Electronic Supplementary Information for

Chiral Discrimination of α-Amino Acids with a C_2-Symmetric Homoditopic Receptor

Sunderraman Sambasivan, Dae-Sik Kim, and Kyo Han Ahn*

Department of Chemistry and the Center for Electro-Photo Behaviors in Advanced Molecular Systems, Pohang University of Science and Technology (POSTECH), San 31, Hyoja-dong, Pohang, 790-784, Republic of Korea

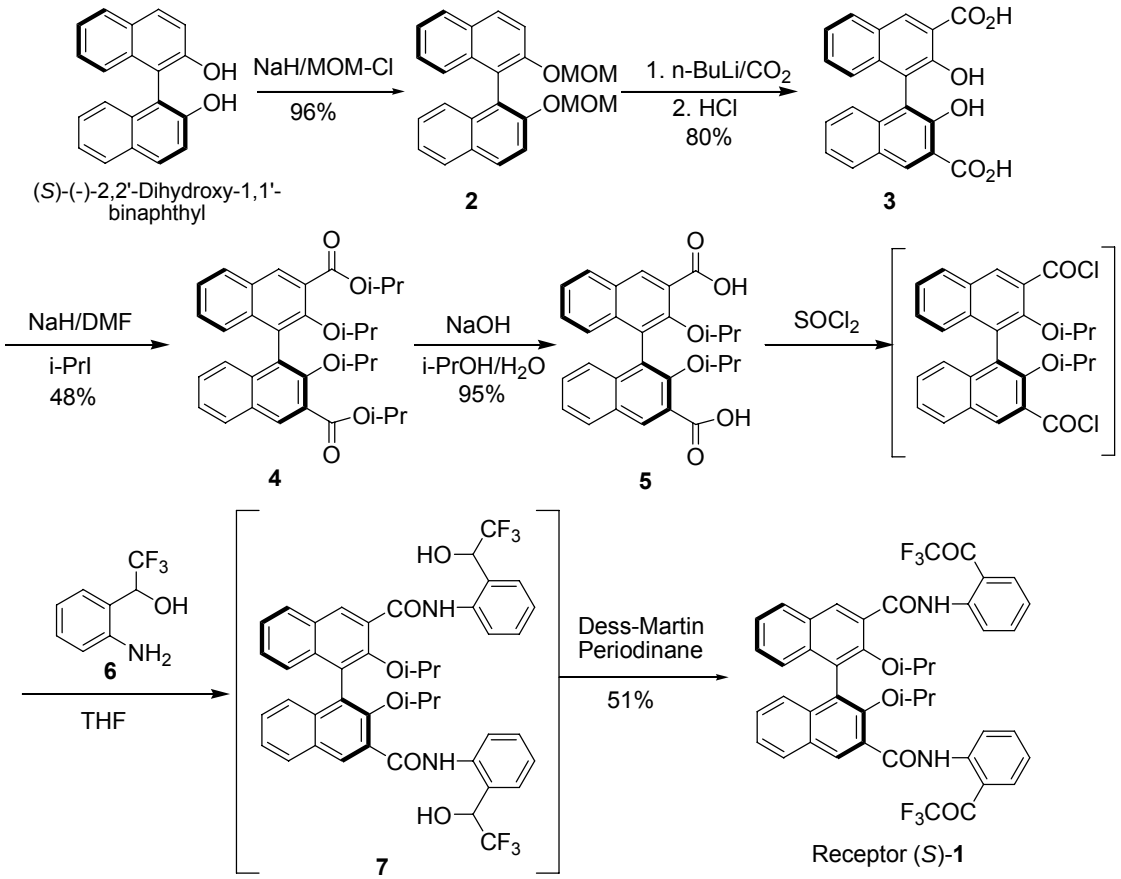
E-mail: ahn@postech.ac.kr

CONTENT

General Methods

All moisture or air sensitive experiments were performed under a positive pressure of argon in oven dried glassware equipped with a rubber septum inlet. Solvents and liquid reagents were transferred by Argon flushed syringes or cannula. Reaction mixtures were stirred with Teflon coated magnetic stir bars. Reaction solvents used were HPLC grade, dried further by passage through a column of appropriate dessicant. Commercial reagents were used as such unless otherwise noted. Analytical thin layer chromatography was performed using Merck 60 F_{524} pre-coated silica gel plates. Subsequent to elution, the plates were visualized by ultra-violet light at 254nm. Preparative thin layer chromatography was also performed using Merck 60 F_{524} pre-coated silica gel plates of thickness 1 mm. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh). Melting points were measured on a capillary melting point apparatus heated by a heating block and are uncorrected. The nuclear magnetic resonance spectra were recorded on an AM-300 Bruker (^{1}H, 300 MHz or 500MHz and ^{13}C, 75 MHz). Chemical shifts are reported in parts per million using the residual solvent peaks as internal reference. The proton coupled ^{19}F NMR spectra are reported in parts per million (ppm) relative to trifluoroacetic acid (δ 0.0 ppm) as an external reference. Mass spectral analysis was recorded on JEOL JMS-AX505WA and is reported in units of mass to charge (m/z). HR-MS was performed at the Korea Basic Science Center, Kyungpook National University

Synthesis and characterization of receptor (*S*)-1



Synthesis of receptor (*S*)-**1** was carried out starting from commercially available and optically pure (*S*)-(–)-2.2′-dihydroxy-1,1′-binaphthyl, according to the scheme above. As all the steps involve known non-racemization processes, we presume that the optical purity of the starting material is transmitted to the final product, receptor (*S*)-**1**. A detailed synthesis of (S)-**1** and its analogues will be reported in a full account.

Receptor (*S*)-**1.** (*S*)-2,2'-Diisopropoxy-1,1'-binaphthyl-3,3'-dicarboxylic acid (**5),** (500 mg, 1.09 mmol) was placed in a dry flask with a stirring bar under argon atmosphere, and freshly distilled $SOCl_2$ (5 mL) was introduced. The mixture was refluxed for 6 h and excess $SOCl_2$ was removed under reduced pressure to give the corresponding diacid

chloride, which was used as such without purification.

To a solution of 1-(2-aminophenyl)-2,2,2-trifluoroethanol (**6**) (835 mg, 4.365 mmol) in anhydrous THF (10 mL) at 0 °C, was added dropwise a solution of the diacid chloride prepared above in anhydrous THF (5 mL). The reaction mixture was stirred for 15 h at room temperature, and the solvent was removed on a rotary evaporator and the resulting residue was purified by column chromatography on silica gel (eluant: 10 → 40% EtOAc in hexane) to give (1*S*)-2,2'-diisopropoxy-N^3,$N^{3'}$-bis[2-(2,2,2-trifluoro-1-hydroxyethyl)phenyl]-1,1'-binaphthyl-3,3'-dicarboxamide (**7**) as a white solid (777 mg). The product which was a mixture of rotamers and diasteromers was used as such in the next step. To a solution of compound **7** (674 mg, 0.838 mmol) in dichloromethane (10 mL), was added a solution of Dess-Martin periodinane (5.92 mL, 15 wt% in CH_2Cl_2, 2.095 mmol) dropwise at 25 °C. The reaction mixture was stirred for 16 h at room temperature, then the insolubles were filtered off and the volatiles were distilled off in vacuo. The residue was dissolved in ethyl acetate (20 mL) and washed with saturated sodium bicarbonate solution, saturated sodium thiosulfate solution, and finally with saturated brine solution. The ethyl acetate solution was then evaporated in vacuo and the residue obtained was subjected to silica gel column chromatography (eluant: 5 → 7% EtOAc in hexane) to afford the product as an off-white solid (490 mg). The product was further purified by preparative TLC (eluant: 15% EtOAc in hexane) to give pure (*S*)-**1** (391 mg, 51 %): Characterization data for (*S*)-**1** : mp 101–103 °C; $[\alpha]^{22}_D$ = +89.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.79 (s, 2H), 8.77 (d, J = 8.5 Hz, 2H), 8.69 (s, 2H), 8.04 (d, J = 8.1 Hz, 2H), 7.94 (d, J = 7.8 Hz, 2H), 7.74 (t, J = 7.7 Hz, 2H), 7.49 (t, J = 7.3 Hz, 2H), 7.39 (t, J = 7 Hz, 2H), 7.28 (m, 2H, overlapped with $CHCl_3$), 7.24 (m, 2H, overlapped with $CHCl_3$), 3.84 (septet, J = 6 Hz, 2H), 0.89 (d, J = 6 Hz, 6H), 0.74 (d,

J = 6 Hz, 6H). ^{1}H NMR (300 MHz, CD_3CN): δ 11.49 (s, 2H), 8.71 (s, 2H), 8.62 (d, J = 8.5 Hz, 2H), 8.18 (dd, J = 8.1,0.36 Hz, 2H), 7.97 (d, J = 8.1 Hz, 2H), 7.84 (ddd, J = 8.1, 7.7, 1.4 Hz, 2H), 7.59 (ddd, J = 10.5, 10.3, 1.1 Hz, 2H), 7.45 (ddd, J = 7.7, 7.6, 1.3 Hz, 2H), 7.39 (ddd, J = 7.7, 7.7, 1 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 3.98 (septet, J = 6.1 Hz, 2H), 0.91 (d, J = 6.1 Hz, 6H), 0.78 (d, J = 6.1 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8 (q, J = 34.5 Hz, –$\underline{C}OCF_3$), 166.5, 151.7, 141.3, 136.6, 135.8, 133.4, 131.2, 130.3, 129.9, 128.9, 126.7, 126.1, 25.9, 123.6, 122.8, 118.8, 116.8 (q, J = 290 Hz, –$\underline{C}F_3$; 114.9 and 111.1 are observed; but other peaks at ~118.8 and 123 are overlapped with other carbons), 78.2, 22.5, 22.1. ^{19}F NMR (300 MHz, CD_3CN) δ 4.8; HRMS calcd for $C_{44}H_{34}F_6N_2O_6$ [M^+] 800.2321; found 800.2318.

Representative procedure for the preparation of various amino acid tetrabutylammonium carboxylates.[2]

To a suspension of L-alanine (250 mg, 2.80 mmol) in water (10 mL) was added tetrabutylammonium hydroxide (1 M in methanol, 2.8 mL, 2.8 mmol). The mixture was stirred and heated to 55 °C for 2 h. The solvents were removed in vacuo and the residue was dissolved in acetonitrile (10 mL) by sonication. The insolubles were filtered off and the filtrate was dried over anhydrous sodium sulfate. The solvent was then evaporated in vacuo and the residue was lyophilized to give the desired amino acid salt as a white solid or semi-solid.

References

1. Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207.
2. Allen, A. R.; Richard, P. L.; Ward, A. J.; Van de Water, L. G. A.; Masters, A. F.; Maschmeyer, T.; *Tetrahedron Lett.* **2006**, *47*, 7367

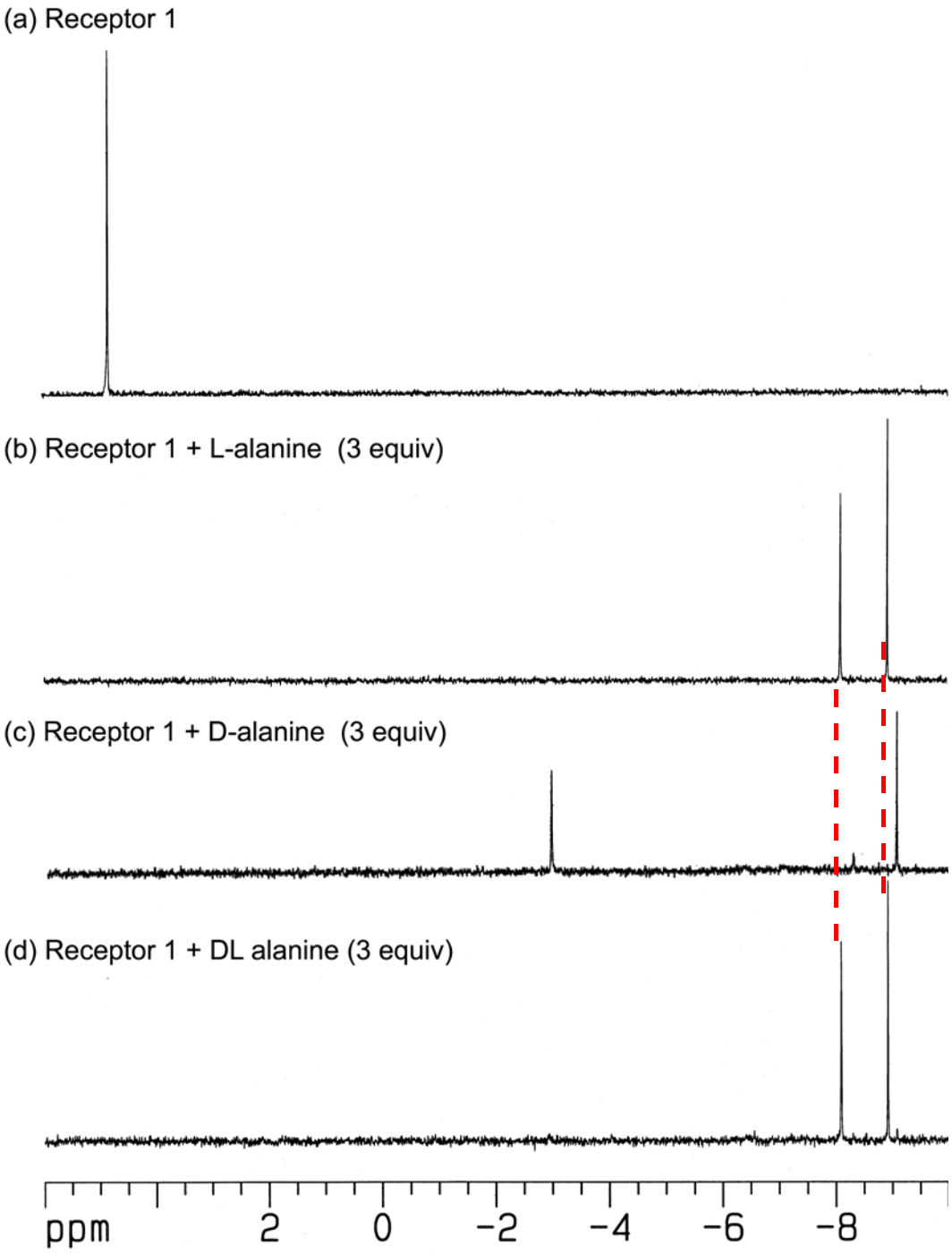


Figure S1. Proton-coupled ^{19}F NMR spectra of (a) receptor (*S*)-**1** [1.0 mM], (b) (*S*)-**1** [1.0 mM] + L-alanine [3.0 mM], (c) (*S*)-**1** [1.0 mM] + D-alanine [3.0 mM], and (d) (*S*)-**1** [1.0 mM] + DL-alanine [3.0 mM]; taken in CD_3CN. Alanine is used as its tetrabutylammonium carboxylate salt.

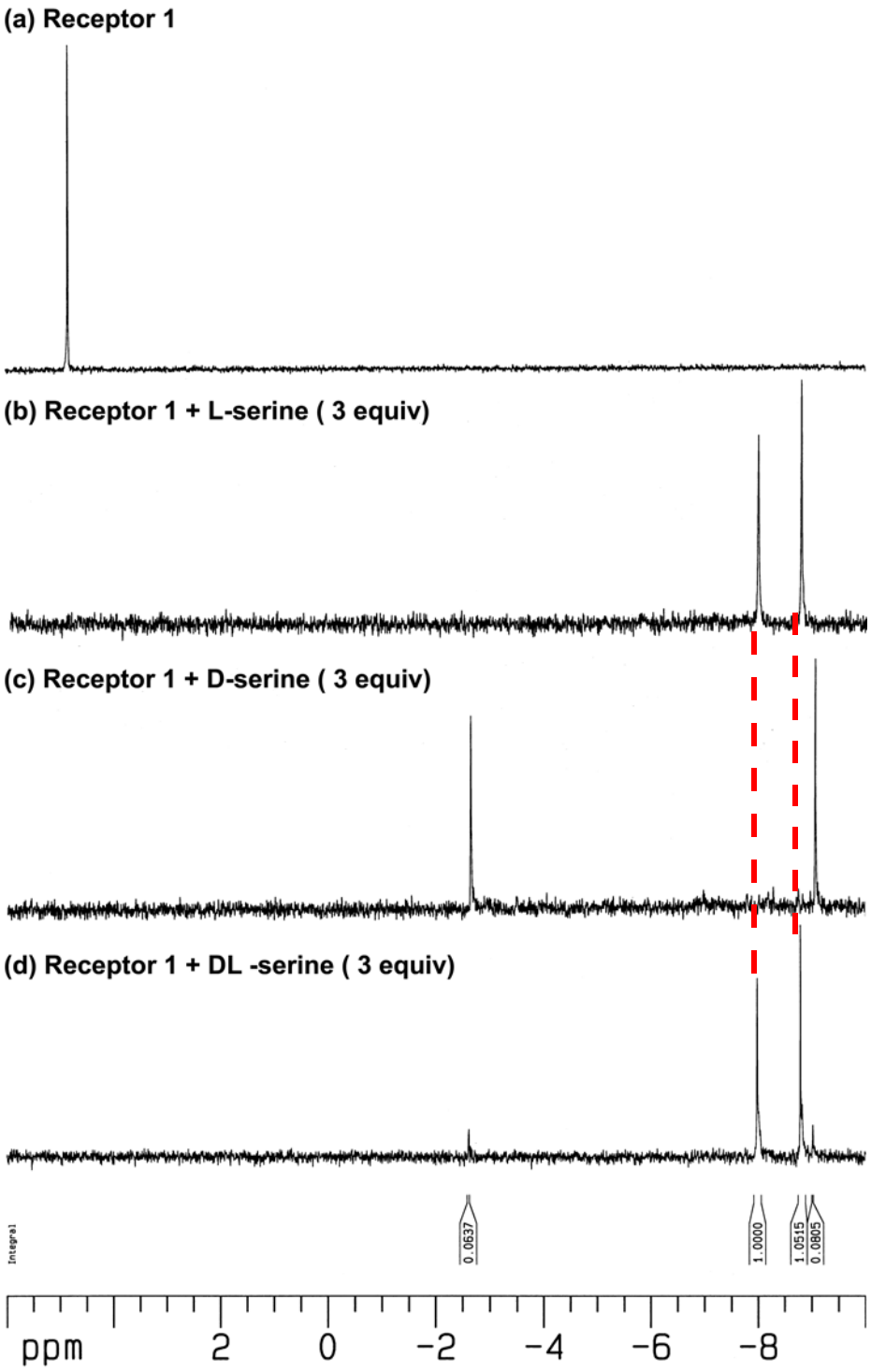


Figure S2. Proton-coupled ^{19}F NMR spectra of (a) receptor (*S*)-**1** [1.0 mM], (b) (*S*)-**1** [1.0 mM] + L-serine [3.0 mM], (c) (*S*)-**1** [1.0 mM] + D-serine [3.0 mM], and (d) (*S*)-**1** [1.0 mM] + DL-serine [3.0 mM]; taken in CD_3CN. Serine is used as its tetrabutylammonium carboxylate salt.

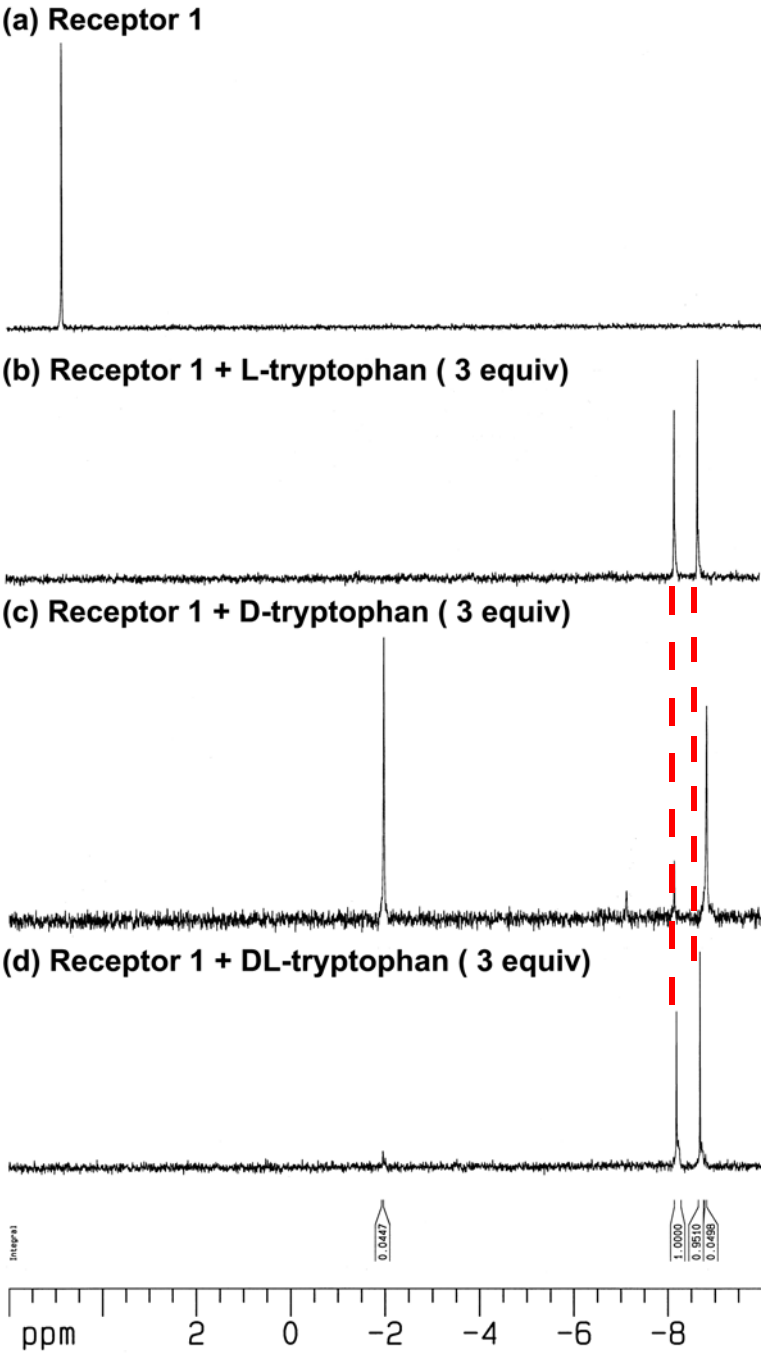


Figure S3. Proton-coupled ^{19}F NMR spectra of (a) receptor (*S*)-**1** [1.0 mM], (b) (*S*)-**1** [1.0 mM] + L-tryptophan [3.0 mM], (c) (*S*)-**1** [1.0 mM] + D-tryptophan [3.0 mM], and (d) (*S*)-**1** [1.0 mM] + DL-tryptophan [3.0 mM]; taken in CD_3CN. Tryptophan is used as its tetrabutylammonium carboxylate salt.

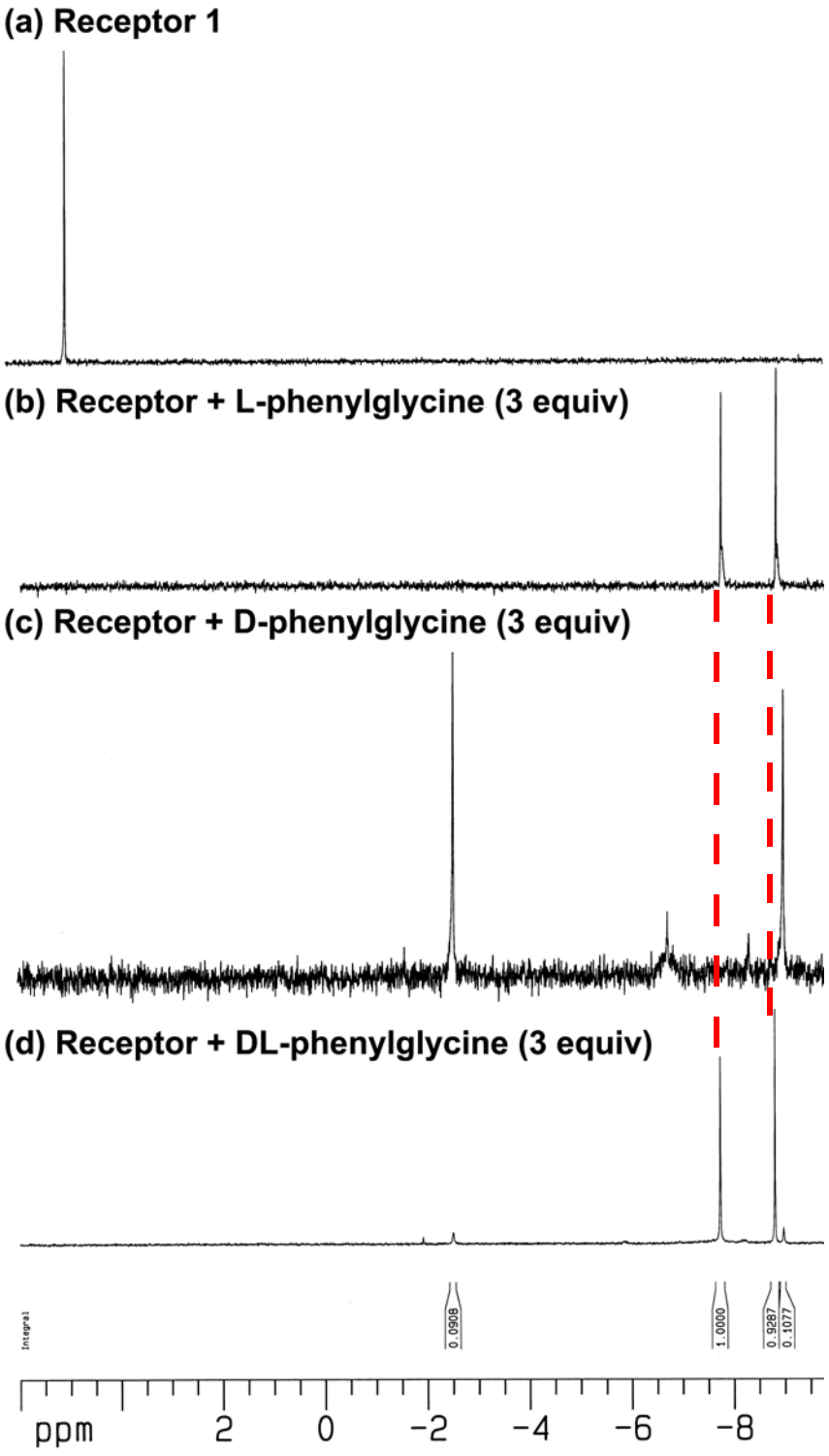


Figure S4. Proton-coupled ^{19}F NMR spectra of (a) receptor (*S*)-**1** [1.0 mM], (b) (*S*)-**1** [1.0 mM] + L-phenylglycine [3.0 mM] (c) (*S*)-**1** [1.0 mM] + D-phenylglycine [3.0 mM], and (d) (*S*)-**1** [1.0 mM] + DL-phenylglycine [3.0 mM]; taken in CD_3CN. Phenylglycine is used as its tetrabutylammonium carboxylate salt.

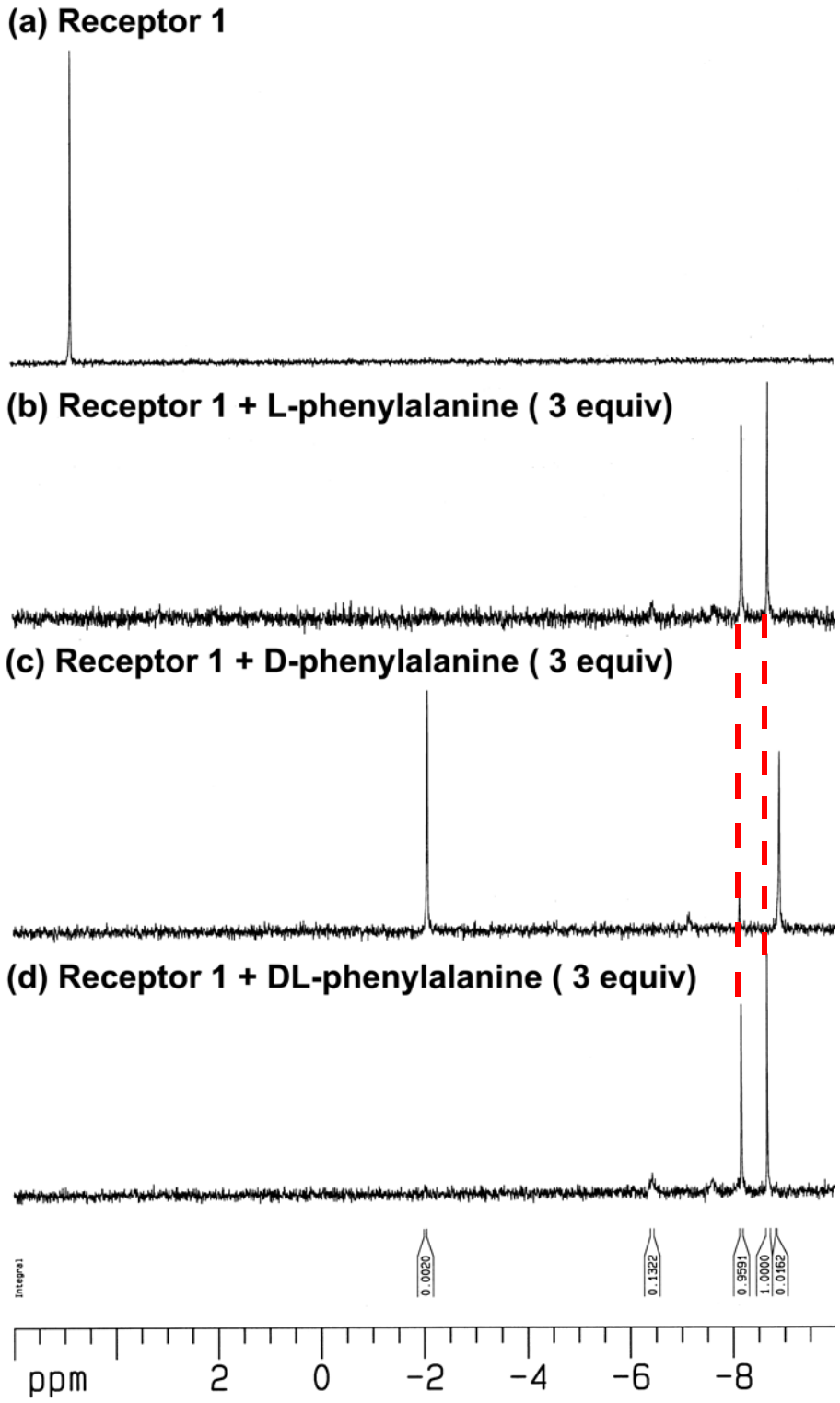


Figure S5. Proton-coupled ^{19}F NMR spectra of (a) Receptor (*S*)-**1** [1.0 mM], (b) (*S*)-**1** [1.0 mM] + D-phenylalanine [3.0 mM], (c) (*S*)-**1** [1.0 mM] + DL-phenylalanine [3.0 mM]. and (d) (*S*)-**1** [1.0 mM] + DL-phenylalanine [3.0 mM]; taken in CD_3CN. Phenylalanine is used as its tetrabutylammonium carboxylate salt.

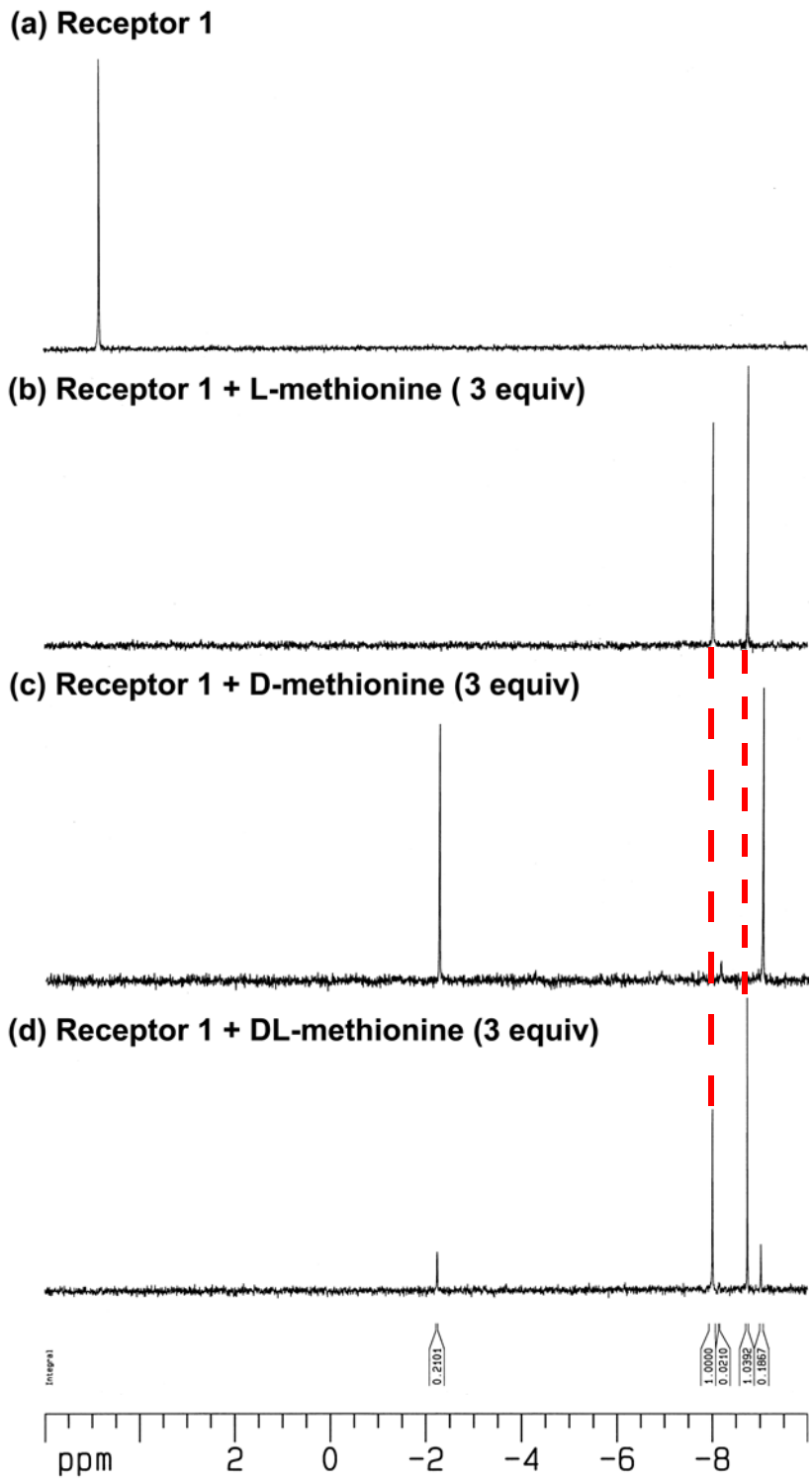


Figure S6. Proton-coupled ^{19}F NMR spectra of receptor (*S*)-**1** [1.0 mM], (b) (*S*)-**1** [1.0 mM] + L-methionine [3.0 mM], (c) (*S*)-**1** [1.0 mM] + D-methionine [3.0 mM], and (d) (*S*)-**1** [1.0 mM] + DL-methionine [3.0 mM]; taken in CD_3CN. Methionine is used as its tetrabutylammonium carboxylate salt.

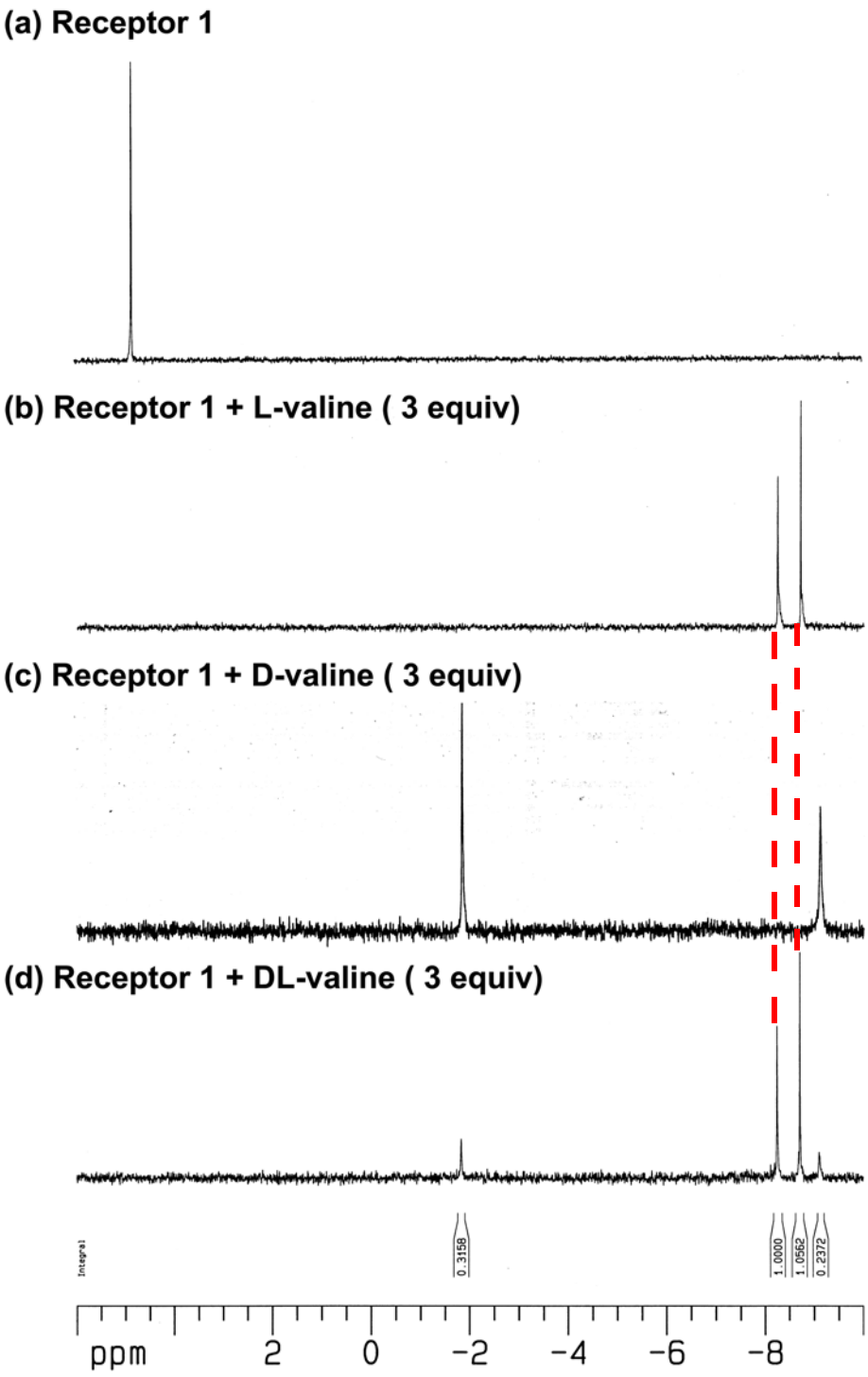


Figure S7. Proton-coupled ^{19}F NMR spectra of (a) receptor (*S*)-**1** [1.0 mM], (b) (*S*)-**1** [1.0 mM] + L-valine [3.0 mM], (c) (*S*)-**1** [1.0 mM] + D-valine [3.0 mM], and (d) (*S*)-**1** [1.0 mM] + DL-valine [3.0 mM]; taken in CD_3CN. Valine is used as its tetrabutylammonium carboxylate salt.

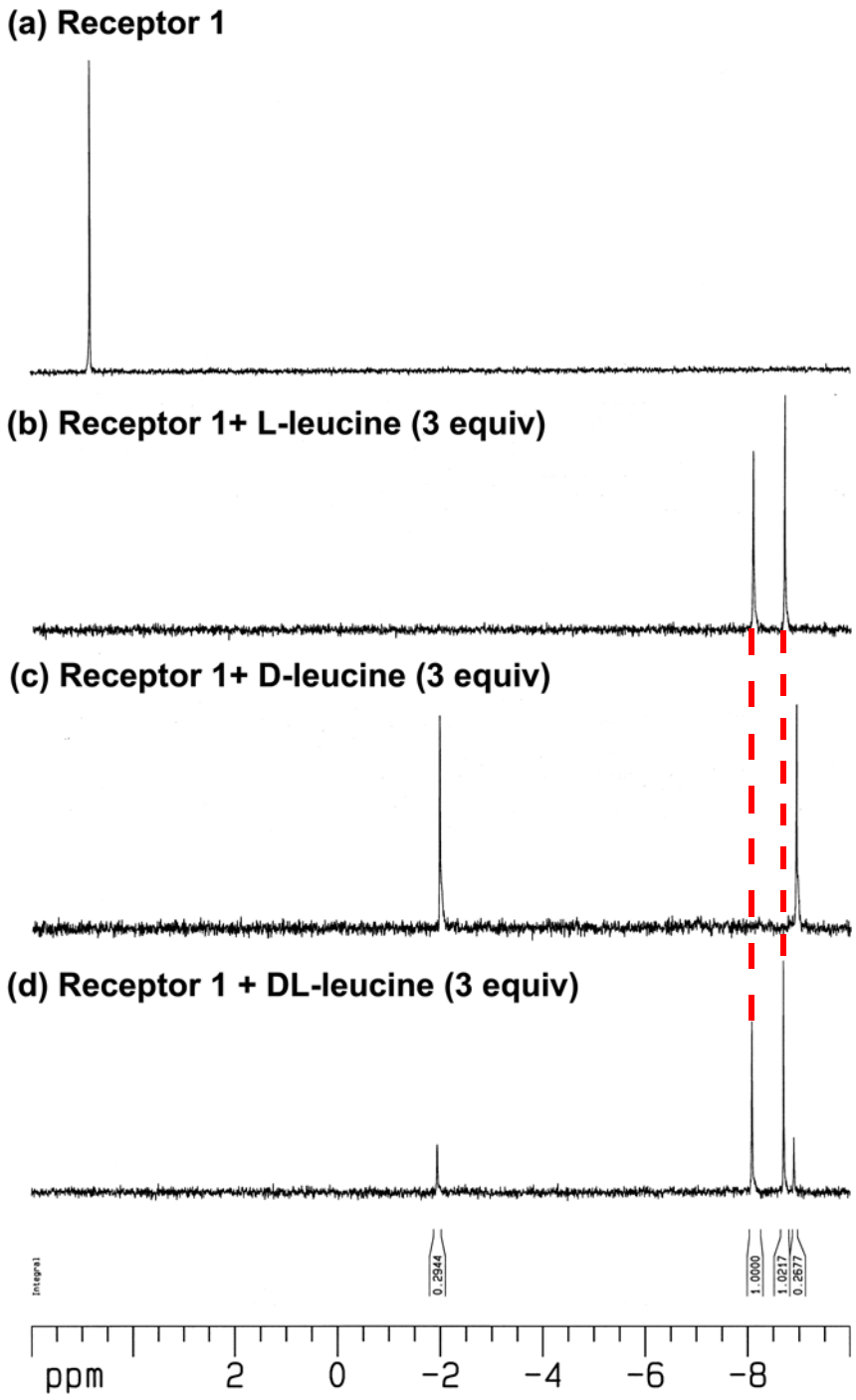


Figure S8. Proton-coupled ^{19}F NMR spectra of (a) receptor (*S*)-**1** [1.0 mM], (b) (*S*)-**1** [1.0 mM] + L-leucine [3.0 mM], (c) (*S*)-**1** [1.0 mM] + D-leucine [3.0 mM], and (d) [1.0 mM] + DL-leucine [3.0 mM]; taken in CD_3CN. Leucine is used as its tetrabutylammonium carboxylate salt.

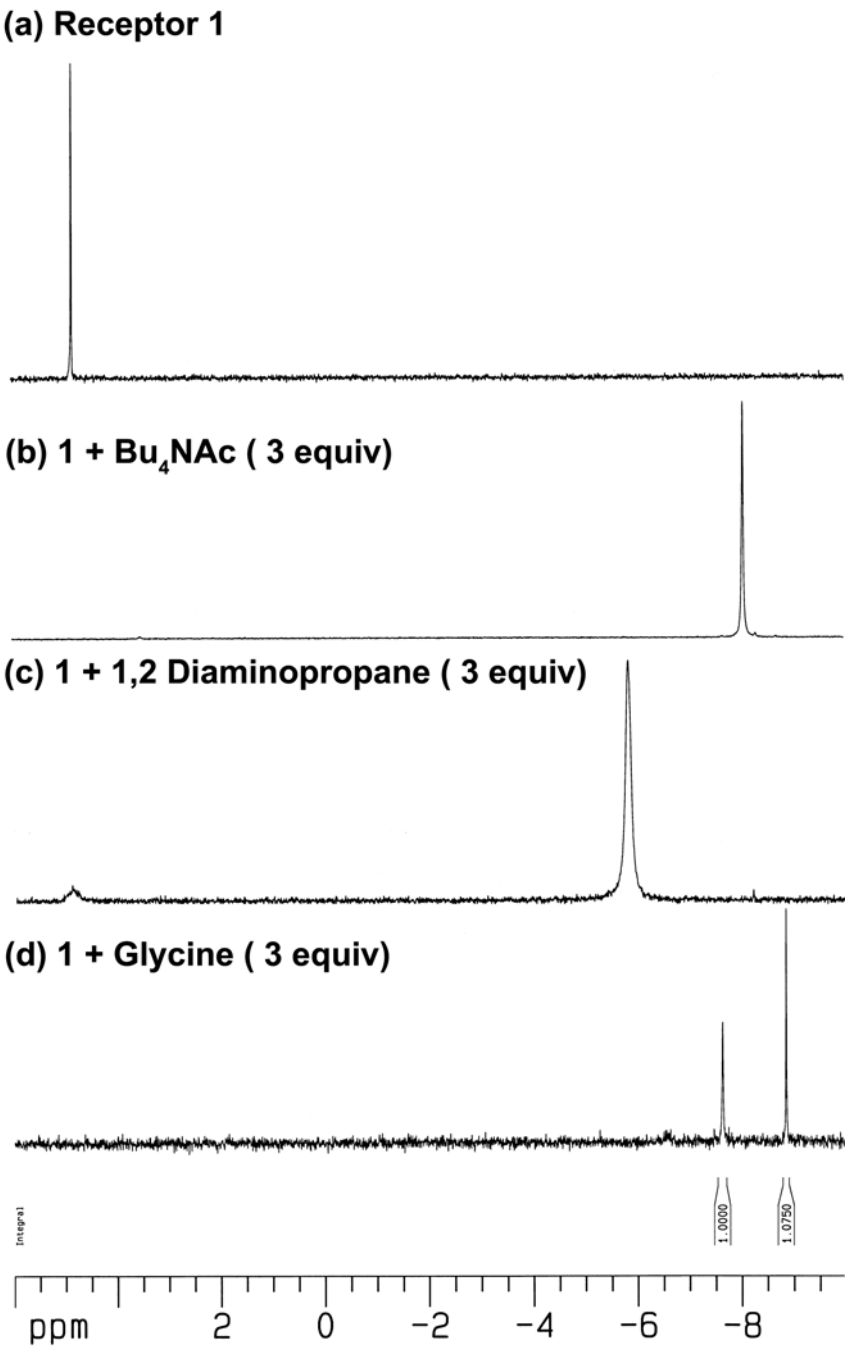


Figure S9. Proton-coupled ^{19}F NMR spectra of (a) receptor (*S*)-**1** [1.0 mM], (b) (*S*)-**1** [6.0 mM] + Bu_4NAc [18.0 mM], (c) (*S*)-**1** [6.0 mM] + 1,2-diaminopropane [18.0 mM], and (d) (*S*)-**1** [6.0 mM] + glycine [18.0 mM]; taken in CD_3CN. Glycine is used as its tetrabutylammonium carboxylate salt.

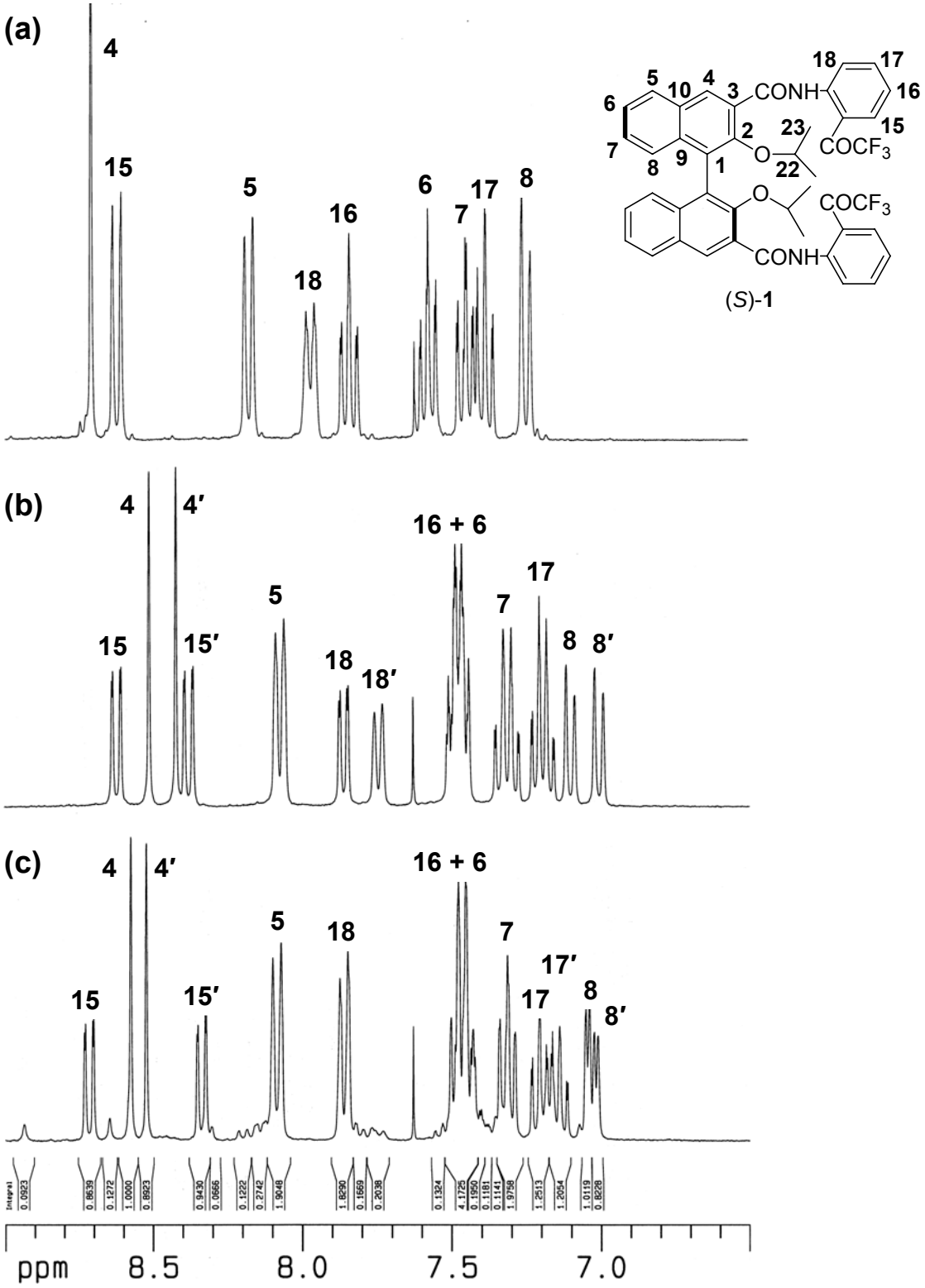


Figure S10. Partial ^{1}H NMR spectra of (a) receptor (*S*)-**1** [0.02M], (b) (*S*)-**1** [0.02M] + L-alanine [0.02M], and (c) (*S*)-**1** [0.02M] + D-alanine [0.02M]; taken in CD_3CN. Alanine is used as its tetrabutylammonium carboxylate salt.

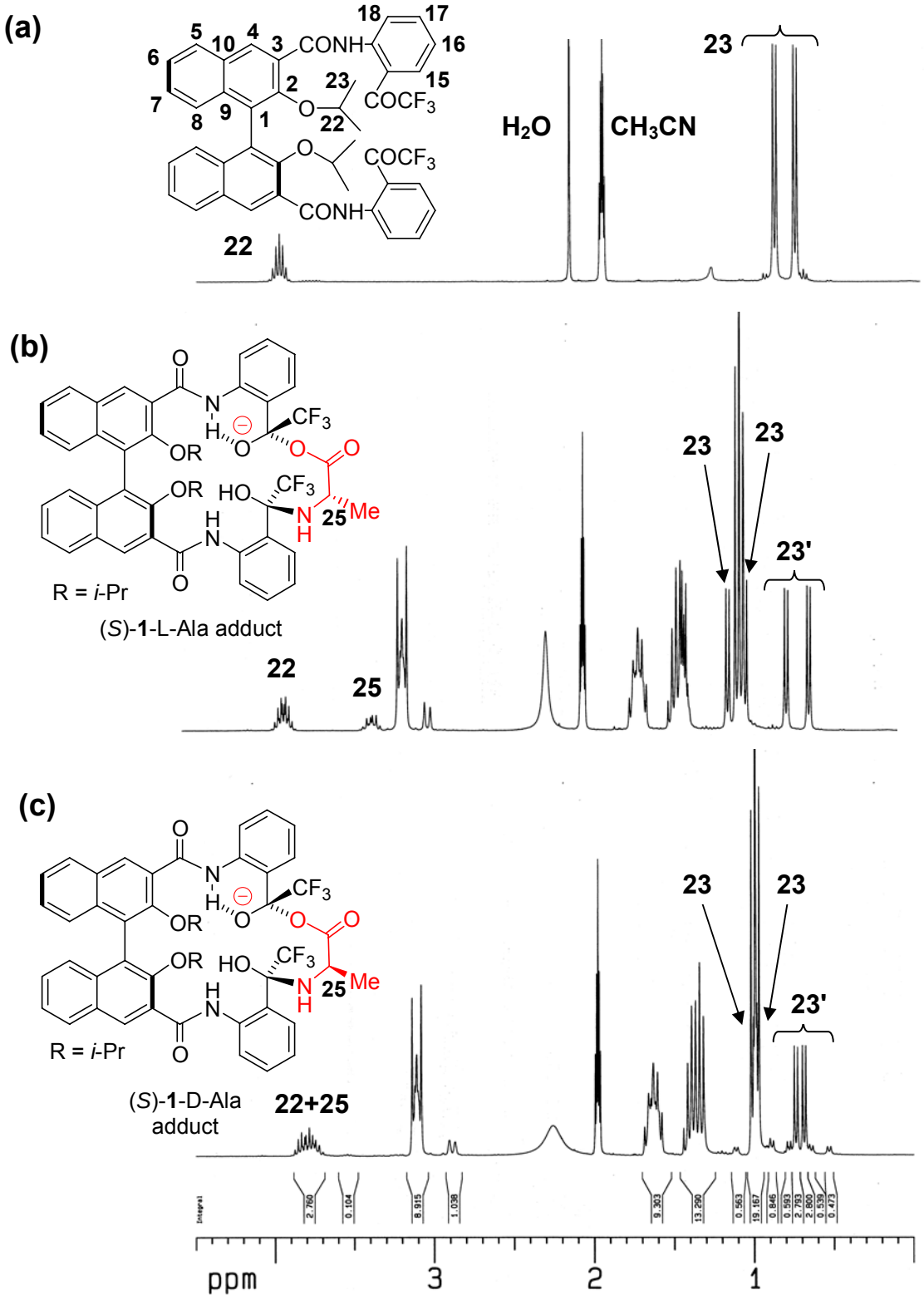


Figure S11. Partial ^{1}H NMR spectra of (a) receptor (*S*)-**1** [0.02M], (b) (*S*)-**1** [0.02M] + L-alanine [0.02M], and (c) (*S*)-**1** [0.02M] + D-alanine [0.02M]; taken in CD_3CN. Alanine is used as its tetrabutylammonium carboxylate salt.

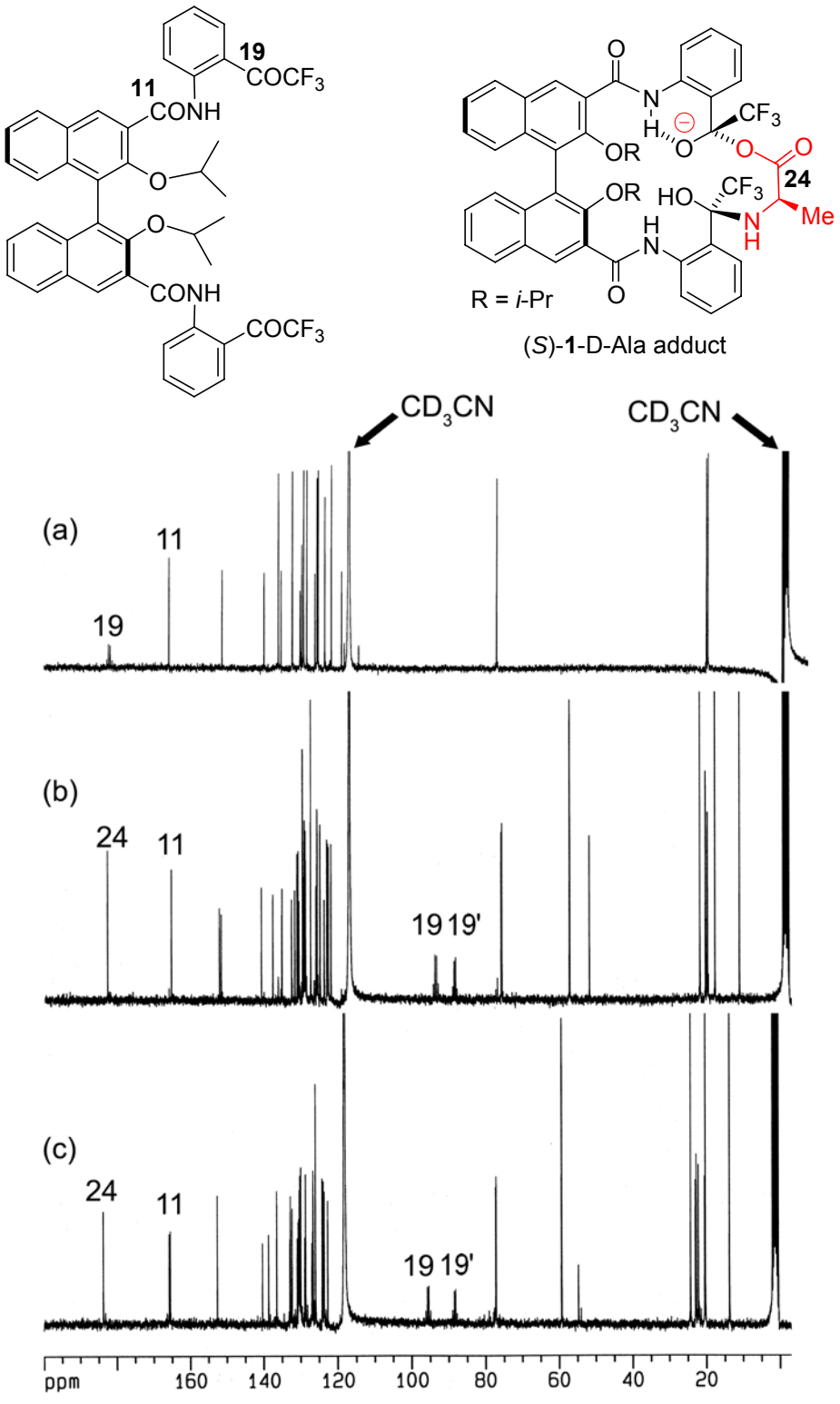


Figure S12. ^{13}C NMR spectra of (a) receptor (*S*)-**1** [0.02M], (b) (*S*)-**1** [0.02M] + L-alanine [0.02M], and (c) (*S*)-**1** [0.02M] + D-alanine [0.02M]; taken in CD_3CN. Alanine is used as its tetrabutylammonium carboxylate salt.

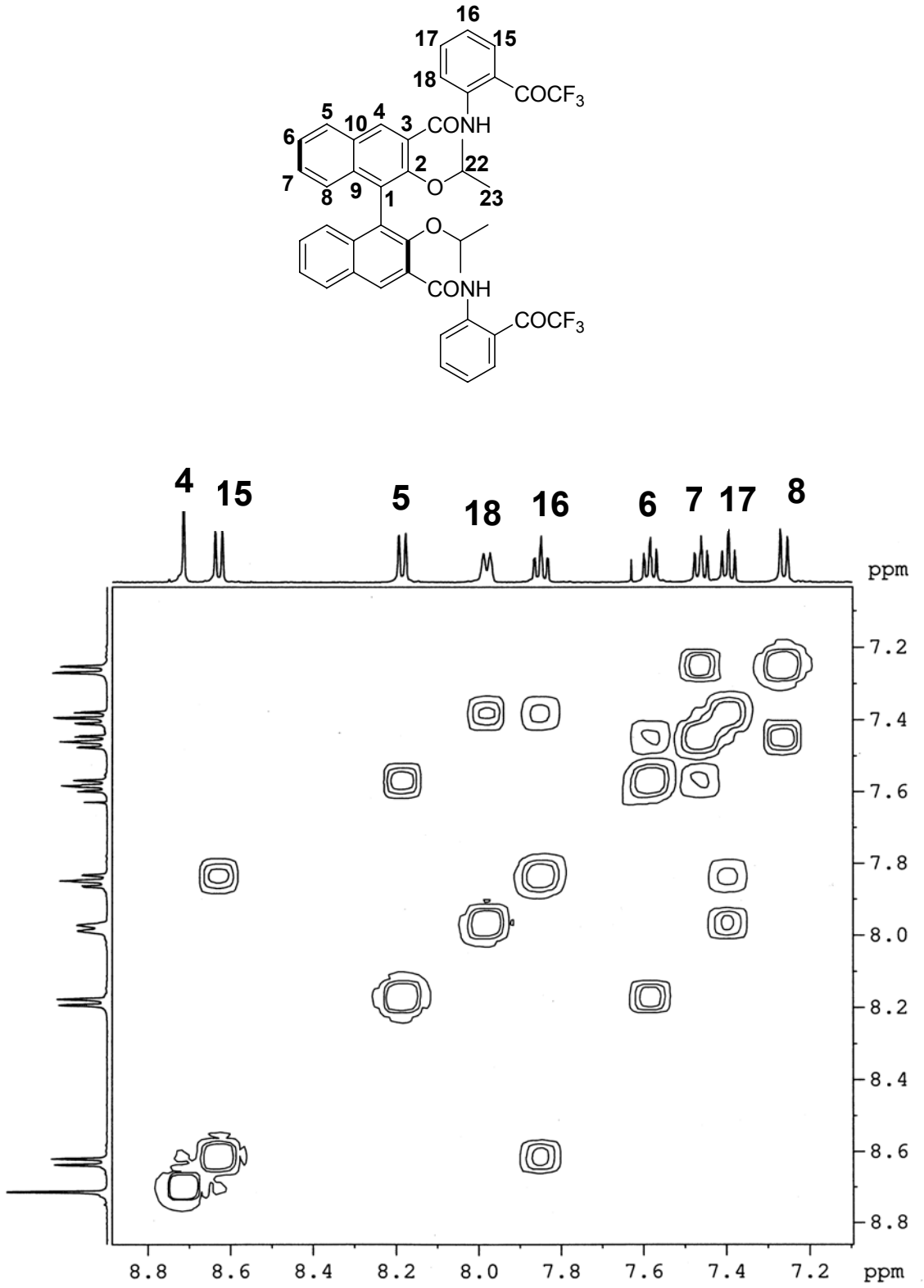


Figure S13. Partial ^{1}H-^{1}H COSY spectrum of receptor (*S*)-**1**, taken in CD_3CN

Isothermal titration calorimetry (ITC).

The binding affinity and the thermodynamic data were determined by ITC using a isothermal titration calorimeter (Microcal Inc.).

Procedure: To a solution of receptor (*S*)-**1** in the calorimeter cell, 5.0 μL of L- or D-alanine tetrabutylammonium carboxylate was injected 40 times at 25 °C. The dilution effects were corrected by carrying out a separate blank titration. The titration data was analyzed by the built-in curve-fitting Origin software, which gave an apparent binding constant (K_{ass}) and the standard enthalpy change $\Delta H°$.

Conditions:

Cell: Receptor (*S*)-**1** (0.2 mM)
Syringe: L- or D-Alanine tetrabutylammonium carboxylate solution (3.0 mM)
Reference power: 26
Temperature: 303 K
Stirring rate: 242 rpm

Although the crude binding isotherms have good features as shown in the next figures, we have difficulty in fitting the raw data by nonlinear least squares regression methods implemented in the software. Thus, the nonlinear squares regression fitting procedure gave a large error value (χ^2 value), particularly in the case of the less stable D-Ala adduct formation. Therefore, the values provided should be taken as ballpark figures. For binding L-alanine tetrabutylammonium carboxylate: $K_{ass} \approx 1.3 \times 10^7\ M^{-1}$, and for binding D-alanine tetrabutylammonium carboxylate: $K_{ass} \approx 1.1 \times 10^6\ M^{-1}$. As shown in the previous reports (references 8 and others reported by Ahn and co-workers for molecular interactions between CATFA-based molecular receptors and carboxylates), the binding process involves favorable enthalpy changes (ΔH = –29 kcal/mol) and unfavorable entropy changes [$-T\Delta S$ = 303 K_{ass} × (–63 eu) = 19 kcal/mol] in the case of L-Ala adduct formation.

Even though the fitting procedures gave the ballpark figures for the association constants, the integration data in Figure S11 clearly show that the titration data for L-Ala follows more steep inflection than the case of D-Ala, indicating that the formation of L-Ala adduct is favored over that of D-Ala. Also, the inflection points occur at 1.0 equivalent molar ratio in both cases, which data are also corroborate with the 1:1 binding modes in both cases.

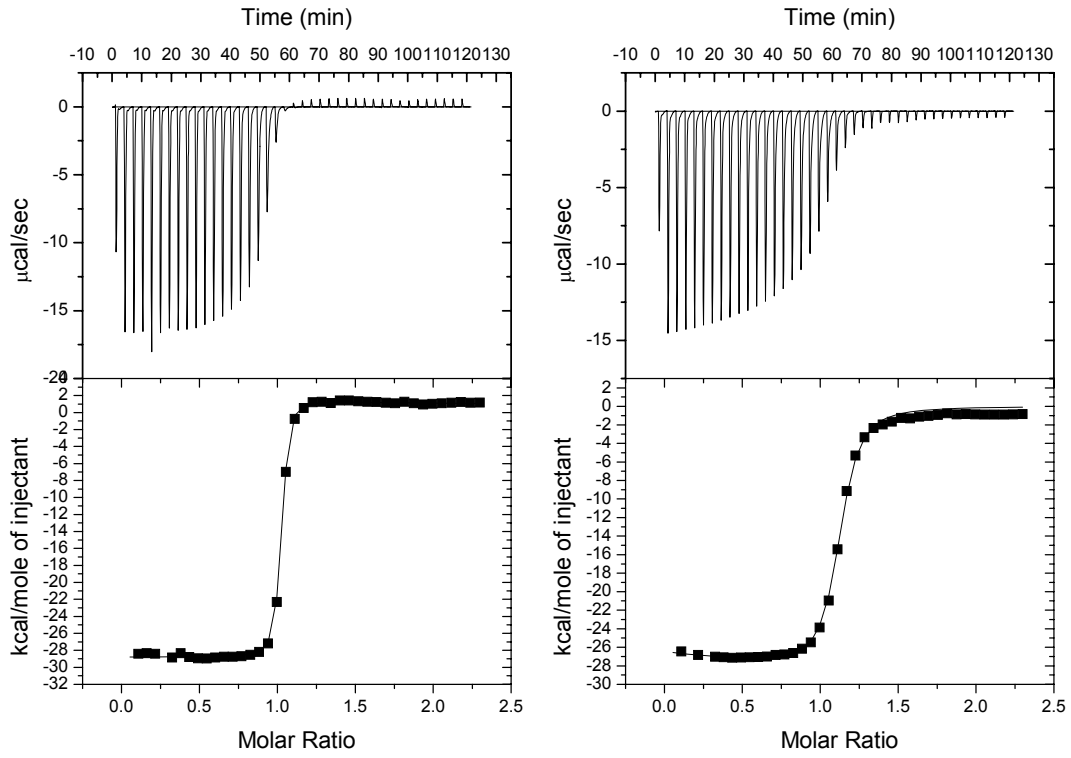


Figure S14: Isothermal titration calorimetry data: (a) receptor (*S*)-**1** (0.2 mM) with L-alanine (3.0 mM) (b) receptor (*S*)-**1** (0.2 mM) with D-alanine (3.0 mM); measured in CH_3CN at 30 °C. Alanine is used as its tetrabutylammonium carboxylate salt.

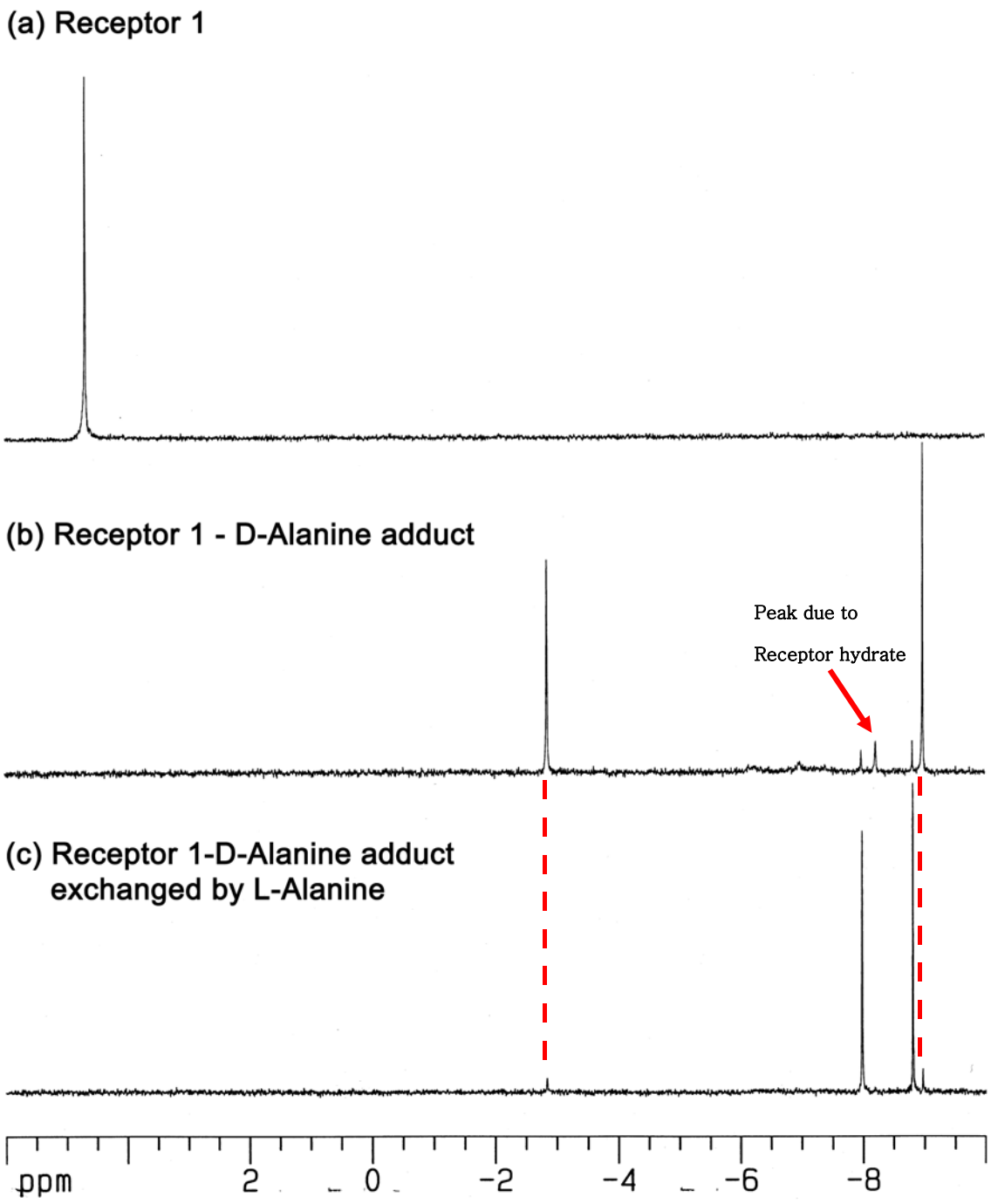
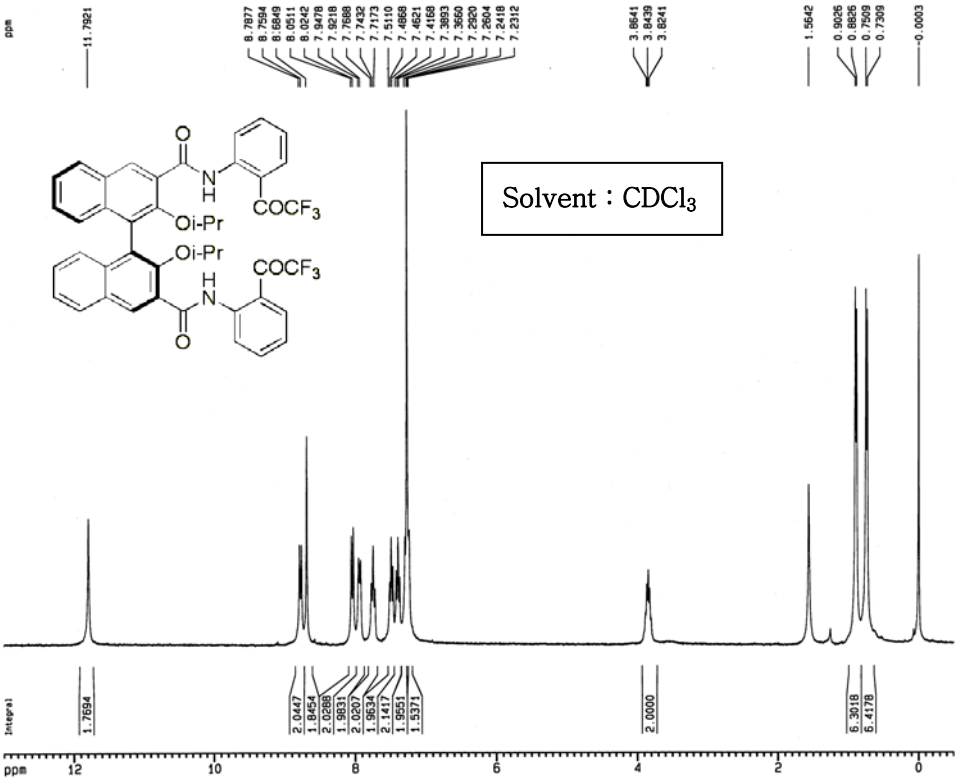
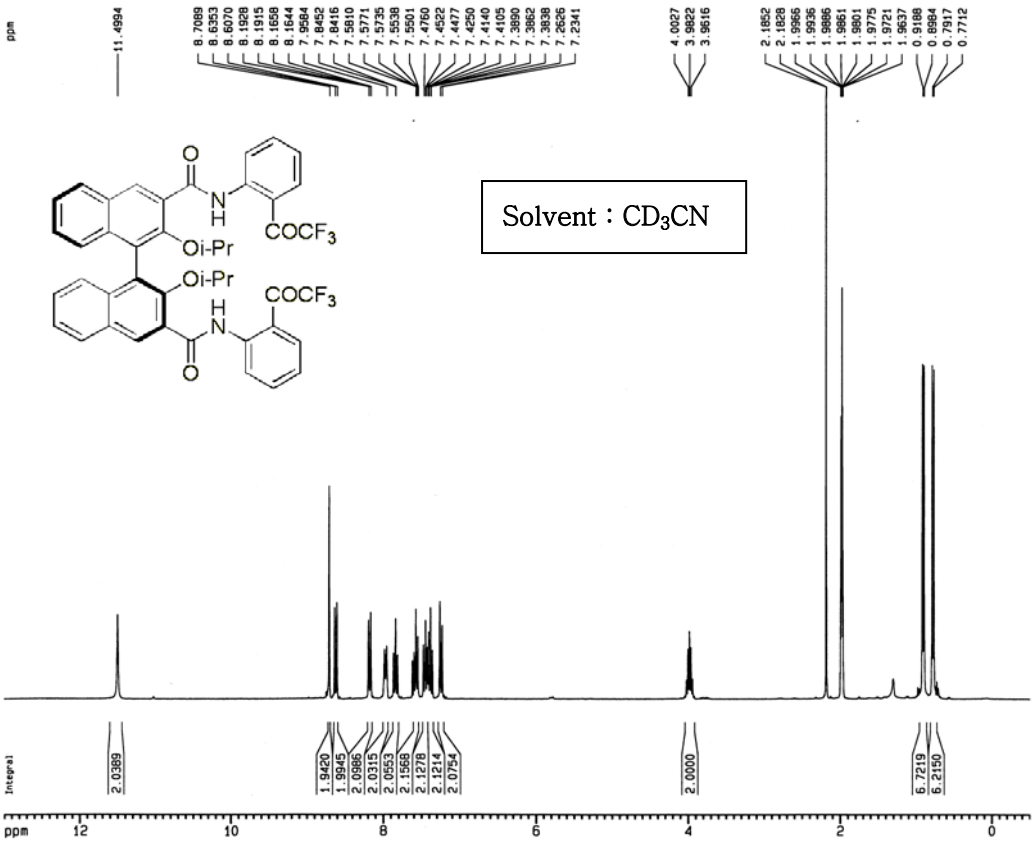
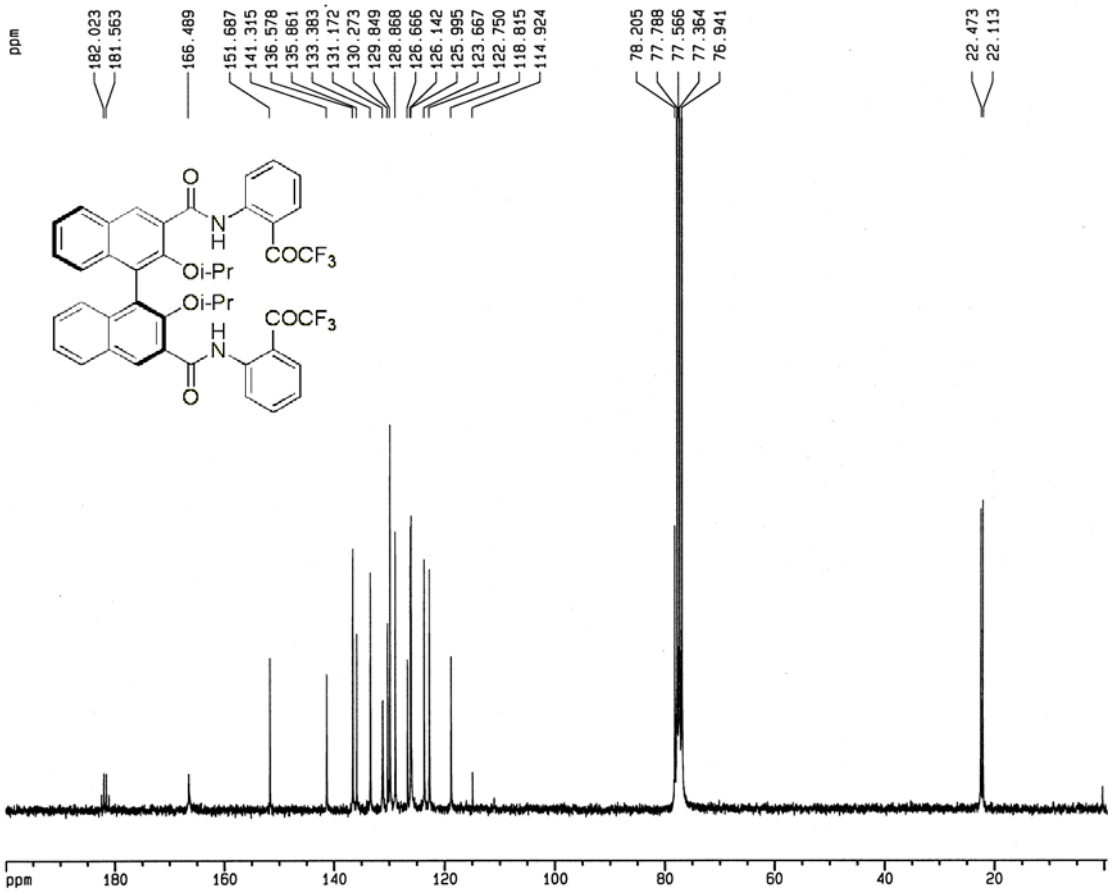


Figure S15. Reversibility of alanine binding to (*S*)-**1**. Proton-coupled ^{19}F NMR spectra of (a) receptor (*S*)-**1** [1.0 mM], (b) (*S*)-**1** [1.0 mM] + D-Alanine [1.5 mM], (c) L-Alanine [1.5 mM] is added to the solution of (b) which contains (*S*)-**1** [1.0 mM] and D-Alanine [1.5 mM] in CD_3CN, taken immediately after the addition. Alanine is used as its tetrabutylammonium carboxylate salt. (The hydrate peak observed this time is due to trace of water presented in the D-Ala sample)


Solvent : $CDCl_3$
Oi-Pr
Oi-Pr
$COCF_3$
$COCF_3$


Solvent : CD_3CN
Oi-Pr
Oi-Pr
$COCF_3$
$COCF_3$


ppm
182.023
181.563
166.489
151.687
141.315
136.578
135.861
133.383
131.172
130.273
129.849
128.868
126.666
126.142
125.995
123.667
122.750
118.815
114.924
78.205
77.788
77.566
77.364
76.941
22.473
22.113
O
N
H
COCF3
Oi-Pr
Oi-Pr
COCF3
H
N
O
ppm
180
160
140
120
100
80
60
40
20