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Asymmetric synthesis of N-stereogenic molecules: Diastereoselective double aza-Michael reaction

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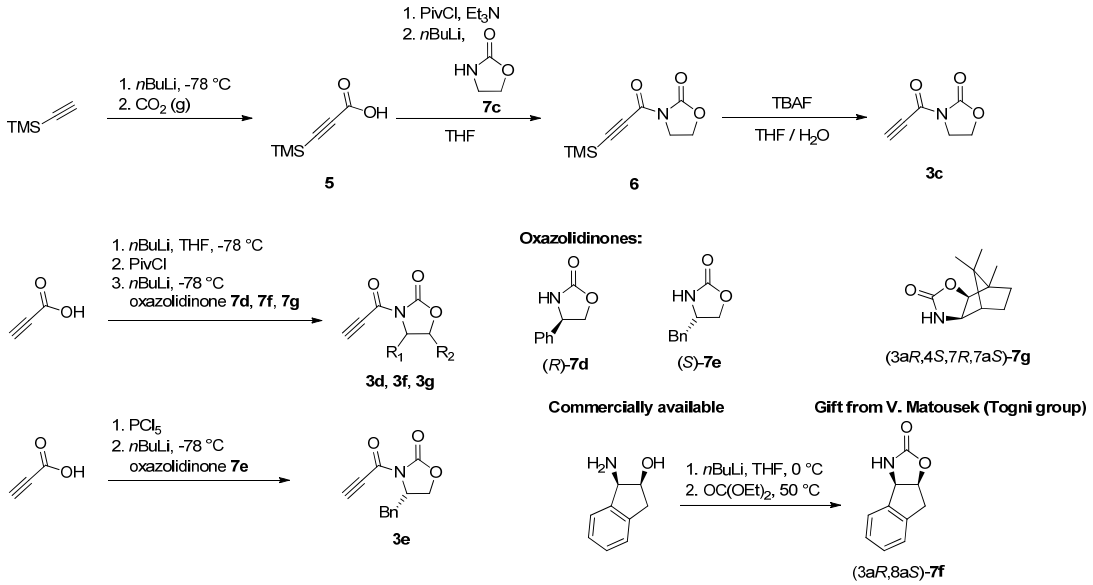
General

Flash chromatography was performed with Fluka silica gel 60. NMR spectra were measured on Bruker Avance III HD Nanobay-300 and III HD Nanobay-400 spectrometers. The chemical shifts are recorded in ppm and are referenced to to tetramethylsilane (^{1}H and ^{13}C). The ^{2}D lock frequency of CD_2Cl_2 or $CDCl_3$ was used as the internal secondary reference in all cases. High-resolution mass spectra were measured by the MS-Service of the "Laboratorium für Organische Chemie der ETH" on a Bruker Daltonics maXis ESI-QTOF. IR spectra were recorded on FT-IR Nicolet 6700 with CsI-optics. Optical rotation was measured on MCP 200 Polarimeter from Anton Paar. Circular dichroism spectra were recorded on a Jasco J-715 CD-spectropolarimeter (10^{-5} M, hexane, 25 °C). X-ray structure of **1a** was measured on a Bruker APEX2 CCD area detector diffractometer with Mo-K_α radiation. Single crystal was coated at room temperature with perfluoroalkylether oil and mounted on a polymer pin. The structures were solved by direct methods in SHELXTL and successive interpretation of the difference Fourier maps, followed by full-matrix least-squares refinement (against F^2). CCDC 938744 (2-(2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocin-13-yl) acetic acid **1a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif and are also available in the supporting information for this article.

Substrate synthesis

Propiolic acid **3a** and methyl propiolate **3b** are commercially available (**3a** from TCI and **3b** from ABCR). The propiolyloxazolidinones **3c**-**3f** were synthesized as depicted in Scheme 1.



Scheme 1. Synthesis of substrates for DAMA.

3-(Trimethylsilyl)propiolic acid (**5**) was prepared from trimethylsilylacetylene according to a modified literature procedure.[1] Subsequently, **5** was transformed into a mixed anhydride with pivaloyl chloride and coupled with lithiated oxazolidin-2-one affording **6**.[2] Finally, the TMS-group was cleaved with TBAF to give propiolyloxazolidinone **3c**. The chiral propiolyloxazolidinones **3d**, **3f** and **3g** were prepared via mixed anhydride

[1] J. Kendall, R. McDonald, M. J. Ferguson, R. R. Tykwinski, *Org. Lett.* **2008**, *10*, 2163-2166.
[2] K.-i. Takao, N. Hayakawa, R. Yamada, T. Yamaguchi, H. Saegusa, M. Uchida, S. Samejima, K.-i. Tadano, *J. Org. Chem.* **2009**, *74*, 6452-6461.

applying the modified procedure reported in the literature.[3] The substrate **3e** was obtained using propioyl chloride.[4] Commercially available (*R*)-(-)-4-phenyl-2-oxazolidinone and (*S*)-4-benzyl-2-oxazolidinone were purchased from Acros or TCI, respectively. Oxazolidinone (3a*R*,8a*S*)-**7f** was synthesized according to a modified literature procedure[5] and oxazolidinone (3a*R*,4*S*,7*R*,7a*S*)-**7g** was obtained as a generous gift from V. Matousek (Togni group).
Tetrahydrodiazocines **2a** and **2b** were prepared by the method reported by Try *et al.*[6]

Synthesis of 3-(trimethylsilyl)propiolic acid (5)

TMS-acetylene (4 g, 41 mmol) was dissolved in dry THF (100 mL) at -78 °C under argon atmosphere. *n*BuLi (1.6 M in hexane, 25.6 mL, 41 mmol) was added dropwise and the resulting mixture was stirred at -78 °C for 30 min. The cooling bath was removed and carbon dioxide was bubbled through the solution for 30 min. A thick white suspension was formed and it was stirred at r.t. for 30 min. Diethylether (80 mL), water (90 mL) and HCl solution (1 M, 45 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the title compound **5** as a white solid (5.8 g, 100%).
^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 0.21 (s, 9H, C*H*$_3$Si), 10.75 (bs, 1H, O*H*).

Synthesis of 3-(3-(trimethylsilyl)propioloyl)oxazolidin-2-one (6)

Pivalolyl chloride (0.98 mL, 7.9 mmol, 1.4 equiv) and NEt_3 (1.1 mL, 7.9 mmol, 1.4 equiv) were added to a solution of 3-(trimethylsilyl)propiolic acid (1.12 g, 7.9 mmol, 1.4 equiv) in THF (52 mL) at -78 °C. The mixture was allowed to warm sequentially to -40 °C and stirred at the same temperature for 15 min. Then it was warmed to 0 °C and the stirring was continued for 1 h. In a separate flask, a solution of *n*BuLi (1.6 M, 3.9 mL, 6.2 mmol, 1.1 equiv) was added to a solution of oxazolidinone **7c** (0.49 g , 5.64 mmol, 0.7 equiv) in THF (16 mL) at -40 °C and the mixture stirred for 15 min at the same temperature. The lithiated oxazolidinone was transferred via syringe to the mixed anhydride. The formed mixture was allowed to warm to r.t. and the stirring was continued for 1 h. The reaction was quenched with a $KHSO_4$ solution (aq, 2 M, 125 mL) and extracted with EtOAc (3 x 100 mL). Combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc 3:1) to afford the title compound **6** as a yellow oil (0.71 g, 59%) which solidifies upon standing.
^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] 4.43 (t, *J* = 7.9 Hz, 2H, C*H*$_2$O), 4.04 (t, *J* = 7.9 Hz, 2H, C*H*$_2$N), 0.29 (s, 9H, C*H*$_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ [ppm] = 151.8 (*C*O), 150.1 (*C*O), 103.2 (*C*C), 94.2 (*C*C), 62.0 (*C*H$_2$O), 42.3 (*C*H$_2$N), -1.0 (*C*H$_3$Si); IR (ATR, neat): 1/λ [cm^{-1}] = 2959, 2168, 2112, 1791, 1652, 1386, 1362, 1321, 1212, 1035, 751, 735, 647; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_9H_{14}NO_3Si$: 212.0737, found: 212.0737.

Synthesis of 3-propioloyloxazolidin-2-one (3c)

A solution of TBAF in THF (1 M, 70 µL, 0.07 mmol, 0.03 equiv) was added to a solution of TMS-protected oxazolidinone **6** in THF/H_2O (15:1, 10 mL) at 0 °C and the resulting mixture stirred for 45 min at the same temperature. The reaction was diluted with H_2O (15 mL), extracted with EtOAc (3 x 10 mL) and the combined organic layers washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc 1:1) to afford the title compound **3c** as a light orange powder (121 mg, 35%).
M.p. = 113.5-114.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 4.44 (dd, *J* = 7.4, 8.6 Hz, 2H, C*H*$_2$O), 4.04 (dd, *J* = 8.5, 7.4 Hz, 2H, C*H*$_2$N), 3.46 (s, 1H, CC*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 151.9 (*C*O), 149.9 (*C*O), 83.6 (*C*C), 74.4 (*C*C), 62.3 (*C*H$_2$O), 42.3 (*C*H$_2$N); IR (ATR, neat): 1/λ [cm^{-1}] = 3249, 2117, 1780, 1651, 1472, 1383, 1364,

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[3] N. A. Eddy, P. D. Morse, M. D. Morton, G. Fenteany, *Synlett* **2011**, 699–701.
[4] Synthesis of propiolyl chloride: a) J. R. Wehler, W. A. Feld, *J. Chem. Eng. Data* **1989**, *34*, 142–143; b) W. J. Balfour, C. C. Greig, S. Visaisouk, *J. Org. Chem.* **1974**, *39*, 725–726.
[5] Matoušek, V.; Togni, A.; Bizet, V.; Cahard, D. *Org. Lett.* **2011**, 13, *5762–5765*.
[6] A. B. Mahon, D. C. Craig, A. C. Try, *Arkivoc.* **2008,** 148-163.

1342, 1213, 1114, 1027, 964, 754, 672; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_6H_5NO_3Na$: 162.0162, found: 162.0158.

Synthesis of (*R*)-4-phenyl-3-propioloyloxazolidin-2-one (3d)

A solution of *n*BuLi in hexane (1.6 M, 2.5 mL, 4.0 mmol, 1.3 equiv) was added dropwise to a solution of propiolic acid (0.23 mL, 3.7 mmol, 1.2 equiv) in THF (10 mL) at -78 °C under argon. The slowly forming white suspension was allowed to warm up to r.t. while being stirred for 45 min. Then it was cooled to 0 °C and pivaloyl chloride (0.46 mL, 3.7 mmol, 1.2 equiv) was added dropwise. The obtained solution was stirred for 2 h at the same temperature. In a separate flask, oxazolidinone **7d** (0.5 g, 3.1 mmol, 1.0 equiv) was dissolved in THF (10 mL) and cooled to -78 °C. A solution of *n*BuLi in hexane (1.6 M, 2.0 mL, 3.4 mmol, 1.1 equiv) was added dropwise and the suspension was stirred for 15 min at the same temperature. The freshly prepared solution of pivaloyl anhydride was transferred to the solution of lithiated oxazolidinone by syringe over 10 min. The formed clear red solution was allowed to warm up to r.t. and then stirred for an additional 1 h at r.t. The reaction was quenched with an NH_4Cl solution (aq, sat, 5 mL) and diluted with H_2O (5 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), the organic layers were washed with a $NaHCO_3$ solution (aq, sat, 10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc 7:3) to afford the title compound **3d** as a white powder (460 mg, 69%)**.**

M.p.: 155-158 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.44-7.29 (m, 5H, Ar), 5.43 (dd, *J* = 8.6, 3.7 Hz, 1H, C*H*N), 4.72 (t, *J* = 9.0 Hz, 1H, C*H*O), 4.33 (dd, *J* = 9.0, 3.7 Hz, 1H, C*H*O), 3.42 (s, 1H, CC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 152.1 (*C*(O)NO), 149.5 (*C*(O)NC), 137.9, 129.5, 129.2, 126.2, 83.4 (*C*(CO)), 74.6 (C*C*H), 70.2 (*C*H_2), 57.6 (*C*HPh); IR (ATR, neat): 1/λ [cm^{-1}] = 3254, 2109, 1777, 1659, 1379, 1323, 777; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{12}H_9NNaO_3$: 238.0475; found: 238.0457; $[\alpha]_D^{20}$ -32.85 (*c* 1.000, $CHCl_3$).

Synthesis of (*S*)-4-benzyl-3-propioloyloxazolidin-2-one (3e)

Synthesis of propiolyl chloride: (*Caution*! Propiolyl chloride is a strong lachrymator which decomposes slowly at r.t. and fast at higher temperatures to spontaneously inflammable chloroacetylene). All operations were conducted in the dark. To a flask containing PCl_5 (32.8 g, 157.5 mmol, 1.05 equiv) connected to two consecutive cooling traps was added dropwise propiolic acid (9.3 mL, 150.0 mmol, 1.00 equiv) at 0 °C. The reaction flask was flushed with a slight stream of Ar until gas evolution stopped (the exhaust was connected to a washing bottle containing ammonia solution (30%, aq)). The first trap was cooled to -78 °C (to capture most of $POCl_3$) and the second to -196 °C (to capture the product). The flask containing the reaction mixture was allowed to warm to r.t. and a vacuum was applied. Propiolyl chloride was collected in the -196 °C trap as a colorless liquid which was redistilled under identical fashion to afford 14.5 g of a colorless mixture of propiolyl chloride as well as smaller amounts of $POCl_3$ and 3-chloroacryloyl chloride as byproducts. The mixture was always stored in the dark at -20 °C or -78 °C when not used for periods longer than 3 days.
^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 3.62 (s, 1H).

A solution of *n*BuLi in hexane (1.6 M, 1.9 mL, 3.10 mmol, 1.1 equiv) was added dropwise to a solution of the oxazolidinone **7e** (0.5 g, 2.82 mmol, 1.0 equiv) in THF (15 mL) at -78 °C and the resulting solution was stirred for 15 min at the same temperature. Propiolyl chloride (0.3 g, 3.39 mmol, 1.2 equiv) was added dropwise to the reaction and stirring was continued for 30 min at -78 °C. The reaction was allowed to warm to r.t. over 30 min, quenched with a NH_4Cl solution (aq, sat, 5 mL), diluted with H_2O (50 mL), extracted with EtOAc (3 x 50 mL) and the combined organic layers washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, hexane/EtOAc 7:3) to afford the title compound **3e** as a white powder (390 mg, 60%).

M.p.: 145-147 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.36-7.18 (m, 5H, Ar*H*), 4.68 (ddt, *J* = 9.6, 7.1, 3.5 Hz, 1H, C*H*N), 4.25- 4.16 (m, 2H, C*H*O), 3.44 (s, 1H, CC*H*), 3.32 (dd, *J* = 13.5, 3.4 Hz, 1H, C*H*Ph), 2.80 (dd, *J* = 13.5, 9.6 Hz, 1H, C*H*Ph); ^{13}C NMR (63 MHz, $CDCl_3$): δ [ppm] = 151.8 (*C*O), 149.9 (*C*O), 134.8, 129.5, 129.2, 127.7, 83.5 (*C*(CO), 74.7 (C*C*H), 66.3 (*C*H_2O), 55.2 (*C*HN), 37.6 (*C*H_2Ph); IR (ATR, neat): 1/λ [cm^{-1}] = 3225, 2110, 1792, 1664,

1354, 704; HRMS (ESI): m /z $[M+H]^+$ calcd for $C_{13}H_{12}NO_2$: 230.0812, found: 230.0812; $[\alpha]_D^{20}$ +72.73 (*c* 0.506, $CHCl_3$).

Synthesis of (3a*R*,8a*S*)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one (7f)

A solution of *n*BuLi in hexane (1.6 M, 26.9 mL, 43.0 mmol, 1.1 equiv) was added dropwise to a suspension of (1*R*,2*S*)-1-amino-2,3-dihydro-1H-inden-2-ol (5.83 g, 39.1 mmol, 1.0 equiv) in THF (250 mL) at 0 °C and the resulting solution was stirred at the same temperature for 15 min. Diethyl carbonate (47.5 mL, 390.8 mmol, 10.0 equiv) was added dropwise and the formed suspension was heated to 50-60 °C for 2 h. The suspension was cooled to 0 °C, the reaction quenched with an NH_4Cl solution (aq, sat, 20 mL) and H_2O (200 mL). The aqueous layer was extracted with EtOAc (3 x 150 mL) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was suspended in $CHCl_3$ (10 mL) and pentane (200 mL) and filtered. The obtained solid was washed with a cold (0 °C) Et_2O/pentane (200 mL, 1:1) mixture to afford title compound **7f** as a greyish crystalline powder (6.4 g, 94%).
^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.34-7.22 (m, 4H, Ar), 6.44 (bs, 1H, O*H*), 5.42 (m, 1H, C*H*), 5.17 (d, *J* = 7.3 Hz, 1H, C*H*), 3.46-3.30 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 159.6 (*C*O), 140.3, 139.9, 129.6, 128.1, 125.8, 124.8, 80.7 (O*C*H), 61.3 (N*C*H), 39.0 (*C*H_2); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{10}NO_2$: 176.0712, found: 176.0706.

Synthesis of (3a*R*,8a*S*)-3-propioloyl-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one (3f)

A solution of *n*BuLi in hexane (1.6 M, 2.3 mL, 3.71 mmol, 1.3 equiv) was added dropwise to a solution of propiolic acid (0.22 mL, 3.43 mmol, 1.2 equiv) in THF (10 mL) at -78 °C and the slowly forming suspension was allowed to warm up to r.t. while being stirred for 45 min. The obtained white suspension was cooled to 0 °C and pivaloyl chloride (0.45 mL, 3.43 mmol, 1.2 equiv) was added dropwise. The resulting solution was stirred for 2 h at the same temperature. In a separate flask, oxazolidinone **7f** (0.5 g, 3.1 mmol, 1.0 equiv) was dissolved in THF (10 mL) and cooled to -78 °C. A solution of *n*BuLi in hexane (1.6 M, 2.0 mL, 3.4 mmol, 1.1 equiv) was added dropwise and the suspension was allowed to stir for 15 min at the same temperature. The freshly prepared pivaloyl anhydride solution was transferred to the lithiated oxazolidinone solution by syringe over 10 min. The formed clear red solution was allowed to warm up to r.t. upon complete addition and then stirred for an additional hour at r.t. The reaction was quenched with an NH_4Cl solution (aq, sat, 10 mL) and diluted with H_2O (10 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with a $NaHCO_3$ solution (aq, sat, 40 mL), H_2O (10 mL) and brine (40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc 2:1) to afford the title compound **3f** as a white powder (320 mg, 49%).
M.p.: 136-139 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.65-7.62 (m, 1H, Ar), 7.40-7.27 (m, 3H, Ar), 5.94 (d, *J* = 7.0 Hz, 1H, C*H*N), 5.33 (ddd, *J* = 7.1, 4.5, 2.7 Hz, 1H, C*H*O), 3.46 (s, 1H, CC*H*), 3.43-3.41 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 151.5 (*C*O), 150.4 (*C*O), 139.5, 138.2, 130.4, 128.5, 127.5, 125.5, 84.0, 78.5, 74.6, 63.1, 38.1; IR (ATR, neat): 1/λ [cm^{-1}] = 3266, 2114, 1795, 1657, 1365, 1176, 1017, 743; HRMS (ESI): m /z $[M+H]^+$ calcd for $C_{13}H_{10}NO_2$: 228.0656, found: 228.0655; $[\alpha]_D^{20}$ -287.35 (*c* 0.506, $CHCl_3$).

Synthesis of (3a*S*, 4*R*, 7*S*, 7a*R*)-7,8,8-Trimethyl-3-propioloylhexahydro-4,7-methanobenzo[*d*]oxazol-2(3*H*)-one (3g)

A solution of *n*BuLi in hexane (1.6 M, 4.2 mL, 6.6 mmol, 1.3 equiv) was added dropwise to a solution of propiolic acid (0.38 mL, 6.2 mmol, 1.2 equiv) in Et_2O (20 mL) at -78 °C and the slowly forming suspension was allowed to warm up to r.t. while being stirred for 45 min. The formed white suspension was cooled to 0 °C and pivaloyl chloride (0.75 mL, 6.2 mmol, 1.2 equiv) was added dropwise. The formed solution was stirred for 2 h at the same temperature. In a separate flask, oxazolidinone **7g** (1.0 g, 5.1 mmol, 1.0 equiv) was dissolved in THF (30 mL) and cooled to -78 °C. A solution of *n*BuLi in hexane (1.6 M, 3.5 mL, 5.6 mmol, 1.1 equiv) was added dropwise and the suspension was allowed to stir for 15 min at the same temperature. The freshly prepared pivaloyl anhydride solution was transferred to the lithiated oxazolidinone solution by syringe over 10 min and

the formed clear red solution was allowed to warm up to r.t. upon complete addition and then stirred at r.t. for an additional 1 h. The reaction was quenched with a NH_4Cl solution (aq, sat, 5 mL) and diluted with H_2O (30 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL), the organic layers washed with a $NaHCO_3$ solution (aq, sat, 50 mL), H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc 2:1) to afford the title compound **3g** as a white powder (0.5 g, 40%).
M.p.: 142-143 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 4.32 (d, *J* = 7.9 Hz, 1H, C*H*O), 4.19 (d, *J* = 7.9, 1H, C*H*N), 3.43 (s, 1H, CC*H*), 2.32 (d, *J* = 4.6 Hz, 1H, C*H*), 1.87-1.77 (m, 1H, CH*H*), 1.64-1.55 (m, 1H, C*H*H), 1.18-1.02 (m, 5H, CH_2, CH_3), 0.98 (s, 3H, CH_3), 0.90 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 152.8 (NCO(O)), 150.2 (*C*O), 85.5, 83.3, 74.9, 62.5, 48.9, 46.8, 46.2, 31.6, 25.1, 23.0, 19.6, 10.7; IR (ATR, neat): 1/λ [cm^{-1}] = 3281, 2961, 2112, 1767, 1659, 1373, 1330, 1049, 757; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{18}NO_3$: 248.1281, found 248.1276; $[\alpha]_D^{20}$ -72.27 (*c* 0.220, $CHCl_3$).

Double aza-Michael conjugate addition

Synthesis of 2-(2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocin-13-yl) acetic acid (1a)

Tetrahydrodiazocine **2a** (160 mg, 0.67 mmol) and propiolic acid (52 mg, 0.74 mmol, 1.1 equiv) were placed into a flask under argon and anhydrous methanol (4 mL) and anhydrous DCM (4 mL, to improve the solubility of propiolic acid) were added. The resulting mixture was stirred at r.t. for 24 h. Solvent was evaporated and the residue was dissolved in DCM (10 mL). A solution of sodium hydroxide (5 mL, 1 M) was added, the organic phase was separated and disposed. A solution of hydrochloric acid (5 mL, 1 M) was added to the aqueous phase and it was extracted with DCM (3x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to yield the title compound **1a** as a yellowish solid (163 mg, 79%). Crystals suitable for X-ray analysis were obtained by vapor diffusion of *n*-pentane into DCE.
M.p.: decarboxylation observed at 85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.00-7.09 (m, 4H, Ar*H*), 6.75 (s, 2H, Ar*H*), 4.74 (d, ^2J = 16.6 Hz, 1H, Ar-CH^{exo}), 4.49-4.56 (m, 2H, Ar-CH^{exo}, NC*H*N), 4.19 (d, ^2J = 16.6 Hz, 1H, Ar-CH^{endo}), 4.07 (d, ^2J = 17.6 Hz, 1H, Ar-CH^{endo}), 2.78 (dd, ^2J = 16.1 Hz, ^3J = 5.6 Hz, 1H, C*H*CO), 2.71 (dd, ^2J = 16.1 Hz, ^3J = 9.7 Hz, 1H, C*H*CO), 2.24 (s, 6H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 171.2, 145.8, 139.6, 135.5, 134.9, 129.4, 128.8, 127.5, 127.4, 126.3, 126.2, 126.1, 125.0, 69.9 (N*C*HN), 59.7 (*C*H^{exo}H^{endo}), 52.0 (*C*H^{exo}H^{endo}), 35.8 (CH_AH_BCO), 21.0 (CH_3); IR (ATR, neat): 1/λ [cm^{-1}] = 824, 1183, 1494, 1717, 2337, 2361, 2856, 2915; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{21}N_2O_2$: 309.1598, found: 309.1595.

Synthesis of methyl 2-(2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocin-13-yl)acetate (1b)

Tetrahydrodiazocine **2a** (200 mg, 0.84 mmol) was placed into the flask and methanol (8 mL) followed by methyl propiolate (83 µL, 0.92 mmol, 1.1 equiv). The resulting mixture was stirred at r.t. for 5 h and the milky solution turned transparent. The solvent was then evaporated and the crude mixture was purified by flash chromatography (SiO_2 (40 g), Hex:EtOAc = 3:1) to give the title compound **1b** as a white solid (258 mg, 95%).
M.p.: 139-141 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.04-6.93 (m, 4H, Ar*H*), 6.71-6.69 (m, 2H, C(1)*H*, C(7)*H*), 4.74-4.66 (m, 2H, C(13)*H*, C(6)H^{exo}), 4.50 (d, ^2J = 17.5 Hz, 1H, C(12)H^{exo}), 4.14 (d, ^2J = 16.5 Hz, 1H, C(6)H^{endo}), 4.03 (d, ^2J = 17.5 Hz, 1H, C(12)H^{endo}), 3.71 (s, 3 H, OCH_3), 2.75 (dd, *J* = 15.5, 6.0 Hz, 1H, C(14)*H*), 2.66 (dd, *J* = 15.5, 8.0 Hz, 1H, C(14)*H*), 2.21 (s, 6 H, CH_3); ^{13} C NMR (75 MHz, $CDCl_3$): δ [ppm] = 171.2, 147.5, 142.7, 133.7, 133.5, 128.7, 128.1, 127.6, 127.4, 127.0, 126.4, 126.2, 124.9, 70.5 (*C(13)*), 60.7 (*C(6)*), 52.7 (*C(12)*), 52.0 (OCH_3), 37.2 (*C(14)*), 21.0 (2 x CH_3); IR (ATR, neat): 1/λ [cm^{-1}] = 2945, 2921, 2850, 1737, 1494, 835; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{20}H_{22}N_2O_2Na$: 345.1573, found: 345.1569.

Synthesis of 3-(2-(2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocin-13-yl)acetyl)oxazolidin-2-one (1c)

Tetrahydrodiazocine **2a** (200 mg, 0.84 mmol) and oxazolidinone **7c** (128 mg, 0.93 mmol, 1.1 equiv) were placed into the flask and methanol (12 mL) was added. The resulting mixture was stirred at r.t. for 1 h. The solvent was then evaporated and the crude mixture was purified by flash chromatography (SiO_2 (20 g), Hex:EA = 1:1) to give the title compound **1c** as a pale brown solid (292 mg, 92%).

M.p.: 98-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.02 (t, ^3J = 8.0 Hz, 2H, Ar), 6.96 (d, ^3J = 7.9 Hz, 2H, Ar), 6.72 (d, ^3J = 8.4 Hz, 2H, Ar), 4.86 (dd, ^3J = 4.8 Hz, ^3J = 8.2 Hz, 2H, NC*H*N), 4.77 (d, ^2J = 16.5 Hz, 2H, Ar-CH^{exo}), 4.62 (d, ^2J = 17.3 Hz, 2H, Ar-CH^{exo}), 4.26 – 4.36 (m, 2H, CH_2O), 4.17 (d, ^2J = 16.5 Hz, 2H, Ar-CH^{endo}), 3.98-4.07 (m, 3H, Ar-CH^{endo}, CH_2N), 3.39 (dd, ^2J = 16.8 Hz, ^3J = 8.3 Hz, 1H, C*H*CO), 3.27 (dd, ^2J = 16.8 Hz, ^3J = 4.9 Hz, 1H, C*H*CO), 2.21 (s, 6H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 170.1, 153.4, 147.5, 142.5, 133.6, 133.4, 128.5, 128.0, 127.6, 127.3, 127.1, 126.3, 126.0, 124.8, 69.4 (N*C*HN), 62.1 (*C*H_2O), 60.6 (*C*H^{exo}H^{endo}), 52.9 (*C*H^{exo}H^{endo}), 42.6 (*C*H_2N), 37.9 (*C*H_2CO), 20.9 (*C*H_3); IR (ATR, neat): 1/λ [cm^{-1}] = 710, 833, 952, 1038, 1110, 1322, 1384, 1492, 1776, 2916; HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{22}H_{23}N_3O_3Na$: 400.1632, found: 400.1638.

Synthesis of (4*R*)-3-(2-(2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocin-13-yl)acetyl)-4-phenyloxazolidin-2-one (1d)

Tetrahydrodiazocine **2a** (21 mg, 0.1 mmol) was placed into the flask and methanol (5 mL) was added followed by oxazolidinone (*R*)-**7d** (21 mg, 0.1 mmol, 1.0 equiv). The resulting mixture was stirred at r.t. for 2 h. The solvent was then evaporated and the crude mixture was purified by flash chromatography (SiO_2, Hex:EtOAc = 1:1) to give the title compound **1d** as white crystals (41 mg, 90%, d.r. 41:59).

^{1}H NMR (700 MHz, $CDCl_3$): δ [ppm] = 7.41-7.29 (m, 5H, -Ph), 7.00-6.92 (m, 4H, Ar), 6.70-6.68 (m, 2H, C(1)*H*, C(7)*H*), 5.50 (dd, *J* = 8.9, 4.6 Hz, 1H, *maj*-C*H*Ph), 5.45 (dd, *J* = 8.6, 3.3 Hz, 1H, *min*-C*H*Ph), 4.82 (t, *J* = 7.2 Hz, 1H, *maj*-C(13)*H*), 4.77 (dd, *J* = 9.1, 3.8 Hz, 1H, *min*-C(13)*H*), 4.70 (d, *J* = 16.6 Hz, 1H, *min*-C(6)H^{exo}), 4.68 (d, *J* = 16.5 Hz, 1H, *maj*-C(6)H^{exo}), 4.67 (t, *J* = 8.9 Hz, 1H, *maj*-H^b), 4.63 (t, *J* = 8.8 Hz, 1H, *min*-H^b), 4.60 (d, *J* = 17.2 Hz, 1H, *min*-C(12)H^{exo}), 4.57 (d, *J* = 17.3 Hz, 1H, *maj*-C(12)H^{exo}), 4.26 (dd, *J* = 8.9, 3.4 Hz, 1H, *min*-H^a), 4.18 (dd, *J* = 8.9, 4.6 Hz, 1H, *maj*-H^a), 4.14-4.09 (m, 1H, C(6)H^{endo}), 4.03 (d, *J* = 17.2 Hz, 1H, *min*-C(12)H^{endo}), 3.95 (d, *J* = 17.4 Hz, 1H, *maj*-C(12)H^{endo}), 3.53 (dd, *J* = 15.6, 7.2 Hz, 1H, *maj*-C(14)*H*), 3.40 (dd, *J* = 17.1, 9.1 Hz, 1H, *min*-C(14)*H*), 3.27 (dd, *J* = 17.1, 3.8 Hz, 1H, *min*-C(14)*H*), 3.17 (dd, *J* = 15.6, 7.1 Hz, 1 H, *maj*-C(14)*H*), 2.21 (s, 3H, *maj*-CH_3), 2.21 (s, 3H, *maj*-CH_3), 2.20 (s, 3H, *min*-CH_3), 2.19 (s, 3H, *min*-CH_3); ^{13}C NMR (176 MHz, $CDCl_3$): δ [ppm] = 169.7 (*maj*-*C*O), 169.6 (*min*-*C*O), 153.7 (*maj*-NCO), 153.7 (*min*-NCO), 147.7 (*maj-C(4a/10a)*), 147.6 (*min-C(4a/10a)*), 142.7 (*maj-C(6a/12a)*), 142.5 (*min-C(6a/12a)*), 138.6 (*Ph*), 133.7 (1C, *C(2/8)*), 133.6 (1C, *C(2/8)*), 133.5 (2C, *C(2/8)*), 129.3, 129.2, 128.9, 128.7, 128.6, 128.6, 128.1, 128.1, 127.8, 127.7, 127.4, 127.4, 127.2, 126.51, 126.4, 126.1, 126.0, 126.0, 125.9, 124.9, 124.8, 70.2 (*min*-CH^aH^b), 70.2 (*maj*-CH^aH^b), 70.0 (*maj-C(13)*), 69.4 (*min-C(13)*), 60.7 (*maj-C(6)*), 60.6 (*min-C(6)*), 57.8 (*min*-CHPh), 57.7 (*maj*-CHPh), 53.0 (*min-C(12)*), 52.7 (*maj-C(12)*), 38.4 (*maj-C(14)*), 38.3 (*min-C(14)*), 21.0 (*C*H_3), 21.0 (*C*H_3); IR (ATR, neat): 1/λ [cm^{-1}] = 2921, 2850, 1778, 1705, 1492, 1384, 1322, 1202, 1064, 1001, 832, 762, 712, 698; HRMS (ESI): m /z [M+H]$^+$ calcd for $C_{28}H_{28}N_3O_3$: 454.2126, found: 454.2125; HPLC (OD-H, hexane/*i*-PrOH 70:30, 0.5 mL/min): t_R = 16.5, 46.5 min.

Synthesis of (4*S*)-4-benzyl-3-(2-(2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocin-13-yl)acetyl)oxazolidin-2-one (1e)

Tetrahydrodiazocine **2a** (39 mg, 0.16 mmol) was placed into the flask and DCM (5 mL) followed by oxazolidinone (*S*)-**7e** (45 mg, 0.19 mmol, 1.2 equiv). The resulting mixture was stirred at r.t. for 3 h. The solvent was then evaporated and the crude mixture was purified by flash chromatography (SiO_2, pentane/Et_2O 2:1) to give the title compound **1e** as a white powder (74 mg, 95%, d.r. 43:57).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.27 (m, 5H, Ph), 7.14-7.00 (m, 4H, Ar), 7.14-7.00 (m, 2H, C(1)*H*, C(7)*H*), 4.95 (q, *J* = 6.2 Hz, 1H, C(13)*H*), 4.88-4.67 (m, 3H, NC*H*, C(6)H^{exo}, C(12)H^{exo}), 4.27-4.09 (m, 4H, OCH_2, C(6)H^{endo}, C(12)H^{endo}), 3.58-3.22 (m, 3H, C(14)*H,* PhCH_2), 2.97 (dd, *J* = 13.6, 8.4 Hz, 1H, *maj*-C(14)*H*), 2.88 (dd, *J* = 13.4, 9.4 Hz, 1H, *min*-C(14)*H*), 2.29-2.26 (m, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 170.1, 170.0, 153.4, 153.4,

147.7, 147.6, 142.7, 142.5, 135.3, 135.0, 133.7, 133.7, 133.5, 133.5, 129.7, 129.6, 129.5, 129.2, 129.1, 129.0, 128.6, 128.1, 128.1, 127.8, 127.7, 127.5, 127.4, 127.4, 127.3, 127.2, 126.5, 126.4, 126.1, 126.1, 125.0, 124.8, 83.5, 72.4, 69.7, 69.6, 66.3, 66.1, 62.0, 60.8, 60.7, 55.5, 55.2, 54.9, 53.1, 52.8, 38.4, 38.1, 37.8, 37.6, 37.6, 21.0; IR (ATR, neat): 1/λ [cm^{-1}] = 2918, 2857, 1774, 1968, 1491, 1389, 1351, 1278, 1209, 1148, 1126, 1109, 1046, 834, 761, 735, 703; HRMS (ESI): m /z $[M+H]^+$ calcd for $C_{29}H_{30}N_3O_3$: 468.2282; found: 468.2284; HPLC (OD-H, hexane/*i*-PrOH 70:30, 0.5 mL/min): t_R = 23.5, 51.4 min.

Synthesis of (3a*R*,8a*S*)-3-(2-(2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocin-13-yl)acetyl)-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazol-2-one (1f)

Tetrahydrodiazocine **2a** (135 mg, 0.56 mmol) was placed into the flask and DCM (50 mL) followed by oxazolidinone (3a*R*,8a*S*)-**7f** (154 mg, 0.68 mmol, 1.2 equiv) were added. The resulting mixture was stirred at r.t. for 24 h. The solvent was then removed under reduced pressure. The crude mixture was dissolved in HFIP (1 mL) and stirred at r.t. for 5 h. The solution was concentrated *in vacuo* and the residue was purified twice by column chromatography (SiO_2, toluene/MTBE 4:1 + 0.1% Et_3N). The (5*S*,11*S*)-diastereomer eluted first as an yellowish solid (177 mg, 71%, d.r. 99:1) which was recrystallized from hexane. The (5*R*,11*R*)-diastereomer eluted afterwards as a white solid (59 mg, 24%, d.r. 2:98). The removal of the residual solvents (especially toluene) from the solids proved highly challenging.

(5*S*,11*S*)-**1f**:

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 7.67 (d, *J* = 7.8 Hz, 1H), 7.37-7.33 (m, 1H, Ar), 7.30-7.25 (m, 2H, Ar), 7.06-6.95 (m, 4H, Ar), 6.74-6.69 (m, 2H, C(1)*H*, C(7)*H*), 5.97 (d, *J* = 6.8 Hz, 1H, NC*H*), 5.21 (dt, *J* = 6.9, 3.5 Hz, 1H, OC*H*), 4.92 (dd, *J* = 8.8, 4.1 Hz, 1H, C(13)*H*), 4.78 (d, *J* = 16.4 Hz, 1H, C(6)H^{exo} or C(12)H^{exo}), 4.60 (d, *J* = 17.3 Hz, 1H, C(6)H^{exo} or C(12)H^{exo}), 4.18 (d, *J* = 16.5 Hz, 1H, C(6)H^{endo} or C(12)H^{endo}), 4.04 (d, *J* = 17.4 Hz, 1H, C(6)H^{endo} or C(12)H^{endo}), 3.42-3.35 (m, 3H, CH_2, C(14)*H*), 3.27 (dd, *J* = 16.9, 4.2 Hz, 1H, C(14)*H*), 2.22 (s, 3H, CH_3), 2.21 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 170.4 ((NC*O*(O)), 152.9 (*C*O), 147.6, 142.5, 139.5, 139.2, 133.7, 133.5, 130.0, 128.6, 128.3, 128.1, 127.7, 127.5, 127.4, 127.2, 126.5, 126.1, 125.3, 124.8, 78.4 (*C*HO), 69.6 (N*C*N), 63.3 (*C*HN), 60.7 (*C(6)* or *(12)*), 53.0 (*C(6)* or *C(12)*), 38.1 (*C*H_2 or *C(14)*), 38.0 (*C*H_2 or *C(14)*), 21.0 (*C*H_3); IR (ATR, neat): 1/λ [cm^{-1}] = 2921, 2852, 1777, 1701, 1491, 1360, 1322, 1278, 1187, 1119, 1043, 955, 823, 754, 678; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{29}H_{28}N_3O_3$: 466.2125, found 466.2124; HPLC (IA, hexane/*i*-PrOH 80:20, 0.5 mL/min): t_R = 11.3 min; $[\alpha]_D^{20}$ -79.8 (*c* 0.460, $CHCl_3$).

(5*R*,11*R*)-**1f**:

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 7.69 (d, *J* = 7.6 Hz, 1H), 7.35-7.23 (m, 3H, Ar), 7.01-6.89 (m, 4H, Ar), 6.70 (bs, 2H, C(1)*H*, C(7)*H*), 5.97 (d, *J* = 6.9 Hz, 1H, NC*H*), 5.20 (ddd, *J* = 7.1, 4.9 2.3 Hz, 1H, OC*H*), 4.84 (t, *J* = 6.9 Hz, 1H, C(13)*H*), 4.76 (d, *J* = 16.5 Hz, 1H, C(6)H^{exo} or C(12)H^{exo}), 4.69 (d, *J* = 17.4 Hz, 1H, C(6)H^{exo} or C(12)H^{exo}), 4.13 (d, *J* = 16.6 Hz, 1H, C(6)H^{endo} or C(12)H^{endo}), 4.05 (d, *J* = 17.4 Hz, 1H, C(6)H^{endo} or C(12)H^{endo}), 3.40 (dd, *J* = 16.0, 7.2 Hz, 1H, C(14)*H*), 3.34-3.26 (m, 3H, CH_2, C(14)*H*), 2.20 (s, 3H, CH_3), 2.19 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 170.3 ((NC*O*(O)), 152.9 (*C*O), 147.7, 142.7, 139.4, 139.1, 133.6, 133.4, 129.8, 128.5, 128.1, 128.0, 127.7, 127.4, 127.3, 127.1, 126.4, 126.0, 125.1, 124.9, 78.3 (*C*HO), 69.7 (N*C*N), 62.9 (*C*HN), 60.7 (*C(6)* or *C(12)*), 52.7 (*C(6)* or *C(12)*), 37.94 (*C*H_2 or *C(14)*), 37.90 (*C*H_2 or *C(14)*), 20.9 (*C*H_3); IR (ATR, neat): 1/λ [cm^{-1}] = 2915, 2854, 1773, 1698, 1491, 1360, 1323, 1278, 1185, 1118, 1040, 954, 831, 752, 677; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{29}H_{28}N_3O_3$: 466.2125, found 466.2124; HPLC (IA, hexane/*i*-PrOH 80:20, 0.5 mL/min): t_R = 17.5 min; $[\alpha]_D^{20}$ -203.9 (*c* 0.590, $CHCl_3$).

Synthesis of (3a*R*,7a*S*)-3-(2-(2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-13-yl)acetyl)-4,8,8-trimethylhexahydro-4,7-methanobenzo[*d*]oxazol-2(3*H*)-one (1g)

Tetrahydrodiazocine **2a** (50.1 mg, 0.21 mmol) was placed into the flask and HFIP (4.2 mL) was added followed by oxazolidinone **7g** (62.2 mg, 0.25 mmol, 1.2 equiv). The resulting mixture was stirred at r.t. for 23 h. The solvent was then evaporated and the crude mixture was purified by flash chromatography (SiO_2, cyclohexane/Et_2O 1:1) to give the title compound **1g** as a white solid (60 mg, 59%, d.r. 65:35).

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.05-6.93 (m, 4H, Ar), 6.72-6.69 (m, 2H, C(1)*H*, C(7)*H*), 4.87-4.81 (m, 1H, C(13)*H*), 4.79-4.58 (m, 2H, C(6)H^{exo}, C(12)H^{exo}), 4.26-3.99 (m, 4H, C(6)H^{exo}, C(12)H^{exo}, C*H*O, C*H*N), 3.46-3.13 (m, 2H, C(14)*H*), 2.37 (d, *J* = 4.5 Hz, 1H, *min*-^{t}C*H*), 2.34 (d, *J* = 4.5 Hz, 1H, *maj*-^{t}C*H*), 2.21-2.19 (m, 6H, CH_3), 1.86-1.74 (m, 1H, C*H*H), 1.61-1.52 (m, 1H, C*H*H), 1.16-0.86 (m, 11H, 3 CH_3, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 170.2 (*maj*-NC*O*(O)), 170.2 (*min*-NC*O*(O)), 154.3 (*min*-NC(O)), 154.3 (*maj*-NC(O)), 147.7, 147.6, 142.7, 142.6, 133.6, 133.5, 133.4, 133.4, 128.5, 128.5, 128.0, 128.0, 127.7, 127.7, 127.4, 127.3, 127.2, 126.5, 126.4, 126.1, 126.0, 124.9, 124.8, 85.3, 69.6, 69.5, 63.0, 62.8, 60.8, 60.6, 53.0, 52.8, 48.7, 47.1, 46.9, 46.1, 46.0, 38.3, 38.2, 31.6, 31.6, 25.1, 25.0, 23.0, 20.9, 19.5, 19.4, 10.7, 10.6; IR (ATR, neat): 1/λ [cm^{-1}] = 2957, 2923, 1771, 1699, 1492, 1375, 1330, 1207, 1129, 907, 726; HRMS (ESI): m /z $[M+H]^+$ calcd for $C_{30}H_{36}N_3O_3$: 486.2751, found 486.2756; HPLC (IA, hexane/*i* -PrOH 80:20, 1.5 mL/min): t_R = 5.5, 6.6 min.

Synthesis of (4*R*)-3-(2-(2,8-dibromo-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-13-yl)acetyl)-4-phenyloxazolidin-2-one (1d)

Tetrahydrodiazocine **2b** (22 mg, 0.06 mmol, 1.0 equiv) and the oxazolidinone (*R*)-**7d** (15 mg, 0.07 mmol, 1.2 equiv) were dissolved in MeOH (3 mL) at r.t. and stirred at the same temperature for 5 h. The solution was concentrated *in vacuo* and the crude product purified by column chromatography (SiO_2, hexane/EtOAc 1:1) to afford the title compound **1d** as a white powder (30 mg, 86%, d.r. 54:46).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.23 (m, 7H, Ar), 7.05-7.03 (m, 2H, Ar) 6.97-6.89 (m, 2H, Ar), 5.50 (dd, *J* = 8.9, 4.4 Hz, 1H, *maj*-NC*H*), 5.44 (dd, *J* = 8.6, 3.4 Hz, 1H, *min*-NC*H*), 4.78-4.54 (m, 4H, C(13)*H*, C(6)H^{exo}, C(12)H^{exo}, H^b), 4.29 (dd, *J* = 8.9, 3.4 Hz, 1H, *min*-H^a), 4.22 (dd, *J* = 8.9, 4.4 Hz, 1H, *maj*-H^a), 4.12-3.91 (m, 2H, C(6)H^{endo}, C(12)H^{endo}), 3.49 (dd, *J* = 15.7, 7.3 Hz, 1H, H-*maj*-C(14)*H*), 3.35 (dd, *J* = 17.0, 8.9 Hz, 1H, *min*-C(14)*H*), 3.23 (dd, *J* = 17.0, 4.2 Hz, 1H, *min*-C(14)*H*), 3.13 (dd, *J* = 15.7, 7.0 Hz, 1H, *maj*-C(14)*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 169.1, 153.7, 153.7, 148.9, 148.9, 144.2, 144.0, 138.9, 138.6, 131.2, 131.2, 130.6, 130.6, 130.0, 129.9, 129.8, 129.8, 129.6, 129.4, 129.3, 129.0, 128.8, 128.7, 128.6, 128.1, 128.0, 126.9, 126.8, 126.1, 125.9, 117.2, 117.2, 117.1, 70.3, 70.2, 69.6, 69.1, 60.3, 60.2, 57.9, 57.7, 52.7, 52.3, 38.0, 37.9; IR (ATR, neat): 1/λ [cm^{-1}] = 3034, 2917, 2856, 1775, 1705, 1473, 1201, 824, 760, 694; HRMS (ESI): m /z $[M+H]^+$ calcd for $C_{26}H_{20}Br_2N_3O_3$ calcd: 582.0023, found: 582.0022.

Post-modifications

Synthesis of (5*S*,11*S*)-methyl 2-(2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[b,f][1,5]diazocin-13-yl)acetate (1b)

Tröger's base analogue (5*S*,11*S*)-**1f** (206 mg, 0.44 mmol, e.r. 99:1) was placed into the Schlenk flask under argon. Then DCM (2 mL), MeOH (2 mL) and dimethyl carbonate (186 µL, 2.21 mmol, 5 equiv) were added and a clear solution was formed. Sodium methoxide (120 mg, 2.21 mmol, 5 equiv) was added in one portion and the resulting mixture was stirred at r.t. for 1 h. The solvent was removed and water (5 mL) and DCM (10 mL) were added. The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). Combined org. layers were dried over $MgSO_4$ and dried. The crude mixture was purified by column chromatography (SiO_2 (20 g), Hex:EtOAc = 1:1 then EtOAc) to give the title compound (5*S*,11*S*)-**1b** as a white solid in the first fraction (93 mg, 65%, e.r. 99:1) and oxazolidinone **7f** as a white solid (66 mg, 86%) in the second fraction.

The spectral data were in agreement with those reported above.

(5*S*,11*S*)-**1b:**

$[\alpha]_D^{20}$ 117.31 (*c* 0.312, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH 90:10, 0.5 mL/min): t_R = 17.0, 21.6 min.

Synthesis of (5*S*,11*S*)-2-(2,8-dimethyl-6,12-dihydro-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-13-yl)ethanol (4)

LAH (113.6 mg, 3.0 mmol, 5 equiv) was added to a solution of the ester (5*S*,11*S*)-**1b** (193.0 mg, 0.6 mmol, 1 equiv, e.r. 99:1) in THF (15 mL) at -78 °C. The suspension was allowed to warm to r.t. and stirred at the same

temperature for 9 h. It was cooled down to 0 °C and water (54 µL), 15% aqueous NaOH solution (54 µL) and water (162 µL) were added. The cooling bath was removed and it was stirred for 30 minutes. Then, $MgSO_4$ was added and stirring was continued for 15 minutes. The suspension was filtered through a pad of celite and concentrated. The crude mixture was purified by column chromatography (SiO_2, Hex:EtOAc 1:3) to give the title compound (5*S*,11*S*)-**4** as a white solid (81 mg, 96%, e.r. 99:1).

M.p.: 60 - 65 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.02-6.95 (m, 4H, Ar), 6.72-6.70 (m, 2H, C(1)*H*, C(7)*H*), 4.71 (d, *J* = 16.5 Hz, 1H, C(6)H^{exo}), 4.57 (d, *J* = 17.2 Hz, 1H, C(12)H^{exo}), 4.34 (m, 2H, O*H*, C(13)*H*), 4.13 (d, *J* = 16.6 Hz, 1H, C(6)H^{endo}), 4.03 (d, *J* = 17.2 Hz, 1H, C(12)H^{endo}), 3.96-3.77 (m, 2H, C(15)*H*), 2.22 (s, 6H, CH_3), 1.98-1.90 (m, 2H, C(14)*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 147.1, 142.1, 134.2, 133.9, 128.9, 128.3, 127.4, 127.2, 127.1, 127.0, 126.0, 125.0, 74.5 (*C(13)*), 62.1 (*C(15)*), 60.3 (*C(6)*), 52.8 (*C(12)*), 32.3 (*C(14)*), 21.0 (CH_3); IR (ATR, neat): 1/λ [cm^{-1}] = 3291, 2911, 2853, 1492, 1199, 1061, 835, 822, 746; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{23}N_2O$: 295.1805, found: 295.1801; $[\alpha]_D^{20}$ 171.5 (*c* 0.490, $CHCl_3$); HPLC (OD-H, hexane/*i*-PrOH 70:30, 0.5 mL/min): t_R = 9.7, 16.1 min.

Determination of the absolute configuration

Our extensive efforts to determine the absolute configuration of the separated diastereomers by X-ray analysis proved fruitless as the attempts to obtain suitable crystals of either of the diastereomers of **1f** met with no success. We have thus resorted to the use of CD-spectroscopy. Given the similarity of the chromophores in alcohol **4** and original Tröger's base we compared the chiroptical properties of **4** obtained from the major diastereomer of **1f** with the spectrum of the commercially available (*R*,*R*)-Tröger's base (Figure 1). Both species displayed opposite Cotton effects over the entire spectral range clearly revealing that the absolute configuration in **4** was (5*S*,11*S*). The experiment simultaneously confirms the absolute configuration of the first eluting diastereomer of **1f** to be (5*S*,11*S*).

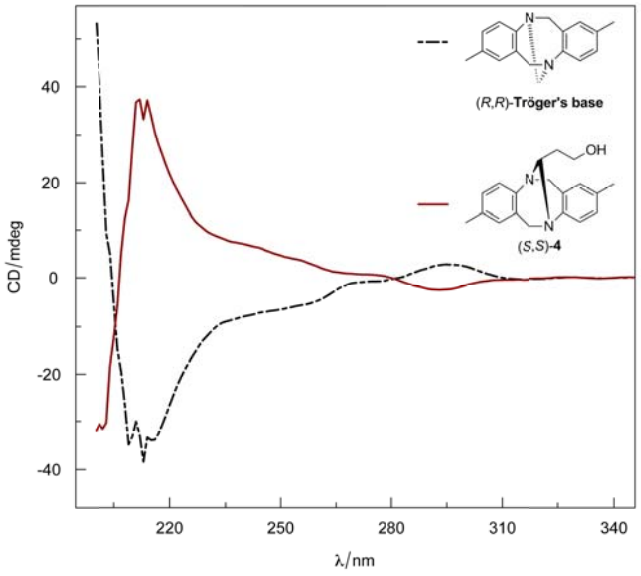
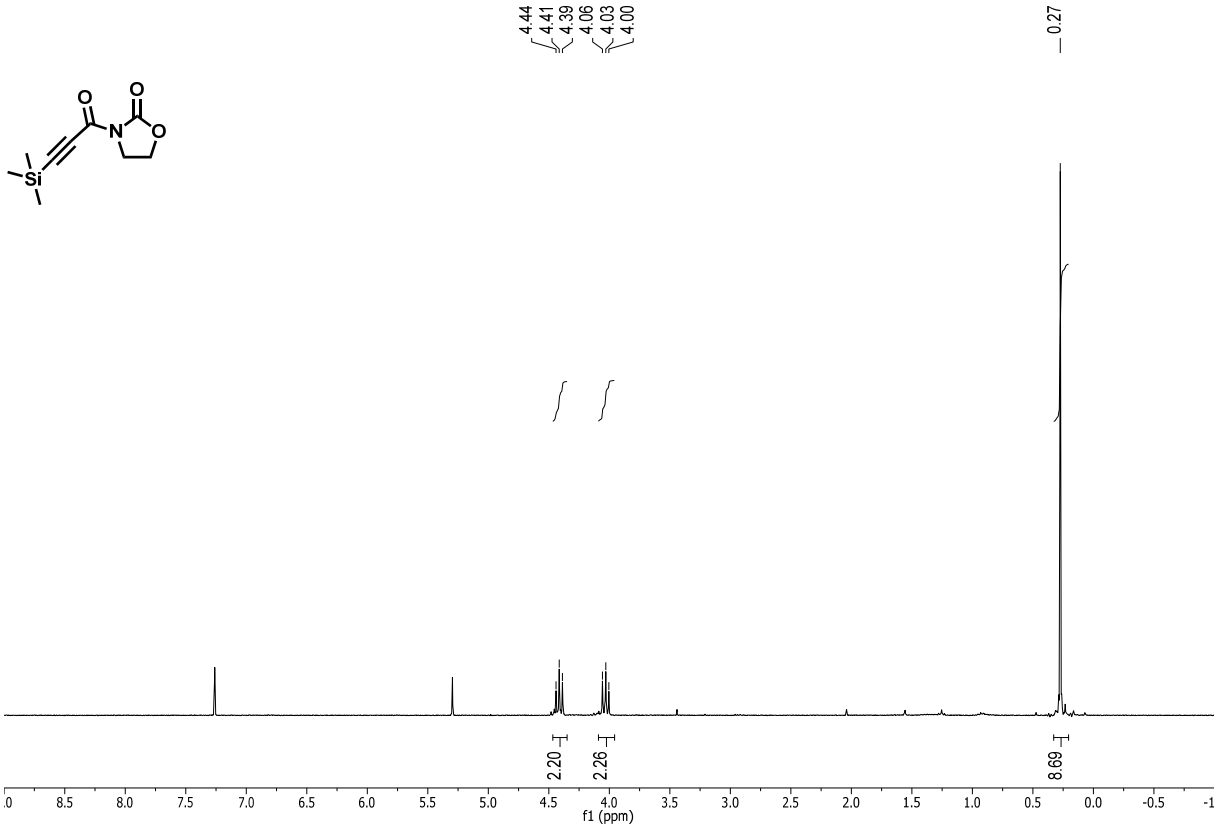


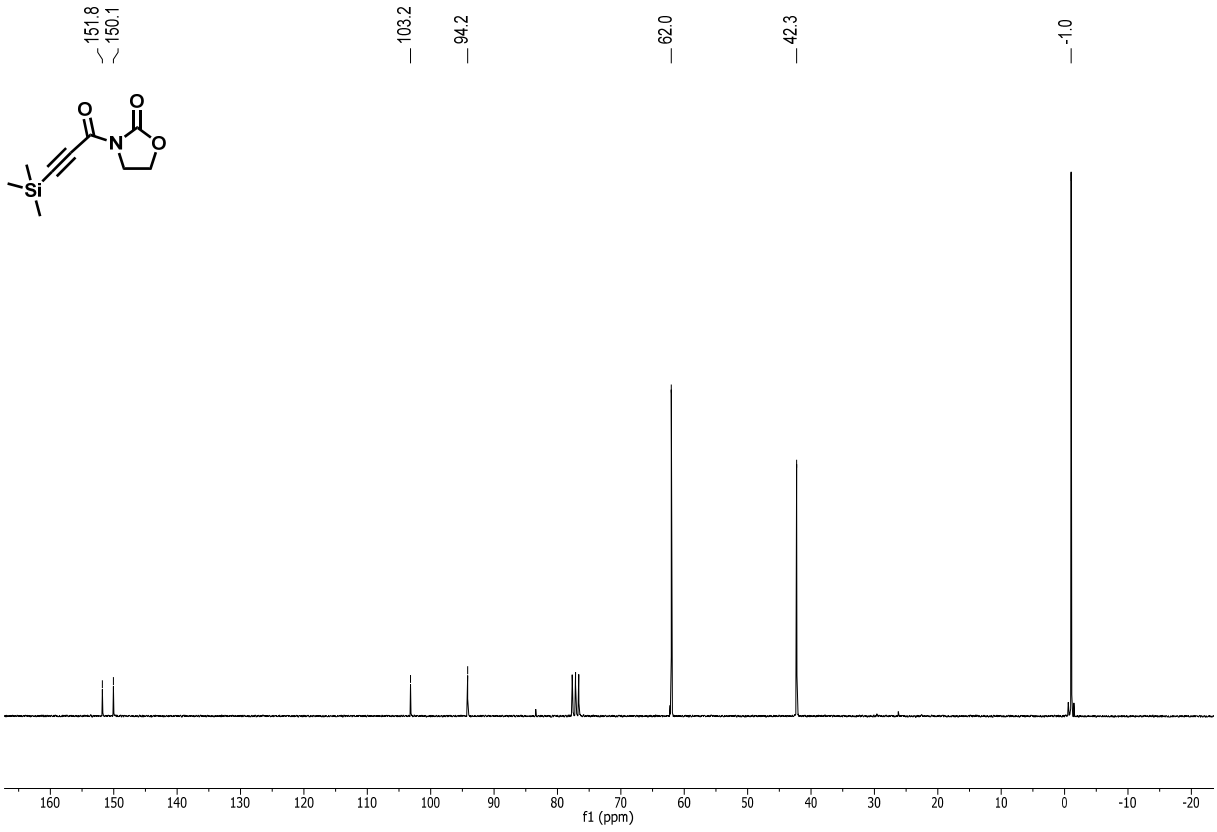
Figure 1. CD spectra of (*R*,*R*)-Tröger's base and (5*S*,11*S*)-**4**.

^{1}H and ^{13}C NMR Spectra of synthesized compounds

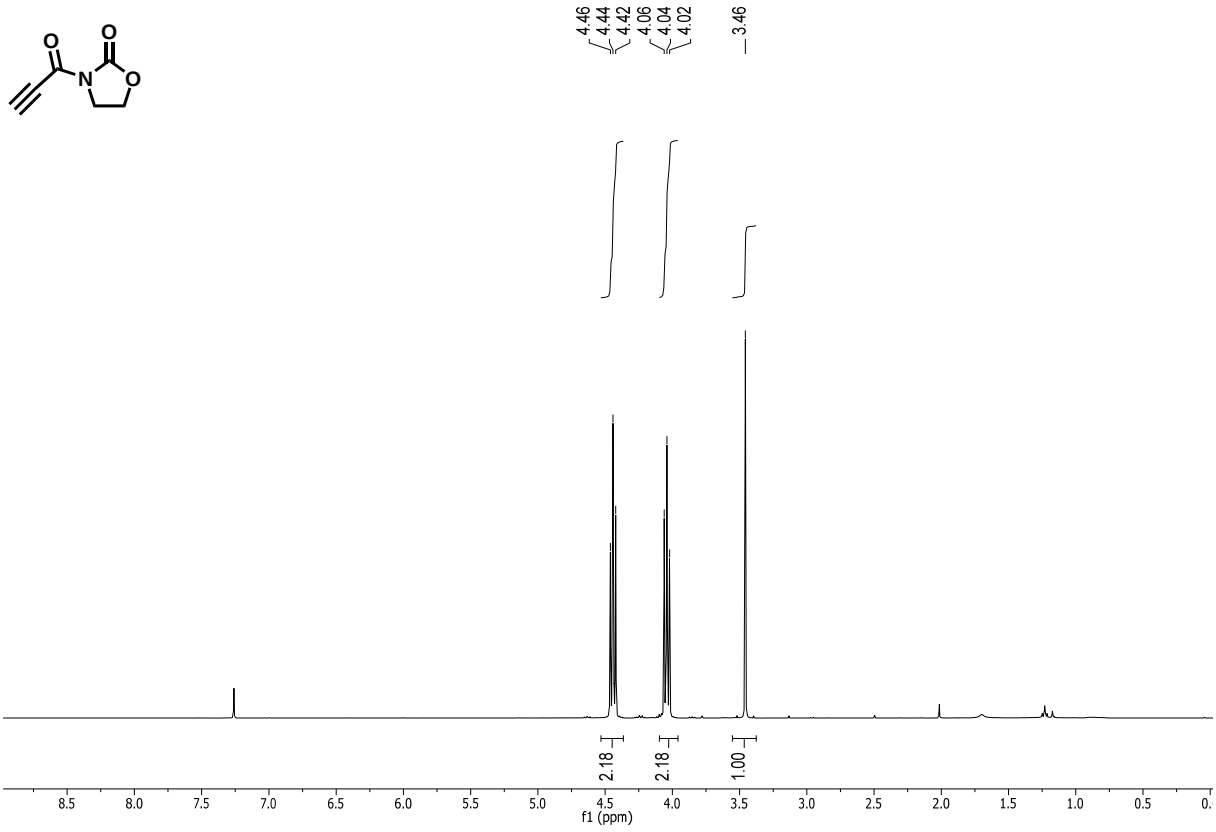
^{1}H NMR of **6**



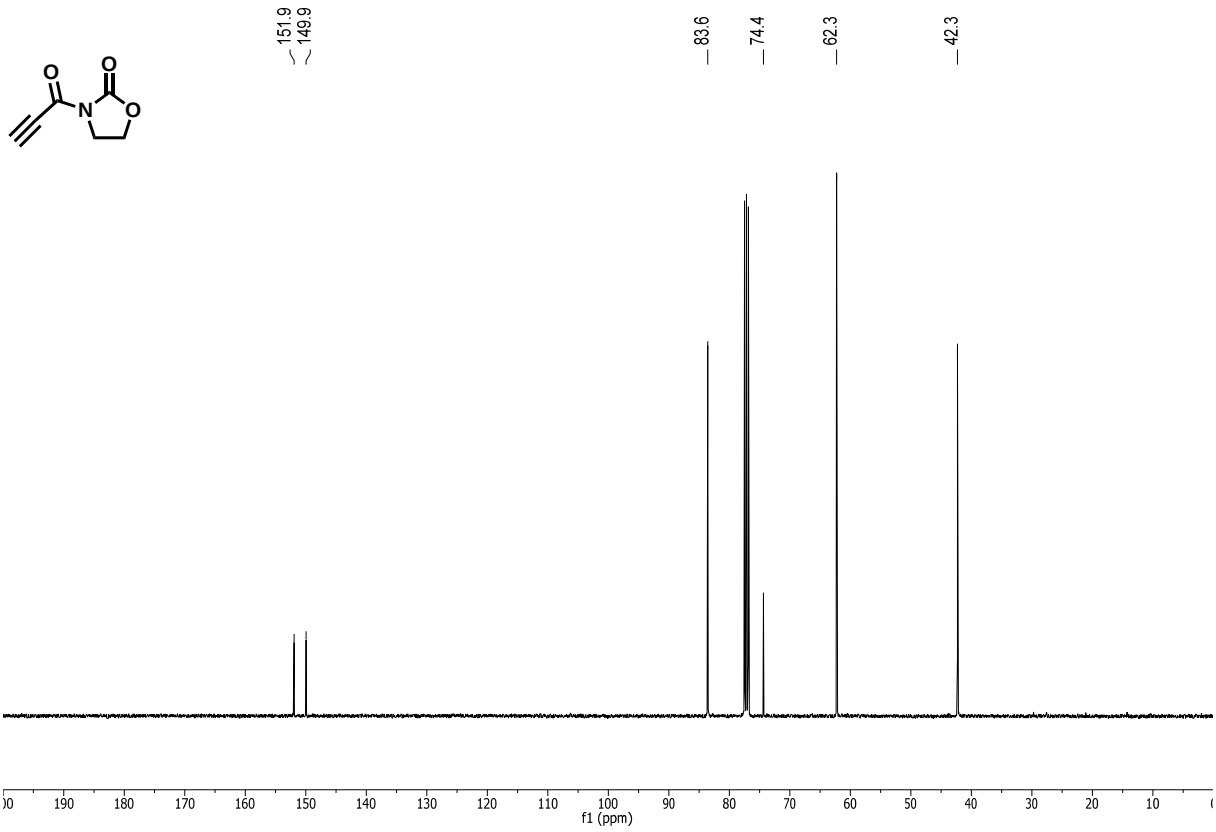
^{13}C NMR of **6**



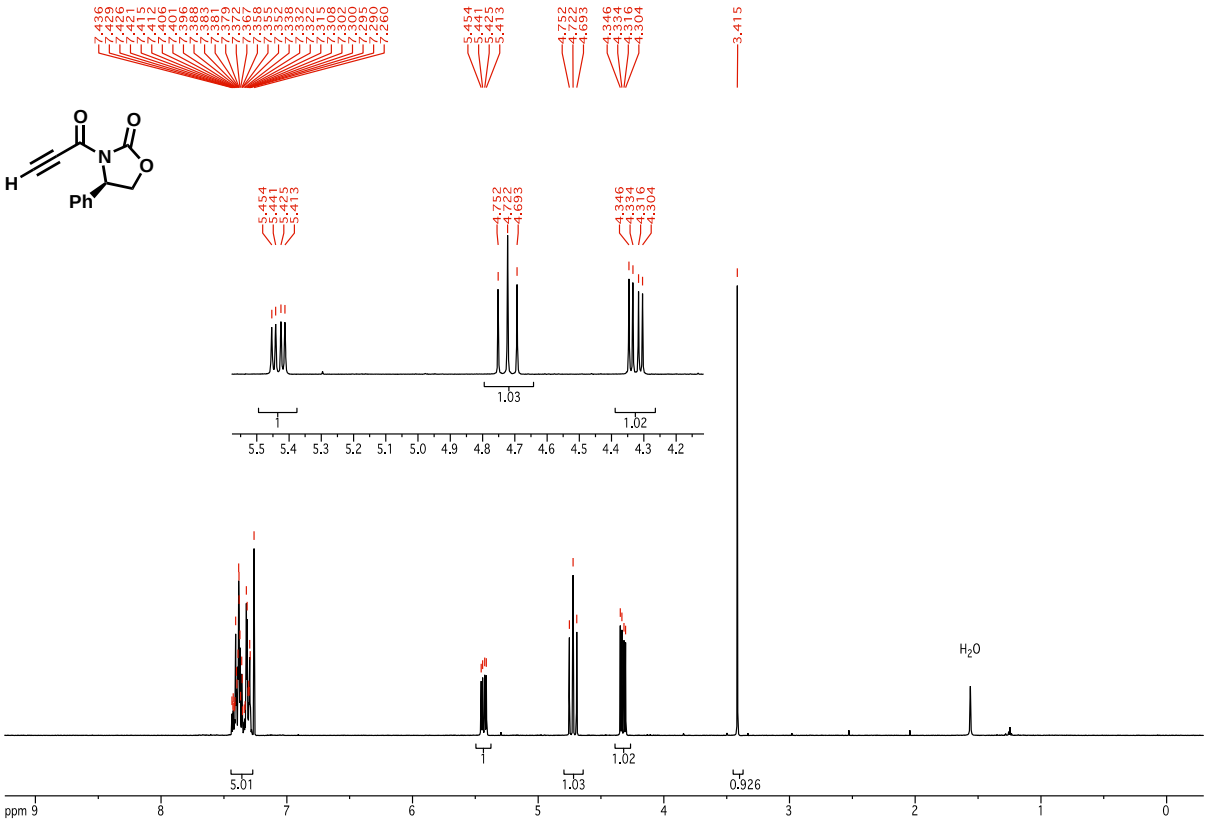
^{1}H NMR of **3c**



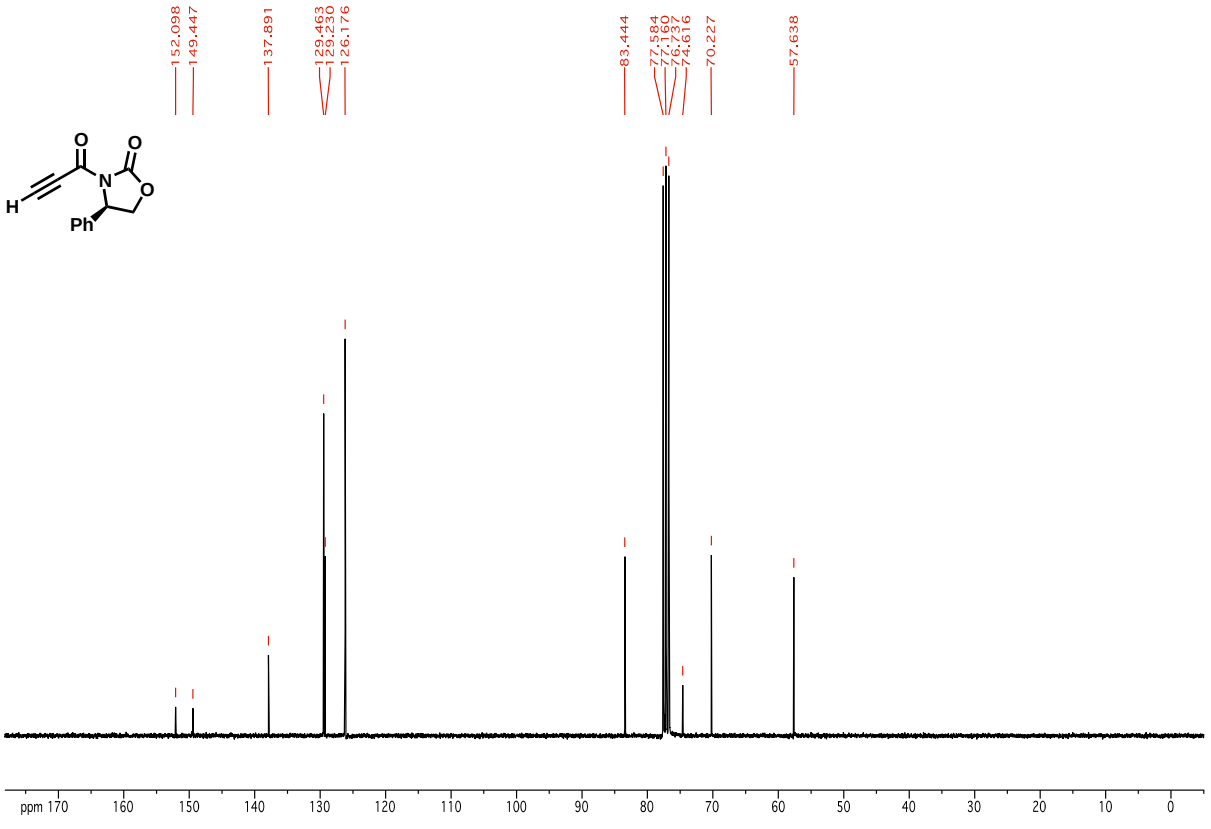
^{13}C NMR of **3c**



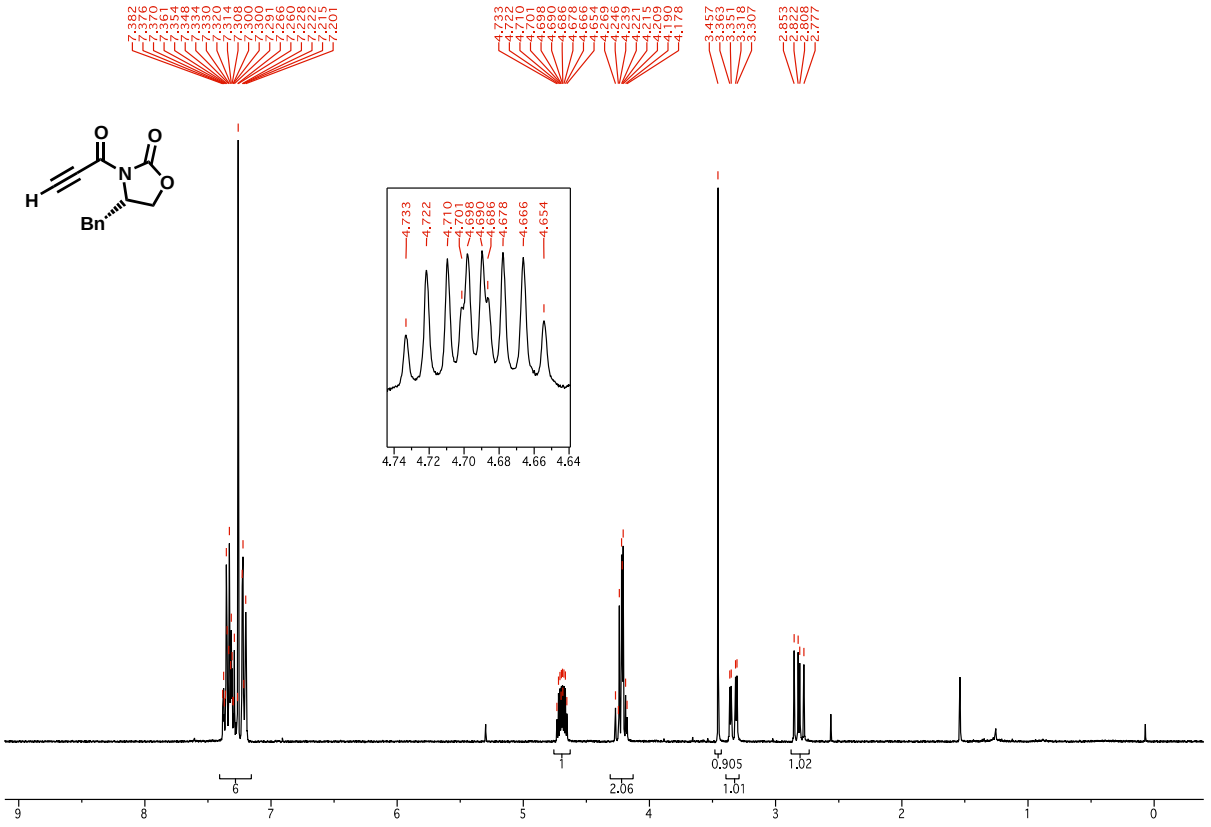
^{1}H NMR of **3d**



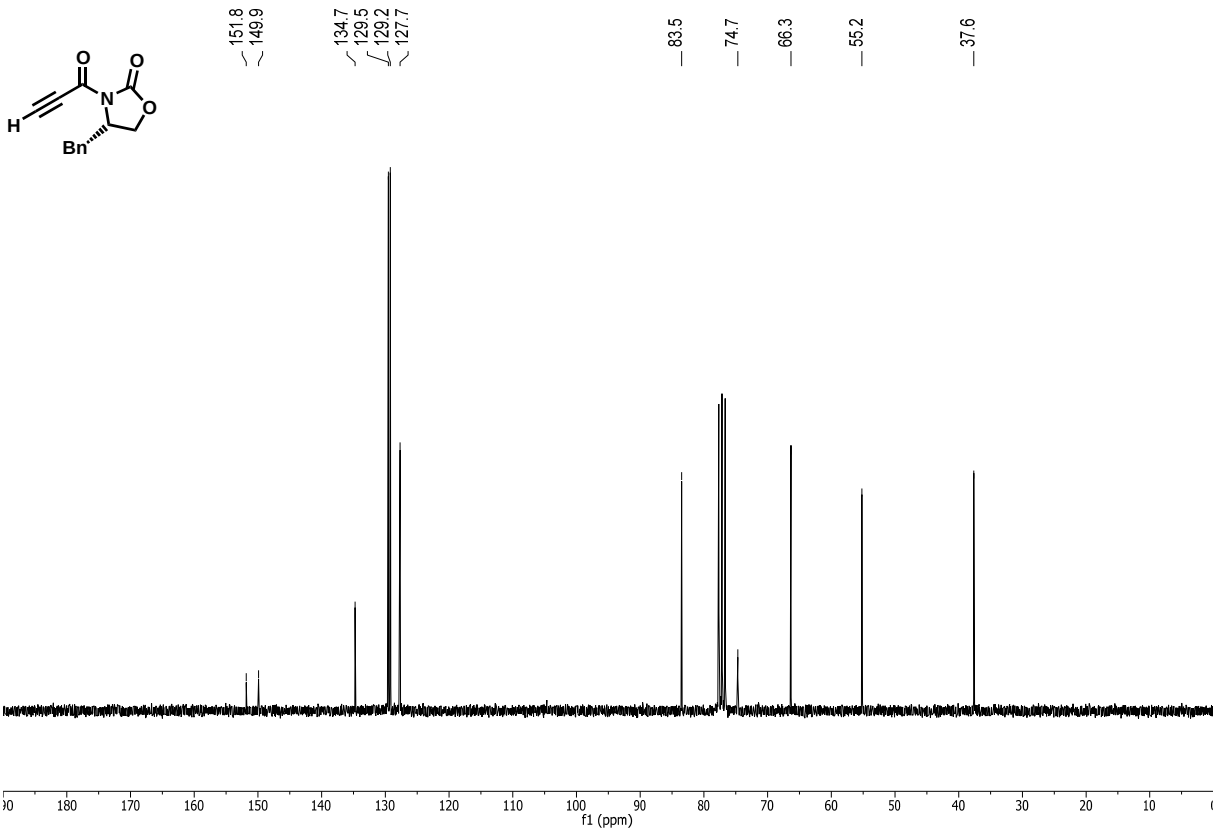
^{13}C NMR of **3d**



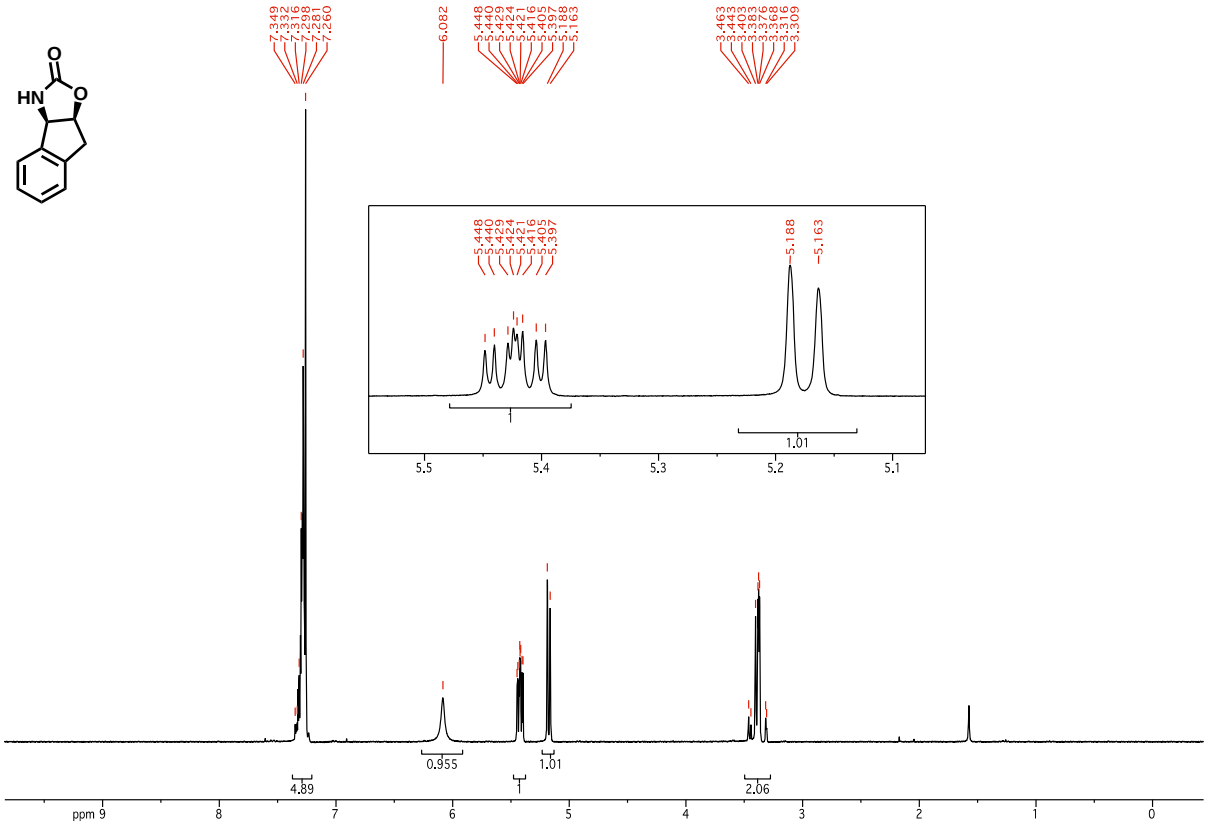
^{1}H NMR of **3e**



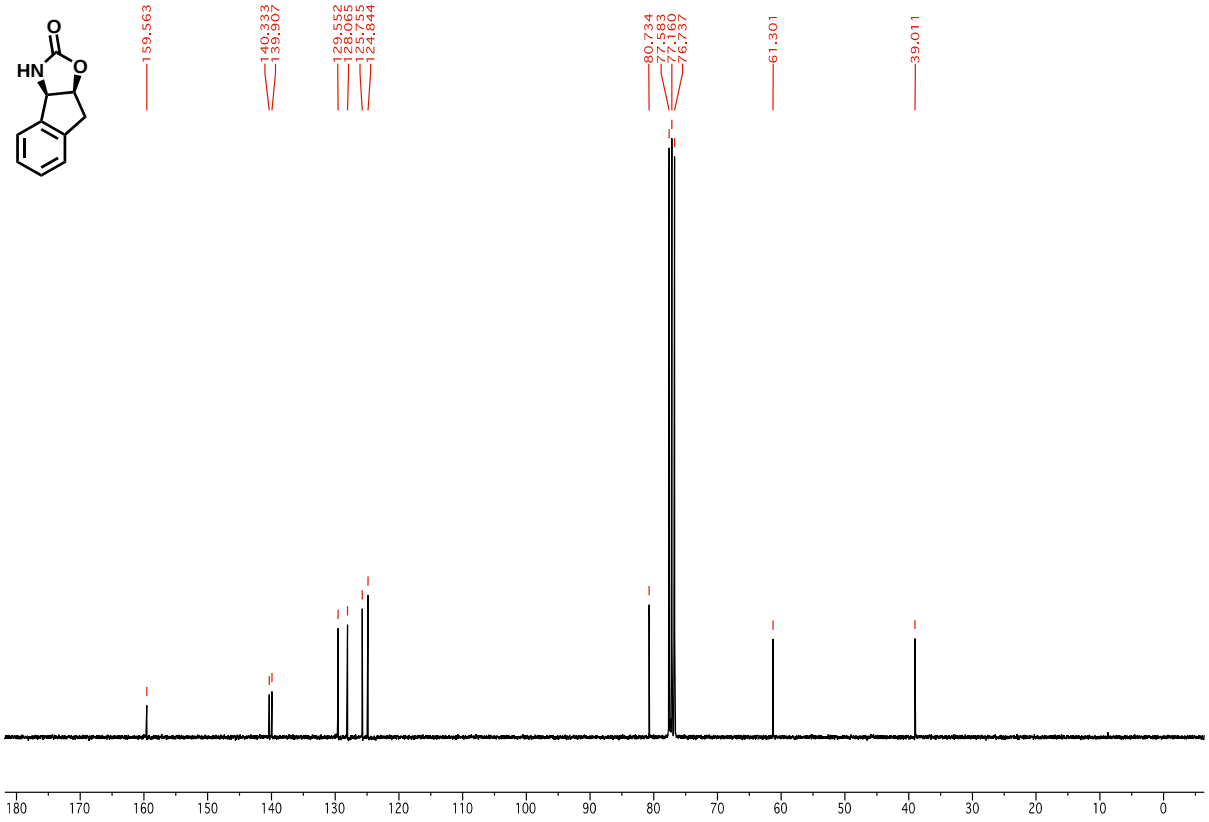
^{13}C NMR of **3e**



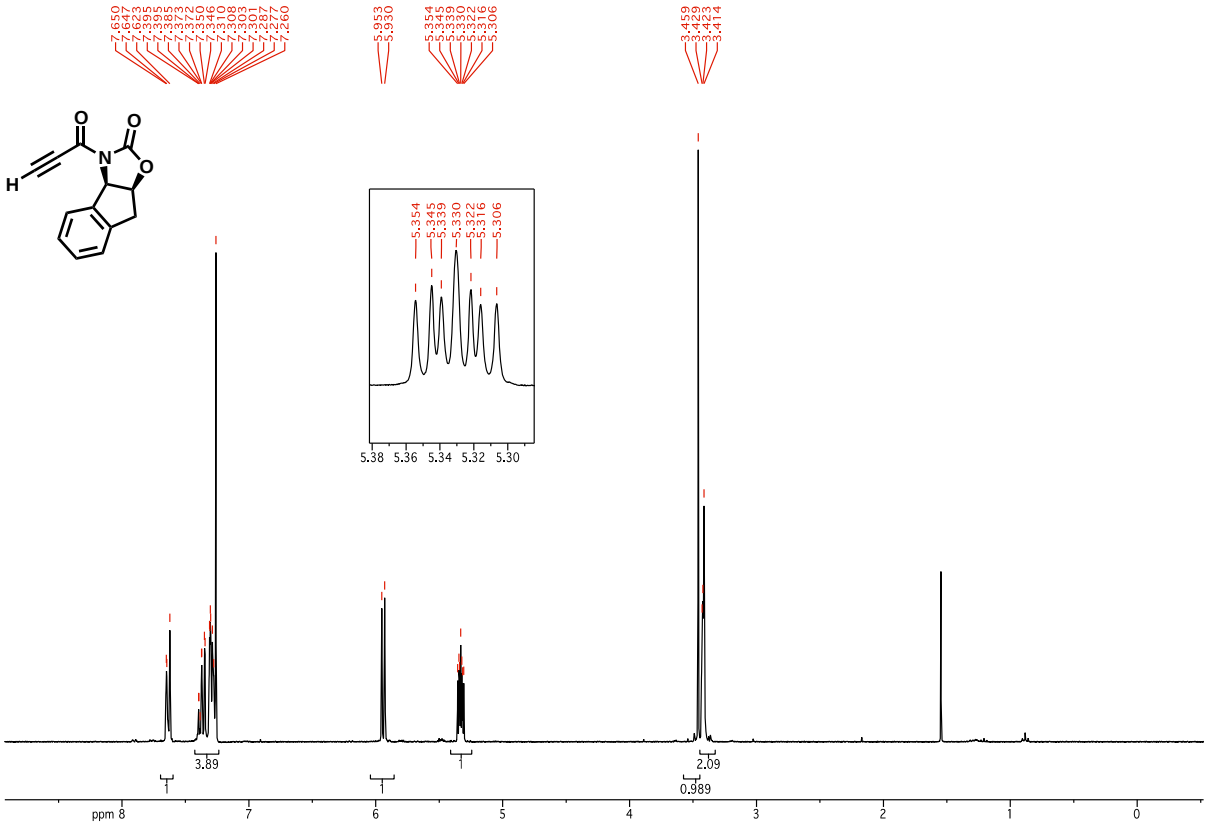
^{1}H NMR of **7f**



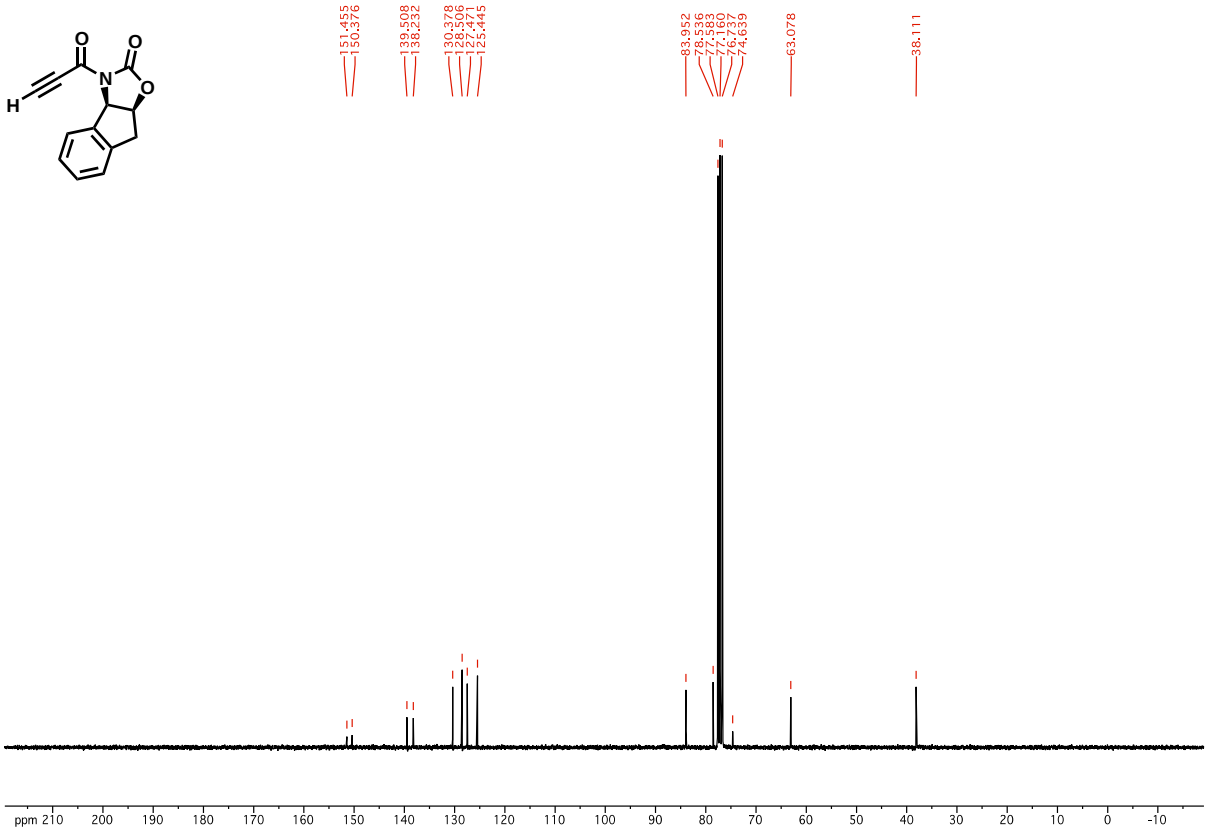
^{13}C NMR of **7f**



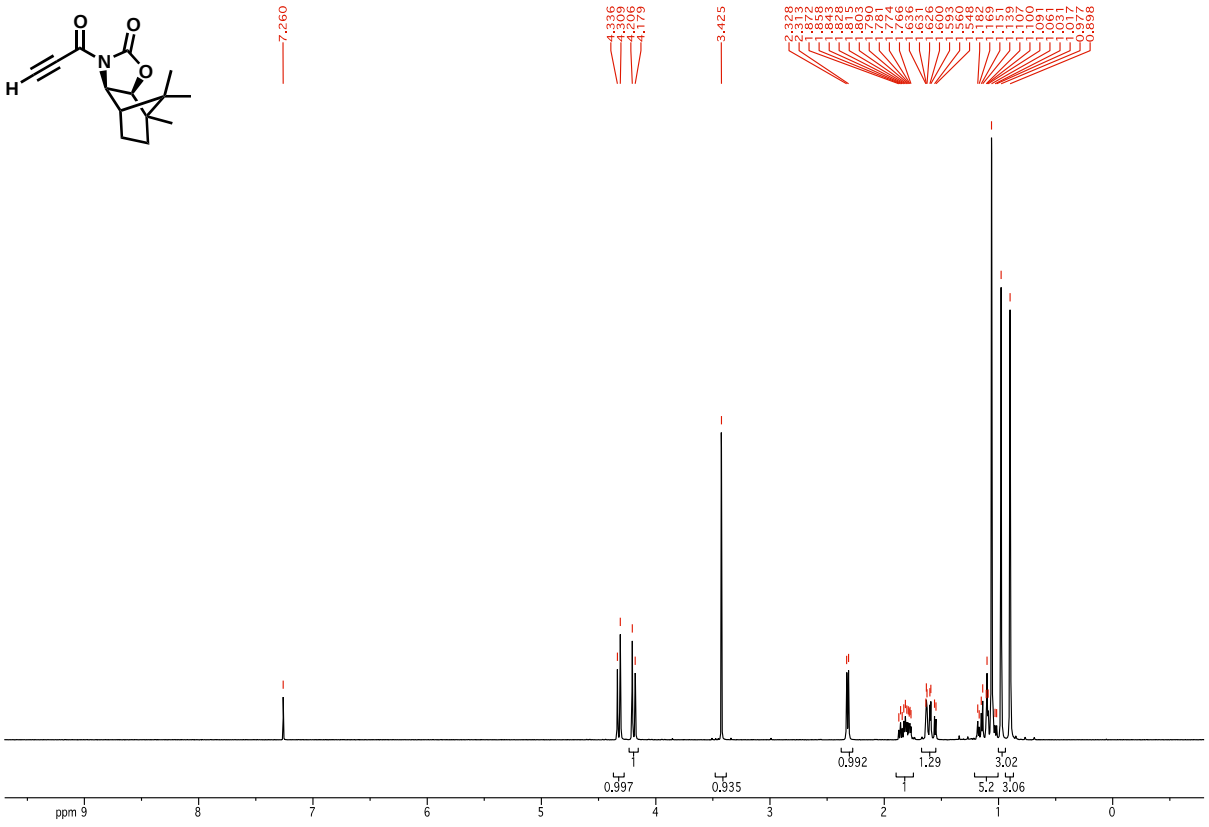
^{1}H NMR of **3f**



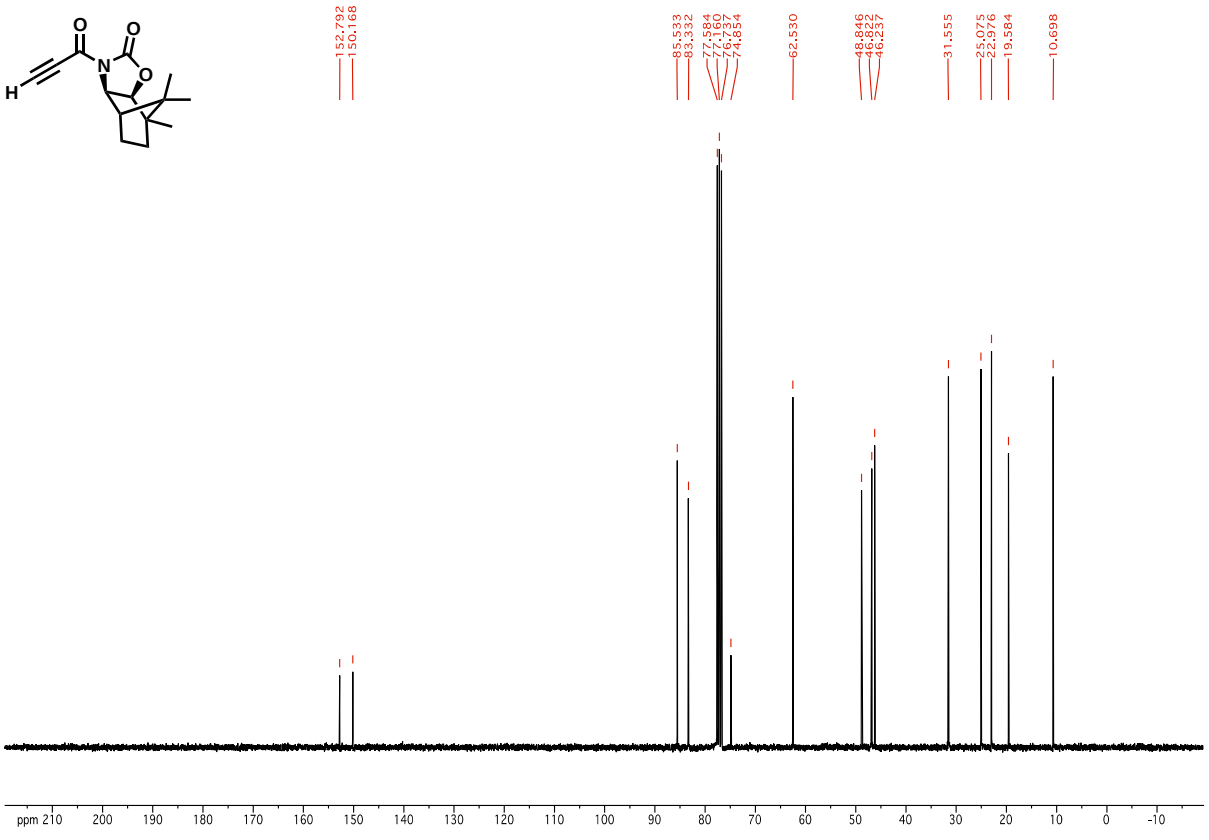
^{13}C NMR of **3f**



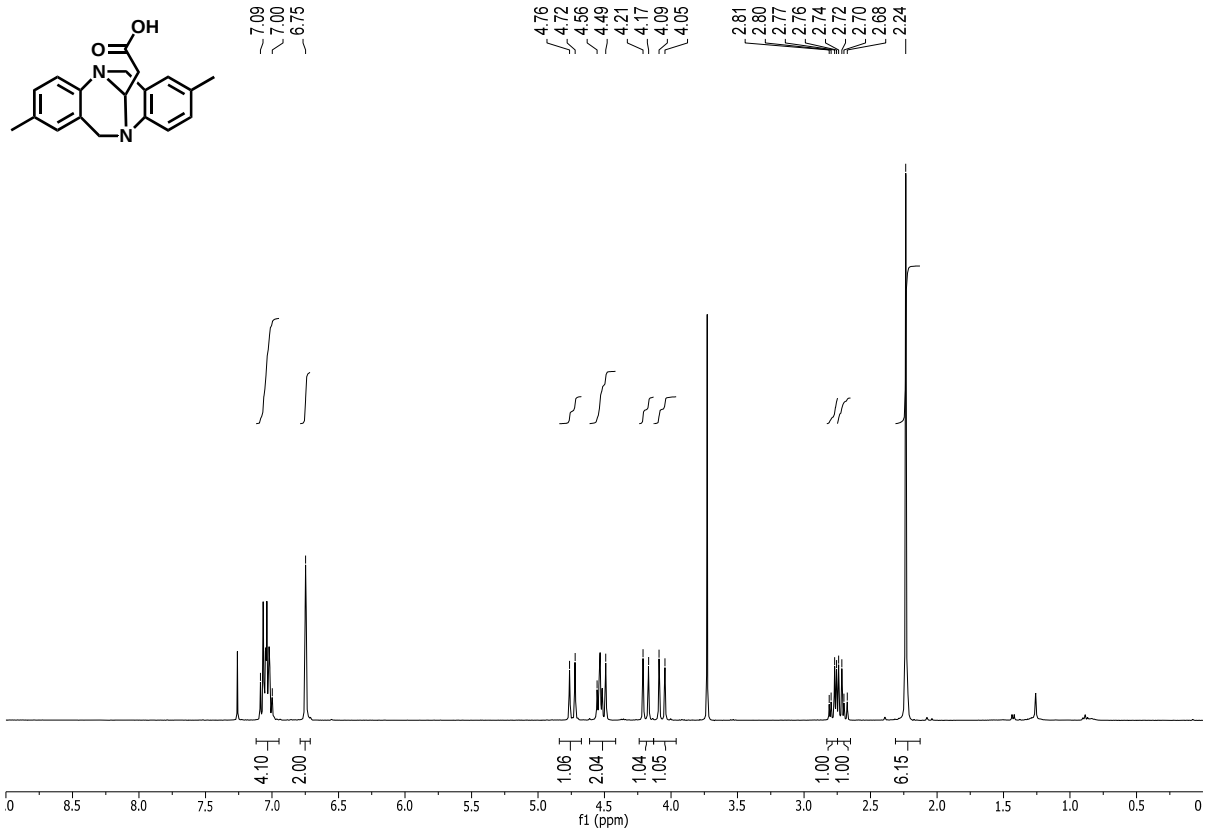
^{1}H NMR of **3g**



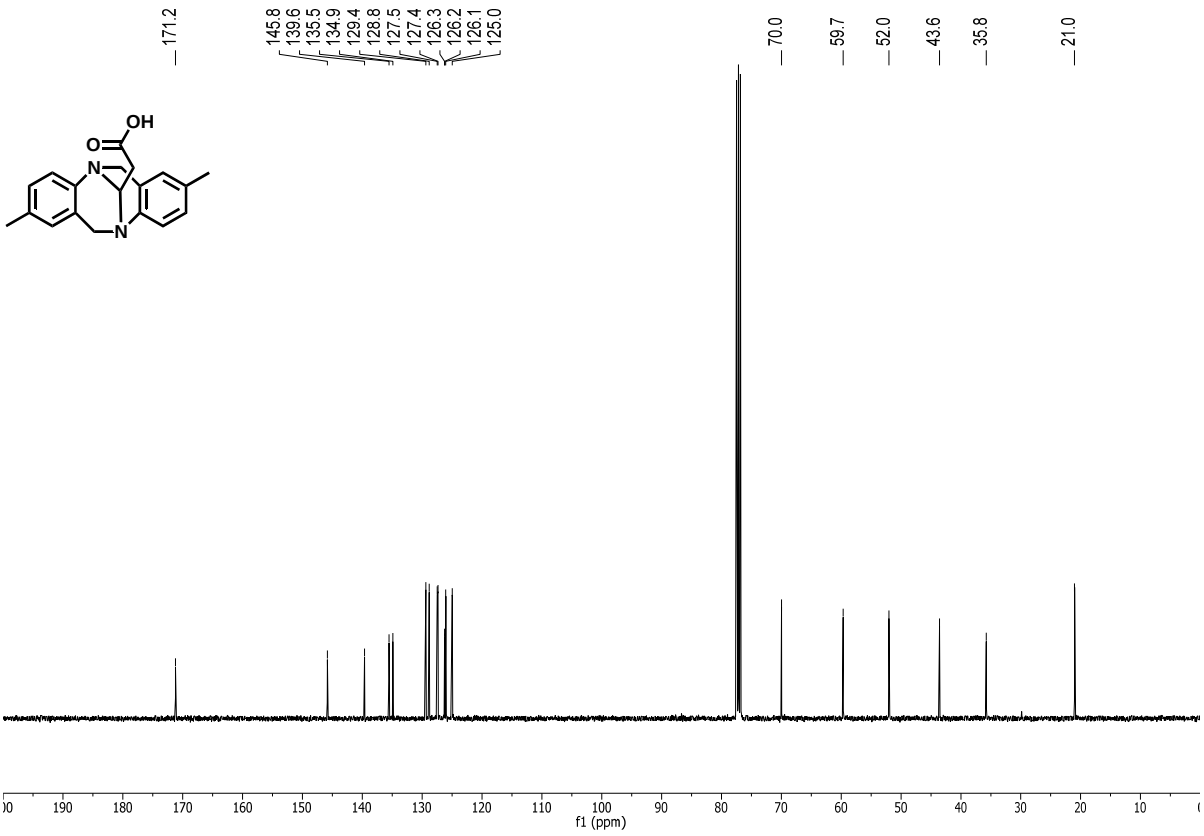
^{13}C NMR of **3g**



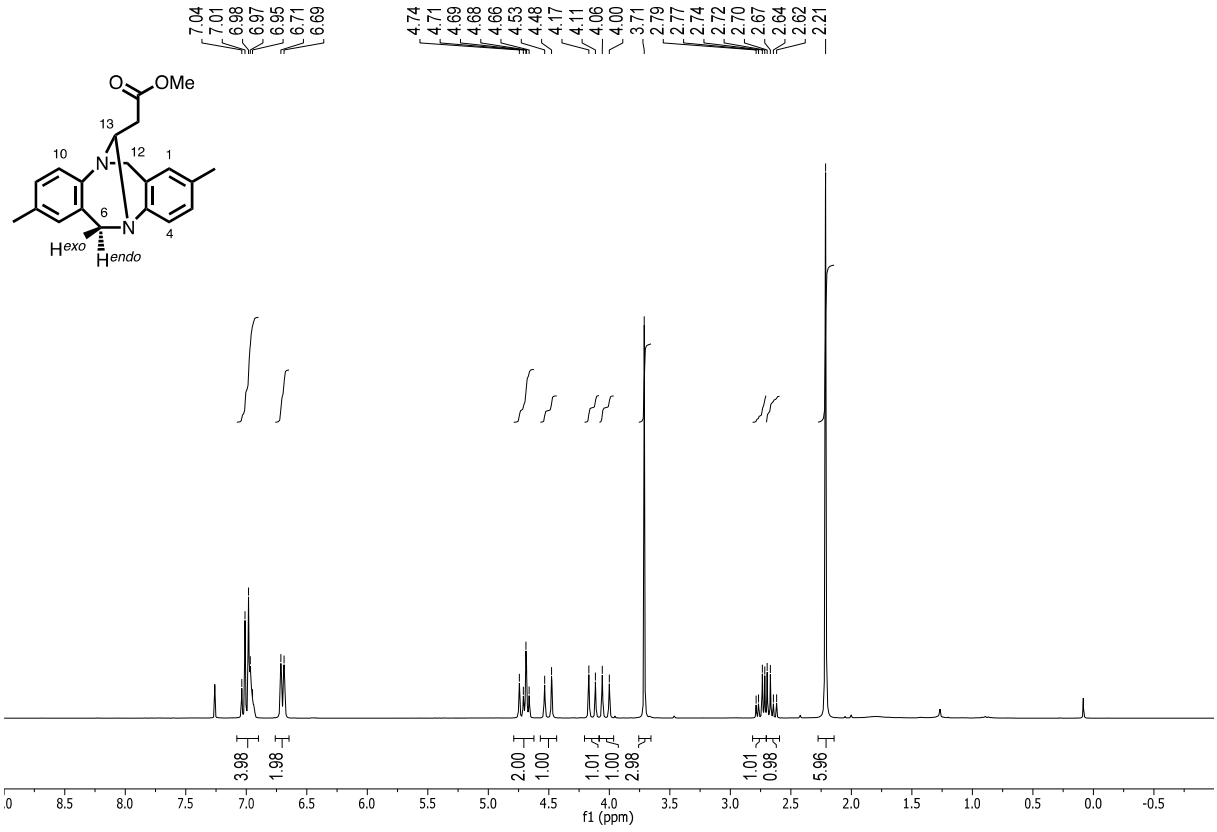
^{1}H NMR of **1a**



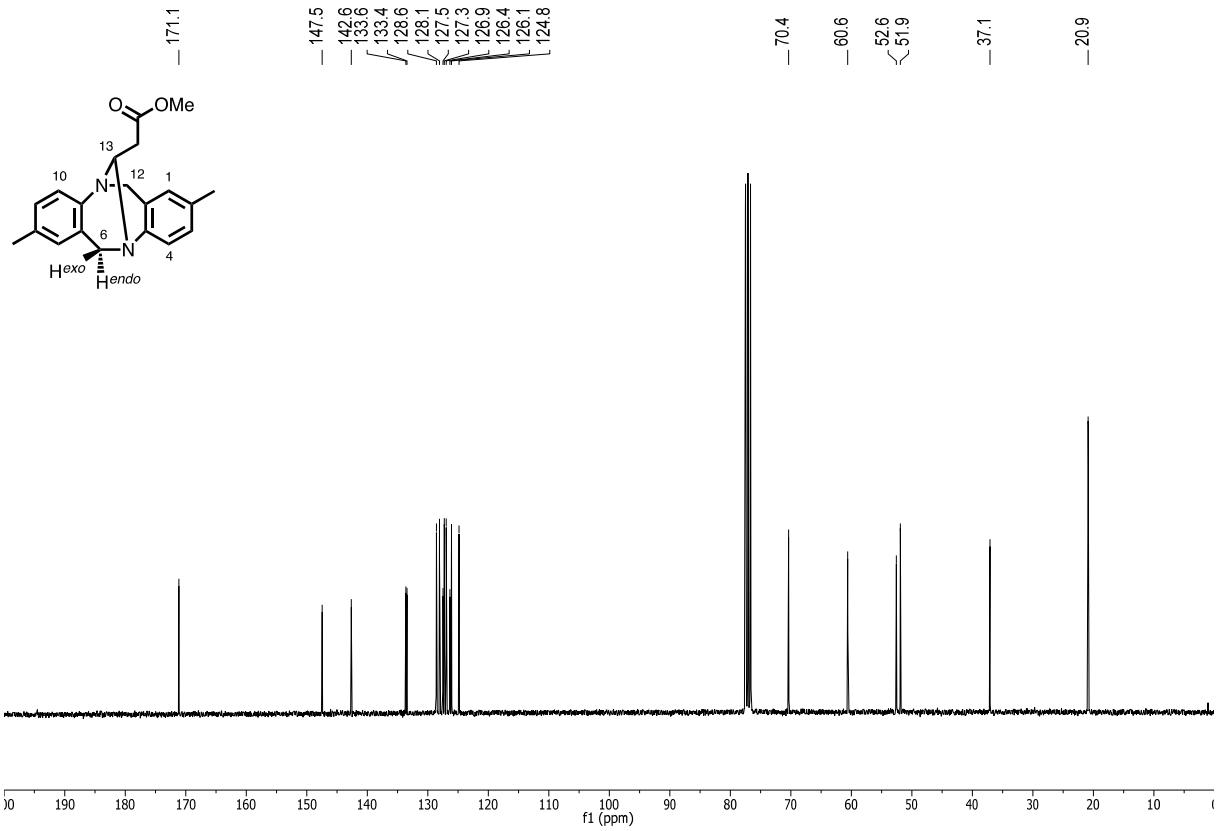
^{13}C NMR of **1a**



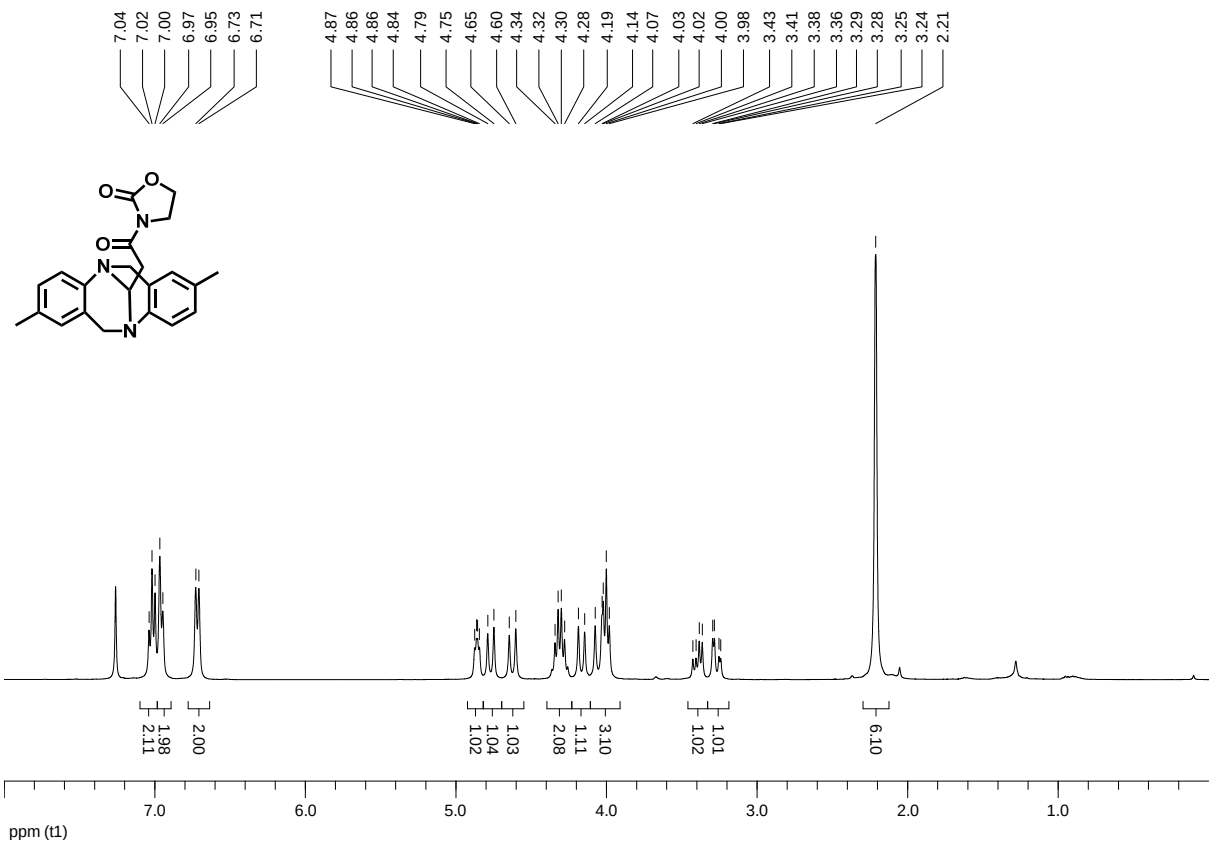
^{1}H NMR of **1b**



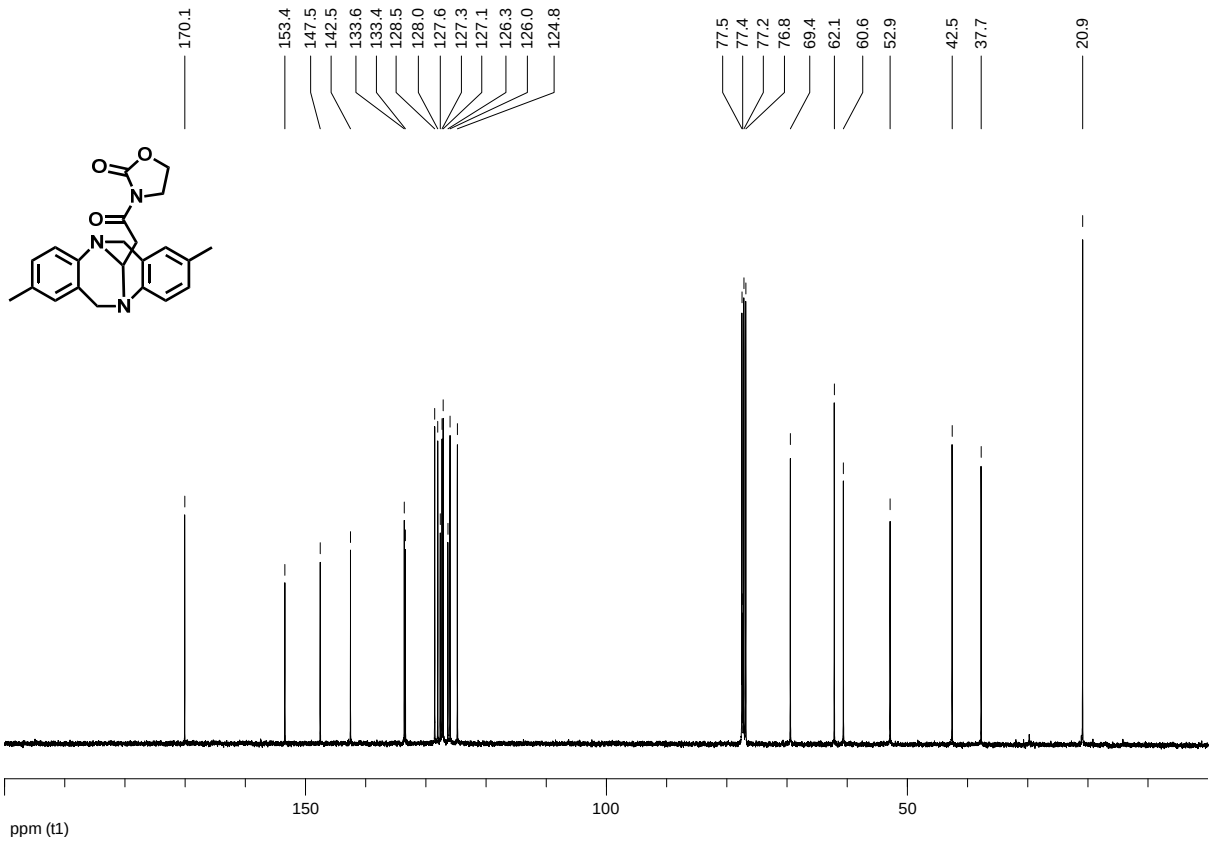
^{13}C NMR of **1b**



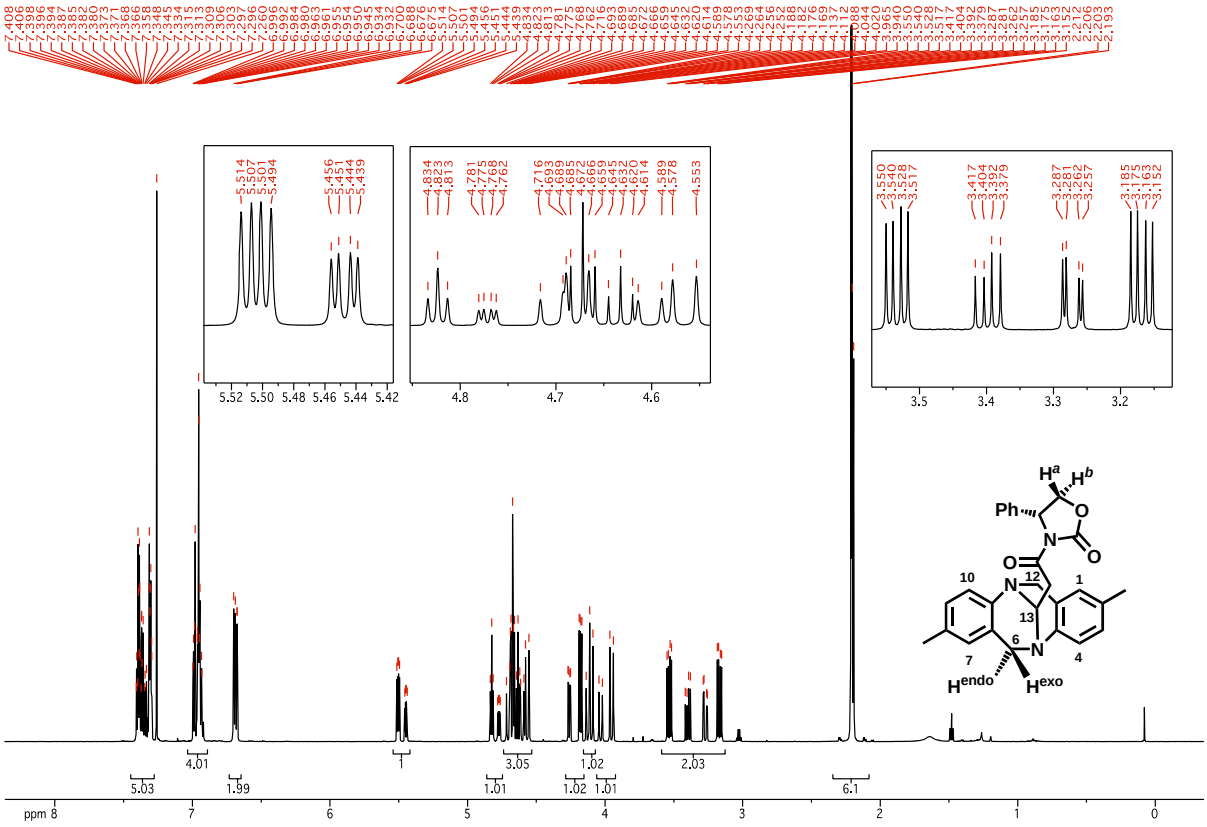
^{1}H NMR of **1c**



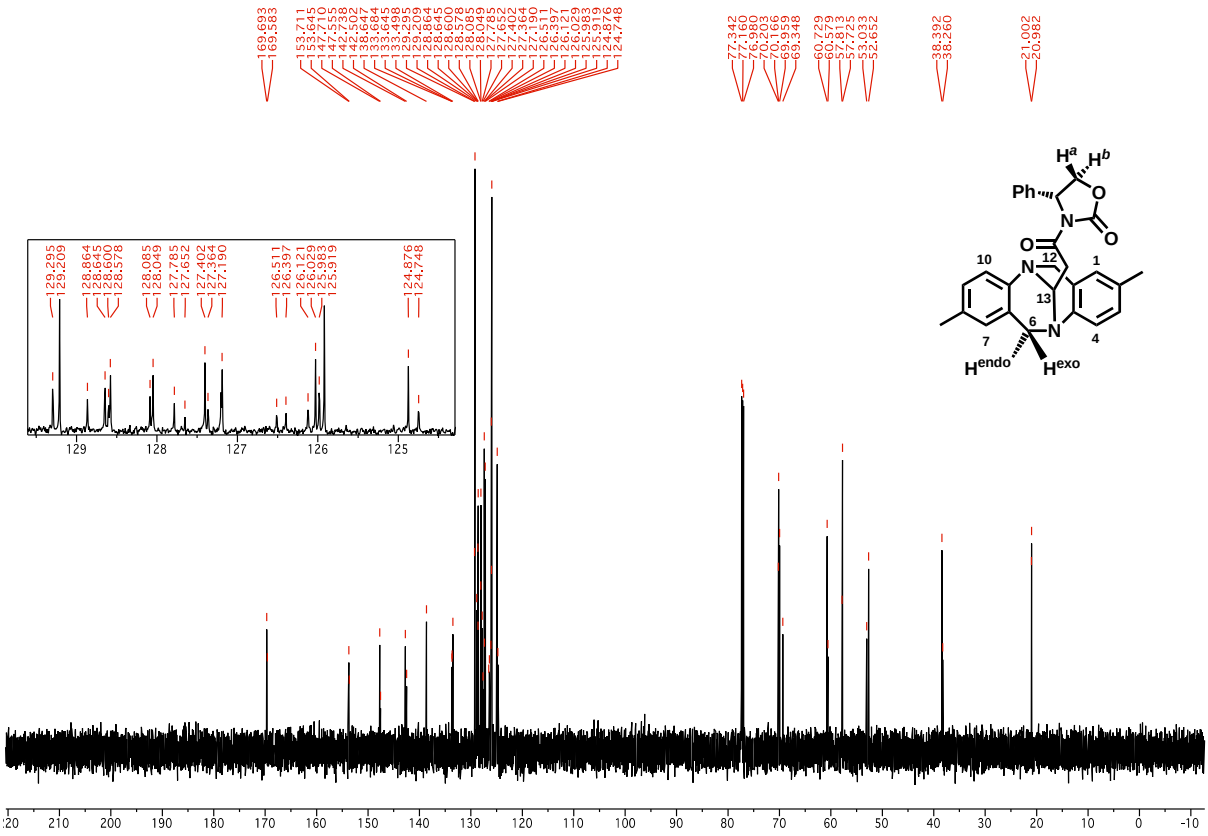
^{13}C NMR of **1c**



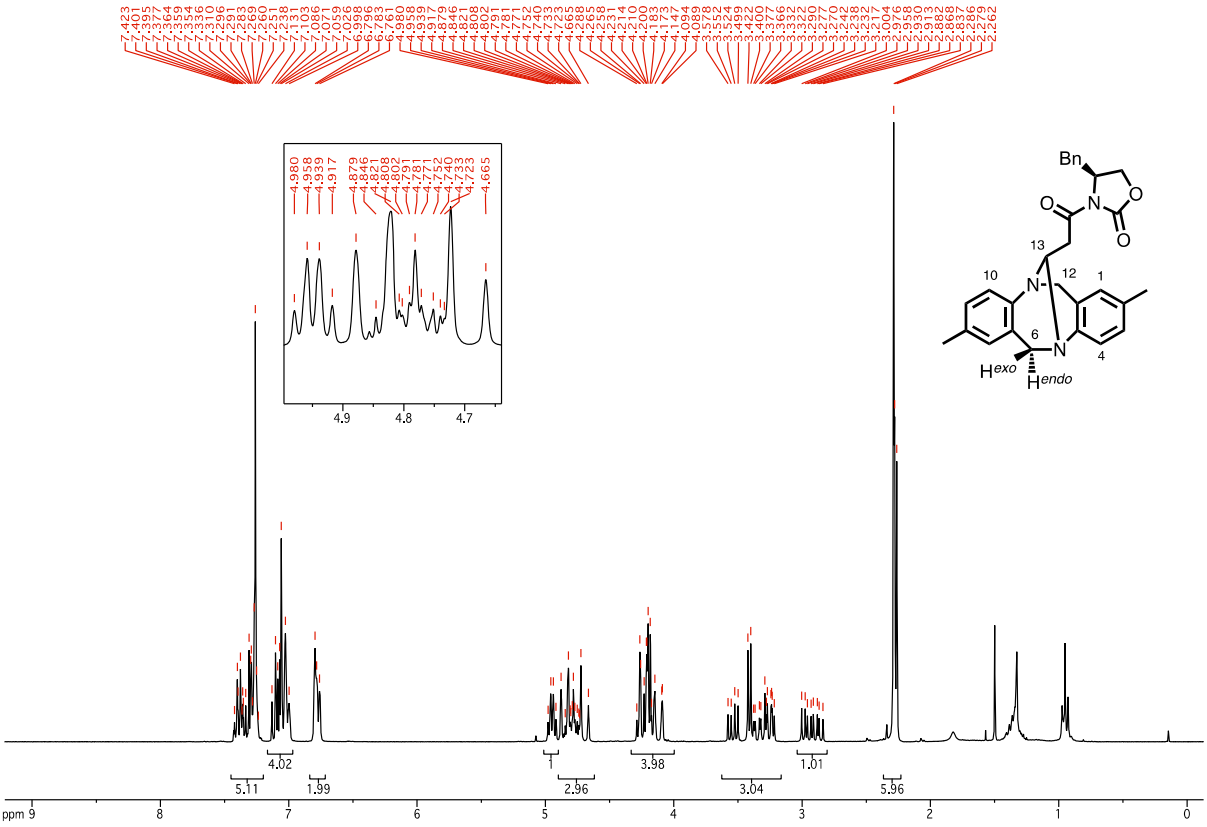
^{1}H NMR of **1d**



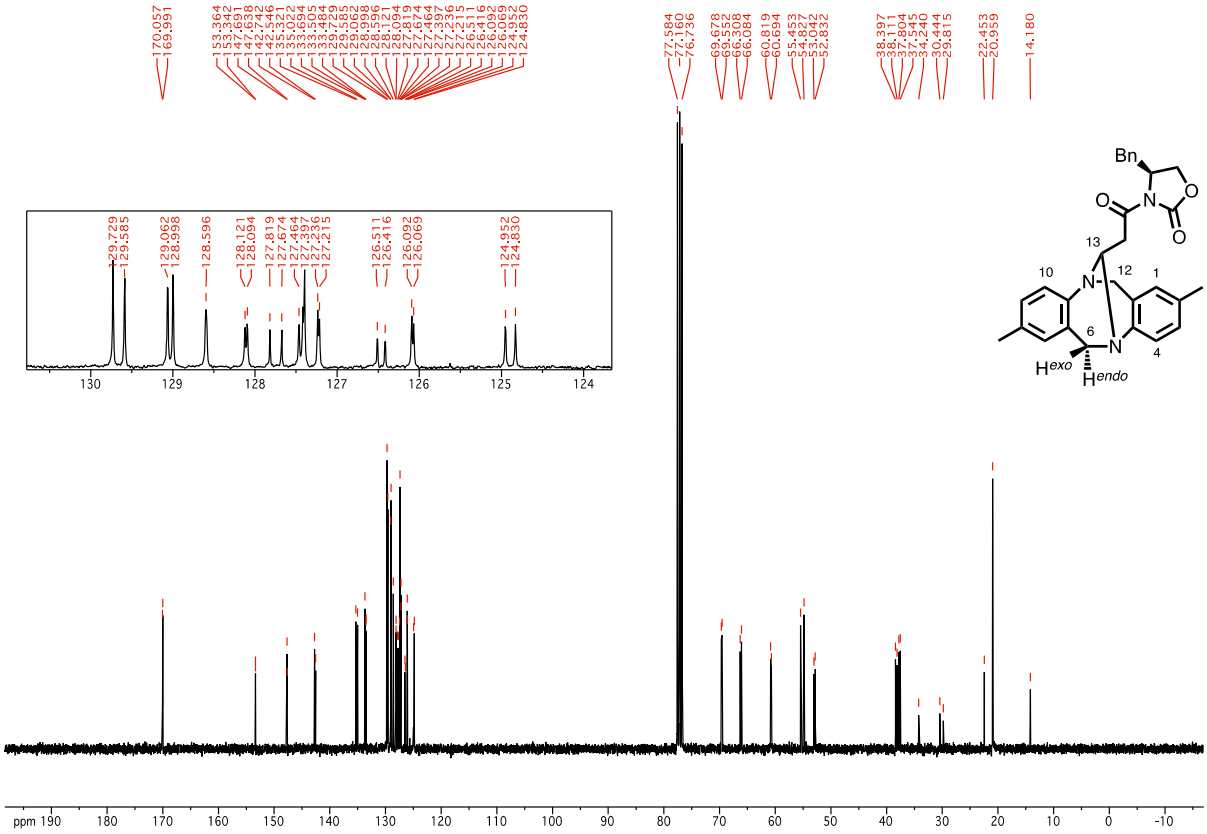
^{13}C NMR of **1d**



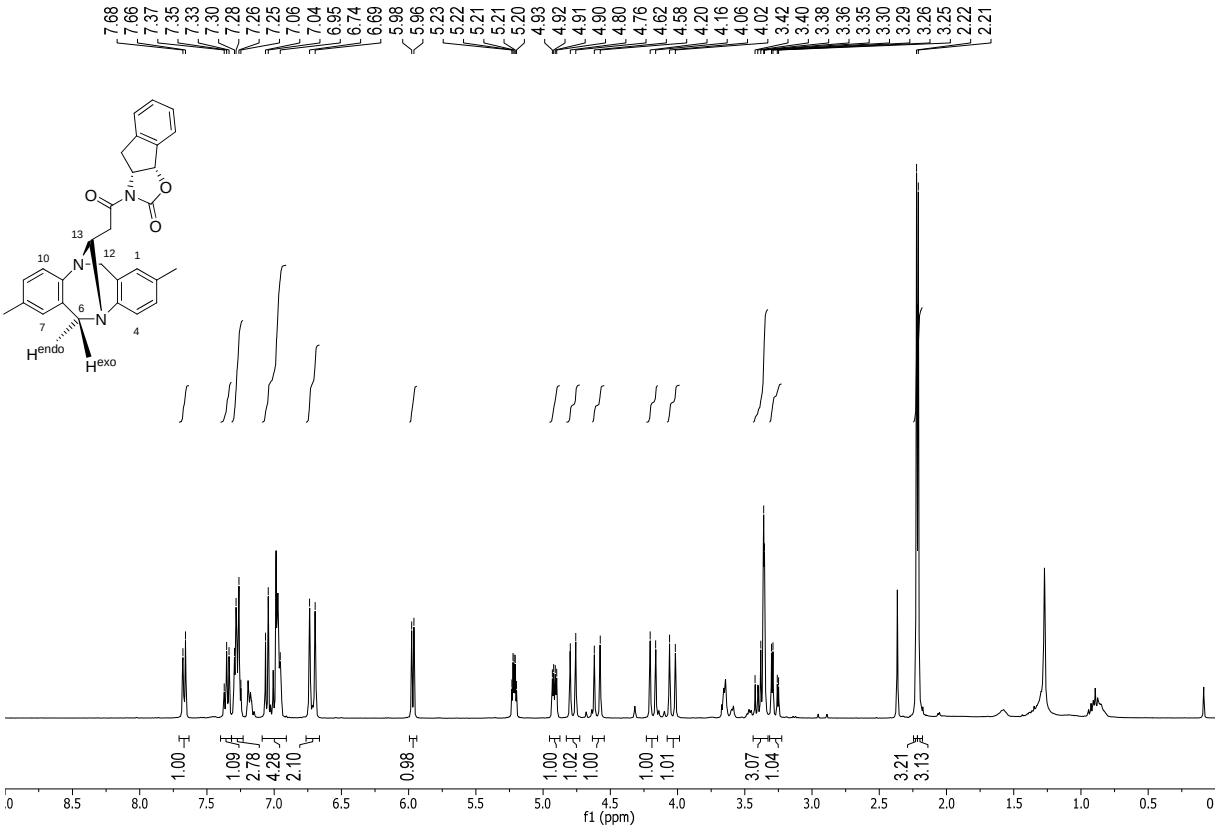
^{1}H NMR of **1e**



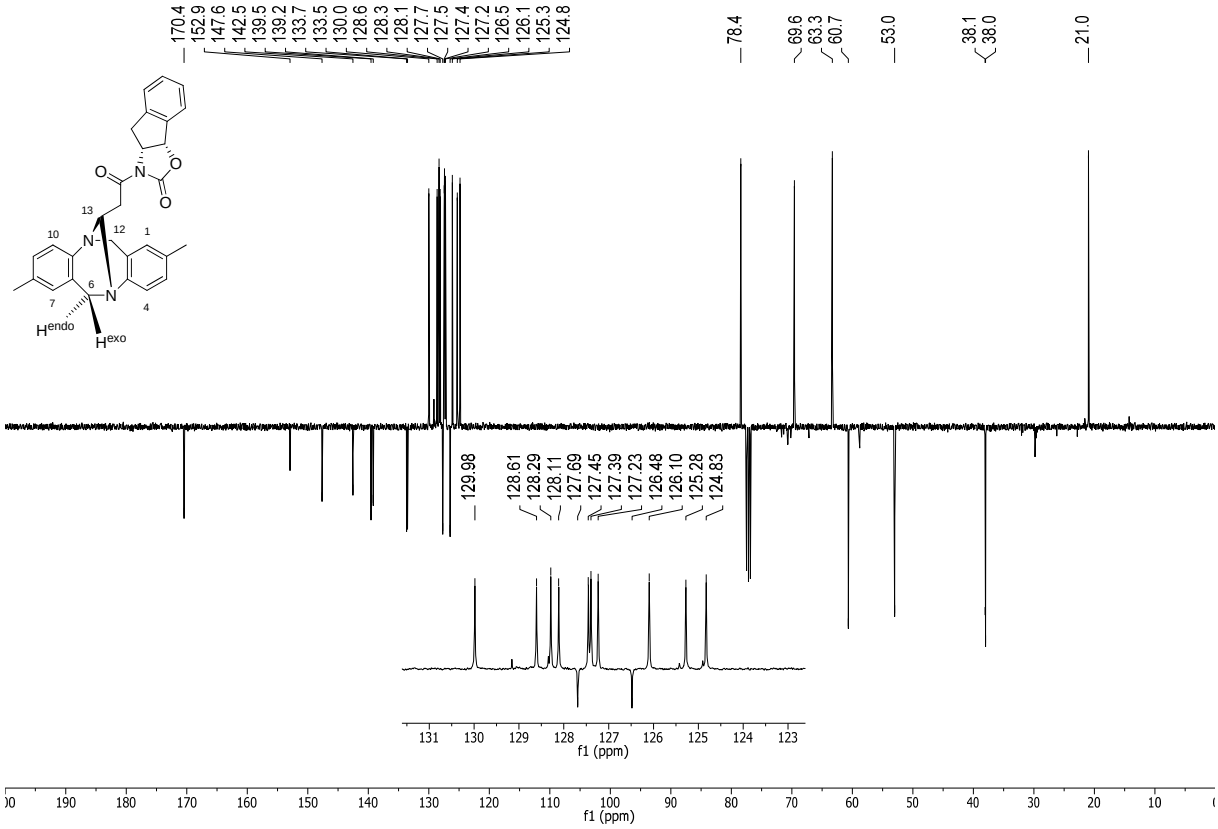
^{13}C NMR of **1e**



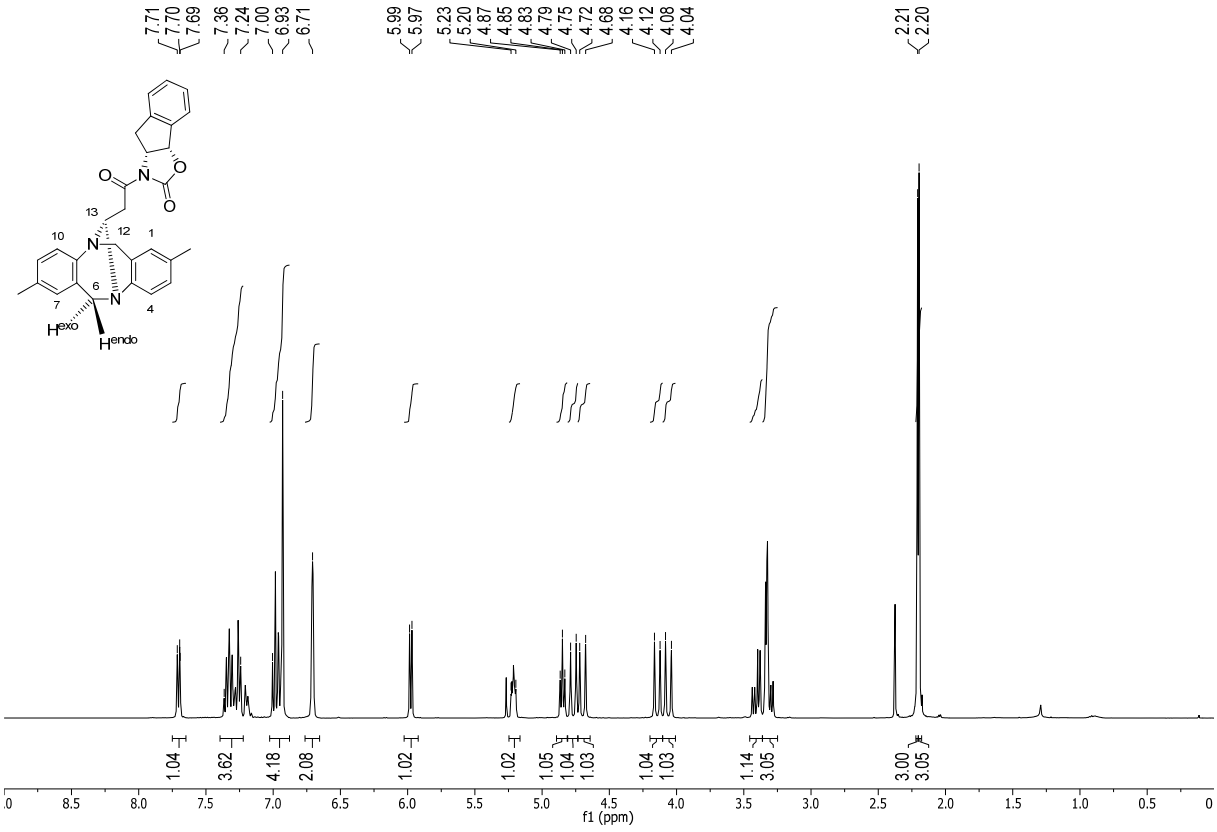
^{1}H NMR of (5*S*,11*S*)-**1f**



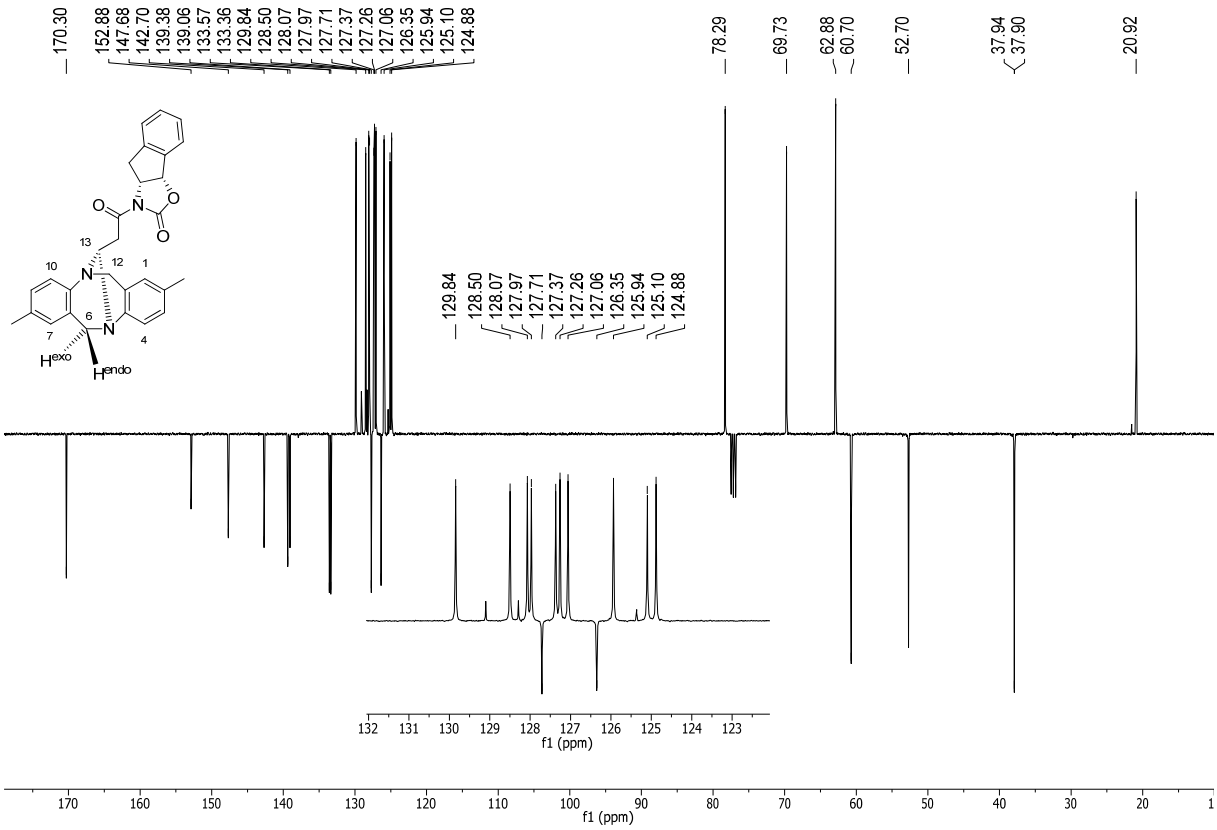
^{13}C NMR of (5*S*,11*S*)-**1f**



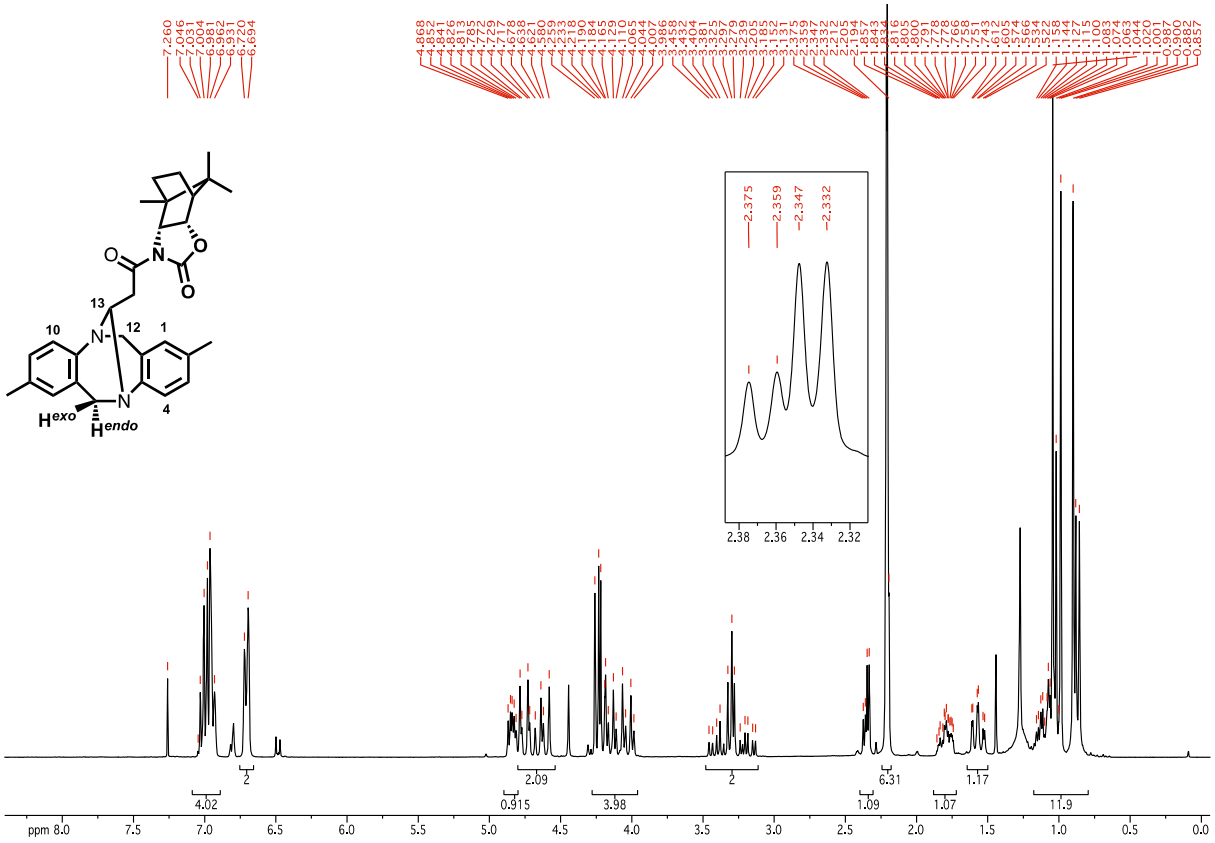
^{1}H NMR of (5*R*,11*R*)-**1f**



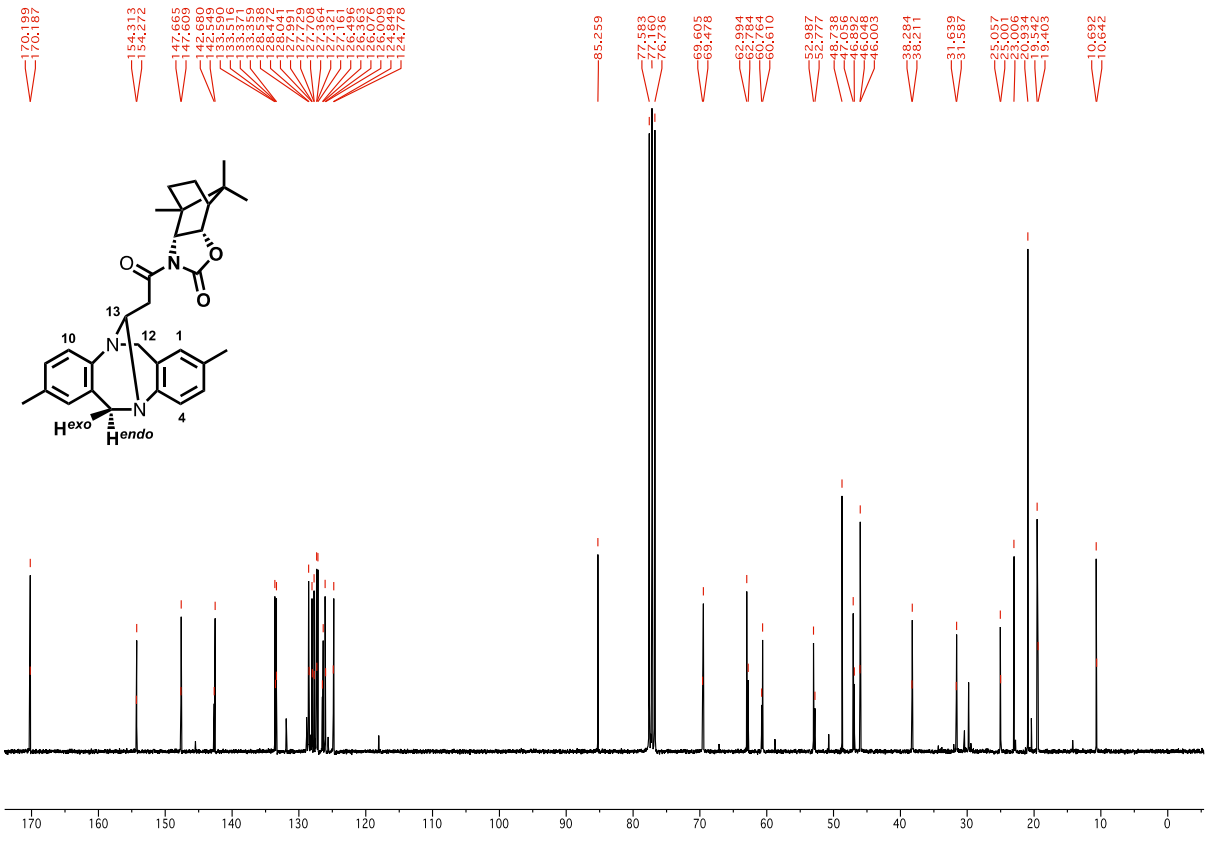
^{13}C NMR of (5*R*,11*R*)-**1f**



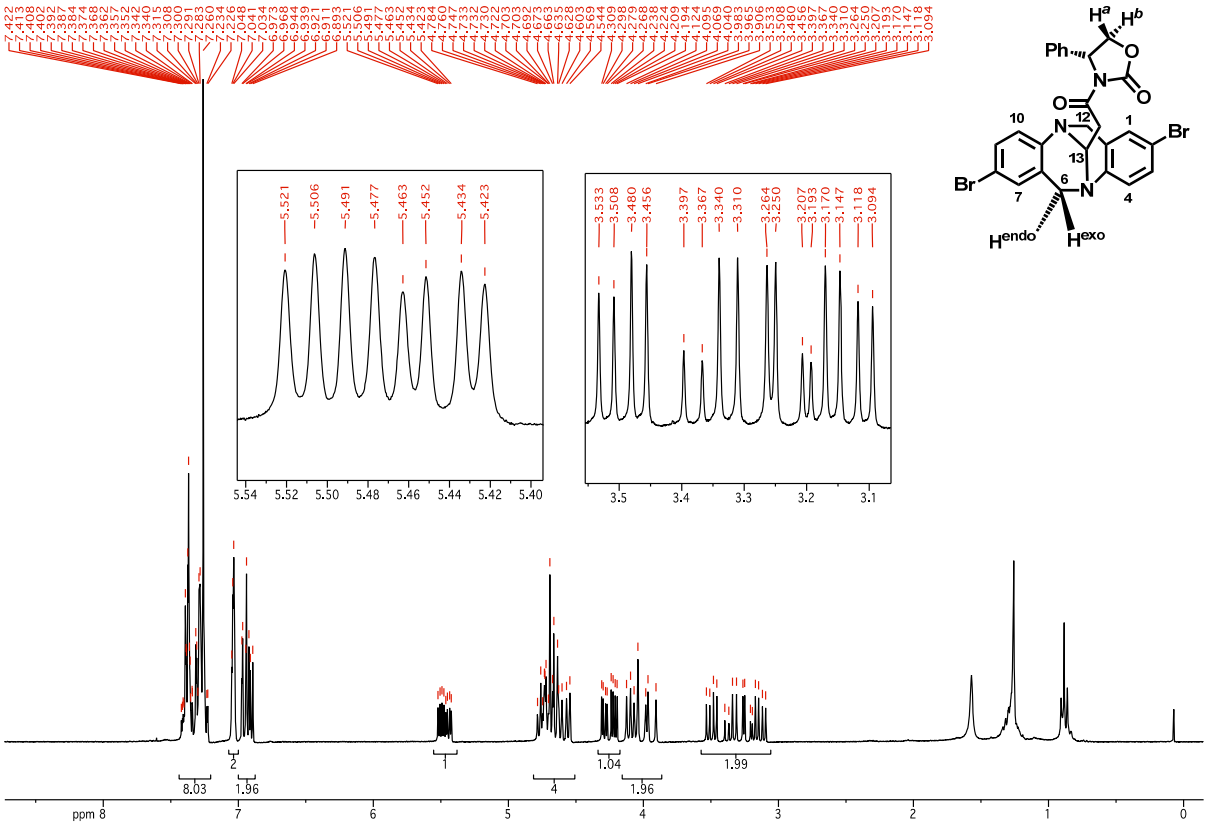
^{1}H NMR of **1g**



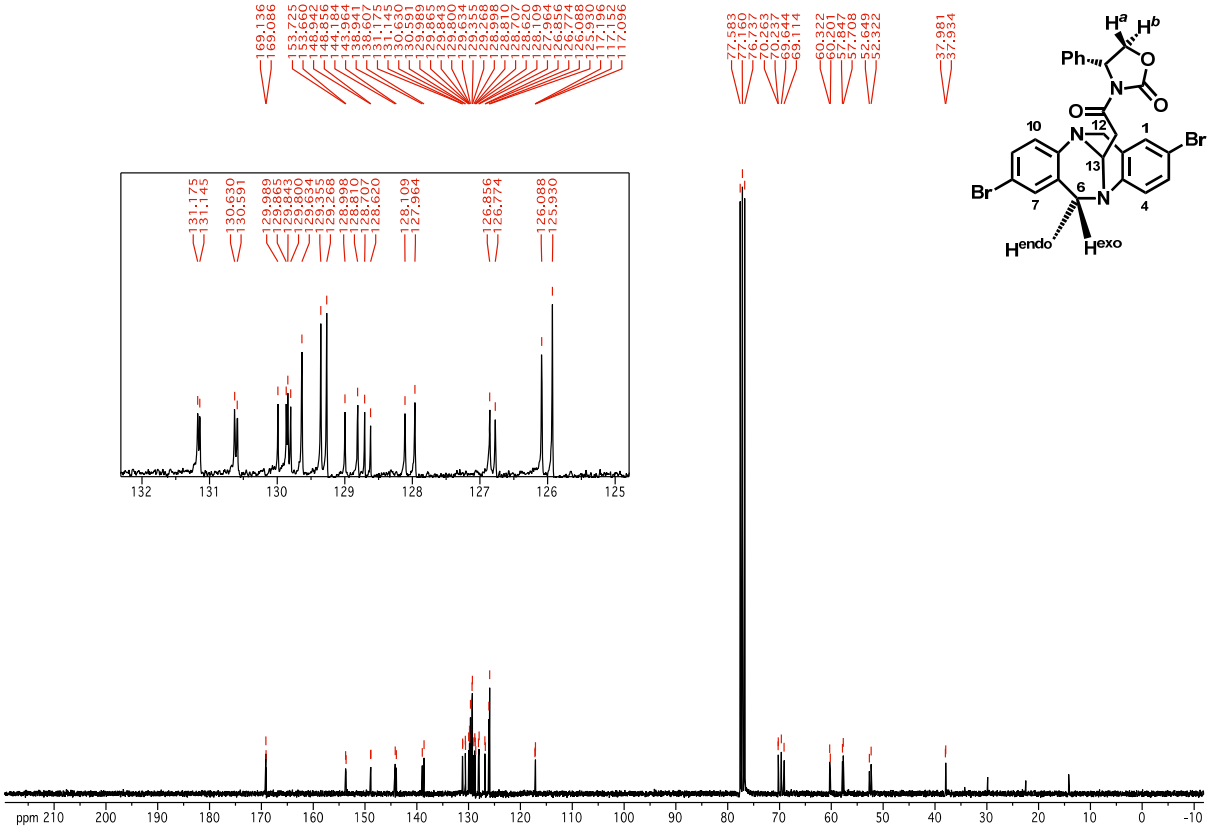
^{13}C NMR of **1g**



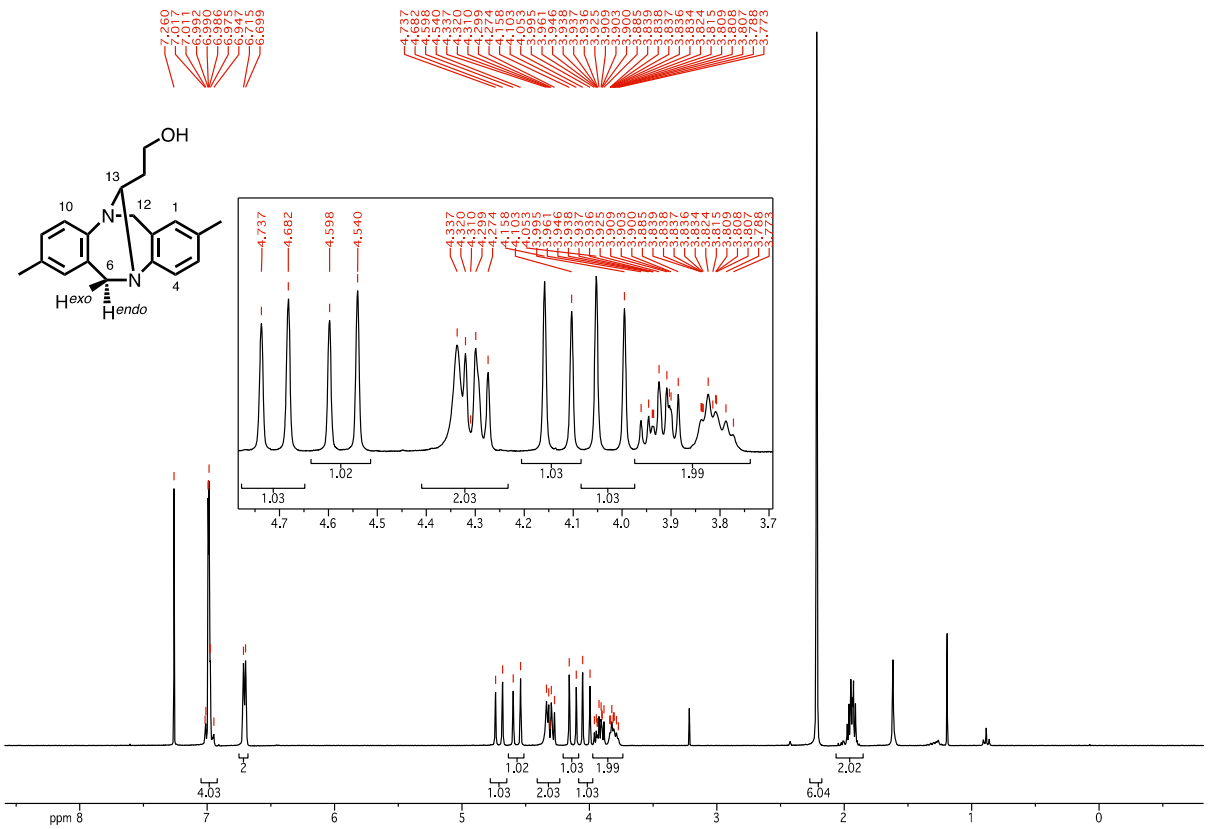
^{1}H NMR of **1h**



^{13}C NMR of **1h**



^{1}H NMR of (5*S*,11*S*)-**4**



^{13}C NMR of (5*S*,11*S*)-**4**