Efficient Synthesis of the Azabicyclo[3.3.1]nonane Ring System in the Alkaloid Methyllycaconitine Using Bis(alkoxymethyl)alkylamines as Aminoalkylating Agents in a Double Mannich Reaction

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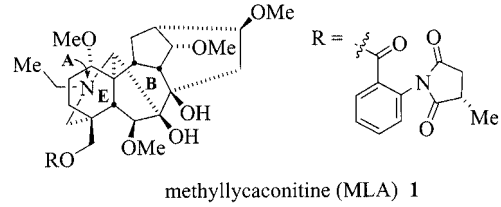
The double Mannich reaction of cyclic β-keto esters with bis-(alkoxymethyl)alkylamines provides an efficient and versatile method for the construction of azabicyclo[3.3.1]nonanes and azabicyclo[3.2.1]octanes. The optimum conditions for efficient reaction involve use of the activator trichloromethylsilane in acetonitrile as solvent at ambient temperature. The utility of this synthetic method is further demonstrated by the facile synthesis of several AE ring analogues **39**, **42** of the alkaloid methyllycaconitine by appendage of the key *N*-(methylsucciniminido)anthranilate pharmacophore to the *N*-(3-phenylpropyl)-substituted double Mannich adducts **18**, **27**.

Introduction

The Mannich reaction is a versatile method for the synthesis of β-amino ketones and esters which are key synthetic intermediates for the construction of nitrogen containing natural products.[1] The inter- and intramolecular version of the Mannich reaction provides a powerful method for the preparation of azacyclic products from acyclic precursors and has formed the crucial step in a number of syntheses of alkaloids.[2] As part of a synthetic programme directed towards the synthesis of simpler bicyclic AE and tricyclic ABE analogues of the complex alkaloid methyllycaconitine (MLA, **1**) (Figure 1)[3] we made use of a classical double Mannich reaction to construct the azabicyclo[3.3.1]-nonane AE ring system.[4] The classical Mannich reaction involved heating a β-keto ester with aqueous formaldehyde in the presence of ethylamine as base, however, we like others,[5] found this procedure only proceeded in low yield and the reaction could not be readily extended to the use of alternative primary amines thus limiting our analogue development programme.

Prompted by the report by Heaney and Papageorgiou[6] on the use of bis(alkoxymethyl)alkylamines derived from primary amines as bis(amino)alkylating agents for use in the synthesis of tertiary amines, we herein report the full details[7] of our study on the bis(amino)alkylation of cyclic β-keto esters using bis(alkoxymethyl)alkylamines as an efficient entry to azabicyclo[3.3.1]nonanes and azabicyclo[3.2.1]octanes. Furthermore we report the conversion of the 3-phenylpropyl-substituted double Mannich adducts **18**, **27** to the AE analogues **39**, **42** of methyllycaconitine.



methyllycaconitine (MLA) **1**

Figure 1. Structure of the alkaloid methyllycaconitine (MLA) illustrating the ABE rings.

Results and Discussion

The bis(alkoxymethyl)alkylamines **2**–**9** (Table 1) were prepared by reaction of the appropriate amine (1.0 equiv.) with paraformaldehyde (2.0 equiv.) and potassium carbonate (1.0 equiv.) in the presence of excess ethanol.[8–11] Purification by vacuum distillation gave the desired products as colourless oils.

Previous studies[6] on Mannich reactions of bis(alkoxymethyl)alkylamines with aromatic nucleophiles provided a number of acidic reagents suitable for activation, including acetyl chloride, trifluoroacetic anhydride, sulfur dioxide and titanium tetrachloride. In these cases, both secondary and tertiary amines were isolated as products. Higher yields of secondary amines were obtained using hydrogen chloride in ether, whereas chlorosilane derivatives promoted the formation of tertiary amines. In order to establish a procedure for double Mannich reactions of bis(alkoxymethyl)alkylamines affording bicyclic tertiary amines, a model reaction of *N,N*-bis(ethoxymethyl)benzylamine (**7**)[6] with ethyl 2-oxocy-

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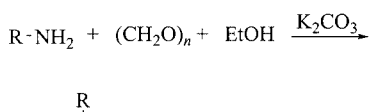
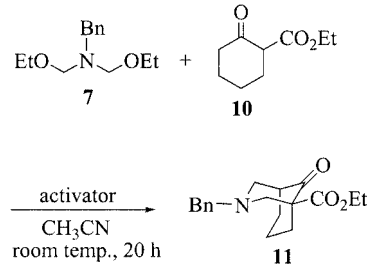
Table 1. Synthesis of bis(alkoxymethyl)alkylamines **2**–**9**.



Entry	R	Product	Yield	Boiling point
1	Et	**2**	47%	105–110 °C/ 100 Torr[6]
2	*i*Pr	**3**	29%	66–72 °C/16 Torr[6]
3	*n*Bu	**4**	28%	66–68 °C/5.3 Torr[6]
4	*t*Bu	**5**	42%	73–76 °C/16 Torr
5	cyclohexyl	**6**	24%	112–118 °C/10 Torr
6	benzyl	**7**	27%	90 °C/0.75 Torr[6]
7	2-phenylethyl	**8**	11%	110 °C/3.5 Torr[12]
8	3-phenylpropyl	**9**	40%	80 °C/0.34 Torr

clohexanecarboxylate (**10**) was investigated. A summary of the different activators used to prepare the bicyclic adduct **11** through a double Mannich reaction is provided (Table 2). Superior results were obtained using trichloromethylsilane as the promoter. Mannich adduct **11** was isolated in 75% yield by treatment of β-keto ester **10** with the bis(alkoxymethyl)alkylamine **7** (2.0 equiv.) and trichloromethylsilane (2.0 equiv.) in acetonitrile at room temperature for 20 h (Entry 8, Table 2).

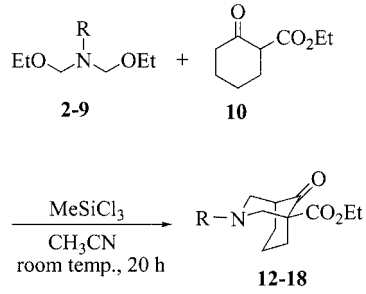
Table 2. Optimization of the double Mannich reaction of bis(alkoxymethyl)alkylamine **7** with β-keto ester **10**.



Entry	Activator	Equiv. of Activator	Equiv. of **7**	Yield of **11** (%)
1	Me_3SiCl	1.1	1.1	–
2	Me_3SiOTf	1.1	1.1	–
3	$Sc(OTf)_3$	0.1	1.1	7
4	$AlCl_3$	1.1	1.1	19
5	$TiCl_4$	0.25	1.1	22
6	$MeSiCl_3$	1.0	1.1	66
7	$MeSiCl_3$	2.0	1.1	64
8	$MeSiCl_3$	2.0	2.0	75
9	$MeSiCl_3$	4.0	4.0	53

A variety of *N*-substituted 3-azabicyclo[3.3.1]nonane derivatives were prepared following these optimized conditions (Table 3). Use of several bis(alkoxymethyl)alkylamines **2**–**6, 8, 9** afforded the corresponding double Mannich products **12**–**18** in good yield after purification by flash chromatography. Conversion of the more sterically demanding *N*-isopropyl- and *N*-benzylbis(alkoxymethyl)-amines was achieved in 75% yield, with the less-hindered bicyclic systems such as the *N*-butyl, *N*-(2-phenylethyl) and *N*-(3-phenylpropyl) derivatives being formed quantitatively.

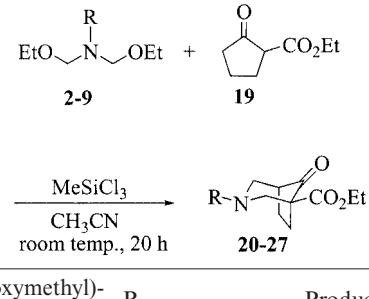
Table 3. Synthesis of 3-azabicyclo[3.3.1]nonanes from bis(alkoxymethyl)alkylamines using a double Mannich reaction.



Entry	Bis(alkoxymethyl)-alkylamine	R	Product	Yield (%)
1	**2**	Et	**12**[5c]	92
2	**3**	*i*Pr	**13**	75
3	**4**	*n*Bu	**14**	>99
4	**5**	*t*Bu	**15**	>99
5	**6**	cyclohexyl	**16**	92
6	**8**	2-phenylethyl	**17**	>99
7	**9**	3-phenylpropyl	**18**	>99

The double Mannich reaction was also applied to the synthesis of smaller *N*-substituted 3-azabicyclo[3.2.1]octane derivatives by reaction of the β-keto ester **19** with bis(alkoxymethyl)alkylamines **2**–**9** (Table 4). In this case, the bicyclic products **20**–**27** were isolated in most cases in an average yield of 80–90%, regardless of the size of the substituent attached to nitrogen.

Table 4. Synthesis of 3-azabicyclo[3.2.1]octanes from bis(alkoxymethyl)alkylamines using a double Mannich reaction.

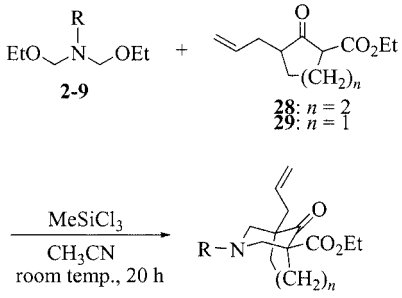


Entry	Bis(alkoxymethyl)-alkylamine	R	Product	Yield (%)
1	**2**	Et	**20**	56
2	**3**	*i*Pr	**21**	81
3	**4**	*n*Bu	**22**	97
4	**5**	*t*Bu	**23**	89
5	**6**	cyclohexyl	**24**	83
6	**7**	benzyl	**25**	83
7	**8**	2-phenylethyl	**26**	81
8	**9**	3-phenylpropyl	**27**	84

Finally, the formation of azabicyclic ring systems containing two quaternary centres at the points of ring fusion was investigated. The allyl-substituted cyclohexanone and cyclopentanone derivatives **28**[13] and **29**[13,14] were con-

verted into the corresponding bicyclic amines in good yield (Table 5). In the case of the cyclohexanone precursor, the allyl derivative **28** gave ca. 20% lower yields of the bicyclic products **30** and **31** than the unsubstituted analogues **11** and **18**. In contrast, the yield of the allylated bicyclic product **32** derived from cyclopentanone precursor **29** was increased by ca. 20% compared to **20**.

Table 5. Application of the double Mannich reaction to the synthesis of allyl-substituted 3-azabicyclic compounds.

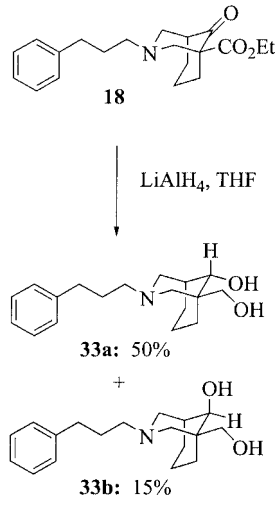


Entry	Starting material	Bis(alkoxymethyl)-alkylamine	R	Product	Yield (%)
1	**28**	**7**	benzyl	**30** (n = 2)	58%
2	**28**	**9**	3-phenylpropyl	**31** (n = 2)	77%
3	**29**	**2**	ethyl	**32** (n = 1)	75%

The results described above demonstrate that double Mannich reactions carried out using preformed bis(alkoxymethyl)alkylamines provides a powerful tool for the synthesis of azabicyclic *N*-substituted ring systems in high yields. The use of mild reaction conditions involving activation of the bis(alkoxymethyl)alkylamines with trichloromethylsilane at room temperature affords significantly improved yields compared to conventional aminomethylation protocols using a refluxing mixture of primary amine and formaldehyde. By applying this new methodology, the yield for the formation of compound **12**[5c] was increased from 47% to 92%, with compound **11** being prepared in 75% rather than 30% yield.

We next focused on the synthesis of biologically active AE ring mimics of methyllycaconitine, in which the key pharmacophore, the *N*-substituted anthranilate ester is attached to the bicyclic AE ring system that in turn is readily prepared using the double Mannich reaction described above. The use of several different preformed bis(alkoxymethyl)alkylamines allows the incorporation of various substituents at the ring nitrogen atom, thus providing access to a library of bicyclic AE ring analogues of methyllycaconitine. Studies on the nicotine-stimulated catecholamine release by nicotinic antagonists have shown that analogues of methyllycaconitine, in which the *N*-ethyl group is replaced by a 3-phenylpropyl group, are more efficient than the corresponding *N*-ethyl-substituted compounds.[15] Therefore, the *N*-(3-phenylpropyl)-substituted bicyclic compounds **18**, **27** were chosen as starting materials for further elaboration to include the *N*-substituted anthranilate pharmacophore.

Reduction of **18** with lithium aluminium hydride in THF gave the corresponding diol as a mixture of diastereomers **33a** and **33b**, which could be separated by flash chromatography (Scheme 1). The stereoisomers were formed in an overall yield of 65% in a ratio of **33a**:**33b** = 3.2:1, favouring the diastereomer containing the equatorial hydroxy group vs. the axial isomer. Evidence for this stereochemistry was obtained by ^{1}H NMR NOESY experiments showing NOE effects between 9-H and 2-H_{ax} in the case of diastereomer **33a**, whereas NOEs between 9-H and 6-H_{ax} as well as 8-H_{ax} were observed for the other diastereomer **33b** (Figure 2).



Scheme 1.

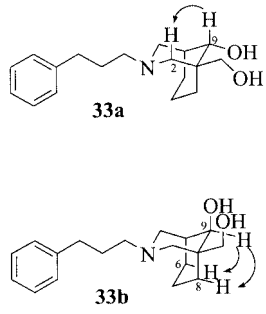
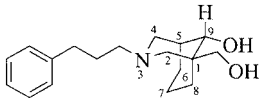


Figure 2. NOE effects observed for the diastereomers **33a** and **33b**. In the case of compound **33a**, no interactions were detected between 9-H and 6-H_{ax} or 8-H_{ax}, while compound **33b** showed no NOE between 9-H and 2-H_{ax}.

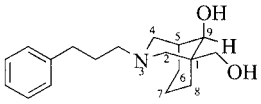
Alternatively, comparison of the ^{13}C NMR spectroscopic data of the alcohols **33a** and **33b** can be used to determine the stereochemistry of the 9-hydroxy group. The 9-OH has a shielding effect on the carbon atoms in the bicyclic ring structure that are *syn* to the hydroxy group. This γ-gauche effect has been extensively studied in 3-azabicyclo[3.3.1]-nonane ring systems.[16] The chemical shifts of the ring carbons that are *syn* to the hydroxy group are shifted upfield when compared to the chemical shifts of the non-hydroxy ring system. Both diastereomers **33a** and **33b** exhibit similar C-7 shifts consistent with a chair-chair conformation of the azabicyclo[3.3.1]nonane ring system as depicted (Figure 2). The resonances assigned to C-6 and C-8 of the azabicy-

clo[3.3.1]nonane ring are shifted 6.8 ppm and 7.0 ppm upfield, respectively, in **33a** compared to **33b**, due to the shielding γ-effect of the 9-hydroxy group (Table 6). Consistent with this analysis, the chemical shifts of C-2 and C-4 appear upfield in **33b** relative to **33a**.

Table 6. Selected ^{13}C NMR chemical shifts δ (ppm) of the 9-hydroxyazabicyclo[3.3.1]nonane diastereomers **33a** and **33b**.



CH2OH

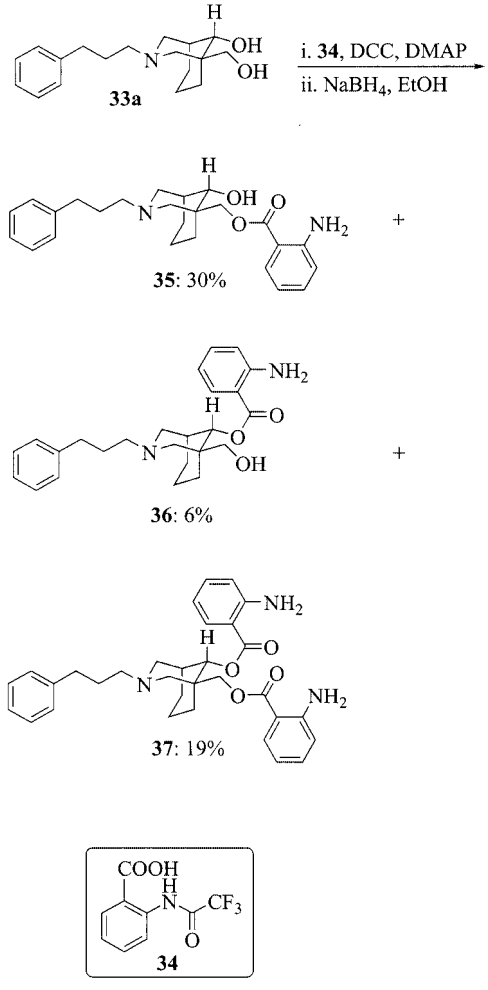


33b

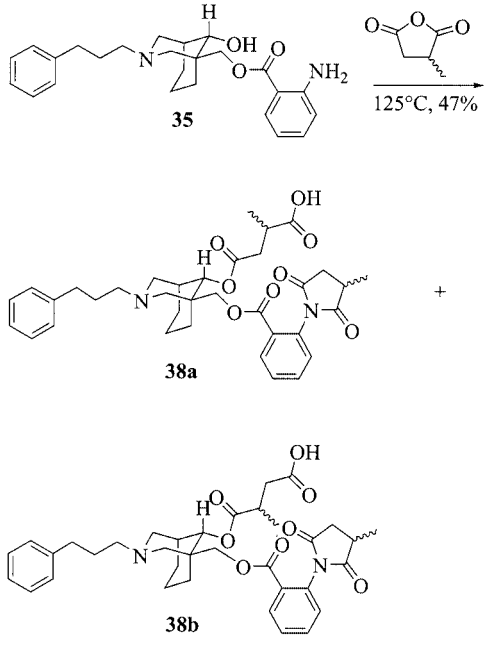
Carbon atom	Diastereomer **33a**	Diastereomer **33b**
C-2	60.9	54.9
C-4	58.7	52.4
C-6	23.9	30.7
C-7	20.6	19.6

The ester side-chain was then introduced by condensing diol **33a** with one equiv. of *N*-(trifluoroacetyl)anthranilic acid (**34**),[17] followed by reductive cleavage of the *N*-protecting group.[18] The condensation was carried out under Steglich conditions,[19] with the reaction occurring predominantly at the primary hydroxy function (Scheme 2). After deprotection with sodium borohydride and subsequent flash chromatography, the corresponding ester **35** was isolated in 30% yield (over two steps). However, the regioisomeric ester **36**, derived from the secondary alcohol, also formed as a by-product in 6% yield together with diester **37** in 19% yield.

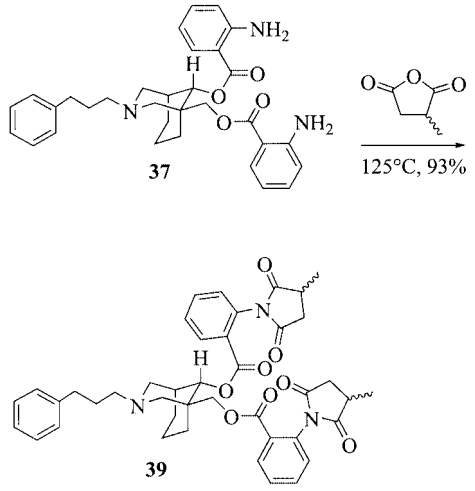
In the final step, the condensation of the aromatic amine with methylsuccinic anhydride was planned in order to obtain the AE ring analogues of methyllycaconitine. Recent structure-activity studies have established that the methyl group of the succinimido moiety is crucial for the binding affinity of methyllycaconitine analogues, although a change in the absolute configuration of this methyl group has no significant effect.[20] The fusion of the amine **35** with racemic methylsuccinic anhydride was carried out as a melt at 125 °C.[21] Under these conditions, the methylsuccinic imide was formed, however, excess reagent also reacted with the secondary hydroxy group to produce the corresponding esters **38a** and **38b** (Scheme 3). After purification by flash chromatography, an inseparable mixture of regioisomers **38a** and **38b** was obtained in 47% yield. The same reaction conditions were then used for fusion of the diester **37** with methylsuccinic anhydride, resulting in the formation of the methyllycaconitine analogue **39**. This compound, which contains two pharmacophoric units as well as the azabicyclic AE methyllycaconitine core structure, was isolated in 93% yield after flash chromatography (Scheme 4).



Scheme 2.

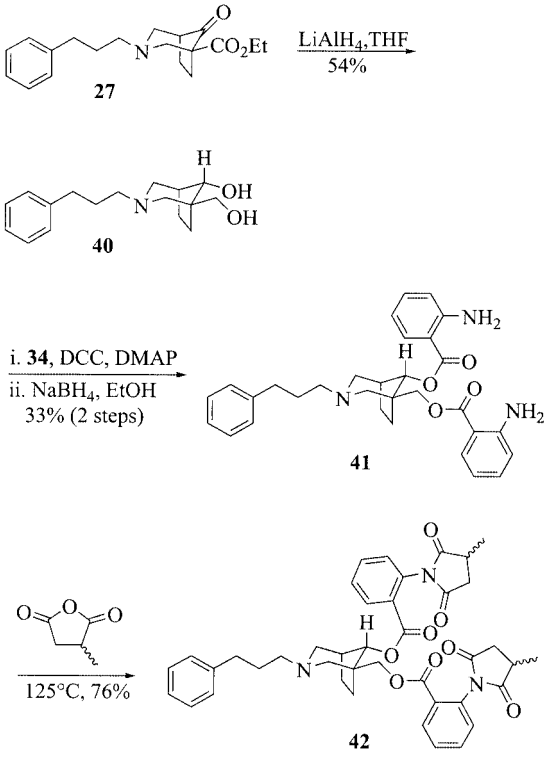


Scheme 3.



Scheme 4.

A similar reaction sequence was performed using 3-azabicyclo[3.2.1]octane derivative **27** as the starting material (Scheme 5). In this case, reduction of **27** with lithium aluminium hydride proceeded diastereoselectively to afford the diol **40** as the only product in 54% yield. The methyllycaconitine noranalogue **42** was then prepared by condensing two equiv. of *N*-(trifluoroacetyl)anthranilic acid **34** with diol **40** to give the corresponding diester **41** in 33% yield (over two steps) after reductive *N*-deprotection. Diester **41** was then converted into the methylsuccinic bisimide **42** in 76% yield.



Scheme 5.

Conclusions

In conclusion, a novel double Mannich reaction has been successfully used as the key step in the synthesis of two methyllycaconitine analogues **39** and **42**, that both contain an azabicyclic AE ring system as well as the crucial *N*-(methylsuccinimido)anthranilate pharmacophore. For the preparation of the bicyclic AE ring precursor, a novel inter- and intramolecular double Mannich reaction has been established using preformed bis(alkoxymethyl)alkylamines as bis(amino)alkylating reagents. The use of mild reaction conditions involving activation of the bis(alkoxymethyl)alkylamines with trichloromethylsilane in acetonitrile at room temperature affords high yields of the azabicyclic products. This new synthetic method provides a powerful tool for the formation of azabicyclic *N*-substituted ring systems present in the alkaloid methyllycaconitine and other related alkaloids.

Experimental Section

General Methods: Analytical thin layer chromatography (TLC) was performed using 0.2 mm thick precoated silica gel plates (Merck Kieselgel 60 F_{254}). Compounds were visualized by ultraviolet fluorescence or by staining with potassium permanganate in aqueous sodium hydroxide. Flash chromatography was performed using Riedel-de Haën silica gel (0.032–0.063 mm) with the indicated solvents. ^{1}H NMR spectra were recorded with a Bruker DRX 300 (300 MHz) or a Bruker DRX 400 (400 MHz) spectrometer at ambient temperature using $CDCl_3$ as a solvent. Chemical shifts are given in parts per million (ppm) downfield shift from tetramethylsilane as an internal standard, and reported as position (δ), multiplicity (s = singlet, s_{br} = broad singlet, d = doublet, dd = double doublet, ddd = double double doublet, dddd = double double double doublet, t = triplet, dt = double triplet, tt = triple triplet, q = quartet, quin = quintet, sept = septet, m = multiplet), relative integral, assignment and coupling constant (J in Hz). ^{13}C NMR spectra were recorded with a Bruker DRX 300 (75 MHz) or a Bruker DRX 400 (100 MHz) spectrometer at ambient temperature with complete proton decoupling. Chemical shifts are expressed in parts per million referenced to the residual chloroform peak (δ = 77.0 ppm), and reported as position (d) and assignment, aided by DEPT 135 experiments. In addition, ^{1}H-^{1}H-COSY and ^{1}H-^{13}C-HSQC correlation spectra were used for the complete assignment of the proton and carbon resonances. ^{1}H-^{1}H-NOESY NMR spectra were recorded in special cases to determine the constitution of diastereomers. The NMR spectroscopic data for the bicyclic analogues of methyllycaconitine were assigned using the following descriptors: bicyclic ring system (no primes), anthranilate ester (one prime ′) and methylsuccinimide (two primes ′′). High resolution mass spectra were recorded with a VG-70SE mass spectrometer operating with an ionisation potential of 70 eV at nominal resolutions of 5000 to 10000 as appropriate. Ionisation methods employed were either electron impact (EI) or fast atom bombardment (FAB) using *m*-nitrobenzyl alcohol as matrix. Major fragments are given as mass to charge ratios. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. β-Keto esters **28** and **29** were prepared as described in the literature.[13,14] *N*-(Trifluoroacetyl)anthranilic acid was prepared as reported.[17]

General Procedure A for the Preparation of *N,N*-Bis(ethoxymethyl)-amines:[8–11] A mixture of dry amine (1 equiv., freshly distilled from calcium hydride where appropriate) and oven-dried potassium carbonate (1 equiv.) in dry ethanol (freshly distilled from magnesium turnings) was treated with paraformaldehyde (2 equiv.) that had been dried overnight under vacuum and the mixture stirred vigorously with a magnetic stirer for 2 days at room temperature. The suspension was filtered, washed with dry ethanol, and excess alcohol was removed from the filtrate by distillation. The residue was purified by fractional vacuum distillation using a Vigreux column to give the *N,N*-bis(ethoxymethyl)amine. Bis(ethoxymethyl)alkylamines **2**–**9** were prepared according to this general procedure. ^{1}H NMR spectroscopic data and boiling points for bis(aminol) ethers **2**, **3**, **4**, **7** were in agreement with that reported in the literature.[6,12]

***N,N*-Bis(ethoxymethyl)-*tert*-butylamine (5):** The title compound was prepared according to general procedure A using *tert*-butylamine (10.00 g, 136.72 mmol), potassium carbonate (18.90 g, 136.72 mmol) and paraformaldehyde (8.21 g, 273.43 mmol) in dry ethanol (30 mL). Yield 10.99 g (58.06 mmol, 42%) of a clear oil; boiling point 73–76 °C/16 Torr. HRMS (EI): *m/z* calcd. for $C_{10}H_{23}NO_2$: 189.1729, found: 189.1729 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.40 [s, 4 H, NCH_2O (2×)], 3.38 [q, ^3J = 7.0 Hz, 4 H, CH_2 (2× Et)], 1.21 [s, 9 H, $NC(CH_3)_3$], 1.18 [t, ^3J = 7.0 Hz, 6 H, CH_3 (2× Et)]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 81.6 [NCH_2O (2×)], 61.6 [CH_2 (2× Et)], 53.3 [N*C*-$(CH_3)_3$], 29.3 [NC(CH$_3$)$_3$], 15.3 [CH_3 (2× Et)].

***N,N*-Bis(ethoxymethyl)cyclohexylamine (6):** The title compound was prepared according to general procedure A using cyclohexylamine (10.00 g, 100.83 mmol), potassium carbonate (13.93 g, 100.83 mmol) and paraformaldehyde (6.06 g, 201.65 mmol) in dry ethanol (25 mL). Yield 5.29 g (24.57 mmol, 24%) of a clear oil; boiling point 112–118 °C/10 mm/Hg. HRMS (EI): *m/z* calcd. for $C_{12}H_{25}NO_2$: 215.1885, found: 215.1882 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.35 [s, 4 H, NCH_2O (2×)], 3.40 [q, ^3J = 7.0 Hz, 4 H, CH_2 (2× Et)], 2.75 (tt, ^3J = 3.5, ^3J = 11.3 Hz, 1 H, 1-H), [1.88–1.85 (m, 2 H), 1.78–1.75 (m, 2 H)] (2-H$_a$, 2-H$_b$, 6-H$_a$, 6-H$_b$)], 1.61–1.59 (m, 2 H, 4-H$_a$, 4-H$_b$), 1.20–1.35 (m, 4 H, 3-H$_a$, 3-H$_b$, 5-H$_a$, 5-H$_b$), 1.18 [t, ^3J = 7.0 Hz, 6 H, CH_3 (2× Et)]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 82.9 [NCH_2O (2×)], 61.8 [CH_2 (2× Et)], 58.7 (C-1), 32.4 (C-2, C-6), 26.2 (C-3, C-5), 26.0 (C-4), 15.3 [CH_3 (2× Et)].

***N,N*-Bis(ethoxymethyl)-3-phenylpropylamine (9):** The title compound was prepared according to general procedure A using 3-phenylpropylamine (25.00 g, 184.90 mmol), potassium carbonate (25.56 g, 184.90 mmol) and paraformaldehyde (11.11 g, 369.80 mmol) in dry ethanol (400 mL). Yield 18.74 g (74.55 mmol, 40%) of a clear oil; boiling point 80 °C/ 0.34 Torr. HRMS (EI): *m/z* calcd. for $C_{15}H_{25}NO_2$: 251.1885, found: 251.1891 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.28–7.16 [m, 5 H, H$_{arom.}$ (Ph)], 4.29 [s, 4 H, NCH_2O (2×)], 3.43 [q, ^3J = 7.0 Hz, 4 H, CH_2 (2× Et)], 2.87 [t, ^3J = 7.3 Hz, 2 H, N(CH_2)$_2$CH_2Ph], 2.63 [t, ^3J = 7.6 Hz, 2 H, NCH_2(CH_2)$_2$Ph], 1.88–1.80 (m, 2 H, $NCH_2CH_2CH_2$Ph), 1.18 [t, ^3J = 7.0 Hz, 6 H, CH_3 (2× Et)]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 142.3 (C-1$_{arom.}$), 128.3 (C-3$_{arom.}$, C-5$_{arom.}$), 128.2 (C-2$_{arom.}$, C-6$_{arom.}$), 125.6 (C-4$_{arom.}$), 84.7 [NCH_2O (2×)], 62.6 [CH_2 (2× Et)], 49.4 [NCH_2(CH_2)$_2$Ph], 33.4 [N(CH_2)$_2$$CH_2$Ph], 30.5 ($NCH_2CH_2CH_2$Ph), 15.1 [$CH_3$ (2× Et)].

General Procedure B for the Double Mannich Reaction Using Preformed Bis(alkoxymethyl)alkylamines: To a mixture of β-keto ester (1 equiv.) and *N,N*-bis(ethoxymethyl)amine (2 equiv.) in acetonitrile was added trichloromethylsilane (2 equiv.). The reaction mixture was stirred for 20 h at room temperature, then quenched with aq. $NaHCO_3$ and extracted with ethyl acetate (3×). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude azabicyclic product was purified by flash chromatography on silica gel (EtOAc/hexane). Compounds **11**–**18**, **20**–**27** and **30**–**32** were prepared according to this general procedure.

Ethyl 3-Benzyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (11): The title compound was prepared according to general procedure B using β-keto ester **10** (100 mg, 0.59 mmol), *N,N*-bis(ethoxymethyl) benzylamine (**7**) (264 mg, 1.18 mmol) and trichloromethylsilane (139 μL, 1.18 mmol) in acetonitrile (2 mL). Yield 133 mg (0.44 mmol, 75%) of a clear oil; R_f = 0.36 (5% EtOAc in hexane). HRMS (EI): *m/z* calcd. for $C_{18}H_{23}NO_3$: 301.1678, found: 301.1670 [M$^+$]. ^{1}H NMR (400 MHz, COSY, $CDCl_3$): δ (ppm) = 7.34–7.26 [m, 5 H, H$_{arom.}$ (Bn)], 4.18 [dq, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.51 [s, 2 H, CH_2 (Bn)], 3.19 [dd, $^2J_{gem}$ = 11.4, $^4J_{2eq,4eq}$ = 2.3 Hz, 1 H, 2-H$_{eq}$], 3.12 (ddd, $^2J_{gem}$ = 11.2, $^3J_{4eq,5}$ = $^4J_{2eq,4eq}$ = 2.3 Hz, 1 H, 4-H$_{eq}$), 3.01–2.91 (m, 1 H, 7-H$_{ax}$), 2.99 (dd, $^2J_{gem}$ = 11.4, $^4J_{2ax,8ax}$ = 1.8 Hz, 1 H, 2-H$_{ax}$), 2.62 (dd, $^2J_{gem}$ = 11.0, $^4J_{4ax,6ax}$ = 2.5 Hz, 1 H, 4-H$_{ax}$), 2.54 (dddd, $^2J_{gem}$ = $^3J_{7ax,8ax}$ = 12.3, $^3J_{7eq,8ax}$ = 6.3, $^4J_{2ax,8ax}$ = 1.6 Hz, 1 H, 8-H$_{ax}$), 2.46–2.43 (m, 1 H, 5-H), 2.27–2.21 (m, 1 H, 8-H$_{eq}$), 2.14–2.07 (m, 2 H, 6-H$_{ax}$, 6-H$_{eq}$), 1.62–1.57 (m, 1 H, 7-H$_{eq}$), 1.26 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)]. ^{13}C NMR (100 MHz, BB, DEPT, HSQC, $CDCl_3$): δ (ppm) = 212.3 (C-9), 170.9 [C=O (ester)], 138.2 (C-1$_{arom.}$), 128.6 (C-2$_{arom.}$, C-6$_{arom.}$), 128.4 (C-3$_{arom.}$, C-5$_{arom.}$), 127.2 (C-4$_{arom.}$), 62.0 [CH_2 (Bn)], 61.7 (C-2), 61.0 [CH_2 (Et)], 60.1 (C-4), 58.8 (C-1), 47.1 (C-5), 36.6 (C-8), 34.0 (C-6), 20.6 (C-7), 14.0 [CH3 (Et)].

Ethyl 3-Ethyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (12):[5c] The title compound was prepared according to general procedure B using β-keto ester **10** (100 mg, 0.59 mmol), *N,N*-bis(ethoxymethyl)ethylamine (**2**) (190 mg, 1.18 mmol) and trichloromethylsilane (139 μL, 1.18 mmol) in acetonitrile (2 mL). Yield 129 mg (0.54 mmol, 92%) of a clear oil; R_f = 0.47 (10% EtOAc in hexane). HRMS (EI): *m/z* calcd. for $C_{13}H_{21}NO_3$: 239.1521, found: 239.1523 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.21 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.21 (dd, $^2J_{gem}$ = 11.4, $^4J_{2eq,4eq}$ = 2.2 Hz, 1 H, 2-H$_{eq}$), 3.15 (ddd, $^2J_{gem}$ = 11.1, $^3J_{4eq,5}$ = $^4J_{2eq,4eq}$ = 2.1 Hz, 1 H, 4-H$_{eq}$), 2.93 (dd, $^2J_{gem}$ = 11.4, $^4J_{2ax,8ax}$ = 1.6 Hz, 1 H, 2-H$_{ax}$), 2.92–2.80 (m, 1 H, 7-H$_{ax}$), 2.59–2.49 (m, 2 H, 4-H$_{ax}$, 8-H$_{ax}$), 2.47–2.45 (m, 1 H, 5-H), 2.41 (dq, ^3J = 7.3 Hz, 2 H, NC$H_2$$CH_3$), 2.26–2.21 (m, 1 H, 8-H$_{eq}$), 2.17–2.03 (m, 2 H, 6-H$_{ax}$, 6-H$_{eq}$), 1.56–1.49 (m, 1 H, 7-H$_{eq}$), 1.28 (t, ^3J = 7.2 Hz, 3 H, CH_3 (Et)], 1.10 (t, ^3J = 7.2 Hz, 3 H, $NCH_2C$$H_3$). ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 212.7 (C-9), 171.1 [C=O (ester)], 61.6 (C-2), 61.0 [CH_2 (Et)], 59.9 (C-4), 58.8 (C-1), 51.0 (NCH_2CH_3), 47.2 (C-5), 36.8 (C-8), 34.1 (C-6), 20.5 (C-7), 14.1 [CH_3 (Et)], 12.7 ($NCH_2$$CH_3$).

Ethyl 3-Isopropyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (13): The title compound was prepared according to general procedure B using β-keto ester **10** (100 mg, 0.59 mmol), *N,N*-bis(ethoxymethyl)isopropylamine (**3**) (207 mg, 1.18 mmol) and trichloromethylsilane (139 μL, 1.18 mmol) in acetonitrile (2 mL). Yield 111 mg (0.44 mmol, 75%) of a clear oil; R_f = 0.57 (10% EtOAc in hexane). HRMS (EI): *m/z* calcd. for $C_{14}H_{23}NO_3$: 253.1678, found: 253.1674 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.22 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.13 (s, 2 H, 2-H$_{ax}$, 2-H$_{eq}$), 3.06 (d, $^2J_{gem}$ = 10.9 Hz, 1 H, 4-H$_{eq}$), 2.87 [sept, ^3J = 6.6 Hz, 1 H, NCH(CH_3)$_2$], 2.81–2.71 (m, 1 H, 7-H$_{ax}$), 2.80 (dd, $^2J_{gem}$ = 11.0, $^3J_{4ax,5}$ = 3.5 Hz, 1 H, 4-H$_{ax}$), 2.54 (ddd, $^2J_{gem}$ = $^3J_{7ax,8ax}$ = 13.6, $^3J_{7eq,8ax}$ = 6.2 Hz, 1 H, 8-H$_{ax}$), 2.47–2.45 (m, 1 H,

5-H), 2.22 (ddd, $^2J_{gem}$ = 13.7, $^3J_{7ax,8eq}$ = $^3J_{7eq,8eq}$ = 4.2 Hz, 1 H, 8-H_{eq}), 2.12–2.07 (m, 2 H, 6-H_{ax}, 6-H_{eq}), 1.52–1.48 (m, 1 H, 7-H_{eq}), 1.29 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)], 1.05 [dd, ^3J = 6.6 Hz, 6 H, NCH(CH_3)$_2$]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 213.0 (C-9), 171.5 [C=O (ester)], 61.0 [CH_2 (Et)], 59.0 (C-1), 57.4 (C-2), 55.5 (C-4), 53.5 [N*C*H(CH$_3$)$_2$], 47.1 (C-5), 36.5 (C-8), 33.8 (C-6), 20.6 (C-7), 18.2, 18.1 [NCH(*C*H$_3$)$_2$], 14.1 [CH_3 (Et)].

Ethyl 3-Butyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (14): The title compound was prepared according to general procedure B using β-keto ester **10** (100 mg, 0.59 mmol), *N,N*-bis(ethoxymethyl)-butylamine (**4**) (223 mg, 1.18 mmol) and trichloromethylsilane (139 μL, 1.18 mmol) in acetonitrile (2 mL). Yield 157 mg (0.59 mmol, >99%) of a clear oil; R_f = 0.67 (10% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{15}H_{25}NO_3$: 267.1834, found: 267.1833 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.21 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.20 (dd, $^2J_{gem}$ = 11.4, $^4J_{2eq,4eq}$ = 2.2 Hz, 1 H, 2-H_{eq}), 3.13 (ddd, $^2J_{gem}$ = 11.1, $^3J_{4eq,5}$ = $^4J_{2eq,4eq}$ = 2.2 Hz, 1 H, 4-H_{eq}), 2.91 (dd, $^2J_{gem}$ = 11.4, $^4J_{2ax,8ax}$ = 1.7 Hz, 1 H, 2-H_{ax}), 2.902.80 (m, 1 H, 7-H_{ax}), 2.57–2.49 (m, 2 H, 4-H_{ax}, 8-H_{ax}), 2.46–2.44 (m, 1 H, 5-H), 2.33 [t, ^3J = 7.0 Hz, 2 H, NCH_2(CH$_2$)$_2$CH$_3$], 2.26–2.21 (m, 1 H, 8-H_{eq}), 2.18–2.02 (m, 2 H, 6-H_{ax}, 6-H_{eq}), 1.56–1.52 (m, 1 H, 7-H_{eq}), 1.52–1.45 (m, 2 H, NCH$_2$CH_2CH$_2$CH$_3$), 1.41–1.35 [m, 2 H, N(CH$_2$)$_2$CH_2CH$_3$], 1.28 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)], 0.94 [t, ^3J = 7.3 Hz, 3 H, N(CH$_2$)$_3$CH_3]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 212.6 (C-9), 171.1 [C=O (ester)], 62.0 (C-2), 61.0 [CH_2 (Et)], 60.4 (C-4), 58.8 (C-1), 56.7 [N*C*H$_2$(CH$_2$)$_2$CH$_3$], 47.2 (C-5), 36.8 (C-8), 34.1 (C-6), 29.3 (NCH$_2$*C*H$_2$CH$_2$CH$_3$), 20.5, 20.4 [C-7, N(CH$_2$)$_2$*C*H$_2$CH$_3$], 14.1 [CH_3 (Et)], 13.9 [N(CH$_2$)$_3$*C*H$_3$].

Ethyl 3-*tert*-Butyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (15): The title compound was prepared according to general procedure B using β-keto ester **10** (100 mg, 0.59 mmol), *N,N*-bis(ethoxymethyl)-*tert*-butylamine (**7**) (223 mg, 1.18 mmol) and trichloromethylsilane (139 μL, 1.18 mmol) in acetonitrile (2 mL). Yield 157 mg (0.59 mmol, >99%) of a clear oil; R_f = 0.47 (10% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{15}H_{25}NO_3$: 267.1834, found: 267.1833 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.22 [dq, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.35 (dd, $^2J_{gem}$ = 11.3, $^4J_{2eq,4eq}$ = 3.0 Hz, 1 H, 2-H_{eq}), 3.27 (ddd, $^2J_{gem}$ = 11.0, $^3J_{4eq,5}$ = $^4J_{2eq,4eq}$ = 2.8 Hz, 1 H, 4-H_{eq}), 3.04 (dd, $^2J_{gem}$ = 11.3, $^4J_{2ax,8ax}$ = 1.3 Hz, 1 H, 2-H_{ax}), 2.78–2.69 (m, 1 H, 7-H_{ax}), 2.73 (dd, $^2J_{gem}$ = 10.8, $^3J_{4ax,5}$ = 3.1 Hz, 1 H, 4-H_{ax}), 2.572.48 (m, 1 H, 8-H_{ax}), 2.44–2.42 (m, 1 H, 5-H), 2.26–2.20 (m, 1 H, 8-H_{eq}), 2.132.08 (m, 2 H, 6-H_{ax}, 6-H_{eq}), 1.50–1.43 (m, 1 H, 7-H_{eq}), 1.29 (t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)], 1.13 [s, 9 H, NC(CH_3)$_3$]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 213.4 (C-9), 171.6 [C=O (ester)], 60.9 [CH_2 (Et)], 59.0 (C-1), 55.5 (C-2), 53.5 (C-4), 53.4 [N*C*(CH$_3$)$_3$], 47.1 (C-5), 36.2 (C-8), 33.6 (C-6), 26.4 [NC(*C*H$_3$)$_3$], 20.6 (C-7), 14.1 [CH_3 (Et)].

Ethyl 3-Cyclohexyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (16): The title compound was prepared according to general procedure B using β-keto ester **10** (100 mg, 0.59 mmol), *N,N*-bis(ethoxymethyl)cyclohexylamine (**6**) (254 mg, 1.18 mmol) and trichloromethylsilane (139 μL, 1.18 mmol) in acetonitrile (2 mL). Yield 157 mg (0.54 mmol, 92%) of a clear oil; R_f = 0.57 (10% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{17}H_{27}NO_3$: 293.1991, found: 293.1984 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.21 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.22–3.16 (m, 2 H, 2-H_{ax}, 2-H_{eq}), 3.11 (ddd, $^2J_{gem}$ = 10.9, $^3J_{4eq,5}$ = $^4J_{2eq,4eq}$ = 1.9 Hz, 1 H, 4-H_{eq}), 2.84 (dd, $^2J_{gem}$ = 11.0, $^3J_{4ax,5}$ = 3.3 Hz, 1 H, 4-H_{ax}), 2.82–2.72 (m, 1 H, 7-H_{ax}), 2.52 (ddd, $^2J_{gem}$ = $^3J_{7ax,8ax}$ = 11.6, $^3J_{7eq,8ax}$ = 6.4 Hz, 1 H, 8-H_{ax}), 2.45–2.43 (m, 1 H, 5-H), 2.43–2.36 (m, 1 H, 1′-H), 2.24–2.18 (m, 1 H, 8-H_{eq}), 2.112.04 (m, 2 H, 6-H_{ax}, 6-H_{eq}), 1.82–1.76 (m, 4 H, 2′-H_a, 2′-H_b, 6′-H_a, 6′-H_b), 1.64–1.59 (m, 1 H, 4′-H_a), 1.53–1.46 (m, 1 H, 7-H_{eq}), 1.28 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)], 1.30–1.21 (m, 4 H, 3′-H_a, 3′-H_b, 5′-H_a, 5′-H_b), 1.17–1.11 (m, 1 H, 4′-H_b). ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 213.0 (C-9), 171.4 [C=O (ester)], 62.4 (C-1′), 60.9 [CH_2 (Et)], 59.1 (C-1), 58.1 (C-2), 56.1 (C-4), 47.3 (C-5), 36.5 (C-8), 33.8 (C-6), 28.8, 28.7, 26.2, 25.6 (C-2′, C-3′, C-4′, C-5′, C-6′), 20.6 (C-7), 14.1 [CH_3 (Et)].

Ethyl 9-Oxo-3-(2-phenylethyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate (17): The title compound was prepared according to general procedure B using β-keto ester **10** (100 mg, 0.59 mmol), *N,N*-bis(ethoxymethyl)-2-phenylethylamine (**8**) (280 mg, 1.18 mmol) and trichloromethylsilane (139 μL, 1.18 mmol) in acetonitrile (2 mL). Yield 185 mg (0.59 mmol, >99%) of a clear oil; R_f = 0.45 (10% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{19}H_{25}NO_3$: 315.1834, found: 315.1829 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.31–7.18 [m, 5 H, $H_{arom.}$ (Ph)], 4.21 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.27 (dd, $^2J_{gem}$ = 11.4, $^4J_{2eq,4eq}$ = 2.0 Hz, 1 H, 2-H_{eq}), 3.18 (d, $^2J_{gem}$ = 11.1 Hz, 1 H, 4-H_{eq}), 3.02 (d, $^2J_{gem}$ = 10.7 Hz, 1 H, 2-H_{ax}), 2.82 (t, ^3J = 7.8 Hz, 2 H, NCH$_2$CH_2Ph), 2.66–2.56 (m, 2 H, 4-H_{ax}, 7-H_{ax}), 2.64 (t, ^3J = 7.9 Hz, 2 H, NCH_2CH$_2$Ph), 2.52–2.42 (m, 2 H, 8-H_{ax}, 5-H), 2.18–2.13 (m, 1 H, 8-H_{eq}), 2.06–2.01 (m, 2 H, 6-H_{ax}, 6-H_{eq}), 1.43–1.38 (m, 1 H, 7-H_{eq}), 1.28 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 212.4 (C-9), 171.0 [C=O (ester)], 140.1 (C-1$_{arom.}$), 128.5 (C-3$_{arom.}$, C-5$_{arom.}$), 128.3 (C-2$_{arom.}$, C-6$_{arom.}$), 126.0 (C-4$_{arom.}$), 61.7 (C-2), 61.0 [CH_2 (Et)], 60.2 (C-4), 58.8 (C-1), 58.5 (N*C*H$_2$CH$_2$Ph), 47.2 (C-5), 36.7 (C-8), 34.0 (C-6), 33.7 (NCH$_2$*C*H$_2$Ph), 20.2 (C-7), 14.1 [CH_3 (Et)].

Ethyl 9-Oxo-3-(3-phenylpropyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate (18): The title compound was prepared according to general procedure B using β-keto ester **10** (100 mg, 0.59 mmol), *N,N*-bis(ethoxymethyl)-3-phenylpropylamine (**9**) (297 mg, 1.18 mmol) and trichloromethylsilane (139 μL, 1.18 mmol) in acetonitrile (2 mL). Yield 193 mg (0.59 mmol, >99%) of a clear oil; R_f = 0.57 (10% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{20}H_{27}NO_3$: 329.1991, found: 329.1988 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.30–7.16 [m, 5 H, $H_{arom.}$ (Ph)], 4.20 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.20 (dd, $^2J_{gem}$ = 11.4, $^4J_{2eq,4eq}$ = 1.9 Hz, 1 H, 2-H_{eq}), 3.13 (d, $^2J_{gem}$ = 11.1 Hz, 1 H, 4-H_{eq}), 2.96–2.86 (m, 1 H, 7-H_{ax}), 2.94 (d, $^2J_{gem}$ = 12.0 Hz, 1 H, 2-H_{ax}), 2.68 [t, ^3J = 7.7 Hz, 2 H, N(CH$_2$)$_2$CH_2Ph], 2.59–2.51 (m, 2 H, 4-H_{ax}, 8-H_{ax}), 2.46–2.43 (m, 1 H, 5-H), 2.35 [t, ^3J = 6.7 Hz, 2 H, NCH_2(CH$_2$)$_2$Ph], 2.27–2.21 (m, 1 H, 8-H_{eq}), 2.16–2.06 (m, 2 H, 6-H_{ax}, 6-H_{eq}), 1.82 (quin, ^3J = 7.3 Hz, 2 H, NCH$_2$CH_2CH$_2$Ph), 1.59–1.54 (m, 1 H, 7-H_{eq}), 1.27 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 212.2 (C-9), 170.9 [C=O (ester)], 141.8 (C-1$_{arom.}$), 128.2 (C-2$_{arom.}$, C-3$_{arom.}$, C-5$_{arom.}$, C-6$_{arom.}$), 125.7 (C-4$_{arom.}$), 61.9 (C-2), 60.9 [CH_2 (Et)], 60.2 (C-4), 58.6 (C-1), 56.2 [N*C*H$_2$(CH$_2$)$_2$Ph], 47.0 (C-5), 36.6 (C-8), 34.0 (C-6), 33.3 [N-(CH$_2$)$_2$*C*H$_2$Ph], 28.9 (NCH$_2$*C*H$_2$CH$_2$Ph), 20.4 (C-7), 14.0 [CH_3 (Et)].

Ethyl 3-Ethyl-8-oxo-3-azabicyclo[3.2.1]octane-1-carboxylate (20): The title compound was prepared according to general procedure B using β-keto ester **19** (100 mg, 0.64 mmol), *N,N*-bis(ethoxymethyl) ethylamine (**2**) (206 mg, 1.28 mmol) and trichloromethylsilane (150 μL, 1.28 mmol) in acetonitrile (2 mL). Yield 80 mg (0.36 mmol, 56%) of a clear oil; R_f = 0.31 (17% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{12}H_{19}NO_3$: 225.1365, found: 225.1366 [M$^+$]. ^{1}H NMR (400 MHz, COSY, $CDCl_3$): δ (ppm) = 4.21 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.15 (dd, $^2J_{gem}$ = 10.9, $^4J_{2eq,4eq}$ = 2.6 Hz, 1 H, 2-H_{eq}), 3.02–2.98 (ddd, $^2J_{gem}$ = 10.5, $^3J_{4eq,5}$ = 4.0, $^4J_{2eq,4eq}$ =

2.8 Hz, 1 H, 4-H_{eq}), 2.70 (d, $^2J_{gem}$ = 10.9 Hz, 1 H, 2-H_{ax}), 2.55 (q, ^3J = 7.2 Hz, 2 H, NCH_2CH$_3$), 2.59 (d, $^2J_{gem}$ = 9.3 Hz, 1 H, 4-H_{ax}), 2.39–2.34 (m, 1 H, 7-H_{exo}), 2.35–2.33 (m, 1 H, 5-H), 2.28–2.21 (m, 1 H, 7-H_{endo}), 2.00–1.91 (m, 2 H, 6-H_{endo}, 6-H_{exo}), 1.28 (t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)], 1.09 (t, ^3J = 7.2 Hz, 3 H, NCH$_2$CH_3). ^{13}C NMR (100 MHz, BB, DEPT, HSQC, $CDCl_3$): δ (ppm) = 213.6 (C-8), 170.3 [C=O (ester)], 62.2 (C-2), 61.1 (C-4), 61.0 [CH_2 (Et)], 57.6 (C-1), 49.7 (NCH_2CH$_3$), 46.3 (C-5), 27.5 (C-7), 21.7 (C-6), 14.1 [CH_3 (Et)], 12.6 (NCH$_2$$CH_3$).

Ethyl 3-Isopropyl-8-oxo-3-azabicyclo[3.2.1]octane-1-carboxylate (21): The title compound was prepared according to general procedure B using β-keto ester **19** (100 mg, 0.64 mmol), *N,N*-bis-(ethoxymethyl)isopropylamine (**3**) (224 mg, 1.28 mmol) and trichloromethylsilane (150 μL, 1.28 mmol) in acetonitrile (2 mL). Yield 125 mg (0.52 mmol, 81%) of a clear oil; R_f = 0.38 (10% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{13}H_{21}NO_3$: 239.1521, found: 239.1521 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.21 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.05 (dd, $^2J_{gem}$ = 10.8, $^4J_{2eq,4eq}$ = 2.7 Hz, 1 H, 2-H_{eq}), 2.97–2.86 [m, 2 H, NCH-(CH_3)$_2$, 4-H_{eq}], 2.87 (d, $^2J_{gem}$ = 10.6 Hz, 1 H, 2-H_{ax}), 2.71 (d, $^2J_{gem}$ = 10.3 Hz, 1 H, 4-H_{ax}), 2.37–2.31 (m, 1 H, 7-H_{exo}), 2.36–2.35 (m, 1 H, 5-H), 2.21–2.14 (m, 1 H, 7-H_{endo}), 1.92–1.87 (m, 2 H, 6-H_{endo}, 6-H_{exo}), 1.28 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)], 1.05 [dd, ^3J = 6.6 Hz, 6 H, NCH(CH_3)$_2$]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 214.1 (C-8), 170.6 [C=O (ester)], 61.0 [CH_2 (Et)], 58.1 (C-1, C-2), 56.8 (C-4), 52.7 [NCH(CH$_3$)$_2$], 46.7 (C-5), 27.6 (C-7), 21.8 (C-6), 18.9, 18.8 [NCH(CH$_3$)$_2$], 14.2 [CH_3 (Et)].

Ethyl 3-Butyl-8-oxo-3-azabicyclo[3.2.1]octane-1-carboxylate (22): The title compound was prepared according to general procedure B using β-keto ester **19** (100 mg, 0.64 mmol), *N,N*-bis(ethoxymethyl)-butylamine (**4**) (242 mg, 1.28 mmol) and trichloromethylsilane (150 μL, 1.28 mmol) in acetonitrile (2 mL). Yield 157 mg (0.62 mmol, 97%) of a clear oil; R_f = 0.66 (10% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{14}H_{23}NO_3$: 253.1678, found: 253.1677 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.21 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.14 (dd, $^2J_{gem}$ = 10.9, $^4J_{2eq,4eq}$ = 2.6 Hz, 1 H, 2-H_{eq}), 2.98 (ddd, $^2J_{gem}$ = 10.5, $^3J_{4eq,5}$ = $^4J_{2eq,4eq}$ = 2.9 Hz, 1 H, 4-H_{eq}), 2.69 (d, $^2J_{gem}$ = 10.9 Hz, 1 H, 2-H_{ax}), 2.50 (d, $^2J_{gem}$ = 10.5 Hz, 1 H, 4-H_{ax}), 2.46 [dt, ^3J = 6.8, ^3J = 1.8 Hz, 2 H, NCH_2(CH$_2$)$_2$CH$_3$], 2.41–2.34 (m, 1 H, 7-H_{exo}), 2.36–2.33 (m, 1 H, 5-H), 2.27–2.20 (m, 1 H, 7-H_{endo}), 1.97–1.91 (m, 2 H, 6-H_{endo}, 6-H_{exo}), 1.49–1.42 (m, 2 H, NCH$_2$CH_2CH$_2$CH$_3$), 1.40–1.35 [m, 2 H, N(CH$_2$)$_2$CH_2CH$_3$], 1.27 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)], 0.93 [t, ^3J = 7.2 Hz, 3 H, N(CH$_2$)$_3$CH_3]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 213.6 (C-8), 170.3 [C=O (ester)], 62.6 (C-2), 61.6 (C-4), 61.0 [CH_2 (Et)], 57.6 (C-1), 55.2 [NCH$_2$(CH$_2$)$_2$CH$_3$], 46.4 (C-5), 29.4 (NCH$_2$$CH_2CH_2CH_3$), 27.5 (C-7), 21.8 (C-6), 20.3 [N(CH$_2$)$_2$-CH$_2$CH$_3$], 14.1 [CH_3 (Et)], 13.9 [N(CH$_2$)$_3$$CH_3$].

Ethyl 3-*tert*-Butyl-8-oxo-3-azabicyclo[3.2.1]octane-1-carboxylate (23): The title compound was prepared according to general procedure B using β-keto ester **19** (100 mg, 0.64 mmol), *N,N*-bis-(ethoxymethyl)-*tert*-butylamine (**5**) (242 mg, 1.28 mmol) and trichloromethylsilane (150 μL, 1.28 mmol) in acetonitrile (2 mL). Yield 144 mg (0.57 mmol, 89%) of a clear oil; R_f = 0.40 (10% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{14}H_{23}NO_3$: 253.1678, found: 253.1678 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.21 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.26 (dd, $^2J_{gem}$ = 10.8, $^4J_{2eq,4eq}$ = 3.2 Hz, 1 H, 2-H_{eq}), 3.11 (ddd, $^2J_{gem}$ = 10.4, $^3J_{4eq,5}$ = $^4J_{2eq,4eq}$ = 3.7 Hz, 1 H, 4-H_{eq}), 2.79 (d, $^2J_{gem}$ = 10.8 Hz, 1 H, 2-H_{ax}), 2.63 (d, $^2J_{gem}$ = 10.1 Hz, 1 H, 4-H_{ax}), 2.34–2.29 (m, 2 H, 5-H, 7-H_{exo}), 2.21–2.14 (m, 1 H, 7-H_{endo}), 1.90–1.86 (m, 2 H, 6-H_{endo}, 6-H_{exo}), 1.28 [t, ^3J = 7.2 Hz, 3 H, CH_3 (Et)], 1.12 [s, 9 H, NC-(CH_3)$_3$]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 214.4 (C-8), 170.7 [C=O (ester)], 61.0 [CH_2 (Et)], 58.1 (C-1), 56.3 (C-2), 54.9 (C-4), 53.1 [NC(CH$_3$)$_3$], 46.7 (C-5), 27.4 (C-7), 27.0 [NC-(CH$_3$)$_3$], 21.6 (C-6), 14.1 [CH_3 (Et)].

Ethyl 3-Cyclohexyl-8-oxo-3-azabicyclo[3.2.1]octane-1-carboxylate (24): The title compound was prepared according to general procedure B using β-keto ester **19** (100 mg, 0.64 mmol), *N,N*-bis-(ethoxymethyl)cyclohexylamine (**6**) (276 mg, 1.28 mmol) and trichloromethylsilane (150 μL, 1.28 mmol) in acetonitrile (2 mL). Yield 147 mg (0.53 mmol, 83%) of a clear oil; R_f = 0.48 (10% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{16}H_{25}NO_3$: 279.1834, found: 279.1833 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.21 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.09 (dd, $^2J_{gem}$ = 10.7, $^4J_{2eq,4eq}$ = 2.7 Hz, 1 H, 2-H_{eq}), 2.93 (ddd, $^2J_{gem}$ = 10.8, $^3J_{4eq,5}$ = $^4J_{2eq,4eq}$ = 3.5 Hz, 1 H, 4-H_{eq}), 2.93 (d, $^2J_{gem}$ = 10.8 Hz, 1 H, 2-H_{ax}), 2.76 (d, $^2J_{gem}$ = 9.7 Hz, 1 H, 4-H_{ax}), 2.49–2.43 (m, 1 H, 1′-H), 2.35–2.30 (m, 2 H, 5-H, 7-H_{exo}), 2.21–2.14 (m, 1 H, 7-H_{endo}), 1.91–1.86 (m, 2 H, 6-H_{endo}, 6-H_{exo}), 1.82–1.75 (m, 4 H, 2′-H_a, 2′-H_b, 6′-H_a, 6′-H_b), 1.64–1.59 (m, 1 H, 4′-H_a), 1.27 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)], 1.30–1.20 (m, 4 H, 3′-H_a, 3′-H_b, 5′-H_a, 5′-H_b), 1.15–1.08 (m, 1 H, 4′-H_b). ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 214.0 (C-8), 170.5 [C=O (ester)], 61.5 (C-1′), 61.0 [CH_2 (Et)], 58.7 (C-2), 58.1 (C-1), 57.4 (C-4), 46.8 (C-5), 29.6, 29.5, 26.1, 25.7 (C-2′, C-3′, C-4′, C-5′, C-6′), 27.5 (C-7), 21.7 (C-6), 14.1 [CH_3 (Et)].

Ethyl 3-Benzyl-8-oxo-3-azabicyclo[3.2.1]octane-1-carboxylate (25): The title compound was prepared according to general procedure B using β-keto ester **19** (100 mg, 0.64 mmol), *N,N*-bis(ethoxymethyl) benzylamine (**7**) (286 mg, 1.28 mmol) and trichloromethylsilane (150 μL, 1.28 mmol) in acetonitrile (2 mL). Yield 151 mg (0.53 mmol, 83%) of a clear oil; R_f = 0.40 (10% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{17}H_{21}NO_3$: 287.1521, found: 287.1523 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35–7.24 [m, 5 H, $H_{arom.}$ (Bn)], 4.17 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.66 [d, $^2J_{gem}$ = 13.3 Hz, 1 H, CH_{2a} (Bn)], 3.60 [d, $^2J_{gem}$ = 13.3 Hz, 1 H, CH_{2b} (Bn)], 3.13 (dd, $^2J_{gem}$ = 10.9, $^4J_{2eq,4eq}$ = 2.6 Hz, 1 H, 2-H_{eq}), 2.96 (ddd, $^2J_{gem}$ = 10.5, $^3J_{4eq,5}$ = $^4J_{2eq,4eq}$ = 3.0 Hz, 1 H, 4-H_{eq}), 2.78 (d, $^2J_{gem}$ = 10.9 Hz, 1 H, 2-H_{ax}), 2.56 (d, $^2J_{gem}$ = 10.5 Hz, 1 H, 4-H_{ax}), 2.41 (ddd, $^2J_{gem}$ = $^3J_{6endo,7exo}$ = 12.1, $^3J_{6exo,7exo}$ = 4.7 Hz, 1 H, 7-H_{exo}), 2.34–2.32 (m, 1 H, 5-H), 2.32–2.27 (m, 1 H, 7-H_{endo}), 2.05–1.92 (m, 2 H, 6-H_{endo}, 6-H_{exo}), 1.25 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 213.2 (C-8), 170.0 [C=O (ester)], 138.3 (C-1$_{arom.}$), 128.5 (C-2$_{arom.}$, C-6$_{arom.}$), 128.3 (C-3$_{arom.}$, C-5$_{arom.}$), 127.2 (C-4$_{arom.}$), 62.3 (C-2), 61.1 (C-4), 61.0 [CH_2 (Et)], 60.0 [CH_2 (Bn)], 57.7 (C-1), 46.3 (C-5), 27.4 (C-7), 21.7 (C-6), 14.0 [CH_3 (Et)].

Ethyl 8-Oxo-3-(2-phenylethyl)-3-azabicyclo[3.2.1]octane-1-carboxylate (26): The title compound was prepared according to general procedure B using β-keto ester **19** (100 mg, 0.64 mmol), *N,N*-bis(ethoxymethyl)-2-phenylethylamine (**8**) (304 mg, 1.28 mmol) and trichloromethylsilane (150 μL, 1.28 mmol) in acetonitrile (2 mL). Yield 157 mg (0.52 mmol, 81%) of a clear oil; R_f = 0.35 (10% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{18}H_{23}NO_3$: 301.1678, found: 301.1674 [M$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.30–7.17 [m, 5 H, $H_{arom.}$ (Ph)], 4.20 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.18 (dd, $^2J_{gem}$ = 10.8, $^4J_{2eq,4eq}$ = 2.5 Hz, 1 H, 2-H_{eq}), 3.01 (ddd, $^2J_{gem}$ = 10.3, $^3J_{4eq,5}$ = $^4J_{2eq,4eq}$ = 2.8 Hz, 1 H, 4-H_{eq}), 2.81–2.73 (m, 5 H, 2-H_{ax}, NCH_2CH_2Ph), 2.60 (d, $^2J_{gem}$ = 10.4 Hz, 1 H, 4-H_{ax}), 2.37–2.30 (m, 2 H, 5-H, 7-H_{exo}), 2.17–2.10 (m, 1 H, 7-H_{endo}), 1.89–1.83 (m, 2 H, 6-H_{endo}, 6-H_{exo}), 1.26 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 213.3 (C-8), 170.2 [C=O (ester)], 140.0 (C-1$_{arom.}$), 128.5 (C-3$_{arom.}$,

C-5$_{arom.}$), 128.2 (C-2$_{arom.}$, C-6$_{arom.}$), 125.9 (C-4$_{arom.}$), 62.3 (C-2), 61.3 (C-4), 61.0 [CH_2 (Et)], 57.5 (C-1), 56.8 (N*C*H_2CH$_2$Ph), 46.3 (C-5), 33.7 (NCH$_2$*C*H$_2$Ph), 27.4 (C-7), 21.6 (C-6), 14.1 [CH_3 (Et)].

Ethyl 8-Oxo-3-(3-phenylpropyl)-3-azabicyclo[3.2.1]octane-1-carboxylate (27): The title compound was prepared according to general procedure B using β-keto ester **19** (100 mg, 0.64 mmol), *N,N*-bis(ethoxymethyl)-3-phenylpropylamine (**9**) (322 mg, 1.28 mmol) and trichloromethylsilane (150 μL, 1.28 mmol) in acetonitrile (2 mL). Yield 169 mg (0.54 mmol, 84%) of a clear oil; R_f = 0.49 (10% EtOAc in hexane). HRMS (EI): *m/z* calcd. for $C_{19}H_{25}NO_3$: 315.1834, found: 315.1833 [M^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.30–7.16 [m, 5 H, H$_{arom.}$ (Ph)], 4.20 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.14 (dd, $^2J_{gem}$ = 10.9, $^4J_{2eq,4eq}$ = 2.5 Hz, 1 H, 2-H$_{eq}$), 2.98 (ddd, $^2J_{gem}$ = 10.4, $^3J_{4eq,5}$ = $^4J_{2eq,4eq}$ = 3.0 Hz, 1 H, 4-H$_{eq}$), 2.72 (d, $^2J_{gem}$ = 10.9 Hz, 1 H, 2-H$_{ax}$), 2.69 [t, ^3J = 7.0 Hz, 2 H, N(CH$_2$)$_2$C*H*$_2$Ph], 2.52–2.44 [m, 3 H, 4-H$_{ax}$, NC*H*$_2$(CH$_2$)$_2$Ph], 2.43-2.38 (m, 1 H, 7-H$_{*exo*}$), 2.37–2.34 (m, 1 H, 5-H), 2.30–2.23 (m, 1 H, 7-H$_{*endo*}$), 2.00–1.93 (m, 2 H, 6-H$_{*endo*}$, 6-H$_{*exo*}$), 1.81 (quin, ^3J = 7.3 Hz, 2 H, NCH$_2$C*H*$_2$CH$_2$Ph), 1.27 [t, 3 H, CH_3 (Et), ^3J = 7.1 Hz]. ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 213.4 (C-8), 170.2 [C=O (ester)], 141.9 (C-1$_{arom.}$), 128.4 (C-3$_{arom.}$, C-5$_{arom.}$), 128.3 (C-2$_{arom.}$, C-6$_{arom.}$), 125.8 (C-4$_{arom.}$), 62.5 (C-2), 61.5 (C-4), 61.0 [CH_2 (Et)], 57.6 (C-1), 54.4 [N*C*H$_2$(CH$_2$)$_2$Ph], 46.3 (C-5), 33.1 [N(CH$_2$)$_2$*C*H$_2$Ph], 28.9 (NCH$_2$*C*H$_2$CH$_2$Ph), 27.6 (C-7), 21.8 (C-6), 14.1 [CH_3 (Et)].

Ethyl 3-Benzyl-9-oxo-5-(2-propenyl)-3-azabicyclo[3.3.1]nonane-1-carboxylate (30): The title compound was prepared according to general procedure B using β-keto ester **28** (100 mg, 0.48 mmol), *N,N*-bis(ethoxymethyl)benzylamine (**2**) (214 mg, 0.96 mmol) and trichloromethylsilane (113 μL, 0.96 mmol) in acetonitrile (2 mL). Yield 95 mg (0.28 mmol, 58%) of a clear oil; R_f = 0.37 (5% EtOAc in hexane). HRMS (EI): *m/z* calcd. for $C_{21}H_{27}NO_3$: 341.1991, found: 341.1994 [M^+]. ^{1}H NMR (400 MHz, COSY, $CDCl_3$): δ (ppm) = 7.34–7.25 [m, 5 H, H$_{arom.}$ (Bn)], 5.78–5.71 (m, 1 H, CH$_2$C*H*=CH$_2$), 5.01 (dd, $^2J_{gem}$ = 2.2, $^3J_{*cis*}$ = 10.2 Hz, 1 H, CH$_2$CH=C*H*$_a$H$_b$), 4.98 (dd, $^2J_{gem}$ = 2.1, $^3J_{*trans*}$ = 16.8 Hz, 1 H, CH$_2$CH=CH$_a$*H*$_b$), 4.17 [dq, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.56 [d, 1 H, CH$_{2a}$ (Bn), $^2J_{gem}$ = 13.1 Hz], 3.43 [d, $^2J_{gem}$ = 13.1 Hz, 1 H, CH$_{2b}$ (Bn)], 3.14 (dd, $^2J_{gem}$ = 11.4, $^4J_{2eq,4eq}$ = 2.3 Hz, 1 H, 4-H$_{eq}$), 3.08–2.98 (m, 1 H, 7-H$_{ax}$), 3.01 (dd, $^2J_{gem}$ = 11.1, $^4J_{2eq,4eq}$ = 2.5 Hz, 1 H, 2-H$_{eq}$), 2.96 (dd, $^2J_{gem}$ = 11.4, $^4J_{4ax,6ax}$ = 1.7 Hz, 1 H, 4-H$_{ax}$), 2.54 (dddd, $^2J_{gem}$ = $^3J_{6ax,7ax}$ = 12.1, $^3J_{6ax,7eq}$ = 6.4, $^4J_{4ax,6ax}$ = 1.8 Hz, 1 H, 6-H$_{ax}$), 2.37 (dd, $^2J_{gem}$ = 11.2, $^4J_{2ax,8ax}$ = 1.8 Hz, 1 H, 2-H$_{ax}$), 2.22–2.17 (m, 1 H, 6-H$_{eq}$), 2.15 (t, ^3J = 7.8 Hz, 2 H, C*H*$_2$CH=CH$_2$), 2.12–2.07 (m, 1 H, 8-H$_{eq}$), 1.84–1.73 (m, 1 H, 8-H$_{ax}$), 1.62–1.55 (m, 1 H, 7-H$_{eq}$), 1.26 (t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)]. ^{13}C NMR (100 MHz, BB, DEPT, HSQC, $CDCl_3$): δ (ppm) = 212.4 (C-9), 171.0 [C=O (ester)], 138.2 (C-1$_{arom.}$), 133.6 (CH$_2$*C*H=CH$_2$), 128.6 (C-2$_{arom.}$, C-6$_{arom.}$), 128.4 (C-3$_{arom.}$, C-5$_{arom.}$), 127.2 (C-4$_{arom.}$), 118.0 (CH$_2$CH=*C*H$_2$), 65.0 (C-2), 62.1 [CH_2 (Bn)], 61.7 (C-4), 61.0 [CH_2 (Et)], 58.9 (C-1), 49.0 (C-5), 39.2 (*C*H$_2$CH=CH$_2$), 39.1 (C-8), 36.6 (C-6), 20.5 (C-7), 14.0 [CH_3 (Et)].

Ethyl 9-Oxo-3-(3-phenylpropyl)-5-(2-propenyl)-3-azabicyclo[3.3.1]-nonane-1-carboxylate (31): The title compound was prepared according to general procedure B using β-keto ester **28** (650 mg, 3.09 mmol), *N,N*-bis(ethoxymethyl)-3-phenylpropylamine (**11**) (1.55 g, 6.18 mmol) and trichloromethylsilane (726 μL, 6.18 mmol) in acetonitrile (15 mL). Yield 882 mg (2.39 mmol, 77%) of a clear oil; R_f = 0.40 (5% EtOAc in hexane). HRMS (EI): *m/z* calcd. for $C_{23}H_{31}NO_3$: 369.2304, found: 369.2301 [M^+]. ^{1}H NMR (400 MHz, COSY, $CDCl_3$): δ (ppm) = 7.31–7.19 [m, 5 H, H$_{arom.}$ (Ph)], 5.82–5.73 (m, 1 H, CH$_2$C*H*=CH$_2$), 5.05 (dd, $^2J_{gem}$ = 2.0, $^3J_{*cis*}$ = 9.9 Hz, 1 H, CH$_2$CH=C*H*$_a$H$_b$), 5.01 (dd, $^2J_{gem}$ = 2.0, $^3J_{*trans*}$ = 16.8 Hz, 1 H, CH$_2$CH=CH$_a$*H*$_b$), 4.21 [q, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.18 (dd, $^2J_{gem}$ = 11.4, $^4J_{2eq,4eq}$ = 2.2 Hz, 1 H, 4-H$_{eq}$), 3.02–2.91 (m, 1 H, 7-H$_{ax}$), 3.00 (dd, $^2J_{gem}$ = 11.2, $^4J_{2eq,4eq}$ = 2.1 Hz, 1 H, 2-H$_{eq}$), 2.94 (dd, $^2J_{gem}$ = 11.8, $^4J_{4ax,6ax}$ = 1.1 Hz, 1 H, 4-H$_{ax}$), 2.68 [t, ^3J = 7.5 Hz, 2 H, N(CH$_2$)$_2$C*H*$_2$Ph], 2.58–2.50 (m, 1 H, 6-H$_{ax}$), 2.34 [t, ^3J = 7.0 Hz, 2 H, NC*H*$_2$(CH$_2$)$_2$Ph], 2.31–2.27 (m, 1 H, 2-H$_{ax}$), 2.24–2.20 (m, 1 H, 6-H$_{eq}$), 2.17 (t, 2 H, C*H*$_2$CH=CH$_2$, ^3J = 6.9 Hz), 2.14–2.08 (m, 1 H, 8-H$_{eq}$), 1.85–1.78 (m, 1 H, 8-H$_{ax}$), 1.82 (quin, ^3J = 7.3 Hz, 2 H, NCH$_2$C*H*$_2$CH$_2$Ph), 1.57–1.53 (m, 1 H, 7-H$_{eq}$), 1.29 [t, ^3J = 7.1 Hz, 3 H, CH_3 (Et)]. ^{13}C NMR (100 MHz, BB, DEPT, HSQC, $CDCl_3$): δ (ppm) = 212.6 (C-9), 171.3 [C=O (ester)], 142.1 (C-1$_{arom.}$), 133.7 (CH$_2$*C*H=CH$_2$), 128.4 (C-2$_{arom.}$, C-3$_{arom.}$, C-5$_{arom.}$, C-6$_{arom.}$), 125.9 (C-4$_{arom.}$), 118.1 (CH$_2$CH=*C*H$_2$), 65.0 (C-2), 62.1 (C-4), 61.2 [CH_2 (Et)], 59.0 (C-1), 56.5 [N*C*H$_2$(CH$_2$)$_2$Ph], 49.0 (C-5), 39.4 (*C*H$_2$CH=CH$_2$), 39.3 (C-8), 36.9 (C-6), 33.5 [N(CH$_2$)$_2$*C*H$_2$Ph], 29.1 (NCH$_2$*C*H$_2$CH$_2$Ph), 20.4 (C-7), 14.2 [CH_3 (Et)].

Ethyl 3-Ethyl-8-oxo-5-(2-propenyl)-3-azabicyclo[3.2.1]octane-1-carboxylate (32): The title compound was prepared according to general procedure B using β-keto ester **29** (100 mg, 0.51 mmol), *N,N*-bis(ethoxymethyl)ethylamine (**5**) (164 mg, 1.02 mmol) and trichloromethylsilane (120 μL, 1.02 mmol) in acetonitrile (2 mL). Yield 101 mg (0.38 mmol, 75%) of a clear oil; R_f = 0.30 (10% EtOAc in hexane). HRMS (EI): *m/z* calcd. for $C_{15}H_{23}NO_3$: 265.1678, found: 265.1676 [M^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.78–5.68 (m, 1 H, CH$_2$C*H*=CH$_2$), 5.06–5.02 (m, 2 H, CH$_2$CH=C*H*$_2$), 4.21 [dq, ^3J = 7.1 Hz, 2 H, CH_2 (Et)], 3.13 (d, $^2J_{gem}$ = 10.8 Hz, 1 H, 4-H$_{eq}$), 2.85 (d, $^2J_{gem}$ = 10.4 Hz, 1 H, 2-H$_{eq}$), 2.69 (d, $^2J_{gem}$ = 10.7 Hz, 1 H, 4-H$_{ax}$), 2.53 (q, ^3J = 7.2 Hz, 2 H, NC*H*$_2$CH$_3$), 2.33 (ddd, $^2J_{gem}$ = $^3J_{*6endo,7exo*}$ = 12.1, $^3J_{*6exo,7exo*}$ = 4.4 Hz, 1 H, 7-H$_{*exo*}$), 2.25–2.12 (m, 4 H, 2-H$_{ax}$, 7-H$_{*endo*}$, C*H*$_2$CH=CH$_2$), 1.99 (ddd, $^2J_{gem}$ = $^3J_{*6exo,7endo*}$ = 12.2, $^3J_{*6exo,7exo*}$ = 4.3 Hz, 1 H, 6-H$_{*exo*}$), 1.75 (ddd, $^2J_{gem}$ = $^3J_{*6endo,7exo*}$ = 12.2, $^3J_{*6endo,7endo*}$ = 4.7 Hz, 1 H, 6-H$_{*endo*}$), 1.27 [t, 3 H, CH_3 (Et), ^3J = 7.1 Hz], 1.08 (t, ^3J = 7.2 Hz, 3 H, NCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, BB, DEPT, $CDCl_3$): δ (ppm) = 213.9 (C-8), 170.3 [C=O (ester)], 133.6 (CH$_2$*C*H=CH$_2$), 117.9 (CH$_2$CH=*C*H$_2$), 65.6 (C-2), 62.2 (C-4), 61.0 [CH_2 (Et)], 58.6 (C-1), 50.7 (C-5), 49.7 (N*C*H$_2$CH$_3$), 35.1 (*C*H$_2$CH=CH$_2$), 27.1 (C-7), 26.6 (C-6), 14.1 [CH_3 (Et)], 12.5 (NCH$_2$*C*H$_3$).

(1*R,5*S**,9*S**)-1-Hydroxymethyl-3-(3-phenylpropyl)-3-azabicyclo-[3.3.1]nonan-9-ol (33a) and (1*R**,5*S**,9*R**)-1-Hydroxymethyl-3-(3-phenylpropyl)-3-azabicyclo-[3.3.1]nonan-9-ol (33b):** To a slurry of lithium aluminium hydride (334 mg, 8.79 mmol) in dry THF (80 mL) was added dropwise a solution of β-keto ester **18** (965 mg, 2.93 mmol) in dry THF (20 mL) under nitrogen. The reaction mixture was stirred for 1 h at room temperature. Sodium sulphate decahydrate (excess, 1 g) was added and stirring was continued for 1 h. The mixture was filtered through Celite and the solvent removed under reduced pressure. The residue was dissolved in diethyl ether (100 mL), washed with aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. The alcohols **33a** and **33b** were isolated by flash chromatography (3% MeOH in CH_2Cl_2). **Diastereomer 33a:** Yield 419 mg (1.45 mmol, 50%) of a yellow oil; R_f = 0.34 (5% MeOH in CH_2Cl_2). HRMS (EI): *m/z* calcd. for $C_{18}H_{27}NO_2$: 289.2042, found: 289.2040 [M^+]. ^{1}H NMR (400 MHz, COSY, NOESY, $CDCl_3$): δ (ppm) = 7.29–7.15 [m, 5 H, H$_{arom.}$ (Ph)], 3.70 (d, $^3J_{5,9}$ = 3.7 Hz, 1 H, 9-H), 3.40 (d, $^2J_{gem}$ = 10.7 Hz, 1 H, C*H*$_a$H$_b$OH), 3.34 (d, $^2J_{gem}$ = 10.8 Hz), , 1 H, CH$_a$*H*$_b$OH3.11 (br., 1 H, OH), 2.94 (d, $^2J_{gem}$ = 10.9 Hz, 1 H, 4-H$_{eq}$), 2.70–2.59 (m, 2 H, 2-H$_{eq}$, 7-H$_{ax}$), 2.64 [t, 2 H, N(CH$_2$)$_2$C*H*$_2$Ph, ^3J = 7.7 Hz], 2.20–2.15 [m, 3 H, 4-H$_{ax}$, NC*H*$_2$(CH$_2$)$_2$Ph], 2.05–1.89 (m, 2 H, 6-H$_{ax}$, 8-H$_{ax}$), 1.85–1.80 (m, 2 H, 2-H$_{ax}$, 5-H), 1.75 (quin, ^3J = 7.4 Hz, 2 H,

$NCH_2CH_2CH_2Ph$), 1.55–1.51 (m, 2 H, 6-H_{eq}, 7-H_{eq}), 1.28 (dd, $^2J_{gem}$ = 13.5, $^3J_{7ax,8eq}$ = 6.2 Hz, 1 H, 8-H_{eq}). ^{13}C NMR (100 MHz, BB, DEPT, HSQC, $CDCl_3$): δ (ppm) = 142.5 (C-$1_{arom.}$), 128.4 (C-$3_{arom.}$, C-$5_{arom.}$), 128.2 (C-$2_{arom.}$, C-$6_{arom.}$), 125.6 (C-$4_{arom.}$), 75.3 (C-9), 71.0 (CH_2OH), 60.9 (C-2), 58.7 (C-4), 57.5 [$NCH_2(CH_2)_2$-Ph], 38.1 (C-1), 36.2 (C-5), 33.4 [$N(CH_2)_2CH_2Ph$], 29.0 ($NCH_2CH_2CH_2Ph$), 26.6 (C-8), 23.9 (C-6), 20.6 (C-7). The ^1H-^1H-NOESY NMR spectra (300 MHz, $CDCl_3$, $T_{mix.}$ = 800 ms) shows NOEs between 9-H and 2-H_{ax}. NOEs between 9-H and 6-H_{ax} or 8-H_{ax} are not observed. **Diastereomer 33b:** Yield 131 mg (0.45 mmol, 15%) of a yellow oil; R_f = 0.26 (5% MeOH in CH_2Cl_2). HRMS (EI): *m*/*z* calcd. for $C_{18}H_{27}NO_2$: 289.2042, found: 289.2041 [M^+]. ^1H NMR (400 MHz, COSY, NOESY, $CDCl_3$): δ (ppm) = 7.29–7.15 [m, 5 H, $H_{arom.}$ (Ph)], 3.62 (d, $^3J_{5,9}$ = 3.0 Hz, 1 H, 9-H), 3.48 (d, $^2J_{gem}$ = 10.9 Hz, 1 H, CH_aH_bOH), 3.40 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, CH_aH_bOH), 2.71 (d, $^2J_{gem}$ = 11.6 Hz, 1 H, 2-H_{ax}), 2.69–2.66 (m, 1 H, 4-H_{ax}), 2.63 [t, ^3J = 7.5 Hz, 2 H, $N(CH_2)_2$-CH_2Ph], 2.50 (d, $^2J_{gem}$ = 11.5 Hz, 1 H, 2-H_{eq}), 2.47–2.38 (m, 1 H, 7-H_{ax}), 2.35 (d, $^2J_{gem}$ = 11.3 Hz, 1 H, 4-H_{eq}), 2.31–2.27 [m, 2 H, $NCH_2(CH_2)_2Ph$], 1.97 (br., 1 H, 5-H), 1.83–1.74 (m, 1 H, 6-H_{eq}), 1.79 (quin, ^3J = 7.4 Hz, 2 H, $NCH_2CH_2CH_2Ph$), 1.61–1.53 (m, 1 H, 6-H_{ax}), 1.45–1.38 (m, 2 H, 7-H_{eq}, 8-H_{eq}), 1.26–1.21 (m, 1 H, 8-H_{ax}). ^{13}C NMR (100 MHz, BB, DEPT, HSQC, $CDCl_3$): δ (ppm) = 142.3 (C-$1_{arom.}$), 128.4 (C-$3_{arom.}$, C-$5_{arom.}$), 128.2 (C-$2_{arom.}$, C-$6_{arom.}$), 125.6 (C-$4_{arom.}$), 75.8 (C-9), 71.3 (CH_2OH), 57.6 [$NCH_2(CH_2)_2Ph$], 54.9 (C-2), 52.4 (C-4), 39.0 (C-1), 36.4 (C-5), 33.6 (C-8), 33.4 [$N(CH_2)_2CH_2Ph$], 30.7 (C-6), 28.7 ($NCH_2CH_2CH_2Ph$), 19.6 (C-7). The ^1H-^1H-NOESY NMR spectra (300 MHz, $CDCl_3$, $T_{mix.}$ = 800 ms) shows NOEs between 9-H and 6-H_{ax} and between 9-H and 8-H_{ax}. NOEs between 9-H and 2-H_{ax} or 4-H_{ax} are not observed.

(1*R,5*S**,8*S**)-1-Hydroxymethyl-3-(3-phenylpropyl)-3-azabicyclo-[3.2.1]octan-8-ol (40):** To a slurry of lithium aluminium hydride (47 mg, 1.23 mmol) in dry THF (10 mL) was added dropwise a solution of β-keto ester **27** (130 mg, 0.41 mmol) in dry THF (5 mL) at 0 °C. The reaction mixture was stirred for 3 h at room temperature. The reaction was quenched by the addition of distilled water (20 mL), and the volatiles were removed at reduced pressure. The remaining aqueous solution was extracted with diethyl ether (3 × 50 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (10% MeOH in CH_2Cl_2). Yield 60 mg (0.22 mmol, 54%) of a yellow oil; R_f = 0.34 (10% MeOH in CH_2Cl_2). HRMS (EI): *m*/*z* calcd. for $C_{17}H_{25}NO_2$: 275.1885, found: 275.1886 [M^+]. ^1H NMR (300 MHz, COSY, $CDCl_3$): δ (ppm) = 7.29–7.16 [m, 5 H, $H_{arom.}$ (Ph)], 3.88 (d, $^3J_{5,8}$ = 4.8 Hz, 1 H, 8-H), 3.61 (s, 2 H, CH_2OH), 2.68–2.61 [m, 3 H, 2-H_{eq}, $N(CH_2)_2CH_2Ph$], 2.53–2.46 (m, 2 H, 4-H_{eq}, 4-H_{ax}), 2.41–2.32 [m, 3 H, 2-H_{ax}, $NCH_2(CH_2)_2Ph$], 2.09 (br., 1 H, 5-H), 1.82–1.62 (m, 5 H, 6-H_{endo}, 6-H_{exo}, 7-H_{exo}, $NCH_2CH_2CH_2Ph$), 1.32–1.22 (m, 1 H, 7-H_{endo}). ^{13}C NMR (75 MHz, BB, DEPT, HSQC, $CDCl_3$): δ (ppm) = 142.5 (C-$1_{arom.}$), 128.5 (C-$3_{arom.}$, C-$5_{arom.}$), 128.2 (C-$2_{arom.}$, C-$6_{arom.}$), 125.6 (C-$4_{arom.}$), 75.9 (C-8), 69.6 (CH_2OH), 56.9 [$NCH_2(CH_2)_2Ph$], 54.7 (C-2), 51.8 (C-4), 44.7 (C-1), 39.7 (C-5), 33.4 [$N(CH_2)_2$-CH_2Ph], 29.0 (C-7), 28.7 ($NCH_2CH_2CH_2Ph$), 24.2 (C-6).

(1*R,5*S**,9*S**)-9-Hydroxy-3-(3-phenylpropyl)-3-azabicyclo[3.3.1]-non-1-ylmethyl 2-Aminobenzoate (35), (1*R**,5*S**,9*S**)-1-Hydroxymethyl-3-(3-phenylpropyl)-3-azabicyclo[3.3.1]non-9-yl 2-Aminobenzoate (36) and (1*R**,5*S**,9*S**)-9-(2-Aminobenzoyl)-3-(3-phenylpropyl)-3-azabicyclo[3.3.1]non-1-ylmethyl 2-Aminobenzoate (37):** To a solution of diol **33a** (280 mg, 0.97 mmol), *N*-(trifluoroacetyl) anthranilic acid (**34**)[17] (226 mg, 0.97 mmol) and 4-(dimethylamino)pyridine (60 mg, 0.49 mmol) in acetonitrile (10 mL) was added 1,3-dicyclohexylcarbodiimide (200 mg, 0.97 mmol), and the reaction mixture was stirred for 8 h at 40 °C. The reaction mixture was cooled, filtered, and the filtrate evaporated to dryness. The residue was dissolved in dichloromethane (30 mL), washed with aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude ester was dissolved in dry ethanol (20 mL), treated with sodium borohydride (73 mg, 1.94 mmol) and stirred for 20 h at room temperature. The reaction mixture was quenched with dist. water (20 mL), and the volatiles were removed at reduced pressure. The residue was dissolved in ethyl acetate (50 mL), washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The title compounds **35**, **36** and **37** were separated by flash chromatography (15% EtOAc in hexane).

Monoester 35: Yield 117 mg (0.29 mmol, 30%) of a yellow oil; R_f = 0.27 (20% EtOAc in hexane); HRMS (EI): *m*/*z* calcd. for $C_{25}H_{32}N_2O_3$: 408.2413, found: 408.2410 [M^+]. ^1H NMR (300 MHz, COSY, $CDCl_3$): δ (ppm) = 7.84 (d, $^3J_{5',6'}$ = 8.1 Hz, 1 H, 6′-$H_{arom.}$), 7.30–7.18 [m, 6 H, $H_{arom.}$ (Ph), 4′-$H_{arom.}$], 6.67–6.63 (m, 2 H, 3′-$H_{arom.}$, 5′-$H_{arom.}$), 5.72 (br., 2 H, NH_2), 4.46 (d, $^2J_{gem}$ = 11.4 Hz, 1 H, CH_aH_bO), 3.66 (d, $^2J_{gem}$ = 11.4 Hz, 1 H, CH_aH_bO), 3.51 (br., 1 H, 9-H), 2.94 (d, $^2J_{gem}$ = 11.1 Hz, 1 H, 4-H_{eq}), 2.85 (d, $^2J_{gem}$ = 10.4 Hz, 1 H, 2-H_{eq}), 2.83 (br., 1 H, OH), 2.68–2.63 (m, 1 H, 7-H_{ax}), 2.65 [t, ^3J = 7.4 Hz, 2 H, $N(CH_2)_2CH_2Ph$], 2.20 [t, ^3J = 7.3 Hz, 2 H, $NCH_2(CH_2)_2Ph$], 2.15 (d, $^2J_{gem}$ = 13.0 Hz, 2 H, 2-H_{ax}, 4-H_{ax}), 2.08–1.94 (m, 1 H, 6-H_{ax}), 1.90 (br., 1 H, 5-H), 1.81–1.72 (m, 3 H, $NCH_2CH_2CH_2Ph$, 8-H_{ax}), 1.57–1.50 (m, 2 H, 6-H_{eq}, 7-H_{eq}), 1.411.35 (m, 1 H, 8-H_{eq}). ^{13}C NMR (75 MHz, BB, DEPT, HSQC, $CDCl_3$): δ (ppm) = 168.7 (C=O (ester)], 150.8 (C-2′$_{arom.}$), 142.5 (C-$1_{arom.}$), 134.4 (C-4′$_{arom.}$), 131.2 (C-6′$_{arom.}$), 128.4 (C-$3_{arom.}$, C-$5_{arom.}$), 128.3 (C-$2_{arom.}$, C-$6_{arom.}$), 125.6 (C-$4_{arom.}$), 116.8 (C-5′$_{arom.}$), 116.3 (C-3′$_{arom.}$), 110.3 (C-1′$_{arom.}$), 71.0 (C-9), 68.9 (CH_2O), 61.1 (C-2), 59.1 (C-4), 57.5 [$NCH_2(CH_2)_2Ph$], 39.0 (C-1), 35.4 (C-5), 33.4 [$N(CH_2)_2CH_2Ph$], 29.1 ($NCH_2CH_2CH_2Ph$), 27.3 (C-8), 24.1 (C-6), 20.7 (C-7).

Monoester 36: Yield 26 mg (0.06 mmol, 6%) of a yellow oil; R_f = 0.33 (20% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{25}H_{32}N_2O_3$: 408.2413, found: 408.2413 [M^+].

Diester 37: Yield 97 mg (0.18 mmol, 19%) of a yellow oil; R_f = 0.44 (20% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{32}H_{37}N_3O_4$: 527.2784, found: 527.2776 [M^+]. ^1H NMR (300 MHz, COSY, $CDCl_3$): δ (ppm) = 7.91 (dd, $^3J_{5',6'}$ = 8.3, $^4J_{4',6'}$ = 1.2 Hz, 1 H, 6′-$H_{arom.}$), 7.85 (dd, $^3J_{5',6'}$ = 8.3, $^4J_{4',6'}$ = 1.4 Hz, 1 H, 6′-$H_{arom.}$), 7.31–7.18 [m, 7 H, $H_{arom.}$ (Ph), 4′-$H_{arom.}$ (2×)], 6.67–6.60 [m, 4 H, 3′-$H_{arom.}$ (2×), 5′-$H_{arom.}$ (2×)], 5.71 (br., 2 H, NH_2), 5.65 (br., 2 H, NH_2), 5.11 (d, $^3J_{5,9}$ = 3.6 Hz, 1 H, 9-H), 4.08 (d, $^2J_{gem}$ = 11.1 Hz, 1 H, CH_aH_bO), 4.01 (d, $^2J_{gem}$ = 11.1 Hz, 1 H, CH_aH_bO), 3.01 (d, $^2J_{gem}$ = 11.5 Hz, 2 H, 2-H_{eq}, 4-H_{eq}), 2.87–2.72 (m, 1 H, 7-H_{ax}), 2.67 [t, ^3J = 7.4 Hz, 2 H, $N(CH_2)_2CH_2Ph$], 2.39 (d, $^2J_{gem}$ = 11.5 Hz, 1 H, 4-H_{ax}), 2.29–2.23 (m, 2 H, 2-H_{ax}, 5-H), 2.25 [t, ^3J = 6.9 Hz, 2 H, $NCH_2(CH_2)_2Ph$], 2.01–1.90 (m, 2 H, 6-H_{ax}, 8-H_{ax}), 1.83–1.73 (m, 3 H, $NCH_2CH_2CH_2Ph$, 8-H_{eq}), 1.68–1.60 (m, 2 H, 6-H_{eq}, 7-H_{eq}). ^{13}C NMR (75 MHz, BB, DEPT, HSQC, $CDCl_3$): δ (ppm) = 167.8, 167.2 [C=O (2× ester)], 150.7, 150.5 [C-2′$_{arom.}$ (2×)], 142.4 (C-$1_{arom.}$), 134.1, 134.0 [C-4′$_{arom.}$ (2×)], 131.1, 131.0 [C-6′$_{arom.}$ (2×)], 128.4 (C-$3_{arom.}$, C-$5_{arom.}$), 128.3 (C-$2_{arom.}$, C-$6_{arom.}$), 125.7 (C-$4_{arom.}$), 116.7, 116.6 [C-5′$_{arom.}$ (2×)], 116.3 [C-3′$_{arom.}$ (2×)], 110.9, 110.7 [C-1′$_{arom.}$ (2×)], 74.3 (C-9), 68.7 (CH_2O), 61.5 (C-2), 58.4 (C-4), 57.3 [$NCH_2(CH_2)_2Ph$], 37.9 (C-1), 33.4 [C-5, $N(CH_2)_2$-CH_2Ph], 29.0 ($NCH_2CH_2CH_2Ph$), 28.6 (C-8), 25.1 (C-6), 20.6 (C-7).

(1*R,5*S**,8*S**)-8-(2-Aminobenzoyl)-3-(3-phenylpropyl)-3-azabicyclo-[3.2.1]oct-1-ylmethyl 2-Amino-benzoate (41):** Diol **40** (75 mg,

0.27 mmol) was converted directly into the diester **41** using a similar procedure to that described above using two equiv. of *N*-(trifluoroacetyl)anthranilic acid **34** (126 mg, 0.54 mmol), two equiv. of 1,3-dicyclohexylcarbodiimide (111 mg, 0.54 mmol) and 0.1 equiv. of 4-(dimethylamino)pyridine (4 mg, 0.03 mmol) in acetonitrile (10 mL). Subsequent *N*-deprotection with four equiv. of sodium borohydride (41 mg, 1.08 mmol) in dry ethanol (10 mL) gave diester **41** after purification by flash chromatography (25% EtOAc in hexane). Yield 44 mg (0.09 mmol, 33% over 2 steps) of a clear oil; R_f = 0.69 (33% EtOAc in hexane). HRMS (EI): *m*/*z* calcd. for $C_{31}H_{35}N_3O_4$: 513.2628, found: 513.2630 [M^+]. ^{1}H NMR (300 MHz, COSY, $CDCl_3$): δ (ppm) = 7.89 (d, $^3J_{5',6'}$ = 7.9 Hz, 1 H, 6′-$H_{arom.}$), 7.76 (d, $^3J_{5',6'}$ = 7.2 Hz, 1 H, 6′-$H_{arom.}$), 7.30–7.17 [m, 7 H, $H_{arom.}$ (Ph), 4′-$H_{arom.}$ (2×)], 6.62 [t, $^3J_{3',4'}$ = $^3J_{4',5'}$ = 8.1 Hz, 3 H, 3′-$H_{arom.}$ (2×), 5′-$H_{arom.}$], 6.52 (t, $^3J_{4',5'}$ = 7.4 Hz, 1 H, 5′-$H_{arom.}$), 5.70 (br., 2 H, NH_2), 5.64 (br. s, 2 H, NH_2), 5.06 (d, $^3J_{5,8}$ = 4.8 Hz, 1 H, 8-H), 4.25 (d, $^2J_{gem}$ = 11.2 Hz, 1 H, C$H_a$$H_b$O), 4.17 (d, $^2J_{gem}$ = 11.2 Hz, 1 H, C$H_a$$H_b$O), 2.69 (t, ^3J = 7.5 Hz, 4 H, NCH_2CH$_2$CH_2Ph), 2.66–2.55 (m, 1 H, 4-H_{eq}), 2.54–2.42 (m, 4 H, 2-H_{ax}, 2-H_{eq}, 4-H_{ax}, 5-H), 2.08–1.96 (m, 1 H, 7-H_{exo}), 1.921.77 (m, 4 H, NCH$_2$CH_2CH$_2$Ph, 6-H_{endo}, 6-H_{exo}), 1.70 (ddd, $^2J_{gem}$ = 15.5, $^3J_{6exo,7endo}$ = $^4J_{5,7endo}$ = 4.4 Hz, 1 H, 7-H_{endo}). ^{13}C NMR (75 MHz, BB, HSQC, $CDCl_3$): δ (ppm) = 167.8, 167.2 [C=O (2× ester)], 150.7, 150.5 [C-2′$_{arom.}$ (2×)], 142.4 (C-1$_{arom.}$), 134.2, 134.0 [C-4′$_{arom.}$ (2×)], 131.2, 131.0 [C-6′$_{arom.}$ (2×)], 128.5 (C-3$_{arom.}$, C-5$_{arom.}$), 128.3 (C-2$_{arom.}$, C-6$_{arom.}$), 125.7 (C-4$_{arom.}$), 116.7, 116.6 [C-5′$_{arom.}$ (2×)], 116.3, 116.2 [C-3′$_{arom.}$ (2×)], 110.9, 110.7 [C-1′$_{arom.}$ (2×)], 74.8 (C-8), 67.3 (CH_2O), 56.8 (C-2), 55.6 [NCH_2(CH$_2$)$_2$Ph], 52.6 (C-4), 44.2 (C-1), 37.4 (C-5), 33.3 [N(CH$_2$)$_2$CH_2Ph], 28.9 (C-7), 28.7 (NCH$_2$CH_2CH$_2$Ph), 23.9 (C-6).

(1*R,5*S**,9*S**)-2-Methyl-4-{[1-({[2-(3-methyl-2,5-dioxo-1-pyrrolidinyl)benzoyl]oxy}methyl)-4-oxo-3-(3-phenylpropyl)-3-azabicyclo[3.3.1]non-9-yl]oxy}butanoic Acid (38a) and (1*R**,5*S**,9*S**)-3-Methyl-4-{[1-({[2-(3-methyl-2,5-dioxo-1-pyrrolidinyl)benzoyl]oxy}methyl)-4-oxo-3-(3-phenylpropyl)-3-azabicyclo[3.3.1]non-9-yl]-oxy}butanoic Acid (38b):** A mixture of the amine **35** (68 mg, 0.17 mmol) and methylsuccinic anhydride (58 mg, 0.51 mmol) was heated at 125 °C for 4 h. The reaction mixture was then dissolved in warm ethyl acetate (30 mL), washed with aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (100% EtOAc). Yield 49 mg (0.08 mmol, 47%) of a yellow oil; R_f = 0.40 (20% hexane in EtOAc). HRMS (FAB): *m*/*z* calcd. for $C_{35}H_{43}N_2O_8$: 619.3019, found: 619.3024 ([M + H]$^+$). ^{1}H NMR (400 MHz, COSY, $CDCl_3$): δ (ppm) = 8.17, 8.09 (2× d, $^3J_{5',6'}$ = 7.3 Hz, 1 H, 6′-$H_{arom.}$), 7.65 (t, $^3J_{3',4'}$ = $^3J_{4',5'}$ = 7.6 Hz, 1 H, 4′-$H_{arom.}$), 7.55 (dd, $^3J_{4',5'}$ = $^3J_{5',6'}$ = 8.1 Hz, 1 H, 5′-$H_{arom.}$), 7.30–7.16 [m, 6 H, $H_{arom.}$ (Ph), 3′-$H_{arom.}$,], 5.08, 4.91 (2× s_b, 1 H, 9-H), 4.00–3.76 (m, 2 H, CH_2O), 3.15–2.82 (m, 5 H, 2-H_{eq}, 4-H_{eq}, {2‴-H, 3‴-H_a, 3‴-H_b} or {2‴-H_a, 2‴-H_b, 3‴-H}), 2.74–2.63 (m, 2 H, 7-H_{ax}, 3″-H), 2.64 [t, ^3J = 7.2 Hz, 2 H, N(CH$_2$)$_2$CH_2Ph], 2.54–2.44 (m, 1 H, 4″-H_a), 2.42–2.24 [m, 5 H, 2-H_{ax}, 4-H_{ax}, NCH_2(CH$_2$)$_2$Ph, 4″-H_b], 2.12, 2.06 (2× br, 1 H, 5-H), 1.90–1.73 (m, 3 H, 6-H_{ax}, NCH$_2$CH_2CH$_2$Ph), 1.64–1.44 (m, 7 H, 6-H_{eq}, 7-H_{eq}, 8-H_{ax}, 8-H_{eq}, 3″-CH_3), 1.30–1.15 (m, 3 H, 2‴-CH_3 or 3‴-CH_3). ^{13}C NMR (75 MHz, BB, HSQC, $CDCl_3$): δ (ppm) = 180.4 (C-1‴), 176.2 (C-2″), 174.0 (C-5″), 171.5 (C-4‴), 170.8 [C=O (ester)], 142.4 (C-1$_{arom.}$), 133.5, 133.4 (C-4′$_{arom.}$), 132.7 (C-2′$_{arom.}$), 131.9, 131.4 (C-6′$_{arom.}$), 129.8, 129.7 (C-3′$_{arom.}$), 129.6, 129.5 (C-5′$_{arom.}$), 128.4 (C-3$_{arom.}$, C-5$_{arom.}$), 128.3 (C-2$_{arom.}$, C-6$_{arom.}$), 127.1 (C-1′$_{arom.}$), 125.7 (C-4$_{arom.}$), 74.5, 73.8 (C-9), 69.1 (CH_2O), 61.5 (C-2), 58.5, 58.3 (C-4), 57.3 [NCH_2(CH$_2$)$_2$Ph], 38.0, 37.8 (C-1), 37.3, 37.2, 37.0, 35.8, 35.7, 35.3 (C-3″, C-4″, C-2‴, C-3‴), 33.4 [N(CH$_2$)$_2$CH_2Ph], 33.1, 32.8 (C-5), 28.9 (NCH$_2$CH_2CH$_2$Ph), 28.3, 28.2 (C-8), 24.7 (C-6), 20.5, 20.4 (C-7), 17.2, 17.1 (2‴-CH_3 or 3‴-CH_3), 16.4, 16.2 (3″-CH_3).

(1*R,5*S**,9*S**)-9-(2-[3-Methyl-2,5-dioxopyrrolidin-1-yl]benzoyl)-3-(3-phenylpropyl)-3-azabicyclo[3.3.1]non-1-ylmethyl 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)benzoate (39):** A mixture of amine **37** (30 mg, 0.057 mmol) and methylsuccinic anhydride (39 mg, 0.342 mmol) was heated at 125 °C for 4 h. The reaction mixture was then dissolved in warm ethyl acetate (20 mL), washed with aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (100% $CHCl_3$). Yield 38 mg (0.053 mmol, 93%) of a yellow oil; R_f = 0.28 (100% $CHCl_3$). HRMS (FAB): *m*/*z* calcd. for $C_{42}H_{46}N_3O_8$: 720.3285, found: 720.3292 ([M + H]$^+$), calcd. for $C_{42}H_{45}N_3O_8$: 719.3207, found: 719.3196 [M^+]. ^{1}H NMR (400 MHz, COSY, $CDCl_3$): δ (ppm) = 8.08 [d, $^3J_{5',6'}$ = 7.5 Hz, 2 H, 6′-$H_{arom.}$ (2×)], 7.64 [t, $^3J_{3',4'}$ = $^3J_{4',5'}$ = 7.5 Hz, 2 H, 4′-$H_{arom.}$ (2×)], 7.51–7.48 [m, 2 H, 5′-$H_{arom.}$ (2×)], 7.30–7.16 [m, 7 H, 3′-$H_{arom.}$ (2×), $H_{arom.}$ (Ph)], 5.03 (br. s, 1 H, 9-H), 4.13–4.02 (m, 2 H, CH_2O), 3.10–2.88 [m, 6 H, 2-H_{eq}, 4-H_{eq}, 3″-H (2×), 4″-H_a (2×)], 2.82–2.72 (m, 1 H, 7-H_{ax}), 2.66 [t, 2 H, N(CH$_2$)$_2$CH_2Ph, ^3J = 7.3 Hz], 2.56–2.36 [m, 2 H, 4″-H_b (2×)], 2.34 (d, $^2J_{gem}$ = 11.1 Hz, 1 H, 4-H_{ax}), 2.24 [t, ^3J = 6.8 Hz, 2 H, NCH_2(CH$_2$)$_2$Ph], 2.24–2.22 (m, 1 H, 2-H_{ax}), 2.16 (s, 1 H, 5-H), 2.02–1.92 (m, 1 H, 6-H_{ax}), 1.92–1.82 (m, 1 H, 8-H_{ax}), 1.78 (quin, ^3J = 7.3 Hz, 3 H, NCH$_2$CH_2CH$_2$Ph), 1.72–1.55 (m, 3 H, 6-H_{eq}, 7-H_{eq}, 8-H_{eq}), 1.40 (s, 3 H, 3″-CH_3), 1.39 (s, 3 H, 3″-CH_3). ^{13}C NMR (100 MHz, BB, DEPT, HSQC, $CDCl_3$): δ (ppm) = 179.8 [C-2″ (2×)], 175.9 [C-5″ (2×)], 163.9 [C=O (2× ester)], 142.4 (C-1$_{arom.}$), 133.3, 133.1 [C-4′$_{arom.}$ (2×)], 133.0 [C-2′$_{arom.}$ (2×)], 131.6, 131.0 [C-6′$_{arom.}$ (2×)], 130.9 [C-1′$_{arom.}$ (2×)], 129.8, 129.6 [C-3′$_{arom.}$ (2×)], 129.3, 129.2 [C-5′$_{arom.}$ (2×)], 128.4 (C-3$_{arom.}$, C-5$_{arom.}$), 128.3 (C-2$_{arom.}$, C-6$_{arom.}$), 125.7 (C-4$_{arom.}$), 75.3 (C-9), 69.1 (CH_2O), 61.2 (C-2), 58.4 (C-4), 57.2 [NCH_2(CH$_2$)$_2$Ph], 37.8 (C-1), 36.9 [C-4″ (2×)], 35.2 [C-3″ (2×)], 33.4 (N(CH$_2$)$_2$CH_2Ph), 33.1 (C-5), 29.0 (NCH$_2$CH_2CH$_2$Ph), 28.3 (C-8), 24.9 (C-6), 20.4 (C-7), 16.3 [3″-CH_3 (2×)].

(1*R,5*S**,8*S**)-8-(2-[3-Methyl-2,5-dioxopyrrolidin-1-yl]benzoyl)-3-(3-phenylpropyl)-3-azabicyclo[3.2.1]oct-1-ylmethyl 2-(3-Methyl-2,5-dioxopyrrolidin-1-yl)-benzoate (42):** A mixture of diamine **41** (37 mg, 0.072 mmol) and methylsuccinic anhydride (49 mg, 0.432 mmol) was heated at 125 °C for 4 h. The reaction mixture was then dissolved in warm ethyl acetate (20 mL), washed with aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (2% MeOH in $CHCl_3$). Yield 39 mg (0.055 mmol, 76%) of a yellow oil; R_f = 0.64 (5% MeOH in $CHCl_3$). HRMS (FAB): *m*/*z* calcd. for $C_{41}H_{44}N_3O_8$: 706.3128, found: 706.3120 ([M + H]$^+$). ^{1}H NMR (400 MHz, COSY, $CDCl_3$), δ (ppm) = 8.09–8.00 [m, 2 H, 6′-$H_{arom.}$ (2×)], 7.65–7.58 [m, 2 H, 4′-$H_{arom.}$ (2×)], 7.46–7.37 [m, 2 H, 5′-$H_{arom.}$ (2×)], 7.29–7.16 [m, 7 H, 3′-$H_{arom.}$ (2×), $H_{arom.}$ (Ph)], 4.95 (d, $^3J_{5,8}$ = 4.8 Hz, 1 H, 8-H), 4.20 (d, $^2J_{gem}$ = 11.0 Hz, 1 H, C$H_a$$H_b$O), 4.10 (d, $^2J_{gem}$ = 11.2 Hz, 1 H, C$H_a$$H_b$O), 3.11–2.95 [m, 4 H, 3″-H (2×), 4″-H_a (2×)], 2.67 [t, ^3J = 7.4 Hz, 2 H, N(CH$_2$)$_2$-CH_2Ph], 2.62–2.40 [m, 7 H, 2-H_{ax}, 2-H_{eq}, 4-H_{ax}, 4-H_{eq}, 5-H, 4″-H_b (2×)], 2.43 [t, ^3J = 6.8 Hz, 2 H, NCH_2(CH$_2$)$_2$Ph], 2.02–1.92 (m, 1 H, 7-H_{exo}), 1.89–1.72 (m, 2 H, 6-H_{endo}, 6-H_{exo}), 1.80 (quin, ^3J = 7.4 Hz, 3 H, NCH$_2$CH_2CH$_2$Ph), 1.72–1.60 (m, 1 H, 7-H_{endo}), 1.42 (s, 3 H, 3″-CH_3), 1.41 (s, 3 H, 3″-CH_3). ^{13}C NMR (100 MHz, BB, DEPT, HSQC, $CDCl_3$): δ (ppm) = 179.8 [C-2″ (2×)], 175.8 [C-5″ (2×)], 164.1, 163.9 [C=O (2× ester)], 142.4 (C-1$_{arom.}$), 133.3 [C-4′$_{arom.}$ (2×)], 132.8 [C-2′$_{arom.}$ (2×)], 131.5, 131.2 [C-6′$_{arom.}$ (2×)], 129.7 [C-3′$_{arom.}$ (2×)], 129.2 [C-5′$_{arom.}$ (2×)], 128.5 (C-3$_{arom.}$, C-5$_{arom.}$), 128.2 (C-2$_{arom.}$, C-6$_{arom.}$), 127.1 [C-1′$_{arom.}$ (2×)], 125.6 (C-4$_{arom.}$), 75.6 (C-8), 67.7 (CH_2O), 56.5 (C-2), 55.2 [NCH_2(CH$_2$)$_2$Ph],

52.3 (C-4), 44.3 (C-1), 37.2 (C-5), 36.9 [C-4′′ (2×)], 35.2 [C-3′′ (2×)], 33.3 [$N(CH_2)_2CH_2Ph$), 28.7 (C-7, $NCH_2CH_2CH_2Ph$), 23.8 (C-6), 16.3 [3′′-CH_3 (2×)].

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