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TOTAL SYNTHESIS OF (±) ASPIDOFRACTININE [1]

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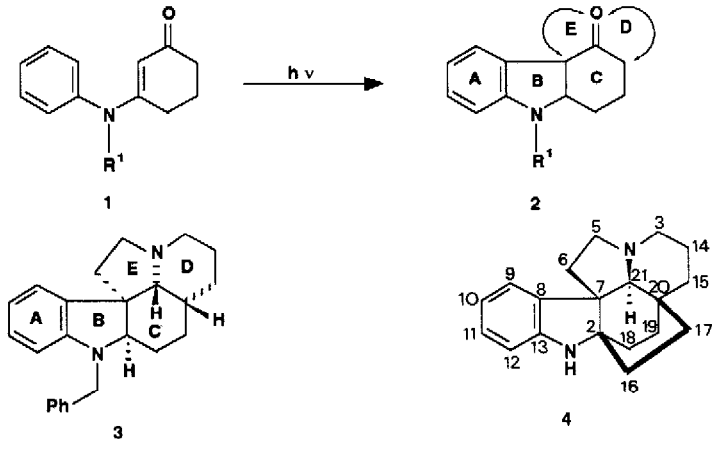
Abstract : The pentacyclic skeleton **10** of the aspidospermine group of indole alkaloids has been constructed from hexahydrocarbazol-4-one **2** with high stereoselectivity. The synthesis of (±) 19-oxo aspidofractinine **12**, a direct precursor of aspidofractinine **4**, illustrates the usefulness of this new general strategy.

The *Aspidosperma* alkaloids belong to a series of natural products useful for the partial synthesis of biologically active compounds (e.g. vincamine and antitumor dimeric indole alkaloids [2]). For these reasons, increasing attention has been paid to their total synthesis [3].

In continuation of our programme aimed at the synthesis of the pentacyclic system of *Aspidosperma* alkaloids, we report herein a straightforward approach to the synthesis of (±) aspidofractinine **4**. Our scheme is based on the fundamentally new approach we have recently described for N-1-benzyl-20-deethyl aspidospermidine **3** [4] from *cis* hexahydrocarbazol-4-ones **2** [5] (Scheme 1).

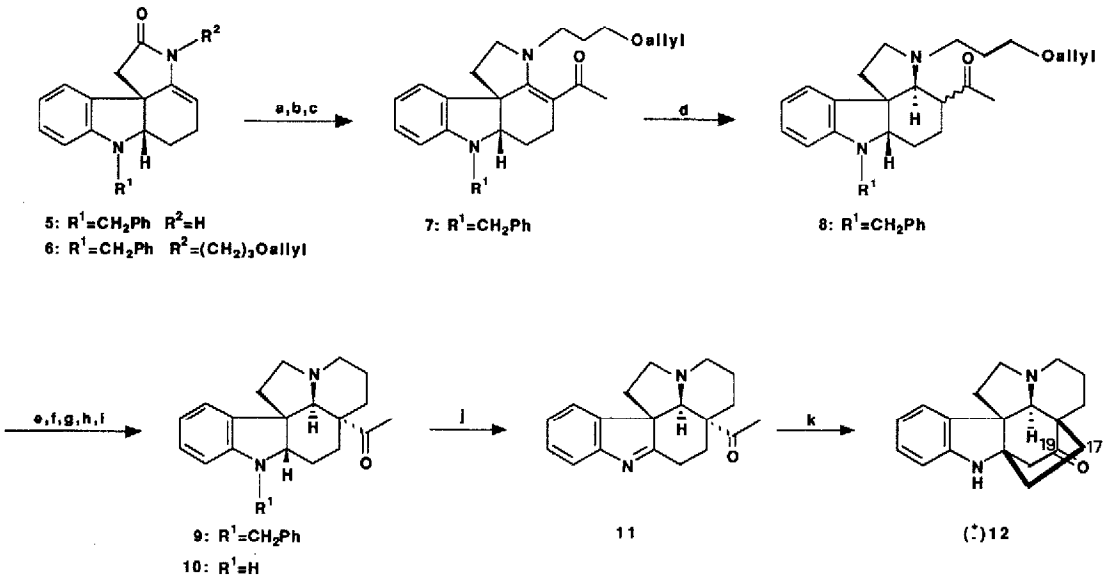


Scheme 1

The tetracyclic enamide **5** (Scheme 2), synthesized in four steps [4] (overall yield : 72 %) from an N-substituted aniline and 1,3-cyclohexanedione, is the key intermediate of considerable interest for the building of the skeleton of the alkaloids we are interested in.

For the generality of our strategy it was necessary to be able to introduce a functionalized C-20 [6] ethyl chain in order to extend our methodology to a large variety of natural products. A ketone at C-19 represents a convenient function since it allows further modification of the side chain [7] and biomimetic Mannich type cyclization to the hexacyclic Aspidofractinine group of type **4** [8].

N-alkylation of amide **5** [4] with 1-iodo-3-allyloxypropane [9] afforded **6** [10] (Scheme 2) which possesses the three carbon atoms necessary for construction of ring D. Selective reduction of the amide function of **6** with $LiAlH_4$ [11] led to an enamine which was directly acylated with CH_3COCl to give enamino ketone **7** (yield : 72 % from **6**) as a stable oil.



Reagents and conditions : (a) KH/THF, $I(CH_2)_3$ O-allyl - (b) $LiAlH_4$/THF, Δ - (c) CH_3COCl, NEt_3, CH_2Cl_2 - (d) $LiAlH_4$/THF, -20°C, 5 min. - (e) DABCO, $RhCl_3$, EtOH/H_2O - (f) H_3O^+, EtOH/H_2O - (g) TsCl, pyr., 48 h, 0°C - (h) NaH, C_6H_6, Δ - (i) H_2, Pd/C, EtOH/$CHCl_3$ - (j) $(COCl)_2$, DMSO, NEt_3 - (k) HCl, MeOH, Δ.

Scheme 2

For ring D closure we envisaged two possible pathways for nucleophilic attack by C-20 at the terminal carbon atom of the chain borne at N-4 : i) use of the enamino ketone itself which is a poor nucleophile or ii) reaction of the ketone formed after reduction of the enamine double bond. We chose the second route, although reduction of enamino ketones is not well documented and has given unpredictable results concerning chemo- and stereoselectivity.

Treatment of **7** with $LiAlH_4$ in very carefully controlled conditions [12] afforded the 1,4 addition products **8** (isolated yield 60 %) as a mixture of epimers at C-20 and with the desired natural stereochemistry at C-21 [13].

The relative stereochemistries of the asymmetric centres of compound **9** are identical to those of natural products of the aspidospermine group (see below). Thus **9** can be considered as a potential intermediate towards a large variety of dihydroindole, indolenine, α-methylene indoline alkaloids, etc. The synthesis of the hexacyclic ring system of aspidofractinine **4** illustrates the usefulness of **9**.

Deprotection [14] of the alcohol function was achieved by treatment with rhodium (III) chloride followed by acidic hydrolysis to give the free alcohol which was tosylated without purification. The anion derived from **8** under thermodynamic control effected the intramolecular cyclization to afford a single pentacyclic product **9** (20 % overall yield from **8** in five steps).

The synthesis of 19-oxo aspidofractinine **12** was completed by hydrogenolysis [15] of the N-1-benzyl appendage of **9**, followed by SWERN oxidation [16] of **10** and direct cyclization of indolenine **11** without isolation (yield : 85 %).

Analytical and spectroscopic data [17] of **12** were identical to those described for the same compound obtained by partial synthesis from minovincine [18] or by total synthesis [8]. This correlation also confirmed the stereochemistry assigned to **9** and **11**. Since the removal of the keto function of **12** has already been performed [8], this work represent a formal total synthesis of (±) aspidofractinine **4**.

In conclusion these latter results illustrate the potential flexibility of our approach to the synthesis of indole alkaloïds from the common tetracyclic compound **5**.

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9. This compound was prepared as follows : $HO\text{-}(CH_2)_3\text{-}OH \xrightarrow{NaH} HO(CH_2)_3ONa \xrightarrow{BrCH_2\text{-}CH=CH_2} HO(CH_2)_3O\text{-allyl} \xrightarrow{TsCl,\ pyr.} TsO(CH_2)_3\text{-}O\text{-allyl} \xrightarrow{NaI,\ acetone} I(CH_2)_3\text{-}O\text{-allyl}$ (overall yield 30 %). For a leading reference see P.G. McDOUGAL, J.G. RICO, Y.I. OH and B.D. CONDON, J. Org. Chem ., 1986, **51**, 3388.
10. The spectral data for all compounds were in accord with their proposed structures. Satisfactory microanalysis and/or high-resolution mass spectra were obtained for these products. Yields are based upon isolated material after silica gel chromatography.
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13. The two C-21 epimers are formed in minor amounts and have not been isolated in this series. Assignment of stereochemistry at C-21 of major epimers **8** was made by comparison with the four epimers obtained in the N-4 allyl series carefully studied by ^1H NMR spectrometry (unpublished results).
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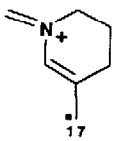
17. Two structural isomers of **12** are possible, with the ketone function at either C-19 or C-17, depending on the stereochemistry of the acetyl chain borne at C-20 before cyclization of **11**. We are able to distinguish between these two isomers, and demonstrate the formation of only the 19-oxo isomer, through use of mass spectrometry. Indeed, 19-oxo aspidofractinine undergoes a typical retro-DIELS-ALDER fragmentation giving an ion at M-42 and another at m/e = 109 [18]. In contrast the same fragmentation leads to ions at M-28 and m/e = 123 for the 17-oxo isomer [19].



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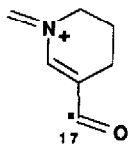

m/e=123

Other new data for **12** not previously available in the literature are as follows : IR ($CHCl_3$) cm^{-1} : 3350, 1705, 1605. ^{13}C NMR ($CDCl_3$) : 212.6 (C-19), 149.2 (C-13), 143.5 (C-8), 127.6 (C-11), 122.2 (C-9), 120.6 (C-10), 111.3 (C-12), 67.2 (C-2), 65.2 (C-21), 57.1 (C-7), 51.2 (C-18), 48.5 (C-5), 47.8 (C-3), 46.7 (C-20), 35.4 (C-6), 27.1 (C-15), 26.2 (C-16), 23.9 (C-17), 17.3 (C-14). ^1H NMR ($CDCl_3$) : 7.2 (d, J = 8 Hz, H-12); 7.05 (t, J = 8 Hz, H-11), 6.8 (t, J = 8 Hz, H-10), 6.7 (d, J = 8 Hz, H-9), 3.1 (s, H-21), 3.3-1.2 (17H, m). HRMS : exact mass m/e = 294.1729 calculated for $C_{19}H_{22}N_2O$ m/e = 294.1732.

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19. We thank Dr. N. KUNESCH (Faculté de Pharmacie, Université Paris XI) for the communication of the mass spectrum of 17-oxo aspidofractinine before publication.

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