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Article

Novel Chiral Ionic Liquid (CIL) Assisted Selectivity Enhancement to (L)-Proline Catalyzed Asymmetric Aldol Reactions

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Melhoras significativas nos rendimentos químicos (até 88%), estereosseletividades (> 99:1) e excessos enantioméricos (até 98%) foram observadas em reações aldólicas assimétricas catalisadas por (L)-prolina, quando líquidos iônicos quirais baseados em prolina (CILs) foram usados como aditivos. Diferentes proporções de DMSO/H_2O como solvente, e líquidos iônicos quirais (CILs) com cátions quirais com diferentes comprimentos de cadeia, foram investigados.

A significant improvement of the chemical yields (up to 88%), stereoselectivity (> 99:1) and enantiomeric excesses (up to 98%) of (L)-proline catalyzed direct asymmetric aldol reaction was found when proline based chiral ionic liquids (CILs) were added as additives. Different ratios of DMSO/H_2O as solvent and chiral ionic liquids (CILs) with chiral cations of different chain length were investigated.

Keywords: aldol reaction, asymmetric synthesis, chiral ionic liquids, chiral additive

Introduction

Room temperature ionic liquids (RTILs) including chiral ionic liquids (CILs) have received growing attentions both from theoretical research and actual productions due to their tuneable features for various chemical tasks and their advantages as homogeneous support, reaction media, etc.[1,2] Since the first example of chiral ionic liquid reported by Howarth *et al*.[3] in 1997, a large number of CILs bearing chiral cations, anions or seldom both were reported by other groups.[4,5] Previous studies have shown that in many asymmetric reactions the use of CILs as reaction media or catalyst can enhance the yield and/or selectivity significantly.[6-8] As most of the asymmetric reactions were carried out using metal/chiral catalysts as chiral sources, which are relatively expensive or environmental unfriendly, searching for a catalyst which is easy to obtain and environmentally benign for the asymmetric reactions is of great significance. In our previous work, a series of (L)-proline based CILs were proved to have the potential to provide a strong chiral environment by ^{19}F NMR study.[9] In this article, a series of reactions were carried out to investigate the catalytic properties of these (L)-proline based CILs, and very high chiral selectivity was obtained.

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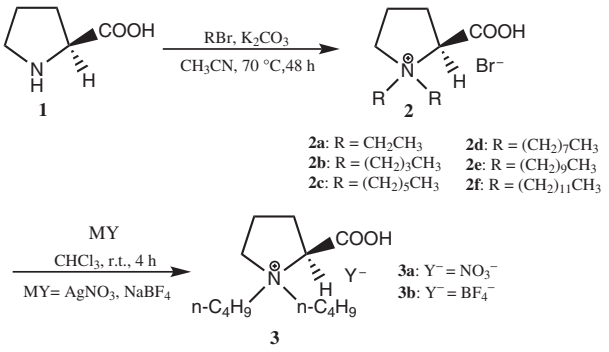
Aldol reaction has been a typical asymmetric reaction used in the search of efficient asymmetric catalyst, especially for environmental friendly and metal-free organic catalyst.[10-13] Since CILs used as catalyst in aldol reaction by Luo *et al*.[14] in 2007, many CILs were developed as catalysts for asymmetric reactions. However, in asymmetric reactions where CILs cannot be applied as catalysts, using CILs as the solvent to investigate the chiral inducing capabilities has rarely been reported. Here we chose the asymmetric aldol reactions as our initial focus to examine the applications of CILs in asymmetric reactions. (L)-Proline and its structural analogs were found to be good catalyst for aldol reaction,[15-19] and (L)-proline combined with ILs were also proved to be an efficient catalytic system for asymmetric aldol reactions.[20-23] However, a systematic study about the relationship between structure and properties of ionic liquids is of great interest to many researchers.

Results and Discussion

In this work, (L)-proline based CILs (Scheme 1) are used as chiral additives for (L)-proline-catalyzed asymmetric aldol reaction between aldehyde and acetone, and the results are listed in Table 1. CILs alone can not promote this reaction (Table 1, entry 1). Upon addition



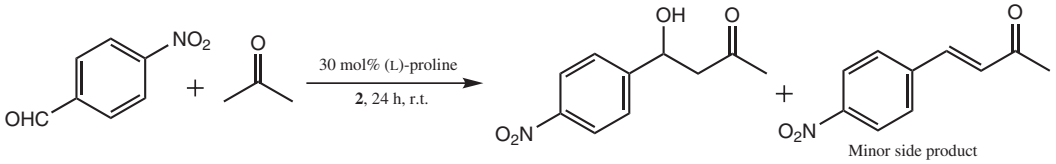
Scheme 1. Synthesis of CILs.

of (L)-proline even with a slight amount the reactions proceeded at room temperature and gave the aldol product.

The yields were obviously increased with increasing amount of (L)-proline (Table 1, entries 2 to 4). When (L)-proline (30 mol%) and **2b** (7.5 mol%) in an acetone mixture of the reactants were used, the reaction proceeded with a superior yield (up to 97%) and a moderate *ee* value (71%). An obvious decrease of the yield but a slight increase of the *ee* values can be observed with decreasing amount of (L)-proline. This result is in accordance with that of Jacobsen's catalytic mechanism.[25] It can be concluded that the amount of catalyst have a direct relationship with the yield but a slight influence on the reaction selectivity. For the CILs, when the amount of CILs varied from 1 mol% to 7.5 mol%, it was found almost no change in the reaction yield, while the by product due to dehydration increased slightly with the increase of CILs. The *ee* values definitely increased with the addition of CILs **2b**, although very slightly. Using different aromatic aldehyde in the (L)-proline catalyzed aldol reaction, adding **2b** as additive and as well good yield and selectivity, the enantiomeric excesses can have up to 24% enhancement.

In summary of the results above, the best reaction ratio of catalyst and additives were found to be 30 mol% (L)-proline as catalyst and 7.5 mol% CILs as additives. Based on this founding, all of the following reactions were carried out on these conditions. The recycle ability of the catalyst and CILs were also studied (Table 1, entry 4 f-h). The reaction was taken 24 h, the solvent was evaporated, and resides were extracted with Et_2O three times. The combined solution was left for analysis, and resides were dried under vacuum for 3 h for the next cycle. The catalytic activity of the catalyst and CILs can be kept after 3 cycles, with only a slight decrease in *ee* values. To investigate the generality of the CILs as additives, a series of aromatic aldehyde acceptors were subjected to the same reaction conditions. From the results above, an obvious *ee* enhancement change can be found when $-NO_2$ was in different positions (entries 4 and 5, entries 9 and 10, entries 14 and 15). In details, the $-NO_2$ in *-o* and *-p* position showed better result than that in the -m position. This is mainly due to the positive effect in nucleophilic addition by $-NO_2$ in *-o* and *-p* position. Furthermore, other aromatic aldehydes with different substituents at *-p* positions (entries 16 and 17, entries 18 and 19, entries 20 and 21, entries 27 and 28, entries 29 and 30) were also investigated to validate the results, it can be seen that all of them react well in this catalytic system and almost no significant change in selectivity which reveals that substituents have less effect in the chemical selectivity. As for the CILs, their solubility can be adjusted by altering the alkyl chain. In details, **2a**, **2b** and **2c** have good solubility in water while the others with longer chain lengths are better miserable with low polarity solvent. The other two kinds of CILs with different (TG) counter ions also have their own unique proprieties. Thermogravimetric measurement reveals that these CILs have T_d (thermal degradation temperature) in the order of $BF_4^- > Br^- > NO_3^-$. Although their widely different proprieties were shown by different chain lengths and different counter ions, they showed no significant change both in chemical yields and selectivity. The mechanism is still under investigation. As temperature is an important factor in most of the asymmetric synthesis, lower the temperature (Table 1, entries 6 and 13) in our system showed only a small change in *ee* values (2% and 5%, respectively).

In addition, the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in the presence of (L)-proline and **2** in DMSO/H_2O solvent was also investigated (Table 2). Similarly, the reactions were carried out using (L)-proline as catalyst with or without CILs. It was very interesting to find that when 10 mol% of CILs was added, the yields, stereo-selectivity and enantiomeric excesses were enhanced significantly. The solvent, which is very important in organic reactions, was optimized by a series of comparison experiments use different ratio of DMSO/H_2O (Table 2, entries 1 to 4). It was found that the best results were

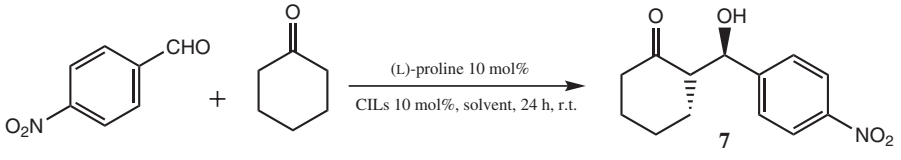


Scheme 2. (L)-proline-catalyzed aldol reaction of aromatic aldehyde with acetone.

Table 1. (L)-Proline-catalyzed aldol reaction of aromatic aldehyde with acetone

entry	4-(R)	(L)-Proline / molar ratio	Product	CILs / molar ratio	Conv. / (%)[a]	Selec. / (%)[b]	*ee* / (%)[c]
1	4-$NO_2C_6H_4$	0	**5a**	7.5% **2b**	—	—	—
2	4-$NO_2C_6H_4$	5%	**5a**	7.5% **2b**	26	95	73
3	4-$NO_2C_6H_4$	10%	**5a**	7.5% **2b**	64	99	75
4	4-$NO_2C_6H_4$	30%	**5a**	7.5% **2b**	96	> 99	74
					— [i]	— [i]	71[f]
					— [i]	— [i]	69[g]
					— [i]	— [i]	69[h]
5	4-$NO_2C_6H_4$	30%	**5a**	0	97[d]	> 99[d]	66[d]
6	4-$NO_2C_6H_4$	30%	**5a**	7.5% **2b**	97[e]	> 99[e]	76[e]
7	4-$NO_2C_6H_4$	30%	**5a**	1% **2b**	96	98	69
8	4-$NO_2C_6H_4$	30%	**5a**	5% **2b**	97	96	71
9	2-$NO_2C_6H_4$	30%	**5b**	7.5% **2b**	98	> 99	79
10	2-$NO_2C_6H_4$	30%	**5b**	0	98[d]	> 99[d]	72[d]
11	2-$NO_2C_6H_4$	30%	**5b**	7.5% **3a**	97	> 99	81
12	2-$NO_2C_6H_4$	30%	**5b**	7.5% **3b**	97	> 99	81
13	2-$NO_2C_6H_4$	30%	**5b**	7.5% **2b**	53[e]	> 99[e]	84[e]
14	3-$NO_2C_6H_4$	30%	**5c**	7.5% **2b**	93	98	72
15	3-$NO_2C_6H_4$	30%	**5c**	0	91[d]	> 99[d]	68[d]
16	C_6H_5	30%	**5d**	7.5% **2b**	85	72	65
17	C_6H_5	30%	**5d**	0	80	61	64[d]
18	4-$CH_3C_6H_5$	30%	**5e**	7.5% **2b**	84	69	70
19	4-$CH_3C_6H_5$	30%	**5e**	0	65[d]	82[d]	64[d]
20	4-FC_6H_4	30%	**5f**	7.5% **2b**	98	> 99	70
21	4-FC_6H_4	30%	**5f**	0	98[d]	> 99[d]	67[d]
22	4-FC_6H_4	30%	**5f**	7.5% **2a**	97	> 99	70
23	4-FC_6H_4	30%	**5f**	7.5% **2c**	98	> 99	71
24	4-FC_6H_4	30%	**5f**	7.5% **2d**	96	> 99	69
25	4-FC_6H_4	30%	**5f**	7.5% **2e**	98	> 99	70
26	4-FC_6H_4	30%	**5f**	7.5% **2f**	97	> 99	69
27	4-ClC_6H_4	30%	**5g**	7.5% **2b**	90	88	71
28	4-ClC_6H_4	30%	**5g**	0	85[d]	88[d]	68[d]
29	4-BrC_6H_4	30%	**5h**	7.5% **2b**	92	89	70
30	4-BrC_6H_4	30%	**5h**	0	90[d]	86[d]	67[d]

[a]Based on the aldehyde recovery after column chromatography. [b]Determined by ^{1}H NMR. [c]Determined by HPLC. [d]Comparison results with (L)-proline as catalyst. [e]The reaction temperature is –15 °C. [f-h]Second, third, forth reuse of the CILs and catalysts, respectively. [i]Not detected.



Scheme 3. CILs as additives for direct aldol reactions between 4-nitrobenzaldehyde and cyclohexanone.

Table 2. CILs as additives for direct aldol reactions between 4-nitrobenzaldehyde and cyclohexanone

entry	Solvent [DMSO:H_2O][a]	No additives			Assisted by CILs			
		Yield / (%)[b]	dr[syn:anti][c]	*ee* / (%)[d]	CILs	Yield / (%)[b]	dr[syn:anti][c]	*ee* / (%)[d]
1	95:5	20	95:5	86	**2b**	60	99:1	93
2	90:10	35	94:6	92	**2b**	85	> 99:1	97
3	80:20	80	93:7	77	**2b**	90	> 99:1	98
4	70:30	60	92:8	73	**2b**	55	98:2	97
5	80:20				**2a**	85	97:3	98
6	80:20				**2c**	87	> 99:1	97
7	80:20				**2d**	85	98:2	97
8	80:20				**2e**	88	> 99:1	98
9	80:20				**2f**	86	> 99:1	98

[a]Volume ratio of DMSO and H_2O. [b]Based on the aldehyde recovery after column chromatography. [c]Determined by ^{1}H NMR. [d]Determined by HPLC.

obtained when the DMSO:H_2O = 4:1(Table 2, entry 3). The other CILs were also used as additives in this catalytic system (Table 2, entries 5 to 9). All of them showed superior co-catalytic effect in aldol reactions.

Conclusions

In summary, a novel asymmetric catalytic system with *N*-substituted pyrrolidine-ionic liquids as chiral additives was developed and their potentials of providing chiral environment by direct asymmetric aldol reaction were demonstrated. This catalytic system can lead to high yields (up to 88%), good stereoselectivities (> 99:1) and superior enantiomeric excesses (up to 98%) for syn-selective aldol reactions. This is the first use of chiral environment as chiral source to lead asymmetric reaction to our knowledge. Further studies on this kind of CILs in other asymmetric reactions are underway in our laboratory.

Experimental

General procedure for chiral ionic liquid (CILs) synthesis

(L)-Proline (0.1 mol) and 1-bromoalkane (0.3 mol) were mixed in a 100 mL round bottom flask with acetonitrile as solvent at 70 °C for 2 days in an inert atmosphere. After filtering, the solvent was removed by distillation and the raw products were washed with ether for several times. After purified by column chromatography ($CHCl_3$:EtOH = 20:1), the product was dried under vacuum for 5 h to afford the chiral ionic liquids (CILs) **2a**-**2f**.

2b (0.02 mol) and silver nitrate (or tetrafluoroborate ammonium) (0.02 mol) were stirred at room temperature for 4 h with chloroform as solvent. After filtering, the solvent was distilled off and the desired raw chiral ionic liquids (CILs) **3a** and **3b** were obtained. After purified by column chromatography ($CHCl_3$:EtOH = 20:1), the product was dried under vacuum for 5 h to afford the final chiral ionic liquids (CILs) **3a** and **3b**.

Characterization of CILs

*CIL **2a***

^{1}H NMR (300 MHz, D_2O) δ 4.19 (dq, 3H, *J* 21.3, 7.3), 3.63 (ddd, 1H, *J* 11.6, 7.7, 4.3), 3.28 (dq, 1H, *J* 14.6, 7.3), 3.17-2.97 (m, 2H), 2.29 (ddd, 2H, *J* 92.6, 11.4, 6.5), 2.05-2.00 (m, 1H), 1.87 (ddd, 1H, *J* 19.6, 14.4, 12.9), 1.15 (dd, 6H, *J* 13.2, 7.1). ^{13}C NMR (75 MHz, D_2O) δ 12.2, 15.1, 24.2, 30.0, 52.7, 56.4, 65.9, 68.3, 171.4).

*CIL **2b***

^{1}H NMR (300 MHz, D_2O) δ 4.42-4.22 (1 H, m), 4.22-4.03 (2 H, m), 3.80-3.57 (m, 1H), 3.33-2.96 (m, 3H), 2.65-2.21 (m, 1H), 2.15-1.76 (m, 3H), 1.69-1.39 (m, 4H), 1.24 (dtd, 4H, *J* 14.8, 7.4, 3.1), 0.76 (td, 5H, *J* 7.3, 2.3). ^{13}C NMR (75 MHz, D_2O) δ 15.7, 15.8, 21.3, 22.0, 25.2, 30.0, 30.9, 31.0, 32.6, 58.1, 58.5, 69.7, 70.4, 172.3.

*CIL **3a***

^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.78-0.92 (m, 6H, CH_3), 1.22-1.38 (m, 4H, CH_2), 1.48-1.78 (m, 4H, CH_2), 2.02-2.26 (m, 3H, CH_2), 2.42-2.56 (m, 1H, CH_2), 3.14-3.46 (m, 3H, NCH_2), 3.84 (s, 1H, NCH_2), 4.14 (t, 2H, *J* 6 Hz, NCH_2), 4.29 (t, 1H, *J* 8.4 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 13.7, 13.8, 19.2, 20.2, 22.5, 28.2, 30.5, 30.5, 55.3, 56.4, 66.9, 67.6, 167.5.

*CIL **3b***

^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.68-0.94 (m, 6H, CH_3), 1.14-1.40 (m, 4H, CH_2), 1.42-1.80 (m, 4H, CH_2),

1.97-2.24 (m, 3H, CH_2), 2.36-2.52 (m, 1H, CH_2), 3.06-3.40 (m, 3H, NCH_2), 3.79 (d, 1H, *J* 4.5 Hz, NCH_2), 4.12 (t, 2H, *J* 6.6 Hz, NCH_2), 4.20-4.32 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 13.5, 13.7, 19.1, 19.7, 22.9, 27.9, 28.7, 30.4, 56.1, 56.4, 67.3, 67.4, 168.8.

*CIL **2c***

^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.68-0.84 (m, 6H, CH_3), 1.08-1.36 (m, 12H, CH_2), 1.44-1.88 (m, 4H, CH_2), 2.02-2.21 (m, 3H, CH_2), 2.42-2.62 (m, 1H, CH_2), 3.13-3.40 (m, 3H, NCH_2), 3.71 (s, 1H, NCH_2), 4.10 (t, 2H, *J* 6.6 Hz, NCH_2), 4.26-4.38 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 14.0, 14.0, 22.1, 22.5, 22.6, 25.6, 25.9, 26.7, 28.5, 28.6, 31.3, 31.5, 53.7, 53.7, 64.9, 67.0, 168.1.

*CIL **2d***

^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.72-0.88 (m, 6H, CH_3), 1.05-1.38 (m, 20H, CH_2), 1.52-1.94 (m, 4H, CH_2), 2.15 (d, 3H, *J* 3.9 Hz, CH_2), 2.47-2.63 (m, 1H, CH_2), 3.13-3.50 (m, 3H, NCH_2), 3.52-3.74 (m, 1H, NCH_2), 4.14 (t, 2H, *J* 6.9 Hz, NCH_2), 4.23-4.38 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 14.2, 14.2, 22.1, 22.7, 22.7, 25.9, 25.9, 27.0, 28.5, 28.5, 29.3, 29.3, 29.3, 29.3, 31.8, 31.9, 53.9, 53.9, 66.9, 66.9, 168.1.

*CIL **2e***

^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.61-0.74 (m, 6H, CH_3), 0.96-1.22 (m, 28H, CH_2), 1.40-1.80 (m, 4H, CH_2), 2.03 (d, 3H, *J* 5.4 Hz, CH_2), 2.45 (d, 1H, *J* 8.1 Hz, CH_2), 3.18-3.39 (m, 3H, NCH_2), 3.70 (s, 1H, NCH_2), 4.00 (t, 2H, *J* 6.6 Hz, NCH_2), 4.42-4.34 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 14.3, 14.3, 22.0, 22.8, 22.8, 26.0, 26.0, 27.1, 28.6, 28.6, 29.2, 29.2, 29.4, 29.4, 29.7, 29.7, 29.7, 29.7, 32.0, 32.0, 53.3, 53.3, 67.0, 67.0, 167.9.

*CIL **2f***

^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.78-0.97(m, 6H, CH_3), 1.05-1.40(m, 36H, CH_2), 1.48-1.98(m, 4H, CH_2), 1.98-2.42(s, 3H, CH_2), 2.60(s, 1H, CH_2), 3.06-3.38(m, 3H, NCH_2), 3.64(s, 1H, NCH_2), 4.04-4.18(m, 3H, NCH_2, CH), 4.20-4.29(m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 14.3, 14.3, 22.3, 22.8, 22.8, 26.0, 26.0, 26.9, 29.2, 29.2, 29.4, 29.4, 29.4, 29.4, 29.7, 29.7, 29.7, 29.7, 32.0, 32.0, 54.4, 54.4, 67.2, 67.2, 168.1.

General procedure for the aldol reactions

(L)-Proline (30 mol%) and the aromatic aldehyde (1 mmol) were added in the acetone (3 mL); after stirred for 1 min, chiral ionic liquids (CILs) (7.5 mol%) were added and the reaction mixture was stirred at room temperature (25 °C (± 3 °C)) for 24 h. The acetone was evaporated, the residue was extracted with diethyl ether (3 mL, three times), separated diethyl ether layer was collected, the residues were dried under vacuum at 40 °C during 5 h for the next cycle, the collected solvent was evaporated and the residues purified by chromatography on SiO_2-column (Petroleum ether:EtOAc = 3:1). All reaction products had the physical constants and NMR spectra in accord with the published data. The petroleum ether used was of boiling range 60-80 °C. Evaporation of solvent was performed at reduced pressure at 25 (±3) °C.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

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Supplementary Information

Novel Chiral Ionic Liquid (CIL) Assisted Selectivity Enhancement to (L)-Proline Catalyzed Asymmetric Aldol Reactions

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General remarks

^{1}H NMR spectra were recorded on a VARIAN Mercury 300 MHz spectrometer or VARIAN Mercury 600 MHz spectrometer. Chemical shifts are reported in ppm with the TMS as internal standard**.** The data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, brs = broad singlet, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded on a VARIAN Mercury 75 MHz or VARIAN Mercury 125 MHz spectrometer. Chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica gel-coated plates. Enantiomeric ratios were determined by HPLC, using a chiralpak AS-H column, a chiralpak AD-H column or a chiralcel OD-H column with hexane and *i*-PrOH as solvents. The configurations were assigned by comparison of the t_R with the reported data.[1,2]

Characterization of CILs

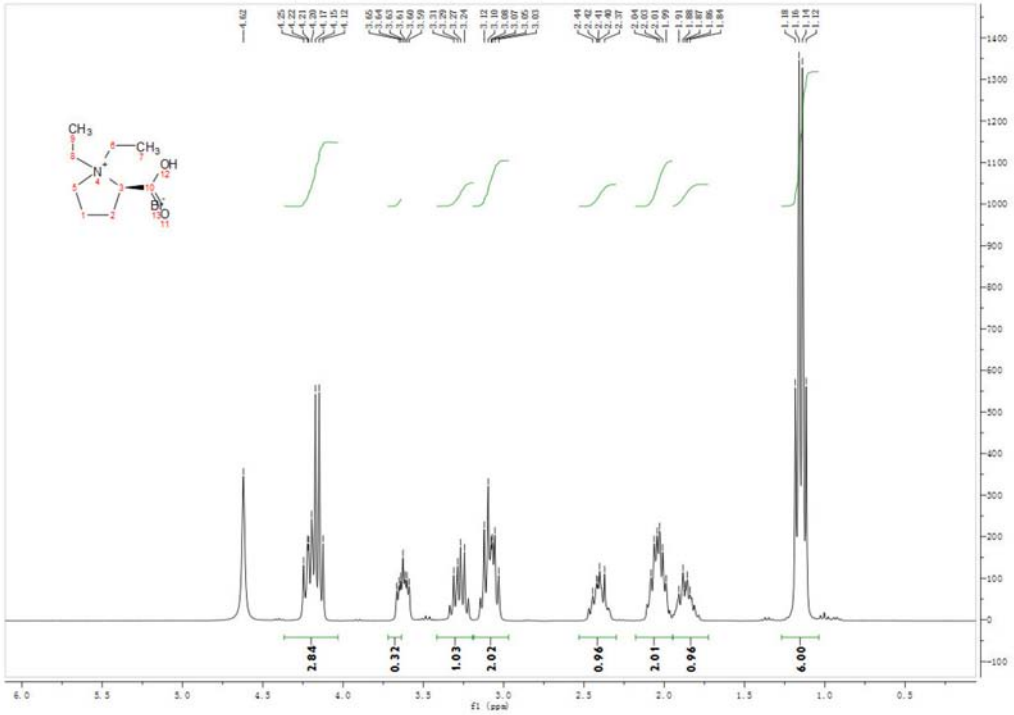

Figure S1. ^{1}H NMR (300 MHZ, D_2O) spectrum of **2a**.

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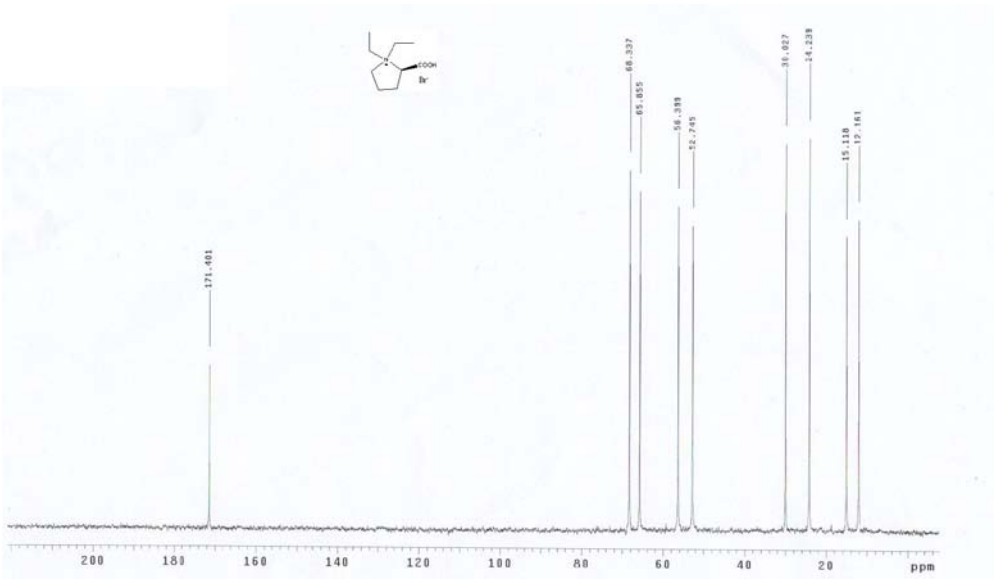


Figure S2. ^{13}C NMR (75 MHZ, D_2O) spectrum of **2a**.

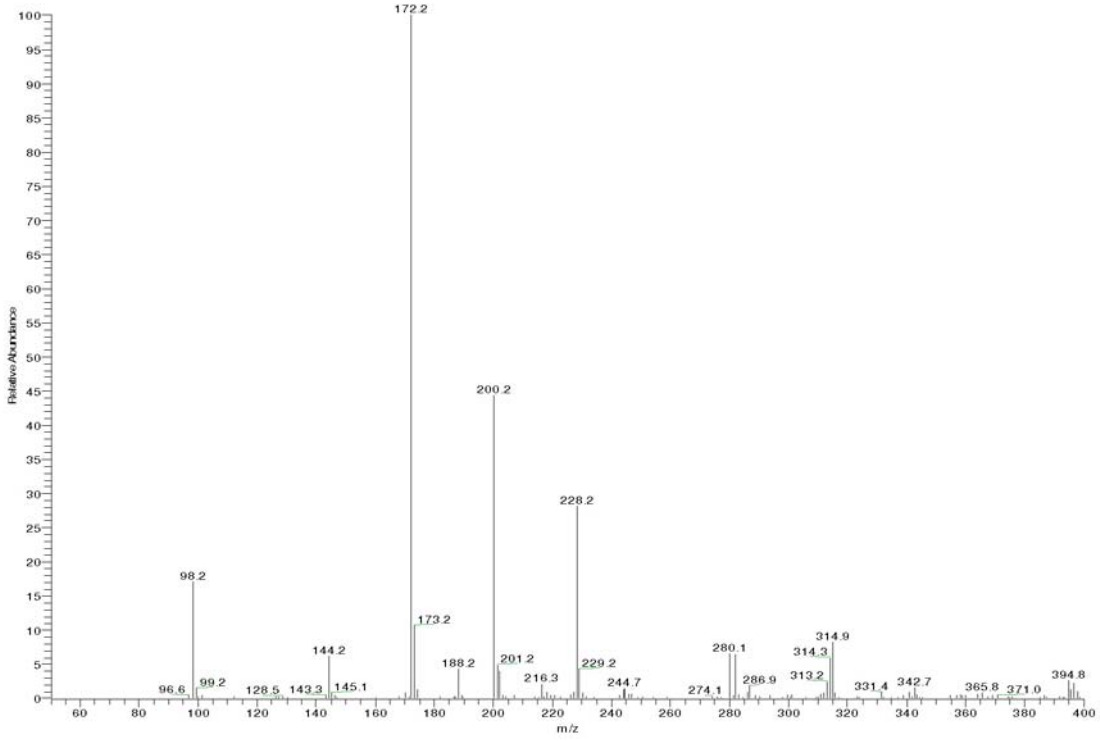


Figure S3. ESI-Mass spectrum of **2a**.

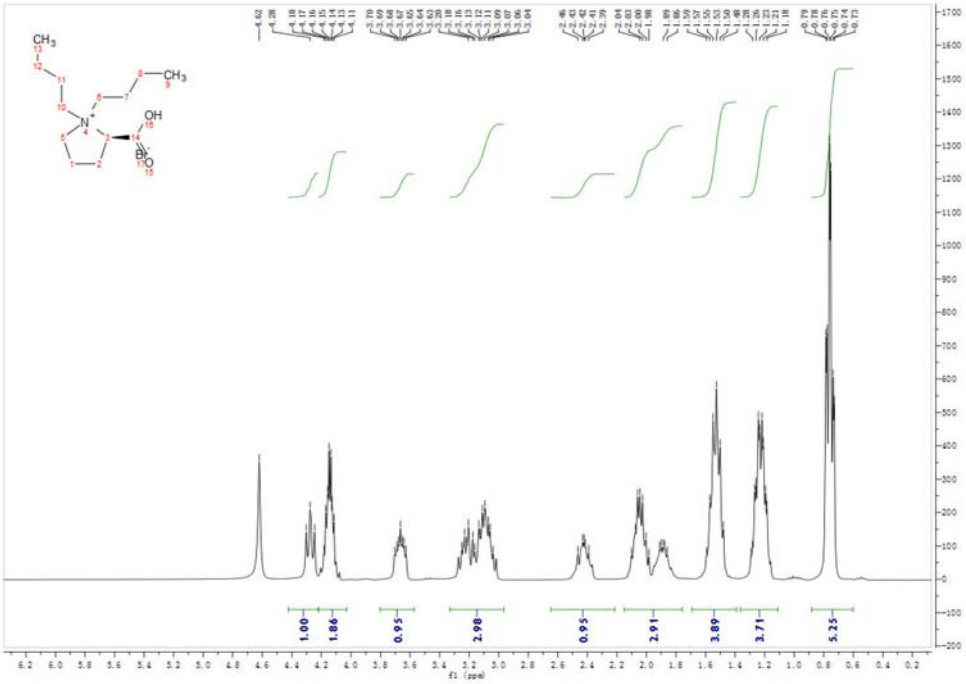


Figure S4. ^{1}H NMR (300 MHZ, D_2O) spectrum of **2b**.

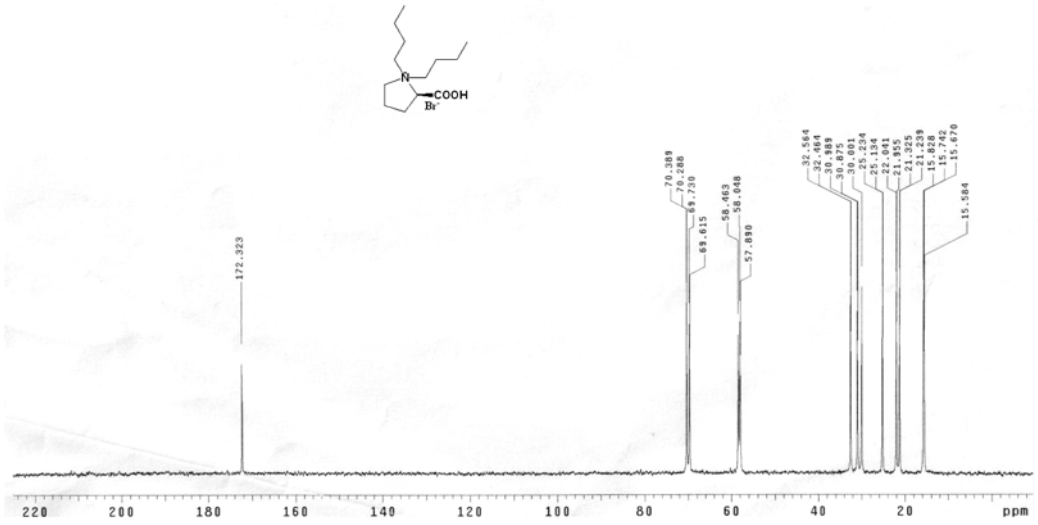


Figure S5. ^{13}C NMR (75 MHZ, D_2O) spectrum of **2b**.

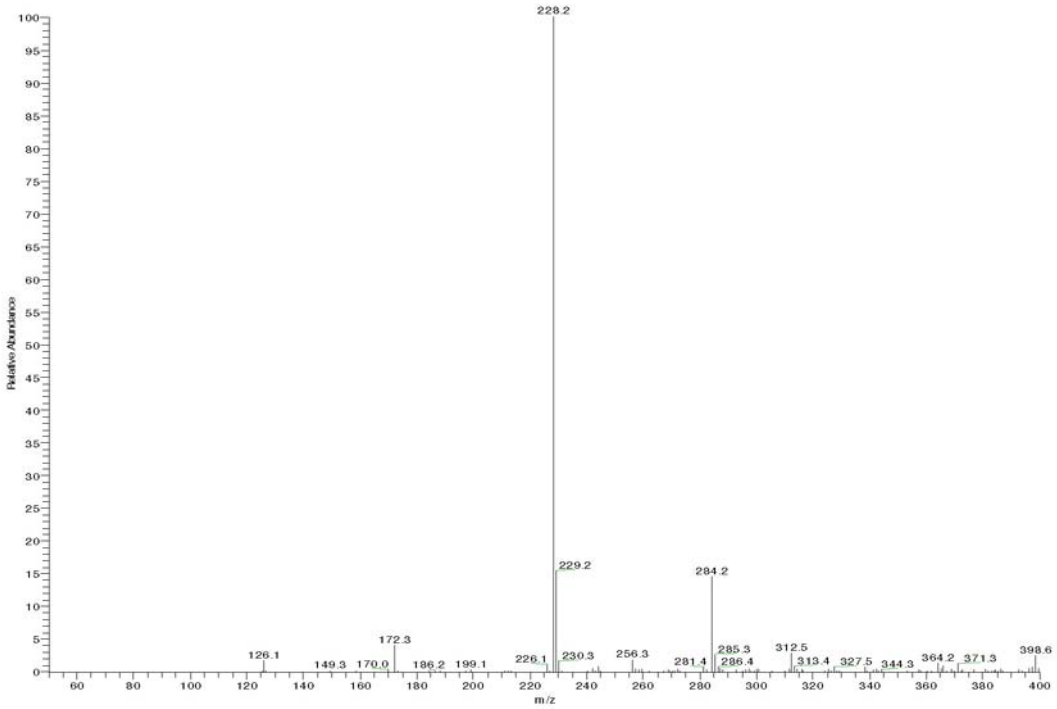


Figure S6. ESI-Mass spectrum of **2b**.

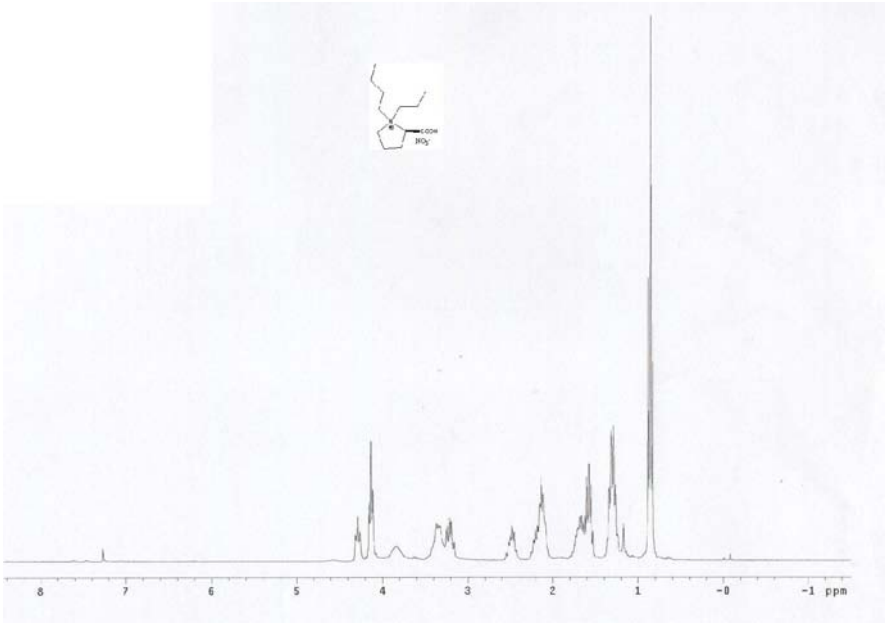


Figure S7. ^{1}H NMR (300 MHZ, $CDCl_3$) spectrum of **3a**.

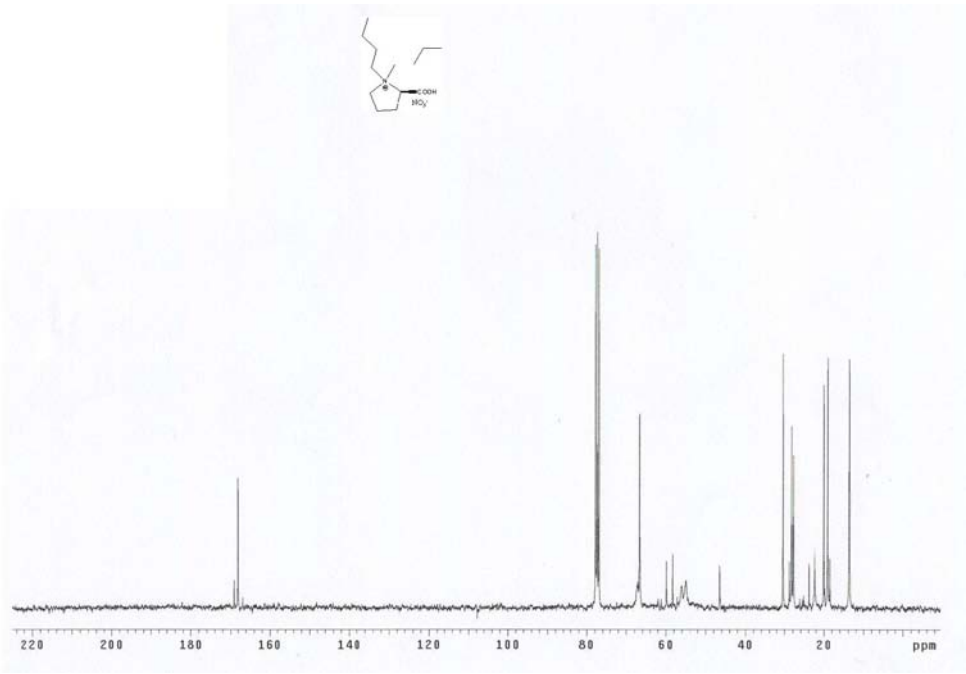


Figure S8. ^{13}C NMR (75 MHZ, $CDCl_3$) spectrum of **3a**.

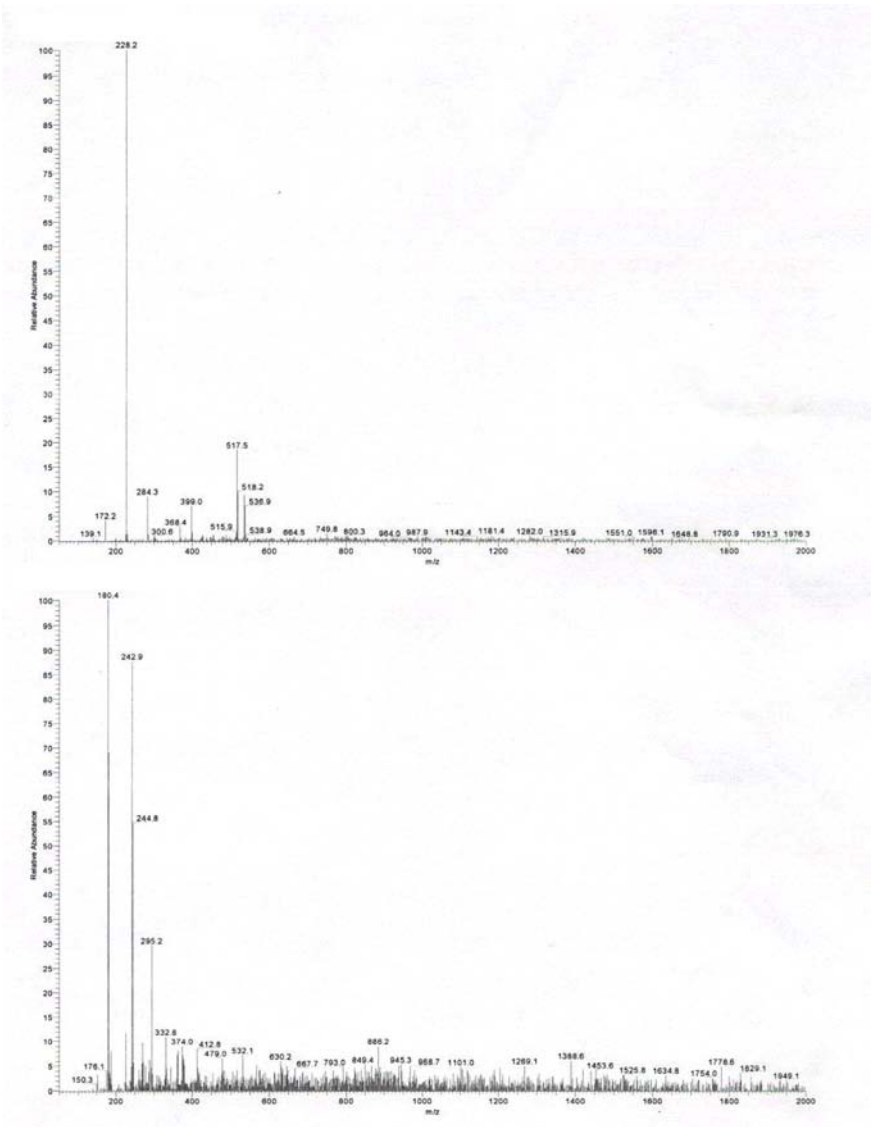


Figure S9. ESI-Mass spectrum of **3a**.

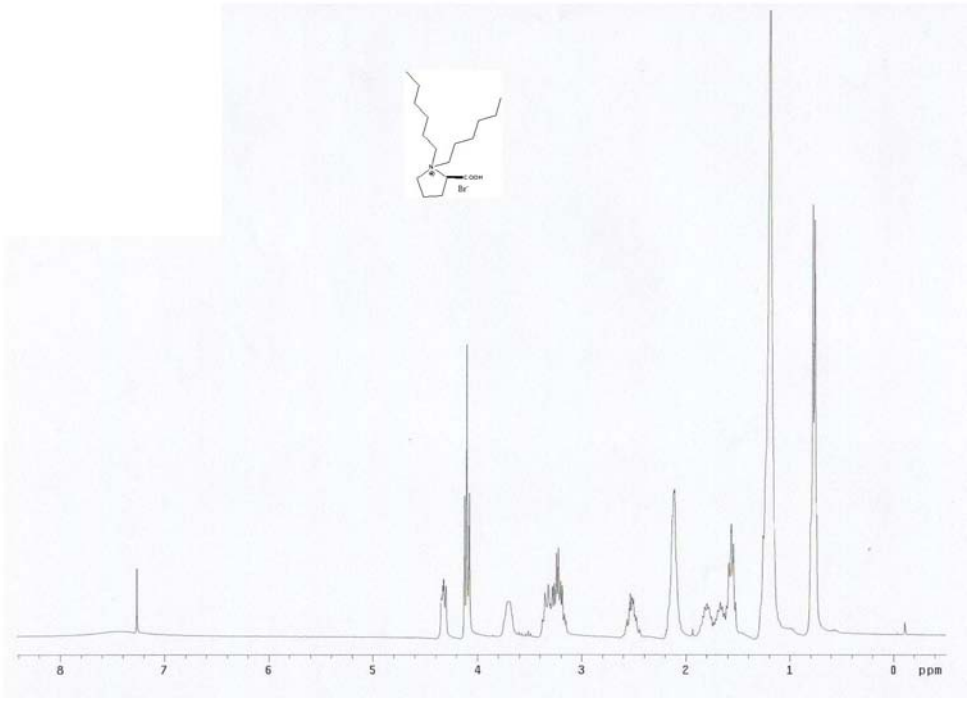


Figure S10. ^{1}H NMR (300 MHZ, $CDCl_3$) spectrum of **2c**.

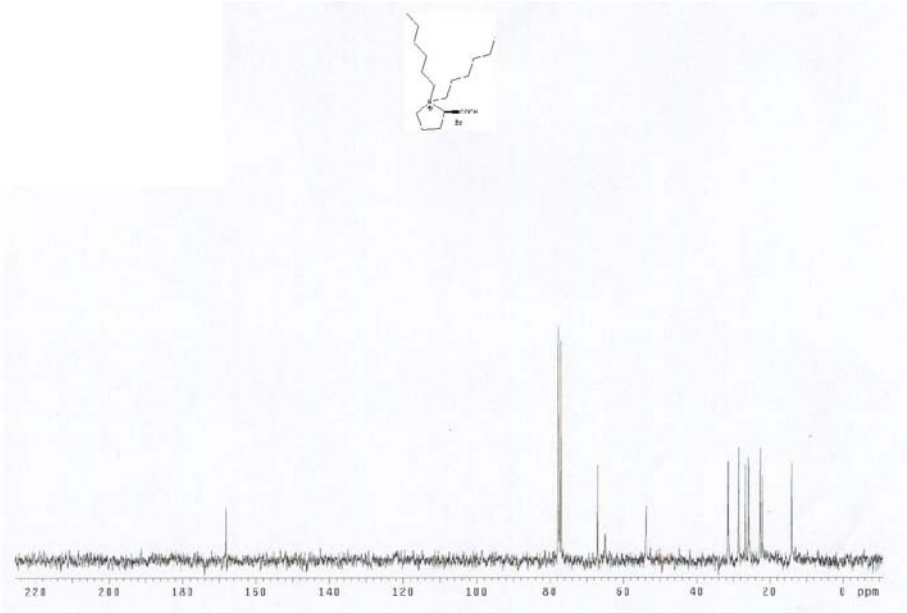


Figure S11. ^{13}C NMR (75 MHZ, $CDCl_3$) spectrum of **2c**.

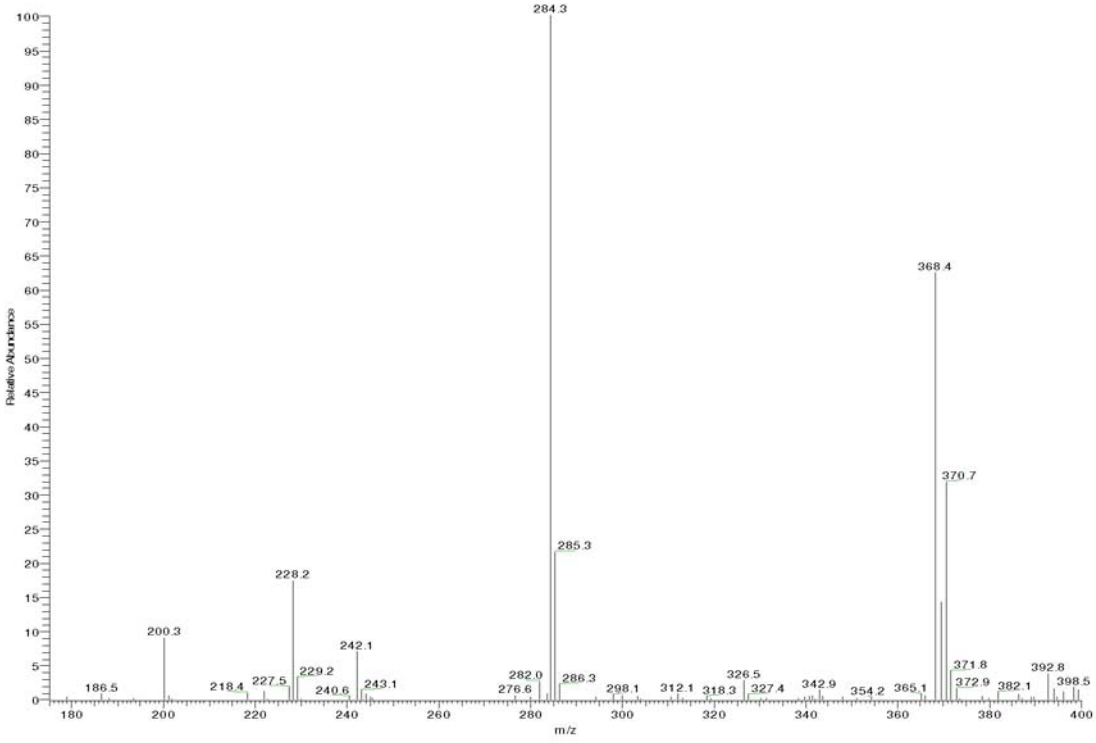


Figure S12. ESI-Mass spectrum of **2c**.

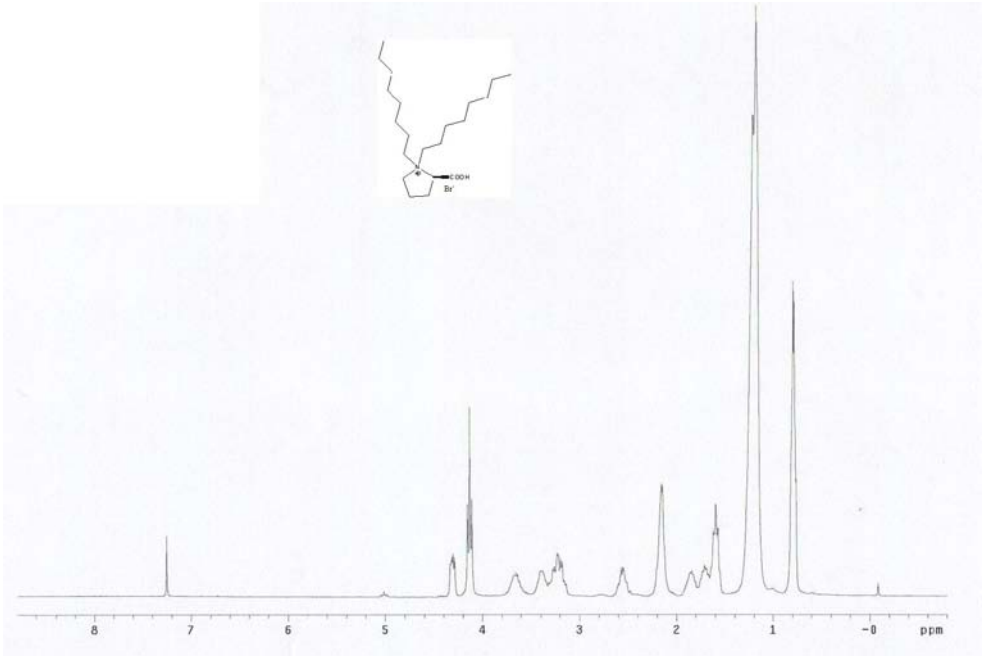


Figure S13. ^{1}H NMR (300 MHZ, $CDCl_3$) spectrum of **2d**.

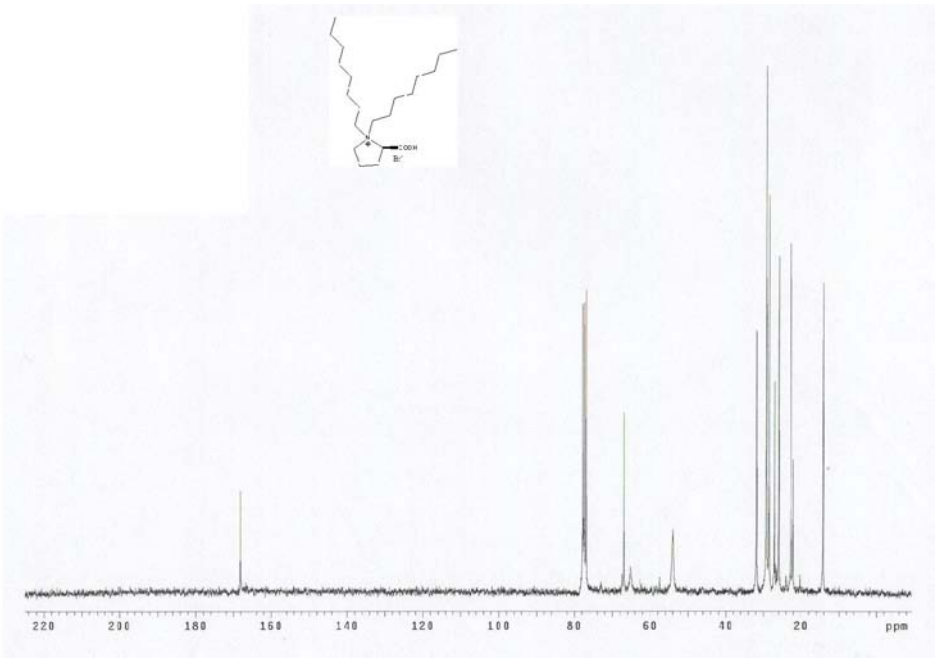


Figure S14. ^{13}C NMR (75 MHZ, $CDCl_3$) spectrum of **2d**.

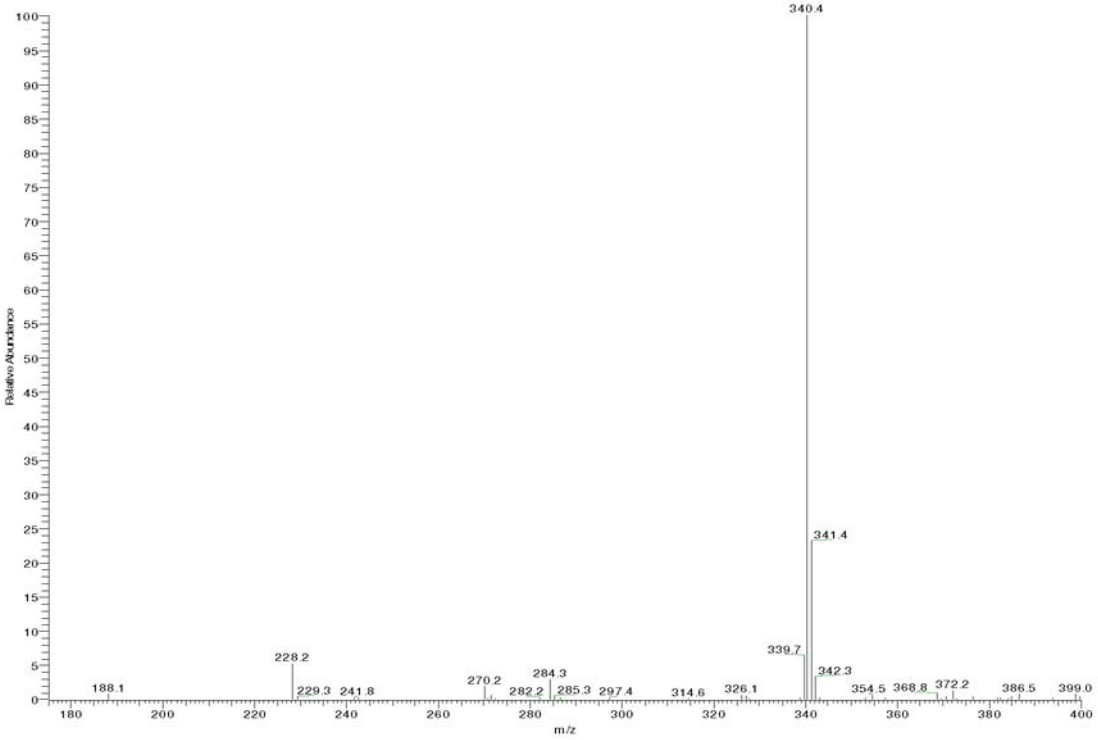


Figure S15. ESI-Mass spectrum of **2d**.

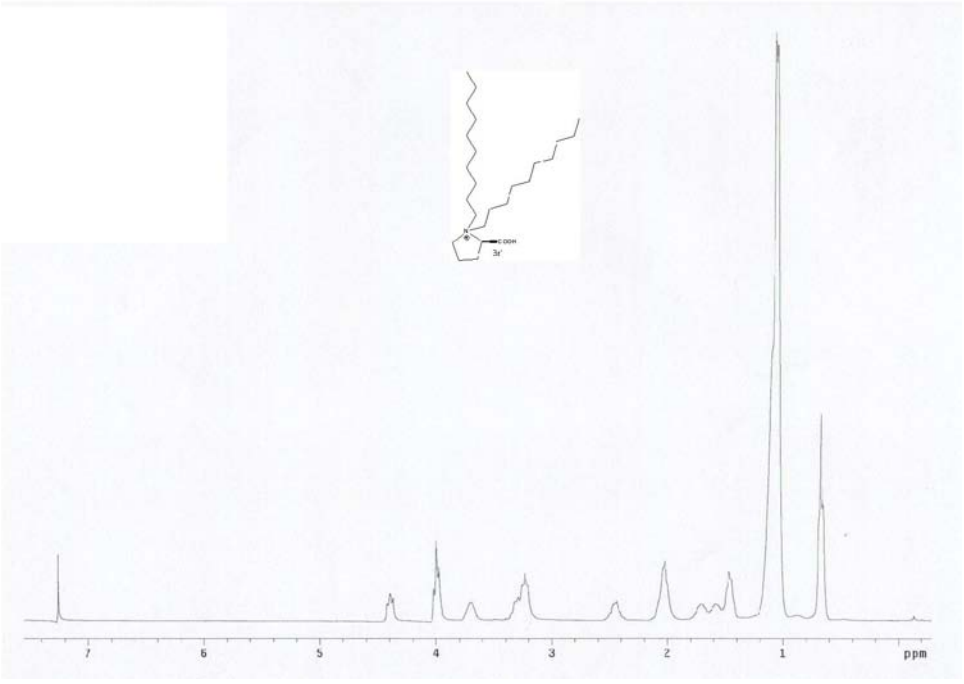


Figure S16. ^{1}H NMR (300 MHZ, $CDCl_3$) spectrum of **2e**.

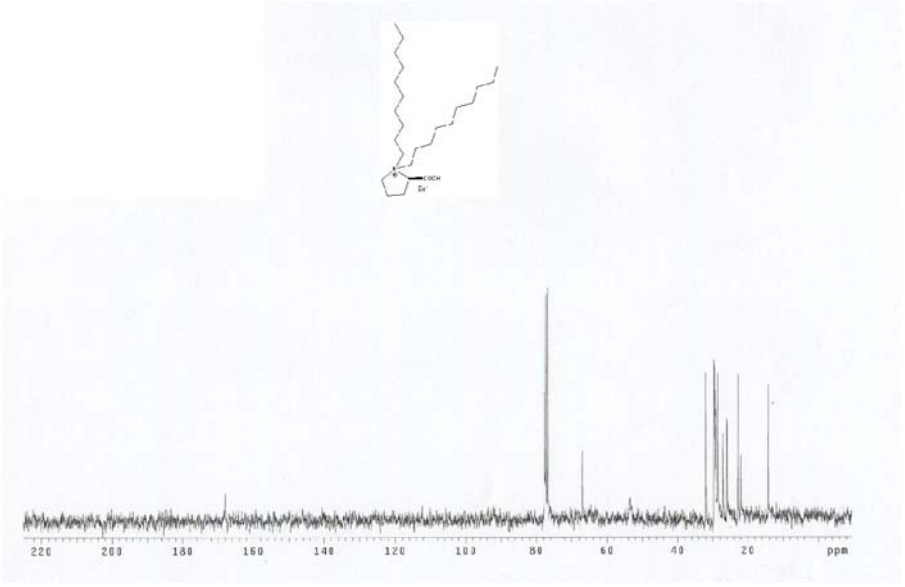


Figure S17. ^{13}C NMR (75 MHZ, $CDCl_3$) spectrum of **2e**.

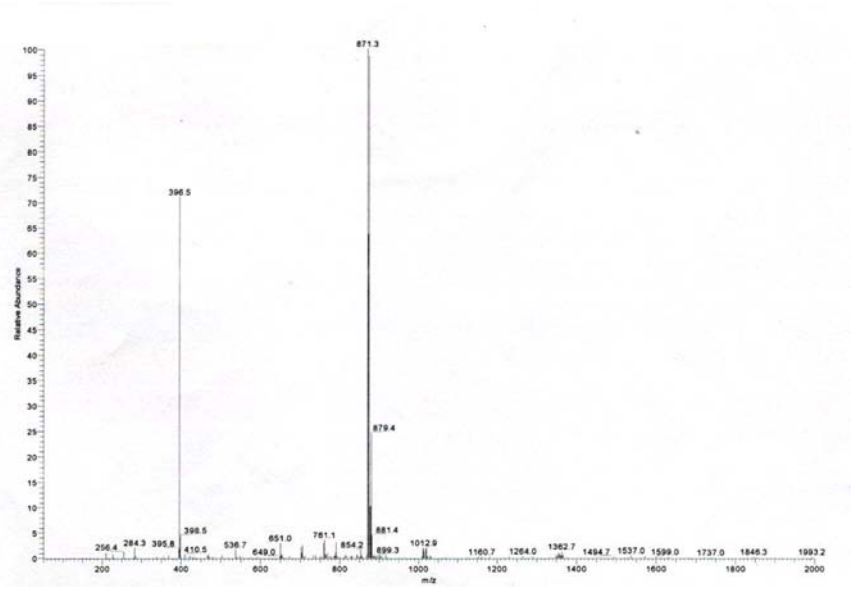


Figure S18. ESI-Mass spectrum of **2e**.

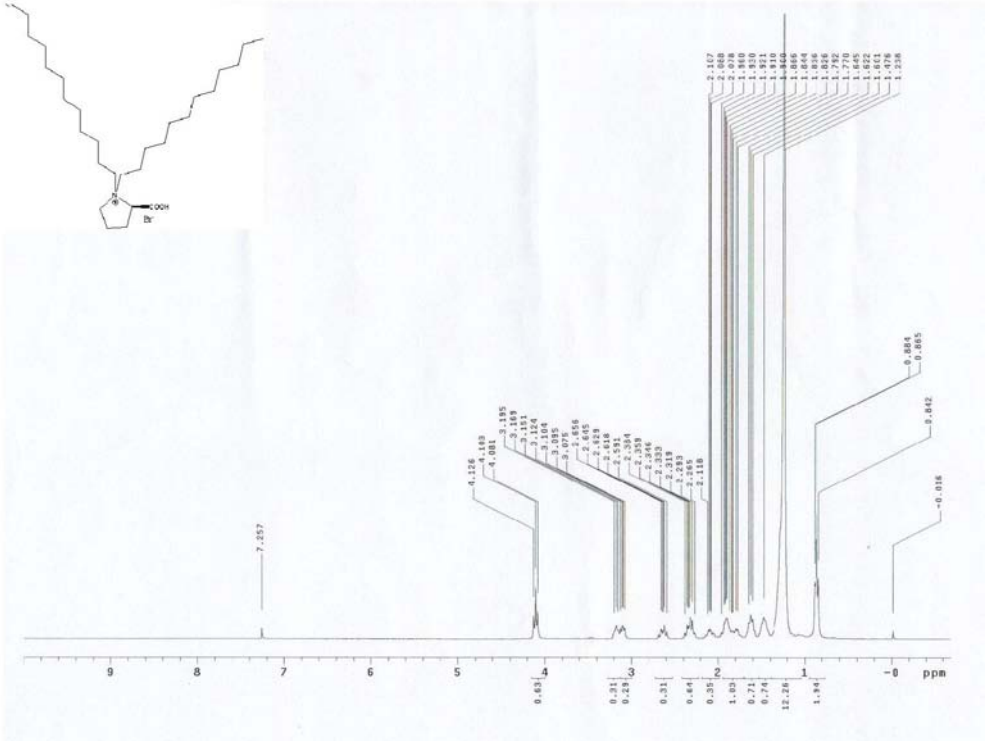


Figure S19. ^{1}H NMR (300 MHZ, $CDCl_3$) spectrum of **2f**.

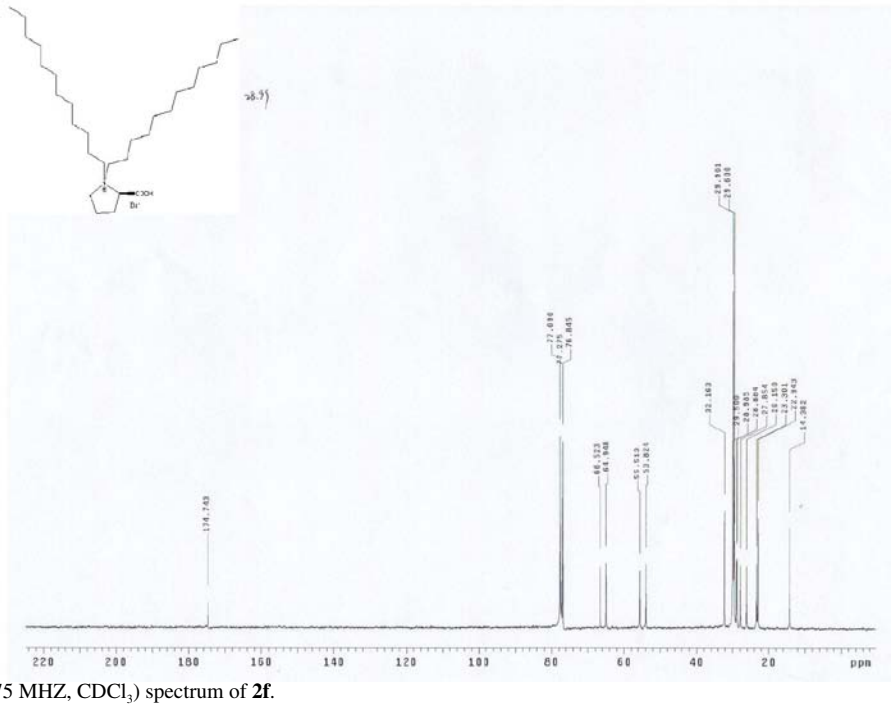


Figure S20. ^{13}C NMR (75 MHZ, $CDCl_3$) spectrum of **2f**.

Characterization of aldol products

NMR data

All available reagents and solvents were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were conducted on Mercury VX-300 (Varian 300 MHz) or Unity-Inova 600 (Varian 600 MHz) spectrometer. Chemical shifts are expressed in ppm use TMS as internal standard and coupling constants are reported in Hz.

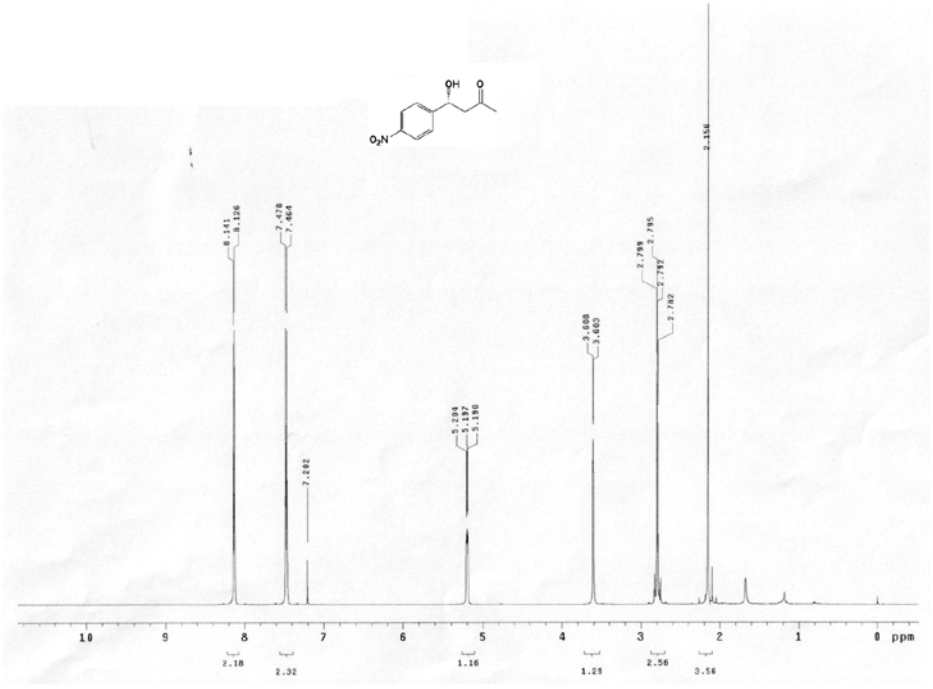


Figure S21. ^{1}H NMR (600 MHZ, $CDCl_3$) spectrum of **5a**.

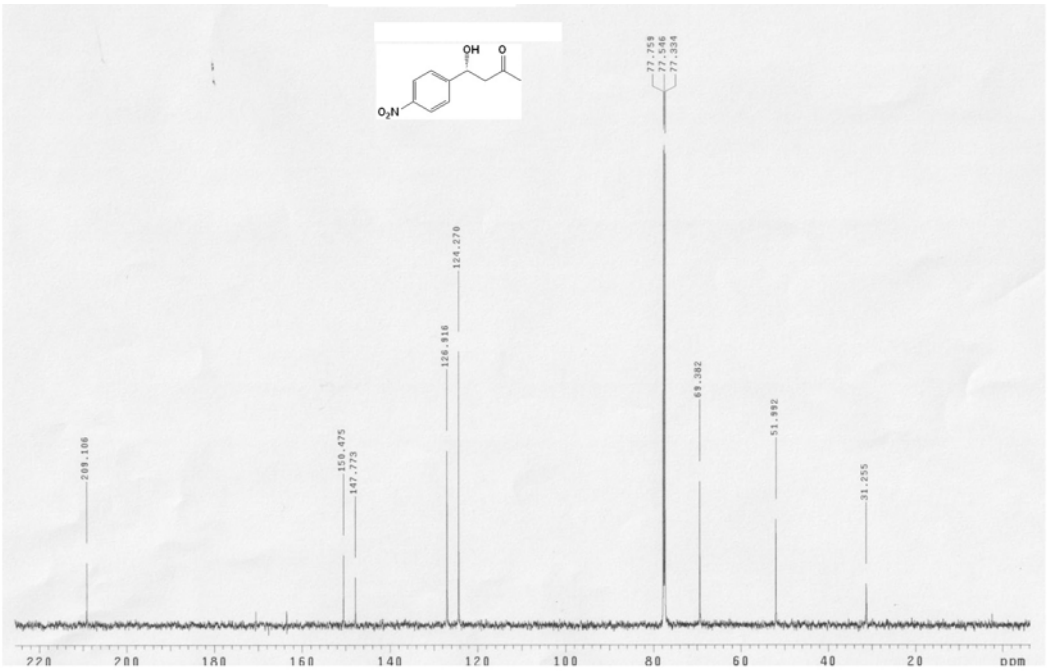


Figure S22. ^{13}C NMR (125 MHZ, $CDCl_3$) spectrum of **5a**.

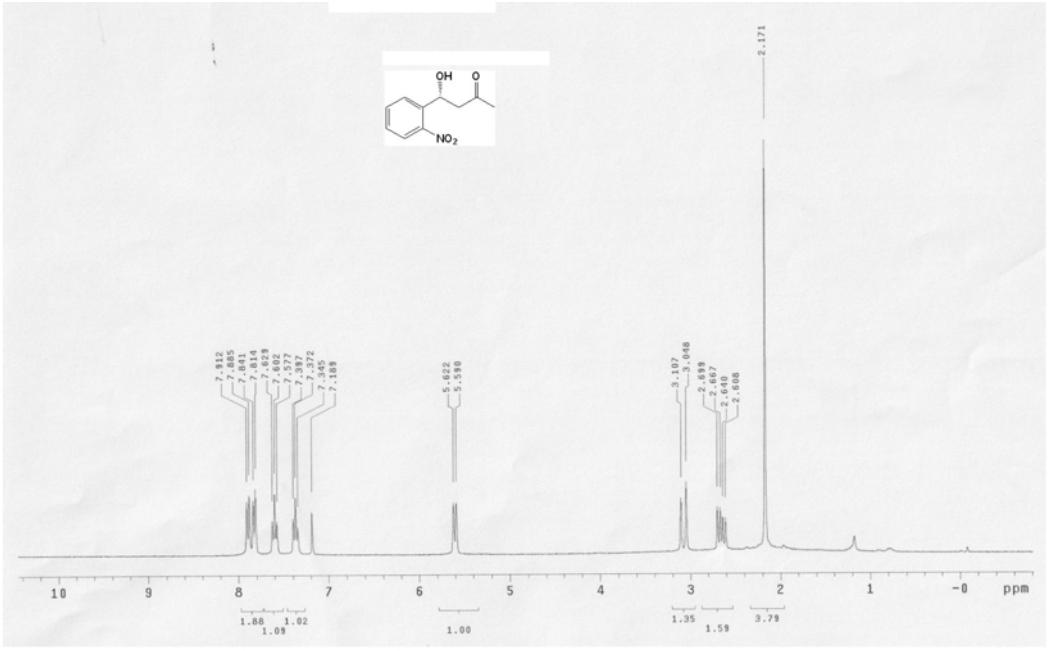


Figure S23. ^{1}H NMR (300 MHZ, $CDCl_3$) spectrum of **5b**.

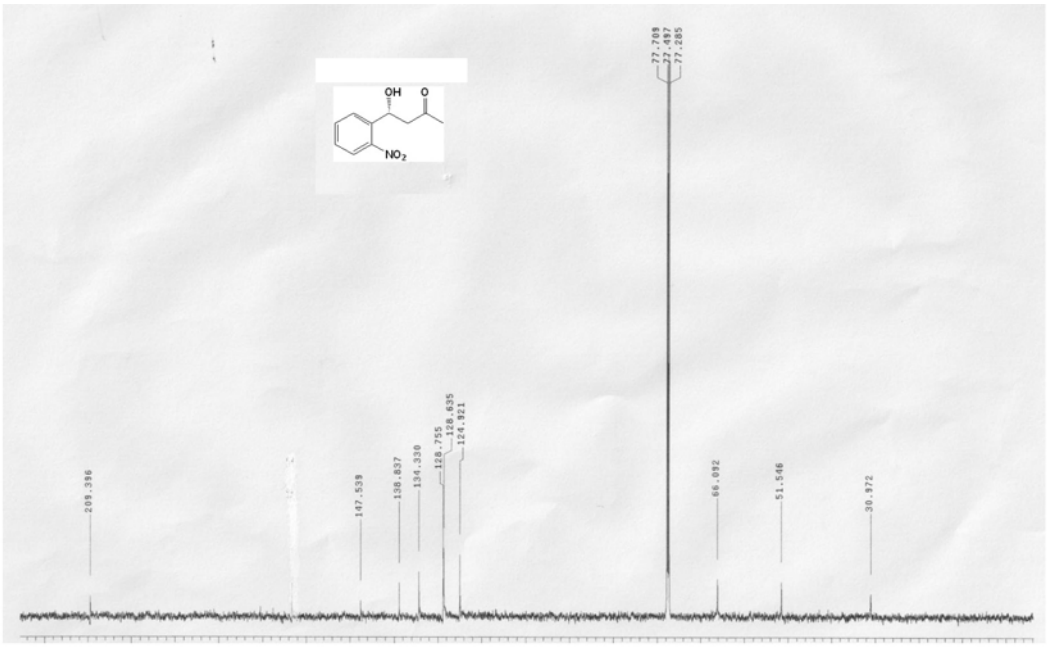


Figure S24. ^{13}C NMR (125 MHZ, $CDCl_3$) spectrum of **5b**.

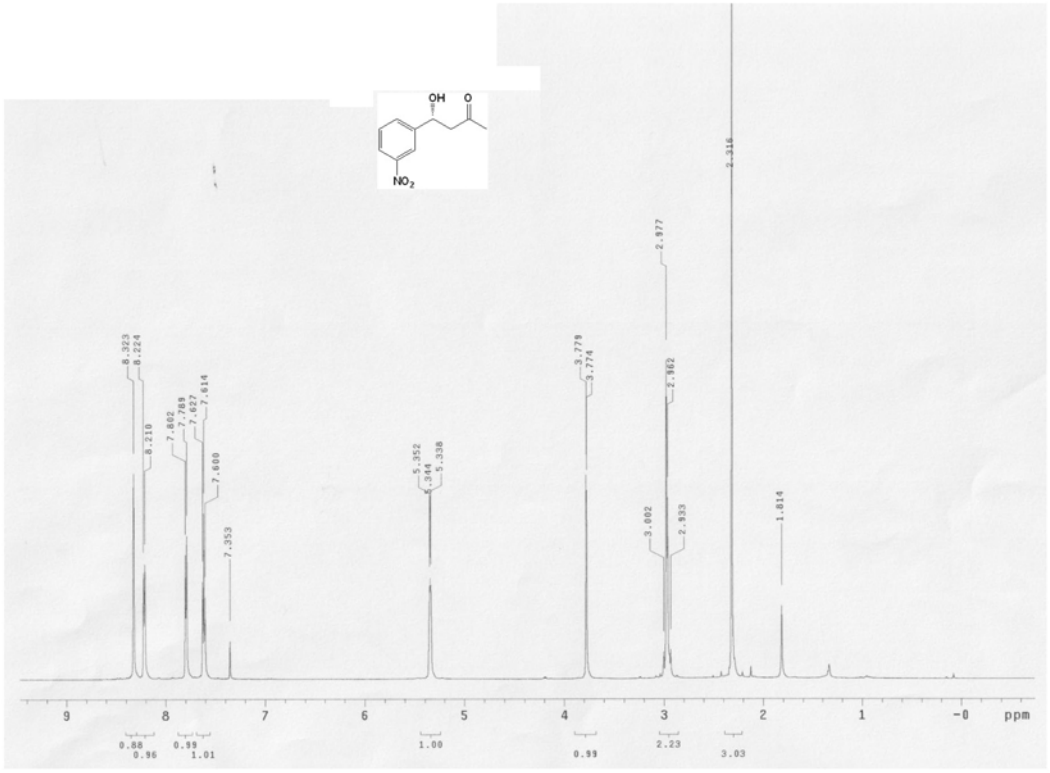


Figure S25. ^{1}H NMR (600 MHZ, $CDCl_3$) spectrum of **5c**.

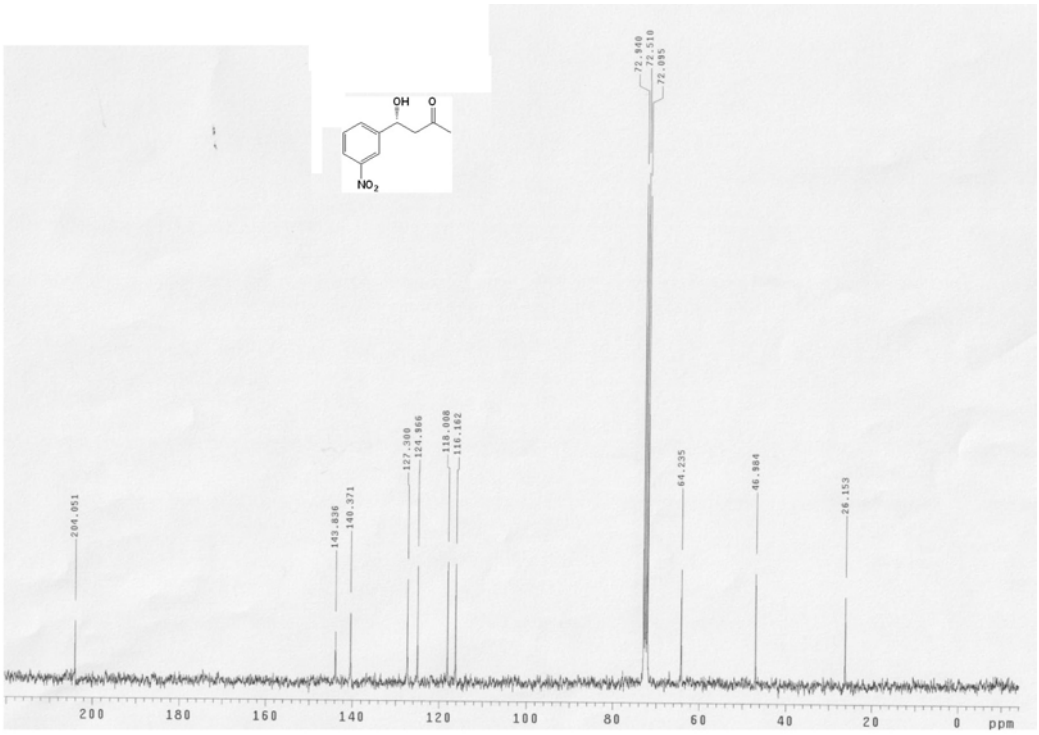


Figure S26. ^{13}C NMR (75 MHZ, $CDCl_3$) spectrum of **5c**.

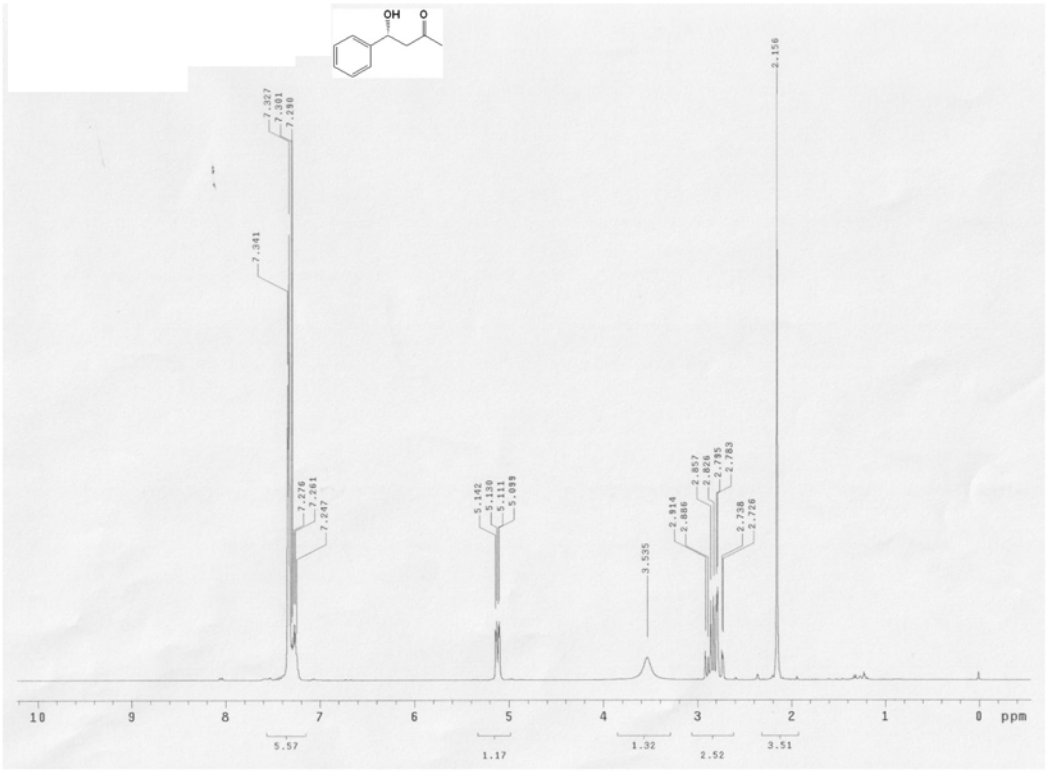


Figure S27. ^{1}H NMR (300 MHZ, $CDCl_3$) spectrum of **5d**.

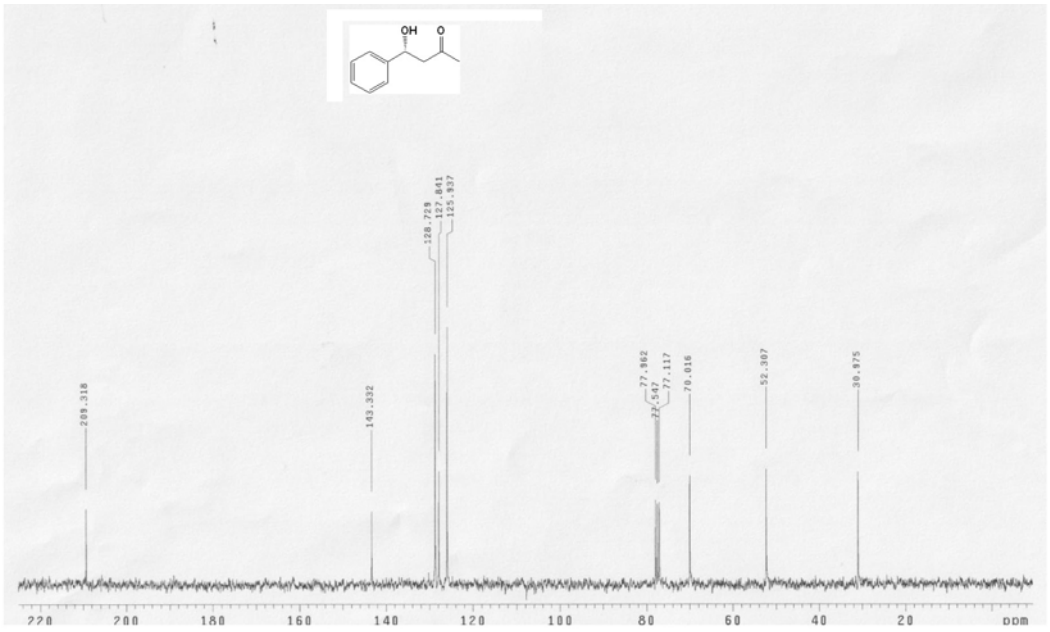


Figure S28. ^{13}C NMR (75 MHZ, $CDCl_3$) spectrum of **5d**.

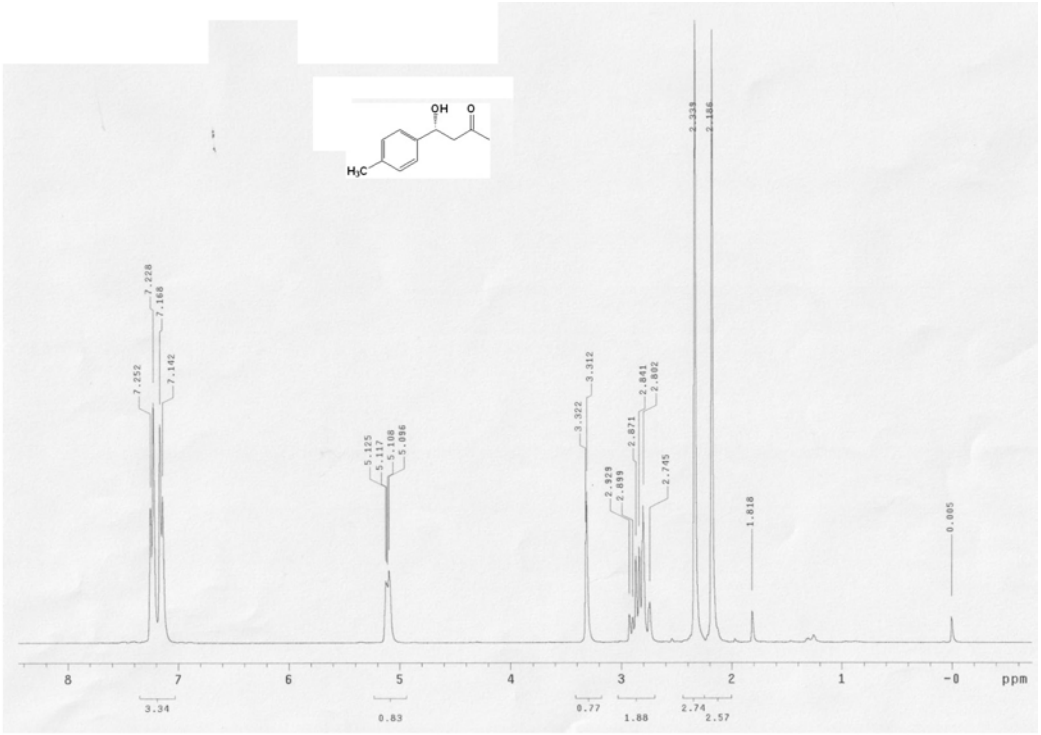


Figure S29. ^{1}H NMR (300 MHZ, $CDCl_3$) spectrum of **5e**.

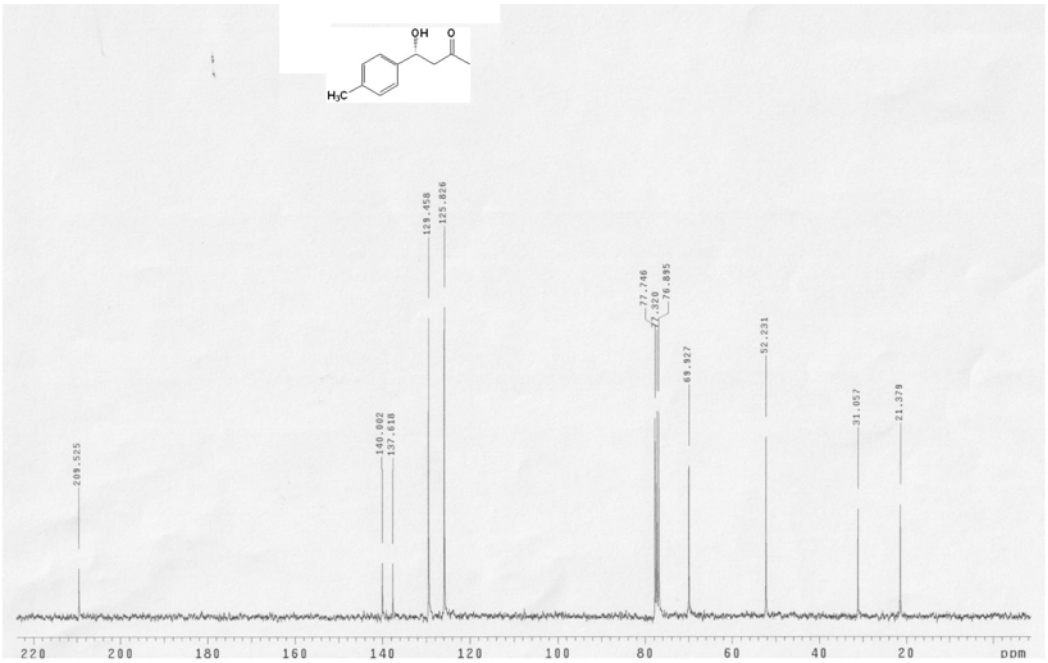


Figure S30. ^{13}C NMR (75 MHZ, $CDCl_3$) spectrum of **5e**.

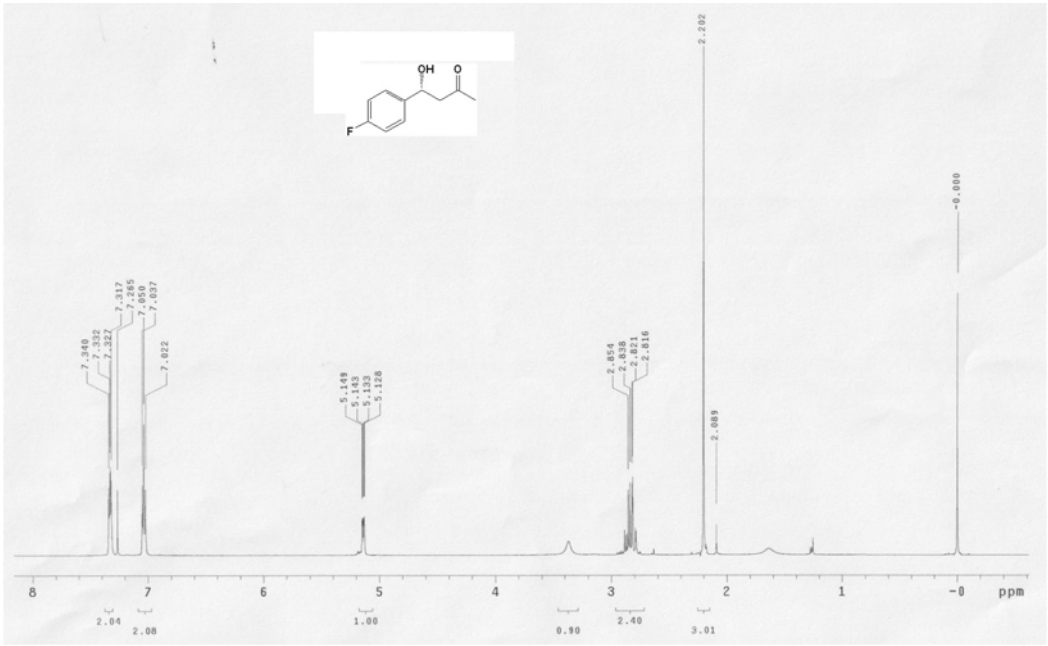


Figure S31. ^{1}H NMR (600 MHZ, $CDCl_3$) spectrum of **5f**.

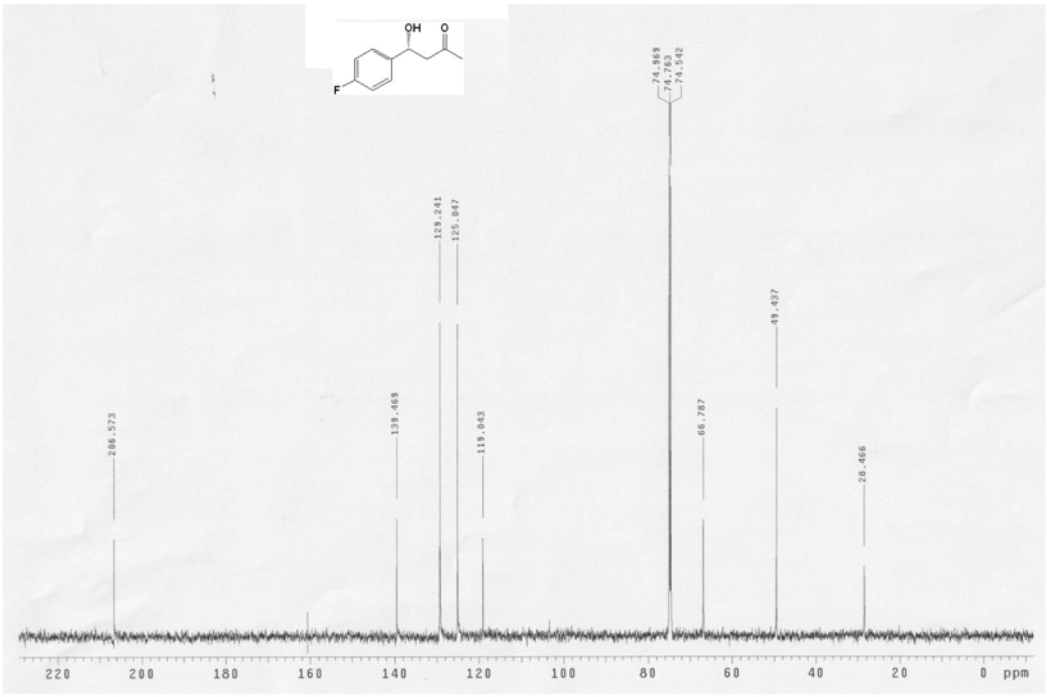


Figure S32. ^{13}C NMR (125 MHZ, $CDCl_3$) spectrum of **5f**.

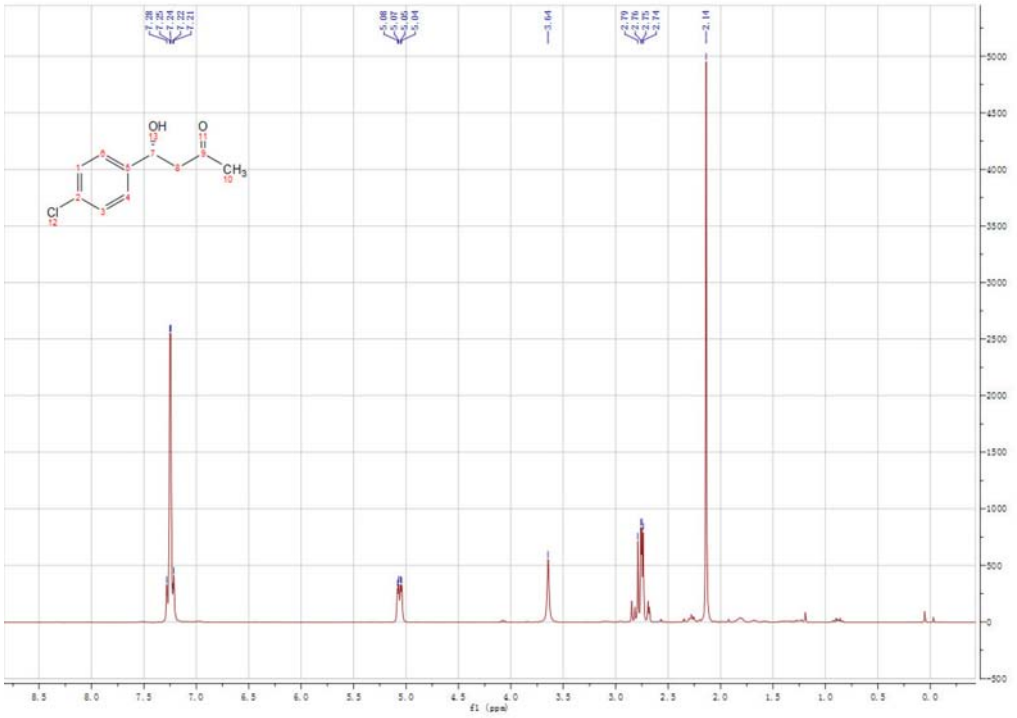


Figure S33. ^{1}H NMR (300 MHZ, $CDCl_3$) spectrum of **5g**.

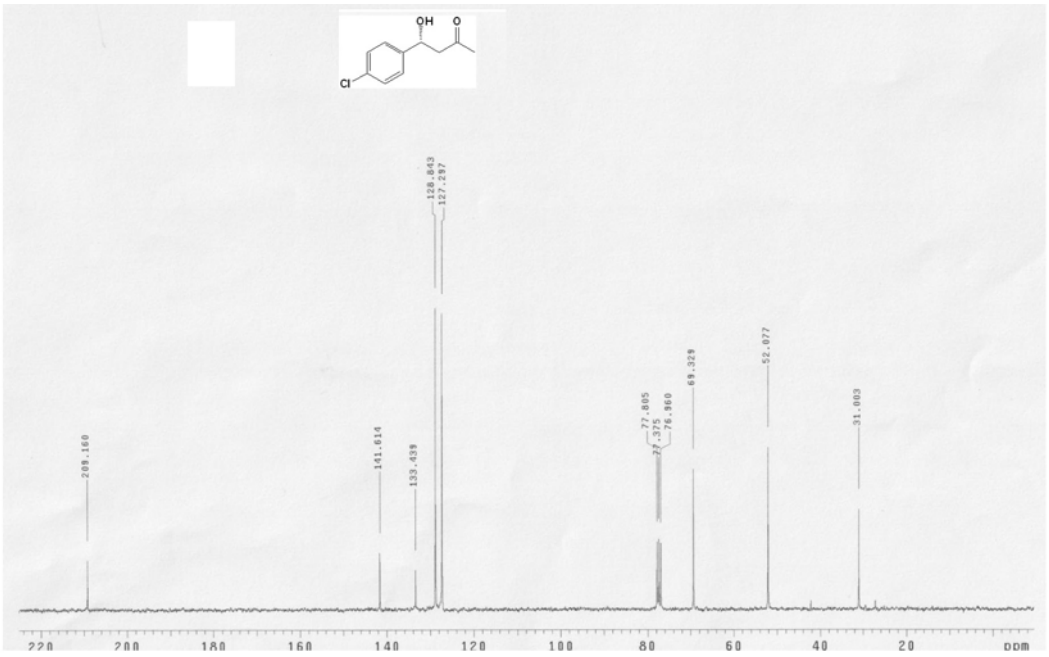


Figure S34. ^{13}C NMR (75 MHZ, $CDCl_3$) spectrum of **5g**.

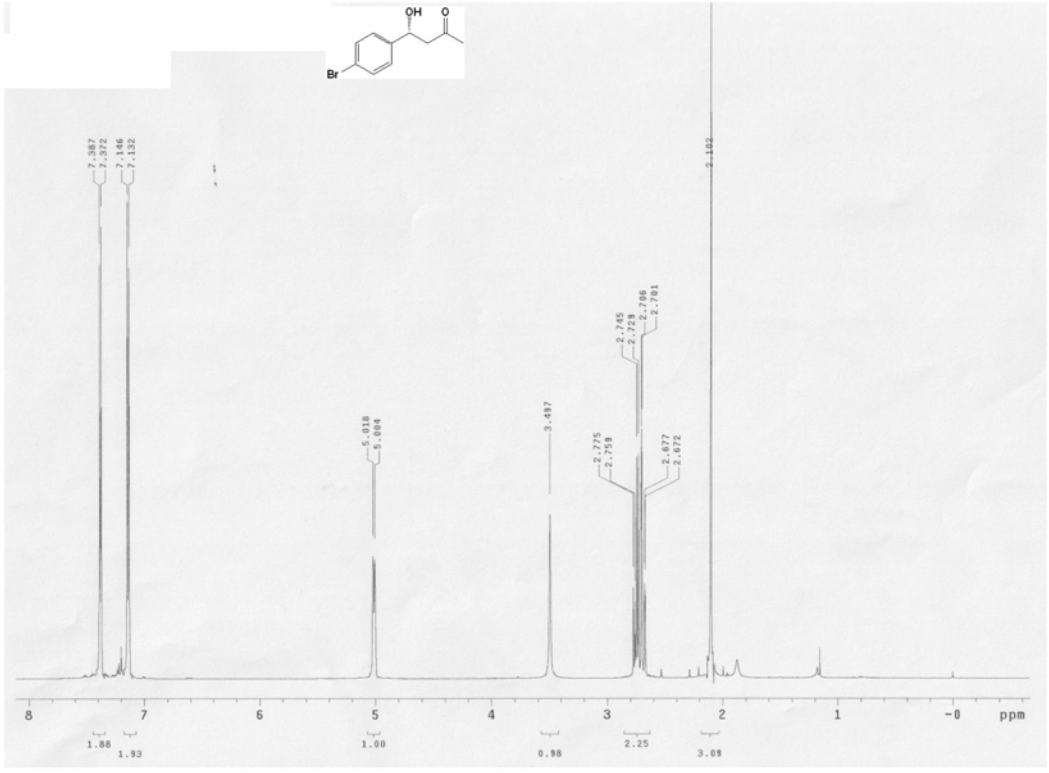


Figure S35. ^{1}H NMR (600 MHZ, $CDCl_3$) spectrum of **5h**.

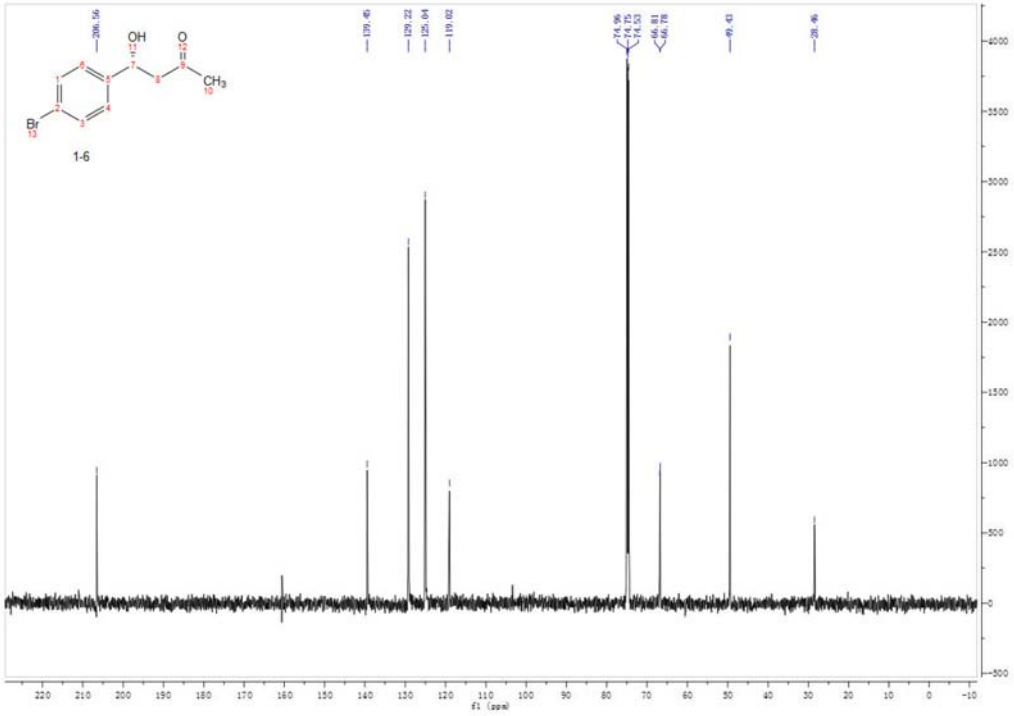


Figure S36. ^{13}C NMR (125 MHZ, $CDCl_3$) spectrum of **5h**.

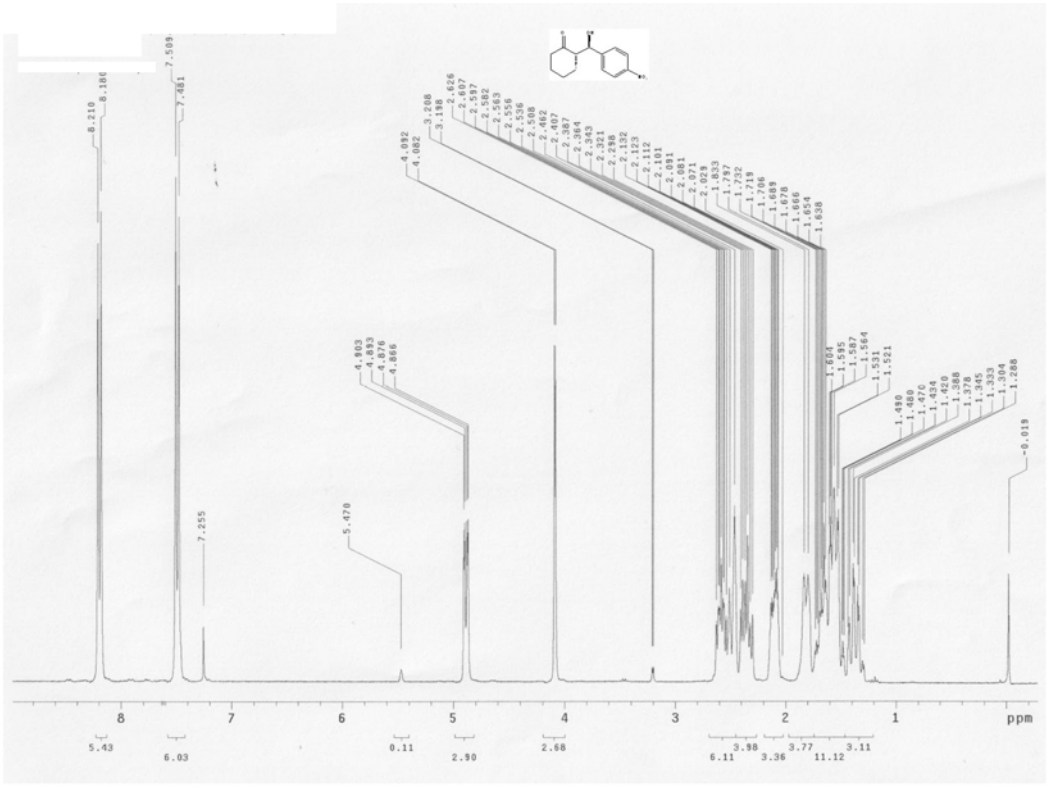


Figure S37. ^{1}H NMR (300 MHZ, $CDCl_3$) spectrum of **7**.

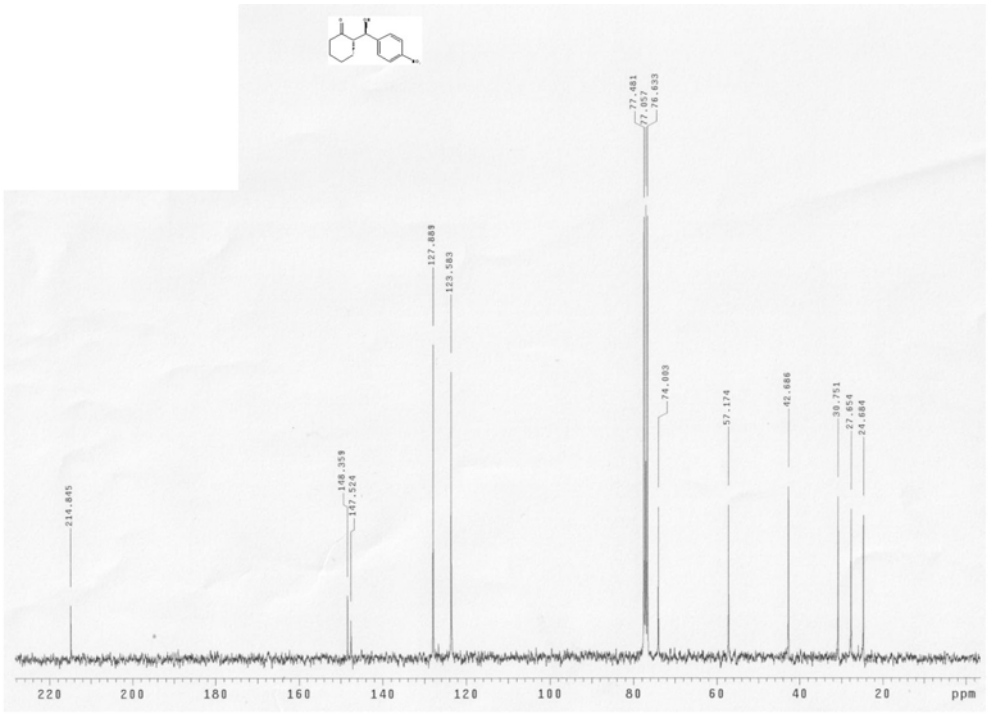
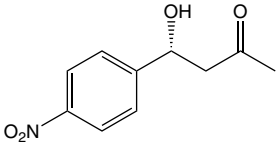


Figure S38. ^{13}C NMR (75 MHZ, $CDCl_3$) spectrum of **7**.

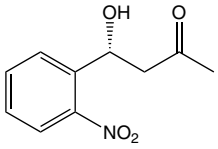
HPLC conditions for the aldol products

*4-Hydroxy-4-(4-nitrophenyl) butan-2-one (**5a**)*



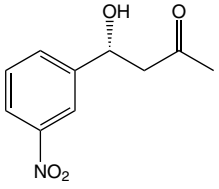
The optical purity was determined by HPLC on chiralpak AS-H column [hexane:2-propanol, 70:30]; flow rate 1.0 mL min^{-1}; λ = 210 nm; major: t_R = 12.8 min and minor: t_R =16.8 min.

*4-Hydroxy-4-(2-nitrophenyl) butan-2-one (**5b**)*



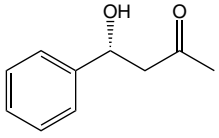
The optical purity was determined by HPLC on chiralpak AS-H column [hexane:2-propanol, 70:30]; flow rate 1.0 mL min^{-1}; λ = 220 nm; minor: t_R =8.3 min and major: t_R =11.2 min.

*4-Hydroxy-4-(3-nitrophenyl) butan-2-one (**5c**)*



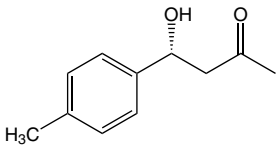
The optical purity was determined by HPLC on chiralpak OJ-H column [hexane:2-propanol, 70:30]; flow rate 1.0 mL min^{-1}; λ = 220 nm; major: t_R = 10.7 min and minor: t_R =12.4 min.

*4-Hydroxy-4-phenylbutan-2-one (**5d**)*



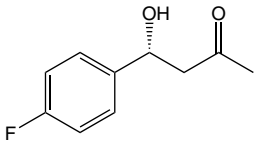
The optical purity was determined by HPLC on chiralpak AD-H column [hexane:2-propanol, 95:5]; flow rate 1.0 mL min^{-1}; λ = 210 nm; major: t_R =14.4 min and minor: t_R = 16.3 min.

*(R)-4-Hydroxy-4-p-tolylbutan-2-one (**5e**)*



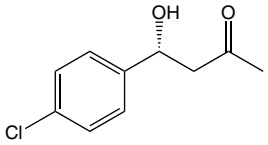
The optical purity was determined by HPLC on chiralpak AS-H column [hexane:2-propanol, 85:15]; flow rate 1.0 mL min^{-1}; λ = 220 nm; major: t_R =9.8 min and minor: t_R =12.2 min.

*4-(4-Fluorophenyl)-4-hydroxybutan-2-one (**5f**)*



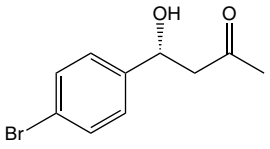
The optical purity was determined by HPLC on chiralpak AS-H column [hexane:2-propanol, 70:3]; flow rate 1.0 mL min^{-1}; λ = 220 nm , major: t_R =7.1 min and minor: 7.6 min.

*4-(4-Chlorophenyl)-4-hydroxybutan-2-one (**5g**)*



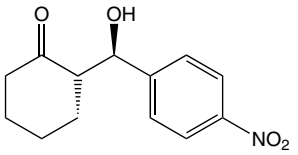
The optical purity was determined by HPLC on chiralpak AS-H column [hexane:2-propanol, 80:20]; flow rate 1.0 mL min^{-1}; λ = 220 nm; major: t_R = 9.0 min and minor: t_R =10.9 min.

*4-(4-Bromophenyl)-4-hydroxybutan-2-one (**5h**)*



The optical purity was determined by HPLC on chiralpak AS-H column [hexane:2-propanol, 70:30]; flow rate 1.0 mL min^{-1}; λ = 220 nm; major: t_R =7.0 min and minor: t_R =8.1 min.

*(S)-2-((R)-Hydroxy(4-nitrophenyl)methyl)cyclohexanone (**7**)*



The optical purity was determined by HPLC on chiralpak AD-H column [hexane:2-propanol, 80:20]; flow rate 0.5 mL min^{-1}; λ = 220 nm; mimor: t_R =21.6 min and 22.7, major: t_R =24.6 and 31.4 min.

HPLC spectra

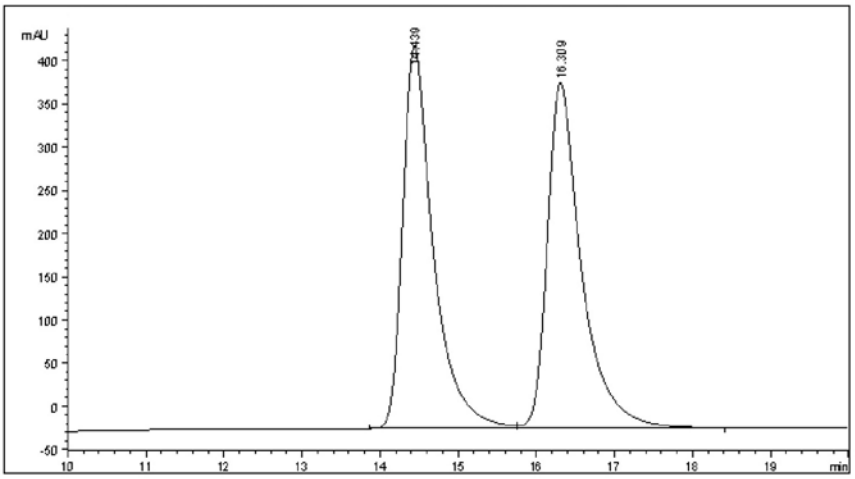


Figure S39. HPLC spectrum of **5a** (racemic).

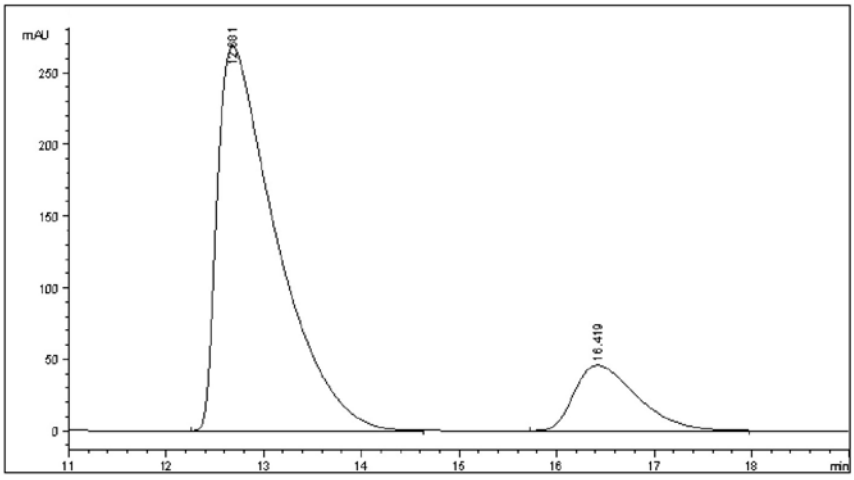


Figure S40. HPLC spectrum of **5a** (Table 1, entry 5).

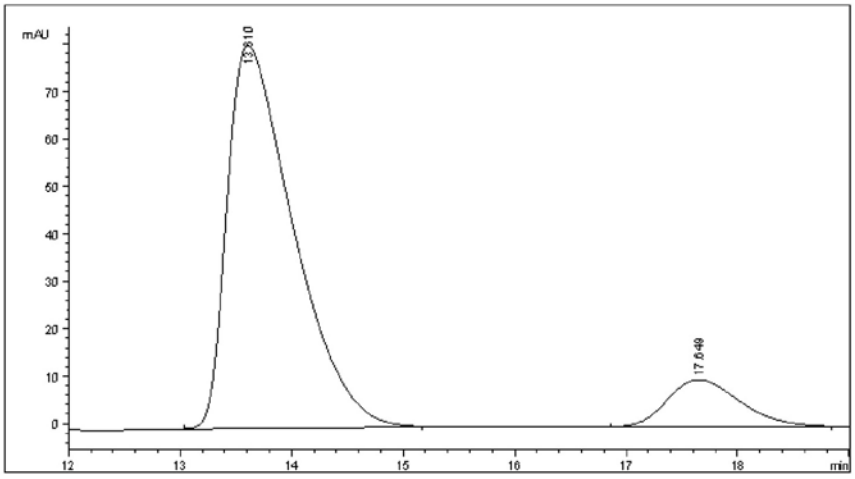


Figure S41. HPLC spectrum of **5a** (Table 1, entry 6).

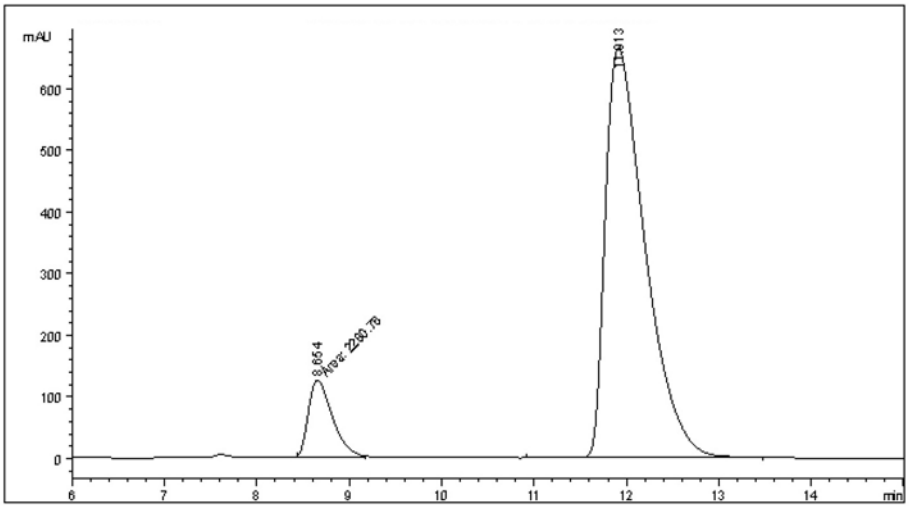


Figure S42. HPLC spectrum of **5b** (Table 1, entry 9).

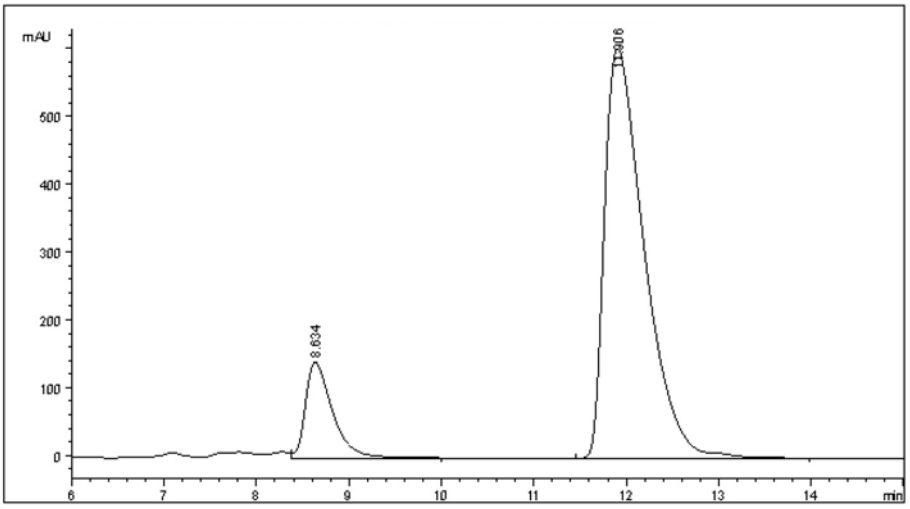


Figure S43. HPLC spectrum of **5b** (Table 1, entry 10).

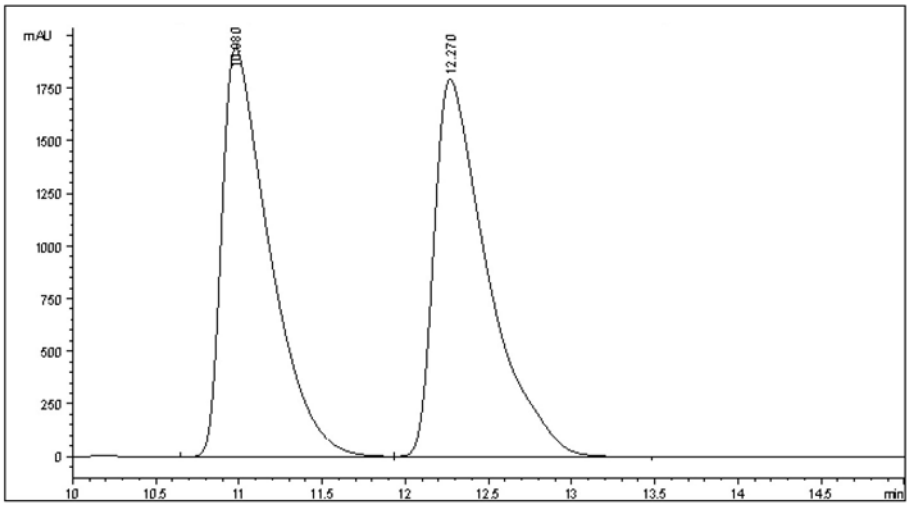


Figure S44. HPLC spectrum of **5c** (racemic).

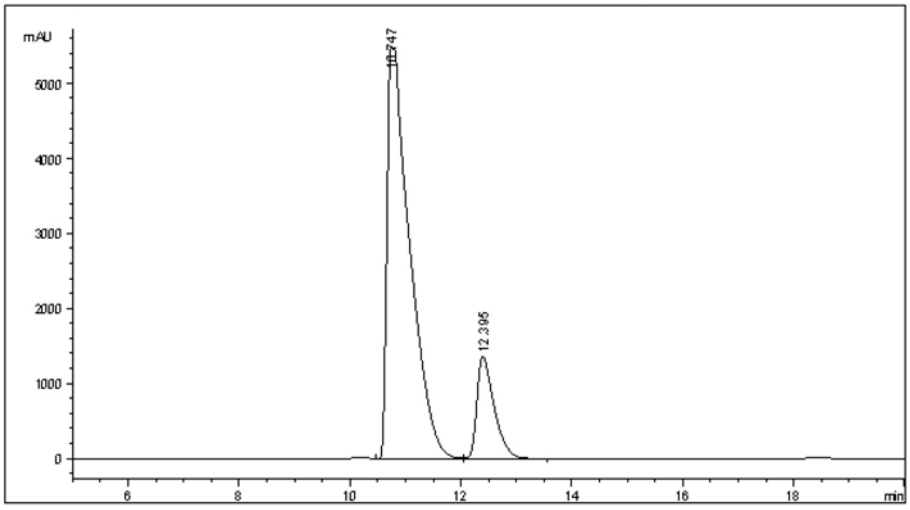


Figure S45. HPLC spectrum of **5c** (Table 1, entry 14).

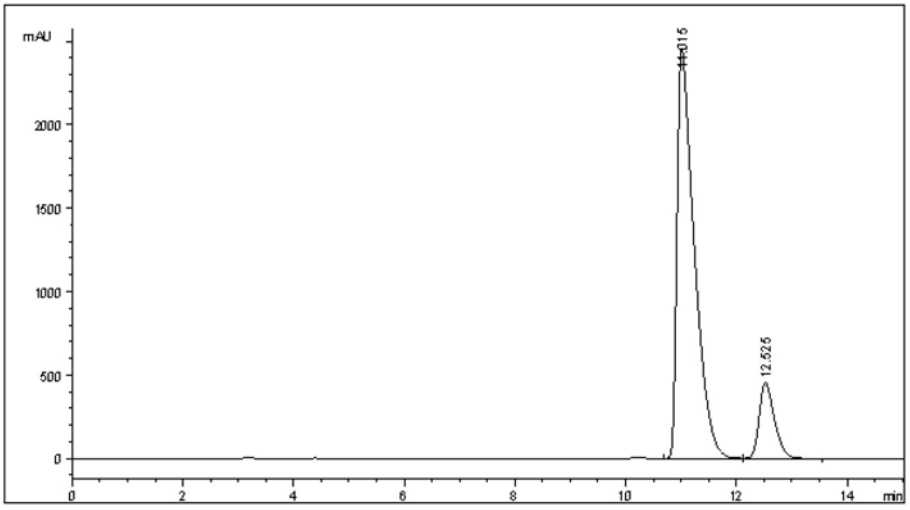


Figure S46. HPLC spectrum of **5c** (Table 1, entry 15).

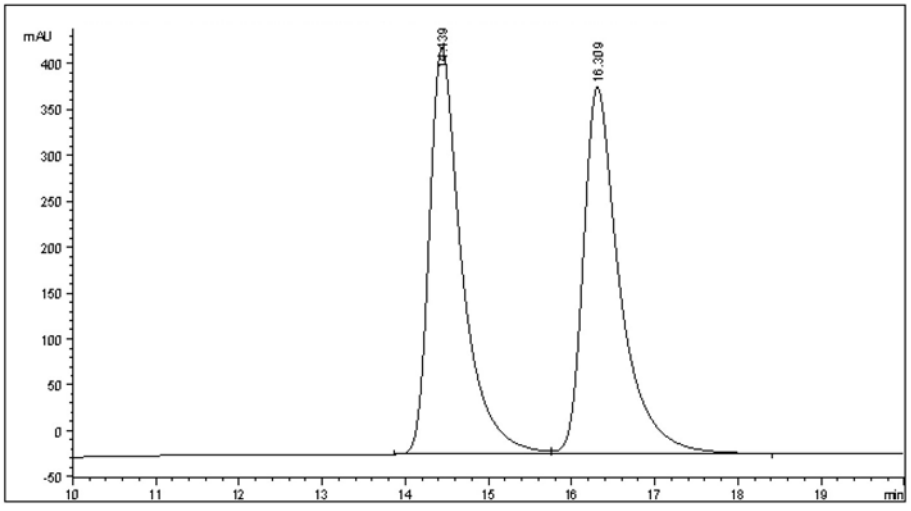


Figure S47. HPLC spectrum of **5d** (racemic).

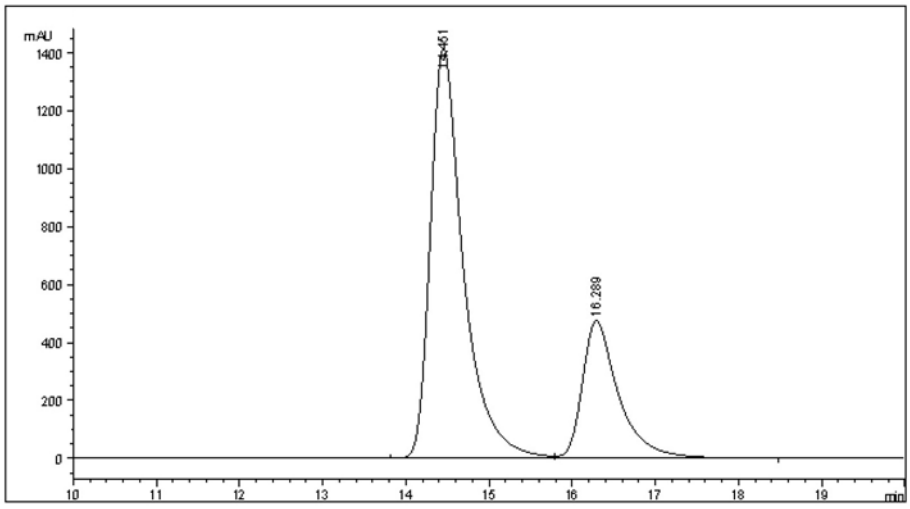


Figure S48. HPLC spectrum of **5d** (Table 1, entry 16).

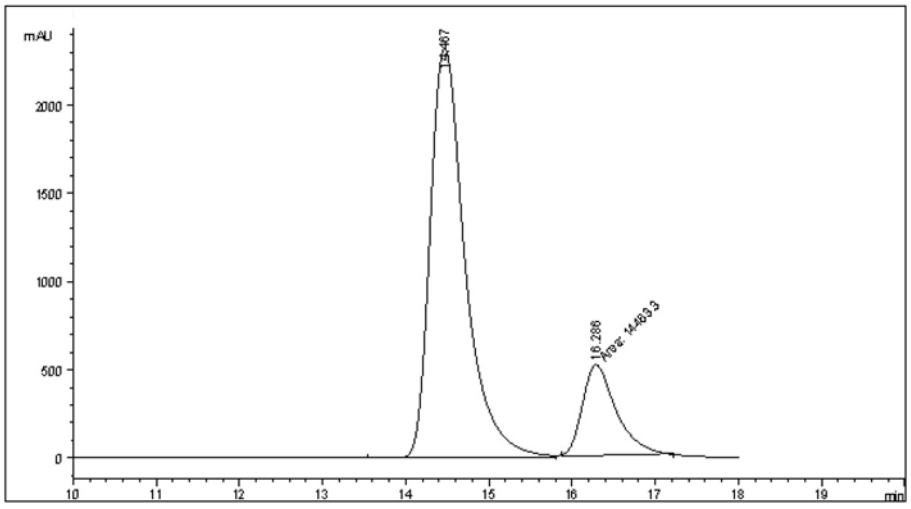


Figure S49. HPLC spectrum of **5d** (Table 1, entry 17).

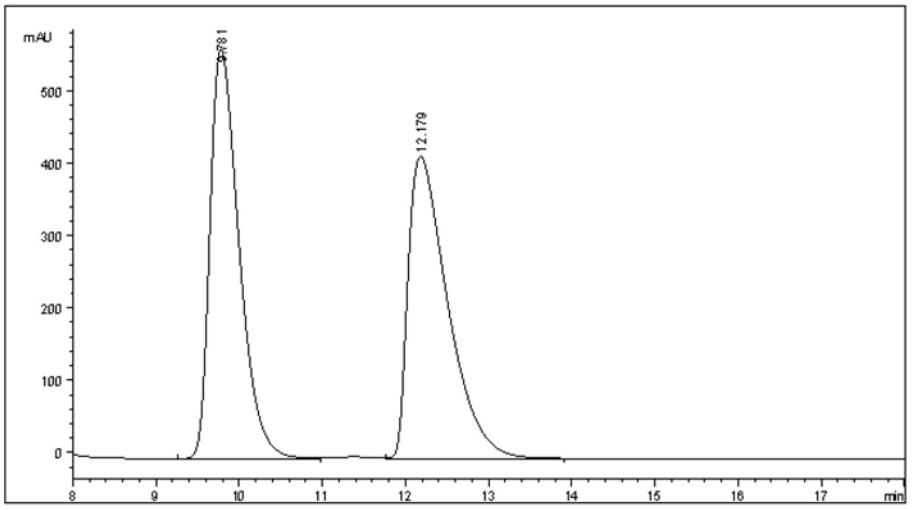


Figure S50. HPLC spectrum of **5e** (racemic).

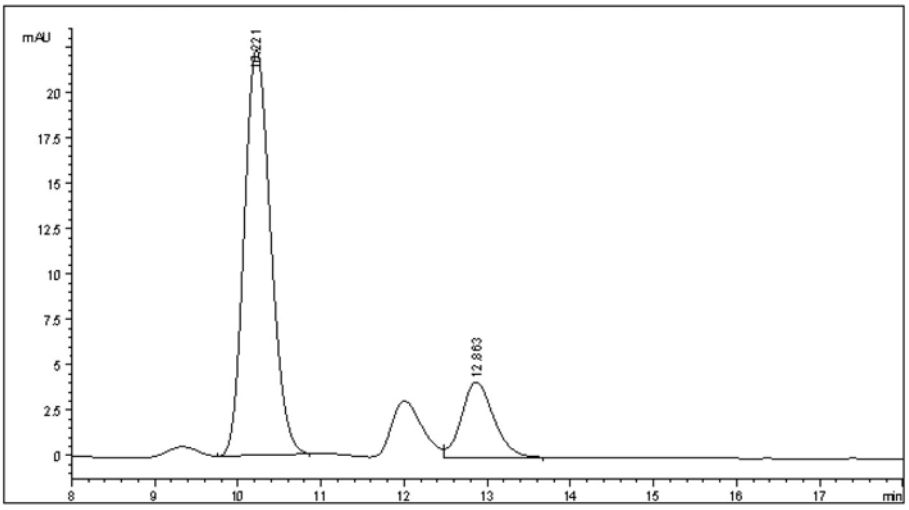


Figure S51. HPLC spectrum of **5e** (Table 1, entry 29).

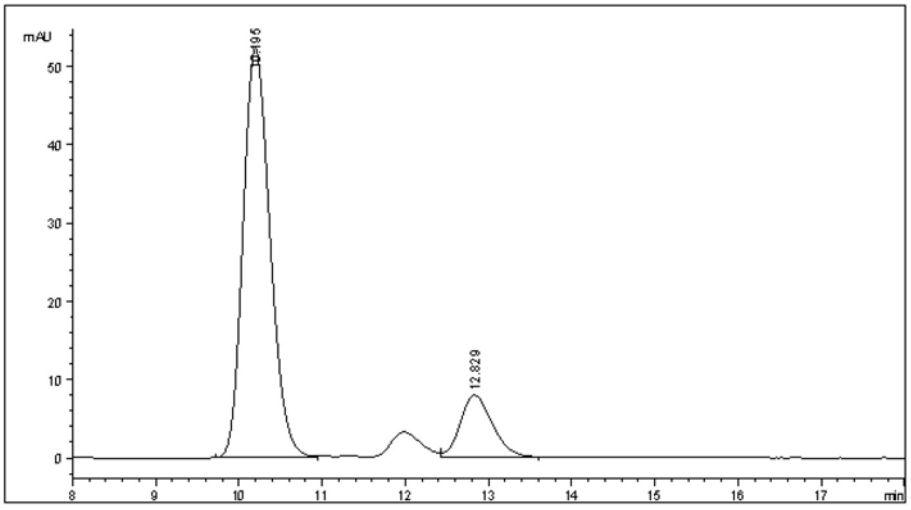


Figure S52. HPLC spectrum of **5e** (Table 1, entry 30).

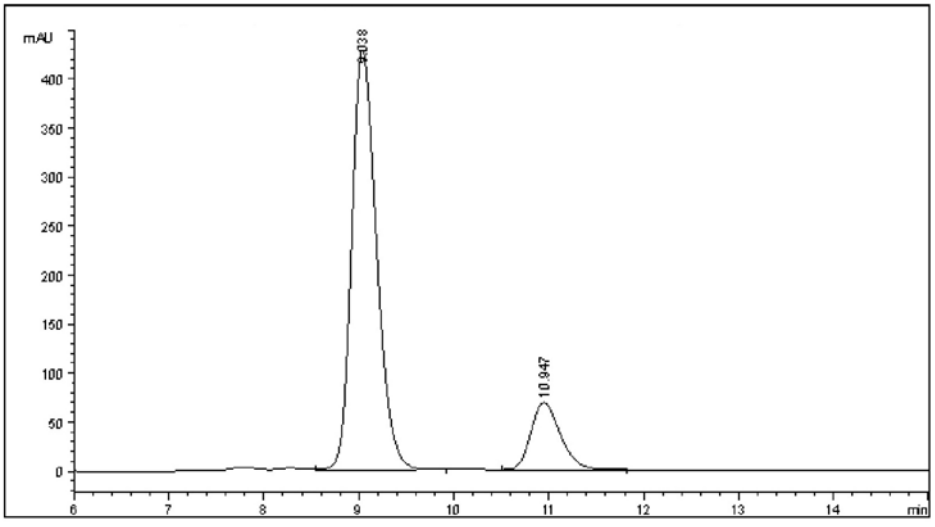


Figure S53. HPLC spectrum of **5f** (Table 1, entry 20).

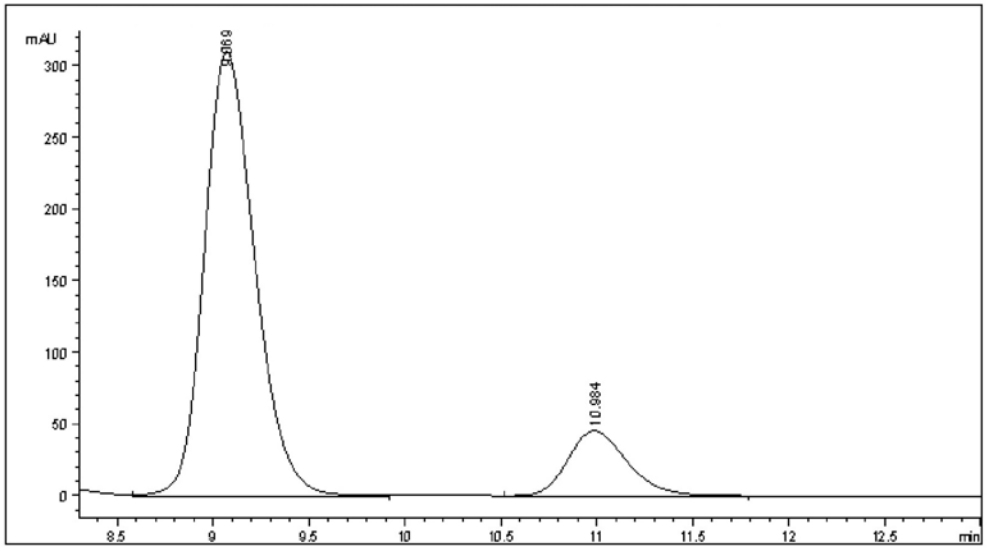


Figure S54. HPLC spectrum of **5f** (Table 1, entry 21).

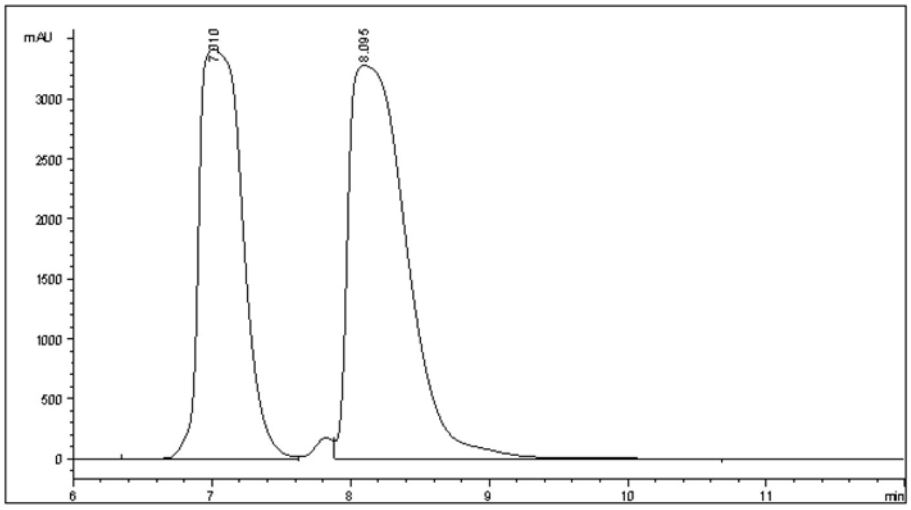


Figure S55. HPLC spectrum of **5g** (racemic).

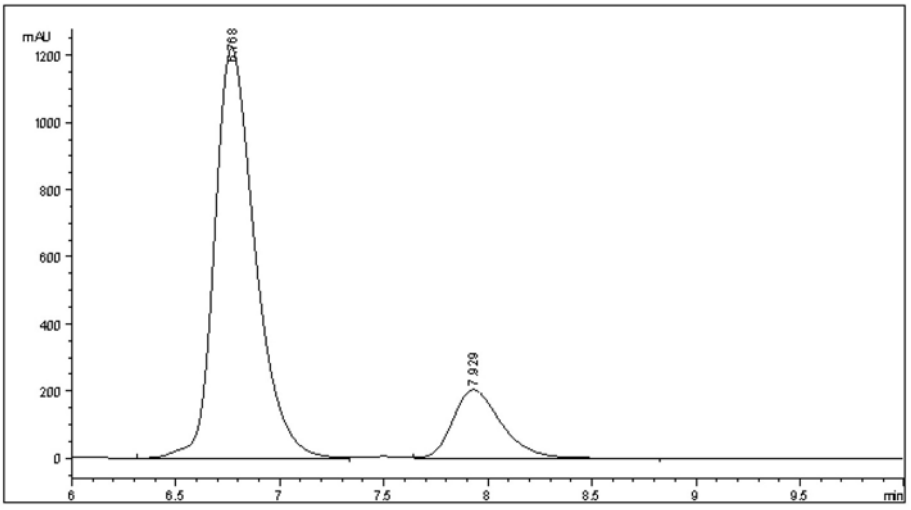


Figure S56. HPLC spectrum of **5g** (Table 1, entry 27).

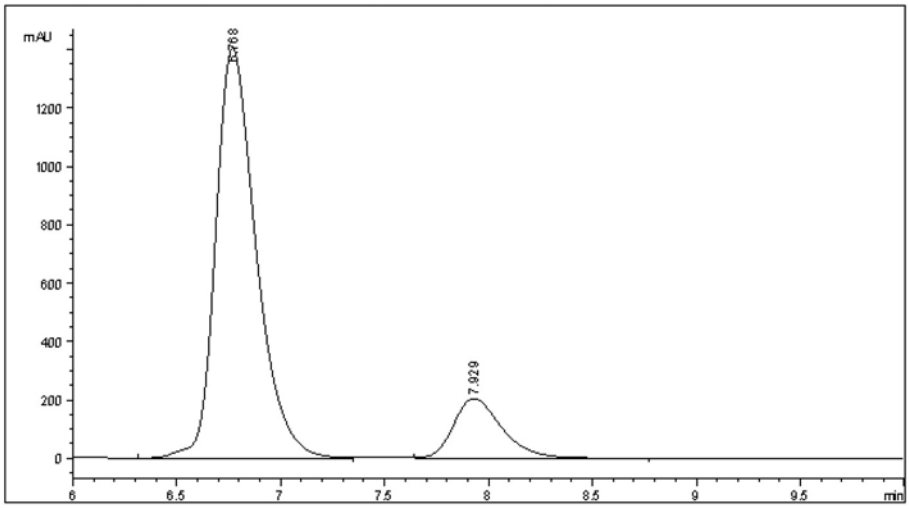


Figure S57. HPLC spectrum of **5g** (Table 1, entry 28).

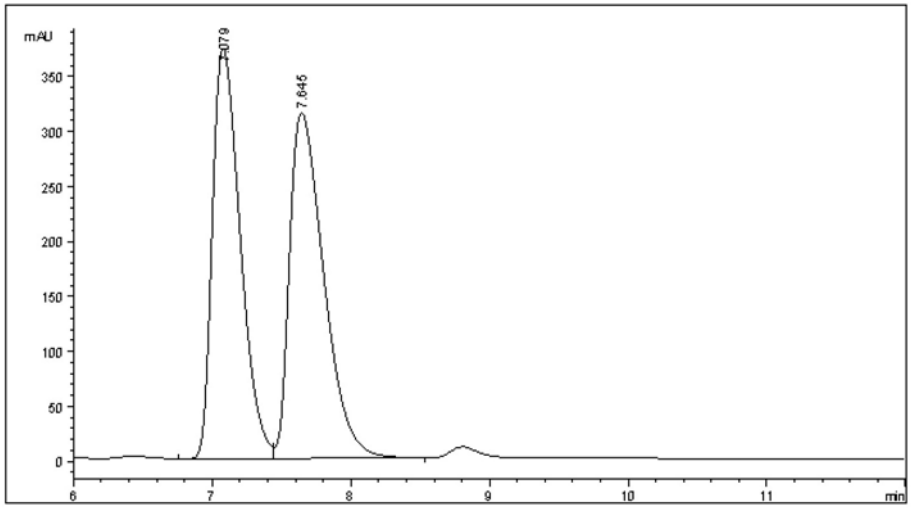


Figure S58. HPLC spectrum of **5h** (racemic).

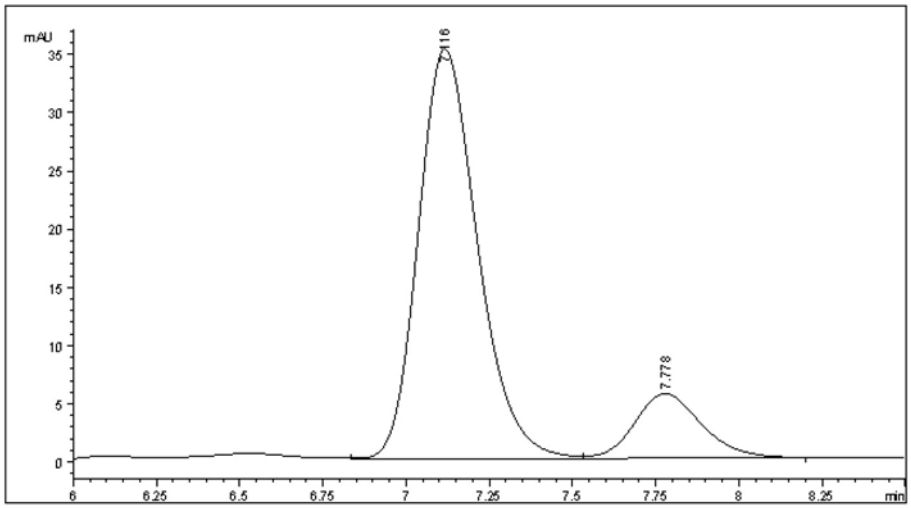


Figure S59. HPLC spectrum of **5h** (Table 1, entry 29).

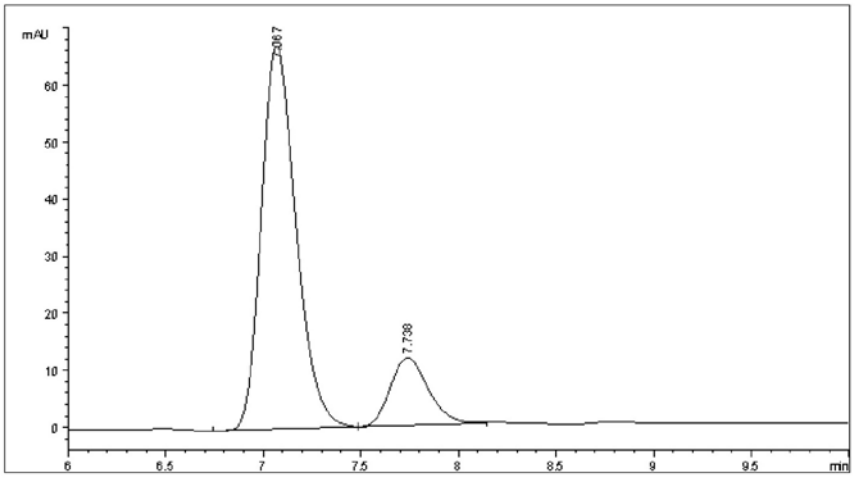


Figure S60. HPLC spectrum of **5h** (Table 1, entry 30).

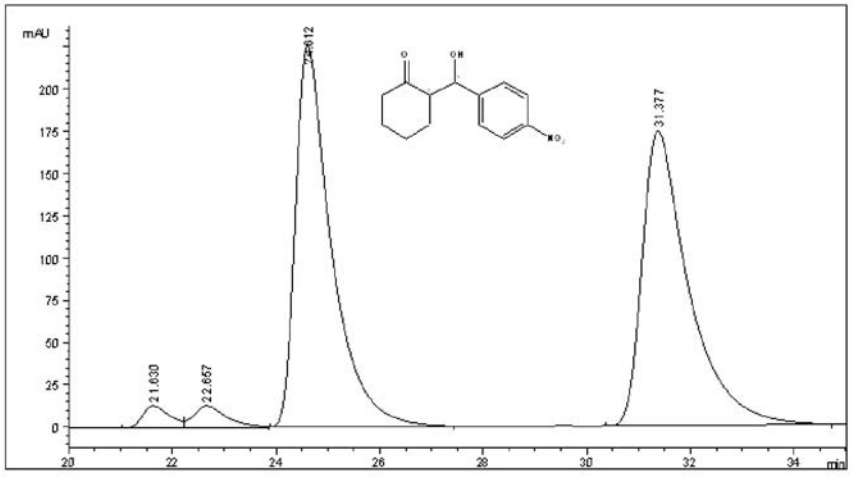


Figure S61. HPLC spectrum of **7** (racemic).

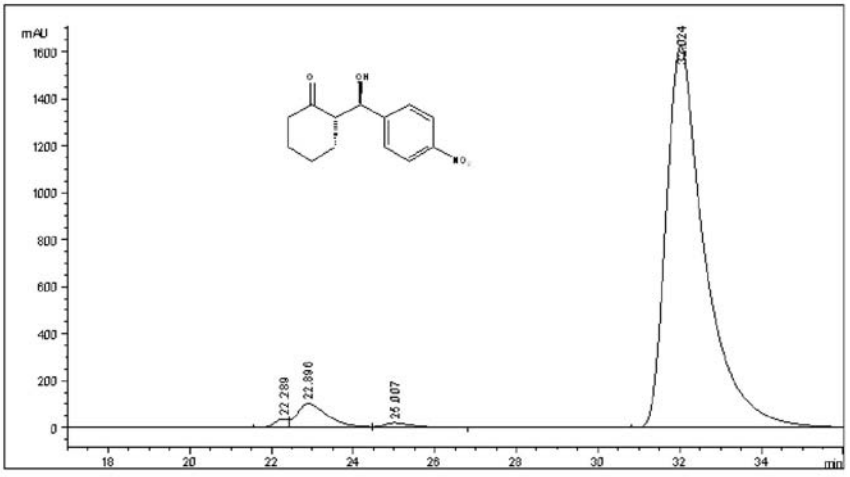


Figure S62. HPLC spectrum of **7** (Table 2, entry 5).

References

1. Zhou Y.; Shan Z.; *Tetrahedron: Asymmetry* **2006**, *17*, 1671.
2. Jia Y. N.; Wu, F. C.; Ma, X.; Zhu, G. J.; Da, C. S.; *Tetrahedron Lett.* **2009**, *50*, 3059.