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Exploiting the regioselectivity of pyroglutamate alkylations for the synthesis of 6-azabicyclo[3.2.1]octanes and 4-azabicyclo[3.3.0]octanes

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Abstract—Depending on the *N*-protecting group of pyroglutamates, the reactivity can be directed to the formation of 6-azabicyclo[3.2.1]-octanes or 4-azabicyclo[3.3.0]octanes, which are conformationally restricted glutamate analogues.

1. Introduction

Azabicyclic systems have been extensively used in recent years as key structural components of various pharmaceutical agents. Consequently, flexible methods for the construction of different azabicycles are of considerable interest.

Among the wide variety of alkaloids, both the 6-azabicyclo[3.2.1]octanes **1** and 4-azabicyclo[3.3.0]octanes **2** have received a lot of attention synthetically (Fig. 1).

Prominent among the early synthetic methods for the preparation of 6-azabicyclo[3.2.1]octane derivatives **1** are the Hofmann–Löffler–Freytag reaction of monocyclic *N*-chloro amines[1] and the reductive cyclisation of aminobenzoic acids or benzamides.[2] More recently, several highly efficient strategies based on rearrangements,[3] cycloadditions[4] and multicomponent couplings have been reported.[5]

The formation of the pyrrolizidine framework **2** generally takes place by cyclisation of a conveniently substituted pyrrolidine moiety. Several types of processes have been reviewed, such as radical and ionic cyclisations.[6] Other procedures such as Claisen-like intramolecular acylation involving α-pyrrolidinyl sulfones,[7] ring-closing metathesis of disubstituted ethenyl pyrrolidines,[8] or intramolecular titanium-mediated coupling reactions of α-substituted succinimides[9] have been described. Other processes include the cis allylation of a chiral lactam skeleton derived from D-malic acid,[10] cyclisations of *N*-propargylaminyl radicals[11] and cycloaddition processes including tandem inter[4+2]/inter[3+2]-additions,[12] hetero Diels–Alder reactions,[13] [2+2]-cycloadditions[14] and 1,3-dipolar cycloadditions.[15] Recently, some other processes for the synthesis of the pyrrolizidine skeleton were described in the literature.[16]

1 2

Figure 1.

During our research on azabicyclic compounds, pyroglutamates were selected for the construction of conformationally restricted molecules. Over the years, pyroglutamates have received a lot of attention because of their importance in several domains and as a versatile starting material for the synthesis of both natural and unnatural products.[17] Intensive study on glutamate analogues resulted in specific inhibitors of different receptor types of the mammalian central nervous system.[18] It has also been used for the synthesis of pyrrolidine alkaloids,[19] kainoids,[20] (−)-bulgecinine,[21] (−)-domoic acid,[22] enantiomerically pure glycine and proline derivatives,[23] a wide variety of non-proteinogenic amino acids,[24] etc. The attractiveness of pyroglutamate as a building block is connected to the fact that the site of alkylation can be directed by changing the protecting group on nitrogen. Alkylation of *N*-Boc protected pyroglutamates results in C-4 functionalised derivatives, whereas alkylation of *N*-benzyl or *N*-unprotected pyroglutamates occurs at the 2-position.[25]

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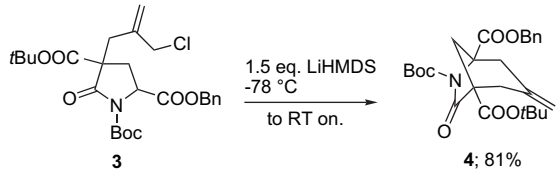
2. Results

2.1. Synthesis of the 6-azabicyclo[3.2.1]octane skeleton by ring closure from C-4 to C-2

Recently we observed that *N*-Boc protected pyroglutamates, substituted at the C-4 position with no or poor electrophilic moieties, undergo a Boc migration.[26] This reaction prevented the synthesis of bicyclic skeletons by alkylation at C-4 followed by ring closure to C-2. Since the Boc migration is competitive with ring closure from C-4 to C-2, a better electrophilic moiety, 3-chloro-2-chloromethyl-1-propene, was introduced at C-4. In this case only ring closure was observed leading to compound **4** in good yield and comprising a new skeleton (Scheme 1).



Scheme 1.

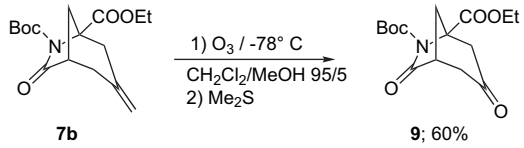
2.2. Synthesis of the 6-azabicyclo[3.2.1]octane skeleton by ring closure from C-2 to C-4

The competing Boc migration prompted us to change the site of ring closure. If an unprotected pyroglutamate is properly functionalised at the C-2 position, subsequent protection with a Boc group (activation of C-4) and treatment with base could also lead to the 6-azabicyclo[3.2.1]octane skeleton.

As we have recently shown, treating a mixture of a pyroglutamate and an electrophile with 2.1 equiv of LiHMDS at −40 °C in THF results in C-2 functionalisation without any reaction on the N-atom.[27] Again, we chose 3-chloro-2-chloromethyl-1-propene as electrophile since the allylic positions increase its electrophilic properties and would thus facilitate both alkylation and ring closure. In order to prevent reaction at the N-atom and accompanying cyclisation to a pyrrolizidinone structure, it is crucial to limit the reaction time to 1 h at −40 °C and 2 h at room temperature. If the reaction was stirred overnight, about 25% of the compound had already cyclised.

In order to activate the C-4 position, compounds **5** were protected with a Boc group under standard conditions using Boc-anhydride and DMAP as a catalyst in acetonitrile at 0 °C. Unfortunately, treating derivatives **6** with 1.1 equiv of LiHMDS at −78 °C did not result in the desired cyclisation to **7**. Only unreacted starting material could be recovered. This lack of reactivity could result from the ability of the Li cation to form a six-membered ring counter-ion complex **8** (Li complex) giving additional stability to the C-4 anion, effectively preventing it from reacting further (Scheme 2).[28] If this extra stabilisation indeed prevents the formation of bicyclic compound **7**, changing to KHMDS as a base should circumvent this problem since the bigger potassium cation does not fit as well in the six-membered ring conformation as the Li cation. Indeed we observed that treating **6** with 1.1 equiv of KHMDS at −78 °C for 2 h resulted in complete conversion to the desired compounds **7**.

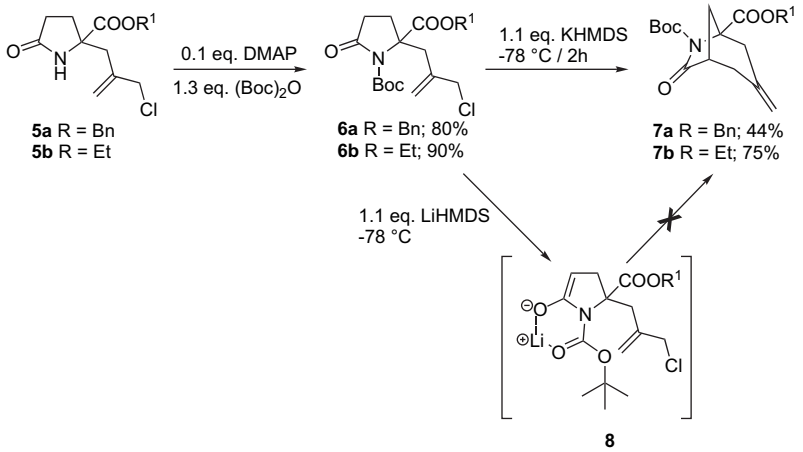
Further functionalisation of compound **7b** was performed by treating it with ozone in CH_2Cl_2/MeOH (95/5) at −78 °C and subsequent work-up with Me_2S leading to compound **9** in 60% yield after purification, a new type of constrained glutamic acid analogue (Scheme 3).



Scheme 3.

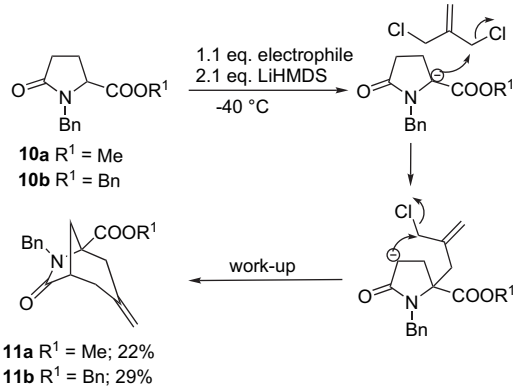
2.3. A one-pot synthesis of the 6-azabicyclo[3.2.1]octane skeleton

Because the abovementioned synthetic strategies involve several steps to get to the 6-azabicyclo[3.2.1]octane skeleton, a one-pot strategy for its synthesis was studied. Therefore, *N*-benzyl protected pyroglutamates **10** were treated with 2.1 equiv of LiHMDS and 1.1 equiv of 3-chloro-2-chloromethyl-1-propene. The first equivalent of LiHMDS



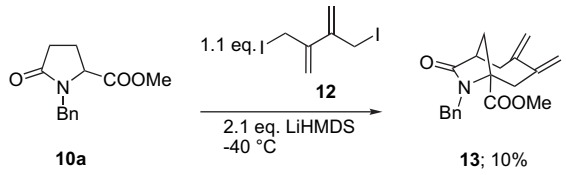
Scheme 2.

deprotonates the C-2 position, which reacts with the electrophile. The second equivalent of LiHMDS then deprotonates at C-4 leading to ring closure. After purification, the 6-azabicyclo[3.2.1]octane **11** was indeed isolated, although in rather poor yields (Scheme 4).



Scheme 4.

In the same way, the 7-azabicyclo[4.2.1]nonane skeleton could be synthesised with 2,3-bis(iodomethyl)-1,3-butadiene **12**[29] as electrophile (Scheme 5). Although the yields of this one-pot strategy were quite poor, a seven-membered ring, which is normally not easily formed, could be obtained.

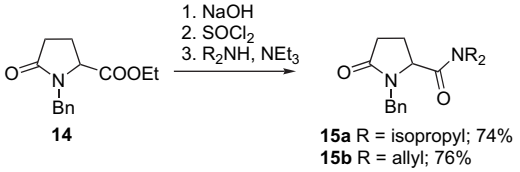


Scheme 5.

Till now, the 7-azabicyclo[4.2.1]nonane skeleton was mainly used in the synthesis of some *Gelsemium* alkaloids, such as gelsemine, gelsedine and gelsemicine. Several synthetic strategies have been published to construct these pharmaceutically interesting products.[30]

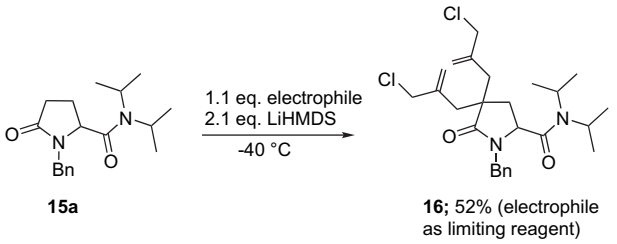
2.4. Pyroglutamides: another regioselectivity

Although the one-pot strategy for the 6-azabicyclo[3.2.1]-octane and 7-azabicyclo[4.2.1]nonane skeleton was successful, the yields after purification were rather low. During earlier research at our laboratory, we observed that formation of an anion at C-2 resulted in fragmentation of the pyroglutamate.[26] This was confirmed by the detection of benzyl alcohol when using benzyl pyroglutamate as starting material. Therefore, the corresponding pyroglutamides **15** were synthesised since it was expected that these compounds would fragment less easily (Scheme 6).



Scheme 6.

Using the pyroglutamides **15** in the same one-pot strategy as mentioned above for the corresponding pyroglutamates, a different regioselectivity was observed. Instead of the formation of the 6-azabicyclo[3.2.1]octane skeleton, double alkylation at C-4 was observed (Scheme 7).



Scheme 7.

Apparently, the most acidic (and the least sterically hindered) protons of *N*-benzyl pyroglutamides are located at the 4-position. With this in mind, treatment of **15b** with 3 equiv of base and 2 equiv of electrophile could lead to the 1-substituted 6-azabicyclo[3.2.1]octane skeleton **18** (Scheme 8). This reaction was indeed successful; although a conversion of 56% was observed, only a 25% yield was obtained after chromatography.

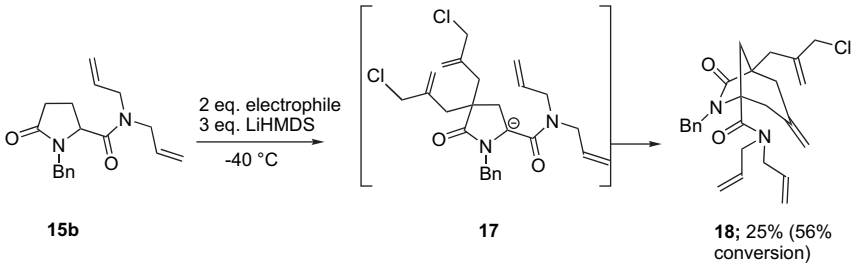
The substitution pattern at the 1-position of the 6-azabicyclo[3.2.1]octane skeleton could be varied by a preceding alkylation at the 4-position of the *N*-benzyl pyroglutamides with subsequent ring closure. To mention one example, **15a** was substituted at the 4-position with a benzyl group after alkylation with benzylbromide. When treating the purified product **19** with 3-chloro-2-chloromethyl-1-propene as electrophile and LiHMDS as base, compound **21** was isolated, besides **19** and **20** (Scheme 9). Apparently, the alkylation and ring closure appears to be slow. The disappointing yield after purification discouraged further efforts in this direction.

2.5. Synthesis of the 4-azabicyclo[3.3.0]octane skeleton by ring closure from C-2 to N

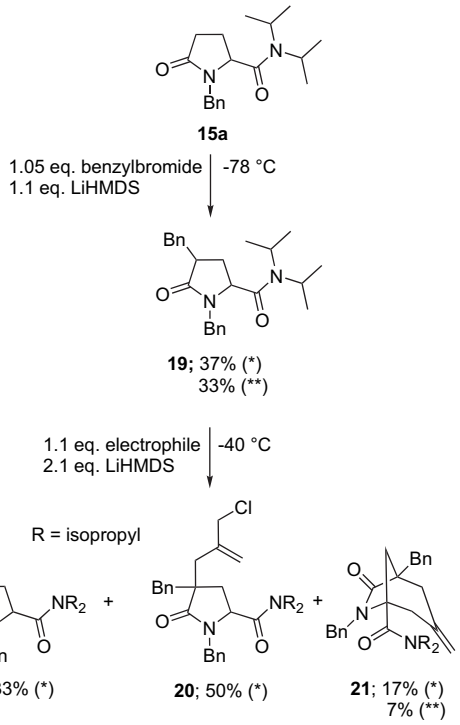
The synthesis of the 4-azabicyclo[3.3.0]octane skeletons **22a** and **22b** was performed by treating **5a** and **5b** (no Boc protection) with 1.5 equiv of NaH in refluxing THF for 16 h and subsequent bulb-to-bulb distillation (Scheme 10).

The pyrrolizidinone **22b** was easily converted to the amino alcohol **23**, a member of an interesting class of compounds,[31] in 70% yield by treatment with $LiAlH_4$ in refluxing THF and subsequent bulb-to-bulb distillation. Compound **22b** was also converted to pyrrolizidinedione **24** by ozonisation followed by work-up with Me_2S (Scheme 11).

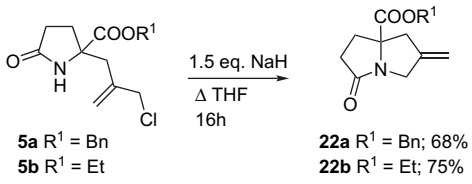
Besides pyrrolizidinones, we were also able to construct an indolizidine skeleton applying the same methodology. Treating a mixture of pyroglutamate **25** and *cis*-1,4-dichloro-2-butene with 2.1 equiv of LiHMDS in THF at −40 °C resulted in a mixture, which consists of compounds **26** and **27** in a 1/3 ratio (Scheme 12). Treatment of this mixture with 1 equiv of NaH in refluxing THF resulted in complete cyclisation of **26**. Indolizidine **27** was obtained in 24% yield



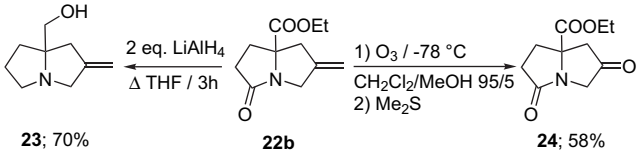
Scheme 8.



Scheme 9. (*) Observed in ^{1}H NMR of crude mixture; (**) after purification.

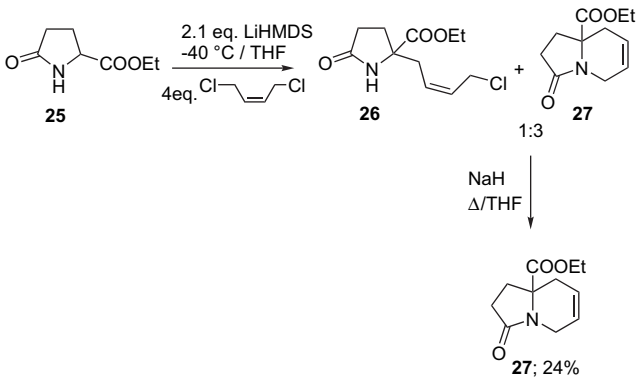


Scheme 10.



Scheme 11.

after purification by column chromatography. The low yield of this procedure can be explained by a severe loss of material during purification.



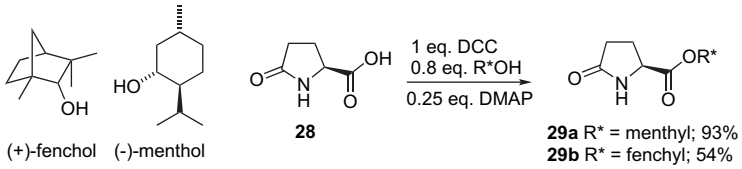
Scheme 12.

2.6. Evaluation of chiral induction during alkylation

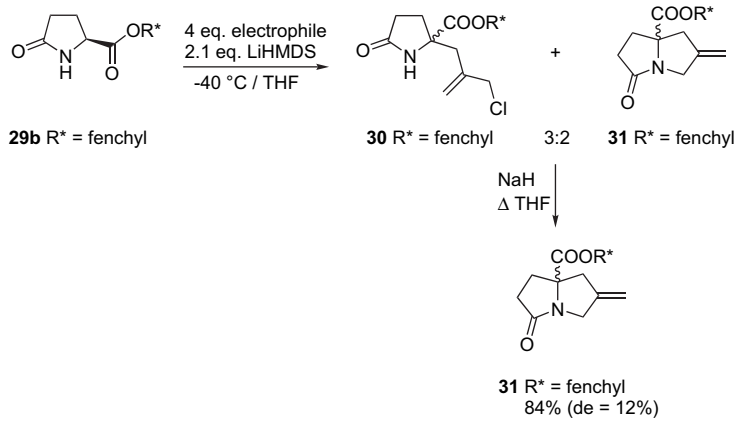
Having this new entry to interesting azabicyclic molecules in hand, the possibility of chiral induction during alkylation was evaluated. Moeller and Rutledge have described an electrochemical method for the enantioselective alkylation of the (+)-menthyl ester of pyroglutamic acid.[32] The ester of (*S*)-pyroglutamic acid and (−)-menthol or (+)-fenchol was prepared using DCC as a coupling agent and DMAP as a catalyst (Scheme 13).

Unfortunately, treatment of **29a** with 2.1 equiv of LiHMDS at −40 °C resulted in complete fragmentation of the ester. Only menthol could be identified in the organic fraction. Treatment of a mixture of **29b** and 3-chloro-2-chloromethyl-1-propene with 2.1 equiv of LiHMDS resulted in a mixture of **30** and **31** in a 3/2 ratio. This mixture was quantitatively converted to pyrrolizidinone **31** upon treatment with NaH in refluxing THF. To our disappointment, **31** was obtained as a mixture of both diastereoisomers with a diastereomeric excess of only 12% (after chromatography and crystallisation). In the crude reaction mixture no diastereomeric excess was observed, showing that the chiral fenchol group has no effect on the diastereoselectivity of the alkylation (Scheme 14).

In conclusion, we have shown that both the 6-azabicyclo[3.2.1]octane and 4-azabicyclo[3.3.0]octane skeletons are accessible from the same precursor depending on the protecting group on the N-atom. Although this approach is straightforward and interesting, the difficulty in purification of the products, reducing the yields considerably, stays problematic. The advantage, however, is the limited number of steps needed to construct these interesting skeletons starting from a readily available precursor.



Scheme 13.



Scheme 14.

3. Experimental

3.1. General

High-resolution ^{1}H NMR (270 MHz or 300 MHz) and ^{13}C NMR (68 MHz or 75 MHz) spectra were run with a Jeol JNM-EX 270 NMR spectrometer or on a Jeol JNM-EX 300 NMR spectrometer. Peak assignments were obtained with the aid of DEPT, 2D-HETCOR, 2D-HSQC and 2D-COSY spectra. The compounds were diluted in deuterated solvents and the used solvent is indicated for each compound. Mass spectra were recorded on a Varian MAT 112 spectrometer (70 eV), using either GC–MS coupling or a direct inlet system. Some volatile samples were recorded on an HP 6890 GC coupled with a HP 5973 MSD (Mass selective detector; quadrupole). Mass spectra of molecules with a high molecular weight were recorded on an Agilent 1100 Series VS (ES, 4000 V) mass spectrometer. The elemental analysis was performed with a Perkin–Elmer 2400 Elemental Analyser. High-resolution mass spectra were recorded on a Finnigan MAT 95 XP-API-GC-Trap tandem Mass spectrometer system (ES, 5000 V). IR-spectra were obtained from a Perkin–Elmer Spectrum One infrared spectrometer. For liquid samples the spectra were collected by preparing a thin film of compound between two sodium chloride plates. The crystalline compounds were mixed with potassium bromide and pressed until a transparent potassium bromide plate was obtained. Melting points of crystalline compounds were measured with a Büchi 540 apparatus and are uncorrected. The purification of reaction mixtures was performed by chromatography using a glass column with silica gel (Across, particle size: 0.035–0.070 mm, pore diameter: ca. 6 nm).

3.2. Typical experimental procedure for the alkylation of pyroglutamates at the C-4 position with di-*tert*-butyldicarbonate and an alkyl halide

A Boc-protected pyroglutamate ester (7.8 mmol) is dissolved in THF (30 mL, freshly distilled from Na metal) and cooled in an acetone bath to −78 °C. At this temperature and under a nitrogen atmosphere, 15.6 mL (15.6 mmol, 2 equiv) of a 1 M LiHMDS solution is added while stirring is continued at this temperature. After 2 h, 11.7 mmol of di-*tert*-butyldicarbonate (1.5 equiv) is added (dissolved in 10 mL of THF) and the reaction mixture is allowed to warm to room temperature. The reaction is quenched with 5 mL of saturated NH_4Cl/NH_4OH solution and 40 mL of water is added. The mixture is extracted with diethyl ether and dried with $MgSO_4$. After filtration and evaporation of the solvent the crude product is purified by means of chromatography.

The purified 4-substituted *N*-Boc pyroglutamate (2.3 mmol) is dissolved in 10 mL of dry THF and kept under a positive N_2-pressure. KO^{t}Bu (2.5 mmol, 1.1 equiv) is added and the mixture is stirred for 30 min when 4.6 mmol of electrophile (2 equiv) is added. The reaction mixture is subsequently refluxed overnight. After cooling, the solution is poured in water and extracted with diethyl ether. The organic layers are combined and dried with $MgSO_4$. Filtering off the drying agent and evaporating the solvent lead to a mixture, which is purified by chromatography to remove the excess of electrophile.

3.2.1. Synthesis of 2-benzyl 1,4-di-*tert*-butyl-4-[2-(chloromethyl)-2-propenyl]-5-oxo-1,2,4-pyrrolidinetricarboxylate (3). The product was obtained as an oil (yield: 60%).

^{1}H NMR (270 MHz, $CDCl_3$) δ: Major: 1.41 (9H, s, *t*-Bu), 1.43 (9H, s, *t*-Bu), 2.32 (1H, dd, J=13.6, 10.2 Hz, CH_AH$_B$ ring), 2.52 (1H, d, J=15.5 Hz, CH_AH$_B$C=CH$_2$), 2.93 (1H, dd, J=13.6, 2.0 Hz, CH$_A$$H_B$ ring), 3.09 (1H, d, J=15.5 Hz, CH$_A$$H_B$C=CH$_2$), 3.92 (2H, s, CH$_2$Cl), 4.61 (1H, dd, J=10.2, 2.0 Hz, CH ring), 5.01 (1H, br s, C=CH_AH$_B$), 5.13 (1H, d, J=12.2 Hz, CH_AH$_B$Ph), 5.19 (1H, br s, C=CH$_A$$H_B$), 5.24 (1H, d, J=12.5 Hz, CH$_A$$H_B$Ph), 7.36 (5H, s, Ph). Minor: 1.41 (9H, s, *t*-Bu), 1.44 (9H, s, *t*-Bu), 1.96 (1H, dd, J=13.8, 6.9 Hz, CH_AH$_B$ ring), 2.60 (1H, d, J=16.0 Hz, CH_AH$_B$C=CH$_2$), 2.88 (1H, dd, J=13.8, 8.9 Hz, CH$_A$$H_B$ ring), 3.01 (1H, d, J=16 Hz, CH$_A$$H_B$C=CH$_2$), 3.99 (2H, s, CH$_2$Cl), 4.64 (1H, dd, J=8.9, 6.9 Hz, CH ring), 4.86 (1H, br s, C=CH_AH$_B$), 5.20 (1H, d, J=13.2 Hz, CH_AH$_B$Ph), 5.24 (1H, d, J=13.2 Hz, CH$_A$$H_B$Ph), 5.28 (1H, br s, C=CH$_A$$H_B$), 7.36 (5H, s, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: Major 28.21 (*t*-Bu), 28.32 (*t*-Bu), 31.61 (CH$_2$ ring), 39.43 (CH$_2$), 48.88 (CH$_2$Cl), 56.91 (CH, C-2), 57.22 (C$_{quat}$, C-4), 67.98 (*C*H$_2$Ph), 83.88 (C$_{quat}$, *t*-Bu), 84.37 (C$_{quat}$, *t*-Bu), 119.35 (C=CH$_2$), 129.04 (CH), 129.15 (CH), 135.72 (C$_{quat}$, Ph), 140.93 (C=CH$_2$), 149.60 (C=O, Boc), 168.09 (C=O), 170.49 (C=O), 170.73 (C=O), 171.54 (C=O). Minor: 28.25 (*t*-Bu), 28.47 (*t*-Bu), 30.39 (CH$_2$ ring), 37.38 (CH$_2$), 48.99 (CH$_2$Cl), 57.22 (CH), 57.45 (C$_{quat}$, C-4), 67.98 (*C*H$_2$Ph), 83.99 (C$_{quat}$, *t*-Bu), 84.71 (C$_{quat}$, *t*-Bu), 119.01 (C=CH$_2$), 129.18 (CH), 129.25 (CH), 135.47 (C$_{quat}$, Ph), 140.93 (C=CH$_2$), 149.60 (C=O, Boc), 168.89 (C=O), 170.73 (C=O), 170.93 (C=O), 171.54 (C=O). IR (cm^{-1}) ν_{max}: 1795, 1725. MS *m*/*z* (%): (ES, Pos) no M$^+$, 354 (30), 352 (85), 91 (100). Chromatography: Hex/EtOAc (64/36). $C_{26}H_{34}ClNO_7$: calcd C 61.47, H 6.75, N 2.76; found C 61.59, H 6.89, N 2.59.

3.3. Synthesis of 5-benzyl 1,6-di-*tert*-butyl-3-methylene-7-oxo-6-azabicyclo[3.2.1]octane-1,5,6-tricarboxylate (4)

2-Benzyl-1,4-di-*tert*-butyl-4-[2-(chloromethyl)-2-propenyl]-5-oxo-1,2,4-pyrrolidinetricarboxylate **3** of 0.28 g (0.55 mmol) was dissolved in 4 mL of dry THF and kept under a positive N_2-pressure during the reaction. The mixture was cooled to −78 °C and 0.66 mL of a LiHMDS solution (0.66 mmol, 1 M solution in hexanes, 1.2 equiv) was added and the solution was slowly allowed to warm up to room temperature overnight keeping the flask in the acetone bath. After quenching the reaction with NH_4Cl/NH_4OH solution, an extra amount of 10 mL of water was added and the reaction mixture was extracted with diethyl ether (3×40 mL). The organic phases were combined and dried with $MgSO_4$. Filtering off the $MgSO_4$ and evaporating the solvent gave the crude product as an oil and was further purified by column chromatography. 5-Benzyl-1,6-di-*tert*-butyl-3-methylene-7-oxo-6-azabicyclo[3.2.1]-octane-1,5,6-tricarboxylate **4** of 0.21 g was obtained as an oil (yield: 81%).

^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.42 (9H, s, *t*-Bu), 1.48 (9H, s, *t*-Bu), 1.96 (1H, d, J=11.2 Hz, CH_AH$_B$), 2.45 (1H, d, J=13.9 Hz, CH_CH$_D$), 2.65 (1H, dd, J=14.4, 1.0 Hz, CH_EH$_F$), 2.79 (1H, d, J=11.2 Hz, CH$_A$$H_B$), 2.87 (1H, d, J=13.9 Hz, CH$_C$$H_D$), 3.04 (1H, d, J=14.4 Hz, CH$_E$$H_F$), 4.94 (1H, br s, C=C$H_AH_B$), 5.00 (1H, br s, C=CH$_A$$H_B$), 5.19 (1H, d, J=12.2 Hz, CH_AH$_B$Ph), 5.24 (1H, d, J=12.2 Hz, CH$_A$$H_B$Ph), 7.35 (5H, br s, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 27.78 (*t*-Bu), 27.89 (*t*-Bu), 37.48 (CH$_2$), 38.10 (CH$_2$), 41.10 (CH$_2$), 56.24 (C$_{quat}$, C-4), 64.71 (C$_{quat}$, C-2), 67.40 (*C*H$_2$Ph), 82.68 (C$_{quat}$, *t*-Bu), 83.95 (C$_{quat}$, *t*-Bu), 117.30 (C=CH$_2$), 128.28 (CH), 128.50 (CH), 128.61 (CH), 135.00 (C$_{quat}$, Ph), 138.36 (C=CH$_2$), 148.80 (C=O, Boc), 167.54 (C=O), 169.86 (C=O), 170.10 (C=O), 177.59 (C=O). IR (cm^{-1}) ν_{max}: 1795, 1728. MS *m*/*z* (%): (ES, Pos) no M$^+$, 316 (M$^+$−COO^{t}Bu, 100), 91 (15). Chromatography: Hex/EtOAc (90/10) R_f=0.31. $C_{26}H_{33}NO_7$: calcd C 66.22, H 7.05, N 2.97; found C 66.17, H 6.87, N 3.11.

3.4. Typical experimental procedure for the alkylation of pyroglutamates at the 2-position

A Boc-protected pyroglutamate ester (12 mmol) is dissolved in THF (15 mL, freshly distilled from Na metal) and the alkyl halide (48 mmol, 4 equiv) is added. The mixture is cooled to −40 °C under a N_2 atmosphere. Over a period of 30–40 min, 25.2 mL of a LiHMDS solution (25.2 mmol, 1 M solution in hexanes, 2.1 equiv) is added at this temperature. The reaction mixture is allowed to stir at room temperature for an additional 2 h. The reaction is quenched by addition of saturated aqueous NH_4Cl until the pH is neutral. The mixture is extracted with EtOAc, and the organic fractions are dried ($MgSO_4$) and filtered. The solvent is removed under reduced pressure.

3.4.1. Synthesis of benzyl 2-(2-chloromethyl-2-propenyl)-5-oxopyrrolidine-2-carboxylate (5a). Recrystallised from hexanes. White crystals (yield: 40%).

^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.17–2.24 (1H, m, CH_AH$_B$ ring, C-3), 2.37–2.50 (3H, m, CH$_A$$H_B$ ring, C-3+CH$_2$ ring, C-4), 2.57 (1H, d, J=14.5 Hz, CH_AH$_B$C=CH$_2$), 2.96 (1H, d, J=14.5 Hz, CH$_A$$H_B$C=CH$_2$), 3.96 (2H, s, CH$_2$Cl), 5.02 (1H, s, C=C$H_AH_B$), 5.20 (1H, d, J=12.0 Hz, CH_AH$_B$Ph), 5.23 (1H, d, J=12.0 Hz, CH$_A$$H_B$Ph), 5.30 (1H, s, C=CH$_A$$H_B$), 7.40 (5H, s, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 29.61 (CH$_2$ ring, C-3), 31.25 (CH$_2$ ring, C-4), 41.71 (*C*H$_2$C=CH$_2$), 48.37 (CH$_2$Cl), 65.14 (C$_{quat}$, C-2), 67.65 (COO*C*H$_2$Ph), 120.09 (C=*C*H$_2$), 128.52 (CH, Ph), 128.68 (CH, Ph), 134.89 (C$_{quat}$, Ph), 139.67 (*C*=CH$_2$), 172.97 (C=O), 177.18 (C=O). IR (cm^{-1}) ν_{max}: 1701 (C=O), 1735 (C=O). MS *m*/*z* (%): 308 (M+H$^+$, 100), 257 (7), 91 (Bn$^+$, 7). Chromatography: Hex/EtOAc (25/75) R_f=0.45. Mp: 47.3–50.3 °C. HRMS calcd for $C_{16}H_{18}{}^{35}ClNO_3$ (M+H$^+$) 308.1048, found 308.1036.

3.4.2. Synthesis of ethyl 2-(2-chloromethyl-2-propenyl)-5-oxopyrrolidine-2-carboxylate (5b). White crystals (yield: 62%).

^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.31 (3H, t, J=7.1 Hz, CH$_2$C*H*$_3$), 2.12–2.22 (1H, m, CH_AH$_B$ ring, C-4), 2.37–2.54 (3H, m, CH$_A$$H_B$ ring, C-4+CH$_2$ ring, C-3), 2.54 (1H, d, J=14.5 Hz, CH_AH$_B$C=CH$_2$), 2.94 (1H, d, J=14.5 Hz, CH$_A$$H_B$C=CH$_2$), 4.00 (2H, s, CH$_2$Cl), 4.22 (2H, q, J=7.1 Hz, C*H*$_2$CH$_3$), 5.06 (1H, s, C=CH_AH$_B$), 5.33 (1H, s, CH$_A$$H_B$), 6.41 (1H, br s, NH). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 14.11 (CH$_2$*C*H$_3$), 29.69 (CH$_2$ ring, C-3), 31.23 (CH$_2$ ring, C-4), 41.74 (*C*H$_2$C=CH$_2$), 48.41 (CH$_2$Cl),

61.99 (CH_2CH_3), 65.07 (C_{quat}, C-2), 120.03 (C=CH_2), 139.91 (C=CH_2), 173.19 (C=O, ring), 177.21 (C=O, COOEt). IR (cm^{-1}) ν_{max}: 1707 (C=O), 1741 (C=O). MS *m/z* (%): 246 ($M+H^+$, 100). Mp: 55.4–56.6 °C. HRMS calcd for $C_{11}H_{16}{}^{35}ClNO_3$ ($M+H^+$) 246.0891, found 246.0894.

3.5. Typical experimental procedure for the Boc protection of 5a and 5b

The pyroglutamate ester **5** (12 mmol) is dissolved in acetonitrile (20 mL). The flask is cooled in an ice bath. To this solution are added DMAP (1.2 mmol, 0.1 equiv) and di-*tert*-butyldicarbonate (15.6 mmol, 1.3 equiv) dissolved in acetonitrile (15 mL). The mixture is allowed to stir overnight after which H_2O (5 mL) and brine (5 mL) are added. The mixture is extracted twice with diethyl ether, and the organic fractions are dried ($MgSO_4$) and filtered. The solvent is removed under reduced pressure.

3.5.1. Synthesis of benzyl 2-(2-chloromethyl-2-propenyl)-1-(*tert*-butoxycarbonyl)-5-oxopyrrolidine-2-carboxylate (6a). Brown oil (yield: 80%).

^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.46 (9H, s, *t*-Bu), 2.01–2.10 (1H, m, CH_AH_B ring, C-3), 2.15–2.24 (1H, m, CH_AH_B ring, C-3), 2.45–2.56 (2H, m, CH_2 ring, C-4), 2.82 (1H, d, J=15.0 Hz, CH_AH_BC=CH_2), 3.33 (1H, d, J=15.0 Hz, CH_AH_BC=CH_2), 3.97 (1H, d, J=12.0 Hz, CH_AH_BCl), 4.04 (1H, d, J=12.0 Hz, CH_AH_BCl), 5.11 (1H, s, C=CH_AH_B), 5.15 (1H, d, J=12.2 Hz, CH_AH_BPh), 5.23 (1H, d, J=12.2 Hz, CH_AH_BPh), 5.40 (1H, s, C=CH_AH_B), 7.35 (5H, s, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 26.61 (CH_2 ring, C-3), 27.80 (*t*-Bu), 30.75 (CH_2 ring, C-4), 36.69 (CH_2C=CH_2), 48.71 (CH_2Cl), 67.60 (CH_2Ph+C_{quat}, C-2), 84.29 (C_{quat}, *t*-Bu), 121.60 (C=CH_2), 128.37 (CH, Ph), 128.61 (CH, Ph), 128.70 (CH, Ph), 134.95 (C_{quat}, Ph), 140.05 (C=CH_2), 149.32 (C=O), 172.25 (C=O), 173.83 (C=O). ^{13}C NMR (68 MHz, C_6D_6) δ: 27.03 (CH_2 ring, C-3), 28.27 (*t*-Bu), 31.02 (CH_2 ring, C-4), 37.07 (CH_2C=CH_2), 49.16 (CH_2Cl), 67.74 (C_{quat}, C-2), 67.87 (CH_2Ph), 83.79 (C_{quat}, *t*-Bu), 121.44 (C=CH_2), 136.24 (C_{quat}, Ph), 141.11 (C=CH_2), 150.96 (C=O), 172.76 (C=O), 172.85 (C=O). IR (cm^{-1}) ν_{max}: 1720 (C=O), 1746 (C=O), 1791 (C=O). MS *m/z* (%): no M^+, 308 (M−Boc+H^+), 201 (21), 199 (7), 91 (12). Chromatography: Hex/EtOAc (60/40) R_f=0.33. $C_{21}H_{26}ClNO_5$: calcd C 61.84, H 6.42, N 3.43; found C 61.80, H 6.68, N 3.46.

3.5.2. Synthesis of ethyl 2-(2-chloromethyl-2-propenyl)-1-(*tert*-butoxycarbonyl)-5-oxopyrrolidine-2-carboxylate (6b). Brown oil (yield: 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=7.1 Hz, CH_2CH_3), 1.51 (9H, s, *t*-Bu), 2.03–2.26 (2H, m, CH_2 ring, C-3), 2.37–2.64 (2H, m, CH_2 ring, C-4), 2.79 (1H, d, J=15.0 Hz, CH_AH_BC=CH_2), 3.29 (1H, d, J=15.0 Hz, CH_AH_BC=CH_2), 3.97 (1H, d, J=12.1 Hz, CH_AH_BCl), 4.03 (1H, d, J=12.1 Hz, CH_AH_BCl), 4.18–4.25 (2H, m, CH_2CH$_3$), 5.11 (1H, s, C=CH_AH_B), 5.40 (1H, s, C=CH_AH_B). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.14 (CH_2CH_3), 26.81 (CH_2 ring, C-3), 27.93 (*t*-Bu), 30.87 (CH_2 ring, C-4), 36.76 (CH_2C=CH_2), 48.83 (CH_2Cl), 62.04 (CH_2CH_3), 67.65 (C_{quat}, C-2), 121.63 (C=CH_2), 140.22 (C=CH_2), 149.41 (C=O, Boc), 172.54 (C=O, ring), 174.08 (C=O, COOEt). IR (cm^{-1}) ν_{max}: 1721 (C=O), 1742 (C=O), 1791 (C=O). MS *m/z* (%): no M^+, 246 (M−Boc+H^+, 100), 210 (15), 172 (15), 136 (10). $C_{16}H_{24}ClNO_5$: calcd C 55.57, H 7.00, N 4.05; found C 55.76, H 7.19, N 4.10.

3.6. Typical experimental procedure for the synthesis of 7a and 7b

The pyroglutamate ester **6** (12 mmol) is dissolved in THF (15 mL, freshly distilled from Na metal). The mixture is cooled to −78 °C under a N_2 atmosphere. Over a period of 5 min, 25.2 mL of a KHMDS solution (25.2 mmol, 1 M solution in toluene, 1.1 equiv) is added at this temperature. The reaction mixture is allowed to stir for an additional 2 h at −78 °C. The reaction is quenched by addition of saturated aqueous NH_4Cl until the pH is neutral. The mixture is extracted twice with diethyl ether (25 mL), and the organic fractions are dried ($MgSO_4$) and filtered. The solvent is removed under reduced pressure. The products are purified by chromatography.

3.6.1. Synthesis of 5-benzyl 6-(*tert*-butyl)-3-methylene-7-oxo-6-azabicyclo[3.2.1]octane-5,6-dicarboxylate (7a). Brown oil (yield: 44%).

^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.42 (9H, s, *t*-Bu), 1.87 (1H, d, J=11.2 Hz, CH_AH_B, C-4), 2.37 (1H, d, J=11.2 Hz, CH_AH_B, C-4), 2.34–2.41 (1H, m, CH_AH_B, C-8), 2.58 (1H, d, J=14.2 Hz, CH_AH_B, C-8), 2.72 (1H, d, J=14.9 Hz, CH_AH_B, C-2), 2.75–2.79 (1H, m, CH, C1), 3.04 (1H, d, J=14.9 Hz, CH_AH_B, C-2), 4.91–5.20 (2H, m, C=CH_2), 5.18 (1H, d, J=12.4 Hz, CH_AH_BPh), 5.20 (1H, d, J=12.4 Hz, CH_AH_BPh), 7.35 (5H, br s, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 27.83 (*t*-Bu), 35.76 (CH_2, C-8), 38.15 (CH_2, C-2), 38.45 (CH_2, C-4), 42.55 (CH, C1), 66.18 (C_{quat}, C-3), 67.31 (CH_2Ph), 83.57 (*t*-Bu, C_{quat}), 116.69 (C=CH_2), 128.30 (CH, Ph), 128.52 (CH, Ph), 128.66 (CH, Ph), 135.04 (C_{quat}, Ph), 139.12 (C=CH_2), 148.89 (C=O, Boc), 170.55 (C=O), 174.12 (C=O). IR (cm^{-1}) ν_{max}: 1716 (C=O), 1747 (C=O), 1790 (C=O). MS *m/z* (%): 272 (M−Boc+H^+, 100), 91 (7). Chromatography: Hex/EtOAc (70/30) R_f=0.27. $C_{21}H_{25}NO_5$: calcd C 67.91, H 6.78, N 3.77; found C 67.88, H 6.82, N 3.59.

3.6.2. Synthesis of 5-ethyl 6-(*tert*-butyl)-3-methylene-7-oxo-6-azabicyclo[3.2.1]octane-5,6-dicarboxylate (7b). Brown oil (yield: 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=7.2 Hz, CH_2CH_3), 1.47 (9H, s, *t*-Bu), 1.86 (1H, d, J=11.3 Hz, CH_AH_B, C-4), 2.34–2.41 (2H, m, CH_AH_B, C-4+CH_AH_B, C-8), 2.59 (1H, br d, J=14.3 Hz, CH_AH_B, C-8), 2.69 (1H, dd, J=15.0, 1.9 Hz, CH_AH_B, C-2), 2.76–2.82 (1H, m, CH, C1), 3.00 (1H, d, J=15.0 Hz, CH_AH_B, C-2), 4.21 (2H, m, CH_2CH$_3$), 4.90–5.95 (2H, m, C=CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.99 (CH_2CH_3), 27.78 (*t*-Bu), 35.66 (CH_2, C-8), 38.06 (CH_2, C-2), 38.40 (CH_2, C-4), 42.49 (CH, C1), 61.52 (CH_2CH_3), 66.07 (C_{quat}, C-3), 83.24 (C_{quat}, *t*-Bu), 116.34 (C=CH_2), 139.35 (C=CH_2), 148.74 (C=O, Boc), 170.60 (C=O), 174.22 (C=O). IR (cm^{-1})

ν_{max}: 1716 (C=O), 1742 (C=O), 1790 (C=O). MS *m/z* (%): no M^+, 210 (M−Boc+H^+, 100), 136 (7). Chromatography: Hex/EtOAc (70/30) R_f=0.21. $C_{16}H_{23}NO_5$: calcd C 62.12, H 7.49, N 4.53; found C 62.07, H 7.42, N 4.55.

3.7. Synthesis of 5-ethyl 6-(*tert*-butyl)-3,7-dioxo-6-azabicyclo[3.2.1]octane-5,6-dicarboxylate (9)

Compound **7b** (1.6 mmol) is dissolved in a mixture of CH_2Cl_2 (10 mL, freshly distilled from CaH_2) and methanol (0.5 mL). The mixture is cooled to −78 °C. Ozone is bubbled through until the mixture remains blue. Air is bubbled through the mixture to remove the excess of ozone after which dimethylsulfide (3.24 mmol, 2 equiv) is added. The flask is put in the freezer (−20 °C) for an overnight period. The mixture is washed twice with brine (10 mL). The aqueous layer is extracted once with CH_2Cl_2 (10 mL). The combined organic fractions are dried ($MgSO_4$) and filtered. The solvent is removed under reduced pressure. The product is purified by chromatography and a brown oil is obtained (yield: 60%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30 (3H, t, J=7.2 Hz, CH_2CH_3), 1.47 (9H, s, *t*-Bu), 2.10 (1H, d, J=11.8 Hz, CH_AH_B, C-4), 2.52–2.61 (2H, m, CH_AH_B, C-4+CH_AH_B, C-8), 2.75 (1H, br d, J=18.4 Hz, CH_AH_B, C-8), 2.97–3.02 (1H, m, CH, C1), 3.00 (1H, d, J=18.6 Hz, CH_AH_B, C-2), 3.18 (1H, br d, J=18.6 Hz, CH_AH_B, C-2), 4.22 (1H, dq, J=13.8, 7.0 Hz, $CH_AH_BCH_3$), 4.23 (1H, dq, J=13.8, 7.0 Hz, $CH_AH_BCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.99 (CH_2CH_3), 27.81 (*t*-Bu), 37.03 (CH_2, C-4), 40.39 (CH, C1), 42.68 (CH_2, C-8), 45.93 (CH_2, C-2), 62.26 (CH_2CH_3), 65.52 (C_{quat}, C-3), 84.56 (C_{quat}, *t*-Bu), 148.38 (C=O, Boc), 169.42 (C=O), 173.20 (C=O), 204.53 (C=O, C-3). IR (cm^{-1}) ν_{max}: 1721 (C=O), 1745 (C=O), 1790 (C=O). MS *m/z* (%): no M^+, 212 (M−Boc+H^+, 100), 166 (7). Chromatography: Hex/EtOAc (50/50) R_f=0.24. $C_{15}H_{21}NO_6$: calcd C 57.87, H 6.80, N 4.50; found C 58.03, H 6.95, N 4.44.

3.8. Typical experimental procedure for the synthesis of 11a, 11b and 13

The pyroglutamate ester **10** (4.29 mmol) is dissolved in THF (15 mL, freshly distilled from Na metal) and the alkyl halide (4.72 mmol, 1.1 equiv) is added. The mixture is cooled to −40 °C under a N_2 atmosphere. Over a period of 30–40 min, 9 mL of a LiHMDS solution (9.01 mmol, 1 M solution in hexanes, 2.1 equiv) is added at this temperature. The reaction mixture is allowed to stir at room temperature for an additional 2 h. The reaction is quenched by addition of saturated aqueous NH_4Cl. An extra amount of 15 mL of water is added and the mixture is extracted with EtOAc (3×15 mL). The organic fractions are dried ($MgSO_4$) and filtered. The solvent is removed under reduced pressure and the crude product is purified by chromatography.

3.8.1. Synthesis of methyl 6-benzyl-3-methylene-7-oxo-6-azabicyclo[3.2.1]octane-5-carboxylate (11a).

Brown oil (yield: 22%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.83 (1H, d, J=11.0 Hz, CH_AH_B, C-8), 2.32 (1H, d, J=14.3 Hz, CH_AH_B, C-2), 2.44 (1H, dd, J=17.7, 2.0 Hz, CH_AH_B, C-4), 2.51–2.61 (3H, m, CH_AH_B, C-8+CH_AH_B, C-2+CH_AH_B, C-4), 2.74–2.77 (1H, m, CH, C1), 3.43 (3H, s, CH_3), 4.22 (1H, d, J=15.0 Hz, CH_AH_BPh), 4.55 (1H, d, J=15.0 Hz, CH_AH_BPh), 4.63 (1H, d, J=2.0 Hz, C=CH_AH_B), 4.90 (1H, d, J=2.0 Hz, C=CH_AH_B), 7.19–7.30 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 35.14 (CH_2, C-2), 37.29 (CH_2, C-4), 40.00 (CH, C1), 40.18 (CH_2, C-8), 44.18 (CH_2Ph), 52.23 (CH_3), 66.39 (C_{quat}, C-5), 116.93 (C=CH_2), 127.33 (CH, Ph), 128.11 (CH, Ph), 128.73 (CH, Ph), 136.90 (C_{quat}, Ph), 138.95 (C=CH_2), 171.03 (C=O), 176.77 (C=O). IR (cm^{-1}) ν_{max}: 1702 (C=O), 1740 (C=O). MS *m/z* (%): (ES, pos) 286 (M+H^+, 100). Chromatography: Hex/EtOAc (70/30) R_f=0.19. HRMS calcd for $C_{17}H_{19}NO_3$ (M+H^+) 286.1438, found 286.1441.

3.8.2. Synthesis of benzyl 6-benzyl-3-methylene-7-oxo-6-azabicyclo[3.2.1]octane-5-carboxylate (11b).

Brown oil (yield: 29%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.83 (1H, d, J=11.0 Hz, CH_AH_B, C-8), 2.31 (1H, br d, J=14.3 Hz, CH_AH_B, C-2), 2.46 (2H, br s, CH_2, C-4), 2.51–2.60 (2H, m, CH_AH_B, C-8+CH_AH_B, C-2), 2.71–2.75 (1H, m, CH, C1), 4.33 (1H, d, J=15.1 Hz, NCH_AH_BPh), 4.43 (1H, d, J=15.1 Hz, NCH_AH_BPh), 4.55 (1H, br s, C=CH_AH_B), 4.75 (1H, d, J=12.4 Hz, OCH_AH_BPh), 4.87 (1H, br s, C=CH_AH_B), 5.01 (1H, d, J=12.4 Hz, OCH_AH_BPh), 7.14–7.36 (10H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 35.11 (CH_2, C-2), 37.45 (CH_2, C-4), 40.12 (CH, C1), 40.25 (CH_2, C-8), 44.17 (NCH_2Ph), 66.60 (C_{quat}, C-5), 67.19 (OCH_2Ph), 116.97 (C=CH_2), 127.37 (CH, Ph), 128.11 (CH, Ph), 128.37 (CH, Ph), 128.54 (CH, Ph), 128.60 (CH, Ph), 128.91 (CH, Ph), 134.91 (C_{quat}, Ph), 136.86 (C_{quat}, Ph), 138.85 (C=CH_2), 170.45 (C=O), 176.67 (C=O). IR (cm^{-1}) ν_{max}: 1649 (C=C), 1704 (C=O), 1735 (C=O). MS *m/z* (%): (ES, pos) 362 (M+H^+, 100). Chromatography: Hex/EtOAc (70/30) R_f=0.33. HRMS calcd for $C_{23}H_{23}NO_3$ (M+H^+) 362.1751, found 362.1749.

3.8.3. Synthesis of methyl 7-benzyl-3,4-dimethylene-8-oxo-7-azabicyclo[4.2.1]-nonane-6-carboxylate (13).

White crystals (yield: 10%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.05 (1H, d, J=12.7 Hz, CH_AH_B, C-9), 2.54–2.62 (3H, m, CH_AH_B, C-9+CH_AH_B, C-2+CH_AH_B, C-5), 2.79–2.84 (2H, m, CH, C1+CH_AH_B, C-2), 2.96 (1H, br d, J=14.9 Hz, CH_AH_B, C-5), 3.29 (3H, s, CH_3), 4.01 (1H, d, J=15.1 Hz, CH_AH_BPh), 4.70 (1H, d, J=15.1 Hz, CH_AH_BPh), 4.79 (1H, br s, C^4=CH_AH_B), 4.82 (1H, t, J=1.9 Hz, C^3=CH_AH_B), 4.85 (1H, d, J=1.4 Hz, C^4=CH_AH_B), 4.90 (1H, br s, C^3=CH_AH_B), 7.19–7.31 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 33.87 (CH_2, C-9), 38.37 (CH, C1), 39.42 (CH, C-2), 42.89 (CH_2, C-5), 44.29 (CH_2, CH_2Ph), 52.25 (CH_3), 67.61 (C_{quat}, C-6), 115.43 (C^3=CH_2), 117.76 (C^4=CH_2), 127.20 (CH, Ph), 128.18 (CH, Ph), 128.54 (CH, Ph), 136.97 (C_{quat}, Ph), 145.45 (C^3=CH_2), 148.13 (C^4=CH_2), 172.07 (C=O), 178.13 (C=O). IR (cm^{-1}) ν_{max}: 1625 (C=C), 1698 (C=O), 1737 (C=O). MS *m/z* (%): (ES, pos) 312 (M+H^+, 100). Chromatography: Hex/EtOAc (70/30) R_f=0.25. Mp: 114–117 °C. HRMS calcd for $C_{19}H_{21}NO_3$ (M+H^+) 312.1594, found 312.1591.

3.9. Typical experimental procedure for the synthesis of 15a and 15b

To 28.83 mmol of pyroglutamate **14** is added 14.4 mL of a 2 N NaOH solution (28.83 mmol, 1.0 equiv). After stirring overnight at room temperature the solvent is removed under reduced pressure. The sodium salt of 1-benzyl-5-oxopyrrolidine-2-carboxylic acid is obtained in 99% yield.

To a suspension of 20.75 mmol 1-benzyl-5-oxopyrrolidine-2-carboxylic acid in 30 mL CH_2Cl_2 is added 62.25 mmol (3 equiv) $SOCl_2$. The reaction mixture is allowed to stir at room temperature for 30 min. After removal of the solvent under reduced pressure, 19.9 mmol of 1-benzyl-5-oxopyrrolidine-2-carbonyl chloride is obtained (yield: 96%).

To a solution of 6.33 mmol of 1-benzyl-5-oxopyrrolidine-2-carbonyl chloride in 15 mL CH_2Cl_2 is added 12.7 mmol of triethylamine (2.0 equiv) and 12.7 mmol of amine (2.0 equiv). After stirring for 1 h at room temperature, 25 mL of water is added. The reaction mixture is extracted with CH_2Cl_2 (3×20 mL). The organic fractions are combined and dried with $MgSO_4$. After filtration and evaporation under reduced pressure, 1-benzyl-*N*,*N*-dialkyl-5-oxopyrrolidine-2-carboxamides are obtained.

3.9.1. Synthesis of 1-benzyl-*N*,*N*-diisopropyl-5-oxopyrrolidine-2-carboxamide (15a). Brown powder (yield: 74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.90 (3H, d, J=6.6 Hz, CH_3), 1.12 (3H, d, J=6.6 Hz, CH_3), 1.39 (3H, d, J=6.6 Hz, CH_3), 1.44 (3H, d, J=6.6 Hz, CH_3), 1.79–1.89 (1H, m, CH_AH$_B$ ring, C-3), 2.11–2.24 (1H, m, CH$_A$$H_B$ ring, C-3), 2.37–2.47 (1H, m, CH_AH$_B$ ring, C-4), 2.54–2.65 (1H, m, CH$_A$$H_B$ ring, C-4), 3.32–3.50 (1H, m, NCH), 3.59 (1H, sept, J=6.6 Hz, NCH), 3.87 (1H, d, J=14.6 Hz, CH_AH$_B$Ph), 4.04 (1H, d, J=8.8, 3.9 Hz, CH ring, C-2), 5.19 (1H, d, J=14.6 Hz, CH$_A$$H_B$Ph), 7.19–7.33 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.21 (CH_3), 20.45 (CH_3), 20.56 (CH_3), 20.77 (CH_3), 22.89 (CH_2 ring, C-3), 29.88 (CH_2 ring, C-4), 45.53 (*C*H$_2$Ph), 46.19 (NCH), 47.82 (NCH), 57.12 (CH ring, C-2), 127.72 (CH, Ph), 128.68 (CH, Ph), 129.02 (CH, Ph), 136.21 (C_{quat}, Ph), 169.07 (C=O), 175.25 (C=O). IR (cm^{-1}) ν_{max}: 1634 (C=O), 1682 (C=O). MS *m*/*z* (%): (ES, pos) 303 (M+H$^+$, 100). Mp: 100.5–102.5 °C. HRMS calcd for $C_{18}H_{26}N_2O_2$ (M+H$^+$) 303.2067, found 303.2079.

3.9.2. Synthesis of 1-benzyl-*N*,*N*-diallyl-5-oxopyrrolidine-2-carboxamide (15b). Brown oil (yield: 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.87–1.97 (1H, m, CH_AH$_B$ ring, C-3), 2.14–2.27 (1H, m, CH$_A$$H_B$ ring, C-3), 2.39–2.49 (1H, m, CH_AH$_B$ ring, C-4), 2.57–2.72 (1H, m, CH$_A$$H_B$ ring, C-4), 3.52 (1H, dd, J=17.6, 5.0 Hz, CH_AH$_B$CH=CH$_2$), 3.66 (1H, dd, J=17.6, 3.9 Hz, CH$_A$$H_B$CH=CH$_2$), 3.76 (1H, d, J=14.9 Hz, CH_AH$_B$Ph), 3.89 (1H, dd, J=15.1, 6.2 Hz, CH_AH$_B$CH=CH$_2$), 4.07 (1H, dd, J=15.1, 5.8 Hz, CH$_A$$H_B$CH=CH$_2$), 4.15 (1H, dd, J=9.0, 3.7 Hz, CH ring, C-2), 4.93–5.07 (2H, m, CH$_2$CH=CH_2), 5.11–5.23 (2H, m, CH$_2$CH=CH_2), 5.20 (1H, d, J=14.9 Hz, CH$_A$$H_B$Ph), 5.41–5.53 (1H, m, CH$_2$C*H*=CH$_2$), 5.68–5.81 (1H, m, CH$_2$C*H*=CH$_2$), 7.17–7.35 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.33 (CH_2 ring, C-3), 29.70 (CH_2 ring, C-4), 45.31 (*C*H$_2$Ph), 48.41 (*C*H$_2$CH=CH$_2$), 48.49 (*C*H$_2$CH=CH$_2$), 56.19 (CH ring, C-2), 117.14 (CH$_2$CH=*C*H$_2$), 118.05 (CH$_2$CH=*C*H$_2$), 127.70 (CH, Ph), 128.51 (CH, Ph), 128.71 (CH, Ph), 132.16 (CH$_2$*C*H=CH$_2$), 132.59 (CH$_2$*C*H=CH$_2$), 136.16 (C_{quat}, Ph), 170.76 (C=O), 175.44 (C=O). IR (cm^{-1}) ν_{max}: 1656 (C=O), 1690 (C=O). MS *m*/*z* (%): (ES, pos) 299 (M+H$^+$, 100). HRMS calcd for $C_{18}H_{22}N_2O_2$ (M+H$^+$) 299.1754, found 299.1761.

3.10. Synthesis of 1-benzyl-4,4-bis-(2-chloromethyl-allyl)-*N*,*N*-diisopropyl-5-oxopyrrolidine-2-carboxamide (16)

1-Benzyl-*N*,*N*-diisopropyl-5-oxopyrrolidine-2-carboxamide **15a** (0.75 g, 2.48 mmol) is dissolved in THF (10 mL, freshly distilled from Na metal) and 0.34 g of 3-chloro-2-chloromethyl-1-propene (2.73 mmol, 1.1 equiv) is added. The mixture is cooled to −40 °C under a N_2 atmosphere. Over a period of 30–40 min, 5.2 mL of a LiHMDS solution (5.2 mmol, 1 M solution in hexanes, 2.1 equiv) is added at this temperature. The reaction mixture is allowed to stir at room temperature for an additional 2 h. The reaction is quenched by addition of saturated aqueous NH_4Cl. An extra amount of 15 mL of water is added and the mixture is extracted with EtOAc (3×15 mL), and the organic fractions are dried ($MgSO_4$). After filtration, the solvent is removed under reduced pressure. Purification by chromatography gives 0.34 g of 1-benzyl-4,4-bis-(2-chloromethyl-allyl)-*N*,*N*-diisopropyl-5-oxopyrrolidine-2-carboxamide (yield: 29%). When considering the electrophile as limiting reagent, the yield is 52%.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, d, J=6.6 Hz, CH_3), 1.12 (3H, d, J=6.6 Hz, CH_3), 1.38 (3H, d, J=6.6 Hz, CH_3), 1.45 (3H, d, J=6.6 Hz, CH_3), 1.92 (1H, dd, J=13.2, 5.2 Hz, CH_AH$_B$ ring, C-3), 2.21 (1H, dd, J=13.2, 9.6 Hz, CH$_A$$H_B$ ring, C-3), 2.30 (1H, d, J=14.2 Hz, CH_AH$_B$(C=CH$_2$)CH$_2$Cl), 2.32 (1H, d, J=14.2 Hz, CH_AH$_B$(C=CH$_2$)CH$_2$Cl), 2.62 (1H, d, J=14.2 Hz, CH$_A$$H_B$(C=CH$_2$)CH$_2$Cl), 2.76 (1H, d, J=14.2 Hz, CH$_A$$H_B$(C=CH$_2$)CH$_2$Cl), 3.36 (1H, sp, J=6.6 Hz, NCH), 3.52 (1H, sept, J=6.6 Hz, NCH), 3.84 (1H, dd, J=9.6, 5.2 Hz, CH ring, C-2), 4.01 (1H, d, J=14.3 Hz, CH_AH$_B$Ph), 4.02 (2H, s, 2×CH_AH$_B$Cl), 4.07 (2H, s, 2×CH$_A$$H_B$Cl), 5.04 (2H, s, 2×C=C$H_AH_B$), 5.16 (1H, d, J=14.3 Hz, CH$_A$$H_B$Ph), 5.30 (2H, s, 2×C=CH$_A$$H_B$), 7.14–7.34 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.26 (CH_3), 20.44 (CH_3), 20.52 (CH_3), 20.66 (CH_3), 30.92 (CH_2 ring, C-3), 40.72 (*C*H$_2$(C=CH$_2$)CH$_2$Cl), 41.00 (*C*H$_2$(C=CH$_2$)CH$_2$Cl), 46.02 (N*C*H$_2$Ph), 46.11 (NCH), 47.29 (C_{quat} ring, C-4), 47.96 (NCH), 48.78 (CH_2Cl), 48.87 (CH_2Cl), 54.55 (CH ring, C-2), 119.03 (C=*C*H$_2$), 119.79 (C=*C*H$_2$), 127.87 (CH, Ph), 128.71 (2×CH, Ph), 129.40 (2×CH, Ph), 135.41 (C_{quat}, Ph), 141.38 (*C*=CH$_2$), 141.57 (*C*=CH$_2$), 168.64 (C=O), 176.70 (C=O). IR (cm^{-1}) ν_{max}: 1649 (C=O), 1683 (C=O). MS *m*/*z* (%): (ES, pos) 480/482/484 (M+H$^+$, 100). Chromatography: Hex/EtOAc (85/15) R_f=0.17. HRMS calcd for $C_{26}H_{36}{}^{35}Cl_2N_2O_2$ (M+H$^+$) 479.2227, found 479.2212.

3.11. Synthesis of 6-benzyl-1-(2-chloromethyl-allyl)-*N*,*N*-diallyl-3-methylene-7-oxo-6-azabicyclo[3.2.1]-octane-5-carboxamide (18)

1-Benzyl-*N*,*N*-diisopropyl-5-oxopyrrolidine-2-carboxamide **15a** of 0.25 g (0.84 mmol) is dissolved in THF (5 mL, freshly distilled from Na metal) and 0.21 g of 3-chloro-2-chloromethyl-1-propene (1.68 mmol, 2.0 equiv) is added. The mixture is cooled to −40 °C under a N_2 atmosphere. Over a period of 30–40 min, 2.5 mL of LiHMDS (2.5 mmol, 1 M solution in hexanes, 3.0 equiv) is added at this temperature. The reaction mixture is allowed to stir at room temperature for an additional 2 h. The reaction is quenched by addition of saturated aqueous NH_4Cl. An extra amount of 10 mL water is added and the mixture is extracted with EtOAc (3×10 mL). The organic fractions are dried ($MgSO_4$) and filtered. The solvent is removed under reduced pressure. A crude reaction mixture of 0.34 g is obtained (conversion: 56%). After purification by chromatography, 0.09 g of 6-benzyl-1-(2-chloromethyl-allyl)-*N*,*N*-diallyl-3-methylene-7-oxo-6-azabicyclo[3.2.1]octane-5-carboxamide **18** is obtained as white crystals (yield: 25%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.74 (1H, d, J=11.6 Hz, CH_AH$_B$, C-8), 2.16 (1H, d, J=13.6 Hz, CH_AH$_B$, C-4), 2.28 (1H, d, J=14.3 Hz, CH_AH$_B$(C=CH$_2$)CH$_2$Cl), 2.30 (1H, d, J=13.6 Hz, CH$_A$$H_B$, C-4), 2.44–2.50 (2H, m, CH_AH$_B$, C-2+CH$_A$$H_B$, C-8), 2.78 (1H, d, J=14.3 Hz, CH$_A$$H_B$(C=CH$_2$)CH$_2$Cl), 2.80 (1H, d, J=14.9 Hz, CH$_A$$H_B$, C-2), 2.94 (1H, dd, J=17.6, 4.7 Hz, CH_AH$_B$CH=CH$_2$), 3.39 (1H, dd, J=13.8, 7.7 Hz, CH_AH$_B$CH=CH$_2$), 3.96 (1H, d, J=12.1 Hz, CH_AH$_B$Cl), 4.03 (1H, d, J=12.1 Hz, CH$_A$$H_B$Cl), 4.17 (1H, d, J=14.6 Hz, CH_AH$_B$Ph), 4.18–4.24 (2H, m, 2×CH$_A$$H_B$CH=CH$_2$), 4.30 (1H, d, J=14.6 Hz, CH$_A$$H_B$Ph), 4.41 (1H, br s, C^3=CH_AH$_B$), 4.74 (1H, br s, C^3=CH$_A$$H_B$), 4.98–5.20 (4H, m, 2×CH$_2$CH=CH_2), 5.07 (1H, br s, CH$_2$(C=CH_AH$_B$)CH$_2$Cl), 5.29 (1H, br s, CH$_2$(C=CH$_A$$H_B$)CH$_2$Cl), 5.44–5.60 (1H, m, CH$_2$CH=CH$_2$), 5.60–5.79 (1H, m, CH$_2$CH=CH$_2$), 7.24–7.35 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 36.34 (*C*H$_2$(C=CH$_2$)CH$_2$Cl), 39.27 (CH$_2$, C-2), 42.02 (CH$_2$, C-8), 42.80 (CH$_2$, C-4), 45.52 (N*C*H$_2$Ph), 48.04 (C$_{quat}$, C1), 48.80 (*C*H$_2$CH=CH$_2$), 49.06 (CH$_2$Cl), 49.99 (*C*H$_2$CH=CH$_2$), 66.63 (C$_{quat}$, C-5), 116.65 (C^3=*C*H$_2$), 117.57 (CH$_2$CH=*C*H$_2$), 118.74 (CH$_2$CH=*C*H$_2$), 118.86 (CH$_2$(C=*C*H$_2$)CH$_2$Cl), 127.80 (CH, Ph), 128.33 (2×CH, Ph), 130.06 (2×CH, Ph), 132.51 (CH$_2$*C*H=CH$_2$), 132.86 (CH$_2$*C*H=CH$_2$), 136.41 (C$_{quat}$, Ph), 139.35 (C$_{quat}$, C-3), 141.05 (CH$_2$(*C*=CH$_2$)CH$_2$Cl), 169.14 (C=O), 177.13 (C=O). IR (cm^{-1}) ν_{max}: 1625 (C=O), 1691 (C=O). MS *m*/*z* (%): (ES, pos) 440/442 (M+H$^+$, 100). Chromatography: Hex/EtOAc (70/30) R_f= 0.56. Mp: 109–111 °C. HRMS calcd for $C_{26}H_{31}{}^{35}ClN_2O_2$ (M+H$^+$) 439.2147, found 439.2142.

3.12. Typical experimental procedure for the synthesis of 22a and 22b

In an oven dry flask, NaH (0.11 g of a 60% suspension in mineral oil washed with hexanes, 3.32 mmol, 1.2 equiv) is dispersed in THF (5 mL, freshly distilled from Na metal). To this dispersion derivative **5** (2.77 mmol, 1 equiv), dissolved in THF (10 mL), is added. The mixture is refluxed under a N_2 atmosphere for 16 h. Very carefully water (5 mL) is added and the mixture is extracted with diethyl ether (3×20 mL). The combined organic fractions are dried ($MgSO_4$) and filtered. The solvent is removed under reduced pressure. The compound is purified by bulb-to-bulb distillation.

3.12.1. Synthesis of benzyl 2-methylene-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (22a). Colourless oil (yield: 68%).

^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.05–2.17 (1H, m, CH_AH$_B$, C-7), 2.33–2.79 (4H, m, CH$_2$, C-6+CH$_A$$H_B$, C-7+C$H_AH_B$, C1), 3.05 (1H, d, J=15.5 Hz, CH$_A$$H_B$, C1), 3.71 (1H, d, J=15.7 Hz, CH_AH$_B$, C-3), 4.28 (1H, d, J=15.7 Hz, CH$_A$$H_B$, C-3), 5.01–5.07 (2H, m, C=CH_2), 5.17 (2H, s, CH_2Ph), 7.28–7.37 (5H, m, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 31.37 (CH$_2$, C-7), 33.30 (CH$_2$, C-6), 43.85 (CH$_2$, C1), 46.54 (CH$_2$, C-3), 67.84 (*C*H$_2$Ph), 72.87 (C$_{quat}$, C-7a), 109.22 (C=*C*H$_2$), 127.96 (CH, Ph), 128.48 (CH, Ph), 128.66 (CH, Ph), 135.27 (C$_{quat}$, Ph), 145.17 (*C*=CH$_2$), 172.94 (C=O), 174.23 (C=O). IR (cm^{-1}) ν_{max}: 1703 (C=O), 1736 (C=O). MS *m*/*z* (%): 272 (M+H$^+$, 100). Bp: 145–160 °C/0.13 mbar. HRMS calcd for $C_{16}H_{17}NO_3$ (M+H$^+$) 272.1281, found 272.1285.

3.12.2. Synthesis of ethyl 2-methylene-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (22b). Colourless oil (yield: 75%).

^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.27 (3H, t, J=7.1 Hz, CH$_2$CH_3), 2.07–2.19 (1H, m, CH_AH$_B$, C-7), 2.40–2.82 (4H, m, CH$_2$, C-6+CH_AH$_B$, C1+CH$_A$$H_B$, C-7), 3.05 (1H, d, J=15.5 Hz, CH$_A$$H_B$, C1), 3.73 (1H, d, J=15.8 Hz, CH_AH$_B$, C-3), 4.21 (2H, q, J=7.1 Hz, CH_2CH$_3$), 4.29 (1H, d, J=15.8 Hz, CH$_A$$H_B$, C-3), 5.03–5.08 (2H, m, C=CH_2). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 14.12 (CH$_2$*C*H$_3$), 31.48 (CH$_2$, C-7), 33.33 (CH$_2$, C-6), 43.86 (CH$_2$, C1), 46.49 (CH$_2$, C-3), 61.80 (*C*H$_2$CH$_3$), 72.79 (C$_{quat}$, C-7a), 109.06 (C=*C*H$_2$), 145.32 (*C*=CH$_2$), 173.15 (C=O), 174.23 (C=O). IR (cm^{-1}) ν_{max}: 1708 (C=O), 1732 (C=O). MS *m*/*z* (%): 210 (M+H$^+$, 100). Bp: 80–90 °C/0.01 mbar. HRMS calcd for $C_{11}H_{15}NO_3$ (M+H$^+$) 210.1125, found 210.1134.

3.13. Synthesis of (2-methylenetetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (23)

In an oven dry flask, 0.23 g of $LiAlH_4$ (5.8 mmol, 2 equiv) is dispersed in THF (10 mL, freshly distilled from Na metal). The flask is put in an ice bath under a N_2 atmosphere. To this dispersion derivative **22b** (2.9 mmol, 1 equiv), dissolved in THF (10 mL), is added. The ice bath is removed and the mixture is refluxed for 3 h under a N_2 atmosphere. Very carefully water is added until all remaining $LiAlH_4$ is decomposed. The mixture is filtered over a combination $MgSO_4$/Celite (50/50) and the solvent is removed under reduced pressure. The compound is purified by bulb-to-bulb distillation and a colourless oil is obtained (yield: 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62–1.94 (4H, m, CH$_2$, C-6+CH$_2$, C-7), 2.32 (1H, dd, J=15.8, 2.0 Hz, CH_AH$_B$, C1), 2.43 (1H, ddd, J=15.8, 2.1, 1.5 Hz, CH$_A$$H_B$, C1),

2.60–2.69 (1H, m, CH_AH$_B$, C-5), 3.02–3.10 (1H, m, CH$_A$$H_B$, C-5), 3.24 (1H, d, J=13.5 Hz, CH_AH$_B$, C-3), 3.25 (1H, d, J=10.9 Hz, CH_AH$_B$OH), 3.27 (1H, d, J=10.9 Hz, CH$_A$$H_B$OH), 3.61 (1H, d, J=13.5 Hz, CH$_A$$H_B$, C-3), 4.87–4.92 (2H, m, C=CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.18 (CH_2, C-6), 34.45 (CH_2, C-7), 41.26 (CH_2, C1), 55.54 (CH_2, C-5), 59.12 (CH_2, C-3), 66.56 (CH_2OH), 74.32 (C$_{quat}$, C-7a), 106.13 (C=CH$_2$), 149.07 (C=CH$_2$). IR (cm^{-1}) ν_{max}: 3368 (br OH). MS m/z (%): 154 (M+H$^+$, 100). Bp: 80–100 °C/0.27 mbar. HRMS calcd for $C_9H_{15}NO$ (M+H$^+$) 154.1226, found 154.1229.

3.14. Synthesis of ethyl 2,5-dioxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (24)

Compound **22b** (1.2 mmol) is dissolved in a mixture of CH_2Cl_2 (10 mL, freshly distilled from CaH_2) and methanol (0.5 mL). The mixture is cooled to −78 °C. Ozone is bubbled through until the mixture remains blue. Air is bubbled through the mixture to remove the excess of ozone after which dimethylsulfide (2.3 mmol, 2 equiv) is added. The flask is put in the freezer (−20 °C) for an overnight period. The mixture is washed twice with brine (10 mL). The aqueous layer is extracted once with CH_2Cl_2 (10 mL). The combined organic fractions are dried ($MgSO_4$) and filtered. The solvent is removed under reduced pressure. After purification by chromatography, a brown oil is obtained (yield: 58%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (3H, t, J=7.1 Hz, CH$_2$CH_3), 2.16 (1H, ddd, J=12.9, 11.1, 9.5 Hz, CH_AH$_B$, C-6), 2.40–2.49 (1H, m, CH_AH$_B$, C-7), 2.52 (1H, d, J=18.0 Hz, CH_AH$_B$, C1), 2.74–2.88 (1H, m, CH$_A$$H_B$, C-7), 2.97–2.99 (1H, m, CH$_A$$H_B$, C-6), 2.97 (1H, d, J=18.0 Hz, CH$_A$$H_B$, C1), 3.54 (1H, d, J=18.5 Hz, CH$_A$H$_B$, C-3), 4.10 (1H, d, J=18.5 Hz, CH$_A$$H_B$, C-3), 4.23 (2H, q, J=7.1 Hz, CH_2CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.05 (CH$_2$$CH_3$), 31.57 ($CH_2$, C-7), 31.66 ($CH_2$, C-6), 48.52 ($CH_2$, C1), 49.74 ($CH_2$, C-3), 62.48 ($CH_2CH_3$), 68.95 (C$_{quat}$, C-7a), 171.53 (C=O), 174.44 (C=O), 208.87 (C=O). IR (cm^{-1}) ν_{max}: 1709 (C=O), 1738 (C=O), 1765 (C=O). MS m/z (%): 212 (M+H$^+$, 100). Chromatography: Hex/EtOAc (35/65) R_f=0.16. HRMS calcd for $C_{10}H_{13}NO_4$ (M+H$^+$) 212.0917, found 212.0918.

3.15. Synthesis of 26 and 27

The procedure is the same as for the synthesis of derivatives **5**. After work-up, a mixture of compounds **26** and **27** is obtained. This mixture is treated with NaH in THF and stirred at room temperature for 16 h. The work-up is the same as described for the synthesis of **22**. After chromatography a brown oil is obtained (yield: 24%).

3.15.1. Synthesis of ethyl 3-oxo-2,3,5,8-tetrahydro-8a(1*H*)-indolizine-carboxylate (27). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (3H, t, J=7.0 Hz, CH$_2$CH_3), 1.95–2.06 (1H, m, CH_AH$_B$, C1), 2.18 (1H, br d, J=15.9 Hz, CH_AH$_B$, C-8), 2.28–2.51 (3H, m, CH$_A$$H_B$, C1+CH$_2$, C-2), 2.96 (1H, ddd, J=15.9, 5.4 Hz, J=1.9 Hz, CH$_A$$H_B$, C-8), 3.66 (1H, dd, J=19.0, 1.4 Hz, CH_AH$_B$, C-5), 4.14 (1H, dq, J=10.9, 7.0 Hz, CH_AH$_B$CH$_3$), 4.17 (1H, dq, J=10.9, 7.0 Hz, CH$_A$$H_BCH_3$), 4.21 (1H, dd, J=19.0, 2.5 Hz, CH$_A$$H_B$, C-5), 5.65–5.77 (2H, m, CH, C-6+CH, C-7). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.19 (CH$_2$$CH_3$), 29.17 ($CH_2$, C1), 31.19 ($CH_2$, C-2), 34.52 ($CH_2$, C-8), 40.02 ($CH_2$, C-5), 61.81 ($CH_2CH_3$), 64.33 (C$_{quat}$, C-8a), 122.92 (CH, C-7), 123.53 (CH, C-6), 173.14 (C=O), 174.66 (C=O). IR (cm^{-1}) ν_{max}: 1701 (C=O), 1732 (C=O). MS m/z (%): 210 (M+H$^+$, 100). Chromatography: Hex/EtOAc (10/90) R_f=0.30. HRMS calcd for $C_{11}H_{15}NO_3$ (M+H$^+$) 210.1125, found 210.1128.

3.15.2. Synthesis of ethyl 2-[(2*Z*)-4-chloro-2-butenyl]-5-oxopyrrolidine-2-carboxylate (26). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30 (3H, t, J=7.1 Hz, CH$_2$CH_3), 2.08–2.13 (1H, m, CH_AH$_B$ ring, C-3), 2.29–2.48 (3H, m, CH$_2$ ring, C-4+CH$_A$$H_B$), 2.57 (1H, dd, J=14.4, 7.3 Hz, CH_AH$_B$HC=CH), 2.67 (1H, dd, J=14.4, 8.5 Hz, CH$_A$$H_B$HC=CH), 4.05 (1H, d, J=8.0 Hz, CH_AH$_B$Cl), 4.03–4.25 (3H, m, CH$_A$$H_B$Cl+C$H_2CH_3$), 5.48–5.57 (1H, m, C$HCH_2$Cl), 5.81–5.89 (1H, m, HC=CHCH$_2$Cl), 6.39 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.16 (CH$_2$$CH_3$), 29.79 (CH$_2$ ring, C-3), 30.30 (CH$_2$ ring, C-4), 36.32 (CH$_2$HC=CH$_2$), 38.76 (CH$_2$Cl), 61.99 (CH$_2$CH$_3$), 65.14 (C$_{quat}$ ring, C-2), 126.90 (CH$_2$HC=CH), 130.06 (HC=CHCH$_2$Cl), 172.94 (C=O), 177.18 (C=O). IR (cm^{-1}) ν_{max}: 1703 (C=O), 1732 (C=O). MS m/z (%): 246 (M+H$^+$, 100). Chromatography: Hex/EtOAc (10/90) R_f=0.30. HRMS calcd for $C_{11}H_{16}{}^{35}ClNO_3$ (M+H$^+$) 246.0891, found 246.0898.

3.16. Synthesis of (2*S*)-[L-(−)-menthyl]-5-oxopyrrolidine-2-carboxylate (29a)

To a solution of (2*S*)-pyroglutamic acid (6.46 g, 50 mmol) in dry CH_2Cl_2 (100 mL, freshly distilled from CaH_2) is added L-(−)-menthol (6.26 g, 40 mmol, 0.8 equiv). Afterwards DMAP (1.52 g, 12.5 mmol, 0.25 g equiv) and DCC (10.34 g, 50 mmol, 1 equiv) are added. The mixture is allowed to stir for 16 h, the volatiles are removed under reduced pressure and the product is purified by chromatography. A yellow oil is obtained (yield: 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.76 (3H, d, J=6.9 Hz, CH$_3$, C-9′), 0.90 (3H, d, J=7.2 Hz, CH$_3$, C-10′), 0.92 (3H, d, J=6.3 Hz, CH$_3$, C-7′), 0.8–1.13 (3H, m, CH_AH$_B$, C-2′+CH_AH$_B$, C-5′+CH_AH$_B$, C-6′), 1.36–1.56 (2H, m, CH, C1′+CH, C-4′), 1.64–1.74 (2H, m, CH$_A$$H_B$, C-5′+CH$_A$$H_B$, C-6′), 1.84 (1H, septd, J=7.1, 2.8 Hz, CH, C-8′), 1.93–2.01 (1H, m, CH$_A$$H_B$, C-2′), 2.13–2.45 (1H, m, CH_AH$_B$, C-3), 2.33–2.41 (2H, m, CH$_2$, C-4), 2.43–2.55 (1H, m, CH$_A$$H_B$, C-3), 4.61 (1H, dd, J=8.7, 5.4 Hz, CH, C-2), 4.78 (1H, dt, J=10.7, 4.4 Hz, CH, C-3′), 5.98 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.33 (CH$_3$, C-9′), 20.82 (CH$_3$, C-10′), 22.04 (CH$_3$, C-7′), 23.40 (CH$_2$, C-5′), 25.13 (CH$_2$, C-3), 26.41 (CH, C-8′), 29.29 (CH$_2$, C-4), 31.45 (CH, C1′), 34.16 (CH$_2$, C-6′), 40.78 (CH$_2$, C-2′), 46.96 (CH, C-4′), 55.48 (CH, C-2), 75.85 (CH, C-3′), 171.64 (C=O), 177.68 (C=O). IR (cm^{-1}) ν_{max}: 1711 (C=O, br), 2871, 2951, 3110, 3230. MS m/z (%): (ES, pos) 268 (M+H$^+$, 53), 225 (7). Chromatography: Hex/EtOAc (30/70) R_f=0.30. Polarimetry: $[\alpha]_{546}$ −77.3 (1.022 g/100 mL, CH_2Cl_2, 27 °C). HRMS calcd for $C_{15}H_{25}NO_3$ (M+H$^+$) 268.1907, found 268.1910.

3.17. Synthesis of (2*S*)-[(1*R*,2*R*,4*S*)-fenchyl]-5-oxopyrrolidine-2-carboxylate (29b)

The procedure is identical as for the synthesis of **29a**. White crystals are obtained (yield: 54%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.78 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.22 (1H, d, J=10.4 Hz, CH_AH$_B$, C-6′); 1.44–1.51 (1H, m, CH_AH$_B$, C-5′), 1.60 (1H, d, J=10.4 Hz, CH$_A$$H_B$, C-6′), 1.07–1.16 and 1.53–1.74 (4H, m, CH$_A$$H_B$, C-5′+CH$_2$, C-7′+CH, C-4′), 2.17–2.32 (1H, m, CH_AH$_B$, C-3), 2.35–2.42 (2H, m, CH$_2$, C-4), 2.44–2.58 (1H, m, CH$_A$$H_B$, C-3), 4.29 (1H, dd, J=8.2, 5.2 Hz, CH, C-2), 4.42 (1H, d, J=1.7 Hz, CH, C-2′), 6.31 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.38 (CH_3), 20.19 (CH_3), 25.23 (CH_2, C-5′), 25.81 (CH_2, C-3), 26.68 (CH_2, C-6′), 29.29 (CH_2, C-4), 29.69 (CH_3), 39.58 (C_{quat}, C-3′), 41.34 (CH_2, C-7′), 48.35 (C_{quat}, C1′), 48.44 (CH, C-4′), 55.68 (CH, C-2), 87.60 (CH, C-2′), 172.34 (C=O, lactam), 177.65 (C=O, ester). IR (cm^{-1}) ν_{max}: 1709 (C=O), 1736 (C=O), 3432 (NH). MS *m/z* (%): (ES, Pos) 266 (M+H$^+$, 100). Chromatography: Hex/EtOAc (20/80) R_f=0.31. Mp: 78.0–81.5 °C. Polarimetry: $[\alpha]_{546}$ +39.60 (1.01 g/100 mL, CH_2Cl_2, 27 °C). HRMS calcd for $C_{15}H_{23}NO_3$ (M+H$^+$) 266.1751, found 266.1757.

3.18. Synthesis of [(1*R*,2*R*,4*S*)-fenchyl]-2-(2-chloromethyl-allyl)-5-oxopyrrolidine-2-carboxylate (30)

The procedure is identical as for the synthesis of **5a** and **5b**. Upon work-up a mixture of **30** and **31** is obtained. In the crude reaction mixture no diastereomeric excess was observed. After purification (chromatography and crystallisation in hexanes) compound **30** is obtained as white crystals (yield: 20%, diastereomeric excess 12%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: Major (in italic), minor, overlap (underlined): 0.78 (6H, s, CH_3), 1.03 (3H, s, CH_3), *1.05* (3H, s, CH_3), 1.08–1.19 (2H, m, CH_AH$_B$, C-7′), 1.11 (6H, s, CH_3), 1.22 (2H, d, J=10.3 Hz, CH_AH$_B$, C-6′), 1.40–1.54 (2H, m, CH$_A$$H_B$, C-7′), 1.60 (2H, d, J=10.3 Hz, CH$_A$$H_B$, C-6′), 1.66–1.72 (2H, m, CH_AH$_B$, C-5′), 1.71 (2H, s, CH, C-4′), 1.72–1.75 (2H, m, CH$_A$$H_B$, C-5′), 2.16–2.25 (2H, m, CH_AH$_B$, C-3), 2.38–2.43 (4H, m, CH_2, C-4), 2.46–2.55 (2H, m, CH$_A$$H_B$, C-3), 2.55 (2H, d, J=15.0 Hz, CH_AH$_B$C=CH$_2$), 2.95 (2H, d, J=15.0 Hz, CH$_A$$H_B$C=CH$_2$), 4.02 (4H, d, J=0.6 Hz, CH_2Cl), 4.38 (2H, t, J=2.1 Hz, CH, C-2′), *5.06* (1H, s, C=CH$_A$H$_B$), 5.07 (1H, s, C=CH$_A$H$_B$), 5.35 (2H, s, C=CH$_A$$H_B$), 6.38 (2H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: Major (in italic), minor, overlap (underlined): 19.81 (CH_3), *19.91* (CH_3), 20.64 (CH_3), *20.72* (CH_3), 26.12 (CH_2, C-7′), 26.96 (CH_2, C-5′), 29.89 (CH_3), 29.95 (CH_2, C-4), *31.86* (CH_2, C-3), 32.01 (CH_2, C-3), 39.94 (C_{quat}, C-3′), *41.60* (CH_2, C-6′), 41.77 (CH_2, C-6′), 42.01 (CH_2HC=CH_2), 48.35 (CH, C-4′), 48.53 (CH, C-4′), *48.82* (C_{quat}, C1′), 48.93 (C_{quat}, C1′), 49.04 (CH_2Cl), *65.41* (C_{quat}, C-2), 65.56 (C_{quat}, C-2), 88.58 (CH, C-2′), *119.99* (C=CH_2), 120.16 (C=CH_2), 140.26 (C=CH$_2$), 173.98 (C=O), 177.11 (C=O). IR (cm^{-1}) ν_{max}: 1699 (C=O), 1745 (C=O), 3193 (br NH). MS *m/z* (%): (ES, pos) 354/356 (M+H$^+$, 100). Chromatography: Hex/EtOAc (40/60) R_f=0.42. Mp: 95 °C. Polarimetry: $[\alpha]_{546}$ +30.41 (0.88 g/100 mL, CH_2Cl_2, 27 °C). HRMS calcd for $C_{19}H_{28}{}^{35}ClNO_3$ (M+H$^+$) 354.1830, found 354.1823.

3.19. Synthesis of [(1*R*,2*R*,4*S*)-fenchyl]-2-methylene-5-oxotetrahydropyrrolizine-7a-carboxylate (31)

The procedure is identical as for the synthesis of **22**. In the crude reaction mixture no diastereomeric excess was observed. After purification (chromatography and crystallisation) white crystals are obtained (yield: 84%, diastereomeric excess 12%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: Major (in italic), minor, overlap (underlined): *0.74* (3H, s, CH_3), 0.75 (3H, s, CH_3), 1.01 (3H, s, CH_3), *1.03* (3H, s, CH_3), 1.11 (6H, s, CH_3), 1.14–1.75 (14H, m, CH, C-4′+CH_2, C-5′+CH_2, C-6′+CH_2, C-7′), 2.08–2.20 (2H, m, CH_AH$_B$, C-7), 2.43–2.54 (4H, m, CH_AH$_B$, C-6 and CH_AH$_B$, C1), 2.62–2.71 (2H, m, CH$_A$$H_B$, C-7), 2.71–2.86 (2H, m, CH$_A$$H_B$, C-6), 3.06 (2H, pseudo t, J=14.2 Hz, CH$_A$$H_B$, C1), *3.73* (1H, d, J=15.7 Hz, CH_AH$_B$, C-3), 3.74 (1H, d, J=15.7 Hz, CH_AH$_B$, C-3), 4.31 (2H, d, J=15.7 Hz, CH$_A$$H_B$, C-3), *4.36* (1H, s, CH, C-2′), 4.37 (1H, s, CH, C-2′), 5.06–5.10 (4H, m, C=CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: Major (in italic), minor, overlap (underlined): 19.37 (CH_3), *19.48* (CH_3), 20.09 (CH_3), 25.84 (CH_2, C-7′), 26.84 (CH_2, C-5′), 29.63 (CH_3), 31.86 (CH_2, C-7), 33.55 (CH_2, C-6), *33.63* (CH_2, C-6), 39.52 (C_{quat}, C-3′), 41.26 (CH_2, C-6′), *43.98* (CH_2, C1), 44.26 (CH_2, C1), 46.61 (CH_2, C-3), 48.32 (CH, C-4′), 48.38 (CH, C-4′ of C_{quat}, C1′), 48.43 (CH, C-4′ of C_{quat}, C1′), 73.16 (C_{quat}, C-7a), 88.02 (CH, C-2′), *88.08* (CH, C-2′), 109.28 (C=CH_2), 145.55 (C=CH$_2$), *173.56* (C=O), 173.70 (C=O), 174.10 (C=O), *174.20* (C=O). IR (cm^{-1}) ν_{max}: 1709 (C=O), 1732 (C=O). MS *m/z* (%): (ES, Pos) 318 (M+H$^+$, 100). Chromatography: Hex/EtOAc (40/60) R_f=0.43. Mp: 214–217 °C. Polarimetry: $[\alpha]_{546}$ +21.93 (0.23 g/100 mL, CH_2Cl_2, 27 °C). HRMS calcd for $C_{19}H_{27}NO_3$ (M+H$^+$) 318.2064, found 318.2051.

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