Asymmetric Michael Addition Reactions of Nitroalkanes to 2-Furanones Catalyzed by Bifunctional Thiourea catalysts†

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Content

1. General methods

^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 400 (400MHz) spectrometer in needful D-reagents with tetramethylsilane (TMS) as an internal reference. Data for ^{1}H NMR were reported as follows:

chemical shift (ppm), and multiplicity (s= singlet, d= doublet, t= triplet, dd= double of doublet, br= broad, m= multiplet), coupling constants (Hz) and integration; Data for ^{13}C NMR were reported as ppm. Melting points were measured on an X4-type micro-melting point apparatus and were uncorrected. HPLC analyses were performed using a Daicel ChiralPak AS or AD column purchased. Crystal structure determination of Michael product 3**a** was carried out on a RigakuMicroMax 002+ diffractometer. HRMS of Michael products were carried out on Brucker Apex IV FTMS.

1.1 Materials

Unless otherwise stated, all reagents were purchased from commercial suppliers, including nitroalkanes, **2a, 2b, 2c**, **2d** and catalysts **I**, **IV**, **V**, **VII**. Ethyl 5,5-disubstituted-2-oxo- 2,5-dihydrofuran-3-carboxylates **1a-c** were prepared according to literature procedures and all the spectral data matches with the desired compounds.[1] Catalysts **II**,[2] **III**,[2] **VI**[3] were prepared according to the literature procedures and all the spectral data matches with the desired compounds. Nitroalkanes **2e**, **2f** and **2g** were prepared according to the literature procedures [4]. All the reactions were monitored by thin layer chromatography (TLC) on GF254 silica gel plates.

Reference

1 W. Wang, J. Wang, S. Zhou, Q. Sun, Z. Ge, X. Wang and R. Li. Chem. Commun.,2013,**49**, 1333.

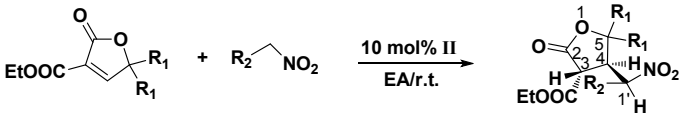
2 C. B. Tripathi, S. Kayal and S. Mukherjee, Org. Lett., 2012, **14**, 3296.

3 F. Yu, Z. Jin, H. Huang, T. Ye, X. Liang and J. Ye, Org. Biomol. Chem., 2010, **8**, 4767.

4 P. Astolfi, L. Charles, D. Gigmes, L. Greci, C. Rizzoli, F. Soranae and P. Stipa, Org. Biomol. Chem., 2013, **11**, 1399.

2. Synthesis and characterization of compounds 3a-k

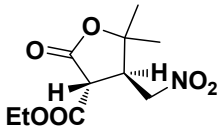
2.1 General procedure for the organocatalytic Michael addition reactions



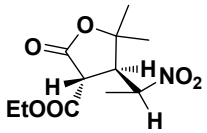
1 2 (3R,4R,1'S)-**3a-k**

To a solution of 10 mol% catalyst **II** (10 or 20 mol% DBU was used for the preparation of racemic samples) in EA (2.0 mL), furanone (0.1 mmol) and nitroalkane (0.5 mmol) was added sequentially at room temperature. The mixture was stirred at room temperature, and the conversion was monitored by TLC. After completion, direct chromatography on silica gel (ethyl acetate/petroleum ether = 2/1) gave corresponding product 3a-m as white solid or oil.

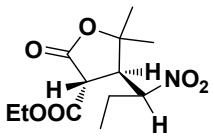
2.2 Scope of the Michael addition reaction



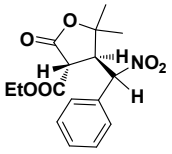
(3R,4R)-ethyl 5,5-dimethyl-4-(nitromethyl)-2-oxotetrahydrofuran-3-carboxylate 3a: Obtained in 98% yield; white solid, m.p. 96.7-99°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.49 (dd, J =12.8 Hz, 6.3Hz, 1H, C*H*HNO_2), δ 4.41 (dd, J = 12.8 Hz, 8.0 Hz, 1H, CH*H*NO_2), $\delta\delta$ 4.23 (q, J = 7.1Hz, 2H, COOC*HH*CH_3), δ 3.55 (d, J = 11.6 Hz, 1H, C*H*$CHCH_2NO_2$), δ 3.46 (ddd, J = 11.6 Hz, 7.9Hz, 6.4 Hz, 1H, CHC*H*CH_2NO_2), δ 1.51 (s, 3H, (CH_3)C(CH_3)), δ 1.28 (s, 3H, (CH_3)C(CH_3)), δ 1.26 (t, J = 7.1 Hz, 3H, $COOCH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.2, 165.2, 82.6, 73.2, 61.8, 50.0, 45.7, 26.4, 21.7, 13.0. HPLC (AD, hexane: *i*-PrOH 80:20, 1.0 mL/min): t_R (major) = 9.71 min, t_R (minor) = 11.08 min; ee 97%; ES-HRMS: Calcd for $C_{10}H_{15}NNaO_6$ $[M+Na]^+$, 268.07916, Found 268.07866.



(3R,4R)-ethyl 5,5-dimethyl-4-((S)-1-nitroethyl)-2-oxotetrahydrofuran-3-carboxylate 3b: Obtained in 97% yield; oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.68 (dq, J = 8.9 Hz, 6.7 Hz, 1H, C*H*(CH_3)NO_2), δ 4.35-4.21 (m, 2H, COOC*HH*CH_3), δ 3.87 (d, J = 11.4 Hz, 1H, C*H*$CHCH_2NO_2$), δ 3.22 (dd, J = 11.2Hz, 9.3 Hz, 1H, CHC*H*CH(CH_3)NO_2), δ 1.67 (d, J = 6.7 Hz, 3H, CHCHCH(CH_3)NO_2), δ 1.65 (s, 3H, (CH_3)C(CH_3)), δ 1.38 (s, 3H, (CH_3)C(CH_3)), δ 1.33 (t, J = 7.1 Hz, 3H, $COOCH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.6, 166.6, 83.8, 82.6, 62.7, 52.1, 51.2, 28.6, 22.7, 19.0, 13.9; HPLC (AS, hexane: *i*-PrOH 80:20, 1.0 mL/min): t_R (major) = 9.30 min, t_R (minor) = 30.71min; dr > 20:1; ee = 96%; ES-HRMS: Calcd for $C_{11}H_{17}NNaO_6$ $[M+Na]^+$, 282.09481, Found 282.09453.

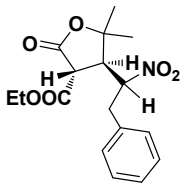


(3R,4R)-ethyl 5,5-dimethyl-4-((S)-1-nitropropyl)-2-oxotetrahydrofuran-3-carboxylate 3c: Obtained in 89% yield; oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.50 (ddd, J = 11.1 Hz, 7.8 Hz, 3.6 Hz, 1H, C*H*(CH_2CH_3)NO_2), δ 4.27 (qd, J = 7.1 Hz, 1.9 Hz, 2H, COOC*HH*CH_3), δ 3.85 (d, J = 11.6 Hz, 1H, C*H*$CHCH_2NO_2$), δ 3.21 (dd, J = 11.5 Hz, 7.8 Hz, 1H, CHC*H*CH(CH_2CH_3)NO_2), δ 2.05 (m, 1H, CHCHCH(C*H*HCH_3)NO_2), δ 1.84 (m, 1H, CHCHCH(CH*H*CH_3)NO_2), δ 1.62 (s, 3H, (CH_3)C(CH_3)), δ 1.35 (s, 3H, (CH_3)C(CH_3)), δ 1.33 (t, J = 7.1 Hz, 3H, $COOCH_2CH_3$) δ 1.00 (t, J = 7.3 Hz, 3H, CHCHCH(CH_2CH_3)NO_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.7, 166.9, 89.1, 84.0, 62.7, 51.2, 50.7, 28.5, 26.7, 22.7, 13.9, 10.4; HPLC (AS, hexane: *i*-PrOH 80:20, 1.0 mL/min): t_R(major) = 9.47 min, t_R(minor) = 35.76min; dr > 20:1; ee>99%, ES-HRMS: Calcd for $C_{12}H_{19}NNaO_6$ $[M+Na]^+$, 296.11046, Found 296.11005.

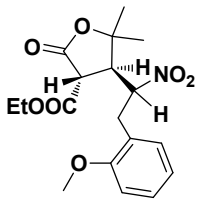


(3R,4R)-ethyl 5,5-dimethyl-4-(nitro(phenyl)methyl)-2-oxotetrahydrofuran-3-carboxylate 3d: mixture of two diastereoisomers, Obtained in 42% yield, white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63–7.36 (m, 5H), δ 5.54 (t, J = 10.6 Hz, 1H), δ 4.37–3.25 (m, 5H), δ 1.62–0.93 (m, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.9, 167.4, 166.0, 165.5, 130.5, 130.3, 130.2, 129.9, 128.4, 128.2, 128.0, 127.5, 90.5, 89.5, 84.1, 83.3, 51.1, 51.0, 50.5, 49.9, 27.2, 27.1, 22.2, 21.9, 12.9, 12.6; HPLC (AD, hexane: *i*-PrOH 90:10, 1.0 mL/min,): t_{R1} (minor) = 10.18 min, t_{R1} (major) = 10.19 min, t_{R2} (major) = 12.30 min,

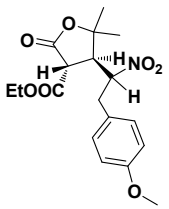
t_{R2} (minor) = 15.77 min; dr=3:2; ee = 72%/41%; ES-HRMS: Calcd for $C_{16}H_{19}NNaO_6$ $[M+Na]^+$, 344.11046, Found 344.11020.



(3R,4R)-ethyl 5,5-dimethyl-4-(1-nitro-2-phenylethyl)-2-oxotetrahydrofuran-3-carboxylate 3e: Obtained in 78% yield, white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19–7.19 (m, 3H, $CH(CH_2C_6H_5)NO_2$), δ 7.11–7.09 (m, 2H, $CH(CH_2C_6H_5)NO_2$), δ 4.72 (ddd, J = 10.0Hz, 6.6 Hz, 5.0 Hz, 1H, $CH(CH_2C_6H_5)NO_2$), δ 4.34–4.11 (m, 2H, $COOCHHCH_3$), δ 3.77 (d, J = 11.8 Hz, 1H, $CHCHCH(CH_2C_6H_5)NO_2$), δ 3.24 (dd, J = 11.8 Hz, 6.6 Hz, 1H, $CHCHCH(CHHC_6H_5)NO_2$), δ 3.20 (dd, J = 14.2 Hz, 10.0 Hz, 1H, $CHCHCH(CHHC_6H_5)NO_2$), δ 3.07 (dd, J = 14.2 Hz, 5.0 Hz, 1H, $CHCHCH(CHHC_6H_5)NO_2$), δ 1.46 (s, 1H, $(CH_3)C(CH_3)$), δ 1.36 (s, 1H, $(CH_3)C(CH_3)$), δ 1.27 (t, J = 7.1 Hz, 3H, $COOCH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.5, 165.8, 133.0, 128.1, 127.7, 127.1, 87.6, 83.0, 61.8, 49.6, 49.5, 38.3, 27.2, 21.7, 13.0; HPLC (AD, hexane:*i*-PrOH 90:10, 1.0 mL/min): t_{R1} (minor) = 15.51 min, t_{R1} (major) = 16.30 min; t_{R2} (major) = 18.97 min, t_{R2} (minor) = 27.78 min. dr = 1:1; ee = 89%/53%; ES-HRMS: Calcd for $C_{17}H_{21}NNaO_6$ $[M+Na]^+$, 358.12611, Found 358.12588.

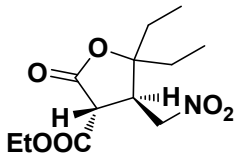


(3R,4R)-ethyl 4-(2-(2-methoxyphenyl)-1-nitroethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate 3f: mixture of two diastereoisomers: Obtained in 89% yield, white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16–7.21 (m, 1H, $CH(CH_2C_6H_4(o\text{-}OCH_3))NO_2$), δ 6.83–6.63 (m, 3H, $CH(CH_2C_6H_4(o\text{-}OCH_3))NO_2$), δ 4.85–4.76 (m, 1H, $CH(CH_2C_6H_4(o\text{-}OCH_3))NO_2$), δ 4.41–4.26 (m, 2H, $COOCHHCH_3$), δ 3.79 (s, 3H, $CH(CH_2C_6H_4(o\text{-}OCH_3))NO_2$), δ 3.82–2.86 (m, 4H, $CHCHCH(CH_2C_6H_4(o\text{-}OCH_3))NO_2$), δ 1.54-1.30 (m, 9H, $(CH_3)C(CH_3)$+$COOCH_2CH_3$); **^{13}C NMR**(100 MHz, $CDCl_3$) δ 168.5, 167.9, 167.7, 166.8, 160.1, 160.0, 135.5, 135.0, 130.2, 130.1, 120.9, 120.8, 114.9, 114.7, 113.2, 113.1, 88.9, 88.5, 84.9, 84.1, 63.1, 62.8, 55.2, 51.8, 50.6, 50.5, 50.5, 39.3, 38.7, 28.2, 27.3, 22.8, 22.6, 14.0, 14.0; HPLC (AS, hexane: i-PrOH 80:20, 1.0 mL/min): t_{R1} (major) = 12.70, t_{R1} (minor) = 17.70 min; t_{R2} (major) = 15.13min., t_{R2} (minor) = 44.06 min; dr = 2:3, ee = 93%/46%; ES-HRMS: Calcd for $C_{18}H_{23}NNaO_7$ $[M+Na]^+$, 388.13667, Found 388.13635.

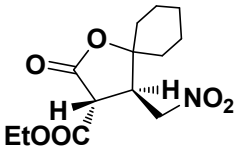


(3R,4R)-ethyl 4-(2-(4-methoxyphenyl)-1-nitroethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate 3g. mixture of two diastereoisomers: Obtained in 79% yield, white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.05 (dd, J = 20.1 Hz, 8.6 Hz, 2H, $CH(CH_2C_6H_4(p\text{-}OCH_3))NO_2$), δ 6.87–6.80 (m, 2H, $CH(CH_2C_6H_4(p\text{-}OCH_3))NO_2$), δ 4.84–4.70 (m, 1H,$CH(CH_2C_6H_4(p\text{-}OCH_3))NO_2$), δ 4.40–4.21 (m, 2H, $COOCHHCH_3$), δ 3.86–2.80 (m, 7H, $CHCHCH(CH_2C_6H_4(p\text{-}OCH_3))NO_2$), δ 1.54–1.31 (m, 9H,

($C\mathit{H}_3$)C($C\mathit{H}_3$)+COOCH$_2$CH_3); **^{13}C NMR (100MHz, CDCl$_3$)** δ 168.7, 168.1, 167.1, 166.9, 159.3, 129.9, 129.7, 125.9, 125.5, 114.5, 114.5, 89.2, 88.9, 84.9, 84.1, 63.0, 62.8, 55.2, 51.8, 50.6, 50.4, 38.5, 38.0, 28.2, 27.3, 22.7, 22.5, 14.0, 14.0; HPLC (AS, hexane: *i*-PrOH 80:20, 1.0 mL/min): t_{R1} (major) = 10.96 min., t_{R1} (minor) = 13.90 min; t_{R2} (major) = 12.08min, t_{R2} (minor) = 32.58min; dr=1:1; ee = 92%/49%; ES-HRMS: Calcd for $C_{18}H_{23}KNO_7$ $[M+K]^+$, 404.11061, Found 404.10966.

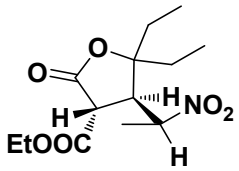


(3R,4R)-ethyl 5,5-diethyl-4-(nitromethyl)-2-oxotetrahydrofuran-3-carboxylate 3h. Obtained in 99% yield, oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.58 (dd, J = 12.8 Hz, 5.2 Hz, 1H, CHHNO$_2$), δ 4.48 (dd, J = 12.6 Hz, 8.8 Hz, 1H, CHHNO$_2$), δ 4.29 (q, J = 7.1Hz, 2H, COOCHHCH$_3$), δ 3.79–3.69 (m, 1H, CHCHCH$_2$NO$_2$), δ 3.65 (d, J = 11.1 Hz, 1H, CHCHCH$_2$NO$_2$), δ 2.03-1.94 (m, 1H, (CH$_3$CHH)(CH$_3$CHH)C), δ 1.75-1.65 (m, 1H, (CH$_3$CHH)(CH$_3$CHH)C), δ 1.63-1.57 (m,2H, (CH$_3$CHH)(CH$_3$CHH)C,), δ 1.32 (t, J = 7.1 Hz, 3H, COOCH$_2$CH_3), δ 1.03 (m, 6H, ($C\mathit{H}_3$CH$_2$)($C\mathit{H}_3$CH$_2$)C); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.9, 166.5, 87.8, 74.6, 62.7, 51.7, 43.2, 29.1, 27.6, 14.0, 7.6, 7.4; HPLC (AS, hexane: *i*-PrOH 80:20, 1.0 mL/min): t_R(major) = 20.73min , t_R(minor) = 31.74 min, ee = 91%; ES-HRMS: Calcd for $C_{12}H_{19}NNaO_6$ $[M+Na]^+$, 296.11046, Found 296.10993.



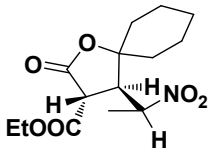
(3*R*,4*R*)-ethyl 4-(nitromethyl)-2-oxo-1-oxaspiro[4.5]decane-3-carboxylate

(3R,4R)-ethyl 4-(nitromethyl)-2-oxo-1-oxaspiro[4.5]decane-3-carboxylate 3i. Obtained in 95% yield, white solid; Mp: 116.7-120.3°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.58 (dd, J = 12.8 Hz, 5.8 Hz, 1H, CHHNO$_2$), δ 4.45 (dd, J = 12.7 Hz, 8.9 Hz, 1H, CHHNO$_2$), δ 4.28 (q, J = 7.1 Hz, 2H, COOCHHCH$_3$), δ 3.64 (d, J = 11.3 Hz, 1H, CHCHCH$_2$NO$_2$), δ 3.46 (ddd, J = 11.3 Hz, 8.8 Hz, 5.8 Hz, 1H, CHCHCH$_2$NO$_2$), δ 1.69 (m, 10H, (CH_2)$_5$C), δ 1.32(t, J = 7.1 Hz, 3H, COOCH$_2$CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.5, 165.4, 84.1, 73.3, 61.7, 49.9, 46.1, 35.3, 30.9, 23.8, 21.25, 20.2 13.0. HPLC (AD, hexane: *i*-PrOH 80:20, 1.0 mL/min): t_R (minor) = 10.76 min, t_R (major) = 14.90 min, ee = 91%; ES-HRMS: Calcd for $C_{13}H_{19}NNaO_6$ $[M+Na]^+$, 308.11046, Found 308.11016.

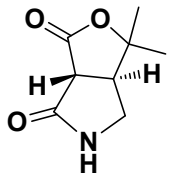


(3R,4R)-ethyl 5,5-diethyl-4-((S)-1-nitroethyl)-2-oxotetrahydrofuran-3-carboxylate 3j. Obtained in 50% yield, oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.76 (dq, J = 9.0 Hz, 6,7 Hz, 1H, CH(CH$_3$)NO$_2$), δ 4.34 (q, J = 7.1 Hz, 2H, COOCHHCH$_3$), δ 3.84 (dd, J = 11.8 Hz, 10.4 Hz, 1H, CHCHCH$_2$NO$_2$), δ 3.47 (d, J = 12.0 Hz, 1H, CHCHCH(CH$_3$)NO$_2$), δ 2.02-1.67 (m, 4H, (CH$_3$CHH)(CH$_3$CHH)C), δ 1.55 (d, J = 6.7 Hz, 3H, CH($C\mathit{H}_3$)NO$_2$), δ 1.41-1.31 (m, 3H, COOCH$_2$CH_3), δ 1.05-1.00 (m, 6H, ($C\mathit{H}_3$CHH)($C\mathit{H}_3$CHH)C); **^{13}C NMR** (100MHz, $CDCl_3$) δ 168.7, 167.3, 88.8, 81.8, 62.8, 50.4, 47.0, 29.5, 28.3, 28.2, 19.0, 14.0, 7.8, 7.7, 7.0; HPLC (AS, hexane: *i*-PrOH 80:20, 1.0 mL/min): t_R (major) = 12.18min, t_R(minor) = 12.79 min; ee = 87%. Calcd for $C_{13}H_{21}NNaO_6$ $[M+Na]^+$, 310.12611, Found

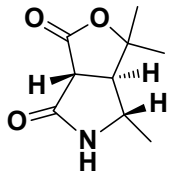
10.12607.



(3R,4R)-ethyl 4-((S)-1-nitroethyl)-2-oxo-1-oxaspiro[4.5]decane-3-carboxylate 3k. Obtained in 85% yield, oil. the signals of the major isomer, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.82–4.71 (m, 1H, C*H*(CH_3)NO_2), δ 4.32 (2H, q, J = 7.1 Hz, COOC*HH*CH_3), δ 3.49–3.35 (2H, m, C*H*C*H*CH_2NO_2), δ 1.88–1.56 (m, 10H, (CH_2)$_5$C), δ 1.53 (d, 3H, J = 6.7 Hz, CH(C*H*$_3$)NO_2), δ 1.34 (t, J = 7.2 Hz, 3H, $COOCH_2CH_3$); **^{13}C NMR** (100MHz, $CDCl_3$) δ 168.2, 167.1, 86.4, 81.6, 62.8, 52.4, 49.8, 36.4, 31.5, 24.7, 22.4, 21.3, 18.6, 14.0; HPLC (AS, hexane: *i*-PrOH 80: 20, 1.0 mL/min): t_{R1}(minor) = 19.51min, t_{R1}(major) = 53.50 min; t_{R2}(minor) = 21.98min, t_{R2}(major) = 29.54 min; dr = 7:1, ee = 77%/64%; ES-HRMS: Calcd for $C_{14}H_{21}NNaO_6[M]^+$, 300.14416, Found 300.14437.



(3aR,6aR)-3,3-dimethyltetrahydro-1H-furo[3,4-c]pyrrole-1,6(6aH)-dione 4a. Zinc powder (570mg, 8.8 mmol) was added in batches to a solution of **3a** (61mg, 0.25 mmol) in 2:1 THF/acetic acid (3mL) at room temperature. After 3h, the reaction mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure followed by high vacuum. The residue was dissolved in dichloromethane (3mL) and an aqueous saturated solution of sodium bicarbonate (1mL) was added into it. After extra 4 hours of reaction at room temperature, the mixture was then diluted with dichloromethane (30 ml). The solution was washed with 10% (w/w) $NaHCO_3$ solution (30 mL) and saturated NaCl solution (30mL) successively, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to give lactam **4a** (35mg, 85%) as oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.63 (s, 1H, N*H*), δ 3.61– 3.52 (m, 3H, C*H*$_2$(NH)CHC*H*CO), δ 3.18–3.13 (m, 1H, CH_2(NH)C*H*CHCO), δ 1.50 (s, 1H, (C*H*$_3$)C(CH_3)), 1.47 (s, 1H, (CH_3)C(C*H*$_3$)); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0, 169.7, 85.0, 49.4, 45.4, 41.8, 30.2, 23.2; ES-HRMS: Calcd for $C_8H_{11}NNaO_3$ $[M+Na]^+$, 192.06311, Found 192.06293.

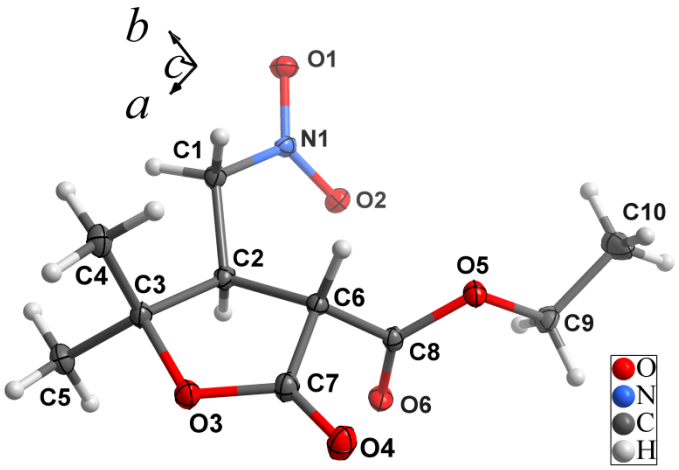


(3aR,4S,6aR)-3,3,4-trimethyltetrahydro-1H-furo[3,4-c]pyrrole-1,6(6aH)-dione 4b. Obtained in 75% yield, oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.2 (s, 1H, N*H*), δ 4.13–4.06 (m, 1H, CH_2(NH)CHC*H*CO), δ 3.58 (d, J = 8.7 Hz, 1H, CH_2(NH)CHC*H*CO), δ 3.04 (dd, J = 8.6 Hz, 6.2 Hz, 1H, CH_2(NH)C*H*CHCO), δ 1.57 (s, 1H, (C*H*$_3$)C(CH_3)), δ 1.55 (s, 1H, (CH_3)C(C*H*$_3$)), δ 1.46 (d, J = 7.0 Hz, 3H, CH_2(NH)CHC*H*CO); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.9, 169.5, 86.1, 51.2, 50.3, 49.7, 30.7, 25.4, 15.6; ES-HRMS: Calcd for $C_9H_{13}NNaO_3$ $[M+Na]^+$, 206.07876, Found206.07854.

3. Determination of the configuration of products 3a-k

3.1 Determination of the absolute configuration of product 3a

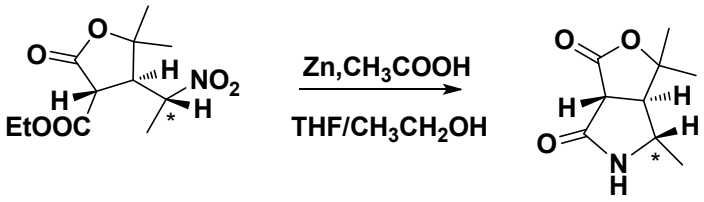
Figure S1. X-ray structure of **3a**



3.2 Determination of the configuration for the newly formed stereocenter

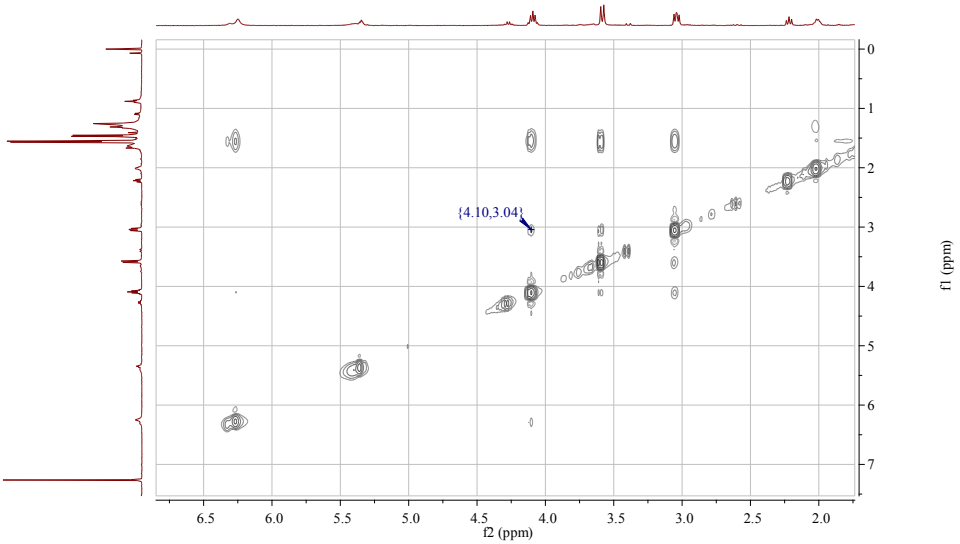
The configuration for the newly formed stereocenter (labelled '*') in **3b** was determined by transformation of **3b** to cyclic lactams **4b** and the NOESY spectra of **3b**.

Figure S2. Transformation of **3b** to cyclic lactams **4b**



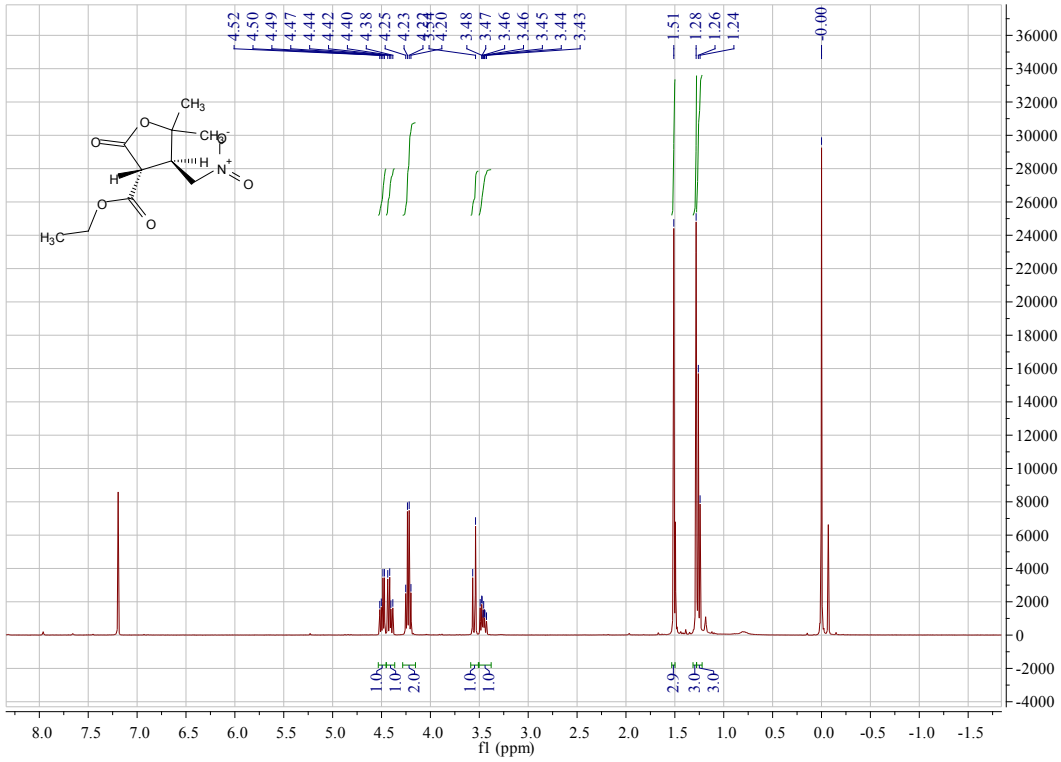
3b **4b**

Figure S3. NOESY for compound **4b**

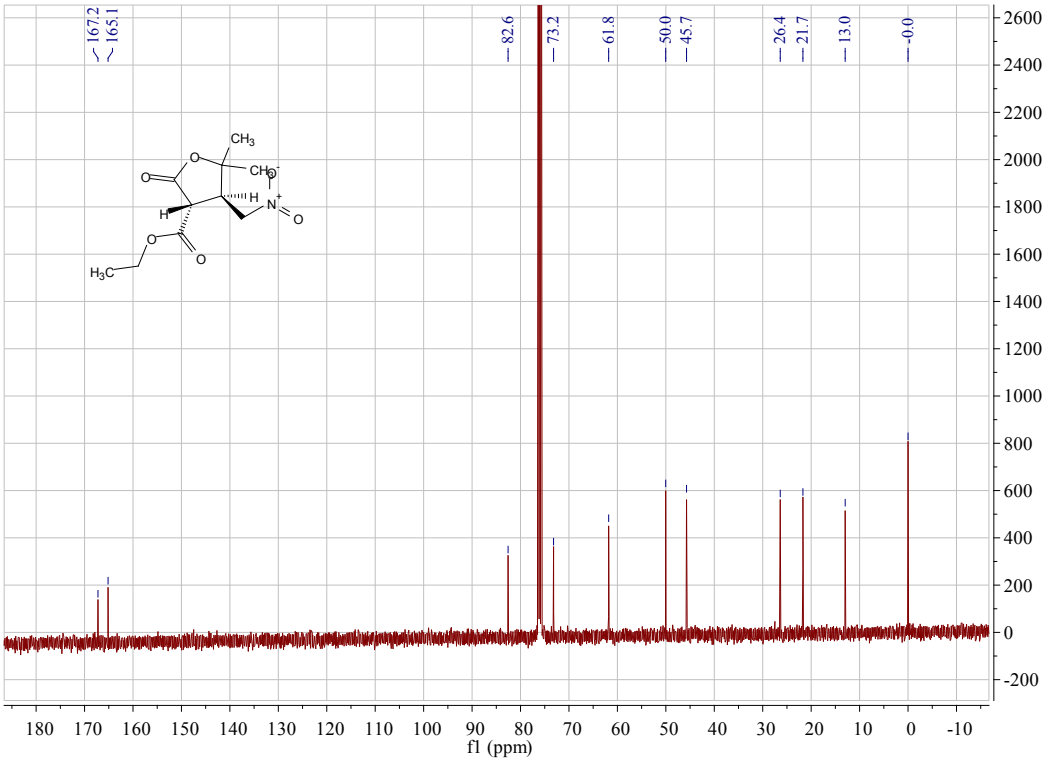


4. NMR Spectra for Michael Product 3a-3k and 4a-4b

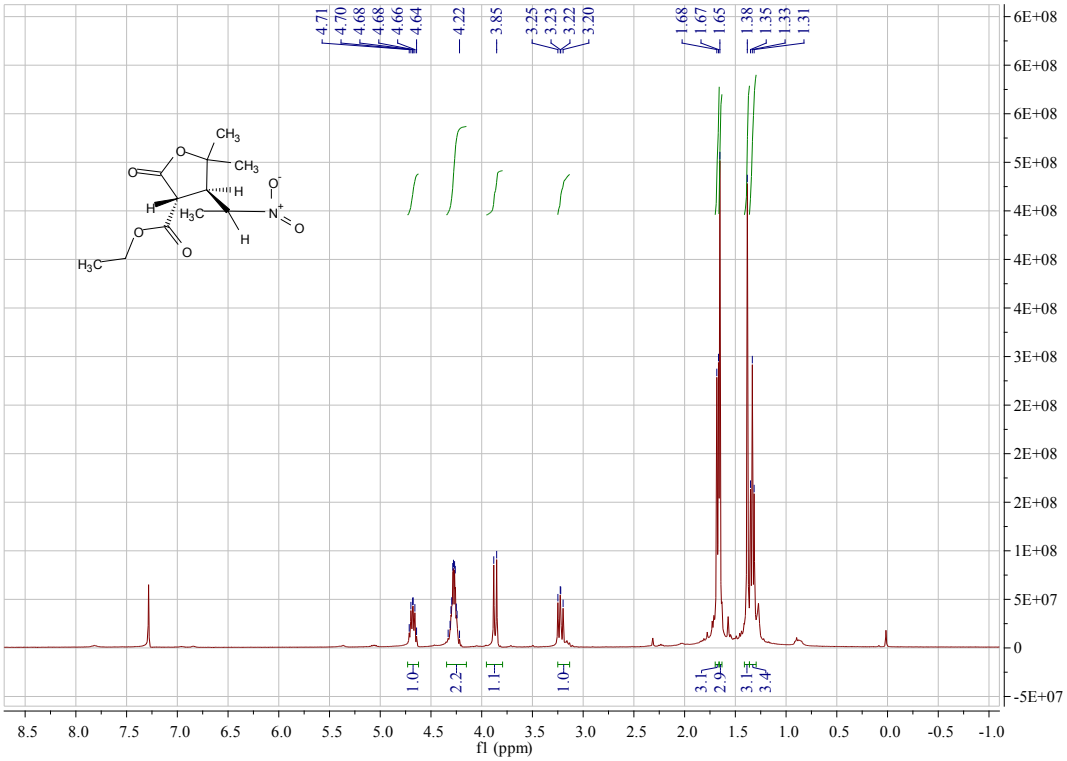
^{1}H NMR of product **3a** (400 MHz, $CDCl_3$)



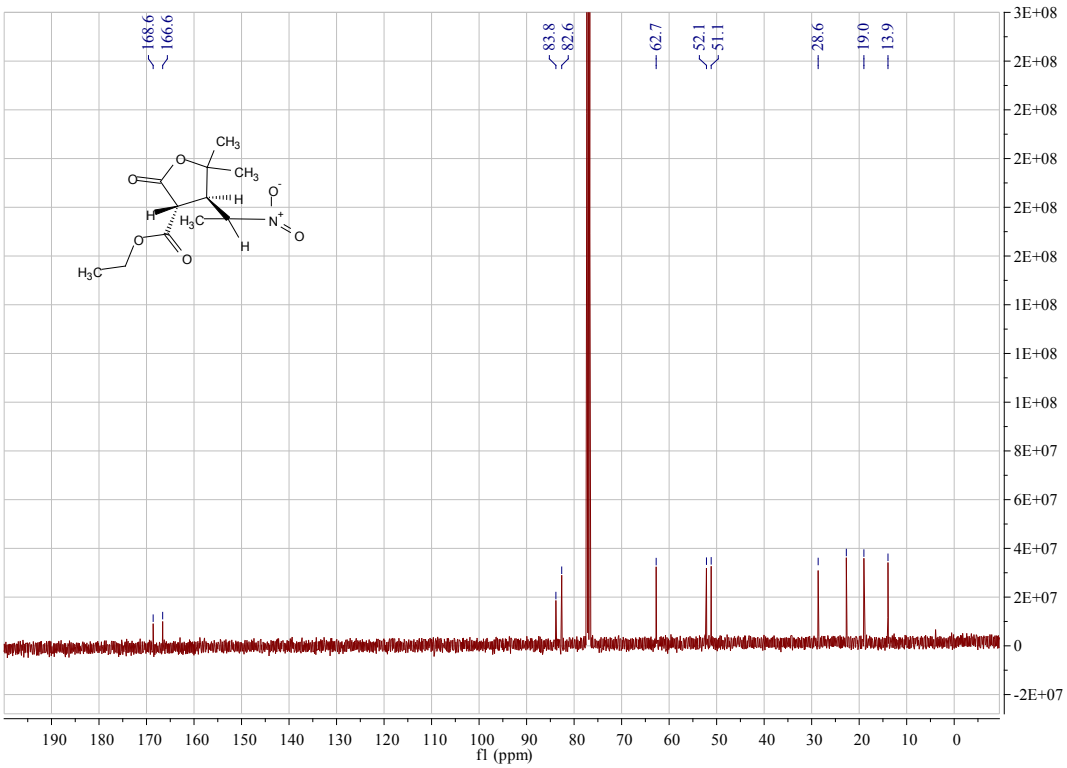
^{13}C NMR of product **3a** (100 MHz, $CDCl_3$)



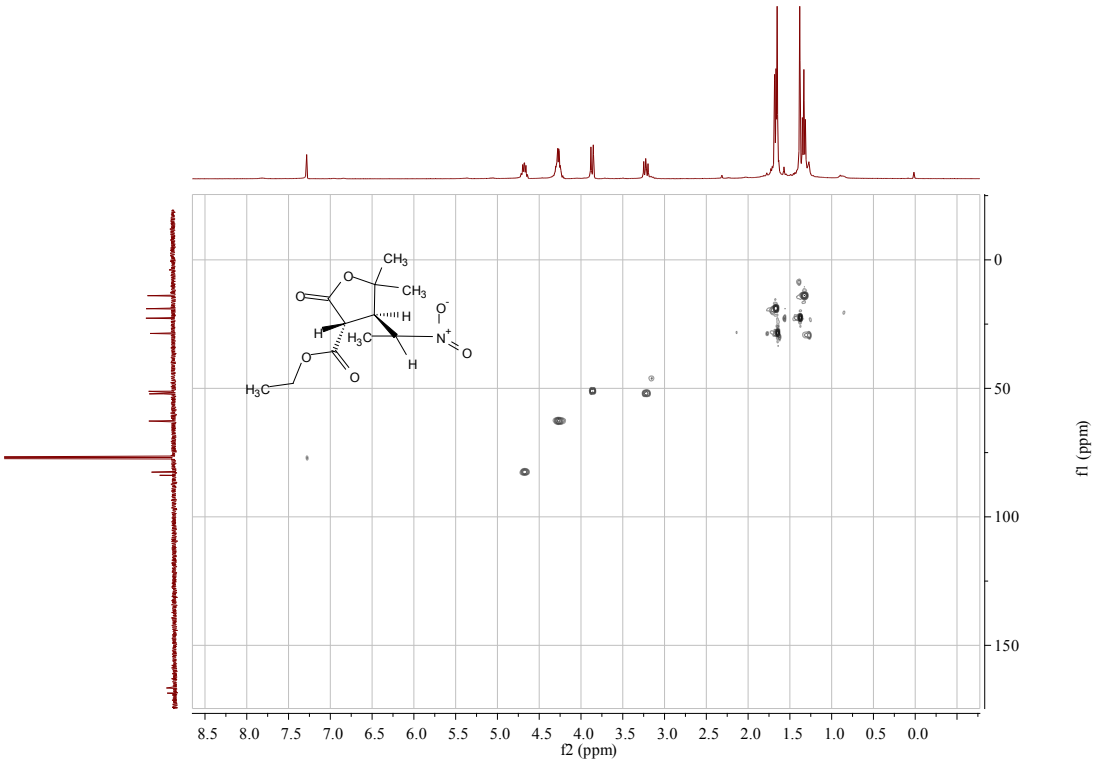
^{1}H NMR of product **3b**(400 MHz, $CDCl_3$)



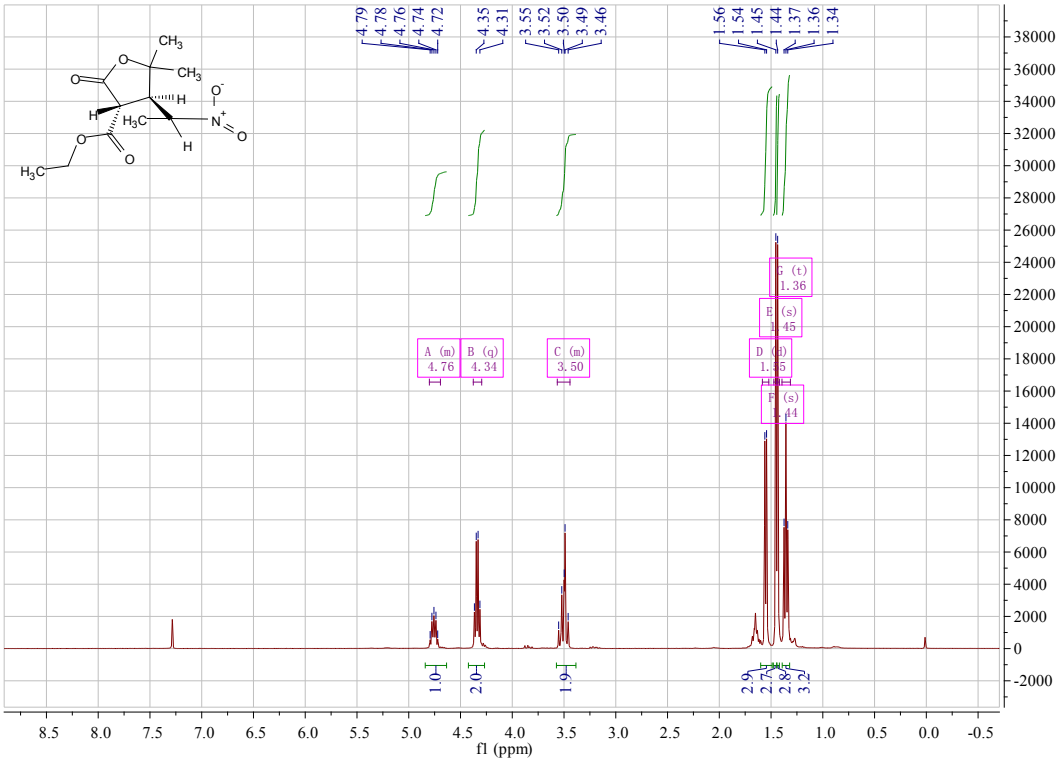
^{13}C NMR of product **3b** (100 MHz, $CDCl_3$)



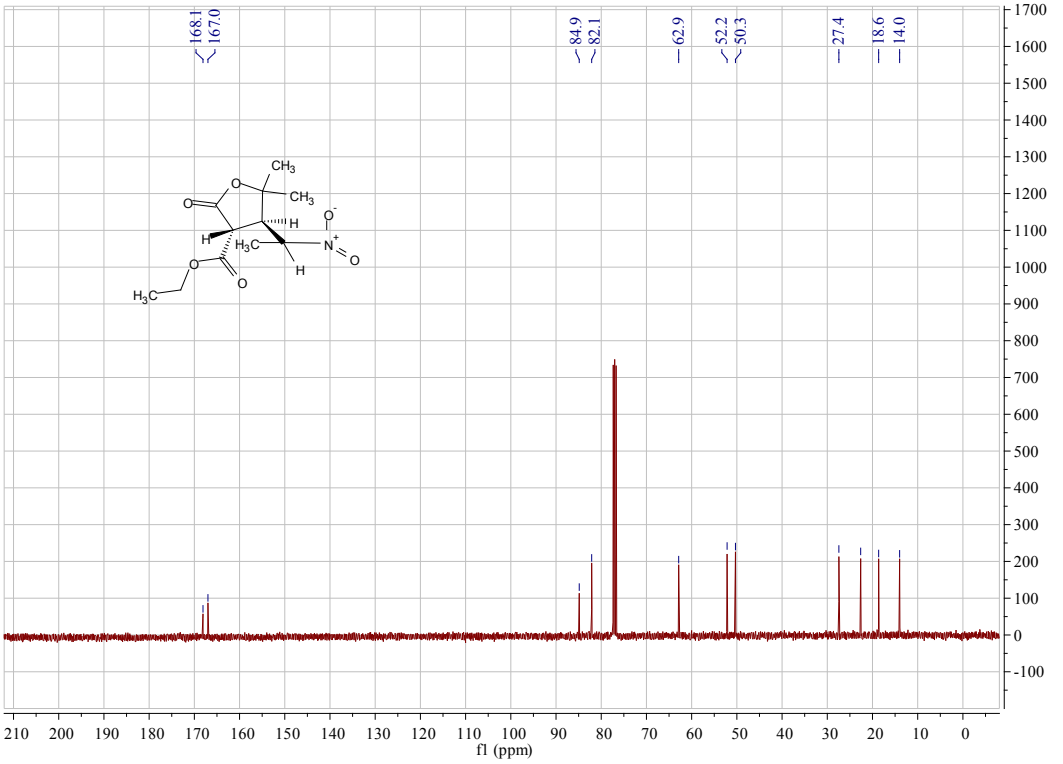
^{1}H-^{13}C HSQC spectra of product **3b**



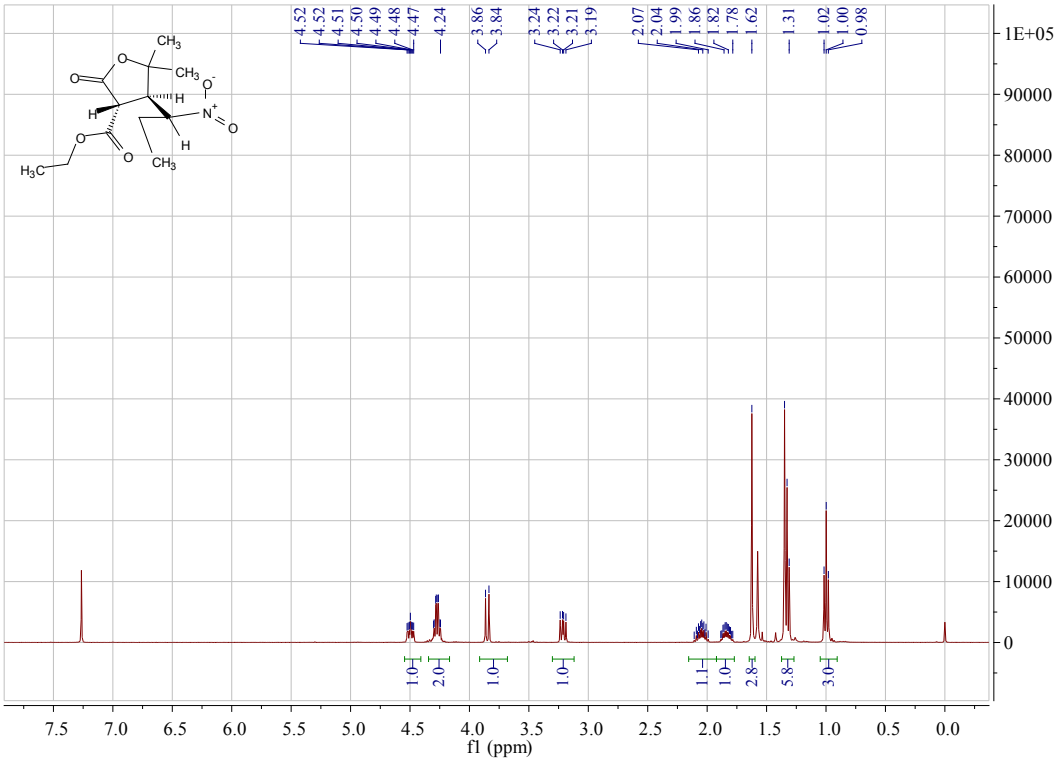
^{1}H NMR of the other diastereoisomer of product **3b** (400 MHz, $CDCl_3$)



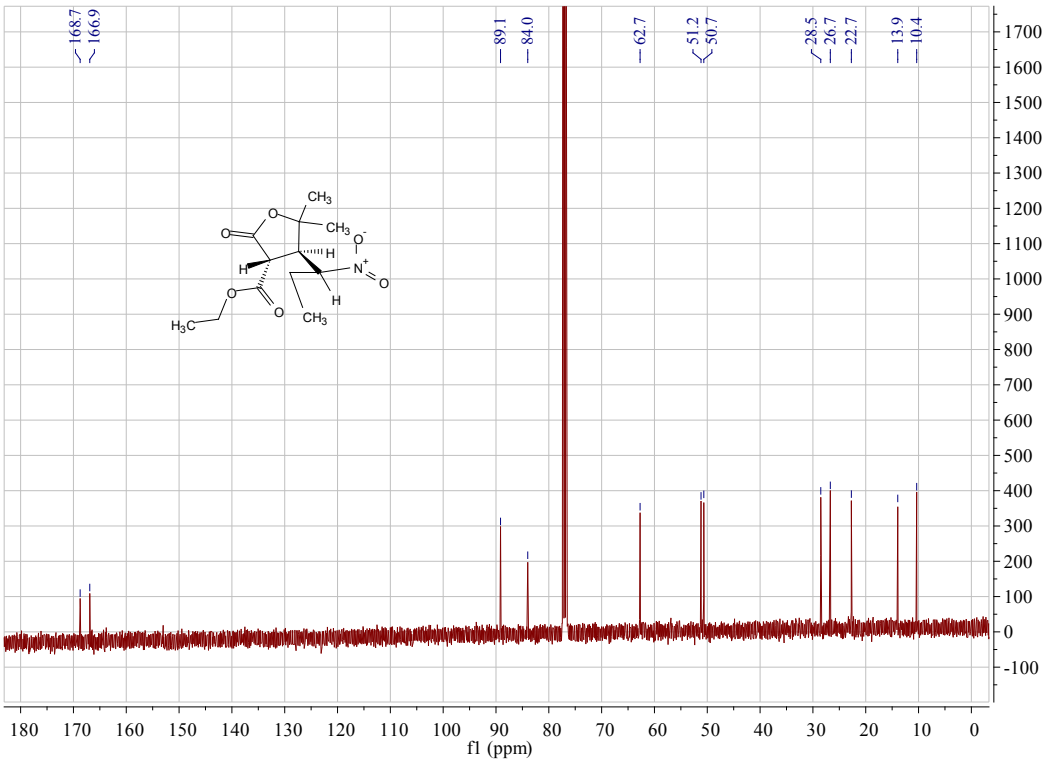
^{13}C NMR of the other diastereoisomer of product **3b** (400 MHz, $CDCl_3$)



^{1}H NMR of product **3c** (400 MHz, $CDCl_3$)

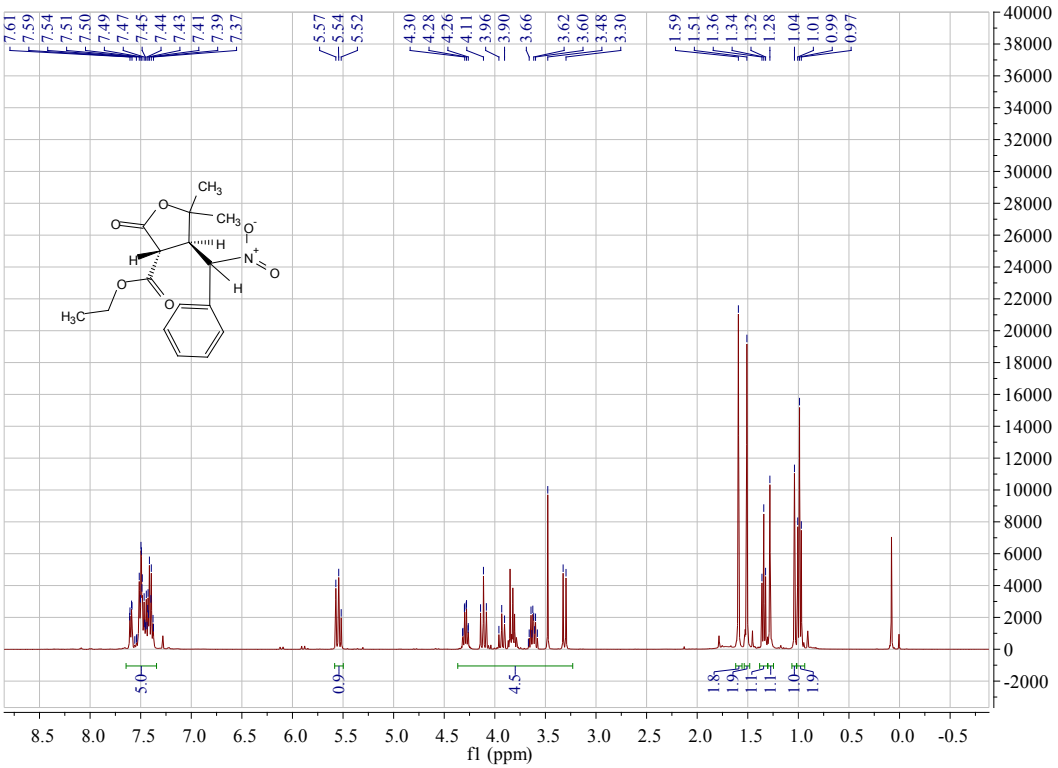


^{13}C NMR of product 3**c** (100 MHz, $CDCl_3$)



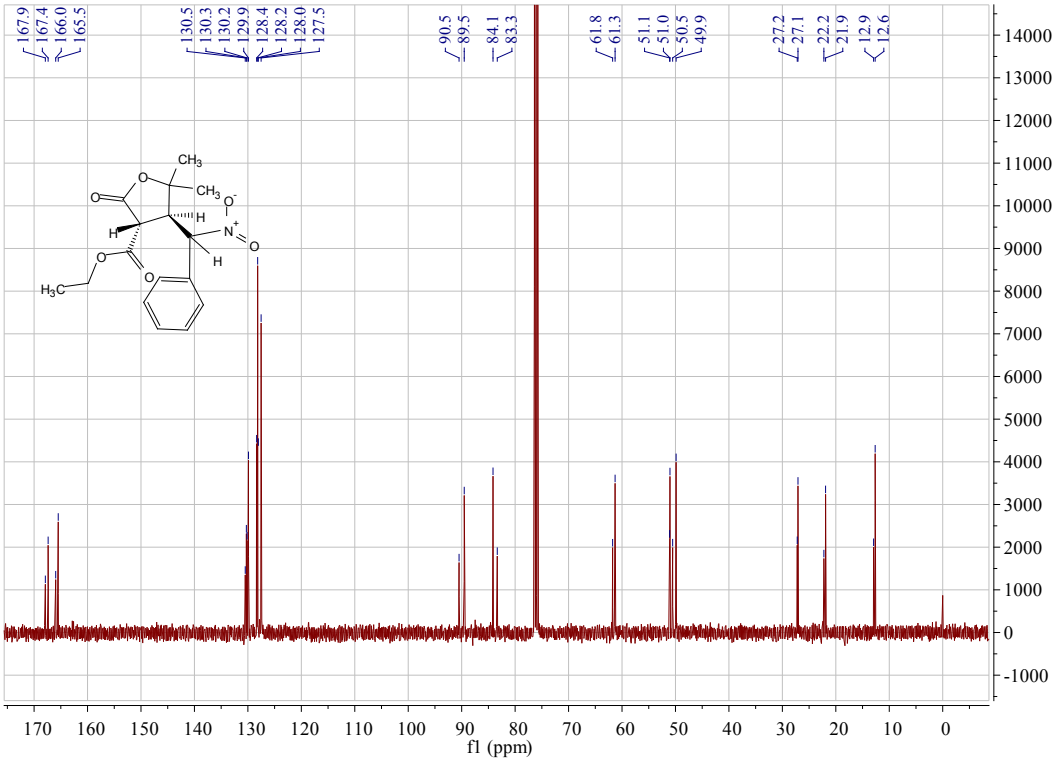
^{1}H NMR of product **3d** (400 MHz, $CDCl_3$)

Mixture of two diastereoisomers



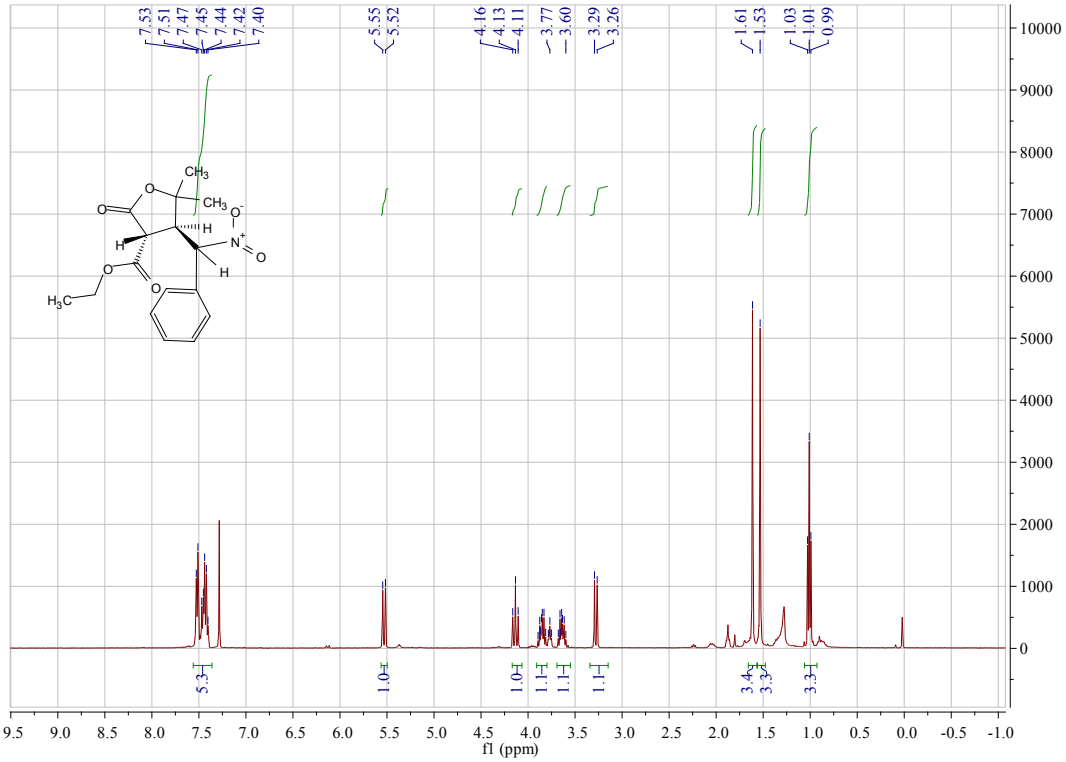
^{13}C NMR of product **3d** (100 MHz, $CDCl_3$)

Mixture of two diastereoisomers



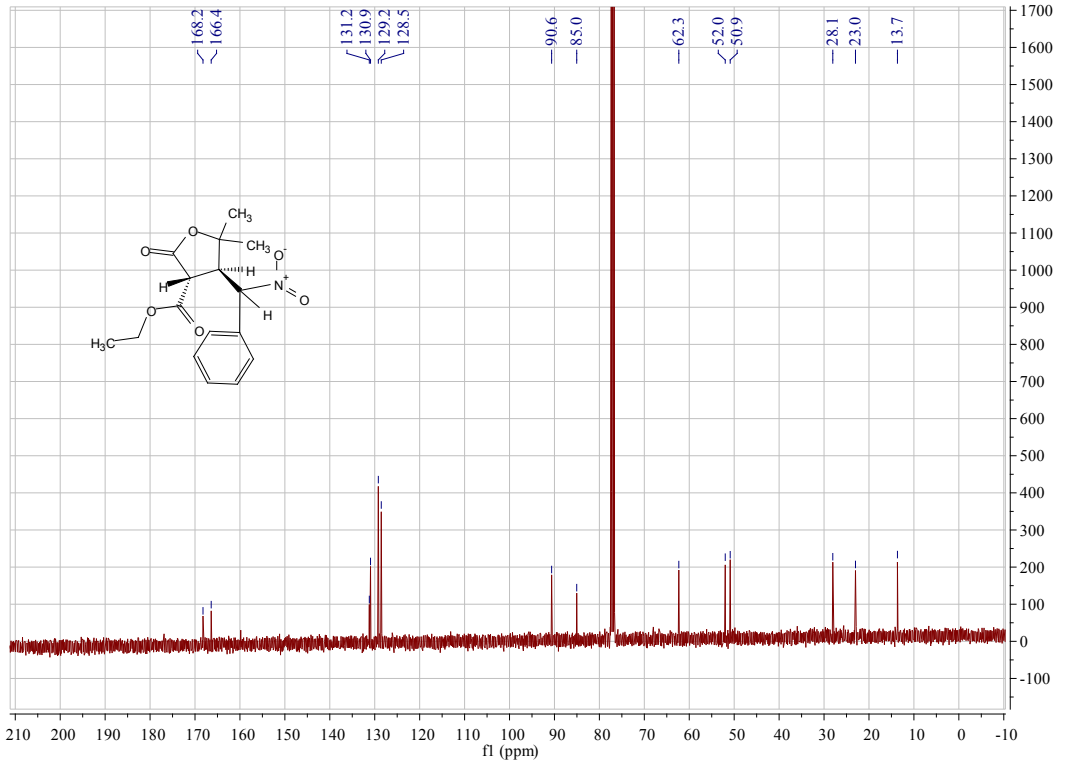
^{1}H NMR of product **3d** (400 MHz, $CDCl_3$)

Single diastereoisomer

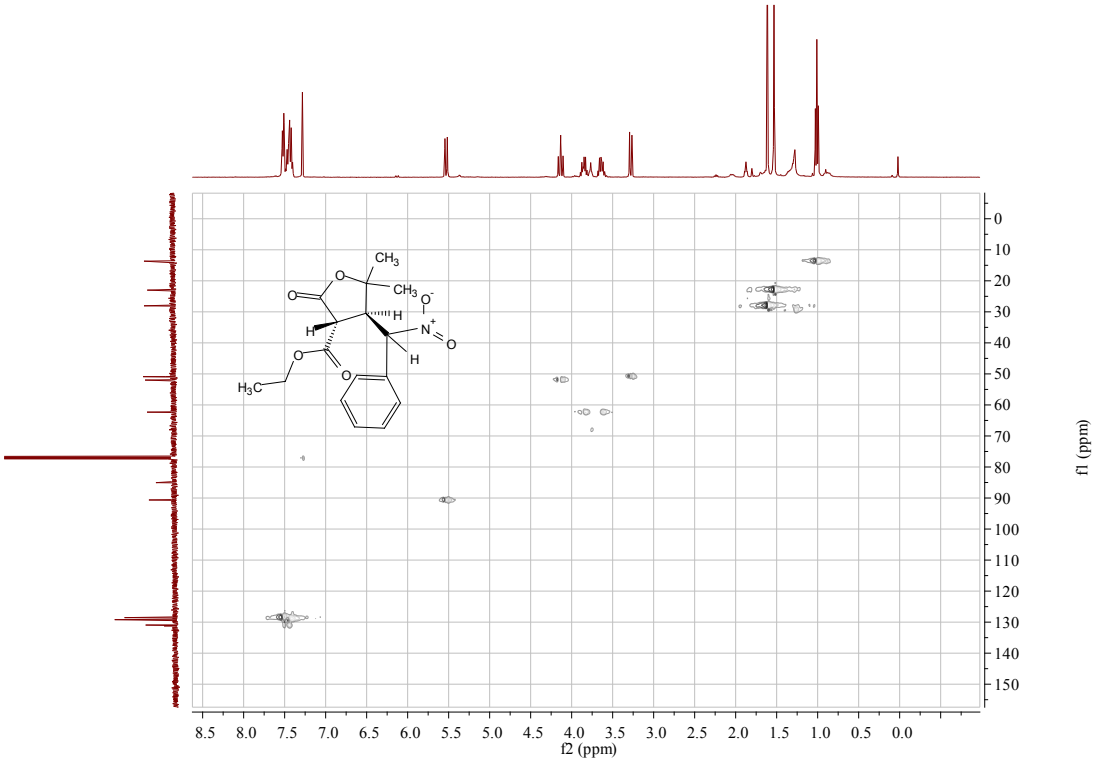


^{13}C NMR of product **3d** (100 MHz, $CDCl_3$)

Single diastereoisomer

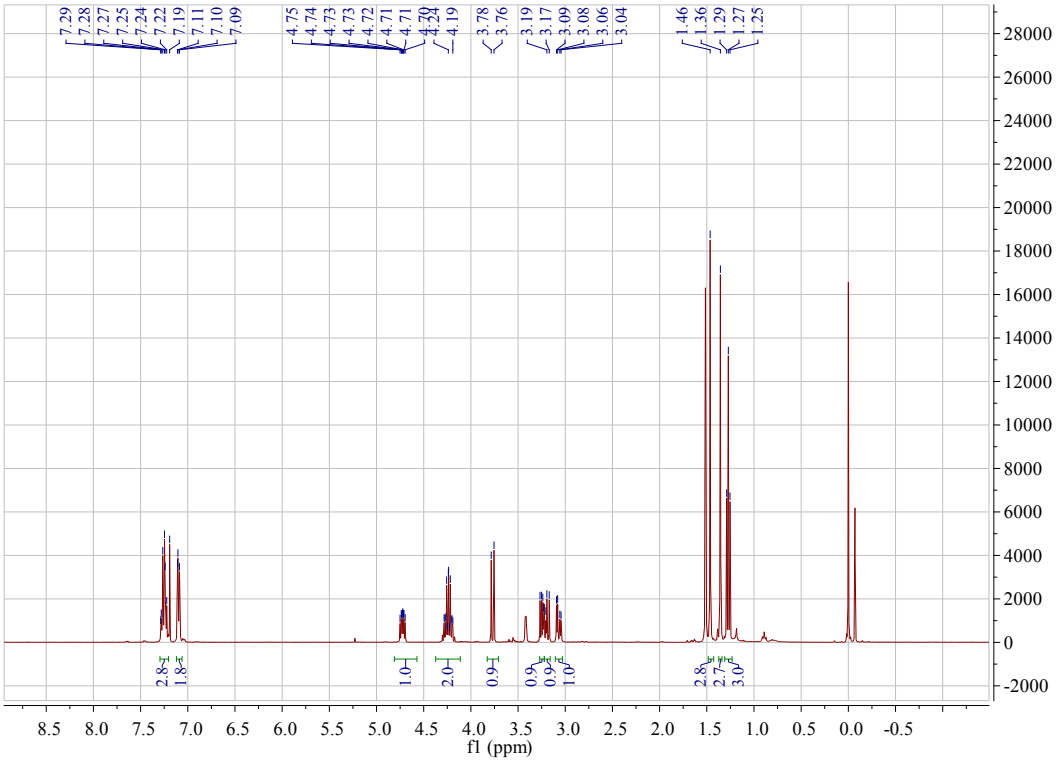


^{1}H-^{13}C HSQC spectra of single diastereoisomer**3d**



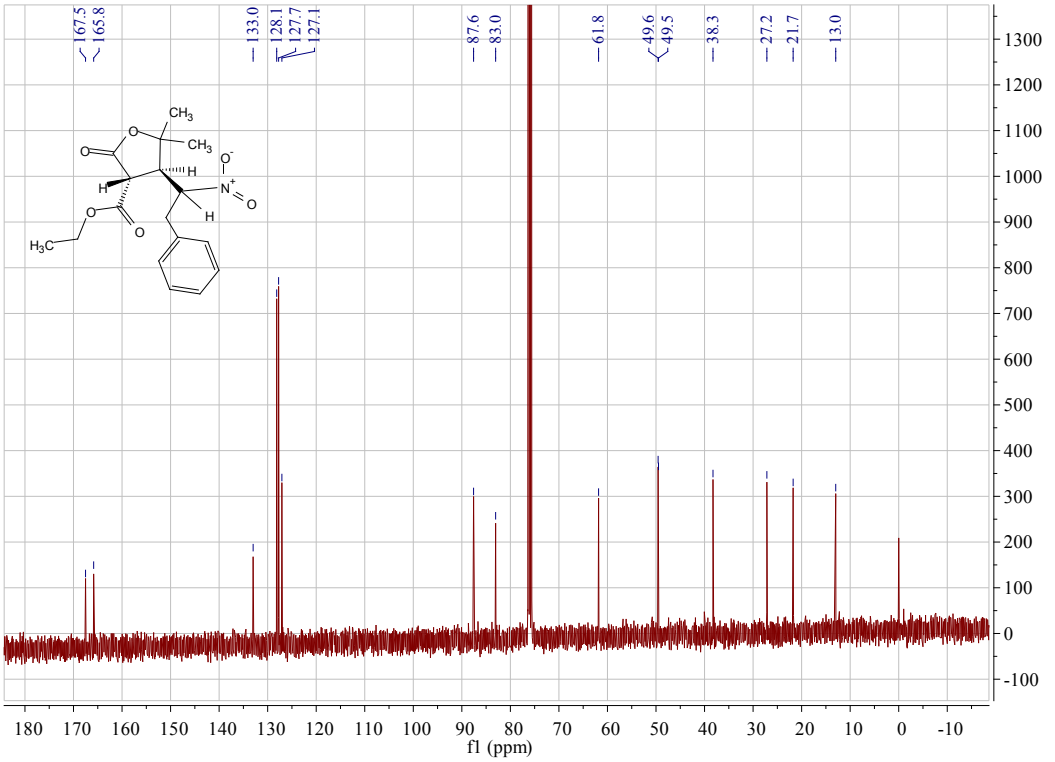
^{1}H NMR of product **3e** (400 MHz, $CDCl_3$)

Single diastereoisomer



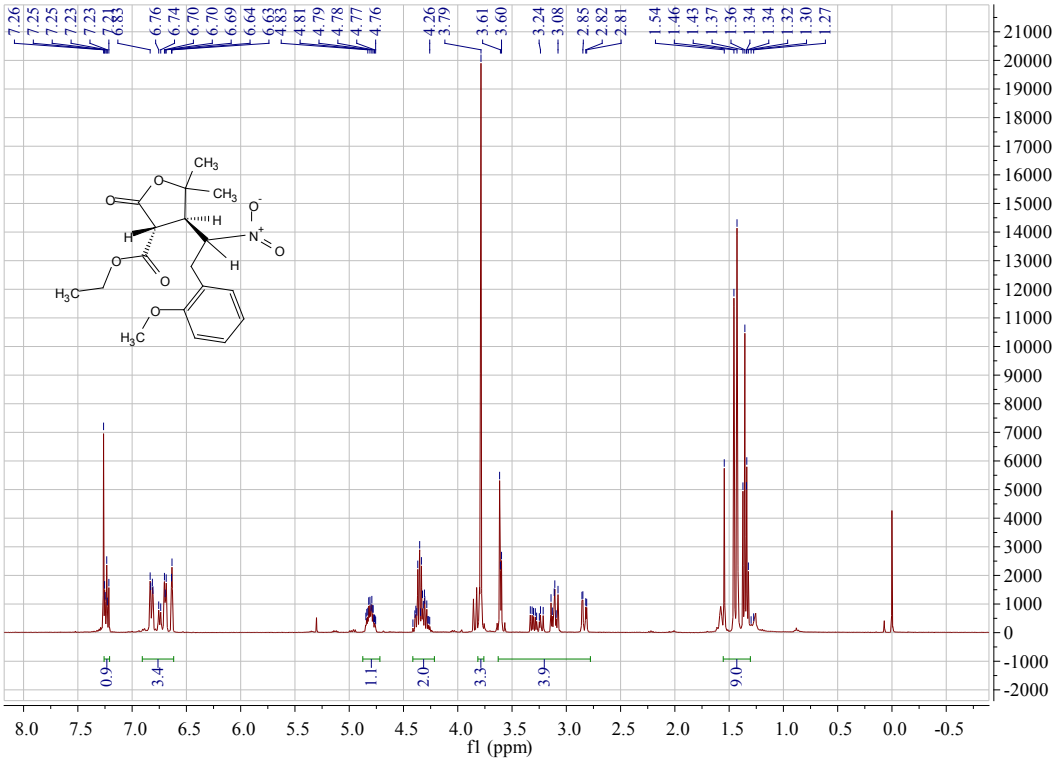
^{13}C NMR of product **3e** (100 MHz, $CDCl_3$)

Single diastereoisomer



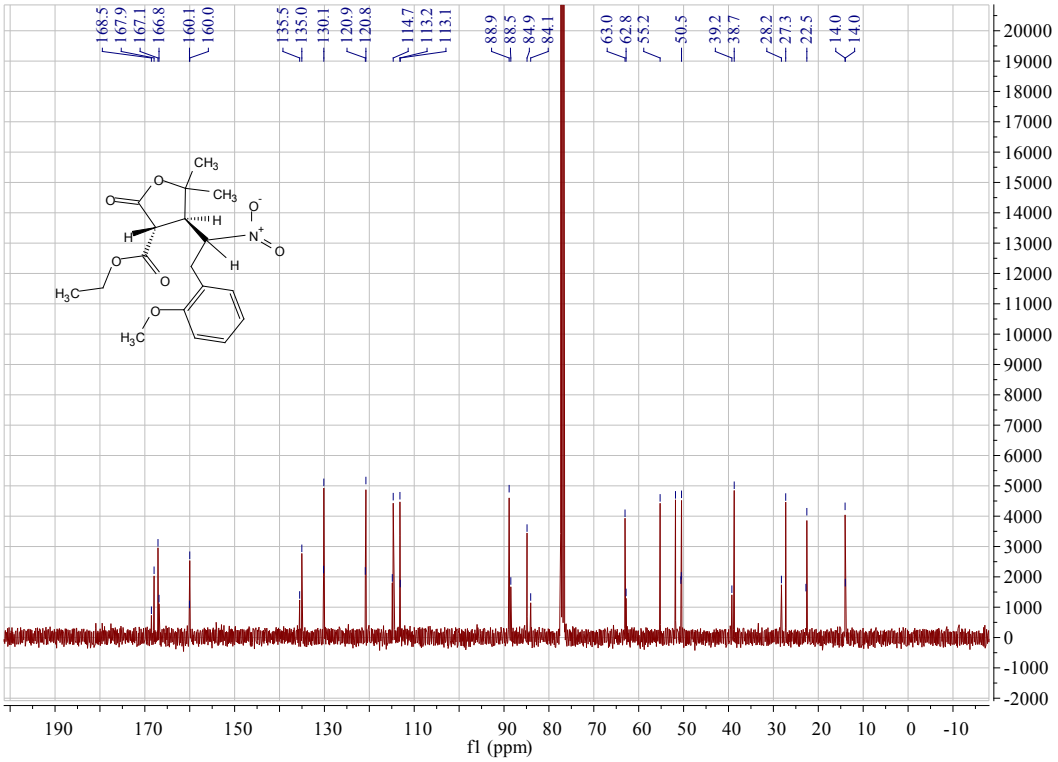
^{1}H NMR of product **3f**(400 MHz, $CDCl_3$)

Mixture of two diastereoisomers



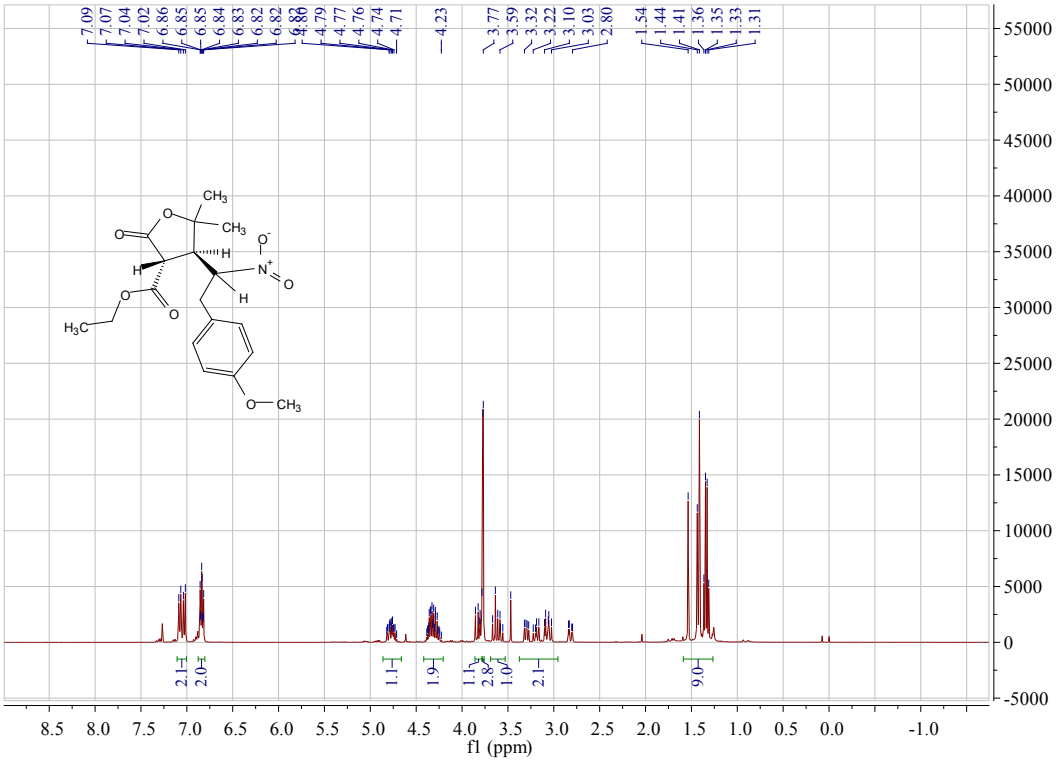
^{13}C NMR of product **3f** (100 MHz, $CDCl_3$)

Mixture of two diastereoisomers



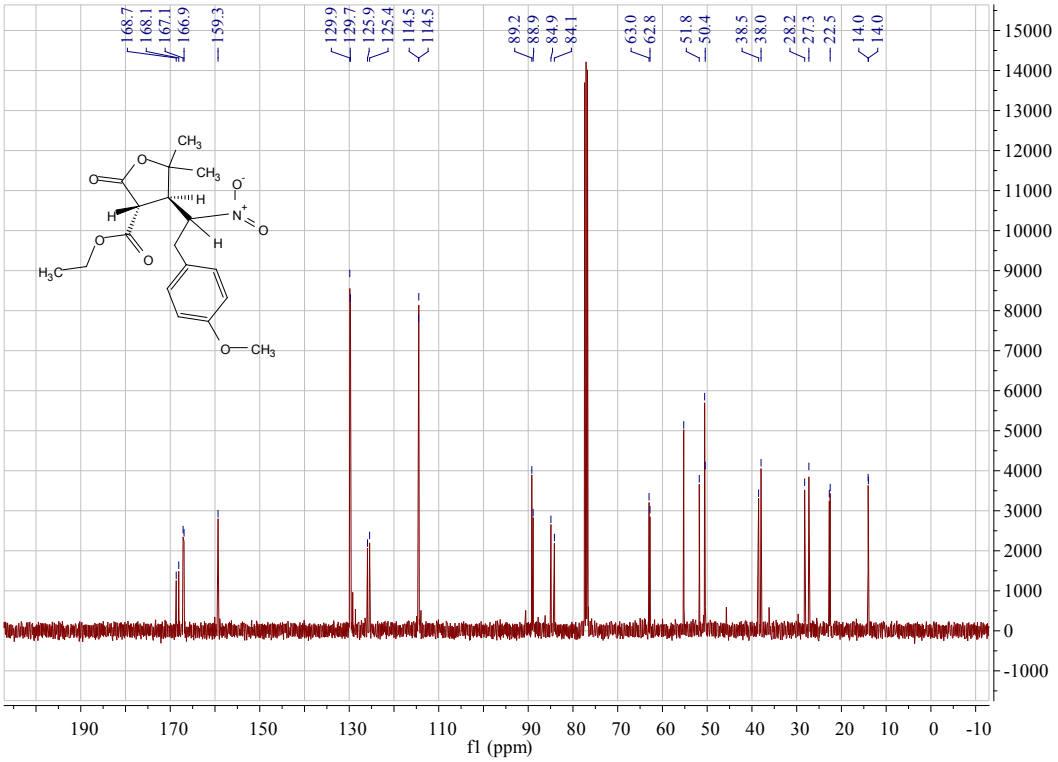
^{1}H NMR of product **3g** (400 MHz, $CDCl_3$)

Mixture of two diastereoisomers



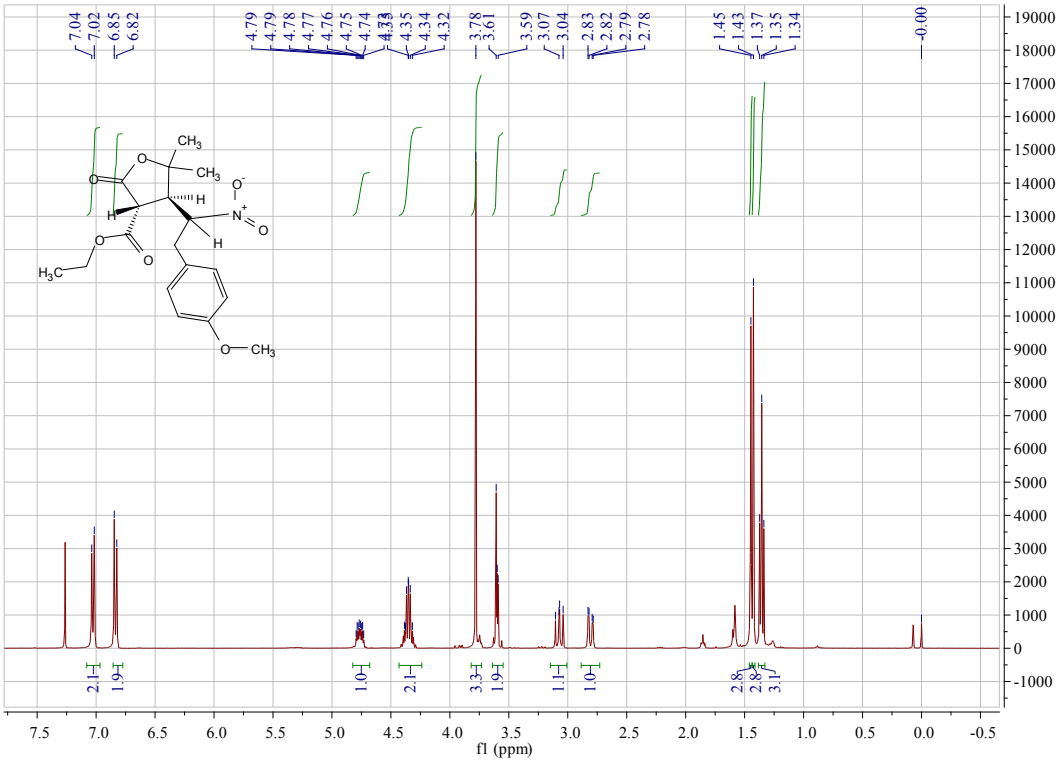
^{13}C NMR of product **3g** (100 MHz, $CDCl_3$)

Mixture of two diastereoisomers



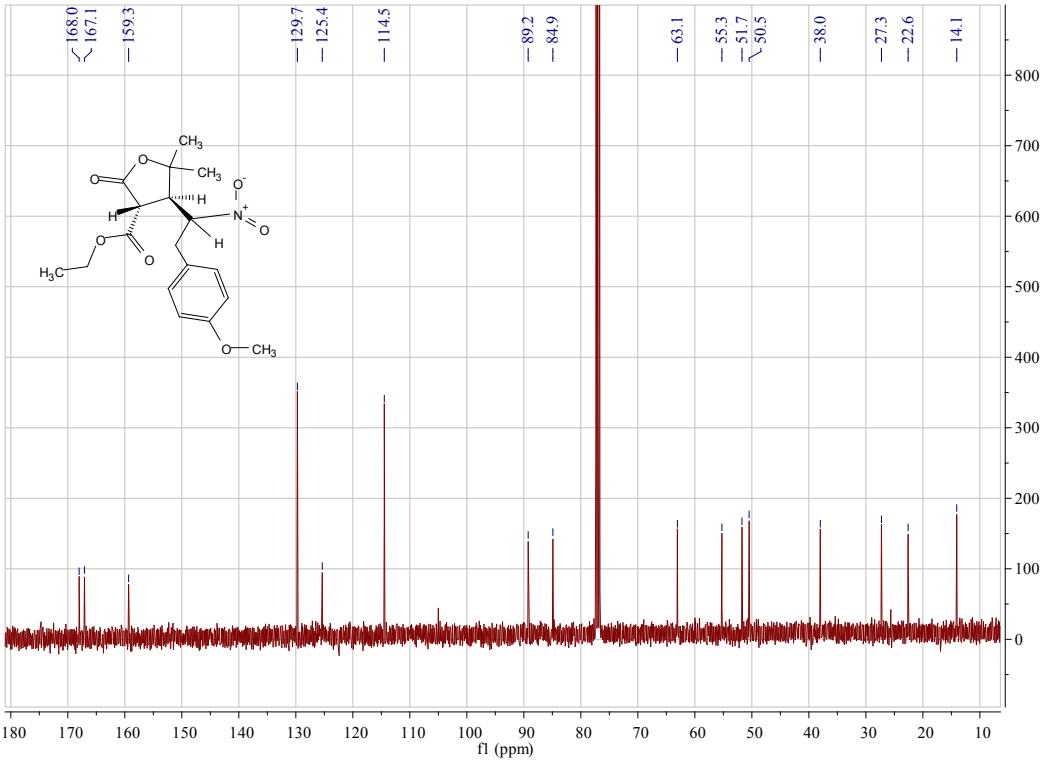
^{1}H NMR of product **3g** (400 MHz, $CDCl_3$)

Single diastereoisomer



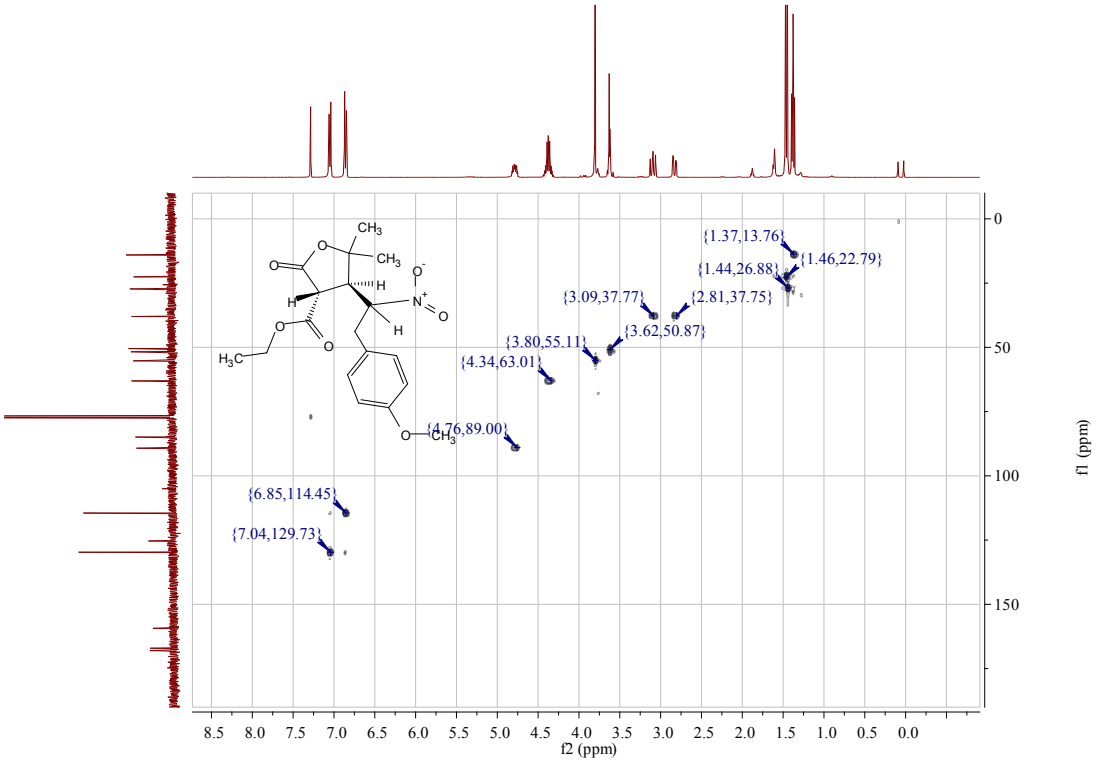
^{13}C NMR of product **3g** (100 MHz, $CDCl_3$)

Single diastereoisomer

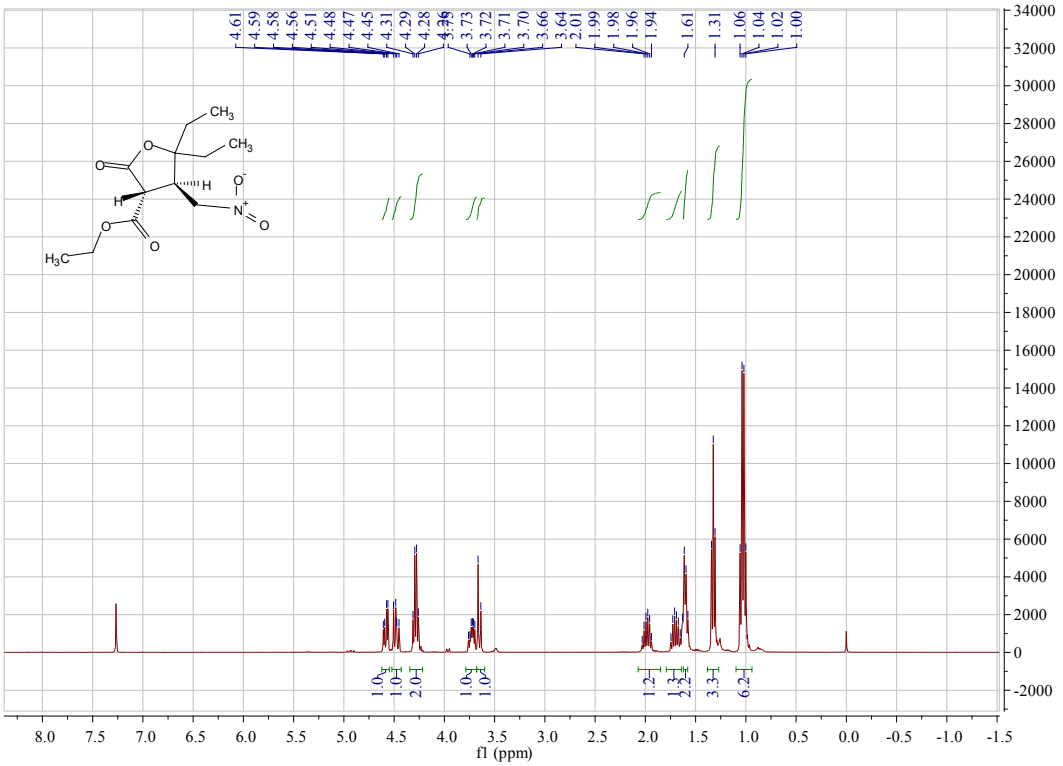


^{1}H-^{13}C HSQC spectra of single diastereoisomer**3g**

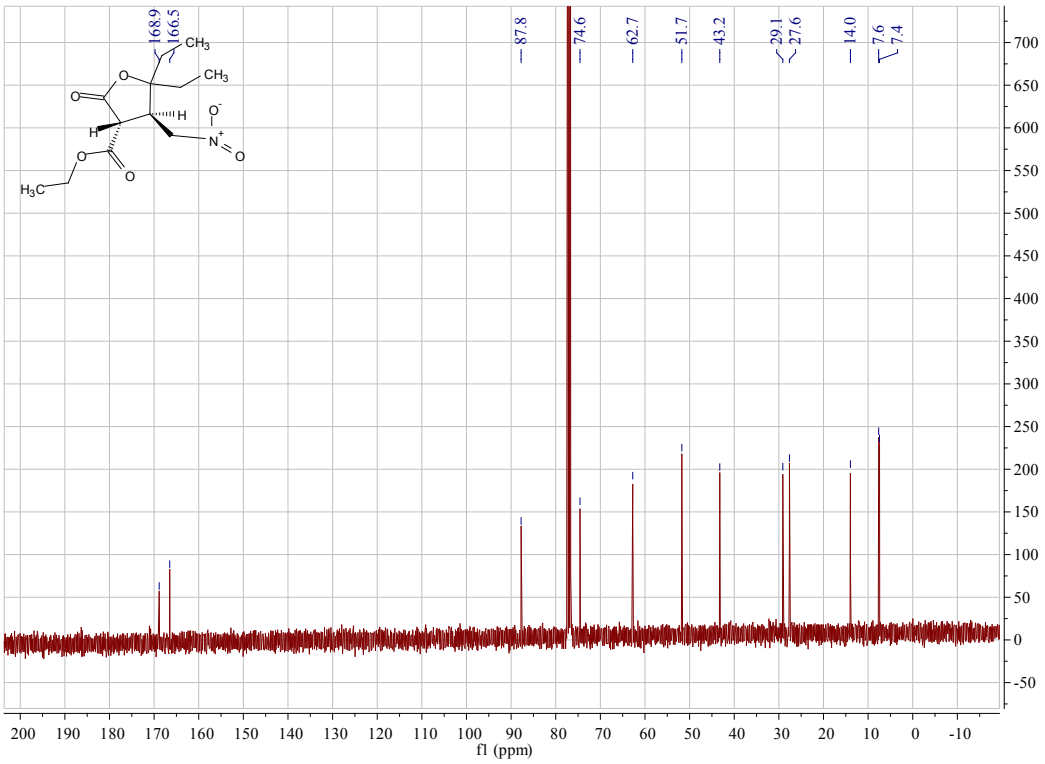
Single diastereoisomer



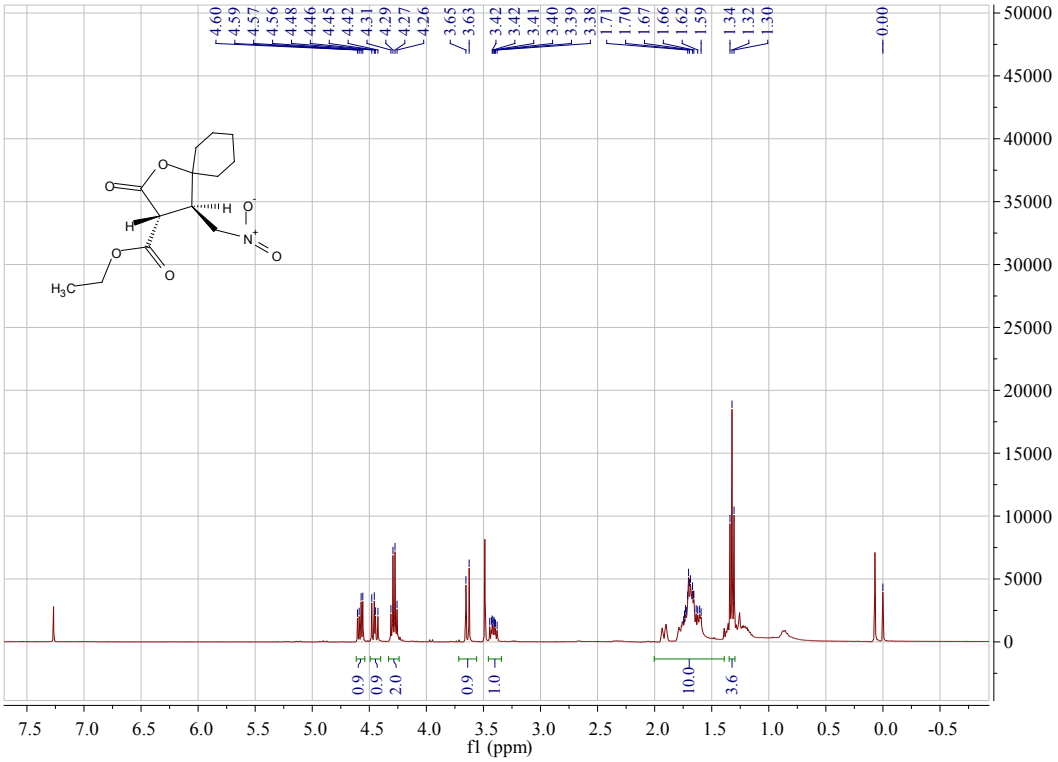
^{1}H NMR of product **3h** (400 MHz, $CDCl_3$)



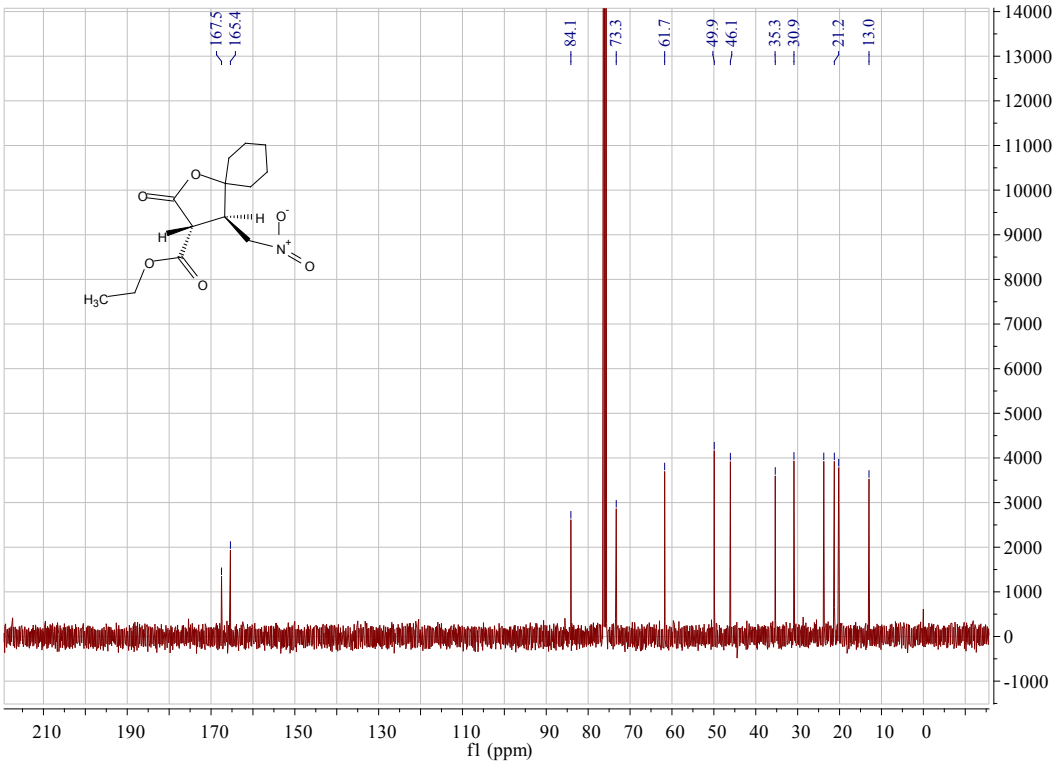
^{13}C NMR of product **3h** (100 MHz, $CDCl_3$)



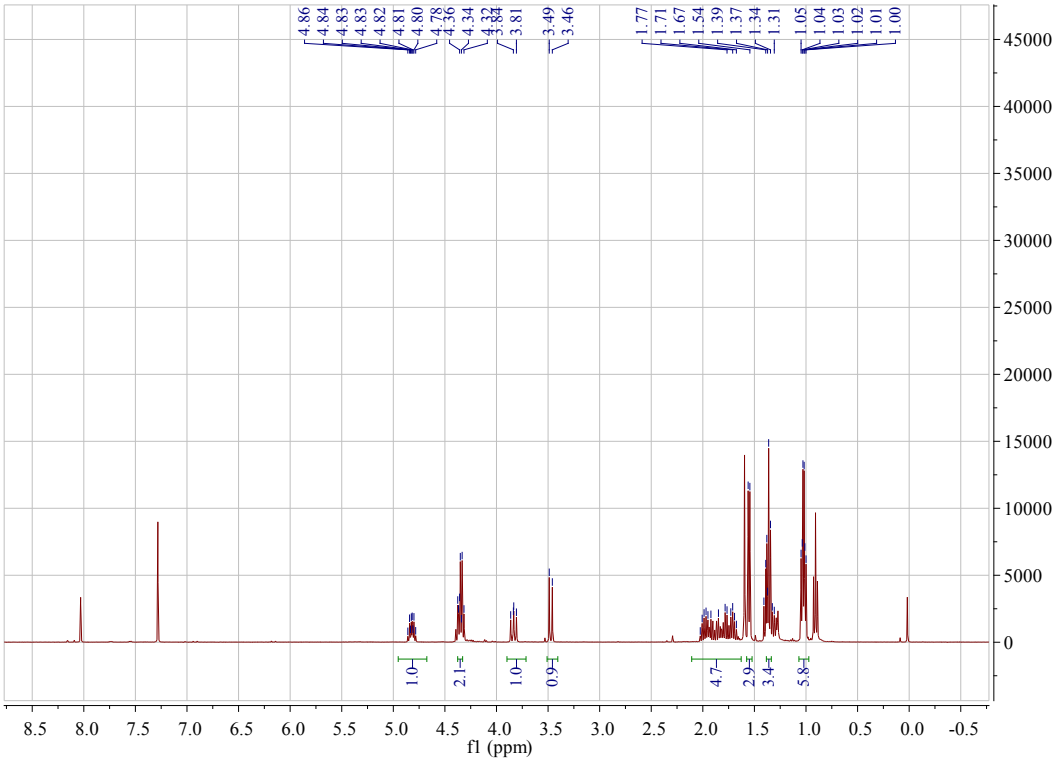
^{1}H NMR of product **3i**(400 MHz, $CDCl_3$)



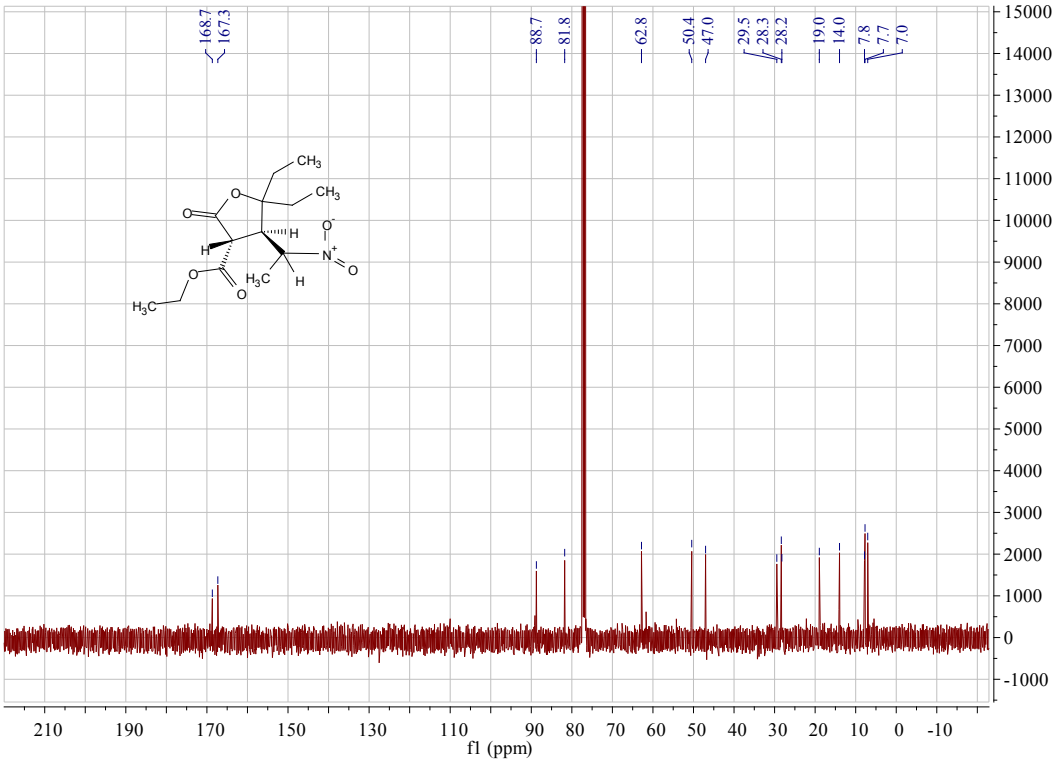
^{13}C NMR of product **3i** (100 MHz, $CDCl_3$)



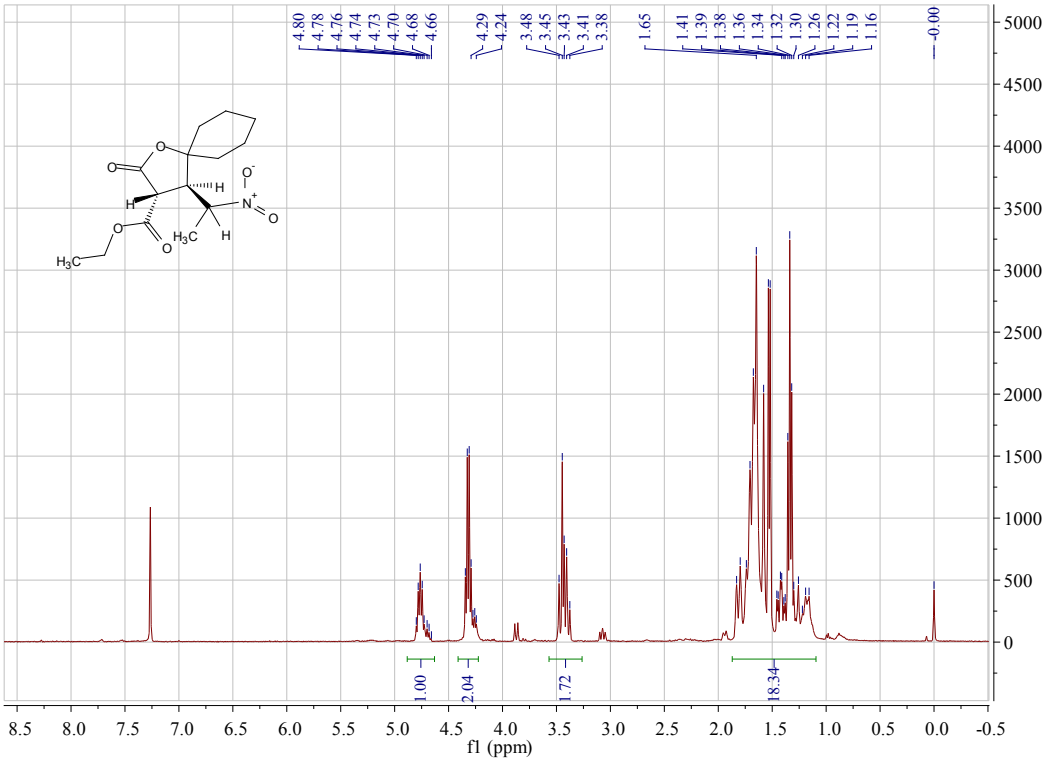
^{1}H NMR of product **3j**(400 MHz, $CDCl_3$)



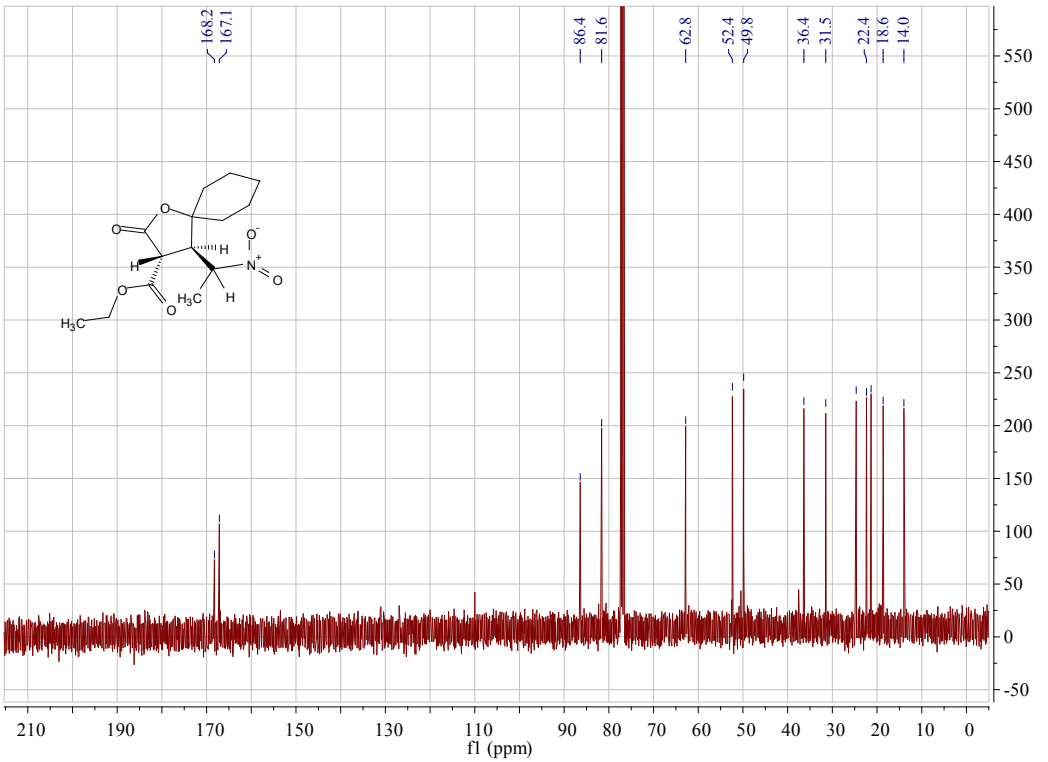
^{13}C NMR of product **3j**(100 MHz, $CDCl_3$)



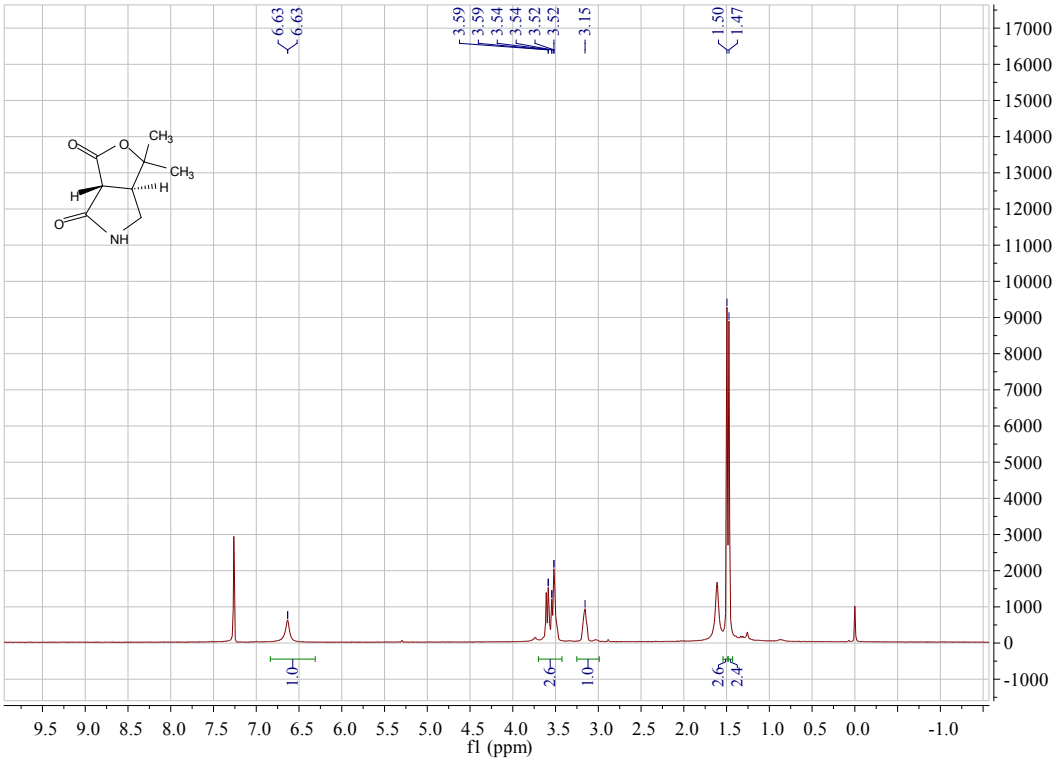
^{1}H NMR of product **3k** (400 MHz, $CDCl_3$)



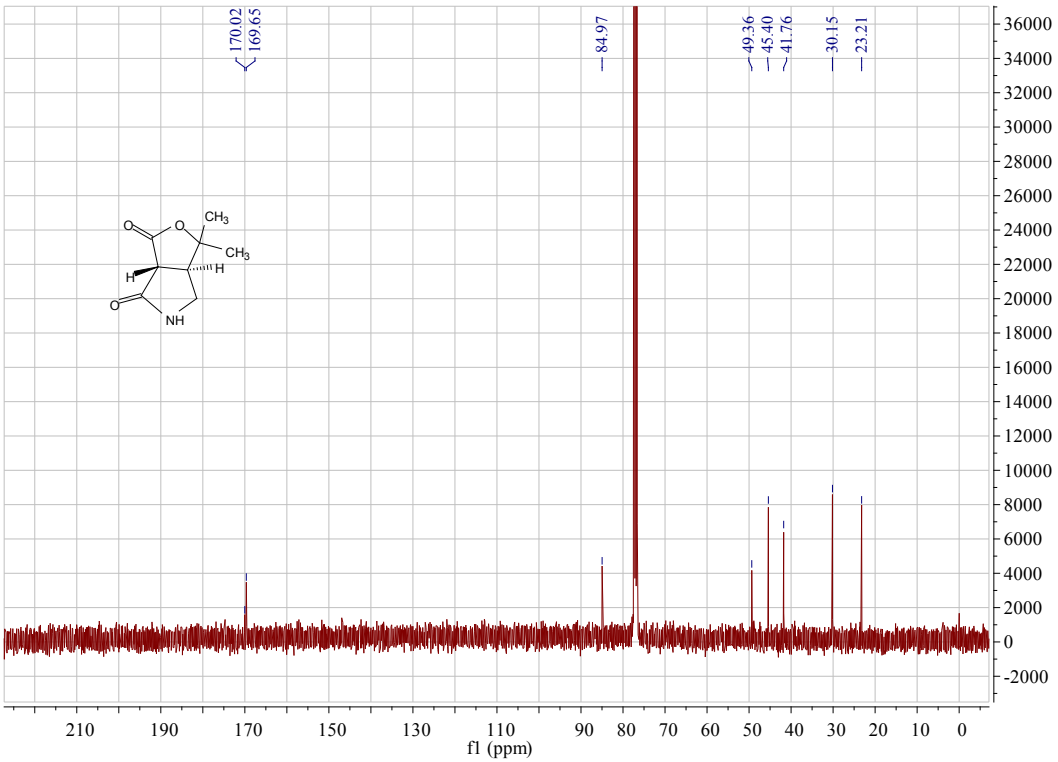
^{13}C NMR of product **3k** (100 MHz, $CDCl_3$)



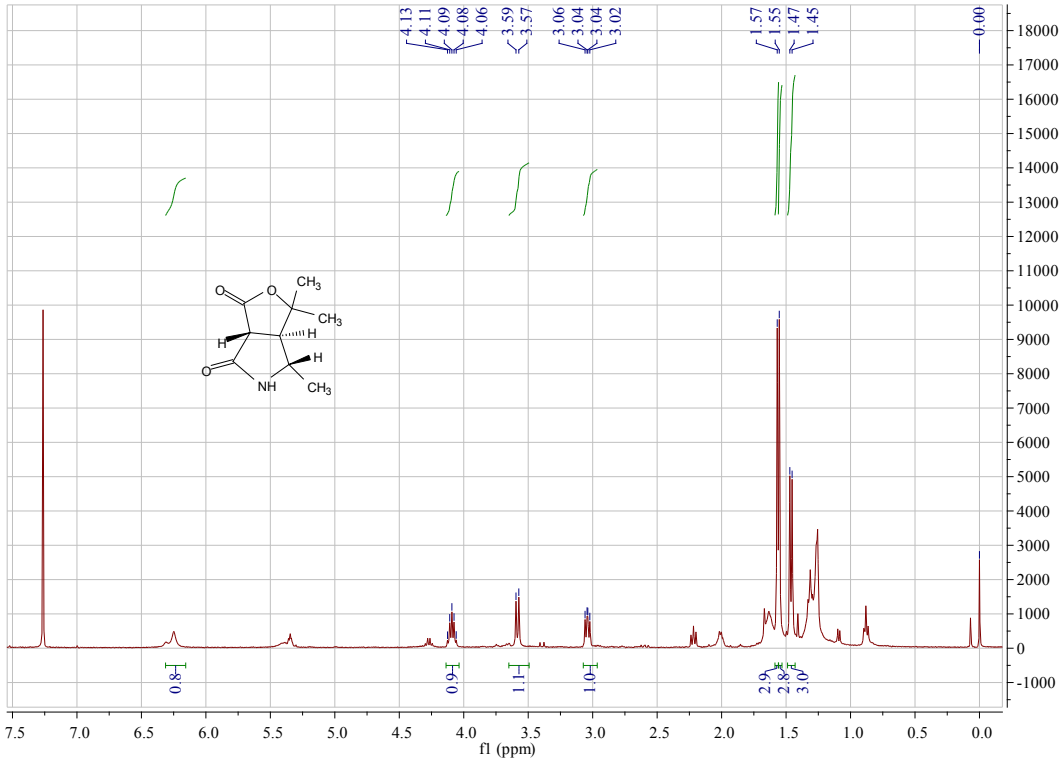
^{1}H NMR of product **4a** (400 MHz, $CDCl_3$)



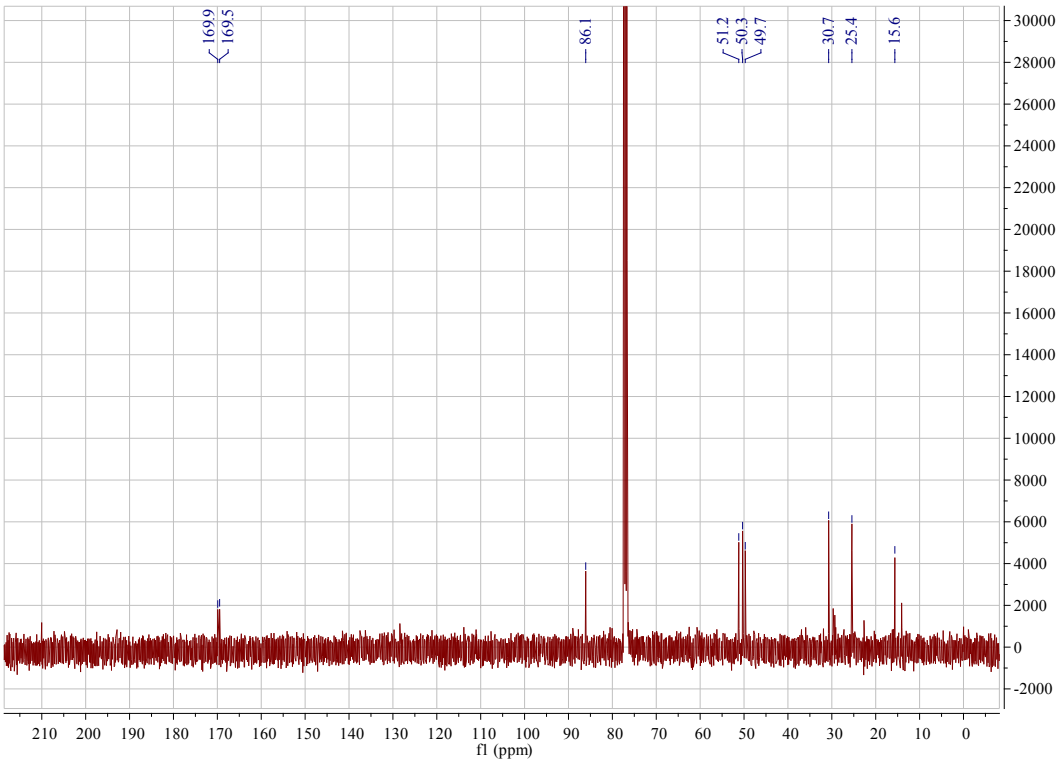
^{13}C NMR of product **4a** (100 MHz, $CDCl_3$)



^{1}H NMR of product **4b** (400 MHz, $CDCl_3$)

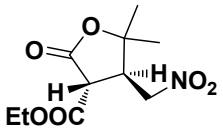


^{13}C NMR of product **4b** (100 MHz, $CDCl_3$)

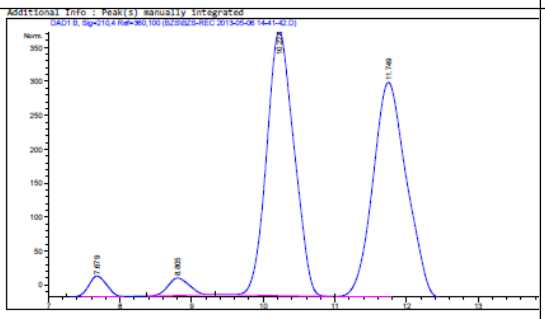


5. HPLCdata for Michael Product 3a-3k

HPLC Chromatogram of compound **3a.**



Racemic mixture	Table 2, Entry 1



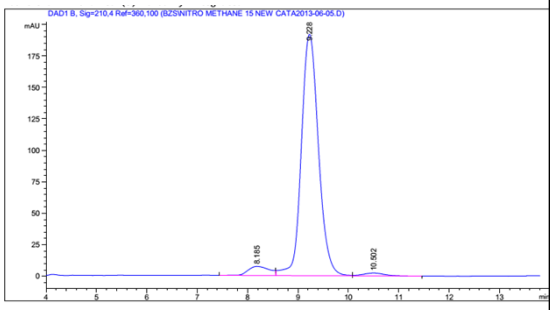
Additional Info : Peak(s) manually integrated

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount: : 1.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=210,4 Ref=360,100

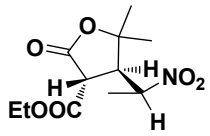
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.679	BB	0.2824	479.43060	27.63348	2.4487
2	8.805	BB	0.3330	479.44849	23.20952	2.4488
3	10.224	BB	0.3972	9334.16406	352.16232	47.6745
4	11.749	BB	0.4873	9285.91602	285.59573	47.4280



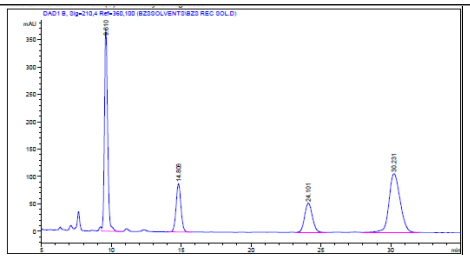
Signal 1: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.185	BV	0.4601	210.45428	7.13534	4.3759
2	9.228	VV	0.3677	4532.08789	191.78981	94.2351
3	10.502	VB	0.4591	66.79924	2.24508	1.3889
Totals :				4809.34142	201.17023	

HPLC Chromatogram of compound **3b.**

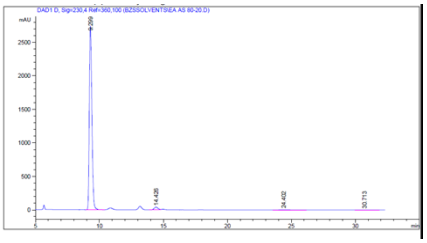


Racemic mixture	Table 2, Entry 2



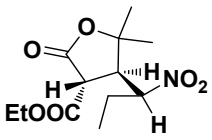
Signal 1: DAD1 B, Sig=210,4 Ref=360,100

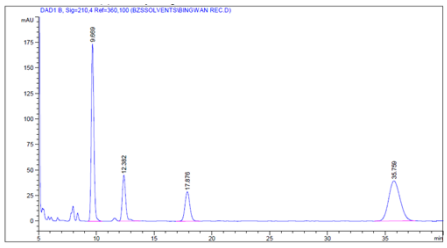
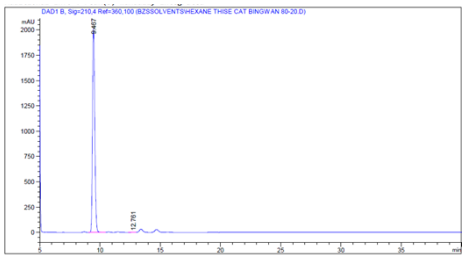
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.610	VB	0.2491	5814.24658	366.43619	36.6460
2	14.806	BB	0.3736	2120.25415	87.85077	13.3635
3	24.101	BB	0.5942	2039.05164	53.31689	12.8517
4	30.231	BB	0.8568	5892.41602	107.28045	37.1387
Totals :				1.58660e4	614.88430	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.299	BV	0.2202	3.86094e4	2743.70239	97.6102
2	14.426	BV	0.3309	874.50488	41.32291	2.2109
3	24.402	BB	0.6529	61.52068	1.43277	0.1555
4	30.713	BB	0.5737	9.26157	1.93732e-1	0.0234
Totals :				3.95547e4	2786.65180	

HPLC Chromatogram of compound **3c.**

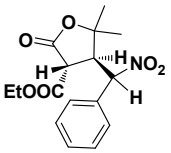


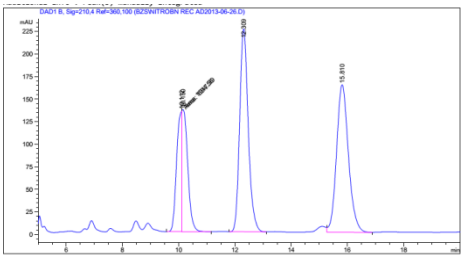
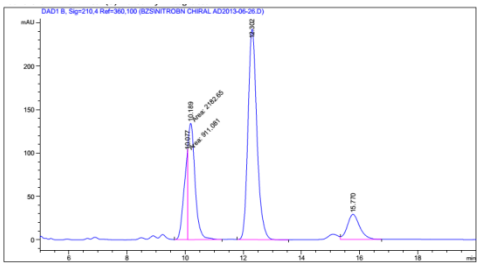
Racemic mixture	Table 2, Entry 3
	

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.669	BB	0.2423	2718.66821	173.94078	37.9743
2	12.382	VB	0.3109	903.26849	44.86479	12.6168
3	17.876	BB	0.4566	850.61334	28.79825	11.8814
4	35.759	BB	1.0626	2686.67407	39.24743	37.5274
Totals :				7159.22412	286.85125	

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.467	BV	0.2082	2.66029e4	2013.35388	99.9197
2	12.761	BV	0.2482	21.37728	1.29763	0.0803
Totals :				2.66242e4	2014.65151	

HPLC Chromatogram of compound **3d.**

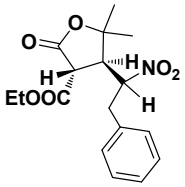


Racemic mixture of **3d**	Table 2, Entry 4
	

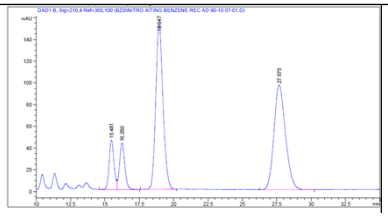
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.112	MF	0.2105	1694.56201	134.15448	12.8474
2	10.150	FM	0.2362	1917.39209	135.31453	14.5368
3	12.309	BB	0.3230	4754.72705	224.60738	36.0483
4	15.810	VB	0.4562	4823.19775	163.50340	36.5674
Totals :				1.31899e4	657.57979	

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.077	MF	0.1493	911.08057	101.67474	10.0110
2	10.189	FM	0.2714	2182.64771	134.03210	23.9831
3	12.302	BB	0.3260	5154.73096	242.48419	56.6406
4	15.770	VB	0.4487	852.30560	28.84732	9.3652
Totals :				9100.76483	507.03835	

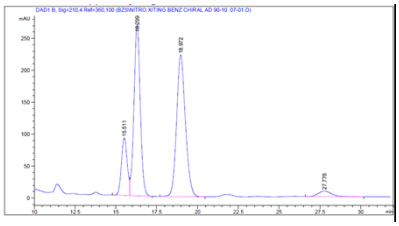
HPLC Chromatogram of compound **3e.**



Racemic mixture	Table 2, Entry 5



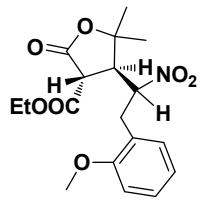
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.481	BV	0.3713	1107.49707	45.60907	8.2500
2	16.250	VB	0.4070	1143.24878	42.88718	8.5163
3	18.947	BB	0.5556	5573.38477	152.06178	41.5173
4	27.675	BB	0.8891	5600.11523	96.48758	41.7164
Totals :				1.34242e4	337.04560	



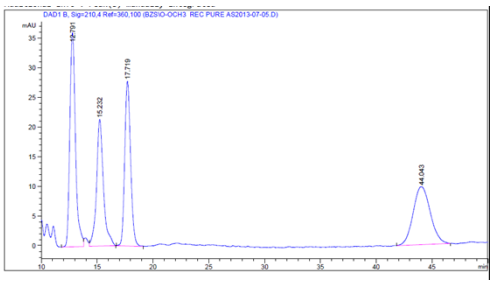
Signal 1: DAD1 B, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.511	BV	0.3803	2224.93896	90.02863	12.2145
2	16.299	VB	0.4103	7179.87451	268.24936	39.4162
3	18.972	BB	0.5692	8312.35547	221.83003	45.6334
4	27.776	BB	0.8489	498.35251	8.74437	2.7359
Totals :				1.82155e4	588.85239	

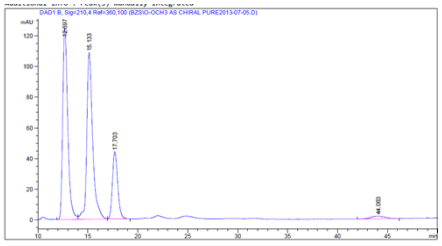
HPLC Chromatogram of compound **3f.**



Racemic mixture	Table 2, Entry 6

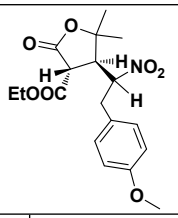


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.791	BV	0.5424	1271.72754	36.15346	29.9096
2	15.232	VB	0.6323	916.45563	21.37193	21.5540
3	17.719	BB	0.5603	1016.23969	27.80877	23.9008
4	44.043	BB	1.2791	1047.47681	9.78359	24.6355
Totals :				4251.89966	95.11776	

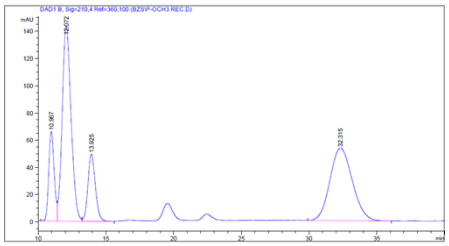


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.697	BV	0.5377	4371.77930	124.50440	41.1632
2	15.133	VV	0.6156	4466.12354	108.65039	42.0515
3	17.703	VB	0.5683	1610.70520	43.87527	15.1658
4	44.063	BB	1.2020	172.00444	1.69779	1.6195
Totals :				1.06206e4	278.72785	

HPLC Chromatogram of compound **3g.**



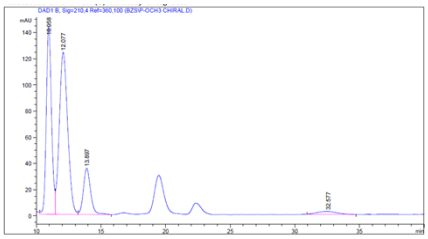
Racemic mixture



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.967	BV	0.4283	1824.89600	65.64371	11.1598
2	12.072	VV	0.6937	6505.58643	143.28404	39.7837
3	13.925	VB	0.5890	1878.09131	49.24165	11.4851
4	32.315	BB	1.7134	6143.83350	53.27548	37.5714

Totals : 1.63524e4 311.44489

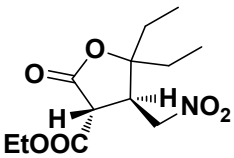
Table 2, Entry 7



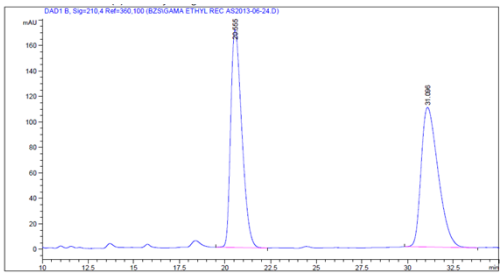
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.958	VV	0.4329	4015.32764	143.29182	35.7800
2	12.077	VV	0.6866	5587.58008	123.79060	49.7901
3	13.897	VB	0.5952	1375.69226	35.41244	12.2586
4	32.577	BB	1.2936	243.67989	2.22874	2.1714

Totals : 1.12223e4 304.72361

HPLC Chromatogram of compound **3h.**



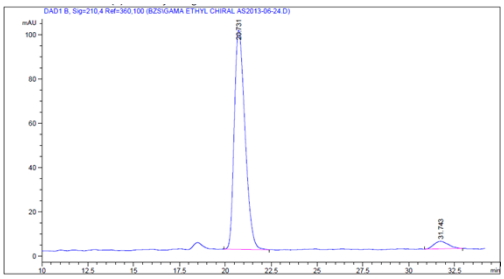
Racemic mixture



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.555	BB	0.6533	7230.00928	170.99091	50.5298
2	31.096	BB	1.0016	7078.39209	109.58506	49.4702

Totals : 1.43084e4 280.57597

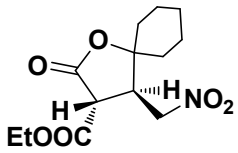
Table 2, Entry 8



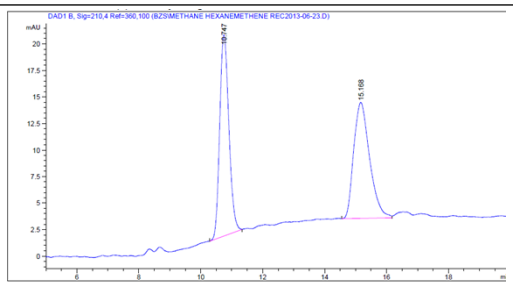
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.731	BB	0.6311	4031.81030	98.99634	95.5873
2	31.743	BB	0.6460	186.12582	3.40334	4.4127

Totals : 4217.93613 102.39968

HPLC Chromatogram of compound **3i.**

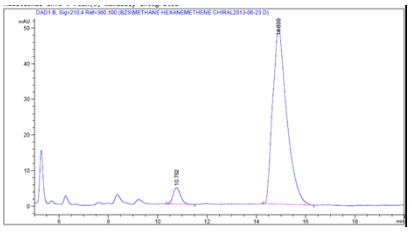


Racemic mixture



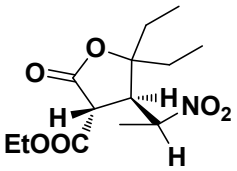
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.747	BB	0.3194	389.12885	18.96127	50.0051
2	15.168	BV	0.5471	389.05005	10.93441	49.9949
Totals :				778.17889	29.89568	

Table 2, Entry 9

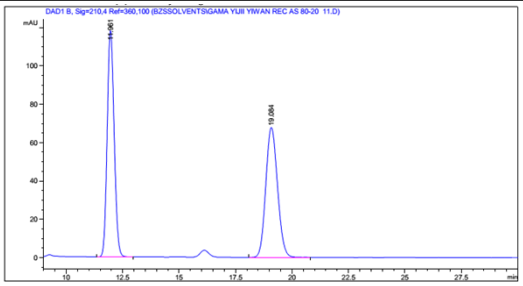


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.762	BB	0.3254	96.06737	4.64319	4.6869
2	14.899	BB	0.5434	1953.63293	49.61015	95.3131
Totals :				2049.70030	54.25334	

HPLC Chromatogram of compound **3j.**

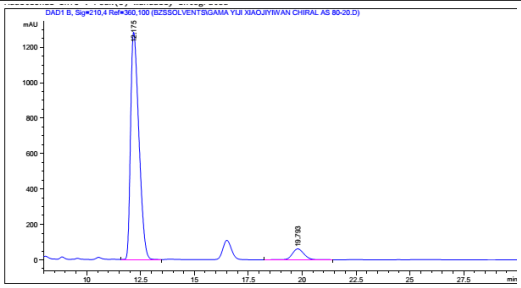


Racemic mixture



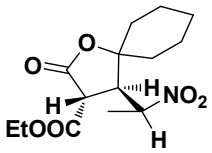
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.961	BB	0.3345	2535.04712	118.04479	50.9108
2	19.084	BB	0.5650	2444.33789	67.73736	49.0892
Totals :				4979.38501	185.78215	

Table 2, Entry 10

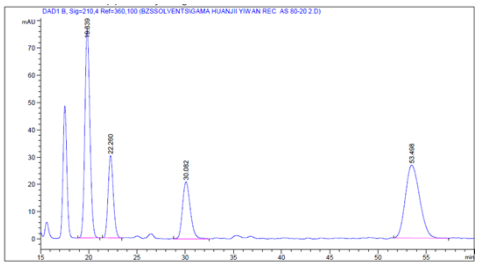


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.175	VV	0.4162	3.43700e4	1284.30383	93.6648
2	19.793	BB	0.5827	2324.68750	61.82207	6.3352
Totals :				3.66947e4	1346.12591	

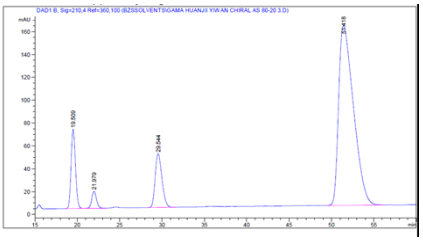
HPLC Chromatogram of compound **3k.**



Racemic mixture	Table 2, Entry 11



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.839	BB	0.5646	2788.66431	76.62232	35.6166
2	22.260	BB	0.5878	1132.90857	30.05264	14.4694
3	30.082	BB	0.8665	1160.43042	20.81116	14.8209
4	53.498	BB	1.6306	2747.66235	26.74439	35.0930
Totals :				7829.66565	154.23052	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.509	BB	0.5646	2497.84912	69.28511	10.0693
2	21.979	BB	0.5983	572.52618	14.83398	2.3080
3	29.544	BB	0.8629	2613.48926	47.13316	10.5355
4	51.418	BB	1.8897	1.91227e4	157.36131	77.0872
Totals :				2.48065e4	288.61356	