Organic Process Research & Development **2010**, *14*, 895–901

Identification of a Manufacturing Route of Novel CRF-1 Antagonists Containing a 2,3-Dihydro-1*H*-pyrrolo[2,3-*b*]pyridine Moiety

Arianna Ribecai,*[,†] Sergio Bacchi,[†] Monica Delpogetto,[†] Simone Guelfi,[†] Angelo Maria Manzo,[†] Alcide Perboni,[†] Paolo Stabile,[†] Pieter Westerduin,[†] Marie Hourdin,[†] Sara Rossi,[†] Stefano Provera,[‡] and Lucilla Turco[‡]

Chemical Development Department and Analytical Chemistry Department, GlaxoSmithKline Medicines Research Centre, Via Fleming 4, 37135 Verona, Italy

Abstract:

A case study on the synthesis of novel CRF-1 antagonists containing the 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine moiety is presented. The development of ever more efficient synthetic routes allowed the progression of three candidates at the same time. A manufacturing route was identified and successfully demonstrated on a pilot-plant scale to prepare 100 kg of the CRF-1 antagonist GW876008.

Introduction

Corticotropin releasing factor (CRF) is a 41-amino acid peptide that plays a central role in mediating the behavioural, neuroendocrine, and autonomic responses to stress.[1] CRF is synthesized in the hypothalamus and liberated into the hypophyseal-portal system, triggering the release of adrenocorticotrophic hormone (ACTH) from the pituitary gland. ACTH, in turn, induces the synthesis and the release of glucocorticoids from the adrenal cortex. In mammals, exposure to stress increases the release of CRF in both hypothalamic and extrahypothalamic brain areas and produces the same effects observed with exogenous administration of CRF, i.e., increase of ACTH and cortisol (human) or corticosterone (rodent) blood levels, enhanced autonomic nervous system activity and anxiety-like behaviour. CRF is responsible, at least in part, for the hypothalamic pituitary adrenal (HPA) axis hyperactivity characteristic of patients with major depression.[2] Several lines of clinical evidence suggest the association between the hyperdrive of CRF and the onset of anxiety and depressive disorders. As a consequence, several pharmaceutical research groups have made significant investments over the past two decades in discovering nonpeptide CRF-1 receptor antagonists as a potential treatment for stress-related illnesses, including anxiety and depression.

As a part of a broad strategy aimed at the discovery of novel CRF-1 antagonists, scientists at GlaxoSmithKline designed and explored the 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine template and identified compounds **1a**−**c** (Figure 1) as the most interesting derivatives belonging to this new series.[3]

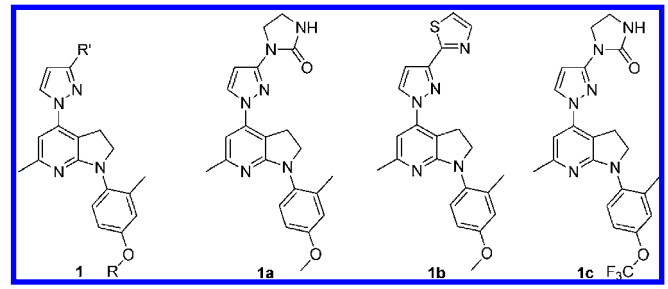


Figure 1. **Exploration of the 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine template.**

Results and Discussion

Initial Supply Routes to CRF-1 Candidates 1a−c. The Medicinal Chemistry retrosynthetic approach used for the synthesis of the initial toxicological batches is depicted in Scheme 1.[3b]

Notably, being a convergent synthesis in the last chemical step, the same chemistry could be applied to prepare all the chosen compounds of general formula **1**, thus allowing the progression of three candidates, **1a**−**c**, at the same time. The synthetic route applied by Medicinal Chemistry is described in Scheme 2.

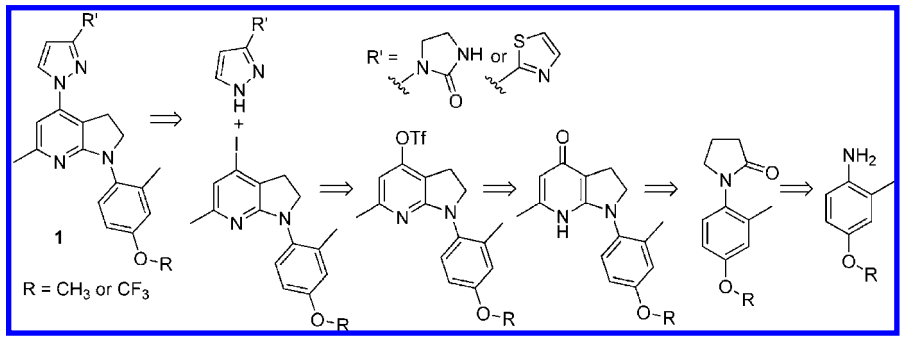
As described in Scheme 2, commercially available anilines **2** were transformed into the corresponding amides **3** by reaction with 4-chlorobutyryl chloride in the presence of K_2HPO_4. These compounds were treated with sodium hydride in DMF at 0 °C to afford the γ-lactam derivatives **4** after chromatographic purification. The reaction of **4** with $POCl_3$ and ethyl 3-aminocrotonate in dry dichloroethane enabled the preparation of crude compounds **5**, which were then dissolved in DMF and heated to 100 °C in the presence of sodium hydride to induce the cyclization. The bicyclic derivatives **6** were obtained after filtration of the crude reaction residue on silica gel, although in limited chemical yield of 10−15%. The resulting intermediates

* To whom correspondence should be addressed. Telephone: 00-390458219360. Fax: 00-390458218117. E-mail: arianna.ribecai@gsk.com.
† Chemical Development Department.
‡ Analytical Chemistry Department.

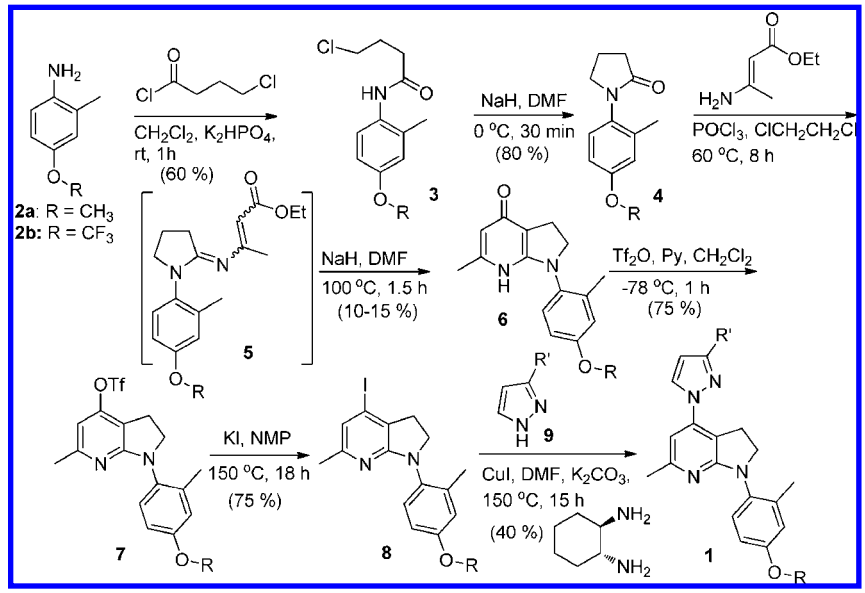
(1) Vale, W.; Spiess, J.; Rivier, C.; Rivier, J. *Science* **1981**, *213*, 1394–1397.
(2) Owen, M. J.; Nemeroff, C. B. *Pharmacol. Res.* **1991**, *43*, 425–473.
(3) (a) Di Fabio, R.; Arban, R.; Bernasconi, G.; Braggio, S.; Blaney, F. E.; Capelli, A. M.; Castiglioni, E.; Donati, D.; Fazzolari, E.; Ratti, E.; Feriani, A.; Contini, S.; Gentile, G.; Ghirlanda, D.; Sabbatini, F. M.; Andreotti, D.; Spada, S.; Marchioro, C.; Worby, A.; St-Denis, Y. *J. Med. Chem.* **2008**, *51*, 7273–7286. (b) Di Fabio, R.; St.-Denis, Y.; Sabbatini, F. M.; Andreotti, D.; Arban, R.; Bernasconi, G.; Braggio, S.; Blaney, F. E.; Capelli, A. M.; Castiglioni, E.; Di Modugno, E.; Donati, D.; Fazzolari, E.; Ratti, E.; Feriani, A.; Contini, S.; Gentile, G.; Ghirlanda, D.; Provera, S.; Marchioro, C.; Roberts, K. L.; Mingardi, A.; Mattioli, M.; Nalin, A.; Pavone, F.; Spada, S.; Trist, D. G.; Worby, A. *J. Med. Chem.* **2008**, *51*, 7370–7379.

10.1021/op100147h
Published on Web 06/28/2010

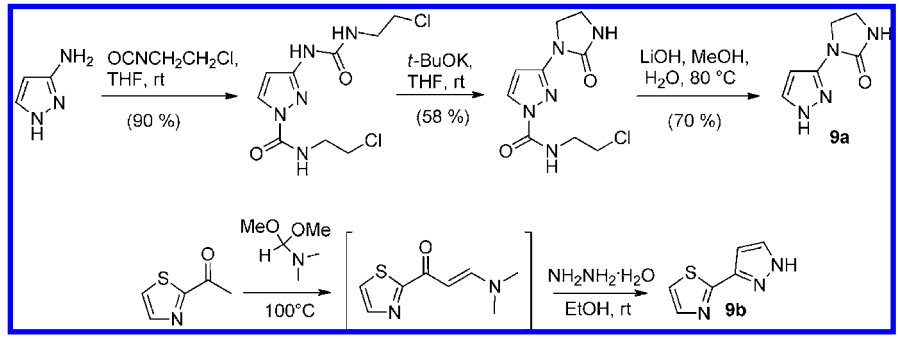
Scheme 1. **Medicinal Chemistry retrosynthetic analysis**



Scheme 2. **Medicinal Chemistry route**



Scheme 3. **Outsourced syntheses of 1*H*-pyrazolyl derivatives 9**



6 were transformed with good yields into the triflate derivatives **7**, which after treatment with potassium iodide in NMP at 150 °C for 18 h afforded the corresponding iodide intermediates **8**. The latter were finally coupled with the substituted pyrazole derivatives **9** under Buchwald conditions[4] to give title compounds **1a**−**c** with very low overall yields of 1−2%. The required compounds **9**, 1-(1*H*-pyrazol-3-yl)imidazolidin-2-one, **9a**, and 2-(1*H*-pyrazol-3-yl)thiazole, **9b**, were purchased from external suppliers and prepared according to the processes depicted in Scheme 3.[5,6]

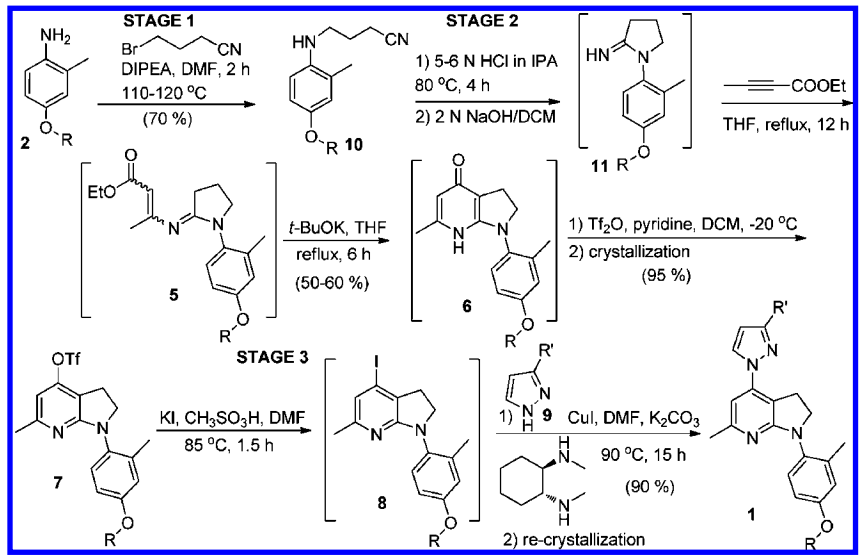
The synthetic route described previously in Scheme 2 was clearly unsuitable to produce multikilogram batches. In fact, it involved very low-yielding steps, made use of a low-temperature triflation process, and employed a large excess of toxic $POCl_3$. Moreover, the large number of impurities generated along the route were difficult to remove even by chromatography (e.g., ethyl 3-aminocrotonate self-condensation product), thus making

(4) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729. (b) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578–5587. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449.

(5) Bacchi, S.; Delpogetto, M.; Guelfi, S.; Perboni, A.; Ribecai, A.; Stabile, P.; Tampieri, M. PCT Int. Appl. WO/2006/108693, 2006.

(6) Andreotti, D.; Bacchi, S.; Delpogetto, M.; Guelfi, S.; Perboni, A.; Ribecai, A.; Spada, S.; Stabile, P.; Tampieri, M. PCT Int. Appl. WO/2006/108689, 2006.

Scheme 4. **Route A to prepare CRF-1 candidates 1a−c**



the cyclisation to the bicyclic pyridones **6** extremely unclean and problematic to perform without using NaH in DMF. In addition, it is known that the combination of NaH and DMF is intrinsically unsafe, behaving as a self-accelerating exothermic reaction.[7] The pyridone derivatives **6** looked attractive as key intermediates to focus on during the development of a new route, and after considerable effort, a completely novel approach to **6** was put in place, as depicted in Scheme 4.

According to the new process (route A), anilines **2** were *N*-alkylated under basic conditions by 4-bromobutyronitrile to generate compounds **10**. The subsequent acid-promoted cyclization in isopropanol provided pyrrolidin-2-imines **11**,[8] which, after a basic wash with a 2 N NaOH solution, were used as crude in the following step. Intermediates **5** were prepared *via* a Michael addition of compounds **11** to 1.1 equiv of ethyl-2-butynoate in refluxing tetrahydrofuran. This successful strategy enabled us to achieve a much cleaner profile for the amidines **5**. Potassium *t*-butoxide (2 equiv) in THF at reflux suitably replaced NaH in DMF for the cyclisation step to form intermediates **6**, which were not isolated but directly subjected to the triflation step. Moreover, the triflate derivatives **7** were isolated by precipitation from an isopropanol/water mixture, significantly improving the quality of the material obtained. Noteworthy improvements were introduced also in other steps of the process. In particular, the iodo-derivatives **8** were obtained under much milder conditions which involved the addition of 1.2 equiv of methanesulfonic acid to activate the triflate displacement by potassium iodide (2 equiv), which occurred at 85 °C in 1.5 h.[9] Also the C−N coupling was optimized considerably, thereby increasing the yield and guaranteeing better-quality final drug substances (DS). In fact, with this being the last chemical transformation, we were committed to finding out more efficient conditions, to identifying the typical impurities, and to gaining understanding of their formation mechanisms. The main issue of the Medicinal Chemistry conditions, apart from the obvious low yield, was the high level of impurities generated by the presence of multiple nitrogen atoms in the pyrazolyl compounds **9**, which can react with the iodides **8** under copper catalysis (Figure 2).[10]

In order to address this issue, we followed two strategies: (*i*) identification of intermediates different from the iodides **8**, such as the corresponding bromo derivatives, less reactive and thus potentially more selective in the C−N coupling; (*ii*) a systematic screening of catalysts/ligands/bases and solvents in the coupling involving the iodides **8**. Notably, triflates **7** were also tested under the aforementioned conditions but proved not stable and gave quantitative hydrolysis to **6**. As for the first approach, bromo derivatives were indeed more selective in the copper-catalysed reaction, generating lower amounts of compounds **12**, **13**, and **14**. However, the required higher temperatures (130−135 °C) and longer reaction times (38−43 h) produced higher levels of aromatized compounds **15**. Furthermore, the reaction became sluggish when scaling up from the laboratory to kilo-lab scale and a certain percentage of the bromides remained unreacted. The second approach proved more successful, and after an extensive screening and considerable process optimization work, we came up with the efficient conditions depicted in Scheme 4. In the optimized procedure, the catalytic system was preformed by mixing 2 mol % of CuI

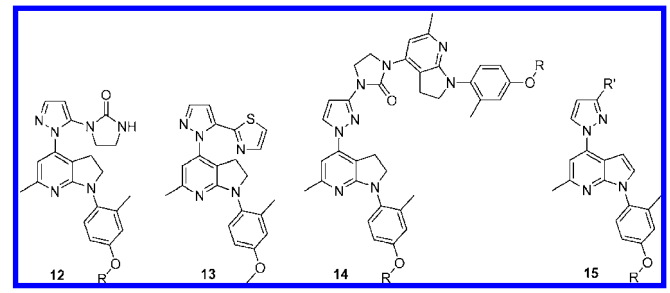
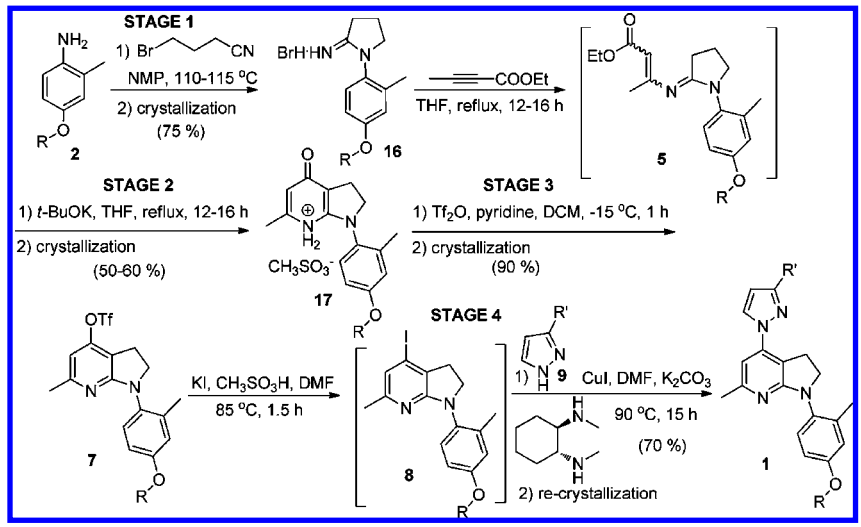


Figure 2. **Main impurities observed in the DS batches produced by route A.**

(7) (a) DeWall, G. *Chem. Eng. News* **1982**, *60*, 5–43. (b) Hesek, D.; Lee, M.; Noll, B. C.; Fisher, J. F.; Mobashery, S. *J. Org. Chem.* **2009**, *74*, 2567–2570.
(8) Kwok, R.; Pranc, P. *J. Org. Chem.* **1967**, *32*, 738–740.
(9) Whitfield, H. J.; Griffin, R. J.; Hardcastle, I. R.; Henderson, A.; Meneyrol, J.; Mesguiche, V.; Sayle, K. L.; Golding, B. T. *Chem. Commun.* **2003**, 2802–2803.
(10) (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428. (b) Stabile, P.; Lamonica, A.; Ribecai, A.; Castoldi, D.; Guercio, G.; Curcuruto, O. *Tetrahedron Lett.* **2010**, *51*, 3232–3235.

Scheme 5. **Route B to prepare CRF-1 candidates 1a−c**



and 0.3 equiv of the ligand (1*R*,2*R*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine in DMF. When a clear solution was obtained, 3 equiv of K_2CO_3 and 2.5 equiv of pyrazolyl derivatives **9** were added, followed by iodides **8**. After 15 h at 90 °C, the final products were precipitated directly from the reaction mixture. Unfortunately, a crystallization step was not sufficient to guarantee a DS of the quality needed for the clinical studies. In fact, the quality umbrella on a clinical batch is not only tight on the impurity control but also on the heavy metal contents which must remain below specific levels.[11] Since we were using copper iodide in the last chemical transformation, we had to develop a suitable treatment to ensure specifications were met. A recrystallisation step was put in place which included dissolution of the DS in a suitable solvent, filtration through CUNO ZetaCarbon cartridge to retain copper and, finally, precipitation by antisolvent addition. By applying those conditions, the measured copper contents were constantly kept below 1 ppm level.

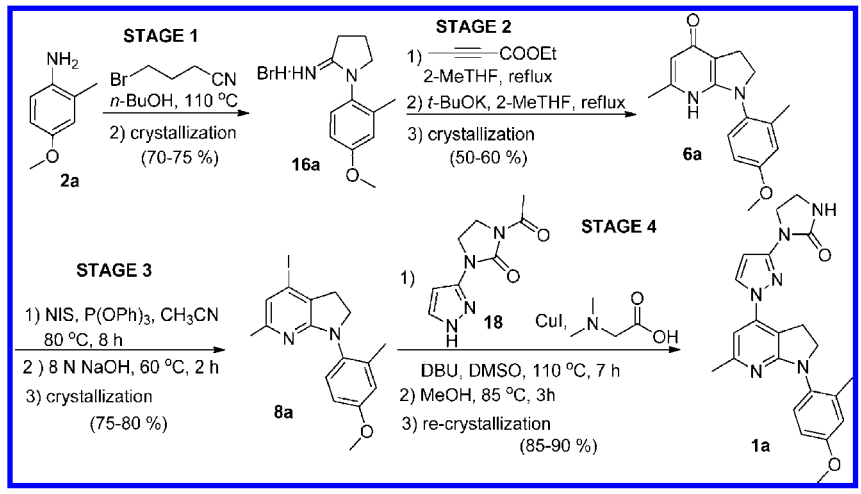
Development of a Robust Supply Route to CRF-1 Candidates 1a−c. The new route A allowed the successful production of the first kilogram-batches of drug substances **1a** and **1b** to support phase I toxicological studies and clinical studies. However, less brilliant results were obtained for compound **1c**. In fact, the presence of a $-CF_3$ group in place of $-CH_3$ substantially influenced the physical properties of butyronitrile **10b**, which was oil and not solid, accessible as a pure material in low yield only after a challenging chromatographic purification. Since the first part of the synthesis of **1c** did not have any isolated intermediate, we made significant efforts to develop an alternative, more robust, and scalable route. As a first option, we thought about introducing a solid version of key intermediates **6** by screening suitable salts. A screening of acids and solvents was run to identify the mesylate in 2-butanone as the best combination of counterion/solvent. Furthermore, a quick win was the observation that, if stage 1 and the first step of stage 2 were telescoped and DIPEA was not added, the hydrobromic acid formed during the alkylation of anilines **2** could remain inside the reaction mixture, promoting the cyclization step and also the precipitation of **11** as the hydrobromide salts **16**. As a consequence, the development work focused mainly on the first stages of the synthesis to efficiently prepare compounds **16** and **17**, while the second part of the process remained basically unchanged. A new route, named route B, shorter and more efficient than the previous one, was developed and successfully scaled up to produce multikilogram batches of **1a−c** (Scheme 5). We were delighted to observe the total yield rising up to 20−25% for all three considered compounds.

Development of a Manufacturing Supply Route to 1a. Once phase I was completed, **1a** was selected among the compounds containing the 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine scaffold as the most promising to progress in the late clinical development. Route B demonstrated viable on scale but still showed limitations when critically analyzed to assess suitability for industrialization. A few weak points were identified: (*i*) toxic and potentially carcinogenic DCM was necessary in stage 2 to extract efficiently the water-soluble pyridone **6a** during workup; (*ii*) the synthesis of triflate **7a** involved a low-temperature triflation reaction employing the humidity-sensitive triflic anhydride; (*iii*) the copper-catalyzed coupling in stage 4 required 0.3 equiv of the very expensive (1*R*,2*R*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine to reach completeness in less than 24 h; (*iv*) a large excess of 2.5 equiv of 1-(1*H*-pyrazol-3-yl)imidazolidin-2-one, **9a**, was needed, again in stage 4, to avoid the competing arylation on the 2-imidazolidinone free nitrogen (up to 25% of bis-arylated product **14** was observed if the temperature was not strictly kept under 95 °C). Notably, (1*R*,2*R*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine and 1-(1*H*-pyrazol-3-yl)imidazolidin-2-one represented, respectively, 20% and 40% of the cost of goods (CoGs) of the entire process.

A thorough process optimization work was undertaken to address all the above-mentioned issues and to come up with a robust and reliable manufacturing route. The new process (named route C) is outlined in Scheme 6.

(11) The tolerated residual level for copper was established by considering the permitted daily exposure according to the European Medicines Agency: *Guideline on the Specification Limits for Residues of Metal Catalysts*, CPMP/SWP/QWP/4446/00; Committee for Human Medicinal Products (CHMP), European Medicines Agency (EMEA): London, 2007; http://www.ema.europa.eu/pdfs/human/swp/444600.pdf.

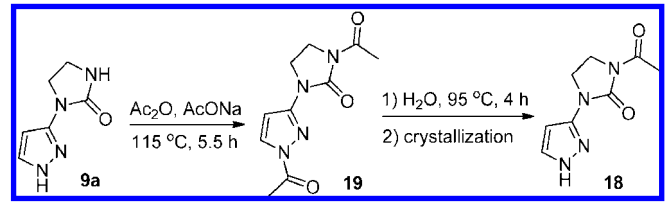
Scheme 6. **Route C, manufacturing route to 1a**



First of all, 2-methyltetrahydrofuran[12] was advantageously introduced in stage 2 as a new solvent; being higher boiling than THF, it shortened reaction times by working at a higher temperature; being nonmiscible with water, it replaced DCM during the workup, and finally, it also revealed an efficient solvent to crystallize pyridone **6a**, thus skipping the methanesulfonate salt formation step. Another significant accomplishment was gained in the following stage 3, where we identified a way to obtain the iodide **8a** directly from pyridone **6a**, thus escaping the triflation step and introducing a new stage 3. This difficult goal was achieved by using *N*-iodosuccinimide (NIS) in the presence of triphenylphosphite,[13] taking advantage of the high affinity for oxygen atom possessed by activated phosphorous derivatives. According to the literature mechanism hypothesis, triphenylphosphite reacts with NIS to generate a very reactive phosphorous adduct which then adds to the oxygen atom of pyridone **6a**, releasing succinimide and creating a good leaving group. The subsequent displacement by iodide provided the iodo-derivative **8a** and generated triphenylphosphate as a byproduct. The reaction was conducted in acetonitrile, by preparing NIS/$P(OPh)_3$ adduct at −10 °C from 3.5 equiv of both reagents. The pyridone **6a** was then added and the mixture heated to 80 °C for 8 h. A subsequent treatment with aqueous 8 N NaOH at 60 °C allowed the hydrolysis of the excess reagent and of triphenylphosphate and triggered the precipitation upon cooling of desired **8a** in high purity and with a typical yield in the range 75−80%.

Stage 4, the C−N coupling, was identified as the key stage of the process since it generated the DS skeleton and all the main impurities which can be found in the final API. For this reason the development of this stage deserved a special attention. In a first instance, a new and enlarged screening (including ligands, copper sources, bases and solvents) was performed, giving a particular focus to cheap aminoacidic ligands and organic bases.[14] As a result, the combination of CuI/*N*,*N*-dimethylglycine/DMSO/DBU was identified as the most advantageous alternative to route B conditions in terms of conversion and impurity profile. In addition, the replacement of the expensive (1*R*,2*R*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine with the cheaper *N*,*N*-dimethylglycine allowed a 10% reduction of the CoGs. Also, the introduction of DBU to replace K_2CO_3 offered the advantage of a homogeneous reaction. Another breakthrough was the idea of a selective protection of the 2-imidazolidinone free nitrogen with an acetyl group,[15] to avoid competing arylation during the coupling. Following this strategy it was possible not only to completely suppress the side reaction but also to employ only 1.3 equiv of pyrazolyl compound **18** with a further reduction of 20% in the CoGs.

Scheme 7. **Synthesis of 1-acetyl-3-(1*H*-pyrrol-3-yl)-imidazolidin-2-one, 18**



The acetylated intermediate **18** was efficiently obtained in high yield and purity from **9a** by a two-step synthesis which consisted of an exhaustive acetylation of the two reactive nitrogen atoms, followed by an *in situ* selective deacetylation of the pyrazolyl moiety promoted by water. Eventually, the desired product was filtered off directly from the reaction mixture (Scheme 7).

Once the C−N coupling reached completeness, the acetyl protecting group was cleaved easily and efficiently *in situ* by adding MeOH to the reaction mixture and heating to 85 °C for 3 h. In fact, the basic environment promoted nucleophilic attack of MeOH to the acetyl group with subsequent formation of methyl acetate. Moreover, methanol acted as an antisolvent, and **1a** was isolated by direct precipitation from the reaction mixture. The quality of the API was remarkable (99.5% a/a HPLC, with an assay of 99% w/w), and also the copper contamination was

(12) Aycock, D. F. *Org. Process Res. Dev.* **2007**, *11*, 156–159.
(13) (a) Sugimoto, O.; Mori, M.; Tanji, K.-I. *Tetrahedron Lett.* **1999**, *40*, 7477–7478. (b) Sugimoto, O.; Mori, M.; Moriya, K.; Tanji, K.-I. *Helv. Chim. Acta* **2001**, *84*, 1112–1118.
(14) (a) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450–1460. (b) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453–2455. (c) Ma, D.; Cai, Q. *Synlett* **2004**, 128–130. (d) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5173.
(15) Kravchenko, A. N.; Sigachev, A. S.; Gazieva, G. A.; Maksareva, E. Y.; Trunova, N. S.; Chegaev, K. A.; Lyssenko, K. A.; Lyubetsky, D. V.; Struchkova, M. I.; Il'in, M. M.; Davankov, V. A.; Lebedev, O. V.; Makhova, N. N.; Tartakovsky, V. A.; Zelinsky, N. D. *Chem. Heterocycl. Compd.* **2006**, *42*, 365–376.

kept under control and reduced to very low level (typically in range of 5−45 ppm) by using 1 equiv of *N*,*N*-dimethylglycine as a scavenger. The aminoacid was dissolved in the MeOH added during the acetyl-group cleavage/precipitation step and kept copper dissolved in the mother liquors as a soluble complex.

The following particle-forming stage developed *ad hoc* for the poorly soluble compound **1a** consisted of dissolution of the crude API in DMSO at 85 °C and subsequent controlled crystallization by addition of 1-propanol at 65 °C. The described methodology gave the desired API form and guaranteed a further reduction of the already low copper contents in order to meet specifications. The entire process demonstrated robustness and reliability in pilot plant, allowing the production up to 100 kg of API with an overall yield of 30−35%, confirming its potential to become the manufacturing route for **1a**. Moreover, the same chemistry could be applied successfully to prepare small batches of compounds **1b** and **1c** as well.

Conclusion

In conclusion, a robust, efficient, and scalable process was developed for the synthesis of CRF-1 antagonists of general formula **1** in 30−35% overall yield. The approach utilized a convergent synthesis which introduced at the last stage the expensive side chain **9**, during a selective copper-catalysed C−N coupling reaction. This more concise and atom-efficient route used readily available starting materials, skipped the formations of expensive intermediates, avoided the use of toxic reagents and extremely low-yielding steps, and also had a more robust final coupling stage. The problem of the clinical grade DS copper contamination was efficiently resolved on-scale by using a cheap and readily available scavenger, *N*,*N*-dimethylglycine, which was also the ligand employed in the C−N coupling reaction.

Experimental Section

All materials obtained from commercial suppliers were used without further purification. ^{1}H NMR spectra were recorded on Varian Inova 400 or 600 spectrometers. LC/MS analyses were performed on an Agilent 1100 series LC/MSD equipped with APCI source.

1-(4-Methoxy-2-methylphenyl)pyrrolidin-2-imine Hydrobromide (16a). To a solution of 4-methoxy-2-methylaniline (**2a**, 20 kg) in *n*-butanol (160 L) at 100 °C was added 4-bromobutyronitrile (1.2 equiv, 17.4 L), and the resulting mixture was heated to 110−115 °C for 6 h. The mixture was then allowed to cool down to 50 °C, and a seed was added. After precipitation occurred, TBME (80 L) was added, and the resulting suspension was cooled down to 20 °C, aged for 6 h, and then filtered. The cake was washed with a 1/1 *n*-butanol/TBME mixture (60 L) and TBME (60 L), and the solid dried overnight at 50 °C (30 kg, 75% yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.1−9.5 (br s, 2H), 7.32 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 2.9 Hz, 1H), 6.94 (dd, J = 8.7, 3.0 Hz, 1H), 3.87 (t, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.05 (t, J = 8.0 Hz, 2H), 2.22 (m, 2H), 2.16 (s, 3H). MS (*m*/*z*): 205 $[M + H]^+$.

1-[2-Methyl-4-(trifluoromethoxy)phenyl]pyrrolidin-2-imine Hydrobromide (16b). To a solution of 2-methyl-4-(trifluoromethoxy)aniline (**2b**, 30 g) in 1-methyl-2-pyrrolidinone (90 mL) at 100 °C was added 4-bromobutyronitrile (1.1 equiv, 17.2 mL), and the resulting mixture was heated to 110−115 °C for 4 h. The mixture was then allowed to cool down to 45 °C, and a seed was added. After precipitation occurred, TBME (270 mL) was added, and the resulting suspension was cooled down to 20 °C, aged for 2 h, and then filtered. The cake was washed with a 3:1 TBME/NMP mixture (3 × 60 mL), and the solid was dried at 70 °C for 6 h (47 g, 88% yield). ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.83 (br s, 1H), 8.62 (br s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.40 (dd, J = 8.7, 1.5 Hz, 1H), 3.92 (t, J = 7.1 Hz, 2H), 3.09 (m, 2H), 2.24 (s, 3H), 2.23 (m, 2H). MS (*m*/*z*): 259 $[M + H]^+$.

1-(4-Methoxy-2-methylphenyl)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-4(7*H*)-one (6a). To a solution of 1-(4-methoxy-2-methylphenyl)pyrrolidin-2-imine hydrobromide (**16a**, 10 kg) in 2-MeTHF (70 L) was added a 10% w/w NaOH aqueous solution (17.5 L). After aqueous phase separation, the organic layer was washed with a 15% w/w NaCl aqueous solution and dried by azeotropic distillation. Ethyl-2-butynoate (1.1 equiv, 4.6 L) was added and the solution was refluxed for 8 h, then it was cooled down to 20 °C. In another vessel, 2-MeTHF (90 L) was charged, KO*t*-Bu (2.5 equiv, 10 kg) was added and the suspension stirred for at least 30 min under nitrogen before being transferred to the first vessel containing the solution of **5a**. The transfer was completed by washing the line with fresh 2-MeTHF (60 L). The resulting mixture was refluxed for 9 h; then it was concentrated down to 120 L, allowed to cool down to 20 °C, washed with a 20% w/w NH_4Cl aqueous solution (40 L) and with a 15% w/w NaCl aqueous solution (20 L), and finally was distilled down to 40 L. Fresh 2-MeTHF was added (80 L). The mixture was concentrated down to 40 L, and then it was cooled down to 20 °C and a seed added. The resulting suspension was aged for 6 h at 20 °C and filtered, and the cake was washed with 2-MeTHF (20 L) and dried *in vacuo* at 50 °C for 18 h (5.2 kg, 55% yield). ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.86 (br s, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.75 (dd, J = 8.7, 2.9 Hz, 1H), 5.93 (s, 1H), 3.74 (s, 3H), 3.70 (t, J = 8.4 Hz, 2H), 2.91 (t, J = 8.5 Hz, 2H), 2.14 (s, 3H), 2.04 (s, 3H). MS (*m*/*z*): 271 $[M + H]^+$.

6-Methyl-1-[2-methyl-4-(trifluoromethoxy)phenyl]-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-4(7*H*)-one (6b). The compound was prepared according to the procedure applied for **6a**.^{1}H NMR (600 MHz, DMSO-d_6): δ 9.78 (br s, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.29 (d, J = 2.7 Hz, 1H), 7.20 (dd, J = 8.7, 2.8 Hz, 1H), 5.95 (s, 1H), 3.72 (t, J = 8.4 Hz, 2H), 2.90 (t, J = 8.5 Hz, 2H), 2.19 (s, 3H), 2.06 (s, 3H). MS (*m*/*z*): 325 $[M + H]^+$.

4-Iodo-1-(4-methoxy-2-methylphenyl)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (8a). To a mixture of *N*-iodosuccinimide (3.5 equiv, 2.9 kg) in CH_3CN (80 L) at 5 °C was added $P(OPh)_3$ (3.5 equiv, 3.4 L) in 1 h. 1-(4-Methoxy-2-methylphenyl)-6-methyl-1,2,3,7-tetrahydro-4*H*-pyrrolo[2,3-*b*]pyridin-4-one, **6a**, (10 kg) was added at 5 °C, and the resulting mixture was refluxed for 8 h. The mixture was then cooled down to 60 °C, and an 8 M NaOH aqueous solution (6.4 L) was slowly added, keeping the temperature at 60−65 °C. The mixture was then stirred for 2 h at 60 °C and cooled

down to 20 °C, and water (30 L) was added in 30 min. The resulting suspension was aged for 3 h at 20 °C before being filtered, and the cake was washed with water (80 L). The collected solid was dried *in vacuo* at 50 °C for 18 h (10.9 kg, 77% yield).^{1}H NMR (600 MHz, DMSO-d_6): δ 7.15 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 2.7 Hz, 1H), 6.78 (dd, J = 8.7, 2.9 Hz, 1H), 6.72 (s, 1H), 3.82 (t, J = 8.5 Hz, 2H), 3.75 (s, 3H), 2.97 (t, J = 8.4 Hz, 2H), 2.13 (s, 3H), 2.08 (s, 3H). MS (*m*/*z*): 381 $[M + H]^+$.

4-Iodo-6-methyl-1-[2-methyl-4-(trifluoromethoxy)phenyl]-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (8b). The compound was prepared according to the procedure applied for **8a**.^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40 (d, J = 8.6 Hz, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.22 (dd, J = 8.7, 2.6 Hz, 1H), 6.81 (s, 1H), 3.90 (t, J = 8.4 Hz, 2H), 3.00 (t, J = 8.4 Hz, 2H), 2.21 (s, 3H), 2.12 (s, 3H). MS (*m*/*z*): 435 $[M + H]^+$.

1-(1-{1-[4-Methoxy-2-methylphenyl]-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl}-1*H*-pyrazol-3-yl)imidazolidin-2-one (1a). DMSO (30 L) was charged under nitrogen followed by CuI (0.10 equiv, 0.5 kg) and *N*,*N*-dimethylglycine (0.30 equiv, 0.82 kg). The suspension was stirred at 25 °C for 30 min. Compound **8a** (10 kg) was added to the solution at 25 °C followed by **18** (1.3 equiv, 6.6 kg) and eventually by DBU (2 equiv, 8 L) and DMSO (10 L). The suspension was heated to 110 °C for 7 h. The temperature was brought down to 85 °C, and methanol (30 L) was added dropwise in 1 h. The resulting suspension was stirred at 85 °C for 3 h. The suspension was cooled down to 70 °C, and *N*,*N*-dimethylglycine (1 equiv, 2.8 kg) was added, followed by MeOH (70 L), that was added dropwise in 1 h. The mixture was aged at 70 °C for 30 min, then it was cooled down to 25 °C and stirred for 12 h at 25 °C. The suspension was filtered under pressure in a pan-filter; the cake was then washed four times upon the filter with MeOH (40 L). The collected solid was dried at 50 °C *in vacuo* to obtain crude grade **1a** as an off-white solid (9.6 kg, 90% yield).^{1}H NMR (600 MHz, DMSO-d_6): δ 8.31 (d, J = 2.7 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.06 (s, 1H), 6.86 (d, J = 2.7 Hz, 1H), 6.78 (d, J = 2.5 Hz, 1H), 6.79 (dd, J = 9.0, 2.7 Hz, 1H), 6.76 (s, 1H), 3.92 (m, 2H), 3.83 (t, J = 8.4 Hz, 2H), 3.76 (s, 3H), 3.46 (m, 4H), 2.17 (s, 3H), 2.15 (s, 3H). MS (*m*/*z*): 405 $[M + H]^+$.

2-(1-{1-[4-Methoxy-2-methylphenyl]-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl}-1H-pyrazol-3-yl)thiazole (1b). The compound was prepared according to the procedure applied for **1a** with 2-(1*H*-pyrazol-3-yl)thiazole (**9b**) used in place of **18** (410 g, 75% yield). ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.59 (d, J = 2.5 Hz, 1H), 7.94 (d, J = 3.3 Hz, 1H), 7.80 (d, J = 3.3 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.07 (d, J = 2.7 Hz, 1H), 6.88 (d, J = 3.3 Hz, 1H), 6.87 (s, 1H), 6.81 (dd, J = 8.5, 3.0 Hz, 1H), 3.90 (t, J = 8.5 Hz, 2H), 3.77 (s, 3H), 3.50 (t, J = 8.4 Hz, 2H), 2.23 (s, 3H), 2.17 (s, 3H). MS (*m*/*z*): 404 $[M + H]^+$.

1-(1-{6-Methyl-1-[2-methyl-4-(trifluoromethoxy)phenyl]-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl}-1*H*-pyrazol-3-yl)imidazolidin-2-one (1c). The compound was prepared according to the procedure applied for **1a** (390 g, 73% yield). ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.33 (d, J = 2.7 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.22 (dd, J = 8.8, 2.7 Hz, 1H), 7.07 (s, 1H), 6.85 (s, 1H), 6.80 (d, J = 2.7 Hz, 1H), 3.91 (m, 4H), 3.47 (m, 4H), 2.24 (s, 3H), 2.21 (s, 3H). MS (*m*/*z*): 459 $[M + H]^+$.

1-acetyl-3-(1H-pyrazol-3-yl)imidazolidin-2-one (18). A suspension of acetic anhydride (40 L), 1-(1*H*-pyrrol-3-yl)imidazolidin-2-one (**9a**) (10 kg) and sodium acetate (1.2 equiv, 6.5 kg) was heated to 115 °C for 5.5 h until formation of **19** was complete. The temperature was then brought to 50 °C, and water (20 L) was cautiously added in 1 h. The mixture was heated to 95 °C and the suspension stirred for 4 h at 95 °C until a complete hydrolysis of **19** to **18** was achieved. The mixture was eventually cooled down to 20 °C and aged for 3 h before filtering. The cake was washed three times upon the filter with 20 L of water, and the wet solid was dried *in vacuo* at 40 °C overnight. (10.9 kg, 86% yield).^{1}H NMR (400 MHz, DMSO-d_6): δ 12.47 (br s, 1H), 7.70 (d, J = 2.2 Hz, 1H), 6.54 (d, J = 2.2 Hz, 1H), 3.83 (m, 4H), 2.41 (s, 3H). M/S (mz): 195 $[M + H]^+$.

Received for review May 25, 2010.

OP100147H