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Ring D Modifications of Ellipticine. Part 1. New Ellipticine Derivatives from 1-Cyano-6-Methylellipticine.

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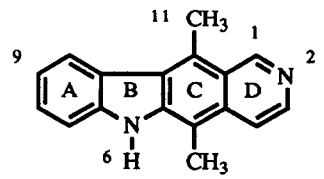
Abstract: *New ellipticine derivatives are synthesized by modification of the cyanogroup of 1-cyano-6-methyl-ellipticine. This resulted in the formation of 1-acetyl- and 1-acetamido-6-methylellipticine. Deprotonation of 1-cyano-6-methylellipticine under the influence of a Palladium catalyst leads to a new annelated ellipticine (9). From the derivatives obtained, 9 showed the highest cytostatic activity.*

INTRODUCTION

The alkaloid Ellipticine **1** (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) was first isolated in 1959 from the leaves of *Ochrosia elliptica Labill.* (family *Apocynaceae*).[1] Subsequently **1** was isolated from various other species of genera *Aspidosperma*, *Tabernaemontana* and *Strychnos*.[2-4] The structure of **1** was definitively established by Woodward et al. by the first total synthesis.[5] Major interest in the synthesis of ellipticine was aroused by the discovery of Dalton et al. of its antitumour properties.[6,7] This has led to numerous syntheses of the ellipticine skeleton which have been reviewed several times.[8-11] Substituents are introduced predominantly by total synthesis using appropriately substituted starting materials.[12-15] Direct substitution or functionalization is restricted to a few positions in **1**, i.e. C-1, N-2, N-6, C-9 and C-11 (Figure 1).[16-21]



1

Figure 1

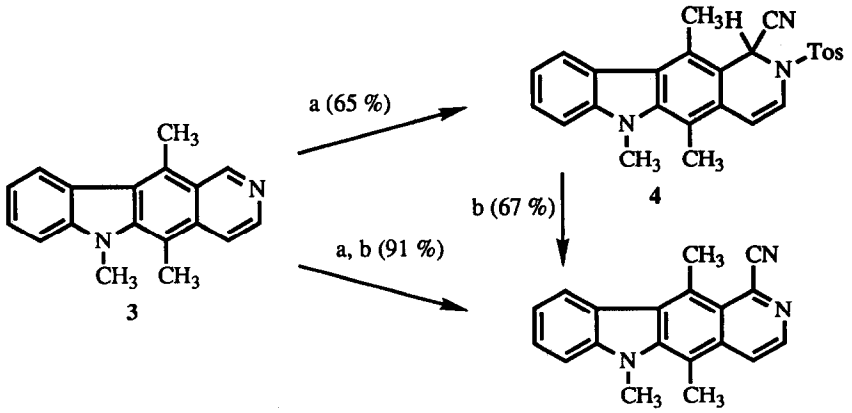
The cyanogroup is a powerful tool in organic chemistry. This group can be easily converted to other functional groups by the application of simple chemistry.[16,22-24] The cyanogroup can easily be introduced at C-1 of **1** using Reissert chemistry.[25-27] Subsequent modification of the cyanogroup has led to the syntheses of several new ellipticine derivatives.[28,29] Furthermore the strong electronegative character of the cyanogroup has been used for the introduction of alkylgroups at C-1.[28,29] Treatment of an ellipticine Reissert compound with NaH followed by the addition of an alkylhalide afforded the corresponding 1-alkylated ellipticines. Debenzoylation was accomplished by reaction with base.

In our group several methods have been developed which can be used to functionalize the 11-methylgroup.[19,21] Treatment of **1** with LDA and quenching with formaldehyde has resulted in the introduction of a hydroxymethylenegroup at C-11. The pyridine nitrogen is capable of stabilizing a negative charge developing at the 11-methylgroup. Substituents attached to the 5-methylgroup can only be introduced via total syntheses of the ellipticine from appropriately substituted or functionalized starting materials.[30-34] Due tot the strong electronegative nature of the cyanogroup, introduction of a cyanogroup at C-1 can possibly lead to direct functionalization of the 5-methylgroup by strong base. The negative charge at the 5-methylgroup can be conjugatively stabilized by the cyanogroup and therefore it is of interest which methylgroup of 1-cyano-6-methylellipticine (**2**) will be deprotonated with strong base.

In this paper we wish to report on the syntheses of new ellipticine derivatives using **2** as starting material.

RESULTS

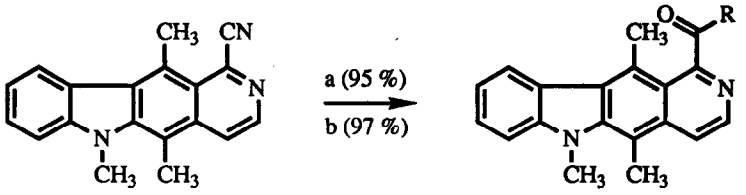
1-Cyano-6-methylellipticine (**2**) was synthesized from **1** by deprotonation with NaH followed by addition of CH_3I giving 6-methylellipticine (**3**) in good yield. The cyanogroup was introduced using TMSCN and p-TosCl followed by treatment with base.[16] It was possible to isolate the intermediate product **4** but this was always accompanied by **2** (Scheme 1).[16,28,35,36] Best results were obtained using a two-phase system with 50 % KOH and tetrabutylammonium hydrogensulfate ($TBAHSO_4$) as a phase-transfer catalyst.[37]



a)TMSCN, TosCl; b) KOH, 50 % w/v.

Scheme 1

The cyanogroup was converted to several other groups (Scheme 2). Reaction of **2** with CH_3MgI gave the corresponding 1-acetyl-6-methylellipticine (**5**) in good yield, reaction with ethanolic KOH gave 1-carboxamido-6-methylellipticine (**6**).[16,23] This substituent could not be introduced directly using a mixture of formamide, hydrogen peroxide and $Fe(II)SO_4$ under acidic conditions, a method which works well for isoquinolines.[38]



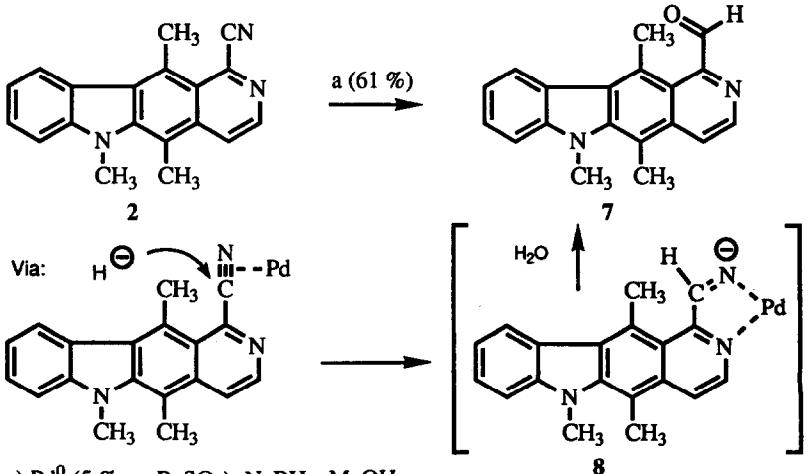
2 **5** R= CH_3, **6** R= NH_2

a) CH_3MgI, THF, -78 °C→ RT; b) KOH, EtOH, reflux.

Scheme 2

Reduction of **2** under a variety of reaction conditions proved to be very difficult. Reduction of the cyanogroup to the aminomethylenegroup could not be achieved. $LiAlH_4$ reduced **2** to 6-methylellipticine (**3**) in 30 % yield, completely removing the cyanogroup and reduction with DIBAH led to untractable mixtures. With other reducing reagents such as BH_3, $SnCl_2$/HCl in ether, Raney-Nickel or $NaBH_4$ no reduction was observed.

In order to increase the susceptibility towards nucleophilic hydrogendonors the cyanogroup can be activated by the use of appropriate Lewis acids.[39-41] A convenient method is reduction with $NaBH_4$ in the presence of Pd-salts which under the conditions used are reduced to their metals. Acidification liberates hydrogen and the cyanogroup is reduced.[42-44] Reduction of **2** with $NaBH_4$ in the presence of Pd^0 (Scheme 3) without acidification in the presence of the catalyst led to the formation of 1-formyl-6-methylellipticine (**7**). After complexation of the Pd-catalyst to the cyanogroup a hydride attacks the complex at the carbon atom.



2 **7** **8**

a) Pd^0 (5 % on $BaSO_4$), $NaBH_4$, MeOH.

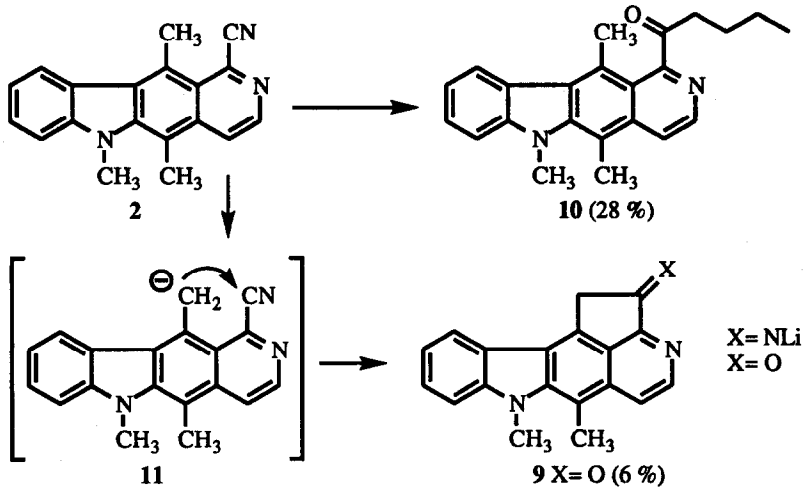
Scheme 3

Whether the catalyst is only bound to the formed imine or has formed a bidentate binding to both nitrogen atoms as represented by structure **8** remains unclear. The complex is resistant to further reduction due to its negative charge.[45] Finally after hydrolysis the aldehyde **7** is liberated.

The formation of **7** is of interest since 2-cyanopyridines or 2-cyanoisoquinolines are usually reduced to to the corresponding aminomethylene or carboxamide derivatives.[46,47] Therefore we examined the reduction of 2-cyanopyridine under the same conditions used for the reduction of **2**. Thus, 2-cyanopyridine was synthesized starting from pyridine-N-oxide, AgCN and TMSCl (74 %).[48] As expected reduction of 2-cyanopyridine with $NaBH_4$ in the presence of Pd^0 gave 2-pyridinecarboxaldehyde in 32 % yield as the only isolable product.

DEPROTONATION STUDIES OF 2.

Deprotonation of **2** with LDA followed by quenching with D_2O only led to deuterium incorporation at the 11-methylgroup. This result was supported by the isolation of a new ellipticine derivative (1,2-dihydro-6,7-dimethyl-7*H*-1-pyrindino[4,4a,5-*bc*]carbazole-2-one, **9**) albeit in low yield, which was isolated after treatment of **2** with excess BuLi. Nucleophilic attack of BuLi followed by hydrolysis leads to **10** (Scheme 4).



Scheme 4

The formation of **9** is the result of an intramolecular addition of the deprotonated 11-methylgroup to the cyanogroup. The possibility of an intermolecular addition leading to a dimer was excluded by I.R., the mass spectrum and exact mass of **9**.[49,50] In order to increase the yield of **9** attempts were made to stabilize the anion **11**. The profound effect of Pd^0 on the reduction of **2** formed a motive to use $Pd^0/BaSO_4$ and finely divided Pd^0 as well as $AlCl_3$ as complexing agents. Upon the addition of $AlCl_3$ or $Pd^0/BaSO_4$ the yield of **9** improved only slightly to 10 % and 18 % respectively, while considerable amounts of **2** were recovered. The use of Pd^0-powder increased the yield of **9** to 70 % supporting the idea of formation of a complex between Pd and the anion **11**.

ANTITUMOUR ACTIVITY

Of the ellipticine derivatives tested only **6**, **7** and **9** showed activity against *in vitro* cultures of L1210 cells (**6**: 662 ng/ml; **7**: 1266 ng/ml) and in vitro cultures of WiDR cells (**9**: 286 ng/ml). Other derivatives showed no activity. In view of the possible role of intercalation in the antitumour activity of ellipticines, the activity of **9** is of considerable interest.

ACKNOWLEDGMENT

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EXPERIMENTAL

General remarks and materials

Infrared spectra (IR) were recorded on a Perkin Elmer 1310 spectrophotometer and the absorptions are given in cm^{-1}. Proton nuclear resonance (^{1}H-N.M.R.) spectra were recorded on Brucker WM 250 and AC 200 instruments. Chemical shifts are given in ppm downfield of tetramethylsilane (TMS). Mass spectra were obtained with a Varian Matt-711 spectrometer and relative intensities are given in percentages. Flash chromatography was performed on silicagel 60 (230 - 390 mesh). Thin layer chromatography was carried out on silica coated plastic sheets (Merck silicagel 60 F_{254}). Melting points are uncorrected. Dry solvents were obtained by distillation from an appropriate drying agent. TMSCN[52], 6-methylellipticine[18] and the Pd-catalyst[53] were synthesized according tot standard procedures.

1-Cyano-2-p-tosyl-1,2-dihydro-5,6,11-trimethylellipticine (4)

To a solution of **3** (52 mg, 0.2 mmol) in CH_2Cl_2 (2 ml) under a dry nitrogen atmosphere was added TMSCN (550 µl, 4.1 mmol). Then a solution of p-TosCl (76 mg, 0.4 mmol) in CH_2Cl_2 (3 ml) was added over a period of 5 minutes and the resulting mixture was stirred for 48 h at R.T. Then $CHCl_3$ (30 ml) and water (20 ml) were added, the organic layer was separated, washed with water (50 ml), 5 % aqueous HCl-solution (50 ml), water (50 ml), 5 % aqueous NaOH solution (50 ml) and water (3 x 50 ml). Drying ($MgSO_4$), filtration, and evaporation of the solvent yielded a residue which was subjected to flash chromatography (silica, eluent: $CHCl_3$/EtOH; 100/0, 2/98, v/v) to give pure **4** (57 mg, 65 %), **2** (11 mg, 19 %) and recovered **3** (8 mg, 15 %). M.p. (EtOAc): 166-7 °C. White needles. I.R. ($CHCl_3$): 3030, 2000, 1620, 1590, 1460, 1360, 1330, 1165, 1090, 980 cm^{-1}. ^{1}H-N.M.R. (200 MHz, $CDCl_3$): 2.37 (s, 3H, pTos-CH_3), 2.75 (s, 3H, 5-CH_3), 2.86 (s, 3H, 11-CH_3), 4.06 (s, 3H, 6-CH_3), 6.56 (d, 1H, J= 1.1 Hz, H-1), 6.56 (d, 1H, J= 7.9 Hz, H-4), 6.80 (dd, 1H, J_1= 0.9 Hz, J_2= 7.9 Hz, H-3), 7.26 (t, 1H, J= 7.8 Hz, H-9), 7.30 (d, 2H, J= 8.3 Hz, p-Tos: H3' and H-5'), 7.39 (d, 1H, J= 7.9 Hz, H-7), 7.50 (t, 1H, J= 7.7 Hz, H-8), 7.80 (d, 2H, J= 8.3 Hz, p-Tos: H2' and H-6'), 8.18 (d, 1H, J= 7.9 Hz, H-10). For spectral data of **2** see below.

1-Cyano-5,6,11-trimethylellipticine (2) from 4

To a solution of **4** (33 mg, 75 μmol) in dry DMF under an atmosphere of dry nitrogen was added NaH (10 mg, 0.4 mmol, previously washed with Et_2O). The reaction mixture was stirred for 1.5 h before 5 ml dry Et_2O was added. Stirring was continued for 0.5 h, then the solution was poured onto ice/water (40 ml, w/v). The product was extracted with $CHCl_3$ (3 x 15 ml) and the combined organic fractions were washed with water (2 x 50 ml), brine (50 ml) and dried ($MgSO_4$). The residue obtained after filtration and evaporation of the solvent was subjected to flash chromatography (silica, eluent: $CHCl_3$/EtOH; 100/0, 98/2, v/v) to give **2** (14 mg, 67 %). For spectral data of **2** see below.

One pot synthesis of 2

To a solution of **3** (1042 mg, 4.0 mmol) in 20 ml dry CH_2Cl_2 under an atmosphere of dry nitrogen was added TMSCN (1.1 ml, 8.2 mmol). To this mixture a solution of p-TosCl (1.5 gr, 7.6 mmol) in dry CH_2Cl_2 (30 ml) was added over a period of 0.5 h. The reaction mixture was stirred for 20 h before TMSCN (0.25 ml, 2 mmol) was added. After 4 h the solution was concentrated to half its volume (25 ml). Then a solution of KOH (50 %, w/v) in water (50 ml) and $TBAHSO_4$ (20 mg, 59 μmol) were added and the mixture was stirred vigorously for an additional h. Extraction with $CHCl_3$ (4 x 50 ml), washing with saturated aqueous $NaHCO_3$ solution (2 x 100 ml) water (3 x 100 ml) and drying ($MgSO_4$) followed by flash chromatography (silica, eluent: $CHCl_3$/EtOH; 100/0, 98/2, v/v) produced **2** (1040 mg, 91 %). M.p. (EtOH): 226-8 °C, dec. Orange needles. I.R. ($CHCl_3$): 2920, 2850, 2220, 1575, 1470, 1370, 1280, 1110, 830 cm^{-1}. ^{1}H-N.M.R. (200 MHz, $CDCl_3$): 3.00 (s, 3H, 5-CH_3), 3.43 (s, 3H, 11-CH_3), 4.08 (s, 3H, 6-CH_3), 7.32 (dt, 1H, J_1= 1.0 Hz, J_2= 7.6 Hz, H-9), 7.39 (d, 1H, J= 8.2 Hz, H-7), 7.62 (dt, 1H, J_1= 1.0 Hz, J_2= 7.7 Hz, H-8), 8.04 (d, 1H, J= 6.0 Hz, H-4), 8.25 (d, 1H, J= 7.9 Hz, H-10), 8.50 (d, 1H, J= 6.0 Hz, H-3). NOE: irradiation at the signal of 5-CH_3 (s, 3.00 ppm) showed a nOe-effect on both 6-CH_3 (s, 4.08 ppm) and H-4 (d, 8.04 ppm): irradiation at the signal of 11-CH_3 (3.43 ppm) showed a nOe-effect on H-10 (d, 8.25 ppm): irradiation at the signal of 6-CH_3 (4.08 ppm) showed a nOe-effect on both 5-CH_3 (s, 3.00 ppm) and H-7 (d, 7.39 ppm). Mass (EI): 285 (100), 270 (38), 242 (8), 28 (40). Acc. mass: Calc. for $C_{19}H_{15}N_3$: 285.1266; Observed: 285.1298.

1-Acetyl-5,6,11-trimethylellipticine (5)

A solution of **2** (143 mg, 0.5 mmol) in dry THF (15 ml) under an atmosphere of dry nitrogen was cooled to -78 °C before a solution of CH_3MgBr in THF (3 ml, 3 M) was added. The resulting mixture was slowly warmed to R.T. during 20 h. The reaction was quenched by the addition of water (25 ml) followed by the extraction with $CHCl_3$ (3 x 10 ml). The combined organic fractions were washed with water (2 x 25 ml), brine (25 ml) and dried ($MgSO_4$). After filtration and evaporation of the solvent the residue was subjected to flash chromatography (silica, eluent: $CHCl_3$/MeOH; 100/0, 95/5, 90/10, 85/15, 80/20, v/v) to give **5** (114 mg, 95 %). M.p. (CH_2Cl_2): 179-83 °C, dec. Yellow needles. I.R. ($CHCl_3$): 2960, 2930, 2860, 1710, 1580, 1470, 1365, 1280, 1255, 1140, 1110, 1095, 895, 860, 825 cm^{-1}. ^{1}H-N.M.R. (200 MHz, $CDCl_3$): 2.79 (s, 3H, 5-CH_3), 3.05 (s, 6H, 11-CH_3 and 1-$COCH_3$), 4.11 (s, 3H, 6-CH_3), 7.30 (t, 1H, J= 7.6 Hz, H-9), 7.39 (d, 1H, J= 8.1 Hz, H-7), 7.57 (t, 1H, J= 7.7 Hz, H-8), 7.90 (d, 1H, J= 6.1 Hz, H-4), 8.26 (d, 1H, J= 7.9 Hz, H-10), 8.41 (d, 1H, J= 6.1 Hz, H-3).

1-Carbamoyl-5,6,11-trimethylellipticine (6)

To a solution of KOH (0.5 gr, 8.9 mmol) in a mixture of water (0.25 ml) and EtOH (2 ml) was added under vigorous stirring **2** (57 mg, 0.2 mmol). The resulting suspension was heated to reflux during 1.5 h then cooled to R.T. before the addition of water (5 ml). The resulting precipitate was filtered off, washed with water (3 x 5 ml) and dried to give **6** (59 mg, 97 %). M.p. ($CHCl_3$/MeOH): 267-75 °C, dec. Yellow needles. I.R. (KBr): 3410, 3330, 3280, 3170, 2920, 2850, 1670, 1600, 1575, 1470, 1445, 1365, 1285, 1250, 1175, 1095, 1045, 1000, 835, 820, 745 cm^{-1}. ^{1}H-N.M.R. (250 MHz, DMSO-D_6): 3.09 (s, 3H, 5-CH_3), 3.20 (s, 3H, 11-CH_3), 4.17 (s, 3H, 6-CH_3), 7.32 (t, 1H, J= 6.8 Hz, H-9), 7.65 (m, 2H, H-7 and H-8), 7.77 (s, 1H, 1-$CONH_2$), 8.10 (d, 1H, J= 6.1 Hz, H-4), 8.19 (s, 1H, 1-$CONH_2$), 8.37 (d, 1H, J= 8.9 Hz, H-10), 8.38 (d, 1H, J= 5.7 Hz, H-3).

1-Formyl-5,6,11-trimethylellipticine (7)

To a suspension of $Pd^0/BaSO_4$ (2 gr, 5 %) in MeOH (10 ml) a small amount of $NaBH_4$ was added. After the evolution of hydrogen gas had ceased **2** (100 mg, 350 μmol) was added under vigorous stirring followed by $NaBH_4$ (100 mg, 2.6 mmol). $NaBH_4$ was added in portions of after the evolution of hydrogen had stopped. This was continued until TLC indicated the disappearance of **2**. The precipitate obtained after filtration over high flow was washed with MeOH (3 x 30 ml) and the filtrate carefully acidified with acetic acid (15 ml). After concentration to about 25 ml, water (100 ml) was added and the pH was raised to 9 with Na_2CO_3 and the solution was extracted with $CHCl_3$ (3 x 30 ml). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated. The residue thus obtained was subjected to flash chromatography (silica, eluent; $CHCl_3$/MeOH; 100/0, 97/3, 95/5, 90/10, 75/25, 50/50, v/v) to give pure **7** (61 mg, 61 %). M.p. (EtOAc): 176-81 °C. Yellow needles. I.R. ($CHCl_3$): 3050, 2940, 2850, 1720, 1585, 1465, 1430, 1380, 1345, 1310, 1290, 1270, 1230, 1160, 1140, 1090, 1020, 985 cm^{-1}. ^{1}H-N.M.R. ($CDCl_3$, 250 MHz): 2.79 (s, 3H, 5-CH_3), 2.93 (s, 3H, 11-CH_3), 3.85 (s, 3H, 6-CH_3), 7.29 (t, 1H, J= 7.9 Hz, H-9), 7.37 (d, 1H, J= 8.1 Hz, H-7), 7.51 (dt, 1H, J_1= 0.9 Hz, J_2= 7.7 Hz, H-8), 7.73 (d, 1H, J= 6.1 Hz, H-4), 8.14 (d, 1H, J= 7.7 Hz, H-10), 8.42 (bd, 1H, J= 5.5 Hz, H-3), 9.51 (bs, 1H, 1-C<u>H</u>O).

Deprotonation of 2 with LDA

A solution of **2** (28 mg, 0.1 mmol) in dry THF (25 ml) under an atmosphere of dry nitrogen was cooled to -78 °C before a freshly prepared solution of LDA in THF (1 ml, 0.1 M) was added. Immediately the solution turned dark red and was stirred for 1.5 h during which the colour of the solution turned dark green. The reaction was quenched with D_2O (250 μl, 0.14 mmol), then warmed to R.T. and poured into water (50 ml). After extraction with $CHCl_3$ (3 x 50 ml), washing with water (100 ml) and drying ($MgSO_4$), the residue obtained was subjected to flash chromatography (silica, eluent: $CHCl_3$/EtOH 100/0, 99/1, 98/2, 96/4, v/v). This gave partially deuterated **2**. ^{1}H-N.M.R. (250 MHz, $CDCl_3$): 3.00 (s, 3H, 5-CH_3), 3.46 (2.7 H, 11-CH_3), 4.08 (s, 3H, 6-CH_3), 7.31 (t, 1H, J= 7.9 Hz, H-9), 7.39 (d, 1H, J= 7.8 Hz, H-7), 7.60 (t, 1H, J= 7.7 Hz, H-8), 8.04 (d, 1H, J= 6.0 Hz, H-4), 8.27 (d, 1H, J= 7.9 Hz, H-10), 8.50 (d, 1H, J= 5.9 Hz, H-3).

Reaction of **2** *with excess BuLi*

To a solution of LDA in dry THF (4 ml), freshly prepared from DiPA (85 µl) and BuLi solution (320 µl, 1.6 M) at -78 °C, was added under an atmosphere of dry nitrogen a solution of **2** (129 mg, 0.45 mmol) in dry THF (7 ml). No change in colour was observed indicating that no deprotonation had occurred. Thus extra BuLi solution was added until a slight colouring could be observed. Then BuLi solution (300 µl, 1.6 M) was added and the reaction mixture was stirred for an additional 15 minutes. The reaction was quenched with benzaldehyde (1 ml) and water (50 ml) and warmed to R.T. After extraction with $CHCl_3$ (5 x 30 ml) the combined organic fractions were washed successively with water (5 x 30 ml), brine (2 x 50 ml) and dried ($MgSO_4$). The residue obtained after filtration and evaporation of the solvent was subjected to flash chromatography (silica, eluent: $CHCl_3$/EtOH; 100/0, 99/1, 98/2, 97/3, 96/4, 95/5, 90/10, v/v). This gave 1,2-dihydro-6,7-dimethyl-7*H*-1-pyrindino[4,4a,5-*bc*]carbazole-2-one (**9**, 7 mg, 6 %), 1-(1-oxopentyl)-5,6,11-trimethylellipticine (**10**, 44 mg, 28 %) as an oil and unreacted **2** (52 mg, 40 %). **10**: I.R. ($CHCl_3$): 3050, 2950, 2860, 1700, 1580, 1470, 1385, 1255, 1095, 830 cm^{-1}. ^{1}H-N.M.R. (250 MHz, $CDCl_3$): 0.96 (t, 3H, J= 7.3 Hz, 1-$COCH_2CH_2CH_2\underline{CH_3}$), 1.45 (q, 2H, J= 7.4 Hz, 1-$COCH_2CH_2\underline{CH_2}CH_3$), 1.88 (m, 2H, 1-$COCH_2\underline{CH_2}CH_2CH_3$), 3.00 (s, 3H, 5-$CH_3$), 3.31 (s, 3H, 11-$CH_3$), 3.48 (t, 2H, J= 8.0 Hz, 1-$COCH_2CH_2CH_2CH_3$), 4.07 (s, 3H, 6-CH_3), 7.30 (t, 1H, J= 7.5 Hz, H-9), 7.38 (d, 1H, J= 8.1 Hz, H-7), 7.56 (t, 1H, J= 7.3 Hz, H-8), 7.75 (d, 1H, J= 6.2 Hz, H-4), 8.30 (d, 1H, J= 7.9 Hz, H-10), 8.36 (d, 1H, J= 6.2 Hz, H-3). For spectral data of **9** see below.

Synthesis of **9**

A solution of **2** (57 mg, 0.2 mmol) in dry THF (50 ml) under an atmosphere of dry nitrogen was cooled to -78 °C. A freshly prepared solution of LDA in THF (400 µl, 0.4 M) was added and the solution was stirred 0.5 h at -78 °C. Pd-powder (61 mg, 0.6 mmol) was added and the resulting suspension was stirred for an additional 2 h at -78 °C. During this time the colour of the solution changed from yellow to dark green. Finally LDA solution (2 ml, 0.4 M) was added upon which the colour immediately changed to dark purple. After 0.5 h of stirring at -78 °C the reaction mixture was poured into 0.1 N HCl solution (100 ml). After 5 minutes the mixture was neutralized ($NaHCO_3$) and filtrated (high flow). To the filtrate was added CH_2Cl_2 (50 ml) and the organic layer separated. The water layer was extracted with CH_2Cl_2 (3 x 25 ml) and the organic fractions were washed with water (2 x 75 ml), brine (2 x 75 ml) and dried ($MgSO_4$). The residue obtained after filtration and evaporation of the solvent was subjected to flash chromatography (silica, eluent: CH_2Cl_2/MeOH; 100/0, 98/2, 95/5,v/v) giving pure **9** (40 mg, 70 %). M.p. ($CHCl_3$): 254-7 °C, dec. Orange needles. I.R. ($CHCl_3$): 3000, 1730, 1600, 1575, 1470, 1385, 1260, 1150, 1005 cm^{-1}. ^{1}H-N.M.R. (200 MHz, $CDCl_3$): 2.95 (s, 3H, 5-CH_3), 3.73 (s, 2H, 11-CH_2), 4.07 (s, 3H, 6-CH_3), 7.33 (t, 1H, J= 7.6 Hz, H-9), 7.39 (d, 1H, J= 7.2 Hz, H-7), 7.63 (t, 1H, J= 7.2 Hz, H-8), 7.82 (d, 1H, J= 6.0 Hz, H-4), 7.85 (d, 1H, J= 7.0 Hz, H-10), 8.78 (d, 1H, J= 6.0 Hz, H-3). Double resonance: upon irradiation at H-3 (8.78 ppm) the signal of H-4 (7.82 ppm) collapsed to a singlet. NOE: irradiation at the signal of 5-CH_3 (s, 2.95 ppm) showed a nOe-effect on both 6-CH_3 (s, 4.07 ppm) and H-4 (d, 7.82 ppm): irradiation at the signal of 11-CH_2 (s, 3.73 ppm) showed a nOe-effect on H-10 (d, 7.85 ppm): irradiation at the signal of 6-CH_3 (s, 4.07 ppm) showed a nOe-effect on both 5-CH_3 (s, 2.95 ppm) and H-7 (d, 7.39 ppm). Mass (EI): 286 (100), 258 (24). Acc. mass: Calc. for $C_{19}H_{14}N_2O$: 286.1106; Observed: 286.1111.

REFERENCES AND NOTES

1. Goodwin, S.; Smith, A.F.; Hornig, E.C. *J. Am. Chem. Soc.* **1959**, *81*, 1903.
2. Büchi, G.; Mayo, D.W.; Hochstein, F.A. *Tetrahedron* **1961**, *15*, 167.
3. Kilminster, K.N.; Sainsbury, M.; Webb, B. *Phytochemistry* **1972**, *11*, 389.
4. Michel, S.; Tillequin, F.; Koch, M.; Ake Assi, L. *J. Nat. Prod.* **1980**, *43*, 294.
5. Woodward, R.B.; Iacobucci, G.A.; Hochstein, F.A. *J. Am. Chem. Soc.* **1959**, *81*, 4434.
6. Dalton, L.K.; Demerac, S.; Elmes, B.C.; Loder, J.W.; Swan, J.M.; Teitei, T. *Aust. J. Chem.* **1967**, *20*, 2715.
7. Svoboda, G.H.; Poore, G.A.; Montfort, J. *J. Pharm. Sci.* **1968**, *57*, 1720.
8. Suffness, M.; Cordell, G.A.: Ellipticine. In: *The Alkaloids*, Brossi, A. ed.; Academic Press, New York **1985**, *25*, pp. 89-142 and 305-324.
9. Gribble, G.W. *Adv. Heterocycl. Nat. Prod. Synth.* **1990**, *1*, 43.
10. Gribble, G.W.: Synthesis and Antitumor Activity of Ellipticine Alkaloids and Related Compounds. In: *The Alkaloids*, Brossi, A. ed.; Academic Press, New York **1990**, *39*, 239.
11. Gribble, G.W. *Synlett.* **1991**, 289.
12. Dolman, D.; Sainsbury, M. *Tetrahedron Letters* **1981**, *22*, 2119.
13. Taylor, G. *J. Chem. Res. Synop.* **1981**, 332.
14. Sainsbury, M.; Weerasinghe, D.; Dolman, D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 587.
15. Gansser, C.; Migambanou, J.; Viel, C.; Mahuteau, J.; Mérienne, C. *Farmaco, Ed. Sci.* **1985**, *40*, 459.
16. Popp, F.D.; Veeraraghavan, S. *J. Heterocycl. Chem.* **1982**, *19*, 1275.
17. Werbel, L.M.; Angelo, M.; Fry, D.W.; Worth, D.F. *J. Med. Chem.* **1986**, *29*, 1321.
18. Langendoen, A.L.; Koomen, G.-J.; Pandit, U.K. *Heterocycles* **1987**, *26*, 69.
19. Langendoen, A.L.; Koomen, G.-J.; Pandit, U.K. *Heterocycles* **1987**, *26*, 91.
20. Honda, T.; Inoue, M.; Kato, M.; Shima, K.; Shimamoto, T. *Chem. Pharm. Bull.* **1987**, *35*, 3975.
21. Langendoen, A.L.; Plug, J.P.M.; Koomen, G.-J.; Pandit, U.K. *Tetrahedron* **1989**, *45*, 1759.
22. Stevens, R.V.; Lai, J.T. *J. Org. Chem.* **1972**, *37*, 2138.
23. Kharash, M.S.; Reinmuth, O. in: *Grignard Reactions of Non-Metallic Substances*, Prentice-Hall, New York, **1954**, Chapter 10.
24. Rappoport, Z. *The Chemistry of the cyanogroup*, **1970**, Interscience, London.
25. Popp, F.D. *Adv. Heterocycl. Chem.* **1968**, *9*, 1.
26. Popp, F.D. *Adv. Heterocycl. Chem.* **1979**, *24*, 187.
27. Popp, F.D. *Heterocycles* **1973**, *1*, 165 and references cited theirin.
28. Veeraraghavan, S.; Popp, F.D. *Synthesis, Commun.* **1985**, 384.
29. Brown, H.C.; Garg, C.P. *J. Am. Chem. Soc.* **1964**, *86*, 1085.
30. Oikawa, Y.; Tanaka, M.; Hirasawa, H.; Yonemitsu, O. *Chem. Pharm. Bull.* **1981**, *29*, 1606.
31. Ross, B.S.; Archer, S. *Tetrahedron Letters* **1986**, *27*, 5343.
32. Archer, S.; Ross, B.S.; Pica-Mattoccia, L.; Cioli, D. *J. Med. Chem.* **1987**, *30*, 1204.
33. Obaza-Nutaitis, J.A.M.; Gribble, G.W. *J. Nat. Prod.* **1986**, *49*, 449.
34. Modi, S.P.; McComb, T.; Zayed, A.H.; Oglesby, R.C.; Archer, S. *Tetrahedron* **1990**, *46*, 5555.
35. Rozwadowska, M.D.; Brózda, D. *Tetrahedron Letters* **1978**, *19*, 589.

36. Rozwadowska, M.D.; Brózda, D. *Can. J. Chem.* **1980**, *58*, 1239.
37. Boger, D.L.; Brotherton, C.E.; Panek, J.S.; Yohannes, D. *J. Org. Chem.* **1984**, *49*, 4056.
38. Joule, J.A.; Smith, G.A. *Heterocyclic Chemistry*, 2nd ed, Van Nostrand Reinhold, Cambridge, **1978**, p. 112.
39. Ho, T.L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, New York, **1977**.
40. Pearson, R.G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827.
41. Pearson, R.G. *J. Chem. Educ.* **1968**, *45*, 581.
42. Brown, H.C.; Brown, C.A. *J. Am. Chem. Soc.* **1962**, *84*, 1495.
43. Brown, H.C.; Brown, C.A. *J. Am. Chem. Soc.* **1963**, *85*, 1003.
44. Pesez, M.; Burtin, J.-F. *Bull. Soc. Chim. France* **1959**, 1996.
45. Card, R.J.; Neckers, D.C. *Inorg. Chem.* **1978**, *17*, 2345.
46. Yasuo, K.; Masashi, K.; Isao, S.; Shunichi, Y. *Chem. Pharm. Bull.* **1973**, *21*, 1927.
47. Kagarlitskaya, N.V.; Volkova, L.D.; Zakumbaeva, G.D., *Izv. Akad. Nak Kaz. SSR, Ser. Khim.*, **1975**, *25*, 19.(Chem. Abstr. **1973**, *83*, 28,065 n)
48. Vorbrüggen, H.; Krolikiewicz, K. *Synthesis* **1983**, 316.
49. Michel, S.; Tillequin, F.; Koch, M. *J. Chem. Soc., Chem. Commun.* **1987**, 229.
50. Delbarre, A.; Roques, B.P.; Le Pecq, J.-B. *C. R. Hebd. Seances Acad. Sci., Ser. D* **1977**, *284*, 81.
51. The antitumour activity was determined at the following laboratories:
TNO, Rijswijk, The Netherlands (P. Lelieveld)
VU Academic Hospital, Amsterdam, The Netherlands (G.J. Peters).
52. Evans, D.A.; Carroll, G.L.; Truesdale, L.K. *J. Org. Chem.* **1974**, *39*, 914.
53. Vogel, Organic Chemistry, 4th ed., 305.

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