Synthesis O. O. Grygorenko et al. Paper

Synthesis of 2-Azabicyclo[n.2.0]alkane-Derived Building Blocks

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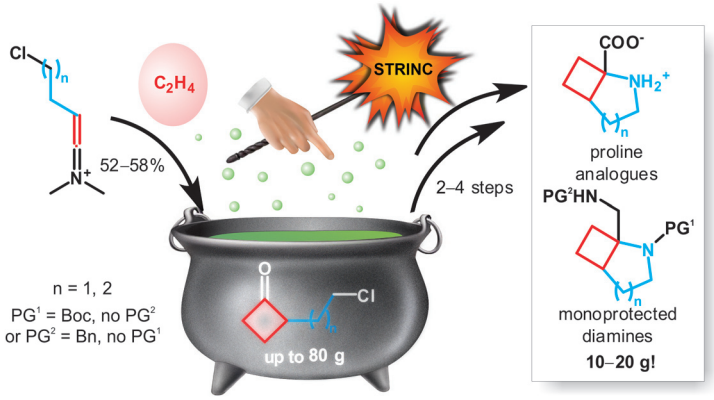

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Abstract An approach to 2-azabicyclo[n.2.0]alkane derivatives (n = 1, 2), which relies on a tandem Strecker reaction–intramolecular nucleophilic cyclization (STRINC) sequence of the corresponding 2-(ω-chloroalkyl)cyclobutanones (in turn prepared by [2+2] cycloaddition of keteniminium salts and ethylene) is described. The utility of the method is demonstrated by multigram syntheses of bicyclic proline analogues, monoprotected diamines, as well as parent 2-azabicyclo[4.2.0]octane.

Key words cycloaddition, bicyclic compounds, amino acids, conformational restriction, cyclobutanes, nitrogen heterocycles, keteniminium salts, Strecker reaction

Bicyclic cyclobutane-derived heteroaliphatic scaffolds have recently attracted attention in synthetic organic and medicinal chemistry as versatile sp^3-rich low-molecular-weight hydrophilic conformationally restricted templates which comply with requirements of lead-oriented synthesis.[1,2] In particular, belaperidone (**1**)[3] and ecenofloxacin (**2**)[4] (derived from 3-azabicyclo[3.2.0]heptane) have reached clinical trials as an antipsychotic and antibacterial agent, respectively (Figure 1). Derivatives of the isomeric 2-azabicyclo[3.2.0]heptane scaffold were evaluated as inhibitors of dipeptidyl peptidase-4 (DPP-4) (**3**),[5] complement factor D (**4**),[6] or nonstructural protein 5A (NS5A).[7]

Despite these promising examples, derivatives of azabicyclo[n.2.0]alkanes remain quite rare in drug discovery.[8] In our opinion, the main reason behind this is the low synthetic accessibility of such structures. A number of papers have appeared describing the synthesis of various C-substituted 2-azabicyclo[3.2.0]heptanes and 2-azabicyclo[4.2.0]octanes. In most cases, intermolecular [2+2] cycloadditions of cyclic enamines or enecarbamates and in situ generated ketenes[5,9–14] or other 2π-components[15–17] were used (Scheme 1, A). Other methods include intramolecular [2+2] photocycloaddition (Scheme 1, B[18] and F[19]), gold- or platinum-catalyzed cycloisomerization of ene-ynamides (Scheme 1, C),[20,21] palladium-catalyzed carboamination of alkylidenecyclopropanes, followed by acid-catalyzed rearrangement (Scheme 1, D),[22] and intramolecular [2+2] cy-

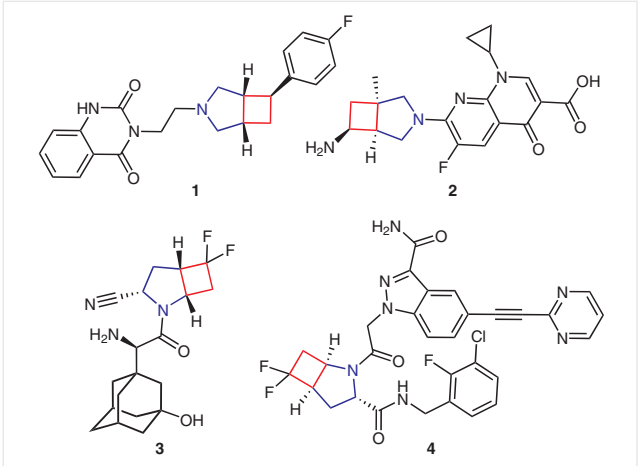
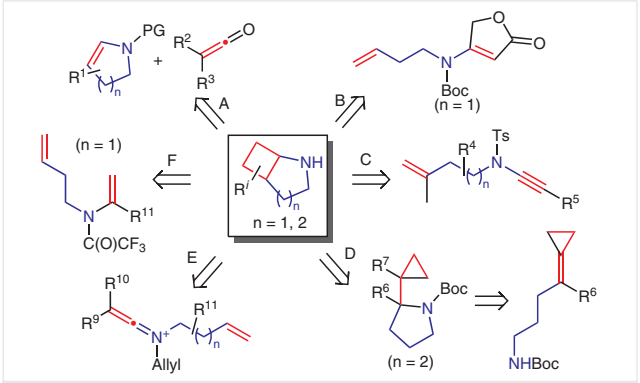


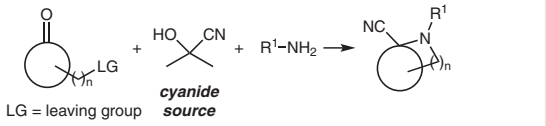
Figure 1 Biologically active azabicyclo[3.2.0]alkanes



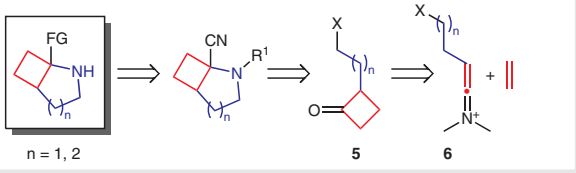
Scheme 1 Known methods for the synthesis of 2-azabicyclo-[3.2.0]heptanes and 2-azabicyclo[4.2.0]octanes

cloaddition involving keteniminium salt intermediates (Scheme 1, E).[23]

All of the above-mentioned methods rely on the annulation of the cyclobutane ring to the pyrrolidine/piperidine moiety, or simultaneous construction of both rings. In this work, we describe an alternative approach to 2-azabicyclo[n.2.0]alkanes, which relies on the formation of the heteroaliphatic ring as the key step. To achieve this, we projected using a one-pot tandem Strecker reaction–intramolecular nucleophilic cyclization (STRINC) sequence (Scheme 2), which had been used previously by our group[24–28] and others[29–33] for the synthesis of various bicyclic ring systems, including bicyclic α-amino acids.[34–43] Application of this retrosynthetic disconnection to 2-azabicyclo[3.2.0]heptane and 2-azabicyclo[4.2.0]octane systems led to 2-(ω-haloalkyl)cyclobutanones **5** (Scheme 3). These ω-halo ketones were not known in the literature; their further retrosynthetic analysis proposed by us relied on [2+2] cycloaddition of keteniminium salts **6** and ethylene.



Scheme 2 STRINC sequence

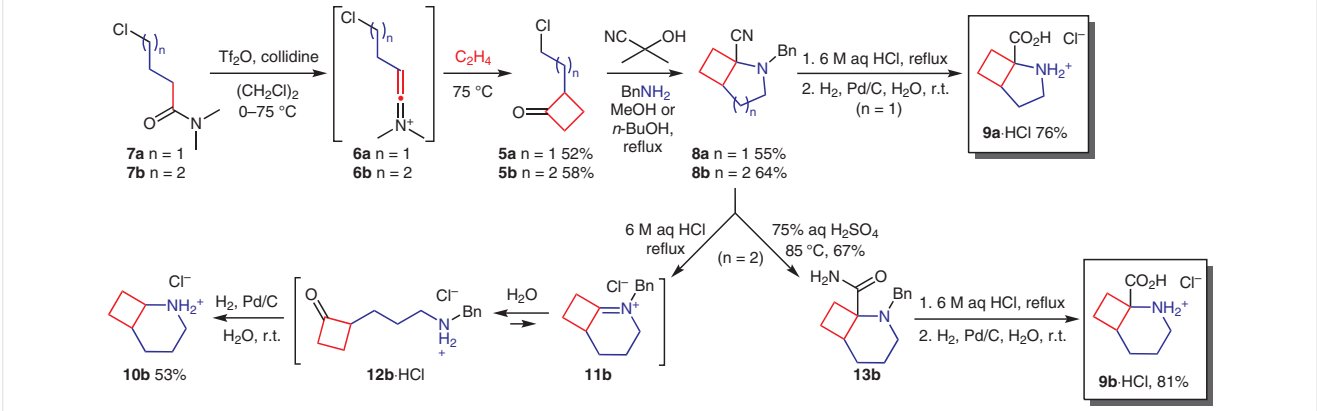


Scheme 3 Retrosynthetic disconnection of 2-azabicyclo[n.2.0]alkanes (n = 1, 2) used in this work

Notably, keteniminium salts **6**[44,45] and ethylene[46] have rarely been used in previous analogous transformations, and, to the best of our knowledge, no examples of their mutual [2+2] cycloaddition have been reported to date. We found that the keteniminium salts **6a** and **6b** (generated in situ from amides **7a** and **7b**) reacted with ethylene at 75 °C at atmospheric pressure to give the corresponding cycloadducts, which provided the target ketones **5a** and **5b** after hydrolysis (Scheme 4). Although the yields of products **5a** and **5b** were moderate (52 and 58%, respectively), they could be obtained on a scale up to 80 grams, since the starting materials are easily accessible. It should be stressed that these novel cyclobutane-derived ω-chloro ketones are versatile sp^3-rich bifunctional building blocks of low molecular weight, which is fully compatible with the lead-oriented synthesis criteria.[1] Since these building blocks have become readily available now, their wide use in medicinal chemistry programs might be anticipated.

First of all, we introduced ω-chloro ketones **5a** and **5b** into the STRINC reaction sequence. Under the standard reaction conditions (benzylamine, acetone cyanohydrin as the cyanide source, MeOH, reflux, 72 h), the target bicyclic nitrile **8a** was obtained from **5a** in 55% yield. In the case of **5b**, a higher reaction temperature was required, so that product **8b** was obtained in 64% yield when *n*-butanol was used as the solvent.

Hydrolysis of nitrile **8a**, followed by catalytic debenzylation, proceeded smoothly and gave the target amino acid **9a**, a bicyclic proline analogue, in 76% overall yield (as a hydrochloride).[47] On the other hand, analogous transformations of **8b** gave the product **10b**·HCl (53% yield) without the carboxylic acid function. Obviously, decyanation occurred at the hydrolysis step, so that iminium intermediate **11b** was initially formed; we were able to isolate amino ketone **12b** (47% yield, as *N*-Boc derivative) from the reaction mixture. Formation of analogous products was observed by us previously for 2-azabicyclo[3.3.0]octane derivatives;[28] it is interesting, however, to outline how subtle conformational differences lead to different reaction outcomes in the following series: bridged bicyclic systems – 2-azabicyclo[3.2.0]heptane – 2-azabicyclo[4.2.0]octane – 2-azabicyclo[3.3.0]octane. It is apparent that the observed regularity can be explained by ring system strain caused by the pres-

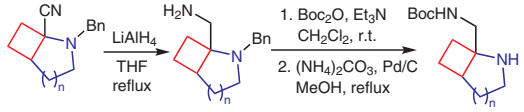


Scheme 4 Synthesis of 2-azabicyclo[n.2.0]alkane-derived proline analogues

ence of a bridgehead sp^2-hybridized carbon atom in the corresponding iminium intermediates (such as **11b**).

Hydrolysis of the nitrile moiety in **8b** was accomplished by using 75% aq H_2SO_4. Under these conditions, amide **13b** formed, and was isolated in 67% yield. Further hydrolysis of **13b**, followed by catalytic hydrogenolysis gave the target amino acid **9b** (81% yield, as hydrochloride).

Alternatively, nitriles **8a** and **8b** were reduced with $LiAlH_4$ to give diamines **14a** and **14b** (98 and 91% yield, respectively) (Scheme 5). Orthogonally protected Boc derivatives **15a** and **15b** were also obtained by using standard protecting group manipulations (68 and 73% yield from **14a** and **14b**, respectively). Compounds **14** and **15** fall into the class of monoprotected bicyclic conformationally restricted diamines, which have proven their utility in drug discovery and other areas.[48]



Scheme 5 Synthesis of monoprotected diamine derivatives **14** and **15**

In conclusion, the tandem Strecker reaction–intramolecular nucleophilic cyclization (STRINC) sequence is an efficient method for the construction of 2-azabicyclo[3.2.0]heptane and 2-azabicyclo[4.2.0]octane systems, which was demonstrated by synthesis of bicyclic conformationally restricted proline analogues and monoprotected diamines on a multigram scale. It was shown that subtle differences in conformational behavior of these bicyclic systems lead to different chemical reactivity (i.e., in hydrolysis of the corresponding α-amino nitriles). Other properties including potential biological activity could also be affected; therefore, series of building blocks derived from 2-azabicyclo[n.2.0]octanes are of special interest for application in drug discovery.

Solvents were purified according to standard procedures.[49] Compounds **7a**[50] and **7b**[51] were obtained by using previously reported methods. All other starting materials were purchased from commercial sources. Melting points were measured on an MPA100 OptiMelt automated melting point system. Analytical TLC was performed on Polychrom SI F254 plates. Column chromatography was performed by using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^1H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (^1H: 500 MHz, ^{13}C: 126 MHz) and a Varian Unity Plus 400 spectrometer (^1H: 400 MHz, ^{13}C: 101 MHz). Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization, APCI) and an Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization, EI). Preparative flash chromatography was performed on a Combiflash Companion chromatograph using 40 g RediSep columns.

2-(2-Chloroethyl)cyclobutanone (5a)

To a solution of amide **7a** (157 g, 1.05 mol) in 1,2-dichloroethane (2.5 L), Tf_2O (355 g, 1.26 mol) was added below 0 °C upon vigorous stirring. The reaction mixture was stirred for 15 min and then heated to 75 °C. At this temperature, collidine (165 g, 1.36 mol) was added dropwise with stirring over 20–30 min; ethylene was bubbled intensively through the reaction mixture during addition. After the addition was complete, ethylene was bubbled at 75 °C for an additional 2 h. The resulting mixture was stirred at this temperature overnight, then cooled to r.t. and evaporated in vacuo. The residue was diluted with H_2O (700 mL), and Na_2CO_3 was added in portions upon stirring to pH 8–9. Hexanes (0.5 L) were added, and the mixture was stirred overnight. Concd aq HCl was added to pH 1, and the organic phase was separated. The aqueous phase was washed with hexanes (2 × 0.5 L), dried over $MgSO_4$, and evaporated in vacuo. The residue was distilled at 1 mmHg to give product **5a**.

Yield: 82.3 g (52%); colorless liquid; bp 41 °C/1 mmHg.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.63–3.51 (m, 2 H), 3.51–3.40 (m, 1 H), 3.12–2.97 (m, 1 H), 2.94–2.82 (m, 1 H), 2.28–2.16 (m, 1 H), 2.16–2.05 (m, 1 H), 1.96–1.83 (m, 1 H), 1.71–1.58 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 209.8, 57.0, 44.2, 42.0, 31.9, 16.3.

MS (EI): *m*/*z* = 132/134 [M^+], 104/106 [$M^+ - C_2H_4$].

Anal. Calcd for C_6H_9ClO: C, 54.35; H, 6.84; Cl, 26.74. Found: C, 54.34; H, 7.05; Cl, 26.80.

2-(3-Chloropropyl)cyclobutanone (5b)

Prepared from **7b** using the procedure described above for **5a**.

Yield: 77.6 g (58%); yellowish liquid; bp 54 °C/1 mmHg.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.57–3.44 (m, 2 H), 3.32–3.18 (m, 1 H), 3.07–2.94 (m, 1 H), 2.94–2.82 (m, 1 H), 2.24–2.11 (m, 1 H), 1.93–1.70 (m, 3 H), 1.70–1.56 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 210.7, 59.0, 44.1, 44.0, 29.6, 26.4, 16.4.

MS (EI): *m*/*z* = 146/148 [M^+], 118/120 [$M^+ - C_2H_4$].

Anal. Calcd for $C_7H_{11}ClO$: C, 57.35; H, 7.56; Cl, 24.18. Found: C, 57.02; H, 7.70; Cl, 23.78.

2-Benzyl-2-azabicyclo[3.2.0]heptane-1-carbonitrile (8a)

To a solution of acetone cyanohydrin (159 g, 1.87 mol) in anhyd MeOH (1.8 L), benzylamine (67.9 g, 0.634 mol) was added under an argon atmosphere, and the resulting mixture was left at r.t. for 30 min. Ketone **11** (80.0 g, 0.603 mol) was added, and the mixture was refluxed for 72 h and then evaporated in vacuo. A solution of 5% aq NaOH was added to pH 12, the mixture was stirred vigorously for 30 min, and then extracted with *t*-BuOMe (2 × 0.5 L). The organic extracts were washed with 2 M aq HCl (1 L) and H_2O (0.5 L). The combined aqueous phases were made alkaline with 25% aq NaOH (to pH 12) and extracted with *t*-BuOMe (2 × 0.5 L). The organic extracts were dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by column chromatography (silica gel, hexanes–*t*-BuOMe–Et_3N, 10:3:1) to give **8a**.

Yield: 70.4 g (55%); yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.32 (m, 4 H), 7.29 (t, *J* = 7.0 Hz, 1 H), 3.95 (d, *J* = 13.0 Hz, 1 H), 3.60 (d, *J* = 13.0 Hz, 1 H), 3.38–3.29 (m, 1 H), 2.98–2.88 (m, 1 H), 2.75 (td, *J* = 9.3, 6.2 Hz, 1 H), 2.39–2.19 (m, 3 H), 2.03–1.92 (m, 1 H), 1.66–1.55 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.9, 128.3, 127.9, 126.9, 120.7, 59.5, 52.7, 50.3, 44.2, 30.1, 23.6, 21.6.

MS (CI): *m*/*z* = 213 [MH^+].

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.6; N, 13.20. Found: C, 79.53; H, 7.39; N, 13.06.

2-Benzyl-2-azabicyclo[4.2.0]octane-1-carbonitrile (8b)

Prepared from **5b** using the procedure described above for **8a** and purified by chromatography (hexanes–*t*-BuOMe–Et_3N, 10:1:1).

Yield: 59.2 g (64%); yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.33 (m, 4 H), 7.29 (t, *J* = 6.7 Hz, 1 H), 3.83 (d, *J* = 13.9 Hz, 1 H), 3.45 (d, *J* = 14.0 Hz, 1 H), 2.93–2.81 (m, 1 H), 2.66–2.56 (m, 1 H), 2.51–2.40 (m, 1 H), 2.34–2.25 (m, 1 H), 2.13–2.02 (m, 2 H), 1.97 (dd, *J* = 17.5, 8.9 Hz, 1 H), 1.79–1.66 (m, 1 H), 1.61–1.48 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.2, 127.9, 126.7, 118.5, 56.4, 55.4, 44.8, 38.5, 30.1, 22.8, 21.9, 21.8.

MS (CI): *m*/*z* = 227 [MH^+].

Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.36; H, 7.83; N, 12.38.

2-Azabicyclo[3.2.0]heptane-1-carboxylic Acid Hydrochloride (9a·HCl)

Amino nitrile **8a** (21.0 g, 99.3 mmol) was refluxed in 6 M aq HCl (300 mL) for 36 h, then cooled and evaporated in vacuo. The residue was made alkaline with 20% aq KOH (100 mL), and the resulting solution was evaporated in vacuo. H_2O (2 × 100 mL) was added, and the mixture was evaporated in vacuo twice to remove residual NH_3. The residue was acidified with 6 M aq HCl to pH 1–2 and evaporated in vacuo again. The resulting solid was triturated with anhyd EtOH (200 mL) and filtered. The filtrate was evaporated in vacuo, and the residue was dissolved in H_2O (200 mL). Then 10% Pd/C (5.02 g) was added, and the resulting mixture was hydrogenated in an autoclave at 70 °C (50 bar) for 36 h (monitored by ^{1}H NMR). The catalyst was filtered off and the filtrates were evaporated in vacuo. The crude product was triturated with acetone (100 mL), filtered, and dried in vacuo to give **9a**·HCl.[47]

Yield: 13.4 g (76%); colorless solid; mp 213–217 °C (dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.79 (br s, 1 H), 10.69 (s, 1 H), 9.05 (s, 1 H), 3.59–3.45 (m, 2 H), 3.17–3.06 (m, 1 H), 2.56–2.35 (m, 2 H), 2.25–2.09 (m, 1 H), 1.99–1.87 (m, 1 H), 1.82 (dd, *J* = 12.6, 4.9 Hz, 1 H), 1.76–1.63 (m, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.8, 67.6, 45.2, 40.4, 29.7, 24.0, 19.8.

MS (CI): *m*/*z* = 142 [MH^+], 96 [M^+ – COOH].

Anal. Calcd for $C_7H_{12}ClNO_2$: C, 47.33; H, 6.81; N, 7.89; Cl, 19.96. Found: C, 47.49; H, 6.93; N, 8.00; Cl, 19.56.

2-Benzyl-2-azabicyclo[4.2.0]octane-1-carboxamide (13b)

Nitrile **8b** (10.0 g, 44.0 mmol) was dissolved in 75% aq H_2SO_4 (100 mL). The resulting solution was stirred at 85 °C for 20 h, then cooled and poured carefully into 25% aq NH_4OH (300 mL) below 25 °C. The resulting mixture was extracted with CH_2Cl_2 (2 × 200 mL). The combined extracts were washed with H_2O (200 mL), dried over Na_2SO_4, and evaporated in vacuo. Et_2O (100 mL) was added, and the mixture was stirred at 0 °C for 15 min. The precipitate was filtered, washed with Et_2O (30 mL), and dried in vacuo to give **13b**.

Yield: 7.25 g (67%); yellowish solid; mp 106–109 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 2 H), 7.26–7.20 (m, 3 H), 7.14 (s, 1 H), 5.52 (s, 1 H), 3.48 (d, *J* = 13.5 Hz, 1 H), 3.16 (d, *J* = 13.5 Hz, 1 H), 2.75 (d, *J* = 10.7 Hz, 1 H), 2.44–1.97 (m, 6 H), 1.69–1.54 (m, 1 H), 1.40–1.28 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 180.2, 138.2, 128.7, 128.4, 127.1, 65.8, 56.2, 46.8, 39.4, 29.4, 23.6, 23.1, 19.4.

MS (CI): *m*/*z* = 245 [MH^+], 200 [MH^+ – CO – NH_3].

Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.34; H, 8.45; N, 11.83.

2-Azabicyclo[4.2.0]octane-1-carboxylic Acid Hydrochloride (9b·HCl)

Amide **13b** (6.95 g, 28.5 mmol) was dissolved in 6 M aq HCl (70 mL). The resulting solution was refluxed for 18 h, and then evaporated in vacuo. The residue was triturated with $CHCl_3$ (140 mL), the precipitate was filtered off, and the filtrate was evaporated in vacuo. The crude product **13b** was dissolved in H_2O (80 mL). Then 10% Pd/C (2.43 g) was added, and the mixture was hydrogenated in an autoclave at 70 °C and 50 bar for 36 h (monitored by ^{1}H NMR). The catalyst was filtered off, and the filtrates were evaporated in vacuo. The residue was triturated with acetone (20 mL), filtered, and dried in vacuo to give **9b** as hydrochloride.

Yield: 4.42 g (81%); white solid; mp 232–236 °C (dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.19 (br s, 1 H), 9.17 (br s, 1 H), 3.16 (dt, *J* = 12.2, 3.5 Hz, 1 H), 2.99–2.89 (m, 1 H), 2.79 (t, *J* = 10.9 Hz, 1 H), 2.42 (dt, *J* = 11.6, 8.6 Hz, 1 H), 2.30 (td, *J* = 18.1, 8.9 Hz, 1 H), 2.21 (ddd, *J* = 11.7, 8.7, 3.0 Hz, 1 H), 2.00–1.87 (m, 2 H), 1.63–1.46 (m, 3 H); COO*H* is exchanged with HDO.

^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.2, 60.8, 40.9, 35.4, 27.1, 22.8, 20.3, 17.3.

MS (CI): *m*/*z* = 156 [MH^+].

Anal. Calcd for $C_8H_{14}ClNO_2$: C, 50.13; H, 7.36; N, 7.31; Cl, 18.50. Found: C, 49.73; H, 7.31; N, 6.96; Cl, 18.90.

(2-Benzyl-2-azabicyclo[3.2.0]heptan-1-yl)methanamine (14a)

To a suspension of $LiAlH_4$ (7.15 g, 0.188 mol) in anhyd THF (200 mL), a solution of **8a** (20.0 g, 94.3 mmol) in anhyd THF (100 mL) was added dropwise with stirring at –78 °C. The mixture was stirred at this temperature for 15 min, then allowed to warm to r.t., stirred for 18 h, and cooled to 0 °C. H_2O (7.2 mL) was added at this temperature dropwise with stirring, followed by 15% aq NaOH (7.2 mL) and H_2O (21.5 mL). The precipitate was filtered and washed with THF (100 mL). The combined filtrates were evaporated in vacuo to give the product **14a**.

Yield: 20.1 g (98%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 4 H), 7.25–7.19 (m, 1 H), 3.65 (d, *J* = 13.4 Hz, 1 H), 3.25 (d, *J* = 13.4 Hz, 1 H), 3.03 (t, *J* = 8.0 Hz, 1 H), 2.78 (d, *J* = 13.4 Hz, 1 H), 2.69 (d, *J* = 13.7 Hz, 1 H), 2.67–2.60 (m, 2 H), 2.18–2.01 (m, 2 H), 1.87 (s, 2 H), 1.80–1.69 (m, 1 H), 1.50–1.38 (m, 2 H), 1.38–1.30 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 139.8, 128.0, 127.8, 126.2, 68.7, 51.4, 51.3, 45.3, 39.5, 29.8, 20.2, 19.6.

MS (CI): *m*/*z* = 217 [MH^+].

Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.64; H, 9.69; N, 12.66.

(2-Benzyl-2-azabicyclo[4.2.0]octan-1-yl)methanamine (14b)

Prepared from **8b** using the procedure described above for **14a**.

Yield: 20.4 g (91%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 4 H), 7.25–7.16 (m, 1 H), 3.74 (d, *J* = 13.9 Hz, 1 H), 3.05 (t, *J* = 13.9 Hz, 1 H), 2.95 (d, *J* = 13.4 Hz, 1 H), 2.72 (d, *J* = 10.8 Hz, 1 H), 2.67 (d, *J* = 13.5 Hz, 1 H), 2.35–2.16 (m, 2 H), 2.05–1.93 (m, 1 H), 1.92–1.82 (m, 1 H), 1.77 (s, 2 H), 1.57–1.48 (m, 1 H), 1.48–1.41 (m, 1 H), 1.41–1.29 (m, 2 H), 1.30–1.18 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 139.6, 128.1, 128.0, 127.7, 127.6, 126.1, 60.4, 52.9, 47.8, 45.3, 35.6, 28.6, 23.3, 22.1, 21.2.

MS (CI): *m*/*z* = 231 [MH^+].

Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 77.93; H, 9.31; N, 11.97.

***tert*-Butyl (2-Azabicyclo[3.2.0]heptan-1-ylmethyl)carbamate (15a)**

To a solution of **14a** (20.6 g, 95.4 mmol) in anhyd CH_2Cl_2 (200 mL), Et_3N (15.6 mL, 114 mmol) was added. The reaction mixture was cooled to 10 °C, and a solution of Boc_2O (22.8 g, 105 mmol) in anhyd CH_2Cl_2 (100 mL) was added. The resulting mixture was stirred at r.t. overnight, then washed with H_2O (2 × 500 mL). The organic phase was dried over Na_2SO_4 and evaporated in vacuo.

$(NH_2)_4CO_3$ (27.9 g, 0.441 mol) and MeOH (300 mL) were added to the residue, followed by 5% Pd/C (26.5 g). The mixture was refluxed for 3 h, and then cooled. The catalyst was filtered off, and the filtrates were evaporated in vacuo. Then 5% aq NaOH was added to pH 12, and the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with H_2O, dried over Na_2SO_4, and evaporated in vacuo to give **15a**.

Yield: 14.7 g (68%); white powder; mp 75–77 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.96 (br s, 0.9 H), 4.77 (br s, 0.1 H), 3.41–3.26 (m, 1 H), 3.26–3.10 (m, 3 H), 2.55–2.43 (m, 1 H), 2.04–1.91 (m, 2 H), 1.81–1.69 (m, 1 H), 1.69–1.59 (m, 1 H), 1.52 (dd, *J* = 12.1, 4.3 Hz, 1 H), 1.46–1.37 (m, 1 H), 1.40 (s, 9 H), 1.35–1.25 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.0, 78.4, 65.3, 46.5, 45.6, 39.3, 32.5, 29.2, 27.9, 18.7.

MS (EI): *m*/*z* = 170 [$M^+ - C_4H_8$], 57 [$C_4H_9^+$].

Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.85; H, 9.69; N, 12.49.

***tert*-Butyl (2-Azabicyclo[4.2.0]octan-1-ylmethyl)carbamate (15b)**

Prepared from **14b** using the procedure described above for **15a**.

Yield: 14.8 g (73%); yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.02 (br s, 0.8 H), 4.83 (br s, 0.2 H), 3.13 (dd, *J* = 13.1, 4.4 Hz, 1 H), 3.04 (dd, *J* = 12.8, 6.0 Hz, 1 H), 2.82–2.70 (m, 1 H), 2.65–2.50 (m, 1 H), 2.07–1.93 (m, 1 H), 1.83–1.62 (m, 5 H), 1.55–1.42 (m, 2 H), 1.39 (s, 9 H), 1.34–1.23 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.1, 78.3, 56.1, 46.5, 40.6, 33.8, 28.0, 27.9, 25.3, 22.5, 20.2.

MS (EI): *m*/*z* = 184 [$M^+ - C_4H_8$], 167 [M^+ – Boc], 110 [$M^+ - CH_2NHBoc$].

Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.97; H, 10.07; N, 11.66. Found: C, 64.82; H, 9.82; N, 12.03.

2-Azabicyclo[4.2.0]octane Hydrochloride (10b·HCl)

Prepared from **8b** using the procedure described above for **9a**·HCl.

Yield: 26.2 g (53%); colorless solid; mp 143–147 °C (dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.60 (br s, 1 H), 9.22 (br s, 1 H), 3.69–3.59 (m, 1 H), 3.09–2.95 (m, 1 H), 2.86–2.72 (m, 1 H), 2.56–2.45 (m, 1 H), 2.28–2.15 (m, 1 H), 2.13–2.00 (m, 1 H), 1.94–1.66 (m, 4 H), 1.59–1.42 (m, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 48.3, 39.3, 31.2, 23.5, 22.7, 22.3, 18.4.

MS (CI): *m*/*z* = 112 [MH^+].

Anal. Calcd for $C_7H_{14}ClN$: C, 56.94; H, 9.56; N, 9.49; Cl, 24.01. Found: C, 56.91; H, 9.91; N, 9.64; Cl, 23.77.

***tert*-Butyl Benzyl[3-(2-oxocyclobutyl)propyl]carbamate (*N*-Boc-12b)**

N-Boc-**12b** was isolated from the crude product obtained by hydrolysis of **8b** (0.500 g, 2.36 mmol) as described above (6 M aq HCl, reflux, 18 h). The residue after evaporation of the reaction mixture was dissolved in anhyd CH_2Cl_2 (30 mL), and Et_3N (2.32 mL, 16.9 mmol) was added. The reaction mixture was cooled to 10 °C, and a solution of Boc_2O (3.38 g, 15.6 mmol) in anhyd CH_2Cl_2 (15 mL) was added. The resulting mixture was stirred at r.t. overnight, then washed with H_2O (2 × 50 mL). The organic phase was dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by using flash chromatography (silica gel, hexane–*t*-BuOMe, 4:1).

Yield: 0.351 g (47%); yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 2 H), 7.25–7.14 (m, 3 H), 4.38 (br s, 2 H), 3.31–3.04 (m, 3 H), 3.02–2.94 (m, 1 H), 2.91–2.79 (m, 1 H), 2.18–2.06 (m, 1 H), 1.68–1.31 (m, 14 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 211.8 and 211.6, 155.9 and 155.6, 138.5, 128.5, 127.7, 127.1, 79.7, 60.0, 50.4 and 49.9, 46.1, 44.4, 28.4, 26.8, 25.6 and 25.4, 16.9.

MS (CI): *m*/*z* = 218 [$MH^+ - CO_2 - C_4H_8$].

Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.83; H, 8.89; N, 4.62.

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Supporting Information

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