SYNTHESIS OF *ASPIDOSPERMA* ALKALOIDS : EIGHT-MEMBERED *vs.* SIX-MEMBERED RING D FORMATION

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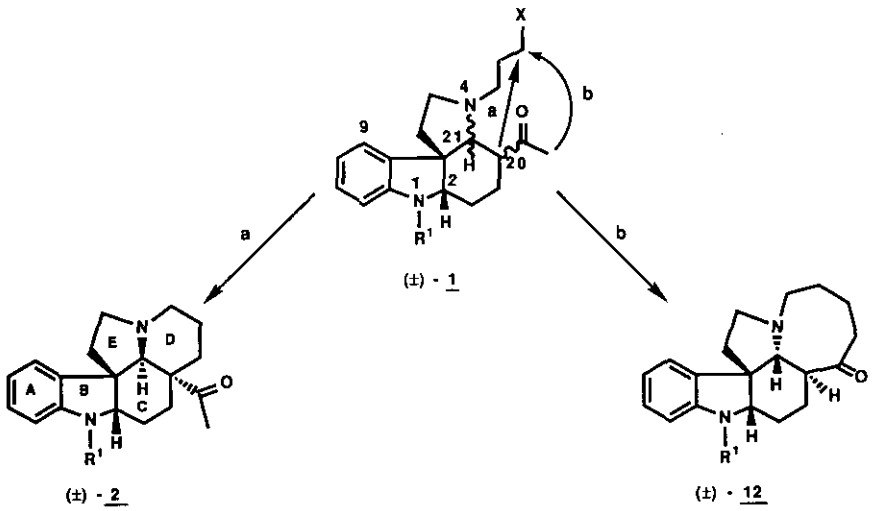
Abstract - Unusual cyclization of the acetyl chain borne at C-20 of a tetracyclic intermediate (**11a**) or (**11b**) led to the formation of a pentacyclic analog of *Aspidosperma* alkaloids with an eight-membered ring D.

In previous papers[1, 2] we have outlined a fundamentally new approach to *Aspidosperma* alkaloids such as **2** (Scheme 1). Our interest in this series led us to consider a general strategy towards its synthesis based on substitution reactions of the key enamine intermediate (**3**) (Scheme 2). Of particular importance was the selective protection of N-1 and N-4[3] atoms and the reduction of the intermediate enamine system. Thus far no selective protection of N-4 has been found. For N-1, an alkyl group is required for the photocyclization step. We thought that an N-4 allyl group might be of interest since it is cleaved in conditions in which a N-benzyl group at N-1 should survive *i.e.* isomerization to an enamine with a transition metal followed by hydrolysis.[4] Finally the resultant secondary amine would be a convenient intermediate for substitution with chains serving as precursors of different ring D found in natural products. According to our previous results, reduction of the enaminoketone double bond of **4** (Scheme 2) afforded the four possible stereomers (**1**) (Scheme 1).



Scheme 1

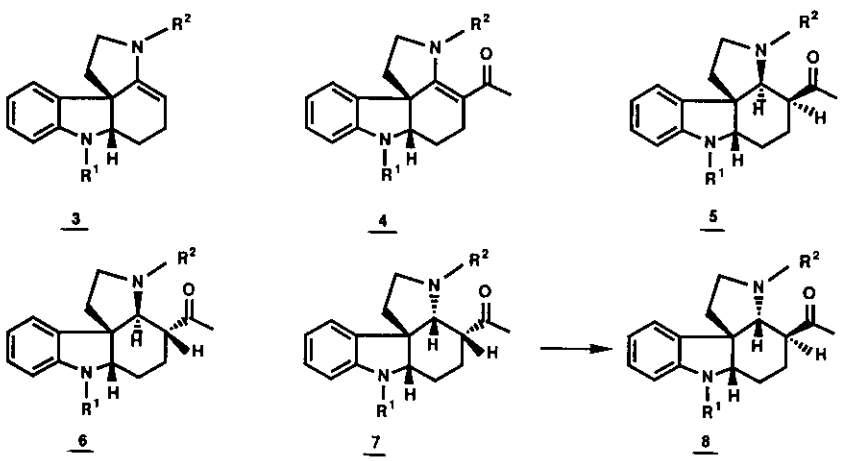
Cyclization of the thermodynamic enolate of 1 in the C-21 α series (natural) gave the *Aspidosperma* skeleton (pathway a, Scheme 1).[2]

In this paper we wish to report the annelation of the C-21 β-epi derivatives (unnatural configuration) leading to an unexpected eight-membered ring D (**12**) (pathway b, Scheme 1).

RESULTS AND DISCUSSION

On reaction of enamine (**3a**)[5] in anhydrous CH_2Cl_2 with acetyl chloride under argon , compound (**4a**) was isolated in 70 % yield (Scheme 2). The reduction of the double bond of the enaminone moiety of **4a** with $NaBH_3CN$[6] in CH_3OH in the presence of CF_3COOH gave a mixture of three of the four possible diastereoisomers **5a** (5 %) , **6a** (10%) , **7a** (35 %). Interestingly when the reduction was performed with $LiAlH_4$[7] in THF the overall yield was better (70%, instead of 50%) and the ratio was different (**5a** + **6a** : 55% ; **7a** 15%). Mechanistic arguments can account for the formation of these isomers. Under kinetic control, protonation at C-20 from the apparently less hindered β face would be more favorable leading to a predominantly α-axial acetyl chain (**6a** and **7a**) despite its strong interaction with the dihydroindole nucleus. Finally,several opposing factors control the reduction of the resultant iminium explaining the apparent lack of selectivity at C-21.

Good selectivity of reduction with $LiAlH_4$ is the result of an 1,4-addition from the α face. It is remarkable that **7a**, the sole product isolated in the unnatural C-21 epi-series, in both cases, is the kinetic one with an axial acetyl side chain. Epimerization of **7a** to the more stable isomer **8a** was possible only in drastic basic conditions (NaH, THF, Δ). On a qualitative basis it is difficult to judge accurately the importance of the various factors which stabilize one conformer relative to another. Indeed, ring C seems highly flexible as shown by examination of Dreiding models and suggested by the variation in coupling constants of H-2 and H-21 with their neighbors.The ^1H nmr spectra of **5a**, **6a**, **7a** and **8a** were highly resolved facilitating determination of their relative stereochemistry. The downfield position for H-9 resonance[1] in the C-21 epi-series (**7a**, **8a**) was characteristic for the C/E *trans* ring juncture due to the proximity of this proton and the nitrogen lone pair. The coupling constant between H-20 and H-21 is diagnostic for their arrangement ; in particular, a value of 8 Hz for **8a** confirmed a *trans* diaxial situation.



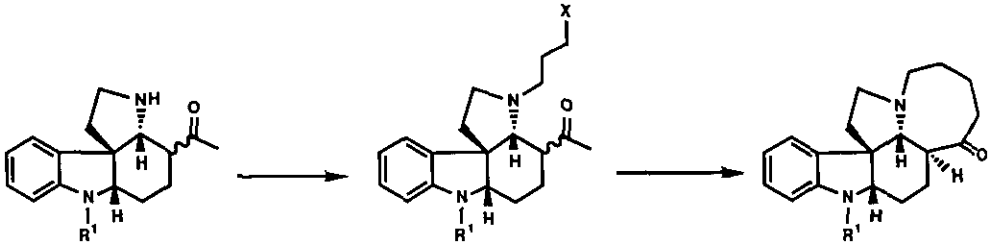
3 **4** **5** **6** **7** **8**

a R^1 = CH_2Ph , R^2 = allyl ; **b** R^1 = $COCH_3$, R^2 = CH_2Ph

Scheme 2

The presence of Bohlmann-Wenkert bands[8] in the ir spectrum of **7a** and **8a** indicated a *trans* relationship between H-21 and the lone pair of N-4. N -Deallylation[4c] of the mixture of **5a** and **6a** (natural C-21 stereochemistry and epimers at C-20) by use of standard methods (DABCO, EtOH/H_2O, Wilkinson's catalyst) gave an intractable mixture of polar compounds in which no desired aminoketone was detected. In contrast, the same reaction performed on the C-21 unnatural epimers (**7a + 8a**) led to the aminoketone (**9a**). From this result we felt that it would be interesting to prepare unnatural series of *Aspidosperma* alkaloids according to our previous experience[9] for the natural compounds.

N-Alkylation of **9a** with 1-chloro-3-iodopropane furnished the chloroketone (**10a**) (70 %) ; an exchange of chloride to iodide was realized with NaI in acetone to give **11a** possessing a better leaving group for the further reaction. Cyclization of intermediate (**11a**) was subsequently accomplished by reaction with NaH in the mixture C_6H_6 / THF (90 / 10) at reflux overnight. Compound (**12a**) was isolated as the sole product (79%) (Scheme 3) . For the determination of the structure of **12a** it was easy to distinguish between a six- and an eight-membered rings on the basis of the following spectral data. In the 300 MHz ^1H nmr spectrum the singlet corresponding to the acetyl methyl group had disappeared and the large coupling constant for H-21 (J = 10 Hz) indicated a *trans* relationship with H-20. The downfield position of the H-9 absorption at δ 7.85ppm was characteristic of the C-21 epi-series (see above). Results of ^1H-^1H and ^1H-^{13}C 2D Cosy experiments were consistent with the structure **12a**. In addition, the fragmentation observed in mass spectroscopy is in good agreement with the pentacyclic structure.[10] The formation of **12a** as a sole product could be explained by the steric hindrance in pentacyclic products : cyclization to a six-membered ring D in the C-21 epi-series would correspond to C/D and C/E *trans* junctions and to an axial acetyl chain experiencing a strong interaction with the dihydroindole nucleus. Calculation of the lower energy conformer (using Alchemy software[11]) for **12a** compared well with the nmr data.



a $R^1 = CH_2Ph$; b $R^1 = COCH_3$

Scheme 3

In order to see if this unusual cyclization reaction was general in this series, we repeated the whole reaction sequence with the C-21 epi-pair **7b + 8b**.[9] N-Debenzylation was performed in standard conditions[12] giving the secondary amine (**9b**) in quantitative yield. Alkylation of N-4 with 1-chloro-3-iodopropane was very sluggish ; compound (**10b**) was formed in poor yield (35%) as a mixture with **11b** due to partial halogen exchange (Cl ---> I) . Compound (**12b**) analog of **12a** was obtained in 75% yield.

In conclusion the development of our synthetic strategy for the total synthesis of the *Aspidosperma* skeleton has proved to be fruitful in the natural series ; however it is impossible to build the same pentacyclic system in the C-21 epi tetracyclic intermediates.

EXPERIMENTAL

Melting points were taken on a Reichert hot stage microscope and are uncorrected. Ir (ν cm^{-1}) spectra were obtained on a Perkin-Elmer 377 spectrophotometer. ^1H Nmr spectra were recorded in $CDCl_3$ on a Bruker MSL 300 or a Jeol C60 H spectrometer with tetramethylsilane as the internal reference; coupling constants , J , are given in Hertz ; s, d, t, and m indicate singlet, doublet, triplet and multiplet, respectively. ^{13}C Nmr spectra ($CDCl_3$, δ = 0 ppm, TMS) were recorded on a Jeol FX 60 or a Bruker MSL 300 spectrometer. Low resolution (70 ev) and high resolution mass spectrometry was performed on a Varian CH5 instrument. Flash chromatography was carried out as previously described[13] in the specified solvent system using silica gel Amicon (35-70 mesh).

Preparation of enamino ketone 4a

To a stirred solution of enamine (**3a**) (0.731 g , 2.1 mmol) and triethylamine (0.222 g , 2.2 mmol) in methylene chloride (50 ml) at 0°C was added, under N_2, a solution of acetyl chloride (0.172 g , 2.2 mmol) in methylene chloride (10 ml). After stirring for 30 min, the reaction mixture was poured into water (200 ml) and extracted three times with methylene chloride (3 x 10 ml). The combined organic layers were washed with water, dried over sodium sulfate and evaporated. The crude product was purified by flash chromatography (ethyl acetate-hexane, 1:1) to give **4a** (0.560 g , 70 %) ; mp 133-134°C (AcOEt) ; ir (CCl_4) : 1690. ^1H Nmr (300 MHz) : 1.69 (m, 4H), 2.05 (s, 3H, CH_3), 2.38 (m, 1H), 2.85 (m, 2H), 3.10 (m, 3H), 3.26 (m, 1H), 4.08 (AB system, J = 15, $\Delta\nu$ = 93 Hz, 2H, N-CH_2Ph), 4.87 (d, J = 10, 1H), 4.99 (d, J = 16.6, 1H), 5.63 (m, 1H), 6.25 (d, J = 7, 1H), 6.57 (t, J = 7, 1H), 6.87 (t, J = 7, 1H), 7.02 (d, J = 7, 1H), 7.21 (m, 5H) . ^{13}C Nmr : 23.1, 28.7, 28.9, 38.5, 48.7, 51.5, 54.5, 57.4, 69.1, 104.0, 105.1, 116.6, 117.7, 122.5, 127.0, 132.8, 133.6, 138.5, 150.6, 159.4, 193.4. Ms, m/z (relative intensity) : 384 (3), 366 (6), 342 (16), 293 (7), 275 (7), 234 (10), 161 (8), 144 (8), 91 (100), 73 (21), 65 (10), 43 (18) ; exact mass m/z 384.2196 (calculated for $C_{26}H_{28}N_2O$ m/z 384.2195). Anal. calcd for $C_{26}H_{28}N_2O$: C, 81.20 ; H, 7.34 ; N, 7.29. Found : C, 81.35 ; H, 7.39 ; N, 7.09.

Reduction of 4a : preparation of compounds 5a, 6a, 7a

A) With sodium cyanoborohydride

To a solution of sodium cyanoborohydride (0.147 g , 2.34 mmol) and trifluoroacetic acid (0.134 g, 1.18 mmol) in methanol (2 ml) at - 25°C, under N_2 , was added a solution of **4a** (0.300 g, 0.78 mmol) in methanol (5 ml). After stirring for 10 min the reaction was quenched with water, then neutralized with aqueous sodium bicarbonate solution. The reaction mixture was extracted with methylene chloride (3 x 20 ml). The organic layers were washed with water, dried over sodium sulfate and evaporated. The crude product was purified by flash chromatography (ethyl acetate-hexane, 1:1) to give :

5a (0.015 g , 5 %) ; mp 137-138°C (ether) ; ir (CCl_4) : 1710. ^1H Nmr (300 MHz) : 1.45 (m, 1H), 1.55 (m, 1H), 1.90 (m, 2H), 1.98 (m, 1H), 2.10 (s, 3H, CH_3), 2.20 (m, 1H), 2.48 (m, 2H), 2.70 (m, 1H), 3.05 (d, J = 7, 1H), 3.10 (m, 1H), 3.30 (m, 2H), 4.20 (AB system, J = 16 , $\Delta\nu$ = 65.7, 2H , N-CH_2Ph), 5.00 (d, J = 8, 1H), 5.10 (d, J = 17, 1H), 5.80 (m, 1H), 6.40 (d, J = 7.5, 1H), 6.70 (t, J = 7.5, 1H), 7.00 (t, J = 7, 1H), 7.10 (d, J = 7.5, 1H), 7.30 (m, 5H) . ^{13}C Nmr : 17.3, 22.8, 28.7, 37.6, 49.9, 50.2, 52.2, 55.1, 57.9, 68.2, 68.5, 107.6, 116.9, 118.3, 122.4, 127.3, 127.5, 128.5, 128.7, 133.4, 135.9, 138.9, 151.6, 211.8 . Ms, m/z (relative intensity) : 386 (8), 302 (16), 240 (23), 225 (37), 196 (49), 179 (49), 168 (46), 91 (100) ; exact mass m/z 386.2351 (calculated for $C_{26}H_{30}N_2O$ m/z 386.2346).

6a (0.031 g , 10 %), oil ; ir (CCl_4) : 1720. ^1H Nmr (300 MHz) : 1.60 (m, 3H), 1.85 (m, 1H), 2.00 (m, 2H), 2.15 (s, 3H, CH_3), 2.48 (m, 1H), 2.96 (m, 2H), 3.12 (m, 2H), 3.20 (m, 1H), 3.40 (m, 1H), 4.20 (AB system J = 17 , $\Delta\nu$ = 66.3 , 2H, N-CH_2Ph), 5.01 (dd, 1H, J = 8.5 and 2), 5.10 (dd, 1H, J = 17 and 2), 5.71 (m, 1H), 6.45 (d, J = 8.5, 1H), 6.70 (t, J = 8.5, 1H), 7.01 (t, J = 8.5, 1H), 7.10 (d, J = 8.5, 1H), 7.30 (m, 5H) . ^{13}C Nmr : 22.2, 23.1, 29.9, 35.5, 50.0, 51.5, 52.5, 57.7, 68.5, 68.8,

107.9, 115.8, 118.4, 123.3, 127.0, 127.3, 127.7, 128.6, 137.0, 138.0, 139.1, 151.4, 211.8 . Ms, m/z (relative intensity) : 386 (20), 371 (2), 345 (3), 301 (20), 247 (2), 234 (5), 220 (10), 183 (2), 169 (8), 156 (2), 148 (10), 140 (10), 130 (2), 96 (8), 91 (100) ; exact mass m/z 386.2362 (calculated for $C_{26}H_{30}N_2O$ m/z 386.2351).

7a (0.105g , 35 %) ; mp 107-108°C (ether) ; ir (CCl_4) : 1710, 2800, 2880, 2930. ^1H Nmr (250 MHz) : 1.06 (m, 1H), 1.55 (m, 2H), 1.71 (m, 2H), 2.05 (m, 1H), 2.22 (s, 3H, CH_3), 2.40 (m, 1H), 2.70 (m, 1H), 2.85 (m, 2H), 3.30 (m, 2H), 3.73 (m, 1H), 4.20 (AB system, J = 14 , Δν = 85, 2H , N-CH_2Ph), 5.10 (d, J = 10, 1H), 5.23 (d, J = 16.6, 1H), 5.90 (m, 1H), 6.20 (d, J = 7, 1H), 6.45 (t, J = 7, 1H), 6.90 (t, J = 7, 1H), 7.31 (m, 6H). ^{13}C Nmr : 22.9, 23.2, 31.6, 38.2, 45.8, 48.6, 50.2, 53.2, 57.5, 67.1, 68.5, 107.2, 116.2, 116.9, 124.9, 126.9, 133.0, 135.5, 138.8, 149.9, 208.2 . Ms, m/z (relative intensity) : 386 (9), 301 (4), 233 (11), 220 (11), 149 (23), 91 (100) ; exact mass m/z 386.2350 (calculated for $C_{26}H_{30}N_2O$ m/z 386.2351). Anal. Calcd for $C_{26}H_{30}N_2O$: C, 80.78 ; H, 7.83 ; N, 7.25. Found : C, 80.81 ; H, 7.80 ; N, 7.23.

B) With $LiAlH_4$

To a suspension of lithium aluminium hydride (1.9 hydride equivalents ; 5.24 ml of a 1M solution in THF) was added rapidly at -25°C, under argon, a solution of **3a** (4.00 g , 10.4 mmol) in 80 ml of THF. After 3 min, ethyl acetate (4 ml) and water (10.4 ml) were added sequentially. After stirring for 1 h at room temperature, the mixture was filtered, dried over sodium sulfate and evaporated. After purification by flash chromatography (ethyl acetate-hexane, 2:8) the following compounds were obtained : **5a + 6a** (2.100 g, 55 %) and **7a** (0.550g, 15 %).

Epimerization of 7a to 8a

To a suspension of NaH (60% in oil ; 0.0071 g ; 0.177 mmol) in THF (2ml) was added a solution of **7a** (0.310 g ; 0.08 mmol) in THF (1ml). The solution was stirred at reflux for 12 h under N_2. After cooling, the mixture was poured in H_2O and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate and evaporated to give **8a** (0.290 g ; 94%) after filtration on silica gel (ethyl acetate-hexane, 2:8).

8a (oil) ; ir (CCl_4) : 1710, 2800, 2860. ^1H Nmr (300 MHz) : 1.25 (m, 1H), 1.41 (m, 1H), 1.61 (m, 2H), 1.91 (m, 2H), 2.08 (s, 3H, CH_3), 2.45 (m, 1H), 2.66 (m, 1H), 2.76 (m, 1H), 3.10 (d, J = 8, 1H), 3.15 (m, 1H), , 3.26 (m, 1H), 3.60 (m, 1H), 4.30 (AB spectrum, J = 17 , Δν = 66 , 2H, N-CH_2Ph), 5.05 (d, J = 9, 1H), 5.20 (d, J = 17, 1H), 5.90 (m, 1H), 6.20 (d, J = 8.5, 1H), 6.60 (t, J = 8.5, 1H), 7.00 (t, J = 8.5, 1H), 7.25 (m, 5H), 7.60 (d, J = 8.5, 1H). ^{13}C Nmr : 22.8, 23.3, 30.4, 38.5, 48.7, 48.9, 50.4, 53.8, 57.9, 64.7, 67.4, 105.4, 116.4, 116.6, 125.8, 127.2, 127.3, 127.9, 128.7, 136.5, 138.8, 150.9, 211.4. Ms, m/z (relative intensity) : 386 (12), 371 (6), 295 (6), 234 (15), 220 (12), 138 (11), 91 (100) ; exact mass m/z 386.2355 (calculated for $C_{26}H_{30}N_2O$ m/z 386.2351).

Deallylation of compound 7a : preparation of 9a

A solution of **7a** (0.640 g , 1.60 mmol), DABCO (0.092 g , 0.82 mmol), and Wilkinson's catalyst (0.103 g , 0.11 mmol) in 10% aqueous ethanol (5 ml) was stirred at reflux for 1 h. After cooling, the mixture was poured in dilute HCl (pH = 2) and was extracted with ether. The organic layer was washed with water, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography (ethyl acetate-hexane, 1:1) to give **9 a** (0.56 g , 98 %) ; mp 98-99°C (AcOEt); ir (CCl_4) : 1720, 2780, 2820, 2880, 3370. ^1H Nmr (300 MHz) : 0.93 (m, 1H), 1.30 (m, 4H), 1.83 (m, 1H), 1.93 (m, 1H), 2.18 (s, 3H, CH_3), 2.63 (m, 1H), 3.08 (m, 1H), 3.25 (m, 1H), 3.35 (d, J = 11, 1H), 3.50 (t, J = 6, 1H), 4.30 (AB system, J = 15, Δν = 115, 2H, N-CH_2Ph), 6.40 (d, J = 7, 1H), 6.65 (t, J = 7, 1H), 7.10 (t, J = 7, 1H), 7.30 (m, 6H). ^{13}C Nmr : 24.6, 28.9, 38.1, 41.7, 48.6, 51.0, 53.0, 61.2, 66.6, 106.9, 117.2, 125.1, 126.7, 133.3, 138.2, 149.3, 211.4 . Ms, m/z (relative intensity) : 346 (20), 233 (16), 220 (60), 167 (17), 149 (56), 91 (100) ; exact mass m/z 346.2038 (calculated for $C_{23}H_{26}N_2O$, m/z 346.2039).

Preparation of amines 10a and 11a

A mixture of **9a** (0.270 g , 0.78 mmol), potassium carbonate (0.216 g, 1.50 mmol) and 1-chloro-3-iodopropane (0.100 g , 1.50 mmol) in DMF (2 ml) was stirred, under N_2, at room temperature for 36 h. Methylene chloride (20 ml) was added, then the mixture was filtered and evaporated. The residue was purified by flash chromatography (ethyl acetate-hexane, 2:8) to give **10a** (0.230 g , 70 %) ; mp 150-151°C (ether) ; ir ($CHCl_3$) : 1705. ^{1}H Nmr (60 MHz) : 1.10 (m, 7H), 2.15 (s, 3H, CH_3), 2.91 (m, 1H), 3.50 (m, 5H), 4.11 (m, 3H), 4.35 (AB system, J = 15 , $\Delta\nu$ = 14, 2H, N-CH_2Ph), 6.85 (m, 9H). ^{13}C Nmr : 21.2, 22.2, 28.7, 32.1, 37.3, 41.4, 44.9, 46.1, 48.2, 52.6, 57.6, 61.7, 66.1, 74.9, 105.3, 116.6, 123.4, 127.1, 128.6, 131.9, 138.4, 151.1, 208.7. Ms, m/z (relative intensity) : 422 (28), 387 (9), 359 (9), 345 (11), 302 (14), 233 (21), 220 (19), 91 (100).

A solution of **10a** (0.230 g, 0.50 mmol) in acetone (10 ml) was then added to a solution of sodium iodide (0.750 g, 5,00 mmol) in acetone (15 ml). The resulting mixture was stirred and heated at reflux for 2 days. After cooling, the majority of acetone was evaporated, water (20 ml) was added,and the aqueous phase was extracted with methylene chloride (3 x 20 ml). The combined organic layers were washed with a 5 % sodium thiosulfate solution dried over sodium sulfate and concentrated to give **11a** (0.270 g).

Cyclization of 11a

To a suspension of sodium hydride (55 % in oil, 0.050 g , 1.14 mmol) in benzene (5 ml), under argon, was added a solution of **11a** (0.37 0g , 0.76 mmol) in benzene (10 ml). The resulting mixture was stirred at reflux for 18 h. After cooling, water was added (10 ml) and the mixture was extracted with methylene chloride. The organic layer was then dried over sodium sulfate and the solvent was evaporated. The crude product was purified by flash chromatography (ethyl acetate-hexane, 1:1) to give **12a** : (0.230 g , 79 %) ; mp 160-161°C (ether) ; ir (CCl_4) : 1690. ^{1}H Nmr (300 MHz) : 1.25 (m, 1H, H-C-16), 1.45 (m, 2H, H-C-17, H-C-18), 1.55 (m, 1H, H-C-17), 1.78 (m, 1H, H-C-15), 1.95 (m, 4H, H-C-16, H-C-6, H-C-18), 2.30 (m, 1H, H-C-14), 2.46 (m, 2H, H-C-14, H-C-3), 2.63 (m, 3H, H-C-5, H-C-15, H-C-21), 2.83 (m, 1H, H-C-3), 3.03 (m, 1H, H-C-20), 3.48 (m, 2H, H-C-2, H-C-5), 4.30 (AB system, J = 15 , $\Delta\nu$ = 76 , 2H, N-CH_2Ph), 6.40 (d, J = 7 ,1H, H-C-12), 6.70 (t, J = 7 ,1H, H-C-10), 7.05 (t, J = 7 ,1H, H-C-11), 7.30 (m, 5H, aromatics), 7.85 (d, J = 7 ,1H, H-C-9) . ^{13} C Nmr : 20.7, (C-15), 24.2 (C-17), 24.3 (C-16), 30.7 (C-18), 37.6 (C-6), 45.1 (C-14), 47.2 (C-20), 49.1 (CH_2Ph), 52.3 (C-3), 53.8 (C-5), 56.1 (C-7), 68.0 (C-2), 73.7 (C-21), 107.6 (C-12), 117.6 (C-10), 125.8 (C-9), 127.1, 127.6, 127.7 (C-11), 128.6, 134.7 (C-ipso), 138.8 (C-8), 150.2 (C-13), 218.6 (C-19) . Ms, m/z (relative intensity) : 386 (50), 295 (7), 260 (12), 233 (20), 220 (65), 204 (2), 194 (2), 180 (2), 172 (5), 166 (50), 156 (2), 149 (10), 138 (15), 111 (15), 91 (100) ; exact mass m/z 386.2353 (calculated for $C_{26}H_{30}N_2O$ m/z 386.2351). Anal. Calcd for $C_{26}H_{30}N_2O$: C, 80.78 ; H, 7.83 ; N, 7.25. Found : C, 80.85 ; H, 7.75 ; N, 7.18.

Preparation of 9b

To a solution of amino ketones (**7b + 8b**) (0.960 g , 2.47 mmol) in $CHCl_3$ (20 ml) and EtOH (30 ml) was added concentrated HCl (2 ml) and catalytic amount of Pd/C (10%) (0.050 g). This mixture was hydrogenated for 8 h at 50 psi (Parr apparatus) and at room temperature. The reaction mixture was filtered through a Celite bed and neutralized with a 5% sodium carbonate solution . The aqueous phase was extracted with methylene chloride .The organic layer was washed with water , dried over sodium sulfate and concentrated to gave the nearly pure amine **9b** which was used directly in the next step ; ir (CCl_4) : 1655,1710, 3380.

Preparation of compounds 10b and 11b

A solution of **9b** (0.390 g , 1.31 mmol) and 1-chloro-3-iodopropane (0.170 ml , 1.60 mmol) in anhydrous DMF (5 ml) was stirred under argon at room temperature during 4 days. DMF was then evaporated under reduced pressure and the crude

product was purified by flash chromatography (ethyl acetate-hexane, 1:1) to give compounds (**10b**) (0.172 g, 35 %) and (**11b**) (in small quantities).

10b ; mp 135-137°C (ether) ; ir (CCl_4) : 2870, 2810, 1710, 1660. ^{1}H Nmr (300 MHz) : 1.20 (m, 1H), 1.50 (m, 1H), 2.25 (m, 15H), 3.25 (m, 1H), 3.35 (d, J = 8, 1H), 3.70 (m, 3H), 4.25 (d, J = 4.5, 1H), 7.00 (t, J = 7.5, 1H), 7.20 (t, J = 7.5, 1H), 7.60 (d, J = 7.5, 1H), 8.15 (d, J = 7.5, 1H) . ^{13}C Nmr : 5.6 , 21.3, 23.6, 26.8 , 30.0 , 31.0 ,38.3, 43.0, 46.9, 49.9, 50.7 , 52.3, 63.6, 65.7 , 116.9 , 124.0, 124.9 , 128.0, 137.0, 142.7, 169.1, 210.2 . Ms, m/z (relative intensity) : 466 (2), 376(4), 374 (12), 340 (17), 339 (73), 331 (18), 312 (20), 311 (92), 297 (100), 144 (36), 143 (33), 130 (45), 96 (26).

Treating **10b** with NaI in reflux ing acetone gives quantitatively the compound **11b**.

Cyclization of 11b

A solution of **11b** (0.020 g, 0.43 mmol) in anhydrous benzene (5 ml) was added under N_2 to a suspension of NaH (60 % in mineral oil, 0.002 g, 0.050 mmol) in benzene (1 ml). The reaction medium was stirred under reflux for 48 h . After cooling, the solvent was evaporated under *vacuum* . The crude product was dissolved in CH_2Cl_2. The organic layer was washed with a solution of NH_4Cl until pH = 8, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography (ethyl acetate-hexane, 1:1) to give **12b** .

12b (0.011 g , 75%) ; mp 151-153°C (ether) ; ir (CCl_4) : 1665, 1700. ^{1}H Nmr (300 MHz) : 1.40 (m, 2H, H-C-16, H-C-17), 1.75 (m, 3H, H-C-15, H-C-17, H-C-18), 1.95 (m, 2H, H-C-6), 2.10 (m, 1H, H-C-16), 2.15 (m, 1H, H-C-18), 2.30 (s, 3H, $NCOCH_3$), 2.40 (m, 3H, H-C-3, H-C-14), 2.60 (m, 2H, H-C-5, H-C-15), 2.75 (d, J = 10.5, 1H, H-C-21), 2.85 (m, 1H, H-C-3), 3.00 (m, 1H, H-C-20), 3.40 (m, 1H, H-C-5), 4.10 (t, J = 6, 1H, H-C-2), 7.10 (t, J = 7.5, 1H, H-C-10), 7.25 (t, J = 7.5 , 1H, H-C-11), 7.95 (d, J = 7.5 , 1H, H-C-9), 8.15 (d, J = 7.5, 1H, H-C-12). ^{13}C Nmr : 20.9 (C-15), 23.5 ($NCOCH_3$) , 23.7 (C-17), 28.0 (C-16), 30.6 (C-18), 37.9 (C-6), 44.9 (C-14), 45.8 (C-20), 52.4 (C-3), 53.5 (C-5), 55.6 (C-7), 66.6 (C-2), 73.3 (C-21), 118.1 (C-12), 124.1 (C-10), 127.0 (C-9), 128.5 (C-11), 136.6 (C-8), 141.3 (C-13), 168.0 ($NCOCH_3$) , 219.0 (C-19) . Ms, m/z (relative intensity) : 338 (94), 337 (100), 309 (35), 295 (30), 268 (35), 267 (47), 170 (59), 168 (35), 166 (35), 149 (35), 144 (53), 143 (41),138 (47),130 (59), 127 (35), 110 (41) ; exact mass m/z 338.1994 (calculated for $C_{21}H_{26}N_2O_2$ m/z 338.1991).

ACKNOWLEDGMENT

We wish to thank Dr G. DAUPHIN for running1H and 13C nmr spectra and for performing the Cosy experiments. The authors would also like to thank Dr D. J. AITKEN for english version of this manuscript.

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Received, 6th April, 1990