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Supporting Information

Detection and Chiral Recognition of α-Hydroxyl Acid through ^{1}H and CEST NMR Spectroscopy Using a Ytterbium Macrocyclic Complex

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1 General

All reagents and solvents were purchased from commercial sources and used as received without other purification unless otherwise noted. ^{1}H, ^{13}C NMR and CEST spectra have been recorded on a Bruker AVANCE III 400 NMR spectrometer.

2. Methods

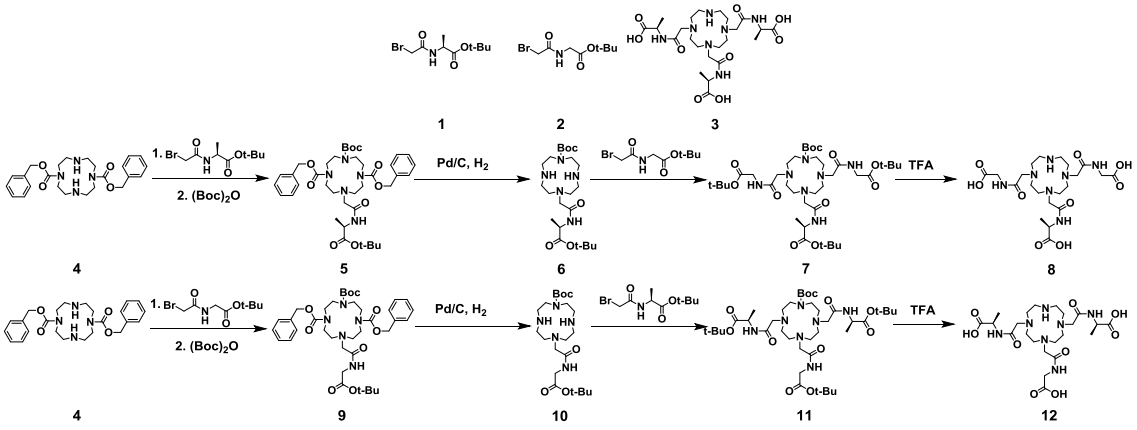
2.1. CEST method

All CEST NMR studies were recorded on a Bruker AVANCE III 400 NMR (9.4 T) spectrometer. Saturation power range was from 14.1 μT. Temperature unit controller Model # 2416 was used to control the temperature to 298 K. CEST spectra were acquired by applying a long, frequency selective pre-saturation pulse over the range of ±200 ppm to cover all potentially exchanging species, including the Yb-bound -OH molecule and amide proton. The chemical shift of bulk water proton was set to 0 ppm.

2.2. Relaxivities measurement

The T1 of the CEST samples were measured at 9.4 T at 298 K using a Bruker AVANCE III 400 MHz vertical bore spectrometer.

3. Synthesis and characterization



Scheme S1. Synthetic pathways of ligands studied in this work.

N-(2-bromoacetyl)-L-glycine tert-butyl ester (1) [1], N-(2-bromoacetyl) L- alanine tertbutyl ester (2) [1], 1,4,7,10–tetraazacyclododecane-1,4,7–tris(2-acetamido)-L-alanine (3) [1] and 1,4,7,10-tetraazacyclododecane-1,7-Bis(benzyloxy carbonyl) (4) [2] were synthesized using established procedures.

1,4,7,10-tetraazacyclododecane-1,7-Bis(benzyloxy carbonyl)-4-(2-acetamido)-L-alanine tertbutyl ester -10-(N-ethylene (tert-butoxycarbonyl) amino acetamide) (5):1,4,7,10-tetraazacyclododecane-1,7-Bis(benzyloxy carbonyl) (2 g, 4.6 mmol) and N-(2-bromoacetyl) - L- alanine tertbutyl ester (1.22 g, 4.6 mmol) were dissolved in anhydrous CH_3CN in the excess amount of K_2CO_3 (3.5 g, 25 mmol). The resulting solution was stirred at 65^oC overnight under N_2 condition for 12 hours and then the solution was filtered and solvents removed under vacuum. The residue was not purified and went to next step directly. The crude product and 4 mL triethylamine were dissolved in anhydrous CH_2Cl_2 (150 mL) and cooled by ice water (0 ^oC). Di-tert-butyl dicarbonate was dissolved CH_2Cl_2 (50 mL) and added dropwise to the mixed solution. The resulting solution was allowed to warm to room temperature and stirred for 8 hours. The solvent was removed under vacuum. The crude product was purified by flash column chromatography on silica, eluted with petroleum ether/ethyl acetate (45:55 v/v) to afford a colorless oil (700 mg, 21%).

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.32 (3H, s br, CHC$\underline{H}_3$), 1.39 (9H, s br, C(C$\underline{H}_3)_3$), 1.44 (9H, s, C(C$\underline{H}_3)_3$), 2.5-3.6 (18H, m, CH_2 on cyclen ring and NC$\underline{H}_2$C=O), 4.40 (1H, s, $CH_3C\underline{H}$), 5.11 (4H, s, OC$\underline{H}_2$Ph), 7.04 (1H, s, NH), 7.34 (10H, m, $CH_2\underline{Ph}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm), 18.44 (CH$\underline{C}H_3$), 27.99 (C($\underline{C}H_3)_3$), 28.46 (C($\underline{C}H_3)_3$), 48.41 ($\underline{C}HCH_3$), 49-55 (cyclen ring $\underline{C}H_2$), 60.50 (N$\underline{C}H_2$C=O), 67.36 ($\underline{C}H_2$Ph), 79.75 (O$\underline{C}CH_3$), 81.57 (O$\underline{C}$CH3), 128.12, 128.53, 136.72 (Ph), 155.74 (N$\underline{C}$=OO), 156.94 (N$\underline{C}$=OO), 170.02 ($CH_2\underline{C}$=OO), 171.94 (CH$\underline{C}$=OO).

1,4,7,10-tetraazacyclododecane-1-(2-acetamido)-L-alanine tertbutyl ester -7-(N-ethylene (tert-butoxycarbonyl) amino acetamide) (6):

Compound 5 (700 mg, 0.96 mmol) was dissolved in ethanol and transferred to a flask with 20% palladium on carbon (200 mg). The mixture was shaken on a Parr hydrogenator under a

H_2 pressure of 80 psi at room temperature for 12 hours. The resulting solution was filtered and solvent was removed under vacuum to afford a colorless oil (422 mg,96%).

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.44 (3H, s br, CHC$\underline{H}_3$), 1.46 (9H, d, C(C$\underline{H}_3)_3$), 1.49(9H, s br, C(C$\underline{H}_3)_3$), 2.7-3.6 (18H, m, CH_2 on cyclen ring and NC$\underline{H}_2$C=O), 4.52 (1H, s, $CH_3C\underline{H}$), 7.82(1H, s, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm), 18.46 (CH$\underline{C}H_3$), 28.04 (C($\underline{C}H_3)_3$), 28.51 (C($\underline{C}H_3)_3$), 47.45 ($\underline{C}HCH_3$), 48-52 (cyclen ring $\underline{C}H_2$), 58.36 (N$\underline{C}H_2$C=O), 80.79 (O$\underline{C}CH_3$), 82.22 (O$\underline{C}$CH3), 155.62 (N$\underline{C}$=OO), 170.60 ($CH_2\underline{C}$=OO), 173.30 (CH$\underline{C}$=OO).

1,4,7,10-tetraazacyclododecane-1,7-di(2-acetamido)-L-glycine tertbutyl ester-4-(2-acetamido)-L-alanine tertbutyl ester-10-(N-ethylene (tert-butoxycarbonyl) amino acetamide) (7)：

Compound 6 and N-(2-b romoacetyl)-L-glycine tertbutyl ester (476 g, 1.9 mmol) were dissolved in anhydrous CH_3CN in the excess amount of K_2CO_3 (2g, 15 mmol). The resulting solution was stirred at 65^oC overnight under N_2 condition for 12 hours and then the solution was filtered and solvents removed under vacuum. The crude product was purified by flash column chromatography on Al_2O_3, eluted with methanol/dichloromethane (2:98 v/v) to afford a pale yellow oil (568 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.38 (3H, d, CHC<u>H</u>$_3$), 1.43 (9H, d, C(C<u>H</u>$_3$)3), 1.47 (27H, d, C(C<u>H</u>$_3$)$_3$), 2.6-3.3 (22H, m, CH_2 on cyclen ring and NC<u>H</u>$_2$C=O), 3.91 (4H, m, NC<u>H</u>$_2$C=O), 4.40 (1H, q br, NC<u>H</u>C=O), 7.55 (1H, d, NH), 7.78 (2H, d, NH).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.10 (CH<u>C</u>H$_3$), 27.81 (C(<u>C</u>H$_3$)$_3$), 27.89 (C(<u>C</u>H$_3$)$_3$), 28.21 (C(<u>C</u>H$_3$)$_3$), 41.49(NCH$_2$C=O), 46.45(NCH$_2$C=O), 48.45 (NCH$_2$C=O), 52-55(cyclen ring <u>C</u>H$_2$), 58.29 (N<u>C</u>HC=O), 79.74 (<u>C</u>(CH$_3$)3), 81.69 (<u>C</u>(CH$_3$)3) 81.90 (<u>C</u>(CH$_3$)3), 155.75 (N<u>C</u>=OO), 168.84 (N<u>C</u>=OCH$_2$), 170.81 (N<u>C</u>=OCH$_2$), 171.51 (CH$_2$<u>C</u>=OO), 172.43 (CH<u>C</u>=OO).

1,4,7,10-tetraazacyclododecane-1,7-di(2-acetamido)-L-glycine-4-(2-acetamido)-L-alanine (8):
Compound 7 (568 mg, 0.78 mmol) was reacted directly with 3 mL TFA for 12 hours. The solvent was then removed under vacuum and the final compound was obtained as a yellow oil (377 mg, 91%).
^{1}H NMR (400 MHz, D_2O): δ (ppm) 1.18 (3H, d, CHC<u>H</u>$_3$), 2.4-3.3 (22H, m, CH_2 on cyclen ring and NC<u>H</u>$_2$C=O), 3.62 (4H, dd, NC<u>H</u>$_2$C=O), 4.02 (1H, q, C<u>H</u>CH$_3$).
^{13}C NMR (100 MHz, D_2O): δ (ppm) 17.75 (CH<u>C</u>H$_3$), 163.10 (N<u>C</u>=OCH$_2$), 42.80 (N<u>C</u>H$_2$C=O), 45.83 (N<u>C</u>H$_2$C=O), 49.09 (N<u>C</u>H$_2$C=O), 50.73, 51.18, 55.12, 56.04 (<u>C</u>H$_2$ on cyclen ring), 59.35 (N<u>C</u>HC=O), 173.87 (N<u>C</u>=OCH$_2$), 176.85 (CH$_2$<u>C</u>=OO), 179.69 (CH<u>C</u>=OO).

1,4,7,10-tetraazacyclododecane-1,7-Bis(benzyloxy carbonyl)-4-(2-acetamido)-L-alanine tertbutyl ester -10-(N-ethylene (tert-butoxycarbonyl) amino acetamide) (9):1,4,7,10-tetraazacyclododecane-1,7-Bis(benzyloxy carbonyl) (2 g, 4.6 mmol) and N-(2-bromoacetyl)-L-glycine tertbutyl ester (1.16 g, 4.6 mmol) were dissolved in anhydrous CH_3CN in the excess amount of K_2CO_3 (3.5 g, 25 mmol). The resulting solution was stirred at 65^{o}C overnight under N_2 condition for 12 hours and then the solution was filtered and solvents removed under vacuum. The residue was not purified and went to next step directly. The crude product and 4 mL triethylamine were dissolved in anhydrous CH_2Cl_2 (150 mL) and cooled by ice water (0 ^{o}C). Di-tert-butyl dicarbonate was dissolved CH_2Cl_2 (50 mL) and added dropwise to the mixed solution. The resulting solution was allowed to warm to room temperature and stirred for 8 hours. The solvent was removed under vacuum. The crude product was purified by flash column chromatography on silica, eluted with petroleum ether/ethyl acetate (45:55 v/v) to afford a colorless oil (751 mg, 23%).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.39 (9H, s br, C(C<u>H</u>$_3$)$_3$), 1.45 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.5-3.9 (20H, m, CH_2 on cyclen ring, NC<u>H</u>$_2$C=O and NHC<u>H</u>$_2$C=O), 5.11 (4H, s, OC<u>H</u>$_2$Ph), 6.91 (1H, s, NH), 7.34 (10H, m, CH$_2$<u>Ph</u>).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm), 28.14 (C(<u>C</u>H$_3$)$_3$), 28.48 (C(<u>C</u>H$_3$)$_3$), 41.76 (<u>C</u>H$_2$CH$_3$), 47-56 (cyclen ring <u>C</u>H$_2$), 60.37 (N<u>C</u>H$_2$C=O), 67.40 (<u>C</u>H$_2$Ph), 79.74 (O<u>C</u>CH$_3$), 81.85 (O<u>C</u>CH3), 128.12, 128.53, 136.70 (Ph), 155.59 (N<u>C</u>=OO), 157.04 (N<u>C</u>=OO), 170.72 (CH$_2$<u>C</u>=OO), 171.12 (CH<u>C</u>=OO).

1,4,7,10-tetraazacyclododecane-1-(2-acetamido)-L-alanine tert-butyl ester -7-(N-ethylene (tert-butoxycarbonyl) amino acetamide) (10):
Compound 9 (751 mg, 1.06 mmol) was dissolved in ethanol and transferred to a flask with

20% palladium on carbon (230 mg). The mixture was shaken on a Parr hydrogenator under a H_2 pressure of 80 psi at room temperature for 12 hours. The resulting solution was filtered and solvent was removed under vacuum to afford a colorless oil (447 mg,95%).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.46 (9H, s, C(C$\underline{H}_3$)$_3$), 1.50 (9H, s, C(C$\underline{H}_3$)$_3$), 2.8-4.0 (20H, m, CH_2 on cyclen ring, NC$\underline{H}_2$C=O and NHC$\underline{H}_2$C=O), 8.22 (1H, s, NH).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm), 28.16 (C(C$\underline{H}_3$)$_3$), 28.54 (C(C$\underline{H}_3$)$_3$), 41.83 (C$\underline{H}_2$CH$_3$), 44-52 (cyclen ring C$\underline{H}_2$), 58.13 (NC$\underline{H}_2$C=O), 80.94 (OC$\underline{C}$H$_3$), 82.28 (OC$\underline{C}$H3), 156.08 (NC$\underline{C}$=OO), 171.40 (CH$_2$C$\underline{C}$=OO), 174.70 (CHC$\underline{C}$=OO).

1,4,7,10-tetraazacyclododecane-1,7-di(2-acetamido)-L-glycine tertbutyl ester-4-(2-acetamido)-L-alanine tertbutyl ester-10-(N-ethylene (tert-butoxycarbonyl) amino acetamide) (11)：
Compound 10 and N-(2-bromoacetyl)-L-alanine tertbutyl ester (534 g, 2.0 mmol) were dissolved in anhydrous CH_3CN in the excess amount of K2CO3 (2g, 15 mmol). The resulting solution was stirred at 65^{o}C overnight under N_2 condition for 12 hours and then the solution was filtered and solvents removed under vacuum. The crude product was purified by flash column chromatography on Al_2O_3, eluted with methanol/dichloromethane (3:97 v/v) to afford a pale yellow oil (714 mg, 83%).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.36 (6H, d, CHC$\underline{H}_3$), 1.43 (9H, s, C(C$\underline{H}_3$)3), 1.45 (27H, d, C(C$\underline{H}_3$)3), 2.6-3.5 (22H, m br, C$\underline{H}_2$ on cyclen ring and NC$\underline{H}_2$C=O), 3.95 (2H, d, NC$\underline{H}_2$C=O), 4.40 (2H, m, NC$\underline{H}$C=O), 7.34(2H, d, NH), 7.81 (1H, s, NH).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.34 (CH$\underline{C}$H$_3$), 27.79 (C(C$\underline{H}_3$)$_3$), 28.05 (C(C$\underline{H}_3$)$_3$), 28.44 (C(C$\underline{H}_3$)$_3$), 41.67(NC$\underline{H}_2$C=O), 46.69 (NC$\underline{H}_2$C=O), 48.30 (NC$\underline{H}_2$C=O), 52-54 (cyclen ring C$\underline{H}_2$), 59.26 (NC$\underline{H}$C=O), 79.72 (C(CH$_3$)$_3$), 81.85 (C(CH$_3$)$_3$), 155.67 (NC$\underline{C}$=OO), 169.15 (NC$\underline{C}$=OCH$_2$), 170.60 (NC$\underline{C}$=OCH$_2$), 171.42 (CH$_2$C$\underline{C}$=OO), 172.15 (CHC$\underline{C}$=OO).

1,4,7,10-tetraazacyclododecane-1,7-di(2-acetamido)-L-glycine-4-(2-acetamido)-L-alanine (12):
Compound 11 (714 mg, 0.88 mmol) was reacted directly with 3 mL TFA for 12 hours. The solvent was then removed under vacuum and the final compound was obtained as a yellow oil (445 mg, 93%).
^{1}H NMR (400 MHz, D_2O): δ (ppm) 1.21 (6H, m, CHC$\underline{H}_3$), 2.4-3.3 (22H, m br, C$\underline{H}_2$ on cyclen ring and NC$\underline{H}_2$C=O), 3.76 (2H, d, NC$\underline{H}_2$C=O), 4.05 (2H, m, NC$\underline{H}$C=O).
^{13}C NMR (100 MHz, D_2O): δ (ppm) 17.44 (CH$\underline{C}$H$_3$), 43.25 (NC$\underline{H}_2$C=O), 45.48 (NC$\underline{H}_2$C=O), 48.94 (NC$\underline{H}_2$C=O), 50-54 (cyclen ring C$\underline{H}_2$), 58.56 (NC$\underline{H}$C=O), 163.00 (NC$\underline{C}$=OO), 172.94 (NC$\underline{C}$=OCH$_2$), 173.90 (NC$\underline{C}$=OCH$_2$), 176.12 (CH$_2$C$\underline{C}$=OO), 180.30 (CHC$\underline{C}$=OO).

General procedure for the preparation of Yb^{3+} complexes.
Yb(III)-1,4,7,10-tetraazacyclododecane-1,7-di(2-acetamido)-L-glycine-4-(2-acetamido)-L-alanine (Yb1): Compound 7 was dissolved in H_2O and 0.95 equivalents of $YbCl_3$ were added. Concentrated solutions of 1N NaOH and 1N HCl were used to adjust the pH to 5.5-6.0. Xylenol Orange tests were performed until no free metal was detected. Samples were filtered using 0.45 μm membrane filter for further experiment.
Yb(III)-1,4,7,10-tetraazacyclododecane-1,7-di(2-acetamido)-L-glycine-4-(2-

acetamido)-L-alanine (Yb2): Compound 10 was dissolved in H_2O and 0.95 equivalents of $YbCl_3$ were added. Concentrated solutions of 1N NaOH and 1N HCl were used to adjust the pH to 5.5-6.0. Xylenol Orange tests were performed until no free metal was detected. Samples were filtered using 0.45 µm membrane filter for further experiment.

Yb (III)- 1,4,7,10–tetraazacyclododecane-1,4,7–tris(2-acetamido)-L-alanine (Yb3): Compound 3 was dissolved in H_2O and 0.95 equivalents of $YbCl_3$ were added. Concentrated solutions of 1N NaOH and 1N HCl were used to adjust the pH to 5.5-6.0. Xylenol Orange tests were performed until no free metal was detected. Samples were filtered using 0.45 µm membrane filter for further experiment.

NMR spectra of compound 7, 8, 11 and 12

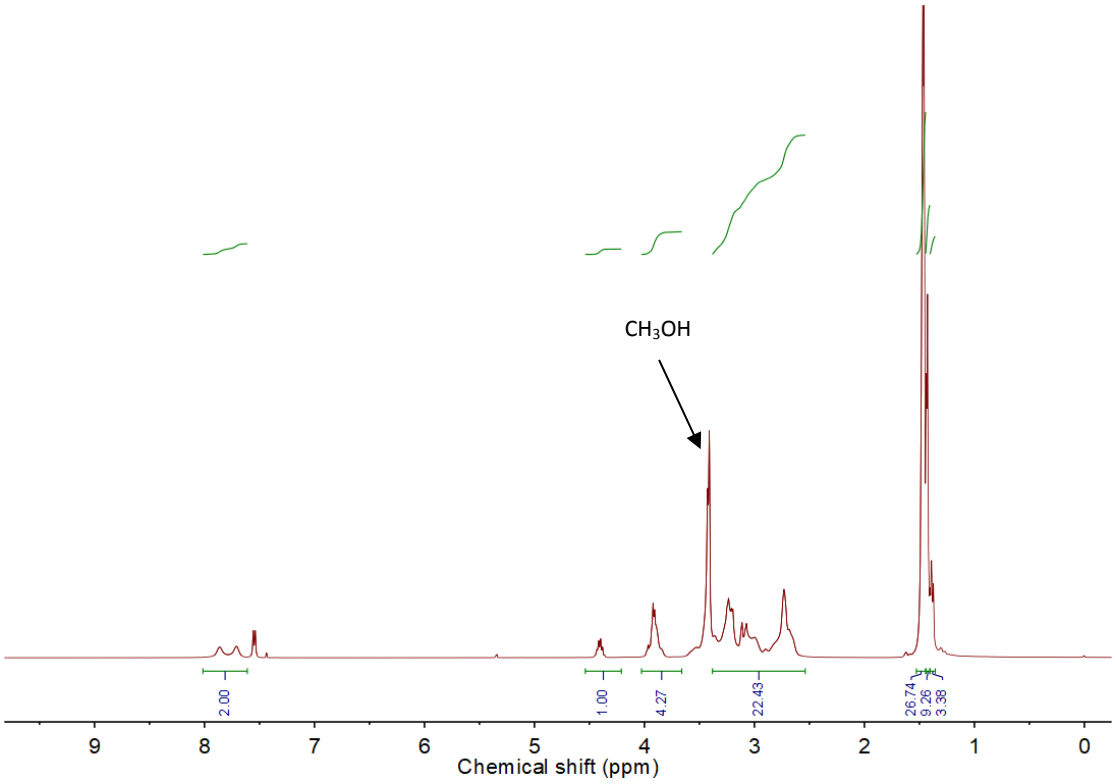


Figure S1. ^{1}H-NMR spectrum of **7** in $CDCl_3$.

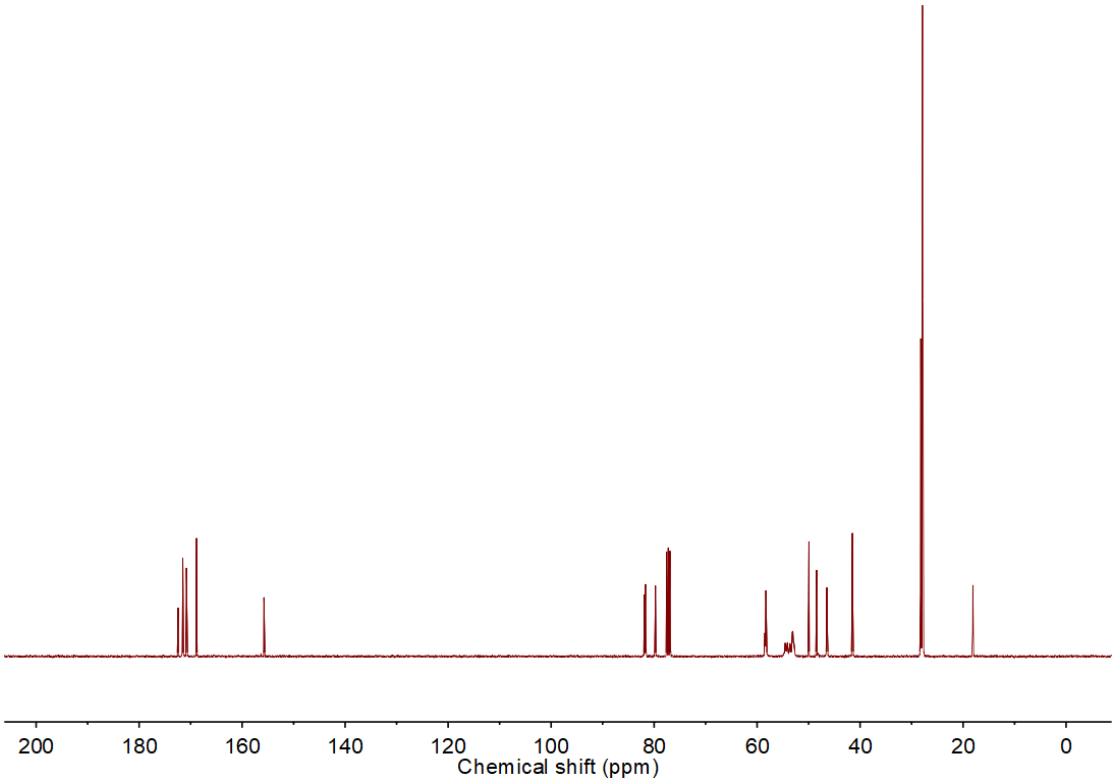


Figure S2. ^{13}C-NMR spectrum of **7** in $CDCl_3$.

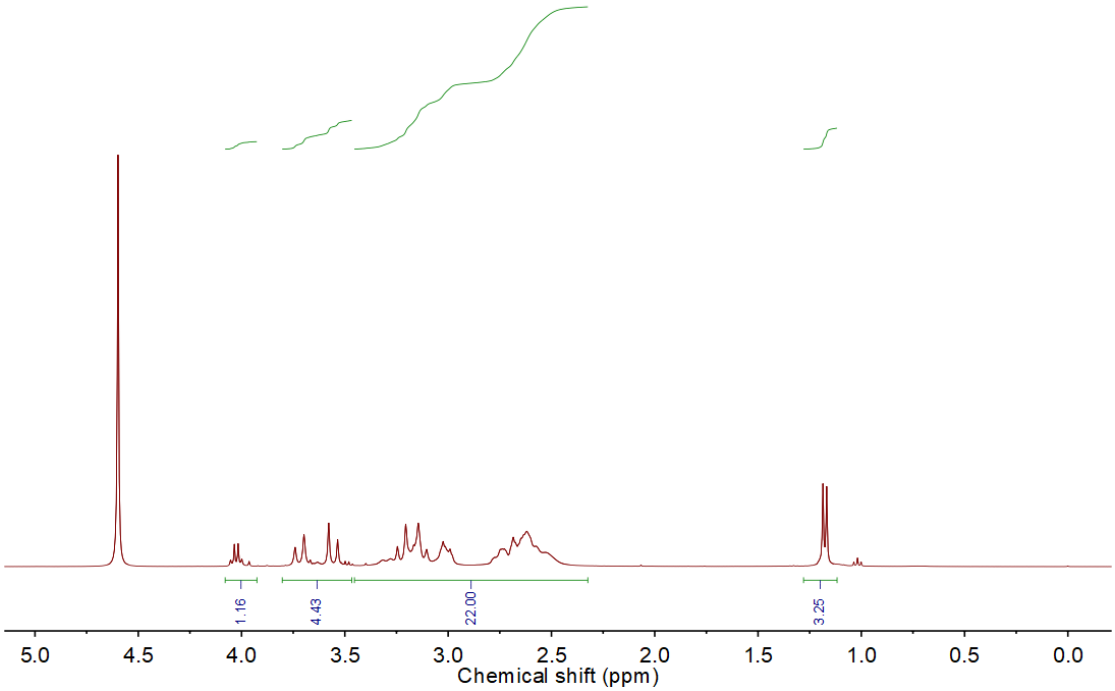


Figure S3. ^{1}H-NMR spectrum of **8** in D_2O.

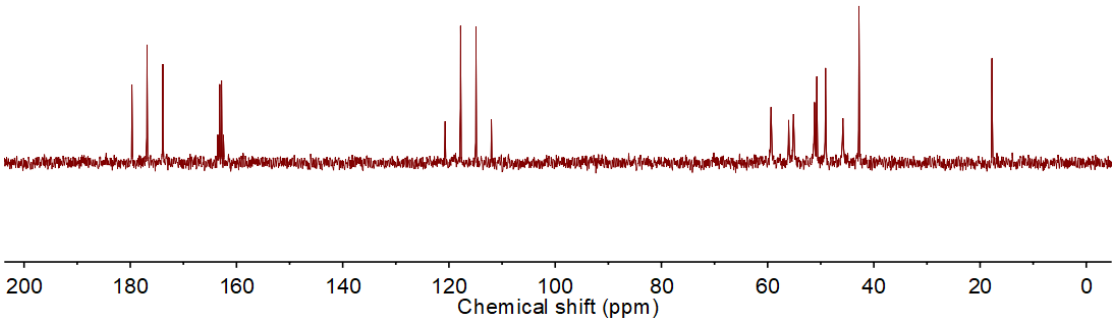


Figure S4. ^{13}C-NMR spectrum of **8** in D_2O.

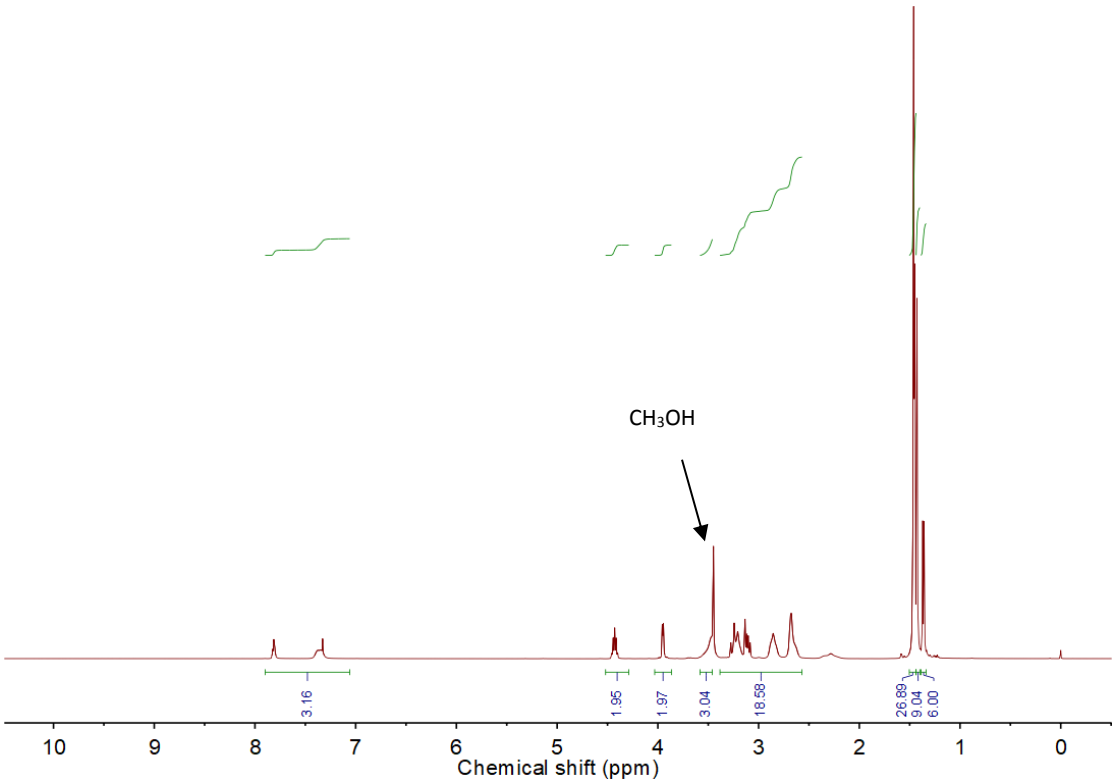


Figure S5. ^{1}H-NMR spectrum of **11** in $CDCl_3$.

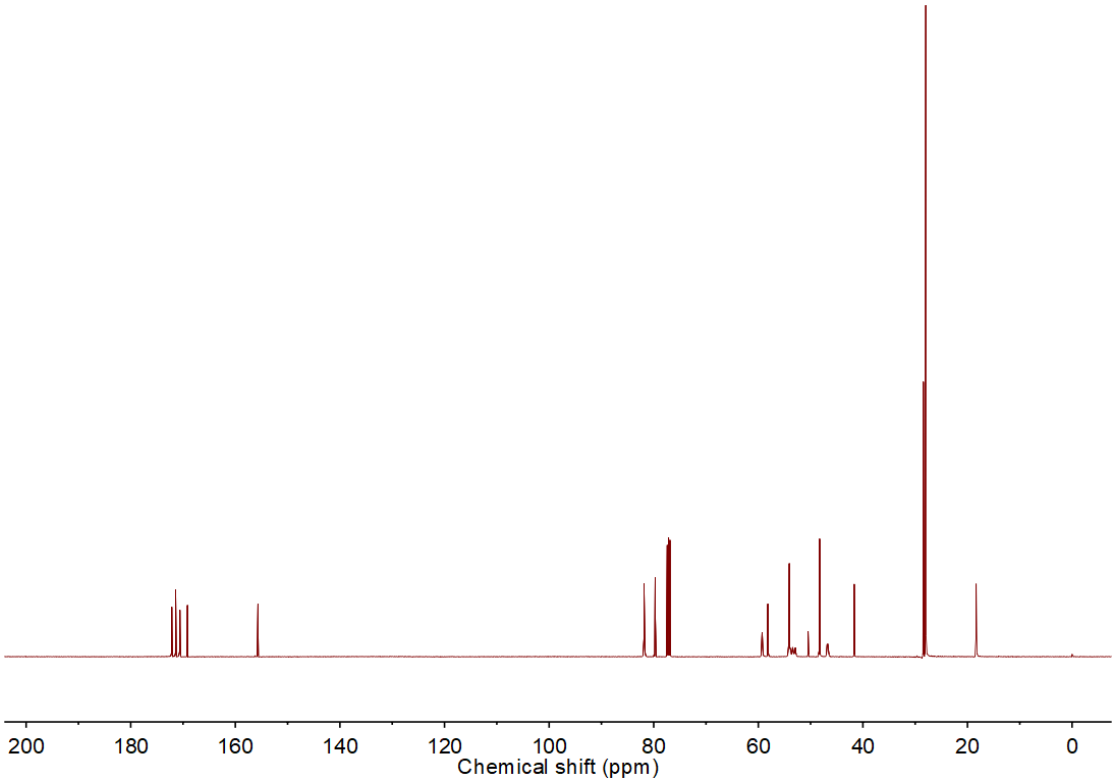


Figure S6. ^{13}C-NMR spectrum of **11** in $CDCl_3$.

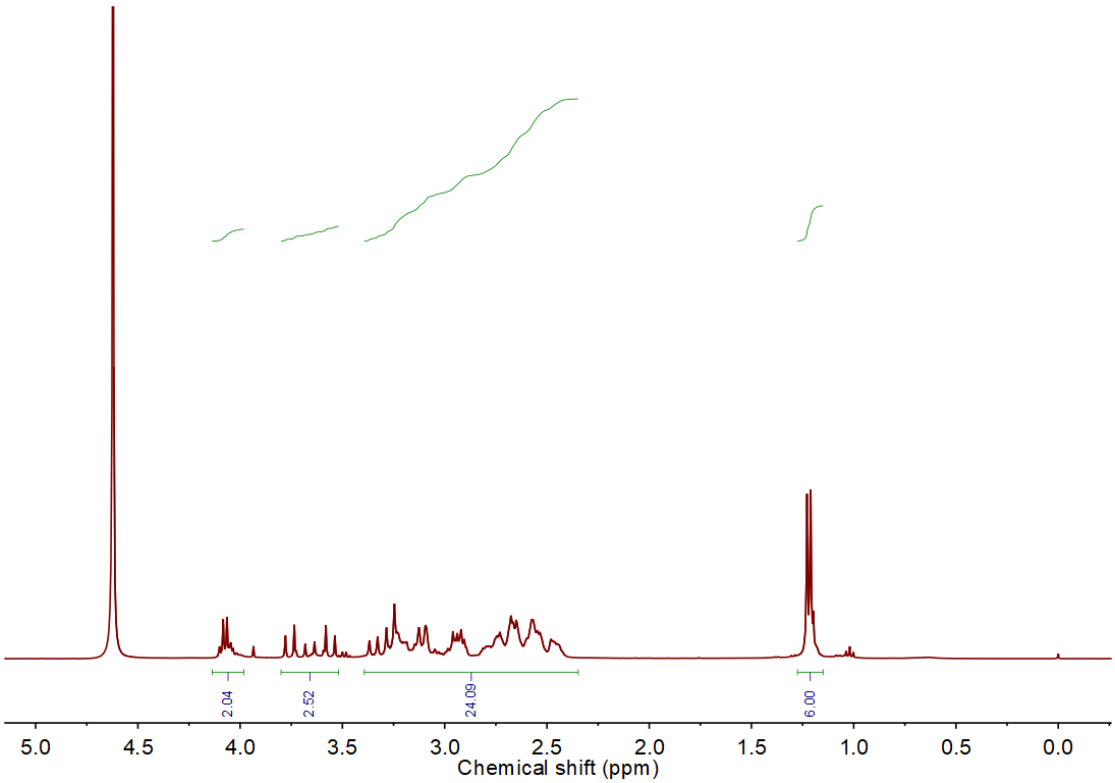


Figure S7. ^{1}H-NMR spectrum of **12** in D_2O.

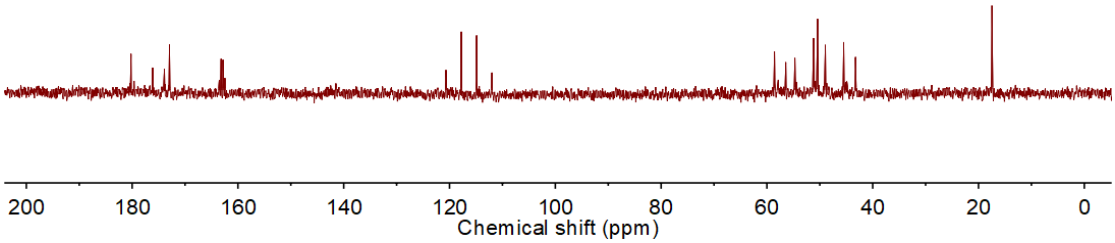


Figure S8. ^{13}C-NMR spectrum of **12** in D_2O.

4. Proton NMR of free Yb-complexes

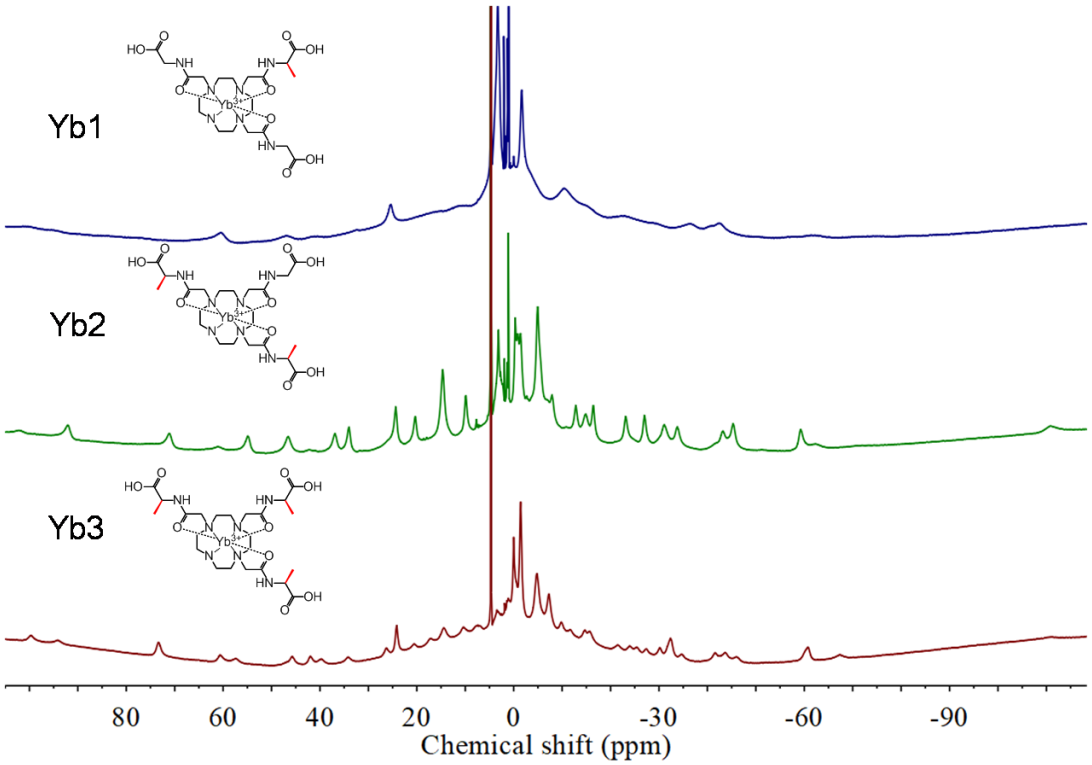


Figure S9. ^{1}H NMR spectra of free Yb-complexes in D_2O.

5. Schematic representation of the two stereoisomers of heptadentate Yb complex binds with α-hydroxyl acids and their arms rotational structure.

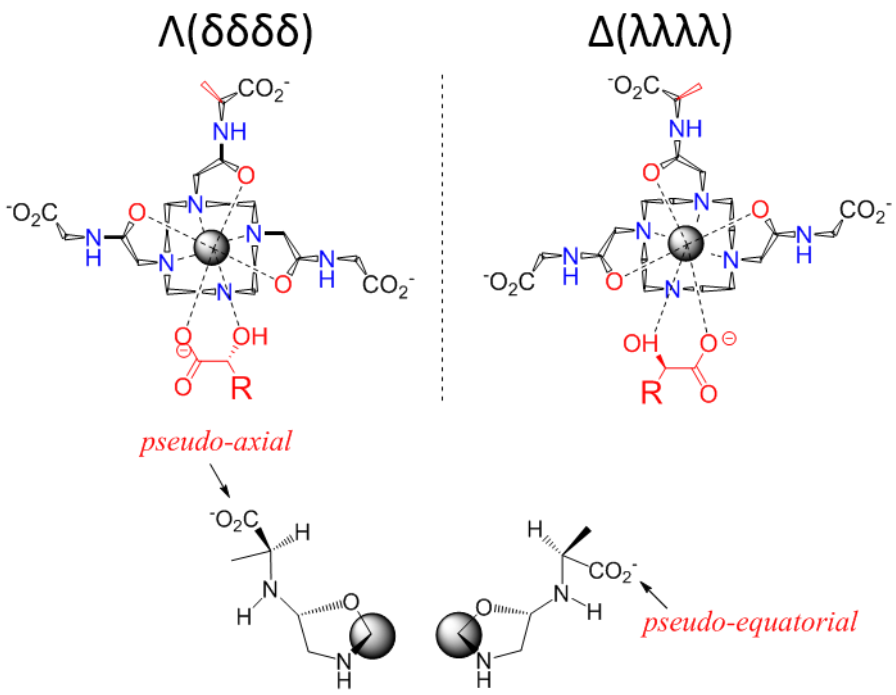


Figure S10. (Top). The complexes are shown from bond-water view. The bond water was deleted for clarity. (Bottom) In a δ-substituted pendent arms, the bulky group preferentially adopts a pseudo-equatorial position (bottom left). All chiral centers on the complexes are in S-configuration.

Reference：

[1] L. Zhang, A. F. Martins, P. Zhao, M. Tieu, D. Esteban-Gomez, G. T. McCandless, C. Platas-Iglesias, A. D. Sherry, *J. Am. Chem. Soc.* **2017**, *139*, 17431-17437.

[2] K. N. Green, S. Viswanathan, F. A. Rojas-Quijano, Z. Kovacs, A. D. Sherry, *Inorg. Chem.* **2011**, *50*, 1648-1655.