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A Short Synthesis of (±) *N*-Benzyl Aspidospermidine[1]

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Key Words: *N*-benzyl-aspidospermidine; photocyclization; Michael reaction; nitroethylene.

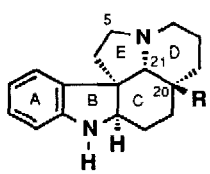
Abstract: (±) *N*-benzyl aspidospermidine is synthesized in seven steps *via* the trisubstituted hexahydrocarbazolone **4**; reductive cyclization of this intermediate which is obtained by photocyclization and Michael reaction with nitroethylene, creates simulteanously both E and D rings of the pentacyclic system.

The *Aspidosperma* alkaloids constitute a large family of natural products. Their presence in biologically active compounds (e.g. vincamine and antitumor dimer alkaloids)[2] accounts for the continuing interests devoted to their total synthesis.[3]

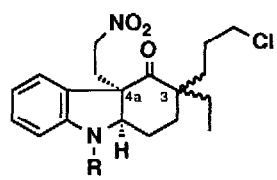
We wish to report here a short and efficient synthesis of (±)-aspidospermidine,[4] the simplest pentacyclic derivative in the series which however shows four asymmetric centers with two quaternary carbons.

Synthesis of the 20-deethyl analogue (R = H) has previously been developed in our laboratory.[5]

A crucial point in the complete skeleton building is the creation of the quaternary C-20 center.[6] Our new strategy is based on the formation of this center at the start of the synthesis and on the intramolecular cyclization of the key intermediate **4** which possesses the future D and E ring chains respectively in C-3 and C-4a.



(+)-aspidospermidine : R = Et
deethylaspidospermidine : R = H



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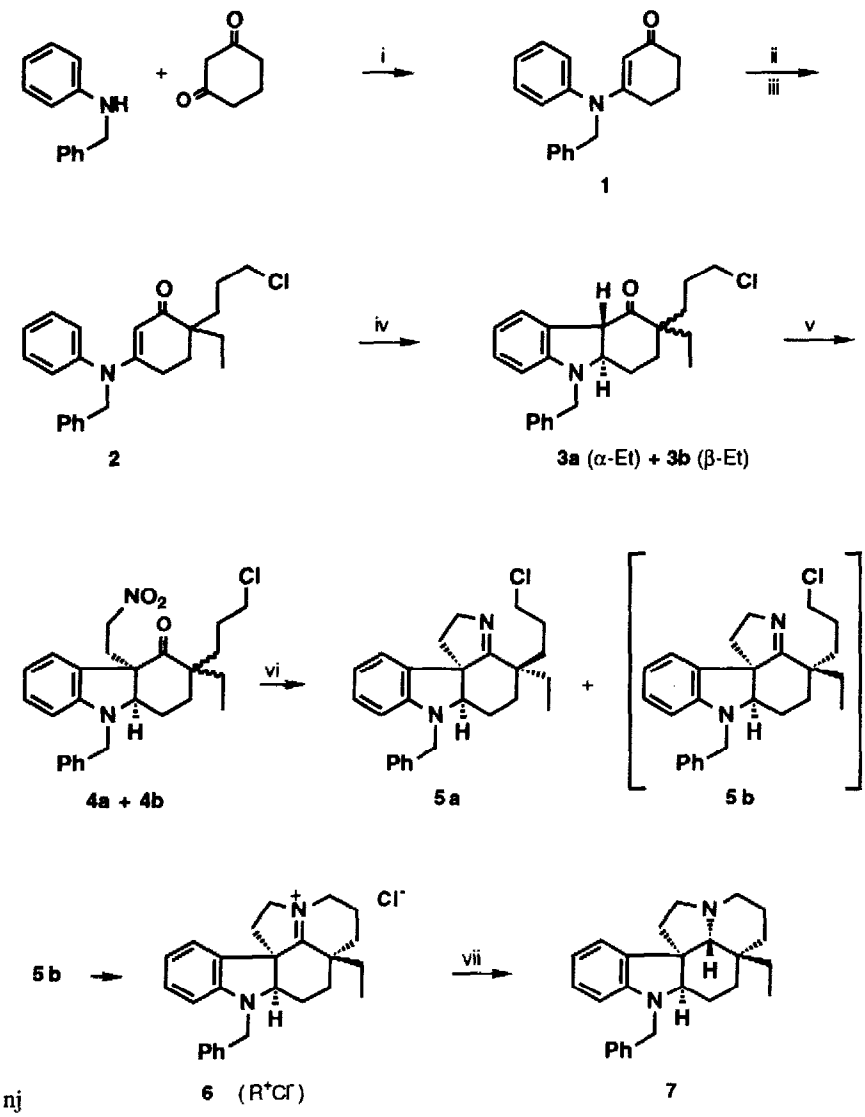
Enaminone **2**[7] is obtained in three steps from *N*-benzyl aniline and cyclohexane-1,3-dione. Then, according to the original process of our laboratory,[8] photocyclization of **2** (carefully deoxygenated benzene solution, 400W medium pressure mercury lamp, 30mn) gives the *trans* hexahydrocarbazolone **3** isolated in 77% yield as a mixture of isomers **3a,b** in approximatively the same amounts.

Creation of the second quaternary carbon α to the keto group is achieved by alkylation of the carbanion derived from **3a,b** (LDA, THF, -78°C) with nitroethylene;[9] the high reactivity of this Michael acceptor allows the introduction of the futur E ring chain - 2C and 1N - and leads in 62% yield to isomers **4a,b** in equal



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Reagents and conditions : i) toluene, Δ, 15h; ii) LDA, C_2H_5I, THF, -78°C; iii) LDA, $I(CH_2)_3Cl$, THF, -78°C; iv) hυ, benzene, argon, 0,5 h ; v) LDA, nitroethylene, THF, -78°C ; vi) $HCOONH_4$, 10 % Pd/C, MeOH, 65 °C, 15 h; vii) H_2, 5 % Pt/Al_2O_3, EtOH, 3 atm., room temperature, 48 h.

quantities. The reaction is stereospecific and gives exclusively compounds with a natural *cis* B/C ring junction as already observed in alkylation of hexahydrocarbazolones with activated electrophiles.[8b,10] Compounds **4a,b** present identical Rf in t.l.c. after five elutions and cannot be separated. Their stereochemistry is supported by spectroscopic IR, ^1H and ^{13}C NMR data.[10]

Reductive cyclization of the isomeric mixture **4a,b** is performed with ammonium formate as hydrogen transfer agent and palladium on carbon as catalyst.[11,12] It produces imine **5a** and iminium chloride **6** in approximatively the same amounts (yield 67%).The reduction of the nitro group in primary amine leads to a spontaneous cyclization into the tetracyclic imines **5a,b**. Imine **5b** which possesses the natural stereochemistry at C-20 cyclizes once more spontaneously into the pentacyclic iminium **6** whereas the unnatural stereochemistry of **5a** prevents any further cyclization. The two compounds are easily separated at this stage. Iminium chloride **6** has been identified by spectroscopic data IR, NMR and mass spectrometry; in particular the e.i. spectrum shows a molecular peak at 406 a.m.u.(R^+Cl^-) while the FAB spectra are characterized by a peak at 371 (R^+) in positive technic and a peak at 441 [(R^+Cl^-)Cl^-] in negative technic.

The synthesis is completed by reduction of the iminium salt **6**. Catalytic hydrogenation (H_2, Pt/Al_2O_3) occurs from the β face of the molecule and affords *N*-benzyl aspidospermidine **7** in 70% yield. The compound obtained has been identified by t.l.c. correlation and by comparaison of its mass, IR, ^1H and ^{13}C NMR spectra[13] with those of an authentic sample prepared from vincadifformine.[14]

This seven step synthesis constitutes one of the shortest synthesis of *Aspidosperma* alkaloids. Our approach is general and can be applied to the synthesis of other indole alkaloids.

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13. Data for **7** : mp 127-129 °C; IR (CCl_4) υ cm^{-1}: 2860, 2790, 2740, 1600; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm : 0.66 (t, 3H, J = 7.5 Hz), 0.91 (dq, 1H, J = 14.0 , 7.0. Hz), 1.07-1.85 (m, 10H), 1.97 (td, 1H, J = 11.0, 4.0 Hz), 2.25 (s, 1H), 2.27 (m, 1H), 2.37 (dt, 1H, J = 13.0 , 8.5 Hz), 3.05 (m, 1H), 3.12 (m, 1H), 3.41 (dd, 1H, J = 10.5 , 5.0 Hz), 4.27 (AB spectrum, 2H, J = 15.0 Hz, $\Delta\upsilon$ = 109 Hz), 6.39 (d, 1H, J = 7.5 Hz), 7.04 (t, 1H, J = 7.5 Hz), 7.08 (d, 1H, J = 7.5 Hz), 7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ ppm : 6.9, 21.8, 22.4, 23.0, 30.2, 34.5, 35.6, 39.1, 48.4, 52.6, 53.0, 53.8, 69.1,71.2, 106.7, 117.4, 122.4, 127.1, 127.2, 127.8, 128.5, 136.7, 138.7, 149.9; HRMS exact mass : calcd 372.2558, found 372.2562.
14. Vincadifformine is transformed in aspidospermidine by acidic treatment[15] and reduction with lithium aluminium hydride.[4e] Then, benzylation with $PhCH_2Br$ (DMF, K_2CO_3) affords *N*-benzyl aspidospermidine.
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