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Multkilogram Scale-Up of a Reductive Alkylation Route to a Novel PARP Inhibitor

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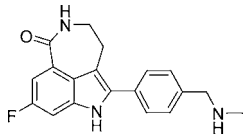
ABSTRACT: Novel PARP inhibitor **1** is a promising new candidate for treatment of breast and ovarian cancer. A modified synthetic route to **1** has been developed and demonstrated on 7 kg scale. In order to scale up the synthesis to multikilogram scale, several synthetic challenges needed to be overcome. The key issues included significant thermal hazards present in a Leimgruber–Batcho indole synthesis, a low-yielding side-chain installation, a nonrobust Suzuki coupling and hydrogen cyanide generation during a reductive amination. In addition to these issues, changing from intravenous to oral delivery required a new salt form and therefore a new crystallization procedure. This contribution describes development work to solve these issues and scaling up of the new process in the pilot plant.

INTRODUCTION

Inhibition of poly(ADP ribose) polymerase, or PARP, is an exciting new mechanism for the treatment of cancer.[1] The PARP enzyme is responsible for repair of damaged DNA in both normal and tumor cells, and inhibition of this repair mechanism is expected to make the cell more likely to undergo apoptosis. Preclinical work has shown that PARP inhibitors coadministered with a standard chemotherapuetic agent are more effective than the standard treatment alone.[2] Several PARP inhibitors, including PF-01367338 (**1**) which is currently in development[3] (Chart 1), have shown promising results in recent clinical trials for the treatment of advanced solid tumors.[4] This contribution details the development work carried out to design and scale up a safe process for the manufacture of **1** on multikilogram scale.

Chart 1. PF-01367338, a PARP inhibitor

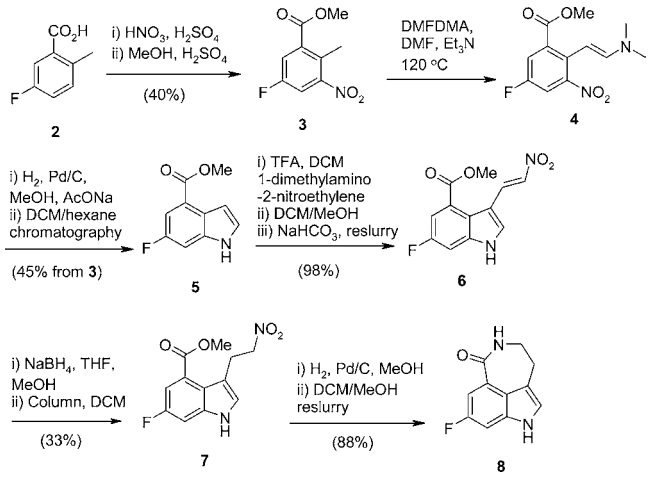


1

The early synthetic route to **1** is shown in Schemes 1 and 2. The key starting material for the in-house synthesis of **1** is indolazepine **8**. The synthesis of indolazepine **8** was outsourced for the first GMP campaign and started with nitration of 2-methyl-5-fluorobenzoic acid (**2**) followed by Leimgruber–Batcho indole synthesis. The resulting indole **5** was then reacted with 1-dimethylamino-2-nitroethylene (DMANE) to append the side chain. Subsequent two-stage reduction then gave the desired lactam **8**.

Indolazepine **8** was selectively brominated with pyridinium tribromide to give **9** which was coupled with boronic acid **10** under standard Suzuki conditions. Reductive amination with methylamine then gave **1** which was converted to the phosphate salt **13** which is the final active pharmaceutical ingredient (API).

Scheme 1. Outsourced route to key starting material indolazepine 8



Whilst this route was successfully used to prepare 2 kg of phosphate salt for use in preclinical and early clinical studies, some challenges still remained for the preparation of larger multikilogram quantities, as outlined below:

(1) Although preparation of indole **5** from **2** had previously been successfully outsourced, whilst running this chemistry in-house we discovered that the onset of an exothermic event during the Leimgruber–Batcho enamine formation (conversion of **3** to **4**) occurred at the current reaction temperature.

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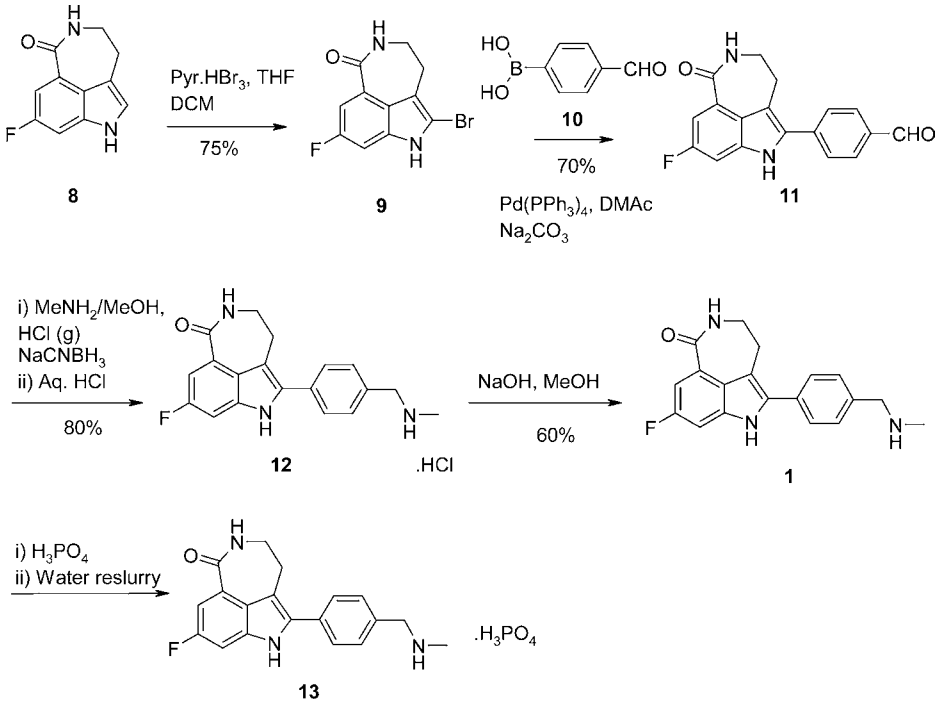
Scheme 2. In-house synthesis of 13 for first GMP campaign



(2) The reduction of nitroalkene **6** to **7** had not performed well on scale, leading to a low yield and the requirement for large-scale chromatography.

(3) The Suzuki coupling between aryl bromide **9** and boronic acid **10** failed to go to completion on scale-up and required an additional catalyst charge.

(4) The generation of HCN during the reductive amination of aldehyde **11** was not desirable, and alternative conditions were sought.

(5) The phosphate salt **13** was initially delivered as an intravenous (IV) formulation during phase I clinical trials; however, we were required to develop an oral product which required a new salt. After screening and evaluation work, the (*S*)-camphorsulfonate salt ((*S*)-CSA) was selected for tablet formulation which meant that a new API crystallization procedure was required.

RESULTS AND DISCUSSION

During the course of our lab development work stocks of indole **5** were required to allow us to address the scale-up issues observed during the reduction of nitroalkene **6**. Routine process safety testing of enamine **4** as a concentrate showed the onset of a significant exothermic event from 75 °C. Preliminary testing of the reaction mixture showed the onset of an exothermic event from 120 °C, which was the same as the intended reaction temperature. Our general purpose lab and plant scale-up facilities are not configured to routinely handle this type of hazard, and thus, inherently safer conditions were sought, either through avoiding this intermediate or through use of alternative conditions. The analogous pyrrolidine enamine was prepared in the hope that the safety profile of the reaction would be improved; however, this was shown not to be the case with the exothermic onset from 90 °C. Replacement of dimethylformamide dimethylacetal (DMFDMA) with Bredereck's reagent[5] did afford complete reaction within 4 h at 50 °C; however, the impurity profile was poor, and the crude mixture did not work in the subsequent reduction step. Tris(dimethylamino)methane (TDMAM)[6] gave complete reaction to the dimethylenamine **4** within 4.5 h at 50 °C, and the reaction profile was better. However, the exothermic onset was also lower with this reagent (75 °C), and unfortunately TDMAM was not readily commercially available on the scale that would have been required for the next campaign (~100 kg), so we discontinued this line of investigation.

In parallel to this work, simply reducing the reaction temperature was also investigated. The reaction rate rapidly dropped off below 90 °C, resulting in extended reaction time and product degradation. A suitable compromise was achieved by running the reaction at 95 °C since isothermal accelerating rate calorimetry (ARC) testing detected no significant thermal events over three days at 100 °C. The yield obtained under these conditions was lower (32% from **3**), but the safety risks were now better understood and manageable in general purpose equipment.[7] The preparation of indole **5** was then outsourced to provide 17.5 kg in 17% yield over four steps from **2**.

With indole **5** now in hand we turned our attention to the sequence of steps to convert it through to **8**. The sodium borohydride reduction of **6** had not performed well on scale due to poor chemoselectivity and the generation of a significant impurity thought to be conjugate addition of the product onto the starting material. In addition to this, it was known that the reaction of **5** with DMANE had some process safety concerns which needed careful management and control.[8] We therefore sought an inherently safer route which would convert indole **5** to **8**, avoiding DMANE and the subsequent reduction steps.

High-throughput screening of a variety of two-carbon electrophiles[9] under both Lewis and Brønsted acid catalysis revealed that the 3-position of this indole was surprisingly unreactive. Even preformation of the indolyl magnesium salt did not improve the reactivity. The only promising hit came

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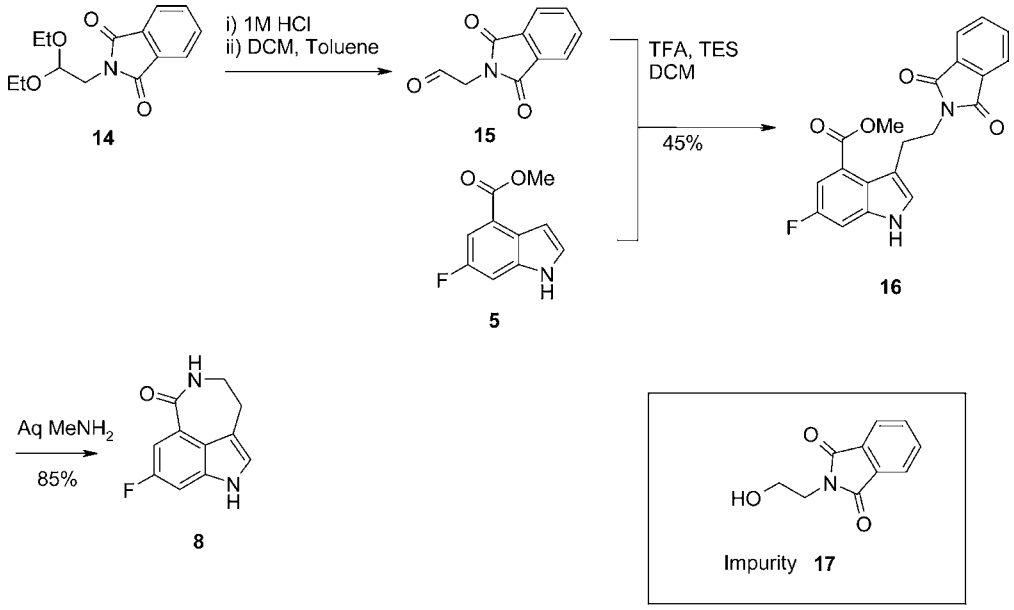
Scheme 3. Alternative reductive alkylation route to azepine 8



with reductive alkylation[10] of phthalimidoacetaldehyde diethyl acetal (**14**) using triethylsilane (TES) and TFA to give **16**; however, this reaction only gave a meager 26% yield after four days with the remainder of the mass balance comprising various adducts arising from reaction of the starting material or product with the intermediate benzylic cation (up to 15%). In order to increase the reaction rate we investigated the use of the deprotected aldehyde **15**.[11] This did indeed speed up the reaction to give complete conversion in 4 h; however, a significant level of alcohol **17** (14% by HPLC) was observed due to direct reduction of the aldehyde, as well as multiple other byproducts (Scheme 3). While the desired product **16** only constituted 40% of the mixture, fortunately **16** crystallized from the reaction mixture with excellent purity, purging all of the byproducts. Although the yield was still relatively low (typically 35−38% isolated yield), given the high quality of the material obtained and the lack of a suitable alternative, this process was selected for scale up. Our main concern was whether the product distribution (and hence the yield) would remain the same at larger scale.

We conducted a series of experiments investigating the order of addition of the various reagents to give an insight into factors affecting impurity formation. Initially we thought that a controlled addition of the triethylsilane (TES) might limit reduction of aldehyde **15** since it would not be present in excess; however, new impurities were formed when the indole **5** was stirred with TFA. Dosing **5** into the reaction mixture resulted in very high levels of aldehyde reduction. The best process involved adding TFA to a solution of the indole **5**, TES, and aldehyde **15**. Increasing the quantity of TFA resulted in an increased level of one of the byproducts, so we decided to add the TFA as a DCM solution to avoid high local concentration upon dosing. It was also noted that cooling the suspension prior to filtration resulted in poor quality product due to incorporation of impurities. This process was successfully run in the pilot plant using 15.7 kg of **5** and delivered 12.9 kg of product **16** in 43% yield as expected. The subsequent deprotection of the phthalimide group was carried out in aqueous methylamine and was scaled up uneventfully to give **8** in 82% yield. The bromination of **8** proceeded with excellent chemical yield, so we turned our attention to the subsequent Suzuki coupling reaction.

$Pd(PPh_3)_4$ is often a capricious catalyst[12] due to its air-sensitivity, and the Suzuki coupling of **9** and **10** had often failed to reach completion using this catalyst. We desired a more robust and active catalyst, and $Pd(dppf)Cl_2$.DCM was identified from a high-throughput screen. This catalyst consistently gave complete reaction in 2 h at 90 °C, compared to variable completion after 18 h at 90 °C for $Pd(PPh_3)_4$.

However, when we ran a use-test of the reagents intended for use in the pilot-plant campaign, no reaction was observed after heating overnight. Repeating the reaction with other batches of substrate **9**/base/boronic acid **10**/catalyst that were known to work from lab trials showed that both the catalyst and the boronic acid **10** intended for use in the pilot plant did not perform well in the reaction; the boronic acid gave only 28% conversion after heating overnight, and the catalyst proved unreactive. Since the catalyst is readily available, we sourced an alternative batch which did work in the use-test. The boronic acid **10** was more problematic as we were limited by supply of this material. A thorough suite of analytical tests (including ^{11}B NMR, residual pH, and sulfated ash) were carried out on the boronic acid **10** in an effort to identify why the reaction was proceeding poorly; however, these tests did not show any differences between this batch of boronic acid and other batches which worked well in the coupling (note that all batches were from a single supplier). Some key experiments suggested that the boronic acid **10** contained a low level of a stoichiometric poison, and that once this had been consumed, a standard reaction profile could be achieved. For example, charging 10 mol % of catalyst instead of the standard 2.5 mol % pushed the reaction to completion in 3 h. Similarly, using a 50:50 mix of 'good' and 'bad' boronic acid gave complete reaction after heating overnight with the same batch of catalyst at 2.5 mol % loading. We therefore decided to see if we could devise a process which would be able to cope with any batch of boronic acid used.

No debromination and no protodeboronation[13] was observed; thus, we hypothesized that deactivation of the catalyst was occurring prior to oxidative insertion. This is

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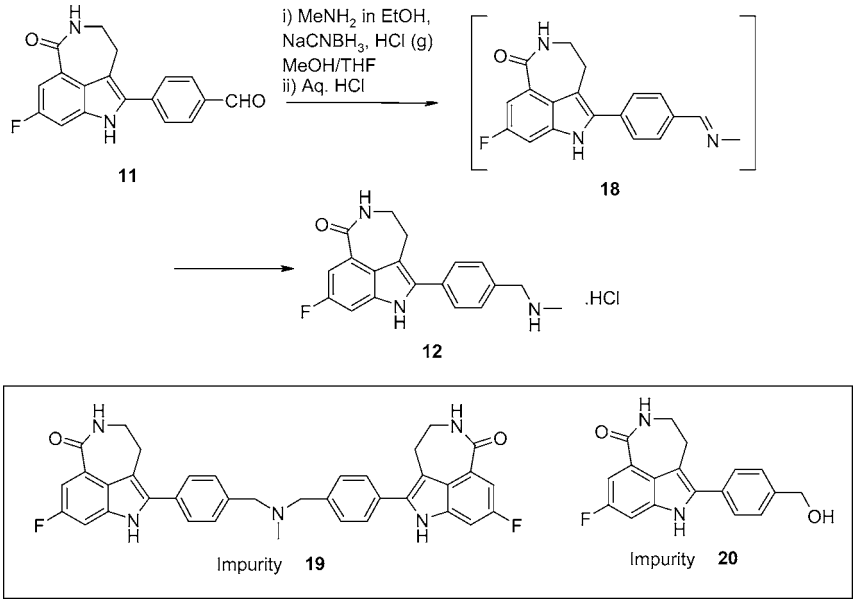
Scheme 4. Reductive amination of 11 and associated impurities



probably not surprising given that all of the reagents are added together and then the reaction is heated to 90 °C. Our aim was to ensure that the catalyst was activated (i.e., converted from Pd^{II} to Pd^{0}) and oxidative insertion had been initiated by the time boronic acid **10** was to be added. Additionally, dosing of **10** should limit the amount of poison that is present in the initial stages of the reaction, allowing the boronic acid to react as it is added, thereby ensuring completion of the reaction prior to catalyst deactivation. The addition mode was therefore changed so that the catalyst and aryl bromide **9** were heated to 90 °C in dimethyl acetamide (DMAc) and held at this temperature for 1 h. In a separate vessel the boronic acid **10** and base were dissolved in a mixture of water and DMAc, and this solution was stirred for 30 min under nitrogen. This was then added to the reaction. Running the reaction in this way gave complete conversion 2 h after the addition of the boronic acid **10** was complete.

We also carried out an experiment to evaluate the stability of the boronic acid and base solution and actually found that the reaction worked better if this solution was stirred at room temperature for 2 h prior to addition. Conversely, using the boronic acid solution immediately after preparation resulted in incomplete reaction. This may be deactivation of the catalyst poison during this time or hydrolysis of boroxines/anhydrides to the more active monomeric[14] or boronate species;[15] however, we did not examine this any further. To summarise, the Suzuki coupling now consistently goes to completion if the substrate **9** and catalyst are preheated to 90 °C and the boronic acid **10** is dosed in after prestirring for 2 h with aqueous base. This reaction was then scaled up in the pilot plant on 7.3 kg scale and was complete in 2 h, giving an excellent 92% yield of aldehyde **11**.

The initial development work on the reductive amination of **11** with sodium cyanoborohydride had shown that a low reaction pH was required to stop addition of the product **12** into the intermediate imine **18**, resulting in impurity **19** (Scheme 4). However, at low pH, HCN was produced as a side product. On smaller scale this was manageable, but we were required to change the conditions for this campaign since scrubbing of HCN from hydrogen-venting vessels is difficult on pilot-plant scale.

Gratifyingly, we found that sodium borohydride could be used as a direct replacement for sodium cyanoborohydride if the HCl is omitted.[16] Although this was a promising hit, we did observe higher levels of alcohol **20** (from reduction of the aldehyde **11**) at larger lab scales. Since this presented a robustness risk and **20** would constitute a new unqualified impurity if still present in the API, this was unacceptable. Further work showed that the intermediate imine **18** is insoluble in methanol and can be isolated in very good yield after removal of THF, thus purging any residual aldehyde **11**. The clean imine **18** can then be redissolved in methanol and THF and reduced with sodium borohydride as before to give the hydrochloride salt **12**. In the previous campaign the aqueous solution of this HCl salt was treated with activated carbon to reduce the palladium to acceptable levels (<20 ppm), so this was incorporated into later experiments when we were assessing the quality of **12** produced by this new route.

Due to a lack of material, development work for the new (*S*)-camphorsulfonate salt **21** was carried out on **1** that had been obtained from neutralization of the phosphate salt **13** prepared in the first GMP campaign. It was acknowledged that this material would have a different impurity profile compared to that of **1** prepared via the new route, but this was unavoidable at this stage of development. From a combination of high-throughput screening and small-scale lab experiments, a process was developed wherein an isopropanol (IPA) solution of (*S*)-camphorsulfonic acid was added to a solution of free base **1** in IPA. Cooling and addition of water then resulted in crystallization of **21** with the desired purity and properties for tablet formulation. When we switched our source of **1** to the free base derived from the new route, the solution turned brown upon addition of (*S*)-camphorsulfonic acid, and the salt **21** was very reluctant to crystallize and was obtained in very low yield. An extensive set of troubleshooting experiments identified the cause: samples of **1** that had not been carbon treated during the reductive amination performed very poorly in the crystallization, whereas samples which had been carbon treated gave (*S*)-CSA salt **21** of the desired purity. Fortunately,

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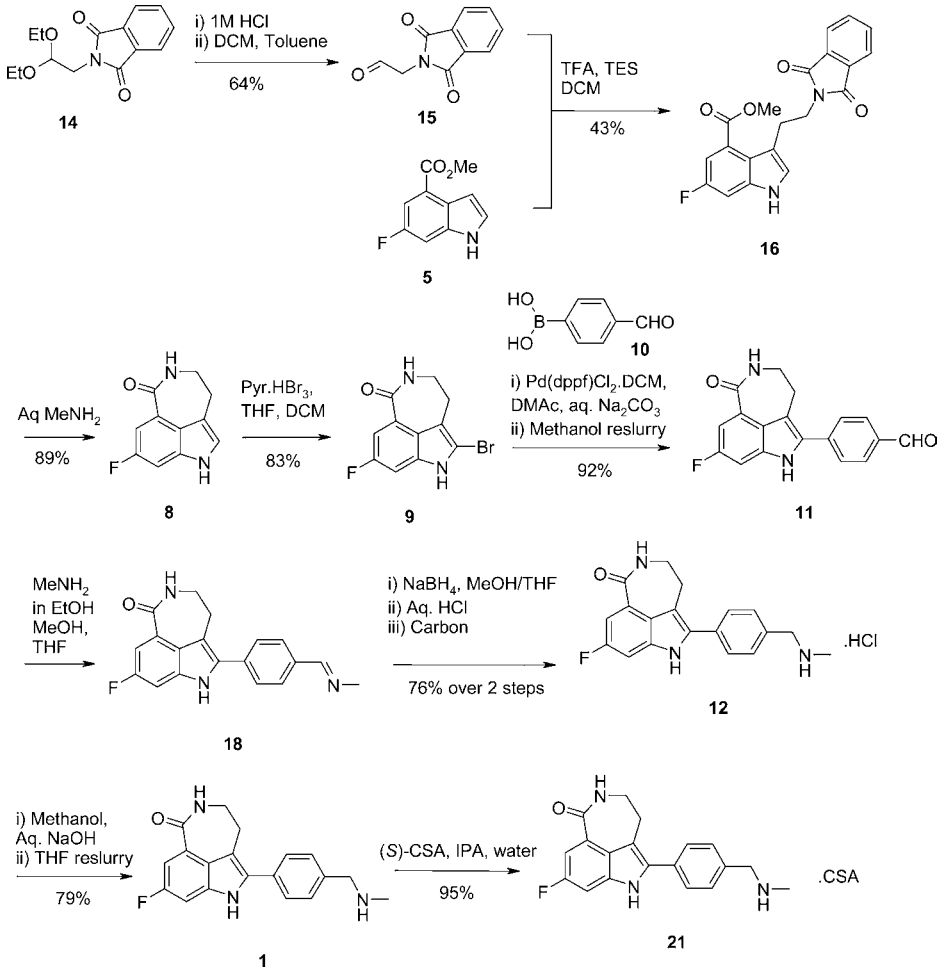
Scheme 5. Modified reductive alkylation route to 21



this was discovered shortly before a planned large lab-scale run to demonstrate the conditions for transfer to the pilot plant. We therefore ensured that the workup incorporated the activated carbon treatment, although a suite of analytical tests did not reveal the nature of the impurity or impurities that were causing the inhibition of the crystallisation in this step. When used on pilot-plant scale this afforded 6.4 kg of product **12** (76% yield; 12 ppm Pd) which performed well in the salt formation. The remaining steps were carried out uneventfully in the pilot plant to deliver 7.1 kg of **21** in 75% yield from Suzuki product **11**.

The final modified synthetic route is shown in Scheme 5.

In conclusion, we have developed an improved, robust process for the synthesis of **21**, a novel PARP inhibitor, and demonstrated the scalability of the route through the manufacture of 7.1 kg of API. Key highlights include thorough understanding of the thermal hazards of the Leimgruber–Batcho indole synthesis, installation of the side chain through a reductive alkylation procedure, improvements in the robustness of the Suzuki coupling, removal of hydrogen cyanide generation during the reductive amination, and reliable generation of good-quality free base for the final salt formation step. The overall yield for the route has been improved from 1.3% to 2.9%.

EXPERIMENTAL SECTION

General. ^{1}H NMR spectra were recorded on a Varian 400 MHz spectrometer or Jeol ECS 400 MHz spectrometer. ^{13}C NMR spectra were recorded on a Jeol ECS spectrometer at 100.5 MHz. Melting points were measured on a Büchi B540 melting point apparatus. Combustion analyses were performed by Warwick Analytical Service, University of Warwick Science Park, The Venture Centre, Sir William Lyons Road, Coventry CV4 7EZ, U.K.

*5-Fluoro-2-methyl-3-nitrobenzoic Acid Methyl Ester (**3**).* To conc. sulfuric acid (349.6 L, 7.6 L/kg) was added 5-fluoro-2-methylbenzoic acid (46.0 kg, 298.4 mol), and the solution was cooled to 0−5 °C. Concentrated nitric acid (70% w/w aqueous solution, 23.18 L, 0.50 L/kg, 1.26 equiv) was added, maintaining the reaction temperature below 40 °C (**CAUTION: HIGHLY EXOTHERMIC!**). The reaction was stirred at 0−5 °C for 30 min before cautiously adding it into water (920 L, 20 L/kg) that had been cooled to 0−5 °C, maintaining the temperature below 30 °C. The reaction mixture was then extracted with methyl *tert*-butylether (MTBE) (2 × 460 L, 10 L/kg) at 30 °C, and the combined organic layers were washed with water (3 × 460 L, 10 L/kg). The organic layer was then dried over anhydrous sodium sulfate (11.5 kg, 0.25 kg/kg) and filtered, washing the filter cake with MTBE (2.5 L/kg, 115 L). The combined filtrate and washings (555 L) were concentrated by distillation under vacuum at 35−40 °C to remove 310 L of solvent. This concentrate was taken directly into the next stage.

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To methanol (230 L, 5 L/kg) was added the concentrated MTBE solution from the previous step (note: quantities based on input of 5-fluoro-2-methylbenzoic acid). Concentrated sulfuric acid (14.72 L, 0.32 L/kg) was added slowly, maintaining the temperature below 40 °C. The reaction mixture was then heated to 65 °C for 24 h. The reaction was cooled to 40−45 °C, and methanol (110 L, 2.5 L/kg) was removed by distillation under vacuum. The reaction was cooled to 30−35 °C, and water (126.5 L, 2.75 L/kg) was added. The slurry was stirred at 30 °C for 30 min, and then the product was isolated by centrifuge. The filter cake was washed with water (2 × 96.6 L, 2.1 L/kg). The product was unloaded from the centrifuge and reslurried in methanol (105.8 L, 2.3 L/kg) at 50 °C for 20 min. Water (52.9 L, 1.19 L/kg) was added, the slurry was stirred for 1 h at 50 °C, and then the product was isolated by centrifuge. The reaction vessel was rinsed with methanol (23.9 L, 0.52 L/kg) at 0−5 °C, and this was used to wash the filter cake. The product was then dried under vacuum at 40 °C to give **3** as a brown solid (32.9 kg, 154.3 mol, 52% yield); mp (methanol) 69 °C; δ_H: (400 MHz, DMSO-d_6) 2.39 (s, 3H), 3.84 (s, 3H), 7.85 (dd, 1H, J = 2.9, 8.6 Hz), 8.06 (dd, 1H, J = 2.9, 8.6 Hz); δ_C (100 MHz, DMSO-d_6) 14.88, 52.86, 114.37 (d, J = 26.8 Hz), 120.37 (d, J = 23.0 Hz), 127.31, 134.76 (d, J = 7.4 Hz), 151.67 (d, J = 8.3 Hz), 158.93 (d, J = 247.9 Hz), 165.33 (d, J = 2.7 Hz).

*6-Fluoro-1H-indole-4-carboxylic Acid Methyl Ester (**5**).* To DMF (87.5 L, 3.5 L/kg) was added **3** (25.0 kg, 117.3 mol) and dimethylformamide dimethylacetal (80 L, 3.2 L/kg). Triethylamine (8.25 L, 0.33 L/kg) was then added, and the reaction was heated to 95−100 °C for 4 h (**CAUTION: STRICT TEMPERATURE CONTROL REQUIRED!**). The reaction mixture was cooled to 60 °C, and 125 L of solvent was removed by distillation under vacuum (**CAUTION: STRICT TEMPERATURE AND VOLUME CONTROL REQUIRED!**). The reaction mixture was then cooled to 25−30 °C and used directly in the next step without further isolation. Reagent quantities are based on 25 kg (117.3 mol) of **3**. To methanol (160 L, 6.3 L/kg) was added the solution of the enamine **4** in DMF (57.4 kg total weight), sodium acetate (9.65 kg, 117.3 mol, 1.0 equiv), and palladium on carbon (10% Pd on carbon, 50% wet Degussa E101 NE/W, 9.5 kg, 0.38 kg/kg). Hydrogen was then applied to the vessel, and the reaction was stirred at 30 °C for 4 h (**CAUTION: HIGHLY EXOTHERMIC**!). The reaction mixture was filtered through Hyflo filter aid to remove the catalyst, and the catalyst bed was washed with methanol (2 × 50 L, 2 L/kg). The solution was stripped to dryness under vacuum at 45 °C and dissolved in DCM (200 L, 8 L/kg) The DCM solution was then washed with water (5 × 125 L, 5 L/kg) and dried over sodium sulfate (17.5 kg, 0.7 kg/kg). The solid was removed by filtration and washed with DCM (2 × 50 L, 2 L/kg), and the washings were combined with the filtrate. The filtrate was then stripped to dryness under vacuum at 30−35 °C to give the crude product **5**. The crude product was then purified as follows. Crude **5** was redissolved in DCM (50 L, 2 L/kg) and purified by column chromatography using 50 kg of silica gel, eluting with DCM (337.5 L, 13.5 L/kg). The product was collected in 4−5 fractions of 62.5−70 L each. The fractions were combined, and silica gel (3.75 kg, 0.15 kg/kg) was added. After the mixture stirred for 30 min, the silica gel was removed by filtration, and the filter was washed with DCM (2 × 25 L, 1 L/kg). The solution was concentrated to 25 L (1 L/kg), and hexane (37.5 L, 1.5 L/kg) was added at 40 °C over 25 min. The solution was cooled to 30 °C and stirred for 3 h before collecting the solid by centrifuge and washing with hexane (2 × 25 L, 1 L/kg). The solid was then dried under vacuum at 45 °C to give **5** as a white crystalline solid (7.30 kg, 37.79 mol, 32% yield); mp (hexane) 119 °C; δ_H: (400 MHz, DMSO-d_6), 3.87 (s, 3H), 6.9 (dd, 1H, J = 0.8, 3.1 Hz), 7.43−7.49 (m, 2H), 7.51 (d, 1H, J = 3.1 Hz), 11.47 (s, br, 1H); δ_C:(100 MHz, DMSO-d_6) 51.85, 102.05, 102.78 (d, J = 25.8 Hz), 109.49 (d, J = 25.8 Hz), 120.79 (d, J = 9.2 Hz), 123.96, 128.49 (d, J = 3.3 Hz), 136.73 (d, J = 12.4 Hz), 157.33 (J = 234.4 Hz), 166.21 (J = 3.2 Hz); Anal. Calcd for $C_{10}H_8FNO_2$ requires: C 62.18; H 4.17; F 9.83; N 7.25. Found: C 62.08; H 4.21; F 9.85; N 7.27.

*Phthalimidoacetaldehyde (**15**).* **14** (45.0 kg, 170.9 mol) was added to aqueous hydrochloric acid (1 M, 200 L, 4.45 L/kg) and heated at 70−75 °C for 1 h. Water (225 L, 5 L/kg) was then added, and the reaction was cooled to 20 °C and stirred for 12 h. Dichloromethane (450 L, 10 L/kg) was added to the reaction, and the phases were separated. The aqueous layer was extracted with a further portion of dichloromethane (112.5 L, 2.5 L/kg), and the layers were separated. The dichloromethane layers were then combined. The solvent was removed by distillation and replaced with toluene to give a final solvent level of 5 L/kg, and the resulting slurry was stirred at 20 °C for 8 h. The product was filtered under pressure, washed with toluene (45 L, 1 L/kg), and dried under vacuum at 50 °C to give **15** as a white solid (20.2 kg, 107 mol, 62% yield); mp (toluene) 116 °C; δ_H: (400 MHz, DMSO-d_6) 4.59 (s, 2H), 7.83−7.90 (m, 4H), 9.56 (s, 1H); δ_C: (100 MHz, DMSO-d_6) 47.29, 123.27, 131.42, 134.67, 167.23, 196.68.

*3-Ethyl-(2-phthalimido)-6-fluoro-1H-indole-4-carboxylic Acid Methyl Ester (**16**).* To a solution of **15** (20 kg, 106 mol) and **5** (15.7 kg, 81.3 mol) in dichloromethane (157 L, 10 L/kg) was added triethylsilane (37.8 kg, 325.2 mol, 4 equiv). A solution of trifluoroacetic acid (18.5 kg, 12.2 L, 2 equiv) in dichloromethane (31.4 L, 2 L/kg) was then added over 30 min, maintaining the temperature below 30 °C. The reaction was then stirred for 28 h at 20 °C, and the resultant slurry was filtered under pressure. The filter cake was washed with dichloromethane (7.9 L, 0.5 L/kg) and then dried under vacuum at 40 °C to give **16** as a pale-yellow solid (12.9 kg, 3.51 mol, 43% yield); mp (dichloromethane) 216 °C; δ_H: (400 MHz, DMSO-d_6) 3.16 (t, 2 H, J = 6.96 Hz) 3.76 (t, 2 H, J = 6.96 Hz) 3.92 (s, 3 H) 7.27 (d, br, 1 H, J = 2.69 Hz) 7.29 (dd, 1 H, J = 10.26, 2.44 Hz,) 7.38 (dd, 1 H, J = 9.28, 2.44 Hz) 7.78−7.82 (m, 4 H) 11.27 (s, br, 1 H); δ_C: (100 MHz, DMSO-d_6) 26.14, 52.72, 102.31 (d, J = 24.9 Hz), 109.93 (d, J = 25.8 Hz), 112.05, 121.58, 123.44, 124.24 (d, J = 8.8 Hz), 127.96 (d, J = 3.2 Hz), 132.05, 134.81, 138.41 (d, J = 12.0 Hz), 157.5 (d, J = 235 Hz), 167.6 (d, J = 2.8 Hz), 168.19.

*8-Fluoro-1,3,4,5-tetrahydro-azepino[5,4,3-cd]indol-6-one (**8**).* **16** (12.9 kg, 35.1 mol) was added to methylamine (40% solution in water, 90 L, 7 L/kg), and the slurry was stirred at 20 °C for 16 h. Water (90 L, 7 L/kg) was charged to the reaction, and the mixture was stirred for 1 h. The solid was then filtered under pressure and washed with water (26 L, 2 L/kg). The solid was then reslurried in water (129 L, 10 L/kg), filtered, washed with water, and dried under vacuum at 70 °C to give the product (**8**) as a tan-brown solid (6.42 kg, 31.4 mol, 89% yield); mp (water) 187 °C; δ_H: (400 MHz, DMSO-d_6) 2.86−2.88 (m, 2H), 3.37 (q, 2H, J = 5.6 Hz), 7.22 (s, br, 1H), 7.30 (dd, 1H, J = 2.4, 9.3 Hz), 7.37 (dd, 1H, J = 2.4, 9.3 Hz), 8.11 (t, br, J = 5.6 Hz), 11.13 (s, br, 1H); δ_C: (100 MHz, DMSO-d_6) 27.91, 42.06, 100.82 (d, J = 25.8 Hz), 109.12 (d, J = 25.8 Hz),

114.40, 121.87, 123.72 (d, J = 3.3 Hz), 125.48 (d, J = 8.7 Hz), 136.71 (d, J = 12.4 Hz), 158.21 (d, J = 233.6 Hz), 168.39.

*2-Bromo-8-fluoro-1,3,4,5-tetrahydro-azepino[5,4,3-cd]-indol-6-one (**9**).* Dichloromethane (96.3 L, 15 L/kg) and THF (96.3 L, 15 L/kg) were mixed together, and **8** (6.42 kg, 31.4 mol) was added. After stirring for 20 min, the slurry was cooled to 0−5 °C. Pyridinium tribromide (11.0 kg, 34.5 mol, 1.1 equiv) was then added, and the solution was stirred at 0−5 °C for 1 h. Water (64.2 L, 10 L/kg) was then charged, and the organic solvents were removed by distillation to give a final volume of 15 L/kg. THF was added (64.2 L, 10 L/kg), and the reaction mixture was added slowly to a solution of saturated aqueous sodium carbonate (481.5 L, 75 L/kg). The resultant slurry was then stirred overnight at 20 °C. The product was filtered under pressure, washed with water (64.2 L, 10 L/kg), and dried under vacuum at 55 °C to give **9** as a beige solid (7.42 kg, 26.2 mol, 83% yield); mp (water) 215 °C dec; δ_H: (400 MHz, DMSO-d_6) 2.73−2.76 (m, 2H), 3.38 (q, 2H, J = 5.6 Hz), 7.25 (dd, 1H, J = 2.4, 9.0 Hz), 7.40 (dd, 1H, J = 2.4, 9.0 Hz), 8.18 (t, br, J = 5.6 Hz), 12.05 (s, br, 1H); δ_C: (100 MHz, DMSO-d_6) 27.70, 41.22, 100.49 (d, J = 26.2 Hz), 109.08 (d, J = 2.8 Hz), 109.85 (d, J = 25.3 Hz), 114.04, 121.78, 124.88 (d, J = 8.8 Hz), 136.53 (d, J = 12.5 Hz), 158.30 (d, J = 235.0 Hz), 167.87; Anal. Calcd for $C_{11}H_8BrFN_2O$: C 46.67; H 2.85; Br 28.22; F 6.71; N 9.90. Found: C 46.81; H 2.82; Br 28.00; F 6.64; N 9.82.

*4-(8-Fluoro-6-oxo-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indol-2-yl)-benzaldehyde (**11**).* 1,1′-Bis-(diphenylphosphino)ferrocene palladium(II) dichloride dichloromethane (0.539 kg, 0.66 mol, 2.5 mol %) was added to a mixture of degassed dimethylacetamide (119 L, 16 L/kg) and **9** (7.41 kg, 26.2 mol) and stirred for 1 h at 20 °C. The mixture was then heated to 95 °C and stirred for 1 h. In a separate vessel, 4-formylbenzene boronic acid (4.71 kg, 31.4 mol, 1.2 equiv) was dissolved in dimethylacetamide (30 L, 4 L/kg) before being added to an aqueous solution of sodium carbonate (5.6 kg in 89 L of water, 2 equiv) and was then stirred for 3 h at 20 °C. The boronic acid solution was then added to the catalyst and substrate solution whilst maintaining the temperature above 90 °C. After stirring for 2 h the reaction was cooled to room temperature and stirred for 4 h. Water (296 L, 40 L/kg) was added, and the slurry was stirred for 1 h before the solid was filtered under pressure and washed with water (74 L, 10 L/kg) to give crude **11**. The product **11** was further purified by resuspending in methanol (59 L, 8 L/kg) and stirring at 60 °C for 1 h. The slurry was cooled to 20 °C and stirred for 1 h. The product was then filtered, washed with methanol (15 L, 2 L/kg), and dried under vacuum to give **11** as an olive-green solid (7.44 kg, 24.1 mol, 92% yield); mp (methanol) 219 °C dec; δ_H: (400 MHz, DMSO-d_6) 3.10 (s, br, 2 H), 3.41 (s, br, 2 H), 7.37 (d, 1 H, J = 7.82 Hz) 7.46 (d, 1 H, J = 10.01 Hz), 7.86 (d, 2 H, J = 6.84 Hz), 8.05 (d, 2 H, J = 7.08 Hz), 8.28 (s, br, 1 H), 10.06 (s, br, 1 H) 11.88 (s, br, 1 H); δ_C: (100 MHz, DMSO-d_6) 28.89, 41.71, 100.75, (J = 25.8 Hz), 110.13 (J = 25.8 Hz), 114.23, 122.95, 126.55 (J = 8.3 Hz), 128.14, 129.83, 133.90, 134.75, 137.20, 158.88 (J = 235.9 Hz), 168.12, 192.49.

*8-Fluoro-2-(4-methylaminomethyl-phenyl)-1,3,4,5-tetrahydro-azepino[5,4,3-cd]indol-6-one Hydrochloride Salt (**12**).* To a mixture of methanol (313 L, 43 L/kg) and THF (153 L, 21 L/kg) was added **11** (7.30 kg, 23.7 mol). A solution of methylamine was then added (8 M in ethanol, 2.0 equiv, 4.44 kg), and the mixture was stirred for 2 h. The reaction mixture was then concentrated by distillation under atmospheric pressure to approximately 73 L, and the solvent was replaced with methanol to give a final solvent volume of 73 L (10 L/kg). The resultant slurry was cooled to 20 °C and stirred for 4 h. The solid was filtered under nitrogen pressure, washed with methanol (37 L, 5 L/kg), and dried under vacuum at 45 °C to give **18** as a solid (6.92 kg, 21.5 mol, 91% yield) which was used directly in the next stage. To a mixture of methanol (298 L, 43 L/kg) and THF (145 L, 21 L/kg) was added **18** (6.92 kg, 21.5 mol), and the slurry was cooled to 0−5 °C. Sodium borohydride (3.0 equiv, 2.44 kg, 64.59 mol) was then added, and the reaction mixture was stirred at 0−5 °C for 2 h. The reaction was warmed to 20 °C over 1 h and then added to a mixture of methanol (69 L, 10 L/kg), water (111 L, 16 L/kg), and conc. hydrochloric acid (27.7 L, 4 L/kg) over 1 h. Methanol (35 L, 5 L/kg) was then added as a line wash. Activated carbon (Norit SX plus, 3.46 kg, 0.5 kg/kg) was added to the reaction mixture as a slurry in methanol (45 L, 6.5 L/kg), and the slurry was stirred for 18 h. The mixture was filtered, and the filter cake was washed with water (28 L, 4 L/kg), THF (43 L, 6L/kg), and methanol (69 L, 10 L/kg). The filtrate was concentrated by vacuum distillation to a level of 130 L, and the resultant slurry was filtered. The filter cake was washed with water (28 L, 4 L/kg) and dried under vacuum at 50 °C to give **12** as an off-white solid (6.44 kg, 17.90 mol, 76% yield); mp (water) 293 °C; δ_H: (400 MHz, DMSO-d_6) 2.52 (t, br, 3H, J = 4.6 Hz), 3.0−3.02 (m, 2H), 3.34−3.36 (m, 2H), 4.12 (t, br, 2H, J = 5.0 Hz), 7.32 (dd, 1H, J = 2.4, 9.3 Hz), 7.40 (dd, 1H, J = 2.4, 11.0 Hz), 7.65 (s, 4H), 8.22 (t, br, J = 5.7 Hz), 9.37 (s, br, 1H), 11.83 (s, 1H); δ_C: (100 MHz, DMSO-d_6) 28.74, 31.94, 41.77, 50.80, 100.63 (d, J = 25.8 Hz), 109.67 (d, J = 25.8 Hz), 112.33, 123.03, 126.00 (d, J = 8.8 Hz), 127.90, 130.28, 131.32, 132.10, 134.59, 136.83 (d, J = 12.4 Hz), 158.48 (d, J = 234 Hz), 168.28.

*8-Fluoro-2-(4-methylaminomethyl-phenyl)-1,3,4,5-tetrahydro-azepino[5,4,3-cd]indol-6-one (**1**).* To a solution of aqueous sodium hydroxide (40% w/w, 3.6 kg, 2.0 equiv) in water (88 L, 14 L/kg) and methanol (35 L, 5.5 L/kg) was added **12** (6.44 kg, 17.90 mol). Water (90 L, 14 L/kg) was then added, and the slurry was stirred for 18 h at 20 °C. The solid was filtered, washed with water (2 × 32 L, 5 L/kg), and dried under vacuum at 50 °C to give **1** as an off-white solid (5.40 kg, 16.70 mol, 93% yield). The product (5.40 kg, 16.70 mol) was further purified by reslurrying in THF (54 L, 10 L/kg) and passing through a high-shear wet mill for 1.5 h. The slurry was then heated to 60 °C for 12 h. After the slurry was cooled to 20 °C, the product was filtered under pressure, washed with THF (16.2 L, 3 L/kg), and dried at 45 °C under vacuum to give **1** as a 1:1 THF solvate (5.57 kg, 14.08 mol, 84% yield); mp (THF) dec at 220 °C; δ_H: (400 MHz, DMSO-d_6) 2.25 (s, 3H), 2.99−3.01 (m 2H), 3.65 (s, 2H), 7.27 (dd, 1H, J = 2.4, 9.3 Hz), 7.39 (dd, 1H, J = 2.4, 9.3 Hz), 7.42 (d, 2H, J = 8.5 Hz), 7.53 (d, 2H, J = 8.3 Hz), 8.18 (t, br, 1H, J = 5.7 Hz), 11.60 (s, 1H); δ_C: (100 MHz, DMSO-d_6) 28.74, 35.58, 41.84, 54.74, 100.47 (d, J = 25.8 Hz), 109.44 (d, J = 25.8 Hz), 111.47, 123.19, 125.72 (d, J = 8.8 Hz), 127.55, 128.20, 129.86, 135.38 (d, J = 3.7 Hz), 136.67 (d, J = 12.4 Hz), 140.52, 158.31 (d, J = 233), 168.39.

*8-Fluoro-2-(4-methylaminomethyl-phenyl)-1,3,4,5-tetrahydro-azepino[5,4,3-cd]indol-6-one (S)-camphorsulfonate Salt (**21**).* To a slurry of **1** (5.32 kg, 13.48 mol) in isopropanol (30 L, 5.5 L/kg) and water (39 L, 7.3 L/kg) was added a solution of (*S*)-camphorsulfonic acid (3.75 kg, 16.18 mol, 1.2 equiv) in water (10.6 L, 2 L/kg). The resultant slurry was then heated to 70 °C and held for 1 h to ensure dissolution. The

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solution was filtered to remove particulates, and then a line wash of water (3.7 L, 0.7 L/kg) and isopropanol (2.1 L, 0.4 L/kg) was added. The solution was cooled to 40 °C, seeded with **21** (0.266 kg, 0.05 equiv), and then held at 40 °C for 8 h. The slurry was then cooled to 20 °C, water was added (4 × 13.3 L, 10 L/kg total), and the slurry was cooled further to 0−5 °C and stirred for 12 h. The product was filtered under pressure, washed with water (10.6 L, 2 L/kg), and dried under vacuum at 50 °C to give **21** as a white crystalline solid (7.09 kg, 12.76 mol, 95% yield); mp (IPA/water) 303 °C; δ_H: (400 MHz, DMSO-d_6) 0.74 (s, 3H), 1.05 (s, 3H), 1.28 (m, 1H), 1.80 (d, 1H, J = 18.0 Hz), 1.81−1.88 (m, 1H), 1.93 (app t, 1H, J = 4.5 Hz), 2.24 (m, 1H), 2.41 (d, 1H, J = 14.6 Hz), 2.62 (s, 3H), 2.66−2.72 (m, 1H), 2.91 (d, 1H, J = 14.7 Hz), 3.04−3.07 (m, br, 2H), 3.36−3.45 (m, br, 2H), 4.20 (s, 2H), 7.37 (dd, 1H, J = 2.4, 9.3 Hz), 7.44 (dd, 1H, J = 2.4, 11.0 Hz), 7.63 (d, 2H, J = 8.3 Hz), 7.71 (d, 2H, J = 8.3 Hz), 8.26 (t, br, 1H, J = 5.5 Hz), 11.76 (s, 1H); δ_C: (100 MHz, DMSO-d_6) 19.51, 20.02, 24.14, 26.37, 28.74, 32.28, 41.77, 42.13, 42.22, 46.71, 47.00, 51.06, 58.21, 100.65 (d, J = 25.8 Hz), 109.72 (d, J = 25.8 Hz), 112.41, 123.03, 126.04 (d, J = 8.7 Hz), 127.98, 130.19, 131.22, 132.22, 134.50, 136.83 (d, J = 12.0 Hz), 158.52 (d, J = 235 Hz), 168.27, 216.24.

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Notes

The authors declare no competing financial interest.

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(7) Further safety evaluation of this process is advised prior to further scale-up.

(8) Differential scanning calorimety (DSC) carried out on DMANE detected an exotherm from 240 °C with ΔH = −2.8 kJ/g. Thermal stability unit (TSU) testing showed that a mixture of trifluoroacetic acid and DMANE in DCM underwent an exothermic runaway from 50 °C with the temperature rising to 220 °C within 2 min. The pressure also increased from 1 to 60 bar in under 30 s. DSC tests were carried out in 40 μL gold HP test cells and heated at 5 K/min from 25 to 400 °C. TSU tests were carried out in glass test cells and heated at 2 K/min from 25 to 250 °C.

(9) Electrophiles included 2-aminoacetaldehyde dimethylacetal, 2-aminoethylchloride hydrochloride, 2-aminoethylhydrogensulfate, *N*-Boc-2-aminoethyl bromide, 2-chloroethyl tosylate, and 2-phthalimidoethyl bromide

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(11) The aldehyde could be easily prepared by deprotection of the commercially available diethyl acetal with aqueous hydrochloric acid. Some care was required in isolating the aldehyde, however, as it appeared to undergo facile dimerisation/trimerisation to give a very insoluble solid. This mixture could be converted back to the monomer by heating in toluene at 80 °C for 3 h.

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