Pergamon

Tetrahedron 55 (1999) 11095–11108

TETRAHEDRON

Synthesis of Aspidospermidine Alkaloids from 1,2,3,4-tetrahydrocarbazole: Total Stereoselective Synthesis of (±)-18-Noraspidospermidine.

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Received 10 May 1999; revised 21 June 1999; accepted 8 July 1999

Abstract: The reactivity of the 1,2,3,4-tetrahydrocarbazol-4-one derivatives has been analysed and applied to the synthesis of (±)-18-noraspidospermidine (**1b**). This was synthesised, starting from 4-(1',3'-dioxolan-2'-yl)cyclohexanone which was successively transformed to 3-methyl-3-(3'-nitropropyl)-1,2,3,4-tetrahydrocarbazol-4-one and to the imine tetracycle **13** by means of nickel boride catalyst. The reduction of **13** to the natural *cis* D ring junction was carried out with the $LiAlH_4/AlCl_3$ system. The construction of the E-ring was carried out by a Pummerer type reaction from the*cis*-7-tosyl-1-phenylthioacetamide derivative **17** by oxidation followed by intramolecular cyclisation, desulfurization and reduction to **1b**.

Keywords: (±)-18-Noraspidospermidine, Tetrahydrocarbazolones, Nickel boride, Stereoselective reduction, Indolisation

INTRODUCTION

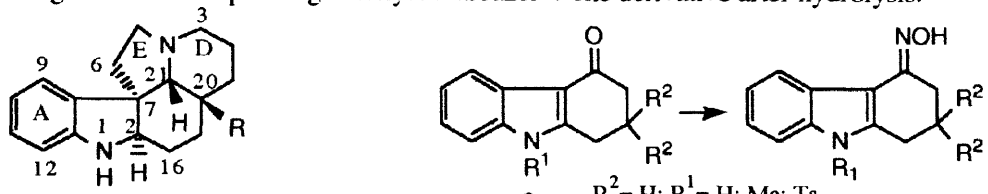
The Aspidosperma type indole alkaloids constitute a large group of alkaloids[1] with important biological activity including the antitumor agents vincristine and vinblastine.[2] These compounds share as part of their structure, the pentacyclic indole ring also found in aspidospermidine **1a**. In the context of our work on 1,2,3,4-tetrahydrocarbazol-4-one (**2**), we were attracted to the possibility of the transformation of the conjugated carbonyl group to prepare analogues of aspidospermidine such as **1b**.

The structure and reactivity of the carbonyl group in **2** or its *N*-methyl or *N*-tosyl derivatives, to prepare C-C and C-N bonds on position 4 has been analysed.[3] The molecular structure in the solid state of all those compounds was elucidated by X-ray diffraction analysis. Two remarkable structural features were observed: i. Compound **2** shows an important intermolecular hydrogen contact between the conjugated N-H and carbonyl groups; ii. compound **2** and its *N*-methyl and *N*-tosyl derivatives exhibit a similar C=O conjugated molecular structure with the cyclohexenone ring moiety in an envelope conformation. Unfortunately, compound **2** and its *N*-methyl, *N*-tosyl and 2,2-dimethyl derivatives, show inactivity to nucleophiles such as Wittig reagents. In this way, the 2,2-dimethyl derivative of **2** was prepared to alter the stable envelope conformation and then avoid the extended conjugation.

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00614-6

Although, oximation at position 4 of the tetrahydrocarbazole ring could be carried out with hydroxylamine in methanol-water (2:1), in practically quantitative yield, the oximes also show an extended conjugation, Scheme 1.[4]

However, the reduction of the corresponding oxime with lithium aluminun hydride affords an imine intermediate which gives the corresponding tetrahydrocarbazol-4-one derivative after hydrolysis.



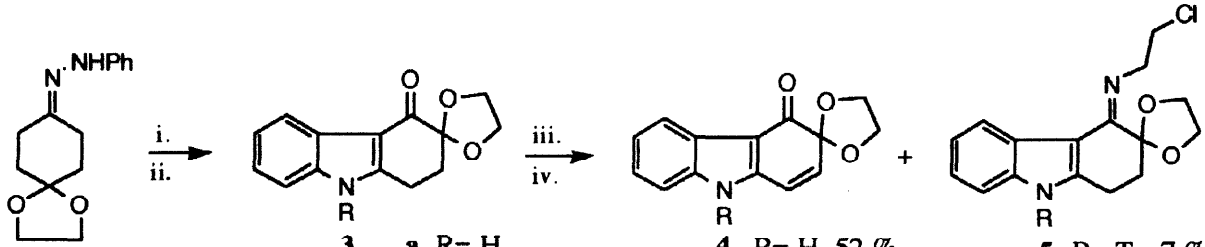
Scheme 1

Moreover, we recently reported the Beckmann rearrangement of those oximes to the corresponding azepin-1(2*H*)-one derivatives, in polyphosphoric acid at 150 °C in good yield.[4] The kinetic analyses for the oximation and its rearrangement reaction, confirm the *N*-tosyl oxime as the most reactive, while the 2,2-dimethyl substituted one shows similar reactivity to the unsubstituted compound **2**.

RESULTS AND DISCUSSION

The reaction of the carbonyl group in 1-(1',3'-dithiolan-2'-yl)-1,2,3,4-tetrahydrocarbazol-4-one with amines has been recently reported for the preparation of the 4-aminotetrahydrocarbazol-1-one derivative as a key step in the synthesis of indole alkaloids.[5,6]

In this way, we undertook the preparation of 3-(1',3'-dioxolan-2'-yl)-1,2,3,4-tetrahydrocarbazol-4-one as a synthon which exhibits a) a hindered 3,3-disubstituted position and b) a convenient functionalization on position 3 to prepare the D ring of aspidospermidine, Scheme 2.



Scheme 2.

The synthesis of 3-(1',3'-dioxolan-2'-yl)-1,2,3,4-tetrahydrocarbazol-4-one (**3**), was achieved in good yield by treatment of 3-(1',3'-dioxolan-2'-yl)-1,2,3,4-tetrahydrocarbazole with 2,6-dichloro-3,4-dicyano-p-benzoquinone (DDQ), in THF:H_2O at 0 °C. Previously, 3-(1',3'-dioxolan-2'-yl)-1,2,3,4-tetrahydrocarbazole was prepared by thermal cyclisation of the phenylhydrazone of 4-(1',3'-dioxolan-2'-yl)cyclohexanone, in ethylene glycol. The 3-(1',3'-dioxolan-2'-yl)-1,2,3,4-tetrahydrocarbazole was hydrolysed with a hydrochloric solution to give 1,2,3,4-tetrahydrocarbazol-3-one (white solid, mp 157-159 °C) which would be an interesting synthon for the alkaloid synthesis.

By comparison with the unsubstituted compound **2**, the spectral data of **3a** in the solid state suggests an associated and conjugated NH···O=C structure; IR spectrum also shows two absorption bands centered at 3240 and 1640 cm^{-1} respectively.

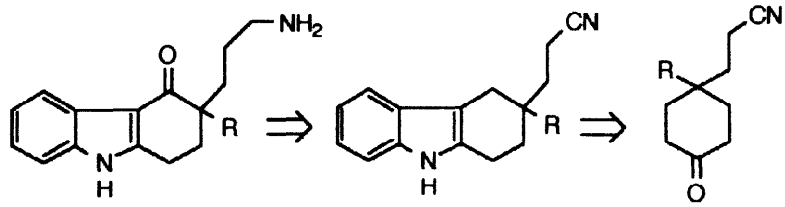
Preparation of an appropriate amino derivative at position 4 in **3a** was tried with 2-chloroethylamine but only the conjugated dehydro derivative **4a** (52 %) was isolated, using titanium tetrachloride as catalyst (0.5 equiv.) in toluene at the reflux temperature.

The reaction of a benzylamine with the *N*-tosyl-3,3-disubstituted derivative of **2**, catalysed by titanium tetrachloride has been recently reported.[7] Thus, to stimulate the reaction of the carbonyl group, we prepared *N*-tosyl-3-(1',3'-dioxolan-2'-yl)-1,2,3,4-tetrahydrocarbazol-4-one **3b**, which on treatment with 2-chloroethylamine (6-15 equiv.), in catalytic presence of titanium tetrachloride (0.5-1.5 equiv., at r.t. or at 120 °C) afforded the iminopropyl derivative **5b** in very low yield (5-8 %). The formation of a crystalline complex between titanium tetrachloride and tetrahydrofuran ($TiCl_4.2THF$) is known,[8] which would explain the formation of a precipitate when titanium tetrachloride is added to **3a** or **3b** perhaps explaing the loss of the catalyst activity.

On the other hand, some synthetic methods to prepare the aspidospermidine derivatives starting from 1,2,3,4,4a,9a-hexahydrocarbazol-4-one have been recently reported. [9,10,11]

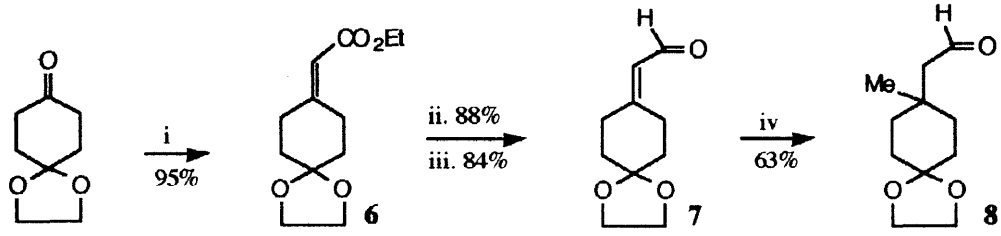
For the preparation of 18-noraspidospermidine (**1b**), we undertook the synthesis of a 3,3-disubstituted-1,2,3,4-tetrahydrocarbazol-4-one to produce some steric effect on the conjugated carbonyl group and also to force the stable envelope conformation of the cyclohexene ring in this molecule, [3,4] Scheme 3.

On the basis of the preceding experiences with **3a**, the preparation of the D ring of **1** was undertaken starting from a 3-alkyl-3-(3´-aminopropyl) compound, which would give the cyclic imino product by condensation with a preformed C=O group at position 4; a retrosynthetic route is shown in Scheme 3.



Scheme 3.

Thus, 4-alkyl-4-cyanoethylcyclohexanone was obtained from aldehyde **7**, which was prepared by the reduction of the ester **6**, Scheme 4. Compound **6** was prepared starting from 4-(1',3'-dioxolan-2'-yl)cyclohexanone by Wittig reaction with the ethyl phosphonoacetate ylide, with rigorous temperature control to avoid the double bond isomerisation into the ring.[12] However, the Michael addition of a methyl group to the ester **6** gave mixtures of the 1,2 and the 1,4 products mainly, employing the following systems: a) Methyl iodide/cuprous chloride in diethyl ether or toluene; b) Lithium dimethylcuprate in diethyl ether at -5 °C (giving mainly the 1,2 product); c) more active cuprates as $Me_5Cu_3Li_2$; d) cuprous iodide and dimethyl sulfide and methyllithium or methylmagnesium iodide (also giving the 1,2 product); e) the $MeCu.BF_3$ complex prepared with methyllithium, cuprous iodide and boron trifluoride etherate (giving the acetal deprotection product).



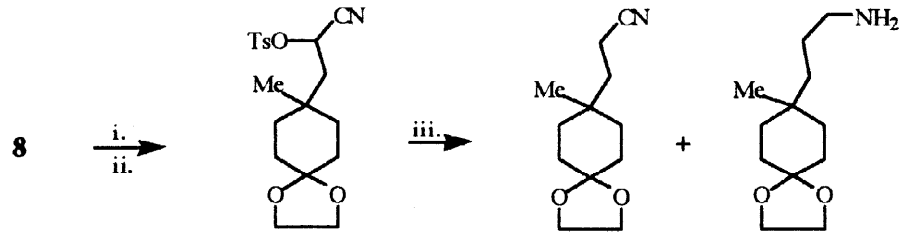
i. $(EtO)_2POCH_2CO_2Et/NaH$; Toluene 80°C; ii. $DIBAL/CH_2Cl_2$, -78°C;
iii. CrO_3-Py, CH_2Cl_2; iv. Me_2CuLi/Et_2O, -5°C.

Scheme 4

Although the rigid chair conformation of the cyclohexane ring due to the acetal group and the β,β-disubstitution of the double bond avoid the 1,4-addition to the conjugate ester, a more active α,β-conjugated aldehyde group was prepared. The ester **6** was reduced with DIBAL in dichloromethane, to the allylic alcohol which was finally oxidised with chromium anhydride in dry pyridine to aldehyde **7** in good yield,[12] Scheme 4.

The 1,4-addition of lithium dimethylcuprate to aldehyde **7** in diethyl ether at -5 °C gave **8** in good yield.

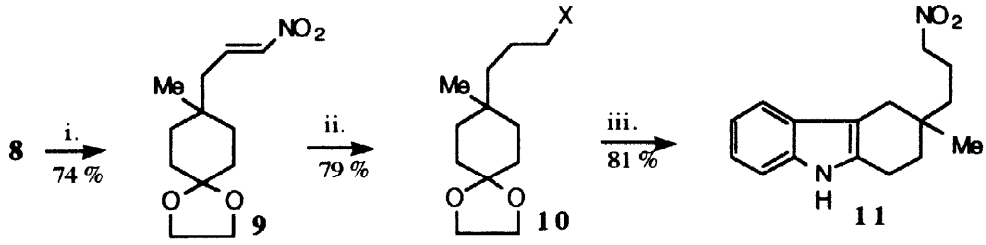
The 4-methyl-1-(1',3'-dioxolan-2'-yl)cyclohexyl-4-γ-propanenitrile (Scheme 3) was obtained (44 %) as a mixture with its reduced amine from the cyanhydrin, prepared by addition of sodium cyanide to aldehyde **8** (97 %). The cyanhydrin was treated with tosyl chloride in presence of triethylamine at 0 °C in dichloromethane (73 %) followed of reduction with sodium borohydride in DMF, Scheme 5. Unfortunately, effective separation of the amine from the mixture results in low efficiency.



i. $NaHSO_3/NaCN$, 97 %; ii. $TsCl/Et_3N$, 73 %;
iii. $NaBH_4/DMF$, 100°C, 44 %.

Scheme 5.

An alternative way was the transformation of the aldehyde **8** into the nitro derivative **9** by condensation with nitromethane in the presence of ammonium acetate (75 %),[13] which by selective reduction of the double bond with sodium borohydride in ethanol at -10 °C, permitted the isolation of the saturated nitropropyl derivative **9** (77 %); its reduced amine was also isolated (10%), Scheme 6.



i. CH_3NO_2/Δ; ii. $NaBH_4$;
iii. $PhNHNH_3Cl$.

X= NO_2,
X= NH_2, 10 %

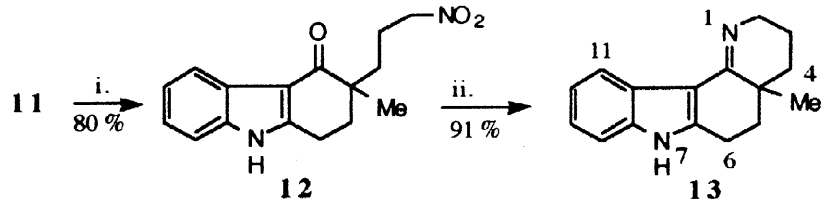
Scheme 6.

The 3-methyl-3-(3′-nitropropyl)-1,2,3,4-tetrahydrocarbazol (**11**) was prepared by means of the Fischer reaction of the nitropropyl derivative **10** with phenylhydrazine hydrochloride in acetic acid. In this reaction, proton-catalysed acetal cleavage, formation of the phenylhydrazone, and cyclisation to the indole **11** all took place in one pot in good yield (81 %), Scheme 6.

Before the reduction of the nitro group in compound **11**, the preparation of compound **12** was achieved by mild treatment of **11** with 2,3-dichloro-5,6-dicyano-1,4-*p*-benzoquinone (DDQ) in THF-H_2O (9:1), in good yield (85 %). The compound **12** in comparison with **2**, shows an important NH···O=C hydrogen bridge association. The IR spectrum (KBr or chloroform solution) shows two absorption bands centered at 3310 and 1610 cm^{-1} for the NH and the C=O groups respectively and the ^1H NMR spectrum shows a deshielding broad singlet at 9.8 ppm for the NH group.

Finally, the reduction of the nitro to amino group in compound **12** was carried out with nickel boride as catalyst, which was prepared *in situ* by reduction of the nickel(II) chloride hexahydrate with sodium borohydride in ethanol,[14] using hydrazine hydrate as the hydrogen generator. During the reduction of the nitro group, an intramolecular condensation took place giving the imine and ring D, **13**. Thus, the double substitution at position 3 in compound **12**, facilitates the intramolecular reaction of the recently formed terminal amino group with the carbonyl group, in one pot to give **13** in excellent yield as a yellow solid (mp 128-9 °C, 91 %), Scheme 7.

Compound **13** exhibits as structural characteristics in the NMR spectra, a deshielding effect of the signal for H-11 at 8.18 ppm, and an imine carbon C-11c, at 168.6 ppm.



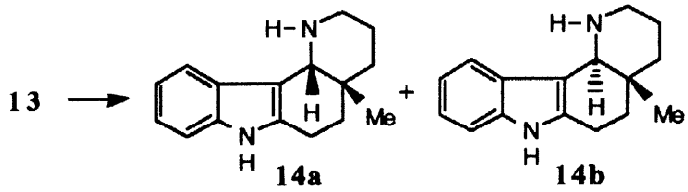
i. DDQ; ii. $NiCl_2.6H_2O/NaBH_4/NH_2NH_2.H_2O$.

Scheme 7.

Recently, the N-*p*-methoxybenzenesulfonyl derivative of **13** was obtained by annulation from a 3-azidoethyl derivative of **12**, but all attempts of reduction of the imine afforded the undesired trans CD ring junction isomer.[7]

The stereoselective reduction of the imine **13** to prepare the natural *cis* C/D ring junction isomer **14a** was examined with different hydride complex systems and solvents. Thus, the reaction of the imine **13** with sodium borohydride, or sodium borohydride-boron trifluoride, in ethanol, isopropanol or THF, and lithium aluminium hydride in diethyl ether, gave only the more stable *trans*-diequatorial fused C/D rings (**14b**), in agreement with the previous work,[7] Table 1.

Table 1. Stereoselective reduction of the imine **8** by hydride complexes.

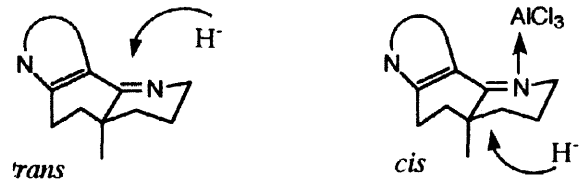


Reagent	Solvent	cis:trans	Reagent	Solvent	cis:trans
$NaBH_4$	iPrOH	0:100	$NaBH_4$-BF_3	THF	0:100
DIBAL	THF	5:95	DIBAL	CH_2Cl	10:90
$LiAlH_4$	Et_2O	0:100	$LiAlH_4$	Et_2O	0:100
$LiAlH_4$	THF	20:80	$LiAlH_4$-$AlCl_3$	Et_2O	0:100
$LiAlH_4/AlCl_3$	toluene:THF 4:1	45:55	$LiAlH_4$-$AlCl_3$	toluene:THF 9:1	50:50
$LiAlH_4$-$AlCl_3$	toluene:THF 20:1	65:35	$LiAlH_4$-$AlCl_3$	toluene:THF 30:1	70:30

However, treatment of the imine **13** with lithium aluminium hydride in the presence of aluminium trichloride, in THF or mixtures with toluene, afforded both *cis* and *trans* isomers, in variable relative amounts depending of the solvent employed, Table 1. Thus, in toluene:THF 30:1, the *cis:trans* ratio was 70:30 respectively (by ^{1}H-

NMR, Me; *cis* 0.92 **14a** and *trans* 0.88 ppm **14b**) and both isomers were isolated by silica gel column chromatography.

On the other hand, the *trans* diequatorial type C/D rings junction in **13** is the more stable (crystallographic data[15]) with both rings in a chair and a half chair conformation respectively, that permits an aproach of hydride attack. Thus, the coordination of the aluminium trichloride to the imine nitrogen by the sterically more accessible face, allows the hydride ion attack on the more hindered side, Scheme 8. The solvent competes with the imine nitrogen in the coordination to the aluminium trichloride which produces increasing in the *trans* isomer product.

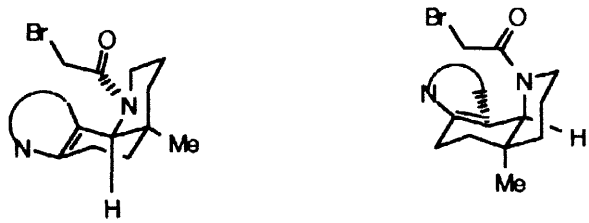


Scheme 8.

The reduction of the imine **13** with the $LiAlH_4/AlCl_3$ system in toluene failed, however we found that addition of a little THF rendered the reaction mixture homogeneous, which favoured the *N*-aluminium trichloride coordination and hence a selectivity of the reduction reaction to the *cis* isomer **14a**.

The *cis* isomer **14a** was used to prepare the 18-noraspidospermidine. According to a previous paper,[11] the cyclopentannulation of the *N*-bromoethyl derivative of **14a**, to the aspidospermidine derivative, resulted unsucessful. In this way, we attempted the preparation and cyclization of the more active *N*-bromoacetyl derivative of **14a**, through the indolylmagnesium salt. The N-bromoacetyl product was obtained by treatment of **14a** with bromoacetyl chloride in toluene in the presence of triethylamine (93 %). The compound shows a conformational equilibrium between two rotamers of the amide (2:1), the main isomer having the carbonyl group on the same side as the hydrogen 11c, on the basis of the anisotropic deshielding effect observed on this proton in the ^1H NMR spectrum.

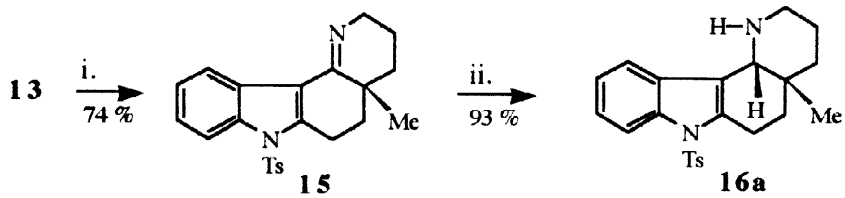
Moreover, according to crystallographic data,[15] the main conformer in a chair conformation for the D ring, shows 4a-methyl in axial and hydrogen 11c in equatorial positions, closing up the C-Br bond to the potential carbanion centre in the *N*-salt, Scheme 9. Unfortunately, although posessing the favourable geometry, the intramolecular cyclisation of the *N*-bromoacetyl derivative through the *N*-indolylmagnesium (or sodium) salt in THF or in toluene, failed to prepare ring E of the aspidospermidine analogue.



Scheme 9

An alternative cyclisation to prepare the E-ring was carried out by a Pummerer type reaction, following the methodology reported by Magnus[16] and applied by Desmaële and d'Angelo.[11] Firstly, we prepared the *N*-tosyl derivative **15** from the conjugated imine **13**, by reaction with tosyl chloride and sodium hydroxide in presence of tetrabutylammonium iodide (74 %).

The stereoselective reduction of **15** to the amine *cis* **16a** was achieved with $LiAlH_4$-$AlCl_3$ system in toluene/THF 30/1 (93 %; *cis*/*trans*, 75/25; white solids, mp 165-7 and 125-7 °C respectively), Scheme 10.

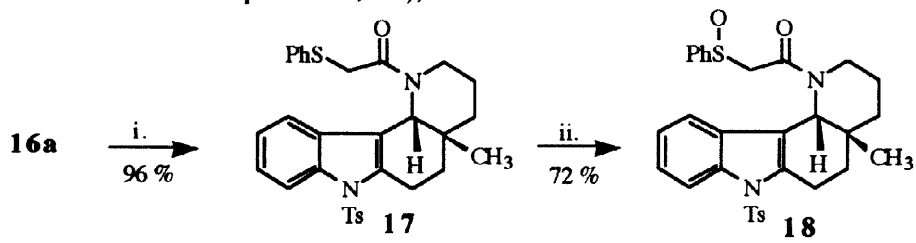


i. TsCl, NaOH, $Bu_4NH_4^+$ I^-; ii. $LiAlH_4$-$AlCl_3$, toluene/THF (30:1), cis/trans 75/25

Scheme 10

Finally, the preparation of the E-ring was carried out by intramolecular rearrangement of the derivative **18** obtained from the N-thioacetyl derivative of **16a**, Scheme 11. Hence, for this purpose, the *N*-tosyl-*cis* isomer **16a** was treated with phenylthioacetyl chloride to prepare **17** (96 %). This thioacetyl amide **17**, exhibits a conformational equilibrium between two rotamers of the amide (5:1), the main one having the carbonyl group on the same side as the hydrogen 11c, (5.62 and 4.72 ppm, respectively, in the ^1H NMR spectrum).

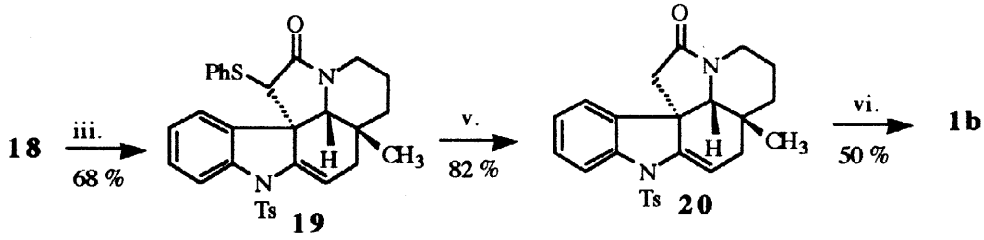
The thioacetyl amide **17** was transformed into the acylsulfinyl derivative **18** by treatment with sodium periodate (72 %, as a conformational equilibrium, 1:1), Scheme 11.



i. $PhSCH_2COCl$; ii. $NaIO_4$

Scheme 11

Pummerer rearrangement of compound **18** was carried out with trifluoroacetic anhydride at room temperature, giving the pentacyclic compound **19** (68 %, as a mixture of diastereoisomers 7:3), by electrophilic attack on the indole ring, through a sulfenium intermediate, Scheme 12.[16]



iii. TFAA, chlorobenzene; iv. Raney nickel; v. $LiAlH_4$.

Scheme 12

Desulfurization of compound **19** was carried out by treatment with Raney nickel at room temperature to give the dihydro derivative **20** (82 %) which was stereospecifically reduced with an excess of $LiAlH_4$ in THF to (±)-18-noraspidospermidine **1b** in moderate yield (50 %), Scheme 12.

The D/E and C/E rings junction are in a *trans* conformation (H-21/C-5 and H-21/C-6 respectively in *trans*) while the C/D one is in a cis conformation (H-21/C-19 in *cis*), which is the same as the stereochemistry of natural aspidospermidine alkaloids, confirmed by X-ray analysis.[15] Moreover, H-2 and C-6 are in a *cis* configuration. In the ^1H NMR spectrum, H-2 appears at 3.51 ppm as a doublet of doublets with J_1 = 10.9 and J_2 = 6.2 Hz in good agreement with that found in its *N*-methyl derivative [7] (3.38 as dd, J_1 = 10.8 and J_2 = 6.0 Hz).

Experimental Section

Melting points were determined on a Reichert hotstage microscope and are uncorrected. IR spectra were obtained as neat films between NaCl plates or KBr pellets. The ^1H and ^{13}C NMR spectra, were recorded at 200 and 50 MHz respectively. Chemical shifts were obtained from $CDCl_3$ solutions with tetramethylsilane as internal standard and are given in δ. Mass spectra analyses were recorded by electron impact at 70 eV on a GC-MS spectrometer.

3-(1',3'-dioxolan-2'-yl)-1,2,3,4-tetrahydrocarbazole (3).

a) Phenylhydrazone of 4-(1',3'-dioxolan-2'-yl)cyclohexanone. In a round-bottomed flask attached to a Dean-Stark system under argon atmosphere, were placed 4-(1',3'-dioxolan-2'-yl)cyclohexanone (4 g, 0.026 mol) and freshly distilled phenylhydrazine (2.5 mL, 0.026 mol) in toluene (160 mL). The mixture was warmed at reflux temperature until evolution of water ceased. After toluene evaporation, phenylhydrazone was isolated as an orange oil, 6.2 g, 98 % yield.

^1H NMR ($CDCl_3$) δ 1.22 (m, 4H), 2.40 (two t, 4H, J= 16.3 and 6.5 Hz), 3.86 (s, 4H), 6.20 (t, 1H, J= 7.4 Hz), 6.92 (d, 2H, J= 7.4 Hz), 7.21 (t, 2H, J= 7.4 Hz); IR (film) 3320 (NH), 1600 (ArH), 1500 (C=N), 760 and 700 (ArH monosubst.).

b) Thermal indolisation of the phenylhydrazone. In a round-bottomed flask, under argon atmosphere, was placed phenylhydrazone of 4-(1',3'-dioxolan-2'-yl)cyclohexanone (6.1 g, 24.6 mmol) in argon saturated ethylene glycol (155 mL). Then, the mixture was warmed at 180 °C for 4 h and then, poured on water (250 mL) at 0 °C, extracted with dichloromethane (50 mL) and dried on $MgSO_4$. After, solvent was removed giving a brown oil which was purified by flash silica gel column chromatography (hexane:ethyl acetate 2:1). The 3-(1',3'-dioxolan-2'-yl)-1,2,3,4-tetrahydrocarbazole was obtained as a rose solid (5.8 g), which was washed with diethyl ether giving a white solid, mp 146-148 °C, 4.8 g, 83 % yield.

^1H NMR ($CDCl_3$) δ 2.05 (t, 2H, J= 6.5 Hz, H-1), 2.85 (t, 2H, J= 6.5 Hz, H-2), 2.96 (s, 2H, H-4), 4.05 (s, 4H, O-CH_2CH_2-O), 7.15 (m, 3H, H-5, H-6, H-7), 7.45 (m, 1H, H-8), 7.8 (s br, 1H, NH); IR (KBr) 3420 (NH), 1595 (ArH), 1100 (O-CH_2-CH_2-O), 750 (ArH 1,2-disubst.). Anal.Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.15; H, 6.72; N, 5.84.

1,2,3,4-Tetrahydrocarbazol-3-one. To a solution of 3-(1',3'-dioxolan-2'-yl)-1,2,3,4-tetrahydrocarbazole (1.74 g, 7.6 mmol) in THF (28 mL), was added HCl (7 mL, 15 %), and the mixture was stirred at room temperature for 2 h, neutralised with sodium carbonate, extracted with dichloromethane and dried on Na_2SO_4. After solvent elimination the residual solid was purified by silica gel column chromatography (THF:ethyl acetate 1:1). The 1,2,3,4-tetrahydrocarbazol-3-one is a white solid, mp 157-159 °C, 1.07g, 76 % yield.

^1H NMR (MeOD) δ 2.78 (t, 2H, J= 6.5 Hz, H-2), 3.15 (t, 2H, J= 6.5 Hz, H-1), 3.62 (s, 2H, H-4), 7.14 (m, 2H, H-6, H-7), 7.38 (m, 2H, H-5, H-8); IR (KBr) 3400 (NH), 1702 (C=O), 750 (ArH 1,2-disubst.). Anal.Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 78.15; H, 5.62; N, 7.54.

3-(1',3'-dioxolan-2'-yl)-1,2,3,4-tetrahydrocarbazol-4-one (3a). To a solution of 3-(1',3'-dioxolan-2'-yl)-1,2,3,4-tetrahydrocarbazole (2 g, 8.73 mmol) in THF (56 mL) and water (6.5 mL) was added a solution of DDQ (4.05 g, 17.84 mmol), in THF (35 mL) at 0 °C during 30 min. The mixture was stirred at room temperature for 7 h and then, with solid K_2CO_3 (9.34 g) for 1 h, and finally the solvent was evaporated. The residual brown solid was purified by silica gel column chromatography (ethyl acetate:hexane 2:1). Compound **3a** was isolated as a white solid, mp 106-107 °C, 1.89 g, 89 % yield.

^1H NMR ($CDCl_3$) δ 2.34 (t, 2H, J= 6.1 Hz, H-1), 3.15 (t, 2H, J= 6.1 Hz, H-2), 4.20 (s, 4H, O-CH_2CH_2-O), 7.20 (m, 2H, H-5, H-7), 7.40 (m, 1H, H-6), 8.15 (m, 1H, H-8), 9.2 (s br, 1H, NH); IR (KBr) 3240 (NH), 1640 (C=O), 1590 (ArH), 1110 (O-CH_2-), 770 (ArH 1,2-disubst.). Anal.Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76.Found: C, 68.85; H, 5.42; N, 5.54.

Reaction of 3a with 2-Chloroethylamine. To a solution of **3a** (150 mg, 0.62 mmol) in toluene (4 mL) under argon atmosphere, was added a solution of 2-chloroethylamine (120 mg, 1.85 mmol) in toluene (2 mL) and a solution of titanium tetrachloride (0.4 mL, 0.32 mmol) in toluene (0.7 mL). The mixture was stirred at 120 °C for 20 h, and the black solid formed was recovered by filtration and then stirred with a saturated solution of HCl in diethyl ether (20 mL) for 30 min. After neutralization with sodium carbonate (25 %), was extracted with dichloromethane and dried on $MgSO_4$. After solvent elimination, a brown oil was isolated, which was purified by silica gel column chromatography (hexane:ethyl acetate 2:1). A yellow oil was isolated and identified as **4**, 77 mg, 52 % yield.

^1H-NMR ($CDCl_3$) δ 3.95 (m, 2H, OCH_2), 4.16 (m, 2H, OCH_2), 6.84 and 7.09 (AB system, 2H, J= 8.1 Hz, H-1 and H-2), 7.20 (m, 2H, H-6 and H-7), 7.38 (m, 1H, H-8), 8.33 (d, 1H, J= 6.5 Hz, H-5); IR (film) 3390 (NH), 1605 (C=O), 1600 (ArH, C=C), 760 (ArH 1,2-disubst.). Anal.Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found:C, 69.45; H,4.42; N, 5.54.

***N*-tosyl-3-(1',3'-dioxolan-2'-yl)-1,2,3,4-tetrahydrocarbazol-4-one (3b).** To a solution of **3a** (1.0 g, 4.12 mmol), under argon atmosphere, in dichloromethane (8 mL), was added a solution of NaOH (164 mg, 4.12 mmol), in water (0.33 mL) and $INBu_4$ (1.52 g, 4.12 mmol), in dichloromethane (2 mL), and the mixture stirred for 20 min at room temperature. Then, a solution of tosyl chloride (1.02 g, 5.35 mmol), in dichloromethane (8 mL) was added, and the mixture was stirred for 5h. The mixture was hydrolysed with water (25 mL) and extracted with dichloromethane (2x25 mL). The organic layer was dried on $MgSO_4$, and after solvent elimination a residual brown oil was obtained. The product was purified by silica gel column chromatography (hexane:ethyl acetate 1:1). Compound **3b** was isolated as a white solid, mp 145-147 °C, 1.39 g, 85 % yield.

^1H NMR ($CDCl_3$) δ 2.31 (s, 3H, CH_3-Ts), 2.40 (t, 2H, J= 6.7 Hz, H-1), 3.55 (t, 2H, J= 6,7 Hz, H-2), 4.2 (m, 4H, O-CH_2CH_2-O), 7.21 (m, 2H, Ts), 7.32 (m, 2H, H-5,H-7), 7.77 (m, 2H, Ts), 8.18 (m, 2H, H-6, H-8); IR (KBr) 1675 (C=O), 1170 (O-CH_2-), 850 (ArH 1,4-disubst.), 760 (ArH 1,2-disubst.); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3-Ts), 22.6 (C-1), 32.8 (C-2), 65.9 (O-CH_2CH_2-O), 103.9 (C-4a), 113.8 (C-8), 116.4 (C-9a), 121.6 (C-6), 124.8 (C-7), 125.4 (C-5), 125.5 (C-4b), 126.5 (Ts C-2'), 130.1 (Ts C-3',5'), 135.0 (C-3), 136.2 (C-8a), 145.8 (Ts C-1'), 150.1 (Ts C-4'), 189.5 (C-4); MS (70eV) m/z 397 (M^+, 4), 242 (100), 198 (15), 170 (29), 156 (23), 128 (17), 91 (26). Anal.Calcd for $C_{21}H_{19}NO_5S$: C, 63.46; H, 4.81; N, 3.52. Found:C, 63.85; H,4.42; N, 3.54.

Reaction of 3b with 2-Chloroethylamine. To a solution of **3b** (131 mg, 0.41 mmol) in toluene (2 mL) under argon atmosphere, was added a solution of 2-chloroethylamine (1.65 mmol) in toluene (2 mL) and titanium tetrachloride (0.18 mL, 1.65 mmol) and the mixture was stirred at 120 °C for 20 h. After cooling, a saturated solution of HCl in diethyl ether (20 mL) was added and stirred for 30 min, neutralised with a sodium carbonate solution (25 %) and extracted with dichloromethane (20 mL). The organic layer was dried on $MgSO_4$. After solvent elimination was isolated a brown oil which was purified by silica gel column chromatography (hexane:ethyl acetate 2:1). A brown oil was isolated and identified as **5**, 10 mg, 7 % yield.

^1H NMR ($CDCl_3$) δ 2.26 (s, 3H, CH_3-Ts), 3.58 (m, 2H, O-CH_2), 3.60 (m, 2H, O-CH_2), 3.98 (m, 2H, $ClCH_2$-), 4.17 (m, 2H, C=N-CH_2-), 7.05 and 7.95 (AB, 2H, J= 8.9 Hz, H-1 and H-2), 7.36 (td, 1H, J= 7.5 and 1.1 Hz, H-6), 7.47 (td, 1H, J= 7.9 and 1.5 Hz, H-7), 8.05 (dd, 1H, J= 7.8 and 1.1 Hz, H-8), 8.33 (d, 1H, J= 7.8 Hz, H-5), 7.09 (m, 2H, H-3', H-5'-Ts), 7.65 (m, 2H, H-2', H-6'-Ts); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3-Ts), 45.5 (CH_2-Cl), 50.3 (=N-CH_2), 61.4 and 71.4 (O-CH_2), 109.2 (C-1), 112.6 (C-8), 114.9 (C-7), 120.2 (C-4a), 122.5 (C-5), 123.9 (C-6), 125.5 (C-4b), 126.4 (C-2',C-6'), 126.8 (C-2), 129.5 (C-3',C-5'), 132.3 (C-9a), 134.2 (C-3), 134.7 (C-8a), 138.8 (C-1'), 144.7 (C-4'), 147.9 (C-4); IR (film) 1590 (ArH), 1490 (C=N), 760 (ArH 1,2-disubst.); MS (70eV) m/z 458 (M^+, 100), 413 (23), 303 (92), 259 (93), 223 (45), 209 (38), 196 (44), 91 (55). Anal. Calcd for $C_{23}H_{23}NO_4Cl$: C, 69.12; H, 5.39; N, 5.76.Found: C, 68.85; H, 5.42; N, 5.54.

Ethyl 4-(1',3'-dioxolan-2'-yl)-1-cyclohexylidene)acetate (6). In a previously flamed round-bottomed flask, under argon atmosphere, were placed sodium hydride (846 mg, 35 mmol) in dry toluene (155 mL) and ethyl phosphonoacetate (7.06 mL, 35 mmol), at 0 °C was droped during 30 min. and the mixture was stirred at room temperature for 1 h. After, a solution of 4-(1',3'-dioxolan-2'-yl)-cyclohexanone (5.0 g, 32 mmol) in dry toluene (35 mL) was added at 0 °C for 30 min. The mixture was warmed at 80 °C for 90 min and then, was hydrolysed with water (35 mL) and extracted with diethyl ether (2x25 mL). Finally, solvent was removed giving a yellow oil which was purified by flash silica gel column chromatography (hexane:ethyl acetate 5:2). Compound **6** was isolated as a transparent oil, 6.85 g, 95 % yield.

^1H NMR ($CDCl_3$) δ 1.26 (t, 3H, J= 7.8 Hz, CH_3), 1.77 (m, 4H, CH_2-2 and CH_2-6), 2.38 (m, 2H, H-2, H-6), 3.02 (m, 2H, H-3, H-5), 3.90 (s, 4H, O-CH_2CH_2-O), 4.15 (q, 2H, J= 7.8 Hz, $COOCH_2$-), 5,68 (s br, 1H, C=CH); IR (film) 1710 (C=O), 1645 (1645), 1100 (O-CH_2). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.45; H, 8.20.

α-[4-(1',3'-dioxolan-2'-yl)-1-(cyclohexyl)]-β-(hydroxymethyl)ethene. To a solution of compound **6** (6.85 g, 30 mmol), in dry dichloromethane (70 mL), was droped a solution of DIBAL (1.5 M, 67 mmol) in toluene (44 mL) at -78 °C and stirred for 1h. After, the mixture was hydrolysed at room temperature with an aqueous saturated solution of amonium chloride (30 mL) with stirring for 15 min. The organic layer was dried on $MgSO_4$ and after solvent elimination, the title compound was obtained as a pale-yellow oil, 4.9 g, 88 % yield.

^1H NMR ($CDCl_3$) δ 1.15 (m, 4H, H-2, H-6), 2.23 (m, 4H, H-3, H-5), 3.10 (s br, 1H, OH), 3.9 (s, 4H, O-CH_2-CH_2), 4.05 (d, 2H, J= 7.3 Hz, CH_2OH), 5.32 (t, 1H, J= 7.3 Hz, C=CH); IR (film) 3400 (OH), 1120 (O-CH_2-), 1090 (C-O). Anal.Calcd for $C_{12}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.87; H, 8.70.

4-(1',3'-dioxolan-2'-yl)(cyclohexylidenyl)acetaldehyde (7). To a solution of dry pyridine (9.2 mL, 114 mmol) in dichloromethane (15 mL), was added CrO_3 (5.71 g, 70 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h. Then, a solution of α-[4-(1',3'-dioxolan-2'-yl)-cyclohexyl)]-β-(hydroxymethyl)ethene (1.5 g, 8 mmol) in dry dichloromethane (9 mL) was added and stirring for 40 min. Finally, dichloromethane (15 mL) was added and the mixture was filtered on a Büchner. The solution at 0 °C, was

successively washed with: i. NaOH (5%, 20 mL); ii. an aqueous saturated aqueous solution of amonium chloride (20 mL) and; iii. an aqueous saturated solution of $NaHCO_3$ (2x15 mL). The organic layer was dried on $MgSO_4$ and after solvent elimination, a yellow oil was obtained, which was purified by silica gel column chromatograpy (ethyl acetate:hexane 2:1). Compound **7** was isolated as a transparent oil, 1.07 g, 70 % yield (air unstable).

^1H NMR ($CDCl_3$) δ 1.84 (m, 4H, H-3, H-5), 2.48 (m, 2H, H-2, H-6), 2.88 (m, 2H, H-2, H-6), 4.00 (s, 4H, O-CH_2CH_2-O), 5.88 (d, 1H, J= 8.2 Hz, C=CH), 10.01 (d, 1H, J= 8.2 Hz, CHO); IR (film) 1670 (C=O), 1655 (C=C), 1120 (O-CH_2-). Anal.Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.52; H, 7.95.

4-methyl-1-(1',3'-dioxolan-2'-yl)cyclohexylacetaldehyde (8). To a solution of Me_2CuLi (10.2 mmol) in diethyl ether (30 mL) at -5 °C, was dropped a solution of 4-(1',3'-dioxolan-2'-yl)(cyclohexylidenyl)acetaldehyde (**7**) (1.55 g, 8.5 mmol) in dry diethyl ether (15 mL) and stirred under argon atmosphere at -5 °C for 2h. The mixture was hydrolysed with a saturated aqueous ammonium chloride solution (25 mL) and extracted with diethyl ether. The solvent was removed giving a residual yellow oil which was purified by silica gel column chromatography (ethyl acetate:hexane 1:1), to provide the aldehyde derivative **8** as a transparent oil, 1.07 g, 63% yield.

^1H NMR ($CDCl_3$) δ 1.13 (s, 3H, CH_3), 1.60 (m, 8H, $(CH_2)_4$), 2.33 (d, 2H, J= 3.1 Hz, CH_2-CO), 3.94 (s, 4H, O-CH_2CH_2-O), 9.86 (t, 1H,J= 3.1 Hz, CHO); IR (film) 1710 (C=O), 1100 (O-CH_2-) cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.35; H, 8.92.

[1-methyl-4-(1',3'-dioxolan-2'-yl)cyclohexyl]-β-propanenitrile.

a) 1. α-[4-(1',3'-dioxolan-2'-yl)-1-(cyclohexyl)]-β-(hydroxymethyl)ethene. To a solution of $NaHSO_3$ (843 mg, 8 mmol) in water (12 mL) was added a solution of **8** (1.07 g, 5.4 mmol) in diethyl ether (2 mL) and stirred at room temperature for 15 min. Then, was added diethyl ether (10 mL) and at 0 °C, a solution of NaCN (397 mg, 8 mmol) in water (5 mL) and stirred for 3h. The organic layer was separated and the aqueous was extracted with diethyl ether. The organic extracts were dried on $MgSO_4$. After the solvent was removed to give the title compound as a yellow oil, 1.18 g, 97 % yield.

^1H NMR ($CDCl_3$) δ 1.06 (s, 3H, CH_3), 1.4-1.7 (m, 8H, $(CH_2)_4$), 1.87 (d, 1H, J= 7.0 Hz, CH_2), 1.89 (d, 1H, J= 6.5 Hz, CH_2), 3.22 (d br, 1H, J= 6.5 Hz, OH), 3.95 (s, 4H, O-CH_2CH_2-O), 4.56 (dt, 1H, J= 6.5 and 6.4 Hz, CH-CN); ^{13}C NMR ($CDCl_3$) δ 23.8 (CH_3), 30.4 (C-3), 34.8 and 34.9 (C-2',6' and C-3',5'), 46.0 (C-1'), 57.9 (C-2), 63.9 (O-CH_2CH_2-O), 108.6 (C-4'), 120.9 (CN); IR (film) 3400 (NH), 2230 (CN), 1100 (O-CH_2-).

a) 2. Tosylation of the cyanhydrin. To a solution of the cyanhydrin (1.18 g, 5.2 mmol) in dry dichloromethane (15 mL) and triethylamine (1.43 mL, 10.2 mmol), under argon atmosphere at 0 °C, was dropped a solution of tosyl chloride (1.29 g, 6.8 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature for 4 h and then hydrolysed with water (10 mL). The aqueous layer was extracted with dichloromethane and dried on $MgSO_4$. Solvent was removed and the residual yellow solid was washed with diethyl ether giving the tosyl derivative as a white solid, mp 96-98 °C, 1.46g, 73 % yield.

^1H NMR ($CDCl_3$) δ 1.04 (s, 3H, CH_3), 1.50 (m, 8H, CH_2), 1.95 (d, 1H, J= 5.8, H-3), 2.01 (d, 1H, J= 7.4, H-3), 2.47 (s, 3H, CH_3-Ts), 3.93 (s, 4H, O-CH_2CH_2-O), 5.14 (dd, 1H, J= 7.4 and 5.8 Hz, H-2), 7.39 (m, 2H, H-3 and H-5 Ts), 7.84 (m, 2H, H-2 and H-6 Ts); IR (KBr) 1590 (ArH), 1100 (O-CH_2), 870 (ArH 1,4-disubst.); MS (70 eV) m/z 364 (M^+, 1), 224 (52), 155 (8), 99 (100), 86 (33), 55 (22).

b) Reduction of the tosyl derivative. To a solution of sodium borohydride (60 mg, 1.6 mmol) in dry DMF (2 mL) was added a solution of the above tosylated cyanhydrin (300 mg, 0.8 mmol) in dry DMF (3 mL). The mixture was warmed at 100 °C for 1 h, and then was hydrolysed with water (15 mL), extracted with dichloromethane (2x15 mL) and dried on $MgSO_4$. Solvent was removed and the residual oil was purified by silica gel column chromatography (hexane:ethyl acetate 1:1), giving ethylenacetal of [1-methyl-4-(1',3'-dioxolan-2'-yl)cyclohexyl]-β-propanenitrile as a yellow oil, 73 mg, 44 % yield.

^1H NMR ($CDCl_3$) δ 0.94 (s, 3H, CH_3), 1.45 (m, 4H, $(CH_2)_2$), 1.65 (m, 6H, $(CH_2)_3$), 2.31 (m, 2H, CH_2CN), 3.96 (s, 4H, OCH_2CH_2O); IR (film) 2240 (CN), 1100 (O-CH_2). Anal.Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.55; H, 9.02; N, 6.46.

4-methyl-1-(1',3'-dioxolan-2'-yl)cyclohexyl-4-γ-propanenitrile (10).

a) A solution of **8** (500 mg, 2.5 mmol) in nitromethane (3 mL) was stirred with ammonium acetate (155 mg, 2.0 mmol) at 80 °C for 1h. Then, the solvent was removed and the residual red oil was purified by silica gel column chromatography (ethyl acetate:hexane 1:1), to obtain compound **9** as a transparent oil, 429 mg, 74 % yield.

^1H NMR ($CDCl_3$) δ1.00 (s, 3H, CH_3), 1.60 (m, 8H, $(CH_2)_4$),2.21(dd, 2H, J = 8.3 and 1.1Hz, H-3), 3.95 (s, 4H, OCH_2CH_2O), 6.99 (dt,1H, J= 13.3 and 1.1 Hz, H-1),7.29 (dt, 1H, J = 13.3 and 8.3 Hz, H-2); IR (film)1640 (C=C),1510 and 1350 (N-O),1100 (O-CH_2-),940 (C=C)cm^{-1}.

b) To a solution of $NaBH_4$ (67 mg, 1.8 mmol) in ethanol (5mL) at -10 °C, was added a solution of the nitropropene **9** (400 mg, 1.8 mmol) in ethanol (1 mL), and stirred for 1h. After the mixture was hydrolysed with a saturated aqueous ammonium chloride solution (25 mL) and extracted with dichloromethane (20 mL). The residual

oil was purified by silica gel column chromatography (ethyl acetate:hexane 1:1), to obtain the nitro propane derivative **10** as a transparent oil, 321 mg, 79 % yield.

^{1}H NMR ($CDCl_3$) δ 0.94 (s, 3H, CH_3), 1.30 (m, 2H, CH_2), 1.40 (m, 4H, CH_2), 1.70 (m, 4H, CH_2), 2.00 (m, 2H, CH_2), 3.93 (s, 4H, OCH_2CH_2O), 4.34 (t, 2H, J= 7.0 Hz, H-1); ^{13}C NMR($CDCl_3$) δ 21.9 (C-2), 23.4 (CH_3), 30.6 (C-3), 31.6 (C-1'), 34.5 (C-2',6'), 37.5 (C-3',5'), 64.0 (OCH_2CH_2O), 76.2 (C-1), 108.7 (C-4'); IR (film) 1545 and 1370 (N-O), 1100 (O-CH_2-) cm^{-1}. MS (70eV) m/z 243 (M^+, 1 %), 242 (5), 99 (100), 86 (21), 55 (19). Anal. Calcd for $C_{12}H_{21}O_4N$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.96; H, 8.65; N, 5.48.

3-methyl-3-(3´-nitropropyl)-1,2,3,4-tetrahydrocarbazole (11). A mixture of phenylhydrazine hydrochloride (1.14 g, 7.9 mmol) and **10** (1.64 g, 7.2 mmol) in acetic acid (99 %, 10 mL) was stirred at 100 °C, under argon atmosphere, during 2h. After cooling, the mixture was neutralised with an aqueous solution of NaOH (10%, 40 mL) and extracted with dichloromethane (30 mL) and dried on magnesium sulfate. The solvent was removed and the residual brown oil was purified by silica gel column chromatography (hexane:ethylacetate 3:2) to obtain **11** as an orange oil,1.58 g, 81%yield.

^{1}HNMR($CDCl_3$)δ1.00 (s, 3H),1.35 (m, 2H), 1.64 (t, 2H, J= 6.3Hz), 2.0 (m, 2H), 2.46 (d, 2H, J= 0.9 Hz), 2.62 (t, 2H, J= 6.3 Hz), 4.25 (t, 2H, J= 7.0 Hz),7.05 (m, 2H),7.20 (m, 1H),7.45(m,1H),7.62 (s br,1H); ^{13}CNMR($CDCl_3$) δ 135.9, 132.6, 127.8, 120.9, 118.9, 117.5, 110.4, 108.5, 76.1, 37.1, 34.0, 33.1, 32.4, 24.1, 22.15, 20.0; IR (film) 3400, 1540, 1380, 740 cm^{-1}; MS (70 eV) m/z 272 (M^+, 25), 226 (8), 182 (18), 143 (100), 77 (6). Anal. Calcd for $C_{16}H_{21}O_2N$: C, 70.30; H, 7.74; N, 10.25. Found: C, 70.07; H, 7.45; N, 9.93.

3-methyl-3-(3-nitropropyl)-1,2,3,4-tetrahydrocarbazol-4-one (12). To a solution of **11** (1.4 g, 5.06 mmol) in THF (35 mL) and H_2O (5 mL) was dropped a solution of DDQ (2.39 g, 10.6 mmol) in THF (10 mL) and stirred at 0 °C for 3 h. Then, was added solid K_2CO_3 (4.74 g) and stirred for 2 h and extracted with dichloromethane (2x20 mL). The solvent was removed and the residual brown solid obtained was purified by silica gel column chromatography (ethyl acetate:hexane 2:1), to provide **12** as a yellow solid, m.p. 137-138°C, 1.25 g, 80% yield.

^{1}H NMR ($CDCl_3$) δ 1.22 (s, 3H), 1.7 (m, 2H), 2.00 (m, 2H), 2.20 (m, 2H), 2.99 (t, 2H, J= 6.1 Hz), 4.14 (t, 2H, J= 7.1 Hz), 7.20 (m, 2H), 7.40(m,1H),8.20(m,1H), 9.8 (s br, 1H); ^{13} NMR ($CDCl_3$) δ 198.5, 150.7, 136.3, 125.0, 123.1, 122.1, 120.7, 111.3, 111.1, 75.7, 44.2, 34.1, 33.5, 22.3, 20.9, 20.0. IR (KBr): 3310, 1615, 1605, 1540, 1370, 740 cm^{-1}. MS (70 eV) m/z 286 (M^+, 26), 240 (47), 199 (16), 157 (100), 129 (58), 102 (16). Anal. Calcd for $C_{16}H_{18}O_3N_2$: C, 67.12; H, 6.34; N, 9.78. Found: C, 66.82; H, 6.28; N, 9.55.

4a-methyl-2,3,4,4a,5,6-hexahydropyrido[4,3-b]carbazole (13). To a solution of $NiCl_2.6H_2O$ (2.98 g, 2.55 mmol) in ethanol (4 mL), under argon atmosphere at 0 °C, were successively dropped a solution of $NaBH_4$ (1 M, 25 mL, 25 mmol) in ethanol and a solution of NaOH (0.1 M, 25 mL) in ethanol and stirred for 30 min at room temperature. Then, a solution of **12** (1.2 g, 4,2 mmol) in ethanol (25 mL) was added, and the mixture heated at 80 °C and then, $NH_2NH_2.H_2O$ (4 mL, 83.7 mmol) was added and stirred at 80 °C for 4 h. The residual catalyst was filtered, and solvent removed to give a yellow solid that was hydrolysed with an aqueous acetic acid solution (10 %) (35 mL). The mixture was neutralised with solid K_2CO_3 and extracted with dichloromethane (2x25 mL). Finally after evaporation of solvent the imine derivative**13**was obtained as a pale-yellow solid, mp 128-129 °C, 0.91g, 91%yield.

^{1}HNMR($CDCl_3$) δ 1.19 (s, 3H), 1.6-2.1 (m, 6H), 2.8 and 3.0 (m, 2H), 3.75 and 4.05 (m, 2H), 7.12 (m, 2H), 7.30 (m, 1H), 8.18 (m,1H); ^{13}CNMR($CDCl_3$) δ 18.8, 20.3, 22.5, 37.5, 34.1, 34.3, 48.3, 109.7, 111.2, 120.4, 120.7, 121.7, 125.3, 137.6, 143.5, 168.6. IR (KBr): 3340, 1605, 740 cm^{-1}; MS (70 eV) m/z 238 (M^+, 100), 210 (83), 209 (53), 195 (22), 156 (28), 155 (61), 55 (23). Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.52; H, 7.45; N, 11.47.

4a-methyl-2,3,4,4a,5,6,7,11c-octahydro-1*H*-pyrido[3,2-c]carbazole (14). In a round bottom flask, under argon atmosphere, was placed compound **13** (100 mg, 0.4 mmol) in dry toluene:THF 30:1 (6 mL) and $AlCl_3$ (0.448 g, 3.4 mmol) and stirred at 0 °C during 5 min and then, was added $LiAlH_4$ (128 mg, 3.4 mmol). The mixture was stirred at room temperature for 2h and then was hydrolysed with THF:H_2O 1:1 (10 mL) and extracted with dichloromethane (15 mL). The solvent was removed and a yellow oil was obtained which was identified as both diastereoisomers *cis:trans* (70:30), 98 mg, 97% yield. The diastereoisomers were isolated by column chromatography using ethyl acetate as the eluent. The natural *cis* isomer was obtained as a white solid, mp 185-7 °C, and the trans isomer as a transparent oil.

cis diastereoisomer, **14a**: ^{1}HNMR(MeOD)δ 0.92(s, 3H),1.30(m, 2H), 1.70 (m, 4H),2.5-2.9 (m, 3H), 3.05 (m, 1H), 3.68 (s, 1H), 7.01 (m, 2H), 7.29 (m, 1H), 7.56 (m, 1H);IR (KBr): 3380,1605, 740cm^{-1}; MS (70 eV) m/z 240 (M^+, 100), 239 (90), 225 (22), 185 (54), 183 (29), 182 (29), 172 (22), 171 (26), 169 (20), 168

(24), 167 (25), 157 (24), 59 (39). Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N2, 11.66 . Found: C, 79.63; H, 8.01; N, 11.42

trans diastereoisomer, **14b**: ^{1}H NMR ($CDCl_3$): δ 0.88 (s, 3H),1.4-1.9 (m, 6H), 2.60 (m, 1H), 2.7 (m, 1H), 2.87(td,1H, J=12.8 and 3.3Hz), 3.27(d,1H, J=5.0Hz), 3.84(t, 1H, J= 2.0Hz),7.05(m,2H),7.23(m, 1H),7.82(sbr,1H),7.91(m,1H); ^{13}C NMR ($CDCl_3$) δ 14.5, 20.2, 22.8, 35.5, 36.1, 37.9, 42.3, 62.8, 110.3, 111.2, 118.7, 120.1, 120.3, 127.0, 133.2, 135.9; IR (film) 3390, 735 cm^{-1}; MS (70 eV) m/z 240 (M^+, 91), 239 (100), 185 (51), 183 (26), 171 (26), 157 (25), 143 (22), 130 (23), 59 (36). Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.96; H; 8.39; N, 11.66. Found: C, 79.90; H; 8.15, N; 11.28.

1-Bromoacetyl-4a-methyl-cis-2,3,4,4a,5,6,7,11c-octahydro-1*H*-pyrido-[3,2-c]-carbazole. In a bottom-flask previouly flamed and under argon atmosphere was placed a solution of **14a** (70 mg, 0,3 mmol) in dichloromethane (5 mL) at 0 °C, and dropped triethylamine (0,04 mL, 0,3 mmol) and bromoacetyl chloride (0,02 mL, 0,3 mmol). The mixture was stirred at 0 °C for 2 h and hydrolysed with water (10 mL) and extracted with dichloromethane (2x10 mL). The organic layer was dried on $MgSO_4$ and then solvent was removed giving the title compound as a mixture of the amide conformers (2:1), as a pale-yellow solid, mp 79-81 °C, 98 mg, 93 % yield.

^{1}H NMR($CDCl_3$) δ 1.00 and 1.18 (two s, 3H, CH_3-4a), 1.2-2.0 (m, 4H, -CH_2-), 2.6-2.9 (m, 4H, -CH_2-), 3.61 (m, 1H, H-2), 4.0-4.5 (m, 3H, CH_2Br and H-2), 4.72 and 5.50 (two s, 1H, H-11c), 6.9-7.3 (m, 4H, H-8, H-9, H-10, H-11), 8.46 and 8.65 (two s br, 1H, NH); IR (film) 3390 and 3280 (NH), 1615 (CO), 740 (ArH 1,4-disubst.). Anal. Calcd for $C_{18}H_{21}NO$: C, 62.25; H, 6.10; N, 4.03. Found: C, 62.37; H, 6.21; N, 3.85.

4a-Methyl-7-(p-toluensulfonyl)-2,3,4,4a,5,6-hexahydropyrido[3,2-c]carbazole (15). In a round bottom flask under argon atmosphere were placed the imine **13** (700 mg, 2.8 mmol) in dichloromethane (25 mL) and at 0 °C was added a solution of tosyl chloride (0.615 mg, 3.5 mmol) in dichloromethane (15 mL), tetrabutylammonium iodide (1.19 g, 3.5 mmol) and a solution of sodium hydroxide 125 mg (3.5 mmol) in water (1.5 mL). The mixture was stirred at 0 °C for 5 min and then, was added water (70 mL), extracted with dichloromethane (2x30 mL), and dried on $MgSO_4$. The solvent was removed giving a brown oil wich was purified by column chromatography (hexane:ethyl acetate 1:1) and compound **15** was isolated as a yellow oil, 0.931 g (74 %).

^{1}H NMR ($CDCl_3$) δ 1.08 (s, 3H, CH_3-4a), 1.5-2.0 (m, 6H, -CH_2-), 2.29 (s, 3H, CH_3-Ts), 3.25 (m, 2H, CH_2-6), 3.70 (m, 1H, H-2), 4.05 (m, 1H, H-2), 7.17 (d, 2H, J= 8,3 Hz, H-3′, H-5′), 7.25 (m, 2H, H-9, H-10), 7.64 (d, 2H, J= 8,3 Hz, H-2′, H-6′), 8.13 (m, 1H, H-8), 8.29 (m, 1H, H-11); ^{13}C-RMN ($CDCl_3$) δ 18.9 (C-4), 21.4 (C-3), 21.8 (CH_3-4a), 33.7 (CH_3-Ts), 33.9 (C-5), 37.1 (C-6), 49.9 (C-2), 64.0 (C-4a), 113.7 (C-11b), 121.7 (C-11), 122.24 (C-6a), 124.0 (C-8), 124.4 (C-10), 126.1 (C-2′ and C-5′ Ts), 126.4 (C-9), 129.8 (C-3′ and C-5′ Ts), 130.1 (C-11a), 137.1 (C-7a), 140.5 (C-1′ Ts), 144.9 (C-4′ Ts), 166.7 (C-11c); IR (KBr) 1620 (C=N), 1590 (ArH), 1170 (SO), 810 (ArH 1,4-disubst.), 750 (ArH 1,2-disubst.). Anal.Calcd for $C_{23}H_{24}N_2SO_2$: C, 70.38; H, 6.16; N, 7.14. Found: C, 70.15; H, 6.21; N, 6.85.

4a-Methyl-7-(*p*-tolensulfonyl)-1,2,3,4,4a,5,6,11c-octahydro-1*H*-pyrido[3,2-c]carbazole (16a, 16b). In a round bottom flask under argon atmosphere were placed the N-tosylimine **15** (0.826 g, 2.1 mmol) in toluene/THF 9:1 (70 mL) and at 0 °C was added $AlCl_3$ (1.12 g, 8.4 mmol) and $LiAlH_4$ (322 mg, 8.4 mmol). The mixture was stirred at 0 °C for 4 h and then hydrolysed with water (70 mL) and treated with a solution of sodium hydroxide (10 %, 100 mL), extracted with dichloromethane (2x50 mL), and dried on $MgSO_4$. The solvent was removed giving a residual solid as a mixture of *cis* and *trans* isomers, which were purified by column chromatography (hexane:ethyl acetate 1:1). Both *cis* and *trans* isomers **16a** and **16b** (75:25) are white solids, mp 165-7 and 125-7 °C respectively, 0.77 g, 93 %.

Compound **16a**:^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3H, CH_3-4a), 1.2-1,7 (m, 6H, -CH_2-), 2.33 (s, 3H, CH_3-Ts), 2.7-3.0 (m, 3H, CH_2-6 and H-2), 3,16 (m, 1H, H-2), 3.57 (s, 1H, H-11c), 7.2 (m, 4H, H-3′, H-5′, H-9 and H-10), 7.50 (m, 1H, H-8), 7.64 (d, 2H, J= 7,7 Hz, H-2′ and H-6′), 8.13 (m, 1H, H-11); ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3-4a), 22.0 (C-4), 22.9 (C-3), 24.9 (CH_3-Ts), 27.8 (C-5), 31.2 (C-4a), 37.7 (C-6), 46.1 (C-2), 56.6 (C-11c), 114.1 (C-11b), 114.3 (C-11), 118.2 (C-8), 119.9 (C-6a), 123.3 (C-10), 123.8 (C-2′ and C-6′), 126.2 (C-9), 129.7 (C-3′ and C-5′), 135.3 (C-11a), 136.1 (C-7a), 136.6 (C-1′), 144,5 (C-4′); IR (KBr) 1590 (ArH), 1170 (SO), 810 (ArH 1,4-disubst.), 750 (ArH 1,2-disubst.). Anal.Calcd for $C_{23}H_{26}N_2SO_2$: C, 70.02; H, 6.64; N, 7.10. Found: C, 69.87; H, 6.61; N, 6.85.

Compound **16b**:^{1}H NMR ($CDCl_3$) δ 0.76 (s, 3H, CH_3-4a), 1.2-1.9 (m, 6H, -CH_2-), 2.31 (s, 3H, CH_3-Ts), 2.3-3.0 (m, 3H, H-6), 3.0-3.3 (m, 2H, H-2), 3.70 (s, 1H, H-11c), 7.16 (d, 2H, J= 8.4 Hz, H-3′, H-5′), 7.1-7.2 (m, 2H, H-9 and H-10), 7.61 (d, 2H, J= 8.4 Hz, H-2′ and H-6′), 8.07 (d, 1H, J= 6.3 Hz, H-8), 8.13 (d, 1H, J= 7.6 Hz, H-11); IR (KBr) 1590 (ArH), 1170 (SO), 810 (ArH 1,4-disubst.), 750 (ArH 1,2-disust.); IR (KBr) 1590 (ArH); 1170 (SO); 810 (ArH 1,4-disubst.); 750 (ArH 1,2-disubst.). Anal.Calcd for $C_{23}H_{26}N_2SO_2$: C, 70.02; H, 6.64; N, 7.10. Found: C, 70.27; H, 6.41; N, 7.15.

***cis*-1-(Phenylsulfinyl)acetyl-7-(p-toluensulfonyl)-4a-methyl-1,2,3,4,4a,5,6,11c-octahydro-1*H*-pyrido-[3,2-c]carbazole (18).**

a) cis-1-(phenylthioacetyl)-4a-methyl-7-(p-toluensulfonyl)-1,2,3,4,4a,5,6,11c-octahydro-1H-pyrido-[3,2-c]-carbazole (17). In a round bottom flask under argon atmosphere were placed a solution of the N-tosylamine **16a** (444 mg, 1.12 mmol) in dichloromethane (5 mL) and at room temperature was added triethylamine (0.16 mL, 1.2 mmol), phenylthioacetyl chloride (0.16 mL, 1.2 mmol) [obtained from thiophenoxyacetic acid, 280 mg, and thionyl chloride, 0.48 mmol]. The mixture was stirred at room temperature for 18 h and then, was added dichloromethane (40 mL) and then washed successively with a hydrochloric acid solution (2N, 20 mL) and water (40 mL). The organic layer was dried on $MgSO_4$ and the solvent was removed to give a brown oil, which was purified by column chromatography (hexane:ethyl acetate 1:1). Compound **17** was isolated as a brown oil, as a conformational equilibrium (5:1, by ^1H NMR), 0.6 g, 96 %.

Compound **17**: ^1H NMR ($CDCl_3$) δ 1.04 and 1.12 (s, 3H, CH_3-4a), 1.2-2.0 (m, 6H, -CH_2-), 2.33 (s, 3H, CH_3-Ts), 2.60 (td, 1H, J= 10.7 and 3.4 Hz, H-2), 3.05 (m, 2H, H-6), 3.59 (m, 1H, H-2); 3.94 and 4.03 (two s, 2H, CH_2SPh), 4.72 and 5.62 (two s, 1H, H-11c), 7.0-7.5 (m, 9H, H-3′, H-5′, H-9, H-10 and PhS), 7.54 (m, 1H, H-8), 7.60 (d, 2H, J= 8.6 Hz, H-2′ and H-6′), 8.13 (d, 1H, J= 8.5 Hz, H-11); IR (film) 1630 (CO), 1600 (ArH), 1170 (SO), 810 (ArH 1,4-disubst.), 735 (ArH 1,2-disubst.). Anal.Calcd for $C_{31}H_{32}N_2S_2O_3$: C, 68.35; H, 5.92; N, 5.14. Found: C, 68.17; H, 6.21; N, 4.95.

b) Periodate oxidation of 17. To a solution of compound **17** (0.48 g, 0.8 mmol) in THF (15 mL) was added a solution of sodium periodate (0.8 g, 7.2 mmol) in water (20 mL). The mixture was stirred at room temperature for 48 h and then was successively added dichloromethane (40 mL) and water (40 mL). The organic layer was dried on $MgSO_4$ and then the solvent was removed giving a dark brown oil, which was purified by column chromatography (ethyl acetate:hexane 4:1). Compound **18** was isolated as a yellow oil, as a conformational equilibrium (1:1, by ^1H NMR), 356 mg, 72 %.

^1H NMR ($CDCl_3$) 0.89 and 1.17 (two s, 3H, CH_3-4a), 1.55-1.92 (m, 6H, -CH_2-), 2.32 (s, 3H, CH_3-Ts), 3.3 (m, 2H, H-6), 3.7-4.3 (m, 4H, H-2 and CH_2SO), 5.60 and 5.65 (two s br, 1H, H-11c), 7.22 (m, 5H, ArH), 7.60 (m, 6H, ArH), 7.88 (m, 2H, ArH), 8.12 (m, 1H, H-11); IR (film) 1630 (CO), 1170 (SO), 1040 (SO), 810 (ArH 1,4-disubst.), 750 (ArH 1,2-disubst.). Anal.Calcd for $C_{31}H_{32}N_2S_2O_4$: C, 66.40; H, 5.75; N, 5.00. Found: C, 66.27; H, 6.05; N, 4.85.

2,16-Didehydro-1-(p-toluensulfonyl)-20-methyl-6-thiophenylaspidospermidin-5-one (19). In a bottom flask under argon atmosphere was placed a solution of compound **18** (356 mg, 0.64 mmol) in dichloromethane (60 mL) and then was slowly added trifluoroacetic anhydride (0.2 mL). The mixture was stirred at room temperature for 25 min and then, was added chlorobenzene (60 mL) and placed at the reflux temperature for 2 h (dichloromethane was removed by distillation). Then, clorobenzene was distilled to give a dark brown oil which was purified by column chromatography (hexane:ethyl acetate 1:1). Compound **19** was isolated as a yellow oil, 240 mg (68 %) as a mixture of diastereomers (7:3).

^1H NMR ($CDCl_3$) δ 0.45 and 0.58 (two s, 3H, CH_3-19), 1.3-1.8 (m, 6H, -CH_2-), 2.19 and 2.25 (s, 3H, CH_3-Ts), 2.35 (m, 1H, H-3), 2.85 (m, 1H, H-3), 3.60 and 3.62 (two s, 1H, H-21), 4.24 (m, 1H, H-6), 6.07 and 6.32 (two dd, 1H, J=10.0 and 4.0 Hz, H-16), 7.0-7.4 (m, 10H, ArH), 7.72 (d, 2H, J= 8.1 Hz, Ts), 7.80 (d, 1H, J= 7.3 Hz, H-12); IR ($CDCl_3$) 1670 (CO), 1590 (ArH), 1170 (SO), 810 (ArH 1,4-disubst.), 740 and 730 (mono and 1,2-disubst.). Anal.Calcd for $C_{31}H_{32}N_2S_2O_3$: C, 68.48; H, 5.75; N, 5.15. Found: C, 68.17; H, 6.11; N, 4.95.

Desulfurization of 19. To a solution of compound **19** (240 mg, 0.44 mmol) in ethanol (20 mL) and DMF (1.2 mL) was added a little amount of Raney nickel. The mixture was stirred at room temperature for 1 h and then, was filtered off on celite, washed successively with ethanol (10 mL) and dichloromethane (10 mL). Finally, the solvent was removed to give a brown oil, which was purified by column chromatography (hexane:ethyl acetate 1:1). Compound **20** was isolated as a yellow oil, 160 mg, 82 %.

^1H NMR ($CDCl_3$) δ 0.60 (s, 3H, CH_3-19), 1.4-1.8 (m, 6H, -CH_2-), 2.29 (s, 3H, CH_3-Ts), 2.65 (m, 2H, H-3), 3.53 (d, 1H, J= 1.8 Hz, H-21), 4.14 (m, 2H, H-6), 6.12 (dd, J= 8.7 and 3.2 Hz, H-16), 7.0-7.3 (m, 4H, H-9, H-10, H-11), 7.13 (d, 2H, J= 8.2 Hz, Ts), 7.54 (d, 2H, J= 8.2 Hz, Ts), 7.77 (d, 1H, J= 8.0 Hz, H-12); IR (film) 1660 (CO), 1600 (ArH), 1170 (SO), 810 (ArH 1,4-disubst.), 740 (1,2-disubst.); MS (70 eV) 434 (M^+, 45), 279 (100), 251 (19), 91 (27). Anal.Calcd for $C_{25}H_{26}N_2SO_3$: C, 69.10; H, 6.03; N, 6.45. Found: C, 69.27; H, 6.25; N, 6.20.

(±)18-noraspidospermidine (1b). In a round bottom flask under argon atmosphere were placed $LiAlH_4$ (0.648 g, 13.5 mmol) in dry THF (5 mL) and then was slowly added a solution of compound **20** (120 mg, 0.27 mmol) in THF (15 mL). The mixture was stirred at room temperature for 48 h and then, was hydrolysed with water (15 mL) and treated with a solution of sodium hydroxide (15 %, 15 mL) extracted with dichloromethane (2x25 mL) and dried on $MgSO_4$. The solvent was removed affords a residual oil, which was purified by column chromatography using ethyl acetate as the eluent. Compound **1b** was isolated as a yellow oil, 35 mg, 50 %.

^1H NMR ($CDCl_3$) δ 0.73 (s, 3H, CH_3), 1.1-1.6 (m, 6H, -CH_2-), 1.7-2.1 (m, 2H, H-16), 2.28 (m, 3H, H-3 and H-21), 2.9 (s br, 1H, NH), 3.15 (m, 2H, H-5), 3.51 (dd, 1H, J= 6.2 and 10.9 Hz, H-2), 6.64 (d, 1H, J=

7.8 Hz, H-12), 6.72 (td, 1H, J= 7.5 and 1.0 Hz, H-10), 7.02 (td, 1H, J= 7.5 and 1.4 Hz, H-11), 7.06 (d, 1H, J= 7.5 Hz, H-9); ^{13}C RMN ($CDCl_3$) δ 21.7 (C-19), 26.7 (C-15), 28.4 (C-17), 29.7 (C-14), 33.0 (C-6), 38.0 (C-16), 39.0 (C-20), 52.7 (C-3), 53.2 (C-7), 53.8 (C-5), 65.1 (C-2), 71.3 (C-21), 110.4 (C-12), 119.1 (C-10), 122.7 (C-9), 127.2 (C-11), 135.4 (C-8), 149.5 (C-13); MS (70 eV) m/z 268 (M^+, 29), 240 (20), 143 (7), 130 (11), 110 (100); IR (film) 3340 (br NH), 1600 (ArH), 745 (ArH 1,2-disubst.). Anal.Calcd for $C_{18}H_{24}N_2$: C, 80.54; H, 9.01; N, 10.44. Found: C, 80.37; H, 9.19; N, 10.35.

ACKNOWLEDGEMENT

This work was supported by the DGICYT PB92-0142-C02-01 and in part by the DGICYT PB97-0060.

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