# SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS, PART LXXXIX. SOME UNEXPECTED REACTIONS OF COMPOUNDS CONTAINING THE D-SECO-ASPIDOSPERMANE RING SYSTEM

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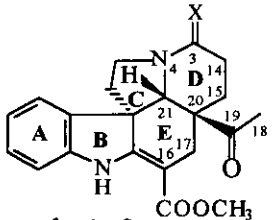
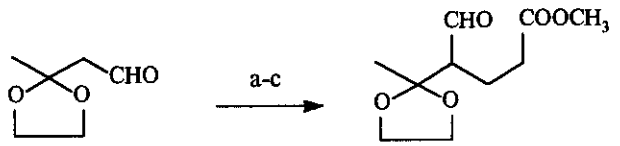
**Abstract** - Interaction of the tryptamine derivative (**3**) with the formyl ester (**4**) gave (±)-20-deethyl-2,16-didehydro-14,16-bis(methoxycarbonyl)-3-phenyl-3,14-seco-20-epiaspidospermidine (**7**) instead of the expected acetal (**6**). The product of the reaction of **3** with the acetoacetic aldehyde derivative (**5**) was ethylene acetal of (±)-2,16-didehydro-16-methoxycarbonyl-3-phenyl-14,15-dinoraspido-spermidin-19-one (**8**), it was readily convertible into the reactive intermediate (**10**). Further build-up starting from secondary amine (**11**) gave the N(4)-substituted derivatives, while **10** afforded products with unexpected structures. The reaction of **10** with acetic anhydride yielded different products depending on the reaction conditions.

A few years ago we reported a convergent synthetic strategy that resulted in the successful synthesis of a number of alkaloids with the aspidospermane-[1] and pseudoaspidospermane[2] ring systems, and of other alkaloid-like compounds.[3,4] In this paper we describe the application of the same strategy with the aim of synthesizing 3-oxominovincine (**1**),[5] a compound isolated from *Tabernaemontana riedelii* (Scheme 1). The total synthesis of this molecule is unknown; the semi-synthesis was achieved by *Cava et al.*[5] starting from minovincine (**2**). We intended to effect the construction of the target alkaloid (**1**) by the interaction of a component possessing the indole ring system (**3**)[1] with the formyl ester (**4**). The latter compound is known from the literature,[6] yet we found a simpler way for its preparation (Scheme 2).




**1:** X = O
**2:** X = $H_2$

Scheme 1

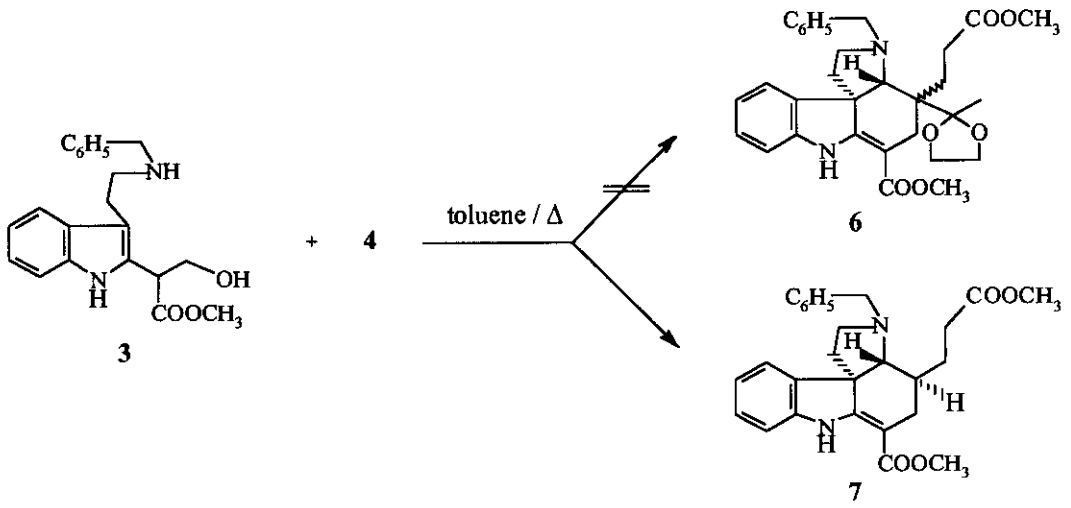



5 4

Conditions: a.) $(CH_2CH_2)_2NH$, $K_2CO_3$ / rt
b.) $CH_2$=CH-$COOCH_3$, $CH_3CN$ / Δ, c.) $CH_3COOH$, $H_2O$ / Δ

Scheme 2

The reaction of **3** with **4** in boiling toluene did not give the expected **6**; the product was **7**, a compound known from our earlier work[3] (Scheme 3).

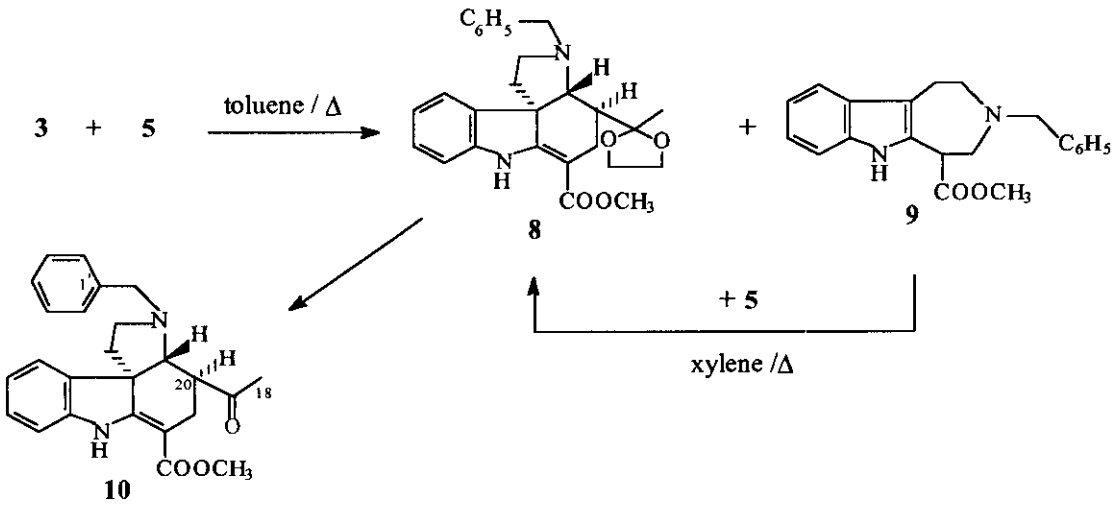



Scheme 3

Splitting of the carbon-carbon bond (retro-Claisen reaction), which occurred in this case, has been reported in the literature for a similar compound,[7] thus the result cannot be considered to be totally unexpected.

In view of this experience the strategy was altered by choosing the acetoacetic aldehyde derivative (**5**)[8] to be the reaction partner of **3**. Under the above conditions the reaction gave the tetracyclic compound (**8**)[9] in a moderate yield. The azepine derivative (**9**)[10] was also isolated from the reaction mixture, and its reaction with **5** in boiling xylene also gave **8**[9] (Scheme 4).

The hydrolysis of the acetal (**8**) was effected in several ways (see Table 1) to obtain the ketone (**10**).[7,9] Catalytic debenzylation of **10** (10 % Pd / C / AcOH, room temperature) led to the secondary amine (**11**)[7] that contains two reactive centers (N4 and C20) for the possible build-up of the aspidospermane ring system. First the N(4) acylation of **11** was effected with 3-chloropropionyl chloride (→**12**), then intramolecular alkylation was attempted to construct ring D of the molecule.[7] The first step was

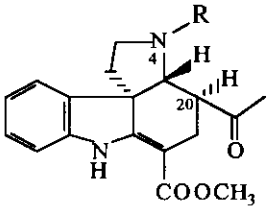



Scheme 4

Table 1. Hydrolysis of 0.1 g (0.224 mmol) of the acetal (**8**) under various conditions to produce the ketone (**10**)

| Reagent | Solvent | Temperature [°C] | Reaction time [h] | Yield [%] |
|---|---|---|---|---|
| Acetic acid (96 %, 5 ml) | Water (5 ml) | 85 | 17 | 7.4 |
| Formic acid (85 %, 5 ml) | Water (5 ml) | 25 | 24 | 25.5 |
| *p*-Toluenesulfonic acid (0.3 g) | Acetone (5 ml) | 25 | 96 | 37.7 |
| Hydrochloric acid (37 %, 5 ml) | THF (5 ml) | 25 | 1.25 | 51.8 |
| Hydrochloric acid (1.0 M, 2 ml) | THF (5 ml) | 55 | 24 | 61.6 |
| Perchloric acid (70 %, 5 ml) | Dichloromethane (5 ml) | 25 | 6 | 64.9 |
| Sulfuric acid (95-98 %, 4 mg) | Acetone (5 ml) | 56 | 24 | 66.3 |

realized in 65% yield, but the expected cyclization did not take place. Compound (**12**) in the presence of bases of different strengths (such as $K_2CO_3$, $CH_3ONa$, NaH, $KOtC_4H_9$, $LiN(iC_3H_7)_2$) gave only one single product (**13**). The cyclization of the isolated **13** also failed in the presence of various bases, in spite of the fact that the acrylamide structural unit readily reacted even with poor nucleophilic reagents (e. g. with methanol at room temperature) to give **14** (Scheme 5).

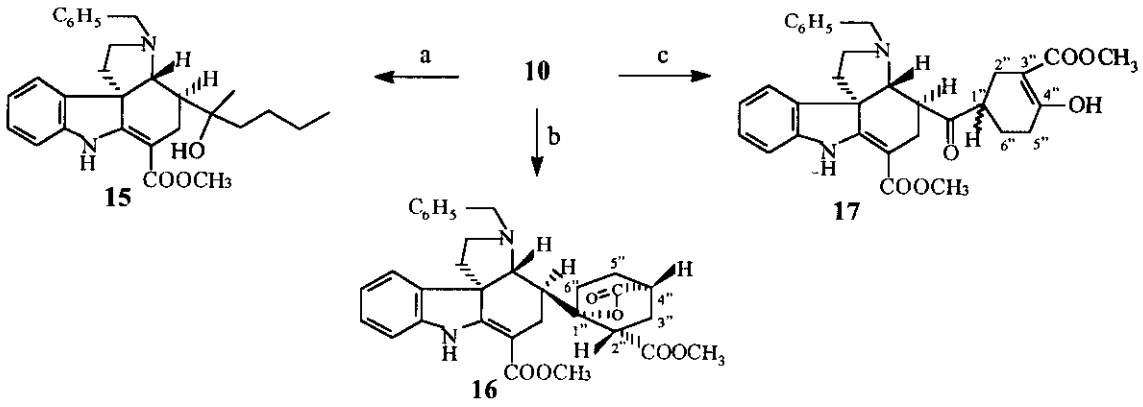


**11**: R = H
**12**: R = $COCH_2CH_2Cl$
**13**: R = $COCH{=}CH_2$
**14**: R = $COCH_2CH_2OCH_3$

Scheme 5

After the failure of these intramolecular alkylation reactions, which were designed to complete the construction of the aspidospermane ring system, we tried to introduce the methoxycarbonylethyl substituent into position 20 of tertiary amine (**10**); removal of the N(4)-benzyl protecting group and

subsequent cyclization would then yield the target molecule (**1**). The first attempt was made with methyl acrylate as the reaction partner in the presence of bases of various strengths. Triethylamine, Triton-B, Hünig's base [$(iC_3H_7)_2NC_2H_5$] and DBU failed in producing any conversion; $nC_4H_9Li$, $LiN(iC_3H_7)_2$ and $NaNH_2$ elicited certain reactions, but the products - although exhibiting interesting structures - did not contain the expected ring system. When $nC_4H_9Li$ was used, methyl acrylate did not react with **10** as expected, only the nucleophilic addition of the base to the carbonyl group took place (**15**). In the presence of $LiN(iC_3H_7)_2$ two molecules of methyl acrylate reacted to give the product (**16**). The structure of **16** was disclosed by NMR experiments. The $^1H$ and $^{13}C$ NMR data showed that the four-ring system remained unchanged, while the substituent at C20 altered. The $^1H$-$^1H$ connections and $^{13}C$-$^1H$ direct and long-range correlations revealed the structure of the substituent. The NOE effects (see Experimental) observed between the protons of the tetracyclic moiety and those of the substituent at C-20 are consistent with the relative stereochemistry portrayed in Scheme 6.




Conditions: a.) $CH_2$=$CHCOOCH_3$, $nC_4H_9Li$, THF / - 78 °C → rt b.) $CH_2$=$CHCOOCH_3$, $LiN(iC_3H_7)_2$, THF / - 78 °C → rt
c.) $CH_2$=$CHCOOCH_3$, $NaNH_2$, THF / rt

Scheme 6

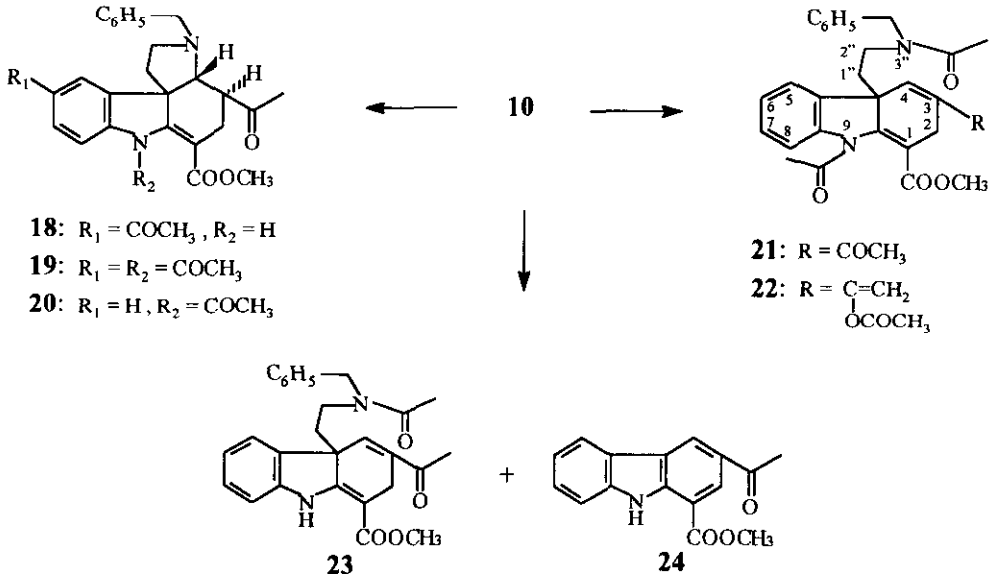
We assume that the process starts with the electrophilic alkylation of the kinetic enol form of the carbonyl group in the side chain of **10**, and this is followed by reaction with a second molecule of methyl acrylate and subsequent cyclization with concomitant lactonization to give the stereohomogeneous final product. That can be, of course, only one of the several possible reaction pathways.

Using sodium amide, the interaction of **10** with two molecules of methyl acrylate took a different course; after double C18 alkylation and subsequent Dieckmann condensation the products were stabilized in the enol form (**17**), consisting of a mixture of epimers, which were separated by chromatography (isomers A and B); however, their unambiguous structural assignments cannot be given. The proton and carbon spectral data indicated the absence of the acetyl methyl group and the formation of a disubstituted cyclohexene ring attached to the C19 carbonyl carbon in both isomers of **17**. The long-range correlation between the methine proton of the cyclohexene ring and the C20 carbon established the structure (**17**) as

depicted in Scheme 6. Moreover, the spatial proximity of the methine proton with the 20-H, 21-H and 17-$H_\beta$ protons, revealed by NOE effects, corroborated this structure for both epimers.

The results described above clearly showed that some other approach had to be found to effect the desired alkylation at C20. It is known from the literature that of the two enol isomers, the proportion of the thermodynamically more stable enol is the highest in the form of the enol acetates.[11] In trying to utilize this experimental fact, we attempted the preparation of the enol acetate of **10**, with the intention of reacting it with methyl acrylate.

The reaction of **10** with acetic anhydride, catalyzed by 70 % aqueous perchloric acid,[11] gave, even at room temperature, **18** and **19** in a ratio 3:1, instead of the expected product. When the catalyst was *p*-toluenesulfonic acid,[12] the reaction followed another course; and at ambient temperature **20** was obtained, whereas at the boiling point of acetic anhydride cleavage of the C-ring resulted in the carbazole derivatives (**21**) and (**22**) in a ratio of 7:1. In view of the unexpected reactions described above, we tried to effect the reaction with acetic anhydride alone and in the absence of catalyst. Compound (**10**) suffered a profound change in this case too. At room temperature **23** was produced, while at the boiling point of the reagent[14] the conversion resulted in **23** and **24**,[13] their ratio being 6:1.




Scheme 7

The structures of the reaction products (**21**, **22** and **23**) were defined by their completely assigned $^1H$ and $^{13}C$ NMR spectra. Comparison of the spectra of these compounds with those of **10** revealed the presence of an olefinic bond instead of the methine groups in these molecules. The NOE effect measured between the olefinic proton and 5-H as well as long-range correlation of the olefinic proton with the C4a, C9a and C2 carbons verified the 4-H position of the olefinic proton in molecules (**21**, **22** and **23**). All these pieces of evidence corroborated the cleavage of the C-ring. The number and location of the acetyl groups were

readily derived from the spectra of the molecules. Due to hindered rotation about the N(3")-CO bond these derivatives appeared as mixtures of rotamers in deuterochloroform solution. The $^{13}C$ and $^{1}H$ NMR spectra of **24** revealed the absence of the C4a substituent and the existence of the fully aromatized three-ring system illustrated in Scheme 7.

The above described experimental facts have unequivocally shown that 3-oxominovincine (**1**) cannot be synthesized in the ways attempted, and a new approach is to be found.

## EXPERIMENTAL

Melting points (uncorrected): Hotstage microscope Boetius. - IR spectra: Specord JR-75 Spectrophotomether. -$^{1}H$ and $^{13}C$ NMR spectra: Varian VXL-400. The assignments noted with $^{x}$ and $^{+}$ may be interchanged. Chemical shifts (in ppm) are relative to $Me_4Si$. Mutual $^{1}H$-$^{1}H$ couplings are given only once, at their first occurrance.- Mass spectra: JEOL-01-SG-2. - Column chromatography: Merck Kieselgel 60 (0.063-0.200 mm). - Preparative thin-layer chromatography: Silica gel plates F254 (Merck). - The organic layers were dried with $MgSO_4$.

**(±)-Methyl 4-(2-Methyl-1,3-dioxolan-2-yl)-4-formylbutanoate (4):** To a cooled (0 °C) suspension of $K_2CO_3$ (20 g, 0.145 mol) in 30 mL of pyrrolidine was added dropwise 10 g (0.077 mol) of 2-formyl-methyl-2-methyl-1,3-dioxolane (**5**)[8] and was stirred at rt for 12 h. After filtration of inorganic salts pyrrolidine was removed from the filtrate in vacuo (0.4 Torr) in a 50 °C oil bath. The residue was dissolved in acetonitrile (50 mL) and to the solution 9 mL (0.1 mol) of methyl acrylate was added. After refluxing for 24 h to the reaction mixture 5 mL of acetic acid and 10 mL of water were added and the mixture was refluxed for 5 h. The cooled mixture was diluted with water (100 mL) and was extracted three times with $CH_2Cl_2$ (20 mL each), the extracts were dried and concentrated in vacuo. The residue was distilled to afford **4** (3.8 g, 23 %) as a colorless liquid, bp 120-130 °C (0.1 Torr). **IR** (film) $\nu_{max}$ 1740, 1732, 1685, 1420, 1374 $cm^{-1}$; **$^{1}H$ NMR** ($CDCl_3$) δ: 1.32 (3H, s, $CH_3$); 1.92 + 2.05 (2 x 1H, 2 x dddd, $J_{gem}$ = 14.0, $J_{2,3}$ = 7.2 + 8.5 and 6.2 + 8.1, $J_{3,4}$ = 3.8 and 9.6 Hz, respectively, 3-$H_2$); 2.32 + 2.41 (2 x 1H, 2 x ddd, $J_{gem}$ = 16.4 Hz, 2-$H_2$); 2.65 (1H, ddd, $J_{CHO}$ = 2.5 Hz, 4-H); 3.67 (3H, s, $OCH_3$); 3.9-4.06 (4H, m, $OCH_2CH_2O$); 9.73 (1H, d, CHO). **$^{13}C$ NMR** ($CDCl_3$) δ: 19.78 (C3), 22.44 ($CH_3$), 31.63 (C2), 51.55 ($OCH_3$), 58.95 (C4), 64.57 + 64.78 ($O\underline{C}H_2\underline{C}H_2O$), 109.39 ($CH_3\underline{C}$), 173.38 ($\underline{C}OOCH_3$), 202.58 (CHO).

**(±)-20-Deethyl-2,16-didehydro-14,16-bis(methoxycarbonyl)-3-phenyl-3,14-seco-20-epiaspidosper-midine (7):** A solution of 1 g (2.84 mmol) of **3**[1] and 1 g (4.63 mmol) of **4** in 100 mL of anhydrous toluene was refluxed under argon for 24 h. The reaction mixture was extracted twice with brine (40 mL each), and the combined aqueous layers were extracted twice with $CH_2Cl_2$ (40 mL each). The combined organic extracts were dried and the solvent was evaporated in vacuo. The residue was purified by column chromatography (eluent: ether / hexane, 1:1) to yield 0.354 g (28 %) of **7**, which has been previously synthesized in our laboratory by an another way.[3]

**Ethylene Acetal of (±)-2,16-Didehydro-16-methoxycarbonyl-3-phenyl-14,15-dinoraspidospermidin-19-one (8):** A solution of 1 g (2.84 mmol) of **3** and 0.55 g (4.23 mmol) of 2-formylmethyl-2-methyl-1,3-dioxolane (**5**) in 100 mL of anhydrous toluene was refluxed under argon for 24 h. The cooled reaction mixture was worked up as described in the case of **7**. The two main components were separated by preparative TLC (eluent: hexane / acetone, 5:1). The more polar compound (**8**) ($R_f$ = 0.36) was obtained as colorless crystals after crystallization from methanol (94 mg, 7.4 %) mp 144-145 °C (lit.,[9] 144-145 °C). Its spectral data ($^1$H and $^{13}$C NMR, IR, MS) were identical to those of a previously described in the literature.[9]

The less polar compound (**9**)[1] ($R_f$ = 0.26, 161 mg,17 %) was converted into the **8** in the presence of **5** by heating in xylene for 4 h (156 mg, 73 %).[9]

**(±)-2,16-Didehydro-16-methoxycarbonyl-3-phenyl-14,15-dinoraspidospermidin-19-one (10):** To a solution of 100 mg (0.22 mmol) of **8** in 10 mL of acetone was added one drop of concd $H_2SO_4$ and after 12 h reflux the mixture was stirred at rt for 12 h. The solution was poured into 50 mL ice-water and the mixture neutralized with a saturated $Na_2CO_3$ solution. The mixture was extracted three times with $CH_2Cl_2$ (10 mL each), the combined organic layers were dried and concentrated in vacuo. The residue was purified by thinlayer chromatography (eluent: hexane / acetone, 5:1) to yield a yellow oil ($R_f$ = 0.28), which was crystallized from methanol to afford **10** (59 mg, 66 %) as colorless crystals: mp 141-142 °C (lit.,[7] 141-142 °C). **IR** (KBr) $\nu_{max}$ 3434, 1695, 1670, 1632, 1600 cm$^{-1}$; **$^1$H NMR** ($CDCl_3$) δ: 1.72 + 2.00 (2 x 1H, 2 x ddd, $J_{gem}$ = 11.6, $J_{5,6}$ = 4.6 + <1 and 12.2 + 6.3 Hz, respectively, 6-$H_2$); 1.98 (3H, s, 18-$H_3$); 2.69 (1H, ddd, $J_{17,20}$ = 4.2 + 2.7, $J_{20,21}$ ~ 1 Hz, 20-H); 2.73 + 2.98 (2 x 1H, 2 x ddd, $J_{gem}$ = 9.0 Hz, 5-$H_2$); 2.74 + 3.18 (2 x 1H, 2 x dd, $J_{gem}$ = 14.9 Hz, 17-$H_2$); 3.72 (1H, br dd, $J_{17B,21}$ = 1.8 Hz, 21-H); 3.76 (3H, s, $OCH_3$); 3.81 + 4.00 (2 x 1H, 2 x d, $J_{gem}$ = 13.0 Hz, C$\underline{H}_2$C$_6$H$_5$); 6.80 (1H, d, 12-H); 6.90 (1H, dd, 10-H); 7.11 (1H, d, 9-H); 7.15 (1H, dd, 11-H); 7.25-7.4 (5H, m, $C_6H_5$); 8.79 (1H, br s, NH). **$^{13}$C NMR** ($CDCl_3$) δ: 21.57 (C17), 28.01 (C18), 41.93 (C6), 51.04 (C5 + $OCH_3$), 53.10 (C20), 55.89 (C7), 58.77 (C$\underline{H}_2$C$_6$H$_5$), 66.51 (C21), 89.24 (C16), 109.36 (C12), 120.94 (C10), 122.01 (C9), 127.18 (C4'), 127.72 (C11), 128.38 + 128.91 (C2' + C3' + C5' + C6'), 137.49 (C8), 138.84 (C1'), 142.64 (C13), 166.15 (C2), 167.99 (C$\underline{O}$OOCH$_3$), 209.75 (C19). **MS**: m/z (int %) 402 (6.0) [$M^+$], 359 (2.0), 269 (20.0), 227 (20.0), 214 (14.0), 188 (20.0), 167 (10.0), 91 (100.0), 43 (16.0).

**(±)-15-Chloro-2,16-didehydro-16-methoxycarbonyl-15,20-secoaspidospermidin-3,19-dione (12):** To a solution of **11**[7] (1 g, 3.21 mmol) and 0.45 mL (324 mg, 3.21 mmol) of triethylamine in anhydrous $CH_2Cl_2$ (20 mL) at 0 °C was added dropwise 3-chloropropionyl chloride (441 mg, 0.33 mL, 3.5 mmol). After stirring at rt for 30 min water was added and the aqueous phase was extracted three times with $CH_2Cl_2$. The combined organic layers were dried and the solvent was evaporated in vacuo. The residue was purified by thinlayer chromatography (eluent: dichloromethane / methanol, 20:1) to yield a yellow oil ($R_f$= 0.50), which was crystallized from methanol to afford **12** (840 mg, 65 %) as colorless crystals: mp 154-156 °C. **IR** (KBr) $\nu_{max}$ 3330, 1710, 1682, 1630, 1607 cm$^{-1}$; **$^1$H NMR** *major rotamer* ($CDCl_3$) δ: 1.97m + 2.37m (2 x 1H, 6-$H_2$); 2.16 (3H, s, 18-$H_3$); 2.49 + 3.20 (2 x 1H, 2 x dd, $J_{gem}$ = 16.0, $J_{17,20}$ = 5.4

and 2.5 Hz, respectively, 17-$H_2$); 2.90 (2H, m, CO-C$\underline{H}_2$); 3.28 (1H, ddd, $J_{20,21}$ = 0.8 Hz, 20-H); 3.76 (3H, s, $OCH_3$); 3.75-3.87 (2H, m, 5-$H_2$); 3.91 (2H, m, C$\underline{H}_2$Cl); 4.88 (1H, br s, 21-H); 6.84 (1H, d, 12-H); 6.91 (1H, dd, 10-H); 7.13 (1H, d, 9-H); 7.19 (1H, dd, 11-H); 8.87 (1H, br s, N1-H).[13]**C NMR** *major rotamer* ($CDCl_3$) δ: 21.96 (C17), 27.89 (C18), 38.04[x] (CO$\underline{C}H_2$), 38.22 (C5), 39.96[x] ($\underline{C}H_2$Cl), 45.68 (C6), 51.04 ($OCH_3$), 51.20 (C20), 54.17 (C7), 61.45 (C21), 89.47 (C16), 109.73 (C12), 121.36[+] (C10), 121.67[+] (C9), 128.56 (C11), 135.05 (C8), 142.91 (C13), 162.37 (C2), 167.77 ($\underline{C}OOCH_3$), 169.23 (N$\underline{C}$O), 207.64 (C19). **MS:** m/z (int%) 404 (12.0) [M+2[+]], 402 (36.0) [M[+]], 366 (9.0) [M-HCl[+]], 268 (34.0), 227 (51.0), $\underline{214}$ (100.0), 195 (84.0), 182 (31.0), 167 (53.0), 153 (58.0), 98 (15.0), 54 (19.0), 41 (41.0); **Anal.** Calcd for $C_{21}H_{23}N_2O_4Cl$ C 62.67, H 5.76, N 6.96, Cl 8.70. Found C 62.54, H 5.83, N 6.93, Cl 9.17.

**(±)-2,14,15,16-Tetradehydro-16-methoxycarbonyl-15,20-secoaspidospermidin-3,19-dione (13):** To a stirred solution of sodium hydride (60 % in mineral oil, 0.110 g, 2.83 mmol, washed with dry ether before use) in THF (20 mL) was added, under nitrogen, a solution of **12** (1 g, 2.48 mmol) in THF (20 mL). The resulting mixture was stirred for 2 h. After cooling, water (50 mL) was added and the aqueous phase was extracted with $CH_2Cl_2$. The organic layer was washed with water, dried and concentrated in vacuo. The residue was purified by thinlayer chromatography (eluent: dichloromethane / methanol, 20:1) to yield a yellow oil ($R_f$ = 0.47), which was crystallized from ether to afford **13** (471 mg, 52 %) as colorless crystals: mp 160-161 °C. **IR** (KBr) $\nu_{max}$ 3325, 1712, 1683, 1640, 1610 $cm^{-1}$; **$^1$H NMR** *major rotamer* ($CDCl_3$) δ: 1.98m + 2.38m (2 x 1H, 6-$H_2$); 2.18 (3H, s, 18-$H_3$); 2.50 + 3.20 (2 x 1H, 2 x dd, $J_{gem}$ = 16.0, $J_{17,20}$ = 5.4 and 2.5 Hz, respectively, 17-$H_2$); 3.35 (1H, ddd, $J_{20,21}$ ~ 1 Hz, 20-H); 3.76 (3H, s, $OCH_3$); 3.8-4.0 (2H, m, 5-$H_2$); 4.92 (1H, br s, 21-H); 5.80 + 6.48 (2 x 1H, 2 x dd, $J_{gem}$ = 2.3, $J_{vic}$ = 10.0 and 16.5 Hz, respectively, =$CH_2$); 6.58 (1H, dd, C$\underline{H}$=$CH_2$); 6.85 (1H, d, 12-H); 6.91 (1H, dd, 10-H); 7.12 (1H, d, 9-H); 7.19 (1H, dd, 11-H); 8.88 (1H, br s, N1-H). **$^{13}$C NMR** *major rotamer* ($CDCl_3$) δ: 21.91 (C17), 27.82 (C18), 38.29 (C5), 45.35 (C6), 50.94 ($OCH_3$), 51.12 (C20), 54.10 (C7), 61.59 (C21), 89.51 (C16), 109.68 (C12), 121.28[x] (C1), 121.64[x] (C9), 128.29 (CO-$\underline{C}$H=), 128.49 (C11), 128.78 (=$CH_2$), 135.14 (C8), 142.93 (C13), 162.44 (C2), 165.04 (NCO), 167.79 ($\underline{C}OOCH_3$), 207.75 (C19). **MS:** m/z (int %) 366 (37.0) [M[+]], 335 (5.0), 323 (8.0), 268 (24.0), 227 (33.0), 214 (61.0), 195 (65.0), 182 (29.0), 167 (58.0), 153 (76.0), 127 (17.0), 98 (34.0), $\underline{54}$ (100.0), 41 (45.0); **Anal.** Calcd for $C_{21}H_{22}N_2O_4$ C 68.82, H 6.06, N 7.65. Found C 68.72, H 6.30, N 7.51.

**(±)-2,16-Didehydro-15-methoxy-16-methoxycarbonyl-15,20-secoaspidospermidin-3,19-dione (14):** To a solution of 100 mg (0.27 mmol) of **13** in 10 mL of anhydrous methanol was added 200 mg (1.44 mmol) of $K_2CO_3$. The suspension was stirred for 72 h at rt and filtered. The filtrate was concentrated in vacuo and the residue was purified by preparative TLC (eluent: dichloromethane / methanol, 20:1) to yield 74 mg (68 %) of **14** as a yellow oil ($R_f$ = 0.44). **IR** (film) $\nu_{max}$ 3400, 1718, 1680, 1650, 1617 $cm^{-1}$; **$^1$H NMR** *major rotamer* ($CDCl_3$) δ: 1.94m + 2.35m (2 x 1H, 6-$H_2$); 2.16 (3H, s, 18-$H_3$); 2.49 + 3.18 (2 x 1H, 2 x dd, $J_{gem}$ = 16.0, $J_{17,20}$ = 5.4 and 2.5 Hz, respectively, 17-$H_2$); 2.63 + 2.74 (2 x 1H, 2 x dt, $J_{gem}$ = 15.4, $J_{vic}$ = 5.8 and 6.6 Hz, respectively, CO-$CH_2$); 3.27 (1H, ddd, $J_{20,21}$ = 0.9 Hz, 20-H); 3.42 (3H, s, $OCH_3$); 3.76 (3H, s, $COOC\underline{H}_3$); 3.75-3.9 (4H, m, 5-$H_2$ + C$\underline{H}_2OCH_3$); 4.84 (1H, br s, 21-H); 6.84 (1H, d,

12-H); 6.90 (1H, dd, 10-H); 7.15 (1H, d, 9-H); 7.18 (1H, dd, 11-H); 8.88 (1H, br s, N1-H). **$^{13}$C NMR** *major rotamer* ($CDCl_3$) δ: 21.96 (C17), 27.90 (C18), 35.36 ($CO\underline{C}H_2$), 38.14 (C5), 45.66 (C6), 51.15 ($COO\underline{C}H_3$ + C20), 54.23 (C7), 59.00 ($OCH_3$), 61.37 (C21), 68.69 ($\underline{C}H_2OCH_3$), 89.54 (C16), 109.66 (C12), 121.29[x] (C10), 121.76[x] (C9), 128.46 (C11), 135.28 (C8), 142.97 (C13), 162.46 (C2), 167.84 ($\underline{C}OOCH_3$), 170.79 (NCO), 207.87 (C19). **MS:** m/z (int%) 398 (31.0) [$M^+$], 367 (5.0), 355 (12.0), 269 (15.0), 227 (41.0), 214 (59.0), 195 (70.0), 182 (28.0), 167 (58.0), 153 (62.0),130 (29.0), 116 (19.0), 100 (27.0), 44 (100.0).

**(±)-19-n-Butyl-2,16-didehydro-16-methoxycarbonyl-3-phenyl-14,15-dinoraspidospermidin-19-ol (15):** A solution of **10** (100 mg, 0.25 mmol) in dry THF (5 mL) was cooled to -78 °C, and n-$C_4H_9Li$ (0.25 mL of a 2.05 M solution in hexane, 0.50 mmol) was added. After 30 min at -78 °C, methyl acrylate (0.05 mL, 0.55 mmol) was added and the resulting solution was stirred at -78 °C for 1 h. The reaction mixture was allowed to warm to 20 °C, stirred at 20 °C for 1 h, and 0.2 mL of water was added dropwise. The solvent was evaporated in vacuo, the residue was dissolved in a mixture of 10 mL of $CH_2Cl_2$ and 10 mL of water, the organic layer was dried and concentrated in vacuo. The residue was purified by thinlayer chromatography (eluent: hexane / acetone, 2:1) to yield a yellow oil ($R_f$ = 0.59), which was crystallized from methanol to afford **15** (98 mg, 86 %) as colorless crystals: mp 113-114 °C. **IR** (KBr) $\nu_{max}$ 3490, 3435, 1665, 1632, 1600 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$) δ: 0.61 (3H, s, 18-$H_3$); 0.90 (3H, t, J = 6.9 Hz, $CH_2C\underline{H}_3$); 1.15-1.53 (6H, m, $(CH_2)_3$); 1.61 (1H, br s, OH); 1.68 + 2.08 (2 x 1H, 2 x ddd, $J_{gem}$ = 11.6, $J_{5,6}$ = 4.6 + <1 and 6.3 + 12.0 Hz, respectively, 6-$H_2$); 1.93 (1H, dd, 20-H); 2.55 + 2.82 (2 x 1H, 2 x dd, $J_{gem}$ = 15.6, $J_{17,20}$ = 4.5 and 2.5 Hz, respectively, 17-$H_2$); 2.71 + 2.93 (2 x 1H, 2 x ddd, $J_{gem}$ = 9.0 Hz, 5-$H_2$); 3.48 (1H, br d, $J_{17B,21}$ = 1.9 Hz, 21-H); 3.79 (3H, s, $OCH_3$); 3.81 + 4.18 (2 x 1H, 2 x d, $J_{gem}$ = 13.4 Hz, $C\underline{H}_2C_6H_5$); 6.79 (1H, d, 12-H); 6.81 (1H, dd, 10-H); 6.92 (1H, d, 9-H); 7.12 (1H, dd, 11-H); 7.25-7.46 (5H, m, $C_6H_5$); 8.94 (1H, br s, N1-H). **$^{13}$C NMR** ($CDCl_3$) δ: 14.01 ($CH_2\underline{C}H_3$), 20.27 (C17), 23.19 ($\underline{C}H_2CH_3$), 25.19 ($\underline{C}H_2CH_2CH_3$), 26.81 (C18), 41.43[x] (C19-$\underline{C}H_2$), 41.49[x] (C6), 48.69 (C20), 49.92 (C5), 50.98 ($OCH_3$), 56.01 (C7), 57.34 ($\underline{C}H_2C_6H_5$), 66.85 (C21), 73.99 (C19), 90.57 (C16), 109.04 (C12), 120.64 (C10), 122.38 (C9), 126.99 (C4'), 127.73 (C11), 128.25 + 129.12 (C2' + C3' + C5' + C6'), 137.59 (C8), 138.94 (C1'), 142.97 (C13), 165. 84 (C2), 168.50 ($\underline{C}OOCH_3$). **MS:** m/z (int%) 460 (10.0) [$M^+$], 403 (18.0), 332 (9.0), 246 (100.0), 227 (14.0), 214 (59.0), 194 (10.0), 167 (19.0), 153 (14.0), 134 (13.0), 91 (86.0), 41 (16.0); **Anal.** Calcd for $C_{29}H_{36}N_2O_3$ C 75.61, H 7.88, N 6.08. Found C 75.42, H 8.10, N 6.09.

**Lactone (16):** To a magnetically stirred solution of 5.0 mmol of lithium diisopropylamide (from 0.76 mL of $HN(iC_3H_7)_2$ and 2.45 mL of 2.05 M n-$C_4H_9Li$ in hexane at -78 °C) in 10 mL of freshly distilled THF under nitrogen at -78 °C was added a solution of 1 g (2.48 mmol) of **10** in 10 mL of freshly distilled THF. After stirring the reaction mixture for 10 min, a solution of 0.45 mL (430 mg, 5 mmol) of methyl acrylate in 3 mL THF was added dropwise. The mixture was warmed to 20 °C over a 30 min period and after stirring for 2 h was poured into 20 mL of water and 20 mL of $CH_2Cl_2$. The organic layer was washed with water, dried and concentrated in vacuo. The residue was purified by thinlayer

chromatography (eluent: hexane / acetone, 2:1) to yield a yellow oil ($R_f$ = 0.40), which was crystallized from methanol to afford **16** (17 mg, 13 %) as colorless crystals: mp 135-136 °C. **IR** (KBr) $\nu_{max}$ 3430, 1760, 1735, 1689, 1650, 1615 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$) δ: 0.71m + 1.17m (2 x 1H, 6"-$H_2$); 1.58 (2H, m, 5"-$H_2$); 1.66 + 2.07 (2 x 1H, 2 x ddd, $J_{gem}$ = 11.5, $J_{5,6}$ = 4.6 + <1 and 6.3 + 12.0 Hz, respectively, 6-$H_2$); 1.95 + 2.23 (2 x 1H, 2 x ddd, $J_{gem}$ = 13.4, $J_{3",4"}$ = 2.2 and 3.5, $J_{2",3"}$ = 10.5 and 3.7 Hz, respectively, 3"-$H_2$); 2.31 (1H, ddd, $J_{17,20}$ = 5.2 + 2.2, $J_{20,21}$ <1Hz, 20-H); 2.61 (1H, m, 4"-H); 2.65 + 3.17 (2 x 1H, 2 x dd, $J_{gem}$ = 16.5 Hz, 17-$H_2$); 2.74 + 2.89 (2 x 1H, 2 x ddd, $J_{gem}$ = 9.0 Hz, 5-$H_2$); 3.04 (1H, dd, 2"-H); 3.53 (1H, br d, $J_{17B,21}$ = 1.8 Hz, 21-H); 3.76 (3H, s, 2"-$COOCH_3$); 3.84 (3H, s, 16-$COOCH_3$); 3.84 + 4.22 (2 x 1H, 2 x d, $J_{gem}$ = 13.5 Hz, $C\underline{H}_2C_6H_5$); 6.74 (1H, br d, $J_{9,10}$ = 7.5 Hz, 9-H); 6.80 (1H, d, $J_{11,12}$ = 7.6 Hz, 12-H); 6.81 (1H, ddd, $J_{10,12}$ = 1.0 Hz, 10-H); 7.14 (1H, ddd, $J_{10,11}$ = 7.5, $J_{9,11}$ = 1.3 Hz, 11-H); 7.25-7.45 (5H, m, $C_6H_5$); 8.92 (1H, br s, N1-H);

NOE: 2.31(20-H) → 3.53 (21-H); 2.65 + 3.17 (17-$H_2$); 4.22 + 3.84 ($C\underline{H}_2C_6H_5$); 3.04 (2"-H); 3.76 (2"-$COOCH_3$); 7.42 (2'-H + 6'-H); 3.04 (2"-H) → 1.95 (3"-$H_A$); 3.17 (17-$H_B$); 2.31 (20-H); 1.17 (6"-$H_B$); 0.71 (6"-$H_A$) → 1.17 (6"-$H_B$); 1.58 (5"-$H_2$); 3.53 (21-H); **$^{13}$C NMR** ($CDCl_3$) δ: 19.52 (C17), 23.87 (C5"), 28.22 (C3"), 28.98 (C6"), 34.35 (C4"), 41.22 (C6), 44.69 (C2"), 46.13 (C20), 48.98 (C5), 51.38 (16-$COO\underline{C}H_3$), 52.24 (2"-$COO\underline{C}H_3$), 55.54 (C7), 56.28 (N4-$\underline{C}H_2C_6H_5$), 65.36 (C21), 85.42 (C1"), 90.40 (C16), 109.16 (C12), 121.05 (C10), 122.74 (C9), 126.92 (C4'), 128.07 (C11), 128.25 (C3' + C5'), 129.30 (C2' + C6'), 136.69 (C8), 138.18 (C1'), 142.64 (C13), 164.89 (C2), 168.30 (16-$\underline{C}OOCH_3$), 172.66 (2"-$\underline{C}OOCH_3$), 174.95 (4"-$\underline{C}OO$). **MS:** m/z (int%) 542 (10.0) [$M^+$], 511 (3.0), 409 (9.0), 328 (77.0), 227 (18.0), 154 (7.0), 91 (100.0).

**Epimers of enol (17):** A solution of **10** (1 g, 2.48 mmol) in dry THF (10 mL) was cooled to 0 °C, and under nitrogen a suspension of $NaNH_2$ (*ca.* 200 mg, 5.12 mmol in toluene) was added. After 30 min at 0 °C, methyl acrylate (430 mg, 5 mmol) was added and the resulting solution was stirred at 0 °C for 1 h and the reaction mixture was allowed to warm to 20 °C. After 1 h 1 mL of water was added dropwise to the cooled mixture and the solvent was evaporated in vacuo. The residue was dissolved in a mixture of 20 mL of $CH_2Cl_2$ and 20 mL of water and the organic layer was dried and concentrated in vacuo. The two main components were separated by preparative TLC (eluent: ether / hexane, 1:1). The more polar compound (epimer B of **17**, $R_f$ = 0.40 ) was obtained as colorless crystals after crystallization from methanol (18 mg, 1.4 %) mp 178-179 °C. **IR** (KBr) $\nu_{max}$ 3420, 1706, 1687, 1610 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$) δ: 1.35 + 1.59 (2 x 1H, 2 x dddd, $J_{gem}$ = 13.0, $J_{1",6"}$ = 11.0 and 2.8, $J_{5",6"}$ = 10.5 + 6.0 and 5.8 + 3.4 Hz, respectively, 6"-$H_2$); 1.75 + 2.02 (2 x 1H, 2 x ddd, $J_{gem}$ = 11.8, $J_{5,6}$ = 4.6 + <1 and 12.5 + 6.3 Hz, respectively, 6-$H_2$); 2.11 (2H, dm, $J_{1",2"}$ = 7.5 Hz, 2"-$H_2$); 2.19 + 2.27 (2 x 1H, 2 x ddddd, $J_{gem}$ = 18.2, $J_{2",5"}$ = 1 + 1 and 1.9 + 1.7 Hz, respectively, 5"-$H_2$); 2.63 (1H, ddt, 1"-H); 2.75 + 3.10 (2 x 1H, 2 x dd, $J_{gem}$ = 15.2, $J_{17,20}$ = 4.5 and 3.0 Hz, respectively, 17-$H_2$); 2.79 + 3.06 (2 x 1H, 2 x ddd, $J_{gem}$ = 9.0 Hz, 5-$H_2$), 2.83 (1H, br dd, 20-H); 3.56 (1H, br d, $J_{17B,21}$ = 1.8 Hz, 21-H); 3.70 (3H, s, 3"-$COOCH_3$); 3.72 (3H, s, 16-$COOCH_3$); 3.92 (2H, s, N4-$C\underline{H}_2C_6H_5$); 6.83 (1H, d,12-H); 6.91 (1H, dd, 10-H); 7.14-7.19 (2H, m, 9-H + 11-H); 7.25-7.40 (5H, m, $C_6H_5$); 8.87 (1H, br s, N1-H); 12.08 (1H, s, OH). **$^{13}$C NMR** ($CDCl_3$) δ: 21.61 (C17), 23.68 (C2"), 24.86 (C6"), 28.49 (C5"), 41.73 (C6), 43.40 (C1"), 50.90 (16-$COO\underline{C}H_3$),

51.15 (C20), 51.41 (3"-COO$\underline{C}H_3$), 51.71 (C5), 56.30 (C7), 59.45 (N4-$\underline{C}H_2C_6H_5$), 67.09 (C21), 88.44 (C16), 96.46 (C3"), 109.53 (C12), 121.02 (C10), 122.02 (C9), 127.26 (C4'), 127.81 (C11), 128.50 (C3' + C5'), 128.99 (C2' + C6'), 137.48 (C8), 139.00 (C1'), 142.72 (C13), 166.42 (C2), 167.89 (16-$\underline{C}OOCH_3$), 170.46 (C4"), 172.63 (3"-$\underline{C}OOCH_3$), 213.45 (C19). **MS:** m/z (int%) 542 (20.0) [$M^+$], 511 (9.0), 409 (4.0), 328 (9.0), 296 (8.0), 227 (20.0), 134 (12.0), 91 (100.0).

The less polar compound ($R_f$ = 0.41 ) was treated with methanol to yield epimer A of **17** as colorless crystals (41 mg, 3.0 %) mp 88-90 °C. **IR** (KBr) $\nu_{max}$ 3390, 1695, 1670, 1600 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$) δ: 1.47 + 1.55 (2 x 1H, 2 x dddd, $J_{gem}$ = 13.5, $J_{1",6"}$ = 10.8 and 3.2, $J_{5",6"}$ = 11.0 + 6.2 and 6.1 + 3.2 Hz, respectively, 6"-$H_2$); 1.74 + 2.02 (2 x 1H, 2 x ddd, $J_{gem}$ = 11.6, $J_{5,6}$ = 4.5 + <1 and 12.4 + 6.2 Hz, respectively, 6-$H_2$); 1.86 + 2.33 (2 x 1H, 2 x dddd, $J_{gem}$ = 15.5, $J_{1",2"}$ = 11.0 and 5.0 Hz, respectively, $J_{2"A,5"}$ = 2.5 + 1.5, $J_{2"B,5"}$ ~ 1, $J_{2"B,6"B}$ = 1.5 Hz, 2"-$H_2$); 2.20-2.31 (2H, m, 5"-$H_2$); 2.61 (1H, dddd, 1"-H); 2.74 + 3.12 (2 x 1H, 2 x dd, $J_{gem}$ = 15.0, $J_{17,20}$ = 4.3 and 2.4 Hz, respectively, 17-$H_2$); 2.78 + 3.06 (2 x 1H, 2 x ddd, $J_{gem}$ = 9.0 Hz, 5-$H_2$), 2.79 (1H, m, 20-H); 3.62 (1H, br s, 21-H); 3.73 (3H, s, 16-$COOCH_3$); 3.76 (3H, s, 3"-$COOCH_3$); 3.90 + 3.95 (2 x 1H, 2 x d, $J_{gem}$ = 13.0 Hz, N4-$C\underline{H}_2C_6H_5$); 6.83 (1H, br d, $J_{11,12}$ = 7.5 Hz, 12-H); 6.91 (1H, ddd, $J_{9,10}$ = 7.3, $J_{10,11}$ = 7.5, $J_{10,12}$ = 1.1 Hz, 10-H); 7.12-7.19 (2H, m, 9-H + 11-H); 7.22-7.42 (5H, m, $C_6H_5$); 8.82 (1H, br s, N1-H); 12.12 (1H, s, OH). **$^{13}$C NMR** ($CDCl_3$) δ: 21.72 (C17), 22.98 (C6"), 25.74 (C2"), 28.23 (C5"), 41.76 (C6), 43.18 (C1"), 50.94 (16-COO$\underline{C}H_3$), 51.08 (C20), 51.47 (3"-COO$\underline{C}H_3$), 51.59 (C5), 56.28 (C7), 59.33 (N4-$\underline{C}H_2C_6H_5$), 66.93 (C21), 88.68 (C16), 96.13 (C3"), 109.56 (C12), 121.08 (C10), 122.04 (C9), 127.33 (C4'), 127.85 (C11), 128.52 (C3' + C5'), 129.04 (C2' + C6'), 137.56 (C8), 138.96 (C1'), 142.71 (C13), 166.46 (C2), 167.90 (16-$\underline{C}OOCH_3$), 171.73 (C4"), 172.48 (3"-$\underline{C}OOCH_3$), 213.63 (C19). **FAB:** m/z (int%) 542 (100.0) [$M^+$].

**(±)-10-Acetyl-2,16-didehydro-16-methoxycarbonyl-3-phenyl-14,15-dinoraspidospermidin-19-one (18) and (±)-1,10-Diacetyl-2,16-didehydro-16-methoxycarbonyl-3-phenyl-14,15-dinor-aspidospermidin-19-one (19):** A solution of **10** (1 g, 2.48 mmol) and five drops of 70 % aqueous $HClO_4$ in 10 mL of $Ac_2O$ was stirred at 20 °C. After 30 min the solution was poured into a cold (0 °C) mixture of 50 mL of water, 20 mL of $CH_2Cl_2$ and 10 mL of saturated aqueous $NaHCO_3$. After excess solid $NaHCO_3$ had been added to neutralize all the acetic acid formed, the organic layer was separated and the aqueous phase was extracted with $CH_2Cl_2$. The two main components were separated by preparative TLC (eluent: dichloromethane / methanol, 20:1). The more polar compound (**19**) ($R_f$ = 0.38) was obtained as colorless crystals after crystallization from methanol (38 mg, 3.1 %) mp 187-188 °C. **IR** (KBr) $\nu_{max}$ 3440, 1702, 1674, 1630, 1602 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$) δ: 1.81 + 2.03 (2 x 1H, 2 x ddd, $J_{gem}$ = 11.6, $J_{5,6}$ = 4.6 + <1 and 12.0 + 6.5 Hz, respectively, 6-$H_2$); 1.98 (3H, s, 18-$H_2$); 2.25 (3H, s, NCO$\underline{C}H_3$); 2.58 (3H, s, 10-$COCH_3$); 2.67 + 2.98 (2 x 1H, 2 x ddd, $J_{gem}$ = 9.4 Hz, 5-$H_2$); 2.82 + 3.25 (2 x 1H, 2 x dd, $J_{gem}$ = 15.0, $J_{17,20}$ = 4.4 and 3.2 Hz, respectively, 17-$H_2$); 2.90 (1H, ddd, $J_{20,21}$ = 1.0 Hz, 20-H); 3.70 (1H, dd, $J_{17B,21}$ = 1.7 Hz, 21-H); 3.78 (3H, s, $OCH_3$); 3.81 + 4.08 (2 x 1H, 2 x d, $J_{gem}$ = 13.2 Hz, N4-$C\underline{H}_2C_6H_5$); 7.25-7.40 (5H, m, $C_6H_5$); 7.80 (1H, d, $J_{9,11}$ = 1.7 Hz, 9-H); 7.87 (1H, dd, $J_{11,12}$ = 8.4 Hz, 11-H); 7.93 (1H, d, 12-H); **$^{13}$C NMR** ($CDCl_3$) δ: 23.02 (C17), 23.27 (NCO$\underline{C}H_3$), 26.57 (10-CO$\underline{C}H_3$), 28.12 (C18), 40.78 (C6), 50.40 (C5), 51.89 ($OCH_3$), 52.01 (C20), 53.39 (C7), 58.25 (N4-$\underline{C}H_2C_6H_5$), 65.41 (C21), 109.68 (C16), 115.14

(C12), 121.21 (C9), 127.40 (C4'), 128.51 (C3' + C5'), 128.81 (C2' + C6'), 129.79 (C11), 133.54 (C10), 138.19 (C8), 138.43 (C1'), 144.89 (C13), 155.94 (C2),165.96 (16-$\underline{C}OOCH_3$), 170.45 (NCO), 196.93 (10-$\underline{C}OCH_3$), 208.09 (C19). **MS:** m/z (int%) 486 (4.5) [$M^+$], 443 (5.0), 353 (4.0), 311 (10.0), 269 (17.0), 188 (64.0), 134 (10.0), 91 (100.0), 42 (47.0).

The less polar compound ($R_f$ = 0.44) was treated with methanol to yield **18** as colorless crystals (110 mg, 10 %) mp 146-147 °C. **IR** (KBr) $\nu_{max}$ 3360, 1690, 1661, 1626, 1595 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$) δ: 1.72 + 1.98 (2 x 1H, 2 x dd, $J_{gem}$ = 11.8, $J_{5,6}$ = 4.6 + <1 and 12.4 + 6.2 Hz, respectively, 6-$H_2$); 1.98 (3H, s, 18-$H_3$); 2.54 (3H, s, 10-$COCH_3$); 2.74 (1H, dd, $J_{17,20}$ = 4.4 + 4.0 Hz, 20-H), 2.75 + 3.18 (2 x 1H, 2 x dd, $J_{gem}$ = 16.5 Hz, 17-$H_2$); 2.79 + 3.00 (2 x 1H, 2 x ddd, $J_{gem}$ = 9.00 Hz, 5-$H_2$); 3.72 (1H, br s, 21-H); 3.77 (3H, s, $OCH_3$); 3.86 + 4.02 (2 x 1H, 2 x d, $J_{gem}$ = 13.2 Hz, N4-$C\underline{H}_2C_6H_5$); 6.82 (1H, d, 12-H); 7.25-7.4 (5H, m, $C_6H_5$); 7.77 (1H, d, 9-H); 7.83 (1H, dd, 11-H); 9.02 (1H, br s, N1-H). **$^{13}$C NMR** ($CDCl_3$) δ: 21.63 (C17), 26.46 (10-$CO\underline{C}H_3$), 28.04 (C18), 42.27 (C6), 50.99 (C5), 51.29 ($OCH_3$), 52.62 (C20), 55.39 (C7), 58.47 (N4-$\underline{C}H_2C_6H_5$), 66.38 (C21), 91.65 (C16), 108.51 (C12), 121.93 (C9), 127.32 (C4), 128.48 (C3' + C5'), 128.97 (C2' + C6'), 130.45 (C11), 130.76 (C10), 137.96 (C8), 138.74 (C1'), 146.99 (C13), 165.36 (C2), 167.82 (16-$\underline{C}OOCH_3$), 196.73 (10-$\underline{C}OCH_3$), 209.77 (C19). **MS:** m/z (int%) 444 (5.0) [$M^+$], 401 (2.0), 311 (16.0), 269 (17.0), 188 (48.0), 134 (19.0), 91 (100.0), 41 (30.0); **Anal.** Calcd for $C_{27}H_{28}N_2O_4$ C 72.94, H 6.35, N 6.30. Found C 72.91, H 6.24, N 6.28.

**(±)-1-Acetyl-2,16-didehydro-16-methoxycarbonyl-3-phenyl-14,15-dinoraspidospermidin-19-one (20):** A solution of **10** (200 mg, 0.50 mmol) and 95 mg (0.50 mmol) of *p*-toluenesulfonic acid monohydrate in 5 mL of $Ac_2O$ was stirred at 20 °C. After 48 h the reaction mixture was worked up as described above and the residue was purified by thinlayer chromatography (eluent: hexane / acetone, 2:1) to yield a yellow oil ($R_f$ = 0.42), which was crystallized from methanol to afford **20** (57 mg, 26 %) as colorless crystals: mp 178-179 °C. **IR** (KBr) $\nu_{max}$ 3430, 1715, 1685, 1663,1602 $cm^{-1}$; **$^1$H NMR** ($CDCl_3$) δ: 1.82 + 2.04 (2 x 1H, 2 x ddd, $J_{gem}$ = 11.6, $J_{5,6}$ = 4.8 + <1 and 12.2 + 6.5 Hz, respectively, 6-$H_2$); 1.97 (3H, s, 18-$H_3$); 2.25 (3H, s, $NCOCH_3$); 2.61 + 2.96 (2 x 1H, 2 x ddd, $J_{gem}$ = 9.2 Hz, 5-$H_2$); 2.81 + 3.20 (2 x 1H, 2 x dd, $J_{gem}$ = 14.5, $J_{17,20}$ = 4.5 and 2.7 Hz, respectively, 17-$H_2$); 2.85 (1H, ddd, $J_{20,21}$ = 1.0 Hz, 20-H); 3.68 (1H, dd, $J_{17B,21}$ = 1.8 Hz, 21-H); 3.77 (3H, s, $OCH_3$); 3.75 + 4.08 (2 x 1H, 2 x d, $J_{gem}$ = 13.2 Hz, N4-$C\underline{H}_2C_6H_5$); 7.09 (1H, ddd, 10-H); 7.12 (1H, dd, 9-H); 7.23 (1H, ddd, 11-H); 7.25-7.4 (5H, m, $C_6H_5$); 7.81 (1H, dd, 12-H); **$^{13}$C NMR** ($CDCl_3$) δ: 23.06 (C17), 23.14 (N1-$CO\underline{C}H_3$), 28.10 (C18), 40.45 (C6), *50.41 (C5), 51.73 ($OCH_3$), 52.50 (C20), 53.39 (C7), 58.44* (N4-$\underline{C}H_2C_6H_5$), *65.53 (C21), 109.76 (C16),* 116.07 (C12), 121.70 (C9), 124.39 (C10), 127.24 (C4'), 127.59 (C11), 128.39 (C3' + C5'), 128.73 (C2' + C6'), 137.44 (C8), 138.41 (C1'), 140.98 (C13), 155.50 (C2), 166.34 (16-$\underline{C}OOCH_3$), 170.00 (NCO), 208.04 (C19). **MS:** m/z (int%) 444 (8.0) [$M^+$], 401 (6.0), 311 (14.0), 269 (17.0), 227 (24.0), 188 (75.0), 167 (14.0), 91 (100.0), 42 (43.0).

**(±)-Methyl 3,9-Diacetyl-4a-[1-(*N*-acetyl-*N*-benzyl-2-aminoethyl)]-2-hydro-9*H*-carbazole-1-carboxylate (21) and Enol Acetate (22):** A solution of 1 g (2.48 mmol) of **10** and 10 mg (0.05 mmol) of *p*-toluenesulfonic acid monohydrate in 10 ml of acetic acid anhydride was refluxed for 1 h. The solvent was

evaporated in vacuo, the residue was dissolved in 10 mL of $CH_2Cl_2$, and was washed with 10 mL of saturated aqueous $NaHCO_3$ and water (10 mL). The organic layer was dried and concentrated in vacuo. The two main components were separated by preparative TLC (eluent: dichloromethane / ether, 100:1). The more polar compound (**21**, $R_f$ = 0.21) was obtained as colorless crystals after crystallization from methanol (253 mg, 21 %) mp 141-142 °C. **IR** (KBr) $\nu_{max}$ 3445, 1712, 1697, 1680, 1647 $cm^{-1}$; **$^1$H NMR** *major rotamer* ($CDCl_3$) δ: 1.70-2.00 (2H, m, 1"-$H_2$); 2.08 (3H, s, N3"-$COCH_3$); 2.25 (3H, s, N9-$COCH_3$); 2.40 (3H, s, 3-$COCH_3$); 2.98 + 3.67 (2 x 1H, $J_{gem}$ = 20.8 Hz, 2-$H_2$); 3.17 + 3.35 (2 x 1H, 2 x ddd, $J_{gem}$ = 13.0 $J_{1",2"}$ = 5.0 + 11.0 and 5.3 + 10.9 Hz, respectively, 2"-$H_2$), 3.77 (3H, s, $OCH_3$), 4.33 + 4.36 (2 x 1H, 2 x d, $J_{gem}$ = 16.2 Hz, $CH_2C_6H_5$); 7.12 (1H, d, $J_{2A,4}$ = 3.0 Hz, 4-H); 7.00-7.40 (8H, m, 5-H + 6-H + 7-H + $C_6H_5$); 7.88 (1H br d, $J_{7,8}$ = 7.9 Hz, 8-H). **$^{13}$C NMR** *major rotamer* ($CDCl_3$) δ: 21.71 (N3"-$COCH_3$), 23.26 (N9-$COCH_3$), 25.62 (3-$COCH_3$), 25.83 (C2), 37.90 (C1"), 41.82 (C2"), 50.51 (C4a), 51.93 ($OCH_3$), 52.44 ($CH_2C_6H_5$), 113.74 (C1), 116.88 (C8), 121.53 (C5), 124.52 (C6), 126.56 (C2' + C6'), 128.33 (C4'), 128.67 (C7), 129.00 (C3' + C5'), 132.72[x] (C4b), 136.05 (C1'), 137.58 (C4), 139.13[x] (C3), 141.39 (C8a), 150.90 (C9a), 165.87 ($COOCH_3$), 169.86 + 170.61 (2 x $NCOCH_3$), 196.83 (3-$COCH_3$). **$^1$H NMR** *minor rotamer* ($CDCl_3$) δ: 1.7-2.0 (2H, m, 1"-$H_2$); 1.92 (3H, s, N3"-$COCH_3$); 2.18 (3H, s, N9-$COCH_3$); 2.39 (3H, s, 3-$COCH_3$); 2.98 + 3.69 (2 x 1H, $J_{gem}$ = 20.8 Hz, 2-$H_2$); 2.97-3.15 (2H, m, 2"-$H_2$), 3.78 (3H, s, $OCH_3$), 4.37 + 4.49 (2 x 1H, 2 x d, $J_{gem}$ = 14.5 Hz, $CH_2C_6H_5$); 7.06 (1H, d, $J_{2A,4}$ ~ 3 Hz, 4-H); 7.0-7.4 (8H, m, 5-H + 6-H + 7-H + $C_6H_5$); 7.83 (1H, br d, $J_{7,8}$ = 8.0 Hz, 8-H). **$^{13}$C NMR** *minor rotamer* ($CDCl_3$) δ: 21.08 (N3"-$COCH_3$), 23.26 (N9-$COCH_3$), 25.62 (3-$COCH_3$), 25.75 (C2), 38.74 (C1"), 42.83 (C2"), 48.30 ($CH_2C_6H_5$), 49.95 (C4a), 52.03 ($OCH_3$), 114.01 (C1), 116.88 (C8), 121.44 (C5), 124.74 (C6), 127.68 (C4'), 127.93 (C3' + C5'), 128.52 (C2' + C6'), 128.95 (C7), 132.02[x] (C4b), 137.04 (C1'), 137.39 (C4), 139.55[x] (C3), 141.55 (C8a), 149.63 (C9a), 165.84 ($COOCH_3$), 169.08 + 170.61 (2 x $NCOCH_3$), 196.41 (3-$COCH_3$). **FAB:** *mixture of two rotamers*, m/z (int%) 486 (100.0) [$M^+$], **MS:** m/z (int%) 455 (30.0) [M-31$^+$], 268 (18.0), 194 (58.0), 177 (100.0), 148 (40.0), 106 (30.0), 91 (94.0), 42 (85.0). **Anal.**Calcd for $C_{29}H_{30}N_2O_5$ C 71.57, H 6.22, N 5.76. Found C 71.42, H 6.56, N 5.73.

The less polar compound (**22**, $R_f$ = 0.38) was yielded as yellow oil (40 mg, 3.0 %). **IR** (film) $\nu_{max}$ 3460, 1776, 1718, 1700, 1690, 1647 $cm^{-1}$; **$^1$H NMR** *major rotamer* ($CDCl_3$) δ: 1.71 + 1.88 (2 x 1H, 2 x ddd, $J_{gem}$ = 13.0, $J_{1",2"}$ = 11.2 + 4.8 and 11.0 + 5.0 Hz, respectively, 1"-$H_2$); 2.05 (3H, s, N3"-$COCH_3$); 2.25 (3H, s, $OCOCH_3$); 2.29 (3H, s, N9-$COCH_3$); 3.13 + 3.37 (2 x 1H, $J_{gem}$ = 19.8 Hz, 2-$H_2$); 3.13 + 3.43 (2 x 1H, 2 x ddd, $J_{gem}$ = 12.5 Hz, 2"-$H_2$); 3.78 (3H, s, $OCH_3$); 4.33 + 4.38 (2 x 1H, 2 x d, $J_{gem}$ = 16.5 Hz, $CH_2C_6H_5$); 4.96 + 5.19 (2 x 1H, 2 x d, $J_{gem}$ = 2.5 Hz, $=CH_2$); 6.22 (1H, d, $J_{2A,4}$ = 2.6 Hz, 4-H); 7.05-7.35 (8H, m, 5-H + 6-H + 7-H + $C_6H_5$); 7.87 (1H, br d, $J_{7,8}$ = 7.9 Hz, 8-H). **$^{13}$C NMR** *major rotamer* ($CDCl_3$) δ: 20.89 ($OCOCH_3$), 21.71 (N3"-$COCH_3$), 23.24 (N9-$COCH_3$), 27.51 (C2), 38.83 (C1"), 42.30 (C2"), 49.85 (C4a), 51.89 ($OCH_3$), 52.49 ($CH_2C_6H_5$), 103.69 ($=CH_2$), 112.75 (C1), 116.71 (C8), 121.43 (C5), 123.71 (C4), 124.44 (C6), 126.63 (C2' + C6'), 127.72 (C4'), 128.57 (C7), 128.89 (C3' + C5'), 131.46 (C3), 133.71 (C4b), 136.43 (C1'), 141.30 (C8a), 151.37 ($C=CH_2$), 152.18 (C9a), 166.03 ($COOCH_3$), 168.83 ($OCOCH_3$), 170.13 (N9-$COCH_3$), 170.68 (N3"-$COCH_3$). **$^1$H NMR** *minor rotamer* ($CDCl_3$) δ: 1.66 + 1.78 (2 x 1H, 2 x ddd, $J_{gem}$ = 13.5, $J_{1",2"}$ = 4.6 + 12.0 and 4.8 + 11.8 Hz, respectively, 1"-$H_2$); 1.95 (3H, s, N3"-$COCH_3$); 2.18 (3H, s, N9-$COCH_3$); 2.28 (3H, s, $OCOCH_3$); 3.08 + 3.18 (2 x 1H, 2 x ddd,

$J_{gem}$ = 14.0 Hz, 2"-$H_2$); 3.13 + 3.37 (2 x 1H, 2 x d, $J_{gem}$ = 19.8 Hz, 2-$H_2$); 3.78 (3H, s, $OCH_3$); 4.27 + 4.54 (2 x 1H, 2 x d, $J_{gem}$ = 14.4 Hz, $C\underline{H}_2C_6H_5$); 5.00 + 5.22 (2 x 1H, 2 x d, $J_{gem}$ = 2.5 Hz, $=CH_2$); 6.19 (1H, d, $J_{2A,4}$ = 2.6 Hz, 4-H); 7.05-7.35 (8H, m, 5-H + 6-H + 7-H + $C_6H_5$); 7.80 (1H, br d, $J_{7,8}$ = 7.9 Hz, 8-H). **$^{13}$C NMR** *minor rotamer* ($CDCl_3$) δ: 20.87 ($OCO\underline{C}H_3$), 21.08 (N3"-$CO\underline{C}H_3$), 23.17 (N9-$CO\underline{C}H_3$), 27.41 (C2), 39.88 (C1"), 43.33 (C2"), 48.50 ($\underline{C}H_2C_6H_5$), 49.21 (C4a), 51.99 ($OCH_3$), 104.20 ($=CH_2$), 113.05 (C1), 116.82 (C8), 121.44 (C5), 123.13 (C4), 124.59 (C6), 127.47 (C4'), 128.17 (C3' + C5'), 128.41 (C2' + C6'), 128.53 (C7), 132.03 (C3), 133.33 (C4b), 137.39 (C1'), 141.25 (C8a), 150.78 (C9a), 151.21 ($\underline{C}=CH_2$), 165.94 ($\underline{C}OOCH_3$), 168.81 ($O\underline{C}OCH_3$), 169.19 (N9-$\underline{C}OCH_3$), 170.17 (N3"-$\underline{C}OCH_3$).**FAB:** *mixture of two rotamers*, m/z (int%) 528 (100.0) [$M^+$], **MS:** m/z (int%) 497 (7.0) [M-31$^+$], 455 (5.0), 267 (13.0), 250 (56.0) 194 (18.0), 177 (82.0), 148 (30.0), 106 (31.0), 91 (100.0), 42 (60.0).

**(±)-Methyl 3-Acetyl-4a-[1-(*N*-acetyl-*N*-benzyl-2-aminoethyl)]-2-hydro-9*H*-carbazole-1-carboxylate (23):** A solution of **10** (200 mg, 0.50 mmol) in 10 mL of $Ac_2O$ was stirred at 20 °C. After 6 h the solution was worked up as in the case of **18** and **19**. The residue was purified by thinlayer chromatography (eluent: benzene / methanol, 10:1, $R_f$= 0.24) to yield a yellow oil (**23**, 62 mg, 28 %). **IR** (film) $\nu_{max}$ 3370, 1690, 1677, 1638, 1600 cm$^{-1}$; **$^1$H NMR** *mixture of two rotamers, ratio 1:1,* ($CDCl_3$) δ: 1.63-1.83 + 1.95 (2H, m, 1"-$H_2$); 2.04s + 1.87s (3H, N-$COCH_3$); 2.36 (3H, s, 3-$COCH_3$); 2.74 + 3.75 and 3.80 (2H, d, $J_{gem}$ = 20.7 Hz, 2-$H_2$), 2.73 + 3.05-3.23 (2H, m, 2"-$H_2$), 3.77s + 3.80s (3H, $OCH_3$), 4.23 + 4.30 ($J_{gem}$ = 16.3) and 4.26 + 4.48 ($J_{gem}$ = 14.3 Hz, $C\underline{H}_2C_6H_5$); 6.82 + 6.85 (1H, 8-H); 6.96-7.44 (8H, m, 5-H + 6-H + 7-H + $C_6H_5$); 7.17d + 7.12d (1H, J = 3.0 Hz, 4-H); 8.96 + 8.98 (1H, br s, N9-H). **$^{13}$C NMR** *mixture of two rotamers, ratio 1:1,* ($CDCl_3$) δ: 21.79 + 20.95 (N-$CO\underline{C}H_3$), 23.92 + 23.87 (C2), 25.74 + 25.72 (3-$CO\underline{C}H_3$), 37.30 + 38.23 (C1"), 41.64 + 42.77 (C2"), 51.18 + 51.04 ($OCH_3$), 52.37 + 51.97 (C4a), 52.39 + 48.46 ($C\underline{H}_2C_6H_5$), 92.66 + 92.81 (C1), 109.99 + 109.70 (C8), 121.15 + 121.30 (C5), 122.72 + 122.03 (C6), 126.60 + 128.42 (C2' + C6'), 128.86 + 128.52 (C3' + C5'), 127.74 + 127.49 (C4'), 128.80 + 129.22 (C7), 129.73 + 130.46$^x$ (C3), 136.21 + 137.14 (C1'), 139.89 + 139.34 (C4), 140.85 + 140.50$^x$ (C4b), 144.26 + 144.45 (C8a), 161.18 + 162.16 (C9a), 168.06 + 167.90 ($\underline{C}OOCH_3$), 170.57 + 170.06 (N-$\underline{C}OCH_3$), 196.98 + 197.30 (3-$\underline{C}OCH_3$). **MS:** m/z (int%) 444 (1.4) [$M^+$], 413 (3.0), 399 (1.2), 268 (22.0), 194 (81.0), 177 (83.0), 148 (35.0), 120 (24.0), 106 (31.0), 91 (100.0), 42 (70.0).

**(±)-Methyl 3-Acetyl-4a-[1-(*N*-acetyl-*N*-benzyl-2-aminoethyl)]-2-hydro-9*H*-carbazole-1-carboxylate (23) and (±)-Methyl 3-Acetyl-9*H*-carbazole-1-carboxylate (24):** A solution of 1 g (2.48 mmol) of **10** in 10 mL of $Ac_2O$ was refluxed for 2 h. The solvent was evaporated in vacuo, the residue was dissolved in 10 mL of $CH_2Cl_2$, and was washed with 10 mL of saturated aqueous $NaHCO_3$ and water (10 mL). The organic layer was dried and concentrated in vacuo. The two main components were separated by preparative TLC (eluent: benzene / methanol, 10:1). The more polar compound (**23**, $R_f$ = 0.24, 210 mg, 19 %) was identical with the product obtained above.

The less polar compound ($R_f$ = 0.58) was treated with methanol to yield **24** as colorless crystals (21 mg, 3.2 %) mp 187-188 °C (lit.,[13] 138 °C). **IR** (KBr) $\nu_{max}$ 3310, 1700, 1652, 1614, 1588 cm$^{-1}$; **$^1$H NMR:**

($CDCl_3$) δ: 2.75 (3H, s, $COCH_3$); 4.06 (3H, s, $COOCH_3$); 7.34 (1H, ddd, $J_{5,6}$ = 7.6, $J_{6,7}$ = 6.4, $J_{6,8}$ = 2.0 Hz, 6-H); 7.52 (1H, ddd, $J_{7,8}$ = 8.2, $J_{5,7}$ = 1.2 Hz, 7-H); 7.54 (1H, dd, 8-H); 8.14 (1H, br d, 5-H); 8.69 (1H, d, $J_{2,4}$ = 1.7 Hz, 2-H); 8.88 (1H, d, 4-H); 10.11 (1H, br s, NH). **$^{13}$C NMR:** ($CDCl_3$) δ: 26.76 ($CO\underline{C}H_3$), 52.30 ($COO\underline{C}H_3$), 111.12 (C1), 111.58 (C8), 120.80 (C5), 121.06 (C6), 122.77$^x$ (C4a), 124.86$^x$ (C4b), 125.61 (C4), 127.43 (C7), 128.36 (C2), 128.56 (C3), 140.25 (C8a), 142.51 (C9a), 167.33 ($\underline{C}OOCH_3$), 197.02 ($\underline{C}OOCH_3$). **MS:** m/z (int%) 267 (90.0) [$M^+$], 252 (100.0), 235 (76.0), 220 (24.0), 192 (32.0), 164 (51.0), 120 (24.0), 110 (23.0), 42 (18.0).

## ACKNOWLEDGMENT

The authors are grateful to the National Scientific Research Foundation (OTKA T / 8-19574) for financial support of this work.

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Received, 3rd March, 1997