Supporting Information

Catalytic asymmetric synthesis of isoxazoline-*N*-oxides under phase-transfer conditions

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General Information. Infrared (IR) spectra were recorded on a Nicolet MAGNA560. ^{1}H NMR spectra were measured on Bruker AV500 (500 MHz) and Bruker AV300 (300 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane (in the case of $CDCl_3$) as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on Bruker AV500 (125 MHz) and Bruker AV300 (75 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using Daicel Chiralpak AD-H and Chiralcel OD-H 4.6 mm × 25 cm columns. High-resolution mass spectra (HRMS) were performed on a Thermo Fisher Scientific LTQ Orbitrap XL and a JEOL JMS-700 MStation. Optical rotations were measured on a JASCO P-1020 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Flash column chromatography was performed with silica gel 60 (Merck 1.09386.9025, 230-400 mesh) or using a Biotage Isolera with prepacked silica cartridges (10 g). In experiments requiring dry solvent, tetrahydrofuran (THF) and CH_2Cl_2 was purchased from Kanto Chemical Co. Inc. as "Dehydrated". Commercially available reagents were used as received. Nitroalkenes[1-4] and phase-transfer catalysts (*R,R*)-**1a**,[5] (*S,S*)-**1b**,[6] (*S,S*)-**1c**[6] and (*S,S*)-**1d**,[6] were synthesized according to literature procedures and used after column chromatography on silica gel.

General procedure for asymmetric synthesis of isoxazoline-*N*-oxides with nitroolefin 1 and diethyl bromomalonate

To a suspension of (*R,R*)-**1a** (0.9 mg, 0.001 mmol), diethyl bromomalonate (23.9 mg, 0.1 mmol) and nitroalkene (0.1 mmol) in mesitylene (0.33 mL) at –35 °C was added 70% Cs_2CO_3 solution (0.12 mL). After stirring for 12 h at –35 °C, the reaction mixture was quenched with saturated NH_4Cl solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by flash column chromatography on silica gel to give the corresponding cyclic nitronate. The product was identified by NMR spectroscopy. The enantiomeric excess of the product was determined by HPLC using a chiral column.

(*S*)-5,5-Bis(ethoxycarbonyl)-3-methyl-4-phenyl-4,5-dihydroisoxazole 2-oxide (Table 3, entry 1)

$[\alpha]_D^{20}$ 2.28 (*c* 1.0, $CHCl_3$; 83% ee); ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.39-7.32 (3H, m, Ar-H), 7.27-7.19 (2H, m, Ar-H), 5.27 (1H, s, Ar-CH), 4.38 (1H, dq, *J* = 11.1, 7.3 Hz, -$CO_2CH_2CH_3$), 4.30 (1H, dq, *J* = 11.1, 7.3 Hz, -$CO_2CH_2CH_3$), 3.78 (1H, dq, *J* = 10.7, 7.2 Hz, -$CO_2CH_2CH_3$), 3.66 (1H, dq, *J* = 10.7, 7.2 Hz, -$CO_2CH_2CH_3$), 1.90 (3H, d, *J* = 1.4 Hz, -C(=N)CH_3), 1.31 (3H, t, *J* = 7.1 Hz, -$CO_2CH_2CH_3$), 0.84 (3H, t, *J* = 7.1 Hz, -$CO_2CH_2CH_3$); ^{13}C-NMR (75MHz, $CDCl_3$) δ 166.3, 163.8, 133.0, 129.14, 129.09, 128.9, 113.1, 84.4, 63.4, 62.3, 56.9, 13.8, 13.4, 11.1; IR (neat) 2984, 1747, 1664, 1457, 1369, 1262, 1208, 1095, 1045 cm^{-1}; HRMS (ESI) Calcd. for $C_{16}H_{20}NO_6$: 322.1284 ($[M + H]^+$), Found: 322.1285 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 254 nm, hexane/2-propanol = 9:1, flow rate 1.0 mL/min, retention time: 10.7 min (*R*) and 12.1 min (*S*).

(*S*)-5,5-Bis(ethoxycarbonyl)-3-ethyl-4-phenyl-4,5-dihydroisoxazole 2-oxide 3b (Table 3, entry 2)

$[\alpha]_D^{20}$ 2.58 (*c* 1.0, $CHCl_3$; 86% ee); ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.39-7.32 (3H, m, Ar-H), 7.28-7.22 (2H, m, Ar-H), 5.26 (1H, s, Ar-CH), 4.39 (1H, dq, *J* = 10.7, 7.1 Hz, -$CO_2CH_2CH_3$), 4.29 (1H, dq, *J* = 10.7, 7.2 Hz, -$CO_2CH_2CH_3$), 3.78 (1H, dq, *J* = 10.7, 7.2 Hz, -$CO_2CH_2CH_3$), 3.68 (1H, dq, *J* = 10.7, 7.2 Hz, -$CO_2CH_2CH_3$), 2.49 (1H, dqd, *J* = 15.3, 7.6, 0.9 Hz, -C(=N)CH_2CH_3), 2.15 (1H, dqd, *J* = 15.3, 7.6, 1.3 Hz, -C(=N)CH_2CH_3), 1.32 (3H, t, *J* = 7.2 Hz, -$CO_2CH_2CH_3$), 1.02 (3H, t, *J* = 7.6 Hz, -C(=N)CH_2CH_3), 0.84 (3H, t, *J* = 7.2 Hz, -$CO_2CH_2CH_3$); ^{13}C-NMR (75MHz, $CDCl_3$) δ 166.4, 163.8, 133.2, 129.2, 129.1, 128.9, 117.6,

84.5, 63.4, 62.3, 55.8, 19.2, 13.8, 13.4, 9.3 ; IR (neat) 2982, 1746, 1654, 1457, 1368, 1279, 1227, 1205, 1093, 1039 cm^{-1}; HRMS (ESI) Calcd. for $C_{17}H_{22}NO_6$: 336.1440 ($[M + H]^+$), Found: 336.1442 ($[M + H]^+$); HPLC analysis: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol = 9:1, flow rate 0.5 mL/min, retention time: 17.2 min (*S*) and 20.2 min (*R*).

(*S*)-3-Butyl-5,5-bis(ethoxycarbonyl)-4-phenyl-4,5-dihydroisoxazole 2-oxide (Table 3, Entry 3)

$[\alpha]_D^{20}$ 2.15 (*c* 1.0, $CHCl_3$; 86% ee); ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.39-7.32 (3H, m, Ar-H), 7.28-7.22 (2H, m, Ar-H), 5.26 (1H, s, Ar-CH), 4.38 (1H, dq, *J* = 10.7, 7.1 Hz, $-CO_2CH_2CH_3$), 4.29 (1H, dq, *J* = 10.7, 7.2 Hz, $-CO_2CH_2CH_3$), 3.78 (1H, dq, *J* = 10.7, 7.2 Hz, $-CO_2CH_2CH_3$), 3.68 (1H, dq, *J* = 10.7, 7.2 Hz, $-CO_2CH_2CH_3$), 2.45 (1H, dt, *J* = 15.1, 7.5 Hz, $-C(=N)CH_2CH_2$), 2.05 (1H, dt, *J* = 14.3, 7.1 Hz, $-C(=N)CH_2CH_2$), 1.50-1.22(4H, m, $-C(=N)CH_2(CH_2)_2CH_3$), 1.31 (3H, t, *J* = 7.1 Hz, $-CO_2CH_2CH_3$), 0.854 (3H, t, *J* = 7.2 Hz, $-C(=N)(CH_2)_3CH_3$), 0.846 (3H, t, *J* = 7.1 Hz, $-CO_2CH_2CH_3$); ^{13}C-NMR (75MHz, $CDCl_3$) δ 166.4, 163.8, 133.2, 129.13, 129.07, 128.8, 116.9, 84.5, 63.3, 62.3, 56.0, 27.0, 25.2, 22.2, 13.8, 13.5, 13.4; IR (neat) 2961, 2934, 1746, 1653, 1457, 1369, 1278, 1208, 1095, 1041 cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{26}NO_6$: 364.1752 ($[M + H]^+$), Found: 364.1755 ($[M + H]^+$); HPLC analysis: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol = 20:1, flow rate 1.0 mL/min, retention time: 22.6 min (*S*) and 26.8 min (*R*).

(*S*)-5,5-Bis(ethoxycarbonyl)-3-isopropyl-4-phenyl-4,5-dihydroisoxazole 2-oxide (Table 3, entry 4)

$[\alpha]_D^{20}$ 2.21 (*c* 1.0, $CHCl_3$; 77% ee); ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.37-7.26 (5H, m, Ar-H), 5.15 (1H, s, Ar-CH), 4.38 (1H, dq, *J* = 10.6, 7.2 Hz, $-CO_2CH_2CH_3$), 4.28 (1H, dq, *J* = 10.6, 7.1 Hz, $-CO_2CH_2CH_3$), 3.79 (1H, dq, *J* = 11.1, 7.0 Hz, $-CO_2CH_2CH_3$), 3.72 (1H, dq, *J* = 11.0, 6.9 Hz, $-CO_2CH_2CH_3$), 2.81 (1H, m, $-C(=N)CH(CH_3)_2$), 1.31 (3H, t, *J* = 7.1 Hz, $-CO_2CH_2CH_3$), 1.15 (3H, d, *J* = 7.0 Hz, $-C(=N)CH(CH_3)_2$), 0.88 (3H, d, *J* = 7.0 Hz, $-C(=N)CH(CH_3)_2$), 0.85 (3H, t, *J* = 7.0 Hz, $-CO_2CH_2CH_3$); ^{13}C-NMR (75MHz, $CDCl_3$) δ 166.6, 163.6, 133.9, 129.2, 129.1, 128.8, 120.9, 84.9, 63.4, 62.3, 55.3, 27.0, 18.5, 18.1, 13.9, 13.4; IR (neat) 2978, 2938, 1747, 1651, 1457, 1369, 1247, 1087, 1038 cm^{-1}; HRMS (ESI) Calcd. for $C_{18}H_{24}NO_6$: 350.1597 ($[M + H]^+$), Found: 350.1598 ($[M + H]^+$); HPLC analysis: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol = 9:1, flow rate 0.5 mL/min, retention time: 13.5 min (*S*) and 12.1 min (*S*).

(*S*)-5,5-Bis(ethoxycarbonyl)-3,4-diphenyl-4,5-dihydroisoxazole 2-oxide (Table 3, entry 5)

$[\alpha]_D^{20}$ 2.51 (*c* 1.0, $CHCl_3$; 81% ee); ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.86-7.76 (2H, m, Ar-H), 7.36-7.24 (8H, m, Ar-H), 5.76 (1H, s, Ar-CH), 4.40 (1H, dq, *J* = 10.7, 7.1 Hz, $-CO_2CH_2CH_3$), 4.31 (1H, dq, *J* = 10.7, 7.1 Hz, $-CO_2CH_2CH_3$), 3.80 (1H, dq, *J* = 10.8, 7.2 Hz, $-CO_2CH_2CH_3$), 3.72 (1H, dq, *J* = 10.7, 7.2 Hz, $-CO_2CH_2CH_3$), 1.32 (3H, t, *J* = 7.1 Hz, $-CO_2CH_2CH_3$), 0.90 (3H, t, *J* = 7.1 Hz, $-CO_2CH_2CH_3$); ^{13}C-NMR (75MHz, $CDCl_3$) δ 166.5, 163.5, 133.9, 129.7, 129.1, 129.0, 128.9, 128.7, 126.9, 125.0, 115.4, 84.8, 63.5, 62.5, 55.4, 13.8, 13.4; IR (neat) 2983, 1747, 1626, 1494, 1448, 1370, 1298, 1233, 1094, 1061, 1041 cm^{-1}; HRMS (ESI) Calcd. for $C_{21}H_{22}NO_6$: 384.1440 ($[M + H]^+$), Found: 384.1442 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 254 nm, hexane/EtOH = 4:1, flow rate 0.5 mL/min, retention time: 19.1 min (*S*) and 24.3 min (*R*).

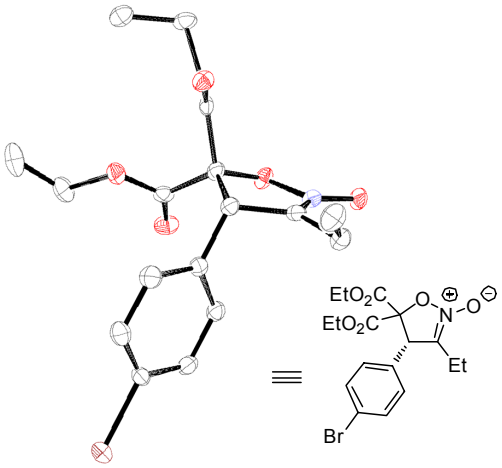
(*S*)-4-(4-Bromophenyl)-5,5-bis(ethoxycarbonyl)-3-ethyl-4,5-dihydroisoxazole 2-oxide (Table 3, entry 6)

$[\alpha]_D^{20}$ 2.12 (*c* 1.0, $CHCl_3$; 85% ee); ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.50 (2H, dd, *J* = 8.5, 2.2 Hz, Ar-H), 7.14 (2H, dd, *J* = 8.5, 2.2 Hz, Ar-H), 5.23 (1H, s, Ar-CH), 4.38 (1H, dq, *J* = 10.7, 7.1 Hz, $-CO_2CH_2CH_3$), 4.29 (1H, dq, *J* = 10.7, 7.1 Hz, $-CO_2CH_2CH_3$), 3.85 (1H, dq, *J* = 10.7, 7.2 Hz, $-CO_2CH_2CH_3$), 3.75 (1H, dq, *J* = 10.7, 7.1 Hz, $-CO_2CH_2CH_3$), 2.48 (1H, dqd, *J* = 15.2, 7.7, 0.9 Hz, $-C(=N)CH_2CH_3$), 2.14 (1H, dqd, *J* = 15.3, 7.7, 1.3 Hz, $-C(=N)CH_2CH_3$), 1.32 (3H, t, *J* = 7.1 Hz, $-CO_2CH_2CH_3$), 1.02 (3H, t, *J* = 7.6 Hz, $-C(=N)CH_2CH_3$), 0.92 (3H, t, *J* = 7.2 Hz, $-CO_2CH_2CH_3$); ^{13}C-NMR (75MHz, $CDCl_3$) δ 166.2, 163.6, 132.3, 132.1, 130.8, 123.4, 116.9, 84.2, 63.5, 62.5, 55.2, 19.1, 13.8, 13.5, 9.3; IR (neat) 2981, 1747, 1654, 1488, 1368, 1280, 1227, 1205, 1093, 1040, 1012 cm^{-1}; HRMS (ESI) Calcd. for $C_{17}H_{21}BrNO_6$: 414.0546 ($[M + H]^+$), Found: 414.0547 ($[M + H]^+$); HPLC analysis: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol = 40:1, flow rate 0.7 mL/min, retention time: 33.2 min (*R*) and 35.5 min (*S*).

Crystal structure analysis of (*S*)-4-(4-Bromophenyl)-5,5-bis(ethoxycarbonyl)-3-ethyl-4,5-dihydroisoxazole 2-oxide

Single crystals of (*S*)-4-(4-Bromophenyl)-5,5-bis(ethoxycarbonyl)-3-ethyl-4,5-dihydroisoxazole 2-oxide for X-ray diffraction experiments was recrystallized from EtOH. The data were collected at –177 °C on a Rigaku R-AXIS RAPID IP area detector with graphite-monochromated Mo-$K\alpha$ radiation (λ = 0.71075 Å). The crystal structure was solved by direct methods using SIR9[7] and expanded using DIRDIF99 Fourier techniques.[8] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically.

The final cycle of full-matrix least-squares refinement[9] on F^2 was based on 4145 observed reflections and 306 variable parameters. Crystallographic data for (c): $C_{17}H_{20}BrNO_6$, colorless block, $0.5 \times 0.4 \times 0.3$ mm^3, orthorhombic, $P2_12_12_1$, a = 10.0497(2), b = 10.3362(3), c = 17.5284(5) Å, V = 1820.77 (8) Å^3, D_{calcd} = 1.511 gcm^{-3}, Z = 4, $2\theta_{max}$ = 55.0°, μ = 22.962 cm^{-1}. A total of 17820 reflections were measured. R = 0.024, and Rw = 0.041 for all reflections. All calculations were performed using the CrystalStructure3.8[10] crystallographic software package. CCDC-796797 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.



(*S*)-5,5-Bis(ethoxycarbonyl)-3-ethyl-4-(4-nitrophenyl)-4,5-dihydroisoxazole 2-oxide (Table 3, entry 7)

$[\alpha]_D^{20}$ 1.85 (*c* 1.0, $CHCl_3$; 87% ee); ^{1}H-NMR (300MHz, $CDCl_3$) δ 8.24 (2H, dd, J = 8.8, 2.2 Hz, Ar-H), 7.49 (2H, dd, J = 8.8, 2.2 Hz, Ar-H), 5.38 (1H, s, Ar-CH), 4.40 (1H, dq, J = 10.8, 7.1 Hz, -$CO_2CH_2CH_3$), 4.31 (1H, dq, J = 10.7, 7.1 Hz, -$CO_2CH_2CH_3$), 3.85 (1H, dq, J = 10.8, 7.1 Hz, -$CO_2CH_2CH_3$), 3.75 (1H, dq, J = 10.8, 7.1 Hz, -$CO_2CH_2CH_3$), 2.51 (1H, dqd, J = 15.2, 7.7, 0.8 Hz, -C(=N)CH_2CH_3), 2.14 (1H, dqd, J = 15.2, 7.7, 1.3 Hz, -C(=N)CH_2CH_3), 1.33 (3H, t, J = 7.1 Hz, -$CO_2CH_2CH_3$), 1.03 (3H, t, J = 7.6 Hz, -C(=N)CH_2CH_3), 0.92 (3H, t, J = 7.1 Hz, -$CO_2CH_2CH_3$); ^{13}C-NMR (75MHz, $CDCl_3$) δ 165.9, 163.4, 148.3, 140.7, 130.2, 124.0, 116.3, 84.1, 63.7, 62.7, 55.1, 19.1, 13.8, 13.5, 9.3; IR (neat) 2983, 2941, 1747, 1655, 1607, 1525, 1351, 1279, 1229, 1205, 1095, 1040, 1014 cm^{-1}; HRMS (ESI) Calcd. for $C_{17}H_{21}N_2O_8$: 381.1291 ([M + H]$^+$), Found: 381.1292 ([M + H]$^+$); HPLC analysis: Daicel Chiralpak AD-H, 254 nm, hexane/2-propanol = 4:1, flow rate 1.0 mL/min, retention time: 13.1 min (*S*) and 19.2 min (*R*).

(*S*)-5,5-Bis(ethoxycarbonyl)-3-ethyl-4-(4-methoxyphenyl)-4,5-dihydroisoxazole 2-oxide (Table 3, entry 8)

$[\alpha]_D^{20}$ 2.42 (*c* 1.0, $CHCl_3$; 87% ee); ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.17 (2H, d, *J* = 8.6 Hz, Ar-H), 6.86 (2H, d, *J* = 8.5 Hz, Ar-H), 5.21 (1H, s, Ar-CH), 4.37 (1H, dq, *J* = 10.7, 7.1 Hz, $-CO_2CH_2CH_3$), 4.28 (1H, dq, *J* = 10.6, 7.1 Hz, $-CO_2CH_2CH_3$), 3.83 (1H, dq, *J* = 10.7, 7.1 Hz, $-CO_2CH_2CH_3$), 3.80 (3H, s, $-OCH_3$), 3.73 (1H, dq, *J* = 10.6, 7.2 Hz, $-CO_2CH_2CH_3$), 2.47 (1H, dq, *J* = 15.2, 7.6 Hz, $-C(=N)CH_2CH_3$), 2.15 (1H, dq, *J* = 15.2, 7.6 Hz, $-C(=N)CH_2CH_3$), 1.31 (3H, t, *J* = 7.1 Hz, $-CO_2CH_2CH_3$), 1.02 (3H, t, *J* = 7.6 Hz, $-C(=N)CH_2CH_3$), 0.91 (3H, t, *J* = 7.1 Hz, $-CO_2CH_2CH_3$); ^{13}C-NMR (75MHz, $CDCl_3$) δ 166.5, 163.9, 160.1, 130.4, 124.9, 117.7, 114.2, 84.6, 63.3, 62.3, 55.3, 55.2, 19.2, 13.9, 13.6, 9.3; IR (neat) 2981, 2362, 1747, 1653, 1611, 1514, 1458, 1368, 1252, 1228, 1206, 1179, 1094, 1036 cm^{-1}; HRMS (ESI) Calcd. for $C_{18}H_{24}NO_7$: 366.1544 ($[M + H]^+$), Found: 366.1547 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 254 nm, hexane/2-propanol = 9:1, flow rate 0.8 mL/min, retention time: 23.0 min (*R*) and 24.9 min (*S*).

(*S*)-4-Butyl-5,5-bis(ethoxycarbonyl)-3-ethyl-4,5-dihydroisoxazole 2-oxide (Table 3, entry 9)

$[\alpha]_D^{20}$ 1.55 (*c* 1.0, $CHCl_3$; 77% ee); ^{1}H-NMR (300MHz, $CDCl_3$) δ 4.42-4.20 (4H, m, $-CO_2CH_2CH_3$), 4.04 (1H, t, *J* = 6.0 Hz, Bu-CH), 2.51 (1H, dq, *J* = 15.1, 7.5 Hz, $-C(=N)CH_2CH_3$), 2.28 (1H, dqd, *J* = 15.1, 7.5, 1.1 Hz, $-C(=N)CH_2CH_3$), 1.75-1.50 (2H, m, $-CH_2-$), 1.45-1.25 (4H, m, $-CH_2-$), 1.33 (3H, t, *J* = 7.1 Hz, $-CH_3$), 1.31 (3H, t, *J* = 7.1 Hz, $-CH_3$), 1.15 (3H, t, *J* = 7.6 Hz, $-C(=N)CH_2CH_3$), 0.90 (3H, t, *J* = 7.0 Hz, $-CH_3$); ^{13}C-NMR (75MHz, $CDCl_3$) δ 166.5, 164.9, 118.5, 84.2, 63.1, 62.7, 49.1, 28.5, 27.9, 22.7, 19.2, 14.0, 13.8, 13.7, 9.3; IR (neat) 2960, 2936, 2874, 1747, 1653, 1458, 1369, 1277, 1230, 1088, 1037 cm^{-1}; HRMS (ESI) Calcd. for $C_{15}H_{26}NO_6$: 316.1754 ($[M + H]^+$), Found: 316.1755 ($[M + H]^+$); HPLC analysis: Daicel Chiralcel OD-H, 235 nm, hexane/2-propanol = 9:1, flow rate 0.5 mL/min, retention time: 12.7 min (*R*) and 14.0 min (*S*).

(*S*)-Diethyl 2-hydroxy-2-(2-(hydroxyimino)-1-phenylbutyl)malonate 4

To a solution of **3b** (200 mg, 0.60 mmol) in MeOH (8 mL) was stirred for 3 h in the presence of 5% palladium on activated carbon (80 mg) at room temperature under H_2 atmosphere. The resulting mixture was filtered to remove the catalyst, and the filtrate was concentrated. Purification of the residue by column chromatography on silica gel (ethyl acetate/hexane = 1:1 as eluent) gave the title compound **4** (188 mg, 0.56 mmol, 93% yield).

$[\alpha]_D^{20}$ 1.68 (*c* 1.0, $CHCl_3$; 86% ee); ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.36-7.34 (2H, m, Ar-H), 7.32-7.27 (3H, m, Ar-H), 7.12 (1H, br, OH) 4.90 (1H, br, OH), 4.63 (1H, s, Ar-CH), 4.31 (1H, dq, *J* = 10.7, 7.1 Hz, -$CO_2CH_2CH_3$), 4.27 (1H, dq, *J* = 10.7, 7.1 Hz, -$CO_2CH_2CH_3$), 4.08 (1H, dq, *J* = 10.7, 7.2 Hz, -$CO_2CH_2CH_3$), 4.04 (1H, dq, *J* = 10.7, 7.2 Hz, -$CO_2CH_2CH_3$), 2.54 (1H, dq, *J* = 13.5, 7.6 Hz, -C(=N)CH_2CH_3), 1.86 (1H, dq, *J* = 13.5, 7.6 Hz, -C(=N)CH_2CH_3), 1.31 (3H, t, *J* = 7.1 Hz, -$CO_2CH_2CH_3$), 1.09 (3H, t, *J* = 7.2 Hz, -$CO_2CH_2CH_3$), 1.00 (3H, t, *J* = 7.6 Hz, -C(=N)CH_2CH_3); ^{13}C-NMR (125MHz, $CDCl_3$) δ 169.9, 167.8, 162.3, 134.0, 130.4, 128.3, 128.0, 82.3, 62.5, 62.4, 53.0, 21.5, 14.0, 13.8, 9.8; IR (neat) 3427, 2980, 2366, 2340, 1741, 1462, 1452, 1367, 1262, 1220, 1149, 1040 cm^{-1}; HRMS (FAB) Calcd. for $C_{17}H_{24}NO_6$: 338.1604 ($[M + H]^+$), Found: 338.1596 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 230 nm, hexane/2-propanol = 9:1, flow rate 1.0 mL/min, retention time: 14.5 min (*R*) and 19.3 min (*S*).

(*S*)-Diethyl 3-ethyl-4-phenylisoxazole-5,5(4H)-dicarboxylate 5

To a solution of **4** (33.7 mg, 0.1 mmol) and Et_3N (21.2 mg, 0.21 mmol) in CH_2Cl_2 (0.5 mL) was added MsCl (11.4 mg, 0.1 mmol) dropwise at 0 °C under argon atmosphere, and the cooling bath was then removed.[11] The reaction mixture was stirred overnight at room temperature and poured into water. After extraction with ethyl acetate, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5:1 as eluent) to give the title compound **5** (29.8 mg, 0.933 mmol, 93% yield).

$[\alpha]_D^{20}$ 3.01 (*c* 1.0, $CHCl_3$; 86% ee); ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.35-7.31 (3H, m, Ar-H), 7.18-7.16 (2H, m, Ar-H), 5.19 (1H, s, Ar-CH), 4.35 (1H, dq, *J* = 10.7, 7.1 Hz, -$CO_2CH_2CH_3$), 4.26 (1H, dq, *J* = 10.7, 7.1 Hz, -$CO_2CH_2CH_3$), 3.78 (1H, dq, *J* = 10.7, 7.1 Hz, -$CO_2CH_2CH_3$), 3.68 (1H, dq, *J* = 10.7, 7.1 Hz, -$CO_2CH_2CH_3$), 2.34 (1H, dq, *J* = 15.1, 7.8 Hz, -C(=N)CH_2CH_3), 2.13 (1H, dq, *J* = 15.4, 7.8 Hz, -C(=N)CH_2CH_3), 1.30 (3H, t, *J* = 7.1 Hz, -$CO_2CH_2CH_3$), 1.12 (3H, t, *J* = 7.5 Hz, -C(=N)CH_2CH_3), 0.81 (3H, t, *J* = 7.2 Hz, -$CO_2CH_2CH_3$); ^{13}C-NMR (125MHz, $CDCl_3$) δ 167.2, 165.0, 162.2, 132.8, 129.3, 128.8, 128.6, 91.6, 62.9, 61.9, 61.3, 19.9, 13.9, 13.4, 10.6; IR (neat) 2980, 1768, 1742, 1462, 1452, 1368, 1268, 1228, 1201, 1128, 1081, 1050 cm^{-1}; HRMS (FAB) Calcd. for $C_{17}H_{22}NO_5$: 320.1498 ($[M + H]^+$), Found: 320.1491 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 230 nm, hexane/2-propanol = 9:1, flow rate 0.5 mL/min, retention time: 14.1 min (*S*) and 18.9 min (*R*).

(4*S*,5*S*)-Ethyl 3-ethyl-5-(hydroxymethyl)-4-phenyl-4,5-dihydroisoxazole-5-carboxylate 6

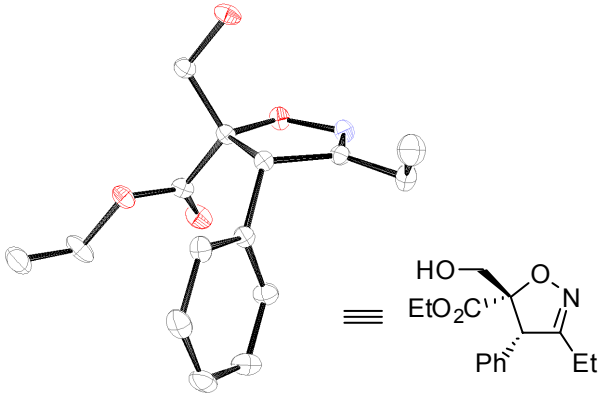
To a solution of **5** (11.6 mg, 0.036 mmol) in THF (0.5 mL) was added $LiAlH(OBu^t)_3$ (1.0 M in THF solution, 180 μl, 0.180 mmol)[12] dropwise at 0 °C, and the cooling bath was then removed. The reaction mixture was stirred for 11 h at room temperature and poured into ice-cooled 1N HCl. After neutrization with $NaHCO_3$ the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane = 1:2 as eluent) to give the title compound **6** (8.7 mg, 0.031 mmol, 86% yield).

$[\alpha]_D^{20}$ 0.68 (*c* 0.5, $CHCl_3$; 85% ee); ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.34-7.28 (3H, m, Ar-H), 7.14-7.12 (2H, m, Ar-H), 4.43 (1H, s, Ar-CH), 3.92 (1H, dd, *J* = 11.8, 5.8 Hz, -CCH_2OH), 3.86 (1H, dd, *J* = 11.8, 8.5 Hz, -CCH_2OH), 3.74 (2H, q, *J* = 7.2 Hz, -$CO_2CH_2CH_3$), 2.54 (1H, dd, *J* = 8.2, 6.4 Hz, -CCH_2OH), 2.34 (1H, dq, *J* = 15.1, 7.8 Hz, -C(=N)CH_2CH_3), 2.12 (1H, dq, *J* = 14.6, 7.6 Hz, -C(=N)CH_2CH_3), 1.11 (3H, t, *J* = 7.5 Hz, -C(=N)CH_2CH_3), 0.84 (3H, t, *J* = 7.2 Hz, -$CO_2CH_2CH_3$); ^{13}C-NMR (125MHz, $CDCl_3$) δ 168.8, 161.9, 133.7, 129.0, 128.7, 128.4, 92.1, 65.5, 61.5, 61.3, 20.1, 13.5, 10.7; IR (neat) 3349, 2979, 2927, 1745, 1461, 1453, 1371, 1277, 1244, 1129, 1096, 1076, 1055, 1040 cm^{-1}; HRMS (FAB) Calcd. for $C_{15}H_{20}NO_4$: 278.1392 ($[M + H]^+$), Found: 278.1388 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 230 nm, hexane/2-propanol = 9:1, flow rate 1.0 mL/min, retention time: 14.0 min (4*S*, 5*S*) and 18.9 min (4*R*, 5*R*).

Crystal structure analysis of (4*S*,5*S*)-ethyl 3-ethyl-5-(hydroxymethyl)-4-phenyl-4,5-dihydroisoxazole-5-carboxylate 6

Single crystals of **6** for X-ray diffraction experiments were recrystallized from EtOH. The data were collected at –177 °C on a Rigaku R-AXIS RAPID IP area detector with graphite-monochromated Mo-$K\alpha$ radiation (λ = 0.71075 Å). The crystal structure was solved by direct methods using SIR92[7] and expanded using DIRDIF99 Fourier techniques.[8] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement[9] on F^2 was based on 3087 observed reflections and 257 variable parameters. Crystallographic data for (c): $C_{15}H_{19}NO_4$, colorless prism, 0.5 × 0.4 × 0.3 mm^3, monoclinic, $P2_1$, a = 9.0974(10), b = 7.7565(9), c = 10.9278(14) Å, V = 724.14 (15) $Å^3$, D_{calcd} = 1.272 gcm^{-3}, Z = 2, $2\theta_{max}$ = 54.9°, μ = 0.921 cm^{-1}. A total of 7136 reflections were measured. R = 0.046, and Rw = 0.104 for all reflections. All calculations were performed using the CrystalStructure3.8[10] crystallographic software package. CCDC-794861 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.



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9) Least Squares function minimized:

$$\Sigma w(Fo^2\text{-}Fc^2)^2 \qquad \text{where w = Least Squares weights.}$$

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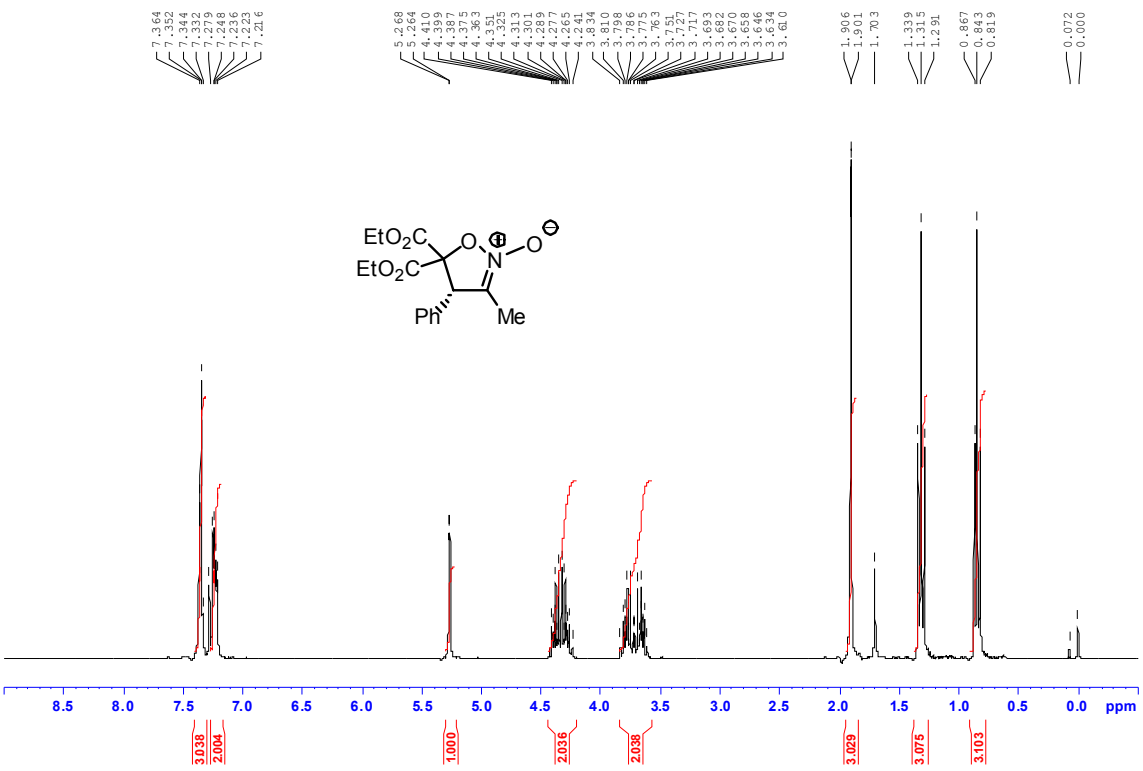
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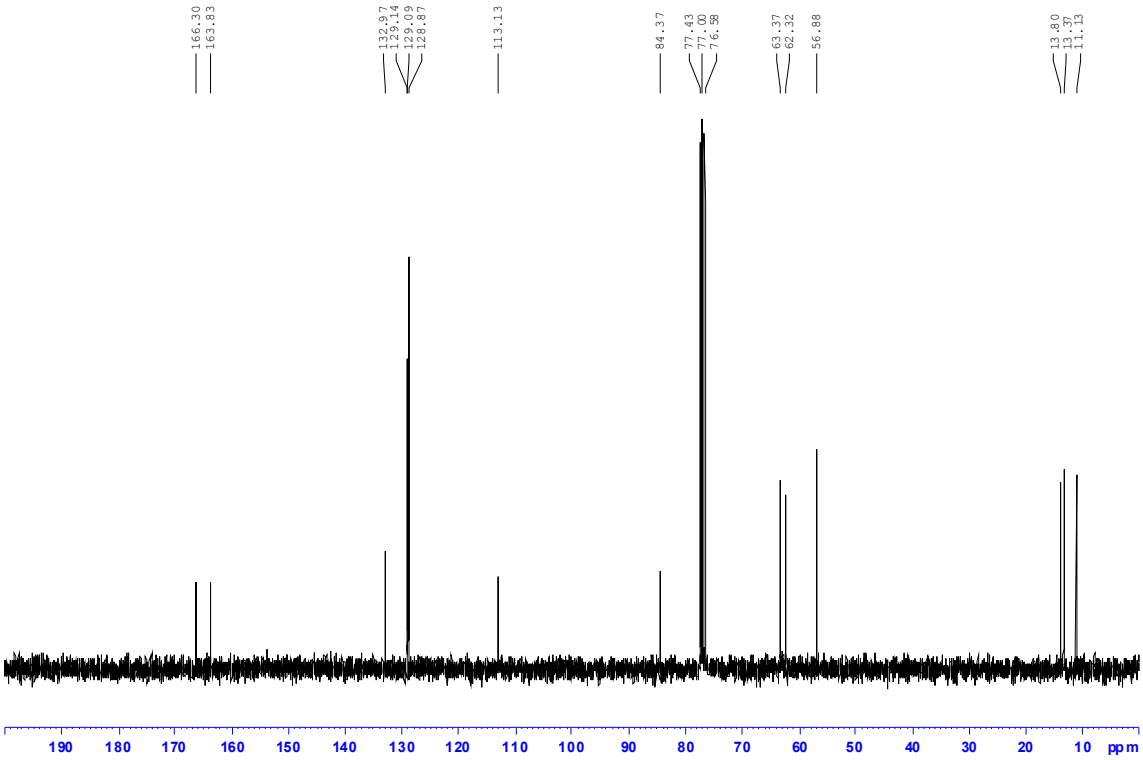
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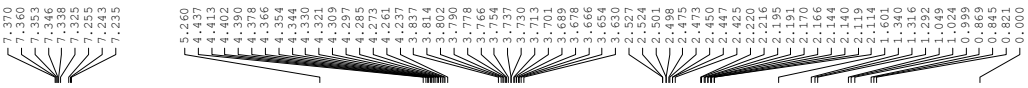
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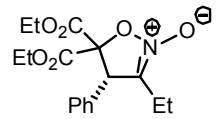
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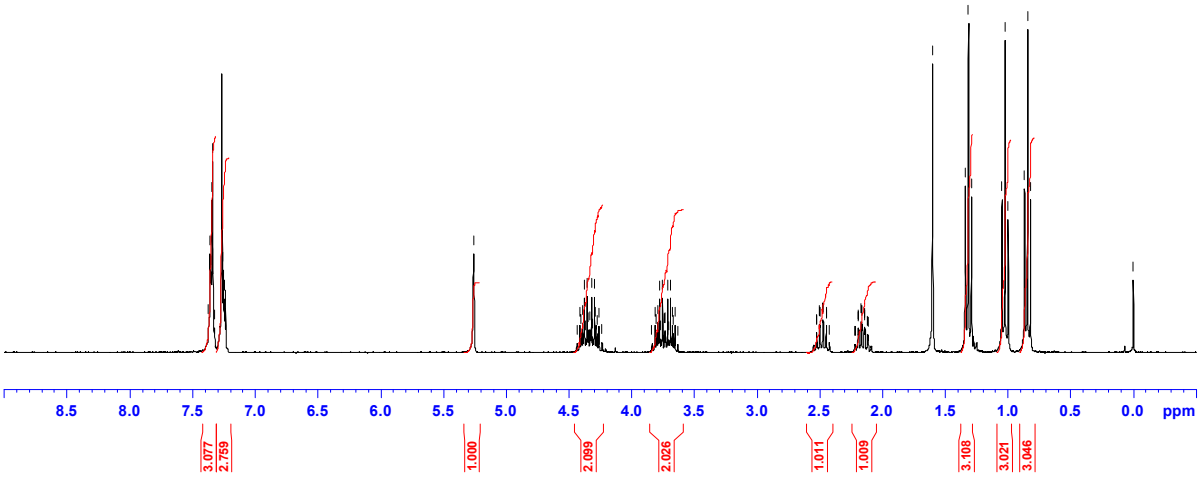
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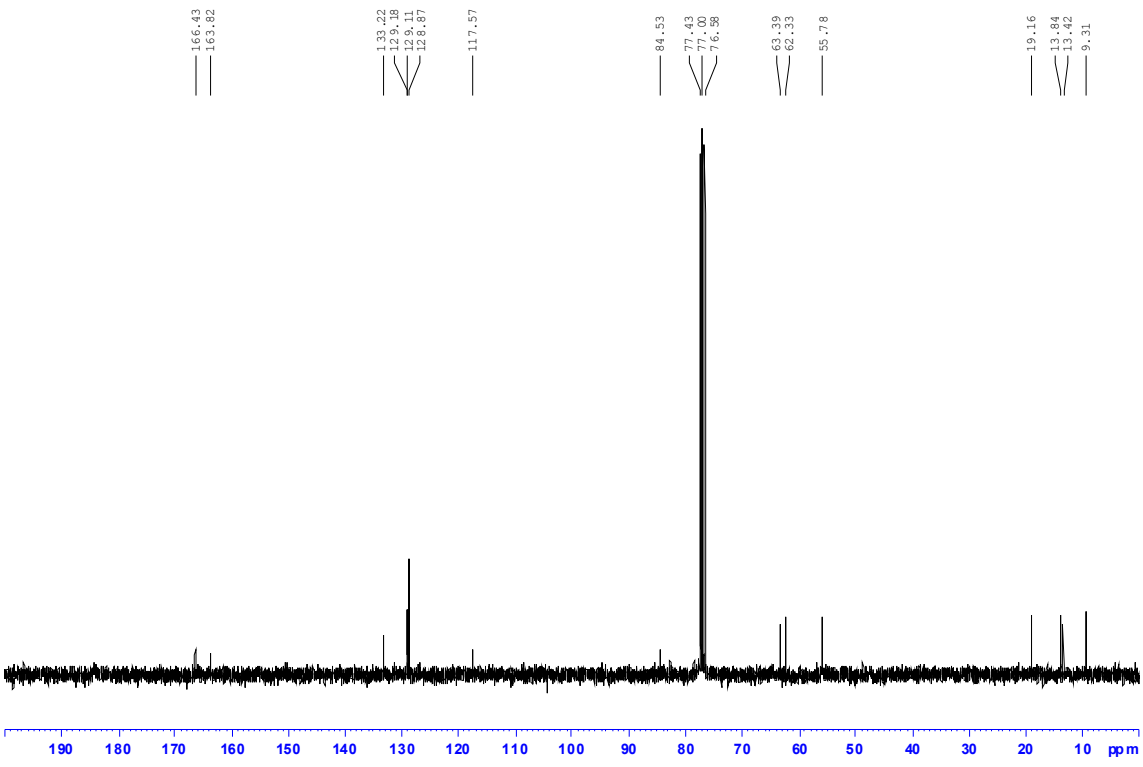
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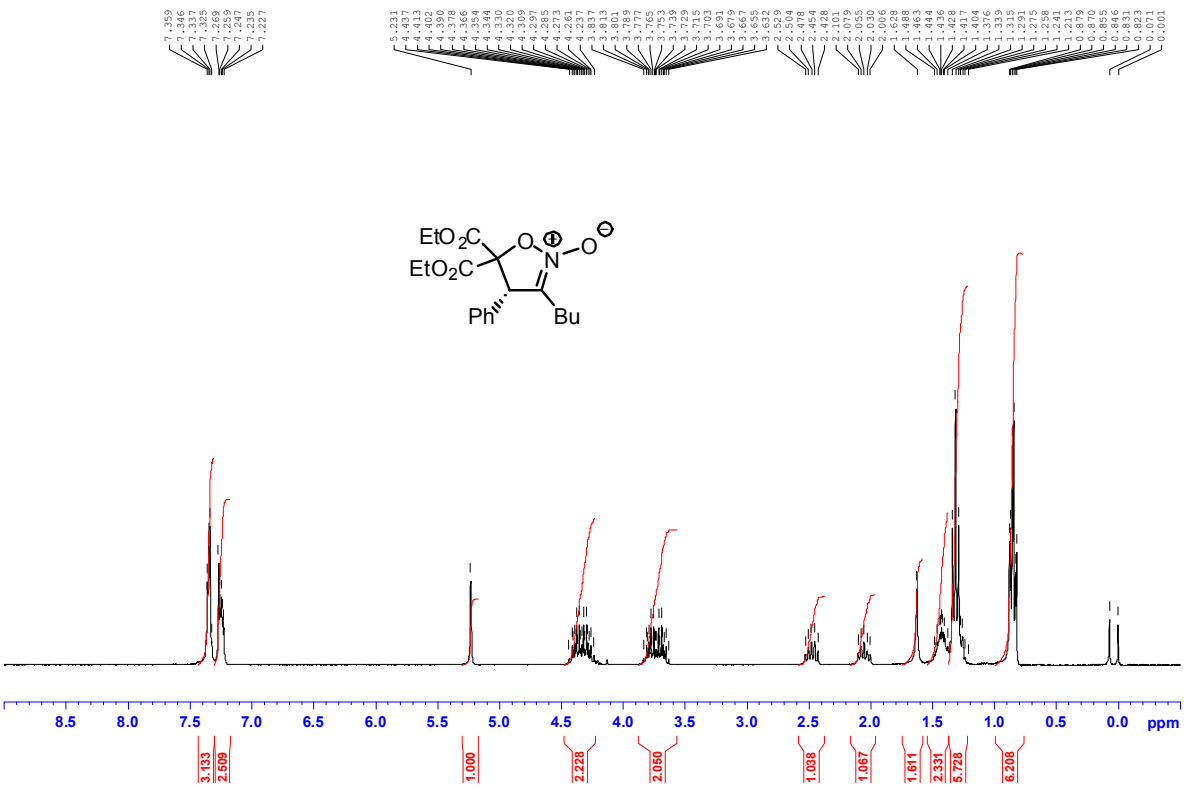
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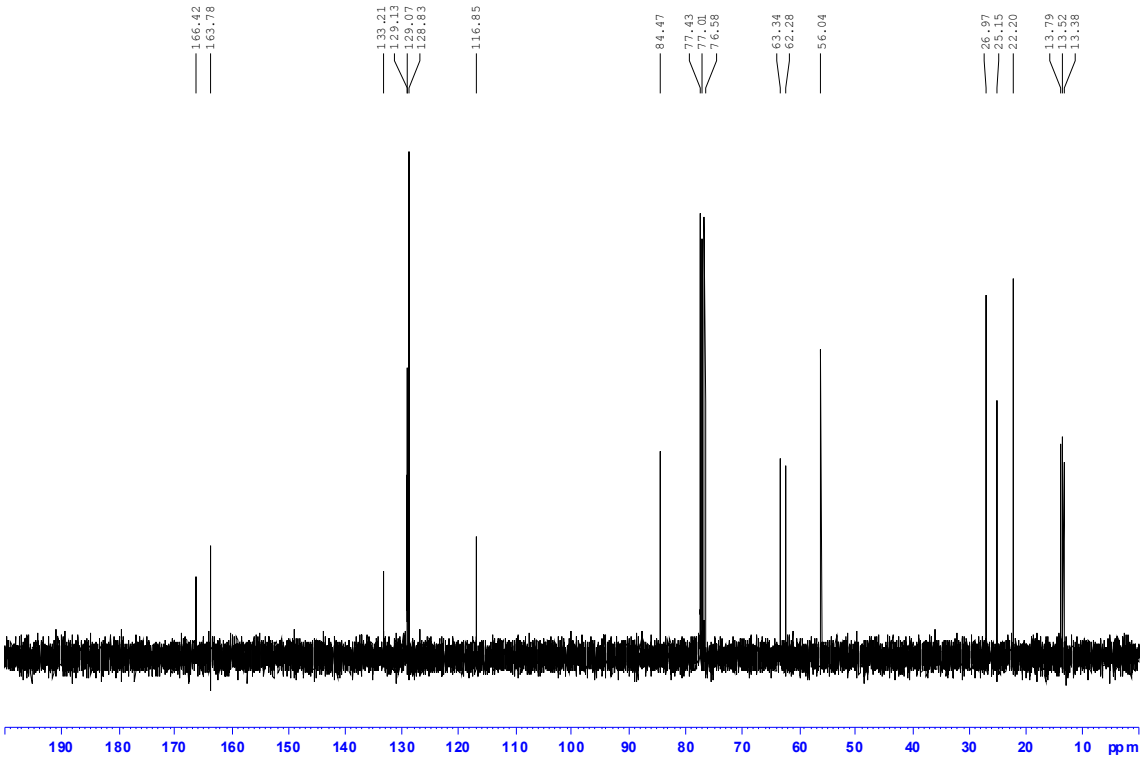
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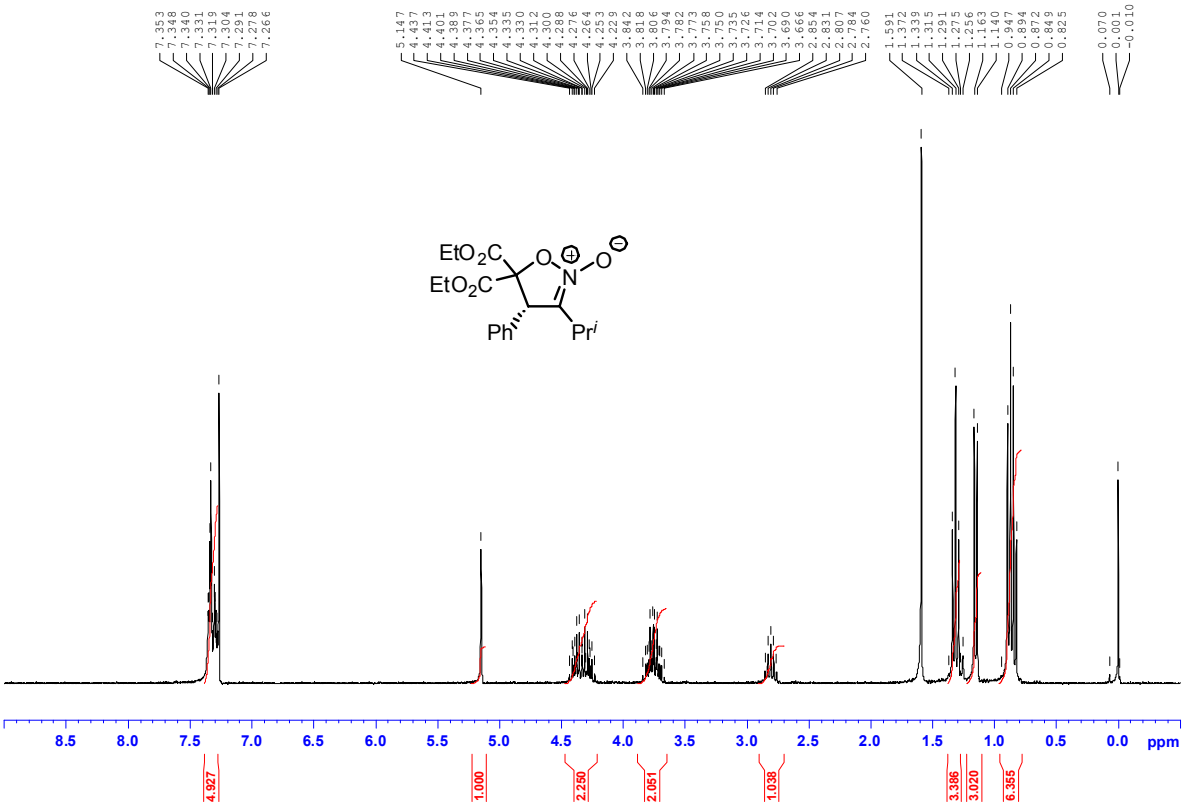
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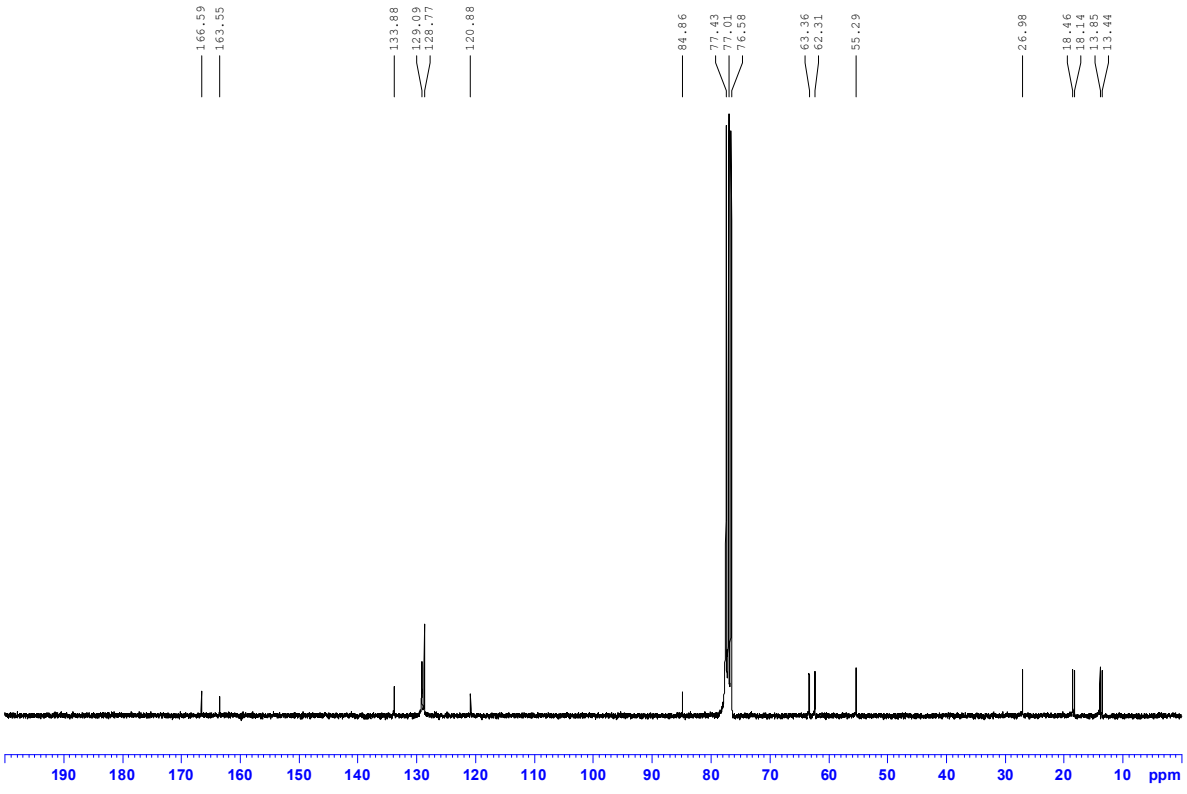
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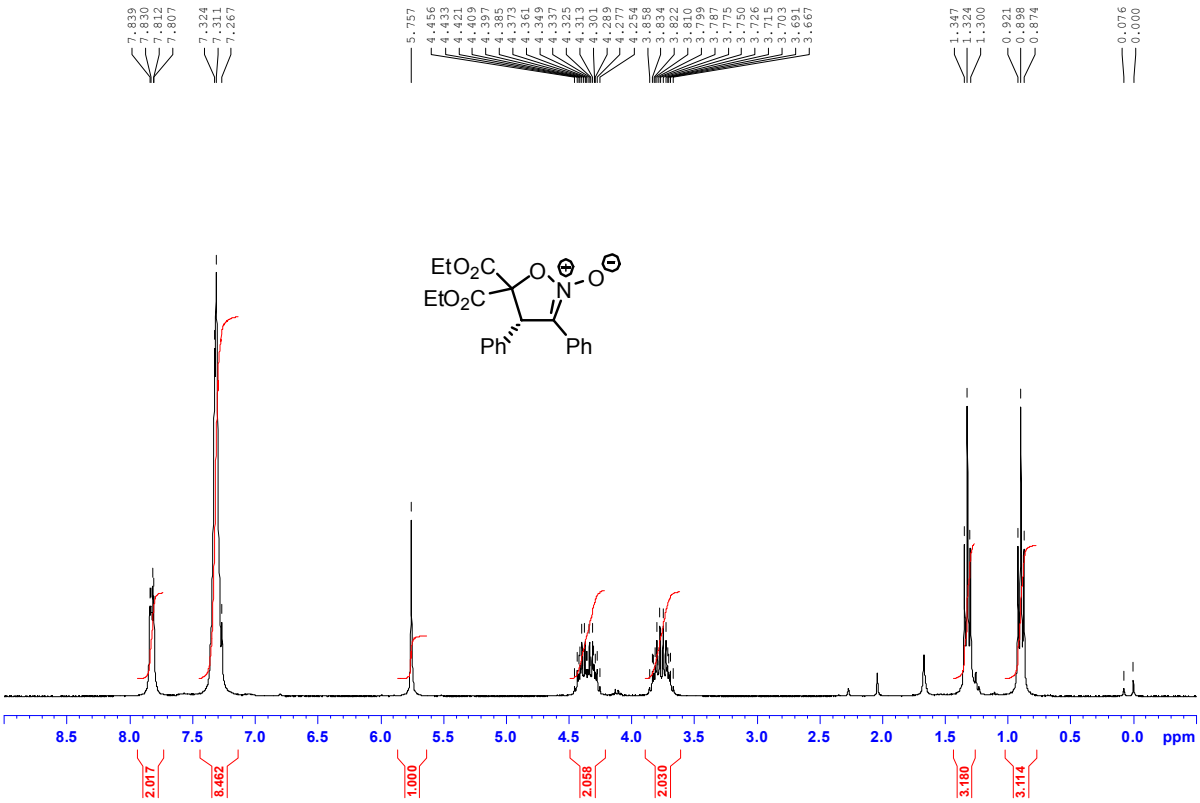
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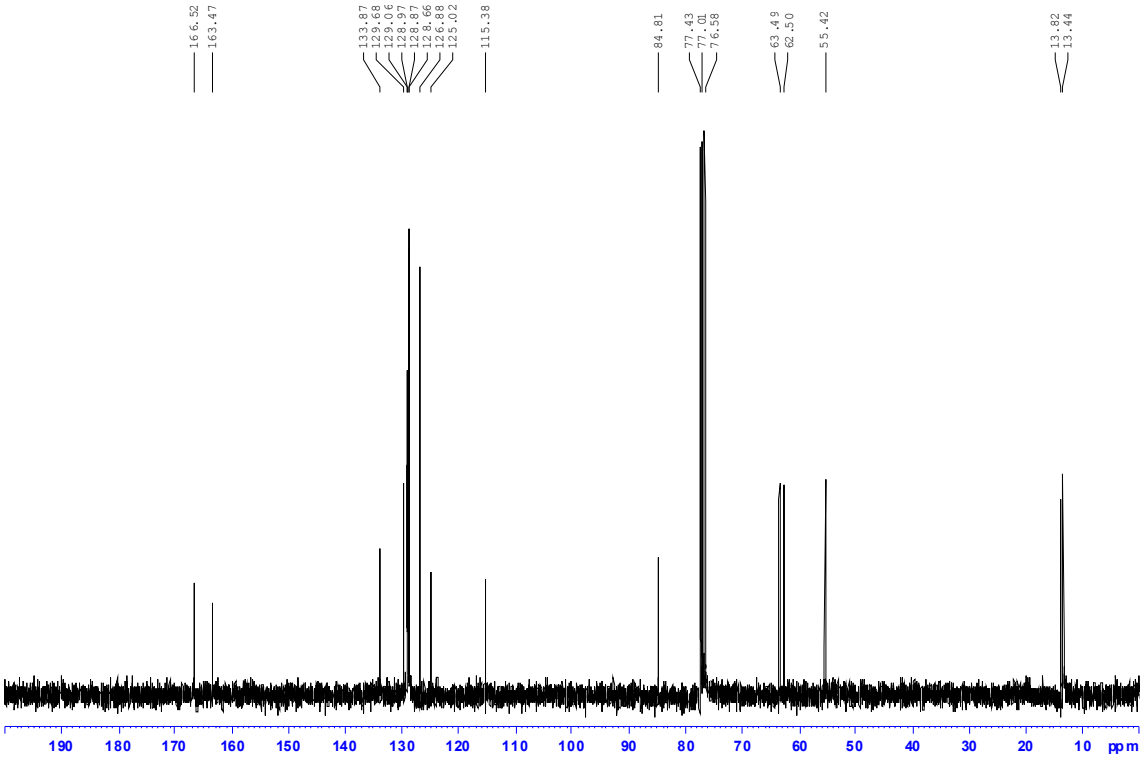
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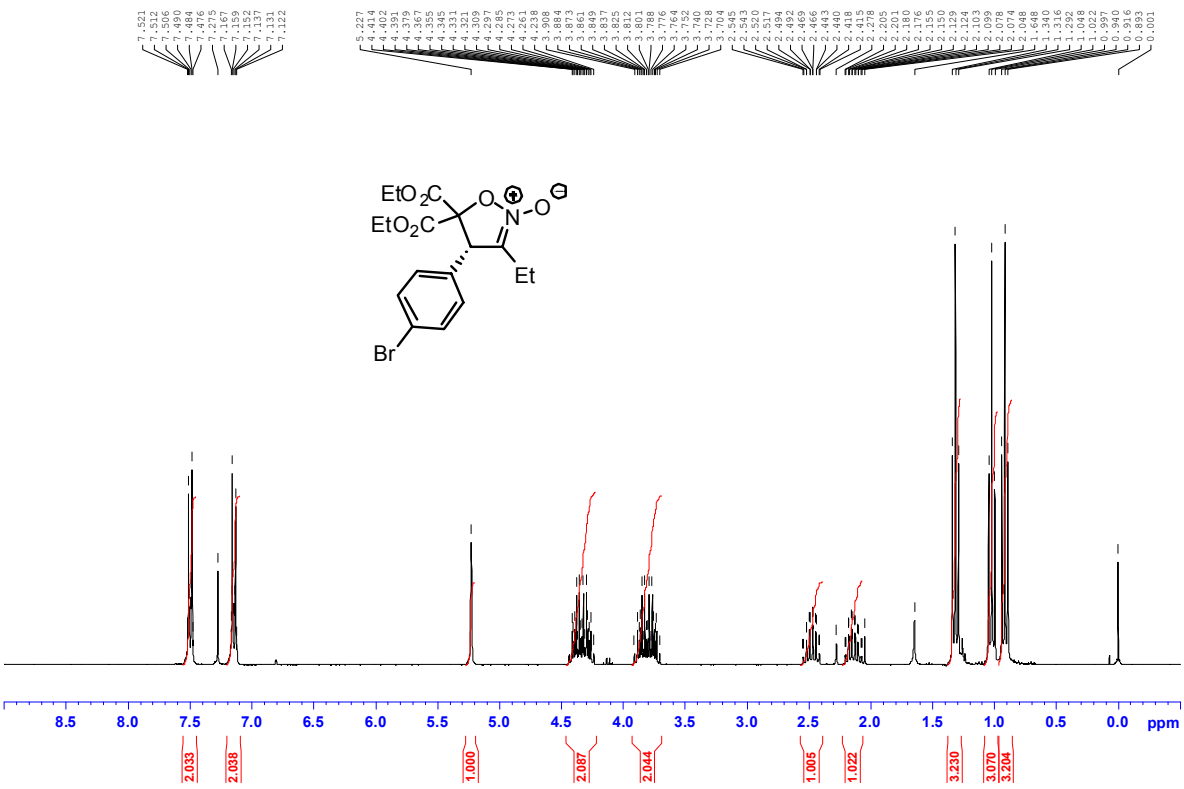
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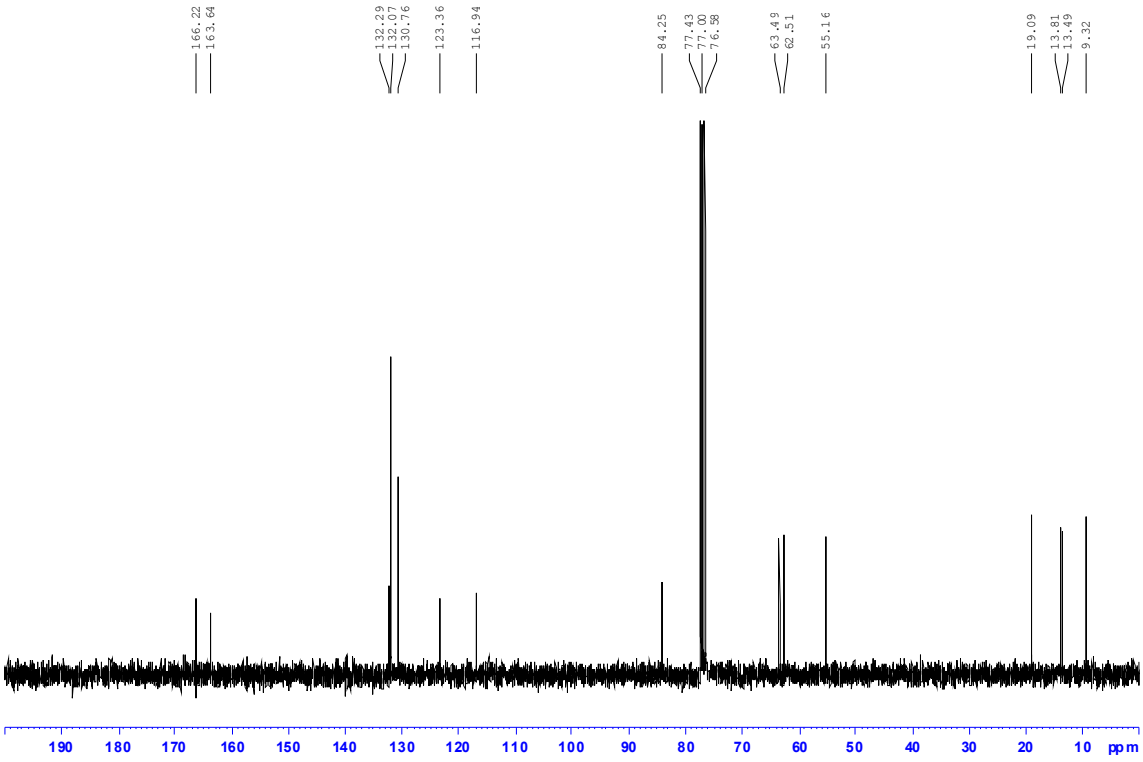
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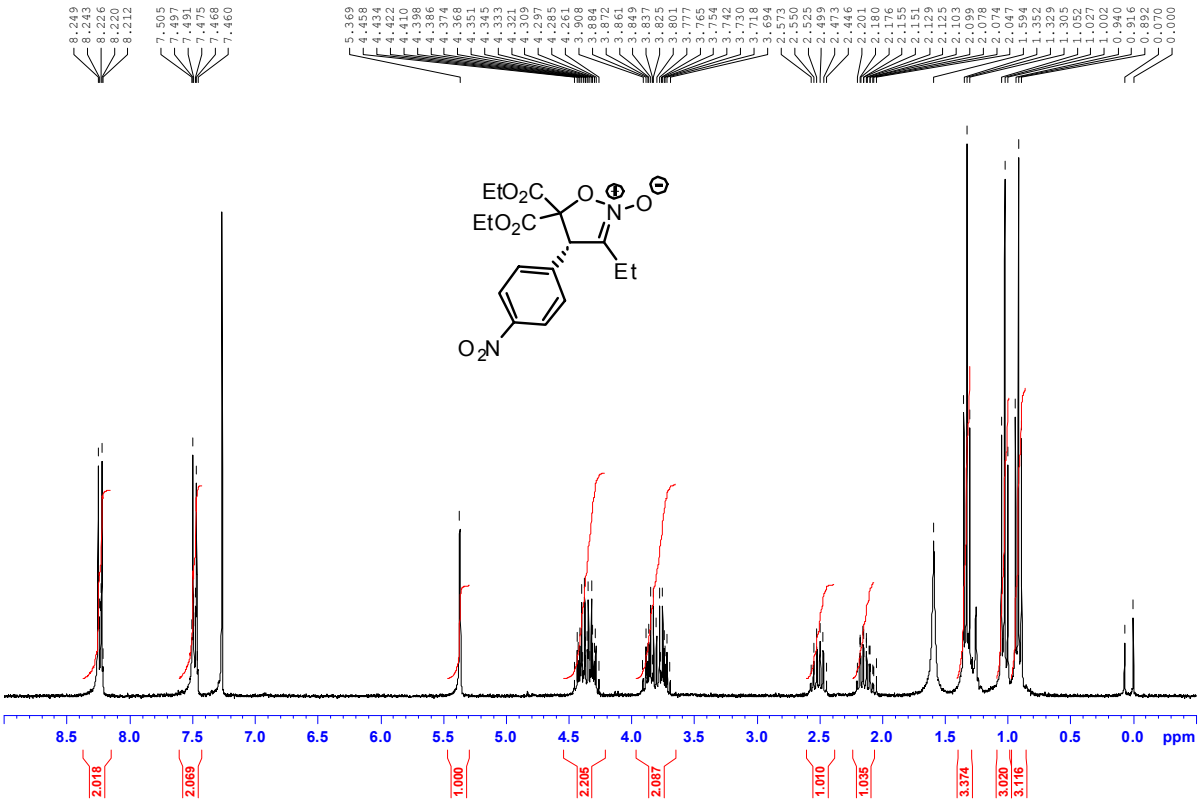
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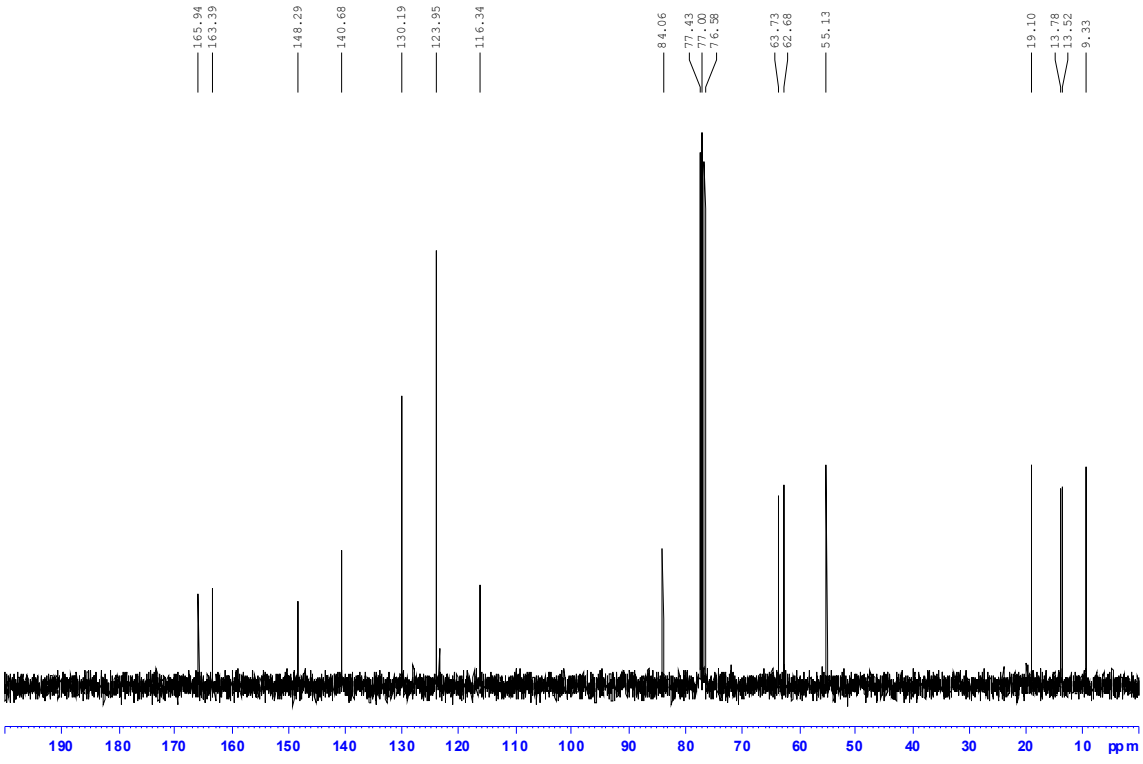
3.116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84.06
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76.58
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62.68
55.13
19.10
13.78
13.52
9.33
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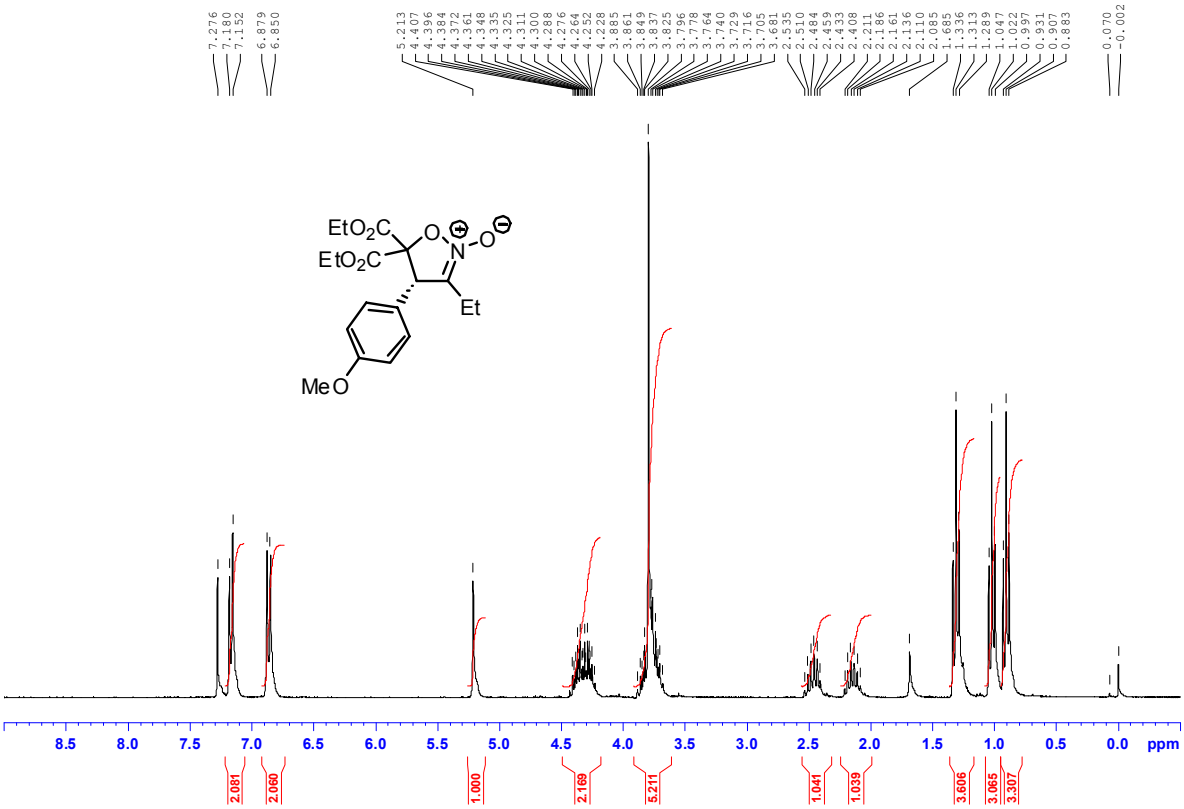
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4.335
4.325
4.311
4.300
4.288
4.276
4.264
4.252
4.228
3.885
3.861
3.849
3.837
3.825
3.796
3.778
3.764
3.740
3.729
3.716
3.705
3.681
2.535
2.510
2.484
2.459
2.433
2.408
2.211
2.186
2.161
2.136
2.110
2.085
1.685
1.336
1.313
1.289
1.047
1.022
0.997
0.931
0.907
0.883
0.070
-0.002
EtO2C
EtO2C
O
N
O
Et
MeO
8.5
8.0
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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2.0
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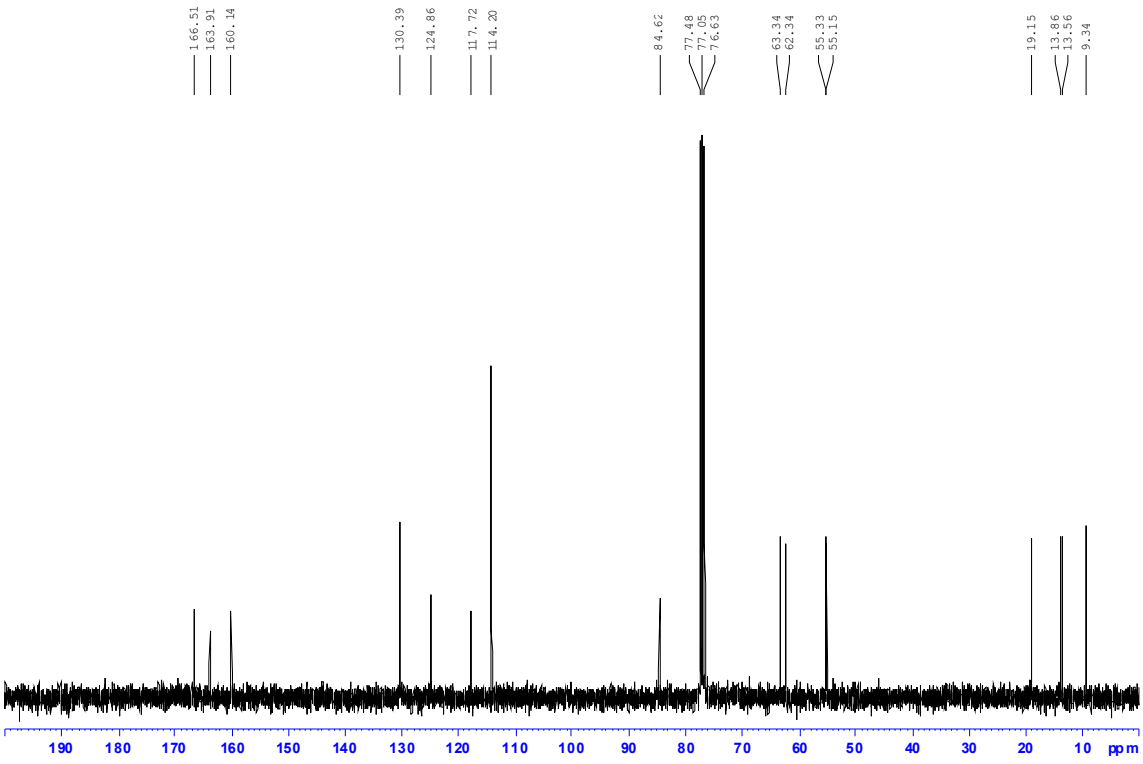
3.307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62.34
55.33
55.15
19.15
13.86
13.56
9.34
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150
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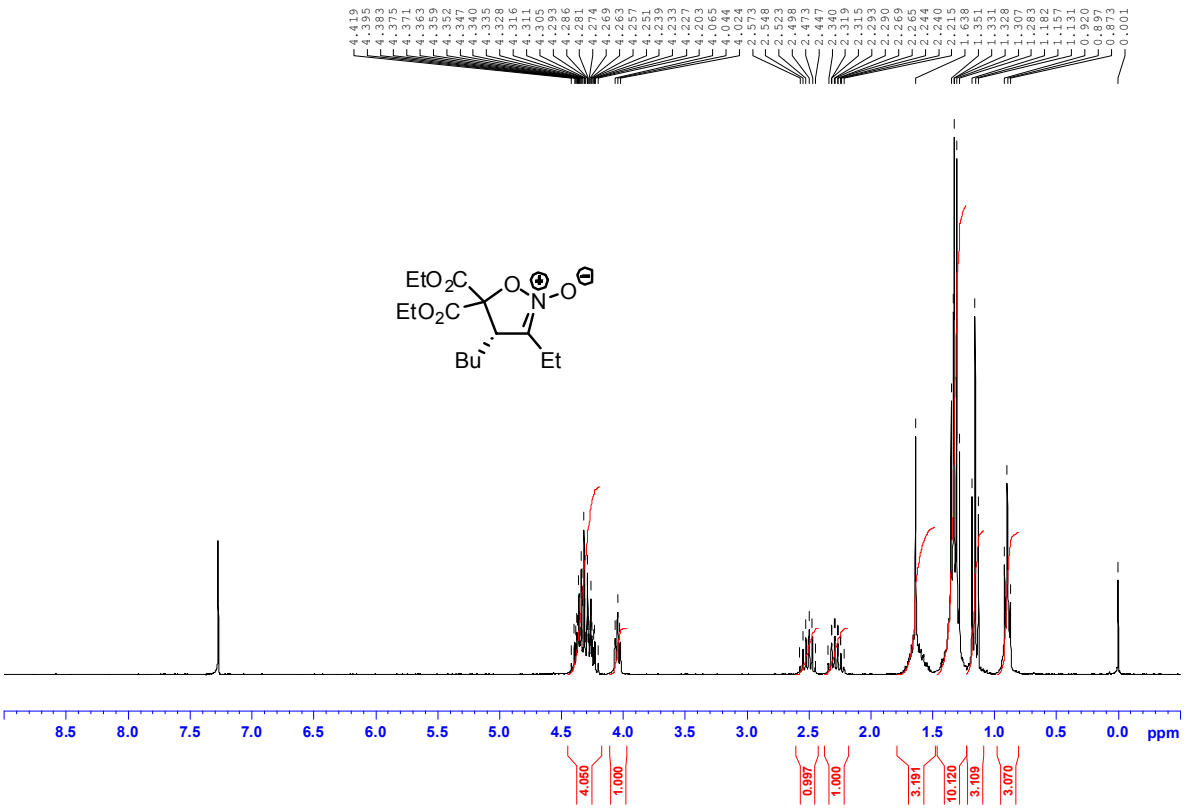
30
20
10
ppm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4.311
4.305
4.293
4.286
4.281
4.274
4.269
4.263
4.257
4.251
4.239
4.233
4.227
4.203
4.065
4.044
4.024
2.573
2.548
2.523
2.498
2.473
2.447
2.340
2.319
2.315
2.293
2.290
2.269
2.265
2.244
2.240
2.215
1.638
1.351
1.331
1.328
1.307
1.283
1.182
1.157
1.131
0.920
0.897
0.873
0.001
EtO2C
EtO2C
O
N
O
Bu
Et
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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0.0
ppm
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0.997
1.000
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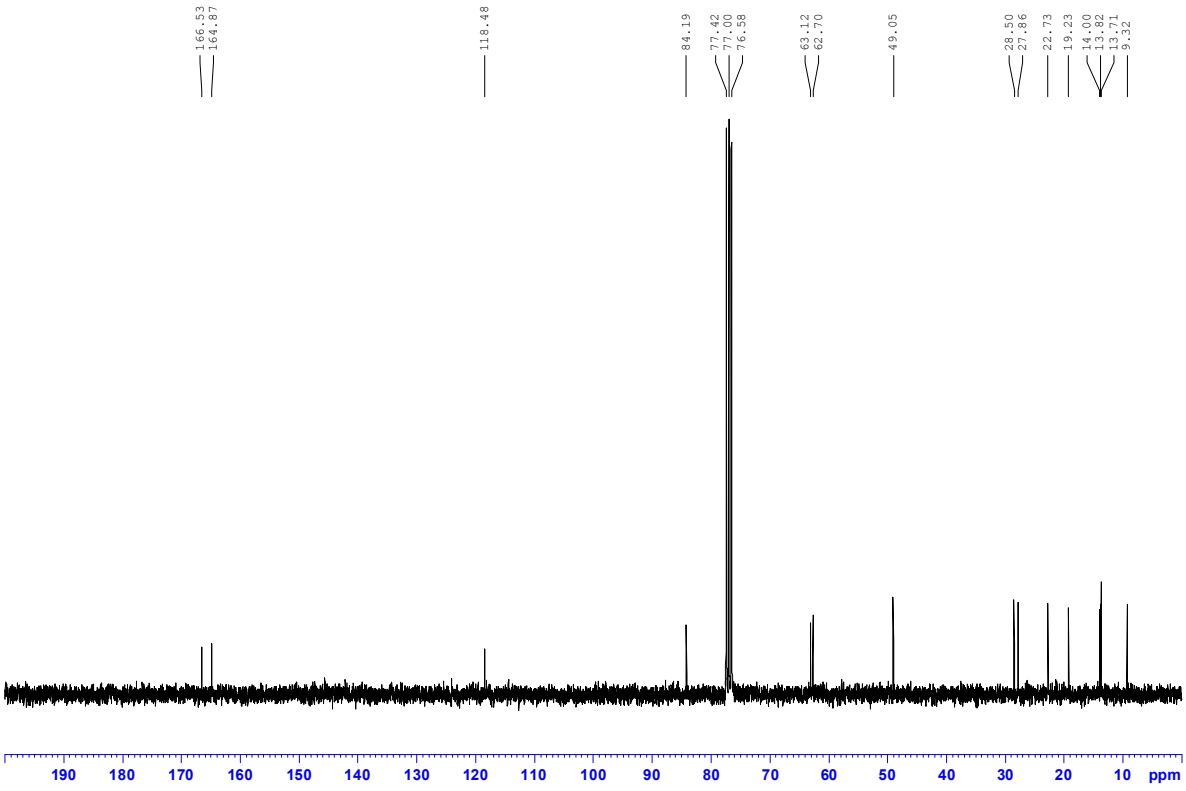
3.070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27.86
22.73
19.23
14.00
13.82
13.71
9.32
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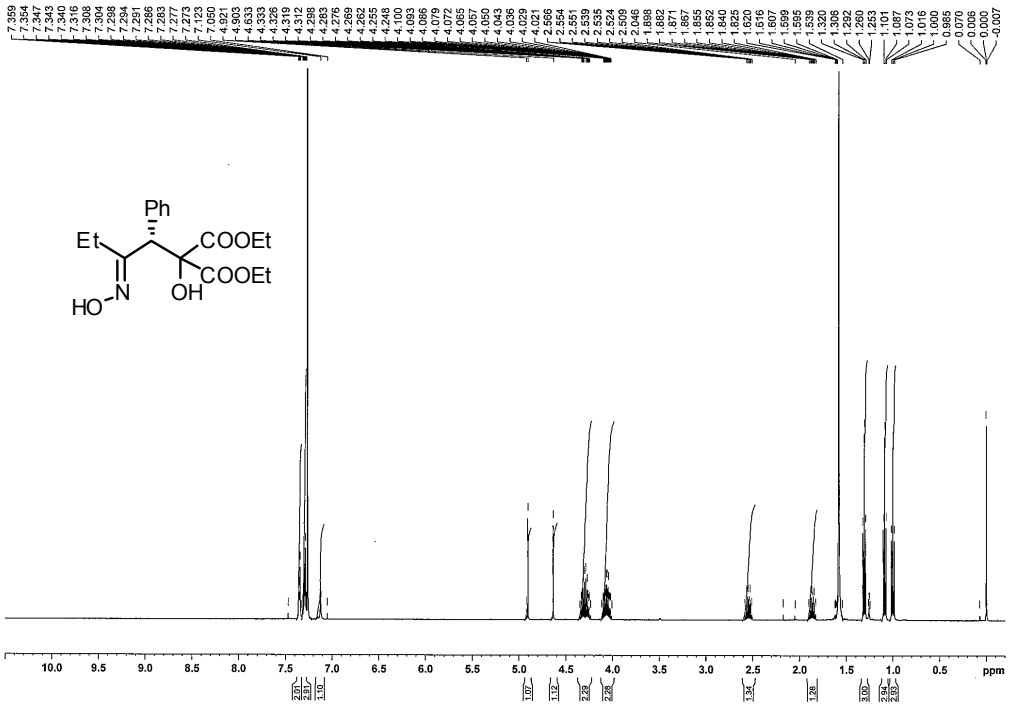
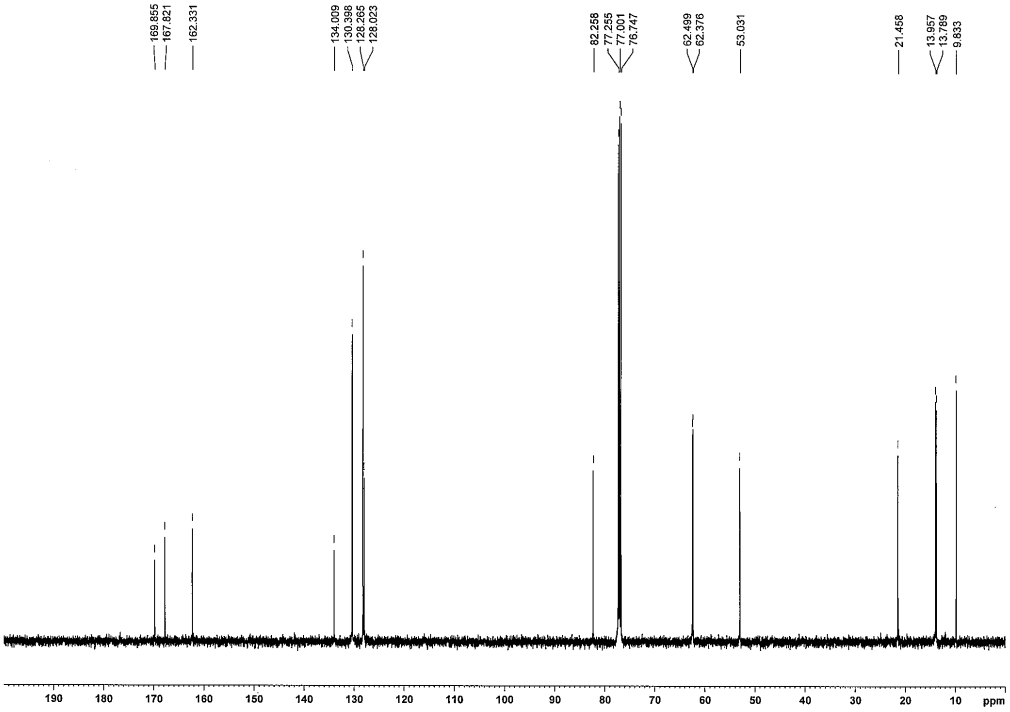
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Ph
Et
COOEt
COOEt
HO
N
OH
ppm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128.023
82.258
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62.376
53.031
21.458
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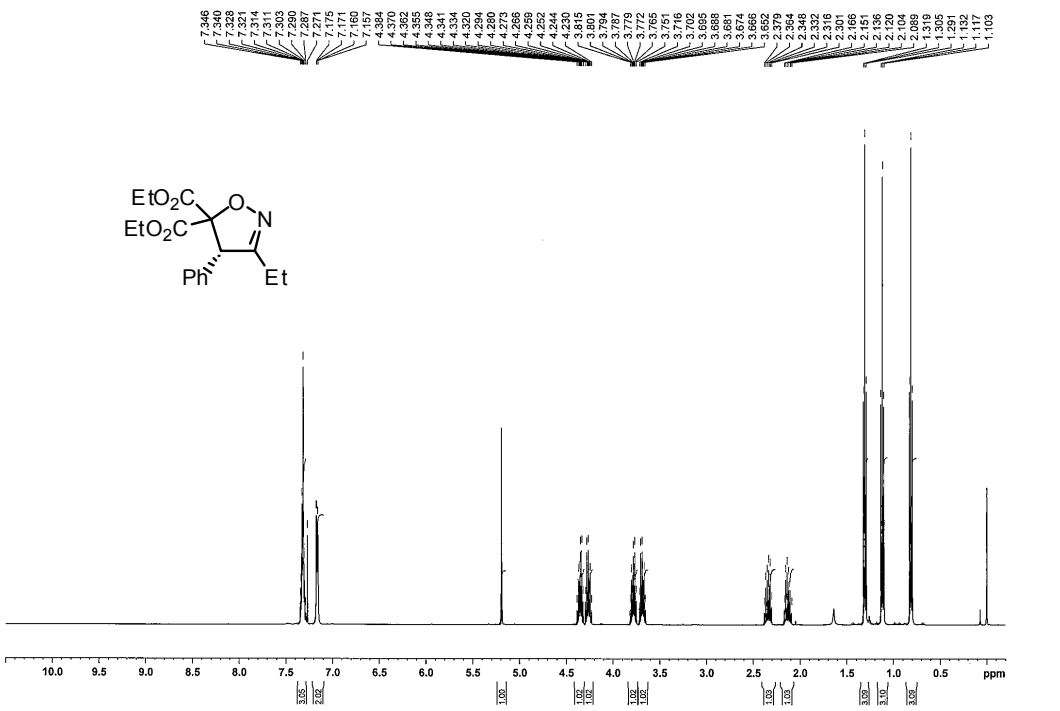
ppm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7.299
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7.171
7.160
7.157
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4.370
4.362
4.355
4.348
4.341
4.334
4.320
4.294
4.280
4.273
4.266
4.259
4.252
4.244
4.230
3.815
3.801
3.794
3.787
3.779
3.772
3.765
3.751
3.716
3.702
3.695
3.688
3.681
3.674
3.666
3.652
2.379
2.364
2.348
2.332
2.316
2.301
2.166
2.151
2.136
2.120
2.104
2.089
1.319
1.305
1.291
1.132
1.117
1.103
EtO2C
EtO2C
O
N
Ph
Et
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
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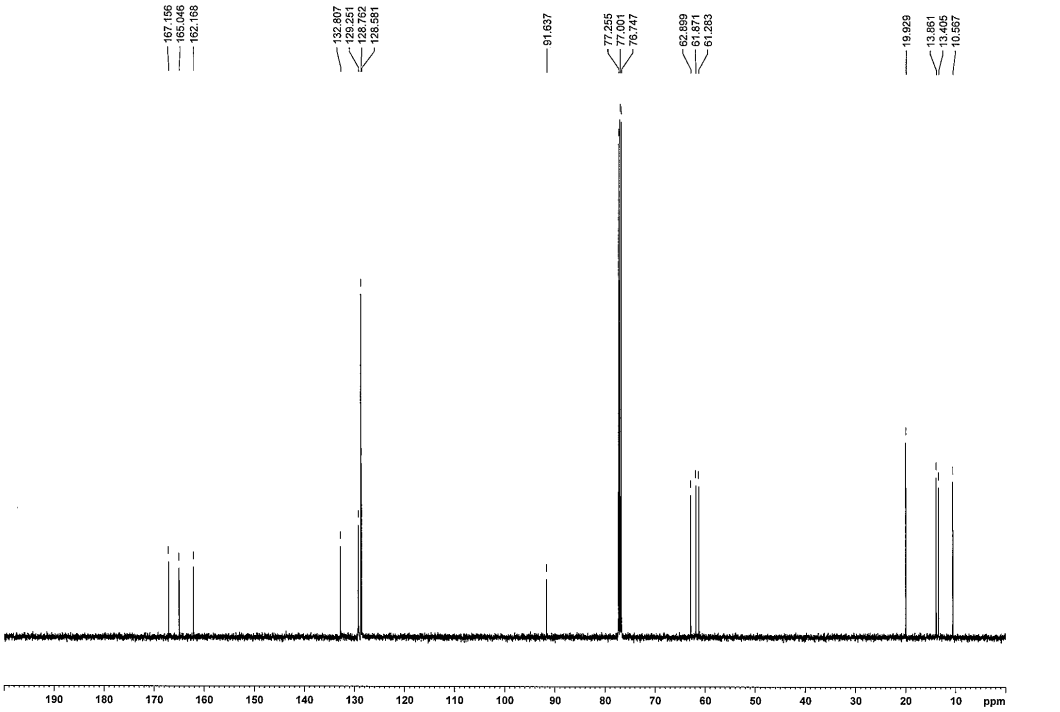
1.02
1.00
1.06
1.06
1.08
1.03
3.08
3.10
3.02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77.001
76.747
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61.283
19.929
13.861
13.405
10.567
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180
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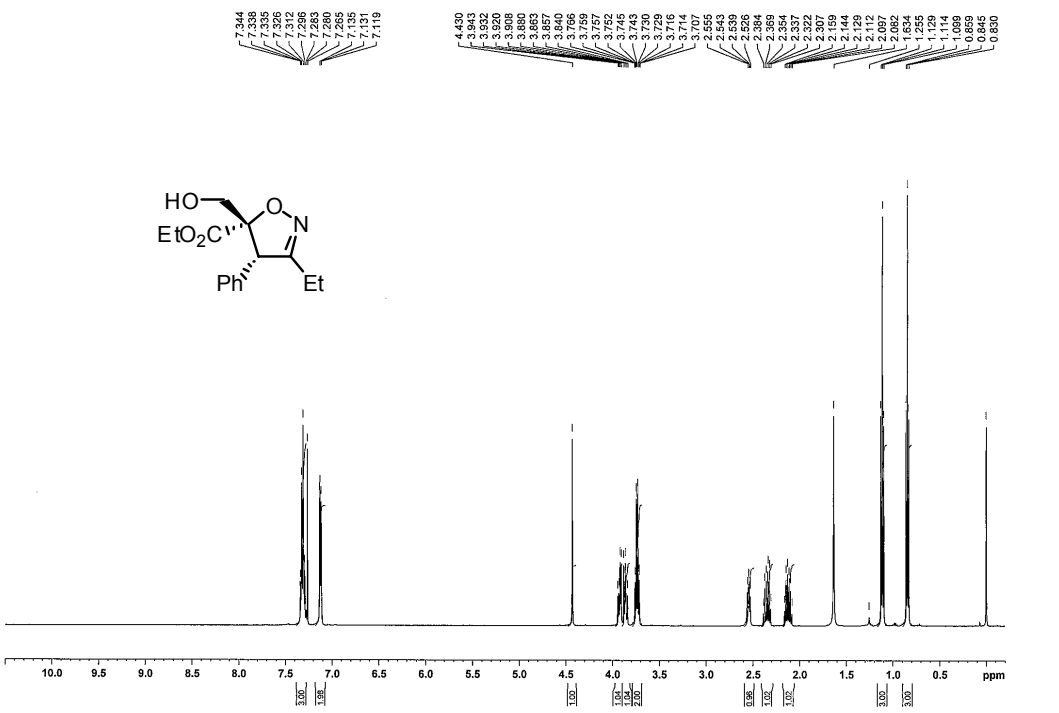
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.280
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7.135
7.131
7.119
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3.943
3.932
3.920
3.908
3.880
3.863
3.857
3.840
3.795
3.759
3.757
3.752
3.745
3.743
3.730
3.729
3.716
3.714
3.707
2.555
2.543
2.539
2.526
2.384
2.369
2.354
2.337
2.322
2.307
2.159
2.144
2.129
2.112
2.097
2.082
1.654
1.255
1.129
1.114
1.099
0.859
0.845
0.830
HO
EtO2C
O
N
Ph
Et
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
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1.00
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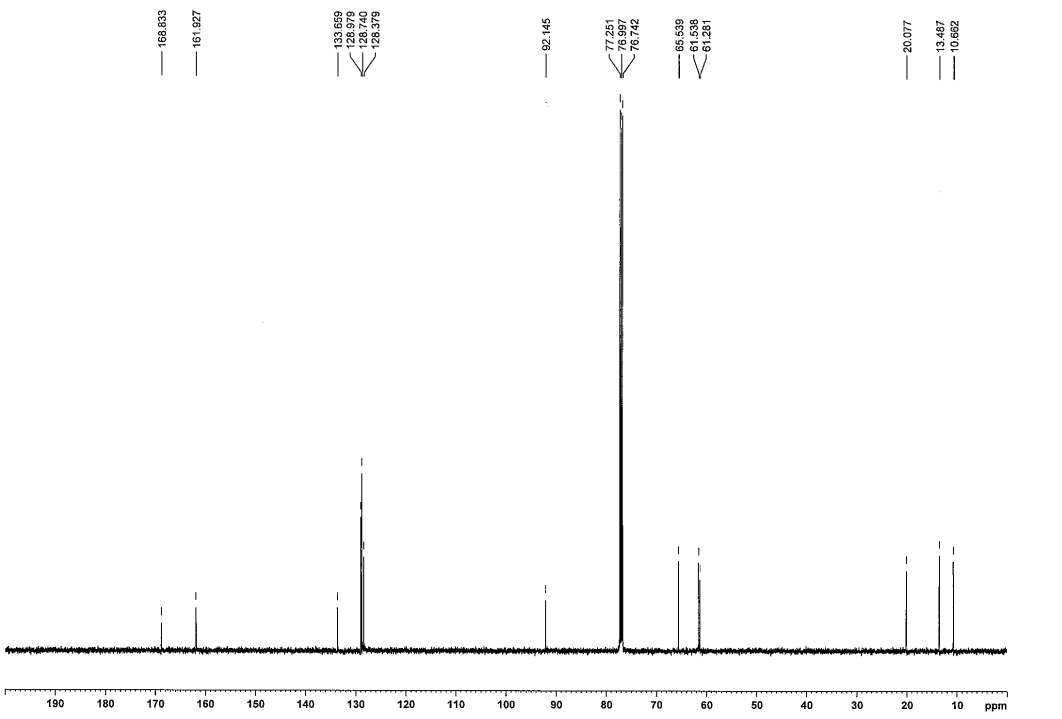
1.94
2.00
0.98
1.02
1.02
3.05
3.09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61.281
20.077
13.467
10.662
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm