Tetrahedron 68 (2012) 1417–1421

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Concise synthesis of new bridged-nicotine analogues

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ARTICLE INFO

Article history:
Received 24 October 2011
Received in revised form 26 November 2011
Accepted 12 December 2011
Available online 16 December 2011

Keywords:
Pyridine metallation
Bridged-nicotine analogue
Suzuki–Miyaura cross-coupling reaction
Nicotinic acetylcholine receptor
Intramolecular reductive amination

ABSTRACT

This study describes a very efficient strategy for the synthesis of two new bridged-nicotine analogues. Starting from either 4- or 3-chloropyridine the desired tricyclic ring systems are accessed in just three steps in 23% and 40% overall yield, respectively.

1. Introduction

The nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels belonging to the Cys-loop receptor family. The involvement of nAChRs in a wide range of diseases as well as neurodegenerative and psychiatric disorders has made this class of receptors a popular target for drug discovery.[1] During the last decades, structural modifications of nicotine have been the starting point for many drug discovery programs.[2] Introduction of conformational restraint to flexible lead molecules is a tried and tested approach in the development of new ligands and nicotine is no exception. Thus, the constrained nicotine scaffolds **1**,[3] **2**[4] and **3**[5] in Fig. 1 have provided new and interesting pharmacological tools.[6]

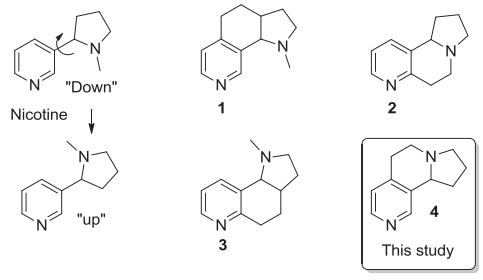

Fig. 1. Structure of nicotine and selected conformational restricted analogues.

Ligands **1** and **2** lock nicotine in the 'down' position,[2a] whereas compound **3** locks nicotine in the 'up' position. Surprisingly, the direct analogue of nicotine locked in the 'up' position, i.e., compound **4** has not yet been described in the literature. Herein we report a very efficient synthesis of this novel bridged-nicotine analogue and the application of this approach to an isomeric ring system using the same methodology.

The first synthetic strategy towards **4** from the three commercially available building blocks **5**–**7** is outlined in Fig. 2. *ortho*-Lithiation of 4-chloropyridine hydrochloride (**5**) and subsequent trapping with *N*-Boc-pyrrolidinone **6**,[7] followed by formation of the pyrrolidine moiety via intramolecular reductive amination, a Suzuki–Miyaura cross-coupling reaction with vinylboronic ester **7**[8] and finally a second reductive amination should deliver the tricyclic ring system.

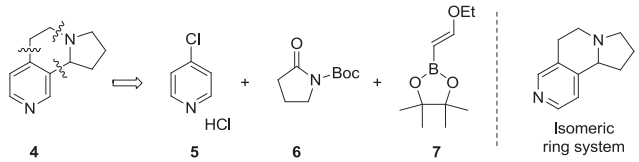

Fig. 2. Retrosynthetic analysis.

2. Results and discussion

For the synthesis of the desired 3,4-disubstituted pyridine **8**, we followed a modified procedure of the method recently published by Jensen and co-workers.[9] Starting material **5** was selectively

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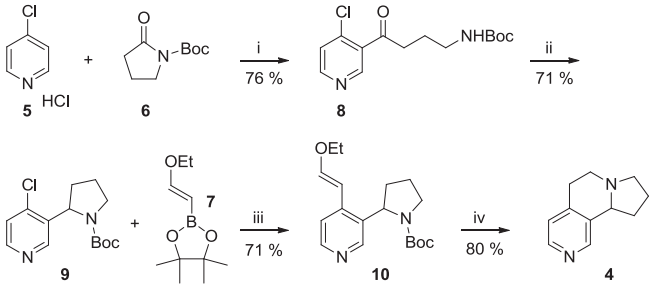
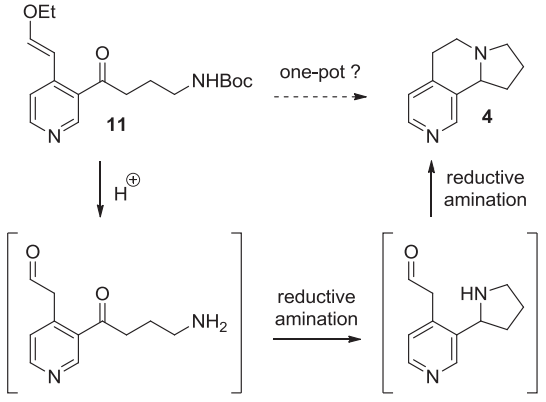
doi:10.1016/j.tet.2011.12.029

metallated at −78 °C in dry THF with freshly prepared lithium diisopropylamide (LDA) and subsequently quenched with pyrrolidinone **6** to give 4-chloropyridine **8** in 76% yield. After deprotection of the Boc group in a mixture TFA/CH_2Cl_2 (1:1) at room temperature, the amine underwent an in situ cyclization resulting in the formation of an imine, which was reduced to the corresponding pyrrolidine using an excess of $NaBH_4$. To ease purification and to obtain a more suitable compound for the Suzuki–Miyaura[10] cross-coupling reaction, the intermediate amine was protected with $(Boc)_2O$ furnishing pyridine **9** in 71% yield on multigram scale over three steps. NMR spectroscopy analysis of **9** showed the existence of two rotamers at room temperature, which was in correlation with the recent results published by Campos and co-workers on *N*-Boc-pyrrolidine derivatives.[11] The recent cross-coupling procedure described by Whelligan and co-workers[8] using boronic ester **7** (1.9 equiv), Pd(OAc) (3 mol %), SPhos[12] (7 mol %) and K_3PO_4 (2 equiv) in a CH_3CN/water (3:2) mixture was successfully applied on our substrate under microwave (MW) conditions at 85 °C for 3 h providing pyridine **10** in 71% yield.[13] Subsequent treatment in a TFA/CH_2Cl_2 (1:1) mixture furnished an iminium salt intermediate, which was reduced with an excess of $NaBH_4$ in MeOH leading to new bridged-nicotine analogue **4** in a four-step synthesis in 31% overall yield (Scheme 1).



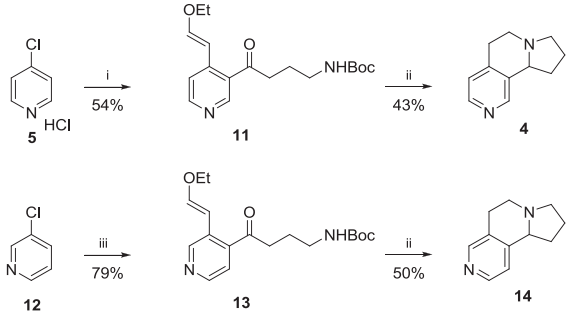
Scheme 1. Reagents and conditions: (i) (a) LDA (2.5 equiv), THF, −78 °C; (b) **6** (1.3 equiv), −78 °C to rt; (ii) (a) TFA/CH_2Cl_2 (1:1), 0 °C to rt; (b) $NaBH_4$ (5 equiv), MeOH, 0 °C to rt; (c) $(Boc)_2O$ (1.5 equiv), DMAP (0.2 equiv), TEA (1.5 equiv), CH_2Cl_2, rt; (iii) **7** (1.9 equiv), SPhos (7 mol %), $Pd(OAc)_2$ (3.5 mol %), K_3PO_4 (2 equiv), CH_3CN/water (3:2), MW, 85 °C; (iv) (a) TFA/CH_2Cl_2 (1:1), 0 °C to rt; (b) $NaBH_4$ (5 equiv), MeOH, 0 °C to rt.

In an attempt to decrease the number of steps we investigated another protocol in which a double intramolecular reductive amination from vinylpyridine **11** would form two rings in one step (Scheme 2). This key intermediate **11** should be available via a Suzuki–Miyaura cross-coupling reaction of **8** with **7**.



Scheme 2. Proposed synthesis of **4** via one-pot double reductive aminaton from **11**.

The synthesis of **4** via **11** is depicted in Scheme 3. Pyridine **5** was *ortho*-lithiated with LDA (2.5 equiv) and subsequently quenched with a slight excess of **6**. After work-up the crude material was immediately employed in the Suzuki–Miyaura cross-coupling reaction with vinylboronic **7** at 85 °C for 70 min under MW conditions giving 3,4-disubstituted pyridine **11** in 54% yield. Subsequent treatment in TFA/CH_2Cl_2 (1:1) and reduction of the intermediate with $NaBH_4$ led to **4** in a three-step synthesis in 23% overall yield (Scheme 3).



Scheme 3. Reagents and conditions: (i) (a) LDA (2.5 equiv), THF, −78 °C; (b) **6** (1.3 equiv), −78 °C to rt; (c) **7** (1.9 equiv), SPhos (6 mol %), $Pd(OAc)_2$ (3 mol %), K_3PO_4 (2 equiv), CH_3CN/water (3:2), MW, 85 °C; (ii) (a) TFA/CH_2Cl_2 (1:1), 0 °C to rt to 40 °C; (b) $NaBH_4$ (5 equiv), MeOH, 0 °C to rt; (iii) (a) LDA (1.2 equiv), THF, −78 °C; (b) **6** (1.3 equiv), −78 °C to rt; (c) **7** (1.9 equiv), SPhos (6 mol %), $Pd(OAc)_2$ (3 mol %), K_3PO_4 (2 equiv), CH_3CN/water (3:2), MW, 85 °C.

To extend the scope of this methodology an isomeric naphthyridine ring **14** has been synthesized. Thus, after metallation of 3-chloropyridine **12** and subsequent quenching with pyrrolidinone **6** the crude intermediate underwent a Suzuki–Miyaura cross-coupling reaction in the presence of boronic ester **7** within 2 h under MW conditions providing the 3,4-disubstituted pyridine **13** in 79% yield. Treatment in acidic media followed by reduction of the iminium salt furnished the novel tricycle **14** in 40% overall yield (Scheme 3).

3. Conclusion

In summary, a mild and short method for the preparation of a new bridged-nicotine analogue has been developed. This strategy can allow the construction of novel substructures and building blocks for applications in medicinal chemistry. Further studies concerning the construction of new scaffolds are in progress in our laboratories. The pharmacological evaluation of the new nicotine derivatives **4** and **14** will be reported elsewhere in due course.

4. Experimental section

4.1. General

Starting materials and reagents were obtained from commercial suppliers and used without further purifications. Syringes, which were used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use. THF was continuously refluxed and freshly distilled from sodium/benzophenone under nitrogen. Other solvents were analytical or HPLC grade and were used as received. *n*-BuLi was titrated following the procedure described by Burchat and co-workers.[14] Yields refer to isolated compounds estimated to be >98% pure as determined by ^1H NMR (25 °C). Thin-layer chromatography (TLC) was carried out on silica gel 60 F_{254} plates from Merck (Germany). Visualization was accomplished by UV lamp (254 nm), or with either cemol dip with heat or iodine on silica as an indicator. Flash column chromatography was performed on chromatography grade, silica 60 Å particle size 35–70 μ from Fisher

Scientific using the solvent system stated. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 300 (Mercury and Gemini) instruments, using $CDCl_3$ as solvent and TMS as internal standard. Coupling constants (*J* values) are given in hertz (Hz). Multiplicities of ^{1}H NMR signals are reported as follows: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; t, triplet; q, quartet; quint: quintet; m: multiplet; br s, broad signal. Microwave-assisted synthesis was carried out in a Biotage Initiator apparatus operating in single mode; the microwave cavity producing controlled irradiation at 2.45 GHz (Biotage AB, Uppsala, Sweden). The reactions were run in sealed vessels. These experiments were performed by employing magnetic stirring and a fixed hold time using variable power to reach (during 1–2 min) and then maintain the desired temperature in the vessel for the programmed time period. The temperature was monitored by an IR sensor focused on a point on the reactor vial glass. The IR sensor was calibrated to internal solution reaction temperature by the manufacturer. High-resolution mass spectra (HRMS) were obtained using a Micromass Q-TOF 2 instrument and are all within 5 ppm of the theoretical values. Melting points (mp) were measured using a MPA100 Optimelt melting point apparatus and are uncorrected. The following abbreviations are used: PE: petroleum ether; THF: tetrahydrofuran; TEA: triethylamine; Cp_2ZrHCl: bis(cyclopentadienyl)zirconium(IV) chloride hydride; SPhos: 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine; $(Boc)_2O$: di-*tert*-butyl dicarbonate; TFA: trifluoroacetic acid; DMAP: 4-dimethylaminopyridine; EtOAc: ethyl acetate.

*4.1.1. N-tert-Butoxycarbonylpyrrolidinone (**6**)[7b].* To a solution of 2-pyrrolidone (5.99 g, 70.38 mmol, 1 equiv) in CH_3CN (130 mL) were added successively $(Boc)_2O$ (18.43 g, 84.46 mmol, 1.2 equiv) and DMAP (0.86 g, 7.04 mmol, 0.1 equiv) at room temperature. The reaction mixture was stirred at this temperature for 14 h then the solvent was removed in vacuo. The crude material was taken up in EtOAc (100 mL) and washed with brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting material was purified by column chromatography using a gradient elution (EtOAc/PE, 1:1 to 2:1) to provide *N-tert*-butoxycarbonylpyrrolidinone **6** (11.01 g, 84%) as a pale yellow oil; R_f=0.45 (Et_2O/PE, 1:20); ^{1}H NMR (300 MHz): δ 3.74 (t, *J*=7.7, 2H), 2.51 (t, *J*=8.0, 2H), 2.00 (m, 2H), 1.94 (s, 9H); ^{13}C NMR (75 MHz): δ 174.5, 150.3, 82.9, 46.7, 33.2, 28.3 (3C), 17.7.

*4.1.2. (E)-2-(2-Ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**7**)[8].* To a cooled solution of ethoxyethyne (ca. 40% w/w solution in hexanes, 5.69 g, 32.47 mmol, 1.3 equiv) in CH_2Cl_2 (70 mL) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.62 mL, 24.98 mmol, 1 equiv) at 0 °C followed by Cp_2ZrHCl (387 mg, 1.50 mmol, 0.06 equiv) under N_2. After 5 min the reaction mixture was allowed to warm up to room temperature and stirred at this temperature for 16 h then solvents were removed in vacuo. The crude material was purified by column chromatography using a gradient elution (heptane/EtOAc, 9:1 to 8:1) to furnish (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **7** (4.01 g, 81%) as a colourless liquid; R_f=0.40 (heptane/EtOAc, 9:1); ^{1}H NMR (300 MHz): δ 7.03 (d, *J*=14.6, 1H), 4.43 (d, *J*=14.6, 1H), 3.84 (q, *J*=6.9, 2H), 1.30 (t, *J*=6.9, 3H), 1.26 (s, 12H); ^{13}C NMR (75 MHz): δ 163.1, 87.6 (br s), 82.8 (2C), 64.5, 25.0 (4C), 14.8.

*4.1.3. tert-Butyl 4-(4-chloropyridin-3-yl)-4-oxobutylcarbamate (**8**).* To a solution of diisopropylamine (266 μL, 1.90 mmol, 2.5 equiv) in dry THF (2 mL) under N_2 at −78 °C was added *n*-BuLi (1.3 M in hexanes, 1.46 mL, 1.90 mmol, 2.5 equiv). The resulting pale yellow solution was stirred at this temperature for 10 min then warmed up to 0 °C, stirred at this temperature for 10 min then cooled back to −78 °C and transferred via cannula to a suspension of 4-chloropyridine hydrochloride **5** (114 mg, 0.76 mmol, 1 equiv) in dry THF (1 mL) over 5 min. The orange reaction mixture was stirred at −78 °C for 1 h prior to the addition of a solution of pyrrolidinone **6** (183 mg, 0.99 mmol, 1.3 equiv) in dry THF (1.5 mL) over 5 min. The resulting reaction mixture was stirred at −78 °C for 2 h then allowed to slowly warm up to room temperature overnight. The resulting solution was quenched with water and extracted with EtOAc (2×20 mL) then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by column chromatography using Et_2O/PE (20:1) as eluent to yield *tert*-butyl 4-(4-chloropyridin-3-yl)-4-oxobutylcarbamate **8** (172 mg, 76%) as a pale yellow oil; R_f=0.45 (Et_2O); ^{1}H NMR (300 MHz): δ 8.70 (s, 1H), 8.55 (d, *J*=5.2, 1H), 7.37 (d, *J*=5.2, 1H), 4.64 (br s, 1H), 3.17–3.28 (m, 2H), 3.02 (t, *J*=6.9, 2H), 1.94 (quint, *J*=6.9, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz): δ 207.8, 156.2, 152.3, 150.1, 141.4, 134.7, 125.6, 79.7, 40.6, 40.1, 28.9 (3C), 24.7; HRMS (EI): MNa^+, found 321.0984. $C_{14}H^{35}_{19}ClN_2O_3$ requires 321.0982.

*4.1.4. tert-Butyl 2-(4-chloropyridin-3-yl)pyrrolidine-1-carboxylate (**9**).* To a solution of pyridine **8** (2.88 g, 9.64 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was added dropwise TFA (20 mL) at 0 °C. The reaction was allowed to warm up to room temperature and stirred at this temperature for 3 h then basified by addition of a saturated aqueous solution of K_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (5×70 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting material was dissolved in MeOH (40 mL) and cooled to 0 °C prior to the portionwise addition of $NaBH_4$ (1.82 g, 48.20 mmol, 5 equiv). The reaction was allowed to warm up to room temperature and stirred at this temperature for 1 h then quenched by addition of an aqueous solution of HCl (1 M, 8 mL). The reaction mixture was basified by addition of a saturated aqueous solution of K_2CO_3 and extracted with CH_2Cl_2 (5×30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting crude was taken up in CH_2Cl_2 (20 mL) then $(Boc)_2O$ (3.16 g, 14.46 mmol, 1.5 equiv), TEA (2.01 mL, 14.46 mmol, 1.5 equiv) and DMAP (236 mg, 1.93 mmol, 0.2 equiv) were successively added at room temperature. The reaction mixture was stirred at this temperature for 14 h then washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by column chromatography using EtOAc as eluent to give *tert*-butyl 2-(4-chloropyridin-3-yl)pyrrolidine-1-carboxylate **9** (1.93 g, 71%) as a yellow oil; the product was identified as a mixture of 2 rotamers in a 1:1 ratio; R_f=0.65 (EtOAc); ^{1}H NMR (300 MHz): δ 8.29–8.39 (m, 2H), 7.25 (d, *J*=5.2, 1H), 5.24 (br d, *J*=7.2, 0.5H), 5.10 (dd, *J*=7.7, 4.7, 0.5H), 3.60–3.72 (m, 1.5H), 3.46–3.59 (m, 0.5H), 2.28–2.47 (m, 1H), 1.75–1.98 (m, 3H), 1.45 (s, 4H), 1.19 (s, 5H); ^{13}C NMR (75 MHz): δ 154.4*, 154.1, 148.9*, 148.8, 148.5, 147.9*, 141.7, 137.9, 136.8*, 124.8*, 124.4, 80.2*, 80.0, 57.4, 57.3*, 47.7*, 47.4, 34.1, 32.9*, 28.8 (3C)*, 28.4 (3C), 23.7*, 23.6; *signal corresponding to the minor rotamer; HRMS (EI): MH^+ found 283.1230. $C_{14}H^{35}_{19}ClN_2O_2$ requires 283.1213.

*4.1.5. (E)-tert-Butyl 2-[4-(2-ethoxyvinyl)pyridin-3-yl]pyrrolidine-1-carboxylate (**10**).* In an MW vial were successively added SPhos (30 mg, 7 mol %), $Pd(OAc)_2$ (8 mg, 3.5 mol %), K_3PO_4 (450 mg, 2.12 mmol, 2 equiv), 4-chloropyridine **9** (300 mg, 1.06 mmol, 1 equiv), boronic ester **7** (399 mg, 2.02 mmol, 1.9 equiv), CH_3CN (3 mL) and water (2 mL). The MW vial was purged with N_2 for 5 min then heated at 85 °C for 3 h under MW conditions. The resulting mixture was filtered through a pad of Celite® and the pad was washed several times with EtOAc. The filtrate was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by column chromatography using EtOAc as eluent to provide (*E*)-*tert*-butyl 2-[4-(2-ethoxyvinyl)pyridin-3-yl]pyrrolidine-1-carboxylate **10** (240 mg, 71%) as an orange

oil; the product was identified as a mixture of 2 rotamers in a 1.2:1 ratio; R_f=0.40 (EtOAc); ^{1}H NMR (300 MHz): δ 8.17–8.34 (m, 2H), 7.11 (d, J=5.3, 1H), 6.99 (d, J=12.4, 1H), 5.89 (d, J=12.4, 1H), 5.14 (br d, J=7.4, 0.45H), 4.89–5.00 (m, 0.55H), 3.86–4.02 (m, 2H), 3.43–3.72 (m, 2H), 2.12–2.37 (m, 1H), 1.67–1.98 (m, 3H), 1.45 (s, 4H), 1.29–1.40 (3H), 1.18 (s, 5H); ^{13}C NMR (75 MHz): δ 154.4*, 154.3, 151.64*, 151.59, 148.1*, 147.9, 147.4, 146.5*, 141.6*, 141.3, 135.6, 134.4*, 119.0*, 118.8, 101.0, 80.0*, 79.8, 66.7, 66.4*, 57.3, 56.9*, 47.6*, 47.4, 34.6, 33.2*, 28.9 (3C)*, 28.5 (3C), 23.5, 15.2; *signal corresponding to the minor rotamer; HRMS (EI): MH$^+$ found 319.2036. $C_{18}H_{26}N_2O_3$ requires 319.2022.

*4.1.6. 5,6,8,9,10,10a-Hexahydropyrrolo[2,1-a][2,7]naphthyridine (**4**) from compound **10**.* To a solution of pyridine **10** (140 mg, 0.44 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was added dropwise TFA (1 mL) at 0 °C. The reaction was allowed to warm up to room temperature and stirred at this temperature for 3 h. After removing solvents in vacuo the resulting material was dissolved in MeOH (4 mL) and cooled to 0 °C prior to the portionwise addition of $NaBH_4$ (83 mg, 2.20 mmol, 5 equiv). The reaction was allowed to warm up to room temperature and stirred at this temperature for 2 h then quenched by addition of an aqueous solution of HCl (1 M, 2 mL). The reaction mixture was basified by addition of a saturated aqueous solution of K_2CO_3 and extracted with CH_2Cl_2 (5×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by column chromatography using EtOAc/MeOH/TEA (30:2:1) as eluent to furnish 5,6,8,9,10,10a-hexahydropyrrolo[2,1-*a*][2,7]naphthyridine **4** (61 mg, 80%) as a pale yellow oil; R_f=0.20 (EtOAc/MeOH/TEA, 30:2:1); ^{1}H NMR (300 MHz): δ 8.31 (d, J=5.0, 1H), 8.29 (s, 1H), 7.02 (d, J=5.0, 1H), 3.38 (br t, J=8.5, 1H), 3.18–3.26 (m, 1H), 3.01–3.15 (m, 2H), 2.82 (br dt, J=17.3, 3.6, 1H), 2.36–2.69 (m, 3H), 1.84–2.05 (m, 2H), 1.68–1.82 (m, 1H); ^{13}C NMR (75 MHz): δ 147.28, 147.27, 143.6, 135.0, 123.5, 61.7, 53.4, 48.2, 29.9, 28.5, 22.5; HRMS (EI): MH$^+$ found 175.1231. $C_{11}H_{14}N_2$ 175.1235.

*4.1.7. (E)-tert-Butyl 4-[4-(2-ethoxyvinyl)pyridin-3-yl]-4-oxobutylcarbamate (**11**).* To a solution of diisopropylamine (701 μL, 5.00 mmol, 2.5 equiv) in dry THF (5 mL) under N_2 at −78 °C was added *n*-BuLi (1.3 M in hexanes, 3.8 mL, 5.00 mmol, 2.5 equiv). The resulting pale yellow solution was stirred at this temperature for 10 min then warmed up to 0 °C, stirred at this temperature for 10 min then cooled back to −78 °C and transferred via cannula to a suspension of 4-chloropyridine hydrochloride **5** (300 mg, 2.00 mmol, 1 equiv) in dry THF (3 mL) over 5 min. The orange reaction mixture was stirred at −78 °C for 1 h prior to the addition of a solution of pyrrolidinone **6** (481 mg, 2.60 mmol, 1.3 equiv) in dry THF (4 mL) over 5 min. The resulting reaction mixture was stirred at −78 °C for 2 h then allowed to slowly warm up to room temperature overnight. The resulting solution was quenched with water and extracted with EtOAc (2×60 mL) then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was dissolved in CH_3CN (6 mL) and added into an MW vial containing SPhos (49 mg, 6 mol %), $Pd(OAc)_2$ (14 mg, 3 mol %), K_3PO_4 (849 mg, 4.00 mmol, 2 equiv), boronic ester **13** (753 mg, 3.80 mmol, 1.9 equiv) and water (4 mL). The MW vial was purged with N_2 for 5 min then heated at 85 °C for 70 min under MW conditions. The resulting mixture was filtered through a pad of Celite® and the pad was washed several times with EtOAc. The filtrate was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by column chromatography using a gradient elution (Et_2O/EtOAc, 10:1 to 10:3) to yield (*E*)-*tert*-butyl 4-[4-(2-ethoxyvinyl)pyridin-3-yl]-4-oxobutylcarbamate **11** (362 mg, 54%) as a yellow oil, which solidified; the product was identified as a mixture of 2 rotamers in a 1.5:1 ratio; mp 90–93 °C; R_f=0.25 (Et_2O/EtOAc, 10:1); ^{1}H NMR (300 MHz): δ 8.79 (s, 0.6H), 8.73 (s, 0.4H), 8.51 (d, J=5.5, 0.4H), 8.45 (d, J=5.5, 0.6H), 8.02 (d, J=5.5, 0.4H), 7.30 (d, J=5.5, 0.6H), 7.20 (d, J=12.9, 0.6H), 6.45–6.52 (m, 1H), 5.79 (d, J=7.2, 0.4H), 4.62 (br s, 1H), 4.07 (q, J=7.2, 0.8H), 3.98 (q, J=7.2, 1.2H), 3.17–3.27 (m, 2H), 2.93–3.01 (m, 2H), 1.87–2.02 (m, 2H), 1.34–1.46 (m, 12H); ^{13}C NMR (75 MHz): δ 202.4, 156.1, 153.4, 151.3, 150.1, 144.5, 130.7, 119.3, 101.8, 79.3, 66.1, 40.1, 39.3, 28.6 (3C), 24.8, 14.9; HRMS (EI): MH$^+$ found 335.1967. $C_{18}H_{26}N_2O_4$ requires 335.1971.

*4.1.8. 5,6,8,9,10,10a-Hexahydropyrrolo[2,1-a][2,7]naphthyridine (**4**) from compound **11**.* To a solution of pyridine **11** (335 mg, 1.00 mmol, 1 equiv) in CH_2Cl_2 (3 mL) was added dropwise TFA (3 mL) at 0 °C. The reaction was allowed to warm up to room temperature and stirred at this temperature for 3 h. After removing solvents in vacuo the resulting material was dissolved in MeOH (6 mL) and cooled to 0 °C prior to the portionwise addition of $NaBH_4$ (189 mg, 5.00 mmol, 5 equiv). The reaction was allowed to warm up to room temperature and stirred at this temperature for 2 h then quenched by addition of an aqueous solution of HCl (1 M, 3 mL). The reaction mixture was basified by addition of a saturated aqueous solution of K_2CO_3 and extracted with CH_2Cl_2 (5×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by column chromatography using EtOAc/MeOH/TEA (30:2:1) as eluent to furnish 5,6,8,9,10,10a-hexahydropyrrolo[2,1-*a*][2,7]naphthyridine **4** (74 mg, 43%) as a pale yellow oil.

*4.1.9. (E)-tert-Butyl 4-[3-(2-ethoxyvinyl)pyridin-4-yl]-4-oxobutylcarbamate (**13**).* To a solution of diisopropylamine (168 μL, 1.20 mmol, 1.2 equiv) in dry THF (2 mL) under N_2 at −78 °C was added *n*-BuLi (2.5 M in hexanes, 480 μL, 1.20 mmol, 1.2 equiv). The resulting pale yellow mixture was stirred at this temperature for 10 min then warmed up to 0 °C and stirred at this temperature for 10 min. After cooling back to −78 °C, a solution of 3-chloropyridine **12** (113 mg, 1.00 mmol, 1 equiv) in dry THF (2 mL) was added dropwise and the reaction was stirred at −78 °C for 1 h. After addition of a solution of pyrrolidinone **6** (241 mg, 1.30 mmol, 1.3 equiv) in dry THF (3 mL) over 2 min, the resulting reaction mixture was stirred at −78 °C for 2 h then allowed to slowly warm up to room temperature and stirred at this temperature for 30 min. The resulting solution was quenched with water and extracted with CH_2Cl_2 (4×20 mL) then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was dissolved in CH_3CN (3 mL) and added into an MW vial containing SPhos (25 mg, 6 mol %), $Pd(OAc)_2$ (7 mg, 3 mol %), K_3PO_4 (425 mg, 2.00 mmol, 2 equiv), boronic ester **7** (376 mg, 1.90 mmol, 1.9 equiv) and water (2 mL). The MW vial was purged with N_2 for 5 min then heated at 85 °C for 2 h under MW conditions. The resulting mixture was filtered through a pad of Celite® and the pad was washed several times with EtOAc. The filtrate was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by column chromatography using Et_2O/PE (20:1) as eluent to yield (*E*)-*tert*-butyl 4-[3-(2-ethoxyvinyl)pyridin-4-yl]-4-oxobutylcarbamate **13** (265 mg, 79%) as a yellow oil; R_f=0.35 (Et_2O/PE, 20:1); ^{1}H NMR (300 MHz): δ 8.63 (s, 1H), 8.43 (d, J=5.0, 1H), 7.28 (d, J=5.0, 1H), 6.90 (d, J=12.9, 1H), 6.12 (d, J=12.9, 1H), 4.71 (br s, 1H), 3.92 (q, J=7.2, 2H), 3.10–3.24 (m, 2H), 2.88 (t, J=7.2, 2H), 1.87 (quint, J=7.2, 2H), 1.41 (s, 9H), 1.34 (t, J=7.2, 3H); ^{13}C NMR (75 MHz): δ 203.8, 156.2, 151.0, 148.3, 147.1, 142.4, 129.8, 121.0, 100.5, 79.6, 66.1, 40.2, 39.5, 28.7 (3C), 24.7, 15.1; HRMS (EI): MH$^+$ found 335.1964. $C_{18}H_{26}N_2O_4$ requires 335.1971.

*4.1.10. 5,6,8,9,10,10a-Hexahydropyrrolo[2,1-a][2,6]naphthyridine (**14**).* To a solution of pyridine **13** (285 mg, 0.85 mmol, 1 equiv) in CH_2Cl_2 (3 mL) was added dropwise TFA (3 mL) at 0 °C. The reaction was allowed to warm up to room temperature and stirred at this temperature for 3 h. After removing solvents in vacuo the resulting material was dissolved in MeOH (5 mL) and cooled to 0 °C prior to the portionwise addition of $NaBH_4$ (161 mg, 4.26 mmol, 5 equiv).

The reaction was allowed to warm up to room temperature and stirred at this temperature for 2 h then quenched by addition of an aqueous solution of HCl (1 M, 3 mL). The reaction mixture was basified by addition of a saturated aqueous solution of K_2CO_3 and extracted with CH_2Cl_2 (5×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by column chromatography using EtOAc/MeOH/TEA (30:2:1) as eluent to give 5,6,8,9,10,10a-hexahydropyrrolo[2,1-*a*][2,6]naphthyridine **14** (74 mg, 50%) as a pale yellow oil; R_f=0.15 (EtOAc/MeOH/TEA, 30:2:1); ^{1}H NMR (300 MHz): δ 8.30 (s, 1H), 8.29 (d, J=5.0, 1H), 6.93 (d, J=5.0, 1H), 3.39 (br t, J=8.5, 1H), 3.15–3.23 (m, 1H), 2.94–3.09 (m, 2H), 2.78 (br dt, J=16.8, 3.6, 1H), 2.59–2.69 (m, 1H), 2.52 (dt, J=8.6 and J=8.0, 1H), 2.26–2.38 (m, 1H), 1.78–1.99 (m, 2H), 1.61–1.75 (m, 1H); ^{13}C NMR (75 MHz): δ 149.8, 147.6, 147.1, 130.2, 120.6, 62.6, 53.2, 48.0, 29.9, 25.7, 22.5; HRMS (EI): MH^+ found 175.1226. $C_{11}H_{14}N_2$ requires 175.1235.

Acknowledgements

The authors thank the Danish Council for Independent Research—Medical Sciences for financial support.

Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for compounds **4**, **11**, **13** and **14**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.12.029.

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