14.88 27.3 35.1 14.876
Total 100.00 200.2 236.1 100.000
racemic
anti isomer
anti isomer
mAU
Min
TI ON
TI OFF

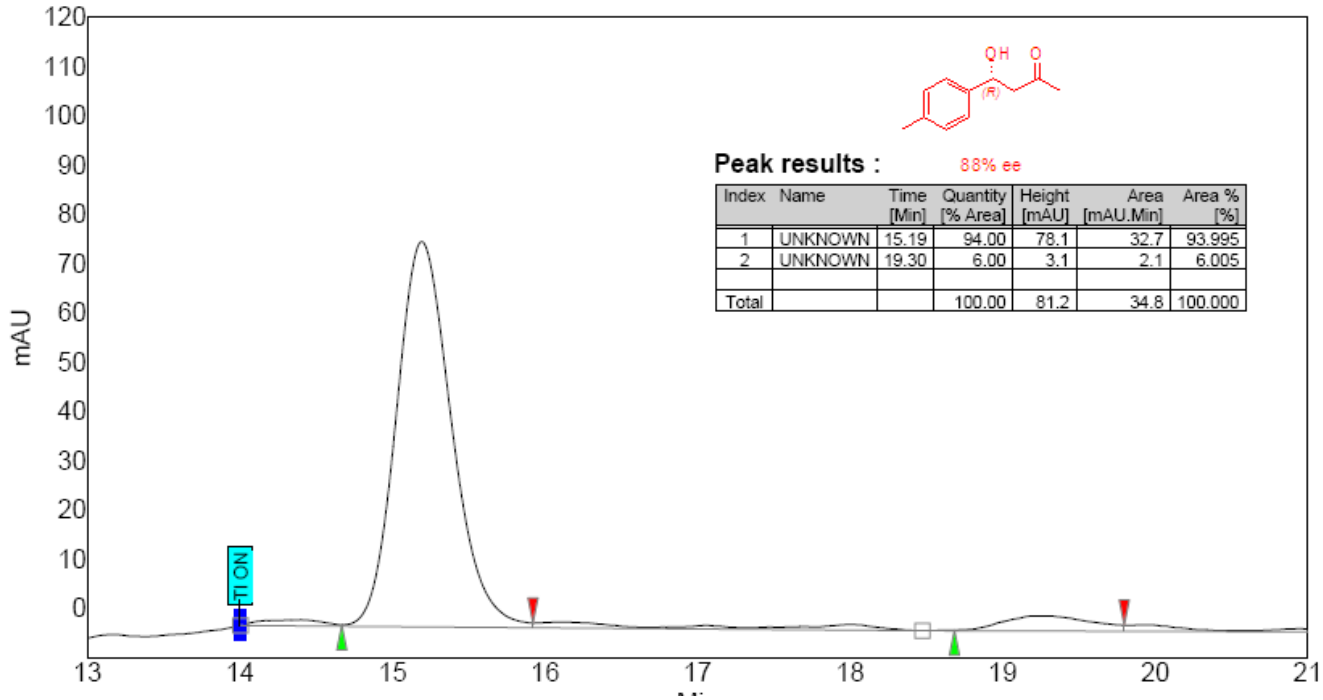

anti isomer
82% ee
Peak results :
Index Name Time [Min] Quantity [% Area] Height [mAU] Area [mAU.Min] Area % [%]
1 UNKNOWN 31.63 17.17 92.4 84.8 17.169
2 UNKNOWN 33.37 70.08 331.9 345.9 70.075
3 UNKNOWN 42.54 5.98 23.9 29.5 5.979
4 UNKNOWN 47.80 6.78 25.1 33.5 6.776
Total 100.00 473.4 493.7 100.000
anti isomer
mAU
Min
TI ON
TI OFF


Peak results :
racemic
Index Name Time [Min] Quantity [% Area] Height [mAU] Area [mAU.Min] Area % [%]
1 UNKNOWN 16.24 49.46 1490.6 729.2 49.456
2 UNKNOWN 19.07 50.54 1135.9 745.2 50.544
Total 100.00 2626.5 1474.3 100.000
mAU
Min
TI ON
TI OFF

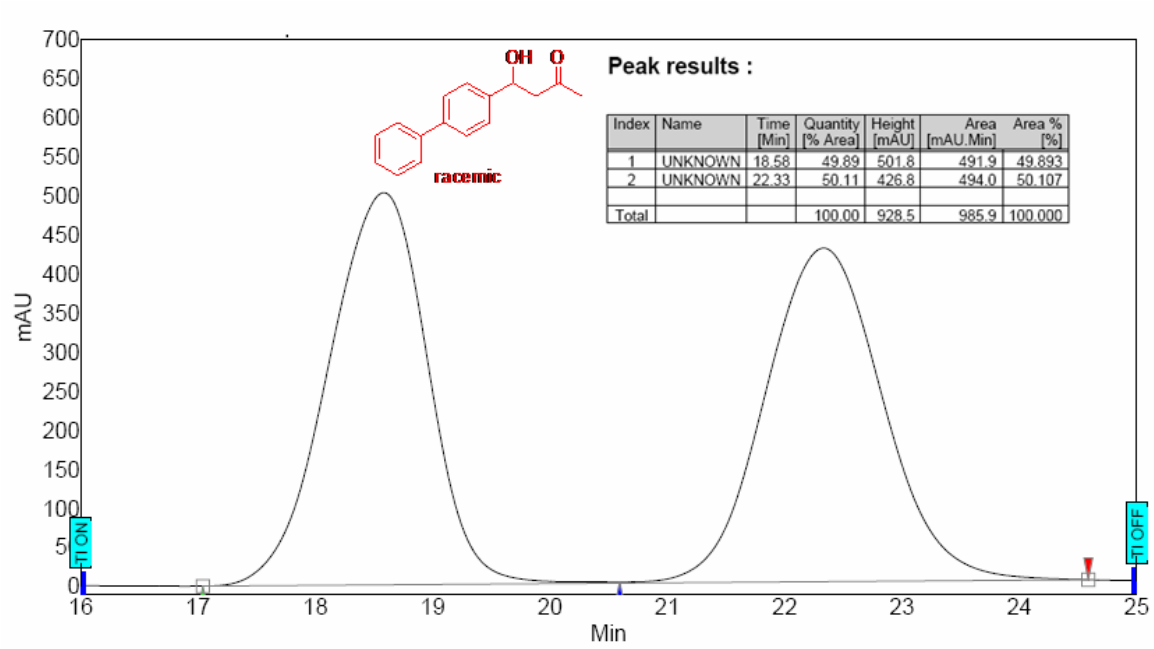

Peak results :
90% ee
Index Name Time [Min] Quantity [% Area] Height [mAU] Area [mAU.Min] Area % [%]
1 UNKNOWN 16.41 95.19 40.5 19.0 95.192
2 UNKNOWN 19.42 4.81 1.8 1.0 4.808
Total 100.00 42.3 19.9 100.000
mAU
Min
TI ON

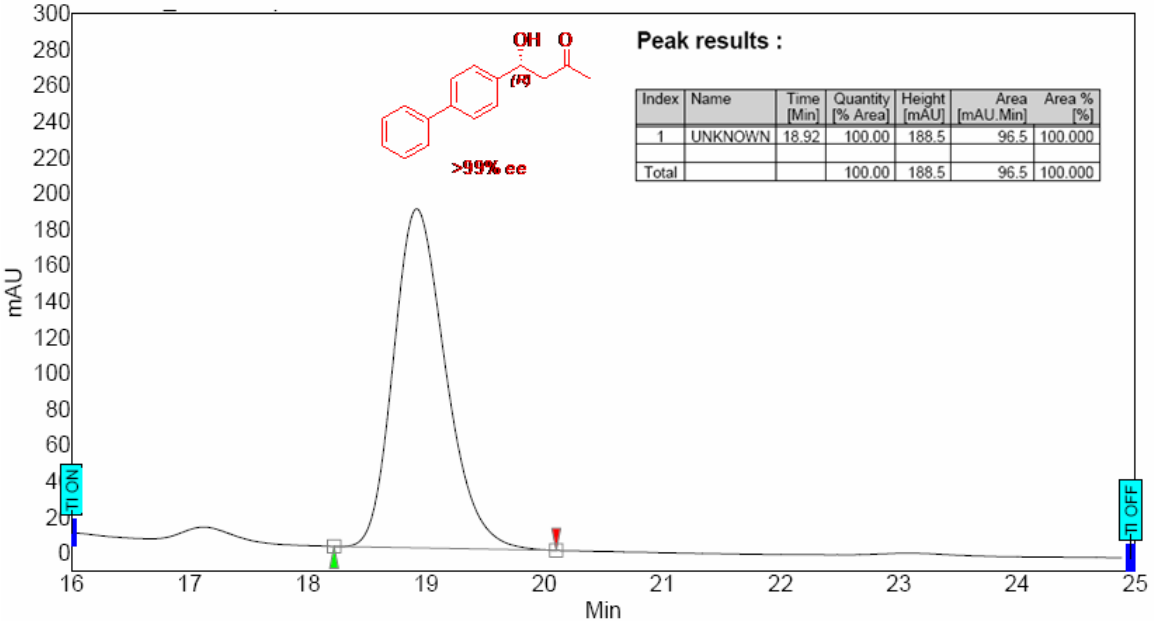


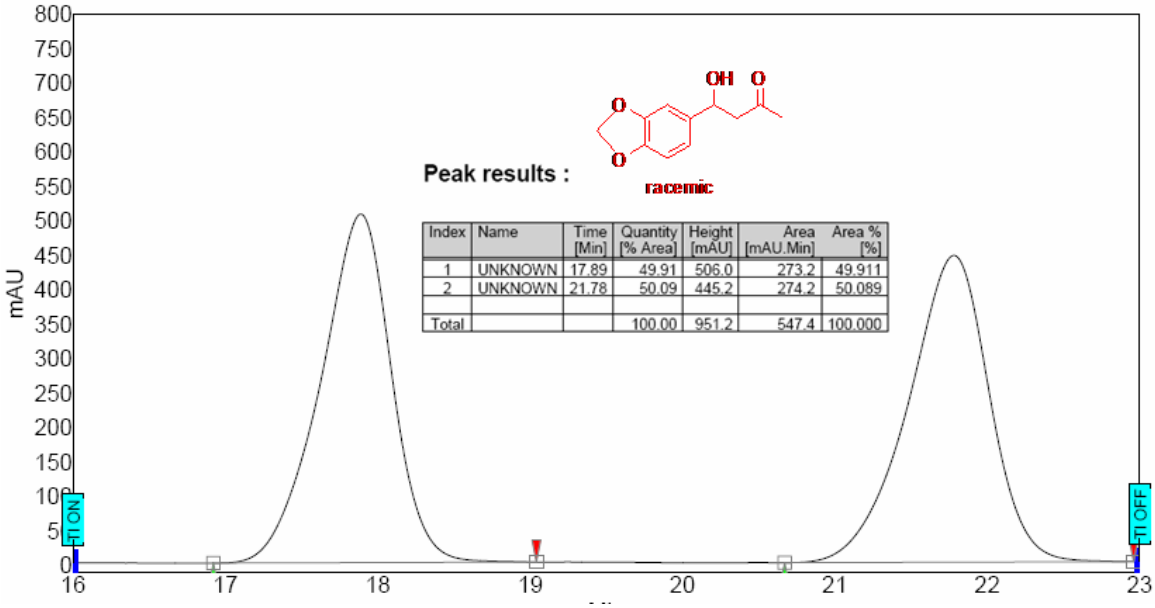
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	14.65	50.22	67.4	37.3	50.219
2	UNKNOWN	18.04	49.78	36.1	37.0	49.781
Total			100.00	103.6	74.3	100.000



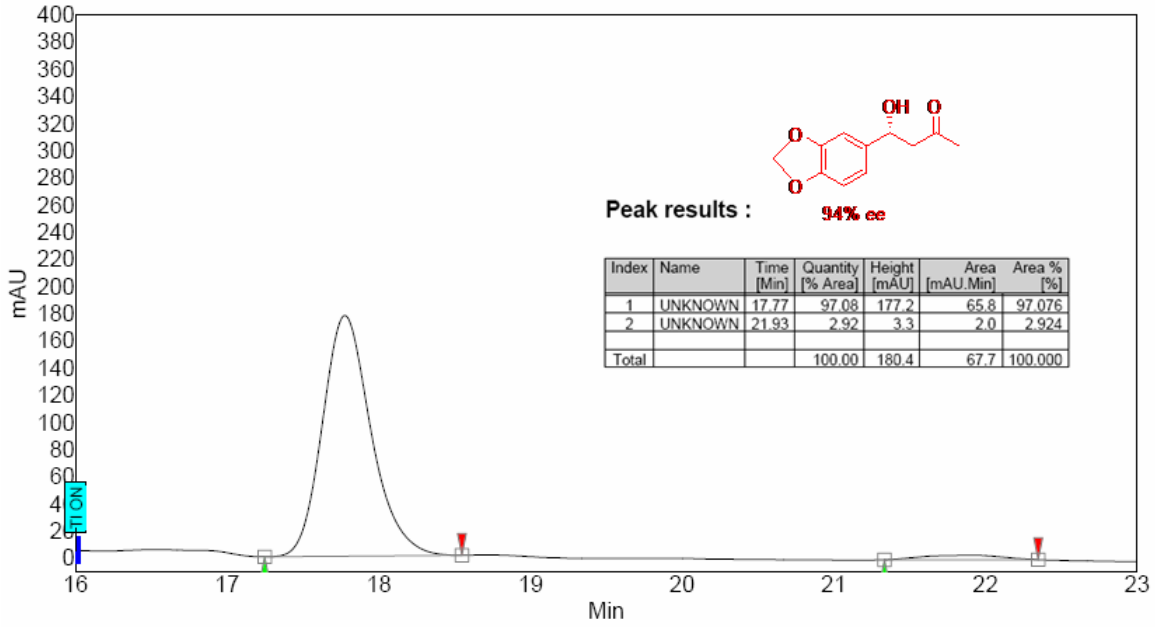
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	15.19	94.00	78.1	32.7	93.995
2	UNKNOWN	19.30	6.00	3.1	2.1	6.005
Total			100.00	81.2	34.8	100.000


racemic
Peak results :
Index | Name | Time [Min] | Quantity [% Area] | Height [mAU] | Area [mAU.Min] | Area % [%]
1 | UNKNOWN | 18.58 | 49.89 | 501.8 | 491.9 | 49.893
2 | UNKNOWN | 22.33 | 50.11 | 426.8 | 494.0 | 50.107
Total | | | 100.00 | 928.5 | 985.9 | 100.000
mAU
Min
TI ON
TI OFF


(R)
>99% ee
Peak results :
Index | Name | Time [Min] | Quantity [% Area] | Height [mAU] | Area [mAU.Min] | Area % [%]
1 | UNKNOWN | 18.92 | 100.00 | 188.5 | 96.5 | 100.000
Total | | | 100.00 | 188.5 | 96.5 | 100.000
mAU
Min
TI ON
TI OFF



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	17.89	49.91	506.0	273.2	49.911
2	UNKNOWN	21.78	50.09	445.2	274.2	50.089
Total			100.00	951.2	547.4	100.000



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	17.77	97.08	177.2	65.8	97.076
2	UNKNOWN	21.93	2.92	3.3	2.0	2.924
Total			100.00	180.4	67.7	100.000

Table S4. Crystal data and structure refinement for CD-1.

Identification code	mx3
Empirical formula	C48 H97 N2 O41.50
Formula weight	1366.28
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P1
Unit cell dimensions	a = 9.9461(19) A alpha = 106.355(3) deg.
	b = 12.038(2) A beta = 103.637(3) deg.
	c = 14.418(3) A gamma = 91.494(2) deg.
Volume	1601.8(6) A^3
Z, Calculated density	1, 1.416 Mg/m^3
Absorption coefficient	0.125 mm^-1
F(000)	731
Crystal size	0.17 x 0.12 x 0.06 mm
Theta range for data collection	1.77 to 27.47 deg.
Limiting indices	-12<=h<=12, -15<=k<=15, -18<=l<=18
Reflections collected / unique	29033 / 7328 [R(int) = 0.0538]
Completeness to theta = 27.47	99.9 %
Absorption correction	Numerical
Max. and min. transmission	0.9925 and 0.9791
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7328 / 3 / 840
Goodness-of-fit on F^2	1.091
Final R indices [I>2sigma(I)]	R1 = 0.0504, wR2 = 0.1282
Absolute structure parameter	-0.2(7)
Extinction coefficient	0.0133(16)
Largest diff. peak and hole	0.443 and -0.234 e.A^-3