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Graphical Abstract

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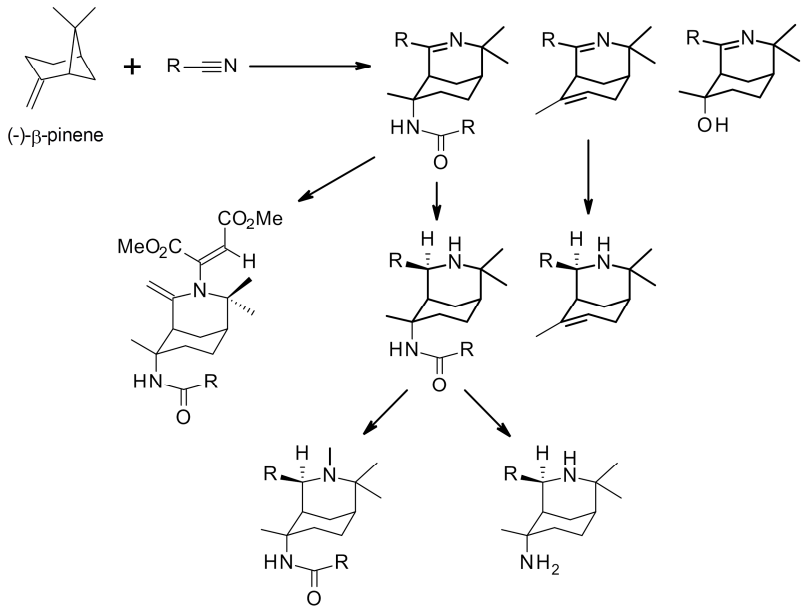

An alkaloid-like 3-azabicyclo[3.3.1]non-3-ene library obtained from the bridged Ritter reaction

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ABSTRACT

A small, diverse library of novel alkaloid-like compounds was synthesised using the bridged Ritter reaction with (–)-β-pinene and subsequent scaffold derivatisation. Structural diversity was achieved by varying the nitrile used in the reaction and thus provided an understanding of the influence nitriles have on the reaction outcome; it was determined that more nucleophilic nitriles, gave higher yields. Steric factors also determined the selectivity of scaffold types produced, with larger groups producing predominantly alkene products. X-ray crystallography and attempts to derivatise the imines obtained from the bridged Ritter reaction, highlighted the way the imino nitrogen reacted either not at all or in a stereospecific mannor, due to crowding by adjacent substituents. As the compounds contain either the 3-azabicyclo[3.3.1]nonane or 3-azabicyclo[3.3.1]non-3-ene core architecture, they will also be explored for their biological properties, due to the prevalence of bioactive alkaloids containing these core structures.

Keywords:
Bridged Ritter reaction
Alkaloid-like
3-aza-bicyclo[3.3.1]nonane
Drug discovery

1. Introduction

Alkaloids and their structurally similar synthetic counterparts are of keen interest in drug discovery due to the diverse range of biological activities reported.[1,2] Although natural products play a significant role in the discovery of bioactive scaffolds, many alkaloids are rare and require complex isolation. These challenges are overcome by obtaining bioactive scaffolds through synthetic pathways. Our previous work has established the use of the bridged Ritter reaction of (–)-β-pinene to generate the 3-azabicyclo[3.3.1]non-3-ene architecture[3] that mimics the core structure of the *Aristotelia* alkaloids (Fig. 1), known to have properties including anti-inflammatory, analgesic and antioxidant activity.[4]

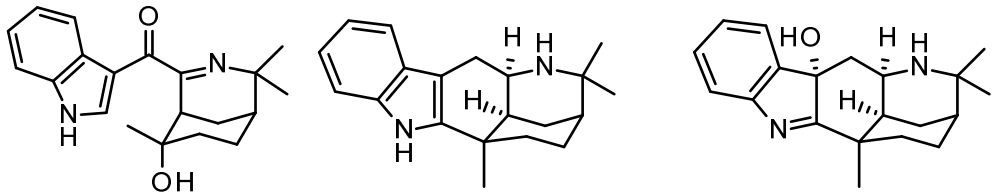
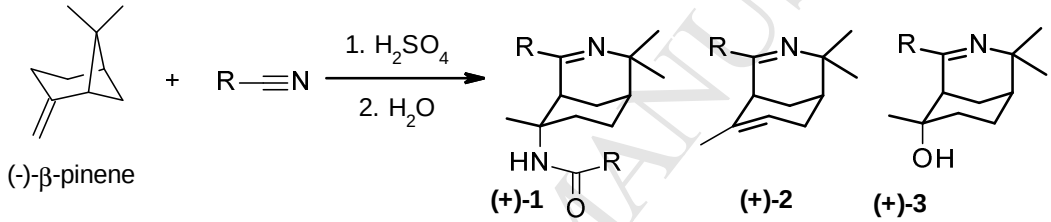


Fig. 1. Structures of *Aristotelia* alkaloids.

Recently, we reported the synthesis of optically active 3-aza-bicyclic [3.3.1]non-3-ene cyclic imines *via* the bridged Ritter reaction. These cyclic imines can be easily obtained in one single step from (–)-β-pinene and various nitriles, as shown in Scheme 1. This synthetic pathway is of significant interest as it provides optically pure products, with three stereocentres, in a one-pot reaction. It is well established that variation in the bridged Ritter reaction conditions, varies the reaction outcome[5] and, therefore, attempts to optimise the conditions to control the ratio of these products were also made, providing interesting results that have allowed further insight into the reaction mechanism.



Scheme 1. The bridged Ritter reaction between (–)-β-pinene and nitriles.

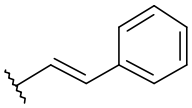
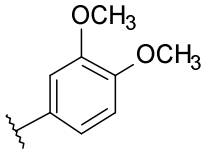
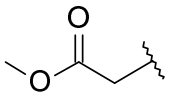
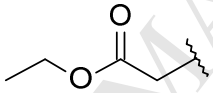
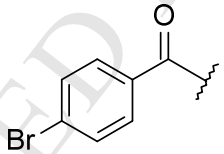
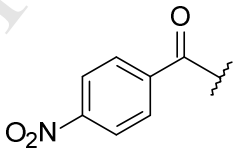
As part of our alkaloid-like drug discovery programme, we aim to develop feasible synthetic pathways that allow quick access to alkaloid-like chemical scaffolds which can be used to produce a library of alkaloid-like compounds for drug discovery. In this paper, we describe the detailed stereospecific synthesis of chiral 3-azabicyclo[3.3.1]non-3-enes *via* the bridged Ritter reaction, starting from (–)-β-pinene with various nitriles. We further explore the selectivity of the product outcome under different reaction conditions and some derivatisation is explored in order to add useful diversity to the library to understand the structure activity relationship (SAR) properties of the alkaloid-like compounds.

2. Results and discussion

2.1 Preparation of 6-*N*-amides, 6-alkene and 6-alcohols with 3-azabicyclo[3.3.1]non-3-ene core structure

The cyclic imines **(+)-1a**, **(+)-2a**, **(+)-1d**, **(+)-2d**, **(+)-1e**, **(+)-2e** and **3e** were previously prepared in our laboratory as the key chemical scaffolds for generating alkaloid-like compounds.[3] The general scheme for the preparation of optically active imino amides **(+)-1**, imino alkenes **(+)-2** and imino alcohols **(+)-3**, from (–)-β-pinene with various nitriles, *via* one-step bridged Ritter reaction is shown in Scheme 1. The reaction outcomes are summarised in Table 1.

Table 1. Products yields obtained from each nitrile with (–)-β-pinene *via* the bridged Ritter reaction.

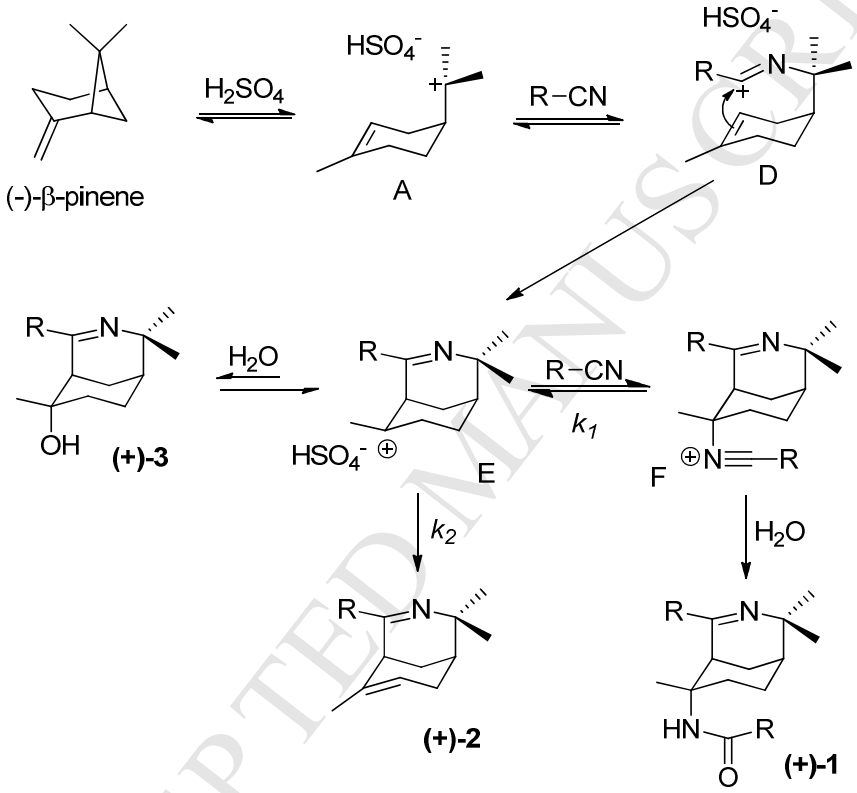
Entry	Nitrile	-R	Product/s (% Yield)
a	Acetonitrile[a]	$-CH_3$	**(+)-1a** (64), **(+)-2a** (23), **(+)-5a** (9)
b	Propionitrile	$-CH_2CH_3$	**(+)-1b** (25), **(–)-2b** (14), **(+)-5b** (4)
c	Valeronitrile	$-CH_2CH_2CH_2\ CH_3$	**(+)-1c** (12), **(+)-2c** (12)
d	Chloroacetonitrile[a]	$-CH_2Cl$	**(+)-1d** (31), **(+)-2d** (23)
e	Benzonitrile[a]	-Ph	**(+)-1e** (42), **(+)-2e** (24)
f	Cinnamonitrile		**(–)-2f** (53)
g	3,4-Dimethoxybenzonitrile		**(+)-2g** (42)
h	Methyl cyanoacetate		**(–)-2h** (2)
i	Ethyl cyanoacetate		**(–)-2i** (7), **(–)-4i**[b] (3)
j	4-Bromophenylacetonitrile		**(–)-8j**[c] (14)
k	4-Nitrophenylacetonitrile		**(–)-8k**[c] (12)
l	Succinonitrile	$-CH_2CH_2CN$	**(–)-2l** (7)

[a] results from nitriles previously published.[3]
[b] **4** results from rearrangement of the cyanoacetate precursor imine **3**, see section 2.2.2.
[c] **8** results from the autoxidation of the precursor alkene **2**, see section 2.2.1.

2.2 Influence of the nitriles

Table 1 summarises the yields of the corresponding products from each nitrile. The results of our early work with acetonitrile (**a**) and benzonitrile (**e**) revealed the formation of **(+)-1** and **(+)-2** in the ratios of 2.78:1 and 1.75:1, respectively.[3] From the results reported herein, there is a clear trend which correlates to the properties of the nitriles used. Notably, the size of the nitrile imposes a steric

factor, the bulky nitriles tending to favour the formation of only imine-alkenes **(+)-2**. However, when benzonitrile was used, despite its relative bulkiness, it provided both **(+)-1** and **(+)-2**. This suggests that the nucleophilicity of the nitriles has a strong influence on the selectivity of these cyclic imines.[6] Attack of the C-6 carbocation intermediate E by a strongly nucleophilic nitrile would eventually favour the formation of the imine-amides **(+)-1** (Scheme 2), as previously reported.[7] Where the imino-amides **(+)-1** are the major product, the data suggest that the transformation of E into F is controlled by the rate k_1, which is influenced by the nucleophilicity of the nitrile, and eventually forms **(+)-1** upon quenching with water. The following explains some of the other interesting outcomes that resulted from the nitrile used.

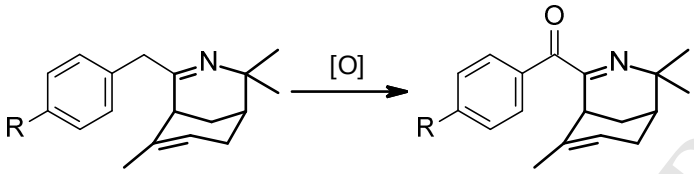


Scheme 2. Proposed mechanism for the bridged Ritter reaction with (–)-β-pinene.

2.2.1 Oxidation of Benzylic products

The reaction of benzyl cyanides (entry **j** and **k**) with (–)-β-pinene, yielded the oxidised product **(–)-8j-k** (Scheme 3). The oxidation of benzylic CH_2 is well established in the literature, and it has also been reported that the use of benzyl cyanides under Ritter reaction conditions give products that underwent spontaneous oxidation to give benzoyl products.[8] Initial evidence for the formation of **(–)-8j** was derived from its molecular weight observed in the crude GC/MS analysis, which showed a product fourteen mass units higher than that of the expected corresponding imine-alkene, **2j**. The IR spectrum presented a band at 1665 cm^{-1}, corresponding to a conjugated ketone carbonyl group. It was further confirmed by the ^{13}C NMR, in which the spectrum of **(–)-8j** showed a resonance at 193.19 ppm, corresponding to the C=O carbon.

Compound **2k** was also initially noted in the crude mixture where GC/MS showed the *m/z* of 298 for the non-oxidised product at 8.48 min while the oxidised product was *m/z* 312 at 8.43 min. Overtime, **2k** underwent air oxidation at the benzylic carbon (C-4α) to provide **(–)-8k** as observed in ^{1}H NMR by the disappearance of the benzylic protons signal at (3.71 ppm). IR spectroscopy indicates the presence of the ketone carbonyl stretch at 1672 cm^{-1}. Due to this oxidation, only the benzoyl products **(–)-8j** and **(–)-8k** were able to be isolated and fully characterised.



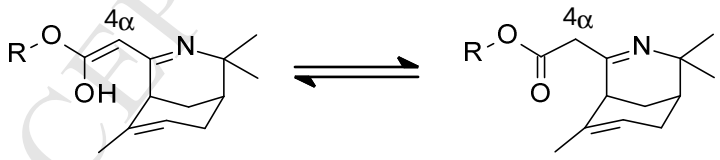
2j: R = Br
2k: R = NO_2

(–)-8j: R = Br
(–)-8k: R = NO_2

Scheme 3. Autoxidation of benzylic products.

2.2.2 Cyanoacetate rearrangement

Two cyanoacetate nitriles were used with the bridged Ritter reaction, methyl and ethyl-cyanoacetate (entry **h** and **i**). The products obtained from these nitriles were low yielding; **(–)-2i** was obtained with 7 % yield after isolation by preparative TLC, while **(–)-2h** was obtained with 2 % yield after column chromatography. Both of these alkenes exist in both the keto and enol form in solution (Scheme 4), as shown by the additional resonances in the NMR spectra. In the ^{1}H NMR spectrum of **(–)-2i**, the OH and 4α-CH resonances of the enol form could be seen at 8.28 and 4.38 ppm respectively, while the 4α-CH_2 of the keto-form occur as singlets at 4.73 and 4.63 ppm. In the ^{13}C NMR spectrum, the enol 4α-CH is observed at 80.00 ppm while the keto 4α-CH_2 is observed at 108.18 ppm. The same was observed for **(–)-2h** as shown in the experimental data. Using the integral values of the ^{1}H NMR resonances, it was determined that the ratio of enol to keto for both **(–)-2i** and **(–)-2h** is 1:2.



enol-form
(–)-2h R = CH_3
(–)-2i R = CH_2CH_3

keto-form
(–)-2h R = CH_3
(–)-2i R = CH_2CH_3

Scheme 4. Interconversion of the enol and keto forms of **(–)-2h** and **(–)-2i**.

The ethyl cyanoacetate also resulted in an unexpected amino-alcohol product **(–)-4i**; isolated in the β-unsaturated carbonyl (keto) form, as a result of imine-enamine tautomerisation. The X-ray structure was obtained from suitable single crystals of **(–)-4i** which were formed in the crude product and re-grown from CH_2Cl_2/hexane. The X-ray structure also shows that the C4 to C4α double bond adopts the *Z*-conformation. The *Z*-configuration is favoured by the intramolecular H-bonding

between NH---O=C (Fig. 2). The structure of **(–)-4i** was also confirmed spectroscopically, characteristic absorbance peaks were also observed in the IR spectrum, notably those corresponding to the alcohol, amine and carbonyl functionality stretches at 3470, 3287 and 1625 cm^{-1} respectively.

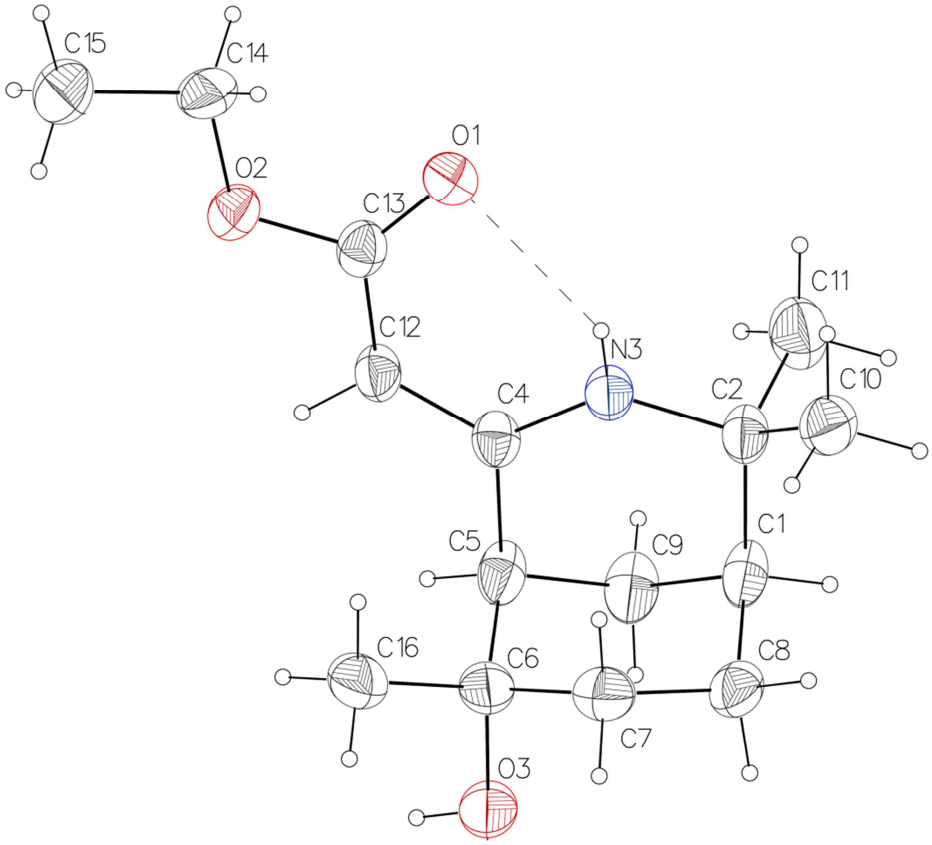


Fig. 2. ORTEP diagram of a **(–)-4i** molecule in the crystal structure of racemic **4i**, showing the intramolecular H-bonding between NH---O=C.

The crystal structure of **4i** was found to be in the *Cc* space group, having four symmetry operations, as this crystal contains the **(–)-4i** (*1R, 5S, 8S*) and **(+)-4i** (*1S, 5R, 8R*) enantiomers (Fig. 3). **(–)-4i** and **(+)-4i** are coloured in grey and magenta, respectively, according to their symmetry operation. This result was unexpected, as the bridged Ritter reaction is asymmetric and should generate optically pure products from chiral starting materials such as (–)-β-pinene.

The presence of both enantiomers in the crystal packing was a result of trace impurities of (+)-β-pinene in the starting material. The (–)-β-pinene used for the reaction was sourced from Sigma-Aldrich, who reported that the product has a 97 % enantiomeric excess and a specific rotation of $[\alpha]_D^{25} - 22$ (neat). We measured the optical rotation of the product to be $[\alpha]_D^{22}$ - 18.85 (neat). The trace amounts of **(+)-4i** in the crude product would have favoured the co-crystallisation of the enantiomers in the sample taken from the crude and recrystallised, while the purified sample of **(–)-4i** was isolated and characterised spectroscopically.

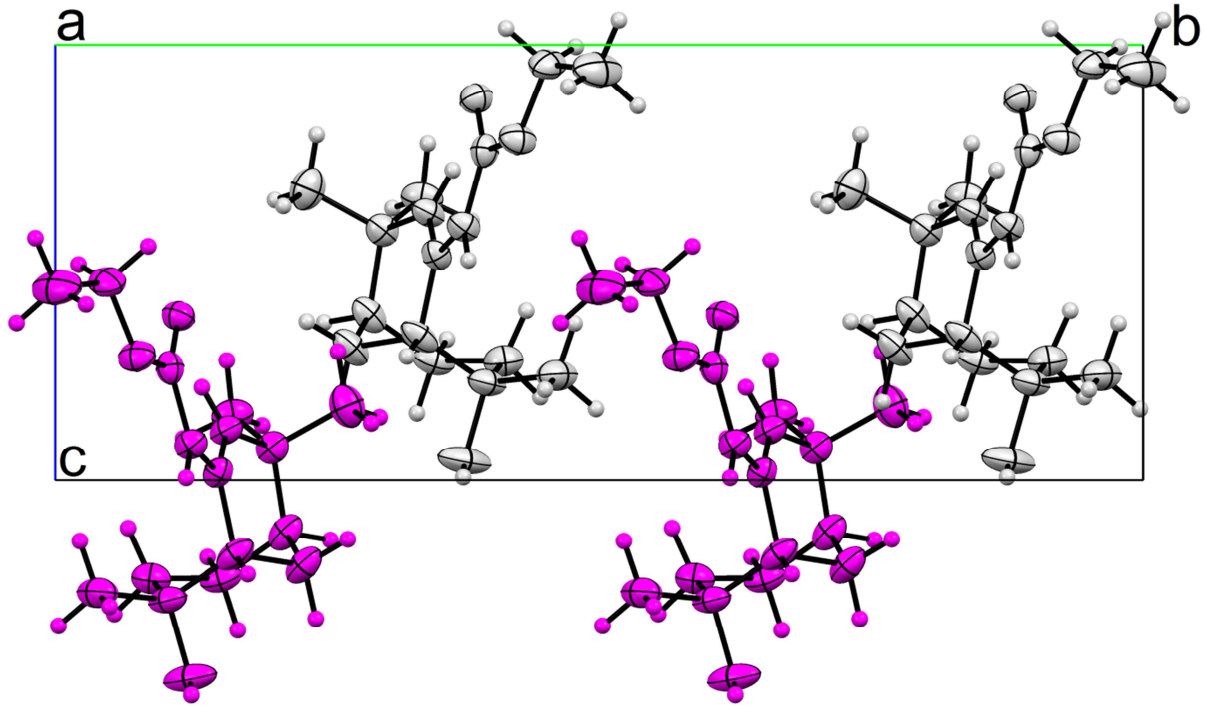
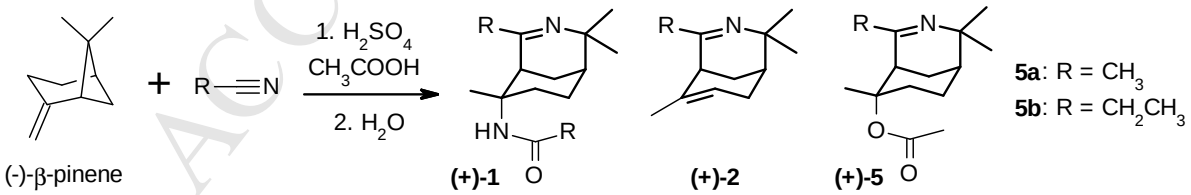


Fig. 3. Enantiomers of **(–)-4i** (grey) and **(+)-4i** (magenta, glide plane related) in the unit cell looking down the *a* axis.

2.3 Optimisation of bridged Ritter reaction conditions

Christol[9] stated that the use of polar solvents increased yields by increasing the nucleophilicity of the nitrile. There are several alternative catalysts for the generation of carbocations reported,[10] however our investigation focused only on the use of concentrated sulfuric acid and the use of acetic acid as a polar solvent in replacement of benzene used in the standard conditions listed in the experimental section. These polar conditions were used with acetonitrile and propionitrile and resulted in the formation of additional acetate products **(+)-5a** and **(+)-5b**, as seen in Scheme 5, however did not result in an increased yield. Formation of the acetate products resulted from the nucleophilic addition of the acetate ion, to the carbocation generated at C-6 as per suggested mechanism shown in Scheme 2.



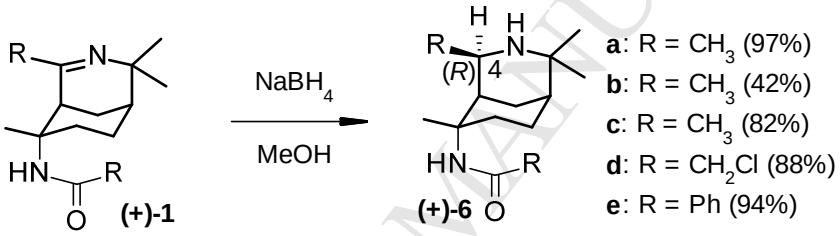
Scheme 5. Formation of acetate products **(+)-5a** and **(+)-5b** under polar bridged Ritter reaction conditions.

The duration of reaction time was also found to influence the product ratio between the imino-amide and imino-alkene for acetonitrile. Under the standard reaction time, the reaction gave a 2.78:1 ratio of imino-amide to imino-alkene. When the reaction time was shortened to only 4

hours, only the amide was formed. On the other hand, when the reaction time was extended to 96 hours, the ratio became 1:3. It appears that the longer reaction times led to higher yields of the alkene product. This would indicate that in the suggested mechanism (Scheme 2), the reaction of E to F is an equilibrium process or that after the maximum amount of F has formed, the remaining carbocation E collapses slowly to the alkene.

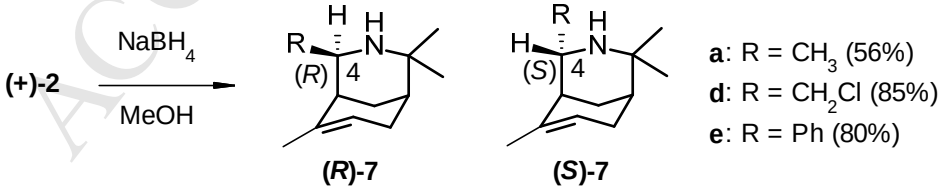
2.4 Reduction of cyclic imines

Both imino-amide (Scheme 6) and imino-alkene (Scheme 7) products prepared *via* the bridged Ritter reaction have been reduced to the corresponding amino structures, using $NaBH_4$.[12] The imine bond of the imino-amides is reduced asymmetrically to give (*R*)-stereocentres exclusively at C-4, with the substituent from the nitrile projecting forward from the *Re* face, as depicted in Scheme 6. This stereoselective outcome resulted from the imino bond being hindered by the cyclohexane ring that projects out from the *Re* face of the imine, only allowing for the hydride ion to approach from the *Si* face side. The amino compounds retain their optical activity, as indicated by the reported optical rotations.



Scheme 6. Reduction of imino-amide scaffolds to amino amides.

Reduction of the imino-alkene **(+)-2a** resulted in a mixture of diastereoisomers, however, this non-facial selectivity of the hydride attack at C-4 was observed only when the -R group was methyl. In this case, the (*R*)-diastereoisomer **(–)-7a** was the major product and the only diastereoisomer isolated. The presence of the (*S*)-diastereoisomer was observed in the GC/MS and NMR analysis of the crude product, in which the ratio between (*R*) and (*S*) is 4.5:1, with GC retention times of 11.1 and 10.7 minutes, respectively. Table 2 lists the corresponding amino-amides (**5**) and amino-alkenes (**6**) that were obtained stereospecifically, containing (*R)*-stereocentres at the C-4 position, *via* hydride reduction using $NaBH_4$.



Scheme 7. Reduction of imino alkene scaffolds to amino alkenes.

Table 2. Yields of amine-scaffolds obtained from the reduction of corresponding imines.

Entry	Imine Used	Amine Product	Yield (%)
1	**(+)-1a**	**(+)-6a**	97
2	**(+)-2a**	**(–)-7a**	56

3	**(+)-1b**	**(+)-6b**	42
4	**(+)-1c**	**(+)-6c**	82
5	**(+)-1d**	**(+)-6d**	88
6	**(+)-2d**	**(–)-7d**	85
7	**(+)-1e**	**(+)-6e**	94
8	**(+)-2e**	**(–)-7e**	80

The stereochemistry at C-4 was confirmed by 1D NOESY experiments, where the orientation of H-4 was determined by observing the NOE (Nuclear Overhauser Effect) when irradiated. Cross-peaks are seen between the H-4 and H-5 signals and the H-4 and CH_3-2α signals, indicating their proximity of less than 3 Å and confirming that H-4 and H-5 are in the *syn* orientation. The spectral analysis of **(+)-6a** and **(+)-6b** and their respective X-ray structures (of single crystals grown from CH_2Cl_2/hexane), unequivocally confirm that C-4 is the (*R*)-stereocentre, with the hydrogen projecting away from the *Re* face of the ring and the substituent forward (Fig. 4).

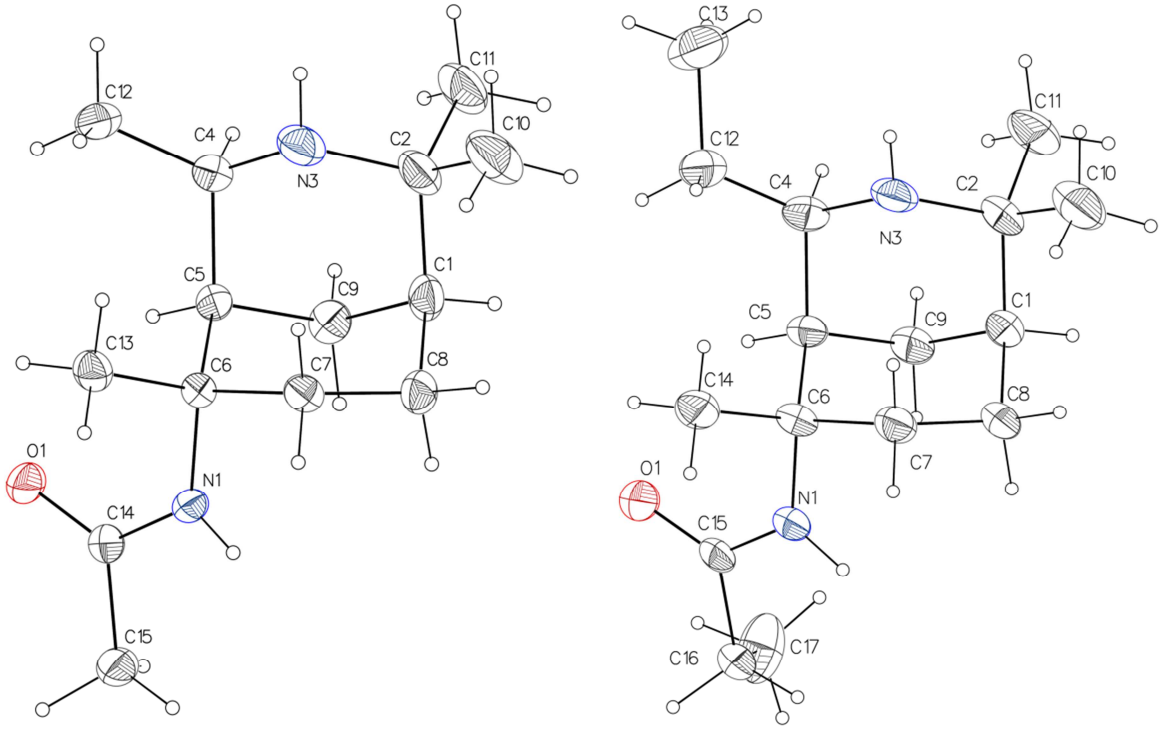


Fig. 4. ORTEP diagram of **(+)-6a** (left) and **(+)-6b** (right), showing the configuration of stereocentre at C-4.

2.4.1 Crystal packing of (+)-6a and (+)-6b

The X-ray analysis of compounds **(+)-6a** and **(+)-6b** revealed a remarkable similarity in the interactions involved in the packing of the molecules in crystals. Between the 2_1 screw related molecules, intermolecular hydrogen bonding was observed between the NH and C=O functionality of the amide groups at position 6 (N1-H1···O1) and two C-H···O contacts (one inter and one intra) between C=O and CH of either the amide CH_3 for **(+)-6a** or CH_2 for **(+)-6b** (Fig. 5 (**a**) and (**b**) respectively). The geometry parameters of the H-bonding interactions are given in Table 3 and Table

4. It should be noted that no hydrogen bonding is observed from the amine NH (N3-H3), this can be accounted for by the fact that the methyl substituents on the adjacent carbons are crowding the nitrogen and hindering any possible interactions. This can clearly be seen in the space filling diagrams for **(+)-6a** and **(+)-6b** in Fig. 6.

Table 3. Hydrogen-bond geometry (Å, °) for **(+)-6a**

D*—H···*A	***D*—H**	**H···*A***	***D*···*A***	***D*—H···*A***
N1—H1···O1$^{'}$	0.88	2.13	2.973 (4)	161
C5—H5···O1	1.00	2.43	3.105 (5)	125
C16—H16*B*···O1$^{'}$	0.99	2.37	3.280 (5)	152

Symmetry codes: (i) −x+2, y+1/2, −z+3

Table 4. Hydrogen-bond geometry (Å, °) for **(+)-6b**

D*—H···*A	***D*—H**	**H···*A***	***D*···*A***	***D*—H···*A***
N1—H1···O1$^{'}$	0.81 (3)	2.22 (2)	3.0097 (18)	166 (2)
C5—H5···O1	0.98 (2)	2.45 (2)	3.1140 (18)	124.8 (17)
C15—H15*B*···O1$^{'}$	0.97 (3)	2.55 (3)	3.414 (2)	147.9 (19)

Symmetry codes: (i) −x+1, y−1/2, −z+1.

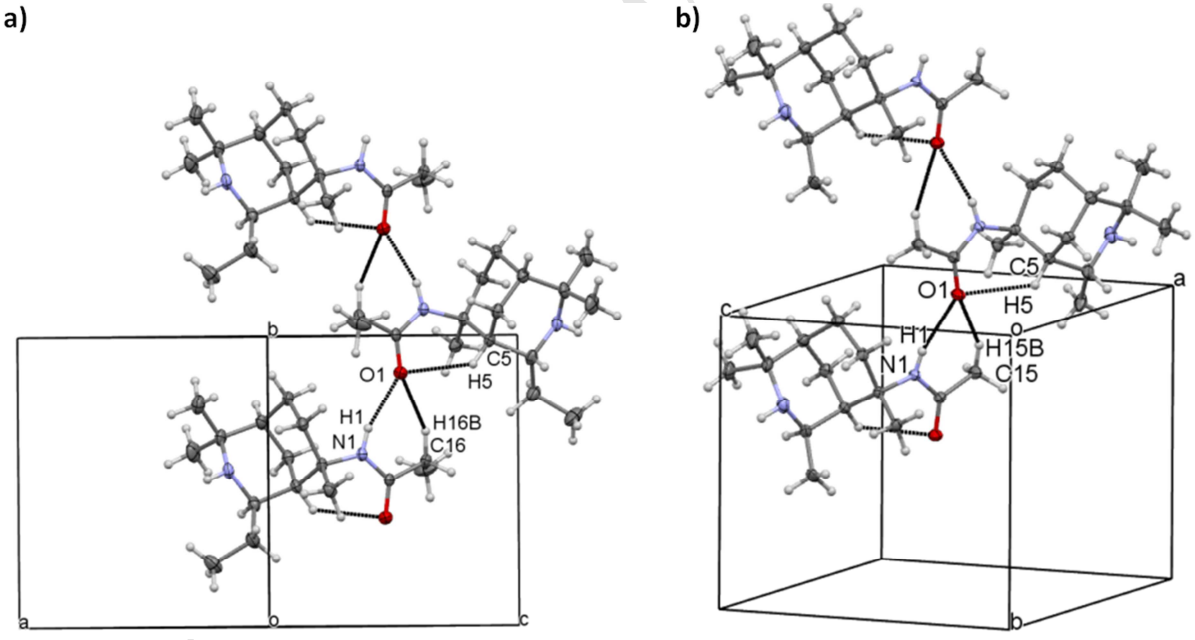


Fig. 5. The NH----O=C and CH---O=C hydrogen bonding observed in the crystal structures of **a**, compound **(+)-6a** and **b**, compound **(+)-6b**.

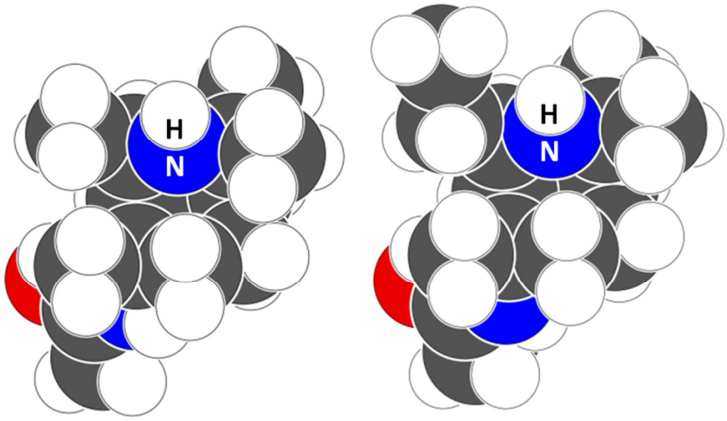
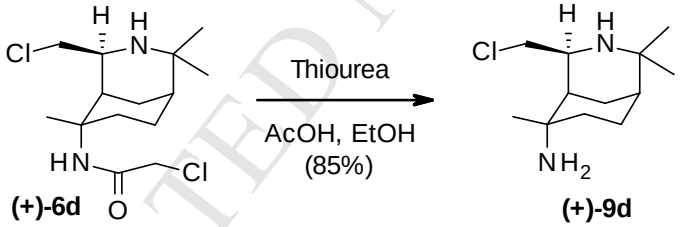


Fig. 6 Space filling diagrams of **(+)-6a** and **(+)-6b**, showing the crowding of the amine NH.

2.5 Derivatisation imino and amino-amides

2.5.1 Amide deprotection of 5d

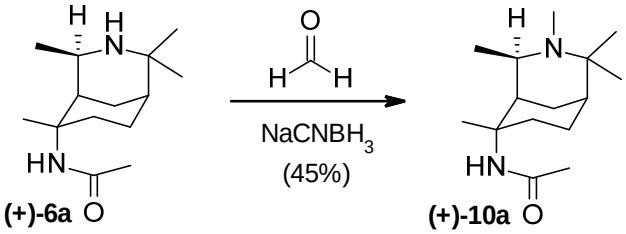
The diamine **(+)-9d** was obtained in one step from the amino-amide **(+)-6d**, *via* amide deprotection (Scheme 8). The presence of the chloroacetamide functional group in **(+)-6d** makes the amide bond labile, allowing it to be hydrolysed under mild conditions to **(+)-9d**. The reaction was performed according to the method outlined by Torres *et al.*,[13] to give the diamine product **(+)-9d**. This primary amine introduces another viable point for further derivatisation and expansion of the alkaloid-like library as it was found that the N-3 amine does not make a viable point for alkylation.



Scheme 8. Amide deprotection of amino amide **(+)-6d** to diamine **(+)-9d**.

2.5.2 Reductive *N*-alkylation

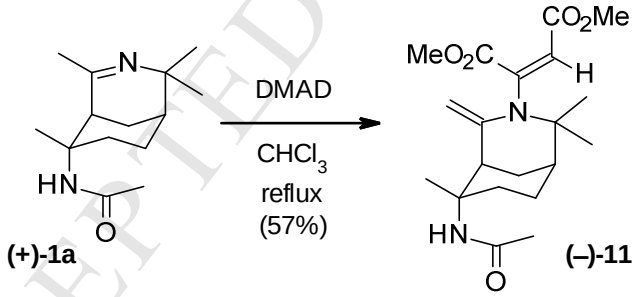
Reductive *N*-methylation was carried out on **(+)-6a**, using the method described by Taylor *et al.*,[12] as shown in Scheme 9, which gave **(+)-10a** in 45 % yield. The reaction was also attempted under the same reaction conditions with propanal, pentanal and benzaldehyde, however, none of these reactions were successful and only starting material was recovered. The outcome of these attempts highlights the significance of the crowding of the amine at position NH-3 in the scaffold, as contributed by the three adjacent methyl groups, illustrated in the X-ray structures (Fig. 4). The hindered nature of NH-3 prevented access of the aldehydes and hence only formaldehyde could successfully react with **(+)-6a** to give **(+)-10a**. The identity of compound **(+)-10a** was confirmed by spectral NMR analysis.



Scheme 9. Reductive N-methylation of amino amide **(+)-6a** to **(+)-10a**.

2.5.3 Reaction of 1a with dimethyl acetylenedicarboxylate

The reaction of compound **(+)-1a** with dimethyl acetylenedicarboxylate (DMAD) was performed by adapting the method published by Ung *et al*.[14] to afford **(–)-11** in 57 % yield. The identity of compound **(–)-11** was confirmed by the following; the ^{1}H NMR spectrum showed new peaks corresponding to functionality added to the scaffold through the amine nitrogen at N-3. These include the singlet at 5.58 ppm due to the alkene C-H (C=C<u>H</u>CO_2Me) and two new CH_3 signals as singlets at 3.73 and 3.70 ppm corresponding to the two methoxy groups. The C-4 CH_3 singlet has been lost and replaced by two singlets for each of the C-4 CH_2 protons; these occur at 4.61 and 4.44 ppm. ^{13}C NMR spectrum reveals the new carbonyl carbons at 167.1 and 166.4 ppm as well as the new N-3α quaternary carbon at 146.8 ppm. The orientation of the two CO_2Me groups were confirmed with 1D NOESY experiments. Upon irradiating the proton (C=C<u>**H**</u>CO_2Me) at 5.58 ppm, two cross-peaks with the two CH_3 groups (1.45 and 1.39 ppm) at C-2 (Figure 2.7) were observed. These indicate that they are within proximity of 3 Å to each other in space, and the two CO_2Me group must be in *cis*-orientation as shown in Scheme 10.



Scheme 10. The reaction of **(+)-1a** with DMAD to give **(–)-11**.

It was expected that compound **(–)-11** could be cyclised through the C-4 CH_2 and the imine as previously reported by Lin *et al*..[15] However, this intermediate adduct product was unable to cyclise due to the highly hindered nature of the imine, as outlined in sections 2.4.1. Even the adsorption of **(–)-11** to silica gel did not result in cyclisation, as reported in a follow up paper by Lin *et al*.,[16] on the reactivity of the adduct. It is likely that for the tri-cyclic scaffolds previously reported by Lin *et al*., the imine nitrogen is relatively less hindered due to the constraints of the ring pulling the carbon adjacent from C-4 away from the nitrogen.

3. Conclusion

In summary, the bridged Ritter reaction is a viable method for generating a chemically diverse library of optically pure alkaloid-like molecules. The nitriles used have the greatest influence on the outcome of the reaction and scaffold type obtained, as well as providing a versatile range of functional group derivatives containing the 3-azabicyclo[3.3.1]non-3-ene core. Most notably, the more electron donating the nature of the group adjacent to the nitrile, the higher the yield. The increase in nucleophilicity of the nitrile favours the affinity towards the carbocation reaction intermediate, generating amides. However, as the size of the nitrile increases (for nitriles larger than benzonitrile), steric hindrance tends to favour the formation of the alkene product. The conformation of the scaffold must also provide a hindering steric effect in decreasing the nitriles ability to attack the carbocation.

Reduction of the imine allowed secondary and tertiary amines to be generated. However, the hindered nature of these amines only allowed for alkylation with formaldehyde. The hindrance resulting from the crowding of the position 3 nitrogen is also observed in the X-ray crystal structures. It was found that the alkene product is extremely stable towards electrophilic addition and therefore is not a suitable functional group for derivatisation. Chloroacetonitrile, however, did provide a labile amide which was readily hydrolysed to give the amine functionality at C-6, which could be further functionalised.

Initial biological screening of several compounds reported have shown anti-cancer activity, however, screening is yet to be completed on the full library and will be reported in the future.

4. Experimental

4.1 General

Reagents and analytical grade solvents were purchased from commercial sources. The progress of reactions was monitored by TLC analysis, performed on aluminium backed Merck 60 GF_{254} silica gel or Merck 60 GF_{254} neutral alumina gel with UV detection at 254 nm, I_2 atmosphere. Compounds were purified by column chromatography using Merck flash either neutral alumina or silica gel (40 – 63 μm). The purity of compounds was determined by ^{1}H NMR and GC/MS. ^{1}H and ^{13}C NMR spectra were recorded on an Agilent 500 MHz spectrometer (500 MHz ^{1}H, 125 MHz ^{13}C) in deuterated chloroform ($CDCl_3$) unless otherwise specified. NMR assignments were based on COSY, HSQC and DEPT experiments. ^{1}H and ^{13}C NMR assignments are based on the numbering system used for the systematic name. Compounds **2h** and **2i** were observed in the NMR as tautomers, thus the NMR assignment reflects this. Low-resolution mass spectra were obtained on an Agilent 6890GC fitted with 5 % polysilphenylene, 95 % polydimethylsiloxane column and an Agilent 5973n MS (EI) spectrometer. High-resolution mass spectra were obtained on an Agilent 6510 Accurate-Mass Q-TOF Mass Spectrometer, equipped with an ESI source. Melting points were measured on a Gallenkamp Melting Point Apparatus equipment and were uncorrected. Optical rotation was measured using a Jasco P-2000 polarimeter.

4.2 General procedures

1. *Standard bridged Ritter reaction conditions*

Sulfuric acid (18 M, 2 mL) was stirred in a flask fitted with a reflux condenser and a drying tube at 0 °C. To the reaction flask, the nitrile (53.4 mmol, 7 mol equiv. of (–)-β-pinene) was added. A solution of (–)-β-pinene (1.2 mL, 7.62 mmol) in benzene (5 mL) was added dropwise to the reaction mixture, *via* the condenser. A further 0.50 mL of benzene was used to wash all traces of (–)-β-pinene into the reaction flask. After 30 min the reaction was allowed to reach room temperature and left to stir for 24 h. The reaction was then quenched by the addition of water (30 mL). The mixture was then basified with 4 M NaOH (until pH > 10). The reaction mix was then extracted with $CHCl_3$ (2 X 15 mL) and dried with Na_2CO_3. Note: if the nitrile used was solid, it is dissolved in 20 mL benzene before addition to sulfuric acid.

4.1.1 N-(4-Ethyl-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-3-en-6-yl)propanamide **1b**

(512 mg, 1.94 mmol, 25 %) as a white solid; m.p. 96-97 °C, R_f (ethyl acetate) 0.69; $[\alpha]_D^{18}$ +125.95 (*c* 0.95, $CHCl_3$); ν_{max}(neat) 3278, 3080, 2972, 2946, 2872, 1637, 1555, 1451, 1348, 1285, 1235, 1110, 955 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (br s, NH), 3.27 (br s, 1H, CH-5), 2.31 (dt, *J* = 7.5, 6.0 Hz, 1H, CH_2-4α), 2.27 (dt, *J* = 7.5, 6.0 Hz, 1H, CH_2-4β), 2.21 (qt, *J* = 7.5, 2.0 Hz, 2H, $COCH_2CH_3$), 1.80-1.83 (m, 1H, CH_2-9a), 1.76 (dt, *J* = 13.0, 2.0 Hz, 1H, CH_2-8a), 1.66-1.63 (m, 2H, CH_2-8b & CH-1), 1.56 (tt, *J* = 13.5, 4.5 Hz, 1H, CH_2-9b), 1.46-1.36 (m, 2H, CH_2-7), 1.42 (br s, 3H, CH_3-6α), 1.28 (br s, 3H, CH_3-2α), 1.16 (t, *J* = 7.5 Hz, 3H, $COCH_2CH_3$), 1.12 (br s, 3H, CH_3-2α), 1.09 (t, *J* = 7.5 Hz, 3H, CH_3-4β); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7 (C-4), 171.7 (C=O), 58.1 (C-6), 56.0 (C-2), 38.3 (CH-5), 36.7 (CH_2-4α), 34.5 (CH-1), 33.6 (CH_2-7), 32.1 (CH_3-2α), 31.0 ($COCH_2CH_3$), 27.4 (CH_3-6α), 26.3 (CH_3-2α), 25.1 (CH_2-9), 24.9 (CH_2-8), 13.0 (CH_3-4β), 12.3 ($COCH_2CH_3$); GC/MS R_t = 18.74 min, *m/z* 264 (72M), 249 (27), 191 (59), 176 (50), 164 (56), 150 (47), 136 (100), 122 (23), 97 (31), 57 (33 %). HRMS (ES): $C_{16}H_{28}N_2O$ calcd: 265.2275 $[M+H]^+$; found: 265.2271 $[M+H]^+$.

4.1.2 4-Ethyl-2,2,6-trimethyl-3-azabicyclo[3.3.1]nona-3,6-diene **2b**

(198 mg, 1.04 mmol, 14 %) as a yellow oil; R_f (1:4 hexane/diethyl ether) 0.6; $[\alpha]_D^{23}$ –22.56 (*c* 1.00, $CHCl_3$); ν_{max}(neat) 2961, 2927, 2868, 1686, 1662, 1453, 1377, 1356 cm^{-1}; ^1H NMR (500 MHz , $CDCl_3$) δ 5.34 (br s, 1H, CH-7), 2.60 (br s, 1H, CH-5), 2.27 (q, *J* = 7.5 Hz, 2H, CH_2-4α), 2.25-2.14 (m, 2H, CH_2-9), 1.87 (br s, 1H, CH-1), 1.79-1.77 (m, 4H, CH_3-6α & CH_2-8a), 1.57 (dt, *J* = 12.0, 2.5 Hz, 1H, CH_2-8b), 1.19 (br s, 3H, CH_3-2α), 1.16 (br s, 3H, CH_3-2α), 1.11 (t, *J* = 7.5 Hz, 3H, CH_3-4β); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (C-4), 135.1 (C-6), 122.5 (CH-7), 58.7 (C-2), 38.5 (CH-5), 34.5 (CH_2-4α), 34.10 (CH-1), 32.2 (CH_3-2α), 29.2 (CH_2-9), 28.2 CH_3-2α), 26.2 (CH_2-8), 24.2 (CH_3-6α), 11.9 (CH_3-4β); GC/MS R_t = 5.431 min, *m/z* 191 (14 M), 176 (5), 136 (23), 121 (11), 93 (100), 77 (14 %). HRMS (ES): $C_{13}H_{21}N$ calcd: 192.1747 $[M+H]^+$; found: 192.1751 $[M+H]^+$.

4.1.3 N-(4-Butyl-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-3-en-6-yl)pentanamide **1c**

(298 mg, 0.931 mmol, 12 %) as a yellow oil; R_f (1:3 ethyl acetate/hexane) 0.47; $[\alpha]_D^{22}$ +81.82 (*c* 1.35, $CHCl_3$); ν_{max}(neat) 3296, 3071, 2959, 2933, 2874, 1642, 1544, 1458, 1378, 1367, 1272, 1110, 929, 910, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.31 (s, 1H, NH), 3.27 (br s, 1H, CH-5), 2.32-2.28 (m, 1H, CH_2-6αc), 2.25-2.20 (m, 1H, CH_2-6αc), 2.17 (td, *J* = 7.5, 3.5 Hz, 2H, CH_2-6αb), 1.84-1.79 (m, 1H, CH_2-8a), 1.75 (dt, *J* = 10.0, 13.0 Hz, 1H, CH_2-9a), 1.75-1.65 (m, 1H, CH_2-9b), 1.63-1.60 (m, 3H, CH-1 & CH_2-4αa), 1.59-1.52 (m, 2H, CH_2-7a & CH_2-8b), 1.45-1.30 (m, 7H, CH_2-7b, CH_2-4αb, CH_2-4αc & CH_2-6αd), 1.42 (br s, 3H, CH_3-2α), 1.28 (br s, 3H, CH_3-2α), 1.12 (br s, 3H, CH_3-6α), 0.94 (t, *J* = 7.5 Hz, 3H, CH_3-

4αd), 0.90 (t, *J* = 7.5 Hz, 3H, CH_3-6αd); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1 (C-4), 170.9 (C=O), 58.2 (C-6), 56.1 (C-2), 42.7 (CH_2-6αc), 38.7 (CH-5), 37.8 (CH_2-6αb), 34.5 (CH-1), 33.5 (CH_2-4αb), 32.1 (CH_2-6α), 31.2 (CH_2-7), 28.2 (CH_2-4αa), 27.4 (CH_3-2α), 25.1 (CH_2-8), 24.7 (CH_2-9), 23.0 (CH_2-6αd), 22.7 (CH_2-4αc), 14.4 (CH_3-6αd), 14.2 (CH_3-4αd); GC/MS R_t = 21.95 min, *m/z* 320 (1 M), 305 (6), 278 (27), 219 (17), 177 (100), 57 (18 %). HRMS (ES): $C_{20}H_{36}N_2O$ calcd: 321.2900 $[M+H]^+$; found: 321.2884 $[M+H]^+$.

4.1.4 4-Butyl-2,2,6-trimethyl-3-azabicyclo[3.3.1]nona-3,6-diene **2c**

(198 mg, 0.903 mmol, 12 %) as a yellow oil; R_f (1:3 ethyl acetate/hexane) 0.97; $[\alpha]_D^{21}$ +9.22 (*c* 1.00, $CHCl_3$); ν_{max}(neat) 2959, 2931, 2874,1698, 1655, 1560, 1542, 1458, 1382, 1361, 1331, 1255, 1207, 1173, 980, 804 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (br s, 1H, CH-7), 2.59 (br s, 1H, H-5), 2.29-2.26 (m, 2H, CH_2-4αa), 2.25-2.16 (m, 2H, CH_2-8), 1.86 (br s, 1H, H-1), 1.80 (br s, 3H, CH_3-6α), 1.78-1.75 (m, 1H, CH_2-9a), 1.57 (dt, *J* = 3.0, 12.0 Hz, 1H, CH_2-9b), 1.52-1.48 (m, 2H, CH_2-4αb), 1.37-1.32 (m, 2H, CH_2-4αc), 1.19 (br s, 3H, CH_3-2α), 1.16 (br s, 3H, CH_3-2α), 0.93 (t, *J* = 7.0 Hz, 3H, CH_3-4αd); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C-4), 135.1 (C-6), 122.5 (CH-7), 58.7 (C-2), 41.3 (CH_2-4αa), 38.7 (CH-5), 34.1 (CH-1), 29.0 (CH_3-2α), 29.8 (CH_2-4αb), 29.3 (CH_2-8), 28.1 (CH_3-2α), 26.1 (CH_2-9), 24.2 (CH_3-6α), 23.0 (CH_2-4αc), 14.4 (CH_3-4αd); GC/MS R_t = 14.26 min, *m/z* 219 (3 M), 204 (3), 190 (4), 177 (31), 162 (8), 136 (9), 121 (9), 93 (100), 77 (12), 41 (12 %). HRMS (ES): $C_{15}H_{25}N$ calcd: 220.2060 $[M+H]^+$; found: 220.2048 $[M+H]^+$.

4.1.5 3-(2,2,6-Trimethyl-3-azabicyclo[3.3.1]nona-3,6-dien-4-yl)propanenitrile ***2l***

(119 mg, 0.552 mmol, 7 %) as a red oil; R_f (1:3 acetone/hexane) 0.70; $[\alpha]_D^{20}$ –45.28 (*c* 1.00, $CHCl_3$); ν_{max}(neat) 2965, 2932, 2910, 2873, 2836, 1665, 1629, 1450, 1431, 1381, 1359, 1205, 1143, 1114, 894, 798 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (br s, 1H, CH-7), 2.72-2.65 (m, 2H, CH_2-4β), 2.64-2.55 (m, 2H, CH_2-4α), 2.44 (br s, 1H, CH-5), 2.20-2.18 (m, 1H, CH_2-9a), 2.16-2.14 (m, 1H, CH_2-9b), 2.90-1.87 (m, 1H, CH-1), 1.83 (dt, *J* = 12.0, 3.0 Hz, 1H, CH_2-8a), 1.79 (d, *J* = 2.0 Hz, 3H, CH_3-6α), 1.57 (dt, *J* = 12.0, 3.0 Hz, 1H, CH_2-8b), 1.17 (br s, 3H, CH_3-2α), 1.12 (br s, 3H, CH_3-2α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9 (C-4), 134.1 (C-6), 123.0 (CH-7), 120.7 (CN), 51.3 (C-2), 40.3 (CH-5), 35.5 (CH_2-4α), 34.0 (CH-1), 31.9 (CH_3-6α), 29.2 (CH_2-9), 28.0 (CH_3-2α), 25.9 (CH_2-8), 24.2 (CH_3-2α), 13.8 (CH_2-4β); GC/MS R_t = 6.455 min, *m/z* 216 (18 M), 177 (27), 136 (27), 121 (14), 93 (100), 77 (18 %). HRMS (ES): $C_{14}H_{20}N_2$ calcd: 217.1699 $[M+H]^+$; found: 217.1705 $[M+H]^+$.

4.1.6 Methyl 2-(2,2,6-trimethyl-3-azabicyclo[3.3.1]nona-3,6-dien-4-yl)acetate ***2h***

(40 mg, 0.17 mmol, 2 %) as a yellow-green oil; R_f ($CHCl_3$) 0.75; $[\alpha]_D^{21}$ –42.38 (*c* 1.00, $CHCl_3$); ν_{max}(neat) 3259, 2960, 2943, 1649, 1595, 1229, 1139, 1049 cm^{-1}; ^{1}H NMR (500 MHz , $CDCl_3$) δ 8.51 (s, 1H, OH), 5.41 (s, 1H, CH-7), 4.75 (s, 1H, CH_2-4αa), 4.64 (s, 1H, CH_2-4αb), 4.38 (s, 1H, CH-4α), 3.63 (s, 3H, OCH_3), 2.47 (s, 1H, CH-5), 2.35-2.32 (m, 1H, CH_2-8a), 2.23-2.22 (m, 2H, CH_2-9), 2.10 (dt, *J* = 6.0, 3.0 Hz, 1H, CH_2-8b), 1.94 (s, 1H, CH-1), 1.73 (br s, 3H, CH_3-6α), 1.31 (br s, 3H, CH_3-2α), 1.24 (br s, 3H, CH_3-2α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1 (C=O), 163.4 (C-4), 136.0 (C-6), 121.8 (CH-7), 108.3 (CH_2-4α, keto), 82.9 (CH-4α, enol), 54.9 (C-2), 50.2 (OCH_3), 47.0 (CH-5), 35.5 (CH-1), 33.0 (CH_3-2α), 30.8 (CH_3-2α), 27.7 (CH_3-6α), 24.4 (CH_2-9), 23.5 (CH_2-8); GC/MS R_t = 6.643 min, *m/z* 235 (50 M), 220 (88), 204 (14), 188 (100), 160 (10), 121 (11), 93 (17), 93 (14 %). HRMS (ES): $C_{14}H_{21}NO_2$ calcd: 236.1645 $[M+H]^+$; found: 236.1639 $[M+H]^+$.

4.1.7 Ethyl 2-(2,2,6-trimethyl-3-azabicyclo[3.3.1]nona-3,6-dien-4-yl)acetate ***2i***

(139 mg, 0.557 mmol, 7 %) as a yellow oil; R_f (1:9 ethyl acetate/ dichloromethane) 0.9; $[\alpha]_D^{22}$ –123.92 (*c* 1.00, $CHCl_3$); ν_{max}(neat) 3261, 2963, 2933, 1647, 1599, 1490, 1468, 1293, 1280, 1140, 1051, 782 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (br s, 1H, OH), 5.40 (br s, 1H, CH-7), 4.73 (s, 1H, CH_2-4αa), 4.63 (s, 1H, CH_2-4αb), 4.38 (s, 1H, CH-4α), 4.11-4.05 (m, 2H, CH_2-4γ), 2.46 (br s, 1H, CH-5), 2.35-2.32 (m, 1H, CH_2-8a), 2.22-2.18 (m, 1H, CH_2-8b), 2.10 (dt, *J* = 12.5, 3.0 Hz, 1H, CH_2-9a), 1.93 (br s, 1H, CH-1), 1.81-1.79 (m, 1H, CH_2-9b), 1.74 (br s, 3H, CH_3-6α), 1.30 (br s, 3H, CH_3-2α), 1.25 (t, *J* = 7.5 Hz, 3H, CH_3-4δ), 1.24 (br s, 3H, CH_3-2α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9 (C=O), 164.2 (C-4), 136.0 (C-6), 121.7 (CH-7), 108.2 (CH_2-4α, keto), 80.0 (CH-4α, enol), 58.6 (CH_2-4γ), 55.2 (C-2), 40.1 (CH-5), 35.0 (CH-1), 33.1 (CH_3-2α), 28.9 (CH_3-2α), 28.6 (CH_2-8), 25.4 (CH_2-9), 22.1 (CH_3-6α), 15.0 (CH_3-4δ); GC/MS R_t = 17.968 min, *m/z* 249 (42 M), 234 (78), 204 (17), 188 (100), 162 (11), 93 (21 %). HRMS (ES): $C_{15}H_{23}NO_2$ calcd: 250.1802 $[M+H]^+$; found: 250.1805 $[M+H]^+$.

4.1.8 (4Z)-4-(2-Ethoxy-2-hydroxy-ethylidene)-2,2,6-trimethyl-3-azabicyclo[3.3.1]nonan-6-ol ***4i***

(56 mg, 0.21 mmol, 3 %) as a pale red solid; m.p. 92 °C, R_f (1:9 ethyl acetate/dichloromethane) 0.66; $[\alpha]_D^{20}$ –33.26 (*c* 1.00, $CHCl_3$); ν_{max}(neat) 3470, 3287, 2984, 2951, 2912, 2874, 1739, 1625, 1578, 1493, 1454, 1365, 1342, 1330, 1272, 1230, 1145, 1133, 1102, 1052, 1029, 962, 907, 784, 714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.50 (br s, 1H, OH), 4.35 (s, 1H, CH-4α), 4.04-4.14 (m, 2H, $O\underline{CH_2}CH_3$), 2.24 (dt, *J* = 13.0, 3.0 Hz, 1H, CH_2-9a), 2.14 (br s, 1H, CH-5), 1.93 (dt, *J* = 13.0, 3.0 Hz, 1H, CH_2-9b), 1.86-1.82 (m, 2H, CH_2-8a, CH_2-7a), 1.79-1.72 (m, 1H, CH_2-7b), 1.68 (br s, 1H, CH-1), 1.44-1.41 (dt, 1H, CH_2-8b), 1.29 (br s, 3H, CH_3-2α), 1.28 (br s, 3H, CH_3-2α), 1.27 (br s, 3H, CH_3-6α), 1.26 (br s, 3H, $OCH_2\underline{CH_3}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C=O), 162.9 (C-4), 83.0 (CH-4α), 71.5 (C-6), 58.3 ($O\underline{C}H_2CH_3$), 54.5 (C-2), 46.6 (CH-5), 35.2 (CH-1) 32.9 (CH_2-7), 32.6 (CH_3-6α), 30.5 (CH_3-2α), 27.3 (CH_3-2α), 24.1 (CH_2-8), 23.2 (CH_2-9), 14.6 ($OCH_2\underline{C}H_3$); GC/MS R_t = 19.42 min, *m/z* 267 (52 M), 252 (100), 222 (26), 206 (70), 197 (17), 182 (17), 148 (19), 96 (30), 43 (26 %). HRMS (ES): $C_{15}H_{25}NO_3$ calcd: 268.1907 $[M+H]^+$; found: 268.1898 $[M+H]^+$.

4.1.9 2,2,6-Trimethyl-4-[(E)-styryl]-3-azabicyclo[3.3.1]nona-3,6-diene ***2f***

(1.067 g, 4.03 mmol, 53 %) as a yellow wax; R_f (0.5:9.5 ethanol/ethyl acetate) 0.69; $[\alpha]_D^{18}$ –35.11 (*c* 0.23, $CHCl_3$); ν_{max}(neat) 3321, 2965, 2929, 1607, 1451, 1331, 1255, 1212, 1186, 1153, 972, 752, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.5 Hz, 2HAr, H-4d), 7.34 (t, *J* = 7.5, 2HAr, H-4e), 7.28 (t, *J* = 7.5 Hz, 1HAr, 4f), 7.16 (d, *J* = 16.5 Hz, 1H, H-4b), 6.88 (d, *J* = 16.5 Hz, 1H, H-4a), 5.38 (br s, 1H, CH-7), 3.19 (br s, 1H, CH-5), 2.19-2.30 (m, 2H, CH_2-8), 1.96 (br s, 1H, CH-1), 1.89 (dt, *J* = 2.5, 12.0 Hz, 1H, CH_2-9a), 1.78 (br s, 3H, CH_3-6α), 1.73 (dt, *J* = 2.5, 12.0 Hz, 1H, CH_2-9b), 1.28 (br s, 3H, CH_3-2α), 1.26 (br s, 3H, CH_3-2α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9 (C-4), 136.7 (C-4c), 135.4 (CH-4b), 135.1 (C-6), 131.8 (CH-4a), 129.0 (CH-4d), 128.9 (CH-4f), 127.5 (CH-4e), 122.8 (CH_2-8), 59.9 (C-2), 35.8 (CH-5), 34.5 (CH-1), 32.5 (CH_3-2α), 29.4 (CH_2-8), 27.8 (CH_3-2α), 25.8 (CH_2-9), 24.1 (CH_3-6α); GC/MS R_t = 6.10 min, *m/z* 265 (50 M), 250 (14), 224 (7), 136 (21), 130 (18), 115 (14) 93 (100) 77 (18 %). HRMS (ES): $C_{19}H_{23}N$ calcd: 266.1903 $[M+H]^+$; found: 266.1901 $[M+H]^+$.

4.1.10 4-(3,4-Dimethoxyphenyl)-2,2,6-trimethyl-3-azabicyclo[3.3.1]nona-3,6-diene **2g**

(948 mg, 3.17 mmol, 42 %) as a pale yellow wax; R_f (1:1 ethyl acetate/hexane) 0.46; $[\alpha]_D^{21}$ +66.64 (*c* 1.00, $CHCl_3$); ν_{max}(neat) 2969, 2937, 2838, 1637, 1608, 1585, 1508, 1458, 1270, 1162, 1134, 1028,

916, 771 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (br s, 1H, CH-7), 7.24 (dd, *J* = 2.0, 8.5 Hz, 1H, Ar-4αf), 6.88 (d, *J* = 2.0 Hz, 1H, Ar-4αb), 6.87 (d, *J* = 2.0 Hz, 1H, Ar-4αe), 4.40 (br s, 1H, CH-5), 3.96 (br s, 3H, OCH_3), 3.94 (br s, 3H, OCH_3), 2.01 (dt, *J* = 2.5 Hz, 13.5, 1H, CH_2-9a), 1.96-1.93 (m, 1H, CH_2-8a), 1.89-1.87 (m, 1H, CH_2-9b), 1.77-1.69 (m, 1H, CH-1), 1.72 (dt, *J* = 4.5, 14.0 Hz, 1H, CH_2-8b), 1.42 (br s, 3H, CH_3-2α), 1.28 (br s, 3H, CH_3-2α) 1.14 (br s, 3H, CH_3-6α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2 (C-4), 152.1 (C-4αa), 149.6 (C-4αc), 149.1 (C-4αd), 128.6 (C-6), 119.0 (C-4αf), 110.7 (CH-4αb), 110.5 (CH-4αe), 110.3 (CH-7), 56.8 (C-2), 56.4 (OCH_3), 56.4 (OCH_3), 35.9 (CH-5), 34.7 (CH-1), 32.1 (CH_3-2α), 27.7 (CH_3-6α), 26.9 (CH_3-2α), 25.3 (CH_2-8), 24.6 (CH_2-9); GC/MS R_t = 22.22 min, *m/z* 299 (46 M), 164 (29), 136 (35), 121 (14) 93 (100), 77 (15 %). HRMS (ES): $C_{19}H_{25}NO_2$ calcd: 300.1958 $[M+H]^+$; found: 300.1963 $[M+H]^+$.

4.1.11 (4-Bromophenyl)-(2,2,6-trimethyl-3-azabicyclo[3.3.1]nona-3,6-dien-4-yl)methanone **8j**
(372 mg, 1.08 mmol, 14 %) as a honey colour oil; R_f (1:3 ethyl acetate/hexane) 0.94; $[\alpha]_D^{22}$ – 31.48 (c 1.00, $CHCl_3$); ν_{max}(neat) 2957, 2929, 2870, 1665, 1655, 1587, 1460, 1384, 1272, 1231, 1071, 1013, 899, 810, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 2H, Ar-4αb), 7.56 (d, *J* = 8.5 Hz, 2H, Ar-4αc), 5.43 (br s, 1H, CH-7), 3.45 (br s, 1H, H-5), 2.32-2.25 (m, 2H, CH_2-8), 1.99 (d, *J* = 3.0 Hz, 1H, H-1), 1.91 (dt, *J* = 2.5, 12.0 Hz, 1H, CH_2-9a), 1.77 (dt, *J* = 2.5, 12.0 Hz, 1H, CH_2-9b), 1.52 (br s, 3H, CH_3-6α), 1.32 (br s, 3H, CH_3-2α), 1.26 (br s, 3H, CH_3-2α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.2 (C=O), 166.5 (C-4), 134.9 (C-4αa), 134.5 (C-4αd), 132.6 (2C, C-4αb & C-4αf), 131.8 (2C, C-4αc & C-4αe), 128.8 (C-6), 122.8 (CH-7), 61.3 (C-2), 35.1 (CH-5), 34.5 (CH-1), 31.3 (CH_3-2α), 29.3 (CH_2-8), 27.8 (CH_3-2α), 25.3 (CH_2-9), 23.3 (CH_3-6α); GC/MS R_t = 8.19 min, *m/z* 345 (29 M), 330 (54), 304 (18), 183 (27), 155 (18), 93 (100), 77 (19 %). HRMS (ES): $C_{18}H_{20}{}^{79}BrNO$ calcd: 346.0801 $[M+H]^+$; found: 346.0803 $[M+H]^+$.

4.1.12 (4-Nitrophenyl)-(2,2,6-trimethyl-3-azabicyclo[3.3.1]nona-3,6-dien-4-yl)methanone **8k**
(211 mg, 0.677 mmol, 12 %) as a deep red oil; R_f (1:3 ethyl acetate/hexane) 0.99; $[\alpha]_D^{23}$ –34.77 (*c* 1.04, $CHCl_3$); ν_{max}(neat) 2967, 2933, 2870, 1672, 1603, 1525, 1460, 1346, 1272, 1231, 1110, 905, 856, 810, 706 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 7.5, 2H, Ar-4αc & Ar-4αe), 8.08 (dd, *J* = 7.0, 2H, Ar-4αb & Ar-4αf), 5.45 (br s, 1H, H-7), 3.52 (br s, 1H, H-5), 2.31-2.33 (m, 2H, CH_2-9), 2.01 (s, 1H, H1), 1.89 (dt, *J* = 3.0, 12.5 Hz, 1H, CH_2-8a), 1.79 (dt, *J* = 3.0, 12.5 Hz, 1H, CH_2-8b), 1.57 (br s, 3H, CH_3-6α), 1.33 (br s, 3H, CH_3-2α) 1.26 (br s, 3H, CH_3-2α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.2 (C=O), 166.4 (C-4), 150.3 (C-4αd), 141.3 (C-4αa), 134.8 (C-6), 132.1 (2C, CH-4αb & CH-4αf), 123.4 (2C, CH-4αc & CH-4αe), 123.0 (CH-7), 61.8 (C-2), 34.5 (CH-5), 34.4 (CH-1), 31.3 (CH_3-2α), 29.3 (CH_2-9), 27.7 (CH_3-2α), 25.3 (CH_2-8), 23.3 (CH_3-6α); GC/MS R_t = 23.44 min, *m/z* 312 (25M), 297 (50), 271 (24), 150 (24), 120 (25), 93 (100), 77 (23 %). HRMS (ES): $C_{18}H_{20}N_2O_3$ calcd: 313.1547 $[M+H]^+$; found: 313.1554 $[M+H]^+$.

2. *Standard conditions for hydride reduction of cyclic imines*

Compound **1a** (0.20 g, 0.85 mmol) was dissolved in dry CH_3OH (10 mL) in a 25 ml round bottom flask and fitted with a rubber septum and needle for ventilation of gases. The mixture was set to stir in an ice bath. To this mixture, $NaBH_4$ (224 mg, 5.93 mmol, 7 mol equiv.) was added and left to stir at 0 °C for about 30 minutes, then at room temperature overnight. Water was added (5 mL), followed by saturated $NaHCO_3$ (15 mL). The product was then extracted with $CHCl_3$ (2 x 20 mL).

The combined extracts were washed with saturated NaCl (20 mL) before drying over anhydrous Na_2CO_3 and the solvent removed under reduced pressure. The same procedure was adapted for the reduction of Imine-amides **1b**, **1c**, **1d** and **1e** and imine-alkenes **2a**, **2d** and **2e**.

4.2.1 N-((1S,4R,5R,6S)-2,2,4,6-Tetramethyl-3-azabicyclo[3.3.1]nonan-6-yl)acetamide **6a**
(195 mg, 0.819 mmol, 97 %) as a pale yellow solid; m.p. 100 °C; $[\alpha]_D^{25}$ +18.30 (*c* 1.43, $CHCl_3$); ν_{max}(neat) 3307, 2954, 2932, 1638, 1544, 1439, 1378, 1292, 1261, 1116, 754, 733, 665 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (s, 1H, NH), 3.37 (qd, *J* = 2.5, 7.5 Hz, 1H, CH-4), 2.46 (td, *J* = 5.5, 15.5 Hz, 1H, CH_2-7a), 2.31 (s, 1H, CH-5), 1.94 (s, 3H, $COCH_3$), 1.90-1.84 (m, 1H, CH_2-8a), 1.82-1.80 (m, 2H, CH_2-9), 1.56-1.54 (m, 2H, CH_2-7a and CH_2-8b), 1.52 (s, 3H, CH_3-6α), 1.30 (s, 1H, CH-1), 1.21 (d, *J* = 7.5 Hz, 3H, CH_3- 4α), 1.19 (s, 3H, CH_3-2α), 1.11 (s, 3H, CH_3-2α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (C=O), 57.9 (C-6), 53.3 (C-2), 51.3 (CH-4), 39.6 (CH-5), 35.6 (CH-1), 34.3 (CH_2-9), 30.1 (CH_2-7), 29.6 (CH_3-2α), 28.0 (CH_3-6α), 27.4 (CH_3-2α), 24.9 (CH_2-8), 24.8 ($CO\underline{C}H_3$), 23.1 (CH_3-4α); GC/MS (EI) R_t = 12.56 min, *m/z* 238 (20, M), 223 (100), 179 (26), 164 (26), 122 (26), 84 (46 %); HRMS (ES): $C_{12}H_{21}N$ calcd: 239.2118 $[M+H]^+$; found: 239.2121 $[M+H]^+$.

4.2.2 (1S,5S)-2,2,4,6-Tetramethyl-3-azabicyclo[3.3.1]non-6-ene **7a**
(125 mg, 0.626 mmol, 56 %) as a red wax; R_f (3:7 MeOH/CH_2Cl_2) 0.47; $[\alpha]_D^{25}$ −15.71 (*c* 0.47, $CHCl_3$); ν_{max}(neat) 2957, 2923, 2886, 1734, 1599, 1458, 1379, 1227, 1160, 1126, 1083, 1035, 1011, 918, 824, 800, 751 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (s, 1H, CH-7), 3.13 (qd *J* = 7.0, 2.5 Hz, 1H, CH-4), 2.20 -2.17 (m, 1H, CH_2-8s), 2.09-2.07 (m, 2H, CH_2-8b & CH_2-9a), 1.94 (d, *J* = 3.0 Hz, 1H, H-5), 1.71 (s, 3H, CH_3-6α), 1.60 (dt, *J* = 3.5, 9.5 Hz 1H, CH_2-9b), 1.43 (dt, *J* = 6.0, 3.0 Hz, 1H, CH-1), 1.21 (s, 3H, CH_3-2), 1.09 (s, 3H, CH_3-2α), 0.98 (d, *J* = 7.0 Hz, 3H, CH_3-4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.4 (C-6), 124.2 (CH-7), 53.6 (C-2) 50.1 (CH-4), 39.7 (CH-5), 34.3 (CH-1), 29.8 (CH_3-2α), 28.9 (CH_2-9), 22.6 (CH_2-8), 25.7 (CH_3-2α), 25.5 (CH_3-6α), 21.7 (CH_3-4α); GC/MS (EI) R_t = 11.09 min, *m/z* 179 (62 M), 164 (47), 136 (34), 124 (43), 93 (100), 44 (32 %); HRMS (ES): $C_{12}H_{21}N$ calcd: 180.1747 $[M+H]^+$; found: 180.1747 $[M+H]^+$.

4.2.3 N-(4-Ethyl-2,2,6-trimethyl-3-azabicyclo[3.3.1]nonan-6-yl)propanamide **6b**
(257 mg, 0.967 mmol, 42 %) as a white solid; m.p. 103 °C, R_f (1:3 ethyl acetate/hexane) 0.13; $[\alpha]_D^{23}$ +26.80 (*c* 1.05, $CHCl_3$); ν_{max}(neat) 3302, 3069, 2957, 2933, 2877, 1637, 1544, 1460, 1432, 1382, 1361, 1261, 1236, 1119, 1086, 974, 808 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29 (br s, NH), 3.02 (ddd, *J* = 2.0, 7.0, 2.5 Hz, 1H, CH-4), 2.53 (td, *J* = 4.5, 13.5, 1H, CH_2-7a), 2.48 (br s, 1H, CH-5), 2.16 (qd, *J* = 1.0, 7.5 Hz, 2H, $CO\underline{CH_2}CH_3$), 1.87-1.93 (m, 1H, CH_2-8a), 1.83 (dt, *J* = 3.0, 13.5 Hz, 1H, CH_2-9a), 1.77-1.76 (m, 1H, CH_2-9b), 1.74-1.66 (m, 1H, CH_2-4αa), 1.52 (br s, 3H, CH_3-6α), 1.50-1.48 (m, 1H, CH_2-8b), 1.47-1.45 (m, 1H, CH_2-7b), 1.40-1.37 (m, 1H, CH_2-4αb), 1.32-1.31 (m, 1H, CH-1), 1.18 (br s, 3H, CH_3-2α), 1.14 (t, *J* = 7.5 Hz, 3H, $COCH_2\underline{CH_3}$), 1.11 (br s, 3H, CH_3-2α), 0.96 (t, *J* = 7.5 Hz, 3H, CH_3-4β); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0 (C=O), 59.4 (CH-4), 57.9 (C-2), 53.6 (C-6), 38.1 (CH-5), 36.5 (CH-1), 35.1 (CH_2-7), 31.2 ($CO\underline{CH_2}CH_3$), 30.7 (CH_2-9), 29.9 (CH_3-2α), 29.7 (CH_2-4α), 27.7 (CH_3-2α), 27.5 (CH_3-6α), 25.4 (CH_2-8), 12.7 (CH_3-4β), 10.5 ($COCH_2\underline{CH_3}$); GC/MS R_t = 7.22 min, *m/z* 266 (5M), 251 (25), 237 (100), 136 (25), 98 (30), 58 (50 %). HRMS (ES): $C_{16}H_{30}N_2O$ calcd: 267.2431 $[M+H]^+$; found: 267.2430 $[M+H]^+$.

4.2.4 N-(4-butyl-2,2,6-trimethyl-3-azabicyclo[3.3.1]nonan-6-yl)pentanamide **6c**

(289 mg, 0.899 mmol, 82 %) as a pale yellow wax; $[\alpha]_D^{19}$ +13.36 (*c* 1.00, $CHCl_3$); ν_{max}(neat) 3325, 3182, 2958, 2931, 2874, 1642, 1541, 1508, 1459, 1438, 1381,1217, 1118, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.29 (s, 1H, NH), 3.12-3.09 (m, 1H, H-4), 2.53 (td, *J* = 4.5, 13.5 Hz, 1H, CH_2-7a), 2.46 (s, 1H, CH-5), 2.13 (t, *J* = 7.0 Hz, 2H, CH_2-6αa), 1.92-1.89 (m, CH_2-8a), 1.82-1.81 (m, 2H, CH_2-4αa), 1.69-1.65 (m, 1H, CH_2-9a), 1.65-1.56 (m, 2H, CH_2-6αb), 1.52 (br s, 3H, CH_3-2α), 1.51-1.42 (m, 2H, CH_2-8b & $CH_2$7b), 1.39-1.32 (m, 8H, CH_2-9b, CH-1, CH_2-4αb, CH_2-4αc, CH_2-6αc), 1.18 (br s, 3H, CH_3-2α), 1.11 (br s, 3H, CH_3-2α), 0.93 (t, *J* = 7.0 Hz, 3H, CH_3-6αd), 0.90 (t, *J* = 6.5 Hz, 3H, CH_3-4αd); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4 (C=O), 58.1 (C-2), 57.61 (CH-4), 53.6 (C-6), 38.6 (CH-5), 38.1 (CH_2-6a), 36.8 (CH_2-9), 36.5 (CH-1), 35.1 (CH_2-7), 30.8 (CH_2-4αa), 30.7 (CH_2-4αb), 29.9 (CH_3-6), 28.4 (CH_2-6αb), 27.7 (CH_3-2α), 27.7 (CH_3-2α), 25.6 (CH_2-8), 23.2 (CH_2-4αc), 22.7 (CH_2-6αc), 14.4 (CH_3-4αd), 14.2 (CH_3-6αd); GC/MS R_t = 22.53 min, *m/z* 322 (2 M), 307 (18), 265 (100), 222 (9), 206 (9), 164 (25), 126 (25), 86 (31 %). HRMS (ES): $C_{20}H_{38}N_2O$ calcd: 323.3057 $[M+H]^+$; found: 323.3037 $[M+H]^+$.

4.2.5 N-((1S,4S,5R,6S)-2,2,6-Trimethyl-4-phenyl-3-azabicyclo[3.3.1]nonan-6-yl)benzamide **6e**

(39 mg, 0.11 mmol, 94 %) as a pale yellow semi-solid; $[\alpha]_D^{20}$ +73.42 (*c* 1.00, $CHCl_3$); ν_{max}(neat) 3337, 2969 , 2933, 1709, 1639, 1525 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.5 Hz, 2H, Ar-6γb & Ar-6γf), 7.49 (d, *J* = 7.5 Hz, 2H, Ar-6γc & Ar-6γe), 7.46 (t, *J* = 7.5 Hz, 1H, Ar-6γd), 7.41 (t, *J* = 7.5 Hz, 2HAr, Ar-4αb & Ar-4αf), 7.32 (t, *J* = 7.5 Hz, 2H, Ar-4αc & Ar-4αe), 7.19 (t, *J* = 7.5 Hz, 1H, Ar-4αd), 5.94 (s, 1H, HNCO), 4.57 (br s, 1H, CH-5), 3.29 (s, 1H, NH), 2.80 (td, *J* = 5.0, 14.5 Hz, 1H, CH-4), 2.08 (s, 1H, CH-1), 2.05-2.02 (m, 2H, CH_2-7), 1.68-1.61 (m, 2H, CH_2-8), 1.48-1.45 (m, 2H, CH_2-9), 1.27 (s, 6H, $2CH_3$-2α). 0.84 (s, 3H, CH_3-6α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2 (C=O), 166.4 (C-4αa), 145.4 (C-6γa), 131.5 (2C, CH-6γb & CH-6γf), 131.0 (CH-4), 129.1 (2C, CH-6γc & CH-6γe), 128.7 (CH-6γd), 128.4 (2C, CH-4αb & CH-4αf), 127.1 (2C, CH-4αc & CH-4αe), 126.7 (CH-4αd), 58.8 (C-6), 53.4 (C-2), 36.0 (CH-5), 34.8 (CH-1), 30.0 (CH_2-7), 29.7 (CH_3-6α), 27.3 (CH_3-2α), 27.0 (CH_3-2α), 25.1 (CH_2-9), 24.9 (CH_2-8). GC/MS (EI): R_t = 27.89 min, *m/z* 362 (38 M), 347 (34), 271 (13), 242 (18), 186 (25), 146 (33) 122 (18), 105 (100), 91 (25), 77 (47 %); HRMS (ES): $C_{24}H_{31}N_2O$ calcd: 363.2436 $[M+H]^+$; found: 363.2324 $[M+H]^+$.

4.2.6 (4S,7S,8S)-2,2,6-Trimethyl-4-phenyl-3-azabicyclo[3.3.1]non-6-ene **7e**

(266 mg, 1.10 mmol, 80 %); R_f (5:80:15, MeOH/EtOAc/n-hexane); $[\alpha]_D^{20}$ –20.84 (*c* 1.00, $CHCl_3$); ν_{max}(neat) 2961, 2922, 2883, 2836, 1600, 1439, 1382 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.5 Hz, 2H, Ar-4αb & Ar-4αf), 7.21 (d, *J* = 7.5 Hz, 2H, Ar-4αc & Ar-4αe), 7.16 (t, *J* = 7.5 Hz, 1H, Ar-4αd), 5.53 (s, 1H, CH-7), 4.26 (s, 1H, CH-5), 2.35 (d, *J* = 3.0 Hz, 1H, CH-4), 2.31-2.25 (m, 2H, CH_2-9) 1.71 (dt, *J* = 3.0, 12.0 Hz, 2H, CH_2-8), 1.64 (s, 1H, NH), 1.51 (t, *J* = 3.0 Hz, 1H, CH-1), 1.30 (s, 3H, CH_3-2α), 1.22 (s, 3H, CH_3-6α), 0.87 (s, 3H, CH_3-2α) ppm; ^{13}C NMR (125MHz, $CDCl_3$) δ 143.6 (C-6) 133.4 (C-4αa), 128.0 (2C, CH-4αb & CH-4αf), 126.6 (CH-4αd), 125.7 (2C, CH-4αc & CH-4αe), 124.1 (CH-7), 57.1 (CH-5), 53.8 (C-2), 42.6 (CH-4), 34.4 (CH-1), 30.1 (CH_3-6α), 29.4 (CH_2-9), 27.7 (CH_2-8), 25.6 (CH_2-2α), 24.2 (CH_2-2α) ppm. GC/MS (EI): R_t = 17.75 min, *m/z* 241 (59 M), 226 (37), 146 (63), 106 (100), 93 (63), 79 (22 %). HRMS (ES): $C_{17}H_{24}N$ calcd: 242.1903 $[M+H]^+$; found: 242.1901 $[M+H]^+$.

4.2.7 2-Chloro-N-((1S,4S,5R,6S)-4-(chloromethyl)-2,2,6-trimethyl-3-azabicyclo[3.3.1]nonan-6-yl)acetamide **6d**

(139 mg, 0.45 mmol, 88 %) as a pale yellow solid; m.p. 88 °C; $[\alpha]_D^{25}$ +76.42 (*c* 0.5, $CHCl_3$); ν_{max}(neat) 3282, 2987, 2963, 2919, 2899, 2876, 2708, 1673, 1643, 1551, 1458, 1438, 1318, 1251, 1110, 720 cm^{-}

[1]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (s, 1H, NHCO), 3.97 (s, 2H, $COCH_2Cl$), 3.78 (dd, *J* = 2.5, 10.5 Hz, 1H, CH_2Cl-4αa), 3.66 (t, *J* = 10.0, 1H, CH_2Cl-4αb), 3.46 (dt, *J* = 2.5, 10.5 Hz, 1H, CH-4), 2.65 (td, *J* = 5.0, 15.5 Hz, 1H, CH_2-7a), 2.54 (br s, 1H, CH-5), 1.98-1.94 (m, 1H, CH_2-8a), 1.83 (q, *J* = 3.0 Hz, 2H, CH_2-9), 1.56-1.50 (m, 2H, CH_2-7b & CH_2-8b), 1.45 (s, 3H, CH_3-6α), 1.38 (t, *J* = 3.0 Hz, 1H, CH-1), 1.21 (s, 3H, CH_3-2α), 1.16 (s, 3H, CH_3-2α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4 (C=O), 59.4 (CH-4), 57.5 (C-6), 53.4 (C-2), 50.5 (CH_2Cl-4α), 43.1 ($CO\underline{C}H_2Cl$), 38.9 (CH-5), 35.9 (CH-1), 34.2 (CH_2-7), 30.0 (CH_2-9), 29.4 (CH_3-2α), 27.4 (CH_3-6α), 26.9 (CH_3-2α), 24.8 (CH_2-8); GC/MS (EI) R_t = 21.44 min, *m/z* 306 (9 M), 291 (100), 271 (81), 257 (29), 121 (32), 58 (41 %); HRMS (ES): $C_{14}H_{24}Cl_2N_2O$ calcd: 307.1266 $[M+H]^+$; found: 307.1266 $[M+H]^+$.

4.2.8 4-(Chloromethyl)-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-6-ene **7d**

(45 mg, 0.21 mmol, 85 %) as a yellow waxy liquid; R_f (diethyl ether) 0.98; $[\alpha]_D^{20}$ –8.63 (*c* 0.24, CH_2Cl_2); ν_{max}(neat) 3412, 3309, 2929, 2956, 1665, 1527, 1458, 1384, 1262, 1115, 1091, 1080, 804 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (br s, 1H, CH-7), 3.37 (dd, *J* = 7.0, 10.5 Hz, 1H, CH_2Cl-4αa), 3.28 (dd, *J* = 2.5, 10.5 Hz, 1H, CH_2Cl-4αb), 3.23 (td, *J* = 2.5, 2.5 Hz, 1H, CH-4), 2.29 (d, *J* = 2.0 Hz, 1H, CH-5), 2.28-2.22 (m, 1H, CH_2-9a), 2.10-2.03 (m, 2H, CH_2-9b & CH_2-8a), 1.71 (br s, 3H, CH_3-6α), 1.64 (dt, *J* = 2.5, 12.5 Hz, 1H, CH_2-8b), 1.48-1.46 (m, 1H, CH-1), 1.21 (br s, 3H, CH_3-2α), 1.11 (br s, 3H, CH_3-2α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8 (C-6), 132.5 (C-2), 125.9 (CH-7), 57.1 (CH-4), 48.0 (CH_2Cl-4α), 36.5 (CH-5), 35.2 (CH-1), 30.2 (CH_3-2α), 29.0 (CH_2-8), 28.1 (CH_2-9), 26.1 (CH_3-2α), 25.2 (CH_3-6α); GC/MS R_t = 6.10 min, *m/z* 213 (28 M), 198 (66), 178 (43), 164 (25), 118 (50), 93 (100), 84 (31), 77 (18 %). HRMS (ES): $C_{12}H_{20}ClN$ calcd: 214.1357 $[M+H]^+$; found: 214.1354 $[M+H]^+$.

3. Polar bridged Ritter reaction conditions

Sulfuric acid (18 M, 2 mL) was stirred in a flask fitted with a reflux condenser and a drying tube at 0 °C. To the reaction flask, the nitrile (53.4 mol, 7 mol equiv. of (–)-β-pinene) was added. A solution of (–)-β-pinene (1.2 mL, 7.62 mmol) in 10 mL glacial acetic acid was added dropwise to the reaction mixture, *via* the condenser. After 30 min the reaction was allowed to reach room temperature and left to stir for 24 h. The reaction was then quenched by the addition of 30 mL of water. The reaction mixture was then washed with CH_2Cl_2 to remove any neutral impurities before being basified with 4 M NaOH (until pH > 10). The reaction mix was then extracted with $CHCl_3$ (2 X 15 mL) and dried with Na_2CO_3.

4.3.1 (2,2,4,6-Tetramethyl-3-azabicyclo[3.3.1]non-3-en-6-yl) acetate **5a**

(154 mg, 0.649 mmol, 9 %) as a pale yellow oily wax; R_f (1:3 ethyl acetate/hexane) 0.83; $[\alpha]_D^{20}$ +72.64 (*c* 1.00, $CHCl_3$); ν_{max}(neat) 2949, 2927, 1732, 1649, 1627, 1458, 1367, 1245, 1220, 1200, 1157, 1099, 1018 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.12 (br s, 1H, CH-5), 2.06 (s, 3H, $COCH_3$), 2.05 (s, 3H, CH_3-4), 1.83 (s, 1H, CH_2-7a), 1.79-1.76 (m, 1H, CH_2-7b), 1.75 (t, *J* = 2.5 Hz, 1H, CH_2-8a), 1.74 (t, *J* = 3.5 Hz, 1H, CH_2-9a), 1.73-1.70 (m, 2H, CH_2-8b & CH_2-9b), 1.63-1.62 (m, 1H, CH-1), 1.57 (s, 3H, CH_3-6α), 1.27 (s, 3H, CH_3-2α), 1.16 (s, 3H, CH_3-2α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 ($\underline{C}OCH_3$), 165.9 (C-4), 82.9 (C-6), 58.5 (C-2), 42.2 (CH-5), 34.2 (CH-1), 33.0 (CH_2-7), 31.9 (CH_3-2α), 29.7 ($CO\underline{CH_3}$), 26.6 (CH_3-2α), 26.5 (CH_3-6α), 24.8 (CH_2-9), 24.1 (CH_2-8), 22.7 (CH_3-4α); GC/MS R_t = 14.658 min, *m/z* 237 (57 M),222 (2),

194 (100), 178 (64), 162 (22), 136 (68), 122 (61), 93 (78), 43 (49 %). HRMS (ES): $C_{14}H_{23}NO_2$ calcd: 238.1802 $[M+H]^+$; found: 238.1805 $[M+H]^+$.

4.3.2 (4-Ethyl-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-3-en-6-yl) acetate **5b**

(77 mg, 0.31 mmol, 4 %) as a yellow wax; R_f (1:3 hexane / diethyl ether) 0.46; $[\alpha]_D^{22}$ +35.72 (*c* 1.00, $CHCl_3$); ν_{max}(neat) 2969, 2933, 2875, 1736, 1652, 1460, 1369, 1242, 1201, 1026, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.19 (br s, 1H, CH-5), 2.67 (qd, *J* = 3.5, 7.5 Hz, 2H, CH_2-4α), 2.05 (s, 3H, $COCH_3$), 1.82-1.78 (m, 3H, CH_2-8, CH_2-9a), 1.75-1.71 (m, 2H, CH_2-7), 1.66-1.63 (m, 2H, CH-1, CH_2-9b), 1.53 (s, 3H, CH_3-6α), 1.28 (s, 3H, CH_3-2α), 1.14 (s, 3H, CH_3-2α), 1.09 (t, *J* = 7.5 Hz, 3H, CH_3-4β); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9 (C=O), 170.6 (C-4), 83.2 (C-6), 58.3 (C-2), 40.0 (CH-5), 35.2 (CH_2-4α), 34.5 (CH-1), 32.9 (CH_2-8), 32.0 (CH_3-2α), 26.5 (CH_3-2α), 26.2 (CH_3-6α), 24.9 (CH_2-7), 24.5 (CH_2-9), 22.7 ($CO\underline{C}H_3$), 12.9 (CH_3-4β); GC/MS R_t = 15.127 min, *m/z* 251 (57 M),236 (18), 208 (100), 192 (82), 176 (31), 150 (27), 136 (81), 93 (42 %). HRMS (ES): $C_{15}H_{25}NO_2$ calcd: 252.1958 $[M+H]^+$; found: 252.1956 $[M+H]^+$.

4.4 Amide deprotection of 5d

A solution of compound **5d** (194.4 mg, 0.64 mmol) dissolved in dry MeOH (10 mL), was added to a solution of thiourea (93.3 mg, 1.23 mmol, dissolved in dry MeOH (5 mL) and acetic acid (1 mL). The reaction mixture was refluxed overnight (24 hr). The resulting suspension was cooled to room temperature before the water (10 mL) was added. The solution was then basified with 2 M NaOH until the pH was 14. The mixture was extracted with $CHCl_3$ (2x15mL). The solvent was then removed under reduced pressure to give **9d** (123.6 mg, 0.54 mmol). NMR and GC/MS analyses indicated that the product was pure and was used for the bioassay without further purification.

4.5.1 (1S,4S,5R,6S)-4-(Chloromethyl)-2,2,6-trimethyl-3-azabicyclo[3.3.1]nonan-6-amine **9d**

(124 mg, 0.537 mmol, 85 %) as a yellow wax; $[\alpha]_D^{23}$ +18.83 (*c* 1.63, MeOH); ν_{max}(neat) 3321, 2923, 2577, 2113, 1523, 1456, 1437, 1379m 1256, 1116, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.67-3.63 (m, 2H, CH_2-4α), 3.43 (dt, *J* = 2.5, 9.5 Hz, 1H, CH-4), 2.49 (td, *J* = 5.0, 14.0 Hz, 1H, CH_2-7a), 2.12 (dt, *J* = 3.0, 14.0 Hz, 1H, CH_2-9a), 1.91-1.86 (m, 2H, CH_2-8a & CH_2-9b), 1.74 (dt, *J* = 5.0, 14.5 Hz, 1H, CH_2-8b), 1.69 (s, 1H, CH-5), 1.39-1.37 (m, 1H, CH-1), 1.37-1.34 (m, 1H, CH_2-7b), 1.26 (s, 3H, CH_3-6α), 1.20 (s, 3H, CH_3-2α), 1.14 (s, 3H, CH_3-2α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.8 (C-6), 60.3 (CH-4), 53.8 (C-2), 51.0 (CH_3-6α), 50.7 (CH_2-4α), 44.2 (CH-5), 36.4 (CH-1), 35.1 (CH_2-7), 29.9 (CH_2-9), 29.5 (CH_3-2α), 27.3 (CH_3-2α), 24.8 (CH_2-8); GC/MS (EI) R_t = 16.64 min, *m/z* 230 (10), 215 (100), 195 (16), 118 (35), 70 (48 %); HRMS (ES): $C_{12}H_{23}ClN_2$ calcd: 231.1623 $[M+H]^+$; found: 231.1618 $[M+H]^+$.

4.5 Reductive alkylation of 5a

Compound **5a** (100.0 mg, 0.42 mmol) was dissolved in MeCN (5 mL), to which sodium cyanoborohydride (502.0 mg, 7.99 mmol), 28 % formaldehyde solution (37 mL) and a few drops of acetic acid were added. The solution was stirred for 3 hours at room temperature. The solvent was removed *via* reduced pressure to give, both yellow and colourless crystals. These were triturated with hexane, the hexane then decanted and the remaining solid dried under reduced pressure to give the yellow crystals of **10a** (48.0 mg, 0.19 mmol, 45 %).

4.4.1 N-((1S,4R,5R,6S)-2,2,3,4,6-Pentamethyl-3-azabicyclo[3.3.1]nonan-6-yl)acetamide **10a**
(48 mg, 0.19 mmol, 45 %) as a pale yellow solid; m.p. 165 °C; $[\alpha]_D^{25}$ +13.89 (*c* 0.37, $CHCl_3$); ν_{max}(neat) 3313,2981, 2960, 2943, 2881, 2846, 2802, 2789, 1638, 1545, 1465, 1439, 1380, 1370, 1310, 1299, 1246, 1223, 1030, 958, 718 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (s, 1H, NH), 2.89 (qd, *J* = 2.0, 7.0 Hz, 1H, CH-4), 2.65 (td, *J* = 4.5, 14.0 Hz 1H, CH_2-7a), 2.41 (br s, 1H, CH-5), 2.08 (s, 3H, NCH_3), 1.96-1.94 (m, 1H, CH_2-8a), 1.94 (s, 3H, $COC\underline{H}_3$), 1.82 (qd, *J* = 3.0, 13.5 Hz, 1H, CH_2-9a), 1.75 (dt, *J* = 3.0, 13.5 Hz, 1H, CH_2-9b), 1.52 (s, 3H, CH_3-6α), 1.46 (dt, *J* = 4.5, 14.0 Hz, 1H, CH_2-8b), 1.42-1.39 (m, 1H, CH_2-7b), 1.29 (br s, 1H, CH-1), 1.21 (d, *J* = 7.0 Hz, 3H, CH_3-4α), 1.17 (s, 3H, CH_3-2α), 0.98 (s, 3H, CH_3-2α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (C=O), 58.2 (CH-4), 57.5 (C-6), 57.4 (C-2), 41.8 (CH-5), 39.9 (CH-1), 34.4 (CH_2-9), 33.7 (CH_3-3α), 30.0 (CH_2-7), 28.5 (CH_3-2α), 28.1 (CH_3-6α), 25.0 (CH_2-8), 24.5 ($CO\underline{C}H_3$), 22.5 (CH_3-4α), 16.9 (CH_3-2α); GC/MS (EI) R_t = 8.28 min, *m/z* 252 (4 M), 237 (100), 178 (22), 58 (37 %); HRMS (ES): $C_{15}H_{28}N_2O$ calcd: 253.2275 $[M+H]^+$; found: 253.2276 $[M+H]^+$.

4.6 DMAD addition of 1a

Compound **1a** (502.3 mg, 2.13 mmol) was dissolved in $CHCl_3$ (15 mL) and then heated to reflux temperature. A solution of DMAD (309 mg, 2.18 mmol) dissolved in $CHCl_3$ (5 mL) was added dropwise to the refluxing solution via the condenser. Once all the DMAD solution was added, the reaction was left to reflux for 4 hours. After which, the reaction was allowed to cool to room temperature before the solvent was removed under reduced pressure to obtain a dark yellow foam like the wax crude product (952 mg). The crude product was purified on an alumina column using a 40 % n-hexane and 60 % ethyl acetate as the mobile phase to give pure **11** as a red-orange solid (458.6 mg, 1.21 mmol, 57 %).

4.6.1 Dimethyl 2-((1S,5S,6S)-6-acetamido-2,2,6-trimethyl-4-methylene-3-azabicyclo[3.3.1]nonan-3-yl)maleate **11**
(459 mg, 1.21 mmol, 57 %) as red orange solid; m.p. 50 °C; R_f (4:6 n-hexane/ethyl acetate) 0.40; $[\alpha]_D^{25}$ −464.16 (*c* 1.02, $CHCl_3$); ν_{max}(neat) 3309, 2950, 1715, 1654, 1585, 1542, 1433, 1370, 1340, 1277, 1234, 1205, 1144, 989, 943, 840, 727 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (s, 1H, H-3β) 5.26 (s, 1H, NH), 4.61 (s, 1H, CH_2-4αa), 4.44 (s, 1H, CH_2-4αb), 3.73 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.34 (br s, 1H, CH-5), 2.63 (td, *J* = 14.5, 5.0 Hz, CH_2-7a), 2.05 (s, 3H, $NCOC\underline{H}_3$), 2.04-2.00 (m, 2H, CH_2-8a & CH_2-9a), 1.96 (s, 3H, CH_3-2α), 1.90 (dt, *J* = 3.0, 10.5 Hz, CH_2-9b), 1.62-1.55 (m, 1H, CH_2-8b), 1.52-1.51 (m, 1H, CH-1), 1.45 (s, 3H, CH_3-6α), 1.40 (s, 3H, CH_3-2α), 1.33 (dd, 1H, *J* = 14.5, 5.0 Hz, CH_2-7b); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6 (C=O), 167.1 (C=O), 166.4 (C=O), 147.1 (C-4), 146.8 ($\underline{C}$=CH), 106.7 (C=$\underline{C}H_2$-4α), 60.5 (C-6), 56.1 (C-2), 52.4 (OCH_3), 51.4 (OCH_3), 41.4 (CH-1), 41.3 (CH-5), 31.0 (CH_2-7), 26.0 ($CO\underline{C}H_3$), 25.9 (CH_3-6α), 25.7 (CH_2-9), 24.7 (CH_3-2α), 24.3 (CH_3-2α), 23.8 (CH_2-8); GC/MS (EI) R_t = 18.27 min, *m/z* 378 (18 M), 363 (18), 319 (100), 287 (79), 260 (67) 208 (18), 70 (31 %); HRMS (ES): $C_{20}H_{30}N_2O_5$ calcd: 379.2227 $[M+H]^+$; found: 379.2229 $[M+H]^+$.

4.7 X-ray Structure Analysis

4.7.1 Diffraction Data Collection

Suitable single crystals of compounds **(+)-6a**, **(+)-6b** and **4i** were selected under the polarizing microscope (Leica M165Z), were picked up on a MicroMount (MiTeGen, USA) consisting of a thin polymer tip with a wicking aperture. The X-ray diffraction measurements were carried out on a Bruker kappa-II CCD diffractometer at 150 K by using graphite-monochromated Mo-Kα radiation (λ = 0.710723 Å). The single crystals, mounted on the goniometer using cryo loops for intensity measurements, were coated with paraffin oil and then quickly transferred to the cold stream using an Oxford Cryo stream attachment.

4.7.2 Solution and Refinement

Symmetry-related absorption corrections using the program SADABS[17] were applied, and the data were corrected for Lorentz and polarisation effects using Bruker APEX2 software.[18] All structures were solved by direct methods and the full-matrix least-square refinements were carried out using SHELXL.[19] The non-hydrogen atoms were refined anisotropically. The molecular graphics were generated using Olex2[20] and Mercury.[21] Key crystallographic data and refinement details are presented in Table 5.

Table 5. Crystal data and structure refinement for compounds **4i**, **(+)-6a**, **(+)-6b**.

	4i	**(+)-6a**	**(+)-6b**
Crystal data			
Chemical formula	$2(C_{15}H_{25}NO_3)$	$C_{14}H_{26}N_2O$	$C_{16}H_{30}N_2O$
M_r	534.72	238.37	266.42
Crystal system, space group	Monoclinic, *Cc*	Monoclinic, $P2_1$	Monoclinic, $P2_1$
Temperature (K)	152	155	151
a, *b*, *c* (Å)	9.9601 (8), 19.406 (2), 7.8544 (6)	8.4055 (5), 9.5712 (5), 9.4883 (5)	9.259 (2), 9.523 (2), 10.244 (3)
β (°)	98.746 (5)	112.922 (1)	115.841 (7)
V (Å^3)	1500.5 (2)	703.06 (7)	813.0 (4)
Z	2	2	2
Radiation type	Mo *K*α	Mo *K*α	Mo *K*α
μ (mm^{-1})	0.08	0.07	0.07
Crystal size (mm)	0.16 × 0.13 × 0.07	0.20 × 0.14 × 0.04	0.23 × 0.13 × 0.03
Data collection			
Diffractometer	Bruker *APEX*-II CCD	Bruker *APEX* II	Bruker *APEX*-II CCD
Absorption correction	Multi-scan *SADABS2014*/5 (Bruker,2014/5) was used for absorption correction. wR2(int) was 0.1524 before and 0.0504 after correction.	Multi-scan *SADABS2007*/4 (Bruker,2007/4) was used for absorption correction. wR2(int) was 0.0482 before and 0.0371 after correction.	Multi-scan *SADABS2014*/5 (Bruker,2014/5) was used for absorption correction. wR2(int) was 0.1284 before and 0.0603 after correction.

	The Ratio of minimum to maximum transmission is 0.8365. The λ/2 correction factor is 0.00150.	The Ratio of minimum to maximum transmission is 0.8847. The λ/2 correction factor is 0.0015.	The Ratio of minimum to maximum transmission is 0.8287. The λ/2 correction factor is 0.00150.
T_{min}, T_{max}	0.624, 0.746	0.660, 0.746	0.618, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	11273, 3088, 2334	5997, 2937, 2874	5777, 2504, 1629
R_{int}	0.056	0.025	0.061
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.640	0.639	0.641
Refinement			
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.047, 0.113, 1.05	0.031, 0.083, 1.05	0.051, 0.121, 0.99
No. of reflections	3088	2937	2504
No. of parameters	177	258	191
No. of restraints	2	1	2
H-atom treatment	H-atom parameters constrained	All H-atom parameters refined	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.17, -0.17	0.22, -0.13	0.21, -0.22
CCDC number	1485895	1485896	1485897

5. Crystal structure data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers 1485895, 1485896 and 1485897. The data can be obtained free of charge via http://www.ccdc.cam.ac.uk or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223/336-033, Tel.: (+44) 1223/336-408.

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