# Reactivity of hexahydrocarbazol-4-ones in Michael reactions: stereocontrolled formation of decahydropyrido[2,3-*d*]carbazoles

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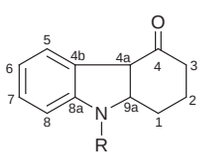
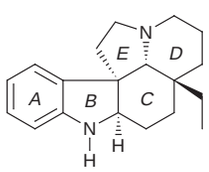
**The reactivity of hexahydrocarbazolones 3 and 7 in Michael reactions has been studied with several reagents: treatment with acrylonitrile, methyl acrylate and the Mannich base of methyl vinyl ketone leads to 4a-substituted compounds 13–16 in good yields (65–93%), as previously observed with nitroethylene. In contrast, unexpected tetracyclic carbazoles 17 and 18 are obtained with methyl vinyl ketone itself. Reductive cyclisation ($H_2$, $PtO_2$) of 4a-cyanoethylhexahydrocarbazolones 13 and 15 affords decahydropyrido[2,3-*d*]carbazoles 20 and 21, potential intermediates in the synthesis of E-homo *Aspidosperma* alkaloids. Compounds 20 and 21 are isolated as single diastereoisomers with a C/E *trans* ring junction.†**

## Introduction

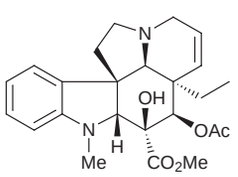
The tricyclic hexahydrocarbazolone ring system is a common structural element of a large variety of indole alkaloids (*e.g.* aspidospermidine and vindoline) which belong to a class of biologically active compounds like vinblastine and vincristine.[1]



hexahydrocarbazolone



aspidospermidine



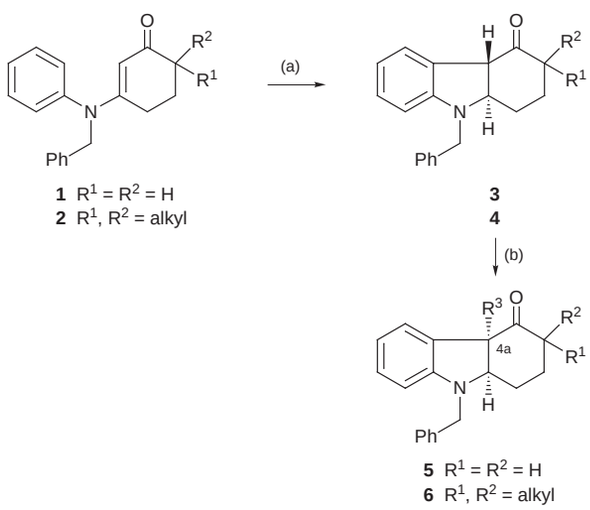
vindoline

Previous work in our laboratory has shown that *trans*-hexahydrocarbazolones **3,4** can be obtained in one stereospecific step by non-oxidative photocyclisation of tertiary aryl enaminones **1,2**.[2,3] The presence of a keto group on these compounds allows the introduction of appropriate $R^3$ substituents *via* carbanionic intermediates. The reaction is regio- and stereoselective; it leads exclusively to 4a-substituted compounds **5,6** with a *cis* B/C ring junction[2–4] which is the stereochemistry of the natural compounds (Scheme 1).

The reactivity of the anion which had been largely studied under alkylating conditions (KH, activated halides)[2,3*b*,4] was then explored in a Michael reaction with nitroethylene[3] which provided the 2C and 1N unit of the *Aspidosperma* E ring (Scheme 2).

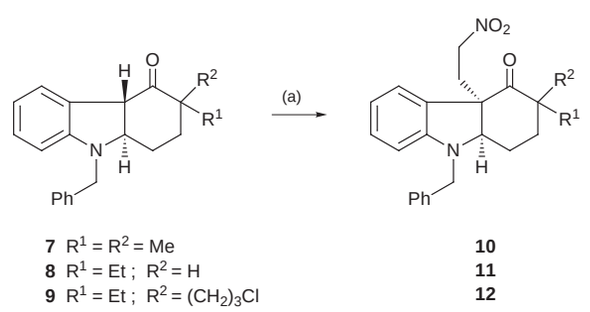
The efficiency of this last reaction which allowed the total synthesis of *N*-benzyl aspidospermidine[3] *via* compound **12** prompted us to investigate further the reactivity of hexahydrocarbazolones with various Michael acceptors. Moreover cyanoalkyl derivatives **13** and **15** obtained in the present study were envisaged as key intermediates in the formation of decahydropyrido[2,3-*d*]carbazoles. These tetracyclic compounds might be direct precursors of E-homo *Aspidosperma* alkaloids as octahydropyrrolo[2,3-*d*]carbazoles are in the *Aspidosperma* series (Scheme 3).[3–5]

In the present paper we report our results on the reactivity of hexahydrocarbazolones with Michael acceptors and we describe the formation of decahydropyrido[2,3-*d*]carbazoles from Michael derivatives **13** and **15**.



**1** $R^1 = R^2 = H$
**2** $R^1, R^2$ = alkyl
**3**
**4**
**5** $R^1 = R^2 = H$
**6** $R^1, R^2$ = alkyl

**Scheme 1** *Reagents and conditions*: (a) *hv*, argon; (b) KH, $R^3X$



**7** $R^1 = R^2$ = Me
**8** $R^1$ = Et ; $R^2 = H$
**9** $R^1$ = Et ; $R^2 = (CH_2)_3Cl$
**10**
**11**
**12**

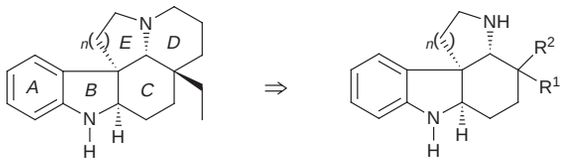
**Scheme 2** *Reagents and conditions*: (a) LDA, $CH_2$=CH-$NO_2$

## Results and discussion

### Reactivity of hexahydrocarbazol-4-ones with Michael acceptors

In addition to nitroethylene,[3] three new reagents were studied in the reaction: acrylonitrile, methyl acrylate and methyl vinyl

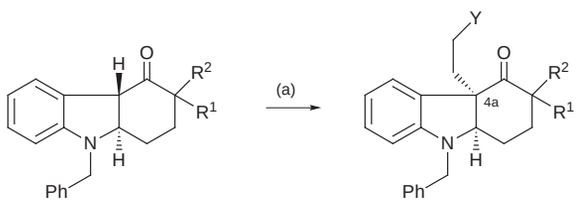
† The ABCDE *Aspidosperma* ring nomenclature has been kept for tetracyclic compounds **20**, **21** and **22**.



| | | |
|---|---|---|
| aspidospermidine | $n = 1$ | octahydropyrrolocarbazole |
| E-homoaspidospermidine | $n = 2$ | decahydropyridocarbazole |

**Scheme 3**

ketone. Reaction of acrylonitrile with **3**[2a] and **7**[3b] led to 4a-cyanoethyl compounds **13** (yield 93%) and **15** (yield 79%) respectively, while 4a-methoxycarbonylethyl compound **14** was obtained in 74% yield from **3** and methyl acrylate (Scheme 4).

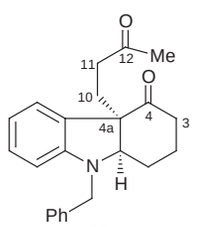


**3** $R^1 = R^2 = H$
**7** $R^1 = R^2 = Me$

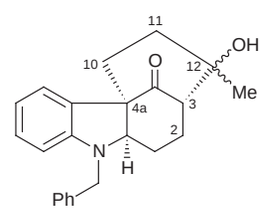
**13** $R^1 = R^2 = H$; Y = CN
**14** $R^1 = R^2 = H$; Y = $CO_2Me$
**15** $R^1 = R^2 = Me$; Y = CN

**Scheme 4** *Reagents and conditions*: (a) LDA, $CH_2$=CH-Y

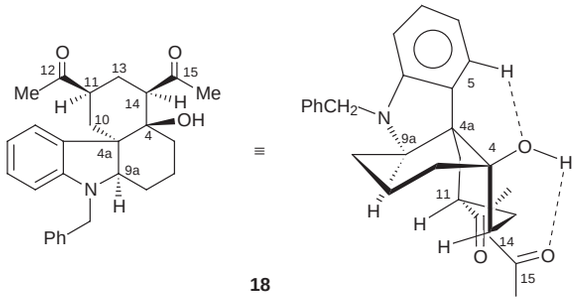
When methyl vinyl ketone was used as Michael acceptor with substrate **3**, the expected 4a-oxobutylhexahydrocarbazolone **16** was surprisingly obtained in low yield (5%). The reaction indeed led essentially to two tetracyclic derivatives **17** and **18**



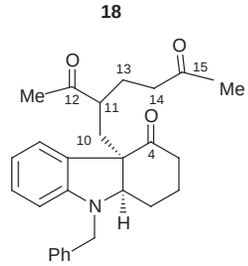
**16**



**17a** α-OH
**17b** β-OH



**18**



**19**

respectively in 30 and 26% yield. Compound **17** was obtained as an inseparable mixture of C-12 epimers **17a**,**b** (60 : 40) resulting from an intramolecular cyclisation of the C-3 carbanion of **16** onto the C-12 carbonyl group. Compound **18** was obtained essentially as one diastereoisomer. Its formation involved two successive alkylations leading to the presumed intermediate **19** followed by intramolecular cyclisation of the C-14 carbanion onto the C-4 carbonyl group. In contrast, reaction of **3** with the methyl iodide salt of the methyl vinyl ketone Mannich base [$MeEt_2N^+$-$(CH_2)_2$-CO-$CH_3$, $I^-$],[6] known to be an excellent masked Michael acceptor,[7] afforded the 4a-oxobutylhexahydrocarbazolone **16** in good yield (65%).

The structure, stereochemistry and conformation of derivatives **13**–**18** were established from IR, 1D NMR ($^1$H and $^{13}$C), and for **17** and **18**, 2D NMR (COSY $^1$H-$^1$H and $^1$H-$^{13}$C) spectral data which allowed identification of all hydrogens and carbons.

The *cis* stereochemistry of hexahydrocarbazolones **13**–**16** was supported by the data in agreement with previous results.[2] In particular, the *cis* compounds were characterized by: (i) a carbonyl adsorption at 1690–1705 $cm^{-1}$ in the IR spectra, (ii) an AB pattern for the NC$H_2$Ph methylene in the $^1$H NMR spectra, (iii) a signal at $\delta_C$ 209.5–214.6 for CO-4 in the $^{13}$C NMR spectra. The corresponding data for the *trans* compounds were respectively $\nu_{CO}$ 1715–1720 $cm^{-1}$, a singlet for NC$H_2$Ph and $\delta_C$ 206–209 (CO-4).[2b]

Compounds **17** and **18** exhibited an OH band ($\nu_{max}$ 3600 $cm^{-1}$) in addition to the expected CO band in the IR spectrum. In the $^1$H NMR spectra of **17a**,**b**, deshielding of the methyl group [$\delta$ 1.33 (**17a**) or 1.30 (**17b**)] compared to its chemical shift in **16** ($\delta$ 2.06) indicated the absence of an α-carbonyl function while in the $^{13}$C NMR spectra a new quaternary carbon characteristic of a C-OH link appeared at $\delta$ 58.6 (**17a**) or 58.3 (**17b**). The mixture of **17a**,**b** also showed in the $^1$H NMR spectrum a doublet of doublets at $\delta$ 3.97 for the 9a-H proton and exhibited an identical pattern for 3-H at $\delta$ 2.50 (**17a**) or 2.65 (**17b**). Those data indicate that both isomers possess the same C/D ring junction which should be *cis* as shown by molecular models. Consequently, they differ from one another by the stereochemistry at C-12 which could be established by analysis of their $^{13}$C NMR spectra. Thus the β-axial configuration of the hydroxy group (**17b**) could be established by virtue of (i) shielding of the C-12 carbon bearing the axial OH substituent ($\Delta\delta$ −2.8),[8a] (ii) shielding of carbon C-2 ($\Delta\delta$ −2.0) owing to the γ gauche effect of the 12-Me group[8b] and (iii) deshielding of the CO carbon ($\Delta\delta$ +0.9) due to an intramolecular hydrogen bond between the CO oxygen and the β-OH hydrogen.[8c]

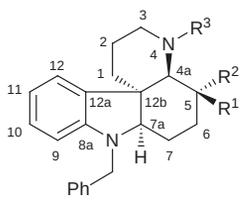
Tetracyclic compound **18** showed: (i) in the $^{13}$C NMR spectrum, two CO resonances at $\delta$ 214.9 and 209.8, three non aromatic CHs at $\delta$ 47.3 (C-11), 50.9 (C-14) and 62.7 (C-9a) and a quaternary carbon at $\delta$ 73.8 (C-OH), (ii) in the $^1$H NMR spectrum, two methyl groups (MeCO) at $\delta$ 2.16 and 2.21, an OH hydrogen at $\delta$ 4.30 and a 5-H aromatic proton at $\delta$ 7.80 whose deshielding is probably due to the proximity of the OH group. Additionally, the sequence 10-$H_{ax}$, 11-H, 13-$H_{ax}$, 14-H deduced from a $^1$H–$^1$H COSY experiment exhibits large coupling constants ($J \approx 13.0$), showing the axial configuration of the 11-H and 14-H hydrogens. An axial configuration may also be attributed to 9a-H from its coupling constants ($J$ 9.5 and 6.0). These data are in agreement with C and D ring chair conformations. Moreover, in the NOE difference spectrum, irradiation of 9a-H ($\delta$ 3.47) led to a nuclear Overhauser effect on 11-$H_{ax}$ ($\delta$ 2.49, 12%) and on 14-$H_{ax}$ ($\delta$ 2.43, 5%). Such effects indicate the α-position of the three hydrogens 9a-H, 11-H and 14-H in a C/D *cis* ring junction. Distances of 9a-H–11-H ≈ 2.5 Å and 9a-H–14-H ≈ 5.5 Å, which can be approximately measured on molecular models, agree with the observed NOE differences. The reasonable stability of **18** compared to its possible isomers at C-4, C-11 and C-14 is probably due to the existence of intramolecular hydrogen bonds between (i) 5-H and the OH oxygen and (ii) the OH proton and the CO-15 oxygen.

### Formation of decahydropyrido[2,3-*d*]carbazoles

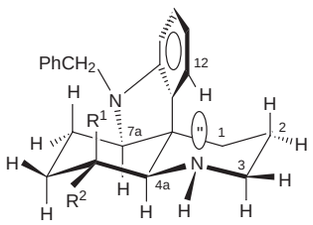
Access to these compounds was envisaged from cyanohexa-

hydrocarbazolones **13** and **15** by reductive cyclisation which would lead directly to tetracyclic amines. The reaction could give two C-4a epimers. Preponderant formation of one isomer required stereochemical control of the reaction.

The reduction was performed in EtOH by catalytic hydrogenation with platinum oxide.[3b,9] It afforded a single compound in both cases *i.e.* amine **20** (80%) from **13** and amine **21** (62%) from **15**. For easier purification amine **20** was transformed in acetamide **22**.



**20** $R^1 = R^2 = H$; $R^3 = H$
**21** $R^1 = R^2 = Me$; $R^3 = H$
**22** $R^1 = R^2 = H$; $R^3 = Ac$



**20** $R^1 = R^2 = H$
**21** $R^1 = R^2 = Me$

Amines **20** and **21** were characterized in the $^{13}C$ NMR spectrum by a new CH-4a signal at $\delta$ 57.3 and 67.9 respectively while the CO moiety of **13** and **15** disappeared. Additionally, in the $^1H$ NMR spectrum, strong deshielding of 12-H [$\delta$ 7.80 (**20**) and 8.20 (**21**)] implied the proximity of the N-4 lone pair in a C/E *trans* ring junction.[3b,4a] This stereochemistry is confirmed (i) for compound **21**, by observation of a nuclear Overhauser effect (3%) between 4a-H and 7a-H; an effect which is only possible in a *trans* ring junction, (ii) for compound **22**, by the $^{13}C$ chemical shift of the CO*Me* group ($\delta$ 25.2) which is in agreement with previously reported data of the C/E *trans* octahydropyrrolocarbazole series ($\delta$ 24.7–24.9) while weaker values ($\delta$ 22.0–23.1) were observed in the *cis* series.[3b] Moreover the coupling constants of the 7a-H hydrogen in compounds **21** ($J$ 8.5 and 5.0) and **22** ($J$ 11.5 and 5.0) and of hydrogen 4a-H in compound **22** ($J$ 10.0 and 5.0) provide further information about the conformations. The observed values are consistent with an axial position for protons 7a-H and 4a-H and a chair conformation for the C and E rings. Exclusive formation of the C/E *trans* isomers outlines the difference between the two series: decahydropyridocarbazole and octahydropyrrolocarbazole. Indeed in this last series, preponderant formation of C/E *cis* compounds was previously observed.[3b] Consequently, the obtained results in both tetracyclic series agree with the higher stability of the *trans* stereochemistry in 9-methyl decalins and the *cis* stereochemistry in 8-methyl hydrindanes respectively,[10] this in spite of (i) a fused indole system and (ii) a N heteroatom in the E ring, both factors which might have considerably modified the theoretical *cis–trans* energy difference.

## Conclusions

The present paper outlines the high reactivity of hexahydrocarbazolones with Michael acceptors. In addition to the nitroethylene already studied,[3] acrylonitrile, methyl acrylate and the Mannich base of methyl vinyl ketone led to 4a-substituted compounds **13**–**16** in good yields (65–93%). In contrast, unexpected tetracyclic cabazoles **17** and **18**, formation of which involved successive di- or tri-alkylations, were obtained with methyl vinyl ketone itself. Reductive cyclisation of 4a-(cyanoethyl)hexahydrocarbazolones **13** and **15**, afforded decahydropyrido[2,3-*d*]carbazoles **20** and **21**. The reaction was stereospecific and gave exclusively isomers with a C/E *trans* ring junction. Those tetracyclic derivatives may be considered as model compounds and key intermediates in an approach to the 4a-epi E-homo *Aspidosperma* series.

## Experimental

Organic layers were dried over $MgSO_4$. 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 mm. Melting points were taken on a Reichert hot-stage microscope and are uncorrected. Infrared spectra were run on a Perkin-Elmer 377 and 881 spectrophotometers. Mass spectra were measured on a Varian CH5 or on a Varian VG 30F apparatus. $^{13}C$ NMR Spectra were recorded on JEOL FX60, Bruker MSL 300 or Bruker AC 400 spectrometers and $^1H$ NMR spectra on Bruker MSL 300 or Bruker AC 400 instruments ($\delta$ values are given in ppm and $J$ values in Hz). The applied pulse sequence was ($\pi$/2), ($t_1$), ($\pi$/4), (FID, $t_2$) for the $^1H$ COSY spectra and ($\pi$/2, $^1H$), ($t_1$/2), ($\pi$, $^{13}C$), ($t_1$/2), ($\tau_1$), ($\pi$/2, $^1H$, $\pi$/2, $^{13}C$), ($\tau_2$), (BB, $^1H$; FID, $t_2$) with $\tau_1 = 0.0035$ s and $\tau_2 = 0.001\,75$ s for the $^1H$-$^{13}C$ COSY spectra. Homonuclear Overhauser effects were generated by presaturating selected proton signals with a low power 4 s decoupler pulse. NOE Difference spectra were obtained by subtracting alternately right-off resonance-free induction decays (FIDs) from right-on resonance-induced FIDs.

### *cis*-4a-(2-Cyanoethyl)-9-benzyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4-one 13

To a solution of LDA (1.3 mmol) at −78 °C [prepared from diisopropylamine (131 mg, 182 mm$^3$, 1.3 mmol), THF (2 cm$^3$) and *n*-butyllithium (870 mm$^3$, 1.3 mmol, 1.5 M in hexane)] was slowly added under argon a solution of hexahydrocarbazolone **3** (277 mg, 1 mmol) in THF (5 cm$^3$) and after 30 min HMPA (269 mg, 261 mm$^3$, 1.5 mmol). The mixture was stirred at this temperature for a further 50 min, allowed to warm up to −50 °C and cooled again to −78 °C. A solution of acrylonitrile (63 mg, 79 mm$^3$, 1.2 mmol) in THF (1 cm$^3$) was then added dropwise. The mixture was stirred again for 50 min at −78 °C and allowed to warm up to 0 °C. The solvent was removed and the residue was dissolved in AcOEt. The solution was washed with brine, dried and concentrated. Flash chromatography on silica gel using 85:15 hexane–AcOEt as eluent afforded **13** (307 mg, 93%) as white crystals, mp 75–78 °C (from cyclohexane) (Found: C, 79.9; H, 6.9; N, 8.3. $C_{22}H_{22}N_2O$ requires C, 79.95; H, 6.7; N, 8.5%); $\nu_{max}(CCl_4)$/cm$^{-1}$ 2240 (CN) and 1700 (CO); $\delta_H$(400 MHz; $CDCl_3$) 1.60 (1 H, m, 2-H$_{ax}$), 1.80 (2 H, m, 2 × 10-H), 1.94 (1 H, m, 1-H$_{ax}$), 2.15–2.45 (6 H, m, 1-H$_{eq}$, 2-H$_{eq}$, 2 × 3-H, 2 × 11-H), 3.79 (1 H, t, $J$ 5.5, 9a-H), 4.40 (2 H, AB, $J$ 15.4, $\Delta\nu$ 117.0,‡ NC$H_2$Ph), 6.52 (1 H, d, $J$ 7.8, 8-H), 6.69 (1 H, t, $J$ 7.4, 6-H), 6.90 (1 H, dd, $J$ 7.4 and 1.0, 5-H), 7.15 (1 H, td, $J$ 7.8 and 1.0, 7-H) and 7.30–7.40 (5 H, m, ArH); $\delta_C$(15 MHz; $CDCl_3$) 12.6 (C-11), 18.2 (C-2), 25.6 (C-10), 31.4 (C-1), 38.1 (C-3), 49.2 (N*C*H$_2$Ph), 59.5 (C-4a), 68.3 (C-9a), 107.2 (C-8), 117.9 (C-6), 119.5 (CN), 123.8 (C-5), 127.4 (C-7), 127.5–129.5 (5 ArCH), 127.6 (C-4b), 137.5 (C-1′), 150.6 (C-8a) and 209.5 (CO); *m*/*z* (EI) 330.1733 (17%, M$^{\cdot+}$. $C_{22}H_{22}N_2O$ requires 330.1727), 302 (11), 220 (8), 105 (11), 91 (44), 77 (12) and 43 (100).

### *cis*-4a-[2-(Methoxycarbonyl)ethyl]-9-benzyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4-one 14

Compound **14** was prepared from hexahydrocarbazolone **3** (277 mg, 1.0 mmol) and methyl acrylate (430 mg, 450 mm$^3$, 5.0 mmol) following the conditions described for the preparation of **13**. Flash chromatography on silica gel with 90:10 hexane–AcOEt afforded **14** (270 mg, 74%) as an oil (Found: C, 75.7; H, 7.1; N, 3.85. $C_{23}H_{25}NO_3$ requires C, 76.0; H, 6.95; N, 3.85%); $\nu_{max}(CHCl_3)$/cm$^{-1}$ 1740 (CO ester) and 1705 (CO ketone); $\delta_H$(400 MHz; $CDCl_3$) 1.65 (1 H, m, 2-H$_{ax}$), 1.74–1.90 (2 H, m, 2-H$_{eq}$, 1-H$_{eq}$), 1.96 (1 H, m, 1-H$_{ax}$), 2.14–2.29 (4 H, m, 2 × 10-H,

‡ $\Delta\nu = \nu_A - \nu_B$ where $\nu_A$ and $\nu_B$ are the resonance frequencies of the A and B protons.

2 × 3-H), 2.31–2.47 (2 H, m, 2 × 11-H), 3.62 (3 H, s, OMe), 3.76 (1 H, t, *J* 4.8, 9a-H), 4.37 (2 H, AB, *J* 15.7, Δ*ν* 98.3, NC$H_2$Ph), 6.46 (1 H, d, *J* 7.8, 8-H), 6.68 (1 H, t, *J* 7.4, 6-H), 7.02 (1 H, dd, *J* 7.4 and 1.0, 5-H), 7.10 (1 H, td, *J* 7.7 and 1.0, 7-H) and 7.25–7.40 (5 H, m, ArH); $\delta_C$(100 MHz; $CDCl_3$) 18.6 (C-2), 25.6 (C-1), 29.8 (C-10), 31.2 (C-11), 38.5 (C-3), 49.9 (N*C*$H_2$Ph), 51.6 ($OCH_3$), 60.0 (C-4a), 68.6 (C-9a), 107.1 (C-8), 117.9 (C-6), 124.5 (C-5), 127.3 (C-7), 127.4–129.1 (5 ArCH), 128.7 (C-4b), 138.1 (C-1′), 151.2 (C-8a), 173.6 (CO ester) and 210.7 (CO ketone); *m*/*z* (EI) 363.1835 (25%, $M^{\cdot+}$. $C_{23}H_{25}NO_3$ requires 363.1828), 335 (7), 279 (13), 275 (10), 220 (8), 106 (15), 91 (100).

### *cis*-3,3-Dimethyl-4a-(2-cyanoethyl)-9-benzyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4-one 15

Compound **15** was prepared from hexahydrocarbazolone **7** (305 mg, 1.0 mmol) and acrylonitrile (63 mg, 79 mm$^3$, 1.2 mmol) following the procedure described for **13**. Flash chromatography on silica gel with 90:10 hexane–AcOEt afforded **15** (283 mg, 79%) as an oil (Found: C, 80.5; H, 7.5; N, 7.6. $C_{24}H_{26}N_2O$ requires C, 80.4; H, 7.3; N, 7.8%); $\nu_{max}(CCl_4)$/cm$^{-1}$ 2250 (CN) and 1690 (CO); $\delta_H$(300 MHz; $CDCl_3$) 0.93 (3 H, s, Me), 1.13 (3 H, s, Me), 1.47 (1 H, m, 2-$H_{ax}$), 1.65–1.87 (3 H, m, 2-$H_{eq}$, 1-$H_{ax}$, 1-$H_{eq}$), 2.05–2.26 (4 H, m, 2 × 10-H, 2 × 11-H), 3.79 (1 H, t, *J* 5.0, 9a-H), 4.42 (2 H, AB, *J* 16.0, Δ*ν* 84.5, NC$H_2$Ph), 6.48 (1 H, d, *J* 7.5, 8-H), 6.64 (1 H, t, *J* 7.5, 6-H), 6.86 (1 H, d, *J* 7.5, 5-H), 7.12 (1 H, t, *J* 7.5, 7-H) and 7.30–7.40 (5 H, m, ArH); $\delta_C$(75 MHz; $CDCl_3$) 12.8 (C-11), 23.3 (C-2), 26.7 ($CH_3$), 29.8 ($CH_3$), 32.4 (C-1), 33.5 (C-10), 44.3 (C-3), 49.2 (N*C*$H_2$Ph), 59.3 (C-4a), 67.8 (C-9a), 106.7 (C-8), 117.7 (C-6), 119.7 (CN), 124.4 (C-5), 127.7 (C-7), 127.6–129.7 (5 ArCH), 128.0 (C-4b), 137.9 (C-1′), 150.7 (C-8a) and 214.6 (CO); *m*/*z* (EI) 358.2045 (18%, $M^{\cdot+}$. $C_{24}H_{26}N_2O$ requires 358.2039), 239 (10), 220 (10), 200 (12), 130 (24), 119 (39), 105 (31), 91 (100), 77 (22), 69 (14), 57 (22), 51 (16) and 41 (33).

### *cis*-4a-(3-Oxobutyl)-9-benzyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4-one 16

Compound **16** was prepared from hexahydrocarbazolone **3** (277 mg, 1.0 mmol) and the methyl iodide salt of methyl vinyl ketone Mannich base [$MeEt_2N^+$-$(CH_2)_2$-CO-$CH_3$, $I^-$][6] (855 mg, 3.0 mmol) following the conditions described for the preparation of **13**. Flash chromatography on silica gel with 90:10 hexane–AcOEt afforded **16** (255 mg, 65%) as an oil (Found: C, 79.3; H, 7.5; N, 3.95. $C_{23}H_{25}NO_2$ requires C, 79.5; H, 7.25; N, 4.05%); $\nu_{max}(CCl_4)$/cm$^{-1}$ 1720 (CO-12) and 1710 (CO-4); $\delta_H$(400 MHz; $CDCl_3$) 1.66 (1 H, m, 2-$H_{ax}$), 1.74–1.91 (2 H, m, 2-$H_{eq}$, 1-$H_{eq}$), 1.96 (1 H, m, 1-$H_{ax}$), 2.06 (3 H, s, Me), 2.07–2.20 (2 H, m, 2 × 10-H), 2.31–2.44 (4 H, m, 2 × 3-H, 2 × 11-H), 3.72 (1 H, t, *J* 4.8, 9a-H), 4.38 (2 H, AB, *J* 15.7, Δ*ν* 109.8, NC$H_2$Ph), 6.48 (1 H, d, *J* 7.8, 8-H), 6.69 (1 H, t, *J* 7.4, 6-H), 7.02 (1 H, dd, *J* 7.4 and 1.0, 5-H), 7.11 (1 H, td, *J* 7.7 and 1.0, 7-H) and 7.22–7.43 (5 H, m, ArH); $\delta_C$(100 MHz; $CDCl_3$) 18.6 (C-2), 25.4 (C-1), 29.8 ($CH_3$), 29.9 (C-10), 38.5 (C-3), 39.2 (C-11), 49.8 (N*C*$H_2$Ph), 59.9 (C-4a), 68.7 (C-9a), 107.2 (C-8), 117.9 (C-6), 124.6 (C-5), 127.3 (C-7), 127.5–129.1 (5 ArCH), 128.9 (C-4b), 138.1 (C-1′), 151.2 (C-8a), 208.0 (CO-12) and 211.0 (CO-4); *m*/*z* (EI) 347.1886 (86%, $M^{\cdot+}$. $C_{23}H_{25}NO_2$ requires 347.1885), 319 (38), 276 (13), 262 (39), 248 (63), 234 (27), 220 (22), 198 (15), 170 (22), 130 (10) and 91 (100).

### *cis*,*cis*-12-Hydroxy-12-methyl-3,4a-propano-9-benzyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4-ones 17a,b and (2*S**,4*R**,4a*R**,7a*R**,12b*R**)-2,4-diacetyl-8-benzyl-4a-hydroxy-1,2,3,4,4a,5,6,7,7a,8-decahydrobenzo[*d*]carbazole 18§

Compounds **17a**,**b** and **18** were prepared from hexahydrocarbazolone **3** (277 mg, 1.0 mmol) and methyl vinyl ketone (105 mg, 122 mm$^3$, 1.5 mmol) following the procedure described for **13**. Flash chromatography on silica gel with 90:10 and 70:30 hexane–AcOEt afforded respectively **18** (108 mg, 26%) and **17a**,**b** (104 mg, ratio 60:40, 30%). Both isomers **17a** and **17b** showed identical $R_f$ values after elutions and could not be separated. The spectroscopic data of each isomer were assigned from the mixture. **17a**: $\delta_H$(400 MHz; $CDCl_3$) 1.33 (3 H, s, Me), 1.38 (1 H, m, 1-$H_{ax}$), 1.63 (1 H, m, 11-$H_B$), 1.66 (1 H, m, 2-$H_{ax}$), 1.90 (1 H, m, 10-$H_B$), 2.02 (1 H, m, 1-$H_{eq}$), 2.11 (1 H, m, 2-$H_{eq}$), 2.12 (1 H, m, 11-$H_A$), 2.45 (1 H, m, 10-$H_A$), 2.50 (1 H, dd, *J* 10.0 and 2.5, 3-H), 3.97 (1 H, dd, *J* 10.5 and 5.0, 9a-H), 4.38 (2 H, AB, *J* 16.5, Δ*ν* 41.3, NC$H_2$Ph), 6.38 (1 H, d, *J* 7.8, 8-H), 6.74 (1 H, td, *J* 7.4 and 1.0, 6-H), 7.09 (1 H, td, *J* 7.8 and 1.0, 7-H), 7.15 (1 H, dd, *J* 7.4 and 1.0, 5-H) and 7.25–7.40 (5 H, m, ArH); $\delta_C$(100 MHz; $CDCl_3$) 24.0 (C-2), 27.2 (C-1), 28.1 ($CH_3$), 29.8 (C-11), 36.6 (C-10), 50.8 (N*C*$H_2$Ph), 57.4 (C-3), 58.6 (C-4a), 71.9 (C-9a), 78.8 (C-12), 106.2 (C-8), 117.2 (C-6), 126.1 (C-5), 127.1 (C-7), 127.0–128.9 (5 ArCH), 127.9 (C-4b), 138.8 (C-1′), 150.7 (C-8a) and 212.3 (CO). **17b**: $\delta_H$(400 MHz; $CDCl_3$) 1.27 (1 H, m, 1-$H_{ax}$), 1.35 (3 H, s, Me), 1.63 (1 H, m, 11-$H_B$), 1.90 (1 H, m, 10-$H_B$), 1.97 (1 H, m, 2-$H_{ax}$), 2.02 (1 H, m, 1-$H_{eq}$), 2.12 (1 H, m, 11-$H_A$), 2.13 (1 H, m, 2-$H_{eq}$), 2.42 (1 H, m, 10-$H_A$), 2.65 (1 H, dd, *J* 10.0 and 2.5, 3-H), 3.97 (1 H, dd, *J* 10.5 and 5.0, 9a-H), 4.39 (2 H, AB, *J* 16.6, Δ*ν* 43.7, NC$H_2$Ph), 6.38 (1 H, d, *J* 7.8, 8-H), 6.73 (1 H, td, *J* 7.4 and 1.0, 6-H), 7.05 (1 H, dd, *J* 7.4 and 1.0, 5-H), 7.10 (1 H, td, *J* 7.8 and 1.0, 7-H) and 7.24–7.40 (5 H, m, ArH); $\delta_C$(100 MHz; $CDCl_3$) 22.0 (C-2), 27.0 (C-1), 27.6 ($CH_3$), 30.8 (C-11), 35.4 (C-10), 50.7 (N*C*$H_2$Ph), 57.9 (C-3), 58.3 (C-4a), 72.1 (C-9a), 76.0 (C-12), 106.2 (C-8), 117.3 (C-6), 125.9 (C-5), 127.1 (C-7), 127.0–128.9 (5 ArCH), 127.2 (C-4b), 138.7 (C-1′), 150.8 (C-8a) and 213.2 (CO).

**17a**,**b** (ratio 60:40): pale yellow foam; $\nu_{max}(CCl_4)$/cm$^{-1}$ 3600 (OH), 1725 and 1710 (CO); *m*/*z* (EI) 347.1886 (100%, $M^{\cdot+}$. $C_{23}H_{25}NO_2$ requires 347.1885), 319 (29), 276 (53), 248 (22), 234 (15), 220 (20), 170 (14), 130 (15), 91 (90), 69 (21), 57 (19), 43 (27). **18**: white crystals, mp 175–178 °C (from cyclohexane–AcOEt) (Found: C, 77.2; H, 7.6; N, 3.2. $C_{27}H_{31}NO_3$ requires C, 77.65; H, 7.5; N, 3.35%); $\nu_{max}(CHCl_3)$/cm$^{-1}$ 3500 (OH) and 1705 (CO); $\delta_H$(400 MHz; $CDCl_3$) 1.20 (1 H, qt, *J* 13.0 and 3.0, 2-$H_{ax}$), 1.25 (1 H, tdd, *J* 13.0, 9.5 and 4.0, 1-$H_{ax}$), 1.53–1.65 (2 H, m, 2-$H_{eq}$, 3-$H_{ax}$), 1.75–1.89 (2 H, m, 3-$H_{eq}$, 1-$H_{eq}$), 1.79 (1 H, dt, *J* 13.0 and 3.0, 13-$H_{eq}$), 1.88 (1 H, t, *J* 13.0, 10-$H_{ax}$), 2.08 (1 H, q, *J* 13.0, 13-$H_{ax}$), 2.16 (3 H, s, Me), 2.21 (3 H, s, Me), 2.25 (1 H, dd, *J* 13.0 and 3.0, 10-$H_{eq}$), 2.49 (1 H, tt, *J* 13.0 and 3.0, 11-$H_{ax}$), 2.93 (1 H, dd, *J* 13.0 and 3.0, 14-$H_{ax}$), 3.47 (1 H, dd, *J* 9.5 and 6.0, 9a-H), 4.26 (2 H, AB, *J* 14.5, Δ*ν* 196.6, NC$H_2$Ph), 4.30 (1 H, s, OH), 6.48 (1 H, d, *J* 7.7, 8-H), 6.73 (1 H, t, *J* 7.4, 6-H), 7.10 (1 H, td, *J* 7.7 and 1.0, 7-H), 7.32–7.46 (5 H, m, ArH) and 7.80 (1 H, dd, *J* 7.4 and 1.0, 5-H); $\delta_C$(100 MHz; $CDCl_3$) 20.0 (C-2), 24.5 (C-1), 26.0 (C-13), 27.7 ($CH_3$), 31.6 ($CH_3$), 32.5 (C-10), 34.0 (C-3), 47.3 (C-11), 48.2 (N*C*$H_2$Ph), 50.9 (C-14), 53.0 (C-4a), 62.7 (C-9a), 73.8 (C-4), 107.9 (C-8), 118.6 (C-6), 126.8 (C-5), 127.4 (C-7), 127.6–128.6 (5 ArCH), 134.8 (C-4b), 138.5 (C-1′), 148.9 (C-8a), 209.8 (CO-12) and 214.9 (CO-15); *m*/*z* (EI) 417.2304 (66%, $M^{\cdot+}$. $C_{27}H_{31}NO_3$ requires 417.2304), 399 (44), 387 (12), 290 (11), 276 (19), 262 (20), 248 (30), 234 (17), 220 (49), 198 (15), 170 (17), 130 (15), 91 (100), 43 (18).

### 8-Benzyl-1,2,3,4,4a,5,6,7,7a,8-decahydropyrido[2,3-*d*]carbazole 20

A solution of hexahydrocarbazolone **13** (231 mg, 0.70 mmol) in EtOH (21 cm$^3$) was hydrogenated at room temperature for 4 days under 3 atm of pressure (Parr apparatus) in the presence of $PtO_2$ (20 mg). The catalyst was removed by filtration through Celite and the filtrate was concentrated. Chromatography on alumina with 20:80 hexane–AcOEt afforded amine **20** (178 mg, 80%) as an amorphous solid; $\nu_{max}$(KBr)/cm$^{-1}$ 3370 (NH); $\delta_H$(300 MHz; [$^2H_6$]DMSO) 0.92–2.00 (10 H, m, 2 × 1-H, 2 × 2-H, 2 × 5-H, 2 × 6-H, 2 × 7-H), 2.94 (1 H, br s, NH), 3.20–3.50

§ The IUPAC numbering system has been used to name this compound. However, for the purposes of describing the $^1$H and $^{13}$C NMR data, the numbering scheme shown in the structural representation of **18** has been used.

(4 H, m, 4a-H, 7a-H, 2 × 3-H), 4.24 (2 H, AB, *J* 15.0, Δ*v* 67.0, NC*H*$_2$Ph), 6.40 (1 H, d, *J* 7.5, 9-H), 6.62 (1 H, t, *J* 7.5, 11-H), 7.04 (1 H, t, *J* 7.5, 10-H), 7.23–7.45 (5 H, m, ArH) and 7.80 (1 H, d, *J* 7.5, 12-H); $\delta_C$(75 MHz, [$^2$H$_6$]DMSO) 18.5 (C-6), 20.3 (C-2), 24.1 (C-7), 25.3 (C-5), 33.2 (C-1), 43.3 (C-3), 47.5 (C-12b), 47.9 (N*C*H$_2$Ph), 57.3 (C-4a), 69.6 (C-7a), 107.8 (C-9), 116.6 (C-11), 125.6 (C-12), 126.9 (C-10), 127.3–128.4 (5 ArCH), 129.9 (C-12a), 138.6 (C-1′) and 150.2 (C-8a); *m*/*z* (EI) 318.2094 (53%, M$^{\bullet+}$. $C_{22}H_{26}N_2$ requires 318.2090), 247 (17), 234 (21), 117 (19), 91 (100), 87 (22), 57 (39) and 47 (64).

**5,5-Dimethyl-8-benzyl-1,2,3,4,4a,5,6,7,7a,8-decahydropyrido-[2,3-*d*]carbazole 21**

This compound was prepared from dimethylcyanohexahydrocarbazolone **15** (179 mg, 0.5 mmol) following the procedure described for **20**. Chromatography on alumina with 50:50 hexane–AcOEt afforded amine **21** (107 mg, 62%) as an amorphous solid; $\nu_{max}$($CCl_4$)/cm$^{-1}$ 3360 (NH); $\delta_H$(300 MHz; $CDCl_3$) 1.07 (3 H, s, Me), 1.36 (3 H, s, Me), 1.20–1.90 (6 H, m, 2 × 2-H, 2 × 6-H, 2 × 7-H), 2.16 (2 H, m, 2 × 1-H), 3.00 (1 H, s, 4a-H), 3.14 (1 H, td, *J* 12.5 and 2.5, 3-H$_{ax}$), 3.24 (1 H, dd, *J* 8.5 and 5.0, 7a-H), 3.93 (1 H, dt, *J* 12.5 and 1.5, 3-H$_{eq}$), 4.30 (2 H, AB, *J* 15.0, Δ*v* 98.5, NC*H*$_2$Ph), 6.42 (1 H, d, *J* 7.5, 9-H), 6.83 (1 H, t, *J* 7.5, 11-H), 7.09 (1 H, t, *J* 7.5, 10-H), 7.30–7.37 (5 H, m, ArH) and 8.20 (1 H, d, *J* 7.5, 12-H); $\delta_C$(75 MHz; $CDCl_3$) 18.9 (C-6), 21.5 (C-2), 21.6 ($CH_3$), 31.3 ($CH_3$), 34.2 (C-7), 36.2 (C-1), 37.0 (C-5), 46.8 (C-3), 47.5 (C-12b), 48.6 (N*C*H$_2$Ph), 67.9 (C-4a), 70.8 (C-7a), 107.4 (C-9), 117.9 (C-11), 127.3 (C-12), 127.6 (C-10), 127.6–128.1 (5 ArCH), 130.2 (C-12a), 138.3 (C-1′) and 149.5 (C-8a); *m*/*z* (EI) 346.2411 (92%, M$^{\bullet+}$. $C_{24}H_{30}N_2$ requires 346.2402), 290 (29), 275 (10), 255 (11), 247 (17), 234 (22), 221 (11), 91 (100), 87 (17), 43 (22).

**21 Hydrochloride**: HCl treatment of an analytical sample of a solution of **21** afforded the hydrochloride salt as white crystals, mp 196–199 °C (from MeOH–diethyl ether) (Found: C, 75.55; H, 7.9; N, 7.35; Cl, 9.45. $C_{24}H_{31}N_2Cl$ requires C, 75.25; H, 8.15; N, 7.3; Cl, 9.25%); $\nu_{max}$(KBr)/cm$^{-1}$ 3440 (NH), 2760, 2740 and 1585 ($^+$NH$_2$); $\delta_H$(400 MHz; $CDCl_3$) 0.75 (3 H, s, Me), 0.95 (3 H, s, Me), 1.15–1.90 (7 H, m, 1-H$_{ax}$, 2 × 2-H, 2 × 6-H, 2 × 7-H), 2.07 (1 H, dt, *J* 12.0 and 3.3, 1-H$_{eq}$), 2.49 (1 H, s, 4a-H), 2.78 (1 H, t, *J* 11.5, 3-H$_{ax}$), 3.12 (1 H, dd, *J* 10.0 and 5.5, 7a-H), 3.32 (1 H, m, 3-H$_{eq}$), 4.27 (2 H, AB, *J* 15.2, Δ*v* 112.5, NC*H*$_2$Ph), 6.33 (1 H, d, *J* 7.5, 9-H), 6.64 (1 H, t, *J* 7.5, 11-H), 7.02 (1 H, t, *J* 7.5, 10-H), 7.26–7.40 (5 H, m, ArH) and 7.83 (1 H, d, *J* 7.5, 12-H).

**4-Acetyl-8-benzyl-1,2,3,4,4a,5,6,7,7a,8-decahydropyrido[2,3-*d*]-carbazole 22**

To a solution of amine **20** (127 mg, 0.40 mmol), $NEt_3$ (45 mg, 60 mm$^3$, 0.44 mmol) and DMAP (catalytic amount) in dry $CH_2Cl_2$ (2 cm$^3$) was added dropwise, under nitrogen, a solution of acetyl chloride (35 mg, 31 mm$^3$, 0.44 mmol) in $CH_2Cl_2$ (2 cm$^3$). After the addition was complete, the solution was stirred for 3 h and then washed with brine. The organic layer was dried and concentrated. Flash chromatography on silica gel with 70:30 hexane–AcOEt afforded acetamide **22** (101 mg, 70%) as an amorphous solid (Found: C, 79.8; H, 7.95; N, 7.4. $C_{24}H_{28}N_2O$ requires C, 79.95; H, 7.85; N, 7.75%); $\nu_{max}$($CCl_4$)/cm$^{-1}$ 1640 (CO); $\delta_H$(300 MHz; $CDCl_3$) 0.85–2.35 (10 H, m, 2 × 1-H, 2 × 2-H, 2 × 5-H, 2 × 6-H, 2 × 7-H), 2.18 (3 H, s, Me), 2.98 (1 H, td, *J* 13.5 and 2.5, 3-H$_{ax}$), 3.20 (1 H, dd, *J* 10.0 and 5.0, 4a-H), 3.30 (1 H, dd, *J* 11.5 and 5.0, 7a-H), 4.26 (1 H, br d, *J* 13.5, 3-H$_{eq}$), 4.27 (2 H, AB, *J* 15.0, Δ*v* 89.0, NC*H*$_2$Ph), 6.39 (1 H, d, *J* 7.8, 9-H), 6.68 (1 H, td, *J* 7.5 and 1.0, 11-H), 7.06 (1 H, td, *J* 7.8 and 1.0, 10-H), 7.21 (1 H, dd, *J* 7.5 and 1.0, 12-H) and 7.30–7.40 (5 H, m, ArH); $\delta_C$(75 MHz; $CDCl_3$) 23.1 (C-2 and C-6), 24.7 (C-7), 25.2 ($CH_3$), 28.8 (C-5), 38.4 (C-1), 48.9 (C-3), 49.6 (C-12b), 50.0 (N*C*H$_2$Ph), 66.3 (C-4a), 71.8 (C-7a), 107.7 (C-9), 117.6 (C-11), 125.6 (C-12), 127.1 (C-10), 127.7–128.6 (5 ArCH), 131.8 (C-12a), 138.7 (C-1′), 150.6 (C-8a) and 169.8 (CO); *m*/*z* (EI) 360.2201 (11%, M$^{\bullet+}$. $C_{24}H_{28}N_2O$ requires 360.2194), 270 (10), 234 (10), 220 (10), 198 (12), 183 (12), 170 (26), 156 (15), 143 (24), 130 (29), 115 (14), 91 (94), 77 (11), 70 (14), 57 (17), 43 (100).

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