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A tandem Diels–Alder/Mannich approach to the synthesis of AE and ABE ring analogues of *Delphinium* alkaloids

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ABSTRACT

The one-pot $TiCl_4$ catalysed Diels–Alder/Mannich reaction of α-cyanoaminoacrylates with 2-silyloxy-1,4-butadienes gives 6-keto-3-azabicyclo[3.3.1]nonane-1-carboxylates. Reduction of the ketone and alkylation of the resultant alcohol gives 6-alkoxy-3-azabicyclo[3.3.1]nonanes mimicking the AE rings of a number of *Delphinium* and *Aconitum* alkaloids, with the same stereochemistry as the natural products.

1. Introduction

6-Alkoxy-3-azabicyclo[3.3.1]nonanes are a common structural motif found in numerous *Delphinium* and *Aconitum* alkaloids, such as eldeline **1** and methyllycaconitine (MLA) **2** (Fig. 1). Substitution at the C-1 position has been found to have a considerable effect on biological activity, to the extent that compounds with a C-1 hydroxyl group, e.g., grandiflorine **3**, exhibits 100–1000 times less binding efficiency than MLA **2**, with a C-1 methoxy group, at the neuronal α7 nicotinic acetylcholine receptor.[1] Other structurally-related *Delphinium* and *Aconitum* alkaloids **4**–**11** exhibit various biological activities, such as inuline **4** and ajacine **5**, which have hypotensive and ganglion-blocking effects,[2] talatisamine **8**, a potassium channel blocker,[3] delcosine **9**, a plant growth inhibitor[4] and takaosamine **11**, an insect antifeedant.[5]

Although there have been previous syntheses of the 3-azabicyclo[3.3.1]nonane core of *Delphinium* and *Aconitum* alkaloids,[6] few have included oxygenated substitution at the C-1 position.[7] This observation led us to investigate the activity of 6-methoxy-9-methylene-3-azabicyclononanes as analogues of the AE rings of MLA **2**.[8] Synthesis of these analogues involved alkylation of a 6-hydroxy-9-oxo-3-azabicyclo[3.3.1]nonane **13**, which itself results from successive Michael/aldol addition of acrolein to an ethyl 4-piperidin-2-onecarboxylate **12**. Methylation of the 6-hydroxy-9-keto-azabicyclononanes **13** required use of the soft base silver (I) oxide to prevent retro-aldol decomposition, however these conditions resulted in epimerisation at C-6, resulting in a mixture of poorly-separable diastereomers **14**, favouring the unnatural stereochemistry **14a**[8] (Fig. 2).

These complications led us to investigate an alternative synthesis of 6-oxygenated azabicyclononanes that did not involve the incorporation of a ketone at C-9. We envisaged that selective reduction of 6-keto azabicyclononane **15** would afford 6-hydroxy azabicyclononane **16**, with the same configuration found in MLA **2** (Fig. 3). Alkylation of alcohol **16** would then proceed readily due to the absence of retro-aldol complicating factors that were previously observed for the alkylation of the 9-keto-6-hydroxy-3-azabicyclononane.[8]

2. Results and discussion

2.1. Synthesis of C6-keto azabicyclononanes

The synthesis of bicyclic ketone **17a**, similar to the desired ketone **15** has been reported[9] from the $TiCl_4$-promoted, one-pot Diels–Alder/Mannich reaction of α-cyanoaminoacrylate **18a** with diene **19a** (Scheme 1). The reaction proceeds by initial Diels–Alder cycloaddition of diene **19a** to dienophile **18a**, forming a cyclic intermediate that undergoes intramolecular Mannich reaction to give the racemic bicyclic product **17a**.

Whilst the synthesis of **17a** has been reported[9] we decided to further develop the synthetic method and demonstrate the utility of the reaction of analogues of **17a** with a range of acrylates and 2-silyloxy-1,4-butadienes. We therefore herein report the

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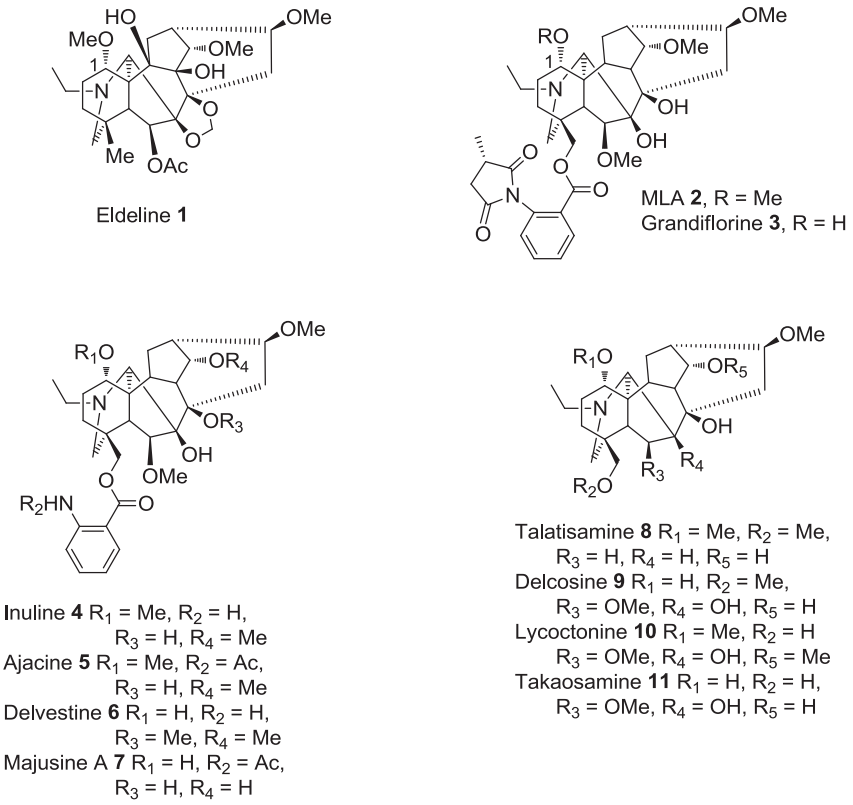


Fig. 1. *Delphinium* and *Aconitum* alkaloids.

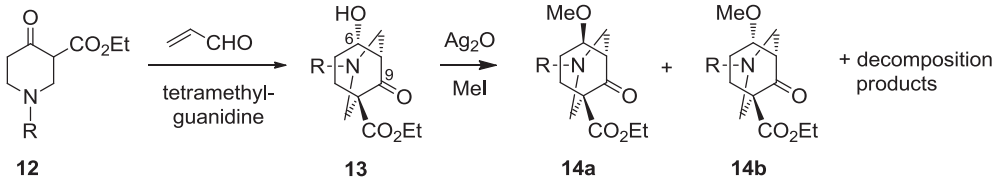


Fig. 2. Epimerisation of C-9 keto-azabicyclononanes.

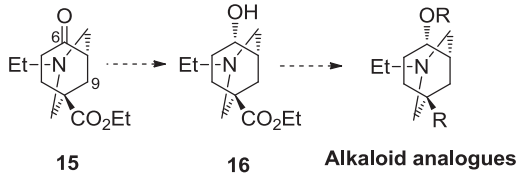
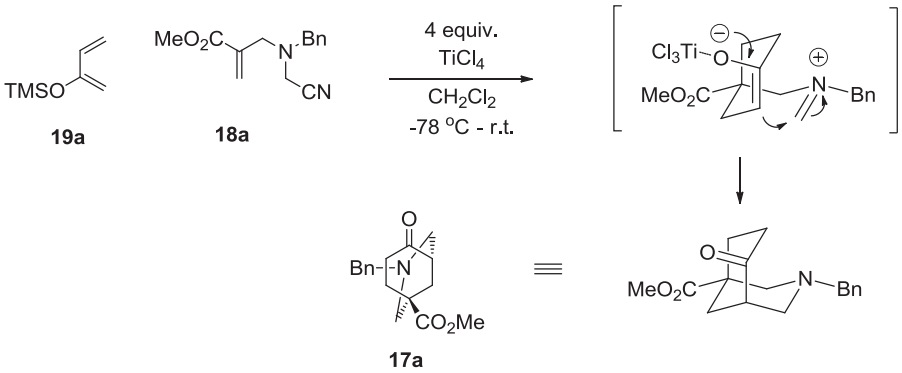


Fig. 3. Key intermediates in the synthesis of 6-alkoxy-3-azabicyclononanes.

synthesis of a series 6-oxygenated-3-azabicyclo[3.3.1]nonanes lacking C-9 oxo-substitution, as analogues of the AE rings of *Delphinium* and *Aconitum* alkaloids using this Diels–Alder/Mannich reaction as the key step.

Cyanoaminoacrylate **18b** was synthesised using literature methods[9] from ethyl 2-(bromomethyl)acrylate,[10,11] and 2-benzylaminoacetonitrile.[12] Diene **19a** was prepared using literature methods[13,14] though yields were generally low due to the



Scheme 1. Titanium tetrachloride catalysed one-pot bicyclization.

difficulties encountered with the purification step that were compounded by the instability of the diene.[15]

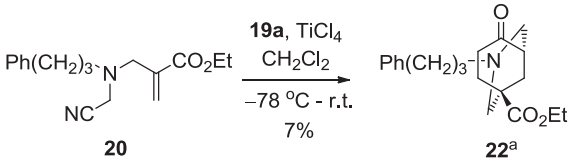
Having prepared both of the required starting materials, attention turned to the key Diels–Alder/Mannich reaction. Initially, 1 equiv of diene **19a** was added to 1 equiv of α-cyanomethylaminoacrylate **18b** (0.5 M in CH_2Cl_2) followed by cooling to −78 °C and the addition of $TiCl_4$ (4 equiv). After 2 h none of the desired product was observed in the crude ^1H NMR spectrum. Increasing the reaction time to 24 h and modifying the workup procedure[16] gave azabicyclononane **17b** in 17% yield (Table 1, entry 1).

The use of $TiCl_4$ as a 1 M solution in CH_2Cl_2,[17] improved the yields to ca. 30% (entry 2), while increasing the amount of diene **19a** to 1.5 equiv increased the yield to 46% (entry 3), with further quantities of diene offering no improvement (entry 4). Reducing the amount of $TiCl_4$ to 3 equiv caused a substantial decrease in yield to 24% (entry 5). Substituting ethyl α-cyanoaminoacrylate **18b** for methyl α-cyanoaminoacrylate **18a** led to no appreciable difference in yields. Yang et al. reported that reverse addition of the reagent to the $TiCl_4$ solution gave improved yields,[16] however the examples cited were all single substrate systems. Adding the combined acrylate-diene mixture to the $TiCl_4$ solution afforded **17b** in 22% yield (Table 1, entry 6). However pre-forming the iminium ion by adding acrylate **18b** to the $TiCl_4$ solution at −78 °C, allowing the mixture to warm to room temperature over 1 h, then adding diene **19a** gave **17b** in 46% yield (entry 7) in only a 4 h reaction time. Under these conditions reaction times longer than 4 h did not improve the yield of **17b**. This yield compares favourably with traditional double Mannich reactions to form 9-keto-azabicyclononanes, which have reported yields in the 20–30% range.[18]

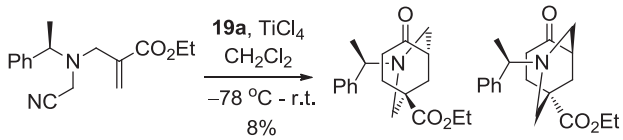
Silyloxydienes bearing larger silyl groups, such as triethylsilyl (TES) and *tert*-butyldimethylsilyl (TBDMS) are more stable than trimethylsilyl (TMS) analogues and may survive the harsh $TiCl_4$ conditions to give an improved yield of azabicyclononane **17b**. TES diene **19b**[19] and TBDMS diene **19c**[19] were therefore subjected to reaction with α-cyanoaminoacrylate **18b** under the conditions previously described (Scheme 2). The results observed however were disappointing, as TES diene **19b** only afforded 12% yield of azabicyclononane **17b**, while TBDMS diene **19c** gave only 2%, establishing that highly reactive trimethylsilyloxydienes are required for this procedure.

Our initial optimisation of the synthesis of C6-keto azabicyclononanes was performed using a benzylamino substituent, however the natural diterpenoid alkaloids of interest have an *N*-ethyl substituent. Bergmeier et al. reported that replacing the *N*-ethyl substituent with an *N*-3-(phenylpropyl) group increased the activity of simple monocyclic analogues at nicotinic acetylcholine receptors.[20] We also envisaged that replacement of the achiral *N*-benzyl moiety with a chiral substituent would afford the opportunity to prepare chiral azabicyclononanes.

N-3-Phenylpropyl α-cyanomethylaminoacrylate **20** and (*R*)-α-methylphenyl-α-cyanomethylaminoacrylate **21** were prepared in a similar manner to acrylates **18a**/**b**, requiring only an alternate base[12] for the synthesis of the more hindered **21**. Both α-cyanoaminoacrylates **20** and **21** underwent $TiCl_4$ catalysed cyclisation with diene **19a** (Scheme 3), however disappointingly, yields of bicycles **22** and **23** never exceeded 8%. Reaction of chiral α-cyanoaminoacrylate **21** produced an inseparable mixture of the two diastereomers of **23** in a 1:1.2 ratio, as determined by ^1H NMR spectroscopy, and the stereochemistry of the individual isomers could not be assigned.



20 **22**[a]



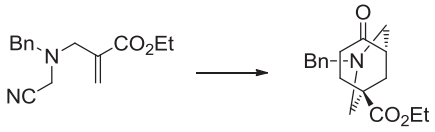
21 **23**

Scheme 3. Diels–Alder/Mannich reaction of different amino-substituted acrylates. [a]**22** is racemic, one enantiomer is shown.

Given the low yields obtained for the above reactions we postulated that the electron donating benzyl group of α-cyanoaminoacrylates **18a**/**b** stabilises the iminium ion intermediate formed in the Mannich reaction. It is plausible that the more hindered nature of the α-methylphenylamino substituent in **21** disfavours the reaction, whilst the 3-(phenylpropyl)amino substituted cyanoacrylate **20** is not electron donating. Fortunately, there are many reported methods for the conversion of an *N*-benzyl group into other substituents.[21]

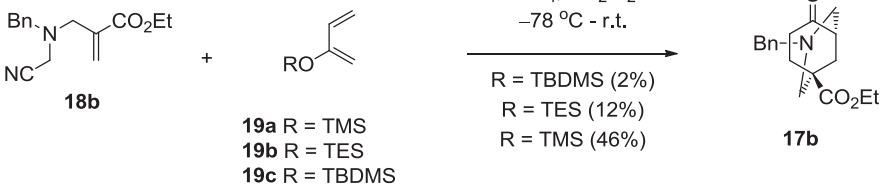
In order to investigate the scope of the Diels–Alder/Mannich reaction with respect to the introduction of substituents at other positions to further elaborate the bicyclic compounds towards the

Table 1
Optimisation of the Diels–Alder/Mannich reaction



18b **17b**

Entry	$TiCl_4$	Diene **16a**	Conditions	Time	Yield **14b**
1	4 equiv, neat	1 equiv	$TiCl_4$ to **18b**+**19a**	24 h	17%
2	4 equiv, 1 M in CH_2Cl_2	1 equiv	$TiCl_4$ to **18b**+**19a**	50 h	31%
3	4 equiv, 1 M in CH_2Cl_2	1.5 equiv	$TiCl_4$ to **18b**+**19a**	18 h	46%
4	4 equiv, 1 M in CH_2Cl_2	2 equiv	$TiCl_4$ to **18b**+**19a**	18 h	41%
5	3 equiv, 1 M in CH_2Cl_2	1.5 equiv	$TiCl_4$ to **18b**+**19a**	18 h	24%
6	4 equiv, 1 M in CH_2Cl_2	1.5 equiv	**18b**+**19a** to $TiCl_4$	18 h	22%
7	4 equiv, 1 M in CH_2Cl_2	1.5 equiv	**18b** to $TiCl_4$ then **19a**	4 h	46%



18b **19a** R = TMS
19b R = TES
19c R = TBDMS

17b

Scheme 2. Synthesis of azabicyclononane **17b** using different silyloxydienes **19a**–**c**.

hexacyclic structure present in the natural alkaloids, methyl substituted cyanoacrylate **24** was prepared. This required the in situ preparation of 2-iodopropionitrile and using a longer reaction time to form the cyanoamine intermediate, affording acrylate **24** in 59% yield over two steps.

Reaction of substituted cyanoacrylate **24** with diene **19a** afforded C4-substituted azabicyclononanes **25a** and **25b** in 9% overall yield, as a 5:1 inseparable mixture of diastereomers (Scheme 4). Whilst the NMR spectra of the **25a**/**b** mixture were complex they could be fully assigned by extensive use of 2D NMR experiments. Significant NOE's between the resonance due to the C4-methyl group and the equatorial 7-H resonance in the major isomer **25a** confirmed the equatorial orientation of the C-4 methyl, while NOE's between the C4-methyl group and axial 2-H and 9-H signals in the minor isomer **25b** confirmed the axial configuration of the C-4 methyl substituent.

The observed stereoselectivity for the equatorial isomer **25a** can be rationalised by the methyl substituent being orientated away from the attacking enolate, thereby minimizing steric interactions in the transition state. Unfortunately, the equatorial stereochemistry of the C-4 methyl group in the major isomer **25a** is opposite to that found in the natural alkaloids.

In order to further investigate the one-pot Diels–Alder/Mannich reaction and to introduce other appropriate substitution for future elaboration of the bicyclic compounds, we prepared known cyclic silyloxydiene **26**.[22,23] Titanium tetrachloride mediated reaction of silyloxydiene **26** with α-cyanoaminoacrylate **18a** proceeded in 20% yield to afford 11-keto-tricyclotridecane **27** as the sole product (Scheme 5).

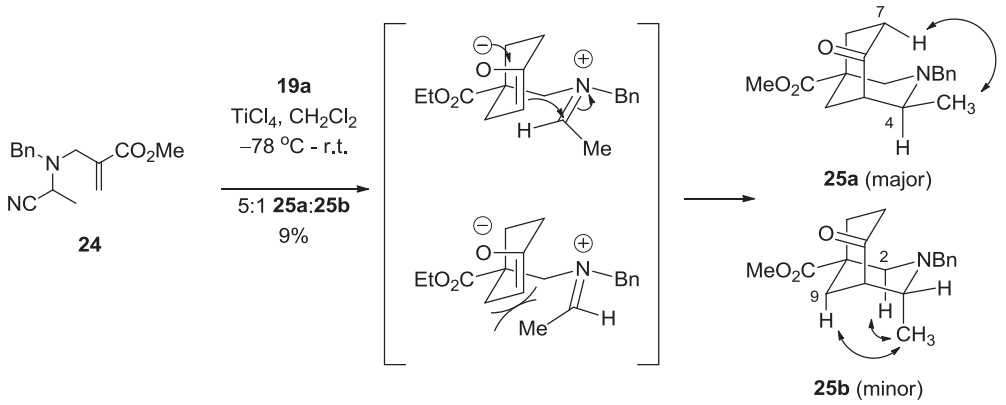
Extensive 2D NMR spectroscopy experiments allowed assignment of all the ring proton signals. From analysis of NOE's, the stereochemistry at C-6 was determined to be *R**, the opposite relationship to that found in the natural alkaloids. The formation of a single diastereomer of the tricyclic compound **27** suggests that the mechanism proceeds by an *endo* Diels–Alder reaction between diene **26** and dienophile **18a**.

2.2. Synthesis of AE and ABE ring analogues of methyllycaconitine and grandiflorine

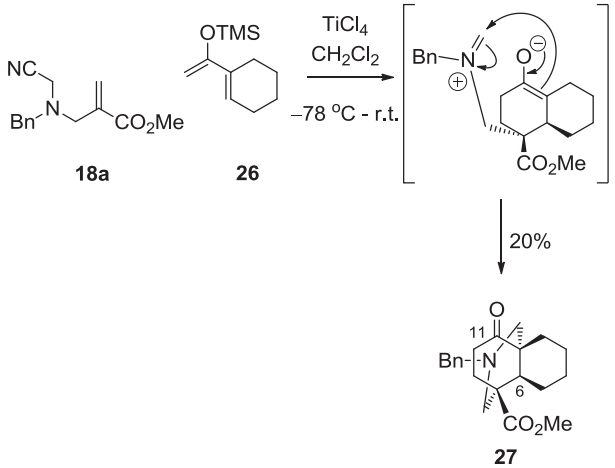
With the racemic 3-azabicyclo[3.3.1]nonanes **17a**/**b** and 9-azatricyclo[5.3.3.0^{1,6}]tridecane **27** in hand, attention turned to reduction and methylation of the ketone (Scheme 6). We envisaged a two step reduction/alkylation procedure to afford the *S** methyl ether present in the parent alkaloids. Accordingly, ketones **17a**/**b** and **27** were separately subjected to sodium borohydride reduction.

Reduction of ketones **17a**/**b** with $NaBH_4$ for 2 h gave alcohols **28a**/**b** in excellent yields of up to 98%, and the reduction was completely specific for the desired 6*S** diastereoisomer. In contrast, the reduction of tricyclic ketone **27** proceeded much more slowly, affording, after 23 h, a 58% combined yield of a 2.9:1 ratio of alcohols **29a**/**b**. The assignment of stereochemistry of alcohols **29a** to 11*S** and **29b** to 11*R** was determined using a range of 2D NMR spectroscopy experiments.[24]

It is postulated that the selectivity of the bicyclic reduction results from the steric influence of the bulky *N*-benzylpiperidine ring hindering hydride attack from the lower face. The slower reaction



Scheme 4. Diels–Alder/Mannich reaction of substituted cyanoacrylate **24**.

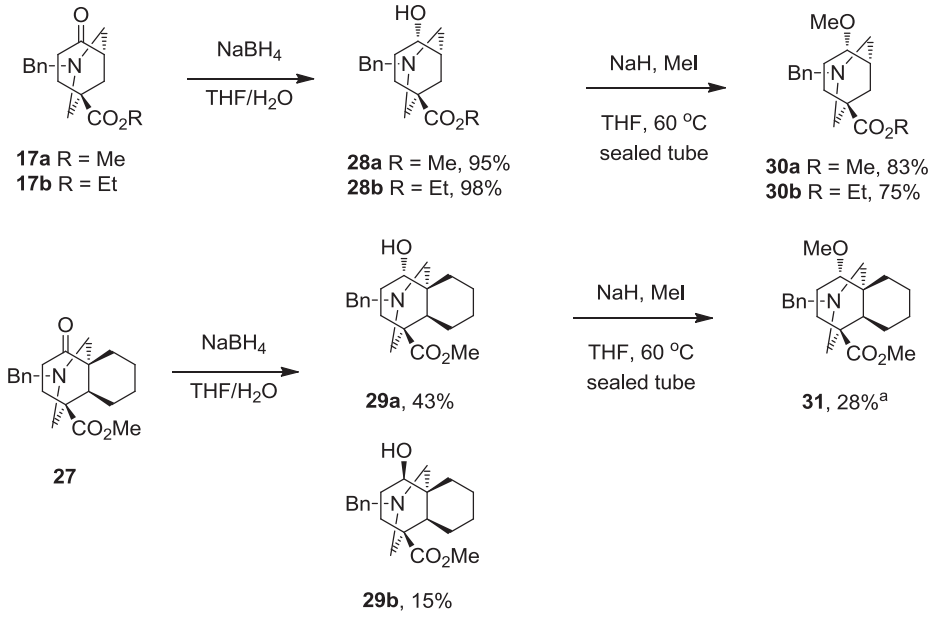


Scheme 5. Synthesis of tricycle **27**.

time and loss of specificity observed in the reduction of tricyclic ketone **24** can be rationalised by increased steric hindrance due to the additional cyclohexyl ring to attack on the top face.

Having prepared alcohols **28a**/**b** and **29a**, we next proceeded with the methylation step, which has proven to be problematic for other azabicyclononanes.[8] When a ketone is present at C-9 in the bicycle, the soft base silver (I) oxide is required to prevent retro-aldol fragmentation of the C5–C6 bond,[8] however in the absence of a C-9 ketone, stronger bases can be used.

Alkylation of alcohol **28b** with iodomethane was attempted under a variety of conditions, utilising different bases and solvents. Attempts were also made using trimethyl phosphate and by using a microwave reactor, however it was not until the use of sealed tubes was trialled that reasonable yields were achieved. Ultimately for this conversion, treatment of **28b** with sodium hydride and methyl iodide in a sealed tube at 60 °C for 3 days afforded ether **30b** in 75% yield, with 16% returned starting material. Ether **30a** was produced in similar yield, however application of these optimised conditions to the methylation of alcohol **29a** proved less effective,



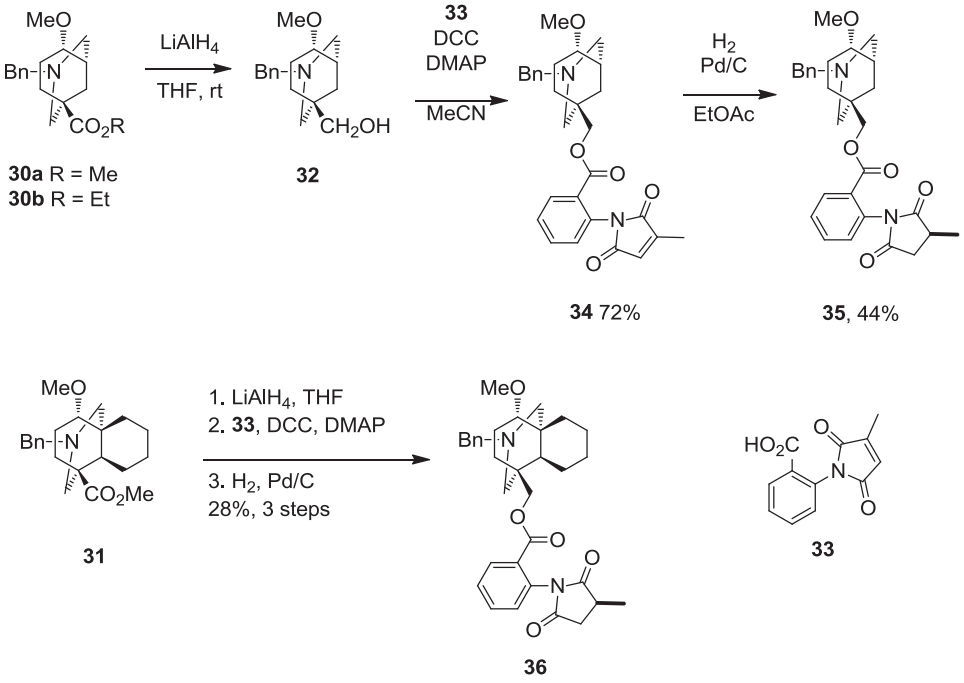
Scheme 6. Synthesis of methyl ethers **30a**/**b** and **31**. [a]60% of **29a** was also returned.

affording only 28% of ether **31**, together with 60% recovered starting material.

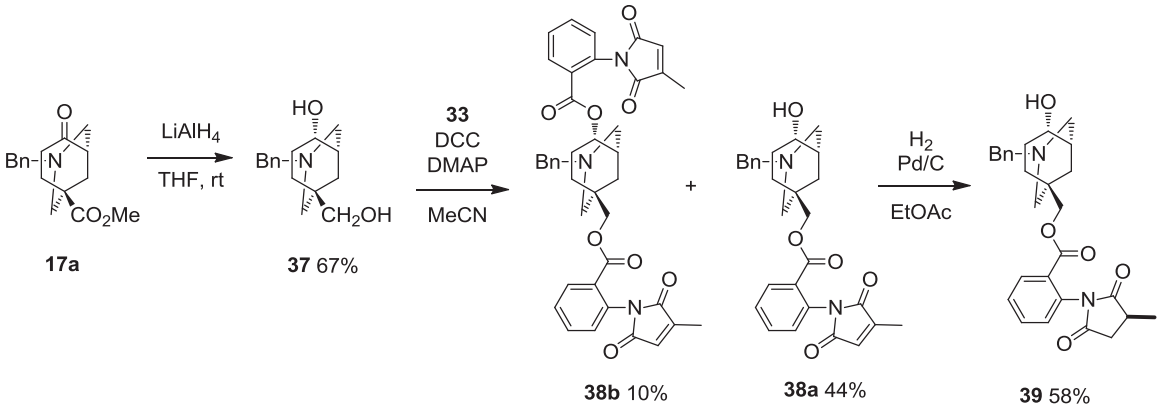
With ethers **30** and **31** in hand, it remained to functionalise C-1 of the bicycle to append the methylsuccinimidoanthranilate moiety. Accordingly, esters **30a**/**b** and **31** were reduced with lithium aluminium hydride, to afford C-1 neopentyl-like alcohols **29** (Scheme 7). These were then coupled with 2-(3-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)benzoic acid[25] **33** to give the respective maleimides, which were then selectively hydrogenated in the presence of the *N*-benzyl moiety to produce MLA analogues **35** and **36**.

The synthesis of grandiflorine analogue **39** could be achieved using a similar approach. In this case ketone **17a** underwent di-reduction to afford diol **37** in 67% yield, retaining the stereoselectivity of the previous ketone reduction (Scheme 8). Diol **37** was coupled with **33** to afford a 4.4:1 mixture of the desired mono-ester **38a** along with diester **38b**. Selective hydrogenation of the maleimide moiety of **38a** gave grandiflorine analogue **39** in 58% yield.

As previously noted, yields of alternatively *N*-substituted 6-keto azabicyclo[3.3.1]nonanes **22** and **23** were disappointingly low, so it was necessary to investigate methods for the interconversion of the *N*-benzyl group to other substituents.



Scheme 7. Synthesis of MLA analogues **35** and **36**.



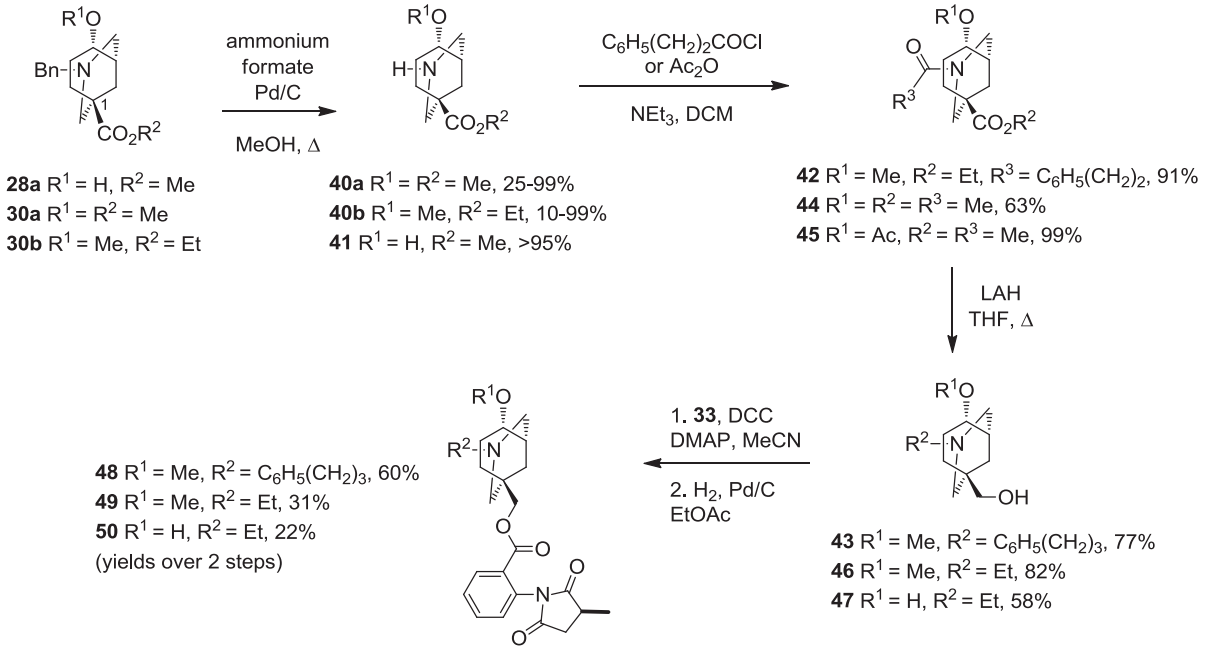
Scheme 8. Synthesis of grandiflorine analogue **39**.

Vafina et al.[26] have reported the N-debenzylation of other azabicyclononanes, while Ismail and Bergmeier[27] have reported acylation and double reduction of piperidine carboxylates to introduce 3-phenylpropyl substitution. Accordingly, we attempted N-debenzylation of C6-ether **30a** using literature procedures,[26] finding the reaction generally successful, though the yields of secondary amine **40a** were erratic, ranging from 25 to 99% (Scheme 9). The same variability was observed in the debenzylation of ether **40b**. N-Debenzylation of C6–alcohol **28a**, however, proceeded much more reliably, affording secondary amine **41** consistently in quantitative yield. Extensive investigation of the debenzylation reaction of azabicyclononanes **28a**/**b**, **30a**/**b** and **32** established that long reaction times and higher catalyst loading were required to effect reliable, quantitative N-debenzylation when the C6-substituent was a methyl ether, rather than an alcohol and changes in the C1-substituent did not appear to influence the reaction. Interestingly, attempted N-debenzylation of C6-ketone **17a** failed completely under all conditions attempted.

N-3-Phenylpropyl substitution[20] was achieved following the procedure of Bergmeier[27] by reaction of secondary amine **40b** with hydrocinnamoyl chloride to form amide **42**, which underwent double reduction with lithium aluminium hydride THF at reflux to afford aminoalcohol **43** in 70% yield over two steps. *N*-Ethyl analogues were formed by reaction of **40a** and **41** with acetic anhydride to give acetamides **44** and **45**, then similarly completely reduced to produce amino alcohols **46** and **47** in 51% and 57% yields, respectively, over two steps. Appendage of the methylsuccimidoanthranilate moiety was achieved by the two step method used above, to afford analogues **48**–**50** in 22–60% yields.

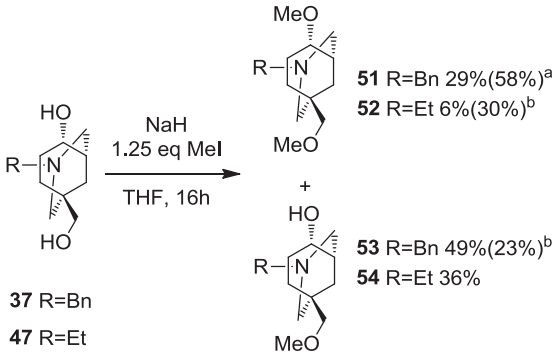
2.3. Synthesis of analogues of other *Delphinium* and *Aconitum* alkaloids

As previously mentioned other *Delphinium* and *Aconitum* alkaloids, that do not contain the methylsuccinimidoanthranilate group, also exhibit interesting biological activity. It was therefore decided to expand the scope of the synthetic route developed to synthesize additional AE bicyclic analogues of other bioactive alkaloids.



Scheme 9. Synthesis of MLA and grandiflorine analogues **48**–**50**.

Notably, synthesized compounds **32**, **37**, **46** and **47** are in themselves bicyclic analogues of the alkaloids lycoctonine **10** and takaosamine **11**. Analogues of talatisamine **8** and delcosine **9** were synthesised by selective methylation of diols **37** and **47** (Scheme 10). Use of 1.25 equiv of methyl iodide resulted in preferentially alkylation of the primary alcohol giving ethers **53** and **54** in 49% and 36%, respectively. Use of 10 equiv of methyl iodide and longer reaction time gave the dialkylated products **51** and **52**, it was, however, found that ether **52** was more easily prepared by methylation of alcohol **46**.



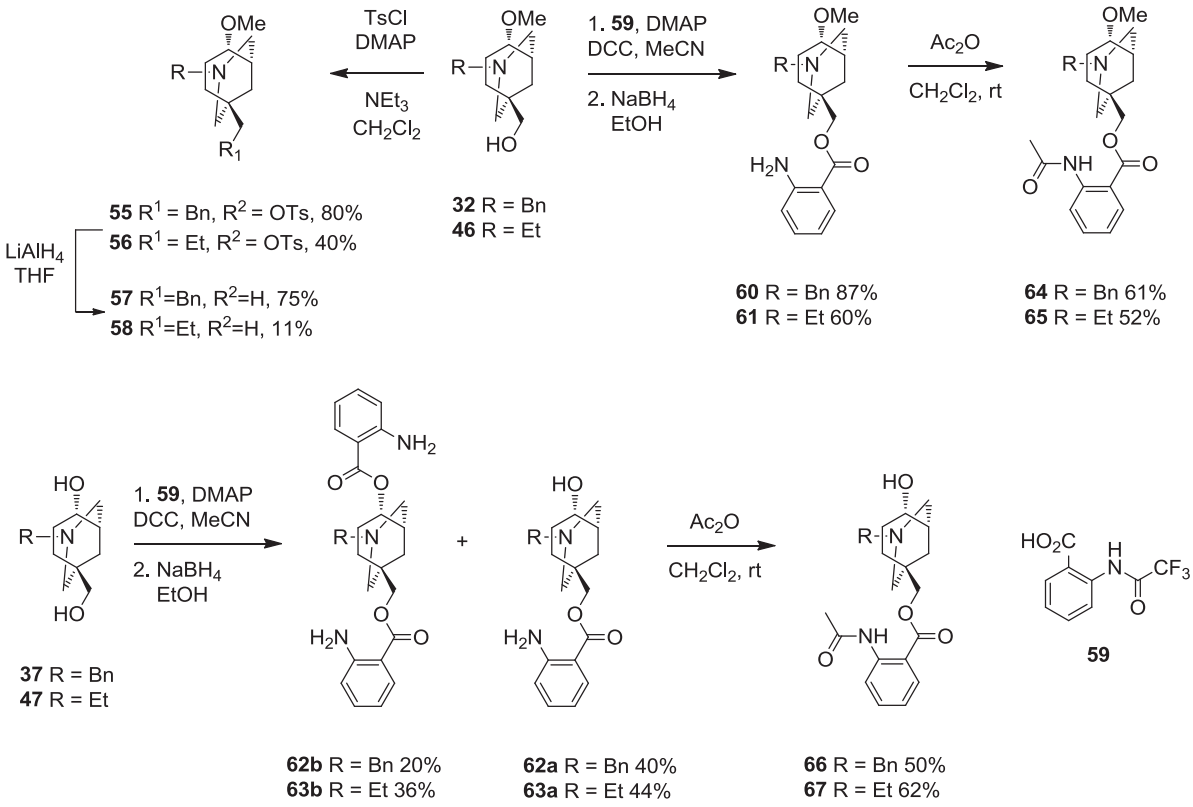
Scheme 10. Synthesis of talatisamine and delcosine analogues **51**–**54**. [a]10 equiv MeI, 3 days; [b]from alcohol **46**.

The synthesis of C1-methyl analogues **57** and **58** of eldeline **1** was achieved via tosylates **55** and **56** (Scheme 11). These were generated by separate reaction of **32** and **46** with tosyl chloride in the presence of triethylamine and DMAP to afford tosylates **55** and **56** in 80% and 40%, respectively. Reduction of **55** with $LiAlH_4$ in THF at reflux gave *N*-benzyl analogue **57** in 75% yield. Similarly, reduction of **56** gave the *N*-ethyl analogue **58**, however in this case only in 11% yield, due to decomposition upon purification by flash chromatography.

The alkaloids inuline **4**, ajacine **5**, delvestine **6** and majusine A **7** contain anthranilate and *N*-acetylanthranilate esters. Coupling of alcohols **32** and **46** with *N*-trifluoroacetylanthranilic acid **59**,[28] gave inuline analogues **60** and **61** in 87% and 60%, respectively. Coupling of diols **37** and **47** with acid **59** gave delvestine analogues **62a** and **63a** in 40% and 44% yields, respectively, with di-adducts **62b** and **63b** also present, no C-6 mono-adduct were produced. This is in contrast to previous examples of the coupling of 3-azabicyclononane diols, with a C-1 and C-9 alcohol,[29] where mono-adducts of both alcohols were formed. The ratio of the desired C-1 mono-adduct to di-adduct was improved, especially in the case of *N*-benzyl analogue **62**. Acetylation of **60** and **61** afforded ajacine analogues **64** and **65** in 61% and 52% yields, respectively. Selective acetylation of amino alcohols **62a** and **63a** afforded majusine A analogues **66** and **67** in 50% and 62% yields, respectively.

3. Conclusions

The preparation of 6-keto-3-azabicyclononanes lacking C-9 oxygenated substituents has been achieved. The key $TiCl_4$ catalysed bicyclization reaction required the use of a reactive trimethylsilyloxydiene with a benzylamino substituent on the dienophile to achieve reasonable yields. Elaboration of the C-6 oxygenated moiety was achieved by selective reduction followed by methylation. Modification of the amino substituent was accomplished via debenzylation with ammonium formate, followed by acylation and reduction. Appendage of a methylsuccinimidoanthranilate moiety at C-1 afforded bicyclic and tricyclic analogues of MLA **2** with various *N*-substituents. AE ring bicyclic analogues of



Scheme 11. Synthesis of eldeline, inuline, ajacine, delvestine and majusine A analogues **56**–**67**.

other biologically active alkaloids **1** and **3**–**11** with *N*-benzyl and *N*-ethyl substitution were produced from the common intermediates **32**, **37**, **46** and **47**.

4. Experimental section

4.1. General methods and materials

Reactions were monitored by TLC, using pre-coated silica gel TLC plates obtained from Merck. Flash chromatography was carried out on silica gel, particle size 0.032–0.063 mm. Melting point determinations were performed on an Electrothermal® melting point apparatus. Infrared (IR) spectra were recorded using a Perkin Elmer Spectrum 1000 FT-IR spectrometer with the absorption peaks expressed in wavenumbers (cm^{-1}) and recorded between 450 cm^{-1} and 4000 cm^{-1}. High resolution mass spectra were recorded using a VG70-SE spectrometer or microTOF-Q mass spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance DRX 300 MHz or 400 MHz spectrometers at ambient temperatures. Chemical shifts δ are expressed in parts per million and coupling constants *J* are reported in hertz. TMS served as internal standard (δ=0 ppm) for ^1H NMR, and $CDCl_3$ served as internal standard (δ=77.0 ppm) for ^{13}C NMR. Resonances were assigned using a mixture of NMR methods including NOESY, COSY HSQC and HMBC. The non-equivalent ring protons of the azabicyclo[3.3.1]nonanes and azatricyclo[5.3.3.0^{1,6}]tridecanes ring systems are designated A or B where H_A are axial and H_B are equatorial. Retention times (R_f) were determined with the solvent mixture used for chromatography unless otherwise stated. 2-(Bromomethyl)acrylates,[10,11] 2-benzylaminoacetonitrile,[12] acid **33**,[25] acid **59**[28] and diene **19a**[13,14] were prepared using literature methods. Diene **19** was also purchased from Fluorochem. All other reagents were purchased from Sigma–Aldrich or Acros and used without purification, unless stated.

4.2. Standard procedures

4.2.1. Standard procedure A: Diels–Alder/Mannich bicyclization. To a solution of titanium tetrachloride (1.00 mL, 1.78 g, 9.37 mmol) in dry DCM (8.40 mL) at −78 °C under an atmosphere of nitrogen was slowly added a solution of acrylate (2.34 mmol) in dry DCM (4.80 mL) and the mixture allowed to warm to room temperature and stirred for 1 h. To this was added dropwise a solution of diene (3.51 mmol) in dry DCM (0.67 mL) and the reaction mixture stirred for a further 4 h. The reaction was quenched by careful addition of saturated aqueous ammonium chloride (10 mL), followed by saturated aqueous potassium sodium tartrate (10 mL) and the mixture allowed to stir for 10 min. The organics were separated and the aqueous residue was extracted with DCM (2×20 mL). The combined organics were washed with brine (30 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography to give the product.

4.2.2. Standard procedure B: alternate Diels–Alder/Mannich bicyclization. To a solution of acrylate (3.48 mmol) in DCM (7 mL) was added diene (5.24 mmol) and the mixture stirred at room temperature for 30 min. The mixture was cooled to −78 °C before titanium tetrachloride (1 M in DCM, 13.9 mmol) was added over 10 min, after which time the reaction mixture was allowed to warm to room temperature and stirred for 17.5 h. The reaction was quenched by slow addition of 5% aqueous sodium carbonate (30 mL) and the organic layer separated. The aqueous residue was extracted with DCM (3×20 mL), then the combined organic extracts washed with brine (30 mL), dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography to give the product.

4.2.3. Standard procedure C: synthesis of α-cyanomethylaminoacrylates. To a solution of α-cyanoamine (10 mmol) in chloroform (22.5 mL) was added a solution of bromoacrylate (10 mmol) in chloroform (22.5 mL) followed by freshly distilled triethylamine (0.73 mL, 10 mmol) and the mixture was heated at reflux for 1.5 h. The reaction mixture was allowed to cool to room temperature, washed with saturated aqueous sodium hydrogen carbonate (50 mL), followed by brine (50 mL), dried (Na_2SO_4), filtered and the solvent removed at reduced pressure to give the product.

4.2.4. Standard procedure D: sodium borohydride reduction of a ketone. To a solution of ketone (3.35 mmol) in THF (8.0 mL) was added dropwise a solution of sodium borohydride (63.0 mg, 1.67 mmol) in 2:1 water/THF (24 mL) and the mixture stirred at room temperature for 2.5 h. Water (32 mL) was added, the volatiles removed under reduced pressure and the aqueous residue extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified by flash chromatography to give the alcohol.

4.2.5. Standard procedure E: sodium hydride-iodomethane methylation of an alcohol. To a 60% dispersion of sodium hydride (128 mg, 5.32 mmol) in oil, washed with pentane (4×2 mL), dried with heating and suspended in anhydrous THF (27 mL) under an atmosphere of nitrogen at 0 °C, was slowly added a solution of alcohol (2.66 mmol) in THF (27 mL) and the mixture stirred at 0 °C for 1 h. Iodomethane (0.83 mL, 13.3 mmol) was added, the reaction vessel sealed and heated to 60 °C with stirring for 3 days (CAUTION: pressure). The reaction was quenched with water (108 mL) and the volatiles removed under reduced pressure. The aqueous residue, was extracted with ethyl acetate (3×100 mL), then the combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography to give the product.

4.2.6. Standard procedure F: LAH reduction of the ester. To a solution of ester (0.10 mmol) in dry THF (8 mL) was added lithium aluminium hydride (38.0 mg, 1.00 mmol) and the mixture stirred under an atmosphere of nitrogen for 15 min. The reaction was quenched by dropwise addition of water (8 mL) and the volatiles removed under reduced pressure. The aqueous residue was filtered through Celite and the solids washed with water (8 mL), ethyl acetate (2×8 mL) and brine (8 mL). The filtrate was separated and the aqueous portion extracted with ethyl acetate (2×8 mL). The organic filtrate and extracts were combined, washed with brine (16 mL), dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography to give the product.

4.2.7. Standard procedure G: preparation of maleimido esters. To a solution of neopentyl-like alcohol (0.20 mmol), 2-(3-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)benzoic acid **30**[25] (93 mg, 0.40 mmol) and DMAP (2.00 mg, 20.0 μmol) in acetonitrile (1.6 mL) was added DCC (83 mg, 0.40 mmol) and the mixture stirred, under an atmosphere of nitrogen, at 40 °C for 18 h. The mixture was cooled, filtered through Celite and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (7.5 mL), washed with aqueous saturated sodium bicarbonate (7.5 mL), brine (7.5 mL), dried ($MgSO_4$),

filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography to give the product.

4.2.8. Standard procedure H: preparation of succinimides. To a solution of maleimide (0.50 mmol) in ethyl acetate (50 mL) was added 10% palladium on charcoal (10%/weight of maleimide) and the mixture stirred under an atmosphere of hydrogen for 24 h. The mixture was filtered through Celite and the solvent removed under reduced pressure. The crude product was purified by flash chromatography to give the product.

4.2.9. Standard procedure I: ammonium formate hydrogenolysis of the benzylamine. To a solution of benzylamine (1.00 mmol) in dry methanol (6.0 mL) was added 10% palladium on charcoal (100%/weight of amine) followed by ammonium formate (315 mg, 5 mmol) and the mixture heated to reflux, with stirring, under an atmosphere of nitrogen for 45 min. The mixture was allowed to cool to room temperature, filtered through Celite, the solids washed with chloroform (6 mL) and the volatiles removed at reduced pressure to give the product.

4.2.10. Standard procedure J: amine acetylation. To a stirred solution of secondary amine (1.00 mmol) in DCM (5.0 mL) was added freshly distilled triethylamine (5.00 mL, 36 mmol) and the mixture cooled to 0 °C. DMAP (1.00 mg, 10.0 μmol) was added, followed by acetic anhydride (0.10 mL, 1.10 mmol), then the mixture was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was acidified with 2 M HCl (20 mL), the organic layers separated and the aqueous residue washed with DCM (2×20 mL). The combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4), filtered and the solvent removed at reduced pressure to give the product.

4.2.11. Standard procedure K: LAH reduction. To a solution of amide (0.186 mmol) in dry THF (7.5 mL) was added LAH (35.0 mg, 0.928 mmol) and the mixture heated at reflux under an atmosphere of nitrogen for 23 h. The reaction was cooled to 0 °C and quenched by dropwise addition of water (15 mL), then the volatiles were removed under reduced pressure. Ethyl acetate (7.5 mL) was added and the residue filtered through Celite, which was washed with water (7.5 mL), ethyl acetate (7.5 mL) and brine (7.5 mL). The filtrate was separated and the aqueous portion extracted with ethyl acetate (2×7.5 mL). The organic filtrate and extracts were combined, washed with brine (15 mL), dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to give the product.

4.2.12. Standard procedure L: preparation of anthranilate esters. To a solution of neopentyl-like alcohol (0.20 mmol) in dry acetonitrile (1.60 mL) under an atmosphere of nitrogen was added *N*-(trifluoroacetyl)anthranilic acid **56**[28] (93.0 mg, 0.40 mmol) and DMAP (2.00 mg, 20.0 μmol) followed by DCC (83.0 mg, 0.40 mmol) and the mixture heated at 40 °C for 24 h. The mixture was cooled to room temperature, filtered through Celite and the solvent removed under reduced pressure. The residue was dissolved in DCM (7.5 mL), washed with saturated aqueous sodium hydrogen carbonate (7.5 mL) and brine (7.5 mL), dried ($MgSO_4$), filtered and the volatiles removed under reduced pressure. The resulting residue was dissolved in absolute ethanol (2.0 mL) then sodium borohydride (0.400 mmol) was added and the mixture stirred at room temperature for 2 h. The reaction was quenched by addition of water (4.0 mL) then the organic volatiles removed under reduced pressure. The aqueous residue was extracted with ethyl acetate (3×5 mL), then the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography to give the product.

4.2.13. Standard procedure M: preparation of acetylanthranilates. To a solution of anthranilate (0.10 mmol) in dry DCM (2.00 mL) under an atmosphere of nitrogen was added dropwise acetic anhydride (28.0 μL, 0.30 mmol) and the mixture was allowed to stir at room temperature for 24 h. The reaction was quenched by addition of saturated aqueous sodium hydrogen carbonate (4 mL), separated, then the organic residue washed with brine (6 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography to give the acetylanthranilate.

4.3. Synthesis of ketones 17a, 17b, 22, 23a/b, 25a/b and 27

*4.3.1. Methyl 2-((benzyl(cyanomethyl)amino)methyl)acrylate **18a**.* The reaction was carried out according to standard procedure C, using 2-(benzylamino)acetonitrile (9.02 g, 61.7 mmol), methyl 2-(bromomethyl)acrylate (11.0 g, 61.7 mmol) and triethylamine (8.60 mL, 61.7 mmol), heating for 2 h to give the *title compound* **18a** (15.0 g, 99%) as a dark orange oil, which was used without further purification. R_f 0.50 (hexane/ethyl acetate 1:1); ν_{max}(NaCl)/cm^{-1} 2952, 2254, 1727, 1635, 1454, 1161, 1120; δ_H(400 MHz; $CDCl_3$) 3.44 (2H, s, NCH_2C≡N), 3.48 (2H, s, NCH_2C=CH_2), 3.73 (2H, s, NCH_2Ar), 3.78 (3H, s, OCH_3), 5.83–5.87 (1H, m, C=CH_AH$_B$), 6.29–6.35 (1H, m, C=CH$_A$$H_B$), 7.26–7.34 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 40.9 (NCH_2C≡N), 51.9 (OCH_3), 54.8 (NCH_2C=CH_2), 58.0 (NCH_2Ar), 114.7 (C≡N), 127.7 (C=CH_2), 127.8 (Ar–CH), 128.5 (Ar–CH), 128.9 (Ar–CH), 136.8 (*C*=CH_2), 136.8 (Ar–C), 166.7 (C=O); *m*/*z* (EI) 244 (M^+, 3%), 204 (13%), 153 (47%), 145 (26%), 121 (34%), 91 ($C_6H_5CH_2$, 100%); found M^+ 244.1216, $C_{14}H_{16}N_2O_2$ requires M^+ 244.1212.

4.3.2. Methyl (1S,5S*)-3-benzyl-6-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate **17a**.* The reaction was carried out according to standard procedure A, using titanium tetrachloride (1.00 mL, 1.78 g, 9.37 mmol), acrylate **18a** (0.572 g, 2.34 mmol) and 2-trimethylsilyloxy-1,3-butadiene **19a** (0.50 g, 3.51 mmol), stirring for 4 h with hexane/ethyl acetate 4:1 as the solvent for flash chromatography to give the *title compound* **17a** (0.31 g, 46%) as a colourless oil. R_f 0.24; ν_{max}(NaCl)/cm^{-1} 2950, 1725, 1495, 1453, 1258, 1128; δ_H(300 MHz; $CDCl_3$) 1.91 (1H, dd, *J*=13.3, 2.4 Hz, 9$_A$-H), 2.10–2.28 (4H, m, 8$_A$-H, 8$_B$-H, 4$_A$-H & 9$_B$-H), 2.37 (1H, d, *J*=11.1 Hz, 2$_A$-H), 2.42–2.53 (2H, m, 7$_B$-H & 5-H), 2.95–3.07 (2H, m, 7$_A$-H & 4$_B$-H), 3.11 (1H, d, *J*=11.1 Hz, 2$_B$-H), 3.43 (1H, d, *J*=13.2 Hz, NCH_AH$_B$Ar), 3.50 (1H, d, *J*=13.2 Hz, NCH$_A$$H_B$Ar), 3.68 (3H, s, OCH_3), 7.20–7.32 (5H, m, Ar–H); δ_C(300 MHz; $CDCl_3$) 31.2 (C-8), 33.3 (C-9), 38.8 (C-7), 41.5 (C-1), 45.2 (C-5), 52.2 (OCH_3), 56.3 (C-4), 61.1 (C-2), 62.9 (NCH_2Ar), 127.2 (Ar–CH), 128.4 (Ar–CH), 128.7 (Ar–CH), 137.7 (Ar–C), 176.0 (C=O), 213.8 (C-6); *m*/*z* (EI) 287 (M^+, 18%), 272 (2%), 256 (M–OCH_3, 5%), 228 (3%), 196 (M–$C_6H_5CH_2$, 7%), 185 (9%), 134 (10%), 91 ($C_6H_5CH_2$, 100%); found M^+ 287.1521, $C_{17}H_{21}NO_3$ requires M^+ 287.1521.

*4.3.3. Ethyl 2-((benzyl(cyanomethyl)amino)methyl)acrylate **18b**.* The reaction was carried out according to standard procedure C, using 2-(benzylamino)acetonitrile (4.20 g, 28.7 mmol), ethyl 2-(bromomethyl)acrylate (5.55 g, 28.7 mmol) and triethylamine (3.98 mL, 2.91 g, 28.7 mmol), heating for 1.5 h to give the *title compound* **18b** (7.42 g, 100%) as an orange oil, which was used without further purification. R_f 0.50 (hexane/ethyl acetate 1:1); ν_{max}(NaCl)/cm^{-1} 2982, 2231, 1717, 1636, 1454, 1177, 1117; δ_H(400 MHz; $CDCl_3$) 1.31 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 3.43 (2H, s, NCH_2C≡N), 3.48 (2H, s, NCH_2C=CH_2), 3.73 (2H, s, NCH_2Ar), 4.24 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 5.83 (1H, s, C=CH_AH$_B$), 6.31 (1H, s, C=CH$_A$$H_B$), 7.25–7.35 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 14.1 (OCH_2CH_3), 40.8 (NCH_2C≡N), 54.8

($NCH_2C{=}CH_2$), 58.0 (NCH_2Ar), 60.8 (OCH_2CH_3), 114.7 (C≡N), 127.4 ($C{=}CH_2$), 127.7 (Ar–CH), 128.5 (Ar–CH), 128.8 (Ar–CH), 136.8 (Ar–C), 136.9 ($C{=}CH_2$), 166.2 (C=O); *m/z* (EI) 258 (M^+, 2%), 218 (14%), 167 ($M-C_6H_5CH_2$, 42%), 145 (28%), 121 (33%), 91 ($C_6H_5CH_2$, 100%); ound M^+ 258.1371, $C_{15}H_{18}N_2O_2$ requires M^+ 258.1368.

4.3.4. Ethyl (1S,5S*)-3-benzyl-6-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***14b***. The reaction was carried out according to standard procedure B, using acrylate **15b** (0.90 g, 3.48 mmol), 2-trimethylsilyloxy-1,3-butadiene **16a** (0.92 mL, 5.24 mmol) and titanium tetrachloride (1 M in DCM, 13.9 mL, 13.9 mmol), stirring for 17.5 h with hexane/ethyl acetate 3:1 as the solvent for flash chromatography to give the *title compound* **14b** (0.478 g, 46%) as a colourless oil. R_f 0.35; ν_{max}(NaCl)/cm^{-1} 2941, 1725, 1453, 1258, 1129; δ_H(400 MHz; $CDCl_3$) 1.24 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.91 (1H, dt, *J*=13.4, 2.5 Hz, 9_A-H), 2.11–2.27 (4H, m, 8_A-H, 8_B-H, 4_A-H & 9_B-H), 2.39 (1H, d, *J*=11.1 Hz, 2_A-H), 2.45–2.53 (2H, m, 7_B-H & 5-H), 2.97–3.07 (2H, m, 7_A-H & 4_B-H), 3.12 (1H, d, *J*=11.1 Hz, 2_B-H), 3.48 (2H, s, NCH_2Ar), 4.13 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 7.20–7.36 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 14.0 (OCH_2CH_3), 31.1 (C-8), 33.2 (C-9), 38.7 (C-7), 41.3 (C-1), 45.1 (C-5), 56.1 (C-4), 60.8 (OCH_2CH_3), 61.1 (C-2), 62.8 (NCH_2Ar), 127.1 (Ar–CH), 128.3 (Ar–CH), 128.6 (Ar–CH), 137.7 (Ar–C), 175.4 (C=O), 213.8 (C-6); *m/z* (EI) 301 (M^+, 28%), 272 (10%), 256 (5%), 210 ($M-C_6H_5CH_2$, 12%), 91 ($C_6H_5CH_2$, 100%); found M^+ 301.1675, $C_{18}H_{23}NO_3$ requires M^+ 301.1678.

4.3.5. Ethyl 2-(((cyanomethyl)(3-phenylpropyl)amino)methyl)acrylate ***20***. The reaction was carried out according to standard procedure C, using 2-((3-phenylpropyl)amino)acetonitrile (1.22 g, 6.99 mmol), ethyl 2-(bromomethyl)acrylate (1.35 g, 6.99 mmol) and triethylamine (0.97 mL, 6.99 mmol), heating for 1 h to give the *title compound* **20** (1.82 g, 91%) as an orange oil, which required no further purification. R_f 0.60 (hexane/ethyl acetate 1:1); ν_{max}(NaCl)/cm^{-1} 2940, 2231, 1716, 1636, 1454, 1176, 1120; δ_H(400 MHz; $CDCl_3$) 1.30 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.79–1.83 (2H, m, $NCH_2CH_2CH_2$), 2.59 (2H, t, *J*=7.1 Hz, $NCH_2CH_2CH_2$), 2.64 (2H, t, *J*=7.7 Hz, $NCH_2CH_2CH_2$), 3.37 (2H, s, $NCH_2C{=}CH_2$), 3.53 (2H, s, $NCH_2C{\equiv}N$), 4.22 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 5.75 (1H, d, *J*=1.2 Hz, $C{=}CH_AH_B$), 6.27 (1H, d, *J*=1.2 Hz, $C{=}CH_AH_B$), 7.15–7.30 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 14.1 (OCH_2CH_3), 28.9 ($NCH_2CH_2CH_2$), 32.9 ($NCH_2CH_2CH_2$), 41.6 ($NCH_2C{\equiv}N$), 53.3 ($NCH_2CH_2CH_2$), 54.5 ($NCH_2C{=}CH_2$), 60.8 (OCH_2CH_3), 114.9 (C≡N), 125.8 (Ar–CH), 127.4 ($C{=}CH_2$), 128.3 (2× Ar–CH), 137.0 ($C{=}CH_2$), 141.5 (Ar–C), 166.2 (C=O); *m/z* (EI) 286 (M^+, 15%), 246 ($M-CH_2C{\equiv}N$, 37%), 181 ($M-C_6H_5CH_2$, 100%), 91 ($C_6H_5CH_2$, 50%), 69 (32%), 42 (CH_2NCH_2, 73%); ound M^+ 286.1685, $C_{17}H_{22}N_2O_2$ requires M^+ 286.1681.

4.3.6. Ethyl (1S,5S*)-3-(3-phenylpropyl)-6-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***22***. The reaction was carried out according to standard procedure A, using titanium tetrachloride (1.11 mL, 1.92 g, 10.1 mmol), acrylate **20** (0.724 g, 2.53 mmol) and diene **19a** (0.67 mL, 3.79 mmol), stirring for 21 h with hexane/ethyl acetate 4:1 as the solvent for flash chromatography to give the *title compound* **22** (57.0 mg, 7%) as a pale yellow oil. R_f 0.31; ν_{max}(NaCl)/cm^{-1} 2943, 1713, 1454, 1257, 1130; δ_H(400 MHz; $CDCl_3$) 1.26 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.74–1.78 (2H, m, $NCH_2CH_2CH_2$), 1.89 (1H, dt, *J*=13.4, 2.4 Hz, 9_A-H), 2.12–2.19 (3H, m, 8_A-H, 8_B-H & 4_A-H), 2.25 (1H, dd, *J*=13.4, 1.6 Hz, 9_B-H), 2.28–2.33 (3H, m, $NCH_2CH_2CH_2$ & 2_A-H), 2.42–2.52 (2H, m, 7_B-H & 5-H), 2.58 (2H, t, *J*=7.5 Hz, $NCH_2CH_2CH_2$), 2.89–2.95 (1H, m, 7_A-H), 3.00 (1H, dt, *J*=11.0, 1.4 Hz, 4_B-H), 3.14 (1H, d, *J*=11.0 Hz, 2_B-H), 4.15 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 7.13–7.29 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 14.1 (OCH_2CH_3), 28.4 ($NCH_2CH_2CH_2$), 31.1 (C-8), 33.0 (C-9), 33.3 ($NCH_2CH_2CH_2$), 38.5 (C-7), 41.2 (C-1), 45.1 (C-5), 56.3 (C-4), 57.1 ($NCH_2CH_2CH_2$), 60.8 (OCH_2CH_3), 61.4 (C-2), 125.7 (Ar–CH), 128.2 (Ar–CH), 128.3 (Ar–CH), 141.9 (Ar–C), 175.5 (C=O), 214.1 (C-6); *m/z* (ESI^+) 330 (100%); found MH^+ 330.2060, $C_{20}H_{28}NO_3$ requires M^+ 330.2064. In a second fraction was returned acrylate **17** (0.177 g, 24%) as a yellow oil.

4.3.7. Ethyl (R)-2-(((cyanomethyl)(1-phenylethyl)amino)methyl)acrylate ***21***. The reaction was carried out according to standard procedure C, using (*R*)-2-((1-phenylethyl)amino)acetonitrile (2.39 g, 14.9 mmol), ethyl 2-(bromomethyl)acrylate (2.88 g, 14.9 mmol) and triethylamine (2.07 mL, 1.51 g, 14.9 mmol), heating for 1 h to give the *title compound* **21** (3.32 g, 82%) as a pale yellow oil, which required no further purification. R_f 0.55 (hexane/ethyl acetate 1:1); ν_{max}(NaCl)/cm^{-1} 2980, 2231, 1719, 1636, 1453, 1177, 1124; δ_H(400 MHz; $CDCl_3$) 1.31 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.45 (3H, d, *J*=6.6 Hz, $CHCH_3$), 3.35–3.58 (4H, m, $NCH_2C{\equiv}N$ & $NCH_2C{=}CH_2$), 3.81 (1H, q, *J*=6.6 Hz, $CHCH_3$), 4.20–4.23 (2H, m, OCH_2CH_3), 5.80–5.82 (1H, m, $C{=}CH_AH_B$), 6.26–6.29 (1H, m, $C{=}CH_AH_B$), 7.23–7.36 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 14.1 (OCH_2CH_3), 20.5 ($CHCH_3$), 39.0 ($NCH_2C{\equiv}N$), 51.7 ($NCH_2C{=}CH_2$), 60.8 (OCH_2CH_3), 61.6 ($NCH(CH_3)Ar$), 115.4 (C≡N), 127.1 ($C{=}CH_2$), 127.2 (Ar–CH), 127.6 (Ar–CH), 128.6 (Ar–CH), 137.4 ($C{=}CH_2$), 143.1 (Ar–C), 166.3 (C=O); *m/z* (EI) 272 (M^+, 2%), 253 ($M-CH_3$, 19%), 232 (11%), 167 (65%), 121 (26%), 105 ($C_6H_5CHCH_3$, 100%), 77 (C_6H_5, 16%); found M^+ 272.1529, $C_{16}H_{20}N_2O_2$ requires M^+ 272.1525.

4.3.8. Ethyl (1S,5S,1′R)-3-(1′-phenylethyl)-6-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate ***23a*** *and ethyl (1R,5R,1′R)-3-(1′-phenylethyl)-6-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***23b***. The reaction was carried out according to standard procedure B, using acrylate **21** (0.280 g, 1.03 mmol), diene **19a** (0.220 g, 1.54 mmol) and titanium tetrachloride (1 M in DCM, 4.10 mL, 4.11 mmol), stirring for 19 h with hexane/ethyl acetate 3:1 as the solvent for flash chromatography to give the *title compound* **23a** and **23b** (26.0 mg, 8%) as a colourless oil, in an inseparable, undetermined, 1:1.2 mixture of diastereomers. R_f 0.36; ν_{max}(NaCl)/cm^{-1} 2935, 1722, 1453, 1250, 1132; [*denotes minor diastereomer] δ_H(400 MHz; $CDCl_3$) 1.21 (3H, t, *J*=7.2 Hz, OCH_2CH_3*), 1.26 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 1.32 (3H, d, *J*=6.9 Hz, $NCH(CH_3)$), 1.35 (3H, d, *J*=6.8 Hz, $NCH(CH_3)$*), 1.80–1.90 (2H, m, 9_A-H & 9_A-H*), 2.09–2.24 (8H, m, 4_A-H, 8_A-H, 8_A-H*, 9_B-H, 9_B-H* & 4_A-H*), 2.27 (1H, dd, *J*=11.2, 1.3 Hz, 2_A-H*), 2.39 (1H, dd, *J*=11.0, 1.1 Hz, 2_A-H), 2.42–2.52 (4H, m, 5-H, 7_B-H, 7_B-H* & 5-H*), 2.91–3.01 (3H, m, 7_A-H, 7_A-H* & 4_B-H), 3.04 (1H, dt, *J*=11.2, 1.8 Hz, 2_B-H*), 3.17 (1H, dd, *J*=10.8, 1.5 Hz, 4_B-H*), 3.22 (1H, dd, *J*=11.0, 1.5 Hz, 2_B-H), 3.40–3.47 (2H, m, $NCH(CH_3)$* & $NCH(CH_3)$), 4.09, (2H, q, *J*=7.2 Hz, OCH_2CH_3*), 4.15 (2H, q, *J*=7.0 Hz, OCH_2CH_3), 7.17–7.36 (10H, m, Ar–H & Ar–H*); δ_C(100 MHz; $CDCl_3$) 14.0 & 14.1 (OCH_2CH_3 & OCH_2CH_3*), 18.1 ($NCH(CH_3)$*), 19.0 ($NCH(CH_3)$), 30.5 & 31.0 (C-8 & C-8*), 33.1 (C-9 & C-9*), 38.6 & 38.7 (C-7 & C-7*), 41.2 & 41.3 (C-1 & C-1*), 45.0 & 45.1 (C-5 & C-5*), 53.3 (C-4*), 53.8 (C-4), 58.1 (C-2), 58.7 (C-2*), 60.7 & 60.8 (OCH_2CH_3 & OCH_2CH_3*), 64.2 & 64.3 ($NCH(CH_3)$ & $NCH(CH_3)$*), 127.1 (Ar–CH & Ar–CH*), 127.4 (Ar–CH & Ar–CH*), 128.3 (Ar–CH & Ar–CH*), 129.2 (Ar–CH & Ar–CH*), 142.5 (Ar–C), 142.9 (Ar–C*), 175.6 (C=O*), 175.8 (C=O), 214.1 (C-6), 214.4 (C-6*); *m/z* (EI) 315 (M^+, 16%), 300 ($M-CH_3$, 82%), 105 ($C_6H_5CH(CH_3)$, 100%); found M^+ 315.1831, $C_{19}H_{25}NO_3$ requires M^+ 315.1834. In a second fraction was returned acrylate **18** (50.0 mg, 18%).

4.3.9. Methyl 2-((benzyl(1-cyanoethyl)amino)methyl)acrylate ***24***. The reaction was carried out according to standard procedure C, using 2-benzylamino-2-methylacetonitrile (0.577 g, 3.60 mmol), methyl 2-(bromomethyl)acrylate (0.645 g, 3.60 mmol) and triethylamine (0.364 g, 3.60 mmol), heating for 2 h, with purification by flash chromatography (hexane/ethyl acetate 3:1) to give the *title compound* **24** (0.84 g, 90%) as a bright yellow oil. R_f 0.50; ν_{max}(NaCl)/cm^{-1} 2952, 2842, 1720, 1636, 1496, 1452, 1263, 1197, 1149, 1133;

δ_H(300 MHz; $CDCl_3$) 1.45 (3H, d, J=7.2 Hz, NCH(CH_3)), 3.18–3.21 (1H, m, NCH_ACH$_B$C=CH$_2$), 3.43 (1H, d, J=13.8 Hz, NCH_ACH$_B$Ar), 3.63–3.66 (1H, m, NCH$_A$CH_BC=CH$_2$), 3.73 (1H, q, J=7.2 Hz, NCH(CH$_3$)), 3.76 (3H, s, OCH$_3$), 3.95 (1H, d, J=13.8 Hz, NCH$_A$CH_BAr), 5.85–5.87 (1H, m, C=CH_AH$_B$), 6.26–6.31 (1H, m, C=CH$_A$$H_B$), 7.27–7.33 (5H, m, Ar–H); δ_C(75 MHz; $CDCl_3$) 17.7 (NCHCH_3), 40.8 (NCHCH$_3$), 51.6 (NCH_2C=CH$_2$), 51.8 (OCH$_3$), 55.7 (NCH_2Ar), 118.1 (C≡N), 127.1 (C=CH_2), 127.6 (Ar–CH), 128.5 (Ar–CH), 128.6 (Ar–CH), 137.4 (C=CH_2), 137.5 (Ar–C), 166.8 (C=O); m/z (ESI$^+$) 281 (MNa$^+$, 100%); found MNa$^+$ 281.1250, $C_{15}H_{18}NaN_2O_2$ requires MNa$^+$ 281.1260.

4.3.10. Methyl (1S,4S*,5S*)-3-benzyl-4-methyl-6-oxo-3-azabicyclo [3.3.1]nonane-1-carboxylate* ***25a*** *and methyl (1S*,4R*,5S*)-3-benzyl-4-methyl-6-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***25b****.* The reaction was carried out according to standard procedure A, using titanium tetrachloride (1.00 mL, 1.78 g, 9.37 mmol), acrylate **24** (0.605 g, 2.34 mmol) and diene **19a** (0.500 g, 3.51 mmol), stirring for 20 h with hexane/ethyl acetate 4:1 as the solvent for flash chromatography to give the *title compound* (61.8 mg, 9%) as an orange oil in a 5:1 inseparable mixture of **25a**/**25b**. R_f 0.26; ν_{max}(NaCl)/cm^{-1} 2951, 1729, 1704, 1495, 1449, 1235, 1153; [*denotes signals from **25b**] δ_H(400 MHz; $CDCl_3$) 1.08 (3H, d, J=6.4 Hz, CCH_3*), 1.19 (3H, d, J=6.4 Hz, CCH_3), 1.92–1.99 (1H, m, 8$_B$-H*), 2.02–2.07 (4H, m, 8$_A$-H, 8$_B$-H, 9$_B$-H* & 9$_B$-H), 2.11–2.15 (1H, m, 8$_A$-H*), 2.16–2.22 (2H, m, 9$_A$-H* & 9$_A$-H), 2.31 (1H, s, 5-H*), 2.38 (1H, d, J=11.2 Hz, 2$_A$-H), 2.43–2.49 (3H, m, 7$_B$-H, 5-H & 7$_B$-H*), 2.54 (1H, m, 4-H), 2.69 (1H, d, J=11.6 Hz, 2$_B$-H*), 2.83 (1H, d, J=11.6 Hz, 2$_A$-H*), 2.93 (1H, m, 7$_A$-H*), 2.99 (1H, d, J=13.4 Hz, NCH_AH$_B$), 3.11 (1H, dd, J=11.2, 2.0, 2$_B$-H), 3.18–3.24 (1H, m, 7$_A$-H), 3.29–3.31 (1H, m, 4-H*), 3.42 (1H, d, J=13.4 Hz, NCH_AH$_B$*), 3.59–3.65 (4H, m, NCH$_A$$H_B$* & OC$H_3$), 3.67 (3H, s, OC$H_3$*), 4.16 (1H, d, J=13.4 Hz, NCH$_A$$H_B$), 7.20–7.34 (10H, m, Ar–H & Ar–H*); δ_C(100 MHz; $CDCl_3$) 7.8 (CCH_3*), 18.6 (CCH_3), 26.7 (C-9*), 30.3 (C-8*), 32.4 (C-8), 35.3 (C-9), 38.2 (C-7*), 39.8 (C-7), 41.2 (C-1*), 41.8 (C-1), 50.3 (C-5*), 52.0 (OCH_3 & OCH_3*), 53.0 (C-5), 53.1 (C-2*), 55.6 (C-4*), 58.0 (NCH_2Ar), 58.4 (C-4), 59.0 (NCH_2Ar*), 59.9 (C-2), 126.9 (Ar–CH), 127.1 (Ar–CH*), 128.3 (Ar–CH & Ar–CH*), 128.6 (Ar–CH & Ar–CH*), 138.4 (Ar–C*), 138.8 (Ar–C), 175.5 (C=O*), 176.2 (C=O), 212.3 (C-6), 214.2 (C-6*); m/z (ESI$^+$) 302 (MH$^+$, 100%); found MH$^+$ 302.1738, $C_{18}H_{24}NO_3$ requires MH$^+$ 302.1751.

4.3.11. Methyl (1S,6R*,7S*)-9-benzyl-11-oxo-9-azatricyclo[5.3.3.0^{1,6}] tridecane-7-carboxylate* ***27****.* The reaction was carried out according to standard procedure A, using titanium tetrachloride (1.07 mL, 1.84 g, 9.71 mmol), acrylate **18a** (0.594 g, 2.45 mmol) and 1-(1-cyclohexenyl)-1-trimethylsilyloxyethene **26** (0.717 g, 3.47 mmol), stirring for 5 h with hexane/ethyl acetate 4:1 as the solvent for flash chromatography to give the *title compound* **27** (0.162 g, 20%) as a bright yellow oil. R_f 0.41; ν_{max}(NaCl)/cm^{-1} 2930, 1728, 1701, 1495, 1453, 1263, 1239, 1128; δ_H(400 MHz; $CDCl_3$) 0.84–0.88 (1H, m, 2$_A$-H), 1.01–1.07 (1H, m, 5$_A$-H), 1.23–1.32 (2H, m, 4$_A$-H, & 3$_A$-H), 1.46–1.55 (2H, m, 5$_B$-H & 3$_B$-H), 1.72–1.77 (1H, m, 4$_B$-H), 1.97–2.07 (3H, m, 6-H, 10$_A$-H & 13$_B$-H), 2.16 (1H, d, J=13.3 Hz, 2$_B$-H),2.33–2.39 (1H, m, 13$_A$-H), 2.47 (1H, dd, J=12.4, 2.5 Hz, 12$_B$-H), 2.55 (1H, dd, J=10.7, 2.1 Hz, 8$_A$-H), 2.70 (1H, dd, J=10.8, 1.4 Hz, 10$_B$-H), 3.00 (1H, dd, J=10.7, 1.6 Hz, 8$_B$-H), 3.08–3.14 (1H, m, 12$_A$-H), 3.33 (1H, d, J=13.2 Hz, NCH_AH$_B$), 3.49 (1H, d, J=13.2 Hz, NCH$_A$$H_B$), 3.66 (3H, s, OCH$_3$), 7.18–7.35 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 22.3 (C-3), 26.2 (C-4), 26.3 (C-5), 26.6 (C-13), 31.2 (C-2), 38.2 (C-12), 46.4 (C-7), 47.4 (C-6), 50.0 (C-1), 52.0 (OCH$_3$), 62.7 (NCH_2Ar), 63.6 (C-8), 64.8 (C-10), 127.2 (Ar–CH), 128.4 (Ar–CH), 128.6 (Ar–CH), 137.7 (Ar–C), 175.1 (C=O), 214.9 (C-11); m/z (EI) 341 (M$^+$, 28%), 250 (M–$C_6H_5CH_2$, 9%), 245 (12%), 218 (9%), 134 (28%), 91 ($C_6H_5CH_2$, 100%); found M$^+$ 341.1993, $C_{21}H_{27}NO_3$ requires M$^+$ 341.1991. In a separate fraction was returned acrylate **18a** (0.281 g, 47%).

4.4. Synthesis of AE ring analogues of methyllycaconitine and grandiflorine 35, 36, 39, 48–50

4.4.1. Methyl (1S,5S*,6S*)-3-benzyl-6-hydroxy-3-azabicyclo[3.3.1] nonane-1-carboxylate* ***28a****.* The reaction was carried out according to standard procedure D, using ketone **17a** (1.53 g, 5.33 mmol) and sodium borohydride (0.101 g, 2.33 mmol), stirring for 3 h, with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give the *title compound* **28a** (1.46 g, 95%) as a pale yellow oil. R_f 0.49; ν_{max}(NaCl)/cm^{-1} 3353, 2949, 1725, 1494, 1453, 1255, 1075, 1209; δ_H(400 MHz; $CDCl_3$) 1.39 (1H, br s, O–H), 1.76–1.85 (3H, m, 9$_A$-H, 9$_B$-H & 8$_A$-H), 1.90–2.00 (3H, m, 7$_B$-H, 8$_B$-H & 5-H), 2.07 (1H, dd, J=11.4, 2.2 Hz, 4$_A$-H), 2.25 (1H, dd, J=11.0, 2.2 Hz, 2$_A$-H), 2.68–2.80 (1H, m, 7$_A$-H), 3.08 (1H, d, J=11.0 Hz, 2$_B$-H), 3.16 (1H, d, J=11.4 Hz, 4$_B$-H), 3.40 (1H, d, J=13.2 Hz, NCH_AH$_B$), 3.45 (1H, d, J=13.2 Hz, NCH$_A$$H_B$), 3.63 (3H, s, OCH$_3$), 3.82–3.93 (1H, m, 6-H), 7.22–7.34 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 31.5 (C-7), 32.6 (C-8), 34.8 (C-9), 35.7 (C-5), 41.8 (C-1), 51.8 (OCH$_3$), 52.1 (C-4), 60.3 (C-2), 63.5 (NCH_2Ar), 71.8 (C-6), 127.0 (Ar–CH), 128.3 (Ar–CH), 128.7 (Ar–CH), 138.7 (Ar–CH), 176.7 (C=O); m/z (EI) 289 (M$^+$, 26%), 272 (M–OH, 28%), 134 (37%), 91 ($C_6H_5CH_2$, 100%), 47 (57%); found M$^+$ 289.1682, $C_{17}H_{23}NO_3$ requires M$^+$ 289.1678.

4.4.2. Ethyl (1S,5S*,6S*)-3-benzyl-6-hydroxy-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***28b****.* The reaction was carried out according to standard procedure D, using ketone **17b** (1.01 g, 3.35 mmol) and sodium borohydride (63.0 mg, 1.67 mmol), stirring for 2.5 h with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give the *title compound* **28b** (0.993 g, 98%) as a pale yellow oil. R_f 0.51; ν_{max}(NaCl)/cm^{-1} 3420, 2916, 1723, 1453, 1255, 1074, 1125; δ_H(400 MHz; $CDCl_3$) 1.21 (3H, t, J=7.1 Hz, OCH$_2$CH_3), 1.64 (1H, br s, O–H), 1.76–1.84 (3H, m, 9$_A$-H, 9$_B$-H & 8$_A$-H), 1.89–2.00 (3H, m, 7$_B$-H, 5-H & 8$_B$-H), 2.05 (1H, dd, J=11.4, 2.8 Hz, 4$_A$-H), 2.25 (1H, dd, J=11.0, 2.2 Hz, 2$_A$-H), 2.69–2.80 (1H, m, 7$_A$-H), 3.07 (1H, d, J=11.0 Hz, 2$_B$-H), 3.15 (1H, d, J=11.4 Hz, 4$_B$-H), 3.42 (2H, s, NCH_2Ar), 3.80–3.92 (1H, m, 6-H), 4.09 (2H, q, J=7.1 Hz, OCH_2CH$_3$), 7.22–7.36 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 14.1 (OCH$_2$CH_3), 31.3 (C-7), 32.5 (C-8), 34.7 (C-9), 35.6 (C-5), 41.6 (C-1), 52.0 (C-4), 60.3 (C-2), 60.4 (OCH_2CH$_3$), 63.4 (NCH_2Ar), 71.8 (C-6), 126.9 (Ar–CH), 128.2 (Ar–CH), 128.6 (Ar–CH), 137.8 (Ar–C), 176.2 (C=O); m/z (EI) 303 (M$^+$, 26%), 286 (M–OH, 50%), 91 ($C_6H_5CH_2$, 100%); found M$^+$ 303.1836, $C_{18}H_{25}NO_3$ requires M$^+$ 303.1834.

4.4.3. Methyl (1S,6R*,7S*,11S*)-9-benzyl-11-hydroxy-9-azatricyclo [5.3.3.0^{1,6}]tridecane-7-carboxylate* ***29a*** *and methyl (1S*,6R*,7S*,11R*)-9-benzyl-11-hydroxy-9-azatricyclo[5.3.3.0^{1,6}]tridecane-7-carboxylate* ***29b****.* The reaction was carried out according to standard procedure D, using ketone **27** (0.374 g, 1.10 mmol) and sodium borohydride (0.165 g, 4.38 mmol), stirring for 23 h with hexane/ethyl acetate 4:1 as the solvent for flash chromatography to give (i) *methyl* (1S*,6R*,7S*,11R*)-9-*benzyl*-11-*hydroxy*-9-*azatricyclo*[5.3.3.0^{1,6}]*tridecane*-7-*carboxylate* **29b** (57.0 mg, 15%) as a bright yellow oil. R_f 0.34; ν_{max}(NaCl)/cm^{-1} 3505, 2924, 1723, 1495, 1448, 1264, 1247, 1160; δ_H(400 MHz; $CDCl_3$) 1.08–1.18 (2H, m, 2$_A$-H & 5$_B$-H), 1.25–1.29 (1H, m, 4$_A$-H), 1.50–1.62 (3H, m, 3$_A$-H, 12$_B$-H & 6-H), 1.63–1.76 (3H, m, 2$_B$-H, 10$_A$-H & 13$_B$-H), 1.77–1.85 (2H, m, 4$_B$-H & 5$_A$-H),2.00–2.07 (1H, m, 3$_B$-H), 2.17 (1H, tdd, J=14.0, 6.4, 2.5 Hz, 13$_A$-H), 2.47–2.52 (2H, m, 8$_A$-H & 10$_B$-H), 2.91 (1H, dd, J=10.9, 0.6, 8$_B$-H), 3.29–3.40 (3H, m, 12$_A$-H & NCH_2Ar), 3.64 (3H, s, OCH$_3$), 3.72–3.85 (1H, m, 11-H), 7.23–7.32 (5H, m, Ar–H); δ_C(400 MHz; $CDCl_3$) 22.7 (C-13), 23.5 (C-3), 23.6 (C-5), 26.4 (C-4), 32.3 (C-12), 35.7 (C-2), 37.5 (C-1), 46.9 (C-6), 47.2 (C-7), 51.6 (OCH$_3$), 63.1 (C-8), 63.2 (NCH_2Ar), 67.2 (C-10), 76.6 (C-11), 126.9 (Ar–CH), 128.3 (Ar–CH), 128.7 (Ar–CH), 138.7

(Ar–C), 176.2 (C=O); *m/z* (ESI$^+$); found MH$^+$ 344.2229, $C_{21}H_{30}NO_3$ requires MH$^+$ 344.2220 and (ii) *methyl* (1*S**,6*R**,7*S**,11*S**)-9-*benzyl*-11-*hydroxy*-9-*azatricyclo*[5.3.3.0^{1,6}]*tridecane*-7-*carboxylate* **29a** (0.160 g, 43%) as a pale yellow oil. R_f 0.23; ν_{max}(NaCl)/cm^{-1} 3439, 2929, 1727, 1495, 1452, 1265, 1240, 1163; δ_H(400 MHz; $CDCl_3$) 0.80–0.84 (1H, m, 2_A-H), 1.13–1.21 (1H, m, 5_B-H), 1.27–1.35 (1H, m, 4_A-H), 1.37 (1H, dd, *J*=12.6, 3.2 Hz, 5_A-H), 1.47–1.51 (2H, m, 3_A-H & 3_B-H), 1.65 (1H, d, *J*=11.3 Hz, 10_A-H), 1.73–1.81 (3H, m, 6-H, 4_B-H & 2_B-H), 1.87 (1H, dd, *J*=13.1, 7.1 Hz, 13_B-H), 2.00–2.06 (2H, m, 12_B-H & 13_A-H), 2.46 (1H, dd, *J*=10.6, 1.7 Hz, 8_A-H), 2.75–2.85 (1H, m, 12_A-H), 2.92 (1H, d, *J*=10.6 Hz, 8_B-H), 3.00 (1H, d, *J*=11.3 Hz, 10_B-H), 3.37 (2H,s, NCH_2Ar), 3.62 (3H, s, OCH_3), 4.15–4.20 (1H, m, 11-H), 7.23–7.31 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 20.7 (C-3), 22.5 (C-5), 26.3 (C-4), 27.2 (C-13), 31.0 (C-12), 31.9 (C-2), 37.5 (C-1), 46.8 (C-7), 47.8 (C-6), 51.7 (OCH_3), 62.0 (C-10), 63.3 (NCH_2Ar), 63.4 (C-8), 67.1 (C-11), 127.0 (Ar–CH), 128.4 (Ar–CH), 128.7 (Ar–CH), 138.7 (Ar–C), 175.8 (C=O); *m/z* (ESI$^+$); ound MH$^+$ 344.2222, $C_{21}H_{30}NO_3$ requires MH$^+$ 343.2220.

4.4.4. Methyl (1S,5S*,6S*)-3-benzyl-6-methoxy-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***30a***. The reaction was carried out according to standard procedure E, using sodium hydride (0.213 g, 5.32 mmol), alcohol **28a** (0.770 g, 2.66 mmol) and iodomethane (0.83 mL, 1.89 g, 13.3 mmol), stirring for 3 days with hexane/ethyl acetate 2:1 as the solvent for flash chromatography to give the *title compound* **30a** (0.670 g, 83%) as a yellow oil. R_f 0.59; ν_{max}(NaCl)/cm^{-1} 2929, 1729, 1493, 1454, 1265, 1102; δ_H(400 MHz; $CDCl_3$) 1.70–1.82 (3H, m, 8_A-H, 9_A-H & 9_B-H), 1.92–1.98 (2H, m, 8_B-H & 7_B-H), 2.08 (1H, dd, *J*=11.0, 2.9 Hz, 4_A-H), 2.13–2.19 (2H, m, 5-H & 2_A-H), 2.75–2.32 (1H, m, 7_A-H), 3.01 (1H, d, *J*=10.9 Hz, 2_B-H), 3.17 (1H, d, *J*=11.0 Hz, 4_B-H), 3.26 (1H, d, *J*=13.4 Hz, NCH_AH$_B$Ar), 3.34 (3H, s, C6–OCH_3), 3.35–3.42 (1H, m, 6-H), 3.57–3.64 (4H, m, NCH$_A$$H_B$Ar & C1–$CO_2CH_3$), 7.19–7.32 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 28.2 (C-7), 31.9 (C-5), 32.4 (C-8), 34.6 (C-9), 42.0 (C-1), 51.7 (CO_2CH_3), 52.7 (C-4), 55.8 (OCH_3), 59.7 (C-2), 63.4 (NCH_2Ar), 80.6 (C-6), 126.7 (Ar–CH), 128.1 (Ar–CH), 128.6 (Ar–CH), 138.6 (Ar–C), 176.7 (C=O); *m/z* (EI) 303 (M$^+$, 11%), 288 (M–OCH_3, 8%), 272 (M–OCH_3, 100%), 212 (6%), 134 (14%), 91 ($C_6H_5CH_2$, 77%); found M$^+$ 303.1832, $C_{18}H_{25}NO_3$ requires M$^+$ 303.1834.

4.4.5. Ethyl (1S,5S*,6S*)-3-benzyl-6-methoxy-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***30b***. The reaction was carried out according to standard procedure E, using sodium hydride (66.0 mg, 1.65 mmol), alcohol **28b** (0.250 g, 0.824 mmol) and iodomethane (0.26 mL, 0.585 g, 4.12 mmol), stirring for 3 days with hexane/ethyl acetate 2:1 as the solvent for flash chromatography to give the *title compound* **30b** (0.197 g, 75%) as a pale yellow oil. R_f 0.63; ν_{max}(NaCl)/cm^{-1} 2926, 1726, 1454, 1263, 1102; δ_H(400 MHz; $CDCl_3$) 1.20 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.71–1.80 (3H, m, 8_A-H, 9_A-H & 9_B-H), 1.93–1.98 (2H, m, 8_B-H & 7_B-H), 2.07 (1H, dd, *J*=11.1, 2.9 Hz, 4_A-H), 2.15–2.20 (2H, m, 5-H & 2_A-H), 2.75–2.80 (1H, m, 7_A-H), 3.02 (1H, d, *J*=11.0 Hz, 2_B-H), 3.16 (1H, d, *J*=11.1 Hz, 4_B-H), 3.29 (1H, d, *J*=13.4 Hz, NCH_AH$_B$Ar), 3.34 (3H, s, OCH_3), 3.38–3.42 (1H, m, 6-H), 3.57 (1H, d, *J*=13.4 Hz, NCH$_A$$H_B$Ar), 4.06 (2H, q, *J*=7.1 Hz, OCH_2CH$_3$), 7.20–7.31 (5H, m, Ar–H); δ_C(400 MHz; $CDCl_3$) 14.1 (OCH_2CH_3), 28.2 (C-7), 32.0 (C-5), 32.4 (C-8), 34.6 (C-9), 41.9 (C-1), 52.6 (C-4), 55.8 (OCH_3), 59.8 (C-2), 60.4 (OCH_2CH$_3$), 63.4 (NCH_2Ar), 80.7 (C-6), 126.7 (Ar–CH), 128.2 (Ar–CH), 128.7 (Ar–CH), 138.7 (Ar–C), 176.3 (C=O); *m/z* (EI) 317 (M$^+$, 9%), 286 (M–OCH_3, 90%), 134 (14%), 91 ($C_6H_5CH_2$, 100%); found M$^+$ 317.19953, $C_{19}H_{27}NO_3$ requires M$^+$ 317.1990.

4.4.6. Methyl (1S,6R*,7S*,11S*)-9-benzyl-11-methoxy-9-azatricyclo[5.3.3.0^{1,6}]tridecane-7-carboxylate* ***31***. The reaction was carried out according to standard procedure E, using sodium hydride (22.3 mg, 0.557 mmol), alcohol **29a** (95.5 mg, 0.278 mmol) and iodomethane (87 μL, 0.198 g, 1.39 mmol), stirring for 3 days with hexane/ethyl acetate 9:1 as the solvent for flash chromatography to give the *title compound* **31** (27.5 mg, 28%) as a yellow oil. R_f 0.37; ν_{max}(NaCl)/cm^{-1} 2925, 1731, 1495, 1451, 1264, 1240, 1111, 1096; δ_H(400 MHz; $CDCl_3$) 0.76–0.80 (1H, m, 2_A-H), 1.14 (1H, dq, *J*=12.3, 3.6 Hz, 5_B-H), 1.27–1.33 (1H, m, 4_A-H), 1.40 (1H, dd, *J*=12.3, 3.6 Hz, 5_A-H), 1.46–1.52 (2H, m, 3_A-H & 3_B-H), 1.66–1.70 (2H, m, 6-H & 10_A-H), 1.75–1.90 (3H, m, 4_B-H, 13_B-H & 2_B-H), 1.96–2.00 (1H, m, 13_A-H), 2.06–2.11 (1H, m, 12_B-H), 2.35 (1H, dd, *J*=10.6, 2.3 Hz, 8_A-H), 2.74–2.86 (2H, m, 12_A-H & 8_B-H), 3.12–3.17 (2H, m, NCH_ACH$_B$ & 10_B-H), 3.38 (3H, s, OCH_3 ether), 3.59 (3H, s, OCH_3 ester), 3.62 (1H, d, *J*=13.4 Hz, NCH$_A$CH_B), 3.71–3.74 (1H, m, 11-H), 7.21–7.31 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 21.0 (C-3), 22.5 (C-5), 26.1 (C-12), 26.4 (C-4), 26.8 (C-13), 32.2 (C-2), 37.6 (C-1), 46.7 (C-7), 48.0 (C-6), 51.6 (OCH_3 ester), 57.3 (OCH_3 ether), 62.8 (C-8), 63.2 (C-10 & NCH_2Ar), 75.9 (C-11), 126.7 (Ar–CH), 128.1 (Ar–CH), 128.7 (Ar–CH), 138.8 (Ar–C), 176.0 (C=O); *m/z* (ESI$^+$); found MH$^+$ 358.2367, $C_{22}H_{32}NO_3$ requires MH$^+$ 358.2377. In a separate fraction was returned alcohol **29a** (57.5 mg, 60%).

4.4.7. ((1S,5S*,6S*)-3-Benzyl-6-methoxy-3-azabicyclo[3.3.1]nonan-1-yl)methanol* ***32***. The reaction was carried out according to standard procedure F, using ester **30b** (0.110 g, 0.347 mmol), stirring for 15 min with hexane/ethyl acetate 1:2 as the solvent for flash chromatography to give the *title compound* **32** (60.0 mg, 63%) as a colourless oil. R_f 0.51; ν_{max}(NaCl)/cm^{-1} 3400, 2916, 1454, 1100, 1065, 1028; δ_H(400 MHz; $CDCl_3$) 1.25–1.27 (1H, m, 9_B-H), 1.35 (1H, tdd, *J*=13.4, 6.3, 2.5 Hz, 8_A-H), 1.42 (1H, dt, *J*=12.5, 3.6 Hz, 9_A-H), 1.60–1.66 (2H, m, 8_B-H & O–H), 1.86 (1H, dd, *J*=11.4, 2.3 Hz, 2_A-H), 1.92–1.94 (1H, m, 7_B-H), 2.07 (1H, dd, *J*=11.0, 2.3 Hz, 4_A-H), 2.14–2.15 (1H, m, 5-H), 2.68 (1H, d, *J*=11.4 Hz, 2_B-H), 2.72–2.78 (1H, m, 7_A-H), 3.17–3.21 (4H, m, CH_2OH, 4_B-H & NCH_AH$_B$Ar), 3.33–3.40 (4H, m, OCH_3 & 6-H), 3.60 (1H, d, *J*=13.4 Hz, NCH$_A$$H_B$Ar), 7.18–7.30 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 27.9 (C-7), 31.8 (C-8), 32.3 (C-5), 34.5 (C-9), 35.3 (C-1), 53.3 (C-4), 55.7 (OCH_3), 60.8 (C-2), 63.6 (NCH_2Ar), 71.7 (CH_2OH), 81.7 (C-6), 126.6 (Ar–CH), 128.1 (Ar–CH), 128.6 (Ar–CH), 139.0 (Ar–C); *m/z* (EI) 275 (M$^+$, 8%), 274 (M–H, 6%), 260 (M–CH_3, 4%), 244 (M–OCH_3, 100%), 134 (18%), 91 ($C_6H_5CH_2$, 61%); found M$^+$ 275.1882, $C_{17}H_{25}NO_2$ requires M$^+$ 275.1885.

4.4.8. ((1″S,5″S*,6″S*)-3″-Benzyl-6″-methoxy-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxo-2′,5′-dihydro-1′H-pyrrol-1′-yl)benzoate* ***34***. The reaction was carried out according to standard procedure G, using alcohol **32** (50.0 mg, 0.182 mmol), acid **33** (84.0 mg, 0.363 mmol), DMAP (2.00 mg, 18.0 μmol) and DCC (75.0 mg, 0.363 mmol), heating for 18 h, with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give the *title compound* **34** (64.0 mg, 72%) as a pale yellow oil. R_f 0.57; ν_{max}(NaCl)/cm^{-1} 2922, 1789, 1710, 1653, 1494, 1453, 1258, 1116, 1084; δ_H(400 MHz; $CDCl_3$) 1.35 (1H, d, *J*=13.0 Hz, $9''_B$-H), 1.39–1.53 (2H, m, $8''_A$-H & $9''_A$-H), 1.70–1.75 (1H, m, $8''_B$-H), 1.89–1.97 (2H, m, $7''_B$-H & $2''_A$-H), 2.07 (1H, dd, *J*=11.2, 2.8 Hz, $4''_A$-H), 2.14 (3H, d, *J*=1.8 Hz, C3′–CH_3), 2.15–2.17 (1H, m, 5″-H), 2.71–2.83 (2H, m, $2''_B$-H & $7''_A$-H), 3.19 (1H, d, *J*=11.2 Hz, $4''_B$-H), 3.25 (1H, d, *J*=13.3 Hz, NCH_AH$_B$Ar), 3.32–3.44 (4H, m, OCH_3 & 6″-H), 3.58 (1H, d, *J*=13.3 Hz, NCH$_A$$H_B$Ar), 3.81 (2H, d, *J*=2.1 Hz, C1″–CH_2O–), 6.46 (1H, q, *J*=1.8 Hz, 4′-H), 7.20–7.31 (6H, m, Ar–H, 3-H) 7.46 (1H, td, *J*=7.7, 1.2 Hz, 5-H), 7.63 (1H, td, *J*=7.7, 1.5 Hz, 4-H), 7.94 (1H, dd, *J*=7.9, 1.5 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 11.1 (C3′–CH_3), 27.7 (C-7″), 32.1 (C-5″ & C-8″), 34.2 (C-1″), 34.7 (C-9″), 53.0 (C-4″), 55.7 (OCH_3), 60.8 (C-2″), 63.4 (NCH_2Ar), 72.8 (C1″–CH_2O), 81.2 (C-6″), 126.6 (Ar–CH), 127.8 (C-1 & C-4′), 128.1 (Ar–CH), 128.6 (Ar–CH), 128.9 (C-5), 130.4 (C-3), 131.2 (C-6), 131.8 (C-2), 133.2 (C-4), 138.7 (Ar–C), 146.1 (C-3′), 164.5 (C=O), 169.6 (C-5′), 170.7 (C-2′); *m/z* (EI) 448 (M$^+$, 16%), 473 (M–CH_3, 4%), 457 (M–OCH_3, 100%), 397 (M–$C_6H_5CH_2$, 3%), 286 (7%), 258

(11%), 214 (13%), 134 (36%), 91 ($C_6H_5CH_2$, 80%); found M^+ 488.2310, $C_{29}H_{32}N_2O_5$ requires M^+ 488.2311.

4.4.9. ((1″S,5″S*,6″S*)-3″-Benzyl-6″-methoxy-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxopyrrolidin-1′-yl)benzoate* ***35***. The reaction was carried out according to standard procedure H, using maleimide **34** (45.0 mg, 92.1 μmol) for 2 h, with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give the *title compound* **35** (20.0 mg, 44%) as a yellow oil. R_f 0.30; ν_{max}(NaCl)/cm^{-1} 2934, 1779, 1709, 1493, 1454, 1260, 1183; δ_H(400 MHz; $CDCl_3$) 1.36 (1H, d, J=12.6 Hz, 9″$_B$-H), 1.40–1.54 (5H, m, C3′–CH_3, 8″$_A$-H & 9″$_A$-H), 1.75 (1H, dd, J=13.5, 6.1 Hz, 8″$_B$-H), 1.89–1.98 (2H, m, 7″$_B$-H & 2″$_A$-H), 2.09 (1H, dd, J=11.0, 2.8 Hz, 4″$_A$-H),2.15–2.19 (1H, m, 5″-H), 2.51–2.53 (1H, m, 4′$_A$-H), 2.70–2.85 (2H, m, 7″$_A$-H & 2″$_B$-H), 2.98–3.11 (2H, m, 4′$_B$-H & 3′-H), 3.18–3.28 (2H, m, 4″$_B$-H & NCH_ACH$_B$), 3.32–3.43 (4H, m, OCH_3 & 6″-H), 3.60 (1H, d, J=13.3 Hz, NCH$_A$CH_B), 3.79–3.84 (2H, m, C1″–CH_2O–), 7.21–7.32 (6H, m, 3-H & Ar–H), 7.48 (1H, td, J=7.7, 1.2 Hz, 5-H), 7.65 (1H, td, J=7.7, 1.6 Hz, 4-H), 7.96 (1H, d, J=7.9 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 16.3 & 16.5 (C3′–CH_3), 27.8 (C-7″), 32.2 (C-5″ & C-8″), 34.3 (C-1″), 34.8 (C-9″), 35.2 & 35.4 (C-3′), 37.0 (C-4′), 53.0 (C-4″), 55.8 (OCH_3), 60.8 (C-2″), 63.4 (NCH_2Ar), 72.8 (C1″–CH_2O), 81.3 (C-6″), 126.4 (C-1), 126.6 (Ar–CH), 128.1 (Ar–CH), 128.8 (Ar–CH), 129.4 (C-5), 129.9 (C-3), 131.4 (C-6), 132.9 (C-2), 133.4 (C-4), 138.8 (Ar–C), 164.1 (C=O), 175.8 & 176.0 (C-5′), 179.9 (C-2′); m/z (ESI^+); found MH^+ 491.2537, $C_{29}H_{35}N_2O_5$ requires MH^+ 491.2540. In a second fraction was returned maleimide **34** (12.5 mg, 28%).

4.4.10. ((1S,6S*,7S*,11S*)-9-Benzyl-11-methoxy-9-azatricyclo[5.3.3.0^{1,6}]tridecan-7-yl)methanol.* The reaction was carried out according to standard procedure F, using ester **31** (50.0 mg, 0.140 mmol), stirring for 10 min with hexane/ethyl acetate 1:2 as the solvent for flash chromatography to give the *title compound* (23.0 mg, 50%) as a pale yellow oil. R_f 0.44; ν_{max}(NaCl)/cm^{-1} 3373, 2926, 1495, 1452, 1097, 1071, 1169; δ_H(400 MHz; $CDCl_3$) 0.75–0.78 (1H, m, 2$_A$-H), 1.23–1.52 (8H, m, 4$_A$-H, 5$_A$-H, 6-H, 5$_B$-H, 13$_B$-H, 3$_B$-H, 13$_A$-H & 3$_A$-H), 1.60 (1H, d, J=10.6 Hz, 10$_A$-H), 1.82 (1H, d, J=11.6 Hz, 4$_B$-H), 1.88 (1H, d, J=13.2 Hz, 2$_B$-H), 2.02–2.09 (2H, m, 12$_B$-H & 8$_A$-H), 2.71 (1H, d, J=10.5 Hz, 8$_B$-H), 2.79–2.80 (1H, m, 12$_A$-H), 3.09–3.19 (3H, m, 10$_B$-H, C7-CH_ACH$_B$OH & NCH_ACH$_B$), 3.32 (1H, d, J=11.0 Hz, C7-CH$_A$CH_BOH), 3.38 (3H, s, OCH_3), 3.59 (1H, d, J=13.4 Hz, NCH$_A$CH_B), 3.73 (1H, dd, J=11.0, 6.7 Hz, 11-H), 7.20–7.33 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 20.5 (C-5), 21.0 (C-3), 26.2 (C-12), 26.5 (C-4), 28.3 (C-13), 32.4 (C-2), 37.7 & 37.8 (C-1 & C-7), 46.2 (C-6), 57.3 (OCH_3), 62.8 (C-8), 63.6 (NCH_2Ar & C-10), 68.8 (CH_2OH), 76.9 (C-11), 126.6 (Ar–CH), 128.1 (Ar–CH), 128.7 (Ar–CH), 139.3 (Ar–C); m/z (ESI^+) found MH^+ 330.2432, $C_{21}H_{32}NO_2$ requires MH^+ 330.2428.

4.4.11. ((1″S,6″S*,7″S*,11″S*)-9″-Benzyl-11″-methoxy-9″-azabicyclo[5.3.3.0^{1,6}]tridecan-7″-yl)methyl 2-(3′-methyl-2′,5′-dioxo-2′,5′-dihydro-1′H-pyrrol-1′-yl)benzoate.* The reaction was carried out according to standard procedure G, using ((1S*,6S*,7S*,11S*)-9-benzyl-11-methoxy-9-azatricyclo[5.3.3.0^{1,6}]tridecan-7-yl)methanol (20.0 mg, 60.7 μmol), acid **33** (28.0 mg, 0.121 mmol), heating for 21.5 h, with hexane/ethyl acetate 2:1 as the solvent for flash chromatography to give the *title compound* (32.0 mg, 97%) as a pale yellow oil. R_f 0.45; ν_{max}(NaCl)/cm^{-1} 2930, 1783, 1710, 1646, 1495 & 1453, 1258, 1099; δ_H(400 MHz; $CDCl_3$) 0.77–0.79 (1H, m, 2″$_A$-H), 1.20–1.61 (9H, m, 4″$_A$-H, 6″-H, 5″$_A$-H, 5″$_B$-H, 3″$_A$-H, 3″$_B$-H, 13″$_B$-H, 13″$_A$-H & 10″$_A$-H), 1.82 (1H, d, J=11.2 Hz, 4″$_B$-H), 1.88 (1H, d, J=13.3 Hz, 2″$_B$-H), 2.01–2.08 (2H, m, 8″$_A$-H & 12″$_B$-H), 2.15 (3H, d, J=1.9 Hz, C3′–CH_3), 2.77–2.86 (2H, m, 12″$_A$-H & 8″$_B$-H), 3.14 (1H, d, J=10.8 Hz, 10″$_B$-H), 3.18 (1H, d, J=13.3 Hz, NCH_AH$_B$Ar), 3.38 (3H, s, OCH_3), 3.58 (1H, d, J=13.3 Hz, NCH$_A$H$_B$Ar), 3.74 (1H, dd, J=11.0, 6.8 Hz, 11″-H), 3.84 (2H, m, C7″–CH_2O–), 6.47 (1H, q, J=1.8 Hz, 4′-H), 7.21–7.33 (6H, m, Ar–H & 3-H) 7.46 (1H, td, J=7.7, 1.2 Hz, 5-H), 7.64 (1H, td, J=7.8, 1.5 Hz, 4-H), 7.86 (1H, dd, J=7.8, 1.5 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 11.2 (C3′–CH_3), 20.7 (C-5″), 20.9 (C-3″), 26.1 (C-12″), 26.5 (C-4″), 28.3 (C-13″), 32.2 (C-2″), 36.9 (C-7″), 37.7 (C-1″), 47.2 (C-6″), 57.3 (OCH_3), 63.0 (C-8″), 63.3 (C-10″ & NCH_2Ar), 70.7 (C7″–CH_2O), 76.5 (C-11″), 126.6 (Ar–CH), 127.9 (C-1 & C-4′), 128.1 (Ar–CH), 128.8 (Ar–CH), 129.0 (C-5), 130.5 (C-3), 131.2 (C-6), 131.9 (C-2), 133.2 (C-4), 139.0 (Ar–C), 146.2 (C-3′), 164.5 (C=O), 169.7 (C-5′), 170.8 (C-2′); m/z (ESI^+) found MH^+ 543.2860, $C_{33}H_{39}N_2O_5$ requires MH^+ 543.2853.

4.4.12. ((1″S,6″S*,7″S*,11″S*)-9″-Benzyl-11″-methoxy-9″-azabicyclo[5.3.3.0^{1,6}]tridecan-7″-yl)methyl 2-(3′-methyl-2′,5′-dioxopyrrolidin-1′-yl)benzoate* ***36***. The reaction was carried out according to standard procedure H, using ((1″*S**,6″*S**,7″*S**,11″*S**)-9″-benzyl-11″-methoxy-9″-azabicyclo[5.3.3.0^{1,6}]tridecan-7″-yl)methyl 2-(3′-methyl-2′,5′-dioxo-2′,5′-dihydro-1′*H*-pyrrol-1′-yl)benzoate (22.0 mg, 40.5 μmol), stirring for 2 h, with hexane/ethyl acetate 2:1 as the solvent for flash chromatography to give the *title compound* **36** (12.5 mg, 57%) as a pale yellow oil. R_f 0.24; ν_{max}(NaCl)/cm^{-1} 2931, 1779, 1713, 1494, 1452, 1260, 1185; δ_H(400 MHz; $CDCl_3$) 0.77–0.80 (1H, m, 2″$_A$-H), 1.20–1.63 (12H, m, 4″$_A$-H, 6″-H, 5″$_A$-H, 5″$_B$-H, C3′–CH_3, 3″$_A$-H, 3″$_B$-H, 13″$_A$-H, 13″$_B$-H & 10″$_A$-H), 1.83 (1H, d, J=11.0 Hz, 4″$_B$-H), 1.90 (1H, d, J=13.2 Hz, 2″$_B$-H), 2.02–2.10 (2H, m, 8″$_A$-H & 12″$_B$-H),2.50–2.52 (1H, m, 4′$_A$-H), 2.78–2.88 (2H, m, 12″$_A$-H & 8″$_B$-H), 3.02–3.11 (2H, m, 4′$_B$-H & 3′-H), 3.13–3.19 (2H, m, 10″$_B$-H & NCH_AH$_B$Ar), 3.39 (3H, s, OCH_3), 3.60 (1H, d, J=13.3 Hz, NCH$_A$H$_B$Ar), 3.75 (1H, dd, J=11.0, 6.8 Hz, 11″-H), 3.80–3.88 (2H, m, C7″–CH_2O–), 7.22–7.33 (6H, m, Ar–H & 3-H), 7.48 (1H, td, J=7.7, 0.9 Hz, 5-H), 7.65 (1H, td, J=7.7, 1.4 Hz, 4-H), 7.88 (1H, dd, J=7.9, 1.5 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 16.3 & 16.5 (C3′–CH_3), 20.7 (C-5″), 21.0 (C-3″), 26.1 (C-12″), 26.5 (C-4″), 28.3 (C-13″), 32.2 (C-2″), 35.2 & 35.4 (C-3′), 36.9 (C-7″), 37.0 (C-4′), 37.7 (C-1″), 47.3 (C-6″), 57.3 (OCH_3), 63.0 (C-8″), 63.3 & 63.4 (C-10″ & NCH_2Ar), 70.6 (C7″–CH_2O), 76.5 (C-11″), 126.6 (Ar–CH), 127.1 (C-1), 128.1 (Ar–CH), 128.8 (Ar–CH), 129.4 (C-5), 129.9 (C-3), 131.3 (C-6), 132.9 (C-2), 133.4 (C-4), 139.0 (Ar–C), 164.1 (C=O), 175.8 (C-5′), 179.9 (C-2′); m/z (ESI^+) found M^+ 545.3008, $C_{33}H_{41}N_2O_5$ requires M^+ 545.3010.

4.4.13. ((1S,5S*,6S*)-3-Benzyl-6-hydroxy-3-azabicyclo[3.3.1]nonan-1-yl)methanol* ***37***. The reaction was carried out according to standard procedure F, using ester **17a** (0.365 g, 1.27 mmol), stirring for 15 min with hexane/ethyl acetate 1:2 as the solvent for flash chromatography to give the *title compound* **37** (0.224 g, 67%) as a colourless oil. R_f 0.20; ν_{max}(NaCl)/cm^{-1} 3375, 2908, 1494, 1453, 1043, 1102; δ_H(400 MHz; $CDCl_3$) 1.29 (1H, dd, J=12.5, 2.0 Hz, 9$_B$-H), 1.34–1.43 (2H, m, 8$_A$-H & 9$_A$-H), 1.65 (1H, dd, J=14.0, 6.7 Hz, 8$_B$-H), 1.84–1.96 (5H, m, 2× O–H, 7$_B$-H, 2$_A$-H & 5-H), 2.04 (1H, dd, J=11.2, 2.8 Hz, 4$_A$-H), 2.65–2.76 (2H, m, 7$_A$-H & 2$_B$-H), 3.16 (1H, d, J=11.2 Hz, 4$_B$-H), 3.19 (2H, s, OCH_2), 3.22 (1H, d, J=13.2 Hz, NCH_AH$_B$Ar), 3.45 (1H, d, J=13.2 Hz, NCH$_A$H$_B$Ar), 3.80–3.83 (1H, m, 6-H), 7.19–7.29 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 31.0 (C-7), 31.9 (C-8), 34.5 (C-9), 34.9 (C-1), 36.0 (C-5), 52.7 (C-4), 61.2 (C-2), 63.6 (NCH_2Ar), 71.4 (OCH_2), 72.6 (C-6), 126.7 (Ar–CH), 128.1 (Ar–CH), 128.5 (Ar–CH), 139.0 (Ar–C); m/z (EI) 261 (M^+, 24%), 244 (M–OH, 58%), 91 ($C_6H_5CH_2$, 100%); found M^+ 261.1726, $C_{16}H_{23}NO_2$ requires M^+ 261.1729.

4.4.14. ((1″S,5″S*,6″S*)-3″-Benzyl-6″-hydroxy-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxo-2′,5′-dihydro-1′H-pyrrol-1′-yl)benzoate* ***38a*** *and (1″S*,5″S*,6″S*)-3″-benzyl-1″-(((2‴-(3‴-methyl-2‴′,5‴′-dioxo-2‴′,5″-dihydro-1‴′H-pyrrol-1‴′-yl)benzoyl)oxy)methyl)-3″-azabicyclo[3.3.1]nonan-6″-yl 2-(3′-methyl-2′,5′-dioxo-2′,5′-dihydro-1′H-pyrrol-1′-yl)benzoate* ***38b***. The reaction was carried out according to standard procedure G, using alcohol **37** (34.0 mg, 0.130 mmol), acid **33** (38.0 mg, 0.163 mmol), heating for 18 h, with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give (i) *diester* **38b** (9.3 mg, 10%) as an orange oil. R_f

0.40; ν_{max}(NaCl)/cm^{-1} 2931, 1782, 1708, 1645, 1493, 1453, 1257, 1084; δ_H(400 MHz; $CDCl_3$) 1.50–1.60 (3H, m, 9″$_B$-H, 8″$_A$-H & 9″$_A$-H), 1.88 (1H, dd, *J*=13.6, 6.0 Hz, 8″$_B$-H), 1.92–2.05 (2H, m, 7″$_B$-H & 4″$_A$-H), 2.10–2.22 (8H, m, 5″-H, C3′–CH_3, C3‴–CH_3, & 2″$_A$-H), 2.94 (1H, d, *J*=10.8 Hz, 2″$_B$-H), 2.99–3.06 (1H, m, 7″$_A$-H), 3.14 (1H, d, *J*=11.2 Hz, 4″$_B$-H), 3.27 (1H, d, *J*=13.2 Hz, NC*H$_A$*H$_B$Ar), 3.60 (1H, d, *J*=13.2 Hz, NCH$_A$*H$_B$*Ar), 3.88 (2H, s, C1″–*CH*$_2$O–), 5.07–5.09 (1H, m, 6″-H), 6.40–6.50 (2H, m, 4′-H & 4‴-H), 7.24–7.41 (8H, m, 3‴-H, 5‴-H, 5× Ar–H & 3-H), 7.51 (1H, td, *J*=7.6, 1.2 Hz, 5-H), 7.60 (1H, td, *J*=7.7, 1.5 Hz, 4‴-H), 7.64–7.69 (2H, m, 4-H & 6‴-H), 8.03 (1H, dd, *J*=7.8, 1.4 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 11.2 (C3′–*C*H$_3$ & C3‴–*C*H$_3$), 26.9 (C-7″), 32.2 (C-8″), 33.0 (C-5″), 34.1 (C-1″), 34.7 (C-9″), 52.7 (C-4″), 62.0 (C-2″), 63.5 (N*C*H$_2$Ar), 72.7 (C1″–*C*H$_2$O), 75.5 (C-6″), 126.8 (Ar–CH), 127.8 (C-1), 127.9 (C-4′ & C-4‴), 128.2 (C-1‴), 128.3 (Ar–CH), 128.9 (Ar–CH & C-5‴), 129.0 (C-5), 130.3 (C-3‴), 130.5 (C-3), 131.3 (C-6), 131.6 (C-6‴), 131.7 (C-2‴), 131.9 (C-2), 133.0 (C-4‴), 133.4 (C-4), 138.9 (Ar–C), 146.2 (C-3′ & C-3‴), 164.0 (O*C*=O), 164.6 (CH$_2$O*C*=O), 169.8 (C-5′ & C-5‴), 170.8 (C-2′ & C-2‴); *m*/*z* (ESI$^+$) 688 (MH$^+$, 100%); found MH$^+$ 688.2641, $C_{40}H_{38}N_3O_8$ requires MH$^+$ 688.2653 and (ii) *ester* **38a** (27.4 mg, 44%) as a yellow oil. R_f 0.24; ν_{max}(NaCl)/cm^{-1} 3420, 2918, 1781, 1708, 1645, 1494, 1258, 1108; δ_H(400 MHz; $CDCl_3$) 1.39 (1H, d, *J*=15.2 Hz, 9″$_B$-H), 1.44–1.52 (2H, m, 8″$_A$-H & 9″$_A$-H), 1.62 (1H, br s, O–H), 1.76 (1H, dd, *J*=13.6, 6.4 Hz, 8″$_B$-H), 1.90–1.94 (1H, m, 7″$_B$-H), 1.95–1.99 (1H, m, 5″-H), 2.02–2.07 (2H, m, 4″$_A$-H & 2″$_A$-H), 2.16 (3H, d, *J*=1.7 Hz, C3′–*CH*$_3$), 2.70–2.78 (1H, m, 7″$_A$-H), 2.83 (1H, d, *J*=10.8 Hz, 2″$_B$-H), 3.18 (1H, d, *J*=11.6 Hz, 4″$_B$-H), 3.39 (1H, d, *J*=13.4 Hz, NC*H$_A$*H$_B$Ar), 3.43 (1H, d, *J*=13.4 Hz, NCH$_A$*H$_B$*Ar), 3.81–3.88 (3H, m, C1″–*CH*$_2$O– & 6″-H), 6.48 (1H, q, *J*=1.7 Hz, 4′-H), 7.21–7.35 (6H, m, Ar–H & 3-H) 7.48 (1H, td, *J*=7.8, 1.2 Hz, 5-H), 7.65 (1H, td, *J*=7.8, 1.7 Hz, 4-H), 7.98 (1H, dd, *J*=7.8, 1.7 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 11.2 (C3′–*C*H$_3$), 31.1 (C-7″), 32.3 (C-8″), 34.1 (C-1″), 34.9 (C-9″), 35.9 (C-5″), 52.4 (C-4″), 61.4 (C-2″), 63.5 (N*C*H$_2$Ar), 72.4 (C-6″), 72.8 (C1″–*C*H$_2$O), 126.9 (Ar–CH), 127.9 (C-1 & C-4′), 128.3 (Ar–CH), 128.7 (Ar–CH), 129.0 (C-5), 130.4 (C-3), 131.3 (C-6), 131.8 (C-2), 133.3 (C-4), 138.8 (Ar–C), 146.2 (C-3′), 164.6 (CO$_2$), 169.7 (C-5′), 170.8 (C-2′); *m*/*z* (ESI$^+$) 475 (MH$^+$, 100%); found MH$^+$ 475.2237, $C_{28}H_{31}N_2O_5$ requires MH$^+$ 475.2227.

4.4.15. ((1″S,5″S*,6″S*)-3″-Benzyl-6″-hydroxy-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxopyrrolidin-1′-yl)benzoate* ***39***. The reaction was carried out according to standard procedure H, using maleimide **38a** (22.0 mg, 46.4 μmol), stirring for 3 h, with hexane/ethyl acetate 1:2 as the solvent for flash chromatography to give the *title compound* **39** (12.8 mg, 58%) as a yellow oil. R_f 0.26; ν_{max}(NaCl)/cm^{-1} 3423, 2926, 1392, 1780, 1712, 1494, 1455, 1262, 1188; δ_H(400 MHz; $CDCl_3$) 1.39–1.53 (6H, m, 9″$_B$-H, C3′–CH_3, 8″$_A$-H & 9″$_A$-H), 1.64 (1H, br s, O–H),1.77–1.80 (1H, m, 8″$_B$-H) 1.88–1.92 (1H, m, 7″$_B$-H), 1.99–2.00 (1H, m, 5″-H), 2.02–2.09 (2H, m, 4″$_A$-H & 2″$_A$-H), 2.52–2.56 (1H, m, 4′$_A$-H), 2.74–2.77 (1H, m, 7″$_A$-H), 2.85 (1H, d, *J*=10.5 Hz, 2″$_B$-H), 2.99–3.16 (2H, m, 4′$_B$-H & 3′-H), 3.19 (1H, d, *J*=11.4 Hz, 4″$_B$-H), 3.38 (1H, d, *J*=13.2 Hz, NC*H$_A$*H$_B$Ar), 3.45 (1H, d, *J*=13.2 Hz, NCH$_A$*H$_B$*Ar), 3.82–3.90 (3H, m, C1″–CH$_2$O–& 6″-H), 7.23–7.32 (6H, m, 3-H & Ar–H), 7.49 (1H, td, *J*=7.7, 1.2 Hz, 5-H), 7.66 (1H, td, *J*=7.7, 1.5 Hz, 4-H), 7.99 (1H, dd, *J*=7.7, 1.5 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 16.3 (C3′–*C*H$_3$), 31.0 (C-7″), 32.3 (C-8″), 34.1 (C-1″), 34.9 (C-9″), 35.2 (C-3′), 35.9 (C-5″), 37.0 (C-4′), 52.4 (C-4″), 61.4 (C-2″), 63.5 (N*C*H$_2$Ar), 72.3 (C-6″), 72.7 (C1″–*C*H$_2$O), 127.0 (C-1 & Ar–C), 128.3 (Ar–CH), 128.8 (Ar–CH), 129.4 (C-5), 129.9 (C-3), 131.3 (C-6), 132.9 (C-2), 133.5 (C-4), 138.8 (Ar–C), 164.0 (CO$_2$), 176.0 (C-5′), 179.9 (C-2′); *m*/*z* (ESI$^+$) 477 (MH$^+$, 100%); found MH$^+$ 477.2407, $C_{28}H_{33}N_2O_5$ requires MH$^+$ 477.2384.

4.4.16. Methyl (1S,5S*,6S*)-6-methoxy-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***40a***. The reaction was carried out according to standard procedure I, using benzylamine **30a** (0.120 g, 0.396 mmol) to give the *title compound* **40a** (84.0 mg, 99%) as a yellow oil, which was used without further purification. ν_{max}(NaCl)/cm^{-1} 3343, 2930, 1722, 1239, 1099; δ_H(400 MHz; $CDCl_3$) 1.81–1.88 (3H, m, N–H, 8$_A$-H & 9$_B$-H), 1.93–1.98 (1H, m, 9$_A$-H), 2.02–2.10 (3H, m, 8$_B$-H, 5-H & 7$_B$-H), 2.25–2.28 (1H, m, 7$_A$-H), 2.75 (1H, dd, *J*=12.6, 2.6 Hz, 4$_A$-H), 3.01 (1H, dd, *J*=12.4, 2.6 Hz, 2$_A$-H), 3.21–3.30 (2H, m, 4$_B$-H & 2$_B$-H), 3.36 (3H, s, OCH_3 ether), 3.43–3.49 (1H, m, 6-H), 3.65 (3H, s, OCH_3 ester); δ_C(100 MHz; $CDCl_3$) 28.5 (C-7), 31.0 (C-5), 31.9 (C-8), 34.1 (C-9), 40.6 (C-1), 44.2 (C-4), 51.7 (OCH_3), 52.9 (C-2), 55.8 (OCH_3), 80.0 (C-6), 176.7 (C=O); *m*/*z* (ESI$^+$) 214 (MH$^+$, 100%); found MH$^+$ 214.1438, $C_{11}H_{20}NO_3$ requires MH$^+$ 214.1438.

4.4.17. Ethyl (1S,5S*,6S*)-6-methoxy-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***40b***. The reaction was carried out according to standard procedure I, using benzylamine **30b** (90.0 mg, 0.284 mmol) to give the *title compound* **40b** as a pale yellow oil (64.0 mg, 99%), which was used without further purification. ν_{max}(NaCl)/cm^{-1} 3584, 2934, 1723, 1240, 1101; δ_H(400 MHz; $CDCl_3$) 1.24 (3H, t, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 1.76–1.88 (3H, m, N–H, 9$_B$-H & 8$_A$-H), 1.97 (1H, ddd, *J*=13.3, 3.3, 3.3 Hz, 9$_A$-H), 2.04–2.10 (3H, m, 5-H, 8$_B$-H & 7$_B$-H), 2.17–2.23 (1H, m, 7$_A$-H), 2.77 (1H, dd, *J*=12.8, 2.2 Hz, 4$_A$-H), 3.02 (1H, dd, *J*=12.6, 2.2 Hz, 2$_A$-H), 3.23–3.32 (2H, m, 2$_B$-H & 4$_B$-H), 3.36 (3H, s, OCH_3), 3.44–3.46 (1H, m, 6-H), 4.11, (2H, q, *J*=7.1 Hz, OC*H*$_2$CH$_3$); δ_C(100 MHz; $CDCl_3$) 14.1 (CH$_3$, OCH$_2$*C*H$_3$), 28.4 (C-7), 30.9 (C-5), 31.8 (C-8), 33.8 (C-9), 40.4 (C-1), 43.9 (C-4), 52.5 (C-2), 55.8 (OCH_3), 60.5 (OCH$_2$CH$_3$), 80.0 (C-6), 176.2 (C=O); *m*/*z* (EI) 227 (M$^+$, 5%), 196 (M–OCH_3, 100%), 154 (M–COOCH$_2$CH$_3$, 11%); found M$^+$ 227.1523, $C_{12}H_{21}NO_3$ requires M$^+$ 227.1521.

4.4.18. Methyl (1S,5S*,6S*)-6-hydroxy-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***41***. The reaction was carried out according to standard procedure I, using benzylamine **28a** (60.0 mg, 0.207 mmol) to give the *title compound* **41** as a yellow oil (41.0 mg, 99%), which was used without further purification. ν_{max}(NaCl)/cm^{-1} 3368, 3350, 2924, 1722, 1255, 1073; δ_H(400 MHz; $CDCl_3$) 1.86–1.93 (3H, m, 9$_B$-H, 8$_A$-H & 9$_A$-H), 1.95–2.00 (1H, m, 5-H), 2.01–2.08 (2H, m, 7$_B$-H & 8$_B$-H), 2.26–2.31 (1H, m, 7$_A$-H), 2.84 (1H, dd, *J*=13.0, 2.0 Hz, 4$_A$-H), 3.08 (1H, dd, *J*=12.4, 2.0 Hz, 2$_A$-H), 3.33 (1H, d, *J*=12.4 Hz, 2$_B$-H), 3.52 (1H, d, *J*=13.0 Hz, 4$_B$-H), 3.57–3.65 (2H, m, N–H & O–H), 3.67 (3H, s, OCH_3), 3.93–3.97 (1H, m, 6-H); δ_C(100 MHz; $CDCl_3$) 30.8 (C-7), 31.8 (C-8), 33.7 (C-9), 34.3 (C-5), 40.1 (C-1), 43.4 (C-4), 51.6 (C-2), 51.99 (OCH_3), 70.9 (C-6), 176.1 (C=O); *m*/*z* (ESI$^+$) 200 (M$^+$, 100%); found MH$^+$ 200.1280, $C_{10}H_{18}NO_3$ requires MH$^+$ 200.1281.

4.4.19. ((1S,5S*,6S*)-6-Methoxy-3-(3-phenylpropyl)-3-azabicyclo[3.3.1]nonan-1-yl)methanol* ***43***. To a solution of amine **40b** (0.174 g, 0.766 mmol) in DCM (3.4 mL) was added triethylamine (3.40 mL, 2.47 g, 24.4 mmol) and the mixture cooled to 0 °C with stirring. DMAP (9.0 mg, 0.077 mmol) was added, followed by hydrocinnamoyl chloride (0.136 mL, 0.155 g, 0.919 mmol), then the mixture was allowed to warm to room temperature and stirred for 22 h. The solvent was removed from the reaction mixture under reduced pressure and the residue was redissolved in ethyl acetate (30 mL). The organic residue was washed with 2 M HCl (2×30 mL) and the combined aqueous washings back-extracted with ethyl acetate (2×30 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (2×30 mL), then brine (30 mL), dried ($MgSO_4$), filtered and the solvent removed at reduced pressure to give a crude amide **42** (0.250 g, 0.682 mmol, 91%) as a colourless oil. To amide **42**, dissolved in dry THF (27 mL), was added lithium aluminium hydride (0.129 g, 3.41 mmol) and the mixture refluxed under an atmosphere of nitrogen for 21 h. The reaction was cooled to 0 °C and quenched by dropwise addition of water (50 mL), then the volatiles were removed under reduced pressure. Ethyl acetate (25 mL) was added and the residue filtered

through Celite, which was washed with water (25 mL), ethyl acetate (25 mL) and brine (25 mL). The filtrate was separated and the aqueous portion extracted with ethyl acetate (2×25 mL). The combined organic filtrate and extracts were extracted with 2 M hydrochloric acid (2×50 mL), then the acidic extracts basified with 4 M aqueous sodium hydroxide. The aqueous residue was extracted with ethyl acetate (3×50 mL), then the combined organic extracts washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the *title compound* **43** (0.160 g, 77%) as an orange oil, which was used without further purification. ν_{max}(NaCl)/cm^{-1} 3363, 2922, 1495, 1217, 1099; δ_H(300 MHz; $CDCl_3$) 1.23–1.28 (1H, m, 9_B-H), 1.30–1.44 (2H, m, 8_A-H & 9_A-H), 1.68–1.82 (4H, m, CH_2–OH, 8_B-H & $NCH_2CH_2CH_2Ar$), 1.87–1.95 (3H, m, 7_B-H, 2_A-H & 4_A-H), 2.09–2.30 (3H, m, 5-H & $NCH_2CH_2CH_2Ar$), 2.48–2.72 (3H, m, $NCH_2CH_2CH_2Ar$ & 7_A-H), 2.80 (1H, d, J=10.4 Hz, 2_B-H), 3.15 (1H, d, J=11.1 Hz, 4_B-H), 3.26 (2H, s, CH_2OH), 3.31–3.39 (4H, m, 6-H & OCH_3), 7.13–7.29 (5H, m, Ar–H); δ_C(75 MHz; $CDCl_3$) 27.7 (C-7), 28.9 ($NCH_2CH_2CH_2Ar$), 32.1 (C-8), 32.5 (C-5), 33.5 ($NCH_2CH_2CH_2Ar$), 34.7 (C-9), 35.3 (C-1), 52.8 (C-4), 55.7 (OCH_3), 58.0 ($NCH_2CH_2CH_2Ar$), 61.4 (C-2), 72.1 (CH_2OH), 81.7 (C-6) 125.5 (Ar–CH), 128.2 (Ar–CH), 128.5 (Ar–CH), 142.8 (Ar–C); m/z (EI) 303 (M^+, 10%), 272 (M–OCH_3, 24%) 198 (M–$CH_2CH_2C_6H_5$, 100%); found M^+ 303.2203, $C_{19}H_{29}NO_2$ requires M^+ 303.2198.

4.4.20. Methyl (1S,5S*,6S*)-3-acetyl-6-methoxy-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***44***. The reaction was carried out according to standard procedure J, using amine **40a** (0.151 g, 0.708 mmol), triethylamine (3.10 mL, 22.2 mmol), DMAP (8.70 mg, 70.8 μmol) and acetic anhydride (86.7 mg, 80 μL, 0.850 mmol), stirring for 42.5 h with the following additional workup. The residue was dissolved in ethyl acetate (15 mL) and washed with water (2×15 mL). The combined aqueous washings were back-extracted with ethyl acetate (15 mL), the combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the *title compound* **44** (0.113 g, 63%) as a pale yellow oil (3.2:1 mixture of rotomers), which was used without further purification. ν_{max}(NaCl)/cm^{-1} 2926, 1726, 1642, 1231, 1100; δ_H(400 MHz; $CDCl_3$) [*denotes minor rotomer] 1.51–1.68 (2H, m, 7_B-H, 7_B-H* & 8_A-H*), 1.77 (1H, tdd, J=13.5, 6.2, 2.6 Hz, 8_A-H), 1.85–2.21 (16H, m, 9_B-H, 9_B-H*, 9_A-H*, 7_A-H*, 7_A-H, 9_A-H, 8_B-H, 8_B-H*, CCH_3*, CCH_3, 5-H & 5-H*), 2.60 (1H, dd, J=13.6, 3.8 Hz, 4_A-H*), 2.81 (1H, dd, J=13.5, 3.0 Hz, 2_A-H), 3.05 (1H, dd, J=13.5, 3.0 Hz, 4_A-H), 3.31–3.45 (9H, m, 2_A-H*, OCH_3 ether*, 6-H*, OCH_3 ether & 6-H), 3.69 (3H, s, OCH_3 ester), 3.72 (3H, s, OCH_3 ester*), 3.96 (1H, d, J=13.2 Hz, 2_B-H*), 4.08 (1H, dd, J=13.5, 1.5 Hz, 4_B-H), 4.75 (1H, d, J=13.6 Hz, 4_B-H*), 4.83 (1H, dt, J=13.5, 1.5 Hz, 2_B-H); δ_C(100 MHz; $CDCl_3$) 22.2 (CCH_3 & CCH_3*), 26.0 (C-7*), 26.1 (C-7), 30.5 (C-5*), 31.6 (C-5), 31.7 (C-8), 32.1 (C-8*), 33.6 (C-9*), 33.9 (C-9), 39.7 (C-4*), 40.6 (C-1 & C-1*), 44.8 (C-4), 47.2 (C-2), 52.0 (OCH_3), 52.2 (OCH_3*), 52.4 (C-2*), 55.8 (OCH_3*), 55.9 (OCH_3), 78.9 (C-6), 79.4 (C-6*), 170.0 (C=O* & C=O), 175.7 (C=O & C=O*); m/z (ESI^+) 278 (MNa^+, 100%), 256 (MH^+, 34%); found MNa^+ 278.1368, $C_{13}H_{21}NNaO_4$ requires MNa^+ 278.1363.

4.4.21. Methyl (1S,5S*,6S*)-3,6-acetyl-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***45***. The reaction was carried out according to standard procedure J, using amine **41** (0.137 g, 0.688 mmol) stirring for 23 h to give the *title compound* **45** (0.193 g, 99%) as an orange oil (1.8:1 mixture of rotomers), which was used without further purification. ν_{max}(NaCl)/cm^{-1} 2941, 1724, 1666, 1643, 1235, 1078; δ_H(400 MHz; $CDCl_3$) [*denotes minor rotomer] 1.72–1.95 (5H, m, 7_B-H, 7_B-H*, 8_A-H, 7_A-H* & 7_A-H), 1.96–2.05 (6H, m, 9_A-H*, 8_A-H*, 9_A-H, 9_B-H, 8_B-H* & 9_B-H*), 2.06–2.23 (15H, m, 8_B-H, 2× CCH_3*, 2× CCH_3, 5-H & 5-H*), 2.65 (1H, d, J=13.7, 3.4 Hz, 4_A-H*), 2.84 (1H, dd, J=13.9, 1.9 Hz, 2_A-H), 3.14 (1H, dd, J=13.3, 2.8 Hz, 4_A-H), 3.35 (1H, dd, J=13.2, 1.9 Hz, 2_A-H*), 3.70 (3H, s, OCH_3), 3.73 (3H, s, OCH_3*), 3.99 (1H, d, J=13.2 Hz, 2_B-H*), 4.07 (1H, d, J=13.3 Hz, 4_B-H), 4.80 (1H, d, J=14.0, 1.3 Hz, 4_B-H*), 4.86 (1H, d, J=13.8 Hz, 2_B-H), 4.89–4.92 (1H, m, 6-H*), 4.99–5.02 (1H, m, 6-H); δ_C(100 MHz; $CDCl_3$) 21.2, 21.3, 22.2 & 22.3 (2× O=CCH_3 & 2× O=CCH_3*), 25.2 (C-7*), 25.5 (C-7), 31.3 (C-5*), 31.6 (C-8), 31.9 (C-8*), 32.0 (C-5), 33.6 (C-9*), 33.9 (C-9), 40.2 (C-4*), 40.3 (C-1), 40.7 (C-1*), 45.4 (C-4), 47.3 (C-2), 52.2 (OCH_3), 52.3 (OCH_3*), 52.5 (C-2*), 72.7 (C-6), 72.9 (C-6*), 169.7, 169.8, 170.0, & 170.7 (2× O=CCH_3 & 2× O=CCH_3*), 175.2 (O=$COCH_3$ & O=$COCH_3$*); m/z (ESI^+) 306 (MNa^+, 100%); found MNa^+ 306.1309, $C_{14}H_{21}NNaO_5$ requires MNa^+ 306.1312.

4.4.22. ((1S,5S*,6S*)-3-Ethyl-6-methoxy-3-azabicyclo[3.3.1]nonan-1-yl)methanol* ***46***. The reaction was carried out according to standard procedure K, using amide **44** (0.100 g, 0.392 mmol) and LAH (74.3 mg, 1.96 mmol), heating for 19 h to give the *title compound* **46** (68.5 mg, 82%) as a yellow oil, which was used without further purification. ν_{max}(NaCl)/cm^{-1} 3391, 2918, 1094, 1040; δ_H(400 MHz; $CDCl_3$) 1.07 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.22–1.26 (2H, m, 9_B-H & O–H), 1.35 (1H, tdd, J=13.4, 6.1, 2.3, 8_A-H), 1.49 (1H, d, J=12.3 Hz, 9_A-H), 1.69–1.72 (1H, m, 8_B-H), 1.85–1.88 (1H, m, 7_B-H), 1.98–2.08 (2H, m, 2_A-H & 4_A-H),2.16–2.18 (1H, m, 5-H), 2.33 (2H, m, NCH_2CH_3), 2.48–2.53 (1H, m, 7_A-H), 2.81 (1H, d, J=10.5 Hz, 2_B-H), 3.12 (1H, d, J=11.2 Hz, 4_B-H), 3.24–3.38 (6H, m, CH_2OH, 6-H & OCH_3); δ_C(100 MHz; $CDCl_3$) 12.1 (NCH_2CH_3), 27.2 (C-7), 31.9 (C-5), 32.0 (C-8), 34.0 (C-9), 35.2 (C-1), 52.1 (C-4), 52.8 (NCH_2CH_3), 55.8 (OCH_3), 60.4 (C-2), 71.8 (CH_2OH), 81.6 (C-6); m/z (EI) 213 (M^+, 12%), 182 (M–OCH_3, 100%); found M^+ 213.1731, $C_{12}H_{23}NO_2$ requires M^+ 213.1729.

4.4.23. ((1S,5S*,6S*)-3-Ethyl-6-hydroxy-3-azabicyclo[3.3.1]nonan-1-yl)methanol* ***47***. The reaction was carried out according to standard procedure K, using amide **45** (0.193 g, 0.681 mmol) and LAH (0.129 g, 3.406 mmol), heating for 21 h to give the *title compound* **47** (78.0 mg, 58%) as a yellow oil, which was used without further purification. ν_{max}(NaCl)/cm^{-1} 3344, 2918, 1111, 1049; δ_H(400 MHz; $CDCl_3$) 1.05 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.24–1.44 (5H, m, 2× O–H, 9_B-H, 9_A-H & 8_A-H), 1.68–1.71 (1H, m, 8_B-H), 1.84–1.87 (1H, m, 7_B-H), 1.91 (1H, dd, J=10.4, 2.4 Hz, 2_A-H), 1.94–1.98 (2H, m, 4_A-H & 5-H), 2.25 (2H, m, NCH_2CH_3), 2.56–2.61 (1H, m, 7_A-H), 2.82 (1H, d, J=10.4 Hz, 2_B-H), 3.22 (1H, d, J=10.0 Hz, 4_B-H), 3.26 (2H, s, CH_2OH), 3.82–3.85 (1H, m, 6-H); δ_C(100 MHz; $CDCl_3$) 12.4 (NCH_2CH_3), 30.8 (C-7), 32.0 (C-8), 34.7 (C-9), 34.9 (C-1), 36.0 (C-5), 52.3 (C-4), 52.7 (NCH_2CH_3), 60.1 (C-2), 71.8 (CH_2OH), 72.7 (C-6); m/z (ESI^+) 200 (MH^+, 100%); found MH^+ 200.1645, $C_{11}H_{22}NO_2$ requires MH^+ 200.1645.

4.4.24. ((1″S,5″S*,6″S*)-6″-Methoxy-3″-(3-phenylpropyl)-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxo-2′,5′-dihydro-1′H-pyrrol-1′-yl)benzoate*. The reaction was carried out according to standard procedure G, using alcohol **43** (0.160 g, 0.527 mmol) and acid **33** (0.244 g, 1.06 mmol) heating for 19 h, with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give the *title compound* (0.170 g, 62%) as a yellow oil. R_f 0.38; ν_{max}(NaCl)/cm^{-1} 2924, 1784, 1713, 1645, 1494, 1259, 1106; δ_H(400 MHz; $CDCl_3$) 1.32 (1H, d, J=12.4 Hz, $9''_B$-H), 1.37–1.49 (2H, m, $8''_A$-H & $9''_A$-H), 1.72–1.82 (3H, m, $NCH_2CH_2CH_2Ar$ & $8''_B$-H), 1.86–1.97 (3H, m, $7''_B$-H, $2''_A$-H & $4''_A$-H), 2.11–2.13 (1H, m, $5''$-H), 2.14 (3H, d, J=1.8 Hz, C3′–CH_3), 2.21 (2H, m, $NCH_2CH_2CH_2Ar$), 2.57–2.72 (3H, m, $NCH_2CH_2CH_2Ar$ & $7''_A$-H), 2.83 (1H, d, J=10.4 Hz, $2''_B$-H), 3.17 (1H, d, J=11.0 Hz, $4''_B$-H), 3.33–3.40 (4H, m, OCH_3 & $6''$-H), 3.86 (2H, s, C1″–CH_2O–), 6.47 (1H, q, J=1.8 Hz, 4′-H), 7.13–7.28 (5H, m, Ar–H), 7.30 (1H, dd, J=7.8, 1.2 Hz, 3-H) 7.50 (1H, td, J=7.8, 1.2 Hz, 5-H), 7.64 (1H, td, J=7.8, 1.6 Hz, 4-H), 8.07 (1H, dd, J=7.9, 1.6 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 11.1 (C3′–CH_3), 27.5 (C-7″), 28.8 ($NCH_2CH_2CH_2Ar$), 32.2 (C-5″), 32.3 (C-8″), 33.3 ($NCH_2CH_2CH_2Ar$), 34.1 (C-1″), 34.8 (C-9″), 52.3 (C-4″), 55.6 (OCH_3),

57.8 ($NCH_2CH_2CH_2Ar$), 61.4 (C-2″), 73.0 (C1″−CH_2O), 81.1 (C-6″), 125.4 (Ar−CH), 127.8 (C-4′), 127.9 (C-1), 128.1 (Ar−CH), 128.4 (Ar−CH), 128.8 (C-5), 130.3 (C-3), 131.2 (C-6), 131.7 (C-2), 133.1 (C-4), 142.6 (Ar−C), 146.1 (C-3′), 164.6 (CO_2), 169.6 (C-5′), 170.6 (C-2′); *m/z* (EI) 516 (M^+, 6%), 411 (M−$CH_2CH_2C_6H_5$, 41%), 214 ($C_5H_4O_2N$-C_6H_4CO, 100%); found M^+ 516.2621, $C_{31}H_{36}N_2O_5$ requires M^+ 516.2624.

4.4.25. ((1″S,5″S*,6″S*)-6″-Methoxy-3″-(3-phenylpropyl)-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxopyrrolidin-1′-yl)benzoate* ***48***. The reaction was carried out according to standard procedure H, using ((1″*S**,5″*S**,6″*S**)-6″-methoxy-3″-(3-phenylpropyl)-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxo-2′,5′-dihydro-1′*H*-pyrrol-1′-yl)benzoate (77.0 mg, 0.149 mmol), stirring for 8 h, with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give the *title compound* **48** (75.0 mg, 97%) as a yellow oil. R_f 0.51; ν_{max}(NaCl)/cm^{-1} 2931, 1777, 1710, 1494, 1261, 1082; δ_H(400 MHz; $CDCl_3$) 1.36 (1H, d, *J*=12.1 Hz, 9″$_B$-H), 1.41−1.53 (5H, m, 8″$_A$-H, C3′−*CH*$_3$ & 9″$_A$-H), 1.73−1.86 (3H, m, $NCH_2CH_2CH_2$ & 8″$_B$-H), 1.87−2.00 (3H, m, 7″$_B$-H, 4″$_A$-H & 2″$_A$-H), 2.12−2.18 (1H, m, 5″H), 2.23 (2H, m, $NCH_2CH_2CH_2$), 2.48−2.52 (1H, m, 4′$_A$-H), 2.60−2.70 (3H, m, $NCH_2CH_2CH_2$ & 7″$_A$-H), 2.86 (1H, d, *J*=10.5 Hz, 2″$_B$-H), 3.02−3.14 (2H, m, 3-′H & 4′$_B$-H), 3.18 (1H, d, *J*=11.0 Hz, 4″$_B$-H), 3.35−3.42 (4H, m, OCH_3 & 6″-H), 3.87 (2H, br s, C1″−CH_2O−), 7.14−7.29 (6H, m, Ar−H & 3-H) 7.53 (1H, t, *J*=7.7 Hz, 5-H), 7.67 (1H, td, *J*=7.7, 1.3 Hz, 4-H), 8.11 (1H, dd, *J*=7.7, 1.3 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 16.3 (C3′−*CH*$_3$), 27.6 (C-7″), 28.9 ($NCH_2CH_2CH_2$), 32.3 (C-5″), 32.4 (C-8″), 33.5 ($NCH_2CH_2CH_2$), 34.3 (C-1″), 34.9 (C-9″), 35.4 (C-3′), 37.0 (C-4′), 52.4 (C-4″), 55.8 (OCH_3), 57.9 ($NCH_2CH_2CH_2$), 61.6 (C-2″), 73.0 (C1″−CH_2O), 81.3 (C-6″), 125.5 (Ar−CH), 127.3 (C-1), 128.2 (Ar−CH), 128.5 (Ar−CH), 129.4 (C-5), 129.9 (C-3), 131.4 (C-6), 132.9 (C-2), 133.5 (C-4), 142.7 (Ar−C), 164.1 (CO_2), 175.9 (C-5′), 179.9 (C-2′); *m/z* (ESI^+) 519 (MNH^+, 100%); found MH^+ 519.2852, $C_{31}H_{39}N_2O_5$ requires M^+ 519.2853.

4.4.26. ((1″S,5″S*,6″S*)-3″-Ethyl-6″-methoxy-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxo-2′,5′-dihydro-1′H-pyrrol-1′-yl)benzoate.* The reaction was carried out according to standard procedure G, using alcohol **46** (67.0 mg, 0.314 mmol) and acid **33** (0.146 g, 0.628 mmol), heating for 20 h, with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give the *title compound* (44.0 mg, 33%) as a pale yellow oil. R_f 0.41; ν_{max}(NaCl)/cm^{-1} 2927, 1784, 1714, 1644, 1494, 1454, 1260, 1105; δ_H(400 MHz; $CDCl_3$) 1.03 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 1.32 (1H, d, *J*=11.4 Hz, 9″$_B$-H), 1.36−1.49 (2H, m, 8″$_A$-H & 9″$_A$-H), 1.74−1.88 (2H, m, 8″$_B$-H & 7″$_B$-H), 1.90−1.95 (2H, m, 4″$_A$-H & 2″$_A$-H), 2.11−2.15 (1H, m, 5″-H), 2.17 (3H, d, *J*=1.8 Hz, C3′−*CH*$_3$), 2.20−2.30 (2H, m, NCH_2CH_3), 2.59−2.67 (1H, m, 7″$_A$-H), 2.85 (1H, d, *J*=10.6 Hz, 2″$_B$-H), 3.15 (1H, d, *J*=11.0 Hz, 4″$_B$-H), 3.31−3.39 (4H, m, OCH_3 & 6″-H), 3.86 (2H, s, C1″−CH_2O−), 6.51 (1H, q, *J*=1.8 Hz, 4′-H), 7.31 (1H, dd, *J*=7.8, 1.1 Hz, 3-H) 7.52 (1H, td, *J*=7.8, 1.1 Hz, 5-H), 7.65 (1H, td, *J*=7.8, 1.6 Hz, 4-H), 8.09 (1H, dd, *J*=7.8, 1.6 Hz, 6-H); δ_C(400 MHz; $CDCl_3$) 11.2 (C3′−*CH*$_3$), 12.4 (NCH_2CH_3), 27.5 (C-7″), 32.1 (C-5″), 32.4 (C-8″), 34.2 (C-1″), 34.9 (C-9″), 52.2 (C-4″), 52.6 (NCH_2CH_3), 55.8 (OCH_3), 61.0 (C-2″), 73.2 (C1″−CH_2O), 81.5 (C-6″), 127.9 (C-4′ & C-1), 129.0 (C-5), 130.4 (C-3), 131.3 (C-6), 131.8 (C-2), 133.2 (C-4), 146.2 (C-3′), 164.7 (CO_2), 169.7 (C-5′), 170.8 (C-2′); *m/z* (EI) 426 (M^+, 14%), 411 (M−CH_3, 23%), 395 (M−OCH_3, 100%); found M^+ 426.2157, $C_{24}H_{30}N_2O_5$ requires M^+ 426.2155.

4.4.27. ((1″S,5″S*,6″S*)-3″-Ethyl-6″-methoxy-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxopyrrolidin-1′-yl)benzoate* ***49***. The reaction was carried out according to standard procedure H, using ((1″*S**,5″*S**,6″*S**)-3″-ethyl-6″-methoxy-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxo-2′,5′-dihydro-1′*H*-pyrrol-1′-yl)benzoate (20.0 mg, 47.0 μmol), stirring for 24 h, with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give the *title compound* **49** (19.0 mg, 95%) as a yellow oil. R_f 0.35; ν_{max}(NaCl)/cm^{-1} 2928, 1777, 1713, 1492, 1454, 1261, 1188; δ_H(300 MHz; $CDCl_3$) 1.03 (3H, t, *J*=7.1 Hz, NCH_2CH_3), 1.35 (1H, d, *J*=13.2 Hz, 9″$_B$-H), 1.39−1.53 (5H, m, 8″$_A$-H, C3′−*CH*$_3$ & 9″$_A$-H), 1.76−1.90 (2H, m, 8″$_B$-H & 7″$_B$-H), 1.91−1.98 (2H, m, 4″$_A$-H & 2″$_A$-H), 2.12−2.16 (1H, m, 5″-H), 2.26 (2H, m, NCH_2CH_3), 2.45−2.71 (2H, m, 4′$_A$-H & 7″$_A$-H), 2.88 (1H, d, *J*=10.7 Hz, 2″$_B$-H), 2.97−3.18 (3H, m, 4″$_B$-H, 4′$_B$-H & 3′-H), 3.31−3.40 (4H, m, OCH_3 & 6″-H), 3.87 (2H, s, C1″−CH_2O−), 7.26 (1H, dd, *J*=7.7, 1.2 Hz, 3-H) 7.53 (1H, td, *J*=7.7, 1.2 Hz, 5-H), 7.67 (1H, td, *J*=7.7, 1.5 Hz, 4-H), 8.11 (1H, dd, *J*=7.7, 1.5 Hz, 6-H); δ_C(75 MHz; $CDCl_3$) 12.4 (NCH_2CH_3), 16.5 (C3′−*CH*$_3$), 27.6 (C-7″), 32.1 (C-5″), 32.5 (C-8″), 34.3 (C-1″), 35.0 (C-9″), 35.3 (C-3′), 37.0 (C-4′), 52.2 (C-4″), 52.6 (NCH_2CH_3), 55.9 (OCH_3), 61.1 (C-2″), 73.1 (C1″−CH_2O), 81.5 (C-6″), 129.4 (C-5), 129.7 (C-1), 129.9 (C-3), 131.4 (C-6), 132.9 (C-2), 133.4 (C-4), 164.0 (CO_2), 175.9 (C-5′), 179.9 (C-2′); *m/z* (EI) 428 (M^+, 9%), 397 (M−OCH_3, 100%), 216 ($C_5H_6O_2NC_6H_4CO$, 14%), 196 (40%); found M^+ 428.2313, $C_{24}H_{32}N_2O_5$ requires M^+ 428.2311.

4.4.28. ((1″S,5″S*,6″S*)-3″-Ethyl-6″-hydroxy-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxo-2′,5′-dihydro-1′H-pyrrol-1′-yl)benzoate and (1″S*,5″S*,6″S*)-3″-ethyl-1″-(((2‴-(3‴-methyl-2‴″,5‴″-dioxo-2‴″,5‴″-dihydro-1‴″H-pyrrol-1‴″-yl)benzoyl)oxy)methyl)-3″-azabicyclo[3.3.1]nonan-6″-yl 2-(3′-methyl-2′,5′-dioxo-2′,5′-dihydro-1′H-pyrrol-1′-yl)benzoate.* The reaction was carried out according to standard procedure G, using alcohol **47** (50.0 mg, 0.251 mmol) and acid **33** (72.5 mg, 0.314 mmol), heating for 20 h, with hexane/ethyl acetate 1:3 as the solvent for flash chromatography to give (i) (1″*S**,5″*S**,6″*S**)-3″-*benzyl*-1″-(((2″-(3‴″-*methyl*-2‴″,5‴″-*dioxo*-2‴″,5‴″-*dihydro*-1‴″*H*-*pyrrol*-1‴″-*yl*)*benzoyl*)*oxy*)*methyl*)-3″-*azabicyclo*[3.3.1]*nonan*-6″-*yl* 2-(3′-*methyl*-2′,5′-*dioxo*-2′,5′-*dihydro*-1′*H*-*pyrrol*-1′-*yl*)*benzoate* (10.0 mg, 6%) as a yellow oil. R_f 0.60; ν_{max}(NaCl)/cm^{-1} 2929, 1785, 1711, 1644, 1494, 1259, 1109, 1085; δ_H(400 MHz; $CDCl_3$) 1.06 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 1.47−1.56 (3H, m, 9″$_B$-H, 9″$_A$-H & 8″$_A$-H), 1.78−1.90 (2H, m, 8″$_B$-H & 7″$_B$-H), 1.96−2.00 (2H, m, 2″$_A$-H & 4″$_A$-H), 2.14−2.18 (7H, m, 5″-H, C3′−CH_3 & C3‴″−CH_3), 2.22−2.34 (2H, m, NCH_2CH_3), 2.77−2.92 (2H, m, 7″$_A$-H & 2″$_B$-H), 3.15 (1H, d, *J*=9.6 Hz, 4″$_B$-H), 3.87 (2H, s, C1″−CH_2O−), 5.08−5.11 (1H, m, 6″-H), 6.49−6.52 (2H, m, 4′-H & 4‴″-H), 7.28−7.33 (2H, m, 3-H & 3‴-H), 7.48−7.55 (2H, m, 5-H & 5‴-H), 7.61−7.69 (2H, m, 4-H & 4‴-H), 8.06−8.11 (2H, m, 6-H & 6‴-H); δ_C(100 MHz; $CDCl_3$) 11.2 (C3′−*CH*$_3$ & C3‴″−*CH*$_3$), 12.4 (NCH_2CH_3), 26.8 (C-7″), 32.3 (C-8″), 33.0 (C-5″), 33.9 (C-1″), 34.9 (C-9″), 52.4 (NCH_2CH_3), 52.7 (C-4″), 61.0 (C-2″), 72.8 (C1″−CH_2O), 76.1 (C-6″), 127.9 (C-4′, C-4‴″, C-1 & C-1‴), 128.9 & 129.0 (C-5‴ & C-5), 130.2 & 130.5 (C-3‴ & C-3), 131.3 & 131.5 (C-6‴ & C-6), 131.6 & 131.9 (C-2‴ & C-2), 133.0 & 133.3 (C-4‴ & C-4),146.2 & 146.3 (C-3′ & C-3‴″), 164.5 (CO_2), 169.8 (C-5′ & C-5‴″), 170.7 (C-2′ & C-2‴″); *m/z* (ESI^+) 626 (MH^+, 100%)l found MH^+ 626.2510, $C_{35}H_{36}N_3O_8$ requires MH^+ 626.2497 and (ii) ((1″*S**,5″*,6″*S**)-3″-*benzyl*-6″-*hydroxy*-3″-*azabicyclo*[3.3.1]*nonan*-1″-*yl*)*methyl* 2-(3′-*methyl*-2′,5′-*dioxo*-2′,5′-*dihydro*-1′*H*-*pyrrol*-1′-*yl*)*benzoate* (26.5 mg, 26%) as an orange oil. R_f 0.03; ν_{max}(NaCl)/cm^{-1} 3337, 2928, 1784, 1708, 1645, 1494,1259, 1108, 1083; δ_H(400 MHz; $CDCl_3$) 1.05 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 1.35−1.48 (4H, m, 9″$_A$-H, 9″$_B$-H, 8″$_A$-H & O−H), 1.76−1.86 (2H, m, 8″$_B$-H & 7″$_B$-H), 1.93−2.00 (3H, m, 5″-H, 4″$_A$-H & 2″$_A$-H), 2.18 (3H, d, *J*=2.0 Hz, C3′−*CH*$_3$), 2.23−2.30 (2H, m, NCH_2CH_3), 2.58−2.63 (1H, m, 7″$_A$-H), 2.86 (1H, d, *J*=10.0 Hz, 2″$_B$-H), 3.25 (1H, d, *J*=10.0 Hz, 4″$_B$-H), 3.82−3.91 (3H, m, 6″-H & C1″−CH_2O−), 6.51 (1H, d, *J*=2.0 Hz, 4′-H), 7.31 (1H, d, *J*=7.8 Hz, 3-H) 7.52 (1H, t, *J*=7.8, 5-H), 7.66 (1H, t, *J*=7.8 Hz, 4-H), 8.08 (1H, d, *J*=7.8 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 11.2 (C3′−*CH*$_3$), 12.4 (NCH_2CH_3), 30.8 (C-7″), 32.4 (C-8″), 33.9 (C-1″), 34.9 (C-9″), 35.8 (C-5″), 51.9 (C-4″), 52.6 (NCH_2CH_3), 61.2 (C-2″), 72.4 (C-6″), 73.1 (C1″−CH_2O), 127.9 (C-1 & C-4′), 129.0 (C-5), 130.4 (C-3), 131.3 (C-6), 131.8 (C-2), 133.3 (C-4), 146.2 (C-3′), 164.7 (CO_2),

169.7 (C-5′), 170.8 (C-2′); *m*/*z* (ESI$^+$) 413 (MH$^+$, 100%); found MH$^+$ 413.2070, $C_{23}H_{29}N_2O_5$ requires MH$^+$ 413.2071.

4.4.29. ((1″S,5″S*,6″S*)-3″-Ethyl-6″-hydroxy-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxopyrrolidin-1′-yl)benzoate* ***50***. The reaction was carried out according to standard procedure H, using ((1″*S**,5″*S**,6″*S**)-3″-benzyl-6″-hydroxy-3″-azabicyclo[3.3.1]nonan-1″-yl)methyl 2-(3′-methyl-2′,5′-dioxo-2′,5′-dihydro-1′*H*-pyrrol-1′-yl)benzoate (14.5 mg, 35.1 μmol), stirring for 4 h, with DCM/methanol 9:1 as the solvent for flash chromatography to give the *title compound* **50** (12.5 mg, 86%) as a yellow oil. R_f 0.40; ν_{max}(NaCl)/cm^{-1} 3408, 2925, 1795, 1714, 1455, 1262, 1188; δ_H(400 MHz; $CDCl_3$) 1.40–1.52 (6H, m, 9″$_B$-H, C3′–CH_3, 8″$_A$-H & 9″$_A$-H), 1.62 (1H, br s, O–H), 1.80–1.89 (2H, m, 8″$_B$-H & 7″$_B$-H), 1.97–2.01 (3H, m, 4″$_A$-H, 2″$_A$-H & 5″-H), 2.28 (2H, qd, *J*=7.1, 1.3 Hz, NCH_2CH$_3$), 2.48–2.69 (2H, m, 4′$_A$-H & 7″$_A$-H), 2.89 (1H, d, *J*=10.5 Hz, 2″$_B$-H), 3.02–3.13 (2H, m, 4′$_B$-H & 3′-H), 3.26 (1H, d, *J*=10.4 Hz, 4″$_B$-H), 3.84–3.88 (3H, m, 6″-H & C1″–CH_2O–), 7.26 (1H, dd, *J*=7.8, 1.1 Hz, 3-H), 7.54 (1H, td, *J*=7.7, 0.9 Hz, 5-H), 7.67 (1H, td, *J*=7.6, 1.6 Hz, 4-H), 8.11 (1H, d, *J*=7.6 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 12.3 (CH_2, NCH$_2$*C*H$_3$), 16.3 & 16.5 (CH_3, br, C3′–*C*H$_3$), 30.7 (CH_2, C-7″), 32.4 (CH_2, C-8″), 34.0 (quat., C-1″), 34.8 (CH_2, C-9″), 35.2 & 35.4 (CH, br, C-3′), 35.7 (CH, C-5″), 37.0 (CH_2, C-4′), 51.9 (CH_2, C-4″), 52.8 (CH_2, N*C*H$_2$CH$_3$), 61.1 (CH_2, C-2″), 72.3 (CH, C-6″), 72.9 (CH_2, C1″-*C*H$_2$O), 127.0 & 127.1 (quat., br, C-1), 129.4 (C-5), 129.9 (CH, C-3), 131.3 (CH, br, C-6), 132.9 (quat., C-2), 133.5 (CH,C-4), 164.1 & 164.2 (quat., C=O ester), 175.9 & 176.0 (quat., br, C-5′), 179.9 (quat., C-2′); *m*/*z* (ESI$^+$) found MH$^+$ 415.2233, $C_{23}H_{31}N_2O_5$ requires MH$^+$ 415.2227.

4.5. Synthesis of analogues of other *Delphinium* and *Aconitum* alkaloids

4.5.1. (1S,5S*,6S*)-3-Benzyl-6-methoxy-1-methoxymethyl-3-azabicyclo[3.3.1]nonane* ***51***. The reaction was carried out according to standard procedure E, using sodium hydride (51.0 mg, 1.29 mmol), diol **37** (84.0 mg, 0.321 mmol) and iodomethane (0.20 mL, 0.457 g, 3.21 mmol), stirring for 3 days at 60 °C, with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give the *title compound* **51** (54.0 mg, 58%) as a yellow oil. R_f 0.67; ν_{max}(NaCl)/cm^{-1} 2924, 1452, 1273, 1194, 1102; δ_H(400 MHz; $CDCl_3$) 1.29 (1H, dd, *J*=12.6, 2.0 Hz, 9$_B$-H), 1.38 (1H, tdd, *J*=13.4, 6.3, 2.4 Hz, 8$_A$-H), 1.42 (1H, ddd, *J*=12.6, 3.6, 3.6 Hz, 9$_A$-H), 1.63–1.67 (1H, m, 8$_B$-H), 1.88–1.94 (2H, m, 7$_B$-H & 2$_A$-H), 2.06 (1H, dd, *J*=10.9, 2.9 Hz, 4$_A$-H), 2.09–2.18 (1H, m, 5-H), 2.68 (1H, d, *J*=10.6 Hz, 2$_B$-H), 2.70–2.80 (1H, m, 7$_A$-H), 2.93 (2H, s, CH_2OCH$_3$), 3.16 (1H, d, *J*=10.9 Hz, 4$_B$-H), 3.22 (1H, d, *J*=13.4 Hz, NCH_AH$_B$Ar), 3.25 (3H, s, CH$_2$OCH_3), 3.33–3.40 (4H, m, C$_6$OCH_3 & 6-H), 3.57 (1H, d, *J*=13.4 Hz, NCH$_A$*H*$_B$Ar), 7.20–7.32 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 28.0 (C-7), 32.4 (C-5 & C-8), 34.8 (C-1), 35.0 (C-9), 53.3 (C-4), 55.7 (C$_6$O*C*H$_3$), 59.4 (CH$_2$O*C*H$_3$), 61.2 (C-2), 63.6 (N*C*H$_2$Ar), 81.7 (C-6), 82.1 (*C*H$_2$OCH$_3$), 126.5 (Ar–CH), 128.1 (Ar–CH), 128.6 (Ar–CH), 139.2 (Ar–C); *m*/*z* (FAB+) 290 (MH$^+$, 40%), 289 (M$^+$, 41%), 288 (M–H, 100%), 258 (M–OCH$_3$, 74%); found MH$^+$ 290.2118, $C_{18}H_{28}NO_2$ requires MH$^+$ 290.2120. In a second fraction was obtained alcohol **50** (20.0 mg, 23%).

4.5.2. (1S,5S*,6S*)-3-Ethyl-6-methoxy-1-methoxymethyl-3-azabicyclo[3.3.1]nonane* ***52***. The reaction was carried out according to standard procedure E, using sodium hydride (11.8 mg, 0.295 mmol), alcohol **46** (31.5 mg, 0.148 mmol) and iodomethane (46.0 μL, 0.105 g, 0.738 mmol), stirring for 3 days at room temperature, with 100% ethyl acetate as the solvent for flash chromatography to give the *title compound* **52** (10.0 mg, 30%) as a yellow oil. R_f 0.08; ν_{max}(NaCl)/cm^{-1} 2907, 1194, 1100, 1121; δ_H(300 MHz; $CDCl_3$) 1.02 (3H, t, *J*=7.2 Hz, NCH$_2$CH_3), 1.23–1.29 (1H, m, 9$_B$-H), 1.31–1.45 (2H, m, 8$_A$-H & 9$_A$-H), 1.70–1.73 (1H, m, 8$_B$-H), 1.79–1.94 (3H, m, 7$_B$-H, 2$_A$-H & 4$_A$-H),2.06–2.10 (1H, m, 5-H), 2.20–2.28 (2H, m, NCH_2CH$_3$), 2.58–2.64 (1H, m, 7$_A$-H), 2.81 (1H, d, *J*=10.5 Hz, 2$_B$-H), 2.98 (2H, s, CH_2OCH$_3$), 3.11 (1H, d, *J*=11.0 Hz, 4$_B$-H), 3.29–3.37 (7H, m, CH$_2$OCH_3, 6-H & C6–OCH$_3$); δ_C(75 MHz; $CDCl_3$) 12.5 (NCH$_2$*C*H$_3$), 27.8 (C-7), 32.4 (C-5), 32.6 (C-8), 34.8 (C-1), 35.2 (C-9), 52.6 (C-4), 52.7 (N*C*H$_2$CH$_3$), 55.8 (C6–O*C*H$_3$), 59.4 (CH$_2$O*C*H$_3$), 61.3 (C-2), 81.9 (C-6), 82.4 (*C*H$_2$OCH$_3$); *m*/*z* (ESI$^+$) 228 (MH$^+$, 100%); found MH$^+$ 228.1965, $C_{13}H_{26}NO_2$ requires MH$^+$ 228.1958.

4.5.3. (1S,5S*,6S*)-3-Benzyl-6-hydroxy-1-methoxymethyl-3-azabicyclo[3.3.1]nonane* ***53***. The reaction was carried out according to standard procedure E, using sodium hydride (14.0 mg, 0.354 mmol), diol **37** (31.0 mg, 0.118 mmol) and iodomethane (0.15 mL, 0.148 mmol, 1 M in THF), stirring for 16 h at 40 °C, with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give the *title compound* **53** (16.0 mg, 49%) as a pale yellow oil. R_f 0.38; ν_{max}(NaCl)/cm^{-1} 3375, 2920, 1657, 1452, 1266, 1194, 1101; δ_H(400 MHz; $CDCl_3$) 1.33 (1H, dd, *J*=12.6, 1.9 Hz, 9$_B$-H), 1.38–1.49 (3H, m, 8$_A$-H, 9$_A$-H & O–H), 1.70 (1H, tdd, *J*=13.6, 6.5, 2.3 Hz, 8$_B$-H), 1.87–1.92 (1H, m, 7$_B$-H), 1.93–1.97 (1H, m, 5-H), 1.98–2.06 (2H, m, 2$_A$-H & 4$_A$-H),2.68–2.73 (1H, m, 7$_A$-H), 2.77 (1H, d, *J*=10.8 Hz, 2$_B$-H), 2.96 (2H, s, CH_2OCH$_3$), 3.14 (1H, d, *J*=11.4 Hz, 4$_B$-H), 3.27 (3H, s, OCH$_3$), 3.36 (1H, d, *J*=13.2 Hz, NCH_AH$_B$Ar), 3.41 (1H, d, *J*=13.2 Hz, NCH$_A$*H*$_B$Ar), 3.80–3.85 (1H, m, 6-H), 7.20–7.31 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 31.4 (C-7), 32.5 (C-8), 34.6 (C-1), 35.1 (C-9), 36.1 (C-5), 52.7 (C-4), 59.4 (OCH$_3$), 61.9 (C-2), 63.7 (NCH$_2$Ar), 72.8 (C-6), 82.0 (*C*H$_2$OCH$_3$), 126.7 (Ar–CH), 128.2 (Ar–CH), 128.6 (Ar–CH), 139.2 (Ar–C); *m*/*z* (EI) 275 (M$^+$, 19%), 258 (M–OH, 41%), 91 (C$_6$H$_5$CH$_2$, 100%); found M$^+$ 275.1879, $C_{17}H_{25}NO_2$ requires M$^+$ 275.1885. In a second fraction was obtained diether **51** (10.0 mg, 29%).

4.5.4. (1S,5S*,6S*)-3-Ethyl-6-hydroxy-1-methoxymethyl-3-azabicyclo[3.3.1]nonane* ***54***. The reaction was carried out according to standard procedure E, using sodium hydride (27.0 mg, 0.675 mmol), diol **47** (45.0 mg, 0.226 mmol) and iodomethane (0.28 mL, 0.282 mmol, 1 M in THF), stirring for 5 h at room temperature, with 100% methanol as the solvent for flash chromatography to give the *title compound* **54** (17.5 mg, 36%) as an orange oil. R_f 0.47; ν_{max}(NaCl)/cm^{-1} 3364, 2923, 1258, 1194, 1099, 1064; δ_H(400 MHz; $CDCl_3$) 1.07 (3H, t, *J*=7.2 Hz, NCH$_2$CH_3), 1.25–1.44 (4H, m, O–H, 9$_B$-H, 8$_A$-H & 9$_A$-H), 1.71–1.73 (1H, m, 8$_B$-H), 1.79–1.83 (1H, m, 7$_B$-H), 1.91–1.98 (3H, m, 5-H, 2$_A$-H & 4$_A$-H), 2.22–2.30 (2H, m, NCH_2CH$_3$), 2.55–2.59 (1H, m, 7$_A$-H), 2.82 (1H, d, *J*=10.9 Hz, 2$_B$-H), 2.99 (2H, s, CH_2OCH$_3$), 3.23 (1H, d, *J*=10.8 Hz, 4$_B$-H), 3.31 (3H, s, OCH$_3$), 3.82–3.87 (1H, m, 6-H); δ_C(100 MHz; $CDCl_3$) 12.1 (NCH$_2$*C*H$_3$), 30.7 (C-7), 32.5 (C-8), 34.4 (C-9), 34.7 (C-1), 35.8 (C-5), 52.2 (C-4), 53.3 (N*C*H$_2$CH$_3$), 59.4 (OCH$_3$), 61.0 (C-2), 72.4 (C-6), 81.9 (*C*H$_2$OCH$_3$); *m*/*z* (ESI$^+$) 214 (MH$^+$, 100%); found MH$^+$ 214.1794, $C_{12}H_{24}NO_2$ requires MH$^+$ 214.1802. In a second fraction was obtained diether **52** (3.00 mg, 6%).

4.5.5. ((1S,5S*,6S*)-3-Benzyl-6-methoxy-3-azabicyclo[3.3.1]nonan-1-yl)methyl 4-methylbenzenesulfonate* ***55***. To a solution of alcohol **32** (50.0 mg, 0.182 mmol) in dry DCM (2.9 mL) under an atmosphere of nitrogen was added DMAP (2.00 mg, 18.2 μmol), *p*-toluenesulfonyl chloride (0.104 g, 0.545 mmol) and triethylamine (76 μL, 55.0 mg, 0.545 mmol) and the mixture stirred at room temperature for 3 days. The mixture was quenched by addition of water (3 mL), separated and the aqueous residue extracted with DCM (2×3 mL). The combined organics were washed with water (6 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate 1:1) to give the *title compound* **55** (62.5 mg, 80%) as a pale yellow oil. R_f 0.63; ν_{max}(NaCl)/cm^{-1}

2918, 1453, 1358, 1174, 1189, 1096, 960; δ_H(400 MHz; $CDCl_3$) 1.23–1.36 (2H, m, 9_B-H & 8_A-H),1.38–1.42 (1H, m, 9_A-H), 1.60 (1H, dd, J=10.9, 5.3 Hz, 8_B-H), 1.80 (1H, dd, J=10.7, 2.1 Hz, 2_A-H), 1.85–2.02 (1H, m, 7_B-H), 2.02 (1H, dd, J=10.5, 2.1 Hz, 4_A-H), 2.10–2.14 (1H, m, 5-H), 2.44 (3H, s, ArCH_3), 2.60 (1H, d, J=10.7 Hz, 2_B-H), 2.68–2.72 (1H, m, 7_A-H), 3.13–3.19 (2H, m, 4_B-H & NCH_AH$_B$Ar), 3.28–3.35 (4H, m, 6-H & OCH_3), 3.52–3.57 (3H, m, NCH$_A$$H_B$Ar & OCH_2), 7.19–7.32 (7H, m, Ar–H), 7.71 (2H, d, J=8.3 Hz, Ar–H); δ_C(100 MHz; $CDCl_3$) 21.5 (ArCH_3), 27.6 (C-7), 31.5 (C-8), 31.9 (C-5), 34.1 (C-9), 34.2 (C-1), 52.8 (C-4), 55.8 (OCH_3), 60.1 (C-2), 63.3 (NCH_2Ar), 77.6 (CH_2OS), 80.9 (C-6), 126.7 (Ar–CH), 127.8 (Ar–CH), 128.1 (Ar–CH), 128.6 (Ar–CH), 129.7 (Ar–CH), 132.7 (Ar–C), 139.2 (Ar–C), 144.6 (Ar–C); m/z (EI) 429 (M^+, 6%), 398 (M–OCH_3, 55%), 91 ($C_6H_5CH_2$, 100%); found M^+ 429.1976, $C_{24}H_{31}NO_4S$ requires M^+ 429.1974.

4.5.6. ((1S,5S*,6S*)-3-Ethyl-6-methoxy-3-azabicyclo[3.3.1]nonan-1-yl)methyl 4-methylbenzenesulfonate* ***56****.* To a solution of alcohol **46** (38.0 mg, 0.178 mmol) in dry DCM (2.85 mL) under an atmosphere of nitrogen was added DMAP (2.00 mg, 17.8 μmol), *p*-toluenesulfonyl chloride (0.102 g, 0.534 mmol) and triethylamine (75 μL, 54.0 mg, 0.534 mmol) and the mixture stirred at room temperature for 5 days. The mixture was quenched by addition of water (3 mL), separated and the aqueous residue extracted with DCM (2×3 mL). The combined organics were washed with brine (6 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate 1:1) to give the *title compound* **56** (26.0 mg, 40%) as an orange oil. R_f 0.14; ν_{max}(NaCl)/cm^{-1} 2924, 1455, 1361, 1176, 1189, 1096, 955; δ_H(300 MHz; $CDCl_3$) 0.98 (3H, t, J=7.2 Hz, NCH$_2$CH_3), 1.19–1.31 (2H, m, 9_B-H & 8_A-H), 1.36 (1H, ddd, J=12.4, 3.6, 3.6 Hz, 9_A-H), 1.66–1.71 (1H, m, 8_B-H), 1.76–1.81 (2H, m, 7_B-H & 2_A-H), 2.89 (1H, dd, J=11.1, 2.9 Hz, 4_A-H), 2.04–2.10 (1H, m, 5-H), 2.20 (2H, m, NCH_2CH$_3$), 2.45 (3H, s, ArCH_3), 2.54–2.61 (1H, m, 7_A-H), 2.73 (1H, d, J=10.6 Hz, 2_B-H), 3.09 (1H, d, J=11.1 Hz, 4_B-H), 3.25–3.29 (1H, m, 6-H), 3.32 (3H, s, OCH_3), 3.59–3.63 (2H, m, OCH_2), 7.35 (2H, d, J=8.1 Hz, Ar–H), 7.77 (2H, d, J=8.3 Hz, Ar–H); δ_C(75 MHz; $CDCl_3$) 12.3 (CH_3, NCH$_2$CH_3), 21.6 (ArCH_3), 27.4 (C-7), 31.9 (C-8), 32.0 (C-5), 34.3 (C-1), 34.4 (C-9), 52.2 (C-4), 52.4 (NCH_2CH$_3$), 55.9 (OCH_3), 60.3 (C-2), 78.1 (CH_2OS), 81.3 (C-6), 127.9 (Ar–CH), 129.8 (Ar–CH), 132.9 (Ar–C), 144.7 (Ar–C); m/z (ESI^+) 369 (MH^+, 100%); found MH^+ 368.1889, $C_{19}H_{30}NO_4S$ requires MH^+ 368.1890.

4.5.7. (1S,5S*,6S*)-3-Benzyl-6-methoxy-1-methyl-3-azabicyclo[3.3.1]nonane* ***57****.* To a suspension of lithium aluminium hydride (24.0 mg, 0.640 mmol) in dry THF (1.3 mL) at 0 °C under an atmosphere of nitrogen was added dropwise a solution of tosylate **55** (55.0 mg, 0.128 mmol) in dry THF (1.3 mL) and the mixture heated under reflux for 9 h, then allowed to cool to room temperature and stirred for a further 15 h. The mixture was then cooled to 0 °C and quenched with sodium hydroxide solution (1 M, five drops), dried ($MgSO_4$), filtered and the volatiles removed under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate 4:1) to give the *title compound* **57** (25.0 mg, 75%) as a pale yellow oil. R_f 0.54; ν_{max}(NaCl)/cm^{-1} 2903, 1494, 1454, 1150, 1103; δ_H(400 MHz; $CDCl_3$) 0.74 (3H, s, C1-CH_3), 1.25–1.43 (3H, m, 9_B-H, 8_A-H & 9_A-H), 1.56–1.61 (1H, m, 8_B-H), 1.74 (1H, dd, J=10.7, 2.3 Hz, 2_A-H), 1.82–1.89 (1H, m, 7_B-H), 2.03 (1H, dd, J=11.0, 2.9 Hz, 4_A-H), 2.09–2.12 (1H, m, 5-H), 2.58 (1H, d, J=10.7 Hz, 2_B-H),2.74–2.79 (1H, m, 7_A-H), 3.14–3.18 (2H, m, NCH_AH$_B$Ar & 4_B-H), 3.33–3.39 (4H, m, OCH_3 & 6-H), 3.58 (1H, d, J=13.4 Hz, NCH$_A$$H_B$Ar), 7.19–7.33 (5H, m, Ar–H); δ_C(100 MHz; $CDCl_3$) 28.4 (C-7), 28.7 (CCH_3), 30.5 (C-1), 33.1 (C-5), 37.1 (C-8), 40.0 (C-9), 53.1 (C-4), 55.8 (OCH_3), 63.6 (NCH_2Ar), 65.3 (C-2), 81.6 (C-6), 126.5 (Ar–CH), 128.1 (Ar–CH), 128.7 (Ar–CH), 139.3 (Ar–C); m/z (EI) 259 (M^+, 18%), 228 (M–OCH_3, 44%), 46 (100%); found M^+ 259.1943, $C_{17}H_{25}NO$ requires M^+ 259.1936.

4.5.8. (1S,5S*,6S*)-3-Ethyl-6-methoxy-1-methyl-3-azabicyclo[3.3.1]nonane* ***58****.* To a suspension of lithium aluminium hydride (13.5 mg, 0.354 mmol) in dry THF (1.15 mL) at 0 °C under an atmosphere of nitrogen was added dropwise a solution of tosylate **56** (26.0 mg, 70.7 μmol) in dry THF (1.15 mL) and the mixture heated under reflux for 2 h. The mixture was allowed to cool to room temperature and stirred for 20 h before being heated under reflux for a further 3.5 h, then stirred at room temperature for another 2 h. The mixture was then cooled to 0 °C and quenched with sodium hydroxide solution (1 M, five drops), dried ($MgSO_4$), filtered and the volatiles removed under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate 1:1) to give the *title compound* **58** (1.5 mg, 11%) as an orange oil. R_f 0.06; ν_{max}(NaCl)/cm^{-1} 2925, 1252, 1159; δ_H(400 MHz; $CDCl_3$) 1.02 (3H, t, J=7.2 Hz, NCH$_2$CH_3), 1.25–1.38 (3H, m, 9_B-H, 8_A-H & 9_A-H), 1.58–1.63 (1H, m, 8_B-H), 1.72–1.79 (2H, m, 2_A-H & 7_B-H), 1.86 (1H, dd, J=10.9, 2.9 Hz, 4_A-H), 2.04–2.10 (1H, m, 5-H), 2.15–2.24 (2H, m, NCH_2CH$_3$), 2.62–2.67 (1H, m, 7_A-H), 2.70 (1H, d, J=10.9 Hz, 2_B-H), 3.10 (1H, d, J=10.7 Hz, 4_B-H), 3.30–3.35 (4H, m, 6-H & OCH_3); δ_C(100 MHz; $CDCl_3$) 12.5 (NCH$_2$CH_3), 28.1 (C-7), 28.8 (CCH_3), 30.4 (C-1), 33.0 (C-5), 37.3 (C-8), 40.1 (C-9), 52.3 (C-4), 52.6 (NCH_2CH$_3$), 55.8 (OCH_3), 65.4 (C-2), 81.8 (C-6); m/z (ESI^+) 198 (MH^+, 100%); found MH^+ 198.1859, $C_{12}H_{24}NO$ requires MH^+ 198.1852.

4.5.9. ((1′S,5′S*,6′S*)-3′-Benzyl-6′-methoxy-3′-azabicyclo[3.3.1]nonan-1′-yl)methyl 2-aminobenzoate* ***60****.* The reaction was carried out according to standard procedure L, using alcohol **32** (50.0 mg, 0.182 mmol) and acid **59** (84.0 mg, 0.363 mmol), with hexane/ethyl acetate 2:1 as the solvent for flash chromatography to give the *title compound* **60** (62.5 mg, 87%) as a yellow oil. R_f 0.47; ν_{max}(NaCl)/cm^{-1} 3476, 3375, 2917, 1689, 1487, 1455, 1243, 1161, 1100; δ_H(400 MHz; $CDCl_3$) 1.40 (1H, d, J=13.7 Hz, $9'_B$-H), 1.46–1.51 (1H, m, $8'_A$-H),1.51–1.58 (1H, m, $9'_A$-H), 1.78 (1H, dd, J=11.6, 5.8 Hz, $8'_B$-H), 1.91–1.98 (1H, m, $7'_B$-H), 2.00 (1H, dd, J=10.8, 2.1 Hz, $2'_A$-H), 2.08 (1H, dd, J=10.8, 2.7 Hz, $4'_A$-H), 2.14–2.20 (1H, m, 5′-H), 2.75–2.84 (2H, m, $7'_A$-H & $2'_B$-H), 3.21 (1H, d, J=10.8 Hz, $4'_B$-H), 3.26 (1H, d, J=13.3 Hz, NCH_AH$_B$Ar), 3.35 (3H, s, OCH_3), 3.38–3.42 (1H, m, 6′-H), 3.59 (1H, d, J=13.3 Hz, NCH$_A$$H_B$Ar), 3.82–3.90 (2H, m, C1′–CH_2O–), 5.68 (2H, br s, NH_2), 6.59–6.64 (2H, m, 3-H & 5-H), 7.20–7.33 (6H, m, Ar–H & 4-H) 7.73 (1H, dd, J=8.0, 1.4 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 27.8 (C-7′), 32.2 (C-5′), 32.3 (C-8′), 34.3 (C-1′), 34.9 (C-9′), 53.0 (C-4′), 55.7 (OCH_3), 61.0 (C-2′), 63.4 (NCH_2Ar), 71.9 (C1′–CH_2O), 81.3 (C-6′), 110.7 (C-1), 116.2 & 116.6 (C-3 & C-5), 126.6 (Ar–CH), 128.1 (Ar–CH), 128.7 (Ar–CH), 130.9 (C-6), 134.0 (C-4), 138.8 (Ar–C), 150.5 (C-2), 167.8 (C=O); m/z (EI) 394 (M^+, 10%), 363 (M–OCH_3, 52%), 137 ($HOOCC_6H_4NH_2$, 64%), 120 ($OCC_6H_4NH_2$, 100%); found M^+ 394.2249, $C_{24}H_{30}N_2O_3$ requires M^+ 394.2256.

4.5.10. ((1′S,5′S*,6′S*)-3′-Ethyl-6′-methoxy-3′-azabicyclo[3.3.1]nonan-1′-yl)methyl 2-aminobenzoate* ***61****.* The reaction was carried out according to standard procedure L, using alcohol **46** (39.0 mg, 0.183 mmol) and acid **59** (85.0 mg, 0.366 mmol), heating for 20 h, with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give the *title compound* **61** (36.4 mg, 60%) as a pale yellow oil. R_f 0.21; ν_{max}(NaCl)/cm^{-1} 3473, 3364, 2926, 1687, 1488, 1455, 1293, 1242, 1160, 1097; δ_H(400 MHz; $CDCl_3$) 1.05 (3H, t, J=7.2 Hz, NCH$_2$CH_3), 1.38 (1H, d, J=13.6 Hz, $9'_B$-H), 1.43–1.49 (1H, m, $8'_A$-H), 1.54 (1H, dt, J=13.6, 3.3 Hz, $9'_A$-H), 1.82–1.90 (2H, m, $8'_B$-H & $7'_B$-H), 1.99–2.04 (2H, m, $4'_A$-H & $2'_A$-H), 2.14–2.19 (1H, m, 5′-H), 2.24–2.34 (2H, m, NCH_2CH$_3$), 2.60–2.66 (1H, m, $7'_A$-H), 2.92 (1H, d, J=10.8 Hz, $2'_B$-H), 3.16 (1H, d, J=11.2 Hz, $4'_B$-H), 3.34–3.41 (4H, m, OCH_3 & 6′-H), 3.92 (2H, s, C1′–CH_2O–), 5.68 (2H, br s, NH_2), 6.63–6.68 (2H, m, 3-H & 5-H), 7.27 (1H, td, J=7.6, 1.4 Hz, 4-H) 7.85

(1H, dd, J=7.8, 1.4 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 12.3 (NCH_2CH_3), 27.5 (C-7′), 32.0 (C-5′), 32.5 (C-8′), 34.2 (C-1′), 34.8 (C-9′), 52.1 (C-4′), 52.6 (NCH_2CH_3), 55.8 (OCH_3), 61.0 (C-2′), 72.2 (C1′–CH_2O), 81.5 (C-6′), 110.8 (C-1), 116.3 & 116.7 (C-3 & C-5), 131.0 (C-6), 134.1 (C-4), 150.5 (C-2), 168.0 (C=O); m/z (ESI^+) 333 (MH^+, 100%) found MH^+ 333.2181, $C_{19}H_{29}N_2O_3$ requires MH^+ 333.2173.

4.5.11. ((1′S,5′S*,6′S*)-3′-Benzyl-6′-hydroxy-3′-azabicyclo[3.3.1]nonan-1′-yl)methyl 2-aminobenzoate* ***62a*** *and (1″S*,5″S*,6″S*)-(6″-((2′-aminobenzoyl)oxy)-3″-benzyl-3″-azabicyclo[3.3.1]nonan-1″-yl) methyl 2-aminobenzoate* ***62b***. The reaction was carried out according to standard procedure L, using alcohol **37** (34.0 mg, 0.130 mmol) and acid **59** (38.0 mg, 0.163 mmol), heating for 21 h, with hexane/ethyl acetate 2:1 as the solvent for flash chromatography to give (i) *diester* **62b** (13.0 mg, 20%) as an orange oil. R_f 0.47; ν_{max}(NaCl)/cm^{-1} 3485, 3375, 2932, 1683, 1487, 1454, 1239, 1161, 1101; δ_H(400 MHz; $CDCl_3$) 1.56–1.71 (3H, m, 9′$_B$-H, 9′$_A$-H & 8′$_A$-H), 1.93–2.06 (3H, m, 8′$_B$-H, 4′$_A$-H & 7′$_B$-H), 2.15–2.20 (1H, m, 5′-H), 2.26 (1H, dd, J=10.8, 2.4 Hz, 2′$_A$-H), 3.01–3.17 (2H, m, 2′$_B$-H & 7′$_A$-H), 3.20–3.27 (2H, m, 4′$_B$-H & NCH_AH$_B$Ar), 3.68 (1H, d, J=13.2 Hz, NCH$_A$$H_B$Ar), 3.96 (2H, s, C1′–$CH_2$O–), 5.20–5.25 (1H, m, 6′-H), 5.63 & 5.72 (4H, br s, 2× NH_2), 6.53–6.72 (4H, m, 3″-H, 5″-H, 3-H & 5-H), 7.19–7.40 (7H, m, 4″-H, 4-H & Ar–H), 7.53 (1H, dd, J=8.1, 1.2 Hz, 6″-H), 7.84 (1H, dd, J=8.4, 1.5 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 27.3 (C-7′), 32.4 (C-8′), 33.3 (C-1′), 34.3 (C-5′), 35.0 (C-9′), 52.9 (C-4′), 62.5 (C-2′), 63.7 (NCH_2Ar), 71.9 (C1′–CH_2O), 74.3 (C-6′), 110.7 (C-1), 111.3 (C-1″), 116.2 (C-5″), 116.3 (C-5), 116.5 (C-3″), 116.7 (C-3), 126.8 (Ar–CH), 128.3 (Ar–CH), 128.8 (Ar–CH), 131.0 (C-6), 131.4 (C-6″), 133.9 (C-4″), 134.2 (C-4), 139.0 (Ar–C), 150.4 (C-2″), 150.6 (C-2), 167.4 (C6′–OC=O), 167.9 (C1′–CH_2OC=O); m/z (ESI^+) 500 (MH^+, 100%); found MH^+ 500.2541, $C_{30}H_{34}N_3O_4$ requires MH^+ 500.2544 and (ii) *ester* **62a** (20.0 mg, 40%) as a yellow oil. R_f 0.34; ν_{max}(NaCl)/cm^{-1} 3485 & 3373 (N–H), 2912, 1686, 1487 & 1454, 1241 (C–O), 1161 & 1104; δ_H(300 MHz; $CDCl_3$) 1.40 (1H, d, J=12.0 Hz, 9′$_B$-H), 1.50–1.60 (2H, m, 8′$_A$-H & 9′$_A$-H), 1.82 (1H, dd, J=13.6, 6.6 Hz, 8′$_B$-H), 1.90–1.98 (1H, m, 7′$_B$-H), 1.99–2.03 (1H, m, 5′-H), 2.04–2.12 (2H, m, 4′$_A$-H & 2′$_A$-H),2.72–2.80 (1H, m, 7′$_A$-H), 2.89 (1H, d, J=10.5 Hz, 2′$_B$-H), 3.19 (1H, d, J=11.4 Hz, 4′$_B$-H), 3.39 (1H, d, J=13.2 Hz, NCH_AH$_B$Ar), 3.45 (1H, d, J=13.2 Hz, NCH$_A$$H_B$Ar), 3.83–3.93 (3H, m, 6′-H & C1′–CH_2O–), 5.69 (2H, br s, NH_2), 6.60–6.66 (2H, m, 3-H & 5-H), 7.20–7.36 (6H, m, Ar–H & 4-H) 7.77 (1H, dd, J=8.4, 1.2 Hz, 6-H); δ_C(400 MHz; $CDCl_3$) 31.2 (C-7′), 32.4 (C-8′), 34.1 (C-1′), 35.0 (C-9′), 35.9 (C-5′), 52.4 (C-4′), 61.6 (C-2′), 63.6 (NCH_2Ar), 71.9 (C1′–CH_2O), 72.5 (C-6′), 110.7 (C-1), 116.2 & 116.7 (C-3 & C-5), 126.9 (Ar–CH), 128.2 (Ar–CH), 128.7 (Ar–CH), 131.0 (C-6), 134.1 (C-4), 138.9 (Ar–C), 150.5 (C-2), 167.9 (C=O); m/z (ESI^+) 381 (MH^+, 100%); found MH^+ 381.2181, $C_{23}H_{29}N_2O_3$ requires MH^+ 381.2173.

4.5.12. ((1′S,5′S*,6′S*)-3′-Ethyl-6′-hydroxy-3′-azabicyclo[3.3.1]nonan-1′-yl)methyl 2-aminobenzoate* ***63a*** *and (1″S*,5″S*,6″S*)-(6″-((2′-aminobenzoyl)oxy)-3″-ethyl-3″-azabicyclo[3.3.1]nonan-1″-yl) methyl 2-aminobenzoate* ***63b***. The reaction was carried out according to standard procedure L, using alcohol **47** (50.0 mg, 0.251 mmol) and acid **59** (73.0 mg, 0.314 mmol), heating for 21 h, with hexane/ethyl acetate 3:1 as the solvent for flash chromatography to give (i) *diester* **63b** (39.5 mg, 36%) as a yellow oil. R_f 0.80; ν_{max}(NaCl)/cm^{-1} 3480, 3372, 2929, 1683, 1487, 1454, 1237, 1160, 1100; δ_H(400 MHz; $CDCl_3$) 1.10 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.56–1.65 (3H, m, 9″$_B$-H, 9′$_A$-H & 8′$_A$-H), 1.90–1.98 (2H, m, 8′$_B$-H & 7′$_B$-H), 2.02 (1H, dd, J=11.2, 2.4 Hz, 4′$_A$-H), 2.08 (1H, dd, J=10.8, 2.4 Hz, 2′$_A$-H), 2.20–2.24 (1H, m, 5′-H), 2.27–2.35 (2H, m, NCH_2CH_3), 2.93–3.04 (2H, m, 2′$_B$-H & 7′$_A$-H), 3.32 (1H, d, J=10.8 Hz, 4′$_B$-H), 3.94 (2H, s, C1′–CH_2O–), 5.18–5.20 (1H, m, 6′-H), 5.74 (4H, br s, 2× NH_2), 6.64–6.70 (4H, m, 3″-H, 5″-H, 3-H & 5-H), 7.23–7.30 (2H, m, 4″-H & 4-H), 7.87 (1H, dd, J=8.4, 1.2 Hz, 6-H), 7.91 (1H, dd, J=8.2, 1.4 Hz, 6″-H); δ_C(100 MHz; $CDCl_3$) 12.5 (NCH_2CH_3), 27.0 (C-7′), 32.4 (C-8′), 33.3 (C-5′), 34.0 (C-1′), 35.0 (C-9′), 52.4 (NCH_2CH_3), 52.7 (C-4′), 61.6 (C-2′), 71.9 (C1′–CH_2O), 74.9 (C-6′), 110.6 (C-1″), 111.4 (C-1), 116.2, 116.3, 116.6, 116.7 (C-5″, C-5, C-3″ & C-3), 131.0 (C-6), 131.1 (C-6″),133.9 (C-4″), 134.1 (C-4), 150.4 (C-2″), 150.5 (C-2), 167.5 (C6′–OC=O), 167.9 (C1′–CH_2OC=O); m/z (ESI^+) 438 (MH^+, 100%); found MH^+ 438.2397, $C_{25}H_{32}N_3O_4$ requires MH^+ 438.2387 and (ii) *ester* **63a** (35.0 mg, 44%) as a yellow oil. R_f 0.15; ν_{max}(NaCl)/cm^{-1} 3471, 3374, 2919, 1684, 1487, 1454, 1241, 1161, 1103; δ_H(400 MHz; $CDCl_3$) 1.06 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.43 (1H, d, J=10.8 Hz, 9′$_B$-H), 1.46–1.56 (2H, m, 8′$_A$-H & 9′$_A$-H), 1.82–1.87 (2H, m, 8′$_B$-H & 7′$_B$-H), 1.97–2.04 (3H, m, 4′$_A$-H, 2′$_A$-H & 5-H), 2.28 (2H, q, J=7.2 Hz, NCH_2CH_3), 2.61–2.68 (1H, m, 7′$_A$-H), 2.93 (1H, d, J=10.4 Hz, 2′$_B$-H), 3.27 (1H, d, J=9.2 Hz, 4′$_B$-H), 3.85–3.92 (3H, m, 6′-H & C1′–CH_2O–), 5.73 (2H, br s, NH_2), 6.64–6.68 (2H, m, 3-H & 5-H), 7.27 (1H, td, J=7.6, 1.8 Hz, 4-H) 7.85 (1H, dd, J=8.2, 1.8 Hz, 6-H); δ_C(100 MHz; $CDCl_3$) 12.5 (NCH_2CH_3), 30.9 (C-7′), 32.5 (C-8′), 34.0 (C-1′), 35.1 (C-9′), 35.9 (C-5′), 52.0 (C-4′), 52.7 (NCH_2CH_3), 61.5 (C-2′), 72.1 (C1′–CH_2O), 72.5 (C-6′), 110.7 (C-1), 116.3 & 116.7 (C-3 & C-5), 131.0 (C-6), 134.1 (C-4), 150.5 (C-2), 168.5 (C=O); m/z (ESI^+) 319 (MH^+, 100%); found MH^+ 319.2024, $C_{18}H_{27}N_2O_3$ requires MH^+ 319.2016.

4.5.13. ((1′S,5′S*,6′S*)-3′-Benzyl-6′-methoxy-3′-azabicyclo[3.3.1]nonan-1′-yl)methyl 2-acetaminobenzoate* ***64***. The reaction was carried out according to standard procedure M, using anthranilate **60** (42.0 mg, 0.107 mmol), stirring for 4 days with hexane/ethyl acetate 2:1 as the solvent for flash chromatography to give the *title compound* **64** (28.3 mg, 61%) as a yellow oil. R_f 0.35; ν_{max}(NaCl)/cm^{-1} 3317, 3278, 2925, 1700, 1685, 1526, 1448, 1258, 1237, 1144, 1086; δ_H(400 MHz; $CDCl_3$) 1.42 (1H, d, J=13.9 Hz, 9′$_B$-H), 1.47–1.52 (1H, m, 8′$_A$-H), 1.56 (1H, ddd, J=13.9, 3.3, 3.3 Hz, 9′$_A$-H), 1.78–1.82 (1H, m, 8′$_B$-H), 1.94–2.02 (2H, m, 7′$_B$-H & 2′$_A$-H), 2.11 (1H, dd, J=11.0, 2.6 Hz, 4′$_A$-H), 2.19–2.24 (4H, m, 5′-H & CCH_3), 2.75–2.85 (2H, m, 7′$_A$-H & 2′$_B$-H), 3.21–3.28 (2H, m, 4′$_B$-H & NCH_AH$_B$Ar), 3.35–3.45 (4H, m, OCH_3 & 6′-H), 3.62 (1H, d, J=13.3 Hz, NCH$_A$$H_B$Ar), 3.91 (2H, br s, C1′–CH_2O–), 7.05 (1H, td, J=8.0, 1.0 Hz, 5-H), 7.23–7.32 (5H, m, Ar–H), 7.54 (1H, td, J=8.0, 1.2 Hz, 4-H), 7.87 (1H, dd, J=8.0, 1.2 Hz, 6-H), 8.69 (1H, dd, J=8.0, 1.0 Hz, 3-H), 11.02 (1H, br s, N–H); δ_C(100 MHz; $CDCl_3$) 25.5 (CCH_3), 27.8 (C-7′), 32.2 (C-5′), 32.3 (C-8′), 34.4 (C-1′), 34.9 (C-9′), 53.0 (C-4′), 55.8 (OCH_3), 60.8 (C-2′), 63.4 (NCH_2Ar), 72.9 (C1′–CH_2O), 81.2 (C-6′), 114.8 (C-1), 120.3 (C-3), 122.4 (C-5), 126.7 (Ar–CH), 128.1 (Ar–CH), 128.7 (Ar–CH), 130.5 (C-6), 134.6 (C-4), 138.7 (Ar–C), 141.6 (C-2), 168.1 (OC=O), 169.0 (NC=O); m/z (EI) 436 (M^+, 17%), 405 (M–OCH_3, 88%), 91 ($C_6H_5CH_2$, 100%); found M^+ 436.2355, $C_{26}H_{32}N_2O_4$ requires M^+ 436.2362.

4.5.14. ((1′S,5′S*,6′S*)-3′-Ethyl-6′-methoxy-3′-azabicyclo[3.3.1]nonan-1′-yl)methyl 2-acetaminobenzoate* ***65***. The reaction was carried out according to standard procedure M, using anthranilate **61** (27.5 mg, 82.7 μmol) stirring for 4 h with 100% ethyl acetate as the solvent for flash chromatography to give the *title compound* **65** (16.0 mg, 52%) (R_f 0.29) as a pale yellow oil. ν_{max}(NaCl)/cm^{-1} 3316, 3282, 2923, 1704, 1684, 1525, 1447, 1257, 1236, 1145, 1086; δ_H(300 MHz; $CDCl_3$) 1.05 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.39 (1H, dd, J=12.5, 1.7 Hz, 9′$_B$-H), 1.44–1.57 (2H, m, 8′$_A$-H & 9′$_A$-H), 1.82–1.92 (2H, m, 8′$_B$-H & 7′$_B$-H), 1.94–2.02 (2H, m, 4′$_A$-H & 2′$_A$-H), 2.13–2.19 (1H, m, 5′-H), 2.21–2.36 (5H, m, CCH_3 & NCH_2CH_3), 2.64–2.70 (1H, m, 7′$_A$-H), 2.92 (1H, d, J=10.3 Hz, 2′$_B$-H), 3.18 (1H, d, J=11.1 Hz, 4′$_B$-H), 3.34–3.43 (4H, m, OCH_3 & 6′-H), 3.96 (2H, s, C1′–CH_2O–), 7.10 (1H, td, J=7.7, 1.3 Hz, 5-H), 7.55 (1H, td, J=7.7, 1.6 Hz, 4-H), 8.02 (1H, dd, J=7.7, 1.6 Hz, 6-H), 8.71 (1H, dd, J=7.7, 1.3 Hz, 3-H), 11.05 (1H, br s, N–H); δ_C(75 MHz; $CDCl_3$) 12.4 (NCH_2CH_3), 25.5 (NHC(=O)CH_3), 27.6 (C-7′), 32.1 (C-5′), 32.5 (C-8′), 34.3 (C-1′), 35.0 (C-9′), 52.2 (C-4′), 52.6 (NCH_2CH_3), 55.9 (OCH_3), 61.2 (C-2′), 73.2 (C1′–CH_2O), 81.5 (C-6′), 114.9 (C-1), 120.4 (C-3), 122.4 (C-5), 130.5 (C-6), 134.7 (C-4),

141.7 (C-2), 168.2 (OC=O), 169.0 (NC=O); *m*/*z* (ESI^+) 375 (MH^+, 100%); found MH^+ 375.2288, $C_{21}H_{31}N_2O_4$ requires MH^+ 375.2275.

4.5.15. ((1′S,5′S*,6′S*)-3′-Benzyl-6′-hydroxy-3′-azabicyclo[3.3.1]nonan-1′-yl)methyl 2-acetaminobenzoate* ***66***. The reaction was carried out according to standard procedure M, using anthranilate **62a** (9.0 mg, 23.7 μmol) stirring for 4 h with hexane/ethyl acetate 1:1 as the solvent for flash chromatography to give the *title compound* **66** (5.0 mg, 50%) as a colourless oil. R_f 0.35; ν_{max}(NaCl)/cm^{-1} 3392, 3314, 3273, 2921, 1683, 1526, 1449, 1260, 1242, 1145, 1089; δ_H(400 MHz; $CDCl_3$) 1.46 (1H, d, *J*=12.7 Hz, 9′$_B$-H), 1.50–1.59 (2H, m, 8′$_A$-H & 9′$_A$-H), 1.83 (1H, dd, *J*=13.8, 6.6 Hz, 8′$_B$-H), 1.93–1.99 (1H, m, 7′$_B$-H), 2.00–2.05 (1H, m, 5′-H), 2.07–2.12 (2H, m, 4′$_A$-H & 2′$_A$-H), 2.22 (3H, s, CCH_3), 2.73–2.80 (1H, m, 7′$_A$-H), 2.89 (1H, d, *J*=10.8 Hz, 2′$_B$-H), 3.22 (1H, d, *J*=11.3 Hz, 4′$_B$-H), 3.44 (2H, m, NCH_2Ar), 3.86–3.93 (1H, m, 6′-H), 3.94 (2H, s, C1′–CH_2O–), 7.07 (1H, t, *J*=7.2 Hz, 5-H), 7.22–7.35 (5H, m, Ar–H), 7.55 (1H, td, *J*=7.2, 1.6 Hz, 4-H), 7.91 (1H, dd, *J*=7.2, 1.6 Hz, 6-H), 8.70 (1H, d, *J*=7.2 Hz, 3-H), 11.02 (1H, br s, N–H); δ_C(100 MHz; $CDCl_3$) 25.5 (CCH_3), 31.2 (C-7′), 32.5 (C-8′), 34.2 (C-1′), 35.0 (C-9′), 35.9 (C-5′), 52.5 (C-4′), 61.5 (C-2′), 63.6 (NCH_2Ar), 72.4 (C-6′), 72.9 (C1′–CH_2O), 114.8 (C-1), 120.4 (C-3), 122.4 (C-5), 127.0 (Ar–CH), 128.3 (Ar–C), 128.7 (2× Ar–CH), 130.5 (C-6), 134.7 (C-4), 138.8 (Ar–C), 141.7 (C-2), 168.1 (OC=O), 169.1 (NC=O); *m*/*z* (ESI^+) 423 (MH^+, 100%); found MH^+ 423.2280, $C_{25}H_{31}N_2O_4$ requires MH^+ 423.2278.

4.5.16. ((1′S,5′S*,6′S*)-3′-Ethyl-6′-hydroxy-3′-azabicyclo[3.3.1]nonan-1′-yl)methyl 2-acetaminobenzoate* ***67***. The reaction was carried out according to standard procedure M, using anthranilate **63a** (22.0 mg, 69.1 μmol) stirring for 2 h with DCM/methanol 9:1 as the solvent for flash chromatography to give the *title compound* **67** (15.5 mg, 62%) as an orange oil. R_f 0.39; ν_{max}(NaCl)/cm^{-1} 3423, 3314, 3273, 2925, 1728, 1685, 1526, 1448, 1258, 1239, 1145, 1088; δ_H(400 MHz; $CDCl_3$) 1.07 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 1.44 (1H, dd, *J*=12.5, 1.9 Hz, 9′$_B$-H), 1.49–1.67 (3H, m, 9′$_A$-H, 8′$_A$-H & O–H), 1.82–1.89 (2H, m, 8′$_B$-H & 7′$_B$-H), 1.99–2.05 (3H, m, 4′$_A$-H, 5′-H & 2′$_A$-H), 2.23 (3H, s, CCH_3), 2.53 (2H, q, *J*=7.2, NCH_2CH_3), 2.86–2.95 (2H, m, 7′$_A$-H & 2′$_B$-H), 3.29 (1H, d, *J*=9.9 Hz, 4′$_B$-H), 3.86–3.92 (1H, m, 6′-H), 3.97 (2H, s, C1′–CH_2O–), 7.11 (1H, td, *J*=7.9, 1.3 Hz, 5-H), 7.56 (1H, td, *J*=7.9, 1.6 Hz, 4-H), 8.01 (1H, dd, *J*=7.9, 1.7 Hz, 6-H), 8.71 (1H, dd, *J* 7.9, 1.3 Hz, 3-H), 11.04 (1H, br s, N–H); δ_C(100 MHz; $CDCl_3$) 12.4 (NCH_2CH_3), 25.5 (CCH_3), 30.8 (C-7′), 32.5 (C-8′), 34.1 (C-1′), 35.1 (C-9′), 35.8 (C-5′), 52.0 (C-4′), 52.7 (NCH_2CH_3), 61.4 (C-2′), 72.5 (C-6′), 73.1 (C1′–CH_2O), 114.9 (C-1), 120.4 (C-3), 122.5 (C-5), 130.5 (C-6), 134.7 (C-4), 141.7 (C-2), 168.2 (OC=O), 169.1 (NC=O); *m*/*z* (ESI^+) 361 (MH^+, 100%); found MH^+ 361.2128, $C_{20}H_{29}N_2O_4$ requires MH^+ 361.2122.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.05.037. These data include MOL files and InChiKeys of the most important compounds described in this article.

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