

# Stereoselectivity of cyclisations *via* *N*-acyliminium ions to form pyrido[2',3':3,4]pyrrolo[2,1-*a*]isoindole, -isoquinoline and -benz[*c*]azepine ring systems

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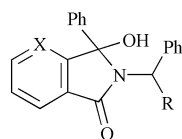
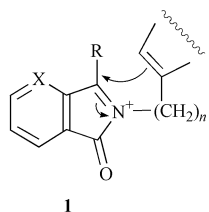
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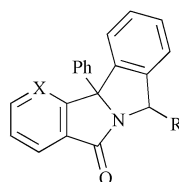
Pyrido[2',3':3,4]pyrrolo[2,1-*a*]isoindole, -isoquinoline and -benz[*c*]azepine derivatives are obtained by heating in polyphosphoric acid (PPA) appropriate hydroxy lactam precursors derived from pyridine-2,3-dicarboximides. The stereoselectivity of ring closure is rationalised by considering the development of A(1,3) strain in the cyclisation step from *N*-acyliminium ion intermediates.

## Introduction

Cyclisations *via* *N*-acyliminium ions provide access to many fused heterocyclic systems<sup>1</sup> and have been widely applied in the synthesis of alkaloids.<sup>2</sup> A variety of 5- and 6-*endo*-cyclisations conform to the general type **1** (X = CH or N), in which the

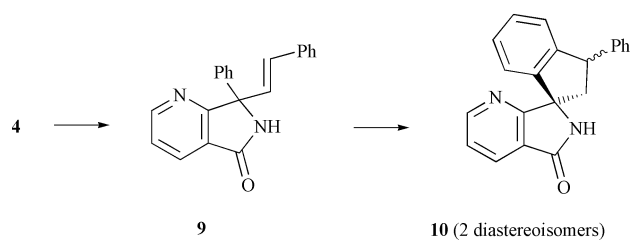


- 2** X = CH, R = H  
**3** X = N, R = H  
**4** X = N, R = Me  
**5** X = N, R = Ph



- 6** X = CH, R = H  
**7** X = N, R = H  
**8** X = N, R = Me

$\pi$ -nucleophile is an aromatic ring attached to nitrogen through one or two carbon atoms.<sup>3-5</sup> In particular, *N*-benzyl hydroxy lactams **2** and **3** on heating in polyphosphoric acid (PPA) undergo cyclisation *via* *N*-acyliminium ion intermediates to give the fused tetracyclic products **6** and **7**, respectively.<sup>3,5</sup> In contrast, hydroxy lactam **4** containing the *N*-(1-phenylethyl) group reacts quite differently, with an extraordinary rearrangement *via* the styrene intermediate **9** to give a 3 : 1 mixture of diastereoisomeric spiro lactams **10** (Scheme 1) instead of the



Scheme 1

expected product(s) **8**.<sup>6</sup> We have described the preparation of a series of spiro lactams related to **10**.<sup>7</sup> In this paper, we return to the possibility of formation of fused heterocyclic products related to **8** and to the stereoselectivity of cyclisation.

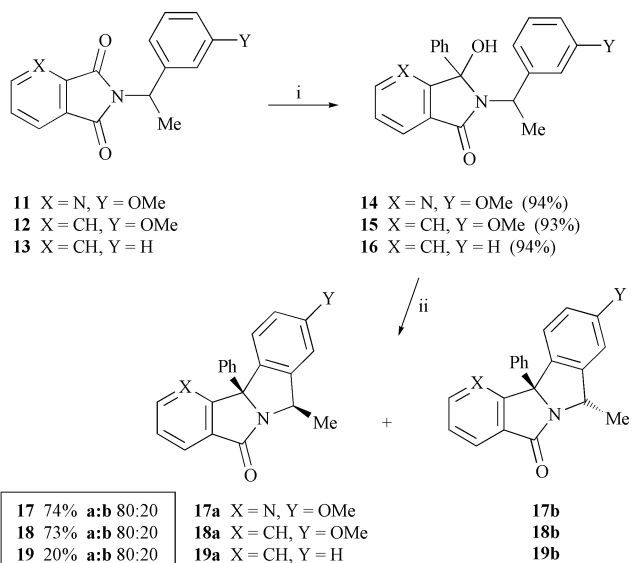
## Results and discussion

The only difference between structures **3** and **4** is the  $\alpha$ -methyl group in the *N*-substituent in **4**, which becomes part of the styryl group in **9** and then part of the indane ring in **10**.<sup>6</sup> Our first strategy to block the rearrangement pathway and thus hopefully to force the alternative cyclisation to **8** was to replace this  $\alpha$ -methyl group by phenyl in the *N*-benzhydryl hydroxy lactam **5**. Maryanoff and co-workers have described 6-*endo*-cyclisations of *N*-acyliminium ions containing 1,2-diphenylethyl or 2,2-diphenylethyl *N*-substituents.<sup>8</sup> However, no identifiable cyclised products were obtainable from **5** by heating in trifluoroacetic acid (TFA) or in PPA, possibly because the benzhydryl group is too easily lost from the *N*-acyliminium ion intermediate.

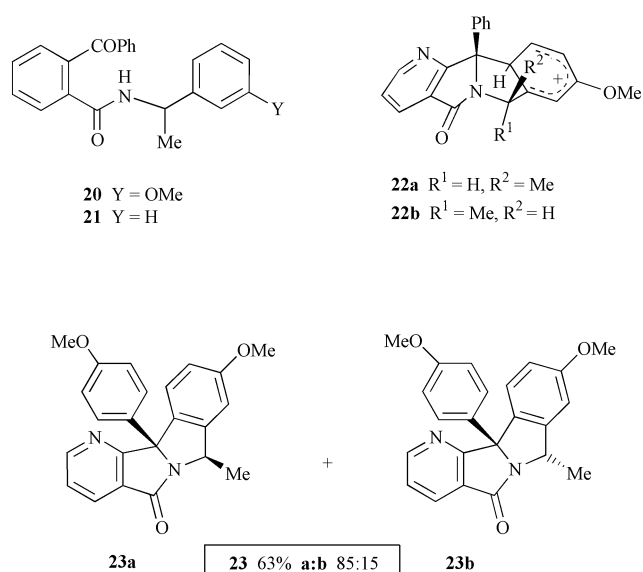
Our second strategy was to activate the ring position for the required 5-*endo*-cyclisation to structure **8** by a *m*-methoxy substituent in the side chain phenyl group. Accordingly, we prepared the hydroxy lactams **14** and **15** by Grignard addition to the corresponding imides **11** and **12** (Scheme 2). Addition to the pyridine-2,3-dicarboximide **11** occurred regioselectively at the more reactive 7-carbonyl group, as shown previously.<sup>5</sup> With a chiral *N*-substituent and a second stereogenic centre at C-7, each of these products **14** and **15** was a mixture of two diastereoisomers, inseparable by chromatography. This is unimportant because the *N*-acyliminium ion intermediate in the ensuing cyclisation step is planar at C-7.

Hydroxy lactam **15**, and likewise **16** (obtained in the same way from imide **13**), were accompanied by the corresponding open chain ketoamides **20** and **21**, respectively,<sup>9</sup> from which they were incompletely separated by chromatography or recrystallisation. For example, the <sup>1</sup>H NMR spectrum of **15** included additional signals for CH ( $\delta$  4.98, quintet) coupled to both NH ( $\delta$  6.32, doublet) and CH<sub>3</sub> ( $\delta$  1.32, doublet) and for OCH<sub>3</sub> ( $\delta$  3.77, singlet). Corresponding <sup>13</sup>C NMR signals were seen for CH, two CH<sub>3</sub> and ketone C=O of **20**. Fortunately, separation was unnecessary, as either hydroxy lactam or ketoamide structure can be the precursor for formation of the same *N*-acyliminium ion intermediate in acidic conditions.

Heating hydroxy lactam **14** in PPA at 100 °C gave a 74% yield of a 4 : 1 mixture of two diastereoisomeric products **17a,b**

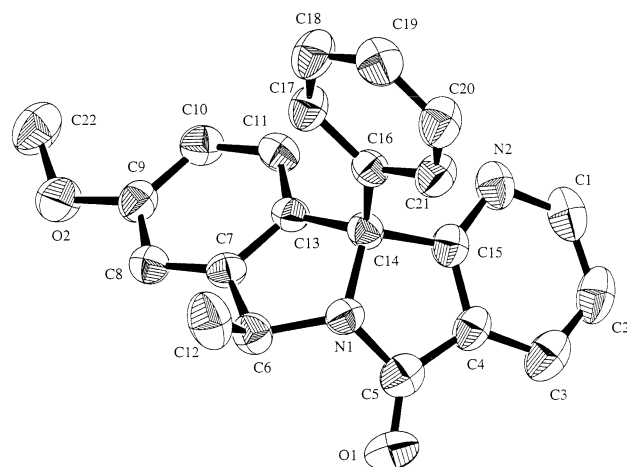


**Scheme 2** Reagents and conditions: (i) PhMgBr; (ii) PPA, 100 °C or AlCl<sub>3</sub>, DCE, -7 °C.



(from the <sup>1</sup>H NMR spectrum), which was inseparable by chromatography. The same result was obtained by heating **14** for 3 days in refluxing TFA. After trials with different binary solvent systems, we succeeded in isolating a pure sample of the major product by fractional crystallisation. When this was reheated to 100 °C in PPA, it was recoverable unchanged, with no equilibration with the minor diastereoisomer, showing that the product ratio is kinetically determined.

NMR spectra provided compelling evidence that the products had the structure **17a,b** and not spiro structures analogous to **10**. In particular, the presence of an extra peak for unprotonated carbon in the aromatic region (not present in the <sup>13</sup>C NMR spectrum of **14**), the splitting pattern of <sup>1</sup>H resonances for the MeO-substituted benzene ring, and the doublet and quartet signals for CH<sub>3</sub>CH (in contrast to the ABX system for ring CH<sub>2</sub>CH in the spiro structure **10**)<sup>6</sup> are consistent with structure **17a,b**. In the <sup>1</sup>H NMR spectra the CH<sub>3</sub> and CH signals were at δ 1.44 and 5.45 for the major isomer, but at δ 2.05 and 4.95 for the minor isomer. If the higher field position in each case is ascribed to shielding by the phenyl group at C-11b,<sup>10</sup> then the major isomer has the *cis*-stereochemistry **17a**. The kinetic preference for formation of the *cis*-isomer can be rationalised in accordance with studies by Hart<sup>11</sup> concerning the effect of substituents *α* to nitrogen on the stereochemical



**Fig. 1** ORTEP drawing of structure **17a** with crystallographic numbering scheme (hydrogen atoms omitted).

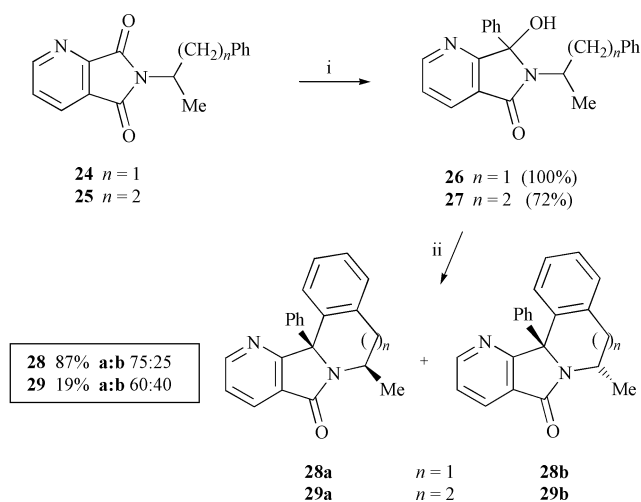
outcome of *N*-acyliminium ion cyclisation to six-membered rings. For reaction of **14**, cyclisation to **17** proceeds *via* structure **22**: A(1,3) strain between the *C*-methyl and carbonyl groups in **22b** determines the preference for the *cis*-stereochemistry **22a**. The fused tetracyclic structure and *cis*-stereochemistry of the major product **17a** were confirmed by single-crystal X-ray diffraction (Fig. 1).

Starting from the same pyridine-2,3-dicarboximide **11** and adding *p*-anisyl Grignard reagent, then heating in PPA, we obtained the fused tetracyclic products **23a,b** in 6 : 1 ratio. The *p*-anisyl group would be expected to stabilise the intermediate *N*-acyliminium ion (*cf.* **1**, R = *p*-anisyl) and thereby to increase the diastereoselectivity of cyclisation.

Analogous cyclisations were also achievable in the phthalimide series, starting from phthalimides **12** and **13** *via* hydroxy lactams **15** and **16** (Scheme 1). The mixture of diastereoisomeric products **18a,b** was obtained by heating **15** in PPA or in TFA and in similar yield and product ratio as for **17a,b**. Again **18a,b** were inseparable by chromatography, and the major component was the *cis*-isomer **18a** with the doublet resonance for CH<sub>3</sub> at higher field (δ 1.34 vs. 2.01 for **18b**). The *m*-methoxy substituent in **14** and **15** is not, after all, essential to obtain cyclisation in the required manner (*cf.* **1**). Although reactions of hydroxy lactam **16** in PPA or TFA were unsuccessful, treatment of **16** with AlCl<sub>3</sub> in 1,2-dichloroethane at -7 °C led to the formation of cyclised products **19a,b** in 20% yield and 4 : 1 ratio in favour of the *cis*-isomer **19a**. This result is consistent with the formation of **6** from **2**,<sup>3</sup> but it is in surprising contrast to the behaviour of **4** in PPA.<sup>6</sup> In spite of the lower yield of fused products **19a,b** from **16**, no spiro by-product analogous to **10** was detected. The presence of the pyridine nitrogen atom in **4** apparently is responsible for the rearrangement *via* **9** to **10**, but the mechanism of this reaction is still partly unexplained.

Further to those 5-*endo*-cyclisations, which are disfavoured by Baldwin's rules, it seemed worthwhile to examine the possibility of 6- and 7-*endo*-cyclisations in related systems and their stereoselectivity. There are, of course, many precedents for *N*-acyliminium ion cyclisations to six-membered rings and several examples of cyclisation to seven-membered rings.<sup>12</sup> Accordingly, we prepared the imides **24** and **25** and from them the hydroxy lactams **26** and **27** (Scheme 3), which are side chain homologues of **4**.

Treatment of **26** with hot PPA afforded a mixture of cyclised products **28a,b** in 87% yield and 3 : 1 ratio (from the <sup>13</sup>C NMR spectrum); reaction in TFA at reflux gave the same products in 89% yield. Assignment of *cis*-stereochemistry **28a** to the major isomer is consistent with earlier results<sup>11</sup> and with a kinetic preference for cyclisation *via* an intermediate, in which the methyl group occupies an axial position in relation to the



**Scheme 3** Reagent and conditions: (i) PhMgBr; (ii) PPA, 100 °C.

newly formed six-membered ring, thereby minimising A(1,3) interaction with the carbonyl group.

The corresponding cyclisation of hydroxy lactam **27** in hot PPA gave the fused azepines **29a,b** in only 19% yield and 3 : 2 ratio. Both the lower yield and lower stereoselectivity are attributable to greater conformational freedom for the longer side chain and for formation of a seven-membered ring. As before, the major product is the *cis*-isomer **29a**, with the CH<sub>3</sub> doublet resonance ( $\delta$  0.54) at higher field than for the *trans*-isomer **29b** ( $\delta$  1.33).

## Experimental

IR Spectra were recorded for Nujol mulls or for solutions in chloroform (Pye-Unicam SP3-2000 or Perkin-Elmer 1420 spectrophotometers) and calibrated with polystyrene. <sup>1</sup>H NMR Spectra were recorded at 90 (JEOL FX90Q) or 270 MHz (JEOL EX 270) and <sup>13</sup>C NMR spectra at 22.5 or 67.5 MHz (on the same instruments) for solutions in deuteriochloroform, unless stated otherwise, and with tetramethylsilane as internal standard. Assignments of <sup>13</sup>C NMR signals were facilitated by recording DEPT spectra. In NMR spectra of diastereoisomeric mixtures, resonances attributed to the minor diastereoisomers are shown in brackets { }. Mass spectra were obtained by electron impact (EI) at 70 eV (VG Autospec). Chromatography was performed on MN-silica gel 60. Tetrahydrofuran (THF) was dried before use. Light petroleum refers to the fraction of bp 60–80 °C.

1-Phenylethylamine was prepared by a Leuckart reaction from acetophenone and ammonium formate.<sup>13</sup> Using the same procedure, 1-(3-methoxyphenyl)ethylamine<sup>14</sup> was prepared from *m*-methoxyacetophenone, 1-phenylpropan-2-ylamine<sup>15</sup> (benzedrine) from phenylacetone, and 4-phenylbutan-2-ylamine<sup>16</sup> from 4-phenylbutan-2-one; all these amines had bp in agreement with literature values and NMR and mass spectra consistent with their structures.

*N*-(1-Phenylethyl)phthalimide **13** was prepared as described in ref. 7. The same procedure using phthalic anhydride (4.4 g, 30 mmol) and 1-(*m*-methoxyphenyl)ethylamine (4.5 g, 30 mmol) afforded *N*-[1-(3-methoxyphenyl)ethyl]phthalimide **12** (5.8 g, 69%), mp 61–62 °C (from toluene–light petroleum) (HREIMS Found: M<sup>+</sup> 281.1044. C<sub>17</sub>H<sub>15</sub>NO<sub>3</sub> requires *M* 281.1052); IR (Nujol)  $\nu_{\max}/\text{cm}^{-1}$  1770 and 1700 (C=O); <sup>1</sup>H NMR (90 MHz)  $\delta$  1.91 (3H, d, *J* 7.3 Hz, CHCH<sub>3</sub>), 3.78 (3H, s, OCH<sub>3</sub>), 5.53 (1H, q, *J* 7.3 Hz, CHCH<sub>3</sub>), 6.79 (1H, ddd, *J* 1.5, 2.6 and 7.7 Hz, ArH), 7.04–7.33 (3H, m, ArH) and 7.59–7.85 (4H, m, ArH); <sup>13</sup>C NMR (22.5 MHz)  $\delta$  17.5 (CH<sub>3</sub>), 48.8 (CH), 54.8 (CH<sub>3</sub>), 112.2 (CH), 112.7 (CH), 118.7 (CH), 122.9 (CH), 129.4 (CH), 131.2 (CH), 134.3 (C), 142.2 (C), 159.2 (C) and 167.6 (C); MS *m/z* 281 (M<sup>+</sup>, 100%), 266 (67), 130 (40), 105 (16) and 77 (15).

## General procedure for preparation of *N*-substituted pyridine-2,3-dicarboximides

Pyridine-2,3-dicarboxylic anhydride was freshly prepared by heating pyridine-2,3-dicarboxylic acid in acetic anhydride under reflux for 2.5 h, then evaporating to dryness. An equimolar amount of the required amine was added, dissolved in dry THF, and the solution heated under reflux for 2 h. The solvent was evaporated and replaced by acetic anhydride. The mixture was heated again under reflux for 3 h, concentrated by removal of most of the solvent, cooled and poured into ice-water. The resulting solid was crushed, filtered, thoroughly washed with water, dried and recrystallised from toluene–light petroleum.

**6-[1-(3-Methoxyphenyl)ethyl]-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione **11**.** Obtained from pyridine-2,3-dicarboxylic acid (9.0 g) and 1-(*m*-methoxyphenyl)ethylamine (8.2 g). Yield 7.3 g (48%), mp 80–81 °C (HREIMS Found M<sup>+</sup> 282.1005. C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> requires *M* 282.1004); IR (Nujol)  $\nu_{\max}/\text{cm}^{-1}$  1715 (C=O); <sup>1</sup>H NMR (270 MHz)  $\delta$  1.94 (3H, d, *J* 7.3 Hz, CH<sub>3</sub>), 3.79 (3H, s, OCH<sub>3</sub>), 5.60 (1H, q, *J* 7.3 Hz, CHCH<sub>3</sub>), 6.80–7.28 (4H, m, ArH), 7.59 (1H, dd, *J* 5.1 and 7.5 Hz, H-3), 8.11 (1H, dd, *J* 1.5 and 7.5 Hz, H-4) and 8.95 (1H, dd, *J* 1.5 and 5.1 Hz, H-2); <sup>13</sup>C NMR (67.5 MHz)  $\delta$  17.6 (CH<sub>3</sub>), 50.0 (CH), 55.2 (CH<sub>3</sub>), 113.2 (CH), 113.4 (CH), 119.8 (CH), 127.2 (C), 127.4 (CH), 129.6 (CH), 131.1 (CH), 141.4 (C), 151.4 (C), 155.2 (CH), 159.7 (C), 166.0 (C) and 166.1 (C); MS *m/z* 282 (M<sup>+</sup>, 100%), 267 (16), 254 (25), 239 (37), 184 (30) and 78 (46).

**6-(1-Phenylpropan-2-yl)-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione **24**.** Obtained from pyridine-2,3-dicarboxylic acid (6.0 g) and 1-phenylpropan-2-ylamine (5.0 g). Yield 7.0 g (70%), mp 94–95 °C (HREIMS Found: M<sup>+</sup> 266.1055. C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> requires *M* 266.1055); IR (CHCl<sub>3</sub>)  $\nu_{\max}/\text{cm}^{-1}$  1720 (C=O); <sup>1</sup>H NMR (90 MHz)  $\delta$  1.55 (3H, d, *J* 7.0 Hz, CH<sub>3</sub>), 3.11 (1H, dd, *J* 7.0 and 13.7 Hz, PhCH<sub>a</sub>), 3.36 (1H, dd, *J* 9.2 and 13.7 Hz, PhCH<sub>b</sub>), 4.76 (1H, m, CH), 7.16 (5H, s, C<sub>6</sub>H<sub>5</sub>), 7.55 (1H, dd, *J* 4.8 and 7.7 Hz, H-3), 8.11 (1H, dd, *J* 1.5 and 7.5 Hz, H-4) and 8.95 (1H, dd, *J* 1.5 and 5.1 Hz, H-2); <sup>13</sup>C NMR (22.5 MHz)  $\delta$  18.2 (CH<sub>3</sub>), 39.6 (CH<sub>2</sub>), 48.9 (CH), 126.5 (CH), 126.7 (CH), 127.2 (CH), 128.3 (C), 128.7 (CH), 130.8 (CH), 137.9 (C), 151.1 (C), 154.9 (CH), 165.9 (C) and 166.1 (C); MS *m/z* 282 (M<sup>+</sup>, 100%), 267 (16), 254 (25), 239 (37), 184 (30) and 78 (46).

**6-(4-Phenylbutan-2-yl)-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione **25**.** Obtained from pyridine-2,3-dicarboxylic acid (1.4 g) and 4-phenylbutan-2-ylamine (1.4 g). The crude product was purified by chromatography on silica, with ethyl acetate–chloroform (1 : 4 v/v) as eluent. Yield 2.1 g (82%), mp 91–92 °C (HREIMS Found: M<sup>+</sup> 280.1216. C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub> requires *M* 280.1212); <sup>1</sup>H NMR (270 MHz)  $\delta$  1.51 (3H, d, *J* 6.9 Hz, CH<sub>3</sub>), 2.05 (1H, m) and 2.48–2.75 (3H, m, 2 × CH<sub>2</sub>), 4.47 (1H, m, NCHCH<sub>3</sub>), 6.96–7.16 (5H, m, ArH), 7.57 (1H, dd, *J* 5.0 and 7.6 Hz, H-3), 8.06 (1H, dd, *J* 1.3 and 7.6 Hz, H-4) and 8.92 (1H, dd, *J* 1.3 and 5.0 Hz, H-2); <sup>13</sup>C NMR (67.5 MHz)  $\delta$  19.0 (CH<sub>3</sub>), 33.4 (CH<sub>2</sub>), 34.5 (CH<sub>2</sub>), 47.9 (CH), 125.7 (CH), 127.0 (C), 127.2 (CH), 128.3 (2 × CH), 130.9 (CH), 140.8 (C), 151.4 (C), 155.0 (CH), 166.3 (C) and 166.4 (C); MS *m/z* 280 (M<sup>+</sup>, 27%), 176 (100), 149 (27), 131 (26), 117 (25), 91 (34) and 79 (40).

## General procedure to prepare hydroxy lactams

The Grignard reagent was prepared from bromobenzene and magnesium in dry THF under nitrogen; reaction was completed by heating under reflux for 1–2 h. The Grignard solution was cooled to 0 °C and the imide dissolved in dry THF was added rapidly with stirring; an excess of the Grignard reagent was employed (typically 4 : 1 mole ratio to imide). The mixture was stirred at 0 °C for 3–4 h, then poured into saturated aqueous NH<sub>4</sub>Cl solution and extracted thrice with chloroform. The combined extracts were washed with water, dried (MgSO<sub>4</sub>),

filtered and the filtrate evaporated to dryness. The crude product was purified by chromatography on silica, eluting with ethyl acetate–chloroform (1 : 4 v/v).

**7-Hydroxy-6-[1-(3-methoxyphenyl)ethyl]-7-phenyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one 14.** Obtained from imide **11** (1.0 g, 3.55 mmol) and Grignard reagent from bromobenzene (2.20 g, 14.0 mmol) and magnesium (0.34 g). Yield 1.2 g (94%), mp 160–162 °C (from toluene–light petroleum) (Found: C, 73.3; H, 5.7; N, 7.7. C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub> requires C, 73.3; H, 5.6; N, 7.8%); <sup>1</sup>H NMR (90 MHz) δ 1.58 and {1.70} (3H, d, *J* 7.2 Hz, CH<sub>3</sub>), {3.58} and 3.63 (3H, s, OCH<sub>3</sub>), 4.32 and {4.45} (1H, s, OH) overlapping {4.40} and 4.61 (1H, q, *J* 7.2 Hz, CHCH<sub>3</sub>), 6.54–6.67 (2H, m, ArH *ortho* to OMe) and 7.00–8.55 (10H, m, other ArH).

**3-Hydroxy-2-[1-(3-methoxyphenyl)ethyl]-3-phenyl-2,3-dihydro-1H-isoindol-1-one 15.** Obtained from imide **12** (1.0 g, 3.56 mmol) and Grignard reagent from bromobenzene (2.26 g, 14.4 mmol) and magnesium (0.35 g). Yield of crude product, which also contains ketoamide **20**, 1.19 g (93%); mp 137.5–139 °C of **15** (from ethyl acetate–light petroleum) (Found: C, 77.0; H, 6.1; N, 3.9. C<sub>23</sub>H<sub>21</sub>NO<sub>3</sub> requires C, 76.9; H, 5.9; N, 3.9%); <sup>1</sup>H NMR (90 MHz) δ 1.63 and {1.73} (3H, d, *J* 7.3 Hz, CH<sub>3</sub>), {3.61} and 3.69 (3H, s, OCH<sub>3</sub>), 3.79 and {3.92} (1H, s, OH), 4.45 and {4.72} (1H, q, *J* 7.3 Hz, CHCH<sub>3</sub>) and 6.58–7.75 (13H, m, ArH); <sup>13</sup>C NMR (22.5 MHz) δ 18.5 and {19.6} (CH<sub>3</sub>), 52.2 and {52.9} (CH), 55.0 and {55.4} (CH<sub>3</sub>), 91.9 and {92.4} (C), 112.4, 112.8, 113.3, 113.9, 120.3, 120.5, 122.5, 123.1, 126.4, 126.7, 128.0, 128.2, 128.3, 128.6, 129.0, 129.3, 129.9, 131.2, 131.3, 132.4, 138.8, 144.1, 144.4, 148.5, 148.7, 158.9, 159.1 and 167.5; MS *m/z* 359 (M<sup>+</sup>, 2%), 210 (27), 209 (30), 151 (29), 150 (100), 105 (14) and 77 (19). Additional NMR signals due to the ketoamide **20**: δ<sub>H</sub> 1.31 (3H, d, *J* 7.2 Hz, CH<sub>3</sub>), 3.76 (3H, s, OCH<sub>3</sub>), 4.96 (1H, quintet, *J* 7.2 Hz, CHCH<sub>3</sub>) and 6.33 br (1H, d, *J* 7.2 Hz, NH); δ<sub>C</sub> 21.3 (CH<sub>3</sub>), 49.5 (CH), 55.3 (CH<sub>3</sub>), 112.3 (CH), 112.9 (CH), 118.6 (CH), 135.6 (C), 137.0 (C), 144.3 (C), 159.8 (C), 166.8 (amide C=O) and 197.8 (ketone C=O).

**3-Hydroxy-2-(1-phenylethyl)-3-phenyl-2,3-dihydro-1H-isoindol-1-one 16.** Obtained from imide **13** (1.0 g, 3.98 mmol) and Grignard reagent from bromobenzene (2.51 g, 16.0 mmol) and magnesium (0.39 g). Yield of crude product, which also contained ketoamide **21**, 1.34 g (94%); mp 111–112 °C (from toluene–light petroleum) (Found: C, 79.9; H, 6.0; N, 4.1. C<sub>22</sub>H<sub>19</sub>NO<sub>2</sub> requires C, 80.2; H, 5.8; N, 4.25%); IR (CHCl<sub>3</sub>) ν<sub>max</sub>/cm<sup>-1</sup> 3370 (OH), 1690 and 1635 (C=O); <sup>1</sup>H NMR (90 MHz) δ 1.67 (3H, d, *J* 6.9 Hz, CH<sub>3</sub>), 3.12 br (1H, s, OH), 4.49 (1H, q, *J* 6.9 Hz, CHCH<sub>3</sub>) and 7.08–7.80 (14H, m, ArH); MS *m/z* M<sup>+</sup> absent, 314 (M – Me, 1%), 313 (2), 298 (1), 210 (20), 209 (28) and 120 (100). Additional NMR signals due to the ketoamide **21**: δ<sub>H</sub> 1.34 (3H, d, *J* 7.2 Hz, CH<sub>3</sub>), 5.02 (1H, quintet, *J* 7.2 Hz, CHCH<sub>3</sub>) and 6.32 br (1H, d, *J* 7.2 Hz, NH); δ<sub>C</sub> 166.6 (amide C=O) and 197.7 (ketone C=O).

**7-Hydroxy-6-(phenylpropan-2-yl)-7-phenyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one 26.** Obtained from imide **24** (1.0 g, 3.76 mmol) and Grignard reagent from bromobenzene (2.39 g, 15.2 mmol) and magnesium (0.37 g). Yield 1.31 g (100%), mp 185–187 °C (from toluene–light petroleum) (Found: M<sup>+</sup>, 344.1531. C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub> requires *M*, 344.1525); IR (CHCl<sub>3</sub>) ν<sub>max</sub>/cm<sup>-1</sup> 3400 (br, OH) and 1700 (C=O); <sup>1</sup>H NMR (90 MHz) δ 1.22 and {1.38} (3H, d, *J* 6.8 Hz, CH<sub>3</sub>), 2.83 (1H, s, OH), 2.90–3.13 (2H, m, overlapping CHCH<sub>3</sub> of two diastereoisomers), 3.30–3.65 (2H, m, CH<sub>2</sub>), 7.08–7.40 (11H, m, ArH), 8.08 (1H, dd, *J* 1.5 and 7.5 Hz, H-4) and 8.46 (1H, dd, *J* 1.5 and 4.8 Hz, H-2); <sup>13</sup>C NMR (22.5 MHz) δ 17.7 and {17.9} (CH<sub>3</sub>), 40.4 and {40.7} (CH<sub>2</sub>), {51.2} and 51.7 (CH), 90.9 and {91.7} (C), 124.3 (CH), 125.5 (CH), 126.1 (CH), 126.6 (2 × CH), 128.4 (2 × CH), 128.5 (2 × CH), 128.7 (CH), 129.1 (C), 129.3 (2 × CH), 131.5 (CH),

136.8 and {137.1} (C), {139.3} and 139.7 (C), {152.6} and 153.0 (CH), 165.7 (C) and 166.3 (C); MS *m/z* 344 (M<sup>+</sup>, 0.2%), 253 (M – CH<sub>2</sub>Ph, 25) and 210 (100).

**7-Hydroxy-6-(4-phenylbutan-2-yl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one 27.** Obtained from imide **25** (1.0 g, 3.57 mmol) and Grignard reagent from bromobenzene (2.26 g, 14.4 mmol) and magnesium 0.35 g. Yield 0.92 g (72%), mp 192–195 °C (from toluene–light petroleum) (HREIMS Found: M<sup>+</sup>, 358.1685. C<sub>23</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> requires *M*, 358.1681); <sup>1</sup>H NMR (270 MHz) δ 1.16 and 1.41 (3H, d, *J* 6.9 Hz, CH<sub>3</sub>), 1.84–2.29 (2H, m, CH<sub>2</sub>Ph), 2.31–2.46 and 2.50–2.71 (2H, m, CHCH<sub>3</sub>), 3.47 and 3.49 (1H, overlapping sext., *J* 7.2 Hz, CHCH<sub>3</sub>), 5.00 and 5.07 (1H, s, OH), 6.85 (1H, dd, *J* 1.5 and 7.8 Hz, ArH), 7.05–7.42 (10H, m, ArH), 8.02 (1H, dd, *J* 1.3 and 7.6 Hz, H-4) and 8.42 (1H, dd, *J* 1.3 and 4.9 Hz, H-2); <sup>13</sup>C NMR (67.5 MHz) δ 17.8 and 18.6 (CH<sub>3</sub>), 33.0 and 33.4 (CH<sub>2</sub>), 35.2 and 36.0 (CH<sub>2</sub>), 48.9 and 49.5 (CH), 91.2 and 91.5 (C), 124.4 (CH), 125.6 and 125.7 (CH), 126.0 and 126.1 (C), 126.6 (2 × CH), 128.1 and 128.2 (CH), 128.3 (2 × CH), 128.5 (CH) 128.7 (CH), 129.0 (CH), 131.8 (CH), 137.3 and 137.5 (C), 141.3 and 141.9 (C), 152.6 (CH), 165.2 and 165.4 (C), 166.3 and 166.4 (C); MS *m/z* 358 (M<sup>+</sup>, 9%), 253 (23), 211 (73), 210 (100), 182 (14), 154 (21), 91 (17) and 77 (18).

#### General procedure for cyclisations in PPA

The hydroxy lactam was dissolved in PPA and heated at 100–125 °C. The hot solution was poured onto crushed ice and the mixture extracted thrice with chloroform. The organic extract was washed by shaking with NaHCO<sub>3</sub> solution, then dried (MgSO<sub>4</sub>), filtered, and the filtrate evaporated to dryness. The residue was chromatographed on silica with ethyl acetate–chloroform (1 : 4 v/v) as eluent.

#### General procedure for cyclisations in TFA

The hydroxy lactam was dissolved in TFA and the solution heated under reflux. The mixture was cooled and poured in small portions into an excess of saturated NaHCO<sub>3</sub> solution. This solution was extracted thrice with chloroform, the combined extracts dried (MgSO<sub>4</sub>), filtered, and the filtrate evaporated to dryness. The residue was chromatographed on silica with ethyl acetate–chloroform (1 : 4 v/v) as eluent.

**9-Methoxy-7-methyl-11b-phenyl-7,11b-dihydro-5H-pyrrolo[2,3':3,4]pyrrolo[2,1-*a*]isoindol-5-ones 17a,b.** Obtained from hydroxy lactam **14** (0.47 g, 1.31 mmol) in PPA (32 g) heated at 100–110 °C for 1 h. Yield 0.33 g (74%), diastereoisomer ratio **17a** : **17b** 80 : 20 unchanged by chromatography and almost unchanged after recrystallisation (toluene–light petroleum), mp 193–195 °C. A sample was dissolved in ethyl acetate and ether added carefully to form an upper layer; the flask was stoppered and left undisturbed while the layers mixed by diffusion and crystals of the pure *cis*-isomer **17a** separated, mp 205–206 °C (Found: C, 77.5; H, 5.6; N, 8.0%; M<sup>+</sup>, 342.1368. C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub> requires C, 77.2; H, 5.3; N, 8.2%; *M*, 342.1368). IR (CHCl<sub>3</sub>) ν<sub>max</sub>/cm<sup>-1</sup> 1720 (C=O); <sup>1</sup>H NMR (90 MHz) δ 1.44 (3H, d, *J* 7.0 Hz, CH<sub>3</sub>), 3.77 (3H, s, OCH<sub>3</sub>), 5.44 (1H, q, *J* 7.0 Hz, H-7), 6.76 (1H, d, *J* 2.4 Hz, H-8), 6.92 (1H, dd, *J* 2.4 and 8.5 Hz, H-10), 7.20–7.50 (6H, m, other ArH), 7.90 (1H, d, *J* 8.5 Hz, H-11), 8.11 (1H, dd, *J* 1.5 and 7.7 Hz, H-4) and 8.70 (1H, dd, *J* 1.7 and 4.8 Hz, H-2); <sup>13</sup>C NMR (22.5 MHz) δ 22.7 (CH<sub>3</sub>), 55.6 (CH<sub>3</sub>), 58.2 (CH), 108.3 (CH), 113.7 (CH), 123.6 (CH), 125.3 (CH), 125.5 (CH), 126.4 (2 × CH), 128.0 (CH), 128.5 (2 × CH), 130.0 (C), 133.0 (CH), 140.9 (C), 147.7 (C), 153.7 (CH), 160.7 (C), 169.5 (C) and 172.5 (C). In CDCl<sub>3</sub> the resonance for quaternary C-11b was masked by solvent signals, but in DMSO-*d*<sub>6</sub> it was seen at δ 81.7. MS *m/z* 342 (M<sup>+</sup>, 42%), 327 (M – Me, 12), 266 (18) and 265 (M – Ph, 100). Hydroxy lactam **14** (0.34 g) was dissolved in TFA (10 ml) and heated under reflux for 72 h. **17a,b**

(0.24 g, 74%) was obtained with the same diastereoisomer ratio as before and mp 193–195 °C after recrystallisation (toluene–light petroleum). <sup>1</sup>H NMR signals for *trans* isomer **17b**: δ 2.05 (3H, d, *J* 7.0 Hz, CH<sub>3</sub>) and 4.95 (1H, q, Hz, H-7); signals for OCH<sub>3</sub> and aromatic H not resolved from corresponding signals for **17a**.

**9-Methoxy-7-methyl-11b-phenyl-7,11b-dihydro-5H-isindolo[1,2-*a*]isindol-5-ones 18a,b.** Obtained from hydroxy lactam **15** (0.56 g, 1.57 mmol) in PPA (35 g) heated at 100–110 °C for 1 h. Yield 0.39 g (73%), diastereoisomer ratio **18a** : **18b** 80 : 20 unchanged by chromatography, mp 107–108 °C (from toluene–light petroleum) (Found: C, 81.3; H, 5.9; N, 4.1%. M<sup>+</sup>, 341.1436. C<sub>23</sub>H<sub>19</sub>NO<sub>2</sub> requires C, 81.0; H, 5.6; N, 4.1%. *M*, 341.1416). IR (CHCl<sub>3</sub>)  $\nu_{\max}/\text{cm}^{-1}$  1710 (C=O); <sup>1</sup>H NMR (270 MHz) δ 1.34 and {2.02} (3H, d, *J* 7.0 Hz, CH<sub>3</sub>), 3.80 (3H, s, OCH<sub>3</sub>), {4.80} and 5.39 (1H, q, *J* 7.0 Hz, H-7), 6.75 (1H, d, *J* 2.2 Hz, H-8), 6.89 (1H, dd, *J* 2.4 and 8.2 Hz, H-10), 7.10–7.80 (10H, m, other ArH) and 7.83 (1H, d, *J* 7.3 Hz, ArH); <sup>13</sup>C NMR (22.5 MHz) δ 21.6 (CH<sub>3</sub>), 55.5 (CH<sub>3</sub>), 57.6 (CH), 78.1 (C), 108.3 (CH), 113.4 (CH), 122.5 (CH), 124.3 (CH), 124.7 (CH), 126.3 (2 × CH), 127.5 (CH), 128.3 (2 × CH), 129.0 (C), 131.2 (C), 131.5 (C), 132.9 (CH), 142.7 (C), 148.2 (C), 151.9 (C), 160.3 (C) and 174.3 (C); MS *m/z* 341 (M<sup>+</sup>, 7%), 326 (M – Me, 4), 265 (19), 264 (M – Ph, 100) and 92 (29).

Hydroxy lactam **15** (0.54 g) was dissolved in TFA (15 ml) and heated under reflux for 72 h. After chromatography, **18a,b** (0.42 g, 82%) was obtained with the same diastereoisomer ratio as before and mp 108–109 °C after recrystallisation (toluene–light petroleum).

**7-Methyl-11b-phenyl-7,11b-dihydro-5H-isindolo[1,2-*a*]isindol-5-ones 19a,b.** Hydroxy lactam **16** (0.71 g, 2.16 mmol) in 1,2-dichloroethane (25 ml) was added slowly to a solution of aluminium trichloride (1.15 g, 8.3 mmol) in 1,2-dichloroethane (20 ml) cooled at –7 °C. The mixture was stirred at this temperature for 4 h. It was then poured onto crushed ice and, after addition of dilute sulfuric acid, extracted with chloroform (2 × 20 ml). The combined extracts were dried (MgSO<sub>4</sub>) and evaporated to dryness. The solid residue was chromatographed on silica with ethyl acetate–chloroform (1 : 15 v/v) as eluent to give **19a,b** (0.13 g, 19%), in the ratio 80 : 20 after recrystallisation from toluene–light petroleum, mp 151–153 °C (HREIMS Found: M<sup>+</sup>, 311.1289. C<sub>22</sub>H<sub>17</sub>NO requires *M*, 311.1310). <sup>1</sup>H NMR (90 MHz) δ 1.35 and {2.03} (3H, d, *J* 7.0 Hz, CH<sub>3</sub>), {4.83} and 5.44 (1H, q, *J* 7.0 Hz, H-7), and 7.26–7.87 (13H, m, ArH); <sup>13</sup>C NMR (22.5 MHz) δ {16.7} and 21.6 (CH<sub>3</sub>), {57.1} and 57.6 (CH), C-11b signal masked by solvent peaks, {122.2} and 122.7 (CH), 123.2 (CH), 123.9 (CH), {124.1} and 124.3 (CH), 126.0 (CH), 126.3 (CH), 127.2 (CH), 127.6 (CH), 128.4 (CH), 128.5 (CH), 131.6 (C), {132.4} and 133.0 (CH), 139.1 (C), 142.4 (C), 146.6 (C), 151.5 (C) and 174.3 (C); MS *m/z* 311 (M<sup>+</sup>, 16%), 296 (34), 235 (18), 234 (M – Ph, 100) and 219 (16). Starting material **16** (0.15 g, 21%) was recovered from later fractions eluted with ethyl acetate–chloroform (1 : 4 v/v).

**9-Methoxy-11b-(4-methoxyphenyl)-7-methyl-7,11b-dihydro-5H-pyrido[2',3':3,4]pyrrolo[2,1-*a*]isindol-5-ones 23a,b.** Imide **11** (1.0 g, 3.55 mmol) was treated with the Grignard reagent prepared from 4-methoxybromobenzene (2.85 g) and magnesium (0.37 g) according to the general procedure. Yield 1.2 g (87%) of a viscous oil, which was a mixture of hydroxy lactam and ketoamide (from <sup>1</sup>H and <sup>13</sup>C NMR spectra). This crude product (0.60 g) was heated with PPA (48 g) at 100–110 °C for 1 h. Work-up according to the general procedure afforded the fused tetracyclic products **23a,b** (0.36 g, 63%) in 85 : 15 ratio (from <sup>1</sup>H NMR spectrum), mp 180–182 °C (from toluene–light petroleum) (Found: C, 74.2; H, 5.5; N, 7.6. C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub> requires C, 74.2; H, 5.4; N, 7.5%); IR (CHCl<sub>3</sub>)  $\nu_{\max}/\text{cm}^{-1}$  1725w (C=O); <sup>1</sup>H NMR (90 MHz) δ 1.44 and {2.03} (3H, d, *J* 6.8 Hz, CH<sub>3</sub>),

3.74 and 3.80 (each 3H, s, OCH<sub>3</sub>), 5.44 (1H, q, *J* 6.8 Hz, CHCH<sub>3</sub>), 6.75–6.96 (4H, m, ArH *ortho* to OCH<sub>3</sub>), 7.24–7.45 (3H, m, other ArH), 7.86 (1H, d, *J* 8.3 Hz, H-3), 8.07 (1H, dd, *J* 1.7 and 7.6 Hz, H-4) and 8.73 (1H, dd, *J* 1.6 and 4.9 Hz, H-2); <sup>13</sup>C NMR (22.5 MHz) δ 16.7 (CH<sub>3</sub>), 55.2 (CH<sub>2</sub>), 55.5 (CH<sub>3</sub>), 58.1 (CH), 78.2 (C), 108.2 (C), 113.4 (CH), 113.8 (CH), 123.2 (CH), 125.1 (CH), 125.3 (CH), 127.2 (CH), 127.6 (CH), 130.5 (C), 132.1 (C), 132.6 (CH), 133.1 (C), 147.7 (C), 153.7 (CH), 159.1 (C), 160.5 (C), 169.7 (C) and 172.3 (C); MS *m/z* 372 (M<sup>+</sup>, 20%), 265 (M – C<sub>6</sub>H<sub>4</sub>OMe, 32) and 91 (100).

**6-Methyl-12b-phenyl-5,12b-dihydropyrido[2',3':3,4]pyrrolo[2,1-*a*]isoquinolin-8(6H)-ones 28a,b.** Obtained from hydroxy lactam **26** (0.45 g, 1.31 mmol) in PPA (36 g) heated at 100–110 °C. Yield 0.37 g (87%), diastereoisomer ratio **28a** : **28b** 75 : 25 after recrystallisation from toluene–light petroleum, mp 215–217 °C (HREIMS Found: M<sup>+</sup>, 326.1421. C<sub>22</sub>N<sub>18</sub>N<sub>2</sub>O requires *M*, 326.1419). IR (CHCl<sub>3</sub>)  $\nu_{\max}/\text{cm}^{-1}$  1690 (C=O); <sup>1</sup>H NMR (90 MHz) δ 1.51 (3H, d, *J* 6.3 Hz, CH<sub>3</sub>), 2.25–3.05 (2H, m, CH<sub>2</sub>), 4.15–4.53 (1H, m, H-6), 7.08–7.55 (9H, m, ArH), 7.93–8.36 (2H, m, H-9 and H-10) and 8.71 (1H, dd, *J* 1.6 and 4.9 Hz, H-11); <sup>13</sup>C NMR (22.5 MHz) δ 18.4 and {21.2} (CH<sub>3</sub>), {35.9} and 36.1 (CH<sub>2</sub>), 47.2 and {47.7} (CH), 71.2 (C), 123.0, 123.2, 125.1, 126.0, 126.2, 126.5, 126.7, 127.7, 127.9, 128.1, 128.3, 128.6, 129.5, 131.8, 132.1, 135.0, 135.7, 135.9, 136.5, 139.5, 141.0, 152.3, 152.5, 166.6, 167.2 and 167.5; MS *m/z* 326 (M<sup>+</sup>, 10%), 311 (M – Me, 11), 250 (18), 249 (M – Ph, 100) and 233 (19).

Hydroxy lactam **26** (0.31 g) was dissolved in TFA (9 ml) and heated under reflux for 24 h. Work-up afforded **28a,b** (0.26 g, 89%) with <sup>1</sup>H and <sup>13</sup>C NMR spectra and diastereoisomer ratio the same as above.

**7-Methyl-13b-phenyl-5,6,7,13b-tetrahydro-9H-pyrido[2',3':3,4]pyrrolo[2,1-*a*]benz[*c*]azepin-9-ones 29a,b.** Obtained from hydroxy lactam **27** (0.60 g, 1.67 mmol) in PPA (32 g) heated at 120–125 °C for 1 h. Yield 0.11 g (19%), diastereoisomer ratio **29a** : **29b** 60 : 40 after recrystallisation from toluene–light petroleum, mp 170–172 °C (HREIMS Found: M<sup>+</sup>, 340.1560. C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O requires *M*, 340.1576). <sup>1</sup>H NMR (270 MHz) δ 0.54 and {1.33} (3H, d, *J* 6.9 Hz, CH<sub>3</sub>), 1.71–3.10 (4H, m, 2 × CH<sub>2</sub>), {3.82–3.91} and 4.91–5.00 (1H, m, H-7), 6.85–6.87 (2H, m, ArH), 7.10–7.41 (8H, m, ArH), {7.66–7.70} and 8.11–8.18 (1H, m, H-10), {8.48–8.53} and 8.70–8.75 (1H, m, H-12); <sup>13</sup>C NMR (67.5 MHz) δ {18.0} and 19.6 (CH<sub>3</sub>), {31.5} and 32.8 (CH<sub>2</sub>), {32.4} and 33.5 (CH<sub>2</sub>), {48.1} and 50.3 (CH), 75.1 and {77.8} (C), 123.3 and {123.5} (CH), 125.1 (C), 125.3 and {126.5} (CH), {126.8} (C), 127.4 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 129.5 (CH), 131.0 (CH), 131.5 (CH), 131.6 (CH), 131.9 (CH) 132.4 (CH), 132.5 (CH), {135.6} and 136.1 (C), {138.8} and 141.3 (C), {142.3} and 142.6 (C), {152.6} and 153.3 (CH), {166.9} and 167.1 (C) and {167.7} and 170.3 (C); MS *m/z* 340 (M<sup>+</sup>, 41%), 326 (17), 325 (M – Me, 65), 264 (21), 263 (M – Ph, 100) and 221 (12).

#### X-Ray analysis of **17a** †

X-Ray analysis of **17a** was carried out on a Rigaku AFC6S four-circle diffractometer with graphite-monochromated Mo-K $\alpha$  radiation,  $\lambda = 0.71070$  Å, at 20 °C. **17a** C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>, *M* = 382.38. The crystal was monoclinic, space group *P*2<sub>1</sub>/*c*, with unit cell *a* = 7.729(2), *b* = 11.983(3), *c* = 18.615(3) Å,  $\beta = 93.13^\circ$ , *V* = 1721.5(6) Å<sup>3</sup>, *Z* = 4, *D*<sub>c</sub> = 1.321 g cm<sup>-3</sup>,  $\mu = 0.86$  cm<sup>-1</sup>. 1756 reflections collected in the range  $5 < 2\theta < 40^\circ$ , of which 1602 were independent (*R*<sub>int</sub> 0.0538). Full matrix least-squares refinement on *F*<sup>2</sup> with 236 variable parameters for 1599 reflections with *I* > 2 $\sigma$ (*I*) gave final *R*<sub>1</sub> = 0.0321 and *wR*<sub>2</sub> = 0.0781.

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