A facile synthesis of pyrrolo-(di)-benzazocinones *via* an intramolecular *N*-acyliminium ion cyclisation†

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A facile, moderate to high yielding synthesis of hexahydro-(di)-benzazocinones is described *via* an intramolecular *N*-acyliminium ion cyclisation. The iminium ion intermediates are formed from the readily available 4,4-diethoxybutyl amides with an excess of triflic acid. For electron-withdrawing substituents, better yields were obtained from the pre-formed 2-hydroxypyrrolidine amides. From NMR studies, at ambient temperatures the pyrrolo-benzazocin-3-ones exist as a slowly equilibrating mixture of two conformations.

Introduction

We have an on-going programme of work directed towards the development of new chemistry to allow the synthesis of privileged structures for the assembly of high quality screening libraries. We are interested in the synthesis of conformationally restricted aryl-substituted alkylamines, privileged structures which are found in CNS drugs,[1–3] and particularly interested in 1,2,3,4-tetrahydro-isoquinoline and its homologues, for which there have been numerous reports on their biological activity.[4–13] As an example of a new synthesis of the 1,2,3,4-tetrahydro-isoquinoline core, we recently described a synthesis of (±)-crispine A *via* an intramolecular cyclisation of a readily synthesized *N*-acyliminium ion.[14] In this paper, we describe the unexpected isolation of a pyrrolo-dibenzazocin-3-one (**3**) from a pyrrolo-isoquinolone synthesis *via* an immimium ion cyclisation and the application of this methodology to related systems.

Results and discussion

Whilst investigating the scope of this tetrahydro-isoquinoline synthesis, we attempted the triflic acid-mediated cyclisation of compound **1**, which was readily prepared from biphenyl-2-acetic acid.[15] On treatment of **1** with triflic acid (10 equivs.) in $CHCl_3$ we isolated the 6-membered cyclisation product **2** (64% yield) as expected (Scheme 1), but in addition a second, isomeric product. ^1H and ^{13}C NMR spectra provided evidence that the product was the dibenzazocine **3** (29% yield). The key difference between the ^{13}C NMR spectra of **2** and **3** were the number of aromatic carbon signals, 10 signals for **2**, 6 of which were C–H, and 12 signals for **3**, 8 of which were C–H. The present observation is, as far as we can ascertain, the first example of an acyliminium ion cyclisation onto an unactivated aromatic to form an 8-membered ring.[16,17]

Although benzo-fused 7-membered rings have been extensively exploited in drug discovery, for example tricyclic antidepressants,[18] benzodiazepines[19] and as enzyme inhibitors,[20] there have only been a few examples of pharmacologically active benzo-fused 8-membered rings described in the literature.[21–24] To date, hexahydro-benzazocines have been prepared either by ring expansion,[21,25–27] by ring-closing metathesis,[28,29] and by intramolecular cyclisation *via* either a Staudinger–aza-Wittig procedure[22] or iminium ion cyclisations of sulfonamides.[30–33] We therefore believed that this finding deserved further investigation.

Following the isolation of **3**, we decided to investigate the synthesis of the simpler hexahydro-benzazocinone **5** from 4-phenylbutyramide **4** (Scheme 2), prepared in a similar manner to **1** from 4-phenylbutyric acid. Cyclisation with triflic acid gave a good yield (70%) of a colourless oil, tentatively assigned as the hexahydrobenzazocinone **5** together with a small amount of 1-tetralone (8% yield). The reaction was carried out at between 0.05–0.1 M concentration demonstrating that no special procedures (*e.g.* high dilution) were required to mediate this ring formation.

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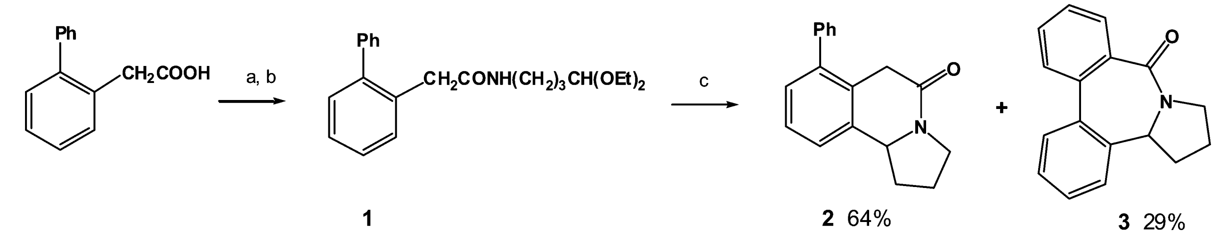
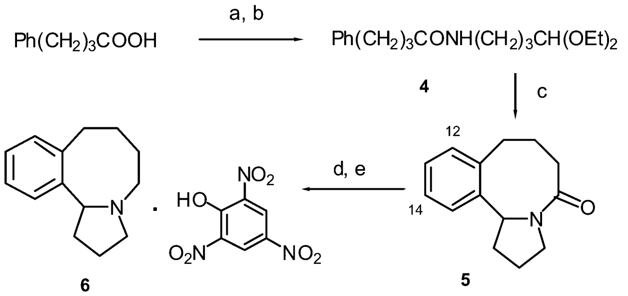


Scheme 1 Synthesis of the tetrahydro-dibenzazocine **3**. *Reagents and conditions*: a) $(COCl)_2$, CH_2Cl_2, DMF, b) $H_2N(CH_2)_3CH(OEt)_2$, $EtNMe_2$, c) CF_3SO_3H, $CHCl_3$, heat.



Scheme 2 Synthesis of benzazocines **5** and **6**. *Reagents and conditions*: a) $(COCl)_2$, CH_2Cl_2, DMF, b) $H_2N(CH_2)_3CH(OEt)_2$, $EtNMe_2$ (100%), c) CF_3SO_3H, $CHCl_3$, heat (70%), d) $LiAlH_4$, THF, heat (88%), e) picric acid.

Under these strongly acidic conditions, it is likely that the acyliminium ion is protonated on the carbonyl to form the dicationic superelectrophile, which undergoes the cyclisation.[34]

At ambient temperatures, the ^1H and ^{13}C NMR spectra of **5** in $CDCl_3$ showed broadened signals for the majority of the peaks, which was attributed to an intramolecular dynamic process with a rate intermediate in the NMR timescale at temperatures near 298 K. Relatively sharp ^1H and ^{13}C NMR spectra were measured at 333 K, which were used for the structural confirmation of **5**. Further variable-temperature ^1H and ^{13}C measurements, including two-dimensional exchange-correlated spectroscopy,[35] revealed the presence of two conformations in the dynamic process. In particular, two sets of peaks were observed at 213 K in the ^1H and ^{13}C NMR spectra of **5** with the integral intensity ratio of 2.7:1. Proton H-2, the bridgehead proton of the major conformer, appeared as a doublet of doublets ($J = 6.4$ and 9.3 Hz), whereas that of the minor conformer showed only a doublet ($J = 7.0$ Hz). Based upon these values and the boundary values of the corresponding $^3J_{HH}$ couplings predicted for L-prolines,[36] the five-membered ring of the major conformer is in the C^4-*exo* conformation, whereas that of the minor comformer is in the C^4-*endo* conformation. Here we use the previously suggested notation for L-proline conformations,[36,37] where the *endo-/exo*-orientation of the C4 atom is determined relative to the C^2–C^1 bond. Overall, the $^3J_{HH}$ couplings of both the five- and eight-membered rings were in favour of a two-site conformational equilibrium shown in Fig. 1, where the C^4-*exo*-C^8-*endo* form is the preferred major conformer. The free energy barrier for the conformational change from the C4-*exo*-C8-*endo* conformer into the C4-*endo*-C8-*exo* conformer for **5** was estimated to be 55 ± 1 kJ mol^{-1} at the coalescence temperature of 266 K. For the reverse interconversion from the C4-*endo*-C8-*exo* conformer into the C4-*exo*-C8-*endo* conformer the free energy barrier was estimated to be 53 ± 1 kJ mol^{-1} at 266 K.

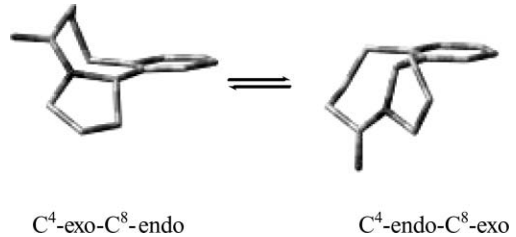


Fig. 1 A representation of the two conformers of **5** from NMR analysis.

In order to obtain a solid derivative to unambiguously confirm the molecular structure, **5** was reduced to the amine with LAH and a solid picrate salt **6** formed. Unfortunately good quality crystals of the picrate could not be obtained. However, the structure of this salt was confirmed by a low resolution X-ray crystal structure analysis. In addition, the structure of the corresponding free base was also confirmed by NMR measurements in $CDCl_3$ (Fig. 2).

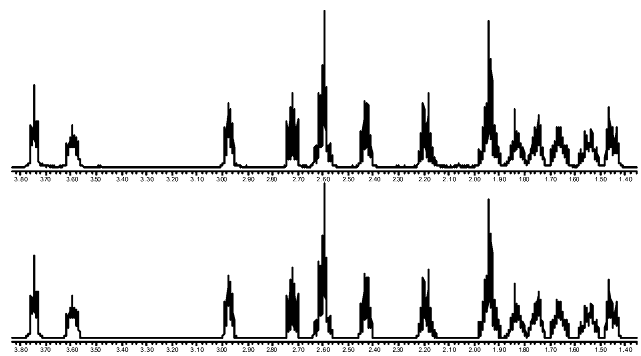


Fig. 2 Experimental (top, in $CDCl_3$, 333 K) and calculated (bottom) 600 MHz ^1H NMR spectra of the free base of **6**. Fifteen protons of the five- and eight-membered aliphatic rings were included in the iterative fittings of the experimental spectrum.

The scope of this method was then investigated with respect to aromatic substituents, and the results are shown in Table 1.

As expected of an electrophilic cyclisation, electron-donating substituents increased the rate of reaction and gave higher yields, as exemplified by the *p*-tolyl and 3,4-dimethoxy analogues (**5a** and **5b** respectively). The 2,5-dimethoxy **5c** gave a much lower yield, though the reaction was still fast and could be run at ambient temperatures. Electron-withdrawing substituents both slowed the reaction and gave lower yields. Thus the 4-Br **4e** and 4-phenyl **4f** gave only poor yields of the benzazocinones **5e** and **5f** respectively. None of the desired product could be detected from the 4-Cl **4d** cyclisation. In all cases, where a poor yield was obtained a significant quantity of insoluble, presumably polymeric material, was produced. For the very electron-rich **4b**, the cyclisation could be achieved using 10 equivs. of TFA (1 h reflux, 90% yield).

In the ^1H and ^{13}C NMR spectra of **5b** and **5e** at 213 K, again two sets of peaks were observed with the integral intensity ratios of 4.3:1 and 3.4:1 respectively. Similar to **5**, the free energy barrier for the conformational change from the C^4-*exo*-C^8-*endo* conformer into the C^4-*endo*-C^8-*exo* conformer for **5e** was estimated to be 56 ± 1 kJ mol^{-1} at the coalescence temperature of 266 K. For the reverse interconversion from the C^4-*endo*-C^8-*exo* conformer into the

Table 1 Synthesis of substitued hexahydrobenzazocin-3-ones **5a–f**

Cpd. no.	R	T (h)[a]	Cpd. no.	R	Isolated yield (%)
4a	4-Me	4	**5a**	14-Me	75
4b	3,4-diMeO	1	**5b**	13,14-diMeO	80
4c	2,5-diMeO	21[b]	**5c**	12,15-diMeO	26
4d	4-Cl	18	**5d**	14-Cl	0
4e	4-Br	18	**5e**	14-Br	17
4f	4-Ph	0.5	**5f**	14-Ph	25

[a] Time of reaction in $CHCl_3$ heated under reflux. [b] At ambient temperatures.

C^4-*exo*-C^8-*endo* conformer the free energy barrier was estimated to be 53 ± 1 kJ mol^{-1} at 266 K (Fig. 3).

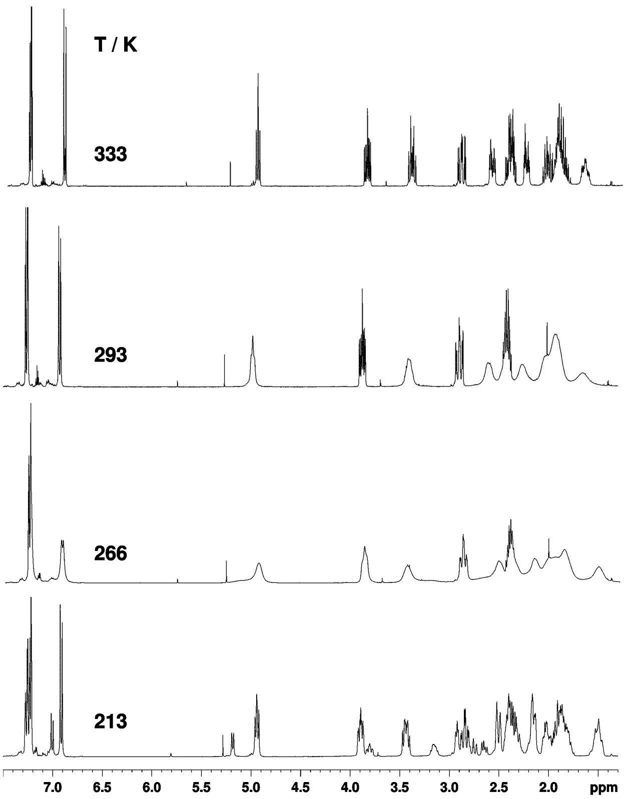


Fig. 3 The temperature dependence of the ^1H NMR spectra of **5e** ($CDCl_3$, 400 MHz).

A sample of **5c** was submitted for X-ray analysis, which confirmed the structure as the benzazocin-3-one (Fig. 4). Unlike the other benzazocinones, **5c** showed sharp ^1H and ^{13}C NMR spectra in $CDCl_3$ at 298 K with the $^3J_{HH}$-couplings indicating of a single C^4-*exo*-C^8-*endo* conformer, in agreement with the solid-state structure. Presumably the steric constraints of the 12- and 15-substituents restricts the conformational freedom of the 8,5 system.

In our previous paper,[14] a higher yield of tetrahydro-isoquinolinone was obtained from the *N*-acyl-2-hydroxy-pyrrolidine,

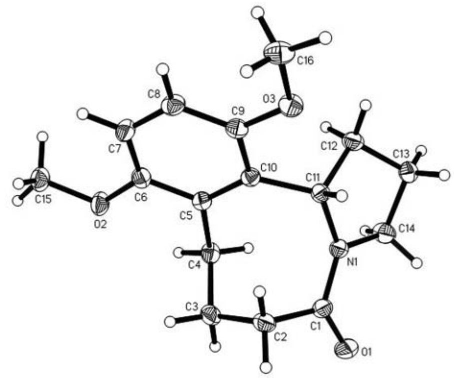
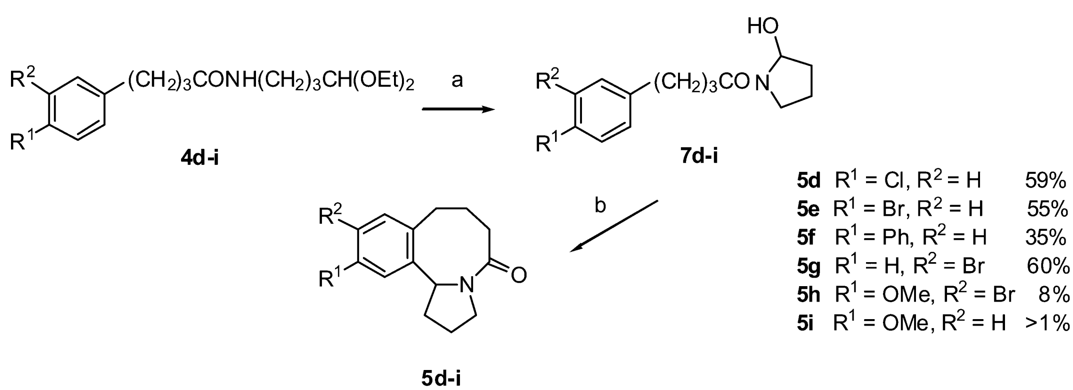


Fig. 4 Structure of hexahydrobenzazocinone **5c** as determined by X-ray crystallography. ORTEP diagram (50% probability ellipsoids) showing the crystallographic atom-numbering scheme.

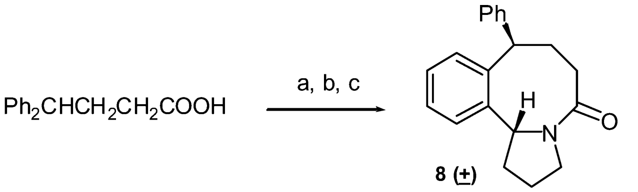
readily prepared by mild acid hydrolysis of the amidoacetal. Thus treatement of an acetone solution **4d–h** with 1 M HCl solution for 15 min gave the intermediate *N*-acyl- 2-hydroxypyrrolidines **7d–h** in essentially quantitative yields (Scheme 3).

Previous experience had shown that *N*-acyl-2-hydroxy-pyrrolidines were too unstable to purify by column chromatography and so **7d–i** were used without further purification. Triflic acid cyclisation of **7d–g** gave higher yields of benzazocines **5d–g**, than previously obtained from the amides (yields quoted are the overall yields from **4d–g**). Cyclisation of the *m*-Br congener **7g** gave almost exclusively the 13-Br product **5g**, with only a trace of a less polar isomer, presumably the 15-Br, detectable by MS. Cyclisation of the 4-methoxy lactam **7i** gave only a trace (TLC, MS) of the hexahydrobenzazocine, but an improved yield was obtained from the 3-Br, 4-MeO lactam **7h** as a single isomer. A similar low yield was reported for the $TiCl_4$-mediated cyclisation of 1-(4-methoxyphenylacetyl)-2-methoxypyrrolidine to the pyrrolidino-tetrahydroisoquinoline.[38]

This methodology also works well for phenyl butyramides substituted in the alkyl chain. Cyclisation of the 4,4-diphenylbutyric acid amide gave a good yield of the phenyl-substituted benzazocinone, which from NMR, the isolated product was a mixture of isomers in a ratio of 20:1 (Scheme 4). The major



Scheme 3 Synthesis of the hexahydrobenzazocines **5d–i** *via* the 2-hydroxypyrolidines **7d–i**. *Reagents and conditions*: a) HCl, acetone, b) CF_3SO_3H, $CHCl_3$, heat.



Scheme 4 Synthesis of benzazocine **8**; *Reagents and conditions:* a) $(COCl)_2$, CH_2Cl_2, DMF, b) $H_2N(CH_2)_3CH(OEt)_2$, $EtNMe_2$ (100%), c) CF_3SO_3H, $CHCl_3$, heat (73%).

isomer **8** was isolated as a solid and its structure confirmed by X-ray analysis (Fig. 5), which shows that the phenyl group is in a pseudo-equatorial orientation '*cis*' to the bridgehead C4 proton.

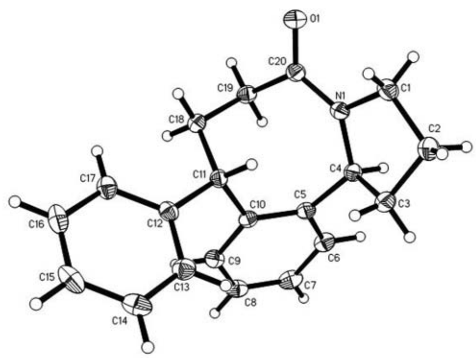


Fig. 5 Structure of hexahydro-benzazocinone **8** as determined by X-ray crystallography. ORTEP diagram (50% probability ellipsoids) showing the crystallographic atom-numbering scheme.

Both the attempted application of this methodology to the synthesis of the 9-membered ring homologue from the 5-phenylpentanoic acid amide **9** and the attempted cyclisation of the 4-phenylbutanoic acid amide of 5-aminopentananal diethylacetal **10** failed to give any cyclised products.

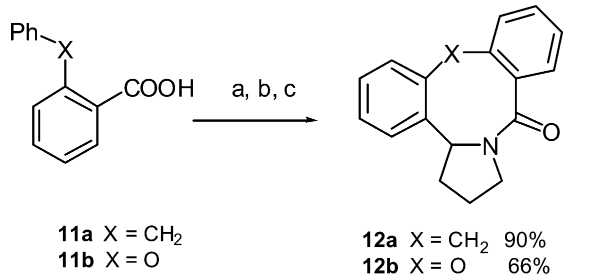
$Ph(CH_2)_4CONH(CH_2)_3CH(OEt)_2$ **9**

$Ph(CH_2)_3CONH(CH_2)_4CH(OEt)_2$ **10**

An alternative system was also evaluated where there is no possibility for the formation of a 6-membered ring (Scheme 5). The commercial α-phenyl-*o*-toluic acid was converted into the 4-aminobutyraldehyde diethylacetal amide derivative *via* the acid chloride. Cyclisation with triflic acid afforded the tetracycle **12a** in an excellent yield. Both the ^1H and ^{13}C NMR spectra were consistent with the proposed structure. The structure of **12a** was confirmed by an X-ray structural analysis (Fig. 6). Cyclisation of the *ortho*-phenoxyamide derived from **11b** also gave the cyclic product **12b**, though in a slightly lower yield.

Although it is well known that acyliminium ions are more electrophilic than iminium ions,[39] for comparison the Pictet–Spengler type cyclisation of the amine **13**, prepared from **4** by reduction with LAH, to **6** was investigated.

$Ph(CH_2)_4NH(CH_2)_3CH(OEt)_2$ **13**



Scheme 5 Synthesis of dibenzoazocines **12a** and **12b**: *Reagents and conditions:* a) $(COCl)_2$, CH_2Cl_2, DMF, b) $H_2N(CH_2)_3CH(OEt)_2$, $EtNMe_2$ (100%), c) CF_3SO_3H, $CHCl_3$, heat.

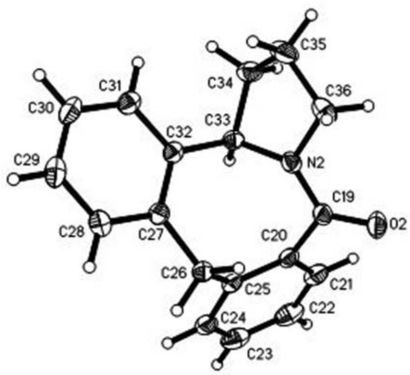


Fig. 6 Structure of hexahydro-dibenzazocinone **12a** as determined by X-ray crystallography. ORTEP diagram (50% probability ellipsoids) showing the crystallographic atom-numbering scheme. There are two independent molecules in the asymmetric unit and only one of these is shown in the figure. The asymmetric unit was selected so that both molecules have the same R-stereochemistry.

No formation of **6** was observed under the acidic conditions of TFA or triflic acid 2 h in refluxing $CHCl_3$, or 2 M aqueous HCl at reflux for 24 h.

Conclusion

In conclusion, we have shown that pyrrolo-benzazocin-3-ones can be readily prepared from the commercially available 4-aminobutyraldehyde diethyl acetal and the appropriate carboxylic acids in moderate to high yield *via* an intramolecular *N*-acyl iminium ion cyclisation. For electron-withdrawing substituents, pre-formation of the 2-hydroxy-pyrrolidine amides gave better yields. Two series of pyrrolo-dibenzazocines were also prepared. This method is not applicable for the synthesis of the 3-aza-benzocyclononanes or the piperidino-benzazocines, nor was the Pictet–Spengler cyclisation successful. Our future work will concentrate on further investigation of the scope of this methodology and on the synthesis of 8-membered analogues of biologically active tetrahydroisoquinolines and benzazepines, and it is our belief that this chemistry will further open up the possibility of 8-membered rings for exploitation in, for example, chemical library synthesis and drug discovery.

Experimental

All reagents were commercially available, unless specified, and used without purification. The chloroform used was stabilised with amylene. All non-crystalline final compounds were found to be >95% pure by HPLC, and all crystalline compounds >98% pure. Solution ^{1}H and ^{13}C NMR spectra (Tables 2, 3 and 4) were recorded on Bruker NMR spectrometers AMX300, Avance III 400, DRX500 and Avance III 600 equipped with z-gradient facilities. ^{1}H and ^{13}C chemical shifts are given relative to TMS. Unless otherwise specified, spectra were recorded at 298 K. The ^{1}H spectra of **5b**, **5c** and **6** were analysed using full lineshape analysis.[40] Low temperature NMR measurements were carried out for hexahydro-benzazocinones **5**, **5b** and **5e**. The value of the free energy of activation for **5** and **5e** was calculated using the procedure described previously.[41]

4-(3-Bromophenyl)-butyric acid

4-(3-Bromophenyl)-4-oxo-butyric acid[42] (4.8 g) and KOH (3.6 g) was dissolved in 35 ml ethylene glycol and hydrazine hydrate (2.4 ml) added. The reaction mixture was heated to reflux (140 °C) for 2 h, then heated to 220 °C (heating block temperature) to distill out the H_2O and excess hydrazine hydrate. After all the distillation had ceased, the reaction mixture was heated for 1 h, the cooled to room temperature, H_2O added (100 ml) and conc. HCl to acidic, then ice (50 g). On scratching with a glass rod, a solid had formed which was collected, dissolved in Et_2O (150 ml) and the product extracted into 1 M NaOH (2 × 50 ml). The aqueous solution was acidified with 2 M HCl and the product extracted into CH_2Cl_2 (3 × 50 ml). The organic extracts were dried (MgSO4) and filter through a SiO_2 bed (~20 g), washing with Et_2O until no more non-polar material was extracted. The combined washings were evaporated *in vacuo* to give 3.1 g of pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (quintet, 2H, $J = 7$ Hz), 2.39 (t, 2H, $J = 7$ Hz), 2.65 (t, 2H, $J = 7$ Hz), 7.10–7.21 (m, 2H), 7.31–7.40 (m, 2H including 7.35, d, 1H, $J = 1.5$ Hz). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 25.6 (CH_2), 33.3 (CH_2), 34.6 (CH_2), 122.5 (C), 127.2 (CH), 129.3 (CH), 130.0 (CH), 133.6 (CH), 143.6 (C), 180.0 (C).

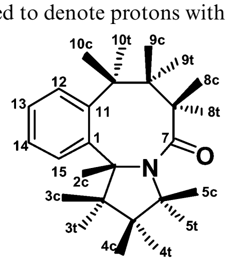
Synthesis of 4-(3-bromo-4-methoxyphenyl)-butyric acid

A solution bromine (0.52 ml, 10 mmol) in $CHCl_3$ (10 ml) was added, drop-wise to a stirred solution of 4-(4-methoxyphenyl)-butyric acid (1.94 g, 10 mmol) in $CHCl_3$ (30 ml) at ambient temperature and the stirring was continued for 1 h. The solvent was removed *in vacuo* and the residue triturated purified by column chromatography on silica, eluting with CH_2Cl_2–10% Et_2O/CH_2Cl_2. and triturated with petrol to give 1.4 g of white solid (50%). Mpt = 78–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (quintet, 2H, $J = 7$ Hz), 2.39 (t, 2H, $J = 7$ Hz), 2.65 (t, 2H, $J = 7$ Hz), 7.10–7.21 (m, 2H), 7.31–7.40 (m, 2H including 7.35, d, 1H, $J = 1.5$ Hz). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 6.2 (CH2), 33.2 (CH2), 33.7 (CH2), 56.3 (CH3), 111.6 (C), 112.0 (CH), 128.4 (CH), 133.3 (CH), 134.9 (C), 154.3 (C), 180.0 (C).

General procedure for the synthesis of the amides

Oxalyl chloride (10 mmol) was added to a stirred solution of the appropriate acid (10 mmol) in DCM (30 mL) and 1–2 drops of

Table 2 ^{1}H NMR chemical shifts (δ_H, ppm) of hexahydrobenzazocinones in $CDCl_3$. The spectrum of **5c** was measured at 298 K, all other spectra were measured at 333 K. The structure shows the proton and carbon numbering used in the NMR assignments in Tables 2–4. The relative orientations of the protons are defined relative to proton H-2c: "c" and "t" are used to denote protons with the *cis* and *trans* orientations relative to proton H-2c



Proton	5	5a	5b	5c	5d	5e	5f	6[a]
2c	5.03	4.98	4.967	5.182	5.00	4.98	5.13	3.746
3c	2.40	2.40	2.412	2.520	2.44	2.42	2.49	2.192
3t	2.07	2.06	2.081	1.719	2.07	2.06	2.17	1.949
4c	1.87	1.86	1.888	1.813	1.90	1.89	1.92	1.832
4t	1.91	1.91	1.960	1.853	1.96	1.95	1.98	1.933
5c	3.87	3.87	3.863	3.838	3.90	3.88	3.94	2.430
5t	3.43	3.44	3.447	3.549	3.44	3.42	3.50	2.974
8c	2.49	2.48	2.508	2.371	2.47	2.44	2.57	1.546
8t	2.26	2.24	2.265	2.106	2.29	2.27	2.32	1.453
9c	1.70	1.66	1.713	1.447	1.70	1.68	1.77	1.662
9t	1.95	1.95	1.935	1.927	1.96	1.95	2.04	1.754
10c	2.66	2.48	2.584	3.207	2.64	2.62	2.73	2.722
10t	2.96	2.92	2.912	2.529	2.95	2.92	3.03	3.593
12	7.05	6.93	6.553	3.747 (OMe)	7.00	6.93	7.15	7.042
13	7.16	6.97	3.833 (OMe)	6.738	7.14	7.27	7.41	7.15
14	7.14	2.29 (Me)	3.836 (OMe)	6.689	—	—	—	7.14
15	7.12	6.92	6.638	3.747 (OMe)	7.13	7.26	7.36	7.13

[a] 2.590 ppm (H-7c) and 2.611 ppm (H-7t).

Table 3 Proton *J*-couplings (in Hz) of hexahydrobenzazocinones **5–5f** and **6** in $CDCl_3$. The spectrum of **5c** was measured at 298 K, all other spectra were measured at 333 K

Protons	5	5a	5b	5c	5d	5e	5f	6
2c–3c	7.1	7.1	6.99	6.15	7.1	7.1	7.1	7.55
2c–3t	7.1	7.1	6.98	9.69	7.1	7.1	7.1	7.74
3c–3t	−12.7	−12.7	−12.80	−12.57	−12.7	−12.9	−12.7	−12.87
3c–4t	5.1	5.0	5.29	3.29	5.2	5.1	5.0	5.29
3c–4c	7.6	7.5	7.58	6.51	7.5	7.4	7.5	10.06
3t–4c	8.7	8.7	8.41	10.81	8.5	8.7	8.6	5.83
3t–4t	7.3	7.2	7.25	6.68	7.0	7.1	7.0	10.72
4c–4t	−12.6	−12.5	−12.63	−12.41	−12.7	−12.6	−12.6	−12.54
4c–5c	8.6	8.5	8.42	8.65	8.4	8.4	8.5	8.63
4c–5t	8.1	8.1	8.12	9.06	7.9	8.2	8.3	3.74
4t–5c	4.1	4.2	4.41	3.44	4.3	4.2	4.3	7.68
4t–5t	8.1	8.1	7.85	7.45	7.9	8.0	8.1	8.38
5c–5t	−12.2	−12.2	−12.17	−12.21	−12.2	−12.1	−12.2	−9.14
8c–8t	−12.4	−12.3	−12.32	−11.88	−12.5	−12.5	−12.4	−15.00
8c–9c	4.8	4.9	4.79	5.38	4.8	4.7	4.9	11.97
8c–9t	12.8	12.8	12.72	13.27	12.7	12.8	12.8	3.34
8t–9c	4.2	4.1	4.03	2.61	4.1	4.0	4.1	3.35
8t–9t	4.2	4.0	4.18	4.47	4.1	3.9	4.1	5.37
9c–9t	−13.0	−12.8	−13.41	−13.06	−12.8	−12.8	−12.8	−13.62
9c–10c	4.0	4.9	3.71	3.90	3.8	3.9	3.9	6.71
9c–10t	11.7	11.9	11.82	13.55	11.8	11.9	11.9	5.31
9t–10c	5.0	4.9	5.04	3.04	5.0	5.0	4.7	5.32
9t–10t	3.9	3.9	3.80	4.09	3.9	3.9	3.9	8.85
10c–10t	−13.8	−13.8	−13.96	−13.29	−13.9	−13.9	−13.8	−12.82
Other	—	7.8 (12–13), 1.7 (13,15)	—	8.94 (13–14)	~8 (12–13), 2.2 (13,15)	~8 (12–13), 2.1 (13,15)	7.9 (12–13), 2.0 (13,15)	−12.57 (7c–7t), 3.09 (7c–8c), 5.27 (7c–8t), 0.85 (7c–9t), 11.28 (7t–8c), 3.13 (7t–8t)

Table 4 ^{13}C NMR chemical shifts (δ_C, ppm) of hexahydrobenzazocinones **5–5f** and **6** in $CDCl_3$. The spectrum of **5c** was measured at 298 K, all other spectra were measured at 333 K. The values of $^1J_{CH}$ couplings (in Hz) are also included in brackets for **5c**

Carbon	5	5a	5b	5c	5d	5e	5f	6
1-C_q	140.54	140.35	132.75	130.09	142.38	142.85	140.90	141.08
2-CH	62.80	62.93	62.53	59.44 (145)	62.35	62.40	63.11	65.65
3-CH_2	36.83	37.12	36.91	36.09 (134)	36.78	36.99	37.33	34.16
4-CH_2	22.75	22.77	22.80	22.50 (131)	22.66	22.77	22.92	22.71
5-CH_2	45.94	46.01	46.04	46.81 (143)	45.93	46.08	46.15	55.30
7	172.48	172.50	172.61	172.71	172.22	172.32	172.65	54.01
8-CH_2	33.81	33.67	33.91	32.26 (131)	33.59	33.63	33.80	24.67
9-CH_2	27.37	27.60	27.61	25.74 (132)	27.22	27.25	27.52	30.17
10-CH_2	32.62	32.03	32.22	21.01 (131)	31.93	32.06	32.32	32.98
11-C_q	138.16	135.01	130.96	127.48	136.60	137.18	137.25	140.19
12	131.49	131.46	115.20	151.02	132.81	133.22	132.17	130.50
13	126.57	128.31	148.66	109.47 (159)	127.58	130.67	126.38	125.92
14	127.61	135.97	147.89	108.31 (159)	132.29	120.29	141.04	126.86
15	126.90	127.63	111.61	150.19	126.91	129.95	125.84	127.13
Other	—	20.97 (14-Me)	56.54 (13-OMe), 56.24 (14-OMe)	56.21(143) (12-OMe), 55.75 (143) (15-OMe)	—	—	139.78 (*i*-Ph), 127.13 (*o*-Ph), 128.96 (*m*-Ph), 127.50 (*p*-Ph)	

DMF were added. After stirring at ambient temperatures for 2 h, by which time gas evolution had ceased, the solvent was removed by rotary evaporation *in vacuo.* The crude acid chloride was re-dissolved in DCM (20 mL) and was added, dropwise, to a stirred, cooled (0 °C) solution of 4-aminobutyraldehyde diethyl acetal (10 mmol) and Et_2NMe (12 mmol) in Et_2O (50 mL) over 5 min. The stirred reaction mixture was warmed to room temperature over 1 h. A 1 M aqueous solution of $NaHCO_3$ (30 mL) was then added and the mixture transferred to s separating funnel, shaken then allowed to settle. The lower aqueous layer was separated and the organic layer washed with brine (30 mL). The organic layer was collected, dried (K_2CO_3), filtered and the filtrate concentrated *in vacuo*, then dried under high vacuum to give the essentially pure amides (>98% by HPLC) which were used without further purification.

2-Biphenyl-2-yl-*N*-(4,4-diethoxybutyl)acetamide (1). Isolated as an oil (95% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, 6H, $J = 7$ Hz), 1.40–1.56 (m, 4H), 3.16 (dt, 2H, $J = 7, 13$ Hz), 3,37–3.66 (m, 4H), 3.52 (s, 2H), 4.42 (t, 1H, $J = 5$ Hz), 5.35 (brs, 1H), 7.24–7.48 (m, 9H): ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 24.6 (CH_2), 30.8 (CH_2), 39.3 (CH_2), 41.4 (CH_2), 61.3 (CH_2), 102.5 (CH), 127.3 (CH), 127.4 (CH), 128.0 (CH), 129.1 (CH), 130.5 (CH), 130.7 (CH), 132.5 (C), 140.9 (C), 142.6 (C), 170.9 (C).

***N*-(4,4-Diethoxybutyl)-4-phenyl-butyramide (4).** Isolated as an oil (100% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, 6H, *J* = 6 Hz), 1.48–1.66 (m, 4H), 1.94 (quintet, 2H, *J* = 7 Hz), 2.13 (t, 2H, *J* = 7 Hz), 2.62 (t, 2H, *J* = 7 Hz), 3.22 (quartet, 2H, *J* = 6 Hz), 3.39–3.52 (m, 2H), 3.56–3.68 (m, 2H), 4.45 (t, 1H, *J* = 5.5 Hz), 5.82 (brs, 1H), 7.10–7.20 (m, 3H), 7.21–7.29 (m, 2H): ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 24.6 (CH_2), 27.2 (CH_2), 31.1 (CH_2), 35.2 (CH_2), 36.0 (CH_2), 39.2 (CH_2),61.5 (CH_2), 102.7 (CH), 125.9 (CH), 128.4 (CH), 128.5 (CH), 141.5 (C), 172.7 (C).

***N*-(4,4-Diethoxybutyl)-4-(4-methylphenyl)-butyramide (4a).** Isolated as an oil (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, 6H, *J* = 7 Hz), 1.53–1.70 (m, 4H), 1.93 (quin., 2H, *J* = 8 Hz), 2.14 (t, 2H, *J* = 8 Hz), 2.31 (s, 3H), 2.60 (t, 2H, *J* = 8 Hz), 3.24 (quartet, 2H, *J* = 6 Hz), 3.43–3.55 (m, 2H), 3.57–3.70 (m, 2H), 4.47 (t, 1H, *J* = 5.5 Hz), 5.62 (brs, 1H), 7.04 (d, 2H, *J* = 5.5 Hz), 7.08 (d, 2H, *J* = 5.5 Hz): ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 21.0 (CH_3), 24.6 (CH_2), 27.3 (CH_2), 31.1 (CH_2), 34.8 (CH_2), 36.0 (CH_2), 39.2 (CH_2), 61.5 (CH_2), 102.7 (CH), 128.4 (CH), 129.1 (CH), 135.4 (C), 138.4 (C), 172.7 (C).

***N*-(4,4-Diethoxybutyl)-4-(3,4-dimethoxy)phenyl-butyramide (4b).** Isolated as an oil (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.22 (m, 6H), 1.45–1.66 (m, 4H), 1.81–1.99 (m, 2H), 2.06–2.19 (m, 2H), 2.46–2.62 (m, 2H), 3.15–3.30 (m, 2H), 3.35–3.50 (m, 2H), 3.51–3.66 (m, 2H), 3.77–3.88 (m, 6H), 4.36–3.49 (m, 1H), 5.63–5.91 (brs, 1H), 6.59–6.80 (m, 3H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 24.6 (CH_2), 27.4 (CH_2), 31.1 (CH_2), 34.8 (CH_2), 35.9 (CH_2), 39.2 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 61.5 (CH_2), 102.7 (CH), 111.2 (CH), 111.8 (CH), 120.3 (CH), 134.2 (C), 147.2 (C), 148.8 (C), 172.7 (C).

***N*-(4,4-Diethoxybutyl)-4-(2,5-dimethoxy)phenyl-butyramide (4c).** Isolated as an oil (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, 6H, J = 7 Hz), 1.52–1.66 (m, 4H), 1.89 (quintet, 2H, J = 7.5 Hz), 2.16 (t, 2H, J = 7.5 Hz), 2.60 (t, 2H, J = 7.5 Hz), 3.24 (q, 2H, J = 6 Hz), 3.43–3.50 (m, 2H), 3.58–3.75 (m, 2H), 3.73 (s, 3H), 3.75 (s, 3H), 4.45 (t, 1H, J = 5.5 Hz), 5.75 (brs, 1H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.38 (CH_3), 24.75 (CH_2), 25.96 (CH_2), 29.82 (CH_2), 31.14 (CH_2), 36.29 (CH_2), 39.27 (CH_2), 55.72 (CH_3), 56.00 (CH_3), 61.48 (CH_2), 102.74 (CH), 111.26 (CH), 111.38 (CH), 116.42 (CH), 131.26 (C), 151.80 (C), 153.57 (C), 172.93 (C).

***N*-(4,4-Diethoxybutyl)-4-(4-chlorophenyl)-butyramide (4d).** Isolated as an oil (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, 6H, J = 7 Hz), 1.45–1.66 (m, 4H), 1.81–1.99 (m, 2H), 2.12 (t, 2H J = 7 Hz), 2.59 (t, 2H, J = 7 Hz), 3.25 (qt, 2H, J = 6.5 Hz), 3.38–3.53 (m, 2H), 3.56–3.68 (m, 2H), 4.44 (t, 1H, J = 7.5 Hz), 5.68 (brs, 1H), 7.08 (d, 2H, J = 8 Hz), 7.22 (d, 2H, J = 8 Hz). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 24.6 (CH_2), 27.0 (CH_2), 31.1 (CH_2), 34.5 (CH_2), 35.7 (CH_2), 39.2 (CH_2), 61.5 (CH_2), 102.7 (CH), 128.4 (CH), 129.8 (CH), 131.6 (C), 140.0 (C), 172.4 (C).

***N*-(4,4-Diethoxybutyl)-4-(4-bromophenyl)-butyramide (4e).** Isolated as an oil (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, 6H, J = 7 Hz), 1.49–1.67 (m, 4H), 1.90 (quin, 2H, J = 7 Hz), 2.11 (t, 2H, J = 7 Hz), 2.57 (t, 2H, J = 7.5 Hz), 3.22 (quartet, 2H, J = 6.5 Hz), 3.39–3.52 (m, 2H), 3.56–3.69 (m, 2H), 4.45 (t, 1H, J = 5 Hz), 5.91 (brs, 1H), 7.02 (d, 2H, J = 8 Hz), 7.36 (d, 2H, J = 8 Hz). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 24.6 (CH_2), 26.9 (CH_2), 31.1 (CH_2), 34.6 (CH_2), 35.7 (CH_2), 39.2 (CH_2), 61.5 (CH_2), 102.7 (CH), 119.7 (C), 130.2 (CH), 131.4 (CH), 140.5 (C), 172.4 (C).

***N*-(4,4-Diethoxybutyl)-4-(4-biphenyl)-butyramide (4f).** Isolated as an oil (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (t, 6H, J = 7 Hz), 1.45–1.66 (m, 4H), 1.99 (quintet, 2H, J = 7 Hz), 2.18 (t, 2H, J = 7 Hz), 2.68 (t, 2H J = 7 Hz), 3.25 (quartet, 2H, J = 6.5 Hz), 3.38–3.53 (m, 2H), 3.56–3.68 (m, 2H), 4.49 (t, 1H, J = 7.5 Hz), 5.83 (brs, 1H), 7.19–7.59 (m, 9H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.4 (CH3), 24.6 (CH_2), 27.1 (CH_2), 31.1 (CH_2), 34.9 (CH_2), 36.0 (CH_2), 39.3 (CH_2), 61.5 (CH_2), 102.7 (CH), 127.0 (CH), 127.1 (CH), 128.7 (CH), 128.9 (CH), 138.9 (C), 140.7 (C), 141.0 (C), 172.7 (C).

***N*-(4,4-Diethoxybutyl)-4-(3-bromophenyl)-butyramide (4g).** Isolated as an oil (100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.18 (t, 6H, J = 7 Hz), 1.49–1.67 (m, 4H), 1.92 (quin, 2H, J = 7 Hz), 2.13 (t, 2H, J = 7 Hz), 2.60 (t, 2H, J = 7.5 Hz), 3.24 (quartet, 2H, J = 6.5 Hz), 3.39–3.52 (m, 2H), 3.56–3.69 (m, 2H), 4.46 (t, 1H, J = 5 Hz), 5.69 (brs, 1H), 7.08–7.16 (m, 2H), 7.26–7.33 (m, 2H): ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 24.6 (CH_2), 26.9 (CH_2), 31.1 (CH_2), 34.9 (CH_2), 35.7 (CH_2), 39.2 (CH_2), 61.5 (CH_2), 102.7 (CH), 122.4 (C), 127.2 (CH), 129.1 (CH), 130.0 (CH), 131.5 (CH), 143.9 (C), 172.3 (C).

***N*-(4,4-Diethoxybutyl)-4-(3-bromo-4-methoxyphenyl)-butyramide (4h).** Isolated as an oil (100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.16 (t, 6H, J = 7 Hz), 1.51–1.65 (m, 4H), 1.88 (quin, 2H, J = 7 Hz), 2.11 (t, 2H, J = 7 Hz), 2.53 (t, 2H, J = 7.5 Hz), 3.24 (quartet, 2H, J = 6.5 Hz), 3.40–3.49 (m, 2H), 3.55–3.64 (m, 2H), 3.83 (s, 3H), 4.45 (t, 1H, J = 5 Hz), 5.76 (brs, 1H), 6.78 (d, 1H, J = 8.5 Hz), 7.04 (dd, 1H, J = 8.5, 2.0 Hz), 7.32 (d, 1H, J = 2.0 Hz).: ^{13}C NMR and DEPT (125 MHz, $CDCl_3$) δ = 15.38 (CH3), 24.62 (CH2), 27.23 (CH2), 31.13 (CH2), 34.00 (CH2), 35.80 (CH2), 39.28 (CH2), 56.33 (CH3), 61.56 (CH2), 102.73 (CH), 111.45 (C), 112.02 (CH), 128.46 (CH), 135.31 (CH), 135.31 (C), 154.17 (C), 172.58 (C).

***N*-(4,4-Diethoxybutyl)-4-(4-methoxyphenyl)-butyramide (4i).** Isolated as an oil (100%) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, 6H, *J* = 7 Hz), 1.45–1.66 (m, 4H), 1.89 (quintet, 2H, *J* = 7 Hz), 2.12 (t, 2H *J* = 7 Hz), 2.55 (t, 2H, *J* = 7 Hz), 3.22 (quartet, 2H, *J* = 6 Hz), 3.38–3.53 (m, 2H), 3.56–3.68 (m, 2H), 3.75 (s, 3H), 4.45 (t, 1H, *J* = 5 Hz), 5.79 (brs, 1H), 6.79 (d, 2H, *J* = 8 Hz), 7.06 (d, 2H, *J* = 8 Hz); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 24.6 (CH_2), 27.4 (CH_2), 31.1 (CH_2), 34.3 (CH_2), 35.9 (CH_2), 39.2 (CH_2), 55.3 (CH_3), 61.5 (CH_2), 102.7 (CH), 113.8 (CH), 129.4 (CH), 133.6 (C), 157.8 (C), 172.8 (C).

***N*-(4,4-Diethoxybutyl)-4,4-diphenyl-butyramide.** Isolated as an oil (88%) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, 6H, *J* = 7 Hz), 1.45–1.66 (m, 4H), 2.07 (t, 2H, *J* = 7 Hz_), 2.39 (qu, 2H, *J* = 7 Hz), 3.21 (quartet, 2H, *J* = 6.5 Hz), 3.38–3.53 (m, 2H), 3.56–3.68 (m, 2H), 3.91 (t, 1H, *J* = 8 Hz), 4.46 (t, 1H, *J* = 7.5 Hz), 5.57 (brs, 1H), 7.10–7.32 (m, 10H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 15.3 (CH_3), 24.6 (CH), 31.1 (CH_2), 31.2

(CH_2), 35.0 (CH_2), 39.2 (CH_2), 50.6 (CH), 61.4 (CH_2), 102.7 (CH), 126.3 (CH), 127.9 (CH), 128.5 (CH), 144.3 (C), 172.4 (C).

5-Phenyl-pentanoic acid (3,3-diethoxybutyl)-amide (9). Isolated as an oil (95%): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$ (t, 6H, $J = 7$ Hz), 1.50–1.73 (m, 8 H), 2.15 (t, 2H, $J = 7$ Hz), 2.61 (t, 2H, $J = 7$ Hz), 3.23 (q, 2H, $J = 6$ Hz), 3.40–3.53 (m, 2H), 3.55–3.69 (m, 2H), 4.46 (t, 1H, $J = 5$ Hz), 5.71 (brs, 1H), 7.12–7.19 (m, 3H), 7.22–7.27 (m, 2H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) $\delta = 15.3$ (CH_3), 24.6 (CH_2), 25.4 (CH_2), 31.1 (CH_2), 35.7 (CH_2), 36.7 (CH_2), 39.2 (CH_2), 61.5 (CH_2), 102.7 (CH), 125.7 (CH), 128.3 (CH), 128.4 (CH), 142.2 (C), 172.8 (C).

***N*-(5,5-Diethoxypentyl)-4-phenyl-butyramide (10).** Isolated as an oil (100%) ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$ (t, 6H, J = 7 Hz), 1.32–1.67 (m, 6H), 1.95 (quintet, 2H, J = 7.4 Hz), 2.15 (t, 2H, J = 7.4 Hz), 2.64 (t, 2H, J = 7.4 Hz), 3.22 (q, 2H, J = 6 Hz), 3.40–3.55 (m, 2H), 3.56–3.71 (m, 2H), 4.45 (t, 1H, J = 5.6 Hz), 5.50 (brs, 1H), 7.13–7.23 (m, 3H), 7.24–7.31 (m, 2H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) $\delta = 15.3$ (CH_3), 22.1 (CH_2), 27.2 (CH_2), 29.5 (CH_2), 33.3 (CH_2), 35.2 (CH_2), 36.0 (CH_2), 39.4 (CH_2), 61.1 (CH_2), 102.8 (CH), 125.9 (CH), 128.4 (CH), 128.5 (CH), 141.5 (C), 172.6 (C).

2-Benzyl-*N*-(4,4-diethoxybutyl)benzamide (11a). Isolated as an oil (100%) ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.16$ (t, 6H, J = 7 Hz), 1.45–1.65 (m, 4H), 3.30 (q, 2H, J = 6 Hz), 3.35–3.50 (m, 2H), 3.53–3.68 (m, 2H), 4.17 (s, 2H), 4.43 (t, 1H, J = 5.3 Hz), 5.90 (brs, 1H), 7.07–7.37 (m, 9H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) $\delta = 15.3$ (CH_3), 24.4 (CH_2), 31.1 (CH_2), 38.9 (CH_2), 39.6 (CH_2), 61.4 (CH_2), 102.6 (CH), 126.0 (CH), 126.3 (CH), 127.1 (CH), 128.4 (CH), 129.0 (CH), 130.9 (CH), 137.0 (C), 138.8 (C), 140.9 (C), 170.0 (C).

***N*-(4,4-Diethoxybutyl)-2-phenoxybenzamide (11b).** Isolated as an oil (95%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.13$ (t, 3H, J = 7 Hz), 1.14 (t, 3H, J = 7 Hz), 1.53–1.67 (m, 4H), 3.30–3.61 (m, 6H), 4.41–4.40 (m, 1H), 6.80 (dd, 1H, J = 8.2, 1.7 Hz), 7.00–7.04 (m, 2H), 7.13–7.20 (m, 2H), 7.29–7.41 (m, 3H), 7.69 (brs, 1H), 8.20 (dt, 1H, J = 7.8, 1.5 Hz). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) $\delta = 15.3$ (CH_3), 24.7 (CH_2), 30.9 (CH_2), 39.5 (CH_2), 61.1 (CH_2), 102.5 (CH), 118.4 (CH), 119.4 (CH), 123.7 (CH), 124.3 (C), 124.6 (CH), 130.1 (CH), 132.2 (CH), 132.5 (CH), 155.3 (C), 155.6 (C), 164.7 (C).

General procedure for the synthesis of the 2-hydroxypyrrolidino-lactams 7d–h

A solution of the 4,4-diethoxybutyl butyramide (3 mmol) in acetone (50 ml) and 1 M HCl (12 ml) was allowed to stand at room temperature for 30 min., by which time TLC showed no starting material remaining. The reaction mixture was basified with 1 M $NaHCO_3$ solution (30 ml) and the acetone removed under reduced pressure on a rotary evaporator. The product was extracted from the aqueous residue with CH_2Cl_2 (3 × 50 ml). The combined organic extracts were dried (K_2CO_3), filtered and evaporated to give the 2-hydroxypyrrolidino-lactam, used without further purification. NMR analysis showed them to be a complex mixture of ~20% aldehyde and amide rotomers.

General procedure for the triflic acid-mediated cyclisation

A solution of the acetal (5 mmol) in chloroform (10 mL) was added over 10 min to a heated (65 °C), stirred mixture of triflic acid (50 mmol) in chloroform (40 mL). The reaction was heated under gentle reflux for a given period. On cooling to ambient temperatures, water (20 ml) was added. The reaction mixture was transferred to a separating funnel and the lower layer separated. The aqueous layer was extracted with DCM (50 ml) and the combined organic extracts dried (K_2CO_3). Filtration and evaporation *in vacuo* gave the crude products that were separated by column chromatography on silica.

7-Phenyl-2,3,6,10b-tetrahydro-1*H*-pyrrolo[2,1-*a*]isoquinolin-5-one (2). Reaction heated to reflux for 3 h, purified by elution with 1:1 CH_2Cl_2/Et_2O to 2%MeOH/Et_2O and fraction 2 isolated as a solid from trituration with Et_2O (64%): mpt 157–9 °C. HRMS Theoretical Mass: 263.12551, found: 263.12589. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.91$–2.25 (m, 3H), 2.61–2.79 (m, 1H), 3.41–3.55 (m, 2H), 3.63 (d, 1H, J = 18 Hz), 3.66–3.77 (m, 1H), 4.63–4.77 (m, 1H), 7.15–7.45 (m, 8H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): $\delta = 23.4$ (CH_2), 31.7 (CH_2), 37.0 (CH_2), 44.8 (CH_2), 59.7 (CH), 123.2 (CH), 126.6 (CH), 127.4 (CH), 128.4 (CH), 129.1 (CH), 129.2 (CH), 130.8 (C), 136.8 (C), 140.2 (C), 140.9 (C), 167.7 (C).

1,2,3,6,10b-Pentahydro-1*H*-pyrrolo[2,1-*a*]-dibenzo[*c*,*e*]azocin-5-one (3). Reaction heated to reflux for 3 h, purified by elution with 1:1 CH_2Cl_2/Et_2O to 2%MeOH/Et_2O and as fraction 1 isolated as an oil (29%). HRMS Theoretical Mass: 263.12551: found: 263.12567. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.66$–1.86 (m, 1H), 1.98–2.20 (m, 2H), 2.35–2.50 (m, 1H), 3.12 (d, 1H, $J = 15$ Hz), 3.57 (d, 1H, $J = 15$ Hz), 3.60–3.80 (m, 2H), 4.27 (t, 1H, $J = 8$ Hz), 7.25–7.55 (m, 8H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): $\delta =$ 23.4 (CH_2), 33.6 (CH_2), 43.3 (CH_2), 48.4 (CH_2), 53.5 (CH_2), 56.7 (CH), 126.0 (CH), 127.5 (CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 130.0 (CH), 132.6 (C), 137.1 (C), 141.2 (C), 142.6 (C), 168.7 (C).

6-Aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-7-one (5). Reaction heated to reflux for 4 h, purified by elution with Et_2O-2% MeOH/Et_2O, isolated as an oil (70% yield). HRMS theoretical 215.13047, found 215.13000: FTIR (film) 2947, 2873, 1624, 1455, 1420, 754 cm^{-1}.

14-Methyl-6-aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-7-one (5a). Reaction heated to reflux for 4 h, purified by elution with Et_2O-2% MeOH/Et_2O, isolated as an oil (70% yield). HRMS Theoretical Mass: 229.14611, found 229.14545.

13,14-Dimethoxy-6-aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-7-one (5b). From the acetal at reflux for 1 h, purified by elution with Et_2O-2% MeOH/Et_2O, isolated as a white solid, recrystallised from EtOAc/petrol (80% yield), m. pt. 116–7 °C. HRMS Theoretical Mass: 275.15160, found 275.15154.

12,15-Dimethoxy-6-aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-7-one (5c). Isolated from the acetal at room temperature for 21 h, purified by elution with Et_2O-2% MeOH/Et_2O, isolated as a white solid, recrystallized from EtOAc/petrol (26% yield), m. pt. 126–7 °C. HRMS Theoretical Mass: 275.15160, found 275.15102. FTIR (solid) 1634, 1471, 1417, 1252, 1141, 1090, 784, 718 cm^{-1}.

14-Chloro-6-aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-7-one (5d). Prepared from the 2-hydroxypyrrolidine, heated to reflux for 18 h, purified by elution with Et_2O-2% MeOH/Et_2O, isolated as an oil (59% yield). HRMS: Theoretical Mass: 249.09149, found 249.09081.

14-Bromo-6-aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-7-one (5e). Prepared from the 2-hydroxypyrrolidine, heated to reflux for 18 h, purified by elution with Et_2O-2% MeOH/Et_2O, isolated as an oil (55% yield). HRMS Theoretical Mass: 293.04098, found 293.03969.

14-Phenyl-6-aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-7-one (5f). Prepared from the 2-hydroxypyrrolidine, heated to reflux for 18 h, purified by elution with Et_2O-2% MeOH/Et_2O, isolated as an oil (45% yield). HRMS Theoretical Mass: 291.16177; found: 291.16191.

13-Bromo-6-aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-7-one (5g). From the 2-hydroxypyrrolidine, heated to reflux for 18 h, purified by elution with Et_2O-4% MeOH/Et_2O, isolated as white solid (Et_2O/petrol) (60% yield). HRMS Theoretical Mass: 293.04098: found 293.04037. ^{1}H NMR (500 MHz, $CDCl_3$) at 332 K: δ = 1.68–1.80 (brm, H-9), 1.87–2.11 (m, H-3,4,4,9), 2.26–2.35 (brm, H-8), 2.40–2.52 (m, H-3, 8), 2.61–2.70 (brm, H-10), 2.96 (ddd, H-10, J = 3.8, 11.9, 13.8 Hz), 3.40–3.50 (brm, H-5), 3.90 (ddd, H-5, J = 4.1, 8.6, 12.4 Hz), 5.01 (t, H-2, J = 7 Hz), 7.02 (d, H-15, J = 8.3 Hz), 7.25 (d, H-12, J = 2.2 Hz), 7.32 (dd, H-14, J = 2.2, 8.3 Hz). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$) at 332 K: δ = 22.60, 26.99, 32.22, 33.48, 36.79, 45.88, 62.34 (2-C), 120.99 (C-13), 128.54 (C-15), 129.50 (C-14), 134.01 (C-12), 139.54 (C-1), 140.27 (C-11), 172.14 (C-7).

13-Bromo-14-methoxy-6-aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-7-one (5h). Isolated from the acetal at reflux for 1 h, purified by elution with Et_2O-2% MeOH/Et_2O, isolated as a white solid, recrystallized from EtOAc/petrol (80% yield), m. pt. 116–7 °C. HRMS Theoretical Mass: 323.05154, found 323.05138. ^{1}H NMR (600 MHz, $CDCl_3$) at 331 K: δ = 1.64–1.77 (brm, 1H), 1.87–2.03 (m, 3H), 2.04–2.13 (m, 1H), 2.26–2.34 (brm, 1H), 2.41–2.52 (m, 2H), 2.54–2.2 (brm, 1H), 2.89 (ddd, 1H, J = 3.8, 12.1, 14 Hz), 3.46 (dt, 1H, J = 8.0, 12.0 Hz), 3.86 (s, 3H), 3.89 (ddd, 1H-5, *J* = 12.1, 8.6, 4.2 Hz), 5.00 (t, 1H, J = 7.1 Hz), 6.66 (s, 1H), 7.26 (s, 1H). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$) at 333 K: δ = 22.86 (CH_2), 27.62 (CH_2), 31.24 (CH_2), 33.43 (CH_2), 46.30 (CH_2), 56.61 (CH_3), 63.01 (CH), 110.68 (C), 111.19 (CH), 131.89 (C), 136.06 (CH), 141.04 (C), 154.65 (C), 172.69 (C).

6-Aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(15),11,13-triene (6). A solution of 6-aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-7-one (0.9 g, 4.2 mmol) in dry THF (5 ml) was added, drop-wise, to a stirred solution of 1 M $LiAlH_4$ (4.2 ml, 4.2 mmol) in dry THF (20 ml) and the reaction mixture heated to reflux for 2 h. On cooling to 0 °C, 2 M NaOH (0.6 ml) was carefully added, drop-wise, the reaction mixture stirred for 30 min. and then Et_2O (50 ml) was added. The white solid was removed, washed with Et_2O (2 × 50 ml) and the combined organics dried (K_2CO_3), filtered and concentrated *in vacuo* to give the title compound as an oil (0.8 g, 88% yield). HRMS Theoretical Mass: 201.15120, found 201.15131. Attempts to form an HCl salt resulted in a sticky, hygroscopic gum. A sample was treated with 1 equivalent of picric acid (35% water) in ethanol to give the picrate, (m pt 162–4 °C).

(2*R*,10*R*)(2*S*,10*S*)-10-Phenyl-6-aza-tricyclo[9.4.0.0*2,6*] pentadeca-1(15),11,13-triene-7-one (8). From the acetal at reflux for 3 h, purified by elution with Et_2O and the solid triturated with petrol (73%), a small sample was re-crystallized from CH_2Cl_2/petrol, m. pt. 162–4 °C. ^{1}H NMR (500 MHz, $CDCl_3$) at 332 K: δ = 1.75–2.60 (m, 7H), 3.60–3.79 (m, 1H), 3.87 (dt, 1H, J = 9.5, 2.4 Hz), 4.53 (dd, 1H, J = 12.3, 3.2 Hz), 4.93 (dd, 1H, J = 10.9, 5.1 Hz), 6.71 (d, 1H, J = 6.8 Hz), 7.05–7.45 (m, 8H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$) at 332 K: δ = 22.4 (CH_2), 31.2 (CH_2), 32.7 (CH_2), 39.5 (CH_2), 43.3 (CH), 46.9 (CH_2), 65.8 (CH), 126.5 (CH), 126.6 (CH), 127.7 (CH), 127.9 (CH), 128.5 (CH), 128.7 (CH), 129.2 (CH), 138.9 (C), 141.0 (C), 142.9 (C), 172.3 (C).

4b,5,6,7-Tetrahydro-14H-dibenzo[*c*,*f*]pyrrolo[1,2-*a*]azocin-9-one (12a). From the acetal at reflux for 3 h, purified by elution with CH_2Cl_2–20% Et_2O/CH_2Cl_2, isolated as a white solid, recrystallised from EtOAc/petrol (95% yield), m. pt. 127–9 °C. HRMS Theoretical Mass: 263.13046, found 263. 12983. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.80–2.17 (m, 3H), 2.55–2.71 (m, 1H), 3.23–3.30 (m, 1H), 3.79 (d, 1H *J* = 14.5 Hz), 3.99–4.13 (m, 1H), 4.3 (d, 1H, *J* = 14.5 Hz), 4.67 (d, 1H, *J* = 5.5 Hz), 7.12–7.41 (m, 7H), 7.52 (dd, 1H, *J* = 7, 1 Hz). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ = 23.0 (CH_2), 29.0 (CH_2), 41.0 (CH_2), 44.4 (CH_2), 60.6 (CH), 125.2 (CH), 125.6 (CH), 127.1 (CH), 127.2 (CH), 127.9 (CH), 129.6 (CH), 130.6 (CH), 131.2 (CH), 134.9 (C), 136.4 (C), 138.0 (C), 139.2 (C), 171.0 (C).

4b,5,6,7-Tetrahydro-14-oxa-dibenzo[*c*,*f*]pyrrolo[1,2-*a*]azocin-9-one (12b). From the acetal at reflux for 2 h, purified by elution with CH_2Cl_2–10% Et_2O/CH_2Cl_2, (66% yield), m. pt. 144–6 °C. HRMS Theoretical Mass: 265.10973, found 265.10973. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.85–1.96 (m, 6–1H), 1.96–2.04 (m, 5–1H), 2.04–2.10 (m, 6–1H), 2.62 (dd, 5–1H, J = 5.3, 12.8 Hz), 3.40–3.48 (m, 7–1H), 3.87–3.95 (m, 7–1H), 4.72 (d, 4d-1H, J = 6.8 Hz), 7.10–7.16 (m, 2H), 7.22 (d, 1H, J = 7.9 Hz), 7.27 (t, 1H, J = 7.9 Hz), 7.32–7.48 (m, 2H), 7.42 (dt, 1H, J = 7.9, 1.2 Hz), 7.58 (dd, 1H, J = 7.6, 1.2 Hz). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$): δ = 23.18 (6-CH_2), 28.75 (5-CH_2), 45.17 (7-CH_2), 58.79 (4b-CH), 122.57 (CH), 122.74 (CH), 124.71 (CH), 125.99 (CH), 126.29 (CH), 127.52 (CH), 129.22 (C), 129.50 (CH), 132.23 (CH), 132.61 (C), 152.82 (C), 157.63 (C), 168.08 (C).

(4,4-Diethoxy-butyl)-(4-phenyl-butyl)-amine (13). A solution of the amide **4** (2.0 g, 6.5 mmol) in dry THF (20 ml) was added to a stirred solution of 1 M LAH (30 ml, 30 mmol) in THF (30 ml) under argon at 0 °C and the reaction was heat under gentle reflux for 24 h. The reaction mixture was cooled to 0 °C and H_2O (1 ml), then 2 M NaOH (2 ml) were carefully add and the reaction mixture stirred until a white solid formed. Et_2O (50 ml) was then addded, the solid collected which was thoroughly washed with Et_2O (4 × 25 ml). The combined organic filtrate and washings were dried (K_2CO_3), filter and concentrate *in vacuo* to give a colourless oil: 1.9 g (~100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (t, 6H, J = 7 Hz), 1.50–1.57 (m, 4H), 1.61–1.70 (m, 4H), 2.58–2.65 (m, 6H), 3.45–3.54 (m, 2H), 3.59–3.67 (m, 2H), 4.48 (t, 1H, J = 5.7 Hz), 7.14–7.18 (m, 3H), 7.24–7.28 (m, 2H); ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 15.41 (CH_3), 25.51 (CH_2), 29.32 (CH_2), 29.83 (CH_2), 31.54 (CH_2), 35.92 (CH_2), 49.89 (CH_2), 49.94 (CH_2), 61.06 (CH_2), 61.16 (CH_2), 102.90 (CH), 125.74 (CH), 128.40 (CH), 128.53 (CH), 142.56 (CH).

Crystal data and structure refinement

12,15-Dimethoxy-6-aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11), 12,14-trien-7-one (5c). Chemical formula $C_{16}H_{21}NO_3$; Formula weight 275.34; Temperature 150(2) K; Radiation, wavelength MoKα, 0.71073 Å; Crystal system, space group monoclinic, $P2_1/c$; Unit cell parameters a = 8.3263(9) Å; α = 90°; b = 18.599(2) Å; β = 107.795(2)°; c = 9.2541(10) Å; γ = 90°; Cell volume 1364.5(3) $Å^3$ Z 4; Calculated density 1.340 g/cm^3; Absorption coefficient μ 0.092 mm^{-1}; F(000) 592; Crystal colour and size colourless, 0.40 × 0.12 × 0.02 mm^3; Data collection method Bruker SMART APEX CCD diffractometer ω rotation with narrow frames; θ range for data collection 2.56 to 28.27°; Index ranges h −10 to 11, k −24 to 24, l −12 to 12; Completeness to θ = 26.00° 99.4%; Reflections collected 11463; Independent reflections 3261 (R_{int} = 0.0276); Reflections with $F^2>2\sigma$ 2760; Absorption correction semi-empirical from equivalents; Min. and max. transmission 0.9641 and 0.9982; Structure solution direct methods; Refinement method Full-matrix least-squares on F^2; Weighting parameters a, b 0.0681, 0.3291; Data/restraints/parameters 3261/0/181; Final R indices [$F^2>2\sigma$] R1 = 0.0439, wR2 = 0.1168; R indices (all data) R1 = 0.0519, wR2 = 0.1221; Goodness-of-fit on F^2 1.066; Largest and mean shift/su 0.000 and 0.000; Largest diff. peak and hole 0.343 and −0.260 e $Å^{-3}$.

2*R*,10*R*)(2*S*,10*S*)-10-Phenyl-6-aza-tricyclo[9.4.0.0*2,6*]-pentadeca-1(15),11,13-triene-7-one (8). Chemical formula $C_{20}H_{21}NO$; Formula weight 291.38; Temperature 150(2) K; Radiation, wavelength MoKα, 0.71073 Å; Crystal system, space group monoclinic, $P2_1/c$; Unit cell parameters a = 7.6569(8) Å α = 90°, b = 9.6582(11) Å β = 90.423(2)°, c = 20.404(2) Å γ = 90°; Cell volume 1508.9(3) $Å^3$; Z 4; Calculated density 1.283 g/cm^3; Absorption coefficient μ 0.078 mm^{-1}; F(000) 624; Crystal colour and size colourless, 0.48 × 0.46 × 0.43 mm^3; Data collection method Bruker SMART APEX CCD diffractometer ω rotation with narrow frames; θ range for data collection 3.34 to 28.29°; Index ranges h −10 to 10, k −12 to 12, l −26 to 26; Completeness to θ = 26.00° 99.3%; Reflections collected 12268; Independent reflections 3580 (R_{int} = 0.0327); Reflections with $F^2>2\sigma$ 3271; Absorption correction semi-empirical from equivalents; Min. and max. transmission 0.9634 and 0.9671;Structure solution direct methods; Refinement method Full-matrix least-squares on F^2; Weighting parameters a, b 0.0720, 0.4836; Data/restraints/parameters 3580/0/200; Final R indices [$F^2>2\sigma$] R1 = 0.0440, wR2 = 0.1201; R indices (all data) R1 = 0.0473, wR2 = 0.1231; Goodness-of-fit on F^2 1.041; Extinction coefficient 0.027(4); Largest and mean shift/su 0.000 and 0.000; Largest diff. peak and hole 0.402 and −0.248 e $Å^{-3}$.

4b,5,6,7-Tetrahydro-14*H*-dibenzo[*c*,*f*]pyrrolo[1,2-*a*]azocin-9-one (12a). Chemical formula $C_{18}H_{17}NO$; Formula weight 263.33; Temperature 150(2) K; Radiation, wavelength MoKα, 0.71073 Å; Crystal system, space group triclinic, $P\bar{1}$; Unit cell parameters a = 9.3106(8) Å α = 75.9490(10)° b = 10.4150(9) Å β = 88.8050(10)° c = 16.0747(14) Å γ = 63.5860(10)°; Cell volume 1347.4(2) $Å^3$ Z 4; Calculated density 1.298 g/cm^3; Absorption coefficient μ 0.080 mm^{-1}; F(000) 560; Crystal colour and size colourless, 0.32 × 0.28 × 0.18 mm^3; Data collection method Bruker SMART APEX CCD diffractometer ω rotation with narrow frames θ range for data collection 2.63 to 28.30°; Index rangesh −12 to 12, k −13 to 13, l −20 to 21; Completeness to θ = 26.00° 97.7%; Reflections collected 11524; Independent reflections 6146 (R_{int} = 0.0221); Reflections with $F^2>2\sigma$ 5332; Absorption correction semi-empirical from equivalents; Min. and max. transmission 0.9748 and 0.9857; Structure solution direct methods; Refinement method Full-matrix least-squares on F^2; Weighting parameters a, b 0.1039, 0.3159; Data/restraints/parameters 6146/0/361; Final R indices [$F^2>2\sigma$] R1 = 0.0520, wR2 = 0.1554; R indices (all data) R1 = 0.0583, wR2 = 0.1641. Goodness-of-fit on F^2 1.079; Largest and mean shift/su 0.000 and 0.000; Largest diff. peak and hole 0.476 and −0.433 e $Å^{-3}$.

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