Multicomponent Synthesis of Pyroglutamic Acid Derivatives via Knoevenagel-Michael-Hydrolysis-Lactamization-Decarboxylation (KMHL-D) Sequence

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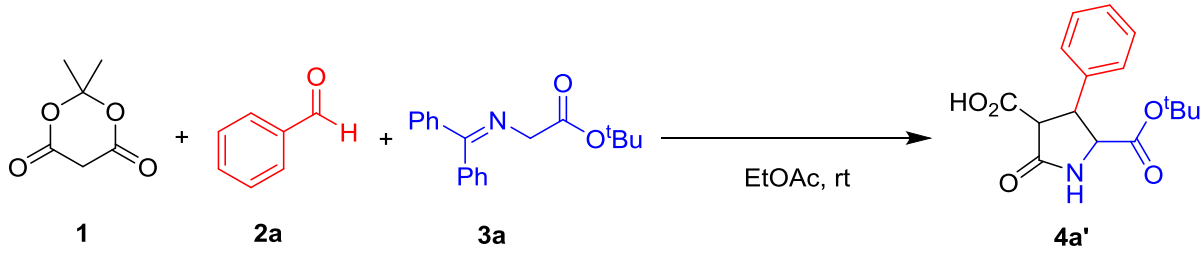
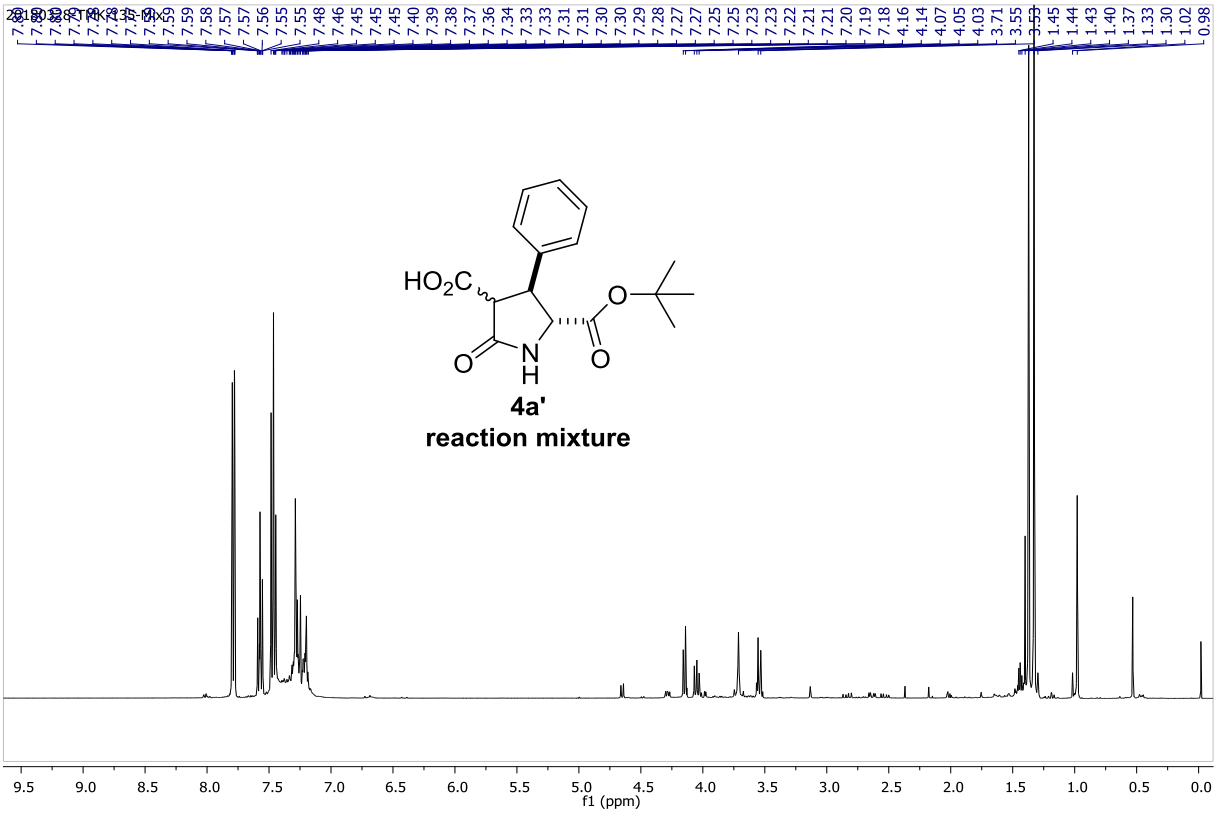
Section 1

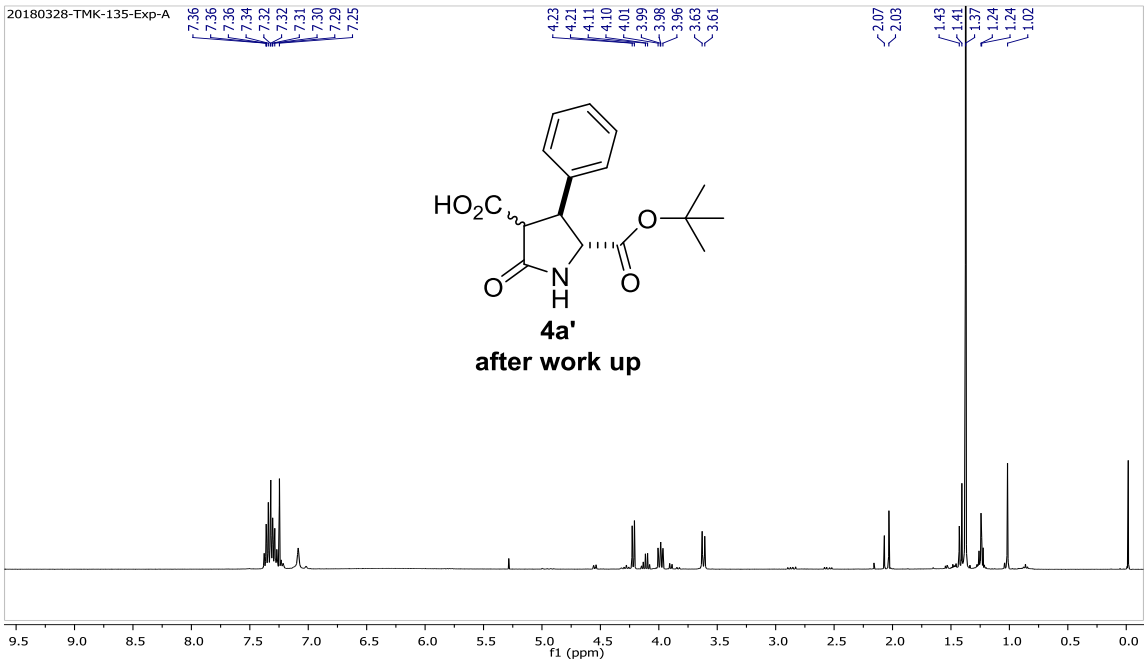
^{1}H NMR studies to prove the intermediates formation



Reaction conditions: In an oven dried 10 mL round bottommed flask with a teflon-coated stir bar, Meldrum's acid **1** (200 mg, 1.39 mmol, 1 equiv.) was dissolved in 6 mL of EtOAc. Then benzaldehyde **2a** (150 µL, 1.47 mmol, 1.06 equiv.) and Schiff's base **3a** (532. 9 mg, 1.8 mmol, 1.3 equiv.) were added subsequently and the reaction mixture was stirred for 24 h at room temperature.

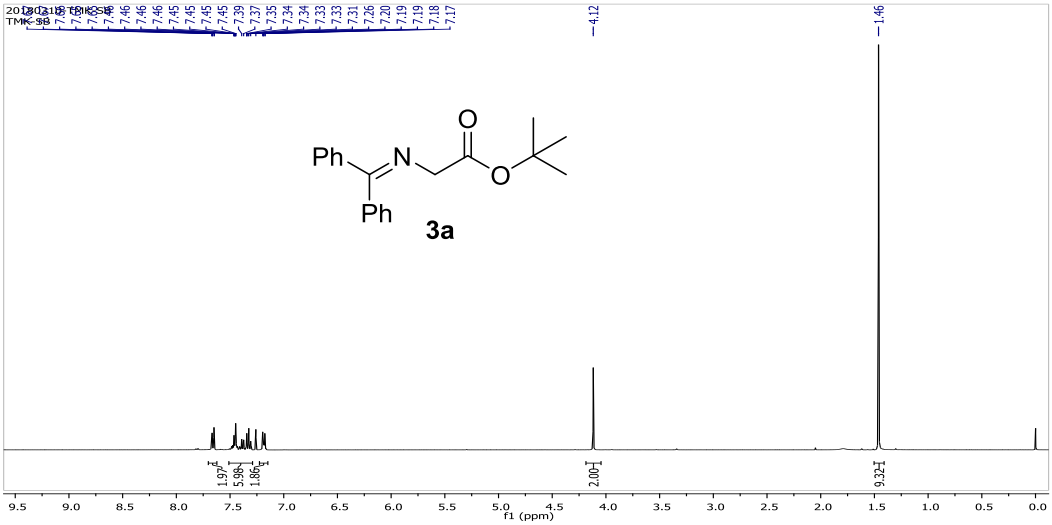


For ^{1}H NMR 100 µL of reaction mixture was taken out and evaporated. The resulting crude mixture was directly submitted for ^{1}H NMR in $CDCl_3$.

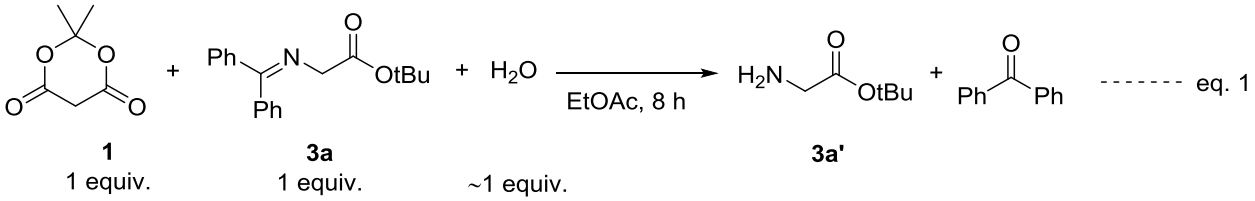


Conditions: Upon completion of the reaction (confirmed by TLC), the reaction mixture was directly transferred in to separating funnel. Then saturated aq. $NaHCO_3$ solution (25 mL) and EtOAc (20 mL) were added to the separating funnel and extracted. The aqueous layer containing pyroglutamic acid derivative **4a'** was separated and the extraction procedure repeated twice. The combined aqueous layer was acidified with 1 N aq. HCl solution till it becomes a turbid solution (~ pH 2). After which, the pyroglutamic acid derivative **4a'** was extracted with EtOAc (3 X 20 mL) and the combined organic layers was washed with brine solution and dried over anhydrous Na_2SO_4. The organic extract was evaporated under vacuuo to afford crude **4a'**. The resulting crude **4a'** was directly submitted for ^1H NMR in $CDCl_3$.

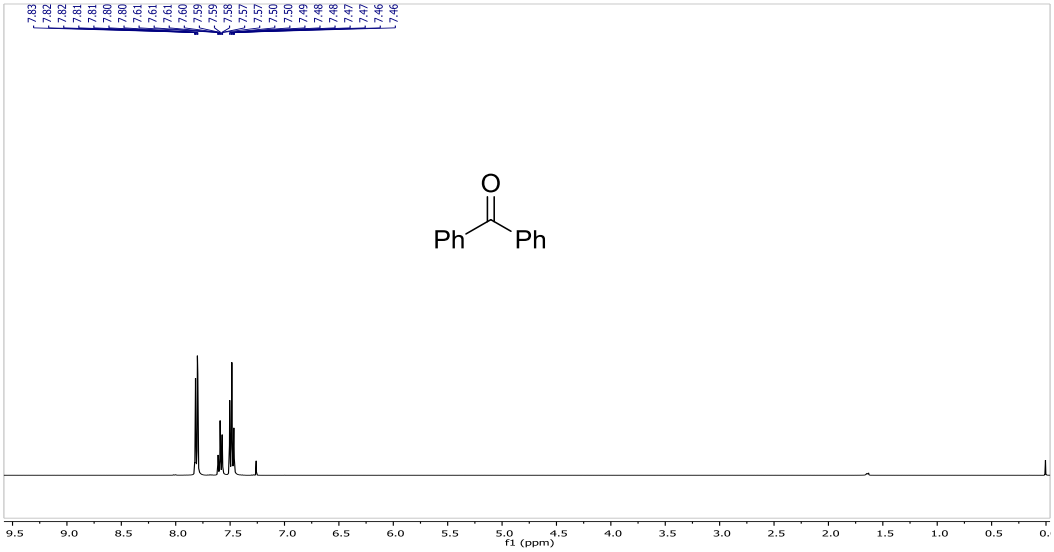
*It is found that imine hydrolysis and lactamization of intermediate **6** takes place in *situ*.

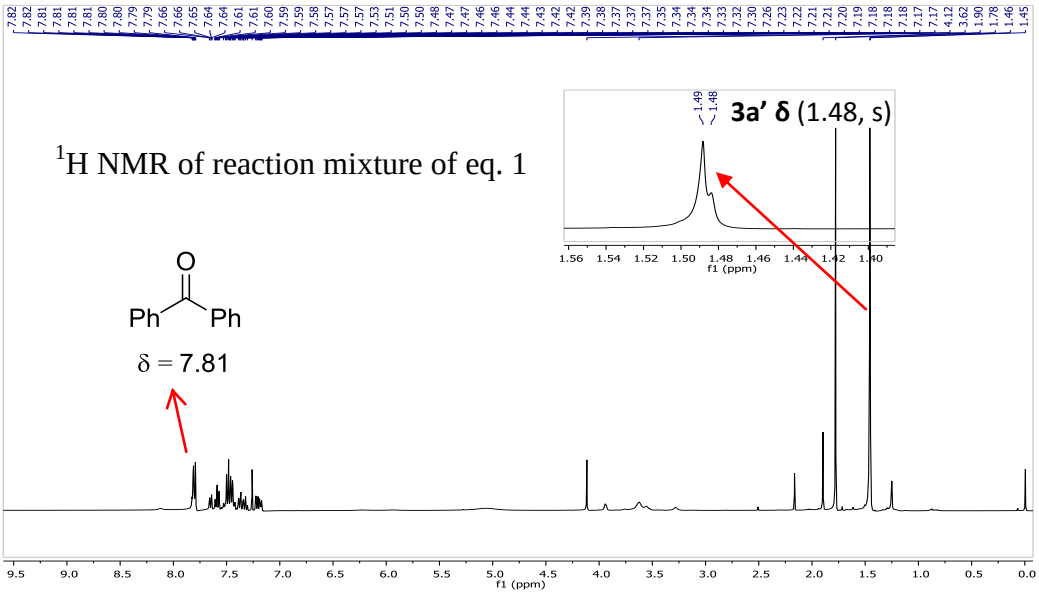


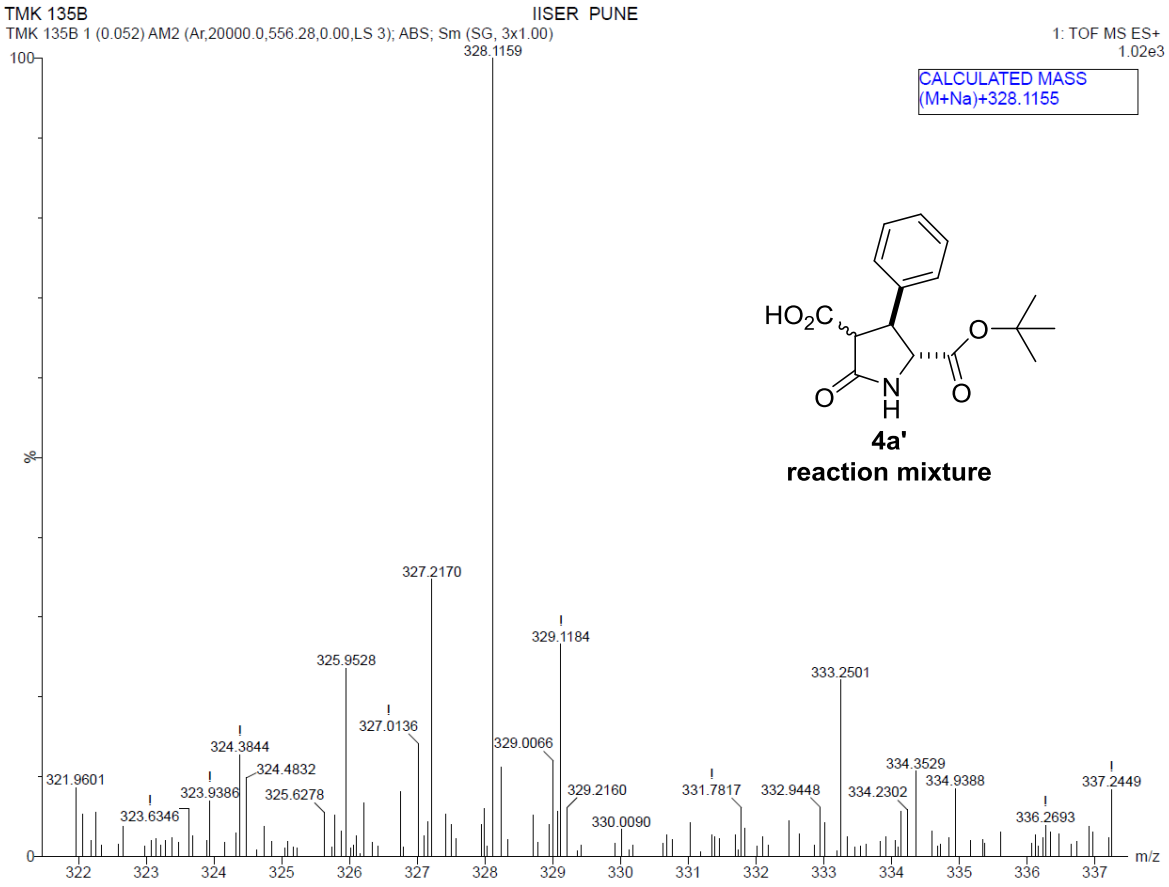
Hydrolysis of Schiff's base 3a catalysed of Meldrum's acid

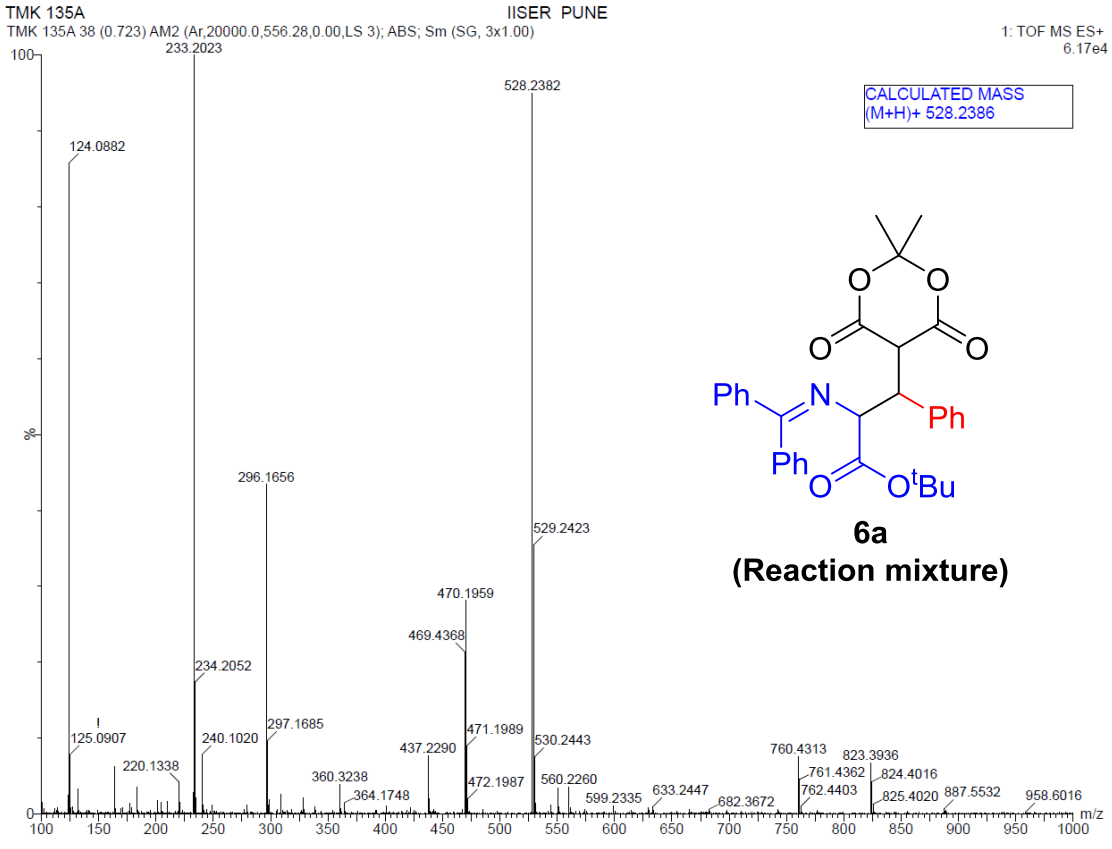


[a]Reaction Conditions: Meldrum's acid **1** (100 mg, 0.69 mmol, 1 equiv.), Schiff's base **3a** (205 mg, 0.69 mmol, 1 equiv.), H_2O (15 µL, 0.72 mmol, 1.04 equiv.) in 1 ml EtOAc for 8 h, then 100 µL of reaction mixture was taken out and evaporated. The resulting crude mixture was directly submitted for ^{1}H NMR.

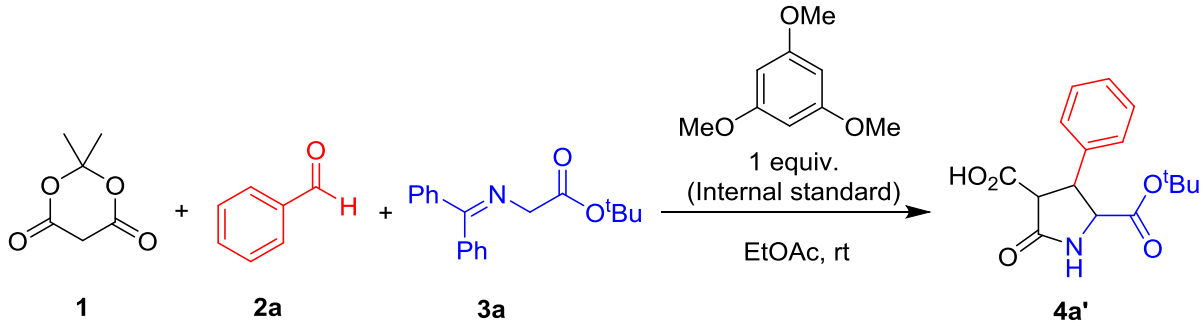




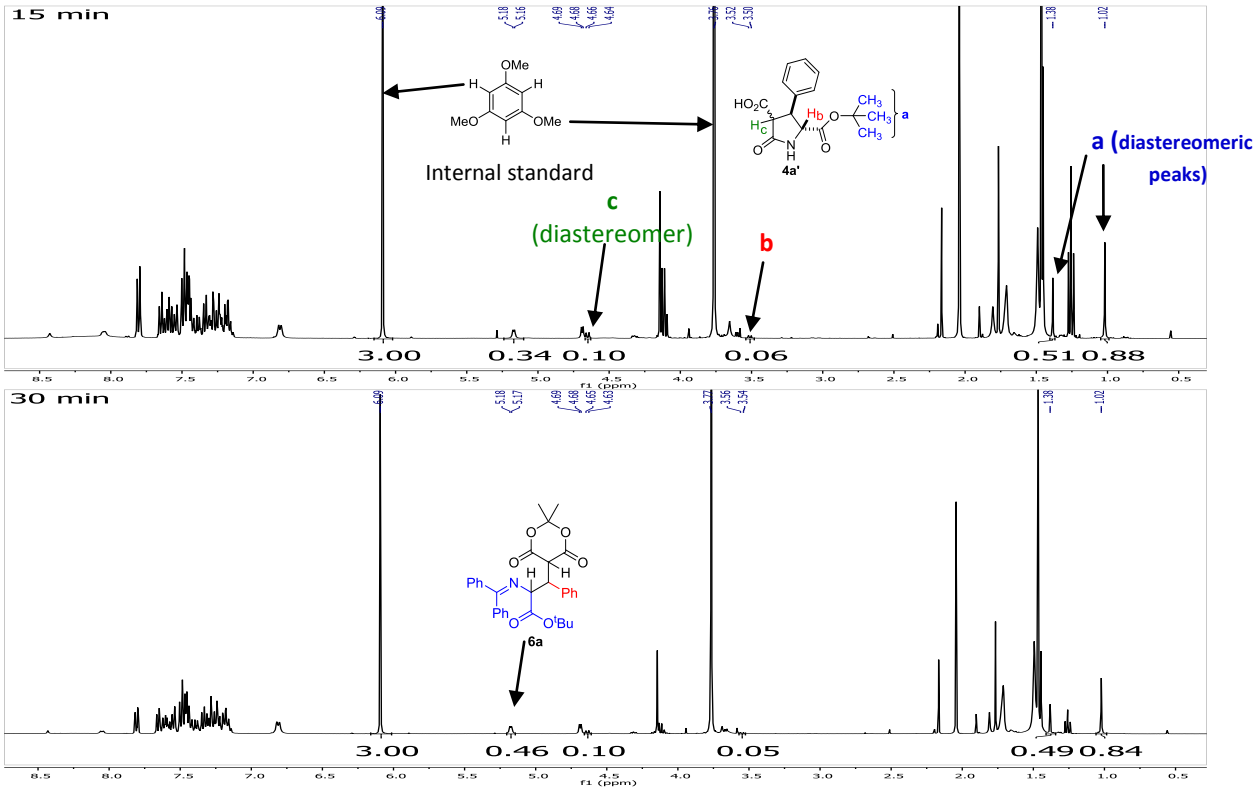

TMK 135B
IISER PUNE
TMK 135B 1 (0.052) AM2 (Ar,20000.0,556.28,0.00,LS 3); ABS; Sm (SG, 3x1.00)
1: TOF MS ES+
1.02e3
CALCULATED MASS
(M+Na)+328.1155
HO2C
O
N
H
O
O
4a'
reaction mixture
%
m/z

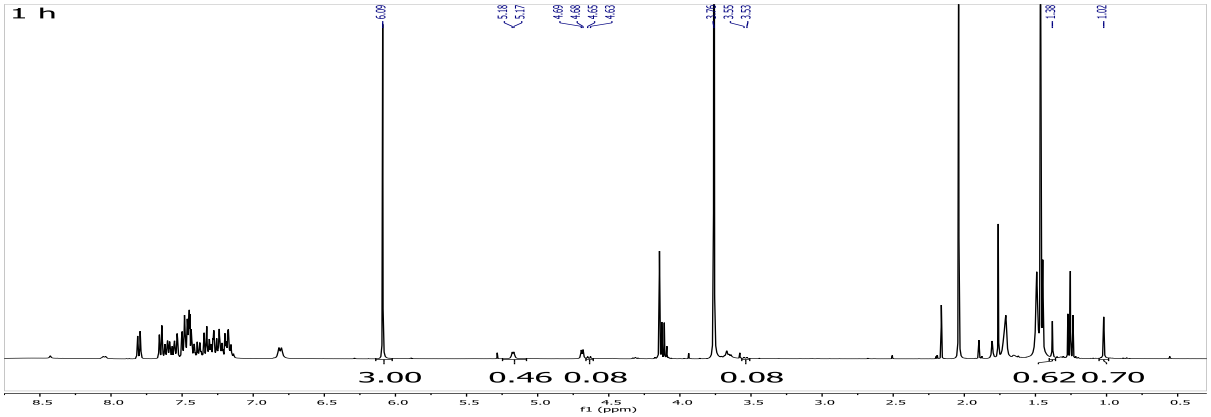

TMK 135A
IISER PUNE
TMK 135A 38 (0.723) AM2 (Ar,20000.0,556.28,0.00,LS 3); ABS; Sm (SG, 3x1.00)
1: TOF MS ES+
6.17e4
CALCULATED MASS
(M+H)+ 528.2386
O
O
O
O
Ph
N
Ph
Ph
O
OtBu
6a
(Reaction mixture)
%
m/z

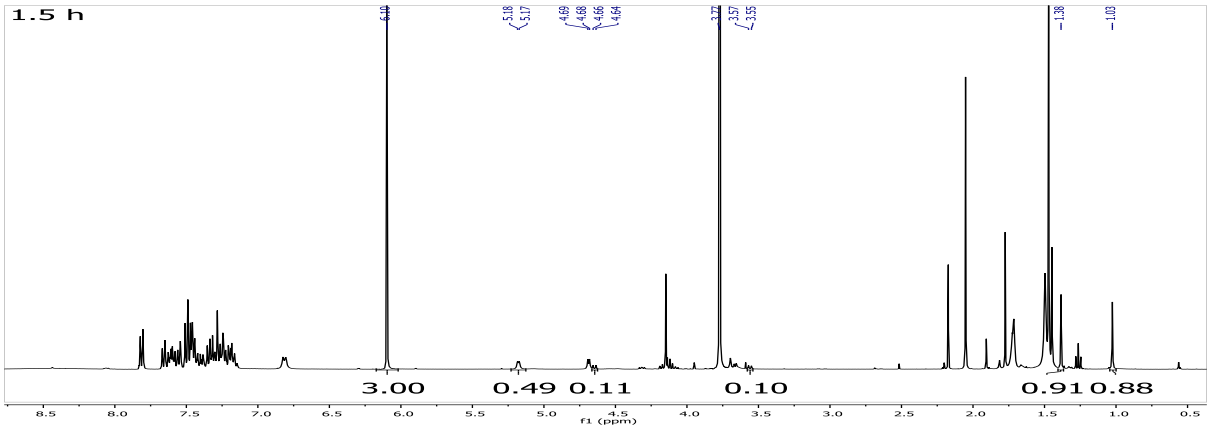
Appendix I: Time dependent ^{1}H-NMR Studies to calculate the yields of **4a'**

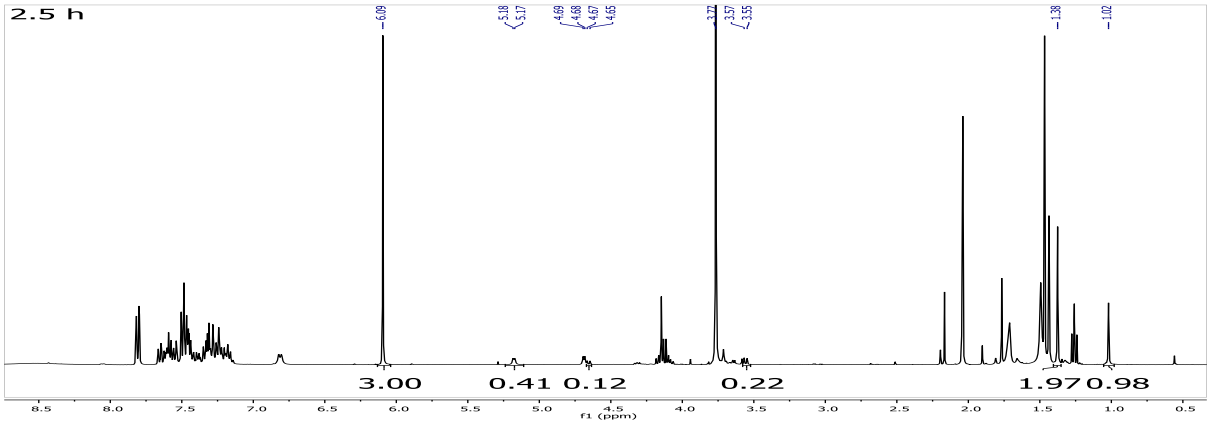


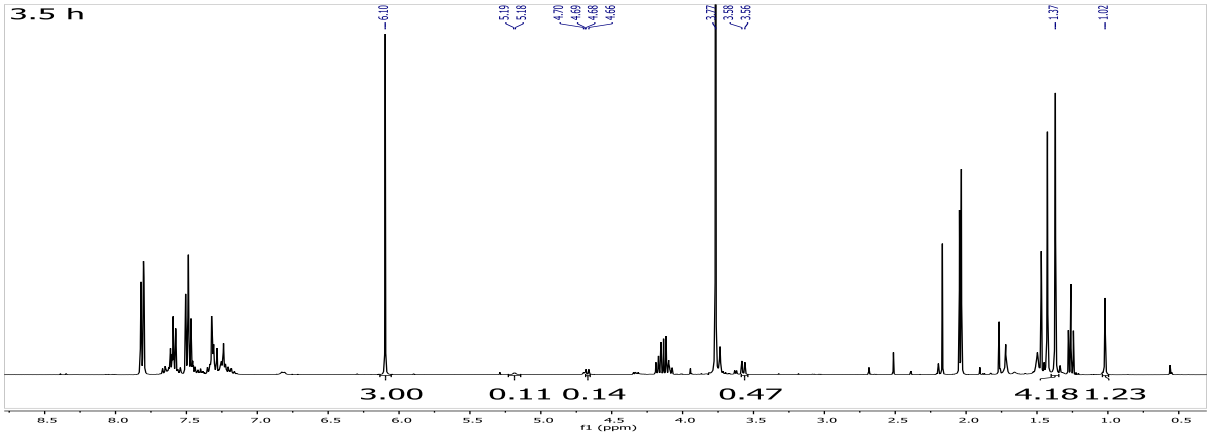
^{1}H NMR kinetic experiments for the reaction of Meldrum's acid (300 mg, 2.08 mmol), Benzaldehyde (225 µL, 2.19 mmol), Schiff's base **3** (799.3 mg, 2.71 mmol) and 1,3,5-trimethoxy benzene (350.1 mg, 2.08 mmol) in 8 ml ethyl acetate at room temperature (25 °C). 1,3,5-Trimethoxy benzene (1 equiv.) was used an internal standard δ (s, 6.09 3H, s, 3.76). ^{1}H-NMR spectra were recorded over a period of time to study the formation of 4a'. Yields were calculated with reference internal standard peak δ (s, 6.09 3H). Based on the time dependent ^{1}H NMR studies we observed that product **4a'** (diastereomers) formation increased significantly after one hour. Using the ^{1}H NMR data kinetics of the reaction was studied (see Fig 2)

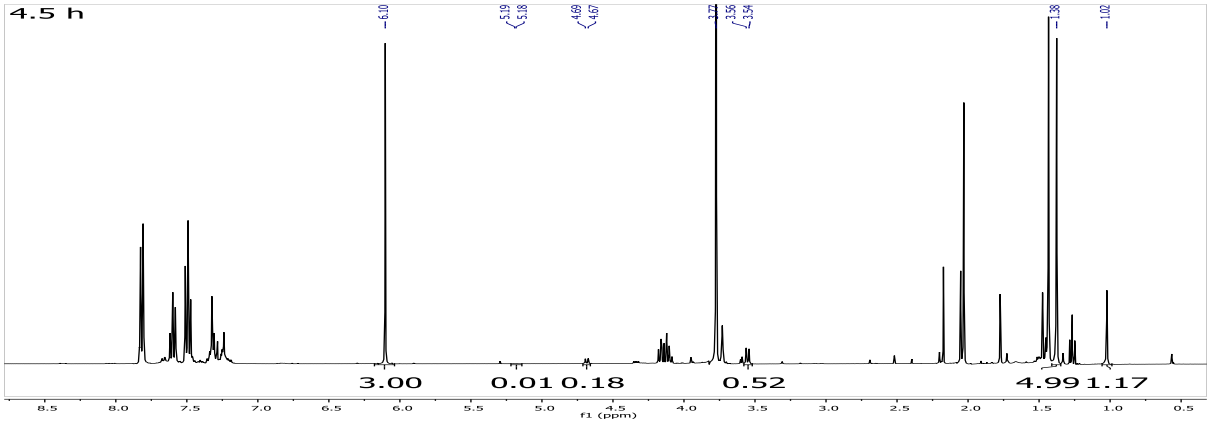


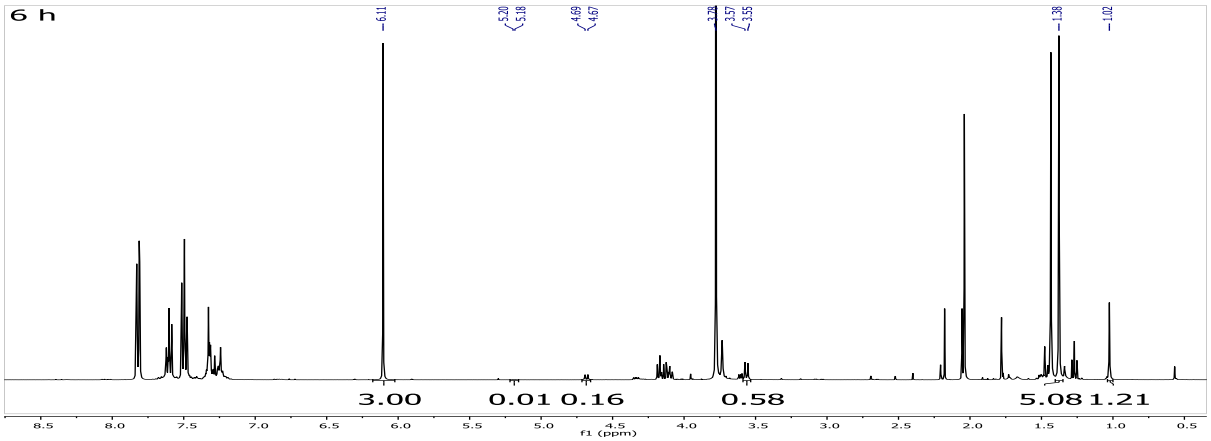

1 h
6.09
5.18
5.17
4.69
4.68
4.65
4.63
3.55
3.53
1.38
1.02
3.00
0.46
0.08
0.08
0.62
0.70
f1 (ppm)

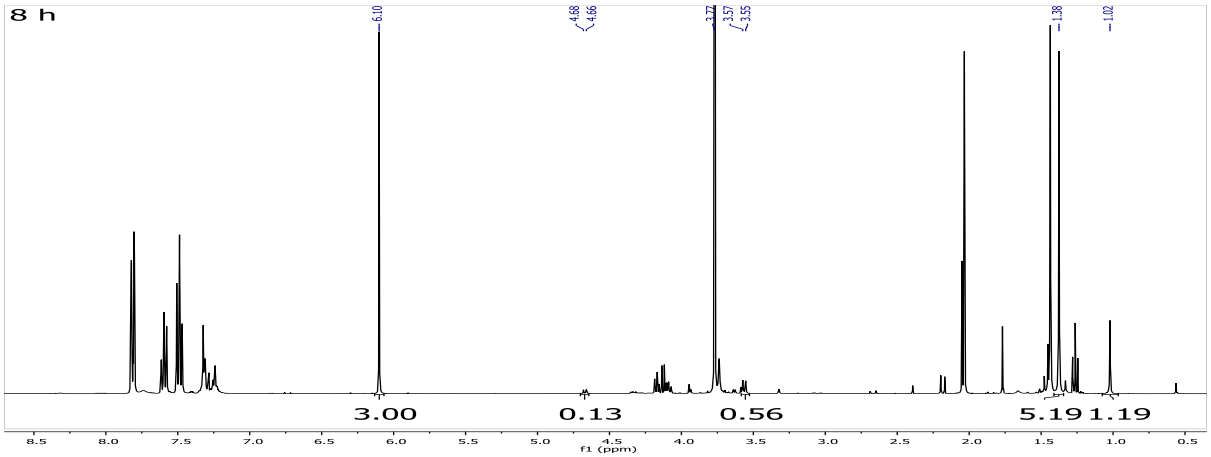

1.5 h
6.10
5.18
5.17
4.69
4.68
4.66
4.64
3.57
3.55
1.38
1.03
3.00
0.49
0.11
0.10
0.91
0.88
f1 (ppm)

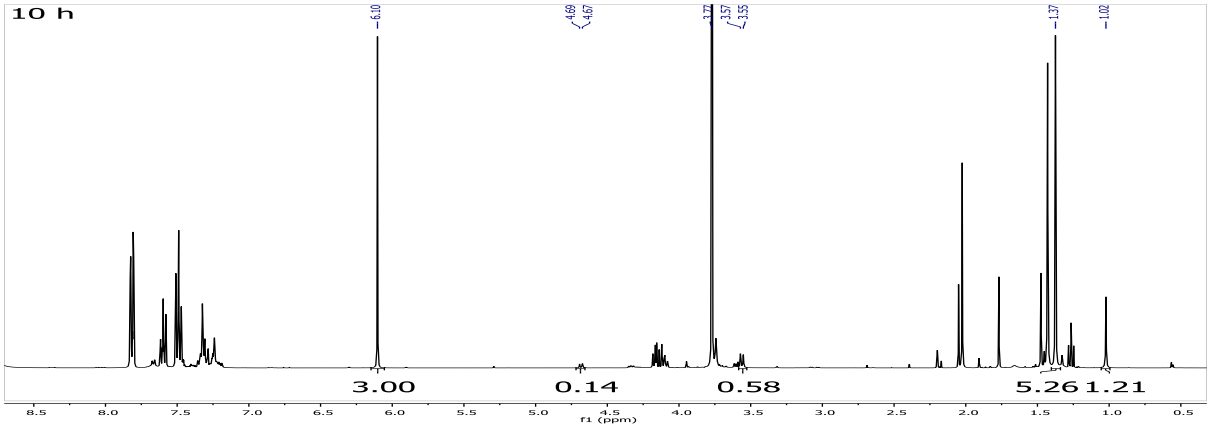

2.5 h
6.09
5.18
5.17
4.69
4.68
4.67
4.65
3.57
3.55
1.38
1.02
3.00
0.41
0.12
0.22
1.97
0.98
f1 (ppm)

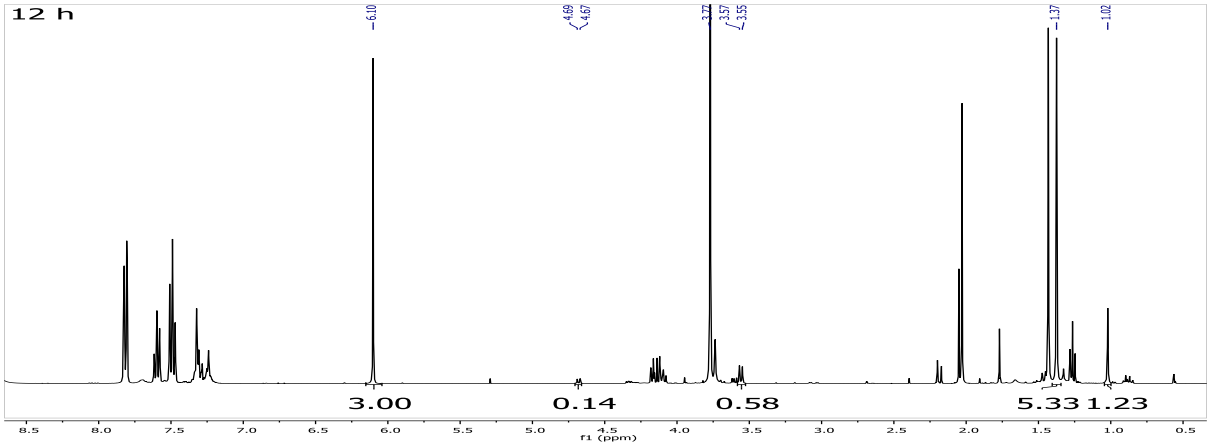

3.5 h
6.10
5.19
5.18
4.70
4.69
4.68
4.66
3.58
3.56
1.37
1.02
3.00
0.11
0.14
0.47
4.18
1.23
f1 (ppm)

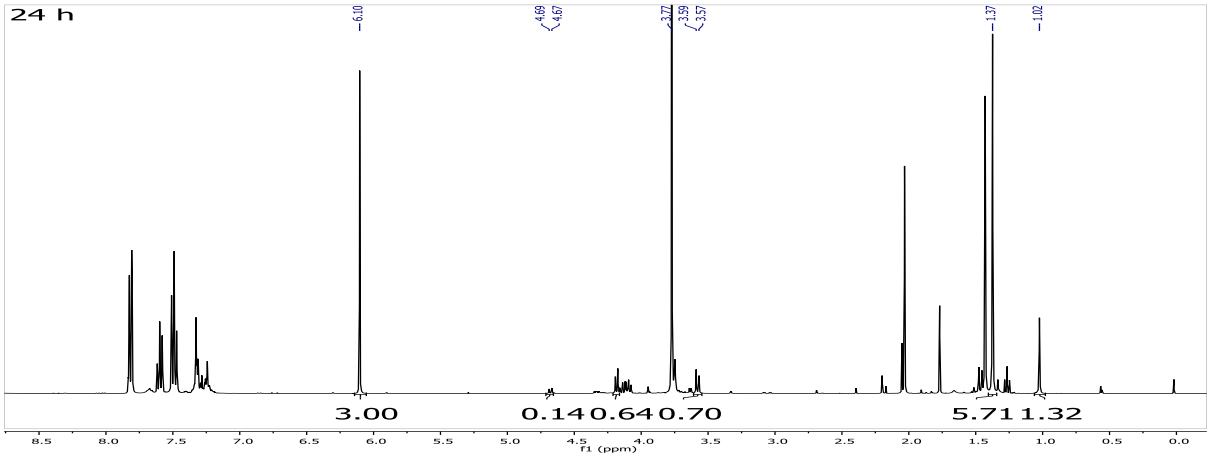

4.5 h
6.10
5.19
5.18
4.69
4.67
3.77
3.56
3.54
1.38
1.02
3.00
0.01
0.18
0.52
4.99
1.17
f1 (ppm)


6 h
6.11
5.20
5.18
4.69
4.67
3.78
3.57
3.55
1.38
1.02
3.00
0.01
0.16
0.58
5.08
1.21
f1 (ppm)

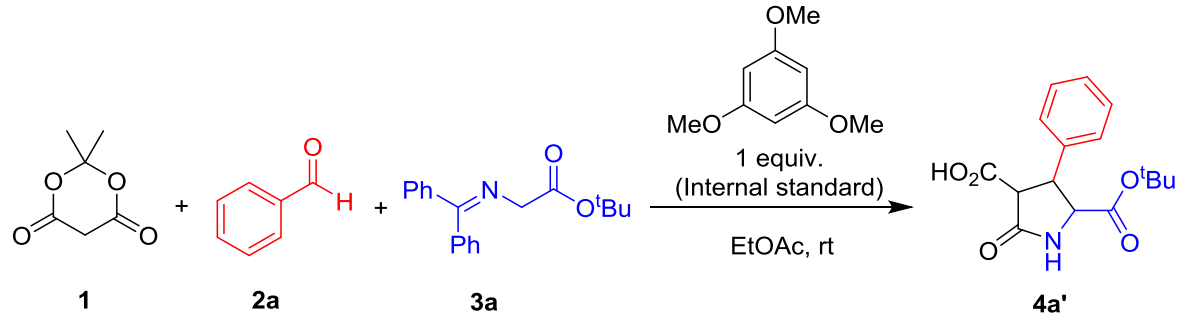

8 h
6.10
4.68
4.66
3.77
3.57
3.55
1.38
1.02
3.00
0.13
0.56
5.19
1.19
f1 (ppm)

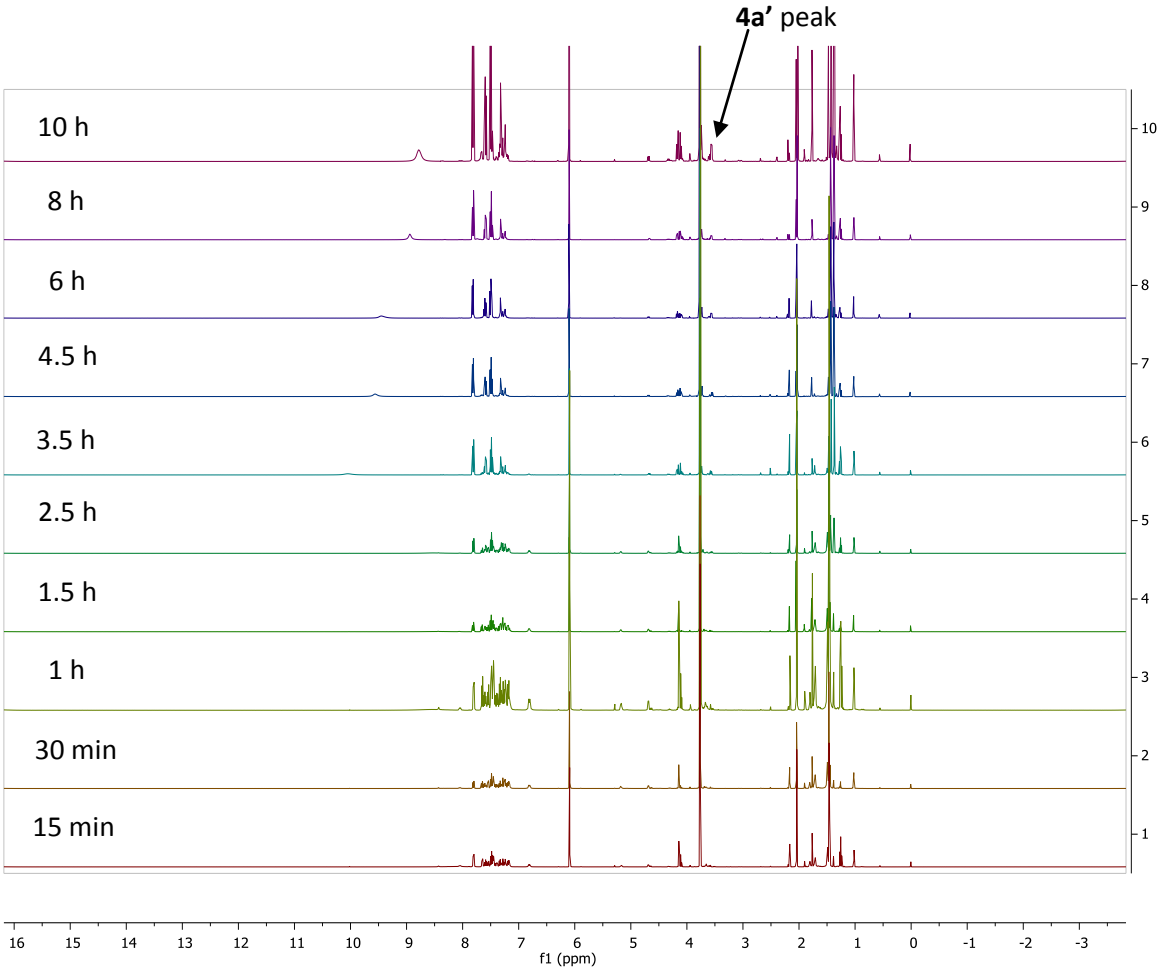

10 h
6.10
4.69
4.67
3.77
3.57
3.55
1.37
1.02
3.00
0.14
0.58
5.26
1.21
f1 (ppm)


12 h
6.10
4.69
4.67
3.77
3.57
3.55
1.37
1.02
3.00
0.14
0.58
5.33
1.23
f1 (ppm)

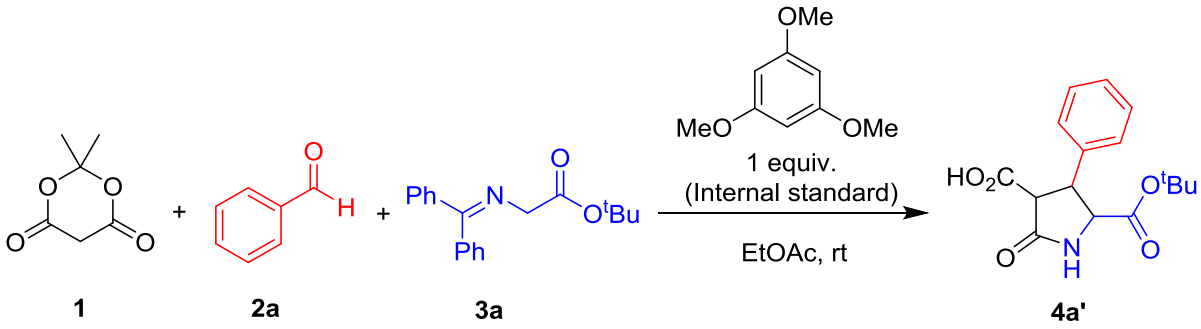

24 h
6.10
4.69
4.67
3.77
3.59
3.57
1.37
1.02
3.00
0.14
0.64
0.70
5.71
1.32
f1 (ppm)

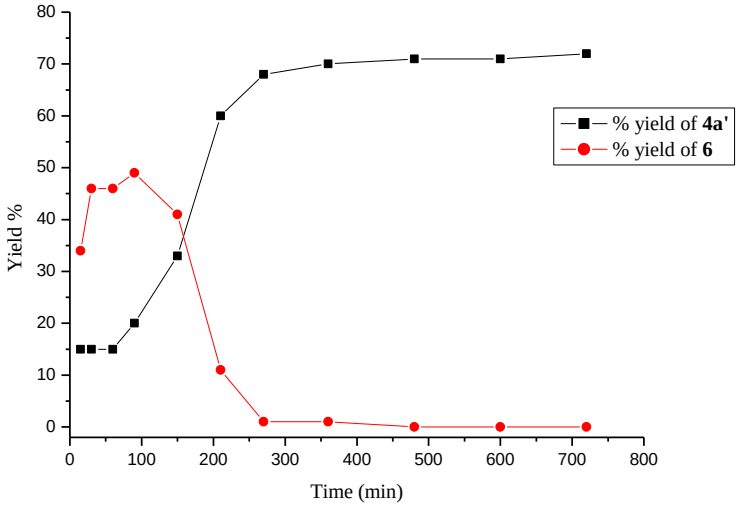
Stacked spectra of reaction mixture at different time interval





Appendix II: ^{1}H NMR Kinetic study of the formation of **4a'**

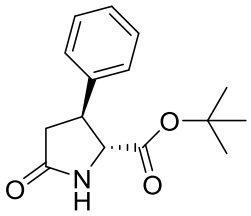




^{1}H NMR kinetic experiments for the reaction of Meldrum's acid (300 mg, 2.08 mmol), Benzaldehyde (225 µL, 2.19 mmol), Schiff's base **3** (799.3 mg, 2.71 mmol) and 1,3,5-trimethoxy benzene (350.1 mg, 2.08 mmol) in 8 ml ethyl acetate at room temperature (25 °C). To quantify the kinetics of this reaction, we followed the production of **4a'** using ^{1}H NMR spectroscopy. The aliquot sampling was taken during different time interval and the solvent (EtOAc) was evaporated and the residue was dissolved in $CDCl_3$. ^{1}H-NMR of the reaction mixture was recorded at different time intervals to calculate the yield of **4a'** and to study the kinetics of the reaction. The yield of **4a'** was calculated by integrating the tert-butyl protons against trimethoxy benzene peak (δ s, 6.09 3H) as an internal standard. Based on the time dependent ^{1}H-NMR studies the kinetics follows the sigmoidal curve which is a characteristic of autocatalytic reaction (black line). Further, autocatalytic process was supported as the concentration of intermediate **6** followed the reverse trend as reaction progressed (red line).

Section 2

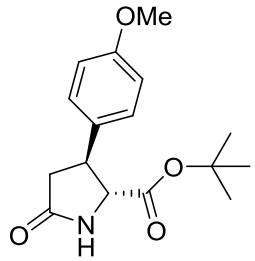
***trans-tert*-butyl 5-oxo-3-phenylpyrrolidine-2-carboxylate (4a)**



Compound **4a** was synthesized following the general procedure. Compound **4a** was obtained as white solid in 65% (235 mg, *trans*/*cis*; 3.6:1, 20:1 after recrystallization from DCM/n-Hexane).

M.p. 108-110 ^{o}C (reported 104-107 °C);[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 2H), 7.30 – 7.26 (m, 3H), 6.31 (s, 1H), 4.15 (d, *J* = 6.0 Hz, 1H), 3.68 – 3.63 (m, 1H), 2.85 (dd, *J* = 17.3, 9.5 Hz, 1H), 2.54 (dd, *J* = 17.3, 7.4 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 170.3, 141.9, 129.1, 127.6, 127.2, 82.8, 63.6, 44.4, 38.4, 28.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{15}H_{20}NO_3$ 262.1443, found 262.1450. FTIR cm^{-1} (neat) 3233, 2978, 2927, 1702, 1453, 1370, 1236, 1154, 845.

***trans-tert*-butyl 3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate (4b)**

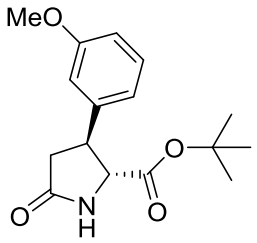


Compound **4b** was synthesized following the general procedure. Compound **4b** was obtained as colourless oil in 58% (235 mg, *trans*/*cis*; >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.18 (s, 1H), 4.09 (d, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.60 (ddd, *J* = 9.4, 7.5, 6.2 Hz, 1H), 2.81 (dd, *J* = 17.2, 9.4 Hz, 1H), 2.50 (dd, *J* = 17.2, 7.5 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 170.4, 159.0, 133.9, 128.3, 114.4, 82.8, 63.8, 55.5, 43.8, 38.5, 28.1; HRMS (ESI-

TOF) *m/z*: $[M + H]^+$ calcd. for $C_{16}H_{22}NO_4$ 292.1549, found 292.1554. FTIR cm^{-1} (neat) 3234, 2976, 2925, 1698, 1614, 1513, 1456, 1369, 1294, 1243, 1153, 1033, 833.

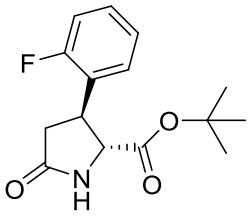
***trans-tert*-butyl 3-(3-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate (4c)**



Compound **4c** was synthesized following the general procedure. Compound **4c** was obtained as colourless oil in 62% (251 mg, *trans*/*cis*; >20:1).

^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (dt, *J* = 7.6, 4.3 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.84 – 6.78 (m, 2H), 6.11 (s, 1H), 4.13 (d, *J* = 5.8 Hz, 1H), 3.81 (s, 3H), 3.68 – 3.58 (m, 1H), 2.83 (dd, *J* = 17.3, 9.5 Hz, 1H), 2.53 (dd, *J* = 17.3, 7.3 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 170.3, 160.1, 143.6, 130.1, 119.4, 113.3, 112.6, 82.9, 63.4, 55.4, 44.3, 38.3, 28.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{16}H_{22}NO_4$ 292.1549, found 292.1548. FTIR cm^{-1} (neat) 3234, 2924, 2853, 1704, 1601, 1489, 1457, 1369, 1245, 1157, 1046, 846.51, 782.

***trans-tert*-butyl 3-(2-fluorophenyl)-5-oxopyrrolidine-2-carboxylate (4d)**



Compound **4d** was synthesized following the general procedure. Compound **4d** was obtained as colourless oil in 70% (270 mg, *trans*/*cis*; 5:1).

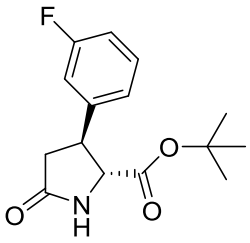
trans isomer- ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 2H), 7.19 – 7.03 (m, 2H), 6.52 (s, 1H), 4.24 (dd, *J* = 16.8, 7.7 Hz, 1H), 3.86 (td, *J* = 8.7, 7.0 Hz, 1H), 2.80 (ddd, *J* = 17.1, 9.5, 0.9 Hz, 1H), 2.60 (dd, *J* = 17.1, 8.4 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 170.1, 160.8 (d, *J* = 246.4 Hz), 129.2 (d, *J* = 8.4 Hz), 128.9 (d, *J* = 4.2 Hz), 128.3 (d, *J*

= 13.0 Hz), 124.6 (d, *J* = 3.6 Hz), 116.0 (d, *J* = 22.0 Hz), 82.8, 62.1, 38.5 (d, *J* = 1.8 Hz), 37.4 (d, *J* = 1.4 Hz), 27.9.

cis isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.18 – 6.94 (m, 2H), 6.52 (s, 1H), 4.54 (d, *J* = 8.1 Hz, 1H), 4.23 (s, 1H), 2.71 (dd, *J* = 15.0, 8.2 Hz, 2H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 169.1, 161.2 (d, *J* = 247.0 Hz), 129.4 (d, *J* = 8.4 Hz), 129.0 (d, *J* = 4.2 Hz), 128.2 (d, *J* = 5.9 Hz), 124.6 (d, *J* = 3.5 Hz), 115.3 (d, *J* = 22.3 Hz), 82.4, 60.2, 36.1 (d, *J* = 3.8 Hz), 34.9, 27.5.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{15}H_{19}FNO_3$ 280.1349, found 280.1355. FTIR cm^{-1} (neat) 3231, 2979, 2929, 1700, 1492, 1455, 1369.80, 1230, 1152, 844, 758.

trans-tert-butyl 3-(3-fluorophenyl)-5-oxopyrrolidine-2-carboxylate (4e)



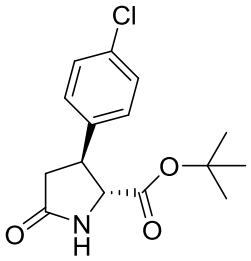
Compound **4e** was synthesized following the general procedure. Compound **4e** was obtained as colourless oil in 69% (267 mg, *trans*/*cis*; 5:1).

trans isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.25 (m, 1H), 7.13 – 7.03 (m, 1H), 7.03 – 6.84 (m, 2H), 6.48 (s, 1H), 4.12 (d, *J* = 6.0 Hz, 1H), 3.73 – 3.57 (m, 1H), 2.93 – 2.76 (m, 1H), 2.51 (dd, *J* = 17.3, 7.4 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 170.1, 163.1 (d, *J* = 246.8 Hz), 144.4 (d, *J* = 7.1 Hz), 130.6 (d, *J* = 8.4 Hz), 122.8 (d, *J* = 2.9 Hz), 114.5 (d, *J* = 19.4 Hz), 114.3 (d, *J* = 20.2 Hz), 83.0, 63.3, 44.1 (d, *J* = 1.7 Hz), 38.3, 28.1.

cis isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (td, *J* = 7.8, 6.1 Hz, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 7.05 – 6.91 (m, 2H), 6.48 (s, 1H), 4.49 (d, *J* = 7.9 Hz, 1H), 3.96 – 3.85 (m, 1H), 2.79 (dd, *J* = 16.8, 8.7 Hz, 1H), 2.65 (dd, *J* = 16.8, 5.9 Hz, 1H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 168.6, 162.8 (d, *J* = 246.7 Hz), 141.7 (d, *J* = 7.2 Hz), 130.3 (d, *J* = 8.1 Hz), 123.5 (d, *J* = 3.0 Hz), 115.2 (d, *J* = 21.8 Hz), 114.7 (d, *J* = 21.0 Hz), 82.6, 61.2, 43.0 (d, *J* = 1.7 Hz), 36.9, 27.6.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{15}H_{19}FNO_3$ 280.1349, found 280.1357. FTIR cm^{-1} (neat) 3233, 2978, 2919, 1705, 1621, 1592, 1489, 1452, 1371, 1241, 115, 786.

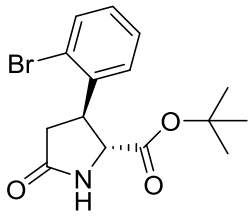
***trans-tert*-butyl 3-(4-chlorophenyl)-5-oxopyrrolidine-2-carboxylate (4f)**



Compound **4f** was synthesized following the general procedure. Compound **4f** was obtained as colourless oil in 72% (295 mg, *trans*/*cis*; 4:1).

trans isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.25 – 7.19 (m, 2H), 6.39 (s, 1H), 4.09 (d, *J* = 6.0 Hz, 1H), 3.68 – 3.58 (m, 1H), 2.83 (dd, *J* = 17.3, 9.4 Hz, 1H), 2.48 (dd, *J* = 17.3, 7.5 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 170.1, 140.4, 133.4, 129.2, 128.6, 83.1, 63.4, 43.8, 38.3, 28.1.
cis isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.39 (s, 1H), 4.49 (d, *J* = 7.9 Hz, 1H), 3.88 (td, *J* = 8.3, 5.6 Hz, 1H), 2.79 (dd, *J* = 15.8, 9.1 Hz, 1H), 2.61 (dd, *J* = 16.8, 5.5 Hz, 1H), 1.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 168.7, 137.8, 133.6, 129.3, 128.8, 82.7, 61.2, 42.6, 37.1, 27.6.
HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{15}H_{19}ClNO_3$ 296.1053, found 296.1058. FTIR cm^{-1} (neat) 3229, 2978, 2927, 1700, 1492, 1369, 1235, 1154, 1093, 1014, 832, 730.

***trans-tert*-butyl 3-(2-bromophenyl)-5-oxopyrrolidine-2-carboxylate (4g)**



Compound **4g** was synthesized following the general procedure. Compound **4g** was obtained as colourless oil in 59% (235 mg, *trans*/*cis*; 2.5:1).

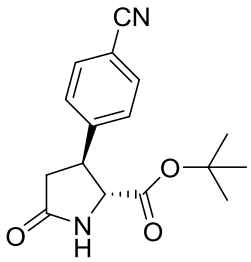
trans isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.46 (m, 1H), 7.35 – 7.28 (m, 2H), 7.20 – 7.08 (m, 1H), 6.31 (s, 1H), 4.27 – 4.06 (m, 1H), 2.88 (ddd, *J* = 10.8, 9.5, 6.2 Hz, 1H), 2.72

(qd, *J* = 16.7, 8.3 Hz, 1H), 2.53 – 2.38 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 170.2, 140.9, 133.4, 129.0, 128.3, 128.0, 124.2, 82.9, 62.3, 43.1, 37.6, 28.0.

cis isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.32 – 7.29 (m, 2H), 7.18 – 7.11 (m, 1H), 6.28 (s, 1H), 4.68 (dd, *J* = 8.3, 0.7 Hz, 1H), 4.43 (q, *J* = 8.3 Hz, 1H), 2.94 – 2.83 (m, 1H), 2.42 (dd, *J* = 4.8, 1.9 Hz, 1H), 1.05 (s, 9H): ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 169.1, 138.0, 133.1, 129.3, 128.2, 128.1, 125.8, 82.5, 59.5, 42.3, 35.6, 27.6.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{15}H_{19}BrNO_3$ 340.0548, found 340.0538. FTIR cm^{-1} (neat) 3233, 2977, 2928, 1699, 1471, 1437, 1369, 1233, 1153, 1024, 845, 754, 663.

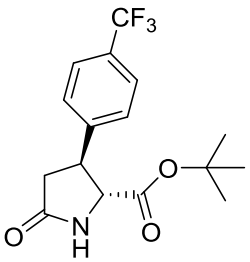
***trans-tert*-butyl 3-(4-cyanophenyl)-5-oxopyrrolidine-2-carboxylate (4h)**



Compound **4h** was synthesized following the general procedure. Compound **4h** was obtained as colourless oil in 68% (270 mg, *trans*/*cis*; >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.66 (m, 2H), 7.44 – 7.32 (m, 2H), 7.03 (s, 1H), 4.14 (d, *J* = 6.0 Hz, 1H), 3.75 – 3.69 (m, 1H), 2.88 (dd, J = 17.3, 9.5 Hz, 1H), 2.51 (dd, J = 17.3, 7.4 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 169.7, 147.2, 132.8, 128.1, 118.5, 111.5, 83.2, 63.1, 44.2, 38.1, 28.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{16}H_{19}N_2O_3$ 287.1395, found 287.1402. FTIR cm^{-1} (neat) 3233, 2924, 2855, 2229, 1697, 1611, 1457, 1421, 1370, 1237, 1153, 972, 839, 784.

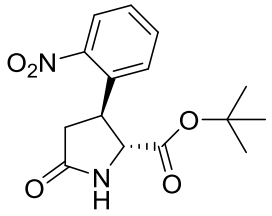
***trans-tert*-butyl 5-oxo-3-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (4i)**



Compound **4i** was synthesized following the general procedure. Compound **4i** was obtained as colourless oil in 71% (324 mg, *trans*/*cis*; >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 6.10 (s, 1H), 4.14 (d, *J* = 6.0 Hz, 1H), 3.87 – 3.59 (m, 1H), 2.87 (dd, *J* = 17.3, 9.5 Hz, 1H), 2.53 (dd, *J* = 17.3, 7.4 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 169.7, 145.7, 129.9 (q, *J* = 37 Hz), 127.5, 126.7(q, *J* = 267 Hz), 126.0 (q, *J* = 3.7 Hz), 83.1, 62.9, 43.9, 38.0, 27.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{16}H_{19}F_3NO_3$ 330.1317, found 330.1328. FTIR cm^{-1} (neat) 3232, 2979, 2925, 1706, 1623, 1424, 1371, 1327, 1240, 1160, 1122, 1069, 842.

***trans*-*tert*-butyl 3-(2-nitrophenyl)-5-oxopyrrolidine-2-carboxylate (4j)**



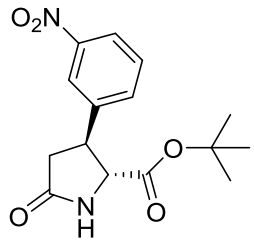
Compound **4j** was synthesized following the general procedure. Compound **4j** was obtained as colourless oil in 61% (259 mg, *trans*/*cis*; 3:1).

trans isomer- ^{1}H NMR (400 MHz, CDCL3) δ 7.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.55 – 7.51 (m, 1H), 7.47 – 7.42 (m, 1H), 6.64 (s, 1H), 4.22 (m, 2H), 3.01 (dt, *J* = 18.0, 8.9 Hz, 1H), 2.56 – 2.39 (m, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 169.8, 149.6, 136.7, 133.7, 128.4, 128.3, 124.8, 83.3, 62.9, 38.5, 38.2, 27.9.

cis isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.82 – 7.78 (m, 1H), 7.61 – 7.56 (m, 1H), 7.49 – 7.34 (m, 1H), 6.57 (s, 1H), 4.66 – 4.57 (m, 2H), 3.26 – 3.16 (m, 1H), 2.81 – 2.74 (m, 1H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 168.9, 150.1, 133.6, 130.2, 128.7, 128.6, 124.9, 82.9, 60.0, 37.8, 36.4, 27.5.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{15}H_{19}N_2O_5$ 307.1294, found 307.1300. FTIR cm^{-1} (neat) 3232, 2923, 2854, 1697, 1453, 1369, 1234, 1151, 1044, 967, 843.

***trans-tert*-butyl 3-(3-nitrophenyl)-5-oxopyrrolidine-2-carboxylate (4k)**



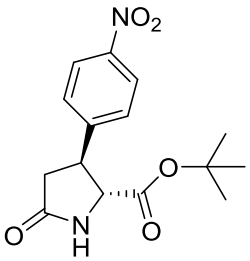
Compound **4k** was synthesized following the general procedure. Compound **4k** was obtained as colourless oil in 65% (276 mg, *trans*/*cis*; 9:1).

trans isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.07 (m, 2H), 7.68 – 7.62 (m, 1H), 7.59 – 7.50 (m, 1H), 6.57 (s, 1H), 4.18 (d, *J* = 6.4 Hz, 1H), 3.79 (ddd, *J* = 9.4, 7.9, 6.4 Hz, 1H), 2.90 (dd, *J* = 17.3, 9.5 Hz, 1H), 2.56 (dd, *J* = 17.3, 7.9 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 169.6, 148.6, 143.7, 133.4, 130.2, 122.7, 122.6, 83.5, 63.1, 43.9, 38.2, 28.0.

cis isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.08 (m, 2H), 7.69 – 7.49 (m, 2H), 6.57 (s, 1H), 4.57 (d, *J* = 7.8 Hz, 1H), 4.08 – 3.97 (m, 1H), 2.87 (dd, *J* = 16.8, 8.7 Hz, 1H), 2.67 (dd, *J* = 16.9, 5.5 Hz, 1H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.6, 130.0, 83.0, 27.6 other peaks were not visible.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{15}H_{19}N_2O_5$ 307.1294, found 307.1298. FTIR cm^{-1} (neat) 3233, 2977, 2925, 1702, 1529, 1451, 1348, 1236, 1154, 812, 737.

***trans-tert*-butyl 3-(4-nitrophenyl)-5-oxopyrrolidine-2-carboxylate (4l)**

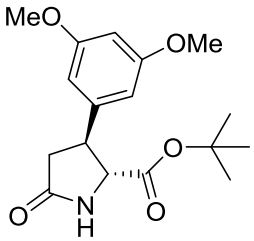


Compound **4l** was synthesized following the general procedure. Compound **4l** was obtained as colourless oil in 56% (238 mg, *trans*/*cis*; >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 6.55 (s, 1H), 4.15 (d, *J* = 6.1 Hz, 1H), 3.94 – 3.60 (m, 1H), 2.89 (dd, *J* = 17.3, 9.5 Hz, 1H), 2.53 (dd, *J* =

17.3, 7.5 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 169.6, 149.1, 147.4, 128.3, 124.4, 83.5, 62.9, 44.0, 38.2, 28.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{15}H_{19}N_2O_5$ 307.1294, found 307.1300. FTIR cm^{-1} (neat) 3234, 2978, 2925, 1702, 1602, 1520, 1454, 1346, 1238, 1155, 1113, 852, 754.

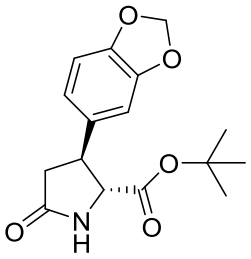
***trans-tert*-butyl 3-(3,5-dimethoxyphenyl)-5-oxopyrrolidine-2-carboxylate (4m)**



Compound **4m** was synthesized following the general procedure. Compound **4m** was obtained as colourless oil in 68% (303 mg, *trans*/*cis*; >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, *J* = 2.2 Hz, 2H), 6.38 – 6.36 (m, 1H), 6.32 (s, 1H), 4.13 (d, *J* = 5.7 Hz, 1H), 3.79 (s, 6H), 3.65 – 3.51 (m, 1H), 2.82 (dd, *J* = 17.4, 9.6 Hz, 1H), 2.51 (dd, *J* = 17.4, 7.1 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 170.3, 161.3, 144.5, 105.3, 99.1, 82.8, 63.4, 55.5, 44.4, 38.2, 28.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{17}H_{24}NO_5$ 322.1654, found 322.1657. FTIR cm^{-1} (neat) 3227, 2925, 2851, 1701, 1598, 1462, 1365, 1295, 1237, 1202, 1151, 1064, 968, 926, 840.

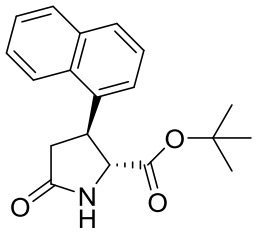
***trans-tert*-butyl 3-(benzo[d][1,3]dioxol-5-yl)-5-oxopyrrolidine-2-carboxylate (4n)**



Compound **4n** was synthesized following the general procedure. Compound **4n** was obtained as colourless oil in 55% (233 mg, *trans*/*cis*; 5:1).

trans isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 – 6.75 (m, 2H), 6.74 – 6.69 (m, 1H), 6.22 (s, 1H), 5.96 (s, 2H), 4.07 (d, *J* = 6.0 Hz, 1H), 3.57 (ddd, *J* = 9.4, 7.4, 6.0 Hz, 1H), 2.89 – 2.73 (m, 1H), 2.47 (dd, *J* = 17.3, 7.4 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 170.3, 148.2, 147.0, 135.7, 120.6, 108.6, 107.3, 101.3, 82.9, 63.7, 44.2, 38.5, 28.1.
cis isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (dd, *J* = 4.7, 3.0 Hz, 1H), 6.74 – 6.68 (m, 1H), 6.22 (s, 1H), 5.96 (s, 1H), 4.48 – 4.41 (m, 1H), 3.90 – 3.76 (m, 1H), 2.76 (dd, *J* = 16.8, 8.7 Hz, 1H), 2.61 (dd, *J* = 16.8, 5.9 Hz, 1H), 1.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 169.9, 147.9, 146.6, 136.6, 121.2, 108.5, 108.3, 101.2, 82.4, 61.4, 43.1, 37.2, 27.7.
HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{16}H_{20}NO_5$ 306.1341, found 306.1348. FTIR cm^{-1}(neat) 3232, 2976, 2924, 1697, 1492, 1445, 1369, 1237, 1152, 1036, 931, 847, 812, 732.

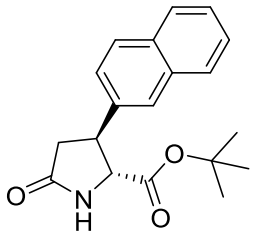
trans-tert-butyl 3-(naphthalen-1-yl)-5-oxopyrrolidine-2-carboxylate (4o)



Compound **4o** was synthesized following the general procedure. Compound **4o** was obtained as colourless oil in 65% (281 mg, *trans*/*cis*; 3:1).

trans isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.3 Hz, 1H), 7.90 (dd, *J* = 6.6, 5.4 Hz, 1H), 7.84 – 7.76 (m, 1H), 7.65 – 7.38 (m, 4H), 6.80 (s, 1H), 4.56 – 4.41 (m, 1H), 4.26 (d, *J* = 3.8 Hz, 1H), 3.06 – 2.94 (m, 1H), 2.73 – 2.61 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 170.8, 137.8, 134.2, 131.0, 129.4, 128.4, 128.2, 126.6, 126.0, 125.6, 122.9, 82.9, 63.1, 38.8, 37.2, 28.0.
cis isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.83 – 7.75 (m, 1H), 7.63 – 7.35 (m, 4H), 6.86 (s, 1H), 4.84 – 4.67 (m, 2H), 3.05 (dd, *J* = 16.7, 8.2 Hz, 1H), 2.76 (dd, *J* = 16.6, 8.1 Hz, 1H), 0.66 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 169.2, 137.7, 133.8, 132.3, 129.1, 129.0, 128.4, 126.5, 125.9, 124.2, 123.4, 81.8, 60.7, 39.5, 35.3, 27.1.
HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{19}H_{22}NO_3$ 312.1599, found 312.1608. FTIR cm^{-1} (neat) 3223, 2976, 2926, 1700, 1425, 1369, 1237, 1151, 967, 84, 780.

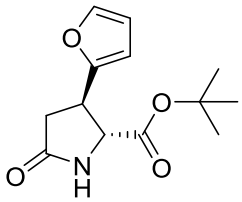
***trans-tert*-butyl 3-(naphthalen-2-yl)-5-oxopyrrolidine-2-carboxylate (4p)**



Compound **4p** was synthesized following the general procedure. Compound **4p** was obtained as colourless oil in 60% (259 mg, *trans*/*cis*; >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.07 (d, *J* = 8.2 Hz, 2H), 7.53 (m, 4H), 6.42 (s, 1H), 5.29 (ddd, *J* = 11.4, 9.0, 7.5 Hz, 1H), 4.81 (d, *J* = 7.3 Hz, 1H), 3.16 (dd, *J* = 18.0, 9.1 Hz, 1H), 3.04 (dd, *J* = 18.0, 11.4 Hz, 1H), 1.20 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 171.0, 147.2, 132.2, 131.9, 128.4, 126.6, 125.0, 123.6, 82.9, 62.2, 38.2, 36.4, 27.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{19}H_{22}NO_3$ 312.1599, found 312.1608. FTIR cm^{-1} (neat) 3209, 2975, 2924, 2855, 1696, 1452, 1369, 1238, 1153, 887, 842.

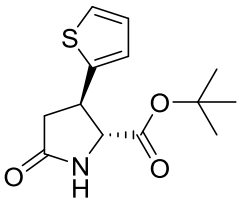
***trans-tert*-butyl 3-(furan-2-yl)-5-oxopyrrolidine-2-carboxylate (4q)**



Compound **4q** was synthesized following the general procedure. Compound **4q** was obtained as colourless oil in 52% (181 mg, *trans*/*cis*; >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 5.93 (s, 1H), 4.23 (d, *J* = 6.4 Hz, 1H), 3.86 – 3.71 (m, 1H), 2.74 (dd, *J* = 17.0, 9.2 Hz, 1H), 2.64 (dd, *J* = 17.0, 7.9 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 169.9, 153.4, 142.3, 110.5, 106.6, 83.1, 60.7, 37.9, 35.4, 28.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{13}H_{17}NO_4$ Na 274.1055, found 274.1057. FTIR cm^{-1} (neat) 3295, 2976, 2927, 1694, 1370, 1241, 1153, 1017, 971, 840.

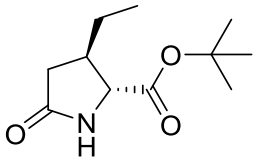
***trans-tert*-butyl 5-oxo-3-(thiophen-2-yl)pyrrolidine-2-carboxylate (4r)**



Compound **4r** was synthesized following the general procedure. Compound **4r** was obtained as colourless oil in 58% (215 mg, *trans*/*cis*; >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.22 (dd, *J* = 3.8, 2.5 Hz, 1H), 6.98 – 6.95 (m, 1H), 6.06 (s, 1H), 4.17 (d, *J* = 6.1 Hz, 1H), 3.98 (ddd, *J* = 9.1, 7.8, 6.2 Hz, 1H), 2.89 (dd, *J* = 17.1, 9.2 Hz, 1H), 2.60 (dd, *J* = 17.1, 7.7 Hz, 1H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 169.8, 144.7, 127.1, 124.9, 124.5, 83.2, 63.8, 39.7, 39.1, 28.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{13}H_{17}NO_3SNa$ 290.0826, found 290.0831. FTIR cm^{-1} (neat) 3227, 2924, 2856, 1704, 1453, 1369, 1240, 1154, 844, 780.

***trans-tert*-butyl 3-ethyl-5-oxopyrrolidine-2-carboxylate (4s)**



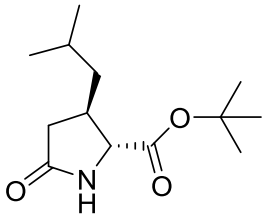
Compound **4s** was synthesized following the general procedure. Compound **4s** was obtained as colourless oil in 35% (104 mg, *trans*/*cis*; 2:1).

trans isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (s, 1H), 4.09 (d, *J* = 8.2 Hz, 1H), 2.59 – 2.47 (m, 1H), 2.42 – 2.33 (m, 1H), 2.21 – 2.11 (m, 1H), 1.63 – 1.52 (m, 1H), 1.46 (s, 9H), 1.33 (m, 1H), 0.95 (t, *J* = 7.4, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 170.4, 82.7, 60.2, 40.6, 35.0, 28.2, 23.4, 12.4.

cis isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H), 3.76 (d, *J* = 5.5 Hz, 1H), 2.61 – 2.47 (m, 1H), 2.37 (dd, *J* = 16.5, 8.2 Hz, 1H), 2.10 – 1.96 (m, 1H), 1.82 – 1.69 (m, 1H), 1.46 (s, 9H), 1.33 (ddd, *J* = 13.4, 9.2, 6.6 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 171.1, 82.5, 61.4, 40.7, 35.8, 29.8, 28.1, 11.7.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{11}H_{19}NO_3Na$ 236.1262, found 236.1264. FTIR cm^{-1} (neat) 3236, 2967, 2926, 1698, 1457, 1422, 1369, 1227, 1154, 844.

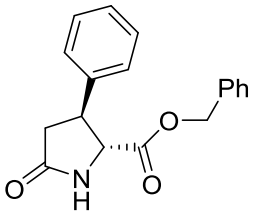
***trans*-*tert*-butyl 3-isobutyl-5-oxopyrrolidine-2-carboxylate (4t)**



Compound **4t** was synthesized following the general procedure. Compound **4t** was obtained as colourless oil in 41% (137 mg, *trans*/*cis*; 1.3:1).

trans isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 4.01 (d, *J* = 7.9 Hz, 1H), 2.55 – 2.39 (m, 1H), 2.34 – 2.22 (m, 1H), 2.19 – 2.05 (m, 1H), 1.65 – 1.49 (m, 1H), 1.46 – 1.36 (m, 9H), 1.33 – 1.15 (m, 2H), 0.92 – 0.77 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 170.5, 82.4, 60.4, 39.3, 36.6, 28.1, 26.0, 23.3, 21.8.
cis isomer- ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 3.69 (d, *J* = 5.4 Hz, 1H), 2.54 – 2.39 (m, 1H), 2.28 (ddt, *J* = 16.4, 8.1, 1.4 Hz, 1H), 2.10 (m, 1H), 2.01 – 1.89 (m, 1H), 1.41 (s, 9H), 1.33 – 1.18 (m, 2H), 0.92 – 0.78 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 171.1, 82.2, 61.9, 44.5, 37.1, 35.4, 28.0, 23.0, 22.0.
HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{13}H_{24}NO_3$ 242.1756, found 242.1763. FTIR cm^{-1} (neat) 3233, 2958, 1698, 1460, 1423, 1368, 1292, 1225, 1152, 844.

***trans*-benzyl-5-oxo-3-phenylpyrrolidine-2-carboxylate (4u)**

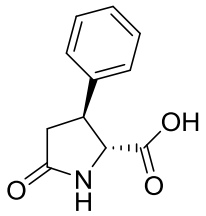


Compound **4u** was synthesized following the general procedure using **3b** as Schiff's base. Compound **4u** was obtained as colourless oil in 56% (229 mg, *trans*/*cis*; 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 10H), 6.78 (s, 1H), 5.23 (d, *J* = 12.2 Hz, 1H), 5.13 (d, *J* = 12.2 Hz, 1H), 4.29 (d, *J* = 5.5 Hz, 1H), 3.67 (ddd, *J* = 9.5, 6.8, 5.6 Hz, 1H), 2.85 (dd, *J* = 17.4, 9.5 Hz, 1H), 2.53 (dd, *J* = 17.4, 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 171.1, 141.6, 135.1, 129.2, 128.8, 128.7, 128.5, 127.7, 127.1, 67.5, 63.1, 44.1, 38.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{18}H_{18}NO_3$ 296.1281, found 296.1287.

Application of the protocol

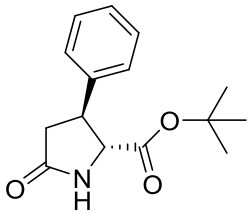
***trans*-5-oxo-3-phenylpyrrolidine-2-carboxylic acid**



To the stirred solution of product **4u** (200 mg) in methanol, 10% Pd/C was added at room temperature. The resulting mixture was stirred for 12 hours under H_2 (1 atm, balloon) and then filtered through celite bed and concentrated under reduced pressure on rotatory evaporator. Further, the crude product **8** was purified by column chromatography on silica gel using dichloromethane/methanol (90:10) as an eluent. The acid **8** obtained as a white solid in 75% (139 mg) yield with 10:1 *dr* ratio.

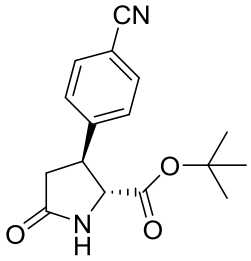
M.p. 141-143 ^{o}C (reported 166.5-167.0 ^{o}C);[2] ^{1}H NMR (400 MHz, CD_3OD) δ 7.38 – 7.24 (m, 5H), 4.22 (d, *J* = 4.9 Hz, 1H), 3.73 – 3.66 (m, 1H), 2.85 (dd, *J* = 17.2, 9.4 Hz, 1H), 2.43 (dd, *J* = 17.2, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 179.7, 175.0, 143.9, 123.0, 128.4, 127.9, 64.6, 45.5, 39.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_{11}H_{12}NO_3$ 206.0812, found 206.0808.

Gram Scale Synthesis of compound 4a



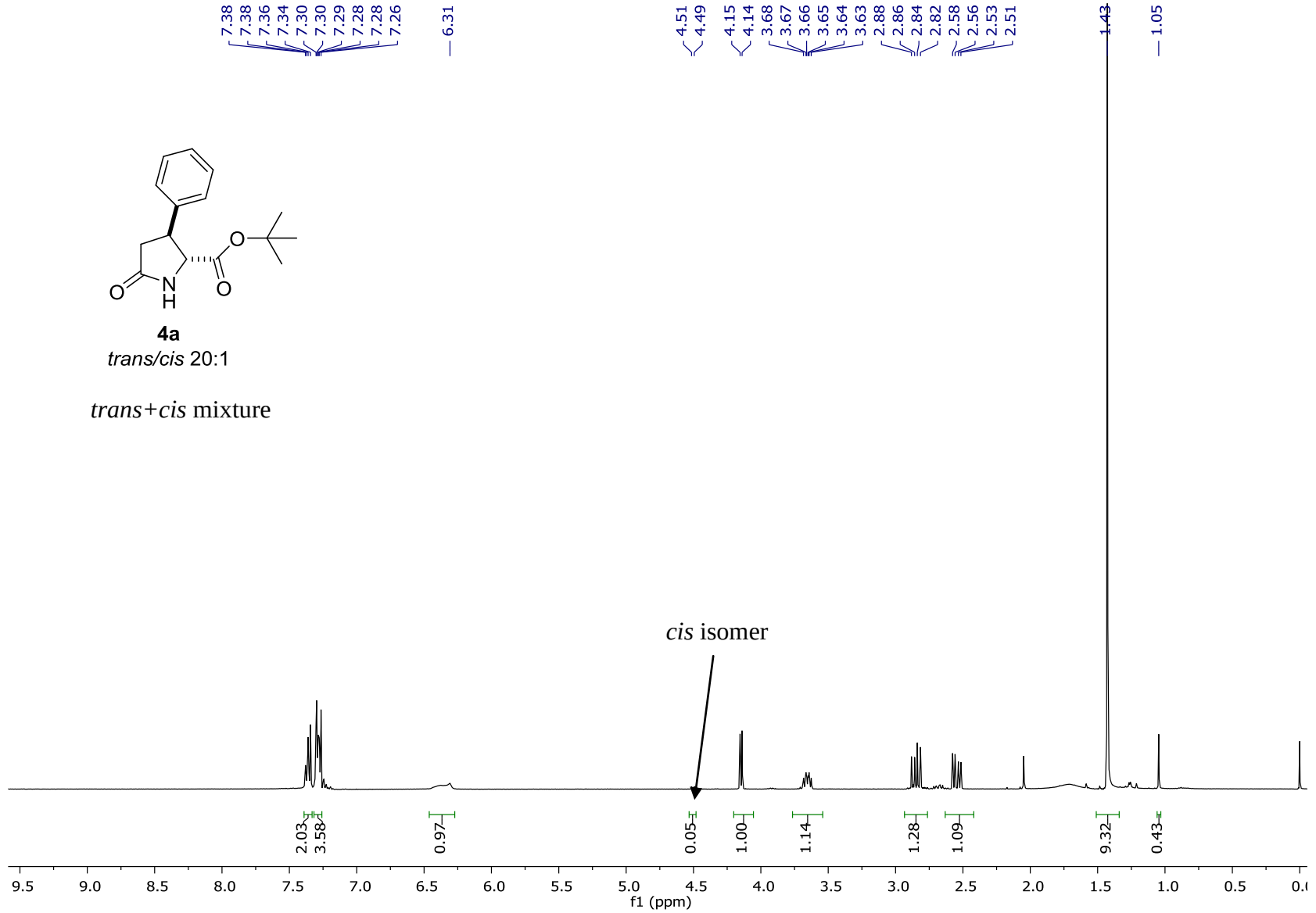
For the gram scale synthesis general procedure described in the manuscript was followed on a higher scale. Meldrum's acid **1** (1 g, 6.95 mmol, 1 equiv.), benzaldehyde **2a** (750 µL, 7.35 mmol, 1.06 equiv.) and Schiff's base **3a** (3.07 g, 10.25 mmol, 1.5 equiv.) in 15 mL of EtOAc. Workup was performed according to general procedure described in the manuscript. Product **4a** obtained as white solid in 55% yield (0.99 g).

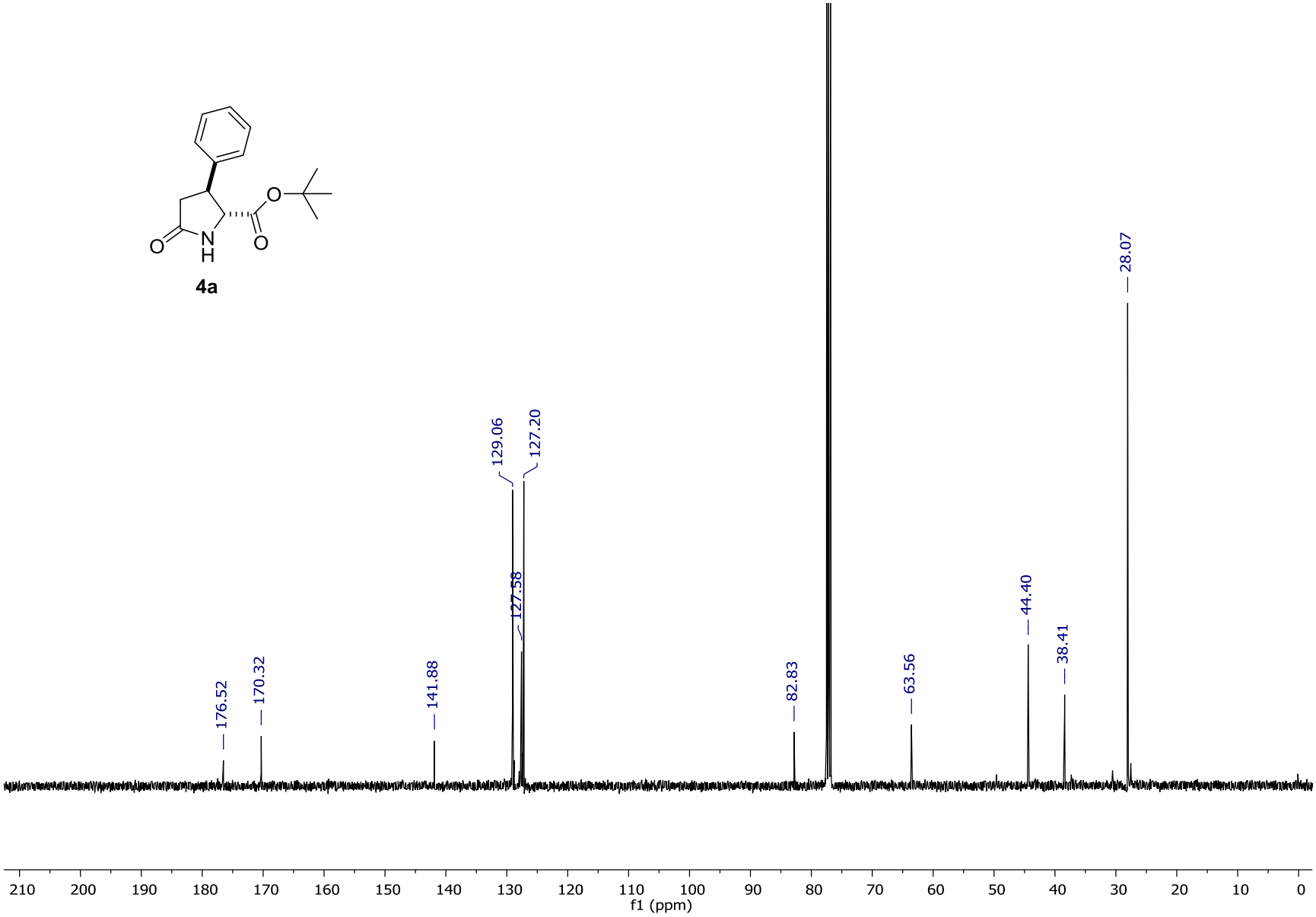
Gram Scale Synthesis of compound 4h



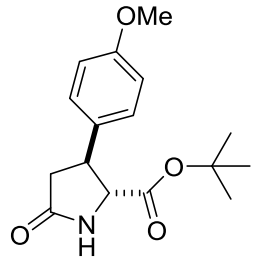
For the gram scale synthesis general procedure described in the manuscript was followed on a higher scale. Meldrum's acid **1** (1 g, 6.95 mmol, 1 equiv.), 4-cyanobenzaldehyde **2h** (955.4 mg, 7.35 mmol, 1.05 equiv.) and Schiff's base **3a** (3.07 g, 10.25 mmol, 1.5 equiv.) in 15 mL of EtOAc. Workup was performed according to general procedure described in the manuscript. Product **4h** obtained as colourless viscous liquid in 59% yield (1.17 g).

Section 3: ^{1}H and ^{13}C Spectra of compounds 4a-4u, 8




4a
176.52
170.32
141.88
129.06
127.58
127.20
82.83
63.56
44.40
38.41
28.07
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

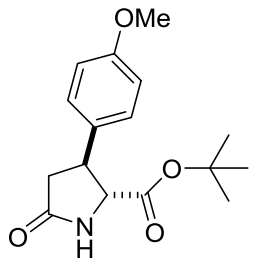
20160830-ADS-155-RGB



4b

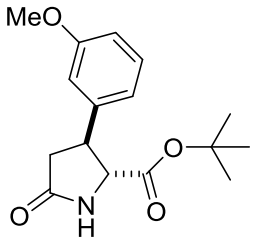
trans/cis >20:1

20160830-ADS-155-RGB



4b

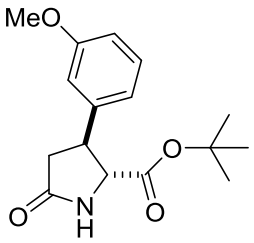
20160907-ADS-165-RGB
ADS-165-RGB



4c

trans/cis >20:1

20160907-ADS-165-RGB
ADS-165-RGB

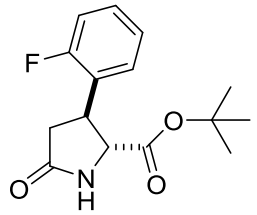


4c

20160907-ADS-168-RGB
ADS-168-RGB

7.3101 7.3064 7.2964 7.2910 7.2876 7.2835 7.2772 7.2720 7.2691 7.2638 7.2605 7.2528 7.2443 7.2397 7.2297 7.2189 6.5245

4.5546 4.5343 4.2750 4.2535 4.2308 4.2137 3.8956 3.8781 3.8737 3.8555 3.8513 3.8338 2.8342 2.8319 2.8104 2.8081 2.7915 2.7891 2.7677 2.7654 2.7405 2.7213 2.7043 2.6826 2.6291 2.6082 2.5864 2.5655 1.3929 1.0479



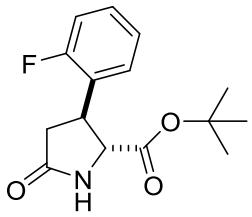
4d

trans/cis 5:1

trans+*cis* mixture

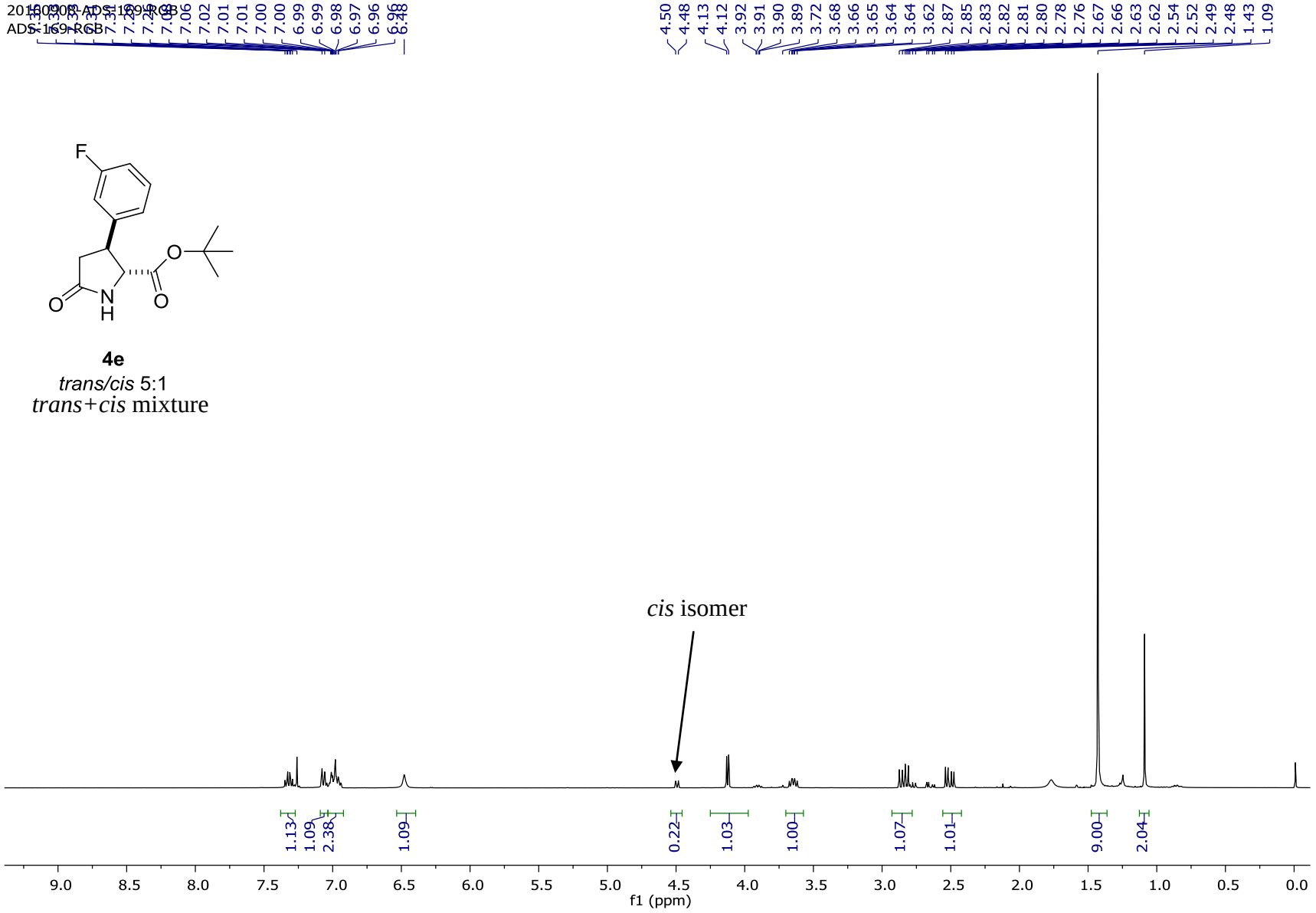
cis isomer

20160907-ADS-168-RGB
ADS-168-RGB

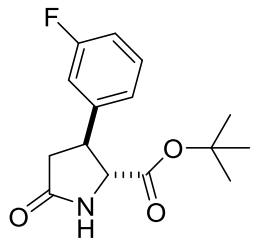


4d

trans+*cis* mixture

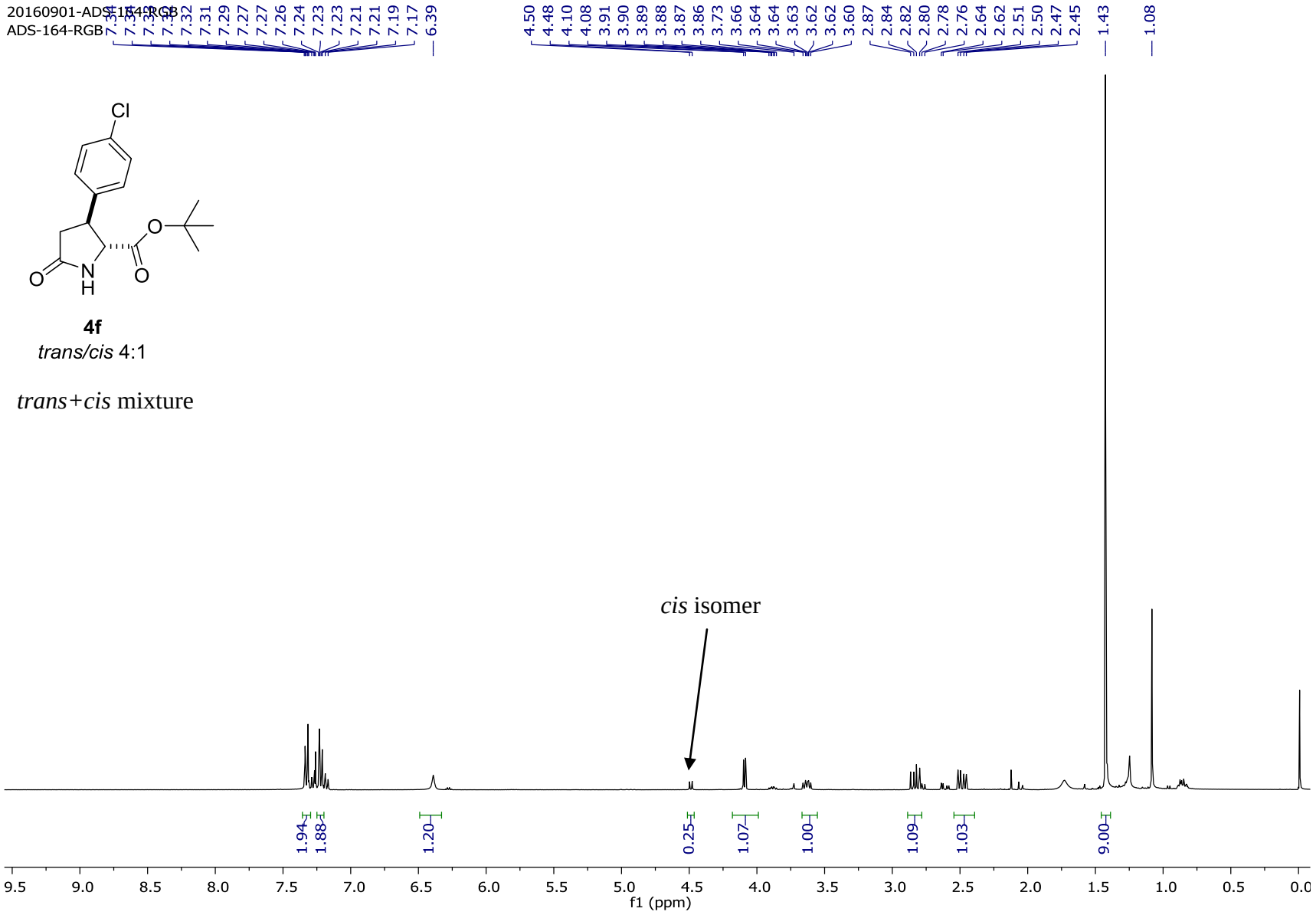

20160908-ADS-169-RGB
ADS-169-RGB
4.50
4.48
4.13
4.12
3.92
3.91
3.90
3.89
3.72
3.68
3.66
3.65
3.64
3.64
3.62
2.87
2.85
2.83
2.82
2.81
2.80
2.78
2.76
2.67
2.66
2.63
2.62
2.54
2.52
2.49
2.48
1.43
1.09
F
O
O
N
H
O
4e
trans/cis 5:1
trans+cis mixture
cis isomer
1.13
1.09
2.38
1.09
0.22
1.03
1.00
1.07
1.01
9.00
2.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

20160908-ADS-169-RGB
ADS-169-RGB

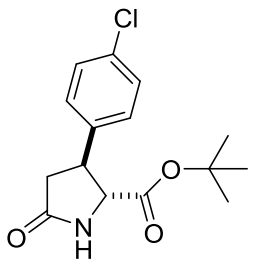


4e

trans+*cis* mixture

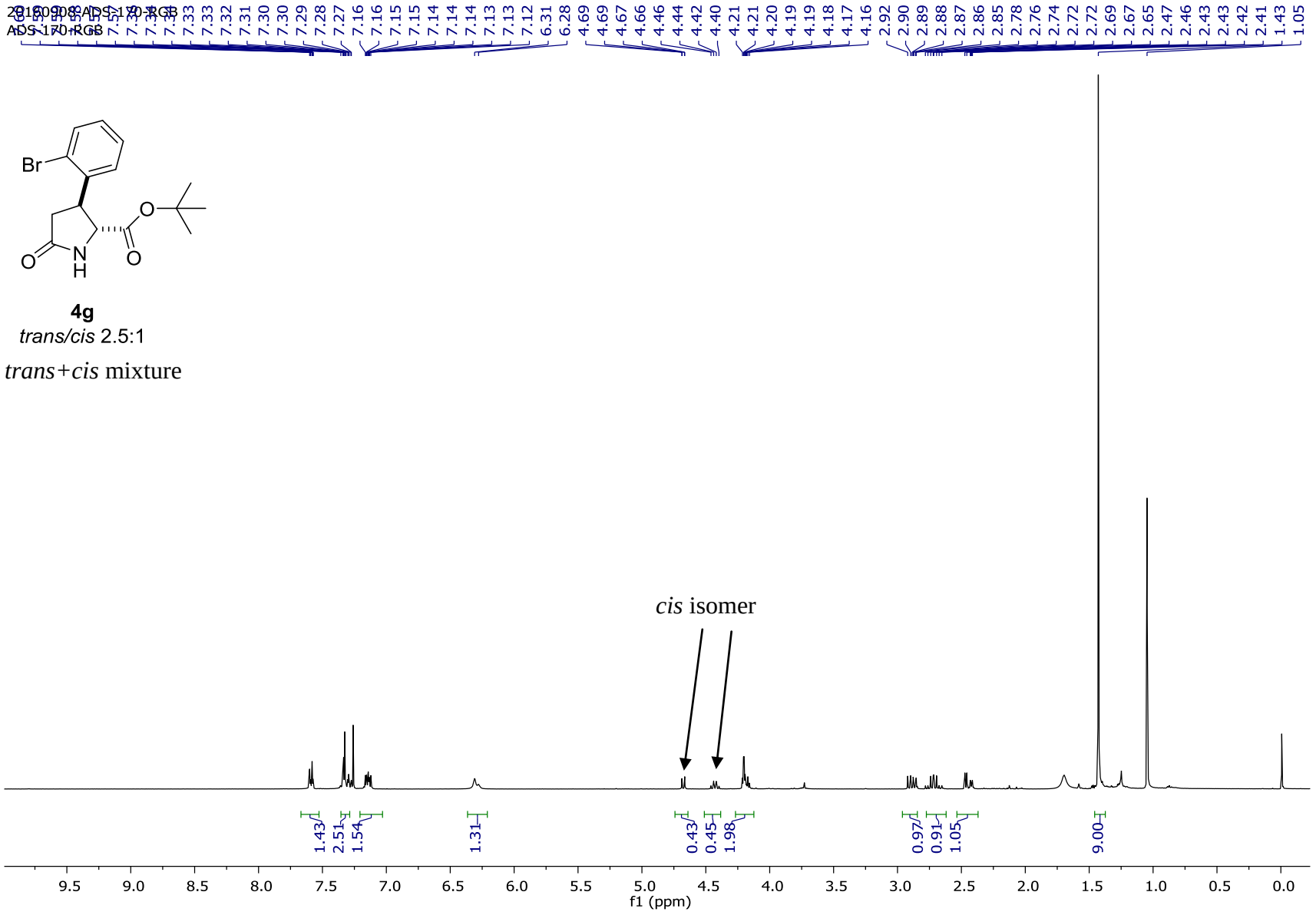

20160901-ADS-154-RGB
ADS-164-RGB
7.34 7.33 7.32 7.31 7.29 7.27 7.27 7.26 7.24 7.23 7.23 7.21 7.21 7.19 7.17 6.39
4.50 4.48 4.10 4.08 3.91 3.90 3.89 3.88 3.87 3.86 3.73 3.66 3.64 3.64 3.63 3.62 3.62 3.60 2.87 2.84 2.82 2.80 2.78 2.76 2.64 2.62 2.51 2.50 2.47 2.45 1.43 1.08
Cl
O
O
N
H
O
4f
trans/cis 4:1
trans+cis mixture
cis isomer
1.94
1.88
1.20
0.25
1.07
1.00
1.09
1.03
9.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

20160901-ADS-164-RGB
ADS-164-RGB

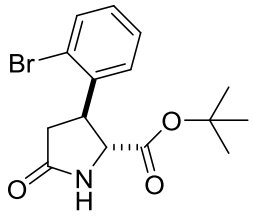


4f

trans+*cis* mixture


20180908ADS-170-RGB
ADS-170-RGB
Br
O
O
N
H
O
4g
trans/cis 2.5:1
trans+cis mixture
cis isomer
1.43
2.51
1.54
1.31
0.43
0.45
1.98
0.97
0.91
1.05
9.00
f1 (ppm)

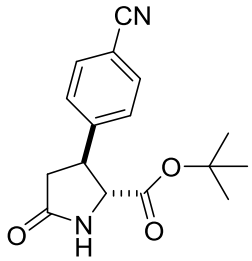
20160908-ADS-170-RGB
ADS-170-RGB



4g

trans+*cis* mixture

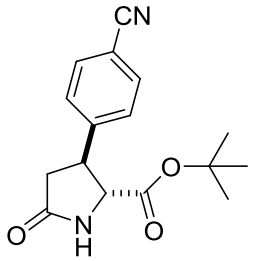
20180416-PKW-4-CYANO
PKW-4-CYANO



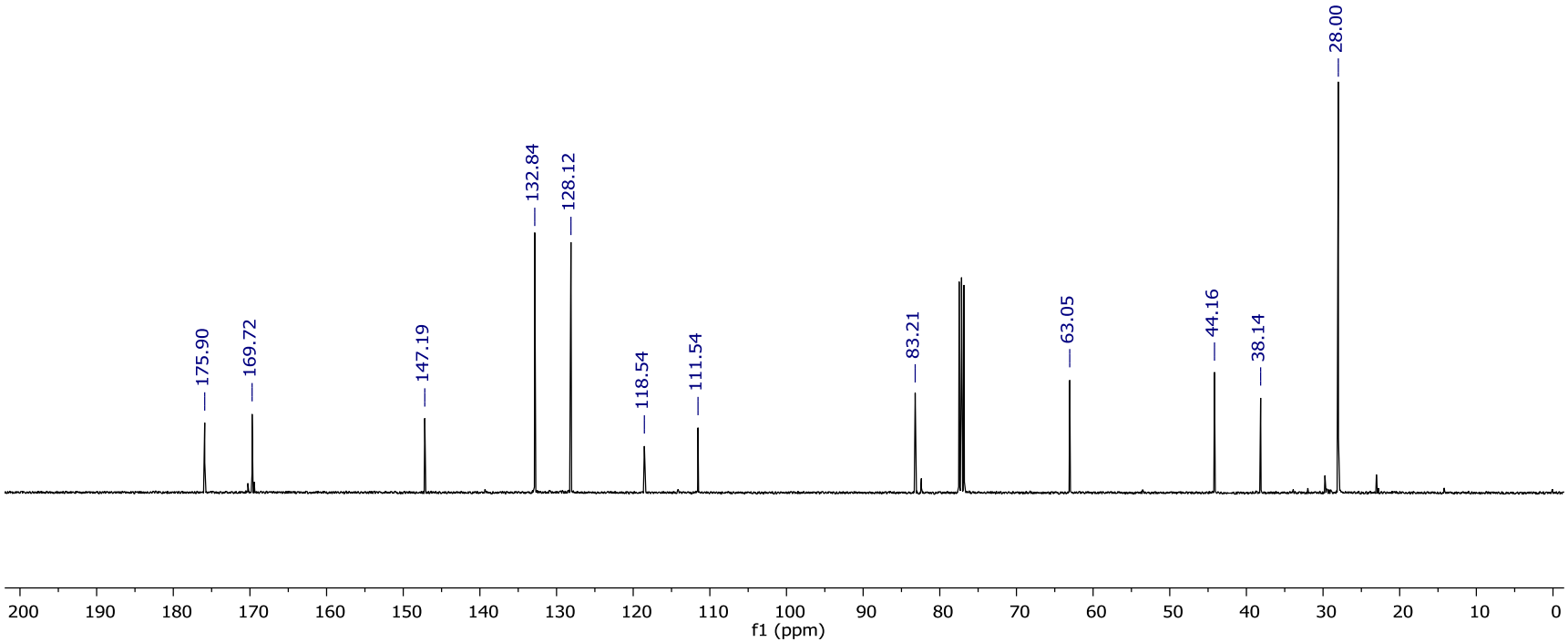
4h

trans/cis >20:1

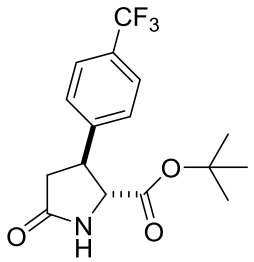
20180416-PKW-4-CYANO
PKW-4-CYANO



4h



20160906-ADS-166-RGB
ADS-166-RGB

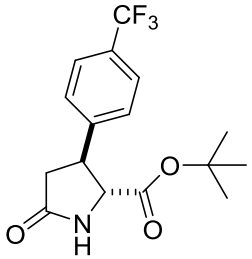


4i

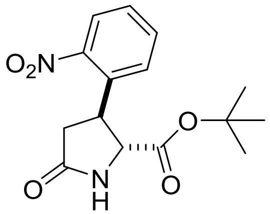
trans/cis >20:1

trans+*cis* mixture

20160907-ADS-166-RGB
ADS-166-RGB

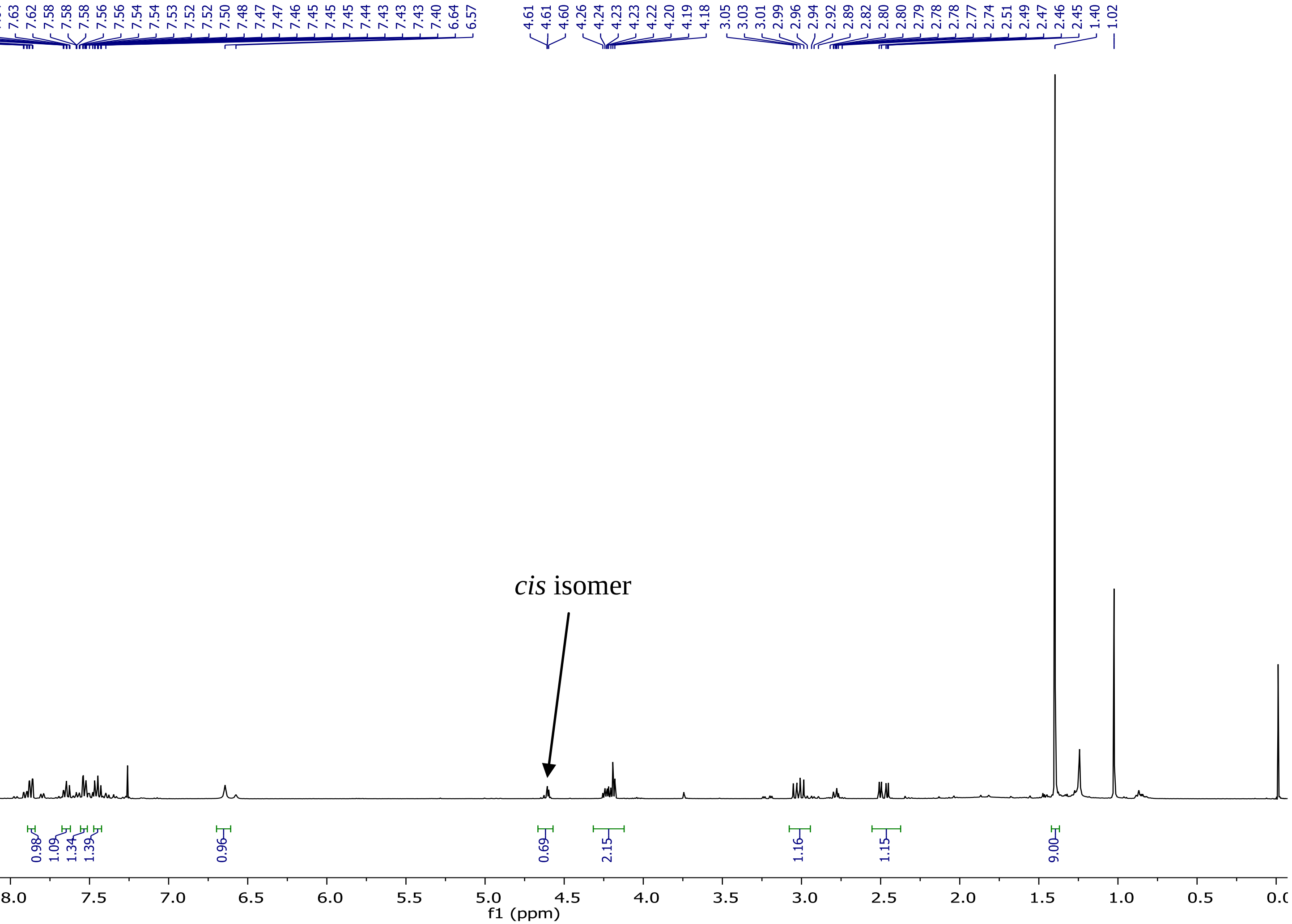


4i

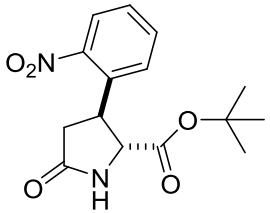


4j
trans/cis 3:1

trans+*cis* mixture

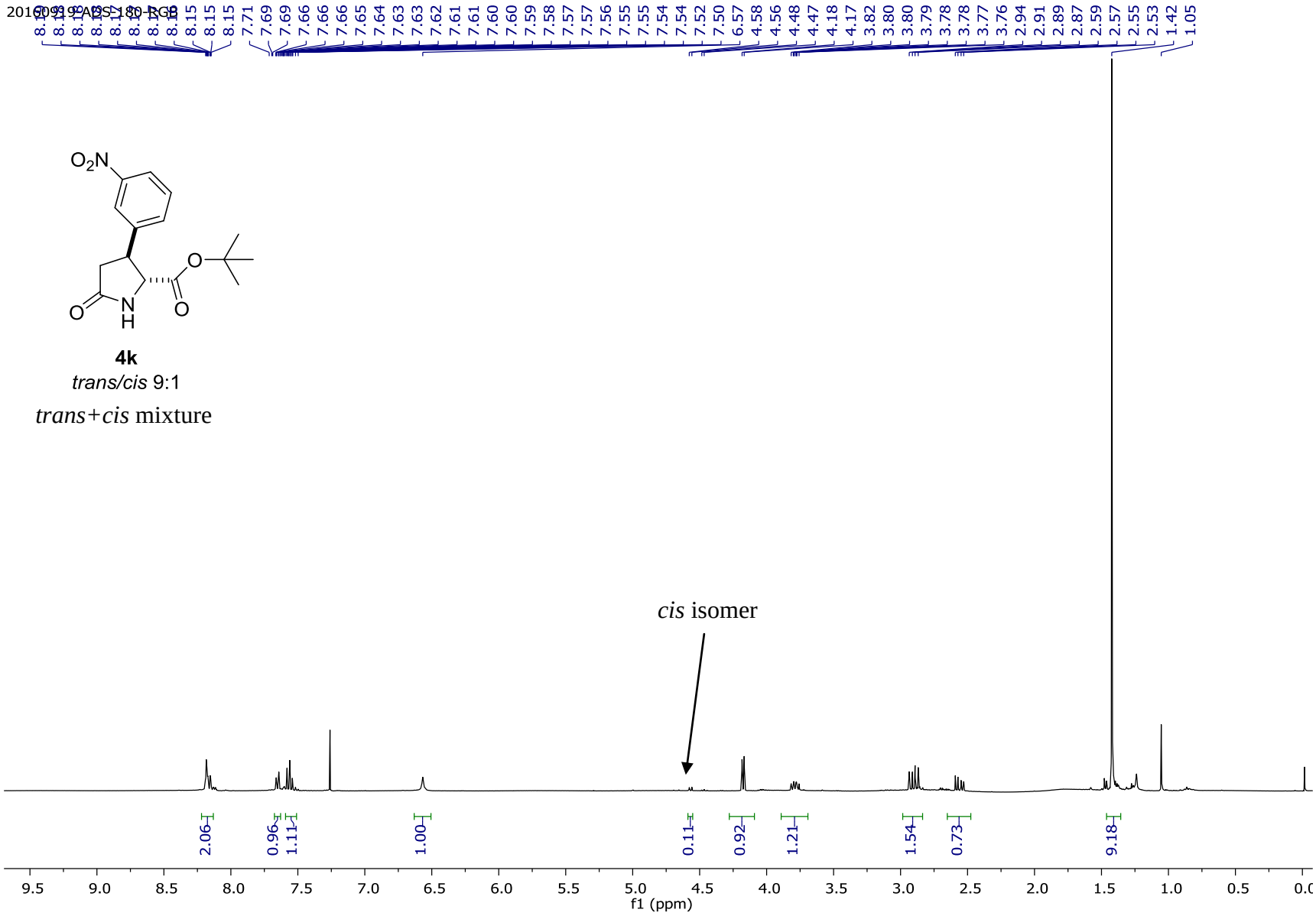


20160824-ADS-149-RGB

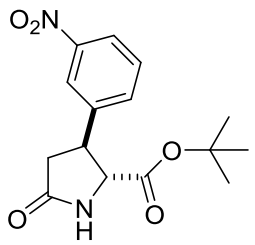


4j

trans+*cis* mixture

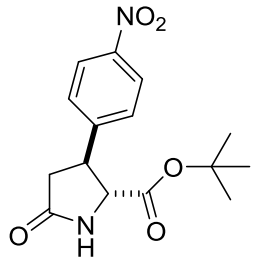

20160919-AJS-180-RGB
8.15 8.15 8.15 7.71 7.69 7.69 7.66 7.66 7.66 7.65 7.64 7.63 7.63 7.62 7.61 7.61 7.60 7.60 7.59 7.58 7.57 7.57 7.56 7.55 7.55 7.54 7.54 7.52 7.50 6.57 4.58 4.56 4.48 4.47 4.18 4.17 3.82 3.80 3.80 3.79 3.78 3.78 3.77 3.76 2.94 2.91 2.89 2.87 2.59 2.57 2.55 2.53 1.42 1.05
O2N
O
O
N
H
O
O
4k
trans/cis 9:1
trans+cis mixture
cis isomer
2.06
0.96
1.11
1.00
0.11
0.92
1.21
1.54
0.73
9.18
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

20160919-ADS-180-RGB



4k

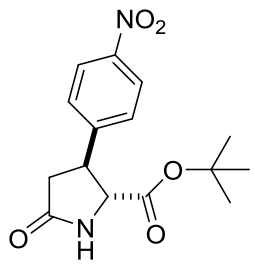
20160831-ADS-161-RGB
ADS-161-RGB



4l

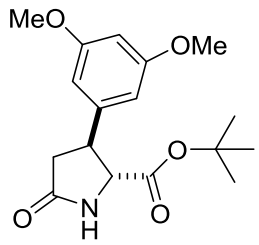
trans/cis >20:1

20160831-ADS-161-RGB
ADS-161-RGB



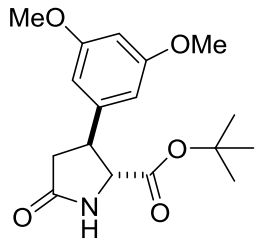
4l

20161024-ADS-1888-RGB
ADS-1888-RGB



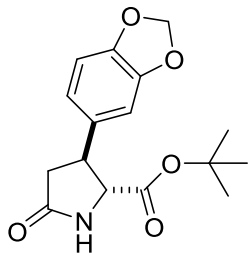
4m
trans/cis >20:1

20161024-ADS-1888-RGB
ADS-1888-RGB



4m

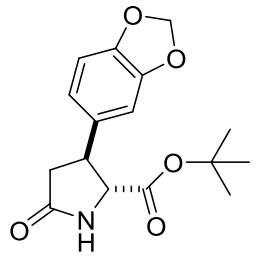
20160910-ADS-171-RGB



4n
trans/cis 5:1

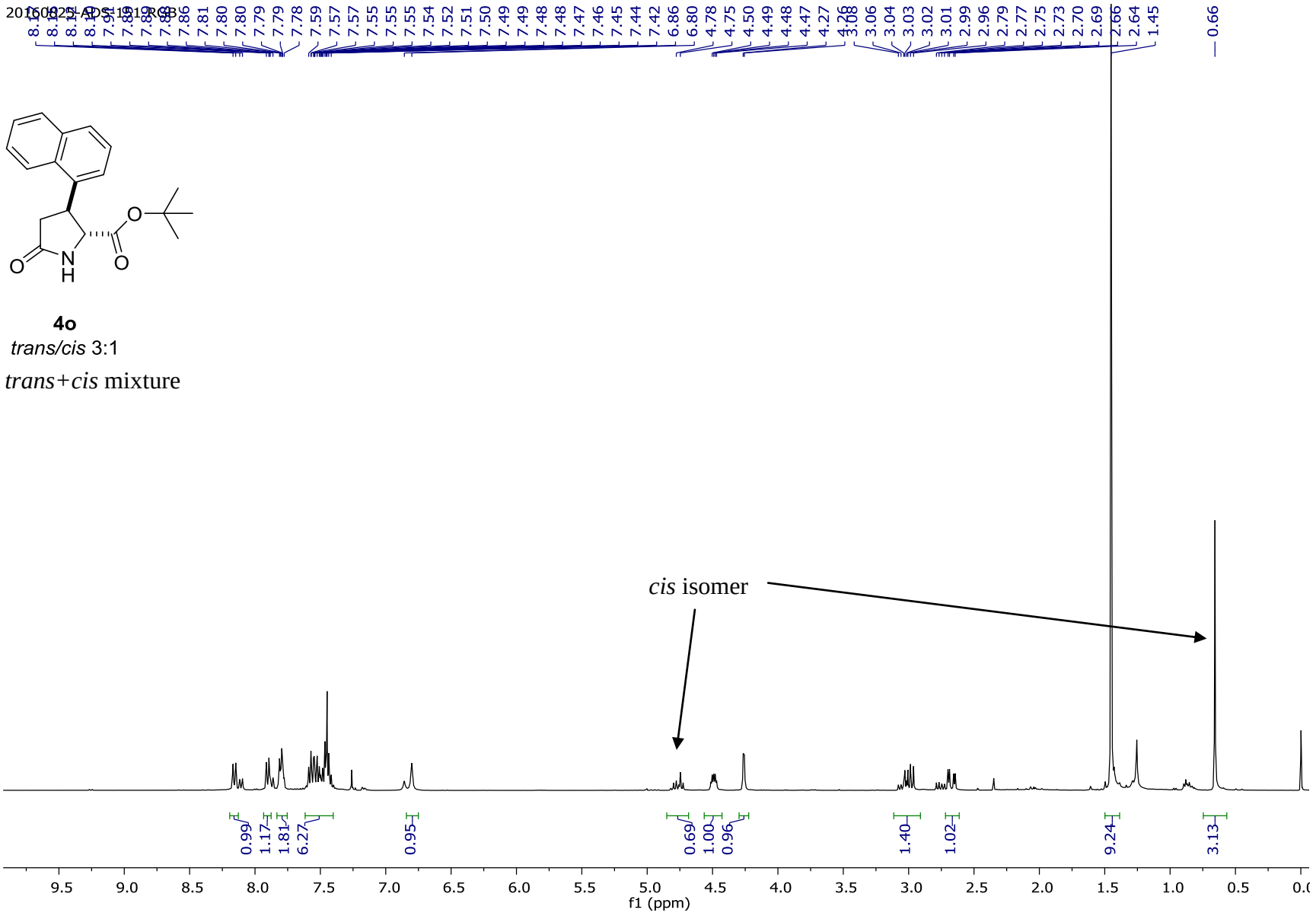
trans+*cis* mixture

20160910-ADS-171-RGB



4n

trans+*cis* mixture

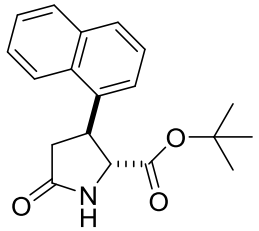


4o

trans/cis 3:1

trans+*cis* mixture

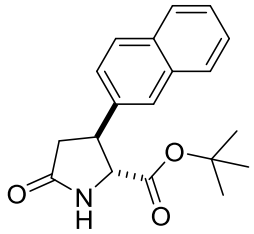
20160825-ADS-151-RGB



4o

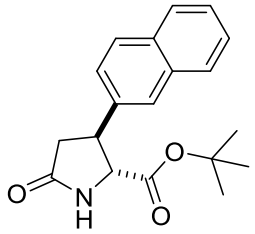
trans+*cis* mixture

20160830-ADS-162-RGB



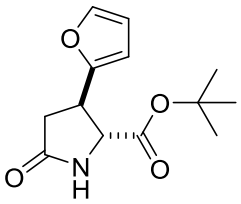
4p
trans/cis >20:1

20160830-ADS-162-RGB



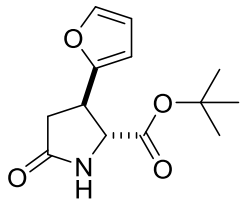
4p

20161228-ADS-FURFURAL-01



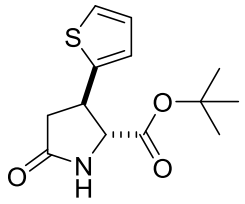
4q
trans/cis >20:1

20161228-ADS-FURFURAL-01



4q

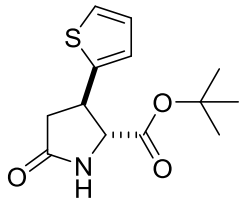
20161219-ADS-THIOPHENE
ADS-THIOPHENE



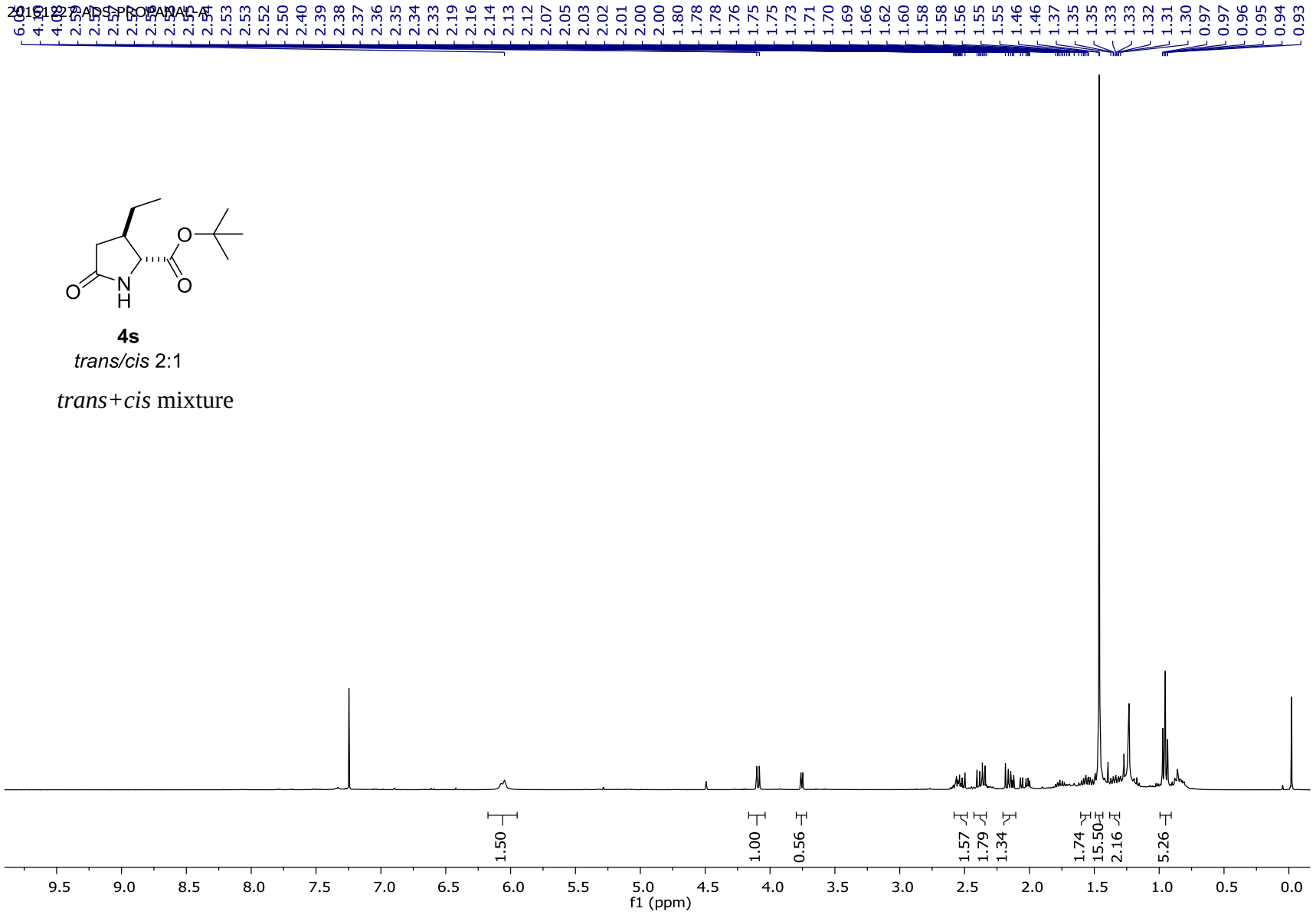
4r

trans/cis >20:1

20161220-ADS-THIOPHENE-01



4r

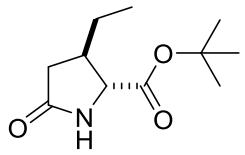


4s

trans/cis 2:1

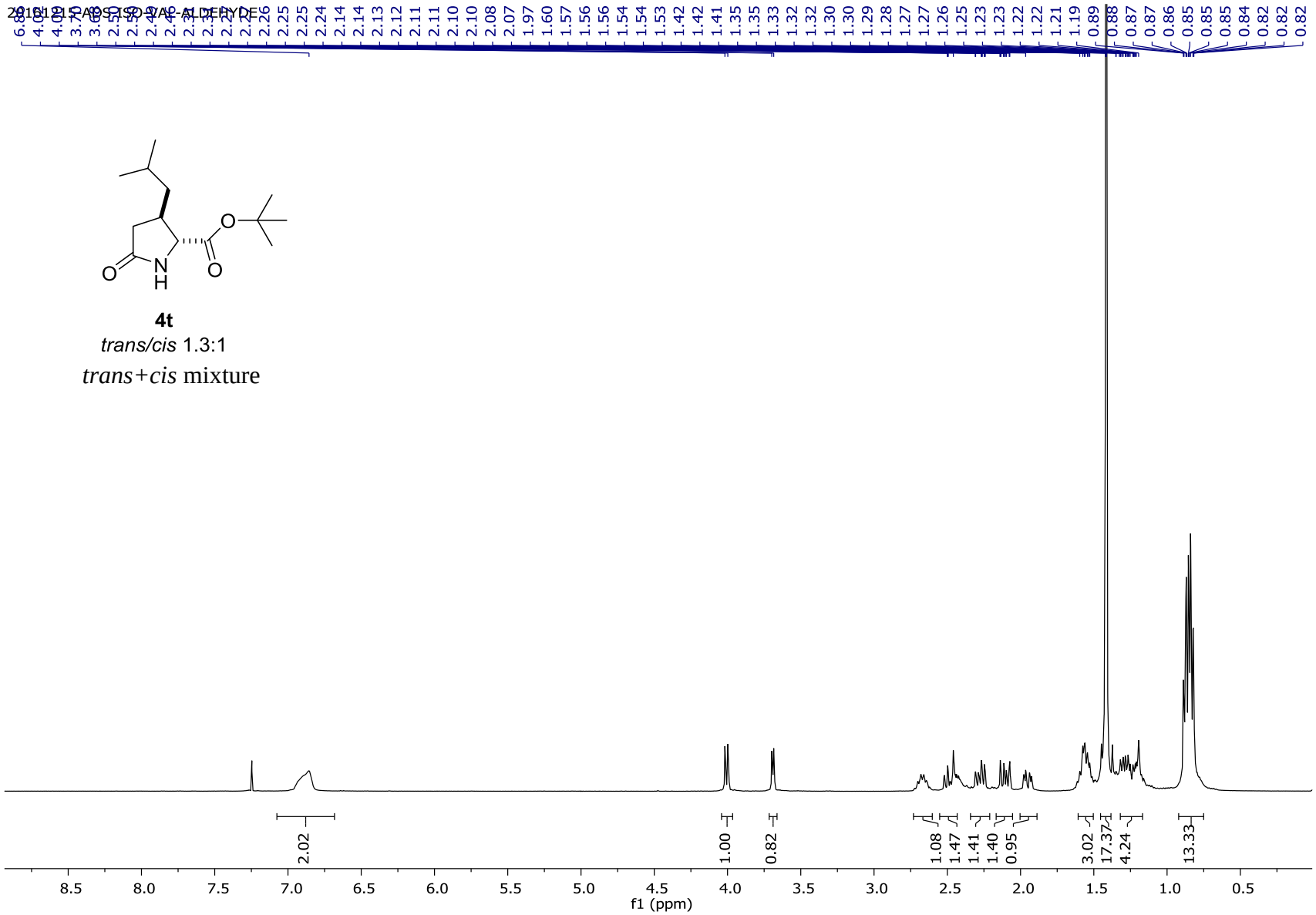
trans+*cis* mixture

20161227-ADS-PROPANAL-A

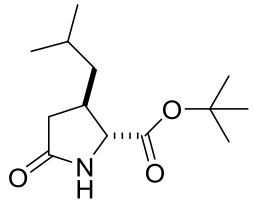


4s

trans+*cis* mixture

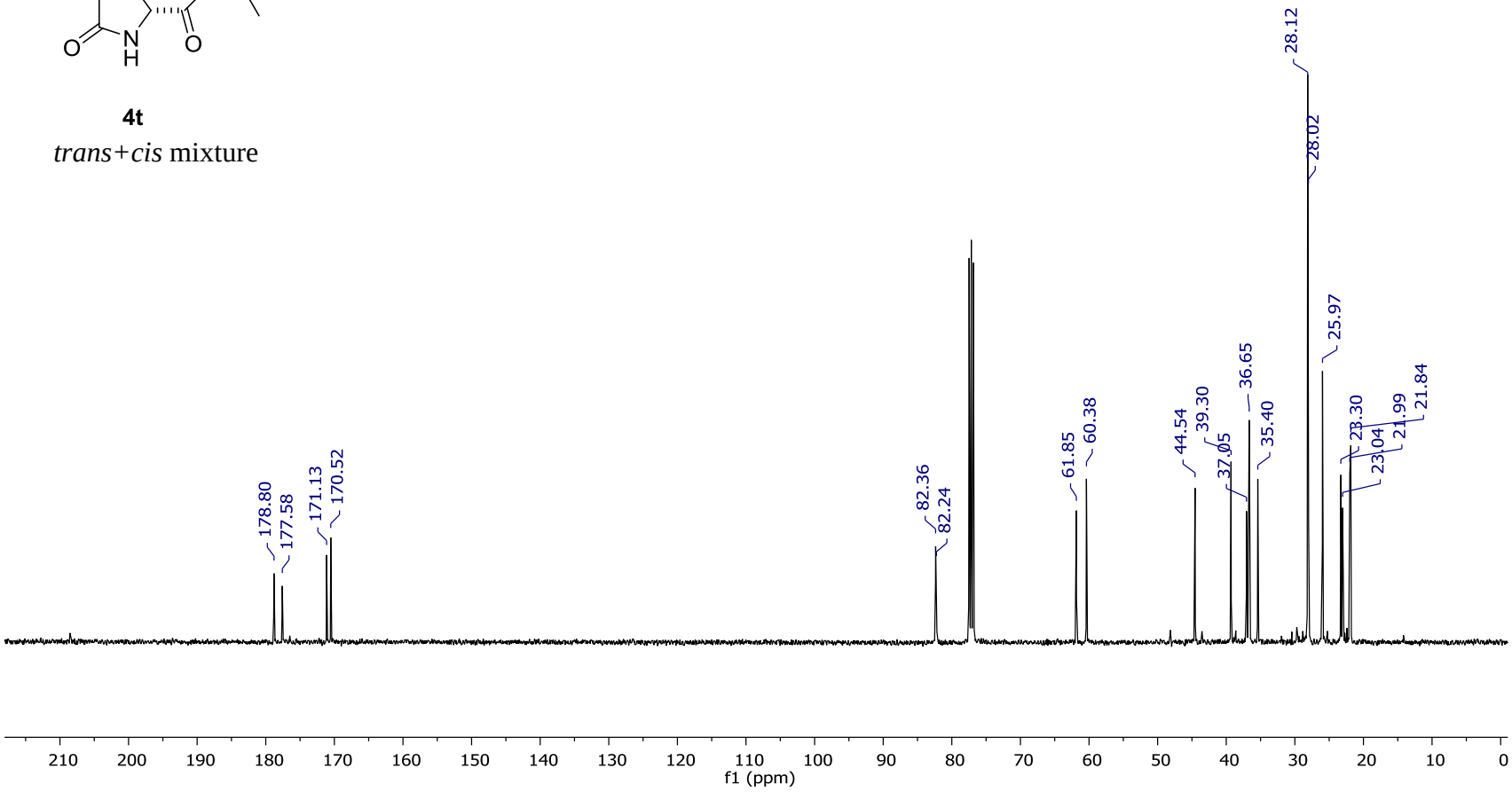

2016121S-AOS-ISO-DA2-ALDEHYDE
6.84 4.01 4.00 3.77 3.65 2.55 2.54 2.43 2.42 2.33 2.32 2.27 2.26 2.25 2.25 2.24 2.14 2.14 2.13 2.12 2.11 2.11 2.10 2.10 2.08 2.07 1.97 1.60 1.57 1.56 1.56 1.54 1.54 1.53 1.42 1.42 1.41 1.35 1.35 1.33 1.32 1.32 1.30 1.30 1.29 1.28 1.27 1.27 1.26 1.25 1.23 1.23 1.22 1.22 1.21 1.19 0.89 0.88 0.87 0.87 0.86 0.85 0.85 0.85 0.84 0.82 0.82 0.82
O
O
N
H
O
O
4t
trans/cis 1.3:1
trans+cis mixture
2.02
1.00
0.82
1.08
1.47
1.41
1.40
0.95
3.02
17.37
4.24
13.33
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

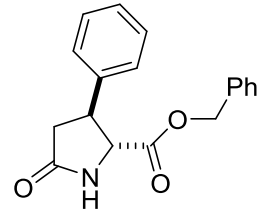
20161215-ADS-ISO-VAL-ALDEHYDE



4t

trans+*cis* mixture

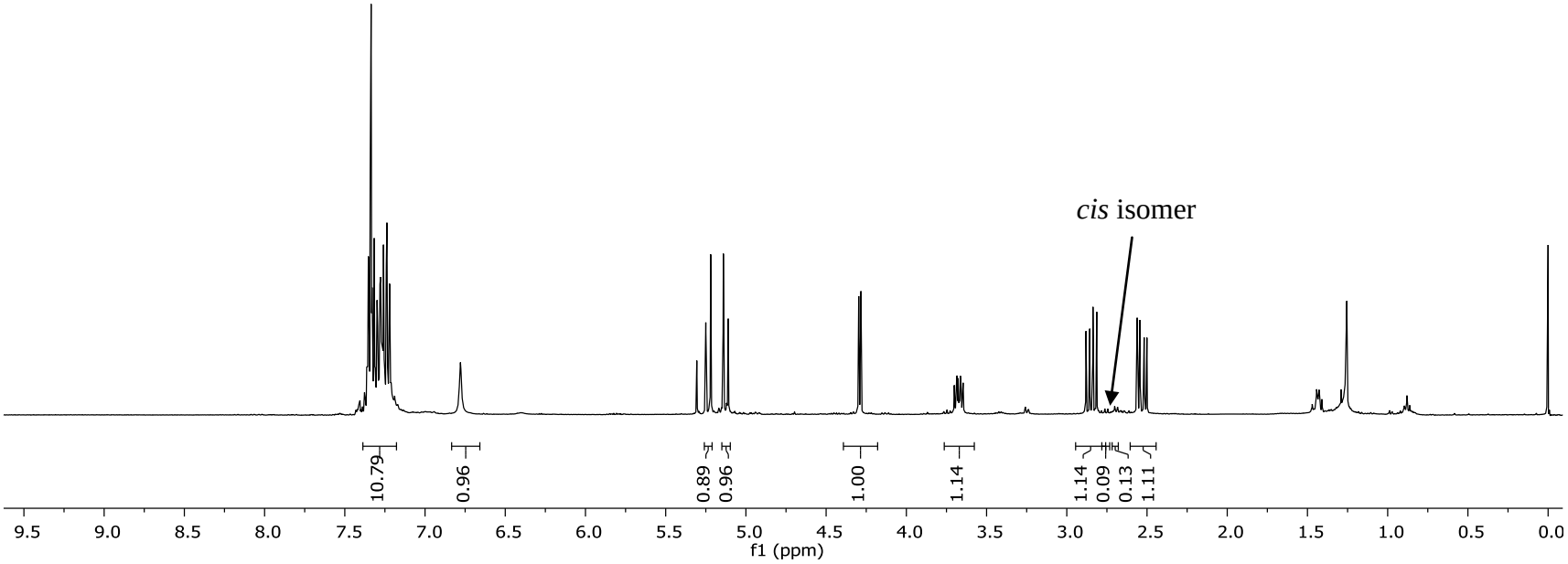




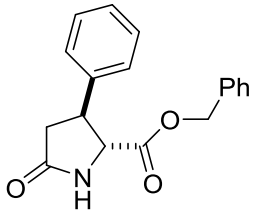
4u

trans/cis >10:1

trans+*cis* mixture



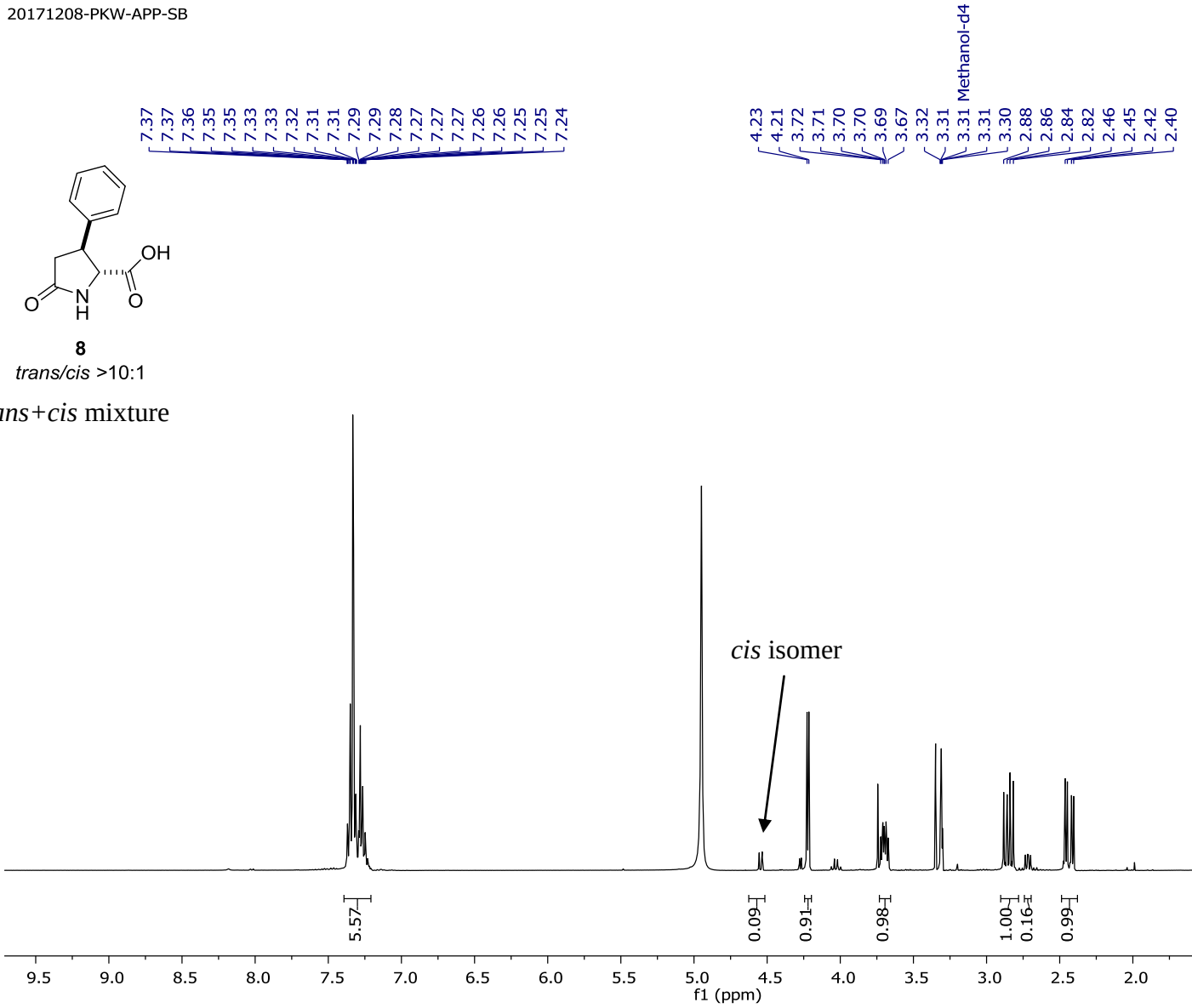
20170923-PKW-335-BSB



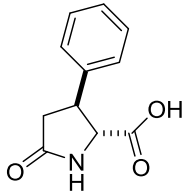
4u

trans+*cis* mixture

20171208-PKW-APP-SB



20171209-PKW-APP-SB



8

trans+*cis* mixture

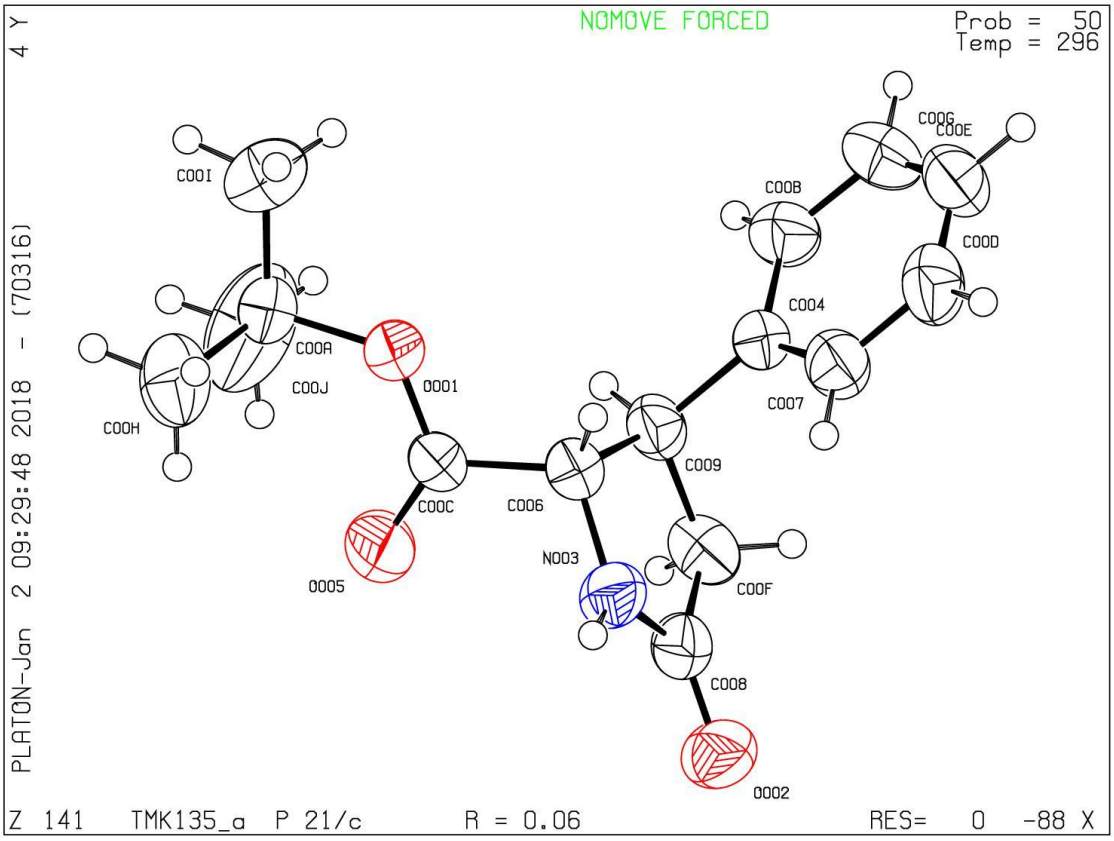
Crystal Structure data 4a-*trans*

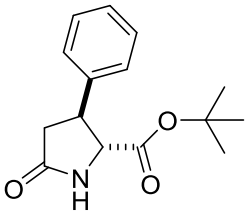
No syntax errors found. CIF dictionary Interpreting this report

Datablock: 4a-*trans*

```
Bond precision:  C-C = 0.0041 A          Wavelength=1.54178

Cell:            a=10.3681(6)    b=11.3036(6)        c=13.4537(8)
                 alpha=90        beta=111.487(4)     gamma=90
Temperature:     296 K

                 Calculated                Reported
Volume           1467.15(15)               1467.15(15)
Space group      P 21/c                    P 21/c
Hall group       -P 2ybc                   -P 2ybc
Moiety formula   C15 H19 N O3              C15 H19 N O3
Sum formula      C15 H19 N O3              C15 H19 N O3
Mr               261.31                    261.31
Dx,g cm-3        1.183                     1.183
Z                4                         4
Mu (mm-1)        0.667                     0.667
F000             560.0                     560.0
F000'            561.72
h,k,lmax         12,13,16                  12,13,16
Nref             2593                      2593
Tmin,Tmax        0.808,0.905               0.105,0.325
Tmin'            0.808

Correction method= # Reported T Limits: Tmin=0.105 Tmax=0.325
AbsCorr = MULTI-SCAN

Data completeness= 1.000          Theta(max)= 66.642

R(reflections)= 0.0622( 1866)     wR2(reflections)= 0.1845( 2573)

S = 1.045                 Npar= 175
```

Datablock 4a-*trans* - ellipsoid plot





4a-*trans*

References

1. C. Alvarez-Ibarra, A. G. Csakye, M. Maroto and M. L. Quiroga, *J. Org. Chem.*, 1995, **60**, 6700-6705.
2. V. A. Soloshonok, C. Cai, V. J. Hruby, L. V. Meervelt and T. Yamazaki, *J. Org. Chem.*, 2000, **65**, 6688-6696.