Synthesis of a Variety of 2-Alkyl-2-Azabicyclo[3.1.1]heptane-1-carbonitriles via a Dynamic Addition–Intramolecular Substitution Sequence

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Abstract: An improved two-step synthetic approach towards 3-(2-chloroethyl)cyclobutanone is described and used in the synthesis of a class of 2-alkyl-2-azabicyclo[3.1.1]heptane-1-carbonitriles. The key step consists of a reversible addition of hydrogen cyanide onto the in situ generated imines, followed by an intramolecular nucleophilic substitution, thereby leading to the bicyclic skeleton in moderate to good yields (47–92%). These bicyclic compounds are stable, and the incorporated cyano group can be easily reduced to the corresponding aminomethyl group in high yields (93–99%), using lithium aluminum hydride.

Key words: nitriles, heterocycles, bicyclic compounds, ring closure, nucleophilic addition

Conformationally restricted amino acids are of paramount value for drug design. In this regard, proline and pipecolic acid have been excellent building blocks to explore the synthesis of azabicyclic amino acids. Their incorporation in targeted peptidomimetics can improve the pharmacokinetic and pharmacodynamic properties of possible drug candidates.[1] An often described example is 2,4-methanoproline (**1**), which is a natural nonproteinogenic amino acid, isolated from the seeds of *Ateleia Herbert smithii* Pittier.[2] The seeds of this legume species are ignored by at least 100 seed predators. Therefore, it is believed that 2,4-methanoproline (**1**), which is present in these seeds, acts as an antifeedant.[3]

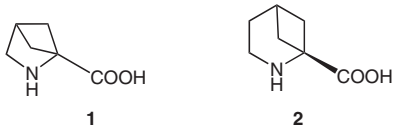
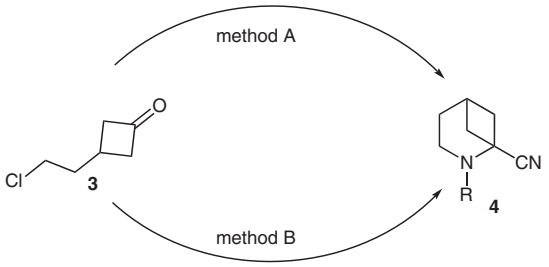


Figure 1 2,4-Methanoproline (**1**) and 2,4-methanepipecolic acid (**2**)

The 2-aza-bicyclo[2.1.1]hexane skeleton has drawn the attention of several groups, developing different strategies for the formation of this bicyclic system. Since its isolation in 1980, several synthetic pathways towards 2,4-methanoproline (**1**) have been developed.[4] Unfortunately, the reaction conditions and reported yields were unsatisfactory, and therefore a new route was elaborated in our research group, starting from 3-(chloromethyl)cyclobutanone.[5] After extensively optimizing the reaction conditions 2,4-methanoproline (**1**) could be synthesized on quite a large scale with an overall yield of 10%.[6]

Since detailed studies yielding satisfactory results of other constrained amino acids like 2,4-methanepipecolic acid (**2**, Figure 1) are scarce,[7] the cyanide-induced dynamic intramolecular cyclization reaction was further developed, leading to 2-alkyl-2-azabicyclo[3.1.1]heptane-1-carbonitriles **4** (Scheme 1). These bicyclic compounds possess the rare 2,4-methanopiperidine as a scaffold. Radchenko et al.[7a] published a similar reaction sequence to form 2-benzyl-2-azabicyclo[3.1.1] heptane-1-carbonitrile (**4a**) from 3-(2-chloroethyl)cyclobutanone (**3**), using a threefold excess amount of acetone cyanohydrin (**13**, compared to 2 equiv in our protocol) and the established yield of **4a** was much lower (42% compared to our 79%). The present paper highlights the different synthetic strategies towards these bicyclic systems, starting from the improved synthesis of the key compound 3-(2-chloroethyl)cyclobutanone (**3**). Furthermore, our method proved to be applicable on a wide range of amines, leading to a variety of bicyclic compounds (Table 1), whereas Radchenko et al. described only one example.



Scheme 1 Synthesis of the bicyclic compounds **4**. *Reagents and conditions*: method A: RNH_2 (1 equiv), acetone cyanohydrin (2 equiv), Et_3N (2 equiv), dry MeOH, temp, 3 d; method B: **14** (1.1 equiv), MeCN, temp, 3 d.

A new synthetic protocol for the key compound, 3-(2-chloroethyl)cyclobutanone (**3**), was developed for its preparation on multigram scale (Scheme 2). In the first step, a [2+2] cycloaddition of in situ generated dichloroketene and homoallyl chloride[8] (**7**) led to the cyclobutanone **9b**.[9] Many different reaction conditions were evaluated to improve the yield of this reaction. The best results were obtained by generating the dichloroketene from trichloroacetyl chloride and a zinc–copper couple.

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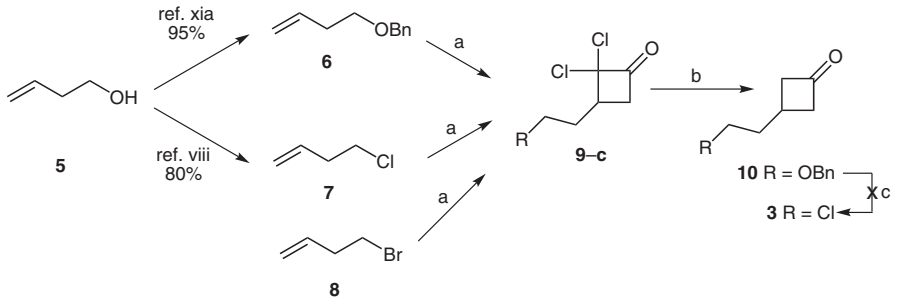


Scheme 2 Synthesis of the key compound 3-(2-chloroethyl)cyclobutanone (**3**). *Reagents and conditions*: (a) Zn–Cu couple, 1,2-DME, Cl_3CCOCl, dry Et_2O, r.t., overnight; **9a** R = OBn, 89%; **9b** R = Cl, 78%; **9c** R = Br, 70%; (b) Zn, AcOH, temp, overnight; **10** R = OBn, 80%; **3** R = Cl, 86%; (c) 12 N HCl, $ZnCl_2$, temp, 1d.

Formation of the ketene from dichloroacetyl chloride, using triethylamine as a base, always led to a complex reaction mixture, probably as a result of the instability of the end product in basic medium. To obtain the 3-(2-chloroethyl)cyclobutanone (**3**), the cycloaddition product **9b** was treated with zinc in acetic acid, reductively removing both geminal chlorine atoms without the formation of any side product.[10]

Another approach leading to 3-(2-halomethyl) cyclobutanones was evaluated, starting from the known cyclobutanone **10**. Slight modification of the literature procedure to prepare **10** from **6**, using 1,2-dimethoxyethane instead of $POCl_3$, gave higher yields than previously reported by other research groups.[11] However, when using a concentrated hydrochloric acid solution with zinc(II) chloride as a catalyst, cyclobutanone **10** could not be converted into the desired 3-(2-chloroethyl)cyclobutanone (**3**).

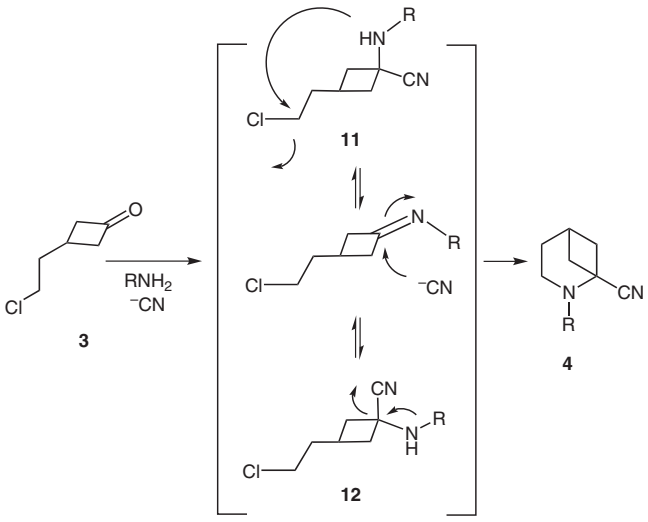
3-(2-Bromoethyl)-2,2-dichlorocyclobutanone (**9c**) could also be prepared, starting from the commercially available homoallyl bromide (**8**). This precursor would be more interesting than compound **9b**, because of the better leaving group capacity of the bromine atom, taking into consideration the subsequent ring closure to form the bicyclic skeleton. Unfortunately, in this case the α-dechlorination step failed. Side products were formed during the reaction, and purification of the reaction mixture by distillation led to the formation of dimers.

The best strategy towards the key compound **3** was the use of a [2+2] cycloaddition with homoallyl chloride (**7**) in the presence of a zinc–copper couple to generate dichloroketene from trichloroacetyl chloride, followed by radical dechlorination of **9b** with zinc in acetic acid.

In an initial experiment to construct the 2-azabicyclo[3.1.1]heptane skeleton, cyclobutanone **3** in dry methanol was treated with a primary amine, triethylamine, and acetone cyanohydrin as a hydrogen cyanide source (Scheme 1, method A). The reaction was performed in a sealed pressure vessel in refluxing methanol for three days. If the reaction was stopped after a few hours of reflux, the starting material was almost completely converted into the adduct **12** (Scheme 3) and only traces of the bicyclic end product **4** could be observed. Especially noteworthy is that only the *cis*-isomer **11** allows ring closure, leading to the desired end product. If the reaction is prolonged to several days, the desired end product **4** is almost completely formed, but some adduct **12** is still present, depending on the R group. The nearly constant ratio of the *cis*/*trans* adducts (**11** and **12**) indicates that the isomerization is relatively fast compared to the ring closure. After three days of reflux, the reaction was complete, and the 2-alkyl-2-azabicyclo[3.1.1]heptane-1-carbonitrile **4** was isolated as the sole product, together with a very small fraction of starting material.[12a]

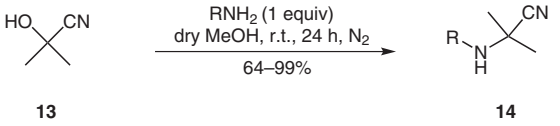
The obtained bicyclic products **4** can be purified by two means in order to remove the excess of acetone cyanohydrin. The first method consists of a purification by column chromatography, which has the disadvantage that the solid-phase silica has a high affinity for the end products, leading to severe losses and consequently lower yields. A more convenient method to remove the acetone cyanohydrin consists of an acid–base extraction. This method is less time-consuming, and the yields after purification are significantly higher compared to the first method.

In a second approach (Scheme 1, method B), based on an earlier reported method of Komarov and co-workers,[13] the 2-azabicyclo[3.1.1]heptane skeleton might be formed using a 'tandem Strecker–intramolecular cyclization reaction'. We investigated the feasibility of applying this



Scheme 3 Mechanism of ring closure

protocol in our research. Adduct **14** was easily prepared in quantitative yield in a separate reaction, starting from acetone cyanohydrin **13** (Scheme 4).[14] Next, it was added to a solution of 3-(2-chloroethyl)cyclobutanone (**3**) in refluxing acetonitrile, again leading to the desired end products. As mentioned before, isolation of the end products was also achieved using column chromatography or an acid–base extraction.[12b]



Scheme 4 Synthesis of adduct **14**

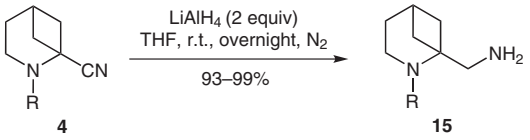
However, when comparing the two methodologies, the previously described method A gave more satisfying results than this second strategy. An overview of the obtained yields is depicted in Table 1. The significant discrepancy in yield between entries **4b** and **4c** can be attributed to difficulties during isolation. Nevertheless, we were capable of preparing a range of derivatives in moderate to good yields.

Table 1 Established Yields of Compound **4** via Methods A and B

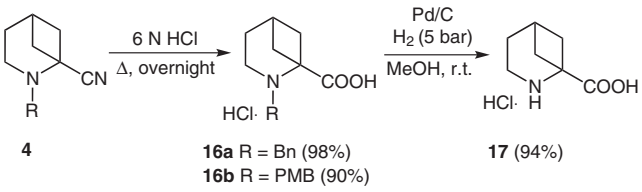
Compound **4**	R	Method A (%)	Method B (%)
4a	Bn	79	70
4b	PMB	85	62
4c	*i*-Pr	59	61
4d	*n*-Pr	73	62
4e	*i*-Bu	78	47
4f	*n*-Bu	79	58
4g	4-Me-Bn	70	59
4h	2,4-DMB	80	60
4i	PMP	72	62
4j	Et	92	–[a]
4k	Me	75	–[a]

[a] Given the volatile properties of $EtNH_2$ and $MeNH_2$ only method A could be applied using 2 equiv of RNH_2.

The bicyclic compounds **4** are stable, and the incorporated cyano group also offers the possibility to elaborate the chemistry further. The cyano group can, for example, be easily reduced to the corresponding aminomethyl group in excellent yields, using lithium aluminum hydride (Scheme 5).[15] Furthermore, the nitrile function can be converted into a carboxylic acid moiety in relatively good yields, using concentrated hydrochloric acid under reflux conditions.[16] After deprotection with Pd/C (10 wt%) 2,4-methanopipecolic acid (**17**) was obtained in 92% overall yield (Scheme 6).[17] Applying these protocols, a series of *N*-alkyl derivatives was synthesized.



Scheme 5 Reduction of the nitrile functionality (R = Bn; PMB; *i*-Pr; *n*-Pr; *i*-Bu; *n*-Bu; 4-MeBn; 2,4-DMB; Et)



Scheme 6 Synthesis of methanepipecolic acid

The results described clearly show the usefulness of 3-(2-chloroethyl)cyclobutanone **3** as a new building block to construct the 2-azabicyclo[3.1.1]heptane skeleton. This key compound is prepared by a two-step methodology, in a way that allows a multigram synthesis. Due to this short sequence, the cyclobutanone **3** forms an ideal precursor for the synthesis of constrained pipecolic acid analogues in only four steps.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(9) **3-(2-Chloroethyl)-2,2-dichlorocyclobutanone (9b)**

In an oven-dried two-necked flask of 500 mL, a solution of homoallyl chloride (15 g, 166 mmol) and a zinc–copper couple (43.32 g, 663 mmol) in dry Et_2O (250 mL) was cooled to 0 °C under a nitrogen atmosphere. A solution of trichloroacetyl chloride (60.24 g, 331 mmol) and 1,2-dimethoxyethane (29.86 g, 331 mmol) in dry Et_2O (150 mL) was added dropwise, after which the reaction mixture was stirred overnight at r.t. The solution was filtered over Celite® and washed with Et_2O. This filtrate was extracted with H_2O (2 × 100 mL), $NaHCO_3$ (4 × 100 mL), brine (2 × 100 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure, leading to the desired 3-(2-chloroethyl)-2,2-dichlorocyclobutanone (26.24 g, 78%) as a clear orange oil. IR (NaCl): 1811 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.05–2.17 (1 H, m, $CHCH_2$), 2.38–2.50 (1 H, m, $CHCH_2$), 3.10 (1 H, dd, *J* = 16.2, 9.4 Hz, CH_2CO), 3.11–3.24 (1 H, m, CH), 3.44 (1 H, dd, *J* = 16.2, 9.4 Hz, CH_2CO), 3.66–3.72 (2 H, m, CH_2Cl). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.94 ($CHCH_2$), 42.12 (CH_2Cl), 43.50 (CH), 47.64 (CH_2CO), 88.51 (C_q), 191.87 (C=O). ESI-MS: *m/z* (%) = 205 (35), 203 (85), 201 (100).

(10) **3-(2-Chloroethyl)cyclobutanone (3)**

A solution of 3-(2-chloroethyl)-2,2-dichlorocyclobutanone (**9b**, 28.23 g, 140 mmol) in AcOH (100 mL) was vigorously stirred, while slowly adding 2 equiv of zinc (18.32 g, 280 mmol). Two extra equiv of zinc (18.32 g, 280 mmol) were added to the reaction mixture, after which it was refluxed overnight. After cooling, the mixture was filtered over Celite® and washed with CH_2Cl_2. The filtrate was neutralized with a sat. $NaHCO_3$ solution. The organic phase was dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. 3-(2-Chloroethyl)cyclobutanone (**3**) was obtained as a bright yellow oil in 86% yield (15.90 g).

IR (NaCl): 1778 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.08 (2 H, dd, *J* = 13.8, 6.6 Hz, $CHCH_2$), 2.54–2.69 (1 H, m, CH), 2.72–2.82 (2 H, m, 2 × CH_2CO), 3.15–3.27 (2 H, m, 2 × CH_2CO), 3.59 (2 H, t, *J* = 6.6 Hz, CH_2Cl). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.71 (CH), 38.57 ($CHCH_2$), 43.41 (CH_2Cl), 52.34 (2 × CH_2CO), 207.01 (C=O). ESI-MS: *m/z* (%) = 135 (45), 133 (100).

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(12) **Typical Procedure for the Synthesis of 2-Alkyl-2-Azabicylo[3.1.1]heptane-1-carbonitriles 4**

(a) In a dry, pressure resistant vessel (20 mL volume) 3-(2-chloroethyl)cyclobutanone (**3**, 2.00 g, 15 mmol, 1 equiv), a primary amine (15 mmol, 1 equiv), acetone cyanohydrin (2.57 g, 30 mmol, 2 equiv), and Et_3N (3.05 g, 30 mmol, 2 equiv) were dissolved in dry MeOH (16 mL). The vessel was closed and heated to 110 °C for 2–3 d. When using ethyl- (pure) or methylamine (2 M in MeOH), the vessel was heated for 4 d, using 30 mmol of the volatile amine. Isolation of the desired end product could be performed by two means. The first method made use of column chromatography. After washing of the reaction mixture with a sat. $NaHCO_3$ solution, 3 g of silica were added to the organic phase (CH_2Cl_2), followed by removal of the solvent under vacuum. The end product was then recovered using column chromatography. The second purification strategy was more convenient and consisted of an acid–base extraction. After removal of the solvent under reduced pressure, 10 mL of a 2 N HCl solution was added. The solution was extracted with Et_2O (3 × 20 mL) to remove the excess of acetone cyanohydrin. A concentrated K_2CO_3 solution was added to the H_2O layer until basic, followed by an extraction of the H_2O layer with CH_2Cl_2 (3 × 30 mL). The combined organic layers (CH_2Cl_2) were dried with $MgSO_4$. After filtration of the solids and removal of the volatiles, the pure 2-R^0-2-azabicyclo[3.1.1]heptane-1-carbonitrile (**4**) was obtained in moderate to good yields, depending on the R^0 group.

(b) In a flame-dried flask of 50 mL, 3-(2-chloroethyl)-cyclobutanone (**3**, 1.00 g, 7.5 mmol) was dissolved in MeCN, together with **14** (8.3 mmol, 1.1 equiv). Hereafter, the reaction mixture was brought to reflux temperature and stirred for 3 d. The pure end product was isolated according to the same procedures as mentioned above in **12a**.

2-(4-Methoxybenzyl)-2-azabicyclo[3.1.1]heptane-1-carbonitrile (4b)

Yellow crystals (3.09 g, 85%). Anal. Calcd (%) for $C_{15}H_{18}N_2O$: C, 74.4; H, 7.5; N, 11.6. Found: C, 74.3; H, 7.6; N, 11.3. R_f = 0.35 (PE–EtOAc = 7:3). IR (ATR): 2359 (CN), 1612, 1515, 1495, 1454 (Ar) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.91 (2 H, td, *J* = 6.6, 3.3 Hz, CH_2), 2.24 (2 H, dd, *J* = 7.2, 2.2 Hz, 2 × $C_qCH_aH_b$), 2.41 (2 H, td, *J* = 7.2, 2.2 Hz, 2 × $C_qCH_aH_b$), 2.49 (1 H, ca. sept, *J* = 3.3 Hz, CH), 2.85 (2 H, t, *J* = 6.6 Hz, NCH_2), 3.79 [5 H, s, NCH_2Ar, OCH_3 (Ar)], 6.86 [2 H, d, *J* = 8.8 Hz, 2 × CH (Ar)], 7.29 [2 H, d, *J* = 8.8 Hz, 2 × CH (Ar)]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.68 (CH_2), 31.25 (CH), 37.21 (2 × $C_qCH_aH_b$), 42.49 (NCH_2), 55.27 [OCH_3 (Ar)], 56.60 (NCH_2Ar), 58.39 (C_q), 113.72 [2 × CH (Ar)], 120.36 (CN), 130.01 [2 × CH (Ar)], 130.79 [C_q (Ar)], 158.83 [C_q (Ar)]. ESI-MS: *m/z* (%) = 291 (20), 214 (15), 213 (100) [MH^+].

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(14) **General Procedure for the Synthesis of 2-Methyl-2-Alkyl/Aryl Aminopropionitriles (14)**

A primary amine (30 mmol) was mixed with acetone cyanohydrin **13** (2.55 g, 30 mmol) in dry MeOH (25 mL).

The solution was stirred at r.t. for 24 h, while N_2 gas was bubbled through. The solvent was removed in vacuo, and the propionitriles **14** were obtained in moderate to excellent yields (64–99%). Analytical samples were obtained after filtration over silica or recrystallization in MeOH.

2-(4-Methoxybenzylamino)-2-methylpropionitrile (14b)

Yellow crystals (6.07 g, 99%). Anal. Calcd (%) $C_{12}H_{16}N_2O$: C, 70.6; H, 7.9; N, 13.7. Found: C, 70.3; H, 8.0; N, 13.5. IR (ATR): 3275 (NH), 2359 (CN), 1611, 1515 (Ar) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51 (7 H, s, 2 × CH_3, NH), 3.80 [3 H, s, OCH_3 (Ar)], 3.83 (2 H, s, NCH_2), 6.87 [2 H, d, *J* = 8.3 Hz, 2 × CH (Ar)], 7.28 [2 H, d, *J* = 8.3 Hz, 2 × CH (Ar)]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.44 (2 × CH_3), 49.00 (NCH_2), 51.68 (C_q), 55.29 [OCH_3 (Ar)], 113.98 [2 × CH (Ar)], 122.85 (CN), 129.60 [2 × CH (Ar)], 131.11 [C_q (Ar)], 158.97 [C_q (Ar)]. ESI-MS: *m/z* (%) = 178 (100) [M – CN]$^+$).

(15) **General Protocol for the Synthesis of (2-Alkyl-2-azabicyclo[3.1.1]hept-1-yl)methylamine 15**

A solution of $LiAlH_4$ (0.19 g, 5 mmol,2 equiv) in dry THF (15 mL) was stirred at –78 °C under a nitrogen atmosphere. A flame-dried syringe was used to slowly add a solution of 2-alkyl-2-azabicyclo[3.1.1]heptane-1-carbonitrile **4** in dry THF (2.5 mmol). Upon completion of the addition, the reaction was stirred overnight at r.t., followed by a careful addition of H_2O to neutralize the excess of $LiAlH_4$. The solution was dried with $MgSO_4$, followed by filtration of the solids and evaporation of the solvent to give the pure {2-alkyl-2-azabicyclo[3.1.1]hept-1-yl}methylamine (**15**, 93–99%). When necessary, the compounds could be further purified using filtration over a short silica column (CH_2Cl_2–MeOH = 9:1).

***C*-{2-(4-Methoxybenzyl)-2-azabicyclo[3.1.1]hept-1-yl}methylamine (15b)**

Bright yellow oil (0.60 g, 97%). IR (ATR): 3365 (NH_2), 1684 (Ar) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.37 (2 H, br s, NH_2), 1.65 (2 H, td, *J* = 6.6, *J* = 2.8 Hz, 2 × $C_qCH_aH_b$), 1.90 (2 H, td, *J* = 6.6, *J* = 3.3 Hz, CH_2), 1.96 (2 H, dd, *J* = 6.6, *J* = 2.8 Hz, 2 × $C_qCH_aH_b$), 2.43 (1 H, sept, *J* = 3.3 Hz, CH), 2.66 (2 H, s, $C_qCH_2NH_2$), 2.92 (2 H, t, *J* = 6.6 Hz, NCH_2), 3.53 (2 H, s, NCH_2Ar), 3.80 [3 H, s, OCH_3 (Ar)], 6.86 [2 H, d, *J* = 8.8 Hz, 2 × CH (Ar)], 7.26 [2 H, d, *J* = 8.8 Hz, 2 × CH (Ar)]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.42 (CH_2), 30.13 (CH), 33.84 (2 × $C_qCH_aH_b$), 43.77 (NCH_2), 48.33 ($C_qCH_2NH_2$), 52.64 (NCH_2Ar), 55.42 [OCH_3 (Ar)], 68.29 (C_q), 113.82 [2 × CH (Ar)], 129.54 [2 × CH (Ar)], 133.53 [C_q (Ar)], 158.51 [C_q (Ar)]. ESI-MS: *m/z* (%) = 247 (100) [MH$^+$]. ESI-HRMS: *m/z* calcd $C_{15}H_{23}ON_2$: 247.18049 [MH$^+$]; found: 247.17857.

(16) **Typical Procedure for the Synthesis of 2-Aryl-2-azabicyclo[3.1.1]heptane-1-carboxylic Acid Hydrochlorides 16**

An amount of the 2-aryl-2-azabicyclo[3.1.1]heptane-1-carbonitrile **4** (0.5 mmol) was dissolved in 6 N HCl (4 mL). The reaction mixture was refluxed overnight. After cooling to r.t., the mixture was kept in the freezer to crystallize the acid from the aqueous solution.

2-(4-Methoxybenzyl)-2-azabicyclo[3.1.1]heptane-1-carboxylic Acid Hydrochloride (16b)

White needles (133.7 mg, 90%). Anal. Calcd (%) for $C_{15}H_{19}NO_3$: C, 68.9; H, 7.3; N, 5.4. Found: C, 68.9; H, 7.4; N, 5.35. IR (ATR): 3358 (br, OH), 1739 (CO), 1637, 1548 (Ar) cm^{-1}. ^1H NMR (300 MHz, D_2O, MeCN): δ = 2.20 (2 H, td, *J* = 6.6, *J* = 3.3 Hz, CH_2), 2.47 (2 H, dd, *J* = 9.4, *J* = 2.8 Hz, 2 × $C_qCH_aH_b$), 2.75 (1 H, sept, *J* = 3.3 Hz, CH), 2.94 (2 H, dd, *J* = 11.8, *J* = 6.6 Hz, 2 × $C_qCH_aH_b$), 3.51 (2 H, t, *J* = 6.6 Hz, NCH_2), 3.86 [3 H, s, OCH_3 (Ar)], 4.60 (2 H, s, NCH_2Ar), 7.08 [2 H, d, *J* = 8.8 Hz, 2 × CH (Ar)], 7.52 [2 H, d, *J* = 8.8 Hz, 2 × CH (Ar)]. ^{13}C NMR (75 MHz, D_2O, MeCN): δ = 24.72 (CH_2), 30.30 (CH), 35.84 (2 × $C_qCH_aH_b$), 46.50 (NCH_2), 50.07 [OCH_3 (Ar)], 58.27 (NCH_2Ar), 59.63 (C_q), 115.39 [2 × CH (Ar)], 121.02 [C_q (Ar)], 133.43 [2 × CH (Ar)], 161.17 [C_q (Ar), COOH]. ESI-MS: *m/z* (%) = 263 (20), 262 (100) [MH$^+$].

(17) **Synthesis of 2,4-Methanepipecolic Acid (17)**

A suspension of 2-benzyl-2-azabicyclo[3.1.1]heptane-1-carboxylic acid hydrochloride (**16a**, 251 mg, 0.94 mmol) and Pd/C (10 wt%, 125 mg) in dry MeOH (2 mL) was placed in a Parr apparatus which was degassed and filled with H_2. The mixture was stirred overnight applying a constant pressure of 5 bar of H_2. Filtration of the heterogeneous suspension over Celite®, followed by evaporation of the solvent in vacuo delivered the crude 2,4-methanepipecolic acid (**17**), which was purified by recrystallization from MeOH; colorless crystals (124.7 mg, 94%). Anal. Calcd (%) for $C_7H_{11}NO_2$: C, 59.6; H, 7.85; N, 9.9. Found: C, 59.6; H, 7.9; N, 9.8. IR (ATR): 3358 (br, OH), 3187 (NH), 1742 (CO) cm^{-1}. ^1H NMR (300 MHz, D_2O, MeCN): δ = 1.87 (2 H, dd, *J* = 8.3, *J* = 2.8 Hz, 2 × $C_qCH_aH_b$), 2.09–2.23 (4 H, m, 2 × $C_qCH_aH_b$, CH_2), 2.60 (1 H, sept, *J* = 3.3 Hz, CH), 2.81 (2 H, br s, OH, NH), 3.53 (2 H, t, *J* = 7.2 Hz, NCH_2). ^{13}C NMR (75 MHz, D_2O, MeCN): δ = 25.75 (CH_2), 29.01 (CH), 33.38 (2 × $C_qCH_aH_b$), 37.66 (NCH_2), 65.21 (C_q), 171.65 (COOH). ESI-MS: *m/z* (%) = 143 (20), 142 (100) [MH$^+$].