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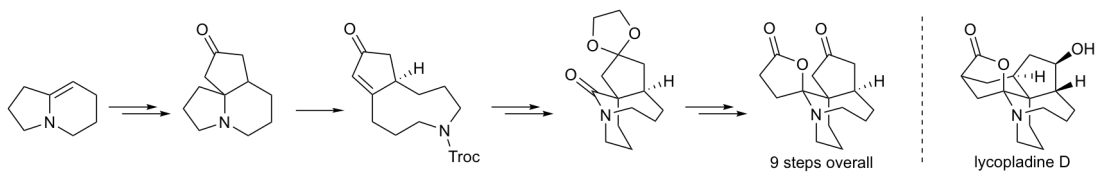
Graphical Abstract

Investigations of an annulation-fragmentation-spirocyclisation approach to fawcettimine-type *Lycopodium* alkaloids

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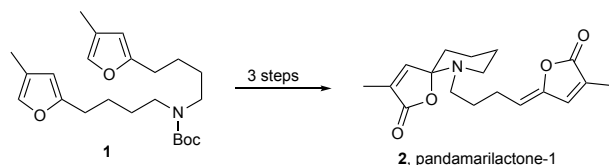
ABSTRACT

This paper reports progress in the development of a furan oxidative *N*-spirocyclisation approach to the fawcettimine alkaloids huperzine Q and lycoplamine D. A short synthesis is described of a key intermediate cyclopentaindolizidine that subsequently fragments by *N*-acylation and β -elimination. The stereochemistry of 1,4-addition of cyanide to the resulting enone is discussed with supporting molecular modelling calculations. *N*-Deprotection is shown to be accompanied by cyclisation onto the nitrile group, resulting in a tricyclic lactam with a twisted amide functionality. Elaboration of this lactam afforded four of the five rings present in lycoplamine D with just the C(8) carbon lacking.

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1. Introduction

The reliable oxidation of furan derivatives combined with intramolecular nucleophilic capture of the so-formed enediones has found extensive application in synthesis,¹ with notable early contributions with oxygen-centred nucleophiles reported by Bohlmann² and Achmatowicz.³ Capture by tethered nitrogen-centred nucleophiles is the basis for the ‘aza-Achmatowicz’ reaction⁴ which we⁵ and others⁶ have extended for alkaloid synthesis. For example, both furan rings in the readily-prepared symmetrical amine **1** (Scheme 1) were oxidised with singlet oxygen, the nitrogen deprotected, and cyclisation and dehydration effected under acidic conditions to yield the butenolide spiro-*N,O*-acetal pandamarilactone-1 **2**.^{5b}



Scheme 1

At the time that our group initiated research into furan oxidative spiro-*N*-cyclisation,⁷ Kobayashi had recently disclosed the structure of lycoplamine D (**3**, Figure 1),⁸ an oxidised stereoisomer of huperzine Q **4**,⁹ both members of the group of *Lycopodium* alkaloids of which fawcettimine **5** is the parent.¹⁰ Aside from the allure of the synthetic challenge and what could be learned from embarking upon it, our initial interest in lycoplamine D was to test

the furan oxidative spiro-*N*-cyclisation in a more challenging synthetic environment than that offered by pandamarilactone-1.

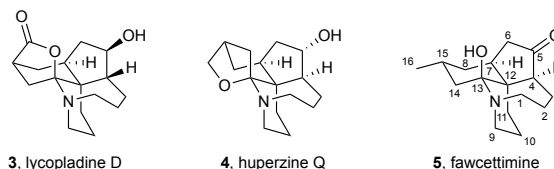
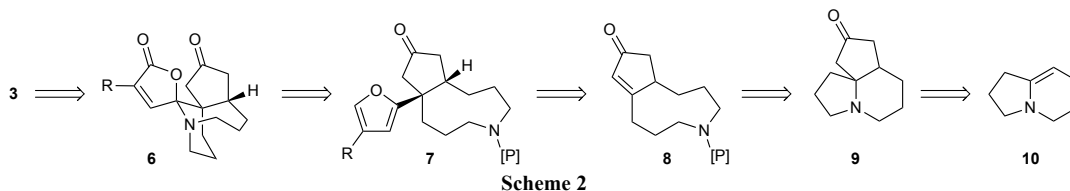


Fig. 1. Selected members of the fawcettimine group of *Lycopodium* alkaloids.

The original synthesis strategy, summarised in Scheme 2, was based on butenolide reduction and subsequent formation of the C(7–8) bond by, for example, enolate alkylation onto a C₁-electrophile (R in compound **6**). Applying the oxidative spirocyclisation transform generated intermediate **7** ([P] = a carbamate *N*-protecting group), originally envisaged to arise by conjugate addition of a furan nucleophile into the enone of azabicyclic ketone **8**, obtained, in turn, by β -elimination¹¹ in tricycle **9**. Beyond developing the overall synthesis, the early stages of this route were felt to be worth pursuing in their own right since they offered the opportunity both to develop the chemistry of enamine **10**¹² and to employ the route to novel tricycle **9**¹³ for new syntheses of related ring systems in complex alkaloids.

This paper details the development of a short synthetic route to a variant of tetracycle **6** that, ultimately, diverged from the furan oxidative spiro-*N*-cyclisation methodology that had inspired the original investigation.

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2. Results and discussion

The unsubstituted iminium ions **A** and enamines **B** (Figure 2), where x and $y = 1$ or 2 , have a long history but surprisingly scant applications in synthesis. Improving upon earlier routes to these species by redox transformations of the partially-reduced parent aromatic heterocycles,¹⁴ Evans introduced a convenient synthesis¹⁵ based on sequential C - and N -alkylations of metalloimines that was later extended by De Kimpe;¹⁶ Pearson generated the same species by intramolecular azide cycloaddition with ω -chloroalkenes.¹⁷ The reported chemistry of these species is, as mentioned, rather limited; however, early research established enamine **10** (that is, **B**; $x = 1$, $y = 2$) to be unique among the enamines studied in its propensity for C - rather than N -methylation.^{12a} Separately, Bohlmann described the annulation reactions of the quinolizidine enamine **B** ($x, y = 2$) with α, β -unsaturated carbonyls.¹⁸ More recently, chemists at Millenium Pharmaceuticals employed a formal *ortho*-quinone methide cycloaddition of the same enamine in a synthesis of an HIV-relevant CCR5 antagonist.¹⁹ Beyond these examples, synthetic transformations in the majority of the rest of the ~80 publications mentioning such species are limited to simple additions to, or reductions of, the iminiums **A**.

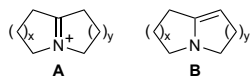


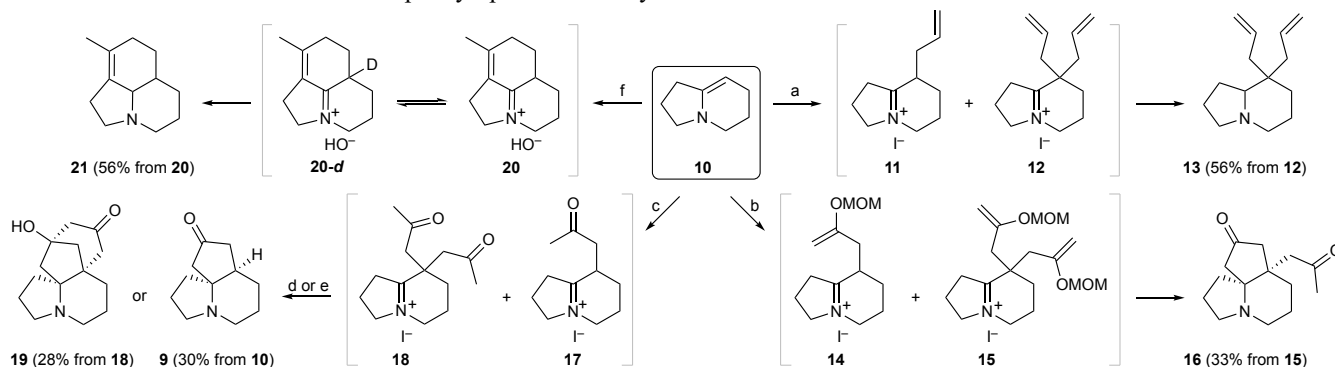
Fig. 2. Bicyclic pyrrolizidine, indolizidine, and quinolizidine iminium ions (**A**) and their corresponding enamines (**B**) ($x, y = 1$ or 2).

With this background, initial studies focused on optimising the preparation of enamine **10** and surveying its alkylation chemistry with functionalised electrophiles. Iminium ion **A** ($x = 1$, $y = 2$; as its chloride salt) was prepared efficiently on decagram scale¹⁶ and converted into enamine **10** by extended stirring in aq. NaOH solution and then extracting the non-polar product into pentane. The isolated enamine was somewhat unstable and was therefore prepared directly prior to its use in alkylation reactions. The enamine is prone to double alkylation; for example, reaction with 1.0 mol. equiv. of allyl iodide produced mono- and diallylated iminium salts **11** and **12** (Scheme 3), in ratios varying from ~25:75 to 35:65. In this case, and in general, only the dialkylated iminium salts could be isolated in an acceptably pure form by

chromatography. The monoalkylated iminium salts, such as **11**, were identified by NMR and MS analysis of the crude products, and by the products of subsequent reactions. Reduction of a sample of iminium salt **12** proceeded as expected to generate diallylindolizidine **13**. Similarly, the crude product from reactions of enamine **10** with 3-iodo-2-(methoxymethoxy)propene²⁰ were enriched in iminium salt **15** (**14/15** ~ 40:60). A sample of separated iminium **15** hydrolysed and cyclised upon heating in aq. acetonitrile, affording tricyclic diketone **16**. With iodoacetone as electrophile, the monoalkylated product **17** was the major (**17/18** ~ 70:30) on scales up to 5.0 mmol; in a single large-scale run (84 mmol) the ratio reversed, possibly as the fast reaction was less well controlled. Iminium ion **18** was isolated and treated with NaOH to afford the tetracycle **19**. The crude product from the 84 mmol alkylation was treated directly with NaOH and the desired tricyclic ketone **9** obtained in 30% overall yield, reflecting the quantity of iminium salt **17** formed in the alkylation step. Finally, in a variant of Bohlmann's work with unsaturated carbonyl electrophiles, addition of methyl vinyl ketone (MVK) initiated a 1,4-addition/enamine aldol annulation to generate tricyclic iminium salt **20**. Rapid deuteration of the acidic methine centre took place in methanol- d_4 (δ_C 25.5 ppm, t, $J = 20$ Hz) that reversed upon dissolution into methanol as NaBH₄ reduction in that solvent produced amine **21** with no deuterium incorporation.

With no direct precedents available for the carbamate-triggered β -elimination of a 1-azaspiro[4.4]nonan-7-one, the conditions employed for a similar transformation in an erythronine substrate were applied to tricyclic amine **9** (Scheme 4).^{11,21} This electrophile-activated fragmentation under mildly basic conditions was very effective and three variants **8a-c** were obtained in excellent yield.

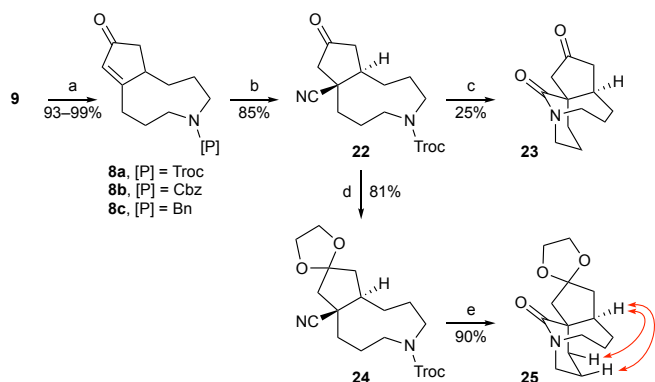
At this point, it was discovered that the enone functionality in **8a** was insufficiently reactive to accept a furan nucleophile or a variety of synthetic equivalents,²² and the research departed from the plan summarised in Scheme 2. However, model studies with 3-butylcyclopentenone demonstrated that Utimoto's conjugate cyanation procedure²³ offered a potentially versatile means to install the C(13) carbonyl latent in the fawcettimine group of



Scheme 3. Reagents and conditions: (a) allyl iodide, THF, RT, 1 h then (from **12**) NaBH₄, MeOH, RT, 1 h; (b) 3-iodo-2-(methoxymethoxy)propene, THF, RT, 6 h then (from **15**) aq. CH₃CN, 80 °C, 16 h; (c) iodoacetone, THF, RT, 1 h; (d) (from **17** → **9**) NaOH, aq. THF, RT, 24 h; (e) (from **18** → **19**) NaOH, aq. THF, RT, 48 h; (f) MVK, THF, RT, 1 h (→ **20-d**, NMR in CD₃OD) then NaBH₄, MeOH, RT, 1 h.

Lycopodium alkaloids. Accordingly, treatment of Troc-protected amine **8a** with trimethylsilyl cyanide and triethylaluminium afforded β -cyanoketone **22** (Scheme 4), after silyl enol ether hydrolysis, apparently as a single diastereomer (discussed below).

Troc-deprotection of amine **22** under standard conditions (Zn, AcOH) proceeded slowly to generate tricyclic lactam **23**, a somewhat twisted amide,²⁴ in low yield. The deprotection and ensuing cyclisation were faster and more efficient when conducted on the ethylenedioxy acetal derivative **24**. The indicated NOE interactions in so-formed lactam **25** (arrows, Scheme 4) confirmed the *exo*-disposition of the bridgehead proton at C(4) (fawcettimine numbering) and hence the potential relevance of the route to the synthesis of huperzine Q (and related *Lycopodium* alkaloids including fawcettimine and lycoplamine B) rather than lycoplamine D.



Scheme 4 Reagents and conditions: (a) TrocCl (or CbzCl or BnBr), K₂CO₃, benzene, RT, 3–16 h; (b) TMSCN, Et₃Al, THF, reflux, 5 h then aq. HCl, THF, RT, 10 min; (c) Zn, AcOH, RT, 48 h; (d) ethylene glycol, *p*-TsOH, benzene, reflux, 1 h; (e) Zn, AcOH, RT, 16 h.

The stereochemistry of the cyanide adduct **22**, determined retrospectively from the structure of lactam **25**, deserves comment. The observed product derives from addition of the cyano group from the enone face *cis*-to the ring substituent at the adjacent stereogenic centre.²⁵ The cyclopentenone ring in compound **8a** is essentially planar so that, stereoelectronically, the two faces in the ground state are equivalent; thus the primary controlling elements in the competing transition states in a kinetically-controlled addition balance the 1,2-steric interaction between the incoming cyanide ion and the adjacent ring substituent (in the observed *cis*-mode of addition) against the developing 1,2-interaction between the two ring substituents (cyanide addition *trans*- to the ring substituent). With 3,4-dimethylcyclopent-2-enone as a simplified model, diastereomeric transition states were located by a DFT calculation (B3LYP/6-31G*)²⁶ for the addition of free cyanide ion; these were found to be essentially equienergetic ($\Delta\Delta G^\ddagger = 0.05$ kJ mol⁻¹) and structural parameters are very similar (Table 1) with the developing *gauche*-interactions between the pseudoaxial C(4)-methyl and the C(1–5) and C(2–3) bonds in the *trans*-addition contributing to the overall picture.

However, upon completion of the addition, the DFT free energies of the first-formed enolates, in each case bearing a pseudoaxial cyano group, diverge further in favour of the *cis*-addition mode with the corresponding values being summarised in Table 2. Here, the axial C(4)-methyl group seems to be the main determinant in raising the energy of the *trans*-mode addition product. Additionally, the two methyl groups move away from each other when the cyanide ion adds in the *cis*-mode, as measured by the C(3)–CH₃ / C(4)–CH₃ dihedral angle that expands from 59.2° in the starting enone, through 63.0° in the transition state, to 72.9° in the intermediate enolate. The converse applies to the *trans*-mode of addition (59.2° → 51° → 41.3°). On this basis, for

a kinetically-controlled addition, a later transition state, as would be expected for cyano transfer to a Lewis-acid complexed enone, would more strongly favour the observed product especially when the extra interactions that would be present with the extended ring substituents in **8a** are factored in.

An analogous DFT calculation of the Boltzmann weighted free energies of the conformers of the cyanoketone diastereomers suggests that a thermodynamically-controlled reaction would also afford the observed *cis*-mode product as the major stereoisomer (Figure 3).

Table 1. Calculated parameters for the transition states for the addition of CN⁻ to 3,4-dimethylcyclopent-2-enone.

Parameter	<i>Cis</i> -addition (observed)	<i>Trans</i> -addition
ΔG^\ddagger ^a	+5.39 kJ mol ⁻¹	+5.44 kJ mol ⁻¹
$r[C(3)\cdots CN]$	2.22 Å	2.15 Å
$\angle[C(2)-C(3)\cdots CN]$	111°	112°
$\theta[CH_3-C(3)-C(4)-CH_3]$ ^b	63.0°	51.0°
$\theta[CH_3-C(4)-C(3)\cdots CN]$ ^b	36.1°	150°
C(3) hybridisation ^c	$\sim sp^{2.66}$	$\sim sp^{2.66}$

^a Relative to $\Sigma\Delta G^\circ$ of 3,4-dimethylcyclopent-2-enone and cyanide ion. ^b θ = [dihedral angle]. ^c Based on the sum of the three bond angles surrounding C(3) connecting to C(2), C(4), and the C(3) methyl group.

Table 2. Calculated parameters for the enolates first-formed from the 1,4-addition of CN⁻ to 3,4-dimethylcyclopent-2-enone.^a

Parameter	<i>Cis</i> -addition (observed)	<i>Trans</i> -addition
ΔG^\ddagger	-46.4 kJ mol ⁻¹	-39.4 kJ mol ⁻¹
$r[C(3)-CN]$	1.48 Å	1.48 Å
$\angle[C(2)-C(3)-CN]$	109°	109°
$\theta[CH_3-C(3)-C(4)-CH_3]$	72.9°	41.3°
$\theta[CH_3-C(4)-C(3)-CN]$	49.2°	162°
C(3) hybridisation	sp^3	sp^3

^a Refer to the Table 1 footnotes for explanations.

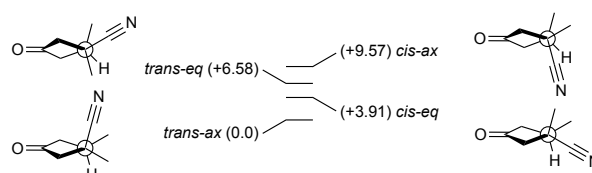
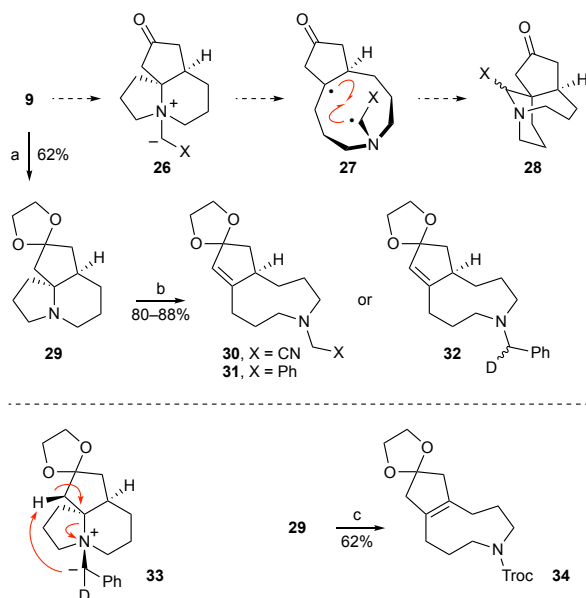


Fig. 3. Relative free energies (ΔG° , B3LYP/6-31G*) for the two (CN pseudoaxial and pseudoequatorial) conformers of the *trans*- and *cis*-3,4-dimethyl nitrile adducts. By this calculation, an 82:18 ratio of *trans*-dimethyl and *cis*-dimethyl diastereomers is predicted under equilibrating conditions.

At this point, an attempt was made to combine the fragmentation of aminoketone **9**, the introduction of the C(13) carbonyl equivalent, and the *N*-cyclisation into a single reaction. A Stevens rearrangement²⁷ was proposed of an ylid (**26**, Scheme 5), formally

derived by addition of an appropriate carbene or carbenoid to **9**, and its subsequent fragmentation (\rightarrow **27**) to generate tricyclic ketone **28** directly. An initial reaction with $\text{KOt-Bu}/\text{CHCl}_3$ returned starting material. Treatment with methyl diazoacetate and $\text{Cu}(\text{acac})_2$ resulted in a complex product mixture, and a similarly unproductive reaction ensued with the ethylenedioxy acetal **29**. In a variant of the approach, the acetal **29** was *N*-alkylated with either cyanomethyl- or benzyl bromide and the so-formed ammonium salt was treated in each case with KOt-Bu to effect ylid formation and Stevens rearrangement. In the event, both reactions resulted in β -elimination to generate products **30** and **31**, respectively. Support for an E_i mechanism was obtained by repeating the latter reaction with α,α -dideutero benzyl bromide²⁸ which afforded the eliminated product enriched in the monodeutero isotopologue **32**.²⁹ Molecular modelling studies of the ylid showed that the benzylic carbon and the relevant *cis*-disposed proton are close (~ 2.2 Å) in a number of accessible conformations of ylid **33**. When acetal **29** was subjected to the fragmentation conditions used to prepare ketone **8a**, the product **34** was obtained, suggesting that an E_i elimination pathway in this system, in contrast to an E_i pathway, leads to preferential formation of the fully-substituted alkene.

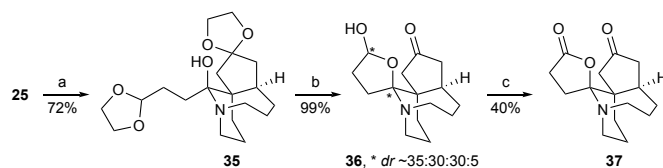


Scheme 5. Reagents and conditions: (a) ethylene glycol, *p*-TsOH, benzene, reflux, 16 h; (b) For **30**: bromoacetonitrile, benzene, RT, 16 h then KOt-Bu , THF, 50 °C, 16 h; For **31**: BnBr, benzene, RT, 16 h then KOt-Bu , THF, RT, 16 h; For **32**: as for **31**, replacing BnBr with PhCD_2Br ; (c) TrocCl, K_2CO_3 , benzene, RT, 16 h.

A brief study was undertaken to establish the potential for protected keto-lactam **25** to be elaborated to the skeleton of huperzine Q and related alkaloids. To this end, the lactam was treated with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane³⁰ as a synthetic equivalent of propionaldehyde homoenolate to furnish hemiaminal **35** (Scheme 6) as a single diastereomer (NOE, Figure 4). Hydrolysis of both carbonyl protecting groups and PCC oxidation of the resulting lactol **36** gave keto-lactone **37**, obtained as the major diastereomer shown whose stereochemistry was established by the key NOE correlations indicated in Figure 4. The stereochemistry in intermediate **35** is presumed to arise from an axial-mode addition to the lactam carbonyl. Although some loss of stereochemical integrity occurred during the hydrolysis, as might be expected, the original sense of stereochemistry was restored during the mildly acidic conditions of the oxidation.

The resulting C(13) stereochemistry in compound **37** is correct for lycoplamine D while the C(4) stereochemistry is correct for

huperzine Q and related alkaloids. However, because the C(4),C(13) combination is epimeric at one of the centres in both series, our investigations were terminated at this point.



Scheme 6. Reagents and conditions: (a) 2-(2-bromoethyl)-1,3-dioxolane/Mg, THF, 0 °C \rightarrow RT, 4 h; (b) aq. HCl, THF, RT, 1 h then 40 °C, 1.5 h; (c) PCC, 4 Å MS, CH_2Cl_2 , RT, 6 h.

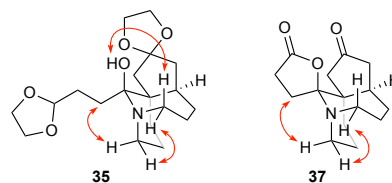


Fig. 4. Diagnostic NOE correlations for the amide/Grignard adduct **35** and the final ketolactone **37**.

3. Conclusion

A furan oxidative spiro-*N*-cyclisation approach to molecules of general structure **6** (Scheme 2) could not be progressed because β -substituted cyclopentenones were found to be insufficiently reactive towards common 2-furyl anion equivalents. Instead, a general route to azonane derivatives **8** (and **30**, **31**, and **34**) was developed that enabled access to a similar tetracyclic motif in nine steps overall from hexahydroindolizine **10**. During the process, an unexpected stereochemical outcome was observed in the conjugate addition of cyanide ion to enone **8a**; some insight into the factors controlling this outcome was obtained through a computational study using 3,4-dimethylcyclopent-2-enone as a model substrate. Finally, although this work did not lead to a synthesis of a complete fawcettimine ring system, the direct formation of lactam **25** offers a potential route to other alkaloids that feature a medium-bridged lactam^{24b} such as tuberostemoninol.³¹

4. Experimental section

4.1. General information

Except where stated, all reagents were purchased from commercial sources and used without further purification. "Petrol" refers to the fraction of light petroleum ether boiling in the range 30–40 °C. "Ether" refers to diethyl ether. Dry ether, dichloromethane and methanol were obtained from Grubbs canisters under argon. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone under a nitrogen atmosphere. All reactions were performed using oven-dried glassware under an atmosphere of argon unless otherwise stated. Reactions were heated, where stated, using oil baths. Thin layer chromatography was carried out using Merck aluminium-backed DC60 F₂₅₄ precoated plates (0.2 mm); spots were visualised by ultraviolet (UV) light ($\lambda_{\text{max}} = 254$ nm) and then stained with anisaldehyde or KMnO_4 dips as appropriate. Flash column chromatography was performed using Merck 60 silica gel (particle size 40–63 μm) and eluted with the described solvent(s). Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on Bruker AVII-500 (500/125 MHz), Bruker AVIII-400 (400/100 MHz), or Bruker AV-400 (400/100 MHz) spectrometers in deuterated solvents. Chemical shifts (δ_{H} and δ_{C}) are quoted in parts per million (ppm), spectra being referenced (in MestReNova) to the appropriate solvent peak: CDCl_3 , 7.26/77.16; CD_2Cl_2 , 5.32/54.00; CD_3OD , 3.31/49.00; toluene-*d*₈, 2.09/20.40. Peak multiplicities are described as singlet

(s), doublet (d), triplet (t), quartet (q), quintet (quin), multiplet (m), and broad (br). Coupling constants (J) are rounded to the nearest 0.5 Hz. Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer. Absorption maxima (ν_{\max}) are reported in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w) and broad (br). High-resolution mass spectra (HRMS) were recorded by the staff of the Chemistry Research Laboratory on a Bruker Daltonics MicroTOF spectrometer; mass to charge ratios (m/z) are reported in Daltons. Melting points were determined using a Griffin MFB-700-010U melting point apparatus and are uncorrected.

4.2. 1,2,3,5,6,7-Hexahydroindolizine (**10**)¹²

n-Butyllithium (53.0 mL, 133 mmol, 2.5 M solution in hexanes) was added dropwise to a stirred solution of diisopropylamine (18.6 mL, 133 mmol) in THF (120 mL) at 0 °C. After 5 min, the solution was cooled to -78 °C and a solution of 2-methyl-1-pyrroline (11.4 mL, 120 mmol) in THF (120 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 2 h. A solution of 1-bromo-3-chloropropane (12.5 mL, 126 mmol) in THF (120 mL) was then added dropwise and the mixture was stirred at RT for 16 h. The mixture was poured into 0.5 M aq. NaOH solution (450 mL), the product extracted into ether (3 × 500 mL), and the combined organic extracts were dried over K_2CO_3 , filtered and concentrated *in vacuo* to afford 2,3,5,6,7,8-hexahydro-1*H*-indolizin-4-ium chloride as a yellow-orange solid (18.0 g, 94%). R_f 0.65 (100:10:1 CHCl_3 :MeOH:aq. NH_3 (18 M)); ν_{\max} (thin film)/ cm^{-1} 3396w, 2950s, 2867m, 1644s, 1431m, 1303m, 1015w; δ_H (400 MHz, C_6D_6) 1.38–1.61 (6 H, m), 1.89–2.00 (4 H, m), 3.12 (2 H, t, J 6.5), 3.73 (2 H, app. tquin, J 7.5, 5.5, 2.0); δ_C (100 MHz, C_6D_6) 22.8, 23.7, 32.5, 32.7, 37.3, 44.8, 61.3, 175.5; m/z (ESI^+) 162 ($\text{M}^{(37)\text{Cl}}\text{H}^+$, 32%), 160 ($\text{M}^{(35)\text{Cl}}\text{H}^+$, 100), 124 ($(\text{M}-\text{Cl})^+$, 35). To a stirred solution of the iminium salt (9.00 g, 56.4 mmol) in water (900 mL) was added powdered NaOH (56.4 g, 1.41 mol) and the reaction mixture was stirred at RT for 16 h. Pentane (900 mL) was added and the mixture was stirred at RT for 1 h. The separated organic layer was dried over K_2CO_3 , filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (5.15 g, 74%). ν_{\max} (thin film)/ cm^{-1} 2930s, 1683m, 1648w, 1445w, 1280m, 1185m; δ_H (400 MHz, C_6D_6) 1.47–1.56 (2 H, m), 1.81–1.88 (2 H, m), 2.12–2.18 (2 H, m), 2.24–2.31 (2 H, m), 2.66 (2 H, t, J 6.5), 2.80 (2 H, t, J 5.5), 4.43 (1 H, tt, J 3.5, 1.5); δ_C (100 MHz, C_6D_6) 21.9, 22.4, 23.5, 29.2, 47.1, 53.1, 88.2 (4° carbon not observed); m/z (ESI^+) 124 (MH^+ , 100%).

4.3. 8,8-Diallyloctahydroindolizine (**13**)

Allyl iodide (23.0 μL , 0.252 mmol) was added to a solution of enamine **10** (31.0 mg, 0.252 mmol) in THF (1 mL) and the reaction mixture was stirred at RT for 1 h. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 6:3:1 CHCl_3 :MeOH:aq. NH_3 (18 M)) afforded 8,8-diallyl-2,3,5,6,7,8-hexahydro-1*H*-indolizin-4-ium iodide (**12**) as a brown oil (49.1 mg, 59%). R_f 0.45 (6:3:1 CHCl_3 :MeOH:aq. NH_3 (18 M)); ν_{\max} (thin film)/ cm^{-1} 3427m, 2935m, 1669s, 1446m, 1314m, 1000m, 927s; δ_H (500 MHz, CDCl_3) 1.84–1.89 (2 H, m), 2.08–2.15 (2 H, m), 2.29 (2 H, quin, J 8.0), 2.49 (2 H, dd, J 14.0, 8.0), 2.67 (2 H, dd, J 14.0, 7.0), 3.29–3.36 (2 H, m), 3.89 (2 H, t, J 6.0), 4.45 (2 H, t, J 8.0), 5.21–5.28 (4 H, m), 5.72–5.84 (2 H, m); δ_C (125 MHz, CDCl_3) 17.7, 18.4, 26.8, 36.8, 41.4, 43.1, 49.7, 62.2, 121.4, 131.1, 194.2; m/z (ESI^+) 127 (I^- , 100%); HRMS (ESI^+) found 204.1749, $\text{C}_{14}\text{H}_{22}\text{N}$ [$(\text{M}-\text{I})^+$] requires 204.1747. To a solution of this iminium salt (11.0 mg, 33.2 μmol) in methanol (1 mL) was added NaBH_4 (2.5 mg, 66.1 μmol) and the reaction mixture was stirred at RT for 1 h then diluted with 1.0 M aq. NaOH solution (2 mL). The methanol was removed *in vacuo*, the aqueous layer diluted with

water (4 mL), and the mixture extracted with ethyl acetate (3 × 4 mL). The combined organic extracts were washed with brine (4 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 CHCl_3 :MeOH:aq. NH_3 (18 M)) afforded the title compound as a pale yellow oil (4.0 mg, 59%). R_f 0.55 (100:10:1 CHCl_3 :MeOH:aq. NH_3 (18 M)); ν_{\max} (thin film)/ cm^{-1} 3407w, 3073w, 2934s, 2780m, 1671m, 1638m, 1454m, 910s; δ_H (500 MHz, CD_3OD) 1.11–1.24 (1 H, m), 1.50–1.88 (7 H, m), 1.99–2.19 (5 H, m), 2.49 (1 H, dd, J 14.0, 8.0), 3.01–3.16 (2 H, m), 3.33–3.39 (1 H, m, obscured by solvent peak), 5.01–5.12 (4 H, m), 5.79–5.95 (2 H, m); δ_C (125 MHz, CD_3OD) 21.1, 22.2, 24.3, 32.4, 35.9, 39.1, 44.2, 54.3, 55.8, 72.6, 117.9, 118.1, 135.8 (two peaks); HRMS (ESI^+) found 206.1907, $\text{C}_{14}\text{H}_{24}\text{N}$ (MH^+) requires 206.1903.

4.4. 7a-(2-Oxopropyl)octahydrocyclopenta[*h*]indolizin-9(1*H*)-one (**16**)

A solution of enamine **10** (40.0 mg, 0.325 mmol) in THF (0.7 mL) was added dropwise to a stirred solution of 3-iodo-2-(methoxymethoxy)propene (74.0 mg, 0.325 mmol) in THF (0.3 mL) and the reaction mixture was stirred at RT for 6 h. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 95:5:1 CHCl_3 :MeOH:aq. NH_3 (18 M)) afforded 8,8-bis[2-(methoxymethoxy)allyl]-2,3,5,6,7,8-hexahydro-1*H*-indolizin-4-ium iodide (**15**) as a brown oil (29.0 mg, 20%). R_f 0.25 (100:10:1 CHCl_3 :MeOH:aq. NH_3 (18 M)); ν_{\max} (thin film)/ cm^{-1} 3445w, 2948w, 1639m, 1447w, 1153m, 1011s; δ_H (400 MHz, CDCl_3) 1.82–1.88 (2 H, m), 2.00–2.07 (2 H, m), 2.30 (2 H, quin, J 7.5), 2.44 (2 H, d, J 14.5), 2.89 (2 H, d, J 14.5), 3.31–3.37 (2 H, m), 3.40 (6 H, s), 3.75–3.83 (2 H, m), 4.19 (2 H, d, J 2.0), 4.24 (2 H, d, J 2.0), 4.45 (2 H, t, J 7.5), 4.90 (2 H, d, J 12.0), 4.92 (2 H, d, J 12.0); δ_C (100 MHz, CDCl_3) 18.4, 18.6, 25.6, 36.01, 41.2, 44.45, 49.3, 57.1, 62.1, 90.4, 94.5, 154.8, 193.9; m/z (ESI^+) 127 (I^- , 100%); HRMS (ESI^+) found 324.2164, $\text{C}_{18}\text{H}_{30}\text{NO}_4$ [$(\text{M}-\text{I})^+$] requires 324.2169. Water (1.5 μL , 83.3 μmol) was added to a solution of this iminium salt (29.0 mg, 64.3 μmol) in dry acetonitrile (0.5 mL) and the mixture was stirred under reflux at 80 °C for 16 h. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 95:5:1 CHCl_3 :MeOH:aq. NH_3 (18 M)) afforded the title compound as a pale yellow oil (5.0 mg, 33%). R_f 0.46 (100:10:1 CHCl_3 :MeOH:aq. NH_3 (18 M)); ν_{\max} (thin film)/ cm^{-1} 2937m, 2797w, 1738s, 1713m, 1405m, 1360m, 1163m; δ_H (500 MHz, CDCl_3) 1.25 (1 H, td, J 14.0, 3.5), 1.42–1.49 (1 H, m), 1.52–1.60 (1 H, m), 1.61–1.95 (6 H, m), 2.16 (3 H, s), 2.29–2.37 (2 H, m) overlays 2.30 (1 H, d, J 18.5), 2.50 (1 H, d, J 16.5), 2.57 (1 H, d, J 18.0), 2.60 (1 H, d, J 18.5), 2.82 (1 H, br d, J 11.0), 3.00 (1 H, br t, J 8.0), 3.16 (1 H, br d, J 16.5); δ_C (125 MHz, CDCl_3) 18.9, 22.0, 29.0, 31.4, 32.2, 36.8, 41.3, 44.9, 45.8, 51.0, 51.2, 69.6, 208.3, 216.7; HRMS (ESI^+) found 236.1643, $\text{C}_{14}\text{H}_{22}\text{NO}_2$ (MH^+) requires 236.1645.

4.5. Octahydrocyclopenta[*h*]indolizin-9(1*H*)-one (**9**)

A solution of enamine **10** (10.3 g, 83.6 mmol) in THF (96 mL) was added dropwise to a stirred solution of iodoacetone (15.4 g, 83.7 mmol) in THF (144 mL) and the reaction mixture was stirred at RT for 1 h. The solvent was removed *in vacuo* to afford a crude mixture of iminium salts **17** and **18** (25.0 g); in this large-scale reaction, the monoalkylated product was the minor component, as judged by NMR and MS analysis, comprising ~30% of the product mixture. The crude product was dissolved in NaOH solution (16.3 g, 408 mmol in 900 mL of THF/water, 1:3) and the reaction mixture was stirred at RT for 24 h. The mixture was extracted with ether (3 × 600 mL), and the combined organic layers were dried over K_2CO_3 , filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 CHCl_3 :MeOH:aq. NH_3 (18

M)) afforded the *title compound* as a pale yellow oil (4.50 g, 30% from enamine **10**). R_f 0.48 (100:10:1 CHCl₃:MeOH:aq. NH₃ (18 M)); ν_{max} (thin film)/cm⁻¹ 2930m, 1740s, 1405w, 1150w; δ_H (500 MHz, CDCl₃) 1.13–1.24 (1 H, m), 1.57–1.71 (2 H, m), 1.73–1.83 (4 H, m), 1.87 (1 H, d, *J* 18.5), 1.91–2.00 (1 H, m), 2.08 (1 H, d, *J* 18.5), 2.10–2.19 (1 H, m), 2.42 (1 H, dd, *J* 18.5, 7.0), 2.52–2.63 (2 H, m), 2.63–2.73 (1 H, m), 2.86 (1 H, dt, *J* 12.5, 3.5), 3.03 (1 H, dt, *J* 9.5, 3.5); δ_C (125 MHz, CDCl₃) 20.1, 22.4, 27.6, 37.0, 38.8, 39.9, 44.9, 45.2, 50.9, 66.7, 217.2; HRMS (ESI⁺) found 180.1386, C₁₁H₁₈NO (MH⁺) requires 180.1383.

4.6. (7*aR*,1*iS*,12*aS*)-11-hydroxyoctahydro-1*H*-7*a*,11-methanocyclohepta[*h*]indolizin-9(5*H*)-one (**19**)

To a solution of iodoacetone (64.5 mg, 0.351 mmol) in THF (0.5 mL) was added dropwise a solution of enamine **10** (43.2 mg, 0.351 mmol) in THF (0.5 mL). The mixture was stirred at RT for 1 h then the solvent was evaporated and the residue purified by flash chromatography (silica, 95:5:1 CHCl₃:MeOH:aq. NH₃ (18 M)). The iminium salt 8,8-bis(2-oxopropyl)-2,3,5,6,7,8-hexahydro-1*H*-indolizin-4-ium iodide (**18**) was obtained as a beige oil (15.0 mg, 12%). R_f 0.50 (40:10:1 CHCl₃:MeOH:aq. NH₃ (18 M)); ν_{max} (thin film)/cm⁻¹ 3453m, 2953w, 1708s, 1674m, 1418w, 1361m, 1174m; δ_H (500 MHz, CD₃OD) 1.83–1.89 (2 H, m), 1.90–1.97 (2 H, m), 2.18 (6 H, s), 2.20–2.26 (2 H, m), 3.06 (2 H, br t, *J* 8.0), 3.17 (2 H, d, *J* 18.5), 3.31 (2 H, d, *J* 18.5), 3.69–3.77 (2 H, m), 4.22 (2 H, t, *J* 8.0); δ_C (125 MHz, CD₃OD) 19.3, 19.5, 29.1, 30.7, 36.6, 40.3, 51.4, 61.0, 194.5, 208.4 (one resonance obscured by solvent peak); *m/z* (ESI⁻) 127 (I⁻, 100%); HRMS (ESI⁺) found 236.1644, C₁₄H₂₂NO₂ [(M-I)⁺] requires 236.1645. To a stirred solution of this iminium salt (14.0 mg, 38.5 μmol) in THF–water (1.3 mL, 1:3) was added powdered NaOH (46.3 mg, 1.16 mmol) and the reaction mixture was stirred at RT for 48 h. Water (1 mL) was added and the mixture was extracted with ether (3 × 3 mL). The combined organic layers were dried over K₂CO₃, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 CHCl₃:MeOH:aq. NH₃ (18 M)) afforded the *title compound* as a pale yellow oil (2.5 mg, 28%). R_f 0.25 (100:10:1 CHCl₃:MeOH:aq. NH₃ (18 M)); ν_{max} (thin film)/cm⁻¹ 3373br, 2944m, 1711s, 1441w, 1327m, 1122m; δ_H (500 MHz, CDCl₃) 1.32 (1 H, td, *J* 14.0, 4.5), 1.37–1.44 (1 H, m), 1.53–1.70 (5 H, m), 1.79 (1 H, td, *J* 12.0, 8.0), 1.87–2.07 (4 H, m), 2.16 (1 H, d, *J* 16.5), 2.23–2.33 (2 H, m), 2.55–2.75 (4 H, m), 3.03 (1 H, dt, *J* 11.5, 3.0), 3.08 (1 H, ddd, *J* 13.0, 10.0, 8.0); δ_C (125 MHz, CDCl₃) 20.5, 21.5, 27.5, 29.7, 44.2, 47.7, 50.8, 52.0, 53.6, 54.6, 56.6, 73.9, 76.6, 209.4; HRMS (ESI⁺) found 236.1645, C₁₄H₂₂NO₂ (MH⁺) requires 236.1645.

4.7. 9-Methyl-1,2,5,6,6*a*,7,8,9*b*-octahydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline (**21**)

Methyl vinyl ketone (27.0 μL, 0.325 mmol) was added to a solution of enamine **10** (40.0 mg, 0.325 mmol) in THF (1.2 mL) and the reaction mixture was stirred at RT for 1 h [a separate NMR experiment in THF-*d*₈ showed the reaction to be complete within minutes]. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 6:3:1 CHCl₃:MeOH:aq. NH₃ (18 M)) afforded 9-methyl-1,2,4,5,6,6*a*,7,8-octahydropyrrolo[3,2,1-*ij*]quinolin-3-ium hydroxide³² (**20/20-d**) as a pale yellow semi-solid (26.4 mg, 42%). R_f 0.20 (6:3:1 CHCl₃:MeOH:aq. NH₃ (18 M)); ν_{max} (thin film)/cm⁻¹ 3383s, 2942w, 1652s, 1430m, 1224w, 1088m; δ_H (500 MHz, CD₃OD) [data for **20-d**] 1.39–1.48 (1 H, m), 1.55–1.65 (1 H, m), 2.03 (3 H, s), 2.00–2.10 (2 H, m), 2.12–2.23 (2 H, m), 2.38–2.48 (1 H, m), 2.53–2.64 (1 H, m), 2.85–2.95 (2 H, m), 3.58–3.72 (1 H, m), 3.77 (1 H, dd, *J* 16.0, 6.0), 4.10 (2 H, t, *J* 7.0); δ_C (125 MHz, CD₃OD) [data for **20-d**] 21.3, 21.9, 24.1 (two peaks), 29.1, 32.7, 35.3 (1:1:1 t, *J* 20.5), 48.1, 58.2, 131.9, 159.5, 180.5; HRMS (ESI⁺) [data for **20**] found 176.1436, C₁₂H₁₈N

[(M-OH)⁺] requires 176.1434. To a solution of this iminium salt **20/20-d** (26.4 mg, 0.137 mmol) in methanol (3 mL) was added NaBH₄ (12.9 mg, 0.341 mmol) and the reaction mixture was stirred at RT for 1 h then diluted with 1.0 M aq. NaOH solution (6 mL). The methanol was removed *in vacuo*, the aqueous layer diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 CHCl₃:MeOH:aq. NH₃ (18 M)) afforded the *title compound* as a pale yellow oil (13.5 mg, 56%). R_f 0.48 (100:10:1 CHCl₃:MeOH:aq. NH₃ (18 M)); ν_{max} (thin film)/cm⁻¹ 3372w, 2924s, 2852m, 1686w, 1436m, 1326m, 1263m; δ_H (500 MHz, CD₃OD) 1.02–1.12 (1 H, m), 1.25–1.34 (2 H, m), 1.58 (3 H, s), 1.66–1.82 (4 H, m), 1.92–2.00 (1 H, m), 2.03–2.10 (2 H, m), 2.14–2.27 (2 H, m), 2.35–2.44 (2 H, m), 3.10–3.17 (2 H, m); δ_C (125 MHz, CD₃OD) 18.4, 26.6, 27.4, 28.4, 31.1, 32.6, 38.9, 54.1 (two peaks), 71.9, 125.7, 131.7; HRMS (ESI⁺) found 178.1596, C₁₂H₂₀N (MH⁺) requires 178.1590.

4.8. 2,2,2-Trichloroethyl-9-oxo-2,3,5,6,7,7*a*,8,9-octahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (**8a**)

2,2,2-Trichloroethyl chloroformate (76.5 μL, 0.556 mmol) and K₂CO₃ (153 mg, 1.11 mmol) were added to a solution of amine **9** (20.0 mg, 0.111 mmol) in benzene (1.2 mL) and the reaction mixture was stirred at RT for 3 h. Water (10 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a colourless viscous oil (39.0 mg, 99%). R_f 0.30 (ether); ν_{max} (thin film)/cm⁻¹ 2925w, 1710s, 1679s, 1605m, 1419m, 1189m, 715m; δ_H (400 MHz, toluene-*d*₈) [at 295 K two rotamers are seen in ratio ~60:40; only partial coalescence seen at 373 K] 0.95–1.07 (2 H, m), 1.24–1.55 (4 H, m), 1.65–1.82 (2.4 H, m), 1.55–2.18 (2.6 H, m), 2.29–2.38 (1 H, m), 2.39–2.53 (1.2 H, m), 2.60–2.77 (1.2 H, m), 3.00–3.14 (1 H, m), 3.21 (0.6 H, ddd, *J* 13.5, 10.0, 4.0), 4.33 & 4.75 (2 × 0.4 H, 2 × d, *J* 12.0), 4.39 & 4.83 (2 × 0.6 H, 2 × d, *J* 12.0), 5.85–5.89 (1 H, m); δ_C (125 MHz, toluene-*d*₈, 373 K) 21.4, 26.6, 28.3, 41.5, 43.2, 50.7, 75.8, 77.8, 96.7, 132.4, 154.8, 180.8, 205.0 [one resonance not observed]; HRMS (EI⁺) found 353.0345, C₁₄H₁₈NO₃³⁵Cl₃ (M⁺) requires 353.0347.

4.9. Benzyl-9-oxo-2,3,5,6,7,7*a*,8,9-octahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (**8b**)

Benzyl chloroformate (20.0 μL, 0.140 mmol) and K₂CO₃ (38.4 mg, 0.278 mmol) were added to a solution of amine **9** (5.0 mg, 0.0279 mmol) in benzene (0.3 mL) and the reaction mixture was stirred at RT for 5 h. Water (5 mL) was added and the mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 99:1 CHCl₃:MeOH) afforded the *title compound* as a *ca.* 60:40 mixture of carbamate rotamers as a colourless viscous oil (8.3 mg, 95%). R_f 0.60 (10:1 CHCl₃:MeOH); ν_{max} (thin film)/cm⁻¹ 2922w, 1684s, 1604w, 1418m, 1189m, 699m; δ_H (500 MHz, CDCl₃) 1.41–1.63 (2 H, m), 1.87–2.00 (2.2 H, m), 2.01–2.12 (1.6 H, m), 2.13–2.26 (1 H, m), 2.33–2.45 (1 H, m), 2.46–2.59 (1.6 H, m), 2.65–2.75 (0.6 H, m), 2.92–3.09 (2.2 H, m), 3.19 (0.4 H, dt, *J* 14.0, 4.5), 3.24–3.39 (1.2 H, m), 3.47 (0.6 H, dt, *J* 14.5, 3.5), 3.66 (0.6 H, ddd, *J* 13.5, 10.0, 4.0), 4.93 (0.6 H, d, *J* 12.0), 5.07 (0.4 H, d, *J* 12.0), 5.17 (0.6 H, d, *J* 12.0), 5.19 (0.4 H, d, *J* 12.0), 5.96 (0.4 H, s), 6.09 (0.6 H, s), 7.28–7.42 (5 H, m); δ_C (125 MHz, CDCl₃) 20.0/20.8, 26.1/27.0, 27.2, 27.8, 28.5, 29.7, 41.1/41.5, 43.2/43.3, 46.9/49.0, 50.4/50.5, 67.4 (two peaks), 128.3, 128.6, 128.7, 131.4/131.8, 136.8, 156.5/157.0, 184.4/184.7, 208.6/208.7; HRMS (ESI⁺) found 336.1581, C₁₉H₂₃NO₃Na (MNa⁺) requires 336.1570.

4.10. 4-Benzyl-2,3,4,5,6,7,7a,8-octahydrocyclopenta[e]azonin-9(1H)-one (8c)

Benzyl bromide (33.0 μ L, 0.277 mmol) and K_2CO_3 (76.7 mg, 0.556 mmol) were added to a solution of amine **9** (10.0 mg, 0.0558 mmol) in benzene (0.6 mL) and the reaction mixture was stirred at RT for 16 h. The mixture was filtered through a cotton plug, washed with dichloromethane (5 mL) and concentrated *in vacuo*. Purification by flash chromatography (silica, ether \rightarrow 10:1 $CHCl_3$:MeOH) afforded the *title compound* as a pale yellow oil (14.0 mg, 93%). R_f 0.30 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/ cm^{-1} 2922w, 1710s, 1683s, 1606m, 1451m, 726m; δ_H (500 MHz, $CDCl_3$) 1.02–1.13 (1 H, m), 1.28–1.38 (1 H, m), 1.56–1.72 (2 H, m), 1.74–1.85 (1 H, m), 2.02 (1 H, dd, J 19.0, 2.0), 2.10–2.20 (1 H, m), 2.22–2.36 (3 H, m), 2.39–2.59 (3 H, m), 2.84 (1 H, ddd, J 13.5, 12.5, 4.0), 3.03–3.08 (1 H, m), 3.41 (1 H, d, J 13.0), 3.68 (1 H, d, J 13.0), 6.09 (1 H, s), 7.23–7.27 (1 H, m), 7.28–7.35 (4 H, m); δ_C (125 MHz, $CDCl_3$) 19.5, 24.5, 26.5, 27.1, 40.9, 44.4, 48.1, 52.4, 60.9, 127.0, 128.3, 129.3, 132.3, 140.0, 187.5, 209.5; HRMS (ESI^+) found 270.1855, $C_{18}H_{24}NO$ (MH^+) requires 270.1852.

4.11. 2,2,2-Trichloroethyl-7a-cyano-9-oxodecahydrocyclopenta[e]azonine-4(1H)-carboxylate (22)

Trimethylsilyl cyanide (47 μ L, 0.376 mmol) was added to a solution of triethylaluminium (0.342 mL, 0.342 mmol, 1.0 M in heptanes) in THF (0.9 mL). A solution of enone **8a** (60.6 mg, 0.171 mmol) in THF (0.5 mL) was then added and the mixture was stirred under reflux for 5 h. Satd. aq. NH_4Cl solution (5 mL) was added and the mixture was extracted with ether (3 \times 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude silyl enol ether was dissolved in THF (1 mL) and dil. HCl (0.5 mL) was added. The mixture was stirred at RT for 10 mins and extracted with ether (3 \times 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless viscous oil (55.2 mg, 85%). R_f 0.50 (ether); ν_{max} (thin film)/ cm^{-1} 2950w, 2215w, 1751m, 1710s, 1422m, 1128m, 714m; δ_H (400 MHz, toluene- d_8) [at 295 K two rotamers are seen in ratio ~55:45; only partial coalescence seen at 373 K] 1.06–1.53 (~6 H, m), 1.53–1.68 (~3 H, m), 1.68–2.26 (~5 H, m), 2.26–2.39 (~1 H, m), 3.37 (~0.6 H, ddd, J 14.0, 6.5, 2.5), 3.47–3.60 (~1 H, m), 3.76 (~0.5 H, ddd, J 14.0, 11.0, 3.5), 4.01 & 4.94 (2 \times 0.55 H, 2 \times d, J 12.0) and 4.14 & 4.79 (2 \times 0.45 H, 2 \times d, J 12.0); δ_C (125 MHz, toluene- d_8 , 363 K) 22.7, 25.9, 31.2, 35.4, 41.4, 45.1, 46.4, 50.3, 75.4, 96.6, 121.6, 154.5, 208.1 (two resonances not seen); HRMS (ESI^+) found 403.0366, $C_{15}H_{19}N_2NaO_3^{35}Cl_3$ (MNa^+) requires: 403.0353.

4.12. (4R,7aS,10aR)-Octahydro-4,7a-methanocyclopenta[e]azonine-9,11(1H)-dione (23)

Zinc (15.5 mg, 0.237 mmol) was added to a solution of nitrile **22** (9.0 mg, 0.0236 mmol) in glacial acetic acid (0.3 mL) and the mixture was stirred at RT for 48 h. Satd. aq. $NaHCO_3$ solution (5 mL) was added and the mixture was extracted with ether (3 \times 5 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (1.2 mg, 25%). R_f 0.40 (ether); ν_{max} (thin film)/ cm^{-1} 2933m, 1743s, 1665m, 1444w, 1321w, 1183m; δ_H (500 MHz, CD_2Cl_2) 1.64–1.81 (4 H, m), 1.82–1.90 (1 H, m), 1.91–2.01 (3 H, m), 2.03–2.14 (2 H, m), 2.40–2.50 (2 H, m), 2.83 (1 H, dt, J 13.5, 5.5), 3.16 (1 H, dd, J 18.5, 2.0), 3.31 (1 H, dtd, J 12.0, 4.5, 1.5), 3.46 (1 H, td, J 12.0, 3.0), 3.88 (1 H, ddd, J 13.5, 8.0, 5.5); δ_C (125 MHz, CD_2Cl_2) 22.2, 24.0, 31.2, 36.2, 43.3, 44.9,

48.4, 49.6, 51.6, 54.4, 184.2, 216.4; HRMS (ESI^+) found 208.1333, $C_{12}H_{18}NO_2$ (MH^+) requires 208.1332.

4.13. 2,2,2-Trichloroethyl-7a-cyano-octahydro-1H-spiro[cyclopenta[e]azonine-9,2'-[1,3]dioxolane]-4(5H)-carboxylate (24)

p-TsOH·H₂O (4.4 mg, 2.32 μ mol) was added to a solution of nitrile **22** (89.0 mg, 0.233 mmol) and ethylene glycol (14.3 μ L, 0.256 mmol) in benzene (3.5 mL) and the mixture was stirred under reflux for 2 h. Satd. aq. $NaHCO_3$ solution (8 mL) was added and the mixture was extracted with ether (3 \times 15 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil as a 50:50 mixture of carbamate rotamers (80.6 mg, 81%). R_f 0.60 (ether); ν_{max} (thin film)/ cm^{-1} 2949w, 2210w, 1712s, 1421m, 1202m, 1127m; δ_H (400 MHz, toluene- d_8) 1.24–1.60 (4 H, m), 1.61–1.86 (6 H, m), 1.95 (0.5 H, dd, J 13.5, 6.5), 2.02–2.08 (1 H, m), 2.10–2.24 (2 H, m), 2.30–2.42 (1 H, m), 3.18–3.43 (4 H, m), 3.53 (0.5 H, ddd, J 14.5, 6.5, 2.0), 3.63 (0.5 H, dt, J 14.5, 6.5), 3.69 (0.5 H, ddd, J 14.5, 8.0, 3.0), 3.85 (0.5 H, ddd, J 14.5, 11.0, 3.5), 4.08 (0.5 H, d, J 12.0), 4.16 (0.5 H, d, J 12.0), 5.00 (0.5 H, d, J 12.0), 5.03 (0.5 H, d, J 12.0); δ_C (100 MHz, toluene- d_8) 22.2/22.8, 25.3/25.9, 30.7/31.0, 36.0 (two peaks), 41.9/42.7, 45.3, 45.7/45.8, 49.4/49.5, 49.6/49.7, 50.0/50.8, 63.9/64.0, 64.5/64.6, 74.8/75.1, 96.1/96.3, 113.4 (two peaks), 122.6/122.8, 154.2 (two peaks); HRMS (ESI^+) found 447.0622, $C_{17}H_{23}N_2NaO_4^{35}Cl_3$ (MNa^+) requires 447.0616.

4.14. (4S,7aR,10aR)-Octahydro-1H-spiro[4,7a-methanocyclopenta[e]azonine-9,2'-[1,3]dioxolan]-11-one (25)

Zinc (37.0 mg, 0.566 mmol) was added to a solution of nitrile **24** (30.0 mg, 0.0705 mmol) in glacial acetic acid (0.9 mL) and the mixture was stirred at RT for 16 h. Satd. aq. $NaHCO_3$ solution (5 mL) was added and the mixture was extracted with ether (3 \times 5 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (15.9 mg, 90%). R_f 0.45 (ether); ν_{max} (thin film)/ cm^{-1} 2930m, 1678s, 1448m, 1321m, 1116m; δ_H (500 MHz, CD_2Cl_2) 1.40–1.54 (4 H, m), 1.57–1.71 (2 H, m), 1.85 (1 H, dt, J 13.5, 6.0), 1.87–1.96 (2 H, m), 2.07–2.19 (2 H, m), 2.25 (1 H, ddd, J 13.5, 8.5, 6.0), 2.84 (1 H, dd, J 13.5, 1.5), 2.88 (1 H, ddt, J 13.5, 5.0, 1.5), 3.15 (1 H, dddd, J 12.5, 7.5, 4.0, 1.0), 3.33 (1 H, dddd, J 12.5, 8.5, 3.5, 1.0), 3.79–3.90 (5 H, m); δ_C (125 MHz, CD_2Cl_2) 22.6, 27.9, 35.3, 37.9, 43.6, 43.9, 45.7, 48.0, 54.9, 64.6, 64.9, 117.1, 185.2 (one resonance obscured by solvent peak); HRMS (ESI^+) found 274.1414, $C_{14}H_{21}NNaO_3$ (MNa^+) requires 274.1414.

4.15. Octahydro-1H-spiro[cyclopenta[h]indolizine-9,2'-[1,3]dioxolane] (29)

p-TsOH·H₂O (34.9 mg, 0.184 mmol) was added to a solution of ketone **9** (30.0 mg, 0.167 mmol) and ethylene glycol (18.6 μ L, 0.334 mmol) in benzene (2.7 mL) and the mixture was stirred under reflux for 16 h. Satd. aq. $NaHCO_3$ solution (5 mL) was added and the mixture was extracted with dichloromethane (3 \times 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a colourless oil (23.0 mg, 62%). R_f 0.15 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/ cm^{-1} 2931s, 2788w, 1437w, 1343m, 1112s, 1066m; δ_H (500 MHz, CD_2Cl_2) 1.35–1.87 (11 H, m), 2.02 (1 H, dd, J 14.0, 7.0), 2.17 (1 H, d, J 14.0), 2.51–2.62 (2 H, m), 2.70 (1 H, dtd, J 12.5, 4.0, 1.0), 2.87 (1 H, td,

J 9.0, 4.5), 3.74–3.88 (4 H, m); δ_{C} (125 MHz, CD_2Cl_2) 20.9, 23.0, 27.5, 37.3, 38.9, 40.8, 42.5, 45.5, 51.2, 64.3, 64.5, 68.5, 116.4; HRMS (ESI^+) found 224.1642, $\text{C}_{13}\text{H}_{22}\text{NO}_2$ (MH^+) requires 224.1645.

4.16. 2-{2,3,6,7,7a,8-Hexahydro-1H-spiro[cyclopenta[e]azonine-9,2'-[1,3]dioxolan]-4(5H)-yl}acetonitrile (**30**)

Bromoacetonitrile (14.0 μL , 0.201 mmol) was added to a solution of amine **29** (9.0 mg, 0.0403 mmol) in benzene (0.5 mL) and the mixture was stirred at RT for 16 h. The solvent was removed *in vacuo* and the white solid was dissolved in THF (0.4 mL). Potassium *tert*-butoxide (80.5 μL , 0.0805 mmol, 1.0 M in THF) was added to the mixture and stirred at 50 °C for 16 h. Water (1 mL) was added and the mixture was extracted with dichloromethane (3 \times 3 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 10:1 CHCl_3 :MeOH) afforded the *title compound* as a colourless oil (8.5 mg, 80%). R_{f} 0.90 (10:1 CHCl_3 :MeOH); ν_{max} (thin film)/ cm^{-1} 2933m, 1647w, 1307m, 1141m, 1087s, 997m; δ_{H} (500 MHz, CD_2Cl_2) 1.31–1.48 (2 H, m), 1.52–1.66 (2 H, m), 1.67–1.77 (2 H, m), 1.85–1.93 (1 H, m), 2.13–2.25 (3 H, m), 2.26–2.35 (2 H, m), 2.63–2.72 (2 H, m), 2.77–2.84 (1 H, m), 3.42 (1 H, dd, J 17.0, 1.5), 3.56 (1 H, d, J 17.0), 3.83–3.90 (4 H, m), 5.47 (1 H, t, J 1.5); δ_{C} (125 MHz, CD_2Cl_2) 20.2, 23.9, 25.9, 26.7, 41.0, 44.4, 45.6, 46.5, 54.1, 64.9, 65.0, 116.9, 119.7, 127.0, 154.3; HRMS (ESI^+) found 263.1751, $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_2$ (MH^+) requires 263.1754.

4.17. 4-Benzyl-2,3,4,5,6,7,7a,8-octahydro-1H-spiro[cyclopenta[e]azonine-9,2'-[1,3]dioxolane] (**31**)

Benzyl bromide (7.2 μL , 0.0605 mmol) was added to a solution of amine **29** (9.0 mg, 0.0403 mmol) in benzene (0.4 mL) and the mixture was stirred at RT for 16 h. The solvent was removed *in vacuo* and the white solid was dissolved in THF (0.4 mL). Potassium *tert*-butoxide (80.5 μL , 0.0805 mmol, 1.0 M in THF) was added to the mixture and stirred at RT for 16 h. Water (1 mL) was added and the mixture was extracted with dichloromethane (3 \times 3 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford the *title compound* as a colourless oil (10.2 mg, 81%). R_{f} 0.70 (1:1 petrol:ether); ν_{max} (thin film)/ cm^{-1} 2922m, 1452w, 1360w, 1087s, 1054m; δ_{H} (500 MHz, CD_2Cl_2) 1.20–1.37 (2 H, m), 1.43–1.53 (2 H, m), 1.63–1.73 (2 H, m), 1.96 (1 H, dq, J 14.0, 4.0), 2.11–2.33 (5 H, m), 2.52 (1 H, td, J 13.5, 4.5), 2.68 (1 H, td, J 13.0, 4.0), 2.78–2.87 (1 H, m), 3.37 (1 H, d, J 13.0), 3.70 (1 H, d, J 13.0), 3.80–3.93 (4 H, m), 5.48 (1 H, t, J 2.0), 7.18–7.25 (1 H, m), 7.27–7.32 (2 H, m), 7.32–7.35 (2 H, m); δ_{C} (125 MHz, CD_2Cl_2) 20.4, 24.1, 25.3, 27.7, 41.1, 45.9, 48.0, 53.0, 61.5, 64.8, 65.0, 119.9, 126.9, 127.2, 128.6, 129.7, 141.2, 155.1; HRMS (ESI^+) found 314.2108, $\text{C}_{20}\text{H}_{28}\text{NO}_2$ (MH^+) requires 314.2115.

4.18. 4-[Deutero(phenyl)methyl]-2,3,4,5,6,7,7a,8-octahydro-1H-spiro[cyclopenta[e]azonine-9,2'-[1,3]dioxolane] (**32**)

α,α -Dideutero benzyl bromide (11.7 mg, 0.0676 mmol) was added to a solution of amine **29** (13.7 mg, 0.0613 mmol) in benzene (0.6 mL) and the mixture was stirred at RT for 16 h. The solvent was removed *in vacuo* and the white solid was dissolved in THF (0.6 mL). Potassium *tert*-butoxide (0.123 mL, 0.123 mmol, 1.0 M in THF) was added to the mixture and stirred at RT for 16 h. Water (1 mL) was added and the mixture was extracted with dichloromethane (3 \times 3 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford the *title compound* as a colourless oil (17.0 mg, 88%). The product was obtained as a 50:50 mixture of diastereomers at the deuterated

centre; the non-deuterated product **31** was also present (**31/32** ~35:65, respectively); R_{f} 0.70 (1:1 petrol:ether); ν_{max} (thin film)/ cm^{-1} 2936w, 1471w, 1362w, 1086s, 1003m, 715m; δ_{H} (500 MHz, CD_2Cl_2) [multiplets complicated by the superposition of resonances due to non-deuterated **31** and the deuterated **32** diastereomers] 1.25–1.38 (2 H, m), 1.44–1.53 (2 H, m), 1.62–1.74 (2 H, m), 1.92–2.00 (1 H, m), 2.10–2.25 (4 H, m), 2.28 (1 H, td, J 12.0, 5.5), 2.47–2.56 (1 H, m), 2.64–2.72 (1 H, m), 2.79–2.86 (1 H, m), 3.34 (0.24 H, s), 3.37 (0.26 H, d, J 13.0), 3.67 (0.24 H, s), 3.70 (0.26 H, d, J 13.0), 3.83–3.92 (4 H, m), 5.49 (1 H, s), 7.19–7.25 (1 H, m), 7.28–7.32 (2 H, m), 7.32–7.36 (2 H, m); δ_{C} (125 MHz, CD_2Cl_2) [resonances marked with an asterisk show fine structure resulting from the mixture of **31** and **32** diastereomers] 20.4*, 24.1, 25.3, 27.7, 41.1, 45.9, 47.9–48.0*, 52.9–53.0*, 61.1 (1:1:1 t, J 20.0), 61.5 (CH_2Ph in **31**), 64.8, 65.0, 119.9, 126.9, 127.2, 128.6, 129.7, 141.1–141.2*, 155.0–155.1*; HRMS (ESI^+) found 315.2165, $\text{C}_{20}\text{H}_{27}\text{DNO}_2$ (MH^+) requires 315.2177.

4.19. 2,2,2-Trichloroethyl-2,3,6,7,8,10-hexahydro-1H-spiro[cyclopenta[e]azonine-9,2'-[1,3]dioxolane]-4(5H)-carboxylate (**34**)

2,2,2-Trichloroethyl chloroformate (28 μL , 0.203 mmol) and K_2CO_3 (27.9 mg, 0.202 mmol) were added to a solution of amine **29** (9.0 mg, 0.0403 mmol) in benzene (0.4 mL) and the reaction mixture was stirred at RT for 16 h. Water (1 mL) was added and the mixture was extracted with dichloromethane (3 \times 2 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless viscous oil (10.0 mg, 62%). R_{f} 0.50 (1:1 petrol:ether); ν_{max} (thin film)/ cm^{-1} 2918w, 1715s, 1483m, 1312m, 1119s, 1018m; δ_{H} (500 MHz, CD_2Cl_2) 1.90 (2 H, quin, J 6.5), 1.95 (2 H, quin, J 6.5), 2.19 (2 H, t, J 6.5), 2.24 (2 H, t, J 6.5), 2.51 (2 H, s), 2.52 (2 H, s), 3.14 (2 H, t, J 6.5), 3.17 (2 H, t, J 6.5), 3.91 (4 H, s), 4.76 (2 H, s); δ_{C} (125 MHz, CD_2Cl_2) 23.7, 23.8, 24.2, 25.4, 45.8 (two peaks), 52.5, 53.7, 64.7, 75.2, 96.6, 116.2, 133.7, 133.8, 155.4; HRMS (ESI^+) found: 420.0496, $\text{C}_{16}\text{H}_{22}\text{NNaO}_4^{35}\text{Cl}_3$ (MNa^+) requires: 420.0507.

4.20. (4S,7aR,10aR,11S)-11-[2-(1,3-Dioxolan-2-yl)ethyl]octahydro-1H-spiro[4,7a-methanocyclopenta[e]azonine-9,2'-[1,3]dioxolan]-11-ol (**35**)

A solution of 2-(2-bromoethyl)-1,3-dioxolane (141 mg, 0.779 mmol) in THF (1.0 mL) was added dropwise to Mg (18.2 mg, 0.749 mmol) at 30 °C and the mixture was stirred for 1 h. A portion of this solution (0.145 mL, ~0.75 M in THF, ~0.109 mmol) was then added to a solution of lactam **25** (22.7 mg, 0.0903 mmol) in THF (0.7 mL) at 0 °C and allowed to warm to RT over 4 h. Satd. aq. NH_4Cl solution (3 mL) was added and the mixture was extracted with dichloromethane (3 \times 5 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a colourless oil (23.0 mg, 72%). R_{f} 0.15 (ether); ν_{max} (thin film)/ cm^{-1} 3471br, 2947m, 1706w, 1452w, 1120s, 1024s; δ_{H} (500 MHz, CD_2Cl_2) 1.23 (1 H, d, J 13.0), 1.31 (1 H, d, J 13.0), 1.34–1.40 (1 H, m), 1.54 (1 H, d, J 13.5), 1.60 (1 H, t, J 12.0), 1.64–1.70 (2 H, m), 1.71–1.81 (3 H, m), 1.82–1.92 (3 H, m), 1.96–2.08 (2 H, m), 2.22 (1 H, dt, J 14.0, 7.0), 2.31 (1 H, d, J 13.0), 2.68 (1 H, d, J 14.5), 2.80 (1 H, dd, J 14.5, 4.5), 2.91 (1 H, td, J 14.5, 2.0), 3.37 (1 H, t, J 14.5), 3.58 (1 H, bs), 3.75–3.99 (8 H, m), 4.86 (1 H, t, J 3.5); δ_{C} (125 MHz, CD_2Cl_2) 23.2, 26.3, 27.4, 31.9, 34.6, 39.0, 46.1, 46.4, 48.1, 49.6, 52.3, 64.6, 64.7, 65.5 (two peaks), 89.2, 105.0, 115.2 (one quaternary carbon resonance not seen); HRMS (ESI^+) found 354.2273, $\text{C}_{19}\text{H}_{32}\text{NO}_5$ (MH^+) requires 354.2275.

4.21. (2'S,4S,7aR,10aR)-5'-Hydroxydecahydro-3'H-spiro[4,7a-methanocyclopenta[e]azonine-11,2'-furan]-9(1H)-one (**36**)

0.5 N aq. HCl (2.1 mL) was added to a solution of hemiaminal **35** (30.2 mg, 0.0854 mmol) in THF (1.3 mL) and the mixture was stirred at RT for 1 h, then at 40 °C for 1.5 h. Satd. aq. NaHCO₃ solution (8 mL) was added and the mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The *title compound* was obtained as a colourless oil as an inseparable mixture of four lactol diastereomers (22.5 mg, 99%, *dr.* 35:30:30:5). R_f 0.20 (10:1 CHCl₃:MeOH); ν_{max} (thin film)/cm⁻¹ 3413br, 2906m, 2855m, 1738s, 1452m, 1183m, 997s; δ_H (500 MHz, CDCl₃) 1.30–1.40 (0.7 H, m), 1.47–1.57 (0.6 H, m), 1.62–2.17 (13.9 H, m), 2.33–2.50 (1 H, m), 2.56 (0.3 H, dd, *J* 19.5, 2.5), 2.61–2.82 (2.1 H, m), 2.90–3.04 (1.1 H, m), 3.14 (0.3 H, dd, *J* 17.5, 2.0), 3.19–3.36 (1.3 H, m), 3.51 (0.1 H, td, *J* 14.0, 4.0), 3.62–3.76 (0.7 H, m), 5.37 (0.3 H, dd, *J* 5.0, 1.5), 5.43 (0.03 H, dd, *J* 5.5, 1.0), 5.57 (0.35 H, dd, *J* 4.5, 2.5), 5.59 (0.3 H, dd, *J* 5.5, 1.0); δ_C (125 MHz, CDCl₃) 22.1, 22.4, 22.7, 23.1, 26.7, 28.3, 29.8, 30.1, 30.9, 31.1, 31.2, 31.3, 32.0, 33.2, 33.9, 34.3, 34.4 (two peaks), 34.6, 39.4, 40.3, 40.5, 40.6, 43.4 (two peaks), 47.5 (two peaks), 47.6, 47.7, 47.8 (two peaks), 47.9, 48.0, 48.4, 48.6, 49.8, 50.3, 50.6, 51.1, 51.2, 52.2, 52.4, 52.7, 96.6, 99.2, 99.4, 100.7, 101.1, 102.0 (two peaks), 102.4, 216.7, 217.4, 217.5; HRMS (ESI⁺) found 266.1749, C₁₅H₂₄NO₃ (MH⁺) requires 266.1751.

4.22. (2'S,4S,7aR,10aR)-Octahydro-3'H-spiro[4,7a-methanocyclopenta[e]azonine-11,2'-furan]-5',9(1H,4'H)-dione (**37**)

Powdered 4 Å molecular sieves (46.0 mg) were added to a solution of lactol **36** (11.3 mg, 0.0426 mmol) in dichloromethane (0.9 mL) and the mixture was stirred at RT for 15 min. Pyridinium

chlorochromate (46.0 mg, 0.213 mmol) was then added and the mixture was stirred at RT for 6 h. The mixture was filtered and washed with dichloromethane. The filtrate was then washed with satd. aq. NaHCO₃ solution (2 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 10:1 CHCl₃:MeOH) afforded the *title compound* as a colourless oil (4.5 mg, 40%) and as a mixture of diastereomers at the aminoacetal centre (*dr.* ~90:10). R_f 0.50 (10:1 CHCl₃:MeOH); ν_{max} (thin film)/cm⁻¹ 2917m, 1782s, 1744s, 1456w, 1194m, 1054m, 916m; δ_H (500 MHz, CD₂Cl₂) [major diastereomer] 1.36–1.42 (1 H, m), 1.60–1.69 (2 H, m), 1.70–1.77 (1 H, m), 1.77–2.17 (6 H, m), 2.24–2.37 (3 H, m), 2.39–2.47 (1 H, m), 2.51–2.67 (2 H, m), 2.72 (1 H, dd, *J* 17.0, 1.5), 2.76–2.82 (1 H, m), 2.98 (1 H, dd, *J* 15.0, 5.5), 3.19 (1 H, td, *J* 15.0, 3.5), 3.32 (1 H, td, *J* 15.0, 4.5) [selected resonances attributed to the minor diastereomer appear at 1.49, 2.21, 2.83, 3.40 and 3.43 (2 × 1 H, 2 × dd, *J* 15.0, 4.0)]; δ_C (125 MHz, CD₂Cl₂) [major diastereomer] 22.3, 27.9, 29.4, 31.6, 34.5, 39.1, 44.9, 47.7, 47.8, 50.0, 50.7, 52.1, 101.8, 177.7, 214.7 [minor diastereomer] 23.0, 26.7, 29.3, 30.2, 31.3, 40.0, 43.6, 48.0, 48.3, 48.6, 52.2, 53.1, 103.2, 176.2, 216.1; HRMS (ESI⁺) found 286.1416, C₁₅H₂₁NNaO₃ (MNa⁺) requires 286.1414.

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Supplementary Material

Copies of ¹H and ¹³C NMR data for novel compounds

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