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# Synthesis of 3-azabicyclo[4.1.0]heptane-1-carboxylic acid

Carmela Napolitano [a], Manuela Borriello [b,†], Francesca Cardullo [b,*], Daniele Donati [b,‡], Alfredo Paio [b], Stefano Manfredini [a,*]

[a] Department of Pharmaceutical Sciences, University of Ferrara, via Fossato di Mortara, 17-19, I-44100 Ferrara, Italy
[b] GlaxoSmithKline, Neurosciences Centre of Excellence for Drug Discovery, Medicine Research Centre, via Fleming, 4, I-37135 Verona, Italy

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ABSTRACT

A full study on the synthesis of 3-azabicyclo[4.1.0]heptane-1-carboxylic acid is described. Three different approaches were investigated in order to achieve an efficient synthesis of this unnatural aminoacid. The optimized synthetic route relies upon three key steps: (i) diazomalonate insertion on 4-phtalimido 1-butene, (ii) intramolecular cyclization and (iii) chemoselective reduction of the resulting lactam. Due to its bicyclic nature and conformational constraints, this aminoacid may be an useful building block in medicinal chemistry.

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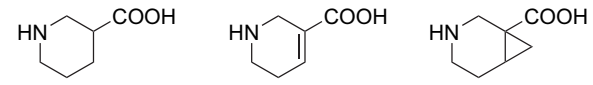
## 1. Introduction

One of the strategies adopted in our lead optimization programmes is the introduction of conformational constraint in the design of new inhibitor structures. The goal is tighter and/or more selective binding of the inhibitor to its target.[1] Reducing the entropic costs of binding can produce the desired effect, but only if enthalpically important contacts are not lost as a result of the structural constraint. The most common tactic toward these ends involves the construction of cyclic isosteres of acyclic structures.[1a,b] The further constraint of cyclic structures can be achieved through the introduction of unsaturation, through fusion to a second ring, or by conversion of a (mono)cyclic system into a bicyclic one.[1c,d,2] Here we report the synthesis of a constrained bicyclic β-amino acid as an example of the latter approach.

The interest in cyclic β-amino acids has increased exponentially in the past few years and they have become a hot topic in synthetic and medicinal chemistry.[3–8] Among these, nipecotic acid and guvacine, which may be considered as conformationally restricted γ-aminobutyric acid (GABA) analogues,[9] have been used as the basis for the design of some lipophilic and highly potent GABA uptake inhibitors (Fig. 1).[10] As part of our efforts to identify novel building blocks for the preparation of modified analogues of biologically active compounds, we became interested in the synthesis of 3-azabicyclo[4.1.0]heptane-1-carboxylic acid (**1**). This β-amino acid, which can be envisioned to derive from nipecotic acid through the fusion of a cyclopropyl ring at the C-1/C-6 positions, might find wide application in the lead optimization phase of different molecular structures: i.e., glycomimetics, peptidomimetics, and secondary-structure inducing elements.

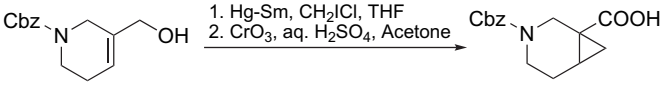



**Nipecotic acid** **Guvacine** **1**

**Figure 1.**

## 2. Results and discussion

At the beginning of this project, a careful survey of the literature revealed only one approach to the synthesis of 3-azabicyclo[4.1.0]heptane-1-carboxylic systems involving the cyclopropanation of the 3-hydroxymethyl tetrahydropyridine. The preparation was accomplished with samarium/mercury amalgam and chloroiodomethane followed by alcohol oxidation (Scheme 1).[11]




**Scheme 1.** Brighty's synthesis of Cbz-protected aminoacid 1.

In a preliminary effort, similarly to the approach used in Scheme 1, arecoline (**2a**) and its simple analogues (**2b**, **2c**) were identified as key precursors (Scheme 2). In order to avoid the use of highly toxic reagents, such as Hg and $CrO_3$, we focused our attention on direct

* Corresponding authors. E-mail address: mv9@unife.it (S. Manfredini).
† Present address: Rothpharma, via Valosa di Sopra, 9, I-20052 Monza (MI), Italy.
‡ Present address: Nerviano Medical Sciences, viale Pasteur, 10, I-20014, Nerviano (MI), Italy.

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cyclopropanation approaches encouraged by the success previously achieved on substrates which are close analogues of the amines **2a**–**c** (structures not reported).


**2a** Pg=Me, R=COOMe
**2b** Pg= Boc, R=COOMe
**2c** Pg=PMB, R=$CH_2OH$

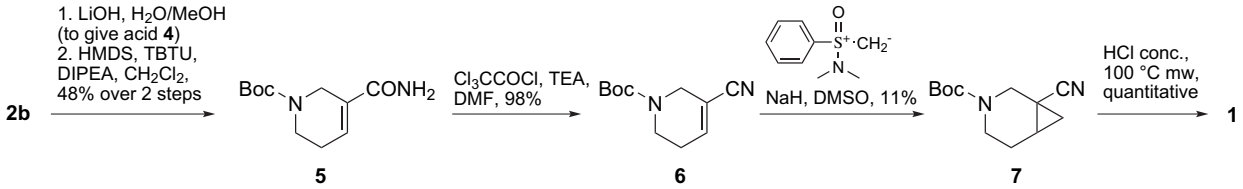
**3a** Pg=Me, R=COOMe
**3b** Pg= Boc, R=COOMe
**3c** Pg=PMB, R=$CH_2OH$

**Scheme 2.** Direct cyclopropanation.

Unfortunately, all our attempts to cyclopropanate those substrates were unsuccessful. In a first effort, we tested Simmons/Smith reaction conditions[12,13] on arecoline (**2a**–**c**). Despite the coordinative potential of the neighboring amino group, arecoline could not be directly applied to the Simmons/Smith reaction due to its propensity to undergo *N*-ylide formation.[14] In order to avoid the supposed formation of ammonium ylides, the methyl amino group was exchanged for the non-nucleophilic *tert*-butylcarbamate group. Cyclopropanation of **2b** using Simmons/Smith conditions and Denmark's activated $IZnCH_2Cl$ reagent[15] afforded only traces of the desired product. Several other reaction conditions (diazomethane,[16] $TMSCHN_2$,[17] Corey's ylide as carbene sources[18]) were then explored without satisfactory results. Hypothesizing that the low reactivity of **2b** under Simmons/Smith conditions was due to the absence of a zinc chelating group[19] (OH or OR), alcohol **2c** was chosen as testing ground for the reaction.

The functional group exchange did not induce an increase in the ring reactivity, suggesting that the methyl ester group and the hydroxymethylene group may be interfering with the cyclopropanation reaction either directly through unfavourable steric interactions or indirectly by altering the conformation of the piperidine ring. In order to verify this hypothesis, the reactivity of two different substrates, in which planar characteristics had been included, was evaluated.

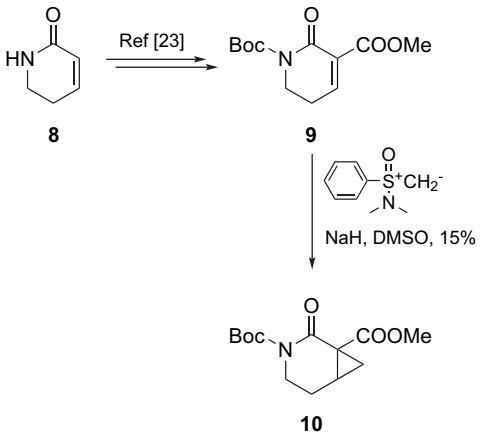
In a first effort, the ester group of **2b** was exchanged for a cyano group. Conversion of the methyl ester into the corresponding amide **5**, followed by dehydration with trichloroacetyl chloride/TEA[20] afforded nitrile **6** in satisfactory overall good yield. The use of Corey's conditions[21] was necessary for cyclopropanation success, even if **7** was isolated only in very low yield (3%). Interestingly, implementation of reaction conditions using dimethylamino-phenylsulfoxonium methylide[22] as the carbene source led to a slight improvement in yield (11%). Treatment of **7** with concd HCl under microwave irradiation allowed a one-pot nitrile hydrolysis and Boc group cleavage to give **1** as the hydrochloride salt in almost quantitative yield (Scheme 3).




**Scheme 3.** Route 1. Synthesis via 3-Boc-3-azabicyclo[4.1.0]heptane-1-carbonitrile intermediate (**7**).

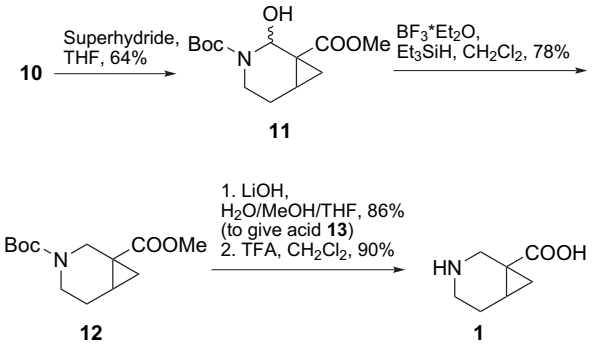
In the second approach the arecoline core was exchanged for a piperidone-like moiety. The preparation of amido ester **9** starting from Boc protected δ-valerolactam (**8**) is well precedented.[23]

To our regret, according with the previous findings the cyclopropanation of piperidone **9** was found poor yielding. Classical Corey's cyclopropanation afforded **10** in 5% yield, while the use of dimethylamino-phenylsulfoxonium methylide led again to a slight, but not satisfactory improvement in yield (15%, Scheme 4).




**Scheme 4.** Route 2. Synthesis of intermediate lactam **10**.

Next we explored the chemoselective reduction of lactam **10**. In an improved protocol,[24] **10** was reduced with lithium triethylborohydride to a diastereomeric mixture of *N*-Boc aminals **11**.[25] Further reduction with triethylsilane and $BF_3 \cdot Et_2O$ followed by acidic work-up gave **12** in 50% overall yield starting from **10**. Next ester hydrolysis followed by Boc group cleavage afforded **1** in excellent yield (Scheme 5).

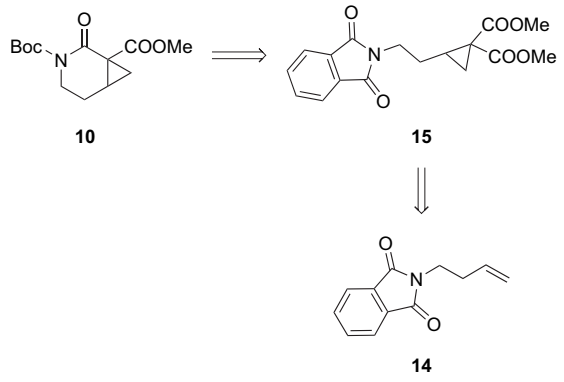



**Scheme 5.** Route 2. Chemoselective reduction and full deprotection.

Critically evaluating our findings, we realized that the cyclopropanation of the six-membered ring was the weak point of our approaches, precluding the access to **1** on multigram scale. In order to avoid the low yielding cyclopropanation step and find a more favorable approach to **1**, we decided to optimize route 2 investigating a de novo synthesis for the key intermediate.

To this end, a rapid and efficient procedure was planned, involving the cyclopropanation of an appropriate amino olefin followed by intramolecular lactamization (Scheme 6). Since the amino group required eventual protection, 4-phthalimido 1-butene (**14**)[26] was employed as starting material.

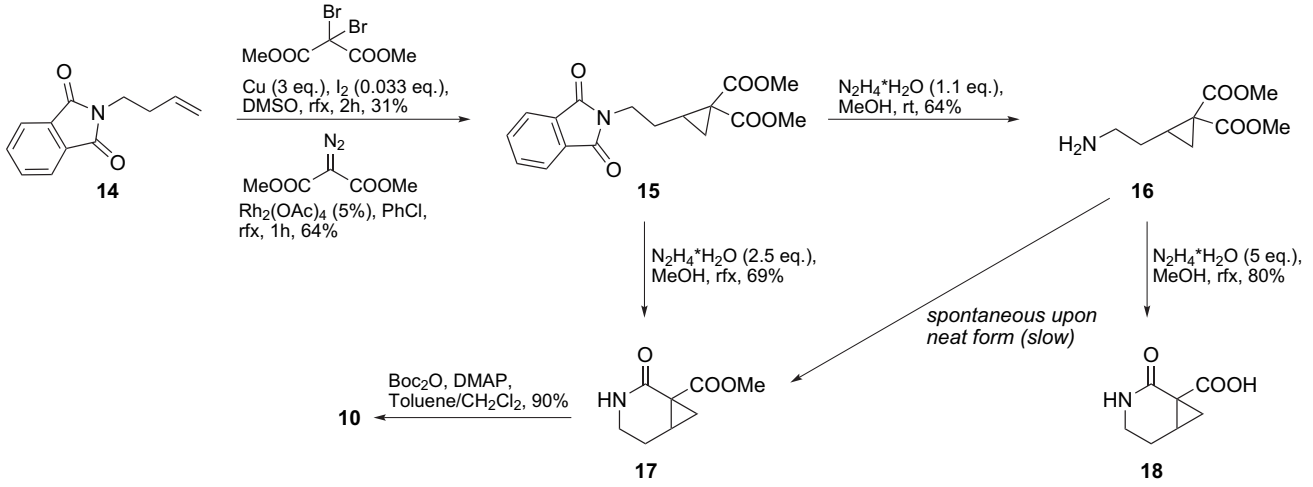
The copper-promoted reaction of dimethyl dibromomalonate[27] with 4-phthalimido 1-butene (**14**) at 75 °C[28] led only to the formation of a small amount of **15**. Unsatisfactory yields (29–31%)




**Scheme 6.** Retrosynthetic approach to **10**.

amine **16** (64% yield). Upon standing in neat form, partial lactamization to **17** was observed by $^1$H NMR spectroscopic analysis (15–30%).

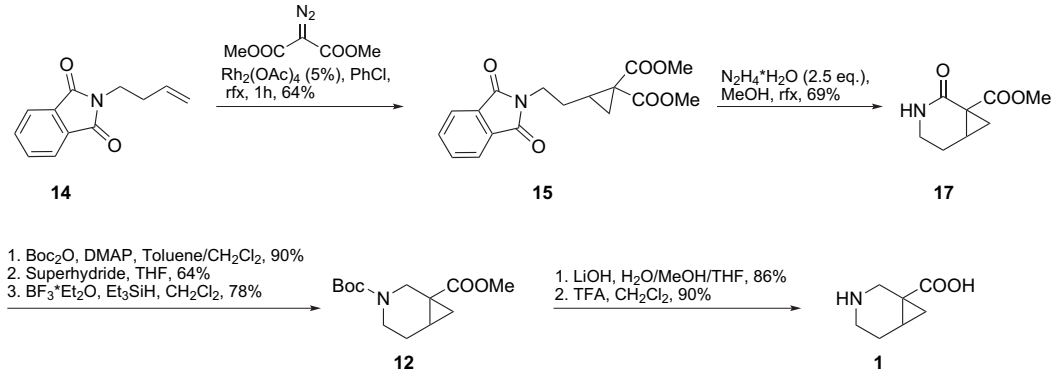
Initial attempts to promote intramolecular cyclization of **16** were unsuccessful, affording multiple products attributed to decomposition of starting material. Optimization efforts included the evaluation of the effect of basic and acidic catalysis in combination with temperature and solvent screening. The most significant improvements were realized employing excess $N_2H_4\cdot H_2O$ (5 equiv) and running the reaction in MeOH at reflux; under these conditions, efficient intramolecular cyclization was observed together with undesired hydrolysis of the ester group and carboxylic acid **18** was isolated in good yield (80%). Intrigued by this finding, we next directed our efforts on the achievement of the complete conversion of phthaloylamine **15** into lactam **17**. Vigorous hydrazinolysis conditions (2.5 equiv $N_2H_4\cdot H_2O$, reflux, 18 h) provided ester **17** in satisfactory yield (69%) after crystallization (Scheme 7).




**Scheme 7.** De novo synthesis of **10**.

were also obtained under stronger thermal and microwave assisted conditions (150–175 °C). Best results were gained replacing dibromomalonate with dimethyl diazomalonate as the carbene source. Indeed Rh(II)-catalysed insertion of diazomalonate[29] on **14** required lower reaction temperatures (70 °C) and afforded **15** in satisfactory yield (64%).[30] For the closure to the six-membered ring, we were encouraged by a Danishefsky and Dynak communication[31] of the spontaneous lactamization of amino diester **15** after N-deprotection. Classical dephthaloylation conditions (1.1 equiv $N_2H_4\cdot H_2O$, MeOH, room temperature) gave access to the deprotected

Finally, N-protection as a *tert*-butylcarbamate, necessary for the two-step chemoselective reduction to **12**, followed by full deprotection gave access to **1** in good yield (16% overall yield starting from **14**) (Scheme 8).




**Scheme 8.** Total synthesis of 3-azabicyclo[4.1.0]heptane-1-carboxylic acid (**1**).

In summary, a straightforward approach to 3-azabicyclo-[4.1.0] heptane-1-carboxylic acid (**1**) has been herein reported (Scheme 8). The synthesis involved three key steps: (i) cyclopropanation of 4-phthalimido 1-butene, (ii) intramolecular cyclization, and (iii) chemoselective reduction of a lactam. Due to its bicyclic nature and conformational constraints, we foresee that **1**

might find application as a building block for the synthesis of glycomimetics, peptidomimetics, and secondary-structure inducing elements.

## 3. Experimental section

### 3.1. General

All moisture-sensitive reactions were performed under a nitrogen atmosphere. All solvents and reagents were used as supplied, unless noted otherwise. Reactions were monitored by TLC (precoated silica gel plates $F_{254}$, Merck). Purifications were performed using Vac Master systems. SPE-Si cartridges are silica solid phase extraction columns supplied by Varian. Mass spectra (MS) were taken on a Micromass ZMD 2000 Mass Spectrometer, operating in ES (+) ionization mode. Total ion current (TIC) and DAD UV chromatographic traces together with MS and UV spectra associated with the peaks were taken on a UPLC/MS Acquity™ system equipped with 2996 PDA detector and coupled to a Waters Micromass ZQ™ mass spectrometer operating in positive or negative electrospray ionization mode. [LC/MS—ES (+/−): analyses performed using an Acquity™ UPLC BEH C18 column (50×2.1 mm, 1.7 μm particle size), column temperature 40 °C, mobile phase: A—water+0.1% HCOOH/B—$CH_3CN$+0.06% HCOOH, flow rate: 1.0 mL/min, run time=1.5 min, gradient: $t$=0 min 3% B, $t$=0.05 min 6% B, $t$=0.57 min 70% B, $t$=1.06 min 99% B, $t$=1.449 min 99% B, $t$=1.45 min 3% B, stop time 1.5 min. Positive ES 100−1000, Negative ES 100−800, UV detection DAD 210−350 nm. The use of this methodology is indicated by 'UPLC/MS' in the analytic characterization of the described compounds. Melting points are determined with a capillary apparatus. IR spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrophotometer (crystals: diamond/ZnSe 14,031). $^1$H and $^{13}$C NMR spectra were recorded on Bruker Advance 400 spectrometer; solvent $CDCl_3$ unless otherwise specified. Wherever necessary, two-dimensional H−H COSY experiments were carried out for complete signal assignments. Combustion analysis was performed using CHNS−O analyzer.

*3.1.1. 5,6-Dihydro-2H-pyridine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (**2b**).* $K_2CO_3$ (18.3 g, 133.0 mmol) was added to a solution of arecoline hydrobromide (25.0 g, 106.0 mmol) in $H_2O$ (60 mL). After 30 min, the mixture was extracted three times with $Et_2O$ (3×60 mL), the combined organic layers were dried ($Na_2SO_4$), filtered, and the solvent evaporated under diminished pressure. The resulting oil was dissolved in toluene (120 mL) and ACE−Cl (14.0 mL, 128 mmol) was added slowly. The reaction was heated to reflux for 16 h. HCl (0.1 N, 100 mL) was added and the mixture was extracted three times with $Et_2O$ (3×100 mL). The combined organics were dried ($Na_2SO_4$), filtered, and the solvent evaporated under diminished pressure. The resulting carbamate was dissolved in MeOH (100 mL) and heated to reflux. After 2 h, solvent was removed under reduced pressure. The resulting amine was dissolved in $CH_2Cl_2$ (150 mL) and cooled to 0 °C. TEA (16.5 mL, 118 mmol) and $Boc_2O$ (31.7 g, 145 mmol) were added. After 24 h, 1 M HCl (100 mL) was added, the layers separated and organic phase extracted twice with $CH_2Cl_2$ (2×150 mL). The combined organics were washed with saturated $NaHCO_3$, dried ($Na_2SO_4$), filtered, and the solvent evaporated under diminished pressure. Flash chromatography of the crude residue (PE/EtOAc=90:10) gave **2b** (20.0 g, 78%) as a white solid: mp 29−31 °C. IR (neat) 1724, 1712, 1652, 1439, 1430, 1390, 1368, 1265, 1221. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.02−7.10 (m, 1H, *CH*=C), 4.08−4.14 (m, 2H, N*CH*$_2$C), 3.76 (s, 3H, O*CH*$_3$), 3.48 (dd, 2H, *J* 10.7, 5.5 Hz N*CH*$_2$CH$_2$), 2.26−2.36 (m, 2H, NCH$_2$*CH*$_2$), 1.48 (s, 9H, C(*CH*$_3$)$_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.8, 154.8, 137.9, 128.1, 80.0, 51.7, 42.6, 39.5, 28.4, 25.5. UPLC/MS ($ES^+$), $m/z$: found 242 [$MH^+$], $C_{12}H_{19}NO_4$ requires 241. $t_R$: 0.67 min. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81; O, 26.52. Found: C, 60.04; H, 8.30; N, 5.77; O, 25.89.

*3.1.2. 5,6-Dihydro-2H-pyridine-1,3-dicarboxylic acid 1-tert-butyl ester (**4**).* To a solution of monohydrate LiOH (1.19 g, 28.2 mmol) in $H_2O$ (10 mL) was added ester **2b** (3.42 g, 14.2 mmol) diluted in a 10:1 mixture of MeOH/THF (11 mL). The mixture was stirred at room temperature for 4 h, acidified with 1 N HCl (15 mL) and extracted three times with $CH_2Cl_2$ (3×30 mL). The combined organics were dried ($Na_2SO_4$), filtered, and the solvent evaporated under diminished pressure to afford acid **5** (3.20 g, quantitative), which did not need any purification. IR (neat) 1725, 1702, 1646, 1445, 1435, 1382, 1366, 1299, 1243. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.40 (br s, 1H, *CH*=C), 4.18 (br s, 4H, N*CH*$_2$C, N*CH*$_2$CH$_2$), 2.34 (br s, 2H, NCH$_2$*CH*$_2$), 1.58 (s, 9H, C(*CH*$_3$)$_3$). $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 169.6, 155.4, 142.1, 129.6, 80.3, 42.4, 42.1, 28.3, 22.4. UPLC/MS ($ES^+$), $m/z$: found 228 [$MH^+$], $C_{11}H_{17}NO_4$ requires 227. $t_R$: 0.62 min. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16; O, 28.16. Found C, 58.31; H, 7.51; N, 6.09; O, 28.09.

*3.1.3. 5-Carbamoyl-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (**5**).* Carboxylic acid **4** (0.550 g, 2.42 mmol), DIPEA (1.86 mL, 10.65 mmol), and TBTU (1.71 g, 5.32 mmol) were dissolved in DMF (12 mL) and the solution was stirred at room temperature for 1 h. HMDS (0.86 g, 5.32 mmol) was added and stirring was prolonged for further 18 h. The mixture was diluted with EtOAc (30 mL) and washed with saturated aq $NH_4Cl$ (2×20 mL). The aqueous layers were backextracted twice with EtOAc (3×20 mL). The combined organics were dried ($Na_2SO_4$), filtered, and the solvent evaporated under diminished pressure. Purification of the crude residue by chromatography over SPE-Si column (25 g, grad. hexane/acetone=95:5 to hexane/acetone=50:50) afforded **5** (0.26 g, 48%) as a colorless oil. IR (neat) 3365, 3179, 1724, 1642, 1623, 1438, 1439, 1385, 1366, 1180. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.70 (br s, 1H, *CH*=C), 5.48 (br s, 2H,CO*NH*$_2$), 4.15−4.18 (m, 2H, N*CH*$_2$C), 3.51 (t, 2H, *J* 9.4 Hz, N*CH*$_2$CH$_2$), 2.27−2.36 (m, 2H, NCH$_2$*CH*$_2$), 1.50 (s, 9H, C(*CH*$_3$)$_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.6, 153.3, 136.8, 127.0, 80.5, 41.4, 41.1, 28.4, 22.7. UPLC/MS ($ES^+$), $m/z$: found 227 [$MH^+$], $C_{11}H_{18}N_2O_3$ requires 226. $t_R$: 0.54 min. Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 58.39; H, 8.02; N, 12.38; O, 21.21. Found C, 58.31; H, 8.04; N, 12.29; O, 21.36.

*3.1.4. 5-Cyano-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (**6**).* Trichloroacetyl chloride (0.974 g, 5.36 mmol) dissolved in dry $CH_2Cl_2$ (3 mL) was added dropwise to a stirred mixture of **5** (1.10 g, 4.87 mmol) and TEA (1.35 mL, 9.74 mmol) in dry $CH_2Cl_2$ (8 mL), which had been pre-cooled to 0 °C. After the addition was finished, the mixture was treated with ice-cooled water (10 mL), 5% NaOH (10 mL), 5% HCl (10 mL), and finally with $H_2O$ (10 mL). The organic layer was dried ($Na_2SO_4$), filtered, and the solvent evaporated under diminished pressure to afford nitrile **6** (1.0 g, 98%) as a pale yellow oil. IR (neat) 2223, 1724, 1648, 1439, 1389, 1365, 1225. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.77 (br s, 1H, *CH*=C), 4.06 (br s, 2H, N*CH*$_2$C), 3.53 (t, 2H, *J* 9.4 Hz, N*CH*$_2$CH$_2$), 2.33 (br s, 2H, NCH$_2$*CH*$_2$), 1.49 (s, 9H, C(*CH*$_3$)$_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.2, 143.5, 119.6, 117.3, 80.9, 42.5, 41.2, 29.0, 25.6. UPLC/MS ($ES^+$), $m/z$: found 209 [$MH^+$], $C_{11}H_{16}N_2O_2$ requires 208. $t_R$: 0.70 min. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 63.44; H, 7.74; N, 13.45; O, 15.36. Found C, 63.54; H, 7.78; N, 13.41; O, 15.27.

*3.1.5. 1-Cyano-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester (**7**).* NaH (0.017 g, 0.720 mmol, 60% oil dispersion) was added to a solution of dimethylamino-phenylsulfoxonium methylide (0.13 g, 0.480 mmol) in DMSO (2 mL). After 20 min a solution of **6** (0.10 g, 0.480 mmol) in DMSO (2 mL) was added and the mixture was stirred at room temperature for 18 h. Brine (10 mL)

was added and the reaction extracted four times with a 50:50 mixture hexane/EtOAc (4×10 mL). The combined organics were dried ($Na_2SO_4$), filtered, and the solvent evaporated under diminished pressure. Purification of the crude residue by chromatography over SPE-Si column (2 g, grad. hexane to hexane/acetone=95:5) gave **7** (12.7 mg, 11%) as a pale yellow oil. IR (neat) 2236, 1723, 1452, 1439, 1390, 1365, 1220. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.97–4.30 (m, 1H, NC*H*$_a$H$_b$C), 3.45–3.70 (m, 2H, NCH$_a$*H*$_b$C, NCH$_a$*H*$_b$CH$_2$), 2.88–3.03 (m, 1H, NC*H*$_a$H$_b$CH$_2$), 1.99–2.13 (m, 1H, NCH$_2$C*H*$_b$H$_a$CH), 1.67–1.84 (m, 2H, CH$_2$C*H*CH$_2$, NCH$_2$CH$_b$*H*$_a$CH), 1.57 (s, 9H, C(C*H*$_3$)$_3$), 1.47 (dd, 1H, *J* 11.6, 7.8 Hz, N≡CCC*H*$_a$H$_b$CH), 0.83 (t, 1H, *J* 8.5 Hz, N≡CCCH$_a$*H*$_b$CH). $^{13}$C NMR (100 MHz, $CDCl_3$) d 156.1, 115.0, 80.5, 52.5, 43.9, 28.2, 26.2, 23.8, 19.8, 19.4. UPLC/MS (ES$^+$), *m*/*z*: found 223 [MH$^+$], $C_{12}H_{18}N_2O_2$ requires 222. $t_R$: 0.70 min. Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60; O, 14.40. Found C, 64.81; H, 8.17; N, 12.63; O, 14.42.

*3.1.6. 2-[2-(1,3-Dihydro-isoindol-2-yl)-ethyl]-cyclopropane-1,1-dicarboxylic acid dimethyl ester (**15**).* Rhodium(II) acetate dimer (0.580 g, 1.31 mmol) was added to a mixture of **14** (5.28 g, 26.2 mmol) in chlorobenzene (50 mL). The suspension was warmed to an internal temperature of +60 °C and dimethyl diazomalonate (6.64 g, 42.0 mmol) was added dropwise keeping the Ti below +70 °C. After 1 h, further dimethyl diazomalonate (6.64 g, 42.0 mmol) was added dropwise keeping the Ti below +70 °C and the reaction mixture was stirred for 1 h. The suspension was cooled to room temperature, diluted with $CH_2Cl_2$ (50 mL), and filtered from the catalyst. Solvent was partially removed under reduced pressure; the crude material was purified by chromatography over SPE-Si column (50 g, cyclohexane/EtOAc=60:40) to afford **15** (5.55 g, 64%) as an off-white solid: mp=124–126 °C; IR (neat) 1769, 1734,1702, 1436, 1292, 1207. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.82–7.89 (m, 2H, Ph), 7.69–7.76 (m, 2H, Ph), 3.76–3.87 (m, 5H, NC*H*$_2$CH$_2$, OC*H*$_3$), 3.73 (s, 3H, OC*H*$_3$), 1.90–2.01 (m, 1H, CH$_2$C*H*CH$_2$), 1.63–1.86 (m, 2H, NCH$_2$C*H*$_2$), 1.37–1.48 (m, 2H, CHC*H*$_2$C). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.4, 168.3, 168.2, 134.0, 132.1, 123.2, 52.7, 52.6, 37.0, 33.7, 27.8, 25.9, 20.5. UPLC/MS (ES$^+$), *m*/*z*: found 332 [MH$^+$], $C_{17}H_{17}NO_6$: requires 331. $t_R$: 0.68 min. Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23; O, 28.97. Found C, 61.78; H, 5.01; N, 3.98; O, 29.23.

*3.1.7. 2-Oxo-3-aza-bicyclo[4.1.0]heptane-1-carboxylic acid methyl ester (**17**).* $N_2H_4\cdot H_2O$ (0.257 mL, 8.19 mmol) was added to a solution of diester **15** (1.08 g, 3.27 mmol) in MeOH (40 mL) and the mixture was heated to reflux. After 18 h the mixture was cooled to room temperature and solvent was partially evaporated under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (20 mL); precipitate was filtered off and the solvent evaporated under reduced pressure. Recrystallization of the crude residue from $Et_2O$/MeOH=95:5 afforded **17** (0.353 g, 69%) as an off-white solid: mp=133–135 °C; IR (neat) 3275, 1720, 1660, 1628, 1437, 1280. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.58 (br s, 1H, NH), 3.77 (s, 3H, $OCH_3$), 3.23–3.32 (m, 1H, NC*H*$_b$H$_a$CH$_2$), 3.04–3.15 (m, 1H, NC*H*$_a$H$_b$CH$_2$), 2.09–2.21 (m, 1H, NCH$_2$C*H*$_a$H$_b$), 1.91–2.00 (m, 2H, NCH$_2$CH$_a$*H*$_b$, CH$_2$C*H*CH$_2$), 1.88–1.94 (m, 1H, CHCH$_a$*H*$_b$C), 1.46 (t, 1H, *J* 10.7 Hz, CHC*H*$_a$H$_b$C). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.5, 168.6, 52.7, 38.0, 28.0, 24.7, 20.3, 16.4. UPLC/MS (ES$^+$), *m*/*z*: found 170 [MH$^+$], $C_8H_{11}NO_3$ requires 169. $t_R$: 0.37 min. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28; O, 28.37. Found C, 56.48; H, 6.03; N, 7.62; O, 29.87.

*3.1.8. 2-Oxo-3-aza-bicyclo[4.1.0]heptane-1,3-dicarboxylic acid 3-tert-butyl ester 1-methyl ester (**10**): method A (starting from **9**).* NaH (0.028 g, 1.185 mmol, 60% oil dispersion) was added portionwise to a solution of dimethylamino-phenylsulfoxonium methylide (0.19 g, 0.711 mmol) in DMSO (3 mL). After 20 min a solution of **9** (0.12 g, 0.474 mmol) in DMSO (3 mL) was added and the stirring was prolonged for further 3 h. Brine (3 mL) was added and the reaction extracted three times with EtOAc (3×10 mL). The combined organics were dried ($Na_2SO_4$), filtered, and the solvent evaporated under diminished pressure. Purification of the crude residue by chromatography over SPE-Si column (2 g, grad. hexane to hexane/EtOAc=95:5) afforded **10** (0.19 g, 15%) as a pale yellow oil. Method B (starting from **17**): to a solution of lactam **17** (0.40 g, 2.36 mmol) in a 2:1 mixture toluene/$CH_2Cl_2$ (15 mL) was added DMAP (0.43 g, 3.55 mmol) followed by $Boc_2O$ (0.659 mL, 2.84 mmol). The resulting mixture was heated to reflux for 2 h, then diluted with $CH_2Cl_2$ (15 mL) and washed with brine (30 mL). The organic layer was dried ($Na_2SO_4$), filtered, and the solvent evaporated under diminished pressure. Purification of the crude residue by chromatography over SPE-Si column (10 g, $CH_2Cl_2$) afforded **10** (0.57 g, 90%) as a pale yellow oil. IR (neat) 1764, 1718, 1439, 1390, 1368, 1295, 1141. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.76–3.85 (m, 4H, $OCH_3$, NC*H*$_b$H$_a$CH$_2$), 3.45–3.54 (m, 1H, NCH$_b$*H*$_a$CH$_2$), 2.15–2.32 (m, 1H, NCH$_2$C*H*$_a$H$_b$), 1.98–2.08 (m, 1H, CH$_2$C*H*CH$_2$), 1.86–1.97 (m, 2H, NCH$_2$CH$_a$*H*$_b$, CHCH$_a$*H*$_b$C), 1.52–1.57 (m, 9H, C(C*H*$_3$)$_3$), 1.47–1.50 (m, 1H, CHC*H*$_a$H$_b$C). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.2, 167.1, 152.8, 83.5, 52.8, 42.7, 31.2, 28.0, 25.5, 22.6, 19.0. UPLC/MS (ES$^+$), *m*/*z*: found 270 [MH$^+$], $C_{13}H_{19}NO_5$ requires 269. $t_R$: 0.63 min. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20; O, 29.71. Found C, 58.03; H, 7.04; N, 5.37; O, 29.56.

*3.1.9. 3-Aza-bicyclo[4.1.0]heptane-1,3-dicarboxylic acid 3-tert-butyl ester 1-methyl ester (**12**).* A solution of Superhydride (1.0 M) in THF (2.49 mL, 2.49 mmol) was added over 30 min to a solution of lactam **10** (0.56 g, 2.08 mmol) in dry THF (5 mL), which had been precooled to −10 °C. After 2 h at 0 °C, further superhydride solution (0.50 mL) was added and the solution was allowed to stir at room temperature for 2 h. The reaction mixture was quenched with water (15 mL) and extracted three times with EtOAc (3×20 mL). The combined organics were dried ($Na_2SO_4$), filtered, and the solvent evaporated under diminished pressure. Purification of the crude residue by chromatography over SPE-Si column (5 g, cyclohexane/EtOAc=60:40) afforded **11** (0.36 g, 64%) as unseparable mixture of diastereoisomeric aminals. A solution of aminals **11** (0.25 g, 0.92 mmol) and triethylsilane (0.15 mL, 0.921 mmol) in $CH_2Cl_2$ (8 mL) was cooled to −78 °C and $BF_3\cdot OEt_2$ (0.12 mL, 0.921 mmol) was added dropwise. After 30 min, further triethylsilane (0.15 mL, 0.921 mmol) and $BF_3\cdot OEt_2$ (0.12 mL, 0.921 mmol) were added. The resulting mixture was stirred 1.5 h at −78 °C, then warmed to room temperature, diluted with $CH_2Cl_2$ (15 mL), and washed with $H_2O$ (2×20 mL). The organic layer was dried ($Na_2SO_4$), filtered, and the solvent evaporated under diminished pressure. Purification of the crude residue by chromatography over SPE-Si column (5 g, cyclohexane/EtOAc=95:5) afforded **12** (0.26 g, 50% over two steps) as a pale yellow oil. IR (neat) 1705, 1691, 1477, 1439, 1388, 1365, 1248, 1164. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.82–4.12 (m, 2H, NC*H*$_2$C), 3.71 (s, 3H, OC*H*$_3$), 3.51 (br s, 1H, NC*H*$_a$H$_b$CH$_2$), 2.87–3.03 (m, 1H, NCH$_a$*H*$_b$CH$_2$), 1.94–2.08 (m, 1H, NCH$_2$C*H*$_a$H$_b$), 1.66–1.86 (m, 2H, NCH$_2$CH$_a$*H*$_b$, CH$_2$C*H*CH$_2$), 1.44–1.53 (m, 9H, C(C*H*$_3$)$_3$), 1.41 (dd, 1H, *J* 9.8, 8.4 Hz CHCH$_a$*H*$_b$C), 0.75 (dd, 1H *J* 10.5, 11.2 Hz, CHC*H*$_a$H$_b$C). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.4, 154.9, 79.7, 52.0, 43.1, 38.3, 28.4, 26.5, 22.2, 19.9, 19.1. UPLC/MS (ES$^+$), *m*/*z*: found 256 [MH$^+$], $C_{13}H_{21}NO_4$ requires 255. $t_R$: 0.67 min. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49; O, 25.07. Found C, 61.23; H, 8.37; N, 5.35; O, 25.05.

*3.1.10. 3-Aza-bicyclo[4.1.0]heptane-1,3-dicarboxylic acid 3-tert-butyl ester (**13**).* To a solution of LiOH (0.034 g, 1.41 mmol) in $H_2O$ (2 mL) was added ester **12** (0.180 g, 0.705 mmol) diluted in a 10:1 mixture MeOH/THF (2.2 mL). The resulting mixture was stirred at room temperature for 3 h, then acidified with 1 M HCl (2 mL), diluted with $H_2O$ (5 mL), and extracted three times with $CH_2Cl_2$ (3×10 mL). The organic layer was dried ($Na_2SO_4$), filtered, and the solvent

evaporated under diminished pressure to afford **13** (0.15 g, 86%) as a colorless oil. IR (neat) 1725, 1705, 1452, 1435, 1384, 1366, 1243. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.94 (br s, 2H, NC$H_2$C), 3.35–3.54 (m, 1H, NC$H_b$H$_a$CH$_2$), 2.94–3.04 (m, 1H, NC$H_a$H$_b$CH$_2$), 1.96–2.10 (m, 1H, NCH$_2$C$H_b$H$_a$), 1.72–1.85 (m, 2H, NCH$_2$C$H_a$H$_b$, CH$_2$C$H$CH$_2$), 1.42–1.54 (m, 10H, C(CH$_3$)$_3$, CC$H_b$H$_a$CH), 0.83 (t, 1H, $J$ 9.3 Hz CC$H_a$H$_b$CH). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 179.8, 156.0, 79.9, 44.7, 38.5, 28.0, 26.7, 22.0, 20.9, 19.8. UPLC/MS (ES$^+$), $m/z$: found 243 [MH$^+$], $C_{12}H_{19}NO_4$ requires 242. $t_R$: 0.62 min. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80; O, 26.52. Found C, 59.95; H, 8.06; N, 5.49; O, 26.50.

*3.1.11. 3-Azabicyclo[4.1.0]heptane-1-carboxylic acid (**1**): method A (starting from **7**).* In a 5 mL microwave vial was added **7** (0.03 g, 0.135 mmol) dissolved in 37% aq HCl (1 mL). The mixture was heated to 150 °C for 10 min under mw irradiation. Volatiles were evaporated under diminished pressure to afford **1** as hydrochloride salt (0.019 g, quantitative). Method B (starting from **13**): compound **13** (0.10 g, 0.415 mmol) was dissolved in a 3:1 mixture $CH_2Cl_2$/TFA (4 mL). The solution was stirred at 0 °C for 45 min; volatiles were evaporated under reduced pressure to give compound **1** (0.095 g, 90%) as trifluoroacetic salt, which did not need any purification. IR (neat) 1674, 1665, 1611, 1517, 1459, 1217. $^1$H NMR (400 MHz, $D_2O$) $\delta$ 4.27 (d, 1H, $J$ 14.4 Hz, NC$H_b$H$_a$C), 3.11–3.19 (m, 1H, NC$H_b$H$_a$CH$_2$), 3.04 (d, 1H, $J$ 14.4 Hz, 1H, NC$H_a$H$_b$C), 2.70 (td, 1H, $J$ 12.3, 4.4 Hz, NC$H_a$H$_b$CH$_2$), 2.02 (dd, 1H, $J$ 14.9, 4.6 Hz, CH$_2$C$H_b$H$_a$CH), 1.98 (dt, 1H, $J$ 14.9, 6.2 Hz, CH$_2$C$H_a$H$_b$CH), 1.85–1.92 (m, 1H, CH$_2$CH$_2$C$H$), 1.66 (dd, 1H, $J$ 9.6, 5.4 Hz, CH$_2$CHC$H_b$H$_a$), 1.07 (dd, 1H, $J$ 7.0, 5.4 Hz, CH$_2$CHC$H_a$H$_b$). $^{13}$C NMR (100 MHz, $D_2O$) $\delta$ 176.6, 43.1, 38.1, 30.3, 21.2, 19.9, 18.6. UPLC/MS (ES$^+$), $m/z$: found 142 [MH$^+$], $C_7H_{11}NO_2$ requires 141. $t_R$: 0.21 min. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92; O, 22.67. Found C, 59.64; H, 8.01; N, 10.03; O, 22.32.

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