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A convenient synthesis of linear pyridinoimidazo[1,2-*a*]pyridine and pyrroloimidazo[1,2-*a*]pyridine cores

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Abstract—Two new imidazo[1,2-*a*]pyridine derivatives, pyridinoimidazo[1,2-*a*]pyridine (**10**) and pyrroloimidazo[1,2-*a*]pyridine (**16**), were synthesised from 2-amino-4-methyl-5-nitropyridine (**1**) by linear cyclisation, making use of dimethylformamide dimethylacetal (DMFDMA) as an agent of vinylamine functionalisation. This report describes first the formation of pyridine and pyrroloimidazopyridine from (**1**), and then the formation of pyridine-fused and pyrrolo-fused pyridine by the Friedländer method and reductive cyclisation followed by treatment of the resulting adduct with chloroacetaldehyde.

For several years, the imidazo[1,2-*a*]pyridine (IP) ring has been known as a core structural unit of bioactive molecules in synthetic and natural core (Zolpidem, Saripidem).[1] Thus, many structural modifications of this scaffold have been intensively investigated with the aim of developing novel therapeutic agents.[2] A perusal of the literature reveals, a large number of different synthetic pathways using functionalisation of the imidazole[3] or pyridine[4] parts to create heterocyclic compounds with potential therapeutic applications. In contrast, the synthetic potential of the pyridine part has long remained largely unexplored, not only because of the problems with functionalisation, but also due to the difficulty of finding commercial reagents to synthesise new rings from this part. Recently we have shown in our laboratory the possibility of reaching in angular systems from monofunctionalisation of pyridine sites.[4b,c] In these works,[4b,c] Chezal et al. reported that during an intramolecular cyclisation the regiospecificity was an angular annulation from C-8 to C-7 and from C-5 to C-6 of IP (see (**3**) in Fig. 1 for numbering). This regiospecificity can be explained by the higher electron densities of the C-5 and C-8 sites, and by thermodynamic stability of angular compounds. In view of all the above reasons, heterocyclisation from C-6 and C-7 poses a significant challenge.

In this study, we decided to synthesise pyridine and pyrrole rings from C-6 and C-7 of IP, because these two kinds of heterocycles can be found as pharmacophores in a wide variety of biologically active compounds, such as antitumourals,[5] antivirals[6] and many other therapeutic agents.[7]

Here, we report a new and efficient synthetic route for the synthesis of linear pyridinoimidazopyridine and pyrroloimidazopyridine cores by the Friedländer and reductive cyclisation reactions. Our retrosynthetic analysis was based on three essential elements. Firstly, in order to direct the reaction for the formation of a linear system, we proposed a bifunctionalised system (in C-6 and C-7 of IP) as shown in the retrosynthetic scheme (Fig. 1, first possibility). Secondly, the reaction of DMFDMA with orthonitrated methyl pyridine (**1**) allowed us access to vinylamine (compound (**3**) or (**5**)) followed by orthonitrated aldehyde synthons by action of sodium periodate. This resulted in the formation of the pyridine and pyrrole cores in a limited number of steps[8] (Fig. 1). Finally, the possibility of forming the pyridine (A-ring) and pyrrole (C-ring) before formation of the imidazole part of IP gave us a second way to obtain the linear pyridine and pyrroloimidazopyridine scaffolds (Fig. 1, second possibility).

To verify the feasibility of this project, we chose to investigate the synthesis of precursors (**3**) and (**8**)

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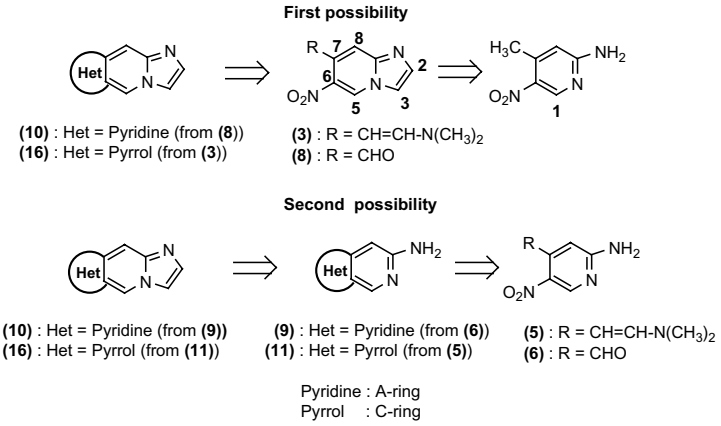
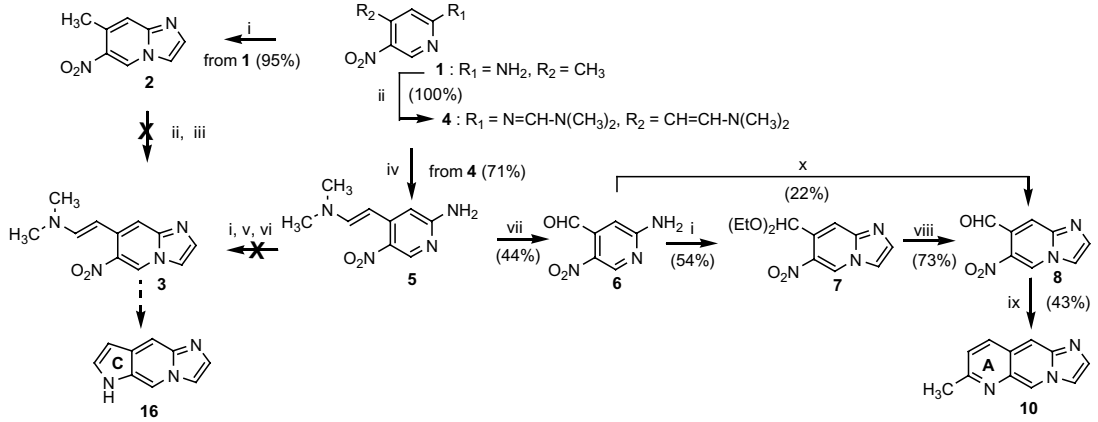


Figure 1. The two possible retrosynthetic pathways for the synthesis of pyridino and pyroloimidazopyridine cores.

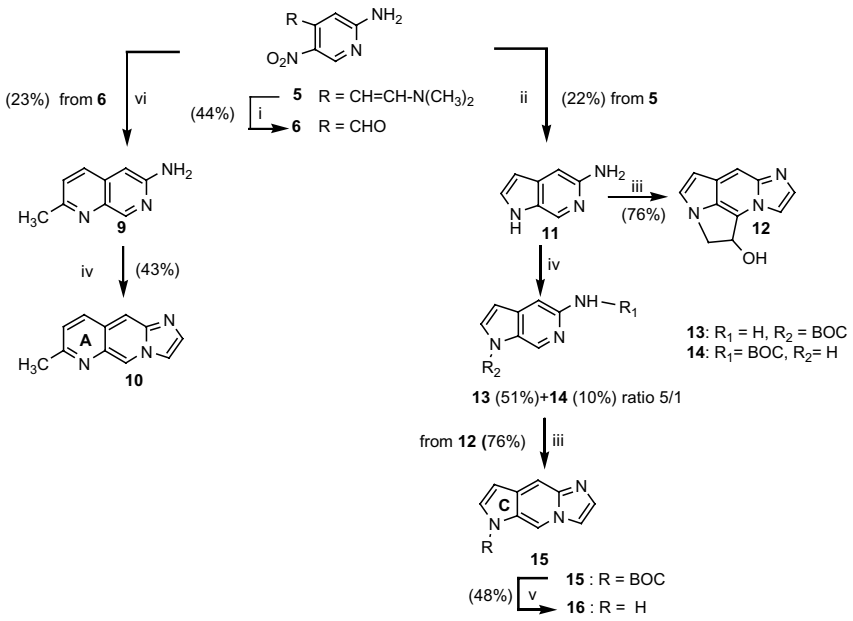
(Scheme 1). Our initial route was based on the formation of (**2**) from 2-amino-4-methyl-5-nitropyridine (**1**) according to the procedure of Tschitschibabin.[9] However, our attempt at formation of the vinylogous enamine (**3**) from compound (**2**) upon treatment with DMFDMA in refluxing DMF was unsuccessful, and use of Bredereck's reagent (*tert*-butoxybisdimethylaminomethane) also failed to produce the desired enamine (**3**). This result can be attributed to the non-delocalisation of π electrons of the pyridine ring in the IP scaffold, which makes the removal of the methyl proton almost impossible. The second route for the formation of enamine (**3**) was the reaction of compound (**1**) with DMFDMA according to the procedure of Filla et al.[10] followed by acid hydrolysis to give amine (**5**) in a yield of 71%. However, several attempts for the formation of the imidazole ring from compound (**5**) with varying solvents (e.g., EtOH, *i*Pr-OH, *n*-butanol, DMF and DME) failed to yield the desired compound (**3**). It seems that either the vinylogous enamine on the C-7 position of IP was unstable, or that the chain on the C-4 position of compound (**5**) reduced the nucleophilicity of the pyridino nitrogen and thus prevented formation of the imidazole ring. Therefore, we concluded that the formation of vinylogous enamine function connected to the IP scaffold in the C-7 position is not possible using this strategy (Scheme 1).

Our strategy for the formation of the A-ring, consisted of condensation of pyridine (**6**) with chloroacetaldehyde in DMF; this gave the desired product (**8**) in a yield of 22%. An alternative strategy would be the treatment of the same pyridine (**6**) with chloroacetaldehyde in refluxing ethanol followed by acidic hydrolysis; this gave the product (**8**) in a better yield of 39% (Scheme 1). For the synthesis of compound (**10**), we chose the Friedländer reaction for the construction of the A-ring. This reaction is traditionally reported from the *ortho* amine aldehyde compounds.[3c] In this work, we decided to apply the same reaction but from the *ortho* nitrated aldehyde compound under the McNaughton conditions,[11] which allowed us to obtain 7-methylimidazo-[2,1-*g*][1,7]naphthyridine (**10**)[12a] in a yield of 43% (Scheme 1).

In the second part of our work, the formation of the A and C rings was considered before accessing the imidazole part. 5-Aminopyrrolopyridine (**11**)[13] was easily synthesised from (**5**) under reductive conditions in the presence of hydrazine monohydrate and Raney nickel



Scheme 1. Reagents and conditions: (i) $ClCH_2CHO$, EtOH, Δ; (ii) DMFDMA, DMF, Δ; (iii) Brederek's reagent, DMF, Δ; (iv) HCl (3 N), Δ; (v) $ClCH_2CHO$, CH_3CN, Δ; (vi) $ClCH_2CHO$, DME, rt; (vii) $NaIO_4$, THF, H_2O, rt; (viii) HCl (10 N), CH_3CN, H_2O, Δ; (ix) acetone, $SnCl_2$, $ZnCl_2$, Δ; (x) $ClCH_2CHO$, DMF, Δ.



Scheme 2. Reagents and conditions: (i) $NaIO_4$, THF, H_2O, rt; (ii) Raney Ni, NH_2NH_2 (8.6 equiv), THF, MeOH, 45–50 °C; (iii) $ClCH_2CHO$, EtOH, Δ; (iv) $(BOC)_2O$, CH_2Cl_2, rt; (v) HCl (3 N), Δ; (vi) acetone, $SnCl_2$, $ZnCl_2$, EtOH, Δ.

as the catalyst. The condensation of compound (**11**) with the chloroacetaldehyde resulted in the formation of the unexpected product (**12**)[12b] (Scheme 2). The formation of compound (**12**) can be explained by three factors: (i) excesses of chloroacetaldehyde (3 equiv) necessary for the Tchichibabin condensation, (ii) the nucleophilic character of N-1 of pyrrole, resulting in the condensation product with chloroacetaldehyde and (iii) a higher electron density at the C-5 position of IP. In addition, a previous report from our laboratory describes the formation of imidazopyridodiazepines from *peri* annulation. The base of this work was a direct intramolecular electrophilic attack of C-5 to vinylimine of the bicyclic ring compound.[14]

To circumvent this obstacle to the synthesis of our linear tricyclic pyrroloimidazopyridine compound, we decided to protect the N-1 group of 5-aminopyrrolo[2,3-*c*]pyridine (**11**) with a BOC group. This yielded the formation of two compounds, (**13**) and (**14**), in a ratio of 5:1 after column chromatography. Thus, the desired compound (**16**)[12c] was obtained by the building of an imidazole ring followed by the removal of the BOC group. The overall yield was 36% (Scheme 2).

Next, the condensation of compound (**6**) with acetone under the McNaughton conditions, allowed us to synthesise aminopyridinopyridine (**9**). The reaction of the latter with chloroacetaldehyde in the ethanol solution at reflux yielded compound (**10**).[12a]

In summary, we have found a convenient route to synthesise linear pyridinoimidazopyridine (**10**) and pyrroloimidazopyridine (**16**) structures by bifunctionalisation of the C-6 and C-7 sites of IP and the C-4 and C-5 sites of the pyridine ring. We have also shown that the C-6 methyl group, *ortho* nitrated on C-7 is not reactive in the presence of DMFDMA and Bredereck's reagents. Furthermore, the synthesis described in this paper allowed us to use known precursor (**5**), which permitted in the synthesised new-fused systems in pyridine series, which ultimately afforded a linear tricycle (**10**) and (**16**). Further work is in progress to develop other hetrocycles (thiophene, furan, pyridazine and pyridinone) from the C-6 and C-7 sites of IP using the same strategy, and reports will follow in due course.

References and notes

1. Renard, S.; Olivier, A.; Granger, P.; Avenet, P.; Graham, D.; Sevrin, M.; George, P.; Besnard, F. *J. Biol. Chem.* **1999**, *274*, 13370.
2. (a) Zeng, F.; Southerland, J. A.; Voll, R. J.; Votaw, J. R.; Williams, L.; Ciliax, B. J.; Levey, A. I.; Goodman, M. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3015; (b) Cai, D.; Byth, K. F.; Shapiro, G. I. *Cancer Res.* **2006**, *66*, 435; (c) Engler, T. A.; Malhotra, S.; Burkholder, T. P.; Henry, J. R.; Mendel, D.; Porter, W. J.; Furness, K.; Diefenbacher, C.; Marquart, A.; Reel, J. K.; Li, Y.; Clayton, J.; Cunningham, B.; McLean, J.; O'Toole, J. C.; Brozinick, J.; Hawkins, E.; Misener, E.; Briere, D.; Brier, R. A.; Wagner, J. R.; Campbell, R. M.; Anderson, B. D.; Vaughn, R.; Bennett, D. B.; Meier, T. I.; Cook, J. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 899; (d) Abadi, A. H. *Arch. Pharm. Pharm. Med. Chem.* **2004**, *337*, 383; (e) Engler, T. A.; Henry, J. R.; Malhotra, S.; Cunningham, B.; Furness, K.; Brozinick, J.; Burkholder, T. P.; Clay, M. P.; Clayton, J.; Diefenbacher, C.; Hawkins, E.; Iverson, P. W.; Li, Y.; Lindstrom, T. D.; Marquart, A. L.; McLean, J.; Mendel, D.; Misener, E.; Briere, D.; O'Toole, J. C.; Porter, W. J.; Queener, S.; Reel, J. K.; Owens, R. A.; Brier, R. A.; Eessalu, T. E.; Wagner, J. R.; Campbell, R. M.; Vaughn, R. *J. Med. Chem.* **2004**, *47*, 3934; (f) Ismail, M. A.; Brun, R.; Wenzler, T.; Tanious, F. A.; Wilson, W. D.; Boykin, D. W. *J. Med. Chem.* **2004**, *47*, 3658; (g)

Gudmundsson, K. S.; Johns, B. A. *Org. Lett.* **2003**, *5*, 1369; (h) Mavel, S.; Renou, J. L.; Galtier, C.; Allouchi, H.; Snoeck, R.; Andrei, G.; De Clercq, E.; Balzarini, J.; Gueiffier, A. *Bioorg. Med. Chem.* **2002**, *10*, 941; (i) Lima, P. C.; Avery, M. A.; Tekwani, B. L.; Alves, H. M.; Barreiro, E. J.; Fraga, C. A. M. *Il Farmaco* **2002**, *57*, 825.

3. (a) Shaabani, A.; Soleimani, E.; Maleki, A. *Tetrahedron Lett.* **2006**, *47*, 3031; (b) Andaloussi, M.; Chezal, J. M.; Moreau, E.; Lartigue, C.; El Laghdach, A.; Teulade, J. C.; Chavignon, O. *Heterocycles* **2005**, *65*, 1071; (c) Desbois, N.; Chezal, J. M.; Fauvelle, F.; Debouzy, J. C.; Lartigue, C.; Gueiffier, A.; Blache, Y.; Moreau, E.; Madelmont, J. C.; Chavignon, O.; Teulade, J. C. *Heterocycles* **2005**, *65*, 1121; (d) Chezal, J. M.; Moreau, E.; Chavignon, O.; Lartique, C.; Blache, Y.; Teaulade, J. C. *Tetrahedron* **2003**, *59*, 5869; (e) Moreau, E.; Chezal, J. M.; Dechambre, C.; Canitrot, D.; Blache, Y.; Lartigue, C.; Chavignon, O.; Teulade, J. C. *Heterocycles* **2002**, *57*, 21; (f) Burkholder, C.; Dolbier, W. R.; Médebielle, M.; Ait-Mohand, S. *Tetrahedron Lett.* **2001**, *42*, 3077; (g) Jouanisson, A.; Couquelet, J.; Teulade, J. C.; Chavignon, O.; Chabard, J. L.; Dauphin, G. *J. Heterocycl. Chem.* **1996**, *33*, 1247; (h) Jouanisson, A.; Chavignon, O.; Couquelet, J.; Teulade, J. C.; Chabard, J. L.; Dauphin, G. *Heterocycles* **1995**, *41*, 21; (i) Chavignon, O.; Teulade, J. C.; Roche, D.; Madesclaire, M.; Blache, Y.; Gueiffier, A.; Chabard, J. L.; Dauphin, G. *J. Org. Chem.* **1994**, *59*, 6413.
4. (a) Kiselyov, A. S. *Tetrahedron Lett.* **2006**, *47*, 2941; (b) Chezal, J. M.; Moreau, E.; Chavignon, O.; Gaumet, V.; Métin, J.; Blache, Y.; Diez, A.; Fradera, X.; Luque, J.; Teulade, J. C. *Tetrahedron* **2002**, *58*, 295; (c) Chezal, J. M.; Moreau, E.; Delmas, G.; Gueiffier, A.; Blache, Y.; Grassy, G.; Lartigue, C.; Chavignon, O.; Teulade, J. C. *J. Org. Chem.* **2001**, *66*, 6576.
5. (a) Berger, D.; Dutia, M.; Powell, D.; Wu, B.; Wissner, A.; DeMorin, F.; Weber, J.; Boschelli, F. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2761; (b) Staker, B. L.; Feese, M. D.; Cushman, M.; Pommier, Y.; Zembower, D.; Stewart, L.; Burgin, A. B. *J. Med. Chem.* **2005**, *48*, 2336; (c) Parrish, J. P.; Kastrinsky, D. B.; Wolkenberg, S. E.; Igarashi, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2003**, *125*, 10971; (d) Bolognese, A.; Correale, G.; Manfra, M.; Lavecchia, A.; Mazzoni, O.; Novellino, E.; La Colla, P.; Sanna, G.; Loddo, R. *J. Med. Chem.* **2004**, *47*, 849.
6. (a) Zhu, Z.; Lippa, B.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2000**, *43*, 2430; (b) Rashad, A. E.; Mohamed, M. S.; Zaki, M. E. A.; Fatahala, S. S. *Arch. Pharm. Chem. Life Sci.* **2006**, *339*, 664; (c) Varaprasad, C. V. N. S.; Ramasamy, K. S.; Girardet, J. L.; Gunic, E.; Lai, V.; Zhong, W.; An, H.; Hong, Z. *Bioorg. Chem.* **2007**, *35*, 25.
7. (a) Vinosova, J.; Cermacova, K.; Tomeckova, A.; Ceckova, M.; Jampilek, J.; Cermak, P.; Kunes, J.; Dolezal, M.; Staud, F. *Bioorg. Med. Chem.* **2006**, *14*, 5850; (b) Marco-Contelles, J.; Leon, R.; de los Rios, C.; Guglietta, A.; Terencio, J.; Lopez, M. G.; Garcia, A. G.; Villaroya, M. *J. Med. Chem.* **2006**, *49*, 7607; (c) Adamec, J.; Beckert, R.; Weiß, D.; Klimesova, V.; Waisser, K.; Möllmann, U.; Kaustova, J.; Buchta, V. *Bioorg. Med. Chem.* **2007**, *15*, 2898; (d) Mai, A.; Massa, S.; Cerbara, I.; Valente, S.; Rango, R.; Bottoni, P.; Scatena, R.; Loidl, P.; Brosch, G. *J. Med. Chem.* **2004**, *47*, 1098; (e) Galm, U.; Heller, S.; Shapiro, S.; Page, M.; Li, S. M.; Heide, L. *Antimicrob. Agents Chemother.* **2004**, *48*, 1307; (f) Biftu, T.; Feng, D.; Ponpipom, M.; Girotra, N.; Liang, G. B.; Qian, X.; Bugianesi, R.; Simeone, J.; Chang, L.; Gurnett, A.; Liberator, P.; Dulski, P.; Leavitt, P. S.; Crumley, T.; Misura, A.; Murphy, T.; Rattray, S.; Samaras, S.; Tamas, T.; Mathew, J.; Brown, C.; Thompson, D.; Schmatz, D.; Fisher, M.; Wyvratt, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3296.
8. (a) Son, J. K.; Son, J. K.; Jahng, Y. *Heterocycles* **2002**, *62*, 1109; (b) Edin, M.; Grivas, S. *ARKIVOC* **2001**, *1*, 144–153.
9. Tschitschibabin, A. E. *Ber.* **1925**, *58*, 1704.
10. Filla, S. A.; Mathes, B. M.; Johnson, K. W.; Phebus, L. A.; Cohen, M. L.; Nelson, D. L.; Zgombick, J. M.; Erickson, J. A.; Schenck, K. W.; Wainscott, D. B.; Branchek, T. A.; Schaus, J. M. *J. Med. Chem.* **2003**, *46*, 3060.
11. McNaughton, B. R.; Miller, B. L. *Org. Lett.* **2003**, *5*, 4257.
12. (a) 7-Methylimidazo[2,1-*g*][1,7]naphthyridine (**10**): mp 147–149 °C; *v* (KBr): 2924, 1610, 1527, 1376, 1259, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.67 (s, 3H), 7.16 (s, 1H), 7.23 (d, 1H, $J = 8.5$ Hz), 7.82 (d, 1H, $J = 8.5$ Hz), 7.90 (s, 1H), 8.57 (s, 1H), 9.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 45.8, 109.6, 121.4, 126.0, 132.1, 134.6, 135.2, 135.4, 140.4, 151.5, 155.7; MS *m*/*z* 183 (M^+, 100), 155 (10), 129 (8), 102 (5), 77 (6), 63 (8), 51 (12); Anal. Calcd for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.25; H, 4.70; N, 22.64.; (b) 1,2-Dihydro-2a,6,8a-triaza-cyclopenta[*cd*]-*s*-indacene-1-ol (**12**): mp 184–186 °C; *v* (KBr): 3410, 1650, 1629, 1349, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.91 (m, 2H), 5.17 (t, 1H, $J = 6.5$ Hz), 6.36 (d, 1H, $J = 3$ Hz), 7.44 (d, 1H, $J = 3$ Hz), 7.52 (s, 1H), 7.53 (s, 1H), 8.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 47.0, 67.1, 101.1, 102.4, 108.7, 122.3, 129.8, 131.7, 134.8, 135.7, 144.6; MS *m*/*z* 199 (M^+, 13), 129 (22), 115 (11), 97 (27), 83 (37), 73 (55), 69 (65), 57 (100); Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09; O, 8.03. Found: C, 66.12; H, 4.81; N, 20.96; O, 8.17.; (c) 6*H*-Imidazo[1,2-*a*]pyrrolo[3,2-*d*]pyridine (**16**): mp = 120–121 °C; *v* (KBr): 2910, 1690, 1550, 1370, 1120 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ: 6.47 (d, 1H, $J = 3$ Hz), 7.51 (d, 1H, $J = 3$ Hz), 7.70 (s, 1H), 7.80 (s, 1H), 8.10 (s, 1H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 101.8, 108.0, 131.6, 132.3, 137.2, 144.1, 144.9, 146.0, 155.8; MS *m*/*z* 157 (M^+, 49), 129 (20), 118 (67), 57 (100); Anal. Calcd for $C_9H_7N_3$: C, 68.78; H, 4.49; N, 26.74. Found: C, 68.48; H, 4.62; N, 26.33.
13. Pineiro, J. L., Chambres, M. S.; Hobbs, S. C.; Matassa, V. G.; Reeve, A. J.; Showell, G. A.; Street, L. J. E.U. Patent 9,532,196, 1995.
14. Dechambre, C.; Chezal, J. M.; Moreau, E.; Estour, F.; Combourieu, B.; Grassay, G.; Gueiffier, A.; Enguehard, C.; Gaumet, V.; Chavignon, O.; Teulade, J. C. *Tetrahedron Lett.* **2002**, *43*, 9119.