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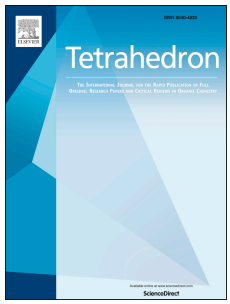

Gas-liquid flow hydrogenation of nitroarenes: Efficient access to a pharmaceutically relevant pyrrolobenzo[1,4]diazepine scaffold

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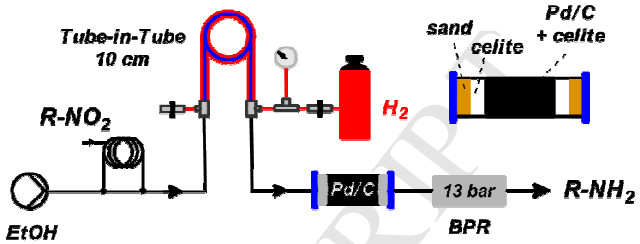

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Gas-liquid flow hydrogenation of nitroarenes: efficient access to a pharmaceutically relevant pyrrolobenzo[1,4]diazepine scaffold

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ABSTRACT

Using a Tube-in-Tube device based on the amorphous Teflon AF-2400 fluoropolymer, a series of nitroarenes was hydrogenated to afford the corresponding aniline compounds. The system was then applied to the construction of a pyrrolobenzo[1,4]diazapene scaffold through a tandem hydrogenation-condensation-hydrogenation sequence.

1. Introduction

The pyrrolobenzodiazepine scaffold **1** (10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine, Figure 1) is a medicinally important heterocycle consisting of a benzo[1,4]diazepine unit fused to a pyrrole. This structure is commonly encountered as a constituent part of important synthetic drug scaffolds, for example, in the development of non-peptidic oxytocin and vasopressin small molecule agonists and antagonists, typified by Lixivaptan **2** (Figure 1).[1]

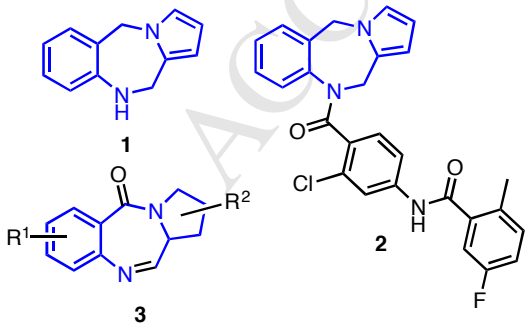
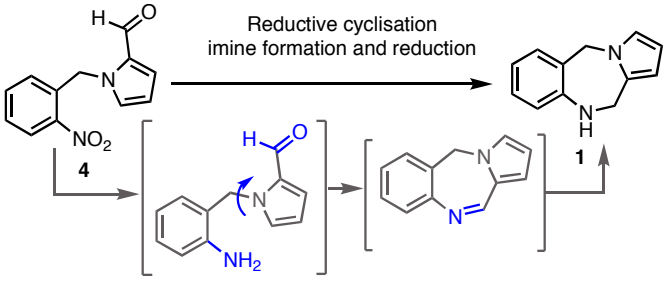


Figure 1. The pyrrolobenzodiazepine scaffold **1**, Lixivaptan **2** and the PDB scaffold **3**.

Also important is the inclusion of the structural template of **1** within the development of pyrrolo[2,1c][1,4]benzodiazepines **3** (PBDs) as DNA interactive agents.[2] Since their discovery in the 1960s the field of PBD research has expanded rapidly and now includes over thirteen different PBD architectures used across synthetic mechanistic and medicinal chemistry and as 'warheads' in therapeutic antibody applications.[3] The utility of **1** requires that efficient synthetic methods to access it are available. Several chemical syntheses of **1** have been reported in the literature[4] and, as their key tricycle-forming step, propose a tandem sequence involving the reduction of the nitro group in pyrroloaldehyde **4**, condensation of the resultant aniline moiety with the pyrrolic aldehyde and finally reduction of the imine to form **1** (Scheme 1).



Scheme 1. Access to **1** (*via* nitro reduction, imine formation and reduction) from pyrroloaldehyde **4**.

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These two transformations are usually completed as a one-step, domino process where nitro reduction, cyclisation and imine reduction are globally effected under hydrogenation conditions.

From a process standpoint, the use of gaseous reagents is in many ways advantageous. Several equivalents of gas can be used to drive reactions to completion and the excess material can easily be removed post reaction simply by opening the container. However, the use of gasses is often accompanied by significant safety issues. As gas concentrations in solution are proportional to pressure in the head space (according to Henry's law[5]), high pressures are often required to achieve sufficient concentrations for reactions to take place. This generally requires the use of specialised high-pressure reactors. As the potential energy stored due to pressurisation (which would be converted to kinetic energy in the event of a mechanical failure) is proportional to the volume of the vessel, this becomes more serious during scale up. Hydrogen is also one of the most flammable of gasses and this leads to additional fire and explosion hazards.[6] Furthermore, as interfacial surface-area scales with the square of dimension, whilst volume scales with its cube, surface-area to volume ratios decrease as the size of the vessel increases (assuming the same shape is maintained). This leads to a scale variant rate of gas transfer, from the head space into the solution, which often becomes rate limiting.

In recent years, continuous flow chemistry has emerged as an alternative to traditional batch based synthetic protocols.[7] Due to the fact that only a small amount of material is being processed at any one time, through relatively small reaction zones, this can often mitigate some of the safety issues associated with the scale-up of batch reactions, particularly for those transformations that involve the formation of hazardous intermediates, or that use high temperatures or pressures.[8] In addition, as interfacial surface contact is often enhanced and well-defined, this can often facilitate more efficient and controllable interfacial mass and energy transfer.[9]

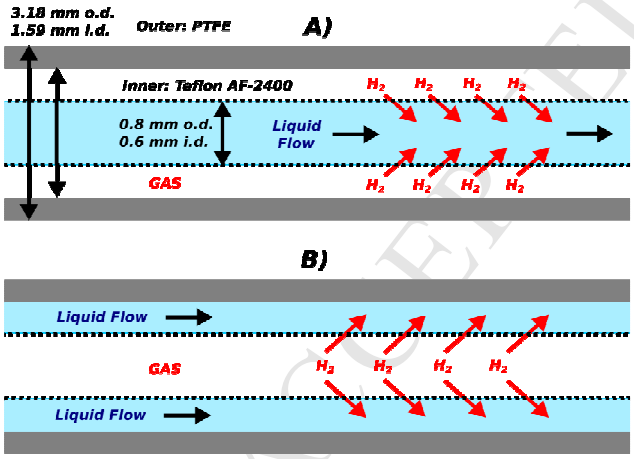


Figure 2. Cartoon schematic of Tube-in-Tube device. A) Configuration with liquid flow within inner AF-2400 tubing, and gas flow in outer jacket (as used in this work). B) Alternative configuration with gas in inner AF-2400 tubing and liquid flow in outer jacket.

As part of a program investigating the use of gas-liquid flow technologies as a replacement for traditional batch hydrogenation and hydrogenolysis processes, we were interested in their application to the synthesis of **1**.

A key consideration when using gases in continuous flow is the nature of the contact between the gas and liquid phases. In systems where biphasic flow streams are generated, governing the morphology of the flow regime is not always straightforward.[10] A number of different approaches to gas-liquid contacting in flow have been developed, many of which provide enhanced mass transfer of gas between the two phases, often by maximising the interfacial surface area.[11] For hydrogenation reactions, the commercially available H-Cube system has also seen growing popularity among synthetic chemists.[12]

We have previously demonstrated that flow reactors based on gas-permeable membranes, such as Teflon AF-2400,[13] which combines very high levels of gas permeability with excellent chemical resistance properties, facilitate the reliable and scale-invariant generation of homogeneous flow streams of reactive gasses in solution.[14] These devices avoid many of the complications associated with heterogeneous biphasic flow regimes which result from 'mechanical mixing' of gas and liquid flow streams. The relationship between gas concentration and operational variables, such as residence time, gas pressure, and tubing dimension, is straightforward and can be reliably modelled using standard mathematical analyses.[15] When high pressures of gas are required to achieve sufficient solution concentrations, the 'tube-in-tube' configuration (Figure 2) is an efficient arrangement which keeps the volume of pressurised gas to a minimum. A simple and inexpensive 'tube-in-tube' device can easily be constructed using just two standard T-piece junctions (e.g. Swagelok), as shown in Figure 3.

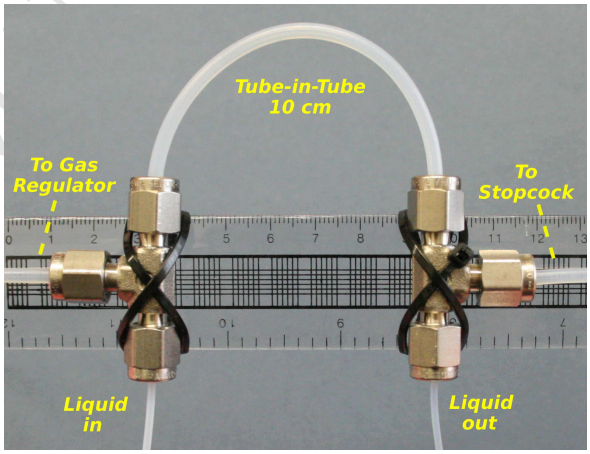


Figure 3. Photograph of the Tube-in-Tube device used in this work. The plastic ruler the Swagelok T-pieces are cable-tied to is used only for attachment and to provide a scale. The left-hand T-piece was connected to the hydrogen cylinder via a standard 2-stage poppet regulator. The right-hand T-piece was connected to a stopcock that was normally closed during operation, so that the jacket of gas remained 'static' (the only flow of gas being through the AF-2400 tubing into the liquid flow stream).

Whilst commercial gas-liquid flow devices tend to be well engineered, and can perform admirably in a wide range of hydrogenation applications, their proprietary nature generally precludes full disclosure of their internal design and workings (including materials). This encourages a 'black box' approach which may inhibit further modification and/or development of the systems by the user. The simple and fully disclosed nature of these Teflon AF-2400 based devices is perhaps one of the reasons (in addition to their low cost) for their rapidly growing popularity.

We, and others, have successfully demonstrated the use of Teflon AF-2400 based reactors with a number of reactive gasses including ozone,[16] oxygen,[17] ammonia,[18] methylamine,[19] carbon dioxide,[15b, 20] carbon monoxide,[19, 21] ethylene,[22] diazomethane[23], formaldehyde,[24] and fluoroform.[25] Importantly, in the context of the current work, they have been used with hydrogen gas,[22c, 26] on its own or as a mixture with carbon monoxide (syngas).[22b, 27]

2. Results and Discussion

2.1. Reduction of Simple Nitroarenes.

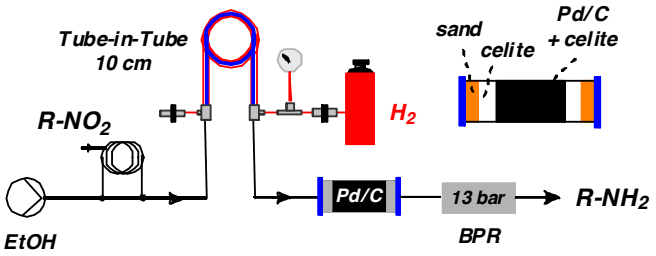
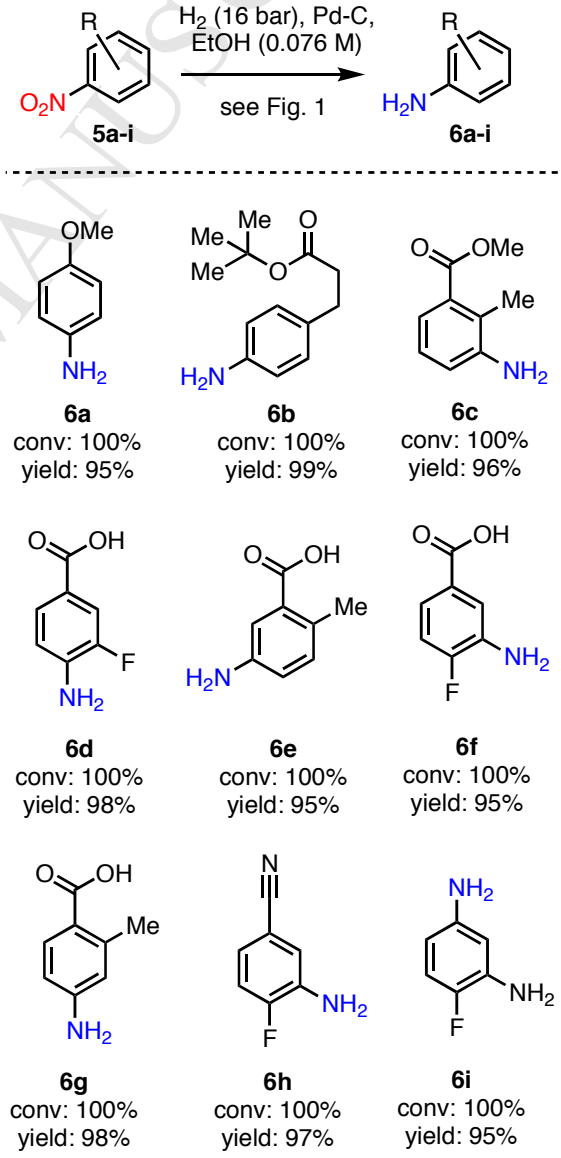


Figure 4. Schematic of the flow setup.

Prior to attempting a synthesis of **1** using gas-liquid flow hydrogenation, we first wanted to establish that the system was capable of effecting the hydrogenation of simple nitroarene compounds **5a-i** in continuous flow[28] using the general setup shown in Figure 4. The starting material was loaded into a flow stream of solvent using an injection loop. The flow stream becomes enriched with hydrogen gas by passing through a relatively short 10 cm Tube-in-Tube device (this single Tube-in-Tube device was used for all the work described in this paper). We have previously found that saturation is rapid using hydrogen gas with Tube-in-Tube reactors. Upon exiting the Tube-in-Tube stage, the flow stream passes through a glass omnifit cartridge containing Pd-C (5%). We found that back-pressure due to compression/blocking of the catalyst powder could be avoided by mixing it with celite (1:1 wt:wt) and packing it into the cartridge with plugs of celite and sand at each end (see Figure 4). Using the powdered supported catalyst by itself led to a significant and variable build up of back-pressure. During a brief initial screening (of solvent, flow rates etc), we used a small cartridge (11.1 mm OD, 6.6 mm ID) containing 370 mg of 5% palladium on carbon (which was used repeatedly). It was found that 15 mg of nitroanisole **5a**, (injected as a 0.027 M EtOH solution in a 3.6 mL loop) could be cleanly converted to the corresponding aniline **6a** with quantitative conversion and in high yield using ethanol as solvent with a flow rate of 0.5 ml min^{-1} and a hydrogen pressure of 16 bar. No premature outgassing (formation of hydrogen bubbles) upstream of the 13 bar back-pressure regulator was observed under these conditions. A noticeable drop in outgassing downstream of the back pressure regulator was observed about 15 minutes after injection, indicating that hydrogen was being used up. This continued until about 20 minutes after injection, at which point the outgassing reached its original level, indicating that the rate of hydrogen consumption had significantly diminished. It should be pointed out that the system was allowed to equilibrate for 30 minutes under H_2 pressure prior to the injection of the substrate solution, after which time the rate of hydrogen outgassing downstream of the back pressure regulator reached a steady state. The product stream was collected at the outlet for 40 min. The reaction was then increased in scale, using a larger cartridge (20.0 mm OD, 15.0 mm ID) containing 1.0 g of palladium on carbon, again with a hydrogen pressure of 16 bar. A 0.152 M solution of **5a** (84 mg in 3.6 mL) was injected into an EtOH flow stream at 0.5 mL min^{-1}. The outlet solution was collected for 120 minutes and the product was isolated by removing the solvent under reduced pressure to afford a mixture of the desired aniline **6a** and the starting material **5a** in a ratio of approximately 3:1. When the concentration of starting material was lowered to 0.076 M (42 mg in 3.6 mL EtOH), under the same conditions, the conversion was complete and the desired product **6a** was isolated in a very high yield of 95 %. Likewise, when the hydrogenation of *tert*-butyl nitrophenylpropanoate **5b** was attempted at a concentration of 0.152 M, the product was isolated alongside unreacted starting material (**6b**:**5b** = 2:1) but when the reaction was carried out at 0.076 M, complete conversion to **6b** was observed. Using a concentration of 0.076 M, a series of nitroarene compounds **5a-i** was cleanly converted to the corresponding anilines **6a-i** which were isolated in very high yields. (Scheme 2). ^{1}H and ^{13}C NMR alongside MS analysis confirmed the desired nitro to aniline conversions had occurred and that nitroso products were not formed. Having thus established that we could perform simple nitro reduction using our gas-liquid flow hydrogenation setup, we next attempted the proposed nitro-reduction/cyclisation/imine-reduction domino process to access **1** from **4**.

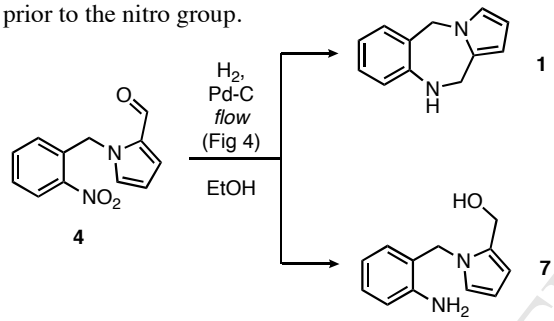


Scheme 2. Results of continuous flow nitroarene hydrogenations. Conversions were determined by ^{1}H NMR. Yields refer to isolated yields based on mass recovery. The starting material for

6i was 2-fluoro-5-nitro-aniline. The same cartridge of Pd-C catalyst was used for all substrates.

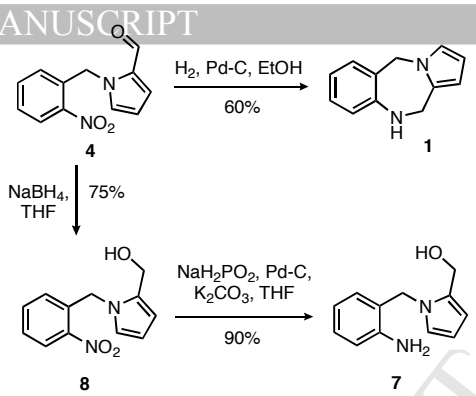
2.2. Pyrrolobenzazepine synthesis using gas-liquid flow hydrogenation.

In our initial investigations for the continuous-flow conversion of **4** into **1**, we reverted to using the smaller cartridge of palladium catalyst (11.1 mm OD, 6.6 mm ID, 370 mg of 5% Pd-C). Again using EtOH as a solvent, nitro-aldehyde **4** (easily obtained from alkylation of 2-nitrobenzyl bromide with pyrrole-2-carbaldehyde[5]) at a concentration of 8.7 mM (7.2 mg in 3.6 mL) was exposed to analogous flow conditions (0.5 mL min^{-1}, 16 bar H_2). The outlet was collected for 45 minutes. Analysis of the isolated product material by ^{1}H NMR suggested that the majority of the starting material, approximately 65%, had not been converted to the desired product **1**, but to another compound with quite similar spectral features. Data reported in the literature for **1** suggested that this was, in fact, the minor component, formed in 35% yield. We were thus interested in firmly establishing the identity of the two products. ^{1}H NMR analysis indicated that, in both products, two CH_2X (X = heteroatom) environments were present. This suggested that aldehyde reduction had occurred and that the amino-alcohol structure **7** was a possibility for the major product. Consistent with this, we found, after chromatographic separation, that the major product also had a significantly lower R_f value than the minor product. It occurred to us that the formation of **7** might result from hydrogenation of the aldehyde prior to the nitro group.



Scheme 3 Reductive cyclisation of pyrrolocarbaldehyde **4** to **1** and formation of the minor reaction by-product **7**.

We separately synthesised **1** and **7** from **4** in batch. To access **1** we used the same solvent and catalyst, but at atmospheric (balloon) pressure of H_2 and isolated the desired product **1** in 60% yield after chromatography. To obtain **4** we used an alternative two-step proces. (68% overall yield, Scheme 4). $NaBH_4$ treatment of **4** proceeded smoothly to deliver novel nitro alcohol **8** in 90% yield. Using mildly basic conditions and H_2 generated *in situ* from sodium hypophosphite (NaH_2PO_2), Pd/C catalysed reduction of **8** delivered **7** smoothly in 75% isolated yield (with no evidence of any cyclisation to **1**). Attempts to access **7** using acidic nitro-reducing conditions (Fe/AcOH) were unsuccessful, leading to extensive material degradation.



Scheme 4. Batch synthesis of anilino-alcohol **7** and pyrrolobenzazepine **1**; i) Pd/C, H_2, EtOH, 60% ii) $NaBH_4$, THF, 75% iii) Pd/C, K_2CO_3, H_2O, THF, 90%.

We compared our NMR data for **7** with the initial gas-liquid flow results as well as with the spectra of pure **1** (selected ^{1}H region shown in Figure 5, bottom, blue line). The product of the hydrogenation of **8** and the major product from the flow hydrogenation had identical ^{1}H and ^{13}C NMR spectra as well as identical R_f values. This corroborated our conclusion that flow hydrogenolysis conditions had converted 65% of **4** to **7** and 35% to **1**. The structures of products **1** and **7** from the batch reactions were further confirmed by Mass Spectrometry and single-crystal X-ray diffraction (see Figure 6).

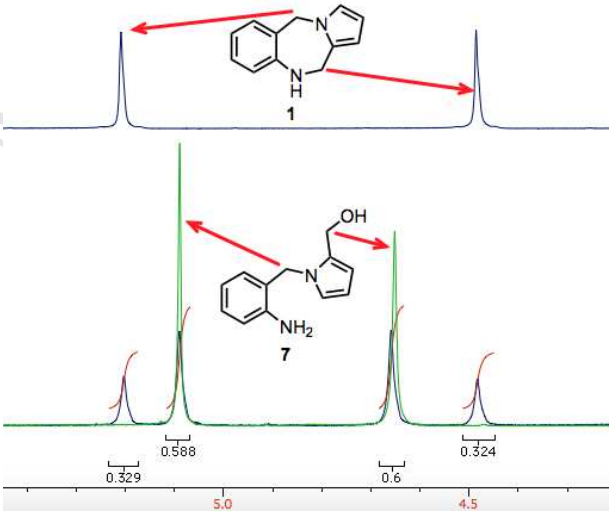
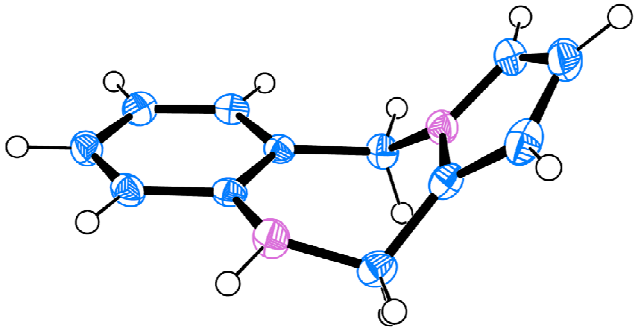


Figure 5. 400 MHz ^{1}H NMR overlays of initial attempted synthesis of **1** using gas-liquid flow hydrogenolysis (bottom, blue line) and using traditional batch conditions[1a,b, 4] (top). The spectra of **7** made in batch *via* hydrogenation of nitro-alcohol **8** is overlaid on the bottom spectrum as a green line.



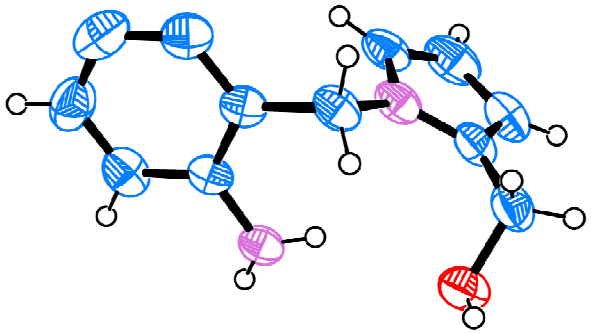


Figure 6. X-ray structures of **1** (top) and **7** (bottom, thermal ellipoids shown at 50%).

It was found that, if the crude 35:65 mixture of **1** and **7** obtained in flow was re-injected into the continuous flow system, then the product that emerged from this second pass (which was isolated with quantitative mass recovery) contained predominantly **7** (now in a 1:12 ratio of **1**:**7**). This suggested the possibility that **1** might be an intermediate in the formation of **7.** To test this hypothesis, we separately passed purified samples of **1** and **7** through the flow system again and found that they were recovered, unaltered, in essentially quantitative yield, which negates the suggestion that **7** is formed from **1**. As the 36:65 ratio mixture of **1** and **7** that was recycled was crude, we cannot rule out the possibility that it contained residual palladium that may have catalysed changes in the time between the two runs (including exposure to NMR solvents etc.). The fact that the relative proportions of **1** and **7** seem to be sensitive to the concentration of **4** at a given hydrogen pressure and flow rate (more **7** being formed at a lower substrate concentration) suggests that the aldehyde in **1** might be undergoing hydrogenative reduction to the alcohol when the hydrogen concentration is higher. If aldehyde hydrogenation occurs either before the nitro group is reduced, or before the formation of the imine intermediate (which is perhaps more likely as reduction of the nitro group might also be expected to proceed more rapidly at higher hydrogen concentration), this would explain the formation of **7**. Whilst transition-metal catalysed hydrogenations of pyrrolic aldehydes are known,[29] literature precedent suggests that the nitro group should be reduced more quickly under these conditions.[30]

Consistent with this, when **4** was injected under the same conditions, but with the addition of 20 equivalents of pyridine (which is a known poison/modifier of palladium catalytic activity[31]) then **1** was obtained in a 2.7:1 ratio with **7**. Also, when 36 mg of nitro-alcohol **8** (in 18 mL EtOH) was subjected to the flow hydrogenation conditions (using the larger 1g Pd-C cartridge, H_2 at 16 bar, 0.5 mL min^{-1}), the amino-alcohol **7** was the sole product, isolated in 97% yield, strongly suggesting that **7** is not a precursor to **1**

Having fully established the identity of the two products from the flow hydrogenation reaction, we were keen to optimise conditions to favour production of the desired material **1**. Whilst the addition of pyridine was observed to have a positive influence in this regard, we noticed that its effect on the smaller catalyst cartridge was not quickly reversed and flushing with copious fresh solvent was required to 'regenerate' the original catalytic activity. Wanting to avoid complications arising from cumulative (and perhaps variable) poisoning effects over time, we investigated whether the same outcome could be obtained by varying simple parameters such as concentration. Pleasingly, when **4** was injected in a higher concentration of 0.0217 M (90 mg in 18 mL EtOH), with a flow rate of 0.5 mL min^{-1} and an H_2 pressure of 16 bar, using the larger catalyst cartridge (1.0 g of Pd-C) the desired compound **1** was obtained in a yield of 95%, and in the absence of the ring-opened by-product **7**.

For larger scale runs, the injection loop became unsuitable and the substrate solution was introduced directly through the pump inlet (Figure 7). When the scale was increased to 500 mg (at the same concentration: 21.7 mM, 500 mg in 100 mL EtOH) then we found that significant amounts of unreacted starting material **4** were obtained, alongside the product **1** and other components (not including **7**), Table 1, entry 1. This reduction in conversion at a higher scale might be explained by the palladium acting as a 'reservoir' of hydrogen. During the equilibration prior to the start of the run, it may take up and store a quantity of hydrogen and, after equilibration is reached, outgassing of hydrogen is then observed downstream of the back pressure regulator. During the run, once the starting material is introduced, this stored hydrogen may (for a while) allow higher conversion than would be possible solely from the hydrogen present in solution. Clearly, any stored hydrogen will be consumed and, during longer runs (i.e. larger scale reactions) may become completely depleted, leading to lower conversions.

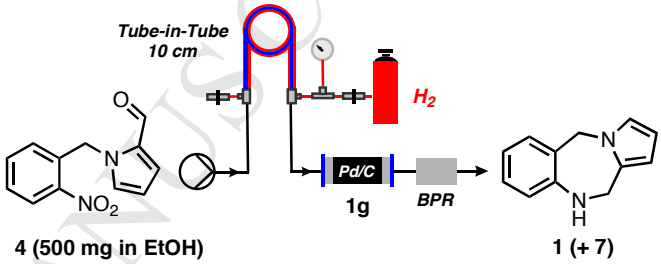


Figure 7. For the larger (500 mg) scale experiments, the starting material **4** was added directly through the pump inlet.

Using a lower concentration of subsrate (14.5 mM, 500 mg in 150 mL) and a higher pressure of hydrogen (25 bar, with the back pressure regulator adjusted to 20 bar), the loss of starting material was complete but now the product **1** was accompanied by a significant amount of amino alcohol **7** (1:7 = 1:0.87, Table 1, entry 2). Lowering the pressure to 20 bar (at this reduced concentration) reduced the quantity of 7 obtained (1:7 = 1:0.40, Table 1, entry 3). Pleasingly, by using this 20 bar pressure with the original concentration (21.7 mM), we were able to obtain a product which contained minimal quantities of 7 (1:7 = 1:0.05) and, after column chromatography, the isolated product 1 was obtained in an 81% yield (356 mg).

Entry	H_2 (bar)	Conc.(mM)	S.M. consumed?	1:7	Yld (1)
1	16	21.7	N	-	-
2	25	14.5	Y	1:0.87	-
3	20	14.5	Y	1:0.40	-
4	20	21.7	Y	1:0.05	81%

Table 1. Results for the 500 mg scale hydrogenations of **1**. Yld refers to the isolated yield of **1** after column chromatography on silica gel.

3. Conclusion

In conclusion, we have developed a simple and effective continuous-flow heterogeneous hydrogenation protocol for

nitroarenes based around an inexpensive Teflon AF-2400 tube-in-tube reactor. This was used to effect the formation of a series of substituted anilines in high yields and high purities. With nitro-aldehyde **4**, the flow conditions could be tuned to preferentially obtain either the desired pyrrolobenzo[1,4]diazapene compound **1** or the amino-alcohol by-product **7**. Despite the fact that 7 was not the desired compound in this particular case, this nevertheless demonstrates that the flow conditions used can provide controlled access to alternative products. There appears to be a relationship between the relative amounts/concentrations of the starting material/H_2 and the product selectivity. We are currently performing investigations aimed at establishing the mechanistic manifold by which 1 and **7** are formed, including a comparison between flow and batch modes across a range of pressures (it should be pointed out that the batch hydrogenation in this work was only carried out at atmospheric pressure). We are also investigating whether the palladium is acting as a hydrogen reservoir (and the effect this has on the reactivity), as well as the extent of any palladium leaching, and will report our findings in due course.

4. Experimental Section

^{1}H NMR spectra were recorded on a Bruker Avance 300 (300.1 MHz) instrument or a Bruker Avance 400 (399.9 MHz) instrument using deuterochloroform (or other indicated solvent) as reference. The chemical shift data for each signal are given as δ in units of parts per million (ppm) relative to tetramethylsilane (TMS) where δ (TMS) = 0.00 ppm. The multiplicity of each signal is indicated by: s (singlet); brs (broad singlet); d (doublet); t (triplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); ddt (doublet of doublet of triplets); sp (septet) or m (multiplet). The number of protons (n) for a given resonance is indicated by nH. Coupling constants (*J*) are quoted in Hz and are recorded to the nearest 0.1 Hz. ^{13}C NMR spectra were recorded on a Bruker Avance 300 (75.5 MHz) instrument using the PENDANT sequence and internal deuterium lock. The chemical shift data for each signal are given as δ in units of ppm relative to TMS where δ (TMS) = 0.00 ppm. Where appropriate, coupling constants (*J*) are quoted in Hz and are recorded to the nearest 0.1 Hz. Melting points were determined using Gallenkamp MF-370 or Electrothermal 9100 melting point apparatuses and are uncorrected. Analytical thin layer chromatography (TLC) was carried out on pre-coated 0.25 mm ICN Biomedicals GmbH 60 F254 silica gel plates. Visualisation was by absorption of UV light, or thermal development after dipping in 5 % H_2SO_4 in MeOH. Manual Column chromatography was carried out on silica gel (Apollo Scientific Ltd 40- 63 micron) under a positive pressure of compressed air. Automatic Column Flash chromatography was carried out on silica gel (Reveleris® X2 system) under a positive pressure of compressed N_2. Dry CH_2Cl_2 and DMF was acquired from an Innovative Technology solvent purification system. Anhydrous MeOH was dried over 4 Å molecular sieves. Chemicals were purchased from Acros UK, Aldrich UK, Avocado UK, Fisher UK or Fluka UK. All solvents and reagents were purified and dried where necessary, by standard techniques. Where appropriate and if not stated otherwise, all non-aqueous reactions were performed under an inert atmosphere of nitrogen, using a vacuum manifold with nitrogen passed through 4 Å molecular sieves and self-indicating silica gel. *In vacuo* refers to the use of a rotary evaporator attached to a diaphragm pump. Brine refers to a saturated aqueous solution of sodium chloride. Hexane refers to *n*-hexane and petroleum ether to the fraction boiling between 40-60 °C. The heterocyclic ring numbering for NMR assignments of **7** and **8** is shown in the supplementary material.

Flow apparatus: A Knauer Azura P-4.1S HPLC pumping unit was used to pump the solvent through the system. Aside from the Tube-in-Tube device, the general liquid flow line consisted of FEP tubing (1/16'' x 1.0 mm ID, VICI-jour) and the tubing interconnects were of the flat seated Omnifit/Diba type (1/4-28-UNF thread). The backpressure regulator was an Upchurch/IDEX type (Kinesis UK) and was manually adjusted to provide the desired back pressure of 13 bar (gauge), as measured using the pressure meter of the Knauer Azura pump. The injection loop was constructed using four Omnifit/Diba 3-way valves (two valves to open/close the loop itself for filling, two valves to connect/disconnect the loop to the flow stream). The hydrogen pressure in the Tube-in-Tube device was regulated at the cylinder outlet using a Gas-Arc Techmaster GA600 multi-stage regulator. As shown in Figure 3, the side-port of one of the Swagelok T-pieces of the Tube-in-Tube device was connected to the regulator outlet, and the side-port of the other T-piece was connected to a Swagelok stopcock (which was closed during normal operation and only used for maintenance/start-up/shutdown etc). With this arrangement, the hydrogen gas could only exit the Tube-in-Tube device during normal operation by passing into the solvent flow stream.

*4.1 Pyrrolobenzodiazepine **1***

Batch: To a stirred solution of 1-[(2-nitrophenyl)methyl]pyrrole-2-carbaldehyde **4** (300 mg, 1.30 mmol, 1.0 equiv.) in EtOH (4 mL), was added 5% Pd-C (5.5 mg, 0.002 equiv.) and the reaction mixture left stirring overnight under a H_2 atmosphere (balloon). Upon completion, as indicated by TLC (1/2, ethyl acetate/hexane), the mixture was filtered through Celite™ and the solution concentrated *in vacuo*. The crude product was purified by Reveleris® automated silica gel flash column chromatography (liquid injection onto column), eluting with ethyl acetate/hexane (0/100, 40/60, 60/40 and 100/0), furnishing **1** (160 mg, 0.79 mmol, 60%) as a brown solid. R_f 0.61 (1/2, ethyl acetate/hexane);

***Flow** (500 mg run)*: The system (see Figure 6), incorporating the 1g Pd-C cartridge (20.0 mm OD, 15.0 mm ID), was primed by pumping through ethanol at a rate of 0.5 mL min^{-1}. No injection loop was used. A 20 bar back pressure regulator was used. To avoid an overpressure of the system in the event of blockage, the upper pressure cut-off limit on the Knauer pump was set to 25 bar. The tube-in-tube device was subjected to 20 bar of hydrogen pressure using a 2-stage regulator on the cylinder. Priming continued for 30 minutes before starting the run (out-gassing of hydrogen downstream of the back-pressure regulator could be observed after about 20 minutes). The starting nitro-aldehyde **4** (500 mg, 2.17 mmol) was dissolved in EtOH (100 mL solution). To introduce the starting material solution, the pump was momentarily stopped and the inlet was switched from the EtOH reservoir to the starting material solution. The pump was then immediately restarted. The level of the inlet solution was monitored and at the moment when it had all been taken in (but before any air could be drawn in to the pump inlet line), the pump was momentarily stopped and the inlet line switched back to the EtOH reservoir. The pump was then immediately restarted. The output from the system was collected for 450 minutes. Solvent was removed under reduced pressure (using a rotary evaporator followed by a 2-stage rotary vane pump) to afford an off-white solid (450 mg crude). The material was purified using column chromatography on silica gel (Merck 9385 grade) eluting with a gradient from petroleum ether to ethyl acetate, to afford **1** as a white solid (356 mg, 81%);

^{1}H NMR (300 MHz; $CDCl_3$) δ 7.08-7.00 (m, 2H, H_4, H_2), 6.71 (t, *J* = 2.1 Hz, 1H, H_5), 6.65 (td, *J* = 7.4, 1.1 Hz, 1H, H_3), 6.52 (dd, *J* = 8.0, 1.0 Hz, 1H, H_1), 6.08-6.05 (m, 2H, H_6, H_7), 5.21 (s, 2H, C*H*$_2$N), 4.49 (s, 2H, C*H*$_2$O), 3.71 (brs, 1H, N*H*); **^{13}C NMR** (75 MHz; $CDCl_3$) δ 146.5, 131.0, 129.9, 128.8, 120.6, 120.0, 117.79, 117.65, 106.2, 105.6, 51.6, 40.7; **MS ESI$^+$** *m/z* 185 ([M+Na]$^+$, 100 %); **HRMS ESI$^+$** *m/z* Found: 185.1071 for $C_{12}H_{13}N_2$ [(M+H)$^+$] requires 185.1073; Data matched those previously reported[1b]; CCDC No: 1584964.

General Procedure for Flow hydrogenation of Nitro Arenes (Scheme 2):

Before each run, the system (see Figure 4) was allowed to equilibrate by pumping solvent through for 30 minutes with the Tube-in-Tube device at 16 bar of hydrogen. An omnifit cartridge (20.0 mm OD, 15.0 mm ID) containing 1g of Pd-C catalyst was used. To avoid an overpressure of the system in the event of blockage, the upper pressure cut-off limit on the Knauer pump was set to 25 bar. With the injection loop disconnected from the flow line, the loop was opened and filled manually (using a syringe) with 3.6 mL of a 0.076 M solution of starting material in ethanol (excess starting material solution exiting the loop was recovered for reuse). The injection loop was then closed off and switched into the flow stream. The outlet from the system (downstream of the back-pressure regulator) was collected for 120 min. The solvent was removed under reduced pressure (using a rotary evaporator followed by a 2-stage rotary vane pump) to afford the product.

4.2. 4-amino methoxybenzene ***6a***
32.0 mg from 41.9 mg **5a** (95%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.3 Hz, 2H), 6.69 (d, *J* = 8.3 Hz, 2H), 3.78 (s, 3H), 3.39 (br.s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.9, 139.9, 116.4, 114.9, 55.8. The data are consistent with values reported in the literature.[32]

4.3. 1 tert-Butyl 3-(4-aminophenyl)propionate ***6b***
59.9 mg from 68.8 mg **5b** (99%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 7.7 Hz, 2H), 6.61 (d, *J* = 7.6 Hz, 2H), 3.57 (br.s, 2H), 2.79 (t, *J* = 7.8 Hz, 2H), 2.47 (t, *J* = 7.8 Hz, 2H), 1.42 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.5, 144.5, 130.9, 129.1, 115.2, 80.2, 37.5, 30.4, 28.1; **HRMS** (**ESI-TOF**, m/z): calculated for $C_{18}H_{20}NO_2$ ([M+ H]$^+$): 222.1489, found: 222.1484. The data are consistent with values reported in the literature.[33]

4.4. Methyl-3-methyl-4-nitro benzoate ***6c***
43.4 mg from 53.4 mg **5c** (96%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.7 Hz, 1H), 7.05 (app.t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 3.88 (s, 3H), 3.73 (br.s, 2H), 2.34 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1, 145.5, 131.6, 126.1, 122.9, 120.4, 118.2, 51.9, 13.8; **HRMS** (**ESI-TOF**, m/z): calculated for $C_9H_{11}NO_2$ ([M+ H]$^+$): 166.0863, found: 166.0857. The data are consistent with values reported in the literature.[34]

4.5. 4-Amino-3-fluoro-benzoic acid ***6d***
41.6 mg from 50.6 mg **5d** (98%).
^{1}H NMR (400 MHz, CD_3CN) δ 7.63 (d, *J* = 8.3 Hz, 1H), 7.59 (s, 1H), 6.84 (t, *J* = 8.4 Hz, 1H); **^{13}C NMR** (101 MHz, CD_3CN) δ 167.1, 151.7, 149.4, 141.5, 127.7, 116.9, 115.6; **HRMS** (**ESI-TOF**, m/z): calculated for $C_6H_7FNO_2$ ([M+ H]$^+$): 156.0455, found: 156.0453.

4.6. 5-Amino-2-methyl-benzoic acid ***6e***
39.3 mg from 49.6 mg **5e** (95%).
^{1}H NMR (400 MHz, CD_3CN) δ 7.20 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 4.26 (br.s, 2H,), 2.42 (s, 3H); **^{13}C NMR** (101 MHz, CD_3CN) δ 169.2, 146.4, 132.8, 130.7, 128.5, 118.8, 116.7, 20.3; **HRMS** (**ESI-TOF**, m/z): calculated for $C_8H_{10}NO_2$ ([M+ H]$^+$): 152.0706, found: 152.0701. The data are consistent with values reported in the literature.[35]

4.7. 3-Amino-4-fluoro-benzoic acid ***6f***
40.3 mg from 50.6 mg **5f** (95%).
^{1}H NMR (400 MHz, CD_3CN) δ 7.48 (d, *J* = 8.8 Hz, 1H), 7.37 – 7.28 (m, 1H), 7.07 (t, *J* = 9.8 Hz, 1H); **^{13}C NMR** (101 MHz, CD_3CN) δ 167.3, 155.9, 153.5, 136.5, 127.4, 120.1, 118.3, 115.7; **HRMS** (**ESI-TOF**, m/z): calculated for $C_7H_7FNO_2$ ([M+ H]$^+$): 156.0455, found: 156.0449. The data are consistent with values reported in the literature.[36]

4.8. 4-Amino-2-methyl-benzoic acid ***6g***
40.5 mg from 49.5 mg **5g** (98%).
^{1}H NMR (400 MHz, CD_3CN) δ 7.79 (d, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 6.8 Hz, 2H); **^{13}C NMR** (101 MHz, CD_3CN) δ 169.3, 152.7, 143.8, 134.1, 117.1, 116.9, 111.5, 22.2; **HRMS** (**ESI-TOF**, m/z): calculated for $C_8H_{10}NO_2$ ([M+ H]$^+$): 152.0706, found: 152.0700.

4.9. 3-Amino-4-fluoro-benzonitrile ***6h***
36.1 mg from 45.4 mg **5h** (97%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 – 6.98 (m, 3H), 3.98 (br.s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ154.9, 152.5, 135.9, 122.9, 119.7, 118.5, 116.3, 108.6.

4.10 2,4-Diamino-1-fluorobenzene ***6i***
32.8 mg from 42.7 mg **5i** (95%).
^{1}H NMR (400 MHz; $CDCl_3$) δ 6.80 (t, *J* = 9.7 Hz, 1H), 6.14 (dd, *J* = 7.6, 2.1 Hz, 1H), 6.03 (d, *J* = 8.5 Hz, 1H), 3.64 (s, 2H), 3.51 (s, 2H); **^{13}C NMR** (101 MHz; $CDCl_3$) δ 115.7, 115.5, 105.1, 105.0, 103.7, 103.7; **HRMS** (**ESI-TOF**, m/z): calculated for $C_6H_8FN_2$ ([M+ H]$^+$): 127.0666, found: 127.0667. The data are consistent with values reported in the literature.[37]

4.11. 1-[(2-aminophenyl)methyl]pyrrole-2-carbinol ***7***

Batch*:* a slurry consisting of **8** (200 mg, 0.86 mmol, 1 equiv.), K_2CO_3 (80 mg, 0.60 mmol, 0.7 equiv.), 5% Pd-C (4 mg, 0.002 equiv.) in H_2O (1.0 mL) and THF (1.5 mL) was heated to 60 °C. To this vigorously stirred mixture was added dropwise a solution of NaH_2PO_2 (350 mg, 3.27 mmol, 3.8 equiv.) in H_2O (1 mL). The reaction was refluxed for 3 h, cooled to room temperature, and toluene (5 mL) was added. The mixture was then filtered through Celite™, the layers separated, and the aqueous extracted with toluene (2 x 10 mL). The combined organic layers were washed with H_2O (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was crystallised from hexane/diethyl ether (1/1) to yield **7** (90 mg, 0.49 mmol, 65%) as a brown powder;

Flow: The system (see Figure 4), incorporating the 1g Pd-C cartridge (20.0 mm OD, 15.0 mm ID), was primed by pumping through ethanol at a rate of 0.5 mL min^{-1}. To avoid an overpressure of the system in the event of blockage, the upper pressure cut-off limit on the Knauer pump was set to 25 bar. The tube-in-tube device was subjected to 16 bar of hydrogen pressure using a 2-stage regulator on the cylinder. Priming continued for 30 minutes before starting the run (out-gassing of hydrogen downstream of the back-pressure regulator could be observed after about 20 minutes). The starting nitro-alcohol **8** (36.0 mg, 0.155 mmol) was dissolved in EtOH (18 mL solution). This solution was loaded into an 18 mL injection loop using a syringe. The injection loop was switched into the flow stream and the

output from the system was collected for 180 min. Solvent was removed under reduced pressure (using a rotary evaporator followed by a 2-stage rotary vane upmp) to afford an off-white solid (27.8 mg, 97%);

R_f 0.17 (1/2, ethyl acetate/hexane); mp 113-115 °C; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.18 (t, *J* = 7.7 Hz, 1H, H_2), 7.01 (d, *J* = 7.3 Hz, 1H, H_4), 6.80 (t, *J* = 7.1 Hz, 1H, H_3), 6.71 (d, *J* = 8.0 Hz, 1H, H_1), 6.64 (t, *J* = 2.2 Hz, 1H, H_5), 6.20 (dd, *J* = 3.3, 1.7 Hz, 1H, H_6), 6.13 (t, *J* = 3.1 Hz, 1H, H_7), 5.10 (s, 2H, CH_2N), 4.66 (s, 2H, CH_2O); **^{13}C NMR** (100 MHz; $CDCl_3$) δ 144.9, 131.6, 129.8, 129.2, 122.4, 121.5, 118.7, 116.3, 109.5, 107.6, 56.6, 47.9; **MS ESI$^+$** *m/z* 225 ([M+Na]$^+$, 100%); **HRMS ESI$^+$** *m/z* Found: 225.1013 for $C_{12}H_{14}N_2ONa$ [(M+Na)$^+$] requires 225.0998; CCDC No: 1816148.

4.12. 1-[(2-nitrophenyl)methyl]pyrrole-2-carbinol ***8***

To a stirred solution of 1-[(2-nitrophenyl)methyl]pyrrole-2-carbaldehyde[1] (200 mg, 0.87 mmol, 1 equiv.) in dry THF (8 mL) at 0 °C was added $NaBH_4$ (60 mg, 1.6 mmol, 1.9 equiv.) and stirring was continued for 48 h at room temperature. The reaction mixture was acidified with 1 M HCl to pH 5 and the solvent removed *in vacuo*. The crude oil was reconstituted between H_2O (25 mL) and CH_2Cl_2 (25 mL) and the aqueous phase extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phases were washed with saturated aqueous sodium chloride (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by Reveleris® automated silica gel flash column chromatography (liquid injection onto column), eluting with ethyl acetate/hexane (0/100, 40/60, 60/40 and 100/0) afforded **8** (180 mg, 0.77 mmol, 93%) as a brown solid. R_f = 0.38 (1/2, ethyl acetate/hexane); m.p. 98-100 °C; **^{1}H NMR** (300 MHz; $CDCl_3$) δ 8.15 (dd, *J* = 8.1, 1.4 Hz, 1H, H_1), 7.53 (td, *J* = 7.6, 1.4 Hz, 1H, H_3), 7.47-7.41 (m, 1H, H_2), 6.70 (dd, *J* = 2.7, 1.8 Hz, 1H, H_5), 6.46 (dd, *J* = 7.7, 1.2 Hz, 1H, H_4), 6.23-6.18 (m, 2H, H_6, H_7), 5.61 (s, 2H, CH_2N), 4.44 (s, 2H, CH_2OH), 1.84 (br.s., 1H, O*H*); **^{13}C NMR** (75 MHz; $CDCl_3$) δ 146.7, 135.5, 134.4, 132.1, 128.2, 128.0, 125.0, 123.5, 109.9, 108.2, 56.5, 48.3; **MS ESI$^-$** *m/z* 231 ([M-H]$^-$, 100%); **HRMS ESI$^-$** *m/z* Found: 231.0776 for $C_{12}H_{11}N_2O_3$ [(M-H)$^-$], requires 231.0775.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at:

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