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An efficient synthesis of 3-alkyl-1,5,3-dioxazepanes and their use as electrophiles in double-Mannich reactions

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ABSTRACT

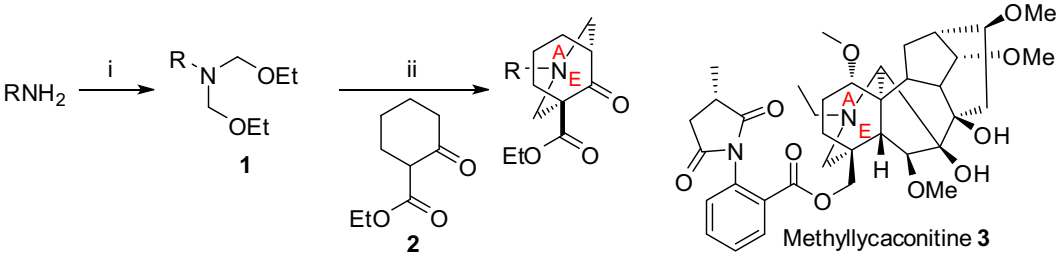
An efficient synthesis of 3-alkyl 1,5,3-dioxazepanes was developed for subsequent use in double-Mannich reactions with a variety of carbon-based nucleophiles. It was found that addition of methyltrichlorosilane to the dioxazepane led to a long-lasting reactive species that reacted rapidly with acid-sensitive ketones and β-ketoesters to afford azabicyclo[3.3.1]nonanes in good yield.

1. Introduction

The use of *N*-alkyl bis(aminol)ethers **1** in double-Mannich reactions with β-ketoester **2** has allowed the rapid, high-yielding synthesis of bicyclic amines as AE ring analogues of methyllycaconitine **3** (Scheme 1).[1] To date, the reported syntheses of bis(aminol)ethers have typically only proceeded in low to moderate yield,[1] have required distillation to isolate the product from oligomeric impurities, and have exhibited low product stability. These problems pose practical barriers for their use with expensive or high molecular weight amines.

2. Results and discussion

In order to improve the overall efficiency of the reaction sequence, alternative bis(iminium) ion precursors were desired. 3-Alkyl-1,5,3-dioxazepanes were first reported by Kapnang and co-workers[2] and were later employed by that group as electrophiles in double-Grignard additions, forming differentially-substituted tertiary amines in good yields.[3] More recently, a double-Mannich reaction of 3-benzyl-1,5,3-dioxazepane with cyclopentanone activated by iodotrimethylsilane was reported by Ooka et al.[4] With these encouraging precedents, a range of 3-alkyl-1,5,3-dioxazepanes **4a**–**g** were synthesized by modification of Kapnang's method[2] via condensation of a primary amine, excess paraformaldehyde and ethylene glycol with azeotropic removal of water (Table 1).



Scheme 1. Reagents and conditions: (i) paraformaldehyde, K_2CO_3, EtOH, 3 d, 11–47%; (ii) **1**+**2**, $MeSiCl_3$, 18 h, 75–99%.

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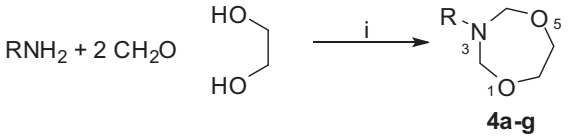
Table 1
Reagents and conditions: (i) paraformaldehyde (1.5 equiv), ethylene glycol (1.1 equiv), amine (1 equiv), benzene or toluene, Δ, Dean–Stark apparatus, 3–16 h



4a-g

Entry	R	Yield	Compound
1	Me	54[a]	**4a**
2	Et	73[b]	**4b**
3	*n*-Bu	97	**4c**
4	*t*-Bu	70[b]	**4d**
5	Bn	Quant.	**4e**
6	$Ph(CH_2)_3$	97	**4f**
7	(*R*)-α-MeBn	89	**4g**

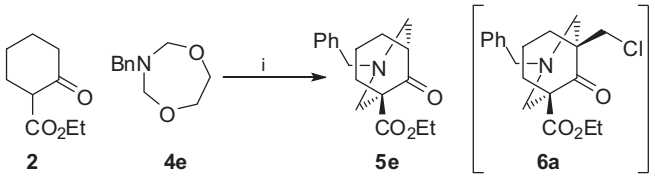
[a] Aqueous methylamine (40%) used.
[b] Product distilled under reduced pressure.

Initially, the products were purified by distillation in good yields (entries 2 and 4). It was subsequently discovered that nearly quantitative yields of spectroscopically pure product could be achieved through dilution of the crude reaction mixture with *n*-hexane and washing with water, thereby eliminating the need for distillation (entries 3, 5–7). The use of more polar solvents than *n*-hexane in the extraction step, such as ethyl acetate or diethyl ether, proved to be ineffective in removing impurities. The synthesis of *N*-methyl-dioxazepane **4a** proved to be low yielding (entry 1), which was likely to be due to the use of a 40% aqueous solution of methylamine for the reaction. The use of methylamine hydrochloride with potassium carbonate however, also resulted in low yields.

2.1. Selection of an efficient activator for *N*-alkyl-1,5,3-dioxazepanes with β-ketoester 2

Having successfully optimized the synthesis of 3-alkyl-1,5,3-dioxazepanes, several Lewis acids were evaluated as activators for the double-Mannich reaction of β-ketoester **2** with 1,5,3-dioxazepane **4e** in dichloromethane (Table 2).

Table 2
Reagents and conditions: (i) activator, CH_2Cl_2

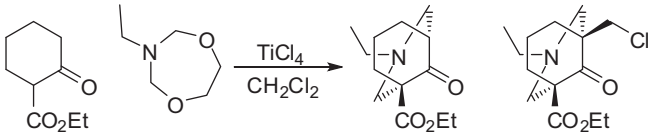


2 **4e** **5e** **6a**

Entry	Activator	Equiv	Temperature (°C)	Time (h)	Yield (%)
1	$SnCl_4$	1.0	0 °C to rt	18	0
2	$BF_3{\cdot}OEt_2$	1.0	0 °C to rt	18	0
3	AcCl	2.0	rt	18	0
4	$Me_2SiCl(OEt)$	1.0	rt	18	55
5	$Sm(OTf)_3$	0.1	rt	20	66
6	$SOCl_2$	1.0	0 °C to rt	5	67
7	Me_2SiCl_2	1.5	rt	18	72
8	Me_3SiCl	3.0	rt	16	85
9	$MeSiCl_3$	1.0	rt	22	88
10	$TiCl_4$	0.25	0 °C to rt	48	90[a]
11	$TiCl_4$	0.5	0 °C to rt	18	90[a]
12	$TiCl_4$	1.0	0 °C to rt	24	90[a]

[a] Crude yield with side product **6a** ca. 2%.

Use of 1 equiv of $SnCl_4$, $BF_3{\cdot}OEt_2$, or 2 equiv of acetyl chloride failed to effect the desired reaction whilst use of 0.1 equiv of samarium(III) triflate (entry 5) gave **5e** in moderate yield. Whilst thionyl chloride (entry 6) also gave **5e** in moderate yield it occurred in a rapid exothermic reaction and was thus not investigated further. Amongst the chlorosilane activators (entries 4, 7–9), methyltrichlorosilane[5] proved to be the most efficient in terms of stoichiometry, reaction time and yield, consistent with related work published in our group.[1] The use of titanium(IV) chloride (entries 10–12) as a Lewis acid activator initially appeared to afford the highest yields. Unfortunately the crude mixture was contaminated with a closely related side product **6a** and product isolation proved difficult with a red gum also forming in the reaction mixture, which complicated silica gel chromatography. The structure of **6a** was determined after the related *N*-ethyl adduct **6b** (Scheme 2) was isolated and characterised in pure form.



2 **4b** **5b** **6b**

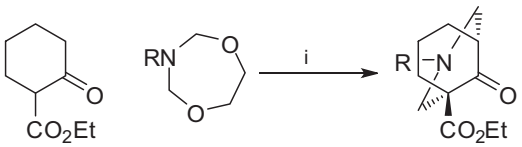
Scheme 2. Reagents and conditions: $TiCl_4$ (0.5 equi.), CH_2Cl_2, 0 °C to rt, 18 h, **5b**, 19%, **6b**, 2.2%.

The incorporation of the chloromethyl substituent into **6b** is thought to occur via a methylenation product based on similar reported examples.[6,7] Having identified $MeSiCl_3$ as the most efficient Lewis acid activator, attention next focused on examining the substrate scope of the reaction.

2.2. Reaction of *N*-alkyl-1,5,3-dioxazepanes 4b–g with β-ketoester 2

The results of the methyltrichlorosilane-activated double-Mannich reaction of β-ketoester **2** with a range of *N*-alkyl-1,5,3-dioxazepanes **4b–g** are summarized in Table 3.

Table 3
Reagents and conditions: (i) 3-alkyl-1,5,3-dioxazepane (1.25 equiv), $MeSiCl_3$ (1.0 equiv), CH_2Cl_2, 0 °C to rt



2 **4b-g** **5b-g**

Entry	Dioxazepane	R	Yield (%)	Product
1	**4b**	Et	89	**5b**
2	**4c**	*n*-Bu	Quant.	**5c**
3	**4d**	*t*-Bu	69	**5d**
4	**4e**	Bn	88	**5e**
5	**4f**	$Ph(CH_2)_3$	Quant.	**5f**
6	**4g**	(*R*)-α-MeBn	Quant.[a]	**5g**

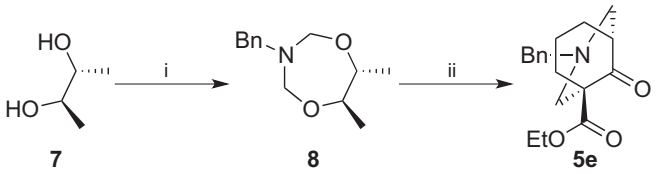
[a] Mixture (1:1) of diastereomers.

Yields were generally high with the exception of adduct **5d** (entry 3), which may be due to the highly acidic conditions cleaving the *N*-*tert*-butyl group. Short-chain aliphatic amines (entries 1 and 2), afforded clean products after carrying out an acid–base wash (see Experimental section). For *N*-benzyl adduct **5f** (entry 4), a short silica gel column purification was required to eliminate polar material. Disappointingly, whilst giving a quantitative yield of adduct

5g, the use of chiral 1,5,3-dioxazepane **4g**, afforded no diastereoselectivity in the double-Mannich reaction.

2.3. Reaction of chiral 1,5,3-dioxazepane 10 with β-ketoester 2

Disappointed with the lack of diastereoselectivity observed for the double-Mannich reaction using chiral dioxazepane **4g**, attention next focused on the use of chiral diol **7** to prepare chiral dioxazepane **8** in order to probe the stereoselectivity upon reaction with β-ketoester **2** (Scheme 3). Disappointingly, use of the methyltrichlorosilane-mediated conditions gave adduct **5e** in 36% yield with no enantioselectivity, as determined by chiral stationary phase HPLC.



Scheme 3. Reagents and conditions: (i) paraformaldehyde (1.5 equiv), diol (1 equiv), benzylamine (1 equiv), toluene, Δ, Dean–Stark apparatus, 16 h, 27% (ii) **8** (1.25 equiv), β-ketoester 2 (1 equiv), $MeSiCl_3$ (1 equiv), CH_2Cl_2, 0 °C to rt, 36%.

2.4. Reaction of *N*-alkyl-1,5,3-dioxazepane 4e with ketones 9a–d

Attention next shifted to investigating the substrate scope of the double-Mannich reaction using alternative carbon nucleophiles (Table 4). The reaction proceeded well with ketone **9a**, cyclic β-ketoester **9b** and diketone **9c** all affording adducts **10a–c** in high yields. Acyclic β-ketoester **9d** gave piperidone **10d** as a single diastereoisomer in modest 49% yield.

2.5. NMR study of the reaction of *N*-ethyl-1,5,3-dioxazepane 5b with methyltrichlorosilane

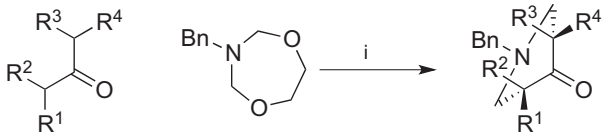
A simple ^1H and ^{13}C NMR study was next carried out to examine the effect of altering the order of addition by initially activating 3-ethyl-1,5,3-dioxazepane **4b** in the absence of a nucleophile. Therefore 0.5, 1.0 and 1.5 equiv of methyltrichlorosilane were added to **4b** in $CDCl_3$ in three separate NMR tubes and their ^1H NMR spectra (Fig. 1) recorded. This latter method of activation would be useful for subsequent reactions with acid-sensitive enols.

After 20 min with periodic agitation, the spectra for the reaction using 1.0 and 1.5 equiv of $MeSiCl_3$ were virtually identical to each other with a new single dominant species being observed. The 0.5 equiv experiment afforded a more complex and line-broadened ^1H spectrum compared to the other experiments with a weak ^{13}C resonance observed at circa δ 160 ppm—within the typical range for an imine or iminium ion species.[8,9] The spectra obtained for the reactions using 1.0 and 1.5 equiv of methyltrichlorosilane remained unchanged after 4 days in the sealed NMR tubes and the presence of an imine or iminium ion was supported by a strong ^{13}C resonance at ~160 ppm.

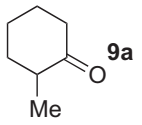
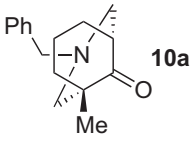
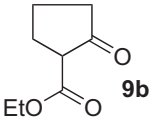
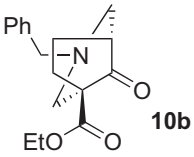
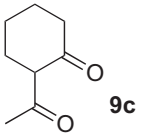
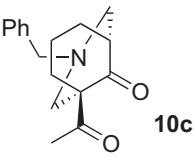
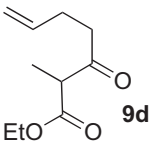
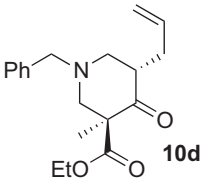
β-Ketoester **2** (1 equiv) was then added to the 1.0 equiv trial reaction and the mixture agitated for ca. 5 min. The ^1H NMR spectrum subsequently indicated the absence of the previously observed peaks, with the appearance of new resonances upfield consistent with formation of an azabicyclo[3.3.1]nonane **5b** (Fig. 2).

After workup of the reaction mixture a quantitative yield of azabicyclo[3.3.1]nonane **5b** was afforded. With this result in hand, the synthesis of double-Mannich adducts using this order of addition of reagents, and stoichiometry, was next attempted with acid-sensitive substrates.

Table 4
Reagents and conditions: (i) **4e** (1.25 equiv), $MeSiCl_3$ (1.0 equiv), CH_2Cl_2, 0 °C to rt, 18 h



9a-d **4e** **10a-10d**

Entry	Nucleophile	Product	Yield (%)
1	 **9a**	 **10a**	Quant.
2	 **9b**	 **10b**	88
3	 **9c**	 **10c**	Quant.
4	 **9d**	 **10d**	49

2.6. Application of the new addition protocol to acid-sensitive enol precursors

*2.6.1. Use of α-oxygenated ketone **11**.* The first sensitive substrate attempted was 2-benzyloxycyclohexanone **11**, a precursor to an AE ring analogue **12** of lappaconitine **13** (Scheme 4).[10] Prior attempts in the literature to apply a double-Mannich reaction to 2-oxygenated cyclohexanones have resulted in a very low 5% yield[11] or a mixture of isomeric products.[12]

2-Benzyloxycyclohexanone **11** was synthesized in two steps by copper(II) tetrafluoroborate-catalyzed opening of commercially available cyclohexene oxide with excess benzyl alcohol.[13] The pre-activation methodology developed above was then applied to the reaction of ketone **11** with *N*-ethyl-dioxazepane **5b** affording the double-Mannich adduct **12** in an improved 35% yield.

*2.6.2. Use of β-ketoester **16** containing a cyclic acetal for the synthesis of C-6 oxygenated AE ring analogues of MLA.* C-6 oxygenated AE ring analogues of MLA **3** have yet to be synthesized via a double-Mannich strategy (Fig. 3).[14] The methyl ether present at C-1 in MLA has been identified as participating in key non-covalent interactions between MLA and *Aplysia* acetylcholine-binding protein; 'a structural and functional surrogate' for the receptor domain in nAChRs.[15] Incorporation of C-6 oxygenation into AE ring analogues of MLA may therefore increase their potency.

It was anticipated that the bicyclic methyl ether **14** could be synthesized diastereoselectively in two steps by reduction of the C-6 ketone from the less-hindered top face, followed by methylation. Protection of the C-6 ketone as a 1,3-dioxolane in **15** facilitates the

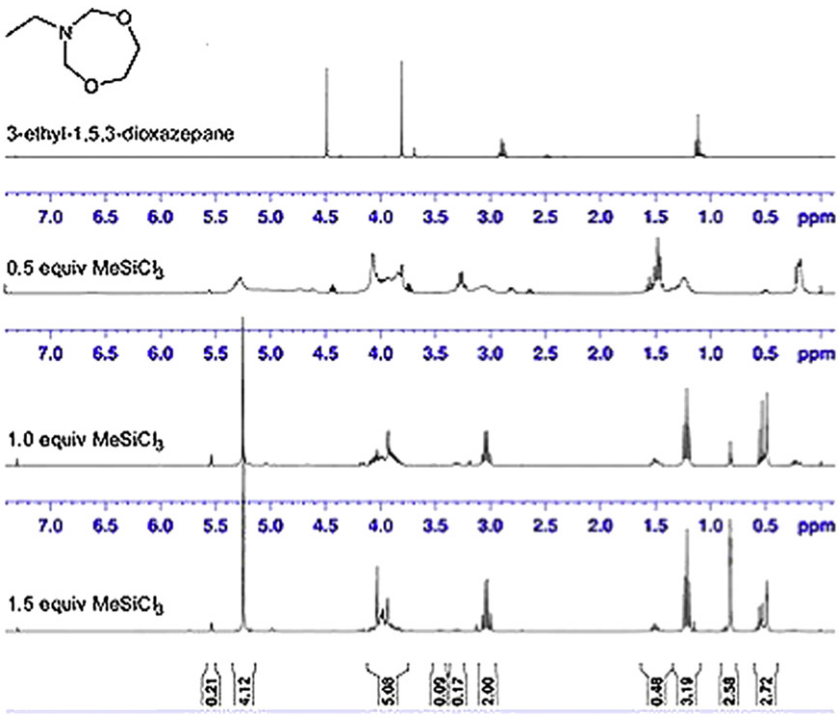


Fig. 1. ^{1}H NMR spectra of 3-ethyl-1,5,3-dioxazepane **4b** and its activated species.

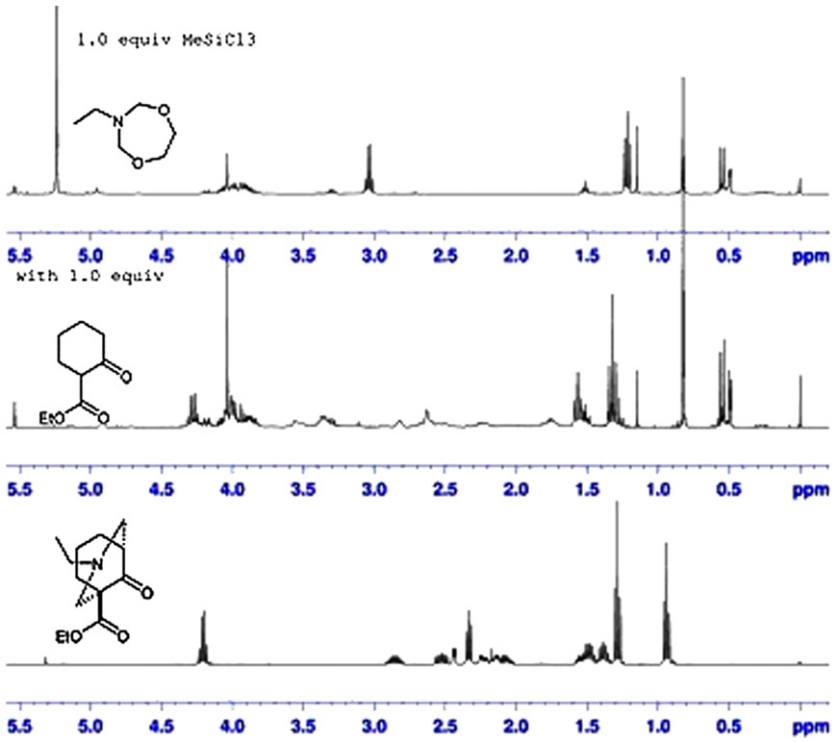
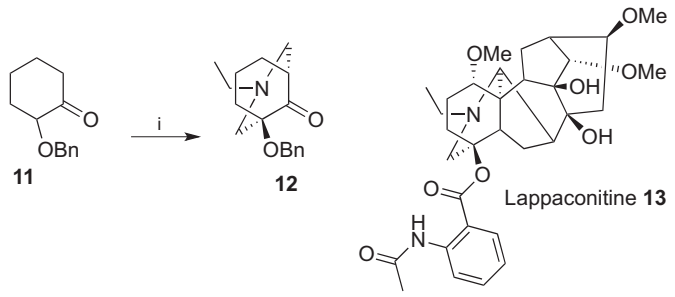


Fig. 2. Reaction of ethyl 2-oxocyclohexane-1-carboxylate 2 with the activated species.

selective functionalisation of the ketone and can be formed from **16** by double-Mannich reaction.

In order to examine this possibility, β-ketoester **16** bearing a cyclic acetal at the C-5 position was synthesized from methyl vinyl ketone and diethyl malonate in a four-step sequence (Scheme 5).

Methyl vinyl ketone and diethyl malonate were condensed in a sealed tube in the presence of potassium carbonate to give the conjugate addition product **17** in 63% yield after purification by fractional distillation.[16] Intramolecular cyclization of diester **17** with sodium ethoxide afforded a crude mixture containing diketo ester **18** that was used without purification in the next reaction. Acetal formation with 1 equiv of ethylene glycol afforded a separable mixture of isomeric ketals **16** and **19** in a combined 58% yield.[17] β-Ketoester **16** was then subjected to the titanium tetrachloride



Scheme 4. Reagents and conditions: (i) **5b** (1.25 equiv), $MeSiCl_3$ (1.0 equiv), CH_2Cl_2, 0 °C to rt, 35%.

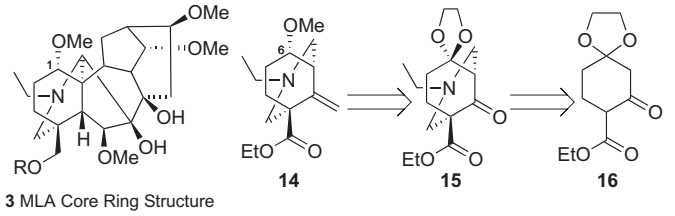


Fig. 3. Proposed synthesis of oxygenated bicyclic analogues of MLA **3**.

activated double-Mannich reaction using the above optimized conditions to afforded bicyclic amine **20** in 53% yield.

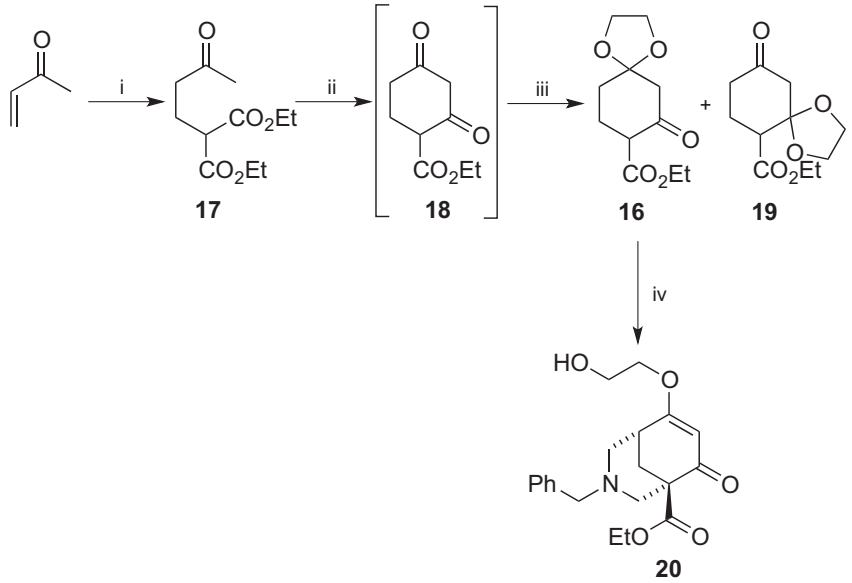
The formation of bicycle **20** can be rationalized if the ring opening of the dioxolane ring to form conjugated vinyl enol ether **21** is faster than the competing Mannich reaction with β-ketoester **16** (Fig. 4). After the initial Mannich reaction of β-ketoester intermediate **21**, isomerization of **22** leads to homoenolate **23** that is in close proximity to the pendant iminium ion enabling rapid Mannich cyclization. The presence of the vinyl enol ether moiety alpha to the ketone prevents the addition of the iminium ion to the desired C-3 position.

To test whether the use of a silyl enol ether could suppress this reaction pathway by increasing the reaction rate of the Mannich reaction over acetal cleavage, trimethylsilyl enol ether **24** was synthesized in 91% yield from β-ketoester **16** (Scheme 6).[18] In order to suppress the ring opening of the dioxolane ring use of methyltrichlorosilane rather than titanium tetrachloride was examined. Thus, silyl enol ether **24** was subjected to the methyltrichlorosilane-activated double-Mannich reaction using *N*-ethyl-1,5,3-dioxazepane **4b** to afford the desired bicyclic amine **15**. The use of dichloromethane or THF gave modest yields of the desired azabicyclo[3.3.1]nonane (entries 1 and 2). However, by changing the solvent to dry dimethylformamide the adduct could be obtained in 70% yield (entry 3). Dimethylformamide is known to be an effective Lewis base for the enhancement of Lewis acidity in chlorosilane complexes and the higher yield may be due to an additional rate enhancement based on this effect.[19]

Adduct **15** was converted to the known ether **14**[14] using the following standard transformations: Wittig olefination, acetal hydrolysis, reduction of the ketone and methylation. Previous double-Mannich approaches to bicycles such as **14** have been unsuccessful due to their incompatibility with acetal containing substrates. The present approach also offers the advantage that bicycle **14** is formed as a single diastereoisomer whilst previously mixtures of isomers were produced.[14]

3. Conclusion

A simple modification of Kapnang's method for the synthesis of *N*-alkyl-1,5,3-dioxazepanes **4a**–**g** involving an aqueous workup procedure afforded quantitative yields of the products that were free of impurities. The resultant *N*-alkyl-1,5,3-dioxazepanes were activated using a variety of Lewis acids and reacted with β-ketoesters to afford double-Mannich products **5a**–**g**, with methyltrichlorosilane providing the best results. Two chiral dioxazepanes were synthesized; one with chirality on the nitrogen **4g**, and another with chirality on the diol backbone **8**. Unfortunately, both chiral dioxazepanes induced no stereoselectivity in their reaction with β-ketoester **2** under the optimized conditions. It was found that in the absence of a nucleophile, 3-ethyl-1,5,3-dioxazepane **4b** and methyltrichorosilane formed a stable intermediate as observed by ^1H NMR. When exposed to β-ketoesters, this intermediate reacted to form a double-Mannich adduct in high yield. This new, pre-activation protocol was applied to double-Mannich reactions with acid-sensitive carbonyl compounds **11**, **16** and **24** to afford azabicyclo[3.3.1]nonanes that are significant AE ring analogues of MLA **3** and lappaconitine **13**.



Scheme 5. Reagents and conditions: (i) diethyl malonate (0.9 equiv), K_2CO_3 (0.1 equiv), neat, sealed tube, 18 h, 63%; (ii) NaOEt, EtOH, 0 °C to rt to Δ, 3 h, 94% crude; (iii) ethylene glycol (1.0 equiv), toluene, cat. *p*-TsA, Δ, Dean–Stark apparatus, 1 h, **16**: 36%, **19**: 22%; (iv) **4e** (1.25 equiv), $TiCl_4$ (1.0 equiv), CH_2Cl_2, 0 °C to rt o/n, 54%.

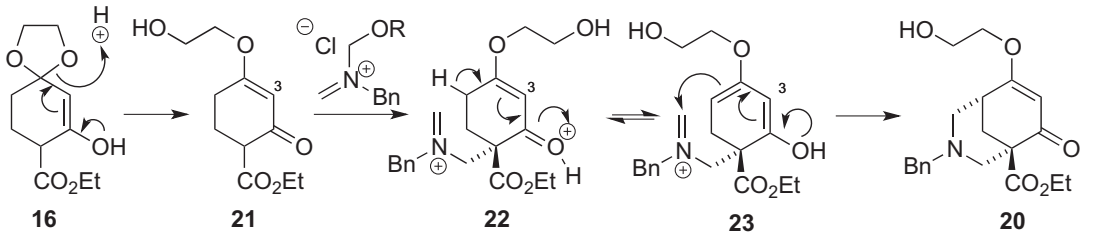
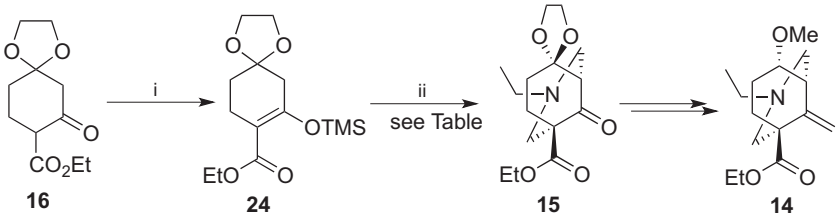


Fig. 4. Proposed mechanism for the formation of amine **20**.



Entry	Solvent	Yield (%)
1	DCM	33
2	THF	40
3	DMF	70

Scheme 6. Reagents and conditions: (i) Me_3SiCl (1.5 equiv), NEt_3 (1.5 equiv), toluene, rt 18 h, 91 %; (ii) 3-ethyl-1,5,3-dioxazepane **4b** (1.25 equiv), $MeSiCl_3$ (1.0 equiv), **24**, solvent, 0 °C to rt, 18 h.

4. Experimental section

4.1. General experimental

All reactions were carried out in oven-dried glassware. HPLC-grade THF and lab-grade DCM distilled from CaH_2 were dried over activated 3 Å molecular sieves. Dried EtOH was freshly distilled from $Mg(OEt)_2$. DMF, DMSO and Et_3N were dried over CaH_2 and distilled onto activated 4 Å molecular sieves. All other reagents were used as received. Thin-layer chromatography (TLC) was carried out using Merck silica gel plates using UV light (254 nm) as the primary visualisation method with supplementary visualisation by staining with vanillin in 95% ethanol, iodine on silica gel or aqueous potassium permanganate. Flash column chromatography was performed using Davisil LC60A 40–63 micron amorphous silica. Melting points were measured on a Reichert™ stage apparatus, Electrothermal™ capillary apparatus or a Stuart Scientific SMP3 melting point apparatus, with the melting points uncorrected. Optical rotations were measured with a Perkin Elmer 341 polarimeter using the sodium D line (589 nm), with the concentration measured in grams per 100 mL. 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}. NMR spectra were recorded on a Bruker Avance-300 or DRX400. High resolution mass spectra were recorded using a VG70-SE spectrometer or microTOF-Q mass spectrometer. Chiral stationary phase HPLC was carried out on a Daicel Chiralpak™ IC column using Dionex Ultimate 3000™ HPLC kit with Chromeleon software.

4.2. Preparation of *N*-substituted dioxazepanes 4a–g

4.2.1. 3-Methyl-1,5,3-dioxazepane ***4a***. Aq methylamine of 40%(10.0 g, 12.9 mmol), ethylene glycol (6.20 g, 10.0 mmol), and paraformaldehyde (7.40 g, 24.6 mmol) were mixed in a sealed tube at 0 °C; heated to 140 °C for 30 min then stirred at room temperature overnight. Benzene (35 mL) was added to the oil and heated under reflux with a Dean–Stark trap for 66 h. The solution was concentrated in vacuo to afford the *title compound* as a crude oil (6.30 g, 54%, circa 90% pure); δ_H (400 MHz, $CDCl_3$, Me_4Si) 2.63 (3H, s, NC*H*$_3$), 3.83 (4H, s, H-6, H-7), 4.45 (4H, s, H-2, H-4); δ_C (100 MHz, $CDCl_3$) 37.2 (*C*H$_3$), 69.1 (CH_2, C-6, C-7), 85.2 (CH_2, C-2, C-4); IR: ν_{max} (film)/cm^{-1} 2941, 2864, 1474, 1446, 1386, 1358, 1329, 1299, 1266, 1234, 1215, 1113, 1078, 1041, 1024, 951, 841, 792. LRMS *m*/*z* (ESI) 117 (M^+, 100), 99 (8); HRMS (ESI^+) found: 117.0804, calculated: 117.0790.

4.2.2. 3-Ethyl-1,5,3-dioxazepane ***4b***. Anhydrous ethylamine (9.50 g, 0.21 mol), ethylene glycol (12.5 g, 0.21 mol), and paraformaldehyde (12.1 g, 0.40 mol) were mixed in a sealed tube at 0 °C then heated to 140 °C for 1.5 h. Benzene (100 mL) was added to the oil and heated under reflux with a Dean–Stark trap for 1 h. The solution was concentrated in vacuo and the crude oil distilled under reduced pressure to afford the *title compound* as a colourless oil (19.0 g, 73%); bp=76–78 °C, 30 mmHg; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.12 (3H, t, *J*=7.2 Hz), 2.89 (2H, q, *J*=7.2 Hz), 3.81 (4H, s, H-6, H-7), 4.49 (4H, s, H-2, H-4); δ_C (75 MHz, $CDCl_3$) 13.3 (CH_3), 43.0 (CH_2), 69.1 (C-6, C-7), 83.2 (C-2, C-4); IR: ν_{max} (film)/cm^{-1} 2967, 2936, 2920, 2910, 2866, 1457, 1380, 1301, 1252, 1211, 1113, 1047, 976, 950, 844, 791, 652, 598; LRMS *m*/*z* (EI^+) 131 (M^+, 2), 129 (2), 118 (7), 114 (3), 103 (2), 99 (2), 85 (66), 83 (100), 74 (5), 71 (6), 62 (3), 58 (37), 47 (31), 42 (23), 35 (14); HRMS (EI^+) found: 131.0946, calculated: 131.0946.

4.2.3. General procedure for the preparation of N-substituted dioxazepanes ***4c–g***. To a mixture of the amine (1 equiv) and ethylene glycol (1.2 equiv) in benzene or toluene was added paraformaldehyde (2.5 equiv). The reaction mixture was heated under reflux with a Dean–Stark trap overnight. The solution was cooled, washed once with deionized water and brine. The aqueous washings were extracted with *n*-hexane and the combined organic layers dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated in vacuo to afford the following dioxazepanes.

4.2.4. 3-n-Butyl-1,5,3-dioxazepane ***4c***. Following the general procedure, from *n*-butylamine (7.70 g, 0.11 mol) in benzene (60 mL): 97% yield as a colourless oil; δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.92 (3H, t,

J=7.2 Hz), 1.27–1.39 (2H, m), 1.43–1.53 (2H, m), 2.83 (2H, t, J=7.2 Hz), 3.80 (4H, s, H-6, H-7), 4.47 (4H, s, H-2, H-4); δ_C (75 MHz, $CDCl_3$) 13.8 (CH_3), 20.1 (CH_2), 30.3 (CH_2), 48.4 (CH_2), 69.2 (C-6, C-7), 83.7 (C-2, C-4); IR: ν_{max} (film)/cm^{-1} 2930, 2863, 1456, 1375, 1302, 1269, 1208, 1112, 1059, 1041, 994, 947, 843, 791, 736, 658, 597; LRMS m/z (EI$^+$) 159 (M$^+$, 8), 116 (27), 98 (29), 86 (21), 72 (7), 57 (49), 42 (100). HRMS (ESI) found: 159.1262, calculated: 159.1259.

4.2.5. 3-tert-Butyl-1,5,3-dioxazepane ***4d***[20]. Following the general procedure, from *tert*-butylamine (7.70 g, 0.11 mol) in benzene (40 mL): 70% yield as a colourless oil; bp: 80 °C; 12 mmHg [lit. bp 80 °C; 12 mmHg][20]; δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.26 (9H, s), 3.86 (4H, s, H-6, H-7), 4.63 (4H, s, H-2, H-4); δ_C (100 Hz, $CDCl_3$) 29.9 ($(H_3C)_3C$), 61.2 ($(H_3C)_3C$) 68.6 (C-6, C-7), 80.8 (C-2, C-4); HRMS (EI$^+$) found: 159.1256, calculated: 159.1259.

4.2.6. 3-Benzyl-1,5,3-dioxazepane ***4e***. Following the general procedure, from benzylamine (10.0 g, 93.3 mmol) in toluene (60 mL): quantitative yield as a colourless oil; δ_H (300 MHz, $CDCl_3$, Me_4Si) 3.86 (4H, s, H-6, H-7), 4.01 (2H, s, CH_2Ph), 4.46 (4H, s, H-2, H-4), 7.22–7.24 (1H, m, *o*-Ph), 7.25–7.27 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 53.1 (CH_2Ph), 69.2 (C-6, C-7), 83.6 (C-2, C-4), 127.1 (CH, Ph), 128.3 (CH, Ph), 128.5 (CH, Ph), 138.3 (C, Ph); IR: ν_{max} (film)/cm^{-1} 3063, 3029, 2911, 2862, 1495, 1476, 1453, 1370, 1301, 1265, 1210, 1175, 1111, 1076, 1036, 1025, 951, 873, 842, 792, 738, 698, 669, 600, 571, 535, 526, 517; LRMS m/z (EI$^+$) 193 (M$^+$, 0.5), 133 (1), 119 (15), 91 (100), 65 (17), 51 (17), 41 (6), 39 (9); HRMS (EI$^+$) found: 193.1103, calculated: 193.1103.

4.2.7. 3-(3-Phenylpropyl)-1,5,3-dioxazepane ***4f***. Following the general procedure, from 3-phenylpropylamine (1.66 g, 12.3 mmol) in toluene (40 mL): 97% yield as a colourless oil; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.77–1.87 (2H, m, H-2'), 2.63 (2H, t, J=7.2 Hz, H-1'), 2.86 (2H, t, J=6.9 Hz, H-3'), 3.79 (4H, s, H-6, H-7), 4.47 (4H, s, H-2, H-4), 7.15–7.19 (3H, m, Ph), 7.25–7.30 (2H, m, Ph); δ_C (75 MHz, $CDCl_3$) 29.7 (CH_2, C-2'), 33.1 (CH_2, C-3'), 48.0 (CH_2, C-1'), 69.1 (2×CH_2, C-6, C-7), 83.7 (2×CH_2, C-2, C-4), 125.7, 128.3 (2×CH, Ph), 141.9 (C, Ph); IR: ν_{max} (film)/cm^{-1} 3025, 2913, 2862, 1496, 1453, 1374, 1355, 1302, 1263, 1207, 1148, 1112, 1032, 978, 951, 843, 792, 744, 698, 656, 598, 523; LRMS m/z (EI$^+$) 221 (M$^+$, 2), 147 (5), 146 (3), 117 (8), 103 (2), 91 (25), 77 (6), 65 (8), 57 (5), 51 (6), 43 (100), 42 (27), 39 (7); HRMS (EI$^+$) found: 221.1419, calculated: 221.1416.

4.2.8. (R)-3-(1'-Phenylethyl)-1,5,3-dioxazepane ***4g***. Following the general procedure, from (*R*)-1-phenylethanamine (1.40 g, 11.6 mmol) in toluene (60 mL): 89% yield as a colourless oil; $[\alpha]_D^{20}$ +54.0 (*c* 1.2, $CHCl_3$); δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.48 (3H, d, J=6.8 Hz, CH_3), 3.88 (4H, s, H-6, H-7), 4.21 (1H, q, J=6.8 Hz, C*H*Ph), 4.38 (2H, d, J=11.3 Hz, H-2$_A$, H-4$_A$), 4.60 (2H, d, J=11.3 Hz, H-2$_B$, H-4$_B$), 7.23–7.26 (1H, m, Ph), 7.29–7.34 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 21.2 (CH_3), 56.7 (*C*HPh), 69.4 (2×CH_2, C-6, C-7), 82.2 (2×CH_2, C-2, C-4), 127.1 (2×CH, Ph), 127.2 (CH, Ph), 128.4 (2×CH, Ph), 144.6 (C, Ph); IR: ν_{max} (film)/cm^{-1} 3028, 2973, 2911, 2865, 1602, 1492, 1452, 1371, 1219, 1199, 1115, 1019, 971, 952, 845, 770, 749, 700, 612, 578, 542, 519; LRMS m/z (EI$^+$) 207 (M$^+$, 2), 192 (4), 162 (2), 133 (5), 118 (5), 105 (100), 91 (12), 79 (12), 77 (16), 51 (9), 40 (15); HRMS (EI$^+$) found: 207.1260, calculated: 207.1259.

*4.2.9. (S)-3-(1-Phenylethyl)-1,5,3-dioxazepane ent-***4g***.* Following the general procedure, from (*S*)-1-phenylethanamine (2.5 g, 20.7 mmol) in toluene (40 mL): 88% yield as a colourless oil; $[\alpha]_D^{20}$ −53.0 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.48 (3H, d, J=6.8 Hz, CH_3), 3.86 (4H, s, H-6, H-7), 4.20 (1H, q, J=6.8 Hz, C*H*Ph), 4.37 (2H, d, J=11.4 Hz, H-2$_A$, H-4$_A$), 4.59 (2H, d, J=11.4 Hz, H-2$_B$, H-4$_B$), 7.20–7.22 (1H, m, Ph), 7.24–7.25 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) 21.1 (CH_3), 56.5 (*C*HPh), 69.3 (2×CH_2, C-6, C-7), 82.1 (2×CH_2, C-2, C-4), 127.0 (2×CH, Ph), 127.1 (CH, Ph), 128.3 (2×CH, Ph), 144.5 (C, Ph); IR: ν_{max} (film)/cm^{-1} 3028, 2973, 2911, 2867, 1602, 1492, 1452, 1371, 1219, 1199, 1115, 1019, 971, 952, 845, 771, 750, 700, 613, 578, 542; LRMS m/z (EI$^+$) 207 (M$^+$, 10), 192 (25), 162 (15), 147 (4), 130 (5), 118 (3), 105 (100), 102 (14), 91 (18), 79 (12), 77 (16), 58 (6), 56 (10), 42 (21); HRMS (EI$^+$) found: 207.12543, calculated: 207.12593.

4.2.10. (6R,7R)-3-Benzyl-6,7-dimethyl-1,5,3-dioxazepane ***10***. Following the general procedure, from benzylamine (3.2 g, 30.1 mmol), (1*R*,2*R*)-butane-1,2-diol (2.7 g, 29.9 mmol) in toluene (50 mL): 27% yield as a colourless oil; $[\alpha]_D^{20}$ −5.8 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.17 (6H, d, J=5.5 Hz, CH_3), 3.57–3.63 (4H, m, H-6, H-7), 4.06 (2H, s, CH_2Ph), 4.32 (4H, d, J=11.4 Hz, H-2, H-4), 4.61 (2H, d, J=11.4 Hz, H-2, H-4), 7.20–7.25 (1H, m, Ph), 7.28–7.34 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) 19.1 (2×CH_3), 53.8 (CH_2Ph), 80.2 (2×CH_2, C-6, C-7), 82.6 (2×CH_2, C-2, C-4), 127.0 (CH, Ph), 128.3 (CH, Ph), 128.7 (CH, Ph), 138.8 (C, Ph); IR: ν_{max} (film)/cm^{-1} 3029, 2972, 2931, 2868, 1603, 1495, 1453, 1368, 1329, 1277, 1251, 1214, 1178, 1136, 1092, 1068, 1035, 1024, 982, 896, 837, 799, 740, 701, 612, 590, 530, 518; LRMS m/z (EI$^+$) 221 (M$^+$, 0.5), 133 (3), 119 (16), 91 (100), 65 (11), 51 (4), 39 (6); HRMS (EI$^+$) found: 221.1416, calculated: 221.1416.

4.3. General methods for the double-Mannich reaction

Method A: To a solution of the ketone (1.0 equiv) and the 3-alkyl-1,5,3-dioxazepane (1.2 equiv) in dry CH_2Cl_2 (2 mL/mmol) was added $MeSiCl_3$ (1.2 equiv). The reaction mixture was stirred until the consumption of the ketone was observed by thin-layer chromatography (3:1 hexane/ethyl acetate). The reaction was quenched with 2 M HCl and diluted with Et_2O. The organic layer was extracted with 2 M HCl and the combined aqueous extracts were basified with solid $NaHCO_3$. The resulting mixture was extracted with Et_2O, dried over $MgSO_4$, concentrated in vacuo, and if necessary, purified by flash column chromatography, using the solvent system stated, to afford the title compounds.

Method B: To a solution of the ketone (1.0 equiv) and the 3-alkyl-1,5,3-dioxazepane (1.3 equiv) in dry CH_2Cl_2 (10 mL/mmol) was added distilled $TiCl_4$ (0.5 equiv) dropwise at 0 °C. The reaction mixture was stirred until the consumption of the ketone was observed by thin-layer chromatography (3:1 hexane/ethyl acetate). The reaction was quenched with satd $NaHCO_3$, extracted with CH_2Cl_2 (using a centrifuge at 3000 rpm for 5 min). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel, using the solvent system stated, to afford the title compounds.

Method C: To a solution of the 3-alkyl-1,5,3-dioxazepane (1.2 equiv) in dry CH_2Cl_2 (circa 2 mL/mmol) was added CH_3SiCl_3 (1.2 equiv). The reaction mixture was stirred for 30 min followed by addition of the ketone (1.0 equiv). The reaction mixture was then stirred until the consumption of the ketone was observed by thin-layer chromatography (3:1 hexane/ethyl acetate). The reaction was quenched with 2 M HCl and diluted with Et_2O. The organic layer was extracted with 2 M HCl and the combined aqueous extracts were basified with solid $NaHCO_3$. The resulting mixture was extracted with Et_2O, dried over $MgSO_4$, concentrated in vacuo, and if necessary, purified by flash chromatography on silica gel, using the solvent system stated, to afford the title compounds.

4.3.1. (1R,5R*)-Ethyl 3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***5b***. Using method A, from ethyl 2-oxocyclohexane-1-carboxylate **2** (0.18 g, 1.10 mmol), 3-ethyl-1,5,3-dioxazepane **4b** (0.17 g, 1.31 mmol), CH_2Cl_2 (2.5 mL) and CH_3SiCl_3 (0.15 mL, 1.30 mmol). Colourless oil (0.25 g, 89%). The ^{1}H and ^{13}C NMR spectra were in agreement with the literature;[1] δ_H (300 MHz,

$CDCl_3$, Me_4Si) 1.10 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.29 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.50–1.55 (1H, m, H-7_{eq}), 2.04–2.18 (2H, m, H-6_{ax}, H-6_{eq}), 2.21–2.27 (1H, m, H-8_{eq}), 2.40 (1H, q, J=7.2 Hz, $NCH_AH_BCH_3$), 2.41 (1H, q, J=7.2 Hz, $NCH_AH_BCH_3$), 2.44–2.48 (1H, m, H-5), 2.49–2.57 (1H, m, H-8_{ax}), 2.57 (1H, ddd, J=0.8, 3.3, 11.4 Hz, H-4_{ax}), 2.80–2.91 (1H, m, H-7_{ax}), 2.94 (1H, dd, J=1.8, 11.4 Hz, H-2_{ax}), 3.15 (1H, dt, J=2.3, 11.4 Hz, H-4_{eq}), 3.22 (1H, dd, J=2.3, 11.4 Hz, H-2_{eq}), 4.21 (2H, q, J=7.0 Hz, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 12.7 ($-NCH_2CH_3$), 14.1 (CH_3, $-OCH_2CH_3$), 20.5 (CH_2, C-7), 34.1 (CH_2, C-6), 36.8 (CH_2, C-8), 47.2 (CH_2, C-5), 51.1 ($-NCH_2CH_3$), 58.8 (C, C-1), 59.9 (CH_2, C-4), 61.0 (CH_2, OCH_2CH_3), 61.6 (CH_2, C-2), 171.2 (OC=O), 212.7 (C=O, C-9).

4.3.2. (1R,5R*)-Ethyl 3-butyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***5c***. Using method A, from ethyl 2-oxocyclohexane-1-carboxylate **2** (0.18 g, 1.1 mmol), 3-butyl-1,5,3-dioxazepane **4c** (0.20 g, 1.3 mmol), CH_2Cl_2 (2.5 mL) and CH_3SiCl_3 (0.15 mL, 1.3 mmol). Colourless oil (0.28 g, quantitative). The ^1H and ^{13}C NMR spectra were in agreement with the literature;[1] δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.10 (3H, t, J=7.2 Hz, $N(CH_2)_3CH_3$), 1.28 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.29–1.59 (5H, m, $-NCH_2(CH_2)_2CH_3$, H-7_{eq}), 2.01–2.28 (3H, m, H-6_{ax}, H-6_{eq}, H-8_{eq}), 2.34 (2H, t, J=6.9 Hz, $-NCH_2(CH_2)_2CH_3$), 2.42–2.48 (1H, m, H-5), 2.49–2.59 (2H, m, H-8_{ax}, H-4_{ax}), 2.78–2.94 (1H, m, H-7_{ax}), 2.91 (1H, dd, J=1.8, 11.7 Hz, H-2_{ax}), 3.14 (1H, dt, J=2.4, 10.8 Hz, H-4_{eq}), 3.20 (1H, dd, J=2.4, 11.4 Hz, H-2_{eq}), 4.20 (2H, q, J=7.2 Hz, $-OCH_2CH_3$); δ_C (75 MHz, $CDCl_3$) 13.7 ($-N(CH_2)_3CH_3$), 13.9 (CH_3, $-OCH_2CH_3$), 20.2 (CH_2, $-N(CH_2)_2CH_2CH_3$), 20.3 (CH_2, C-7), 29.1 (CH_2, $-NCH_2CH_2Et$), 33.9 (CH_2, C-6), 36.6 (CH_2, C-8), 47.1 (CH_2, C-5), 56.5 ($-NCH_2Pr$), 58.6 (C, C-1), 60.2 (CH_2, C-4), 60.7 (CH_2, $-OCH_2CH_3$), 61.8 (CH_2, C-2), 170.8 (OC=O), 212.1 (C=O, C-9).

4.3.3. (1R,5R*)-Ethyl 3-tert-butyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***5d***[1]. Using method A, from ethyl 2-oxocyclohexane-1-carboxylate **2** (0.19 g, 1.1 mmol), 3-*tert*-butyl-1,5,3-dioxazepane **4d** (0.20 g, 1.3 mmol), CH_2Cl_2 (2.5 mL) and CH_3SiCl_3 (0.15 mL, 1.3 mmol). Colourless oil (0.21 g, 69%). The ^1H and ^{13}C NMR spectra were in agreement with the literature;[1] δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.13 (9H, s, *t*-Bu), 1.29 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.46–1.49 (1H, m, H-7_{eq}), 2.05–2.12 (2H, m, H-6_{ax}, H-6_{eq}), 2.21–2.25 (1H, m, H-8_{eq}), 2.43–2.44 (1H, m, H-5), 2.49–2.57 (1H, m, H-8_{ax}), 2.69–2.76 (2H, m, H-4_{ax}, H-7_{ax}), 3.04 (1H, d, J=11.3 Hz, H-2_{ax}), 3.28 (1H, dd, J=2.3, 11.0 Hz, H-4_{eq}), 3.35 (1H, dd, J=2.3, 11.3 Hz, H-2_{eq}), 4.20 (1H, q, J=7.2 Hz, $OCH_AH_BCH_3$), 4.21 (1H, q, J=7.2 Hz, $OCH_AH_BCH_3$); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3, OCH_2CH_3), 20.5 (CH_2, C-7), 26.3 (CH_3, *t*-Bu), 33.5 (CH_2, C-6), 36.1 (CH_2, C-8), 46.9 (CH_2, C-5), 53.3 (CH_2, C-4), 53.4 (C, *t*-Bu), 55.3 (CH_2, C-2), 58.8 (C, C-1), 60.8 (CH_2, $-OCH_2CH_3$), 171.4 (C, C=O), 213.3 (C, C=O, C-9); IR: ν_{max} (film)/cm^{-1} 2971, 2928, 2862, 2821, 1732, 1715, 1458, 1393, 1359, 1299, 1262, 1239, 1219, 1202, 1188, 1162, 1097, 1069, 1040, 1024, 1006, 967, 657; LRMS m/z (EI^+) 267 (M^+, 15), 252 (100), 250 (25), 224 (10), 222 (7), 206 (35), 194 (10), 136 (5), 123 (6), 110 (5), 95 (4), 81 (10), 70 (26), 57 (26), 41 (38); HRMS (EI^+) found: 267.1838, calculated: 267.1834.

4.3.4. (1R,5R*)-Ethyl 3-benzyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***5e***. Using method A, from ethyl 2-oxocyclohexane-1-carboxylate **2** (0.20 g, 1.20 mmol), 3-benzyl-1,5,3-dioxazepane **4e** (0.25 g, 1.32 mmol), CH_2Cl_2 (2.5 mL) and CH_3SiCl_3 (0.17 mL, 1.4 mmol). Colourless oil (0.35 g, 88%). The ^1H and ^{13}C NMR spectra were in agreement with the literature;[1] δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.26 (3H, t, J=7.7 Hz, OCH_2CH_3), 1.56–1.63 (1H, m, H-7_{eq}), 2.01–2.15 (2H, m, H-6_{ax}, H-6_{eq}), 2.21–2.27 (1H, m, H-8_{eq}), 2.43–2.46 (1H, m, H-5), 2.47–2.55 (1H, m, H-8_{ax}), 2.62 (1H, dd, J=2.3, 11.5 Hz, H-4_{ax}), 2.99 (1H, dd, J=1.8, 11.4 Hz, H-2_{ax}), 2.94–3.03 (1H, m, H-7_{ax}), 3.12 (1H, dt, J=2.3, 11.5 Hz, H-4_{eq}), 3.20 (1H, dd, J=2.4, 11.4 Hz, H-2_{eq}), 3.51 (2H, s, $-CH_2Ph$), 4.17 (1H, q, J=7.2 Hz, $OCH_AH_BCH_3$), 4.18 (1H, q, J=7.2 Hz, $OCH_AH_BCH_3$), 7.25–7.35 (5H, m, Ph); δ_C (75 MHz, $CDCl_3$) 14.1 (CH_3, $-OCH_2CH_3$), 20.7 (CH_2, C-7), 34.0 (CH_2, C-6), 36.6 (CH_2, C-8), 47.1 (CH_2, C-5), 58.8 (C, C-1), 60.2 (CH_2, C-4), 61.1 (CH_2, $-OCH_2CH_3$), 61.8 (CH_2, C-2), 62.0 (CH_2, $-CH_2Ph$), 127.2 (CH, Ph), 128.2 (CH, Ph), 128.7 (CH, Ph), 138.3 (C, Ph), 170.9 (C, C=O), 212.4 (C, C=O, C-9); IR: ν_{max} (film)/cm^{-1} 2928, 2860, 2813, 1732 (C=O), 1716 (C=O), 1585, 1494, 1455, 1365, 1242, 1186, 1163, 1110, 1072, 1052, 1027, 951, 912, 859, 797, 739, 698, 654, 606; LRMS m/z (EI^+) 301 (M^+, 12), 300 (11), 284 (38), 272 (3), 258 (34), 256 (7), 226 (5), 212 (3), 210 (2), 182 (3), 164 (2), 132 (3), 120 (8), 106 (2), 91 (100), 81 (4), 65 (9), 55 (3), 42 (8), 41 (7); HRMS (EI^+) found: 301.1676, calculated: 301.1678.

4.3.5. (1R,5R*)-Ethyl 3-(3-phenylpropyl)-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***5f***. Using method A, from ethyl 2-oxocyclohexane-1-carboxylate **2** (0.20 g, 1.20 mmol), 3-(3-phenylpropyl)-1,5,3-dioxazepane **4f** (0.33 g, 1.51 mmol), CH_2Cl_2 (2.5 mL) and CH_3SiCl_3 (0.17 mL, 1.39 mmol). Colourless oil (0.40 g, quantitative). The ^1H and ^{13}C NMR spectra were in agreement with the literature;[1] δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.28 (3H, t, J=6.9 Hz, $-OCH_2CH_3$), 1.54–1.61 (1H, m, H-7_{eq}), 1.82 (2H, quin, J=7.2 Hz, $-NCH_2CH_2Bn$), 2.06–2.29 (3H, m, H-6_{ax}, H-6_{eq}, H-8_{eq}), 2.35 (2H, t, J=6.9 Hz, $-NCH_2(CH_2)_2Ph$), 2.45–2.61 (3H, m, H-5, H-8_{ax}, H-4_{ax}), 2.69 (2H, t, J=7.5 Hz, $-N(CH_2)_2CH_2Ph$), 2.86–2.97 (1H, m, H-7_{ax}), 2.94 (1H, dd, J=1.5, 11.7 Hz, H-2_{ax}), 3.14 (1H, dt, J=2.1, 11.1 Hz, H-2_{eq}), 3.21 (1H, dd, J=2.1, 11.4 Hz, H-4_{eq}), 4.21 (2H, q, J=6.9 Hz, $-OCH_2CH_3$), 7.16–7.25 (3H, m, Ph), 7.25–7.31 (2H, m, Ph); δ_C (75 MHz, $CDCl_3$) 14.1 (CH_3, $-OCH_2CH_3$), 20.5 (CH_2, C-7), 29.0 (CH_2, $-NCH_2CH_2Bn$), 33.4 (CH_2, $-N(CH_2)_2CH_2Ph$), 34.1 (CH_2, C-6), 36.7 (CH_2, C-8), 47.1 (CH, C-5), 56.3 (CH_2, $-NCH_2(CH_2)_2Ph$), 58.7 (C, C-1), 60.3 (CH_2, $-OCH_2CH_3$), 61.0 (CH_2, C-2), 61.9 (CH_2, C-4), 125.8, 128.3 (2×CH, Ph), 141.9 (C, Ph), 171.0 (C, C=O), 212.4 (C, C-9); IR: ν_{max} (film)/cm^{-1} 2929, 2860, 2808, 1732, 1715, 1602, 1496, 1454, 1365, 1259, 1187, 1162, 1115, 1053, 1028, 1008, 962, 909, 859, 731, 699, 655; LRMS m/z (EI^+) 329 (M^+, 32), 312 (44), 300 (2), 286 (35), 224 (100), 196 (7), 180 (3), 160 (10), 152 (9), 117 (5), 91 (36), 55 (10), 43 (19); HRMS (EI^+) found: 329.1988, calculated: 329.1991.

4.3.6. (1R,5R*)-Ethyl 3-((R)-1-phenylethyl)-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***5g***. Using method A, from ethyl 2-oxocyclohexane-1-carboxylate **2** (0.19 g, 1.18 mmol), 3-((*R*)-1-phenylethyl)-1,5,3-dioxazepane **4g** (0.30 g, 1.53 mmol), CH_2Cl_2 (2.5 mL) and CH_3SiCl_3 (0.17 mL, 1.39 mmol). Colourless oil (0.37 g, quantitative). 1:1 Diastereomeric ratio. The ^1H NMR was in agreement with the literature;[21] δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.22 (3H, t, J=6.8 Hz, $-OCH_2CH_3$), 1.27 (3H, t, J=7.2 Hz, $-OCH_2CH_3$), 1.37–1.41 (6H, m, $-CH(CH_3)Ph$, $-CH(CH_3)Ph$*), 1.54–1.59 (2H, m, H-7_{eq}, H-$7_{\ddot{e}q}$), 2.02–2.06 (2H, m, H-6_{ax}, H-6_{eq}), 2.06–2.29 (4H, m, H-$6_{\ddot{a}x}$, H-$6_{\ddot{e}q}$, H-$8_{\ddot{e}q}$, H-8_{eq}), 2.34–2.45 (1H, m, H-5), 2.44–2.54 (4H, m, H-4_{ax}, H-8_{ax}, H-$8_{\ddot{a}x}$, H-5*), 2.63 (1H, dd, J=2.4, 11.2 Hz, H-$4_{\ddot{a}x}$), 2.87–2.98 (3H, m, H-7_{ax}, H-$7_{\ddot{a}x}$, H-4_{eq}), 2.99–3.03 (1H, m, H-$2_{\ddot{a}x}$), 3.10 (1H, dd, J=2.4, 11.6 Hz, H-2_{eq}), 3.29 (1H, d, J=10.8 Hz, H-$4_{\ddot{e}q}$), 3.36 (1H, dd, J=2.0, 11.0 Hz, H-$2_{\ddot{e}q}$), 3.41 (1H, q, J=6.8 Hz, $-CH(CH_3)Ph$), 4.11–4.21 (4H, m, $-OCH_2CH_3$, $-OCH_2CH_3$), 7.22–7.32 (10H, m, Ph).

4.3.7. (1R,5R*)-Ethyl 5-(chloromethyl)-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***6b***. Using method B, from ethyl 2-oxocyclohexane-1-carboxylate **2** (0.18 g, 1.03 mmol), 3-ethyl-1,5,3-dioxazepane **4b** (0.18 g, 1.29 mmol), CH_2Cl_2 (2.5 mL) and $TiCl_4$ (55 μL, 0.5 mmol). Purified by flash column chromatography (19:1 *n*-hexane/EtOAc). Colourless oil (30 mg, 2.2%); δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.12 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.29 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.53–1.60 (1H, m H-7_{ax}), 1.79 (1H, dddd, J=2.0, 6.0, 11.6, 13.6 Hz, H-8_{ax}), 2.21–2.27 (1H, m, H-6_{ax}), 2.35 (1H, dd, J=2.0, 10.8 Hz, H-4_{ax}), 2.41–2.47 (1H, m, H-8_{eq}), 2.45 (2H, q, J=7.2 Hz, NCH_2CH_3), 2.54 (1H, dddd, J=2.0, 6.4, 12.0, 14.0 Hz, H-6_{eq}),

2.84–2.95 (1H, m, H-7_{eq}), 2.98 (1H, dd, J=2.0, 11.6 Hz, H-2_{ax}), 3.20 (1H, dd, J=2.4, 11.6 Hz, H-2_{eq}), 3.34 (1H, dd, J=2.4, 10.8 Hz, H-4_{eq}), 3.58 (2H, d, J=2.8 Hz, CH_2Cl), 4.22 (2H, q, J=7.1 Hz, −OCH_2CH$_3$); δ_C (100 MHz, $CDCl_3$) 12.5 (CH_3, −NCH_2CH$_3$), 14.1 (CH_3, −OCH_2CH_3), 20.0 (CH_2), 36.7 (CH_2, C-6), 37.4 (CH_2, C-8), 49.3 (CH_2, CH_2Cl), 49.9 (C, C-5), 51.0 (CH_2, −NCH_2CH$_3$), 58.9 (C, C-1), 61.2 (CH_2, −OCH_2CH$_3$), 61.5 (CH_2, C-2), 62.6 (CH_2, C-4), 170.7 (C, C=O), 211.5 (C, C-9); IR: ν_{max} (film)/cm^{-1} 2977, 2937, 2815, 1730, 1716, 1673, 1455, 1442, 1368, 1258, 1201, 1175, 1156, 1125, 1097, 1047, 1018, 985, 961, 910, 859, 807, 731, 712; LRMS m/z (EI$^+$) 289 (M$^+$ [^{37}Cl], 4), 287 (M$^+$ [^{35}Cl], 5), 272 (3), 270 (4), 253 (15), 252 (100), 244 (7), 238 (14), 195 (5), 192 (3), 183 (3), 167 (4), 137 (7), 93 (7), 83 (10), 51 (12), 44 (6); HRMS (EI$^+$) Found: 287.1284, calculated: 287.1288.

4.3.8. (1S,5R*)-3-Benzyl-1-methyl-3-azabicyclo[3.3.1]nonan-9-one* ***10a***. Using method A, from 2-methylcyclohexanone **9a** (0.13 g, 1.14 mmol), 3-benzyl-1,5,3-dioxazepane **4e** (0.26 g, 1.43 mmol), CH_2Cl_2 (3 mL) and CH_3SiCl_3 (0.16 mL, 1.4 mmol). Colourless oil (0.28 g, quantitative); δ_H (400 MHz, $CDCl_3$, Me_4Si) 0.87 (3H, d, J=1.6 Hz, CH_3), 1.46–1.56 (1H, m, H-7_{eq}), 1.67–1.75 (1H, m, H-8_{ax}), 1.91–2.12 (3H, m, H-6_{ax}, H-6_{eq}, H-8_{eq}), 2.21 (1H, br d, J=9.2 Hz, H-4_{ax}), 2.38 (1H, br s, H-5), 2.49 (1H, d, J=9.2 Hz, H-2_{ax}), 2.98 (1H, d, J=9.2 Hz, H-4_{eq}), 3.10–3.20 (1H, m, H-7_{ax}), 3.13 (1H, dd, J=1.6, 10.4 Hz, H-2_{eq}), 3.40 (2H, s, −CH_2Ph), 7.17–7.32 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 20.8 (CH_3), 21.2 (CH_2, C-7), 34.6 (CH_2, C-6), 42.4 (CH_2, C-8), 46.9 (C, C-1), 47.7 (CH, C-5), 60.3 (CH_2, C-2), 62.0 (CH_2, −CH_2Ph), 66.7 (CH_2, C-4), 126.9 (2×CH, Ph), 128.7 (CH, Ph), 138.4 (C, Ph), 218.3 (C=O, C-9); IR: ν_{max} (film)/cm^{-1} 2971, 2926, 2856, 2821, 1721 (C=O), 1458, 1393, 1359, 1298, 1263, 1240, 1217, 1202, 1188, 1164, 1097, 1069, 1042, 1025, 1006, 657; LRMS m/z (ESI$^+$) 243 (M$^+$, 100), 166 (13); HRMS (ESI$^+$) found: 243.1619, calculated: 243.1623.

4.3.9. (1R,5R*)-Ethyl 3-benzyl-8-oxo-3-azabicyclo[3.2.1]octane-1-carboxylate* ***10b***. Using method A, from ethyl 2-oxocyclopentane-1-carboxylate **9b** (0.16 g, 1.0 mmol), 3-benzyl-1,5,3-dioxazepane **4e** (0.23 g, 1.2 mmol), CH_2Cl_2 (2 mL) and CH_3SiCl_3 (0.13 mL, 1.1 mmol). Colourless oil (0.30 g, 88%). The ^{1}H NMR was in agreement with the literature;[1] δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.25 (3H, t, J=7.2 Hz, −OCH$_2$CH_3), 1.92–2.05 (2H, m, H-6_{exo}, H-6_{endo}), 2.27–2.32 (1H, m, H-7_{endo}), 2.32–2.34 (1H, m, H-5), 2.41 (1H, ddd, J=1.2, 4.8, 12.1 Hz, H-7_{exo}), 2.56 (1H, d, J=10.4 Hz, H-4_{ax}), 2.78 (1H, d, J=11.0 Hz, H-2_{ax}), 2.96 (1H, ddd, J=1.4, 3.0, 10.4 Hz, H-4_{eq}), 3.13 (1H, dd, J=2.6, 11.0 Hz, H-2_{eq}), 3.60 (1H, d, J=13.2 Hz, −CH_2Ph), 3.66 (1H, d, J=13.2 Hz, −CH_2Ph), 4.17 (2H, q, J=7.2 Hz, −OCH_2CH$_3$), 7.24–7.36 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3, −OCH$_2$CH_3), 21.8 (CH_2, C-6), 27.6 (CH_2, C-7), 46.4 (CH, C-5), 57.8 (C, C-1), 60.1 (CH_2, −CH_2Ph), 61.0 (CH_2, −OCH_2CH$_3$), 61.1 (CH_2, C-4), 62.4 (CH_2, C-2), 127.2 (CH, Ph), 128.3 (CH, Ph), 128.5 (CH, Ph), 138.0 (C, Ph), 170.2 (C, C=O), 213.4 (C=O, C-8).

4.3.10. (1S,5R*)-1-Acetyl-3-benzyl-3-azabicyclo[3.3.1]nonan-9-one* ***10c***. Using method A, from 2-acetylcyclohexanone **9c** (0.18 g, 1.3 mmol), 3-benzyl-1,5,3-dioxazepane **4e** (0.33 g, 1.7 mmol), CH_2Cl_2 (2.5 mL) and CH_3SiCl_3 (0.18 mL, 1.5 mmol). Colourless oil (0.35 g, quantitative); δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.57–1.61 (1H, m, H-7_{eq}), 2.02–2.17 (3H, m, H-6_{ax}, H-6_{eq}, H-8_{eq}), 2.18 (3H, s, C(=O)CH_3), 2.26–2.34 (1H, m, H-8_{ax}), 2.42–2.46 (1H, m, H-5), 2.61 (1H, dd, J=3.8, 11.5 Hz, H-4_{ax}), 2.82–2.90 (1H, m, H-7_{ax}), 2.89 (1H, d, J=11.1 Hz, H-2_{ax}), 3.07 (1H, dt, J=2.1, 11.1 Hz, H-2_{eq}), 3.12 (1H, dd, J=2.1, 11.5 Hz, H-4_{eq}), 3.47 (1H, d, J=13.1 Hz, CH_2Ph), 3.53 (1H, d, J=13.1 Hz, CH_2Ph), 7.23–7.32 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 20.1 (CH_2, C-7), 27.7 (CH_3, C(=O)CH_3), 33.6 (CH_2, C-6), 35.7 (CH_2, C-8), 47.2 (CH, C-5), 59.9 (CH_2, C-4), 60.9 (CH_2, C-2), 61.8 (CH_2, CH_2Ph), 62.6 (C, C-1), 127.1 (CH, Ph), 128.2 (CH, Ph), 128.5 (CH, Ph), 137.9 (C, Ph), 207.1 (C, C=O), 214.7 (C, C-9); IR: ν_{max} (film/cm^{-1}) 2928, 2859, 2806, 1704 (C=O), 1494, 1454, 1355, 1314, 1253, 1235, 1162, 1104, 1072, 1028, 985, 948, 907, 829, 727, 698, 648, 614, 580; LRMS m/z (EI$^+$) 287 (MH$^+$, 5), 272 (100), 260 (7), 134 (4).HRMS (EI$^+$) found: 272.1636, calculated: 272.1645.

4.3.11. (3R,5R*)-Ethyl 5-allyl-1-benzyl-3-methyl-4-oxopiperidine-3-carboxylate* ***10d***. Using method A, from ethyl 2-methyl-3-oxohept-6-enoate **9d** (0.21 g, 1.2 mmol), 3-benzyl-1,5,3-dioxazepane **4e** (0.28 g, 1.48 mmol), CH_2Cl_2 (2.5 mL) and CH_3SiCl_3 (0.17 mL, 1.39 mmol). Purified by flash chromatography on silica gel (9:1 *n*-hexane/EtOAc). Colourless oil (0.17 g, 49%). R_f (9:1 *n*-hexane/EtOAc) 0.35; δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.18 (3H, s, −CH_3), 1.22 (3H, t, J=6.8 Hz, −OCH$_2$CH_3), 1.94 (1H, dt, J=7.3, 14.8 Hz, −CH_2C=CH_2), 2.02 (1H, d, J=11.6 Hz, H-2), 2.05 (1H, t, J=11.2 Hz, H-6), 2.59 (1H, dtt, J=1.2, 6.0, 14.4 Hz, −CH_2C=CH_2), 3.00–3.07 (1H, m, H-5), 3.16 (1H, ddd, J=3.2, 6.4, 11.2 Hz, H-6), 3.48 (1H, d, J=13.6 Hz, −CH_AH$_B$Ph), 3.50 (1H, dd, J=3.2, 11.2 Hz, H-2), 3.66 (1H, d, J=13.6 Hz, −CH$_A$CH_BPh), 4.10–4.18 (1H, m, −OCH_2CH$_3$), 4.19–4.27 (1H, m, −OCH_2CH$_3$), 4.98 (1H, d, J=10.4 Hz, −CH=CH_2), 5.02 (1H, d, J=1.2, 13.2 Hz, −CH=CH_2), 5.71–5.81 (1H, m, −CH=CH$_2$), 7.25–7.34 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3, −OCH$_2$CH_3), 17.6 (CH_3), 31.0 (CH_2, −CH_2C=CH$_2$), 47.6 (CH, C-5), 56.9 (C, C-3), 59.5 (CH_2, C-6), 61.1 (CH_2, −OCH_2CH$_3$), 61.5 (CH_2, −CH_2Ph), 62.8 (CH_2, C-2), 116.2 (CH_2, −CH=CH_2), 127.1 (2×CH, Ph), 128.1 (2×CH, Ph), 128.6 (CH, Ph), 135.7 (CH, −CH=CH$_2$), 137.6 (C, Ph), 172.8 (C, C=O), 206.6 (C, C=O, C-4); IR: ν_{max} (film/cm^{-1}) 2979, 2804, 1716 (C=O), 1657, 1585, 1489, 1469, 1452, 1361, 1272, 1252, 1206, 1118, 1152, 1114, 1066, 1025, 987, 915, 856, 829, 740, 698, 523; LRMS m/z (FAB$^+$) 316 (MH$^+$, 100), 270 (2), 202 (8), 170 (53), 140 (5), 118 (1); HRMS (FAB$^+$) found: (MH$^+$) 316.1915, calculated: 316.1907.

4.4. Synthesis of 1-oxygenated-3-azabicyclo[3.3.1]nonan-9-ones

4.4.1. 2-(Benzyloxy)cyclohexanol[22]. To a suspension of $Cu(BF_4)_2 \cdot xH_2O$ (90 mg, ~0.40 mmol) in benzyl alcohol (3.90 g, 36.0 mmol) under a nitrogen atmosphere was added cyclohexene oxide (3.50 g, 36.2 mmol) dropwise. The reaction mixture was stirred overnight and the crude mixture purified by flash column chromatography (19:1 *n*-hexane/EtOAc) to afford the *title compound* as a colourless oil (3.6 g, 49%). The ^{1}H and ^{13}C NMR spectra were in agreement with the literature.[23] R_f (9:1 *n*-hexane/EtOAc) 0.50; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.18–1.32 (4H, m, H-3B, H-4B, H-5B, H-6B), 1.65–1.77 (2H, m, H-4A, H-5A), 1.98–2.17 (2H, m, H-3A, H-6A), 2.78 (1H, br s, OH), 3.15–3.24 (1H, m, H-2), 3.45–3.54 (1H, m, H-1), 4.48 (1H, d, J=11.3 Hz, CH_2Ph), 4.70 (1H, d, J=11.3 Hz, CH_2Ph), 7.26–7.40 (5H, m, Ph); δ_C (75 MHz, $CDCl_3$) 23.9 (CH_2, C-4), 24.2 (CH_2, C-5), 29.2 (CH_2, C-3), 32.0 (CH_2, C-6), 70.8 (CH_2, CH_2Ph), 73.8 (CH, C-1), 83.5 (CH, C-2), 127.7 (3×CH, Ph), 128.5 (2×CH, Ph), 138.5 (C, Ph).

4.4.2. 2-(Benzyloxy)cyclohexanone ***11***. Oxalyl chloride (1.5 mL, 17.4 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under a nitrogen atmosphere and cooled to −78 °C. Dry DMSO (2.7 mL, 37.7 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise and stirred for 20 min. 2-(Benzyloxy)cyclohexanol (3.2 g, 15.5 mmol) in dry CH_2Cl_2 (7 mL) was added dropwise to form a suspended white precipitate. The mixture was stirred for 30 min, warmed to −60 °C and dry Et_3N (11 mL, 78.9 mmol) was added dropwise. The reaction mixture was held at −60 °C for 5 min then warmed to room temperature. The reaction was quenched with H_2O (80 mL) and the organic layer separated. The organic extract was washed with 2 M HCl (30 mL), H_2O (30 mL) and satd $NaHCO_3$ (30 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 *n*-hexane/EtOAc) to afford the *title compound* as a colourless oil (2.5 g, 75%). The ^{1}H and ^{13}C NMR spectra were in agreement with the literature.[24] R_f (9:1 *n*-hexane/

EtOAc) 0.65; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.60–1.75 (2H, m), 1.77–1.86 (1H, m), 1.89–1.98 (2H, m), 2.14–2.32 (2H, m), 2.51–2.59 (1H, m), 3.88 (1H, ddd, *J*=1.2, 5.5, 9.8 Hz), 4.48 (1H, d, *J*=12.1 Hz, C*H*$_2$Ph), 4.76 (1H, d, *J*=12.1 Hz, C*H*$_2$Ph), 7.27–7.33 (1H, m, Ph), 7.34–7.39 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 23.1 (CH_2, C-4), 27.6 (CH_2, C-5), 34.6 (CH_2, C-3), 40.6 (CH_2, C-6), 71.6 (CH_2, *C*H$_2$Ph), 81.7 (CH, C-2), 127.7 (2×CH, Ph), 127.8 (CH, Ph), 128.4 (2×CH, Ph), 138.0 (C, Ph), 210.1 (C, C-1).

4.4.3. (1R,5R*)-1-(Benzyloxy)-3-ethyl-3-azabicyclo[3.3.1]nonan-9-one* ***12***. To a solution of 2-(benzyloxy)cyclohexanone **11** (0.18 g, 0.88 mmol) and 3-ethyl-1,5,3-dioxazepane **4b** (0.14 g, 1.03 mmol) in dry CH_2Cl_2 (2 mL) was added CH_3SiCl_3 (0.13 mL, 1.12 mmol) under a nitrogen atmosphere. The mixture was stirred for 90 min and quenched with 2 M HCl (3 mL). The mixture was diluted with Et_2O (10 mL), the aqueous phase was separated and the organic phase was extracted with 2 M HCl (3×10 mL). The combined aqueous extracts were washed with Et_2O (1×20 mL) and neutralized with solid $NaHCO_3$. The alkaline solution was extracted with Et_2O (3×20 mL), the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 *n*-hexane/EtOAc) to afford the *title compound* as a colourless oil (85 mg, 35%); δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.08 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 1.57–1.64 (1H, m, H-7$_{eq}$), 1.96–2.15 (2H, m, H-6$_{ax}$, H-6$_{eq}$), 2.19–2.34 (2H, m, H-8$_{ax}$, H-8$_{eq}$), 2.38 (1H, q, *J*=7.2 Hz, $-NCH_AH_BCH_3$), 2.39 (1H, q, *J*=7.2 Hz, $NCH_AH_BCH_3$), 2.53–2.58 (2H, m, H-4$_{ax}$, H-5), 2.62 (1H, dd, *J*=1.6, 10.8 Hz, H-2$_{ax}$), 2.85–2.97 (1H, m, H-7$_{ax}$), 3.08 (1H, d, *J*=10.8 Hz, H-4$_{eq}$), 3.22 (1H, dd, *J*=1.6, 10.8 Hz, H-2$_{eq}$), 4.68 (1H, d, *J*=11.4 Hz, $-CH_2$Ph), 4.74 (1H, d, *J*=11.4 Hz, $-CH_2$Ph), 7.23–7.37 (3H, m, Ph), 7.41–7.42 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 12.6 (CH_3, NCH_2CH_3), 21.3 (CH_2, C-7), 33.8 (CH_2, C-6), 39.3 (CH_2, C-8), 49.0 (CH, C-5), 51.0 (CH_2, NCH_2CH_3), 59.4 (C, C-4), 64.1 (CH_2, C-2), 66.1 (CH_2, $-CH_2$Ph), 81.0 (C, C-1), 127.1 (2×CH, Ph), 127.5 (CH, Ph), 128.1 (2×CH, Ph), 139.2 (C, Ph), 214.6 (C, C-9); LRMS *m*/*z* (EI$^+$) 296 (MNa^+, 9), 274 (MH^+, 100), 182 (1); HRMS (EI$^+$) found (MH^+): 274.1805, calculated: 274.1802.

4.5. Synthesis of 1-oxygenated-3-azabicyclo[3.3.1]nonanes

4.5.1. Diethyl 2-(3'-oxobutyl)malonate ***17***. Diethyl malonate (65.6 g, 0.41 mol), K_2CO_3 (6.00 g, 0.04 mol) and methyl vinyl ketone (32.2 g, 0.46 mol) were stirred in a sealed tube [caution: exothermic] overnight. The reaction was quenched with 2 M H_2SO_4 (21 mL) and diluted with Et_2O (30 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (50 mL). The combined organic extracts were washed with H_2O (50 mL), brine (20 mL) and dried over $MgSO_4$. The product was purified by distillation under reduced pressure to afford the *title compound* as a colourless oil (59.4 g, 63%). The ^1H and ^{13}C NMR spectra were in agreement with the literature;[25] bp 124–126 °C; 1 mmHg; δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.27 (6H, t, *J*=7.2 Hz, $-OCH_2CH_3$), 2.15 (3H, s, H-4'), 2.15 (2H, m, H-1'), 2.55 (2H, t, *J*=7.2 Hz, H-2'), 2.55 (1H, t, *J*=7.5 Hz, H-2), 4.18 (4H, dq, *J*=0.9, 7.2 Hz, $-OCH_2CH_3$); δ_C (75 MHz, $CDCl_3$) 13.9 (CH_3, $-OCH_2CH_3$), 22.3 (CH_2, C-1'), 29.8 (CH_2, C-4'), 40.3 (CH_2, C-2'), 50.6 (CH, C-2), 61.3 (CH_2, $-OCH_2CH_3$), 169.0 (C, $-CO_2CH_2CH_3$), 207.0 (C, C-3'); IR: ν_{max} (film)/cm^{-1} 2984, 2941, 2905, 1745, 1726, 1718, 1466, 1447, 1415, 1369, 1249, 1227, 1176, 1151, 1096, 1026, 950, 860, 753; LRMS *m*/*z* (EI$^+$) 230 (M^+, 5), 215 (3), 185 (43), 173 (15), 169 (17), 160 (81), 156 (5), 139 (71), 133 (17), 127 (21), 111 (21), 99 (8), 86 (10), 71 (6), 55 (26), 43 (100); HRMS (EI$^+$) found: 230.11508, calculated: 230.11542.

4.5.2. Ethyl 2,4-dioxocyclohexanecarboxylate ***18***[26]. Diethyl 2-(3-oxobutyl)malonate 17 (23.6 g, 0.1 mol) was added dropwise to a solution of sodium ethoxide in EtOH [made from Na (2.3 g, 0.1 mol) and EtOH (42 mL)] at −12 °C under a N_2 atmosphere. The reaction mixture was allowed to warm to room temperature before heating under reflux for 3 h. The crude material was dissolved in brine (350 mL) and washed with Et_2O (2×100 mL). The aqueous layer was cooled to 0 °C and acidified with 2 M H_2SO_4. The mixture was extracted with Et_2O (3×200 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to afford the *title compound* as a colourless solid (17.7 g, 94%); mp 58–63 °C [lit. mp[26] 56–60 °C]; multiple keto–enol tautomers: δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.27–1.39 (3H, m, $-OCH_2CH_3$), 2.15–2.64 (4H, m, H-5, H-6), 3.16 (0.6H, s, H-3), 3.36–3.67 (1H, m, H-1), 4.20–4.30 (2H, m, $-OCH_2CH_3$), 5.39 (0.1H, s, H-3), 5.54 (0.4H, s, H-3), 7.82 (0.5H, br s, OH enol), 12.22 (0.3H, s, OH, enol); δ_C (100 MHz, $CDCl_3$) 14.1, 14.2 (CH_3, $-OCH_2CH_3$), 20.1 (CH_2), 21.5 (CH_2), 24.2 (CH_2), 27.3 (CH_2), 29.4 (CH_2), 37.8 (CH_2), 38.9 (CH_2), 42.9 (CH_2), 49.0 (CH, C-1), 52.2 (CH, C-1), 55.1 (CH, C-1), 57.8 (CH_2), 60.8 (CH_2, $-OCH_2CH_3$), 61.3 (CH_2, $-OCH_2CH_3$), 61.9 (CH_2, $-OCH_2CH_3$), 64.7 (CH_2, $-OCH_2CH_3$), 97.9 (C), 102.0 (CH), 104.9 (CH), 167.5 (C, C=O), 168.7 (C), 170.3(C), 170.8(C), 171.4 (C), 187.0 (C), 188.2 (C), 198.4 (C), 202.4 (C), 206.2 (C, C=O); IR: ν_{max} (film)/cm^{-1} 3156, 3063, 2983, 2955, 2914, 1728 (C=O), 1644, 1601, 1571, 1458, 1308, 1193, 1173, 1153, 1088, 1024, 845, 605; LRMS *m*/*z* (EI$^+$) 184 (M^+, 100), 156 (16), 142 (12), 138 (40), 127 (14), 114 (48), 110 (78), 96 (57), 86 (17), 82 (37), 68 (46), 55 (48), 42 (49), 39 (70); HRMS (EI$^+$) found: 184.0732, calculated: 184.0736.

4.5.3. Ethyl 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxylate ***16*** *and ethyl 9-oxo-1,4-dioxaspiro[4.5]decane-6-carboxylate* ***19***. Ethyl 2,4-dioxocyclohexane-1-carboxylate 18 (17.7 g, 96.1 mmol), ethylene glycol (6.00 g, 96.7 mmol), *p*-TSA (0.20 g, 1.16 mmol) and toluene (200 mL) were combined and heated under reflux in a Dean–Stark apparatus for 1 h. The crude mixture was concentrated in vacuo and purified by flash column chromatography (9:1 *n*-hexane/EtOAc) to afford the *title compounds* **16** (7.8 g, 36%) and **19** (4.8 g, 22%) as colourless oils.

A mixture of keto/enol tautomers. *Compound* ***16***: δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.26–1.40 (3H, m, $-OCH_2CH_3$), 1.73–1.78 (1.6H, m), 1.87–1.94 (0.3H, m), 1.87–1.94 (0.3H, m), 1.99–2.08 (0.7H, m), 2.20–2.27 (0.4H, m), 2.39–2.45 (1.4H, m), 2.53 (1.3H, m), 2.64 (0.3H, d, *J*=13.9 Hz), 2.77 (0.3H, d, *J*=13.9 Hz), 3.35 (0.3H, dd, *J*=5.2, 8.1 Hz), 3.93–4.03 (4H, m), 4.16–4.25 (2H, m, $-OCH_2CH_3$), 12.20 (0.5H, s, O*H* enol); δ_C (100 MHz, $CDCl_3$) 14.1, 14.2 (CH_3, $-OCH_2CH_3$), 20.2 (CH_2), 23.3 (CH_2), 31.3 (CH_2), 32.6 (CH_2), 39.2 (CH_2), 51.1 (CH_2), 55.6 (CH), 60.3 (CH_2), 61.3 (CH_2), 64.5, 64.8 (2×CH_2, C-2, C-3), 96.9 (C), 107.2 (C), 109.6 (C), 168.5 (C), 169.4 (C), 172.2 (C), 201.7 (C, C-7); IR: ν_{max} (film)/cm^{-1} 2980, 2954, 2890, 1741, 1718, 1654, 1616, 1466, 1443, 1404, 1365, 1300, 1262, 1216, 1175, 1153, 1107, 1069, 1036, 1017, 947, 926, 823, 704; LRMS *m*/*z* (EI$^+$) 228 (M^+, 22), 213 (1), 200 (2), 183 (6), 154 (3), 141 (3), 127 (2), 113 (10), 99 (31), 86 (100), 69 (5), 55 (8), 42 (14), 35 (5); HRMS (EI$^+$) found: 228.1001, calculated: 228.0998.

Compound ***19***: δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.30 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 2.09–2.18 (2H, m, H-7), 2.33 (1H, ddt, *J*=1.6, 5.8, 14.1 Hz, H-8), 2.52 (1H, dt, *J*=1.5, 14.4 Hz, H-10), 2.59 (1H, ddd, *J*=5.5, 9.2, 14.1 Hz, H-8), 2.95 (1H, dt, *J*=1.2, 5.3 Hz, H-6), 3.14 (1H, dd, *J*=1.0, 14.4 Hz, H-10), 3.94–3.98 (2H, m, C-2/C-3), 4.00–4.02 (2H, m, C-2/C-3), 4.21 (2H, q, *J*=7.2 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3, $-OCH_2CH_3$), 23.2 (CH_2 C-7), 37.3 (CH_2, C-8), 47.9 (CH, C-6), 49.9 (CH_2, C-10), 60.8 (CH_3, $-OCH_2CH_3$), 64.5, 64.8 (CH_2, C-2, C-3), 109.4 (C, C-5), 171.5 (C, C=O), 206.7 (C, C=O, C-9); IR: ν_{max} (film)/cm^{-1} 2981, 2952, 2888, 1756, 1712, 1654, 1616, 1469, 1443, 1363, 1302, 1260, 1210, 1152, 1104, 1067, 1038, 1014, 947, 927, 824; LRMS *m*/*z* (EI$^+$) 228 (M^+, 10), 212 (20), 183 (24), 171 (40), 167 (40), 155 (5), 139 (25), 128 (40), 112 (37), 99 (20), 86 (100), 84 (60), 69 (53), 68 (54), 55 (62), 43 (39); HRMS (EI$^+$) found: 228.10058, calculated: 228.09977.

4.5.4. (1R,5R*)-Ethyl 3-benzyl-6-(2'-hydroxyethoxy)-8-oxo-3-azabicyclo[3.3.1]non-6-ene-1-carboxylate* ***20***. Ethyl 7-oxo-1,4-

dioxaspiro[4.5]decane-8-carboxylate **16** (0.32 g, 1.44 mmol) and 3-benzyl-1,5,3-dioxazepane **4e** (0.37 g, 1.92 mmol) were dissolved in dry CH_2Cl_2 (5 mL) under a N_2 atmosphere and cooled to 0 °C. Distilled $TiCl_4$ (0.15 mL, 1.4 mmol) was added dropwise and the mixture was left to warm to room temperature overnight. The reaction was quenched with satd $NaHCO_3$ (10 mL), extracted [centrifuge] with EtOAc (3×20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash column chromatography (1:1 *n*-hexane/EtOAc) to afford the *title compound* as a colourless gum (0.27 g, 54%). R_f (1:1 *n*-hexane/EtOAc) 0.2; δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.23 (3H, t, J=7.1 Hz, $-OCH_2CH_3$), 1.76 (1H, dd, J=2.9, 12.5 Hz, H-9), 2.11 (1H, dd, J=1.8, 11.0 Hz, H-4), 2.36 (1H, d, J=11.1 Hz, H-2), 2.59 (1H, br s, O*H*), 2.64 (1H, t, J=2.5 Hz, H-5), 2.70 (1H, d, J=12.5 Hz, H-9), 2.80 (1H, d, J=11.0 Hz, H-4), 3.31 (1H, d, J=11.1 Hz, H-2), 3.49 (1H, d, J=13.7 Hz, CH_2Ph), 3.61 (1H, d, J=13.7 Hz, CH_2Ph), 3.82–3.84 (2H, m, $HOCH_2CH_2OR$), 3.91–3.96 (1H, m, $HOCH_2CH_2OR$), 3.98–4.03 (1H, m, $HOCH_2CH_2OR$), 4.16 (2H, q, J=7.1 Hz, $-OCH_2CH_3$), 5.59 (1H, s, H-7), 7.16–7.32 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3, $-OCH_2CH_3$), 35.0 (CH_2, C-9), 35.9 (CH, C-5), 51.5 (CH_2, C-4), 54.1 (C, C-1), 56.8 (CH_2, C-2), 60.1 (CH_2, $HOCH_2CH_2OR$), 60.9 (CH_2, $-OCH_2CH_3$), 61.3 (CH_2, CH_2Ph), 70.1 (CH_2, $HOCH_2CH_2OR$), 104.2 (CH, C-7), 126.9 (CH, Ph), 128.1 (CH, Ph), 128.3 (CH, Ph), 137.8 (C, Ph), 171.3 (C, C=O), 178.4 (C, C-6), 196.8 (C, C-8); IR: ν_{max} (film)/cm^{-1} 3026, 2936, 2798, 1733, 1651, 1601, 1494, 1452, 1388, 1365, 1299, 1259, 1235, 1188, 1144, 1065, 1026, 902, 861, 835, 740, 699, 644; LRMS m/z (EI^+) 359 (M^+, 31), 314 (45), 298 (3), 268 (22), 252 (2), 244 (2), 222 (2), 134 (9), 120 (6), 91 (100), 65 (7), 42 (14); HRMS (EI^+) found: 359.1727, calculated: 359.1733.

*4.5.5. Ethyl 7-(trimethylsilyloxy)-1,4-dioxaspiro[4.5]dec-7-ene-8-carboxylate **24**.* To a solution of ketone **16** (7.80 g, 34.2 mmol) in dry toluene (140 mL) under a N_2 atmosphere was added dry Et_3N (7.5 mL, 53.8 mmol) followed by chlorotrimethylsilane (6.5 mL, 51.5 mmol) and the mixture stirred overnight. The reaction was quenched with satd $NaHCO_3$ (40 mL), the aqueous layer extracted with *n*-hexane (50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to afford the *title compound* as a colourless oil (9.3 g, 91%); δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.23 (9H, s, $-Si(CH_3)_3$), 1.28 (3H, t, J=7.1 Hz, $-OCH_2CH_3$), 1.73 (2H, t, J=6.5 Hz, H-10), 2.40 (2H, s, H-6), 2.45–2.49 (2H, t, J=6.5 Hz, H-9), 3.97 (4H, s, H-2, H-3), 4.17 (2H, q, J=7.1 Hz, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 0.6 ($Si(CH_3)_3$), 14.4 (CH_3, $-OCH_2CH_3$), 22.7 (CH_2, C-9), 30.9 (CH_2, C-10), 42.3 (CH_2, C-6), 59.7 (CH_2, $-OCH_2CH_3$), 64.5 (2×CH_2, C-2, C-3), 107.5 (C, C-5), 108.7 (C, C-1), 155.7 (C, C-2), 167.0 (C, C=O); IR: ν_{max} (film)/cm^{-1} 2955, 2897, 1714, 1686, 1632, 1446, 1393, 1373, 1298, 1249, 1194, 1108, 1063, 1022, 1007, 984, 948, 931, 841, 787, 753, 688, 631, 578; LRMS m/z (CI^+) 301 (MH^+, 36), 285 (87), 271 (3), 265 (37), 228 (12), 214 (12), 199 (12), 185 (9), 171 (15), 141 (6), 113 (7), 99 (26), 91 (18), 86 (100), 75 (34), 73 (34); HRMS (CI^+) found: 301.1479; calculated: 301.1471.

4.5.6. (1R,5R*)-Ethyl 3-ethyl-9-oxo-3-azaspiro[bicyclo[3.3.1]nonane-6,2′-[1,3]dioxolane]-1-carboxylate **15**.* To a solution of 3-ethyl-1,5,3-dioxazepane **4b** (0.14 g, 1.13 mmol) in dry DMF (2 mL) was added CH_3SiCl_3 (0.13 mL). The mixture was stirred for 25 min, ethyl 7-(trimethylsilyloxy)-1,4-dioxaspiro[4.5]dec-7-ene-8-carboxylate **24** (0.33 g, 1.13 mmol) was added dropwise and then left to stir overnight. The reaction was quenched with 2 M HCl (5 mL) and the aqueous layer washed with Et_2O (3×10 mL). The aqueous extract was basified with solid $NaHCO_3$, extracted with Et_2O (3×20 mL) and dried over $MgSO_4$, The filtrate was concentrated in vacuo and purified by flash column chromatography (4:1 *n*-hexane/EtOAc) to afford the *title compound* as a colourless oil (0.23 g, 70%). R_f (4:1 *n*-hexane/EtOAc) 0.25; δ_H (300 MHz, $CDCl_3$; Me_4Si) 1.09 (3H, t, J=7.0 Hz, $-NCH_2CH_3$), 1.28 (3H, t, J=7.6 Hz, $-OCH_2CH_3$), 1.78 (1H, dd, J=6.9, 13.2 Hz, H-7_{ax}), 2.02 (1H, ddd, J=0.9, 6.9, 13.8 Hz, H-8_{eq}), 2.41 (2H, q, J=7.2 Hz, $-NCH_2CH_3$), 2.39–2.46 (2H, m, H-4_{ax}, H-8_{eq}), 2.49–2.51 (1H, m, H-5), 2.93 (1H, dd, J=2.1, 11.4 Hz, H-2_{ax}), 3.18–3.29 (2H, m, H-2_{aq}, H-7_{ax}), 3.33 (1H, dt, J=2.1, 11.4 Hz, H-4_{eq}), 3.87–4.03 (4H, m, C-2′, C-3′, $-O(CH_2)_2O-$), 4.22 (2H, q, J=7.0 Hz, $-OCH_2CH_3$); δ_C (75 MHz, $CDCl_3$) 12.4 (CH_3, $-NCH_2CH_3$), 14.0 (CH_3, $-OCH_2CH_3$), 29.6 (CH_2, C-8), 31.9 (CH_2, C-7), 50.6 (CH_2, $-NCH_2CH_3$), 55.4 (CH, C-4), 56.5 (CH, C-5), 58.0 (C, C-1), 61.1 (CH_2, $-OCH_2CH_3$), 61.8 (CH_2, C-2), 64.4 (CH_2, C-2′/C-3′), 64.8 (CH_2, C-2′/C-3′), 112.6 (C, C-6), 170.5 (C, C=O), 206.8 (C, C-9); IR: ν_{max} (film)/cm^{-1} 2975, 2936, 2808, 1733 (C=O), 1719 (C=O), 1596, 1475, 1452, 1426, 1367, 1308, 1259, 1232, 1164, 1138, 1095, 1024, 946, 906, 881, 860, 846, 776, 759, 732, 663; LRMS m/z (EI^+) 320 (MNa^+, 100), 298 (MH^+, 38), 252 (15), 186 (35), 141 (3); HRMS (EI^+) found: 298.1642, calculated: 298.1649.

4.5.7. (1S,5S*)-Ethyl 3-ethyl-9-methylene-3-azaspiro[bicyclo[3.3.1]nonane-6,2′-[1,3]dioxolane]-1-carboxylate.* To a suspension of methyltriphenylphosphonium bromide (2.1 g, 5.9 mmol) in dry THF (20 mL) under a N_2 atmosphere at −78 °C was added *n*-BuLi in *n*-hexane (3.2 mL, 1.6 M, 5.1 mmol). The mixture was warmed to 0 °C then re-cooled to −78 °C. Ketone **15** (0.7 g, 2.4 mmol) dissolved in dry THF (5 mL) was then added dropwise and the mixture warmed to 0 °C. After 1 h, the reaction mixture was warmed to room temperature, quenched with satd NH_4Cl (15 mL), extracted with EtOAc (3×15 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash column chromatography (9:1 *n*-hexane/EtOAc) to afford the *title compound* as an amber oil (0.52 g, 74%); δ_H (300 MHz, $CDCl_3$, Me_4Si) 1.06 (3H, t, J=7.2 Hz, $-NCH_2CH_3$), 1.28 (3H, t, J=7.6 Hz, $-OCH_2CH_3$), 1.71 (1H, dd, J=7.6, 11.4 Hz, H-7/8_{ax}), 1.90 (1H, dd, J=7.4, 12.0 Hz, H-7/8_{eq}), 2.12 (1H, dd, J=4.0, 11.6 Hz, H-4_{ax}), 2.25 (1H, dtd, J=1.2, 4.0, 14.8 Hz, H-8/7_{ax}), 2.33 (2H, q, J=7.2 Hz, $-NCH_2CH_3$), 2.35 (1H, s, H-5), 2.57 (1H, dd, J=4.0, 11.5 Hz, H-2_{ax}), 3.04 (1H, dt, J=8.0, 11.4 Hz, H-8/7_{eq}), 3.07 (1H, d, J=11.5 Hz, H-2_{aq}), 3.22 (1H, d, J=11.2 Hz, H-4_{eq}), 3.89–3.96 (2H, m, C-4′/C-5′, $-O(CH_2)_2O-$), 3.98–4.02 (2H, m, C-4′/C-5′, $-O(CH_2)_2O-$), 4.17–4.24 (2H, m, $-OCH_2CH_3$), 4.63 (1H, s, C=CH_2), 4.84 (1H, s, C=CH_2); δ_C (75 MHz, $CDCl_3$) 12.3 (CH_3, $-NCH_2CH_3$), 14.2 (CH_3, $-OCH_2CH_3$), 32.0 (CH_2, C-8/C-7), 32.1 (CH_2, C-7/C-8), 49.6 (CH, C-5), 49.8 (C, C-1), 51.5 (CH_2, $-NCH_2CH_3$), 56.6 (CH, C-4), 60.6 (CH_2, $-OCH_2CH_3$), 61.7 (CH_2, C-2), 64.3 (CH_2, C-2′/C-3′), 64.5 (CH_2, C-2′/C-3′), 106.5 (C=CH_2), 111.1 (C, C-6), 148.2 (C, C-9), 173.8 (C, C=O); IR: ν_{max} (film)/cm^{-1} 2973, 2924, 2807, 1723, 1655, 1473, 1450, 1425, 1380, 1366, 1313, 1249, 1231, 1180, 1144, 1097, 1060, 1022, 949, 908, 891, 860, 840, 805, 754, 732, 692; LRMS m/z (EI^+) 296 (MH^+, 100); HRMS (EI^+) found: 296.1849, calculated: 296.1862.

4.5.8. (1S,5S*)-Ethyl 3-ethyl-9-methylene-6-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate.* The above dioxolane (0.27 g, 0.9 mmol), acetone (30 mL) and 10% HCl (20 mL) were mixed and heated under reflux overnight. The reaction mixture was concentrated in vacuo to ca. 20 mL volume, basified with solid $NaHCO_3$ and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash column chromatography (4:1 *n*-hexane/EtOAc) to afford the *title compound* as an amber oil (0.11 g, 49%). R_f (4:1 *n*-hexane/EtOAc) 0.35; δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.99 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.30 (3H, t, J=7.6 Hz, $-OCH_2CH_3$), 1.98–2.06 (1H, m, H-8), 2.35 (2H, t, J=7.2 Hz, 7-CH_2), 2.45–2.61 (2H, m, H-8, H-4_{ax}), 2.63 (2H, t, J=7.2 Hz, $-NCH_2CH_3$), 2.69 (1H, d, J=8.8 Hz, H-2_{ax}), 2.98 (1H, s, H-5), 3.00 (1H, dd, J=1.5, 14.4 Hz, H-4_{eq}), 3.12 (1H, dt, J=2.4, 8.8 Hz, H-2_{eq}), 4.23 (2H, q, J=7.6 Hz, OCH_2CH_3), 4.69 (1H, s, C=CH_2), 4.87 (1H, s, C=CH_2); δ_C (75 MHz, $CDCl_3$) 12.1 (CH_3, $-NCH_2CH_3$), 14.2 (CH_3, $-OCH_2CH_3$), 29.9 (CH_2, C-8), 39.0 (CH_2, C-7), 49.8 (C, C-1), 51.2 (CH_2, $-NCH_2CH_3$), 56.6 (CH, C-5), 58.4 (CH_2, C-4), 61.0 (CH_2, $-OCH_2CH_3$), 62.4 (CH_2, C-2), 108.6 (C=CH_2), 145.2 (C, C-9), 173.5 (C,

C=O), 212.6 (C, C-6); IR: ν_{max} (film)/cm^{-1} 2976, 2934, 2866, 1743, 1726, 1657, 1470, 1410, 1365, 1304, 1253, 1220, 1177, 1149, 1101, 1065, 1018, 948, 805, 754; LRMS *m*/*z* (EI$^+$) 252 (MH$^+$, 16), 208 (17), 194 (10), 179 (25), 162 (100), 151 (42), 134 (24); HRMS (EI$^+$) [MH$^+$] found: 252.1596, calculated: 252.1600.

4.5.9. (1S,5S*,6S*)-Ethyl 3-ethyl-6-hydroxy-9-methylene-3-azabicyclo[3.3.1]nonane-1-carboxylate.* To a solution of the above ketone (66 mg, 0.26 mmol) in EtOH (5 mL) was added $NaBH_4$ (30 mg, 0.79 mmol). After 1 h the reaction was quenched with satd NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (5×10 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash column chromatography (4:1 *n*-hexane/EtOAc) to afford the *title compound* as an amber oil (40 mg, 60%). R_f (4:1 *n*-hexane/EtOAc) 0.25; δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.99 (3H, t, *J*=7.2 Hz, −NCH$_2$C*H*$_3$), 1.24 (3H, t, *J*=7.2 Hz, −OCH$_2$C*H*$_3$), 1.56–1.74 (2H, m, H-7$_{eq}$, H-8$_{ax}$), 2.17–2.28 (2H, m, H-4$_{ax}$, H-8$_{eq}$), 2.29 (2H, q, *J*=7.2 Hz, −NC*H*$_2$CH$_3$), 2.44 (1H, d, *J*=11.2 Hz, H-2$_{ax}$), 2.56 (1H, br s, H-5), 2.59–2.76 (1H, m, H-7$_{ax}$), 2.87 (1H, d, *J*=11.2 Hz, H-2$_{eq}$), 3.02 (1H, d, *J*=11.4 Hz, H-4$_{eq}$), 3.98–4.01 (1H, m, H-6), 4.14 (2H, q, *J*=7.2 Hz, −OC*H*$_2$CH$_3$), 4.60 (1H, s, C=CH$_2$), 4.82 (1H, s, C=CH$_2$); δ_C (75 MHz, $CDCl_3$) 12.2 (CH$_3$, NCH$_2$*C*H$_3$), 14.2 (CH$_3$, OCH$_2$*C*H$_3$), 28.7 (CH$_2$, C-8), 39.2 (CH$_2$, C-7), 49.6 (C, C-1), 51.1 (CH$_2$, −N*C*H$_2$CH$_3$), 56.6 (CH, C-5), 58.4 (CH$_2$, C-4), 61.1 (CH$_2$, −O*C*H$_2$CH$_3$), 62.3 (CH$_2$, C-2), 70.5 (CH, C-6), 106.9 (C=*C*H$_2$), 146.2 (C, C-9), 173.4 (C, C=O); IR: ν_{max} (film)/cm^{-1} 3394 (O–H), 2973, 2917, 2807, 2770, 1726, 1652, 1473, 1450, 1381, 1367, 1301, 1249, 1230, 1185, 1155, 1131, 1040, 1061, 1022, 978, 951.7, 894, 861, 845, 804, 752, 721, 678, 652; LRMS *m*/*z* (EI$^+$) 254 (MH$^+$, 26), 208 (20), 194 (14), 179 (22), 162 (100), 151 (54), 134 (31); HRMS (EI$^+$) [MH$^+$] found: 254.1768, calculated: 254.1756.

4.5.10. (1S,5S*,6S*)-Ethyl 3-ethyl-6-methoxy-9-methylene-3-azabicyclo[3.3.1]nonane-1-carboxylate* ***14***[14]. NaH (60 wt %, 21 mg, 0.53 mmol) was washed with *n*-pentane (3×1 mL) and suspended in dry THF (5 mL) under a N_2 atmosphere. The mixture was cooled to 0 °C and the above alcohol (38 mg, 0.15 mmol) in dry THF (3 mL) was added dropwise. The mixture was warmed to room temperature for 30 min then re-cooled to 0 °C. Iodomethane (12 μL, 0.19 mmol) was added dropwise, the reaction flask was sealed and the reaction mixture left to warm to room temperature overnight. The mixture was heated to 50 °C in a sealed tube for a further 2 days then quenched with satd NH_4Cl (10 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (9:1 *n*-hexane/EtOAc) to afford the *title compound* as a colourless oil (10 mg, 25%). The ^{1}H NMR spectrum was in agreement with the literature.[14] R_f (4:1 *n*-hexane/EtOAc) 0.6; δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.99 (3H, t, *J*=7.2 Hz, −NCH$_2$C*H*$_3$), 1.19 (3H, t, *J*=7.2 Hz, −OCH$_2$C*H*$_3$), 1.56–1.74 (2H, m, H-7$_{eq}$, H-8$_{ax}$), 2.13–2.18 (2H, m, H-4$_{ax}$, H-8$_{eq}$), 2.30 (2H, q, *J*=7.2 Hz, −NC*H*$_2$CH$_3$), 2.45 (3H, d, *J*=11.2 Hz, H-2$_{ax}$), 2.50 (1H, br s, H-5), 2.55–2.72 (1H, m, H-7$_{ax}$), 2.86 (1H, d, *J*=11.2 Hz, H-2$_{eq}$), 2.95 (1H, d, *J*=11.4 Hz, H-4$_{eq}$), 3.26 (3H, s, −OC*H*$_3$), 3.44–3.45 (1H, m, H-6), 4.12 (2H, q, *J*=7.2 Hz, −OC*H*$_2$CH$_3$), 4.56 (1H, s, C=CH$_2$), 4.77 (1H, s, C=CH$_2$); LRMS *m*/*z* (EI$^+$) 268 (MH$^+$, 35), 236 (42), 208 (27), 194 (17), 179 (28), 162 (100), 151 (63), 134 (24), 119 (3), 105 (14); HRMS (EI$^+$) [MH$^+$] found: 268.1905, calculated: 268.1907.

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References and notes

1. Brimble, M. A.; Brocke, C. *Eur. J. Org. Chem.* **2005**, 2385–2395.
2. Kapnang, H.; Charles, G.; Sondengam, B. L.; Hemo Hentchoya, J. *Tetrahedron Lett.* **1977**, 3469–3472.
3. Kapnang, H.; Charles, G. *Tetrahedron Lett.* **1983**, *24*, 1597–1600.
4. Ooka, K.; Inoue, H. Japanese Patent 2008094744, 2008.
5. Rochin, C.; Babot, O.; Dunogues, J.; Duboudin, F. *Synthesis* **1986**, 228–229.
6. Miller, R. B.; Smith, B. F. *Synth. Commun.* **1973**, *3*, 129–133.
7. Hon, Y.-S.; Hsu, T.-R.; Chen, C.-Y.; Lin, Y.-H.; Chang, F.-J.; Hsieh, C.-H.; Szu, P.-H. *Tetrahedron* **2003**, *59*, 1509–1520.
8. Olah, G. A.; Donovan, D. J. *J. Org. Chem.* **1978**, *43*, 860–865.
9. Mayr, H.; Ofial, A. R.; Wurthwein, E.-U.; Aust, N. C. *J. Am. Chem. Soc.* **1997**, *119*, 12727–12733.
10. Tashkhodzhaev, B. *Chem. Nat. Compd.* **2010**, *46*, 421–425.
11. Halliday, J. I.; Chebib, M.; Turner, P.; McLeod, M. D. *Org. Lett.* **2006**, *8*, 3399–3401.
12. Darout, E.; Basak, A. *Tetrahedron Lett.* **2010**, *51*, 2998–3001.
13. Jiang, D.; Mallat, T.; Krumeich, F.; Baiker, A. *J. Catal.* **2008**, *257*, 390–395.
14. Barker, D.; Lin, D. H. S.; Carland, J. E.; Chu, C. P. Y.; Chebib, M.; Brimble, M. A.; Savage, G. P.; McLeod, M. D. *Bioorg. Med. Chem.* **2005**, *13*, 4565–4575.
15. Hansen, S. B.; Sulzenbacher, G.; Huxford, T.; Marchot, P.; Taylor, P.; Bourne, Y. *EMBO J.* **2005**, *24*, 3635–3646.
16. Greenhill, J. V.; Chaaban, I.; Steel, P. J. *J. Heterocycl. Chem.* **1992**, *29*, 1375–1383.
17. Ko, S. S.; Batt, D. G.; Delucca, G. V.; Duncia, J. V.; Gardner, D. S.; Santella, J. B. U.S. Patent 7,291,744, 2004.
18. Langer, P.; Schneider, T. *Synlett* **2000**, 497–500.
19. Sakata, K.; Fujimoto, H. *Organometallics* **2010**, *29*, 1004–1011.
20. Kapnang, H.; Charles, G. *Tetrahedron Lett.* **1980**, *21*, 2949–2950.
21. Buckley, B. R.; Page, P. C. B.; Heaney, H.; Sampler, E. P.; Carley, S.; Brocke, C.; Brimble, M. A. *Tetrahedron* **2005**, *61*, 5876–5888.
22. Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *Org. Lett.* **2002**, *4*, 2817–2819.
23. Masaki, Y.; Miura, T.; Ochiai, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 195–205.
24. Lauktien, G.; Volk, F.-J.; Frahm, A. W. *Tetrahedron: Asymmetry* **1997**, *8*, 3457–3466.
25. Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1999**, *55*, 3937–3948.
26. Spencer, T. A.; Newton, M. D.; Baldwin, S. W. *J. Org. Chem.* **1964**, *29*, 787–789.