Supporting Information

A Novel Amine Receptor Based on the Binol Scaffold Functions as a Highly Effective Chiral Shift Reagent for Carboxylic Acids

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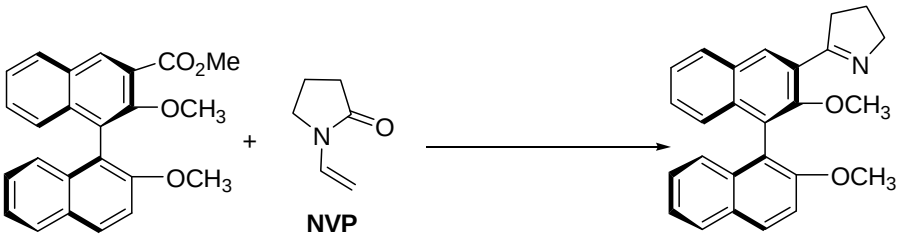
General Information: All synthetic operations were performed under air atmosphere and all solvent was used without purification, unless otherwise stated. **Py-binol 1-1** was prepared from commercial ***R*-Binol** according to reference (7a, text), others Chemicals were either purchased or purified by standard techniques. Melting points were obtained with a Yuhua X-5 micromelting point apparatus and uncorrected. Optical rotation was tested in PolAAr-3005 polarimeter and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured on 300 or 500 MHz Brucker spectrometer in $CDCl_3$ solutions with tetramethylsilane (TMS). *J* values are given in Hz. Column chromatography was performed using Silica gel (300-400 mesh). de of **Py-binol 1-4** was checked by HPLC, and absolute configuration of **(*R, R*)-Py-Binol 1** was confirmed with X-ray. Infrared spectra was measured on a Bruker Vector-55 spectrometer. HRMS was recorded with a Waters Micromass GCT Premier instrument.

Synthetic Procedures of Py-Binol 1-2



Py-Binol 1-1 **Py-Binol 1-2**

LiHMDS (171 mL, 171 mmol) was added to stirring freshly distilled N-vinylpyrrolidinone (19.98 g, 180 mmol) in THF (50 mL, anhydrous) at -78 ^{o}C. The mixture was stirred for 1 h and a solution of **Py-Binol 1-1** (33.5 g. 90 mmol) in THF was added dropwise. After the reaction mixture was stirred at -78 ^{o}C for 2-3 h, the reaction was allowed to warm to room temperature naturally and stirred overnight. Concentrated HC1(30 mL), diluted with H_2O (50 mL), was added, and the THF was removed on a rotary evaporator. The mixture is added slowly to refluxing 6 N hydrochloric acid (150 mL) and heated under reflux overnight, cooled to room temperature. The pH of solution was adjusted to 12 with concentrated aqueous NaOH (ice-bath cooling), which resulted in precipitation of the crude product (**Py-Binol 1-2**), and then extracted with methylene chloride (2 X 250 mL). The combined extracts were washed with H_2O (100 mL), dried with $MgSO_4$ and concentrated under reduced pressure to afford 21 g (60%) of crude product which can

be used directly without further purification.

White solid. mp: 59-60 ^{o}C. $[\alpha]_D^{20}$: +64.6 (c 1.76, $CHCl_3$). IR (KBr): ν 1715, 1619, 1593, 1508, 1355, 1266, 1248, 1088, 810, 751 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ: 1.91-2.01 (m, 2H), 3.00 (t, *J* = 7.6 Hz, 2H), 3.25 (s, 3H), 3.67 (s, 3H,), 3.98 (t, *J* = 7.6 Hz, 2H), 7.03 (dd, J_1 = 7.8 Hz, J_2 = 8.7 Hz, 2H), 7.13 (dd, J_1 = 7.2 Hz, J_2 = 7.8 Hz, 2H), 7.19-7.30 (m, 2H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.76(d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* =9.0 Hz, 1H), 8.26 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ: 23.29, 38.06, 56.48, 60.19, 61.12, 113.46, 118.72, 123.64, 125.08, 125.27, 125.37, 126.70, 127.23, 127.91, 128.74, 128.87, 128.98, 129.91, 130.26, 130.55, 133.90, 134.94, 154.45, 154.87, 175.29.. HRMS (ESI) calcd for $C_{26}H_{24}NO_2$ $(M+H)^+$: 382.1807; Found: 382.1802.

Figure S1: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) of Py-Binol 1-2.

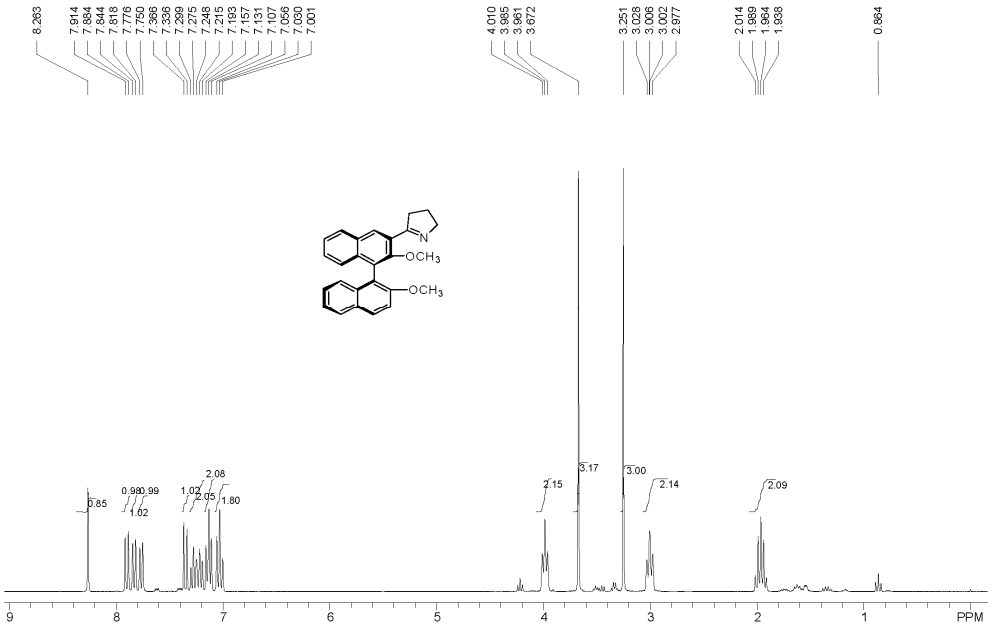
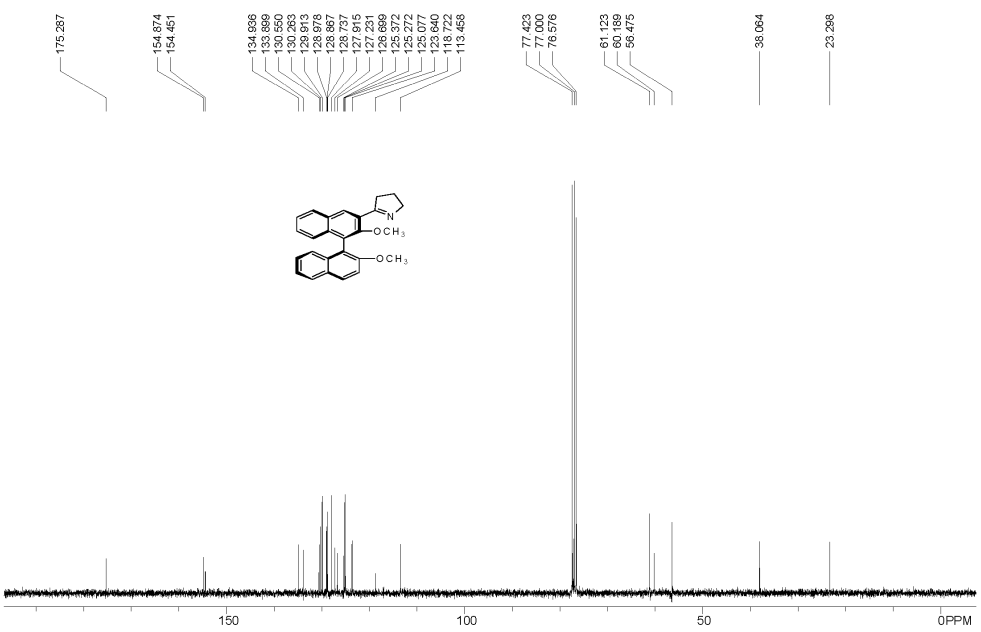
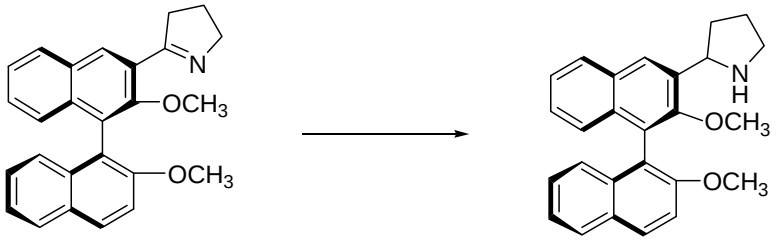


Figure S2: ^{13}C NMR (125 MHz, $CDCl_3$) of Py-Binol 1-2.



Synthesis of Py-Binol 1-3



Py-Binol 1-2 **Py-Binol 1-3**

$NaBH_4$ (2.84 g, 75 mmol) was added portionwise over 20 min, with vigorous stirring, to a solution of **Py-Binol 1-2** (11.5 g, 30 mmol) in methanol (50 mL) cooled to -40 ^oC. After warmed to room temperature slowly, most of the solvent was removed with a rotary evaporator. H_2O (100 mL) was added, and the solution was made basic with NaOH and extracted with methylene chloride (2 x 150 mL). The combined extract was washed with saturated aqueous NaC1 (100 mL), dried over $MgSO_4$, concentrated on a rotary evaporator to give 9.9 g (86%) of crude product (**Py-Binol 1-3**) as yellow solid. The crude product (**Py-Binol 1-3**) was purified by flash column chromatography on silica gel (eluent: CH_2Cl_2 : CH_3OH, from 40:1 to 20:1) to give the product (9.21 g, 93%) as a white solid.

White solid. mp: 77-79 ^{o}C. $[\alpha]_D^{20}$: +77.1 (c 1.05, $CHCl_3$). IR (KBr): ν 2935, 1710, 1592, 1507, 1455, 1358, 1248, 1148, 1087, 809, 749 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ: 1.76-2.1 (m, 3H), 2.23 (s, 1H), 2.31-2.40 (m, 1H), 3.03-3.12 (m, 1H), 3.26-3.31 (m, 1H), 3.33 (s, 1.3H), 3.34 (s, 1.7H), 3.77 (s, 1.7H), 3.79 (s, 1.3H), 4.55-4.62 (m, 1H), 7.08-7.36 (m, 6H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 2H), 7.98 (d, *J* = 9.0 Hz, 1H), 8.07 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ: 25.24, 25.27, 33.08, 33.39, 46.65, 56.48, 56.56, 57.69, 57.84, 58.31, 60.68, 60.70, 113.50, 113.62, 119.36, 119.40, 123.66, 124.15, 124.67, 125.12, 125.22, 125.38, 125.79, 125.83, 126.07, 126.11, 126.70, 127.85, 127.88, 127.95, 128.00, 129.05, 129.85, 130.58, 130.61, 133.31, 133.96, 135.95, 154.74, 154.83, 154.90, 154.93. HRMS (ESI) calcd for $C_{26}H_{26}NO_2$ $(M+H)^+$384.1964; Found: 384.1958.

Figure S3: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) of Py-Binol 1-3.

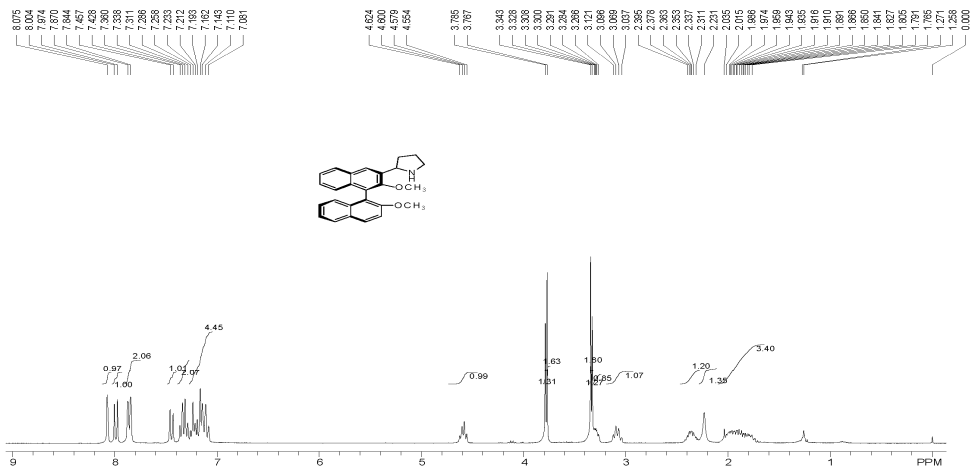
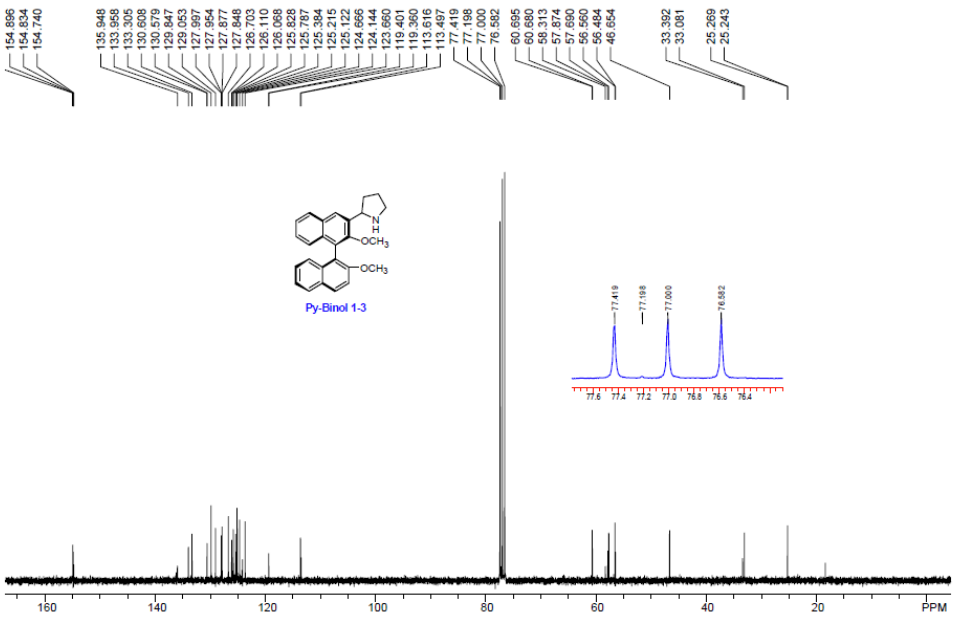
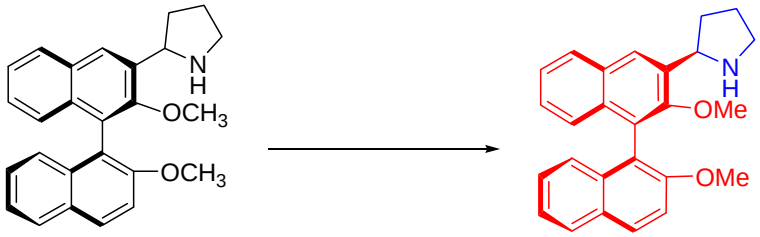


Figure S4: ^{13}C NMR (125 MHz, $CDCl_3$) of Py-Binol 1-3.



Synthesis of (*R*, *R*)-Py-Binol 1-4



Py-Binol 1-3 **(*R*,*R*)-Py-Binol 1-4**

L-Tartaric acid (7.96 g, 53 mmol) was added to the solution of **Py-Binol 1-3** (20.3 g, 53 mmol) in EtOH (200 mL, g/v = 1:10), and heated to reflux for 1-2 h, then cooled to room temperature naturally, white salt precipitated, after filtration, the salt was solvled in water and made basic with 10% aqueous NaOH, extracted with methylene chloride (2 x 100 mL). The combined extract was washed with 100 mL of saturated aqueous NaC1, dried over $MgSO_4$, concentrated on a rotary evaporator to give 5.5 g product of (*R*, *R*)-**Py-Binol 1-4** as white solid with over 99% de.

White solid. mp: 78-79 ^{o}C. $[\alpha]_D^{20}$: +84.4 (c 1.92, $CHCl_3$). IR (KBr): ν 2935, 1710, 1592,

1507, 1455, 1358, 1248, 1148, 1087, 809, 749 cm^{-1}. ^{1}H NMR (500 MHz, d_6-DMSO): δ:1.58-1.66 (m, 1H), 1.78-1.95 (m, 2H), 2.26-2.34 (m, 1H), 2.97-3.02 (m, 1H), 3.15-3.20 (m, 1H), 3.30 (s, 3H), 3.30-3.4 (br, 1H), 3.81 (s, 3H), 4.52 (t, *J* = 7.5 Hz, 1H), 6.95 (dd, *J* = 9.0, *J* = 8.7 Hz, 2H), 7.22 (dd, *J* = 7.0 Hz, *J* = 1.0 Hz, 1H), 7.25-7.28 (m, 1H), 7.34-7.41 (m, 2H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 9.0 Hz, 1H), 8.21 (s, 1H). ^{13}C NMR(125 MHz, $CDCl_3$): δ: 25.27, 33.17, 46.68, 56.53, 57.51, 60.67, 113.59, 119.42, 123.61, 124.13, 124.60, 125.10, 125.35, 125.72, 125.96, 126.66, 127.82, 127.96, 129.02, 129.79, 130.59, 133.21, 133.94, 136.41, 154.86, 154.90. HRMS (ESI) calcd for $C_{26}H_{26}NO_2$ $(M+H)^+$384.1964; Found: 384.1958.

Figure S5: ^{1}H NMR (500 MHz, d_6-DMSO) of (*R*, *R*)-Py-Binol 1-4.

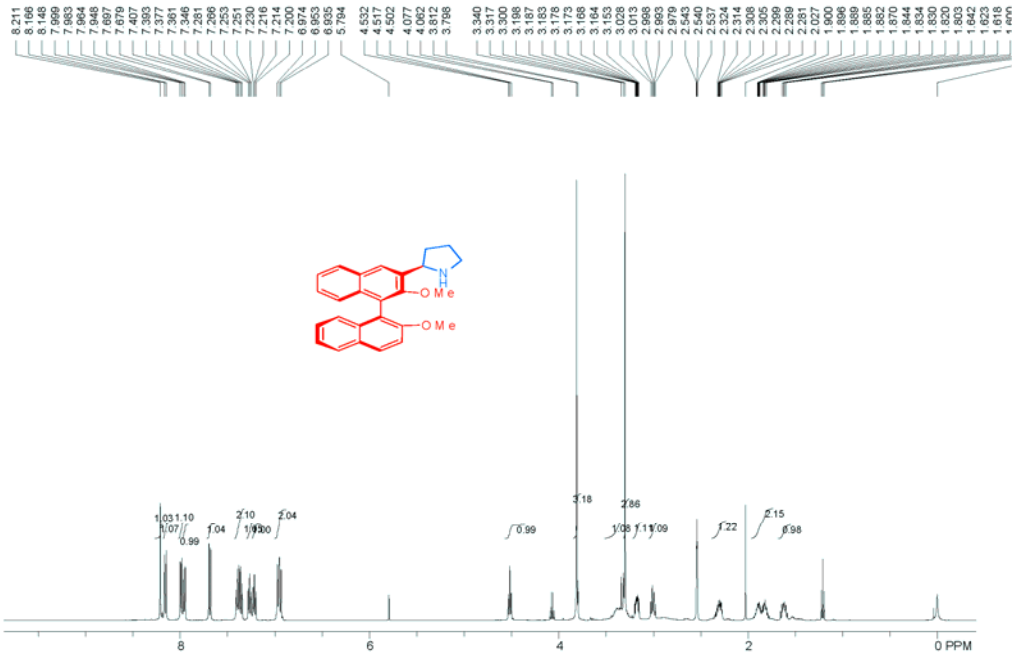
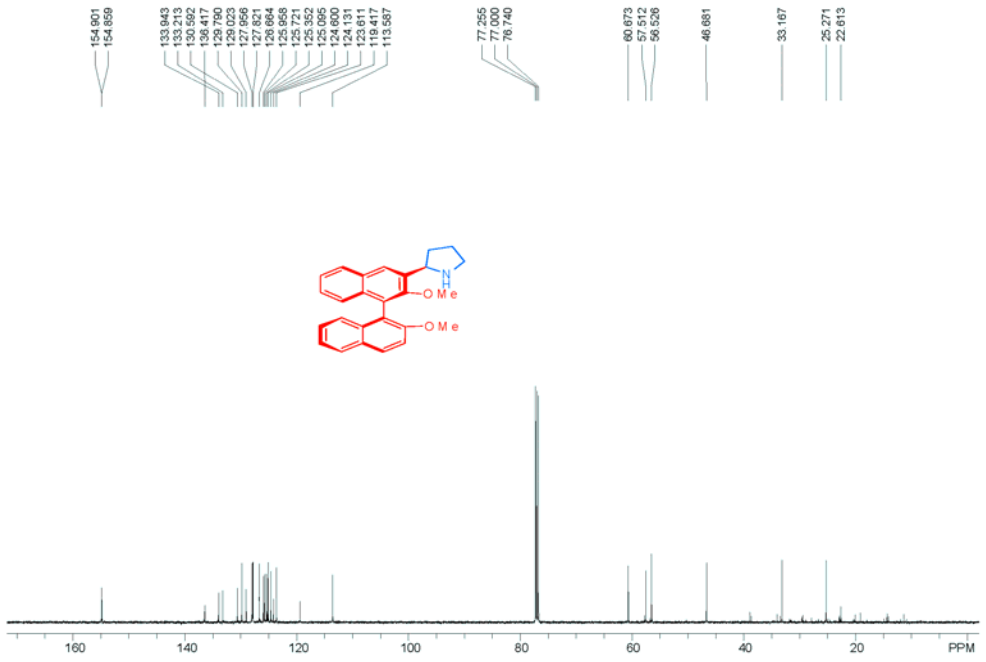
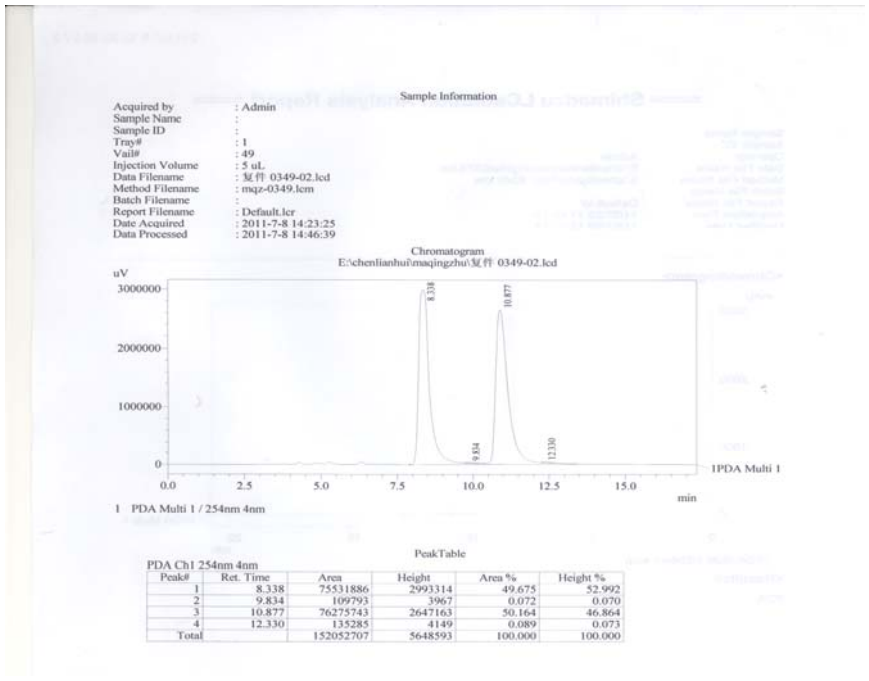


Figure S6: ^{13}C NMR (125 MHz, $CDCl_3$) of (*R*, *R*)-Py-Binol 1-4



Determination of de for **Py-Binol 1-4.** Boc group before chiral HPLC was used. Chiral AD column; λ = 254 nm; eluent: Hexane/Isopropanol = 98/2; Flow rate: 0.7 mL/min; t_1 = 8.38 min; t_2 = 10.88 min.

Figure S7: HPLC of Boc protected Py-Binol 1-4, determination of de.



Sample Information

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Sample Name	:
Sample ID	:
Tray#	: 1
Vail#	: 49
Injection Volume	: 5 uL
Data Filename	: 复件 0349-02.lcd
Method Filename	: mqz-0349.lcm
Batch Filename	:
Report Filename	: Default.lcr
Date Acquired	: 2011-7-8 14:23:25
Data Processed	: 2011-7-8 14:46:39

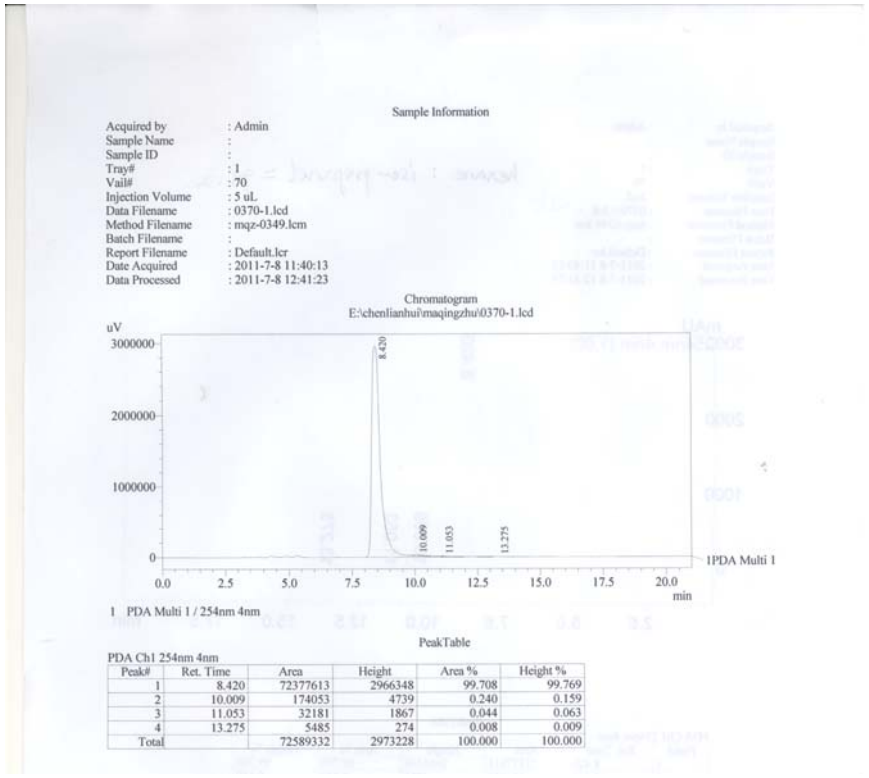
Chromatogram
E:\chenlianhui\maqingzhu\复件 0349-02.lcd

1 PDA Multi 1 / 254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.338	75531886	2993314	49.675	52.992
2	9.834	109793	3967	0.072	0.070
3	10.877	76275743	2647163	50.164	46.864
4	12.330	135285	4149	0.089	0.073
Total		152052707	5648593	100.000	100.000



Sample Information

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Sample Name	:
Sample ID	:
Tray#	: 1
Vail#	: 70
Injection Volume	: 5 uL
Data Filename	: 0370-1.lcd
Method Filename	: mqz-0349.lcm
Batch Filename	:
Report Filename	: Default.lcr
Date Acquired	: 2011-7-8 11:40:13
Data Processed	: 2011-7-8 12:41:23

Chromatogram
E:\chenlianhui\maqingzhu\0370-1.lcd

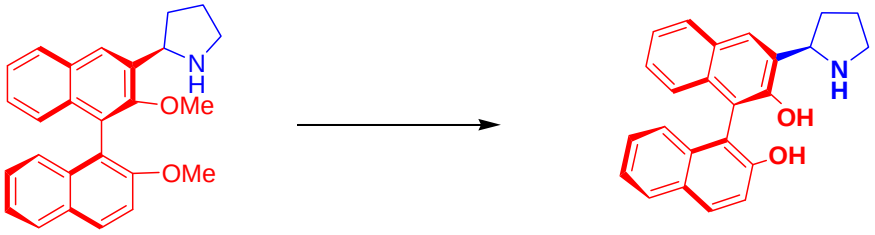
1 PDA Multi 1 / 254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.420	72377613	2966348	99.708	99.769
2	10.009	174053	4739	0.240	0.159
3	11.053	32181	1867	0.044	0.063
4	13.275	5485	274	0.008	0.009
Total		72589332	2973228	100.000	100.000

Synthesis of receptor (*R*, *R*)-Py-Binol 1



(*R*,*R*)-Py-Binol 1-4 **(*R*,*R*)-Py-Binol 1**

(*R*,*R*)-Py-Binol 1-4 (1.3 g, 3.4 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to-40 ^oC, BBr_3 (1 mL ,10 mmol) was added slowly, and the reaction mixture was stirred for 4-5 h at -40 ^oC. H_2O (30 mL) was carefully added. The phases were separated, extracted with CH_2Cl_2 (2 x 50 mL). The combined extract organic phase was washed with H_2O (50 mL) and saturated aqueous NaCl (50 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to give the crude product **(*R*,*R*)-Py-Binol 1** , then the crude product was purified by flash column chromatography on silica gel to give the product (eluent: CH_2Cl_2 : CH_3OH, from 40:1 to 20:1) as a white solid. (1.13 g, 87%).

white solid. mp: 101-103 ^oC. $[\alpha]_D^{20}$: +43.5 (c 1.75, $CHCl_3$). IR (KBr): ν 3027, 2928, 1716, 1710, 1424, 1371, 1358, 1221, 1199 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$, TMS): δ: 1.18 (s, 1H), 1.82-1.97 (m, 3H), 2.19-2.23 (m, 1H), 2.96-2.99 (m, 1H), 3.04-3.07 (m, 1H), 4.45-4.47 (m, 1H), 5.83 (br, 2H), 7.03 (d, *J* = 8.5 Hz, 1H), 7.08-7.23 (m, 6H), 7.56 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.75-7.80 (m, 2H), ^{13}C NMR (125 MHz, DMSO): δ: 24.64, 33.97, 44.93, 62.27, 115.84, 116.25, 118.55, 121.86, 122.09, 123.99, 124.58, 125.14, 125.67, 126.02, 127.22, 127.45, 127.76, 128.07, 128.27, 128.86, 133.02, 134.23, 152.80, 155.14. HRMS (ESI) calcd for $C_{24}H_{22}NO_2$ $(M+H)^+$ 356.1651; Found: 356.1645.

Figure S8: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) of (*R*, *R*)-Py-Binol 1

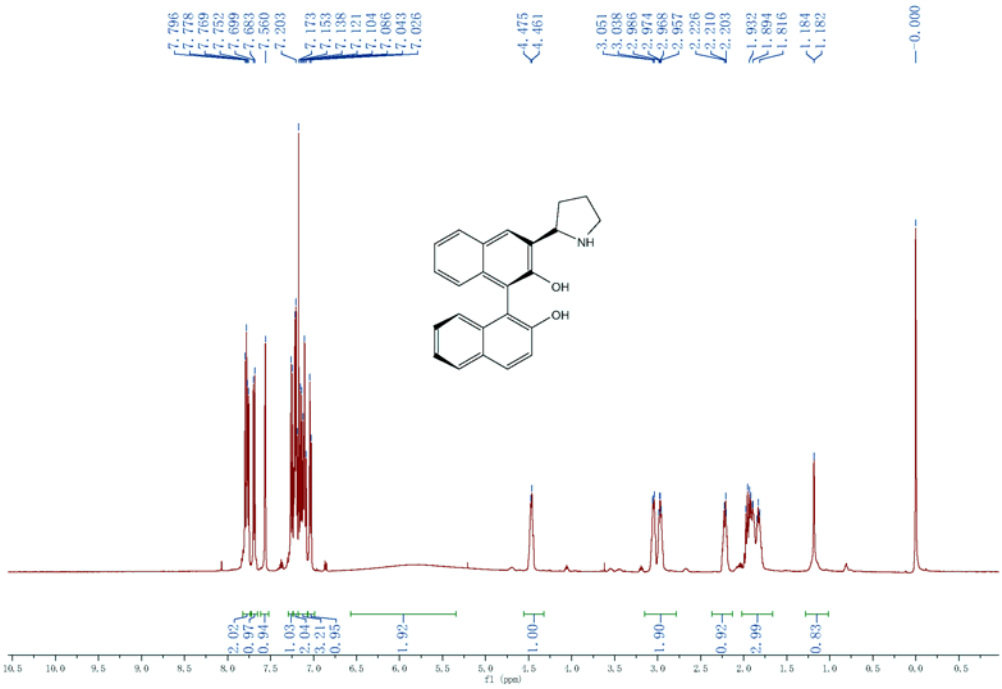


Figure S9: ^{13}C NMR (125 MHz, d_6-DMSO) of (*R*, *R*)-Py-Binol 1

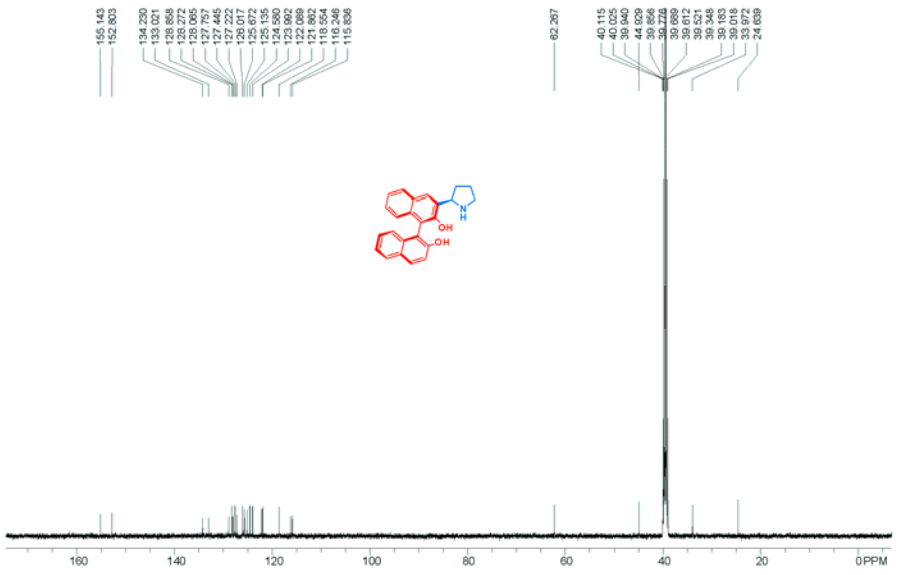
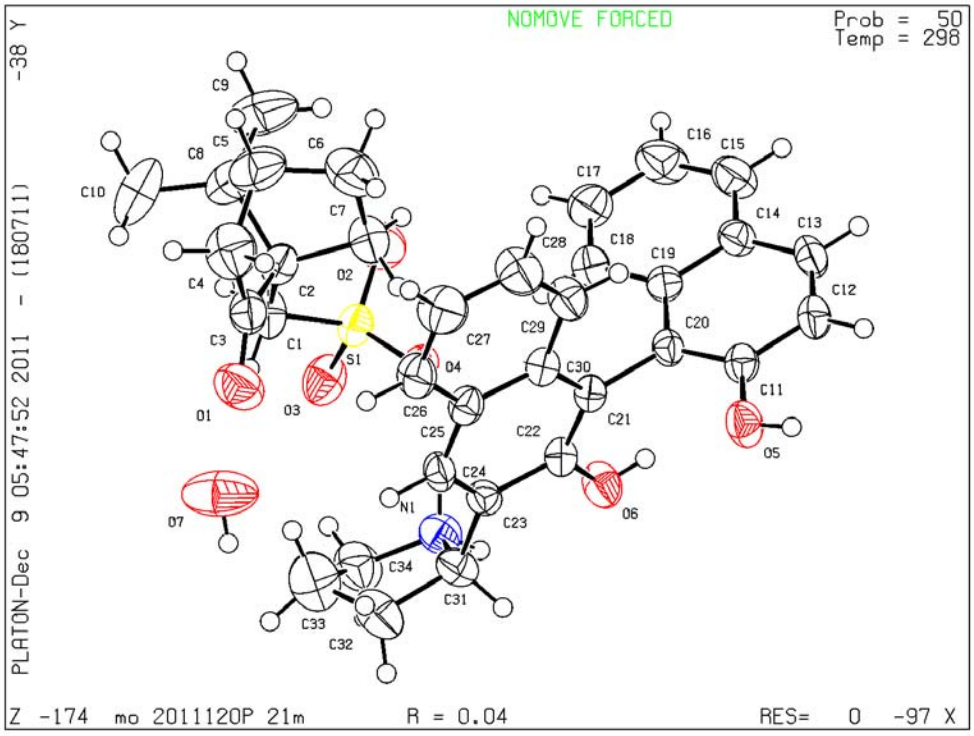


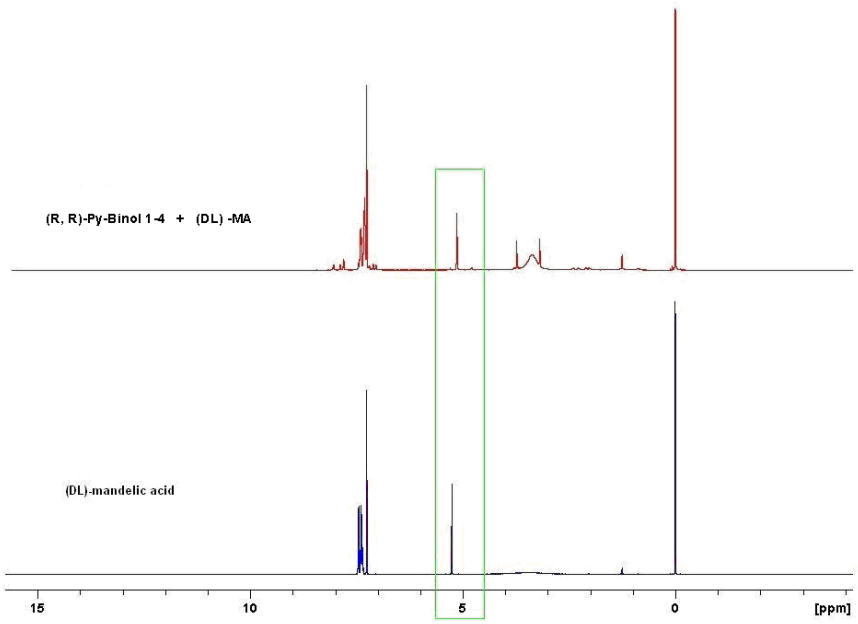
Figure S10: X-ray of D-(+)- Camphorsulfonic Acid salt of (*R*, *R*)-Py-Binol 1, determination of the absolute configuration.



NMR Experiments

NMR spectra were collected on a spectrometer 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR and reported as parts per million (ppm) from the internal standard TMS(solvent, $CDCl_3$).

Figure S11. The overlaid ^{1}H NMR spectra of free mandelic acid (blue), and the 1:1 mixture of compound **(*R, R*)-Py-Binol 1-4** and mandelic acid (10 mM).



NMR Enantiodifferentiation of carboxylic acids 1-13 (5 mM) by the receptor (10 mM).

Figure S12. ^{1}H NMR Spectra of CSR and carboxylic acid 1

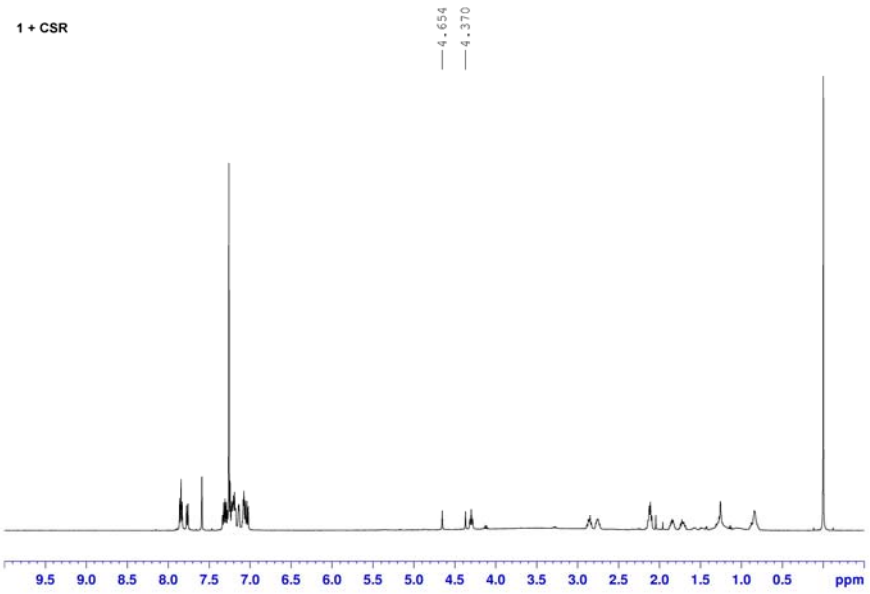


Figure S13. ^{1}H NMR Spectra of CSR and carboxylic acid 2

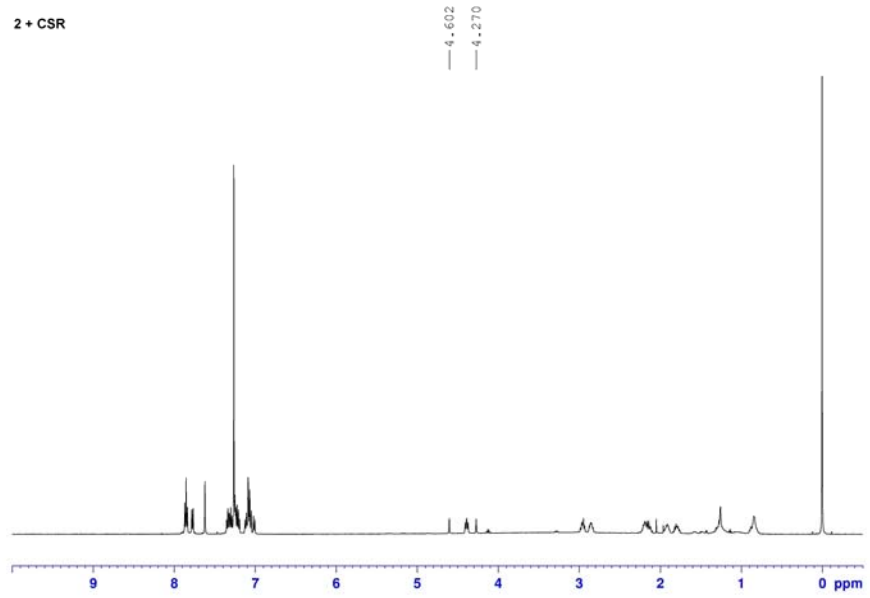


Figure S14. ^{1}H NMR Spectra of CSR and carboxylic acid 3

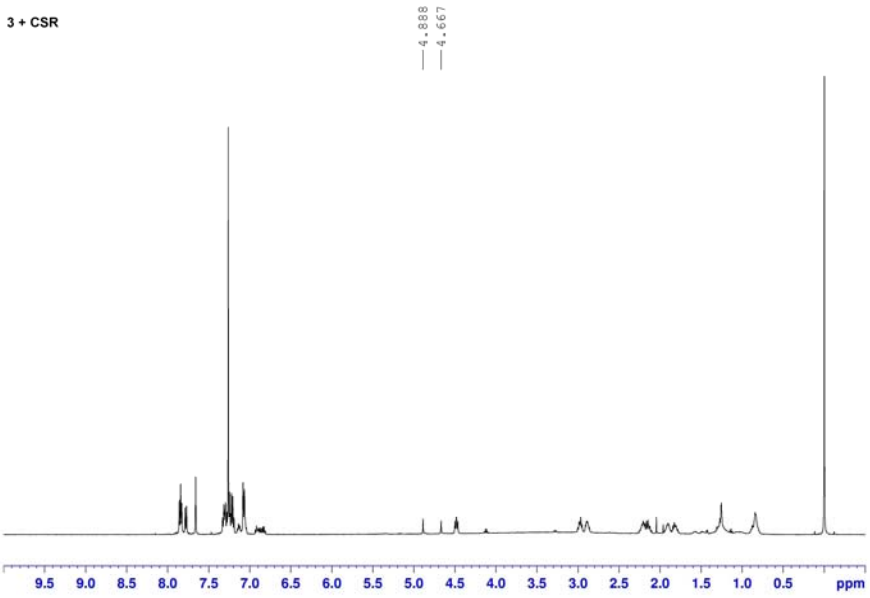


Figure S15. ^{1}H NMR Spectra of CSR and carboxylic acid 4

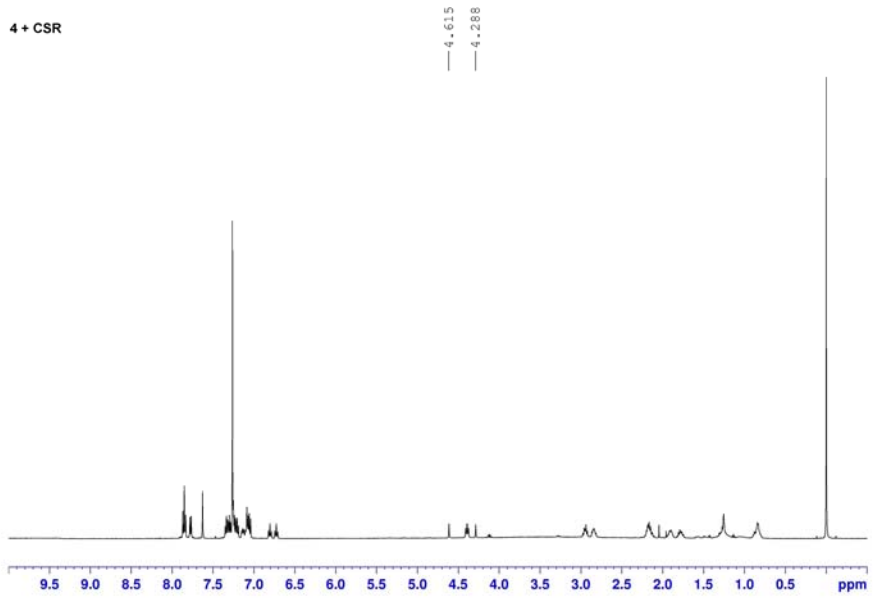


Figure S16. ^{1}H NMR Spectra of CSR and carboxylic acid 5

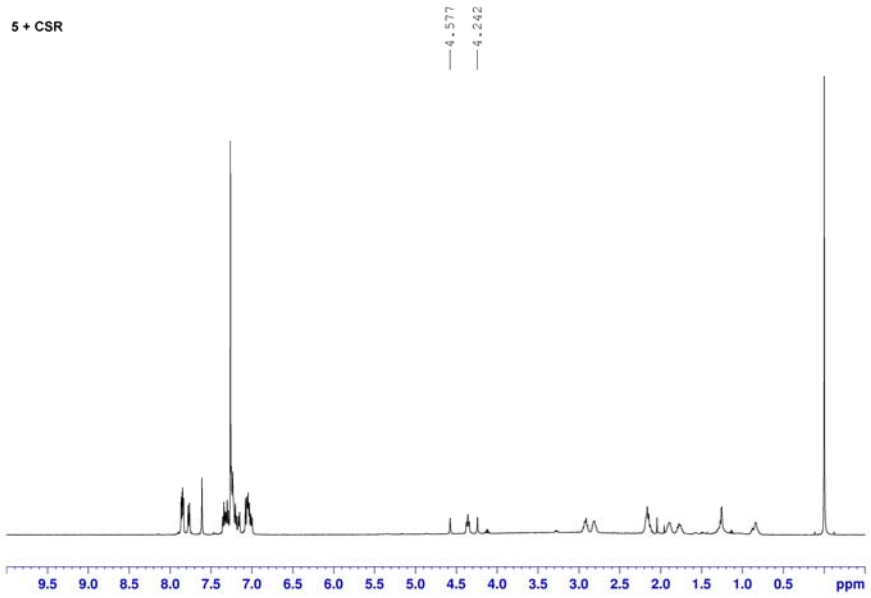


Figure S17. ^{1}H NMR Spectra of CSR and carboxylic acid 6

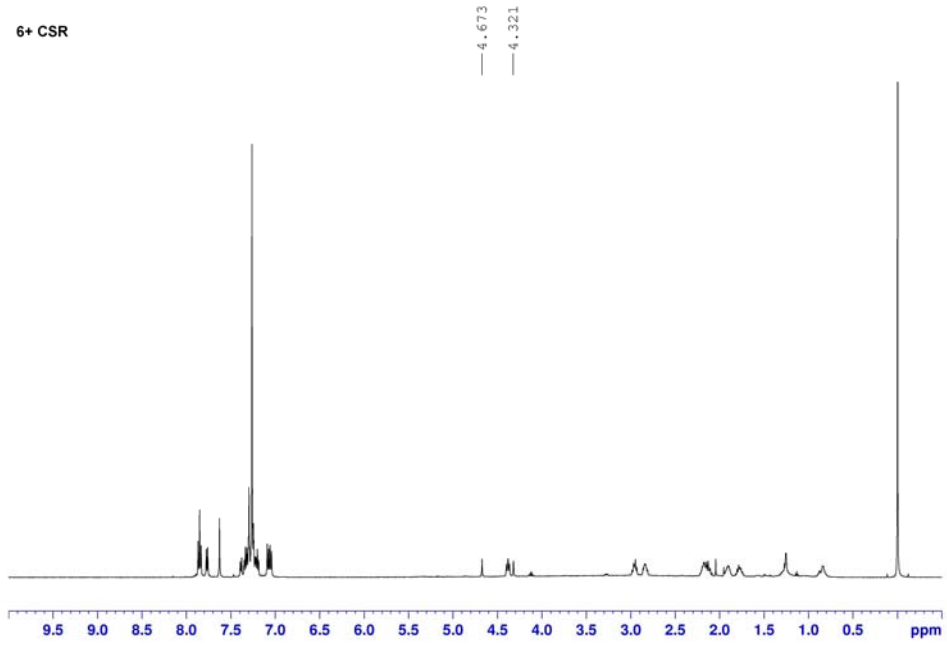


Figure S18. ^{1}H NMR Spectra of CSR and carboxylic acid 7

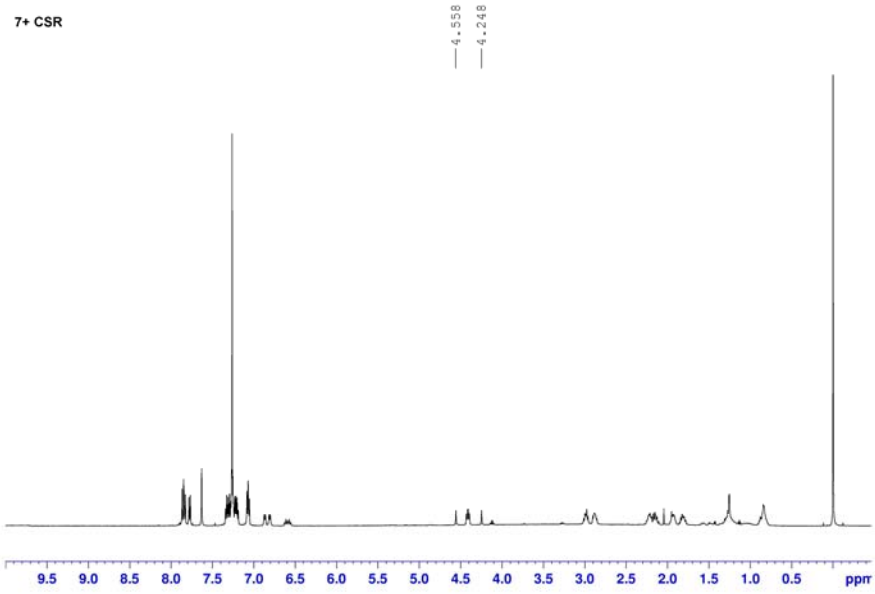


Figure S19. ^{1}H NMR Spectra of CSR and carboxylic acid 8

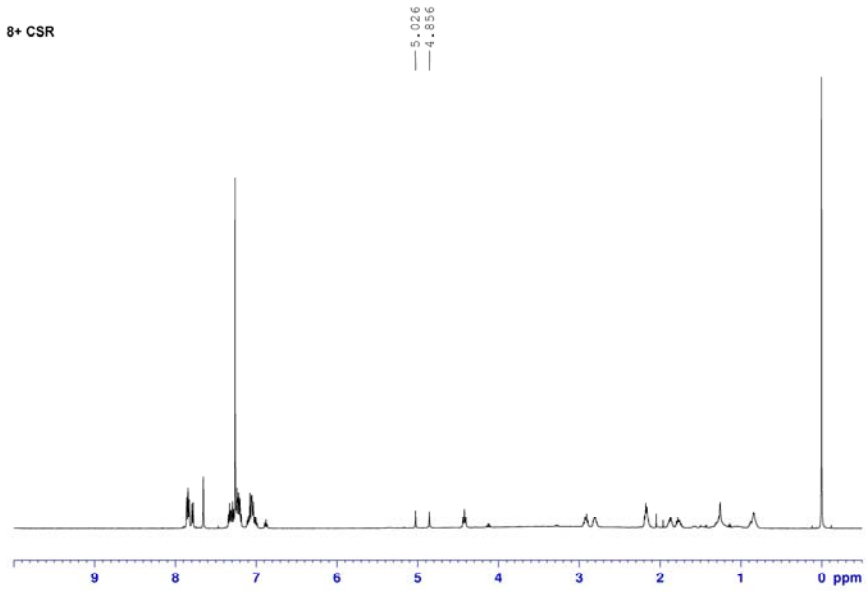


Figure S20. ^{1}H NMR Spectra of CSR and carboxylic acid 9

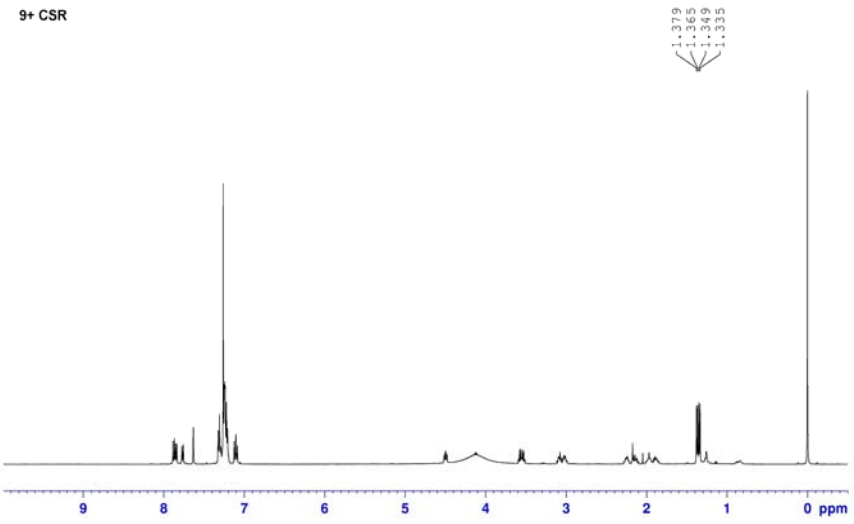


Figure S21. ^{1}H NMR Spectra of CSR and carboxylic acid 10

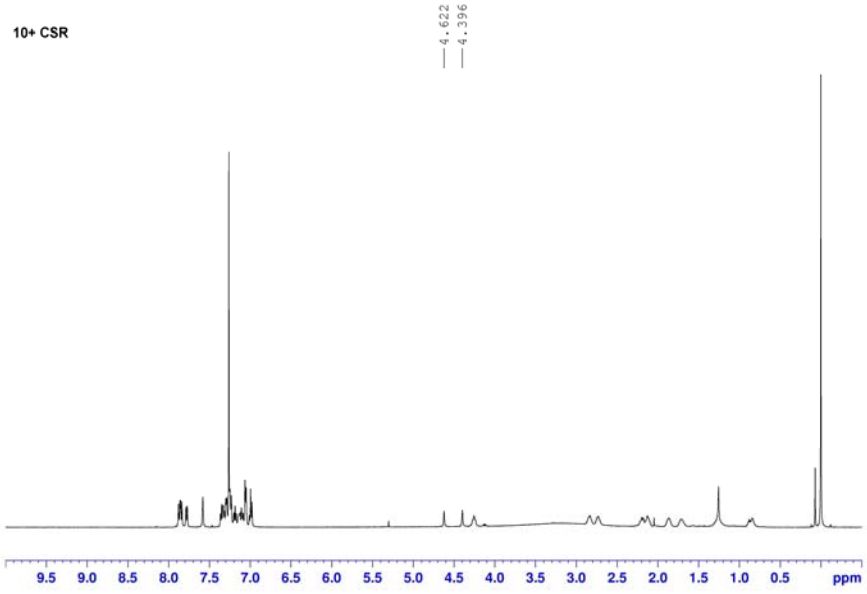


Figure S22. ^{1}H NMR Spectra of CSR and carboxylic acid 11

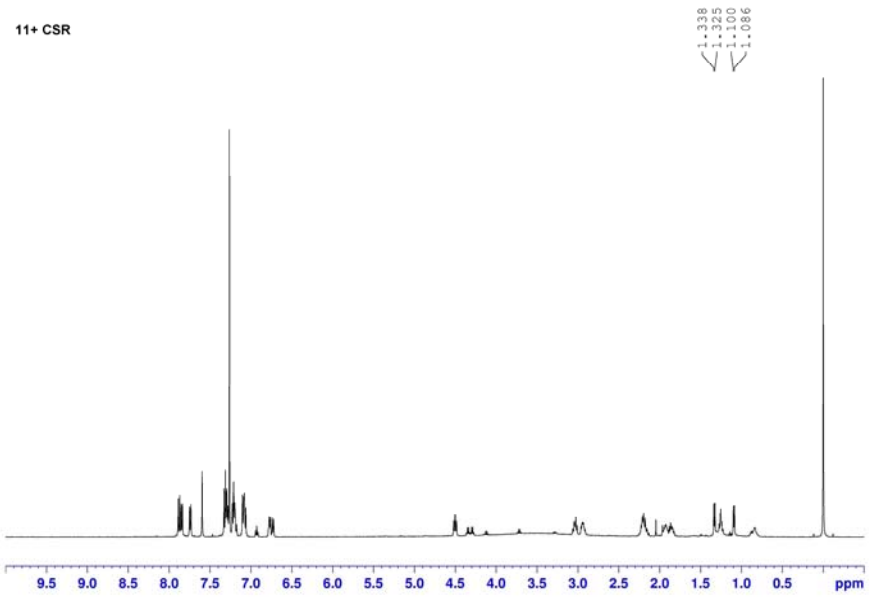


Figure S23. ^{1}H NMR Spectra of CSR and carboxylic acid 12

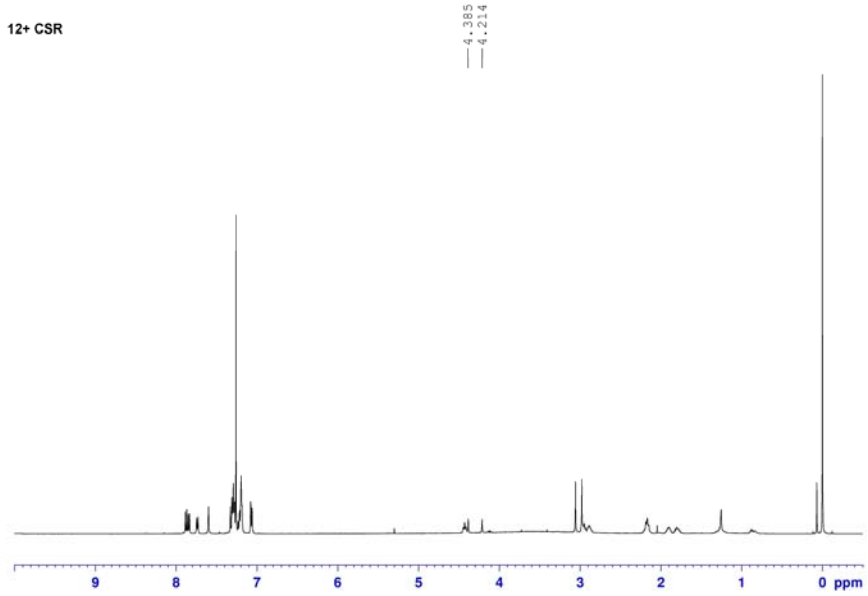


Figure S24. ^{1}H NMR Spectra of CSR and carboxylic acid 13