Electronic Supplementary Material (ESI) for RSC Advances.

Selective C-H Bond Hydroxylation of Cyclohexanes in Water by Supramolecular Control

Bin Yang,[a,b] Jian-Fang Cui*[a,b] and Man Kin Wong*[a,b]

a. The Hong Kong Polytechnic University Shenzhen Research Institute, Shenzhen, PR China.

b. State Key Laboratory of Chirosciences and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, PR China.

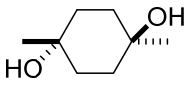
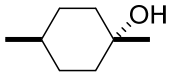
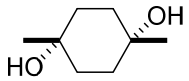
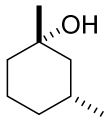
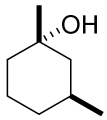
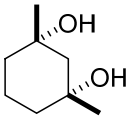
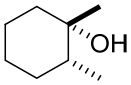
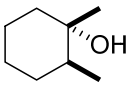
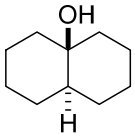
E-mail: mankin.wong@polyu.edu.hk

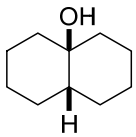
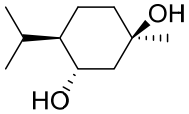
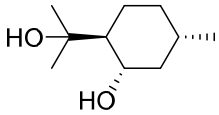
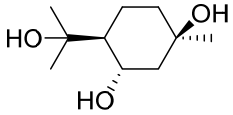
jian-fang.cui@polyu.edu.hk

Fax: +852 2364 9932

Supporting Information

Literature References

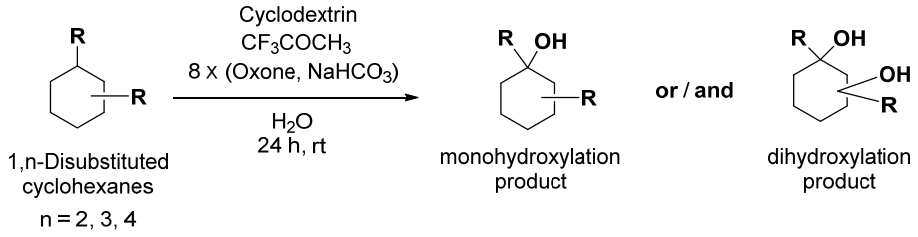
 **1a**	Z. Cohen, E. Keinan, Y. Mazur and T. H. Varkony, *J. Org. Chem.*, 1975, **40**, 2141-2142.
 **2a**	S. Lee and P. L. Fuchs, *J. Am. Chem. Soc.*, 2002, **124**, 13978-13979.
 **2b**	Z. Cohen, E. Keinan, Y. Mazur and T. H. Varkony, *J. Org. Chem.*, 1975, **40**, 2141-2142.
 **3a**	K. Maruoka, T. Itoh, M. Sakurai, K. Nonoshita and H. Yamamoto, *J. Org. Chem.*, 2006, **71**, 2283-2292.
 **4a**	P. Dai, T. K. Trullinger, X. Liu and P. H. Dussault, *J. Org. Chem.*, 2006, **71**, 2283-2292.
 **4b**	S. Kasuya, S. Kamijo and M. Inoue, *Org. Lett.*, 2009, **11**, 3630-3632.
 **5a**	R. Mello, M. Fiorentino, C. Fusco and R. Curci, *J. Am. Chem. Soc.,* 1989, **111**, 6749-6757.
 **6a**	R. Mello, M. Fiorentino, C. Fusco and R. Curci, *J. Am. Chem. Soc.,* 1989, **111**, 6749-6757.
 **7a**	S. Rozen, M. Brand and M. Kol, *J. Am. Chem. Soc.*, 1989, **111**, 8325-8326.

 **8a**	B. H. Brodsky and J. D. Bois, *J. Am. Chem. Soc.,* 2005, **127**, 15391-15393.
 **9a**	Y. Asakawa, R. Matsuda, M. Tori and T. Hashimoto*, Phytochemistry*. 1988, **27**, 3861-3869.
 **9b**	Y. Asakawa, R. Matsuda, M. Tori and T. Hashimoto*, Phytochemistry*, 1988, **27**, 3861-3869.
 **9c**	S. G. Musharraf, M. A. Ahmed, R. A. Ali and M. I. Choudhary, *Biocatal. Biotransformat.*, 2011, **29**, 77-82.

General Methods

All chemicals were purchased from commercially available sources and used without further purification. Flash column chromatography was performed using silica gel 60 (230–400 mesh ASTM) with EtOAc/n-hexane as eluent. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-400. 2D ROESY was recorded on Bruker DPX-600. The chemical shifts are expressed in ppm and coupling constants are given in Hz. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; brs, broad singlet; d, doublet; dd, double doublet; t, triplet; td, triplet doublet; m, multiplet), coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). High resolution mass spectra (HR-MS) were obtained on Agilent 6540 UHD Accurate-Mass Q-TOF LC/MS system equipped with an ion spray source in the positive ion mode.

General procedure for C-H bond hydroxylation of cycloalkanes by using β-CD or γ-CD as supramolecular hosts



To a mixture of cyclohexane substrate (1.0 mmol) and β- or γ-CD (1.1 mmol) in H_2O (50 mL) was added 1,1,1-trifluoroacetone (1.0 mmol) and stirred for 1 h. Then, 8 portions of a mixture of Oxone (2.5 mmol × 8) and $NaHCO_3$ (7.75 mmol × 8) were added within 7 h (one portion was added per hour). After stirring for a total of 24 h at room temperature, the resulting mixture was extracted with ethyl acetate (100 mL × 4). The combined organic extract was dried over anhydrous Na_2SO_4 and filtered, and the organic solvent was evaporated under reduced pressure. Purification by flash column chromatography on silica gel using 10~20% EtOAc/n-hexane gave monohydroxylation product as colorless oil and using 50~75% EtOAc/n-hexane gave dihydroxylation product as a white solid.

Procedure for selective C-H bond hydroxylation of a 1:1 mixture of 3 and 4

To a mixture of **3** (0.5 mmol) and **4** (0.5 mmol) and β- or γ-CD (1.1 mmol) in H_2O (50 mL) was added 1,1,1-trifluoroacetone (1.0 mmol) and stirred for 1 h. Then, 8 portions of a mixture of Oxone (2.5 mmol × 8) and $NaHCO_3$ (7.75 mmol × 8) were added within 7 h (one portion was added per hour). After stirring for a total of 24 h at room temperature, the resulting mixture was extracted with ethyl acetate (100 mL × 4). The combined organic extract was dried over anhydrous Na_2SO_4 and filtered, and the organic solvent was evaporated under reduced pressure. Purification by flash column chromatography on silica gel (15% EtOAc/n-hexane) gave the mixture product of **3a** and **4a** as colorless oil (9% total yield of **3a** and **4a**, the ratio of **3a**/**4a** = 1:1 when β-CD was used as supramolecular host; 26% total yield of **3a** and **4a**, the ratio of **3a**/**4a** = 2:1 when γ-CD was used as supramolecular host)

Procedure for selective C-H bond hydroxylation of a 1:1 mixture of 7 and 8

To a mixture of **7** (0.5 mmol) and **8** (0.5 mmol) and γ-CD (1.1 mmol) in H_2O (50 mL) was added 1,1,1-trifluoroacetone (1.0 mmol) and stirred for 1 h. Then, 8 portions of a mixture of Oxone (2.5 mmol × 8) and $NaHCO_3$ (7.75 mmol × 8) were added within 7 h (one portion was added per hour). After stirring for a total of 24 h at room temperature, the resulting mixture was extracted with ethyl acetate (100 mL × 4). The combined organic extract was dried over anhydrous Na_2SO_4 and filtered, and the organic solvent was evaporated under reduced pressure. Purification by flash column chromatography on silica gel using 5% EtOAc/n-hexane as eluent gave product **7a** in 13% yield (20 mg) and using 10% EtOAc/n-hexane as eluent gave product **8a** in 38% yield (58 mg).

Procedure for C-H bond oxidation of (+)-menthol (9) with β- or γ-CD

To a mixture of **9** (1.0 mmol) and β- or γ-CD (1.1 mmol) in H_2O (50 mL) was added 1,1,1-trifluoroacetone (1 mmol) and stirred for 1 h. Then, 8 portions of a mixture of Oxone (2.5 mmol × 8) and $NaHCO_3$ (7.75 mmol × 8) were added within 7 h (one portion was added per hour). After stirring for a total of 24 h at room temperature, the resulting mixture was extracted with ethyl acetate (100 mL × 4). The combined organic extract was dried over anhydrous Na_2SO_4 and filtered, and the organic solvent was evaporated under reduced pressure. Purification by flash column chromatography on silica gel using 30% EtOAc/n-hexane as eluent gave product **9b**, using 60% EtOAc/n-hexane as eluent gave product **9a**, and using 75% EtOAc/n-hexaneas eluent gave product **9c**.

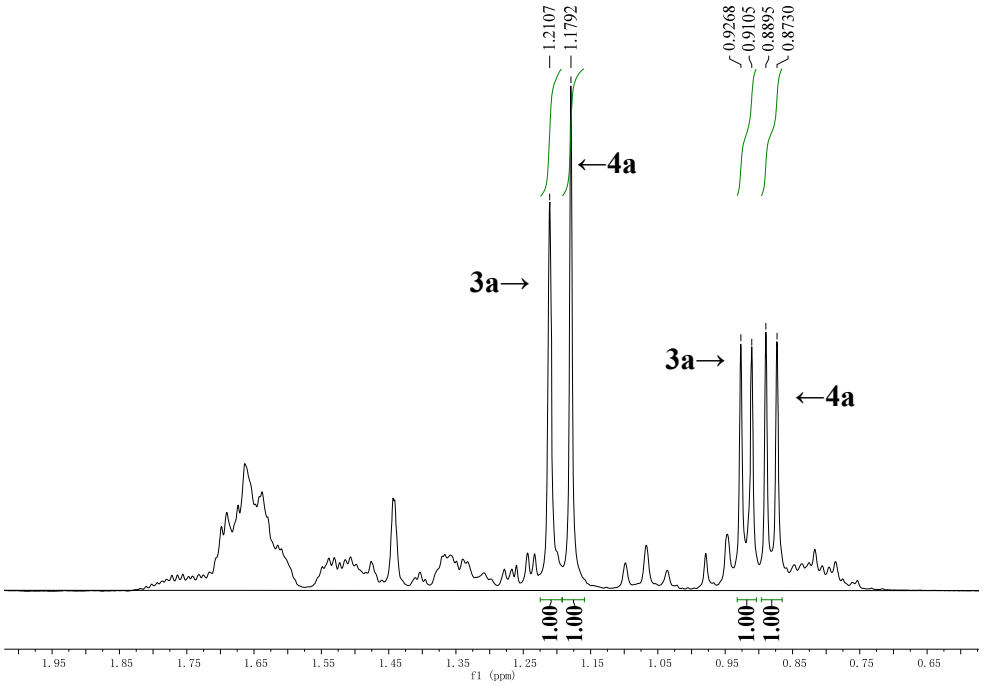


Fig. S1 Partial ^{1}H NMR spectra of **3a** and **4a** when β-CD was used as the supramolecular host.

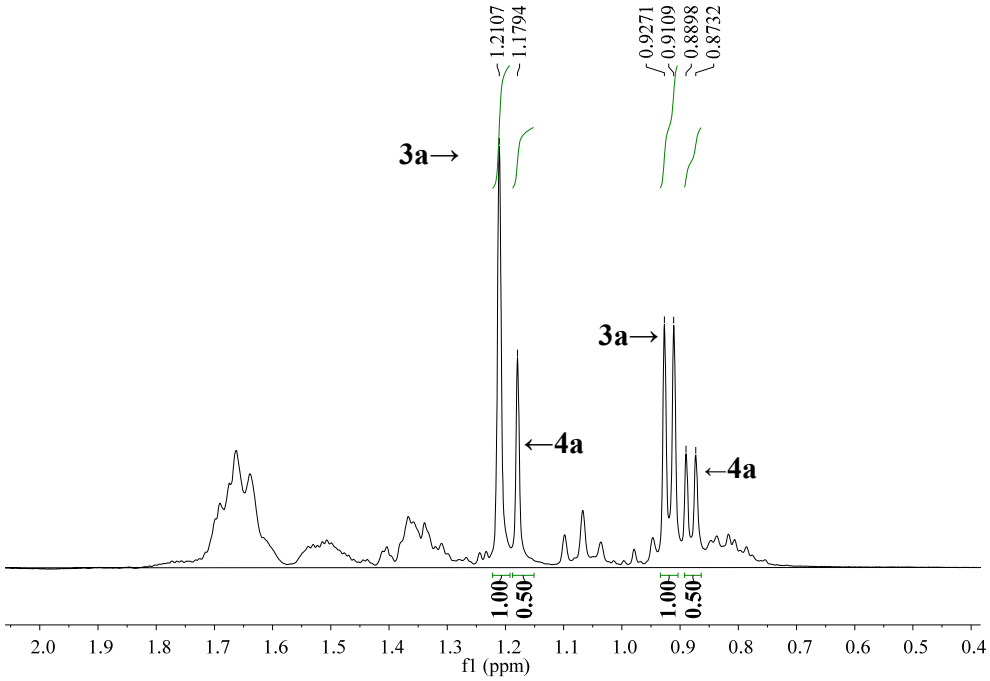


Fig. S2 Partial ^{1}H NMR spectra of **3a** and **4a** when γ-CD was used as the supramolecular host.

^{1}H NMR titration experiments of *trans*-1,4-dimethylcyclohexane (1) [or (1R,2R,5S)-(+)-menthol (9)] with β-CD

The mixtures of *trans*-1,4-dimethylcyclohexane (**1**) [or (1R,2R,5S)-(+)-menthol (**9**)] with β-CD for the ^{1}H NMR titration experiments were prepared by mixing indicated volume of (i) **1** (or **9**) stock solutions [100 mM, 0.1 mmol of **1** (or **9**) in 1.0 mL of d^6-acetone), (ii) β-CD stock solution (4 mM, 0.04 mmol of β-CD in 10 mL of D_2O), and (iii) volume of β-CD stock solution is ~500 μL (**Table S1**).

Table S1

Entry	Molar ratio of **1** (or **9**) : β-CD	Volume of **1** (or **9**) stock solutions (μL)	Volume of β-CD stock solution (μL)
1	0:10	0	500
2[a]	1:10	2	500
3	2:10	4	500
4	4:10	8	500
5	6:10	12	500
6	8:10	16	500
7	10:10	20	500
8	12:10	24	500
9	15:10	30	500
10	20:10	40	500

Remarks: In general, the mixtures with high ratio of β-CD are opaque and viscous (entries 1-7) while transparent solutions are observed in the mixtures with low ratio of β-CD (entries 8-9). [a] Data of this entry was not used for (1R,2R,5S)-(+)-menthol (**9**) with β-CD.

The mixtures were subjected to ^{1}H NMR analysis. The changes of the chemical shift of H3 of β-CD (with the chemical shift of H4 of β-CD as the internal reference) are obtained as $\Delta\delta_{obs}$ which is used for the calculation of the binding constant.

The binding constants (K) of **1** (or **9**) to β-CD were calculated by fitting $\Delta\delta_{obs}$ into Scott's plot as the equation shown below (R. L. Scott, *Recl. Trav. Chim. Pays-Bas*, 1956, **75**, 787):

$$[\mathbf{1}\ (\text{or}\ \mathbf{9})] / \Delta\delta_{obs} = [\mathbf{1}\ (\text{or}\ \mathbf{9})] / \Delta\delta_{max} + \Delta\delta_{max} / K$$

where [**1** (or **9**)] is the concentration of **1** (or **9**) with normalized concentration of β-CD; $\Delta\delta_{obs}$ is the observed change of the chemical shift of H3 of β-CD at different concentrations of **1** (or **9**); $\Delta\delta_{max}$ is the maximum change of the chemical shift of H3 of β-CD.

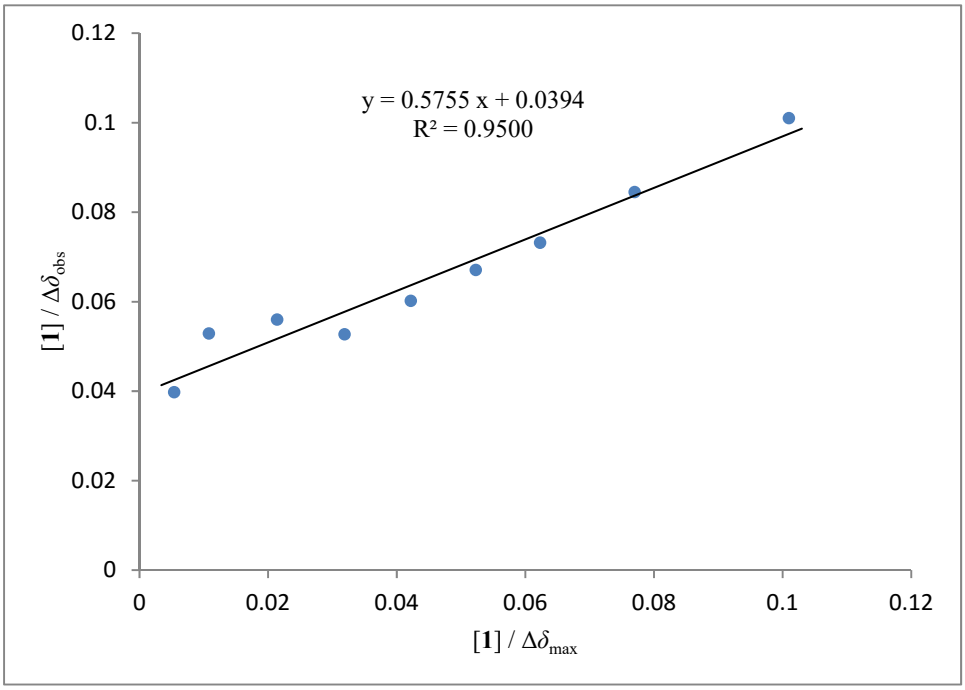


Fig. S3 Scott's plot of ^{1}H NMR titration of **1** and β-CD

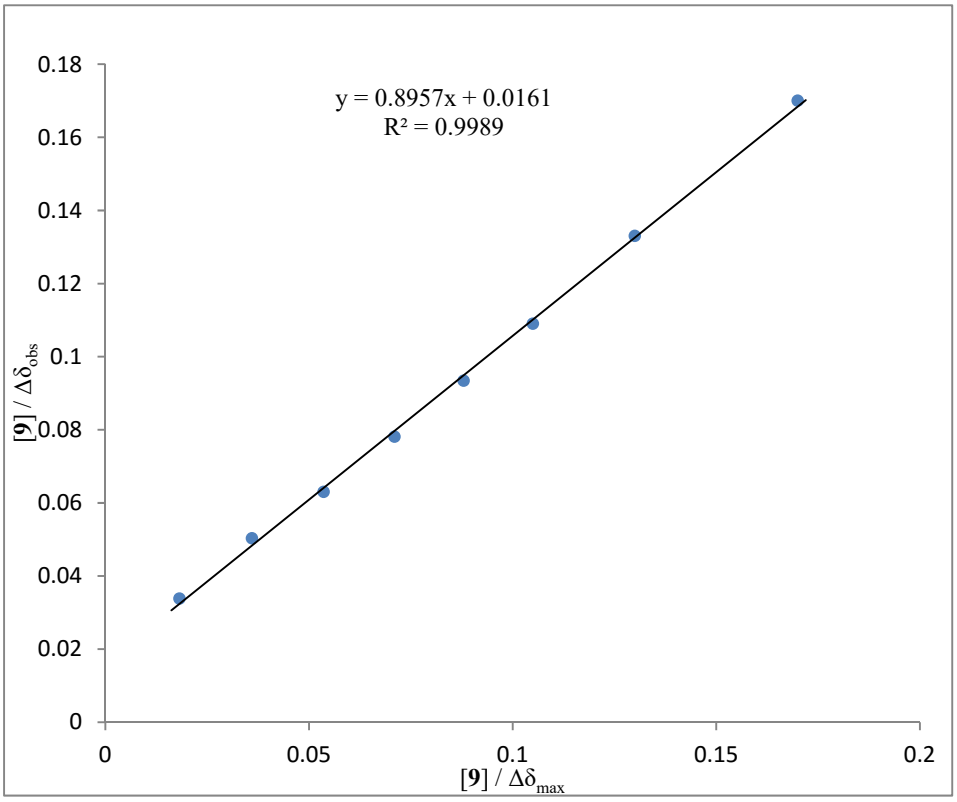


Fig. S4 Scott's plot of ^{1}H NMR titration of **9** and β-CD

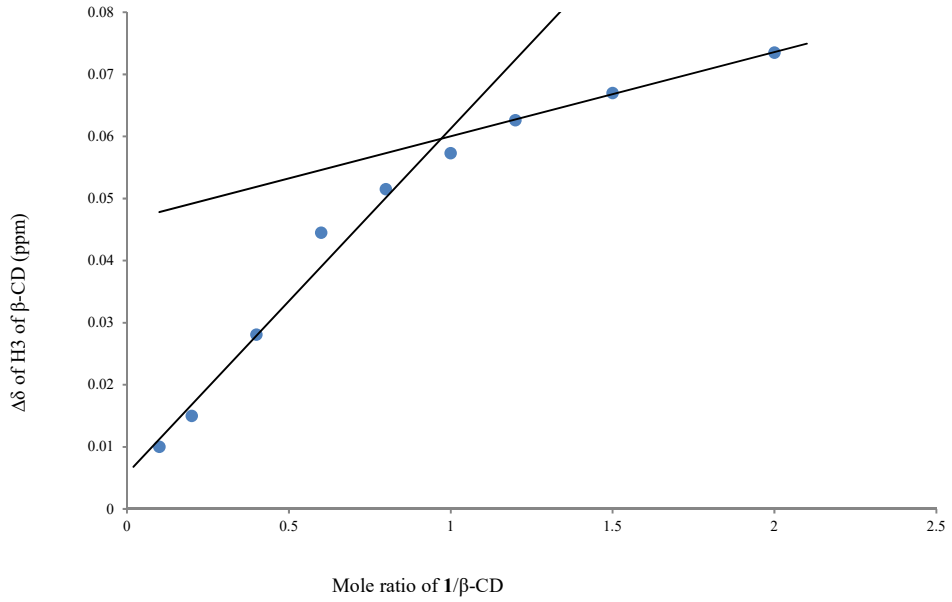


Figure S5. ^{1}H NMR titration curve for **1** and β-CD

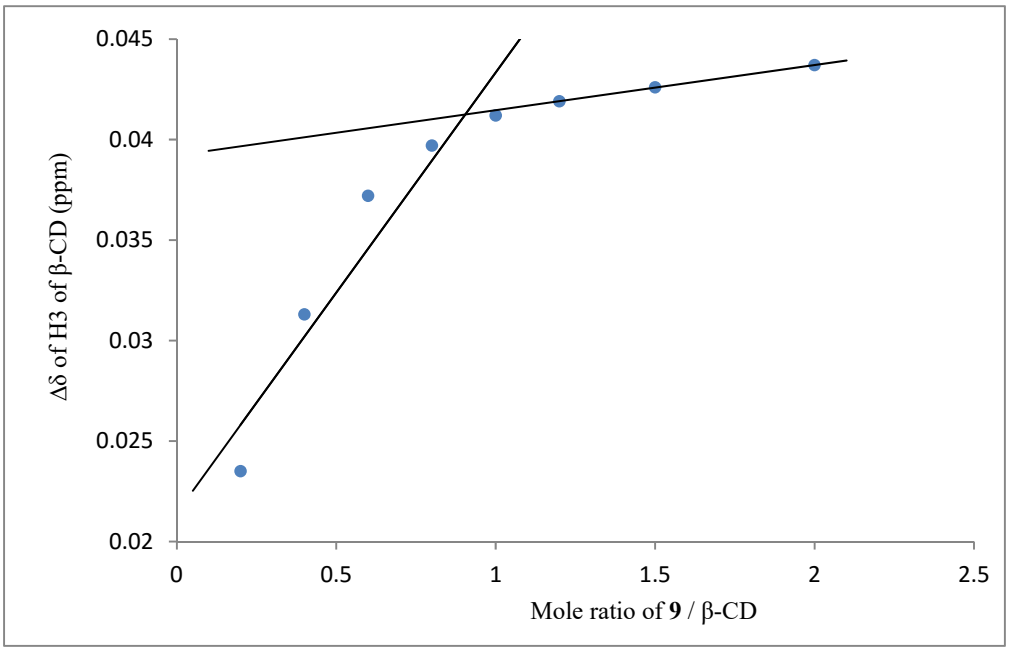


Figure S6. ^{1}H NMR titration curve for **9** and β-CD

^{1}H NMR titration experiments of *trans*-1,4-dimethylcyclohexane (1) [or (1R,2R,5S)-(+)-menthol (9)] with γ-CD

The mixtures of **1** (or **9**) with γ-CD for the ^{1}H NMR titration experiments were prepared by mixing indicated volume of (i) **1** (or **9**) stock solutions (100 mM, 0.1 mmol of **1** (or **9**) in 1 mL of d^6-acetone), (ii) γ-CD stock solution (4 mM, 0.04 mmol of γ-CD in 10 mL of D_2O), (iii) Volume of γ-CD stock solution is ~500 μL (**Table S2**).

Table S2

Entry	Mole Ratio of **1** (or **9**) : γ-CD	Volume of **1** (or **9**) stock solutions (μL)	Volume of γ-CD stock solution (μL)
1	0:10	0	500
2	1:10	2	500
3	4:10	8	500
4	7:10	14	500
5	10:10	20	500
6	12:10	24	500
7	15:10	30	500
8	18:10	36	500
9	20:10	40	500
10	25:10	50	500
11	30:10	60	500
12	35:10	70	500
13	40:10	80	500

Remarks: In general, the mixtures with high ratio of γ-CD are opaque and viscous (entries 1-4) while transparent solutions are observed in the mixtures with low ratio of γ-CD (entries 5-13).

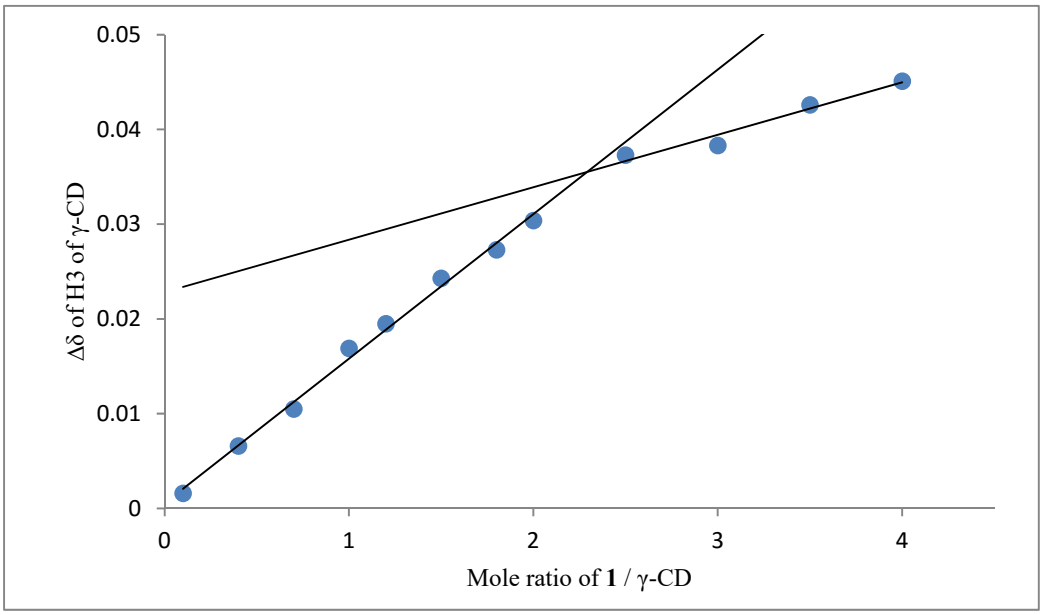


Figure S7. ^{1}H NMR titration curve for **1** and γ-CD

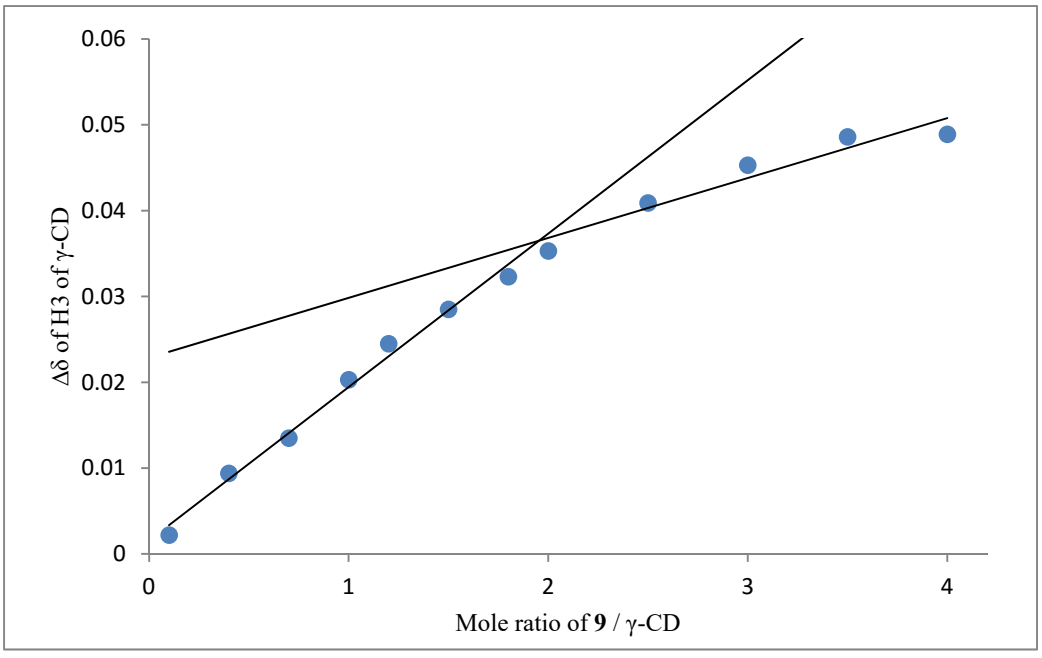
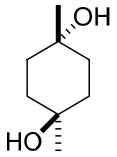


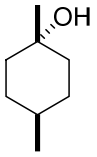
Figure S8. ^{1}H NMR titration curve for **9** and γ-CD

Characterization Data of Compounds



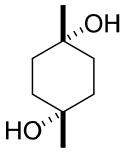
1a

White solid, analytical TLC (silica gel 60, 70% EtOAc in n-hexane), R_f = 0.30;
^{1}H NMR (400 MHz, d^6-DMSO): δ 3.85 (s, 2H), 1.56 (d, J = 8.9 Hz, 4H), 1.27 (d, J = 8.3 Hz, 4H), 1.07 (s, 6H);
^{13}C NMR (100 MHz, CD_3OD): δ 68.1, 33.9, 29.4.



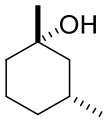
2a

Colorless liquid, analytical TLC (silica gel 60, 10% EtOAc in n-hexane), R_f = 0.36;
^{1}H NMR (400 MHz, CD_3OD): δ 1.66 (t, J = 10.9 Hz, 1H), 1.52-1.31 (m, 1H), 1.17 (d, J = 28.2 Hz, 1H), 1.08 (dd, J = 22.1, 11.6 Hz, 1H), 0.93 (d, J = 6.6 Hz, 1H);
^{13}C NMR (100 MHz, $CDCl_3$): δ 70.8, 39.8, 32.3, 31.8, 26.0, 21.5.



2b

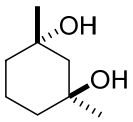
Colorless liquid, analytical TLC (silica gel 60, 70% EtOAc in n-hexane), R_f = 0.18;
^{1}H NMR (400 MHz, d^6-DMSO): δ 4.01 (s, 2H), 1.58 (dd, J = 12.5, 8.0 Hz, 4H), 1.25 (dd, J = 12.2, 7.7 Hz, 4H), 1.06 (s, 6H);
^{13}C NMR (100 MHz, $CDCl_3$): δ 69.5, 36.3, 27.8.



3a

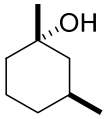
Colorless liquid, analytical TLC (silica gel 60, 10% EtOAc in n-hexane), R_f = 0.34;

^{1}H NMR (400 MHz, d^{6}-DMSO): δ 4.21 (s, 1H), 1.64-1.46 (m, 4H), 1.45-1.33 (m, 1H), 1.3-1.12 (m, 2H), 1.08 (s, 3H), 0.96 (t, J = 12.3 Hz, 1H), 0.84 (d, J = 6.5 Hz, 3H), 0.77-0.67 (m, 1H);
^{13}C NMR (100 MHz, $CDCl_3$): δ 71.3, 49.5, 40.2, 34.6, 30.6, 26.0, 23.8, 22.6.



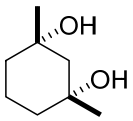
3b

White solid, analytical TLC (silica gel 60, 50% EtOAc in n-hexane), R_f = 0.43;
^{1}H NMR (400 MHz, d^{6}-DMSO): δ 3.91 (s, 2H), 1.43 (dd, J = 11.6, 5.9 Hz, 2H), 1.39 (s, 2H), 1.28 (dd, J = 9.8, 5.0 Hz, 4H), 1.11 (s, 6H);
^{13}C NMR (100 MHz, CD_3OD): δ 70.2, 50.7, 48.2, 48.0, 38.7, 28.9, 19.6.



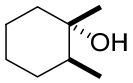
4a

Colorless liquid, analytical TLC (silica gel 60, 10% EtOAc in n-hexane), R_f = 0.34;
^{1}H NMR (400 MHz, d^{6}-DMSO): δ 3.83 (s, 1H), 1.79-1.60 (m, 1H), 1.59-1.40 (m, 4H), 1.42-1.31 (m, 1H), 1.12-0.96 (m, 4H), 0.85-0.73 (m, 4H), 0.72-0.57 (m, 1H);
^{13}C NMR (100 MHz, $CDCl_3$): δ 70.0, 47.6, 38.3, 34.4, 31.7, 28.0, 22.5, 21.8.



4b

White solid, analytical TLC (silica gel 60, 50% EtOAc in n-hexane), R_f = 0.20;
^{1}H NMR (400 MHz, CD_3OD): δ 2.00-1.86 (m, 1H), 1.67 (d, J = 13.0 Hz, 3H), 1.56-1.48 (m, 1H), 1.40 (d, J = 13.8 Hz, 1H), 1.31 (dt, J = 7.5, 6.3 Hz, 2H), 1.17 (s, 6H);
^{13}C NMR (100 MHz, $CDCl_3$): δ 71.2, 48.1, 38.3, 31.2, 17.5.

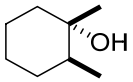


5a

Colorless liquid, analytical TLC (silica gel 60; 10% EtOAc in n-hexane), R_f = 0.40;

^{1}H NMR (400 MHz, CD_3OD): δ 1.72-1.54 (m, 3H), 1.53-1.23 (m, 6H), 1.18 (s, 3H), 0.93 (d, J = 6.0 Hz, 1H);

^{13}C NMR (100 MHz, CD_3OD): δ 70.5, 40.3, 39.6, 30.2, 27.5, 25.7, 21.7, 14.2.

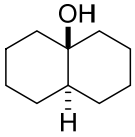


6a

Colorless liquid, analytical TLC (silica gel 60; 10% EtOAc in n-hexane), R_f = 0.28;

^{1}H NMR (400 MHz, d^6-DMSO): δ 3.99 (s, 1H), 1.61-1.46 (m, 4H), 1.42-1.31 (m, 1H), 1.30-1.19 (m, 2H), 1.20-1.06 (m, 1H), 1.04-0.92 (m, 1H), 0.91 (s, 3H), 0.80 (d, J = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, d^6-DMSO): δ 68.2, 48.0, 38.5, 34.7, 32.4, 27.7, 23.1, 21.8.

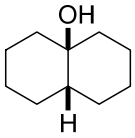


7a

White solid, analytical TLC (silica gel 60, 10% EtOAc in n-hexane), R_f = 0.52;

^{1}H NMR (400 MHz, d^6-DMSO): δ 3.51 (s, 1H), 1.67-1.56 (m, 4H), 1.43-1.39 (m, 2H), 1.36-1.24 (m, 4H), 0.98-0.76 (m, 1H), 1.21-0.99 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 70.1, 44.2, 39.7, 28.6, 26.3, 21.6.

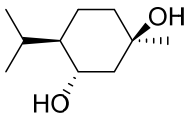


8a

White solid, analytical TLC (silica gel 60, 10% EtOAc in n-hexane), R_f = 0.38;

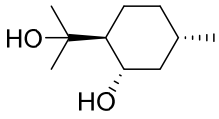
^{1}H NMR (400 MHz, d^6-DMSO): δ 3.87 (s, 1H), 1.71-1.49 (m, 5H), 1.49-1.33 (m, 4H), 1.33-1.06 (m, 8H).

^{13}C NMR (100 MHz, d^6-DMSO): δ 69.9, 42.6, 28.0 (brs), 23.1 (brs).



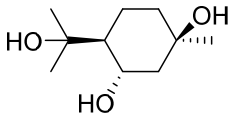
9a

White solid, analytical TLC (silica gel 60, 10% EtOAc in n-hexane), R_f = 0.40;
^{1}H NMR (400 MHz, d^6-DMSO): δ 4.11 (d, J = 6.0 Hz, 1H), 3.92 (s, 1H), 3.54-3.40 (m, 1H), 2.23-2.11 (m, 1H), 1.78 (d, J = 12.2 Hz, 1H), 1.48 (d, J = 12.9 Hz, 1H), 1.27 (d, J = 8.1 Hz, 2H), 1.17-1.03 (m, 5H), 1.01-0.89 (m, 1H), 4.11 (d, J = 6.0 Hz, 1H), 0.75 (d, J = 6.9 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): δ 71.5, 68.5, 50.1, 48.2, 38.4, 31.6, 25.8, 21.0, 19.0, 16.2.



9b

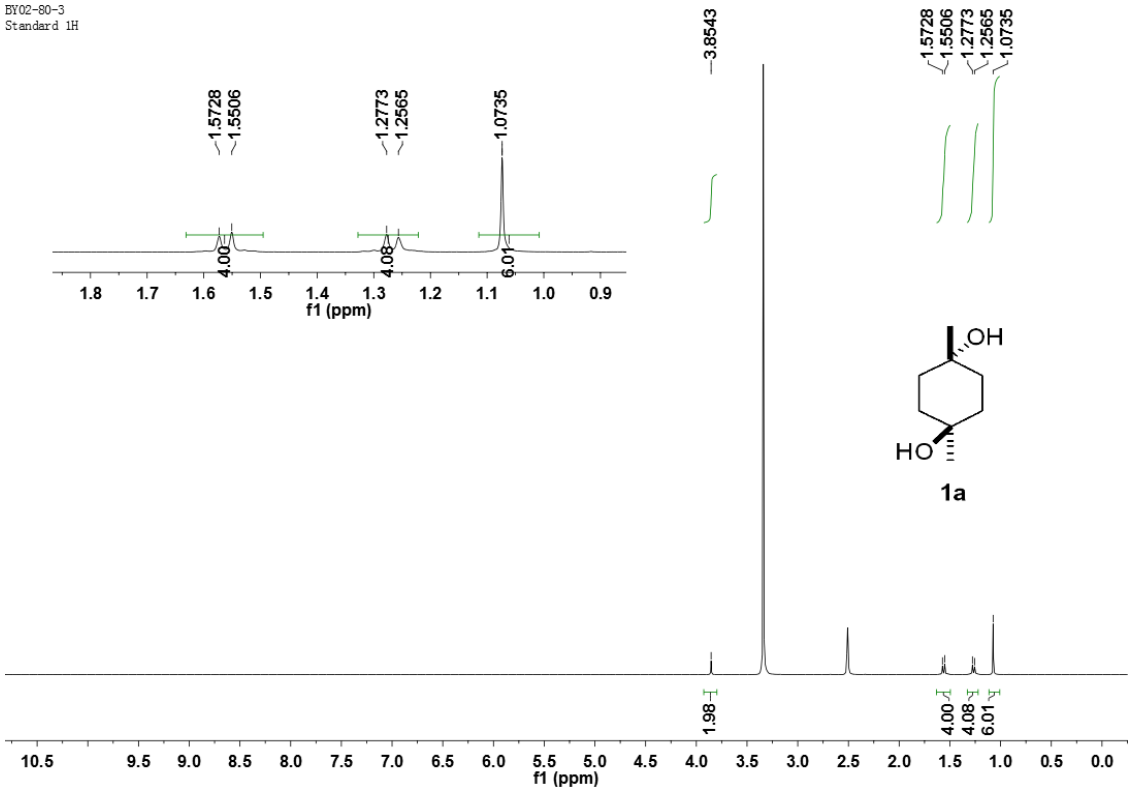
White solid, analytical TLC (silica gel 60, 10% EtOAc in n-hexane), R_f = 0.40;
^{1}H NMR (400 MHz, CD_3OD): δ 3.68 (td, J = 10.5, 4.3 Hz, 1H), 1.94-1.85 (m, 1H), 1.78-1.64 (m, 2H), 1.54-1.38 (m, 1H), 1.38-1.30 (m, 1H), 1.18 (d, J = 9.7 Hz, 6H), 1.08-0.94 (m, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.90-0.80 (m, 1H);
^{13}C NMR (100 MHz, CD_3OD): δ 74.2, 72.4, 52.9, 44.3, 34.4, 31.2, 28.3, 26.5, 22.7, 21.0.

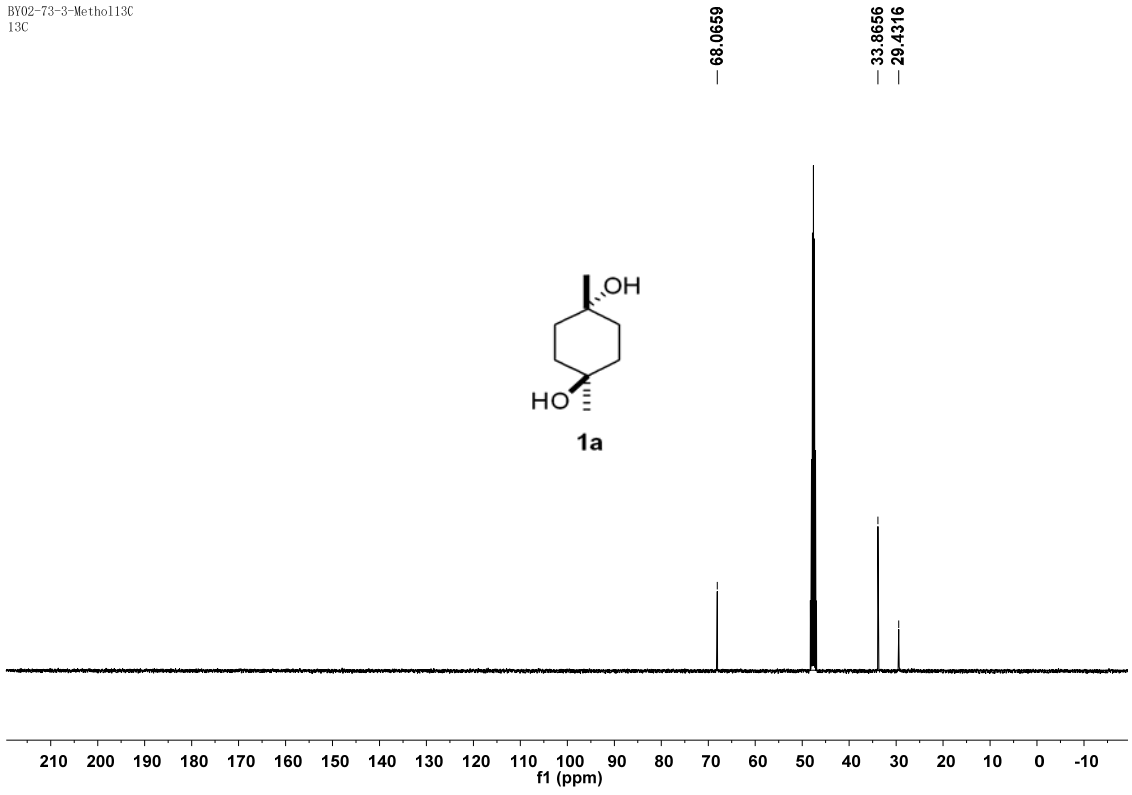


9c

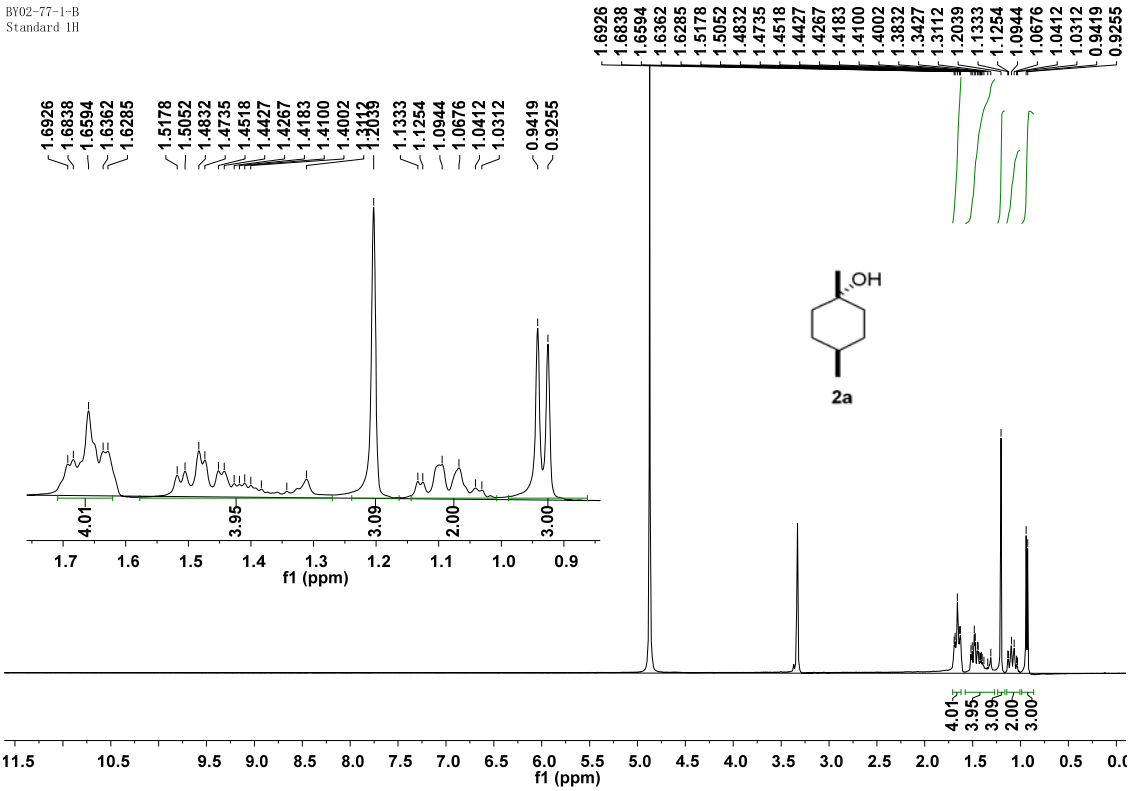
White solid, analytical TLC (silica gel 60, 70% EtOAc in n-hexane), R_f = 0.16;
^{1}H NMR (400 MHz, CD_3OD): δ 4.10-3.94 (m, 1H), 1.97-1.81 (m, 1H), 1.72-1.58 (m, 1H), 1.58-1.48 (m, 1H), 1.46-1.29 (m, 4H), 1.22 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H);
^{13}C NMR (100 MHz, $CDCl_3$): δ 75.2, 71.1, 69.6, 53.4, 48.0, 38.4, 31.4, 30.2, 23.9, 22.9.

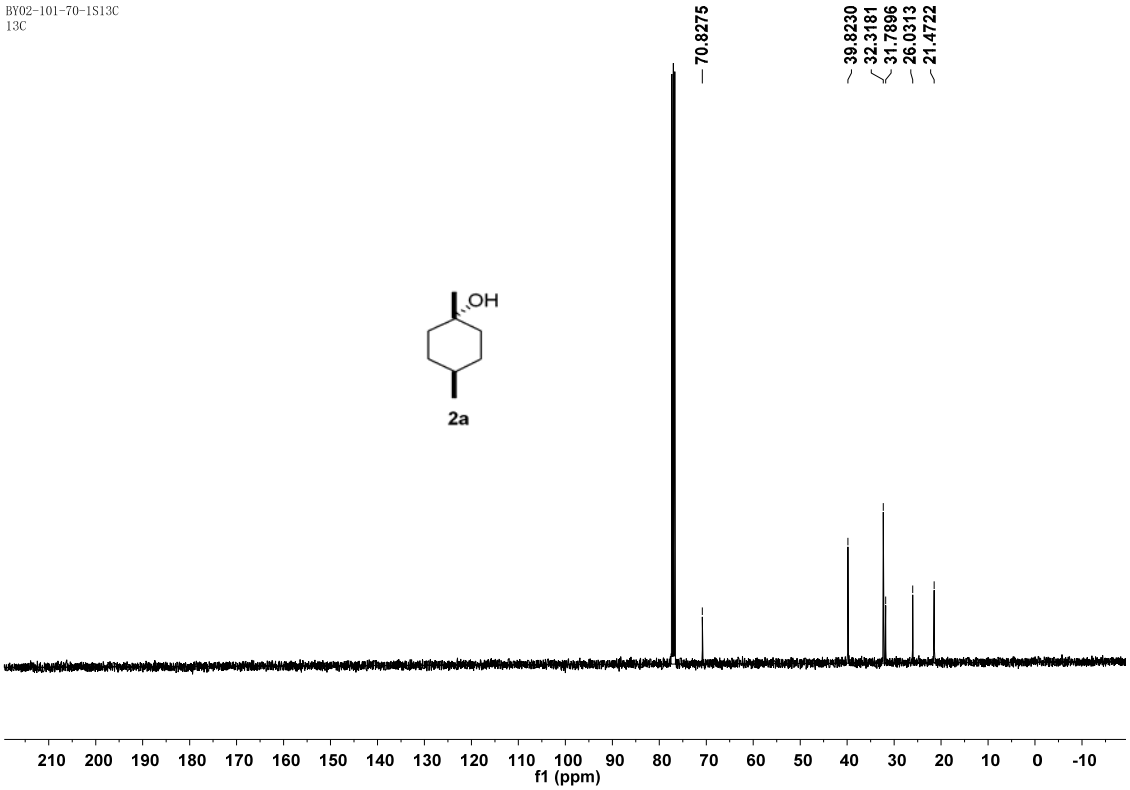
^{1}H NMR (400 MHz, d^{6}-DMSO) and ^{13}C NMR (100 MHz, CD_3OD) of **1a**



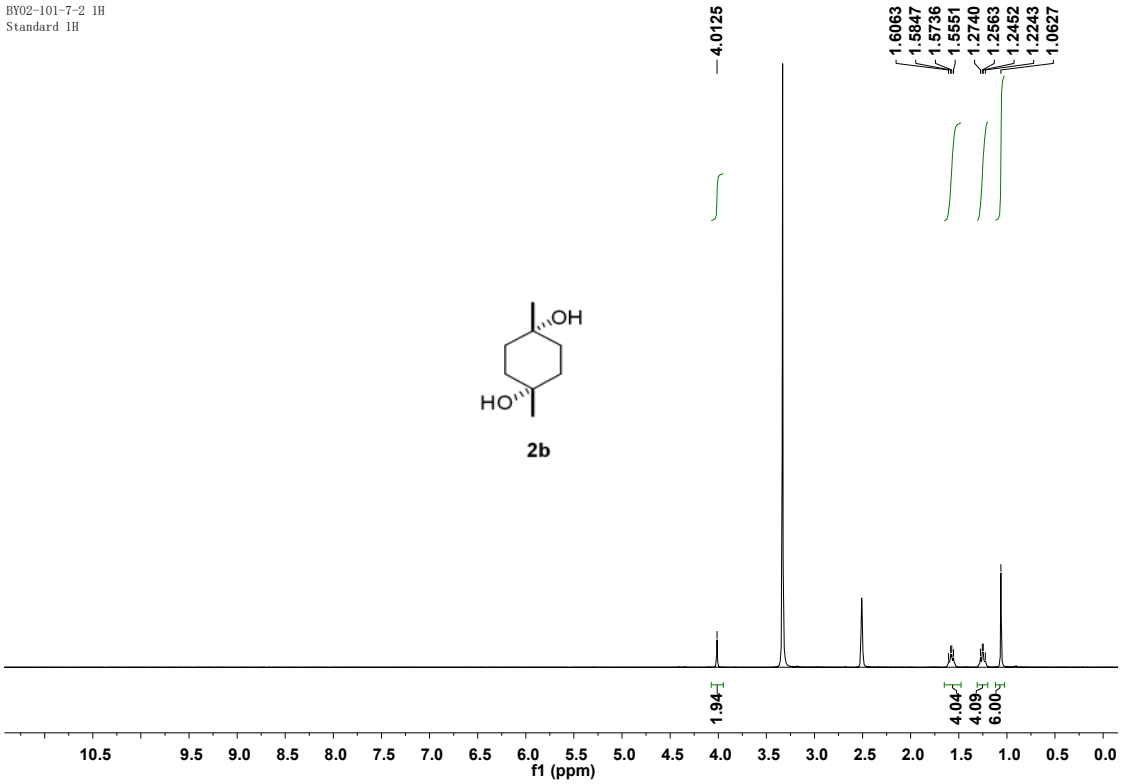


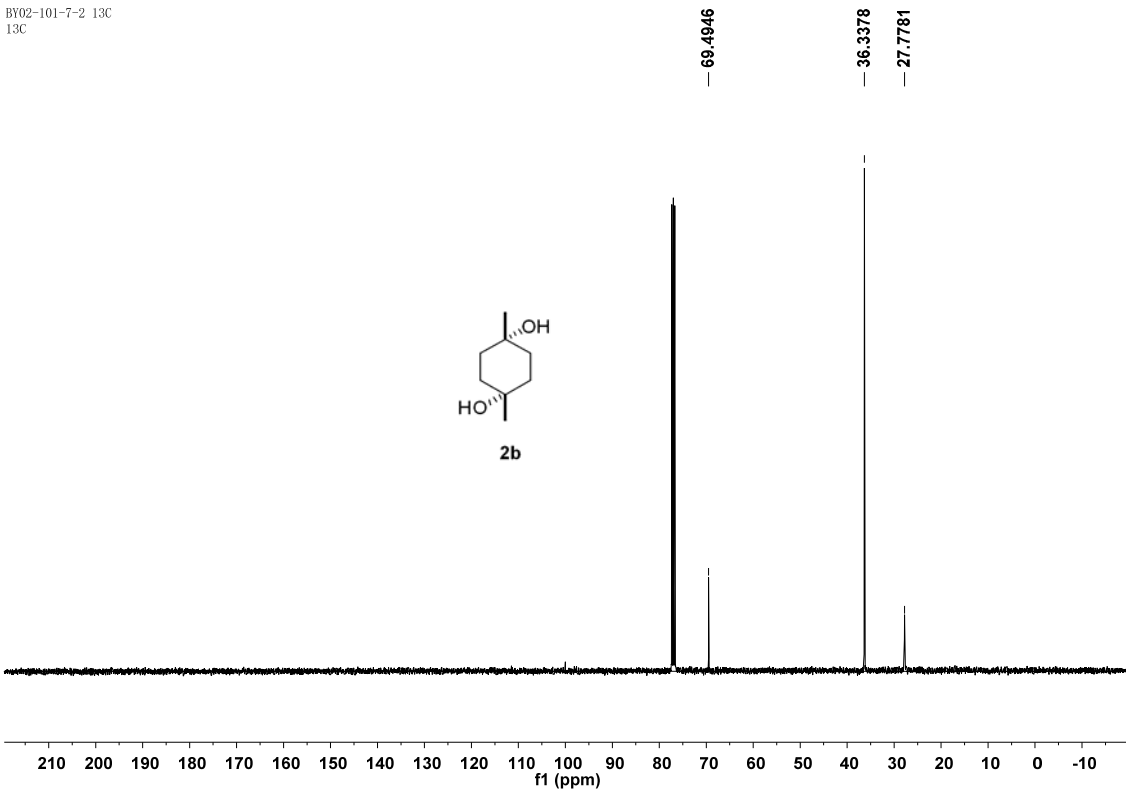
^{1}H NMR (400 MHz, CD_3OD) and ^{13}C NMR (400 MHz, $CDCl_3$) of **2a**



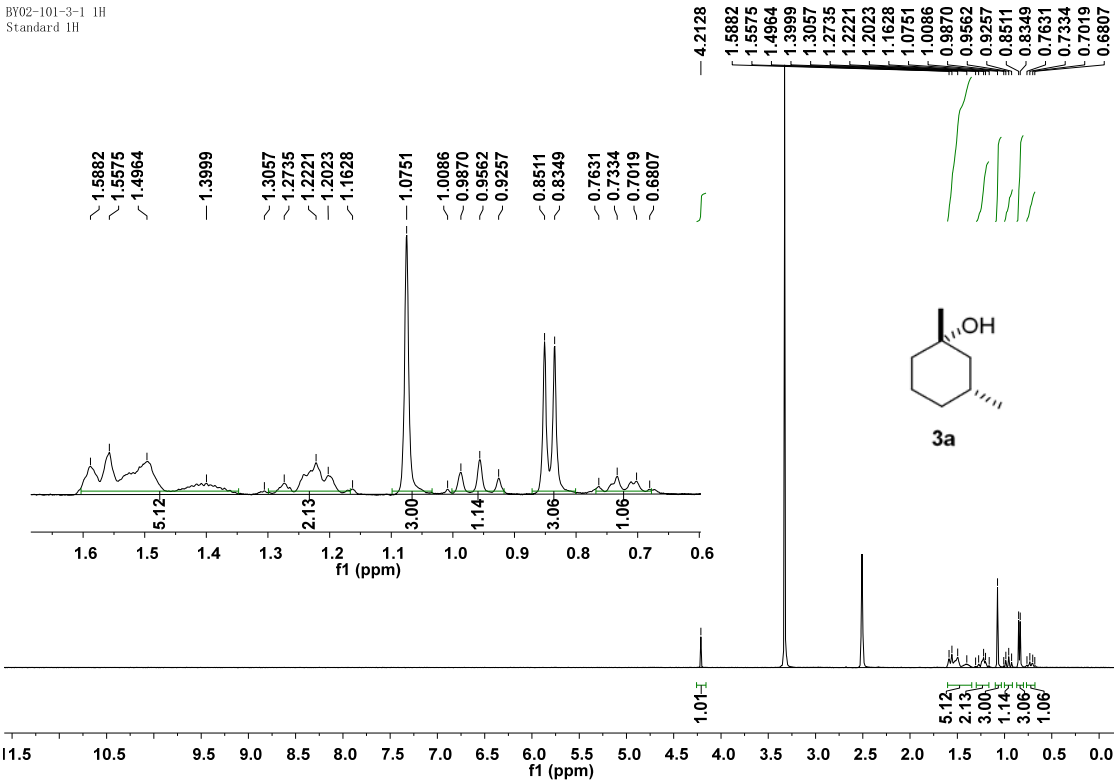


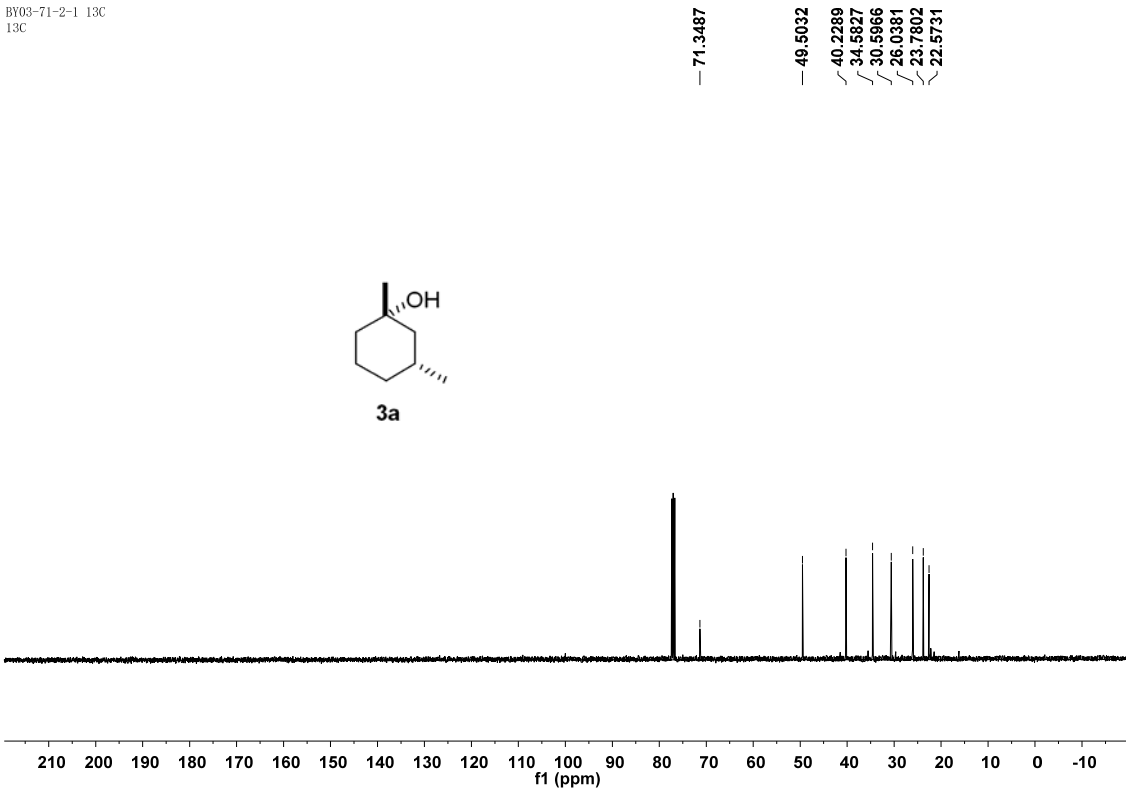
^{1}H NMR (400 MHz, d^{6}-DMSO) and ^{13}C NMR (100 MHz, $CDCl_3$) of **2b**



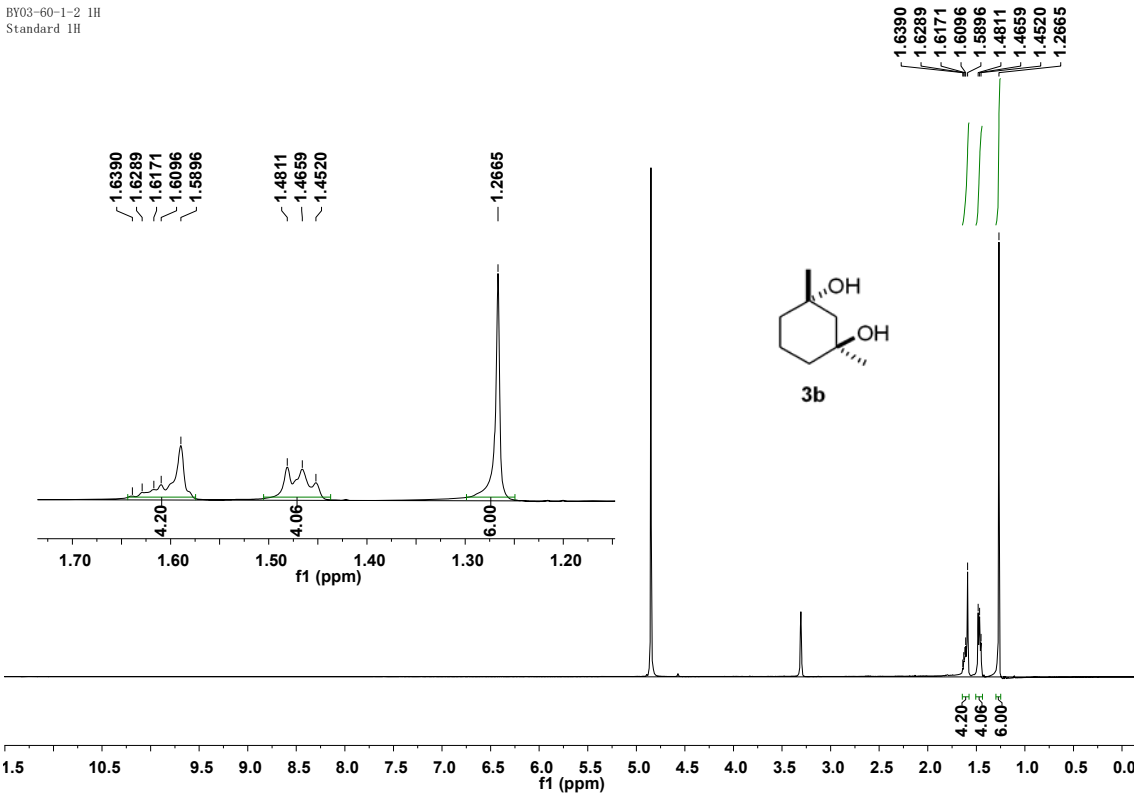


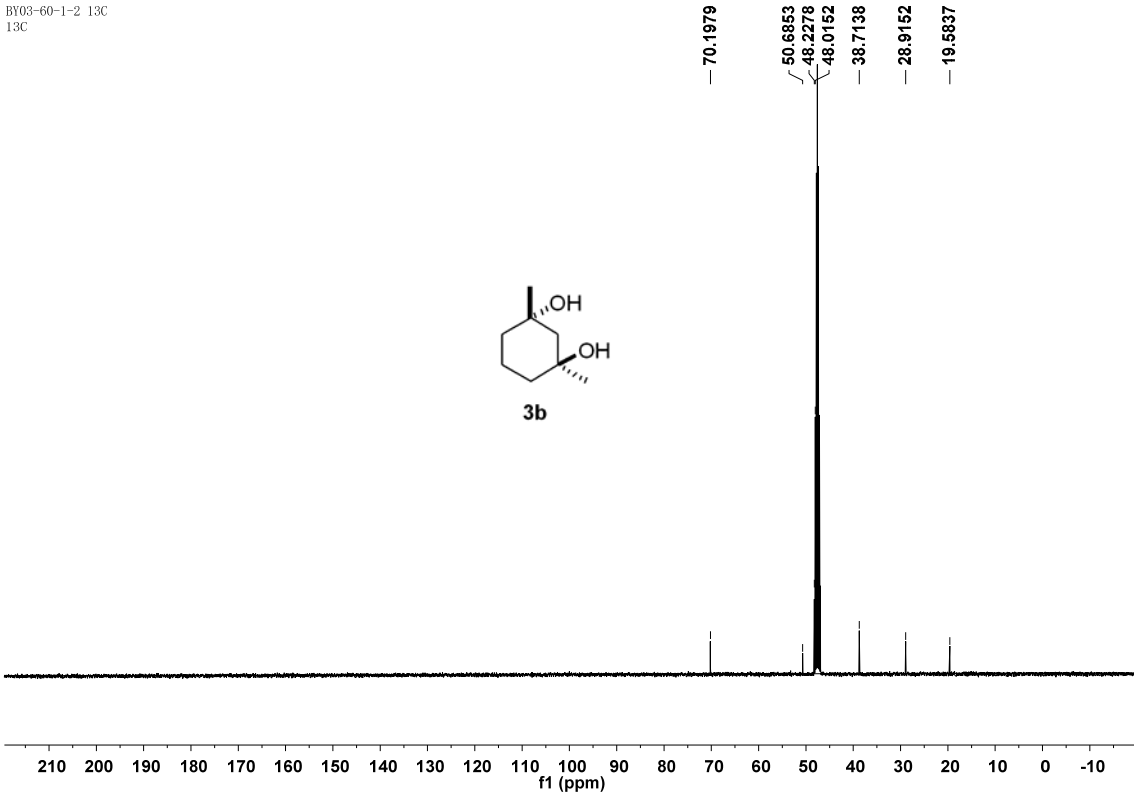
^{1}H NMR (400 MHz, d^{6}-DMSO) and ^{13}C NMR (100 MHz, $CDCl_3$) of **3a**



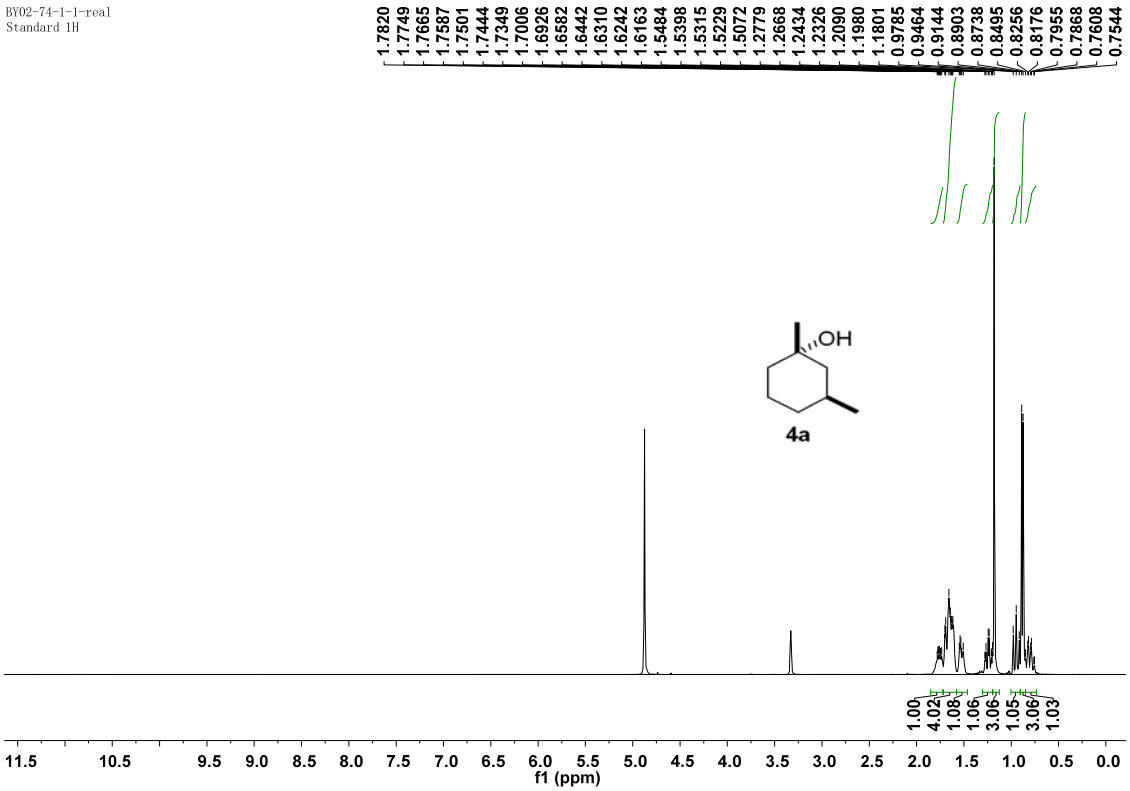


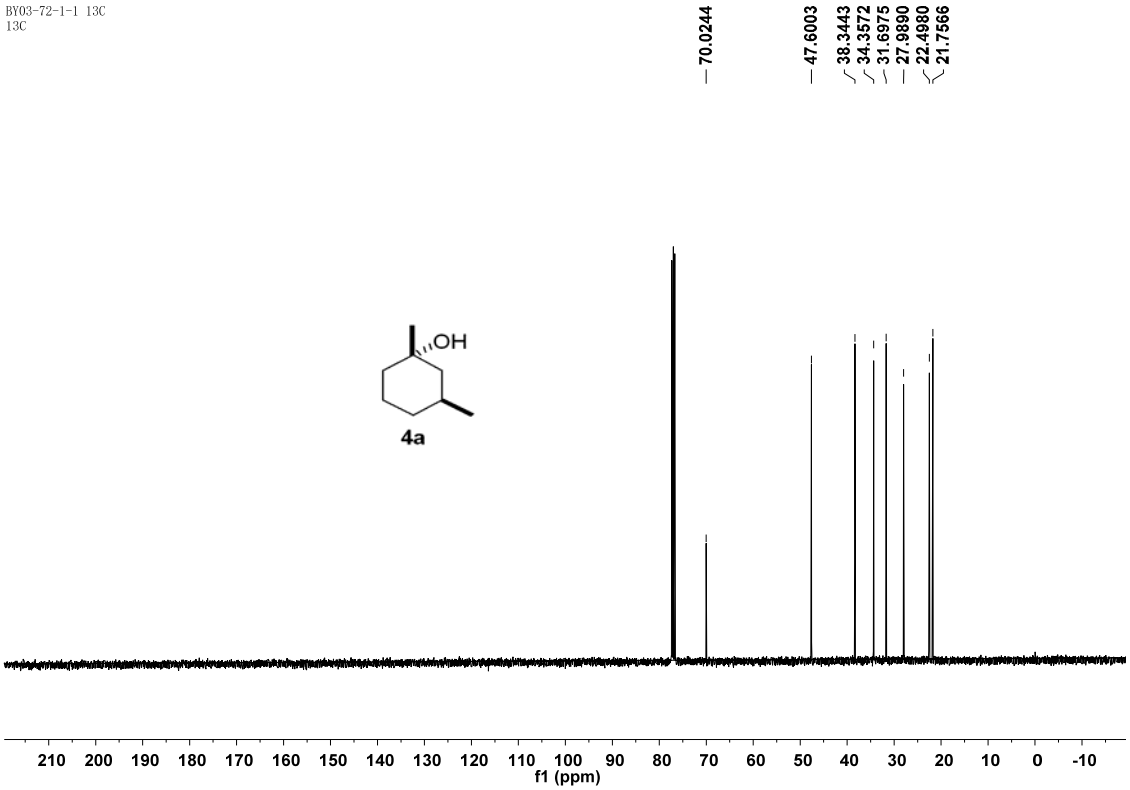
^{1}H NMR (400 MHz, CD_3OD) and ^{13}C NMR (100 MHz, CD_3OD) of **3b**



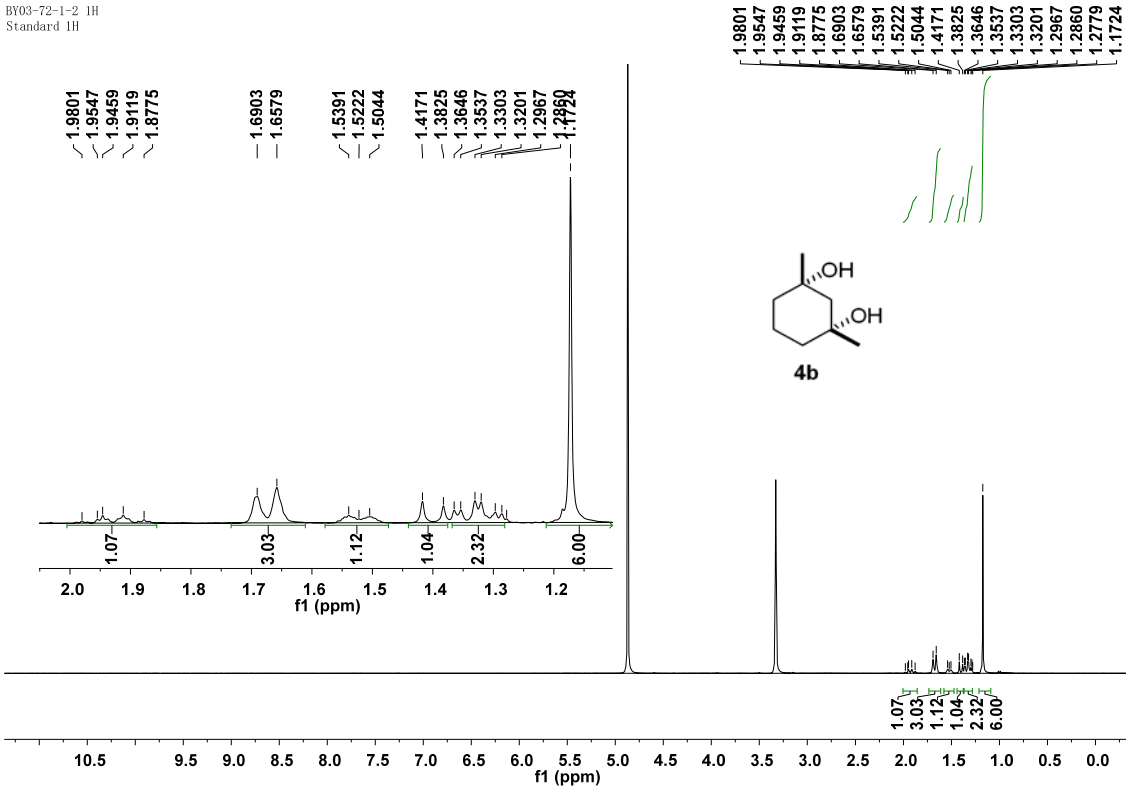


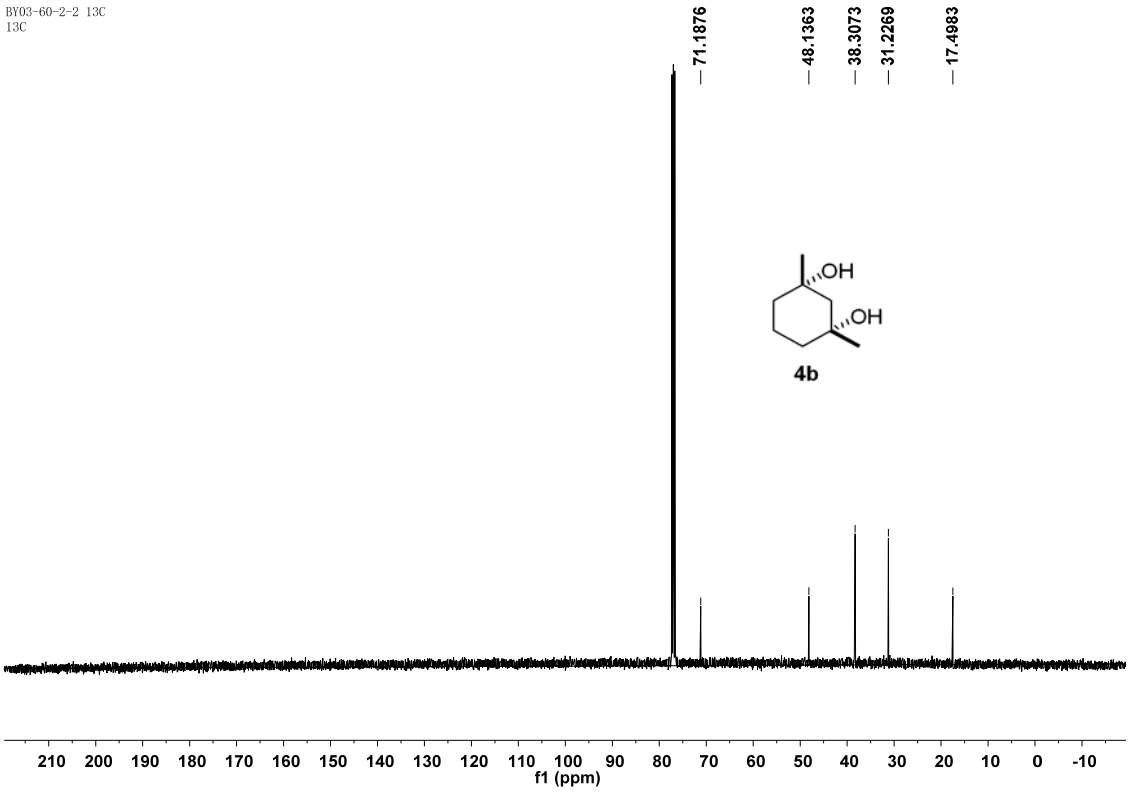
^{1}H NMR (400 MHz, CD_3OD) and ^{13}C NMR (100 MHz, $CDCl_3$) of **4a**



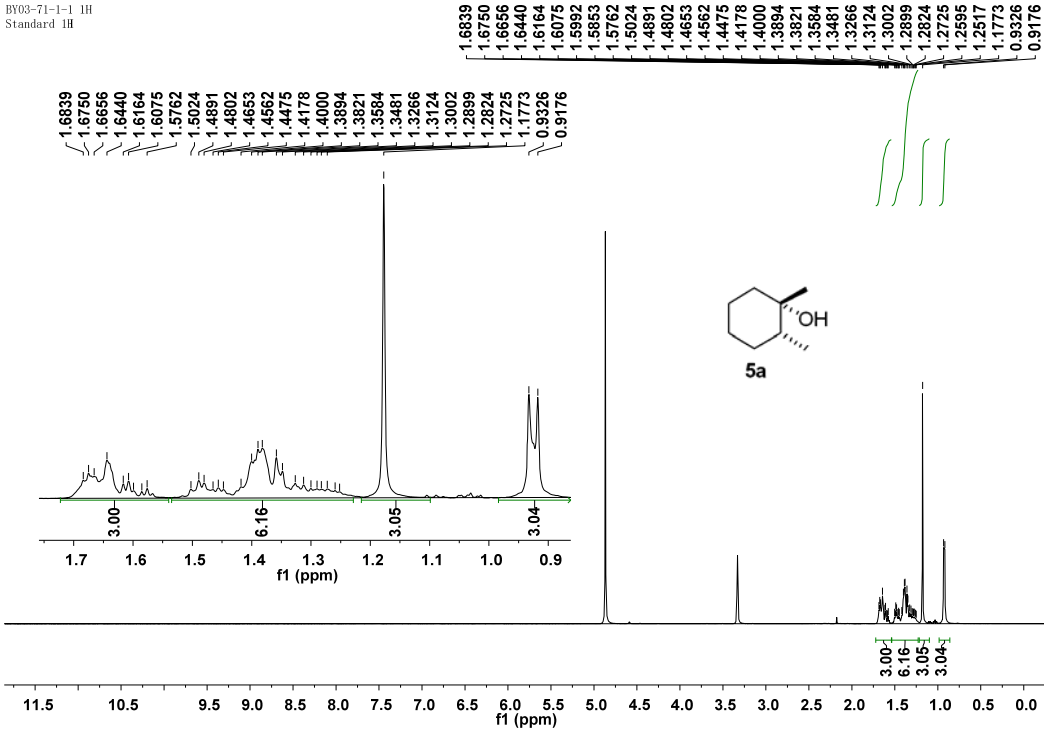


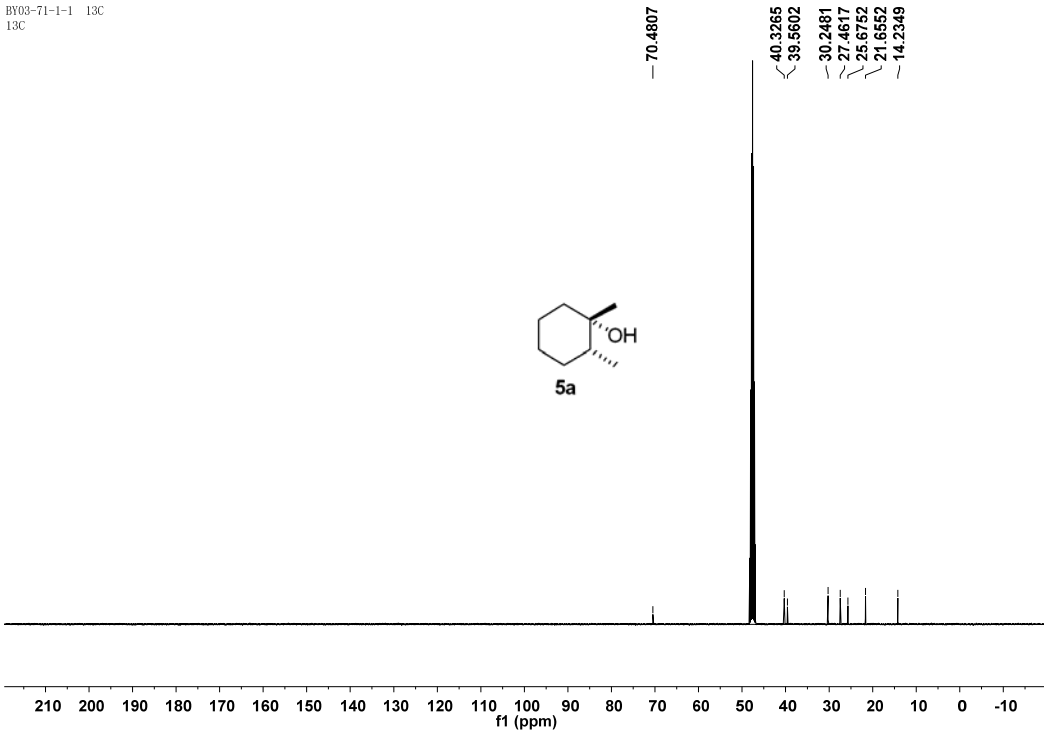
^{1}H NMR (400 MHz, CD_3OD) and ^{13}C NMR (100 MHz, $CDCl_3$) of **4b**



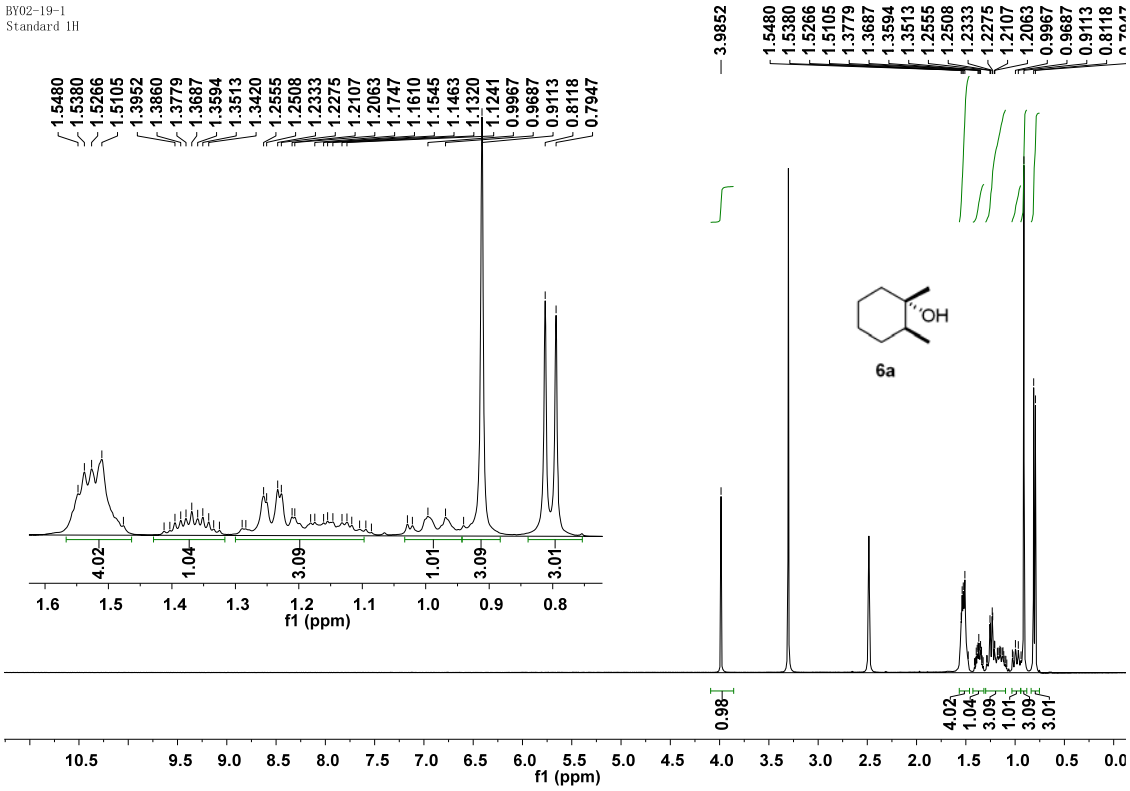


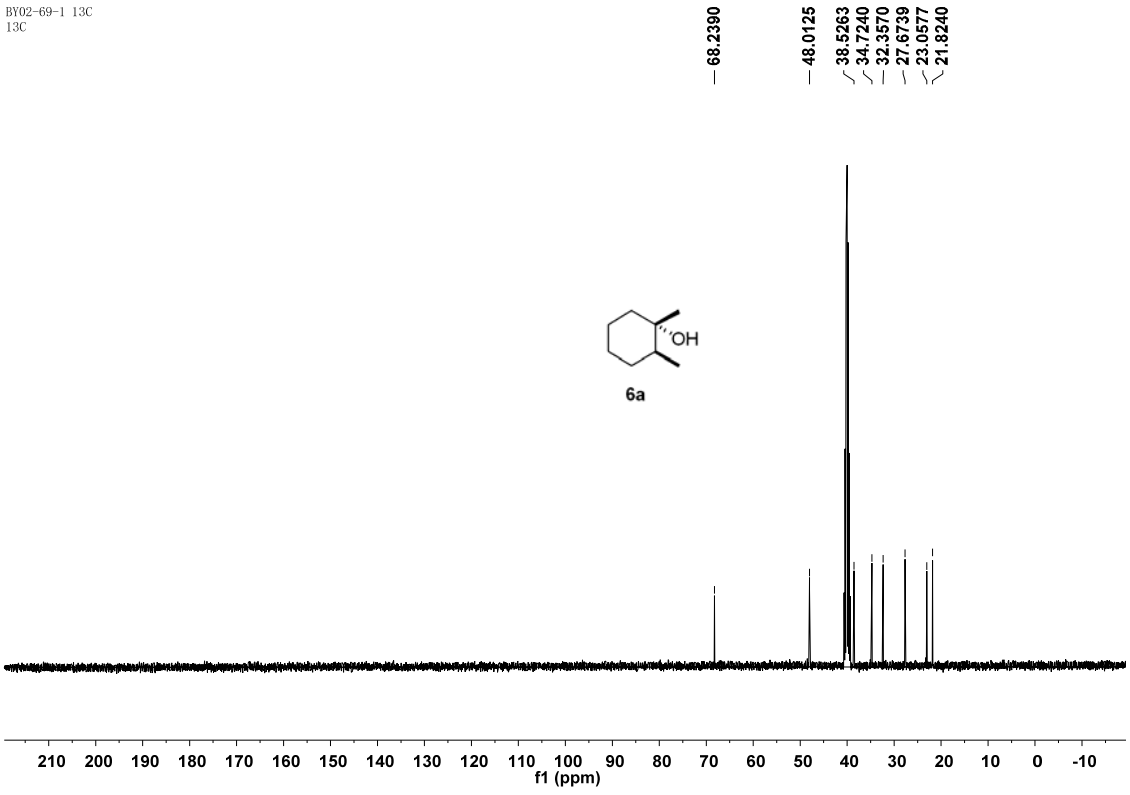
^{1}H NMR (400 MHz, CD_3OD) and ^{13}C NMR(100 MHz, CD_3OD) of **5a**



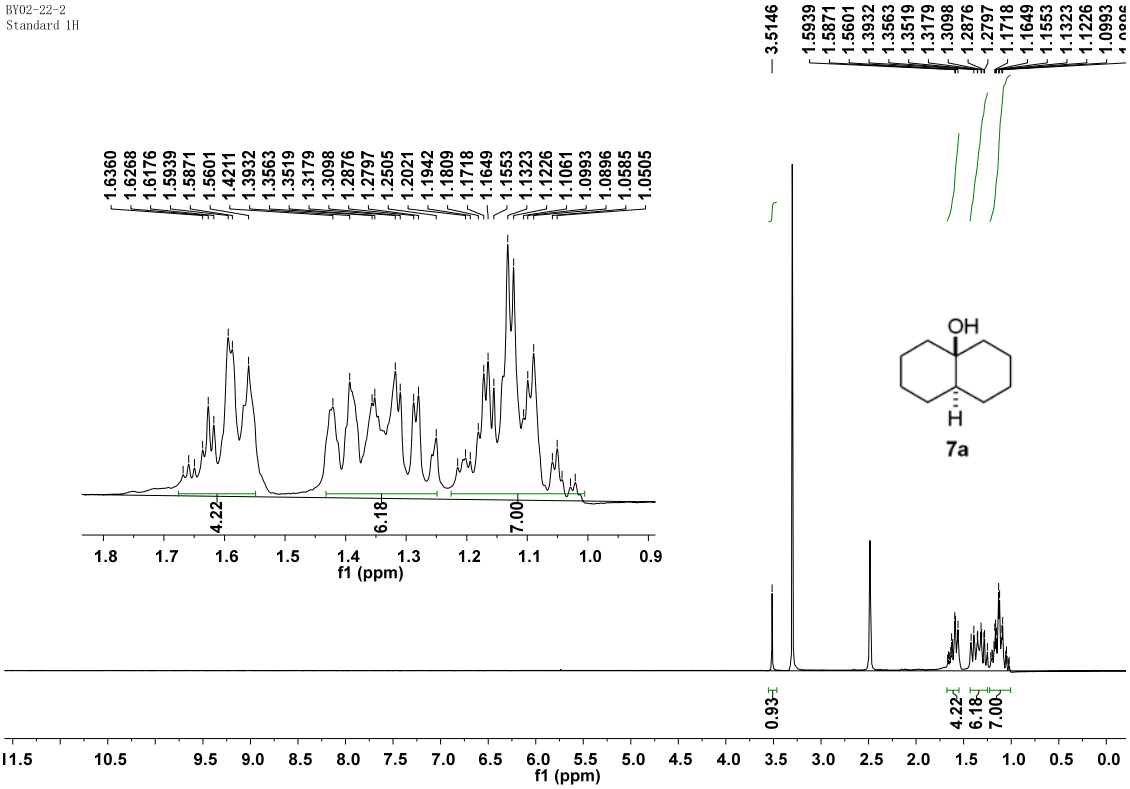


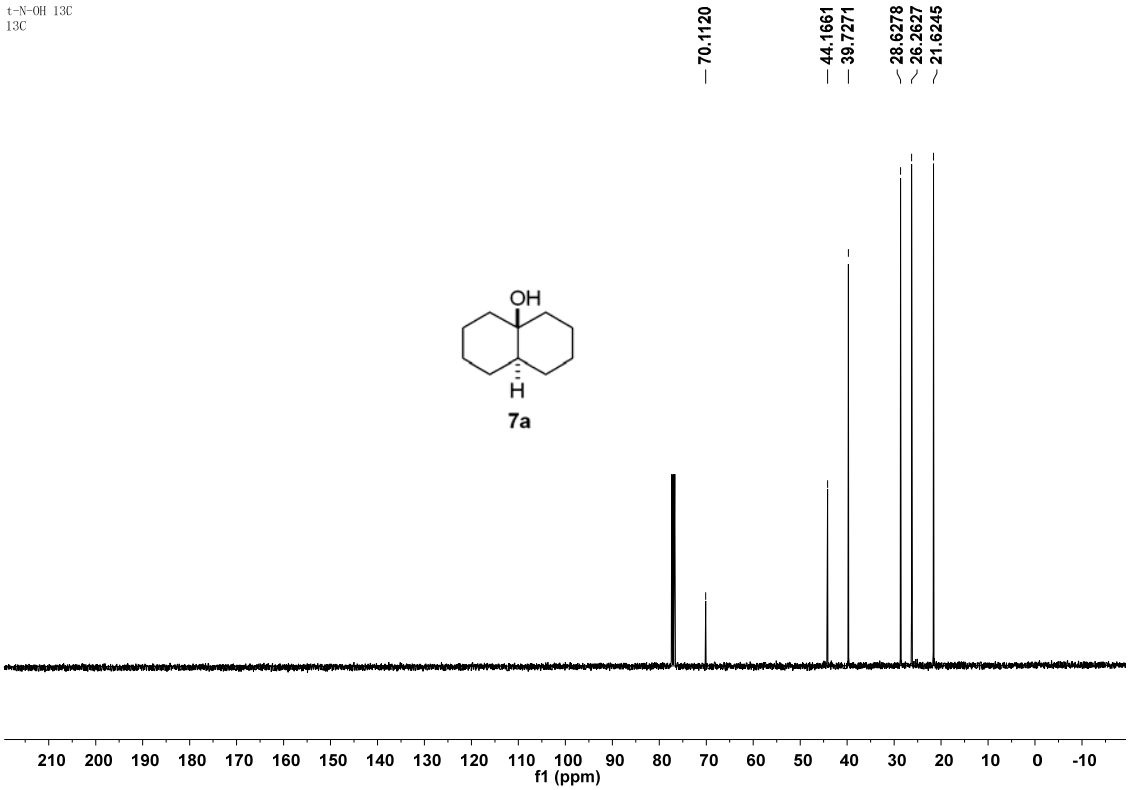
^{1}H NMR (400 MHz, d^{6}-DMSO) and ^{13}C NMR (100 MHz, d^{6}-DMSO) of **6a**



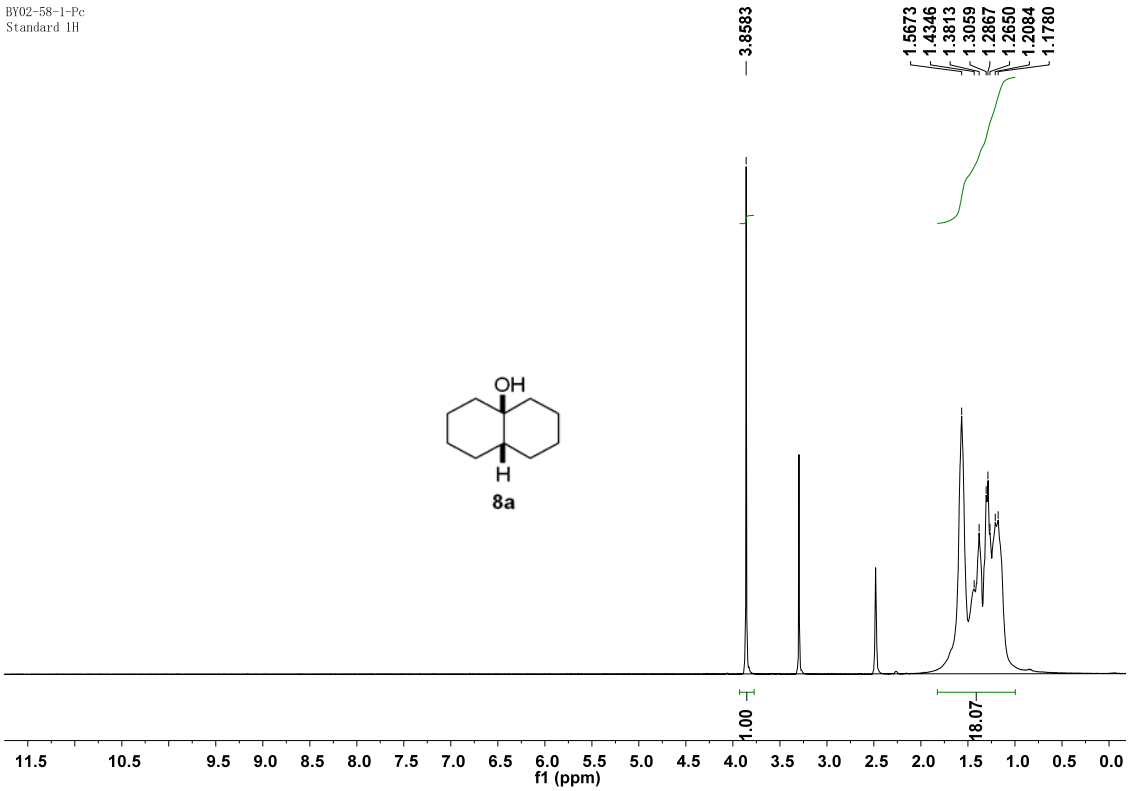


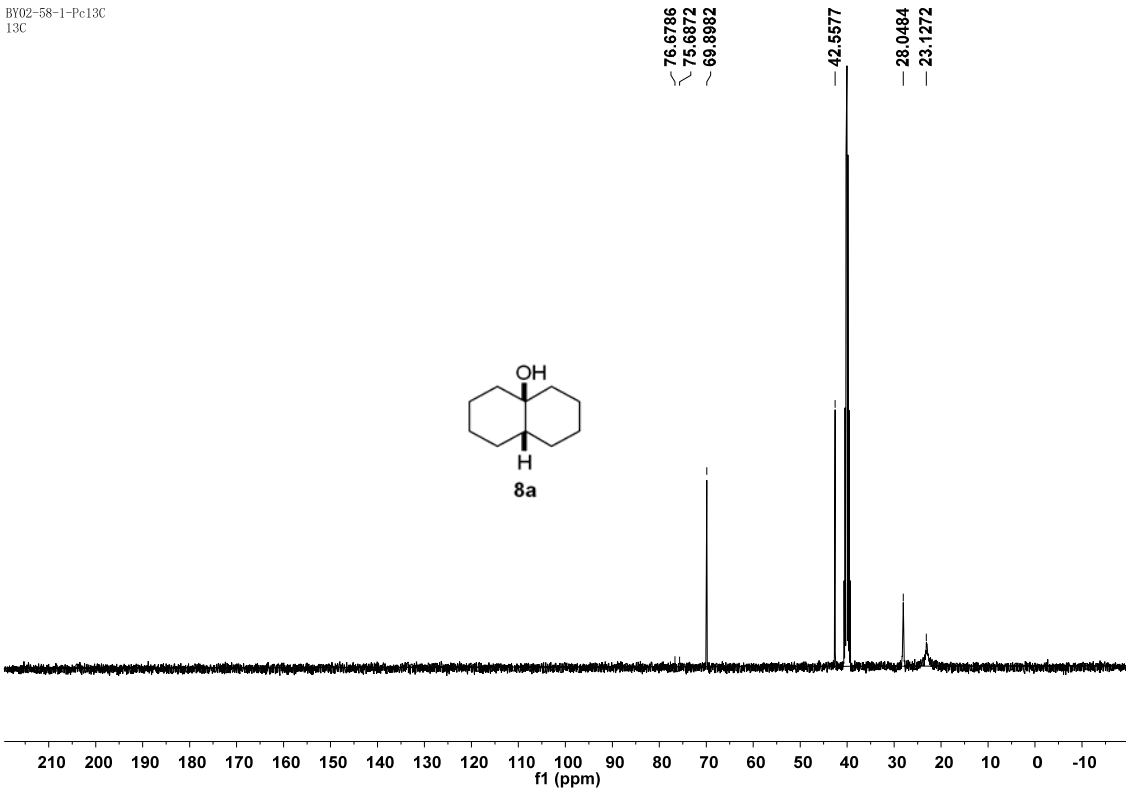
^{1}H NMR (400 MHz, d^{6}-DMSO) and ^{13}C NMR (100 MHz, $CDCl_3$) of **7a**



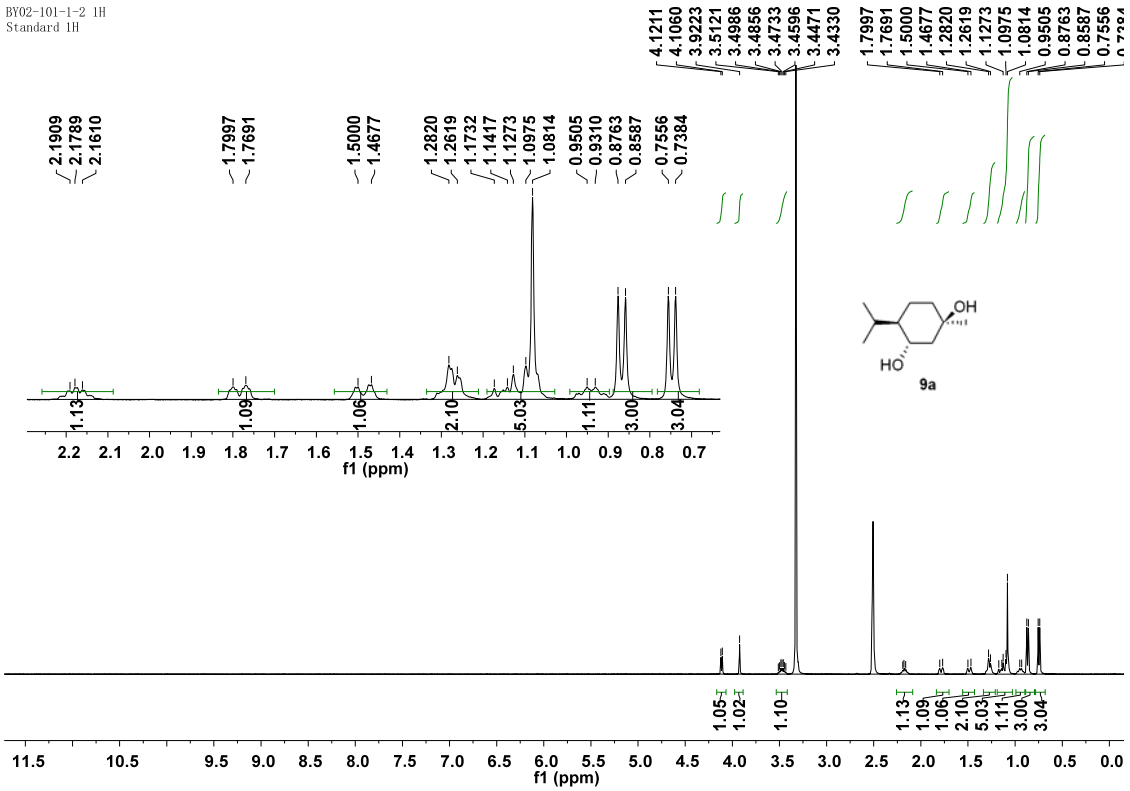


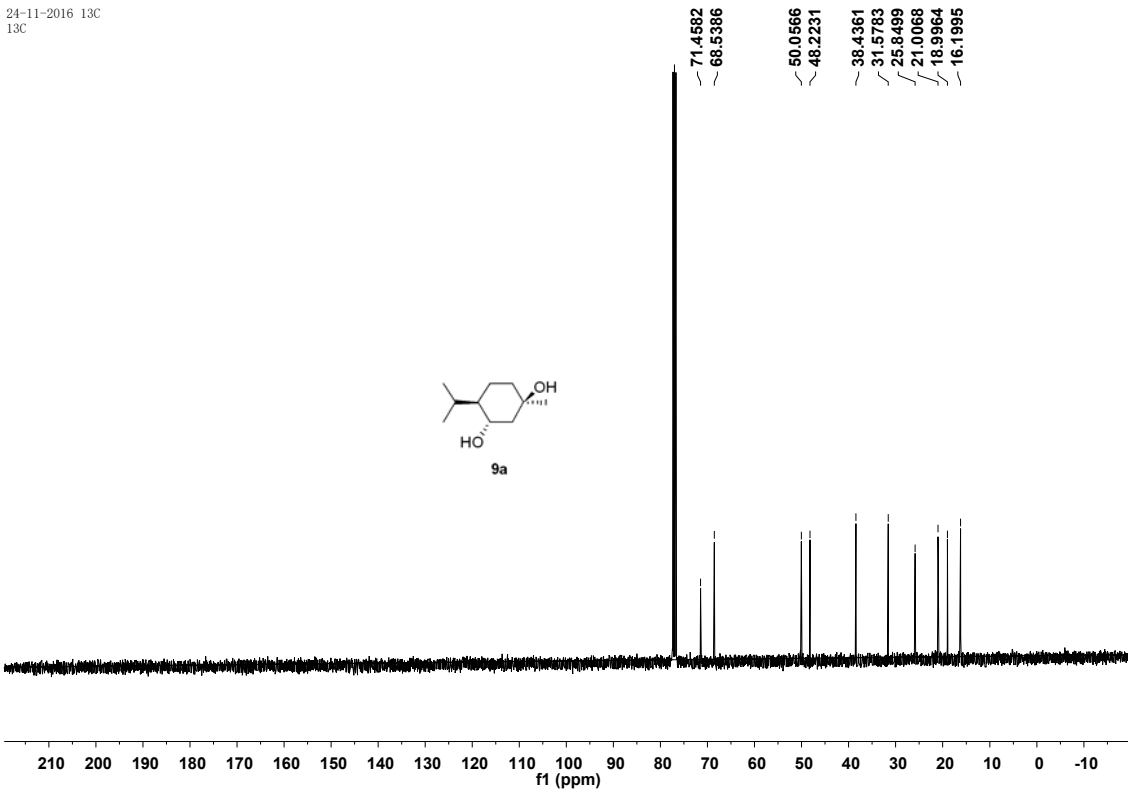
^{1}H NMR (400 MHz, d^{6}-DMSO) and ^{13}C NMR (100 MHz, d^{6}-DMSO) of **8a**



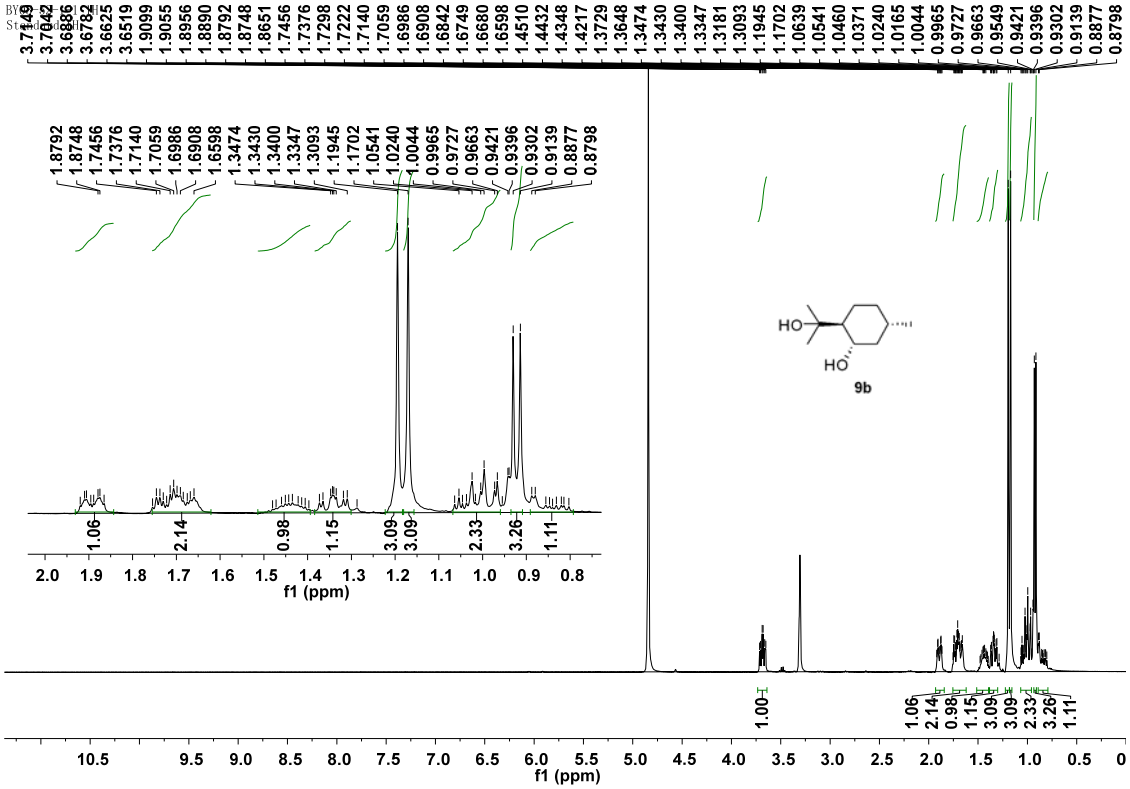


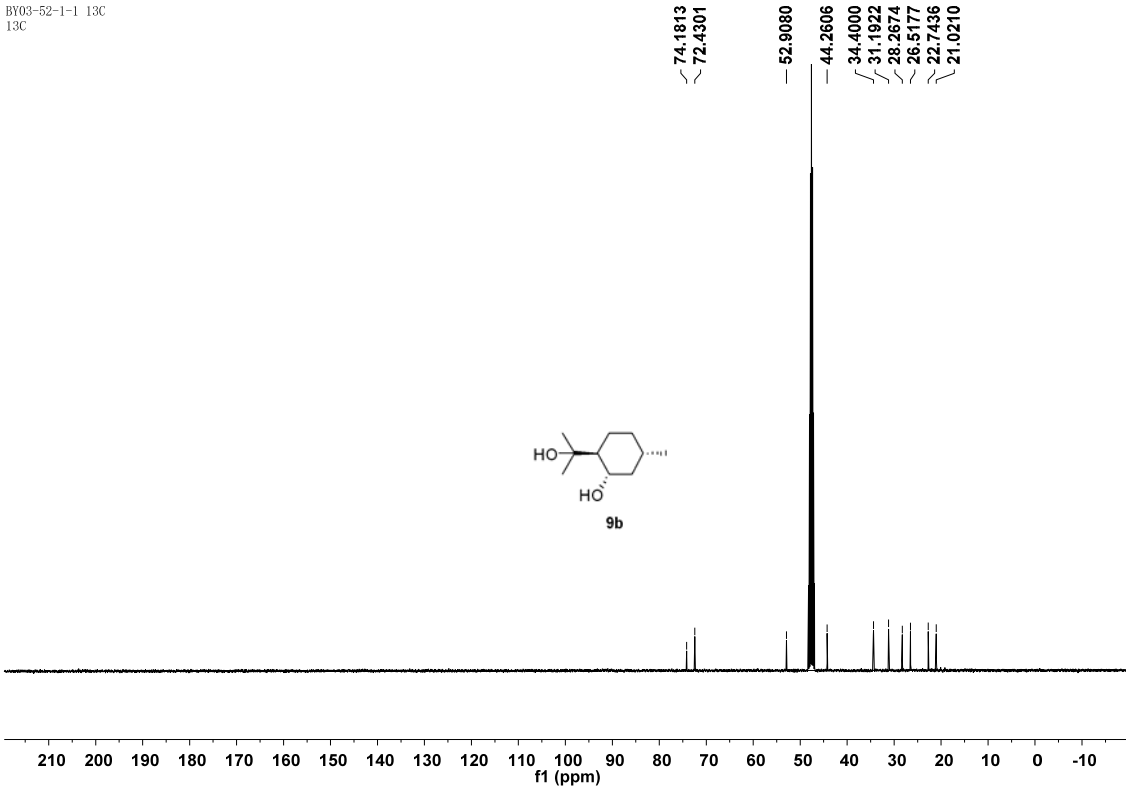
^{1}H NMR (400 MHz, d^{6}-DMSO) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9a**





^{1}H NMR (400 MHz, CD_3OD) and ^{13}C NMR (100 MHz, CD_3OD) of **9b**





^{1}H NMR (400 MHz, CD_3OD) and ^{13}C NMR (100 MHz, $CDCl_3$) of **9c**