

SHORT SYNTHESIS OF (±)-CORYNANTHEIDOL AND  
(±)-3-EPICORYNANTHEIDOL

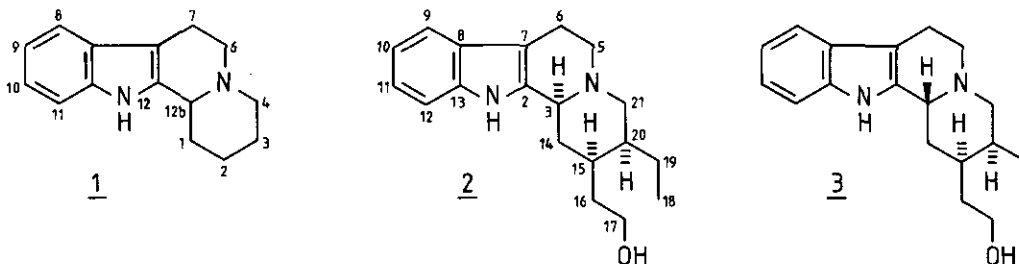
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**Abstract** - A short synthesis for (±)-corynantheidol and (±)-3-epicorynantheidol is described.

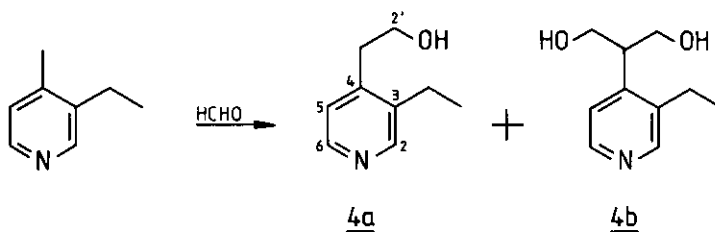
Recent reports from our laboratory have described a new general method,<sup>1-5</sup> which permits the preparation of 1-, 2- and 3-substituted 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (**1**) derivatives possessing the C(12b)H-C(1)H, C(12b)H-C(2)H and C(12b)H-C(3)H relationship [corresponding to the C(3)H-C(14)H, C(3)H-C(15)H and C(3)H-C(20)H relationship, respectively, when the biogenetic numbering of indole alkaloids is used<sup>6</sup>] cis or trans at will.

Our method appeared to be ideally suited for a short synthesis of both (±)-corynantheidol (**2**) and (±)-3-epicorynantheidol (**3**) (biogenetic numbering<sup>6</sup>) of which the former is the racemic form of the known indole alkaloid (-)-corynantheidol found in *Mitragyna parvifolia* (Roxb.) Korth. (Rubiaceae).<sup>7</sup> In the present paper we describe the results obtained.



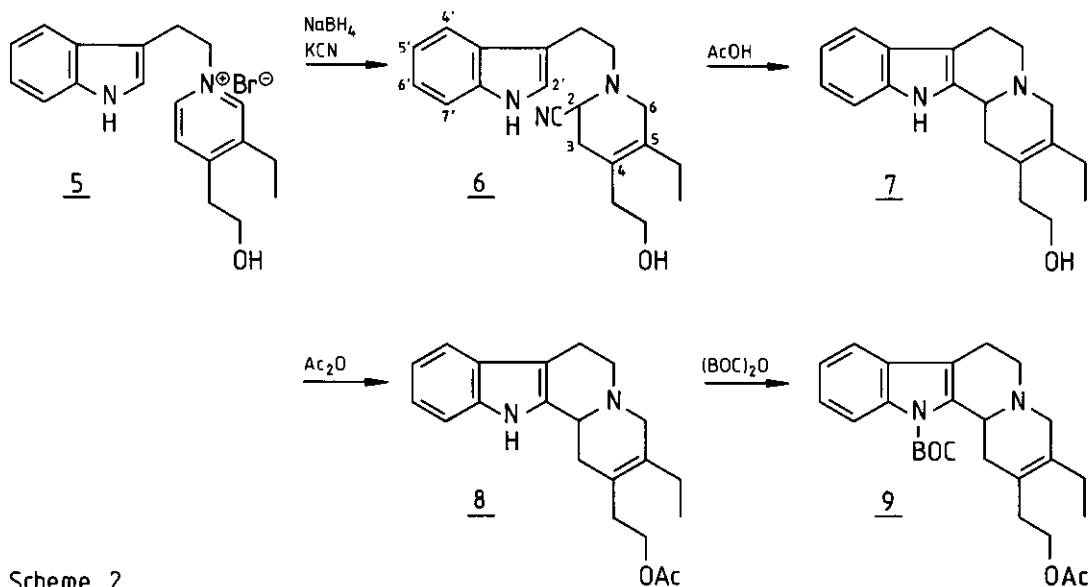
RESULTS AND DISCUSSION

Alkylation of 3-ethyl-4-(2'-hydroxyethyl)pyridine (**4a**) [prepared together with compound (**4b**) from 3-ethyl-4-methylpyridine<sup>8</sup> and formaldehyde; Scheme 1] with tryptophyl bromide<sup>9</sup> yielded the pyridinium salt (**5**).



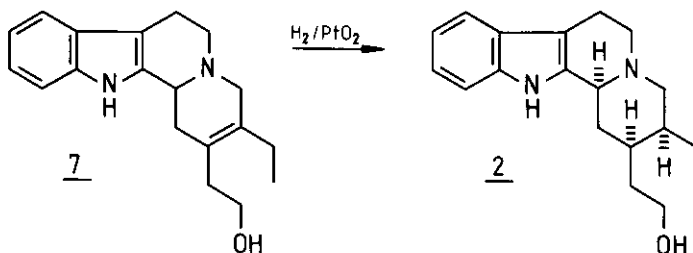
Scheme 1

The pyridinium salt (5) was transformed by  $\text{NaBH}_4$  reduction and cyanide trapping<sup>10-13</sup> to  $\alpha$ -aminonitrile (6), which by  $\text{AcOH}$  treatment<sup>14-16</sup> afforded compound (7). A part of compound (7) was acetylated to compound (8) which was then transformed with di-*t*-butyl dicarbonate [ $(\text{BOC})_2\text{O}$ ] to the corresponding BOC-protected compound (9) (Scheme 2).<sup>13,17,18</sup>



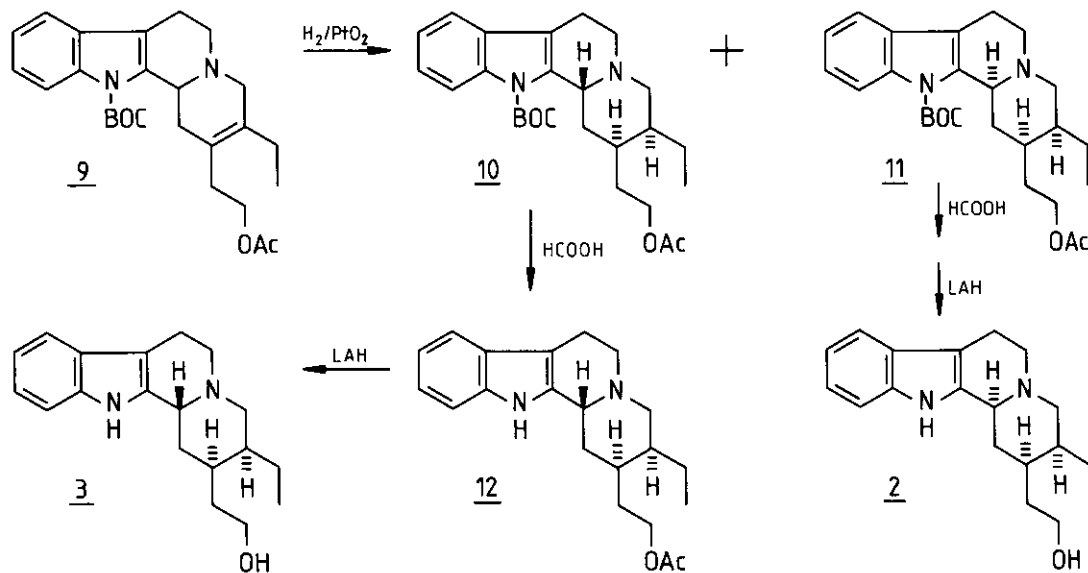
Scheme 2

Catalytic hydrogenation ( $\text{PtO}_2$ ) of compound (7) led directly to (+)-corynantheidol (2) [C(3)H-C(15)H *cis*; C(3)H-C(20)H *cis*]. Thus a very short stereoselective synthesis of (+)-corynantheidol (2) was in hand (Scheme 3).



Scheme 3

Catalytic hydrogenation ( $\text{PtO}_2$ ) of the BOC-protected compound (9) instead of compound (7) led to a 60/40 mixture of compound (10) [C(3)H-C(15)H trans; C(3)H-C(20)H trans] and compound (11) [C(3)H-C(15)H cis; C(3)H-C(20)H cis], which were separated by tlc. Acid-induced cleavage ( $\text{HCOOH}$ ) of compound (10) afforded compound (12), which by LAH treatment yielded ( $\pm$ )-3-epicorynantheidol (3). Compound (11) was transformed by consecutive  $\text{HCOOH}$  and LAH treatments to ( $\pm$ )-corynantheidol (2) without the isolation of the acetate intermediate [cf. compound (12)] (Scheme 4<sup>19</sup>).



Scheme 4

$^{13}\text{C}$  Nmr data of all the compounds formed are given in Figure 1. The proper shift assignment was confirmed by recording single frequency, off-resonance decoupled (sford) spectra.

Comparison of the chemical shifts found for compounds (2), (3), (7), (8), (9), (10), (11) and (12) with those given earlier,<sup>1,3,20</sup> taking into account the conformational considerations relevant for indolo[2,3-*a*]quinolizidines, provides clear evidence of the stereostructures depicted in the formulae.

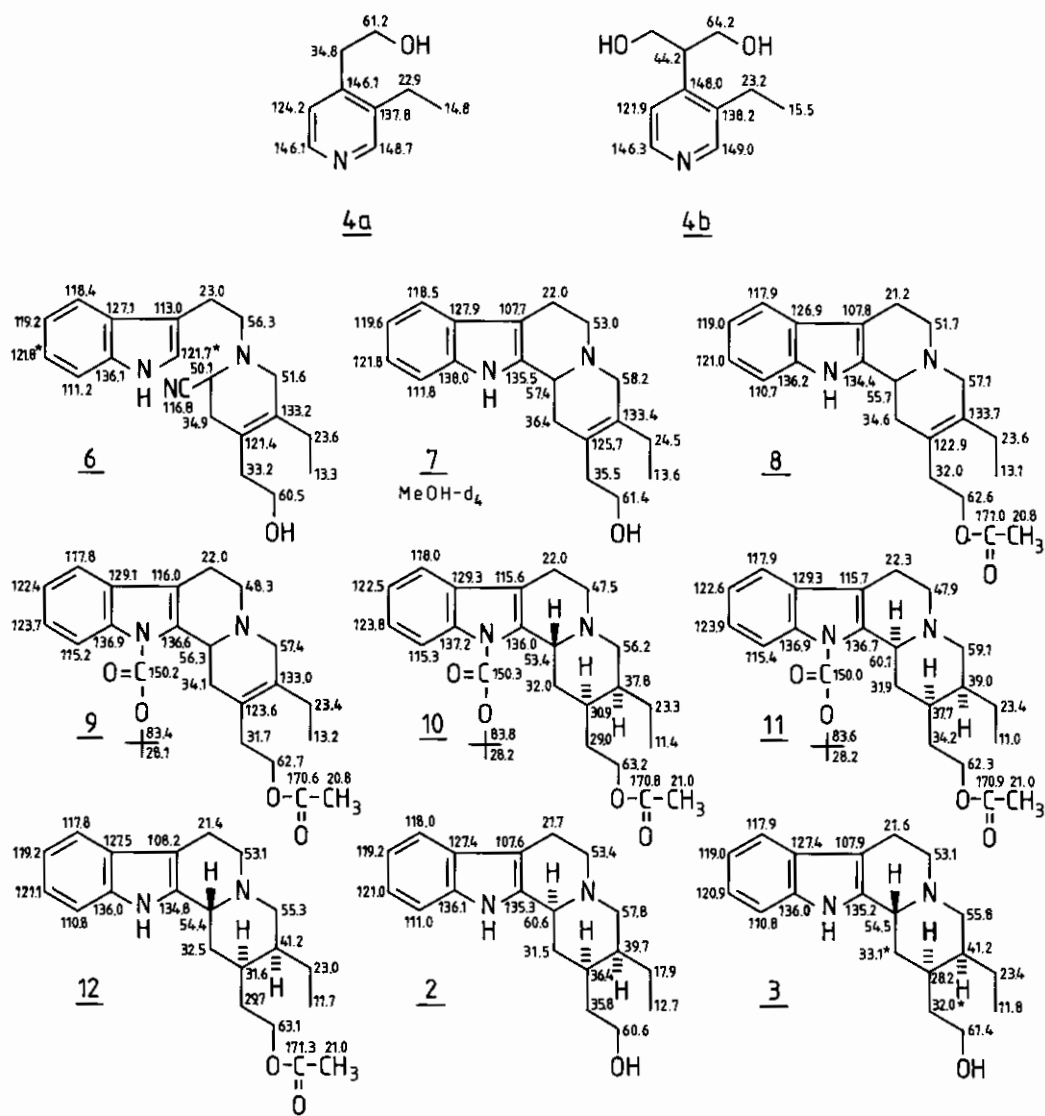


Figure 1

## CONCLUSIONS

The results clearly demonstrate that our recently developed method<sup>1-5</sup> can successfully be applied to a short synthesis of both (+)-corynantheidol (2) and (+)-3-epicorynantheidol (3). Compared with some earlier syntheses<sup>21-27</sup> our method affords an easier access to these compounds.

## EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 spectrophotometer. Absorption bands are expressed in reciprocal centimetres ( $\text{cm}^{-1}$ ) using polystyrene calibration.  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra were recorded in  $\text{CDCl}_3$  (if not otherwise stated) with a JEOL JNM-FX 60 spectrometer working at 59.80 MHz ( $^1\text{H}$  nmr) and 15.04 MHz ( $^{13}\text{C}$  nmr). Chemical shift data are given in ppm downfield from TMS. Abbreviations s, d, t, m and br are used to designate singlet, doublet, triplet, multiplet and broad, respectively. For  $^{13}\text{C}$  nmr data see Figure 1. Mass spectrometry was done on a JEOL DX 303/DA 5000 instrument.

Compounds (4a) and (4b)

Commercial 3-ethyl-4-methylpyridine<sup>8</sup> (10.00 g, 82.64 mmol) and formaldehyde (35%, 15 ml) were refluxed for 60 h (Ar-atm). The crude product was purified by column chromatography (alumina, first  $\text{CH}_2\text{Cl}_2$ , then increasing the polarity of the eluent with gradual MeOH addition). Three compounds were isolated: unreacted starting compound, monoalcohol (4a) and dialcohol (4b).

Compound (4a). Yield: 2.50 g (20%). Oil. Ir 3300 (OH), pmr 1.20 (3H, t,  $J=7.0$  Hz,  $-\text{CH}_3$ ), 2.67 (2H, q,  $J=7.0$  Hz,  $-\text{CH}_2-\text{CH}_3$ ), 2.89 (2H, t,  $J=7.0$  Hz,  $-\text{CH}_2-\text{CH}_2\text{OH}$ ), 3.87 (2H, t,  $J=7.0$  Hz,  $-\text{CH}_2\text{OH}$ ), 4.83 (1H, s, -OH), 7.14 (1H, d,  $J=6.0$  Hz, H-5), 8.20 (1H, d,  $J=6.0$  Hz, H-6), 8.23 (1H, s, H-2),  $m/z$  151 ( $\text{M}^+$ ), 132, 120, 118 (100%), 106; exact mass: 151.1010 (calcd for  $\text{C}_9\text{H}_{13}\text{NO}$ : 151.0997).

Compound (4b). Yield: 3.74 g (25%). mp 102-103°C (MeOH). Ir 3200 (OH), pmr 1.18 (3H, t,  $J=7.0$  Hz,  $-\text{CH}_3$ ), 2.67 (2H, q,  $J=7.0$  Hz,  $-\text{CH}_2-\text{CH}_3$ ), 3.88 (4H, 2xd,  $J=6.0$  Hz,  $-\text{CH}_2\text{OH}$ ), 4.71 (1H, s, -OH), 7.12 (1H, d,  $J=5.0$  Hz, H-5), 8.12 (1H, d,  $J=5.0$  Hz, H-6), 8.17 (1H, s, H-2),  $m/z$  182 ( $\text{M} + 1$  peak<sup>28</sup>), 181 ( $\text{M}^+$ ), 145, 133, 118 (100%), 106; exact mass: 181.1110 (calcd for  $\text{C}_{10}\text{H}_{15}\text{NO}_2$ : 181.1103).

Compound (5)

Alkylation of compound (4a) (1.21 g, 8.01 mmol) with tryptophyl bromide (1.80 g, 8.04 mmol) afforded salt (5). Yield: 2.79 g (93%).

Compound (6)

Hydrochloric acid (6N, 4 ml) was added dropwise to a cooled (0°C) stirred solution of KCN (3.02 g, 46.46 mmol) in  $\text{H}_2\text{O}$  (4 ml) and layered with  $\text{Et}_2\text{O}$  (20 ml). MeOH (7 ml) and the salt (5) (2.79 g, 7.44 mmol) were added, after which  $\text{NaBH}_4$  (0.37 g, 9.78 mmol) was added during 0.5 h keeping the solution at 0°C. Stirring was continued for 4 h at room temperature. The ethereal layer was separated and the aqueous layer was extracted several times with ether. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and evaporated to yield nitrile (6), which was used without purification in the next step. Yield: 2.35 g (98%). Amorphous material. Ir 3420 (NH), 3300 (OH), 2280 (CN), pmr 0.99 (3H, t,  $J=7.5$  Hz,  $-\text{CH}_3$ ), 6.94 (1H, d,  $J=2.4$  Hz, H-2'), 7.19-7.66 (4H, m, H-4', 5', 6', 7'), 8.26 (1H, br s, NH),  $m/z$  323 ( $\text{M}^+$ ), 308, 296, 168, 144 (100%), 130; exact mass: 323.1984 (calcd for  $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}$ : 323.1998).

#### Compound (7)

Compound (6) (2.17 g, 6.72 mmol) in 50% AcOH (200 ml) was stirred (at room temperature) for 68 h. After evaporation and neutralization (2N Na<sub>2</sub>CO<sub>3</sub>) the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The product was purified by column chromatography (alumina, first CH<sub>2</sub>Cl<sub>2</sub>, then increasing the polarity of the eluent with gradual MeOH addition) to yield compound (7). Yield: 1.18 g (59%). mp 223-224°C (MeOH). Ir 3410 (NH), 3210 (OH), pmr 0.97 (3H, t, J=7.5 Hz, -CH<sub>3</sub>), 7.04-7.53 (4H, m, H-9, 10, 11, 12), 8.64 (1H, m, NH), m/z 296 (M<sup>+</sup>), 295, 170 (100%), 169; exact mass: 296.1906 (calcd for C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O: 296.1889).

#### (±)-Corynantheidol (2)

Catalytic hydrogenation (PtO<sub>2</sub>, 24 h) of compound (7) (180 mg, 0.61 mmol) in MeOH afforded crude compound (2), which was purified by tlc (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH; 95:5). Yield: 100 mg (55%) (after recycling the unreacted starting material). mp 163-165°C (CH<sub>2</sub>Cl<sub>2</sub>) (lit. 158-162°C;<sup>21</sup> 158-160°C;<sup>22</sup> 157-159°C;<sup>23</sup> 160-161°C;<sup>25</sup> 162-164°C<sup>26</sup>). Ir 3430 (NH), 3280 (OH), 2830 and 2780 (Bohlmann bands), pmr 0.88 (3H, t, J=7.0 Hz, -CH<sub>3</sub>), 6.96-7.56 (4H, m, H-9, 10, 11, 12), 8.54 (1H, br s, NH), m/z 298 (M<sup>+</sup>), 297 (100%), 170, 169; exact mass: 298.2061 (calcd for C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>O: 298.2041).

#### Compound (8)

Compound (7) (0.60 g, 2.03 mmol), Ac<sub>2</sub>O (6.2 ml) and two drops of pyridine were stirred (room temperature, Ar-atm) for 20 h. The solution was poured into ice water, neutralized with aq. NH<sub>4</sub>OH and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> to afford pure compound (8). Yield: 0.64 g (93%). Amorphous material. Ir 3400 (NH), 1740 (C=O), pmr 1.00 (3H, t, J=7.0 Hz, -CH<sub>3</sub>), 2.00 (3H, s, AcO-), 7.02-7.55 (4H, m, H-9, 10, 11, 12), 8.40 (1H, br s, NH), m/z 338 (M<sup>+</sup>), 170 (100%), 169; exact mass: 338.1981 (calcd for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>: 338.1990).

#### Compound (9)

To compound (8) (310 mg, 0.92 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (2 ml) were added 4-dimethylaminopyridine (DMAP) (12 mg, 0.1 equiv.) and di-*t*-butyl dicarbonate [(BOC)<sub>2</sub>O] (242 mg, 1.2 equiv.) with stirring (room temperature, Ar-atm). After 2 h the mixture was evaporated and purified by column chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH/Et<sub>3</sub>N; 99:0.75:0.25) to afford pure compound (9). Yield: 361 mg (90%). Viscous oil. Ir 1740 (2 x C=O), pmr 1.03 (3H, t, J=7.0 Hz, -CH<sub>3</sub>), 1.66 (9H, s, -C(CH<sub>3</sub>)<sub>3</sub>), 2.02 (3H, s, AcO-), 4.10 (1H, t, J=6.0 Hz, H-3), 7.14-7.42 (3H, m, H-9, 10, 11), 8.06 (1H, m, H-12), m/z 438 (M<sup>+</sup>), 383, 382, 214 (100%), 170, 169; exact mass: 438.2516 (calcd for C<sub>26</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>: 438.2519).

#### Compounds (10) and (11)

Catalytic hydrogenation (PtO<sub>2</sub>, 20 h) of compound (9) (344 mg, 0.79 mmol) in MeOH afforded a mixture of compounds [(10) and (11) (60:40)] and unreacted compound (9), which was recycled. Compounds (10) and (11) were separated by tlc (silica gel,

CH<sub>2</sub>Cl<sub>2</sub>/MeOH; 95:5).

Compound (10). Yield: 198 mg (57%). Amorphous material. Ir 1730 (2 x C=O), pmr 0.93 (3H, t, J=6.0 Hz, -CH<sub>3</sub>), 1.68 (9H, s, -C(CH<sub>3</sub>)<sub>3</sub>), 2.05 (3H, s, AcO-), 4.35 (1H, m, H-3), 7.14-7.50 (3H, m, H-9, 10, 11), 7.98 (1H, m, H-12), m/z 440 (M<sup>+</sup>), 384, 383 (100%), 339; exact mass: 440.2663 (calcd for C<sub>26</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>: 440.2675).

Compound (11). Yield: 132 mg (38%). Amorphous material. Ir 1730 (2 x C=O), pmr 0.98 (3H, t, J=6.0 Hz, -CH<sub>3</sub>), 1.67 (9H, s, -C(CH<sub>3</sub>)<sub>3</sub>), 2.04 (3H, s, AcO-), 4.09 (1H, m, H-3), 7.14-7.43 (3H, m, H-9, 10, 11), 8.07 (1H, m, H-12), m/z 440 (M<sup>+</sup>), 384, 383 (100%), 339; exact mass: 440.2666 (calcd for C<sub>26</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>: 440.2675).

#### Compound (12)

Compound (10) (92 mg, 0.21 mmol) was stirred in HCOOH (2 ml) for 70 h (room temperature, Ar-atm). After evaporation and neutralization (10% Na<sub>2</sub>CO<sub>3</sub>) the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to yield compound (12). Yield: 57 mg (80%). Amorphous material. Ir 3400 (NH), 1730 (C=O), pmr 0.93 (3H, t, J=5.0 Hz, -CH<sub>3</sub>), 2.06 (3H, s, AcO-), 4.20 (1H, m, H-3), 7.05-7.53 (4H, m, H-9, 10, 11, 12), 8.28 (1H, m, NH), m/z 340 (M<sup>+</sup>, 100%), 339, 170, 169; exact mass: 340.2153 (calcd for C<sub>21</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>: 340.2151).

#### (±)-3-Epicorynantheidol (3)

LAH treatment of compound (12) (57 mg, 0.17 mmol) in dry THF for 2.5 h (room temperature, Ar-atm) afforded crude product (3), which was purified by tlc (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH; 90:10). Yield: 25 mg (50%). mp 189-191°C (CH<sub>2</sub>Cl<sub>2</sub>) (lit. 191-192°C;<sup>21,22</sup> 192-194°C<sup>23</sup>). Ir 3350-3200 (NH and OH), pmr 0.90 (3H, t, J=5.0 Hz, -CH<sub>3</sub>), 3.74 (1H, m, H-3), 7.01-7.42 (4H, m, H-9, 10, 11, 12), 8.49 (1H, m, NH), m/z 298 (M<sup>+</sup>), 297 (100%), 170, 169; exact mass: 298.2019 (calcd for C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>O: 298.2041).

#### (±)-Corynantheidol (2)

Consecutive HCOOH and LAH treatments (vide supra) of compound (11) (60 mg, 0.14 mmol) led to crude compound (2), which was purified by tlc (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH; 90:10). Yield: 18 mg (45%). mp 163-165°C (CH<sub>2</sub>Cl<sub>2</sub>) (lit. 158-162°C;<sup>21</sup> 158-160°C;<sup>22</sup> 157-159°C;<sup>23</sup> 160-161°C;<sup>25</sup> 162-164°C<sup>26</sup>).

Spectral data were identical with those described above.

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