

**UNEXPECTED RESULTS IN THE REDUCTION OF TETRACYCLIC ENAMIDES.  
STRUCTURE, STEREOCHEMISTRY AND CONFORMATION OF A 20 $\beta$ -HYDROPEROXYIMINE**

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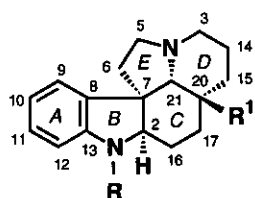
**Abstract** - Reduction of *N<sub>B</sub>*-allyl-20-ethyltetracyclic enamide (7) with lithium aluminium hydride afforded the expected enamine (12) and 4a-oxoethylhexahydrocarbazolones (18a,b). Reduction of *N<sub>B</sub>*-unsubstituted enamide (6), under the same conditions, gave imine (9), enamine (11) and a 20 $\beta$ -hydroperoxytetracyclic imine (19) resulting from the peroxydation of 9 and 11. The C-20 stereochemistry of 19 was established by means of 2D <sup>1</sup>H nmr and NOE difference spectroscopy.

Alkaloids of the *Aspidosperma* genus are biologically important<sup>1</sup> and their pharmacological activity has stimulated a great deal of work on their synthesis. In our program devoted to studies in this series,<sup>2,3</sup> tetracyclic enamides (4)<sup>2</sup> and (5)<sup>3</sup> were used as key intermediates in a total synthesis of *N<sub>A</sub>*-benzyl-20-desethylaspidospermidine (1). Reduction of 4 with LiAlH<sub>4</sub> afforded imine (8)<sup>2</sup> while reduction of 5 afforded enamine (10)<sup>3</sup> (Scheme 1). However most of the *Aspidosperma* alkaloids possess an ethyl chain in C-20<sup>4</sup> [e.g. aspidospermidine (2)]. One possible strategy involves the introduction of the 20-ethyl group at the first step of the synthesis *i.e.* into the original *N*-benzylenaminone from which hexahydrocarbazolones (13a,b) were synthesized.<sup>5</sup> We report herein our results on the reduction of 20-ethyl tetracyclic enamides (6) and (7).

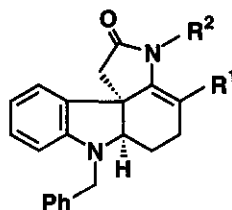
Compounds (6) and (7) were prepared from 13a,b which were isolated in a 30:70 ratio as previously described.<sup>5</sup> The thermodynamic enolates of 13a,b were alkylated with iodoacetamide or *N*-allyliodoacetamide according to published methods.<sup>2,3</sup> The reaction afforded a mixture of 4a-carbamoylmethylhexahydrocarbazolones (14a) and tetracyclic hydroxyamides (15a,b) in a 10:90 ratio and 70% yield in the *N<sub>B</sub>*-unsubstituted series and a mixture of (16a,b) and (17a,b) in a 60:40 ratio and 69% yield in the *N<sub>B</sub>*-allyl series (Scheme 2). In contrast to the results observed in the absence of a C-3 substituent (R<sup>1</sup> = H),<sup>2,3</sup> the cyclization of 14 and 16 to 15 and 17 is not completely spontaneous. Compounds (16a) and (16b) were separated easily while 15a,b and 17a,b were both isolated as a mixture of C-20 isomers. The stereochemistry of the B/C ring junction has been found to be *cis* for compounds (14-17).<sup>5-7</sup> and thermodynamic considerations led us to assign a *cis* C/E ring junction for 15 and 17 as previously mentioned in the series R<sup>1</sup> = H.<sup>2,3</sup> Moreover 15, 16 and 17 were obtained as a mixture of isomers at C-20. Although the C-3 (future C-20) stereochemistry of the ethyl chain would have to be destroyed in the subsequent dehydration step, we established it for 14a, 16a and 16b. This stereochemistry is supported by spectroscopic data in agreement with a previous article.<sup>5</sup> Thus, in <sup>1</sup>H nmr <sup>3</sup>J<sub>9a-1ax</sub> and <sup>3</sup>J<sub>9a-1eq</sub> are almost identical for the  $\beta$ -ethyl compound (16b) ( $\approx$  4 Hz) and different for the  $\alpha$ -ethyl derivatives (14a) and (16a) ( $\approx$  9 and 6 Hz). Concerning amido alcohols (15a,b) and (17a,b), the C-20

stereochemistry was attributed tentatively by comparison with some other tetracyclic compounds, in particular with tetracyclic nitrones and amines.<sup>8</sup> In the <sup>1</sup>H and <sup>13</sup>C nmr, Me-18 of tetracyclic derivatives appears at higher field for β-ethyl isomers than for α-ethyl isomers.

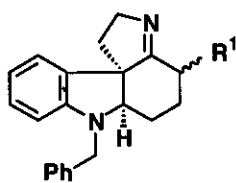
## Scheme 1



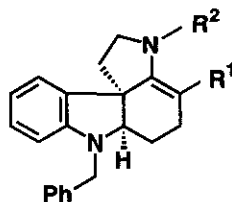
- 1: R = CH<sub>2</sub>Ph ; R<sup>1</sup> = H  
 2: R = H ; R<sup>1</sup> = Et  
 3: R = Ac ; R<sup>1</sup> = OH



- 4: R<sup>1</sup> = R<sup>2</sup> = H  
 5: R<sup>1</sup> = H ; R<sup>2</sup> = allyl  
 6: R<sup>1</sup> = Et ; R<sup>2</sup> = H  
 7: R<sup>1</sup> = Et ; R<sup>2</sup> = allyl



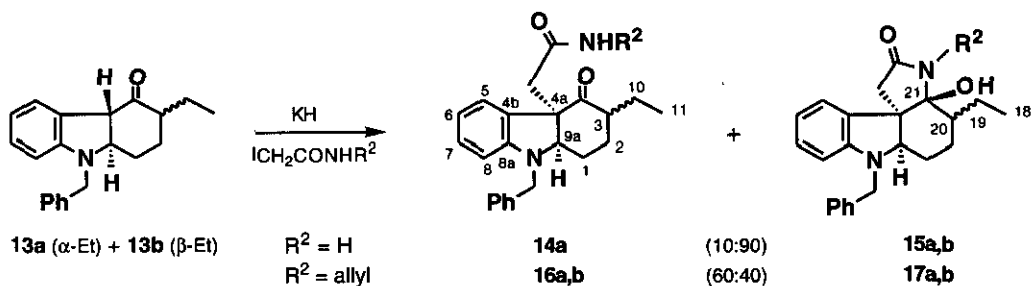
- 8: R<sup>1</sup> = H  
 9: R<sup>1</sup> = Et



- 10: R<sup>1</sup> = H ; R<sup>2</sup> = allyl  
 11: R<sup>1</sup> = Et ; R<sup>2</sup> = H  
 12: R<sup>1</sup> = Et ; R<sup>2</sup> = allyl

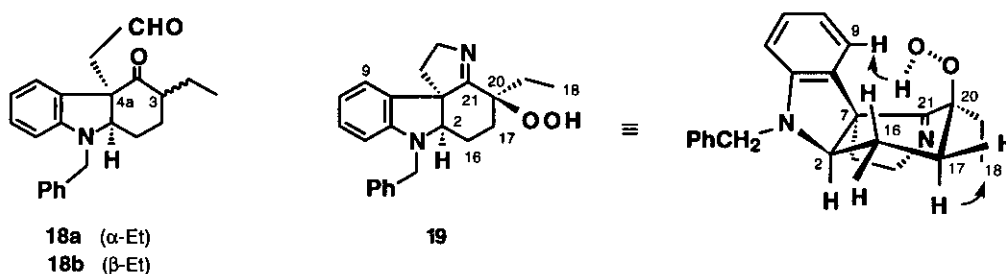
Acidic treatment of **15a,b** and **17a,b** (CH<sub>2</sub>Cl<sub>2</sub>, reflux, camphorsulfonic acid, molecular sieves) led to enamides (**6**) and (**7**) respectively, in good yield (≈90%). Formation of **6** from **14a** and formation of **7** from **16a** or **16b** required stronger conditions (C<sub>6</sub>H<sub>6</sub>, reflux, camphorsulfonic acid, Dean Stark).

## Scheme 2



Reduction of **6** and **7** was performed under the usual conditions<sup>2,3,9</sup> ( $\text{LiAlH}_4$ , THF,  $65^\circ\text{C}$ ). In the  $N_B$ -allyl series, the reaction gave the expected and unstable enamine (**12**) in a yield estimated to be 25-30% and afforded essentially 4a-oxoethylhexahydrocarbazolones (**18a,b**) (25:75) as a mixture of isomers at C-3 (isolated yield 62%) (Scheme 3). Compounds **18a** and **18b** are characterized by a singlet at  $\delta \approx 9.6$  ppm (aldehydic H) in the  $^1\text{H}$  nmr spectra and by a signal at  $\delta \approx 200$  ppm (formyl CO) in the  $^{13}\text{C}$  nmr spectra. The  $\alpha$  or  $\beta$ -ethyl stereochemistry was established as previously indicated for **14** and **16**. In both compounds, the ethyl group is quasi-equatorial and the two isomers correspond to the two chair forms of the C ring.<sup>5</sup>

Scheme 3



In the  $N_B$ -unsubstituted series, the reaction led to the unstable enamine (**11**) in equilibrium with its imine tautomer (**9**) and to a tetracyclic hydroperoxyimine (**19**) in a range of 30-50% yield depending on the reaction conditions (air or inert atmosphere) (Scheme 3). Compound (**19**) was isolated as a single isomer. It shows OH and C=N absorptions at 3620 and  $1640\text{ cm}^{-1}$  respectively in the ir spectrum and a C-21 signal (C=N) at  $\delta 177.4$  ppm in the  $^{13}\text{C}$  nmr spectrum. Its C-20 stereochemistry was established by 2D  $^1\text{H}$  nmr and NOE difference spectroscopy. The sequence H-2, H-16ax, H-17ax with large coupling constants ( $J = 8.0\text{-}9.5$  Hz) was deduced from a  $^1\text{H}$ - $^1\text{H}$  COSY experiment, and it is characteristic of a chair C ring conformation with an axial H-2 proton. Moreover irradiation of the H-17ax hydrogen (1.45 ppm) led to a nuclear Overhauser effect on the  $\text{CH}_3$ -18 group (0.95 ppm, 8%) and irradiation of OOH (7.08 ppm) produces a nuclear Overhauser effect on H-9 proton (6.96 ppm, 7%). Such effects which would occur exclusively on the isomer with an axial OOH enable us to conclude unambiguously on a  $\beta$ -OOH stereochemistry for carbon C-20 (Scheme 3). Distances of  $\approx 2.0\text{-}2.5$  Å can be approximately measured, on molecular models, between the concerned hydrogens. The distance  $\text{H}_9\text{-H}_{\text{OOH}}$  has been estimated in a favored conformation which allowed the formation of an hydrogen bond between the hydrogen  $\text{H}_{\text{OOH}}$  and the nitrogen  $N_B$ .

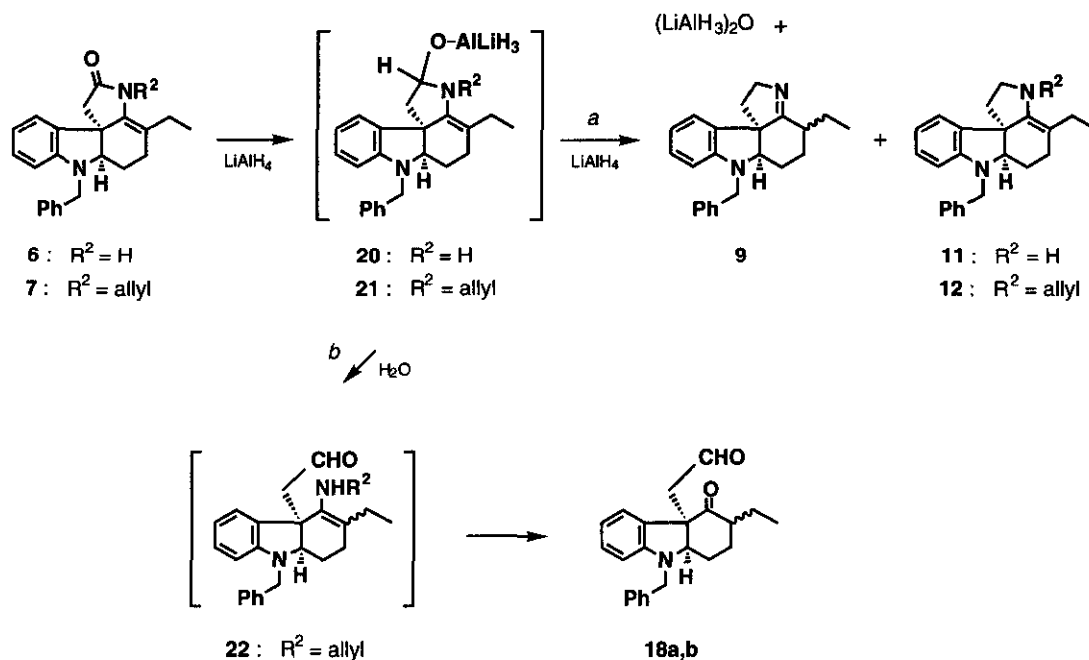
## DISCUSSION

### \* Formation of 4a-oxoethyl hexahydrocarbazolones (**18a,b**)

The mechanism of amide reduction postulated by Weygand<sup>10,11</sup> invokes a tetrahedral intermediate type **20** or **21**. This presumed complex can react further by different routes: (i) a nucleophilic attack by a second hydride on the carbon-oxygen bond will form imine (**9**) and enamine (**11**) from **20** or enamine (**12**) from **21** (path a); (ii) a hydrolysis will prevent the second step of the reduction and convert the intermediate (**20**) or (**21**) into the keto aldehydes (**18a,b**) via a presumed enamino aldehyde (**22**) (path b) (Scheme 4). Thus, aldehydes (**18a,b**) corresponds to partial reduction derivatives. In the

$N_b$ -unsubstituted series, the reaction evolves exclusively by path *a* as usually observed on reduction of secondary amides.<sup>11</sup> It leads to the mixture of imine (**9**) and enamine (**11**). In contrast, both pathways are followed in the  $N_b$ -allyl series as mentioned for the reduction of tertiary amides.<sup>11</sup> The reaction gives rise to enamide (**12**) and 4-oxoethylhexahydrocarbazolones (**18a,b**).

Scheme 4

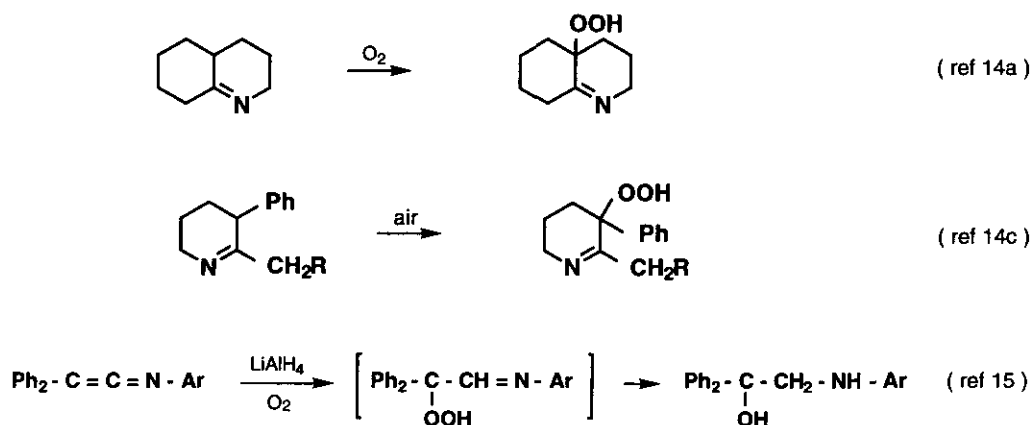


\* Formation of the hydroperoxyimine (**19**)

The literature relates few examples of the introduction of an hydroperoxy linkage  $\alpha$  to an imine function. Thus, autoxidation of cyclic imines or enamines by molecular oxygen is known to give the corresponding hydroperoxyimine.<sup>12 - 14</sup> On another hand, it has been observed that molecular oxygen intervenes in the metal hydride reduction of compounds containing carbon-nitrogen double bonds; thus reduction by  $\text{LiAlH}_4$  of an arylketimine is reported to lead to the corresponding  $\alpha$ -hydroxyamine via an hydroperoxy intermediate<sup>15</sup> (Scheme 5).

In the case concerning us, cyclic imine (**9**) and enamine (**11**) undergo reduction with hydride. The resulting metal salt is very reactive to molecular oxygen as was the Stevens and Gasser's analogue.<sup>15</sup> It gives hydroperoxide (**19**) whose fair stability in a crystalline state is probably due to its tertiary nature in a crowded polycyclic molecule and to the existence of intramolecular hydrogen bonds.

Scheme 5



## CONCLUSION

Reduction of tetracyclic enamides (**6**) ( $R^2 = H$ ) and (**7**) ( $R^2 = \text{allyl}$ ) by  $\text{LiAlH}_4$  gives unexpected results. In the  $N_B$ -allyl series, formation of 4a-oxoethylhexahydrocarbazolones (**18a,b**) prevents further investigations towards the building of the pentacyclic framework. In contrast isolation of the hydroperoxyimino (**19**), in the  $N_B$ -unsubstituted series, represents an interesting result. This compound, with an appropriate side chain on carbon C-20 [ $R^1 = (\text{CH}_2)_3\text{X}$ ] could be a key intermediate in the synthesis of alkaloids which possess a 20 $\beta$ -hydroxy group such as deoxyaspidodispermine (**3**).

## EXPERIMENTAL

Organic layers were dried over  $\text{MgSO}_4$ . Thin layer chromatography was performed with Merck silica gel 60 F254 and flash column chromatography was carried out with Merck silica gel 0.040-0.063 nm. Melting points were taken on a Reicher hot-stage microscope and are uncorrected. Infrared spectra were run on a Perkin-Elmer 377 spectrophotometer ( $\nu$  values in  $\text{cm}^{-1}$ ). Mass spectra were measured on a Varian CH5 or on a Varian VG 30F apparatus under electronic impact (ei).  $^{13}\text{C}$  Nmr spectra were recorded on Jeol FX60 or Bruker MSL 300 spectrometers and  $^1\text{H}$  nmr spectra on Jeol C60H, Bruker MSL 300 or Bruker AC 400 instruments ( $\delta$  values in ppm,  $J$  values in Hz). The applied pulse sequence was  $(\pi/2)$ ,  $t_1$ ,  $(\pi/4)$ , FID,  $t_2$ , for the  $^1\text{H}$  nmr COSY spectrum. Homonuclear Overhauser effects were generated by saturating selected proton signals with a low-power 4s decoupler pulse. NOE difference spectra were obtained by subtracting alternately right-off resonance-free induction decays (FIDs) from right-on resonance-induced FIDs.

### *cis*-3-Ethyl-4a-(carbamoylmethyl)-9-benzylhexahydrocarbazol-4-one (**14a**)

### 21-Hydroxy-20-ethyl-5-oxo-1-benzyl-octahydropyrrolocarbazoles (**15a,b**)

A solution of **13a,b** (30:70) (915 mg, 3.0 mmol) in THF (18 ml) was added dropwise to a suspension of KH (33% in oil, 468 mg, 3.9 mmol) in THF (9 ml) and stirred at room temperature for 15 min under an atmosphere of argon. The resulting medium was added to a solution of iodoacetamide (666 mg, 3.6 mmol) in THF (18 ml). The mixture was stirred again for 30 min, then water was added and the majority of THF was distilled. The aqueous phase was extracted with AcOEt. The

organic layer was dried and concentrated. The crude product was purified by flash chromatography with 60:40 hexane-AcOEt to give **14a** (76 mg, 7%) and **15a,b** (684 mg, 63%, ratio 75:25).

**14a**: white crystals; mp 155-157°C (hexane-AcOEt); ir (CHCl<sub>3</sub>) 3505, 3395 (NH), 1685, 1635 (C=O), 1595; <sup>1</sup>H nmr (CDCl<sub>3</sub>, 300 MHz) δ 0.80 (t, 3H, Me-11, *J* = 7.0), 1.35 (ddq, 1H, H-10B, *J* = 14.0, 7.0, 7.0), 1.47 (m, 2H, H-1ax, H-2ax), 1.75-1.90 (m, 3H, H-10A, H-1eq, H-2eq), 2.00 (m, 1H, H-3), 2.76 (AB, 2H, CH<sub>2</sub>CO, *J* = 16.0, Δ*v* = 128.0), 4.06 (dd, 1H, H-9a, *J* = 9.5, 5.5), 4.25 (AB, 2H, NCH<sub>2</sub>Ph, *J* = 15.5, Δ*v* = 49.0), 5.45 (d, 2H, NH<sub>2</sub>, *J* = 34.0), 6.30 (d, 1H, H-8, *J* = 8.0), 6.56 (t, 1H, H-6, *J* = 8.0), 6.81 (d, 1H, H-5, *J* = 8.0), 7.00 (t, 1H, H-7, *J* = 8.0), 7.30 (m, 5H, ArH); <sup>13</sup>C nmr (CDCl<sub>3</sub>, 75 MHz) δ 11.4 (CH<sub>3</sub>-11), 22.4 (C-10), 24.1 (C-1), 25.4 (C-2), 41.9 (CH<sub>2</sub>CO), 48.7 (C-3), 49.2 (NCH<sub>2</sub>Ph), 58.6 (C-4a), 70.1 (C-9a), 107.4 (C-8), 117.9 (C-6), 123.3 (C-5), 127.3 (C-7), 127.5-129.2 (5 Ar CH), 129.6 (C-4b), 138.3 (C-1'), 149.8 (C-8a), 173.3 (CONH<sub>2</sub>), 209.6 (CO); ms (*m/z*, %) 362 (M<sup>+</sup>, 6), 304 (30), 290 (1), 275 (18), 246 (11), 234 (48), 220 (44), 198 (10), 169 (8), 156 (14), 144 (11), 119 (17), 117 (21), 91 (100), 85 (16), 77 (16), 65 (16), 47 (37), 35 (29); exact mass calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub> 362.1994, found 362.1991. Anal. Calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>: C, 76.21; H, 7.23; N, 7.73. Found: C, 75.97; H, 7.38; N, 7.45.

**15a,b**: white solid; mp 100-105°C (ether); ir (CHCl<sub>3</sub>) 3510 (OH), 3400 (NH), 1690 (CO), 1600; <sup>1</sup>H nmr (CD<sub>3</sub>COCD<sub>3</sub>, 400 MHz) δ 0.75 and 0.90\* (major isomer peak is indicated by an asterisk) (2t, 3H, Me-18, *J* = 7.5), 1.05-2.10 (m, 7H, 2H-16, 2H-17, 2H-19, H-20), 2.58\* (AB, 2H, 2H-6, *J* = 15.0, Δ*v* = 96.0) and 2.60 (AB, 2H, 2H-6, *J* = 17.0, Δ*v* = 66.5), 2.90 (s, 1H, OH), 3.45\* (t, 1H, H-2, *J* = 4.5) and 3.54 (dd, 1H, H-2, *J* = 7.0, 5.0), 4.28 (AB, 2H, NCH<sub>2</sub>Ph, *J* = 16.5, Δ*v* = 78.3) and 4.30\* (AB, 2H, NCH<sub>2</sub>Ph, *J* = 16.5, Δ*v* = 129.0), 6.37 and 6.45\* (2d, 1H, H-12, *J* = 7.8), 6.62 and 6.66\* (2t, 1H, H-10, *J* = 7.8), 6.90 and 7.03\* (2t, 1H, H-11, *J* = 7.8), 7.22 and 7.23\* (2d, 1H, H-9, *J* = 7.8), 7.35 (m, 5H, ArH), 9.10 (br s, 1H, NH); <sup>13</sup>C nmr (CD<sub>3</sub>COCD<sub>3</sub>, 15 MHz) δ 11.9 and 12.7\* (CH<sub>3</sub>-18), 21.2\* and 23.3 (C-19), 21.5\* and 25.0 (C-16), 23.0\* and 26.2 (C-17), 42.6\* and 46.3 (C-6), 47.2\* and 49.9 (C-20), 50.3 and 50.9\* (NCH<sub>2</sub>Ph), 54.9\* and 58.1 (C-7), 69.1\* and 70.1 (C-2), 90.8 and 90.9\* (C-21), 107.0 and 108.9\* (C-12), 117.6 and 119.1\* (C-10), 124.8\* and 124.9 (C-9), 126.7 and 127.7\* (C-11), 128.2-129.5 (5 Ar CH), 131.0 and 131.7\* (C-8), 139.9 (C-1'), 152.1 and 153.5\* (C-13), 173.3 and 174.3\* (CO); ms (*m/z*, %) 362 (M<sup>+</sup>, 19), 344 (10), 304 (23), 290 (5), 275 (10), 253 (7), 246 (6), 234 (12), 220 (10), 130 (6), 91 (100), 65 (8), 41 (6); exact mass calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub> 362.1994, found 362.1991.

#### ***cis*-3-Ethyl-4a-(*N*-allylcarbamoylmethyl)-9-benzylhexahydrocarbazol-4-one (16a,b)**

#### **21-Hydroxy-20-ethyl-5-oxo-4-allyl-1-benzyl-octahydropyrrolocarbazoles (17a,b)**

These compounds were prepared from hexahydrocarbazolones (**13a,b**) (30:70) (915 mg, 3.0 mmol) and *N*-allyl-iodoacetamide (810 mg, 3.6 mmol) following the conditions described for the preparation of **14a** and **15a,b**. Flash chromatography on silica gel, with 80:20 hexane-AcOEt, gave **16a** (274 mg, 23%), **16b** (225 mg, 19%) and **17a,b** (333 mg, 27%, ratio 30:70).

**16a**: white solid; mp 124-125°C (cyclohexane); ir (CCl<sub>4</sub>) 3445 (NH), 1675 (CO), 1590; <sup>1</sup>H nmr (CDCl<sub>3</sub>, 300 MHz) δ 0.80 (t, 3H, Me-11, *J* = 7.5), 1.33 (ddq, 1H, H-10B, *J* = 14.0, 7.5, 7.5), 1.46 (m, 2H, H-1ax, H-2ax), 1.70-1.90 (m, 3H, H-1eq, H-2eq, H-10A), 2.0 (m, 1H, H-3), 2.75 (AB, 2H, CH<sub>2</sub>CO, *J* = 17.0, Δ*v* = 135.0), 3.70 (t, 2H, NCH<sub>2</sub>-CH=CH<sub>2</sub>, *J* = 5.5), 4.10 (dd, 1H, H-9a, *J* = 9.0, 5.0), 4.27 (AB, 2H, NCH<sub>2</sub>Ph, *J* = 16.0, Δ*v* = 47.0), 5.03 (m, 2H, NCH<sub>2</sub>-CH=CH<sub>2</sub>), 5.50 (br s, 1H, NH), 5.70 (m, 1H, NCH<sub>2</sub>-CH=CH<sub>2</sub>), 6.30 (d, 1H, H-8, *J* = 8.0), 6.56 (t, 1H, H-6, *J* = 8.0), 6.80 (d, 1H, H-5, *J* = 8.0), 6.98 (t, 1H, H-7, *J* = 8.0), 7.30 (m, 5H, ArH); <sup>13</sup>C nmr (CDCl<sub>3</sub>, 15 MHz) δ 11.4 (CH<sub>3</sub>-11), 22.4 (C-10), 24.0 (C-1), 25.3 (C-2), 41.8 (CH<sub>2</sub>CO), 42.4 (NCH<sub>2</sub>-CH=CH<sub>2</sub>), 48.7 (C-3), 49.2 (NCH<sub>2</sub>Ph), 58.7 (C-4a), 70.0 (C-9a), 107.4 (C-8), 116.2 (NCH<sub>2</sub>-CH=CH<sub>2</sub>), 117.9 (C-6), 123.3 (C-5), 128.6 (C-7), 127.5-129.1 (5 Ar CH), 129.8 (C-4b), 134.2 (NCH<sub>2</sub>-CH=CH<sub>2</sub>), 138.4 (C-

1'), 149.8 (C-8a), 170.6 (CONH), 211.1 (CO); ms (*m/z*, %) 402 ( $M^{+}$ , 9), 304 (90), 275 (8), 246 (6), 234 (12), 220 (8), 130 (7), 91 (100); exact mass calcd for  $C_{26}H_{30}N_2O_2$  402.2307, found 402.2321. Anal. Calcd for  $C_{26}H_{30}N_2O_2$ : C, 77.58; H, 7.51; N, 6.96. Found: C, 78.01; H, 7.59; N, 6.66.

**16b**: yellow crystals; mp 114-115°C (cyclohexane); ir ( $CCl_4$ ) 3440 (NH), 1680 (CO), 1590;  $^1H$  nmr ( $CDCl_3$ , 300 MHz)  $\delta$  0.80 (t, 3H, Me-11,  $J = 7.5$ ), 1.17 (ddq, 1H, H-10B,  $J = 14.0, 7.0, 7.5$ ), 1.57-1.70 (m, 2H, H-10A, H-2ax), 1.77-1.92 (m, 3H, H-2eq, 2H-1), 2.30 (dddd, 1H, H-3,  $J = 9.0, 7.0, 7.0, 6.0$ ), 2.82 (AB, 2H,  $CH_2CO$ ,  $J = 16.0$ ,  $\Delta\nu = 196.0$ ), 3.76 (t, 2H,  $NCH_2-CH=CH_2$ ,  $J = 5.5$ ), 4.16 (dd, 1H, H-9a,  $J = 4.5, 3.5$ ), 4.38 (AB, 2H,  $NCH_2Ph$ ,  $J = 16.0$ ,  $\Delta\nu = 47.0$ ), 5.10 (m, 2H,  $NCH_2-CH=CH_2$ ), 5.68 (br s, 1H, NH), 5.75 (m, 1H,  $NCH_2-CH=CH_2$ ), 6.35 (d, 1H, H-8,  $J = 8.0$ ), 6.56 (t, 1H, H-6,  $J = 8.0$ ), 6.88 (d, 1H, H-5,  $J = 8.0$ ), 7.04 (t, 1H, H-7,  $J = 8.0$ ), 7.30 (m, 5H, ArH);  $^{13}C$  nmr ( $CDCl_3$ , 300 MHz)  $\delta$  11.7 ( $CH_3-11$ ), 22.5 (C-10), 25.0 (C-1), 26.4 (C-2), 41.8 ( $CH_2CO$ ), 45.5 ( $NCH_2-CH=CH_2$ ), 49.8 ( $NCH_2Ph$ ), 50.2 (C-3), 58.3 (C-4a), 69.1 (C-9a), 106.4 (C-8), 116.2 ( $NCH_2-CH=CH_2$ ), 117.2 (C-6), 124.2 (C-5), 127.3-129.3 (5 Ar CH), 128.1 (C-4b), 134.2 ( $NCH_2-CH=CH_2$ ), 138.6 (C-1'), 151.3 (C-8a), 170.3 (CONH), 211.9 (CO); ms (*m/z*, %) 402 ( $M^{+}$ , 12), 304 (100), 290 (3), 275 (8), 246 (6), 234 (12), 220 (7), 198 (2), 130 (7), 91 (70); exact mass calcd for  $C_{26}H_{30}N_2O_2$  402.2307, found 402.2301. Anal. Calcd for  $C_{26}H_{30}N_2O_2$ : C, 77.58; H, 7.51; N, 6.96. Found: C, 77.44; H, 7.55; N, 6.82.

**17a,b**: white solid; mp 144-149°C (ether); ir (KBr) 3315 (br, OH) 1670 (CO), 1600;  $^1H$  nmr ( $CD_3COCD_3$ , 300 MHz)  $\delta$  0.84\* and 0.88 (major isomer peak is indicated by an asterisk) (2t, 3H, Me-18,  $J = 7.5$ ), 1.17-2.05 (m, 7H, 2H-16, 2H-17, 2H-19, H-20), 2.60 (AB, 2H, 2H-6,  $J = 17.5$ ,  $\Delta\nu = 18.0$ ) and 2.61\* (AB, 2H, 2H-6,  $J = 16.5$ ,  $\Delta\nu = 91.0$ ), 2.86 (s, 1H, OH), 3.32\* (dd, 1H, H-2,  $J = 7.0, 5.0$ ) and 3.58 (dd, 1H, H-2,  $J = 4.0, 3.0$ ), 3.91 (m, 2H,  $NCH_2-CH=CH_2$ ), 4.32 (AB, 2H,  $NCH_2Ph$ ,  $J = 16.0$ ,  $\Delta\nu = 90.0$ ) 5.13 (m, 2H,  $NCH_2-CH=CH_2$ ), 5.90 (m, 1H,  $NCH_2-CH=CH_2$ ), 6.45\* and 6.47 (2d, 1H, H-12,  $J = 8.0$ ), 6.65\* and 6.70 (2t, 1H, H-10,  $J = 8.0$ ), 7.03\* and 7.05 (2t, 1H, H-11,  $J = 8.0$ ), 7.12 and 7.28\* (2d, 1H, H-9,  $J = 8.0$ ), 7.40 (m, 5H, ArH);  $^{13}C$  nmr ( $CD_3COCD_3$ , 75 MHz)  $\delta$  12.5\* and 12.8 ( $CH_3-18$ ), 19.2 and 20.8\* (C-19), 20.0 and 21.3\* (C-16 and C-17), 42.1\* and 42.6 (C-6), 42.9 ( $NCH_2-CH=CH_2$ ), 43.6 and 44.0\* (C-20), 50.1\* and 51.3 ( $NCH_2Ph$ ), 53.2 and 53.9\* (C-7), 69.9 and 70.2\* (C-2), 93.6 and 94.6\* (C-21), 108.4\* and 108.9 (C-12), 116.8\* and 117.0 ( $NCH_2-CH=CH_2$ ), 118.8\* and 119.1 (C-10), 124.9 and 125.5\* (C-9), 127.7\* and 127.9 (C-11), 128.2-129.7 (5 Ar CH), 131.5\* and 131.6 (C-8), 136.0 ( $NCH_2-CH=CH_2$ ), 139.7\* and 140.0 (C-1'), 152.5\* and 153.8 (C-13), 172.9 and 173.8\* (CO); ms (*m/z*, %) 402 ( $M^{+}$ , 25), 331 (5), 304 (46), 275 (5), 246 (6), 234 (9), 220 (21), 198 (4), 144 (5), 130 (9), 91 (100), 65 (7), 41 (12), 32 (29), 28 (98); exact mass calcd for  $C_{26}H_{30}N_2O_2$  402.2307, found 402.2313. Anal. Calcd for  $C_{26}H_{30}N_2O_2$ : C, 77.58; H, 7.51; N, 6.96. Found: C, 77.49; H, 7.54; N, 6.88.

## 20-Ethyl-5-oxo-1-benzylhexahydropyrrolocarbazole (6)

**Method A**: A solution of **15a,b** (615 mg, 1.7 mmol) and ( $\pm$ )-10-camphorsulfonic acid (10 mg) in  $CH_2Cl_2$  (85 ml) was refluxed in the presence of molecular sieves (4 Å) (17 g) for 8 h. The reaction mixture was then neutralized at room temperature with solid  $K_2CO_3$ . After filtration and concentration of the organic phase, compound (**6**) (550 mg, 94%) was purified by crystallization from AcOEt.

**Method B**: A solution of **14a** (72 mg, 0.2 mmol) and ( $\pm$ )-10-camphorsulfonic acid (2 mg) in benzene (20 ml) was refluxed under a Dean-Stark trap for 10 h. The reaction mixture was then neutralized at room temperature with solid  $K_2CO_3$ . After filtration and concentration of the organic phase, compound (**6**) (63 mg, 92%) was purified by crystallization from AcOEt. White crystals; mp 196-198°C (AcOEt); ir ( $CHCl_3$ ) 3430 (NH), 1735, 1695 (C=O), 1600;  $^1H$  nmr ( $CDCl_3$ , 300 MHz)  $\delta$  0.92 (t, 3H, Me-18,  $J = 7.0$ ), 1.50-2.10 (m, 6H, 2H-16, 2H-17, 2H-19), 2.58 (s, 2H, 2H-6), 3.77 (br s, 1H, H-2), 4.34 (AB, 2H,

NCH<sub>2</sub>Ph,  $J = 16.0$ ,  $\Delta\nu = 49.5$ ), 6.32 (d, 1H, H-12,  $J = 7.5$ ), 6.57 (t, 1H, H-10,  $J = 7.5$ ), 6.99 (t, 1H, H-11,  $J = 7.5$ ), 7.13 (d, 1H, H-9,  $J = 7.5$ ), 7.30 (m, 5H, ArH); <sup>13</sup>C nmr (CDCl<sub>3</sub>, 75 MHz)  $\delta$  12.1 (C-18), 22.9 (C-19), 24.7 (C-16), 26.7 (C-17), 47.3 (C-6), 50.2 (NCH<sub>2</sub>Ph), 50.3 (C-7), 67.2 (C-2), 106.5 (C-8), 116.1 (C-20), 117.6 (C-10), 121.7 (C-9), 127.1 (C-11), 127.1-128.6 (5 Ar CH), 132.6 (C-8), 135.2 (C-21), 138.7 (C-1'), 150.2 (C-13), 175.5 (CO); ms ( $m/z$ , %) 344 (M<sup>+</sup>, 35), 305 (75), 258 (65), 253 (40), 220 (40), 130 (70), 91 (100), 81 (40), 71 (35), 69 (45), 57 (50); exact mass calcd for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O 344.1883, found 344.1884. Anal. Calcd for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O: C, 80.20; H, 7.02; N, 8.13. Found: C, 79.79; H, 6.91; N, 7.83.

### 20-Ethyl-5-oxo-4-allyl-1-benzylhexahydropyrrolocarbazole (7)

This compound was prepared from **17a,b** (30:70) (321 mg, 0.8 mmol), **16a** (241 mg, 0.6 mmol) or **16b** (201 mg, 0.5 mmol) following the conditions described for the preparation of **6** (method A from **17a,b**; method B from **16a** or **16b**). A quick filtration on a neutral alumina pad with 70:30 hexane-AcOEt as the eluent, gave **7** in 89% yield: white crystals; mp 88-90° (hexane); ir (CCl<sub>4</sub>) 1720, 1675 (CO), 1595; <sup>1</sup>H nmr (CDCl<sub>3</sub>, 300 MHz)  $\delta$  0.97 (t, 3H, Me-18,  $J = 7.5$ ), 1.50-2.32 (m, 4H, 2H-16, 2H-17), 2.13 (q, 2H, 2H-19,  $J = 7.5$ ), 2.61 (AB, 2H, 2H-6,  $J = 14.0$ ,  $\Delta\nu = 14.3$ ), 3.80 (t, 1H, H-2,  $J = 4.0$ ), 4.20-4.58 (m, 2H, NCH<sub>2</sub>-CH=CH<sub>2</sub>), 4.37 (AB, 2H, NCH<sub>2</sub>Ph,  $J = 16.0$ ,  $\Delta\nu = 50.0$ ), 5.25 (m, 2H, NCH<sub>2</sub>-CH=CH<sub>2</sub>), 5.90 (m, 1H, NCH<sub>2</sub>-CH=CH<sub>2</sub>), 6.36 (d, 1H, H-12,  $J = 8.0$ ), 6.58 (t, 1H, H-10,  $J = 8.0$ ), 6.97 (d, 1H, H-9,  $J = 8.0$ ), 7.03 (t, 1H, H-11,  $J = 8.0$ ), 7.32 (m, 5H, ArH); <sup>13</sup>C nmr (CDCl<sub>3</sub>, 75 MHz)  $\delta$  13.2 (CH<sub>3</sub>-18), 25.1 (C-19), 25.5 (C-16), 26.6 (C-17), 45.1 (NCH<sub>2</sub>-CH=CH<sub>2</sub>), 46.9 (C-6), 50.3 (C-7), 50.4 (NCH<sub>2</sub>Ph), 67.3 (C-2), 106.6 (C-12), 117.0 (NCH<sub>2</sub>-CH=CH<sub>2</sub>), 117.7 (C-10), 118.8 (C-20), 121.7 (C-9), 128.6 (C-11), 127.2-128.9 (5 Ar CH), 133.2 (NCH<sub>2</sub>-CH=CH<sub>2</sub>), 134.5 (C-21), 135.1 (C-8), 138.8 (C-1'), 150.6 (C-13), 173.5 (C-5); ms ( $m/z$ , %) 384 (M<sup>+</sup>, 12), 356 (3), 293 (14), 233 (6), 202 (6), 183 (6), 174 (6), 144 (3), 130 (10), 105 (6), 91 (100), 77 (10), 65 (8), 55 (7), 41 (30); exact mass calcd for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O 384.2200, found 384.2203. Anal. Calcd for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O: C, 81.21; H, 7.34; N, 7.29. Found: C, 81.10; H, 7.29; N, 7.27.

### Imine (9), Enamine (11) and Hydroperoxyimine (19)

A solution of enamide (**6**) (516 mg, 1.5 mmol) in THF (30 ml) was added to a suspension of LiAlH<sub>4</sub> (171 mg, 4.5 mmol) in THF (60 ml). The mixture was refluxed for 16 h, cooled and water (1.5 ml) was added. After filtration, the inorganic salts were washed with CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were combined, dried and evaporated. The residue was partially dissolved in AcOEt. Filtration of the mixture provided a first fraction of **19** (190 mg, 35%). The filtrate was then evaporated, and the residue was chromatographed on a short column of neutral alumina to afford a second fraction of **19** (65 mg, 12%) (elution with 70:30 hexane-AcOEt) and a mixture of imine (**9**) and enamine (**11**) (163 mg, 33%) (elution with AcOEt).

**9** and **11**: ir (CHCl<sub>3</sub>) 3400 (br, NH enamine), 1690 (N=C enamine), 1640 (C=N imine), 1600; <sup>1</sup>H nmr (CDCl<sub>3</sub>, 60 MHz)  $\delta$  0.93 (t, 3H, Me-18,  $J = 7.5$ ), 1.3-2.8 (m, 9H, 2H-19, 2H-17, 2H-16, 2H-6, H-20 imine), 3.4-3.8 (m, 1H, H-2), 3.85-4.15 (m, 2H, 2H-5), 4.40 (AB, 2H, NCH<sub>2</sub>Ph,  $J = 16.5$ ,  $\Delta\nu = 14.0$ ), 6.4-7.5 (m, 9H, ArH); ms ( $m/z$ , %) 330 (M<sup>+</sup>, 5), 263 (21), 234 (13), 144 (10), 130 (4), 117 (7), 91 (100), 77 (11), 65 (20), 55 (20), 43 (41), 41 (43), 29 (54); exact mass calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub> 330.2096, found 330.2092.

**19**: white crystals; mp 147-150°C (AcOEt); ir (CHCl<sub>3</sub>) 3620 (OH), 1630 (C=N), 1600; <sup>1</sup>H nmr COSY <sup>1</sup>H-<sup>1</sup>H (CDCl<sub>3</sub>, 300 MHz)  $\delta$  0.95 (t, 3H, Me-18,  $J = 7.5$ ), 1.45 (ddd, 1H, H-17ax,  $J = 15.0$ , 9.5, 4.0), 1.56-1.80 (m, 2H, 2H-16), 1.75 (dq, 1H, H-19B,  $J = 14.0$ , 7.0), 1.91 (ddd, 1H, H-17eq,  $J = 15.0$ , 7.0, 4.0), 2.07 (ddd, 1H, H-6ax,  $J = 12.5$ , 10.0, 9.5), 2.34 (ddd, 1H, H-6eq,  $J = 12.5$ , 6.5, 1.0), 2.39 (dq, 1H, H-19A,  $J = 14.0$ , 7.0), 3.57 (dd, 1H, H-2,  $J = 8.0$ , 5.0), 3.92 (ddd, 1H, H-5ax,  $J = 15.5$ , 10.0, 6.5), 4.08 (ddd, 1H, H-5eq,  $J = 15.5$ , 9.5, 1.0), 4.37 (AB, 2H, NCH<sub>2</sub>Ph,  $J = 15.5$ ,  $\Delta\nu = 68.0$ ), 6.49 (d, 1H, H-12,



$J = 7.5$ ), 6.67 (t, 1H, H-10,  $J = 7.5$ ), 6.96 (d, 1H, H-9,  $J = 7.5$ ), 7.08 (br s, 1H, OH), 7.11 (t, 1H, H-11,  $J = 7.5$ ), 7.37 (m, 5H, ArH);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  7.0 (CH<sub>3</sub>-18), 21.7 (C-19), 26.0 (C-16), 28.9 (C-17), 42.8 (C-6), 49.8 (NCH<sub>2</sub>Ph), 57.8 (C-5), 61.1 (C-7), 71.9 (C-2), 83.3 (C-20), 107.8 (C-12), 117.7 (C-10), 121.1 (C-9), 127.3 (C-11), 127.6-128.9 (5 Ar CH), 132.7 (C-8), 138.3 (C-1'), 150.0 (C-13), 177.4 (C-21); ms ( $m/z$ , %) 362 ( $\text{M}^+$ , 3), 346 (14), 330 (3), 289 (6), 278 (6), 234 (21), 220 (9), 144 (8), 91 (100), 77 (6), 65 (9), 57 (6), 28 (84); exact mass calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub> 362.1994, found 362.2000. Anal. Calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.09; H, 7.21; N, 7.76.

#### Enamine (12) and 4a-Oxoethylhexahydrocarbazolones (18a,b)

Those compounds were prepared from enamide (7) (384 mg, 1.0 mmol) following the conditions described for the preparation of 9, 11 and 19. The crude material was filtered on a short column of neutral alumina to give hexahydrocarbazolones (18a,b) (elution with 80:20 hexane-AcOEt), and enamine (12) (100 mg, 27%) (elution with AcOEt). A flash chromatography of the diastereoisomeric mixture (18a,b), on silica gel (elution with 80:20 hexane:AcOEt), afforded pure 18a (55 mg, 16%) and 18b (160 mg, 46%).

**12**: oil (unstable); ir ( $\text{CHCl}_3$ ) (N=C=C), 1600;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 60 MHz)  $\delta$  0.90 (t, 3H, Me-18,  $J = 7.5$ ), 1.3-3.2 (m, 8H, 2H-19, 2H-17, 2H-16, 2H-6), 3.5-4.7 (m, 5H, H-2, 2H-5, NCH<sub>2</sub>-CH=CH<sub>2</sub>), 4.35 (AB, 2H, NCH<sub>2</sub>Ph,  $J = 17.0$ ,  $\Delta\nu = 12.0$ ), 5.0-6.0 (m, 3H, NCH<sub>2</sub>-CH=CH<sub>2</sub>), 6.4-7.4 (m, 9H, ArH);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , 15 MHz)  $\delta$  13.3 (CH<sub>3</sub>-18), 24.5 (C-19), 25.6 (C-16), 30.0 (C-17), 38.8 (C-6), 50.1 (NCH<sub>2</sub>Ph), 52.8 (C-7), 57.6 (NCH<sub>2</sub>-CH=CH<sub>2</sub>), 62.6 (C-5), 68.5 (C-2), 106.5 (C-12), 115.6 (NCH<sub>2</sub>-CH=CH<sub>2</sub>), 116.8 (C-10), 117.7 (C-20), 123.2 (C-9), 127.5 (C-11), 127.3-128.9 (5 Ar CH), 136.6 (NCH<sub>2</sub>-CH=CH<sub>2</sub>), 137.0 (C-8), 139.1 (C-1'), 141.4 (C-21), 150.0 (C-13).

**18a**: amorphous solid; ir ( $\text{CCl}_4$ ) 2820 and 2725 (CH aldehyde), 1725 (CO aldehyde), 1705 (CO ketone), 1605;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.84 (t, 3H, Me-11,  $J = 7.5$ ), 1.36 (ddq, 1H, H-10B,  $J = 14.0, 7.5, 7.0$ ), 1.40-1.55 (m, 2H, H-1ax, H-2ax), 1.75-1.90 (m, 2H, H-1eq, H-10A), 1.93-2.10 (m, 2H, H-2eq, H-3), 2.96 (AB, 2H, CH<sub>2</sub>CO,  $J = 18.0$ ,  $\Delta\nu = 86.4$ ), 3.72 (dd, 1H, H-9a,  $J = 10.0, 5.0$ ), 4.27 (AB, 2H, NCH<sub>2</sub>Ph,  $J = 16.0$ ,  $\Delta\nu = 78.4$ ), 6.37 (d, 1H, H-8,  $J = 8.0$ ), 6.62 (t, 1H, H-6,  $J = 8.0$ ), 6.84 (d, 1H, H-5,  $J = 8.0$ ), 7.04 (t, 1H, H-7,  $J = 8.0$ ), 7.20-7.30 (m, 5H, ArH), 9.56 (s, 1H, CHO);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  11.3 (CH<sub>3</sub>-11), 22.3 (C-10), 24.4 (C-1), 25.4 (C-2), 48.8 (C-3), 49.0 (NCH<sub>2</sub>Ph), 50.3 (CH<sub>2</sub>CO), 57.8 (C-4a), 70.7 (C-9a), 107.7 (C-8), 118.3 (C-6), 123.4 (C-5), 126.2 (C-4b), 127.5 (C-7), 127.6-129.3 (5 Ar CH), 137.9 (C-1'), 149.6 (C-8a), 200.9 (CHO), 210.0 (CO); ms ( $m/z$ , %) 347 ( $\text{M}^+$ , 27), 319 (3), 290 (9), 276 (4), 256 (6), 234 (5), 228 (13), 220 (12), 200 (7), 144 (4), 130 (4), 91 (100), 65 (7), 55 (4), 41 (7); exact mass calcd for C<sub>23</sub>H<sub>25</sub>NO<sub>2</sub> 347.1885, found 347.1886.

**18b**: white solid; mp 86-88°C (hexane); ir ( $\text{CCl}_4$ ) 2820 and 2725 (CH aldehyde), 1725 (CO aldehyde), 1700 (CO ketone), 1600;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.83 (t, 3H, Me-11,  $J = 7.5$ ), 1.19 (ddq, 1H, H-10B,  $J = 14.0, 7.5, 7.0$ ), 1.59-1.74 (m, 2H, H-2ax, H-10A), 1.84-1.96 (m, 3H, H-2eq, 2H-1), 2.34 (dddd, 1H, H-3,  $J = 9.0, 7.0, 7.0, 5.0$ ), 3.08 (AB, 2H, CH<sub>2</sub>CO,  $J = 18.0$ ,  $\Delta\nu = 187.0$ ), 3.83 (dd, 1H, H-9a,  $J = 4.0, 3.0$ ), 4.40 (AB, 2H, NCH<sub>2</sub>Ph,  $J = 16.0$ ,  $\Delta\nu = 70.0$ ), 6.43 (d, 1H, H-8,  $J = 8.0$ ), 6.62 (t, 1H, H-6,  $J = 8.0$ ), 6.91 (d, 1H, H-5,  $J = 8.0$ ), 7.09 (t, 1H, H-7,  $J = 8.0$ ), 7.30-7.40 (m, 5H, ArH), 9.61 (s, 1H, CHO);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  11.8 (CH<sub>3</sub>-11), 22.7 (C-10), 24.4 (C-1), 26.6 (C-2), 49.4 (NCH<sub>2</sub>Ph), 50.1 (C-3), 53.3 (CH<sub>2</sub>CO), 57.1 (C-4a), 69.3 (C-9a), 106.5 (C-8), 117.4 (C-6), 124.3 (C-5), 126.2 (C-4b), 127.4 (C-7), 127.3-129.5 (5 Ar CH), 138.3 (C-1'), 151.2 (C-8a), 200.4 (CHO), 211.0 (CO); ms ( $m/z$ , %) 347 ( $\text{M}^+$ , 23), 319 (3), 290 (9), 276 (4), 256 (3), 234 (5), 228 (11), 220 (14), 200 (6), 144 (5), 130 (5), 115 (3), 91 (100), 65 (10), 55 (6), 41 (10); exact mass calcd for C<sub>23</sub>H<sub>25</sub>NO<sub>2</sub> 347.1885, found 347.1883. Anal. Calcd for C<sub>23</sub>H<sub>25</sub>NO<sub>2</sub>: C, 79.50; H, 7.25; N, 4.03. Found: C, 79.57; H, 7.63; N, 3.60.

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