An investigation into the electrophilic cyclisation of *N*-acyl-pyrrolidinium ions: a facile synthesis of pyrrolo-tetrahydroisoquinolones and pyrrolo-benzazepinones†

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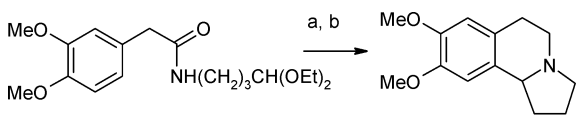
The triflic acid-mediated cyclisation of *N*-arylmethyl- and *N*-arylethyl-acylpyrrolidinium ions gave moderate to good yields of pyrrolo-tetrahydroisoquinolones and pyrrolo-benzazepinones respectively. Electron-donating R substituents enhanced the rate of reaction and gave higher yields than electron-withdrawing substituents. Substituents on the methyl or ethyl chain in general enhanced the reaction, unless sterically encumbered. The equivalent acylpiperidinium ions cyclised much slower and in lower yield.

Introduction

Tetrahydroisoquinoline can be regarded as a privileged structure,[1] in that it occurs in a number of pharmacologically active molecules.[2–10] We are therefore interested in developing synthetic approaches to tetrahydroisoquinolines, and homologues, for use in the generation of diverse compound collections for pharmacological testing. In an earlier paper, we described the synthesis of the tetrahydroisoquinoline (±)-crispine A **2** *via* an aromatic electrophilic cyclisation of an acylpyrrolidinium ion, generated *in situ* from the readily available amide **1** (Scheme 1).[11] Previously, for this type of cyclisation the iminium ion precursors were prepared by anodic oxidation of the pyrrolidine amide,[12,13] and the cyclisation was restricted to electron rich aromatics.[12,14] A single example of cyclisation onto an unsubstituted phenyl was described, but no further work was reported.[13] In this paper, we describe our study of the electrophilic cyclisation of *N*-arylacetyl- and the homologous *N*-3-arylpropionyl-pyrrolidinium ions with less activated aromatic rings in order to investigate the scope and utility of this reaction.



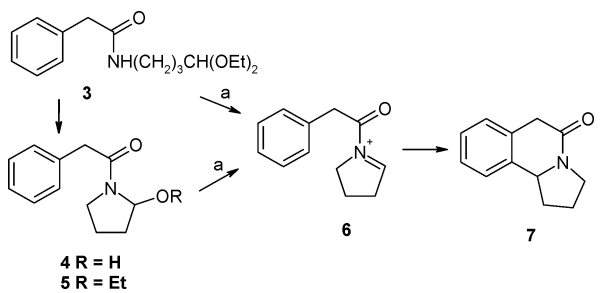
1 **2** (±) crispine A

Scheme 1 Synthesis of (±)-crispine A **2**. *Reagents and conditions*: a) CF_3SO_3H, $CHCl_3$, heat, b) AlH_3

Results and discussion

2.1 Cyclisation of phenylacetamides

We began our investigation with the phenylacetamide **3**, shown in the generalised Scheme 2. The three possible precursors to the iminium ion, the phenylacetamide **3**, the hydroxypyrrolidine **4** and the ethoxypyrrolidine **5**, can all be synthesized by the procedure described in our earlier paper.[11] Thus, the hydroxy pyrrolidine **4** was readily prepared from **3** by mild aqueous acid hydrolysis. The ethoxy-pyrrolidine **5** was obtained in moderate yield directly from **3** by treatment with a catalytic quantity of TFA in the presence of 4A molecular sieves, but the reaction was not reproducible. A more reliable method was the conversion of **4** to **5** which was achieved using TFA in the presence of 3A molecular sieves.[11]



Scheme 2 The electrophilic cyclisation of *N*-acyl-pyrrolidinium ions to give pyrrolo-tetrahydroisoquinolones. *Reagents*: a) acid (see Table 1)

The conversion of the 2-methoxy analogue of **5** into **7** had previously been reported using conc. H_2SO_4.[13] However, we found that treatment of **5** with conc. H_2SO_4 gave no evidence of the formation of the lactam **7**, but instead gave a single product in an 85% yield, for which the NMR spectrum was complex and the mass spectrum indicated a molecular weight consistent with the formation of a dimer of the iminium ion **6**. An X-ray diffraction study determined the structure to be **9** (Fig. 1), presumably formed by addition of the *N*-acyl dihydropyrrole **8** to the iminium ion **6**, followed by deprotonation (Scheme 3). Although only one enantiomer was found in the X-ray structure, chiral HPLC showed, as expected, that the bulk material of **9** was

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† Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR for all compounds, and crystal structure details for **9**. CCDC reference number 727741. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b907400g

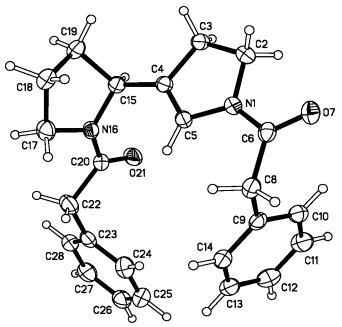
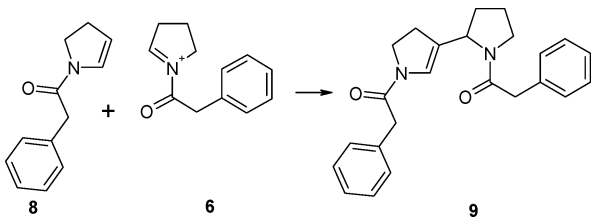


Fig. 1 A view of a molecule of **9** from the crystal structure, showing the numbering scheme employed. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms are displayed with an arbitrarily small radius.



Scheme 3 Proposed reaction to form **9**.

a 1 : 1 mixture of enantiomers. Similar dimerisations of cyclic iminium ions have been reported.[15,16]

The formation of **8** requires the loss of a proton, so to minimise this, stronger acids were investigated, including the Lewis acids used for the synthesis of **2**.[11] The results are summarised in Table 1.

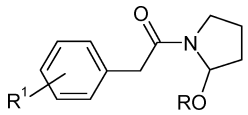
The Lewis acids $TiCl_4$, $BF_3.OEt_2$, and the Brønsted acids HBr/AcOH and $MeSO_3H$ all failed to give the desired lactam **7**. However, the use of 2 equivalents of $AlCl_3$ gave a good yield of **7**. Increasing the quantity of $AlCl_3$ to 4 equivalents gave a slightly lower yield. A 10-fold excess of triflic acid also gave a good yield of **7** when **5** was added to a mixture of triflic acid in $CHCl_3$ heated under reflux. A smaller quantity of triflic acid, or the addition of **5** at ambient temperatures, gave lower yields of **7** and led to an increased quantity of **9**. The progress of the reaction can be monitored by thin layer chromatography (TLC) of a basified aliquot of the reaction mixture. A non-polar product is rapidly formed, which then disappears with time and is followed by the production of either **9** or **7**. Attempts to characterise this non-polar intermediate were unsuccessful, as the compound decomposed on attempted purification. However, we speculate that it is the enamide **8**. The 2-hydroxypyrrolidine **4** also underwent cyclisation with triflic acid and, as the synthesis of **4** is simpler and higher yielding, it offers an advantage over **5** as the preferred precursor. It was found that the lactam **7** was relatively unstable and rapidly darkened on storage in air.

Table 1 Successful cyclisation conditions for the conversion of **4** or **5** into **7**

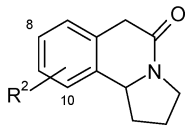
Comp.	Acid	Equiv.	Yield (%)[b]
5	$AlCl_3$	3.0	73
5	$AlCl_3$	4.0	61
5	Triflic[a]	7	35
5	Triflic[a]	10	60
4	Triflic[a]	10	60

[a] A solution of **4** or **5** was added over 10 min. to a mixture of triflic acid in $CHCl_3$ at reflux, then heated for 1 h. [b] Isolated yield of **7** after purification by column chromatography.

Table 2 Triflic acid-mediated cyclisation of substituted phenylacetamido-pyrrolidines[a]



5a-d, 4e



7a-e

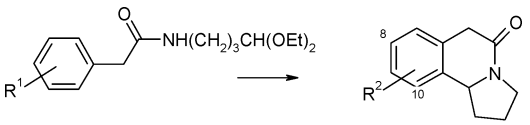
Comp.	R^1	Time/h	R^2	Yield (%)	Product
5a	3-MeO	0.5	10-MeO	33	**7a**
			8-MeO	46	**7a′**
5b	3,4-diMeO	0.5	8,9-diMeO	100	**7b**
5b	3,4-diMeO	18[b]	8,9-diMeO	85	**7b**
5c	4-Cl	6	9-Cl	40	**7c**
5d	4-MeO	6	9-MeO	0	**7d**
4e	4-Br	1[c]	9-Br	60	**7e**

[a] A solution of the substrate was added over 10 min to a mixture of 10 equiv. of triflic acid in $CHCl_3$ at reflux. [b] Reaction carried out at ambient temperatures. [c] Reaction carried out in 1,2-dichloroethane at reflux.

Following the success of this cyclisation with triflic acid, the effect of substitution on the phenyl ring was investigated (Table 2). Although triflic acid gave slightly lower yields than $AlCl_3$, it was chosen for investigation as the reaction work-up was simpler and the crude products cleaner and easier to purify. The choice of substituents was dictated by their electron-donating/withdrawing character and their potential for further synthetic manipulation.

As expected, the results were consistent with those we would expect from an electrophilic substitution. Thus, the 3-methoxy **5a** cyclised rapidly and gave a high combined yield of the two isomers formed by cyclisation onto the ortho- (**7a**) and para- (**7a′**) positions respectively. Interestingly, the ratio of **7a**:**7a′** (0.7 : 1) is different from that reported for the $TiCl_4$-mediated cyclisation of the 2-methoxypyrrolidinyl amide (0.35 : 1).[12] Following this result, we re-investigated the cyclisation of the 3,4-dimethoxy-phenylacetamde **5b** and an excellent yield of **7b** was obtained, even at ambient temperatures. As previously described for the $AlCl_3$-induced cyclisation of **5b**,[11] only one isomer was formed. Studies were also carried out with electron-withdrawing substituents and the 4-chloro analogue **5c** required prolonged heating and gave only a moderate yield of the lactam **7c**. The 4-methoxy amide **5d** gave no lactam, which is a similar outcome to the previously reported $TiCl_4$-mediated cyclisation.[12] Cyclisation of the 4-bromo-phenylacetyl-2-hydroxypyrrolidine **4e** also required forcing conditions, however a good yield of lactam **7e** was obtained in a shorter reaction time using the higher boiling solvent 1,2-dichloroethane at reflux. This study shows that the electrophilic cyclisation of the 1-phenylacetyl-2-ethoxy- or 2-hydroxy-pyrrolidines can be achieved with electron-withdrawing substituents on the aromatic ring. However, an alternative direct conversion of the acetal **3** into the isoquinolone **7** would be more convenient than the current three-step synthesis. We therefore investigated the cyclisation of the 3,4-dimethoxy-phenyl-acetamide **3b** and **7b** was obtained an 80% yield (Table 3). With this result in hand, we further explored the cyclisation of amido-acetals and the results of these studies are presented in Table 3.

Table 3 Triflic acid-mediate cyclisations of substituted phenylacetamides



3-3o 7-7o

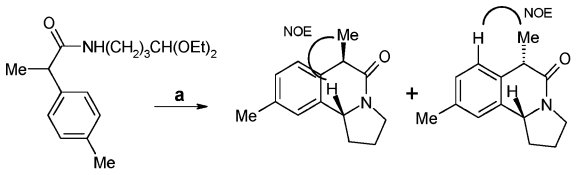
Comp.	R^1	Time/h[a]	R^2	Product	Yield (%)
3	H	0.5	H	**7**	60
3b	3,4-diMeO	0.5	8,9-diMeO	**7b**	80
3c	4-Cl	18	9-Cl	**7c**	45
3e	4-Br	18	9-Br	**7e**	55
			8-Br	**7f**	45
3f	3-Br	18	10-Br	**7f′**	26
3h	2-Br	18	7-Br	**7h**	20
3i	4-Phth[c]	3	9-Phth	**7i**	0
3j	4-NO_2	24[d]	9-NO_2	**7j**	0
3k	4-Me	1.5	9-Me	**7k**	75
			8-Me	**7l**	78[b]
3l	3-Me	1.5	10-Me	**7l′**	
3m	2-Me	1.5	7-Me	**7m**	95
3n	2,3-Benzo	1	7,8-Benzo	**7n**	79
3o	3,4-Benzo	1.5	9,10-Benzo	**7o**	71

[a] Add solution of acetal over 10 min to refluxing solution of 10 equivs of triflic acid in$CHCl_3$. [b] Inseparable mixture. [c] Phth. = Phthalimido [d] In 1,2-dichloroethane

The unsubstituted phenyl-acetamide **3** gave a 60% yield of the lactam **7** which is comparable with that obtained from both **4** and **5** (Table 1). The incorporation of electron-withdrawing substituents again necessitated more forcing conditions and the 4-chloro **3c** and the 4-bromo **3e** derivatives gave the lactams **7c** and **7e**, respectively, again in comparable yields to those obtained earlier (Table 2). The 3-bromo analogue **3f** gave a good overall yield of 71% of a mixture of **7f** and **7f′**, readily separated by column chromatography. However, the 2-bromo analogue **3h** gave only a poor yield (20%) of **7h**. Less success was also obtained in the attempted cyclisation of the 4-phthalimido-phenylacetamide **3i**, which after 3 hours gave none of the desired product and no evidence of starting material or intermediate. We assume that the lack of success is a consequence of the sensitivity of the phthalimido group to the strongly acidic reaction conditions. We have not yet found an arylamine protecting group that can withstand the cyclisation conditions. Also notable is the lack of success in the attempted cyclisation of **3j**, which contains the strongly electron-withdrawing 4-nitro group. However, cyclisation of the methyl-substituted **3k**, **3l** and **3m** all gave high yields of cyclised product (75, 78 and 95% respectively), with the *meta*-methyl **3l** giving a 3 : 1 mixture of isomers that were inseparable by column chromatography. On recording the NMR spectrum of the mixture in C_6D_6, separate aromatic peaks were observed. No large splitting of *ca.* 7 Hz was found for proton 7-H in the major isomer, which was thus assigned as the 8-methyl isomer **7l**. Both the 1- and 2-naphthalene acetamides (**3n** and **3o** respectively) cyclised rapidly and in high yield, with **3o** giving a single isomer resulting from cyclisation onto the more reactive 1-position.

2.2 Cyclisation of α-substituted phenylacetamides

The effect of phenylacetyl α-substitutents on the cyclisation was then investigated. Cyclisation of the dimethyl amide **3p** (Scheme 4) gave a readily separable 1 : 1 ratio of a mixture of isomers. From

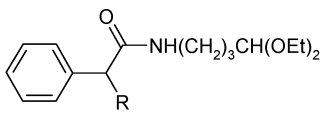


3p **7p** more polar 40% **7p'** less polar 43%

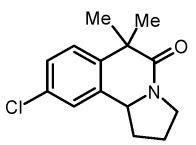
Scheme 4 Synthesis of the 6,9-dimethyl pyrrolo-tetrahydro-isoquinolones **7p** and 7p′. *Reagents and conditions*: a) CF_3SO_3H, $CHCl_3$, heat.

an NMR study, for the more polar isomer, an nuclear Overhauser effect (NOE) was observed between the methyl and the bridgehead proton, which is only possible if the methyl group were '*cis*' to the bridgehead proton **7p** in the boat conformation of the central six-membered ring. In contrast, for the less polar isomer **7p′**, no such NOE was observed, instead a strong NOE was observed between the methyl protons and the peri-aromatic hydrogen, consistent with the methyl being equatorially orientated and '*trans*' to the bridgehead proton. Treatment of **7p′** with a catalytic quantity of $KOBu^t$ rapidly gave exclusively **7p**, whereas similar treatment of **7p** led to no change.

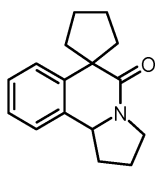
Similar treatment of the 4-chlorophenyl-α,α-dimethyl-acetamide **3q** for 5 h gave the dimethyl product **7q** in a 44% yield. Thus the cyclisation was faster than for the equivalent 4-chlorophenylacetamide **3c**, but the yield of cyclised product was no better. Notably, **7q** was surprisingly unstable, decomposing at ambient temperatures over a period of about 7 days, so the low yield may be due to the instability of the product. Instability of the cyclic product may be the reason for the lack of any product **7r** from the cyclisation of the spirocyclopropyl amide **3r**.



3q R = Me_2; p-Cl
3r R = -$(CH_2)_4$-
3s R = Phthalimido
3t R = Ph
3u R = Ph_2
3v R = CH_2Ph



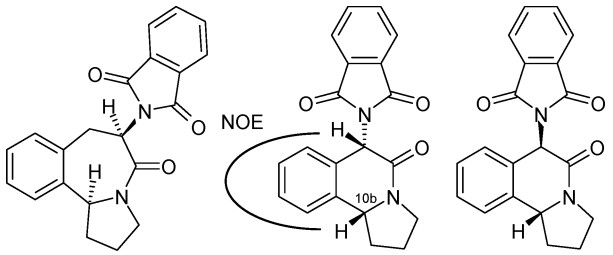
7q



7r

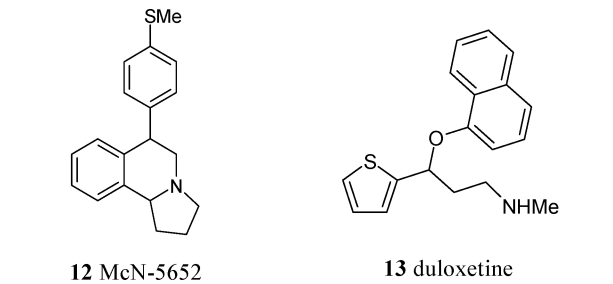
The cyclisation of the α-phthalimido amide **3s**, readily prepared from phenylglycine, gave a good yield (85%) of a mixture of two isomers in a ratio of 2.5 : 1. These products are of interest as the benzazepine homologue **10** has been used as an intermediate for enkephalinase inhibitors.[17,18] The isomers were separated by careful chromatography on silica. From an NMR study on the less polar, minor isomer, irradiation of the bridgehead 10b-H proton showed a NOE enhancement of the 6-H proton observed as a doublet at $\delta = 5.92$ ppm, consistent with the phthalimido group being equatorially orientated and *trans* to the 10b-H proton, **11a**. In addition, the aryl protons of the phthalimido group of **11a** showed up as 4 distinct multiplets, and the ^{13}C NMR showed three inequivalent carbonyl C signals, indicative of restricted

rotation about the C-6–N phthalimide bond. In contrast, for the more polar, major isomer, irradiation of the signal for the 10b-H proton showed no such enhancement and was therefore assigned as the '*trans*' isomer **11b**, with the phthalimido group axially orientated. Treatment of the NMR solutions of both the isomers in $CDCl_3$ with Et_3N at ambient temperatures overnight reversed the ratio to 2 : 1 of **11a**:**11b**. Thus **11b** is probably the kinetically favoured product, whereas **11a** is the thermodynamically more stable isomer.



10 **(±) 11a** **(±) 11b**

We were also interested in application of our methodology to the synthesis of analogues of potent serotonin, dopamine and norepinephrine reuptake inhibitors, as exemplified by McN-5652, **12**.[9] Interest in such mixed pharmacology compounds has been rekindled with the success of the recently marketed duloxetine (**13**) for the treatment of depressive disorders.[19] Triflic acid cyclisation of the diphenylacetamide **3t** gave an excellent yield of a mixture of the 6-phenyl lactams (**14a**:**14b**) in a ratio of 2.5 : 1. The isomers were separated by column chromatography on silica and the less polar, major isomer crystallised from Et_2O.



12 McN-5652 **13** duloxetine

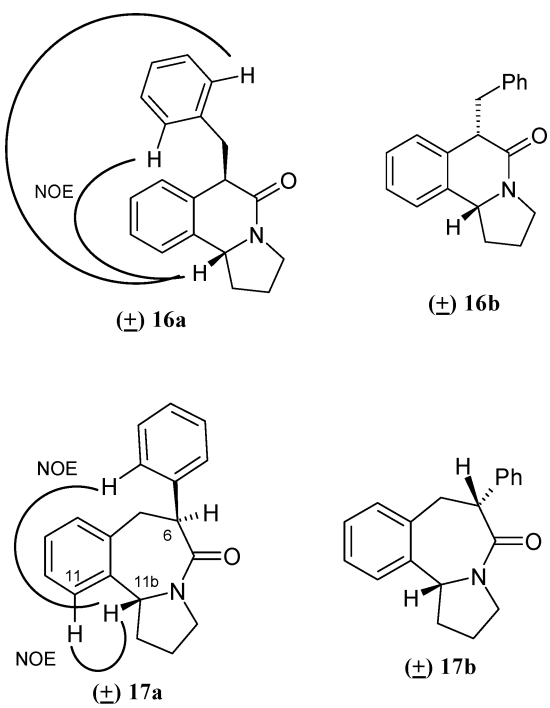
(±) 14a **(±) 14b** **15**

Despite considerable effort, the more polar isomer failed to crystallise. From NMR studies on the less polar, major isomer, the *ortho*-protons of the phenyl substituent at $\delta = 7.12$ ppm showed relatively strong NOEs with protons 6-H and 10b-H, thus confirming that the phenyl group is on the same face of the tricyclic system as the bridgehead 10b hydrogen. The less polar isomer was therefore assigned with the phenyl group axially orientated, **14a**. Heating either of **14a** and **14b** with 0.2 equiv. of KBu^{t}O in MeOH led to a 9 : 1 mixture of **14a**:**14b**.

The attempted cyclisation of the triphenyl-acetamide **3u** led to the isolation of the lactam **15** in only 18% yield. However, unlike the *gem*-dimethyl lactam **7q**, **15** was stable and therefore the low yield is probably a consequence of steric hindrance.

Cyclisation of the 2,3-diphenylpropionamide **3v** gave the 6-benzyl isoquinolone (**16b**), and the 6-phenyl benzazepinones (**17a**) and (**17b**). Initial separation on silica gave two components, the first of which was a mixture of two products from which the 6-phenylbenzazepinone **17a** was crystallised from Et_2O–petrol in a 3% yield. The remainder of this material was determined to be a 6 : 1 mixture of **16b** and **17a** (32% yield). The stereochemical assignment of **17a** was based upon the observation of an NOE enhancement at $\delta = 7.30$ (*o*-phenyl) and $\delta = 7.37$ (11-H proton) on irradiation of the bridgehead 11b proton at $\delta = 5.31$, the phenyl group being on the same face of the molecule as the bridgehead proton. Treatment of **16b** with KBu^{t}O generated a 4 : 1 mixture of **16b**:**16a**, which was readily separated by silica column chromatography. The stereochemistry of **16a** was assigned by virtue of the chemical shift of the 10b proton is at $\delta = 3.61$, which in **16b** is at $\delta = 4.55$. For **16a**, NOE enhancement was observed at $\delta = 6.78$ for the ortho protons of the benzyl substituent and at $\delta = 3.09$ and 3.15 for the benzylic CH_2 protons when $\delta = 3.61$ was irradiated, which is all consistent with the benzyl group positioned over the 10b proton.

The second component from the column gave a solid which was determined to be the 6-phenylbenzazepinone **17b** in a 60% yield. Again the assignment of stereochemistry was based upon NOE. Enhancement for the 6-H proton at $\delta = 4.30$ was observed when bridgehead 11b proton at $\delta = 5.19$ was irradiated. This is consistent with both protons being positioned on the same face of the seven-membered ring. It is notable that the combined yield of the benzazepinones **17a** and **17b** was higher than that of the tetrahydro-isoquinolone **16b**, suggesting that cyclisation to form the seven-membered ring is more favoured. Treatment of **17b** with catalytic KBu^{t}O in ethanol gave a 1 : 1 mixture of **17a** and **17b** from which a pure sample of **17a** was obtained.



(±) 16a **(±) 16b**

(±) 17a **(±) 17b**

2.3 Cyclisation of 3-phenylpropionamides

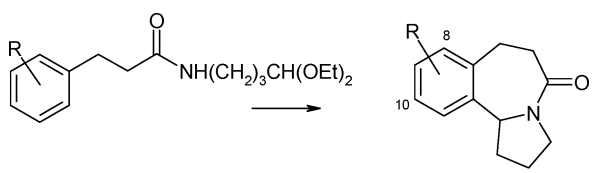
The formation of the benzazepinones **17a** and **17b** prompted us to investigate the generality of applying this cyclisation to the synthesis of benzazepinones. A limited amount of work on the triflic acid-mediated cyclisation of *N*-3-phenylpropionylpyrrolidinium ions to form benzazepinones has been reported for the synthesis of dipeptide mimetics.[17,18]

In those patents, the iminium ion was prepared by oxidative cleavage of an olefin to form the amido-aldehyde. We therefore undertook a study to compare the effectiveness of iminium ion formation from the amido-acetals and to further investigate the scope of the cyclisation to the benzazepinones. A preliminary study on the cyclisation of substrates containing the 3-arylpropionyl group and the results are shown in Table 4

In general, the cyclisation to form the benzazepinones was more rapid and higher yielding than the formation of equivalent isoquinolones (for example **7** *vs.* **19a**, **7c** *vs.* **19l**). In contrast to the phenacetyl cyclisations, products were obtained from both the 2- and 4-methoxy derivatives, compounds **18b** and **18d**, albeit in poor yield. However, the yield of **19d** was improved by pre-hydrolysing the acetal of **18d** in acetone/2 M HCl followed by triflic acid-mediated cyclisation of the crude 2-hydroxypyrrolidinamide to give **19d** in a 31% overall yield. As expected, the cyclisation of amides incorporating electron-withdrawing substituents (**18h–18l**) was generally slower and required prolonged heating to ensure complete reaction. It was also noteworthy that, unlike the isoquinolones, the benzazepinones were stable in air.

We also investigated the synthesis of the previously reported benzazepinone **10**, an intermediate to enkephalinase inhibitors.[17,18] From the L-phthalimdo-phenylglycine amide **20**, a quantitative yield of **10** was obtained as a glass which could not be crystallized.

Table 4 Cyclisations of 3-phenylpropionamides

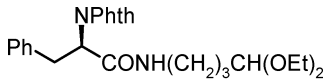


18 **19**

Comp.	R	Time/h	Comp.	Isomer	Yield (%)
18a	H	0.5	**19a**	—	80
18b	2-MeO	1	**19b**	8	13
			19c	9-	68
18c	3-MeO	0.5	**19c′**	11-	11
18d	4-MeO	1	**19d**	10	15
					32%[b]
18e	3,4-diMeO	0.5	**19e**	9,10	86
18f	3,4,5-triMeO	1[a]	**19f**	9,10,11	90
18g	4-Me	1	**19g**	10	75
18h	4-F	6	**19h**	10	77
18i	3-Br	1	**19i**	9	75
18j	4-Br	6	**19j**	10	78
			19k	9-	78
18k	3-Cl	4	**19k′**	11	9
181	4-Cl	4	**19l**	10	90

[a] In DCM at reflux [b] Overall yield from pre-hydrolysis to the hydroxypyrrolidine.

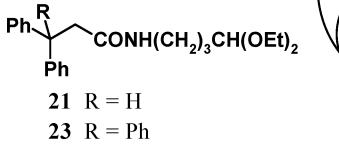
We were pleased to note that, without taking any special precautions against racemization throughout the reaction sequence, chiral HPLC analysis showed that the product obtained had an ee of 97.7%. The relative stereochemistry of **10** was confirmed by NMR. At room temperature there was restricted rotation about the *N*-phthalimido group such that heating to 263K was required to obtain good ^{1}H and ^{13}C NMR spectra. Further studies showed that the energy barrier to rotation is 61 ± 1 KJmol^{-1}. An NOE enhancement of the 6-H proton, α- to the *N*-phthalimido group, was observed on irradiation of the 11b-H bridghead proton consistent with the structure as shown. Interestingly, the product obtained from cyclisation of the racemic form of **20** gave the racemic form of **10**, **10′** in an 80% yield as a crystalline solid.



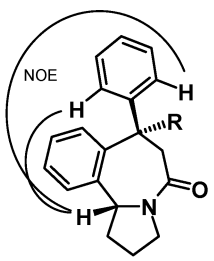
20

We investigated the application of this methodology to the synthesis of the homologues of the re-uptake inhibitors derived from **14a/b**. Thus cyclisation of the 3,3-diphenylpropionamide **21** gave an excellent yield (86%) of cyclic product from which a single, crystalline isomer **22** was obtained in 76% yield. The stereochemistry was assigned by NMR, with a strong NOE enhancement of the *ortho*-protons of the phenyl substituent on irradiation of the bridgehead proton. In contrast to the triphenyacetamide **3u**, the cyclisation of **23** was rapid and gave an excellent (90%) yield of **24**.

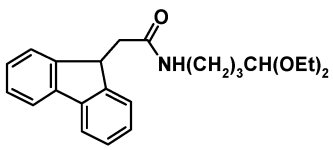
As a continuation of our interest in the synthesis of polyphenylated amines, the cyclisation of the fluorenylacetamide **25** also gave an excellent yield (90%) of the pentacyclic lactam **26**.



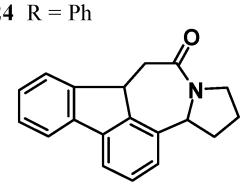
21 R = H
23 R = Ph



(±) **22** R = H
24 R = Ph



25



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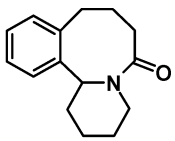
2.4 Formation of piperidino-tetrahydroisoquinolones and -benzazepinones

We recently reported that the triflic acid-mediated cyclisation of **27** failed to give the piperidino-benzazocine **28**.[21] However, for the six- and seven-membered analogues we found that the cyclisations were successful, allowing the synthesis of the piperidino-tetrahydroisoquinolones **31** and **32** and the piperidino-benzazapinone **34** from the amides *N*-(5,5-diethoxypentyl)-2-phenylacetamide **29**, *N*-(5,5-diethoxypentyl)-2-(3,4-dimethoxyphenyl)

acetamide **30** and *N*-(5,5-diethoxypentyl)-3-phenylpropionamide **33** respectively. In all cases, the cyclisations with triflic acid were much slower than the equivalent pyrrolidino cases and lower yields were obtained. In the case of **31**, a 31% yield was obtained which is less than the previously reported yield of 51% for the $AlCl_3$-mediated cyclisation of the 2-methoxypiperidinyl amide, obtained from anodic oxidation of the amide.[22]

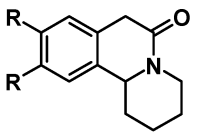
$Ph(CH_2)_3CONH(CH_2)_4CH(OEt)_2$

27

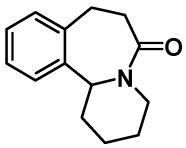


28

However, using this methodology it was possible to synthesise the 3,4-dimethoxy **32**, which was not possible by the anodic oxidation method due to oxidation of the benzylic position. The reaction to form the benzazepinone **33** was more rapid than that for **30** but the isolated yield of 39% was poorer than for the pyrrolidine analogue **19a**. However, using the previously described two-step procedure involving a separate acetal hydrolysis followed by triflic acid-mediated cyclisation, yields could be improved to 49% for **30** and 86% for **33**.



31 R = H: 24h reflux, 31%
33 R = MeO: 1h reflux 60%



34

Conclusion

In this paper we have further demonstrated that commercially available 4-aminobutyraldehyde diethylacetal can be used as a precursor to *N*-arylacetylpyrrolidinium ions as an alternative to anodic oxidation. These *N*-arylacetyl-pyrrolidinium ion precursors can be cyclised to pyrroloisoquinolinones in moderate to high yields using either strong Lewis acids or triflic acid. As previously reported,[12] the pyrrolo-isoquinolinones are relatively unstable in air, though stability is improved with substitution at the 6-position. This methodology is also suitable for the synthesis of the homologous pyrrolo-benzazepinones. From this and our earlier publication[20] the rate of cyclisation is related to the size of the ring such that 7>6>8. The rate and yields are adversely affected by electron-withdrawing substituents in the aryl ring, whereas substitution on the alkyl chain between the aryl and amide generally favours cyclisation.

Experimental

Melting points are uncorrected. All solvents and reagents were of commercial grade and used without purification. All evaporations of solvents were carried out under reduced pressure. High-resolution mass spectrometry (HRMS) measurements were performed with a Micromass Q-Tof 2 hybrid quadrupole time-of-flight mass spectrometer, equipped with a Z-spray interface, and the elemental composition was calculated using MassLynx version 4.0. All crystalline final compounds were >97% pure, all oils were >95% pure by NMR and HPLC immediately following purification. Infrared spectra were run neat on a Perkin Elmer 100 FTIR spectrometer. Solution ^1H and ^{13}C NMR spectra were recorded on Bruker NMR spectrometers AMX300, Avance III 400, DRX500 and Avance III 600 equipped with z-gradient facilities. ^1H and ^{13}C chemical shifts are given relative to TMS.

General procedure for the synthesis of the arylalkyl-carboxamides (3) and (18)

In a 100 mL round-bottomed flask connected to a drying tube, oxalyl chloride (5 mmol, 0.35 mL) and 1–2 drops of DMF were added to a stirred solution of the acid (5 mmol) in DCM (40 mL). After stirring at ambient temperatures for 2 h, by which time gas evolution had ceased, $CHCl_3$ (10 mL) was added and the solvent was removed by rotary evaporation under reduced pressure. The residue was re-dissolved in 10 mL of DCM and added, dropwise, over 10 min. to a cooled (0°C) stirred solution of 4-aminobutyraldehyde diethylacetal (Aldrich) (5 mmol, 0.9 mL) and dimethylethylamine (6 mmol, 0.7 mL) in Et_2O (100 mL). The reaction mixture was allowed to warm to ambient temperatures over 2 h, when 0.2 M NaOH (30 mL) was added, after which the white solid suspension dissolved. The reaction mixture was transferred to a separating funnel, shaken and the lower aqueous layer separated. The upper organic layer was then washed with saturated NaCl solution (30 mL). The lower layer was combined with the previous aqueous wash and the upper organic layer was dried (K_2CO_3). The combined aqueous layers were back-washed with Et_2O (50 mL) and the upper organic layer separated and added to the previously separated organic extract. The combined organic extracts were separated and concentrated *in vacuo* to give the amides as either oils, used without further purification, or as solids, isolated by trituration with petrol (40–60°C).

In this way the following amide was prepared:

***N*-(4,4-Diethoxybutyl)-2-phenylacetamide (3).** Prepared from the commercially available acid chloride and isolated as an oil (95% yield). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.16$ (t, $J = 7$ Hz, 6H), 1.48–1.60 (m, 4H), 3.24 (q, $J = 7$ Hz, 2H), 3.40–3.49 (m, 2H), 3.51 (s, 2H), 3.54–3.65 (m, 2H), 4.43 (t, $J = 5$ Hz, 1H), 5.57 (brs, 1H), 7.20–7.35 (m, 5): ^{13}C NMR and distortionless enhancement with polarisation transfer (DEPT) (75 MHz, $CDCl_3$) $\delta = 15.3$ (CH_3), 24.5 (CH_2), 30.8 (CH_2), 39.3 (CH_2), 43.8 (CH_2), 61.3 (CH_2), 102.5 (CH), 127.2 (CH), 128.9 (CH), 129.4 (CH), 135.1 (C), 171.0 (C); ν_{max}/cm^{-1} 2974, 2878, 1638, 1405, 1096, 1065, 719, 696.

General procedure for the synthesis of the *N*-acyl-2-hydroxypyrrolidines

A solution of the appropriate *N*-(4,4-diethoxybutyl)acetamide (5 mmol) in acetone (50 mL) was treated with 1M HCl (8 mL) for 15 min at ambient temperatures. The reaction mixture was basified with an excess of 1 M $NaHCO_3$ solution and the acetone removed by rotary evaporation. The aqueous residue was extracted with DCM (3 × 50 mL), the combined extracts dried (K_2CO_3), filtered and concentrated *in vacuo* to give essentially a quantitative yield of the 2-hydroxypyrrolidine, used without further purification.

1-(2-Hydroxypyrrolidin-1-yl)-2-phenylethanone (4). Isolated as an oil (95% yield), which gave a waxy solid on standing mpt 46–9°C. ^1H NMR (400 MHz, $CDCl_3$) as a mixture of rotomers: $\delta = 1.78$–2.15 (m, 4H), 2.97 (brs, 0.14H) 3.31–3.42 (m, 1H),

3.55–3.68 (m, 2.72H), 3.80 (d, J = 15 Hz, 0.14H), 3.86 (d, J = 15 Hz, 0.14H), 4.21 (brs, 0.86H), 5.44 (brs, 0.14H), 5.66 (dd, J = 6, 3 Hz, 0.86H), 7.20–7.37 (m, 5H).

2-(4-Bromophenyl)-1-(2-hydroxypyrrolidin-1-yl)ethanone (4d). Isolated as a white solid (100% yield), mpt 110–2°C: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78–2.15 (m, 4H), 3.31–3.42 (m, 1H), 3.50–3.80 (m, 3H including 3.58, s, 2H), 4.20 (brs, 1H), 5.63 (dd, J = 5.5, 2.5 Hz, 1H), 7.13 (d, J = 7 Hz, 2H), 7.44 (d, J = 7 Hz, 2H): ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 23.2 (CH_2), 32.0 (CH_2), 41.4 (CH_2), 46.7 (CH_2), 82.0 (CH), 121 (C), 130.9 (CH), 131.8 (CH), 133.1 (C), 170.9 (C).

General procedure for the synthesis of the *N*-acyl-2-ethoxypyrrolidines

A solution of the appropriate *N*-acyl-2-hydroxypyrrolidine (2 mmol) in DCM (50 mL) and EtOH (0.5 mL) was stirred with 3A molecular sieves (5 g) and TFA (0.5 mL) at ambient temperatures for 18 h. The reaction mixture was filtered and washed with an excess of 1 M $NaHCO_3$ solution, then dried (K_2CO_3), filtered and evaporated *in vacuo* to give the 2-ethoxy compounds, used without further purification.

1-(2-Ethoxypyrrolidin-1-yl)-2-phenylethanone (5). Isolated as an oil (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) as a mixture of rotomers: δ = 1.16 (t, J = 7.2 Hz, 1.5H), 1.27 (t, J = 7.2 Hz, 1.5H), 1.64–2.21 (m, 4H), 3.31–3.72 (m, 6H), 5.08 (d, J = 4.8, 0.5H), 5.55 (d, J = 4.8, 0.5H), 7.12–7.35 (m, 5H).

2-(4-Chlorophenyl)-1-(2-ethoxypyrrolidin-1-yl)ethanone (5c). Isolated as an oil (85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) as a mixture of rotomers: δ = 1.13 (t, J = 7 Hz, 1.5H), 1.22 (t, J = 7 Hz, 1.5H), 1.60–2.20 (m, 4H), 3.22–3.76 (m, 6H), 5.05 (d, J = 4 Hz, 0.5H), 5.51 (d, J = 4 Hz, 0.5H), 7.12–7.29 (m, 4H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 15.4 (CH_3), 21.1 (CH_2), 23.1 (CH_2), 31.5 (CH_2), 31.9 (CH_2), 40.3 (CH_2), 41.3 (CH_2), 45.9 (CH_2), 46.4 (CH_2), 62.1 (CH_2), 64.6 (CH_2), 86.0 (CH), 87.6 (CH), 128.6 (CH), 128.7 (CH), 130.6 (CH), 130.7 (CH), 132.6 (C), 132.7 (C), 133.1 (C), 133.7 (C), 170.3 (C), 170.6 (C).

2-Phenyl-1-(1′-phenylacetyl-2,3,4,5,4′,5′-hexahydro-1′H-[2,3′]-bipyrrol-1-yl)ethanone (9). The amide (**5**) (1.2 g, 5 mmol) was stirred with conc. H_2SO_4 (5 mL) according to the literature procedure.[13] The reaction mixture was carefully treated with ice (~20 g) and basified with solid K_2CO_3. The product was extracted into DCM (2 × 50 mL), dried (K_2CO_3), filtered, concentrated *in vacuo* and purified by column chromatography on SiO_2, eluting with EtOAc to give a white crystalline solid (0.79 g, 85% yield). A small sample was recrystallised from EtOAc to yield crystals for X-ray analysis, mpt 104–8°C. HRMS theoretical mass: 375.2072, measured mass: 375.2075. ^{1}H NMR (400 MHz, $CDCl_3$) as a mixture of rotomers: δ = 1.65–2.05 (m, 4H), 2.46–2.72 (m, 2H), 3.40–3.70 (m, 6H), 3.75–3.98 (m, 2H), 4.41 (d, J = 8 Hz, 0.24H), 4.49 (d, J = 8 Hz, 0.16H), 4.77 (dd, J = 10, 8 Hz, 0.6H), 6.06 (dd, J = 3, 3 Hz, 0.4H), 6.15 (d, J = 1 Hz, 0.3H), 6.66 (dd, J = 3.5, 2 Hz, 0.18H), 6.83 (d, J = 1 Hz, 0.12H), 7.09 (d, J = 7 Hz, 0.75H), 7.12–7.48 (m, 9.25H). Chiral HPLC was run on a Chiracel OJ 4.6 × 250 mm column with 10 μm particle size, eluting with heptane–EtOH 7 : 3 at a flow rate of 1 mL min^{-1}. Retention times of 28 and 45 min. were obtained for each enantiomer.

General procedure for the triflic acid-mediated cyclisation

A solution of the appropriate acetamide (2 mmol) in $CHCl_3$ (10 mL) was added, dropwise, over 10 min. to a stirred mixture of triflic acid (20 mmol) in $CHCl_3$ (40 mL), heated to gentle reflux. The reaction was monitored by taking a small aliquot of the reaction mixture, adding a few drops of water, basifying with K_2CO_3 and then analysing the $CHCl_3$ layer on silica TLC, eluting with EtOAc. The reaction was heated until the high running spot had disappeared. The reaction mixture was then cooled, water was added (10 mL) and the aqueous layer basified with K_2CO_3. The organic layer was separated and the aqueous layer extracted with DCM (2 × 30 mL). The combined organic extracts were dried (K_2CO_3), separated and concentrated *in vacuo.* The residue was purified by column chromatography on silica, initially absorbing the compound from a DCM solution, and then eluting with Et_2O containing appropriate amounts of MeOH up to 5%.

2,3,6,10b-Tetrahydro-1*H*-pyrrolo[2,1-a]isoquinolin-5-one (7). Purified by column chromatography on SiO_2, eluting with Et_2O and isolated as an orange oil (60% yield); FTIR (film) ν_{max}: 2968, 2879, 1627, 1454, 1410, 767, 736 cm^{-1}; HRMS: theoretical mass: (MH^+) 188.1075, measured mass: (MH^+) 188.1077. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.75–1.86 (m, 1H), 1.87–1.97 (m, 1H), 1.97–2.06 (m, 1H), 2.55 (tt, J = 5.8, 11.6 Hz, 1H), 3.39 (dd, J = 8.7, 7.7 Hz, 1H), 3.44 (d, J = 18.1 Hz, 1H), 3.52 (d, J = 18.1 Hz, 1H) 3.59 (t, J = 11.2 Hz, 1H), 4.50–4.56 (m, 1H), 7.04–7.15 (m, 2H), 7.15–7.21 (m, 2H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 23.2 (CH_2), 31.3 (CH_2), 38.7 (CH_2), 59.6 (CH), 124.0 (CH), 126.8 (CH), 127.2 (CH), 127.6 (CH), 133.0 (C), 136.2 (C), 167.5 (C).

2-((6s,10bR/6R10bS)-5-Oxo-1,2,3,6,10b-hexahydro-pyrrolo[2,1-a]isoquinolin-6-yl)isoindole-1,3-dione (11a). The less polar isomer was isolated as a pale yellow solid from a SiO_2 column purification, eluting with 1 : 1 Et_2O–petrol (24% yield) mpt 249–51°C (Et_2O). Alternatively treatment of the crude product with Et_3N (5 equiv.) in DCM, concentration and column as before gave **11a** (57% yield). HRMS theoretical mass: (MH^+) 332.1155, measured mass: (MH^+) 332.1163. ^{1}H NMR (500 MHz, 298K, $CDCl_3$): δ = 2.01–2.25 (m, 3H), 2.67–2.77 (m, 1H), 3.58–3.67 (dd, J = 8.1, 11.7 Hz, 1H), 3.70–3.77 (dt, J = 8.2, 11.0 Hz, 1H), 4.69–4.73 (brs, 1H), 5.92 (d, J = 1.1 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 7.24–7.29 (m, 2H), 7.32 (t, J = 7.6 Hz, 1H), 7.72–7.80 (m, 2H), 7.85 (dd, J = 1.7, 5.8 Hz, 1H), 7.95 (dd, J = 1.5, 5.8 Hz, 1H); ^{13}C NMR and DEPT (125.8 MHz, $CDCl_3$) δ = 23.3 (CH_2), 31.5 (CH_2), 45.3 (CH_2), 52.5 (CH), 58.8 (CH), 123.8 (CH), 123.8 (C), 124.1 (CH), 124.5 (CH), 127.8 (CH), 128.0 (CH), 131.6 (C), 132.2 (C), 134.2 (CH), 134.3 (CH), 134.7 (C), 162.9 (C), 167.1 (C), 168.6 (C); ν_{max}/cm^{-1} 1713, 1655, 1441, 1386, 904, 763, 742, 725, 697.

2-((6R,10bR/6S10bS)-5-Oxo-1,2,3,6,10b-hexahydro-pyrrolo[2,1-a]isoquinolin-6-yl)isoindole-1,3-dione (11b). The more polar isomer was isolated as a pale yellow solid from a SiO_2 column purification, eluting with 3 : 1 Et_2O–petrol (61% yield), mpt 210–4°C. HRMS theoretical mass: (MH^+) 332.1155, measured mass: (MH^+) 332.1164. ^{1}H NMR (500 MHz, 298K, $CDCl_3$): δ = 1.87 (tt, J = 8.0, 11.8 Hz, 1-H), 2.03–2.22 (m, 2,2-H), 2.71 (tt, J = 6.5, 12 Hz, 1-H), 3.69–3.81 (m, 4,4-H), 5.10 (dd, J = 5.4, 11.8 Hz, 10b-H), 5.95 (d, J = 1.9 Hz, 6-H), 7.21–7.37 (m, 4H), 7.67 (dd, J = 5.5, 3 Hz, 2H), 7.78 (dd, J = 5.5, 3 Hz, 2H): ^{13}C NMR and DEPT

(125.8 MHz, $CDCl_3$) δ = 22.2 (2-C), 32.1 (1-C), 45.3 (3-C), 51.0 (6-C), 60.1 (10b-C), 123.5 (CH), 124.8 (CH), 128.2 (CH), 128.6 (CH), 128.6 (CH), 131.7 (C), 132.0 (C), 134.3 (CH), 136.9 (C), 163.3 (C), 167.5 (C) ν_{max}/cm^{-1} 1709, 1657, 1387, 1111, 893, 773, 717.

(6S, 10bS)/(6R, 10bR)-6-Phenyl-2,3,6,10b-tetrahydro-1*H*-pyrrolo[2,1-a]isoquinolin-5-one (14a). Isolated as pale yellow solid (71% yield), mpt 126–8°C (lit. 120°C[22]). HRMS theoretical mass: 263.1305, measured mass: 263.1305. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.86–1.97 (m, 2H), 2.06–2.15 (m, 1H), 2.58–2.67 (m, 1H), 3.51–3.60 (m, 1H), 3.60–3.65 (m, 1H), 4.53 (dd, J = 5.7, 10.1 Hz, H-10b), 4.92 (s, H-6), 7.12 (dd, J = 7.3, 0.5 Hz, 2H), 7.17–7.31 (m, 5H), 7.31–7.37 (m, 2H): ^{13}C NMR and DEPT (125.8 MHz, $CDCl_3$) δ = 23.0 (2-CH_2), 31.7 (1-CH_2), 45.3 (3-CH_2), 54.4 (6-CH), 59.0 (10b-CH), 124.5 (CH), 127.1 (CH), 127.4 (CH), 127.5 (CH), 128.2 (CH), 128.6 (CH), 128.7 (CH), 135.9 (C), 137.1 (C), 138.1 (C), 168.6 (C). NOE irradiation of *ortho*-CH of phenyl substituent enhanced both 10b-H and 6-H.

(6S, 10bR)/(6R, 10bS)-6-Phenyl-2,3,6,10b-tetrahydro-1*H*-pyrrolo[2,1-a]isoquinolin-5-one (14b). Isolated as a foam (29% yield). HRMS theoretical mass: 263.1305, measured mass: 263.1306. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.97–2.32 (m, 3H), 2.66–2.80 (m, 1H), 3.58 (q, J = 9.5 Hz, 1H), 3.77 (dd, J = 12, 7 Hz, 1H), 4.63–4.77 (m, 2H including 4.67 s, 1H), 6.65 (d, J = 8 Hz, 1H), 7.12–7.56 (m, 8H): ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 23.3 (CH_2), 31.5 (CH_2), 45.3 (CH_2), 53.8 (CH), 58.9 (CH), 123.7 (CH), 126.8 (CH), 127.3 (CH), 127.5 (CH), 128.5 (CH), 128.9 (CH), 131.1 (CH), 136.8 (C), 137.4 (C), 137.7 (C), 168.2 (C).

6,6-Diphenyl-2,3,6,10b-tetrahydro-1*H*-pyrrolo[2,1-a]iso-quinolin-5-one (15). Isolated as white solid (18% yield), mpt 176–9°C. HRMS theoretical mass: 339.1618, measured mass: 339.1611; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78–2.19 (m, 3H), 2.53–2.65 (m, 1H), 3.56–3.83 (m, 2H), 4.09 (dd, J = 10, 6 Hz, 1H), 6.62 (d, J = 8 Hz, 1H), 6.66–6.91 (m, 2H), 7.08 (dd, J = 7, 3 Hz, 2H), 7.15–7.40 (m, 9H): ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 23.0 (CH_2), 31.4 (CH_2), 45.8 (CH_2), 57.8 (CH), 64.4 (C), 123.8 (CH), 126.7 (CH), 127.0 (CH), 127.4 (CH), 128.3 (CH), 129.0 (CH), 129.7 (CH), 131.0 (CH), 138.2 (C), 139.3 (C), 141.7 (C), 143.5 (C), 170.2 (C). ν_{max}/cm^{-1} 1649, 1446, 1413, 752, 727, 704, 676.

(6R, 10bR)/(6S, 10bS)-6-Benzyl-2,3,6,10b-tetrahydro-1*H*-pyrrolo[2,1-a]isoquinolin-5-one (16a). Isolated from the cyclisation of **3v**, purified on SiO_2 and eluting with Et_2O to isolate the less polar fraction. From this, **17a** was crystallised from Et_2O–petrol. Concentration of the mother liquors gave an oil (1.09 g) which was treated with KBu^{t}O (0.1 g) in Et_2O (20 mL) at ambient temperatures for 4 days. The reaction mixture was then acidified with 2 M HCl and the organic layer separated, dried (K_2CO_3) and concentrated *in vacuo*. Purification by column chromatography on SiO_2, eluting with Et_2O + 25% petrol gave a more polar fraction, which on concentration afforded the title compound as an oil (7% yield). MS theoretical mass: 277.1461, measured mass: 277.1463; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.57–1.67 (m, 1-H), 1.71–1.82 (m 2-H), 1.95–2.03 (m 2-H), 2.39 (tt, J = 5.9, 11.7 Hz, 1-H), 3.09 (dd, J = 12.9, 4.8 Hz, 1′-H), 3.15 (dd, J = 12.9, 4.8 Hz, 1′-H), 3.61 (dd, J = 11.1, 5.6 Hz, 10b-H), 3.80 (t, J = 5.5 Hz, 6-H), 6.78 (d, J = 7.0 Hz, 5′,5′-H), 6.84 (d, J = 7.4 Hz, 1H), 7.01 (d, J = 7.4 Hz, 1H), 7.08 (t, J = 7.0 Hz, 2′, 4′-H), 7.13 (t, J = 7.0 Hz, 3′-H), 7.14 (t, J = 7.4 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H: ^{13}C NMR and DEPT (125.8 MHz, $CDCl_3$) δ = 22.5 (2-C), 31.8 (1-C), 40.7 (1′-C), 44.7 (3-C), 50.5 (6-C), 58.7 (10b-C), 124.0 (CH), 126.5 (CH), 126.7 (CH), 127.3 (CH), 127.8 (CH), 127.8 (CH), 129.6 (CH), 135.5 (C), 136.0 (C), 137.4 (C), 169.4 (C);ν_{max}/cm^{-1} 1712, 1655, 1386, 1109, 904, 725.

(6S, 10bR)/(6R, 10bS)-6-Benzyl-2,3,6,10b-tetrahydro-1*H*-pyrrolo[2,1-a]isoquinolin-5-one (16b). Isolated from the cyclisation of **3v**, purified on SiO_2 and eluting with Et_2O to isolate the less polar fraction, from which **17a** was crystallised from Et_2O–petrol. Concentration of the mother liquors gave the title compound as an oil (29% yield, 90% pure by NMR, the remainder being **17a**); MS theoretical mass: 277.1461, measured mass: 277.1465; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.72 (m, 1H), 1.86–2.07 (m, 2H), 2.41 (m, 0.1H), 2.49 (ddt, 0.9H), 2.65 (dt, 0.1H), 2.98 (dd, 0.1H), 3.37–3.89 (m, 4.8 H), 4.46–4.57 (m, 0.9H), 5.29 (t, 0.1H), 7.10–7.39 (m, 9H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 23.3 (CH_2), 31.2 (CH_2), 33.8 (CH_2), 44.9 (CH_2), 46.2 (CH), 59.0 (CH), 123.9 (CH), 125.8 (CH), 126.0 (CH), 126.6 (CH), 127.5 (CH), 128.2 (CH), 128.9 (CH), 129.9 (C), 136.2 (C), 137.1 (C) 139.9 (C), 169.0 (C).

(6S,11bR/6R,11bS)-6-Phenyl-1,2,3,6,7,11b-hexahydro-benzo-[*c*]pyrrolo[1,2-a]azepin-5-one (17a). Isolated from the cyclisation of **3v**, purified on SiO_2 and eluting with Et_2O to isolate the less polar fraction. From this, **17a** was crystallised from Et_2O–petrol (3% yield), mpt 125–7°C. MS theoretical mass: 277.1461, measured mass: 277.1466; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.90–2.10 (m, 2H), 2.41 (quintet, J = 7.2 Hz, 1H), 2.65 (quintet, J = 6.3 Hz, 1H), 2.99 (dd, J = 14.7, 5.4 Hz, 1H), 3.53 (dd, J = 12.9, 14.6 Hz, 1H), 3.72 (t, J = 6.8 Hz, 1H), 3.81 (dd, J = 12.9, 5.4 Hz, 1H), 5.31 (dd, J = 7.0, 6.2 Hz, 1H), 7.26–7.33 (m, 5H), 7.35–7.38 (m, 4H). NOE irradiation of 1-H at δ = 5.31 showed an enhancement of the *ortho*-phenyls at δ = 7.30 and 7.37.^{13}C NMR and DEPT (125 MHz, $CDCl_3$) δ = 22.5 (CH_2), 29.9 (CH_2), 38.2 (CH_2), 48.5 (CH_2), 53.6 (CH), 56.1 (CH), 123.4 (CH), 126.7 (CH)126.8 (CH), 127.6 (CH), 128.2 (CH), 128.7 (CH), 129.1 (CH), 139.1 (C), 139.5 (C), 142.8 (C), 170.7 (C). HRMS theoretical mass: 277.14612, measured mass: 277.14580; ν_{max}/cm^{-1} 1610, 1599, 1583, 1421, 776, 748, 703, 658.

(6S,11bS/6R,11bR)-6-Phenyl-1,2,3,6,7,11b-hexahydro-benzo-[*c*]pyrrolo[1,2-a]azepin-5-one (17b). Isolated from the cyclisation of **3v**, purified on SiO_2 and eluting with Et_2O + 1% MeOH to isolate the more polar fraction, which on concentration gave an oil which gave the title compound as a solid from Et_2O (47% yield) mpt 150–2°C. MS theoretical mass: 277.1461, measured mass: 277.1458; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.88–1.99 (m, 1H), 2.01–2.09 (m, 1H), 2.48–2.52 (m, 2H), 3.13 (d,d J = 15.4, 7.4 Hz, 1H), 3.48–3.58 (m, 2H), 4.02 (dddd, J = 12.0, 7.7, 3.5, 0.8 Hz, 1H), 4.30 (dd, J = 7.3, 3.6 Hz, 1H), 5.19 (dd, J = 8.2, 6.9 Hz, 1H), 6.77 (ddd, J = 7.5, 1.5, 0.4 Hz, 1H), 6.90 (dd, J = 7.6, 1.3 Hz, 2H), 7.10 (tdd, J = 7.4, 1.3, 0.4 Hz, 1H), 7.14–7.25 (m, 4H), 7.34 (d, 1H, J = 7.9 Hz): NOE irradiation of 1-H at δ = 5.19 showed an enhancement of the 11-H proton at δ = 7.34 and the 6-H proton at δ = 4.30: ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 22.9 (CH_2), 31.7 (CH_2), 37.6 (CH_2), 48.2 (CH_2), 50.4 (CH_2), 58.1 (CH),

124.8 (CH), 126.5 (CH), 126.5 (CH), 127.5 (CH), 128.0 (CH), 128.5 (CH), 130.5 (CH), 137.7 (C), 138.2 (C), 141.0 (C), 171.8 (C)

General procedure for the aluminium chloride-mediated synthesis of the 2,3,6,10b-tetrahydro-1*H*-pyrrolo[2,1-a]isoquinolin-5-ones

To a stirred solution of the phenyl acetamide (2 mmol) in $CHCl_3$ (30 mL) was added $AlCl_3$ (6 mmol) at ambient temperature. The reaction was monitored by taking a small aliquot of the reaction mixture, adding a few drops of water, basifying with K_2CO_3 and then analysing the $CHCl_3$ layer on silica TLC, eluting with EtOAc. The reaction was stirred until the high running spot had disappeared. The reaction mixture was then cooled, water was added (2 mL) and the aqueous layer basified, then saturated with K_2CO_3. The organic layer was separated and the solid residue extracted with DCM (2×30 mL). The combined organic extracts were dried (K_2CO_3), separated and concentrated *in vacuo.* The residue was purified by column chromatography on silica, initially absorbing the compound from a DCM solution, and then eluting with Et_2O containing appropriate amounts of MeOH up to 5%.

***N*-(4,4-Diethoxybutyl)-3-phenylpropionamide (18a).** Isolated as an oil (100% yield). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$ (t, $J = 7.1$ Hz, 6H), 1.44–1.62 (m, 4H), 2.43 (t, $J = 7.5$ Hz, 2H), 2.93 (t, $J = 7.5$ Hz, 2H), 3.20 (q, $J = 6.3$ Hz, 2H), 3.40–3.52 (m, 2H), 3.55–3.67 (m, 2H), 4.42 (t, $J = 5$ Hz, 1H). 5.73 (brs, 1H), 7.12- 7.30 (m, 5H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) $\delta =$ 15.3 (CH_3), 24.5 (CH_2), 31.0 (CH_2), 31.8 (CH_2), 38.5 (CH_2), 39.2 (CH_2), 61.4 (CH_2), 102.6 (CH), 126.2 (CH), 128.3 (CH), 128.5 (CH), 140.9 (CH), 172.1 (C); ν_{max}/cm^{-1} 2974, 2928, 2874, 1643, 1589, 1453, 1373, 1125, 1058, 994, 749.

1,2,3,6,7,11b - hexahydro - benzo[c]pyrrolo[1,2 - a]azepin - 5 - one (19a). Isolated as an oil (80% yield), HRMS theoretical mass: 201.1148, measured mass: 201.1154. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.76$–2.02 (m, 2H), 2.22–2.55 (m, 3H), 2.78–2.95 (m, 2H), 3.15–3.29 (m, 1H), 3.36–3.50 (m, 1H), 3.70–3.81 (m, 1H), 5.04 (t, $J =$ 7.7 Hz, 1H,), 7.19–2.28 (m, 5H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) $\delta = 22.8$ (CH_2), 29.1 (CH_2), 30.6 (CH_2), 35.9 (CH_2), 48.1 (CH_2), 56.9 (CH), 124.4 (CH), 126.5 (CH), 128.2 (CH), 128.9 (CH), 138.2 (C), 140.8 (C), 170.7 (C); ν_{max}/cm^{-1} 1596, 1446, 1401, 1306, 754, 696.

(S)-*N*-(4,4-Diethoxybutyl)-2-[4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-phenylpropionamide (20). Isolated as a white solid (91% yield), mpt 78–80°C. (Et_2O–petrol). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.11$ (t, $J = 7$ Hz, 3H), 1.13 (t, $J = 7$ Hz, 3H), 1.51–1.67 (m, 4H), 3.18–3.62 (m, 8H), 4.44 (t, $J = 5$ Hz, 1H), 5.07 (dd, $J = 6$, 10 Hz, 1H), 6.40 (brs, 1H), 7.06–7.20 (m, 5H), 7.63–7.71 (m, 2H), 7.71–7.79 (m, 2H); ν_{max}/cm^{-1} 2973, 1712, 1642, 1545, 1380, 1103, 1065, 874, 721, 707.

2-((6S,11bS)-5-Oxo-2,3,5,6,7,11b-hexahydro-1*H*-benzo[c]pyrrolo[1,2-a]azepin-6-yl)-isoindole-1,3-dione (10). Isolated as a glass (70% yield); ^{1}H NMR (500 MHz, $CDCl_3$ at 263 K): $\delta =$ 1.85–1.97 (m, 1H, H-2), 2.01–2.19 (m, 1H, H-2), 2.48–2.59 (m, 2H, H-1,1), 3.41 (dd, $J = 16.2$, 3.9 Hz, 1H, H-7), 3.43–3.51 (m, 1H, H-3), 3.76 (dd, $J = 16.2$, 8.7 Hz, 1H, H-7), 3.88–3.95 (m, 1H, H-8), 5.19 (t, $J = 7.2$ Hz, 1H, H-11b), 5.38 (dd, $J = 8.7$, 3.9 Hz, 1H, H-6), 7.05 (d, $J = 7.5$ Hz, 1H, H-8), 7.17 (t, $J = 7.5$ Hz, 1H, H-9), 7.26 (t, $J = 7.5$ Hz, 1H, H-10), 7.32 (d, $J = 7.5$ Hz, 1H, H-9), 7.52–7.25 (m, 3H), 7.82 (d, $J = 6.3$ Hz, 1H, 1-H); ^{13}C NMR (125.8 MHz, $CDCl_3$ at 263 K) $\delta = 23.1$, 31.9, 35.0, 48.1. 52.1, 58.6, 123.4, 123.5, 125.4, 127.1, 127.9, 130.1, 131.5, 131.9, 134.1, 134.3, 136.4, 137.4, 167.2, 167.6, 168.2. ^{1}H NMR (500 MHz, $CDCl_3$ at 333 K): $\delta = 1.87$–1.98 (m, 1H), 1.99–2.07 (m, 1H), 2.51–2.60 (m, 2H), 3.41 (dd, $J = 15.8$, 4.5 Hz, 1H), 3.45–3.53 (m, 1H), 3.84 (dd, $J = 16.2$, 8.9 Hz, 1H), 3.88–3.94 (m, 1H), 5.10 (dd, $J = 7.8$, 8.9 Hz, 1H), 5.39 (dd, $J = 8.8$, 3.7 Hz, 1H), 7.07 (d, $J = 6.8$ Hz, 1H), 7.15 (t, $J = 7.3$ Hz, 1H), 7.22 (t, $J = 7.4$ Hz, 1H), 7.29 (d, $J = 7.8$ Hz, 1H), 7.63–7.67 (m, 2H), 7.76–7,78 (m, 2H). Chiral HPLC was run on a Chiracel OJ 4.6×250 mm column with 10 μm particle size, eluting with heptane–EtOH 1 : 1 at a flow rate of 1 mL/min. Retention times of 8.1 and 11.4 min. were obtained for each enantiomer.

***N*-(4,4-Diethoxybutyl)-3,3-diphenylpropionamide (21).** Isolated as an oil which solidified on standing (95% yield), mpt 61–4°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$ (t, $J = 7$ Hz, 6H), 1.31–1.49 (m, 4H), 2.86 (d, $J = 8$ Hz, 2H), 3.10 (q, $J = 6$ Hz, 2H), 3.39–3.50 (m, 2H), 3.52–3.75 (m, 2H), 4.36 (t, $J = 5$ Hz, 1H), 4.56 (t, $J = 8$ Hz, 1H), 5.56 (brs, 1H), 7.14–7.31 (m, 10H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) $\delta = 15.4$ (CH_3), 24.5 (CH_2), 30.8 (CH_2), 39.1 (CH_2), 43.5 (CH_2), 47.5 (CH), 102.6 (CH), 126.5 (CH), 127.8 (CH), 128.6 (CH), 143.7 (C), 171.0 (C).

7-Phenyl-1,2,3,6,7,11b-hexahydro-benzo[*c*]pyrrolo[1,2-a]azepin-5-one (22). Isolated as a solid (76% yield) mpt 118–9°C (Et_2O/–petrol), HRMS theoretical mass: 277.1461, measured mass: 277.1467. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.79$–1.89 (m, H-2), 1.92–2.02 (m, H-2), 2.27–2.36 (m, H-1), 2.50–2.58 (m, H-2), 2.83 (dd, $J = 5$, 15.1 Hz, H-6), 3.37–3.50 (m, H-3, H-6), 3.72–3.79 (m, H-3), 4.49 (dd, $J = 5$, 10.5 Hz, H-7), 7.08 (d, $J = 8.3$ Hz, 1H), 7.12 (dd, $J = 1.4$, 8.4 Hz, 2H), 7.16–7.23 (m,3H), 7.24–7.31 (m, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) $\delta = 23.1$ (CH2), 30.4 (CH2), 42.6 (CH2), 46.0 (CH), 46.5 (CH2), 57.6 (CH), 124.9 (CH), 126.5 (CH), 127.5 (CH), 127.9 (CH), 128.7 (CH), 132.5 (CH), 137.4 (C), 141.8 (C), 145.7 (C), 170.3 (C); ν_{max}/cm^{-1} 1636, 1448, 1430, 1304, 755, 701.

***N*-(4,4-Diethoxybutyl)-3,3,3-triphenylpropionamide (23).** Isolated as a white solid (96% yield), mpt 110–2°C (Et_2O–petrol). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1,17$ (t, $J = 7$ Hz, 6H), 1.25–1.40 (m, 2H), 2.93 (q, $J = 6$ Hz, 2H), 3.35–3.48 (m, 2H), 3.50–3.64 (m, 4H including 3.54, s, 2H), 4.33 (t, $J = 5.5$ Hz, 1H), 4.85 (brs, 1H), 7.10–7.32 (m, 15H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) $\delta = 15.4$ (CH_3), 24.2 (CH_2), 30.8 (CH_2), 39.2 (CH_2), 48.8 (CH_2), 56.2 (C), 61.1 (CH_2), 102.5 (CH), 126.5 (CH), 128.1 (CH), 129.3 (CH), 146.3 (C), 170.5 (C).

7,7-Diphenyl-1,2,3,6,7,11b-hexahydro-benzo[c]pyrrolo[1,2-a]azepin-5-one (24)

Isolated as a white solid (90% yield), mpt 153–6°C (Et_2O–petrol). HRMS theoretical mass: 353.1774, measured mass: 353.1785. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.60$–1.79 (m, 1H), 1.83–1.97 (m, 1H), 2.21–2.40 (m, 1H), 2.45–2.59 (m, 1H), 3.00–3.13 (m, 1H), 3.40 (d, $J = 15$ Hz, 1H), 3.84 (brt, $J = 9$ Hz, 1H), 3.92 (d, $J = 15$ Hz, 1H), 4.87 (dt, $J = 2.7$, 7 Hz, 1H), 6.64 (d, $J = 7$ Hz, 1H), 7.01–7.41 (m, 13H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) $\delta = 22.9$ (CH_2), 33.7 (CH_2), 46.6 (CH_2), 49.2 (CH_2), 54.8 (C), 59.4 (CH_2), 126.6 (CH), 126.7 (CH), 126.7 (CH), 126.9 (CH), 127.0 (CH), 127.7

(CH), 128.3 (CH), 128.5 (CH), 129.7 (CH), 133.1 (CH), 137.9 (C), 144.8 (C), 145.2 (C), 148.2 (C), 170.3 (C); ν_{max}/cm^{-1} 1650, 1430, 761, 727, 740, 700, 678.

***N*-(4,4-Diethoxybutyl)-2-(9H-fluoren-9-yl)-acetamide (25).** Isolated as a white solid (93% yield), mpt 82–6°C (Et_2O–petrol). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, J = 7 Hz, 6H), 1.48–1.67 (m, 4H), 2.58 (d, J = 7.4 Hz, 2H), 3.33 (q, J = 6 Hz, 2H), 3.40–3.51 (m, 2H), 3.53–3.75 (m, 2H), 4.46 (t, J = 5.2 Hz, 1H), 4.51 (t, J = 7.4 Hz, 1H), 5.55 (brs, 1H), 7.29 (t, J = 7.4 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 7.49 (d, J = 7.3 Hz, 2H), 7.75 (d, J = 7.4 Hz, 2H), ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 24.6 (CH_2), 31.0 (CH_2), 39.4 (CH_2), 41.0 (CH_2), 44.0 (CH), 61.4 (CH_2), 47.5 (CH), 102.6 (CH), 119.9 (CH), 124.5 (CH), 127.2 (CH), 127.4 (CH), 140.7 (C), 146.5 (C), 171.1 (C).

1,3,4,5,6,14b-Hexahydro-fluoreno[1,9-cd]-pyrrolo[3,4-a]azepine-2-one (26). Isolated as a white solid (90% yield) mpt 156–8°C. HRMS theoretical mass: 275.1305, measured mass: 275.1305. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.82–2.08 (m, 4H), 2.23–2.40 (m, 2H), 2.72 (t, J = 13 Hz, 1H), 2.75–2.89 (m, 1H), 3.24 (dd, J = 13, 1.4 Hz, 1H), 3.40–3.52 (m, 1H), 4.05–4.22 (m, 2H), 5.00 (t, J = 8 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 7.28–7.44 (m, 3H), 7.57 (d, J = 7.3 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 6.7 Hz, 1H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 22.7 (CH_2), 34.5 (CH_2), 38.3 (CH_2), 44.1 (CH), 48.0 (CH_2), 60.3 (CH), 118.8 (CH), 120.2 (CH), 123.7 (CH), 124.1 (CH), 127.4 (CH), 127.5 (CH), 128.0 (CH), 135.6 (C), 140.0 (C), 140.8 (C), 144.3 (C), 145.7 (C), 174.1 (C).

***N*-(5,5-Diethoxypentyl)-2-phenylacetamide (29).** Isolated as an oil (98% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, J = 7 Hz, 6H), 1.21–1.31 (m, 2H), 1.33–1.46 (m, 2H), 1.48–1.59 (m, 2H), 3.17 (q, J = 6.5 Hz, 2H), 3.36–3.49 (m, 2H), 3.50–3.64 (m, 4H including 3.52, s, 2H), 4.40 (t, J = 5.5 Hz, 1H), 5.52 (brs, 1H), 7.18–7.35 (m, 5H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 22.0 (CH_2), 29.3 (CH_2), 33.2 (CH_2), 39.6 (CH_2), 43.8 (CH_2), 61.0 (CH_2), 102.7 (CH), 127.3 (CH), 129.0 (CH), 129.4 (CH), 135.1 (C), 170.9 (C).

***N*-(5,5-Diethoxypentyl)-2-(3,4-dimethoxyphenyl) acetamide (30).** Isolated as an oil (88% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, J = 7 Hz, 6H), 1.21–1.31 (m, 2H), 1.33–1.46 (m, 2H), 1.48–1.59 (m, 2H), 3.17 (q, J = 6.5 Hz, 2H), 3.36–3.49 (m, 4H including 3.46, s, 2H), 3.50–3.64 (m, 2H), 3.86 (s, 6H), 4.40 (t, J = 5.5 Hz, 1H), 5.45 (brs, 1H), 6.74–6.86 (m, 3H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 22.1 (CH_2), 29.5 (CH_2), 39.5 (CH_2), 43.7 (CH_2), 55.9 (CH_2), 61.1 (CH_3), 61.3 (CH_3), 102.5 (CH), 111.5 (CH), 112.4 (CH), 121.6 (C), 127.5 (C), 148.3 (C), 149.2 (C), 171.3 (C).

1,2,3,4,7,11b-hexahydro-benzo[a]quinolizin-6-one (31). Isolated as a pale yellow solid (31% yield), mpt 47–49°C (Et_2O–petrol) (lit. 49–52°C[21]), HRMS theoretical mass: 201.1148, measured mass: 201.1146. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.40–1.58 (m, 2H), 1.65–1.79 (m, 2H), 1.92–2.10 (m, 2H), 2.61 (td, J = 12.7, 2.5 Hz, 1H), 3.62 (d, J = 21.0 Hz, 1H), 3.67 (d, J = 21.0 Hz, 1H), 4.42 (d, J = 11.8 Hz, 1H), 4.89 (ddt, J = 13.1, 4.2, 2.0 Hz, 1H), 7.08–7.35 (m, 4H); ^{13}C NMR and DEPT (125.8 MHz, $CDCl_3$) δ = 25.1 (CH_2), 25.3 (CH_2), 35.1 (CH_2), 36.4 (CH_2), 43.9 (CH_2), 61.7 (CH). 125.5 (CH), 126.7 (CH), 127.4 (CH), 127.6 (CH), 130.3 (C), 134.1 (C), 166.7 (C).

9,10-Dimethoxy-1,2,3,4,7,11b-hexahydro-benzo[a]-quinolizin-6-one (32). Isolated as a pale yellow solid (60% yield) mpt 103–6°C (Et_2O–petrol), HRMS theoretical mass: 261.1359, measured mass: 261.1362. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.40–1.58 (m, 2H), 1.68–1.76 (m, 2H), 1.97 (dd, J = 12.8, 1.7 Hz, 1H), 2.07 (dd, J = 12.1, 1.2 Hz, 1H), 2.59 (dt, J = 10.5, 2.5 Hz, 1H), 3.52 (d, J = 21.0 Hz, 1H), 3.60 (d, J = 21.0 Hz, 1H), 3.85 (s, 6H), 4.34 (dd, J = 11.8, 1.7 Hz, 1H), 4.89 (dt, J = 13.0, 2.3 Hz, 1H), 6.50 (s, 1H), 6.62 (s, 1H); ^{13}C NMR and DEPT (125.8 MHz, $CDCl_3$) δ = 25.08 (CH_2), 25.2 (CH_2), 34.6 (CH_2), 36.6 (CH_2), 43.8 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 61.5 (CH), 108.2 (CH), 109.8 (CH), 122.3 (C), 126.0 (C), 148.1 (C), 148.6 (C), 166.7 (C); ν_{max}/cm^{-1} 2937, 2847, 1641, 1521, 1464, 1321, 1269, 1246, 1227, 1119, 1015, 998, 846, 761.

***N*-(5,5-Diethoxypentyl)-3-phenylpropionamide (33).** Isolated as an oil (94% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, J = 7 Hz, 6H), 1.21–1.31 (m, 2H), 1.33–1.46 (m, 2H), 1.48–1.59 (m, 2H), 2.42 (t, J = 7.5 Hz, 2H), 2.93 (t, J = 7.5 Hz, 2H), 3.17 (q, J = 6.5 Hz, 2H), 3.36–3.49 (m, 2H), 3.50–3.64 (m, 2H), 4.42 (t, J = 5.5 Hz, 1H), 5.62 (brs, 1H), 7.12–7.28 (m, 5H), ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.4 (CH_3), 22.0 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 33.3 (CH_2), 38.5 (CH_2), 39.4 (CH_2), 61.1 (CH_2), 102.8 (CH), 126.2 (CH), 128.3 (CH), 128.5 (CH), 140.9 (C), 172.0 (C).

1,3,4,7,8,12b-Hexahydro-2*H*-pyrido[2,1-a][2]benzazepin-6-one (34). *N*-(5,5-Diethoxypentyl)-3-phenylpropionamide (0.8 g) was dissolved in acetone (50 mL) and 5 mL of 2 M HCl added. After standing at ambient temperatures for 30 min., an excess of solid K_2CO_3 was added and the acetone removed by rotary evaporation. The residue was extracted with DCM (3 × 50 mL), dried (K_2CO_3) and the solvent removed by rotary evaporation to give a clear oil (0.7 g). This oil was dissolved in $CHCl_3$ and cyclised with triflic acid (2.3 mL) by the previously described procedure to give the product as an oil which crystallised on trituration with 1 : 1 Et_2O–petrol (86% yield), mpt 91–3°C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.58–1.96 (m, 5H), 2.10–2.20 (m, 1H), 2.71–2.83 (m, 1H), 2.89–3.04 (m, 2H), 3.12–3.25 (m, 1H), 3.49–3.57 (m, 1H), 3.60–3.75 (m, 1H), 4.90 (dd, J = 4.4, 7.9 Hz, 1H), 7.06–7.30 (m, 4H); ^{13}C NMR and DEPT (125.8 MHz, $CDCl_3$) δ = 23.3 (CH_2), 24.7 (CH_2), 29.4 (CH_2), 30.4 (CH_2), 36.2 (CH_2), 42.6 (CH_2), 59.8 (CH), 126.2 (CH), 127.5 (CH), 127.8 (CH), 129.9 (CH), 138.6 (C), 139.4 (C), 172.7 (C).

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