Enantioselective Synthesis of 8-Azabicyclo[3.2.1]octanes via Asymmetric 1,3-Dipolar Cycloadditions of Cyclic Azomethine Ylides Using a Dual Catalytic System

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Experimental section

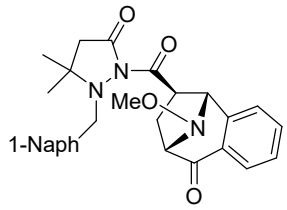
General.

Melting points were determined on a Yanaco MP-13 melting point apparatus and are uncorrected. IR spectra were taken with a JASCO FT/IR-5300S spectrophotometer. ^{1}H NMR spectra were recorded on BRUKER AVANCE III Fourier 300 (300 MHz), Ascend 500 (500 MHz), or JEOL JNM-GX400 (400 MHz) spectrometers. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on BRUKER AVANCE III Fourier 300 (75 MHz), Ascend 500 (125 MHz), or JEOL JNM-GX400 (100 MHz) spectrometers using broadband proton decoupling. Chemical shifts are expressed in parts per million using the middle resonance of $CDCl_3$ (77.0 ppm), C_6D_6 (128.06 ppm), CD_3OD (49.00 ppm), and DMSO-*d*$_6$ (39.52 ppm) as an internal standard. Hydrogen multiplicity (C, CH, CH_2, CH_3) information was obtained from carbon DEPT spectra. High-resolution mass spectra were obtained on BRUKER micrOTOF II ESI-TOF or HITACHI M-80B spectrometers. Wakogel C-300HG (FUJIFILM Wako) were employed for preparative column chromatography. Unless otherwise noted, all reactions were carried out under an argon atmosphere in dried glassware.

Materials.

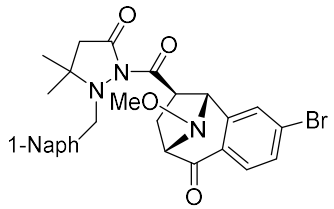
2-(2-Diazoacetyl)benzaldehyde *O*-methyloxime (**1a**) and 2-acryloyl-5,5-dimethyl-3-pyrazolidinones **2a** and **2b** were prepared according to the literature.[1,2] Chiral binaphthyldiimine ligands **A** – **D** were prepared by the reported procedure.[3] $Ni(ClO_4)_2{\cdot}6H_2O$, $Co(ClO_4)_2{\cdot}6H_2O$, $Zn(ClO_4)_2{\cdot}6H_2O$, $Cu(ClO_4)_2{\cdot}6H_2O$, and $Cu(OTf)_2$ are commercially available, and used without further purification. Powdered 4Å molecular sieves (MS 4A) was commercially available and dried in vacuo over 200 °C for 12 h before use.

General procedure for the cycloaddition of the cyclic azomethine ylide generated from *O*-methyloxime 1, exemplified by the reaction of 2-(2-diazoacetyl)benzaldehyde *O*-methyloxime (1a) with acryloylpyrazolidinone 2b. To a 30 mL two-necked flask equipped with a stir bar was added MS 4A (254.0 mg), $Cu(OTf)_2$ (36.2 mg, 0.10 mmol, 20 mol %), and ligand **E** (56.6 mg, 0.10 mmol, 20 mol %). After the flask was purged with oxygen, $CHCl_3$ (4.0 mL) was added, and then the mixture was stirred at 35 °C for 6 h. After the addition of $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol, 2 mol %) and acryloylpyrazolidinone **2b** (308.2 mg, 1.0 mmol), a solution of *O*-methyloxime **1a** (101.6 mg, 0.50 mmol) in $CHCl_3$ (5.0 mL) was added dropwise over a period of 3 h at 35 °C using a syringe pump under an oxygen atmosphere. Subsequently, the syringe was washed with $CHCl_3$ (1.0 mL) and the wash was added to the reaction mixture. The mixture was filtered through a plug of silica gel-Celite (SiO_2: 1.5 g), rinsed with a mixture of Hexane/EtOAc (25 mL/25 mL), and then concentrated. Flash column chromatography (SiO_2: 30 g, Hexane:EtOAc = 85:15, v/v) yielded cycloadduct *exo*-**3b** (234.3 mg, 97%, *exo*:*endo* = >99:1).



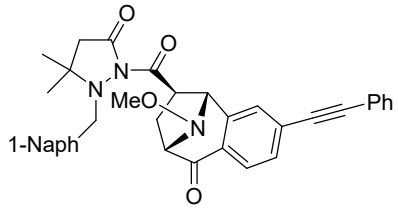
(1*R*,9*S*,11*R*)-11-{[5,5-Dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl]carbonyl}-12-methoxy-8-oxo-12-azatricyclo[7.2.1.$0^{2,7}$]dodeca-2,4,6-triene (*exo*-3b). Colorless prisms; Mp. 183-185 °C; $[\alpha]_D^{25}$ -10.2 (*c* 1.0, $CHCl_3$, 99% ee); R_f = 0.20 (Hexane:EtOAc = 70:30, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 0.73 (3H×2/5, s), 0.76 (3H×2/5, s), 0.767 (3H×3/5, s), 0.774 (3H×3/5, s), 1.75 (1H, m), 2.07 (1H×3/5, d, *J* = 17.4 Hz), 2.09 (1H×2/5, d, *J* = 16.8 Hz), 2.13 (1H×2/5, d, *J* = 17.4 Hz), 2.26 (1H×3/5, d, *J* = 16.8 Hz), 2.69 (1H×2/5, ddd, *J* = 3.9, 8.2, 14.0 Hz), 3.12 (3H×3/5, s), 3.20 (3H×2/5, s), 3.43-3.53 (1H×3/5+1H×3/5, m), 3.62 (1H×2/5, dd, *J* = 3.9, 10.3 Hz), 4.08 (1H×2/5, d, *J* = 14.0 Hz), 4.18 (1H×2/5, d, *J* = 14.0 Hz), 4.27 (1H×3/5, d, *J* = 14.6 Hz), 4.28 (1H×2/5, d, *J* = 8.2 Hz), 4.33 (1H×3/5, d, *J* = 14.6 Hz), 4.54 (1H×3/5, m), 4.90 (1H×2/5, s), 5.16 (1H×3/5, s), 6.98 (1H, m), 7.17-7.33 (3H, m), 7.38-7.48 (1H+1H×2/5, m), 7.58 (1H, d, *J* = 8.1 Hz), 7.65 (1H, m), 7.79 (1H×3/5+1H×2/5, m), 7.98 (1H×3/5, d, *J* = 6.9 Hz), 8.17 (1H×3/5, dd, *J* = 1.3, 7.7 Hz), 8.22 (1H×2/5, dd, *J* = 1.3, 7.7 Hz),

8.39 (1H×2/5, d, J = 8.4 Hz), 8.47 (1H×3/5, d, J = 8.4 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 25.0 (CH_2), 25.3 (CH_3), 25.7 (CH_3), 25.8 (CH_3), 25.9 (CH_2), 26.2 (CH_3), 43.1 (CH_2), 43.6 (CH_2), 48.0 (CH), 52.6 (CH), 54.3 (CH_2), 54.7 (CH_2), 59.4 (CH_3), 60.4 (CH_3), 60.70 (C), 60.74 (C), 65.7 (CH), 68.0 (CH), 73.4 (CH), 75.5 (CH), 124.4 (CH), 124.5 (CH), 125.6 (CH), 125.7 (CH), 125.89 (CH), 125.94 (CH), 126.0 (CH), 126.2 (2CH), 127.2 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.35 (2CH), 128.44 (CH), 129.05 (CH), 129.10 (CH), 130.4 (C), 131.1 (C), 131.8 (C), 132.1 (C), 133.7 (CH), 134.0 (C), 134.1 (CH), 134.28 (C), 134.31 (C), 134.6 (C), 141.6 (C), 145.4 (C), 168.1 (C), 168.6 (C), 173.7 (C), 173.8 (C), 195.0 (C), 196.6 (C); IR (KBr) 3058, 2970, 2936, 1743, 1698, 1602, 1460, 1305, 1241, 1044, 800, 752 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{29}H_{29}N_3NaO_4$ $[M+Na]^+$ 506.2060, found 506.2047. The ^{1}H and ^{13}C NMR analysis showed that *exo*-**3b** exists as a 3:2 mixture of nitrogen invertomers at room temperature. The enantiomeric excess of *exo*-**3b** was determined by chiral-phase HPLC after hydrogenation.



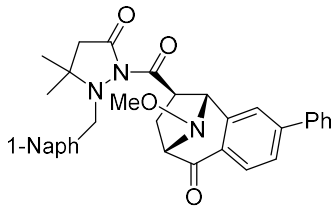
(1*R*,9*S*,11*R*)-4-Bromo-11-{[5,5-dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl]carbonyl}-12-methoxy-8-oxo-12-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene (*exo*-3c). Isolated as colorless prisms (217.8 mg, 77%, *exo*:*endo* = >99:1) by silica gel column chromatography (30 g, Hexane:EtOAc = 85:15, v/v) following the general procedure using *O*-methyloxime **1b** (141.0 mg, 0.50 mmol). Mp. 172-173 °C; $[\alpha]_D^{26}$ -8.44 (*c* 1.0, $CHCl_3$, 95% ee); R_f = 0.20 (Hexane:EtOAc = 70:30, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 0.75 (3H×1/2, s), 0.77 (3H+3H×1/2, s), 1.63 (1H×1/2, ddd, J = 0.7, 9.5, 14.2 Hz), 1.69 (1H×1/2, ddd, J = 10.5, 14.0 Hz), 2.07 (1H×1/2, d, J = 17.5 Hz), 2.10 (1H×1/2, d, J = 17.0 Hz), 2.13 (1H×1/2, d, J = 17.5 Hz), 2.21 (1H×1/2, d, J = 17.0 Hz), 2.59 (1H×1/2, ddd, J = 4.1, 8.1, 14.0 Hz), 3.11 (3H×1/2, s), 3.17 (3H×1/2, s), 3.20-3.46 (1H+1H×1/2, m), 4.04 (1H×1/2, d, J = 13.8 Hz), 4.16 (1H×1/2, m), 4.17 (1H×1/2, d, J = 14.3 Hz), 4.22 (1H×1/2, d, J = 13.8 Hz), 4.30 (1H×1/2, d, J = 14.3 Hz), 4.45 (1H×1/2, d, J = 8.0 Hz), 4.69 (1H×1/2, s), 4.95 (1H×1/2, s), 7.09 (1H, dd, J = 1.8, 8.2 Hz), 7.20-7.32 (2H, m), 7.41 (1H, m), 7.53-7.73 (1H×1/2+2H+1H×1/2, m), 7.76 (1H×1/2, d, J = 8.2 Hz), 7.82 (1H×1/2, d, J = 8.2

Hz), 7.87-8.00 (1H×1/2+1H×1/2, m), 8.35 (1H×1/2, d, J = 8.4 Hz), 8.44 (1H×1/2, d, J = 8.5 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 24.9 (2CH_2), 25.5 (CH_3), 25.7 (CH_3), 25.9 (CH_3), 26.1 (CH_3), 42.9 (CH_2), 43.4 (CH_2), 47.7 (CH), 52.2 (CH), 54.4 (CH_2), 54.9 (CH_2), 59.5 (CH_3), 60.5 (CH_3), 60.9 (C), 61.0 (C), 65.0 (CH), 68.0 (CH), 72.5 (CH), 75.3 (CH), 124.2 (CH), 124.3 (CH), 125.5 (CH), 125.7 (CH), 125.9 (CH), 126.0 (CH), 126.3 (CH), 127.7 (CH), 127.9 (CH), 128.2 (CH), 128.27 (CH), 128.33 (CH), 128.6 (CH), 128.7 (CH), 128.98 (C), 129.05 (CH, C), 129.1 (CH), 129.2 (C), 129.7 (C), 130.9 (2CH), 131.3 (CH), 131.7 (CH), 131.9 (C), 132.2 (C), 133.7 (C), 134.21 (C), 134.23 (C), 134.3 (C), 143.4 (C), 146.9 (C), 167.8 (C), 168.2 (C), 173.8 (C), 174.0 (C), 194.1(C), 195.9 (C); IR (KBr) 3063, 2968, 2933, 1744, 1702, 1590, 1308, 1240, 798, 778, 695 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{29}H_{28}BrN_3NaO_4$ $[M+Na]^+$ 584.1155, found 584.1151. The ^{1}H and ^{13}C NMR analysis showed that *exo*-**3c** exists as a 1:1 mixture of nitrogen invertomers at room temperature. The enantiomeric excess of *exo*-**3c** was determined by chiral-phase HPLC after hydrogenation.



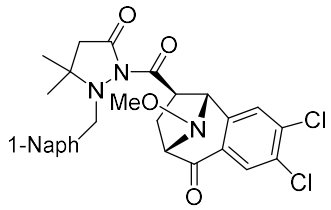
(1*R*,9*S*,11*R*)-11-{[5,5-Dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl]carbonyl}-12-methoxy-8-oxo-4-phenylethynyl-12-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene (*exo*-3d). Isolated as colorless prisms (194.7 mg, 67%, *exo*:*endo* = >99:1) by silica gel column chromatography (30 g, Hexane:EtOAc = 85:15, v/v) following the general procedure (reaction temperature: 50 °C) using *O*-methyloxime **1c** (151.6 mg, 0.50 mmol), Cu(OTf)$_2$ (54.3 mg, 0.15 mmol), and ligand **E** (84.9 mg, 0.15 mmol). Mp. 105-106 °C; $[\alpha]_D^{26}$ -71.1 (*c* 1.0, $CHCl_3$, 91% ee); R_f = 0.20 (Hexane:EtOAc = 70:30, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 0.75 (3H×1/2, s), 0.77 (3H×1/2, s), 0.79 (3H×1/2, s), 0.80 (3H×1/2, s), 1.74 (1H, m), 2.11 (1H×1/2, d, J = 17.1 Hz), 2.15 (1H×1/2, d, J = 16.8 Hz), 2.17 (1H×1/2, d, J = 17.1 Hz), 2.25 (1H×1/2, d, J = 16.8 Hz), 2.65 (1H×1/2, ddd, J = 4.0, 8.1, 13.7 Hz), 3.15 (3H×1/2, s), 3.21 (3H×1/2, s), 3.31-3.66 (1H+1H×1/2, m), 4.07 (1H×1/2, d, J = 13.8 Hz), 4.20 (1H×1/2, d, J = 13.8 Hz), 4.23-4.30 (1H×1/2+1H×1/2, m), 4.34 (1H×1/2, d, J = 14.5 Hz), 4.52 (1H×1/2, d, J = 7.7 Hz), 4.83 (1H×1/2, s), 5.11 (1H×1/2, s), 6.96-7.07 (3H, m), 7.20-7.32 (2H, m), 7.34 (1H×1/2, d, J = 8.0 Hz), 7.35

(1H×1/2, d, J = 8.0 Hz), 7.37-7.52 (3H, m), 7.60 (1H×1/2, d, J = 8.2 Hz), 7.61 (1H×1/2, d, J = 8.1 Hz), 7.66 (1H, d, J = 8.2 Hz), 7.69 (1H×1/2, s), 7.74 (1H×1/2, d, J = 7.1 Hz), 7.94 (1H×1/2, d, J = 7.0 Hz), 8.04 (1H×1/2, d, J = 8.0 Hz), 8.07 (1H×1/2, s), 8.09 (1H×1/2, d, J = 7.9 Hz), 8.37 (1H×1/2, d, J = 8.4 Hz), 8.45 (1H×1/2, d, J = 8.5 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 25.1 (CH_2), 25.5 (CH_3), 25.6 (CH_3), 26.0 ($2CH_3$), 26.2 (CH_2), 43.0 (CH_2), 43.5 (CH_2), 47.8 (CH), 52.4 (CH), 54.4 (CH_2), 54.8 (CH_2), 59.5 (CH_3), 60.4 (CH_3), 60.8 (C), 60.9 (C), 65.3 (CH), 68.1 (CH), 72.9 (CH), 75.4 (CH), 89.7 (C), 89.9 (C), 93.3 (C), 93.4 (C), 123.3 (C), 123.4 (C), 124.3 (CH), 124.4 (CH), 125.6 (CH), 125.7 (CH), 125.9 (CH), 126.0 (CH), 126.1 (CH), 126.27 (CH), 126.29 (CH), 127.3 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.70 (CH), 128.72 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH, C), 129.4 (C), 129.7 (C), 130.3 (C), 130.9 (CH), 131.1 (CH), 131.2 (CH), 131.5 (CH), 131.9 (C), 132.1 (CH), 132.2 (CH, C), 133.8 (C), 134.25 (C), 134.27 (C), 134.5 (C), 141.8 (C), 145.5 (C), 168.0 (C), 168.4 (C), 173.7 (C), 173.9 (C), 194.3 (C), 196.1 (C); IR (KBr) 3058, 2969, 2938, 2210, 1743, 1698, 1603, 1443, 1307, 1043, 798, 757, 691 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{37}H_{33}N_3NaO_4$ $[M+Na]^+$ 606.2362, found 606.2361. The ^{1}H and ^{13}C NMR analysis showed that *exo*-**3d** exists as a 1:1 mixture of nitrogen invertomers at room temperature. The enantiomeric excess of *exo*-**3d** was determined by chiral-phase HPLC analysis (Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C): t_{minor} = 41.9 min, t_{major} = 53.6 min.



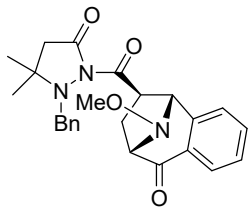
(1*R*,9*S*,11*R*)-11-{[5,5-Dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl]carbonyl}-12-methoxy-8-oxo-4-phenyl-12-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene (*exo*-3e). Isolated as colorless prisms (184.8 mg, 66%, *exo*:*endo* = >99:1) by silica gel column chromatography (30 g, Hexane:EtOAc = 85:15, v/v) following the general procedure (reaction temperature: 50 °C) using *O*-methyloxime **1d** (139.6 mg, 0.50 mmol), $Cu(OTf)_2$ (54.3 mg, 0.15 mmol), and ligand **E** (84.9 mg, 0.15 mmol). Mp. 235-237 °C; $[\alpha]_D^{25}$ -51.4 (*c* 1.0, $CHCl_3$, 95% ee); R_f = 0.20 (Hexane:EtOAc = 70:30, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 0.71 (3H×2/5, s), 0.75 (3H+3H×3/5, s), 1.79 (1H×3/5, ddd, J = 0.8, 10.1, 14.2 Hz), 1.85

(1H×2/5, dd, *J* = 10.2, 14.1 Hz), 2.06 (1H×3/5, d, *J* = 17.4 Hz), 2.08 (1H×2/5, d, *J* = 16.8 Hz), 2.11 (1H×2/5, d, *J* = 17.4 Hz), 2.21 (1H×3/5, d, *J* = 16.8 Hz), 2.71 (1H×3/5, ddd, *J* = 3.9, 8.3, 14.2 Hz), 3.16 (3H×3/5, s), 3.25 (3H×2/5, s), 3.41-3.57 (1H×3/5+1H×3/5, m), 3.62 (1H×2/5, m), 4.05 (1H×3/5, d, *J* = 14.0 Hz), 4.18 (1H×3/5, d, *J* = 14.0 Hz), 4.25 (1H×2/5, d, *J* = 14.5 Hz), 4.32 (1H×2/5, m), 4.33 (1H×2/5, d, *J* = 14.5 Hz), 4.58 (1H×3/5, m), 4.97 (1H×2/5, s), 5.22 (1H×3/5, s), 7.06-7.22 (3H, m), 7.22-7.34 (3H, m), 7.41 (1H, m), 7.46-7.66 (4H, m), 7.74 (1H×2/5, s), 7.75 (1H×2/5, d, *J* = 6.6 Hz), 7.93 (1H×3/5, d, *J* = 7.0 Hz), 8.10 (1H×3/5, s), 8.21 (1H×3/5, d, *J* = 8.0 Hz), 8.27 (1H×2/5, d, *J* = 8.0 Hz), 8.38 (1H×2/5, d, *J* = 8.6 Hz), 8.49 (1H×3/5, d, *J* = 8.5 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 25.2 (CH_2), 25.3 (CH_3), 25.6 (CH_3), 25.9 (CH_3), 26.1 (CH_3), 26.3 (CH_2), 43.0 (CH_2), 43.6 (CH_2), 48.1 (CH), 52.6 (CH), 54.4 (CH_2), 54.8 (CH_2), 59.4 (CH_3), 60.5 (CH_3), 60.7 (C), 60.8 (C), 65.9 (CH), 68.2 (CH), 73.5 (CH), 75.6 (CH), 124.4 (CH), 124.5 (CH), 125.5 (CH), 125.7 (CH), 125.9 (CH), 126.0 (CH), 126.3 (2CH), 126.5 (CH), 126.6 (CH), 126.7 (CH), 126.9 (CH), 127.2 (2CH), 127.8 (CH), 127.85 (CH), 127.89 (CH), 128.1 (CH), 128.2 (CH), 128.4 (2CH), 128.5 (C), 128.9 (C), 129.0 (CH), 129.07 (CH), 129.10 (CH), 129.2 (CH), 129.9 (C), 131.9 (C), 132.2 (C), 133.9 (C), 134.27 (C), 134.29 (C), 134.5 (C), 140.6 (C), 140.7 (C), 142.2 (C), 145.9 (C), 146.7 (C), 147.1 (C), 168.1 (C), 168.6 (C), 173.7 (C), 173.9 (C), 194.7 (C), 196.4 (C); IR (KBr) 3063, 2963, 2938, 1699, 1607, 1304, 1233, 801, 766, 699 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{35}H_{33}N_3NaO_4$ $[M+Na]^+$ 582.2347, found 582.2371. The ^{1}H and ^{13}C NMR analysis showed that *exo*-**3e** exists as a 3:2 mixture of nitrogen invertomers at room temperature. The enantiomeric excess of *exo*-**3e** was determined by chiral-phase HPLC after hydrogenation.



(1*R*,9*S*,11*R*)-4,5-Dichloro-11-{[5,5-dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl]-carbonyl}-12-methoxy-8-oxo-12-azaticyclro[7.2.1.0^{2,7}]dodeca-2,4,6-triene (*exo*-3f). Isolated as colorless prisms (199.7 mg, 72%, *exo*:*endo* = >99:1) by silica gel column chromatography (30 g, Hexane:EtOAc = 85:15, v/v) following the general procedure using *O*-methyl oxime **1e** (136.0 mg, 0.50 mmol). Mp. 155-157 °C; $[\alpha]_D^{26}$ -3.02 (*c* 1.0, $CHCl_3$, 90% ee); R_f = 0.20 (Hexane:EtOAc = 70:30, v/v);

^{1}H NMR (300 MHz, C_6D_6) δ 0.76 (3H+3H×1/2, s), 0.78 (3H×1/2, s), 1.64 (1H, m), 2.07 (1H×1/2, d, *J* = 17.2 Hz), 2.10 (1H×1/2, d, *J* = 16.9 Hz), 2.14 (1H×1/2, d, *J* = 17.2 Hz), 2.20 (1H×1/2, d, *J* = 16.9 Hz), 2.51 (1H×1/2, m), 3.11 (3H×1/2, s), 3.17 (3H×1/2, s), 3.18-3.42 (1H+1H×1/2, m), 3.99 (1H×1/2, d, *J* = 13.6 Hz), 4.11 (1H×1/2, d, *J* = 7.8 Hz), 4.18 (1H×1/2, d, *J* = 13.6 Hz), 4.18 (1H×1/2, d, *J* = 14.2), 4.30 (1H×1/2, d, *J* = 14.2 Hz), 4.39 (1H×1/2, d, *J* = 7.9 Hz), 4.62 (1H×1/2, s), 4.87 (1H×1/2, s), 7.20-7.31 (2H+1H×1/2, m), 7.40 (1H, m), 7.55-7.75 (3H, m), 7.86 (1H×1/2, brs), 8.00 (1H×1/2, s), 8.07 (1H×1/2, s), 8.31 (1H×1/2, d, *J* = 8.4 Hz), 8.40 (1H×1/2, d, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 25.0 (CH_2), 25.5 (CH_3), 25.6 (CH_3), 25.9 (CH_3), 26.1 (CH_3), 26.3 (CH_2), 42.9 (CH_2), 43.4 (CH_2), 47.6 (CH), 52.1 (CH), 54.5 (CH_2), 55.0 (CH_2), 59.5 (CH_3), 60.5 (CH_3), 60.9 (C), 61.0 (C), 64.3 (CH), 67.7 (CH), 71.8 (CH), 75.0 (CH), 124.1 (CH), 124.2 (CH), 125.5 (CH), 125.7 (CH), 125.95 (CH), 126.02 (CH), 126.3 (CH), 126.4 (CH), 127.9 (CH), 128.4 (CH), 128.6 (2CH), 128.7 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 129.7 (CH), 129.8 (C), 129.9 (CH), 130.5 (C), 131.9 (C), 132.2 (C), 132.7 (C), 133.1 (C), 133.4 (C), 134.1 (C), 134.20 (C), 134.23 (C), 138.0 (C), 138.3 (C), 141.0 (C), 144.4 (C), 167.7 (C), 168.0 (C), 173.9 (C), 174.0 (C), 192.8 (C), 194.7 (C); IR (KBr) 3049, 2968, 2933, 1744, 1707, 1592, 1304, 1240, 1043, 907, 798, 779 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{29}H_{27}N_3NaO_4$ $[M+Na]^+$ 574.1271, found 574.1250. The ^{1}H and ^{13}C NMR showed that compound *exo*-**3f** exists as a 1:1 mixture of nitrogen invertomers at room temperature. The enantiomeric excess of *exo*-**3f** was determined by chiral-phase HPLC analysis (Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C) t_{minor} = 33.6 min, t_{major} = 42.1 min.

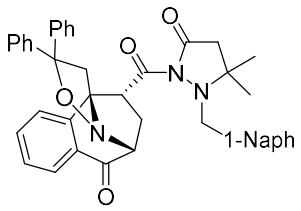


(1*R*,9*S*,11*R*)-11-[(1-Benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)carbonyl]-12-methoxy-8-oxo-12-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene (*exo*-3a). Isolated as colorless prisms (154.0 mg, 71%, *exo*:*endo* = 98:2) by silica gel column chromatography (15 g, Hexane:EtOAc = 85:15 – 70:30, v/v) following the general procedure (reaction temperature: 26 °C, under an argon atmosphere) using *O*-methyloxime **1a** (101.6 mg, 0.50 mmol), acryloylpyrazolidinone **2a** (258.3 mg, 1.0 mmol),

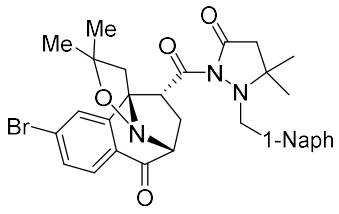
$Ni(ClO_4)_2$•$6H_2O$ (36.6 mg, 0.10 mmol), and ligand **A** (59.1 mg, 0.10 mmol). Mp. 210-211 °C; $[\alpha]_D^{25}$ -22.9 (*c* 1.0, $CHCl_3$, *exo*:*endo* = 82:18, 63% ee (*exo*)); R_f = 0.43 (Hexane:EtOAc = 50:50, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H×3/5, s), 1.26 (3H×2/5, s), 1.28 (3H×3/5, s), 1.29 (3H×2/5, s), 1.86 (1H×3/5, dd, *J* = 9.4, 13.9 Hz), 1.98 (1H×2/5, dd, *J* = 10.3, 14.1 Hz), 2.55 (1H×3/5, d, *J* = 16.8 Hz), 2.59 (1H×2/5, d, *J* = 16.8 Hz), 2.67 (1H×2/5, d, *J* = 16.8 Hz), 2.70 (1H×2/5, ddd, *J* = 4.1, 7.6, 14.1 Hz), 2.74 (1H×3/5, d, *J* = 16.8 Hz), 3.35 (1H×3/5, ddd, *J* = 4.1, 8.2, 13.9 Hz), 3.47 (3H, s), 3.58 (1H×3/5, dd, *J* = 4.1, 9.4 Hz), 3.67 (1H×2/5, dd, *J* = 4.1, 10.3 Hz), 4.11 (1H×3/5, d, *J* = 14.5 Hz), 4.13 (1H×2/5, d, *J* = 13.7 Hz), 4.17 (1H×2/5, d, *J* = 13.7 Hz), 4.18 (1H×2/5, d, *J* = 7.6 Hz), 4.20 (1H×3/5, d, *J* = 14.5 Hz), 4.44 (1H×3/5, d, *J* = 8.2 Hz), 4.75 (1H×2/5, s), 5.03 (1H×3/5, s), 7.22-7.35 (3H, m), 7.38-7.44 (1H+1H×2/5, m), 7.48-7.54 (2H, m), 7.60 (1H, m), 7.67 (1H×3/5, m), 7.99 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6 (CH_2), 25.5 (CH_2), 25.7 (CH_3), 25.8 (CH_3), 26.6 (CH_3), 26.8 (CH_3), 43.5 (CH_2), 43.9 (CH_2), 47.1 (CH), 51.6 (CH), 56.2 (CH_2), 56.5 (CH_2), 59.8 (CH_3), 60.7 (CH_3), 60.8 (2CH), 64.7 (CH, C), 67.4 (CH), 72.5 (CH), 74.8 (CH), 125.4 (CH), 126.8 (CH), 127.15 (2CH), 127.22 (CH), 127.3 (CH), 127.7 (CH), 128.0 (CH), 128.1 (2CH), 128.6 (CH), 128.7 (CH), 129.2 (C), 129.8 (C), 133.9 (CH), 134.4 (CH), 137.3 (C), 137.9 (C), 140.8 (C), 144.6 (C), 168.0 (C), 168.3 (C), 174.2 (2C), 195.4 (C), 197.2 (C); IR (KBr) 1736, 1696, 1373, 1335, 1263, 1238, 1200, 1179, 1049 cm^{-1}; MS (EI) m/z 345 (M^+), 232, 189, 170. Anal. calcd for $C_{25}H_{27}N_3O_4$: C, 69.27; H, 6.28; N, 9.73 %, found: C, 69.48; H, 6.18; N, 9.58 %. The ^{1}H and ^{13}C NMR showed that compound *exo*-**3a** exists as a 3:2 mixture of nitrogen invertomers at room temperature. The enantiomeric excess of *exo*-**3a** was determined by chiral-phase HPLC after hydrogenation.

General procedure for the cycloaddition of the cyclic azomethine ylide generated from diazo isoxazoline 4, exemplified by the reaction of 3-[2-(2-diazoacetyl)phenyl]-4,4-diphenyl-2-isoxazoline (4e) with acryloylpyrazolidinone 2b. To a 30 mL two-necked flask equipped with a stir bar was added MS 4A (254.0 mg), $Ni(BF_4)_2$•$6H_2O$ (34.0 mg, 0.10 mmol, 20 mol %), and ligand **A** (56.2 mg, 0.10 mmol, 20 mol %). After the flask was purged with argon, $CHCl_3$ (4.0 mL) was added, and then the mixture was stirred at 26 °C for 6 h. After the addition of $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol, 2 mol %) and acryloylpyrazolidinone **2b** (308.4 mg, 1.0 mmol), a solution of isoxazoline **4e** (183.7 mg, 0.50 mmol) in

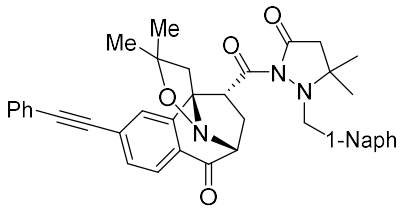
$CHCl_3$ (5.0 mL) was added dropwise over a period of 3 h at 50 °C using a syringe pump under an argon atmosphere. Subsequently, the syringe was washed with $CHCl_3$ (1.0 mL) and the wash was added to the reaction mixture. The mixture was filtered through a plug of silica gel-Celite (SiO_2: 1.5 g), rinsed with a mixture of Hexane/EtOAc (25 mL/25 mL), and then concentrated. Flash column chromatography (SiO_2: 20 g, Hexane:EtOAc = 85:15, v/v) yielded cycloadduct *endo*-**5e** (234.3 mg, 60%, *endo*:*exo* = >99:1).



(3a*S*,9*R*,11*R*)-11-{[5,5-Dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl]carbonyl}-2,2-diphenyl-8-oxo-3,3a,8,9-tetrahydro-2*H*-3a,9-ethanoisoxazolo[2,3-*a*]isoquinoline (*endo*-5e). Colorless amorphous; $[\alpha]_D^{25}$ = +61.0 (*c* 1.0, $CHCl_3$, 89% ee); R_f = 0.30 (Hexane:EtOAc = 75:25, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 0.58 (3H, s), 0.60 (3H, s), 1.99 (1H, d, *J* = 17.0 Hz), 2.20 (1H, d, *J* = 17.0 Hz), 2.32 (1H, dd, *J* = 2.8, 12.4 Hz), 2.73 (1H, ddd, *J* = 7.2, 10.0, 12.4 Hz), 3.50 (1H, d, *J* = 12.2 Hz), 3.57 (1H, d, *J* = 14.5 Hz), 3.88 (1H, d, *J* = 14.5 Hz), 4.62 (1H, dd, *J* = 2.8, 10.0 Hz), 4.76 (1H, d, *J* = 12.2 Hz), 4.86 (1H, d, *J* = 7.2 Hz), 6.63 (1H, m), 6.88-6.98 (3H, m), 7.06-7.14 (4H, m), 7.25 (1H, m), 7.29-7.38 (3H, m), 7.47 (1H, d, *J* = 8.2 Hz), 7.58-7.65 (2H, m), 7.65-7.72 (2H, m), 7.82-7.88 (2H, m), 7.96 (1H, d, *J* = 7.7 Hz), 8.10 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 25.1 (CH_3), 26.0 (CH_3), 32.1 (CH_2), 43.4 (CH_2), 49.8 (CH_2), 52.3 (CH), 53.7 (CH_2), 59.8 (C), 75.8 (CH), 81.9 (C), 88.1 (C), 123.9 (CH), 124.6 (CH), 125.7 (CH), 125.8 (CH), 126.0 (CH), 126.2 (CH), 126.79 (CH), 126.84 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 128.0 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 129.1 (CH), 131.5 (C), 132.7 (C), 133.1 (CH), 134.08 (C), 134.14 (C), 143.3 (C), 145.1 (C), 149.4 (C), 168.7 (C), 173.3 (C), 193.9 (C); IR (KBr) 2972, 1745, 1699, 1600, 1306, 1227, 800, 754, 700 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{42}H_{37}N_3NaO_4$ $[M+Na]^+$ 670.2676, found 670.2688. The enantiomeric excess of *endo*-**5e** was determined by chiral-phase HPLC analysis (Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C): t_{major} = 38.1 min, t_{minor} = 45.5 min.

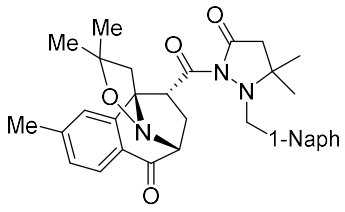


(3a*S*,9*R*,11*R*)-5-Bromo-2,2-dimethyl-11-{[5,5-dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl]carbonyl}-8-oxo-3,3a,8,9-tetrahydro-2*H*-3a,9-ethanoisoxazolo[2,3-*a*]isoquinoline (*endo*-5a). Isolated as colorless amorphous (200.8 mg, 67%, *endo*:*exo* = >99:1) by silica gel column chromatography (30 g, Toluene:EtOAc = 96:4, v/v) following the general procedure using diazo isoxazoline **4a** (161.0 mg, 0.50 mmol). $[\alpha]_D^{22}$ +95.2 (*c* 1.0, $CHCl_3$, 96% ee); R_f = 0.35 (Toluene:EtOAc = 90:10, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 0.59 (3H, s), 0.79 (3H, s), 1.37 (3H, s), 1.65 (3H, s), 2.03 (1H, d, *J* = 17.1 Hz), 2.12 (1H, d, *J* = 17.1 Hz), 2.15 (1H, d, *J* = 11.7 Hz), 2.26 (1H, dd, *J* = 4.2, 13.1 Hz), 2.67 (1H, ddd, *J* = 7.4, 10.3, 13.1 Hz), 3.14 (1H, d, *J* = 11.7 Hz), 3.90 (1H, d, *J* = 14.2 Hz), 4.04 (1H, d, *J* = 14.2 Hz), 4.64 (1H, d, *J* = 7.4 Hz), 5.07 (1H, dd, *J* = 4.2, 10.3 Hz), 6.78 (1H, dd, *J* = 1.8, 8.2 Hz), 7.18-7.30 (3H, m), 7.39 (1H, m), 7.51 (1H, d, *J* = 8.2 Hz), 7.62 (1H, d, *J* = 8.0 Hz), 7.71-7.75 (2H, m), 8.33 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5 (CH_3), 26.1 (CH_3), 27.2 (CH_3), 29.8 (CH_3), 31.4 (CH_2), 44.0 (CH_2), 47.7 (CH_2), 51.3 (CH), 53.8 (CH_2), 60.3 (C), 74.1 (CH), 81.1 (C), 81.2 (C), 123.5 (CH), 125.3 (CH), 125.6 (CH), 126.1 (CH), 127.8 (CH), 128.08 (CH), 128.13 (CH), 128.4 (C), 128.65 (CH), 128.72 (CH), 130.1 (C), 131.3 (C), 131.4 (CH), 132.7 (C), 133.6 (C), 145.2 (C), 169.1 (C), 174.3 (C), 193.4 (C); IR (KBr) 2974, 1742, 1702, 1592, 1308, 1227, 887, 791, 680, 616 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{32}H_{32}BrN_3NaO_4$ $[M+Na]^+$ 624.1468, found 624.1479. The enantiomeric excess of *endo*-**5a** was determined by chiral-phase HPLC analysis (Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C): t_{major} = 30.2 min, t_{minor} = 51.5 min.



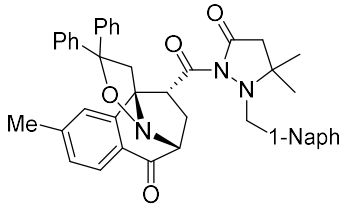
(3a*S*,9*R*,11*R*)-2,2-Dimethyl-11-{[5,5-dimethyl-1-(1-naphthylmethyl)-3-oxo-2-

pyrazolidinyl]carbonyl}-5-phenylethynyl-8-oxo-3,3a,8,9-tetrahydro-2*H*-3a,9-ethanoisoxazolo[2,3-*a*]isoquinoline (*endo*-5b). Isolated as colorless prisms (212.6 mg, 68%, *endo*:*exo* = >99:1) by silica gel column chromatography (25 g, Toluene:EtOAc = 95:5, v/v) following the general procedure using diazo isoxazoline **4b** (171.7 mg, 0.50 mmol). Mp. 186-188 °C; $[\alpha]_D^{26}$ +57.8 (*c* 1.0, $CHCl_3$, 94% ee); R_f = 0.56 (Hexane:EtOAc = 75:25, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 0.58 (3H, s), 0.75 (3H, s), 1.43 (3H, s), 1.69 (3H, s), 1.98 (1H, d, *J* = 16.9 Hz), 2.13 (1H, d, *J* = 16.9 Hz), 2.31 (1H, d, *J* = 11.7 Hz), 2.40 (1H, dd, *J* = 4.2, 13.2 Hz), 2.73 (1H, ddd, *J* = 7.0, 10.2, 13.2 Hz), 3.33 (1H, d, *J* = 11.7 Hz), 3.93 (1H, d, *J* = 14.2 Hz), 4.12 (1H, d, *J* = 14.2 Hz), 4.70 (1H, d, *J* = 7.0 Hz), 5.13 (1H, dd, *J* = 4.2, 10.2 Hz), 6.97-7.05 (4H, m), 7.10-7.30 (3H, m), 7.36-7.48 (4H, m), 7.58 (1H, m), 7.80 (1H, d, *J* = 7.4 Hz), 7.96 (1H, d, *J* = 8.2 Hz), 8.35 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1 (CH_3), 26.4 (CH_3), 27.2 (CH_3), 29.9 (CH_3), 31.3 (CH_2), 44.1 (CH_2), 47.8 (CH_2), 51.3 (CH), 53.5 (CH_2), 60.2 (C), 74.3 (CH), 81.2 (C), 81.3 (C), 88.6 (C), 93.1 (C), 122.5 (C), 123.4 (CH), 125.3 (CH), 125.4 (CH), 126.0 (CH), 127.1 (CH), 127.6 (CH), 127.8 (CH), 127.9 (CH), 128.1 (C), 128.3 (C), 128.4 (CH), 128.6 (CH), 128.9 (CH), 130.6 (C), 131.2 (CH), 131.7 (CH), 133.0 (C), 133.5 (C), 143.5 (C), 169.1 (C), 174.2 (C), 193.6 (C); IR (KBr) 2968, 2217, 1740, 1691, 1604, 1309, 1240, 802, 758, 688, 616 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{40}H_{37}N_3NaO_4$ $[M+Na]^+$ 646.2676, found 646.2677. The enantiomeric excess of *endo*-**5b** was determined by chiral-phase HPLC analysis (Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C): t_{major} = 27.0 min, t_{minor} = 49.2 min.



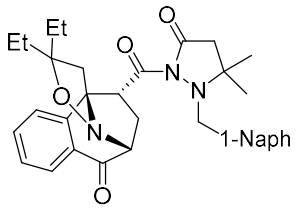
(3a*S*,9*R*,11*R*)-2,2-Dimethyl-5-methyl-11-{[5,5-dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl]carbonyl}-8-oxo-3,3a,8,9-tetrahydro-2*H*-3a,9-ethanoisoxazolo[2,3-*a*]isoquinoline (*endo*-5c). Isolated as colorless amorphous (144.7 mg, 54%, *endo*:*exo* = >99:1) by silica gel column chromatography (25 g, Hexane:EtOAc = 90:10, v/v and then 40 g, Toluene:EtOAc = 98:2, v/v) following the general procedure using diazo isoxazoline **4c** (128.6 mg, 0.50 mmol). R_f = 0.35 (Hexane:EtOAc = 60:40, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 0.59 (3H, s), 0.67 (3H, s), 1.44 (3H, s), 1.73

(3H, s), 1.83 (3H, s), 2.03 (1H, d, J = 17.0 Hz), 2.20 (1H, d, J = 17.0 Hz), 2.37 (1H, dd, J = 4.3, 13.0 Hz), 2.40 (1H, d, J = 11.6 Hz), 2.72 (1H, ddd, J = 7.4, 10.3, 13.0 Hz), 3.32 (1H, d, J = 11.6 Hz), 3.85 (1H, d, J = 14.3 Hz), 4.03 (1H, d, J = 14.3 Hz), 4.72 (1H, d, J = 7.4 Hz), 5.16 (1H, dd, J = 4.3, 10.3 Hz), 6.51 (1H, dd, J = 0.9, 7.8 Hz), 6.76 (1H, s), 7.15 (1H, m), 7,25 (1H, m), 7.35 (1H, m), 7.49 (1H, d, J = 8.1 Hz), 7.60 (1H, d, J = 8.1 Hz), 7.67 (1H, d, J = 7.0 Hz), 8.07 (1H, d, J = 7.8 Hz), 8.28 (1H, d, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7 (CH_3), 25.2 (CH_3), 26.5 (CH_3), 27.2 (CH_3), 29.8 (CH_3), 31.2 (CH_2), 43.9 (CH_2), 47.7 (CH_2), 51.1 (CH), 54.1 (CH_2), 60.2 (C), 74.3 (CH), 81.0 (C), 81.5 (C), 123.3 (CH), 125.3 (CH), 125.5 (CH), 126.0 (CH), 127.2 (CH), 127.7 (CH), 128.0 (CH), 128.1 (C), 128.3 (CH), 128.7 (CH), 128.9 (CH), 131.2 (C), 132.8 (C), 133.6 (C), 143.5 (C), 144.2 (C), 169.3 (C), 174.1 (C), 194.1 (C); IR (KBr) 2970, 1697, 1609, 1226, 954, 888, 862, 803, 615 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{33}H_{36}N_3O_4$ $[M+H]^+$ 538.2700, found 538.2692. The enantiomeric excess of *endo*-**5c** was determined by chiral-phase HPLC analysis (Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 93:7, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C): t_{major} = 41.9 min, t_{minor} = 88.3 min.



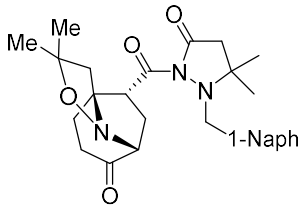
(3a*S*,9*R*,11*R*)-5-Methyl-11-{[5,5-dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl]carbonyl}-2,2-diphenyl-8-oxo-3,3a,8,9-tetrahydro-2*H*-3a,9-ethanoisoxazolo[2,3-*a*]isoquinoline (*endo*-5d). Isolated as colorless amorphous (185.2 mg, 56%, *endo*:*exo* = >99:1) by silica gel column chromatography (30 g, Toluene:EtOAc = 95:5 and then Hexane:EtOAc = 85:15, v/v) following the general procedure using diazo isoxazoline **4d** (190.7 mg, 0.50 mmol). $[\alpha]_D^{25}$ +70.3 (*c* 1.0, $CHCl_3$, 88% ee); R_f = 0.33 (Hexane:EtOAc = 60:40, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 0.53 (3H, s), 0.56 (3H, s), 1.82 (3H, s), 1.96 (1H, d, J = 17.0 Hz), 2.15 (1H, d, J = 17.0 Hz), 2.40 (1H, dd, J = 3.2, 12.8 Hz), 2.77 (1H, ddd, J = 7.0, 10.1, 12.8 Hz), 3.52 (1H, d, J = 12.1 Hz), 3.62 (1H, d, J = 14.3 Hz), 3.85 (1H, d, J = 14.3 Hz), 4.66 (1H, dd, J = 3.2, 10.1 Hz), 4.78 (1H, d, J = 12.1 Hz), 4.88 (1H, d, J = 6.9 Hz), 6.42 (1H, dd, J = 0.8, 7.8 Hz), 6.80 (1H, s), 6.95 (1H, m), 7.08-7.17 (4H, m), 7.23 (1H, m), 7.30-7.36 (3H, m), 7.46 (1H, d, J = 8.2 Hz), 7.56-7.65 (2H, m), 7.68-7.73 (2H, m), 7.84-7.89 (2H, m), 7.95

(1H, d, J = 7.8 Hz), 8.17 (1H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8 (CH_3), 25.3 (CH_3), 26.3 (CH_3), 31.4 (CH_2), 43.5 (CH_2), 49.2 (CH_2), 51.7 (CH), 53.9 (CH_2), 60.4 (C), 74.6 (CH), 80.9 (C), 87.3 (C), 123.2 (CH), 125.2 (CH), 125.4 (2CH), 125.5 (CH), 125.8 (CH), 126.1 (CH), 126.6 (CH), 127.06 (CH), 127.11 (CH), 128.1 (CH), 128.15 (2CH), 128.22 (CH), 128.7 (CH), 129.0 (CH), 129.2 (C), 131.3 (C), 132.4 (C), 133.5 (C), 143.0 (C), 144.1 (C), 144.7 (C), 148.3 (C), 169.0 (C), 173.5 (C), 194.0 (C); IR (KBr) 1721, 1439, 1271, 1106, 912, 835, 784, 758, 703 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{43}H_{40}N_3O_4$ $[M+H]^+$ 662.3013, found 662.3039. The enantiomeric excess of *endo*-**5d** was determined by chiral-phase HPLC analysis (Daicel Chiralcel OZ-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C): t_{major} = 82.2 min, t_{minor} = 70.6 min.



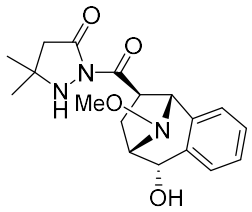
(3a*S*,9*R*,11*R*)-2,2-Diethyl-11-{[5,5-dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl]-carbonyl}-8-oxo-3,3a,8,9-tetrahydro-2*H*-3a,9-ethanoisoxazolo[2,3-*a*]isoquinoline (*endo*-5f). Isolated as colorless amorphous (154.5 mg, 56%, *endo*:*exo* = >99:1) by silica gel column chromatography (30 g, CH_2Cl_2:EtOAc = 98:2 – 97:3, v/v) following the general procedure using diazo isoxazoline **4f** (135.7 mg, 0.50 mmol). $[\alpha]_D^{22}$ = +112.9 (*c* 1.0, $CHCl_3$, 89% ee); R_f = 0.31 (Hexane:EtOAc = 75:25, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 0.63 (3H, s), 0.68 (3H, s), 0. 91 (3H, t, J = 7.4 Hz), 1.10 (3H, t, J = 7.4 Hz), 1.56 (1H, m), 1.94-2.15 (3H, m), 2.04 (1H, d, J = 17.0 Hz), 2.20 (1H, d, J = 17.0 Hz), 2.30 (1H, dd, J = 4.0, 12.7 Hz), 2.32 (1H, d, J = 11.8 Hz), 2.70 (1H, m), 3.41 (1H, d, J = 11.8 Hz), 3.78 (1H, d, J = 14.3 Hz), 4.01 (1H, d, J = 14.3 Hz), 4.70 (1H, d, J = 6.7 Hz), 5.04 (1H, dd, J = 4.0, 10.3 Hz), 6.70 (1H, m), 6.87-6.98 (2H, m), 7.15 (1H, m), 7.26 (1H, m), 7.37 (1H, m), 7.49 (1H, d, J = 8.1 Hz), 7.59-7.70 (2H, m), 8.09 (1H, dd, J = 0.9, 7.7 Hz), 8.21 (1H, d, J = 8.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.2 (CH_3), 9.1 (CH_3), 25.2 (CH_3), 26.8 (CH_3), 28.4 (CH_2), 30.0 (CH_2), 31.4 (CH_2), 43.8 (CH_2), 45.4 (CH_2), 51.5 (CH), 54.3 (CH_2), 60.4 (C), 74.3 (CH), 80.9 (C), 86.6 (C), 123.2 (CH), 124.5 (CH), 125.4 (CH), 125.6 (CH), 126.1 (CH), 127.1 (CH), 128.0 (2CH), 128.2 (CH), 128.8 (CH), 131.3 (C), 131.4 (C), 132.5 (C), 133.2 (CH), 133.6 (C), 143.6 (C), 169.5 (C), 174.0 (C), 194.5 (C); IR (KBr) 2969, 1742, 1698, 1602,

1458, 1305, 1227, 914, 770, 732 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{34}H_{37}N_3NaO_4$ $[M+Na]^+$ 574.2676, found 574.2671. The enantiomeric excess of *endo*-**5f** was determined by chiral-phase HPLC analysis (Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C): t_{major} = 20.1 min, t_{minor} = 116.6 min.



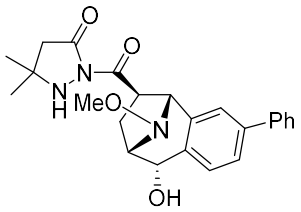
(3a*S*,7*R*,9*R*)-2,2-Dimethyl-9-{[5,5-dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl]-carbonyl}-6-oxo-3,3a-dihydro-2*H*-3a,7-ethanoisoxazolo[2,3-*a*]piperidine (*endo*-5g). Isolated as colorless amorphous (144.3 mg, 63%, *endo*:*exo* = >99:1) by silica gel column chromatography (20 g, Hexane:EtOAc = 85:15, v/v) following the general procedure using diazo isoxazoline **4g** (97.6 mg, 0.50 mmol). $[\alpha]_D^{26}$ = +20.6 (*c* 1.0, $CHCl_3$, 63% ee); R_f = 0.29 (Hexane:EtOAc = 60:40, v/v); ^1H NMR (C_6D_6, 500 MHz) δ 0.68 (3H, s), 0.82 (3H, s), 1.30-1.34 (2H, m), 1.41 (3H, s), 1.58 (1H, d, *J* = 12.0 Hz), 1.60 (3H, s), 1.93-2.01 (2H, m), 2.08 (1H, d, *J* = 17.3 Hz), 2.12 (1H, d, *J* = 17.3 Hz), 2.42 (1H, m), 2.56 (1H, d, *J* = 12.0 Hz), 2.77 (1H, dt, *J* = 18.1, 9.9 Hz), 3.99 (1H, d, *J* = 13.9 Hz), 4.10 (1H, d, *J* = 13.9 Hz), 4.22 (1H, d, *J* = 7.1 Hz), 4.86 (1H, m), 7.23 (1H, m), 7.28 (1H, m), 7.42 (1H, m), 7.55 (1H, d, *J* = 8.2 Hz), 7.63 (1H, d, *J* = 8.0 Hz), 7.71 (1H, d, *J* = 7.1 Hz), 8.30 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3 (CH_3), 26.8 (CH_3), 27.1 (CH_3), 28.6 (CH_2), 29.6 (CH_3), 32.5 (CH_2), 33.2 (CH_2), 43.5 (CH_2), 48.7 (CH), 51.2 (CH_2), 55.1 (CH_2), 61.0 (C), 74.2 (CH), 78.0 (C), 81.4 (C), 123.6 (CH), 125.2 (CH), 125.9 (CH), 126.5 (CH), 128.6 (CH), 128.8 (2CH), 131.9 (C), 132.1 (C), 133.7 (C), 171.5 (C), 174.9 (C), 205.8 (C); IR (KBr) 2972, 1743, 1723, 1511, 1455, 1365, 1302, 1225, 803, 755 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{28}H_{33}N_3NaO_4$ $[M+Na]^+$ 498.2363, found 498.2381. The enantiomeric excess of *endo*-**5g** was determined by chiral-phase HPLC analysis (Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C) t_{major} = 25.8 min, t_{minor} = 31.9 min.

General procedure for the hydrogenation of cycloadducts *exo*-3 exemplified by the reaction of *exo*-3b. To a solution of *exo*-**3b** (48.3 mg, 0.10 mmol) in MeOH (2.0 mL) was added $Pd(OH)_2/C$ (20%, 10.0 mg, 0.02 mmol). After the flask was purged with hydrogen, the mixture was stirred at 26 °C for 18 h under a hydrogen atmosphere with a balloon of hydrogen (1 atm). The mixture was filtered through a plug of Celite, rinsed with MeOH (50 mL), and then concentrated. Flash column chromatography (SiO_2: 10 g, EtOAc) yielded alcohol **6** (31.1 mg, 90%). The reactions of *exo*-**3a** and *exo*-**3c** by the same procedure also gave alcohol **6**.



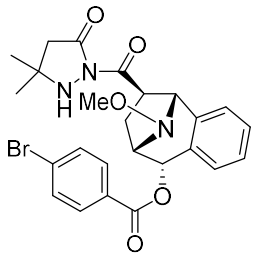
(1*R*,9*S*,8*S*,11*R*)-8-Hydroxy-11-[(5,5-dimethyl-3-oxo-2-pyrazolidinyl)carbonyl]-12-methoxy-12-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene (6). Colorless needles; Mp. 152-153 °C; $[\alpha]_D^{25}$ -6.33 (*c* 0.6, $CHCl_3$, 99% ee); R_f = 0.20 (EtOAc); ^{1}H NMR (300 MHz, CD_3OD) δ 1.295 (3H×1/10, s), 1.304 (3H×1/10, s), 1.33 (3H×9/10, s), 1.35 (3H×9/10, s), 2.18 (1H×9/10, ddd, *J* = 1.1, 9.5, 13.9 Hz), 2.26-2.47 (2H×1/10, m), 2.59 (1H×1/10, d, *J* = 16.8 Hz), 2.65 (1H×1/10, d, *J* = 16.8 Hz), 2.65 (2H×9/10, s), 2.78 (1H×9/10, ddd, *J* = 3.6, 7.7, 13.9 Hz), 3.39 (1H, dd, *J* = 3.6, 9.5 Hz), 3.47 (3H×9/10, s), 3.49 (3H×1/10, s), 3.84 (1H×1/10, m), 4.08 (1H×9/10, m), 4.50 (1H×1/10, s), 4.83 (1H×9/10, s), 5.07 (1H×9/10, d, *J* = 5.4 Hz), 5.23 (1H×1/10, d, *J* = 4.9 Hz), 7.18-7.32 (2H, m), 7.39-7.52 (2H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 22.1 (CH_2), 22.6 (CH_2), 25.4 (CH_3), 25.60 (CH_3), 25.62 (CH_3), 25.8 (CH_3), 48.2 (CH_2), 48.3 (CH_2), 55.0 (2CH), 56.7 (C), 56.9 (C), 59.3 (CH_3), 60.5 (CH_3), 61.7 (CH), 65.8 (CH), 67.1 (CH), 70.9 (CH), 71.8 (CH), 72.4 (CH), 127.2 (2CH), 127.6 (CH), 128.1 (CH), 128.4 (CH), 128.55 (CH), 128.64 (CH), 128.9 (CH), 136.8 (C), 138.1 (C), 138.2 (C), 139.3 (C), 171.8 (C), 172.6 (C), 175.8 (C), 176.2 (C); IR (KBr) 3552, 3338, 3210, 2981, 2966, 1727, 1708, 1467, 1309, 1256, 1037, 941, 755, 682 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{18}H_{23}N_3NaO_4$ $[M+Na]^+$ 368.1581, found 368.1571. The ^{1}H and ^{13}C NMR analysis showed that compound **6** exists as a 9:1 mixture of nitrogen invertomers at room temperature. The enantiomeric excess of **6** was determined by chiral-phase HPLC analysis (Daicel Chiralpak AD-H, Hexane:*i*-PrOH = 86:14, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C):

t_{major} = 49.1 min, t_{minor} = 56.1 min.



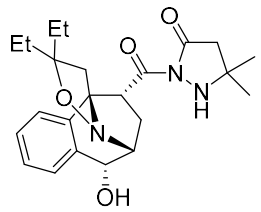
(1*R*,9*S*,8*S*,11*R*)-8-Hydroxy-11-[(5,5-dimethyl-3-oxo-2-pyrazolidinyl)carbonyl]-12-methoxy-4-phenyl-12-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene. Isolated as colorless needles (33.4 mg, 79%) by silica gel column chromatography (10 g, EtOAc:Hexane = 90:10, v/v) following the general procedure (reaction time: 10 h) using *exo*-**3f** (56.0 mg, 0.10 mmol). Mp. 120-122 °C; $[\alpha]_D^{25}$ -55.3 (*c* 0.4, $CHCl_3$, 95% ee); R_f = 0.10 (EtOAc:Hexane = 90:10, v/v); ^{1}H NMR (300 MHz, CD_3OD) δ 1.29 (3H×1/13, s), 1.30 (3H×1/13, s), 1.32 (3H×12/13, s), 1.35 (3H×12/13, s), 2.20 (1H×12/13, ddd, *J* = 0.8, 9.4, 13.7 Hz), 2.38 (1H×1/13, m), 2.46 (1H×1/13, m), 2.60 (1H×1/13, d, *J* = 16.6 Hz), 2.66 (2H×12/13, s), 2.67 (1H×1/13, d, *J* = 16.6 Hz), 2.83 (1H×12/13, ddd, *J* = 3.5, 7.7, 13.7 Hz), 3.45 (1H×1/13, dd, *J* = 3.5, 9.4 Hz), 3.48 (3H×12/13, s), 3.51 (1H×1/13, m), 3.54 (1H×1/13, s), 3.88 (1H×1/13, m), 4.11 (1H×12/13, m), 4.56 (1H×1/13, s), 4.89 (1H×12/13, s), 5.11 (1H×12/13, d, *J* = 5.4 Hz), 5.27 (1H×1/13, d, *J* = 4.8 Hz), 7.32 (1H, m), 7.38-7.46 (2H, m), 7.49-7.57 (2H, m), 7.58-7.67 (2H, m), 7.74 (1H, brs); ^{13}C NMR (75 MHz, CD_3OD) δ 22.0 (CH_2), 22.3 (CH_2), 25.5 (CH_3), 25.6 (CH_3), 25.7 (CH_3), 25.8 (CH_3), 48.2 (CH_2), 48.3 (CH_2), 53.2 (CH), 55.1 (CH), 56.9 (C), 57.9 (C), 59.4 (CH_3), 60.6 (CH_3), 61.7 (CH), 66.2 (CH), 66.9 (CH), 71.0 (CH), 71.6 (CH), 72.7 (CH), 124.6 (CH), 125.7 (CH), 126.3 (CH), 126.9 (CH), 127.4 (CH), 127.5 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 129.1 (CH), 129.9 (CH), 135.8 (C), 137.3 (C), 138.7 (C), 139.8 (C), 141.5 (C), 141.6 (C), 142.0 (C), 142.2 (C), 171.7 (C), 172.5 (C), 175.8 (C), 176.1 (C); IR (KBr) 3430, 2961, 2924, 2851, 1765, 1744, 1686, 1307, 1253, 1039, 867, 761, 700 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{24}H_{27}N_3NaO_4$ $[M+Na]^+$ 444.1894, found 444.1877. The ^{1}H and ^{13}C NMR analysis showed that this compound exists as a 9:1 mixture of nitrogen invertomers at room temperature. The enantiomeric excess of this compound was determined by chiral-phase HPLC analysis (Daicel Chiralpak AD-H, Hexane:*i*-PrOH = 75:25, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C): t_{major} = 28.3 min, t_{minor} = 57.6 min.

Conversion of alcohol 6 to *p*-bromobenzoate 7. To a solution of **6** (34.6 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) were added 4-bromobenzoic acid (24.2 mg, 0.12 mmol), DCC (32.8 mg, 0.16 mmol), and DMAP (18.4 mg, 0.15 mmol) successively, and then the mixture was stirred at 26 °C for 24 h. The mixture was filtered through a plug of Celite, rinsed with Et_2O (30 mL), and then concentrated. Flash column chromatography (SiO_2: 10 g, Hexane:EtOAc = 50:50, v/v) yielded **7** (45.1 mg, 84%).



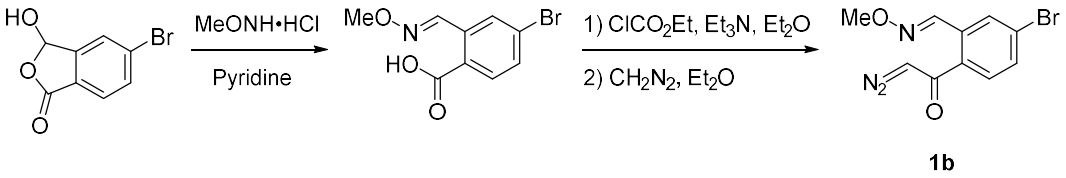
(1*R*,9*S*,8*S*,11*R*)-8-*p*-Bromobenzoyloxy-11-[(5,5-dimethyl-3-oxo-2-pyrazolidinyl)carbonyl]-12-methoxy-12-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene (7). Colorless needles; Mp. 93-95 °C; $[\alpha]_D^{25}$ +31.2 (*c* 0.5, $CHCl_3$); R_f = 0.20 (EtOAc:Hexane = 80:20, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 0.70 (3H×1/6, s), 0.72 (3H×5/6+3H×1/6, m), 0.82 (3H×5/6, s), 1.88 (1H×1/6, d, *J* = 16.6 Hz), 1.90 (1H×5/6, d, *J* = 16.6 Hz), 1.95 (1H×1/6, d, *J* = 16.6 Hz), 2.00 (1H×5/6, d, *J* = 16.6 Hz), 2.32 (1H×5/6, ddd, *J* = 1.0, 9.5, 13.8 Hz), 2.55 (1H×1/6, ddd, *J* = 1.0, 9.9, 13.9 Hz), 2.67 (1H×1/6, ddd, *J* = 3.6, 7.4, 13.9 Hz), 3.28 (1H×5/6, ddd, *J* = 3.3, 7.7, 13.8 Hz), 3.38 (3H×5/6, s), 3.43 (3H×1/6, s), 3.78 (1H×4/5, dd, *J* = 3.3, 9.5 Hz), 3.79 (1H×1/6, m), 4.38 (1H×1/6, m), 4.52 (1H×1/6, s), 4.63 (1H×5/6, m), 4.65 (1H×5/6, s), 4.92 (1H×1/6, s), 5.12 (1H×5/6, s), 6.75 (1H×5/6, d, *J* = 5.5 Hz), 7.03 (1H, m), 7.07-7.29 (4H+1H×1/6, m), 7.50 (1H×1/6, m), 7.74-7.81 (2H, m), 7.86 (1H×5/6, m); ^{13}C NMR (75 MHz, C_6D_6) δ 22.9 ($2CH_2$), 25.4 (CH_3), 25.67 (CH_3), 25.69 (CH_3), 26.0 (CH_3), 47.2 (CH_2), 47.4 (CH_2), 49.3 (CH), 54.5 (CH), 54.8 (C), 54.9 (C), 57.9 (CH), 59.5 (CH_3), 60.5 (CH_3), 65.4 (CH), 67.0 (CH), 71.5 (CH), 71.9 (CH), 74.2 (CH), 127.3 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 129.4 (C), 129.6 (C), 131.6 (2CH), 132.0 (CH), 132.1 (CH), 132.2 (C), 133.4 (C), 138.2 (C), 139.7 (C), 165.4 (C), 165.8 (C), 168.3 (C), 169.3 (C), 171.5 (C), 171.8 (C), two quaternary carbons of the product are overlapped in C_6D_6 signals; IR (KBr) 2963, 1720, 1589, 1308, 1260, 1101, 1011, 848, 755, 683 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{25}H_{26}BrN_3O_5$ $[M+Na]^+$ 550.0948, found 550.0948.

Hydrogenation of *endo*-5f. To a solution of *endo*-**5f** (55.2 mg, 0.10 mmol) in MeOH (0.5 mL) was added $Pd(OH)_2/C$ (20%, 10.1 mg, 0.02 mmol). After the flask was purged with hydrogen, the mixture was stirred at 26 °C for 12 h with a balloon of hydrogen (1 atm). The mixture was filtered through a plug of Celite, rinsed with MeOH (50 mL), and then concentrated. Flash column chromatography (SiO_2: 12 g, $CHCl_3$:MeOH = 98:2, v/v) yielded the corresponding alcohol (33.0 mg, 79%).



(3a*S*,8*R*,9*R*,11*R*)-2,2-Diethyl-8-hydroxy-11-[(5,5-dimethyl-3-oxo-2-pyrazolidinyl)-carbonyl]-3,3a,8,9-tetrahydro-2*H*-3a,9-ethanoisoxazolo[2,3-*a*]isoquinoline. Colorless amorphous; $[\alpha]_D^{26}$ +120.5 (*c* 0.2, $CHCl_3$); R_f = 0.30 (Hexane:EtOAc = 67:33, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 0.59 (3H, s), 0.68 (3H, s), 0.94 (3H, t, *J* =7.4 Hz), 1.11 (3H, t, *J* = 7.6 Hz), 1.60 (1H, dq, *J* = 7.4, 14.7 Hz), 1.89 (1H, d, *J* = 16.7 Hz), 1.95 (1H, d, *J* = 16.7 Hz), 1.97-2.09 (3H, m), 2.28 (1H, d, *J* = 12.0 Hz), 2.63 (1H, ddd, *J* = 6.5, 10.6, 13.3 Hz), 2.92 (1H, dd, *J* = 3.0, 13.3 Hz), 3.45 (1H, d, *J* = 12.0 Hz), 3.83 (1H, brs), 4.25 (1H, brs), 4.41 (1H, t, *J* = 6.5 Hz), 4.77 (1H, dd, *J* = 3.0, 10.6 Hz), 5.41 (1H, m), 6.74 (1H, dd, *J* = 1.1, 7.6 Hz), 6.95 (1H, m), 7.06 (1H, dt, *J* = 1.1, 7.6 Hz), 7.59 (1H, d, *J* = 7.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 8.7 (CH_3), 9.3 (CH_3), 25.4 (CH_3), 25.4 (CH_3), 26.1 (CH_3), 28.2 (CH_2), 29.0 (CH_2), 31.1 (CH_2), 46.2 (CH_2), 47.5 (CH_2), 53.8 (CH), 53.9 (C), 69.5 (CH), 71.8 (CH), 81.0 (C), 86.2 (C), 123.1 (CH), 127.1 (CH), 128.2 (CH), 128.7 (CH), 139.0 (C), 139.1 (C), 170.7 (C), 170.8 (C); IR (KBr) 3443, 2972, 2361, 1731, 1454, 1200, 1159, 1081, 761, 702 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{23}H_{30}N_3O_4$ $[M-H]^-$ 412.2242, found 412.2226.

Preparation of diazo compounds 1b – 1e

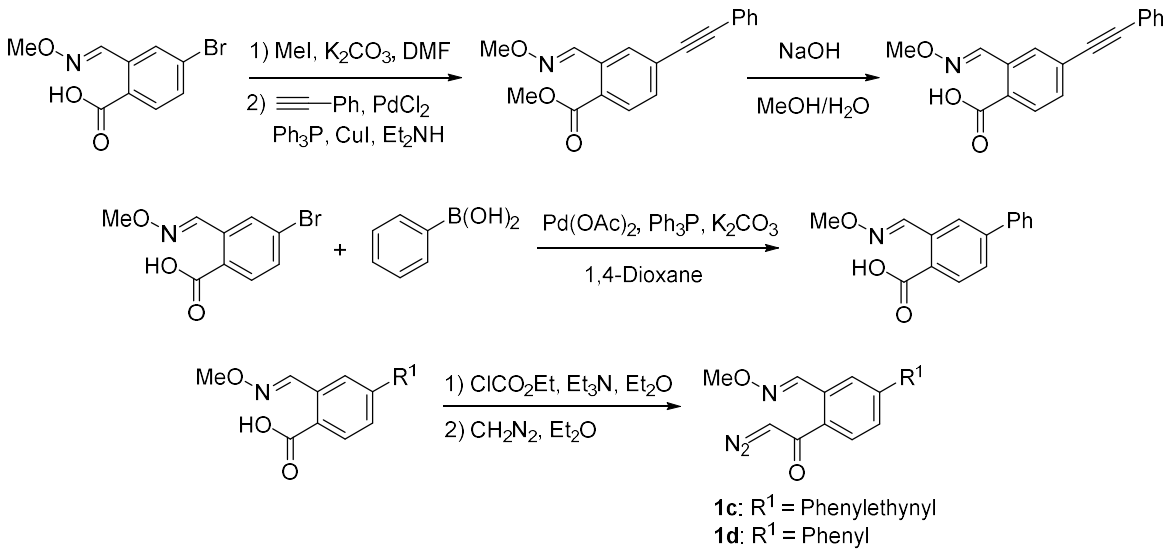


1b

4-Bromo-2-methoxyiminomethylbenzoic acid. To a solution of 5-bromo-3-hydroxyphthalide[4] (1.49 g, 6.50 mmol) in pyridine (20 mL) was added $MeONH_2$•HCl (1.03 g, 12.4 mmol). The mixture was stirred at room temperature for 18 h, and then concentrated. After adding 1 M H_3PO_4 aq (30 mL), the mixture was extracted with EtOAc (40 mL×3). The combined EtOAc extracts were dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was recrystallized from CH_2Cl_2 (50 mL) to give 4-bromo-2-methoxyiminomethylbenzoic acid (1.12 g, 67%) as colorless needles. Mp. 191-193 °C; R_f = 0.20 (Hexane:EtOAc = 50:50, v/v); ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 3.93 (3H, s), 7.74 (1H, dd, *J* = 2.1, 8.4 Hz), 7.86 (1H, d, *J* = 8.4 Hz), 7.93 (1H, d, *J* = 2.1 Hz), 8.78 (1H, s); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 62.0 (CH_3), 125.9 (C), 129.1 (CH), 129.2 (C), 132.5 (CH), 132.7 (CH), 134.3 (C), 147.0 (CH), 167.0 (C); IR (KBr) 2936, 1689, 1551, 1304, 1272, 1051, 934, 802 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_9H_7BrNO_3$ $[M-H]^-$ 255.9615, found 255.9601.

2-Diazoacetyl-5-bromobenzaldehyde *O*-methyloxime (1b). To a solution of 4-bromo-2-methoxyiminomethylbenzoic acid (1.00 g, 3.80 mmol) in Et_2O (30 mL) were added methyl chloroformate (0.30 mL, 4.20 mmol) and Et_3N (0.60 mL, 4.20 mmol) successively. The mixture was stirred for 2 h at room temperature, and then filtered to remove Et_3N•HCl. The filtrate was diluted with Et_2O (15 mL), and then the diluted filtrate was added at 0 °C over a period of 30 min to a solution of CH_2N_2 in Et_2O. The mixture was stirred at room temperature for 1 day, and then concentrated. Silica gel column chromatography (60 g, Hexane:EtOAc = 95:5, v/v) yielded **1b** (393.1 mg, 36%) as yellow prisms. Mp. 163-164 °C; R_f = 0.23 (Hexane:EtOAc = 80:20, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (3H, s), 5.62 (1H, s), 7.32 (1H, d, *J* = 8.3 Hz), 7.53 (1H, dd, *J* = 2.0, 8.3 Hz), 8.10 (1H, d, *J* = 2.0 Hz), 8.51 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.2 (CH), 62.3 (CH_3), 125.9 (C), 128.8 (CH), 130.1 (CH), 132.2 (CH), 132.6 (C), 135.6 (C), 145.6 (CH), 187.1 (C); IR (KBr) 3087, 2933, 2117, 1606, 1546, 1374,

1088, 1053, 940, 890, 759, 578 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{10}H_8BrN_3NaO_2$ $[M+Na]^+$ 303.9692, found 303.9688.



Methyl 2-methoxyiminomethyl-4-phenylethynylbenzoate. To a solution of 4-bromo-2-methoxyiminomethylbenzoic acid (2.14 g, 8.30 mmol) in DMF (29 mL) were added K_2CO_3 (2.29 g, 16.6 mmol) and CH_3I (1.54 mL, 24.9 mmol) at 0 °C, and then the mixture was stirred at 40 °C for 1 h. After cooling the mixture to room temperature, EtOAc (50 mL) was added, and the resulting solution was washed with water (50 mL×3) and brine (50 mL×3). The organic layer was dried over Na_2SO_4, and then concentrated. The crude ester (2.54 g) was used for Sonogashira coupling without purification. To a solution of the crude ester in Et_2NH (25 mL) were added $PdCl_2$ (148.3 mg, 0.83 mmol), Ph_3P (439.0 mg, 1.70 mmol), CuI (318.7 mg, 1.70 mmol), and phenylacetylene (1.36 mL, 12.5 mmol), and then the mixture was refluxed for 8 h. After cooling the mixture to room temperature, Et_2NH was removed under reduced pressure. Water (50 mL) was added to the residue, and the organic phase was extracted with EtOAc (50 mL×3). The organic extracts were dried over Na_2SO_4 and concentrated. Silica gel column chromatography (60 g, Hexane:EtOAc = 90:10, v/v) yielded methyl 2-methoxyiminomethyl-4-phenylethynylbenzoate (2.26 g, 90%) as colorless prisms. Mp. 86-88 °C; R_f = 0.16 (Hexane:EtOAc = 90:10, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (3H, s), 4.02 (3H, s), 7.33-7.41 (3H, m), 7.51-7.60 (3H, m), 7.95 (1H, dd, J = 0.4, 8.1 Hz), 8.07 (1H, d, J = 1.7 Hz), 8.86 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ

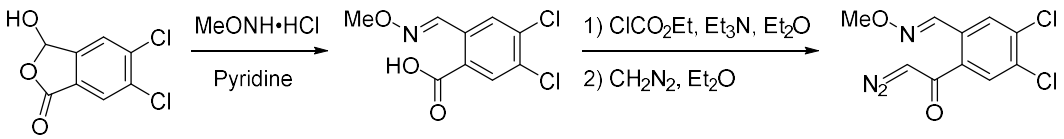
52.4 (CH_3), 62.2 (CH_3), 88.1 (C), 92.5 (C), 122.6 (C), 127.6 (C), 128.1 (C), 128.4 (CH), 128.8 (CH), 130.4 (CH), 130.8 (CH), 131.8 (CH), 131.9 (CH), 133.3 (C), 147.5 (CH), 166.5 (C); IR (KBr) 2936, 2215, 1719, 1610, 1550, 1436, 1293, 1254, 1053, 916, 781, 763, 529 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{18}H_{15}NNaO_3$ $[M+Na]^+$ 316.0941, found 316.0950.

2-Diazoacetyl-5-phenylethynylbenzaldehyde *O*-methyloxime (1c). To a solution of 2-methoxyiminomethyl-4-phenylethynylbenzoate (2.26 g, 7.60 mmol) in MeOH (114 mL) and water (29 mL) was added NaOH (1.17 g, 29.3 mmol), and the mixture was refluxed for 2 h. After cooling the mixture to room temperature, the mixture was acidified (pH 1) with 1 M HCl aq, and then extracted with CH_2Cl_2 (50 mL×3). The organic extracts were dried over Na_2SO_4 and concentrated. The resulting crude carboxylic acid was used without purification for the synthesis of **1c**. To a solution of crude carboxylic acid in Et_2O (40 mL) were added methyl chloroformate (0.49 mL, 7.00 mmol) and Et_3N (1.00 mL, 7.00 mmol) successively. The mixture was stirred for 2 h at room temperature, and then filtered to remove Et_3N•HCl. The filtrate was diluted with Et_2O (15 mL), and then the diluted filtrate was added at 0 °C over a period of 30 min to a solution of CH_2N_2 in Et_2O. The mixture was stirred at room temperature for 1 day, and then concentrated. Silica gel column chromatography (60 g, Hexane:EtOAc = 95:5, v/v) yielded **1c** (382.5 mg, 33%) as yellow prisms. Mp. 109-111 °C; R_f = 0.10 (Hexane:EtOAc = 95:5, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (3H, s), 5.66 (1H, s), 7.31-7.40 (3H, m), 7.43 (1H, d, *J* = 7.9 Hz), 7.48-7.58 (3H, m), 8.08 (1H, d, *J* = 1.6 Hz), 8.56 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.1 (CH), 62.2 (CH_3), 88.1 (C), 92.2 (C), 122.5 (C), 126.6 (C), 127.5 (CH), 128.4 (CH), 128.8 (CH), 130.2 (CH), 131.0 (C), 131.7 (CH), 131.9 (CH), 136.0 (C), 146.4 (CH), 187.3 (C); IR (KBr) 3423, 3086, 2125, 1602, 1377, 1226, 1053, 913, 753, 687 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{18}H_{13}N_3NaO_2$ $[M+Na]^+$ 326.0900, found 326.0905.

2-Methoxyiminomethyl-4-phenylbenzoic acid. To a solution of K_2CO_3 (1.59 g, 11.5 mmol) in 1,4-dioxane (30 mL) were added 4-bromo-2-methoxyiminomethylbenzoic acid (2.06 g, 8.0 mmol), $Pd(OAc)_2$ (68.3 mg, 0.30 mmol), Ph_3P (419.6 mg, 1.60 mmol), and phenylboronic acid (1.46 g, 12.0 mmol), and then the mixture was refluxed for 20 h. After cooling the mixture to room temperature, saturated NH_4Cl aq (30 mL) was added, and then the mixture was washed with hexane (30 mL). The water layer was acidified (pH 1) with 1 M HCl aq and extracted with CH_2Cl_2 (50 mL×3). The organic

extracts were dried over Na_2SO_4 and concentrated. Silica gel column chromatography (55 g, Hexane:EtOAc = 90:10, v/v) yielded 2-methoxyiminomethyl-4-phenylbenzoic acid (1.46 g, 72%) as colorless needles. Mp. 172-173 °C; R_f = 0.15 (Hexane:EtOAc = 90:10, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (3H, s), 7.38-7.53 (3H, m), 7.64-7.73 (3H, m), 8.16-8.23 (2H, m), 9.04 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.2 (CH_3), 126.1 (C), 126.4 (CH), 127.4 (CH), 127.9 (CH), 128.5 (CH), 129.0 (CH), 132.4 (CH), 134.5 (C), 139.3 (C), 146.1 (C), 148.3 (CH), 171.8 (C); IR (KBr) 2940, 1688, 1426, 1306, 1061, 748, 689 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{15}H_{13}NNaO_3$ $[M+Na]^+$ 278.0788, found 278.0799.

2-Diazoacetyl-5-phenylbenzaldehyde *O*-methyloxime (1d). To a solution of 2-methoxyiminomethyl-4-phenylbenzoic acid (1.27 g) in Et_2O (30 mL) were added methyl chloroformate (0.36 mL, 5.00 mmol) and Et_3N (0.77 mL, 5.50 mmol) successively. The mixture was stirred for 2 h at room temperature, and then filtered to remove Et_3N•HCl. The filtrate was diluted with Et_2O (15 mL), and then the diluted filtrate was added at 0 °C over a period of 30 min to a solution of CH_2N_2 in Et_2O. The mixture was stirred at room temperature for 1 day, and then concentrated. Silica gel column chromatography (60 g, Hexane:EtOAc = 95:5, v/v) yielded **1d** (684.1 mg, 49%) as colorless prisms. Mp. 119-120 °C; R_f = 0.17 (Hexane:EtOAc = 90:10, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (3H, s), 5.70 (1H, s), 7.31-7.53 (4H, m), 7.55-7.67 (3H, m), 8.15 (1H, d, J = 1.9 Hz), 8.64 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.9 (CH), 62.1 (CH_3), 125.8 (CH), 127.2 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 128.9 (CH), 131.2 (C), 135.5 (C), 139.3 (C), 144.1 (C), 147.1 (CH), 187.7 (C); IR (KBr) 3085, 2932, 2118, 1605, 1372, 1228, 1063, 936, 903, 749, 693, 578 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{16}H_{13}N_3NaO_2$ $[M+Na]^+$ 302.0900, found 302.0894.



1e

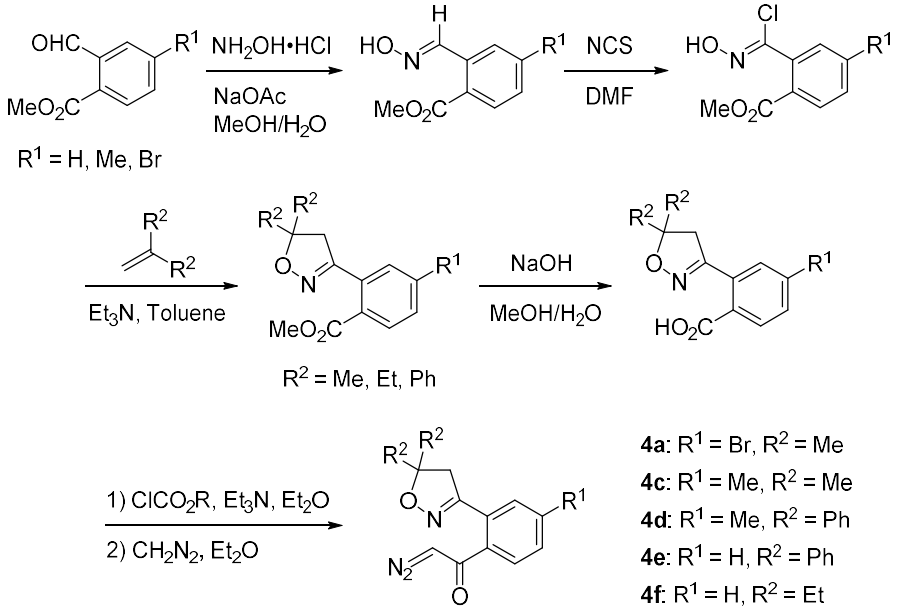
4,5-Dichloro-2-methoxyiminomethylbenzoic acid. Isolated as colorless powder (2.24 g, 87%) following the preparation of 4-bromo-2-methoxyiminomethylbenzoic acid (5,6-dichloro-3-hydroxyphthalide[5]: 2.24 g, 10.2 mmol; $MeONH_2$•HCl: 1.03 g, 12.4 mmol; pyridine: 30 mL). Mp. 173-

175 °C; R_f = 0.20 (Hexane:EtOAc = 50:50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (3H, s), 8.09 (1H, s), 8.18 (1H, s), 8.87 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.5 (CH_3), 126.7 (C), 129.3 (CH), 133.3 (CH), 133.6 (C), 133.7 (C), 138.2 (C), 146.0 (CH), 169.5 (C); IR (KBr) 3432, 2954, 1727, 1539, 1266, 1233, 1204, 1099, 1053, 923, 717, 574 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_9H_6Cl_2NO_3$ $[M-H]^-$ 245.9730, found 245.9725.

2-Diazoacety1-4,5-dichlorobenzaldehyde *O*-methyloxime (1e). To a solution of 4,5-dichloro-2-methoxyiminomethylbenzoic acid (3.28 g, 13.3 mmol) in Et_2O (100 mL) were added methyl chloroformate (1.05 mL, 14.7 mmol) and Et_3N (2.10 mL, 14.7 mmol) successively. The mixture was stirred for 2 h at room temperature, and then filtered to remove Et_3N•HCl. The filtrate was diluted with Et_2O (50 mL), and then the diluted filtrate was added at 0 °C over a period of 30 min to a solution of CH_2N_2 in Et_2O. The mixture was stirred at room temperature for 1 day, and then concentrated. Silica gel column chromatography (60 g, Hexane:EtOAc = 95:5, v/v) yielded **1e** (359.2 mg, 10%) as yellow powder. Mp. 155-157 °C; R_f = 0.15 (Hexane:EtOAc = 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (3H, s), 5.64 (1H, s) 7.54 (1H, s), 8.05 (1H, s), 8.46 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.5 (CH), 62.4 (CH_3), 128.8 (CH), 129.2 (CH), 130.5 (C), 133.4 (C), 135.8 (C), 136.0 (C), 144.9 (CH), 185.6 (C); IR (KBr) 3112, 2967, 2934, 2818, 2158, 2120, 1593, 1531, 1472, 1379, 1359, 1329, 1228, 1182, 1127, 1059, 938, 923 cm^{-1}; The corresponding molecular ion peak was not observed because of instability of **1d**.

Preparation of diazo compounds 4a and 4c – 4f

Methyl 2-[(chlorohydroxyimino)methyl]benzoate, and its 4-Me and 4-Br derivatives were prepared from the corresponding methyl 2-formylbanzoates[4] by two step sequences according to the literature.[1,6] These methyl 2-[(chlorohydroxyimino)methyl]benzoates were used without purification after extraction by Et_2O due to their instability.



General procedure for the preparation of 3-(2-methoxycarbonyl)phenylisoxazolines, exemplified by the reaction of methyl 2-[(chlorohydroxyimino)methyl]-4-methylbenzoate with 2-methylpropene. To a solution of methyl 2-[(chlorohydroxyimino)methyl]-4-methylbenzoate (1.82 g, 8.00 mmol) and 2-methylpropene (10% *i*-Pr_2O solution, 25.3 mL, 320 mmol) in toluene (32 mL) was added Et_3N (1.67 mL, 12.0 mmol), and then the mixture was refluxed for 14.5 h. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (50 g, Hexane:EtOAc = 92:8, v/v) to provide 3-(2-methoxycarbonyl-5-methyl)phenyl-5,5-dimethylisoxazoline (1.57 g, 79%) as colorless oil.

3-(2-Methoxycarbonyl-5-methyl)phenyl-5,5-dimethylisoxazoline. R_f = 0.40 (Hexane:EtOAc = 86:14, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (6H, s), 2.40 (3H, s), 3.06 (2H, s), 3.88 (3H, s), 7.24-7.28 (2H, m), 7.82 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1 (CH_3), 27.1 (CH_3), 49.8 (CH_2), 52.0 (CH_3), 84.9 (C), 127.1 (C), 129.7 (CH), 130.2 (CH), 130.3 (CH), 131.6 (C), 142.5 (C), 157.9 (C), 166.9 (C); IR ($CHCl_3$) 3019, 1719, 1216, 755, 669, 495, 468, 455 cm^{-1}; HRMS (ESI): Exact

mass calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$ 248.1281, found 248.1276.

3-(5-Bromo-2-methoxycarbonyl)phenyl-5,5-dimethylisoxazoline. Isolated as pale yellow prisms (568.4 mg, 49%) by silica gel column chromatography (30 g, Hexane:EtOAc = 95:5, v/v) following the general procedure (methyl 4-bromo-2-[(chlorohydroxyimino)methyl]benzoate: 1.08 g, 3.70 mmol; 2-methylpropene (10% *i*-Pr_2O solution): 11.7 mL, 148 mmol; Et_3N: 0.78 mL, 5.60 mmol; toluene: 15 mL; reflux: 10 h). Mp. 63-65 °C; R_f = 0.28 (Hexane:EtOAc = 86:14, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (6H, s), 3.05 (2H, s), 3.89 (3H, s), 7.58-7.62 (2H, m), 7.76 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.3 (CH_3), 49.5 (CH_2), 52.6 (CH_3), 85.8 (C), 126.5 (C), 129.1 (C), 131.7 (CH), 132.4 (CH), 132.7 (CH), 133.4 (C), 156.5 (C), 166.6 (C); IR (KBr) 1727, 1552, 1436, 1267, 1099, 1042, 911, 782, 741, 698 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{13}H_{15}BrNO_3$ $[M+H]^+$ 312.0230, found 312.0231.

3-(2-Methoxycarbonyl-5-methyl)phenyl-5,5-diphenylisoxazoline. Isolated as colorless prisms (866.5 mg, 58%) by silica gel column chromatography (55 g, Hexane:EtOAc = 92:8, v/v) following the general procedure (methyl 2-[(chlorohydroxyimino)methyl]-4-methylbenzoate: 911.0 mg, 4.00 mmol; diphenylethylene: 2.26 mL, 16.0 mmol; Et_3N: 0.84 mL, 6.00 mmol; toluene: 16 mL; reflux: 17 h). Mp. 150-151 °C; R_f = 0.35 (Hexane:EtOAc = 86:14, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (3H, s), 3.46 (3H, s), 3.94 (2H, s), 7.21 (1H, m), 7.25-7.40 (7H, m), 7.46-7.52 (4H, m), 7.82 (1H, d, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 (CH_3), 51.7 (CH_2), 51.8 (CH_3), 92.0 (C), 126.1 (CH), 127.4 (C), 127.5 (CH), 128.3 (CH), 130.2 (CH), 130.5 (C), 130.6 (CH), 130.7 (CH), 142.7 (C), 144.4 (C), 157.8 (C), 167.2 (C); IR (KBr) 1721, 1604, 1439, 1271, 1106, 912, 835, 784, 758, 703 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{24}H_{22}NO_3$ $[M+H]^+$ 372.1594, found 372.1592.

3-(2-Methoxycarbonyl)phenyl-5,5-diphenylisoxazoline. Isolated as colorless powder (1.79 g, 56%) by recrystallization from EtOAc (6 mL) following the general procedure (methyl 2-[(chlorohydroxyimino)methyl]benzoate: 1.92 g, 8.99 mmol; diphenylethylene: 6.60 mL, 40.0 mmol; Et_3N: 2.00 mL, 15.0 mmol; toluene: 65 mL; reflux: 17 h). R_f = 0.30 (Hexane:EtOAc = 67:33, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50 (3H, s), 3.95 (2H, s), 7.26-7.55 (13H, m), 7.88 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.4 (CH_2), 52.1 (CH_3), 92.2 (C), 126.2 (CH), 127.6 (CH), 128.4 (CH), 129.6 (CH), 129.8 (CH), 130.3 (C), 130.4 (CH), 130.6 (C), 131.9 (CH), 144.3 (C), 157.4 (C), 167.5 (C); IR (KBr) 3064, 2957, 1717, 1488, 1336, 1092, 1000, 893, 754, 700 cm^{-1}; HRMS (ESI): Exact mass calcd for

$C_{23}H_{20}NO_3$ $[M+H]^+$ 358.1438, found 358.1436.

3-(2-Methoxycarbonyl)phenyl-5,5-diethylisoxazoline. Isolated as colorless oil (1.99 g, 51%) by silica gel column chromatography (60 g, Hexane:EtOAc = 95:5, v/v) following the general procedure (methyl 2-[(chlorohydroxyimino)methyl]benzoate: 3.20 g, 15.0 mmol; 2-ethyl-1-butene: 7.32 mL, 60.0 mmol; Et_3N: 3.14 mL, 22.5 mmol; toluene: 60 mL; reflux: 8.5 h). R_f = 0.34 (Hexane:EtOAc = 86:14, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (6H, t, *J* = 7.4 Hz), 1.775 (2H, q, *J* = 7.4 Hz), 1.780 (2H, q, *J* = 7.4 Hz), 3.04 (2H, s), 3.89 (3H, s), 7.42-7.56 (3H, m), 7.83 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.1 (CH_3), 30.5 (CH_2), 44.9 (CH_2), 52.4 (CH_3), 90.7 (C), 129.1 (CH), 129.4 (CH), 129.9 (CH), 130.6 (C), 131.2 (C), 131.6 (CH), 156.6 (C), 167.7 (C); IR (neat) 2969, 1728, 1434, 1294, 759, 447, 431, 421, 411 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{15}H_{19}O_3NNa$ $[M+Na]^+$ 284.1257, found 284.1266.

3-(5-Bromo-2-diazoacetyl)phenyl-5,5-dimethylisoxazoline (4a). To a solution of 3-(5-bromo-2-methoxycarbonyl)phenyl-5,5-diphenylisoxazoline (1.40 g, 4.50 mmol) in MeOH (64 mL) and water (16 mL) was added NaOH (0.684 g, 17.1 mmol), and the mixture was refluxed for 1 h. After cooling the mixture to room temperature, the mixture was acidified (pH 1) with 1 M HCl aq, and then extracted with $CHCl_3$ (30 mL×3). The organic extracts were dried over $MgSO_4$ and concentrated. The corresponding crude carboxylic acid was obtained as white solid and was used without purification for the synthesis of **4a**. To a solution of the resulting acid in Et_2O (40 mL) were added methyl chloroformate (0.31 mL, 4.00 mmol) and Et_3N (0.61 mL, 4.40 mmol) successively. The mixture was stirred for 2 h at room temperature, and then filtered to remove Et_3N•HCl. The filtrate was added at 0 °C over a period of 30 min to a solution of CH_2N_2 in Et_2O. The mixture was stirred at room temperature for 1 day, and then concentrated. Silica gel column chromatography (40 g, Hexane:EtOAc = 80:20, v/v) yielded **4a** (0.985 g, 68% (3 steps)) as yellow prisms. Mp. 115-116 °C; R_f = 0.25 (Hexane:EtOAc = 75:25, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (6H, s), 3.04 (2H, s), 5.61 (1H, brs), 7.33 (1H, d, *J* = 8.2 Hz), 7.57 (1H, dd, *J* = 2.0, 8.2 Hz), 7.67 (1H, d, *J* = 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.2 (CH_3), 49.0 (CH_2), 57.0 (CH), 86.0 (C), 125.1 (C), 128.9 (CH), 131.0 (C), 132.3 (CH), 132.4 (C), 136.7 (C), 155.7 (C), 187.7 (C); IR (KBr) 3073, 2108, 1605, 1550, 1360, 1227, 1107, 1024, 907, 873, 829, 748 cm^{-1}.

3-(2-Diazoacetyl-5-methyl)phenyl-5,5-dimethylisoxazoline (4c). To a solution of 3-(2-methoxy-

carbonyl-5-methyl)phenyl-5,5-dimethylisoxazoline (1.53 g, 6.20 mmol) in MeOH (72 mL) and water (18 mL) was added NaOH (0.94 g, 23.6 mmol), and the mixture was refluxed for 1 h. After cooling the mixture to room temperature, the mixture was acidified (pH 1) with 1 M HCl aq, and then extracted with $CHCl_3$ (30 mL×3). The organic extracts were dried over $MgSO_4$ and concentrated. The corresponding crude carboxylic acid was obtained as white solid and was used without purification for the synthesis of **4c**. To a solution of the resulting acid in Et_2O (30 mL) were added ethyl chloroformate (0.40 mL, 4.20 mmol) and Et_3N (0.60 mL, 4.20 mmol) successively. The mixture was stirred for 2 h at room temperature, and then filtered to remove Et_3N•HCl. The filtrate was added at 0 °C over a period of 30 min to a solution of CH_2N_2 in Et_2O. The mixture was stirred at room temperature for 1 day, and then concentrated. Silica gel column chromatography (35 g, Hexane:EtOAc = 90:10, v/v) yielded **4c** (0.544 g, 34% (3 steps)) as brown plates. Mp. 78-80 °C; R_f = 0.45 (Hexane:EtOAc = 60:40, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (6H, s), 2.39 (3H, s), 3.05 (2H, s), 5.65 (1H, brs), 7.24 (1H, d, *J* = 7.9 Hz), 7.32 (1H, m), 7.37 (1H, d, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 (CH_3), 27.2 (CH_3), 49.5 (CH_2), 56.5 (CH), 85.4 (C), 127.5 (CH), 129.2 (C), 129.9 (CH), 130.2 (CH), 135.1 (C), 141.5 (C), 157.3 (C), 188.5 (C); IR (KBr) 3067, 2106, 1604, 1358, 911, 847, 765, 697, 611 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{14}H_{15}N_3NaO_2$ $[M+Na]^+$ 280.1056, found 280.1070.

3-(2-Diazoacetyl-5-methyl)phenyl-5,5-diphenylisoxazoline (4d). To a solution of 3-(2-methoxycarbonyl-5-methyl)phenyl-5,5-diphenylisoxazoline (1.48 g, 4.00 mmol) in MeOH (48 mL) and water (12 mL) was added NaOH (0.608 g, 15.2 mmol), and the mixture was refluxed for 2.5 h. After cooling the mixture to room temperature, the mixture was acidified (pH 1) with 1 M HCl aq, and then extracted with $CHCl_3$ (30 mL×3). The organic extracts were dried over $MgSO_4$ and concentrated. The corresponding crude carboxylic acid was obtained as white solid and was used without purification for the synthesis of **4d**. To a solution of the resulting acid in Et_2O (21 mL) were added ethyl chloroformate (0.25 mL, 2.60 mmol) and Et_3N (0.40 mL, 2.90 mmol) successively. The mixture was stirred for 2 h at room temperature, and then filtered to remove Et_3N•HCl. The filtrate was added at 0 °C over a period of 30 min to a solution of CH_2N_2 in Et_2O. The mixture was stirred at room temperature for 1 day, and then concentrated. Silica gel column chromatography (15 g, CH_2Cl_2) yielded **4d** (0.588 g, 38% (3 steps)) as yellow prisms. Mp. 128-130 °C; R_f = 0.66 (Hexane:EtOAc = 50:50, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ

2.37 (3H, s), 3.92 (2H, s), 5.18 (1H, brs), 7.24-7.50 (13H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2 (CH_3), 51.0 (CH_2), 57.3 (CH), 92.5 (C), 126.1 (CH), 127.7 (CH), 127.9 (CH, C), 128.4 (CH), 130.2 (CH), 130.6 (CH), 135.4 (C), 141.6 (C), 143.8 (C), 157.5 (C), 188.1 (C); IR (KBr) 2110, 1607, 1448, 1351, 915, 821, 749, 698, 509 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{24}H_{19}N_3NaO_2$ $[M+Na]^+$ 404.1369, found 404.1392.

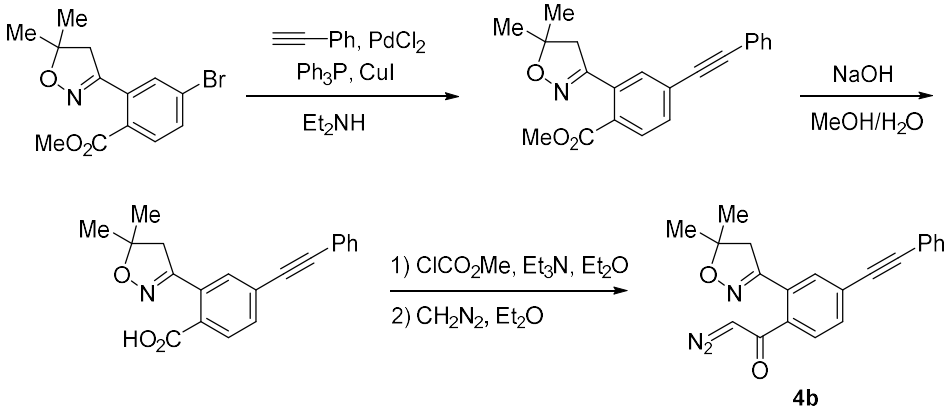
3-(2-Diazoacetyl)phenyl-5,5-diphenylisoxazoline (4e). To a solution of 3-(2-methoxycarbonyl)-phenyl-5,5-diphenylisoxazoline (3.57 g, 10.0 mmol) in MeOH (134 mL) and water (33 mL) was added NaOH (0.600 g, 15.0 mmol), and the mixture was refluxed for 6 h. After cooling the mixture to room temperature, the mixture was acidified (pH 1) with 1 M HCl aq, and then extracted with $CHCl_3$ (50 mL×3). The organic extracts were dried over $MgSO_4$ and concentrated. The corresponding crude carboxylic acid (2.40 g) was obtained as white solid and was used without purification for the synthesis of **4e**. The preparation of the carboxylic acid was repeated. To a solution of the resulting acid (4.12 g in total) in Et_2O (40 mL) were added ethyl chloroformate (1.30 mL, 13.2 mmol) and Et_3N (3.40 mL, 24.0 mmol) successively. The mixture was stirred for 2 h at room temperature, and then filtered to remove Et_3N•HCl. The filtrate was added at 0 °C over a period of 30 min to a solution of CH_2N_2 in Et_2O. The mixture was stirred at room temperature for 1 day, and then concentrated. Silica gel column chromatography (40 g, Hexane:EtOAc = 80:20, v/v) yielded **4e** (0.973 g) as yellow plates. R_f = 0.32 (Hexane:EtOAc = 80:20, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (2H, s), 5.21 (1H, brs), 7.22-7.36 (6H, m), 7.40-7.49 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.6 (CH_2), 57.4 (CH), 92.5 (C), 126.0 (CH), 127.6, (CH), 128.3 (CH), 129.4 (CH), 129.8 (CH), 129.9 (CH), 130.8 (CH), 138.1 (2C), 143.7 (C), 156.9 (C), 188.3 (C); IR (KBr) 3114, 3060, 2116, 1600, 1350, 1218, 1141, 899, 754, 699 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{23}H_{17}N_3NaO_2$ $[M+Na]^+$ 390.1213, found 390.1204.

3-(2-Diazoacetyl)phenyl-5,5-diethylisoxazoline (4f). To a solution of 3-(2-methoxycarbonyl)phenyl-5,5-diethylisoxazoline (1.57 g, 6.00 mmol) in MeOH (90 mL) and water (20 mL) was added NaOH (0.920 g, 23.0 mmol), and the mixture was refluxed for 1 h. After cooling the mixture to room temperature, the mixture was acidified (pH 1) with 1 M HCl aq, and then extracted with $CHCl_3$ (30 mL×3). The organic extracts were dried over $MgSO_4$ and concentrated. The corresponding crude carboxylic acid was obtained as white solid and was used without purification for the synthesis of **4f**. To

a solution of the resulting acid in Et_2O (20 mL) were added ethyl chloroformate (0.70 mL, 6.00 mmol) and Et_3N (1.60 mL, 10.8 mmol) successively. The mixture was stirred for 2 h at room temperature, and then filtered to remove Et_3N•HCl. The filtrate was added at 0 °C over a period of 30 min to a solution of CH_2N_2 in Et_2O. The mixture was stirred at room temperature for 1 day, and then concentrated. Silica gel column chromatography (40 g, Hexane:EtOAc = 80:20, v/v) yielded **4f** (0.499 g, 30% (3 steps)) as yellow prisms. Mp. 52-54 °C; R_f = 0.24 (Hexane:EtOAc = 80:20, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (6H, t, *J* = 7.5 Hz), 1.75 (4H, q, *J* = 7.5 Hz), 3.04 (2H, s), 5.58 (1H, brs), 7.40-7.53 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.0 (CH_3), 30.5 (CH_2), 44.4 (CH_2), 56.7 (CH), 90.8 (C), 127.3 (CH), 128.8 (C), 129.2 (2CH), 130.6 (CH), 137.9 (C), 156.0 (C), 189.0 (C); IR (KBr) 3075, 2973, 2101, 1613, 1468, 1361, 1226, 904, 759, 706 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{15}H_{17}N_3NaO_2$ $[M+Na]^+$ 294.1213, found 294.1206.

Preparation of diazo compound 4b

Diazo compound **4b** was prepared form 3-(5-bromo-2-methoxycarbonyl)phenyl-5,5-dimethylisoxazoline using Sonogashira coupling as shown in the scheme below.

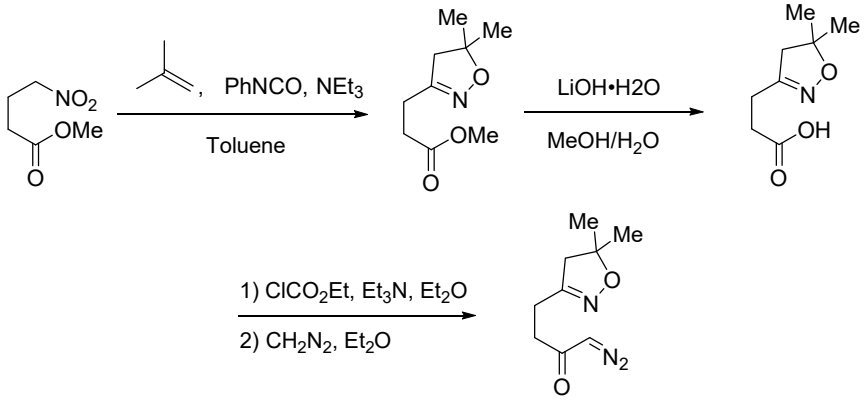


3-(2-Methoxycarbonyl-5-phenylethynyl)phenyl-5,5-dimethylisoxazoline. To a solution of 3-(5-bromo-2-methoxycarbonyl)phenyl-5,5-dimethylisoxazoline (936.5 mg, 3.0 mmol) in Et_2NH (9 mL) were added $PdCl_2$ (53.2 mg, 0.30 mmol), Ph_3P (157.4 mg, 0.60 mmol), CuI (114.3 mg, 0.60 mmol), and phenylacetylene (0.49 mL, 4.50 mmol), and then the mixture was refluxed for 10 h. After cooling the mixture to room temperature, Et_2NH was removed under reduced pressure. Water (20 mL) was added to

the residue, and the organic phase was extracted with EtOAc (20 mL×3). The organic extracts were dried over Na_2SO_4 and concentrated. Silica gel column chromatography (46 g, Hexane:EtOAc = 92:8, v/v) yielded 3-(2-methoxycarbonyl-5-phenylethynyl)phenyl-5,5-dimethylisoxazoline (736.5 mg, 74%) as brown plates. Mp. 89-90 °C; R_f = 0.29 (Hexane:EtOAc = 86:14, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (6H, s), 3.09 (2H, s), 3.91 (3H, s), 7.35-7.39 (3H, m), 7.52-7.55 (2H, m), 7.58-7.61 (2H, m), 7.87 (1H, dd, *J* = 0.6, 7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.3 (CH_3), 49.6 (CH_2), 52.5 (CH_3), 85.5 (C), 87.8 (C), 92.7 (C), 122.4 (C), 127.3 (C), 128.4 (CH), 128.9 (CH), 129.4 (C), 130.3 (CH), 131.75 (CH), 131.77 (C), 131.9 (CH), 132.6 (CH), 157.0 (C), 166.8 (C); IR (KBr) 2211, 1721, 1602, 1440, 1341, 1287, 1140, 901, 795, 760, 690 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{21}H_{19}NNaO_3$ $[M+Na]^+$ 356.1257, found: 356.1262.

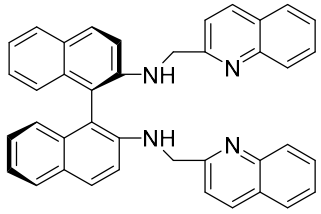
3-(2-Diazoacetyl-5-phenylethynyl)phenyl-5,5-dimethylisoxazoline (4b). To a solution of 3-(2-methoxycarbonyl-5-phenylethynyl)phenyl-5,5-dimethylisoxazoline (1.37 g, 4.10 mmol) in MeOH (60 mL) and water (15 mL) was added NaOH (0.624 g, 15.6 mmol), and the mixture was refluxed for 1.5 h. After cooling the mixture to room temperature, the mixture was acidified (pH 1) with 1 M HCl aq, and then extracted with $CHCl_3$ (30 mL×3). The organic extracts were dried over $MgSO_4$ and concentrated. The corresponding crude carboxylic acid was obtained as white solid and was used without purification for the synthesis of **4b**. To a solution of the resulting acid in Et_2O (40 mL) were added methyl chloroformate (0.28 mL, 3.70 mmol) and Et_3N (0.56 mL, 3.00 mmol) successively. The mixture was stirred for 2 h at room temperature, and then filtered to remove Et_3N•HCl. The filtrate was added at 0 °C over a period of 30 min to a solution of CH_2N_2 in Et_2O. The mixture was stirred at room temperature for 1 day, and then concentrated. Silica gel column chromatography (50 g, Hexane:EtOAc = 90:10, v/v) yielded **4b** (1.10 g, 78% (3 steps)) as yellow prisms. Mp. 115-116 °C; R_f = 0.25 (Hexane:EtOAc = 75:25, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (6H, s), 3.09 (2H, s), 5.64 (1H, brs), 7.34-7.40 (3H, m), 7.45 (1H, d, *J* = 7.9 Hz), 7.51-7.59 (3H, m), 7.66 (1H, dd, *J* = 0.5, 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.1 (CH_3), 49.0 (CH_2), 56.8 (CH), 85.6 (C), 87.7 (C), 92.2 (C), 122.4 (C), 126.2 (C), 127.6 (CH), 128.4 (CH), 128.8 (CH), 129.4 (C), 131.6 (CH), 131.9 (CH), 132.3 (CH), 136.9 (C), 156.3 (C), 187.9 (C); IR (KBr) 3124, 2116, 1604, 1483, 1348, 1136, 929, 859, 793, 759, 688, 522 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{21}H_{17}N_3NaO_2$ $[M+Na]^+$ 366.1213, found: 366.1208.

Preparation of diazo compound 4g.



3-(4-Diazo-3-oxopropyl)-5,5-dimetylisoxazoline (4g). To a solution (0 °C) of methyl 4-nitrobutyrate (3.11 g, 21.2 mmol) in toluene (53 mL) were added 2-methylpropene (10% *i*-Pr_2O solution, 101 mL, 106 mmol), Et_3N (5.90 mL, 42.3 mmol), and phenyl isocyanate (6.90 mL, 63.5 mmol) successively, and then the mixture was stirred at 25 °C for 66 h. The mixture was filtered through a plug of Celite, rinsed with toluene, and then concentrated. The resulting isoxazoline was used without purification. A solution of the isoxazoline in MeOH (30 mL) and water (30 mL) was added LiOH•H_2O (4.44 g, 106 mmol), and then the mixture was stirred at 50 °C for 19 h. After cooling the mixture at room temperature, the mixture was filtered through a plug of Celite, and then washed with hexane (30 mL×3). The mixture was acidified (pH 2) with 0.2 M HCl aq, and then extracted with CH_2Cl_2 (120 mL×3). The organic extracts were dried (Na_2SO_4) and concentrated. The resulting carboxylic acid was used without purification. To a solution of the resulting acid in Et_2O (38 mL) were added ethyl chloroformate (1.07 ml, 11.3 mmol) and Et_3N (3.13 mL, 22.5 mmol) successively. The mixture was stirred for 2 h at room temperature, and then filtered to remove Et_3N•HCl. The filtrate was added at 0 °C over a period of 30 min to a solution of CH_2N_2 in Et_2O. The mixture was stirred at room temperature for 1 day, and then concentrated. Silica gel column chromatography (22 g, Hexane:EtOAc = 80:20, v/v) yielded **4g** (703 mg, 17% (4 steps)) as yellow liquid. R_f = 0.30 (Hexane:EtOAc = 67:33, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (6H, s), 2.60-2.70 (6H, m), 5.34 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1 (CH_2), 26.9 (CH), 36.4 (CH_2), 49.2 (CH_2), 54.6 (CH), 83.6 (C), 157.4 (C), 193.0 (C); IR (neat) 3090, 2974, 2928, 2105, 1642, 1369, 1321, 1145, 895 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_9H_{13}N_3NaO_2$ $[M+Na]^+$ 218.0900, found 218.0897.

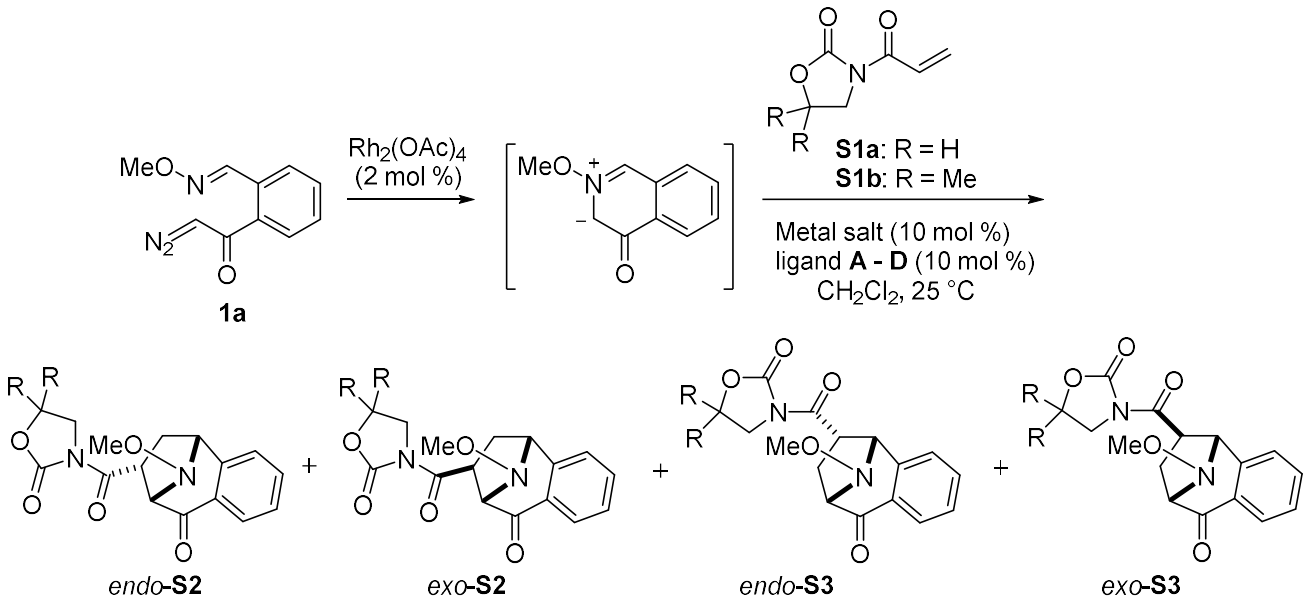
Preparation of ligand E.



(*R*)-*N*,*N*'-Bis(2-quinolylmethyl)-1,1'-binaphthyl-2,2'-diamine (ligand E). $NaBH_4$ (79.4 mg, 2.10 mmol) was added to a solution of ligand **A** (300.0 mg, 0.53 mmol) in CH_2Cl_2/MeOH (5 mL/1 mL), and then the mixture was stirred at room temperature for 6 h. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (8.5 g, Hexane:EtOAc = 85:15, v/v) to provide ligand **E** (298.3 mg, 99%) as yellow prisms. Mp. 81-84 °C; $[\alpha]_D^{26}$ +50.6 (*c* 1.0, $CHCl_3$); R_f = 0.30 (Hexane:EtOAc = 85:15, v/v); ^{1}H NMR (300 MHz, C_6D_6) δ 4.20-4.33 (4H, m), 5.18 (2H, t, *J* = 5.8 Hz), 6.95 (2H, d, *J* = 8.5 Hz), 7.04-7.14 (6H, m), 7.24-7.36 (8H, m), 7.42-7.48 (2H, m), 7.69-7.78 (4H, m), 7.97-8.03 (2H, m); ^{13}C NMR (75 MHz, C_6D_6) δ 49.7 (CH_2), 113.0 (C), 114.7 (CH), 119.3 (CH), 122.4 (CH), 124.7 (CH), 126.1 (CH), 127.3 (CH), 127.5 (C), 127.6 (CH), 128.5 (C), 128.7 (CH), 129.4 (CH), 129.6 (CH), 130.2 (CH), 134.9 (C), 136.1 (CH), 144.7 (C), 148.1 (C), 159.9 (C); IR (KBr) 3362, 3053, 1686, 1618, 1595, 1503, 1425, 817, 772, 748 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{40}H_{30}N_4Na$ $[M+Na]^+$ 589.2362, found 589.2363.

Reactions of diazo *O*-methyloxime 1a with acryloyloxazolidinone S1

Table S1. Reactions of diazo *O*-methyloxime **1a** with acryloyloxazolidinone **S1** in the presence of metal salts as a Lewis acid catalyst[a]

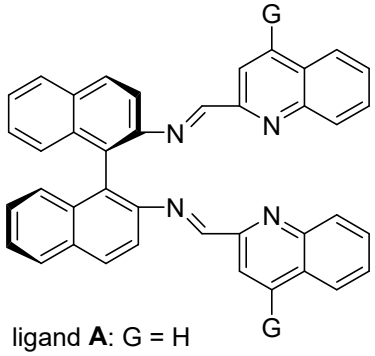


Entry	R	Metal salt	Ligand	Yield (%)	Ratio[b]	Ee (%)[c]
1	H	$Yb(OTf)_3$[d]	none	15	0:0:34:66	-, -, -
2	H	$Sc(OTf)_3$[d]	none	14	26:0:24:50	-, -, -
3	H	$Ni(ClO_4)_2•6H_2O$[d]	none	50	29:6:46:19	-, -, -
4	H	$Co(ClO_4)_2•6H_2O$[d]	none	40	41:0:59:0	-, -, -
5	H	$Ni(BF_4)_2•6H_2O$[d]	none	59	25:8:52:15	-, -, -
6	H	$Ni(ClO_4)_2•6H_2O$	**B**	85	22:13:33:32	41, 36, 46
7	H	$Ni(ClO_4)_2•6H_2O$	**C**	78	19:5:49:27	49, 37, 70
8	H	$Ni(ClO_4)_2•6H_2O$	**D**	79	16:2:46:36	41, 40, 71
9	Me	$Ni(ClO_4)_2•6H_2O$[d]	**A**	90	24:21:28:27	62, 25, 38
10	Me	$Ni(ClO_4)_2•6H_2O$	**B**	62	28:9:38:25	73, 69, 49
11	Me	$Ni(ClO_4)_2•6H_2O$[d]	**B**	91	27:21:27:25	81, 75, 47

Table S1. (*Continued*)

Entry	R	Metal salt	Ligand	Yield (%)	Ratio[b]	Ee (%)[c]
12	Me	$Ni(ClO_4)_2•6H_2O$[d]	**C**	76	24:14:45:17	79, 76, 47
13	Me	$Ni(ClO_4)_2•6H_2O$[d]	**D**	71	29:9:38:24	84, 83, 55
14[e]	Me	$Ni(ClO_4)_2•6H_2O$[d]	**D**	91	28:5:41:26	88, 74, 51

[a]The reaction was carried out by adding a solution of diazo compound **1a** (0.5 mmol) over a period of 3 h to a solution of oxazolidinone **S1a** or **S1b** (1.0 mmol), and $Rh_2(OAc)_4$ (0.01 mmol) in CH_2Cl_2. [b]The ratio of *endo*-**S2**, *exo*-**S2**, *endo*-**S3**, and *exo*-**S3** was determined by ^1H NMR analysis. [c]The ee values of *endo*-**S2**, *endo*-**S3**, and *exo*-**S3** were determined by chiral-phase HPLC. [d]20 mol % of catalyst was used. [e]Addition of **1a** over a period of 6 h.

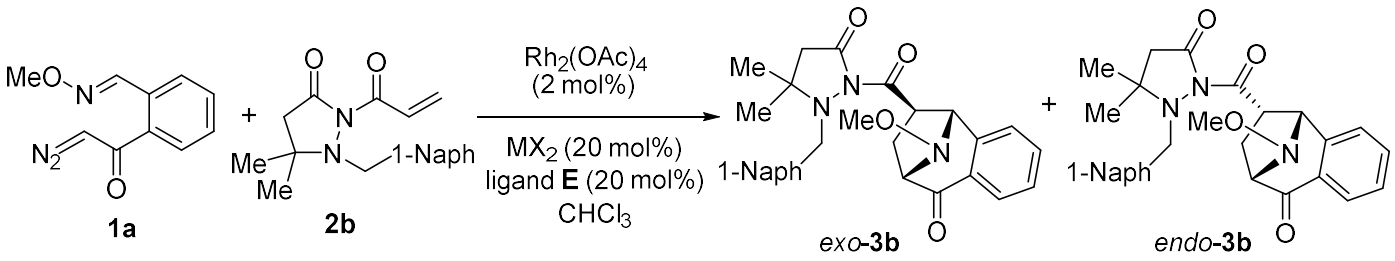


ligand **A**: G = H
ligand **B**: G = Me
ligand **C**: G = Ph
ligand **D**: G = 3,5-xylyl

Optimization of conditions for asymmetric cycloadditions using *O*-methyloxime 1a

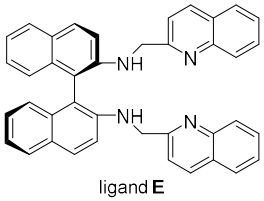
Preparation of the chiral Cu(II) catalyst and the cycloaddition under oxygen atmosphere showed satisfactory results in terms of reproducibility.

Table S2. Optimization of conditions for the reaction of *O*-methyloxime **1a** with pyrazolidinone **2b**[a]



Entry	Metal salt (mol%)	Atmosphere	Temp (°C)	Yield (%)	*endo*:*exo*[b]	Ee (%)[c]
1	$Cu(OTf)_2$ (20)	Argon	26	47 - 91	68:32 - >99:1	3 - 99
2	$Cu(OTf)_2$ (30)	Argon	26	73 - 80	69:31 - 95:5	65 - 93
3	$Cu(OTf)_2$ (30)	Air	26	93	>99:1	97
4	$Cu(OTf)_2$ (20)	Air	26	76 - 98	96:4 - >99:1	93 - 97
5	$Cu(OTf)_2$ (20)	Air	35	98	>99:1	97
6	$Cu(OTf)_2$ (20)	Oxygen	35	95 - 97	>99:1	97 - 99
7	$CuPF_4(MeCN)_4$ (20)	Oxygen	35	64	47:53	-22
8	$Zn(OTf)_2$ (20)	Argon	35	87	90:10	89
9	$Zn(ClO_4)_2 \cdot 6H_2O$ (20)	Argon	35	86	98:2	91

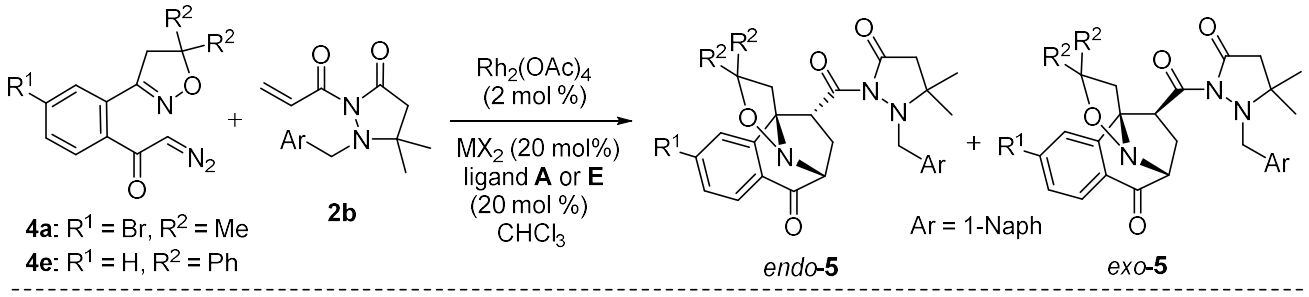
[a]The reaction was carried out by adding a solution of diazo compound **1a** over a period of 3 h to a solution of pyrazolidinone **2b** (1.0 mmol), $Rh_2(OAc)_4$ (0.01 mmol), and a chiral Lewis acid prepared from MX_2 (0.1 mmol) and ligand **E** (0.1 mmol) in $CHCl_3$. [b]Determined by ^1H NMR analysis. [c]The ee values for *exo*-**3b** was determined by chiral-phase HPLC after hydrogenation.

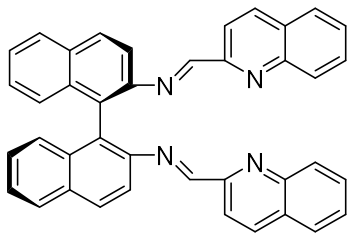


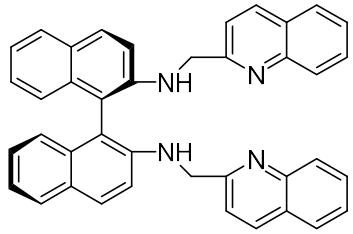
ligand **E**

Optimization of chiral Lewis acids for asymmetric cycloadditions using diazo isoxazolines 4

Table S3. Reactions of diazo isoxazolines **4** with pyrazolidinone **2b** in the presence of several chiral Lewis acids[a]




ligand **A**


ligand **E**

Entry	**4**	MX_2	Ligand	Temp (°C)	Yield (%)	*endo*:*exo*[b]	Ee (%)[c]
1	**4a**	$Ni(BF_4)_2•6H_2O$	**A**	50	67	>99:1	96
2	**4a**	$Cu(OTf)_2$	**E**	26	28	>99:1	0
3	**4e**	$Ni(ClO_4)_2•6H_2O$	**A**	26	40	>99:1	86
4	**4e**	$Ni(ClO_4)_2•6H_2O$	**A**	50	57	>99:1	86
5	**4e**	$Ni(BF_4)_2•6H_2O$	**A**	50	60	>99:1	89
6	**4e**	$Co(ClO_4)_2•6H_2O$	**A**	50	42	>99:1	69
7	**4e**	$Co(BF_4)_2•6H_2O$	**A**	50	42	>99:1	35
8	**4e**	$Cu(ClO_4)_2•6H_2O$	**E**	26	21	>99:1	1

[a]The reaction was carried out by adding a solution of diazo compound **4a** or **4e** (0.5 mmol) over a period of 3 h to a solution of pyrazolidinone **2b** (1.0 mmol), $Rh_2(OAc)_4$ (0.01 mmol), and a chiral Lewis acid prepared from MX_2 (0.1 mmol) and ligand **A** or **E** (0.1 mmol) in $CHCl_3$. [b]Determined by ^1H NMR analysis. [c]The ee values for *endo*-**5** were determined by chiral-phase HPLC.

X-ray crystallographic analysis

To determine the absolute configuration of cycloadduct *exo*-**3b**, X-ray analysis was carried out using the single crystal of *p*-bromobenzoyl ester **7**, which was obtained by the hydrogenation followed by esterification of *exo*-**3b**. The crystal was grown in CH_2Cl_2 under hexane atmosphere (Figure S1).

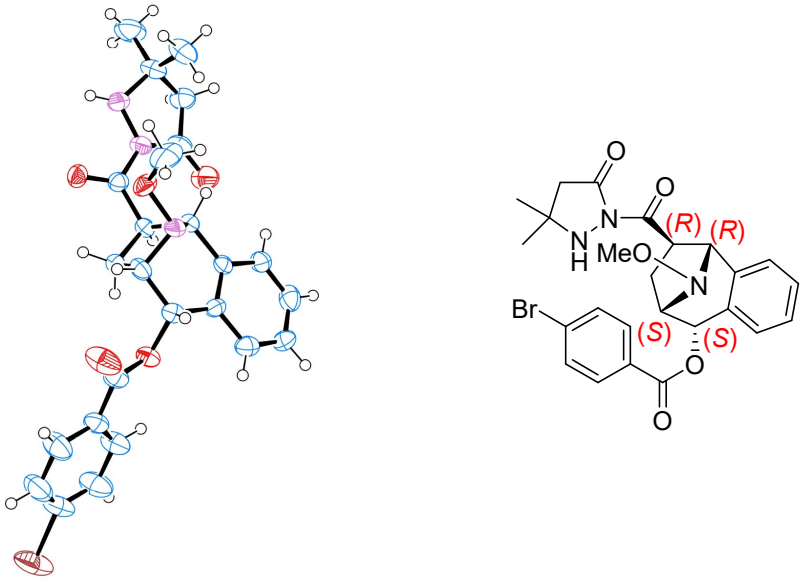


Figure S1. ORTEP drawing (50% probability ellipsoids) of **7**.

Determination of the absolute configuration of alcohol S4 derived from *endo*-5f

To determine the absolute configuration of cycloadduct *endo*-**5f**, modified Mosher's method[7] was used for secondly alcohol **S4**. The corresponding (*S*)-MTPA-**S4** and (*R*)-MTPA-**S4** were prepared using (*R*)-MTPACl and (*S*)-MTPACl in the normal procedure, respectively.[8] Chemical shifts of H_a – H_e (^{1}H NMR) for (*S*)-MTPA-**S4** and (*R*)-MTPA-**S4**, and $\Delta\delta^{SR} = \delta^S - \delta^R$ were shown in Figure S2. Chemical shifts of C_a – C_d (^{13}C NMR) for (*S*)-MTPA-**S4** and (*R*)-MTPA-**S4**, and $\Delta\delta^{SR} = \delta^S - \delta^R$ were shown in Figure S3. The sign of $\Delta\delta^{SR}$ values indicates that secondly alcohol **S4** possesses (*R*)-configuration.

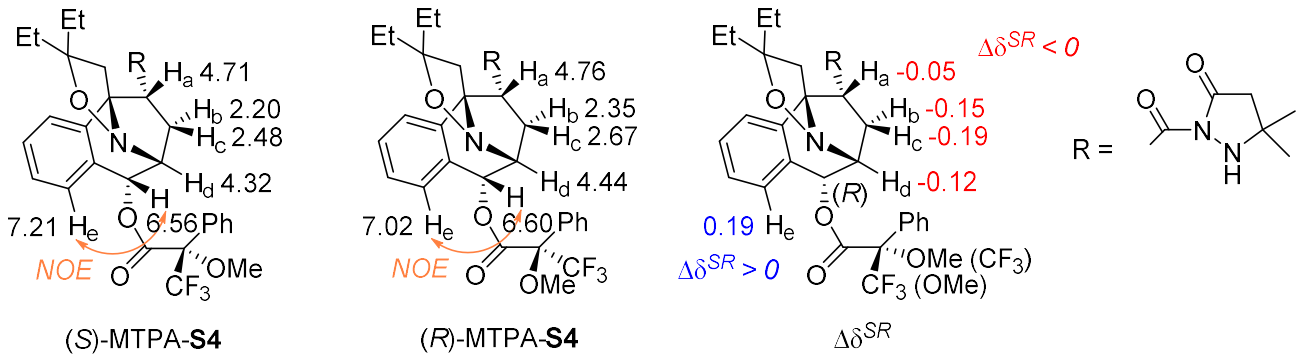


Figure S2. $\Delta\delta^{SR}$ values from ^{1}H NMR spectra of different MTPA esters.

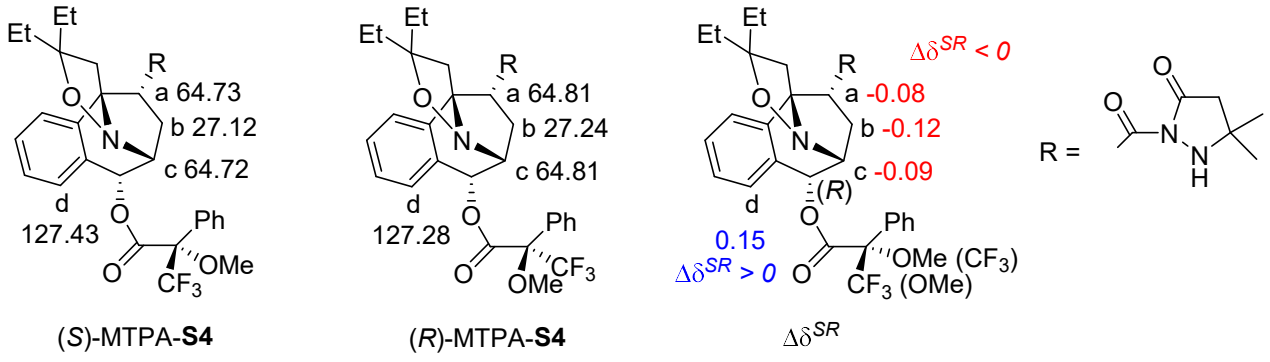


Figure S3. $\Delta\delta^{SR}$ values from ^{13}C NMR spectra of different MTPA esters.

^{19}F NMR of (*S*)-MTPA-S4 and (*R*)-MTPA-S4

The chemical shift of the CF_3 (^{19}F NMR) group on (*S*)-MTPA-**S4** was observed at a higher field than that of (*R*)-MTPA-**S4** by 0.25 ppm (Figure S4). (*R*)-MTPA-**S4** probably exists in a conformation in which the methine proton, the carbonyl, and the CF_3 groups are situated in the same plane where the phenyl ring is opposite to the least bulky substituent of the corresponding alcohol.[7] This observation indicates that the CF_3 group of (*S*)-MTPA-**S4** would be shielded with the carbonyl group of MTPA ester.

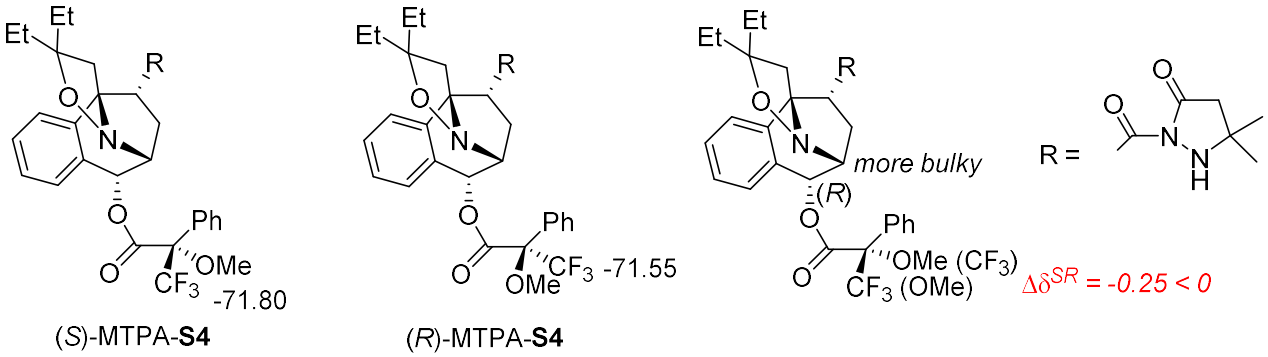
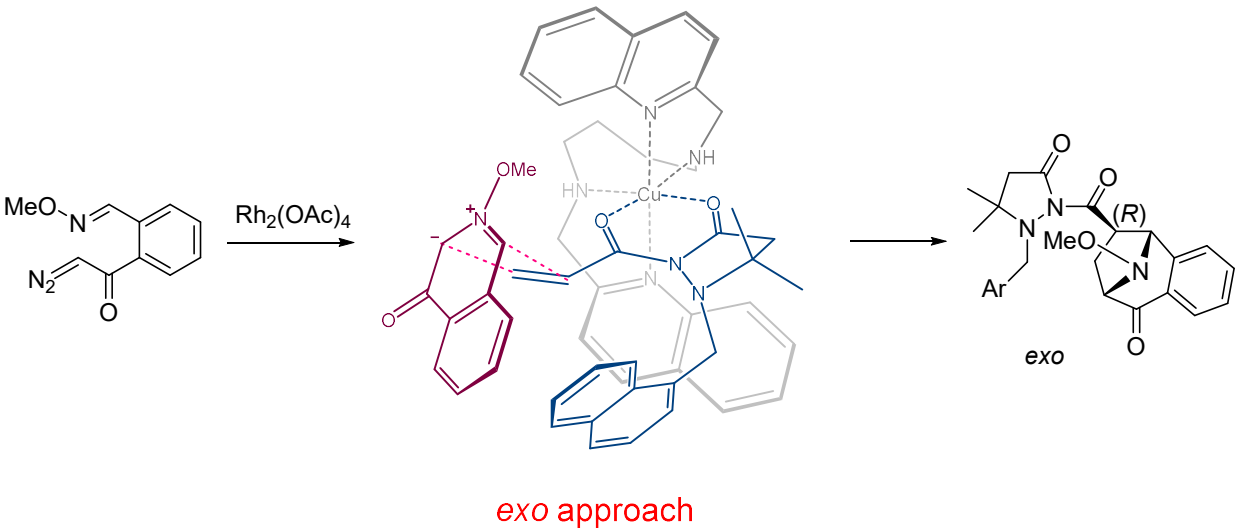
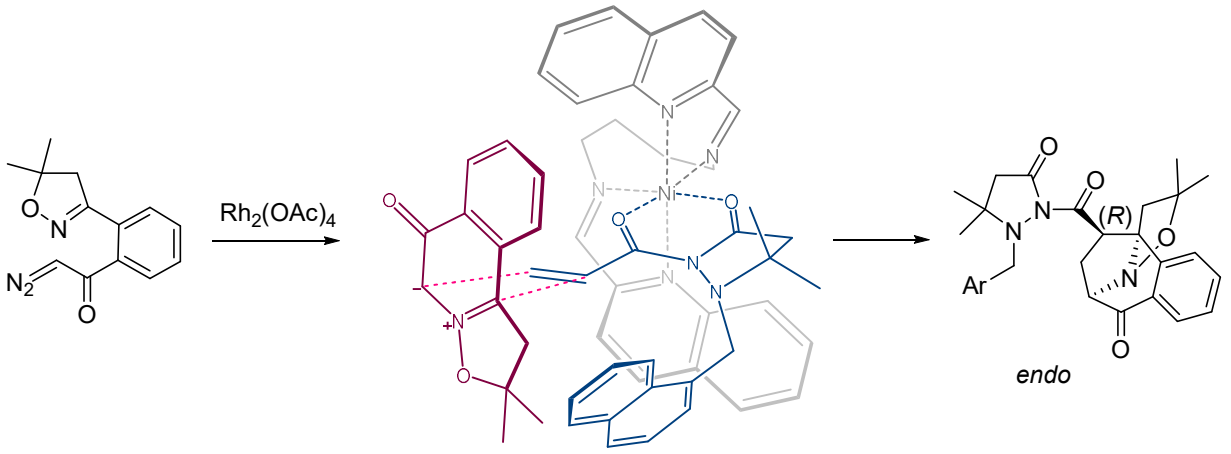


Figure S4. ^{19}F NMR spectra of different MTPA esters.

Proposed transition state models for the cyclic azomethine ylides



exo approach



endo approach

Scheme S1. Proposed *exo* and *endo* approach for the cyclic azomethine ylides using Cu(II)-ligand **E** and Ni(II)-ligand **A** complexes

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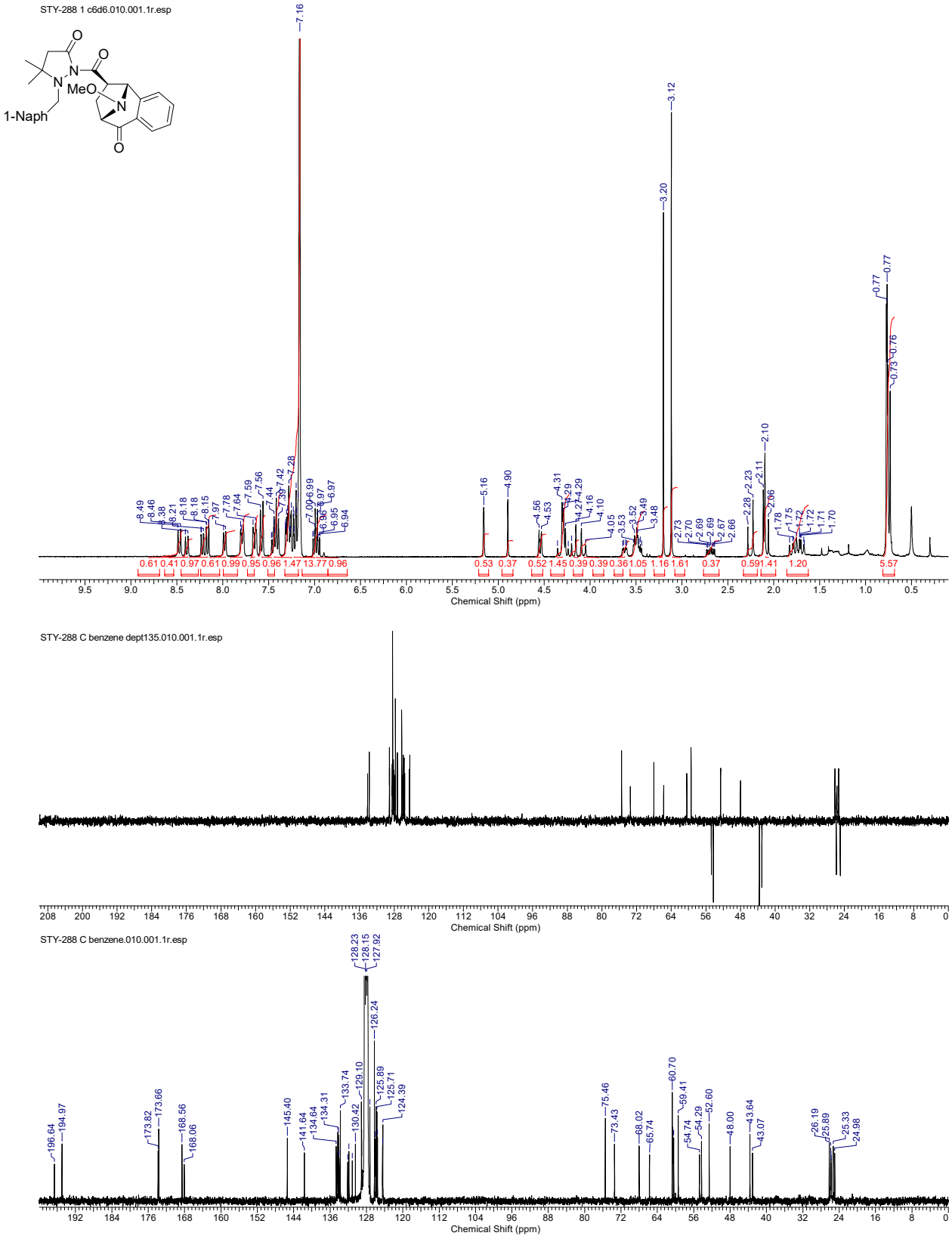
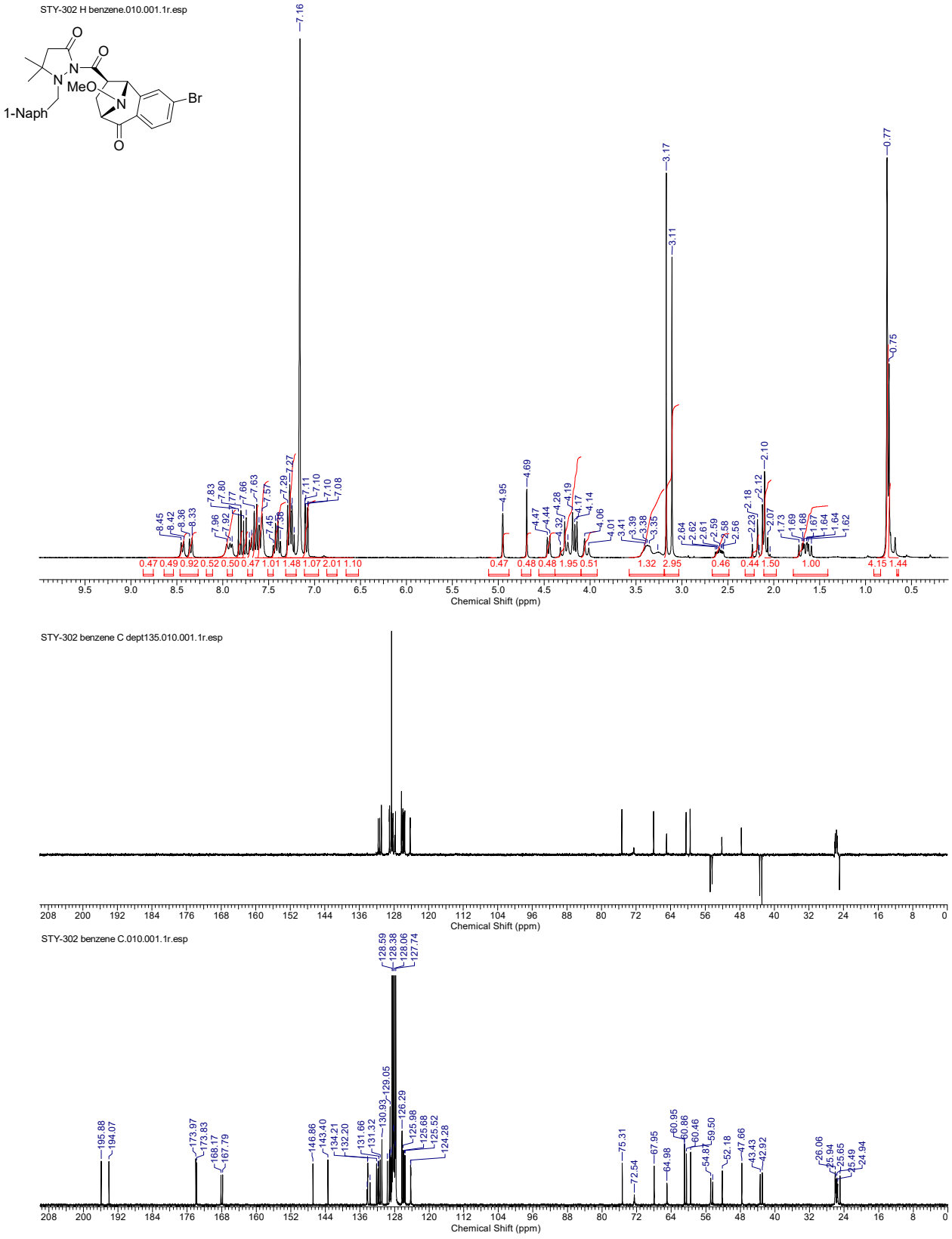
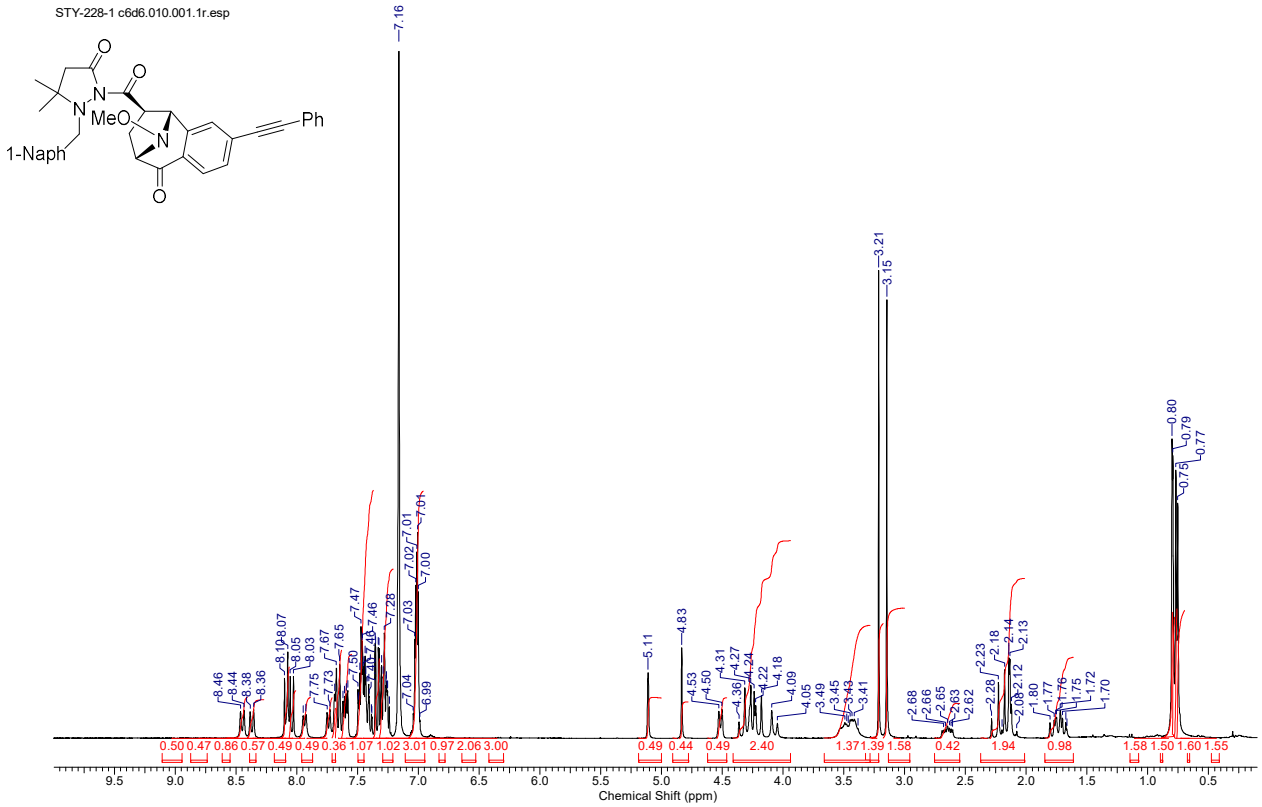
^{1}H and ^{13}C NMR of *exo*-**3b**

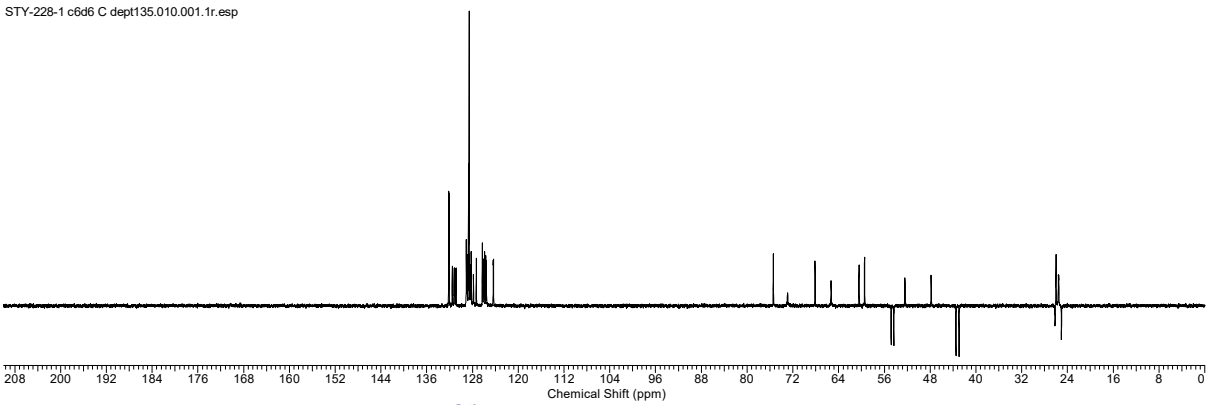


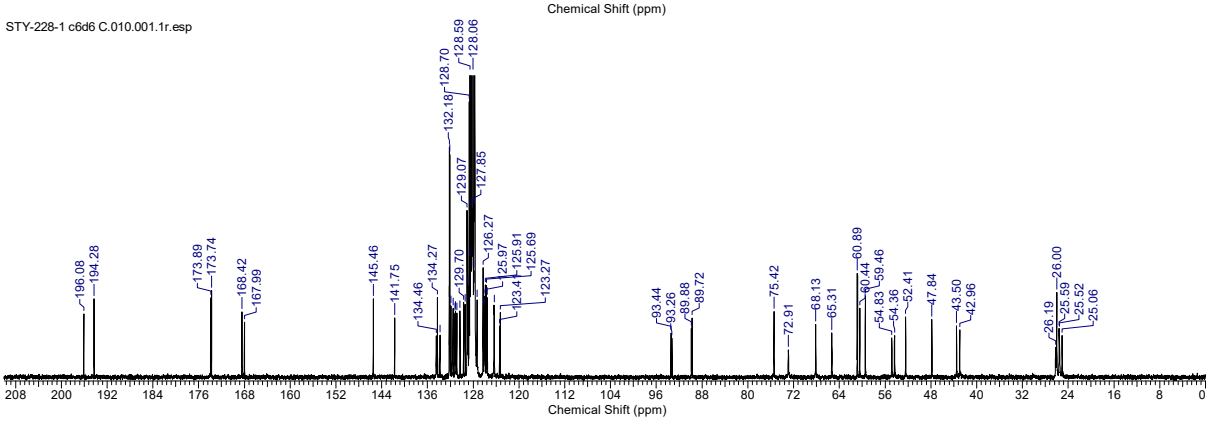
^{1}H and ^{13}C NMR of *exo*-**3c**



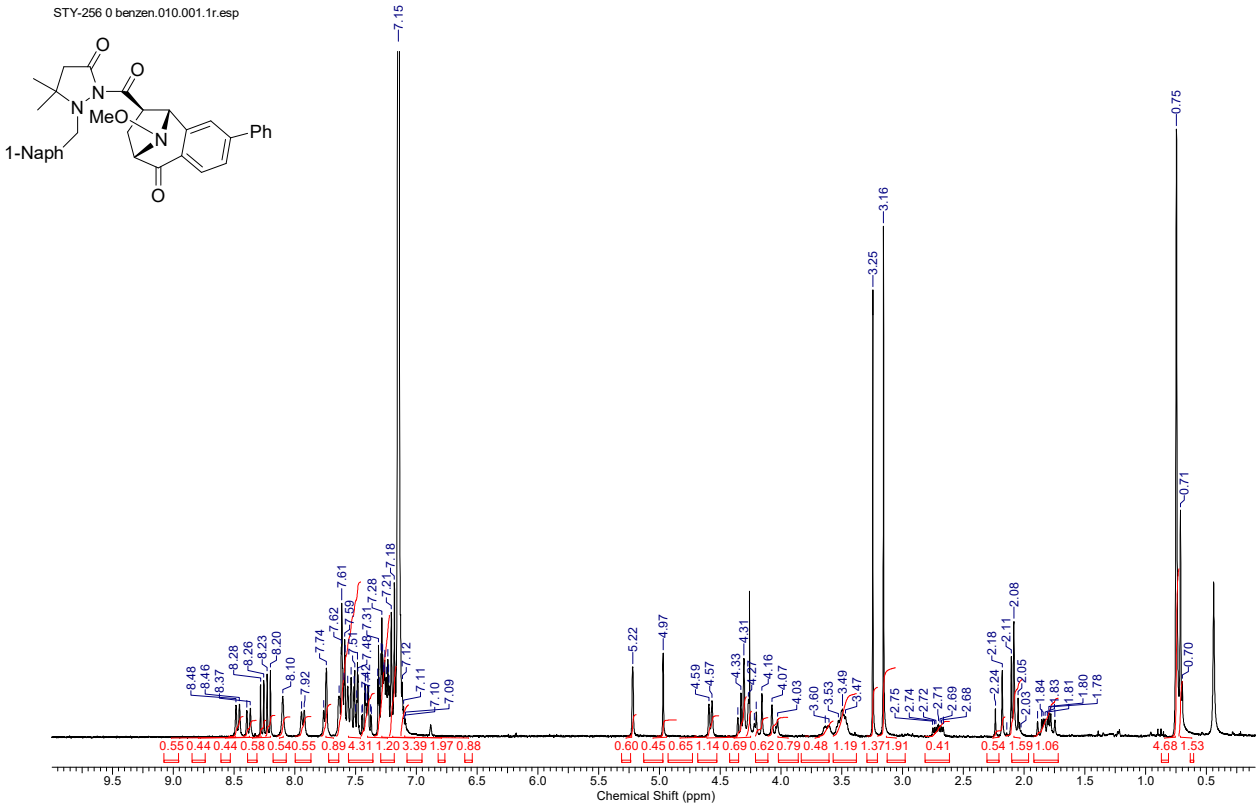
^{1}H and ^{13}C NMR of *exo*-**3d**

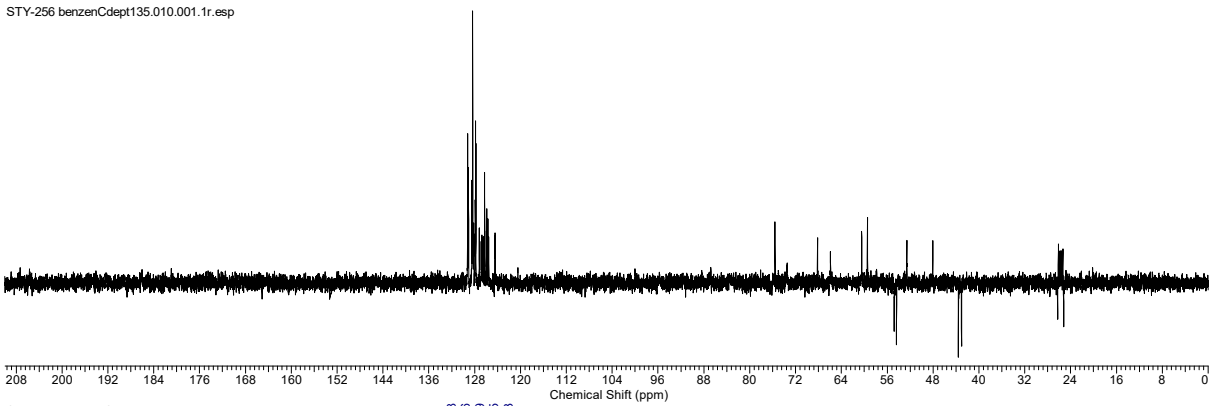


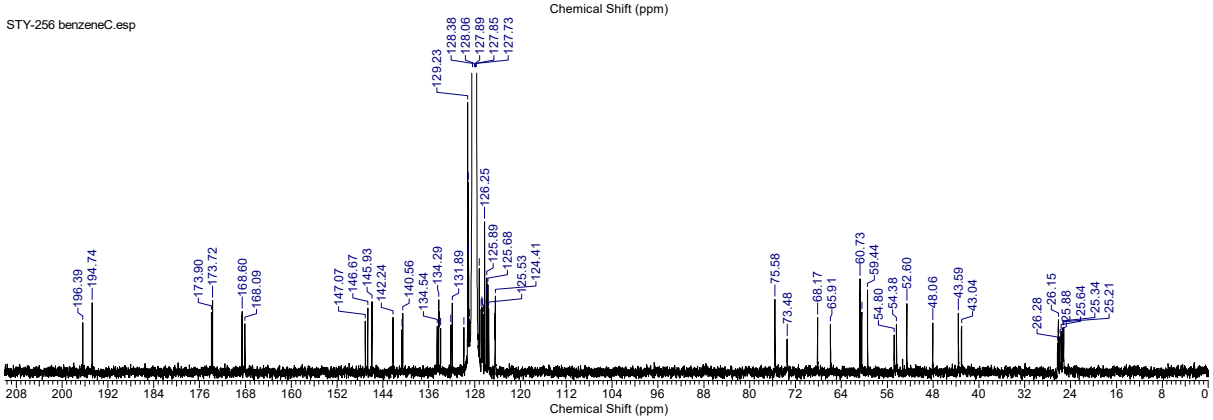




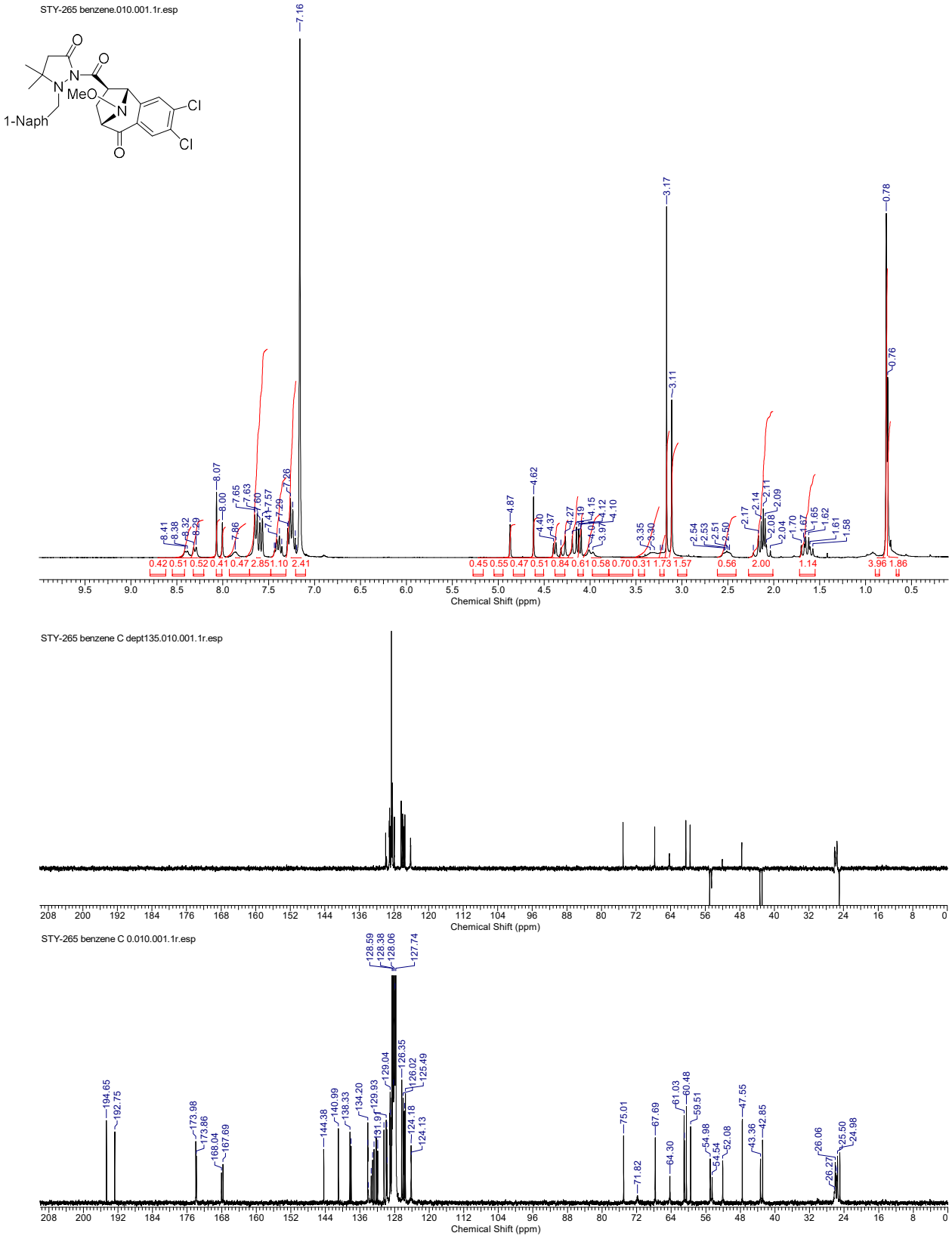
^{1}H and ^{13}C NMR of *exo*-**3e**



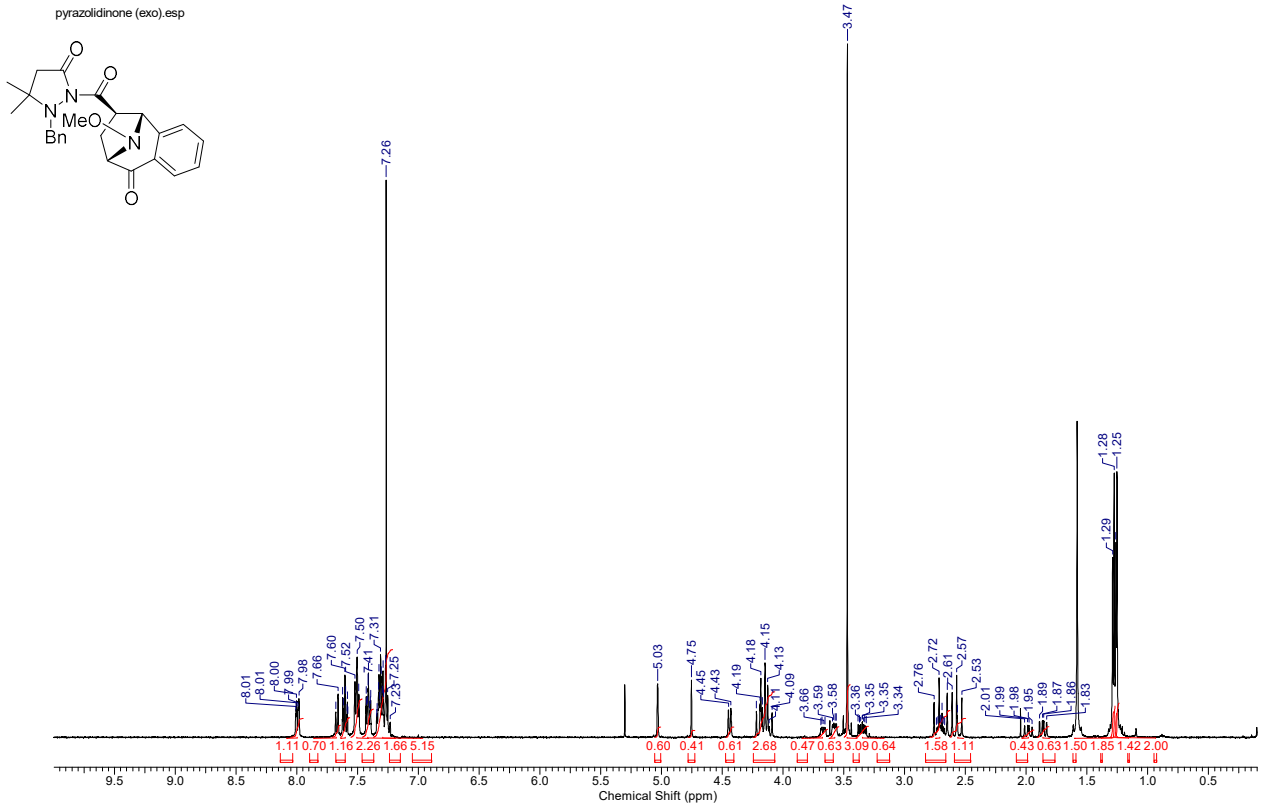


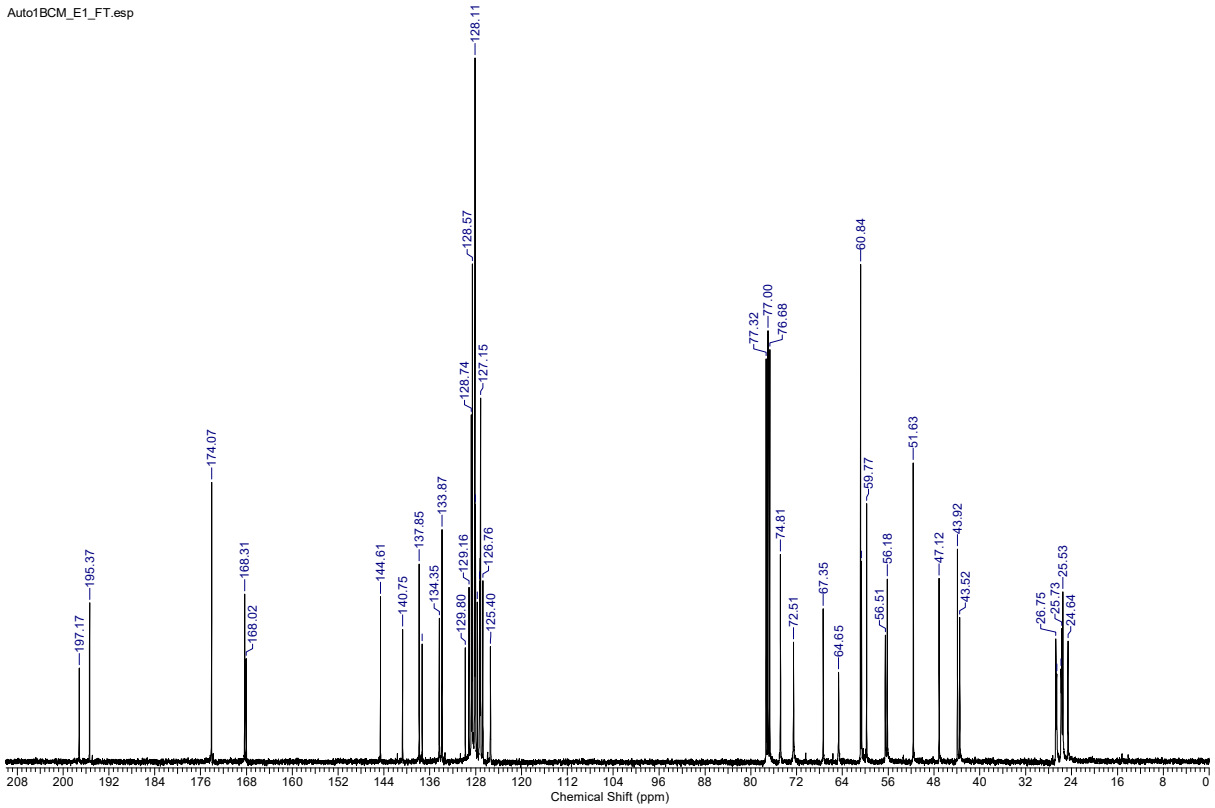


^{1}H and ^{13}C NMR of *exo*-**3f**

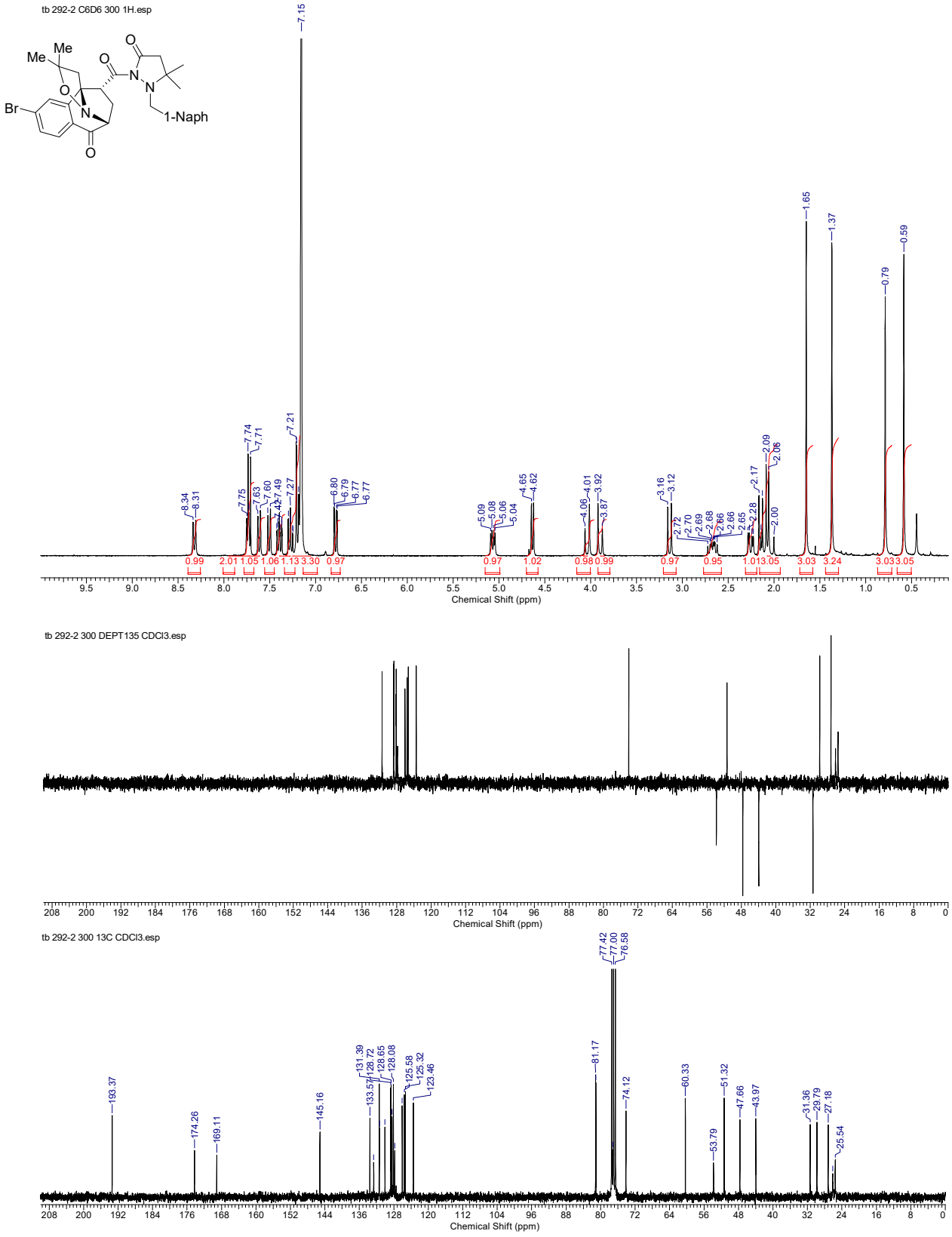


^{1}H and ^{13}C NMR of *exo*-**3a**

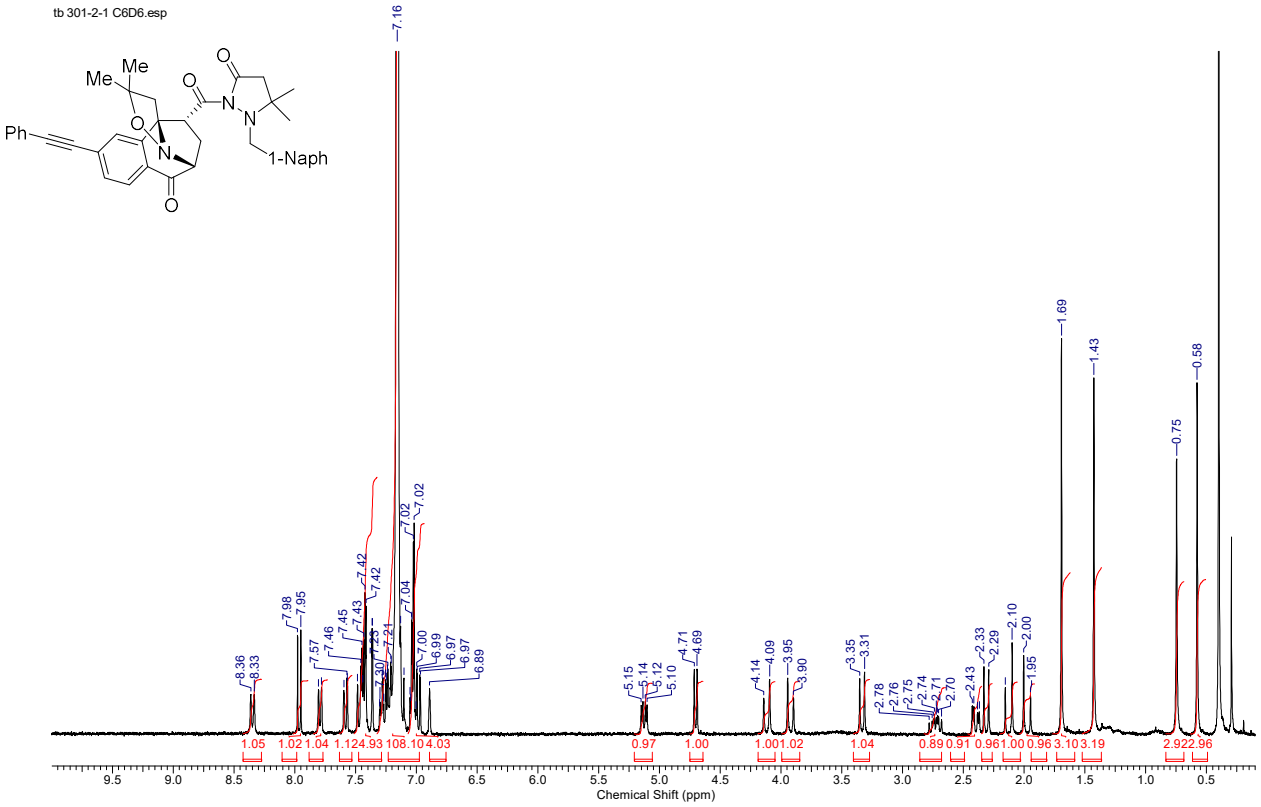


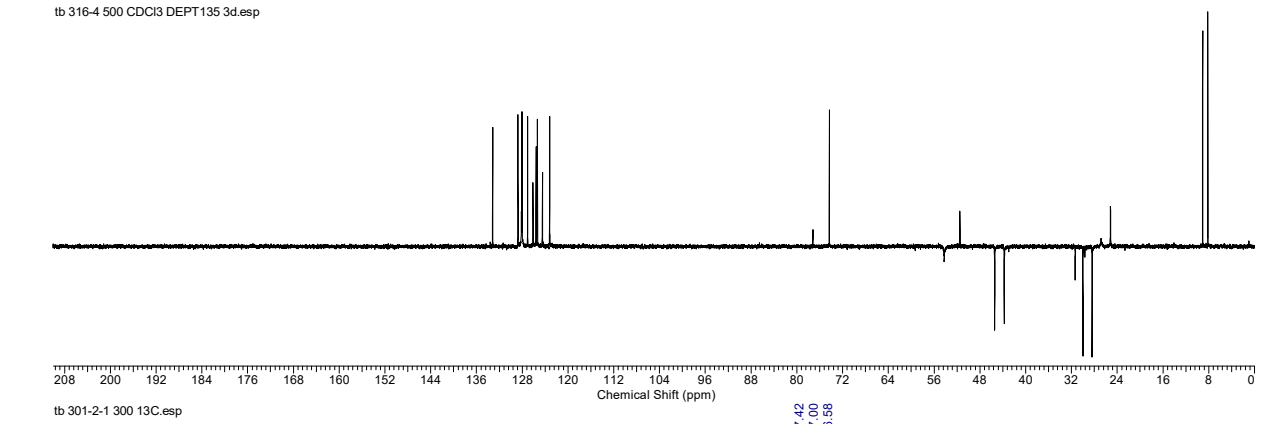


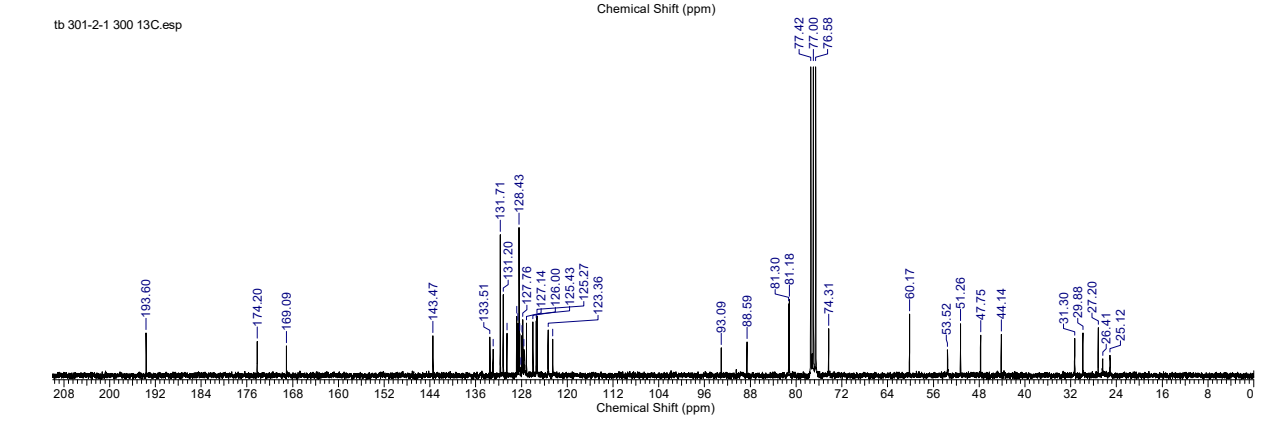
^{1}H and ^{13}C NMR of *endo*-**5a**



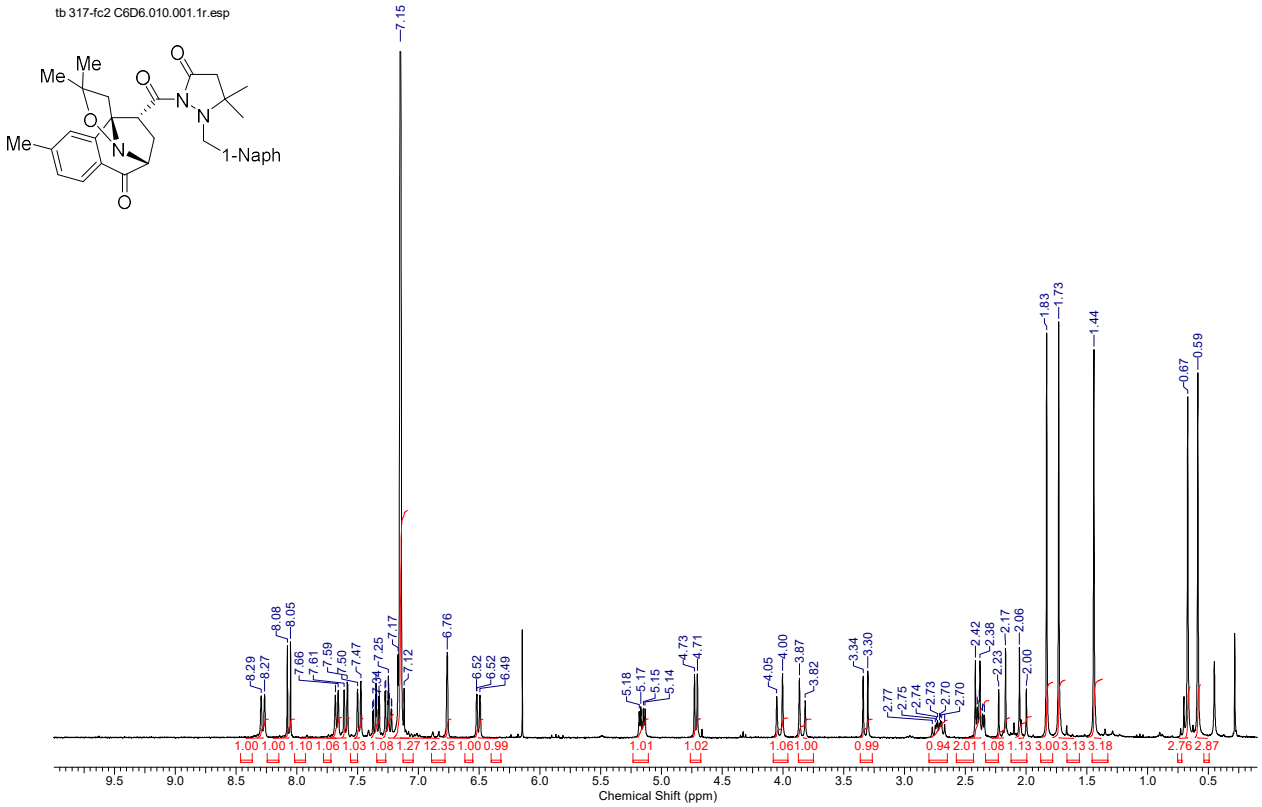
^{1}H and ^{13}C NMR of *endo*-**5b**

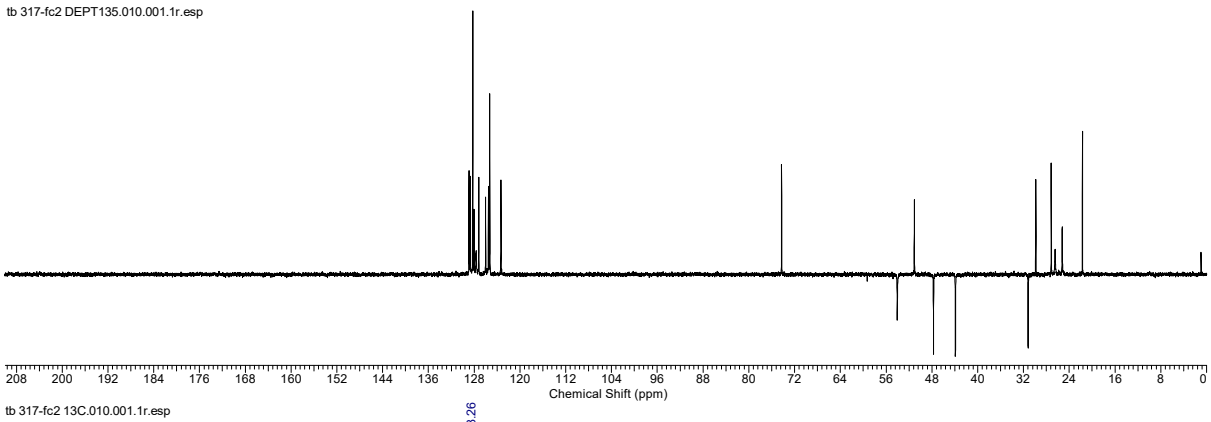


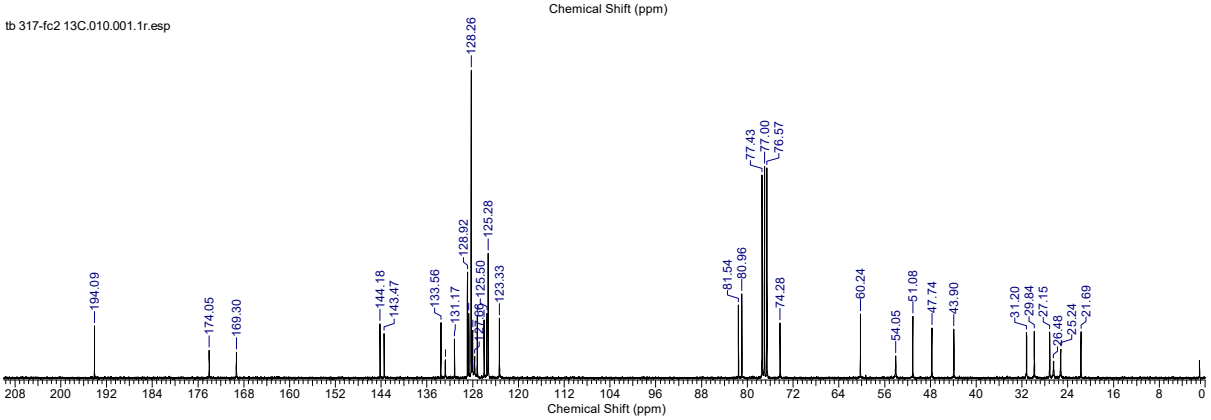




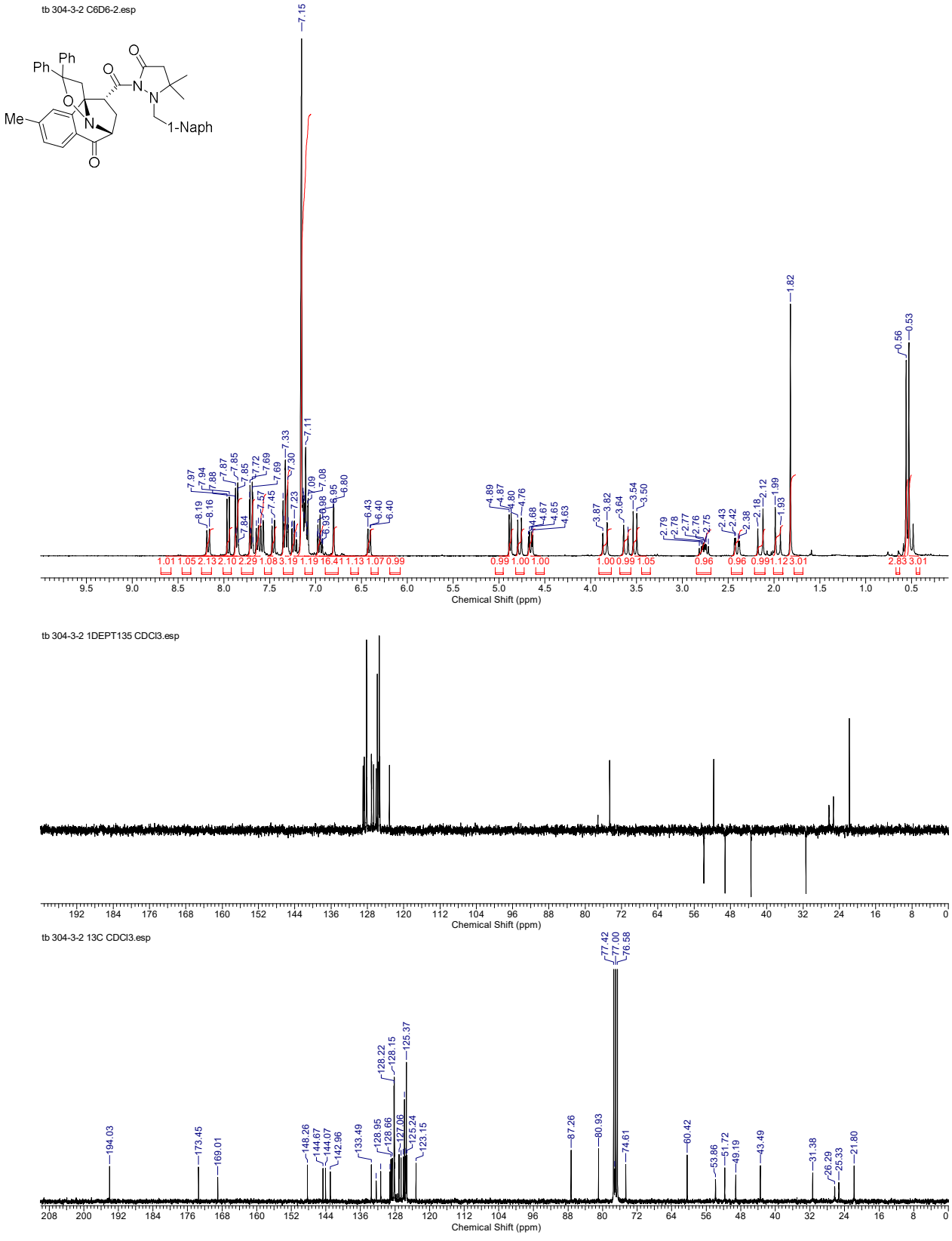
^{1}H and ^{13}C NMR of *endo*-**5c**



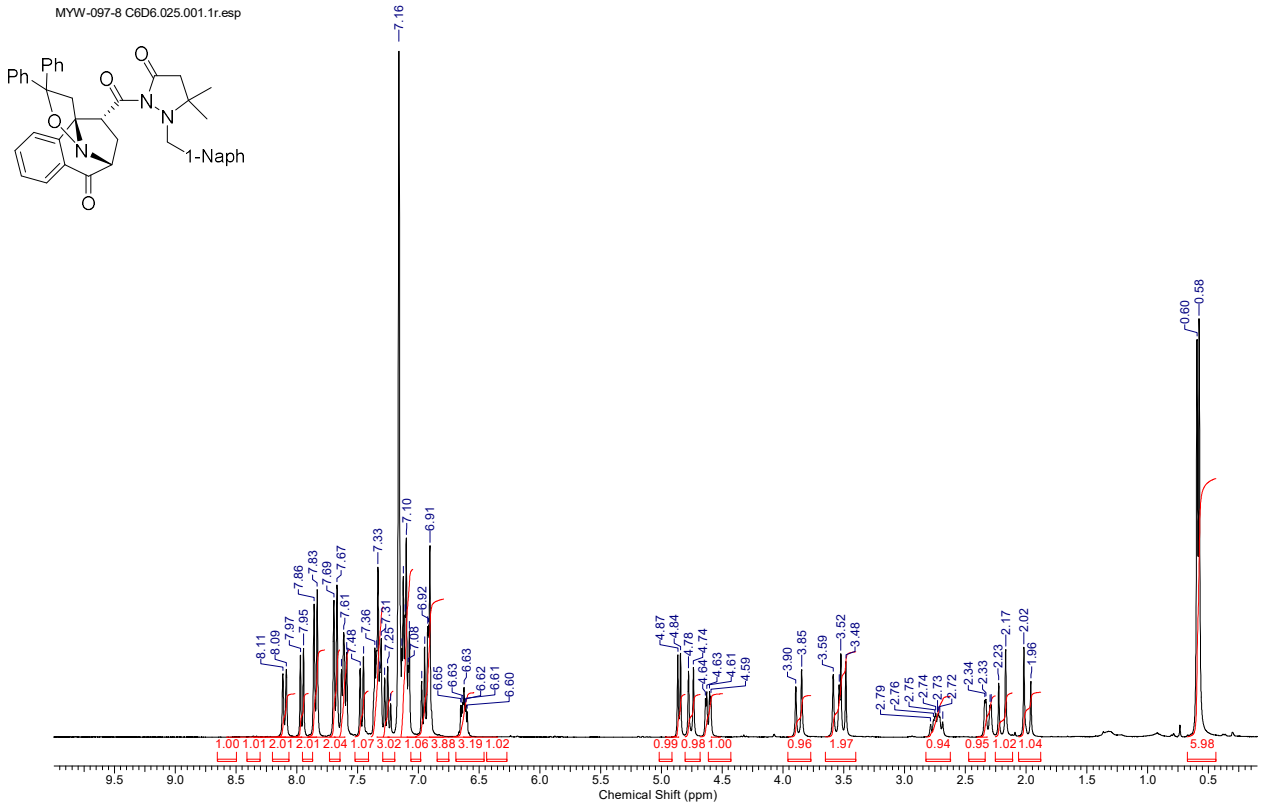


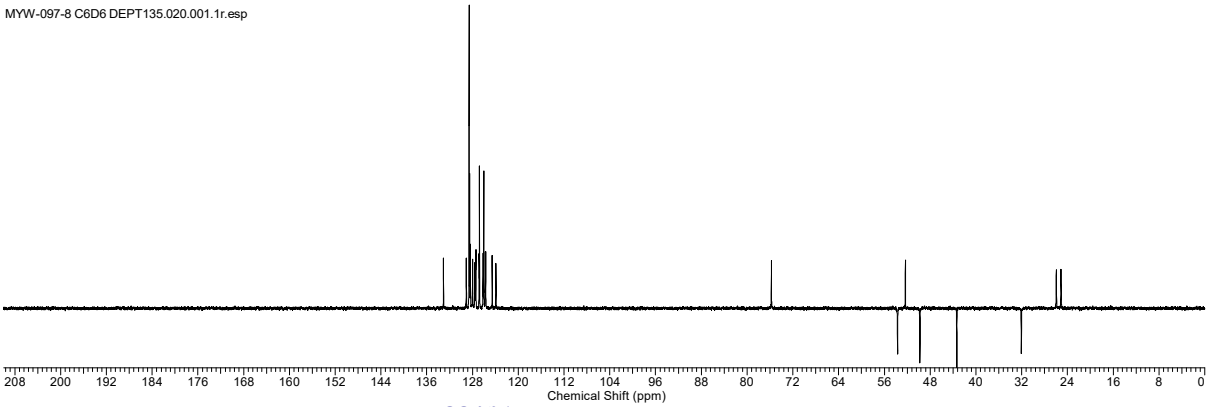


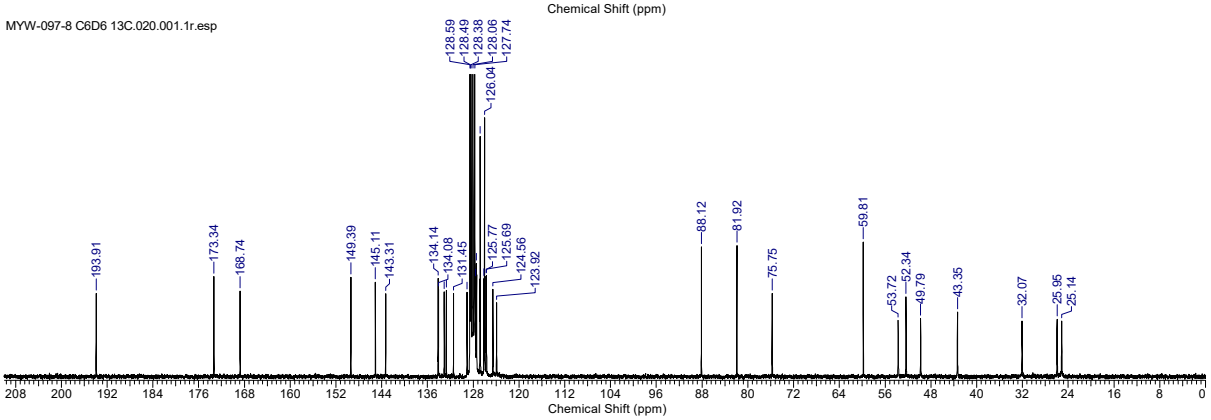
^{1}H and ^{13}C NMR of *endo*-**5d**



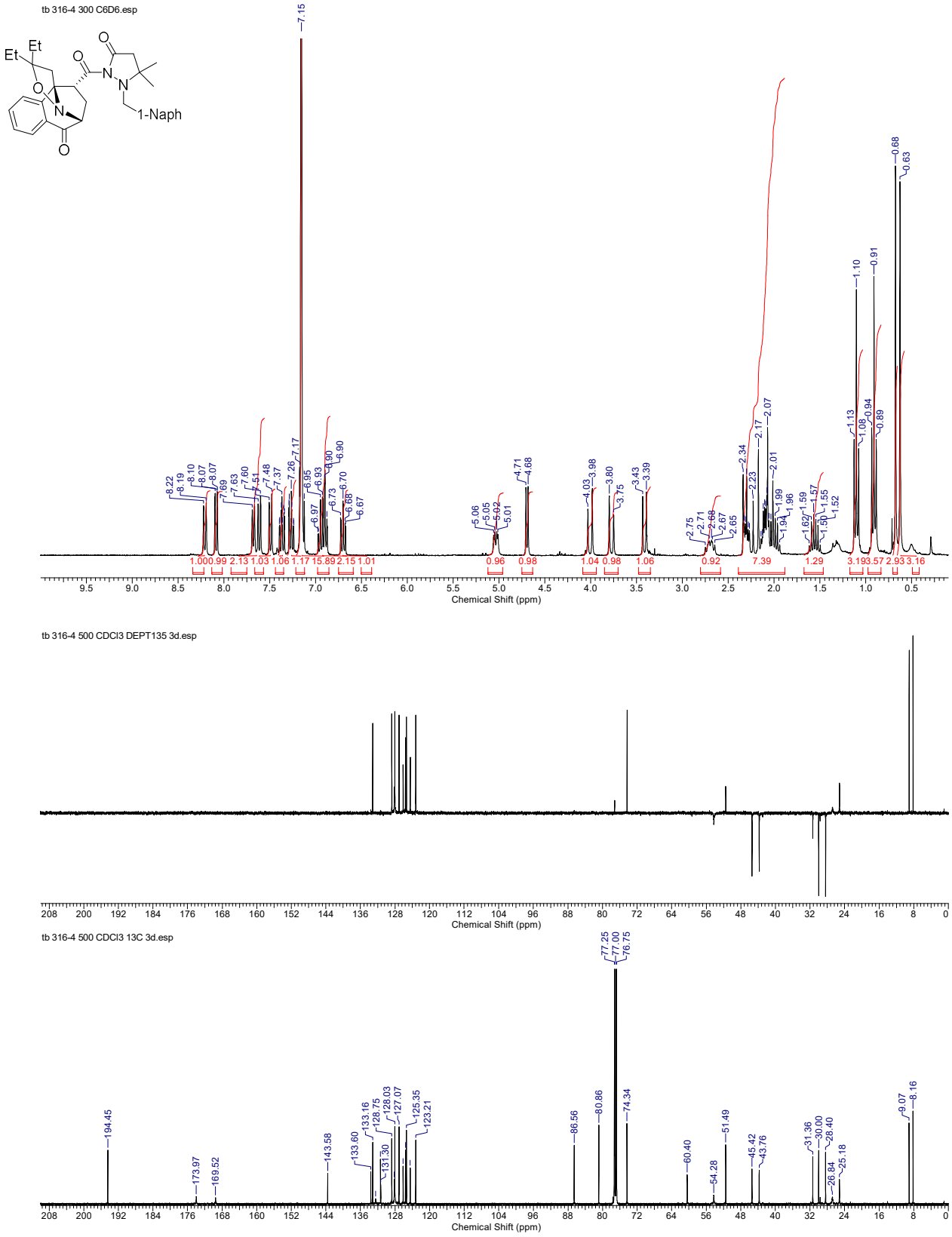
^{1}H and ^{13}C NMR of *endo*-**5e**



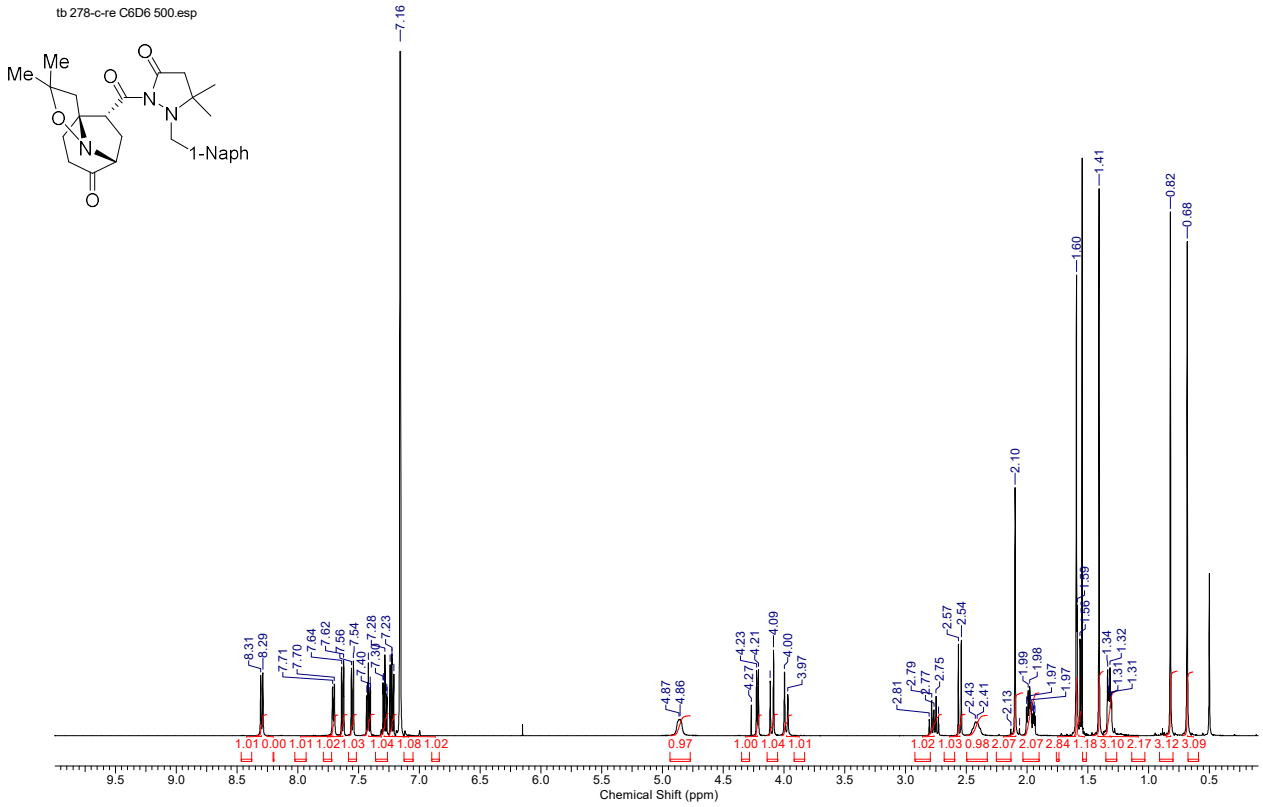


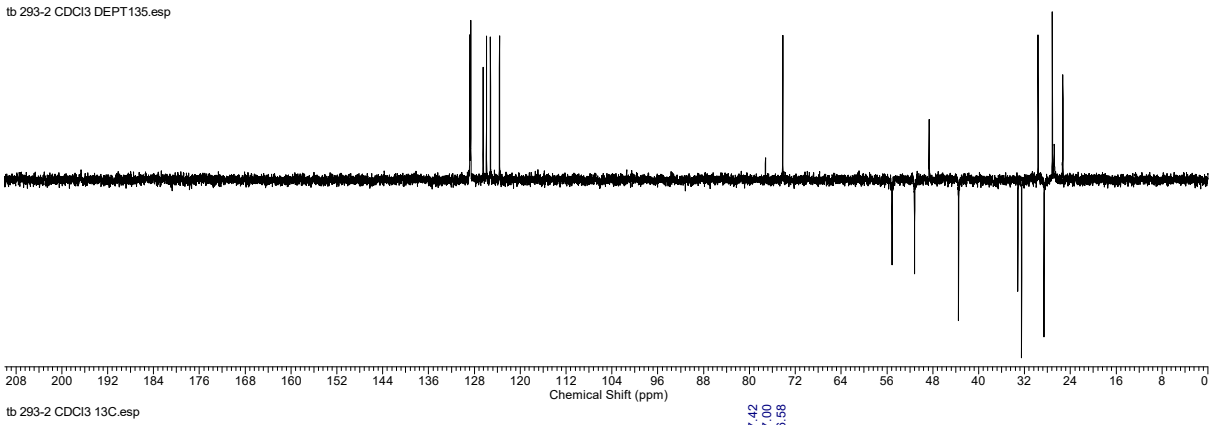


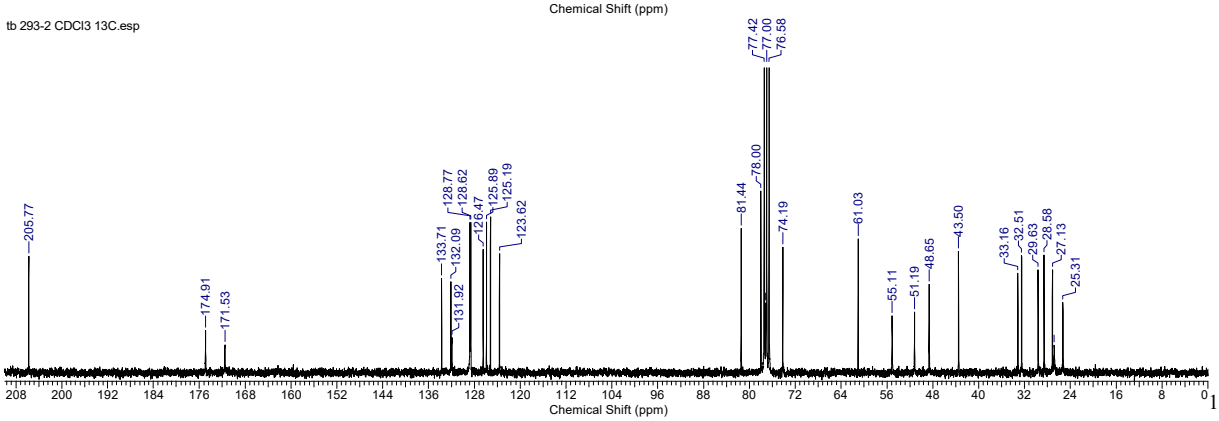
^{1}H and ^{13}C NMR of *endo*-**5f**



^{1}H and ^{13}C NMR of *endo*-**5g**

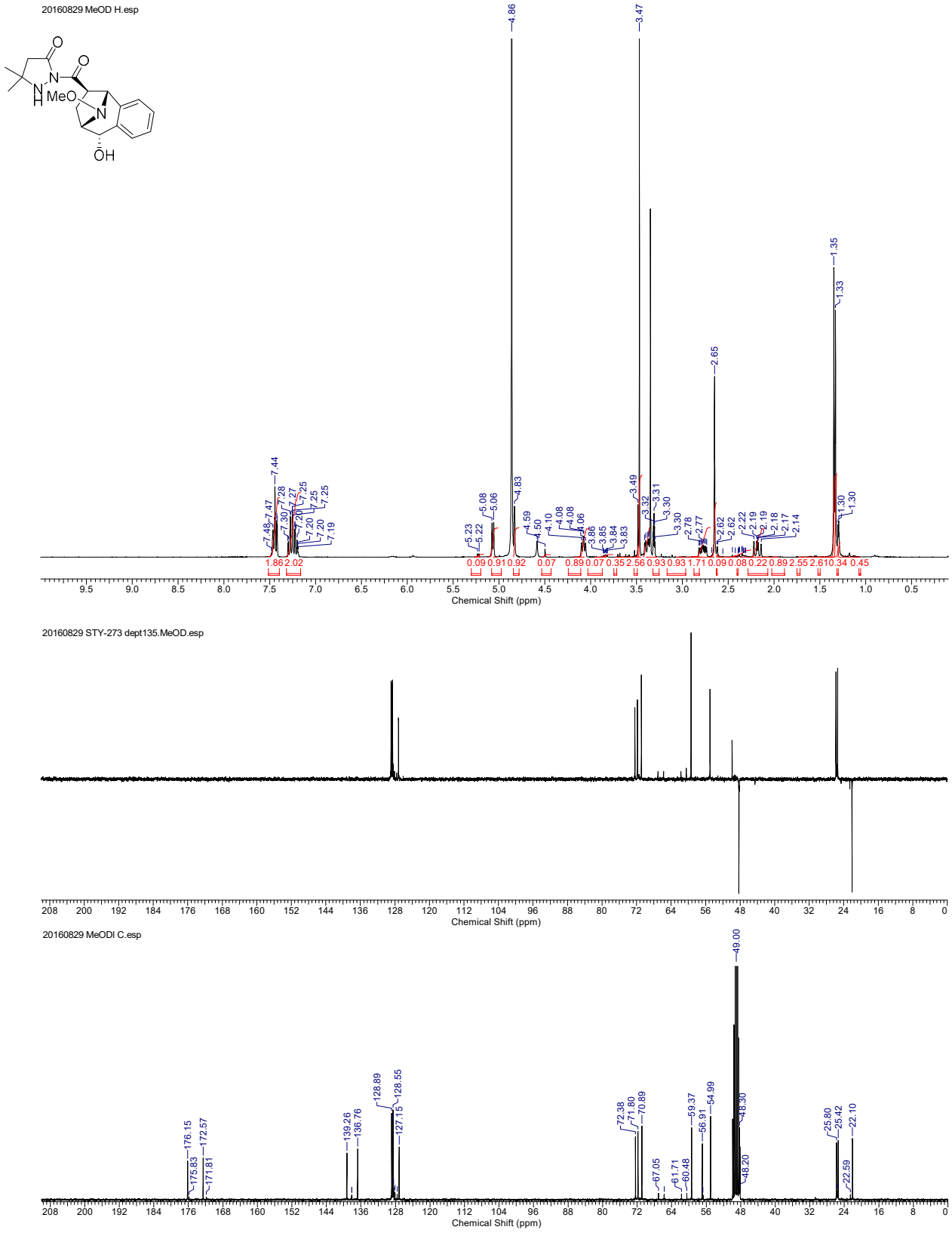




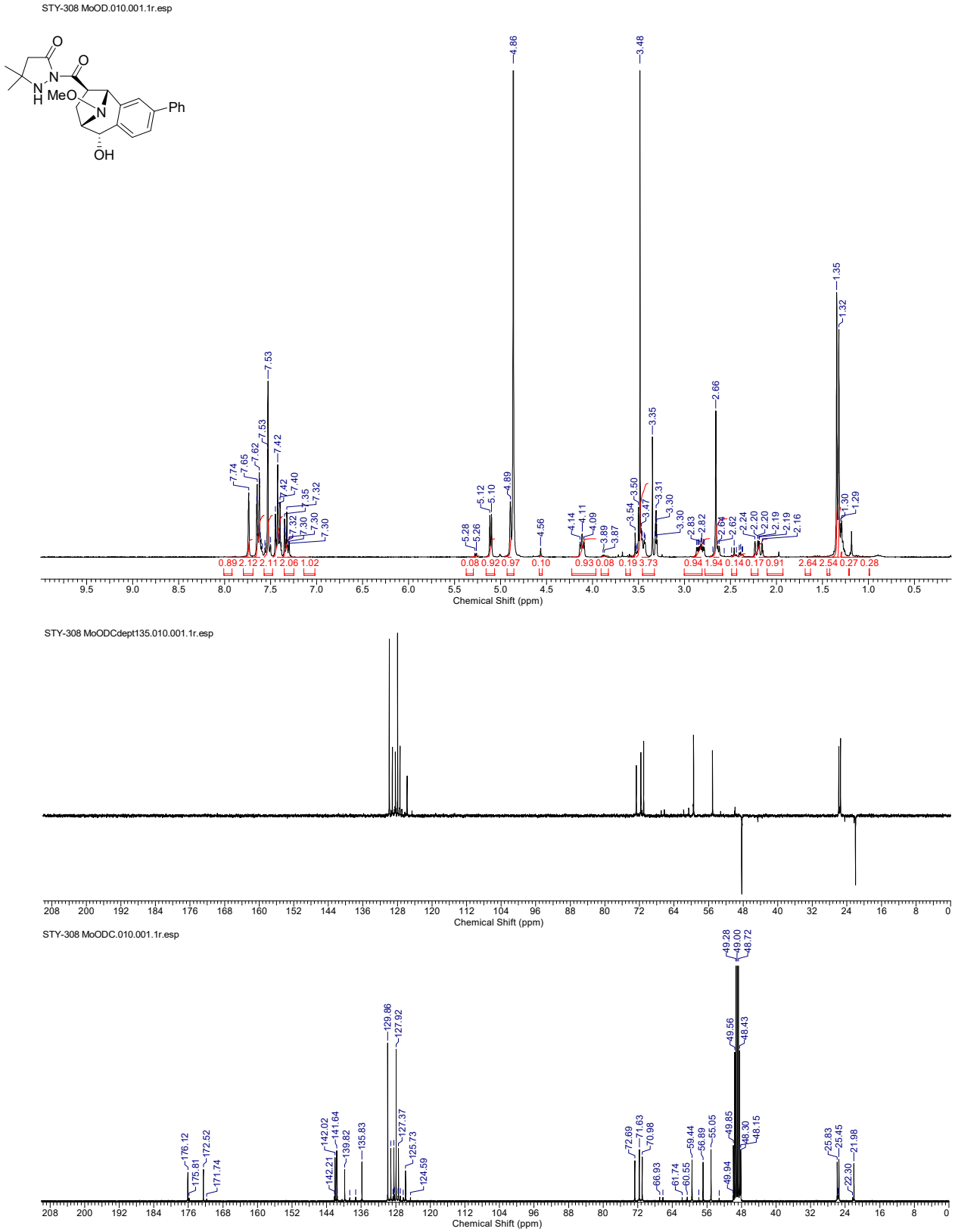


^{1}H and

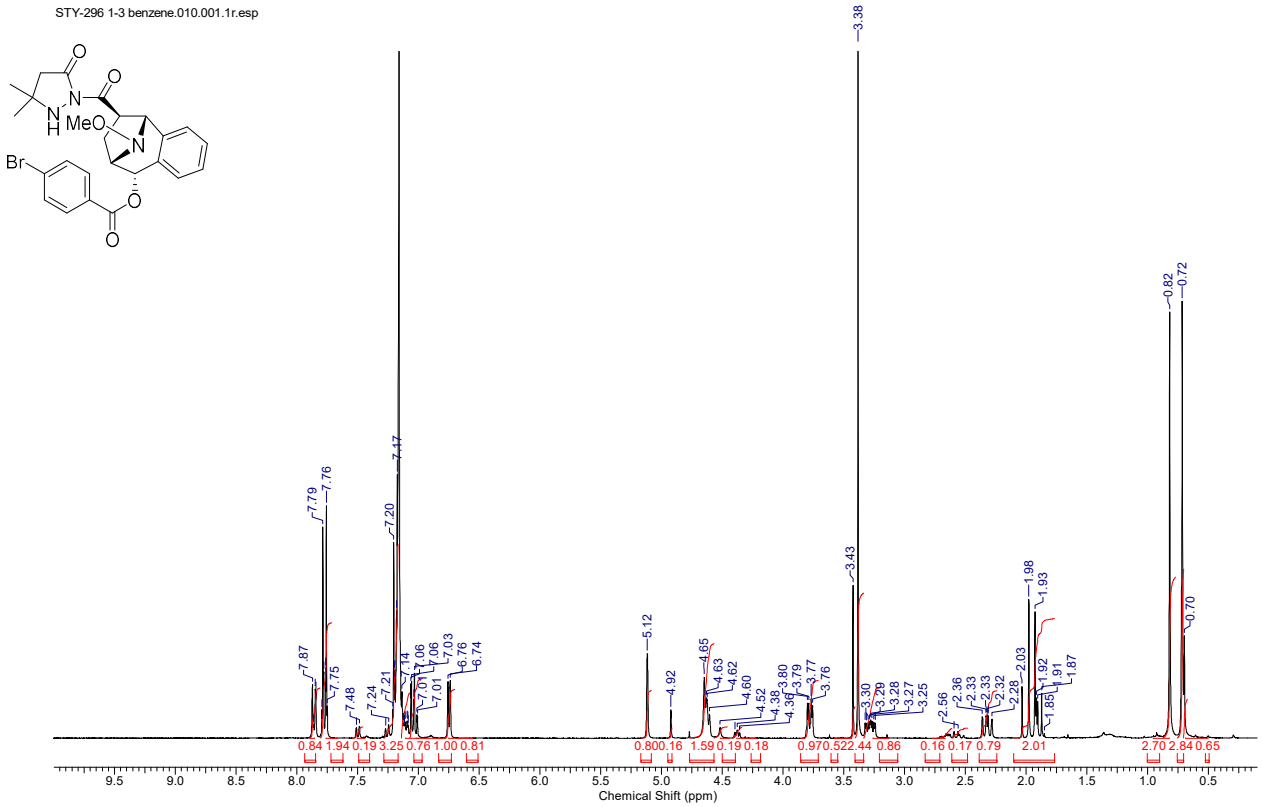
^{13}C NMR of **6**

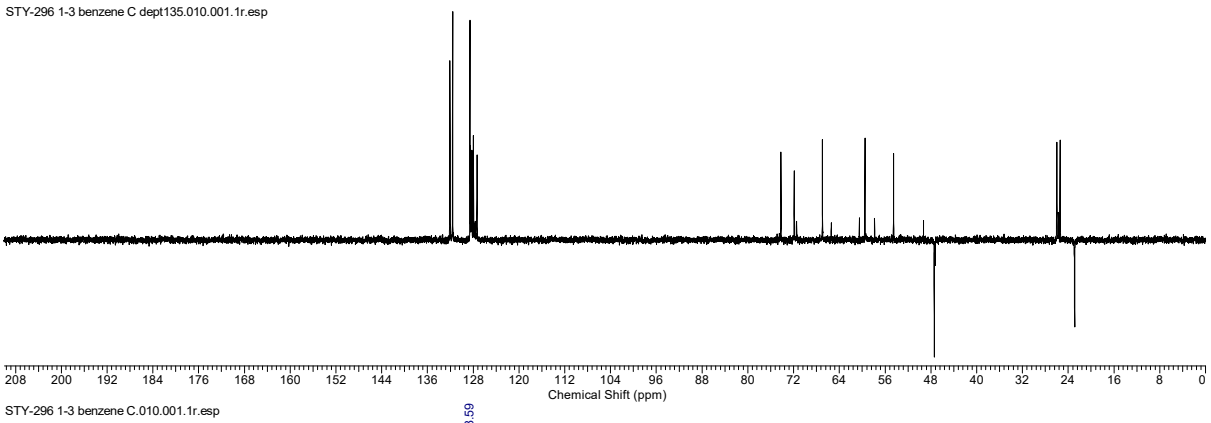

20160829 MeOD H.esp
20160829 STY-273 dept135.MeOD.esp
20160829 MeODl C.esp
Chemical Shift (ppm)

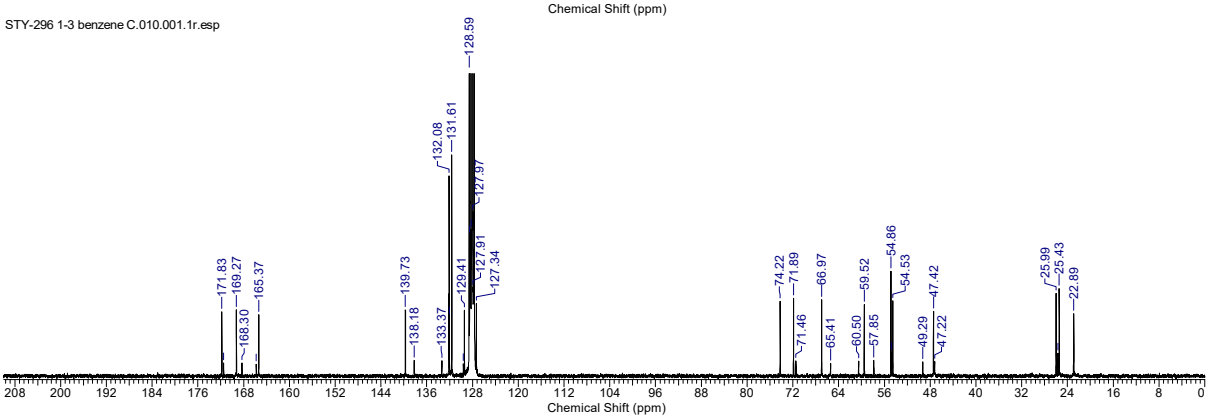
^{1}H and ^{13}C NMR of the alcohol obtained from *exo*-**3e**



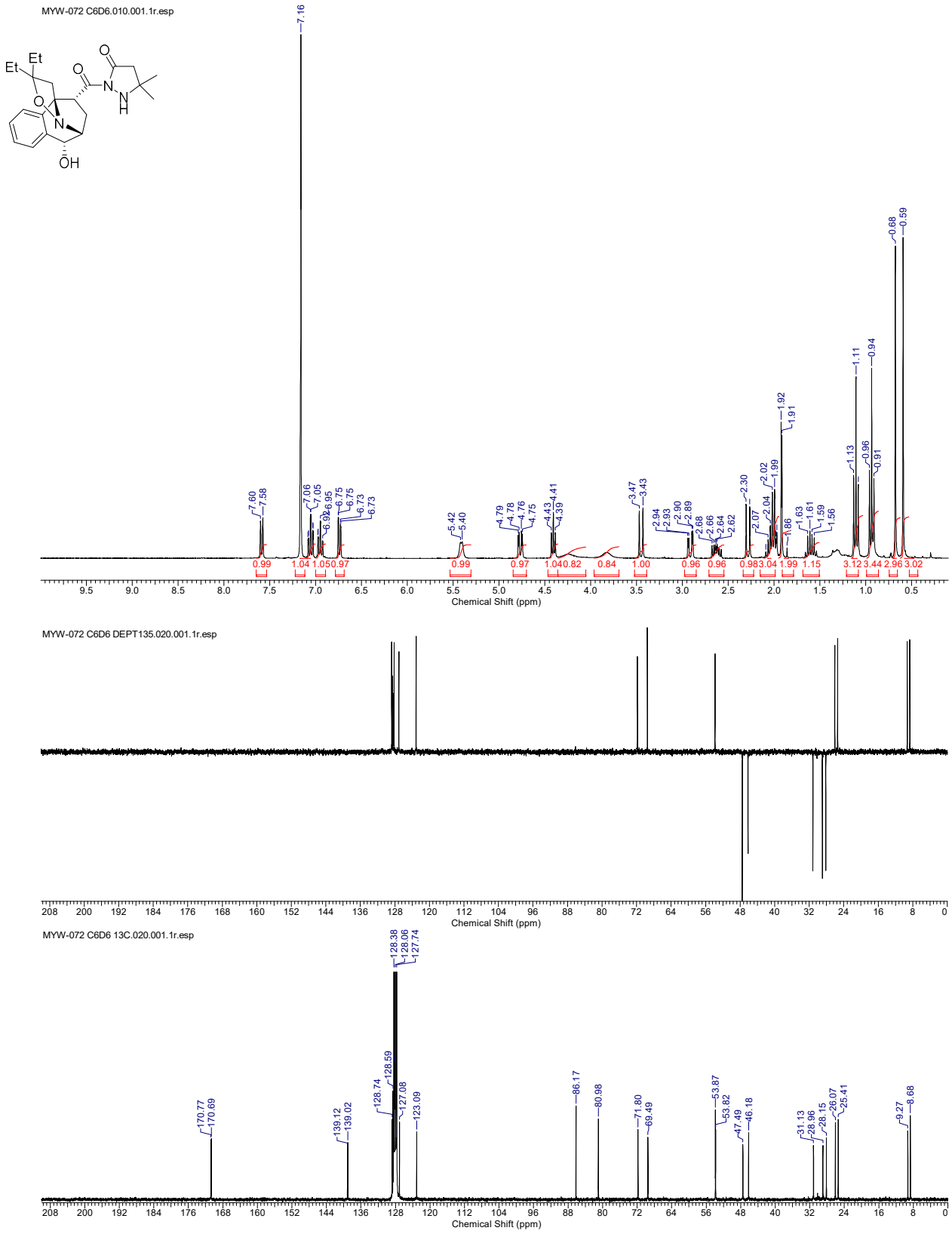
^{1}H and ^{13}C NMR of **7**



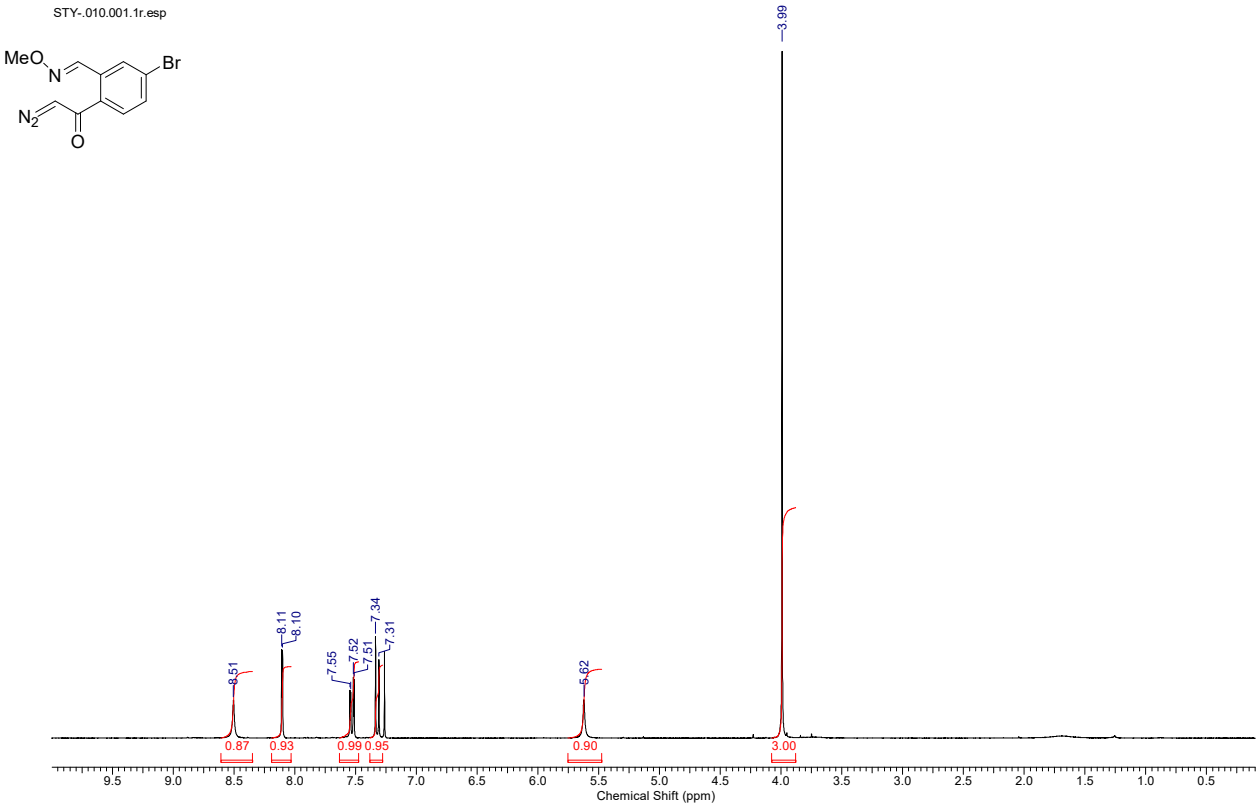


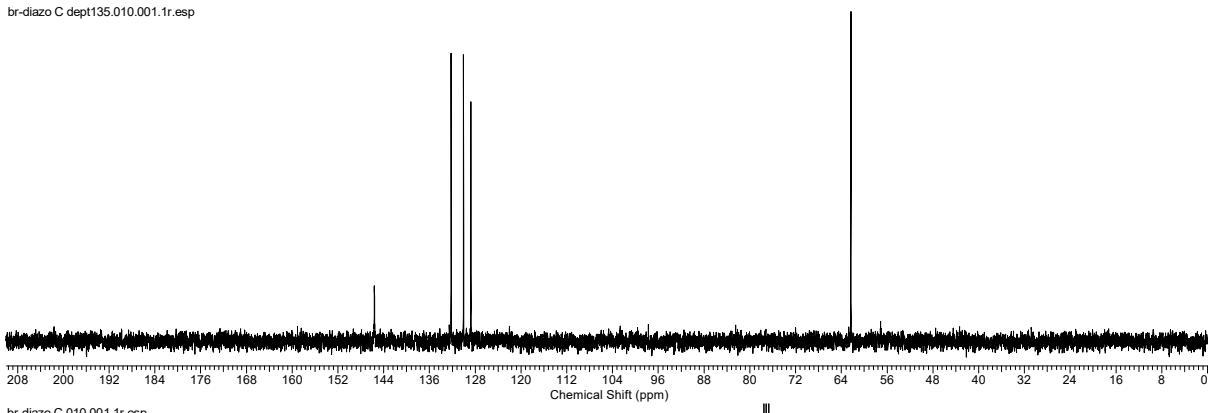


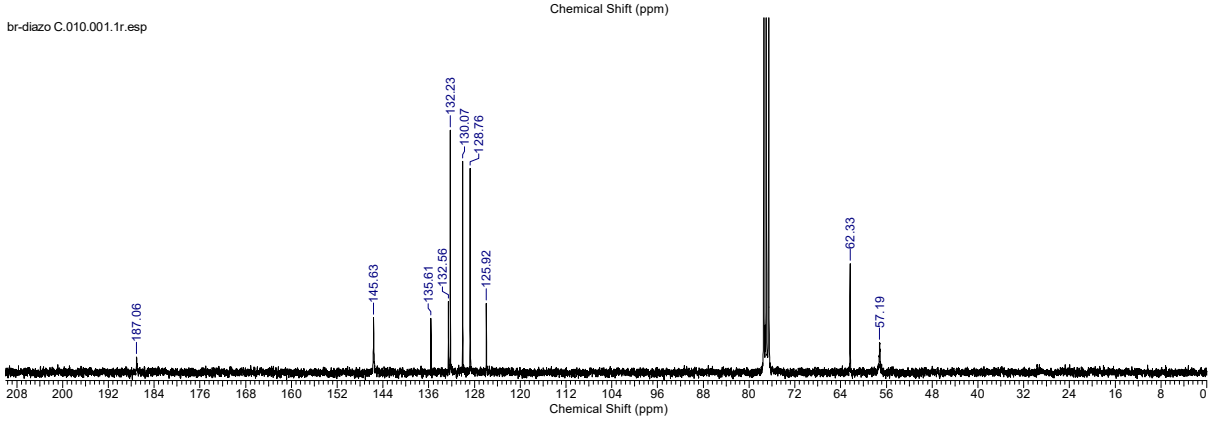
^{1}H and ^{13}C NMR of **S4**



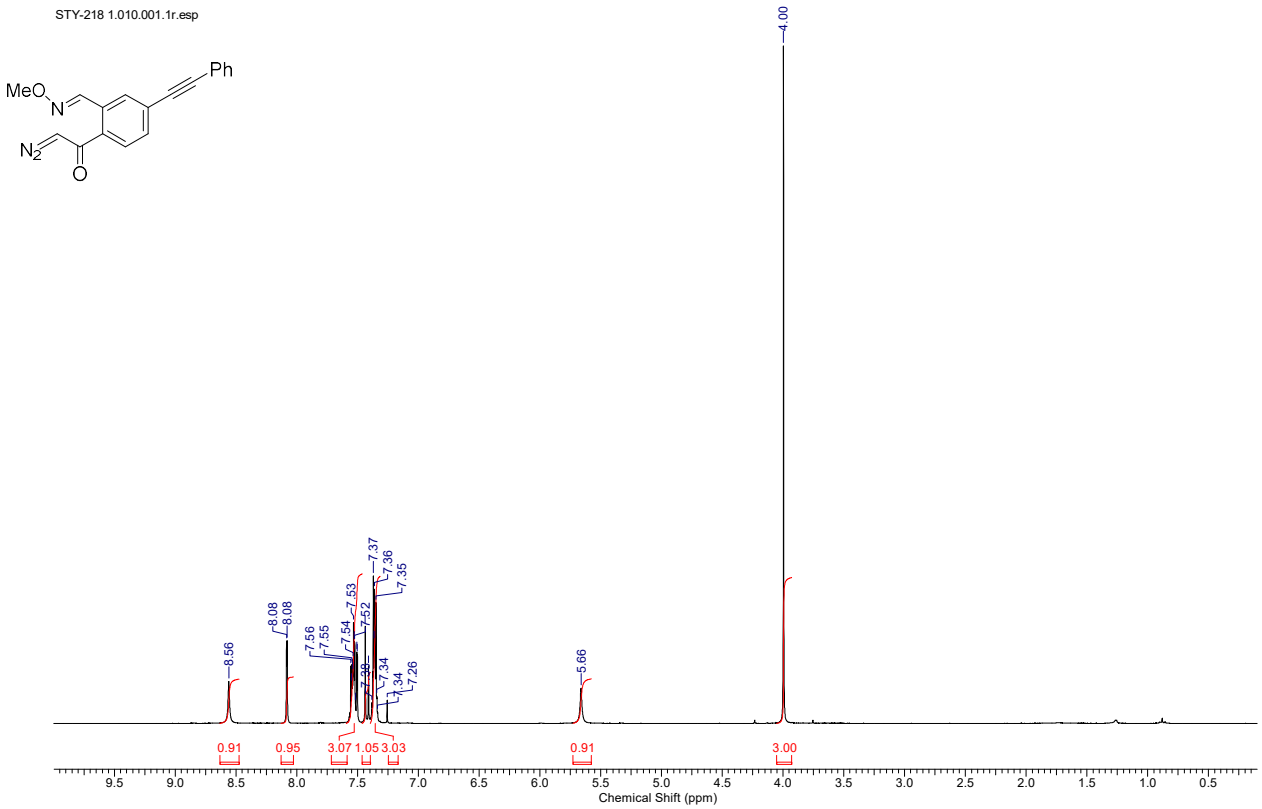
^{1}H and ^{13}C NMR of **1b**

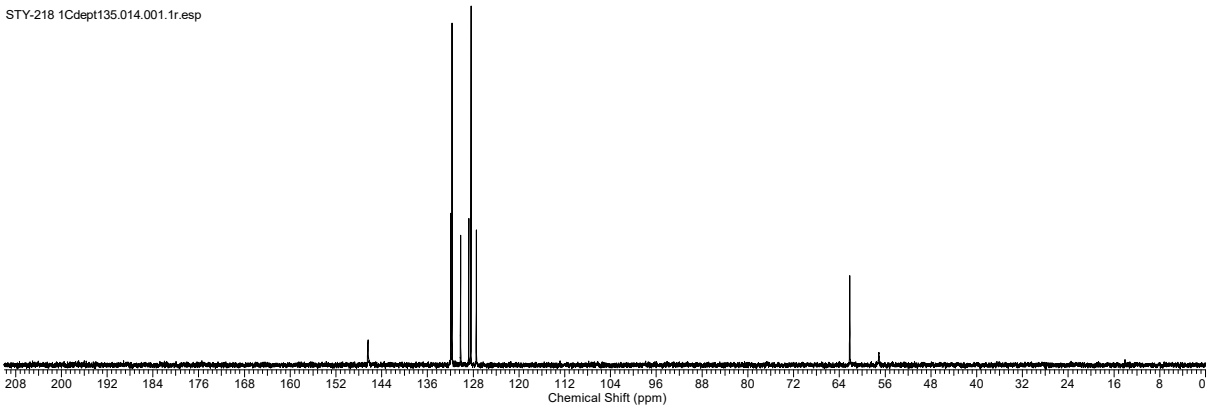


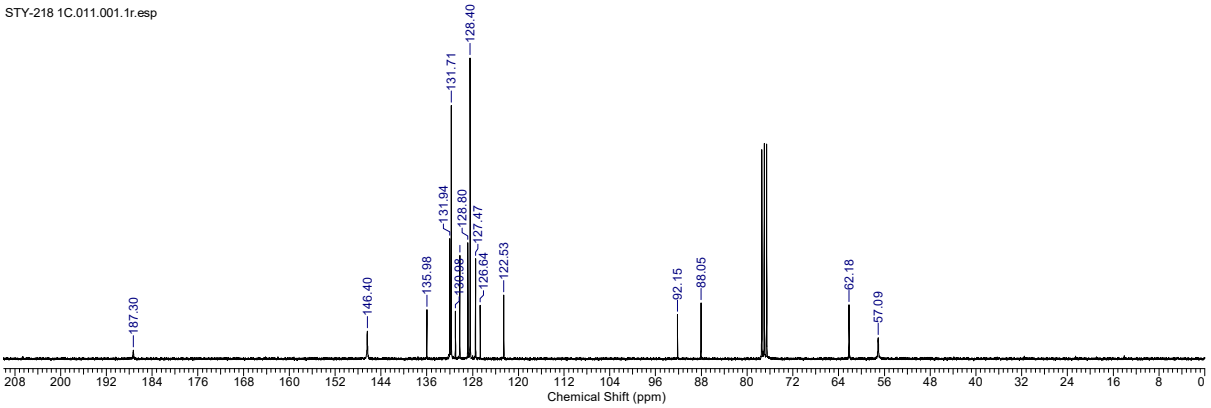




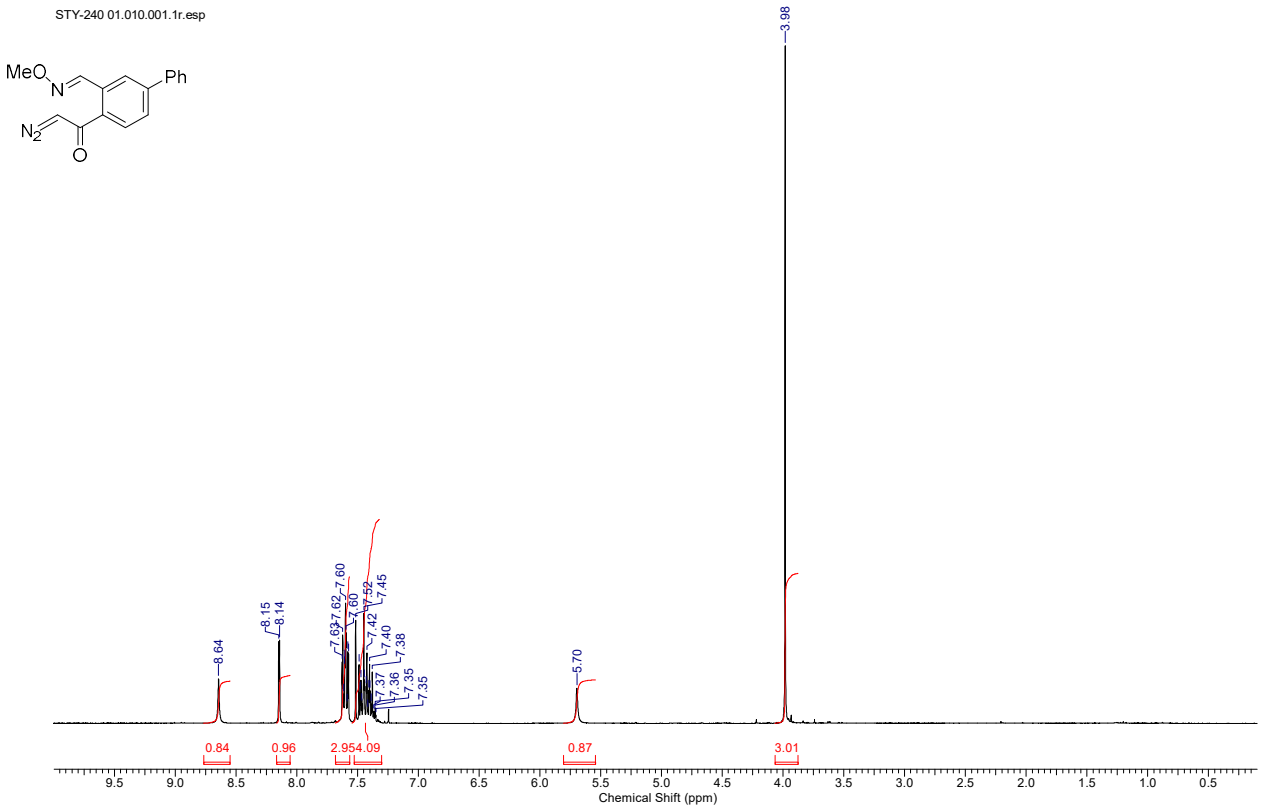
^{1}H and ^{13}C NMR of **1c**

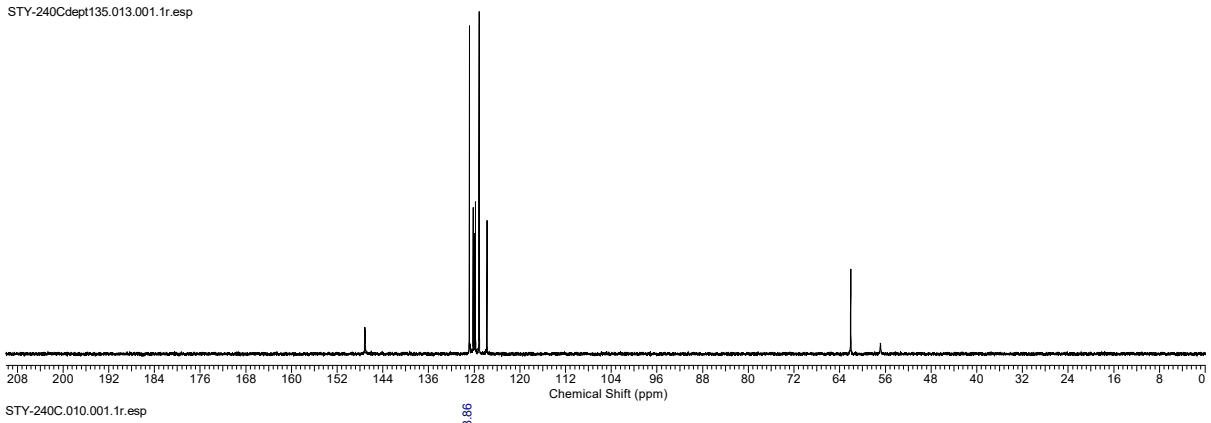


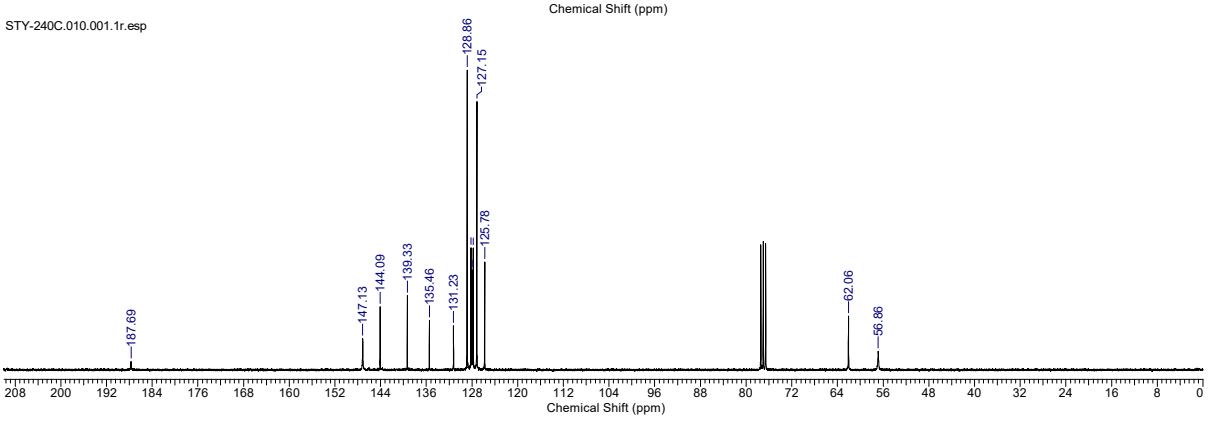




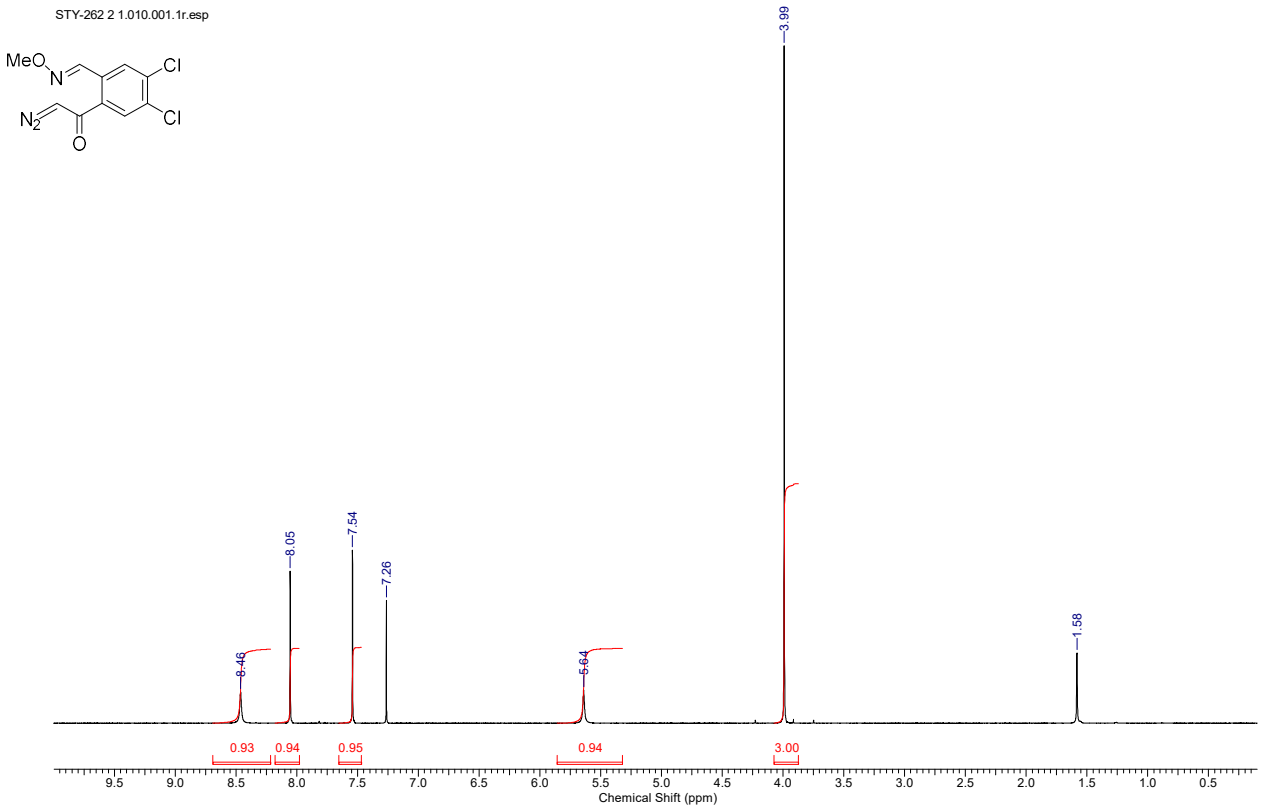
^{1}H and ^{13}C NMR of **1d**

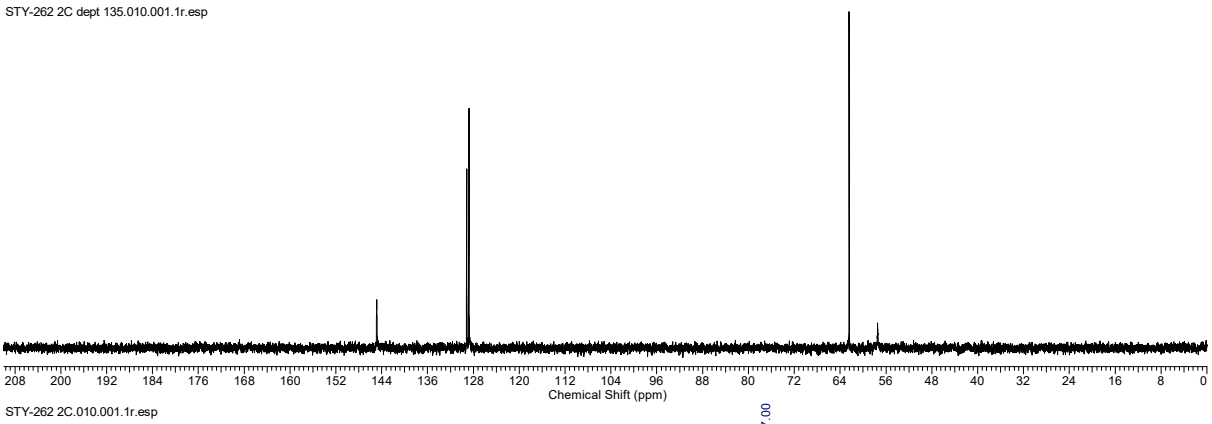


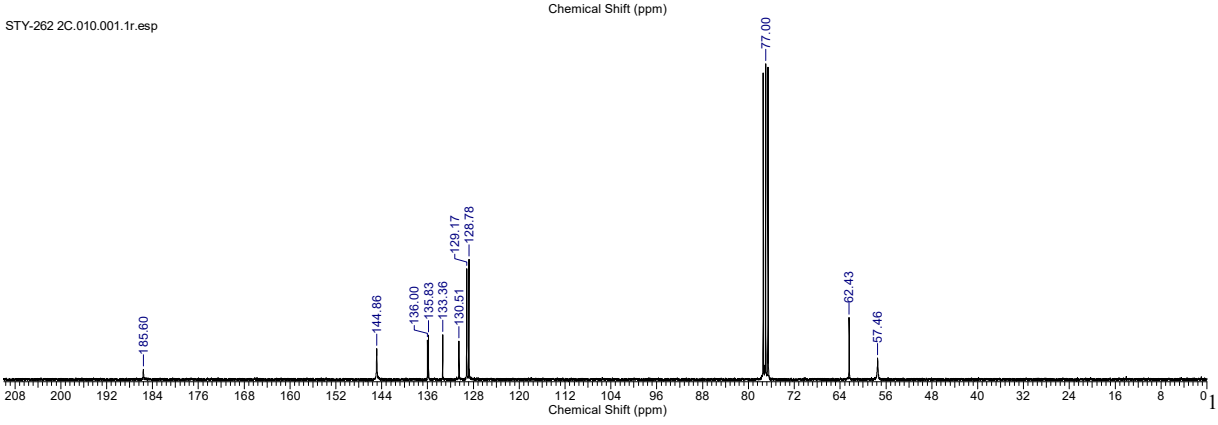




^{1}H and ^{13}C NMR of **1e**

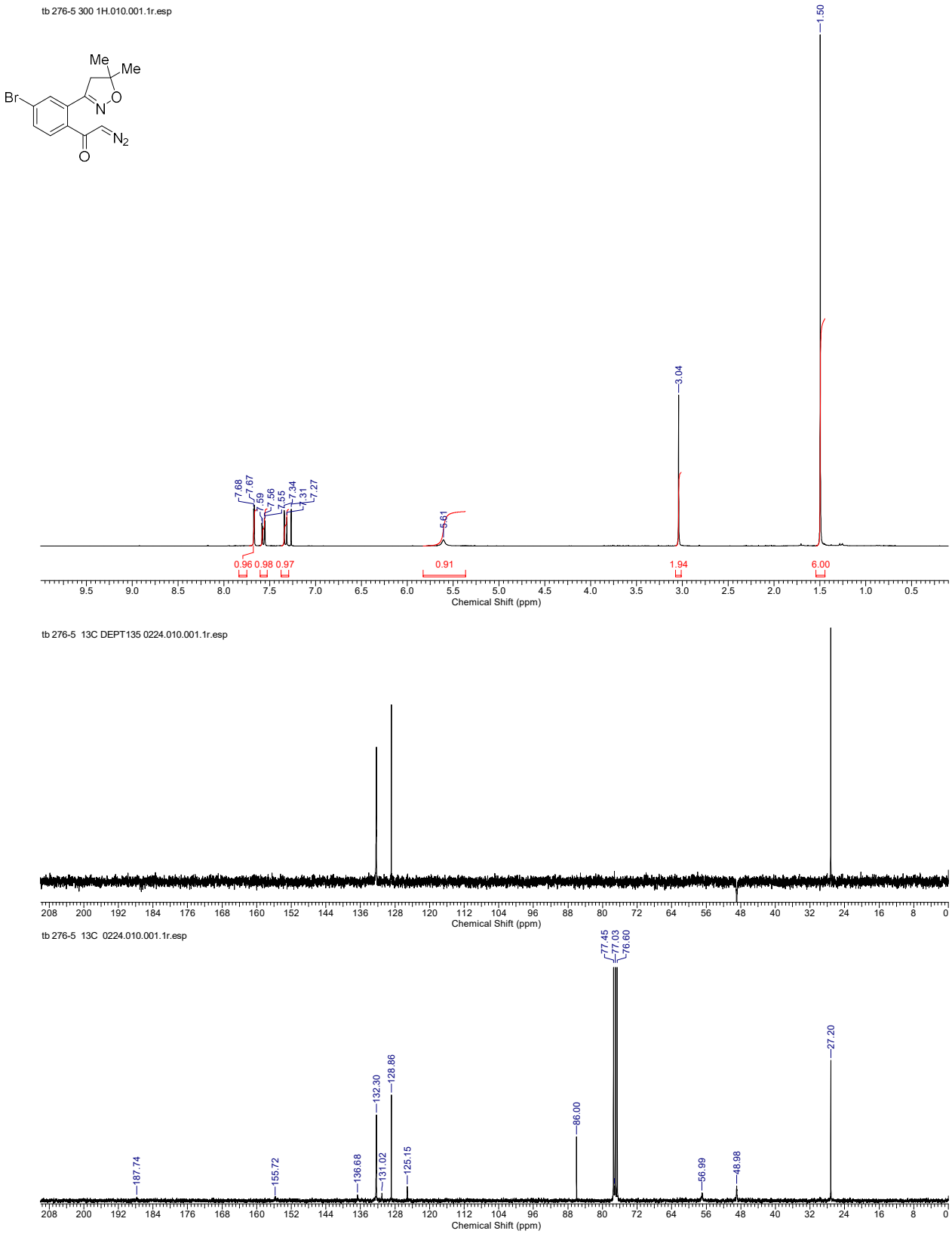




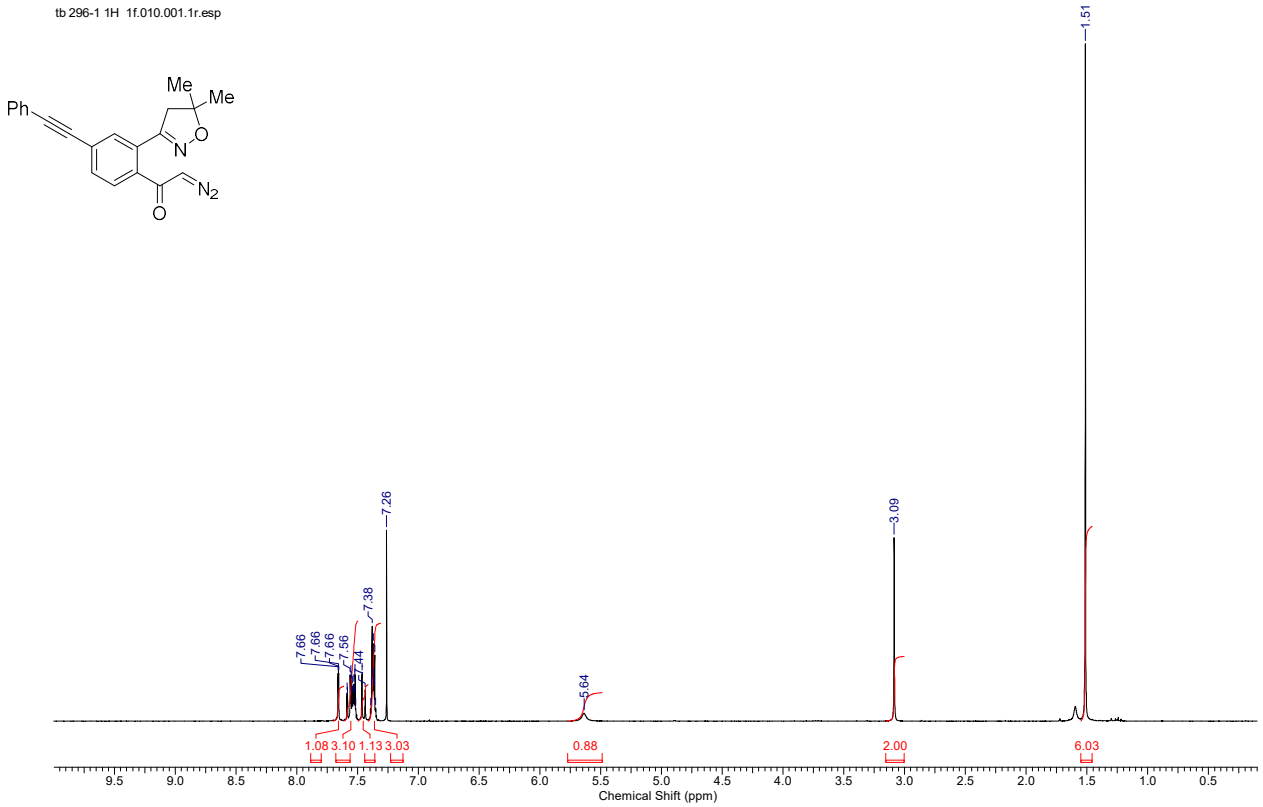


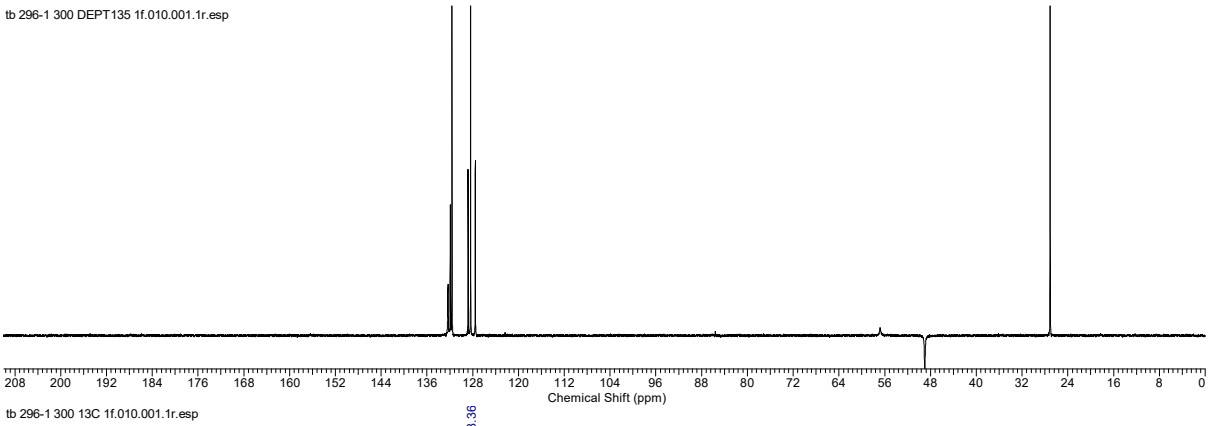
^{1}H and

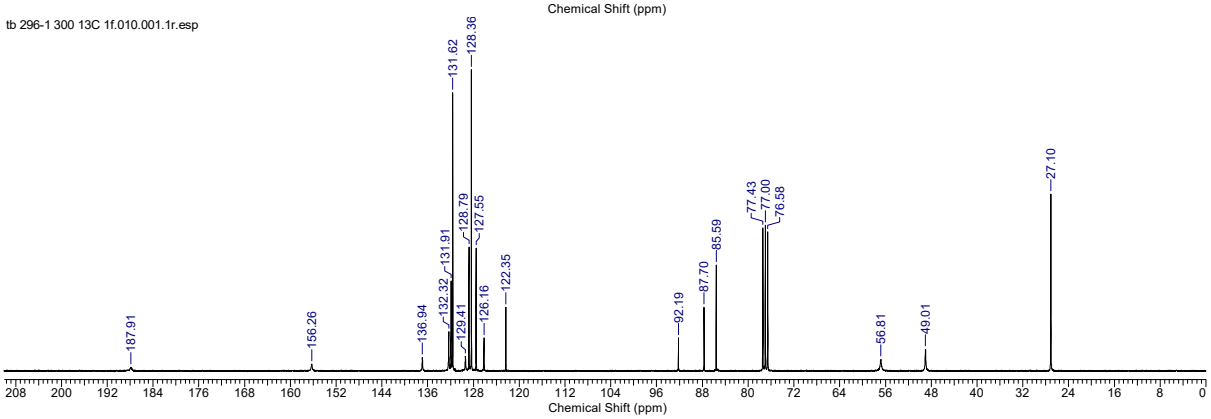
^{13}C NMR of **4a**


tb 276-5 300 1H.010.001.1r.esp
Me
Me
Br
O
N
O
N2
1.50
3.04
7.68
7.67
7.59
7.56
7.55
7.34
7.31
7.27
5.61
0.96
0.98
0.97
0.91
1.94
6.00
Chemical Shift (ppm)
tb 276-5 13C DEPT135 0224.010.001.1r.esp
Chemical Shift (ppm)
tb 276-5 13C 0224.010.001.1r.esp
77.45
77.03
76.60
27.20
128.86
132.30
86.00
187.74
155.72
136.68
131.02
125.15
56.99
48.98
Chemical Shift (ppm)

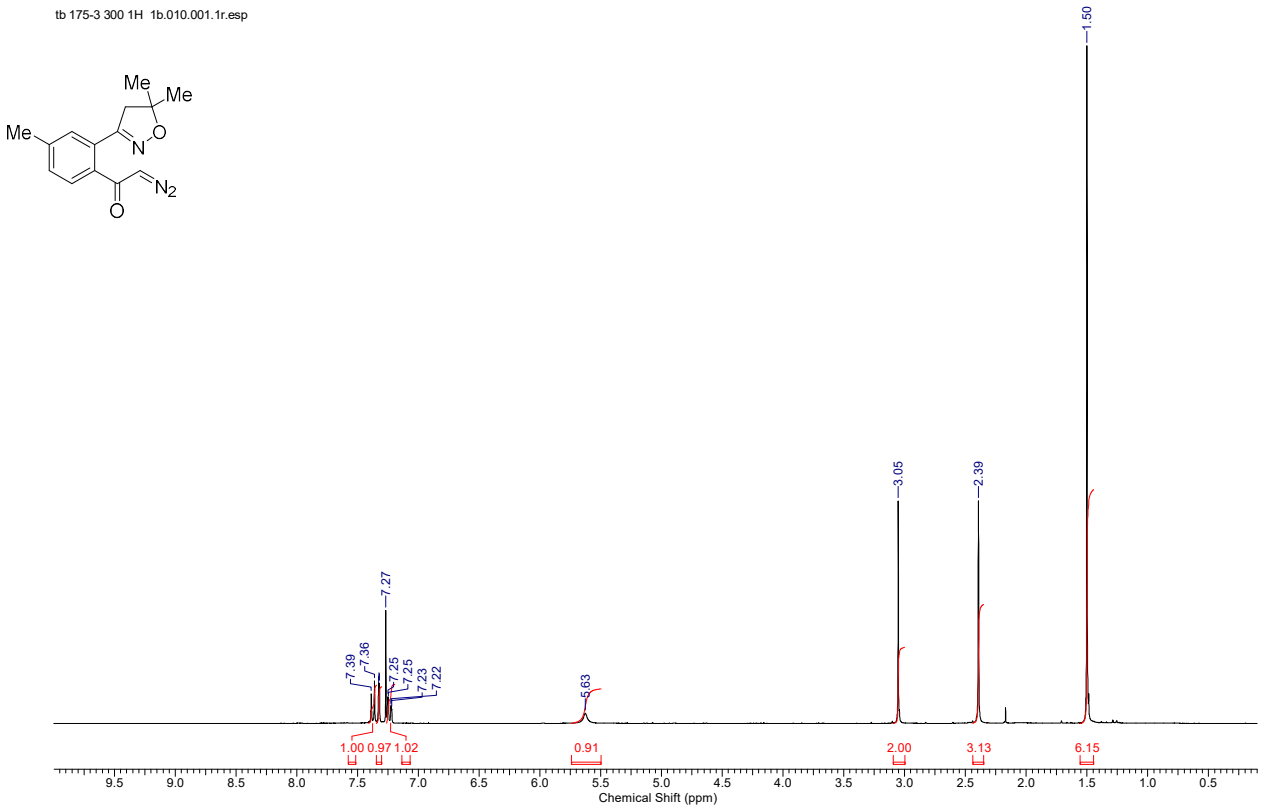
^{1}H and ^{13}C NMR of **4b**

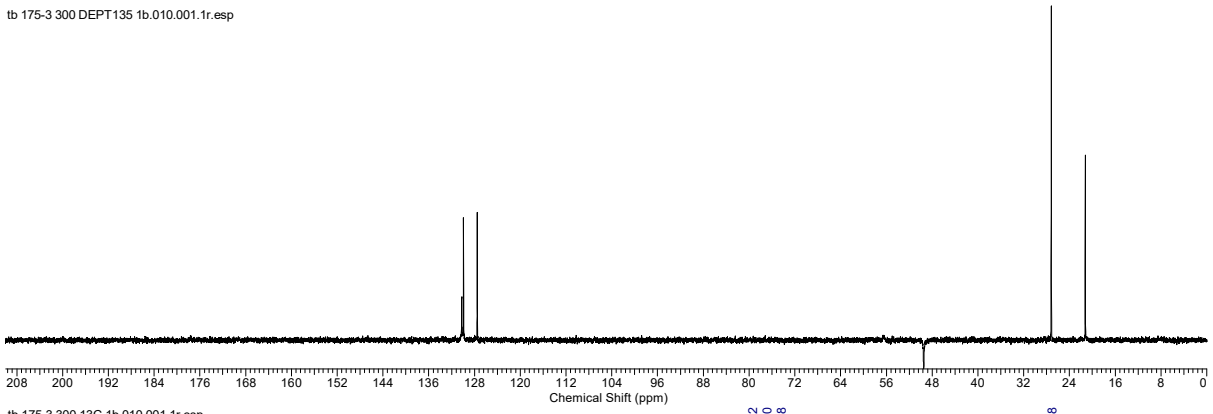


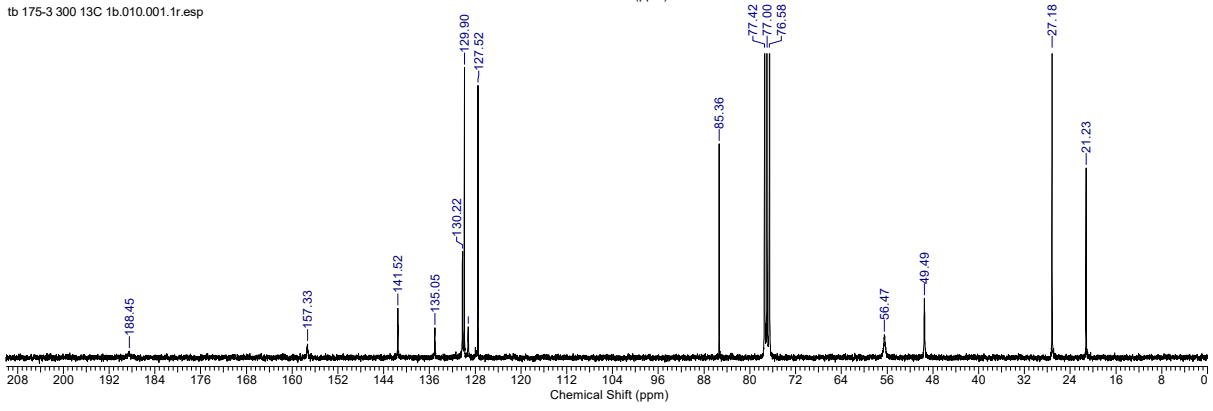




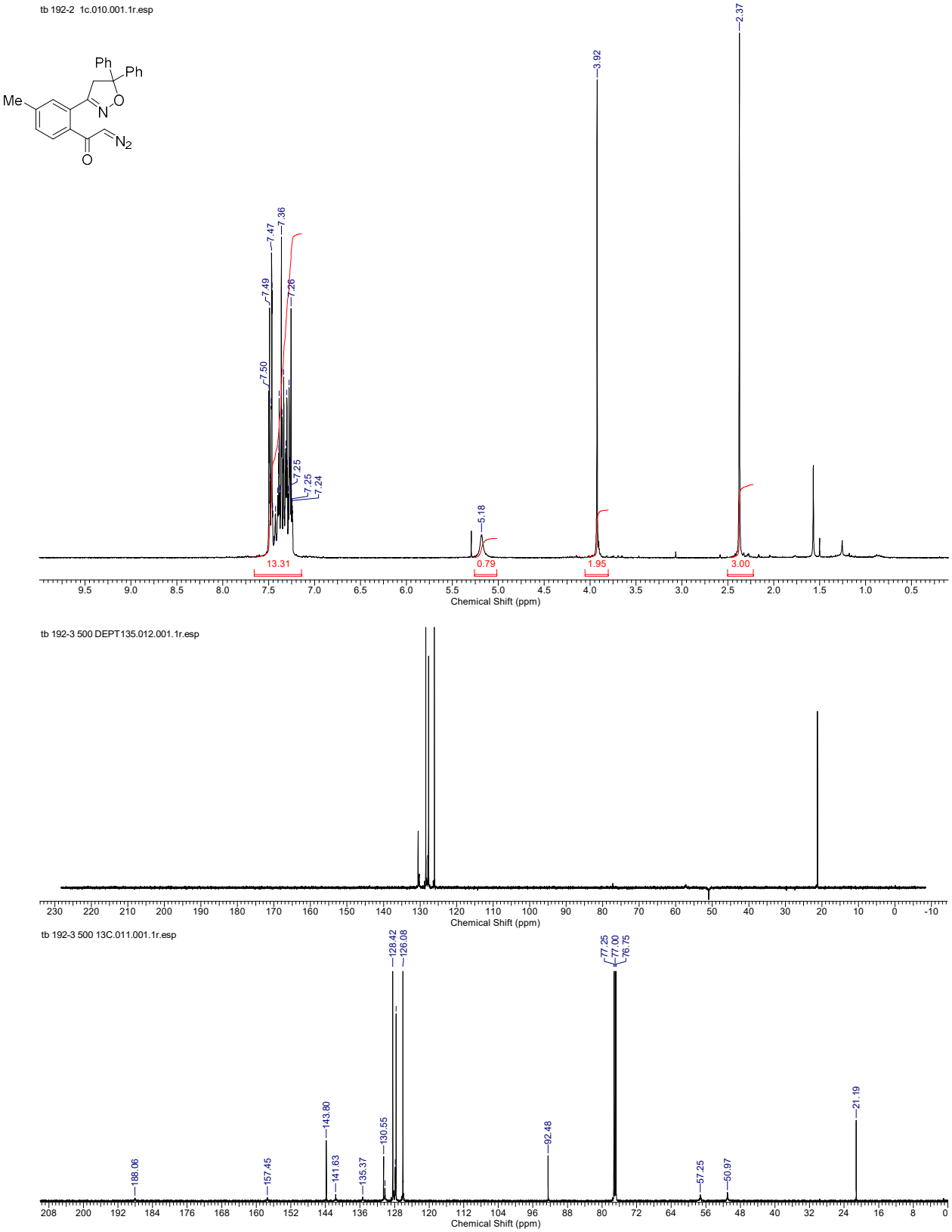
^{1}H and ^{13}C NMR of **4c**



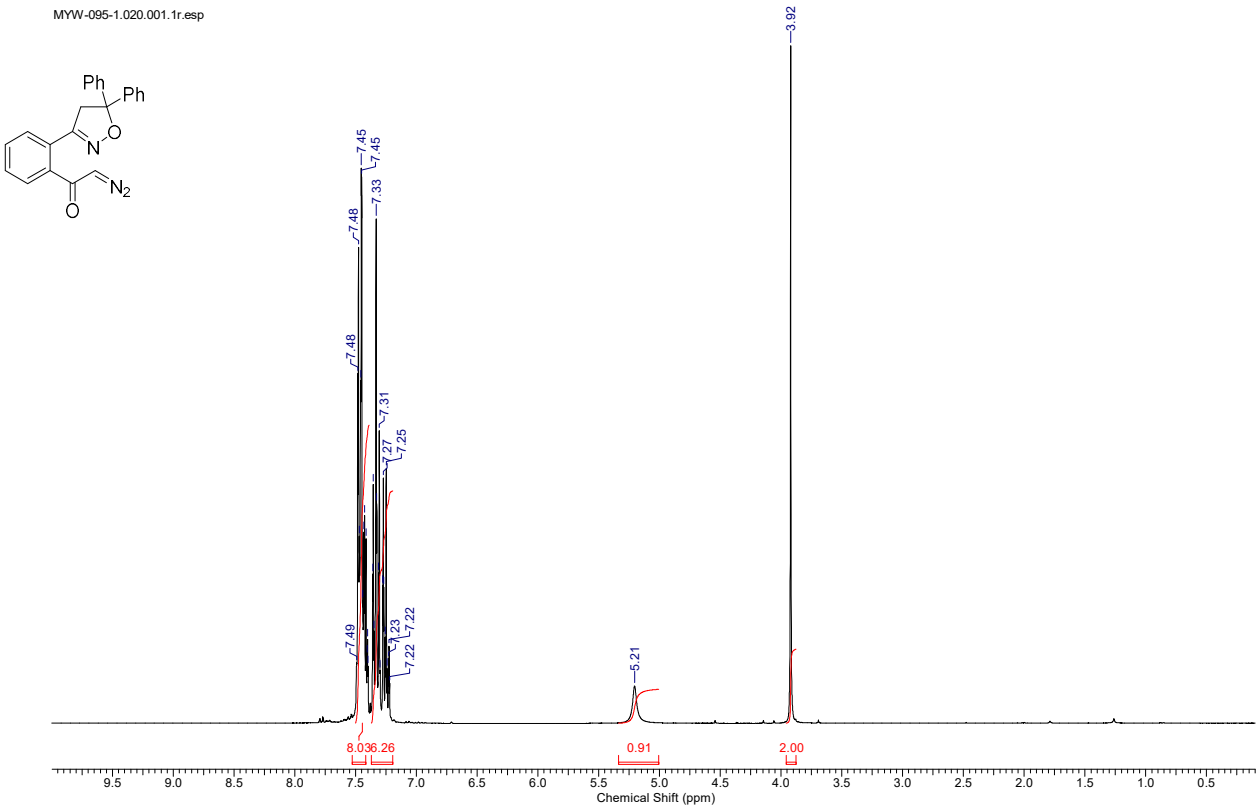


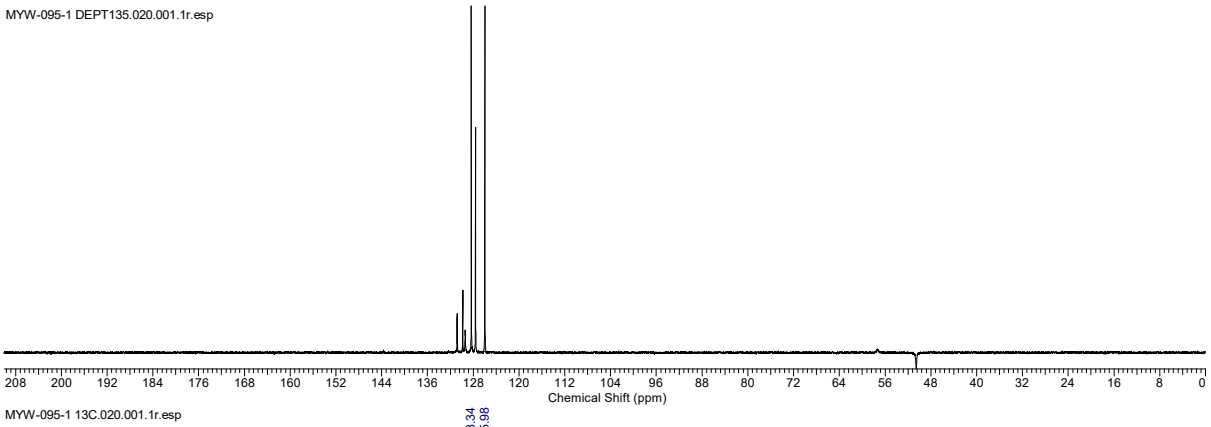


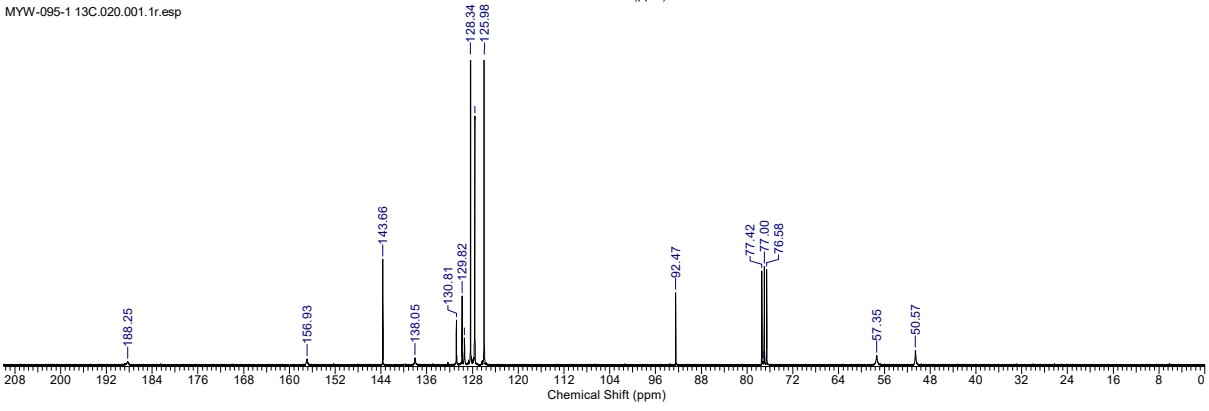
^{1}H and ^{13}C NMR of **4d**



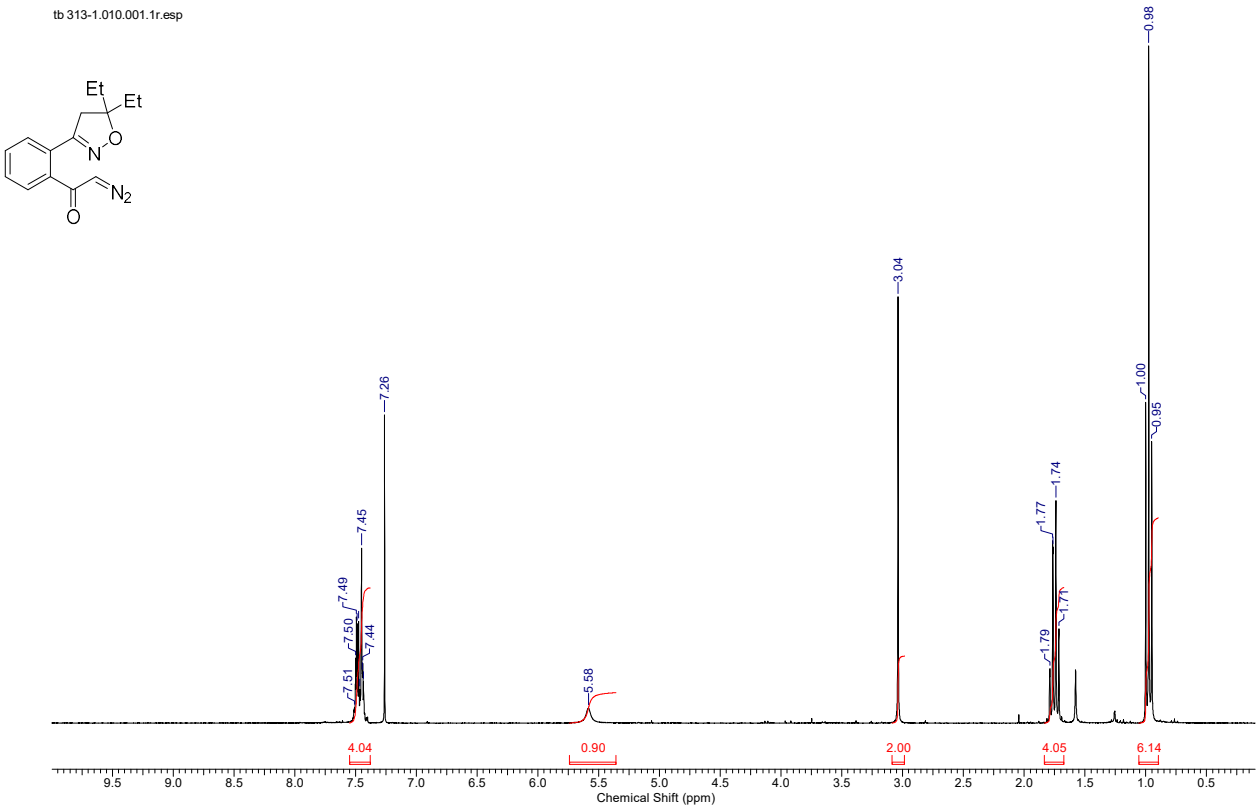
^{1}H and ^{13}C NMR of **4e**

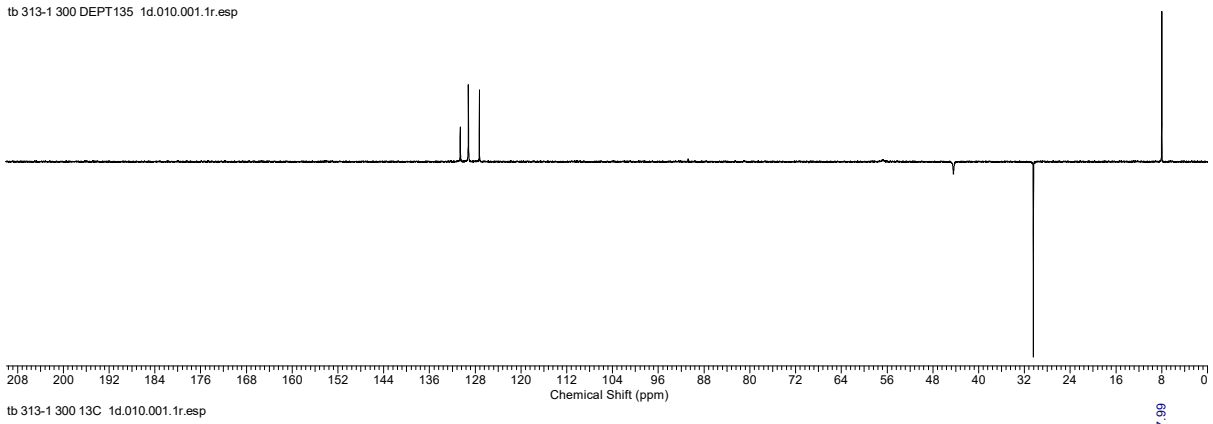


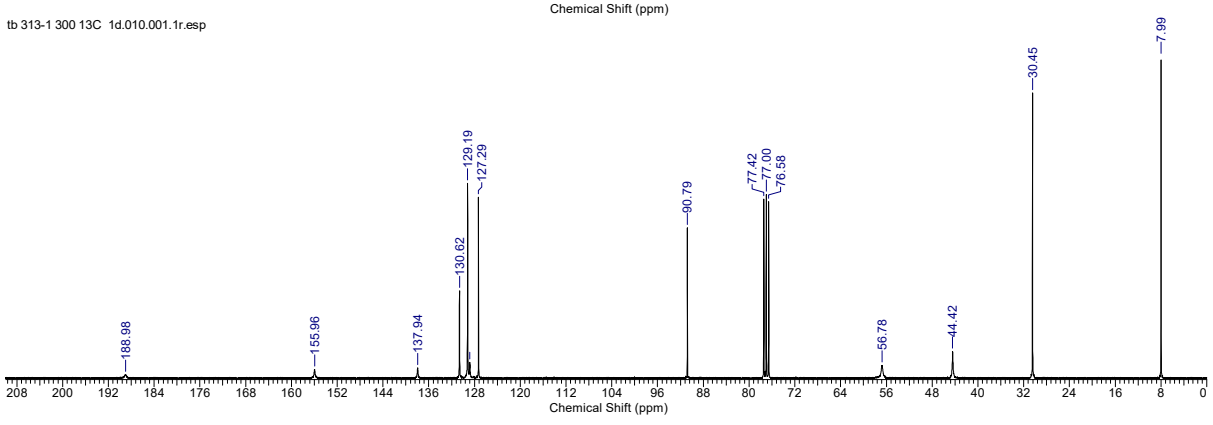




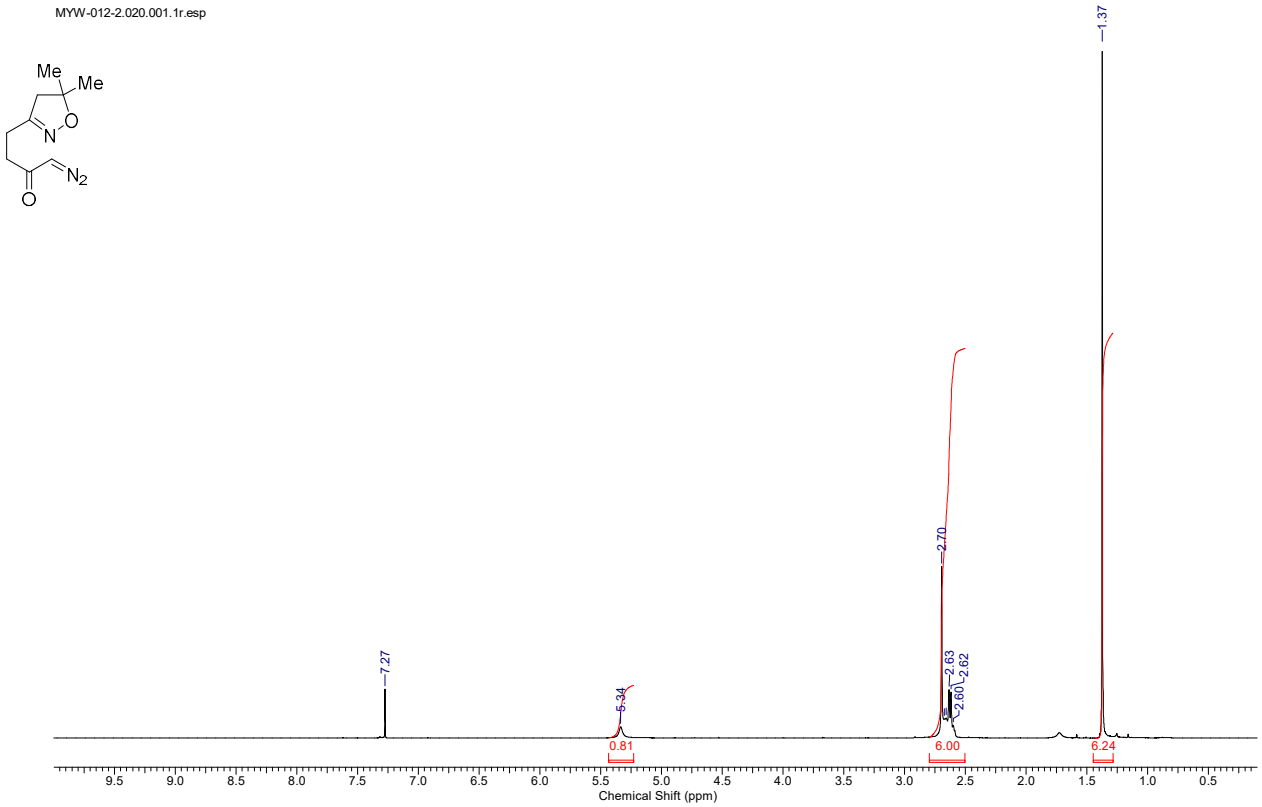
^{1}H and ^{13}C NMR of **4f**

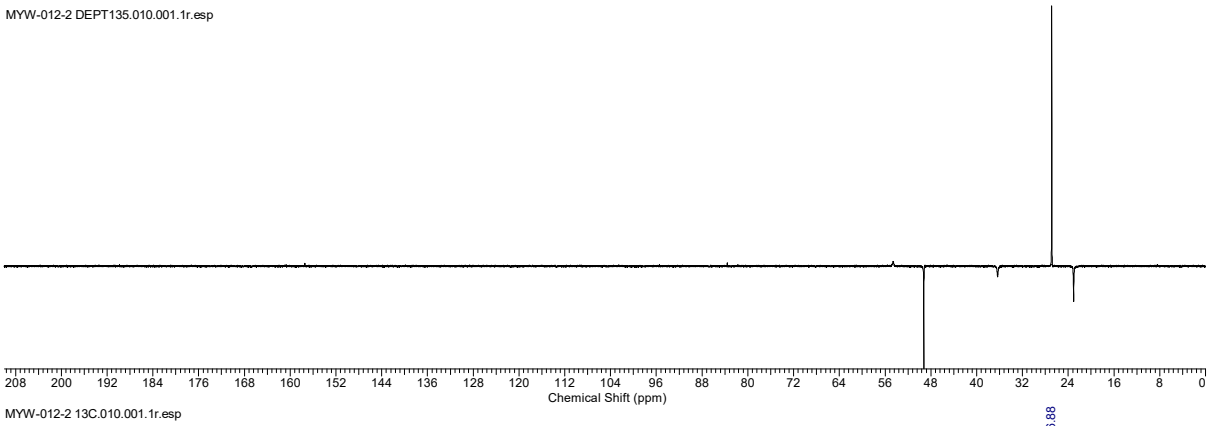


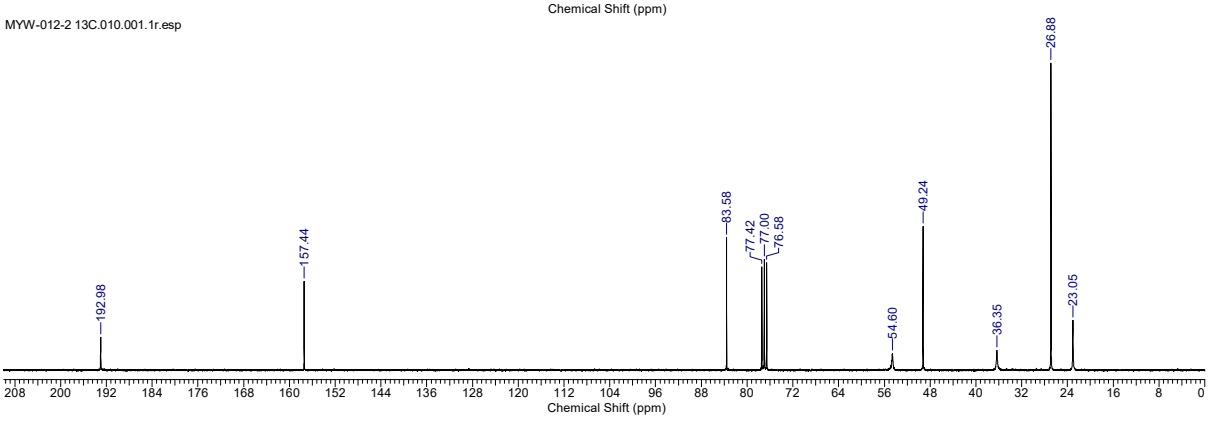




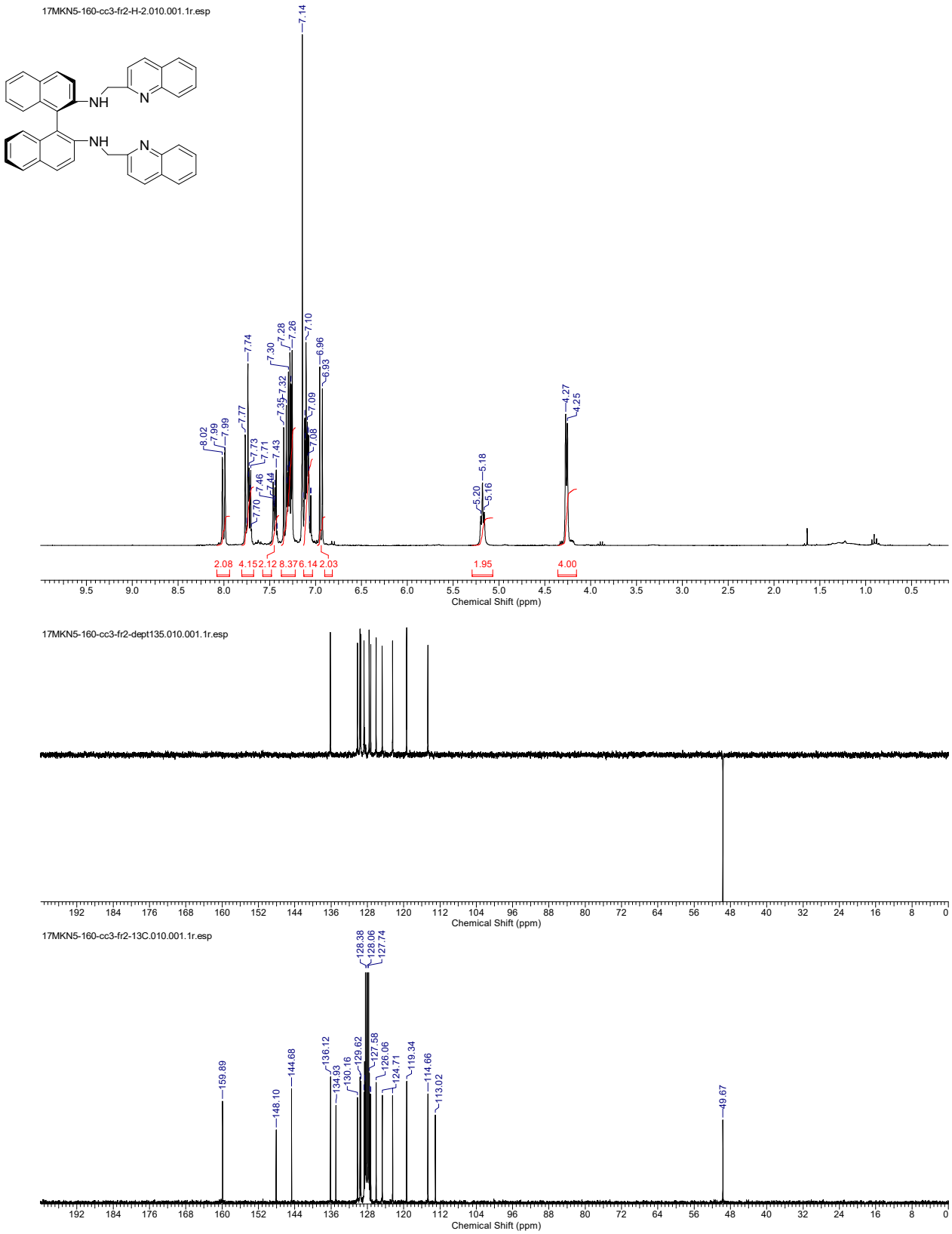
^{1}H and ^{13}C NMR of **4g**



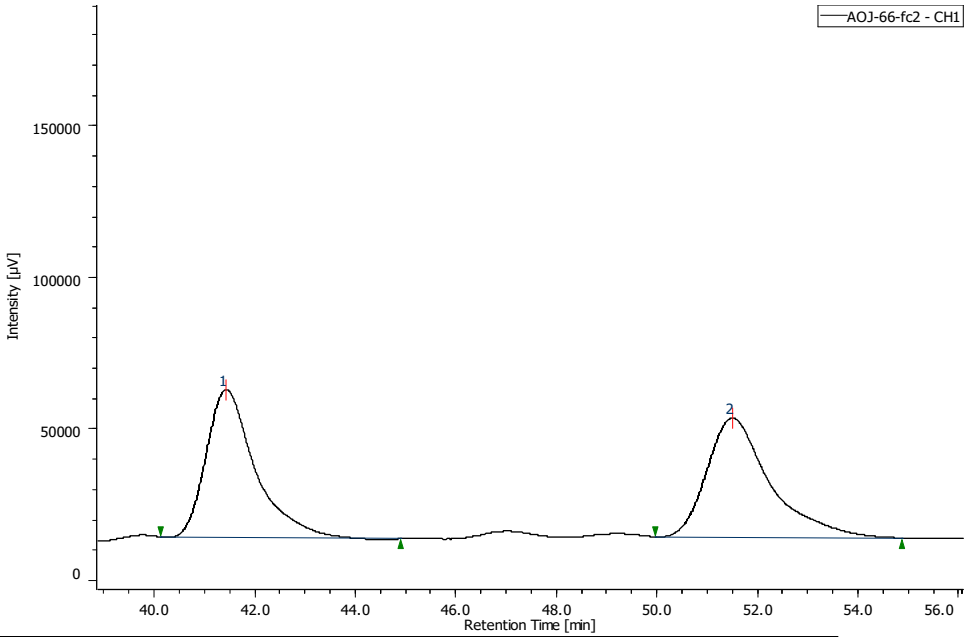




^{1}H and ^{13}C NMR of ligand **E**

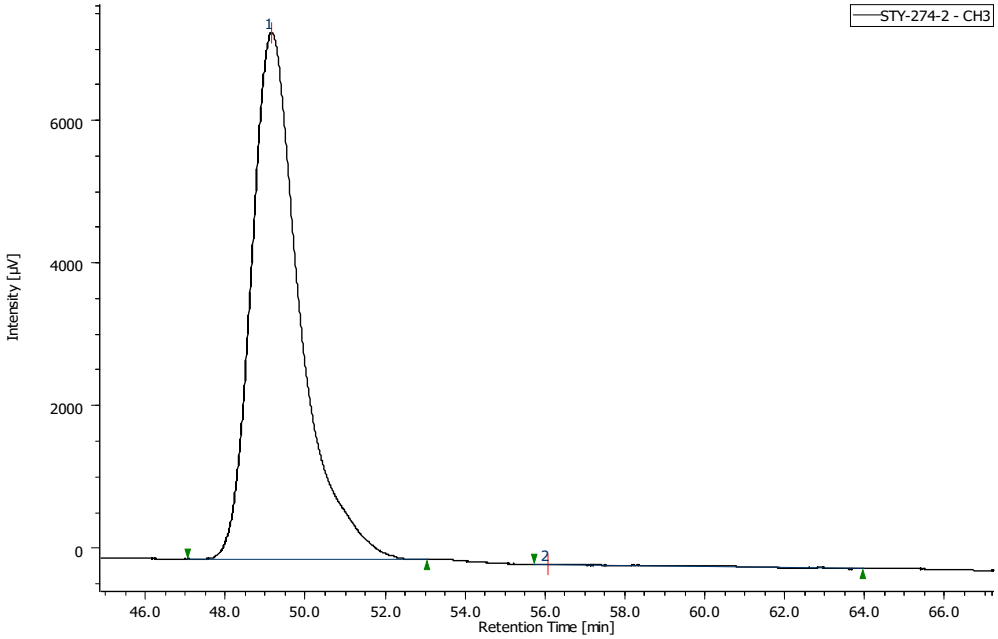


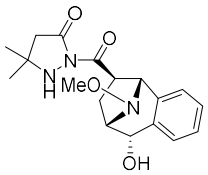
HPLC analysis of **6**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	41.433	3300235	48609	49.271
2	3	51.475	3397943	39137	50.729

Racemate



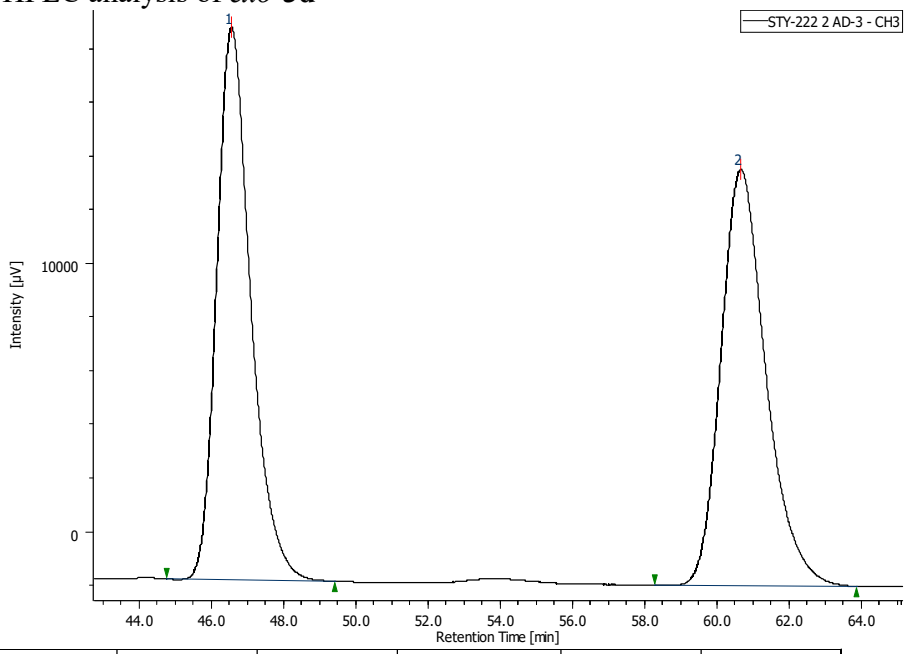


# Peak	CH	tR (min)	Area	Height	Area%
1	3	49.15	621255	7373	99.711
2	3	56.075	1800	7	0.289

99% ee

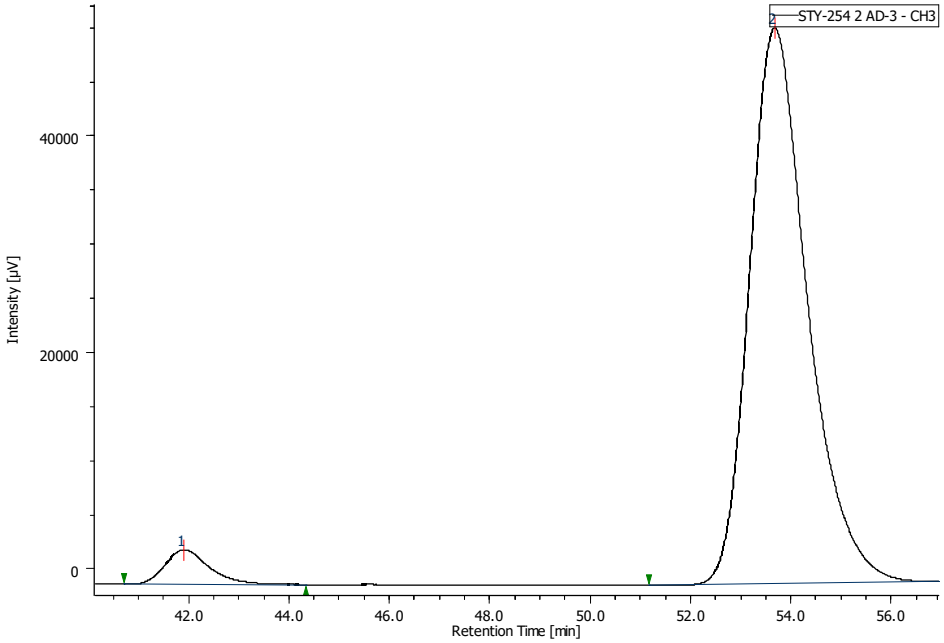
Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 86:14, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C

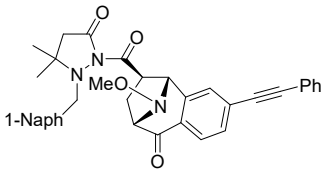
HPLC analysis of *exo*-**3d**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	46.567	1341488	20557	50.036
2	3	60.642	1339575	15483	49.964

Racemate



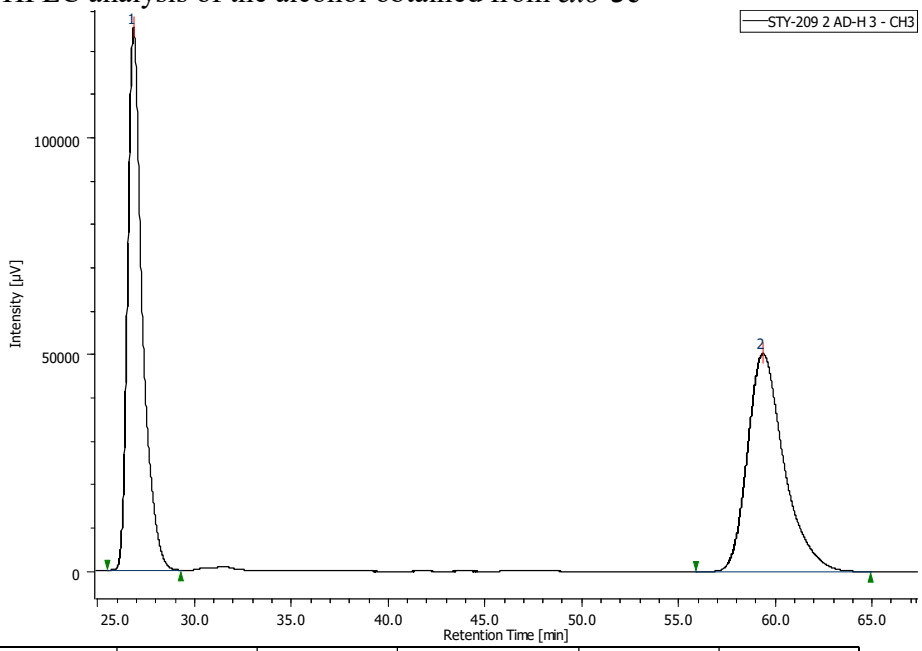


# Peak	CH	tR (min)	Area	Height	Area%
1	3	41.917	195873	3198	4.497
2	3	53.658	4160103	51382	95.503

91% ee

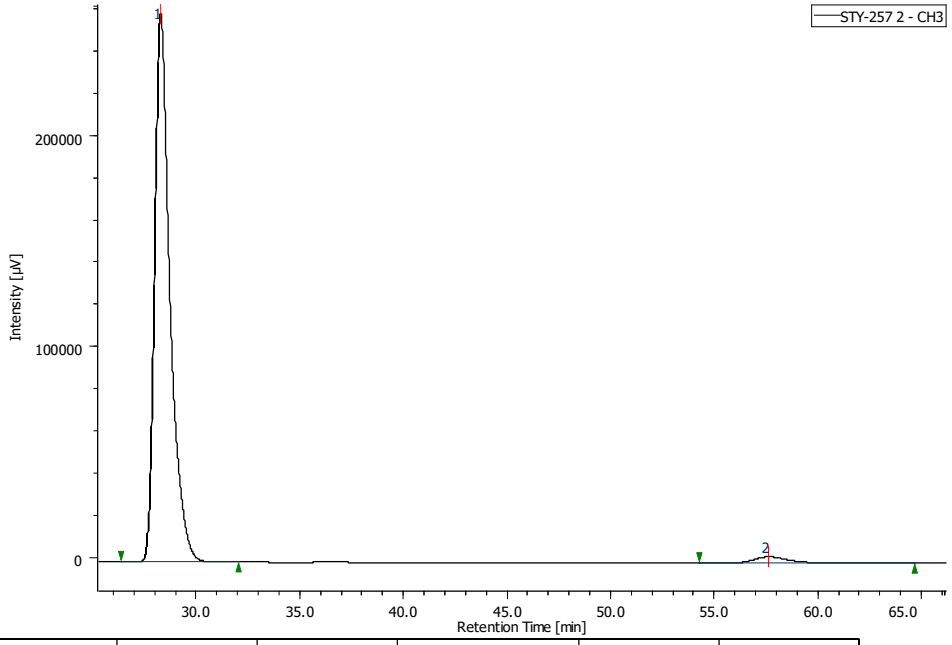
Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C

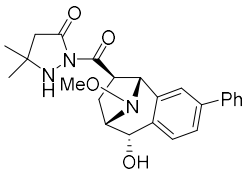
HPLC analysis of the alcohol obtained from *exo*-**3e**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	26.85	6577525	124970	49.995
2	3	59.308	6578731	50244	50.005

Racemate



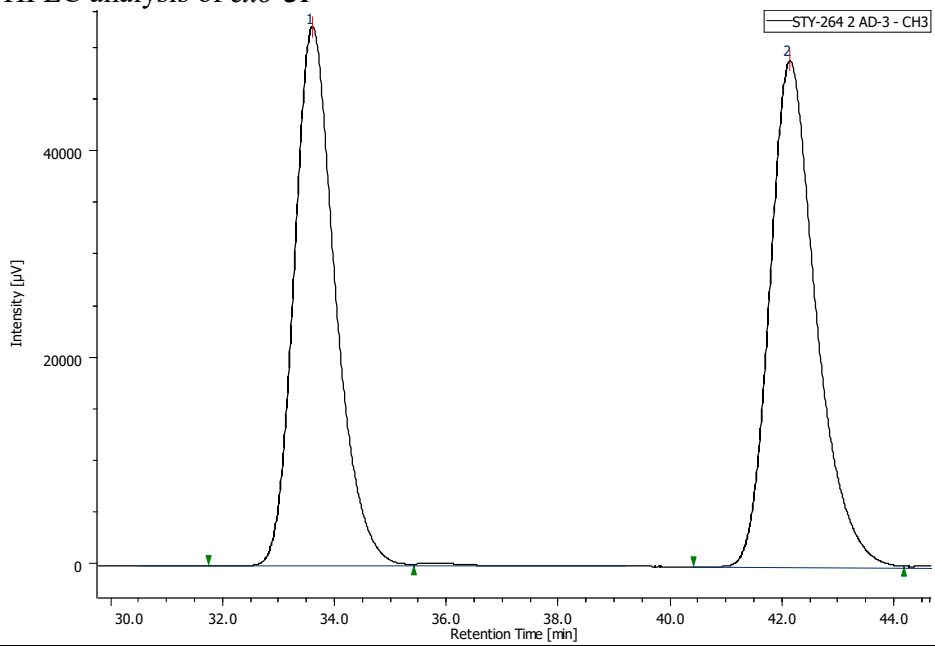


# Peak	CH	tR (min)	Area	Height	Area%
1	3	28.292	13286393	258632	97.428
2	3	57.608	350735	3004	2.572

95% ee

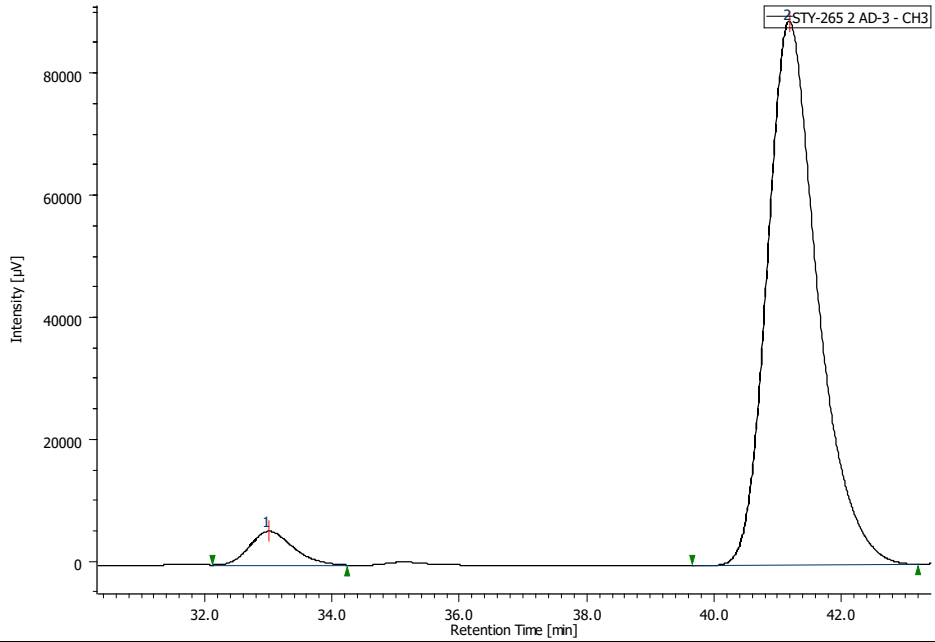
Daicel Chiralpak AD-H, Hexane:*i*-PrOH = 75:25, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C

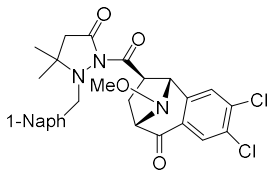
HPLC analysis of *exo*-**3f**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	33.6	2663794	52172	48.654
2	3	42.125	2811130	48915	51.346

Racemate



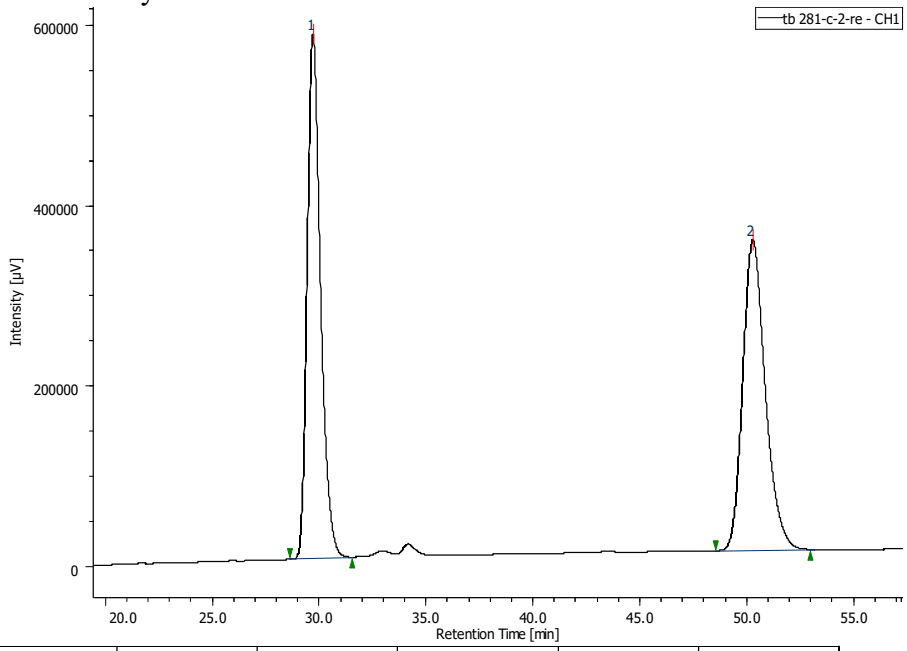


# Peak	CH	tR (min)	Area	Height	Area%
1	3	33	260727	5503	5.074
2	3	41.167	4877446	88911	94.926

90% ee

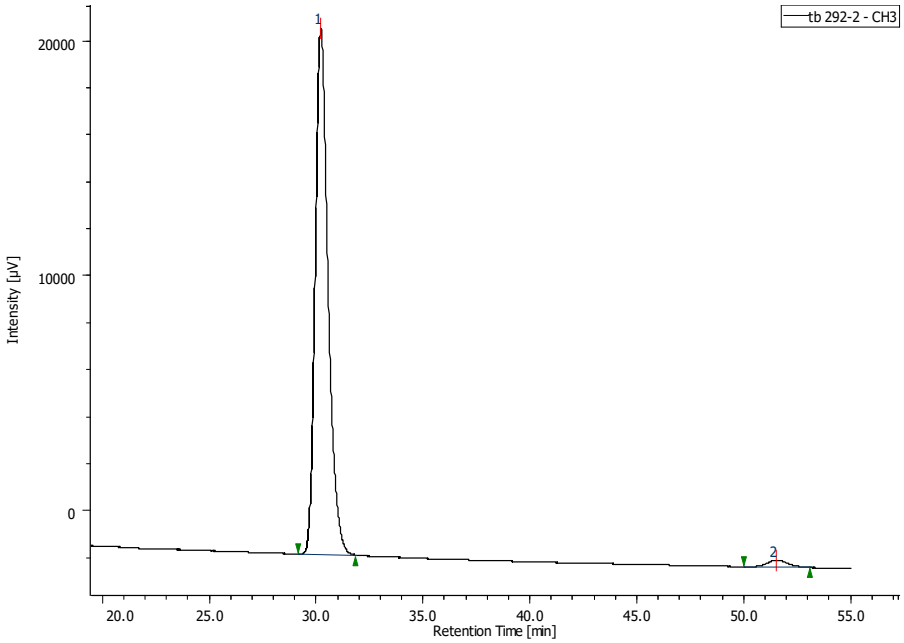
Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C

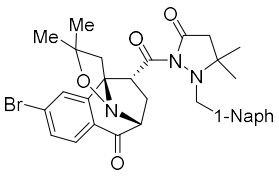
HPLC analysis of *endo*-**5a**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	29.7	25081371	579688	50.049
2	3	50.25	25032188	343096	49.951

Racemate



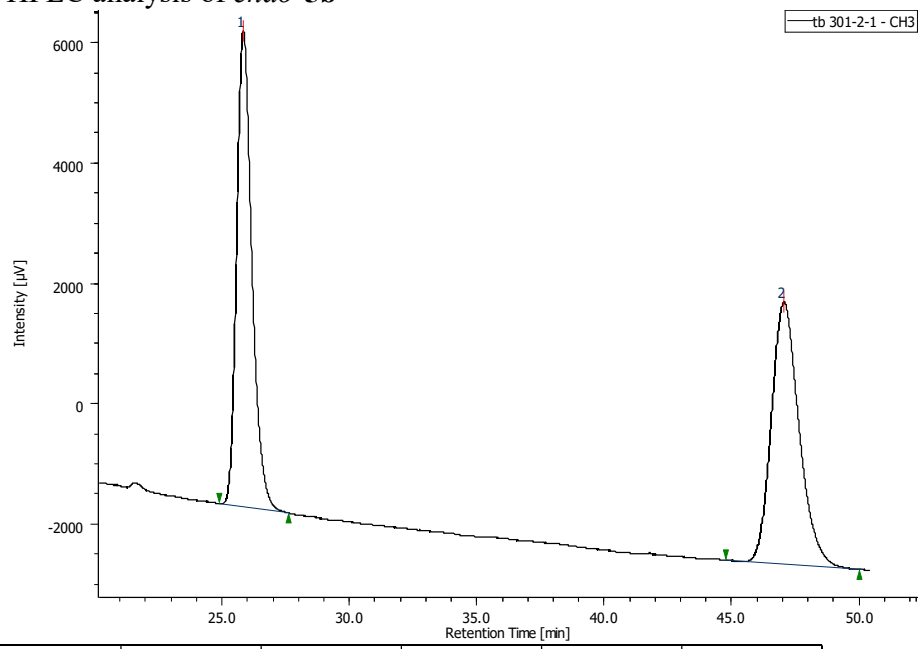


# Peak	CH	tR (min)	Area	Height	Area%
1	3	30.208	934011	22346	97.931
2	3	51.492	19733	290	2.069

96% ee

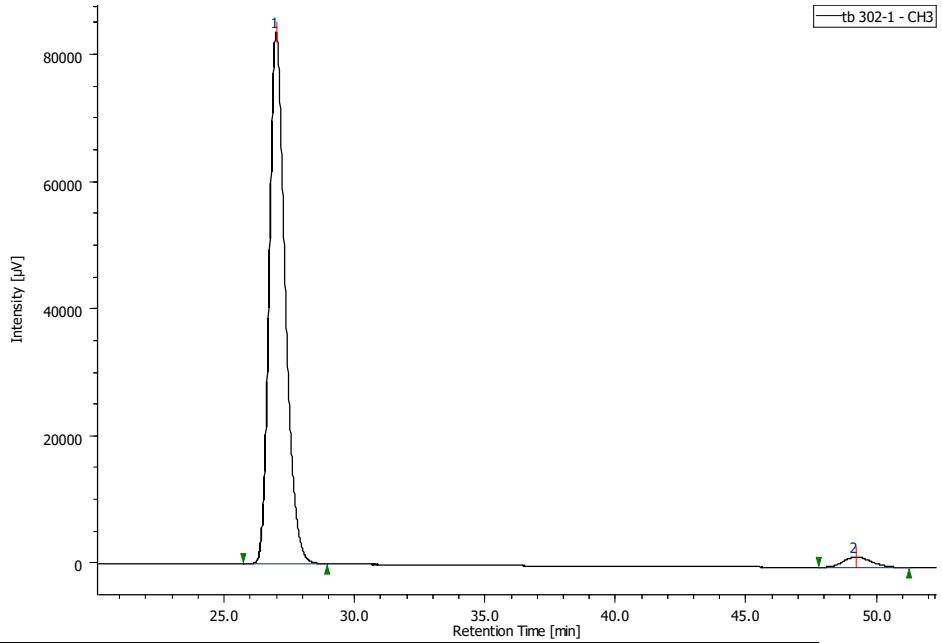
Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C

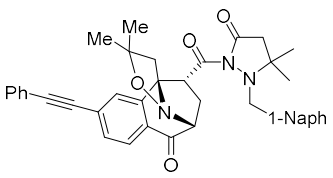
HPLC analysis of *endo*-**5b**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	25.833	327842	7890	49.978
2	3	47.017	328133	4345	50.022

Racemate



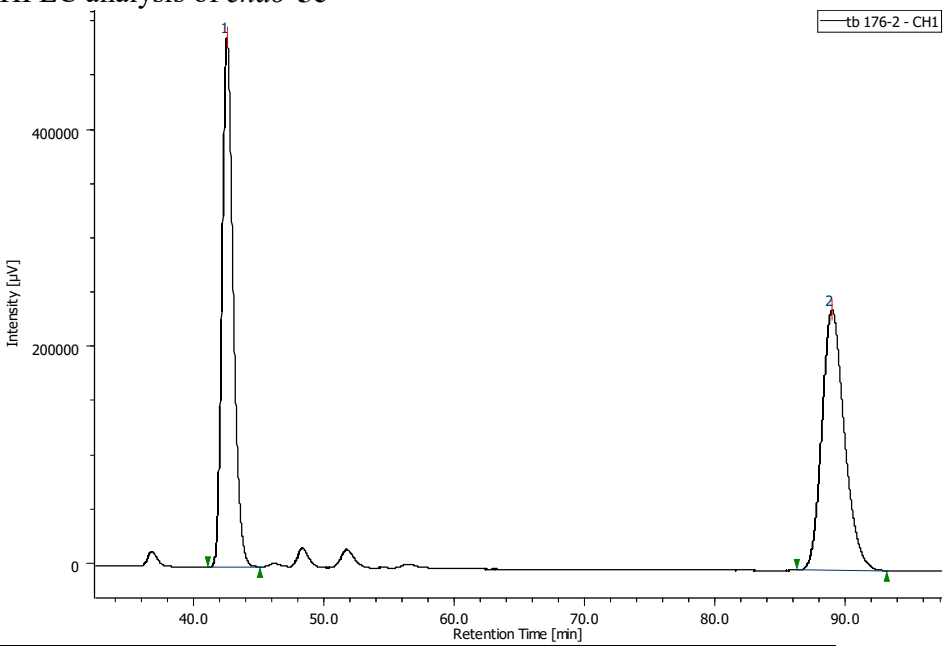


# Peak	CH	tR (min)	Area	Height	Area%
1	3	26.992	3542790	83457	96.888
2	3	49.208	125990	1677	3.112

94% ee

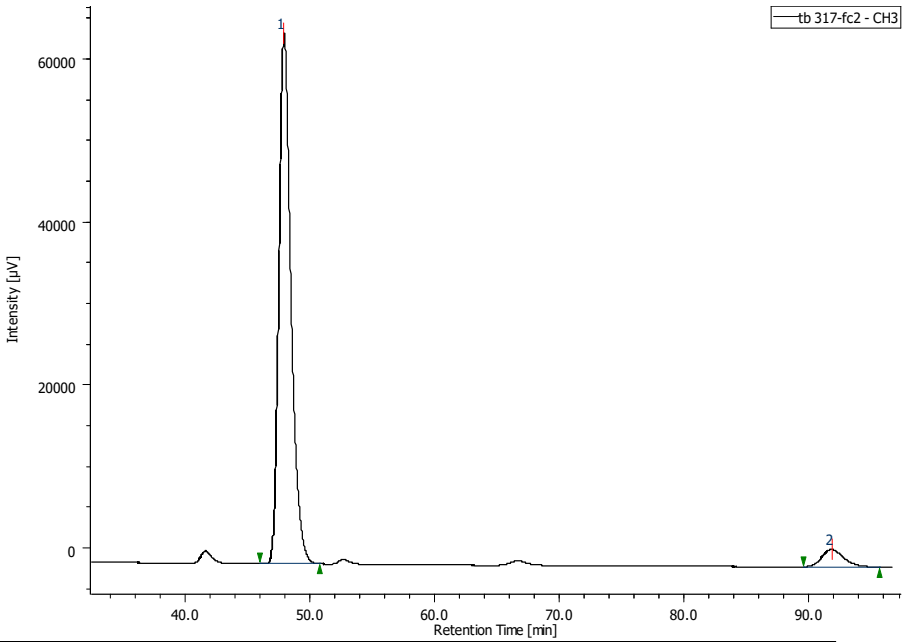
Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C

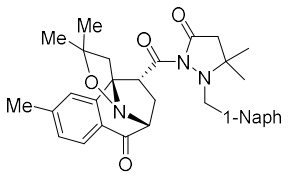
HPLC analysis of *endo*-**5c**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	42.558	28837730	487288	50
2	3	88.958	28837545	239525	50

Racemate



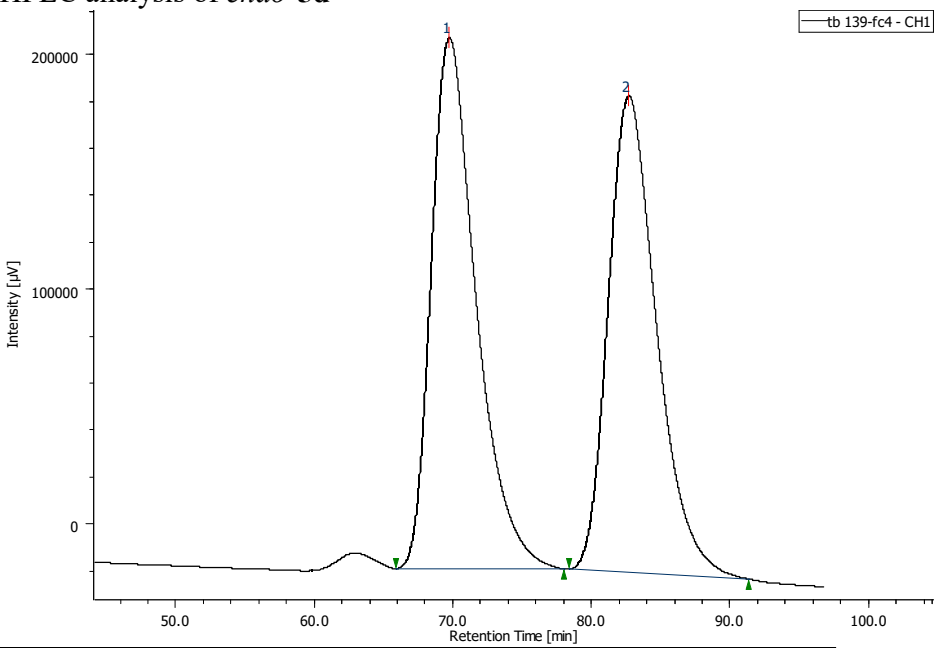


# Peak	CH	tR (min)	Area	Height	Area%
1	3	47.933	4381988	65018	94.284
2	3	91.825	265644	2156	5.716

89% ee

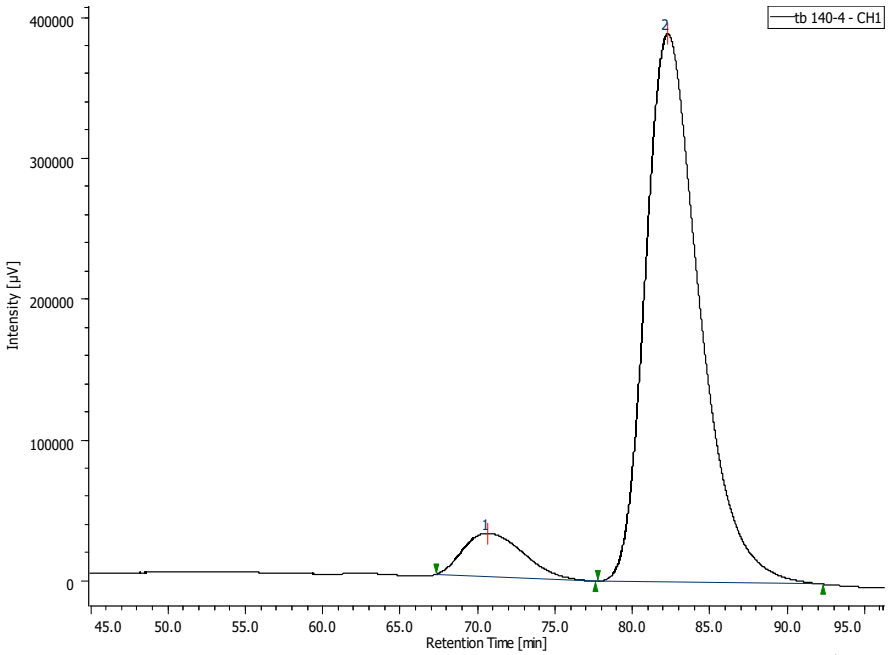
Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 93:7, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C

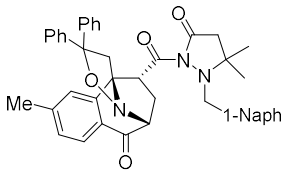
HPLC analysis of *endo*-**5d**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	69.717	50830197	225708	50.829
2	3	82.658	49172665	202683	49.171

Racemate



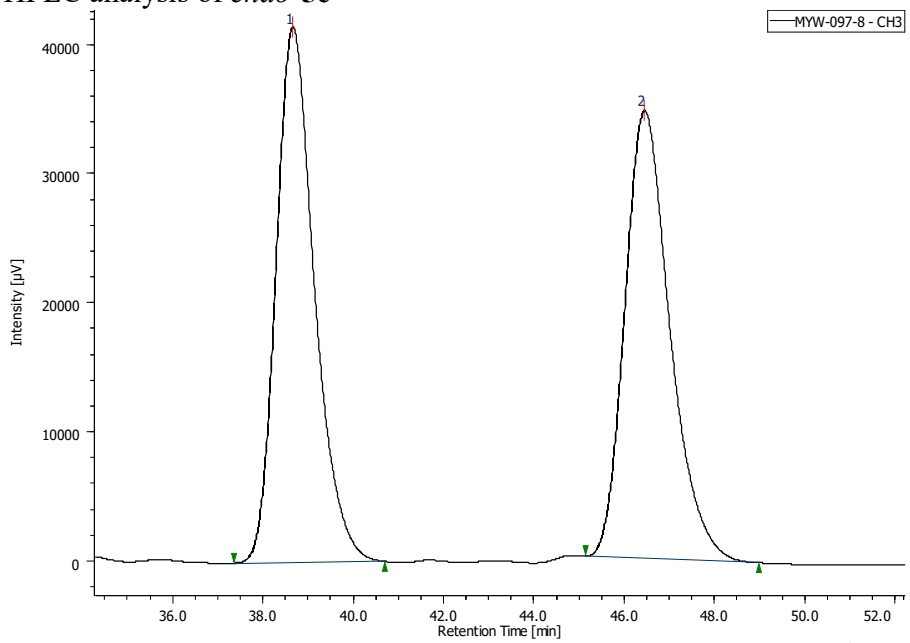


# Peak	CH	tR (min)	Area	Height	Area%
1	3	70.617	8289119	30527	8.088
2	3	82.242	94201168	388347	91.912

84% ee

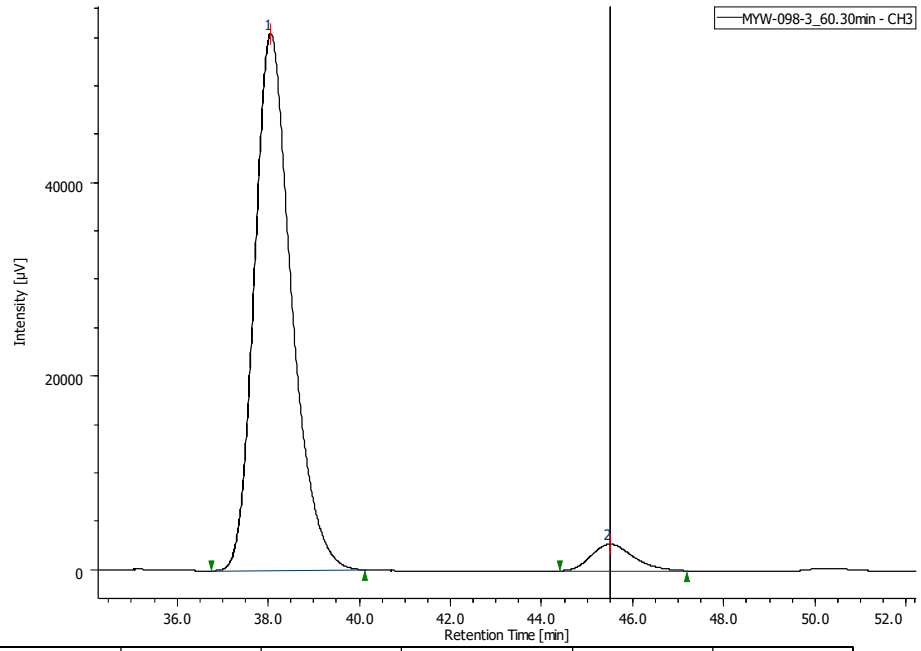
Daicel Chiralcel OZ-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C

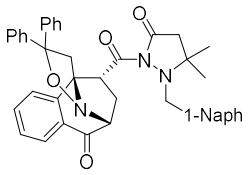
HPLC analysis of *endo*-**5e**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	38.658	2441408	41379	50.437
2	3	46.433	2399102	34629	49.563

Racemate



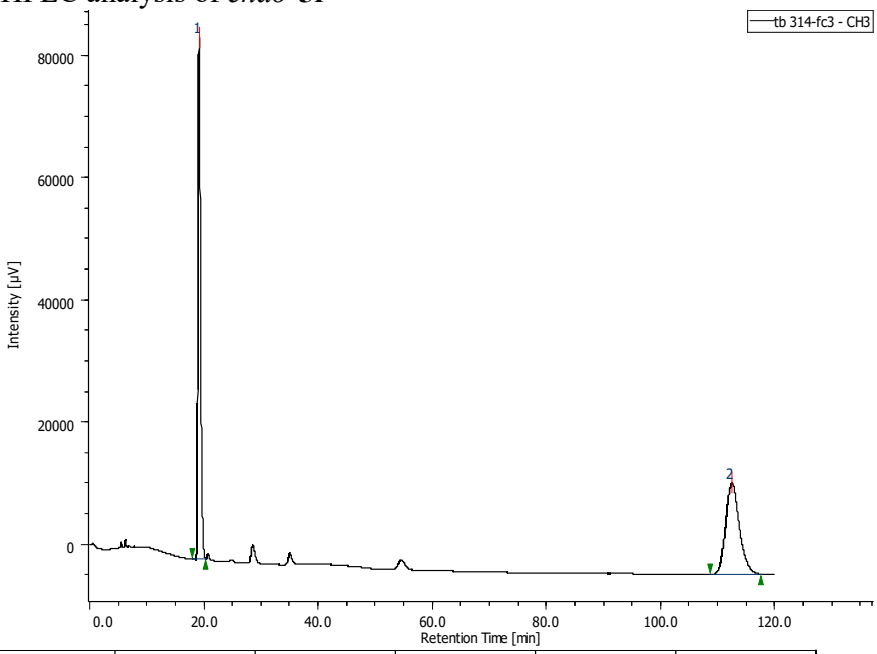


# Peak	CH	tR (min)	Area	Height	Area%
1	3	38.05	3126691	55381	94.6
2	3	45.492	178463	2766	5.4

89% ee

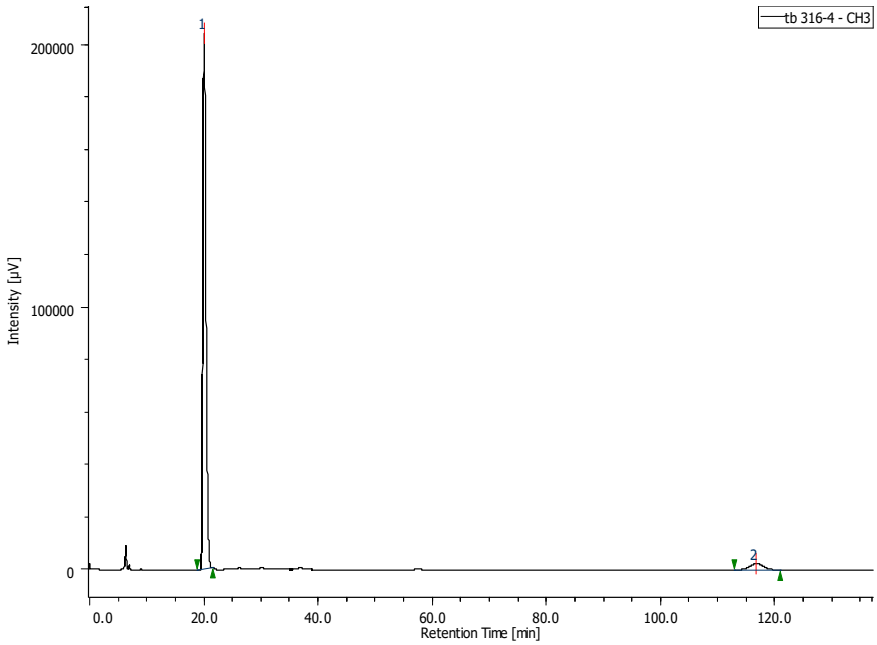
Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C

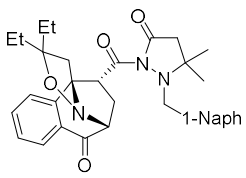
HPLC analysis of *endo*-**5f**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	19.15	2528274	85261	50.305
2	3	112.35	2497627	14928	49.695

Racemate



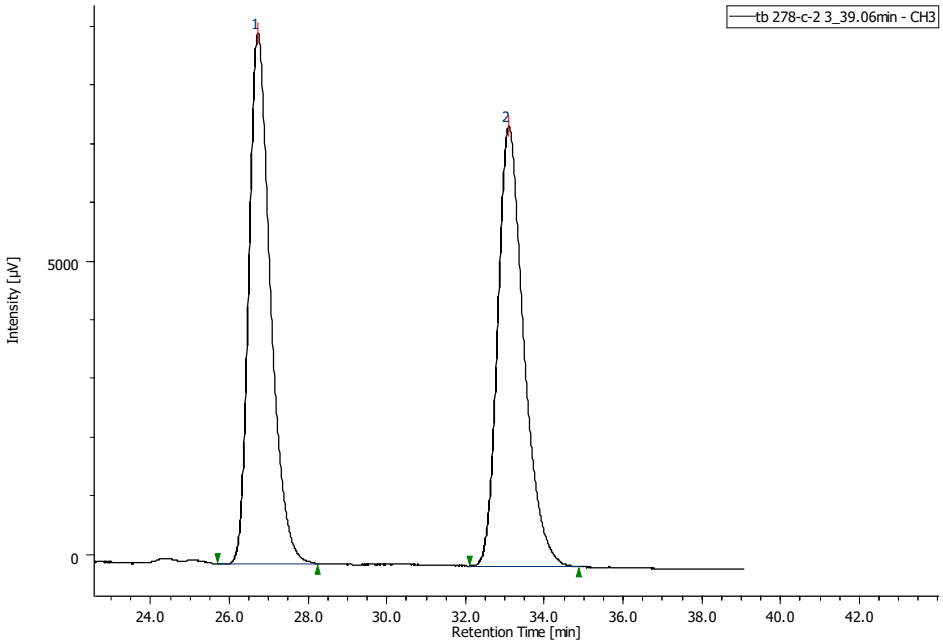


# Peak	CH	tR (min)	Area	Height	Area%
1	3	20.05	7539283	203689	94.371
2	3	116.558	449685	2533	5.629

89% ee

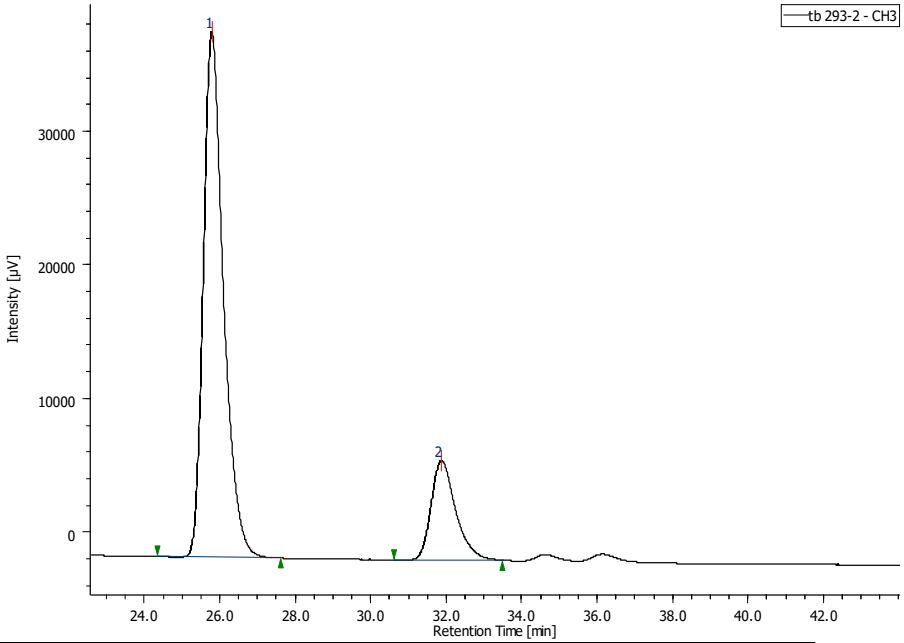
Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C

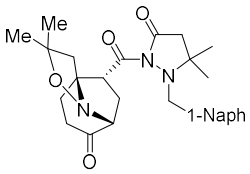
HPLC analysis of *endo*-**5g**



# Peak	CH	tR (min)	Area	Height	Area%
1	3	26.725	342220	9031	49.961
2	3	33.083	342751	7480	50.039

Racemate





# Peak	CH	tR (min)	Area	Height	Area%
1	3	25.783	1450775	39243	81.323
2	3	31.867	333186	7404	18.677

63% ee

Daicel Chiralpak AD-3, Hexane:*i*-PrOH = 90:10, v/v, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C