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# Synthesis of Regioisomeric Pyrido[*c*]azocanones from Azaindanone Derivatives

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A ring enlargement reaction with methylamine gave new pyrido[2,3-*c*]-, pyrido[3,4-*c*]- and pyrido[3,2-*c*]azocanone derivatives from cyclic β-oxo esters with a cyclopentapyridine skeleton and a 1,4-diketone moiety. The starting materials for this ring transformation were either prepared from halogenopyridine carboxylates by Heck reaction and subsequent hydrogenation, or (halogenomethyl)pyridine carboxylates were submitted to $S_N$ reaction with diethyl malonate. Both routes were completed by Dieckmann condensation to build the cyclic β-oxo ester structure and alkylation with phenacylbromide to install the 1,4-diketone motif.

## Introduction

The efficient construction of medium sized nitrogen-containing rings is an ongoing challenge for synthetic chemists, as the entropic penalty for ring closure is typically higher than for five- and six-membered systems. Nevertheless, fused nitrogen-containing eight-membered ring systems (azocines) are common in nature, being found in a number of bioactive molecules and pharmaceuticals. These include natural products such as apparicine (**1**),[1] uleine (**2**),[2] dasycarpidone (**3**),[3] and cycloechinulin (**4**)[4] (Figure 1) as well as other compounds that are promising for medicinal chemistry.[5]

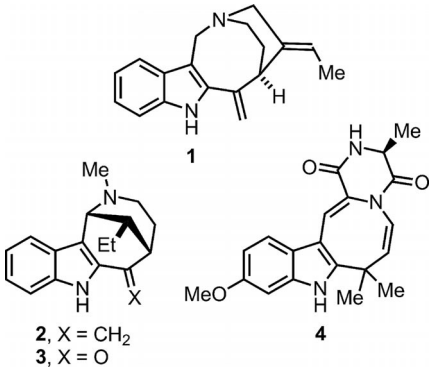


Figure 1. Examples of natural products with annulated azocine moieties.

Due to their attractive structures, fused benzo[*c*]azocines have previously been prepared through the application of methods such as nucleophilic[6] and electrophilic (aromatic) substitutions,[7] electrophilic cyclizations,[8] 2,3-sigmatropic rearrangements of *N*-benzylammonium ylides (Sommelet–Hauser rearrangements),[9] radical chain insertions,[10] and ring closing metatheses.[11] However, one area that remains poorly developed is the synthesis of heterocycle-fused ring systems, in particular those that contain a pyridine ring, which is one of the key molecular binding sites in medicinal chemistry.[12]

In 2006 we discovered a transformation of 1,4-diketones with primary amines that furnished eight-membered ring lactams, i.e., hexahydroazocinones, which defined new scaffolds for combinatorial chemistry.[13] This transformation was subsequently used for the preparation of a library of almost five thousand compounds for the discovery of new lead structures.[14] Furthermore, we have used pyrrolidine and tetrahydrothiophene derivatives in the ring-expansion reaction to form eight-membered ring lactams with a second N-heteroatom (diazocanones)[15] or an additional S-heteroatom (thiazocanones).[16] The latter have been used for the preparation of a combinatorial library consisting of more than one hundred compounds. Finally, we recently introduced a benzo[*c*] annulation at the azocanone ring.[17] Since the pyridine moiety is one of the privileged structural motifs in medicinal chemistry,[18] we report herein on an extension of our investigations towards the preparation of pyrido[*c*] annulated azocanones **5**–**8** as part of our continuing efforts to provide new heterocyclic scaffolds for combinatorial chemistry (Scheme 1).[19] The retrosynthetic approach to all four target structures **5**–**8** is the same and can therefore be exemplified for the pyrido[2,3-*c*] congener **5**. Our key reaction for eight-membered lactam formation is actually the ring enlargement of the 1,4-diketone **9** with $MeNH_2$. Compound **9** should be obtained by alkylation of azaindanone carboxylate **10** with phenacylbromide (**11**). The cyclic β-oxo ester moiety of **10** can be derived from di- (*n* = 1; **13a**) or triesters (*n* = 2; **13b**) by Dieckmann condensation.[20] The synthesis of **13** was actually the major

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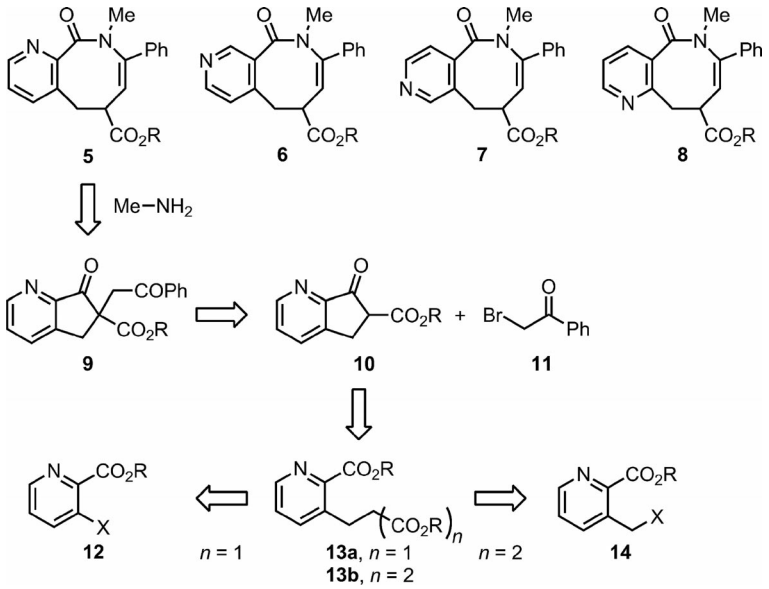
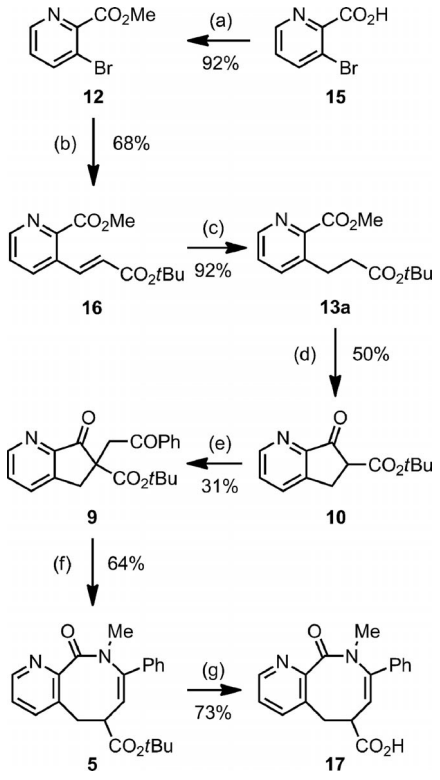



Scheme 1. Target structures and their retrosynthetic approach.

challenge of this project. For $n$ = 1, diester **13a** is available by Heck reaction of halo (X = Cl, Br) pyridine **12** followed by hydrogenation. When $n$ = 2, triester **13b** could be obtained by substitution of (halomethyl)pyridines **14** with malonates.

## Results and Discussion

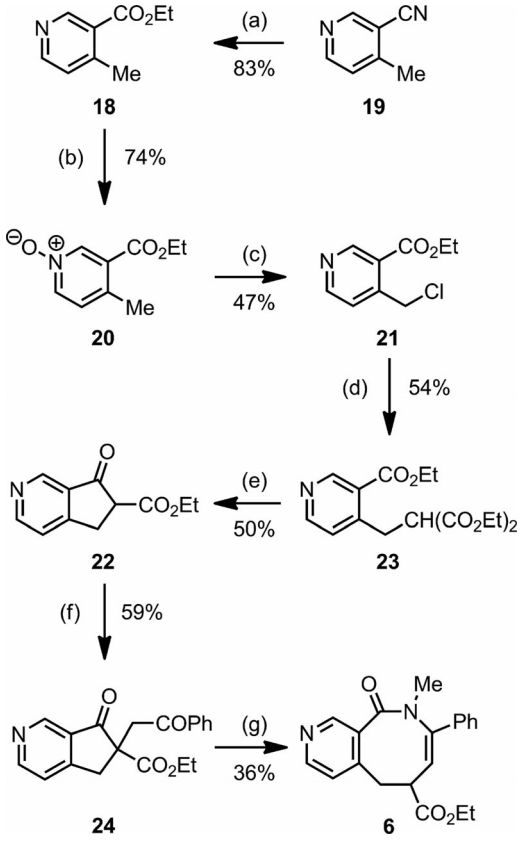
Synthesis of pyrido[2,3-*c*]azocanone **5** was accomplished through the Heck route and started with commercially available 3-bromopicolinic acid (**15**), which was esterified according to a published procedure (92% yield of product **12**; Scheme 2).[21] The subsequent Heck reaction was accomplished according to a standard protocol[22] with an excess of *tert*-butyl acrylate (68% of product **16**), which was followed by catalytic hydrogenation (92%). Actually, in initial experiments, two ethyl ester functions were present in the intermediate product, which led to very low yield in the Dieckmann condensation. With the *tert*-butyl methyl diester **13a** this step still gave moderate, but preparatively useful, yield of β-oxo ester **10**. The latter could be alkylated with α-bromoketone **11** to give 1,4-diketone **9** (31%). The yield-limiting process was competing *O*-alkylation, which is well-known for sterically congested β-dicarbonyl compounds.[23] Ring enlargement reaction with $MeNH_2$ in tetrahydrofuran (THF) was performed at 100 °C in a tightly closed reaction vial. Compound **5** was obtained with good yield. In the NMR spectra of the latter, a doubled signal set was observed, which was due to two slowly interconverting diastereoisomeric conformers. Whereas C-6 is clearly a stereogenic center, a second stereogenic element is defined by the plane of the pyridine ring, which becomes a chirality plane due to the restricted torsion of the folded boat conformation of the eight-membered ring (for structural details see below). This stereochemical issue was previously observed for the benzo-annulated analogues and discussed in detail.[17] Finally, the *tert*-butyl ester function was smoothly cleaved under acidic conditions to furnish carboxylic acid **17** (73%).




Scheme 2. Synthesis of pyrido[2,3-*c*]azocanones **5** and **17**. Reagents and conditions: (a) $SOCl_2$ (4 equiv.), MeOH, 0–85 °C, 24 h; (b) $CH_2{=}CHCO_2tBu$ (10 equiv.), $Pd(OAc)_2$ (0.1 equiv.), $PPh_3$ (0.2 equiv.), $NEt_3$ (5 equiv.), DMF, 110 °C, 18 h; (c) Pd–C (cat.), $H_2$ (1 atm), *i*PrOH, 23 °C, 22 h; (d) NaH (2.5 equiv.), THF, 0–50 °C, 1 h; (e) $PhCOCH_2Br$ (**11**; 1.2 equiv.), $K_2CO_3$ (1.2 equiv.), acetone, 40 °C, 2 h; (f) $MeNH_2$ (2 equiv.), THF, 100 °C, 16 h; (g) TFA, $CH_2Cl_2$, 23 °C, 19 h.

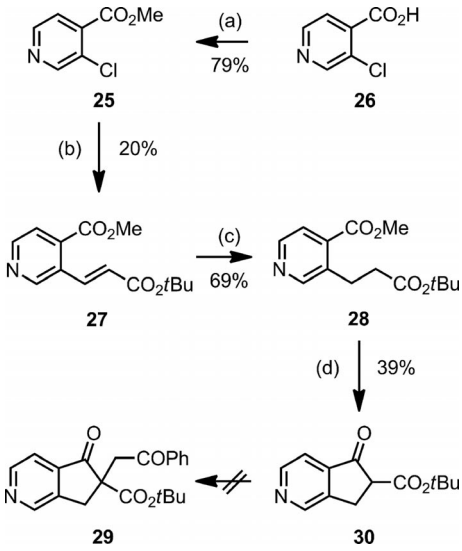
  

Synthesis of pyrido[3,4-*c*]azocanone **6** was accomplished through the malonate route and started with nitrile **19**, which was prepared in three steps from commercially available cyano acetamide and ethyl acetoacetate according to a published procedure.[24] The nitrile function was first solvolyzed to give ethyl ester **18** (Scheme 3).[25] Since all attempts at direct α-halogenation of the 4-Me group failed, we followed a literature report[26] and achieved the synthesis via the *N*-oxide **20** (74% with *m*CPBA), which could be converted with TosCl to give 4-chloromethyl derivative **21**. Nucleophilic displacement with diethyl malonate gave triester **23** (54%), which was submitted to Dieckmann condensation to furnish β-oxo ester **22** (50%).[27] The last two steps proceeded analogously to the preparation of compound **5**: Alkylation with bromoketone **11** (59% yield of 1,4-diketone **24**) and ring transformation with $MeNH_2$ (36%). As observed in the previous case, product **6** showed doubled signal sets in the NMR spectra.

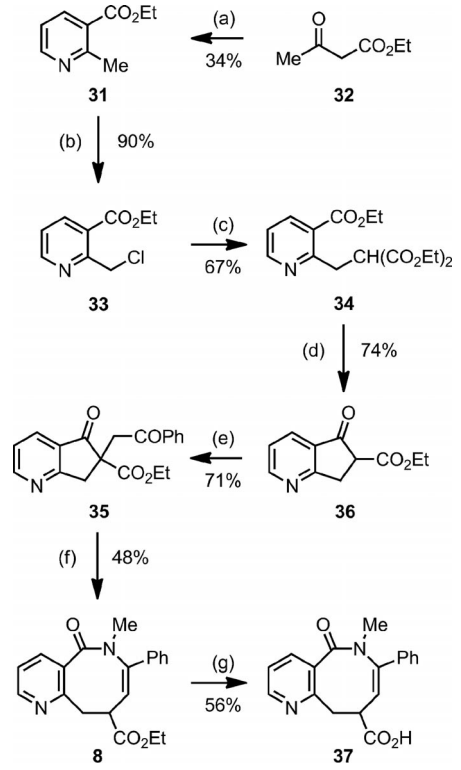



Scheme 3. Synthesis of pyrido[3,4-*c*]azocanone **6**. Reagents and conditions: (a) 1. $H_2SO_4/H_2O$, 130 °C, 17 h; 2. EtOH, 80 °C, 4 h; (b) *m*CPBA (2 equiv.), $CHCl_3$, 0–23 °C, 19 h; (c) TosCl (2 equiv.), 1,4-dioxane, 100 °C, 1.5 h; (d) Na (3 equiv.) in EtOH, $CH_2(CO_2Et)_2$ (3 equiv.), THF, 0–23 °C, 2 h; (e) Na (4 equiv.) in EtOH, 65 °C, 2 h; (f) $PhCOCH_2Br$ (**11**; 1.2 equiv.), $K_2CO_3$ (1.2 equiv.), acetone, 40 °C, 3 h; (g) $MeNH_2$ (2 equiv.), THF, 100 °C, 17 h.

Attempts at the preparation of pyrido[4,3-*c*]azocanone **7** were made by using both the malonate and Heck routes. The latter actually started with commercially available chloro isonicotinic acid **26**, which was first esterified to give compound **25** (Scheme 4).[28] However, severe problems




Scheme 4. Attempts at the synthesis of pyrido[4,3-*c*]azocanone **7**. Reagents and conditions: (a) $SOCl_2$ (4 equiv.), MeOH, 0–80 °C, 24 h; (b) $CH_2{=}CHCO_2tBu$ (20 equiv.), $Pd(OAc)_2$ (0.1 equiv.), $PPh_3$ (0.2 equiv.), $NEt_3$ (5 equiv.), DMA, 120 °C, 18 h; (c) Pd–C (cat.), $H_2$ (1 atm), *i*PrOH, 23 °C, 3 d; (d) KO*t*Bu (2.5 equiv.), THF, 0 °C, 0.5 h.




Scheme 5. Synthesis of pyrido[3,2-*c*]azocanone **8**. Reagents and conditions: (a) 1. $NH_4OAc$ (1.1 equiv.), toluene, 110 °C, 2 h; 2. $CH_2{=}CHCHO$ (3 equiv.), 110 °C, 2.5 h; (b) DMF (0.1 equiv.), trichloroisocyanuric acid (1.5 equiv.), $CH_2Cl_2$, 23 °C, 16 h; (c) Na (3 equiv.) in EtOH, $CH_2(CO_2Et)_2$ (3 equiv.), THF, 0–23 °C, 4 h; (d) NaH (1.5 equiv.), THF, 65 °C, 1 h; (e) $PhCOCH_2Br$ (**11**; 1.2 equiv.), $K_2CO_3$ (1.2 equiv.), acetone, 56 °C, 3 h; (f) $MeNH_2$ (2 equiv.), THF, 100 °C, 15 h; (g) NaOH (10 equiv.), $H_2O$, EtOH, 23 °C, 1 h.

then started with the Heck reaction. After tedious optimization (key was the change of solvent to DMA) product **27** could be obtained, but with only 20% yield. Even by following procedures developed particularly for the conversion of aryl chlorides,[29] no improvements were achieved. Catalytic hydrogenation (69% of product **28**) and Dieckmann condensation (39% of product **30**) could be achieved, but both showed problems with reproducibility. Finally, no conditions for a successful $S_N2$ reaction of oxo ester **30** with phenacyl bromide (**11**) could be found. Along the malonate route, the β-oxo ethyl ester analogous to compound **30** could be obtained, however, alkylation with phenacyl bromide (**11**) could also not be achieved with this derivative. Therefore, the third of our target compounds (i.e., **7**) could so far not be obtained.

Synthesis of pyrido[3,2-*c*]azocanone **8** was successfully accomplished through the malonate route, starting with the synthesis of nicotinic acid derivative **31**, which was obtained in one step from ethyl acetoacetate (**32**), ammonia, and acroleine according to a published procedure (Scheme 5).[30] For side chain α-halogenation, we chose trichloroisocyanuric acid as the source of electrophilic chlorine,[31] which was superior to *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) (90% yield of product **33**).[32] Nucleophilic substitution with diethyl malonate (67% of triester **34**)[33] and Dieckmann condensation (74% of oxo ester **36**) were straightforward. The C-alkylation with bromoketone **11** also worked well, giving 1,4-diketone **35** in 71% yield. Finally, ring enlargement with $MeNH_2$ was achieved under the previously established conditions, giving the target compound **8** (48%). After ester saponification (56%) the structural features of the annulated ring system were established by X-ray crystallographic analysis of carboxylic acid **37**.[34] Figure 2 shows the structure in the solid state. The top view gives an impression of the conformation of the eight-membered ring. The amide moiety is planar, as expected (dihedral angle O1–C5–N6–C11 0.7°), with a formal C–N double bond (C5–N6 135 pm). The enamine C–C double bond is not in conjugation with the amide moiety (dihedral angle C11–N6–C7–Ph 71°). The eight-membered ring is in a folded, boat-shaped conformation. It can be clearly seen from Figure 2 (bottom view) that the pyridine ring becomes a chirality plane, thus leading to the two slowly interconverting diastereoisomeric conformations causing the doubled signal sets in the NMR spectra. We had previously determined the energy barrier for this ring inversion to be about 70 kJ mol$^{-1}$ (in the case of benzo instead of pyrido annulation).[17]

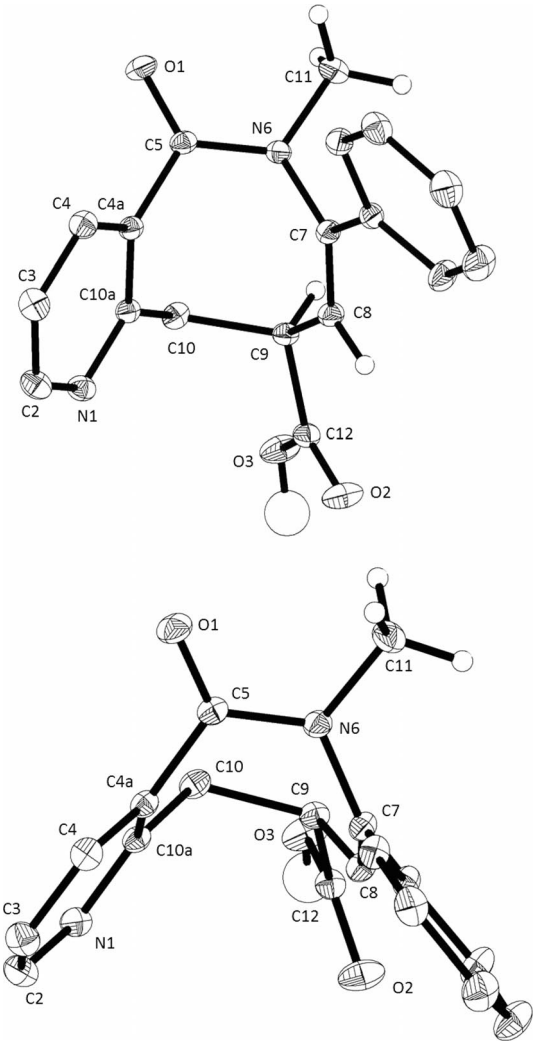



Figure 2. ORTEP representations of the structure of compound **37** in the solid state.

## Conclusions

Three cyclopentapyridine derivatives **10**, **22**, and **36** with β-oxo ester moieties were alkylated with phenacylbromide (**11**) to 1,4-diketones **9**, **24** and **35** as intermediate products (31–71% yield). The latter three compounds were submitted to ring-enlargement reactions with methylamine, furnishing three new pyridoazocanone derivatives with 36–64% yield, namely pyrido[2,3-*c*]azocanone **5**, pyrido[3,4-*c*]azocanone **6** and pyrido[3,2-*c*]azocanone **8**. The synthesis of a fourth regioisomeric compound **7** with pyrido[4,3-*c*]azocanone structure failed at the stage of the β-oxo ester **30**. The preparation of β-oxo esters **10**, **22**, **30** and **36** were accomplished through two routes with a Dieckmann condensation in each case as the last step. By following the Heck route, pyridinecarboxylates **12** and **25**, with a halogen atom in the α-position to the ester function, were converted with *tert*-butylacrylate (20–68%) and, after hydrogenation (69–92%), submitted to Dieckmann condensation (39–50%) to give β-oxo esters **10** and **30**. In the malonate route, (chloromethyl)pyridinecarboxylates **21** and **33** were first prepared by side-chain chlorination of the respective pyridinecarboxylates **18** and **31** with a methyl group α to the ester function and then submitted to nucleophilic substitution with diethyl malonate (54–67%). Dieckmann condensation (50–74%) gave β-oxo esters **22** and **36**.

## Experimental Section

**General:** Preparative column chromatography was carried out using Merck $SiO_2$ (35–70 μm, type 60 A) with hexane, *tert*-butyl methyl

ether (MTBE), ethyl acetate (EtOAc), $CH_2Cl_2$, or MeOH as eluents. TLC was performed on Merck aluminum plates coated with $SiO_2$ $F_{254}$. $^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker Avance DRX 500 instrument. Multiplicities of carbon signals were determined on the basis of DEPT experiments. MS and HRMS spectra were obtained with a Finnigan MAT 95 (EI) and a Waters Q-TOF Premier (ESI) spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond ATR unit. Elemental analyses were determined with a Euro EA-CHNS instrument from HEKAtech.

**Methyl 3-Bromopicolinate (12):** $SOCl_2$ (16.7 g, 140 mmol) was added to a cooled (ice-water bath) solution of acid **15** (7.10 g, 35.1 mmol) in MeOH (10 mL) and the mixture was stirred at 85 °C for 24 h. All volatile materials were then removed in vacuo and the residue dissolved in satd. aqueous $NaHCO_3$ solution (75 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3× 40 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. Ester **12** (6.99 g, 32.4 mmol, 92%) was isolated as a colorless solid; mp. 37–38 °C. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 3.99 (s, 3 H), 7.29 (dd, $J$ = 4.6, 8.2 Hz, 1 H), 7.99 (dd, $J$ = 1.4, 8.2 Hz, 1 H), 8.59 (dd, $J$ = 1.2, 4.6 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 53.31 ($CH_3$), 119.45 (C), 126.73 (CH), 142.23 (CH), 147.95 (CH), 149.18 (C), 165.47 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3056 (w), 3002 (w), 2953 (w), 1735 (vs), 1570 (w), 1446 (w), 1419 (m), 1296 (s), 1206 (m), 1133 (m), 1058 (m), 1023 (m), 959 (w), 837 (w), 794 (m), 723 (w), 635 (w) $cm^{-1}$. HRMS (ESI): calcd. for $C_7H_6BrNNaO_2$ [M + $Na^+$] 237.9480; found 237.9485.

**(*E*)-Methyl 3-[2-(*tert*-Butoxycarbonyl)ethenyl]picolinate (16):** *tert*-Butyl acrylate (17.9 g, 139 mmol), $Pd(OAc)_2$ (312 mg, 1.39 mmol), $PPh_3$ (729 mg, 2.78 mmol) and $NEt_3$ (7.03 g, 69.5 mmol) were added under an inert atmosphere ($N_2$) to a solution of pyridine **12** (3.00 g, 13.9 mmol) in anhydrous DMF (35 mL) and the resulting mixture was stirred at 110 °C for 18 h. Water (20 mL) was then added and the aqueous layer was extracted with MTBE (3× 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvents were evaporated to give **16** (2.48 g, 9.42 mmol, 68%) after column chromatography ($SiO_2$; hexane/MTBE = 1:1; $R_f$ = 0.17) as a yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.51 (s, 9 H), 3.99 (s, 3 H), 6.27 (d, $J$ = 16.0 Hz, 1 H), 7.45 (dd, $J$ = 4.6, 8.0 Hz, 1 H), 7.93 (dd, $J$ = 1.4, 8.0 Hz, 1 H), 8.21 (d, $J$ = 16.0 Hz, 1 H), 8.65 (dd, $J$ = 1.3, 5.1 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 28.33 (3 $CH_3$), 53.27 ($CH_3$), 81.25 (C), 125.13 (CH), 126.51 (CH), 132.49 (C), 135.93 (CH), 139.56 (CH), 147.18 (CH), 149.98 (C), 165.37 (C), 165.98 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3004 (w), 2980 (w), 2956 (w), 2935 (w), 1710 (vs), 1638 (m), 1445 (m), 1424 (m), 1370 (m), 1293 (s), 1259 (m), 1241 (m), 1197 (m), 1150 (vs), 1087 (s), 978 (m), 877 (m), 847 (m), 808 (m), 770 (m), 707 (m), 667 (m) $cm^{-1}$. HRMS (ESI): calcd. for $C_{14}H_{17}NNaO_4$ [M + $Na^+$] 286.1055; found 286.1056.

**Methyl 3-[2-(*tert*-Butoxycarbonyl)ethyl]picolinate (13a):** A suspension of Pd/C (4 mg, 10% on charcoal), pyridine **16** (100 mg, 380 μmol) and *i*PrOH (1 mL) was degassed (three times freeze, pump, thaw) and then stirred under an atmosphere of hydrogen (1 bar) at 23 °C for 22 h. The mixture was then filtered and the solvent was evaporated to give **13a** (92 mg, 0.35 mmol, 92%) as a colorless oil. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.39 (s, 9 H), 2.59 (t, $J$ = 7.5 Hz, 2 H), 3.20 (t, $J$ = 7.5 Hz, 2 H), 3.98 (s, 3 H), 7.36 (dd, $J$ = 4.6, 7.9 Hz, 1 H), 7.70 (dd, $J$ = 0.9, 7.9 Hz, 1 H), 8.57 (dd, $J$ = 1.3, 4.6 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 28.31 (3 $CH_3$), 28.58 ($CH_2$), 36.42 ($CH_2$), 52.95 ($CH_3$), 80.83 (C), 126.29 (CH), 138.58 (C), 139.95 (CH), 147.22 (C), 147.53 (CH), 166.40 (C), 172.05 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2977 (w), 2952 (w), 2932 (w), 1722 (vs), 1452 (m), 1429 (m), 1367 (m), 1301 (m), 1255 (m), 1233 (m), 1199 (m), 1147 (s), 1135 (s), 1091 (s), 845 (m), 804 (m), 753 (m), 717 (m), 660 (m) $cm^{-1}$. HRMS (ESI): calcd. for $C_{14}H_{19}NNaO_4$ [M + $Na^+$] 288.1212; found 288.1211.

***tert*-Butyl 7-Oxo-5,6-dihydrocyclopenta[*b*]pyridine-6-carboxylate (10):** NaH (60% in mineral oil, 45 mg, 1.13 mmol) was added under an inert atmosphere ($N_2$) to a cooled (ice-water bath) solution of diester **13a** (120 mg, 0.45 mmol) in anhydrous THF (1.4 mL) and the mixture was stirred at 50 °C for 1 h. Water (10 mL) was added and the solution was acidified with hydrochloric acid (1 M, 5 mL) to pH 1. The aqueous layer was extracted with $CH_2Cl_2$ (3× 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and the solvents were evaporated. β-Oxo ester **10** (52 mg, 0.22 mmol, 50%) was isolated after column chromatography ($SiO_2$; $CH_2Cl_2$/MeOH = 20:1; $R_f$ = 0.38) as a colorless solid; m.p. 100–101 °C. A doubled signal set is observed due to keto-enol tautomers (ratio 1:5). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ (ketone form) = 1.47 (s, 9 H), 3.31 (dd, $J$ = 8.8, 18.2 Hz, 1 H), 3.49–3.53 (m, 1 H), 3.66 (dd, $J$ = 3.7, 8.2 Hz, 1 H), 7.44 (dd, $J$ = 4.5, 7.7 Hz, 1 H), 7.88 (d, $J$ = 7.7 Hz, 1 H), 8.77 (d, $J$ = 3.9 Hz, 1 H) ppm; $\delta$ (enol form) = 1.57 (s, 9 H), 3.43 (s, 2 H), 7.26 (dd, $J$ = 5.0, 7.4 Hz, 1 H), 7.73 (d, $J$ = 7.6 Hz, 1 H), 8.61 (d, $J$ = 4.6 Hz, 1 H), 10.16 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ (ketone form) = 28.23 (3 $CH_3$), 29.92 ($CH_2$), 53.24 (CH), 82.83 (C), 127.94 (CH), 135.33 (CH), 151.48 (CH), 152.78 (C), 155.46 (C), 167.00 (C), 205.23 (C) ppm; $\delta$ (enol form) = 28.66 (3 $CH_3$), 30.67 ($CH_2$), 81.93 (C), 108.16 (C), 123.11 (CH), 132.28 (CH), 137.06 (C), 149.13 (CH), 152.78 (C), 155.46 (C), 168.64 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3284 (w, br), 3010 (w), 2977 (w), 2932 (w), 2918 (w), 2900 (w), 1653 (m), 1610 (m), 1567 (m), 1393 (m), 1361 (m), 1279 (m), 1236 (m), 1206 (m), 1181 (m), 1157 (s), 1130 (s), 1121 (s), 1098 (s), 781 (m), 759 (m), 714 (m) $cm^{-1}$. HRMS (ESI): calcd. for $C_{13}H_{15}NNaO_3$ [M + $Na^+$] 256.0950; found 256.0957.

***tert*-Butyl 7-Oxo-6-(2-oxo-2-phenylethyl)-5,6-dihydrocyclopenta[*b*]-pyridine-6-carboxylate (9):** Phenacylbromide (**11**; 58 mg, 0.29 mmol) and $K_2CO_3$ (40 mg, 0.29 mmol) were added to a solution of β-oxo ester **10** (50 mg, 0.24 mmol) in acetone (0.5 mL) and the mixture was stirred at 40 °C for 2 h. Water (10 mL) and brine (5 mL) were added and the aqueous layer was extracted with MTBE (3× 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. Diketone **9** (27 mg, 77 μmol, 31%) was isolated after column chromatography ($SiO_2$; hexane/EtOAc = 1:1; $R_f$ = 0.37) as a brownish resin. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.30 (s, 9 H), 3.10 (d, $J$ = 17.5 Hz, 1 H), 3.49 (d, $J$ = 18.5 Hz, 1 H), 3.91 (d, $J$ = 17.4 Hz, 1 H), 4.15 (d, $J$ = 18.5 Hz, 1 H), 7.42–7.47 (m, 3 H), 7.55 (t, $J$ = 7.3 Hz, 1 H), 7.87 (d, $J$ = 7.8 Hz, 1 H), 7.93 (d, $J$ = 8.0 Hz, 2 H), 8.78 (d, $J$ = 4.5 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 27.82 (3 $CH_3$), 36.34 ($CH_2$), 43.86 ($CH_2$), 58.01 (C), 82.90 (C), 127.87 (CH), 128.30 (2 CH), 128.91 (2 CH), 133.75 (CH), 134.92 (CH), 136.46 (C), 148.68 (C), 151.14 (CH), 152.91 (C), 168.34 (C), 197.08 (C), 201.01 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3062 (w), 2977 (w), 2930 (w), 2880 (w), 1742 (m), 1716 (s), 1684 (m), 1449 (w), 1369 (m), 1354 (w), 1289 (w), 1271 (m), 1256 (m), 1224 (m), 1149 (vs), 1050 (m), 1001 (m), 910 (m), 845 (w), 755 (w), 729 (s), 690 (m), 646 (m), 631 (m) $cm^{-1}$. HRMS (ESI): calcd. for $C_{21}H_{21}NNaO_4$ [M + $Na^+$] 374.1368; found 374.1357.

***tert*-Butyl (*Z*)-9-Methyl-10-oxo-8-phenyl-5,6,9,10-tetrahydropyrido-[2,3-*c*]azocine-6-carboxylate (5):** A solution of $MeNH_2$ (2 M in THF, 0.34 mmol, 0.17 mL) was added to a solution of 1,4-diketone **9** (60 mg, 0.17 mmol) in THF (0.7 mL) and the mixture was stirred

for 16 h at 100 °C in a closed reaction vial. Subsequently, the solvent was evaporated and lactam **5** (40 mg, 0.11 mmol, 64%) was isolated after column chromatography ($SiO_2$; hexane/EtOAc = 1:3; $R_f$ = 0.47) as a yellowish oil. A doubled signal set is observed in the NMR spectra (ratio 4:1). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (major conformer) = 1.52 (s, 9 H), 2.93 (dd, $J$ = 10.5, 16.0 Hz, 1 H), 3.10 (s, 3 H), 3.62 (dd, $J$ = 8.1, 16.0 Hz, 1 H), 3.86 (dd, $J$ = 8.6, 18.9 Hz, 1 H), 5.82 (d, $J$ = 8.8 Hz, 1 H), 7.13 (dd, $J$ = 4.8, 7.8 Hz, 1 H), 7.27–7.31 (m, 4 H), 7.35 (d, $J$ = 7.8 Hz, 1 H), 7.37–7.39 (m, 1 H), 8.43 (d, $J$ = 4.6 Hz, 1 H) ppm; $\delta$ (minor conformer) = 1.51 (s, 9 H), 3.00–3.04 (m, 1 H), 3.02 (s, 3 H), 3.37–3.43 (m, 1 H), 3.48–3.53 (m, 1 H), 5.59 (d, $J$ = 8.6 Hz, 1 H), 7.19 (dd, $J$ = 4.8, 7.7 Hz, 1 H), 7.37–7.39 (m, 5 H), 7.42 (d, $J$ = 7.9 Hz, 1 H), 8.49 (d, $J$ = 4.8 Hz, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ (major conformer) = 28.10 (3 $CH_3$), 33.09 ($CH_3$), 35.29 ($CH_2$), 45.52 (CH), 82.18 (C), 123.02 (CH), 124.00 (CH), 126.82 (2 CH), 128.98 (2 CH), 129.30 (CH), 130.58 (C), 134.82 (C), 137.57 (CH), 144.01 (C), 147.88 (CH), 154.07 (C), 170.33 (C), 172.32 (C) ppm; $\delta$ (minor conformer) = 28.10 (3 $CH_3$), 32.83 ($CH_2$), 33.46 ($CH_3$), 46.57 (CH), 82.06 (C), 121.52 (CH), 124.59 (CH), 126.52 (2 CH), 128.80 (2 CH), 128.94 (CH), 132.06 (C), 137.21 (C), 135.60 (CH), 144.54 (C), 148.73 (CH), 154.98 (C), 168.89 (C), 170.60 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3057 (w), 2978 (w), 2931 (w), 2874 (w), 1727 (s), 1663 (s), 1449 (m), 1371 (s), 1325 (m), 1315 (m), 1291 (m), 1258 (m), 1208 (m), 1151 (vs), 1108 (m), 1051 (m), 1033 (m), 848 (m), 774 (m), 735 (m), 700 (m) cm$^{-1}$. HRMS (ESI): calcd. for $C_{22}H_{24}N_2NaO_3$ [M + Na$^+$] 387.1685; found 387.1672.

**(*Z*)-9-Methyl-10-oxo-8-phenyl-5,6,9,10-tetrahydropyrido[2,3-*c*]-azocine-6-carboxylic Acid (17):** TFA (812 mg, 7.12 mmol) was added to a solution of ester **5** (65 mg, 0.18 mmol) in $CH_2Cl_2$ (0.9 mL) and the mixture was stirred at 23 °C for 19 h. All volatile materials were removed in vacuo and the residue was dissolved in water (10 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated to give carboxylic acid **17** (40 mg, 0.13 mmol, 73%) after column chromatography ($SiO_2$; $CH_2Cl_2$/MeOH = 10:1; $R_f$ = 0.16) as a colorless solid; m.p. 222–224 °C. A doubled signal set is observed in the NMR spectra (ratio 3:1). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (major conformer) = 3.08 (dd, $J$ = 5.7, 16.1 Hz, 1 H), 3.13 (s, 3 H), 3.72 (dd, $J$ = 8.1, 16.0 Hz, 1 H), 4.05 (dd, $J$ = 8.6, 18.7 Hz, 1 H), 5.89 (d, $J$ = 8.7 Hz, 1 H), 7.19 (dd, $J$ = 4.8, 7.8 Hz, 1 H), 7.29–7.32 (m, 4 H), 7.40–7.42 (m, 2 H), 8.48 (d, $J$ = 4.5 Hz, 1 H) ppm; $\delta$ (minor conformer) = 3.05 (s, 3 H), 3.58–3.64 (m, 3 H), 5.68 (d, $J$ = 8.3 Hz, 1 H), 7.19 (dd, $J$ = 4.8, 7.8 Hz, 1 H), 7.25–7.27 (m, 1 H), 7.35–7.37 (m, 1 H), 7.40–7.42 (m, 3 H), 7.48 (d, $J$ = 7.2 Hz, 1 H), 8.55 (d, $J$ = 4.8 Hz, 1 H) ppm; no $CO_2H$ signal was observed. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ (major conformer) = 33.51 ($CH_3$), 35.09 ($CH_2$), 41.81 (CH), 122.57 (CH), 124.43 (CH), 126.80 (2 CH), 129.05 (2 CH), 129.50 (CH), 130.90 (C), 134.55 (C), 138.30 (CH), 144.23 (C), 147.45 (CH), 153.41 (C), 169.77 (C), 176.26 (C) ppm; $\delta$ (minor conformer) = 33.19 ($CH_2$), 33.69 ($CH_3$), 45.36 (CH), 120.96 (CH), 125.01 (CH), 126.55 (2 CH), 129.05 (2 CH), 129.40 (CH), 132.13 (C), 136.43 (CH), 136.63 (C), 145.02 (C), 148.26 (CH), 154.30 (C), 168.34 (C), 175.00 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2924 (w), 2899 (w), 2853 (w), 1709 (s), 1656 (vs), 1579 (m), 1434 (m), 1414 (m), 1379 (s), 1338 (m), 1303 (m), 1241 (m), 1186 (s), 1130 (m), 1108 (m), 1080 (m), 1051 (m), 925 (m), 881 (m), 801 (m), 771 (s), 743 (m), 700 (s), 682 (m), 660 (m), 635 (m) cm$^{-1}$. HRMS (ESI): calcd. for $C_{18}H_{16}N_2NaO_3$ [M + Na$^+$] 331.1059; found 331.1066.

**Ethyl 4-Methylnicotinate (18):** A solution of nitrile **19** (5.00 g, 42.3 mmol) in 75% aqueous $H_2SO_4$ (85 mL) was stirred at 130 °C for 17 h. EtOH (210 mL) was added and stirring was continued for 4 h under reflux. The pH was adjusted to pH 8 with aqueous NaOH (10 M, 240 mL) and the aqueous layer was extracted with MTBE (3 × 75 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated to give ester **18** (5.77 g, 34.9 mmol, 83%) as a colorless liquid, which did not require further purification. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.38 (t, $J$ = 7.1 Hz, 3 H), 2.59 (s, 3 H), 4.36 (q, $J$ = 7.1 Hz, 2 H), 7.14 (d, $J$ = 4.9 Hz, 1 H), 8.52 (d, $J$ = 4.8 Hz, 1 H), 9.04 (s, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ = 14.47 ($CH_3$), 21.38 ($CH_3$), 61.34 ($CH_2$), 126.24 (C), 126.56 (CH), 149.51 (C), 151.78 (CH), 152.28 (CH), 166.36 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2982 (w), 2933 (w), 2907 (w), 1718 (s), 1592 (m), 1443 (m), 1366 (m), 1307 (m), 1274 (s), 1222 (m), 1171 (m), 1104 (s), 1063 (m), 1018 (m), 857 (m), 839 (m), 773 (m) cm$^{-1}$. HRMS (ESI): calcd. for $C_9H_{11}NNaO_2$ [M + Na$^+$] 188.0687; found 188.0688.

**3-(Ethoxycarbonyl)-4-methylpyridine 1-Oxide (20):** *m*CPBA (70%, 5.61 g, 22.8 mmol) was added while stirring to a cooled (ice-water bath) solution of ester **18** (1.89 g, 11.4 mmol) in $CHCl_3$ (12 mL) and the mixture was stirred at 23 °C for 19 h. $CHCl_3$ (40 mL) and $K_2CO_3$ (6.30 g, 45.6 mmol) were added and stirring was continued for 10 min. The mixture was filtered and the filtrate was dried ($MgSO_4$), filtered, and the solvent was removed in vacuo to give *N*-oxide **20** (1.53 g, 8.44 mmol, 74%) as a colorless solid (mp 67–69 °C), which did not require further purification. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.37 (t, $J$ = 7.2 Hz, 3 H), 2.58 (s, 3 H), 4.36 (q, $J$ = 7.2 Hz, 2 H), 7.16 (d, $J$ = 6.6 Hz, 1 H), 8.20 (dd, $J$ = 1.8, 6.6 Hz, 1 H), 8.73 (d, $J$ = 1.7 Hz, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ = 14.31 ($CH_3$), 20.65 ($CH_3$), 62.27 ($CH_2$), 128.82 (C), 129.11 (CH), 140.53 (CH), 140.82 (CH), 141.11 (C), 163.52 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3075 (w), 3031 (w), 2984 (w), 1704 (s), 1480 (m), 1453 (m), 1363 (m), 1301 (s), 1278 (m), 1253 (m), 1217 (m), 1200 (m), 1094 (s), 1020 (m), 1008 (m), 890 (m), 866 (m), 782 (m), 768 (m), 551 (m) cm$^{-1}$. MS (70 eV, EI): *m*/*z* (%) = 181 (100) [M$^+$], 152 (44), 135 (47), 107 (31). HRMS (70 eV, EI): calcd. for $C_9H_{11}NO_3$ [M$^+$] 181.0733; found 181.0727; $C_9H_{11}NO_3$ (181.19): calcd. C 59.66, H 6.12, N 7.73; found C 59.65; H 6.12; N 7.81.

**Ethyl 4-(Chloromethyl)nicotinate (21):** *p*TosCl (1.05 g, 5.52 mmol) was added to a solution of *N*-oxide **20** (500 mg, 2.76 mmol) in dioxane (4.5 mL), the mixture was stirred for 1.5 h under reflux and then acidified with hydrochloric acid (1 M, 15 mL) to pH 1. The aqueous layer was washed with MTBE (2 × 20 mL) and the organic extracts were discarded. Sat. aqueous $NaHCO_3$ solution (20 mL) was added to the aqueous layer to adjust to pH 8. The aqueous phase was then extracted with MTBE (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. After column chromatography ($SiO_2$; hexane/MTBE = 1:1; $R_f$ = 0.33) compound **21** (261 mg, 1.31 mmol, 47%) was obtained as a yellowish oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.43 (t, $J$ = 7.1 Hz, 3 H), 4.43 (q, $J$ = 7.1 Hz, 2 H), 5.05 (s, 2 H), 7.61 (d, $J$ = 5.1 Hz, 1 H), 8.76 (d, $J$ = 5.1 Hz, 1 H), 9.16 (s, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ = 14.33 ($CH_3$), 43.20 ($CH_2$), 61.90 ($CH_2$), 124.12 (C), 124.58 (CH), 147.68 (C), 151.82 (CH), 153.29 (CH), 165.38 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3053 (w), 2984 (w), 2940 (w), 2911 (w), 2875 (w), 1717 (vs), 1592 (m), 1564 (w), 1447 (w), 1408 (w), 1394 (w), 1369 (m), 1312 (m), 1280 (s), 1233 (m), 1221 (m), 1207 (m), 1175 (m), 1146 (w), 1108 (s), 1057 (m), 1018 (m), 860 (w), 846 (w), 772 (m), 737 (m), 693 (m) cm$^{-1}$. HRMS (ESI): calcd. for $C_9H_{10}ClNNaO_2$ [M + Na$^+$] 222.0298; found 222.0305. $C_9H_{10}ClNO_2$ (199.63): calcd. C 54.15, H 7.02, N 5.05; found C 54.10, H 7.03, N 5.03.

**Diethyl 2-{[3-(Ethoxycarbonyl)-4-pyridyl]methyl}malonate (23):** Diethyl malonate (241 mg, 1.50 mmol) was added to a cooled (ice-

water bath) solution of Na (35 mg, 1.5 mmol) in EtOH/THF (1:1; 2 mL). Subsequently, a solution of **21** (100 mg, 501 μmol) in THF (1 mL) was added and the resulting mixture was stirred while cooling for 1 h and then at 23 °C for 1 h. All volatile materials were removed in vacuo and the residue was diluted with water (10 mL) and extracted with MTBE (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated to give malonate **23** (88 mg, 0.28 mmol, 54%) after column chromatography ($SiO_2$; hexane/MTBE = 1:1; $R_f$ = 0.29) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.22 (t, $J$ = 7.1 Hz, 6 H), 1.42 (t, $J$ = 7.1 Hz, 3 H), 3.57 (d, $J$ = 7.7 Hz, 2 H), 3.87 (t, $J$ = 7.7 Hz, 1 H), 4.16 (dq, $J$ = 10.8, 7.1 Hz, 2 H), 4.17 (dq, $J$ = 10.8, 7.1 Hz, 2 H), 4.42 (q, $J$ = 7.1 Hz, 2 H), 7.27 (s, 1 H), 8.60 (d, $J$ = 5.1 Hz, 1 H), 9.15 (s, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ = 14.12 (2 $CH_3$), 14.30 ($CH_3$), 33.08 ($CH_2$), 52.26 (CH), 61.84 (2 $CH_2$), 61.90 ($CH_2$), 126.22 (CH), 127.01 (C), 150.26 (CH), 151.22 (CH), 151.24 (C), 165.32 (C), 168.55 (2 C) ppm. IR (ATR): $\tilde{\nu}$ = 2983 (w), 2940 (w), 2907 (w), 1718 (vs), 1591 (w), 1558 (w), 1466 (w), 1446 (w), 1406 (w), 1392 (w), 1368 (m), 1328 (w), 1303 (m), 1275 (s), 1247 (m), 1216 (m), 1175 (m), 1147 (m), 1107 (s), 1052 (m), 1030 (m), 858 (m), 787 (m), 728 (w), 701 (w), 602 (w), 580 (w), 549 (m) cm$^{-1}$. HRMS (ESI): calcd. for $C_{16}H_{21}NNaO_6$ [M + Na$^+$] 346.1267; found 346.1262.

**Ethyl 7-Oxo-5,6-dihydrocyclopenta[*c*]pyridine-6-carboxylate (22):** A solution of malonate **23** (250 mg, 773 μmol) in abs. EtOH (1.5 mL) was added under an inert atmosphere ($N_2$) to a solution of Na (71 mg, 3.1 mmol) in abs. EtOH (1.5 mL) and the mixture was stirred at 65 °C for 2 h. Water (10 mL) was added and the solution was acidified with hydrochloric acid (1 M, 5 mL) to pH 3. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. β-Oxo ester **22** (80 mg, 0.39 mmol, 50%) was obtained after column chromatography ($SiO_2$; $CH_2Cl_2$/MeOH = 20:1; $R_f$ = 0.41) as a colorless solid; m.p. 92–93 °C. A doubled signal set is observed due to keto-enol tautomers (ratio 4:3). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ketone form) = 1.29 (t, $J$ = 7.1 Hz, 3 H), 3.37 (dd, $J$ = 18.1, 8.4 Hz, 1 H), 3.58 (dd, $J$ = 18.1, 4.0 Hz, 1 H), 3.72 (dd, $J$ = 8.4, 4.1 Hz, 1 H), 4.21–4.25 (m, 2 H), 7.47 (d, $J$ = 5.1 Hz, 1 H), 8.73 (d, $J$ = 5.2 Hz, 1 H), 8.99 (s, 1 H) ppm; $\delta$ (enol form) = 1.34 (t, $J$ = 7.1 Hz, 3 H), 3.55 (s, 2 H), 4.31 (q, $J$ = 7.1 Hz, 2 H), 7.42 (d, $J$ = 5.0 Hz, 1 H), 8.61 (d, $J$ = 4.9 Hz, 1 H), 8.88 (s, 1 H), 10.32 (br. s, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ (ketone form) = 14.25 ($CH_3$), 30.33 ($CH_2$), 53.03 (CH), 62.18 ($CH_2$), 121.99 (CH), 131.25 (C), 147.40 (CH), 154.33 (CH), 161.57 (C), 168.36 (C), 198.23 (C) ppm; $\delta$ (enol form) = 14.50 ($CH_3$), 33.00 ($CH_2$), 60.56 ($CH_2$), 103.26 (C), 120.24 (C), 133.64 (C), 142.56 (CH), 149.42 (CH), 151.45 (C), 167.59 (C), 168.87 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2979 (m), 2913 (w), 1689 (vs), 1615 (s), 1584 (s), 1564 (s), 1476 (w), 1458 (w), 1443 (m), 1414 (m), 1405 (m), 1384 (w), 1367 (w), 1320 (m), 1296 (m), 1253 (m), 1205 (s), 1175 (s), 1155 (s), 1119 (s), 1099 (s), 1027 (s), 925 (s), 863 (m), 839 (m), 826 (m), 766 (s), 729 (m), 669 (w), 646 (m), 580 (m) cm$^{-1}$. HRMS (ESI): calcd. for $C_{11}H_{11}NNaO_3$ [M + Na$^+$] 228.0637; found 228.0643.

**Ethyl 7-Oxo-6-(2-oxo-2-phenylethyl)-5,6-dihydrocyclopenta[*c*]pyridine-6-carboxylate (24):** Phenacylbromide (**11**; 84 mg, 0.42 mmol) and $K_2CO_3$ (58 mg, 0.42 mmol) were added to a solution of β-oxo ester **22** (72 mg, 0.35 mmol) in acetone (0.7 mL) and the mixture was stirred at 40 °C for 3 h. Water (10 mL) and brine (5 mL) were added and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. Diketone **24** (67 mg, 0.21 mmol, 59%) was isolated after column chromatography ($SiO_2$; hexane/MTBE = 1:2; $R_f$ = 0.21) as a brownish solid; m.p. 130–132 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.15 (t, $J$ = 7.1 Hz, 3 H), 3.17 (d, $J$ = 18.2 Hz, 1 H), 3.58 (d, $J$ = 18.5 Hz, 1 H), 4.00 (d, $J$ = 18.2 Hz, 1 H), 4.14 (q, $J$ = 7.11 Hz, 2 H), 4.16 (d, $J$ = 18.5 Hz, 1 H), 7.45–7.48 (m, 2 H), 7.50 (d, $J$ = 5.2 Hz, 1 H), 7.57–7.60 (m, 1 H), 7.94–7.96 (m, 2 H), 8.77 (d, $J$ = 5.2 Hz, 1 H), 9.06 (s, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ = 14.02 ($CH_3$), 38.19 ($CH_2$), 43.74 ($CH_2$), 58.24 (C), 62.41 ($CH_2$), 121.89 (CH), 128.26 (2 CH), 128.89 (2 CH), 131.35 (C), 133.91 (CH), 136.03 (C), 147.27 (CH), 154.14 (CH), 161.72 (C), 169.40 (C), 196.81 (C), 200.63 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2963 (w), 2909 (w), 1737 (vs), 1702 (s), 1682 (vs), 1620 (w), 1597 (vs), 1478 (w), 1449 (m), 1416 (m), 1397 (m), 1353 (m), 1326 (w), 1292 (s), 1224 (s), 1207 (s), 1180 (vs), 1157 (s), 1096 (m), 1066 (m), 1044 (m), 1033 (m), 1020 (m), 999 (m), 943 (w), 909 (s), 859 (m), 850 (m), 749 (s), 689 (s), 600 (m), 561 (m), 536 (m) cm$^{-1}$. HRMS (ESI): calcd. for $C_{19}H_{17}NNaO_4$ [M + Na$^+$] 346.1055; found 346.1054.

**Ethyl 9-Methyl-10-oxo-8-phenyl-5,6,9,10-tetrahydropyrido[3,4-*c*]-azocine-6-carboxylate (6):** A solution of $MeNH_2$ (2 M in THF, 0.45 mmol, 0.25 mL) was added to a solution of 1,4-diketone **24** (73 mg, 0.23 mmol) in THF (0.25 mL) and the mixture was stirred for 17 h at 100 °C in a closed reaction vial. The solvent was evaporated and lactam **6** (27 mg, 81 μmol, 36%) was isolated after column chromatography ($SiO_2$; hexane/EtOAc = 1:2; $R_f$ = 0.36) as a yellowish resin. A doubled signal set is observed in the NMR spectra (ratio 5:1). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (major conformer) = 1.34 (t, $J$ = 7.2 Hz, 3 H), 3.05 (dd, $J$ = 11.3, 16.6 Hz, 1 H), 3.12 (s, 3 H), 3.64 (dd, $J$ = 7.5, 16.4 Hz, 1 H), 3.95 (ddd, $J$ = 7.5, 9.2, 11.3 Hz, 1 H), 4.24–4.31 (m, 2 H), 5.94 (d, $J$ = 9.2 Hz, 1 H), 6.98 (d, $J$ = 5.2 Hz, 1 H), 7.28–7.35 (m, 5 H), 8.41 (d, $J$ = 5.1 Hz, 1 H), 8.64 (s, 1 H) ppm; $\delta$ (minor conformer) = 1.33 (t, $J$ = 7.9 Hz, 3 H), 3.03 (s, 3 H), 3.05 (dd, $J$ = 16.6, 11.3 Hz, 1 H), 3.52–3.59 (m, 1 H), 3.64 (dd, $J$ = 16.4, 7.5 Hz, 1 H), 4.23–4.32 (m, 2 H), 5.70 (d, $J$ = 8.3 Hz, 1 H), 7.08 (d, $J$ = 5.0 Hz, 1 H), 7.22–7.24 (m, 2 H), 7.28–7.35 (m, 3 H), 8.52 (d, $J$ = 5.0 Hz, 1 H), 8.74 (s, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ (major conformer) = 14.35 ($CH_3$), 33.77 ($CH_3$), 36.56 ($CH_2$), 41.32 (CH), 61.83 ($CH_2$), 122.31 (CH), 124.17 (CH), 126.20 (2 CH), 129.09 (2 CH), 129.52 (CH), 132.86 (C), 134.08 (C), 143.78 (C), 143.98 (C), 148.74 (CH), 149.83 (CH), 169.87 (C), 172.62 (C) ppm; $\delta$ (minor conformer) = 14.38 ($CH_3$), 33.95 ($CH_3$), 34.08 ($CH_2$), 44.89 (CH), 61.88 ($CH_2$), 120.82 (CH), 122.78 (2 CH), 125.92 (2 CH), 129.34 (2 CH), 133.33 (C), 136.51 (C), 144.93 (C), 145.41 (C), 147.51 (CH), 150.92 (CH), 168.91 (C), 171.29 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3057 (w), 2934 (w), 1730 (s), 1641 (vs), 1590 (m), 1559 (w), 1465 (w), 1446 (m), 1428 (m), 1405 (m), 1372 (s), 1327 (m), 1255 (m), 1190 (s), 1117 (m), 1079 (m), 1028 (s), 950 (w), 919 (w), 892 (w), 856 (m), 769 (s), 731 (m), 697 (m), 648 (w), 635 (w), 585 (m), 552 (w) cm$^{-1}$. HRMS (ESI): calcd. for $C_{20}H_{20}N_2NaO_3$ [M + Na$^+$] 359.1372; found 359.1373.

**Methyl 3-Chloroisonicotinate (25):** $SOCl_2$ (4.53 g, 38.1 mmol) was added to a cooled (ice-water bath) solution of acid **26** (1.50 g, 9.52 mmol) in MeOH (50 mL) and the mixture was stirred for 24 h at 80 °C. All volatile materials were removed in vacuo and the residue was diluted with satd. aqueous $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated to obtain ester **25** (1.28 g, 7.48 mmol, 79%) as a colorless liquid. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 3.95 (s, 3 H), 7.63 (d, $J$ = 4.9 Hz, 1 H), 8.57 (d, $J$ = 4.9 Hz, 1 H), 8.70 (s, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ = 53.17 ($CH_3$), 124.27 (CH), 130.37 (C), 137.05 (C), 148.22 (CH), 151.60 (CH), 164.70 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3047 (w), 3027 (w), 3014 (w), 2957 (w), 1739 (s), 1437 (m), 1398 (m), 1305 (m), 1272 (vs), 1219 (m), 1196 (m), 1180 (m), 1132 (m), 1090 (m), 1040 (m), 961 (m), 851

(m), 834 (m), 782 (m), 742 (m), 704 (m), 665 (m) $cm^{-1}$. HRMS (ESI): calcd. for $C_7H_7ClNO_2$ [M + $H^+$] 172.0165; found 172.0161.

**Methyl (*E*)-3-[(2-*tert*-Butoxycarbonyl)ethenyl]isonicotinate (27):** *tert*-Butyl acrylate (1.49 g, 11.7 mmol), $Pd(OAc)_2$ (13 mg, 58 μmol), $PPh_3$ (31 mg, 0.12 mmol) and $NEt_3$ (295 mg, 2.92 mmol) were added under an inert atmosphere ($N_2$) to a solution of pyridine **25** (100 mg, 0.583 mmol) in anhydrous DMA (1.5 mL) and the mixture was stirred at 120 °C for 18 h. Water (10 mL) was added and the aqueous layer was extracted with MTBE (3× 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvents were evaporated to give **27** (31 mg, 0.12 mmol, 20%) after column chromatography ($SiO_2$; hexane/MTBE = 1:1; $R_f$ = 0.39) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.53 (s, 9 H), 3.95 (s, 3 H), 6.32 (d, *J* = 16.0 Hz, 1 H), 7.72 (d, *J* = 5.0 Hz, 1 H), 8.19 (d, *J* = 16.0 Hz, 1 H), 8.68 (d, *J* = 4.6 Hz, 1 H), 8.86 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 28.40 (3 $CH_3$), 53.11 ($CH_3$), 81.28 (C), 123.45 (CH), 124.94 (CH), 130.76 (C), 136.48 (C), 139.10 (CH), 149.61 (CH), 150.80 (CH), 165.44 (C), 166.03 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2977 (w), 2933 (w), 2872 (w), 1722 (s), 1480 (w), 1454 (w), 1439 (w), 1367 (m), 1319 (w), 1274 (m), 1257 (m), 1222 (w), 1145 (s), 1101 (m), 980 (w), 845 (m), 702 (w), 671 (m), 628 (m) $cm^{-1}$. HRMS (ESI): calcd. for $C_{14}H_{17}NNaO_4$ [M + $Na^+$] 286.1055; found 286.1057.

**Methyl 3-[(2-*tert*-Butoxycarbonyl)ethyl]isonicotinate (28):** A suspension of Pd/C (6 mg, 10% on charcoal), pyridine **27** (30 mg, 0.11 mmol) and *i*PrOH (0.5 mL) was degassed (three times freeze, pump, thaw) and then stirred under an atmosphere of hydrogen (1 bar) at 23 °C for 3 d. Subsequently, the mixture was filtered and the solvent was evaporated to give **28** (21 mg, 79 μmol, 69%) after column chromatography ($SiO_2$; hexane/MTBE = 1:1; $R_f$ = 0.36) as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.39 (s, 9 H), 2.55 (t, *J* = 7.6 Hz, 2 H), 3.20 (t, *J* = 7.6 Hz, 2 H), 3.92 (s, 3 H), 7.65 (d, *J* = 5.0 Hz, 1 H), 8.56 (d, *J* = 5.0 Hz, 1 H), 8.60 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 27.18 ($CH_2$), 28.29 (3 $CH_3$), 36.69 ($CH_2$), 52.73 ($CH_3$), 80.84 (C), 123.58 (CH), 136.20 (C), 136.70 (C), 148.64 (CH), 153.02 (CH), 166.56 (C), 171.90 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2977 (w), 2955 (w), 2930 (w), 2850 (w), 1727 (vs), 1453 (w), 1436 (w), 1408 (w), 1367 (w), 1275 (m), 1231 (w), 1209 (w), 1150 (m), 1103 (w), 673 (m), 631 (s) $cm^{-1}$. HRMS (ESI): calcd. for $C_{14}H_{19}NNaO_4$ [M + $Na^+$] 288.1212; found 288.1209.

***tert*-Butyl 5-Oxo-6,7-dihydrocyclopenta[*c*]pyridine-6-carboxylate (30):** KO*t*Bu (37 mg, 0.33 mmol) was added under an inert atmosphere ($N_2$) at 0 °C to a solution of diester **28** (35 mg, 0.13 mmol) in anhydrous THF (0.4 mL) and the mixture was stirred for 30 min at this temperature. Water (10 mL) was added and the solution was acidified with hydrochloric acid (1 M, 4 mL) to pH 1 and then extracted with $CH_2Cl_2$ (3× 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated to give β-oxo ester **30** (12 mg, 51 μmol, 39%) as a colorless oil. A doubled signal set is observed due to keto-enol tautomerism (ratio 1:6). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ketone form) = 1.46 (s, 9 H), 3.39 (dd, *J* = 8.4, 17.2 Hz, 1 H), 3.55 (dd, *J* = 3.8, 17.6 Hz, 1 H), 3.72–3.80 (m, 1 H), 7.56 (d, *J* = 4.9 Hz, 1 H), 8.69 (d, *J* = 5.1 Hz, 1 H), 8.94 (s, 1 H) ppm; $\delta$ (enol form) = 1.56 (s, 9 H), 3.63 (s, 2 H), 7.68 (d, *J* = 5.3 Hz, 1 H), 8.65 (d, *J* = 5.3 Hz, 1 H), 8.77 (s, 1 H), 9.03 (br. s, 1 H) ppm.

**Ethyl 2-Methylnicotinate (31):** A solution of ethyl acetoacetate **32** (10.0 g, 76.8 mmol) and $NH_4OAc$ (6.64 g, 86.2 mmol) in toluene (310 mL) was heated to reflux for 2 h in a Dean–Stark trap. Subsequently, freshly distilled acroleine (12.9 g, 230 mmol) was slowly added over 1.5 h under reflux and the mixture was then stirred for 1 h at the same temperature. The solvents were evaporated and the residue was purified by chromatography ($SiO_2$; hexane/MTBE = 1:1; $R_f$ = 0.35) to give ester **31** (4.27 g, 25.8 mmol, 34%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.39 (t, *J* = 7.1 Hz, 3 H), 2.85 (s, 3 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 7.22–7.25 (m, 1 H), 8.22 (d, *J* = 7.4 Hz, 1 H), 8.60 (dd, *J* = 1.5, 4.8 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 14.47 ($CH_3$), 24.64 ($CH_2$), 61.64 ($CH_3$), 121.31 (CH), 126.26 (C), 139.18 (CH), 151.27 (CH), 159.75 (C), 166.52 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2982 (w), 2934 (w), 1720 (s), 1584 (m), 1571 (m), 1439 (m), 1296 (m), 1275 (s), 1243 (s), 1140 (m), 1081 (s), 754 (s) $cm^{-1}$. MS (70 eV, EI): *m*/*z* (%) = 165 (27) [$M^+$], 120 (40), 86 (62), 84 (98), 49 (100). HRMS (70 eV, EI): calcd. for $C_9H_{11}NO_2$ [$M^+$] 165.1790; found 165.0782.

**Ethyl 2-(Chloromethyl)nicotinate (33):**[32] DMF (263 mg, 3.60 mmol) and trichloroisocyanuric acid (12.6 g, 54.0 mmol) were added to a solution of ester **31** (5.95 g, 36.0 mmol) in $CH_2Cl_2$ (36 mL) and the resulting mixture was stirred for 16 h at 23 °C. The mixture was then filtered, the residue was washed with $CH_2Cl_2$ (2× 40 mL) and the combined filtrates were washed with satd. aqueous $NaHCO_3$ solution (2× 50 mL) and brine (50 mL) and dried ($MgSO_4$). After filtration, the solvents were evaporated to give **33** (6.45 g, 32.3 mmol, 90%) as a yellow oil, which did not require further purification. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.41 (t, *J* = 7.2 Hz, 3 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 5.10 (s, 2 H), 7.34 (dd, *J* = 4.8, 7.9 Hz, 1 H), 8.26 (d, *J* = 7.9 Hz, 1 H), 8.70 (d, *J* = 4.8 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 14.34 ($CH_3$), 45.74 ($CH_2$), 62.10 ($CH_2$), 123.40 (CH), 126.02 (C), 139.34 (CH), 152.34 (CH), 157.39 (C), 165.66 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2983 (w), 2940 (w), 1719 (s), 1583 (m), 1572 (m), 1442 (m), 1300 (m), 1262 (s), 1129 (m), 1081 (s), 1058 (m), 740 (m), 692 (m) $cm^{-1}$. MS (70 eV, EI): *m*/*z* (%) = 199 (53) [$M^+$], 171 (23), 164 (46), 154 (56), 136 (100), 126 (24), 84 (48), 49 (47). HRMS (70 eV, EI): calcd. for $C_9H_{10}ClNO_2$ [$M^+$] 199.0400; found 199.0399.

**Ethyl 2-[2,2-Bis(ethoxycarbonyl)ethyl]nicotinate (34):**[33] Diethyl malonate (6.00 g, 37.5 mmol) was added to a cooled (ice-water bath) solution of Na (862 mg, 37.5 mmol) in EtOH/THF (1:1, 26 mL). Subsequently, a solution of compound **33** (2.50 g, 12.5 mmol) in THF (13 mL) was added and the mixture was further stirred with cooling for 2 h and then at 23 °C for 2 h. All volatile materials were removed in vacuo and the residue was diluted with water (60 mL) and extracted with MTBE (3× 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated to give malonate **34** (2.69 g, 8.32 mmol, 67%) after column chromatography ($SiO_2$; hexane/MTBE = 2:1; $R_f$ = 0.28) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.22 (t, *J* = 7.1 Hz, 6 H), 1.38 (t, *J* = 7.1 Hz, 3 H), 3.82 (d, *J* = 7.6 Hz, 2 H), 4.35–4.39 (m, 5 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 7.20 (dd, *J* = 4.1, 8.4 Hz, 1 H), 8.19 (d, *J* = 7.9 Hz, 1 H), 8.56 (d, *J* = 4.8 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 14.26 (2 $CH_3$), 14.44 ($CH_3$), 35.29 (CH), 50.49 ($CH_2$), 61.50 (2 $CH_2$), 61.69 ($CH_2$), 121.50 (CH), 125.90 (C), 138.74 (CH), 151.45 (CH), 158.93 (C), 166.33 (C), 169.82 (2 C) ppm. IR (ATR): $\tilde{\nu}$ = 2982 (w), 2939 (w), 2907 (w), 1746 (m), 1721 (s), 1571 (m), 1442 (m), 1368 (m), 1277 (m), 1253 (m), 1174 (m), 1136 (m), 1089 (m), 1055 (m), 1033 (m), 1019 (m), 858 (m), 758 (m) $cm^{-1}$. MS (70 eV, EI): *m*/*z* (%) = 323 (4) [$M^+$], 278 (60), 250 (90), 232 (83), 204 (100), 176 (73), 148 (27). HRMS (70 eV, EI): calcd. for $C_{16}H_{21}NO_6$ [$M^+$] 323.1369; found 323.1370. $C_{16}H_{21}NO_6$ (323.34): calcd. C 59.43, H 6.55, N 4.33; found C 59.35, H 6.51, N 4.47.

**Ethyl 5-Oxo-6,7-dihydrocyclopenta[*b*]pyridine-6-carboxylate (36):** Under an inert atmosphere ($N_2$), a solution of malonate **34** (3.83 g, 11.8 mmol) in anhydrous THF (24 mL) was added to a suspension

of NaH (60% in mineral oil, 708 mg, 17.7 mmol) in anhydrous THF (35 mL), while heating to reflux. The mixture was further stirred at this temperature for 1 h, then acidified with hydrochloric acid (1 M, 18 mL) to pH 5 and the aqueous layer was extracted with $CH_2Cl_2$ (3× 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated to give β-oxo ester **36** (1.78 g, 8.68 mmol, 74%) after column chromatography ($SiO_2$; hexane/MTBE = 1:5; $R_f$ = 0.40) as a yellow solid; m.p. 53–55 °C. A doubled signal set is observed due to keto-enol tautomers (ratio 2:1). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ketone form) = 1.28 (t, $J$ = 7.1 Hz, 3 H), 3.49 (dd, $J$ = 8.5, 18.0 Hz, 1 H), 3.66 (dd, $J$ = 4.6, 17.4 Hz, 1 H), 3.79 (dd, $J$ = 4.1, 8.5 Hz, 1 H), 4.21–4.25 (m, 2 H), 7.34 (dd, $J$ = 4.8, 7.8 Hz, 1 H), 8.02 (dd, $J$ = 1.6, 7.8 Hz, 1 H), 8.82 (dd, $J$ = 1.6, 4.8 Hz, 1 H) ppm; $\delta$ (enol form) = 1.35 (t, $J$ = 7.1 Hz, 3 H), 3.65 (s, 2 H), 4.32 (q, $J$ = 7.1 Hz, 2 H), 7.31 (dd, $J$ = 5.0, 7.7 Hz, 1 H), 7.90 (dd, $J$ = 1.1, 7.7 Hz, 1 H), 8.58 (dd, $J$ = 1.1, 5.0 Hz, 1 H), 10.47 (s, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ (ketone form) = 14.37 ($CH_3$), 33.33 ($CH_2$), 53.24 (CH), 61.97 ($CH_2$), 123.13 (CH), 133.06 (CH), 131.33 (C), 156.66 (CH), 168.72 (C), 173.18 (C), 198.10 (C) ppm; $\delta$ (enol form) = 14.61 ($CH_3$), 35.02 ($CH_2$), 60.54 ($CH_2$), 102.86 (C), 122.19 (CH), 128.89 (CH), 133.42 (C), 149.43 (CH), 163.50 (C), 167.22 (C), 169.43 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3067 (w), 2989 (w), 2976 (w), 2900 (w), 1694 (s), 1650 (s), 1623 (s), 1608 (m), 1575 (s), 1563 (s), 1403 (m), 1342 (m), 1324 (m), 1280 (m), 1244 (m), 1214 (s), 1183 (s), 1161 (m), 1102 (m), 1088 (s), 1039 (m), 1024 (m), 923 (m), 814 (m), 765 (s), 726 (m) cm$^{-1}$. MS (70 eV, EI): *m*/*z* (%) = 205 (100) [M$^+$], 193 (33). HRMS (70 eV, EI): calcd. for $C_{11}H_{11}NO_3$ [M$^+$] 205.0739; found 205.0734. $C_{11}H_{11}NO_3$ (205.21): calcd. C 64.38, H 5.40, N 6.83; found C 64.36, H 5.40, N 6.77.

**Ethyl 5-Oxo-6-(2-oxo-2-phenylethyl)-6,7-dihydrocyclopenta[*b*]pyridine-6-carboxylate (35):** Phenacylbromide (**11**; 1.28 g, 6.43 mmol) and $K_2CO_3$ (889 mg, 6.43 mmol) were added to a solution of β-oxo ester **36** (1.10 g, 5.36 mmol) in acetone (11 mL) and the mixture was heated for 3 h at reflux. Water (15 mL) and brine (15 mL) were added and the aqueous layer was extracted with MTBE (3× 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was evaporated. Diketone **35** (1.23 g, 3.80 mmol, 71%) was isolated after column chromatography ($SiO_2$; hexane/MTBE = 1:2; $R_f$ = 0.23) as a brownish resin. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.12 (t, $J$ = 7.1 Hz, 3 H), 3.25 (d, $J$ = 18.1 Hz, 1 H), 3.70 (d, $J$ = 18.6 Hz, 1 H), 4.00 (d, $J$ = 18.1 Hz, 1 H), 4.10–4.14 (m, 2 H), 4.12 (d, $J$ = 18.5 Hz, 1 H), 7.37 (dd, $J$ = 5.2, 7.2 Hz, 1 H), 7.43 (t, $J$ = 7.7 Hz, 2 H), 7.55 (t, $J$ = 7.4 Hz, 1 H), 7.92 (d, $J$ = 8.0 Hz, 2 H), 8.07 (d, $J$ = 7.7 Hz, 1 H), 8.82–8.83 (m, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ = 14.09 ($CH_3$), 40.83 ($CH_2$), 43.83 ($CH_2$), 58.13 (C), 62.37 ($CH_2$), 123.01 (CH), 128.33 (2 CH), 128.91 (2 CH), 129.11 (C), 133.04 (CH), 133.88 (CH), 136.13 (C), 156.04 (CH), 169.84 (C), 172.93 (C), 196.76 (C), 200.56 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3060 (w), 2977 (w), 2938 (w), 1740 (s), 1713 (vs), 1698 (s), 1596 (m), 1578 (s), 1470 (m), 1449 (m), 1417 (m), 1406 (m), 1354 (m), 1284 (m), 1258 (m), 1237 (m), 1215 (s), 1196 (vs), 1096 (m), 1040 (m), 1001 (m), 914 (m), 753 (m), 690 (m), 625 (m) cm$^{-1}$. HRMS (ESI): calcd. for $C_{19}H_{17}NNaO_4$ [M + Na$^+$] 346.1055; found 346.1066.

**Ethyl (*Z*)-6-Methyl-5-oxo-7-phenyl-5,6,9,10-tetrahydropyrido[3,2-*c*]azocine-9-carboxylate (8):** A solution of $MeNH_2$ (2 M in THF, 1.24 mmol, 0.62 mL) was added to a solution of 1,4-diketone **35** (200 mg, 0.62 mmol) in THF (0.62 mL) and the mixture was stirred for 15 h at 100 °C in a closed reaction vial. The solvent was then evaporated and lactam **8** (101 mg, 300 μmol, 48%) was isolated after column chromatography ($SiO_2$; hexane/EtOAc = 1:2; $R_f$ = 0.25) as a yellowish resin. A doubled signal set is observed in the NMR spectra (ratio 2:1). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (major conformer) = 1.27 (t, $J$ = 7.1 Hz, 3 H), 3.05 (s, 3 H), 3.30 (dd, $J$ = 11.7, 16.7 Hz, 1 H), 3.72 (dd, $J$ = 7.6, 16.6 Hz, 1 H), 3.92 (ddd, $J$ = 7.7, 9.1, 11.7 Hz, 1 H), 4.16–4.25 (m, 2 H), 6.02 (d, $J$ = 9.1 Hz, 1 H), 7.08 (dd, $J$ = 4.9, 7.4 Hz, 1 H), 7.21–7.27 (m, 5 H), 7.65 (dd, $J$ = 1.7, 7.8 Hz, 1 H), 8.39 (dd, $J$ = 1.7, 4.8 Hz, 1 H) ppm; $\delta$ (minor conformer) = 1.26 (t, $J$ = 7.0 Hz, 3 H), 2.97 (s, 3 H), 3.21–3.23 (m, 1 H), 3.65–3.68 (m, 2 H), 4.16–4.25 (m, 2 H), 5.70 (d, $J$ = 7.7 Hz, 1 H), 7.11 (dd, $J$ = 4.9, 7.7 Hz, 1 H), 7.14–7.16 (m, 2 H), 7.21–7.27 (m, 3 H), 7.76 (dd, $J$ = 1.7, 7.7 Hz, 1 H), 8.44 (dd, $J$ = 1.7, 4.9 Hz, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ (major conformer) = 14.43 ($CH_3$), 33.74 ($CH_3$), 39.98 ($CH_2$), 41.43 (CH), 61.73 ($CH_2$), 121.76 (CH), 125.95 (CH), 126.19 (2 CH), 129.11 (2 CH), 129.41 (CH), 132.48 (C), 134.41 (C), 136.46 (CH), 143.38 (C), 150.03 (C), 154.30 (CH), 170.89 (C), 172.62 (C) ppm; $\delta$ (minor conformer) = 14.47 ($CH_3$), 34.13 ($CH_3$), 37.21 ($CH_2$), 44.51 (CH), 61.73 ($CH_2$), 121.76 (2 CH), 121.84 (CH), 122.33 (CH), 129.11 (2 CH), 129.24 (CH), 132.52 (C), 134.86 (CH), 137.01 (C), 144.69 (C), 150.70 (C), 156.02 (CH), 170.05 (C), 171.75 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3058 (w), 2980 (w), 2937 (w), 2907 (w), 1730 (s), 1461 (s), 1446 (m), 1420 (m), 1372 (s), 1264 (m), 1186 (m), 1161 (m), 1102 (m), 1029 (m), 770 (m), 734 (m), 698 (m), 632 (m) cm$^{-1}$. MS (70 eV, EI): *m*/*z* (%) = 336 (1) [M$^+$], 260 (100), 245 (47), 195 (28), 165 (17), 105 (35), 91 (6), 77 (6). HRMS (70 eV, EI): calcd. for $C_{20}H_{20}N_2O_3$ [M$^+$] 336.1468; found 336.1460.

**(*Z*)-6-Methyl-5-oxo-7-phenyl-5,6,9,10-tetrahydropyrido[3,2-*c*]-azocine-9-carboxylic Acid (37):** A solution of NaOH (512 mg, 12.8 mmol) in water (6.5 mL) was added to a solution of ester **8** (430 mg, 1.28 mmol) in EtOH (1.5 mL) and the mixture was stirred at 23 °C for 1 h. Subsequently, water (10 mL) was added and the mixture was acidified with hydrochloric acid (1 M, 15 mL) to pH 1. The aqueous layer was extracted with $CH_2Cl_2$ (3× 20 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and the solvents were evaporated to give carboxylic acid **37** (220 mg, 710 μmol, 56%) after column chromatography ($SiO_2$; $CH_2Cl_2$/MeOH = 10:1; $R_f$ = 0.03) as a brown solid; m.p. 201–205 °C. A doubled signal set is observed in the NMR spectra (ratio 3:1). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (major conformer) = 2.99 (s, 3 H), 3.26 (dd, $J$ = 11.1, 16.5 Hz, 1 H), 3.68 (dd, $J$ = 7.9, 16.4 Hz, 1 H), 3.88 (dt, $J$ = 8.3, 11.0 Hz, 1 H), 6.06 (d, $J$ = 8.8 Hz, 1 H), 7.30–7.38 (m, 6 H), 7.90–7.94 (m, 1 H), 8.47 (dd, $J$ = 1.6, 4.9 Hz, 1 H), 12.89 (br. s, 1 H) ppm; $\delta$ (minor conformer) = 2.87 (s, 3 H), 3.26 (dd, $J$ = 11.1, 16.5 Hz, 1 H), 3.68 (dd, $J$ = 7.9, 16.4 Hz, 1 H), 3.88 (dt, $J$ = 8.3, 11.0 Hz, 1 H), 5.98 (d, $J$ = 8.9 Hz, 1 H), 7.25–7.27 (m, 2 H), 7.30–7.38 (m, 3 H), 7.43–7.51 (m, 1 H), 7.90–7.94 (m, 1 H), 8.51 (dd, $J$ = 1.6, 4.9 Hz, 1 H), 12.89 (br. s, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ (major conformer) = 33.03 ($CH_3$), 38.44 ($CH_2$), 40.56 (CH), 121.92 (CH), 123.59 (C), 125.72 (2 CH), 128.29 (CH), 129.00 (2 CH), 132.20 (C), 133.97 (C), 136.66 (CH), 142.38 (C), 149.01 (CH), 153.61 (C), 169.17 (C), 173.47 (C) ppm; $\delta$ (minor conformer) = 32.96 ($CH_3$), 36.22 ($CH_2$), 43.13 (CH), 122.32 (CH), 123.07 (CH), 125.39 (2 CH), 127.04 (CH), 129.06 (2 CH), 132.40 (C), 134.79 (CH), 136.02 (C), 142.79 (CH), 149.79 (CH), 155.24 (C), 168.62 (C), 172.71 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2915 (w, br), 2477 (w, br), 1656 (m), 1638 (s), 1582 (m), 1444 (m), 1419 (m), 1379 (m), 1322 (m), 1248 (m), 1198 (m), 1186 (m), 1165 (m), 1110 (m), 815 (m), 769 (s), 752 (m), 695 (m) cm$^{-1}$. MS (70 eV, EI): *m*/*z* (%) = 308 (4) [M$^+$], 264 (9), 246 (13), 235 (8), 118 (100), 91 (8), 77 (10). HRMS (70 eV, EI): calcd. for $C_{18}H_{16}N_2O_3$ [M$^+$] 308.1155; found 308.1146.

**Supporting Information** (see footnote on the first page of this article): $^1$H and $^{13}$C{$^1$H} NMR spectra of all products.

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