

# A Short and Efficient Synthesis of 4a-Substituted *cis*-Hexahydro-1,2,3,4,4a,9a-Carbazol-4-ones

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Received January 7, 1987

Photocyclization of tertiary aryl enamines **1** gave *trans*-hexahydrocarbazol-4-ones **2** which were subsequently alkylated with a series of electrophiles *via* the corresponding thermodynamic anion. The 4a-substituted derivatives formed were shown to have the *cis*-hexahydrocarbazol-4-one structure by comparison with the previously prepared *trans* isomer.

*J. Heterocyclic Chem.*, **25**, 201 (1988).

Hexahydrocarbazole systems are present in the framework of a number of indole alkaloids of biological interest. The presence of a keto group at the C-4 position of this heterocycle theoretically permits further substitutions at the C-4a and C-3 positions and this possibility can be exploited for instance to build the pentacyclic skeleton of *Aspidosperma* alkaloids. We have recently achieved a short and efficient synthesis of *trans*-hexahydrocarbazol-4-ones substituted at 4a position [1]. However the formation of a *trans* relationship at the B/C ring junction is undesirable for the synthesis of the natural products. It was thus necessary to rely on a regio- and stereospecific alkylation of the still unknown unsubstituted hexahydrocarbazol-4-ones **2**. Indeed a survey of the literature for 1-tetralone [2a-c] revealed that *cis*-fused 4a-alkylated derivatives should be obtained *via* the thermodynamic anion derived from **2**.

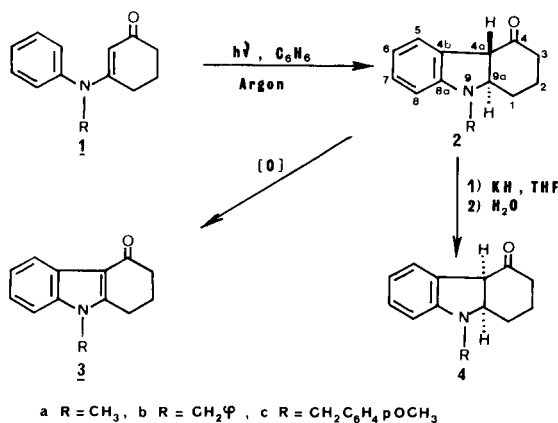
We now wish to report a simple and high-yield procedure for the synthesis of *cis*-alkylated hexahydrocarbazol-4-ones from the readily available *trans*-hexahydrocarbazol-4-ones **2a-c**. Compounds **2a-c** can be prepared in

excellent yield (85-100%) by irradiation, using pyrex filter, of the easily available tertiary aryl enamines **1a** [3], **1b** [4] and **1c** in carefully deoxygenated benzene solution, for one hour (Scheme 1). In fact compounds **2** were found to be rather unstable, oxidizing rapidly in solution to the known tetrahydro derivatives **3a** [5] or **3b** [6]. We found that insufficient deoxygenation of the solution led to the formation of **3** which then acted as internal photochemical filter (due to high molecular extinction coefficient  $\epsilon$ ) lowering both the yield and the rate of the photochemical process.

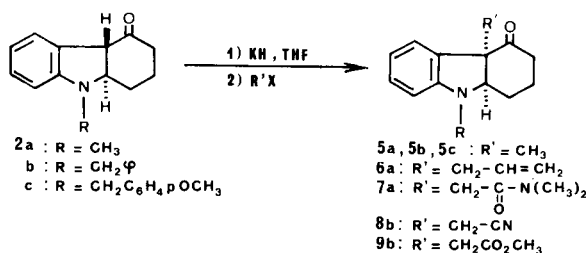
However compounds **2** could be purified by flash chromatography [7] and stored neat at  $-15^\circ$ , under an argon atmosphere, without notable decomposition after several days.

Structures and stereochemical purities of the newly synthesized compounds **2** have been determined on the basis of their spectral properties and in particular their  $^{13}\text{C}$  nmr. The *trans* ring junction of **2** was inferred from analogy with our previous results for the photocyclization of substituted enamines [1] and from quantitative transformation of **2b** into its more stable *cis*-isomer **4**. Thus the reaction of potassium hydride [8-9] with **2b** in THF at room temperature [10] for a few minutes resulted in the formation of **4** *via* the thermodynamic enolate [11], after quenching with water.

Scheme 1



Scheme 2



We decided to exploit the abovementioned conditions for the preparation of the *cis*-fused compounds we were looking for. Carefully controlled reaction of the enolates derived from **2a-c** with a series of electrophiles (methyl iodide, allyl bromide, dimethyl iodoacetamide, iodoacetonitrile and methyl bromoacetate) led to the formation of *cis*-4a-substituted hexahydrocarbazol-4-ones **5-9** in yields ranging from 80% to 94% (Scheme 2).

All the compounds are stereochemically pure, showing that the angular alkylation proceeds with 100% stereoselectivity.

The B/C ring junction of compounds **5-9** is *cis* as expected what is confirmed by comparison with their *trans*-isomers previously synthesized [1].

Having in hand three pairs of *cis* and *trans*-hexahydrocarbazol-4-ones (*cis*-compounds **5a**, **5b** and **6a** and their *trans*-analogues previously described [1]) it was interesting to consider the possibility of establishing their stereochemistry by comparison of <sup>1</sup>H and <sup>13</sup>C nmr data. Examination of molecular models shows rather important modification of the situation of the aromatic H-5 with respect to the strongly anisotropic carbonyl group at C-4. One can thus expect a systematic difference of the chemical shift of this hydrogen in both series. Indeed H-5 appears at 7.2 ppm in the *cis*-series and at 7.5 ppm in the *trans*-series.

The <sup>13</sup>C nmr spectra of both *cis* and *trans*-series are quite similar with the exception of the carbonyl carbons which appear at higher field for the *trans*-compounds (Table 1). Although these data are coherent for the three pairs of compounds it seems necessary to possess both isomers in order to assign their stereochemistry on the basis of nmr data only.

Table I

Chemical Shift (in ppm, TMS = 0, deuteriochloroform) of C-4 (carbonyl) in Substituted *cis* and *trans*-Hexahydrocarbazol-4-ones (*cis* this work, *trans*, see ref [1])

	<i>cis</i>	<i>trans</i>
<b>5a</b>	212.7	209.2
<b>5b</b>	212.1	209.1
<b>6a</b>	211.3	207.7

In conclusion we have devised a very efficient regio- and stereoselective method for the synthesis of variously 4a-substituted *cis*-hexahydrocarbazol-4-ones in high yield (up to 85% in three steps).

A total synthesis of (±) desethylaspidospermidine has recently been achieved using this sequence of reaction [12].

## EXPERIMENTAL

Melting points were determined on a hot stage microscope and are un-

corrected. Infrared spectra (ir) were recorded in solution on a Perkin-Elmer 377 spectrophotometer and values are expressed in reciprocal centimeters with polystyrene calibration. The <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance spectra (nmr) were recorded in deuteriochloroform (tetramethylsilane as an internal standard, δ = 0) on a JEOL C 60 H and on a JEOL FX 60 (15.08 MHz) spectrometers at the "Centre Regional de Mesures Physiques" under the responsibility of Professor D. Besserre whom we wish to thank.

Chemical shift data are reported in parts per million downfield from tetramethylsilane, where s, d, dd, t, q, and m designate singlet, doublet, doublet of doublet, triplet, quadruplet and multiplet, respectively. Low resolution (70 eV) and high resolution mass spectrometry were performed on a Varian CH5 instrument.

Irradiations were carried out in a pyrex glass vessel using a medium pressure mercury lamp (Philips 400w). Before irradiation the reaction mixture was flushed with a stream of argon for ten minutes in order to remove oxygen.

Potassium hydride was freed from oil by centrifugation and washed with dry pentane. It was then transferred to the reaction flask where it was dried by a stream of argon.

### Tertiary Alkyl Enaminones **1a,b,c**.

Enaminones **1a** and **1b** were prepared according to literature [3,4]. Enaminone **1c** was prepared by the same procedure and was obtained as a viscous oil (75%); ir (carbon tetrachloride): 1645 cm<sup>-1</sup> (N-C=C-O); <sup>1</sup>H nmr: δ 1.7-2.5 (m, 6H), 3.7 (s, 3H), 4.8 (s, 2H), 5.4 (s, 1H), 6.7-7.5 (m, 9H); <sup>13</sup>C nmr: δ 21.5, 27.7, 35.1, 54.2, 55.1, 100.2, 113.1, 126.6, 126.9, 127.5, 128.1, 128.7, 143.3, 158.0, 164.2, 196.5; ms: exact mass m/z, 307.1574; Calcd. for C<sub>20</sub>H<sub>21</sub>NO<sub>2</sub> m/z 307.1572.

Anal. Calcd. for C<sub>20</sub>H<sub>21</sub>NO<sub>2</sub>: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.05; H, 6.78; N, 4.48.

### *Trans*-Hexahydro-1,2,3,4,4a,9a-carbazol-4-ones **2a,b,c**.

A degassed solution of **1a**, **1b**, **1c** (1.0 g, 5.0 mmoles) in benzene (200 ml) was irradiated for 1 hour under an atmosphere of argon. The solvent was then evaporated and the crude product was purified by chromatography on silica gel eluting with hexane-ethyl acetate (8:2).

#### Compound **2a**.

This compound was obtained as an oil (85%); ir (carbon tetrachloride): 1715 cm<sup>-1</sup> (C=O); <sup>1</sup>H nmr: δ 1.7-2.1 (m, 4H), 2.2-2.6 (m, 2H), 2.7 (s, 3H), 3.6-3.9 (m, 2H), 6.3-7.4 (m, 4H); <sup>13</sup>C nmr: δ 19.2, 24.6, 32.8, 39.7, 54.0, 67.2, 107.5, 118.0, 125.5, 126.4, 128.4, 152.4, 209.6; ms: exact mass m/z 201.1157; Calcd. for C<sub>13</sub>H<sub>15</sub>NO m/z 201.1153.

#### Compound **2b**.

This compound was obtained as a colourless solid, mp 165-166°, quantitative yield; ir (carbon tetrachloride): 1710 cm<sup>-1</sup> (C=O); <sup>1</sup>H nmr: δ 1.4-2.6 (m, 6H), 3.4-3.6 (m, 2H), 4.2 (s, 2H), 6.3-7.6 (m, 9H); <sup>13</sup>C nmr: δ 23.7, 29.4, 40.9, 52.7, 57.6, 73.0, 108.9, 119.5, 124.9, 127.2, 127.9, 138.6, 152.6, 205.6; ms: exact mass m/z, 277.1466; Calcd. for C<sub>15</sub>H<sub>19</sub>NO m/z 277.1462.

#### Compound **2c**.

This compound was obtained in quantitative yield; ir (carbon tetrachloride): 1710 cm<sup>-1</sup> (C=O); <sup>1</sup>H nmr: δ 1.3-2.6 (m, 7H), 3.4 (m, 1H), 3.7 (s, 3H), 4.1 (s, 2H), 6.4-7.5 (m, 8H); <sup>13</sup>C nmr: δ 23.7, 29.4, 40.9, 52.0, 55.2, 57.6, 72.7, 108.9, 113.9, 119.3, 123.2, 124.9, 125.3, 127.5, 127.9, 128.8, 129.4, 130.5, 152.7, 158.8, 205.8; ms: exact mass m/z 307.1571; Calcd. for C<sub>20</sub>H<sub>21</sub>NO<sub>2</sub> m/z 307.1572.

Compounds **2a**, **2b**, **2c** and **4** were susceptible to air oxidation and did not give satisfactory microanalyses. They were homogenous by tlc and <sup>13</sup>C nmr spectroscopy gave additional evidence of their structures.

General Procedure for the Alkylation of Ketones **2**. *Cis*-Hexahydrocarbazolone **5a**.

The apparatus was comprised of two 50 ml flasks (A and B), fitted with magnetic stirring bars, argon inlets and serum caps, and linked together

by 2 mm i.d. teflon tubing allowing the transfer of a solution from one flask to the other by means of argon pressure. Potassium hydride (2.66 mmoles, 0.304 g, 35% in oil), freed from oil (see above), was placed in flask A to which THF (5 ml) was added. To the resulting suspension was added a solution of **2a** (0.508 g, 2.53 mmoles) in THF (10 ml) from flask B, *via* the teflon tubing. The mixture was stirred at room temperature for five minutes and then was added to a solution of methyl iodide (0.37 g, 2.60 mmoles) in THF (20 ml) prepared in flask B by reverse addition through the same teflon tubing under argon pressure. After stirring for an additional ten minutes, water was added to the mixture in order to solubilize the precipitate. The majority of THF was evaporated and the aqueous phase was extracted three times with methylene chloride. The combined organic layers were washed with water, dried over sodium sulfate and concentrated. The crude product was purified by filtration through a column of silica gel, eluting with hexane-ethyl acetate (8:2). Compound **5a** was isolated as an oil (80%); ir (carbon tetrachloride): 1710  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr:  $\delta$  1.45 (s, 3H,  $\text{C}_{4a}\text{-CH}_3$ ), 1.6-2.2 (m, 4H), 2.2-2.5 (m, 2H), 2.7 (s, 3H, N- $\text{CH}_3$ ), 3.4 (m, 1H, N- $\text{C}_9\text{aH}$ ), 6.3-7.3 (m, 4H);  $^{13}\text{C}$  nmr:  $\delta$  19.6, 22.7, 23.6, 33.0, 38.2, 56.5, 74.8, 107.5, 118.2, 124.4, 128.5, 131.7, 152.0, 212.7; ms: exact mass  $m/z$  215.1309; Calcd. for  $\text{C}_{14}\text{H}_{17}\text{NO}$   $m/z$  215.1310.

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{17}\text{NO}$ : C, 78.10; H, 7.96; N, 6.51. Found: C, 78.14; H, 7.88; N, 6.44.

#### *Cis*-Hexahydrocarbazolone **5b**.

This compound was obtained in 90% yield; ir (carbon tetrachloride): 1725  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr:  $\delta$  1.45 (s, 3H,  $\text{C}_{4a}\text{-CH}_3$ ), 1.6-2.5 (m, 6H), 3.75 (m, 1H, N- $\text{C}_9\text{aH}$ ), 4.35 (2H, AB spectrum,  $J = 15$  Hz,  $\Delta\nu = 13.2$  Hz), 6.4-7.5 (m, 9H);  $^{13}\text{C}$  nmr:  $\delta$  19.4, 23.1, 24.4, 38.1, 50.3, 56.6, 72.6, 107.5, 118.1, 124.2, 127.0, 127.2, 128.5, 131.4, 138.3, 151.1, 212.1; ms: exact mass  $m/z$  291.1624; Calcd. for  $\text{C}_{20}\text{H}_{21}\text{NO}$   $m/z$  291.1623.

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{21}\text{NO}$ : C, 82.44; H, 7.26; N, 4.81. Found: C, 82.32; H, 7.32; N, 4.75.

#### *Cis*-Hexahydrocarbazolone **5c**.

This compound was obtained as an oil in 87% yield; ir (carbon tetrachloride): 1705  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr:  $\delta$  1.4 (s, 3H,  $\text{C}_{4a}\text{-CH}_3$ ), 1.6-2.0 (m, 4H), 2.1-2.5 (m, 2H), 3.4-3.6 (m, 1H, N- $\text{C}_9\text{aH}$ ), 3.7 (s, 3H, OCH<sub>3</sub>), 4.2 (2H, AB spectrum,  $J = 15$  Hz,  $\Delta\nu = 12.5$  Hz; N- $\text{CH}_2\text{Ph}$ ), 6.3-7.3 (m, 8H);  $^{13}\text{C}$  nmr:  $\delta = 19.4, 23.0, 24.2, 38.0, 49.4, 55.0, 56.4, 72.2, 107.5, 113.8, 117.9, 124.1, 128.4, 130.0, 131.4, 150.1, 158.7, 212.0$ ; ms: exact mass  $m/z$  321.1729; Calcd. for  $\text{C}_{21}\text{H}_{23}\text{NO}_2$   $m/z$  321.1728.

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{23}\text{NO}_2$ : C, 78.47; H, 7.21; N, 4.36. Found: C, 78.33; H, 7.07; N, 4.27.

#### *Cis*-Hexahydrocarbazolone **6a**.

This compound was obtained as an oil in 86% yield; ir (carbon tetrachloride): 1710  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr:  $\delta$  1.7-3.0 (m, 8H), 2.7 (s, 3H, N- $\text{CH}_3$ ), 3.65 (m, 1H,  $\text{C}_9\text{aH}$ ), 4.8-6.0 (m, 3H), 6.4-7.3 (m, 4H);  $^{13}\text{C}$  nmr:  $\delta$  18.6, 24.5, 32.6, 38.8, 41.4, 60.2, 70.0, 106.9, 117.8, 118.3, 124.4, 128.8, 130.7, 134.1, 151.8, 211.3; ms: exact mass  $m/z$  241.1458; Calcd. for  $\text{C}_{16}\text{H}_{19}\text{NO}$   $m/z$  241.1461.

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{19}\text{NO}$ : C, 79.63; H, 7.94; N, 5.80. Found: C, 79.60; H, 7.89; N, 5.74.

#### *Cis*-Hexahydrocarbazolone **7a**.

This compound was obtained as an oil in 94% yield; ir (carbon tetrachloride): 1650 (N-C=O), 1710  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr:  $\delta$  1.2-2.7 (m, 6H), 2.75 (s, 3H, N- $\text{CH}_3$ ), 2.85 (s, 6H, N- $(\text{CH}_2)_2$ ), 2.95 (2H, AB spectrum,  $J = 17$  Hz,  $\Delta\nu = 27$  Hz, CO- $\text{CH}_2\text{-N}$ ), 3.85 (m, 1H,  $\text{C}_9\text{aH}$ ), 6.2-7.3 (m, 4H);  $^{13}\text{C}$  nmr:  $\delta$  18.3, 24.9, 31.1, 35.1, 38.9, 42.2, 57.4, 71.1, 106.2, 117.1, 123.4, 128.8, 129.0, 150.5, 170.7, 209.3; ms: exact mass  $m/z$  286.1683; Calcd. for  $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2$   $m/z$  286.1681.

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2$ : C, 71.30; H, 7.74; N, 9.78. Found: C, 71.12; H, 7.70; N, 9.62.

Equilibration of *trans*-Hexahydro-1,2,3,4,4a,9a-carbazol-4-one **2b** into its *cis*-Epimer **4**.

#### *Cis*-Hexahydrocarbazolone **8b**.

This compound was obtained as a colourless solid, mp 141-142° (88%); ir (chloroform): 2250  $\text{cm}^{-1}$  (C $\equiv$ N), 1705  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr:  $\delta$  1.5-2.1 (m, 4H), 2.2-2.6 (m, 2H), 2.7 (2H, AB spectrum,  $J = 17$  Hz,  $\Delta\nu = 22$  Hz,  $\text{C}_{4a}\text{-CH}_2\text{-CN}$ ), 3.9 (m, 1H,  $\text{C}_9\text{aH}$ ), 4.4 (2H, AB spectrum,  $J = 14$  Hz,  $\Delta\nu = 14.3$  Hz, N- $\text{CH}_2$ ), 6.4-7.1 (m, 9H);  $^{13}\text{C}$  nmr:  $\delta$  18.4, 24.4, 25.7, 37.9, 49.4, 58.6, 69.8, 107.8, 117.5, 118.4, 123.4, 126.8, 127.4, 127.5, 128.5, 128.8, 130.3, 137.5, 150.0, 207.1; ms: exact mass  $m/z$  316.1572; Calcd. for  $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}$   $m/z$  316.1576.

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}$ : C, 79.71; H, 6.37; N, 8.85. Found: C, 79.67; H, 6.41; N, 8.72.

#### *Cis*-Hexahydrocarbazolone **9b**.

This compound had mp 104-105° (ether) (84%); ir (carbon tetrachloride): 1740  $\text{cm}^{-1}$  (CO<sub>2</sub>Me), 1710  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr:  $\delta$  1.5-2.1 (m, 4H), 2.2-2.5 (m, 2H), 2.9 (2H, AB spectrum,  $J = 17$  Hz,  $\Delta\nu = 31$  Hz,  $\text{C}_{4a}\text{-CH}_2$ ), 3.6 (s, 3H, OCH<sub>3</sub>), 3.9 (m, 1H,  $\text{C}_9\text{aH}$ ), 4.3 (2H, AB spectrum,  $J = 16$  Hz,  $\Delta\nu = 12$  Hz, N- $\text{CH}_2$ ), 6.3-7.4 (m, 9H);  $^{13}\text{C}$  nmr:  $\delta$  18.0, 25.6, 38.4, 41.2, 48.7, 51.2, 57.5, 69.4, 106.8, 117.6, 123.4, 127.1, 128.0, 128.4, 129.1, 137.9, 149.8, 172.0, 208.6; ms: exact mass  $m/z$  337.1677; Calcd. for  $\text{C}_{21}\text{H}_{23}\text{NO}_3$   $m/z$  337.1678.

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{23}\text{NO}_3$ : C, 74.75; H, 6.87; N, 4.15. Found: C, 74.72; H, 6.82; N, 4.17.

To a suspension of potassium hydride (2.54 mmoles, 0.290 g, 35% in oil) in THF (10 ml) was added a solution of **2b** (0.670 g, 2.42 mmoles) in THF (10 ml). The resulting mixture was stirred at room temperature for five minutes and then water was added (5 ml). After stirring for five minutes the THF was evaporated. The residue was taken with methylene chloride, the resulting solution was dried over sodium sulfate and evaporated to give **4** as an oil (quantitative yield); ir (carbon tetrachloride): 1710  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr:  $\delta$  1.6-2.0 (m, 4H), 2.1-2.5 (m, 2H), 3.6-4.1 (m, 2H), 4.5 (2H, AB spectrum,  $J = 15$  Hz, N- $\text{CH}_2\text{Ph}$ ), 6.3-7.4 (m, 9H);  $^{13}\text{C}$  nmr:  $\delta$  19.1, 25.0, 39.4, 50.3, 54.0, 65.1, 107.5, 118.1, 125.4, 126.0, 127.1, 127.3, 127.8, 128.6, 138.3, 151.7, 209.4; ms: exact mass  $m/z$  277.1460; Calcd. for  $\text{C}_{19}\text{H}_{19}\text{NO}$   $m/z$  277.1462.

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