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Synthesis of Epibatidine Analogues Having a 2-Substituted 2-Azabicyclo[2.2.2]octane Skeleton

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The synthesis of 1-cyano-2-aza-[2.2.2]bicyclooctanes has been studied using the dynamic cyanide addition to cyclohexanone derivatives. These compounds were further elaborated into a new class of epibatidine derivatives from which a number of examples were fully deprotected to give the potentially active compounds. The highly hydrophilic character of the compounds resulted in a difficult isolation and purification of the epibatidine analogues.

Introduction

Chronic pain presents a major challenge to the citizens and economy of Europe, as one in five Europeans is estimated to suffer from chronic pain, and this burden is likely to worsen with an ageing population and a greater pressure for people to work longer.[1–3] Current pain management is mostly reliant on pharmacological intervention, using analgesics [(non)-opioids, e.g., morphine (**1**) and codeine (**2**)] and NSAIDs (non-steroidal anti-inflammatory drugs), as well as adjuvant therapies such as antidepressants and anticonvulsants.

Given the complexity and unfavourable side-effects of pain treatment, combined with a high cost, the development of new drug candidates to counter chronic pain is still of paramount value for the industry.[4] One strategy focusses on interaction with neuronal nicotinic acetylcholine receptors (nAChRs),[5] pentameric ion channels structurally composed of 17 subunits [α(1–10), β(1–4), γ, δ, and ε].[6] The predominant receptor subtypes in the central nervous system (CNS) are of the α4β2 and α7 varieties, whereas the α3β4 receptor subtype predominates in the peripheral nervous system.[7,8] Of these receptor subtypes, the first accounts for approximately 90% of all nAChRs.[4] In 1974, Daly et al. discovered that alkaloids extracted from the skin of the Ecuadorian tree frog *Epipedobates tricolor* produced a Straub tail response in mice (a rigid, erect, S-shaped tail), similar to that produced by opioids.[9] The alkaloid epibatidine (**3**) was shown to have an analgesic potency about 200 times higher than that of morphine (**1**). The high potency of epibatidine (**3**) spurred interest in this field. However, the toxicity of the natural product is too high for it to be used clinically.[10] Many analogues have been synthesized, aiming to reduce the toxicity, while maintaining or improving the efficacy of the compound (the so-called therapeutic ratio). Epiboxidine (**4**) and ABT-594 (**5**) are among the most successful examples (Figure 1).[11]

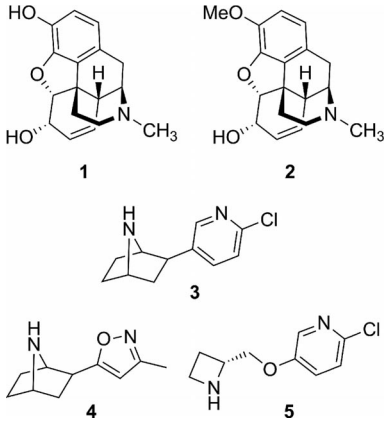

Figure 1. Morphine (**1**), codeine (**2**), epibatidine (**3**), epiboxidine (**4**), and ABT-594 (**5**).

Moreover, the 2-azabicyclo[2.2.2]octane core or isoquinuclidine skeleton is omnipresent in nature. A series of plant alkaloids with a variety of interesting properties have been isolated. Ibogaine (**6**), isolated from the root of the African plant *Tabernanthe iboga*, is a tricyclic secondary plant metabolite that causes hallucinations. However, despite these side-effects, it has been used in the treatment of opiate, nicotine, and alcohol addiction.[12] Another interesting alkaloid is dioscorine (**7**), the prototype molecule from *Dioscorea hispida*, a tropical yam and edible tuber. This toxic alkaloid shows insecticidal and antifeedant properties

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through interaction with the AChRs and suppression of the central nervous system (Figure 2).[13] Several synthetic routes towards the isoquinuclidine scaffold have been reported, the majority of which used a Diels–Alder cycloaddition[14] or an intramolecular ring closure.[15]

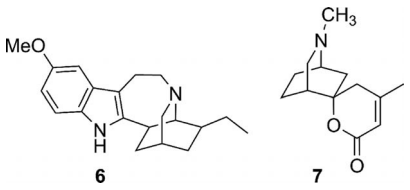
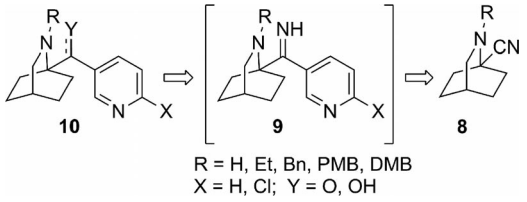


Figure 2. Ibogaine (**6**) and dioscorine (**7**).

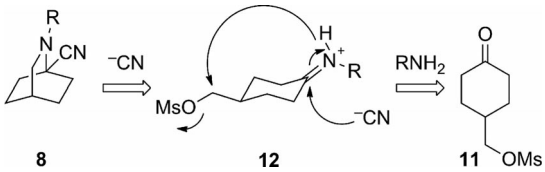
By combining these two structural moieties, the azabicyclo[2.2.2]octane skeleton and the pyridyl side-chain, we have developed a new series of epibatidine analogues. This paper highlights the different synthetic strategies towards these epibatidine analogues, starting from the interesting 2-substituted 2-azabicyclo[2.2.2]octane-1-carbonitriles **8**, as presented in Scheme 1. To preserve epibatidine's very important "internitrogen distance" of approximately 5.5 Å, an extra carbon atom was introduced between the pyridine substituent and the azabicycle.



Scheme 1. Retrosynthetic approach (PMB = 4-methoxybenzyl; DMB = 2,4-dimethoxybenzyl).

Results and Discussion

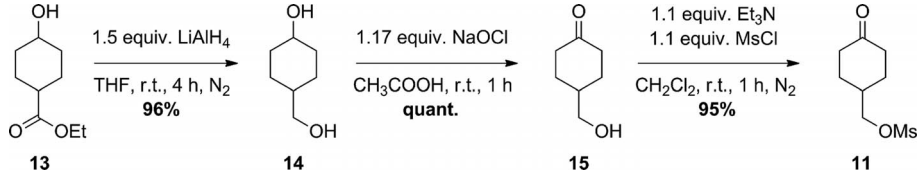
A new strategy towards scaffold **8** was pursued, implementing our cyanide-induced dynamic intramolecular cyclization reaction.[16–18] The synthesis of the precursor 4-(methanesulfonyloxymethyl)cyclohexanone (**11**) was designed such that the bicyclic core would be formed in a single reaction step (Scheme 2).



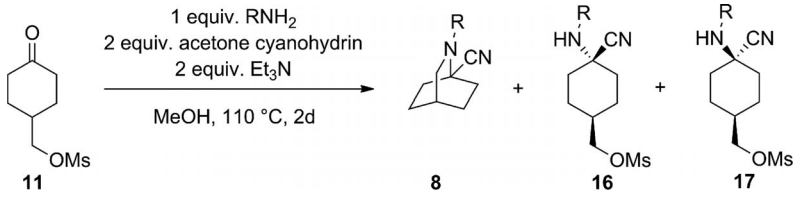
Scheme 2. Retrosynthetic analysis of **8**.

First, the envisaged precursor (i.e., **11**) was prepared from commercially available racemic ethyl 4-hydroxycyclohexane-1-carboxylate (**13**) by reduction of the ester moiety with lithium aluminium hydride to give the corresponding diol (i.e., **14**) in nearly quantitative yield, followed by selective oxidation of the secondary alcohol in the presence of sodium hypochlorite in glacial acetic acid to give ketone **15**.[19] Final mesylation to transform the alcohol functionality into a good leaving group led to precursor **11** in an overall yield of 90% (Scheme 3).

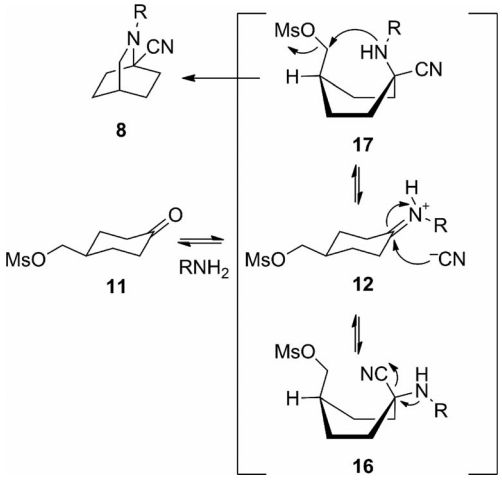
Having synthesized precursor **11**, several experiments were carried out to construct the isoquinuclidine core, using our cyanide-induced dynamic intramolecular cyclization reaction with acetone cyanohydrin as a hydrogen cyanide source.[17] 4-(Methanesulfonyloxymethyl)cyclohexanone (**11**) in dry methanol was treated with a primary amine, triethylamine, and acetone cyanohydrin in a sealed pressure vial at 110 °C for 2 d (Scheme 4). The mechanism of ring closure is illustrated below (Scheme 5). If the reaction was stopped after a few hours of reflux, adduct **16** and/or **17** was the major component of the mixture, along with traces of the bicyclic end product (i.e., **8**). It is especially noteworthy that only the *cis* isomer (i.e., **17**) allows the ring closure to give the envisaged isoquinuclidine skeleton (i.e., **8**) to take place. When the reaction time was prolonged to 2 d, azabicyclic compound **8** was isolated as the major product, but still some of adducts **16** and/or **17** could be detected, depending on the R group.



Scheme 3. Precursor synthesis.

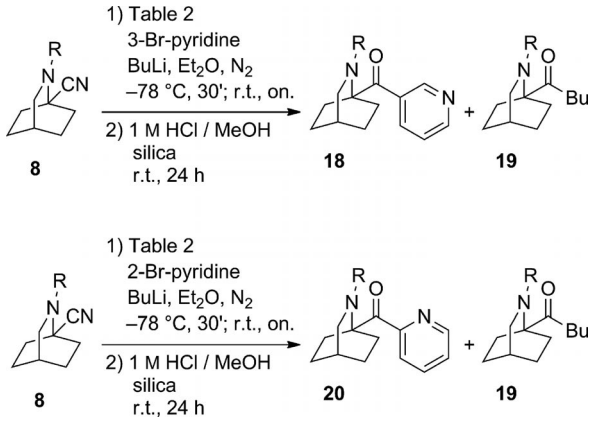


Scheme 4. Synthesis of azabicyclic core **8**.



Scheme 5. Reaction mechanism.

cleophilic attack of a pyridin-2-yl group onto the nitrile, however, proved to be more efficient.



Scheme 6. Synthesis of epibatidine analogues.

After extraction with sodium hydrogen carbonate, the crude bicyclic products **8** could be purified by column chromatography or recrystallization from methanol, the latter method being less time-consuming. Using a variety of primary amines, a range of derivatives was successfully prepared in moderate to good yields, as shown in Table 1. The significant discrepancy in yield between entries 1 and 7 can be attributed to a difficult isolation in the latter case.

Because of the introduction of a chloropyridyl side-chain and its subsequent deprotection were troublesome in a previously reported series of epibatidine analogues,[17] and because it is known that omitting the chlorine atom does not greatly affect the binding affinity towards the nAChRs,[20] only 2- and 3-bromopyridine were evaluated as pyridyl nucleophiles for this series of epibatidine derivatives.

Avenoza et al. published a reaction sequence towards α-aminoketones using organolithium reagents derived from 3-bromopyridine.[21] Based on these published results, along with our own experience of introducing a 2- or 3-pyridyl side-chain in previous series of compounds,[18] we developed an analogous route starting from the 2-substituted 2-azabicyclo[2.2.2]octane-1-carbonitriles (i.e., **8**; Scheme 6). An overview of the compounds synthesized and their yields is presented in Table 2. In none of the cases could complete consumption of the starting material be obtained. The nu-

The imines formed by the nucleophilic attack of the pyridyl anion onto the nitrile functionality proved to be quite resistant to acidic hydrolysis, and intermediate ketimine **18d′** could be isolated in 30% yield by column chromatography instead of the expected product, **18d** (^{1}H NMR spectroscopic analysis, recorded in $CDCl_3$; C_qCHN at δ = 9.1 ppm instead of δ = 9.8 ppm for the ketone). Further hydrolysis of **18d′** resulted in the formation of the desired ketone (i.e., **18d**; Scheme 7). However, when the reaction was performed on a smaller scale, no imine was detected, and **18d** was obtained directly (Table 2). Consequently, the hydrolysis was found to be a critical step in obtaining the epibatidine analogues in good yields. It must be carried out for 24 h to guarantee the transformation of the imine into the ketone.

To enhance the potential activity or binding affinity with the nAChRs, the nitrogen atom of the bicyclic core had to be deprotected. Large groups, e.g., benzyl, *p*-methoxybenzyl, or 2,4-dimethoxybenzyl, prevent efficient interaction, and thus reduce the activity of the analogues. Based on our experience of removing the benzyl groups from our previous series of epibatidine analogues, the current series were deprotected using a reductive deprotection strategy as shown in Scheme 8. The use of ammonium formate and palladium on carbon (10 wt.-%) led to the complete re-

Table 1. , yields of 2-substituted 2-azabicyclo[2.2.2]octane-1-carbonitriles **8**.

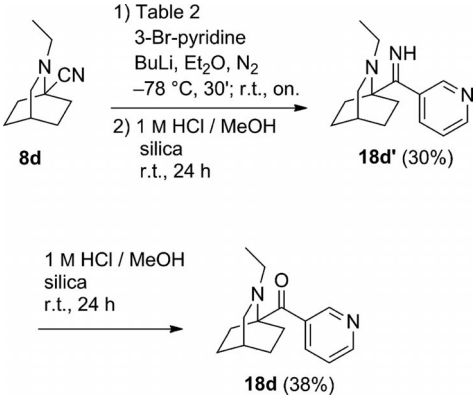
	R	Compd.	Yield of **8** [%]	Compd. **16/17**	Yield of **16/17** [%]
1	Bn	**8a**	83[a]	**a**	–
2	PMB	**8b**	72[b]	**b**	–
3	2,4-DMB	**8c**	59[b]	**c**	–
4	Et	**8d**	73[a,d]	**d**	–
5	pyridin-2-ylmethyl	**8e**	68[c]	**e**	9[e]
6	pyridin-3-ylmethyl	**8f**	55[c]	**f**	17[e]
7	pyridin-4-ylmethyl	**8g**	25[a]	**g**	25[e]

[a] Yield after column chromatography (SiO_2). [b] Yield after recrystallization. [c] Determined from the ^{1}H NMR spectrum of the crude material, co-elution impeded further purification. [d] Given the volatile properties of $EtNH_2$, 2 equiv. of RNH_2 were used. [e] Determined from the ^{1}H NMR spectrum of the crude material.

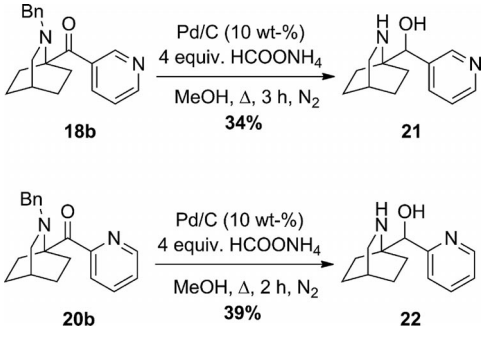
Table 2. Synthesis of 2-substituted 1-pyridinylcarbonyl-2-azabicyclo[2.2.2]octanes using 2- or 3-bromopyridine.

Entry	R		Time/temp. After adding **8**	Compound **8** [%][a]	Compound **19** [%][a]	Compound **18** or **20** [%]
18 Using 3-bromopyridine						
1	PMB	**a**	30 min, –78 °C; overnight, room temp.	36	8	56[b]
2	Bn	**b**	30 min, –78 °C; overnight, room temp.	45	18	37[b]
3	2,4-DMB	**c**	30 min, –78 °C; overnight, room temp.	49	12	31[c]
4	Et	**d**	30 min, –78 °C; overnight, room temp.	15	47	38[b]
20 Using 2-bromopyridine						
5	PMB	**a**	30 min, –78 °C; overnight, room temp.	16	20	64[b]
6	Bn	**b**	30 min, –78 °C; overnight, room temp.	15	18	63[c]
7	Et	**c**	30 min, –78 °C; overnight, room temp.	17	21	62[b]

[a] Determined from the ^{1}H NMR spectrum of the crude material. [b] Yield after column chromatography (SiO_2). [c] Yield after recrystallization.



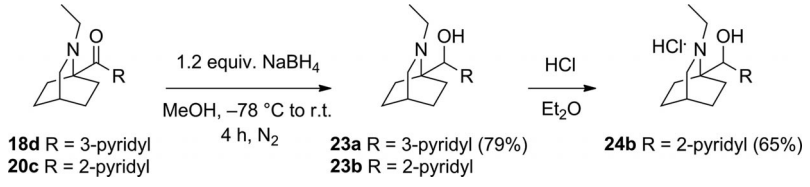
Scheme 7. Synthesis of intermediate ketimine **18d′**.



Scheme 8. Deprotection of epibatidine analogues **18b** and **20b**.

moval of the benzyl group within 3 h. In the presence of the palladium catalyst, ammonium formate decomposes to produce the reducing agent, hydrogen gas, along with carbon dioxide and ammonia. The reaction times are especially noteworthy, and they varied depending on the substrate, as shown in Scheme 8. Unnecessary extension of the reaction time led only to decomposition of the final product in the reaction medium.

Given the difficulties associated with deprotection, and since QSAR (quantitative structure–activity relationship) studies of epibatidine analogues have shown that derivatives with small alkyl groups on the nitrogen atom may still show activity against the nAChRs,[22] ethyl-protected compounds were further derivatized by reducing the carbonyl moiety to the corresponding racemic alcohol with sodium borohydride in dry methanol. When necessary, an extra purification step was implemented to isolate the racemic alcohol as its hydrochloride salt (i.e., **24b**) in 65% yield, using a saturated solution of hydrochloric acid in ether. Two such deriv-



Scheme 9. Derivatisation of analogues **18d** and **20c**.

Table 3. Screening of ligand-gated ion channel and CNS-related receptor modulatory activity at 1 μM concentration. Values below 30% are considered to be insignificant

Receptor	Inhibition [%]						
	18d	**20b**	**20c**	**21**	**22**	**23a**	**24b**
D1(h)[a]	4	–11	–14	–13	–10	–13	–24
D3(h)[a]	2	7	0	–20	2	–8	5
D3(h)[b]	4	–12	7	12	6	–2	5
D5(h)[a]	–9	–2	7	–3	11	6	8
D5(h)[b]	0	–14	–65	–5	7	–9	–14
N neuronal α-BGTX-insensitive (α4β2)[b]	7	–6	–4	–1	–6	–5	–2
N neuronal α-BGTX-sensitive (α7)[a]	9	–15	–12	–11	–5	–7	–2
N muscle-type (h)[a]	4	7	8	6	0	–1	1

[a] Antagonist radioligand. [b] Agonist radioligand.

atives were prepared accordingly, and an overview of the yields is given in Scheme 9.

Seven analogues containing the 2-azabicyclo[2.2.2]octane skeleton were selected and evaluated for their biological activity. To get a general idea of the activity profile of these compounds, they were submitted to a series of competitive binding assays. A series of neurotransmitter recognition sites relevant to the pharmacology of nicotinic acetylcholine receptors was chosen as a testing panel. Representatives of the major classes, the ligand-gated ion channels (nicotinic acetylcholine) and other CNS-related receptors relevant to pain mechanisms such as the dopaminic receptors were included.[23] The percentage inhibition was obtained from a competitive binding assay using known radioligands, and the results are shown in Table 3. Values are expressed as the percentage decrease of control-specific binding in the presence of the compounds, as determined by scintillation counting. As can be seen from Table 3, no significant (>30%) binding to any of these receptors could be detected for the selected compounds.

Conclusions

The results described clearly show the utility of 4-(methanesulfonyloxymethyl)cyclohexanone as a building block for the construction of the 2-azabicyclo[2.2.2]octane skeleton, using our cyanide-induced dynamic intramolecular cyclization reaction. This cyclohexanone forms the ideal precursor for the synthesis in only four steps of the isoquinuclidine skeleton that is omnipresent in nature. Due to the versatility of the interesting nitrile derivative, a new series of epibatidine analogues could be synthesized, starting from 2-substituted 2-azabicyclo[2.2.2]octane-1-carbonitriles. A lithium–halogen exchange to prepare a pyridyl nucleophile plays a central role in the route towards these interesting rigid skeletons. The azabicyclo[2.2.2]octane epibatidine derivatives did not show significant activity as potential analgesic compounds.

Experimental Section

General Remarks: High-resolution ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with a Jeol JNM-EX 300 NMR spectrometer. Peaks were assigned with the aid of DEPT, 2D-HSQC, and 2D-COSY spectra. The compounds were dissolved in deuterated solvents, and the solvent used is indicated for each compound. Multiplicities are indicated using the following abbreviations: s singlet, d doublet, t triplet, q quadruplet, quint quintuplet, sext sextuplet, sept septuplet, oct octuplet, non nonuplet, m multiplet, br. broad, ~ resembles. Low-resolution mass spectra were recorded with an Agilent 1100 Series VS (ES, 4000V) mass spectrometer. Infrared spectra were recorded with a Perkin–Elmer Spectrum BX FTIR spectrometer. Compounds were analyzed in neat form with an ATR (Attenuated Total Reflectance) accessory. Only selected absorbances ($\tilde{\nu}$) are reported. Melting points of crystalline compounds were measured with a Büchi 540 apparatus. The purification of reaction mixtures was performed by flash chromatography using a glass column with silica gel (Acros, particle size 0.035–0.070 mm, pore diameter ca. 6 nm).

4-(Hydroxymethyl)cyclohexanol (14): A suspension of $LiAlH_4$ (1.5 equiv., 3.31 g, 87.1 mmol) in dry THF (300 mL) was stirred at 0 °C under an inert nitrogen atmosphere. A solution of commercially available ethyl 4-hydroxycyclohexane-1-carboxylate **13** (1 equiv., 10.00 g, 58.1 mmol) in dry THF (50 mL) was carefully added dropwise to the solution, using a dropping funnel with a bypass. After the addition was complete, the cooling equipment was removed, and the reaction mixture was stirred at room temperature for 4 h. Then, water was added carefully to neutralize the excess lithium aluminium hydride. The solution was dried with magnesium sulfate, and then the solids were removed by filtration. Evaporation of the filtrate under reduced pressure gave pure diol **14** (7.60 g, 96%) as a translucent oil. The spectroscopic data were consistent with literature data.[24]

4-(Hydroxymethyl)cyclohexanone (15): In a 250 mL flask, **14** (1 equiv., 7.60 g, 58.1 mmol) was dissolved in glacial acetic acid (40 mL), and then commercially sourced sodium hypochlorite solution (La Croix Traditional Bleach, 39.93 g/L; 1.17 equiv., 127 mL, 68 mmol) was carefully added at room temperature. The mixture was stirred form 1 h, and then the solvent was removed in vacuo. The oily residue was re-dissolved in dry diethyl ether (50 mL) to precipitate the salts. The solids were removed by filtration, and the filtrate was evaporated to give compound **15** (7.44 g; quantitative yield) as a colourless oil, with a purity of 94%. IR: $\tilde{\nu}$ = 1705 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.45 (dq, J = 12.1, J = 5.5 Hz, 2 H, 2 CHCH_aH$_b$), 1.89–2.06 (m, 1 H, CH), 2.08–2.13 (m, 2 H, 2 CHCH$_a$$H_b$), 2.34–2.48 (m, 4 H, 2 COCH_2), 3.58 (d, J = 6.6 Hz, 2 H, CH_2OH), 5.27 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.12 (2 CHCH$_a$H$_b$), 38.51 (CH), 40.38 (2 COCH$_2$), 66.54 (CH$_2$OH), 212.88 (C=O) ppm. MS (ES): *m*/*z* (%) = 129 (100) [M + H]$^+$, 130 (20). HRMS (ESI): calcd. for $C_7H_{13}O_2$

[M + H]$^+$ 129.0916; found 129.0919. Chromatography, 30:70, EtOAc/petroleum ether; R_f = 0.10.

4-(Methanesulfonyloxymethyl)cyclohexanone (11): In an oven-dried 250 mL flask, compound **15** (1 equiv., 7.40 g, 58.1 mmol) was dissolved in dry dichloromethane (150 mL) together with triethylamine (1.1 equiv., 6.47 g, 63.9 mmol). The mixture was cooled to 0 °C under an inert nitrogen atmosphere. A solution of mesyl chloride (1.1 equiv., 7.32 g, 63.9 mmol) in dry dichloromethane (50 mL) was added dropwise, and then the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was poured into a saturated $NaHCO_3$ solution, and then the mixture was extracted with CH_2Cl_2 (2× 50 mL). The combined organic extracts were dried with $MgSO_4$. The solvent was removed in vacuo, and the residue was recrystallized from ethyl acetate to give compound **11** (11.4 g; 95%) as white crystals. The crystals needed to be stored at –18 °C, as they were unstable at room temperature. IR: $\tilde{\nu}$ = 1705 (C=O), 1344, 1339 (S=O), 932 (S-O). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.54 (dq, J = 12.4, J = 5.2 Hz, 2 H, 2 CHCH_aH$_b$), 2.11–2.30 (m, 3 H, CH, 2 CHCH$_a$$H_b$), 2.31–2.48 (m, 4 H, 2 COCH_2), 3.05 [s, 3 H, CH_3 (Ms)], 4.16 (d, J = 6.6 Hz, 2 H, CH_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.67 (2 CHCH$_a$H$_b$), 35.86 (CH), 37.42 [CH$_3$ (Ms)], 39.94 (2 COCH$_2$), 72.70 (CH$_2$O), 210.34 (C=O) ppm. MS (ES): m/z (%) = 224 (100) [M + NH$_4^+$]. HRMS (ESI): calcd. for $C_8H_{17}NO_4S$ [M + NH$_4$]$^+$ 223.0878; found 223.0192, m.p. 66.2–68.3 °C.

2-Substituted 2-Azabicyclo[2.2.2]octane-1-carbonitriles (8): In a dry, pressure-resistant 150 mL vial, 4-(methanesulfonyloxymethyl)cyclohexanone (**11**; 1 equiv., 14.7 mmol, 3.00 g), a primary amine (1 equiv., 14.7 mmol), acetone cyanohydrin (2 equiv., 2.50 g, 29.4 mmol), and triethylamine (2 equiv., 2.98 g, 29.4 mmol) were dissolved in dry methanol (100 mL). When using pure ethylamine, the volatile amine (2 mL, 30 mmol) was used. The vessel was closed and heated to 110 °C for 2 d. The reaction mixture was poured into a saturated $NaHCO_3$ solution, the mixture was extracted with dichloromethane (3× 50 mL), and the combined organic extracts were dried with $MgSO_4$. The crude 2-substituted 2-azabicyclo[2.2.2]octane-1-carbonitriles **8** could be further purified by column chromatography or by recrystallization from methanol.

2-Benzyl-2-azabicyclo[2.2.2]octane-1-carbonitrile (8a): Yield 83%. IR: $\tilde{\nu}$ = 2237 (C≡N), 1494, 1454 (Ph). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.56–1.78 (m, 5 H, 2 CHCH_2, CH), 1.99 (dt, J = 12.0, J = 4.4 Hz, 2 H, 2 CH_aH$_b$), 2.33–2.45 (m, 2 H, 2 CH$_a$$H_b$), 2.62 (br. s, 2 H, CHC$H_2$N), 3.96 (s, 2 H, NC$H_2$Ph), 7.22–7.39 [m, 5 H, 5 CH (Ph)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.21 (2 CHCH$_2$), 25.00 (CH), 30.27 (2 C$_q$CH$_a$H$_b$), 52.42 (C_q), 55.11 (CHCH$_2$N), 59.02 (NCH$_2$Ph), 122.19 (C≡N), 127.18 [CH (Ph)], 128.38 [2 CH (Ph)], 128.81 [2 CH (Ph)], 138.67 [C_q (Ph)] ppm. MS (ES): m/z (%) = 227 (100) [M + H]$^+$, 228 (15). $C_{15}H_{18}N_2$ (226.32): calcd. C 79.6, H 8.0, N 12.4; found C 79.2, H 7.9, N 12.1, m.p. 99.3 °C. Chromatography, 10:90, EtOAc/petroleum ether; R_f = 0.30. Yellow crystals.

2-(4-Methoxybenzyl)-2-azabicyclo[2.2.2]octane-1-carbonitrile (8b): Yield 72%. IR: $\tilde{\nu}$ = 2234 (C≡N), 1610, 1586, 1510 (Ar). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.56–1.77 (m, 5 H, 2 CHCH_2, CH), 1.97 (dt, J = 12.1, J = 4.4 Hz, 2 H, 2 CH_aH$_b$), 2.31–2.44 (m, 2 H, 2 CH$_a$$H_b$), 2.60 (br. s, 2 H, CHC$H_2$N), 3.79 [s, 3 H, OC$H_3$ (Ar)], 3.89 (s, 2 H, NCH_2Ar), 6.86 [d, J = 8.3 Hz, 2 H, 2 CH (Ar)], 7.28 [d, J = 8.3 Hz, 2 H, 2 CH (Ar)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.22 (2 CHCH$_2$), 25.00 (CH), 30.26 (2 C$_q$CH$_a$H$_b$), 52.33 (C_q), 54.90 (CHCH$_2$N), 55.36 [OCH$_3$ (Ar)], 58.30 (NCH$_2$Ar), 113.76 [2 CH (Ar)], 122.26 (C≡N), 129.94 [2 CH (Ar)], 130.66 [C_q (Ar)], 158.83 [C_q (Ar)] ppm. MS (ES): m/z (%) = 257 (100) [M + H]$^+$, 258 (15). $C_{16}H_{20}N_2O$ (256.35): calcd. C 75.0, H 7.9, N 10.9; found C 74.7, H 8.3, N 10.5, m.p. 75.0 °C. Chromatography, 10:90, EtOAc/petroleum ether; R_f = 0.26. Yellow crystals.

2-(2,4-Dimethoxybenzyl)-2-azabicyclo[2.2.2]octane-1-carbonitrile (8c): Yield 59%. IR: $\tilde{\nu}$ = 2238 (C≡N), 1611, 1586, 1504 (Ar). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.56–1.80 (m, 5 H, 2 CHCH_2, CH), 1.98 (dt, J = 12.1, J = 4.4 Hz, 2 H, 2 CH_aH$_b$), 2.35–2.48 (m, 2 H, 2 CH$_a$$H_b$), 2.71 (br. s, 2 H, CHC$H_2$N), 3.80 [s, 3 H, OC$H_3$ (Ar)], 3.81 [s, 3 H, OCH_3 (Ar)], 3.93 (s, 2 H, NCH_2Ar), 6.43 [d, J = 2.2 Hz, 1 H, C$_q$CHC$_q$ (Ar)], 6.48 [dd, J = 8.3, J = 2.2 Hz, 1 H, C$_q$CHCH (Ar)], 7.33 [d, J = 8.3 Hz, 1 H, C$_q$CHCH (Ar)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.21 (2 CHCH$_2$), 25.13 (CH), 30.38 (2 C$_q$CH$_a$H$_b$), 52.41 (C_q, NCH$_2$Ar), 55.16 (CHCH$_2$N), 55.46 [2 OCH$_3$ (Ar)], 98.44 [C$_q$CHC$_q$ (Ar)], 104.15 [C$_q$CHCH (Ar)], 119.35 [C_q (Ar)], 122.40 (C≡N), 130.46 [C$_q$CHCH (Ar)], 158.49 [C_q (Ar)], 159.87 [C_q (Ar)] ppm. MS (ES): m/z (%) = 151 (60), 152 (5), 287 (100) [M + H]$^+$, 288 (20). $C_{17}H_{22}N_2O_2$ (286.37): calcd. C 71.3, H 7.7, N 9.8; found C 70.9, H 8.0, N 9.7, m.p. 72.7 °C. Chromatography, 10:90, EtOAc/petroleum ether; R_f = 0.18. Orange crystals.

2-Ethyl-2-azabicyclo[2.2.2]octane-1-carbonitrile (8d): Yield 73%. IR: $\tilde{\nu}$ = 2241 (C≡N). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.12 [t, J = 7.2 Hz, 3 H, CH_3 (Et)], 1.56–1.77 (m, 5 H, 2 CHCH_2, CH), 1.85–1.96 (m, 2 H, 2 CH_aH$_b$), 2.24–2.36 (m, 2 H, 2 CH$_a$$H_b$), 2.75–2.78 (m, 2 H, CHCH_2N), 2.81 [q, J = 7.2 Hz, 2 H, NCH_2 (Et)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.34 [CH$_3$ (Et)], 24.11 (2 CHCH$_2$), 24.76 (CH), 29.93 (2 C$_q$CH$_a$H$_b$), 48.75 [NCH$_2$ (Et)], 52.40 (C_q), 54.61 (NCH$_2$), 122.02 (C≡N) ppm. MS (ES): m/z (%) = 165 (100) [M + H]$^+$, 166 (11). HRMS (ESI): calcd. for $C_{10}H_{17}N_2$ [M + H]$^+$ 165.1392; found 165.1390. Chromatography, 40:60, EtOAc/petroleum ether; R_f = 0.33. Yellow oil.

2-(Pyridin-4-ylmethyl)-2-azabicyclo[2.2.2]octane-1-carbonitrile (8g): Yield 25%. IR: $\tilde{\nu}$ = 2240 (C≡N), 1602, 1561, 1493 (pyr.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.59–1.80 (m, 5 H, m, 2 CHCH_2, CH), 1.95–2.07 (m, 2 H, 2 CH_aH$_b$), 2.33–2.45 (m, 2 H, 2 CH$_a$$H_b$), 2.64 (br. s, 2 H, CHC$H_2$N), 3.98 (s, 2 H, NC$H_2$pyr.), 7.32 [d, J = 5.5 Hz, 2 H, 2 CH (pyr.)], 8.56 [d, J = 5.5 Hz, 2 H, 2 CH (pyr.)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.91 (2 CHCH$_2$), 24.78 (CH), 30.09 (2 C$_q$CH$_a$H$_b$), 52.23 (C_q), 55.48 (CHCH$_2$N), 58.02 (NCH$_2$pyr.), 121.73 (C≡N), 123.50 [2 CH (pyr.)], 147.95 [C_q (pyr.)], 149.69 [2 CH (pyr.)] ppm. MS (ES): m/z (%) = 228 (100) [M + H]$^+$, 229 (15). HRMS (ESI): calcd. for $C_{14}H_{18}N_3$ [M + H]$^+$ 228.1501; found 228.1497. $C_{14}H_{17}N_3$ (227.31): calcd. C 74.0, H 7.5, N 18.5; found C 73.9, H 7.6, N 18.3, m.p. 43.3 °C. Chromatography, 30:70, EtOAc/petroleum ether; R_f = 0.19. Orange crystals.

2-Substituted 1-(Pyridin-3-ylcarbonyl)-2-azabicyclo[2.2.2]octanes (18): In a dry 50 mL flask, a 2-substituted 2-azabicyclo[2.2.2]-octane-1-carbonitrile **8** (1 equiv., 5.7 mmol) and 3-bromopyridine (1.1 equiv., 0.99 g, 6.3 mmol) were dissolved in dry diethyl ether (35 mL). The flask was placed under an inert N_2 atmosphere and cooled to –78 °C. Using a syringe, BuLi (2.5 M solution; 1.1 equiv., 2.5 mL, 6.3 mmol) was added over a period of 10 min. The reaction mixture was stirred for 30 min at –78 °C, and then it was allowed to slowly warm up to room temperature. The mixture was left stirring for 24 h. Methanol was added to neutralize the excess BuLi, and the volatile components were removed in vacuo. The reaction mixture was redissolved in a 1:1 mixture of methanol and HCl (1 M) (30 mL). Silica gel (0.5 g) was added to improve the hydrolysis, and the mixture was stirred for 24 h at room temperature. The pH of the solution was adjusted to 8 by the addition of a concentrated $NaHCO_3$ solution. Compound **18** was extracted using dichloromethane (3× 50 mL), and the combined organic extracts were dried with $MgSO_4$. The solids were removed by filtration, and the

volatile components were evaporated. The residue was purified by column chromatography to give compound **18**. Crystalline materials were recrystallized from methanol.

2-(4-Methoxybenzyl)-1-(pyridin-3-ylcarbonyl)-2-azabicyclo[2.2.2]-octane (18a): Yield 56%. IR: $\tilde{\nu}$ = 1674 (C=O), 1611, 1582, 1511 (Ar, pyr.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.62–1.85 (m, 7 H, 2 CHCH_2, CH, 2 CH_aH$_b$), 2.42–2.54 (m, 2 H, 2 CH$_a$$H_b$), 2.82 (br. s, 2 H, CHC$H_2$N), 3.54 (s, 2 H, NC$H_2$Ar), 3.75 [s, 3 H, OC$H_3$ (Ar)], 6.79 [d, J = 8.3 Hz, 2 H, 2 CH (Ar)], 7.12 [d, J = 8.3 Hz, 2 H, 2 CH (Ar)], 7.37 [dd, J = 8.3, J = 5.0 Hz, 1 H, C$_q$CHCH (pyr.)], 8.71 [~dd, J = 5.0, J = 1.7 Hz, 1 H, NCHCH (pyr.)], 8.76 [~dt, J = 8.3, J = 1.7 Hz, 1 H, C$_q$CHCH (pyr.)], 9.97 [d, J = 1.7 Hz, 1 H, C$_q$CHN (pyr.)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.64 (2 CHCH$_2$), 26.67 (CH), 27.93 (2 C$_q$$CH_aH_b$), 54.75 (CH$CH_2$N), 55.25 [O$CH_3$ (Ar)], 57.98 (NCH$_2$Ar), 65.28 (C_q), 113.71 [2 CH (Ar)], 123.15 [C$_q$CHCH (pyr.)], 129.54 [2 CH (Ar)], 130.64 [C_q (Ar)], 130.89 [C_q (pyr.)], 137.61 [C$_q$$C$HCH (pyr.)], 151.96 [C$_q$$C$HN (pyr.)], 152.84 [N$C$HCH (pyr.)], 158.63 [$C_q$ (Ar)], 202.59 (C=O) ppm. MS (ES): m/z (%) = 337 (100) [M + H]$^+$, 338 (28). HRMS (ESI): calcd. for $C_{21}H_{25}N_2O_2$ [M + H]$^+$ 337.1916; found 337.1909. Chromatography, 30:70, EtOAc/petroleum ether; R_f = 0.29. Yellow oil.

2-Benzyl-1-(pyridin-3-ylcarbonyl)-2-azabicyclo[2.2.2]octane (18b): Yield 37%. IR: $\tilde{\nu}$ = 1666 (C=O), 1580, 1494, 1476 (Ph, pyr.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.64–1.87 (m, 7 H, 2 CHCH_2, CH, 2 CH_aH$_b$), 2.45–2.56 (m, 2 H, 2 CH$_a$$H_b$), 2.85 (br. s, 2 H, CHC$H_2$N), 3.61 (s, 2 H, NC$H_2$Ph), 7.16–7.29 [m, 5 H, 5 CH (Ph)], 7.36 [dd, J = 7.7 Hz, J = 5.0 Hz, 1 H, C$_q$CHCH (pyr.)], 8.70 [d, J = 5.0 Hz, 1 H, NCHCH (pyr.)], 8.76 [~dt, J = 7.7, J = 1.7 Hz, 1 H, C$_q$CHCH (pyr.)], 9.97 [s, 1 H, C$_q$CHN (pyr.)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.64 (2 CHCH$_2$), 26.68 (CH), 28.00 (2 C$_q$$CH_aH_b$), 55.07 (CH$CH_2$N), 58.70 (N$CH_2$Ph), 65.33 ($C_q$), 123.16 [C$_qCHC$H (pyr.)], 126.98 [$C$H (Ph)], 128.39 [2 CH (Ph)], 128.41 [2 CH (Ph)], 130.90 [C_q (pyr.)], 137.61 [C$_q$$C$HCH (pyr.)], 138.70 [$C_q$ (Ph)], 152.03 [C$_q$$C$HN (pyr.)], 152.93 [N$C$HCH (pyr.)], 202.66 ($C$=O) ppm. MS (ES): m/z (%) = 307 (100) [M + H]$^+$, 308 (24). HRMS (ESI): calcd. for $C_{20}H_{23}N_2O$ [M + H]$^+$ 307.1810; found 307.1803. $C_{20}H_{22}N_2O$ (306.41): calcd. C 78.4, H 7.2, N 9.1; found C 78.3, H 7.6, N 9.1, m.p. 91.4 °C. Chromatography, 30:70, EtOAc/petroleum ether; R_f = 0.16. Yellow crystals.

2-(2,4-Dimethoxybenzyl)-1-(pyridin-3-ylcarbonyl)-2-azabicyclo-[2.2.2]octane (18c): Yield 31%. IR: $\tilde{\nu}$ = 1670 (C=O), 1613, 1591, 1581, 1504, 1457 (Ar, pyr.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.63–1.86 (m, 7 H, 2 CHCH_2, CH, 2 CH_aH$_b$), 2.43–2.57 (m, 2 H, 2 CH$_a$$H_b$), 2.92 (br. s, 2 H, CHC$H_2$N), 3.57 (s, 2 H, NC$H_2$Ar), 3.64 [s, 3 H, OC$H_3$ (Ar)], 3.77 [s, 3 H, OCH_3 (Ar)], 6.32 [d, J = 2.2 Hz, 1 H, C$_q$CHC$_q$ (Ar)], 6.44 [dd, J = 8.3, J = 2.2 Hz, 1 H, C$_q$CHCH (Ar)], 7.27 [d, J = 8.3 Hz, 1 H, C$_q$CHCH (Ar)], 7.29 [dd, J = 7.7, J = 5.0 Hz, 1 H, C$_q$CHCH (pyr.)], 8.64 [d, J = 5.0 Hz, 1 H, NCHCH (pyr.)]; 8.71 [~dt, J = 7.7, J = 1.7 Hz, 1 H, C$_q$CHCH (pyr.)], 9.87 [s, 1 H, C$_q$CHN (pyr.)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.61 (2 CHCH$_2$), 26.79 (CH), 28.13 (2 C$_q$$CH_aH_b$), 52.50 (N$CH_2$Ar), 55.05 [O$CH_3$ (Ar)], 55.37 (CHCH$_2$N), 55.40 [OCH$_3$ (Ar)], 65.39 (C_q), 98.14 [C$_q$$CHC_q$ (Ar)], 103.74 [C$_q$$C$HCH (Ar)], 119.19 [$C_q$ (Ar)], 122.92 [C$_q$CHCH (pyr.)], 129.74 [C$_q$CHCH (Ar)], 131.12 [C_q (pyr.)], 137.64 [C$_q$$C$HCH (pyr.)], 152.05 [C$_q$$C$HN (pyr.)], 152.52 [N$C$HCH (pyr.)], 158.22 [$C_q$ (Ar)], 159.64 [C_q (Ar)], 202.80 (C=O) ppm. MS (ES): m/z (%) = 367 (100) [M + H]$^+$. 368, (30). $C_{22}H_{26}N_2O_3$ (366.46): calcd. C 72.1, H 7.15, N 7.6; found C 72.1, H 7.3, N 7.4, m.p. 83.7 °C. Chromatography, 30:70, EtOAc/petroleum ether; R_f = 0.14. Orange crystals.

2-Ethyl-1-(pyridin-3-ylimino)-2-azabicyclo[2.2.2]octane (18d′): The importance of sufficient hydrolysis, and the resistance of the imine formed after nucleophilic attack of the pyridyllithium onto the nitrile moiety towards hydrolysis, was proved by isolation of compound **18d′** after column chromatography in 30% yield as a representative example. IR: $\tilde{\nu}$ = 1676 (C=N), 1607, 1582, 1448 (pyr.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.00 [t, J = 7.2 Hz, 3 H, CH_3 (Et)], 1.58–1.81 (m, 7 H, 2 CHCH_2, CH, 2 CH_aH$_b$), 2.05–2.19 (m, 2 H, 2 CH$_a$$H_b$), 2.48 [q, J = 7.2 Hz, 2 H, NCH_2 (Et)], 2.93 (br. s, 2 H, CHCH_2N), 7.28 [dd, J = 8.0, J = 5.0 Hz, 1 H, C$_q$CHCH (pyr.)], 8.20 [dt, J = 8.0, J = 1.7 Hz, 1 H, C$_q$CHCH (pyr.)], 8.60 [dd, J = 5.0, J = 1.7 Hz, 1 H, NCHCH (pyr.)], 9.10 [s, 1 H, C$_q$CHN (pyr.)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.61 [CH$_3$ (Et)], 24.85 (2 CHCH$_2$), 26.41 (CH), 28.55 (2 C$_q$$CH_aH_b$), 47.91 [N$CH_2$ (Et)], 54.33 (CHCH$_2$N), 61.51 (C_q), 122.70 [C$_q$CHCH (pyr.)], 135.32 [C_q (pyr.)], 135.84 [C$_q$$C$HCH (pyr.)], 149.47 [C$_q$$C$HN (pyr.)], 150.10 [N$C$HCH (pyr.)], 181.78 ($C$=N) ppm. MS (ES): m/z (%) = 244 (100) [M + H]$^+$, 245 (15). HRMS (ESI): calcd. for $C_{15}H_{22}N_3$ [M + H]$^+$ 244.1814; found 244.1817. Chromatography, 98:2, CH_2Cl_2/MeOH; R_f = 0.05. Yellow oil.

2-Ethyl-1-(pyridin-3-ylcarbonyl)-2-azabicyclo[2.2.2]octane (18d): Yield 38%. IR: $\tilde{\nu}$ = 1675 (C=O), 1580, 1448, 1412 (pyr.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.92 [t, J = 7.2 Hz, 3 H, CH_3 (Et)], 1.62–1.77 (m, 6 H, 2 CHCH_2, 2 CH_aH$_b$), 1.79–1.84 (m, 1 H, CH); 2.25–2.35 (m, 2 H, 2 CH$_a$$H_b$), 2.39 [q, J = 7.2 Hz, 2 H, NCH_2 (Et)], 2.94 (br. s, 2 H, CHCH_2N), 7.36 [dd, J = 7.7, J = 5.0 Hz, 1 H, C$_q$CHCH (pyr.)], 8.71 [dd, J = 5.0, J = 1.7 Hz, 1 H, NCHCH (pyr.)], 8.78 [dt, J = 7.7, J = 1.7 Hz, 1 H, C$_q$CHCH (pyr.)], 9.84 [s, 1 H, C$_q$CHN (pyr.)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.25 [CH$_3$ (Et)], 24.74 (2 CHCH$_2$, C$_q$$CH_aH_b$), 26.65 ($C$H), 27.95 (C$_q$$CH_aH_b$), 49.45 [N$CH_2$ (Et)], 54.87 (CHCH$_2$N), 65.59 (C_q), 123.04 [C$_q$CHCH (pyr.)], 131.32 [C_q (pyr.)], 137.73 [C$_q$$C$HCH (pyr.)], 152.14 [C$_q$$C$HN (pyr.)], 152.77 [N$C$HCH (pyr.)], 202.97 ($C$=O) ppm. MS (ES): m/z (%) = 196 (40), 245 (100) [M + H]$^+$, 246 (15). HRMS (ESI): calcd. for $C_{15}H_{21}N_2O$ [M + H]$^+$ 245.1654; found 245.1646. Chromatography, 30:70, EtOAc/petroleum ether; R_f = 0.20. Yellow oil.

2-Substituted 1-(Pyridin-2-ylcarbonyl)-2-azabicyclo[2.2.2]octanes (20): The protocol for the preparation of 2-substituted 1-(pyridin-2-ylcarbonyl)-2-azabicyclo[2.2.2]octanes **20** is similar to that for the synthesis of 2-substituted 1-(pyridin-3-ylcarbonyl)-2-azabicyclo [2.2.2]octanes **18**, except that 3-bromopyridine was replaced by 2-bromopyridine.

2-(4-Methoxybenzyl)-1-(pyridin-2-ylcarbonyl)-2-azabicyclo[2.2.2]-octane (20a): Yield 64%. IR: $\tilde{\nu}$ = 1685 (C=O), 1610, 1583, 1568, 1509, 1463 (Ar, pyr.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.62–1.83 (m, 5 H, 2 CHCH_2, CH), 1.96 (td, J = 12.0, J = 5.0 Hz, 2 H, 2 CH_aH$_b$), 2.61–2.73 (m, 2 H, 2 CH$_a$$H_b$), 2.77 (br. s, 2 H, CHC$H_2$N), 3.52 (s, 2 H, NC$H_2$Ar), 3.75 [s, 3 H, OC$H_3$ (Ar)], 6.73 [d, J = 8.8 Hz, 2 H, 2 CH (Ar)], 6.98 [d, J = 8.8 Hz, 2 H, 2 CH (Ar)], 7.37 [ddd, J = 7.7, J = 5.0, J = 1.1 Hz, 1 H, C$_q$CHCHCH (pyr.)], 7.75 [td, J = 7.7, J = 1.1 Hz, 1 H, C$_q$CHCH (pyr.)], 8.25 [dd, J = 7.7, J = 1.1 Hz, 1 H, C$_q$CH (pyr.)], 8.74 [d, J = 5.0 Hz, 1 H, NCH (pyr.)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.84 (2 CHCH$_2$), 26.88 (CH), 27.95 (2 C$_q$$CH_aH_b$), 55.07 (CH$CH_2$N), 55.34 [O$CH_3$ (Ar)], 58.42 (NCH$_2$Ar), 65.14 (C_q), 113.57 [2 CH (Ar)], 124.78 [C$_q$$C$H (pyr.)], 125.74 [C$_q$CHCH$C$H (pyr.)], 129.59 [2 CH (Ar)], 131.62 [C_q (Ar)], 136.39 [C$_q$CHCH (pyr.)], 149.04 [NCH (pyr.)], 155.00 [C_q (pyr.)], 158.58 [C_q (Ar)], 204.94 (C=O) ppm. MS (ES): m/z (%) = 337 (100) [M + H]$^+$, 338 (25). HRMS (ESI): calcd. for $C_{21}H_{25}N_2O_2$ [M + H]$^+$ 337.1916; found 337.1910. Chromatography, 30:70, EtOAc/petroleum ether; R_f = 0.12. Yellow oil.

2-Benzyl-1-(pyridin-2-ylcarbonyl)-2-azabicyclo[2.2.2]octane (20b): Yield 63%. IR: $\tilde{\nu}$ = 1681 (C=O), 1581, 1567, 1493, 1450 (Ph, pyr.).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.63–1.83 (m, 5 H, 2 CHCH_2, CH), 1.91–2.03 (m, 2 H, 2 CH_aH$_b$), 2.62–2.74 (m, 2 H, 2 CH$_a$$H_b$), 2.79 (br. s, 2 H, CHC$H_2$N), 3.60 (s, 2 H, NC$H_2$Ar), 7.05–7.10 [m, 2 H, 2 CH (Ph)], 7.13–7.22 [m, 3 H, 3 CH (Ph)], 7.35 [ddd, J = 7.7, J = 5.0, J = 1.1 Hz, 1 H, C$_q$CHCHCH (pyr.)], 7.73 [td, J = 7.7, J = 1.7 Hz, 1 H, C$_q$CHCH (pyr.)], 8.25 [dd, J = 7.7, J = 1.1 Hz, 1 H, C$_q$CH (pyr.)], 8.73 [dd, J = 5.0, J = 1.7 Hz, 1 H, NCH (pyr.)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.76 (2 CHCH$_2$), 26.82 (*C*H), 27.91 (2 C$_q$*C*H$_a$H$_b$), 55.27 (CH*C*H$_2$N), 59.05 (N*C*H$_2$Ar), 65.10 (*C$_q$*), 124.70 [C$_q$*C*H (pyr.)], 125.71 [C$_q$CHCH*C*H (pyr.)], 126.74 [*C*H (Ph)], 128.09 [2 *C*H (Ph)], 128.46 [2 *C*H (Ph)], 136.34 [C$_q$CH*C*H (pyr.)], 139.53 [*C$_q$* (Ph)], 148.98 [N*C*H (pyr.)], 154.89 [*C$_q$* (pyr.)], 204.82 (*C*=O) ppm. MS (ES): *m*/*z* (%) = 307 (100) [M + H]$^+$, 308 (29). HRMS (ESI): calcd. for $C_{20}H_{23}N_2O$ [M + H]$^+$ 307.1810; found 307.1803. $C_{20}H_{22}N_2O$ (306.41): calcd. C 78.4, H 7.2, N 9.1; found C 78.4, H 7.4, N 9.1, m.p. 74.4–74.8 °C. Chromatography, 30:70, EtOAc/petroleum ether; R_f = 0.25. Yellow crystals.

2-Ethyl-1-(pyridin-2-ylcarbonyl)-2-azabicyclo[2.2.2]octane (20c): Yield 62%. IR: $\tilde{\nu}$ = 1686 (C=O), 1581, 1567, 1462 (pyr.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.89 [t, J = 7.2 Hz, 3 H, CH_3 (Et)], 1.58–1.82 (m, 5 H, 2 CHCH_2, CH), 1.90 (td, J = 12.1, J = 5.0 Hz, 2 H, 2 CH_aH$_b$), 2.34–2.44 (m, 2 H, 2 CH$_a$$H_b$), 2.43 [q, J = 7.2 Hz, 2 H, NCH_2 (Et)], 2.93 (br. s, 2 H, CHCH_2N), 7.37 [dd, J = 7.7, J = 5.0 Hz, 1 H, C$_q$CHCHCH (pyr.)], 7.78 [td, J = 7.7, J = 1.1 Hz, 1 H, C$_q$CHCH (pyr.)], 8.47 [dd, J = 7.7, J = 1.1 Hz, 1 H, C$_q$CH (pyr.)], 8.73 [dd, J = 5.0, J = 1.1 Hz, 1 H, NCH (pyr.)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.39 [*C*H$_3$ (Et)], 24.68 (2 CHCH$_2$), 26.50 (*C*H), 27.65 (2 C$_q$*C*H$_a$H$_b$), 49.40 [N*C*H$_2$ (Et)], 56.11 (CH*C*H$_2$N), 65.19 (*C$_q$*), 125.15 [C$_q$*C*H (pyr.)], 125.64 [C$_q$CHCH*C*H (pyr.)], 136.17 [C$_q$CH*C*H (pyr.)], 149.24 [N*C*H (pyr.)], 154.16 [*C$_q$* (pyr.)], 203.70 (*C*=O) ppm. MS (ES): *m*/*z* (%) = 245 (100) [M + H]$^+$, 246 (20). HRMS (ESI): calcd. for $C_{15}H_{21}N_2O$ [M + H]$^+$ 245.1654; found 245.1650. Chromatography, 98:2, CH_2Cl_2/MeOH; R_f = 0.08. Yellow oil.

Removal of the N-Protecting Group: As a representative example, the synthesis of 1-(pyridin-3-ylhydroxymethyl)-2-azabicyclo[2.2.2]-octane (**21**) is described here. In a 25 mL flask, 2-benzyl-1-(pyridin-3-ylcarbonyl)-2-azabicyclo[2.2.2]octane (**18b**; 1 equiv., 0.18 g, 0.59 mmol) and ammonium formate (4 equiv., 0.15 g, 2.36 mmol) were dissolved in dry methanol (15 mL). Palladium on activated carbon (10 wt.-%; 0.05 g) was added, and the suspension was heated at reflux under an inert nitrogen atmosphere for 3 h. The heterogeneous mixture was filtered through Celite®, and the methanol was evaporated. Dichloromethane (5 mL) was added, and the excess of ammonium formate was removed by filtration. The dichloromethane was evaporated, and te residue was further purified by recrystallization from diethyl ether to give compound **21**. When 2-benzyl-1-(pyridin-2-ylcarbonyl)-2-azabicyclo[2.2.2]octane (**20b**) was used as a substrate for the reductive deprotection, the reaction was already complete after 2 h of reflux.

1-(Pyridin-3-ylhydroxymethyl)-2-azabicyclo[2.2.2]octane (21): Yield 34%. IR: $\tilde{\nu}$ = 3254 (NH), 3047 (br., OH), 1575, 1472, 1420 (pyr.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.22–1.34 (m, 2 H, 2 CHCH_aH$_b$), 1.34–1.84 (m, 7 H, 2 CHCH$_a$$H_b$, C$H$, 2 C$H_a$$H_b$), 3.03 (br. s, 2 H, CHC$H_2$N), 3.48 (br. s, 1 H, O$H$), 4.44 (s, 1 H, C$H$OH), 7.25 [dd, J = 7.7, J = 5.0 Hz, 1 H, C$_q$CHCH (pyr.)], 7.65 [dt, J = 7.7, J = 2.8 Hz, 1 H, C$_q$CHCH (pyr.)], 8.49 [dd, J = 5.0, J = 2.8 Hz, 2 H, NCHCH, C$_q$CHN (pyr.)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.41 (*C*H$_2$), 24.68 (*C*H$_2$), 24.78 (*C*H$_2$), 25.29 (*C*H), 29.33 (*C*H$_2$), 47.81 (CH*C*H$_2$N), 54.44 (*C$_q$*), 77.04 (*C*HOH), 123.07 [C$_q$CH*C*H (pyr.)], 135.33 [C$_q$*C*HCH (pyr.)], 136.09 [*C$_q$* (pyr.)], 148.92 [N*C*HCH (pyr.)], 149.24 [C$_q$*C*HN (pyr.)] ppm. MS (ES): *m*/*z* (%) = 219 (100) [M + H]$^+$, 220 (15). HRMS (ESI): calcd. for $C_{13}H_{19}N_2O$ [M + H]$^+$ 219.1497; found 219.1495. $C_{13}H_{18}N_2O$ (218.30): calcd. C 71.5, H 8.3, N 12.8; found C 71.3, H 8.2, N 12.7, m.p. 103.3 °C. White crystals.

1-(Pyridin-2-ylhydroxymethyl)-2-azabicyclo[2.2.2]octane (22): Yield 39%. IR: $\tilde{\nu}$ = 3276 (NH), 3049 (br., OH), 1588, 1567, 1470, 1454 (pyr.); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.37–1.43 (m, 2 H, 2 CHCH_aH$_b$), 1.43–1.86 (m, 7 H, 2 CHCH$_a$$H_b$, C$H$, 2 C$H_a$$H_b$), 2.97 (br. s, 1 H, O$H$), 3.02 (br. s, 2 H, CHC$H_2$N), 4.37 (s, 1 H, C$H$OH), 7.19 [dd, J = 7.7, J = 5.0 Hz, 1 H, C$_q$CHCHCH (pyr.)], 7.30 [d, J = 7.7 Hz, 1 H, C$_q$CH (pyr.)], 7.65 [td, J = 7.7, J = 1.7 Hz, 1 H, C$_q$CHCH (pyr.)], 8.55 [dd, J = 5.0, J = 1.7 Hz, 1 H, NCH (pyr.)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.97 (*C*H$_2$), 25.10 (*C*H$_2$), 25.61 (*C*H), 27.17 (*C*H$_2$), 29.40 (*C*H$_2$), 48.07 (CH*C*H$_2$N), 53.83 (*C$_q$*), 78.76 (*C*HOH), 122.58 [C$_q$CHCH*C*H (pyr.)], 122.90 [C$_q$*C*H (pyr.)], 136.08 [C$_q$CH*C*H (pyr.)], 148.42 [N*C*H (pyr.)], 159.65 [*C$_q$* (pyr.)] ppm. MS (ES): *m*/*z* (%) = 219 (100) [M + H]$^+$, 220 (20). HRMS (ESI): calcd. for $C_{13}H_{19}N_2O$ [M + H]$^+$ 219.1497; found 219.1495. $C_{13}H_{18}N_2O$ (218.30): calcd. C 71.5, H 8.3, N 12.8; found C 71.6, H 8.5, N 12.8, m.p. 144.1–144.9 °C. White crystals.

Reduction of Epibatidine Analogues: In a dry 25 mL flask, compound **18d** or **20c** (1 equiv., 1 mmol) was dissolved in dry methanol (15 mL). The flask was placed under an inert N_2 atmosphere at –78 °C. $NaBH_4$ (1.2 equiv., 45.4 mg, 1.2 mmol) was added. The reaction mixture was stirred for 4 h at room temperature, and then water was carefully added to neutralize the excess $NaBH_4$. The mixture was extracted with dichloromethane (3× 15 mL). The combined organic extracts were dried with $MgSO_4$ and, after filtration of the solids and removal of the volatile components in vacuo, racemic alcohol **23a** was obtained in good yield.

When necessary the crude alcohol could be further purified. The residue was redissolved in dry diethyl ether and bubbled through with hydrogen chloride. Compound **24b** was isolated as the hydrochloric salt in 65% yield. The melting point could not be recorded, due to degradation upon heating.

2-Ethyl-1-(pyridin-3-ylhydroxymethyl)-2-azabicyclo[2.2.2]octane (23a): Yield 79%. IR: $\tilde{\nu}$ = 3355 (OH), 1590, 1577, 1447 (pyr.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.05–1.15 (m, 1 H, CH_aH$_b$), 1.15 [t, J = 7.2 Hz, 3 H, CH_3 (Et)], 1.24–1.36 (m, 2 H, CH_aH$_b$, C$_q$CH_aH$_b$), 1.42–1.95 (m, 6 H, CH, 2 CH$_a$$H_b$, C$_qCH_a$$H_b$, C$_qCH_a$$H_b$), 2.42 [dq, J = 11.6, J = 7.2 Hz, 1 H, NCH_aH$_b$ (Et)], 2.67 (dt, J = 11.6, J = 3.0 Hz, 1 H, NCH_aH$_b$), 3.08–3.17 [m, 2 H, NCH$_a$$H_b$, NCH$_a$$H_b$ (Et)], 4.40 (br. s, 1 H, OH), 4.76 (s, 1 H, CHOH), 7.25 [dd, J = 7.7, J = 4.6 Hz, 1 H, C$_q$CHCH (pyr.)], 7.68 [d, J = 7.7 Hz, 1 H, C$_q$CHCH (pyr.)], 8.47 [br. s, 2 H, NCHCH, C$_q$CHN (pyr.)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.35 [*C*H$_3$ (Et)], 23.11 (*C*H$_a$H$_b$), 24.30 (C$_q$*C*H$_a$H$_b$), 24.33 (C$_q$*C*H$_a$H$_b$), 25.66 (*C*H$_a$H$_b$), 26.39 (*C*H), 44.43 [N*C*H$_2$ (Et)], 55.04 (CH*C*H$_2$N), 57.19 (*C$_q$*), 73.51 (*C*HOH), 122.77 [C$_q$CH*C*H (pyr.)], 135.42 [C$_q$*C*HCH (pyr.)], 136.46 [*C$_q$* (pyr.)], 148.43 [N*C*HCH or C$_q$*C*HN (pyr.)], 148.12 [N*C*HCH or C$_q$*C*HN (pyr.)] ppm. MS (ES): *m*/*z* (%) = 247 (100) [M + H]$^+$, 248 (20). HRMS (ESI): calcd. for $C_{15}H_{23}N_2O$ [M + H]$^+$ 247.1810; found 247.1806. $C_{15}H_{22}N_2O$ (246.35): calcd. C 73.1, H 9.0, N 11.4; found C 72.9, H 8.7, N 11.3, m.p. 79.0 °C. Yellow crystals.

2-Ethyl-1-(pyridin-2-ylhydroxymethyl)-2-azabicyclo[2.2.2]octane Hydrochloride (24b): Yield 65%. IR: $\tilde{\nu}$ = 3198 (OH), 1589, 1570, 1470, 1453 (pyr.). ^{1}H NMR (300 MHz, D_2O, 25 °C): δ = 1.27–1.39 (m, 1 H, CH_aH$_b$), 1.45 [t, J = 7.2 Hz, 3 H, CH_3 (Et)], 1.57–1.87 (m, 5 H, CH_aH$_b$, 2 C$_q$C$H_a$$H_b$), 2.02–2.29 (m, 3 H, C$H$, 2 CH$_a$$H_b$), 3.20–3.35 [m, 2 H, NC$H_aH_b$, NC$H_aH_b$ (Et)], 3.65 (d, J = 12.1 Hz,

1 H, NCH_aH_b), 3.78 [dq, J = 12.1, J = 7.2 Hz, 1 H, NCH_aH_b (Et)], 5.07 (s, 1 H, C*H*OH); 7.43 [ddd, J = 7.7, J = 5.0, J = 1.1 Hz, 1 H, $C_qCHCHCH$ (pyr.)], 7.64 [d, J = 7.7 Hz, 1 H, C_qCH (pyr.)], 7.96 [td, J = 7.7, J = 1.7 Hz, 1 H, C_qCHCH (pyr.)], 8.55 [d, J = 5.0 Hz, 1 H, NC*H* (pyr.)] ppm. ^{13}C NMR (75 MHz, D_2O, CH_3CN): δ = 9.53 [CH_3 (Et)], 21.29 (CH_aH_b), 22.33 ($C_qCH_aH_b$), 22.40 ($C_qCH_aH_b$), 22.77 (CH_aH_b), 23.90 (*C*H), 46.08 [NCH_2 (Et)], 55.67 (CH_2N), 65.05 (C_q), 73.60 (*C*HOH), 124.26 [C_qCH (pyr.)], 124.59 [$C_qCHCHCH$ (pyr.)], 138.55 [C_qCHCH (pyr.)], 148.49 [N*C*H (pyr.)], 157.92 [C_q (pyr.)] ppm. MS (ES): *m*/*z* (%) = 247 (100) $[M + H]^+$, 248 (20). HRMS (ESI): calcd. for $C_{15}H_{23}N_2O$ $[M - Cl^-]^+$ 247.1810; found 247.1811. White powder.

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

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