

## Contents

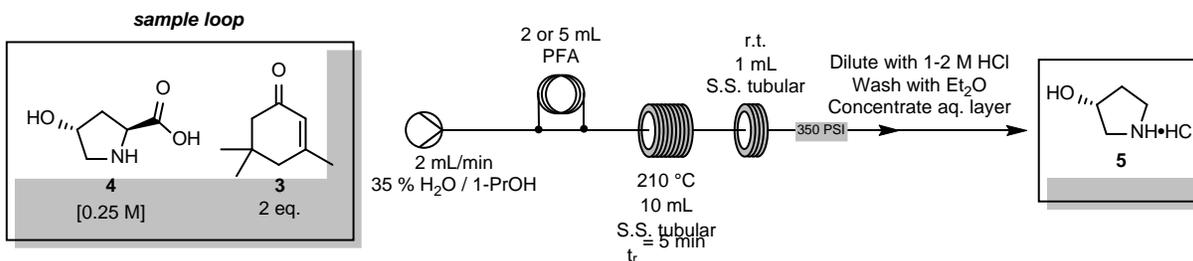
<b>General Experimental Details .....</b>	<b>2</b>
<b>Decarboxylation in flow reactor.....</b>	<b>3</b>
Procedure for Small Scale Preparation of <b>5</b> .....	3
Procedure for 70 g Scale Preparation of <b>5</b> .....	3
<b>Procedure for batch decarboxylation .....</b>	<b>6</b>
<b>Cbz protection procedure.....</b>	<b>7</b>
<b>NMR Spectra .....</b>	<b>8</b>

## GENERAL EXPERIMENTAL DETAILS

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Bruker AV 300 MHz or Bruker AS 500 MHz spectrometers under standard conditions and referenced with residual solvent peaks ( $\text{CDCl}_3$   $^1\text{H}$  = 7.26 ppm,  $^{13}\text{C}$  = 77.16 ppm;  $\text{D}_2\text{O}$   $^1\text{H}$  = 4.79 ppm;  $\text{MeOD}$   $^1\text{H}$  = 3.31 ppm). Dimethylsulfone was used as a  $^1\text{H}$  NMR internal standard during optimisation experiments. NMR data were processed using MestreNova version 14. Flash column chromatography was run using Merck silica gel 60 (230–400 mesh). Fractions were initially visualised using UV irradiation and subsequently by heating TLC plates exposed potassium permanganate stain. TLC was performed with Merck silica gel plates, precoated with silica gel 60 F254 (0.2 mm). Optical rotations were measured using a Jasco P-2000 Polarimeter. Batch decarboxylation reactions were performed in a Parr 4562 Mini Bench Top Reactor with mechanical overhead stirring, internal temperature probe, and attached Parr 4842 control unit. A Teflon™ liner was used inside the stainless steel reaction vessel. Before heating was commenced the reaction chamber was flushed twice with  $\text{N}_2$  to remove any oxygen. For the batch reactions, 1-propanol was distilled before use. 1-Propanol used in the flow reactions was commercial (RCI Labscan) and used without purification. Isophorone (TCI) and *trans*-4-hydroxy-L-proline (Cayman Chemical) were commercially sourced and used as received. Other commercially available chemicals were used without further purification unless specified otherwise. The flow apparatus consisted of a Vapourtec (Cambridge, UK) R2/R4 pumping module and reactor manifold. The reactor coil was a tubular stainless steel high temperature jacketed reactor manufactured by Vapourtec (part 50-1121) with an internal volume of 10 mL. Other tubing was 1/16 inch internal diameter PFA. Unions were PEEK or PFA construction. The thermal reactor was equipped with an in-line check-valve at its inlet. A stainless steel cooling loop with an internal volume of 1 mL at ambient temperature was situated immediately at the exit of the thermal reactor. Pressurisation was achieved using in-line back pressure regulator (BPR) cartridges (IDEX), comprising 250 + 100 PSI. The reaction mixture was introduced *via* a sample loop (2 or 5 mL, supplied by Vapourtec) and the rotary injection port of the R2 pumping module. Small scale flow reactions were collected for at least 1.5 residence times. No precautions were taken to exclude oxygen during solution preparation or from the solvent reservoirs. Infra-red monitoring of the flow reaction was achieved using a ReactIR® instrument (Mettler Toledo, Part 14000003). The instrument was placed in-line between two BPRs. Prior to the flow run, the instrument signal was calibrated against the pure solvent system. During the flow run, IR absorbance at multiple arbitrary wavelengths ( $1646\text{ cm}^{-1}$  and  $2342\text{ cm}^{-1}$ ) were recorded and the intensity changes used to identify the steady state. The changes in IR absorbance are due to slight differences in solvent composition of the ‘pure’ solvent reservoir and the reaction solution rather than the presence of new compounds.

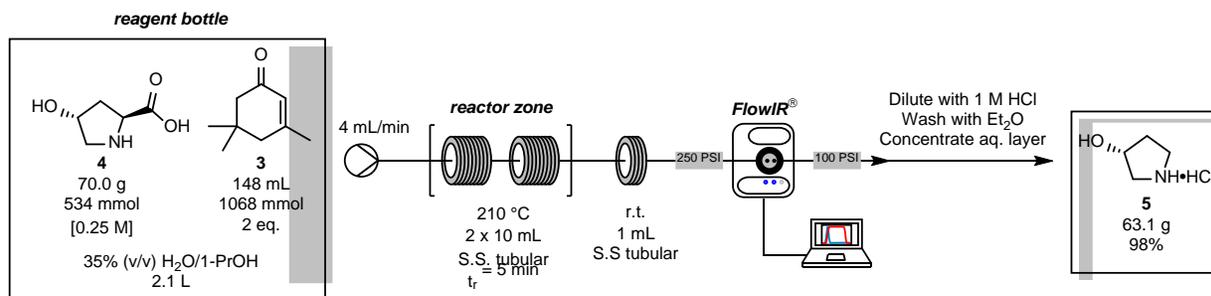
# DECARBOXYLATION IN FLOW REACTOR

## Procedure for Small Scale Preparation of **5**



A solution of *trans*-4-hydroxy-L-proline (**4**, 0.25 M) and isophorone (**3**, 2 eq.) in 35 % (v/v) 1-PrOH/H<sub>2</sub>O was prepared volumetrically with enough volume to completely fill the sample loop (2 or 5 mL). The mixture was sonicated briefly to aid dissolution of the material. At the same time, the Vapourtec R2/R4 flow reactor equipped with a stainless steel high temperature tubular reactor coil (10 mL) and heat exchanger (1 mL) was primed, pressurised (350 PSI) by pumping solvent (35 % (v/v) 1-PrOH/H<sub>2</sub>O: 2 mL/min for 5 minutes residence time), then the thermal reactor was set to 210 °C. The reactant mixture was injected into the sample loop situated between the pump and the reactor coil, then injected via the 6-way rotary stator. The eluent solution was collected for 1.5 residence times. The product mixture was diluted with 1-2 M HCl (aq.) and the aqueous phase washed with diethyl ether (3 × 10 mL). The obtained aqueous layer was concentrated under reduced pressure to provide (*R*)-3-hydroxypyrrolidine hydrochloride (**5**) as a hygroscopic brown solid (optimum yield: 85 %). Further purification of the solid was achieved by washing with acetone. Analytical data are in accordance with literature and identical to the large scale decarboxylation.<sup>1</sup>

## Procedure for 70 g Scale Preparation of **5**



A 2 L Schott bottle equipped with a magnetic stirrer was charged with *trans*-4-hydroxy-L-proline (**4**, 70.0 g, 533.8 mmol), followed by water (747 mL), 1-PrOH (1241 mL) and isophorone (**3**, 148 mL, 1067.6 mmol, 2 eq.) with stirring until a homogenous solution was obtained. The Vapourtec R2/R4 flow reactor system was equipped with two stainless steel high temperature tubular reactor coils (total volume 20 mL), connected in series by a short stainless steel connector tube. The stainless steel heat exchanger (1 mL) situated after the thermal reactor was

submerged in water to accommodate efficient cooling at the higher flow rate. A FlowIR® unit (Mettler Toledo®) was situated in-line after the cooling loop. The flow rate was set (4 mL/min for 5 minute residence time) pumping a stock H<sub>2</sub>O/1-PrOH (35 % v/v) solvent and the system pressurised (350 PSI) prior to heating the thermal reactor coils to 210 °C. The solvent source was switched to the reaction mixture *via* the Vapourtec R2 manifold. The reaction front was collected and its volume recorded until the system had reached steady state as judged by IR band intensity. Then the major fraction was collected and its volume recorded. Once the reactant mixture was almost consumed, additional solvent was added (3 x 20 mL volumes) and the tail volume was separately collected once steady state was lost as judged by IR monitoring. In portions (~500 mL), the obtained steady state crude reaction mixture (2066 mL) was diluted with 1 M HCl and washed with diethyl ether (3 x 100 mL). The aqueous phase was concentrated under reduced pressure to provide the crude amine hydrochloride as a brown solid. The solid was washed with acetone and diethyl ether, then dried in a vacuum oven (60 °C, 0.1 mPa, 5 h) to provide (*R*)-3-hydroxypyrrolidine hydrochloride (**5**) as a hygroscopic brown solid (63.1 g, 511 mmol, 98 % yield from the steady state). The reaction front and tail were subjected to the same workup procedure, and samples were obtained of the crude material for <sup>1</sup>H NMR analysis of conversion. The retained ether phases were concentrated and the residue filtered through a plug of silica gel. The obtained residue was evaporated under reduced pressure to yield isophorone (85.0 g, 60 % recovery from the steady state) in exceptional purity as judged by <sup>1</sup>H NMR. Data are in accordance with literature.<sup>1</sup>

$[\alpha]_D^{24}$  -8.6 (c 1.5, MeOH) (lit.<sup>2</sup>  $[\alpha]_D^{26}$  -8.5 (c 1.5, MeOH); lit<sup>1</sup>  $[\alpha]_D^{26}$  -9.2 (c 1.74, MeOH))

<sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O)  $\delta$  4.69-4.65 (m, 1H), 3.50-3.45 (m, 2H), 3.40-3.30 (m, 2H), 2.24-2.06 (m, 2H).  
 (500 MHz, MeOD)  $\delta$  4.57 (s, 1H), 3.44-3.40 (m, 2H), 3.25 (m, 2H), 2.08-2.07 (m, 2H).

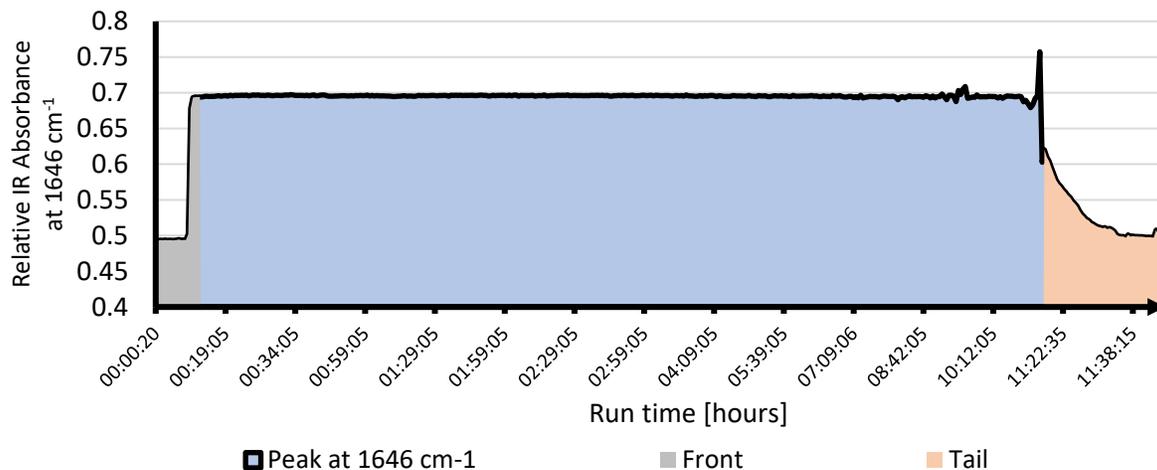


Figure S1: IR absorbance trace showing front, steady-state, and tail portions of 70 g scale flow reaction.

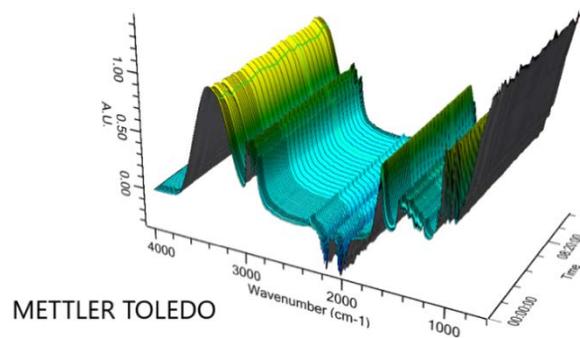


Figure S2: IR spectrum of the continuous flow reaction recorded over the entire run-time.

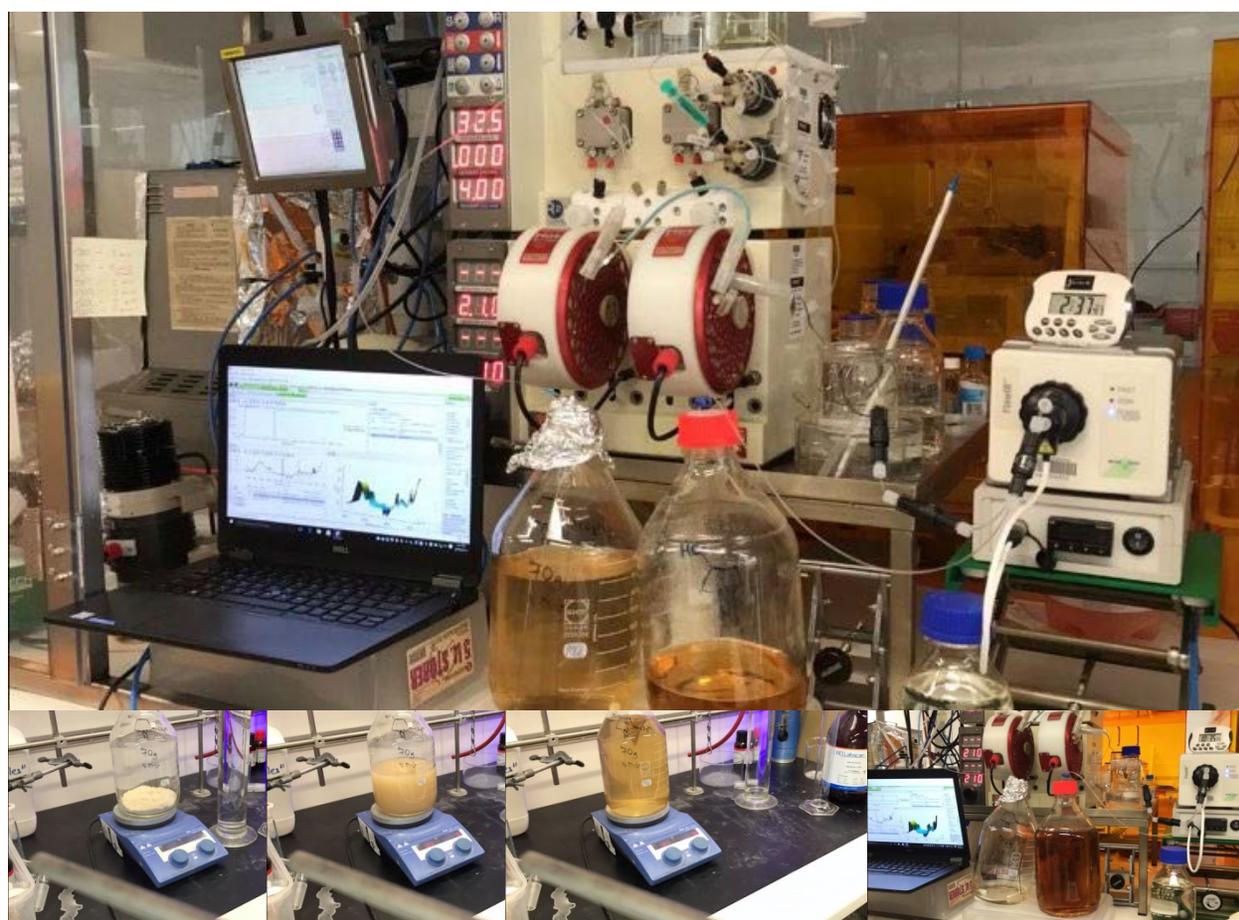
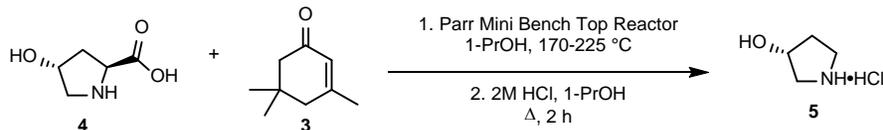


Figure S3 Images of the Continuous Experiment

A timelapse of the continuous flow experiment can be viewed at this link:

<https://www.dropbox.com/s/jcxj50dwvd2ubdc/video-1571094595%20low%20q%20.mp4?dl=0>

## PROCEDURE FOR BATCH DECARBOXYLATION



A Teflon™ liner for a 450 mL 4562 Parr Mini Bench Top Reactor was charged with *trans*-4-hydroxy-L-proline (**4**, 5.0 g, 38.1 mmol), isophorone (**3**, 11.5 mL, 76.2 mmol, 2 eq.) and 1-propanol (38 mL). The reactor was assembled as per the manufacturer instructions and two N<sub>2</sub> flushes of the reaction chamber were performed. The reaction was stirred while the temperature was raised to a target of 170 °C (see below), in all runs the high temperature limit switch was triggered at 190 °C and the reactor was allowed to cool to approximately 50 °C before being opened and the reaction mixture transferred to a 500 mL round bottom flask. If any starting material (solid) was visible it was collected by filtration. 2M HCl (114 mL, 228 mmol, 6 eq) was slowly added and the mixture was refluxed for 2 hours. After cooling, the acidic solution was split into two equal volumes and each was washed with Et<sub>2</sub>O (1x100 mL, 3 x 50 mL). The aqueous phases were then combined and washed a final time with Et<sub>2</sub>O (50 mL). The water was distilled from the salt product, first at atmospheric pressure then under gentle vacuum, until a thick oil remained. The oil was dried under high vacuum (0 °C → 60 °C) to provide a hygroscopic brown solid or thick oil. <sup>1</sup>H NMR indicated the presence of **5**, data identical to the large scale flow decarboxylation product, as well as decomposition products.

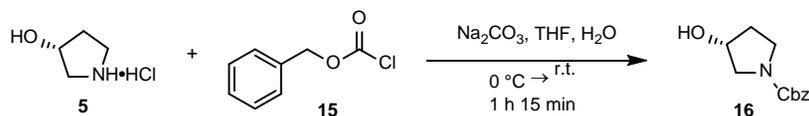
### Reaction details:

**Batch 1:** With the heating set to 170 °C, heating rate II was used to reach 160 °C after which the rate was slowed to setting I until 170 °C when the heating was turned off. The internal temperature continued to rise to 225 °C, and the internal pressure reached approximately 300 psi. The reactor was allowed to cool to 50 °C before venting and disassembling. The dark red reaction mixture was taken through to the acidic reflux step. After work up and drying under reduced vacuum a viscous brown oil remained.

**Batch 2:** Using heating rate II, the temperature was raised to 75 °C and then heating was ceased. Pleasingly the temperature rose and stabilised at 170 °C before starting to fall. After the temperature fell to 160 °C the heater was turned back on to heating rate I and set to 170 °C in order to maintain the reaction temperature for 1 h. The high-temperature shut off switch activated at 190 °C and the temperature rose to over 200 °C. The reactor was allowed to cool to 50 °C before venting and disassembly. The dark red reaction mixture was taken through to the acidic reflux step. Work up and drying under reduced vacuum provided a dark brown, extremely hygroscopic solid.

**Batch 3:** Heating rate II was used to reach 100 °C after which the heater was turned off. The internal reaction temperature continued to rise to a maximum of 184 °C and an internal pressure of approximately 200 psi. The reaction was allowed to slowly cool to 50 °C and upon opening a small amount (276 mg) of the insoluble starting material (**4**) was still visible, which was collected by filtration before the reaction mixture was taken through to the acidic reflux step. Work up and drying under reduced vacuum provided a dark brown, hygroscopic solid.

## CBZ PROTECTION PROCEDURE



A 100 mL rbf was charged with (*R*)-pyrrolidin-3-ol hydrochloride salt from the previous step (**5**, 1.0 g, 8.1 mmol) and a 1:1 mixture of water and THF (20 mL). To this was slowly added Na<sub>2</sub>CO<sub>3</sub> (2.5 g, 23.3 mmol, 2.9 eq.), and the mixture was cooled in an ice bath. Benzyl chloroformate (**15**, 2 mL, 13.8 mmol, 1.7 eq.) was added dropwise to the cooled solution and stirred at 0 °C for 15 minutes. The reaction was removed from the ice bath and stirred for a further 1 h, after which it was quenched with 2M HCl (13 mL). The biphasic reaction mixture was separated, and the aqueous layer extracted with DCM (2 x 20 mL). The combined organic phases were washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give a crude brown oil. Purification by column chromatography (1:1 Hex/EtOAc → 1:2 Hex/EtOAc → EtOAc) provided benzyl (*R*)-3-hydroxypyrrolidine-1-carboxylate (**16**) as an orange oil in the yields listed below in Table S1. Spectroscopic data were in accordance with literature.

<sup>1</sup>H NMR (lit.<sup>3,4</sup>) (500 MHz, CDCl<sub>3</sub>) δ 7.38–7.29 (5H, m), 5.13 (2H, app s), 4.47 (1H, brs), 3.59–3.51 (3H, m), 3.48–3.41 (1H, m), 2.03–1.90 (3H, m).

<sup>13</sup>C NMR (lit.<sup>4</sup>) (125 MHz, CDCl<sub>3</sub>) δ 155.2, 137.0, 128.6, 128.1, 128.0, 71.3 and 70.4, 66.9, 54.9 and 54.3, 44.2 and 43.9, 34.3 and 33.7.

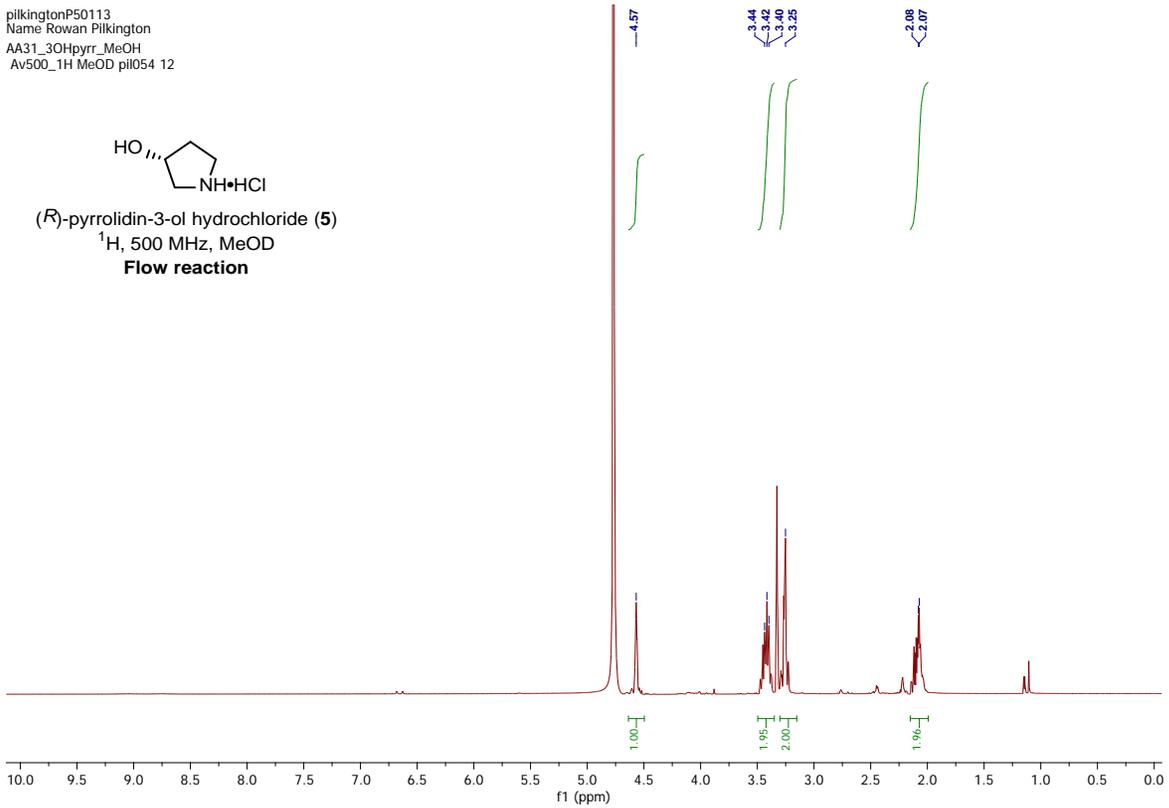
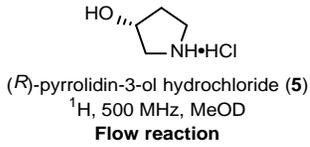
Table S1: Summary of flow, batch decarboxylation reaction temperatures and Cbz protection yields.

Run	Target temperature	Maximum temperature	Recovered SM ( <b>4</b> )	Mass yield	Yield of <b>16</b>
Flow	210	210	none	98 % <sup>a</sup>	76%
<b>1</b>	170 °C	225 °C	none	98%	9%
<b>2</b>	170 °C	200 °C	none	98%	30%
<b>3</b>	170 °C	184 °C	276 mg	95 % (98% <sup>b</sup> )	53%

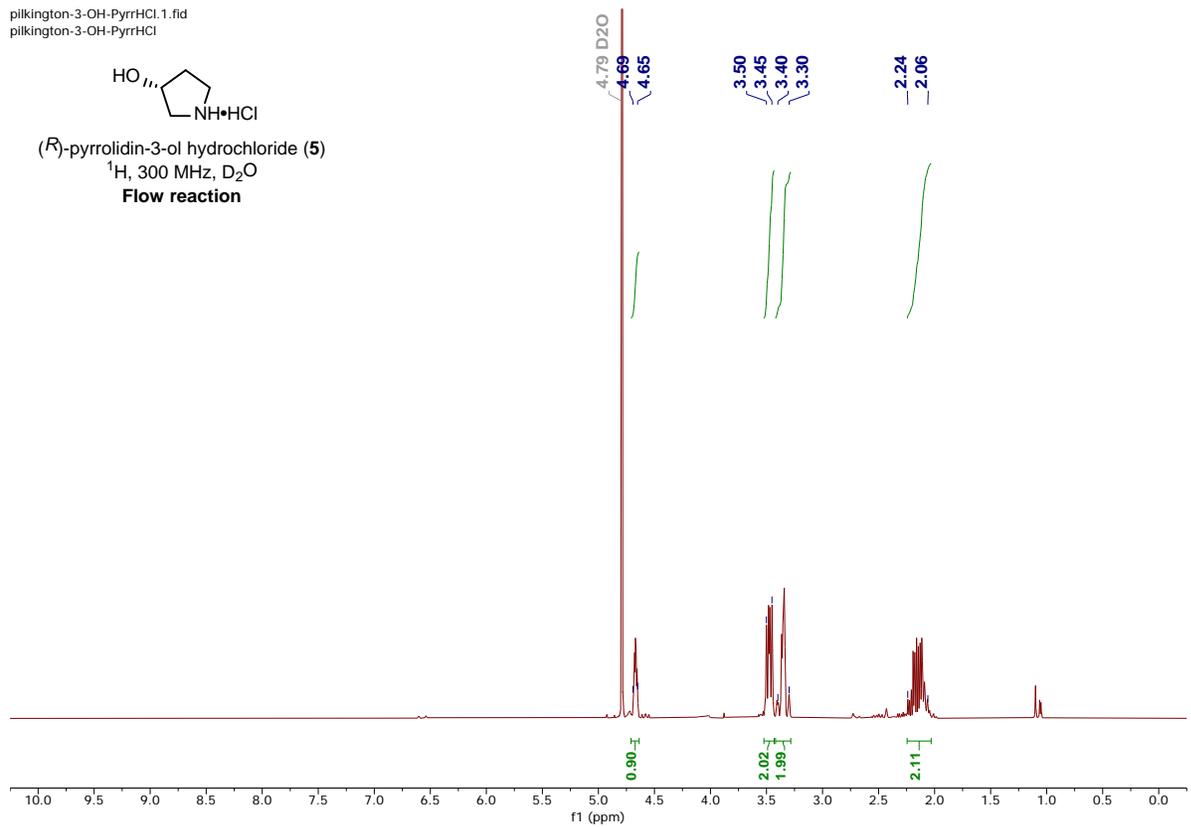
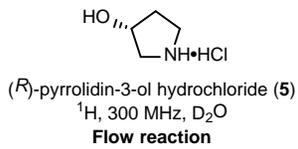
[a]Steady-state yield; [b] based on recovered starting material

# NMR SPECTRA

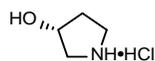
pilkingtonP50113  
Name Rowan Pilkington  
AA31\_3OHpyrr\_MeOH  
Av500\_1H MeOD pil054 12



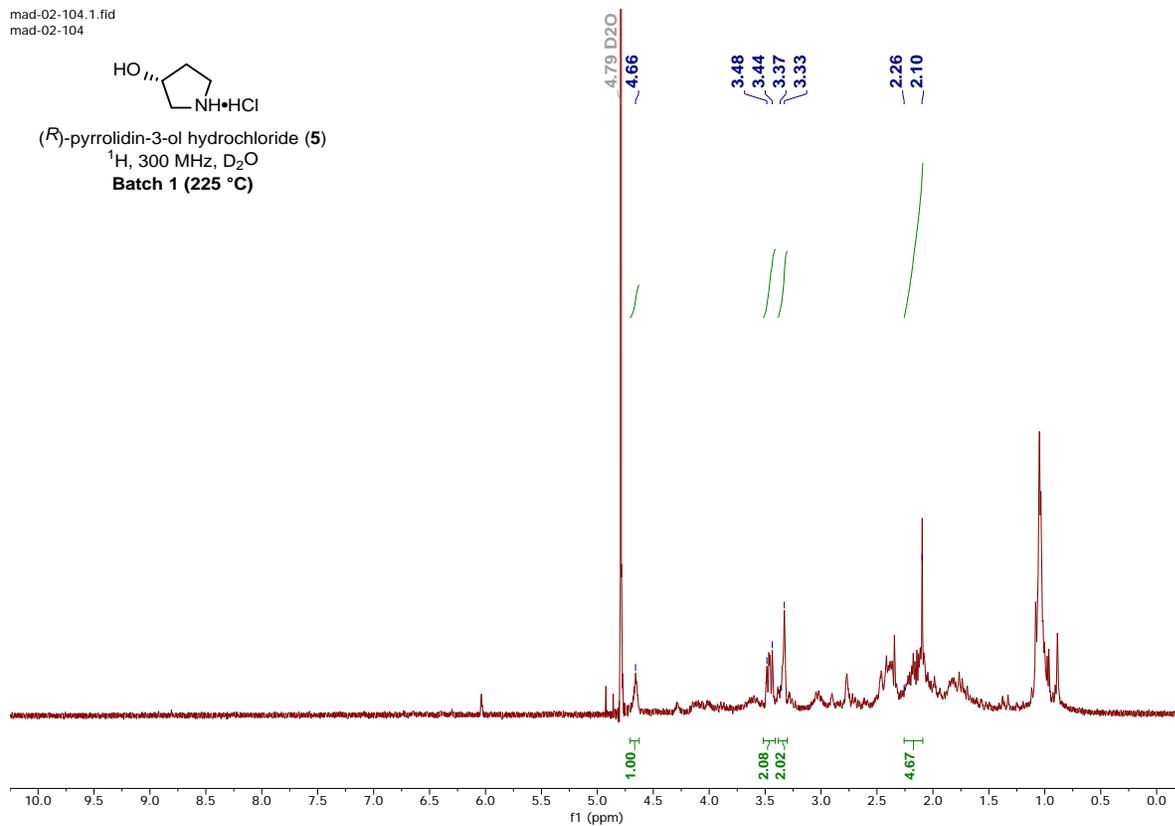
pilkington-3-OH-PyrrHCl.1.fid  
pilkington-3-OH-PyrrHCl



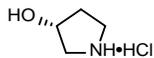
mad-02-104.1.fid  
mad-02-104



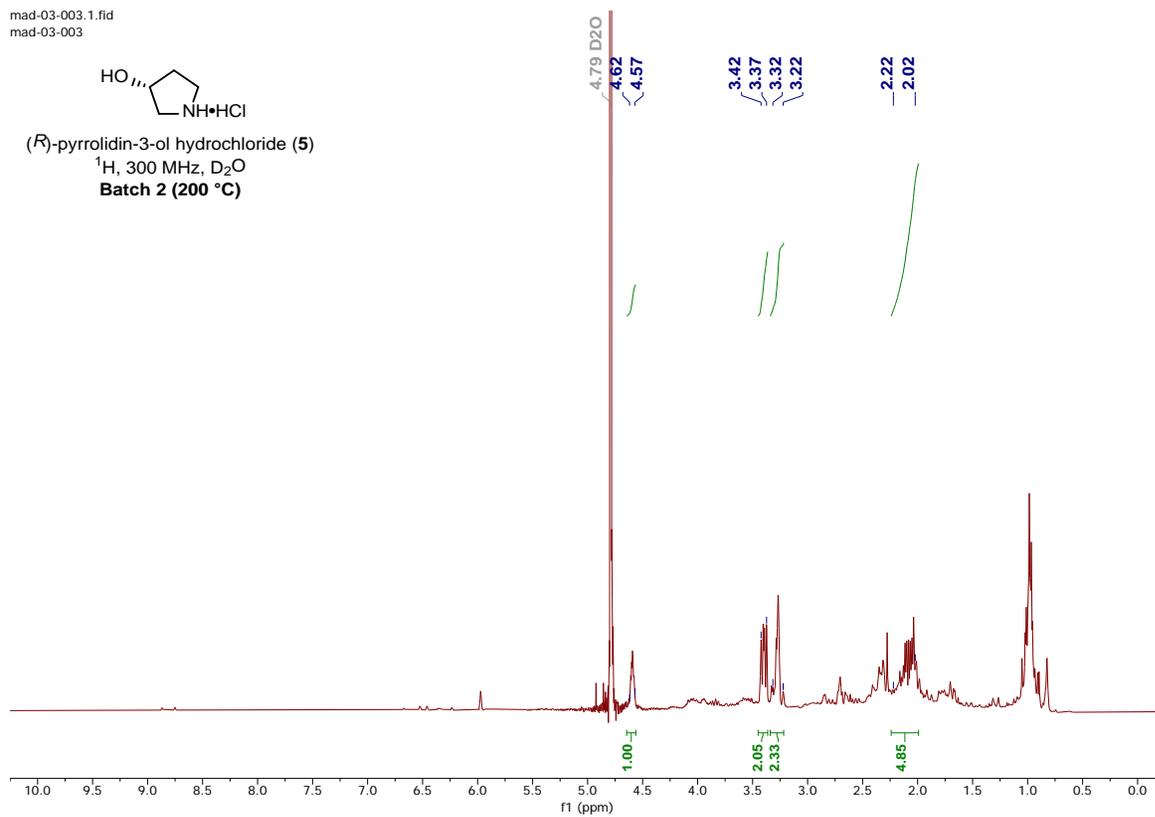
(*R*)-pyrrolidin-3-ol hydrochloride (**5**)  
<sup>1</sup>H, 300 MHz, D<sub>2</sub>O  
Batch 1 (225 °C)



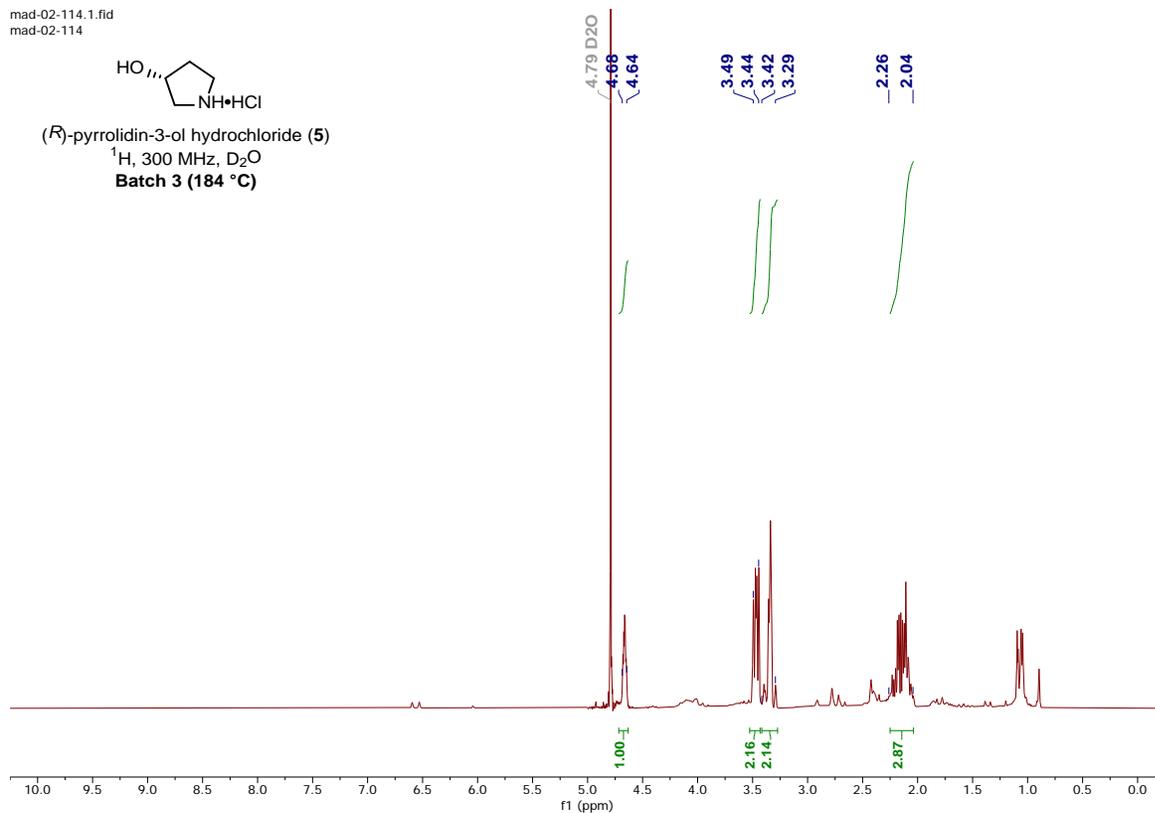
mad-03-003.1.fid  
mad-03-003



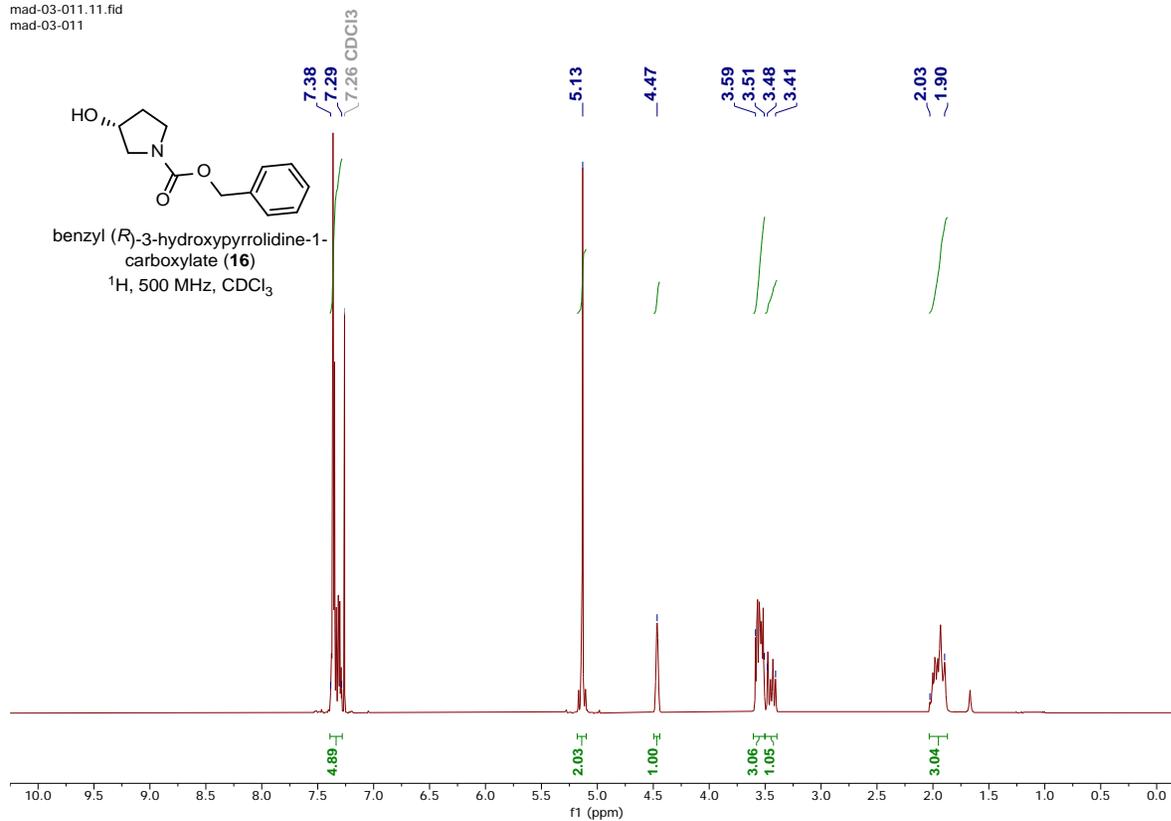
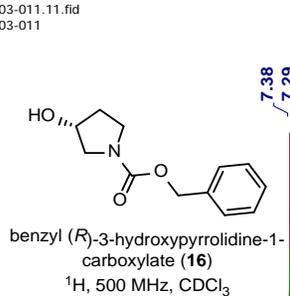
(*R*)-pyrrolidin-3-ol hydrochloride (**5**)  
<sup>1</sup>H, 300 MHz, D<sub>2</sub>O  
Batch 2 (200 °C)



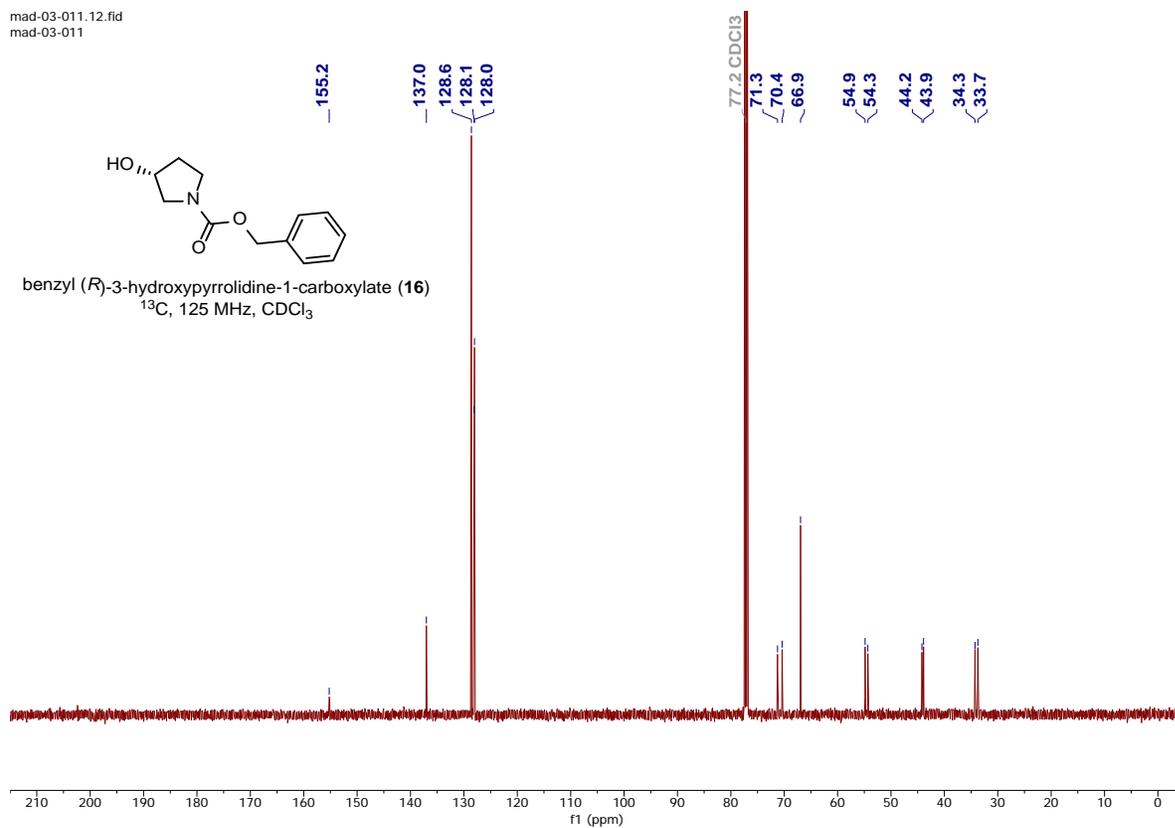
mad-02-114.1.fid  
mad-02-114



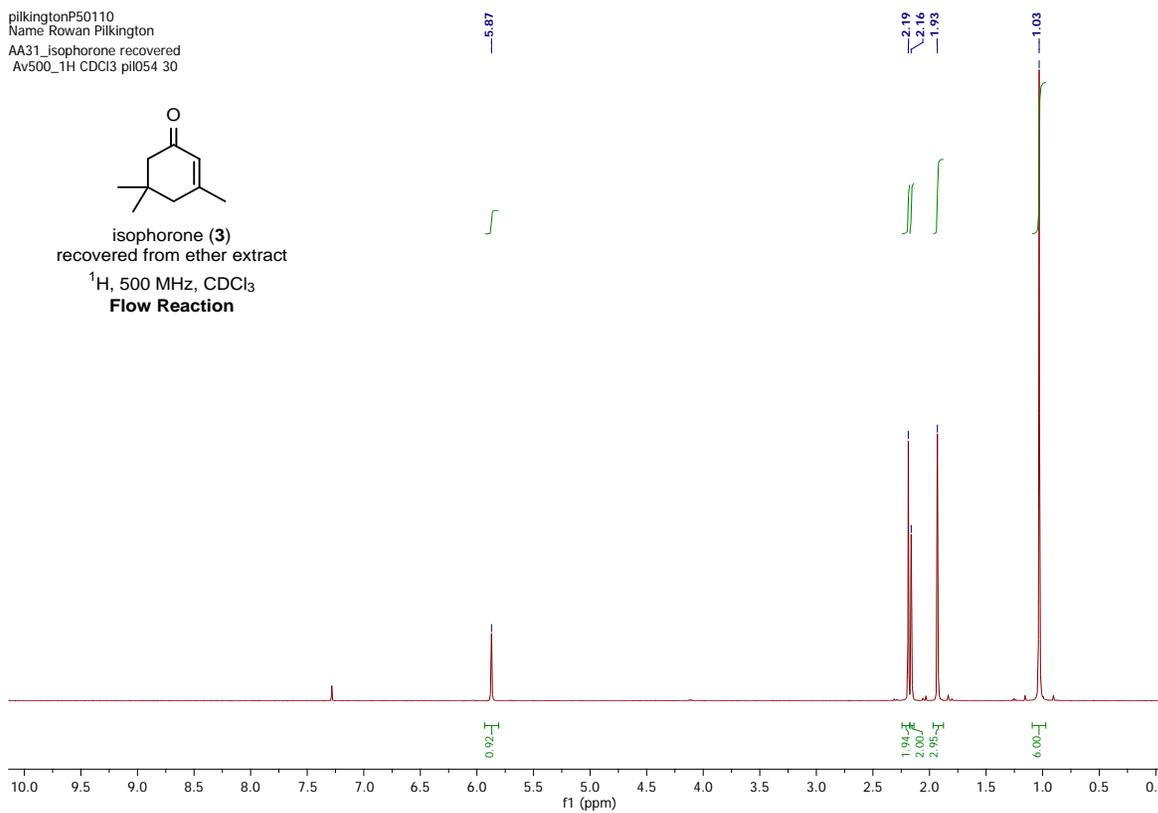
mad-03-011.11.fid  
mad-03-011



mad-03-011.12.fid  
mad-03-011



pilkingtonP50110  
Name Rowan Pilkington  
AA31\_isophorone recovered  
Av500\_1H CDCl3 pil054 30



1. H. Yamazaki, H. Horikawa, T. Nishitani and T. Iwasaki, *Chem. Pharm. Bull. (Tokyo)* **1990**, *38*, 2024–2026.
2. E. García-Urdiales, F. Rebolledo, V. Gotor, *Tetrahedron: Asymmetry* **1999**, *10*, 721–726.
3. J. Katarzyńska, A. Mazur, M. Bilska, E. Adamek, M. Zimecki, S. Jankowski and J. Zabrocki, *J. Pept. Sci.* **2008**, *14*, 1283–1294.
4. A. Raghuraman, E. Ko, L. M. Perez, T. R. Ioerger and K. Burgess, *J. Am. Chem. Soc.* **2011**, *133*, 12350–12353.