Supplementary Information

Synthesis of biphenyl-based chiral amine catalysts from dibromopyrenes and their application in enamine catalysis

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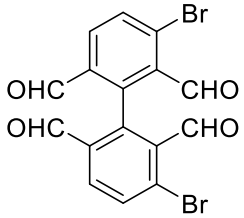
General information

^{1}H NMR spectra were measured on a JEOL JNM-ECA500 (500 MHz) spectrometer. Chemical shifts were reported in ppm from tetramethylsilane as an internal standard. Data were reported as follow: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on a JEOL JNM-FX500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 20A instruments using Daicel CHIRALPAK AD-H, IA-3, and IC-3 4.6 mm × 25 cm column. The high resolution mass spectra (HRMS) were performed on Thermo Scientific EXACTIVE PLUS. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60N (Kanto Chemical Co. Inc., 40–50 μm).

Both 1,6- and 1,8-dibromopyrenes are commercially available and their mixture is readily obtained by bromination of pyrene.[1] In experiments requiring dry solvents, dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), and toluene were purchased from Kanto Chemical Co. Inc. as "Dehydrated". A 1.6M hexane solution of butyllithium (BuLi) was purchased from Nacalai Tesque, Inc. The commercially available aldehydes were distilled and stored under a nitrogen atmosphere at 5 °C.

Synthesis of biphenyl-based chiral secondary amine catalysts

3,3'-Dibromo-[1,1'-biphenyl]-2,2',6,6'-tetracarbaldehyde[2] (5)



A mixture of 1,6-dibromopyrene and 1,8-dibromopyrene (1.80 g, 5 mmol) was dissolved in CH_2CI_2 (300 mL), and the solution was cooled to –78 °C. Ozone was introduced to the stirred solution at –78 °C for 2.5 h, maintaining the temperature at –

78 °C. The excess of ozone was removed by bubbling O_2 and N_2 through the solution at –78 °C. NaI (3.74 g, 25 mmol) and acetic acid (5.7 mL, 100 mmol) were added to the reaction mixture at –78 °C, and the stirring was continued at –78 °C to room temperature overnight. The reaction mixture was successively washed with an aqueous $Na_2S_2O_3$ solution, a saturated aqueous $NaHCO_3$ solution, and water. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 4/1) to give **5** as a white solid (1.35 g, 3.2 mmol, 64% yield).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 10.24 (s, 2H), 9.54 (s, 2H), 8.00 (d, J = 8.2 Hz, 2H), 7.96 (d, J = 8.2 Hz, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 191.8, 188.7, 140.5, 134.9, 134.7 (2 peaks overlapped), 133.8, 132.8.

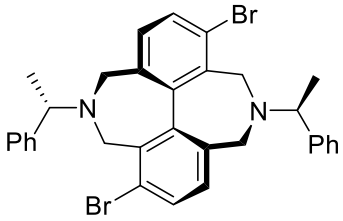
HRMS (ESI, positive) Calcd. For $C_{16}H_8Br_2NaO_4$: 444.8682, 446.8662, 448.8641 ([M + Na]$^+$), Found: 444.8685, 446.8663, 448.8643 ([M + Na]$^+$)

(*R*)-3,9-Dibromo-5,11-bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene ((*R*,*S*,*S*)-8),

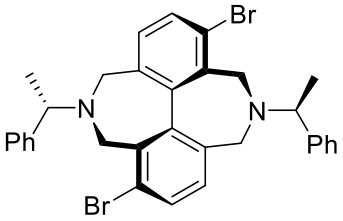
(*S*)-3,9-Dibromo-5,11-bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene ((*S*,*S*,*S*)-8),

(*S*)-3,7-Dibromo-5,11-bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene ((*S*,*S*,*S*)-9),

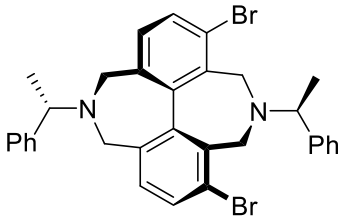
and (*R*)-3,7-Dibromo-5,11-bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene[3] ((*R*,*S*,*S*)-9)



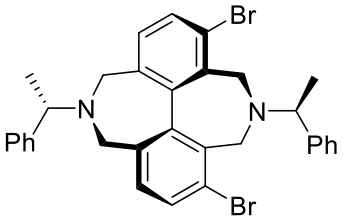
(*R*,*S*,*S*)-**8**



(*S*,*S*,*S*)-**8**



(*S*,*S*,*S*)-**9**



(*R*,*S*,*S*)-**9**

To a solution of **5** (0.209 g, 0.49 mmol) in MeCN (10 mL) was added (*S*)-1-phenylethylamine (0.19 mL, 1.47 mmol). After being stirred at room temperature for 15 min, $NaBH_3CN$ (0.154 g, 2.45 mmol) was added and the reaction was stirred at room temperature for 20 h before the addition of acetic acid (0.28 mL, 4.9 mmol). After 1 h, the reaction was quenched with 1N aqueous NaOH solution and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 20/1 to 5/1) to give (*R*,*S*,*S*)-**8**, (*S*,*S*,*S*)-**8**, (*S*,*S*,*S*)-**9**, and (*R*,*S*,*S*)-**9** (1.6: 1.5: 2.2: 1) as white solid (0.222 g, 0.368 mmol, 75% yield). The absolute configurations of the axial chirality of **8** and **9** were determined by conversion to the

known compounds through removal of the bromine atoms by hydrogenation using Pd on carbon and hydrogen.[3]

(*R*,*S*,*S*)-**8**

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 7.9 Hz, 2H), 7.53 (d, J = 7.1 Hz, 4H), 7.39 (t, J = 7.7 Hz, 4H), 7.30 (t, J = 7.5 Hz, 2H), 7.04 (d, J = 7.9 Hz, 2H), 4.44 (d, J = 11.6 Hz, 2H), 3.74 (q, J = 6.5 Hz, 2H), 3.57 (d, J = 13.0 Hz, 2H), 3.03 (d, J = 13.0 Hz, 2H), 2.91 (d, J = 11.9 Hz, 2H), 1.40 (d, J = 6.5 Hz, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 146.5, 141.9, 135.1, 133.6, 132.5, 130.1, 128.6, 127.6, 127.0, 124.6, 62.2, 52.5, 51.8, 22.6.

HRMS (ESI, positive) Calcd. For $C_{32}H_{31}Br_2N_2$: 601.0849, 603.0829, 605.0808 ([M + H]$^+$), Found: 601.0864, 603.0836, 605.0812 ([M + H]$^+$)

$[\alpha]_D^{31}$ = –61.1 (c 1.00, $CHCl_3$)

(*S*,*S*,*S*)-**8**

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 7.9 Hz, 2H), 7.37 (d, J = 7.4 Hz, 4H), 7.31 (t, J = 7.5 Hz, 4H), 7.25 (d, J = 7.1 Hz, 2H), 7.10 (d, J = 7.9 Hz, 2H), 4.17 (d, J = 12.5 Hz, 2H), 3.73 (d, J = 13.3 Hz, 2H), 3.57 (q, J = 6.4 Hz, 2H), 2.99 (d, J = 13.3 Hz, 2H), 2.84 (d, J = 12.5 Hz, 2H), 1.64 (d, J = 6.2 Hz, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 144.9, 141.9, 134.8, 133.6, 132.6, 130.0, 128.6, 127.6, 127.2, 124.7, 62.1, 52.5, 51.8, 23.0.

HRMS (ESI, positive) Calcd. For $C_{32}H_{31}Br_2N_2$: 601.0849, 603.0829, 605.0808 ([M + H]$^+$), Found: 601.0851, 603.0835, 605.0803 ([M + H]$^+$)

$[\alpha]_D^{31}$ = –7.3 (c 1.00, $CHCl_3$)

(*S*,*S*,*S*)-**9**

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 7.9 Hz, 2H), 7.62 (d, J = 7.7 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.27 (t, J = 6.1 Hz, 1H), 7.12 (d, J = 7.9 Hz, 2H), 4.29 (d, J = 12.5 Hz, 2H), 4.07 (q, J = 6.6 Hz, 1H), 3.71 (d, J = 12.5 Hz, 2H), 3.54 (q, J = 6.4 Hz, 1H), 3.05 (d, J = 12.5 Hz, 2H),

2.96 (d, *J* = 12.5 Hz, 2H), 1.39 (d, *J* = 7.0 Hz, 3H) , 1.37 (d, *J* = 7.0 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 147.0, 146.1, 141.8, 135.0, 133.9, 132.5, 130.2, 128.9, 128.1, 127.7, 127.6, 127.2, 126.7, 124.8, 62.7, 61.6, 52.6, 51.6, 22.7, 22.7.

HRMS (ESI, positive) Calcd. For $C_{32}H_{31}Br_2N_2$: 601.0849, 603.0829, 605.0808 ([M + H]$^+$), Found: 601.0859, 603.0834, 605.0808 ([M + H]$^+$)

$[\alpha]_D^{30}$ = –20.5 (c 1.10, $CHCl_3$)

(*R*,*S*,*S*)-**9**

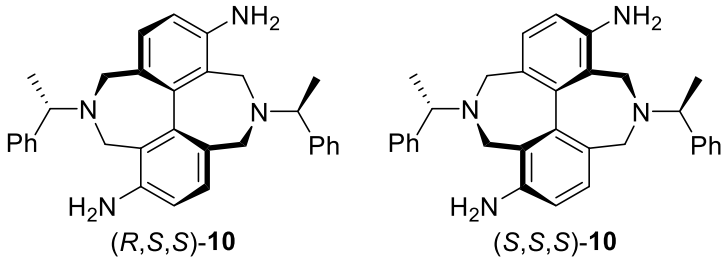
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 7.1 Hz, 2H), 7.34-7.29 (m, 6H), 7.27-7.23 (m, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 4.23 (d, *J* = 13.0 Hz, 2H), 3.70 (q, *J* = 6.5 Hz, 1H), 3.66 (d, *J* = 12.8 Hz, 2H), 3.46 (q, *J* = 6.4 Hz, 1H), 2.95 (d, *J* = 12.8 Hz, 2H), 2.90 (d, *J* = 13.0 Hz, 2H), 1.75 (d, *J* = 6.2 Hz, 3H), 1.57 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 144.94, 144.91, 141.9, 134.7, 133.8, 132.5, 130.0, 128.7, 128.5, 127.7, 127.5, 127.24, 127.19, 124.8, 62.3, 61.9, 52.3, 52.0, 23.6, 22.6.

HRMS (ESI, positive) Calcd. For $C_{32}H_{31}Br_2N_2$: 601.0849, 603.0829, 605.0808 ([M + H]$^+$), Found: 601.0851, 603.0832, 605.0802 ([M + H]$^+$)

$[\alpha]_D^{30}$ = –64.0 (c 1.10, $CHCl_3$)

(*R*)-5,11-Bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-3,9-diamine ((*R*,*S*,*S*)-10)
and (*S*)-5,11-Bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-3,9-diamine[4] ((*S*,*S*,*S*)-10)



(*R*,*S*,*S*)-**10** (*S*,*S*,*S*)-**10**

A mixture of (*R*,*S*,*S*)-**8** (0.304 g, 0.51 mmol), benzophenone imine (0.20 mL, 1.2 mmol), *rac*-BINAP (62.9 mg, 0.11 mmol), $Pd_2(dba)_3$ (546 mg, 0.051 mmol), and NaO*t*-

Bu (136 mg, 1.41 mmol) in toluene (10 mL) was heated at 110 °C and stirred for 65 h under an nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered through a Celite pad, and the filter cake was washed with ethyl acetate. The filtrate was concentrated in vacuo. The residue was dissolved in 1N aqueous HCl solution (3.0 mL) and THF (14 mL). After refluxing for 2 h, the mixture was then quenched with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate =3/1, 1% Et_3N) to give (*R*,*S*,*S*)-**10** and (*S*,*S*,*S*)-**10** (dr = 1/1.3) as a diastereomer mixture (0.184 g, 0.39 mmol, 77% yield).

Minor diastereomer (*R*,*S*,*S*)-**10**

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 4H), 7.40 (t, *J* = 7.5 Hz, 4H), 7.30 (app t, *J* = 7.4 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.72 (d, *J* = 7.9 Hz, 2H), 3.83 (d, *J* = 13.5Hz, 2H), 3.78 (br s, 4 H), 3.67 (q, *J* = 6.5 Hz, 2H), 3.59 (d, *J* = 12.8 Hz, 2H), 3.02 (d, *J* = 12.5 Hz, 2H), 2.89 (d, *J* = 12.8 Hz, 2H), 1.38 (d, *J* = 6.5 Hz, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 146.9, 144.4, 142.1, 129.4, 128.7, 127.5, 127.0, 125.1, 120.5, 115.1, 62.4, 53.1, 47.0, 23.0.

HRMS (ESI, positive) Calcd. For $C_{32}H_{35}N_4$: 475.2856 ($[M + H]^+$), Found: 475.2861 ($[M + H]^+$)

$[\alpha]_D^{32}$ = –36.4 (c 0.30, $CHCl_3$)

Major diastereomer (*S*,*S*,*S*)-**10**

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.9 Hz, 4H), 7.31 (t, *J* = 7.5 Hz, 4H), 7.24 (app t, *J* = 7.5 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.69 (d, *J* = 7.9 Hz, 2H), 3.85 (d, *J* = 13.9 Hz, 2H), 3.65 (br s, 4H), 3.51 (q, *J* = 6.3 Hz, 2H), 3.46 (d, *J* = 12.5 Hz, 2H), 3.25 (d, *J* = 13.9 Hz, 2H), 2.59 (d, *J* = 12.5 Hz, 2H), 1.59 (d, *J* = 6.2 Hz, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 146.0, 144.0, 142.1, 129.0, 128.7, 127.2, 127.1, 124.0, 120.9, 115.2, 62.1, 51.1, 48.8, 22.9.

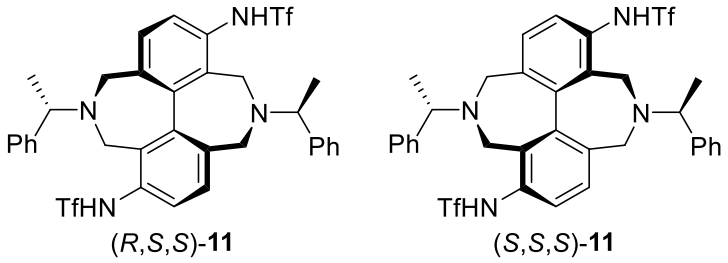
HRMS (ESI, positive) Calcd. For $C_{32}H_{35}N_4$: 475.2856 ($[M + H]^+$), Found: 475.2860 ([M

+ H]$^+$)

$[\alpha]_D^{29}$ = –11.2 (c 0.30, $CHCl_3$)

_N_,_N_'-((_R_)-5,11-Bis((_S_)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[_ef_,_kl_]heptalene-3,9-diyl)bis(1,1,1-trifluoromethanesulfonamide) ((_R_,_S_,_S_)-11)

and _N_,_N_'-((_S_)-5,11-Bis((_S_)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[_ef_,_kl_]heptalene-3,9-diyl)bis(1,1,1-trifluoromethanesulfonamide) ((_S_,_S_,_S_)-11)



(_R_,_S_,_S_)-**11** (_S_,_S_,_S_)-**11**

To a stirred solution of a mixture of amine (_R_,_S_,_S_)-**10** and (_S_,_S_,_S_)-**10** (0.027 g, 0.057 mmol, dr = 1/1.3) in CH_2Cl_2 (0.66 mL) was added Tf_2O (50 μL, 0.30 mmol) by syringe pump for 30 min at –78 °C. The reaction mixture was stirred at –78 °C to room temperature overnight. The mixture was then quenched with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane/ethyl acetate = 2/1). The product was used for the next reaction without further purification. The roughly purified product was dissolved in 1,2-dichloroethane (1.1 mL), and *p*-nitrophenol (0.020 g, 0.14 mmol) was added to this solution. After being stirred at 80 °C for 24 h, the reaction mixture was cooled to room temperature. Solvent was removed in vacuo, and the residue was then purified by flash column chromatography on silica gel (ethyl acetate/MeOH = 50/1 to 30/1) to give (_R_,_S_,_S_)-**11** and (_S_,_S_,_S_)-**11** (dr = 1.6/1) as yellow solid (0.031 g, 0.042 mmol, 73% yield).

Major diastereomer (*R*,*S*,*S*)-**11**

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.61-7.58 (m, 4H), 7.54-7.51 (m, 6H), 7.40 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 5.28 (d, J = 12.5 Hz, 2H), 4.32 (q, J = 6.6 Hz, 2H), 3.82 (d, J = 13.9 Hz, 2H), 3.54 (d, J = 13.9 Hz, 2H), 3.44 (d, J = 11.9 Hz, 2H), 1.89 (d, J = 6.8 Hz, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 150.1, 141.0, 136.6, 133.3, 130.8, 130.6, 129.0, 127.0, 125.4, 121.9 (q, $J_{C\text{-}F}$ = 325.4), 120.0, 64.3, 51.4, 50.0, 19.5.

^{19}F-NMR (466 MHz, $CDCl_3$) δ –75.0.

HRMS (ESI, positive) Calcd. For $C_{34}H_{33}F_6N_4O_4S_2$: 739.1842 ($[M + H]^+$), Found: 739.1839 ($[M + H]^+$)

$[\alpha]_D^{31}$ = –16.1 (c 0.10, $CHCl_3$)

Minor diastereomer (*S*,*S*,*S*)-**11**

^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.41 (br s, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.53-7.31 (m, 10H), 5.26 (d, J = 12.8 Hz, 2H), 4.25 (app t, J = 7.4 Hz, 2H), 3.49 (d, J = 10.5 Hz, 2H), 3.37 (d, J = 9.4 Hz, 2H), 2.99-2.94 (m, 2H), 2.18 (d, J = 6.2 Hz, 6H).

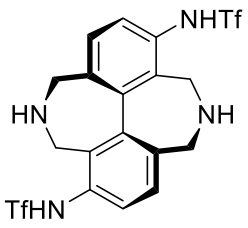
^{13}C-NMR (125 MHz, $CDCl_3$) δ 149.8, 140.7, 136.1, 133.2, 129.8 (2 peaks overlapped), 128.2, 123.9, 121.8 (q, $J_{C\text{-}F}$ = 326.6 Hz), 120.9, 120.4, 65.0, 54.9, 45.7, 19.6.

^{19}F-NMR (466 MHz, $CDCl_3$) δ –76.9.

HRMS (ESI, positive) Calcd. For $C_{34}H_{33}F_6N_4O_4S_2$: 739.1842 ($[M + H]^+$), Found: 739.1844 ($[M + H]^+$)

$[\alpha]_D^{31}$ = –66.2 (c 1.00, $CHCl_3$)

(*R*)-*N*,*N*'-(4,5,6,10,11,12-Hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-3,9-diyl)bis(1,1,1-trifluoromethanesulfonamide) ((*R*)-6)

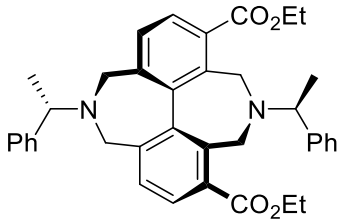


To a stirred solution of (*R*,*S*,*S*)-**11** (0.022 g, 0.03 mmol) in MeOH (0.98 mL) were

added 2.4N aqueous HCl solution (50 μL, 0.12 mmol) and 10% palladium on carbon (6.4 mg) at room temperature. The mixture was then hydrogenated under H_2 (balloon) at room temperature for 17 h. The reaction was quenched with $NaHCO_3$, and filtered through a Celite pad. The filter cake was washed with ethyl acetate. The filtrate was concentrated and dried under vacuum. The crude product was dissolved in a few drops of MeOH, and CH_2Cl_2 was added to this solution. Resulting precipitate was filtered, washed with CH_2Cl_2, and dried under vacuum to give (*R*)-**6** as a white solid (0.011 g, 0.021 mmol, 70% yield).

^{1}H-NMR (500 MHz, CD_3OD) δ 7.48 (m, 4H), 4.83 (d, J = 12.8 Hz, 2H), 4.15 (d, J = 13.0 Hz, 2H), 3.57 (d, J = 13.3 Hz, 2H), 3.38 (d, J = 13.0 Hz, 2H).
^{13}C-NMR (125 MHz, CD_3OD) δ 148.7, 142.0, 132.8, 126.7, 125.7, 124.4, 123.3 (q, $J_{C\text{-}F}$ = 327.9 Hz), 46.7, 42.0.
^{19}F-NMR (466 MHz, CD_3OD) δ –77.6.
HRMS (ESI, positive) Calcd. For $C_{18}H_{17}F_6N_4O_4S_2$: 531.0590 ($[M + H]^+$), Found: 531.0595 ($[M + H]^+$)
$[\alpha]_D^{29}$ = –17.1 (c 0.40, MeOH)

Diethyl (*S*)-5,11-bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-3,7-dicarboxylate ((*S*,*S*,*S*)-12)



To a stirred solution of (*S*,*S*,*S*)-**9** (1.20 g, 2 mmol) in THF (12 mL) was added *n*-BuLi (2.75 mL, 1.6M in hexane, 4.4 mmol) at –78 °C dropwise under a nitrogen atmosphere. The reaction mixture was stirred at –78 °C for 30 min. This solution was transferred to a THF (8 mL) solution of ethyl chloroformate (1.9 mL, 20 mmol) at –78 °C by syringe, and the solution was stirred at –78 °C to room temperature overnight. The mixture was then quenched with a saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The

residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give (*S*,*S*,*S*)-**12** as a white solid (0.776 g, 1.32 mmol, 66% yield).

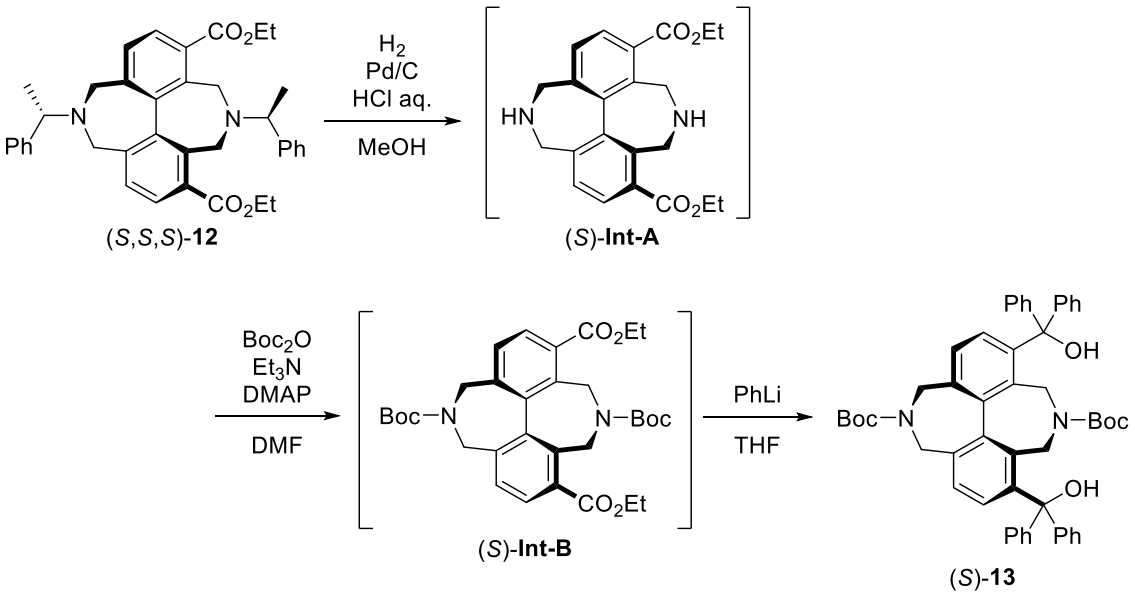
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.4 Hz, 4H), 7.40 (t, J = 7.7 Hz, 2H), 7.35-7.29 (m, 5H), 7.24 (t, J = 7.2 Hz, 1H), 4.66 (d, J = 12.8 Hz, 2H), 4.33-4.24 (m, 2H), 4.19-4.13 (m, 2H), 3.76 (d, J = 12.5 Hz, 2H), 3.64 (q, J = 6.5 Hz, 1H), 3.52 (q, J = 6.4 Hz, 1H), 3.02 (d, J = 12.5 Hz, 2H), 2.98 (d, J = 12.5 Hz, 2H), 1.36 (d, J = 6.5 Hz, 3H), 1.29 (d, J = 6.5 Hz, 3H), 1.25 (t, J = 7.1 Hz, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.6, 147.0, 146.1, 141.3, 137.8, 134.5, 131.6, 129.8, 128.9, 128.6, 128.4, 127.6, 127.3, 127.2, 126.8, 62.7, 61.6, 61.4, 52.9, 47.9, 23.2, 22.7, 14.3.

HRMS (ESI, positive) Calcd. For $C_{38}H_{41}N_2O_4$: 589.3061 ($[M + H]^+$), Found: 589.3067 ($[M + H]^+$)

$[\alpha]_D^{29}$ = –15.3 (c 1.00, $CHCl_3$)

Di-*tert*-butyl (*S*)-3,7-bis(hydroxydiphenylmethyl)-10,12-dihydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-5,11(4*H*,6*H*)-dicarboxylate ((*S*)-13)



To a stirred solution of (*S*,*S*,*S*)-**12** (0.719 g, 1.22 mmol) in MeOH (38 mL) were added 2.4N aqueous HCl solution (2 mL, 4.88 mmol) and 10% palladium on carbon (260 mg) at room temperature. The mixture was then hydrogenated under H_2 (balloon) at room temperature for 63 h and filtered through a Celite pad. The filtrate was basified with 1N aqueous NaOH solution and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The product (*S*)-**Int-A** was used for the next reaction without further purification.

Amine (*S*)-**IntA** (*ca*. 1.2 mmol), Et_3N (0.85 mL, 6.1 mmol), Boc_2O (1.4 mL, 6.1 mmol) and DMAP (0.075 g, 0.61 mmol) were dissolved in DMF (6.1 mL). After being stirred for 48 h, the reaction mixture was diluted with H_2O and extracted with a mixture of hexane and ethyl acetate (1/1). The combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5/1). The product (*S*)-**Int-B** was used for the next reaction without further purification.

To a stirred solution of (*S*)-**Int-B** (*ca*. 1 mmol) in THF (20 mL) was added PhLi (3.66 mL, 2M in *n*-Bu_2O, 7.32 mmol) at 0 °C dropwise under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 5 h. The mixture was then quenched with a saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5/1 to 3/1) to give (*S*)-**13** as a white solid (0.458 g, 0.57 mmol, 47% yield for three steps).

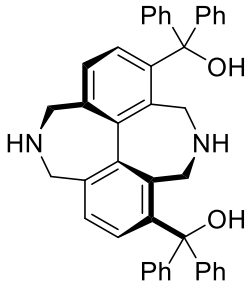
^{1}H-NMR (500 MHz, CD_3CN) δ 7.30-7.19 (m, 20H), 7.14 (d, J = 7.7 Hz, 2H), 6.72 (d, J = 7.9 Hz, 1H), 6.66 (d, J = 7.9 Hz, 1H), 5.96 (s, 1H), 5.36 (d, J = 13.0 Hz, 1H), 4.88 (d, J = 14.7 Hz, 1H), 4.78 (m, 2H), 4.72 (d, J = 12.8 Hz, 1H), 3.57-3.38 (m, 2H), 2.99 (d, J = 14.5 Hz, 1H), 2.97 (d, J = 13.0 Hz, 1H), 1.45 (s, 9H), 1.33 (s, 9H).
^{13}C-NMR (125 MHz, CD_3CN) δ 156.0, 154.8, 150.1, 148.7, 148.0, 147.8, 146.8, 146.6, 142.9, 141.8, 135.2, 134.9, 134.3, 133.3, 131.5, 131.2, 129.2, 128.8 (2 peaks overlapped), 128.7 (2 peaks overlapped), 128.63, 128.59, 128.55, 128.4, 128.1, 128.0, 127.9, 127.6 (2 peaks overlapped), 83.2 (2 peaks overlapped), 81.8 (2 peaks overlapped), 81.3, 80.6, 45.0,

43.4, 28.5, 28.5.

HRMS (ESI, positive) Calcd. For $C_{52}H_{52}N_2NaO_6$: 823.3718 ($[M + Na]^+$), Found: 823.3714 ($[M + Na]^+$)

$[\alpha]_D^{31}$ = –306.4 (c 1.00, $CHCl_3$)

(*S*)-(4,5,6,10,11,12-Hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-3,7-diyl)bis(diphenylmethanol) ((*S*)-7)



To a stirred solution of (*S*)-**13** (0.024 g, 0.03 mmol) in 1,4-dioxane (0.44 mL) was added 9N aqueous HCl solution (0.21 mL). The reaction mixture was stirred at room temperature for 28 h. The reaction was quenched with 1N aqueous NaOH solution and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give (*S*)-**7** as a white solid (0.015 g, 0.026 mmol, 85% yield).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31-7.21 (m, 20H), 7.06 (d, J = 7.9 Hz, 2H), 6.68 (d, J = 7.9 Hz, 2H), 3.98 (d, J = 12.8 Hz, 2H), 3.69 (d, J = 12.5 Hz, 2H), 3.40 (d, J = 12.5 Hz, 2H), 2.82 (d, J = 12.8 Hz, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 147.9, 147.6, 145.9, 142.0, 134.9, 134.5, 130.0, 128.2, 128.1, 128.0, 127.7, 127.3, 127.1, 126.9, 83.0, 48.3, 44.8.

HRMS (ESI, positive) Calcd. For $C_{42}H_{37}N_2O_2$: 601.2850 ($[M + H]^+$), Found: 601.2857 ($[M + H]^+$)

$[\alpha]_D^{31}$ = –165.1 (c 0.80, $CHCl_3$)

Procedures for asymmetric reactions catalyzed by biphenyl-based amines

Procedure for the catalytic asymmetric Mannich reaction of *N*-PMP-protected α-iminoacetate 14[5]

To a stirred solution of (*R*)-**6** (1.3 mg, 0.0025 mmol) in dioxane (2.5 mL) were added 3-methylbutanal (80.7 μL, 0.75 mmol) and ethyl (4-methoxyphenylimino)acetate **14** (48.9 μL, 0.25 mmol) in this order at room temperature. After being stirred at room temperature for 45 min, the reaction mixture was then quenched with a saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 8/1 to 4/1) to give the corresponding Mannich adduct **15** (59 mg, 0.20 mmol, 80% yield, dr = 11/1, 96% ee).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.74 (d, J = 3.4 Hz, 1H), 6.76 (app d, J = 8.8 Hz, 2H), 6.65 (app d, J = 9.1 Hz, 2H), 4.35 (br s, 1H), 4.14 (app q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 2.59 (m, 1H), 2.09 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H), 1.11 (d, J = 7.1 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H) ; HPLC analysis: Daicel CHIRALPAK IC-3, hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, λ = 240 nm, retention time; t_R(major) = 25.0 min, t_R(minor) =33.2 min. Spectroscopic data were in agreement with the ones previously reported in literature[5].

Procedure for the direct asymmetric aminoxylation reaction[6]

To a stirred solution of (*R*)-**6** (1.6 mg, 0.003 mmol) in $CHCl_3$ (100 μL) were added 3-phenylpropanal (39.5 μL, 0.30 mmol) and nitrosobenzene (10.7 mg, 0.10 mmol) in this order at 0 °C. After being stirred at 0 °C for 1 h, EtOH (200 μL) and $NaBH_4$ (20 mg) were added at the same temperature. After 30 min, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 4/1 to 2/1) to afford the corresponding aminoxylation product **16** (18 mg, 0.75 mmol, 75% yield, 91% ee).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.33-7.19 (m, 7H), 7.06 (br s, 1H), 6.95 (t, J = 7.4 Hz, 1H),

6.85 (d, *J* = 7.4 Hz, 2H), 4.18-4.14 (m, 1H), 3.88-3.85 (m, 1H), 3.76-3.72 (m, 1H), 3.06 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.86 (dd, *J* = 13.6, 7.1 Hz, 1H), 2.40 (s, 1H); HPLC analysis: Daicel CHIRALPAK AD-H, hexane/*i*-PrOH = 10/1, flow rate = 1.0 mL/min, λ = 206 nm, retention time; t_R(major) = 18.0 min, t_R(minor) = 23.0 min.

Spectroscopic data were in agreement with the ones previously reported in literature[6].

Procedure for the asymmetric α-hydroxyamination reaction[7]

A mixture of (*S*)-**7** (3.0 mg, 0.005 mmol) and nitrosobenzene (5.4 mg, 0.05 mmol) in THF (0.25 mL) was stirred at 0 °C for 3 minutes. To the mixture was then added 3-phenylpropanal (19.7 μL, 0.15 mmol) dropwise at –40 °C. After being stirred at –40 °C for 12 h, MeOH (0.25 mL) and $NaBH_4$ (5.7 mg) were added at 0 °C. After 15 minutes, the reaction mixture was treated with a saturated aqueous NaCl solution, extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 10/1 to 3/1) to give the corresponding hydroxyamination product **17** (9.7 mg, 0.04 mmol, 80% yield, 97% ee).

^{1}H-NMR (500 MHz, CD_3OD) δ 7.25-7.20 (m, 4H), 7.14-7.11 (m, 5H), 6.86 (app t, *J* = 7.2 Hz, 1H), 3.84-3.76 (m, 2H), 3.57 (dd, *J* = 10.3, 4.1 Hz, 1H), 2.86 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.75 (dd, *J* = 13.9, 7.7 Hz, 1H); HPLC analysis: Daicel CHIRALPAK AD-H, hexane/*i*-PrOH = 10/1, flow rate = 1.0 mL/min, λ = 254 nm, retention time; t_R(minor) = 10.3 min, t_R(major) = 14.2 min.

Spectroscopic data were in agreement with the ones previously reported in literature[7].

Procedure for the asymmetric conjugate addition to α,β-unsaturated ketone[8]

To a solution of (*S*)-**7** (3.0 mg, 0.005 mmol) in MeCN (0.1 mL) in a small vial were added 3-phenylpropanal (13.2 μL, 0.10 mmol) and enone **18** (9.5 mg, 0.05 mmol) at room temperature. The reaction mixture was stirred to give a clear, homogeneous solution (less than 1 min) before H_2O (0.1 mL) was added. After capping the vial the reaction was vigorously stirred for 6 h. The organic phase was extracted with CH_2Cl_2, dried over

Na_2SO_4, filtered, and concentrated. To the crude mixture in CH_2Cl_2 (1 mL) was added benzyl 2-(triphenylphosphoranylidene)acetate **19** (61.6 mg, 0.15 mmol) and the olefination reaction was allowed to proceed until complete consumption of the conjugate addition adduct. After solvent removal, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 10/1 to 5/1) to give the corresponding product **20** as an inseparable diastereomeric mixture (18 mg, 0.04 mmol, 80% yield, dr = 1.9/1, 97% ee).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.93-7.92 (m, 2H), 7.58-7.55 (m, 1H), 7.47-7.44 (m, 2H), 7.37-7.31 (m, 5H), 7.29-7.24 (m, 2H), 7.23-7.18 (m, 1H), 7.16-7.15 (m, 2H), 6.94 (dd, *J* = 15.7, 9.2 Hz, 1H), 5.74 (d, *J* = 15.6 Hz, 1H), 5.15 (app t, *J* = 12.0 Hz, 2H), 3.69 (s, 3H), 3.55 (dd, *J* = 17.7, 9.8 Hz, 1H), 3.34 (dt, *J* = 10.0, 4.5 Hz, 1H), 3.02-2.94 (m, 2H), 2.88-2.84 (m, 1H), 2.74 (dd, *J* = 13.6, 8.5 Hz, 1H); HPLC analysis: Daicel CHIRALPAK IA-3, hexane/*i*-PrOH = 85/15, flow rate = 0.75 mL/min, λ = 236 nm, retention time; t_R(minor) = 14.4 min, t_R(major) = 16.6 min.

Spectroscopic data were in agreement with the ones previously reported in literature[8].

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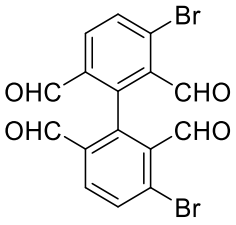
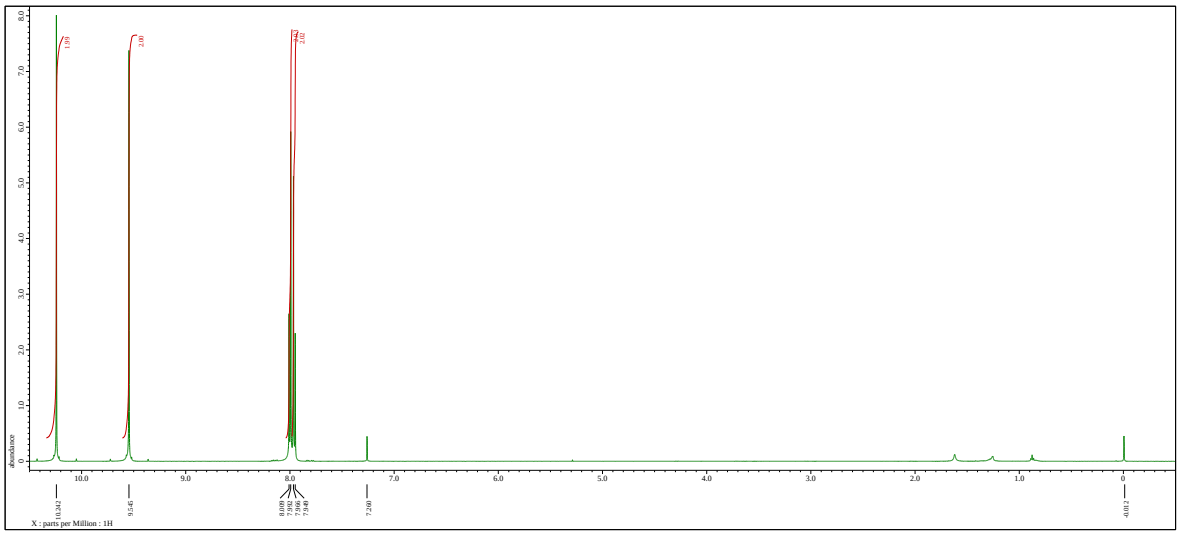
^{1}H and ^{13}C NMR spectra

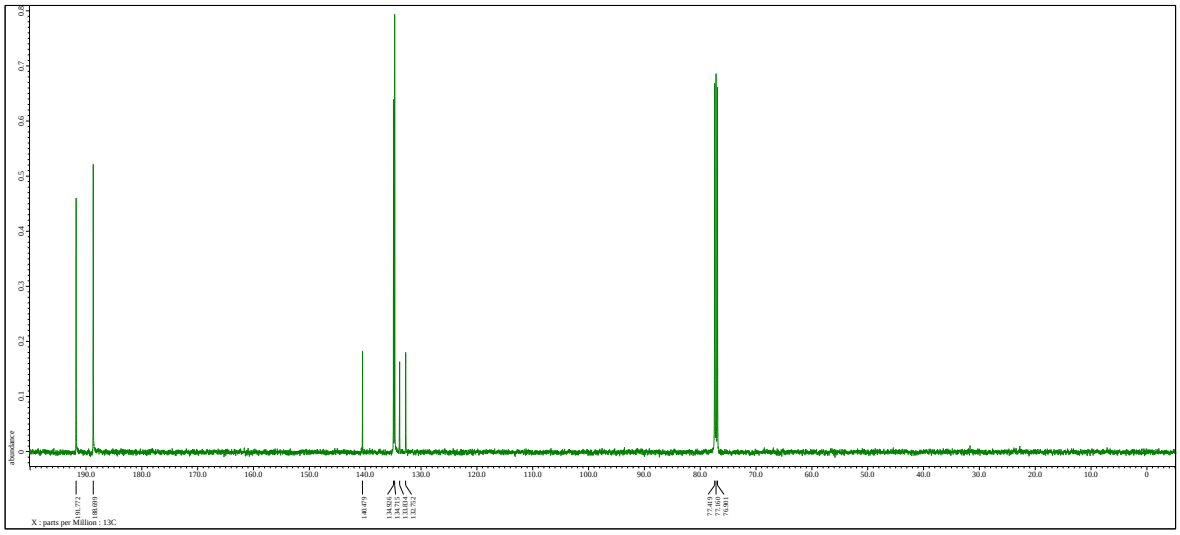
3,3'-Dibromo-[1,1'-biphenyl]-2,2',6,6'-tetracarbaldehyde (5)



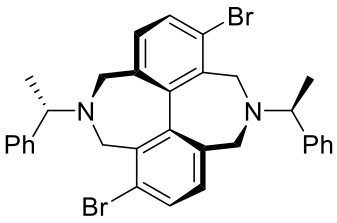
^{1}H-NMR (500 MHz, $CDCl_3$)



^{13}C-NMR (125 MHz, $CDCl_3$)



3,9-Dibromo-5,11-bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene ((*R*,*S*,*S*)-8)



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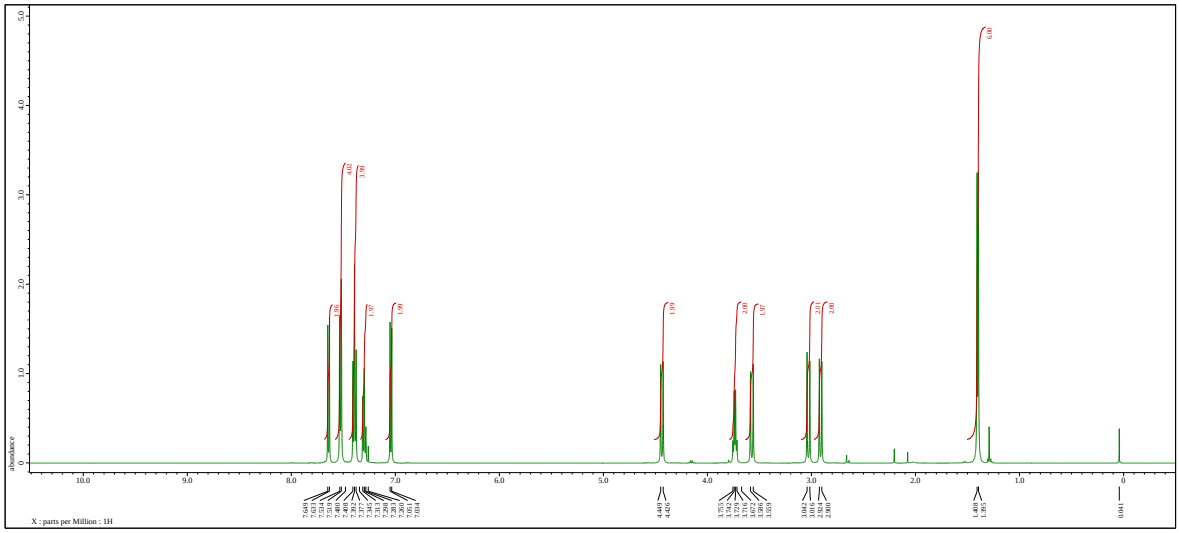

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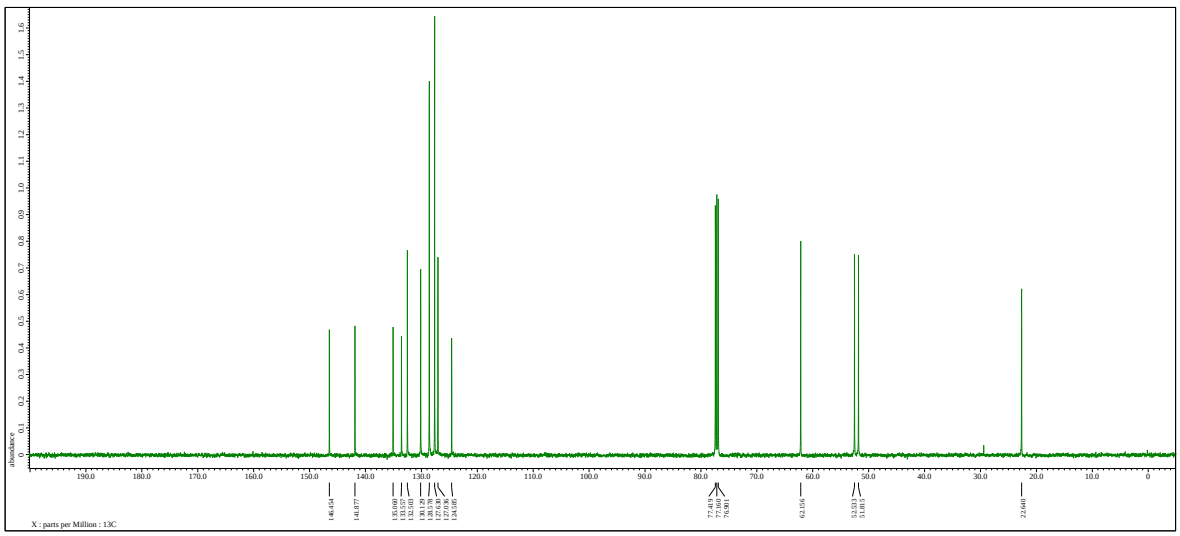
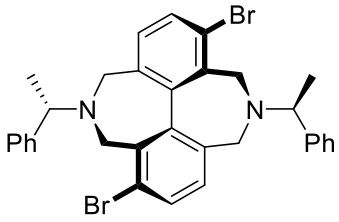


3,9-Dibromo-5,11-bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene ((*S*,*S*,*S*)-8)



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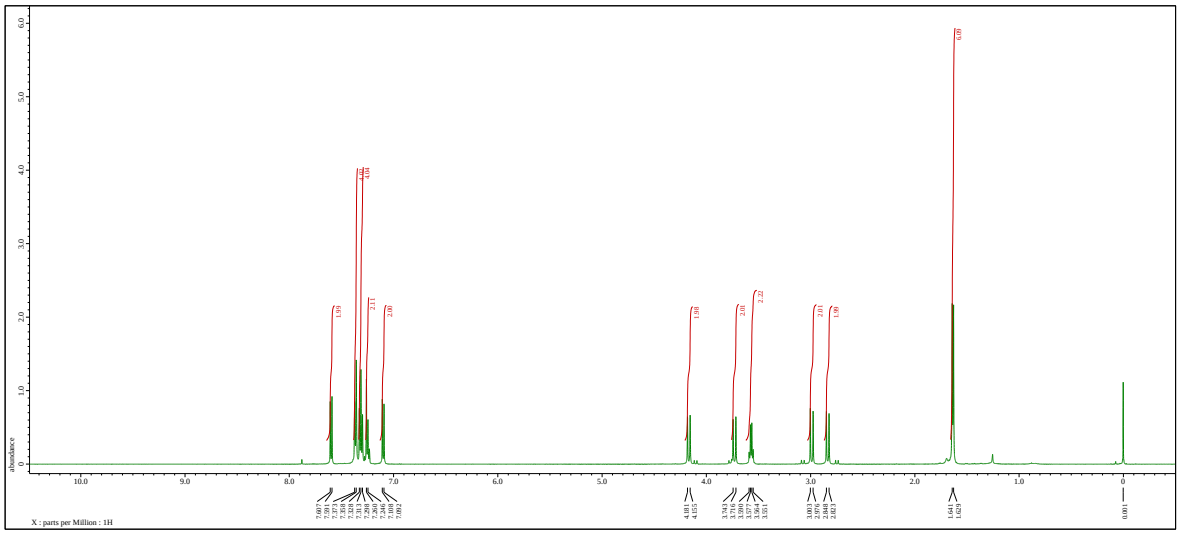

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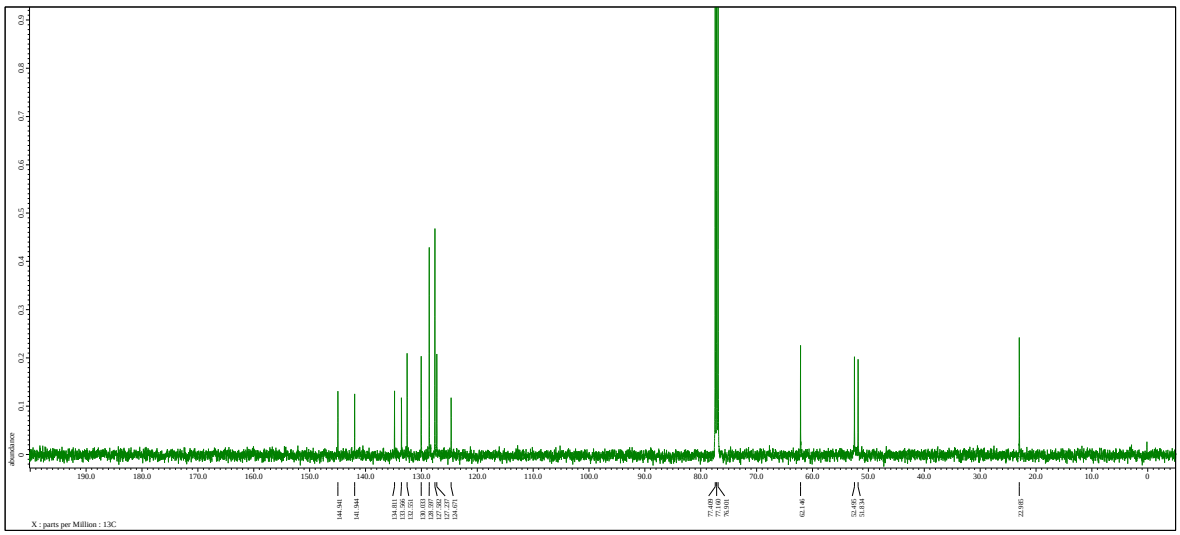
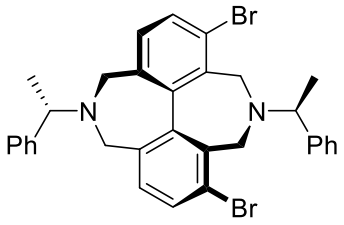


(*S*)-3,7-Dibromo-5,11-bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene ((*S*,*S*,*S*)-9)



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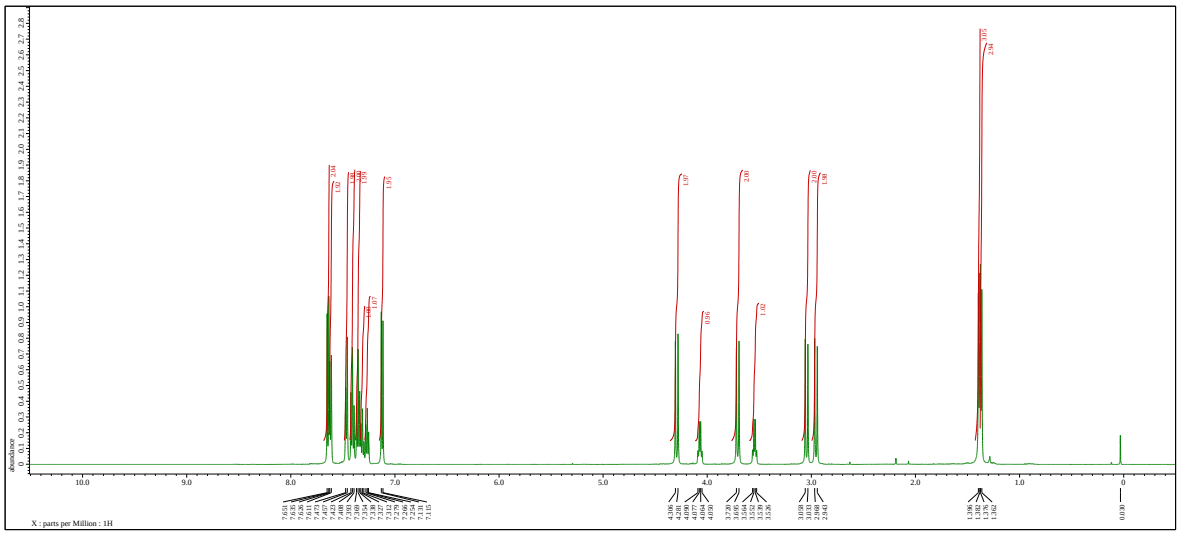

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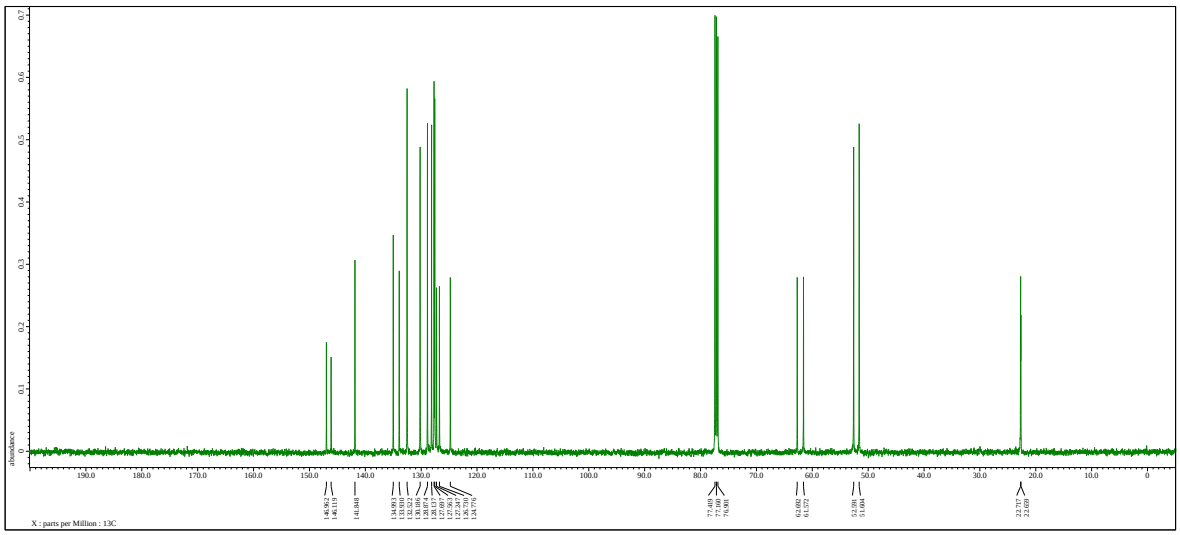

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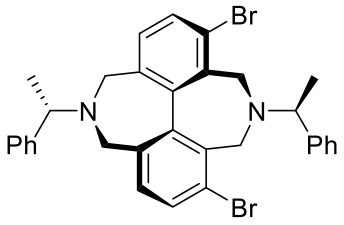

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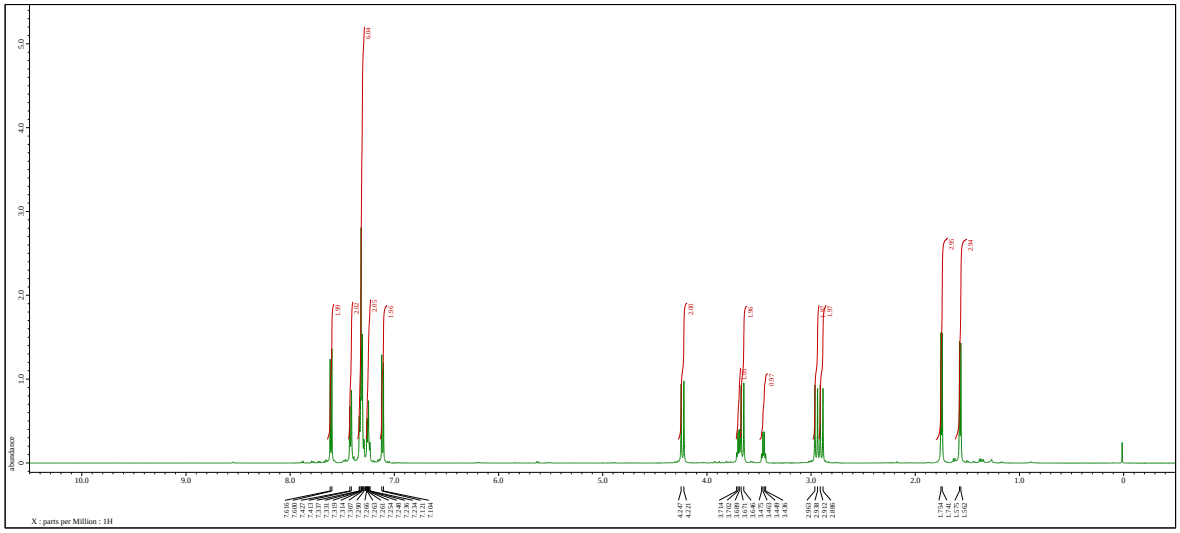
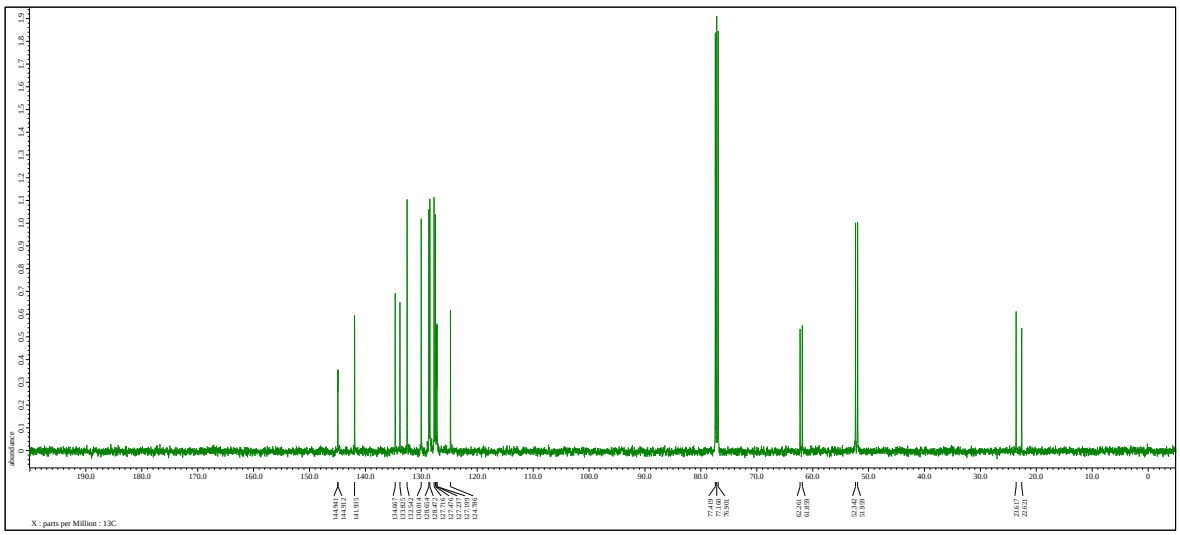
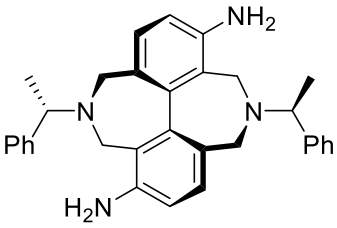


^{13}C-NMR (125 MHz, $CDCl_3$)



(*R*)-5,11-Bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-3,9-diamine ((*R*,*S*,*S*)-10)



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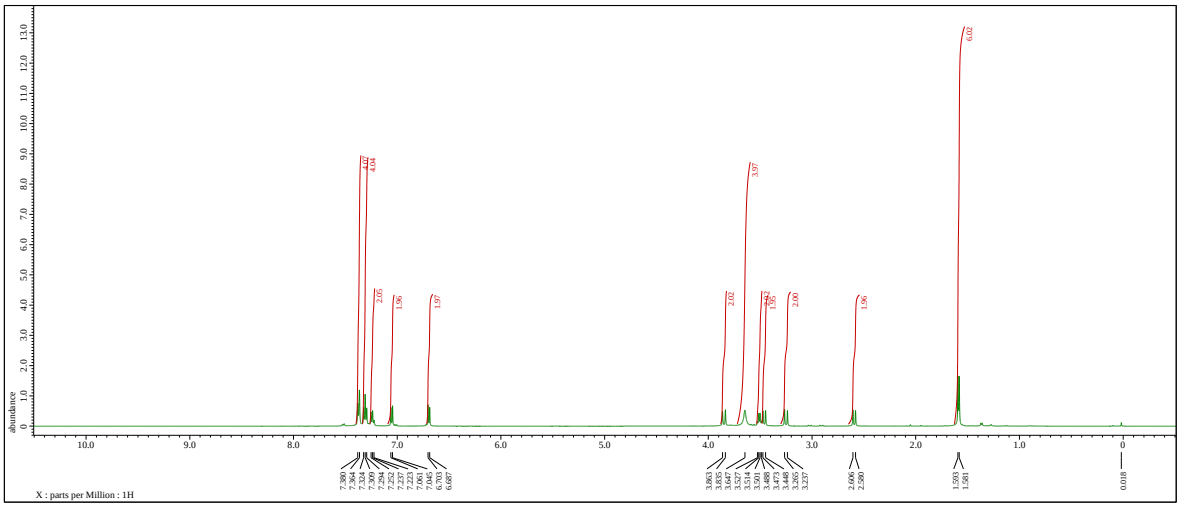

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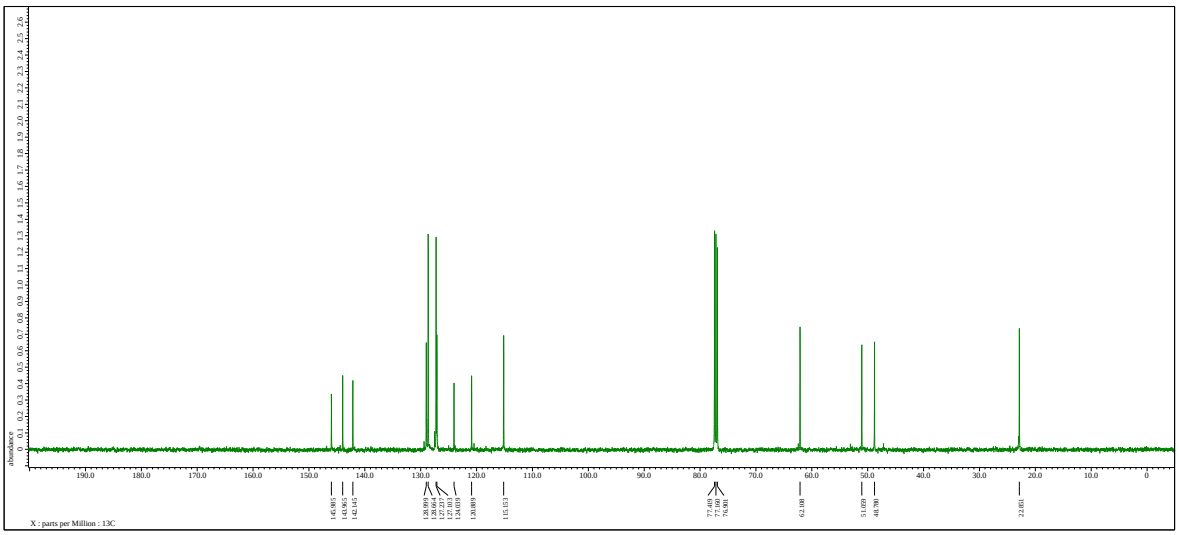
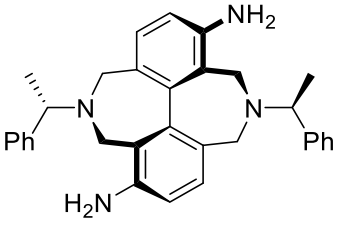
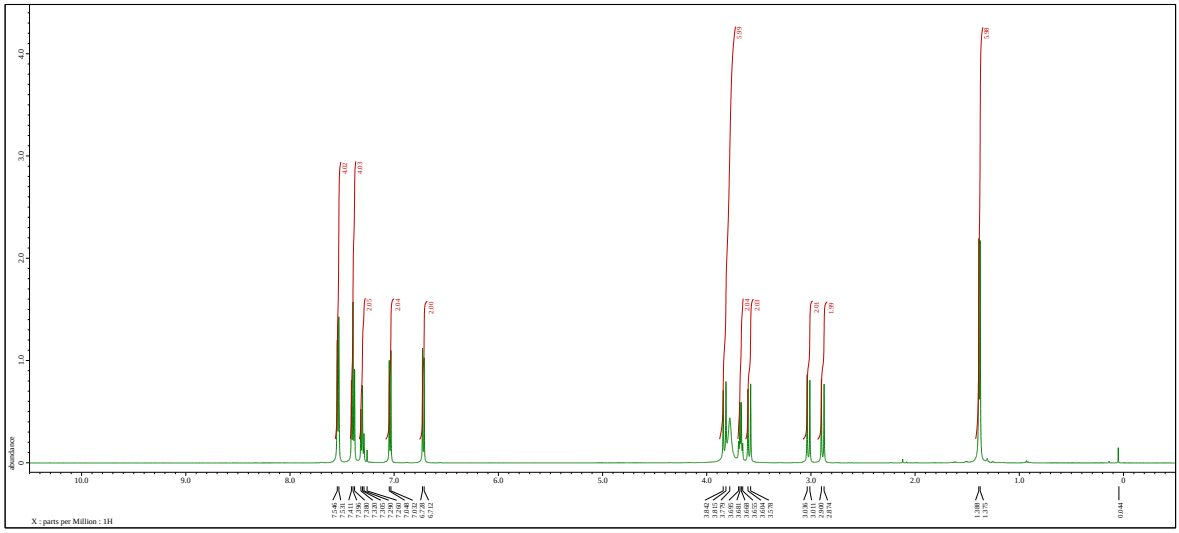


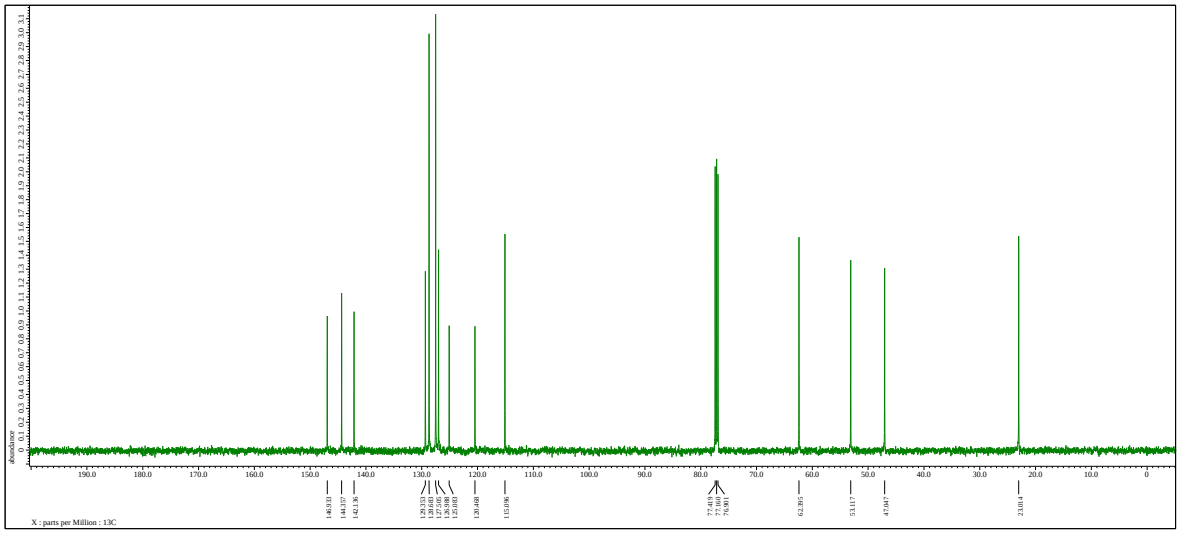
(*S*)-5,11-Bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-3,9-diamine ((*S*,*S*,*S*)-10)



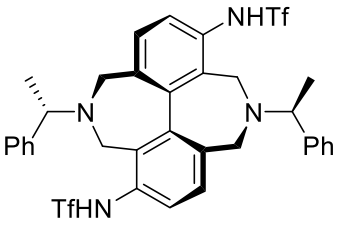
^{1}H-NMR (500 MHz, $CDCl_3$)



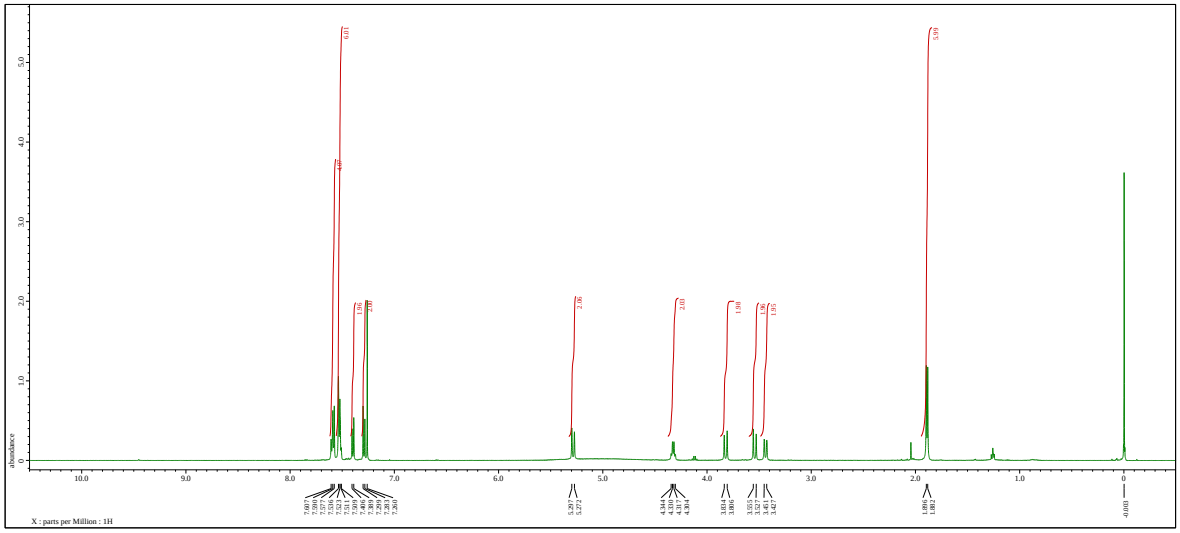
^{13}C-NMR (125 MHz, $CDCl_3$)



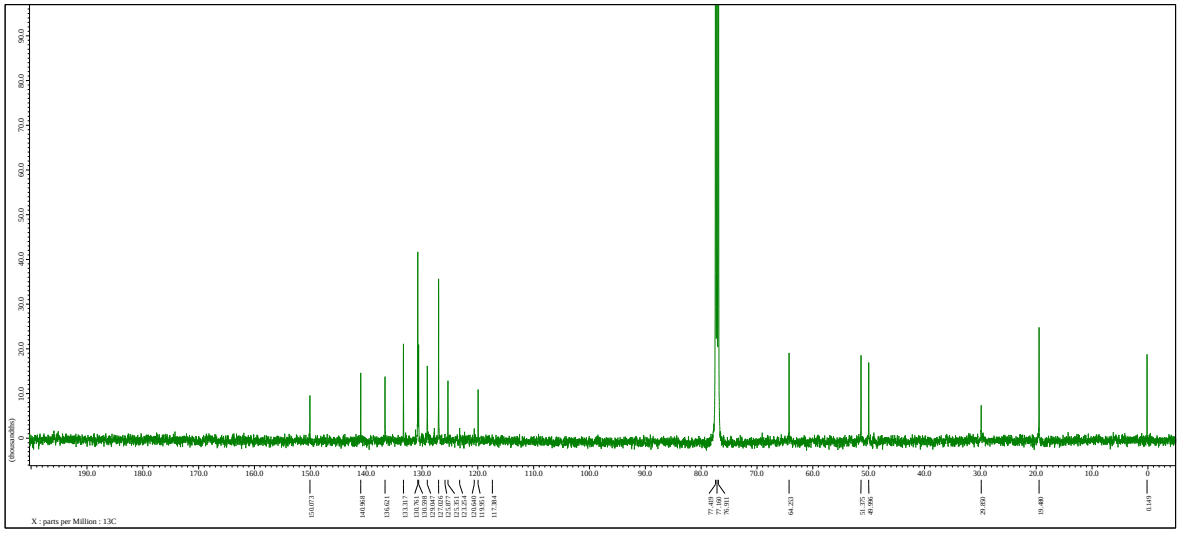
***N*,*N*'-((*R*)-5,11-Bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-3,9-diyl)bis(1,1,1-trifluoromethanesulfonamide) ((*R*,*S*,*S*)-11)**



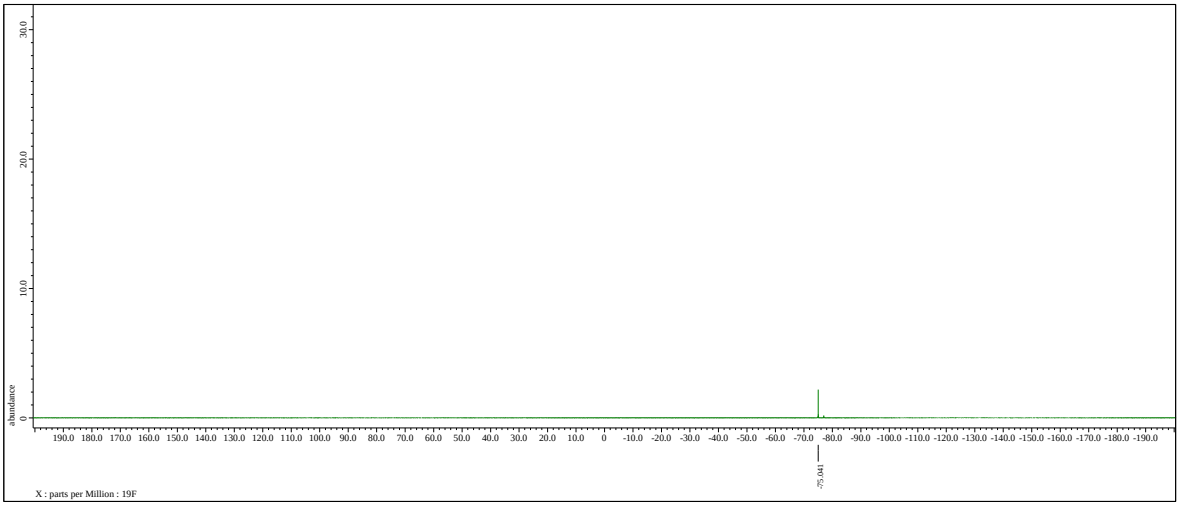
^{1}H-NMR (500 MHz, $CDCl_3$)



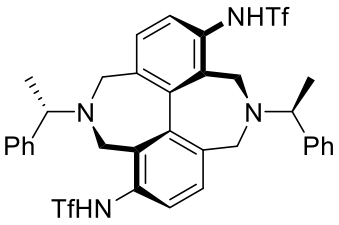
^{13}C-NMR (125 MHz, $CDCl_3$)



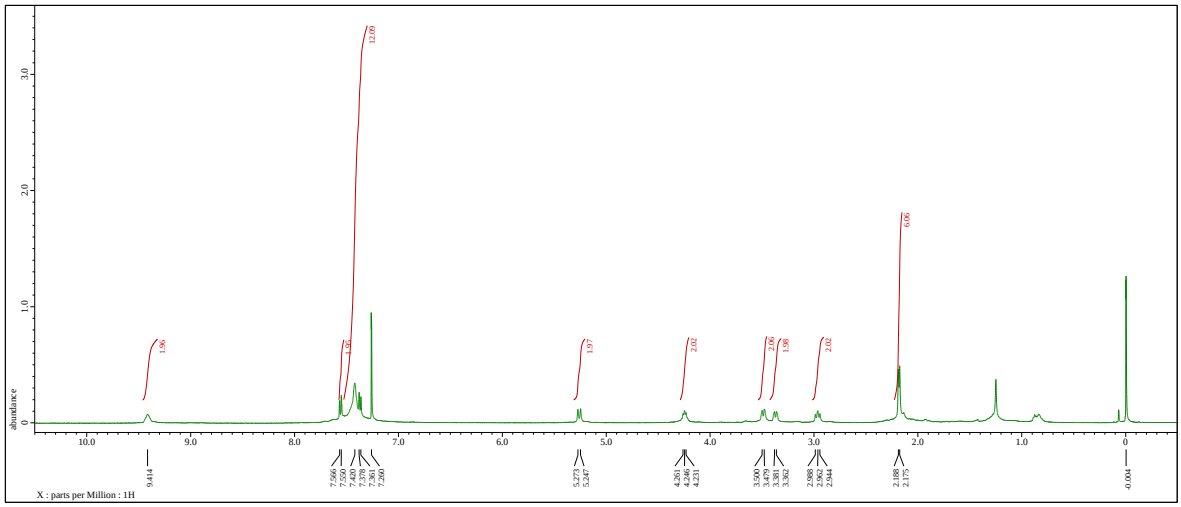
^{19}F-NMR (466 MHz, $CDCl_3$)



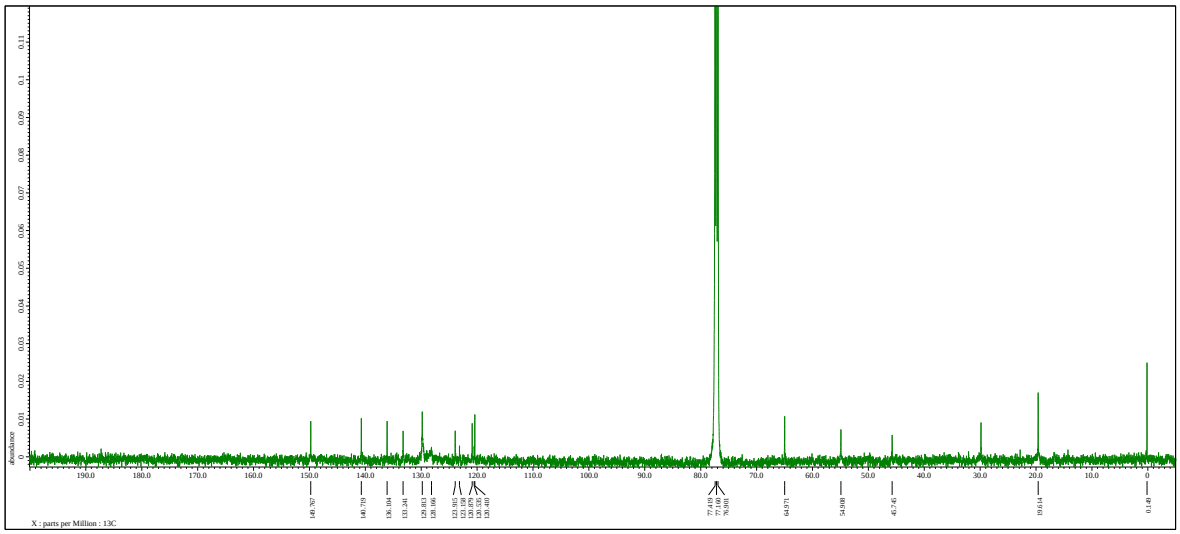
***N*,*N*'-((*S*)-5,11-Bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-3,9-diyl)bis(1,1,1-trifluoromethanesulfonamide) ((*S*,*S*,*S*)-11)**



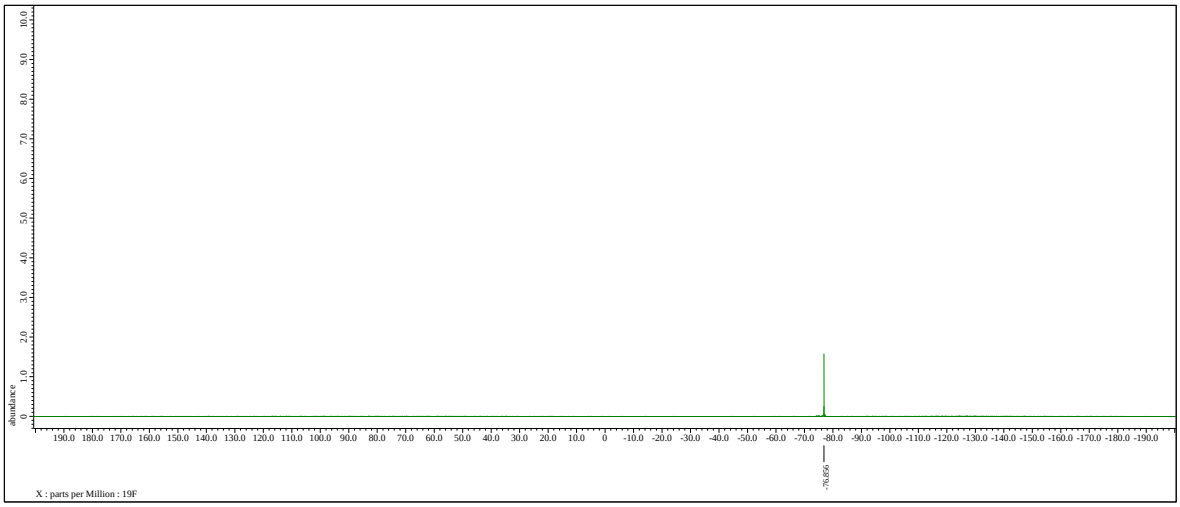
^{1}H-NMR (500 MHz, $CDCl_3$)



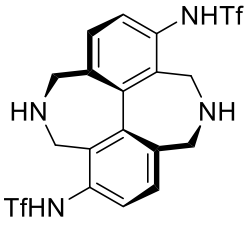
^{13}C-NMR (125 MHz, $CDCl_3$)



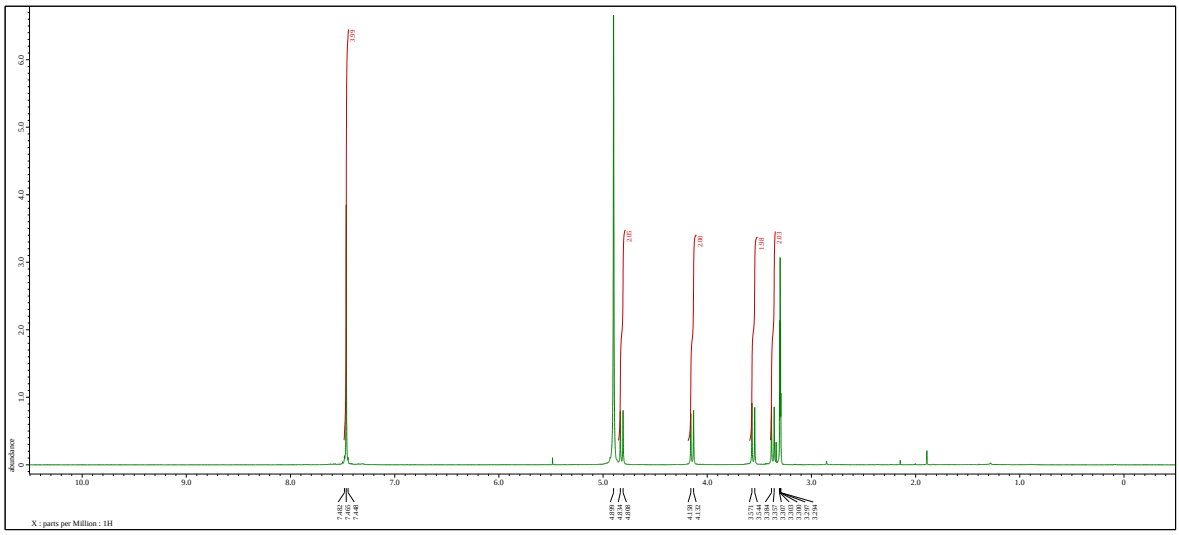
^{19}F-NMR (466 MHz, $CDCl_3$)



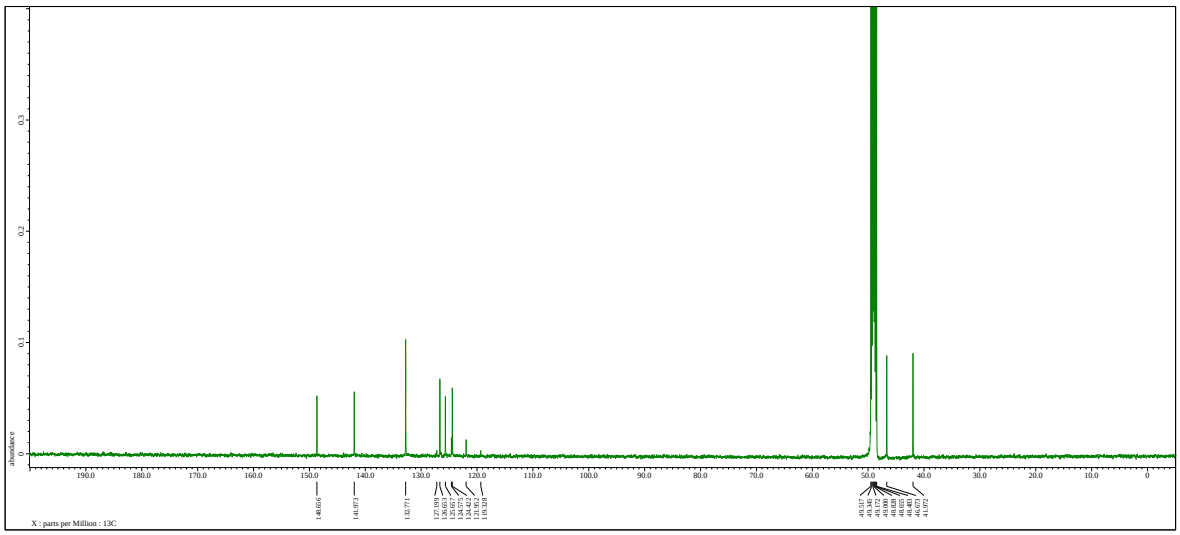
(*R*)-*N*,*N*'-(4,5,6,10,11,12-Hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-3,9-diyl)bis(1,1,1-trifluoromethanesulfonamide) ((*R*)-6)



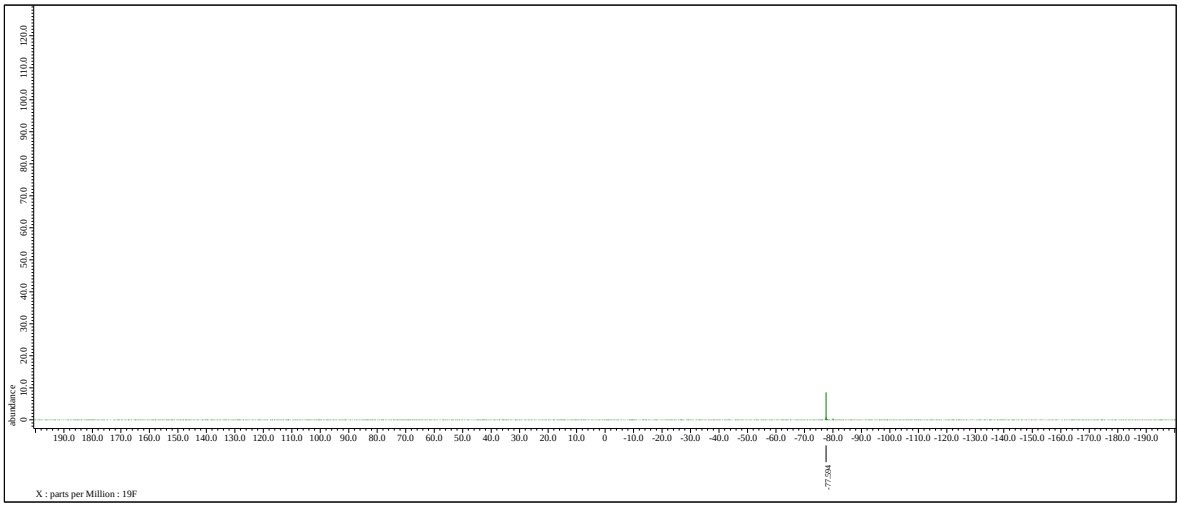
^{1}H-NMR (500 MHz, CD_3OD)



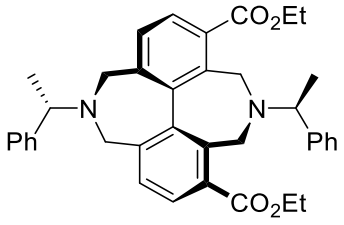
^{13}C-NMR (125 MHz, CD_3OD)



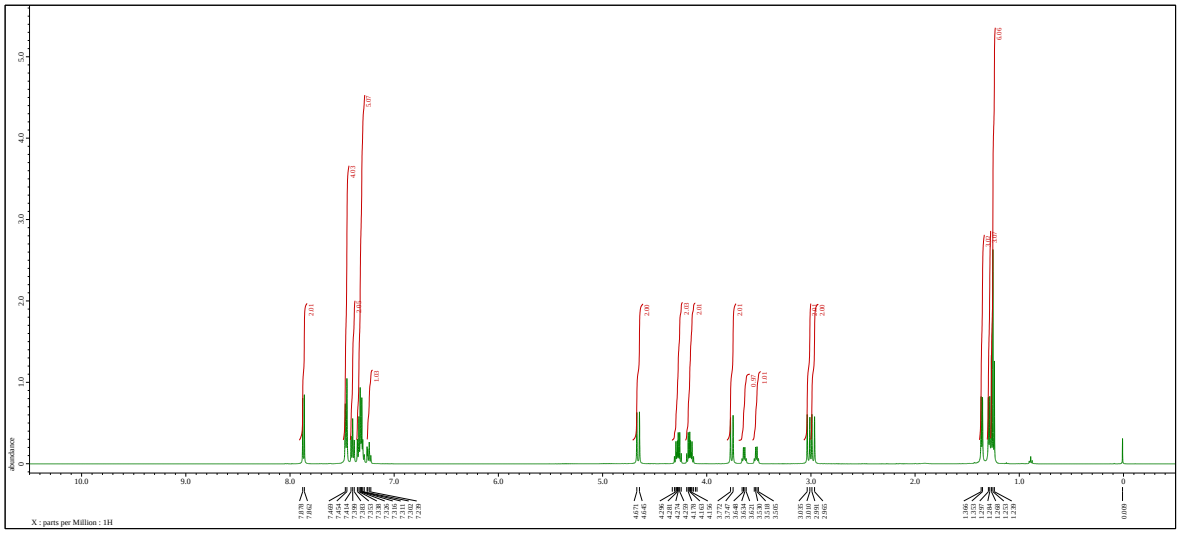
^{19}F-NMR (466 MHz, CD_3OD)

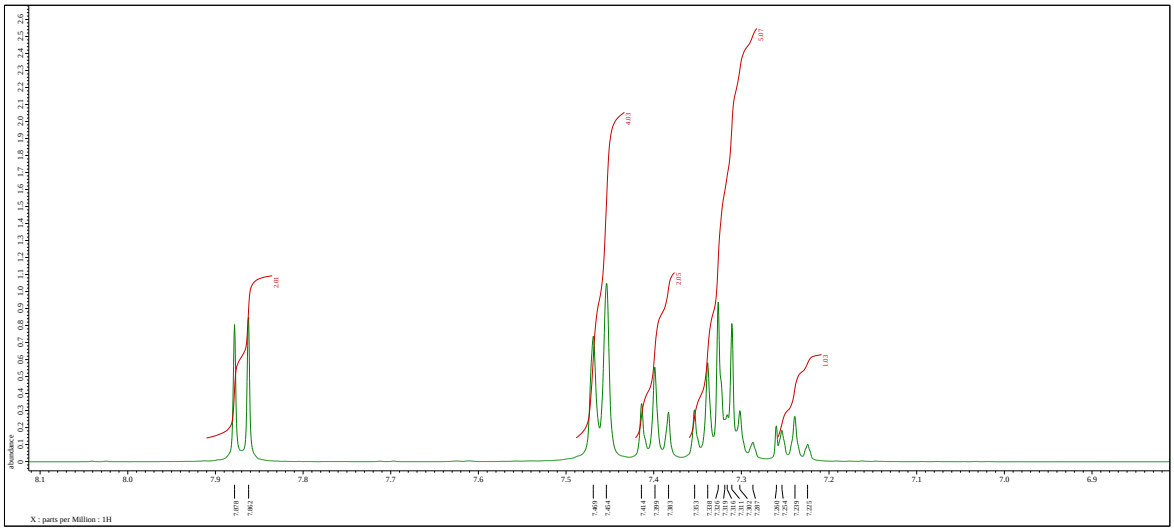


Diethyl (*S*)-5,11-bis((*S*)-1-phenylethyl)-4,5,6,10,11,12-hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-3,7-dicarboxylate ((*S*,*S*,*S*)-12)

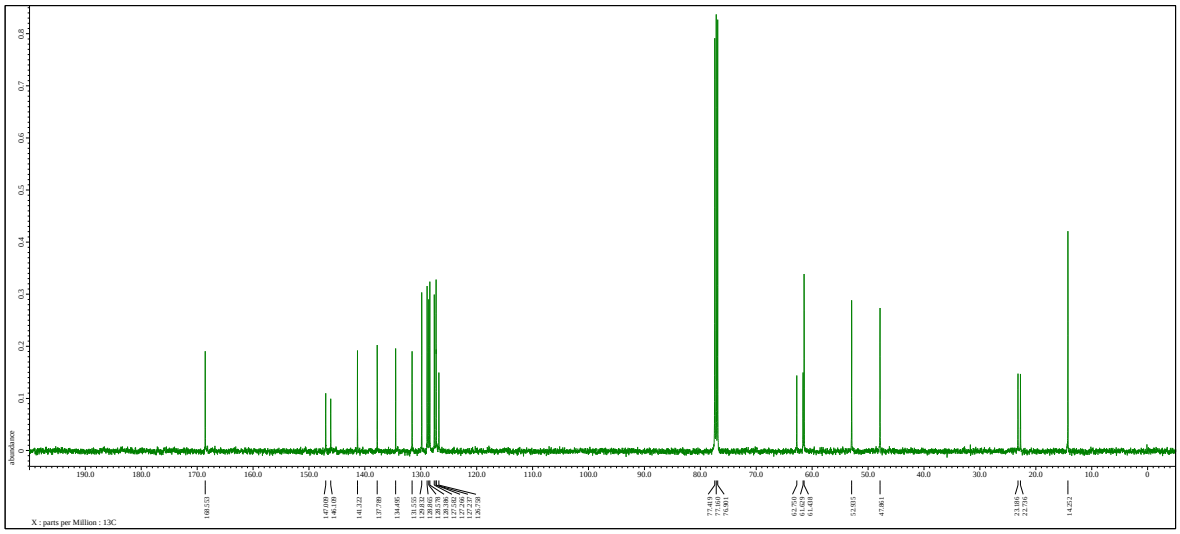


^{1}H-NMR (500 MHz, $CDCl_3$)

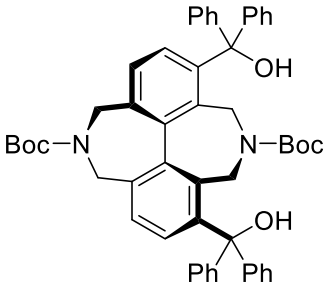




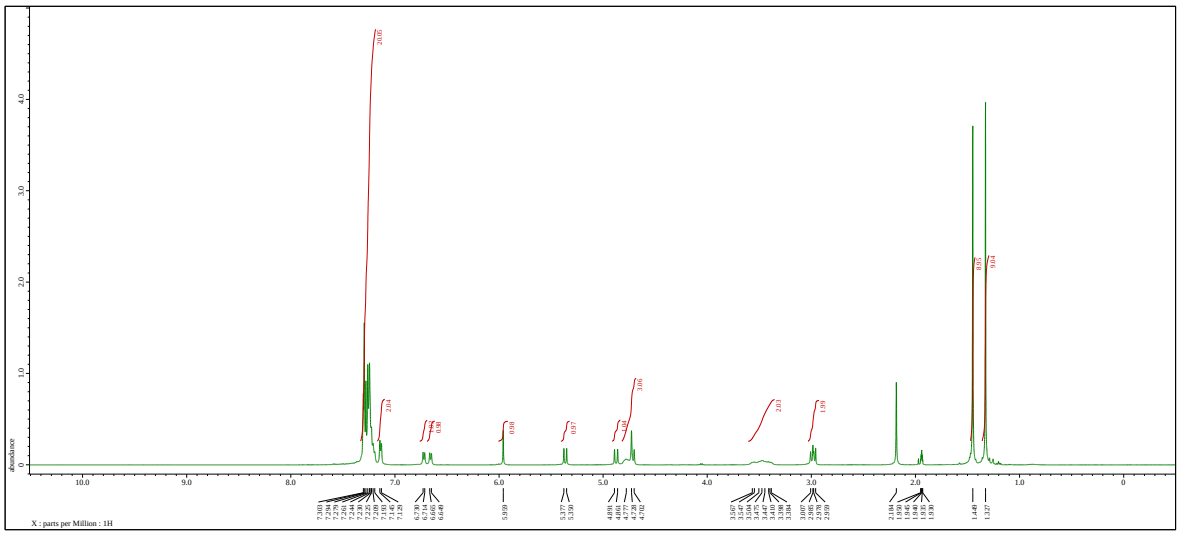
^{13}C-NMR (125 MHz, $CDCl_3$)



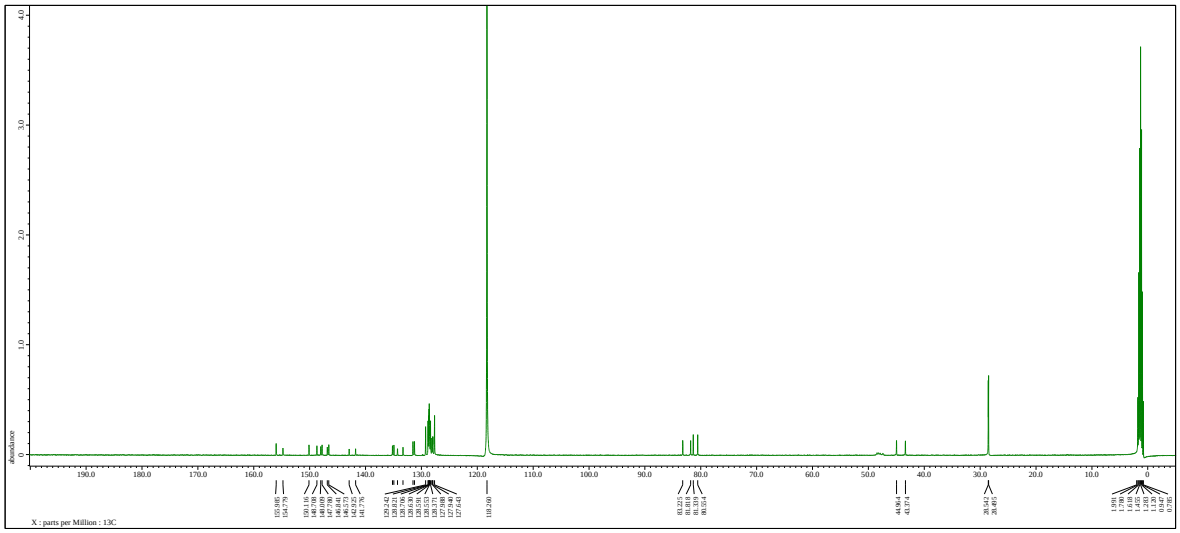
Di-*tert*-butyl (*S*)-3,7-bis(hydroxydiphenylmethyl)-10,12-dihydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-5,11(4*H*,6*H*)-dicarboxylate ((*S*)-13)



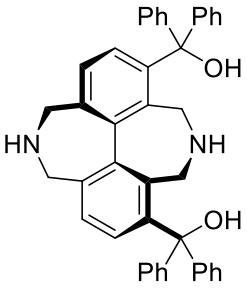
^{1}H-NMR (500 MHz, CD_3CN)



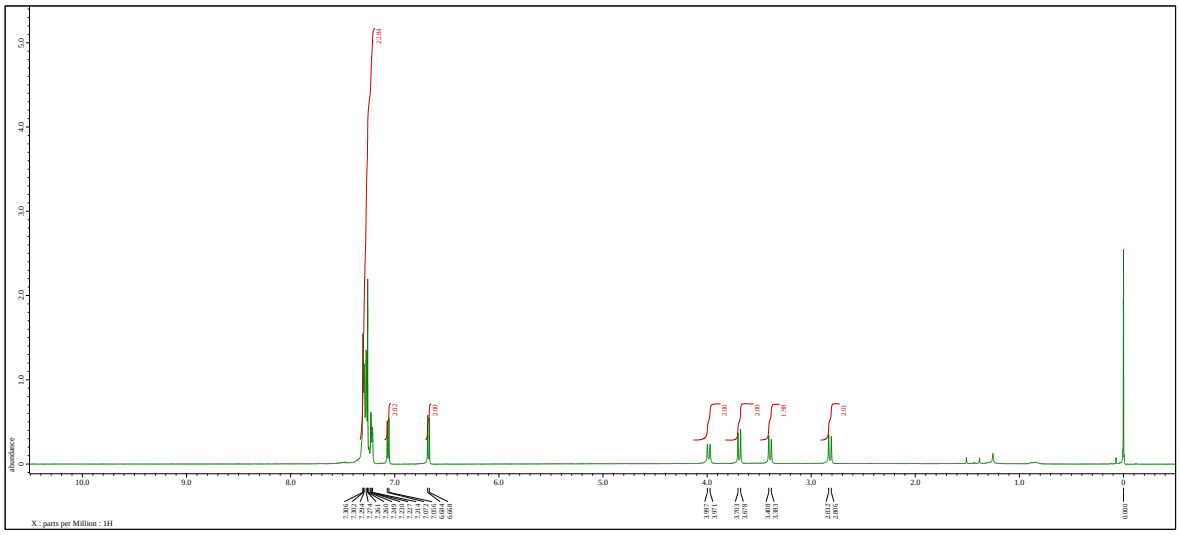
^{13}C-NMR (125 MHz, CD_3CN)



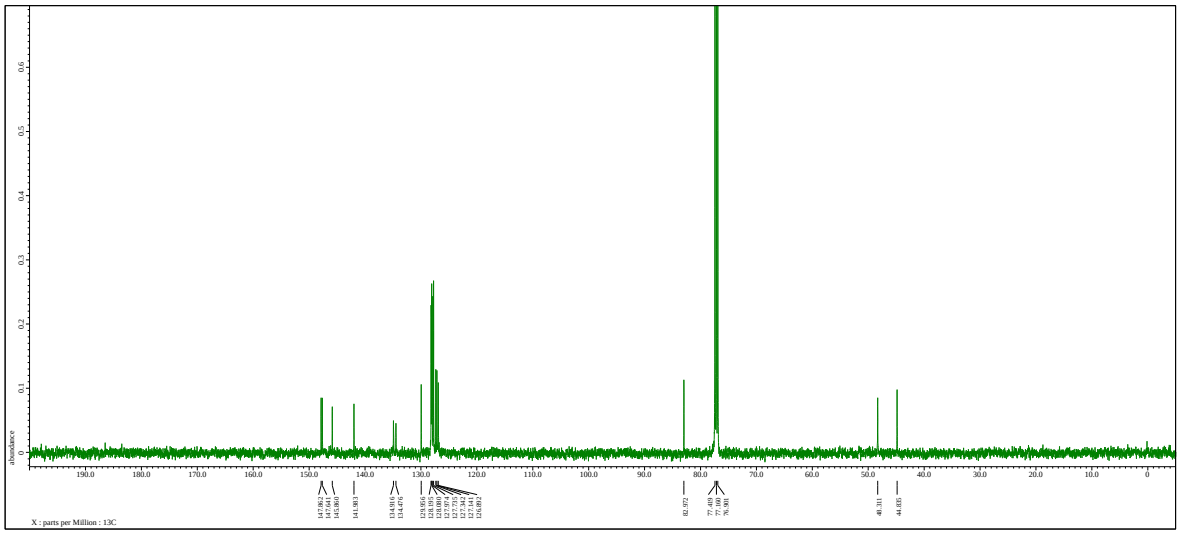
(*S*)-(4,5,6,10,11,12-Hexahydro-5,11-diazadibenzo[*ef*,*kl*]heptalene-3,7-diyl)bis(diphenylmethanol) ((*S*)-7)

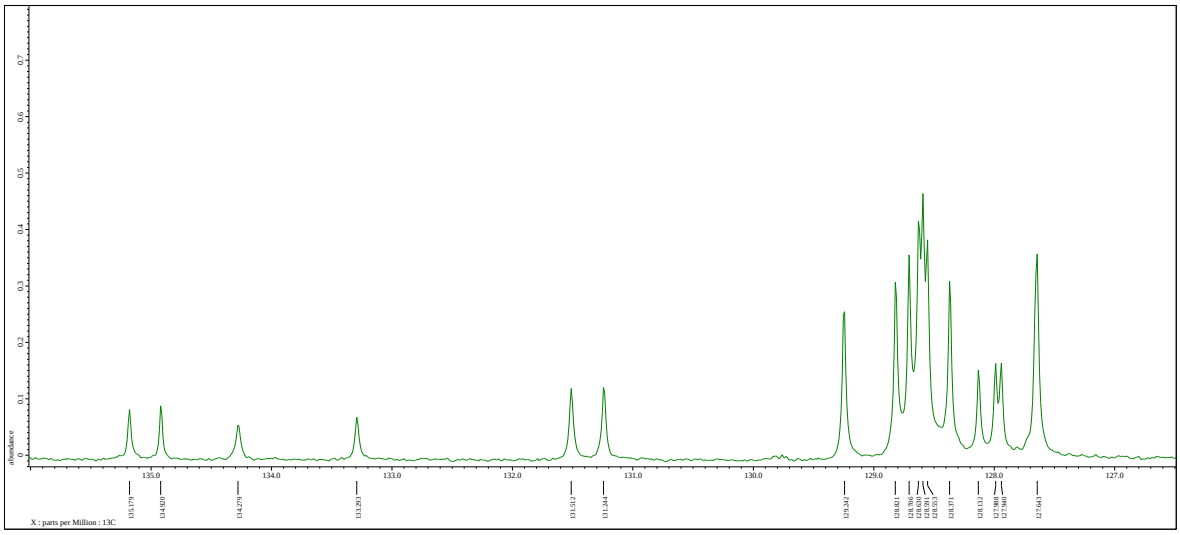


^{1}H-NMR (500 MHz, $CDCl_3$)



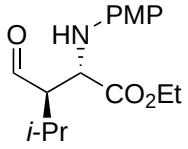
^{13}C-NMR (125 MHz, $CDCl_3$)



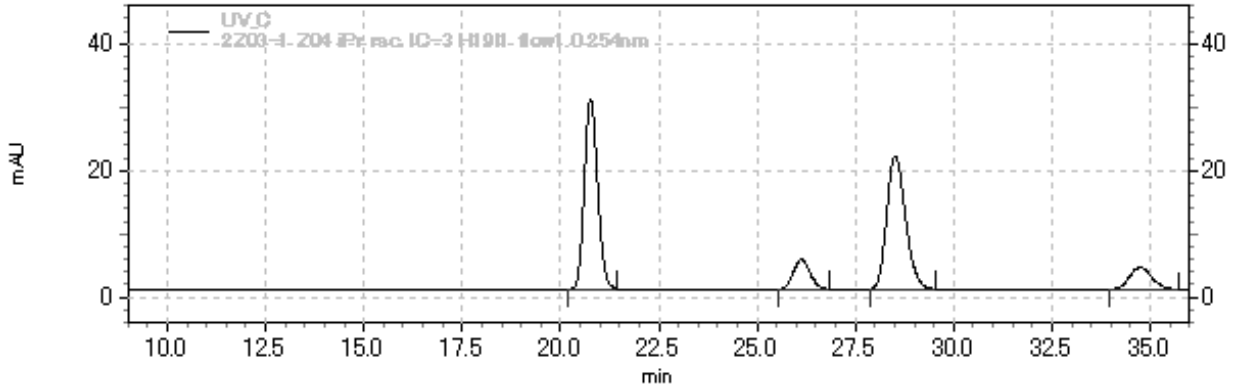


HPLC traces

Ethyl (2*S*,3*R*)-3-formyl-2-((4-methoxyphenyl)amino)-4-methylpentanoate (15)

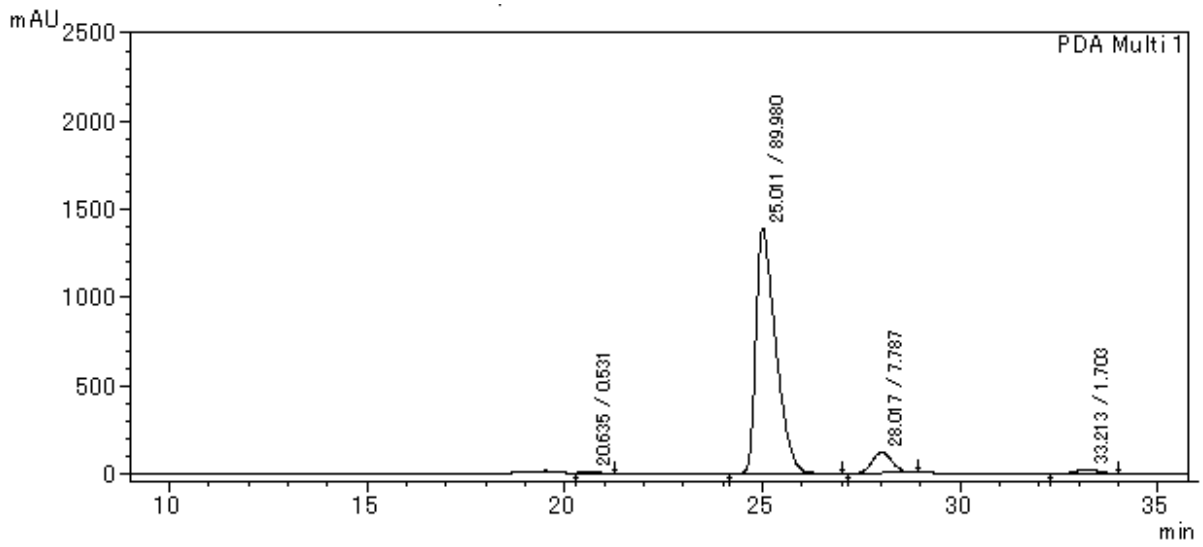


HPLC analysis: Daicel CHIRALPAK IC-3, hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, λ = 240 nm, retention time; t_R(major) = 25.0 min, t_R(minor) =33.2 min.

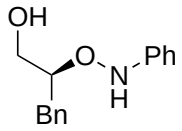


UV C結果

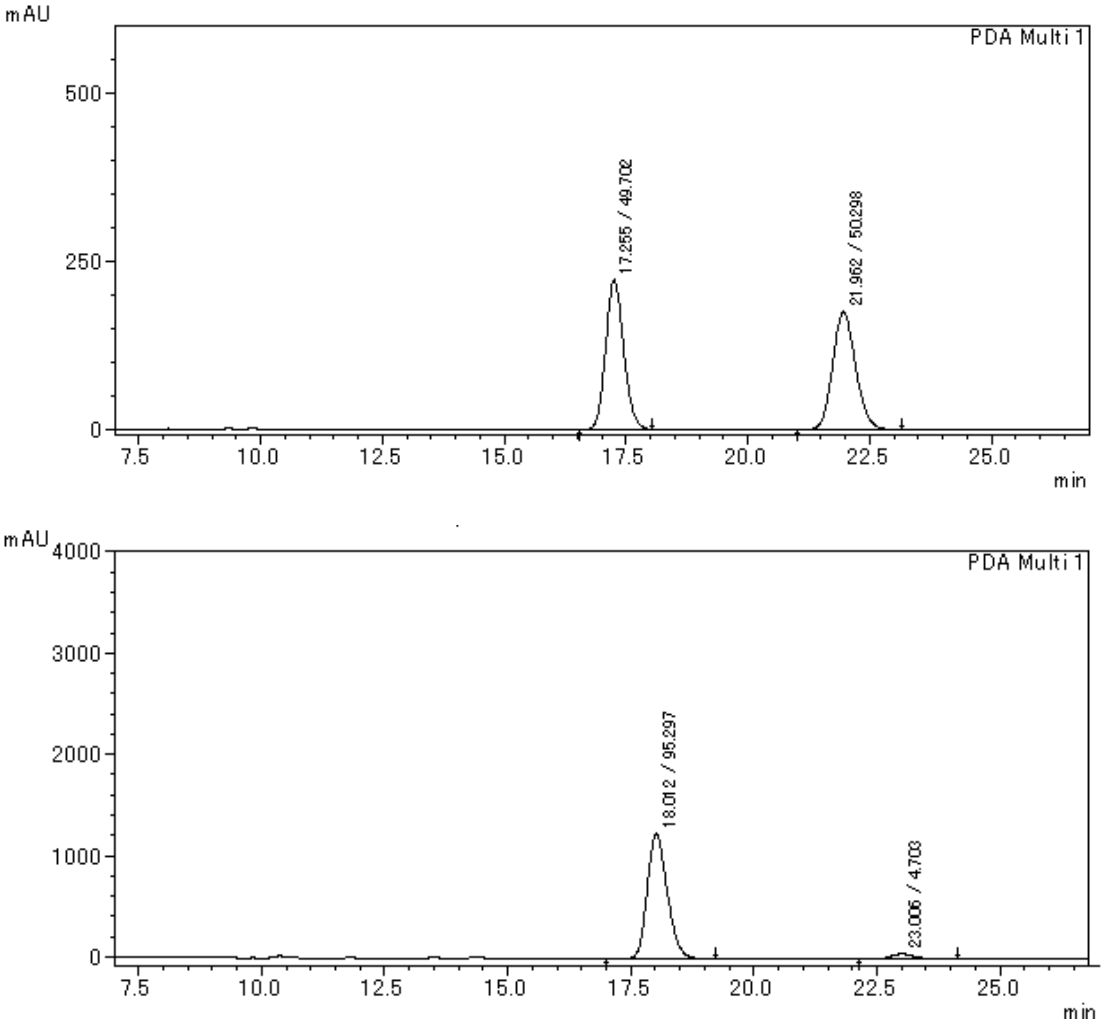
No	RT	Area	Area%
1	20.77	699246	41.689
2	26.12	140687	8.388
3	28.52	698190	41.626
4	34.74	139188	8.298
トータル		1677311	100.000



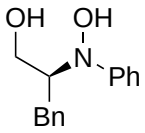
(*S*)-3-Phenyl-2-((phenylamino)oxy)propan-1-ol (16)



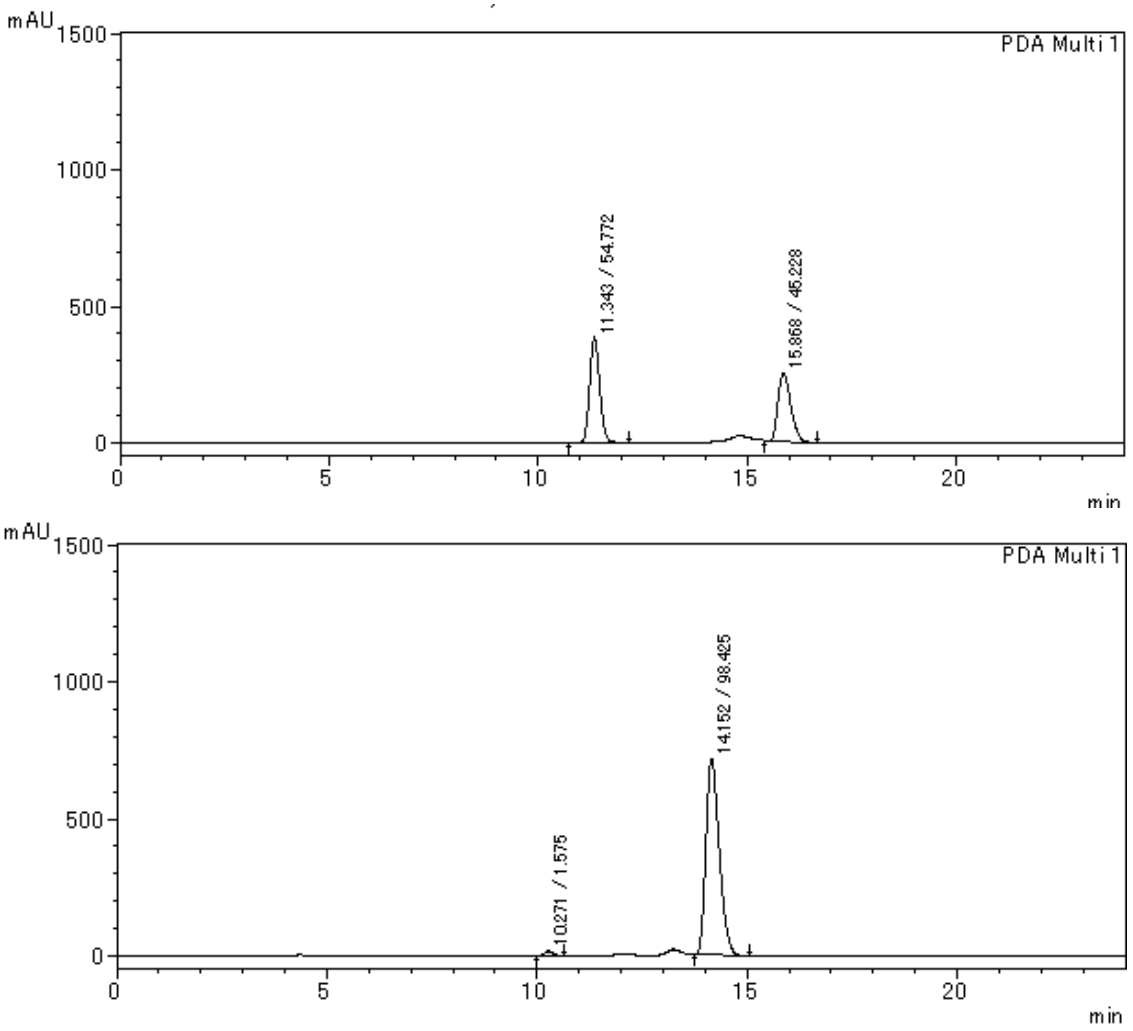
Daicel CHIRALPAK AD-H, hexane/*i*-PrOH = 10/1, flow rate = 1.0 mL/min, λ = 206 nm, retention time; t_R(major) = 18.0 min, t_R(minor) = 23.0 min.



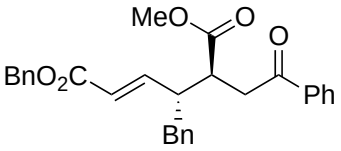
(*S*)-2-(Hydroxy(phenyl)amino)-3-phenylpropan-1-ol (17)



HPLC analysis: Daicel CHIRALPAK AD-H, hexane/*i*-PrOH = 10/1, flow rate = 1.0 mL/min, λ = 254 nm, retention time; t_R(minor) = 10.3 min, t_R(major) = 14.2 min.



1-Benzyl 6-methyl (4*R*,5*S*,*E*)-4-benzyl-5-(2-oxo-2-phenylethyl)hex-2-enedioate (20)



Daicel CHIRALPAK IA-3, hexane/*i*-PrOH = 85/15, flow rate = 0.75 mL/min, λ = 236 nm, retention time; t_R(minor) = 14.4 min, t_R(major) = 16.6 min.