Supplementary Material (ESI) for Chemical Communications
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Supporting Information

To accompany

Organocatalytic Asymmetric Aza-Nazarov Cyclization of an Azirine Accompanied by a Kinetic Resolution

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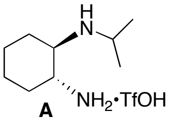
Table of Contents

General Experimental:

^1H NMR and ^{13}C NMR spectra were recorded either at 300 MHz (^1H) and 75 MHz (^{13}C) or at 500 MHz (^1H) and 125 MHz (^{13}C). Chemical shifts are reported in parts per million (δ) and are referenced to the solvent, i.e. 7.26/77.0 for $CDCl_3$ or 3.30/49.0 for CD_3OD. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). Thin layer chromatography (TLC) was performed on glass plates 250 μm, particle size 5-17 μm, pore size 60 Å. Flash column chromatography was performed on silica gel, 200-400 mesh or premium silica gel, 60 Å, 40-75 μm. All moisture sensitive reactions were performed under a static atmosphere of nitrogen or argon in oven dried or flame dried glassware. Purity and homogeneity of all materials was determined from TLC, ^1H NMR, ^{13}C NMR, and HPLC.

Screening of catalysts

In addition to **7**, catalysts **A**, **B**, **C** and **D** were examined for activity. Catalyst **A** gave results that were essentially the same as with **7**, whereas catalysts **B**-**D** did not lead to any reaction of **4**, indicating the importance of the primary amino group.



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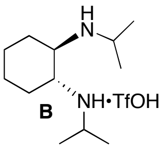

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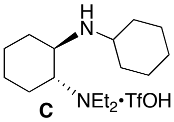

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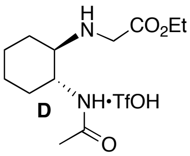
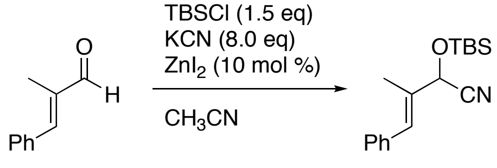


D

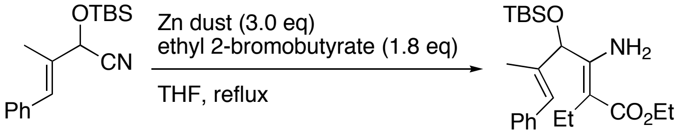
(*E*)-2-(*tert*-butyldimethylsilyl)oxy-3-methyl-4-phenylbut-3-enenitrile (**1**)



90% **1**

To a stirred solution of α-methylcinnamaldehyde (5.24 g, 35.8 mmol, 1.0 eq) in CH_3CN (180 mL), was added sequentially KCN (18.6 g, 286.4 mmol, 8.0 eq), TBSCl (6.49 g, 42.9 mmol, 1.2 eq) and ZnI_2 (1.14 g, 3.6 mmol, 10 mol %) at 21°C. After 18 h, the mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, hexane to 50:1 hexane/EtOAc) provided cyanohydrin **1** (9.24 g, 90% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.23 (m, 5H), 6.66 (s, 1H), 4.91 (s, 1H), 1.96 (s, 3H), 0.92 (br s, 9H), 0.20 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 132.6, 128.8, 128.7, 128.1, 127.3, 118.6, 67.6, 25.4, 18.0, 13.4, –5.3.

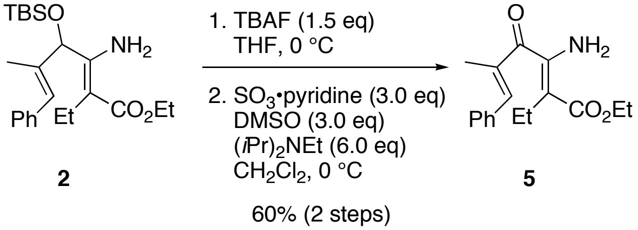
(2*Z*,5*E*)-ethyl 3-amino-4-(*tert*-butyldimethylsilyl)oxy-2-ethyl-5-methyl-6-phenylhexa-2,5-dienoate (**2**)



1 80% **2**

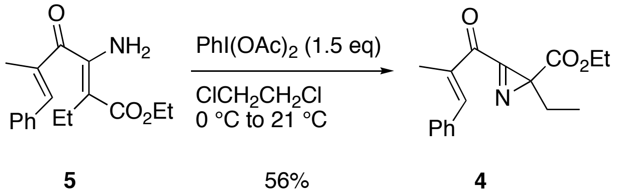
To a stirred suspension of activated Zn dust (680 mg, 10.4 mmol, 3.0 eq) in THF (9 mL) under reflux, a solution of cyanohydrin **1** (1.00 g, 3.4 mmol, 1.0 eq) in THF (3 mL) was transferred by cannula. Then ethyl-2-bromobutyrate (0.90 mL, 6.0 mmol, 1.8 eq) was added dropwise over a period of 1 h while maintaining steady reflux. After an additional hour the reaction mixture was cooled to 21°C and poured into a vigorously stirred mixture of 50% aq K_2CO_3 (5 mL) and THF (25 mL). After 30 min the clear solution was decanted off, dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, 50:1 hexane/EtOAc) provided enamino ester **2** (1.12 g, 80% yield) as a clear oil. IR (neat) 3482, 3313, 2955, 2858, 1660, 1595, 1510, 1236, 1064, 873, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.39 (m, 3H), 7.26–7.23 (d, *J* = 8.4 Hz, 2H), 6.54 (br s, 1H), 5.08 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.47-2.10 (m, 2H), 1.81 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.96–0.90 (m, 12 H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 158.1, 137.0, 136.9, 128.7, 128.0, 126.6, 93.8, 76.0, 58.5, 25.6, 18.8, 18.0, 14.8, 14.4, 12.5, –4.8, –5.3; HRMS (EI) calcd. for $C_{23}H_{37}NO_3Si$: 403.2542 found: 403.2539.

(2*Z*,5*E*)-ethyl 3-amino-2-ethyl-5-methyl-4-oxo-6-phenylhexa-2,5-dienoate (**5**)



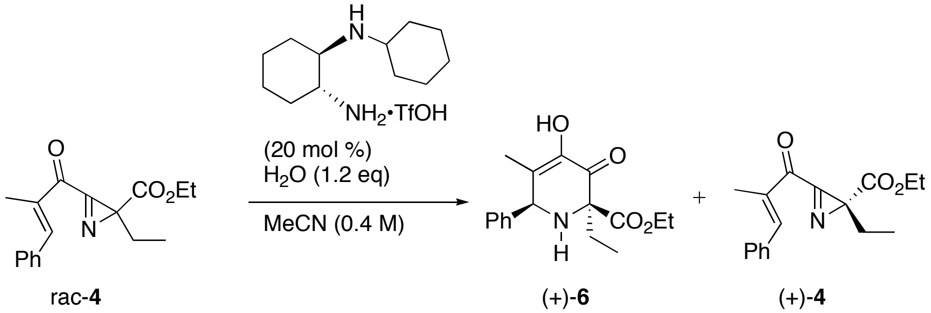
Tetrabutylammonium fluoride monohydrate (587 mg, 1.86 mmol, 1.5 eq) was added to a stirred solution of enamino ester **2** (500 mg, 1.24 mmol, 1.0 eq) in THF (6 mL) at 0 °C. After stirring at this temperature for 20 min, the reaction was quenched by addition of water. The mixture was extracted with EtOAc, and the combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by short column chromatography (silica gel, 4:1 hexane/EtOAc) provided alcohol **3** (quantitative yield) as a pale yellow oil. SO_3•pyridine complex (591 mg, 3.72 mmol, 3.0 eq), DMSO (0.26 mL, 3.72 mmol, 3.0 eq), *N*,*N*-diisopropylethylamine (1.33 mL, 7.43 mmol, 6.0 eq) was added to a solution of the above alcohol **3** in CH_2Cl_2 (6 mL) at 0 °C. The solution was stirred at this temperature for 20 min. Then water was added and aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, 10:1 hexane/EtOAc) provided aminodienone **5** (215 mg, 60% yield, overall for 2 steps) as a yellow oil. IR (film) 3430, 3316, 1659, 1605 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.65 (s, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.12 (s, 3H), 1.97 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 198.1, 171.6, 158.0, 147.2, 136.5, 131.2, 130.6, 129.7, 126.3, 95.9, 60.2, 22.1, 15.5, 14.9, 12.2; HRMS (EI) calcd for $C_{17}H_{21}NO_3$ (M^+) 287.1521, found 287.1510.

Ethyl 2-ethyl-3-((*E*)-2-methyl-3-phenylacryloyl)-2*H*-azirine-2-carboxylate (**4**)



To a solution of the aminodienone **5** (200 mg, 0.67 mmol, 1.0 eq) in 1,2-dichlorethane (7 mL) was added $PhI(OAc)_2$ (336 mg, 1.04 mmol, 1.5 eq) in a portionwise at 0°C. After the stirring at this temperature for 30 min the cooling bath was removed and stirring was continued at 21°C for 1 h. Upon completion of the reaction, the reaction mixture was filtered through a pad of Celite® and the pad was washed with EtOAc. The filtrate was concentrated *in vacuo* followed by column chromatography (silica gel, 20:1 hexane/ EtOAc) provided azirine **4** (111 mg, 56% yield) as a yellow oil. IR (neat) 2976, 1720, 1682, 1651, 1614, 1448, 1256, 1214, 1015, 694 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.15 (s, 1H), 7.54–7.57 (m, 2H), 7.42–7.49 (m, 3H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 2.16 (qd, *J* = 7.5, 3.0 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 184.9, 171.3, 163.9, 148.6, 135.8, 134.8, 130.6, 130.1, 128.7, 61.7, 44.3, 23.2, 14.2, 12.5, 10.0; HRMS (EI) calcd for $C_{17}H_{19}NO_3$: 285.1365 found 285.1365.

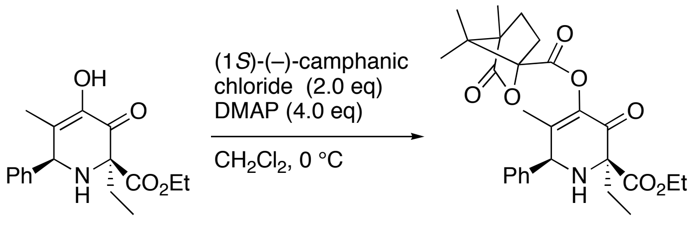
(2*S*,6*S*)-ethyl 2-ethyl-1,2,3,6-tetrahydro-4-hydroxy-5-methyl-3-oxo-6-phenylpyridine-2-carboxylate (**6**)



To a solution of the azirine **4** (28.5 mg, 0.10 mmol 1.0 eq) in MeCN (130 μL) was added water (1.0 M in MeCN, 120 μL, 0.12 mmol. 1.2 eq), 1,2-diamine **7** (1.0 M in CH$_2$Cl$_2$, 20 μL, 0.02 mmol, 20 mol %) at 21°C. After stirring at this temperature for 9 days brine was added and the whole was extracted with EtOAc. The combined organic layers were dried over anhydrous Na$_2$SO$_4$. Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, 20:1 hexane/EtOAc) provided piperidinone **6** (8.5 mg, 28% yield) as a colorless oil and optically active azirine **4** (10.4 mg, 36% yield, $[\alpha]_D^{23}$ +5.4 (*c* 0.58, MeOH)) as a colorless oil.

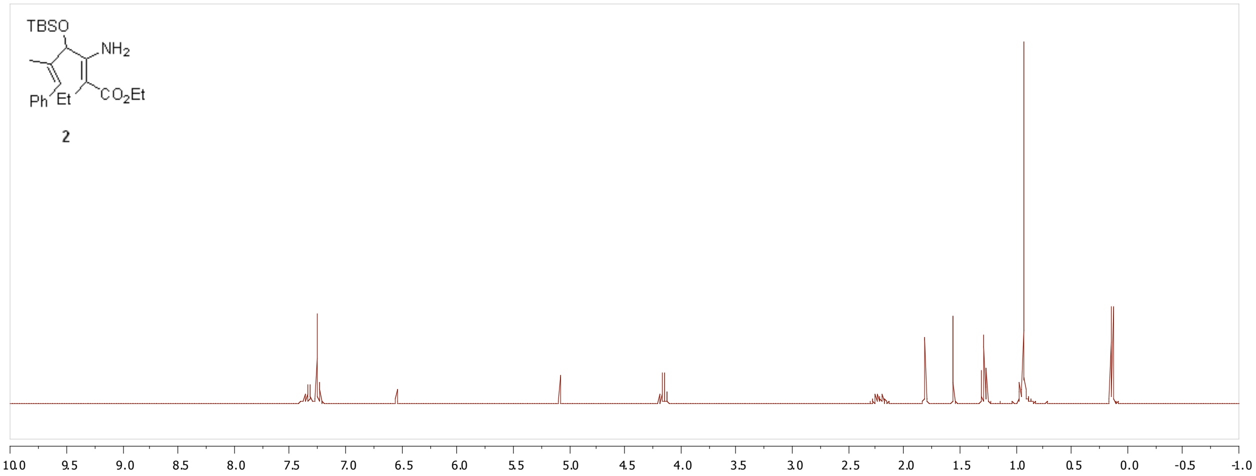
Compound (+)-**6**: $[\alpha]_D^{25}$ = +57.5 (*c* = 0.36, CHCl$_3$); IR (neat) 3425, 2979, 2937, 1730, 1678, 1652, 1452, 1388, 1237 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.19–7.34 (m, 5H), 6.13 (s, 1H), 4.57 (s, 1H), 3.86–4.00 (m, 2H), 2.63 (s, 1H), 1.87–1.96 (m, 2H), 1.63 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 190.4, 170.1, 142.8, 140.7, 130.2, 129.2, 128.9, 128.5, 68.8, 62.1, 59.4, 27.3, 14.6, 14.1, 8.9; HRMS (ESI+) calcd. for $C_{17}H_{22}NO_4$ (M+H) 304.1549, found 304.1535; Chiral HPLC (5% *i*-PrOH / Hexanes, Chiralcel AD-H®, 4.6 mm x 250 mm, UV detection at 261 nm, 1 mL/min) t_R = 12.2 min (major), t_R = 15.1 min (minor).

(2*S*,6*S*,4(1*S*))-ethyl 2-ethyl-1,2,3,6-tetrahydro-4-(4,7,7-trimethyl-3-oxo-2-oxabicyclo [2.2.1]heptane-1-carbonyl)oxy-5-methyl-3-oxo-6-phenylpyridine-2-carboxylate (**8**)



(+)-**6** **8**

(–)-Camphanoyl chloride (5.9 mg, 27.8 μmol, 2 eq) was added to a stirred solution of piperidone **6** (4.0 mg, 13.9 μmol, 1.0 eq) and DMAP (6.8 mg, 55.6 μmol, 4 eq) in CH_2Cl_2 (1 mL) at 0 °C. After stirring at 21°C for 30 min, the reaction was quenched by addition of water and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with 10% aq HCl solution, saturated aq $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, 4:1 hexane/EtOAc) provided camphanic ester **8** (6.0 mg, 92% yield) as a white solid. Dissolution in EtOAc and slow diffusion of hexane in a sealed vessel yielded a colorless crystal suitable for single crystal X-ray analysis. ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.42 (m, 5H), 4.68 (s, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 2.80 (br s, 1H), 2.56 (m, 1H), 1.95–2.18 (m, 4H), 1.73 (m, 1H), 1.64 (s, 3H), 1.21 (s, *J* = 7.2 Hz, 2H), 1.17 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.4, 178.0, 169.3, 165.0, 147.3, 139.6, 139.3, 129.3, 128.7, 128.3, 91.0, 70.0, 62.0, 59.9, 55.0, 54.8, 30.9, 28.9, 26.0, 16.6, 15.2, 13.9, 9.6, 8.5; HRMS (EI) calcd for $C_{27}H_{33}NO_7$ (M^+) 483.2257, found 483.2243.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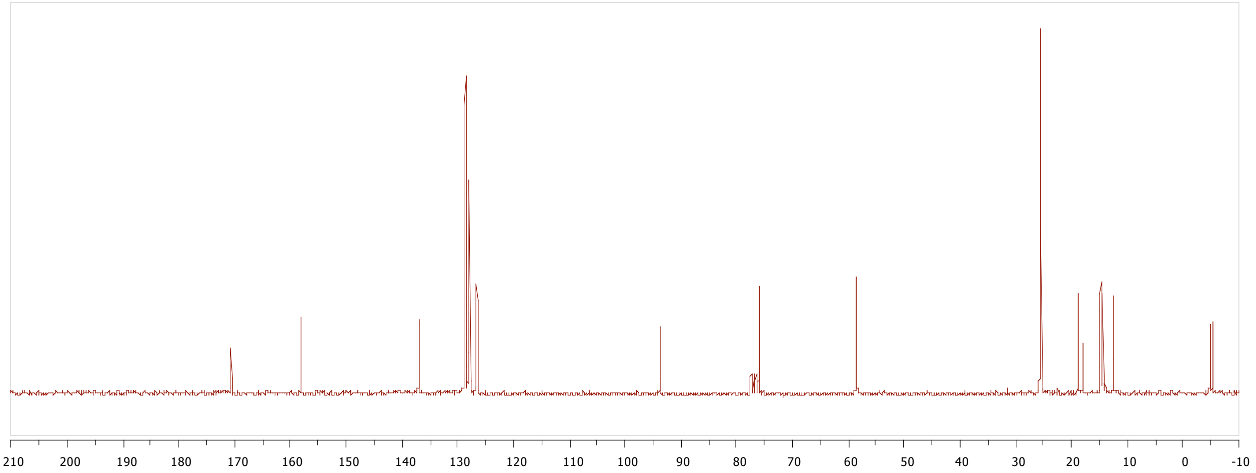
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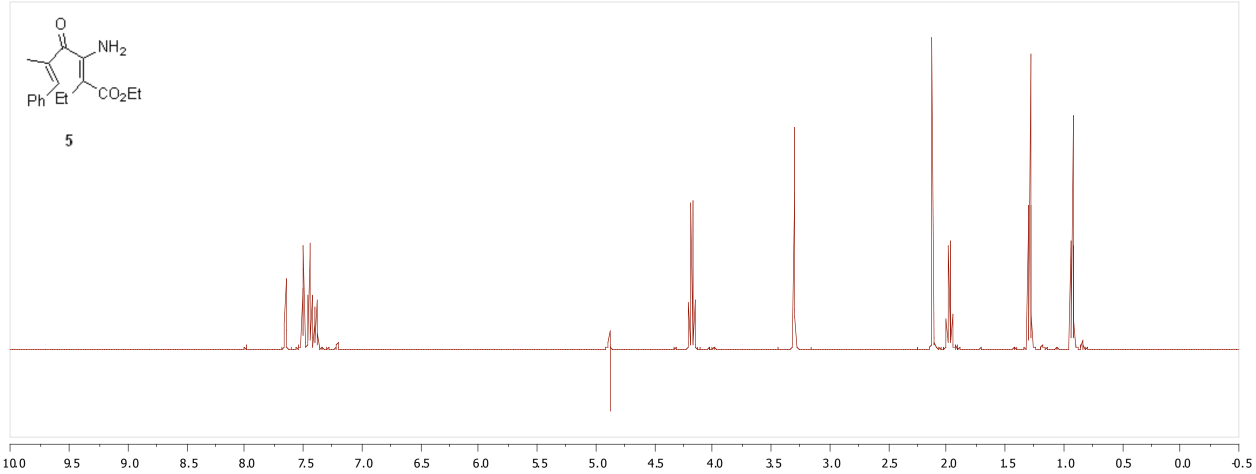
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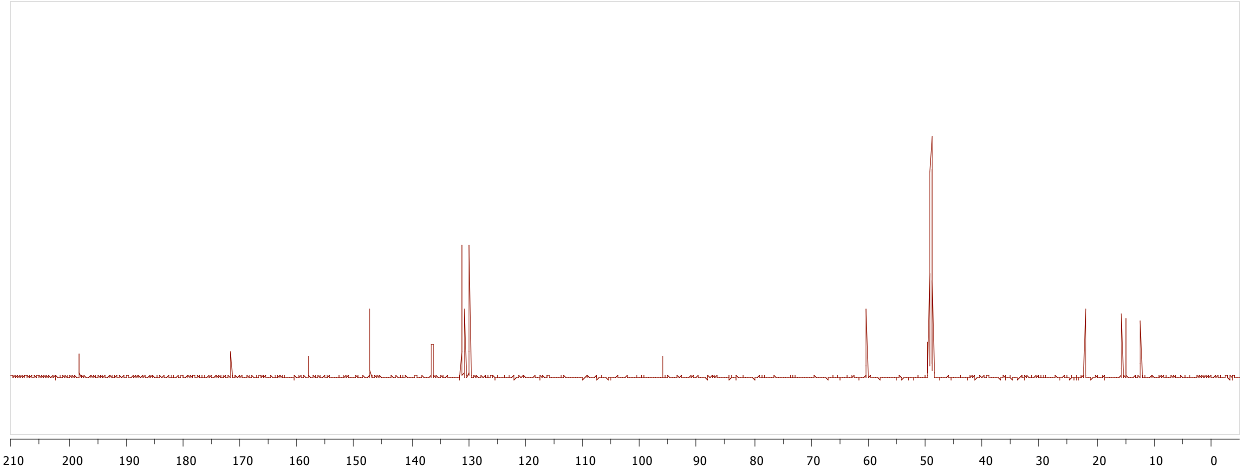
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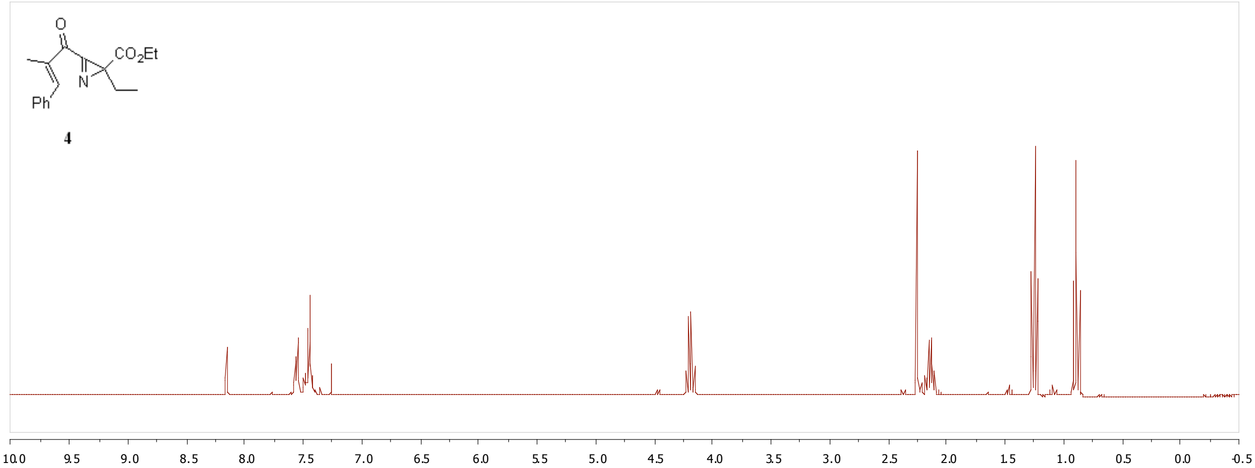
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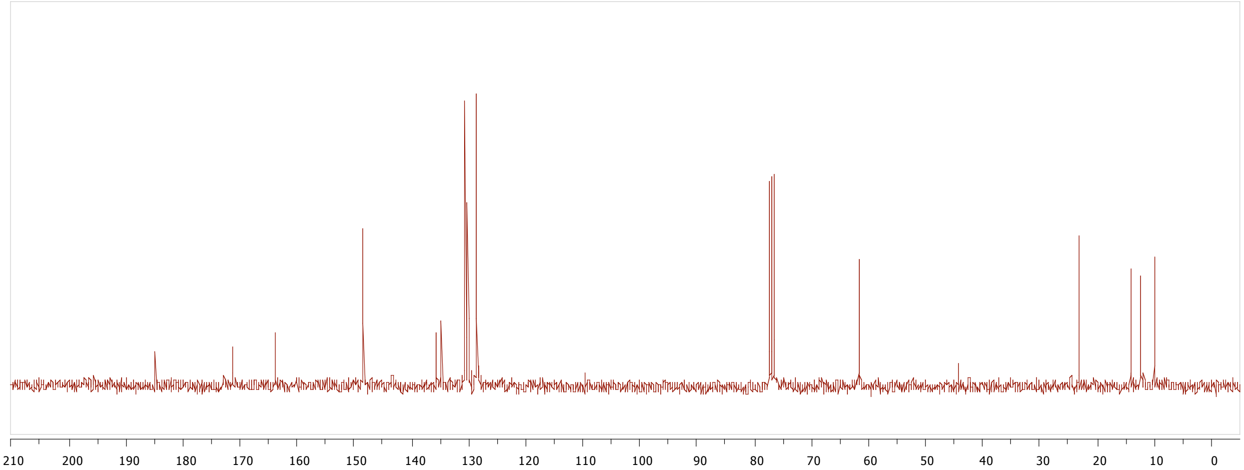
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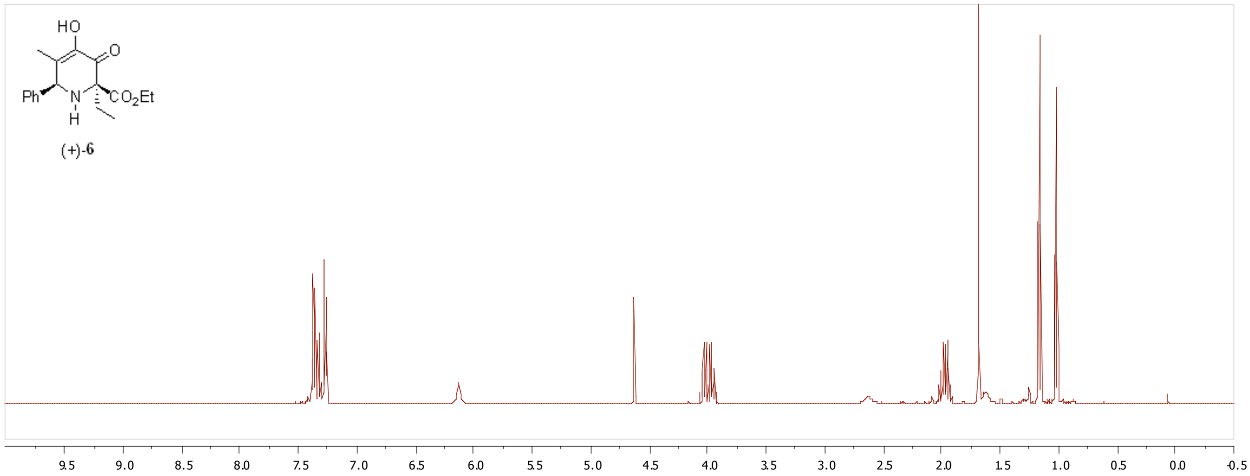
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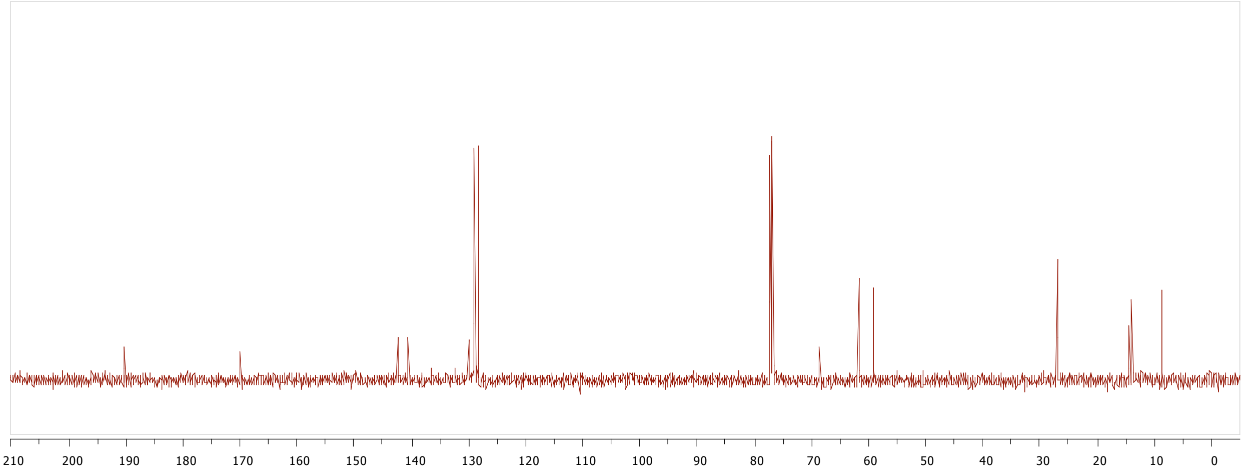
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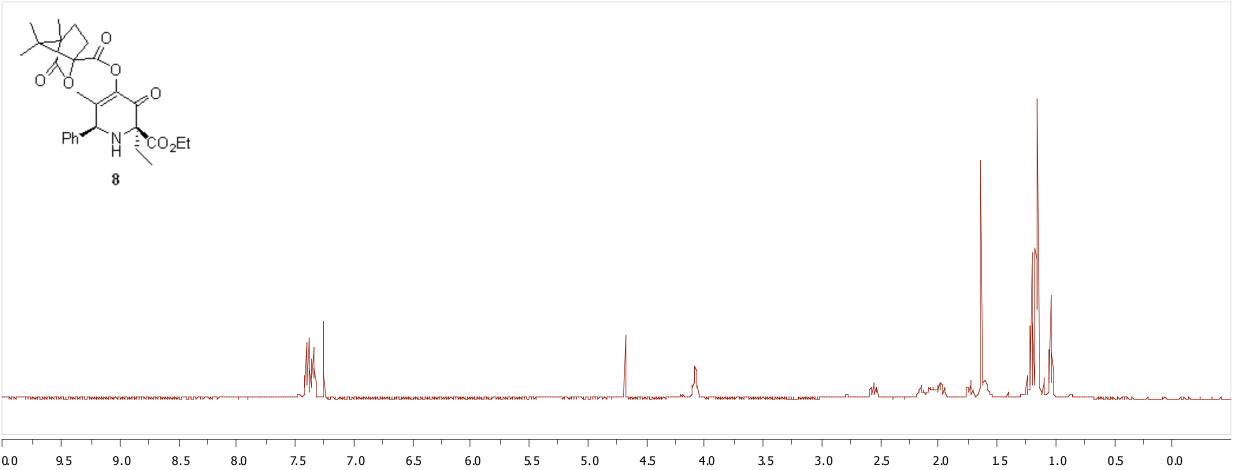

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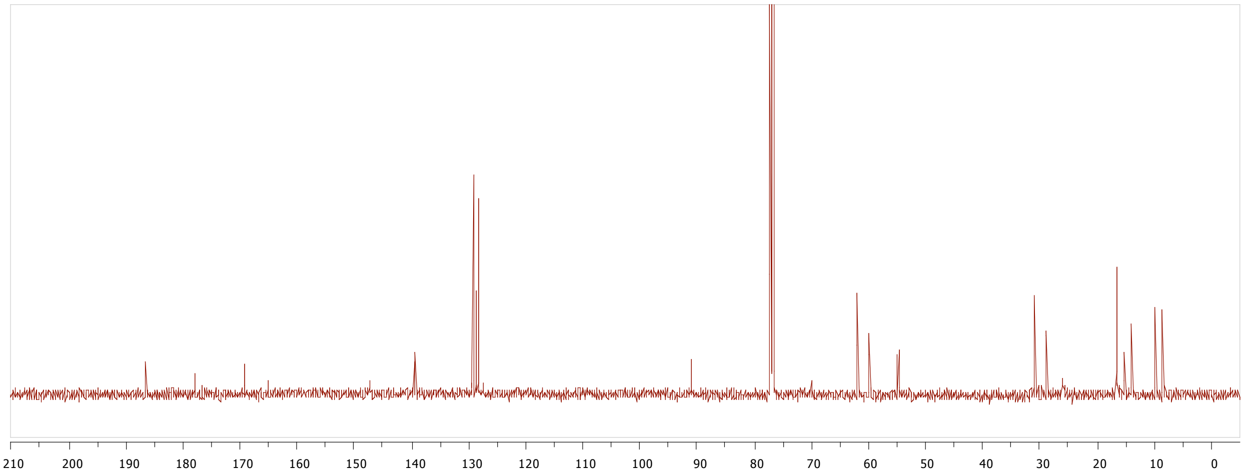

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