DOI: 10.1002/ejoc.201000936

A New Sequential Intramolecular Cyclization Based on the Boekelheide Rearrangement

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Keywords: Pyridine *N*-oxides / Boekelheide rearrangement / Cyclization / Intramolecular reactions / Nitrogen heterocycles / Synthetic methods

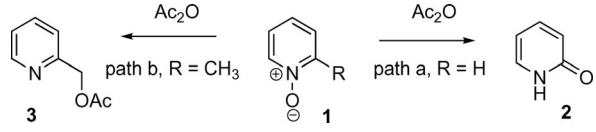
Pyrrolidines and piperidines were synthesized from (aminoalkyl)pyridine *N*-oxides with a general and quite efficient method developed by using di-*tert*-butylsilyl bis(trifluoromethanesulfonate) as a new promoter for a Boekelheide-type reaction. The use of a new Boekelheide promoter, which is compatible with amino groups, opens new perspectives in view of its application in intramolecular cyclizations.

Introduction

The development of new synthetic methodologies has reached a level, which allows organic chemists to plan and perform almost any kind of functional-group transformation. Nevertheless, despite such an achievement, investigations in this field are still highly desirable and required to solve problems, which we are now facing with respect to sustainable development. Multistep syntheses are now less desirable in view of the needs for economically and ecologically justifiable processes. Modern syntheses must deal carefully with our resources and must be designed in a way that allows easy and short access to diversified substance libraries. A general way to improve synthetic efficiency and also to give access to a multitude of diversified molecules is the development of sequential reactions, which allow the formation of complex compounds, starting from simple substrates in a single transformation consisting of several steps.[1] In this respect, we decided to investigate in detail the Boekelheide rearrangement[2] as a tool for a new one-step intramolecular cyclization to give heterocycles.

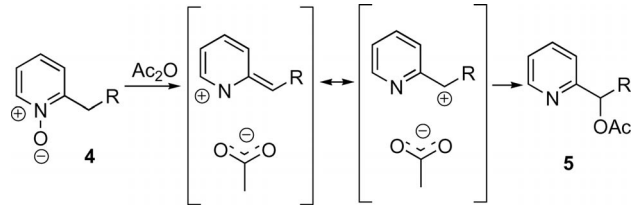
Results and Discussion

Since the late 1940s, the reactivity of pyridine *N*-oxide, mediated by *N*-oxide activators, has attracted the interest of several research groups. The transformation of pyridine *N*-oxide **1** to the corresponding 2-pyridone **2** with acetic anhydride (Scheme 1, path a) was the first example reported in this field.[3–5]



Scheme 1.

A few years later, Boekelheide[6–8] established a different procedure, which allowed oxygen functionalities to be transferred onto alkyl groups in the 2-position of pyridine rings. It was also clearly established that oxygen migration could occur on the alkyl chain of substituents attached to position 4 of the heteroaromatic ring. This process, which is now known as Boekelheide reaction, requires the activation of pyridine *N*-oxides[9] by electrophilic agents such as Ac_2O, as in the original example, or others like P_2O_5, TFAA, or TsCl. Despite many efforts, the mechanism[10–16] of this rearrangement is not completely understood, and its interpretation has evolved with time. At present, the generally accepted explanation involves an ion-pair mechanism[17,18] as shown in Scheme 2 for the rearrangement occurring in position 2.



Scheme 2.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000936.

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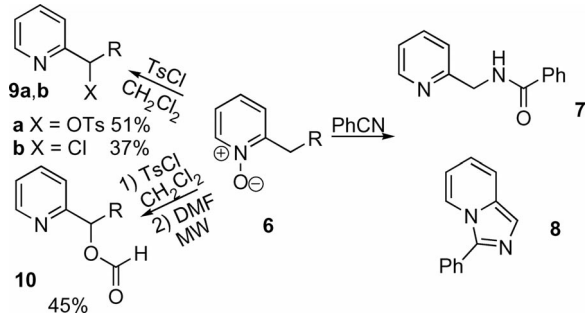
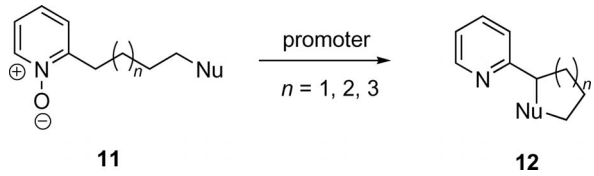
Although it has potential, the Boekelheide reaction has found only a limited number of applications so far, mainly due to the need for protection of other functional groups in the molecule that cannot tolerate the use of highly reactive promoters such as Ac_2O, P_2O_5, TFAA and TsCl. The Boekelheide rearrangement can be formally considered as an activation of the pyridine ring followed by a nucleophilic attack; but only a few nucleophiles, other than acetate, are compatible with the activation conditions usually employed. The resulting lack of extensive studies on nucleophilic reactions induced by the Boekelheide rearrangement coupled with our interest in developing new efficient synthetic procedures, were the driving force to initiate the investigation described here.

An early observation by Cohen demonstrated that Boekelheide reactions carried out in benzonitrile[19] lead to the formation of products derived from trapping the Boekelheide cationic intermediate with the nitrile species, albeit in minor amounts (**7** and **8**). In our experiments on classical Boekelheide rearrangements, when tosyl chloride was used as promoter, we isolated the product derived from nucleophilic attack of the chloride (**9b**) as well as the expected transposition product **9a**. On the other hand, upon subjection of the tosylate derivative to microwave (MW) irradiation in DMF, the nucleophilic attack of formate occurred, leading to compound **10** (Scheme 3).

These results clearly demonstrated that a nucleophile present in the reaction medium during the rearrangement, other than the oxygenated species derived from the pyridine *N*-oxide, could be trapped by the Boekelheide intermediate. This allowed us to plan a new strategy in which the nucleophile would be bonded to the pyridine ring (as in **11**), and could then lead to heterocyclic compounds **12** through an intramolecular telescopic process (Scheme 4).

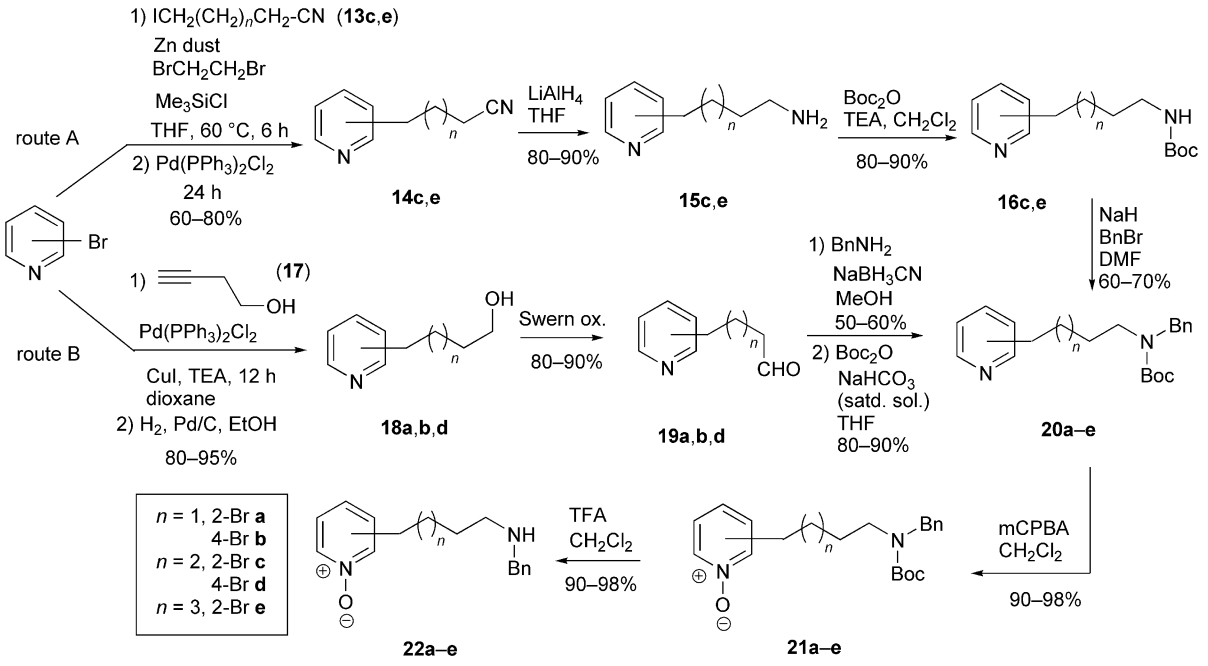


Scheme 3.



Scheme 4.

In this paper we report our initial systematic investigation on these new intramolecular Boekelheide reactions as a function of the reaction conditions, the length and the position of the lateral chain (i.e. the size of the newly formed ring), and the promoter. The choice of the latter is crucial, because the usual promoters greatly limit the scope of this strategy, which – in order to become synthetically useful – needs to be free from these limitations. For this reason, we have also envisaged a new possible promoter, which would allow a broader range of nucleophiles to be employed. Several (aminoalkyl)pyridine *N*-oxides were prepared for this purpose according to the procedure outlined in Scheme 5.



Scheme 5.

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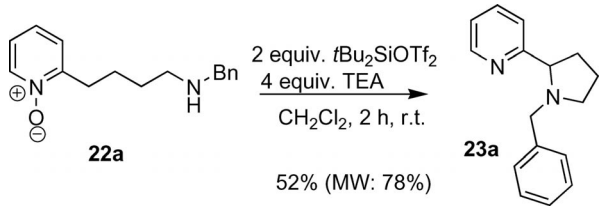
We synthesized the intermediates **20a**–**e** according to two possible routes. Route A involved a Pd^{II}-catalyzed cross-coupling[21] between 2-bromopyridine and the required iodoalkanenitrile **13c**,**e** (obtained from the commercially available chloroalkyl cyanide by chlorine/iodine exchange[20]) to give the intermediates **14c**,**e**, which – after reduction of the nitrile functionality, protection with Boc anhydride, and substitution with benzyl bromide – led to the [(benzylamino)alkyl]pyridines **20c**,**e**. Route B consited of a Sonogashira coupling[22] of 2- or 4-bromopyridine with the commercially available alkynol **17** to give the intermediates **18a**,**b**,**d**, which – by oxidation, reductive amination with benzylamine, and Boc protection – led to **20a**,**b**,**d**. The pyridine rings of these intermediates were then oxidized with *m*CPBA[23] (**21a**–**e**), and final deprotection with TFA afforded **22a**–**e**, starting materials for the cyclization reactions.

Due to the incompatibility of the traditional promoters with amino groups, we envisaged the possibility of using silyl derivatives as activators for the Boekelheide reaction. Their oxophilic nature was deemed compatible with the presence of unprotected basic amines that could participate by intramolecular reaction with the activated pyridine *N*-oxide. Our reagent of choice for testing the intramolecular rearrangements was di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (tBu$_2$SiOTf$_2$), which is commercially available and features the presence of a non-nucleophilic counterion. We were pleased to find that when the amino pyridine *N*-oxide **22a** was treated with tBu$_2$SiOTf$_2$ and triethylamine in dichloromethane, the 2-(*N*-benzylpyrrolidin-2-yl)pyridine[24] **23a** was obtained as planned.

A careful screening of all the parameters involved in the reaction was done on the cyclization of **22a** to **23a** (see Supporting Information), from which some clear conclusions can be drawn: (i) there are no differences among the bases used [triethylamine, (dimethylamino)pyridine, diisopropylethylamine]; (ii) all the solvents used [dichloromethane, *N*,*N*-dimethylformamide (DMF), acetonitrile, tetrahydrofuran, toluene] except acetonitrile lead to the cyclization, although the yields are lower with DMF; (iii) at least 2 equiv. of promoter are required, but an additional amount does not improve the yields; (iv) 2 equiv. of base are required per equivalent of promoter; (v) increasing the temperature does not increase the yields. The cyclized product **23a** was obtained in 52% yield, which could be increased up to 78% by MW irradiation (50 °C, 250 W, 20 min) (Scheme 6).



Scheme 6.

This is, to the best of our knowledge, the first intramolecular cyclization induced by a Boekelheide reaction reported so far, and opens interesting synthetic perspectives.

Upon monitoring the reaction course by NMR spectroscopy, we observed a very fast activation of the pyridine *N*-oxide indicated by downfield shifts of all proton and carbon chemical shifts of the aromatic ring. In addition, the ^{1}H NMR spectra showed that the amine nitrogen atom was quaternarized – probably due to protonation by the triflic acid deriving from the promoter. Addition of TEA restored the original nucleophilicity. Subsequent aqueous quench led to the formation of two major identifiable species: the expected cyclised product **23a** and compound **24**, derived from a simple Boekelheide rearrangement, which was isolated in about 30% yield (Figure 1).

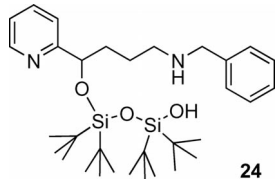
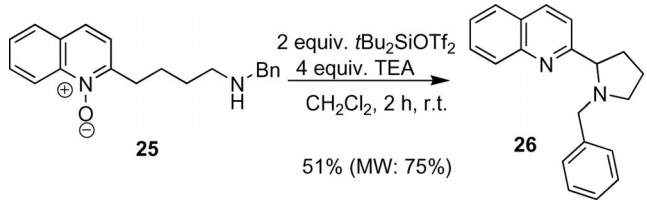


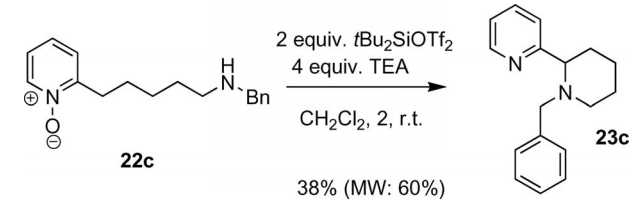
Figure 1. Side product obtained during cyclization of **22a**.

The analogous quinoline *N*-oxide **25** (prepared according to a procedure similar to that reported in Scheme 5, route A) behaves in the same way giving, after treatment with tBu$_2$SiOTf$_2$ and triethylamine in dichloromethane, the corresponding 2-(*N*-benzylpyrrolidin-2-yl)quinoline **26** in comparable yield (Scheme 7).



Scheme 7.

We also investigated the length of the chain carrying the amino group, and we obtained similar results with the amino pyridine *N*-oxides **22c** having one more carbon atom. The corresponding 2-(*N*-benzylpiperidin-2-yl)pyridine **23c** was obtained under the same reaction conditions as described above, although with lower yield (38%), which was increased to 60% by MW irradiation (Scheme 8).



Scheme 8.

The longer analogue **22e**, which would give the corresponding azepine, did not cyclize under the same reaction conditions.

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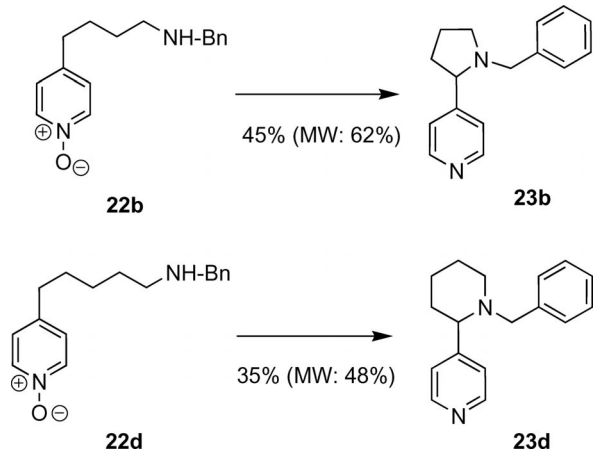
In order to extend the scope of our intramolecular Boekelheide reaction, we decided to investigate some additional (aminoalkyl)pyridine *N*-oxides. Our aim was to better understand some features of this new process. We chose substrates **22b**,**d** to verify the possibility of inducing an intramolecular cyclization at position 4 of the pyridine ring, and amines **27a**–**e** to investigate the effect of substituents on the lateral chain both on the chemical and stereochemical behaviour. Compounds **22b**,**d** were synthesized as described for the analogues with the lateral chain in the 2-position (**22a**), whereas the fully protected precursors of **27a**–**e** are commercially available. Both compounds **22b** and **22d** behave in the same manner as the analogue with substitution in position 2 (**22a**,**c**), giving the corresponding pyrrolidine **23b** and piperidine **23d** (Scheme 9). Although the yields were lower (45 and 35%, respectively), they were again slightly increased by MW irradiation (62% and 48%, respectively). Indeed, in our experiments we have found that the Boekelheide rearrangement to alkyl chains in position 4 generally occurrs with lower yields than the one in position 2.

The presence of substituents on the alkyl chain in position 2 has some effect on the yield of the cyclised products (Scheme 10). As a general trend, we have observed that the closer the methyl group is with respect to the picoline carbon atom, the lower is the yield. In the case of **27e**, the methyl group attached to carbon atom 2 of the chain forbids the attack of the amino group, leaving unreacted starting material.

In all other cases, the reaction takes place with unoptimized moderate yields (25–50%) and diastereoselectivities (from 2:1 up to 3:1) that could be improved by using the microwave irradiation.



Scheme 9.

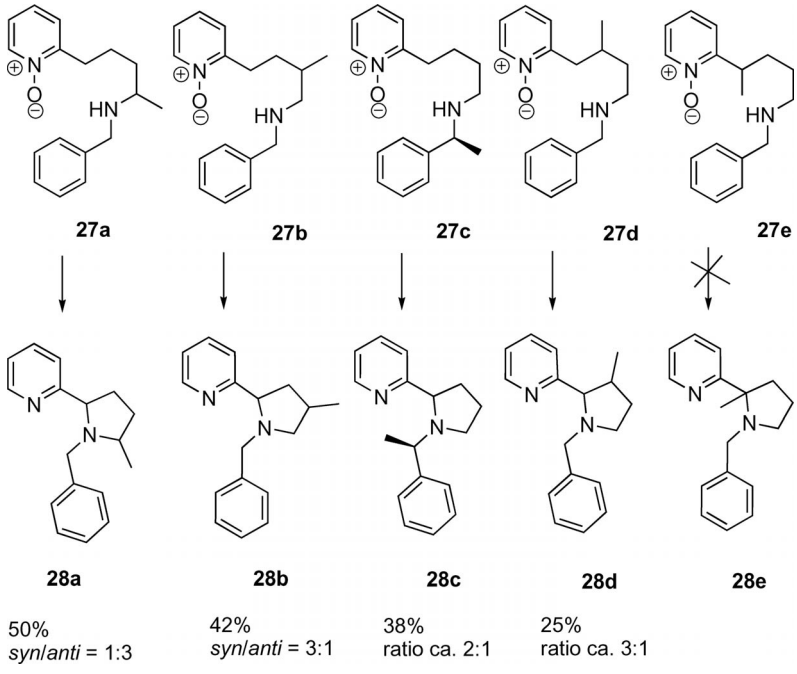
Conclusions

We have developed a general and quite efficient method to synthesize pyrrolidines and piperidines from (aminoalkyl)pyridine *N*-oxides using di-*tert*-butylsilyl bis(trifluoromethanesulfonate) as a new promoter for a Boekelheide-type reaction.

The use of a new Boekelheide promoter, which is compatible with amino groups, opens new perspectives in view of its application in intramolecular cyclizations.

Experimental Section

General Procedures: Air- and moisture-sensitive compounds were stored in Schlenk tubes or in Schlenk burettes. They were protected by and handled under 99.99% pure nitrogen. Purifications by flash



Scheme 10.

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column chromatography were performed using glass columns (10–50 mm wide); silica gel (230–400 mesh) was chosen as stationary phase, with an elution rate of 5 cm/min. ^{1}H NMR spectra were recorded at 200, 400 and 500 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: δ = 7.26 ppm). Coupling constants (*J*) were measured in Hz. Coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (doublet of a doublet), m (multiplet), br. s (broad singlet). ^{13}C NMR spectra were recorded at 50.4 and 100.6 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: δ = 77.0 ppm). Mass spectra were obtained at a 70 eV ionization potential. LC-MS analyses were performed by operating in ESI positive or negative mode. The phases used were: (A) 10 mM aqueous solution of NH_4HCO_3 (adjusted to pH = 10 with ammonia); (B) acetonitrile. The gradient was: *t* = 0 min, 97% A, 3% B; *t* = 1.06 min, 1% A, 99% B; *t* = 1.45 min, 1% A, 99% B; *t* = 1.46 min 97% A, 3% B, followed by 1 min of reconditioning. Retention times are indicated in min. Protections of amines with Boc_2O, oxidations of pyridines with *m*CPBA and deprotection of *N*-Boc-amines with TFA have been described in detail only for one example; the others were almost identical.

Materials: Starting materials were commercially available unless otherwise stated. All commercial reagents were used without further purification except triethylamine, which was distilled from calcium hydride. Anhydrous tetrahydrofuran was distilled from sodium diphenylketyl. DMF was distilled from calcium hydride and then stored over molecular sieves (4 Å). Dichloromethane was dried with calcium chloride and stored over molecular sieves (4 Å). Petroleum ether, unless specified, was the fraction with boiling range 40–70 °C.

Preparation of the (Benzylamino)pyridines

Synthesis of [4-(1-Oxido-2-pyridinyl)butyl](phenylmethyl)amine (22a): Scheme 5, route B.

4-(2-Pyridinyl)-3-butyn-1-ol: To a solution of 2-bromopyridine (6.04 mL, 63.3 mmol), CuI (0.603 g, 3.16 mmol), TEA (13.23 mL, 95 mmol), and $(PPh_3)_2PdCl_2$ (1.3 g, 1.852 mmol) in 1,4-dioxane (100 mL) stirred under nitrogen at room temp., 3-butyn-1-ol (5.75 mL, 76 mmol) was added dropwise during 15 min. Upon addition of the alcohol, the yellow solution became first red, then orange with a white precipitate. The reaction mixture was stirred at room temp. overnight, then the solvent was evaporated, and the crude reaction mixture was dissolved in EtOAc and washed with water (pH = 6). The water phase was extracted with EtOAc (4 × 30 mL), and the combined organic phases were washed with brine and dried (Na_2SO_4). The crude product was purified on silica gel (EtOAc/cyclohexane, 70:30) to give pure product (7.97 g, 85%) as a red oil. The spectroscopic data are in full agreement with literature data.[22] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.72 (t, *J* = 6.30 Hz, 2 H), 3.36 (br. s, 1 H), 3.87 (t, *J* = 6.30 Hz, 2 H), 7.18–7.22 (m, 1 H), 7.38 (d, *J* = 7.78 Hz, 1 H), 7.63 (td, *J* = 7.72, 1.88 Hz, 1 H), 8.51 (dd, *J* = 4.80, 1.5 Hz, 1 H) ppm. LC-MS: t_R = 0.46 min; *m*/*z* = 148 [M + H$^+$].

4-(2-Pyridinyl)-1-butanol (18a): To a solution of 4-(2-pyridinyl)-3-butyn-1-ol (7.97 g, 54.2 mmol) in ethanol (108 mL), palladium on carbon (2.6 g, 2.443 mmol) was added, and the reaction mixture was stirred under hydrogen at room temp. for 18 h. The mixture was filtered through a pad of Celite, and the solvent was evaporated to give **18a** (7.618 g, 93%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.52–1.73 (m, 2 H), 1.76–1.89 (m, 2 H), 2.01–2.57 (br. s, 1 H), 2.84 (t, *J* = 7.40 Hz, 2 H), 3.69 (t, *J* = 6.40 Hz, 2 H), 7.04–7.21 (m, 2 H), 7.60 (td, *J* = 7.58, 1.52 Hz, 1 H), 8.50 (d, *J* = 4.80 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 25.80, 32.06, 37.43, 62.26, 76.69, 77.32, 121.05, 122.91, 136.48, 148.95, 161.92 ppm. LC-MS: t_R = 0.46 min; *m*/*z* = 152 [MH$^+$].

4-(2-Pyridinyl)-butanal (19a): To a solution of oxalyl chloride (546 mg, 4.30 mmol) in CH_2Cl_2 (10 mL) cooled to –78 °C, DMSO (672 mg, 8.6 mmol) was added, and the mixture was stirred for 30 min. A solution of 4-(pyridin-2-yl)butan-1-ol (**18a**, 500 mg, 3.31 mmol) in CH_2Cl_2 (2 mL) was then added, and the reaction mixture was stirred at –78 °C for 1 h. TEA (1.7 mL) was added, and the reaction mixture was stirred for an additional 30 min. The reaction was quenched with water and the mixture extracted with EtOAc. The organic layer was concentrated to give crude product **19a** (460 mg, 95%) as a yellow oil, which was used as such without further purification. The spectroscopic data are in full agreement with the literature data.[25] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.00–2.17 (m, 2 H), 2.50 (td, *J* = 7.30, 1.51 Hz, 2 H), 2.84 (t, *J* = 7.50 Hz, 2 H), 7.01–7.21 (m, 2 H), 7.50–7.69 (m, 1 H), 8.53 (d, *J* = 5.04 Hz, 1 H), 9.77 (d, *J* = 1.51 Hz, 1 H) ppm. LC-MS: t_R = 0.48 min; *m*/*z* = 150 [MH$^+$].

1,1-Dimethylethyl (Phenylmethyl)[4-(2-pyridinyl)butyl]carbamate (20a): (1) To a solution of benzylamine (2.63 mL, 24.13 mmol) in MeOH (160 mL) stirred under nitrogen at room temp., a solution of 4-(2-pyridinyl)butanal (**19a**) (3.6 g, 24.13 mmol) in MeOH (20 mL) was added dropwise over 15 min. Acetic acid (4.14 mL, 72.4 mmol) was then added, and the mixture was stirred for 3 h. After this time, sodium cyanoborohydride (1.516 g, 24.13 mmol) was added, and the stirring was continued for 4 h. (2) The methanol was evaporated, and the crude (phenylmethyl)[4-(2-pyridinyl)butyl]-amine (6.60 g, 27.5 mmol) was dissolved in a mixture of THF (75 mL) and a saturated solution (1 M) of $NaHCO_3$. Boc_2O (17.98 g, 82 mmol) was then added, and the reaction mixture was vigorously stirred overnight, then extracted with EtOAc (3 × 40 mL). The organic phase was washed with brine, dried with Na_2SO_4, and the solvent was evaporated to give the crude product (6.66 g) as yellow oil. The product was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 2:1) to give pure **20a** (2.05 g, 25% over two steps) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.48 (br. s, 9 H), 1.54–1.64 (m, 4 H), 1.70 (d, *J* = 7.91 Hz, 2 H), 2.79 (t, *J* = 7.59 Hz, 2 H), 4.44 (s, 2 H), 7.10–7.18 (m, 2 H), 7.23–7.31 (m, 3 H), 7.32–7.39 (m, 2 H), 7.58–7.65 (m, 1 H), 8.49–8.54 (m, 1 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 26.96, 27.72, 28.15, 37.80, 44.80, 46.95, 84.60, 120.86, 122.63, 126.93, 128.32, 128.45, 136.14, 136.37, 148.95, 154.29, 161.67 ppm. LC-MS: t_R = 1.00 min; *m*/*z* = 341 [MH$^+$]. $C_{28}H_{28}N_2O_2$ (424.54): calcd. C 74.08, H 8.29, N 8.23, O 9.40; found C 74.04, H 8.31, N 8.25, O 9.38.

1,1-Dimethylethyl [4-(1-Oxido-2-pyridinyl)butyl](phenylmethyl)-carbamate (21a): To a solution of 1,1-dimethylethyl (phenylmethyl)[4-(2-pyridinyl)butyl]carbamate (**20a**) (1.845 g, 5.42 mmol) in CH_2Cl_2 (25 mL), *m*CPBA (1.47 g, 5.46 mmol) was added, and the reaction mixture was stirred at room temp. for 2 h. A saturated solution of $Na_2S_2O_3$ was added, and the CH_2Cl_2 was evaporated. EtOAc was added, and the organic phase was washed with $Na_2S_2O_3$ (4 × 30 mL), $NaHCO_3$ (2 × 30 mL), and brine. The organic phase was then dried (Na_2SO_4), and the solvent was evaporated to give crude **21a** (1.92 g, 99%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.40–1.51 (m, 9 H), 1.57–1.81 (m, 4 H), 2.92 (br. s, 2 H), 3.19 (br. s, 1 H), 3.29 (br. s, 1 H), 4.44 (d, *J* = 16.45 Hz, 2 H), 7.16 (d, *J* = 5.82 Hz, 1 H), 7.21 (br. s, 2 H), 7.23–7.28 (m, 3 H), 7.29–7.35 (m, 2 H), 8.27 (d, *J* = 6.26 Hz, 1 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 23.10, 27.63, 27.89, 29.92, 45.96, 49.96, 79.29, 123.14, 125.30, 126.74, 128.08, 128.17, 137.46, 138.16, 139.22, 151.77, 154.38 ppm. LC-MS: t_R = 0.81 min;

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m/z = 357 [MH$^+$]. $C_{21}H_{28}N_2O_3$ (356.46): calcd. C 70.76, H 7.92, N 7.86, O 13.47; found C 70.79, H 8.01, N 7.84, O 13.45.

[4-(1-Oxido-2-pyridinyl)butyl](phenylmethyl)amine (22a): To a solution of 1,1-dimethylethyl [4-(1-oxido-2-pyridinyl)butyl](phenylmethyl)carbamate (**21a**) (500 mg, 1.403 mmol) in CH_2Cl_2 (14 mL), stirred under nitrogen at room temp., TFA (1.081 mL, 13.03 mmol) was added, and the reaction mixture was stirred at room temp. for 4 h. The solvent and the excess TFA were evaporated, and the crude mixture was dissolved in EtOAc and washed with $NaHCO_3$ containing some NaOH pellets. The organic phase was dried with Na_2SO_4, filtered, and the solvent was evaporated to afford **22a** (355 mg, 99%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.61–1.68 (m, 2 H), 1.76–1.84 (m, 2 H), 1.92 (br. s, 1 H), 2.72 (t, *J* = 6.84 Hz, 2 H), 2.93–2.97 (m, 2 H), 3.81 (s, 2 H), 7.13–7.17 (m, 1 H), 7.19–7.30 (m, 3 H), 7.31–7.38 (m, 4 H), 8.26 (d, *J* = 6.41 Hz, 1 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 23.66, 28.87, 30.18, 48.38, 53.48, 123.38, 125.43, 125.86, 127.17, 128.31, 128.38, 138.57, 139.52, 152.04 ppm. LC-MS: t_R = 0.46 min; *m/z* = 257 [MH$^+$]. $C_{16}H_{20}N_2O$ (256.35): calcd. C 74.97, H 7.86, N 10.93, O 6.24; found C 75.00, H 7.84, N 10.91, O 6.21.

Synthesis of 5-(1-Oxido-2-pyridinyl)-*N*-(phenylmethyl)-1-pentanamine (22c): Scheme 5, route A. 5-Iodopentanenitrile (**13c**), necessary for this synthesis, was prepared according to a literature procedure:[20] 5-Chloropentanenitrile (1.34 mL, 13.52 mmol) and NaI (6.08 g, 40.55 mmol) were stirred and refluxed in acetone (130 mL) under N_2 for 2 d. After distilling off the solvent, the residue was diluted with water and extracted with ethyl acetate (200 mL + 100 mL). The organic extracts were successively washed with 1 M $Na_2S_2O_3$ and saturated $NaHCO_3$, dried (Na_2SO_4), concentrated, and distilled under reduced pressure to give 6-iodopentanenitrile (**13c**) (2.60 g, 99%) as a colourless liquid. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.54–2.12 (m, 4 H), 2.24–2.49 (m, 2 H), 3.07–3.31 (m, 2 H) ppm.

5-(2-Pyridinyl)pentanenitrile (14c): A known procedure[21] was used for the synthesis of **14c**. To a round-bottom flask containing Zn dust (1.30 g, 20.0 mmol), dibromoethane (305.2 mg, 1.62 mmol) was added, and the resulting mixture was warmed to 60 °C and then allowed to cool for 1 min. This heating/cooling process was repeated three more times, and then the flask was allowed to cool for an additional 3 min. Trimethylsilyl chloride (26.5 mg, 0.24 mmol) in THF (20 mL) was then added. The resulting mixture was warmed to 60 °C, and a solution of 5-iodopentanenitrile (**13c**) (6.5 mmol) in THF (1 mL) was added. The mixture was stirred at 60 °C until all the alkyl iodide had been consumed (ca. 4 h, TLC control). The resulting solution of alkylzinc iodide was transferred by a syringe fitted with a 0.45 μm filter to a second flask charged with 2-bromopyridine (1.3 mmol) and $(Ph_3P)_2PdCl_2$ (45 mg, 0.06 mmol). The resulting mixture was stirred at 60 °C under N_2 for 18 h, cooled to room temperature, and the reaction quenched with saturated aqueous NH_4Cl solution (5 mL). The resulting mixture was stirred at room temp. for 20 min and diluted with ethyl acetate (200 mL). The organic phase was washed with saturated aqueous NH_4Cl (50 mL), brine (50 mL), and dried with Na_2SO_4. The organic phase was concentrated, and the crude product was purified by flash column chromatography on silica gel using petroleum ether/EtOAc (3:1), then EtOAc as eluent to afford **14c** (416 mg, 40%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.52–1.98 (m, 2 H), 2.22–2.48 (m, 2 H), 2.80 (t, *J* = 6.96 Hz, 4 H), 7.02–7.20 (m, 2 H), 7.49–7.66 (m, 1 H), 8.49 (d, *J* = 4.76 Hz, 1 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 16.99, 24.90, 28.55, 37.17, 121.15, 122.64, 136.31, 137.33, 149.15, 160.73 ppm. GC-MS: *m/z* (%) = 51 (76), 78 (100) [Py], 106 (2), 159 (26), 160 (2) [M$^+$]. $C_{10}H_{12}N_2$ (160.22): calcd. C 74.97, H 7.55, N 17.48; found C 74.95, H 7.53, N 17.51.

5-(2-Pyridinyl)-1-pentanamine (15c): Lithium aluminium hydride (231 mg, 6.09 mmol) was suspended in dry THF (8 mL) and cooled to 0 °C. A solution of 5-(2-pyridinyl)pentanenitrile (**14c**) (650 mg, 4.06 mmol) in THF (4 mL) was added, and the mixture was stirred at 0 °C for 2 h, then warmed to room temp. and filtered through Celite. The solvent was evaporated to give **15c** (619 mg, 93%) as a red oil, which was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.21–1.95 (m, 6 H), 2.40 (br. s, 2 H), 2.61–2.79 (m, 4 H), 7.02–7.26 (m, 2 H), 7.54 (dt, *J* = 7.80, 1.60 Hz, 1 H), 8.48 (d, *J* = 4.00 Hz, 1 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 26.58, 29.29, 29.66, 38.29, 42.08, 120.79, 122.59, 136.12, 137.36, 149.04 ppm. $C_{10}H_{16}N_2$ (164.25): calcd. C 73.13, H 9.82, N 17.06; found C 73.10, H 9.79, N 17.03.

1,1-Dimethylethyl [5-(2-Pyridinyl)pentyl]carbamate (16c): 5-(2-Pyridinyl)-1-pentanamine (**15c**) (1.21 g, 7.38 mmol) was dissolved in CH_2Cl_2 (50 mL), and Boc_2O (1.93 g, 8.85 mmol) was added. The solution was cooled to 0 °C, and TEA (1.54 mL, 11.07 mmol) and DMAP (catalytic amount) were added. The mixture was stirred overnight, then the reaction was quenched with $NaHCO_3$ and the mixture extracted several times with CH_2Cl_2. The organic layers were dried (Na_2SO_4), and the solvent was evaporated to give the crude product (2.80 g), which was was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 2:1) to afford pure **16c** (1.40 g, 74%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.40 (s, 9 H), 1.24–1.56 (m, 4 H), 1.63–1.68 (m, 2 H), 2.74 (t, *J* = 7.60 Hz, 2 H), 3.02–3.12 (m, 2 H), 3.52 (br. s, 1 H), 7.02–7.11 (m, 2 H), 7.54 (dt, *J* = 7.40, 2.00 Hz, 1 H), 8.46–8.49 (m, 1 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 26.38, 28.38, 29.37, 29.80, 38.11, 40.37, 78.85, 120.82, 122.61, 136.15, 149.03, 155.85, 161.90 ppm. $C_{15}H_{24}N_2O_2$ (264.37): calcd. C 68.15, H 9.15, N 10.60, O 12.10; found C 68.13, H 9.18, N 10.57, O 12.08.

1,1-Dimethylethyl (Phenylmethyl)[5-(2-pyridinyl)pentyl]carbamate (20c): 1,1-Dimethylethyl [5-(2-pyridinyl)pentyl]carbamate (**16c**) (315 mg, 1.19 mmol) was dissolved in dry DMF (6 mL) and added to a suspension of NaH (70 mg, 1.43 mmol, 50% in mineral oil) in DMF (6 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and at room temp. for 2 h, then benzyl bromide (118 μL, 0.99 mmol) and tetrabutylammonium iodide (catalytic amount) were added. The mixture was stirred at room temp. overnight, then the reaction was quenched with saturated aq. NH_4Cl and the mixture extracted with EtOAc (3 × 20mL). The organic phase was dried with Na_2SO_4, and the solvent was evaporated to give the crude product, which was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 2:1) to afford pure **20c** (255 mg, 60%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.24–1.53 (m, 4 H), 1.50 (s, 9 H), 1.62–1.78 (m, 2 H), 2.74 (t, *J* = 7.60 Hz, 2 H), 3.05–3.25 (m, 2 H), 4.39 (s, 2 H), 7.04–7.33 (m, 7 H), 7.55 (dt, *J* = 7.60, 1.80 Hz, 1 H), 8.49 (d, *J* = 4.20 Hz, 1 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 26.58, 27.91, 28.42, 29.55, 38.25, 46.43, 50.36, 79.42, 120.81, 122.59, 126.92, 127.10, 128.29, 136.14, 138.58, 149.06, 154.30, 161.96 ppm. GC-MS: *m/z* (%) = 57 (100) [*t*Bu], 91 (31) [py-CH_2], 106 (86) [pyCH_2CH_2], 148 (13) [py$(CH_2)_5$], 163 (36) [py$(CH_2)_5$NH], 253 (14) [py$(CH_2)_5$NBn], 354 (3) [M$^+$]. $C_{22}H_{30}N_2O_2$ (354.49): calcd. C 74.54, H 8.53, N 7.90, O 9.03; found C 74.52, H 8.49, N 7.87, O 9.06.

1,1-Dimethylethyl [5-(1-Oxido-2-pyridinyl)pentyl](phenylmethyl)-carbamate (21c): See the procedure used for **21a**. The product obtained as a yellow oil (98%) was used as such without further purification. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.47 (s, 9 H), 1.35–1.83 (m, 6 H), 2.92 (t, *J* = 7.60 Hz, 2 H), 3.12–3.32 (m, 2 H),

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4.45 (s, 2 H), 7.12–7.38 (m, 8 H), 8.25 (d, J = 5.80 Hz, 1 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 25.49, 26.36, 28.18, 29.38, 30.20, 46.07, 50.12, 79.08, 122.95, 124.94, 125.13, 126.54, 127.55, 127.91, 130.16, 138.03, 139.05, 151.70 ppm. GC-MS: *m*/*z* (%) = 57 (100) [*t*Bu], 91 (53) [$pyCH_2$], 106 (25) [$pyCH_2CH_2$], 148 (11) [$py(CH_2)_5$], 163 (9) [$py(CH_2)_5NH$], 253 (33) [$py(CH_2)_5NBn$], 354 (3). 370 (1) [M^+]. $C_{22}H_{30}N_2O_3$ (370.49): calcd. C 71.32, H 8.16, N 7.56, O 12.96; found C 71.29, H 8.14, N 7.59, O 12.99.

5-(1-Oxido-2-pyridinyl)-*N*-(phenylmethyl)-1-pentanamine (22c): See the procedure used for **22a**. The product obtained as a yellow oil (63%) was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.29–1.84 (m, 6 H), 2.41–2.72 (m, 3 H), 2.87 (t, J = 7.60 Hz, 2 H), 3.76 (s, 2 H), 6.98–7.43 (m, 8 H), 8.20 (d, J = 6.23 Hz, 1 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 25.96, 27.04, 29.59, 30.42, 49.03, 53.84, 123.28, 125.32, 125.68, 126.93, 128.13, 128.33, 139.56, 139.78, 152.38 ppm. GC-MS: *m*/*z* (%) = 91 (100) [Bz], 119 (30), 120 (6), 158 (56), 193 (3), 253 (2). $C_{17}H_{22}N_2O$ (270.37): calcd. C 75.52, H 8.20, N 10.36, O 5.92; found C 75.49, H 8.17, N 10.33, O 5.96.

Synthesis of [4-(1-Oxido-4-pyridinyl)butyl](phenylmethyl)amine (22b): Scheme 5, route B.

4-(Pyridin-4-yl)but-3-yn-1-ol: See procedures used for **18a**, but starting from 4-bromopyridine. The crude product was purified by flash chromatography on silica gel [from EtOAc/petroleum ether (2:1) to EtOAc 100%, then EtOAc/MeOH (10:1)] to afford the pure product (77%) as an orange oil. The spectroscopic data are in complete agreement with the literature's data.[26] ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.91 (br. s, 1 H), 2.71 (t, J = 6.6 Hz, 2 H), 3.78–3.95 (m, 2 H), 7.24 (dd, J = 4.40, 1.40 Hz, 2 H), 8.51 (dd, J = 4.40, 1.40 Hz, 2 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 23.98, 60.81, 79.84, 92.23, 125.73, 128.26, 149.37 ppm. GC-MS: *m*/*z* (%) = 31 (63), 63 (41), 90 (57), 117 (100) [$pyC{\equiv}CCH_3$], 147 (53) [M^+].

4-(Pyridin-4-yl)butan-1-ol (18b): See procedure used for **18a**. The product obtained as a yellow oil (90%) was used without further purification. The spectroscopic data are in complete agreement with the literature's data.[26] ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.46–1.79 (m, 4 H), 1.93 (br. s, 1 H), 2.64 (t, J = 7.0 Hz, 2 H), 3.66 (t, J = 7.00 Hz, 2 H), 7.10 (dd, J = 4.40, 1.40 Hz, 2 H), 8.44 (dd, J = 4.40, 1.40 Hz, 2 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 26.57, 32.22, 35.01, 62.40, 123.77, 149.35, 151.20 ppm. GC-MS: *m*/*z* (%) = 31 (29), 65 (24), 93 (22) [$pyCH_3$], 105 (100) [$pyCH_2CH_3$], 151 (10) [M^+].

4-(Pyridin-4-yl)butanal (19b): See procedure used for **19a** The product obtained as a red oil (99%) was used without further purification. The spectroscopic data are in complete agreement with the literature's data.[25] ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.95 (t, J = 7.60 Hz, 2 H), 2.47 (dt, J = 8.00, 1.00 Hz, 2 H), 2.64 (t, J = 7.60 Hz, 2 H), 7.09 (d, J = 5.80 Hz, 2 H), 8.48 (dd, J = 4.40, 1.40 Hz, 2 H), 9.76 (t, J = 1.40 Hz, 1 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 22.51, 34.30, 42.95, 149.50, 150.05, 150.20, 201.02 ppm. GC-MS: *m*/*z* (%) = 51 (24), 65 (32), 78 (18) [Py], 92 (24) [$pyCH_2$], 106 (100) [$pyCH_2CH_2$], 149 (14) [M^+].

1,1-Dimethylethyl (Benzyl)[4-(pyridin-4-yl)butyl]carbamate (20b): See procedure used for **20a**. The crude product was purified by flash chromatography on silica gel [petroleum ether/EtOAc (3:1 → 1:1)] to give the pure product (27% over two steps) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.44 (s, 9 H), 1.40–1.50 (m, 2 H), 1.61–1.73 (m, 2 H), 2.58 (t, J = 6.80 Hz, 2 H), 3.05–3.25 (m, 2 H), 4.40 (br. s, 2 H), 7.06 (d, J = 5.80 Hz, 2 H), 7.18–7.38 (m, 5 H), 8.46 (d, J = 5.20 Hz, 2 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 27.46, 28.46, 28.47, 34.81, 46.15, 50.34, 79.69, 123.79, 127.09, 127.50, 128.40, 138.39, 146.64, 149.54, 151.10 ppm. GC-MS: *m*/*z* (%) = 41 (36), 57 (100) [*t*Bu], 91 (67) [Bz], 106 (50) [$pyCH_2CH_2$], 120 (28) [$py(CH_2)_3$], 240 (6) [M^+ – Boc], 340 (1) [M^+]. $C_{21}H_{28}N_2O_2$ (340.46): calcd. C 74.08, H 8.29, N 8.23, O 9.40; found C 74.10, H 8.32, N 8.21, O 9.38.

1,1-Dimethylethyl [4-(1-Oxido-4-pyridinyl)butyl](phenylmethyl)-carbamate (21b): See procedure used for **21a**. The product obtained as a yellow oil (80%) was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.45 (s, 9 H), 1.40–1.58 (m, 4 H), 2.50–2.62 (m, 2 H), 3.10–3.32 (m, 2 H), 4.40 (br. s, 2 H), 7.04 (d, J = 6.20 Hz, 2 H), 7.18–7.38 (m, 5 H), 8.13 (d, J = 7.00 Hz, 2 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 27.44, 27.86, 28.54, 34.00, 46.12, 50.49, 79.81, 125.81, 127.08, 127.09, 128.35, 132.05, 138.67, 141.40, 154.17 ppm. GC-MS: *m*/*z* (%) = 57 (100) [*t*Bu], 91 (76) [Bz], 106 (54) [$pyCH_2CH_2$], 120 (27) [$py(CH_2)_3$], 240 (7) [M^+ – Boc], 284 (8) [M^+ – *t*BuBoc], 340 (1%). $C_{21}H_{28}N_2O_3$ (356.46): calcd. C 70.76, H 7.92, N 7.86, O 13.47; found C 70.74, H 7.89, N 7.83, O 13.45.

[4-(1-Oxido-4-pyridinyl)butyl](phenylmethyl)amine (22b): See procedure used for **22a**. The product obtained as a yellow oil (99%) was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.50–1.57 (m, 2 H), 1.63–1.70 (m, 3 H), 2.60 (t, J = 7.60 Hz, 2 H), 2.65 (t, J = 6.80 Hz, 2 H), 3.77 (s, 2 H), 7.06 (d, J = 6.80 Hz, 2 H), 7.22–7.38 (m, 5 H), 8.11 (d, J = 6.80 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 27.87, 29.48, 34.22, 48.84, 54.03, 125.96, 126.98, 128.07, 128.42, 138.77, 140.27, 142.14 ppm. GC-MS: *m*/*z* (%) = 91 (100) [Bz], 106 (8) [$pyCH_2CH_2$], 120 (22) [$py(CH_2)_3$], 240 (1). $C_{16}H_{20}N_2O$ (256.35): calcd. C 74.97, H 7.86, N 10.93, O 6.24; found C 75.00, H 7.83, N 10.90, O 6.21.

Synthesis of [5-(1-Oxido-4-pyridinyl)pentyl](phenylmethyl)amine (22d): In this case a different procedure for the preparation of the alcohol **18d** was used.

5-(4-Pyridinyl)-1-pentanol: To a cooled (0 °C) solution of 4-penten-1-ol (1.0 g, 11.61 mmol) in THF (10 mL), 9-BBN (0.5 M in THF, 34.83 mmol) was slowly added. The mixture was slowly warmed to 25 °C and then stirred over a weekend to give a solution of the *B*-alkyl-9-BBN derivative. This solution was transferred into a separate flask containing 4-bromopyridine hydrochloride (2.71 g, 13.93 mmol), $Pd(PPh_3)_4$ (1.26 g, 1.16 mmol), and potassium carbonate (32 mL, 3 M in H_2O, 92.90 mmol) in DMF (80 mL). The mixture was stirred at 70 °C for 24 h, and then it was diluted with EtOAc and poured into water. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to afford the crude product, which was then purified by flash chromatography on silica gel (EtOAc 100%) to give the pure alcohol (870 mg, 45%) as a yellow oil. The spectroscopic data are in complete agreement with the literature's data.[27] ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.40–1.75 (m, 7 H), 2.65 (t, J = 7.70 Hz, 2 H), 3.66 (t, J = 6.50 Hz, 2 H), 7.09 (d, J = 5.80 Hz, 2 H), 8.48 (d, J = 5.80 Hz, 2 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 25.19, 29.78, 32.28, 34.87, 61.78, 123.79, 149.00, 151.77 ppm.

5-(4-Pyridinyl)pentanal (19d):[28] See procedure used for **19a**. The product obtained as a yellow oil (96%) was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.55–1.75 (m, 4 H), 2.38–2-45 (m, 2 H), 2.46–2.62 (m, 2 H), 7.02 (d, J = 6.00 Hz, 2 H), 8.38 (dd, J = 4.40, 1.60 Hz, 2 H), 9.67 (t, J = 1.60 Hz, 1 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 21.38, 29.47, 34.78, 43.36, 123.48, 149.29, 150.37, 201.45 ppm. GC-MS: *m*/*z* (%) = 106 (100) [$pyCH_2CH_2$], 92 (31) [$pyCH_2$], 120 (7) [$py(CH_2)_3$].

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***N*-(Phenylmethyl)-5-(4-pyridinyl)-1-pentanamine:** 5-(4-Pyridinyl)-pentanal (**19d**) (680 mg, 4.17 mmol) was dissolved in dry MeOH (40 mL) and benzylamine (0.54 mL, 5.00 mmol). Acetic acid (0.71 mL, 12.51 mmol) and sodium cyanoborohydride (1 M, THF solution, 4.17 mmol) were then added. The mixture was stirred at room temp. overnight, and then the solvent was evaporated. The crude product was dissolved in EtOAc and washed with $NaHCO_3$. The organic phase was dried with Na_2SO_4, filtered and the solvent was evaporated to give the product (864 mg, 82%) as a yellow oil, which was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.20–1.62 (m, 6 H), 2.40–2.78 (m, 5 H), 3.74 (s, 2 H), 7.03 (d, J = 5.40 Hz, 2 H), 7.18–7.40 (m, 5 H), 8.40 (d, J = 5.60 Hz, 2 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 26.78, 29.79, 30.10, 35.19, 49.09, 53.89, 123.77, 126.78, 127.89, 128.17, 140.08, 149.29, 151.56 ppm. $C_{17}H_{22}N_2$ (254.37): calcd. C 80.27, H 8.72, N 11.01; found C 80.24, H 8.69, N 10.98.

1,1-Dimethylethyl (Phenylmethyl)[5-(4-pyridinyl)pentyl]carbamate (20d): See procedure used for **16c**. The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 2:1) to afford pure **20d** (25%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.22–1.38 (m, 2 H), 1.46 (s, 9 H), 1.42–1.65 (m, 2 H), 1.80–1.98 (m, 2 H), 2.57 (t, J = 7.20 Hz, 2 H), 3.09–3.18 (m, 2 H), 4.41 (br. s, 2 H), 7.07 (d, J = 5.80 Hz, 2 H), 7.19–7.38 (m, 5 H), 8.47 (d, J = 5.80 Hz, 2 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 26.39, 27.78, 28.46, 29.89, 35.08, 46.37, 50.40, 79.48, 123.67, 126.89, 127.88, 128.19, 138.28, 149.29, 149.78, 151.20 ppm. GC-MS: m/z (%) = 175 (10) [M^+ – Ph – Boc], 174 (100), 91 (95) [Ph – CH_2]. $C_{22}H_{30}N_2O_2$ (354.49): calcd. C 74.54, H 8.53, N 7.90, O 9.03; found C 74.51, H 8.49, N 7.94, O 9.00.

1,1-Dimethylethyl [5-(1-Oxido-4-pyridinyl)pentyl](phenylmethyl)-carbamate (21d): See procedure used for **21a**. The product obtained as a yellow oil (99%) was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.38–1.64 (m, 15 H), 2.58 (t, J = 7.20 Hz, 2 H), 3.05–3.13 (m, 2 H), 4.20 (br. s, 2 H), 7.08 (d, J = 6.60 Hz, 2 H), 7.20–7.38 (m, 5 H), 8.17 (d, J = 6.60 Hz, 2 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 21.08, 26.27, 28.48, 29.78, 34.37, 46.29, 50.38, 79.89, 125.78, 126.86, 128.27, 134.38, 135.89, 138.56, 153.67, 161.18 ppm. GC-MS: m/z (%) = 57 (100) [tBu], 91 (95) [Ph – CH_2], 106 (30), 253 (33) [M^+ – BocO], 354 (2) [M^+ – O]. $C_{22}H_{30}N_2O_3$ (370.49): calcd. C 71.32, H 8.16, N 7.56, O 12.96; found C 71.29, H 8.14, N 7.53, O 13.00.

[5-(1-Oxido-4-pyridinyl)pentyl](phenylmethyl)amine (22d): See procedure used for **22a**. The product obtained as a yellow oil (69%) was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.12–1.65 (m, 7 H), 2.58 (app. q, J = 7.00 Hz, 4 H), 3.76 (s, 2 H), 7.03 (d, J = 7.00 Hz, 2 H), 7.17–7.34 (m, 5 H), 8.07 (d, J = 7.00 Hz, 2 H) ppm. ^{13}C NMR (50.4 MHz, $CDCl_3$, 25 °C): δ = 26.73, 29.82, 30.03, 34.26, 49.09, 54.01, 125.68, 126.68, 127.80, 128.14, 138.49, 140.07, 141.80 ppm. GC-MS: m/z (%) = 32 (100), 91 (78) [Ph – CH_2], 106 (25), 120 (12), 254 (2) [M^+ – O]. $C_{17}H_{22}N_2O$ (270.37): calcd. C 75.52, H 8.20, N 10.36, O 5.92; found C 75.49, H 8.18, N 10.38, O 5.89.

Intramolecular Ring Closures

2-[1-(Phenylmethyl)-2-pyrrolidinyl]pyridine (23a):[24] To a solution of [4-(1-oxido-2-pyridinyl)butyl](phenylmethyl)amine (**22a**) (300 mg, 1.170 mmol) in CH_2Cl_2 (10 mL) bis(1,1-dimethylethyl)silanediyl bis(trifluoromethanesulfonate) (0.758 mL, 2.341 mmol) was added, and the reaction mixture was stirred at room temp. for 30 min. Then TEA (0.652 mL, 4.68 mmol) was added (the yellow solution became orange), and the mixture was stirred for an additional 2 h. The reaction was quenched by adding saturated aq. NH_4Cl to the red mixture and extracting with CH_2Cl_2. The organic phase was dried with Na_2SO_4, and the solvent was evaporated to give the crude product as orange oil, which was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 5:1) to give pure **23a** (144 mg, 52%) as a yellow oil. The same reaction was repeated under microwave irradiation (50 °C, 250 W, 20 min) in a closed vessel to give **23a** with 78% yield after purification. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.68–1.99 (m, 3 H), 2.25–2.38 (m, 2 H), 3.10–3.17 (m, 1 H), 3.24 (d, J = 10.40 Hz, 1 H), 3.66 (t, J = 6.40 Hz, 1 H), 3.85 (d, J = 10.00 Hz, 1 H), 7.13–7.18 (m, 1 H), 7.19–7.35 (m, 5 H), 7.62–7.72 (m, 2 H), 8.52–8.57 (m, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 22.78, 33.76, 53.58, 58.52, 70.65, 121.11, 121.92, 126.74, 128.10, 128.67, 136.78, 139.42, 148.86, 164.14 ppm. LC-MS: t_R = 0.89 min; m/z = 239 [MH^+].

2-[1-(Phenylmethyl)-2-piperidinyl]pyridine (23c):[29] See procedure used for **23a**. The crude product was purified by flash chromatography on silica gel [petroleum ether/EtOAc (3:1) → EtOAc 100%] to afford pure **23c** (38%; 60% by MW) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.55–1.64 (m, 4 H), 1.76–1.90 (m, 3 H), 2.92–3.02 (m, 2 H), 3.33–3.40 (m, 1 H), 3.66 (app. d, J = 12.00 Hz, 1 H), 7.11–7.22 (m, 2 H), 7.25–7.27 (m, 4 H), 7.59–7.69 (m, 2 H), 8.51–8.54 (m, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 24.76, 25.78, 35.37, 53.03, 60.03, 70.46, 121.57, 121.95, 126.65, 128.05, 128.72, 136.76, 140.46, 148.88, 165.02 ppm. GC-MS: m/z (%) = 91 (100) [Ph – CH_2], 106 (89) [py$(CH_2)_3$], 147 (22) [py$(CH_2)_5$], 161 (79) [M – Bz], 174 (11) [M – Py], 252(1) [M^+].

4-[1-(Phenylmethyl)pyrrolidin-2-yl]pyridine (23b): See procedure used for **23a**. The crude product was purified by flash chromatography on silica gel [petroleum ether/EtOAc (3:1) → petroleum ether/EtOAc (1:1)] to afford pure **23b** (45%; 62% by MW) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.38–1.43 (m, 1 H), 1.55–1.90 (m, 2 H), 2.18–2.34 (m, 2 H), 3.10–3.18 (m, 2 H), 3.42 (t, J = 8.00 Hz, 1 H), 3.80 (d, J = 13.20 Hz, 1 H), 7.21–7.31 (m, 5 H), 7.39 (d, J = 5.20 Hz, 2 H), 8.55 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 23.74, 35.02, 53.44, 58.24, 68.16, 122.67, 127.13, 128.18, 128.60, 134.93, 149.82, 155.01 ppm. ESI-MS: m/z = 239.17 [M + H^+]. $C_{16}H_{18}N_2$ (238.33): calcd. C 80.63, H 7.61, N 11.75; found C 80.61, H 7.58, N 11.78.

4-[1-(Phenylmethyl)-2-piperidinyl]pyridine (23d): See procedure used for **23a**. The crude product was purified by flash chromatography on silica gel [petroleum ether/EtOAc (3:1) → petroleum ether/EtOAc (1:1)] to afford pure **23d** (35%; 48% by MW) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.25–1.64 (m, 4 H), 1.73–1.82 (m, 2 H), 1.95 (dt, J = 11.60, 3.60 Hz, 1 H), 2.87 (d, J = 13.60 Hz, 1 H), 2.94–3.10 (m, 1 H), 3.14 (dd, J = 11.20, 2.80 Hz, 1 H), 3.68 (d, J = 13.60 Hz, 1 H), 7.25–7.32 (m, 5 H), 7.41 (d, J = 6.00 Hz, 2 H), 8.55 (d, 6.00 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 24.78, 25.67, 36.56, 52.89, 59.88, 68.10, 122.70, 126.78, 128.10, 128.47, 138.78, 149.78, 155.00 ppm. GC-MS: m/z (%) = 252 (9) [M^+], 175 (17) [M^+ – Ph], 174 (100), 161 (15) [M^+ – Bn], 91 (72) [Bn], 65 (15). $C_{17}H_{20}N_2$ (252.36): calcd. C 80.91, H 7.99, N 11.10; found C 80.89, H 7.97, N 11.14.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data of all intermediates and final compounds not reported here; ^{1}H and ^{13}C NMR of compounds **22a**–**d** and **23a**–**d**.

Acknowledgments

We acknowledge GlaxoSmithKline of Verona for its financial support.

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Received: July 2, 2010
Published Online: November 25, 2010

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