Organic Process Research & Development **2003**, *7*, 209–213

A Practical Synthesis of 7-Azaindolylcarboxy-*endo*-tropanamide (DF 1012)

Marcello Allegretti,*,† Roberto Anacardio,† M. Candida Cesta,† Roberto Curti,† Marco Mantovanini,† Giuseppe Nano,† Alessandra Topai,† and Giuseppe Zampella‡

Chemistry Section, Dompé S.p.A. Research Centre, Via Campo di Pile, 67100 L'Aquila, Italy, and Biotechnologies and Biosciences Department of Milano-Bicocca University, Piazza della Scienza 2, 20126 Milan, Italy

Abstract:

An optimised cost-effective synthesis of the new antitussive drug, DF1012, is herewith reported. The new synthetic route to the key intermediate DF1005 is based on the unusual deprotection step of the 1-*tert*-butyl-3-cyano-7-azaindole intermediate, which can also be regarded as a convenient way for the industrial production of the expensive 7-azaindole 1. The second key intermediate, *endo*-tropanamine 6, was obtained in high yield by a novel one-pot stereoselective process using a Pd-catalysed reductive amination procedure.

Introduction

7-Azaindolylcarboxy-*endo*-tropanamide (**DF 1012**) (Figure 1) is the selected candidate drug in a new class of nonnarcotic antitussive compounds and is actually under investigation in phase II clinical trials.

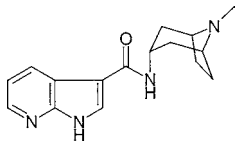
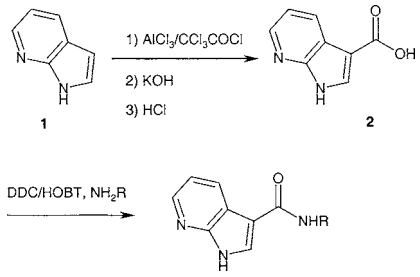


Figure 1. **DF 1012.**

DF 1012 and the class-related compounds were synthesised from the common intermediate 7-azaindolyl-3-carboxylic acid **2** via the general route outlined in Scheme 1.

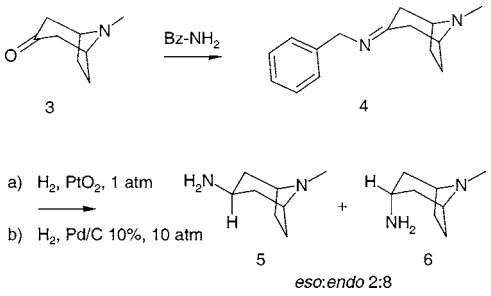
Scheme 1



endo-Tropanamine **6** is not a commercially available reagent and therefore was prepared, in the discovery phase, from commercial tropinone **3**, according to an established synthetic method[1] described in Scheme 2.

The synthetic process was a satisfactory general strategy for a laboratory-scale preparation, but it was not a suitable starting point for scaling-up studies due to the extremely high cost of the starting materials **1** and **3**.

Scheme 2



Considering the number of competitors in the antitussive-active drug area, the final price of the new product is one of the main issues to be evaluated because it could play a crucial role for its commercial success. The active principle high cost could then become, in this scenario, a serious drawback for an antitussive drug once on the market.

Results and Discussion

Preparation of 7-Azaindolyl-3-carboxylic Acid (2). The proposed pathway for the industrial preparation of **2** is represented in Scheme 3.

The cheap starting materials, succinonitrile and ethylformate, were condensed in the presence of sodium methoxide to give the corresponding salt of 2-hydroxymethylenebutyronitrile the latter of which was treated, in the reaction medium, with *tert*-butylamine to obtain the enaminonitrile **7**. The base-catalyzed internal condensation of **7** led to 1-*tert*-butyl-2-amino-4-cyanopyrrole **8** in high yield. In the fourth step, the 7-azaindole structure was easily built up by reaction of the intermediate **8** with 1,1,3,3-tetramethoxypropane in the presence of catalytic *p*-toluenesulfonic acid. Treatment of **9** with $AlCl_3$ (3 equiv) allowed the removal of the *tert*-butyl protecting group; the acidic hydrolysis of the cyano functionality in controlled conditions (step 6a) led to the desired 7-azaindolyl-3-carboxylic acid **2**.

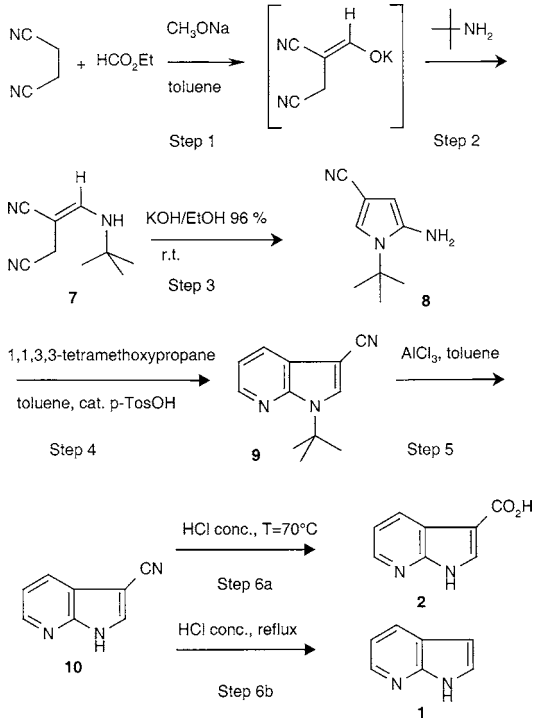
This process is based on an already existing method.[2] Broderick proposed a general preparation method for 1-substituted-2-aminopyrroles and pointed to their use as intermediates in the synthesis of 1-substituted-3-cyano-7-azaindoles. Even if 1-*H*-7-azaindoles were not accessible by means of this procedure, Broderick showed the synthesis of the attractive intermediate *N*-benzyl-3-cyano-7-azaindole.

* Author for correspondence. E-mail: marcello.allegretti@dompe.it.
† Dompé S.p.A. Research Centre.
‡ Milano-Bicocca University.

(1) Bagley, J. R.; Riley, T. N. *J. Heterocycl. Chem.* **1977**, *14*, 599.
(2) Brodrick, A.; Wibberley, D. G. *J. Chem. Soc. Perkin Trans. I* **1975**, *19*, 1910.

10.1021/op025570t CCC: $25.00
Published on Web 02/21/2003

Scheme 3



Therefore, in the first phase of our work, we tried to synthesise compound **2** through *N*-benzyl-3-cyano-7-azaindole, but any attempt[3,4] (Pd/C- or PtO_2-catalysed hydrogenation, Na/liq.NH_3, Na/naphthalene, ethylchloroformate/CF_3-COOH) to remove the benzyl group completely failed. These results were in agreement with the reported low reactivity of *N*-benzyl pyrroles in debenzylation conditions.

The use of *tert*-butylamine in the first step of the synthesis allowed us to perform the final deprotection step using a Lewis acid reagent with surprisingly high yield.

The *tert*-butyl group is not known as a protecting group for indole or pyrrole nitrogen; the cyano group-activating effect in position 3 is essential to determine the unusual high reactivity of our intermediate **9**. In fact, the reaction proceeded in very low yield, as the 3-carboxy or 3-carboxyamide **9**-analogues were the starting materials.

We could then argue that the 3-cyano-group coordination by 1 equiv of $AlCl_3$ is crucial for the activation of the Lewis acid-mediated C−N bond cleavage (as depicted in Figure 2).

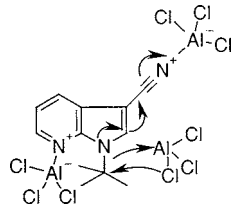
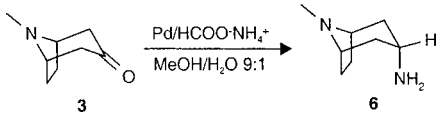


Figure 2. **Effect of the Lewis acid in the deprotection step.**

The final hydrolytic step to **2** requires carefully controlled conditions to avoid contemporary product decarboxylation-(step 6b). Under reflux the quantitative transformation of **9**

Scheme 4



to **1** was in fact obtained. Considering this result, the overall process from succinonitrile can thus be considered both as an advantageous synthetic method for the intermediate **2** preparation (step 6a) and as a new alternative convenient method for the synthesis of the expensive compound **1**.

The overall high yield obtained at kilogram-lab scale, together with the low cost of the starting materials and the ease of purification, makes this process an economic and efficient way to the 3-carboxy-7-azaindole **2** synthesis.

Preparation of *endo*-Tropanamine 6. The most widely used method[1] for the preparation of *endo*-tropanamine **6** is the catalytic debenzylation (PtO_2, EtOH) of the Schiff base **4** derived from tropinone and benzylamine coupling (Scheme 2). The iminic intermediate **4** reduction leads to a disappointing 8:2 ratio of *endo*/*eso* isomers; however, the pure *endo*-tropanamine **6** can be easily isolated in the final step by crystallisation of the corresponding bis-hydrochloride. Few years ago Eli-Lilly's researchers studied how to increase the stereoselectivity in the *endo*-tropanamine **6** synthesis.[5] They found that the use of bulky reducing agents such as sodium tris[(2-ethylhexanoyloxy)borohydride] enabled the set up of a new, highly stereoselective (*endo*/*eso* > 50:1) process for the preparation of the *endo*-*N*-benzyl-tropanamine. This method is surely appealing in terms of yield and stereoselectivity; however, it makes necessary a careful recovery of the valuable reagent.

At some stage in our initial attempts to scale-up the Scheme 2 method we faced unexpected difficulties.

The higher **4** concentration, due to the necessary solvent reduction at kilogram-lab scale, favoured the catalyst poisoning, thus decreasing the hydrogenolysis rate. Even a second addition of the same amount of catalyst did not afford the complete transformation of the intermediate *N*-benzyltropanamines.

More, in our hands, the formation of undesired by-products, mainly *N*-ethyltropanamines, unexpectedly increased. The combination of these two factors lowered the final yield of **6** (52% vs 75%) and compromised its isolation.

To bypass the deprotection step we studied and developed a novel one-step reductive amination procedure using ammonium formate both as nitrogen and hydrogen source (see Scheme 4).[6]

The new method, if compared with the classical Borch reductive amination procedure,[7,8] led to very good results not only in terms of yield but also in terms of stereoselec-

(3) Lim, M.-I.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 3826.
(4) Anderson, H. J.; Groves, J. K. *Tetrahedron Lett.* **1971**, *34*, 3165.
(5) Burks, J. E., Jr.; Espinosa, L.; LaBell, E. S.; McGill, J. M.; Ritter, A. R.; Speakman, J. L.; Williams, M.; Bradley, D. A.; Haehl, M. G.; Schmid, C. R. *Org. Process Res. Dev.* **1997**, *1*, 198.
(6) Allegretti, M.; Berdini, V.; Cesta, M. C.; Curti, R.; Nicolini, L.; Topai, A. *Tetrahedron Lett.* **2001**, *42*, 4257.
(7) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(8) Yoon, N. M.; Kim, E. G.; Son, H. S.; Choi, J. *Synth. Commun.* **1993**, *23*, 1595.

Table 1. [a]

entry no.	solvent	*T* (h)	10% Pd−C (% w/w)	molar ratio $HCO_2^-NH_4^+$/3	**6** (yield%)
1	EtOH	24	3	10	2
2	MeOH	24	3	5	12
3	MeOH	24	3	10	42
4	MeOH	24	3	30	58
5	MeOH	30	3	10	43
6	MeOH/H_2O, 9:1	24	3	10	40
7	MeOH/H_2O, 9:1	30	3	10	65
8	MeOH/H_2O, 9:1	24	3	20	55
9	MeOH/H_2O, 8:2	24	3	20	50
10	MeOH/H_2O, 9:1	24	6	20	66
11	MeOH/H_2O ,9:1	24	12	20	79
12	MeOH/H_2O, 9:1	24	12	10	81

[a] Note: All reactions were carried out at 25 °C.

tivity. No traces of the *eso* isomer **5** were detected in the reaction mixture before the crystallisation.

As shown in Table 1, we tested a number of conditions to optimise yield, reaction time, and catalyst amount. Initially the reaction was performed in methanol and led to the pure **6** product in low yield but good stereoselectivity (entry 2). Optimisation in alcoholic media did not proceed beyond fair yields (entries 3−5). A surprisingly favourable effect on the reaction course due to water addition was observed (entries 6−12). In the optimised conditions an hydro alcoholic (MeOH/H_2O, 9:1) mixture was the chosen solvent.

The catalyst amount was found to be a crucial parameter in reducing the reaction time. As detailed in the Experimental Section, we preferred to use a quite high catalyst/substrate ratio (1:4 w/w) to ensure reaction completion in 3 h, as the catalyst can be recovered in excellent yield. The reductive amination reaction is generally supposed to proceed through an iminic intermediate

The unexpected reactivity of ketones in the hydro alcoholic mixture led us to the hypothesis of the hemi-aminal species as the reaction key intermediates. At this point it is also important to keep in mind that the observed stereochemistry was never affected by relative changes in the optimisation process (GC−MS *endo*/*eso* ratio >99:1).

The different reactivity of the two possible hemi-aminals in the Pd-catalysed hydrogenolytic step justifies the absolute stereoselectivity toward the *endo*-tropanamine, according to the mechanism shown (Figure 3).

The new reductive amination procedure was applied to a wide number of substrates and was shown to be a general, straightforward, and mild route for the synthesis of primary amines from ketones. The overall results of the mechanistic and reactivity studies have been extensively discussed in our recent work.[9]

The reported results of the kilogram-lab scale-up trials confirmed the proposed process as a simple, high-yielding, one-pot alternative to the procedures of Borch[7,8] and Leuckart[10,11] for primary amines synthesis. The observed absolute stereoselectivity referring to the tropanonic ring functionality

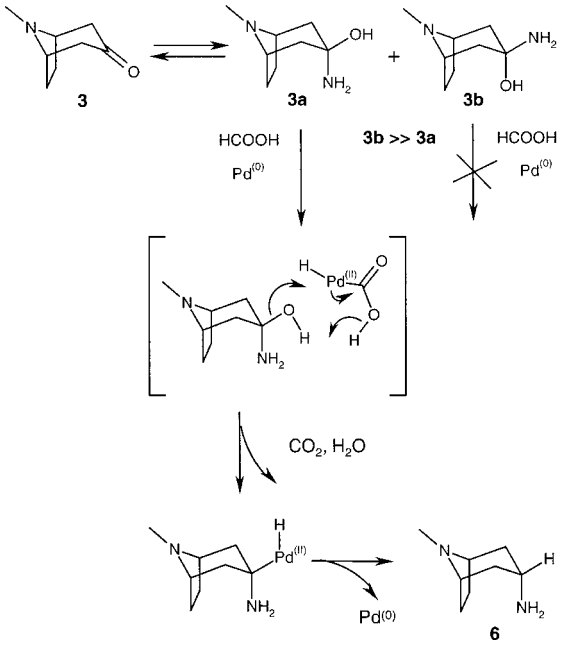


Figure 3. **Proposed reaction mechanism of the *endo*-tropanamine stereoselective synthesis via hemi-aminal.**

makes this process, from our point of view, extremely advantageous for the industrial preparation of the *endo*-tropanamine **6** as confirmed by the excellent results at kilogram-lab scale (see Experimental Section).

Preparation of DF1012 (*N-endo*-8-Methyl-8-azabicyclo-[3.2.1.]oct-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl-carboxamide). The condensation of the two key-intermediates **2** and **6** to **DF 1012** was generally performed using the DCC/HOBT system. Despite the satisfactory yield obtained in these conditions, several attempts were made to avoid the use of expensive (HOBT) and toxic (DCC) reagents in the final step.

The need for an alternative condensation route prompted us to study the acyl chloride coupling. However, the low solubility of the formed acyl chloride hydrochlorides strongly limited the choice of the solvent, and in most cases, a very low yield was obtained.

The best results were obtained using dioxane at room temperature in the presence of triethylamine to give **DF 1012** with 82% yield.

Experimental Section

General Procedures. Ten percent palladium on activated charcoal was purchased of "purissimum" grade from Fluka. Other commercial reagent grade solvents and chemicals were used as obtained unless otherwise noted. Melting points were obtained on a Buchi 530 apparatus and are uncorrected. Thin-layer chromatography was carried out with Macherey-Nagel-DURASIL-25 silica gel plates. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 MHz. GC−MS analyses were performed on a Varian 3400 chromatograph (analytical column: Supelwax-10 fused silica capillary column) and an Incos 50 XL (Finnigan Mat) spectrometer. Mass spectra were recorded on a Finnigan TSQ 700, a triple-quadrupole mass spectrometer, equipped with electrospray ionisation (ESI) source (Thermo Finnigan, San Jose, CA).

(9) Allegretti, M.; Berdini, V.; Cesta, M. C.; Curti, R.; Di Bello, N.; Nano, G.; Nicolini, L.; Topai, A. *Tetrahedron* **2002**, *58*, 5669.
(10) Moore, L. M. *Org. React.* **1949**, *5*, 301.
(11) Carlson, R.; Lejon, T.; Lundsted, T.; Le Clouerec, E. *Acta Chim. Scand.* **1993**, *47*, 1046.

***N-tert*-Butylaminomethylenesuccinonitrile (7).** A 250-L steel reactor in nitrogen atmosphere was loaded with sodium methoxide (4 kg, 74 mol) and anhydrous toluene (60 L). The suspension was cooled to 5 °C under stirring, and a solution of ethyl formate (6.17 kg, 83.3 mol) and succinonitrile (5.60 kg, 69.9 mol) in anhydrous toluene (60 L) was added dropwise. The addition rate was controlled to avoid the inner temperature exceeding 20 °C. Once the addition was done, the mixture was stirred for 2.5 h at room temperature, still under nitrogen atmosphere. *tert*-Butylamine (5.22 kg, 71.4 mol) and acetic acid (5.0 kg, 83.3 mol) were subsequently added to the reaction mixture, ensuring that the temperature did not exceed 40 °C.

The mixture was refluxed for 2.5 h and then cooled to room temperature; an 18% NaCl solution (17 L) was added, and the two phases were separated. The aqueous layer was extracted twice with toluene (7.5 L), and the collected organic extracts were evaporated under reduced pressure to give **7** (10.28 kg, 63.0 mol) as a brown solid (*E*/*Z* isomers mixture 2:1). Typically, the obtained solid was subsequently used without further purification. An analytically pure sample was recrystallised from acetone/diethyl ether: mp 118−119 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 3.18 (s, 2H), 5.0 (bs, 1H), 6.88 (d, 1H, (*E* isomer), J = 14.2 Hz), 6.99 (d, 1H, (*Z* isomer), J = 14.5 Hz); IR (Nujol) 3300, 2170, 1650, 1210 cm^{-1}. Anal. Calcd for $C_9H_{13}N_3$: C, 66.23; H, 8.03; N, 25.74. Found: C, 65.98; H, 8.01; N, 25.81. ESI-MS *m*/*z* 164 $[M + H]^+$.

2-Amino-1-*tert*-butyl-4-cyanopyrrole (8). In a 250-L steel reactor 85% KOH (7.35 kg, 111.3 mol) was dissolved in denatured ethanol (60 L) at 50 °C ,and the opalescent solution was then cooled at room temperature. To the latter, a solution of **7** (10.00 kg, 61.3 mol) in denatured ethanol (17 L) was added while stirring. This mixture was continuously stirred for 4 h at room temperature and then concentrated under reduced pressure until a solid started to separate. The mass was then diluted with water (50 L) and stirred at room temperature for another hour. The precipitate was separated by centrifugation, washed with water (15 L), and desiccated at 50 °C to give **8** (6.73 kg, 41.2 mol) as brown solid. The yield based on succinonitrile was 60.6%. Typically, the solid was used in subsequent reactions without further purification. An analytically pure sample was recrystallised from isopropyl ether: mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 (s, 9H), 3.15 (bs, 2H), 5.76 (d, 1H, J = 2.2 Hz), 6.96 (d, 1H, J = 2.2 Hz); IR (Nujol) 3380, 3320, 2190, 1640, 1200, 785, 715 cm^{-1}. Anal. Calcd for $C_9H_{13}N_3$: C, 66.23; H, 8.03; N, 25.74. Found: C, 66.06; H, 8.04; N, 25.76. ESI-MS *m*/*z* 164 $[M + H]^+$.

1-*tert*-butyl-3-cyano-7-azaindole (9). To a solution of **8** (6.50 kg, 39.8 mol) in toluene (65 L) in a 250-L glass-lined reactor were added 1,1,3,3-tetramethoxypropane (7.11 kg, 43.3 mol) and then *p*-toluenesulfonic acid monohydrate (758 g, 3.98 mol). The reaction mixture was gently heated to reflux temperature, thus removing methanol (reaction by-product) by azeotropic distillation. After 1 h the reaction mixture was cooled at 40 °C, transferred into a 100-L steel reactor and evaporated under reduced pressure. Isopropyl ether (45 L) was added to the residue, and then it was refluxed and stirred for 15 min. The latter mixture was cooled again to room temperature, and the solid was filtered off and washed with isopropyl ether. The organic layers were collected, and the solvent was distilled at reduced pressure. A solid from the latter residue was crystallised from *n*-heptane (18 L), separated by centrifugation and desiccated at 40 °C to give **9** (6.35 kg, 31.9 mol) as yellow powder in 80% yield (mp 84−92 °C). The product was subsequently used without further purification. An analytically pure sample was recrystallised from cyclohexane: mp 91−92 °C; ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 9H), 7.15−7.22 (m, 1H), 7.85 (s, 1H), 8.05 (d, 1H, J = 8 Hz), 8.45 (m, 1H); IR (Nujol) 2190, 1590, 1515, 760 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.33; H, 6.58; N, 21.09. Found: C, 72.16; H, 6.61; N, 21.11. ESI-MS *m*/*z* 200 $[M + H]^+$.

3-Cyano-7-azaindole (10). In nitrogen atmosphere at room temperature, **9** (6.00 kg, 30.1 mol) was added portionwise to a suspension of $AlCl_3$ (90 mol in 50 L of chlorobenzene). The mixture was stirred in a 250-L glass-lined reactor. At the end of additions the reaction mixture was refluxed for 8 h. The resulting mixture was cooled to room temperature and by means of a dosing pump added to precooled 2 N HCl (120 L) in a 250-L glass-lined reactor and then stirred for 2 h. Celite (4 kg) was added to the mixture, which was then transferred through a filter into a 250-L glass-lined reactor. The phases were separated, and the organic one was washed with 2 N HCl (20 L): the collected aqueous layers were washed again with chlorobenzene (20 L). The strongly acidic aqueous solution was adjusted to pH = 2.2−2.4 with 50% aqueous NaOH while cooling. The mixture was stirred while a precipitate formed; the solid was separated from mother liquors by centrifugation, washed with water, and desiccated at T = 70 °C to give **10** (3.93 kg, 27.5 mol) in 91.2% yield, as a slightly violet powder. The powder was subsequently used without further purification. An analytically pure sample was recrystallised from isopropyl alcohol: mp = 259−260 °C; ^{1}H NMR (DMSO-d_6) δ 7.30 (dd, 1H, J_1 = 8.0 Hz, J_2 = 4.7 Hz), 8.12 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.5 Hz), 8.41 (dd, 1H, J_1 = 4.7 Hz, J_2 = 1.6 Hz), 8.45 (s, 1H), 12.8 (bs, 1H); IR (Nujol) 3070, 2190, 1580, 1280, 760 cm^{-1}. Anal. Calcd for $C_8H_5N_3$: C, 67.12; H, 3.52; N, 29.35. Found: C, 67.09; H, 3.50; N, 29.32. ESI-MS *m*/*z* 144 $[M + H]^+$.

7-Azaindol-3-carboxylic acid (2). A 250-L glass-lined reactor was loaded with **10** (3.21 kg, 22.4 mol) and 32% HCl (32 L). The suspension was heated to 70 °C to give a homogeneous solution, which was stirred at 70 °C for 20 h; water (25 L) and charcoal (320 g) were then added. The resulting mixture was stirred at 70 °C for 1 h; Celite (320 g) was then added, and the mixture was left stirring for an additional hour at 70 °C. The warm solution was transferred into a 250-L glass-lined reactor through a filter, the filtrate cooled by brine to 8−10 °C, and the pH adjusted to 2.5 with 50% NaOH. A white precipitate formed; after the suspension stirred for 2 h at room temperature, the solid was separated by centrifugation, washed with copious water till disappearance of chloride ions, and dried at T = 70 °C to give **2** (3.43

kg, 21.15 mol) in 94.3% yield as a white solid. An analytically pure sample was recrystallised from ethanol/2 N HCl, 4:1: mp 245−246 °C; ^{1}H NMR (DMSO-d_6) δ 7.18−7.25 (m, 1H), 8.13 (s, 1H), 8.29−8.33 (m, 2H) 11.7−12.5 (bs, 2H); IR (Nujol) 3460, 2920, 2570, 1685, 1350, 1195, 1140, 1040,805, 750 cm^{-1}. Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.12; H, 3.74; N, 17.25. ESI-MS *m*/*z* 163 $[M + H]^+$.

7-Azaindole (1). A 250-L glass-lined reactor was loaded with **10** (3.21 kg, 22.4 mol) and HCl 32% (32 L). The suspension was refluxed for 24 h. The solution was cooled to 70 °C, and additional HCl 32% (32 L) was poured into the mixture; the mass was then reheated to reflux for an additional 24 h. Finally, the mixture was cooled to room temperature and diluted with water (40 L), and the pH was adjusted to 2.5 with 50% aqueous NaOH. Charcoal (320 g) was added, and the mixture was stirred for 1 h at room temperature. Celite (320 g) was added to the mixture which was then stirred for 1 h at the same temperature and then transferred into a 250-L steel reactor through a filter. The filtrate was cooled by brine to 8−10 °C; methylene chloride was added (25 L), and the pH was adjusted to 12 with 50% aqueous NaOH. The phases were separated, and the aqueous layer was extracted again with methylene chloride (25 L). Solvent was distilled under reduced pressure to give **1** (1.93 kg, 16.3 mol) in 72.9% yield as a white solid: mp = 105−106 °C, ^{1}H NMR ($CDCl_3$) δ 6.55 (d, 1H, J = 3.0 Hz), 7.1 (dd, 1H J_1 = 8.0 Hz, J_2 = 4.7 Hz), 7.45 (d, 1H, J = 3.0 Hz), 7.98 (m, 1H), 8.32 (bs, 1H), 9.7 (bs, 1H); IR (Nujol) 3040, 1580, 1280, 1120, 890, 760 cm^{-1}. Anal. Calcd for $C_7H_6N_2$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.20; H, 5.11; N, 23.69. ESI-MS *m*/*z* 119 $[M + H]^+$.

3-*Endo*-amino-8-methyl-8-azabicyclo[3.2.1.]octane Bis-hydrochloride (6·Bis-hydrochloride). In a 50-L glass reactor under nitrogen atmosphere **3** (600 g, 4.31 mol) was dissolved in 90% aqueous MeOH (15 L) and stirred with ammonium formate (2500 g, 39.64 mol). After complete dissolution, 10% Pd/C (0.15 kg, 0.14 mol) was added, and the reaction mixture was stirred for 3 h. The catalyst was filtered under vacuum on a Celite panel and washed with 90% MeOH. The filtrate was concentrated under reduced pressure in a 25-L glass reactor. The so-obtained oil was dissolved in absolute ethyl alcohol (10 L), and 37% HCl (0.75 L) was added dropwise while stirring. The solution was seeded and left stirring at room temperature for 1 h and for 5 h at 4 °C.

The precipitate was filtered, washed with absolute ethyl alcohol, and desiccated at 40 °C in a vacuum oven to give **6**·bis-hydrochloride (760 g, 3.56 mol) as a white solid in 82.7% yield: mp > 250 °C; ^{1}H NMR (DMSO-d_6) δ 2.4−2.05 (m, 6H), 2.8−2.55 (m, 5H), 3.7−3.5 (m, 1H), 4.0−3.8 (bs, 2H), 8.7−8.2 (bs, 3H), 11.2−11.0 (bs, 1H). IR (Nujol) 3300, 3210, 3150, 2700, 2560, 1550, 1040 cm^{-1}. Anal. Calcd for $C_8H_{18}N_2Cl_2$: C, 45.08; H, 8.51; N, 13.14; Cl, 33.26. Found: C, 45.09; H, 8.50; N, 13.12; Cl, 33.26. ESI-MS *m*/*z* 141 $[M + H]^+$.

***N*-*endo*-8-Methyl-8-azabicyclo[3.2.1.]oct-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl-carboxamide (DF1012).** In a 25-L glass reactor **2** (1.3 kg, 8.02 mol) and toluene (10 L) were mixed. The suspension was stirred and heated to T = 70 °C. Thionyl chloride (0.75 L, 10.2 mol) was dripped into the mixture slowly, and this mixure was then refluxed for 2 h. After cooling at room temperature the solid was separated by vacuum filtration, washed with toluene, and then dried at 60 °C in a vacuum oven to give **2** chloride hydrochloride as a white solid (1.4 kg, 6.45 mol).

6·bis-hydrochloride (900 g, 4.22 mol), placed in 25-L glass reactor, was dissolved in water (1 L) and cooled at T = 5 °C. Dichloromethane (2 L) was added, and 32% aqueous NaOH (1 L; 10.8 mol) was slowly dripped under stirring and cooling. The two phases were separated, and the aqueous one was re-extracted with dichloromethane (2 L). Solvent was distilled off under reduced pressure to give **6** (0.55 kg, 3.92 mol) as a yellow oil.

The compound **2** chloride hydrochloride (0.705 kg, 3.25 mol) was suspended in a 25-L glass reactor with dioxane (5 L), then triethylamine (0.724 kg, 7.15 mol) was added under stirring. A solution of **6** (0.55 kg, 3.92 mol) in dioxane (5 L) was added dropwise and the mixture kept under stirring overnight. The reaction mixture was concentrated under reduced pressure, water (10 L) was added to the residue, and the pH was adjusted to 1.5 with 2 N HCl. The aqueous solution was first washed with dichloromethane (2 × 5 L), and then 50% aqueous NaOH was slowly added while stirring and cooling until pH > 10. The mixture was stirred overnight at T = 5 °C; the precipitate was vacuum-filtered, washed with water (10 L), and dried under vacuum at T = 60 °C to give a pale-pink solid (0.74 kg, 2.6 mol). The crude product was resuspended in ethanol (3 L) and refluxed for 2 h; the mixture was then cooled at room temperature and refrigerated at T = 5 °C overnight. The resulting solid was vacuum-filtered, washed with cooled ethanol (3 × 0.25 L), and dried under vacuum at T = 80 °C to give **DF1012** (0.718 kg, 2.53 mol) as a white solid in 78% yield: mp = 281−282 °C; ^{1}H NMR (DMSO-d_6) δ 1.9−2.2 (m, 8H), 2.25 (s, 3H) 3.12 (bs, 2H), 4.05 (m, 1H), 7.25 (dd, 1H, J_1 = 7.9, J_2 = 4.6), 7.50 (d, 1H, J = 4.6 Hz), 8.20 (s, 1H), 8.43 (d, 1H), 8.5 (d, 1H), 12.1−12.3 (bs, 1H); IR (Nujol) 3300, 3100, 1620, 1530, 1290, 1200 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09; N, 19.70. Found: C, 67.60; H, 7.07; N, 19.71. ESI-MS *m*/*z* 285 $[M + H]^+$.

Acknowledgment

We sincerely thank Professor Carmelo Gandolfi in whose memory this paper is dedicated.

Received for review July 18, 2002.

OP025570T