A Flexible Three-Component Synthesis of Novel δ-Amino Acids Incorporating an Imidazo[1,2-*a*]pyridine Backbone

Ivana Veljkovic, Reinhold Zimmer, Hans-Ulrich Reissig,* Irene Brüdgam, Hans Hartl

Freie Universität Berlin, Institut für Chemie und Biochemie, Takustrasse 3, 14195 Berlin, Germany
Fax +49(30)83855367; E-mail: hans.reissig@chemie.fu-berlin.de

Received 3 March 2006; revised 18 April 2006

In Memory of Professor Ivar Ugi

Abstract: Methyl 2-trimethylsiloxycyclopropanecarboxylates **1**, 2-aminopyridine (**2**), and isonitriles **3** combine in a one-pot reaction to provide a series of novel δ-amino acids **4** incorporating an imidazo[1,2-*a*]pyridine backbone. Scope and limitations of this new three-component synthesis were investigated. Several reactions of compounds **4** affording suitably protected derivatives such as **5**, **6** and **9** were performed to allow couplings with L-alanine derivatives. The expected peptides **11** and **12** were obtained by standard coupling reactions with excellent or moderate yield. Cyanide-catalyzed reactions converted compounds **4e** and **4h** into tricyclic δ-lactams **10e** and **10h** in very good yields.

Key words: amino acids, cyclopropanes, pyridines, lactams, peptides

Synthesis as well as structural and biological evaluation of amino acids and peptides derived thereof with modified – in particular restricted – conformations are recent topics in bioorganic and medicinal chemistry.[1] Simple, efficient and highly flexible methods to generate new 'unnatural' amino acids are of particular importance, and among other strategies multicomponent reactions have found numerous applications to approach this goal.[2] In many of these reactions aldehydes are crucial components in the proceeding reaction cascades. In several examples we could demonstrate that methyl 2-siloxycyclopropanecarboxylates are equivalents of functionalized and substituted carbonyl compounds.[3] They are prepared from the trimethylsiloxycyclopropane derivatives under very mild conditions (either neutral, with fluoride or slightly acidic or basic media) and thus these cyclopropane derivatives can directly be introduced into multicomponent reactions.[4,5] Recent reports on the synthesis of imidazo[1,2-*a*]pyridines by an Ugi-type reaction of 2-aminopyridine with aldehydes and isonitriles attracted our attention,[6] since a related process with methyl 2-siloxycyclopropanecarboxylates as aldehyde equivalents should directly provide compounds **A**. The expected products are δ-amino acids incorporating an imidazo[1,2-*a*]pyridine backbone, which can be regarded as a conformationally altered dipeptide **B** (Figure 1). In addition, imidazo[1,2-*a*]pyridine derivatives are of general interest because of their broad range of physiological effects (e.g. antibacterial, antiviral, anti-inflammatory, analgesic activities).[7]

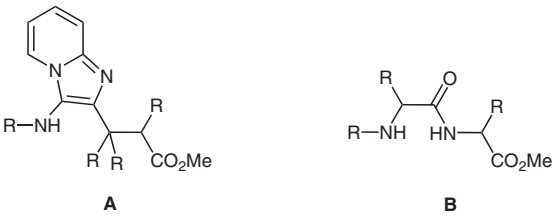


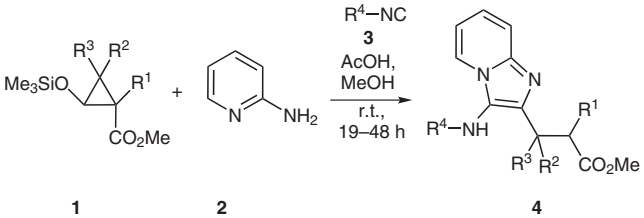
Figure 1 Equivalence of methyl (3-aminoimidazo[1,2-*a*]pyridin-2-yl)propanoates **A** to **B**

In this paper we report on scope and limitations of the synthesis of compounds **A** starting from siloxycyclopropanes and we also reveal first model reactions to couple these novel δ-amino acids with L-alanine derivatives to produce small peptides.

Methyl 2-siloxycyclopropanecarboxylates **1** (1 to 1.1 equiv), 2-aminopyridine (**2**) (1 equiv), and isonitriles **3** (1 equiv) were stirred in a mixture of acetic acid (2 equiv) and methanol for 19–48 hours at room temperature. After acidic work up (which destroys remaining isonitrile) and chromatographic purification we obtained methyl (3-aminoimidazo[1,2-*a*]pyridin-2-yl)propanoates **4** in moderate to good yields (Scheme 1). With respect to the cyclopropanes **1**, the parent compound (entries **a**, **b**), monomethyl substituted (entry **c**), dimethyl substituted (entries **d**, **e**, **f**, **g**), and trimethyl substituted (entry **h**) derivatives were also suitable aldehyde equivalents. The isonitrile component can bear a tertiary alkyl, a benzyl, or an aryl substituent. Although not examined, other 2-aminopyridine derivatives may also be used. Hence, this one-pot three-component reaction leading to δ-amino acid derivatives **4** with an imidazo[1,2-*a*]pyridine backbone seems to allow a fairly broad substitution pattern. For the synthesis of compound **4g** (entry **g**) the yield was 62% when the mixture was exposed to microwave irradiation,[8] whereas only 43% yield was obtained under the standard conditions applied for all other entries of Scheme 1.

For heterocycle **4g**, we could also obtain suitable crystals for an X-ray analysis, which not only proved the constitution of the product but also showed that the propanoate side chain is spatially in close proximity to the arylamino group (Figure 2).

SYNTHESIS 2006, No. 16, pp 2677–2684
Advanced online publication: 19.07.2006
DOI: 10.1055/s-2006-942506; Art ID: T03306SS



1 2 4

Entry	R^1	R^2	R^3	R^4	Yield
a	H	H	H	*t*-Bu	56%
b	H	H	H	$CMe_2CH_2CMe_3$	79%
c	H	Me	H	*t*-Bu	57%
d	H	Me	Me	*t*-Bu	46%
e	H	Me	Me	Bn	57%
f	H	Me	Me	$CMe_2CH_2CMe_3$	56%[a]
g	H	Me	Me	*p*-$MeOC_6H_4$	62%[b]
h	Me	Me	Me	Bn	40%

[a] In addition of 30% of compound **7**.
[b] Under microwave conditions.

Scheme 1 Synthesis of methyl (3-aminoimidazo[1,2-*a*]pyridin-2-yl)propanoates **4** by one-pot reaction of siloxycyclopropanes **1**, 2-aminopyridine **2** and isonitriles **3**

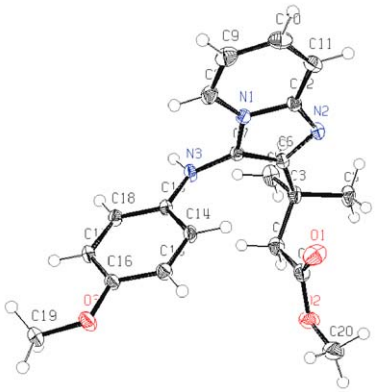
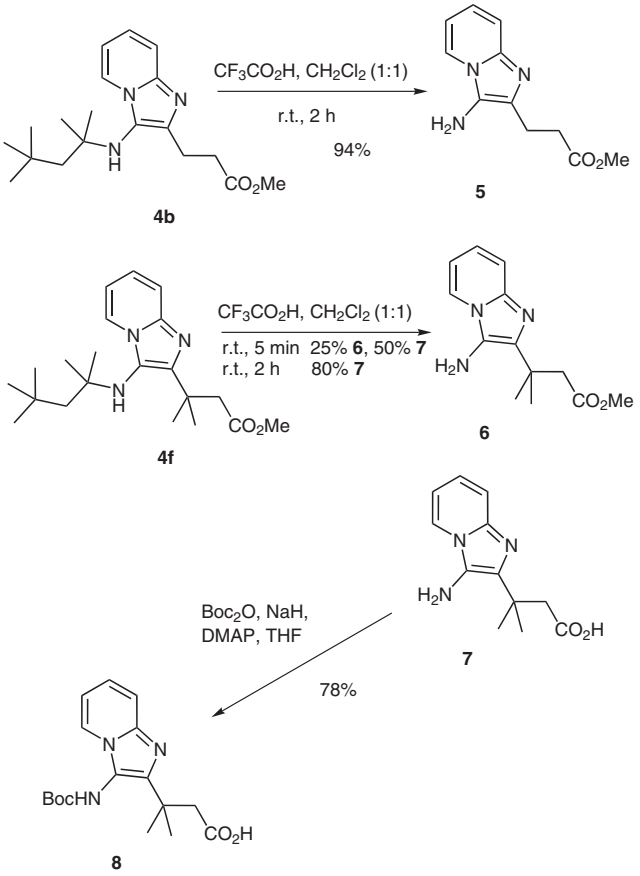


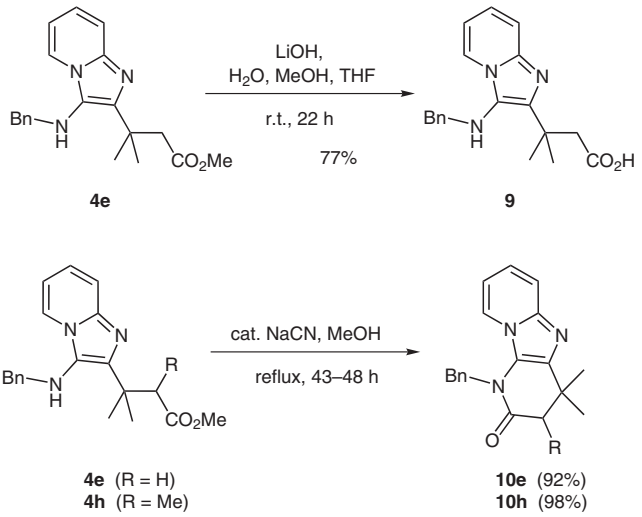
Figure 2 X-ray crystal structure of compound **4g**

Since we wanted to prepare small model peptides including δ-amino acids derived from **4**, we had to convert these compounds into suitably protected intermediates. Treatment of compound **4b** with trifluoroacetic acid for two hours at room temperature furnished the expected amino ester **5** in excellent yield (Scheme 2).[9] Surprisingly, when identical conditions were applied to the higher substituted analog **4f** not only the tetramethylbutyl group was displaced, but in addition the methyl ester was cleaved providing the amino acid **7** in 80% yield. Precursor **4f** seems to be particular sensitive to acid since amino acid **7** was isolated as a by-product in 30% yield during synthesis of **4f**. We therefore shortened the reaction time of **4f** with trifluoroacetic acid to five minutes at room temperature and obtained a mixture of the required amino ester **6** (25% yield) and of the amino acid **7** (50% yield). The deprotection reactions of **4f** thus occur under milder acidic conditions. We speculate that the particular conformation of the ammonium salt derived from **4f** facilitates the cleavage of the methyl ester. According to the X-ray crystal structure of the related dimethyl substituted compound **4g**, the methoxycarbonyl is in close proximity of the amino substituents (Figure 2) which might exhibit a neighboring group effect. No further attempts have been made to selectively deprotect compound **4f**. Employing sodium hydride, DMAP and Boc-anhydride, compound **7** was converted into the N-protected δ-amino acid **8** with reasonable efficacy (Scheme 2). We had to recognize already here that the amino groups of imidazo[1,2-*a*]pyridine derivatives are fairly unreactive under acylation conditions.



Scheme 2 Trifluoroacetic acid promoted deprotections of **4b** and **4f** leading to amino esters **5, 6** and amino acid **7** and Boc-protection of **7** to δ-amino acid **8**

Saponification of the amino ester **4e** proceeded without problem and afforded the expected *N*-benzyl-protected amino acid **9** in 77% yield (Scheme 3). It should be mentioned here that attempts to debenzylate compounds such as **4e** and **4h** were not successful and in general led to decomposition of the heterocycles. However, we discovered a smooth cyclization method to transform δ-amino acid derivatives into tricyclic δ-lactam derivatives. By cyanide catalysis in refluxing methanol[10] (most likely via the corresponding acyl cyanides[11]) precursors **4e** and **4h** delivered the dipyrido[1,2-*a*;3′,2′-*d*]imidazol-2-ones **10e** and **10h** in excellent yields (Scheme 3).

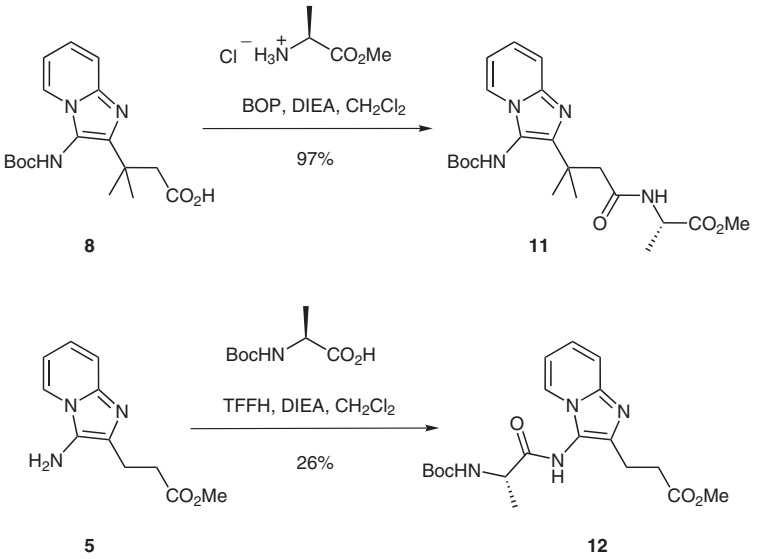


Scheme 3 Preparation of δ-amino acid **9** and of dipyrido[1,2-*a*;3′,2′-*d*]imidazol-2-ones **10e** and **10h**

With amino acid derivatives **8** and **5** we tried model reactions to generate small peptides. The peptide coupling of acid **8** with L-alanine methyl ester was conventionally performed with benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate[12] (BOP) as activating agent and furnished almost quantitatively compound **11**, which may be regarded as a tripeptide equivalent (Scheme 4). On the other hand, reaction at the amino group of ester **5** with *N*-Boc-protected L-alanine required the very powerful coupling reagent tetramethylfluoroformamidinium hexafluorophosphate[13] (TFFH) and still only 26% of the desired product **12** was obtained. It should be mentioned that experiments employing the dimethyl substituted compound **6** did not result in peptide formation. This may again be the effect of the conformations of these compounds (see discussion above and Figure 2). Further investigations are required to overcome this problem and take profit of the apparently restricted conformation of this particular skeleton.

In conclusion, we have demonstrated that the novel three-component synthesis of siloxycyclopropanes **1** with 2-aminopyridine (**2**) and isonitriles **3** efficiently provided new δ-amino acid derivatives **4** incorporating a 2-imidazo[1,2-*a*]pyridine backbone. This transformation again proved the equivalence of siloxycyclopropanes **1** to substituted and functionalized aldehydes, which are difficult to prepare by alternative methods. In various model reactions the heterocyclic amino acid derivatives **4** were suitably protected and coupled with L-alanine derivatives to afford the expected peptides **11** or **12**. Furthermore, a mild method was found to convert compounds **4** into the tricyclic δ-lactams **10**. Future studies should be devoted to the synthesis of longer peptide chains – optionally under multiple inclusion of derivative **4** – and to the elucidation of the influence of the 2-imidazo[1,2-*a*]pyridine backbone on the conformation of the resulting constructs.

All reactions were performed under argon in flame-dried flasks, and the components were added by means of syringes. All solvents were dried by standard methods. TLC was carried out on commercial Polygram Sil G/UV$_{254}$ or Polygram Alox N/UV$_{254}$ (Macherey & Nagel). Column chromatography was performed using 70–230 mesh silica gel (Merck) or neutral aluminum oxide (activity grade-III; Fluka or Merck). Nucleosil 50-5 (Macherey & Nagel) was used for HPLC. Unless stated otherwise, ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker (AM-270, AC-500) or JEOL (Eclipse 500) instruments. The chemical shifts are related to TMS or to the $CDCl_3$ signal ($\delta_H = 7.26$, $\delta_C = 77.0$). Higher order NMR spectra were approximately interpreted as first-order spectra, if possible. Missing signals could not be unambiguously identified due to low intensity. IR spectra were measured on Nicolet spectrometer FTIR 5 SXC. MS and HRMS analyses were performed on Finnigan MAT 711 (EI, 80 eV, 8 kV), MAT CH7A (EI, 80 eV, 3 kV) and CH5DF (FAB, 80 eV, 3 kV) instruments. Elemental analyses were performed on a Perkin Elmer CHN analyzer 2400. Melting points were determined with a Büchi MP 510 apparatus and are uncorrected.



Scheme 4 Couplings of L-alanine derivatives with amino acid **8** to peptide **11** and with amino ester **5** to peptide **12**

Boiling points of compounds obtained in small-scale experiments refer to the temperature in a Büchi Kugelrohrofen. Starting materials **1**[14] and *p*-methoxyphenylisocyanide[15] were prepared using known procedures. All other chemicals were commercially available and were used as received.

Ugi-Type Reaction of Methyl Siloxycyclopropanecarboxylates 1 and Isonitriles 3 with 2-Aminopyridine (2), General Procedure

Methyl siloxycyclopropanecarboxylate **1** (1–1.1 equiv), 2-aminopyridine (**2**; 1 equiv) and the corresponding isonitrile **3** (1 equiv) were dissolved in anhyd MeOH (2.5–3 mL/mmol of **2**) under argon. After addition of AcOH (2 equiv), the mixture was stirred at r.t. for the time indicated in the individual experiment. Then 1 M HCl solution was added to adjust pH 1, the mixture was stirred for 30 min to destroy unreacted isocyanide **3** and then evaporated to dryness. The residue was taken up in sat. aq $NaHCO_3$ solution (2 mL/mmol of **2**) and extracted with EtOAc (3 × 10 mL/mmol of **2**). The combined organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (EtOAc–hexane, 2:1) and in some cases followed by HPLC (20% *i*-PrOH–hexane).

Methyl 3-(3-*tert*-Butylaminoimidazo[1,2-*a*]pyridin-2-yl)propanoate (4a)

According to general procedure, a mixture of methyl 2-trimethylsiloxycyclopropanecarboxylate (0.510 g, 2.71 mmol), 2-aminopyridine (0.258 g, 2.74 mmol), *tert*-butyl isocyanide (0.225 g, 2.67 mmol) and AcOH (0.325 g, 5.41 mmol) in MeOH (8 mL) gave after 12 h at r.t., 0.420 g (56%) of **4a** as a foamy resin.

IR (neat): 3330–3220 (N–H), 3060–2800 (=C–H, C–H), 1730 (C=O), 1630 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): δ = 1.20 (s, 9 H, *t*-C_4H_9), 2.75 (t, *J* = 7 Hz, 2 H, CH_2), 3.00 (t, *J* = 7 Hz, 2 H, CH_2), 3.40 (s, 1 H, NH), 3.55 (s, 3 H, OCH_3), 6.60 (dd, *J* = 7, 7.5 Hz, 1 H, 6-H), 7.05 (dd, *J* = 7.5, 9 Hz, 1 H, 7-H), 7.45 (d, *J* = 9 Hz, 1 H, 8-H), 8.10 (d, *J* = 7 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 22.6 (t, CH_2), 30.2, 55.4 (q, s, *t*-C_4H_9), 33.3 (t, CH_2), 51.5 (q, OCH_3), 110.7 (d, C-6), 116.5 (d, C-8), 123.4 (d, 2 C, C-5, C-7), 124.1 (s, C-3), 138.8 (s, C-2), 141.9 (s, C-9), 174.1 (s, C=O).

MS (EI): *m*/*z* (%) = 275 (41, $[M]^+$), 260 (2, $[M - CH_3]^+$), 244 (9, $[M - OMe]^+$), 218 (100, $[M - C_4H_9]^+$), 191 (12), 186 (10), 160 (28), 159 (13), 78 (45, $[C_5H_4N]^+$), 57 (7, $[t\text{-Bu}]^+$), 41 (5, $[C_3H_5]^+$), 29 (5, $[C_2H_5]^+$).

HRMS: *m*/*z* calcd for $C_{15}H_{21}N_3O_2$: 275.1638; found: 275.1656.

Methyl 3-{3-(1,1,3,3-Tetramethylbutyl)aminoimidazo[1,2-*a*]pyridin-2-yl}propanoate (4b)

According to general procedure, a mixture of methyl 2-trimethylsiloxycyclopropanecarboxylate (0.827 g, 4.40 mmol), 2-aminopyridine (0.376 g, 4.00 mmol), 1,1,3,3-tetramethylbutyl isocyanide (0.558 g, 4.00 mmol) and AcOH (0.500 g, 8.00 mmol) in MeOH (12 mL) gave after 48 h at r.t., 1.07 g (79%) of **4b** as a yellowish oil.

IR (neat): 3335 (N–H), 3090–2870 (C–H), 1735 (C=O), 1630 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): δ = 1.05, 1.12 (2 s, 9 H, 6 H, CH_3), 1.64 (s, 2 H, CH_2), 2.76 (t, *J* = 6.8 Hz, 2 H, CH_2), 3.01 (t, *J* = 6.8 Hz, 2 H, CH_2), 3.21 (br s, 1 H, NH), 3.56 (s, 3 H, OCH_3), 6.63 (td, *J* = 6.8, 1.2 Hz, 1 H, 6-H), 6.86 (ddd, *J* = 9.0, 6.8, 1.2 Hz, 1 H, 7-H), 7.34 (dt, *J* = 9.0, 1.2 Hz, 1 H, 8-H), 8.11 (dt, *J* = 6.8, 1.2 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 22.8 (t, CH_2), 29.1 (q, CH_3), 31.7 (s, *C*Me_3), 31.9 (q, CH_3), 33.3 (t, CH_2), 51.4 (q, OCH_3), 56.8 (t, CH_2), 59.5 (s, N*C*Me_2), 110.6 (d, C-6), 116.6 (d, C-8), 123.2 (d, C-7), 123.5 (d, C-5), 123.8 (s, C-3), 139.2 (s, C-2), 142.0 (s, C-9), 173.9 (s, C=O).

MS (EI): *m*/*z* (%) = 331 (27, $[M]^+$), 220 (14), 219 (100), 218 (79), 186 (22), 161 (12), 160 (71), 159 (16), 158 (12), 146 (21), 131 (16), 119 (11), 85 (53), 84 (71), 79 (11), 78 (40), 57 (42), 55 (18), 49 (14), 47 (18), 43 (20), 41 (23), 29 (15), 28 (34).

HRMS: *m*/*z* calcd for $C_{19}H_{29}N_3O_2$: 331.2260; found: 331.2264.

Methyl 3-(3-*tert*-Butylaminoimidazo[1,2-*a*]pyridin-2-yl)butanoate (4c)

According to general procedure, a mixture of methyl 3-methyl-2-trimethylsiloxycyclopropanecarboxylate (0.202 g, 1.00 mmol), 2-aminopyridine (0.094 g, 1.00 mmol), *tert*-butyl isocyanide (0.084 g, 1.00 mmol) and AcOH (0.120 g, 2.00 mmol) in MeOH (3 mL) gave after 12 h at r.t., 0.166 g (57%) of **4c** as amber crystals; mp 63–65 °C.

IR (KBr): 3320–3220 (N–H), 3060–2850 (=C–H, C–H), 1730 (C=O), 1635 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): δ = 1.20 (s, 9 H, *t*-C_4H_9), 1.45 (d, *J* = 7 Hz, 3 H, CH_3), 1.65 (s, 1 H, NH), 2.60 (d, *J* = 7 Hz, 2 H, CH_2), 2.80 (d, *J* = 7 Hz, 2 H, CH_2), 3.45 (br s, 1 H, NH), 3.48–3.53 (m, 1 H, CH), 3.55 (s, 3 H, CO_2CH_3), 6.65 (dd, *J* = 7, 7.5 Hz, 1 H, 6-H), 7.05 (dd, *J* = 7.5, 9 Hz, 1 H, 7-H), 7.45 (d, *J* = 9 Hz, 1 H, 8-H), 8.15 (d, *J* = 7 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 20.1 (q, CH_3), 27.5 (d, CH), 30.1, 54.9 (q, s, *t*-C_4H_9), 41.2 (t, CH_2), 51.3 (q, OCH_3), 110.5 (d, C-6), 116.6 (d, C-8), 123.2 (d, C-5), 123.3 (s, C-3), 123.5 (d, C-7), 142.1, 142.9 (2 s, C-2, C-9), 173.6 (s, C=O).

MS (EI): *m*/*z* (%) = 289 (37, $[M]^+$), 274 (10, $[M - CH_3]^+$), 258 (7, $[M - OMe]^+$), 233 (37, $[M - C_4H_8]^+$), 232 (100, $[M - C_4H_9]^+$), 160 (28), 79 (16, $[C_5H_5N]^+$), 78 (46, $[C_5H_4N]^+$), 57 (13, $[t\text{-Bu}]^+$), 41 (12, $[C_3H_5]^+$), 29 (8, $[C_2H_5]^+$).

HRMS: *m*/*z* calcd for $C_{16}H_{23}N_3O_2$: 289.1790; found: 289.1772.

Methyl 3-(3-*tert*-Butylaminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoate (4d)

According to general procedure, a mixture of methyl 3,3-dimethyl-2-trimethylsiloxycyclopropanecarboxylate (0.648 g, 3.00 mmol), 2-aminopyridine (0.283 g, 3.00 mmol), *tert*-butyl isocyanide (0.253 g, 3.00 mmol) and AcOH (0.361 g, 6.00 mmol) in MeOH (9 mL) gave after 12 h at r.t., 0.419 g (46%) of **4d** as colorless crystals; mp 183–185 °C.

IR (KBr): 3300–3230 (N–H), 3080–2860 (=C–H, C–H), 1730 (C=O), 1630 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): δ = 1.25 (s, 9 H, *t*-C_4H_9), 1.55 (br s, 1 H, NH), 1.65 (s, 6 H, CH_3), 3.05 (s, 2 H, CH_2), 3.55 (s, 3 H, OCH_3), 7.15 (dd, *J* = 7.5, 8.0 Hz, 1 H, 6-H), 7.60 (dd, *J* = 7.5, 9.0 Hz, 1 H, 7-H), 8.35 (d, *J* = 9.0 Hz, 1 H, 8-H), 8.50 (d, *J* = 8.0 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 28.7 (q, CH_3), 31.2, 54.8 (q, s, *t*-Bu), 34.8 (s, *C*Me_2), 45.5 (t, CH_2), 51.6 (q, OCH_3), 113.4 (d, C-6), 115.5 (d, C-8), 124.3 (s, C-3), 124.7 (d, C-5), 131.2 (d, C-7), 133.8, 137.2 (2 s, C-2, C-9), 171.9 (s, C=O).

MS (EI): *m*/*z* (%) = 303 (35, $[M]^+$), 287 (3, $[M - CH_4]^+$), 272 (6, $[M - OMe]^+$), 247 (27, $[M - C_4H_8]^+$), 246 (100, $[M - t\text{-Bu}]^+$), 214 (29), 198 (10), 78 (29, $[C_5H_4N]^+$), 73 (18, $[C_4H_{11}N]^+$), 57 (85, $[t\text{-Bu}]^+$), 43 (65, $[C_3H_7]^+$), 29 (19, $[C_2H_5]^+$).

HRMS: *m*/*z* calcd for $C_{17}H_{25}N_3O_2$: 303.1947; found: 303.1911.

Methyl 3-(Benzylaminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoate (4e)

According to general procedure, a mixture of methyl 3,3-dimethyl-2-siloxycyclopropanecarboxylate (0.216 g, 1.00 mmol), 2-aminopyridine (0.094 g, 1.00 mmol), benzyl isocyanide (0.118 g, 1.00 mmol) and AcOH (0.120 g, 2.00 mmol) in MeOH (3 mL) gave after 19 h at r.t., 0.201 g (57%) of **4e** as a pale yellow oil.

IR (KBr): 3375 (N–H), 3085–2950 (=C–H, C–H), 1735 (C=O), 1630 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.58 (s, 6 H, CH_3), 2.82 (s, 2 H, CH_2), 3.50 (s, 3 H, OCH_3), 3.62 (br s, 1 H, NH), 4.13 (s, 2 H, CH_2Ph), 6.69 (td, *J* = 6.8, 1.2 Hz, 1 H, 6-H), 7.06 (ddd, *J* = 9.0, 6.8, 1.2 Hz, 1 H, 7-H), 7.25–7.49 (m, 6 H, 8-H, C_6H_5), 7.94 (dt, *J* = 6.8, 1.2 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 28.4 (q, CH_3), 35.3 (s, *C*Me_2), 46.5 (t, CH_2), 51.1 (q, OCH_3), 52.9 (t, *C*H_2Ph), 111.1 (d, C-6), 117.1 (d, C-8), 122.2 (d, C-5), 123.2 (d, C-7), 124.8 (s, C-3), 127.5, 128.0, 128.6 (3 d, C_6H_5), 139.2 (s, C_6H_5), 140.4 (s, C-2), 143.1 (s, C-9), 172.6 (s, C=O).

MS (EI): *m*/*z* (%) = 337 (32, $[M]^+$), 247 (16), 246 (100), 219 (22), 214 (21), 105 (32), 78 (29), 73 (13).

HRMS: *m*/*z* calcd for $C_{20}H_{23}N_3O_2$: 337.1790; found: 337.1784.

Methyl 3-{3-(1,1,3,3-Tetramethylbutyl)imidazo[1,2-*a*]pyridin-2-yl}-3-methylbutanoate (4f)

According to general procedure, a mixture of methyl 3,3-dimethyl-2-trimethylsiloxycyclopropanecarboxylate (0.951 g, 4.40 mmol), 2-aminopyridine (0.376 g, 4.00 mmol), 1,1,3,3-tetramethylbutyl isocyanide (0.558 g, 4.00 mmol) and AcOH (0.480 g, 8.00 mmol) in MeOH (12 mL) gave after 48 h at r.t., 0.797 g (56%) of **4f** as a pale yellow oil and 0.280 g (30%) of **7** as colorless crystals (for analytical and spectral data of **7**, see below).

IR (neat): 3370 (N–H), 3075–2870 (=C–H, C–H), 1735 (C=O), 1630 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): δ = 1.08, 1.22, 1.58 (3 s, 9 H, 3 H, 3 H, CH_3), 1.69, 2.91 (2 s, 2 H, 2 H, CH_2), 3.11 (s, 1 H, NH), 3.52 (s, 3 H, OCH_3), 6.63 (td, *J* = 6.8, 1.2 Hz, 1 H, 6-H), 6.99 (ddd, *J* = 9.0, 6.8, 1.2 Hz, 1 H, 7-H), 7.38 (dt, *J* = 9.0, 1.2 Hz, 1 H, 8-H), 8.16 (dt, *J* = 6.8, 1.2 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 29.0, 30.3, 31.9 (3 q, CH_3), 32.0, 35.9 (2 s, *C*Me_3, *C*Me_2), 46.6 (t, CH_2), 51.1 (q, OCH_3), 57.8 (t, CH_2), 58.8 (s, N*C*Me_2), 110.3 (d, C-6), 116.8 (d, C-8), 122.5 (d, C-5), 123.1 (d, C-7), 123.8 (s, C-3), 140.8 (s, C-2), 144.9 (s, C-9), 172.6 (s, C=O).

MS (EI): *m*/*z* (%) = 359 (66, $[M]^+$), 328 (11), 248 (18), 247 (86), 246 (100), 219 (29), 215 (13), 214 (51), 188 (17), 174 (44), 105 (17).

HRMS: *m*/*z* calcd for $C_{21}H_{33}N_3O_2$: 359.2573; found: 359.2554.

Anal. Calcd for $C_{21}H_{33}N_3O_2$ (359.5): C, 70.16; H, 9.25; N, 11.69. Found: C, 69.90; H, 9.14; N, 11.70.

Methyl 3-{(4-Methoxyphenyl)aminoimidazo[1,2-*a*]pyridin-2-yl}-3-methylbutanoate (4g)

According to general procedure, a mixture of methyl 3,3-dimethyl-2-trimethylsiloxycyclopropanecarboxylate (0.238 g, 1.10 mmol), 2-aminopyridine (0.094 g, 1.00 mmol), 4-methoxyphenyl isocyanide (0.133 g, 1.00 mmol) and AcOH (0.120 g, 2.00 mmol) in MeOH (3 mL) gave after 60 min under microwave conditions (200 W, T_{max} = 30 °C), 0.218 g (62%) of **4g** as pale brownish crystals; mp 140–143 °C.

IR (KBr): 3270 (N–H), 3105–2825 (=C–H, C–H), 1730 (C=O), 1675 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.50 (s, 6 H, CH_3), 2.82 (s, 2 H, CH_2), 3.55, 3.72 (2 s, 3 H, 3 H, OCH_3), 5.79 (s, 1 H, NH), 6.20–6.26 (m, 2 H, Ar), 6.50 (td, *J* = 6.8, 1.2 Hz, 1 H, 6-H), 6.54–6.60 (m, 2 H, Ar), 6.94 (ddd, *J* = 9.1, 6.8, 1.2 Hz, 1 H, 7-H), 7.34 (dt, *J* = 9.1, 1.2 Hz, 1 H, 8-H), 7.58 (dt, *J* = 6.8, 1.2 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 28.3 (q, CH_3), 35.3 (s, *C*Me_2), 46.0 (t, CH_2), 51.1 (q, OCH_3), 55.6 (q, ArO*C*H_3), 111.4 (d, C-6), 114.0 (d, C-8), 115.1 (d, C-5), 117.2 (d, C-7), 118.6 (s, C-3), 122.6, 124.0 (2 d, Ar), 139.2 (s, Ar), 141.4 (s, C-2), 146.3 (s, C-9), 153.1 (s, Ar), 172.9 (s, C=O).

MS (EI): *m*/*z* (%) = 354 (100, $[M]^+$), 294 (30), 281 (38), 151 (11), 147 (25), 112 (15), 95 (12), 94 (42), 86 (21), 85 (16), 84 (42), 83 (17), 78 (28), 73 (21), 71 (23), 70 (20), 69 (32), 67 (15), 60 (22), 57 (46), 56 (19), 55 (35), 45 (37), 44 (37), 43 (71), 42 (14), 39 (19).

Anal. Calcd for $C_{20}H_{23}N_3O_3$ (353.4): C, 67.97; H, 6.56; N, 11.89. Found: C, 67.83; H, 6.47; N, 11.44.

Crystal Data

$C_{20}H_{23}N_3O_3$, M_r = 353.4; T = 173(2) K; crystal size: 0.5 × 0.2 × 0.1 mm; monoclinic, space group *P*2(1)/*c*, *a* = 9.870(4), *b* = 10.817(4), *c* = 17.218(7) A; *Z* = 4; D_c = 1.290 Mg/m^3; F(000) = 752; μ(Mo-K) = 0.088 mm^{-1}. Θ Range for data collection: 2.08–30.55°, index ranges: $-12 \le h \le 14$, $-15 \le k \le 14$, $-22 \le l \le 24$; reflections collected/unique: 13376/5119 (R_{int} = 0.0296); final R [$I > 2\sigma(I)$]: *R*1 = 0.0526, *wR*2 = 0.1400. For structure solution and refinement, the programs SHELXS97 and SHELXL97 were used.[16,17]

Methyl 3-(Benzylaminoimidazo[1,2-*a*]pyridin-2-yl)-2,3-dimethylbutanoate (4h)

According to general procedure, a mixture of methyl 1,3,3-trimethyl-2-trimethylsiloxycyclopropanecarboxylate (0.277 g, 1.20 mmol), 2-aminopyridine (0.094 g, 1.00 mmol), benzyl isocyanide (0.118 g, 1.00 mmol) and AcOH (0.120 g, 2.00 mmol) in MeOH (3 mL) gave after 17 h at r.t., 0.140 g (40%) of **4h** as a pale yellow oil.

IR (KBr): 3375 (N–H), 3085–2950 (=C–H, C–H), 1735 (C=O), 1630 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.06 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.54 (s, 6 H, CH_3), 3.17 (q, *J* = 7.2 Hz, 1 H, CH), 3.44 (t, *J* = 6.4 Hz, 1 H, NH), 3.50 (s, 3 H, OCH_3), 4.07 (d, *J* = 6.4 Hz, 2 H, CH_2Ph), 6.66 (td, *J* = 6.8, 1.1 Hz, 1 H, 6-H), 7.04 (ddd, *J* = 9.0, 6.8, 1.1 Hz, 1 H, 7-H), 7.24–7.55 (m, 6 H, 8-H, C_6H_5), 7.91 (dt, *J* = 6.8, 1.1 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 13.1, 24.0, 26.0 (3 q, CH_3), 38.5 (s, *C*Me_2), 48.5 (d, CH), 51.0 (q, OCH_3), 52.8 (t, *C*H_2Ph), 111.2 (d, C-6), 117.0 (d, C-8), 122.1 (d, C-5), 123.3 (d, C-7), 125.3 (s, C-3), 127.5, 127.9, 128.6 (3 d, C_6H_5), 139.0 (s, C_6H_5), 140.2 (s, C-2), 142.3 (s, C-9), 176.2 (s, C=O).

MS (EI): *m*/*z* (%) = 351 (34, $[M]^+$), 264 (14), 261 (20), 260 (100), 233 (16), 229 (12), 228 (66), 201 (10), 174 (16), 176 (15), 158 (14), 121 (21) 105 (19), 91 (10, $[Bn]^+$), 78 (13).

HRMS: *m*/*z* calcd for $C_{21}H_{25}N_3O_2$: 351.1947; found: 351.1963.

Methyl 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)propanoate (5)

Compound **4b** (0.643 g, 1.94 mmol) was dissolved in trifluoroacetic acid–CH_2Cl_2 solution (1:1; 5 mL) and stirred for 2 h at r.t. The mixture was loaded on a Dowex cation exchange resin, washed with MeOH until it was acid-free and then eluted with MeOH saturated with ammonia. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 19:1); yield: 0.399 g (94%) of **5** as yellowish oil.

IR (KBr): 3320–3180 (N–H), 2950–2850 (=C–H, C–H), 1730 (C=O), 1670 (C=N) cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.78 (t, *J* = 6.7 Hz, 2 H, CH_2), 3.02 (t, *J* = 6.7 Hz, 2 H, CH_2), 3.52 (s, 3 H, OCH_3), 6.05 (br s, 2 H, NH_2), 6.76 (t, *J* = 6.8 Hz, 1 H, 6-H), 7.03–7.19 (m, 1 H, 7-H), 7.42 (d, *J* = 9.1 Hz, 1 H, 8-H), 8.00 (d, *J* = 6.8 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 21.6, 33.2 (2 t, CH_2), 51.6 (q, OCH_3), 111.6 (d, C-6), 116.7 (d, C-8), 122.1 (d, C-5), 123.3 (d, C-7), 123.4 (s, C-3), 132.7 (s, C-2), 140.2 (s, C-9), 174.1 (s, C=O).

MS (EI): *m*/*z* (%) = 219 (58, $[M]^+$), 188 (16), 161 (14), 160 (100), 159 (19), 146 (52), 133 (14), 121 (16), 119 (25), 115 (14), 80 (24), 79 (82), 55 (15), 51 (17).

HRMS: *m*/*z* calcd for $C_{11}H_{13}N_3O_2$: 219.1008; found: 219.1016.

Methyl 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoate (6) and 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoic Acid (7)

Compound **4f** (0.116 g, 0.32 mmol) was dissolved in trifluoroacetic acid–CH_2Cl_2 solution (1:1; 2 mL) and stirred for 5 min at r.t. The mixture was loaded on a Dowex cation exchange resin, washed with MeOH until it was acid-free and then eluted with MeOH saturated with ammonia. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 19:1); yield: 0.020 g (25%) of **6** as a yellow oil and 0.037 g (50%) of **7** as colorless crystals; mp 250–251 °C.

According to the preparation described above, compound **4f** (0.861 g, 2.40 mmol) was dissolved in trifluoroacetic acid–CH_2Cl_2 solution (1:1; 5 mL) and stirred for 2 h at r.t. Purification by column chromatography (silica gel, CH_2Cl_2–MeOH, 19:1) gave 0.450 g (80%) of **7** as colorless crystals.

Compound 6

IR (KBr): 3380–3085 (N–H, O–H), 2950–2875 (=C–H, C–H), 1720 (C=O), 1610 (C=N) cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.35 (s, 6 H, CH_3), 2.54 (s, 2 H, CH_2), 3.91 (s, 3 H, OCH_3), 6.75 (td, *J* = 6.7, 1.2 Hz, 1 H, 6-H), 7.02 (ddd, *J* = 9.0, 6.7, 1.2 Hz, 1 H, 7-H), 7.49 (dt, *J* = 9.0, 1.2 Hz, 1 H, 8-H), 8.09 (dt, *J* = 6.7, 1.2 Hz, 1 H, 5-H); the NH_2 signal could not be detected.

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 27.0 (q, CH_3), 32.2 (s, *C*Me_2), 42.8 (t, CH_2), 53.7 (q, OCH_3), 111.8 (d, C-6), 117.1 (d, C-8), 121.5 (d, C-5), 122.4 (d, C-7), 127.5 (s, C-3), 135.8 (s, C-2), 141.9 (s, C-9), 165.9 (s, C=O).

MS (EI): *m*/*z* (%) = 229 (100, $[M - NH_4]^+$), 215 (14), 214 (95), 200 (15), 199 (14), 91 (12, $[Bn]^+$), 85 (21), 83 (21), 78 (21), 55 (40), 45 (25), 43 (74), 41 (46).

HRMS: *m*/*z* calcd for $C_{13}H_{13}N_2O_2$ $[M - NH_4]^+$: 229.0978; found: 229.0982.

Compound 7

IR (KBr): 3335–2865 (O–H, N–H, =C–H, C–H), 1680 (C=O), 1570 (C=N) cm^{-1}.

^{1}H NMR (CD_3OD, 500 MHz): δ = 1.47 (s, 6 H, CH_3), 2.78 (s, 2 H, CH_2), 6.88 (td, *J* = 6.8, 1.2 Hz, 1 H, 6-H), 7.13 (ddd, *J* = 9.2, 6.8, 1.2 Hz, 1 H, 7-H), 7.44 (dt, *J* = 9.2, 1.2 Hz, 1 H, 8-H), 8.06 (dt, *J* = 6.8, 1.2 Hz, 1 H, 5-H).

^{13}C NMR (CD_3OD, 125.8 MHz): δ = 27.2 (q, CH_3), 33.1 (s, *C*Me_2), 48.0 (t, CH_2), 113.8 (d, C-6), 117.5 (d, C-8), 121.3 (d, C-5), 122.5 (d, C-7), 123.9 (d, C-3), 139.3 (s, C-2), 142.1 (s, C-9), 172.4 (s, C=O).

MS (EI): *m*/*z* (%) = 215 (87, $[M - H_2O]^+$), 201 (29), 200 (100), 173 (13), 172 (11), 158 (12), 145 (20), 79 (19), 78 (57), 52 (10), 51 (17), 41 (12), 39 (12), 28 (16), 27 (10).

HRMS: *m*/*z* calcd for $C_{12}H_{13}N_3O$ $[M - H_2O]^+$: 215.1059; found: 215.1063.

3-{3-[(*tert*-Butoxycarbonyl)amino]imidazo[1,2-*a*]pyridin-2-yl}-3-methylbutanoic Acid (8)

A stirred solution of amino acid **5** (0.090 g, 0.386 mmol) in THF (6 mL) was treated with NaH (0.016 g, 0.038 mmol; 60% suspension in oil), and further stirred for 1 h at r.t. Boc_2O (0.168 g, 0.772 mmol) was then added to the mixture, stirred for 1 h, and then treated with a catalytic amount of DMAP followed by stirring for 1 h. The mixture was partitioned between EtOAc and sat. aq NH_4Cl solution and the organic phase was separated and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography (silica gel; 10% *i*-PrOH–hexane) to give 0.100 g (78%) of **8** as brownish oil.

IR (KBr): 3445 (N–H), 3050–2875 (=C–H, C–H), 1785, 1740 (C=O), 1635 (C=N), 1290 (C–O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.36 (s, 6 H, CH_3), 1.49 (s, 9 H, *t*-C_4H_9), 2.57 (s, 2 H, CH_2), 6.75 (t, *J* = 6.9 Hz, 1 H, 6-H), 7.07 (t, *J* = 6.9 Hz, 1 H, 7-H), 7.43–7.53 (m, 2 H, 8-H, 5-H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 26.0 (q, CH_3), 27.7, 85.2 [q, s, $C(CH_3)_3$], 31.6 (s, *C*Me_2), 50.4 (t, CH_2), 111.8 (d, C-6), 117.5 (d, C-8), 118.0 (s, C-3), 122.7 (d, C-5), 123.0 (d, C-7), 140.4 (s, C-2), 142.3 (s, C-9), 148.5, 172.4 (2 s, C=O).

MS (EI): *m*/*z* (%) = 315 (2, $[M - H_2O]^+$), 215 (62), 200 (100), 78 (15), 57 (27).

HRMS: *m*/*z* calcd for $C_{17}H_{21}N_3O_3$ $[M - H_2O]^+$: 315.1583; found: 315.1573.

3-[3-(Benzylamino)imidazo[1,2-*a*]pyridin-2-yl]-3-methylbutanoic Acid (9)

To a solution of compound **4e** (0.109 g, 0.320 mmol) in MeOH–THF (1 mL/3 mL), was added a solution of $LiOH·H_2O$ (0.041 g, 0.096 mmol) in H_2O (1 mL), and the resulting mixture was stirred for 22 h at r.t. Then aq 2 M HCl was added to adjust the pH to 7, followed by Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O, the combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. Purification of the crude product by column chromatography (silica gel, hexane–EtOAc, 1:2) gave 0.080 g (77%) of **9** as a pale yellow solid; mp 111–115 °C.

IR (KBr): 3230–3030 (O–H, N–H), 2960–2870 (=C–H, C–H), 1680 (C=O), 1235 (C–O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.38 (s, 6 H, CH_3), 2.74 (s, 2 H, CH_2), 5.23 (s, 2 H, CH_2Ph), 6.65 (td, *J* = 6.9, 1.2 Hz, 1 H, 6-H), 7.01 (ddd, *J* = 9.1, 6.9, 1.2 Hz, 1 H, 7-H), 7.24–7.40 (m, 5 H, C_6H_5), 7.56 (dt, *J* = 9.1, 1.2 Hz, 1 H, 8-H), 7.76 (dt, *J* = 6.9, 1.2 Hz, 1 H, 5-H); the NH signal could not be detected.

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 26.4 (q, CH_3), 31.6 (s, *C*Me_2), 46.6 (t, CH_2), 48.5 (t, *C*H_2Ph), 112.8 (d, C-6), 118.2 (d, C-8), 121.8 (d, C-5), 121.9 (d, C-7), 122.1 (s, C-3), 126.8, 127.8, 129.0, 136.7 (3 d, s, C_6H_5), 138.6 (s, C-2), 141.5 (s, C-9), 171.0 (s, C=O).

MS (EI): *m*/*z* (%) = 323 (31, $[M]^+$), 305 (32), 233 (16), 232 (100, $[M - Bn]^+$), 215 (14), 214 (94), 205 (42), 121 (31), 105 (17), 91 (39, $[Bn]^+$), 83 (11), 79 (14), 78 (59), 41 (11).

HRMS: *m*/*z* calcd for $C_{19}H_{21}N_3O_2$: 323.1634; found: 323.1663.

1-Benzyl-4,4-dimethyl-3,4-dihydro-1*H*-dipyrido[1,2-*a*;3′,2′-*d*]-imidazol-2-one (10e)

Compound **4e** (0.060 g, 0.178 mmol) was dissolved in anhyd MeOH (2 mL) under argon, followed by addition of NaCN (1 mg, 0.02 mmol). The mixture was heated at 85 °C for 43 h, and then the solvent was evaporated to dryness. EtOAc and H_2O were added and the layers were separated. The aqueous layer was extracted with EtOAc, the combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography (alumina, activity

III; hexane–EtOAc, 1:1) leading to 0.050 g (92%) of **10e** as colorless crystals; mp 138–140 °C.

IR (KBr): 3065–2865 (=C–H, C–H), 1680 (C=O), 1630 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.38 (s, 6 H, CH_3), 2.74 (s, 2 H, CH_2), 5.23 (s, 2 H, CH_2Ph), 6.64 (td, *J* = 6.9, 1.2 Hz, 1 H, 6-H), 7.01 (ddd, *J* = 9.1, 6.9, 1.2 Hz, 1 H, 7-H), 7.23–7.37 (m, 5 H, C_6H_5), 7.55 (dt, *J* = 9.1, 1.2 Hz, 1 H, 8-H), 7.77 (dt, *J* = 6.9, 1.2 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 26.3 (q, CH_3), 31.5 (s, CMe_2), 46.5, 48.4 (2 t, CH_2), 112.6 (d, C-6), 118.2 (d, C-8), 121.6 (d, C-5), 121.8 (d, C-7), 122.0 (s, C-3), 126.7, 127.7, 128.9, 136.6 (3 d, s, C_6H_5), 138.6 (s, C-2), 141.4 (s, C-9), 170.9 (s, C=O).

MS (EI): *m*/*z* (%) = 305 (32, $[M]^+$), 215 (14), 214 (100, $[M - Bn]^+$), 91 (13, $[Bn]^+$), 78 (18).

HRMS: *m*/*z* calcd for $C_{19}H_{19}N_3O$: 305.1528; found: 305.1536.

1-Benzyl-3,4,4-trimethyl-3,4-dihydro-1*H*-dipyrido[1,2-*a*;3′,2′-*d*]imidazol-2-one (10h)

According to the preparation of **10e**, compound **4h** (0.414 g, 1.12 mmol), NaCN (6 mg, 0.12 mmol) and MeOH (14 mL) gave after 48 h at 85 °C and purification by column chromatography (alumina, activity III; hexane–EtOAc, 1:1), 0.350 g (98%) of **10h** as colorless crystals; mp 114–115 °C.

IR (KBr): 3085–2870 (=C–H, C–H), 1680 (C=O), 1635 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.11 (s, 3 H, CH_3), 1.19 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 2.66 (q, *J* = 7.1 Hz, 1 H, 10-H), 5.16, 5.23 (2 dd, *J* = 16.3 Hz, 2 H, CH_2), 6.62 (td, *J* = 6.9, 1.2 Hz, 1 H, 6-H), 6.98 (ddd, *J* = 9.1, 6.9, 1.2 Hz, 1 H, 7-H), 7.19–7.33 (m, 5 H, C_6H_5), 7.54 (dt, *J* = 9.1, 1.2 Hz, 1 H, 8-H), 7.72 (dt, *J* = 6.9, 1.2 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 10.0, 21.3, 25.3 (3 q, CH_3), 34.3 (s, CMe_2), 46.6 (t, CH_2), 48.8 (d, CH), 112.5 (d, C-6), 118.1 (d, C-8), 121.3 (d, C-5), 121.5 (d, C-7), 121.7 (s, C-3), 126.6, 127.6, 128.8, 136.7 (3 d, s, C_6H_5), 139.0 (s, C-2), 141.2 (s, C-9), 173.9 (s, C=O).

MS (EI): *m*/*z* (%) = 319 (53, $[M]^+$), 258 (17), 229 (17), 228 (100, $[M - Bn]^+$), 121 (30), 108 (22), 106 (17), 94 (25), 91 (38, $[Bn]^+$), 86 (37), 84 (64), 78 (33), 70 (37), 69 (15), 67 (17), 55 (23), 47 (16), 43 (21), 41 (24).

HRMS: *m*/*z* calcd for $C_{20}H_{21}N_3O$: 319.1685; found: 319.1666.

Methyl *N*-(3-{3-[(*tert*-Butoxycarbonyl)amino]imidazo[1,2-*a*]pyridin-2-yl}-3-methylbutanoyl)-l-alaninate (11)

Acid **8** (0.074 g, 0.222 mmol), H-Ala-OMe·HCl (0.036 g, 0.26 mmol) and BOP (0.115 g, 0.26 mmol) were dissolved in anhyd CH_2Cl_2 (2 mL), and then DIEA (0.1 mL, 0.66 mmol) was added. The reaction was stirred for 10 d at r.t. EtOAc and H_2O were added and the layers were separated. The organic layer was successively washed with sat. aq $NaHCO_3$ solution, brine and H_2O, dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification by column chromatography [silica gel; hexane–EtOAc (1:2), then MeOH–CH_2Cl_2 (1:1), and finally HPLC 50% *i*-PrOH–hexane, 64 mL/min, 124 bar] yielded 0.089 g (97%) of **11** as a colorless solid; mp 70–72 °C; $[\alpha]_D$ –27.4 (*c* = 0.95, MeOH).

IR (KBr): 3290 (N–H), 3055–2880 (=C–H, C–H), 1725 (C=O), 1655 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.06 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.54, 1.55 (2 s, 9 H, 6 H, *t*-C_4H_9, CH_3), 2.60–2.82 (m, 2 H, CH_2), 3.60 (s, 3 H, OCH_3), 4.35 (q, *J* = 7.2 Hz, 1 H, CH), 6.64, 6.74 (2 br s, 1 H, 1 H, NH), 6.82 (t, *J* = 6.2 Hz, 1 H, 6-H), 7.11–7.24 (m, 1 H, 7-H), 7.52 (d, *J* = 9.0 Hz, 1 H, 8-H), 7.86 (d, *J* = 6.2 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 17.7, 28.2 [2 q, CH_3, $C(CH_3)_3$], 36.0 (s, CMe_2), 47.7 (d, CH), 50.6 (t, CH_2), 52.1 (q, OCH_3), 81.3 (s, CMe_3), 112.0 (d, C-6), 117.0 (d, C-8), 122.9 (d, C-5), 124.7 (d, C-7), 128.0 (s, C-3), 142.5 (s, C-2), 148.7 (s, C-9), 154.1, 171.4, 171.5 (3 s, C=O).

MS (EI): *m*/*z* (%) = 418 (6, $[M]^+$), 345 (15), 344 (48), 318 (39), 242 (20), 223 (14), 216 (15), 215 (71), 214 (45), 200 (85), 188 (57), 175 (13), 174 (100), 173 (14), 158 (13), 147 (11), 121 (12), 79 (12), 78 (30), 57 (32).

HRMS: *m*/*z* calcd for $C_{21}H_{30}N_4O_5$: 418.2216; found: 418.2235.

Methyl 3-(3-{[*N*-(*tert*-Butoxycarbonyl)-l-alanyl]amino}imidazo[1,2-*a*]pyridin-2-yl)propanoate (12)

Amino ester **5** (0.026 g, 0.12 mmol), Boc-Ala-OH (0.022 g, 0.12 mmol) and DIEA (0.06 mL, 0.36 mmol) were dissolved in anhyd CH_2Cl_2 (3 mL), cooled in an ice bath, and then TFFH (0.042 g, 0.15 mmol) was added. The temperature was allowed to rise to r.t. After 4 d, the mixture was successively washed with aq 1 M HCl, sat. aq $NaHCO_3$ solution and brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification by column chromatography [silica gel; hexane–EtOAc (4:1), then MeOH–CH_2Cl_2 (4:1), and finally HPLC 50% *i*-PrOH–hexane, 64 mL/min, 124 bar] gave 0.012 g (26%) of **12** as pale yellow oil; $[\alpha]_D$ –25.6 (*c* = 0.09, MeOH).

IR (KBr): 3295 (N–H), 3055–2855 (=C–H, C–H), 1715 (C=O), 1635 (C=N) cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.46 (s, 9 H, *t*-C_4H_9), 1.55 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.75–2.82 (m, 2 H, CH_2), 2.91–2.97 (m, 2 H, CH_2), 3.60 (s, 3 H, OCH_3), 4.43 (q, *J* = 7.2 Hz, 1 H, CH), 5.15 (br s, 1 H, NH), 6.75 (td, *J* = 6.8, 1.1 Hz, 1 H, 6-H), 7.13 (ddd, *J* = 9, 6.8, 1.1 Hz, 1 H, 7-H), 7.46 (dt, *J* = 9, 1.1 Hz, 1 H, 8-H), 7.73 (d, *J* = 6.8 Hz, 1 H, 5-H), 8.75 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 18.2 (q, CH_3), 21.9 (t, CH_2), 28.3 [q, $C(CH_3)_3$], 33.0 (t, CH_2), 38.6 (s, CMe_2), 50.6 (d, CH), 51.7 (q, OCH_3), 80.3 (s, CMe_3), 111.8 (d, C-6), 115.5 (s, C-3), 117.1 (d, C-8), 123.6 (d, C-5), 124.2 (d, C-7), 138.6 (s, C-2), 142.8 (s, C-9), 155.8, 172.7, 174.6 (3 s, C=O).

MS (EI): *m*/*z* (%) = 390 (15, $[M]^+$), 334 (12), 247 (13), 246 (86), 219 (56), 218 (18), 214 (16), 186 (20), 160 (38), 159 (14), 146 (15), 131 (15), 79 (42), 73 (19), 59 (29), 57 (100), 55 (16), 44 (59), 43 (42).

HRMS: *m*/*z* calcd for $C_{19}H_{26}N_4O_5$: 390.1903; found: 390.1914.

Acknowledgment

Support by the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 'Hydrogen Bridges and Hydrogen Transfer'), the Fonds der Chemischen Industrie and the Schering AG is most gratefully acknowledged. We also thank Simon Braun for his experimental help.

References

(1) Sewald, N.; Jakubke, H.-D. *Peptides: Chemistry and Biology*; Wiley-VCH: Weinheim, **2002**, Chap. 7.
(2) For excellent up to date reviews, see: (a) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, **2005**. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (c) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (d) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168; *Angew. Chem.* **2000**, *118*, 3300. (e) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. (f) Ugi, I.; Lohberger, S.; Karl, R. In *Comprehensive Organic*

Synthesis, Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, Chap. 4.6. (g) Ugi, I. *J. Prakt. Chem.* **1997**, *339*, 499.
(3) (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73.
(4) Zimmer, R.; Ziemer, A.; Gruner, M.; Brüdgam, I.; Hartl, H.; Reissig, H.-U. *Synthesis* **2001**, 1649.
(5) Veljkovic, I.; Al-Ajmi, H.; Özbek, H.; Reissig, H.-U., manuscript in preparation.
(6) (a) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661. (b) Mandair, G. S.; Light, M.; Russell, A.; Hursthouse, M.; Bradley, M. *Tetrahedron Lett.* **2002**, *43*, 4267. (c) Lyon, M. A.; Kercher, T. S. *Org. Lett.* **2004**, *6*, 4989. (d) Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635. Alternative methods for the preparation of imidazo[1,2-*a*]pyridines: (e) Krasovsky, A. L.; Nenajdenko, V. G.; Balenkova, E. S. *Synthesis* **2002**, 1379.
(7) (a) Katritzky, A. R.; Xu, Y.-J.; Tu, H. *J. Org. Chem.* **2003**, *68*, 4935. (b) Jaramillo, C.; de Diego, E.; Hamdouchi, C. *Synlett* **2002**, 1544; and references cited therein.
(8) (a) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250; *Angew. Chem.* **2004**, *116*, 6408. (b) Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, **2002**. For microwave-assisted synthesis of fused 3-aminoimidazolines, see: (c) Ireland, S. M.; Tye, K.; Whittaker, M. *Tetrahedron Lett.* **2003**, *44*, 4369. (d) Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 7665.
(9) Blackburn, C.; Guan, B. *Tetrahedron Lett.* **2000**, *41*, 1495.
(10) Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033.
(11) Hünig, S.; Schaller, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 36; *Angew. Chem.* **1982**, *94*, 1.
(12) (a) Campagne, J.-M.; Coste, J.; Jouin, P. *J. Org. Chem.* **1995**, *60*, 5214. (b) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, 1219.
(13) Carpino, L. A.; El-Faham, A. *J. Am. Chem. Soc.* **1995**, *117*, 5401.
(14) Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 512.
(15) Casanova, J.; Newton, D. W.; Schuster, R. E. *J. Am. Chem. Soc.* **1966**, *88*, 3473.
(16) Sheldrick, G. M. *SHELX97 (Includes SHELXS97, SHELXL97, CIFTAB) Programs for Crystal Structure Analysis (Release 97-2)*; Universität Göttingen: Germany, **1998**.
(17) Atomic coordinates and further crystallographic details have been deposited at the Cambridge Crystallographic Data Centre, deposition number CCDC 601760, and copies of this data can be obtained in application to CCDC, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).