An Approach to Skeletal Diversity Using "Functional Group Pairing" of Multifunctional Scaffolds

Supporting Information

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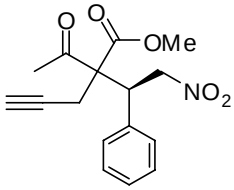
1. General Experimental Information:

^{1}H NMR and ^{13}C spectra were recorded at 400 MHz and 100.0 MHz respectively at ambient temperature with $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^{1}H, δ 7.26; ^{13}C, δ 77.0). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dt = doublet of triplets, dq = doublet of quartets, m = multiplet, br = broad), coupling constant, and integration. Coupling constants are reported as values in hertz (Hz). All ^{13}C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet Nexus 670 FTIR spectrophotometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and are reported as $[\alpha]_D^{20}$ (concentration in grams/100 mL solvent). High-resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory using a Finnegan MAT-90 spectrometer. Analytical and preparative HPLC were performed on a Waters FractionLynx System with a Waters 600 HPLC pump, MicroMass ZQ 2000 mass spectrometer, Waters 996 diode array, and a Sedere Sedex 75 ELS detector. Analytical thin layer chromatography was performed using Whatman Reagent 0.25 mm silica gel 60-A plates. Flash chromatography was carried out using an Isco CombiFlash system. Methylene chloride, THF, Diethyl ether, and toluene were purified and dried by passing through two packed columns of neutral alumina (Innovative Technologies, MA). Microwave reactions were performed using the Discover™ Explorer System (CEM Corp., Matthews, NC). A GeneVac HT-4 or EZ-2 (Genevac Inc.), was used for concentration and drying of solutions in vials or test tubes. The ArthurTM Suite Reaction Planner (Symyx Technologies, Inc.) was used for experimental procedure planning. Chiral high pressure liquid chromatography (HPLC) analyses were performed on compounds **4a**, **4b** and **4d** on a Hewlett-Packard 1100 Series instrument equipped with a quaternary pump using a Daicel Chiralcel OJ or OD Column (250 x 4.6 mm) with UV detection monitored at 220 nm or 215 nm. Chiral HPLC analyses on all other compounds was performed on a Waters 717 plus autosampler instrument equipped with a Waters binary 1525 pump, using a Daicel Chiralcel OD-H Column. UV detection was monitored at 214 nm and at 254 nm.

2. Stereoselective generation of multifunctional scaffolds

(*E*)-*o*-Allyl-β-nitrostyrene 3b. To a solution of *trans*-2-bromo-β-nitrostyrene[1] (**3c**) (877 mg, 3.84 mmol) in THF (10 mL) was added allyltributyltin (1.6 mL, 5.0 mmol) and tetrakis(triphenylphosphine)palladium(0) (400 mg, 0.4 mmol) under argon. The reaction was heated under microwave conditions at 140°C (300 watts) for 30 min. The reaction was concentrated and then dissolved in acetonitrile. Hexanes were then used to extract the tin-containing byproducts and the reaction was concentrated under vacuum. Chromatography over SiO_2 (10% EtOAc in pet. ether) provided nitromalonate **3b** (674 mg, 93%) as a yellow oil. This material had properties in good agreement with that reported in the literature.[2]

1-(3-Methoxyprop-1-ynyl)-2-((*E*)-2-nitrovinyl)benzene 3d. To a solution of *trans*-2-bromo-β-nitrostyrene[1] (**3c**) (200 mg, 0.9 mmol) in THF (3 mL) was added *N*,*N*-diisopropylamine (1 mL). Argon was bubbled through this solution for 15 min. To the reaction was added tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.03 mmol), copper (I) iodide (10 mg, 0.05 mmol) and methyl propargyl ether (96 μL, 1.1 mmol). The reaction was irradiated under microwave conditions at 100°C (300 watts) for 40 min. The reaction was concentrated under vacuum. Chromatography over SiO_2 (10% EtOAc in pet. ether) provided **3d** (130 mg, 70%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 13.8, 1H), 7.71 (d, *J* = 13.8, 1H), 7.59-7.56 (m, 2H), 7.46-7.37 (m, 2H), 4.41 (s, 2H), 3.51 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 138.5, 137.1, 133.9, 131.7, 131.7, 129.3, 127.6, 124.9, 92.9, 83.5, 60.6, 58.2; IR (thin film) ν_{max} 2931, 2824, 1520, 1341, 1100 cm^{-1}; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{12}H_{12}NO_3$ 218.0817, found 218.0795.



4a

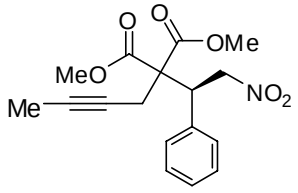
Methyl 2-acetyl-2-((*S*)-2-nitro-1-phenylethyl)pent-4-ynoate 4a: To a solution of *trans*-β-nitrostyrene[3] (15 mg, 0.1 mmol) in THF (0.1 mL) was added ketoester **2a**[4] (30 mg, 0.2 mmol). The solution was stirred at -20 °C for 1 h. To this solution was added catalyst **5c**[5] (10 mol%). The reaction mixture was stirred at -20 °C for 16 h then filtered through a plug of silica gel for removal of the catalyst using diethyl ether as eluant. The filtrate was concentrated *in vacuo* to afford a crude mixture of two compounds which are diastereomeric at the ester-bearing stereocenter. Chromatography over SiO_2 (10% EtOAc in pet. ether) provided the major and minor adducts of **4a** (22 mg, 73%) in a ratio of 2.6/1. The major diastereoisomer was isolated in 99% ee (as determined by HPLC analysis [Daicel chiralcel OD, Hexanes:IPA, 90:10, 1.0 mL/min, λ 220 nm, t (major) = 13.5 min, t (minor) = 10.7 min]) as a white

(1) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829.
(2) Knight, J.; Parsons, P. J. *J. Chem. Soc. Perkin Trans 1* **1989**, *5*, 979.
(3) Commercially available from Aldrich.
(4) Prepared according to the procedure of; Cruciani, P.; Stammler, R.; Corinne, A.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699.
(5) Prepared according to the procedure of; Wang, H. Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc*. **2004**, *32*, 9906.

solid mp 132-134 ºC (from EtOAc/Hexane). The minor diastereoisomer was isolated in 88% ee as determined by HPLC analysis [Daicel Chiralcel OD, Hexanes:IPA, 90:10, 1.0 mL/min, λ 220 nm, t (major) = 13.0 min, t (minor) = 10.3 min] as a white solid. m.p. 88-90ºC (from EtOAc/Hexane).

Major diastereoisomer; ^{1}H NMR (400 MHz $CDCl_3$): δ 7.25 (m, 3H), 7.16 (m, 2H), 5.19 (ddd, *J* = 0.6, *J* = 3.5, *J* = 13.7, 1H), 5.04 (dd, *J* = 11.4, *J* = 13.6, 1H), 4.46 (dd, *J* = 3.3, *J* = 11.5, 1H), 3.62 (s, 3H), 2.78 (ddd, *J* = 10.2, *J* = 18.0, *J* = 20.5, 2H), 2.16 (t, *J* = 2.8, 1H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.1, 169.5, 135.1, 129.2, 129.1, 128.9, 78.7, 76.8, 74.0, 65.2, 53.3, 46.4, 28.3, 22.1; IR (thin film) ν_{max} 3290, 2924, 1718, 1652, 1554, 1217, 1089 cm^{-1}; $[\alpha]_D^{23}$ = -2.8^o (c = 0.8, CH_2Cl_2). HRMS (CI/NH_3) $[M+Na]^+$ calcd for $C_{16}H_{17}NO_5Na$ 326.1004, found 326.1014.

Minor diastereoisomer: ^{1}H NMR (400 MHz) δ 7.25 (m, 3H), 7.09 (m, 2H), 5.02 (dd, *J* = 3.3, *J* = 13.7, 1H,), 4.83 (dd, *J* = 11.3, *J* = 13.6, 1H), 4.39 (dd, *J* = 3.2, *J* = 11.3, 1H), 3.79 (s, 3H), 2.48 (ddd, *J* = 2.7, *J* =17.8, *J* = 13.9, 1H), 2.65 (dd, *J* = 2.7, *J* = 17.8, 1H,), 2.31 (dd, *J* = 2.7, *J* = 17.8, 1H,), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 170.2, 135.1, 129.2, 128.9, 128.9, 77.8, 77.6, 74.1, 65.2, 53.4, 45.0, 27.1, 23.4 IR (thin film) ν_{max} 3289, 2923, 1718, 1554, 1218, 1090 cm^{-1}; $[\alpha]_D^{23}$ = 6.7^o (c = 0.2, CH_2Cl_2). HRMS (CI/NH_3) $[M+Na]^+$ calcd for $C_{16}H_{17}NO_5Na$ 326.1004, found 326.1019.

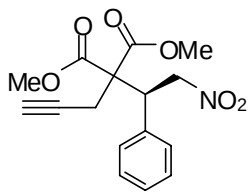


4b

Dimethyl 2-(but-2-ynyl)-2-((*S*)-2-nitro-1-phenylethyl)malonate 4b: To a solution of *trans*-β-nitrostyrene[3] (15 mg, 0.1 mmol) in THF (0.1 mL) was added dimethyl 2-(but-2'-yn-1'-yl)malonate (**5**)[6] (37 mg, 0.2 mmol). The solution was stirred at -20 ^{o}C for 1 h. To the solution was added catalyst **5a**[7] (3.1 mg, 10 mol %).The reaction mixture was stirred at -20 ^{o}C for 48 h and then filtered through a plug of silica gel for the removal of the catalyst using diethyl ether as eluant. The filtrate was concentrated *in vacuo.* Chromatography over SiO_2 (10% EtOAc in pet. ether) provided **4b** (28 mg, 85%) in 90% ee (as determined by HPLC analysis [Daicel Chiralcel OJ, Hexanes:IPA, 90:10, 1.0 mL/min, λ 220 nm, t (major) = 20.7 min, t (minor) = 24.7 min]) as a white solid. m.p. 76-78ºC (from EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H) 7.18 (m, 2H), 5.31 (dd, *J* = 3.2, 13.7, 1H), 5.03 (dd, *J* = 11.4, 13.7, 1H), 4.50 (dd, *J* = 3.2, 11.4, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.74 (dq, *J* = 2.5, 17.2, 1H), 2.35 (dq, *J* = 2.6, 17.2, 1H), 1.86 (t, *J* = 2.6, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.6, 131.2, 125.2, 125.1, 125.0, 77.3, 74.0, 69.1, 56.3, 49.5, 49.4, 41.8, 20.5, 0.0 ; IR (thin film) ν_{max} 2956, 1737, 1555, 1216, 1088 cm^{-1}; $[\alpha]_D^{23}$ = -14.2^o (c = 0.7, CH_2Cl_2). HRMS (CI/NH_3) $[M+Na]^+$ calcd for $C_{17}H_{20}NO_6$ 334.1291, found 334.1298.

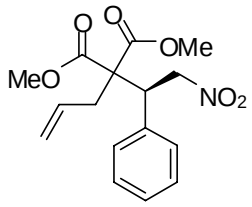
(6) Prepared according to the procedure of; Zhao, L.; Lu, X.; Xu W. *J. Org. Chem.* **2001**, *70*, 4059.

(7) Li, H., Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105.



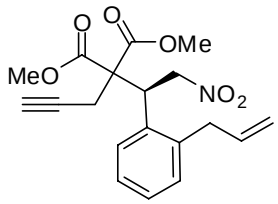
4c

Dimethyl 2-((*S*)-2-nitro-1-phenylethyl)-2-(prop-2-ynyl)malonate 4c: To a solution of *trans*-β-nitrostyrene[3] (30 mg, 0.2 mmol) in THF (0.2 mL) was added dimethyl propargylmalonate[8] **2d** (68 mg, 0.4 mmol). The solution was stirred at -40 °C for 3 h. To this solution was added catalyst **5c**[5] (9.8 mg, 10 mol%). The reaction mixture was stirred at -40 °C for 3 d and then filtered through a plug of silica gel for the removal of the catalyst using diethyl ether as eluant. The filtrate was concentrated *in vacuo*. Chromatography over SiO_2 (20% EtOAc in pet. ether) provided nitromalonate **4c** (29 mg, 45%) in 92% ee (as determined by HPLC analysis [Daicel Chiralcel OD-H, Hexanes:IPA, 98:2, 1.0 mL/min, λ 214 nm, t (major) = 16.8 min, t (minor) = 14.2 min]) as a white waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 3H) 7.19 (m, 2H), 5.30 (dd, *J* = 3.1, *J* = 13.7, 1H), 5.02 (dd, *J* = 11.3, *J* = 13.7, 1H), 4.52 (dd, *J* = 3.1, *J* = 11.3, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 2.79 (dd, *J* = 2.7, *J* = 17.4, 1H), 2.39 (dd, *J*=2.7, *J*=17.4, 1H) 2.23 (t, *J* = 2.7, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 169.2, 134.8, 129.2, 129.0, 128.9, 78.3, 77.8, 73.6, 59.8, 53.5, 53.4, 45.6, 24.2 ; IR (thin film) ν_{max} 3290, 2956, 1737, 1556, 1216, 1089 cm^{-1}; $[\alpha]_D^{23}$ = 3.2° (c = 0.8, CH_2Cl_2); HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{16}H_{18}NO_6$ 320.1134, found 320.1159.



4d

(*S*)-dimethyl 2-allyl-2-(2-nitro-1-phenylethyl)malonate 4d: To a solution of *trans*-β-nitrostyrene[3] (15 mg, 0.1 mmol) in THF (0.2 mL) was added dimethyl allylmalonate[3] **2e** (34 mg, 0.2 mmol). The solution was cooled to -20 °C for 3 h. To this solution was added catalyst **5c**[5] (5 mg, 10 mol%). The reaction mixture was cooled at -30 °C for 5 d and then then filtered through a plug of silica gel for the removal of the catalyst using diethyl ether as eluant. The filtrate was concentrated *in vacuo*. Chromatography over SiO_2 (15% EtOAc in pet. ether) provided nitromalonate **4d** (14 mg, 44%) in 90% ee (as determined by HPLC analysis [Daicel Chiralcel OD, Hexanes:IPA, 98:2, 1.0 mL/min, λ 214 nm, t (major) = 14.6 min, t (minor) = 7.7 min] as a yellow oil.) This material had properties in good agreement with those reported in the literature for (±) **4d**[9]. $[\alpha]_D^{23}$ = 36.4° (c = 0.3, CH_2Cl_2).



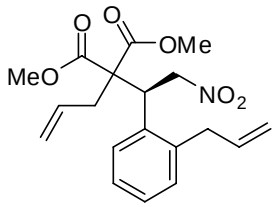
4e

Dimethyl 2-((*S*)-1-(2-allylphenyl)-2-nitroethyl)-2-(prop-2-ynyl)malonate 4e: To a solution of (*E*)-*o*-allyl-β-nitrostyrene (**3b**) (380 mg, 2.0 mmol) in THF (2 mL) was added dimethyl propargylmalonate[3] (600 μL, 4.0 mmol). The solution was stirred at -20 °C for 1 h. To this was added catalyst **5c** (100 mg, 10 mol%). The reaction mixture was stirred at -20 °C for 7 d and then then filtered through a plug of silica gel for the removal of the catalyst using diethyl ether as eluant. The filtrate was concentrated *in vacuo.* Chromatography over SiO_2 (20% EtOAc in pet. ether) provided **4e** (254 mg, 35%) in 95% ee (as determined by HPLC analysis [Daicel Chiralcel OD-H,

(8) Commercially available from Fluka.

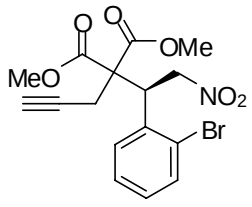
(9) Tu, Z.; Jang, Y.; Lin, C.; Liu, J.-T.; Hsu, J.; Sastry, M. N. V.; Yao, C.-F. *Tetrahedron* **2005**, *61*, 10541.

Hexanes:IPA, 90:10, 1.0 mL/min, λ 254 nm, t (major) = 6.1 min, t (minor) = 8.7 min]) as a white solid. mp 84-86 ºC (from EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 7.16 (m, 1H), 6.93 (m, 1H), 5.92 (m, 1H), 5.32 (dd, *J* = 3.0, 13.2, 1H), 5.15 (m, 1H), 5.12 (t, *J* = 1.4, 1H), 4.97 (dd, *J* = 10.8, 13.1, 1H), 4.86 (dd, *J* = 3.0, 10.9, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.66 (m, 2H), 2.82 (dd, *J* = 2.8, 17.3, 1H,), 2.38 (dd, *J* = 2.7, 17.3, 1H), 2.16 (t, *J* = 2.7, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.4, 141.0, 137.1, 133.1, 130.5, 128.6, 126.9, 126.6, 117.0, 79.0, 78.9, 73.3, 60.8, 53.5, 53.4, 40.3, 36.4, 23.9; IR (thin film) ν_{max} 3288, 2953, 1737, 1556, 1211cm^{-1}; $[\alpha]_D^{23}$ = 17.0^o (c = 0.4, CH_2Cl_2). HRMS (CI/NH_3) $[M+Na]^+$ calcd for $C_{19}H_{21}NO_6Na$ 382.1267, found 382.1264.



4f

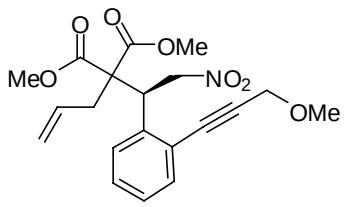
Dimethyl 2-allyl-2-((*S*)-1-(2-allylphenyl)-2-nitroethyl)malonate 4f: To a solution of (*E*)-*o*-allyl-β-nitrostyrene (**2b**) (238 mg, 1.3 mmol) in THF (1.3 mL) was added dimethyl allylmalonate[3] (600 μL, 4.0 mmol). The solution was stirred at -20 ^{o}C for 2 h. To this was added catalyst **5c** (100 mg, 10 mol%).The reaction mixture was stirred at -20 ^{o}C for 15 d and then filtered through a plug of silica gel for the removal of the catalyst using diethyl ether as eluant. The filtrate was concentrated *in vacuo.* Chromatography over SiO_2 (20% EtOAc in pet. ether) provided **4f** (248 mg, 55%) in 92% ee (as determined by HPLC analysis [Daicel chiralcel OD-H, Hexanes:IPA, 99:1, 1.0 mL/min, λ 214 nm, t (major) = 18.0 min, t (minor) = 7.2 min]) as a white solid. m.p. 81-83 ºC (from EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 2H) 7.17 (m, 1H), 6.97 (m, 1H), 5.91 (m, 1H), 5.74 (m, 1H), 5.16 (m, 1H,), 5.12 (m, 1H), 5.03 (m, 2H), 4.98 (m, 2H), 4.70 (t, *J* = 7.0, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.62 (m, 1H), 3.49 (dd, *J* = 7.2, *J* = 15.9, 1H), 2.47 (dd, *J* = 6.1, *J* = 14.1, 1H), 2.26 (dd, *J* = 8.2, *J* = 14.1, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.3, 140.4, 137.0, 133.4, 133.0, 131.0, 128.4, 127.0, 126.5, 119.3, 117.1, 79.3, 62.4, 52.9, 52.9, 42.2, 39.3, 36.7 ; IR (thin film) ν_{max} 2955, 1737, 1649, 1555, 1208, 1087cm^{-1}; $[\alpha]_D^{23}$ = 23.2^o (c = 0.3, CH_2Cl_2); HRMS (CI/NH_3) $[M+Na]^+$ calcd for $C_{19}H_{23}NO_6Na$ 384.1423, found 384.1417.



4g

Dimethyl 2-((*R*)-1-(2-bromophenyl)-2-nitroethyl)-2-(prop-2-ynyl)malonate 4g: To a solution of (*E*)-2-bromo-β-nitrostyrene (**3c**)[1] (395 mg, 1.73 mmol) in THF (1.7 mL) was added dimethyl propargylmalonate[8] (589 mg, 3.46 mmol). The solution was stirred at -20 ^{o}C for 2 h. To the solution was added catalyst **5c** (85 mg, 10 mol%). The reaction mixture was stirred at -20 ^{o}C for 5 d and then filtered through a plug of silica gel for the removal of the catalyst using diethyl ether as eluant. The filtrate was concentrated *in vacuo.* Chromatography over SiO_2 (20% EtOAc in pet. ether) provided **4g** (598 mg, 87%) in 97% ee (as determined by HPLC analysis [Daicel Chiralcel OD-H, Hexanes:IPA, 95:05, 1.0 mL/min, λ 254 nm, t (major) = 18.2 min, t (minor) = 13.6 min]) as a white solid. m.p. 58-60 ºC (from Methylene chloride/2,2,4-Trimethylpentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9, 1H), 7.27 (t, *J* = 7.3, 1H,), 7.14 (m, 2H), 5.19 (dd, *J* = 1.9, *J* = 12.3, 1H,), 5.07 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 2.73 (m, 2H), 2.08 (t, *J* = 2.3, 1H); δ

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 169.2, 134.7, 134.2, 130.2, 128.6, 128.3, 127.4, 78.9, 78.1, 72.9, 60.9, 53.6, 53.4, 44.9, 23.9; IR (thin film) ν_{max} 3291, 2955, 1736, 1650, 1556, 1211, 1087 cm^{-1}; $[\alpha]_D^{23}$ = 13.9^o (c = 0.8, CH_2Cl_2); HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{16}H_{17}NO_6Br$ 398.0239, found 398.0259.

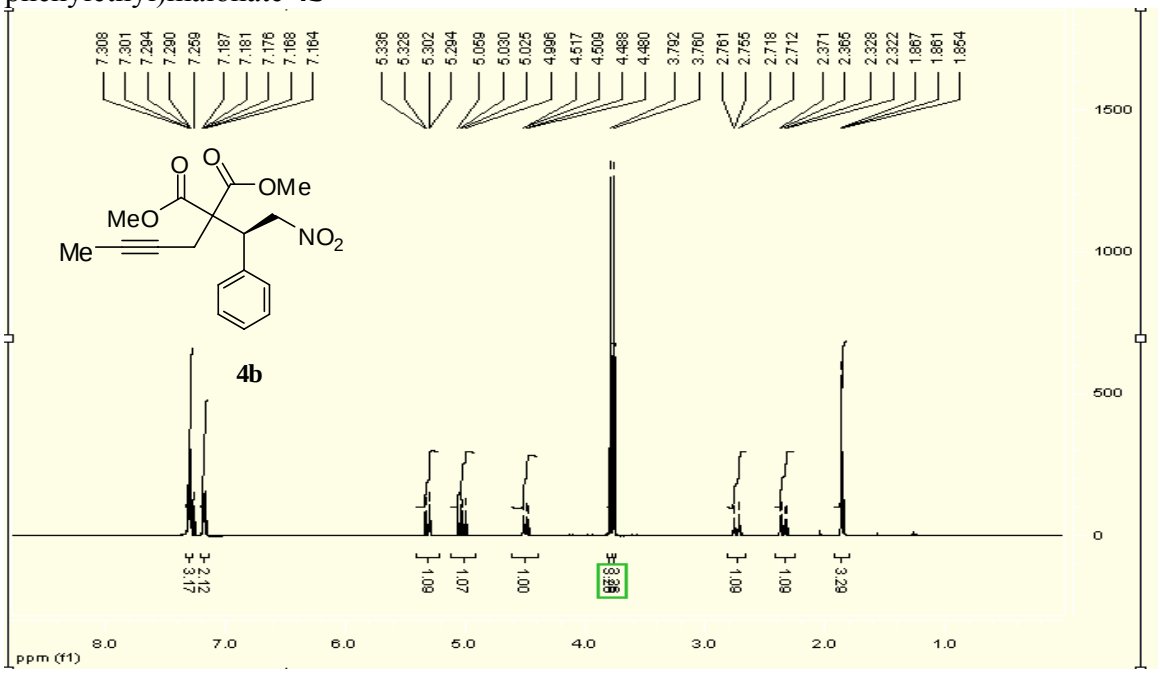


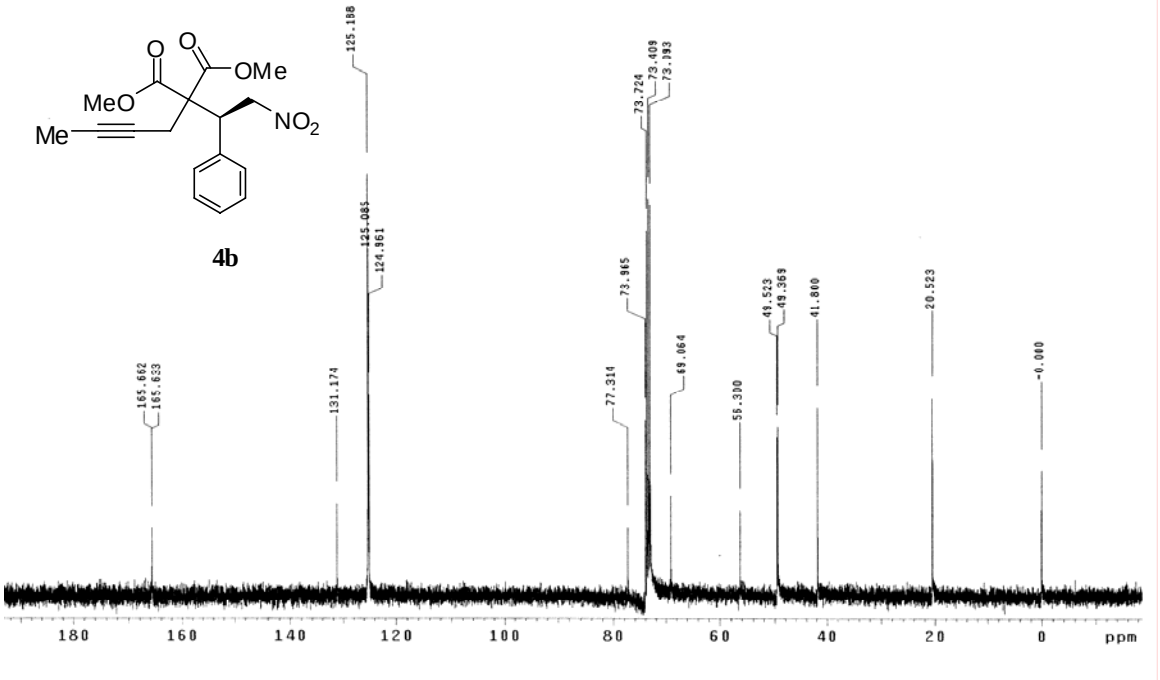
4h

Dimethyl 2-allyl-2-((*S*)-1-(2-(3-methoxyprop-1-ynyl)phenyl)-2-nitroethyl)malonate 4h: To a solution of 1-(3-methoxyprop-1-ynyl)-2-((*E*)-2-nitrovinyl)benzene **3d** (180 mg, 0.83 mmol) in THF (0.8 mL) was added dimethyl allylmalonate[3] **2d** (400 µl, 2.0 mmol). The solution was stirred at -20 ^{o}C for 2 h. To this was added catalyst **5c** (40 mg, 10 mol%).The reaction mixture was stirred at -20 ^{o}C for 5 d and then filtered through a plug of silica gel for the removal of the catalyst using diethyl ether as an eluant. The filtrate was concentrated *in vacuo.* Chromatography over SiO_2 (20% EtOAc / pet. ether) provided **4h** (133 mg, 41%) in 96% ee (as determined by HPLC analysis [Daicel Chiralcel OD-H, Hexanes:IPA, 90:10, 1.0 mL/min, λ 254 nm, t (major) = 13.6 min, t (minor) = 4.9 min]) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 1H), 7.27 (m, 2H), 7.27 (m, 1H), 5.86 (tdd, *J* = 17.5, *J* = 10.4, *J* = 7.3, *J* = 7.3, 1H), 5.02 (m, 5H), 4.41 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 3.53 (s, 3H), 2.48 (m, 2H); ^{13}CNMR (100 MHz, d6-acetone) δ 170.0, 169.7, 137.6, 133.6, 133.1, 129.4, 128.4, 127.1, 125.3, 118.5, 91.0, 84.4, 78.6, 62.3, 60.0, 57.1, 52.5, 52.4, 44.8, 39.1; IR (thin film) ν_{max} 3074, 2988, 2829, 1733, 1556, 1437, 1218, 1098 cm^{-1}; $[\alpha]_D^{23}$ = 10.7^o (c = 0.9, CH_2Cl_2); HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{20}H_{24}NO_7$ 390.1553, found 390.1556.

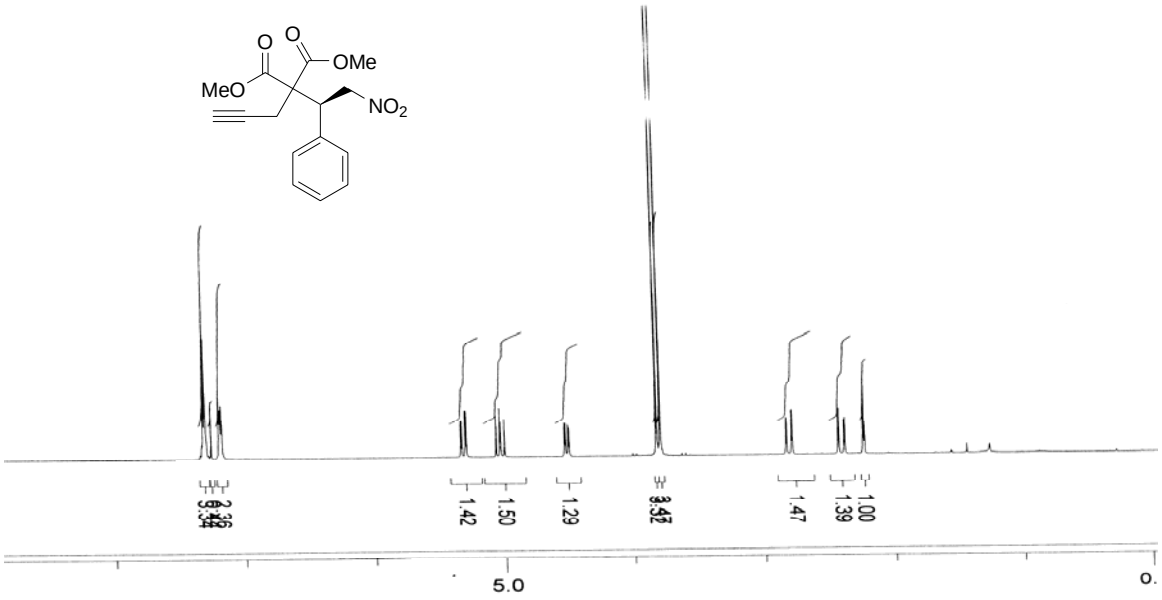
3. Select NMR spectra for multifunctional scaffolds

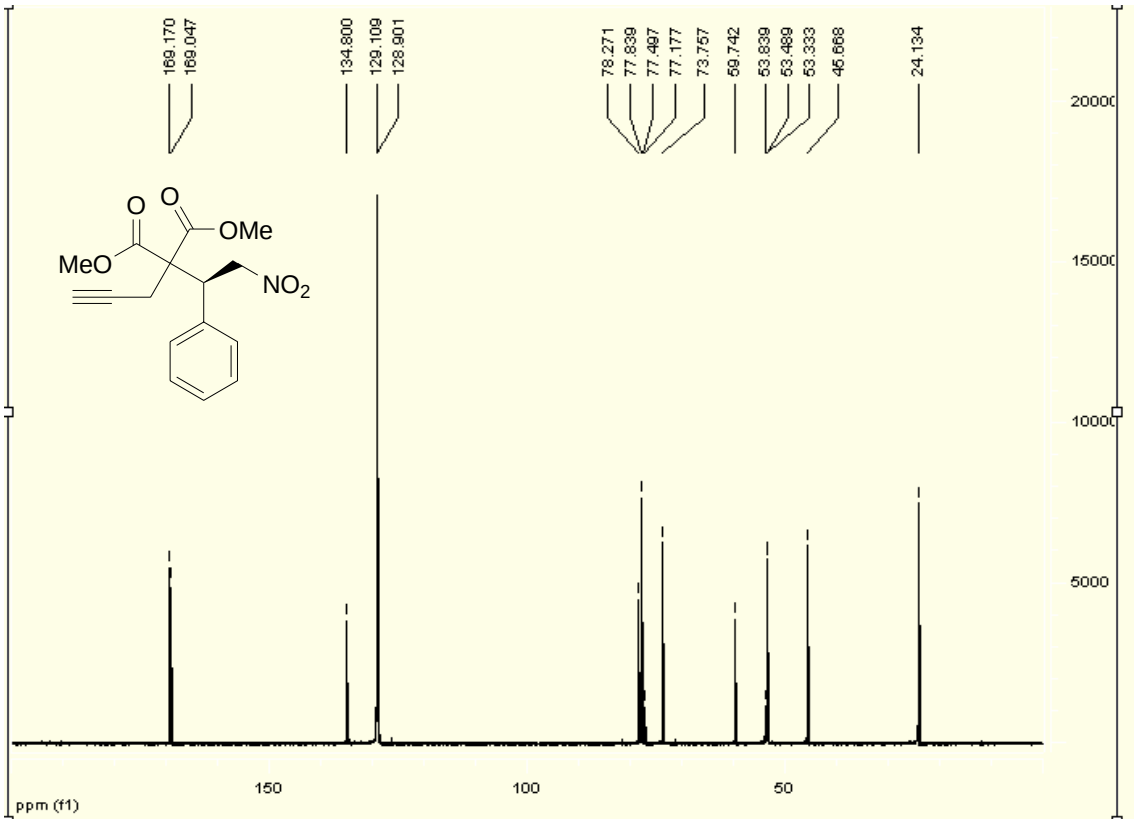
^{1}H and ^{13}C NMR spectra for dimethyl 2-(but-2-ynyl)-2-((*S*)-2-nitro-1-phenylethyl)malonate **4b**



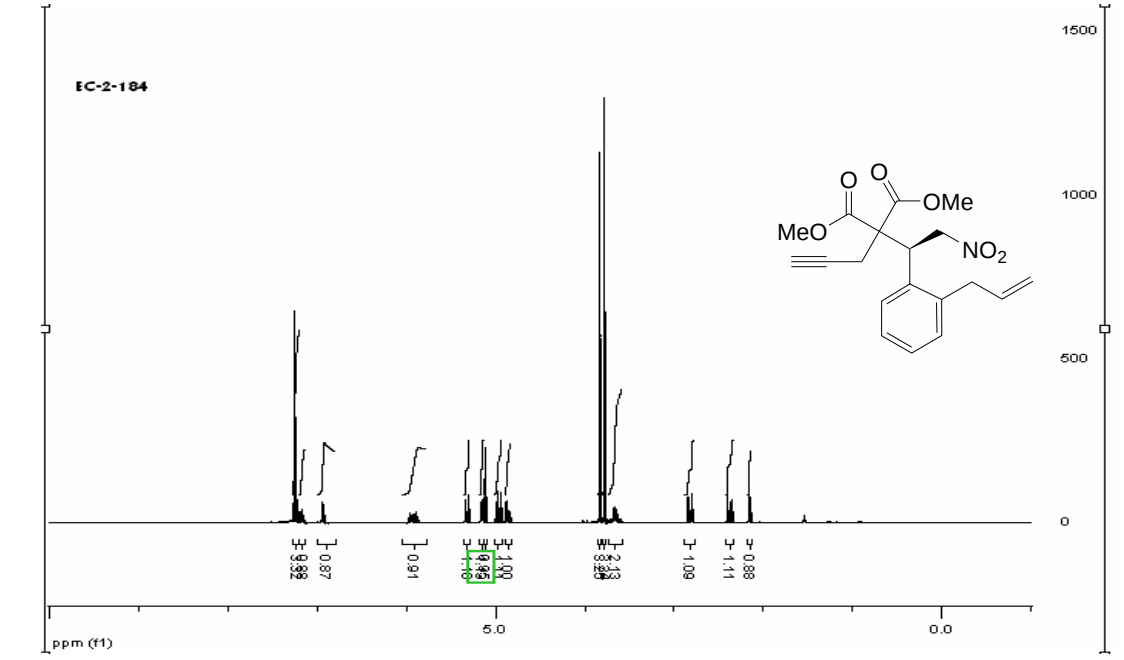


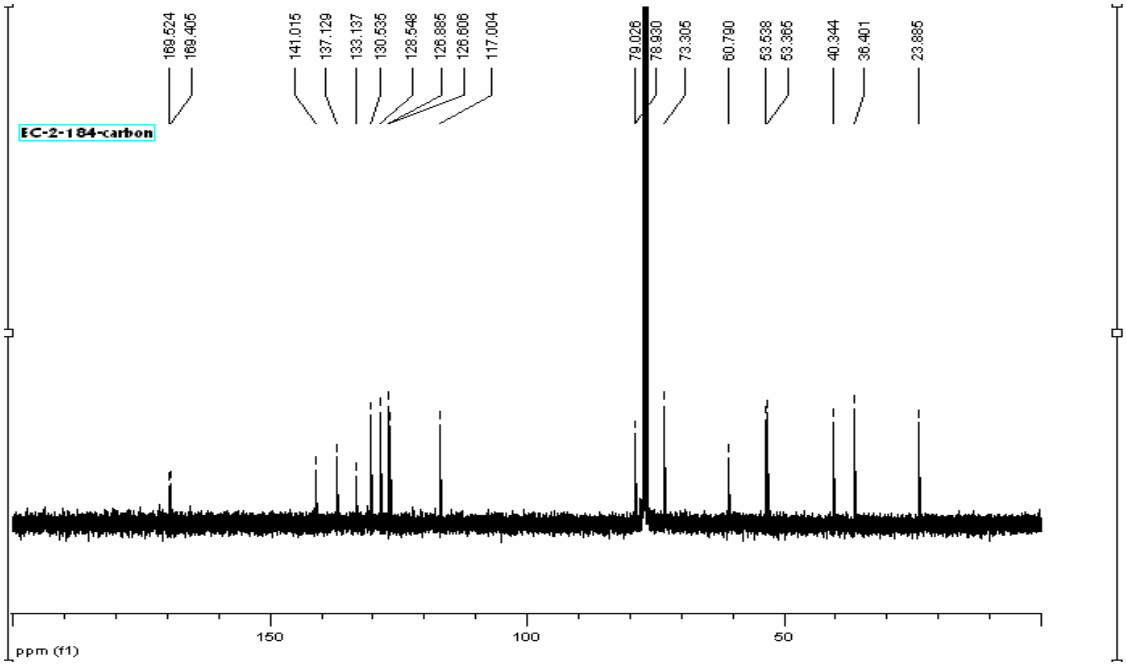
^{1}H and ^{13}C NMR spectra for dimethyl 2-((*S*)-2-nitro-1-phenylethyl)-2-(prop-2-ynyl)malonate **4c**



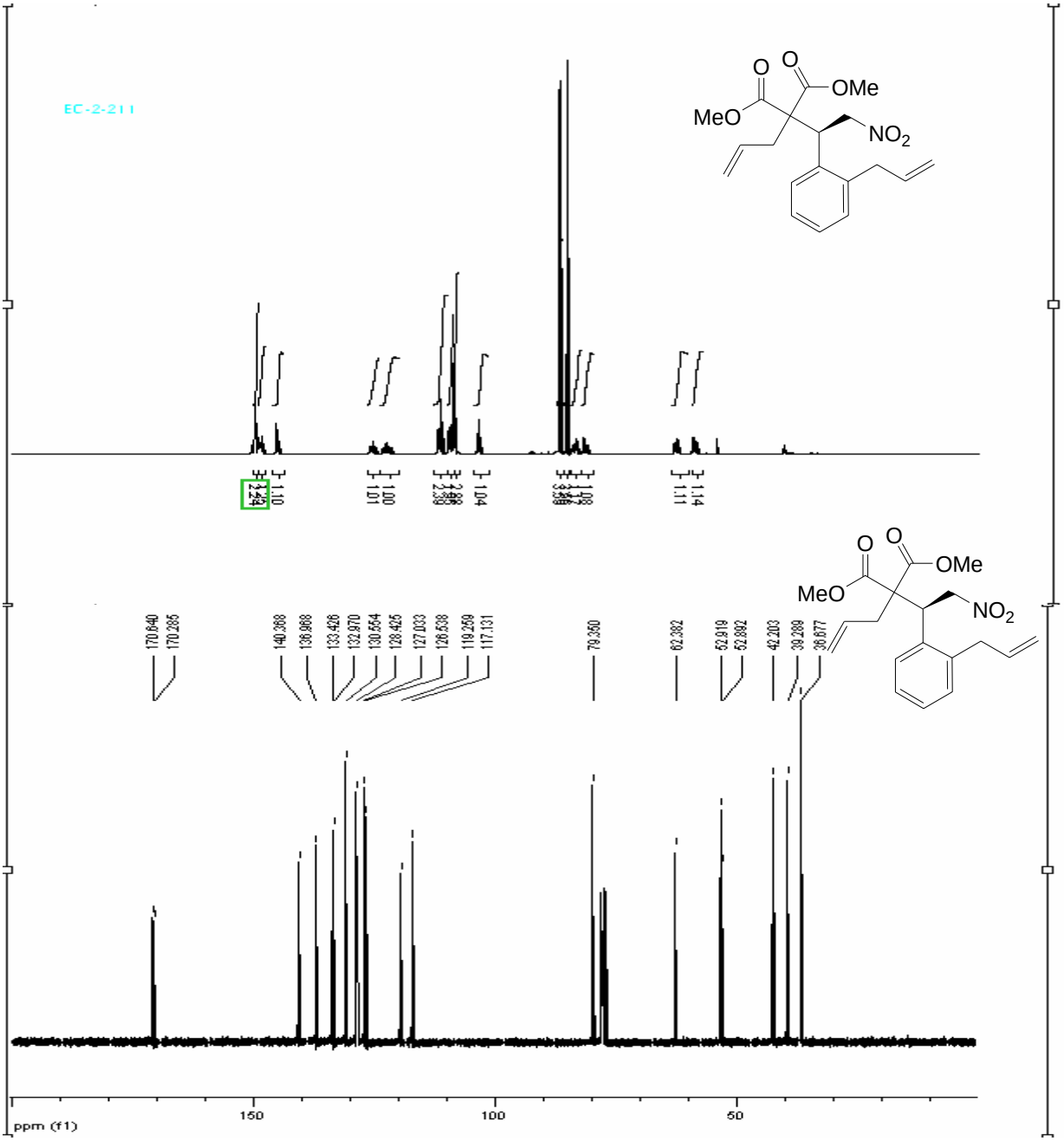


^{1}H and ^{13}C NMR spectra for dimethyl 2-((*S*)-1-(2-allylphenyl)-2-nitroethyl)-2-(prop-2-ynyl)malonate **4e**

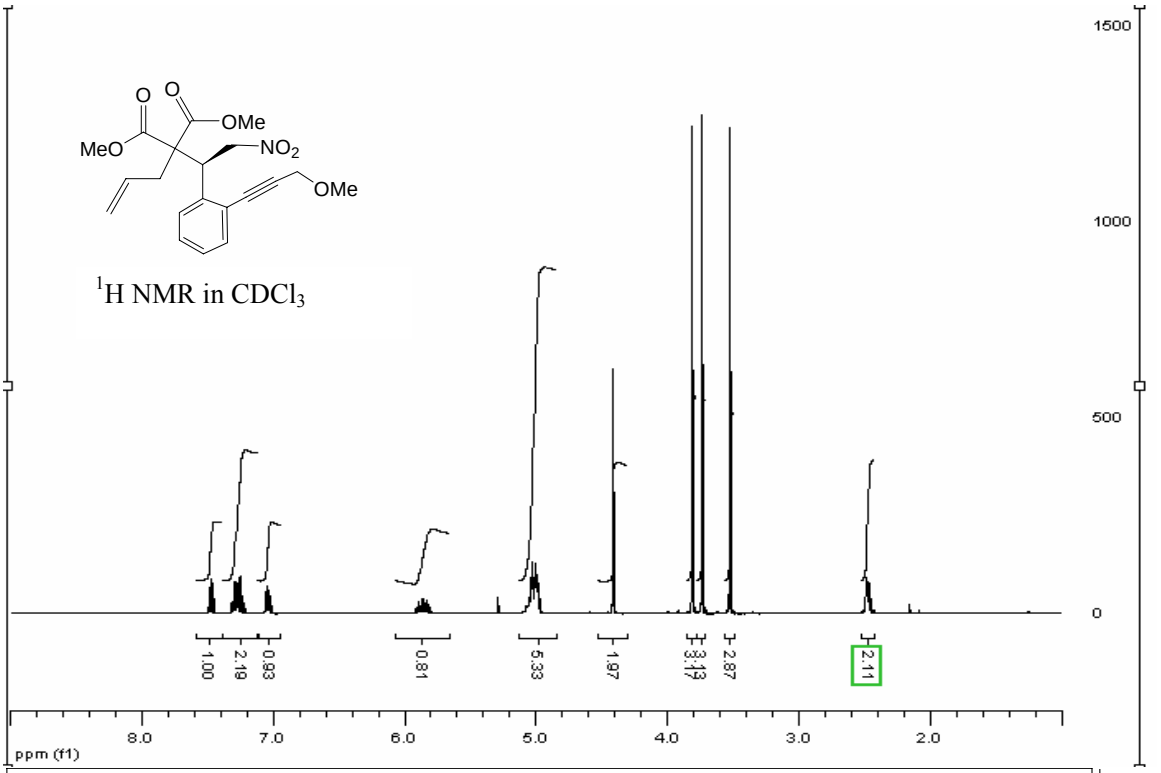


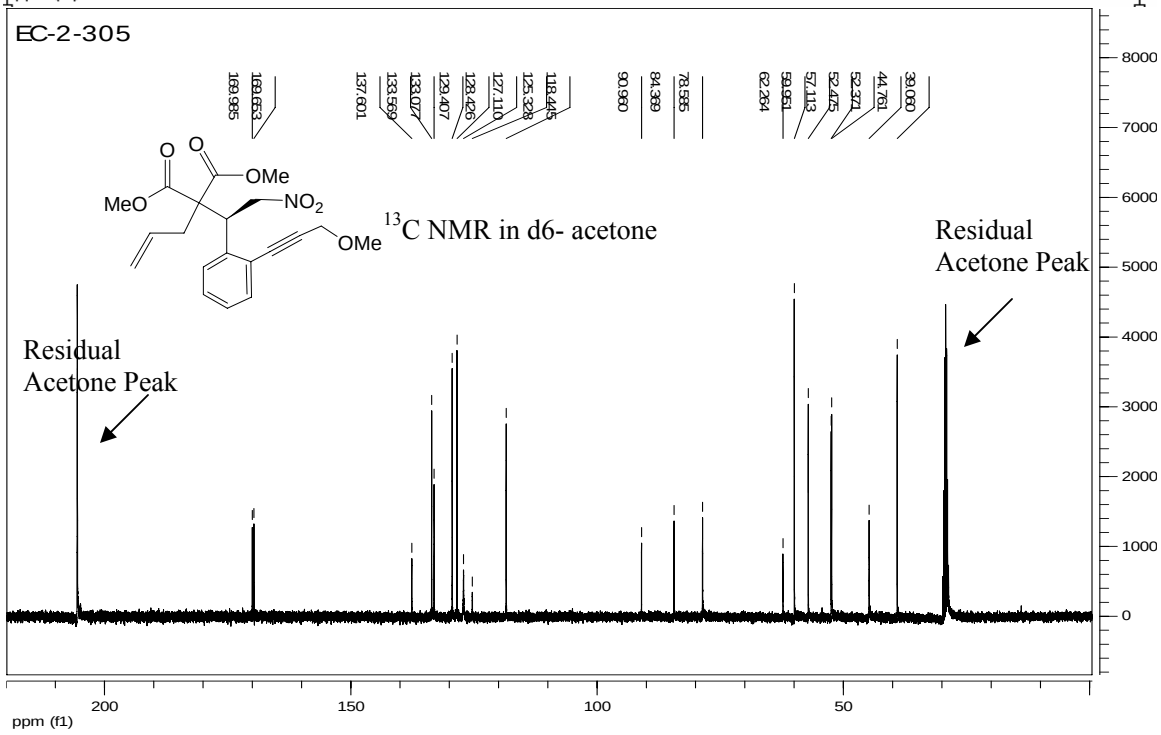


^{1}H and ^{13}C NMR for dimethyl 2-allyl-2-((*S*)-1-(2-allylphenyl)-2-nitroethyl)malonate **4f**

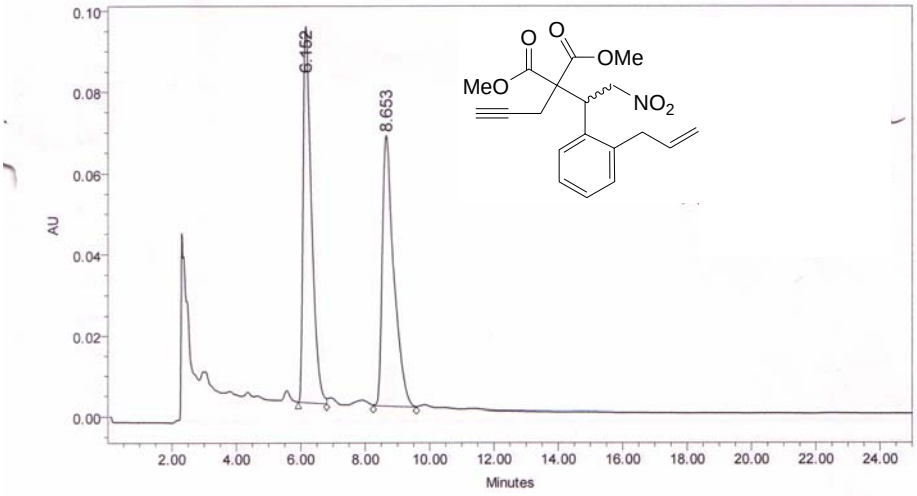


^{1}H and ^{13}C NMR spectra for dimethyl 2-allyl-2-((*S*)-1-(2-(3-methoxyprop-1-ynyl)phenyl)-2-nitroethyl)malonate **4h**.



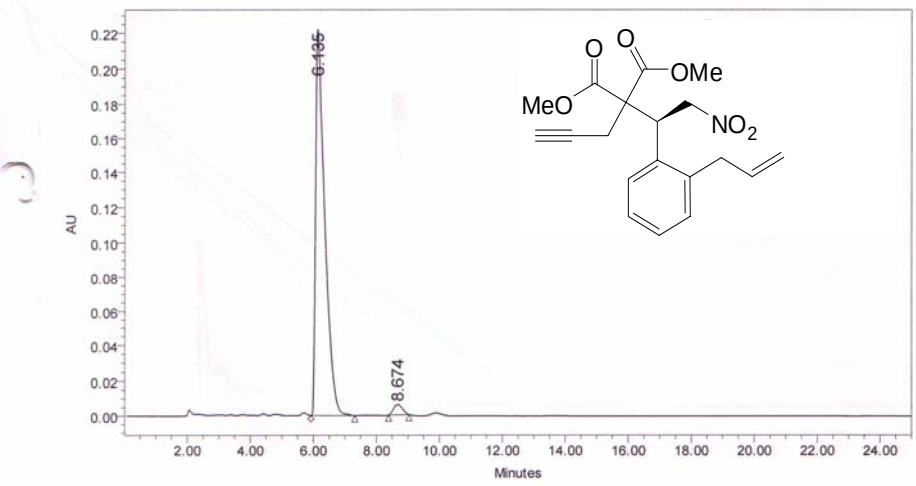


4. Select chiral HPLC analyses of multifunctional scaffolds



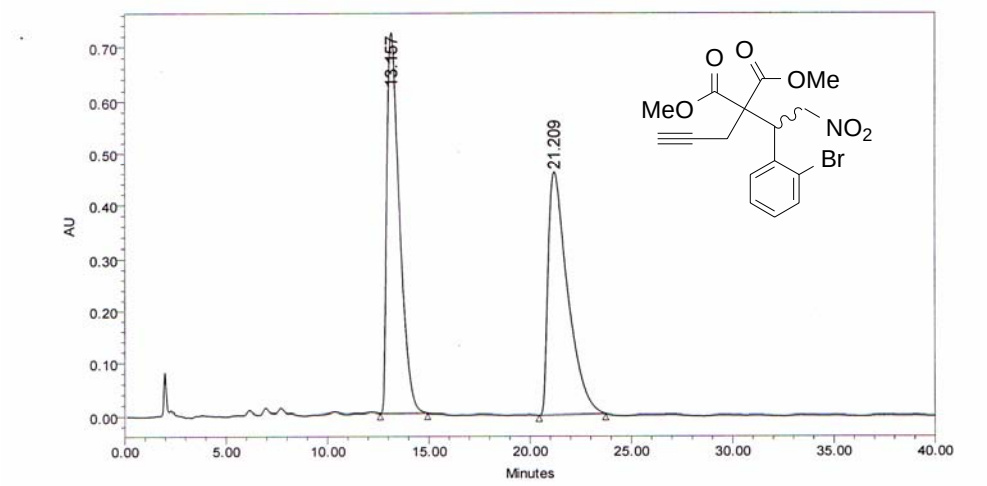
	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)	Baseline Start (min)
1	6.152	Unknown	1687305	50.22	92946	58.14	BV	52	5.917	6.800	5.917
2	8.653	Unknown	1672504	49.78	66924	41.86	VV	80	8.250	9.583	7.283

Chiral HPLC analysis for racemic Michael Adduct **4e**
Column: Daicel Chiralcel OD-H
Conditions: Hexanes:IPA, 90:10, 1.0 mL/min, λ 254 nm, t = 6.2 min, t = 8.7 min



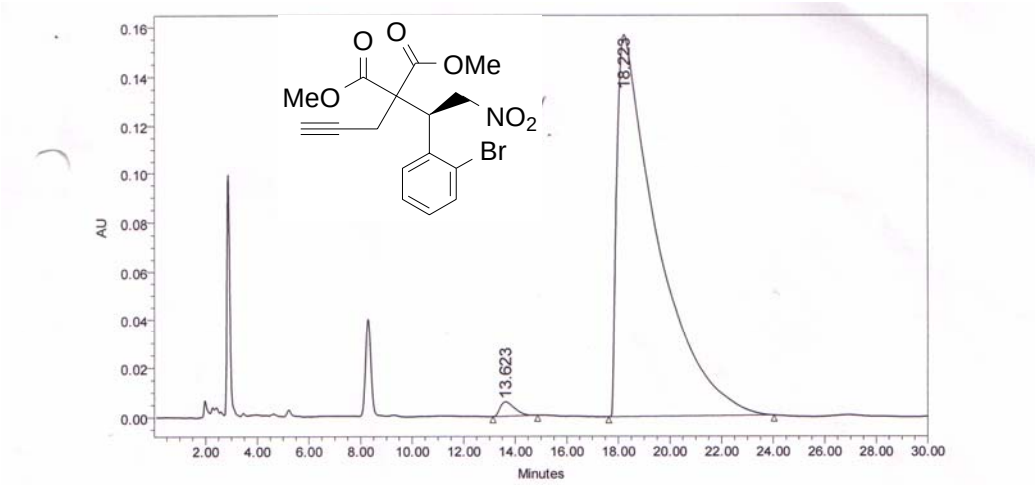
	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)	Baseline Start (min)
1	6.135	Unknown	4495688	97.41	222149	97.35	VB	83	5.917	7.317	5.467
2	8.674	Unknown	119493	2.59	6041	2.65	bb	38	8.383	9.033	8.383

Chiral HPLC trace of Michael Adduct **7e** obtained using **5c** as catalyst
Column: Daicel Chiralcel OD-H
Conditions: Hexanes:IPA, 90:10, 1.0 mL/min, λ 254 nm, t (major) = 6.1 min, t (minor) = 8.7 min



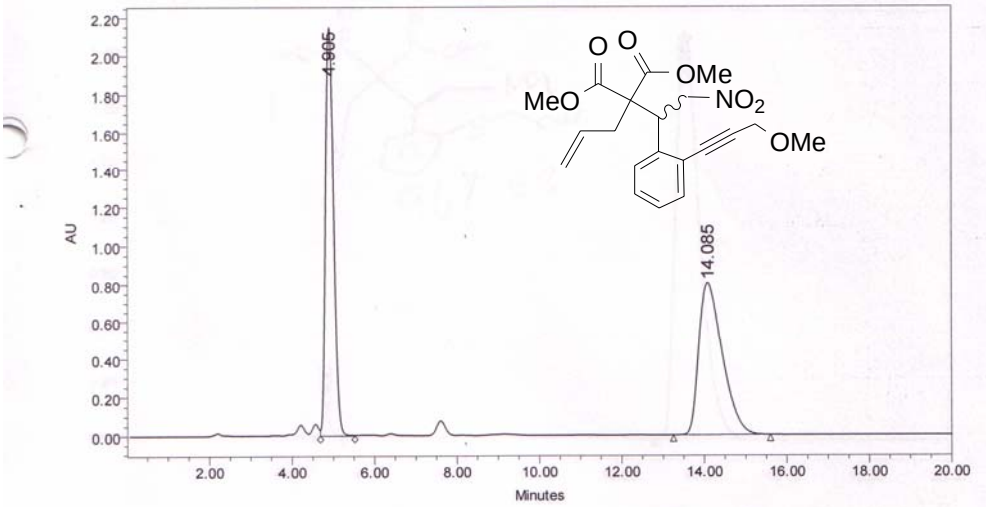
	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	13.157	Unknown	31297625	50.23	721832	61.05	BB	139	12.600	14.933
2	21.209	Unknown	31005017	49.77	460481	38.95	BB	196	20.450	23.733

Chiral HPLC analyses for racemic Michael Adduct **4g**
Column: Daicel Chiralcel OD-H
Conditions: Hexanes:IPA, 95:05, 1.0 mL/min, λ 254 nm, t = 21.2 min, t = 13.2 min



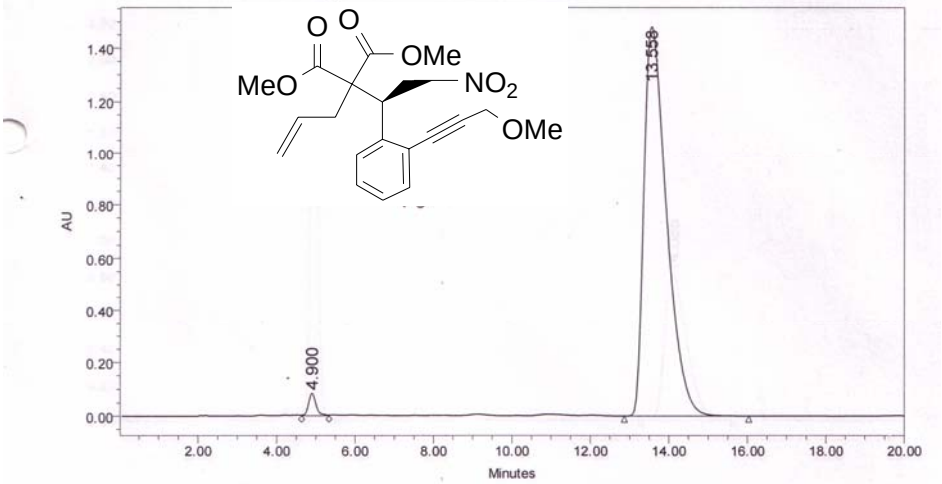
	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	13.623	Unknown	228784	1.33	5858	3.60	BB	103	13.133	14.867
2	18.223	Unknown	16984867	98.67	156775	96.40	BB	383	17.633	24.033

Chiral HPLC analyses for Michael Adduct **4g** obtained using **5c** as catalyst
Column: Daicel Chiralcel OD-H
Conditions: Hexanes:IPA, 95:05, 1.0 mL/min, λ 254 nm, t (major) = 18.2 min, t (minor) = 13.6 min



	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	4.905	Unknown	29312921	48.33	2152679	72.84	VV	49	4.683	5.517
2	14.085	Unknown	31338222	51.67	802826	27.16	BB	141	13.250	15.600

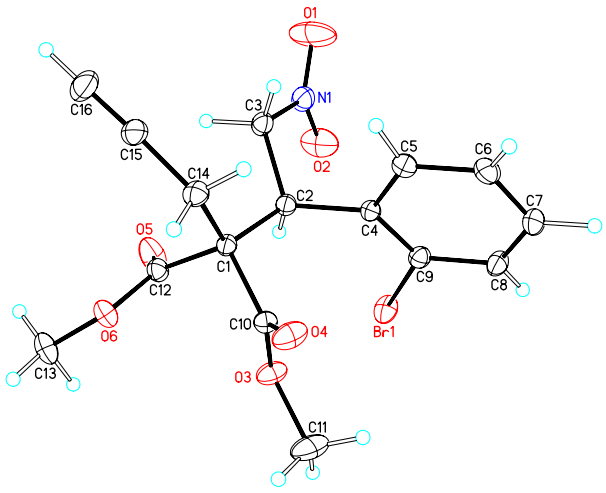
Chiral HPLC analyses for racemic Michael Adduct **4h**
Column: Daicel Chiralcel OD-H
Conditions: Hexanes:IPA, 90:10, 1.0 mL/min, λ 254 nm, t = 13.6 min, t = 4.9 min



	RT (min)	Peak Type	Area (μV*sec)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	4.900	Unknown	1132136	1.87	84040	5.37	VV	42	4.633	5.333
2	13.558	Unknown	59275671	98.13	1480331	94.63	BB	189	12.867	16.033

Chiral HPLC analyses for Michael Adduct **4h** obtained using **5c** as catalyst
Column: Daicel Chiralcel OD-H
Conditions: Hexanes:IPA, 90:10, 1.0 mL/min, λ 254 nm, t (major) = 13.6 min, t (minor) = 4.9 min

5. X-ray crystal structure analysis of malonate 4g



Crystals of compound **4g** suitable for x-ray analysis were obtained by slow evaporation from CH_2Cl_2/isooctane. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC # 627519). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

Table 1. Crystal data and structure refinement for **4g**.

Identification code	**4g**	
Empirical formula	C16 H16 Br N O6	
Formula weight	398.21	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.4518(6) Å	α= 90°.
	b = 7.1699(6) Å	β= 97.485(4)°.
	c = 14.2192(11) Å	γ = 90°.
Volume	854.32(11) Å3	
Z	2	
Density (calculated)	1.548 Mg/m^3	
Absorption coefficient	2.437 mm^{-1}	
F(000)	404	
Crystal size	0.40 x 0.30 x 0.20 mm^3	
Theta range for data collection	1.44 to 33.14°.	

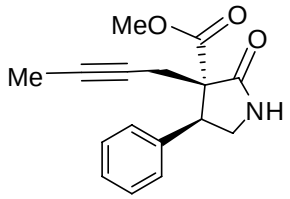
Index ranges	-12<=h<=13, -11<=k<=11, -21<=l<=21
Reflections collected	28101
Independent reflections	6350 [R(int) = 0.0350]
Completeness to theta = 33.14°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6414 and 0.4423
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6350 / 1 / 282
Goodness-of-fit on F2	0.987
Final R indices [I>2sigma(I)]	R1 = 0.0256, wR2 = 0.0556
R indices (all data)	R1 = 0.0326, wR2 = 0.0572
Absolute structure parameter	0.002(4)
Largest diff. peak and hole	0.434 and -0.296 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for **4g**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	5275(1)	284(1)	7535(1)	28(1)
O(1)	187(3)	2012(2)	5166(1)	67(1)
O(2)	1621(2)	433(2)	6210(1)	45(1)
O(3)	4839(1)	3758(2)	9026(1)	27(1)
O(4)	5030(1)	6674(2)	8509(1)	30(1)
O(5)	1011(2)	2529(2)	8717(1)	38(1)
O(6)	1706(1)	5068(2)	9581(1)	24(1)
N(1)	976(2)	1863(2)	5929(1)	28(1)
C(1)	2572(2)	4945(2)	8076(1)	17(1)
C(2)	2640(2)	3540(2)	7238(1)	18(1)
C(3)	1077(2)	3548(2)	6572(1)	23(1)
C(4)	4087(2)	3779(2)	6715(1)	18(1)
C(5)	4225(2)	5301(3)	6114(1)	24(1)
C(6)	5548(2)	5540(3)	5645(1)	28(1)
C(7)	6769(2)	4232(2)	5749(1)	28(1)
C(8)	6651(2)	2702(2)	6323(1)	25(1)
C(9)	5328(2)	2486(2)	6798(1)	20(1)

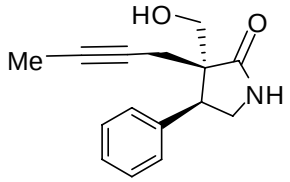
C(10)	4280(1)	5261(3)	8553(1)	19(1)
C(11)	6463(2)	3899(3)	9481(2)	41(1)
C(12)	1654(2)	4013(2)	8808(1)	21(1)
C(13)	1073(2)	4225(3)	10382(1)	31(1)
C(14)	1846(2)	6890(2)	7809(1)	23(1)
C(15)	95(2)	6892(2)	7635(1)	28(1)
C(16)	-1311(2)	6895(3)	7526(1)	39(1)

6. Functional group pairing of multifunctional scaffolds



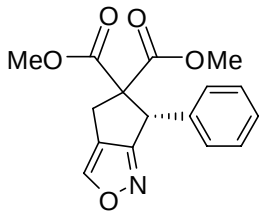
6

(*S*)-3-But-2-ynyl-2-oxo-4-phenyl-pyrrolidine-3-carboxylic acid methyl ester 6: To a solution of nitro malonate **4b** (79 mg, 0.24 mmol) in THF (1 mL) and acetic acid (1 mL) was added zinc powder (570 mg, 8.8 mmol) in small portions at room temperature. The reaction mixture was stirred for 2 h at room temperature and then filtered through Celite washing with THF. The solution was concentrated *in vacuo* and then redissolved in methylene chloride. A solution of saturated aqueous sodium carbonate (1 mL) was added and the mixture was stirred for 14 h. The mixture was extracted with methylene chloride and the organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to afford a 11.9/1 mixture of diastereomers. Chromatography over SiO_2 (50% EtOAc in pet. ether) provided **6** (59 mg, 92%) as a mixture of diastereomers in the form of a clear film. (Major isomer only) ^{1}H NMR (400 MHz, $CDCl_3$) 7.31 (m, 5H), 7.05 (s, 1H), 4.36 (t, J = 7.4, 1H,), 3.85 (m, 4H), 3.76 (m, 1H), 2.43 (m, 2H), 1.73 (t, J = 2.6, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 167.4, 133.3, 125.0, 124.9, 124.2, 74.5, 70.7, 55.9, 49.6, 44.1, 42.0, 17.0, 0.0; IR (thin film) ν_{max} 2957, 2914, 1737, 1701, 1255 cm^{-1}; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{17}H_{18}NO_3$ 272.1287, found 272.1272. $[\alpha]_D^{23}$ = 42.1^o (c = 1.1, CH_2Cl_2).



23

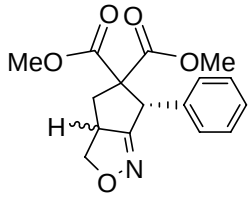
(3*R*,4*S*)-3-(but-2-ynyl)-3-(hydroxymethyl)-4-phenylpyrrolidin-2-one 23: To a solution of lactam **6** (50 mg, 0.087 mmol) in THF (1.2 mL) was added lithium tetrahydroborate (20 mg, 0.9 mmol) at room temperature. The reaction mixture was stirred for 4 h at room temperature and then quenched with 2M HCl. The solution was extracted with ethyl acetate and the organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. Chromatography over SiO_2 (70% EtOAc in pet. ether) provided **23** (32 mg, 71%) as a white film. ^{1}H NMR (400 MHz, $CDCl_3$) 7.38-7.26 (m, 5H), 6.20 (br s, 1H), 3.91 (dt, J = 9.18, J =9.14, J =2.55, 1H) 3.82-3.78 (m, 2H), 3.64-3.58 (m, 2H), 3.00 (br s, 1H), 2.31-2.26 (m, 1H), 1.94-1.88 (m, 1H), 1.74-1.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 132.9, 125.4, 125.0, 124.0, 74.4, 71.1, 61.5, 48.4, 42.5, 41.0, 16.4, 0.0; IR (thin film) ν_{max} 3284, 2920, 1695, 1044 cm^{-1}; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{15}H_{18}NO_2$, 244.1338 found 244.1355. $[\alpha]_D^{23}$ = 122.2^o (c = 0.18, CH_2Cl_2).



7

(*S*)-6-Phenyl-4*H*,6*H*-cyclopenta[c]isoxazole-5,5-dicarboxylic acid dimethyl ester 7: To a solution of nitro malonate **4c** (30 mg, 0.094 mmol) in toluene (1 mL) was added *di*-tert -butyldicarbonate (62 mg, 0.28 mmol) and 4-dimethylaminopyridine (1 mg, 0.01 mmol) at room temperature. The reaction mixture was stirred at room temperature for 48 h. The mixture was concentrated *in vacuo* to afford a crude material. Chromatography over SiO_2 (35% EtOAc in pet. ether) provided **7** (21 mg, 74%) as a white solid, m.p. 115-116 ^{o}C (from EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (m, 1H), 7.26 (m, 3H),

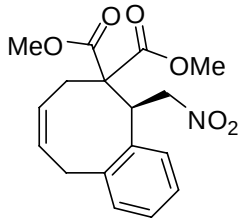
7.18 (m, 2H), 5.32 (s, 1H), 3.80 (s, 3H), 3.72 (dd, *J* = 1.4, *J* = 16.5, 1H), 3.20 (s, 3H), 3.14 (dd, *J* = 1.3, *J* = 16.6, 1H); ^{13}C NMR 172.0, 171.1, 168.8, 150.5, 136.2, 129.1, 128.6, 128.2, 121.1, 73.0, 53.5, 52.6, 48.7, 29.7; IR (thin film) ν_{max} 2952, 1740, 1565 cm^{-1}; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{16}H_{16}NO_6$ 302.1028, found 302.1029. $[\alpha]_D^{23}$ = -40.7^o (c = 0.3, CH_2Cl_2).



8, 9

(3a*S*,6*S*) and (3a*R*,6*S*)-6-Phenyl-3a,4-dihydro-3*H*,6*H*-cyclopenta[c]isoxazole-5,5-dicarboxylic acid dimethyl ester 8 and 9: To a solution of nitro malonate **4d** (200 mg, 0.62 mmol) in toluene (6 mL) was added *di-tert*-butyldicarbonate (400 mg, 1.83 mmol) and 4-dimethylaminopyridine (8 mg, 0.06 mmol) at room temperature. The reaction mixture was stirred at room temperature for 48 h. The mixture was concentrated *in vacuo* to afford a crude 1.1 / 1 mixture of diastereomers (^{1}H NMR). Chromatography over SiO_2 (50% EtOAc in pet. ether) provided the major diastereoisomer **8** (96 mg, 51%) as a clear solid, m.p. 98-100 ^{o}C, and the minor diastereomer **9** (64 mg, 34%) as a clear oil.
Major diastereomer **8** (α–H): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 5H), 5.01 (d, *J* = 1.2, 1H), 4.64 (dd, *J* = 8.2, *J* = 9.7, 1H), 4.09 (m, 1H), 3.86 (m, 1H), 3.80 (s, 3H), 3.10 (s, 3H), 2.69 (dd, *J* = 11.3, *J* = 13.6, 1H), 2.55 (dd, *J* = 8.3, *J* = 13.6, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.6, 170.7, 168.7, 135.6, 130.1, 128.4, 128.2, 75.4, 70.5, 53.7, 52.5, 52.2, 47.0, 35.4; ν_{max} 2928, 2858, 1728, 1274, 1204 cm^{-1}; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{16}H_{18}NO_5$,304.1173, found 304.1161. $[\alpha]_D^{23}$ = -113.8 ^{o} (c = 0.88 CH_2Cl_2).
Minor diastereomer **9** (β–H): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 5H), 5.00 (s, 1H), 4.67 (dd, *J* = 7.7, *J* = 9.6, 1H), 4.58 (m, 1H), 3.90 (dd, *J* = 7.7, *J* = 12.1, 1H), 3.79 (s, 3H), 3.03 (s, 3H), 2.86 (m, 1H), 1.80 (dd, *J* = 11.1, *J* = 12.8, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.9, 169.9, 136.9, 128.9, 128.5, 127.9, 75.4, 71.7, 55.6, 53.4, 52.4, 46.1, 36.7 ; IR (thin film) ν_{max} 2955, 1732, 1285, 1212 cm^{-1}; HRMS (CI/NH_3) $[M+Na]^+$ calcd for $C_{16}H_{17}NO_5Na$, 326.1002, found 326.1004. $[\alpha]_D^{23}$ = 5.5^o (c = 1.4, CH_2Cl_2).

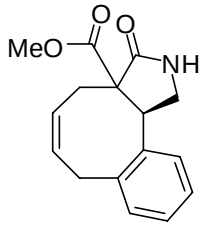
The relative stereochemistry of **8** and **9** was assigned based on the stereochemistry of **4d** and comparison of our spectral data to literature data for the (±) compounds for which x-ray analysis was obtained.[9]



10

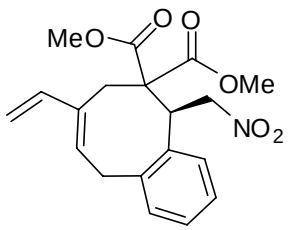
Nitromalonate 10: To a solution of nitrodiene **4f** (150 mg, 0.415 mmol) in methylene chloride (2 mL) was added Grubbs 2nd generation catalyst (40 mg, 0.04 mmol). The solution was heated by microwave irradiation at 50 ^{o}C (150 watts) for 5 min. The reaction mixture was concentrated *in vacuo* and chromatographed over SiO_2 (20% EtOAc in pet. ether) to provided **10** (135 mg, 98%) as a sticky white solid, m.p. 92-94 ^{o}C (from Methylene chloride/2,2,4-Trimethylpentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 3H), 6.89 (dd, *J* = 4.2, *J* = 8.1, 1H), 5.92 (dddd, *J* = 1.4, *J* = 3.5, *J* = 4.9, *J* = 11.8, 1H), 5.35 (m, 1H), 5.22 (dd, *J* = 3.4, *J* = 14.4, 1H), 5.09 (dd, *J* = 11.4, *J* = 14.4, 1H), 4.80 (dd, *J* = 3.4, *J* = 11.4, 1H), 3.96 (d, *J* = 19.6, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.38 (dd, *J* = 3.8, J = 19.9, 1H), 2.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.7, 139.7, 135.2, 134.8, 130.7, 128.5, 127.4, 125.0, 121.6, 76.3, 60.4, 53.3, 52.9, 40.5,

38.5, 30.0 ; IR (thin film) ν_{max} 3025, 2952, 1732, 1561, 1278, 1200 cm^{-1}; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{17}H_{20}NO_6$ 334.1291, found 334.1290. $[\alpha]_D^{23}$ = 93.2° (c = 1.2, CH_2Cl_2);



11

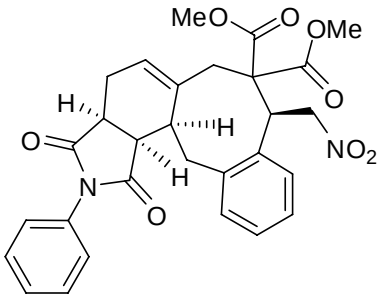
Lactam 11: To a solution of nitro malonate **10** (32 mg, 0.096 mmol) in THF (0.4 mL) and acetic acid (0.4 mL) was added zinc powder (230 mg, 3.6 mmol) in small portions at room temperature. The reaction mixture was stirred for 14 h at room temperature and then filtered through Celite washing with methylene chloride. The solution was concentrated *in vacuo* and then redissolved in methylene chloride. To the solution was added saturated sodium carbonate (1 mL) and the mixture was stirred overnight. The mixture was extracted with methylene chloride and the organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford a mixture of diastereomers as a yellow oil. Chromatography over SiO_2 (50% EtOAc in pet. ether) provided **11** (12 mg, 46%) as a mixture of diastereomers (1.51/1) in the form of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 1H), 7.26 (m, 4H), 7.18 (m, 3H), 6.67 (s, 1H, major isomer), 6.61 (s, 1H, minor isomer), 5.90 (m, 1H, major isomer), 5.74 (m, 2H, major and minor isomers), 5.57 (m, 1H, minor isomer), 4.50 (d, *J* = 6.3, 1H, minor isomer), 4.28 (dd, *J* = 10.7, *J* = 8.6, 1H, major isomer), 4.18 (dd, *J* = 10.8, *J* = 7.3, 1H, major isomer), 4.00 (dd, *J* = 10.4, *J* = 6.3, 1H, minor isomer), 3.78 (s, 3H, major isomer), 7.78 (m, 1H, major or minor isomer), 3.69 (m, 2H, major and minor isomers), 3.53 (s, 3H, minor isomer), 3.45 (m, 1H, major or minor isomers), 3.29 (dd, *J* = 18.1, *J* = 7.1, 1H, major or minor isomers), 3.20 (dd, *J* = 14.5, *J* = 8.4, 1H, major or minor isomers), 3.07 (dd, *J* = 12.9, *J* = 7.6, 1H, major or minor isomers), 2.53 (m, 2H, major and minor isomers), 1.58 (m, 1H, major or minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$) (major and minor isomers) 174.6, 173.2, 170.5, 169.0, 142.7, 139.4, 137.9, 133.5, 133.2, 131.9, 130.8, 129.5, 128.6, 127.9, 127.9, 127.7, 126.3, 126.1, 125.7, 125.1, 64.6, 58.3, 53.2, 52.2, 49.6, 44.8, 43.6, 42.9, 36.5, 33.6, 33.0, 26.6; IR (thin film) ν_{max} 3227, 3018, 2913, 1705, 1204 cm^{-1}; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{16}H_{18}NO_3$ 272.1287, found 272.1277.$[\alpha]_D^{23}$ = 183.9° (c = 0.7, CH_2Cl_2).



12

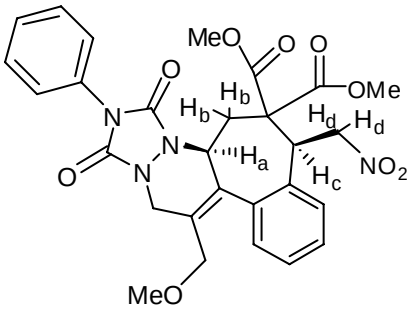
Diene 12: To a solution of enyne **4e** (75 mg, 0.21 mmol) in methylene chloride (3 mL) was added Grubbs 1st generation catalyst (20 mg, 0.02 mmol) under an atmosphere of ethylene gas. The reaction was heated by microwave irradiation at 60°C (150W) for 30 min. The reaction mixture was concentrated *in vacuo* and chromatography over SiO_2 (20% EtOAc in pet. ether) provided diene **12** (71 mg, 95%) as a white solid, m.p. 128-130 °C(from EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.19 (m, 3H), 6.93-6.91 (m, 1H), 6.28 (dd, *J* = 17.4, *J* = 11.0, 1H), 6.00 (t, *J* = 4.4, 1H), 5.20 (dd, *J* = 14.5, *J* = 11.4, 1H), 5.07 (dd, *J* = 14.5, *J* = 3.2, 1H), 5.00 (d, *J* = 17.5, 1H), 4.88 (d, *J* = 10.9, 1H), 4.75 (dd, *J* = 11.4, *J* = 3.2, 1H), 4.11 (dd, *J* = 20.0, *J* = 4.3, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 3.52 (dd, *J* = 20.7, *J* = 4.9, 1H), 2.69 (d, *J* = 14.8, 1H), 2.35 (dd, *J* = 14.9, *J* = 1.1, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 170.0, 141.6, 139.1, 135.1, 135.0, 131.9, 130.6, 128.6, 127.6, 124.6, 110.2, 76.2, 60.1, 53.0, 53.0, 40.8, 38.5, 28.0; IR (thin film) ν_{max} 2948, 1732, 1553, 1282, 1220 cm^{-1}; HRMS (CI/NH_3)

$[M+Na]^+$ calcd for $C_{19}H_{21}NO_6Na$ 382.1265, found 382.1267. $[\alpha]_D^{23}$ = 41.7° (c = 0.43, CH_2Cl_2).



13

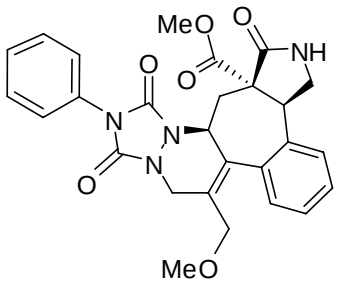
Nitromalonate 13: To a solution of enyne **4e** (44 mg, 0.12 mmol) in methylene chloride (2 mL) was added Grubbs 1st generation catalyst (10 mg, 0.01 mmol) under an atmosphere of ethylene gas. The reaction was heated by microwave irradiation at 60°C (150W) for 30 min. The reaction mixture was concentrated *in vacuo* to afford a crude sample of intermediate **12** as a dark brown oil which was dissolved in toluene (3 mL) under argon. To this solution was added *N*-phenylmaleimide (50 mg, 0.3 mmol). The reaction was heated by microwave irradiation (300W, 160°C, 40 min.). Chromatography over SiO_2 (50% EtOAc in pet. ether) provided **13** (64 mg, 98%) as a 15/1 mixture of diastereomers; white solid, m.p. 109-111°C (from Methylene chloride/2,2,4-Trimethylpentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.41 (m, 3H), 7.38-7.35 (m, 1H), 7.21-7.14 (m, 4H), 6.91 (d, *J* = 10.9, 1H), 5.60 (s, 1H), 5.25-5.13 (m, 2H), 4.55 (dd, *J* = 10.1, *J* = 3.8, 1H), 3.86-3.78 (m, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.64-3.55 (m, 1H), 3.40 (dd, *J* = 10.1, *J* = 3.8, 1H), 3.34-3.00 (m, 2H), 2.68-2.59 (m, 2H), 2.52 (d, *J* = 14.4, 1H), 2.33-2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 177.3, 170.3, 169.5, 139.9, 139.5, 133.9, 132.8, 131.9, 129.4, 128.9, 128.3, 127.9, 127.1, 126.7, 124.7, 76.4, 62.7, 53.1, 53.0, 47.9, 40.5, 40.4, 39.0, 38.0, 36.5, 25.5 ; IR (thin film) ν_{max} 2959, 2842, 1713, 1546, 1386, 1204 cm^{-1}; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{29}H_{29}N_2O_8$ 533.1935, found 533.1924. $[\alpha]_D^{23}$ = 41.8° (c = 0.6, CH_2Cl_2).



15

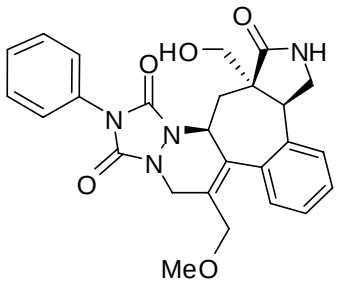
Nitromalonate 15: To a solution of enyne **4h** (8 mg, 0.021 mmol) in methylene chloride (0.6 mL) was added Grubbs 1st generation catalyst (2 mg, 0.002 mmol) under an atmosphere of ethylene gas. The reaction was heated by microwave irradiation at 50°C, (150 watts) for 45 min. The reaction mixture was concentrated *in vacuo*. Chromatography over SiO_2 (50% EtOAc in pet. ether) provided intermediate **14** (7.5 mg, 94%) as a dark yellow oil. ^{1}H NMR (400 MHz $CDCl_3$) 7.29-7.09 (m, 4H), 6.15 (br m, 1H), 5.26 (s, 1H), 5.20 (br m, 1H), 5.10 (s, 1H), 5.02 (br s, 1H), 4.27 (br s, 1H), 4.10 (br s, 1H), 3.99 (br s, 1H), 3.70 (br s, 2H), 3.63 (s, 3H), 3.26 (s, 3H), 2.56 (br s, 1H), 2.07 (br s, 1H) . The crude intermediate was dissolved in toluene (3 mL) under argon. To this solution was added *N*-phenylmaleimide (50 mg, 0.3 mmol). The reaction was heated by microwave irradiation at 160°C (300 W) for 20 min. The reaction mixture was concentrated *in vacuo* and chromatographed on SiO_2 (50% EtOAc in pet. ether) to provide **15** (9.4 mg, 86%) as a white solid, m.p. 105-107°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.57 (m, 2H), 7.50-7.39 (m, 2H), 7.37 (m, 1H), 7.28 (m, 3H), 7.06 (dd, *J* = 7.1, 1.7, 1H), 5.11 (d, *J* = 10.4, 1H), 5.03-5.01 (m, 2H), 4.69 (d, *J* = 17.0, 1H), 4.49 (t, *J* = 7.5, 1H), 4.22 (d, *J* = 17.2, 1H), 3.93 (s, 2H), 3.78 (s, 3H), 3.55 (s, 3H), 3.29 (s, 3H), 3.04 (dd, *J* = 13.5, 3.9, 1H), 2.06 (m, 1H); NOED ^{1}H NMR (400 MHz, $CDCl_3$): Irradiation at δ 2.07 (diastereotopic proton H_b): 7% enhancement at proton H_d, Irradiation at δ 2.56 (diastereotopic proton

H_b): 5% enhancement at proton Ha, ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 168.1, 153.9, 150.9, 136.7, 133.7, 133.3, 132.8, 131.4, 130.5, 129.4, 129.2, 129.0, 128.3, 125.3, 125.3, 75.7, 70.3, 59.2, 57.8, 53.9, 53.2, 51.8, 48.1, 45.9, 33.8; IR (thin film) ν_{max} 2959, 1713, 1553, 1413, 1266, 1223 cm^{-1}; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{28}H_{29}N_4O_9$ 565.1935, found 565.1935. $[\alpha]_D^{23} = 97.4^o$ (c = 0.9, CH_2Cl_2).



16

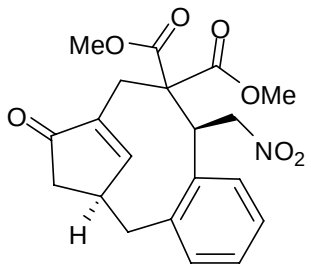
Lactam 16: To a solution of nitro malonate **15** (20 mg, 0.036 mmol) in THF (0.4 mL) and acetic acid (0.4 mL) was added zinc powder (86 mg, 1.3 mmol) in small portions at room temperature. The reaction mixture was stirred at 90 ^oC for 3 h, then filtered through Celite washing with THF. The solution was concentrated *in vacuo* and then redissolved in methylene chloride. A solution of saturated sodium carbonate (1 mL) was added and the reaction mixture was stirred overnight. The mixture was extracted with methylene chloride and the organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford a crude mixture of diastereomers. Chromatography over SiO_2 (50% EtOAc in pet. ether) provided **16** (8 mg, 45%) as a 5/1 mixture of diastereomers (^1H NMR) as a slightly yellow oil. (Major isomer only) ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.54 (m, 2H), 7.48-7.44 (m, 2H), 7.38-7.33 (m, 3H), 7.27-7.25 (m, 1H), 7.11 (dd, *J* = 6.8, 2.1, 1H), 6.24 (s, 1H), 4.69 (m, 1H), 4.54 (d, *J* = 16.8, 1H), 4.21 (dd, *J* = 16.6, 2.3, 1H), 4.13 (t, *J* = 8.7, 1H), 3.87 (s, 2H), 3.77 (s, 3H), 3.65 (t, *J* = 9.4, 1H), 3.29 (m, 1H), 3.26 (s, 3H), 3.11 (dd, *J* = 15.0, 6.0, 1H), 2.47 (dd, *J* = 15.1, 4.6, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 152.6, 151.4, 136.0, 135.7, 133.2, 132.2, 131.5, 130.3, 129.3, 129.3, 128.6, 128.3, 127.9, 126.0, 125.5, 70.6, 59.2, 55.4, 53.5, 53.1, 49.6, 46.3, 44.4, 32.4 ; IR (thin film) ν_{max} 3239, 2940, 2701, 1425, 1270, 1235, 1076 cm^{-1}; HRMS (CI/NH_3) $[M+Na]^+$ calcd for $C_{27}H_{26}N_4O_6Na$ 525.1750, found 525.1763. $[\alpha]_D^{23} = 16.7^o$ (c = 0.3, CH_2Cl_2).



24

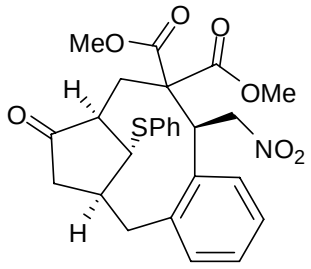
Lactam alcohol 24. To a solution of lactam **16** (11 mg, 0.022 mmol) in THF (1.5 mL) was added lithium tetrahydroborate (2 mg, 0.092 mmol) at 0^oC. The reaction mixture was stirred for 6 h at 0^oC and was then quenched by addition of 2M HCl. The solution was extracted with EtOAc and the organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Chromatography over SiO_2 (10% EtOH in EtOAc) provided lactam alcohol **24** (5 mg, 48%) as a white film. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.53 (m, 2H), 7.48-7.44 (m, 2H), 7.37-7.33 (m, 3H), 7.26-7.24 (m, 1H), 7.13-7.10 (m, 1H), 6.15 (s, 1H), 4.63 (s, 1H), 4.45 (d, *J* = 16.8, 1H), 4.22 (d, *J* = 16.6, 1H), 3.84 (s, 2H), 3.74 (d, *J* = 10.6, 1H), 3.72-3.67 (m, 2H), 3.61 (t, *J* = 9.7, 1H), 3.43 (d, *J* = 11.0, 1H), 3.26 (s, 3H), 3.20-3.15 (m, 2H), 1.64 (dd, *J* = 15.5, 5.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 151.9, 138.1,135.3, 132.3, 131.6, 131.5, 130.1, 129.4, 129.3, 129.2, 128.4, 128.2, 127.9, 126.2, 70.7, 68.5, 59.2, 54.2, 49.0, 46.9,

45.8, 43.9, 29.9; IR (thin film) ν_{max} 3332, 2924, 1710, 1427, 1091 cm^{-1}; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{26}H_{27}N_4O_5$, found. $[\alpha]_D^{23} = 32.8^o$ (c = 0.3, CH_2Cl_2).



17

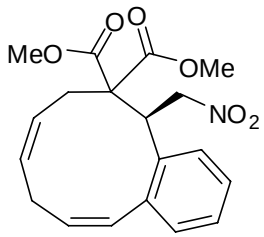
Nitromalonate 17: Dicobalt octacarbonyl (94 mg, 0.27 mmol) was weighed in a glove box. To the solid catalyst was added enyne **4e** (82 mg, 0.23 mmol) in methylene chloride (1 mL) under an atmosphere of argon. The reaction stirred at room temperature for 30 min. upon which all the starting material had fully converted to a cobalt complex (monitored by TLC). The reaction was heated by microwave irradiation at 80°C (150 W) for 15 min. The reaction mixture was concentrated *in vacuo* and chromatographed over SiO_2 (90% pet. ether in EtOAc to 40% pet. ether in EtOAc) to provide **17** (59 mg, 67%) as a white solid m.p. 234-236 °C (from Methylene chloride/2,2,4-Trimethylpentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.32-7.29 (m, 1H), 7.23-7.17 (m, 2H), 6.98 (d, *J* = 7.5, 1H), 4.99 (dd, *J* = 13.0, 2.3, 1H), 4.68 (t, *J* = 12.0, 1H), 4.21 (d, *J* = 10.6, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.51 (br s, 1H), 3.09 (d, *J* = 13.5, 1H), 3.01 (d, *J* = 17.3, 1H), 2.88 (dd, *J* = 13.8, *J* = 4.8, 1H), 2.82 (d, *J* = 17.4, 1H), 2.07 (dd, *J* = 16.5, 4.7, 1H), 1.97 (dd, *J* = 16.8, 1.1, 1H); NOED ^{1}H NMR (400 MHz, $CDCl_3$): Irradiation at δ 4.21 (methine proton β to nitro group): 4% enhancement at vinyl proton at 7.54 ppm, Irradiation at δ 7.54 ppm 5% enhancement at methine proton β to nitro group at 4.21 ppm,^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 172.7, 170.7, 159.8, 138.1, 137.5, 136.2, 133.9, 129.3, 128.7, 128.3, 80.4, 62.1, 54.0, 53.7, 41.8, 40.5, 38.3, 37.9, 26.8; IR (thin film) ν_{max} 2955, 1729, 1706, 1557, 1268 cm^{-1}; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{20}H_{22}NO_7$ 388.1396, found 388.1376. $[\alpha]_D^{23} = 49.2^o$ (c = 0.5, CH_2Cl_2).



19

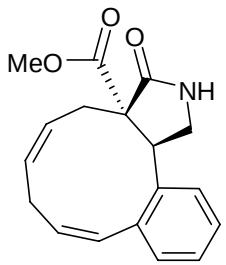
Nitromalonate 19. To a solution of **17** (11 mg, 0.028 mmol) and triethylamine (0.4 μL, 0.003 mmol) in toluene (0.6 mL) was added thiophenol (9 μL, 0.08 mmol) at room temperature. The reaction was monitored by TLC analysis which showed complete consumption of the starting material after 40 min. The reaction mixture was concentrated *in vacuo*. Chromatography over SiO_2 (20% EtOAc in pet. ether) provided **19** (10 mg, 71%) as a white solid, m.p. 158-160°C (from Methylene chloride/2,2,4-Trimethylpentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2H), 7.34-7.30 (m, 2H), 7.28-7.25 (m, 1H), 7.19-7.16 (m, 2H), 7.02-7.00 (m, 1H), 6.84-6.82 (m, 1H), 5.19-5.16 (m, 1H), 4.79-4.68 (m, 2H), 4.21 (s, 1H), 3.73 (s, 3H), 3.37 (s, 3H), 3.37-3.33 (m, 1H), 2.86-2.70 (m, 2H), 2.58 (dd, *J* = 19.0, 8.5, 1H), 2.25-2.07 (m, 3H), 0.92 (dd, *J* = 14.3, 8.4, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.39, 170.19, 169.74, 138.55, 135.08, 134.44, 134.19, 133.47, 129.55, 128.81, 128.56, 128.00, 126.56, 77.92, 58.65, 53.31 (2 ester carbons, see HMQC page S39), 52.27, 49.38, 41.41, 39.79, 39.08, 36.03, 30.31; ν_{max} 2955, 2923, 1733, 1558 cm^{-1}; HRMS (CI/NH_3) $[M+Na]^+$ calcd for $C_{26}H_{27}NO_7NaS$ 520.1406, found 520.1509. $[\alpha]_D^{23} = 101.4^o$ (c = 0.11, CH_2Cl_2).

Nitromalonate 21. To a solution of nitro malonate **4e** (40 mg, 0.11 mmol) in toluene (1.1 mL) was added $AuCl(PPh)_3$ (30 mg, 0.4 mmol) at room temperature. To the resulting mixture was added AgOTf (20 mg, 0.5 mmol) and the reaction was heated at 50°C for 14 h. The reaction mixture was concentrated *in vacuo*. Chromatography over SiO_2 (10% EtOAc in pet. ether) provided **21** (23 mg, 58%) as a white film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.08-7.06 (m, 1H), 6.86-6.84 (m, 1H), 6.32 (d, *J* = 10.8, 1H), 5.96-5.77 (m, 2H), 5.19 (dd, *J* = 12.8, 2.9, 1H), 4.96 (dt, *J* = 11.2, 11.0, 5.7, 1H), 4.73 (dd, *J* = 12.8, 11.2, 1H), 4.42 (dd, *J* = 11.1, 2.9, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 3.03-2.74 (m, 1H), 2.58-2.44 (m, 2H), 2.33-2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.3, 140.6, 134.4, 132.9, 131.2, 130.3, 128.3, 128.2, 128.0, 126.3, 123.1, 80.2, 60.0, 53.2, 53.1, 42.1, 31.0, 27.9; HRMS (CI/NH_3) $[M+Na]^+$ calcd for $C_{19}H_{21}NO_6Na$ 382.1267, found 382.1247. $[\alpha]_D^{23}$ = 210.1° (c = 0.7, CH_2Cl_2).



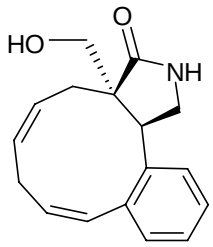
21

Lactam 22. To a solution of nitro malonate **21** (18 mg, 0.05 mmol) in THF (0.3 mL) and acetic acid (0.3 mL) was added zinc powder (120 mg, 1.8 mmol) in small portions at room temperature. The reaction mixture was stirred for 4 h at room temperature, then filtered through Celite washing with THF. The solution was concentrated *in vacuo* and then redissolved in methanol (0.8 mL). 6M NaOH (0.7 mL) was added and the reaction mixture was stirred for 20 min at room temperature. The mixture was extracted with methylene chloride and the organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. Chromatography over SiO_2 (80% EtOAc in pet. ether) provided **22** (9 mg, 60%) as a white film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.13 (m, 2H), 7.07-7.00 (m, 2H), 6.25 (d, *J* = 11.3, 1H), 5.95 (br s, 1H), 5.83-5.71 (m, 2H), 5.50-5.33 (m, 1H), 4.10-4.00 (m, 1H), 3.77 (s, 3H), 3.40 (dd, *J* = 10.50, *J* = 9.27, 1H), 3.31-3.27 (m, 1H), 3.09 (q, *J* = 12.0, 1H), 2.76 (dd, *J* = 13.93, *J* = 10.21, 1H), 2.50 (dd, *J* = 14.0, *J* = 6.4, 1H) 2.40-2.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 172.2, 138.8, 133.6, 132.5, 130.5, 130.4, 127.9, 127.4, 127.3, 126.9, 124.1, 58.3, 52.6, 47.4, 43.7, 28.3, 27.4; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{18}H_{20}NO_3$ 298.1443, found 298.1448. $[\alpha]_D^{23}$ = 155.8° (c = 0.5 CH_2Cl_2).



22

(±) Lactam alcohol 25. The (±) analogue of lactam **22** (22 mg, 0.067 mmol) was prepared using the procedure reported for **22** with the exception that (±) **4e** was prepared using DABCO as catalyst**.** This compound was dissolved in THF (1 mL) and lithium tetrahydroborate (6 mg, 0.267 mmol) was added at room temperature. The reaction mixture was stirred for 6 h at room temperature and then quenched through the addition of 2M HCl. The solution was extracted with EtOAc and the organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. Chromatography over SiO_2 (90% EtOAc / pet. ether) provided lactam alcohol **25** (18 mg, 70%) as an off white film. ^{1}H

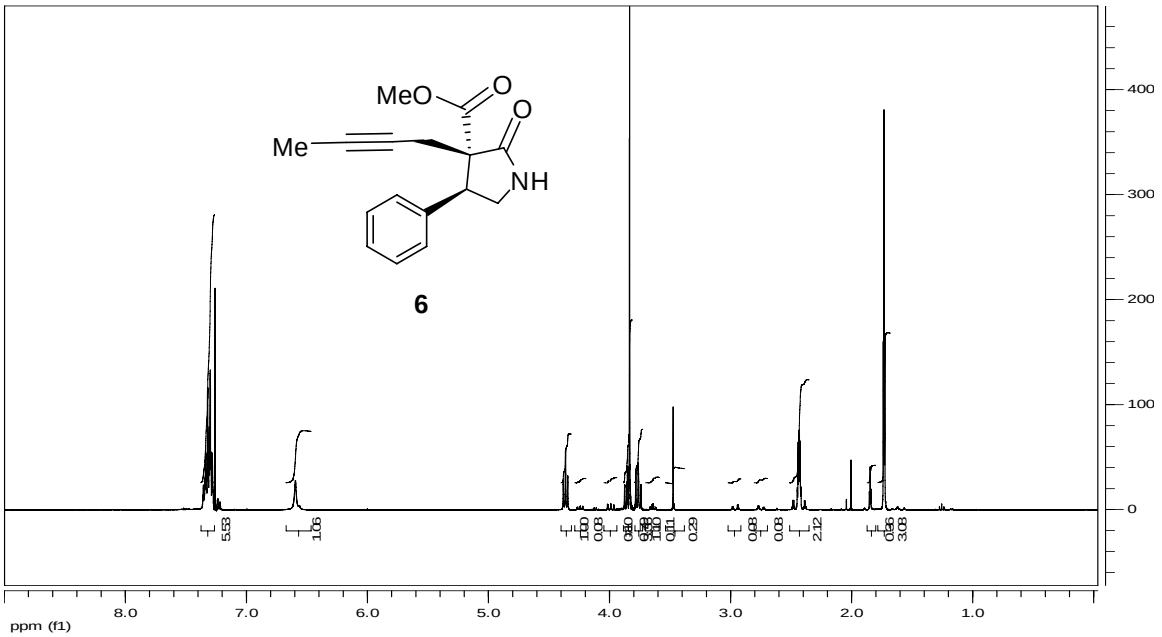


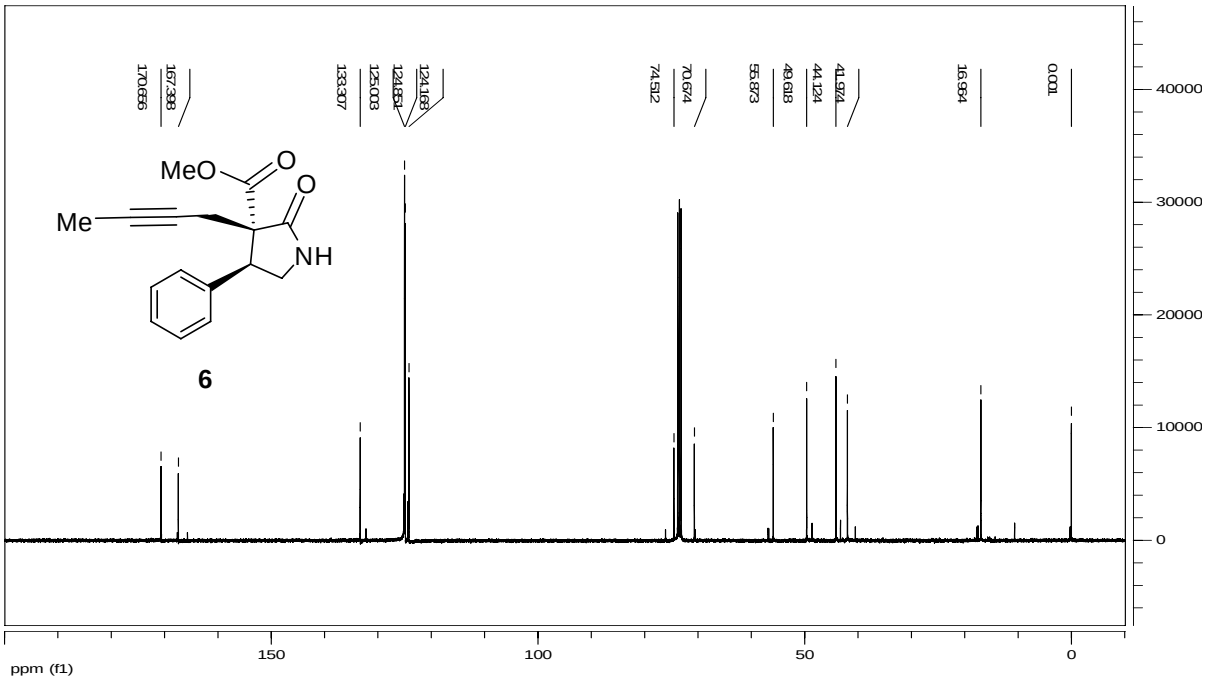
(±) 25

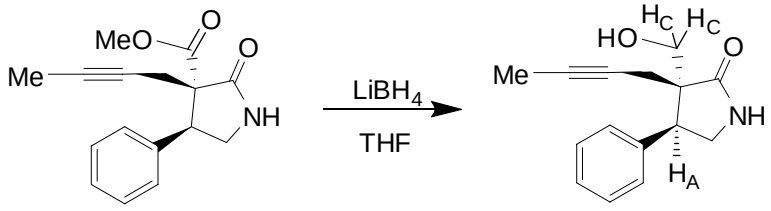
NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.6, 1.6, 1H), 7.27-7.15 (m, 2H), 7.06 (dd, *J* = 7.1, 1.8, 1H), 6.27 (d, *J* = 11.2, 1H), 5.98 (br s, 1H), 5.77 (dt, *J* = 11.5, 11.4, 5.0, 1H), 5.70 (dt, *J* = 11.2, 11.0, 4.4, 1H), 5.46-5.40 (br s, 1H), 4.08-3.95 (m, 1H), 3.93 (d, *J* = 10.5, 1H), 3.77 (d, *J* = 10.6, 1H), 3.33 (t, *J* = 9.8, 1H), 3.26 (t, *J* = 8.3, 1H), 3.02 (dd, *J* = 24.5, 12.0, 1H), 2.57-2.46 (m, 1H), 2.39-2.26 (m, 1H), 2.16 (dd, *J* = 13.1, 6.5, 1H), 2.11-2.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 139.2, 134.8, 131.6,130.3, 130.3, 130.2, 127.5, 127.5, 127.4, 124.4, 66.8, 60.7, 48.0, 42.0, 28.2, 28.1; IR (thin film) ν_{max} cm^{-1} 3440, 2923, 2852, 1677, 1258; HRMS (CI/NH_3) $[M+H]^+$ calcd for $C_{17}H_{20}NO_2$ 270.1494, found 270.1494.

7. Select NMR spectra for functional group pairing products

^{1}H and ^{13}C NMR spectra for (S)-3-but-2-ynyl-2-oxo-4-phenyl-pyrrolidine-3-carboxylic acid methyl ester **6** (major and minor diastereomers).

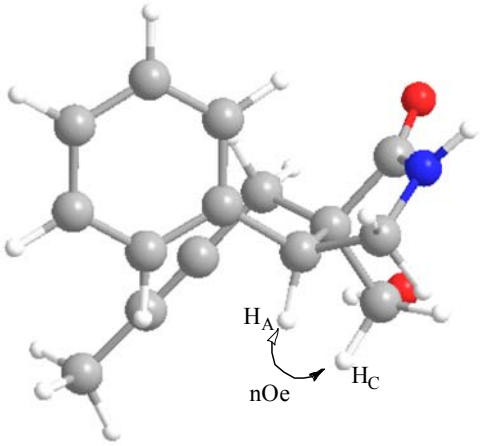






6 **23**

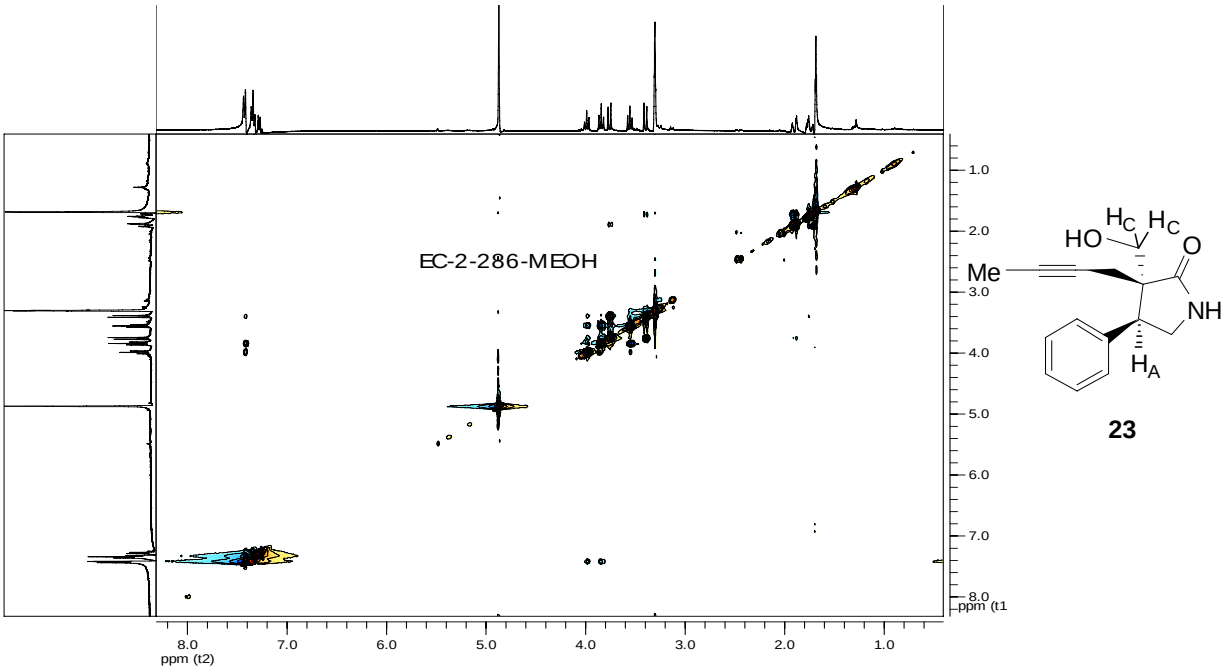
- The stereochemistry of the quaternary carbon of **6** was assigned based on nOe data of the corresponding alcohol **23** in d_6-MeOH.
- The chemical shifts of methine and methylene protons of **23** were established through HMQC and GCOSY analysis.



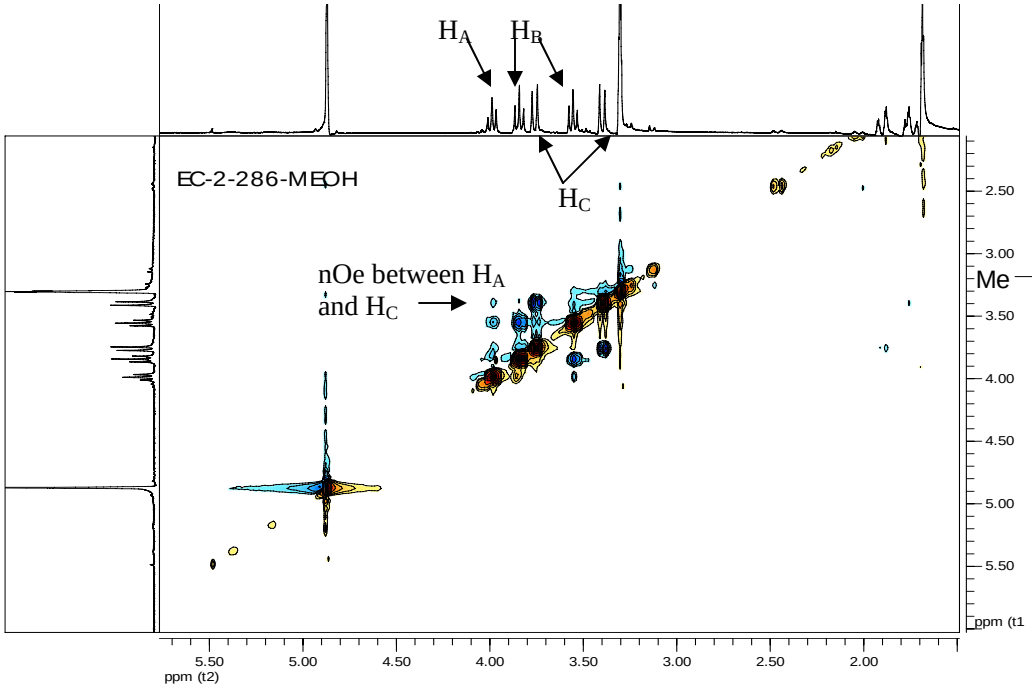
23

Figure A, Chem 3D representation of **23** showing observed nOe

NOESY spectrum of alcohol **23** (d_6-MeOH).

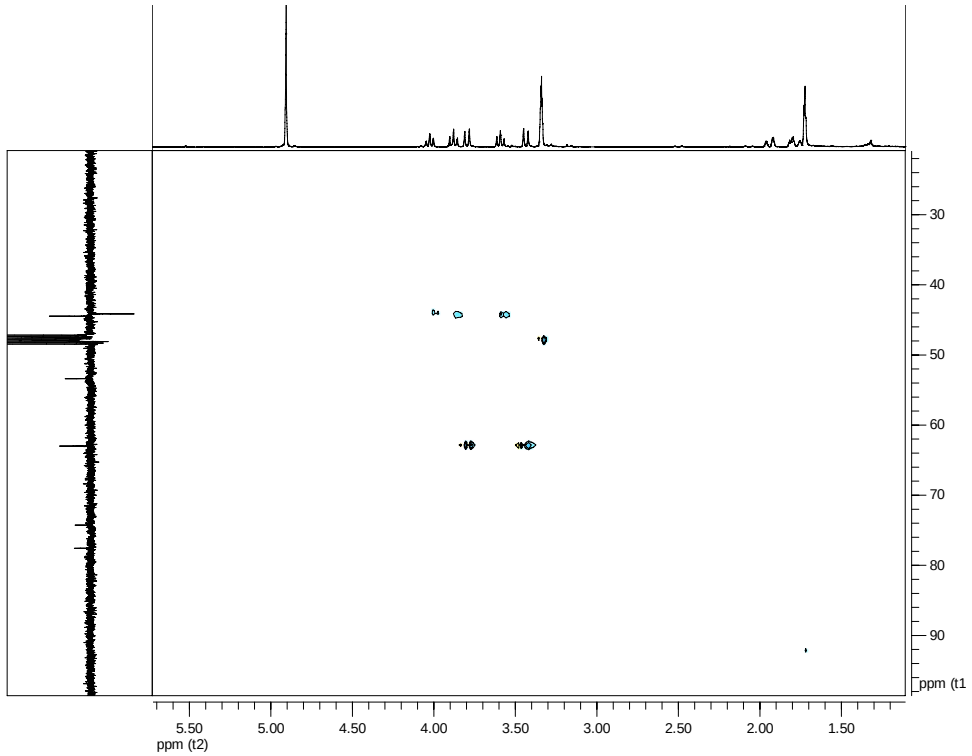


NOESY spectrum (expansion plot) for alcohol **23** (d_6-MeOH).

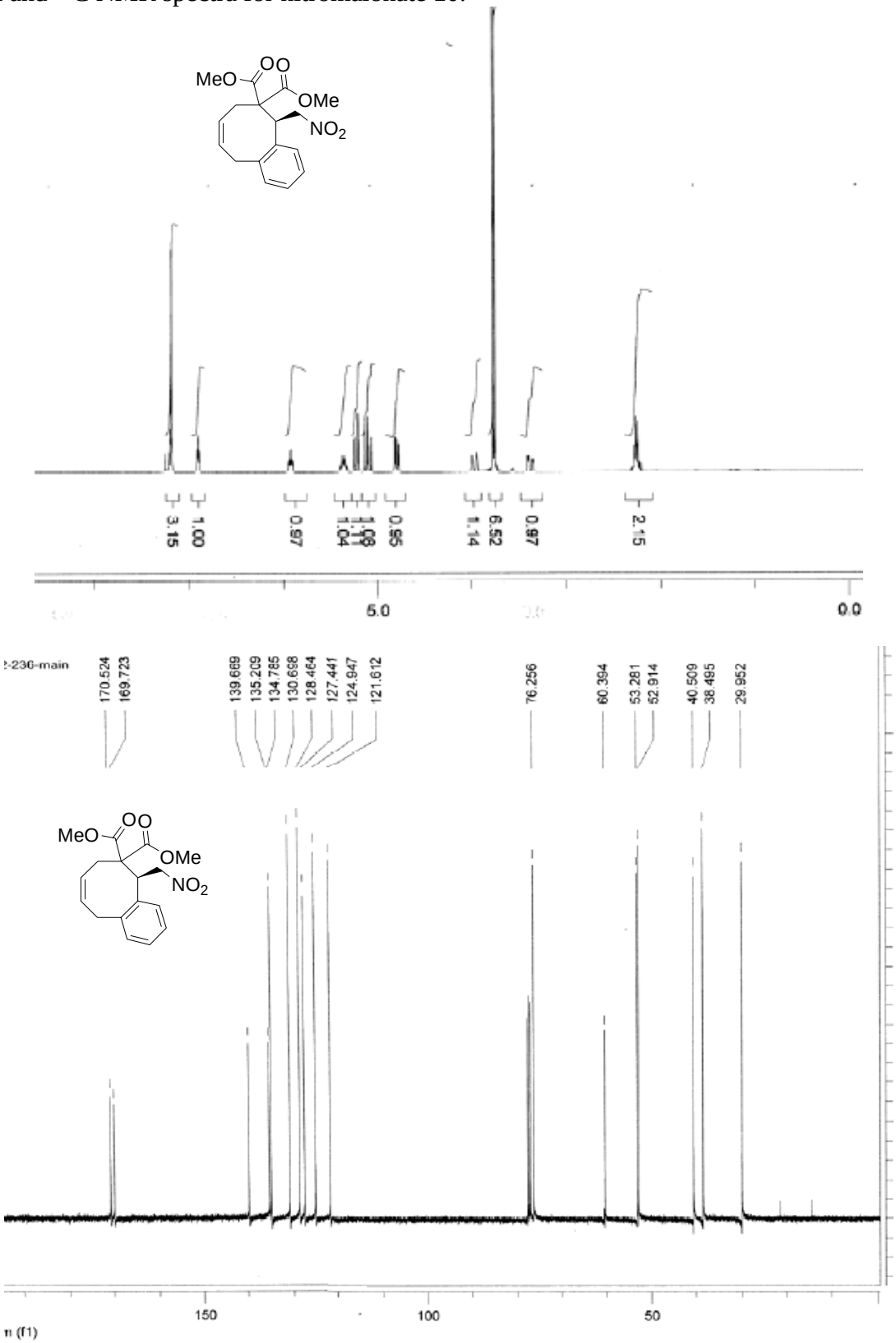


23

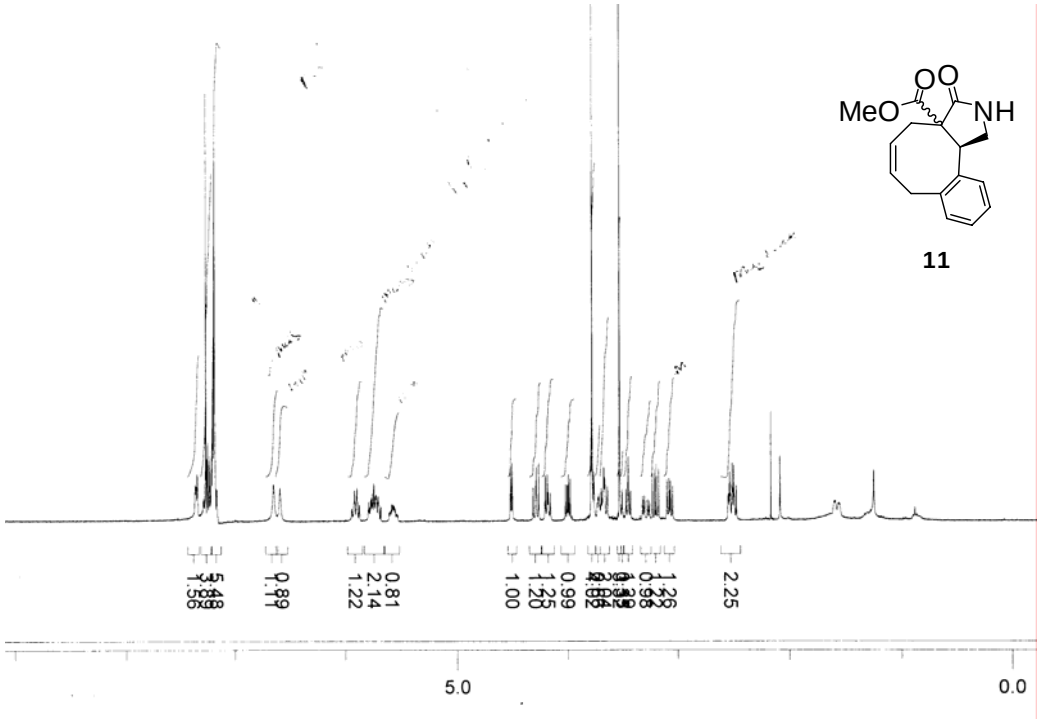
HMQC spectrum (expansion plot) for alcohol **23** (d_6-MeOH).

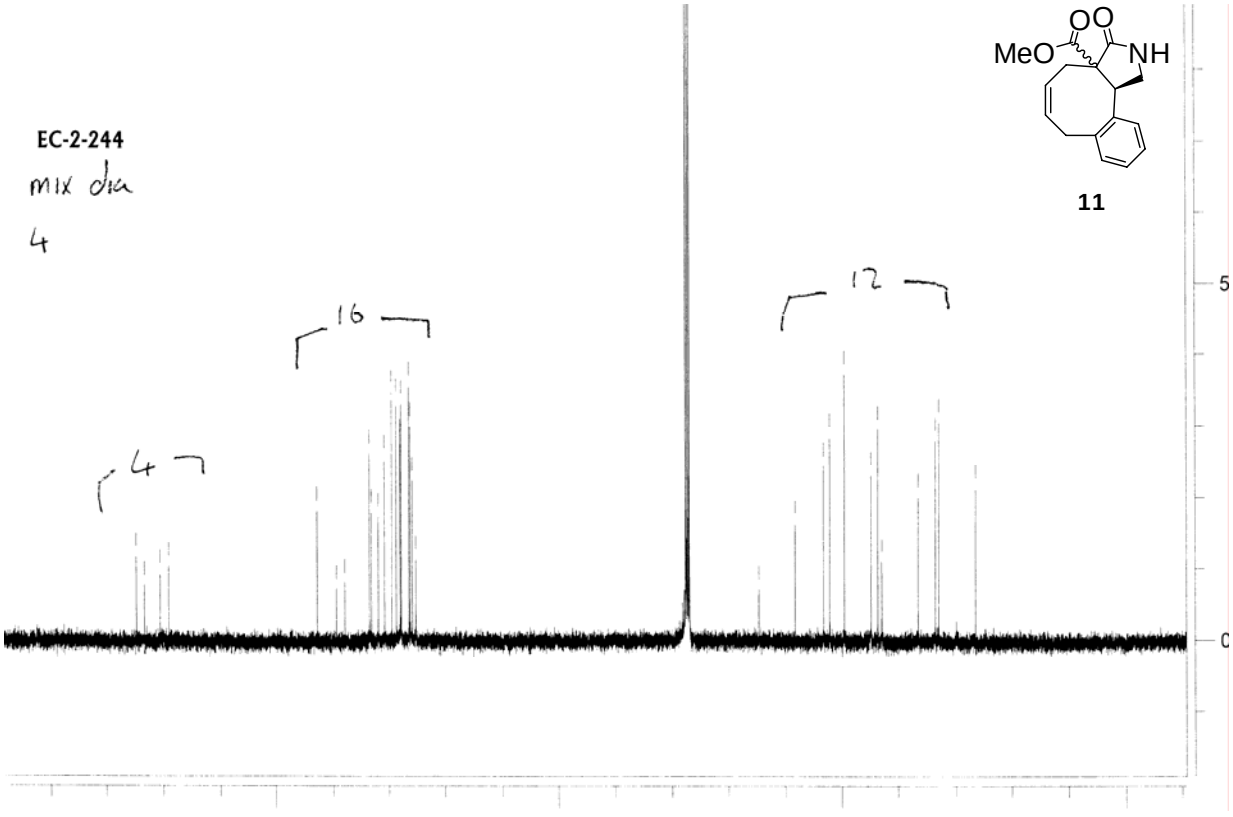


^{1}H and ^{13}C NMR spectra for nitromalonate **10**.

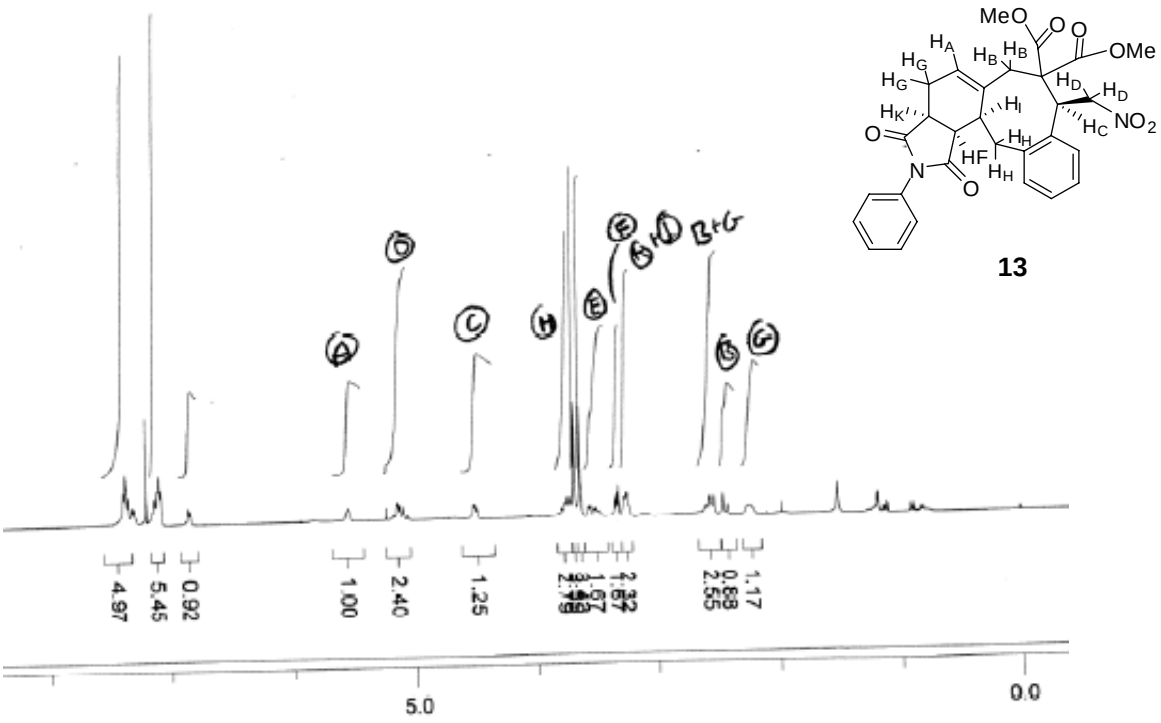


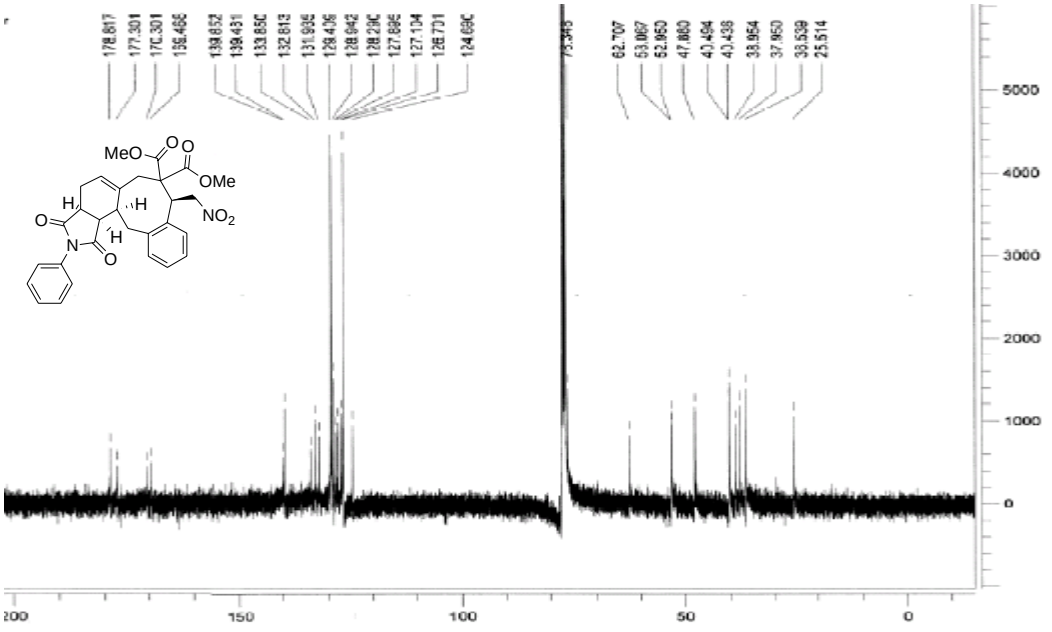
^{1}H and ^{13}C NMR spectra for lactam **11** (major and minor diastereomers).



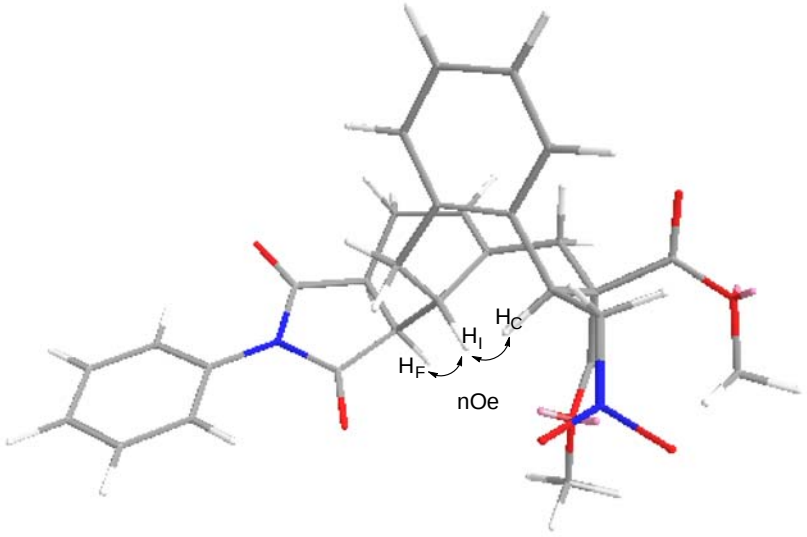


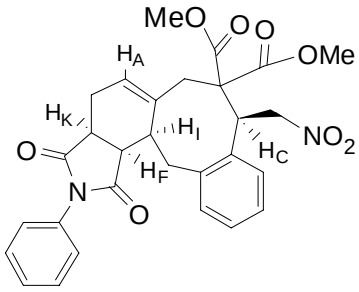
^{1}H and ^{13}C NMR spectra for nitromalonate **13**.





- HMQC and GCOSY analyses facilitated assignment of methine protons H_C, H_I and H_F.



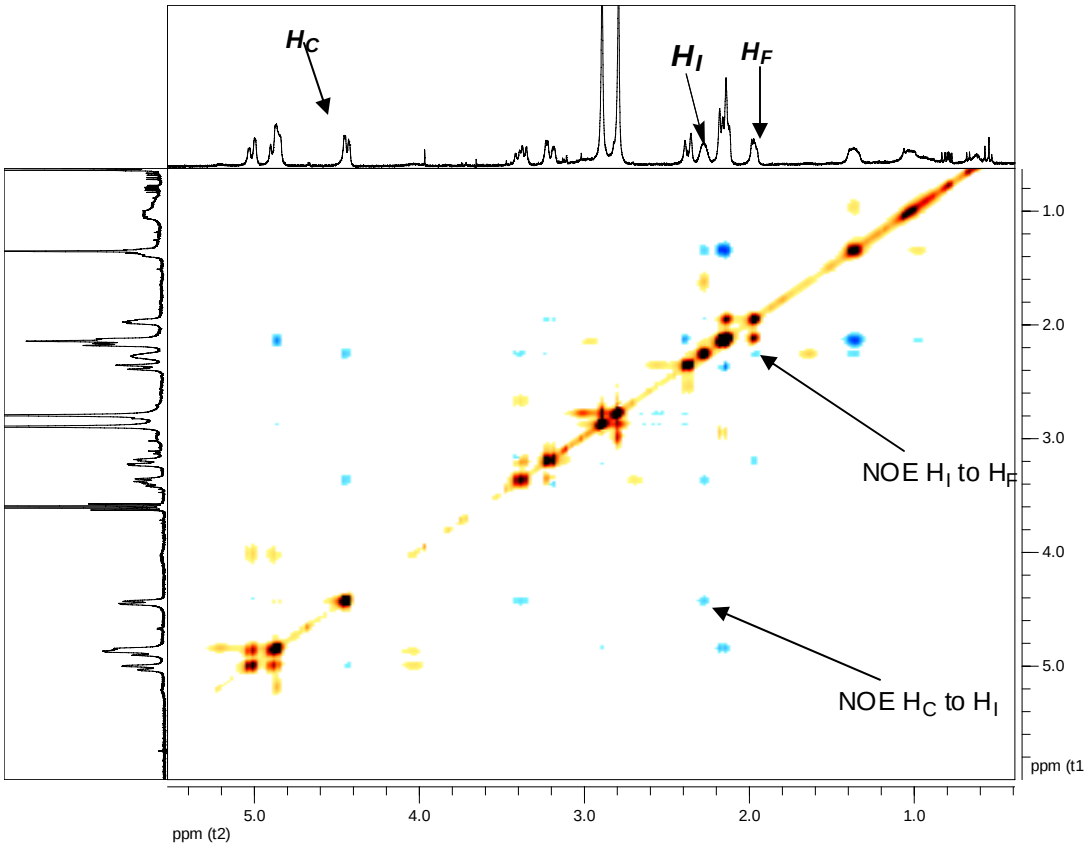


13

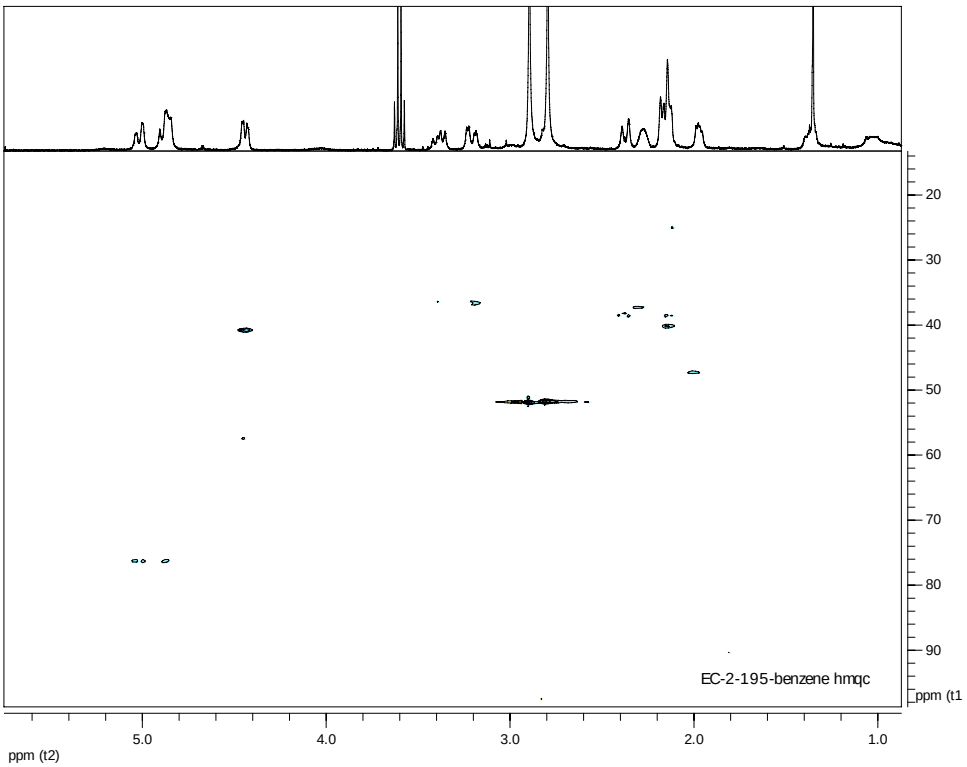
Figure B, Chem 3D representation for **13** showing observed nOes

- The NOESY spectrum shows an nOe from H_C to H_I. H_C is on α face which means that Hi is also on the α face. There is also an nOe from H_I to H_F which shows that H_F and therefore H_K are also on the α face.

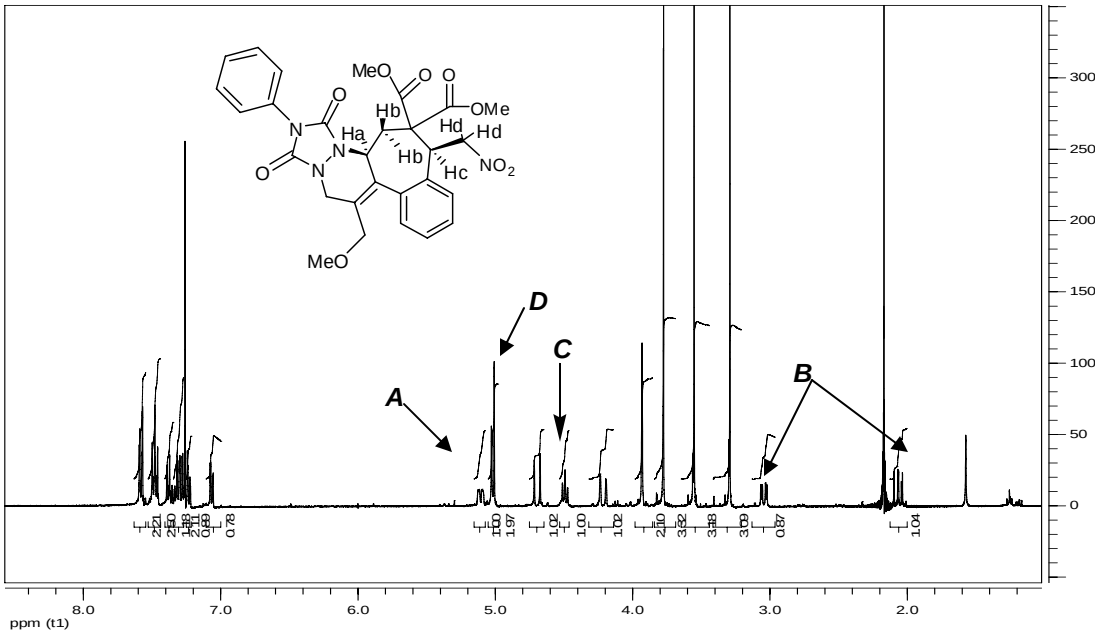
NOESY spectrum for tetracycle **13** in d_6-benzene.

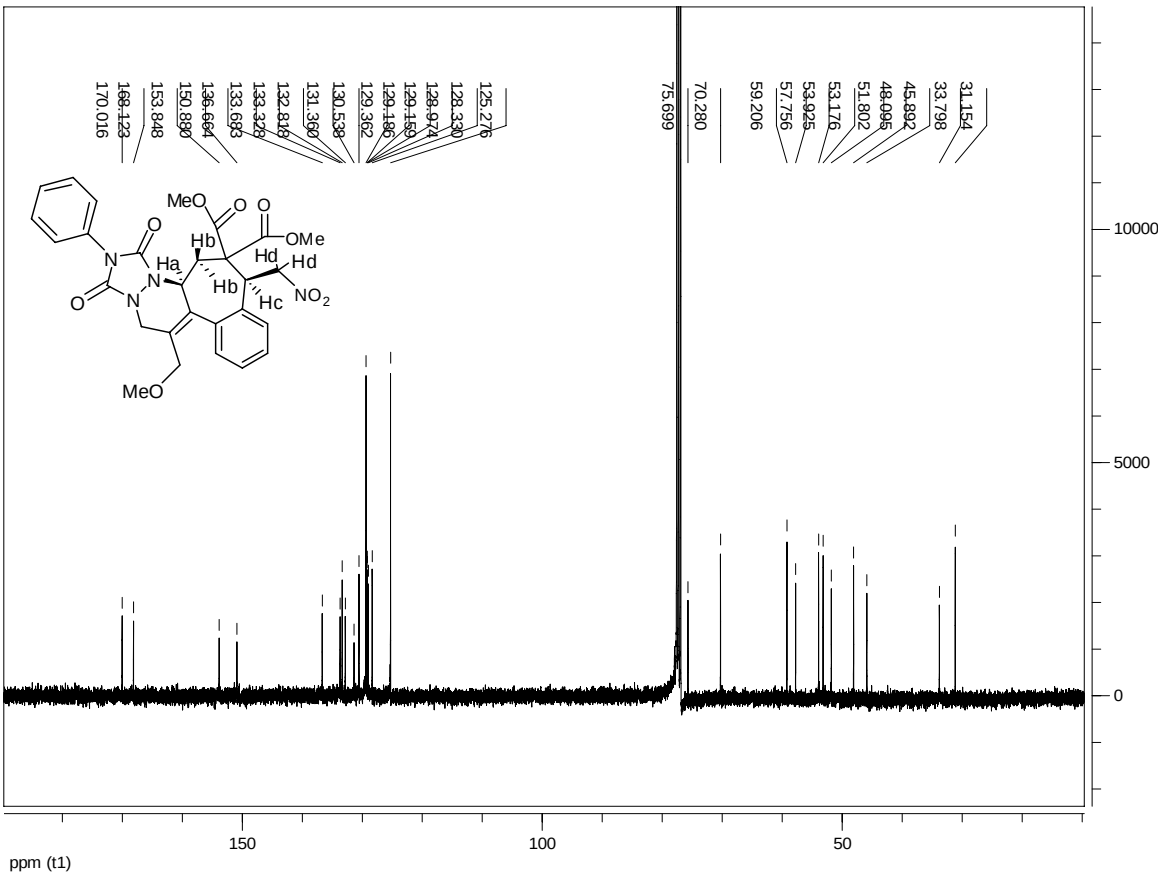


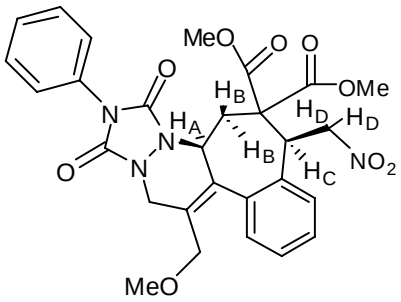
HMQC spectrum for tetracycle **13** in d_6-benzene.



^{1}H and ^{13}C NMR spectra of tetracycle **15**







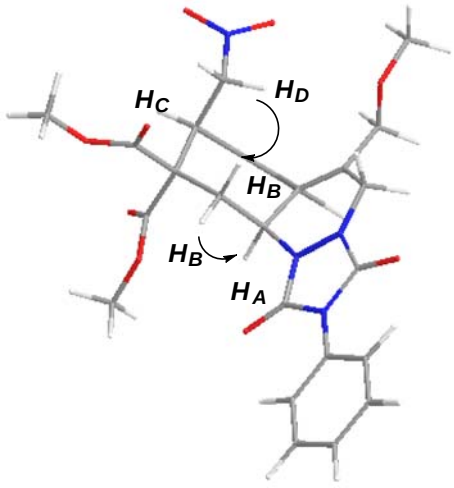
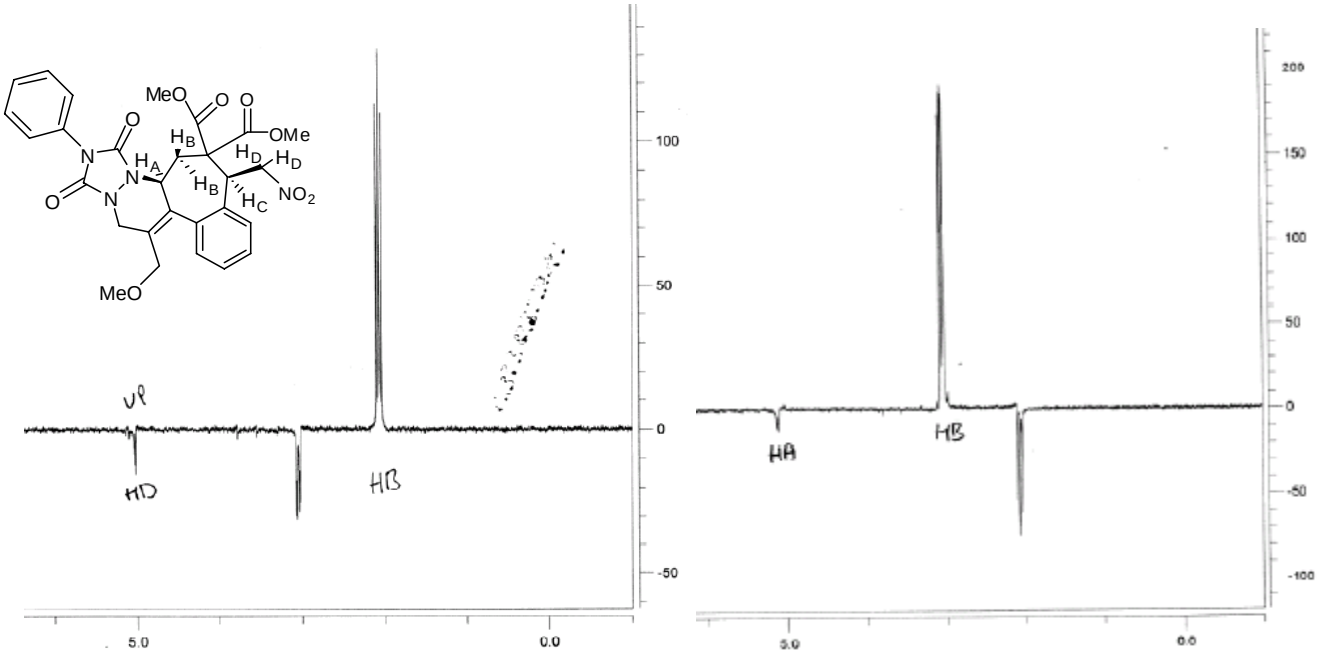


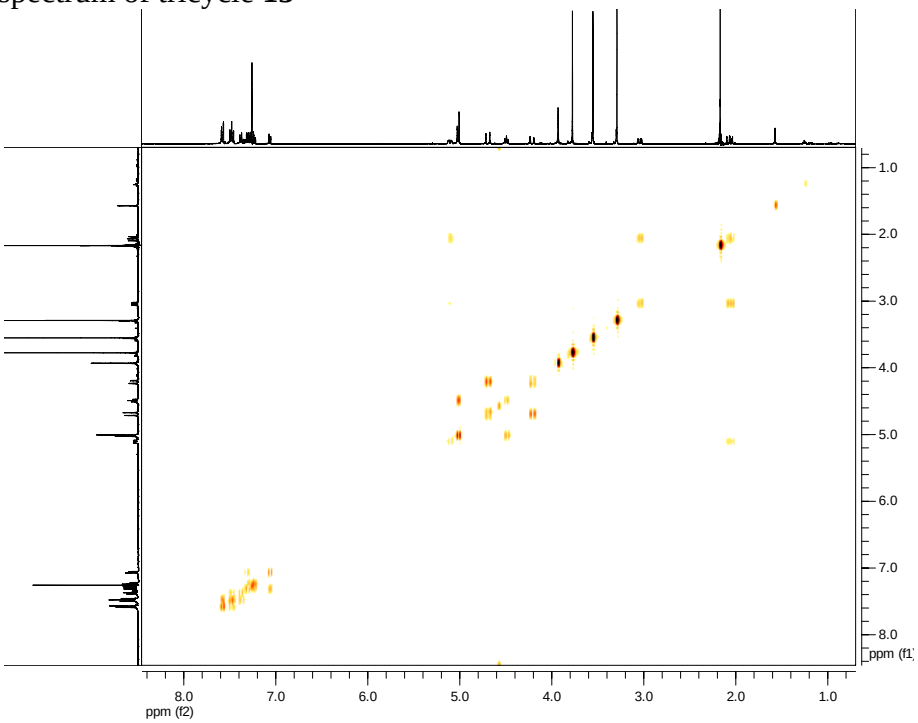
Figure C, Chem 3D representation of **15** showing observed nOes

- HMQC and GCOSY analyses of **15** facilitated the assignment of peaks corresponding to protons H_D (2 protons), H_B (2 protons) and H_A.
- From 1D nOe analysis of tricycle **15**; Proton H_B at δ 2.07 ppm has an nOe with H_D, thus this proton is on the same face as H_D which is the β face. Proton H_B at δ 2.56 must be on the opposite α face. This proton has an nOe with H_A, thus H_A is on the α face.

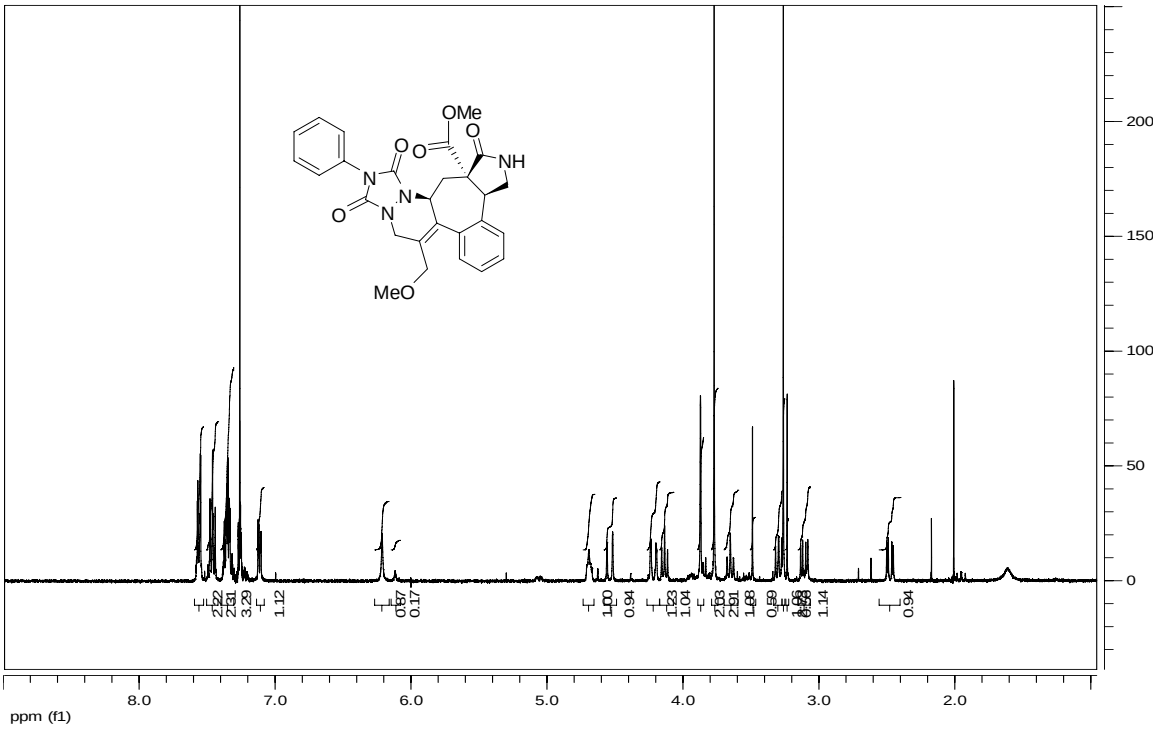
1D nOe analysis of tricycle **15**.

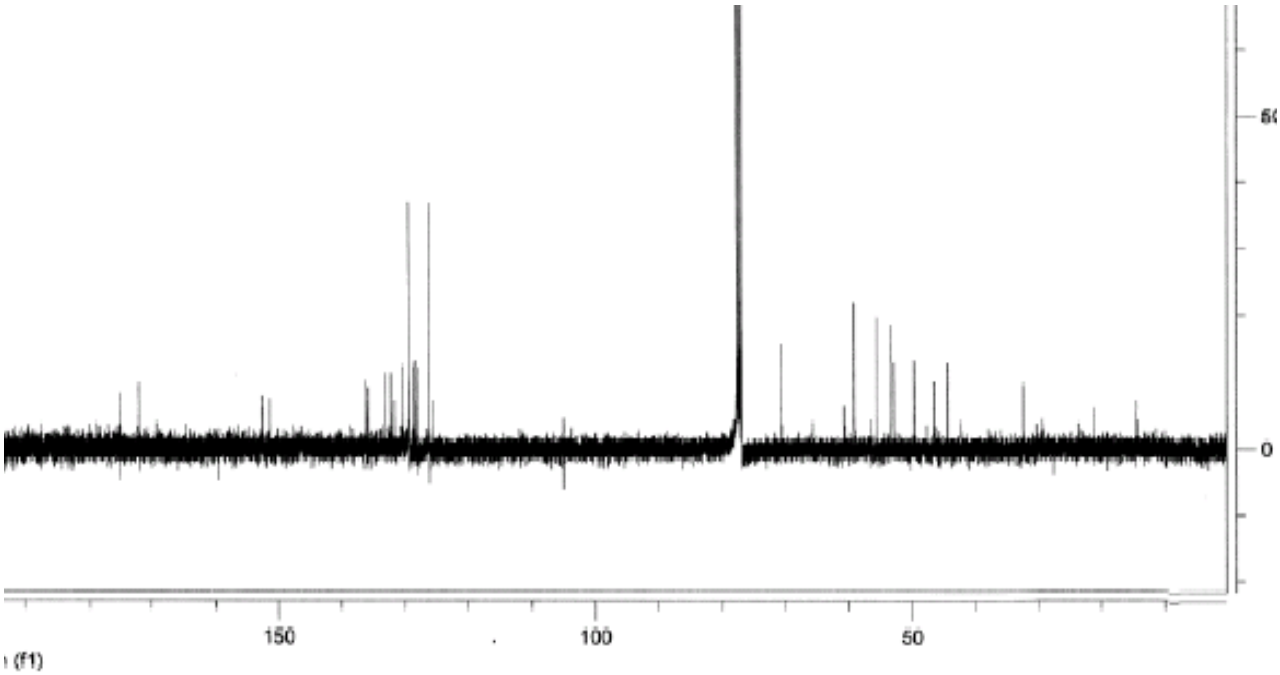


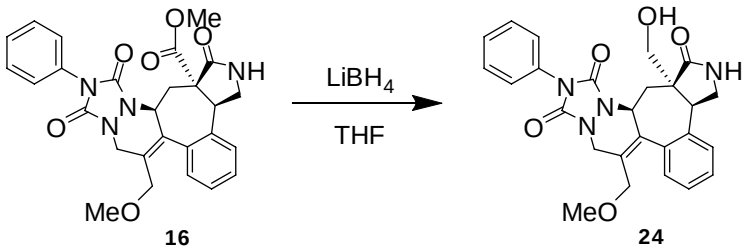
GCOSY spectrum of tricycle **15**



^{1}H and ^{13}C NMR spectra for tetracycle **16** (Major and minor diastereomers).







16 **24**

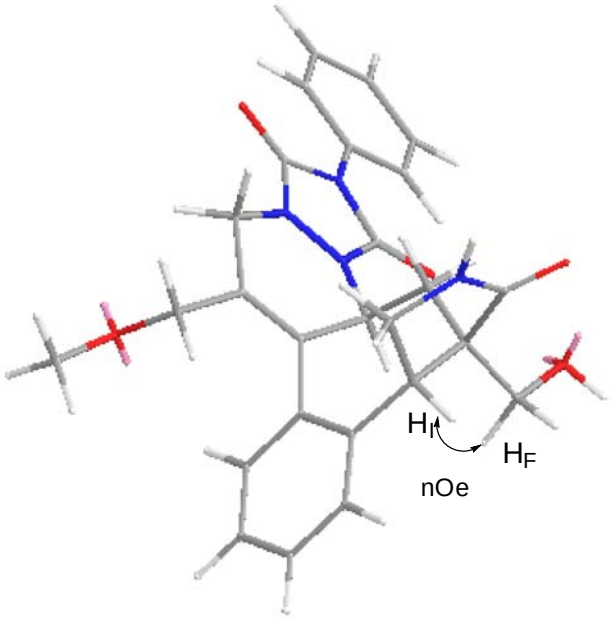
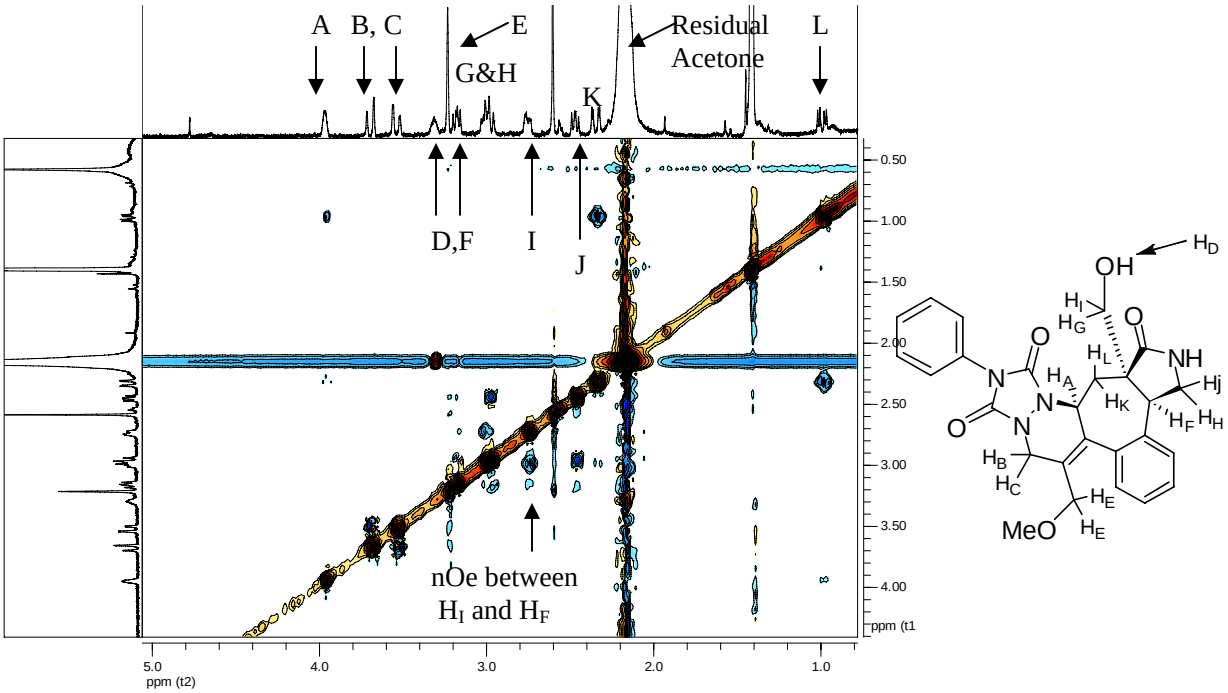


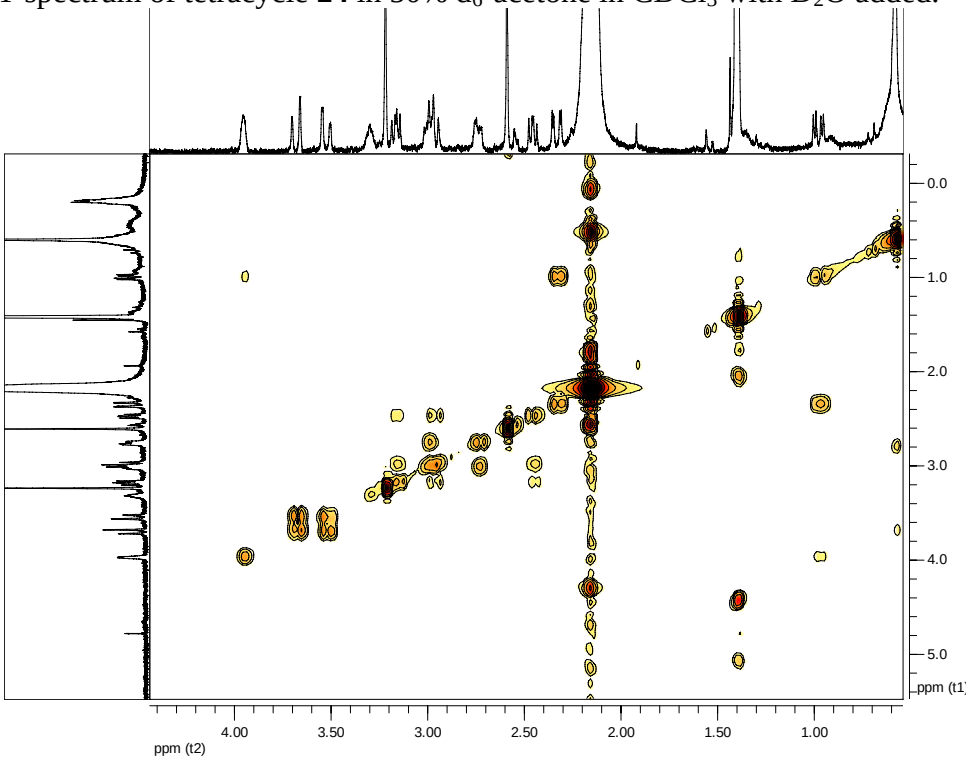
Figure D, Chem 3D representation for **24** showing observed nOe

- The stereochemistry of the quaternary carbon of lactam **16** was assigned based on NOESY data of the corresponding alcohol **24** in a 50% mixture of d_6-acetone in $CDCl_3$.
- HMQC and GCOSY analyses of **24** facilitated the assignment of peaks.
- An nOe was observed between the methine proton H_F on the lactam ring of **24** and one of the methylene protons H_I of the primary alcohol which is only possible with the *cis* fused lactam configuration.

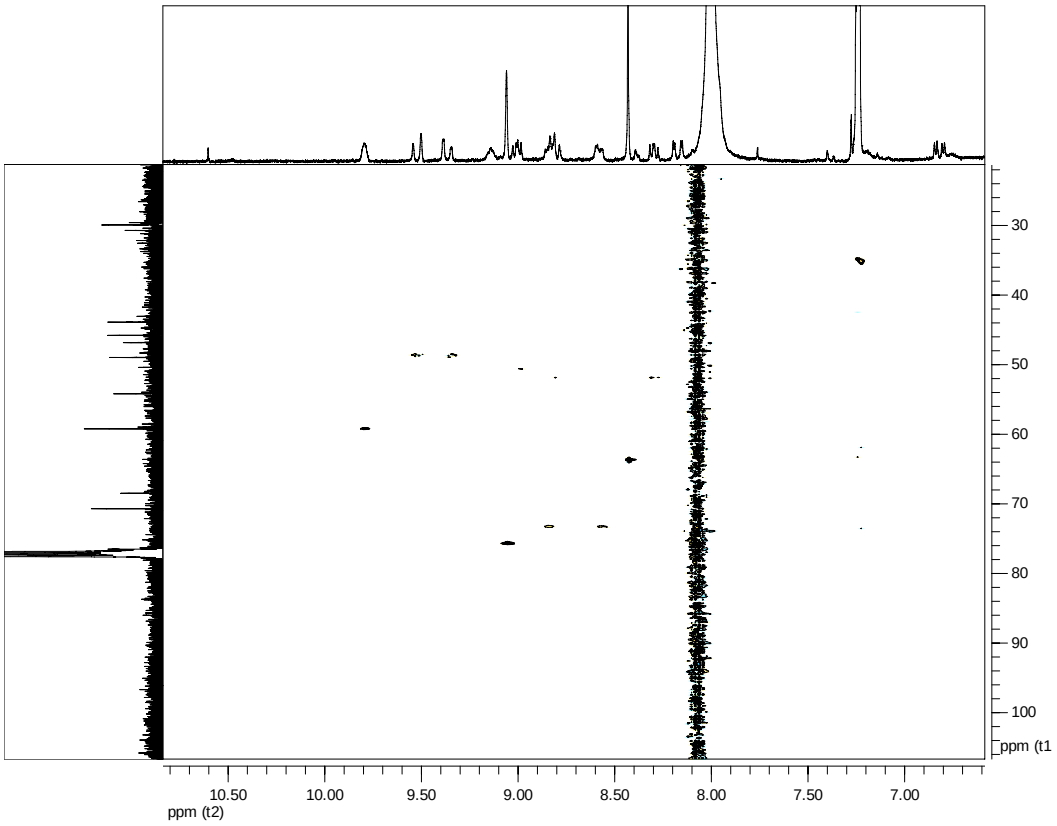
NOESY spectrum of tetracycle **24** in 50% d_6-acetone in $CDCl_3$.



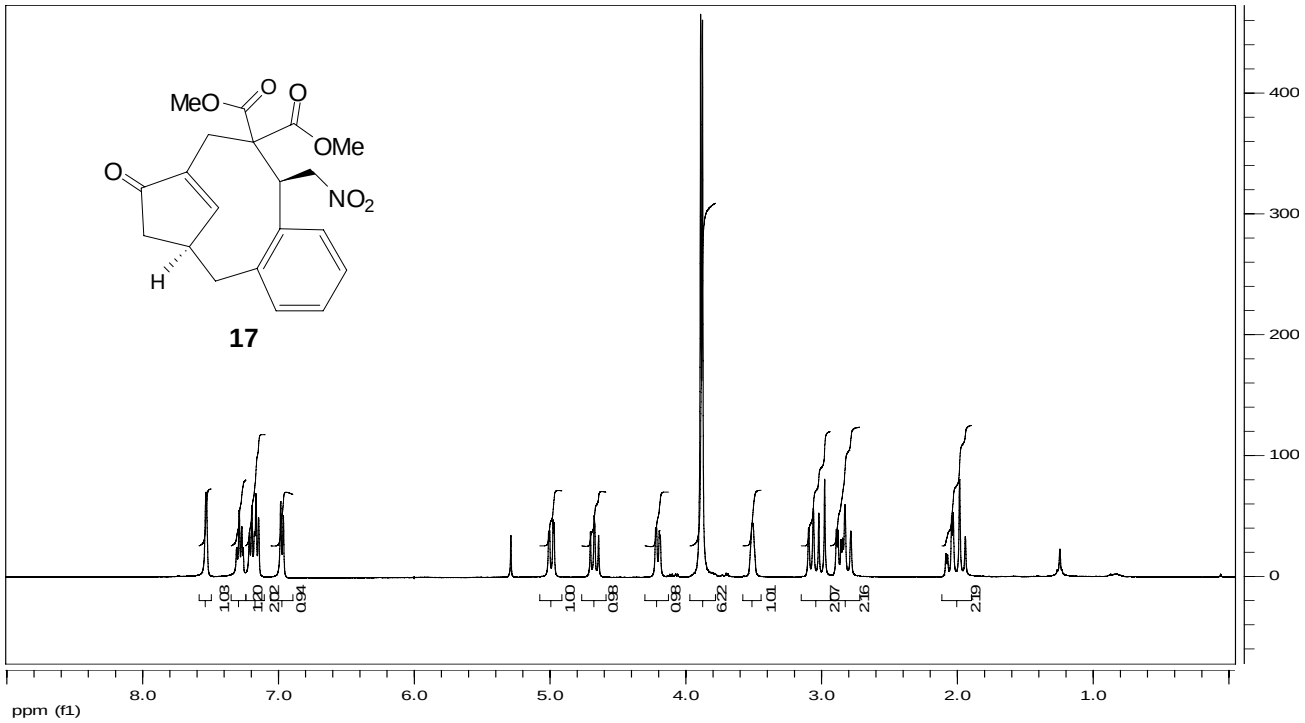
GCOSY spectrum of tetracycle **24** in 50% d_6-acetone in $CDCl_3$ with D_2O added.

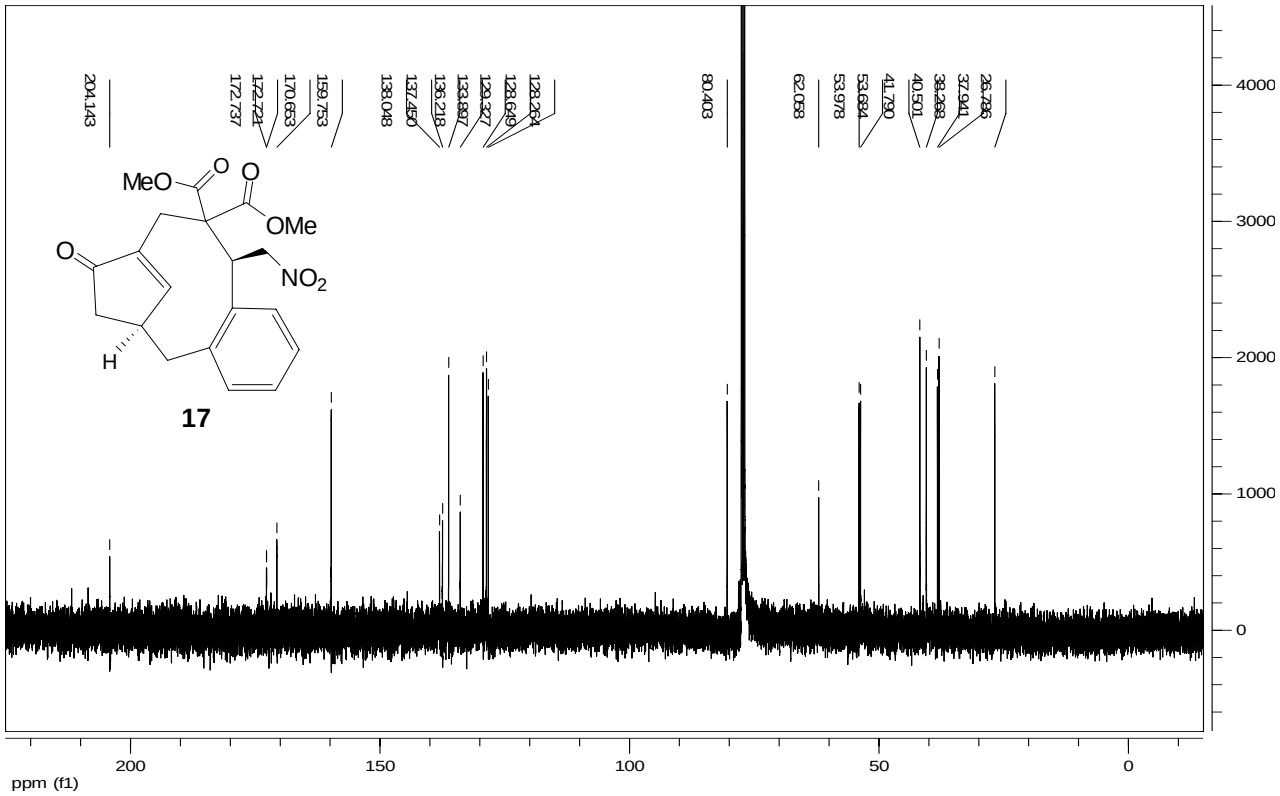


HMQC spectrum of tetracycle **24** in 50% d_6-acetone in $CDCl_3$.



^{1}H and ^{13}C NMR spectra of tricycle **17**.





1D nOe analysis of tricycle **17**.

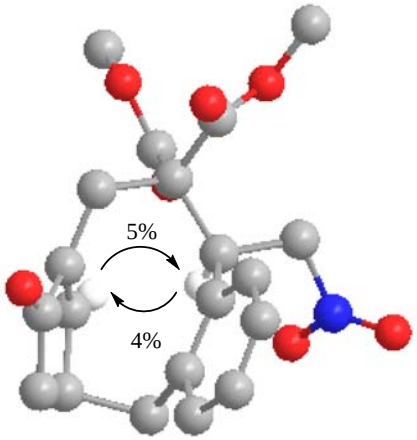
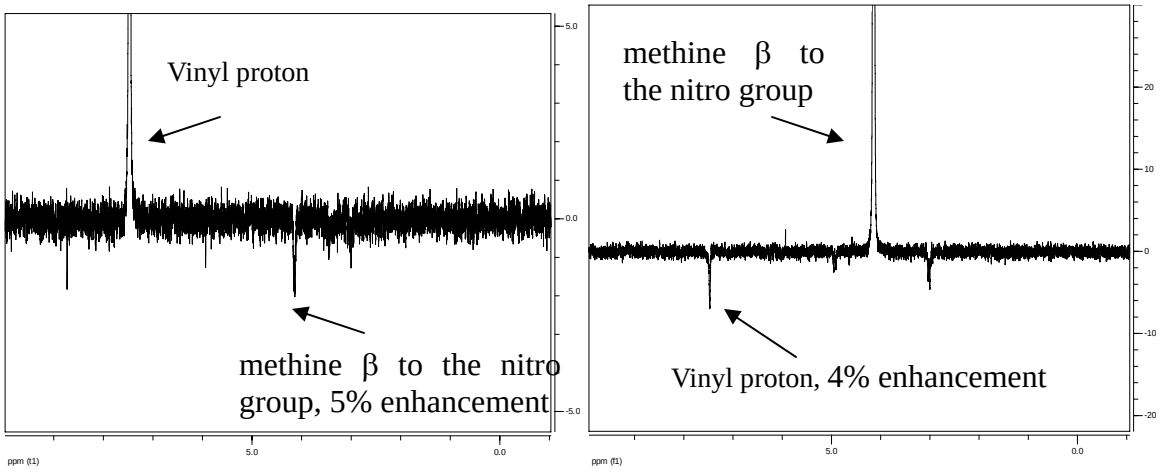
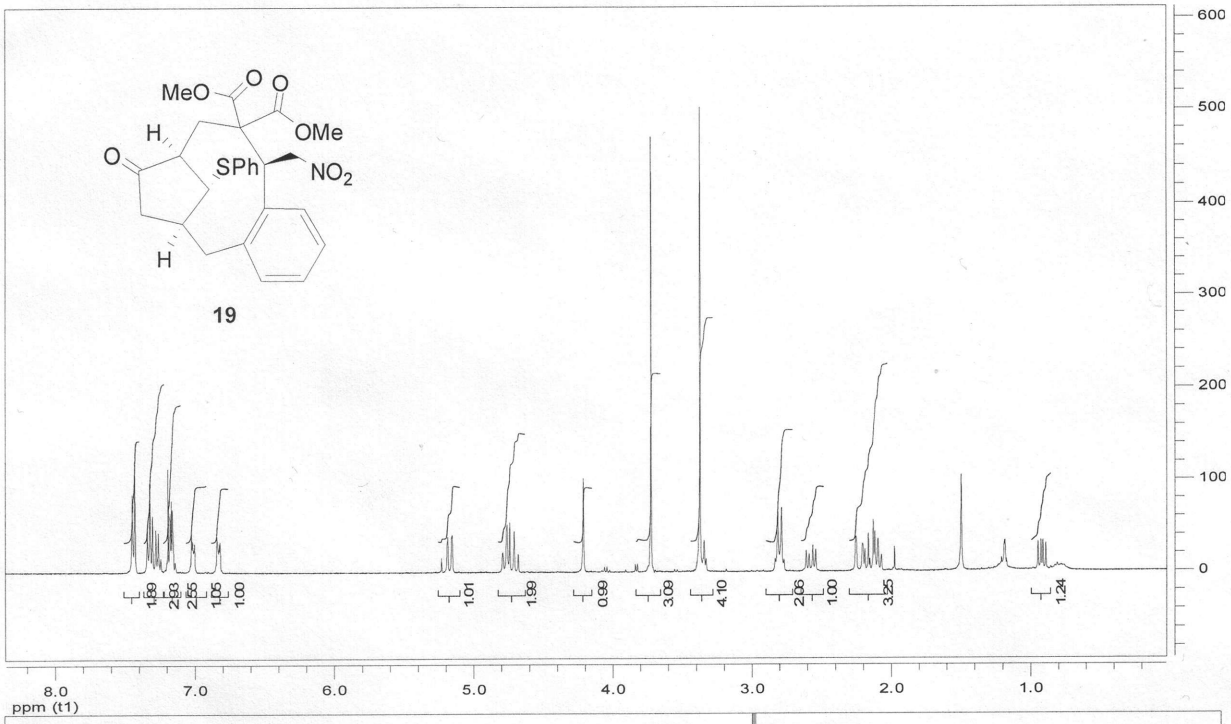


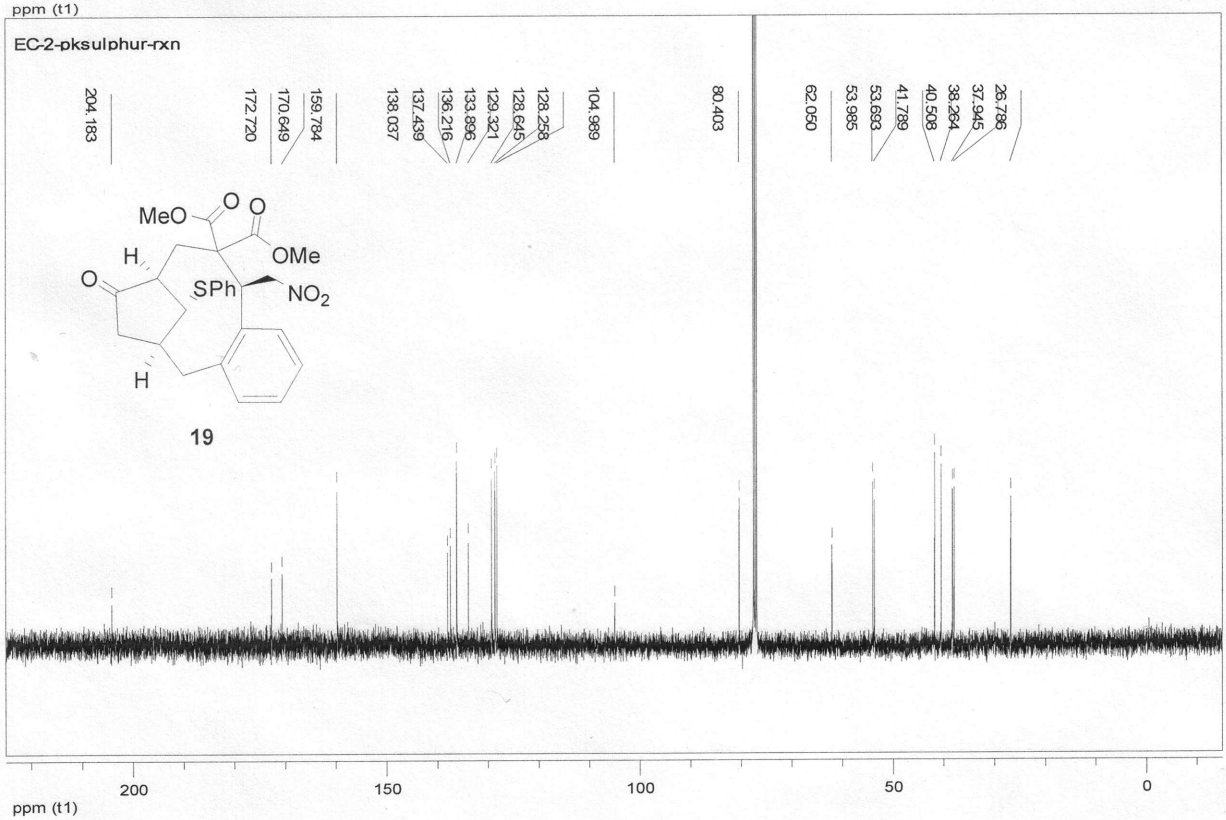
Figure E, Chem 3D representation for **17** showing observed nOes



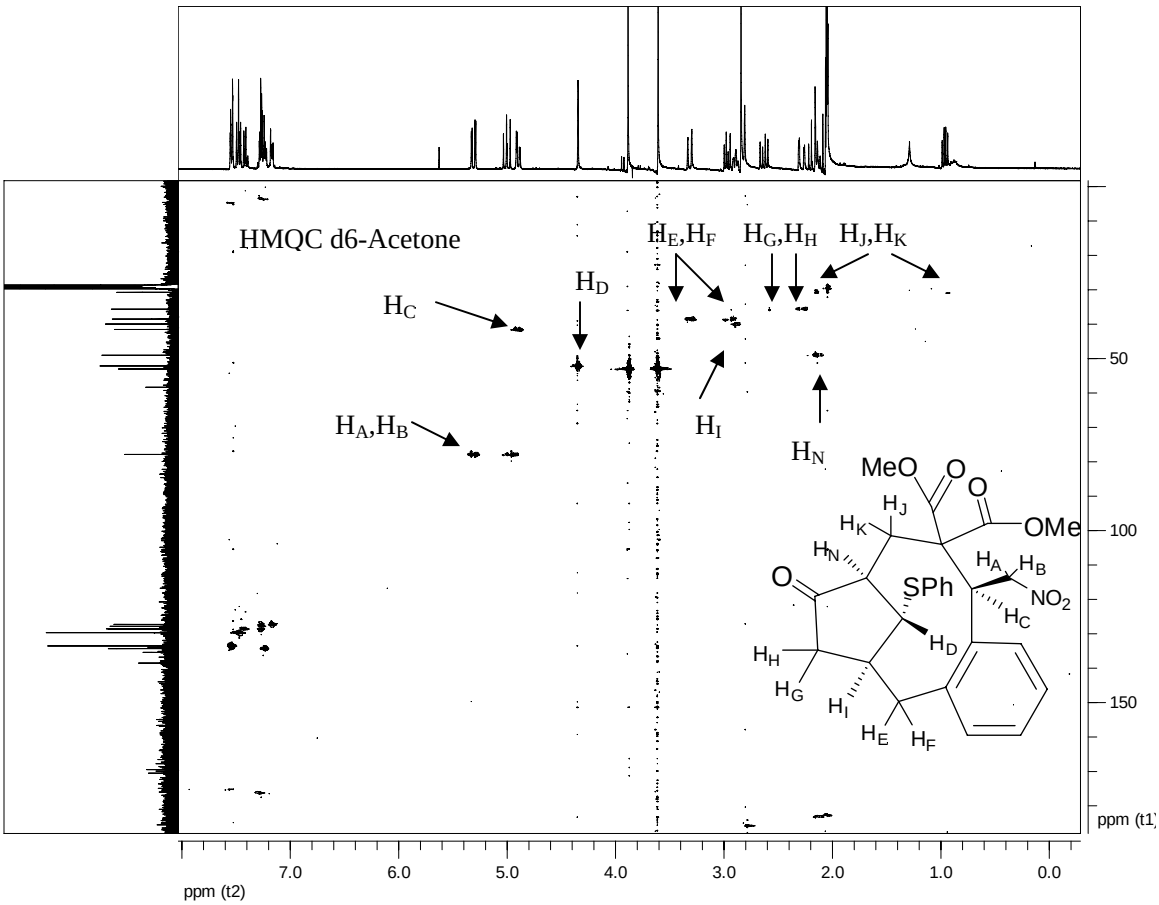
- The above nOes demonstrate that the solution phase conformation of **17** is similar to the x-ray structure shown in the main text (figure 2).

^{1}H and ^{13}C NMR spectra of tricycle **19** in $CDCl_3$.





HMQC spectrum of tricycle **19** in d6-acetone.



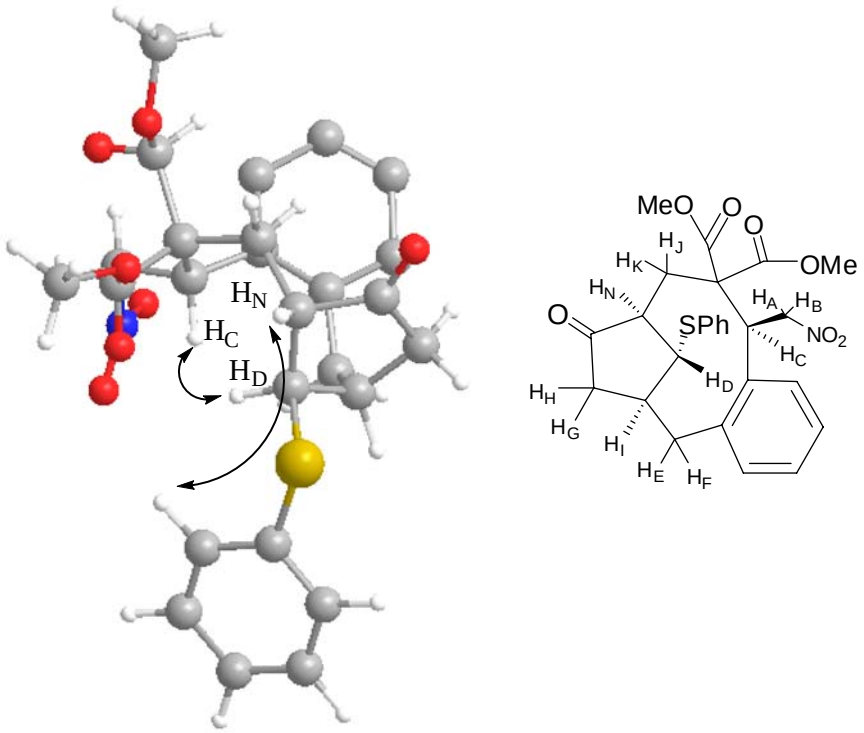
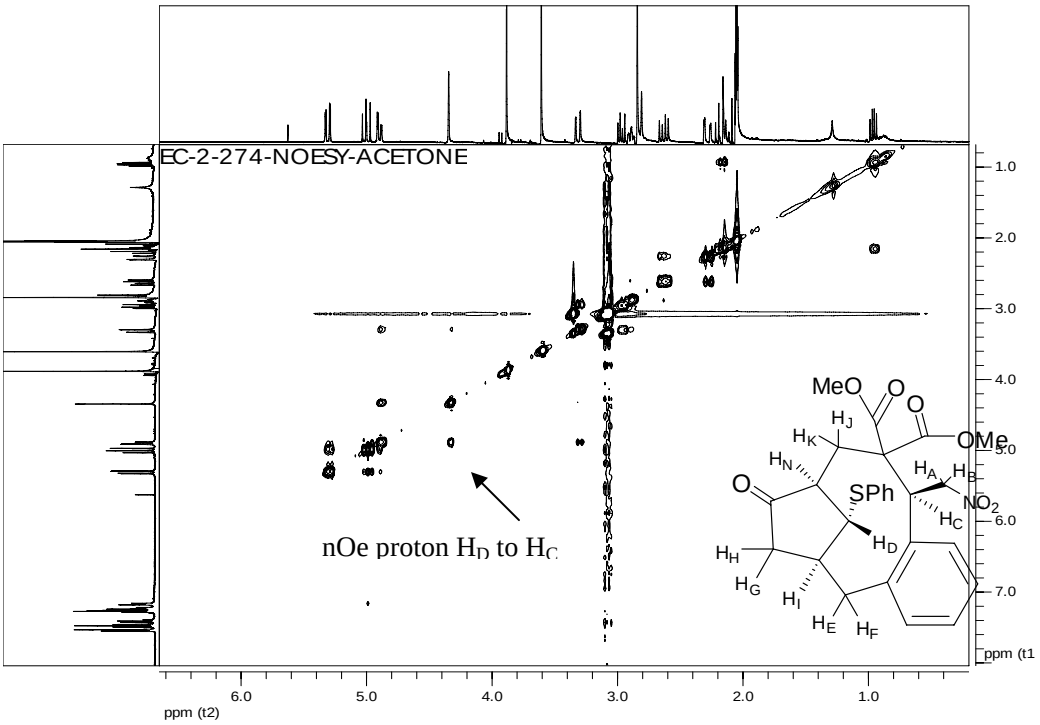


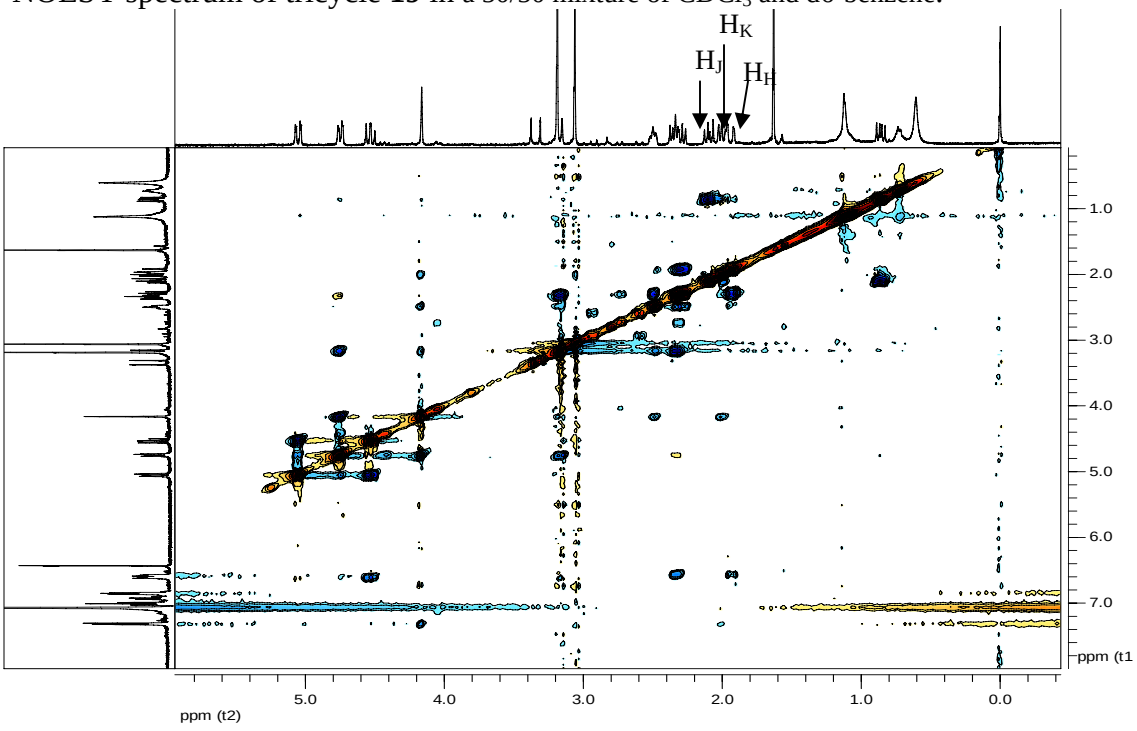
Figure F, Chem 3D representation for **19** showing observed nOes

- HMBC analysis of **19** in d_6-acetone shows that H_E and H_F couple to three aromatic carbons. Thus H_E and H_F are benzylic hydrogens.
- HMBC analysis indicates that the malonate quaternary carbon couples with H_J and H_K.
- Protons H_A and H_B are identified from their chemical shifts thus the remaining diastereotopic protons are H_H and H_G.
- GCOSY establishes H_I, as this proton couples with H_G. H_D is a singlet at 4.21 ppm, which suggests that the remaining high field methine proton is H_N.
- The stereochemistry of proton H_I was established as α from x-ray analysis of **17.**
- NOESY analysis of **19** shows a strong nOe from H_D to H_C. Thus H_D is in the β face as in Figure F.
- NOESY analysis of **19** (50/50 mixture of $CDCl_3$/d_6-benzene) shows an nOe from H_D to an aromatic proton which must belong to the SPh group. NOESY analysis also shows an nOe from H_N to the same aromatic proton established as a SPh group suggesting that H_N is on the α-face as shown in Figure F.

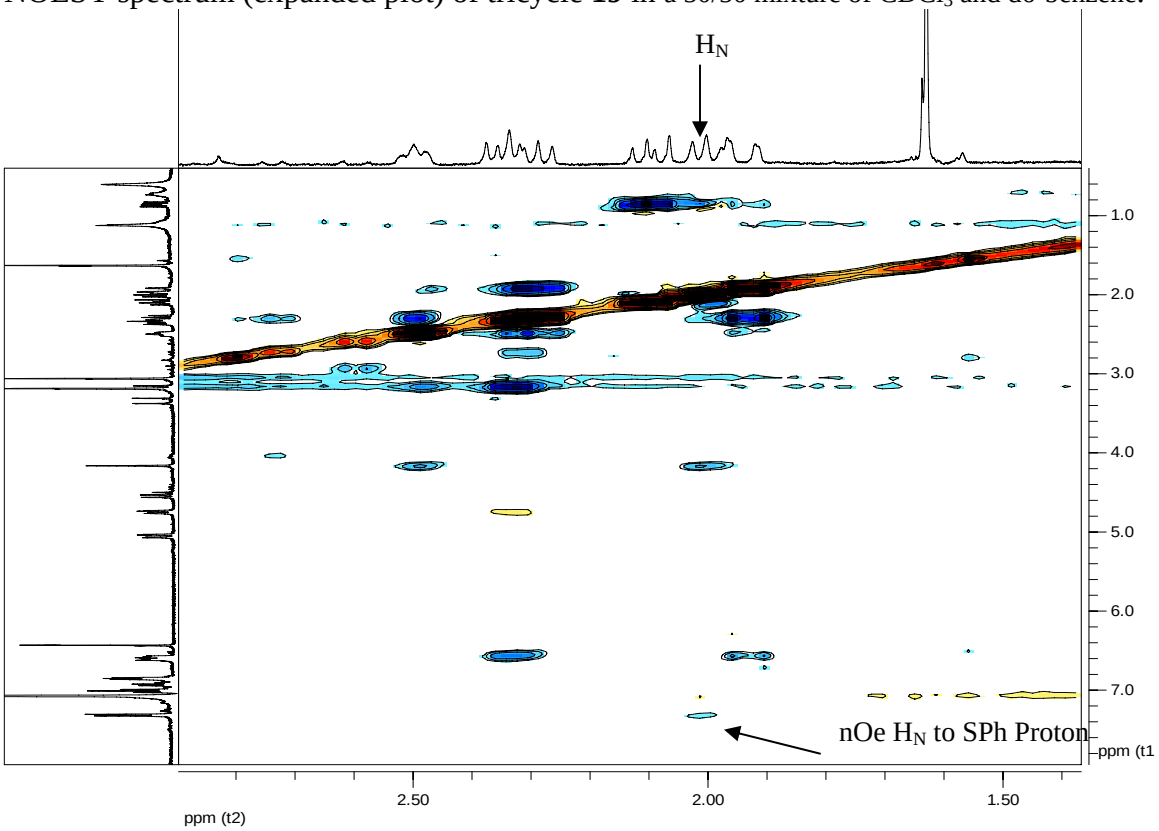
NOESY spectrum of tricycle **19** in d6-acetone.



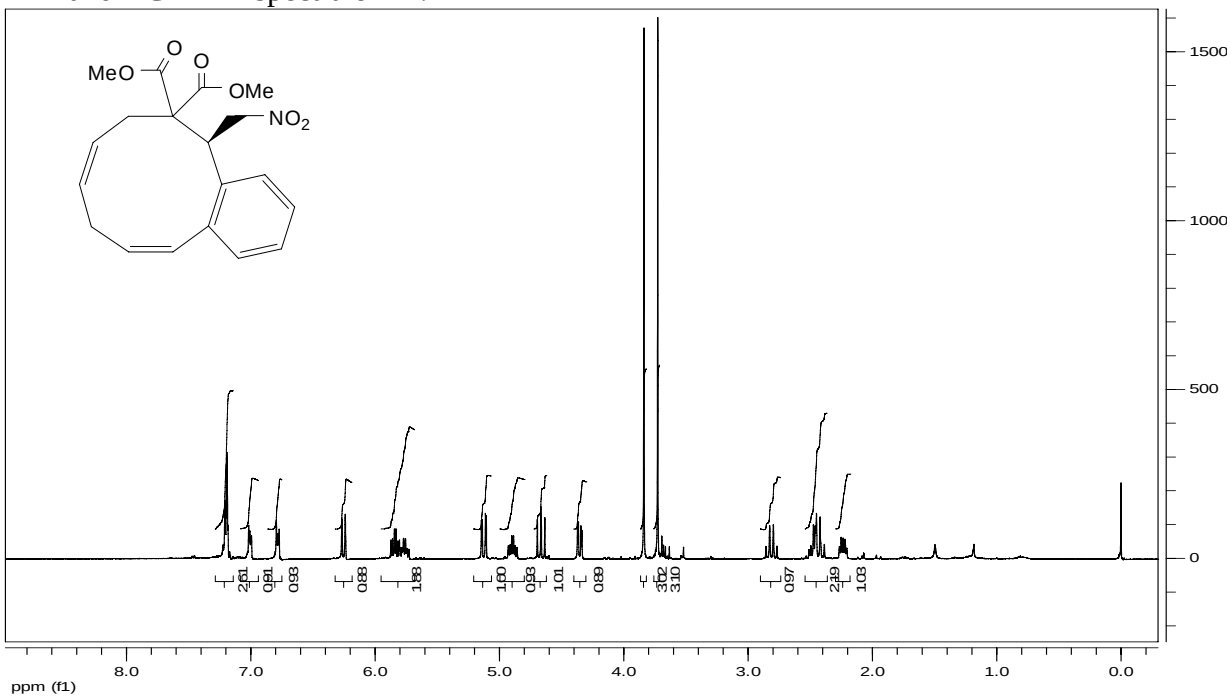
NOESY spectrum of tricycle **19** in a 50/50 mixture of $CDCl_3$ and d6-benzene.

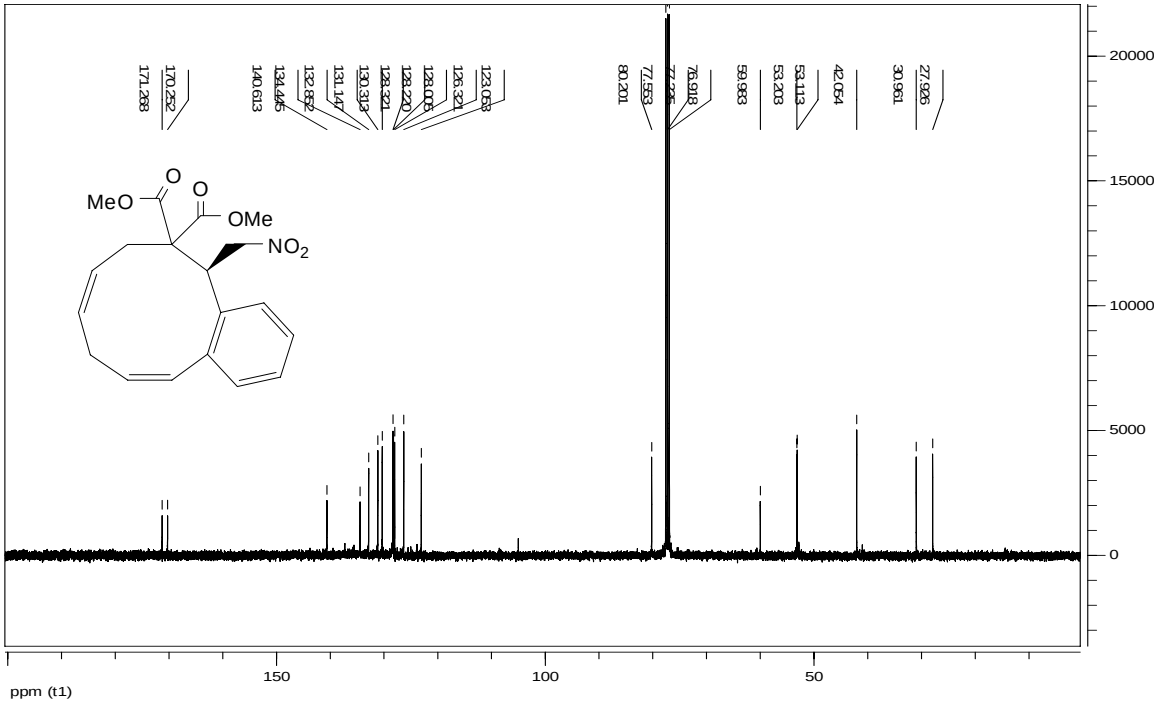


NOESY spectrum (expanded plot) of tricycle **19** in a 50/50 mixture of $CDCl_3$ and d6-benzene.

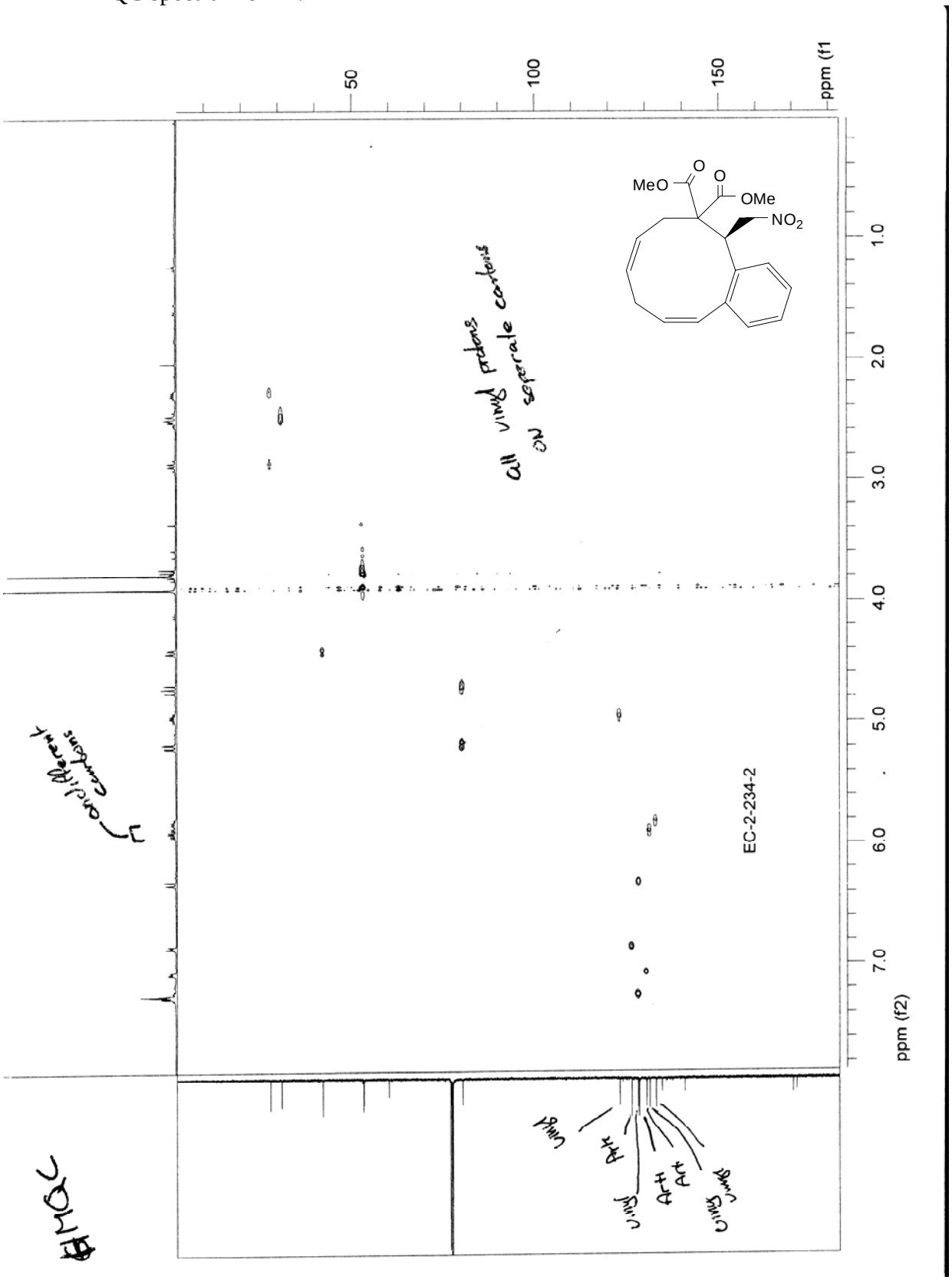


^{1}H and ^{13}C NMR spectra of **21**.

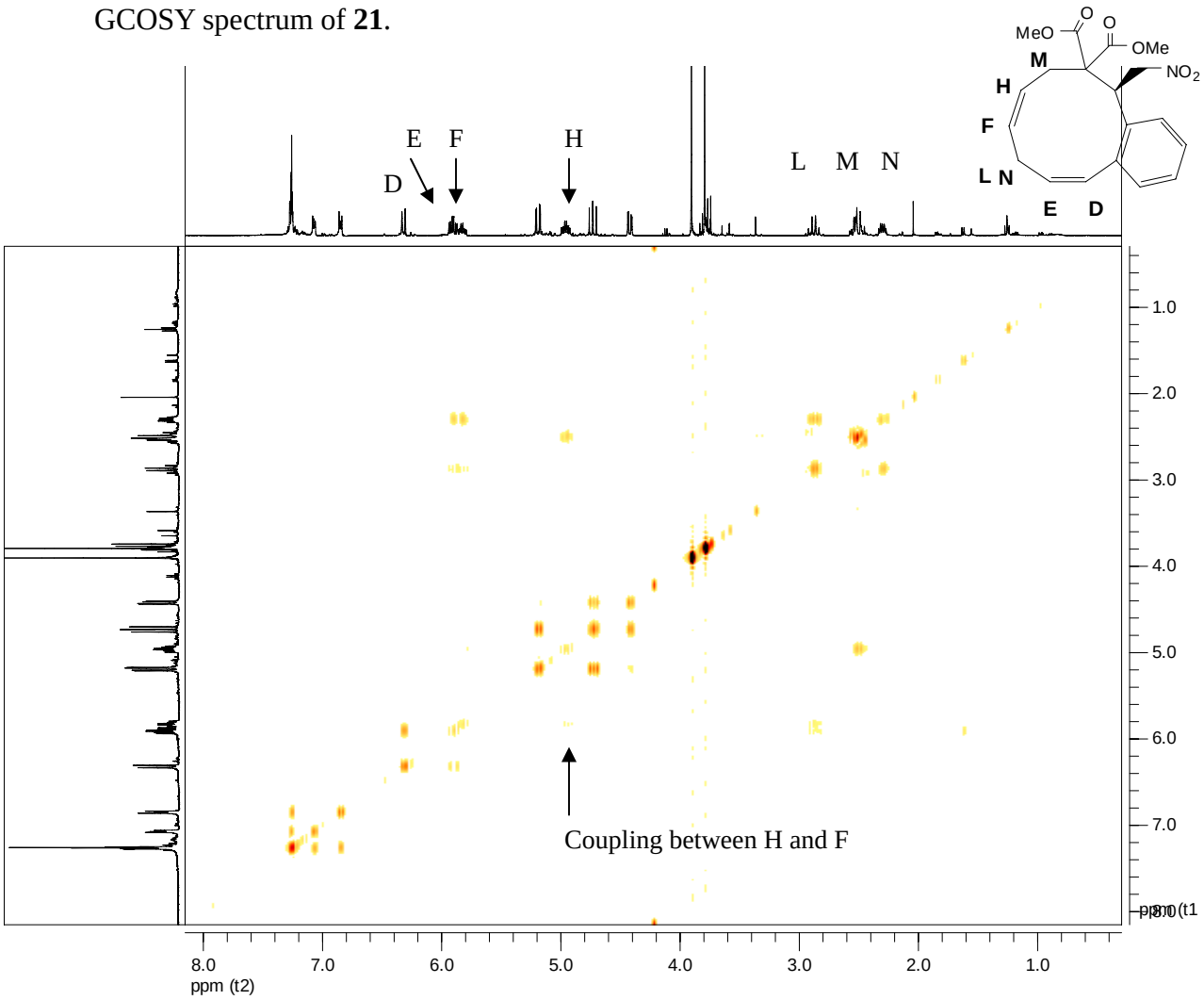




HMQC spectrum of **21**.

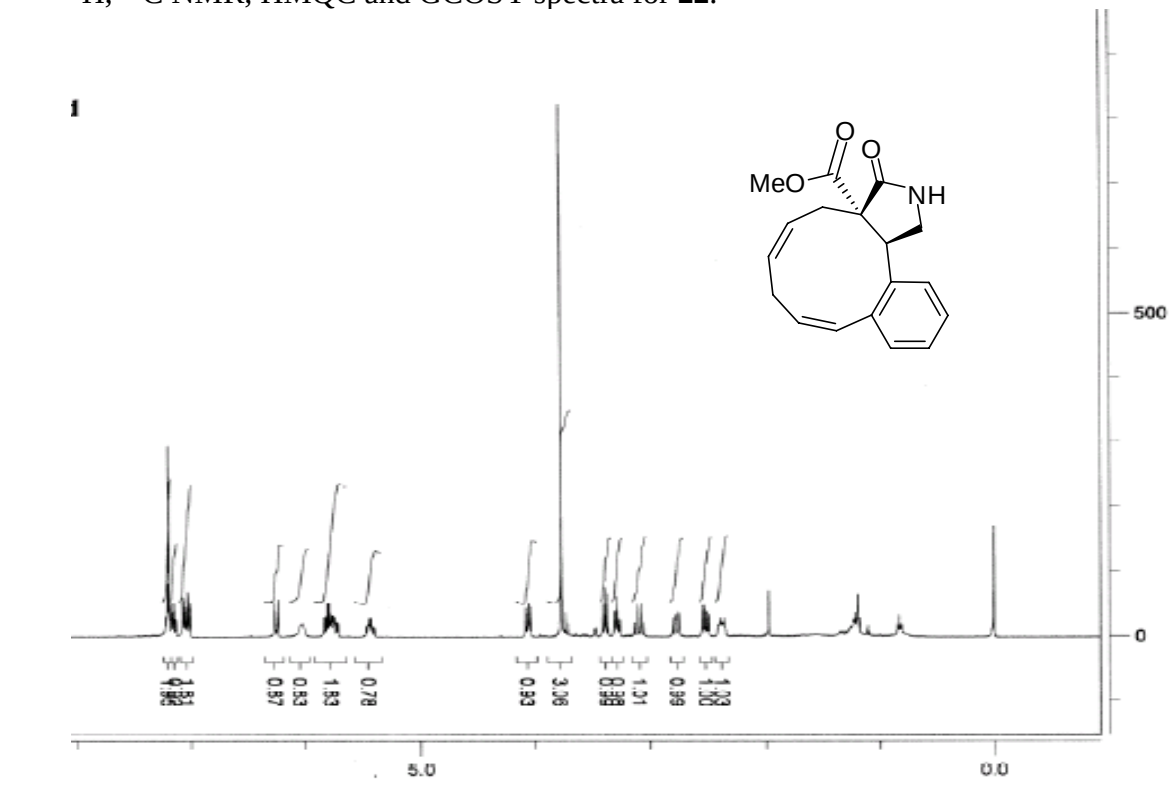


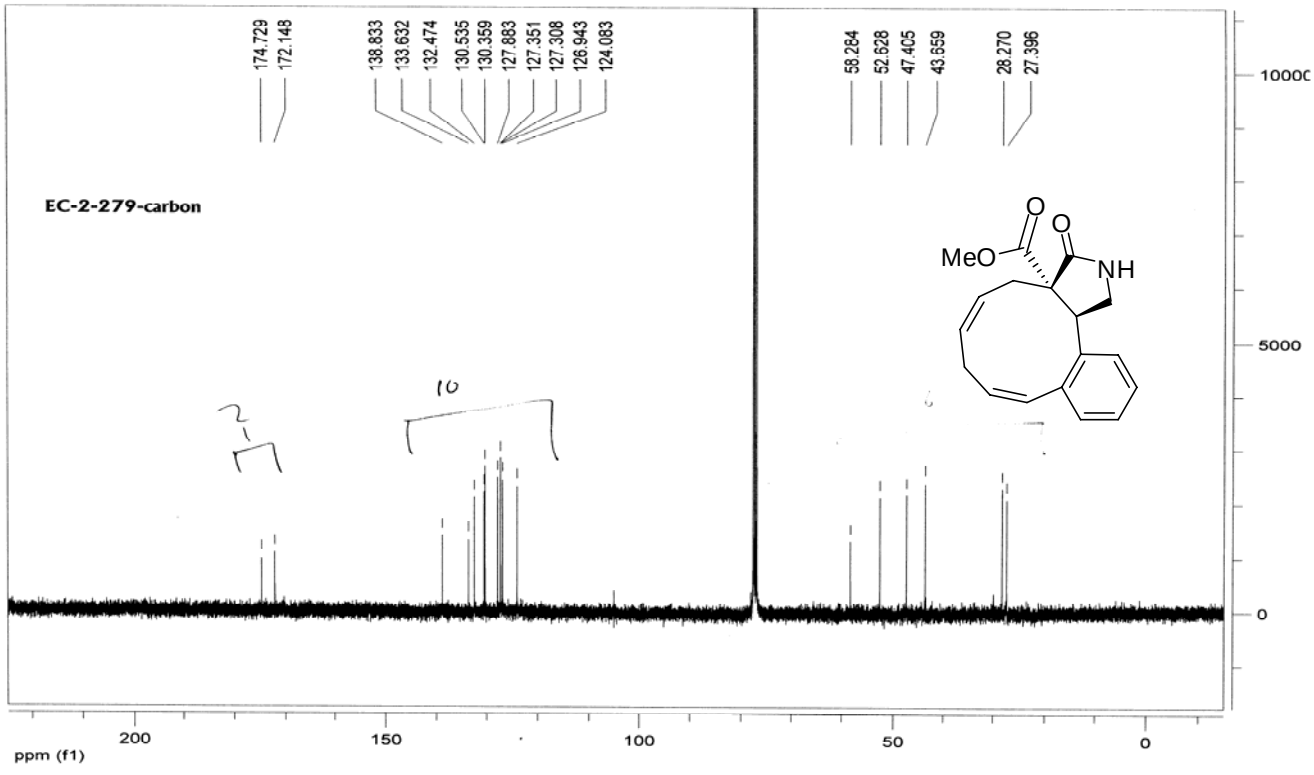
GCOSY spectrum of **21**.



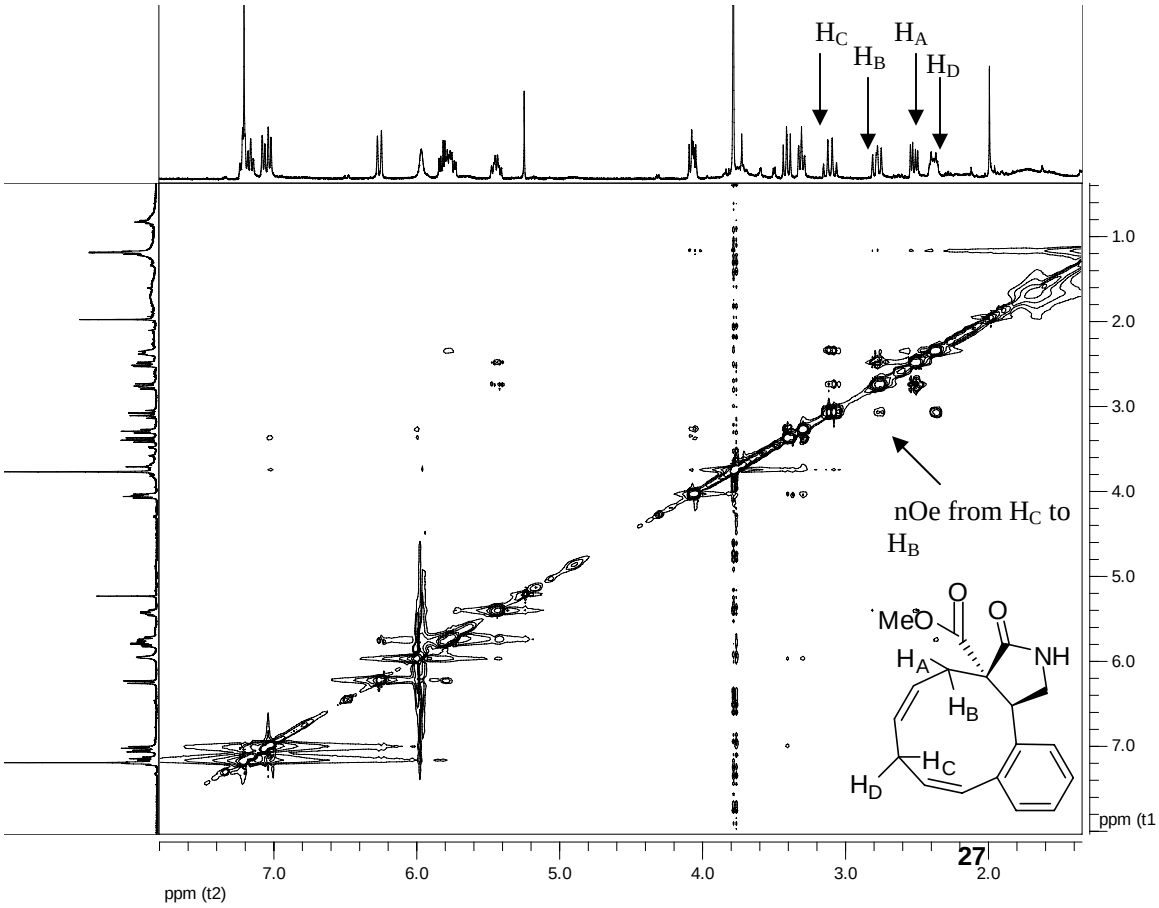
GCOSY spectrum of **21** shows the connectivity and correlation of protons to each other. Proton **D** couples with proton **E** which couples with protons **L** and **N.** Proton **L** couples with protons **F** which couples with protons **H.** Proton **H** couples with protons **M**.

^{1}H, ^{13}C NMR, HMQC and GCOSY spectra for **22**.

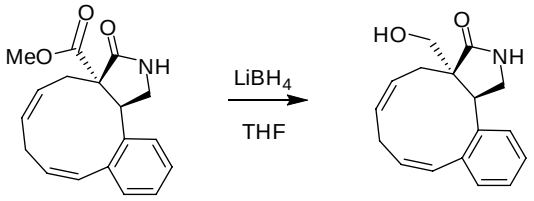




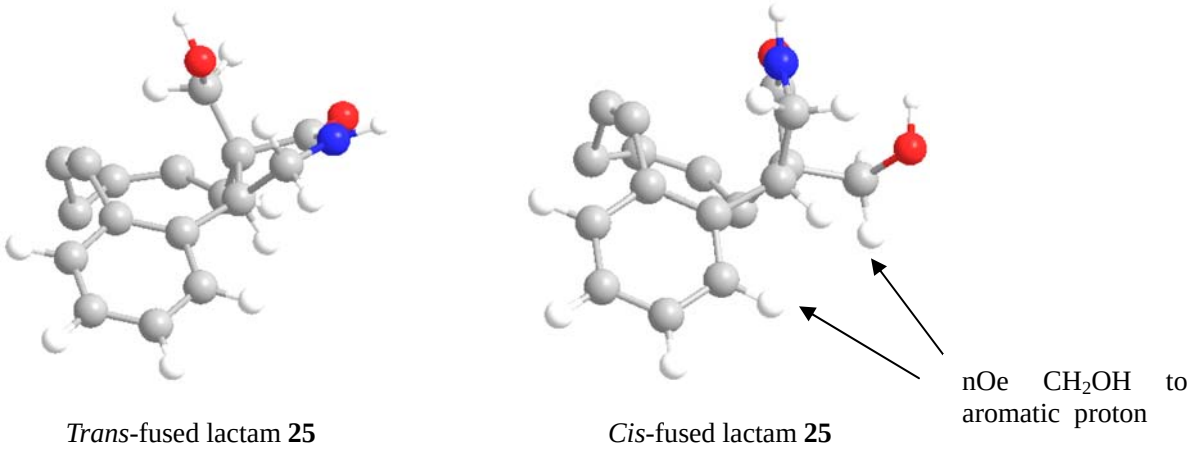
NOESY spectrum for **22**.



The stereochemistry of **22** was assigned as the *cis* fused lactam based on examination of the minimum-energy conformers for the *cis* and *trans* fused ring system derived from a conformational search (MMFF[10]) of **25** and nOe analysis of **25.**

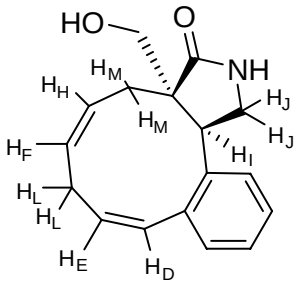


22 **25**



Trans-fused lactam **25** *Cis*-fused lactam **25**

Figure G. Minimum-energy conformers for the *cis* and *trans* fused ring system derived from a conformational search (MMFF[10]) of **25**

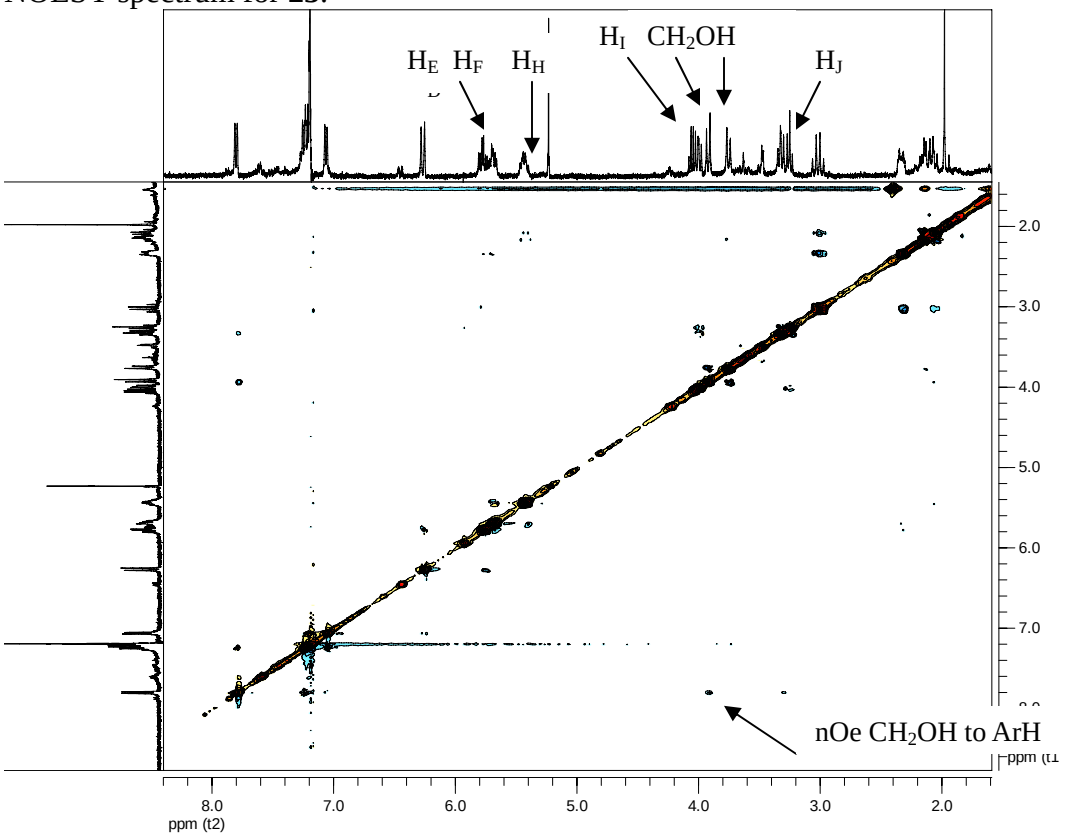


25

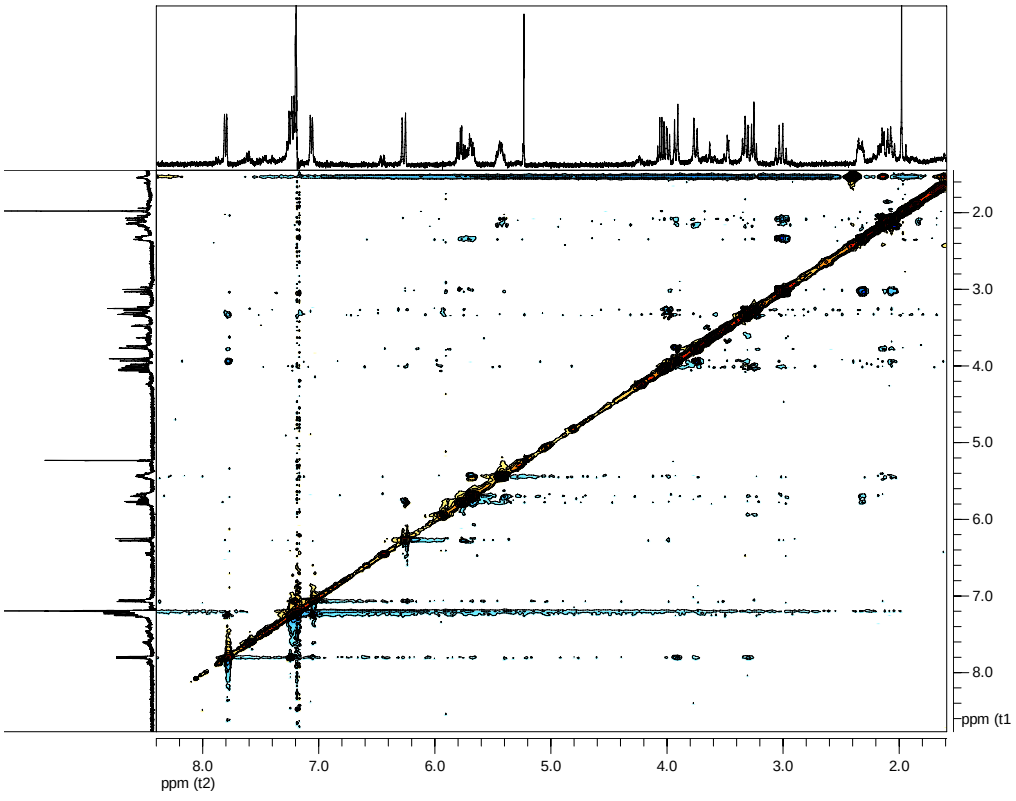
- Peaks corresponding to the methylene protons of the primary alcohol of **25** were easily identified using GCOSY and HMQC analyses.
- An nOe was observed between the methylene protons of the primary alcohol and an aromatic proton.
- Examination of the minimum conformations (calculated using MMFF) (Figure G) show that this nOe should only be observable for *cis* fused lactam **25.**
- Additionally, proton H_I, previously assigned as α, also has a weak nOe to the same aromatic proton.

[10] Conformational searches (Merck Molecular Mechanics Fourse Field) were performed using Spartan '04 Windows (Wavefunction, Irvine, CA).

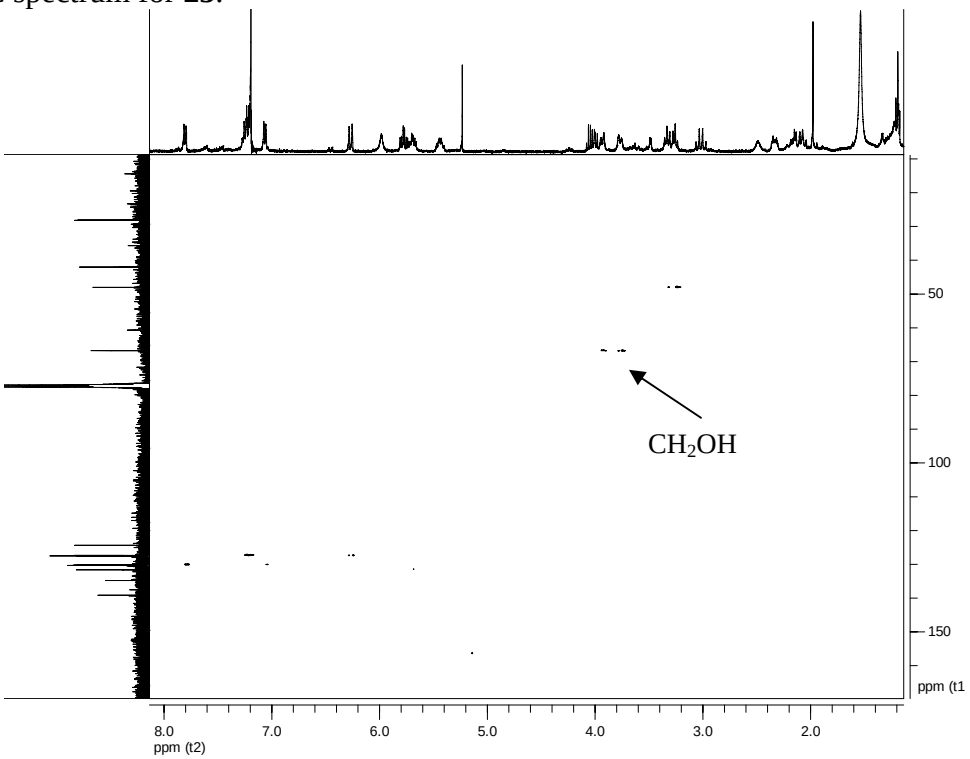
NOESY spectrum for **25**.



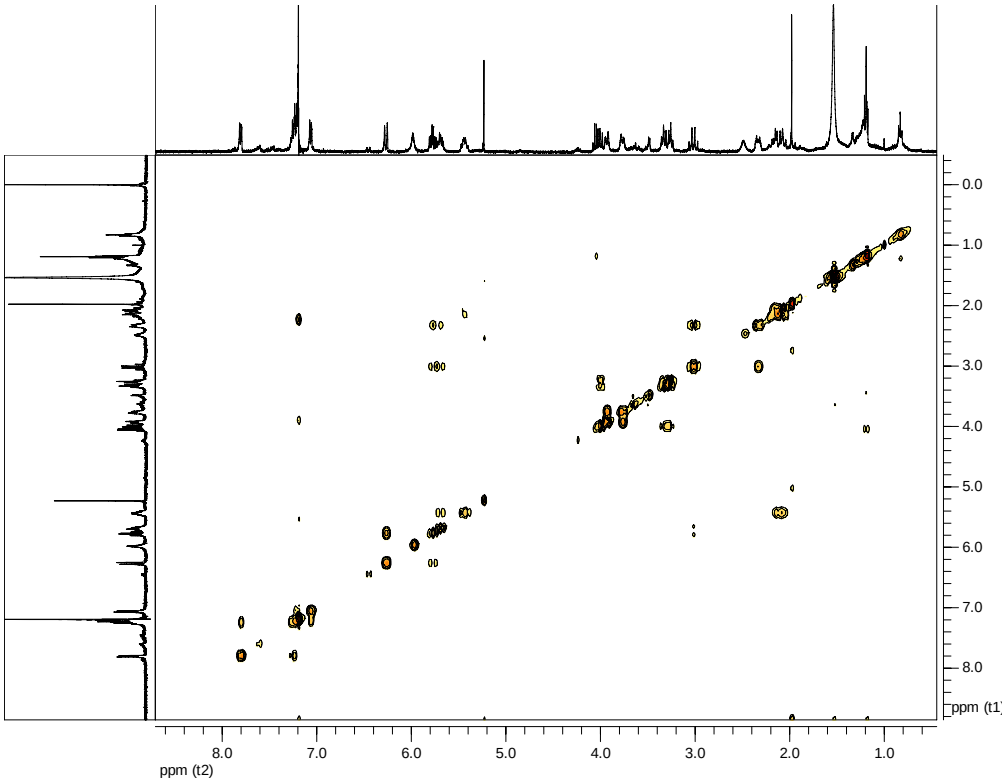
NOESY spectrum for **25** (expansion plot).



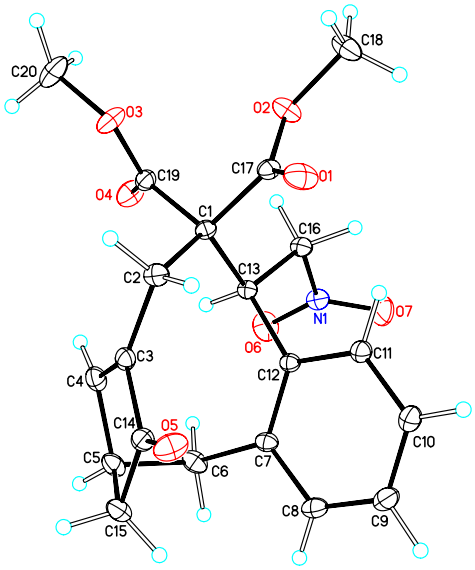
HMQC spectrum for **25**.



GCOSY spectrum for **25**.



5. X-ray crystal structure analysis for Pauson-Khand product 17.



Crystals of compound **17** suitable for x-ray analysis were obtained by slow evaporation from CH_2Cl_2/isooctane. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC #627520). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

Table 3. Crystal data and structure refinement for **17**.

Empirical formula	C20 H21 N O7	
Formula weight	387.38	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.8302(5) Å	α= 90°.
	b = 13.5528(8) Å	β= 90°.
	c = 14.9410(8) Å	γ = 90°.
Volume	1788.05(17) $Å^3$	
Z	4	
Density (calculated)	1.439 Mg/m^3	
Absorption coefficient	0.110 mm^{-1}	

F(000)	816
Crystal size	0.60 x 0.55 x 0.50 mm^3
Theta range for data collection	2.03 to 36.32°.
Index ranges	-13<=h<=13, -21<=k<=21, -24<=l<=23
Reflections collected	19695
Independent reflections	4578 [R(int) = 0.0247]
Completeness to theta = 36.32°	95.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9472 and 0.9371
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4578 / 0 / 337
Goodness-of-fit on F^2	1.111
Final R indices [I>2sigma(I)]	R1 = 0.0367, wR2 = 0.0920
R indices (all data)	R1 = 0.0415, wR2 = 0.0950
Absolute structure parameter	1.2(5)
Largest diff. peak and hole	0.367 and -0.376 e.$Å^{-3}$

Table 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for **23**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-2226(1)	9320(1)	2410(1)	28(1)
O(2)	-2414(1)	10955(1)	2261(1)	23(1)
O(3)	-2499(1)	10733(1)	345(1)	25(1)
O(4)	-352(1)	11607(1)	385(1)	25(1)
O(5)	1216(1)	7265(1)	1034(1)	25(1)
O(6)	3109(1)	12018(1)	1844(1)	29(1)
O(7)	2759(1)	11933(1)	3268(1)	35(1)
N(1)	2344(1)	11812(1)	2498(1)	19(1)
C(1)	-619(1)	10154(1)	1334(1)	14(1)
C(2)	-549(1)	9131(1)	856(1)	18(1)
C(3)	964(1)	8915(1)	465(1)	16(1)

C(4)	1924(1)	9523(1)	45(1)	19(1)
C(5)	3530(1)	9202(1)	179(1)	20(1)
C(6)	4087(1)	9752(1)	1041(1)	20(1)
C(7)	3325(1)	9400(1)	1893(1)	16(1)
C(8)	4122(1)	8712(1)	2408(1)	20(1)
C(9)	3531(1)	8305(1)	3183(1)	22(1)
C(10)	2097(1)	8578(1)	3463(1)	21(1)
C(11)	1296(1)	9270(1)	2975(1)	17(1)
C(12)	1869(1)	9689(1)	2189(1)	13(1)
C(13)	950(1)	10487(1)	1728(1)	13(1)
C(14)	1768(1)	7982(1)	677(1)	18(1)
C(15)	3377(1)	8091(1)	336(1)	20(1)
C(16)	795(1)	11392(1)	2341(1)	17(1)
C(17)	-1848(1)	10077(1)	2060(1)	16(1)
C(18)	-3586(1)	10962(1)	2940(1)	27(1)
C(19)	-1114(1)	10931(1)	646(1)	16(1)
C(20)	-3090(2)	11409(1)	-317(1)	33(1)