Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2011, **9**, 1547

www.rsc.org/obc

PAPER

A novel synthesis of (di)-benzazocinones *via* an endocyclic *N*-acyliminium ion cyclisation†

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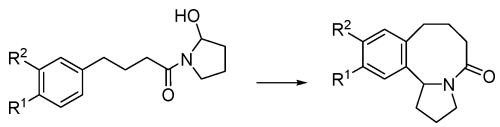
Received 10th August 2010, Accepted 24th November 2010
DOI: 10.1039/c0ob00559b

The triflic acid-mediated endocyclic *N*-acyliminium ion cyclisation provides a facile synthesis of (di)-benzazocinones. On reduction of the 10-phenyl derivative, an unusually non-polar tertiary alkylamine was obtained.

Introduction

We have an on-going interest in the synthesis of conformationally restricted benzylamines as potential CNS drugs.[1] We recently described the synthesis of pyrrolo-benzazocin-7-ones *via* a triflic acid-mediated cyclisation of acyliminium ions in which the acyl group was exocyclic to the cyclic iminium ion precursor (Scheme 1).[2]



Scheme 1 The exocyclic *N*-acyliminium ion cyclisation to pyrrolo-benzazocin-7-ones.[2]

The success of this methodology prompted us to investigate the triflic acid-mediated cyclisation of the endocyclic acyliminium ion derived from **1**, in which the acyl group is now within the ring of the cyclic iminium ion precursor, for the synthesis of pyrrolobenzazepin-5-ones **2** (Scheme 2). Such endocyclic acyliminium ion cyclisations have been reported for the synthesis of tetrahydro-isoquinolinones and benzazepinones.[3]

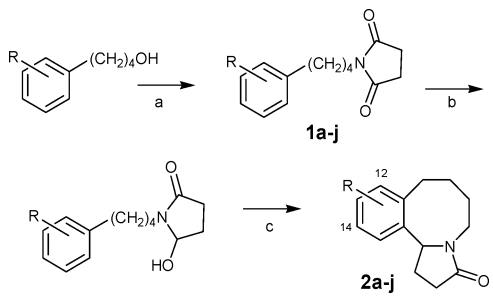
Results and discussion

The succinimides **1a–j** were readily prepared either from the 4-arylbutan-1-ols *via* a Mitsunobu reaction with dried succinimide[4] or from the amines and succinic anhydride.[5] Reduction with $NaBH_4$ in EtOH buffered with 15% $H_2O/KHCO_3$ gave the hydroxyamides, which were cyclised using a 10 fold excess of triflic acid in refluxing $CHCl_3$ to give the pyrrolobenzazocin-5-ones **2a–j** (Table 1). For the bromo compounds **2c–e**, we found

Table 1 Synthesis of substituted benzazocin-5-ones **2a–j**

Cpd. No.	*R*	T (h)[a]	Isolated yield (%)
2a	H	1	78
2b	14-Cl	3	65
2c	14-Br	3	73
2d[b]	13-Br	3	73
2e[b]	15-Br	3	18
2f	13,15-di-Br	3	80
2g[c]	13,14-di-MeO	0.25	74
2h	14-MeO	1	0
2i	14-Me	1	80
2j	14-NO_2	48	0

[a] Time of reaction in $CHCl_3$, heated under reflux. [b] Two isomers formed from reduction and cyclisation of N-(3-bromophenyl) butyl succinimide in a total yield of 91%. [c] A single isomer was obtained.



Scheme 2 The endocyclic *N*-acyliminium ion cyclisation for the synthesis of benzazocinones **2a-j**. *Reagents and conditions*: a) Ph_3P, succinimide, DEAD, b) $NaBH_4$, $KHCO_3$, c) CF_3SO_3H, $CHCl_3$, heat.

that borohydride reduction resulted in ~5% debromination and so for these examples DIBAL was used for the reduction.[6] As previously observed in related cyclisations,[1,2] the p-methoxy analogue failed to give any of the desired product. We believe this is because of O-demethylation and subsequent reaction to form an insoluble material. This cyclisation works well for mildly deactivated phenyls, such as the dibromo **2f** but not for the strongly deactivated nitro **2j**. At room temperature, the NMR spectra of the pyrrolobenazocinones were often poorly resolved, with peak broadening, and peaks were often missing in the ^{13}C spectrum.

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† Electronic supplementary information (ESI) available: ^1H NMR and ^{13}C NMR for all compounds. CCDC reference numbers 787503. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00559b

However, running the spectra at 60 °C improved the resolution, as the exchange of conformers becomes fast in the NMR time scale at higher temperatures. Interestingly, the presence of a substituent at the C-15 position also reduced conformational freedom and sharp spectra were obtained at ambient temperatures. We were able to obtain sufficiently good crystals of **2f** for an X-ray crystallographic determination which confirmed the structure (Fig. 1).

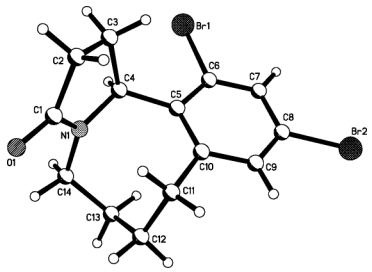
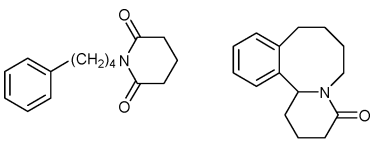


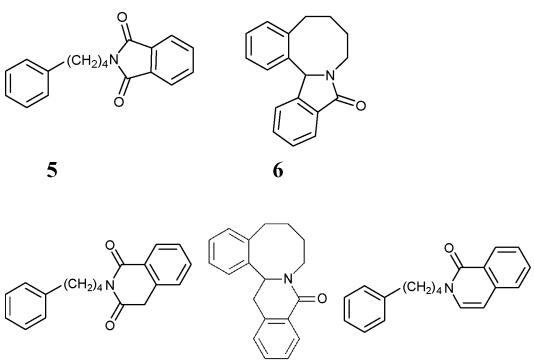
Fig. 1 Structure of **2f** from X-ray structure analysis: CCDC 787503.†

This endocyclic acyliminium ion cyclisation can be readily applied to the synthesis of products not readily achievable by the exocyclic acyliminium ion methodology.[2] Thus, whereas cyclisation of the 6-membered exocyclic N-acyliminium ion failed,[2] reduction and cyclisation of the imide **3** readily gave the piperidinobenzazocine **4** in 74% yield.



3 **4**

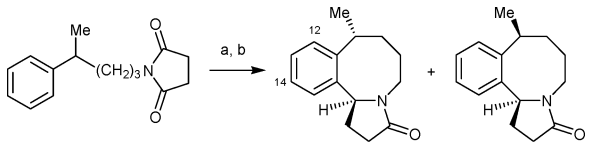
For the phthalimide **5**,[7] reduction and cyclisation gave the cyclic product **6** (73% yield). With **5**, we found that low temperatures and buffering of the $NaBH_4$ to avoid ring opening was not necessary. The NMR of **6** at room temperature was poorly resolved. However, on cooling to –60 °C, two distinct conformers were observed in a ratio of 2.4 : 1, whereas heating to 125 °C gave a simplified time-averaged spectrum. Although reduction and acid-mediated intramolecular cyclisations of *N*-arylethyl-homo-phthalimides onto indole and phenyls to give 6-membered rings has been reported,[8] the reduction and cyclisation of the homophthalimide **7** did not give **8a**, but instead gave the isoquinolone **8b** (95% yield).[8b] Prolonged heating of **8b** with triflic acid failed to convert it into **8a**.



5 **6**

7 **8a** **8b**

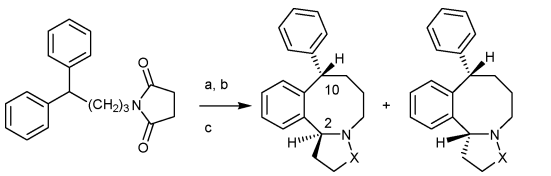
The reduction/cyclisation also worked well for the synthesis of 10-substituted analogues. Thus, the 4-methyl-4-phenylbutyl imide **9** was reduced and cyclised to give the '*trans*' **10** and '*cis*' **11** isomers, readily separable by column chromatography, in a ratio of 5.5 : 1 with an overall yield of 90% (Scheme 3).



(±)**9** (±) **10** (±) **11**

Scheme 3 Synthesis of benzazocinones **10** and **11.** *Reagents and conditions*: a) $NaBH_4$, $KHCO_3$, b) CF_3SO_3H, $CHCl_3$, heat.

Similarly, reduction and cyclisation of the 4,4-diphenylbutyl imide **12** gave a mixture of the '*trans*' **13** and the '*cis*' **14** isomers in an overall yield of 70%, although this time they were inseparable by column chromatography (Scheme 4). However, the major '*trans*' isomer was isolated from the mixture by crystallization from EtOAc/petrol.

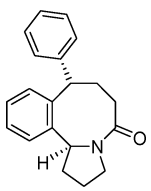


12 (±)**13** X = C=O (±) **14** X = C=O
(±) **15** X = CH_2 (±) **16** X = CH_2

Scheme 4 Synthesis of benzazocinones (±)**13** and (±)**14** and (±)**15** and (±)**16**. *Reagents and conditions*: a) $NaBH_4$, $KHCO_3$, b) CF_3SO_3H, $CHCl_3$, heat, then c) $LiAlH_4$.

An NMR study confirmed that the 10-phenyl group was orientated '*trans*' with respect to the pyrrolidinone ring. The '*trans*' isomer has also been reported to be the major isomer obtained from the equivalent exocyclic acyliminium ion cyclisation.[2]

Reduction of the mother liquors from the crystallization (which contained a mixture of **13** and **14**) with $LiAlH_4$ gave the amines **15** and **16** in an overall yield of 95%. Similar reduction of **13** with $LiAlH_4$ gave only **15**. The amines **15** and **16** were readily separable by column chromatography on silica. Surprisingly, **15** was non-polar (rf 0.7 on SiO_2, elution with DCM) and rapidly eluted from a SiO_2 column with DCM, whereas **16** required the addition of 10% MeOH and 1% 0.88 aqueous ammonia solution. Amine **15** rapidly degraded on exposure to air.[9] An aqueous ethanolic solution of **15** was found to have a neutral pH, but it was possible to form a solid HCl salt, which was more stable.



17

A strong nuclear Overhauser effect (NOE) between 2-H and 10-H protons was observed in **16**, showing that they are on

the same side of the 8-membered ring, whereas no such NOE was observed for **15**. In **15**, NOEs were observed between the 3t-H (t = *trans* to 2-H) and 10-H protons. These NOEs confirm the *trans*-configuration of the two methine protons 2-H and 10-H in **15** and their *cis*-configuration in **16**. Furthermore, the same amine **15** was formed by $LiAlH_4$ reduction of our previously reported 10-phenylbenzazocin-7-one **17**, for which we had structural confirmation from X-ray analysis.[2]

The NMR analysis of the HCl salt of **15** showed that it exists as a mixture of two forms, the '*trans*' form **15a** and the '*cis*' form **15b**, in a ratio of **15a** : **15b** = 57 : 43. The more polar amine **16** also readily formed a solid HCl salt and NMR analysis showed that this also existed as a mixture of the '*cis*' **16a** and '*trans*' **16b** ring junction, but now the '*cis*' form was the major form, with a ratio of **16a** : **16b** = 62 : 38 (Fig. 2).

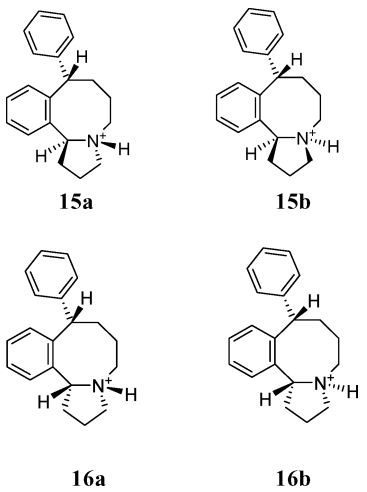
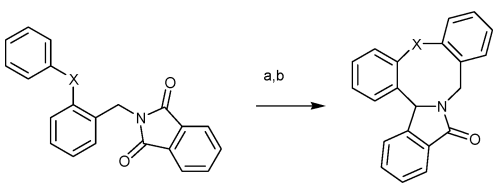


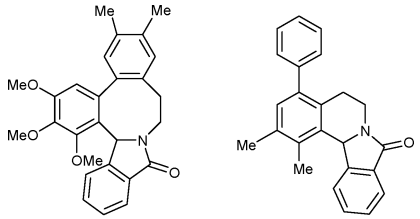
Fig. 2 The structures of the major (**15a**) and minor (**15b**) forms of the hydrochloride of **15** and the major (**16a**) and minor (**16b**) forms of the hydrochloride of **16** in $CDCl_3$ solution.

We were also interested in investigating the use of this methodology in the synthesis of dibenzazocinones as conformationally restricted analogues. It was found that both the 2-(2-benzyl) benzyl imide **18** and the 2-(2-phenoxy) benzyl imide **19** reduced and cyclised to give the 8-membered ring compounds **20** (95% yield) and **21** (86% yield), respectively (Scheme 5).

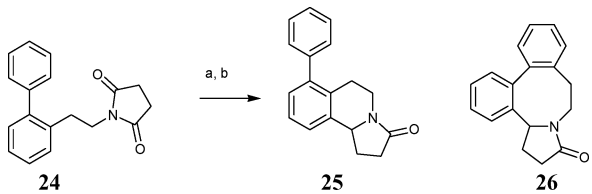


Scheme 5 Synthesis of di-benzazocinones **20** and **21**. *Reagents and conditions*: a) $NaBH_4$, b) CF_3SO_3H, $CHCl_3$, heat.

The formation of 8-membered rings by reduction/cyclisation of phthalimides has previously been reported only for the highly electron rich phenyl **22**, with 6-membered cyclisation occurring without the activation of the 2-phenyl with electron donating substituents **23**.[10] In contrast, we have previously reported that the cyclisation of the exocyclic pyrrolidinium ion onto phenyl gave a 1 : 2 ratio of the 8 : 6 membered cyclisation.[2]



In order to determine whether these contrasting results were due either to the position of the acyl group, or to the structural differences between phthalimide and pyrrolidinone, we carried out the reduction/cyclisation of **24**. This led to the exclusive formation of the isoquinolinone **25** (78% yield), with none of the dibenzazocinone **26** detected (Scheme 6). Thus, in the absence of strongly electron donating groups, reduction/cyclisation of both the phthalimide and pyrrolidinone form the 6-membered ring exclusively.



Scheme 6 Synthesis of the isoquinolone **25**. *Reagents and conditions*: a) $NaBH_4$, b) CF_3SO_3H, $CHCl_3$, heat.

Conclusion

In conclusion, we have shown that the benzo-fused 8-membered benzazocinones and dibenzazocinones can be readily prepared in good yield by triflic acid-mediated *endo*-cyclic iminium ion cyclisation. This method offers an alternative to our previously reported *exo*-cyclic iminium ion cyclisation and allows the synthesis of analogues not readily available by that route. We have also identified a conformationally restricted tertiary amine that is unusually non-polar.

Experimental

All reagents were commercially available, unless otherwise 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. Infrared spectra were run neat on a Perkin Elmer 100 FT IR 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. Unless otherwise specified, spectra were recorded at 25 °C. Both NOE and ROE measurements were undertaken for establishing spatial proximities of protons. The latest implementations of the corresponding 2D NMR experiments—NOESY with the elimination of zero-quantum interference and EASY-ROESY—were used, which offer considerably improved selectivity for NOE

and ROE measurements with minimum interference from other sources.[11]

General procedure for the preparation of the N-substituted imides

A stirred solution of the appropriate alcohol (10 mmol), triphenyl phosphine (11 mmol) and the dried NH-imide (11 mol) was dissolved in DCM (50 ml), cooled to 0 °C and treated with DEAD (11 mmol) until a yellow colour remained. The reaction mixture was left overnight at ambient temperature, the solvent removed and the residue purified by column chromatography on SiO_2, eluting with DCM.

General procedure for the reduction of the N-substituted succinimides to the hydroxy-amides using $NaBH_4$

A stirred solution of the appropriate N-substituted succinimide (5 mmol) was dissolved in EtOH (30 ml) and saturated aqueous $KHCO_3$ solution (3 ml) added together with H_2O (2 ml). On cooling to 0–5 °C, $NaBH_4$ (25 mmol) was added and the reaction stirred at that temperature for 2–4 h, until most of the succinimide had been reduced by TLC. Water (150 ml) was then added and the product extracted into DCM (3 × 50 ml), dried (K_2CO_3), concentrated and the residue purified by column chromatography on SiO_2, eluting with DCM and 2–4% MeOH to give the desired products.

General procedure for the reduction of the N-substituted phthalimides to the hydroxy-amides using $NaBH_4$

To a stirred, ethanolic (40 ml) suspension of the phthalimide (5 mmol) and water (4 ml) was added $NaBH_4$ (25 mmol) at ambient temperature and the reaction stirred at ambient temperature for 1 h until no starting material was observed by TLC. Water (150 ml) was then added and the solid product collected and dried.

General procedure for the triflic acid-mediated cyclisation

A solution of the hydroxy-amide (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 temperature, water (20 ml) was added and the aqueous layer carefully basified with solid K_2CO_3 (vigorous effervescence). 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 which were separated by column chromatography on silica.

1-(4-Phenyl-butyl)-pyrrolidine-2,5-dione (1a)

A stirred solution of 4-phenylbutyl-1-amine (2.4 ml, 15 mmol) and succinic anhydride (1.5 g, 15 mmol) in $CHCl_3$ (30 ml) was heated under reflux for 30 min. The reaction mixture was then cooled to 0 °C and MeOH (20 ml), thionyl chloride (1.3 ml, 18 mmol) then added and the reaction heated under reflux for 3 h. On cooling, the reaction was concentrated under reduced pressure on a rotary evaporator, and the residue dissolved in toluene (50 ml) and again concentrated as before. The residue was dissolved in toluene (50 ml) and treated with 0.5 g NaOBu-t and heated under reflux for 1 h. On cooling to room temperature, water (50 ml) was added and the product extracted into 4 : 1 Et_2O–DCM (3 × 100 ml). The combined organic extracts were dried (K_2CO_3), concentrated and trituration with petrol afforded the title compound **1a** as a beige solid 2.4 g (78% yield), mpt 46–48 °C (EtOAc/petrol); FT-IR (neat) 3307, 2946, 1736, 1673, 1641, 1562, 1435, 1339, 1155, 1137, 743, 711, 702, 696 cm^{-1}. HRMS theoretical mass: 231.12538; measured mass: 231.12579. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.54–1.67 (4H, m), 2.53–2.70 (6H, m, including 2.87, 4H, s), 3.45–3.55 (2H, m), 7.10–7.30 (5H, m): ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ = 27.3 (CH_2), 28.2 (CH_2), 28.6 (CH_2), 35.3 (CH_2), 38.6 (CH_2), 125.8 (CH), 128.3 (CH), 128.4 (CH), 141.9 (C), 177.2 (C).

6-Aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-5-one (2a)

The title compound was prepared as described in the general procedures. **1a** was reduced with $NaBH_4$ to give the 5-hydroxy-1-(4-phenyl-butyl)-pyrrolidin-2-one in an 80% yield as an oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.45–1.66 (4H, m), 1.87 (1H, dt, J = 11.6, 1.6 Hz), 2.19–2.31 (2H, m), 2.50 (1H, quintet, J = 10.2 Hz), 2.56–2.68 (2H, m), 3.08–3.17 (1H, m), 3.40–3.51 (1H, m), 4.18 (0.4H, brs), 4.31 (0.6H, brs), 4.14 (1H, brs), 7.10–7.20 (3H, m), 7.21–7.32 (2H, m); ^{13}C NMR and DEPT (125 MHz, $CDCl_3$) δ = 27.4 (CH_2), 28.3 (CH_2), 28.8 (CH_2), 29.1 (CH_2), 35.6 (CH_2), 39.7 (CH_2), 83.2 (CH), 125.9 (CH), 128.4 (CH), 128.5 (CH), 142.2 (C), 175.0 (C). Cyclisation of 5-hydroxy-1-(4-phenyl-butyl)-pyrrolidin-2-one with triflic acid as described in the general procedure, with heating for 1 h, gave the title compound **2a** as a white solid (78% yield): mpt 72–4 °C (EtOAc/petrol). HRMS theoretical mass: 215.13047; measured mass: 215.13125. FT-IR (neat) 1672, 1410, 1357, 1310, 1259, 1238, 771 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) at 60 °C: δ = 1.43–1.51 (1H, m), 1.63–1.71 (1H, brm), 1.73–1.80 (1H, m), 1.84–1.92 (1H, brm), 1.98–2.70 (1H, m), 2.38–2.43 (1H, m), 2.47 (1H, dd, J = 8.9, 17.5 Hz), 2.49–2.56 (1H, m), 2.72 (1H, ddd, J = 4.5, 6.6, 13.7 Hz), 3.05 (1H, ddd, J = 4.3, 10.0, 13.8 H), 3.10–3.16 (1H, brm), 3.60–3.69 (1H, brm), 4.80 (1H, t, J = 7.5 Hz), 7.11 (1H, dd, J = 1.5, 7.4 Hz), 7.16 (1H, dd, J = 1.4, 7.6 Hz), 7.21 (1H, dt, J = 1.6, 7.6 Hz), 7.25 (1H, dt, J = 1.6, 7.3 Hz). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$) δ = 24.8 (8-C), 28.2 (3-C), 29.2 (9-C), 31.0 (4-C), 31.6 (10-C), 41.6 (7-C), 63.1 (2-C), 126.5 (CH), 127.3 (15-C), 128.2 (CH), 131.5 (12-C), 139.0 (11-C), 140.2 (1-C), 174.6 (5-C).

6-Aza-benzo[c]tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-5-one (6)

To a stirred suspension of **5**[7] (0.9 g, 3.2 mmol) in ethanol (30 ml) at ambient temperature was added $NaBH_4$ (0.6 g, 16 mmol) and water (3 ml), and the reaction mixture was stirred at ambient temperatures until TLC shows no **5** (~1 h). Water (200 ml) was then added and the solid hydroxyamide that precipitated was collected and dried (0.83 g, 92% yield), mpt 114–5 °C. FT-IR (neat) 3314, 1683, 1671, 1468, 1450, 1421, 1044, 751, 704, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.51–1.70 (4H, m), 2.61 (2H, t, J = 5.8 Hz), 3.20–3.28 (1H, m), 3.39–3.48 (1H, m), 3.56 (1H, d, J = 11.9 Hz), 5.67 (1H, d, J = 11.9 Hz), 7.11–7.17 (3H, m), 7.24 (2H, t, J = 7.5 Hz), 7.42 (1H, dt, J = 0.95, 7.4 Hz), 7.52–7.60 (3H, m); ^{13}C NMR and DEPT (125 MHz, $CDCl_3$) δ = 27.83 (CH_2), 28.75 (CH_2), 35.52 (CH_2), 38.89 (CH_2), 81.69 (CH), 123.25 (CH), 123.35 (CH),

125.87 (CH), 128.39 (CH), 128.48 (CH), 129.79 (CH), 131.55 (C), 132.20 (CH), 142.12 (C), 143.93 (C), 167.50 (C).

A solution of the hydroxyamide (0.44 g, 1.5 mmol) in $CHCl_3$ (5 ml) was added to a stirred mixture of triflic acid (1.5 ml) in $CHCl_3$ (20 ml) and the reaction mixture heated under reflux for 2 h. On cooling, water was added (10 ml) and the aqueous layer made basic by careful addition of solid K_2CO_3. The product was extracted into DCM (3 × 50 ml), dried (K_2CO_3), concentrated and purified by column chromatography on SiO_2, eluting with 1 : 1 petrol : DCM to give the title compound **6** as a white solid (0.30 g, 73% yield), mpt 150–152 °C. FT-IR (neat) 1683, 1465, 1407, 1365, 1315, 1301, 755, 743, 720, 688 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, −60 °C): two conformations in a ratio of 2.4 : 1: δ = 1.4–1.72 (2H, m), 1.94–2.06 (0.29H, m), 2.15–2.43 (2H, m), 2.55–2.68 (0.29H, m), 2.98–3.18 (1.14H, m), 3.36 (0.29H, d, J = 14.0 Hz), 4.48 (0.71H, dd, J = 9.5, 13.9 Hz), 4.57 (0.29H, ddd, J = 5.1, 12.3, 13.9 Hz), 5.63 (0.29H, s), 5.94 (0.71H, s), 6.55 (0.71H, d, J = 7.8 Hz), 7.01 (0.29H, d, J = 7.4 Hz), 7.06–7.16 (0.71H, m), 7.22 (0.29H, d, J = 7.2 Hz), 7.25–7.67 (5H, m), 7.87 (0.29H, d, J = 7.5 Hz), 7.94 (0.71H, d, J = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, −60 °C) δ = 22.4, 26.9, 28.7, 30.5, 31.8, 34.2, 39.1, 42.0, 122.9, 123.4, 123.7, 123.8, 126.8, 127.4, 127.6, 128.5, 128.7, 129.6, 130.2, 130.9, 131.9, 132.2, 133.5, 134.0, 135.9, 138.7, 143.3, 144.4, 144.8. ^1H NMR (400 MHz, $CDCl_3$, 125 °C): δ = 1.52–1.90 (4H, m), 2.68–2.87 (2H, m), 3.56 (H-8, t, J = 11.5 Hz), 3.68 (H-8, dt, J = 3.2, 11.2 Hz), 5.93 (H-14b, s), 7.08 (H-1, d, J = 7.4 Hz), 7.16 (H-4, dd, J = 1.4, 7.4 Hz), 7.24 (H-2, dt, J = 1.6, 7.4 Hz), 7.30 (H-3, dt, J = 1.4, 7.4 Hz), 7.33 (H-14, d, J = 7.6 Hz), 7.40 (H-12, dt, J = 1.3, 7.4 Hz), 7.57 (H-13, t, J = 7.4 Hz), 7.75 (H-11, d, J = 7.4 Hz)

2-(4-Phenyl-butyl)-4*H*-isoquinoline-1,3-dione (7)[12]

A solution of 4-phenylbutyl-1-amine (1.6 g, 11 mmol) (10 ml) and homophthalic anhydride (1.8 g, 11 mmol) in $CHCl_3$ was stirred at ambient temperature for 5 min, then heated to 200 °C (heating block temperature), driving off the $CHCl_3$ and H_2O for 30 min. The reaction mixture was cooled and the residue dissolved in DCM (5 ml) and purified by column chromatography on SiO_2, eluting with DCM to give **7**, 2.8 g (87% yield), as a white solid, recrystallized from EtOAc/petrol, mpt 84–86 °C. Theoretical mass: 291.14103; measured mass: 291.14156. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.64–1.75 (4H, m), 2.66 (2H, t, J = 6.8 Hz), 3.99–4.06 (4H, m), 7.12–7.18 (3H, m), 7.20–7.28 (3H, m), 7.44 (1H, t, J = 7.8 Hz), 7.58 (1H, t, J = 7.5 Hz), 8.20 (1H, d, J = 8.0 Hz): ^{13}C NMR and DEPT (125 MHz, $CDCl_3$) δ = 27.8 (CH_2), 29.0 (CH_2), 35.7 (CH_2), 36.5 (CH_2), 40.1 (CH_2), 125.5 (C), 125.8 (CH), 127.2 (CH), 127.8 (CH), 128.4 (CH), 128.5 (CH), 129.2 (CH), 133.6 (CH), 134.2 (C), 142.3 (C), 164.9 (C), 170.0 (C).

2-(4-Phenyl-butyl)-2*H*-isoquinolin-1-one (8b)

A stirred solution of **7** (1.9 g, 6.5 mmol) in EtOH (50 ml) was cooled to 5 °C and treated with $NaBH_4$ (1.2 g, 0.32 mmol), saturated $KHCO_3$ solution (3 ml) and water (5 ml), and cooling and stirring was continued for 3 h. Water (200 ml) was added and the solid collected, dissolved in DCM and purified by column chromatography on SiO_2, eluting with 1 : 5 ether : DCM to give the hydroxyamide as a white solid (1.47 g, 77% yield) that started to go yellow on standing with formation of the title compound **8b**. A stirred solution of the hydroxyamide (0.89 g, 2.9 mmol) in $CHCl_3$ (30 ml) was treated with triflic acid (2.9 ml) and heated under reflux for 30 min. On cooling, water (10 ml) was added and the reaction carefully basified by addition of solid K_2CO_3. The product was extracted into DCM (3 × 50 ml), dried (K_2CO_3), concentrated *in vacuo* and the residue purified by column chromatography on SiO_2, eluting with DCM + 1% MeOH to give **8b** as a white solid (0.77 g, 95% yield), mpt 58–59 °C (ether/petrol). FT-IR (neat) 1641, 1623, 1598, 1491, 1373, 1296, 794, 750, 690 cm^{-1}. Theoretical mass: 277.14612; measured mass: 277.14557. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.71 (2H, quintet, J = 7.3 Hz), 1.82 (2H, quintet, J = 7.4 Hz), 2.66 (2H, t, J = 7.6 Hz), 4.01 (2H, t, J = 7.3 Hz), 6.47 (1H, d, J = 7.3 Hz), 7.02 (1H, d, J = 7.3 Hz), 7.14–7.20 (3H, m), 7.24–7.29 (2H, m), 7.46–7.52 (2H, m), 7.62 (1H, ddd, J = 1.3, 7.1, 8.3 Hz), 8.43 (dd, J = 0.5, 8.1 Hz). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$) δ = 28.66 (CH2), 28.99 (CH2), 35.64 (CH2), 49.30 (CH2), 106.05 (CH), 125.89 (CH), 125.92 (CH), 126.40 (C), 126.84 (CH), 127.92 (CH), 128.43 (CH), 128.50 (CH), 131.72 (CH), 132.10 (CH), 137.07 (C), 142.05 (C), 162.18 (C).

2-(4,4-Diphenyl-butyl)-pyrrolidine-2,5-dione (12)

A stirred solution of 4,4-diphenylbutan-1-ol[13] (2.4 g, 11 mmol), triphenylphosphine (2.9 g, 12 mmol) and dried succinimide (1.1 g, 12 mmol) in DCM (50 ml) was cooled to 0 °C and DEAD (1.8 ml, 12 mmol) was added dropwise. The reaction mixture was stirred at ambient temperatures overnight and then concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2, eluting with 2 : 3 petrol : DCM to 1 : 4 petrol : DCM to give the title product as a white solid (3.2 g, 84% yield), mpt 91–93 °C (Et_2O/petrol); theoretical mass: 307.15668; measured mass: 307.15655. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.20–1.56 (2H, m), 2.03 (2H, q, J = 7.9 Hz), 2.65 (4H, s), 3.52 (2H, t, J = 7.3 Hz), 3.90 (1H, t, J = 7.9 Hz), 7.15–7.28 (10H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.3 (CH_2), 28.2 (CH_2), 32.8 (CH_2), 38.7 (CH_2), 51.0 (CH), 126.2 (CH), 127.9 (CH), 128.6 (CH), 144.6 (C), 177.3 (C)

(2*R*,10R; 2*S*,10*S*)-10-Phenyl-6-aza-tricyclo[9.4.0.0*2,6*]-pentadeca-1(11),12,14-trien-5-one (13) and (2*R*,10S; 2*S*,10*R*)-10-phenyl-6-aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-5-one (14)

A stirred suspension of **12** (2.0 g, 6.6 mmol) in ethanol (90 ml) was cooled to 5 °C and $NaBH_4$ (1.0 g, 27 mmol) was added followed by saturated aqueous $KHCO_3$ (9 ml) and the reaction was stirred at 5 °C for 4 h. Water (300 ml) was then added and the product extracted into $CHCl_3$ (3 × 100 ml). The combined organic extracts were dried (K_2CO_3), concentrated and purified by column chromatography, eluting with ether to give recovered **12** (0.13 g, 20% yield) and the hydroxyamide (1.32 g, 65% yield) as an oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.40–1.55 (2H, m), 1.80–1.89 (1H, m), 1.94–2.02 (2H, m), 2.10–2.21 (2H, m), 2,44–2.52 (2H, m), 3.12 (2H, tt, J = 5.9, 7.6 Hz), 3.47 (2H dt, J = 7.8, 13.6 Hz), 3.86 (2H, t, J = 8.1 Hz), 5.08 (1H, dd, J = 2.6, 6.3 Hz), 7.09–7.28 (10H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.2 (CH_2), 28.3 (CH_2), 29.0 (CH_2), 32.9 (CH_2), 39.7 (CH_2), 51.1 (CH), 83.1 (CH), 126.3 (CH), 127.9 (CH), 128.6 (CH), 144.8 (C), 174.9 (C).

A solution of the hydroxyamide (1.32 g, 4.2 mmol) in $CHCl_3$ (15 ml) was added, dropwise, to a stirred mixture of triflic acid

(4.2 ml, 45 mmol) in $CHCl_3$ (60 ml) at 65 °C over 5 min. The reaction was heated under reflux for 1 h, cooled to r.t., then water was added (20 ml) and the aqueous layer made basic by careful addition of solid K_2CO_3. The product was extracted into DCM (3 × 100 ml), dried (K_2CO_3), concentrated and purified by column chromatography on SiO_2, eluting with Et_2O/1% MeOH to give a 9 : 1 mixture of **13** and **14** (0.93 g, 77% yield), from which pure **13** was obtained by crystallization from Et_2O (0.45 g, 37% yield), mpt 152–3 °C (DMSO/water). FT-IR (neat) 1669, 1488, 1445, 1414, 1358, 1273, 1153, 762, 747, 697 cm^{-1}. Theoretical mass: 291.16177; measured mass: 291.16051. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.4–1.55 (m, 1H), 1.7–1.8 (m, 1H), 1.89–2.0 (m, 1H), 2.10 (dt, *J* = 2.5, 9.5 Hz, 1H), 2.22–2.32 (m, 1H), 2.43–2.62 (m, 3H), 3.02 (d, *J* = 13.5 Hz, 1H), 4.24 (brs, 1H), 4.80 (dd, *J* = 7.4, 8.9 Hz, 1H), 5.01 (dd, *J* = 4.6, 11.6 Hz, 1H), 6.76 (dd, 1H, *J* = 1.9, 7.5 Hz, 1H), 7.08–7.37 (m, 8H); ^{13}C NMR and DEPT (125 MHz, CDCl3) δ = 23.4 (CH_2), 30.5 (CH_2), 31.3 (CH_2), 32.7 (CH_2), 42.3 (CH_2), 42.6 (CH), 65.8 (CH), 126.2 (CH), 126.4 (CH), 127.8 (CH), 128.4 (CH), 128.4 (CH), 128.5 (CH), 129.8 (CH), 139.6 (C), 142.9 (C), 144.1 (C), 175.2 (C).

(2*R*,10R; 2*S*,10*S*)-10-Phenyl-6-aza-tricyclo[9.4.0.0*2,6*]-pentadeca-1(11),12,14-trienene (15) and (2*R*,10S; 2*S*,10*R*)-10-phenyl-6-aza-tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trienene (16)

The mother liquors from the crystallization of **13** (0.48 g, 1.6 mmol) was dissolved in dry THF (20 ml) with stirring under argon and a 1 M solution of $LiAlH_4$ in THF (1.0 ml, 1 mmol) was added and the reaction heated under reflux for 1 h. The reaction mixture was then cooled, Et_2O (50 ml) added, followed by careful addition of 2 M NaOH (0.3 ml). The reaction was stirred for 30 min, filtered through celite and the celite and aluminium salts were washed thoroughly with DCM (2 × 50 ml). The combined organics were concentrated *in vacuo*, and the residue purified by column chromatography in SiO_2, eluting with DCM to give **15** as an oil (0.35 g, 78% yield), then DCM + 10% MeOH + 1% 0.88 ammonia to give **16** as an oil (0.075 g, 17% yield). **15**: theoretical mass: 277.18250; measured mass: 277.18159. ^{1}H NMR (600 MHz, $CDCl_3$, 60 °C): δ = 1.50 (1H, m, 8c-H (c = *cis* to 2-H)), 1.56 (1H, m, 8t-H (t = *trans* to 2-H)), 1.77 (1H, m, 4c-H), 1.91 (1H, m, 3t-H), 1.92 (1H, m, 4t-H), 1.94 (1H, m, 9t-H), 2.14 (1H, tdd, *J* 12.7, 3.7 and 5.4, 9c-H), 2.22 (1H, m, 5c-H), 2.23 (1H, m, 3c-H), 2.55 (1H, m, 7c-H), 3.04 (1H, ddd, *J* = 13.2, 12.0, 5.2 Hz, 7t-H), 3.14 (1H, m, 5t-H), 3.49 (1H, dd, *J* = 9.4, 7.4 Hz, 2-H), 6.47 (1H, dd, *J* = 12.0, 5.5 Hz, 10-H), 6.62 (1H, dd, *J* = 7.8, 1.5 Hz, 12-H), 7.00 (1H, td, *J* = 7.5, 1.8 Hz, 13-H), 7.06 (1H, td, *J* = 7.6, 1.5 Hz, 14-H), 7.09 (1H, dd, *J* = 7.7, 1.8 Hz, 15-H), 7.22 (1H, m, *p*-H 10-Ph), 7.32 (2H, m, *o*-H 10-Ph), 7.33 (2H, m, *m*-H 10-Ph); ^{13}C NMR (150 MHz, $CDCl_3$) at 60 °C: δ = 22.2 (C4), 24.4 (C8), 33.1 (C9), 37.4 (C3), 43.3 (C10), 55.7 (C7), 56.3 (C5), 71.1 (C2), 125.2 (C14), 125.7 (C_p of 10-Ph), 126.4 (C13), 127.4 (C15), 128.1 (C_m of 10-Ph), 128.9 (C_o of 10-Ph), 129.1 (C12), 142.2 (C11), 142.7 (C1), 145.5 (C_q of 10-Ph). **16**: theoretical mass: 277.18250; measured mass: 277.18147. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.38 (1H, m, 8t-H (c = *cis* to 2-H)), 1.86 (1H, m, 8c-H (t = *trans* to 2-H)), 1.90 (1H, m, 9t-H), 2.02 (1H, m, 4c-H), 2.11 (1H, m, 4t-H), 2.25 (1H, m, 9c-H), 2.32 (1H, dddd, *J* = 13.1, 10.0, 7.9, 6.3 Hz, 3c-H), 2.43 (1H, dddd, *J* = 13.1, 10.3, 6.1, 5.2 Hz, 3t-H), 2.67 (1H, m, 5c-H), 2.67 (2H, m, 7-H), 3.01 (1H, ddd, *J* = 9.5, 8.1, 4.4 Hz, 5t-H), 4.35 (1H, t, *J* = 7.5 Hz, 2-H), 4.80 (1H, dd, *J* = 11.9, 3.5 Hz, 10-H), 6.47 (1H, dd, *J* = 12.0, 5.5 Hz, 10-H), 6.74 (1H, dd, *J* = 7.9, 1.5 Hz, 12-H), 7.10 (1H, td, *J* = 7.6, 1.5 Hz, 13-H), 7.20 (1H, td, *J* = 7.4, 1.5 Hz, 14-H), 7.25 (1H, m, *p*-H 10-Ph), 7.33 (2H, m, *o*-H 10-Ph), 7.35 (2H, m, *m*-H 10-Ph), 7.41 (1H, dd, *J* = 7.9, 1.5 Hz, 15-H); ^{13}C NMR (150 MHz, $CDCl_3$) at 25 °C: δ = 23.1 (C4), 25.3 (C8), 30.9 (C3), 35.9 (C9), 42.7 (C10), 52.8 (C7), 55.5 (C5), 60.7 (C2), 125.9 (C15), 126.3 (C_p of 10-Ph), 126.3 (C14), 127.8 (C13), 127.8 (C12), 128.4 (C_o of 10-Ph), 128.8 (C_m of 10-Ph), 138.1 (C1), 145.2 (C11), 145.4 (C_q of 10-Ph).

15 appeared to have limited stability in air and therefore both **15** and **16** were converted to their HCl salts by treatment of an ethereal solution of the amines with an excess of ethereal HCl to give the hydrochlorides **15a**/**15b** and **16a**/**16b**, respectively. **15a**/**15b**: mpt 188–90 °C. FT-IR 2417 (br), 1452, 1424, 1031, 770, 749, 721, 703, 667 cm^{-1}. **15a** ^{1}H NMR (in a mixture with **15b**, ratio **15a** : **15b** = 57 : 43, 600 MHz, $CDCl_3$, 60 °C): δ = 1.65 (1H, m, 4c-H (c = *cis* to 2-H)), 1.77 (1H, m, 3c-H), 1.95 (1H, m, 8t-H (t = *trans* to 2-H)), 1.97 (1H, m, 8c-H), 2.01 (1H, m, 9t-H), 2.30 (1H, m, 4t-H), 2.62 (1H, m, 3t-H), 2.70 (1H, m, 5c-H), 2.84 (1H, m, 7t-H), 2.97 (1H, m, 9c-H), 3.15 (1H, br dd, *J* = 14.1, 7.5 Hz, 7c-H), 3.69 (1H, m, 5t-H), 3.87 (1H, ddd, *J* = 11.8, 10.4, 6.6 Hz, 2-H), 4.46 (1H, t, *J* = 4.5 Hz, 10-H), 7.08 (2H, m, *o*-H 10-Ph), 7.23 (1H, m, *p*-H 10-Ph), 7.28 (1H, br d, *J* = 7.6 Hz, 12-H), 7.31 (2H, m, *m*-H 10-Ph), 7.42 (1H, br t, *J* = 7.6 Hz, 13-H), 7.49 (1H, br t, *J* = 7.6 Hz, 14-H), 8.07 (1H, br d, *J* = 7.6 Hz, 15-H), 12.39 (1H, br s, 6-H). ^{13}C NMR (150 MHz, $CDCl_3$, 60 °C): δ = 16.8 (C8), 20.6 (C4), 27.3 (C3), 33.5 (C9), 48.6 (C7), 48.7 (C10), 51.1 (C5), 62.2 (C2), 126.3 (C_o of 10-Ph), 126.8 (C_p of 10-Ph), 128.9 (C14), 129.1 (C_m of 10-Ph), 129.2 (C1), 130.5 (C15), 131.0 (C13), 132.2 (C12), 141.7 (C_q of 10-Ph), 144.1 (C11). **15b** ^{1}H NMR (in a mixture with **15a**, ratio **15a**:**15b** = 4 : 3, 600 MHz, $CDCl_3$, 60 °C): δ = 2.00 (1H, m, 8t-H (t = *trans* to 2-H)), 2.15 (1H, m, 9t-H), 2.17 (1H, m, 7t-H), 2.21 (1H, m, 4t-H (c = *cis* to 2-H)), 2.36 (1H, m, 3t-H), 2.46 (1H, m, 4c-H), 2.63 (1H, m, 3c-H), 2.64 (1H, m, 5t-H), 2.67 (1H, m, 8c-H), 2.90 (1H, m, 9c-H), 3.20 (1H, br d, *J* = 13.2 Hz, 7c-H), 3.51 (1H, m, 5c-H), 4.42 (1H, dd, *J* = 8.5, 5.4 Hz, 10-H), 5.22 (1H, br dd, *J* = 7.8, 4.5 Hz, 2-H), 7.04 (2H, m, *o*-H 10-Ph), 7.18 (1H, m, *p*-H 10-Ph), 7.24 (1H, br d, *J* = 7.2 Hz, 15-H), 7.26 (2H, m, *m*-H 10-Ph), 7.35 (1H, br d, *J* = 7.2, 12-H), 7.38 (1H, td, *J* = 7.3, 1.5 Hz, 14-H), 7.40 (1H, br t, *J* = 7.3 Hz, 13-H), 12.72 (1H, br s, 6-H); ^{13}C NMR (150 MHz, $CDCl_3$, 60 °C): δ = 22.9 (C8), 21.7 (C4), 27.6 (C3), 33.0 (C9), 48.2 (C7), 51.0 (C10), 51.5 (C5), 60.6 (C2), 126.7 (C_o of 10-Ph), 126.9 (C_p of 10-Ph), 128.1 (C14), 128.6 (C15), 129.2 (C_m of 10-Ph), 130.6 (C13), 131.3 (C1), 133.5 (C12), 142.7 (C_q of 10-Ph), 145.3 (C11).

16a/**16b**: mpt = 144–146 °C (phase change) 196–198 °C, FT-IR 2927, 2513 (br), 1495. 1447, 1410, 741, 698, 661 cm^{-1}. **16a** ^{1}H NMR (in a mixture with **16b**, ratio **16a** : **16b** = 62 : 38, 600 MHz, $CDCl_3$, 60 °C): δ = 1.83 (1H, tdd, *J* = 13.4, 11.7, 3.6 Hz, 9t-H (t = *trans* to 2-H)), 1.95 (1H, dt, *J* = 13.3, 9.0 Hz, 7t-H), 2.24 (1H, m, 8t-H), 2.35 (1H, m, 4t-H), 2.52 (1H, m, 9c-H (c = *cis* to 2-H)), 2.54 (1H, m, 3t-H), 2.62 (1H, m, 8c-H), 2.63 (1H, m, 4c-H), 2.76 (1H, m, 5t-H), 3.08 (1H, m, 3c-H), 3.28 (1H, ddd, *J* = 13.3, 9.5, 1.8 Hz, 7c-H), 3.54 (1H, m, 5c-H), 4.53 (1H, dd, *J* = 11.7, 0.9 Hz, 10-H), 5.62 (1H, dd, *J* = 8.3, 4.5 Hz, 2-H), 6.94 (1H, m, 12-H), 7.22 (1H, m, 15-H), 7.22 (2H, m, *o*-H 10-Ph), 7.26 (1H, m, 13-H), 7.26 (1H, m, *p*-H 10-Ph), 7.27 (1H, m, 14-H), 7.34 (2H, m, *m*-H 10-Ph), 12.98 (1H, br s, 6-H); ^{13}C NMR (150 MHz, $CDCl_3$, 60 °C): δ = 22.1 (C4), 25.3 (C8), 28.4 (C3), 35.5 (C9), 45.8 (C10),

48.6 (C7), 51.2 (C5), 59.2 (C2), 126.8 (C_p of 10-Ph), 127.0 (C15), 127.0 (C14), 128.4 (C_o of 10-Ph), 128.7 (C_m of 10-Ph), 129.3 (C12), 129.8 (C1), 130.7 (C13), 144.4 (C_q of 10-Ph), 147.5 (C11). **16b** ^{1}H NMR (in a mixture with **16a**, ratio **16a** : **16b** = 62 : 38, 600 MHz, $CDCl_3$, 60 °C): δ = 1.65 (1H, m, 8t-H (t = *trans* to 2-H)), 1.98 (1H, m, 9t-H), 2.00 (1H, m, 8c-H (c = *cis* to 2-H)), 2.20 (1H, m, 4c-H), 2.24 (1H, m, 9c-H), 2.42 (1H, m, 3c-H), 2.49 (1H, m, 4t-H), 3.01 (1H, m, 5t-H), 3.05 (1H, m, 7c-H), 3.08 (1H, m, 3t-H), 3.53 (1H, dt, m, 7t-H), 4.13 (1H, m, 5c-H), 4.58 (1H, dd, J = 12.3, 4.0 Hz, 10-H), 4.79 (1H, ddd, J = 11.5, 9.5, 6.3 Hz, 2-H), 6.78 (1H, dd, J = 7.9, 1.4 Hz, 12-H), 7.26 (1H, m, 13-H), 7.26 (1H, m, *p*-H 10-Ph), 7.29 (2H, m, *o*-H 10-Ph), 7.33 (1H, m, 14-H), 7.36 (2H, m, *m*-H 10-Ph), 7.89 (1H, dd, J = 8.0, 1.4 Hz, 15-H), 12.46 (1H, br s, 6-H); ^{13}C NMR (150 MHz, $CDCl_3$, 60 °C): δ = 21.5 (C4), 21.7 (C8), 29.7 (C3), 34.8 (C9), 42.8 (C10), 53.2 (C7), 55.4 (C5), 64.9 (C2), 127.0 (C_p of 10-Ph), 127.5 (C14), 128.0 (C15), 128.2 (C12), 128.5 (C_o of 10-Ph), 128.6 (C_m of 10-Ph), 129.2 (C1), 130.7 (C13), 143.0 (C11), 144.7 (C_q of 10-Ph).

6-Aza-dibenzo[c,f]tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-5-one (20)

2-Benzyl-phenyl-methanol[14] (1.46 g, 7.3 mmol) was converted to the imide **18** by the previously described general procedure, with **18** being purified on SiO_2, eluting with 1 : 1 petrol : DCM and isolated by crystallization from Et_2O as a white solid, 1.8 g (75% yield), mpt 130–133 °C. FT-IR (neat) 1768, 1697, 1421, 1390, 1358, 1331, 1108, 1073, 958, 939, 753, 736, 719, 709, 699 cm^{-1}. Theoretical mass: 327.12538; measured mass: 327.12450. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.27 (2H, s), 4.80 (2H, s), 7.06–7.12 (3H, m), 7.15 (1H, dd, J = 1.7, 7.3 Hz), 7.17–7.25 (4H, m), 7.37 (1H, dd, J = 1.7, 7.1 Hz), 7.68 (2H, dd, J = 3.0, 5.5 Hz), 7.78 (2H, dd, J = 3.0, 5.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.8 (CH_2), 39.3 (CH_2), 123.3 (CH), 126.0 (CH), 126.9 (CH), 128.1 (CH), 128.5 (CH), 129.5 (CH), 131.0 (CH), 132.1 (C), 134.0 (CH), 138.4 (C), 140.5 (C), 168.2 (C). A solution of **18** (0.81 g, 2.5 mmol) was reduced to the hydroxyamide by the procedure described for **7**, extracting the product into $CHCl_3$ (3 × 50 ml), drying and concentrating *in vacuo* to give the hydroxyamide as a white solid (0.75 g, 93% yield), mpt 128–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.33 (1H, d, J = 11 Hz), 4.09 (1H, d, J = 16 Hz), 4.11 (1H, d, J = 16 Hz), 4.18 (1H, d, J = 15 Hz), 4.77 (1H, d, J = 15 Hz), 5.37 (1H, d, J = 11 Hz), 7.05–7.10 (3H, m), 7.14–7.28 (6H, m), 7.31–7.35 (1H, m), 7.44–7.49 (2H, m), 7.56 (1H, d, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.6 (CH_2), 40.0 (CH_2), 81.0 (CH), 123.3 (CH), 123.4 (CH), 126.1 (CH), 127.0 (CH), 128.1 (CH), 128.5 (CH), 128.8 (C), 129.7 (CH), 130.0 (CH), 131.2 (CH), 132.2 (CH), 134.9 (C), 140.5 (C), 143.8 (C), 167.1 (C). A solution of the hydroxyamide (0.65 g, 2 mmol) was cyclised following the general procedure with 2 ml of triflic acid with heating at 50 °C for 15 min. Purification was by column chromatography on SiO_2, eluting with DCM + 20% Et_2O to give **20** as a white solid, mpt 220–222 °C ($CHCl_3$/petrol). FT-IR (neat) 1674, 1467, 1451, 1432, 1401, 1360, 1324, 773, 751, 734, 708, 688 cm^{-1}. Theoretical mass: 311.13047; measured mass: 311.12969. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.34 (1H, d, J = 14.3 Hz), 3.83 (1H, d, J = 14.3 Hz), 4.50 (1H, d, J = 16.6 Hz), 5.20 (1H, d, J = 16.6 Hz), 5.76 (1H, s), 7.11–7.21 (4H, m), 7.23–7.34 (4H, m), 7.45–7.55 (3H, m), 7.88 (1H, d, J = 7.5 Hz): ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.8 (CH_2), 46.2 (CH_2), 67.8 (CH), 122.9 (CH), 123.9 (CH), 127.2 (CH), 127.2 (CH), 127.5 (CH), 128.5 (CH), 128.7 (CH), 129.4 (CH), 129.8 (CH), 131.1 (CH), 131.4 (C), 132.1 (CH), 132.4 (CH), 133.6 (C), 134.6 (C), 137.2 (C), 137.3 (C), 145.0 (C), 168.5 (C).

6-Aza-10-oxa-dibenzo[c,f]tricyclo[9.4.0.0*2,6*]pentadeca-1(11),12,14-trien-5-one (21)

2-Phenoxy-phenyl-methanol[15] (1.5 g, 7.5 mmol) was converted to the imide **19** by the previously described general procedure but with the product **19** being purified on SiO_2, eluting with 3 : 1 petrol : DCM and isolated as a white solid from ether/petrol (1.6 g, 65% yield), mpt 91–93 °C. FT-IR (neat) 1703, 1484, 1428, 1391, 1349, 1330, 1235, 1076, 935, 751, 711, 689 cm^{-1}. Theoretical mass: 329.10464; measured mass: 329.10354. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.97 (2H, s), 6.88 (1H, dd, J = 0.8, 8.1 Hz), 6.95 (2H, dd, J = 0.9, 7.7 Hz), 7.00 (1H, t, J = 7.4 Hz), 7.09 (1H, dt, J = 0.9, 7.5 Hz), 7.20–7.29 (3H, m), 7.32 (1H, dd, J = 1.1, 7.6 Hz), 7.66–7.70 (2H, m), 7.78–7.82 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.0 (CH_2), 118.2 (CH), 119.3 (CH), 123.0 (CH), 123.3 (CH), 123.9 (CH), 127.5 (C), 129.1 (CH), 129.5 (CH), 129.7 (CH), 132.2 (C), 134.0 (CH), 154.4 (C), 157.4 (C), 168.0 (C). A solution of **19** (0.7 g, 2.1 mmol) was reduced to the hydroxyamide by the procedure described for **7**, extracting the product into $CHCl_3$ (3 × 50 ml), drying and concentrating *in vacuo* (0.68 g, 96% yield), isolating as an oil, and used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.85 (1H, d, J = 10.2 Hz), 4.67 (1H, d, J = 15.3 Hz), 4.79 (1H, d, J = 15.3 Hz), 5.72 (1H, d, J = 10.2 Hz), 6.87 (1H, dd, J = 0.6, 8.2 Hz), 6.96 (2H, dd, J = 1.0, 8.7 Hz), 7.05 (1H, dt, J = 0.9, 7.4 Hz), 7.08 (1H, t, J = 7.4 Hz), 7.21 (1H, dt, J = 1.6, 8.0 Hz), 7.28–7.34 (3H, m), 7.38 (1H, dt, J = 0.7, 7.5 Hz), 7.50 (1H, dt, J = 1.0, 7.4 Hz), 7.55 (1H, d, J = 7.5 Hz), 7.65 (1H, d, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.6 (CH_2), 81.5 (CH), 118.1 (CH), 119.2 (CH), 123.3 (CH), 123.5 (CH), 124.3 (CH), 129.2 (CH), 129.8 (CH), 129.9 (CH), 130.5 (C), 130.7 (CH), 131.4 (C), 132.3 (CH), 143.9 (C), 154.60 (C), 157.3 (C), 167.6 (C). A solution of the hydroxyamide (0.66 g, 2 mmol) was cyclised following the general procedure with 2 ml of triflic acid with heating at 50 °C for 15 min. Purification was by column chromatography on SiO_2, eluting with DCM + 20% Et_2O, and gave **21** as a white solid (0.57 g, 86% yield), mpt 234–236 °C ($CHCl_3$/petrol). FT-IR (neat) 1687, 1483, 1464, 1450, 1429, 1390, 1354, 1318, 1215, 811, 779, 761, 748, 737, 713, 686 cm^{-1}. Theoretical mass: 313.10973; measured mass: 313.10919. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.53 (1H, d, J = 16.4 Hz), 4.92 (1H, d, J = 16.4 Hz), 5.80 (1H, s), 7.07–7.16 (m, 2H), 7.18–7.38 (m, 6H), 7.40 (1H, dd, J = 1.1, 7.5 Hz), 7.46 (1H, t, J = 7.3 Hz), 7.51 (1H, dt, J = 0.8, 7.3 Hz), 7.85 (1H, d, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 44.1 (CH_2), 64.56 (CH), 122.5 (CH), 122.8 (CH), 123.8 (CH), 124.0 (CH), 124.9 (CH), 125.8 (CH), 128.2 (C), 128.6 (CH), 129.4 (C), 129.7 (CH), 130.2 (CH), 130.7 (CH), 131.8 (CH), 131.9 (C), 144.5 (C), 155.0 (C), 156.7 (C), 168.8 (C).

4-Phenyl-5,12b-dihydro-6*H*-isoindolo[1,2-a]isoquinolin-8-one (25)

2-Biphenylethan-2-ol[16] was converted to the imide **24** by the previously described general procedure, with **24** being purified on SiO_2, eluting with 1 : 1 petrol : DCM, and isolated as a white solid (~100% yield), mpt 98–101 °C. FT-IR (neat) 1691, 1435, 1399, 1347, 1314, 1255, 1164, 1151, 1111, 921, 820, 761, 741, 716, 666 cm^{-1}. Theoretical mass: 279.12538; measured mass: 279.12539.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.56 (4H, s), 2.88 (2H, t, J = 7.5 Hz), 3.58 (2H, t, J = 7.5 Hz), 7.19–7.50 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0 (CH_2), 30.8 (CH_2), 39.5 (CH_2), 126.7 (CH), 127.1 (CH), 127.4 (CH), 128.3 (CH), 129.2 (CH), 129.7 (CH), 130.4 (CH), 135.3 (C), 141.2 (C), 142.5 (C), 176.8 (C). The imide **24** (0.8 g) was reduced with $NaBH_4$ by the method described in the general procedure to give the hydroxyamide, 0.43 g as an oil, purified on SiO_2, eluting with DCM + 2% MeOH (53% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.70–1.78 (1H, m), 2.06–2.20 (2H, m), 2.34–2.44 (1H, m), 2.76–2.92 (2H, m), 3.09–3.18 (1H, m), 3.24 (1H, d, J = 7.7 Hz), 3.44–3.52 (1H, m), 4.70 (1H, dt, J = 2.3, 7.7 Hz), 7.20–7.45 (9H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.1 (CH_2), 28.9 (CH_2), 31.2 (CH_2), 40.9 (CH_2), 83.3 (CH), 126.7 (CH), 127.2 (CH), 127.7 (CH), 128.3 (CH), 129.3 (CH), 129.9 (CH), 130.3 (CH), 136.2 (C), 141.7 (C), 142.2 (C), 174.7(C). The amide (0.43 g) was cyclised with triflic acid (1.5 ml) following the general procedure and the product purified on SiO_2, eluting with DCM + 1% MeOH to give **25**, 0.33 g (80% yield) as an oil: theoretical mass: 263.13047; measured mass: 262.12977. FT-IR (neat) 1676, 1462, 1416, 1363, 1316, 907, 760, 726, 702 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.97 (1H, tt, J = 9.5, 11.4 Hz), 2.51 (1H, ddd, J = 1.3, 9.3, 16.5 Hz), 2.57–2.65 (2H, m), 2.68–2.75 (1H, m), 2.83–2.90 (1H, m), 2.97–3.03 (1H, m), 4.12 (1H, ddd, J = 3.3, 6.1, 12.9 Hz), 4.84 (1H, t, J = 8.0 Hz), 7.15 (1H, d, J = 7.8 Hz), 7.17 (1H, d, J = 7.4 Hz), 7.25–7.29 (2H, m), 7.31 (1H, t, J = 7.6 Hz), 7.33–7.37 (1H, m), 7.39–7.43 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.4 (CH_2), 27.9 (CH_2), 32.0 (CH_2), 37.3 (CH_2), 57.0 (CH), 124.1 (CH), 126.7 (CH), 127.4 (CH), 128.4 (CH), 128.6 (CH), 129.2 (CH), 131.6 (C), 138.1 (C), 141.0 (C), 142.4 (C), 173.3 (C).

Acknowledgements

The authors would like to thank Dr Lisa D. Haigh for the mass spectra.

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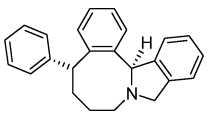

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